NOVEL [3+2] ANNULATION REACTION OF NITRONES WITH BURGESS REAGENT AND A FEW RELATED REACTIONS

Thesis submitted to the
Cochin University of Science and Technology
In partial fulfilment of the requirements for the degree of

Doctor of Philosophy
In
Chemistry

In the Faculty of Science

By

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Under the supervision of

Dr. P. A. Unnikrishnan

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KOCHI – 682 022, Kerala, INDIA

February 2014

DECLARATION

I hereby declare that the work presented in the thesis entitled **"*Novel [3+2] annulation reaction of nitrones with Burgess reagent and a few related reactions*"** is the result of genuine research carried out by me under the supervision of **Dr. P. A. Unnikrishnan**, Assistant Professor, 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 **Sajitha T. S.**

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CERTIFICATE

This is to certify that the thesis entitled *"**Novel [3+2] annulation reaction of nitrones with Burgess reagent and a few related reactions**"* is a genuine record of research work carried out by **Mrs. Sajitha T. S.** under my supervision, in partial fulfilment of the requirements for the degree of Doctor of Philosophy of Cochin University of Science and Technology, and further that no part thereof has been presented before for the award of any other degree.

Kochi-22 **P. A. Unnikrishnan**
February 19, 2014 (Supervising Guide)

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Sajitha T. S.

PREFACE

Burgess reagent first prepared by E. M. Burgess in 1968, is a mild and selective dehydrating agent for secondary and tertiary alcohols and due to the amphipolar nature it is gainfully employed in a number of creative synthetic ventures. A close examination of the structure of Burgess reagent reveals that it can act as a 1,2-dipole. To the best of our knowledge, no attempts have been made to tap full synthetic potential of the amphipolar nature of this reagent and no reports on 1,3-dipolar addition to a σ-bond in acyclic systems are available in literature. In this context, we propose to unravel novel applications of Burgess reagent based on its amphipolar nature.

Rich and multifaceted chemistry of nitrones form the basis of many successful chemical transformations used in attractive synthetic strategies. For the last 50 years special attention has been given to nitrones due to their successful application as building blocks in the synthesis of various natural and biologically active compounds. Our interest in nitrones stems out of its unique character: *i.e.* it is a 1,3-dipole exhibiting distinct nucleophilic activity.

We reasoned that 1,3-dipole possessing significant nucleophilicity should react with amphipolar Burgess reagent with elimination of triethylamine to give the corresponding five-membered ring product by formal dipolar addition to a σ bond. To test this hypothesis we studied the reaction of nitrones with Burgess reagent. This thesis reveals our attempts to explore the [3+2] annulation reaction of nitrones with Burgess reagent which was found to be followed by a rearrangement

involving C-to-N aryl migration, ultimately resulting in diarylamines and carbamates.

We have also examined the reaction of cyanuric chloride with nitrones in DMF with a view to exploit the nucleophilicty of nitrones and to unravel the migratory aptitude, if any, observed in this reaction

The thesis is divided into six chapters. **Chapter 1** gives a brief introduction to Burgess reagent, nitrones and [3+2] annulation reactions with useful applications. Research problem is defined at the end of this chapter. **Chapter 2** deals with the synthesis of nitrones. Reactions of various nitrones with Burgess reagent are presented in **Chapter 3**. In **Chapter 4**, reaction of Burgess reagent with a few selected α,α,*N*-triarylnitrones with different substituents on the α-aryl ring to establish the actual mechanism of migration is described. Study of the reactions of various nitrones with cyanuric chloride given in **Chapter 5** provides additional evidence for the nucleophilic character of nitrones. Potential application of the new C-to-N aryl migration reaction discovered by us is described in **Chapter 6.** In this chapter we present an attractive route for the synthesis of a variety of diarylamines. The novel procedure developed by us is especially suited for the generation of unsymmetrically substituted diarylamines for which there is increasing demand due to their applications.

The structural formulae, schemes, tables and figures are numbered chapter-wise as each chapter of the thesis is organised as an independent unit. All new compounds are fully characterised on the basis of their spectral and analytical data. A comprehensive list of references is given at the end of each chapter.

List of Abbreviations

AcOH	:acetic acid
br	: broad
C	: centigrade
CSI	: chlorosulphonyl isocyanate
DBA	: dibenzoylacetylene
DCM	: dichloromethane
DEPT	: distortionless enhancement by polarisation transfer
DIPEA	: *N*,*N*-Diisopropylethylamine
DMF	: dimethylformamide
d	: doublet
dd	: doublet of doublet
dt	: doublet of triplet
E	: entgegen
ESR	: electron spin resonance
ESI	: electrospray ionization
FT IR	: fourier transform infrared
g	: gram
h	:hour
GC-MS	: gas chromatography-mass spectrometry
HCl	: hydrochloric acid
Hz	: hertz
m	: multiplet
Me	: methyl
mg	: milligram
min	: minute
mL	: millilitre
mp	: melting point
MS	: mass spectrometry
m-CPBA	: *m*- chloroperbenzoic acid
$Mo_2(acac)_2$	: Bis(acetylacetonato)dioxomolybdenum(VI)
nm	: nanometre
NMR	: nuclear magnetic resonance
ORTEP	: oak ridge thermal ellipsoid plot program
KBr	: potassium bromide
Ph	: phenyl
ppm	: part per million
KOH	: potassium hydroxide

RT	: room temperature
NaOH	: sodium hydroxide
s	: singlet
S_N	: substitution
t	: triplet
TCT	: 2,4,6-trichloro-1,3,5-triazine
td	: triplet of doublet
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	: tetramethylsilane
XRD	: X-ray diffraction
Z	: zusammen

CONTENTS

CHAPTER 3

REACTIONS OF NITRONES WITH BURGESS REAGENT

CHAPTER 4

MIGRATORY APTITUDE

CHAPTER 5

REACTION OF NITRONES WITH CYANURIC CHLORIDE

CHAPTER 6

SYNTHETIC APPLICATION OF REACTION OF NITRONES WITH BURGESS REAGENT: SYNTHESIS OF UNSYMMETRICAL DIARYLAMINES

CHAPTER 1

A Short Introduction to Burgess reagent, Nitrones and [3+2] Annulation Reactions

1.1 Abstract

This chapter reviews the reactivity and applications of Burgess reagent and also gives a brief introduction to nitrones. A brief discussion on [3+2] annulation reactions is also presented in this chapter.

1.2 Burgess Reagent

Methyl-*N*-(triethylammoniumsulphonyl)carbamate (**1**) (Figure 1.1), also known as Burgess reagent was first prepared by E. M. Burgess in 1968.[1] It was Peter Wipf who brought this reagent to the attention of organic chemists through its extensive use in the formation of 5-membered heterocycles [2,3,4] from their acyclic precursors and now it is gainfully employes in a number of creative synthetic ventures. It is a mild and selective dehydrating agent for secondary and tertiary alcohols and can produce urethanes from primary alcohols.

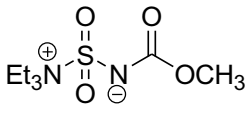

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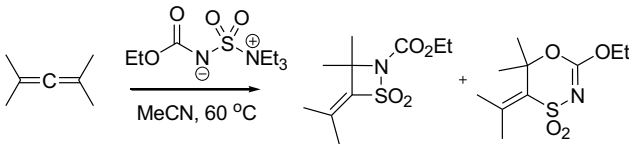
Figure 1.1

Burgess reagent is highly soluble in most of the common organic solvents including nonpolar ones, even though it is formulated as a salt and the dehydration reaction can be effected below 100 °C. The reagent has received wide acceptance because of the mild conditions required and the selectivity observed in the reactions mediated by it and has been employed in the synthesis of natural products and other complex molecules such as in Rigby's synthesis of narciclasine[5] and cedrene,[6] Nicolaou's synthesis of efrotomycin,[7] Uskokovic's synthesis of pravastatin,[8] and Holton's synthesis of Taxol.[9]

1.2.1 Discovery and Initial Applications

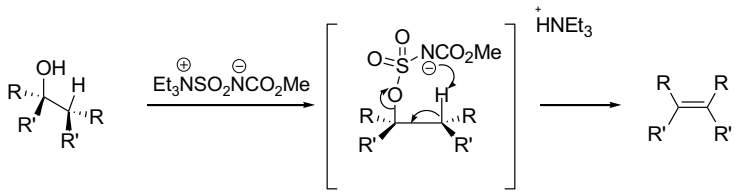
Burgess first explained the synthesis of Methyl-*N*-(triethylammoniumsulphonyl)carbamate **1** during his work on the cycloadditive reactivity of electrophilic *N* sulphonylamines with olefins and the reagent that now bears his name. Along with this synthetic procedure he also reported an observation on cycloaddition of this inner salt with tetramethylallene[2,10] to form isomeric cycloadducts (Scheme 1.1).



Scheme 1.1. Cycloadditions of inner salt with tetramethylallene.

1.2.2 Synthesis of olefins from secondary and tertiary alcohols

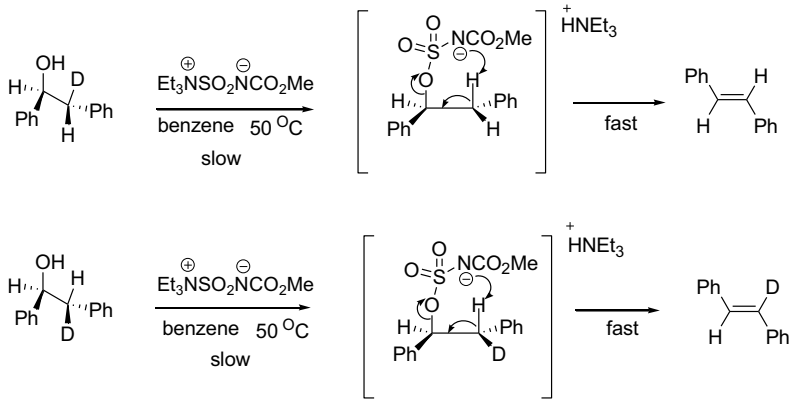
In 1970 Burgess and coworkers also found that the newly discovered inner salt, Methyl-*N*-(triethylammoniumsulphonyl)carbamate was a mild dehydrating agent for the dehydration of secondary and tertiary alcohols to the corresponding olefins.[2] According to them, during this dehydration process Burgess reagent first ionizes at low temperatures in non-polar solvents to provide tight ion pairs which then react with alcohol. The proposed mechanism involves the attack of the hydroxyl functionality onto the sulphur followed by *syn*-elimination of the intermediate sulphamate to give high yields of olefin and *N*-carboalkoxysulphamic acid salt (Scheme 1.2).



Scheme 1.2. Reaction of Burgess Reagent with secondary alcohols.

Evidence for *syn*- elimination was obtained from kinetic isotopic studies of *erythro*- and *threo*-2-deuterio-l,2-diphenylethyl-*N*-carbo-methoxysulphamate salts[11] in benzene at 50 ^{o}C. The *erythro* compound provided only *trans*-stilbene containing deuterium while the *threo* gave only protio-*trans*-stilbene with the elimination of *syn* deuterium (Scheme

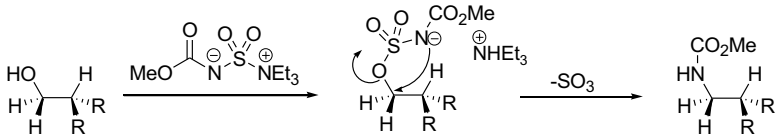
1.3). The same result is obtained in dimethylformamide also which indicate a *syn* elimination independent of solvent polarity. Kinetic isotopic studies reveals a small β-hydrogen isotope effect with k_H/k_D = 1.05 ±0.02 and 1.08 ± 0.03 for the *erythro* and *threo* isomers, respectively, in ethanol at 35 ^oC. These kinetic and stereochemical results supports the mechanism with an initial rate-limiting formation of an ion pair followed by a fast cis-*β*- proton transfer to the departing anion at a rate greater than the rotational interconversion of the *erythro*- and a *threo*-derived ion pairs. The product formation in dehydration of tertiary alcohols with the Burgess reagent follows Saytzef's rule in majority of cases.



Scheme 1.3. Kinetic and stereochemical considerations of the Burgess reagent mediated eliminations.

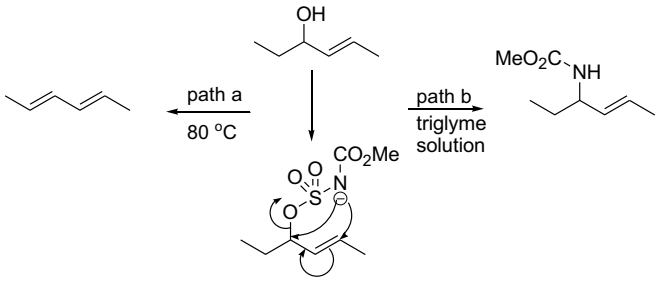
1.2.3 Synthesis of urethanes from primary alcohols

Though primary alcohols are expected to give terminal olefins as final product similar to the case of secondary and tertiary alcohols, it is observed that the reaction gives the corresponding carbamates (Scheme 1.4) in excellent yields. The mechanism involves the initial formation of an *N*-carbomethoxysulphamate salts derived from primary alcohols, which then prefers an energetically more favorable S_N2 pathway as compared to the Ei counterpart and urethanes results from the thermolysis of these salts.[11]



Scheme 1.4. Burgess reagent-mediated carbamate formation from primary alcohols.

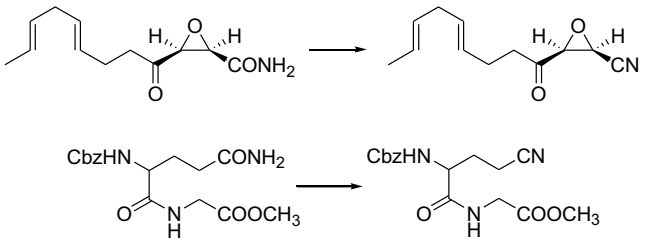
Reaction of allylic alcohols with the Burgess reagent forms an intermediate which can either produce a diene or a carbamate depending on the reaction conditions (Scheme 1.5).[11,12] While in triglyme at room temperature carbamate product predominates, the diene results from thermal decomposition in solid form at 80 °C.



Scheme 1.5. Reactivity of allylic alcohol with the Burgess reagent.

1.2.4 Nitrile formation from primary amides

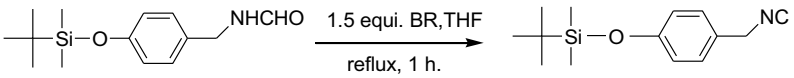
In addition to the application in dehydration reactions, Burgess reagent also finds application in the preparation of many other important functional groups like isocyanides, nitriles etc. Claremon and Phillips first reported the dehydration of primary amides to the corresponding nitriles.[13] The reagents commonly used for this transformation cannot be applied in the presence of other sensitive functional groups.[14] It requires an entirely alternative synthesis or protection of intermediate. Burgess reagent is a mild and efficient reagent for this transformation, and these reactions proceed with excellent chemoselectivity - Burgess reagent dehydrate selectively the amide to nitrile leaving other functional groups intact. The formation of nitriles as demonstrated in Scheme 1.6 is selective over epoxide openings and dehydration of secondary alcohols.



Scheme 1.6. Conversion of primary amides to nitriles.

1.2.5 Isocyanides formation from formamides

Burgess reagent can effectively convert formamides containing halide sensitive trimethylsilyl ether groups to isocyanides (Scheme 1.7) in high yields.[15,16]

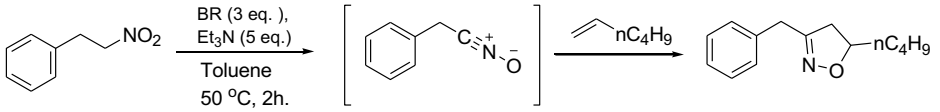


Scheme 1.7. Conversion of formamides to isocyanides.

1.2.6 Isoxazolines formation from nitrile oxides

Nitrile oxides are highly reactive intermediates and when generated *in situ* in the presence of dipolarophile, can readily undergo 1,3-dipolar cycloadditions with alkenes to give isoxazolines or dimerised to furoxans. In 1960 Mukaiyama developed a method for the dehydration of primary nitro compounds to nitrile oxides using 4-chlorophenylisocyanate[17] but the application of this procedure for the synthesis of complex natural products is limited since it requires high

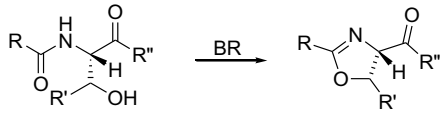
temperature and large excess of reagents leading to the formation of by products which are difficult to remove.[18] Later in 1997 Mioskowski published a very mild and efficient method[19] for the preparation of nitrile oxides from primary nitroalkanes using Burgess reagent (Scheme 1.8). In the presence of a terminal alkene, the corresponding isoxazolines were obtained in moderate yield, with some dimerization.



Scheme 1.8. Isoxazoline formation from nitroalkanes *via* a nitrile oxide intermediate.

1.2.7 Heterocycles from hydroxyl aminoacids

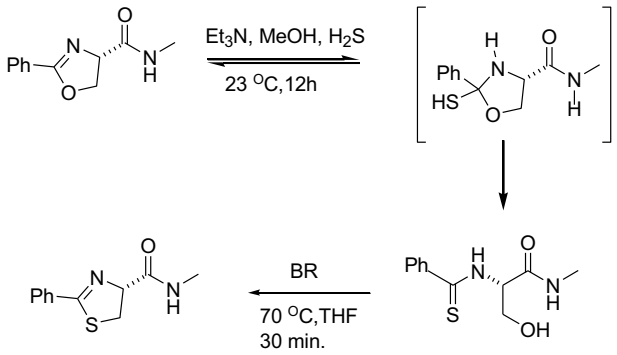
Wipf developed a cyclodehydration method using Burgess reagent for preparation of a variety of heterocycles. A single-step approach for the synthesis of 4,5-dihydrooxazolines by the cyclization of hydroxyl aminoacids (Scheme 1.9) with Burgess reagent is an example.[20] Similarly peptide analogs of serine and threonine were converted to dihydrooxazolines without any detectable side products like β-lactam, aziridines, or dehydroaminoacids.[21]



Scheme 1.9. Synthesis of dihydrooxazolines from β-hydroxy-α-amino acids**.**

1.2.8 Thiazolines from oxazolines

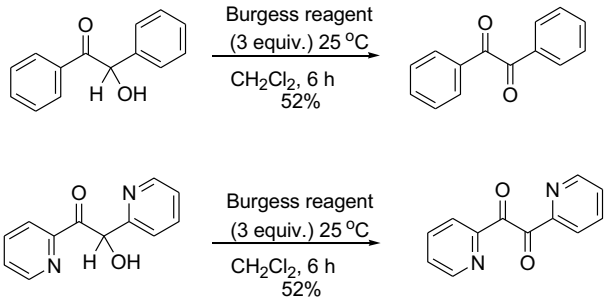
A high yielding and chemoselective direct conversion of oxazolines to thiazolines can be achieved using Burgess reagent.[22,23] Thiolysis of oxazolines with H_2S in methanol/triethylamine, followed by cyclodehydration with Burgess reagent gives thiazolines (Scheme 1.10).



Scheme 1.10. Synthesis of thiazolines from oxazolines.

1.2.9 Benzil from benzoins

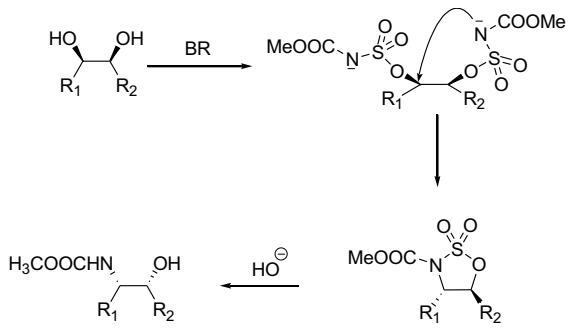
The oxidation of benzoin to benzil has been accomplished by several reagents such as nitric acid, Fehling's solution[24] etc. but the yields in the case of heteroaromatic compounds are poor with most of these reagents. Burgess reagent can smoothly oxidize benzoins to the corresponding benzils in good yield under very mild conditions (Scheme 1.11). In contrast to the other methods of oxidation, the yields are higher and the reactions are faster in the case of heteroaromatic compounds.[25]



Scheme 1.11. Synthesis of benzil from benzoin.

1.2.10 Stereoselective Synthesis of Sulphamidates from 1,2-Diols: A Facile Entry into β-Aminoalcohols

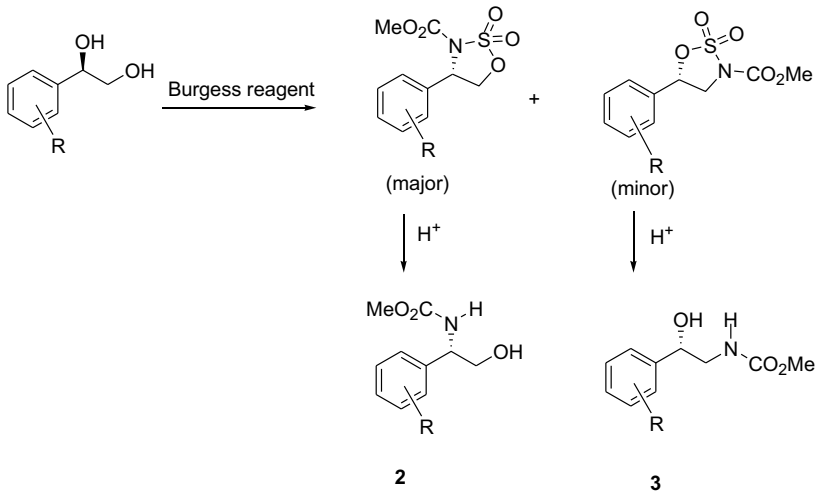
Nicolaou's group has reported various applications of Burgess reagent in the synthesis of a variety of sulphonyl-containing heterocycles, like for the preparation of sulphamidates from 1,2-diols,[26] (Scheme 1.12). The reaction follows an S_N2 mechanism in preference to typical pathways that involve the loss of water.



Scheme 1.12. Synthesis of sulphamidates from 1,2-diols.

Styrene-derived diols react with Burgess reagent giving sulphamidates with excellent regio- and stereoselectivity. This

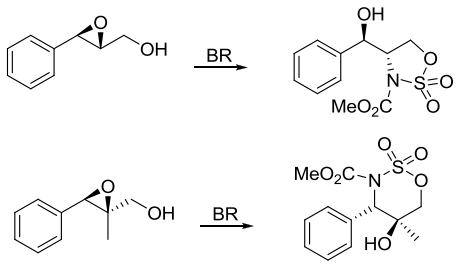
selectivity is reduced in the presence of strong electron withdrawing groups (R = -NO_2, -CF_3). Deprotection of cyclic sulphamidates using aqueous HCl in 1,4-dioxane at ambient temperature gives β-aminoalcohols **2** and **3** (Scheme 1.13).[27] This method provides easy access to chiral β-aminoalcohols which can be used as chiral ligands to perform asymmetric synthesis or as molecular probes to explore problems in chemical biology.



Scheme 1.13. Two-step synthesis of β-amino alcohols from 1,2-diols.

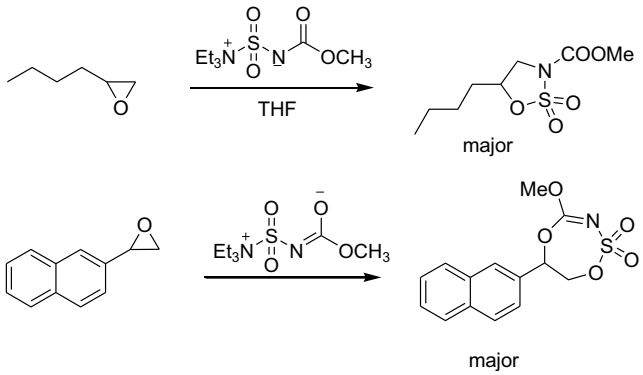
1.2.11 Epoxides to sulphamidates

Hydroxyepoxides derived from allylic alcohols on reaction with 1.3 equivalents of the Burgess reagent for 3 h in a 4:1 solvent mixture of THF/CH_2Cl_2, followed by chromatographic purification using a slightly basic material Florisil gives either 5- or 6-membered sulphamidates (Scheme 1.14).[28]



Scheme 1.14. Synthesis of 5-and 6-membered sulphamidates from epoxy alcohols.

Simple epoxides were believed to be inert to the action of Burgess reagent, but in 2003 Hudlicky[29] reported the reactions of epoxides with Burgess reagent. Aliphatic epoxides yield 5-membered cyclic sulphamidates (Scheme 1.15) while aromatic epoxides like styrene oxide gave mostly 7-membered sulphamidate and only trace amounts of 5-membered sulphamidate. The sulphamidates can serve as precursors to both *cis* and *trans* aminoalcohols, which are commonly used in the pharmaceutical sector (Figure 1.2), but only a very few methods are reported in the literature for the synthesis of sulphamidates.



Scheme 1.15. Synthesis of 5- and 7-membered cyclic sulphamidates from epoxides.

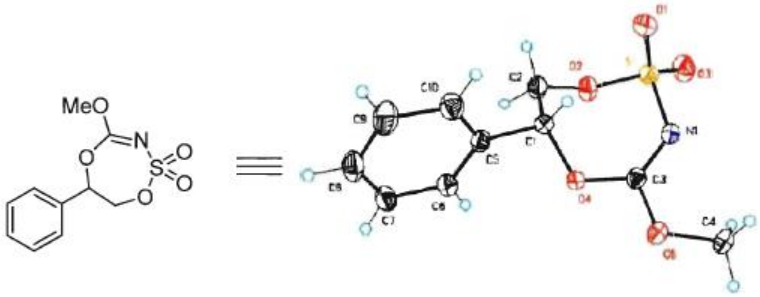
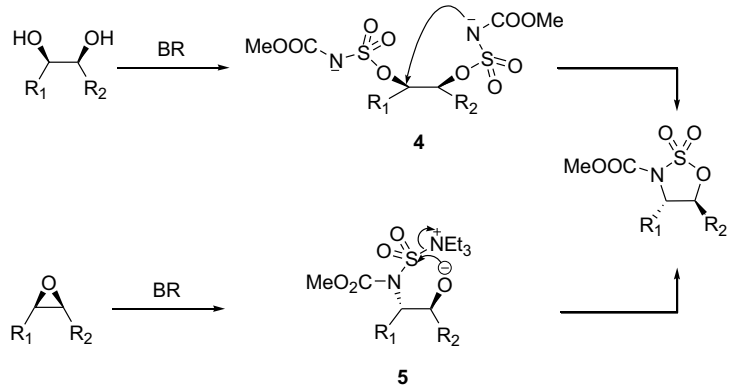


Figure 1.2. X-ray crystal structure of sulphamidate.[29]

Nicolaou and Hudlicky proposed mechanisms for the formation of *trans*-fused cyclic sulphamidates from 1,2-diols and oxiranes (Scheme 1.16). In case of 1,2-diols each alcohol group attacks an equivalent of the Burgess reagent displacing triethylamine and forming intermediate **4**, this is followed by S_N2 displacement at the more activated position. In

the second case, epoxide is opened with one equivalent of the Burgess reagent, followed by attack of the oxyanion **5** on the sulphur.



Scheme 1.16. Proposed mechanism for formation of *trans*-sulphamidate from 1,2-diol and epoxide**.**

The reaction of the chiral version of the Burgess reagent (Figure 1.3) with epoxides yields diastereomeric pairs of sulphamidates, which lead to *cis* and *trans* amino alcohols in each enantiomeric series (Scheme 1.17).

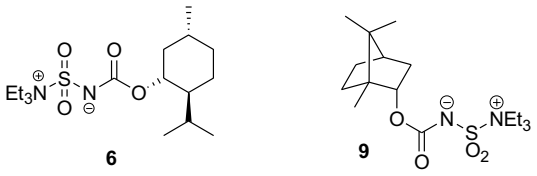
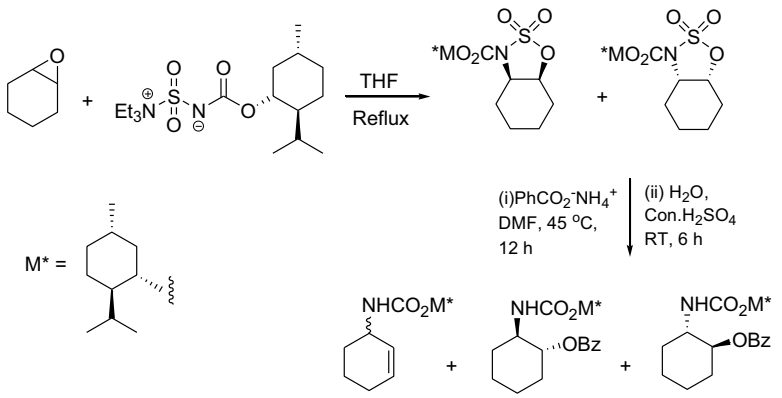


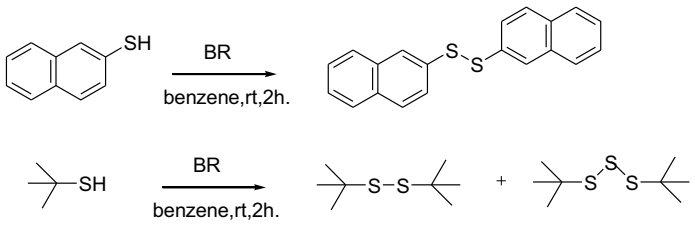
Figure 1.3. Chiral Burgess reagent.[30]



Scheme 1.17. Diastereomeric sulphamidates from epoxides.

1.2.12 Disulfides and trisulfides from thiols

The reaction of Burgess reagent with primary thiols[31] gives unexpected products, disulfides were produced from primary thiols, while secondary and tertiary thiols gives trisulfides along with trace amounts of disulfides (Scheme 1.18).

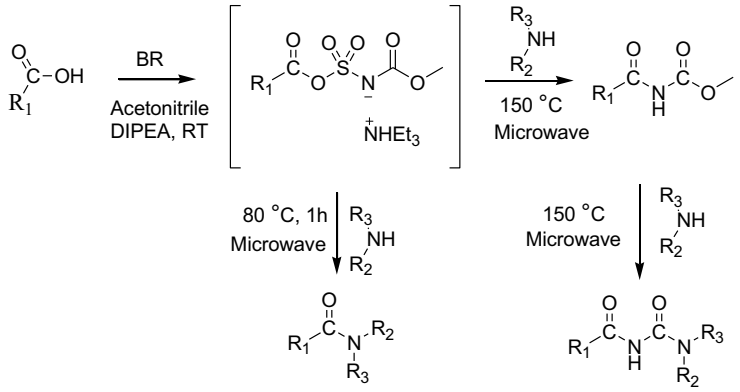


Scheme 1.18. Synthesis of disulfides and trisulfides.[31]

1.2.13 Acyl urea and amide from carboxylic acids

Makara reported that carboxylic acids upon treatment with Burgess reagent was converted to novel mixed sulphocarboxy

anhydrides,[32] subsequent treatment of such mixed anhydrides with amines at elevated temperature yielding acylureas and amides. The ratio of the products is temperature dependant. The method provides a simple and convenient route to diverse acylureas starting from carboxylic acids and amines (Scheme 1.19)

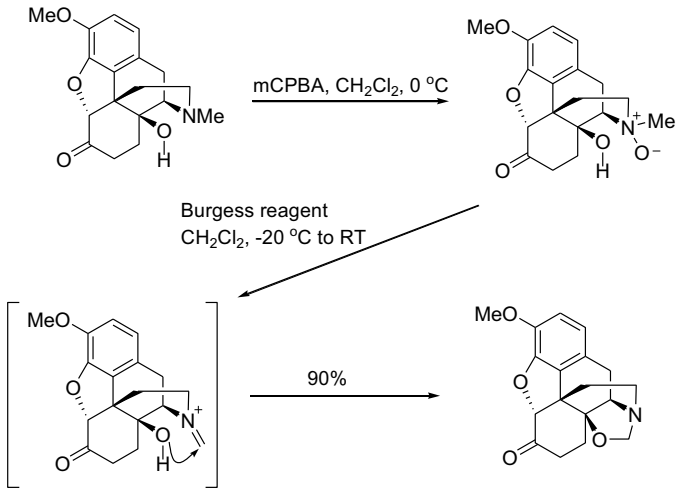


Scheme 1.19. Preparation of acylureas and amides from carboxylic acids.

1.2.14 Unexpected *N*-Demethylation of Oxymorphone and Oxycodone *N*-Oxides

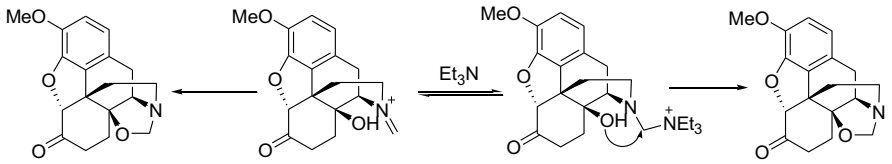
N-Oxides derived from oxycodone and *O*-acyloxymorphone were treated with the Burgess reagent to provide the corresponding oxazolidines in excellent yields.[33] This oxazolidines were further hydrolyzed to noroxymorphone, alkylation of which furnished naltrexone, naloxone, and nalbuphone,[34,35] which can be converted to nalbuphine, the mixed agonist-antagonist[36] analgesic. The entire sequence from oxymorphone to the various antagonists was reduced to three one-pot operations, proceeding in excellent overall yields (Scheme

1.20). Thus Burgess reagent provides an easy route to high yielding conversion of *N*-oxide from oxycodone to oxazolidine compared to other methods.[37,38]



Scheme 1.20. Reaction of oxycodone *N*-oxide with burgess reagent to oxazolidine.

The reaction proceeds *via* the formation of an intermediate iminium species, in the absence of a nucleophile, iminium species trapped, by the C-14 hydroxy group to form the oxazolidine. Such a process would represent the formally forbidden 5-endo-trig closure. An alternative to this procedure involves reaction with triethylamine which trap the iminium species and a subsequent S_N2-type alkylation, as shown below in Scheme 1.21.

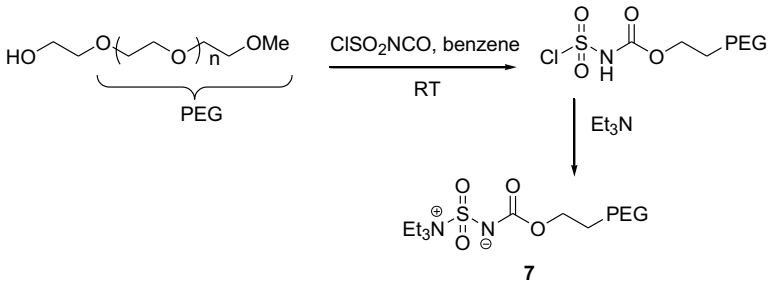


Scheme 1.21. Mechanism of oxazolidine formation.

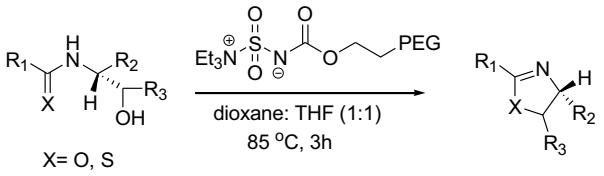
1.3 Important analogues of Burgess reagent

1.3.1 PEG supported Burgess reagent

The standard Burgess reagent is sensitive to moisture and oxidation and often needs to be stored at low temperature. In 1996, Wipf developed a poly(ethyleneglycol)-linked version of the reagent **7**[39,40] which is more stable compared to the standard reagent. This can be prepared from chlorosulphonyl isocyanate, PEG, and triethylamine *via* a two-step preparation, involving the conversion of chlorosulphonyl isocyanate to carbamate followed by its reaction with triethylamine (Scheme 1.22). Cyclodehydration of β-hydroxy amides [41,42] using PEG supported Burgess reagent gives oxazolines in good yield (Scheme 1.23). After completion of the reaction the reagent can be conveniently removed by filtration through silica gel using hexane/EtOAc (1:1) and other side products remained adsorbed on PEG matrix and the silica gel. Thiazoline formation from thioamides[42] can also be achieved under similar conditions using PEG supported Burgess reagent.

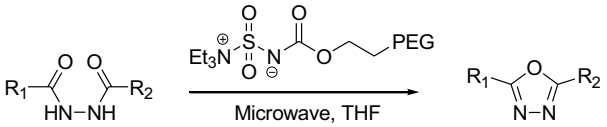


Scheme 1.22. Synthesis of PEG linked Burgess reagent.



Scheme 1.23. Formation of oxazolines from hydroxyl amides.

Cyclodehydration of 1,2-diacylhydrazines using PEG supported Burgess reagent under single-mode microwave conditions gives 1,3,4-oxadiazole[43] (Scheme 1.24).

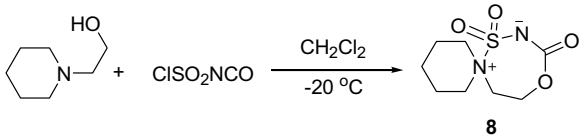


Scheme 1.24. Formation of 1,3,4-oxadiazole from 1,2-diacylhydrazines.

1.3.2 Cyclic Burgess reagent

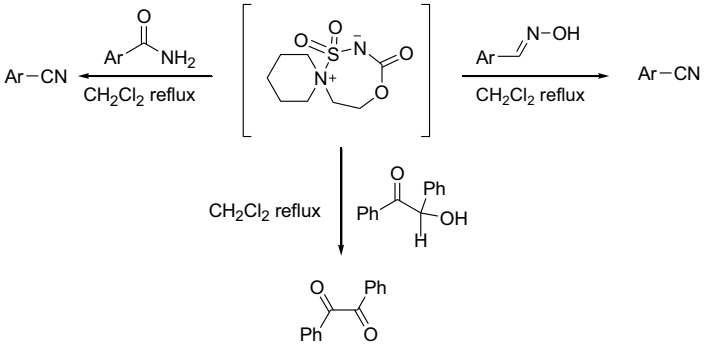
Treatment of chlorosulphonyl isocyante with a suitable β-aminoalcohol should yield a cyclic Burgess-type reagent **8** in one step (Scheme 1.25).[44] This version of the reagent can be used as such without

isolation and purification for various transformations like dehydration of amides, oximes and oxidation of benzoins etc. (Scheme 1.26).



8

Scheme 1.25. Synthesis of cyclic Burgess reagent.



Scheme 1.26. Transformations with cyclic Burgess reagent.

1.3.3 Chiral Burgess reagent

Structures of Burgess reagent incorporated with menthol and camphor are given in Figure 1.3. The menthol-containing reagent **6** was prepared easily by reacting menthol with chlorosulfonyl isocyanate followed by triethylamine. Reaction of **6** (2.3 equiv.) with cyclohexene oxide produced a 1:1 mixture of diastereomers of sulphamidates.[30]

1.3.4 Thermally Stable Versions of the Burgess Reagent

Several attempts have been made to render Burgess reagent more resistant to moisture and oxidation and thermally more stable. It was noted that the stability as well as the reactivity of the original Burgess reagent can be improved by modifying the triethylamine and methoxy component of the conventional reagent. Examples for thermally stable versions of the Burgess reagent[45] (**10**, **11** and **12**) are given below (Figure 1.4).

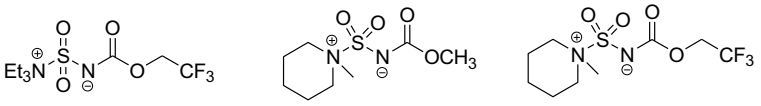


Figure 1.4. Thermally stable versions of Burgess Reagent.

The half-life of conventional Burgess reagent and its chiral version at 50 ^{o}C is 216 and 198 min. respectively. At reflux, the corresponding half-lives reduced to 19min and 13min respectively. The Burgess reagent as well as the menthyl chiral version completely decompose in less than an hour at 78 ^{o}C. The reagents derived from *N*-methylpiperidine **11** and **12** are stable even at refluxing temperatures for 3 h or more.

In short, the above examples have underlined the impressive power of Burgess reagent to effect various transformations of synthetic interest under very mild conditions. Compatibility of Burgess reagent with many functionalities, *e.g.* halogens, epoxides, alkenes, alkynes,

aldehydes, ketones, acetals, esters, secondary amides, etc. makes it an attractive reagent for the introduction of C-C double bonds into highly functionalized molecules.[46] Even though Burgess reagent is already known to bring about a large number of transformations new applications are certainly to be expected in the future. The amphipolar nature of Burgess reagent is equally impressive: nucleophiles attack the sulphur[2] end while electrophiles attack its nitrogen.[26] To the best of our knowledge, no attempts have been made to tap full synthetic potential of the amphipolar nature of Burgess reagent. In this context, we propose to unravel novel applications of Burgess reagent.

1.4 Nitrones

Nitrones, first prepared by Beckmann in 1890,[47,48] represent a powerful substrate in synthetic chemistry due to their reactivity in cycloaddition reactions and nucleophilic addition reactions.[49] For the last 50 years special attention has been given to nitrones due to their successful application as building blocks in the synthesis of various natural and biologically active compounds. The general structure of nitrone is given below (Figure 1.5).

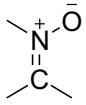
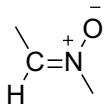


Figure 1.5

The name nitrone was derived from abbreviation of *'nitrogen-ketones'* by Pfeiffer in 1916 to highlight their resemblance to ketones.[50] The reactivity of aromatic *N*-oxides resembles that of *N*-oxides so they retain the name *N*-oxide even though it contains nitrone moiety. The terms aldo and keto nitrones (Figure 1.6) are used to distinguish between those with or without proton on the α-carbon respectively. Nitrones (acyclic) can exist in either *E*- or *Z*- form[51] and they can be readily interconverted either thermally[52] or photochemically.[53] Occurrence of geometrical isomerism in unsymmetrical nitrones further support the existence of dipolar structure with negative charge concentrated on oxygen.

Aldonitrone 

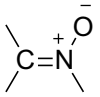
Ketonitrone 

Figure 1.6

Nitrones are *N*-substituted 1,3-dipolar compounds[54,55] (Figure 1.7) capable of reacting with a wide variety of dipolarophiles giving rise to a vast array of products.

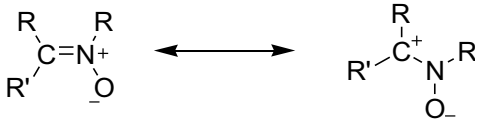
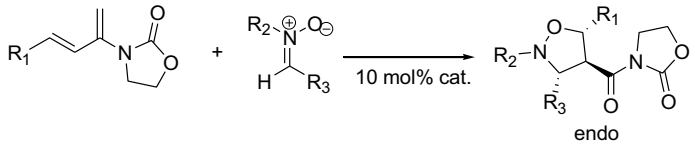


Figure 1.7

1.4.1 Reaction of nitrones with alkenes

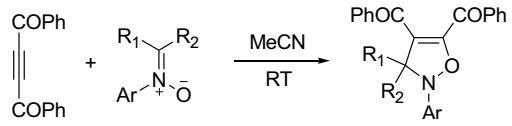
1,3-Dipolar cycloaddition reaction of nitrones with alkenes gives *endo* isoxazolidine product in presence of a catalyst (Scheme 1.27).[56]



Scheme 1.27. 1,3-dipolar cycloaddition reaction of nitrones with alkenes.

Reaction of nitrones with alkenes both in the inter and intramolecular versions gives important class of compounds, isoxazolidines,[56-61] which are convenient precursors of 1,3-aminoalcohols, a structural fragment present in a number of organic compounds of interest.[62] They can also react with allenes,[63,64] ketenes,[65] isocyanates,[66,67] isothiocyanates,[68] nitriles,[69] *etc*. to give a number of heterocycles.

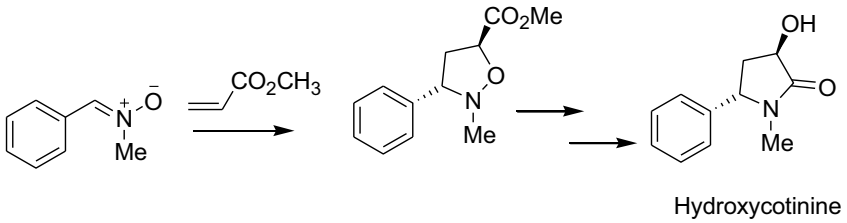
1,3-Dipolar cycloaddition reaction of nitrones and dibenzoylacetylene (DBA) gives isoxazoline derivatives (Scheme 1.28). In this cycloaddition nitrone act as a 1,3-dipole and DBA as dipolarophile,[70] and the reaction proceeds through a zwitterionic intermediate. Cyclisation of the zwitterionic intermediate to the formal cycloadduct is only one of the several possible pathways and this method is an efficient method for the synthesis of pharmacologically as well as synthetically important 3(*2H*)-furanones and quinolines.



Scheme 1.28. Cycloaddition reaction of nitrone with DBA.

1.4.2 Synthesis of hydroxycotinine from nitrones

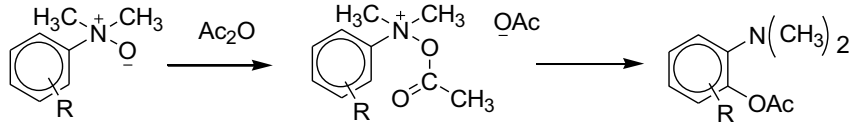
The structure of hydroxycotinine, a human metabolite of nicotine was confirmed in an independent synthesis employing nitrone-olefin cycloaddition[71] (Scheme 1.29).



Scheme 1.29. Synthesis of hydroxycotinine.

1.4.3 Reaction of *N*-arylnitrones with acetic anhydride

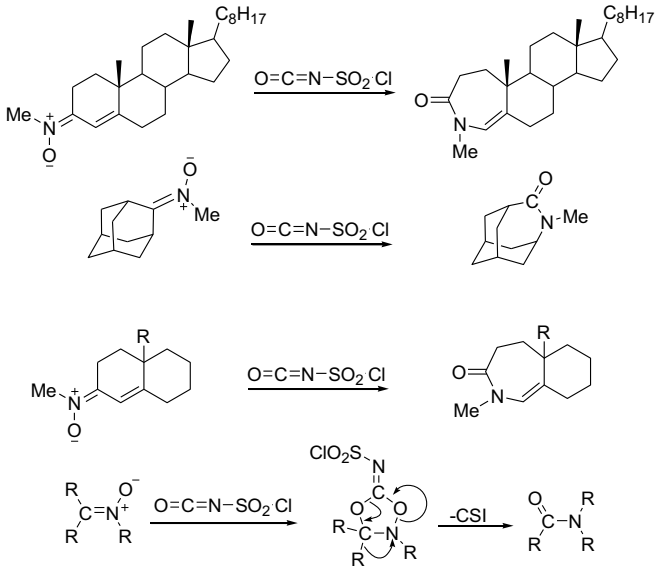
The classes of *N*-aryl nitrogen oxides react with acid chlorides and anhydrides to yield corresponding ring substituted products. For example reaction of *N,N*-dimethylaniline *N*-oxides with acetic anhydride gives ortho-acetylated *N,N*-dimethylanilines.[72] The reaction proceeds via the formation of *N*-acetoxy-*N,N*-dimethylanilinium acetate as shown in Scheme 1.30.



Scheme 1.30. Reaction of *N*-arylnitrones with acetic anhydride.

1.4.4 Reaction of nitrones with chlorosulphonyl isocyanate

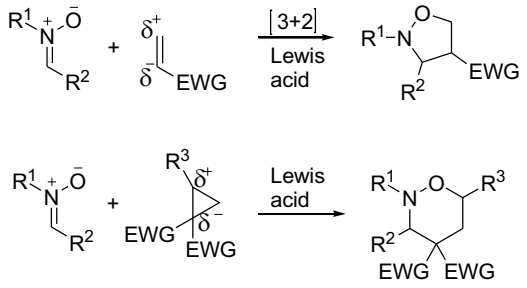
The rearrangement of nitrones to amides is a potentially useful reaction as it provides a viable synthetic route to differently substituted amides and amines. In the reaction of α,α,*N*-triaryl nitrones with chlorosulphonyl isocyanate,[73] (CSI) the C=O group of CSI which adds[74] to nitrone dipole[75] under very mild reaction conditions gives amide product (Scheme 1.31). The rearrangement has synthetic importance, since it can be used for the synthesis of several hitherto inaccessible amides and amines.



Scheme 1.31. Reaction of nitrones with CSI.

1.4.5 Reaction of nitrones with cyclopropane

Reaction of nitrones with cyclopropanes represents the first example of a dipolar homo [3+2] cycloaddition. Nitrones on reaction with cyclopropane in the presence of 5 mol% $Yb(OTf)_3$ in dichloromethane gives tetrahydro-1,2-oxazines.[76] This reaction of nitrone is a dipolar homo [3+2]cycloaddition (Scheme 1.32) and this "cycloaddition" can be applied to the synthesis of the [3.3.1]bicyclic core of FR-900482[77] and related compounds. Cyclopropane undergoes a significant degree of charge separation in the presence of a Lewis acid such as $Yb(OTf)_3$. Such a charge separation would be enhanced by the presence of a carbocation-stabilizing group on the cyclopropane unit.[78] The reaction follows an annulation mechanism involving an initial attack of the nitrone oxygen atom onto the cyclopropane followed by the attack of the resulting malonate onto the iminium species.



Scheme 1.32. Reaction of nitrones with cyclopropane.

1.4.6 Nitrones as spin trap agents

Apart from constituting an efficient class of compounds capable of acting as 1,3-dipoles in cycloaddition reactions, nitrones also can act as spin traps for distinguishing free radical species, especially when direct detection of some free radicals (for *e.g.*, superoxide and hydroxyl radical) becomes very difficult. Upon addition of radicals, nitrones form nitroxides in high yields (Scheme 1.33), the ESR spectra of this long lived spin adducts can be recorded and analyzed. Nitrones commonly used as spin traps are α-phenyl-*N*-*tert*-butylnitrone (PBN) and 5,5-dimethyl-1-Pyrroline N-oxide (DMPO)[79,80] (Figure 1.8).

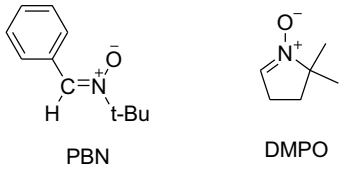
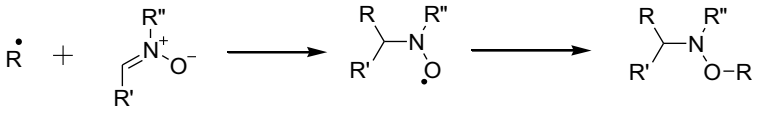


Figure 1.8



Scheme 1.33 Spin trapping reaction between nitrone and radical.

Thus, the radical spin capturing reaction can lead to the synthesis and fast assembly of complex molecular architectures. Nitrone-mediated radical coupling (NMRC)[81-83] works very efficiently with macromolecules.

Nitrones are also used as antioxidants in biological systems and therapeutics in age related diseases. Clinical studies revealed that they can be hepatocarcinogenic in rats.[84]

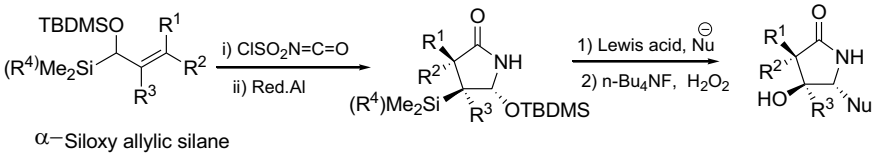
Rich and multifaceted chemistry of nitrones form the basis of many successful chemical transformations used in attractive synthetic strategies. In recent years, the effect of catalysts on the rate and selectivity of the nitrone nucleophilic addition reaction has been examined from which impressive results have begun to emerge. The wide range of chemistry incorporating nitrone cycloaddition shows no sign of having reached its limits and novel applications are expected to appear in the future. Our interest in nitrones stems out of its unique character: it is a 1,3-dipole exhibiting distinct nucleophilic activity.

1.5 [3+2] Annulation reactions

Annulation reactions are important in the construction of a wide variety of carbocyclic and heterocyclic frameworks.[85] Among various annulations, [3+2] annulation represents a breakthrough in the field of organic synthesis. The reaction between a 1,3-dipole and 1,2-dipole should yield five membered ring structures[86] *via* a formal [3+2] annulation sequence, a few examples are given below.

1.5.1 [3+2] Annulation of α-Siloxy Allylic Silanes with Chlorosulphonyl Isocyanate

The [3+2] annulation of α-siloxy allylic silanes with *N*-chlorosulphonyl isocyanate ($ClSO_2NCO$) gives highly substituted γ-lactams,[87] and further oxidation of the silyl group leads to complex *α*-hydroxy-*γ*-lactams (Scheme 1.34). This annulations[88,89] provides the key ring systems for the syntheses of (+)-blastmycinone[90] and (±)-peduncularine.[91] Application of α-siloxy allylic silanes in [3+2]annulations are particularly attractive because of their convenient syntheses,[92] the facile preparation of asymmetric variants,[93] and the functionality available in the annulation products.

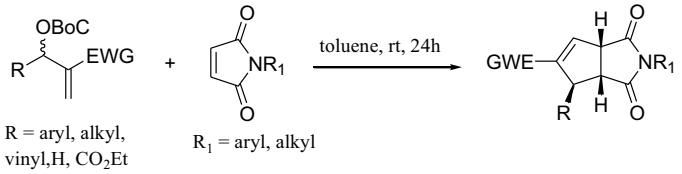


α−Siloxy allylic silane

Scheme 1.34. Synthesis of highly substituted γ-lactams.

1.5.2 Functionalized Bicyclic Imides *via* [3+2] Annulation of MBH Carbonates

A highly enantioselective [3+2] annulation of Morita-Baylis-Hillman (MBH) carbonates[94] and maleimides catalyzed by chiral phosphines gives functionalized bicyclic imides (Scheme 1.35)



Scheme 1.35 Synthesis of bicyclic imides.

1.5.3 Radical Approach to [3+2] Annulation

In principle, reaction between a 1,3-dipole and 1,2-dipole should yield five membered ring structures *via* a formal [3+2] annulation sequence. Huisgen and co-workers have refined this methodology for general application in organic synthesis. Several 1,3-dipoles were investigated by Huisgen. Invariably, the dipolarophile was a π-system. To the best of our knowledge, 1,3-dipolar addition to a σ-bond in acyclic systems has not been reported in literature. Identification of appropriate substrates is the key to successful demonstration of this novel concept. Close examination of the structure of Burgess reagent reveals that it can act as a 1,2-dipole. Based on the reactions of Burgess reagent detailed in the first part of this chapter, it is clear that Burgess reagent exhibit both electrophilic and nucleophilic activity. Hence, in principle, any 1,3-dipole possessing significant nucleophilicity should react with Burgess reagent with elimination of triethylamine to give the corresponding five-membered ring product by formal dipolar addition to a σ bond. To test this hypothesis, we selected nitrones as the dipole since significant nucleophilic activity of nitrones is well documented in literature.

1.6 Objectives

1. Synthesis of substituted triphenyl nitrones
2. Reaction of Nitrones with Burgess reagent – Mechanism
3. Migratory aptitude study
4. Comparative study of Reaction of Nitrones with Cyanuric chloride and burgess reagent
5. Synthetic application of reaction of nitrones with Burgess Reagent - synthesis of unsymmetrical diarylamines

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CHAPTER 2

SYNTHESIS OF NITRONES

2.1 Abstract

Syntheses of a few selected ketonitrones and aldonitrones required for various studies included in the thesis are described in this chapter.

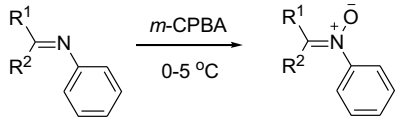
2.2 Introduction: General Methods of Synthesis of Nitrones

Several methods are available for the synthesis of nitrones. In general the synthesis procedures are classified into oxidative and non-oxidative methods. Oxidative method includes oxidation of *i*) secondary amines using urea-hydrogen peroxide complex *ii*) hydroxylamines using manganese dioxide, and *iii)* imines using peracids. Reaction between *i*) aldehydes and hydroxylamines and *ii*) diazo compounds and nitroso compounds constitute typical examples for non-oxidative processes for nitrone synthesis.

2.2.1 Oxidative Methods

2.2.1.1 Oxidation of Imines

Oxidation of imines can be achieved by the use of several reagents like peracids, dimethyldioxirane (DMD), $KMnO_4$ etc. Oxidation of imines using peracids leads to oxaziridines (Scheme 2.1), which then rearrange to the corresponding nitrones.[1-5]



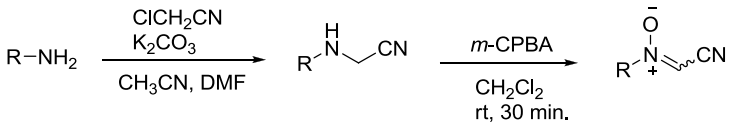
Scheme 2.1

Diarylnitrones can be synthesized by the oxidation diarylimines with oxone (potassium peroxymonosulphate) in an aqueous solution of $NaHCO_3$, in acetonitrile or in acetone.[6] Photochemical oxidation (λ 350 *nm*) of aldimines in acetonitrile, in the presence of O_2 over a TiO_2 suspension is another method for the synthesis of nitrones.[7,8] Oxidation of imines to nitrones can also be achieved by using methyl(trifluoromethyl)dioxirane as an oxidant.

2.2.1.2 Oxidation of Amines

Oxidation of secondary amines provides a more convenient route to nitrones. The commonly used reagents for secondary amine oxidation include urea complex with hydrogen peroxide (UHP), *m*-chloroperbenzoic etc. Secondary amines can be converted to nitrones by oxidation using urea complex with hydrogen peroxide (UHP) in methanol and the reaction is catalyzed

by Mo, W, or SeO_2.[9] Oxidation of secondary amines with alkylhydroxyperoxides in presence of titanium alkoxide or selenium compound gives nitrones quickly and with good selectivity.[10,11] Most frequently used oxidant for secondary amines is *m*-chloroperbenzoic acid (Scheme 2.2).[12] *m*-CPBA first oxidizes tertiary amines to amine *N*-oxides which then undergo Cope or Meisenheimer rearrangement to give nitrones.[13]



Scheme 2.2

This method can be used for the one-pot synthesis of asymmetrical acyclic nitrones starting from aromatic aldehydes. The aldehydes are first converted to imines which are then reduced to secondary amines and finally oxidized to nitrones.

2.2.1.3 Oxidation of Hydroxylamines

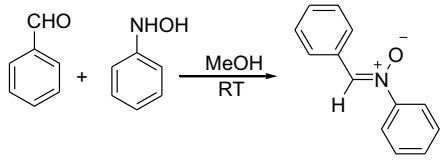
Oxidation of hydroxylamines containing one or more α-hydrogens is another common method for the synthesis of nitrones, common reagents being air, H_2O_2, *m*-CPBA and metal oxides like MnO_2, PbO_2, HgO. The hydroxylamines first form nitroxyl radicals which then undergo a disproportionation reaction with excess of the oxidant, giving nitrones in good yield under mild conditions.[14,15] Oxidation using HgO proceeds with high regioselectivity[16] depending on the electronic nature of substituents.[17-19] Both acyclic

and cyclic nitrones can be prepared in high yield under mild conditions (-78 ^{o}C) using diazabicycloundecene (DBU) in CH_2Cl_2.

2.2.2 Non-oxidative Methods

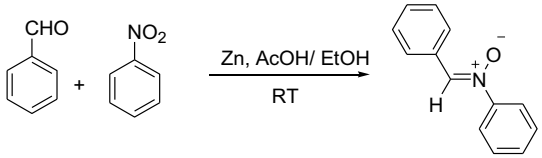
2.2.2.1 Condensation of *N*-Monosubstituted Hydroxylamines with Carbonyl Compounds

A direct route for the synthesis of diarylnitrones is via the condensation of *N*-monosubstituted hydroxylamines with carbonyl compounds (Scheme 2.3).[20]



Scheme 2.3

Hydroxylamines can be prepared *in situ* by the reduction of nitro compounds with zinc powder in the presence of weak acids (NH_4Cl or AcOH) (Scheme 2.4).[21,22] The condensation is carried out under mild conditions and it is possible to synthesize a variety of *N*-alkylnitrones using this method without affecting other functional groups.[23,24] Condensation of *N*-substituted hydroxylamines with aldehydes and ketones is widely used in the synthesis of various spin traps and biologically active nitrones.[25,26]

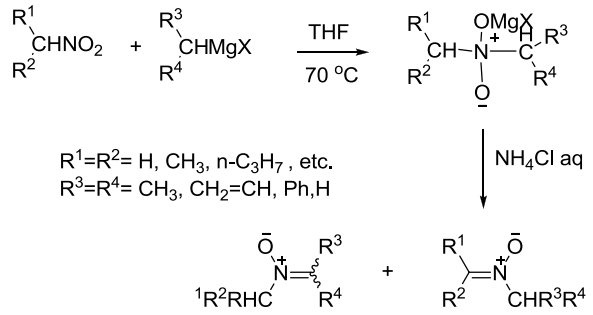


Scheme 2.4

α-Aryl-*N*-methylnitrones can be synthesized using silica gel-NaOH catalytic system and the reaction proceeds without solvents in good yields, irrespective of the electron-donor or electron-acceptor nature of the substituents on benzaldehyde. Under similar reaction conditions only aldehydes can be converted to nitrones. Hence it is possible to carry out selective syntheses in cases where the system contain both aldehyde and ketone functionalities[27]. Synthesis of novel glycolipidic nitrones have been demonstrated using 4A molecular sieves, these nitrones are potential antioxidant drugs for neurodegenerative disorders.[28] *N*-Benzylketonitrones were obtained in the condensation reaction of *N*-benzylhydroxylamine with ketones in methylene chloride using $ZnCl_2$.[29]

2.2.2.2 Synthesis from Nitro Compounds

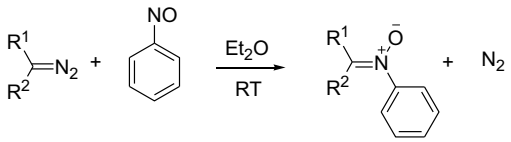
Addition of benzyl and allyl Grignard reagents to aryl- and alkylnitro compounds gives nitrones in good yields with excellent chemoselectivity (Scheme 2.5). The stereochemistry of newly generated double bond is determined by the nature of the employed Grignard reagent. Benzylmagnesium halides give exclusively *Z*-isomers of nitrones[30] whereas 2-butenylmagnesium chloride gives predominantly *E*-isomers of the conjugated nitrone.



Scheme 2.5

2.2.2.3 Synthesis from Nitroso Compounds

Condensation of diazo compounds with nitrosoarenes gives nitrones (Scheme 2.6) and this is the common method used for the synthesis of triarylnitrones.[31,32]



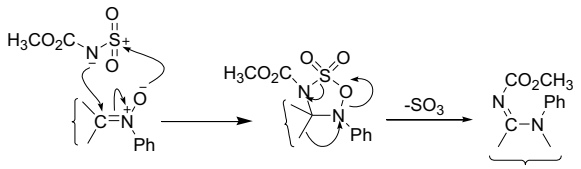
Scheme 2.6

In the present study, we have adopted two simple methods for the synthesis of the target nitrones considering the availability of the required substrates and easy workup. N-(diphenylmethylene)aniline-N-oxides were synthesized *via* the condensation of nitrosoarenes with diazo compounds and N-(benzylidene)aniline-N-oxide were obtained by the condensation reaction of hydroxylamines with benzaldehyde.

2.3 Results and Discussion

In the present investigation, we have extensively employed Burgess reagent and nitrones. Burgess reagent exhibits differential

reactivity towards several classes of compounds.[33-41] Close examination of the structural features of Burgess reagent reveals that it can be considered as a 1,2-dipole. To the best of our knowledge, exploitation of this structural aspect of Burgess reagent is not reported in literature. Similarly, nitrones constitute an important class of 1,3-dipoles. Several reports are available on exploiting the 1,3-dipolar nature of nitrones. Comprehensive listing of reports on such reactions is beyond the scope of this thesis. Interestingly, a few stray reports on the nucleophilic character of nitrones are also available in literature. Our group has made a few significant contributions in this area.[42,43] In several of their reactions, nitrones exhibit distinct nucleophilic character.[44-47] We reasoned that 1,3-dipoles like nitrones possessing significant nucleophilicity should react with a 1,2-dipole such as Burgess reagent with elimination of triethylamine to give the corresponding five-membered ring product – a novel example for formal dipolar addition to a σ-bond (Scheme 2.7). In order to validate our assumption, we examined the reaction between several nitrones and Burgess reagent. Structure of nitrones selected for this study is given in the Figure 2.1.



Scheme 2.7

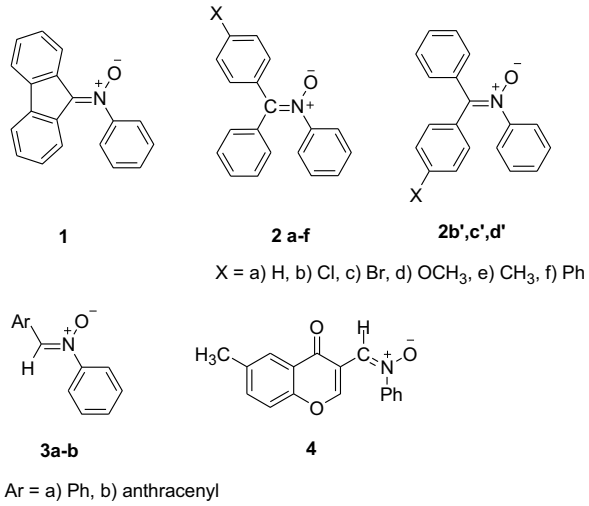
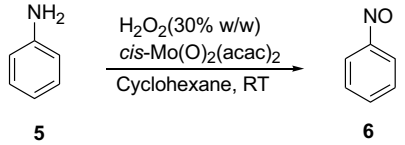


Figure 2.1

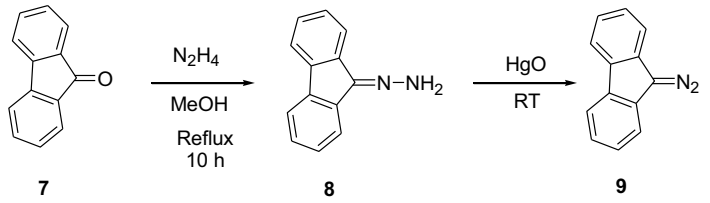
2.3.1 Synthesis of *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide

N-(9H-fluoren-9-ylidene)aniline-*N*-oxide was synthesized by the condensation of nitrosoarenes with 9-diazofluorene. Usually nitrosoarenes are synthesized by a conventional lengthy procedure which involves the reduction of aromatic nitro compounds to the corresponding phenylhydroxylamine followed by oxidation and purification by steam distillation.[48] We prepared the required nitrosoarene **6** by a very simple protocol developed by Porta *et al*. This procedure involves oxidation of aromatic primary amines using H_2O_2 (30% w/w) in presence of catalytic amounts of *cis*-$Mo(O)_2(acac)_2$ at room temperature under aerobic conditions (Scheme 2.8).[49]



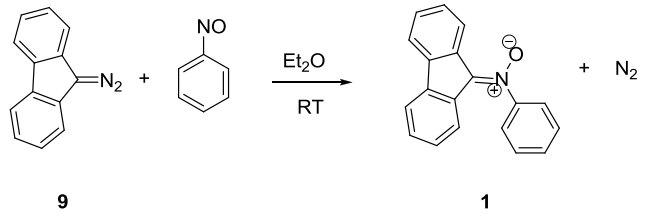
Scheme 2.8

9-Diazofluorene[50] (**9**) was prepared by the oxidation of fluorenone hydrazine with mercuric oxide (HgO) (Scheme 2.9).[51]



Scheme 2.9

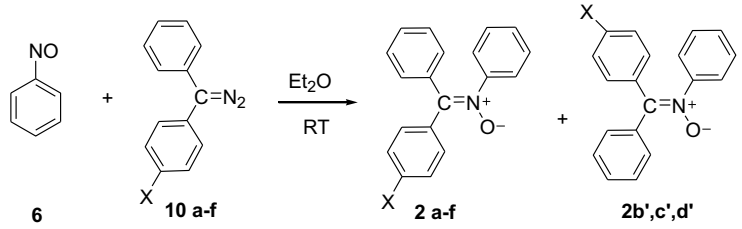
N-(9H-fluoren-9-ylidene)aniline-*N*-oxide (**1**) was prepared by the reaction between diazofluorene and nitrosobenzene.[5,31] (Scheme 2.10).



Scheme 2.10

2.3.2 Synthesis of *N*-(diphenylmethylene)aniline-*N*-oxide

N-(diphenylmethylene)aniline-*N*-oxide **2** was prepared by the condensation of nitrosobenzene **6** with diaryldiazomethane (**10a-f**) at room temperature (Scheme 2.11).[31]

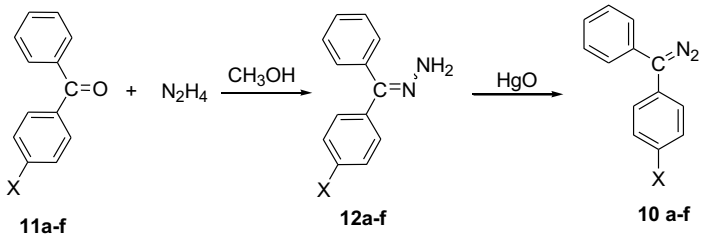


X = a) H, b) Cl, c) Br, d) OCH_3, e) CH_3, f) Ph

Scheme 2.11

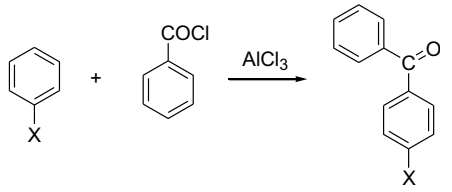
Triarylnitrones exhibit *syn-anti* isomerism and both these isomers can potentially be generated in the reaction between diazo compounds and nitrosoarenes. Indeed, both *syn*- and *anti*-isomers were generated as inseparable mixtures in some of our reactions. In a few cases, only a single nitrone isomer was generated. Though a structure-srtereoselectivity relationship was evident, we did not explore the mechanistic details of this reaction to establish the observed stereoselectivity. We could however, establish the isomer ratio on the basis of ^{1}H NMR spectrum of the isomer mixtures. Earlier reports suggest that *ortho* protons on the aryl group *syn* to oxygen appear downfield with respect to *ortho* protons of the *anti*-aryl group.[52] We established the stereochemistry of one of the nitrones by single crystal X-ray diffraction analysis and this compound's ^{1}H NMR spectrum was benchmarked for estimating isomer ratios, where appropriate, of product mixtures. Since both *syn*- and *anti*-isomers are formed in some cases, we adopted the following numbering schemes for the nitrone isomers: **2b** denotes the *syn*-isomer while the corresponding *anti*-isomer is numbered **2b**'. All nitrones were identified by spectral and analytical data.

Diaryldiazomethanes **10a-f** required for the synthesis of nitrones were obtained by the oxidation of the corresponding benzophenone hydrazones **12a-f** with mercuric oxide (Scheme 2.12).[51]



Scheme 2.12

Diarylketones **11b-f** required for the synthesis of diarylketone hydrazones **12b-f** were in turn prepared by the Friedel-Crafts acylation[53] of corresponding arenes with benzoyl chloride, in the presence of anhydrous aluminum chloride (Scheme 2.13)

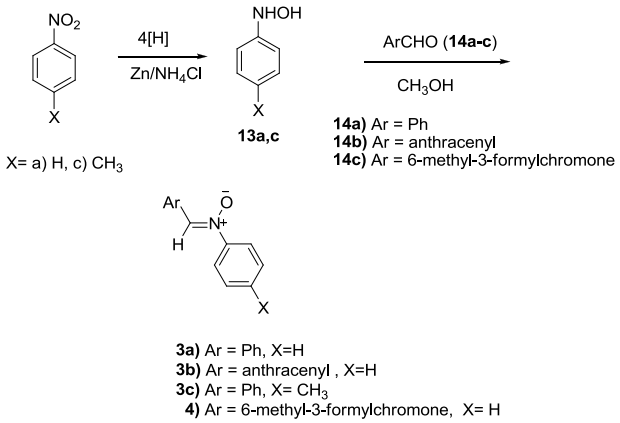


X = b) Cl, c) Br, d) OCH_3, e) CH_3, f) Ph

Scheme 2.13

2.3.3 Synthesis of *N*-(benzylidene)aniline-*N*-oxide

N-(benzylidene)aniline-*N*-oxide **3a-c** were prepared by the method developed by Chapoulaud *et al*.[21] Zinc mediated reduction of nitroarenes produced hydroxylamines **13a-c** quantitatively.[54] Hydroxylamines **13a-c** were reacted with aromatic aldehydes **14a-c** to give the corresponding diarylnitrones **3a-c**, **4**, and **14a-c** in good to excellent yields (Scheme 2.14).



Scheme 2.14

2.4 Experimental Section

2.4.1 General Techniques

All reactions were carried out in oven dried glassware. All starting materials were purchased from *Sigma-Aldrich* or from *S. D. Fine Chemicals* and were used without further purification unless otherwise mentioned. Progress of reactions were monitored by thin layer chromatography using dried and activated silica gel TLC plates (aluminium sheets coated with silica gel, *E. Merck*). Visualisation of TLC plates was done by exposure to iodine vapours or using a UV lamp. Solvents used for the experiments were distilled and dried by employing standard protocols. Separation and purification of compounds were done by column chromatography using silica gel (*S. D. Fine Chemicals*, 60-120 mesh). Mixtures of ethyl acetate and hexane were used as the eluent. After chromatographic separation, solvent was removed using *Heidolph* rotary evaporator. The products were further

purified by recrystallization from appropriate solvent system. Melting points were recorded on *Neolab* melting point apparatus. Elemental analysis was performed on *Elementar Systeme* (*Vario EL III*). FAB mass spectra were recorded on *JEOL JMS 600*. IR spectra were recorded on *ABB Bomem* (*MB Series*) FT-IR spectrometer and *JASCO-FTIR 4100* spectrometer. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively on *Bruker* FT-NMR spectrometer using $CDCl_3$ as the solvent. Chemical shifts are given in δ scale with TMS as internal standard.

2.4.2 Nitrosobenzene (6)

Nitrosobenzene was prepared by a known procedure (62 % yield, mp 66 ^{o}C).[49]

2.4.3 Fluorenone hydrazone (8)

Fluorenone hydrazone was prepared by a reported procedure (85% yield, mp 146 ^{o}C).[51]

2.4.4 9-Diazofluorene (9)

9-Diazofluorene was prepared by a procedure reported in literature (84% yield, mp 94 ^{o}C).[50]

2.4.5 4-Chlorobenzophenone (11b)

4-Chlorobenzophenone was prepared by a known procedure (72% yield).[51,53]

2.4.6 4-Bromobenzophenone (11c)

4-Bromobenzophenone was prepared by a reported procedure (70% yield).[51, 53]

2.4.7 4-Methoxybenzophenone (11d)

4-Methoxybenzophenone hydrazone was prepared by a reported procedure (62% yield).[51,53]

2.4.8 4-Methylbenzophenone (11e)

4-Methylbenzophenone hydrazone was prepared by a known procedure (60% yield).[51,53]

2.4.9 4-Phenylbenzophenone (11f)

4-Phenylbenzophenone was prepared as per a literature report (64% yield).[51,53]

2.4.10 Benzophenone hydrazone (12a)

Benzophenone hydrazone was prepared by a known procedure (82% yield, mp 95 ^{o}C).[51]

2.4.11 4-Chlorobenzophenone hydrazone (12b)

4-Chlorobenzophenone hydrazone was prepared by a known procedure (72% yield).[51]

2.4.12 4-Bromobenzophenone hydrazone (12c)

4-Bromobenzophenone hydrazone was prepared by a reported procedure (70% yield).[51]

2.4.13 4-Methoxybenzophenone hydrazone (12d)

4-Methoxybenzophenone hydrazone was prepared by a reported procedure (62% yield).[51]

2.4.14 4-Methylbenzophenone hydrazone (12e)

4-Methylbenzophenone hydrazone was prepared by a known procedure (60% yield).[51]

2.4.15 4-Phenylbenzophenone hydrazone (12f)

4-Phenylbenzophenone hydrazone was prepared as per a literature report (64% yield).[51]

2.4.16 Diphenyldiazomethane (10a)

Diphenyldiazomethane was prepared by a known procedure and the product being unstable was stored as a pink solution in hexane under low temperature and was used as such in the synthesis of nitrones.[49]

2.4.17 (4-Chlorophenyl)(phenyl)diazomethane (10b)

(4-Chlorophenyl)(phenyl)diazomethane was prepared using a reported procedure.[49]

2.4.18 (4-Bromophenyl)(phenyl)diazomethane (10c)

(4-Bromophenyl)(phenyl)diazomethane was prepared by a reported procedure.[49]

2.4.19 (4-Methoxyphenyl)(phenyl)diazomethane (10d)

(4-Methoxyphenyl)(phenyl)diazomethane was prepared according to a known procedure.[49]

2.4.20 (4-Methylphenyl)(phenyl)diazomethane (10e)

(4-Methylphenyl)(phenyl)diazomethane was prepared by a reported procedure.[49]

2.4.21 (4-Phenylphenyl)(phenyl)diazomethane (10f)

(4-Phenylphenyl)(phenyl)diazomethane was prepared by a known procedure.[49]

2.4.22 *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide (1a)

N-(9H-fluoren-9-ylidene)aniline-*N*-oxide was prepared by a reported procedure (85%, mp 194 ^{o}C).[31]

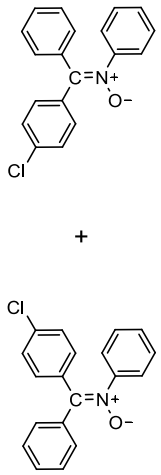
2.4.23 *N*-(diphenylmethylene)aniline-*N*-oxide (2a)

N-(diphenylmethylene)aniline-*N*-oxide was prepared by a known procedure (83% yield, mp 227 ^{o}C).[31]

2.4.24 *N*-((4-chlorophenyl)(phenyl)methylene)aniline-*N*-oxide (2b, b')

Nitrosobenzene (1.07g, 10 mmol) was added to a well stirred solution of (4-chlorophenyl)(phenyl)diazomethane (2.28g, 10 mmol) in diethyl ether. During the course of the reaction pink color of solution vanished with evolution of nitrogen and a white precipitate was formed. The precipitate was filtered, dried and recrystallized to get colorless crystals of *N*-((4-chlorophenyl)(phenyl)methylene)aniline-*N*-oxide isomers **2b**, **b'** as an inseparable mixture. The product gave two spots on TLC with negligible difference in their Rf value, indicating the presence of isomeric mixture of nitrones. NMR analysis also supports the presence of geometrical isomers in an 8:1 (*syn*:*anti*) ratio. However we could not separate nitrone isomers in pure form. ^{1}H NMR spectrum exhibited characteristic signal for all aromatic protons at δ 8.05-7.02 ppm.

2.4.24.1 Spectral data of 2b, b'



Yield 2.10 g, 68%

IR ν_{max} (KBr): 3052, 1573, 1581 1509, 1464, 1239, 764, 695 cm^{-1};

^{1}H NMR ($CDCl_3$): δ 8.05-8.04 (t, 3H), 7.42-7.40 (m, 2H), 7.38-7.35 (dd, 3H), 7.29-7.26 (m, 2H), 7.22-7.17 (m, 10H), 7.09-7.08 (m, 3H), 7.03-7.02 (dd, 1H);

MS: *m/z* calculated for $C_{19}H_{14}ClNO$: 307 (M^+); found: 308 (M^++1), 310.

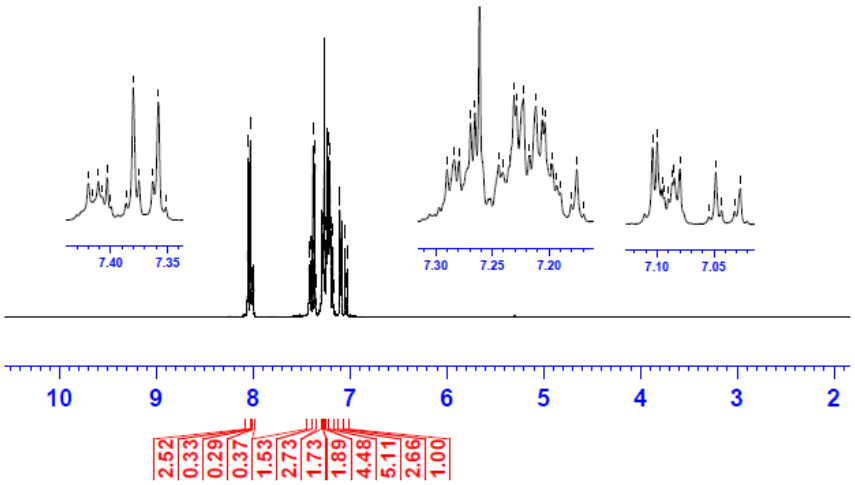


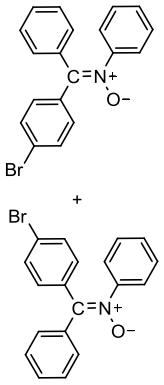
Figure 2.2. ^{1}H NMR spectrum of **2b, b'**.

2.4.25 *N*-((4-bromophenyl)(phenyl)methylene)aniline-*N*-oxide (2c, c')

Nitrosobenzene (1.07 g 10 mmol) was added to a well stirred solution of 4-bromodiphenyldiazomethane (2.72 g 10 mmol) in diethylether. Pink color of the solution got vanished during the course of reaction with evolution of nitrogen and a light yellow precipitate was formed. The precipitate was filtered, washed with

hexane, dried and recrystallized to get colorless crystals of nitrone isomers **2c**, **c'**. As in the above reaction, the product in this case was also a mixture of geometrical isomers. NMR analysis also supports the existence of geometrical isomers in a 2:5 ratio (*syn*:*anti*). The isomeric nitrones could not be separated in pure form.

2.4.25.1 Spectral data of compound 2c, c'



Yield 2.40 g, 68%; mp 120 ^{o}C

IR ν_{max} (KBr): 3049, 1577, 1586 1509, 1483, 1240, 762, 695 cm^{-1};

^{1}H NMR ($CDCl_3$): δ 7.97-7.95 (q, 1H), 7.53-7.51 (dd, 3H), 7.41-7.40 (m, 2H), 7.35-7.33 (dd, 1H), 7.28-7.26 (m, 4H), 7.24 (d, 1H), 7.23-7.22 (m, 3H), 7.21-7.19 (m, 4H), 7.10-7.07 (m, 3H), 6.98-6.97 (d, 1H);

^{13}C NMR ($CDCl_3$): δ 148.49, 135.15, 133.82, 133.00, 132.69, 132.04, 131.61, 131.18, 131.11, 130.41, 130.29, 128.97, 128.92, 128.76, 128.65, 128.43, 128.07, 124.54, 124.48, 124.23, 123.13;

MS: *m/z* calculated for $C_{19}H_{14}BrNO$: 351, 353 (M^+); found: 352, 354 (M^++1).

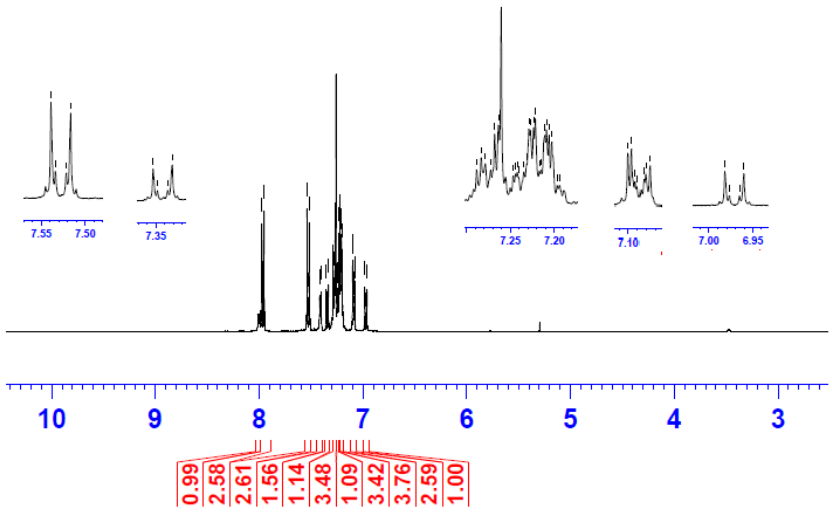


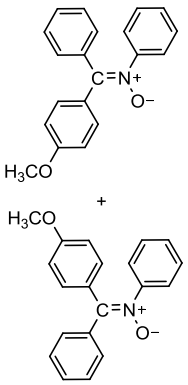
Figure 2.3. ^{1}H NMR spectrum of **2c**.

2.4.26 *N*-((4-methoxyphenyl)(phenyl)methylene)aniline-*N*-oxide (2d, d')

A mixture of 4-methoxydiazofluorene (2.24 g, 10 mmol) and nitrosobenzene (1.07 g, 10 mmol) in 40 mL of dry diethyl ether was stirred for about 1h. Change of the pink color of solution and evolution of nitrogen was noted and a light yellow precipitate was formed. The precipitate was filtered, washed with hexane, dried and recrystallized to get light yellow crystals of **2d**, **d'**. The product appears as two spots on TLC with negligible difference in their Rf value indicating a mixture of geometrical isomers of nitrones. ^{1}H NMR analysis supports the existence of geometrical isomers in a 2:1 (*syn*:*anti*) ratio. ^{1}H NMR spectrum exhibited characteristic peak of methoxy protons at δ 3.85 ppm and 3.75 ppm in a 2:1 ratio corresponding to the two methoxy groups in isomeric nitrones. ^{13}C NMR spectrum also gave evidence for the formation of geometrical

isomers. Two signals were obtained for the methoxy carbons at δ 55.38 ppm and 55.22 ppm.

2.4.26.1 Spectral data of 2d, d'



Yield 1.63 g, 54%; mp 84 ^{o}C

IR ν_{max} (KBr): 3032, 1601, 1591, 1505, 1227, 1026, 756, 691 cm^{-1};

^{1}H NMR ($CDCl_3$): δ 8.13-8.11 (dd, 2H), 7.40 (d, 2H), 7.38-7.10 (m, 13H), 7.01-6.99 (q, 1H), 6.92-6.90 (q, 2H), 6.72-6.70 (d, 1H), 3.85 (s, 3H), 3.75 (s, 1.5H);

^{13}C NMR ($CDCl_3$): δ 160.80, 159.65, 148.57, 147.28, 135.77, 134.53, 132.56, 131.20, 130.63, 129.99, 128.76, 128.64, 128.61, 128.37, 128.22, 127.90, 126.66, 124.66, 124.60, 113.71, 113.22, 55.38, 55.22;

MS: *m/z* calculated for $C_{20}H_{17}NO_2$: 303 (M^+); found: 304 (M^++1)

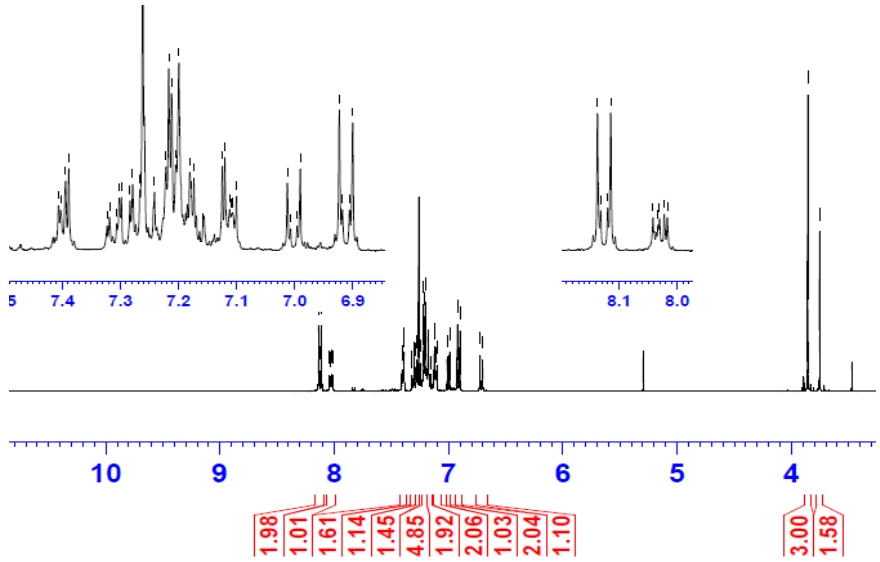


Figure 2.4. ^{1}H NMR spectrum of **2d, d'**.

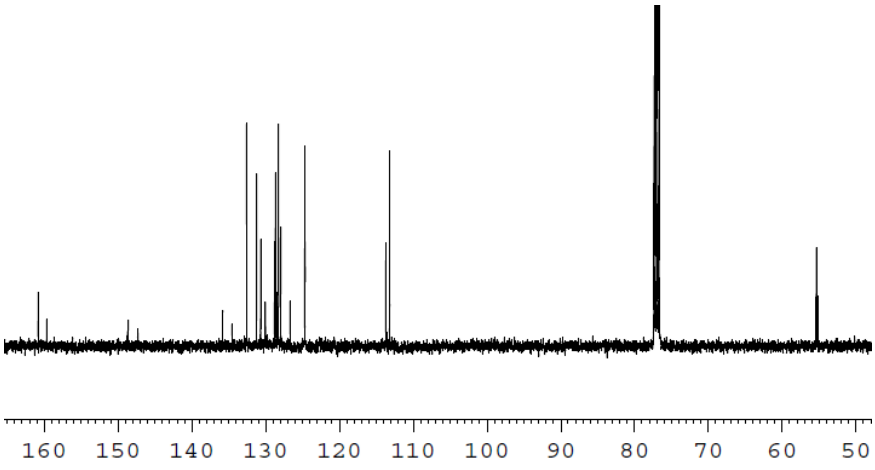


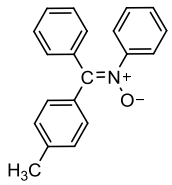
Figure 2.5. ^{13}C NMR spectrum of **2d, d'**.

2.4.27 *N*-(phenyl(p-tolyl)methylene)aniline-*N*-oxide (2e)

A concentrated solution of 4-methyldiphenyl-diazomethane in hexane was added drop wise to a solution of nitrosobenzene (1.07g, 10 mmol) in 40 mL of dry diethyl ether with

vigorous stirring till the reaction mixture turned pale pink in color. It was stirred for about 1h. The precipitate was then filtered, washed with hexane, dried and purified by recrystallization. The product obtained gave a single spot on TLC which indicated the presence of a single geometrical isomer. The nitrone product was identified as *syn*-isomer by XRD analysis (Figure 2.5). ^{1}H NMR spectrum exhibited a characteristic 3H signal for CH_3 at δ 2.38 ppm and 14 aromatic protons at δ 7.98-7.08 ppm.

2.4.27.1 Spectral data of compound 2e



Yield 1.49 g, 51% yield; mp 98 °C

IR ν_{max} (KBr): υ 3029, 1591, 1506, 1346, 1237, 823, 754, 695 cm^{-1};

^{1}H NMR ($CDCl_3$): δ 7.98-7.96 (d, 2H), 7.29-7.25 (m, 2H), 7.22-7.16 (m, 8H), 7.11-7.08 (m, 2H), 2.38 (s, 3H);

MS: *m/z* calculated for $C_{20}H_{17}NO$: 287 (M^+); found: 288 (M^++1)

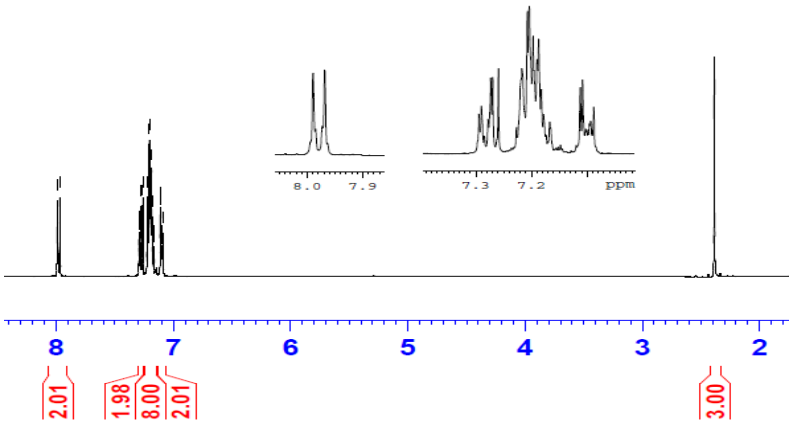


Figure 2.6. ^{1}H NMR spectrum of **2e**.

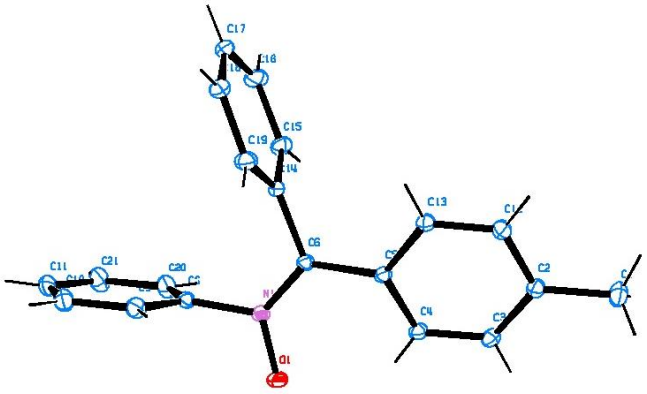
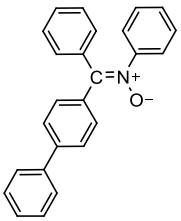


Figure 2.7. X-ray crystal structure of **2e**.

2.4.28 *N*-(biphenyl-4-yl(phenyl)methylene)aniline-*N*-oxide (2f)

A mixture of 4-phenyldiazofluorene (2.70 g, 10 mmol) and nitrosobenzene (1.07 g, 10 mmol) in 40 mL of dry diethyl ether was stirred for about 1h. Decolorisation of red solution with nitrogen evolution was followed by formation of a pale yellow precipitate. The precipitate was filtered, washed with hexane, dried and recrystallized to get light yellow crystals of **2f**. Appearance of a single spot on TLC analysis indicates the existence of a single isomer. ^{1}H NMR analysis also supports the formation of single geometrical isomer.

2.4.28.1 Spectral data of compound 2f



Yield 2.30 g, 66%; mp 92 °C

IR ν_{max} (KBr): 3049, 1582, 1506, 1237, 829, 743, 695 cm^{-1};

^{1}H NMR ($CDCl_3$): δ 8.17-8.14 (m, 2H), 7.65-7.62 (m, 4H), 7.47-7.43 (t, 2H), 7.38-7.36 (tt, 1H), 7.32-7.29 (dt, 2H), 7.25-7.16 (m, 6H), 7.14-7.13 (m, 2H);

^{13}C NMR ($CDCl_3$): δ 148.57, 147.23, 142.63, 140.33, 135.62, 133.02, 131.22, 131.01, 128.87, 128.73, 128.71, 128.49, 128.31, 127.30, 127.13, 126.51, 124.62;

MS: *m/z* calculated for $C_{25}H_{19}NO$: 349 (M^+); measured: 350 (M^++1).

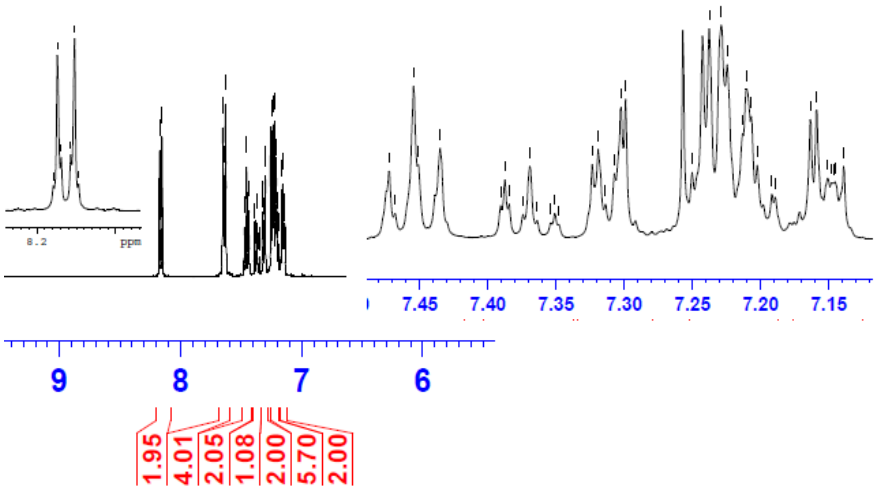


Figure 2.8. ^{1}H NMR spectrum of **2f**.

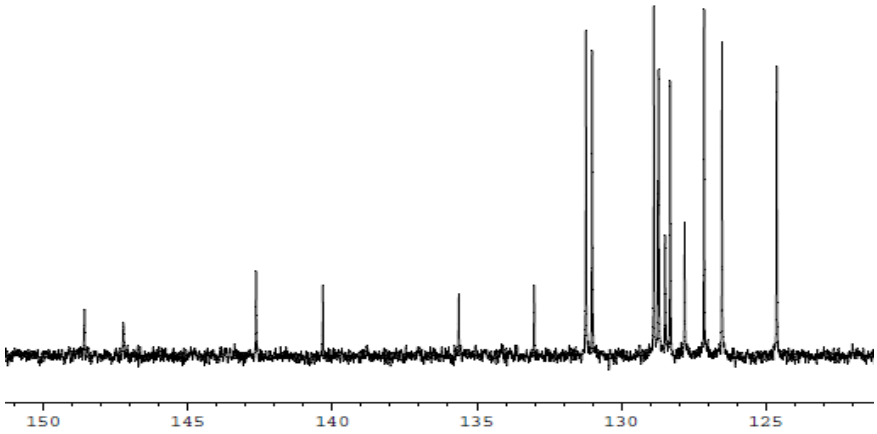


Figure 2.9 ^{13}C NMR spectrum of **2f**.

2.4.29 Phenylhydroxylamine (13a)

Phenylhydroxylamine was prepared by a known procedure (83% yield).[37]

2.4.30 4-Methylphenylhydroxylamine (13c)

Zinc mediated reduction of 4-methylnitrobenzene in the presence of NH_4Cl gives 4-methylphenylhydroxylamine (75% yield).[54]

2.4.31 *N*-(benzylidene)aniline-*N*-oxide (3a)

N-(benzylidene)aniline-*N*-oxide was prepared by a reported procedure (80% yield).[21]

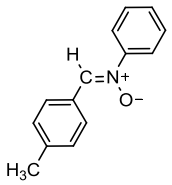
2.4.32 *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide (3b)

N-(anthracen-9-ylmethylene)aniline-*N*-oxide was prepared by a reported procedure (72% yield).[21]

2.4.33 *N*-benzylidene-4-methylaniline-*N*-oxide (3c)

Zinc mediated reduction of 4-methylnitrobenzene **13c** in the presence of benzaldehyde produced *N*-benzylidene-4-methylaniline-*N*-oxide **3c** quantitatively.

2.4.33.1 Spectral data of compound 3c



Yield 1.60 g, 76%; mp 73 ^{o}C

^{1}H NMR ($CDCl_3$): δ 7.87-7.85 (t, 2H), 7.77 (s, 1H), 7.54-7.47 (m, 5H), 7.18-7.17 (d, 2H), 2.34 (s, 3H);

^{13}C NMR ($CDCl_3$): δ 135.34, 135.10, 134.27, 131.76, 129.61, 128.78, 126.98, 120.25, 20.91;

MS: *m/z* calculated for $C_{14}H_{13}NO$: 211 (M^+); found: 212 (M^++1).

2.4.34 C-(4-oxo-4*H*[1]benzopyran-3-yl)-N-phenylnitrone (4)

C-(4-oxo-4*H*[1]benzopyran-3-yl)-N-phenylnitrone **(4)** was prepared by a known procedure.[55]

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CHAPTER 3

REACTIONS OF NITRONES WITH BURGESS REAGENT

3.1 Abstract

This chapter deals with the reactions of various nitrones with Burgess reagent. 1,3-Dipolar species such as nitrones and azomethine imines undergo annulation reactions with Burgess reagent. Preliminary studies indicated that nitrones undergo useful transformations with Burgess reagent. The reaction involves a [3+2] annulation followed by a rearrangement involving C-to-N aryl migration. Based on the available experimental evidence, plausible mechanisms for the rearrangement and the overall conversion have been proposed.

3.2 Introduction

Burgess reagent (**1**) is a versatile reagent in organic synthesis[1,2] and its reactivity with a number of functional groups like alcohols, epoxides[3], 1,2-diols[4-6], thiols[7,8] are well documented. Newer applications[9] of the reagent as well as several modified forms of the reagents with improved thermal stability[10] are being reported. Now, chiral versions of the reagent are also known[11] and the reagent has been extensively used in natural product syntheses.

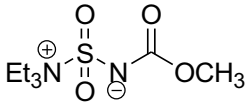

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Figure 3.1

A recent report shows an unexpected *N*-demethylation of oxymorphone and oxycodone-*N*-oxide using Burgess reagent to the corresponding oxazolidines providing a direct synthetic route to naltrexone, naloxone, and other antagonists from oxymorphone.[9] Though several reagents like cyanogen bromide (von Braun reaction),[12] ethyl chloroformate[13] etc. are available for this transformation the conversion still remains a challenge in terms of efficiency and greenness of the reagent and conditions. The conversion of oxymorphone to naloxone and other analgesics include several steps, but use of Burgess reagent for *N*-demethylation reduces the entire sequence to three one-pot operations, proceeding in excellent overall yields.[9] Burgess reagent shows unexpected reactivity with *N*-oxides and the results are interesting and applicable in synthesis of several heterocyclic compounds, particularly those with pharmaceutical applications.

Nitrones being *N*-substituted 1,3-dipolar systems can undergo cycloaddition[14] reactions with a variety of carbon–carbon, carbon–nitrogen, carbon–sulphur, nitrogen–phosphorus multiple bonded systems to give various heterocyclic systems. Nitrones also find application in the synthesis of a wide range of natural product target types – from sugars and nucleoside analogues through

lactams to alkaloids and other nitrogen heterocyclic natural products, both bridgehead bicyclic and monocyclic systems. Thus, nitrones represent a useful substrate for fabrication of heterocyclic[15,16] systems in modern synthetic chemistry. A dipolar homo [3+2] cycloaddition reaction of nitrone with cyclopropane has also been reported.[17]

Annulation reactions are important synthetic processes for constructing a wide variety of carbocyclic and heterocyclic frameworks.[18] Among various annulations, [3+2] annulation represents a breakthrough in the field of organic synthesis. In principle, reaction between a 1,3-dipole and 1,2-dipole should yield five membered ring structures *via* a formal [3+2] annulation sequence. Huisgen and co-workers have refined this methodology for general application in organic synthesis.[19,20] Several 1,3-dipoles were investigated by Huisgen. Invariably, the dipolarophile was a π-system.

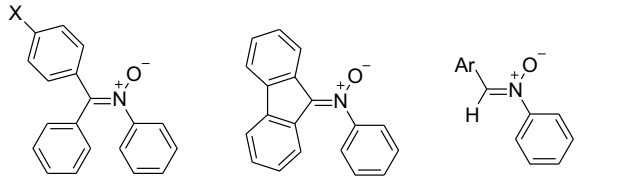
3.2.1 Objectives

To the best of our knowledge, 1,3-dipolar addition to a σ-bond in acyclic systems is not reported in literature. A close examination of the structure of Burgess reagent reveals that it can act as a 1,2-dipole. In principle, any 1,3-dipole possessing significant nucleophilicity should react with Burgess reagent with elimination of triethylamine to give the corresponding product having a five-membered ring by a formal dipolar addition to a σ-bond. With a view to verify this hypothesis, we selected nitrones

as the dipole component since significant nucleophilic activity of nitrones has been well documented.[21,22]

3.3 Results and Discussion

In the present investigation, we have exploited the 1,2-dipolar nature of Burgess reagent that should enable it to undergo annulation reactions with 1,3-dipolar species possessing significant nucleophilicity such as nitrones. In this preliminary investigation, we examined the reaction of two ketonitrones *viz.* *N*-(diphenylmethylene)aniline-*N*-oxide (**2**) and *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide (**3**), and two aldonitrones *viz.* *N*-(benzylidene)aniline-*N*-oxide (**4a**) and *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide (**4b**) with Burgess reagent. Structure of different nitrones employed in the present study is given in Figure 3.2. The required nitrones were prepared according to procedures reported in literature.[23-27]



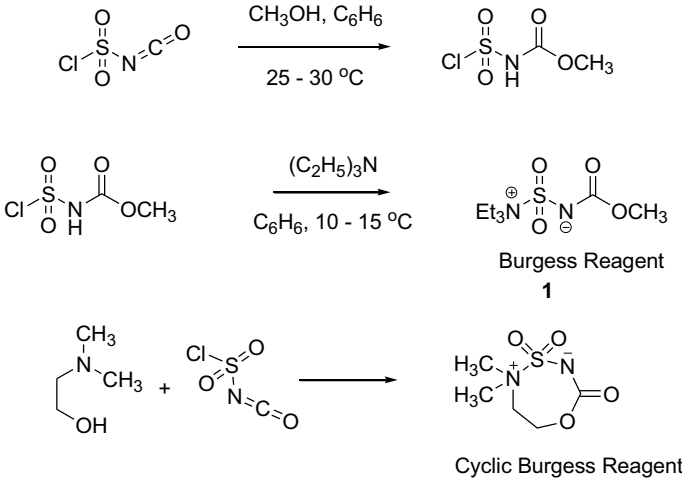
2 **3** **4a,b**

Ar = a) Ph, b) anthracenyl

Figure 3.2

Burgess reagent was prepared from chlorosulphonyl isocyanate and triethylamine *via* a two-step reaction[28,29] (Scheme 3.1). In the first step, chlorosulphonyl isocyanate was treated with methanol to give methyl-(chlorosulphonyl)carbamate, which was

then reacted with triethylamine to give Burgess reagent (Methyl-*N*-(triethylammoniumsulphonyl)carbamate **1**) in excellent overall yield. The reagent is oxidation and moisture sensitive, and needs to be stored under dry, oxygen free conditions at low temperature. A cyclic Burgess reagent was also prepared in a more convenient one-step process starting with an appropriate β-aminoalcohol[30] (Scheme 3.1).

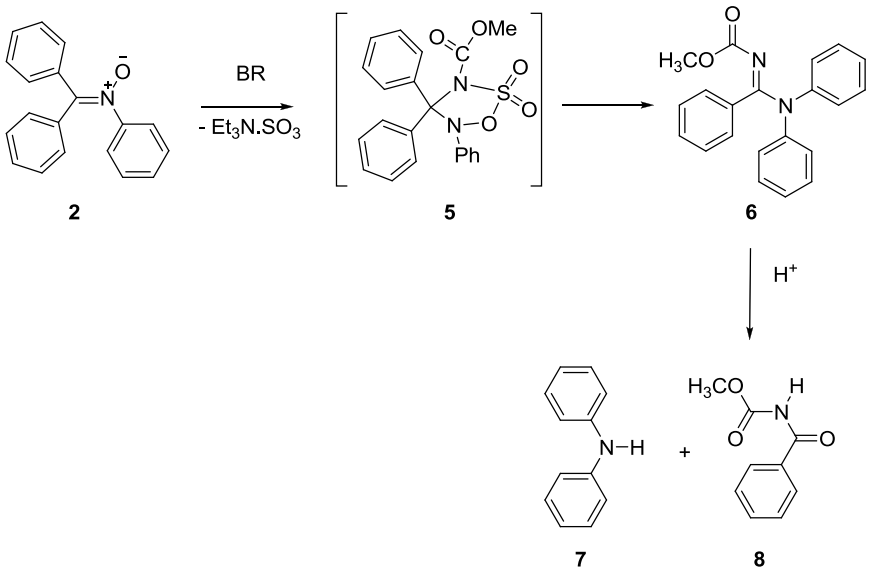


Scheme 3.1

3.3.1 Reactions of *N*-(diphenylmethylene)aniline-*N*-oxide with Burgess reagent

1,3-Dipolar reaction between *N*-(diphenylmethylene)-aniline-*N*-oxide (**2**) and Burgess reagent (**1**) was conducted in a 1:3 molar ratio in dry dichloromethane at room temperature. The product **6** precipitated on adding hexane was separated, purified and further characterized by ^{1}H NMR, ^{13}C NMR, and MS (FAB). ^{1}H NMR spectrum exhibited a characteristic signal of ester methyl proton at δ 3.40 ppm. Similarly ^{13}C NMR spectrum exhibited

characteristic carbon signal at 52.70 ppm for ester methyl group and a signal at 163.4 ppm for carbonyl carbon. IR spectrum exhibited characteristic carbonyl absorption at 1713 cm^{-1} and C=N absorption at 1616 cm^{-1}. These spectral characteristics support the presence of carbamate group in structure **6**. MS (FAB) analysis gave molecular ion peak at 331.17 corresponding to the molecular formula $C_{21}H_{18}O_2N_2$. All data were consistent with the proposed structure **6**. In a repeat run, careful work up of the reaction mixture under absolutely moisture free conditions afforded, in addition to **6**, triethylamine-sulphur trioxde complex as colorless needles. Generation of **6** in the reaction between **2** and Burgess reagent mandates carbon to nitrogen aryl group migration. This rearrangement is reminiscent of a similar C to N aryl migration observed in the chlorosulphonyl isocyanate mediated transformation of nitrones.[21,22] Though Burgess reagent is known to exhibit myriad reactivity, this is the first example for a C to N aryl migration overseen by this versatile reagent. We focused our attention on unraveling the mechanistic underpinnings, generality and possible synthetic utility of the novel C to N aryl migration discovered by us.



Scheme 3.2

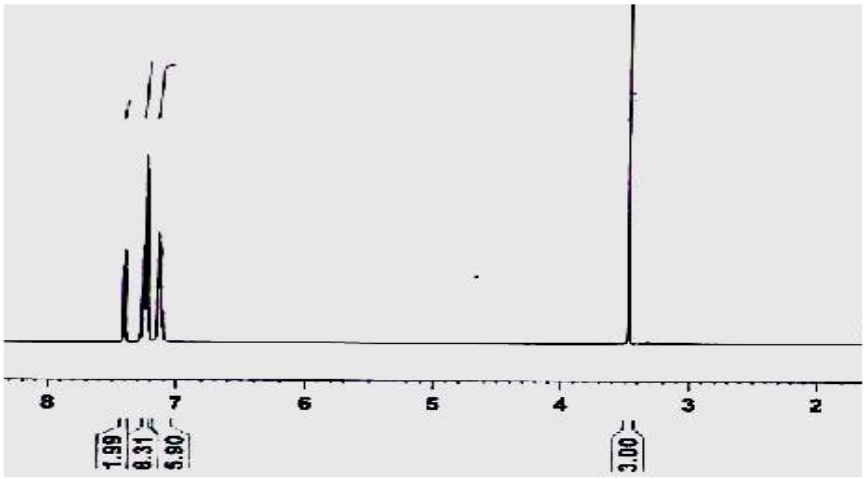


Figure 3.3. ^{1}H NMR spectrum of **6**.

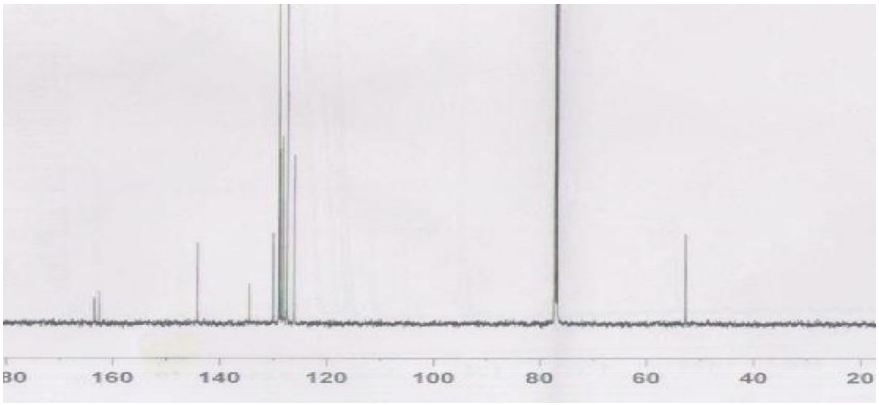


Figure 3.4. ^{13}C NMR spectrum of **6**.

Structure of carbamate **6** was further confirmed by chemical transformations. Acid hydrolysis of **6** gave diphenylamine (**7)** along with **8** in quantitative yields. Structure of **8** was arrived at on the basis of spectral and analytical data. IR spectrum of **8** showed a peak at 3278 cm^{-1} attributable to NH stretch and two carbonyl stretching frequencies at 1778 and 1651 cm^{-1}. In the ^{1}H NMR spectrum of **8**, a broad singlet (1H, D_2O-exchangeable) was observed at δ 8.2. A sharp singlet (3H) attributable to methoxy group was observed at δ 3.8 and three sets of multiplets (5H) attributable to a mono-substituted benzene ring were observed in the δ 7.4-7.8 range. Based on available data, this new compound was identified as methyl benzoylcarbamate (**8**).

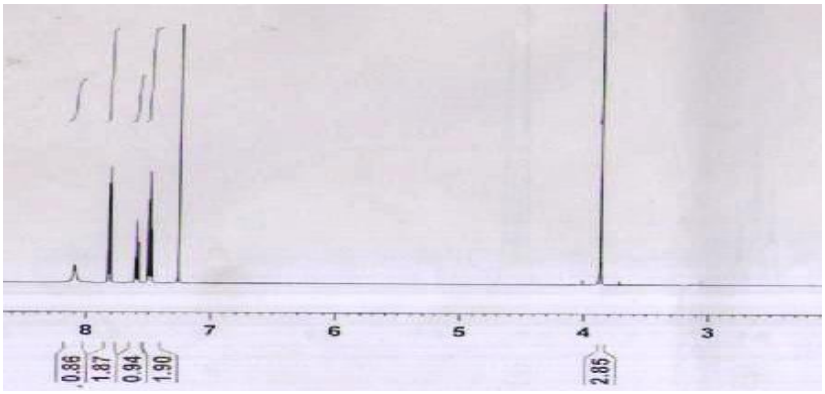
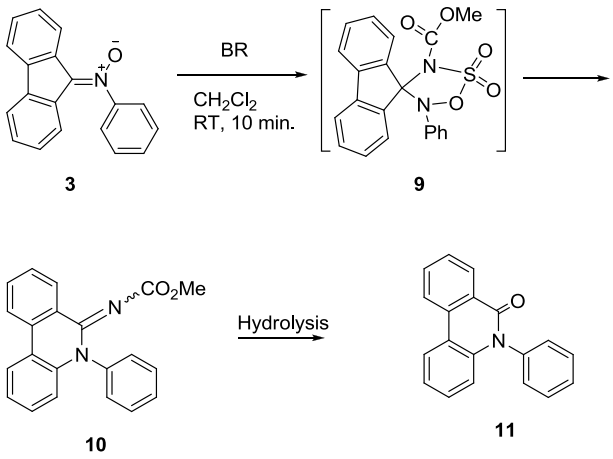


Figure 3.5 ^{1}H NMR spectrum of **8**.

3.3.2 Reaction of *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide (3) with Burgess reagent

In order to establish the generality of the novel C to N aryl migration observed by us, we examined the reaction of *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide **3** with Burgess reagent (Scheme 3.3). The product **10** precipitated on adding hexane was separated, purified and characterized on the basis of ^{1}H NMR, ^{13}C NMR, MS (FAB) data.



3 **9** **10** **11**

Scheme 3.3

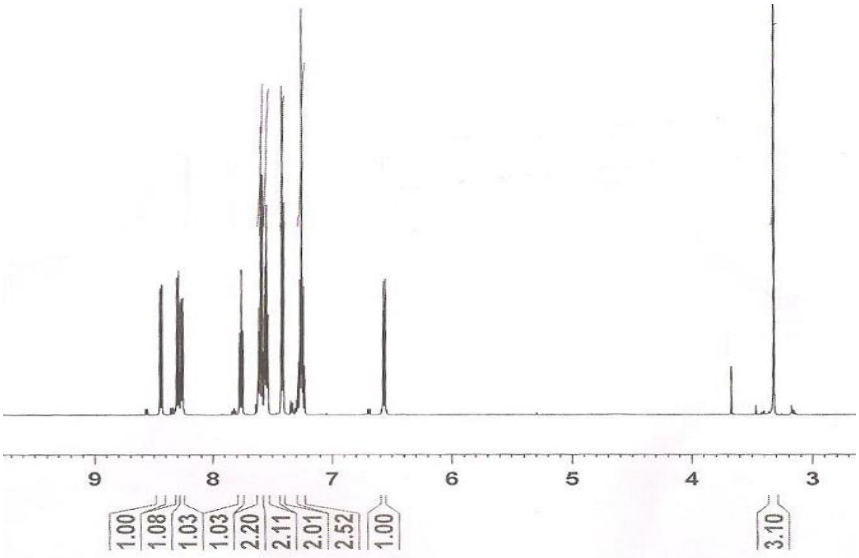


Figure 3.6. ^{1}H NMR spectrum of compound **10**.

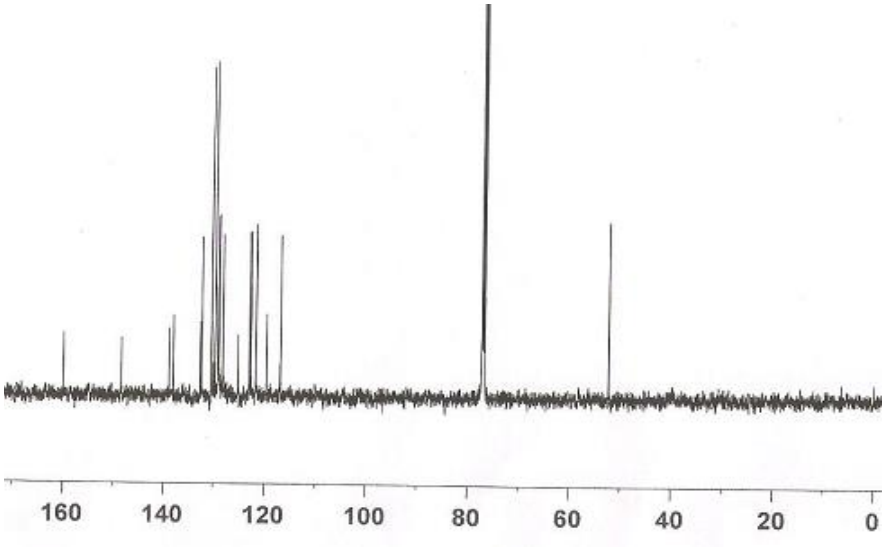


Figure 3.7. ^{13}C NMR spectrum of compound **10**.

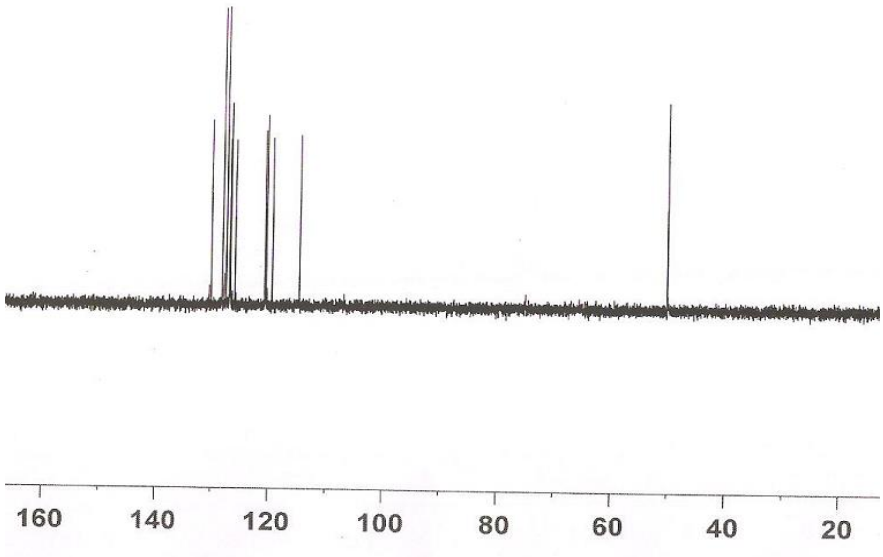


Figure 3.8. ^{13}C DEPT-135 spectrum of **10**.

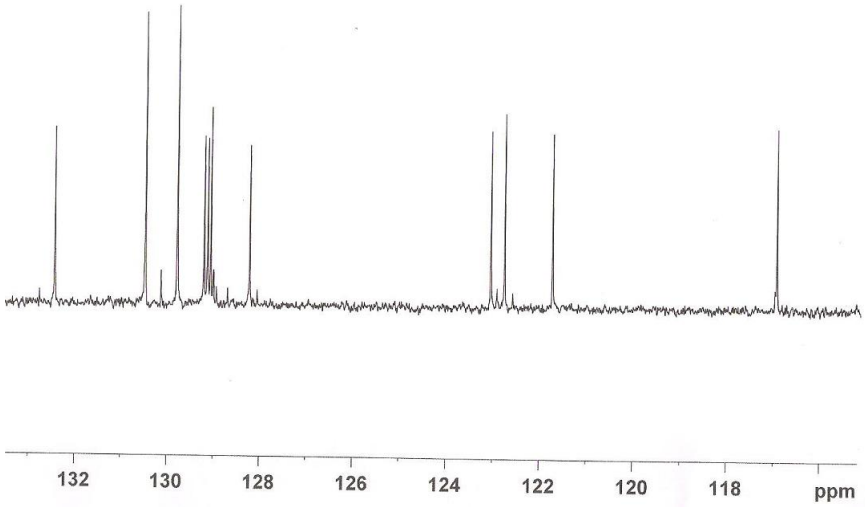


Figure 3.9. ^{13}C DEPT-90 spectrum of **10**.

^{1}H NMR spectrum of **10** exhibited the characteristic peak of methyl proton at δ 3.32 ppm. The ^{13}C NMR spectrum exhibited characteristic carbon peak at δ 52.20 ppm for ester methyl group

and a peak at δ 160.0 ppm for carbonyl carbon. IR spectrum showed characteristic carbonyl absorption at 1683 cm^{-1} and C=N absorption at 1640 cm^{-1}. Hence the spectral data support the presence of carbamate group in structure **10**. MS (FAB) analysis gave molecular ion peak at 329.26 corresponding to the molecular formula $C_{21}H_{16}N_2O_2$. All data were consistent with the proposed structure **10** arising through a C to N aryl migration sequence. Structure of **10** was further confirmed on the basis of chemical transformations. Carbamate **10** on hydrolysis using oxalic acid adsorbed on silica gave compound **11** that was characterized on the basis of ^1H NMR, ^{13}C NMR, and MS (FAB) data. IR spectrum of compound **11** shows C=O stretch at 1658 cm^{-1}, but the ester carbonyl at 1740 cm^{-1} was missing indicating the cleavage of ester group on hydrolysis and existence of another carbonyl group. ^1H NMR spectrum exhibited characteristic signal for 13 aromatic hydrogens at δ 8.49-6.60 while the signal corresponding to carbamate methyl proton at δ 3.32 disappeared confirming the cleavage of carbamate group on hydrolysis. ^{13}C NMR spectrum exhibited only one carbonyl signal at δ 160.60. FAB-MS analysis gave molecular ion peak at 272.4 which corresponds to the molecular formula $C_{19}H_{13}NO$. The above spectral characteristics suggest cleavage of ester group on hydrolysis and compound was identified as 5-phenylphenanthridin-6(5*H*)-one (**11)** confirming a C to N migration in this case well.

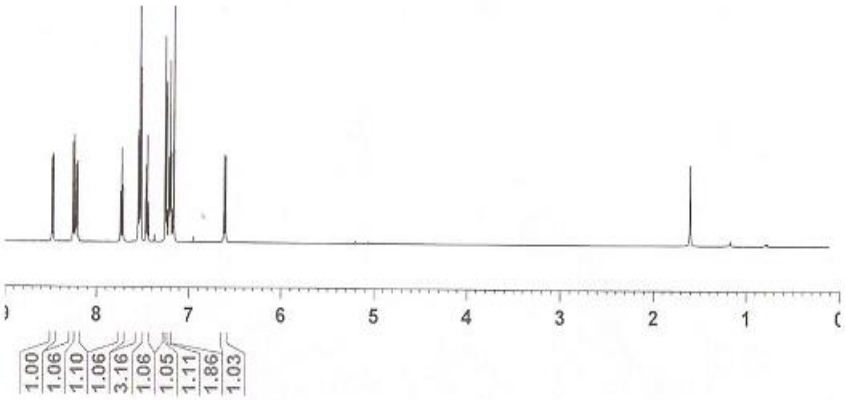


Figure 3.10. ^{1}H NMR spectrum of **11**.

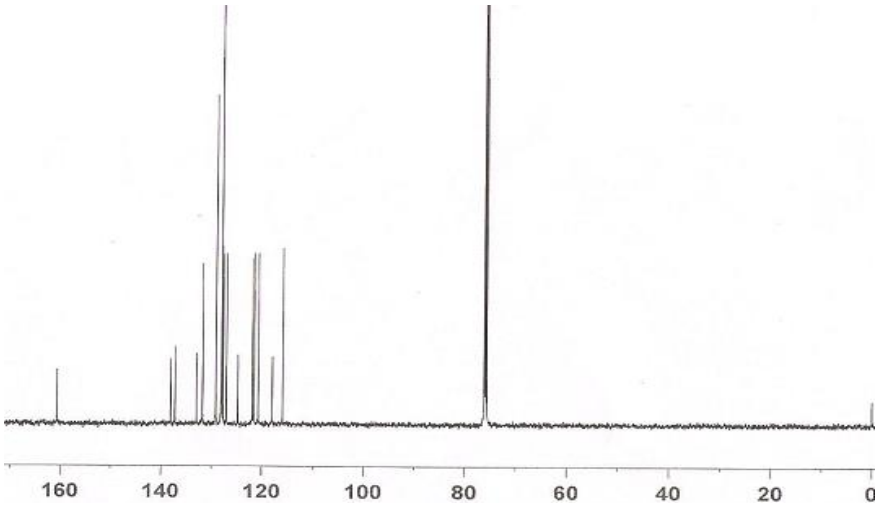
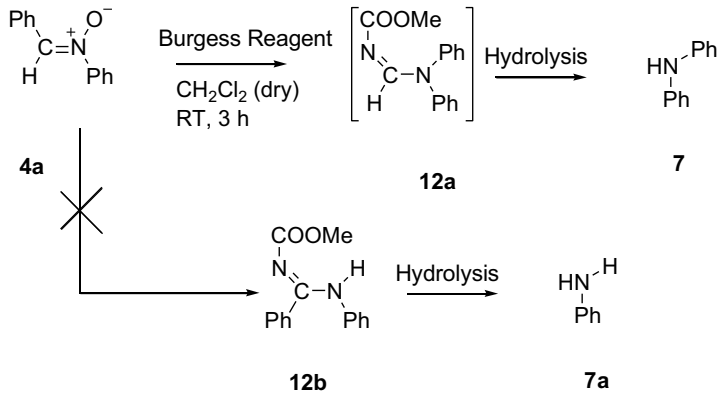


Figure 3.11. ^{13}C NMR spectrum of **11.**

3.3.3 Reaction of *N*-(benzylidene)aniline-*N*-oxide with Burgess reagent

N-(benzylidene)aniline-*N*-oxide (**4a**) on reaction with Burgess reagent gave products arising through carbon to nitrogen

phenyl migration. In the reactions of nitrone **4a,** the carbamate intermediates **12a** could not be isolated and the corresponding diarylamine **7** was the only isolable product (Scheme 3.4). The product obtained was identified by comparing melting point, TLC and IR spectra with those of authentic sample. Though we could not isolate the carbamate intermediate **12a**, generation of diarylamine **7** is consistent with the C to N aryl migration pathway proposed by us. It may be noted that C to N hydrogen migration is an alternative possibility here. In order to verify this, we carried out careful GC-MS analysis of the reaction mixture. GC-MS analysis ruled out aniline generation and hence the C to N hydrogen migration possibility.

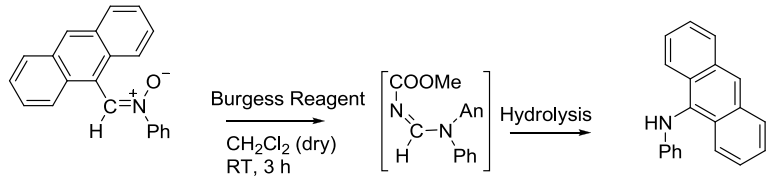


Scheme 3.4

3.3.4 Reaction of *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide with Burgess reagent

Difficulty in isolating intermediate **12a** in the above reaction, prompted us to conduct a similar reaction with a different nitrone, *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide (**4b**) and

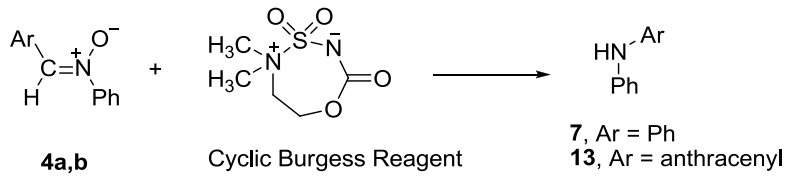
Burgess reagent. However in this case also the diarylamine **13** (arising through the proposed C to N aryl migration pathway) was the only isolable product (Scheme 3.5).



4b **12b** **13**

Scheme 3.5

We explored the possibility of isolating the carbamate intermediate in the reaction of nitrones **4a-b** with a cyclic Burgess reagent.[28] It was noted that the corresponding diarylamines **7** and **13** were the only isolable products in these reactions as well (Scheme 3.6). Though we were unsuccessful in isolating the carbamate intermediate, this experiment demonstrated that other variants of Burgess reagent also can initiate C to N aryl migration.



4a,b

Scheme 3.6

3.3.5 Conclusions

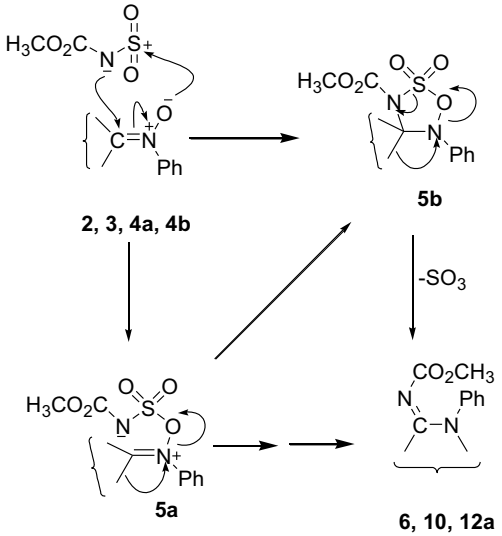
On the basis of the results obtained in the reaction of classic Burgess reagent with different nitrones and a novel cyclic variant of Burgess reagent with nitrones, we demonstrated that the novel C to N aryl migration in the Burgess reagent–nitrone reaction is a general reaction as well. Another striking feature of this

rearrangement is the remarkable migratory aptitude observed here. In the case of **2** and **3**, migratory aptitude cannot be ascertained. However, with **4a, b**, the aryl group migrates preferentially. Observed migratory aptitude can be explained in two different ways: *i*) it is the more electron rich group that migrates; *ii*) it is the *syn* group that migrates. Since only limited data is available at this stage, any conclusion made on this regard at best will be half-baked. Detailed analysis of migratory aptitude is presented in Chapter 4 of this thesis.

A plausible mechanism for the rearrangement can be proposed on the basis of available experimental evidences. Migration of the aryl group to the electron deficient nitrogen is the key step in the overall transformation. Such migrations are possible *via* different intermediates. Involvement of a cyclic intermediate promotes migration of the more electron rich aromatic ring. Conversely, migratory aptitude in a Beckmann type rearrangement should be controlled by geometrical constraints with the *anti* group migrating preferentially. Two possible mechanisms for the observed C to N aryl migration are presented in Scheme 3.7.

We have taken cues from available literature while presenting the two mechanistic possibilities. In Burgess reagent mediated dehydration of alcohols, the reagent first ionizes at low temperature in non-polar solvents to provide tight ion pairs,[31-33] which then react with alcohol. In a similar way here also Burgess reagent undergoes ionization with the elimination of triethylamine part leaving a positive charge on sulphur. Then an attack of the

oxygen centre on dipole to sulphur followed with concomitant formation of C-N bond leads to a 1,2,3,5-oxathiadiazolidine intermediate **5b**. Subsequent elimination of the SO_3 group[5] with concomitant C to N aryl migration gives the carbamate product (Scheme 3.6). Loss of SO_3 from **5b** generates a nitrenium ion intermediate setting the stage for a carbon to electron deficient nitrogen migration. Needless to mention, the more electron rich entity will migrate preferentially. Isolation of triethylamine-sulphur trioxide complex in certain cases endorses credence to this proposal.



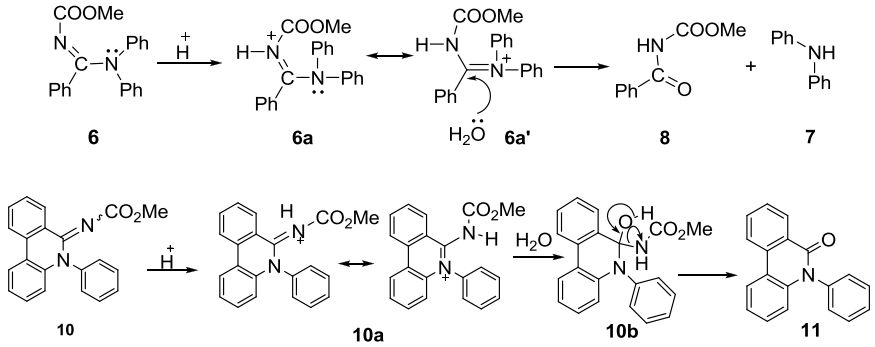
Scheme 3.7

Alternatively, a Beckmann type mechanism can also be proposed for the Burgess reagent mediated rearrangement of nitrones. Herein, nitrone attacks Burgess reagent in a nucleophilic fashion as in the earlier case to give the open-chain intermediate **5a**. Intermediate **5a** has the right structural features to undergo Beckmann rearrangement such as an efficient nucleofuge as

N-substituent and an *anti* group that is set to migrate. However, migratory aptitude in this case should be controlled by stereoelectronic factors and only the *anti* group can migrate. On the contrary, in the case of aldonitrone-Burgess reagent reaction, we observed exclusive migration of the *syn* group. Hence, a Beckmann type rearrangement involving the open-chain intermediate **5a** is improbable in this case. Intermediate **5a** at best will serve as a precursor to 1,2,3,5-oxathiadiazolidine intermediate **5b (**Scheme 3.7). Based on these considerations, we endorse the mechanism involving intermediate **5b** to account for the observed C to N aryl migration with the more electron rich group migrating preferentially. Exclusive migration of the *syn* group, thus, is just a fortuitous event. A more detailed investigation of migratory aptitude in the nitrone-Burgess reagent reaction is presented in Chapter 4 of this thesis.

Hydrolysis of carbamate intermediates also provided interesting results. Generally, carbamates during hydrolysis are first converted to carbamic acid which then decarboxylates to afford the corresponding amines. Similarly, alkylidenecarbamates are expected to undergo hydrolysis to imines that might undergo further hydrolysis to give the corresponding ammonia derivative and carbonyl compound. But in the hydrolysis of Compound **6,** C=N and ester group remain intact and only C-N bond is cleaved on hydrolysis and the products obtained are diphenylamine and benzoylcarbamate. On the other hand, hydrolysis of compound **10** apparently follows the expected hydrolysis pathway of carbamate.

The observed dichotomy, however, is easily explainable on the basis of the mechanism presented in Scheme 3.8. In the case of **10**, intermediate **10b** undergoes C-N bond cleavage to give a stable phenanthridinone product **11**. Thus, both **6** and **10** undergo hydrolysis through the same mechanism; but with difference preference for CN bond cleavage. Product stability control is operating here. Furthermore, this type of hydrolysis occurs only under acidic conditions. Both **6** and **10** are inert towards bases.



Scheme 3.8

3.4 Experimental Section

3.4.1 General Techniques

General experimental techniques and instruments used are described in the experimental section of Chapter 2.

Yields reported are for compounds separated and purified in analytically pure form.

Required nitrones and Burgess reagent were prepared using the reported procedure as detailed in the experimental section of Chapter 2. All the reactions were carried out under nitrogen atmosphere.

3.4.2 General Procedure for Reaction of Nitrones 2 and 3 with Burgess reagent

Three equivalents of Burgess reagent were added under nitrogen to a well stirred solution of nitrone in dry dichloromethane at room temperature and the stirring was continued for 3h. The progress of the reaction was monitored by TLC using ethyl acetate:hexane (8:92). The intermediate carbamate product was isolated from the reaction mixture by adding hexane. Addition of hexane to this reaction mixture give two layers - a brown coloured bottom layer containing the decomposition products of Burgess reagent and the upper layer containing the precipitated carbamate product which was carefully decanted. The filtrate was allowed to settle and washed repeatedly with hexane to get the colorless precipitate of carbamate in pure form it was further characterized by IR, ^{1}H NMR,^{13}C NMR, MS (FAB) analysis. Triethylamine-sulphur trioxide complex separated as colourless needles could be isolated under carefully controlled conditions.

3.4.3 Reaction of Nitrone 4a with Burgess Reagent.

Nitrone **4a** was dissolved in dry dichloromethane and after purging the reaction mixture with N_2, three equivalent Burgess reagent were added and mechanically stirred for 3h. at room temperature. Column chromatography (silica) of reaction mixture using hexane-ethyl acetate (9:1) gave diphenylamine **7** (68% yield). The product obtained was identified by comparing melting point, TLC and IR spectra with those of authentic sample.[34] GC-MS data indicates exclusive formation of a single amine product with

retention time 13.02, major peak at 169 corresponds to diphenylamine.

3.4.4 Reaction of Nitrone 4b with Burgess Reagent.

Nitrone **4b** was stirred with three equivalent Burgess reagent for 3h. at room temperature. Column chromatography (silica) of reaction mixture using hexane-ethyl acetate (17:3) gave diarylamine **13** (60% yield). The product obtained was identified by melting point, TLC and IR spectra, ^{1}H NMR and ESI (MS) data.

3.4.5 Reaction of Nitrones 4a and 4b with Cyclic Burgess Reagent (CBR)

Insitu generated CBR[30] was reacted with 3 equivalents of nitrones **4a,b** for 3h. at room temperature. The solvent removed under reduced pressure, and the residue was purified by column chromatography on silica gel using a mixture of hexane-ethyl acetate (9:1) as eluent gave diarylamine **7** and **13**. We repeated the reaction of nitrones **4a, b** with cyclic Burgess reagent with a view to isolate the carbamate intermediate. However, the corresponding diarylamines **7** and **13** were the only isolable products in these reactions as well.

3.4.6 Hydrolysis of Carbamate 6

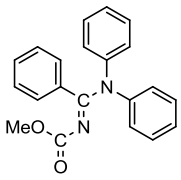
Hydrolysis of carbamate **6** was achieved by acid medium like dilute HCl. After hydrolysis, excess acid was neutralized with sodium bicarbonate solution and the products were isolated by solvent extraction using hexane.

3.4.7 Hydrolysis of Carbamate 10

Hydrolysis of carbamate **10** was achieved by acid medium like oxalic acid adsorbed on silica gel. After hydrolysis, excess acid was neutralized with sodium bicarbonate solution and the products were isolated by solvent extraction.

3.4.8 Spectral and Analytical Data of Novel Compounds

3.4.8.1 Compound 6



Yield 2.60 g (78%); mp 172 ^{o}C

IR ν_{max} (KBr): 1713, 1616, 1577, 1490, 1372, 1236, 1195, 1118 cm^{-1}

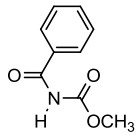
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.39(m, 2H), 7.26-7.20(m, 7H), 7.14-7.10(m, 6H), 3.4(s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.44, 162.58, 144.25, 134.49, 130.10, 129.04, 128.76, 128.29, 127.51, 126.16, 52.74

FAB-MS: *m/z* calculated for $C_{21}H_{18}N_2O_2$:330.36 (M^+); found: *m/z* 331.17 (M^++1)

Elemental analysis calculated for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48; found: C, 74.55; H, 3.98; N, 9.57.

3.4.8.2 Compound 8



Yield 1.6 g (64%); mp 116 ^{o}C

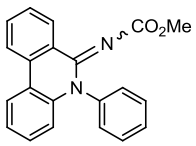
IR ν_{max} (KBr); 3278, 1778, 1751, 1529, 1209, 1018, 702 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09(1H, s), 7.83-7.81(2H, td), 7.61-7.58(1H, tt), 7.50-7.47(2H, m), 3.87(3H, s)

FAB-MS: *m/z* calculated for $C_9H_9NO_3$:179.16 (M^+); found: *m/z* 180.12 (M^++1)

Elemental analysis calculated for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82, O, 26.79 %; found: C, 61.05; H, 3.08; N, 5.96, O,24.32%

3.4.8.3 Compound 10



Yield 2.68 g (82%); mp 149 ^{o}C

IR ν_{max} (KBr): 3055, 2949, 1683, 1640, 1601, 1488, 1357, 1191, 1119, 1096 cm^{-1}

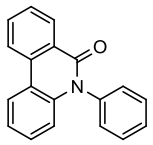
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45-8.43(dd, 1H), 8.30-8.27(dd, 1H), 8.26-8.25(t, 1H), 7.78-7.74(m, 1H), 7.62-7.58(dt, 2H), 7.57-7.53(m, 2H), 7.42-7.41(m, 2H), 7.27-7.24(m, 2H), 6.58-6.56(m, 1H), 3.32(s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.04, 148.53, 139.01, 138.16, 132.81, 132.52, 130.57, 130.21, 129.88, 129.30, 129.23, 129.16, 128.32, 125.32, 123.13, 122.84, 121.81, 119.70, 117.00, 52.26

FAB-MS: *m/z* calculated for $C_{21}H_{16}N_2O_2$: 328.35 (M^+); found: *m/z* 329.26 (M^++1)

Elemental analysis calculated for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53; found: C, 73.23; H, 5.07; N, 7.68

3.4.8.4 Compound 11



Yield 1.97 g (73%); mp 202 ^{o}C

IR ν_{max} (KBr): 3066, 1658, 1604, 1486, 1324, 1261, 810, 747 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49-8.47(q, 1H), 8.26-8.22(q, 1H), 8.22-8.21(t, 1H), 7.74-7.71(dt, 1H), 7.55-7.51(m, 3H), 7.47-7.44(m, 1H), 7.26-7.25(t, 1H), 7.24(d, 1H), 7.23-7.20(m, 2H), 6.62-6.60(m, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): 160.69, 138.14, 137.26, 132.98, 131.81, 129.18, 128.06, 127.99, 127.76, 127.11, 124.83, 121.96, 121.63, 120.76, 118.00, 116.00

FAB-MS: *m/z* calculated for $C_{19}H_{13}NO$: 271.30 (M^{+}); found: *m/z* 272.40 (M^{+}+1)

mental analysis calculated for $C_{21}H_{16}N_2O_2$: C, 84.11; H, 4.83; N, 5.16; found: C, 81.92; H, 5.12; N, 3.76

3.5. References

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CHAPTER 4

MIGRATORY APTITUDE

4.1 Abstract

Reaction of Burgess reagent with a few selected α,α,N-triarylnitrones with different substituents on the C-aryl ring was studied with a view to establish the migratory aptitudes and thereby to establish the actual mechanism of migration. These results are presented in this chapter.

4.2 Introduction

Rearrangement reactions are one of the most important classes of organic reactions[1]. Rearrangements involving electron deficient carbon and nitrogen atoms and pericyclic reaction are well studied and also find several applications in organic synthesis. Wagner-Meerwein rearrangement and pinacol rearrangements involving carbocations and Hofmann and Beckmann rearrangements involving electron deficient nitrogen are common examples. Cope and Claisen rearrangements are two well-known pericyclic reactions governed by Woodward-Hoffmann rules.[2]

Migratory aptitude is the relative tendency of a group to undergo migration in a rearrangement reaction. It is usually related to electronic factors and a wide range of other factors such as steric and conformational effects may also play important roles in

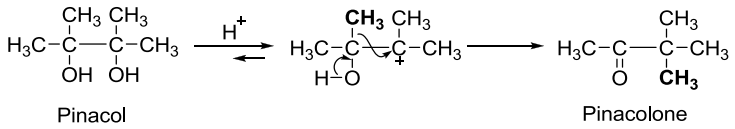
determining the migratory aptitude of a particular group in a particular rearrangement. Examination of migratory aptitudes provides insightful information on reaction mechanisms.

4.2.1 Rearrangements to electron-deficient carbon

Rearrangements involving carbocations are the major reactions in this class Wagner-Meerwein rearrangement[3] and pinacol rearrangement are typical examples.

4.2.1.1 Pinacol rearrangement

Acid-mediated rearrangement of 1,2-diols to carbonyl compounds is known as pinacol-pinacolone rearrangement (Scheme 4.1). Pinacol first dehydrates to form a carbocation that initiates 1,2-migration of an appropriate β-substituent to yield the pinacolone product.[4-14]



Scheme 4.1

In pinacol and similar rearrangements, more electron rich group migrates in preference to others and the general trend in migratory aptitude is as follows: hydrogen > aryl > alkyl.

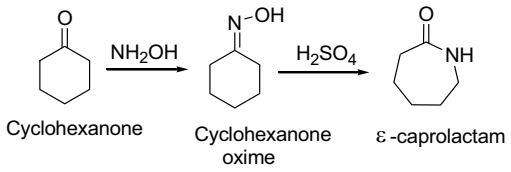
4.2.2 Rearrangements to electron-deficient nitrogen

Rearrangements to electron deficient nitrogen include Hofmann, Beckmann, Schmidt, Neber, Curtius, Lossen, and

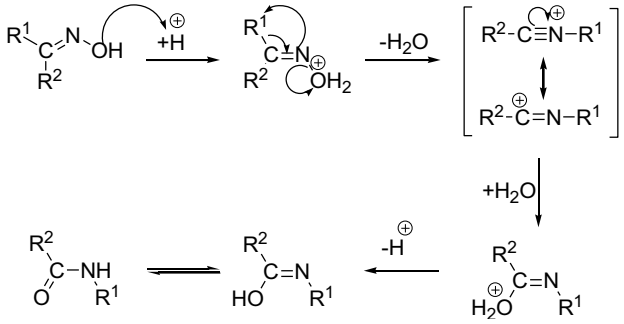
Stieglitz rearrangements. The most important and well-studied one is Beckmann rearrangement

4.2.2.1 Beckmann rearrangement

Beckmann rearrangement is an acid catalysed rearrangement of oximes to amides and where applicable to lactams[15-21] (Scheme 4.2). Mechanism of the Beckmann rearrangement in general consists of an alkyl/aryl migration with expulsion of the protonated hydroxyl group to form a nitrilium ion followed by its hydrolysis (Scheme 4.3).



Scheme 4.2

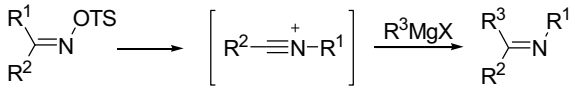


Scheme 4.3

A general observation on this rearrangement is that the group *anti* to the leaving group migrates preferentially to the nitrogen atom in a concerted fashion as shown in Scheme 4.3.[2]

4.2.2.2 Neber Rearrangement

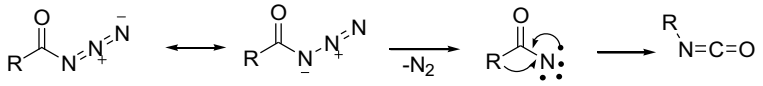
A rearrangent similar to Beckmann Rearrangement involving an oxime sulphonate in basic medium is known as the Neber rearrangement (Scheme 4.4). Geometry of the oxime sulphonate has no influence in Neber rearrangement. Here the substituent possessing the more acidic α-position migrates in preference and not necessarily the one located at *anti* position.



Scheme 4.4

4.2.2.3 Curtius rearrangement

Curtius rearrangement involves the rearrangement of acylazides to isocyanates.[22]



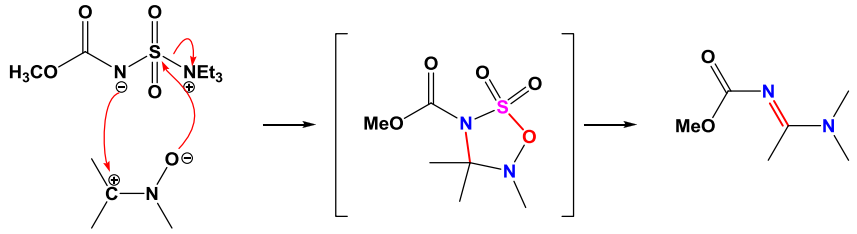
Scheme 4.5

4.2.3 Burgess reagent mediated rearrangement of nitrones

Our studies on Burgess reagent mediated conversion of nitrones to carbamates and amides reveals that a C—N migration reaction is a key step here as in many other rearrangement reactions like the Beckmann rearrangement.

As mentioned earlier, nitrone being a 1,3-dipole can add on to Burgess reagent (a potential 1,2-dipole) resulting in an

intermediate five membered heterocycle containing four heteroatoms and then rearrange to a carbamate (Scheme 4.6).



Scheme 4.6

One of the objectives of the present study is to analyse the migratory aptitude of different groups in this reaction. With this in view, synthesis[23-28] of a few suitably substituted triarylnitrone derivatives was undertaken and the reaction of these compounds with Burgess reagent was studied. The result of this study is also expected to throw more light on the mechanism of this reaction.

4.3 Results and discussion

In order to study the migratory aptitude of different groups, we examined the reactions of suitably designed *N*-(diphenylmethylene)aniline-*N*-oxides with one of the α-aryl rings having either electron withdrawing or electron releasing substituents. The desired nitrones were synthesized exclusively as *syn* isomer in some cases and a mixture of *anti* and *syn* isomers in other cases providing us the additional advantage of verifying the role of electronic *vs* stereochemical (geometric) factors in the rearrangement. In addition to *N*-(diphenylmethylene)aniline-*N*-oxide (**1**) described in Chapter 3, the following *C*-unsymmetrically substituted triarylnitrones were employed in this study:

(Z)-*N*-(phenyl(p-tolyl)methylene)aniline-*N*-oxide (**2a**), *N*-(biphenyl-4-yl(phenyl)methylene)aniline-*N*-oxide (**3a**), (Z)-*N*-((4-methoxyphenyl)(phenyl)methylene)aniline-*N*-oxide (**4a**), (E)-*N*-((4-methoxyphenyl)(phenyl)methylene)aniline-*N*-oxide (**4a'**), (Z)-*N*-((4-bromophenyl)(phenyl)methylene)aniline-*N*-oxide (**5a**), (E)-*N*-((4-bromophenyl)(phenyl)methylene)aniline-*N*-oxide (**5a'**), and (Z)-*N*-((4-chlorophenyl)(phenyl)methylene)aniline-*N*-oxide (**6a**), (E)-*N*-((4-chlorophenyl)(phenyl)methylene)aniline-*N*-oxide (**6a'**). Structure of nitrones **1-6** is presented in Figure 4.1. Note that the *Z*-isomers are numbered **xa** while the corresponding *E*-isomers are numbered **xa'**. All the required nitrones (Figure 4.1) were prepared according to reported[23-29] or modified procedures. Details of preparation, purification and characterization are presented in Chapter 2 of this thesis. In a few cases, (**4-6**) nitrones were prepared as a mixture of *syn* and *anti* isomers. Where it was difficult to separate the individual isomers in pure form, we used the isomer mixtures as such. Fortunately, it turned out to be advantageous to do so (*vide infra*).

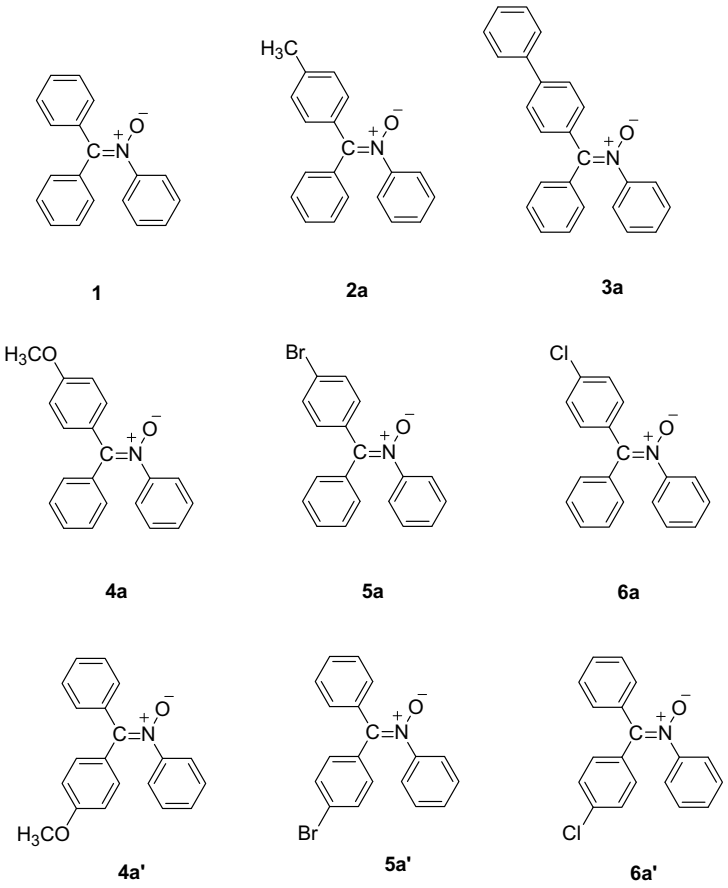
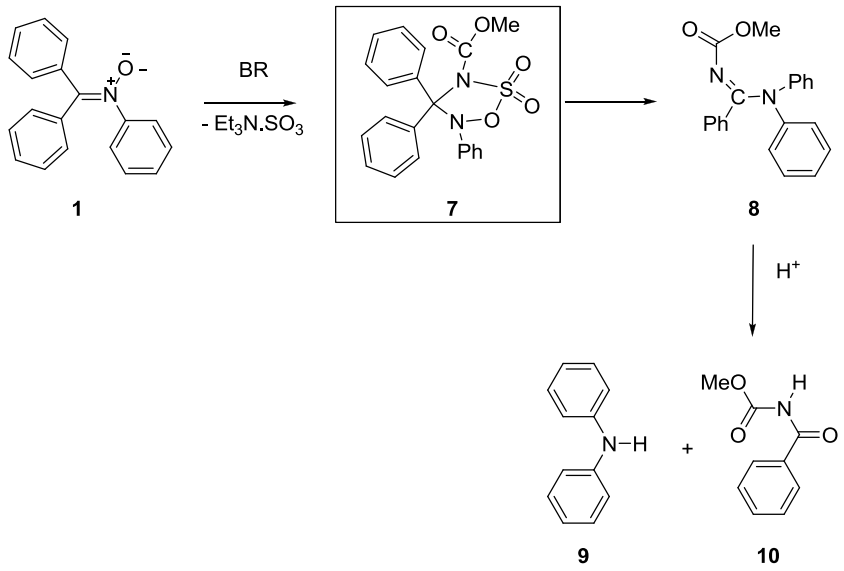


Figure 4.1

4.3.1 Reaction of *N*-(diphenylmethylene)aniline-*N*-oxide (1) with Burgess reagent

Details of this reaction are available in Chapter 3. Since the α–C is symmetrically substituted, migratory aptitude is irrelevant here (Scheme 4. 7).



Scheme 4.7

4.3.2 Reaction of (Z)-*N*-(phenyl(p-tolyl)methylene)aniline-*N*-oxide (2) with Burgess reagent

The title compound, shown to be the *Z*-isomer (with the N—O bond and the 4-methylphenyl group in *syn* (*Z*) arrangement) from single crystal XRD studies (Figure 4.2) and ^{1}H NMR characteristics was treated with Burgess reagent to identify the *C*-aryl group that migrates to nitrogen.

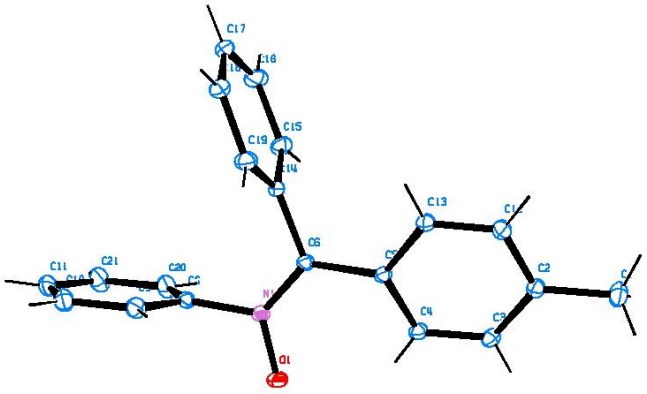
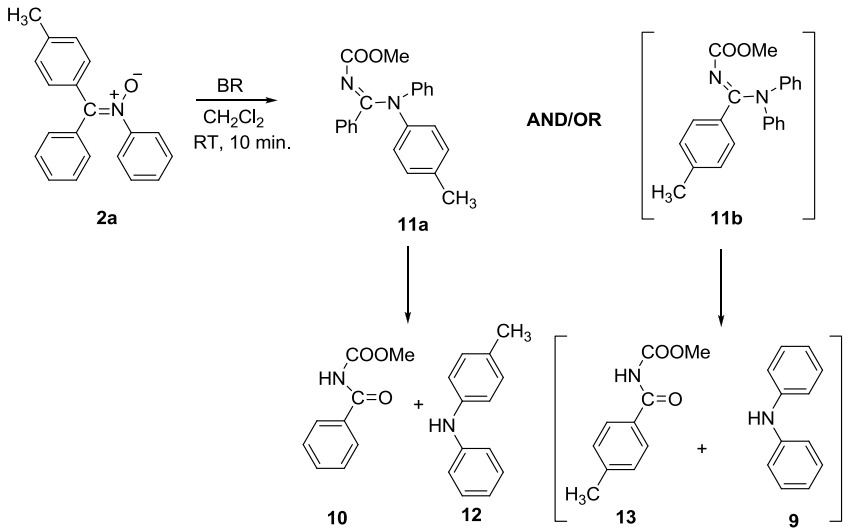


Figure 4.2. XRD structure of nitrone **2a**.

Either the phenyl or the 4-methylphenyl group could migrate in this case. Consequently, rearrangement reaction of **2a** can lead to the carbamates **11a** or **11b** depending on the group that migrates (Scheme 4.8). If the 4-methylphenyl group *syn* to N—O bond in **2a** migrates to nitrogen carbamate **11a** will be formed. On the other hand, if the group *anti* to N—O migrates, carbamate **11b** will be formed. We have already established that carbamate **11a** on hydrolysis gives benzoyl carbamate (**10)** and 4-methyl-*N*-phenylaniline (**12)**, whereas carbamate **11b** on hydrolysis gives 4-methylbenzoylcarbamate (**13)** and diphenylamine (**9**).



Scheme 4.8

It is interesting to note that in our experiments we could isolate products **10** and **12** only, suggesting the exclusive formation of the carbamate **11a** which in turn indicated the migration of 4-methylphenyl group in preference to phenyl. Note that 4-methylphenyl group is *syn* with respect to the N—O bond. It may also be noted that 4-methylphenyl group is comparatively more electron rich in comparison with phenyl. We could account for the observed migratory aptitude based on either of the following conclusions: *i*) the *syn* group migrates preferentially; *ii*) it is the more electron rich group that migrates. Based on this experiment alone, we could not pinpoint the driving force behind migratory aptitude, but it is clear that a Beckmann type mechanism is not operating here.

^{1}H NMR spectrum of the carbamate **11a** exhibited a characteristic signal of ester methyl protons at δ 3.50 ppm and a

three proton singlet of 4-methyl group at δ 2.30 ppm. Similarly ^{13}C NMR spectrum exhibited characteristic carbon signal at 52.73 ppm for ester methyl group, carbon signal at 21.01 corresponding to methyl carbon and signals at 163.57 ppm and 162.64 for carbonyl carbon and C=N carbon respectively. IR spectrum exhibited characteristic carbonyl absorption at 1712 cm^{-1} and C=N absorption peak at 1690 cm^{-1}. MS (ESI) analysis gave molecular ion peak at 345.3 corresponding to the molecular formula $C_{22}H_{20}N_2O_2$. All data were consistent with the carbamate structure **11a**.

In various schemes presented in this chapter, structures appearing in square brackets are expected products that were not formed under the conditions employed by us.

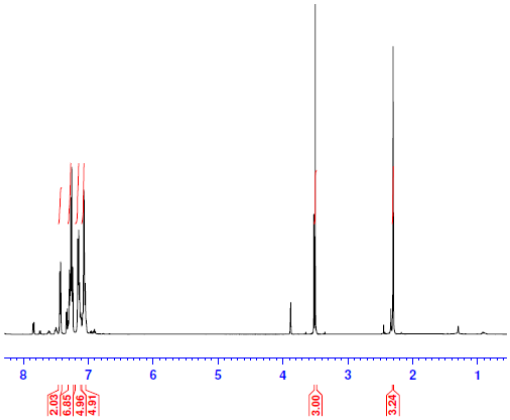


Figure 4.3 ^{1}H NMR spectrum of **11a**.

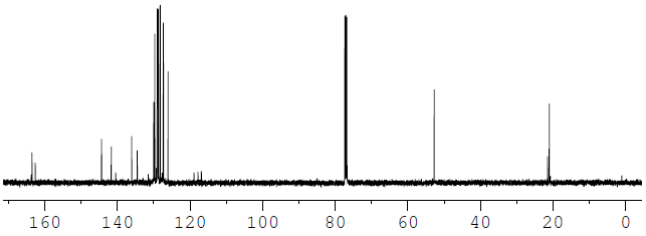
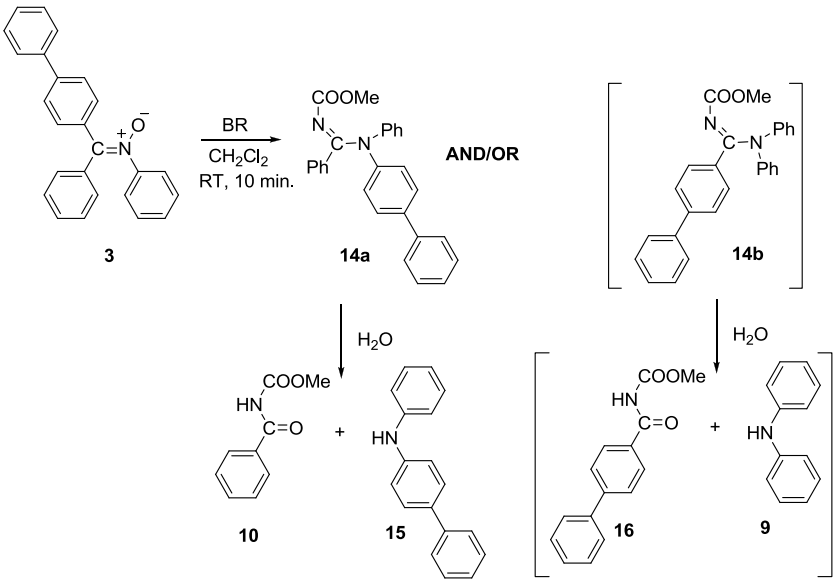


Figure 4.4 ^{13}C NMR spectrum of **11a**.

4.3.3 Reaction of *N*-(biphenyl-4 yl(phenyl)methylene)aniline-*N*-oxide (3) with Burgess reagent

Nitrone **3** on reaction with Burgess reagent afforded carbamate **14a** (Scheme 4.9). ^{1}H NMR spectrum of **14a** exhibited a characteristic signal of ester methyl protons at δ 3.54 ppm and ^{13}C NMR spectrum had characteristic carbon signal at 52.80 ppm for ester methyl group, and signals at 162.12 ppm and 160.32 for carbonyl carbon and C=N carbon respectively. IR spectrum exhibited characteristic carbonyl absorption at 1712 cm^{-1} and C=N absorption peak at 1692 cm^{-1}. All these spectral data supports the structure **14a**. MS (ESI) analysis gave molecular ion peak at 407.3 corresponding to the molecular formula $C_{27}H_{22}N_2O_2$. All data were consistent with the proposed structure **14a** in Scheme 4.9.

Structure of **14a** was further confirmed by chemical transformations. Hydrolysis of **14a** gave benzoylcarbamate **10** and *N*-phenylbiphenyl-4-amine (**15)**. As in the above case, formation of **10** and **15** points to the formation of **14a**, the precursor for **10** and **15** through the migration of more electron rich biphenyl group in preference to phenyl group.



Scheme 4.9

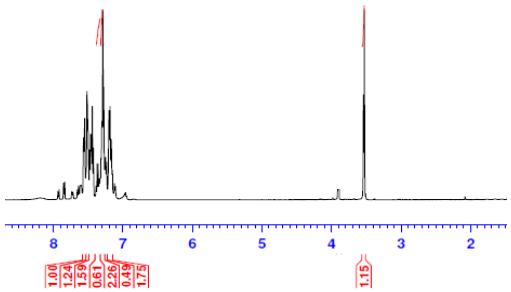


Figure 4.5. ^{1}H NMR spectrum of **14a**.

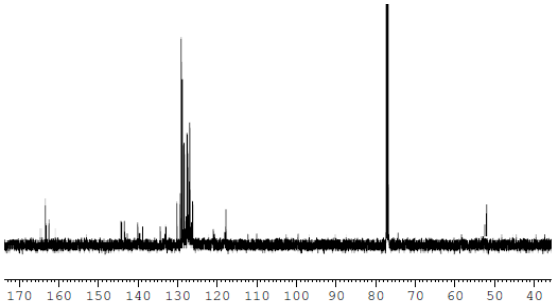
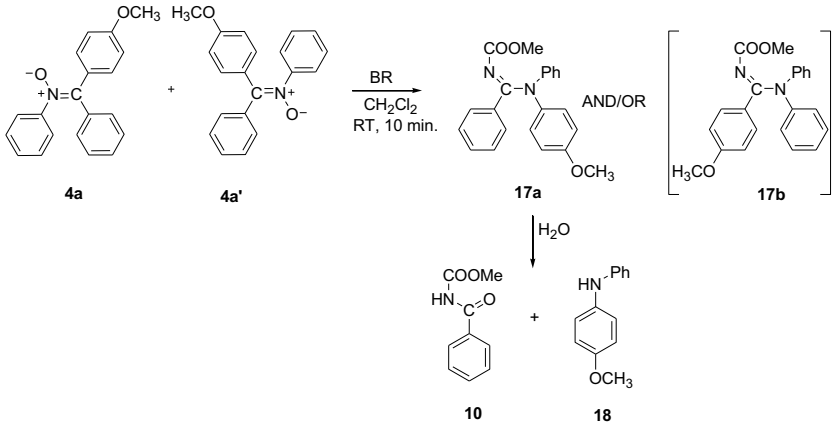


Figure 4.6 ^{13}C NMR spectrum of **14a**.

4.3.4 Reaction of *N*-((4-methoxyphenyl) (phenyl)methylene) aniline-*N*-oxide (4a+4a') with Burgess reagent

Here, the title compound obtained as a 2:1 mixture of geometrically isomeric nitrones **4a** and **4a'** was subjected to reaction with Burgess reagent to get a single carbamate product which on hydrolysis gave methyl benzoylcarbamate (**10**) and 4-methoxy-*N*-phenylaniline (**18)**, indicating the exclusive formation of **17a** as the immediate rearrangement product.



Scheme 4.10

This was the defining result of our investigations. Complete conversion of mixture of nitrones **4a** and **4a'** to give a single product **17a** (Scheme 4.10) showed that geometry of the substrate nitrone has no commanding role in dictating migratory aptitude in this rearrangement and as indicated, but not confirmed, by the previous examples of **2** and **3**, the more electron rich group migrated in preference (Scheme 4.8). Reaction of **4a**,**4a'** mixture to give a single product supported our view that the more electron rich aryl group migrates preferentially.

In this case it was possible to isolate the carbamate **17a**. Structure of **17a** was established from the following spectral characteristics. ^{1}H NMR spectrum exhibited a characteristic signal of ester methyl protons at δ 3.77 ppm and a three proton singlet of 4-methoxy group at δ 3.50 ppm. Similarly ^{13}C NMR spectrum exhibited characteristic carbon signal at 52.73 ppm for ester methyl group, carbon signal at 55.38 ppm corresponding to methoxy carbon and signals at 163.67 ppm and 162.28 ppm for carbonyl carbon and C=N carbon respectively. IR spectrum exhibited characteristic carbonyl absorption at 1703 cm^{-1} and C=N absorption peak at 1615 cm^{-1}. MS (ESI) analysis gives molecular ion peak at 361.2 corresponds to the molecular formula $C_{22}H_{20}NO_3$. All data were consistent with structure **17a** (Scheme 4.10). Proposed structure for the rearranged product was further confirmed by chemical transformation. Acidic hydrolysis of **17a** gave methyl benzoylcarbamate (**10**) and 4-methoxy-*N*-phenylaniline (**18**) in near-quantitative amounts.

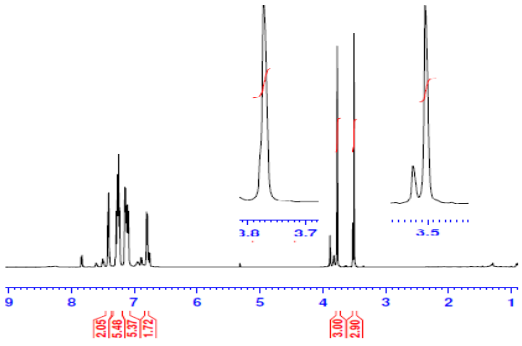


Figure 4.7. ^{1}H NMR spectrum of **17a**.

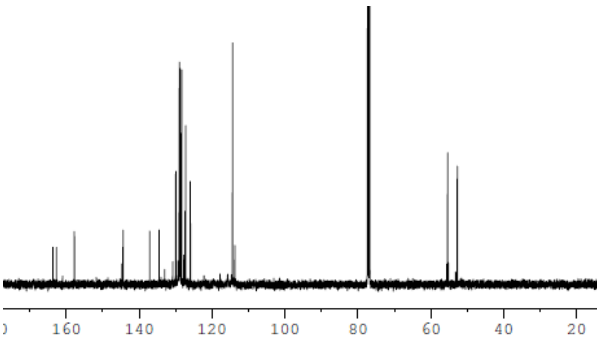
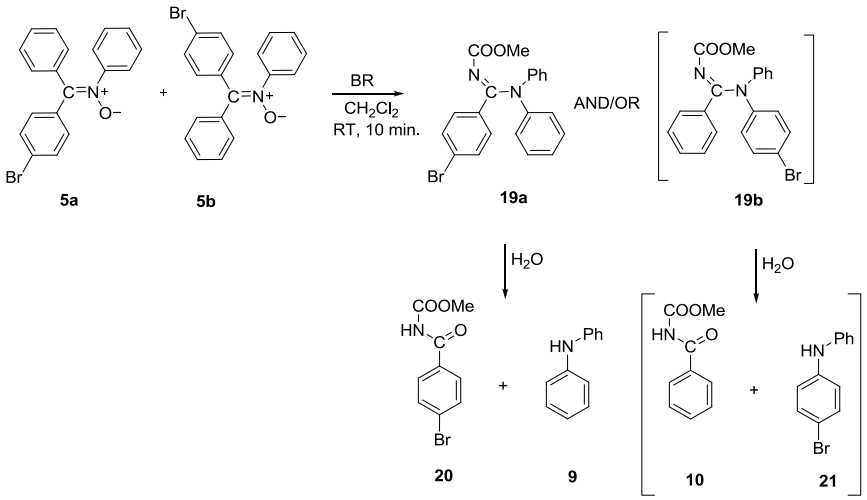


Figure 4.8. ^{13}C NMR spectrum of **17a**.

4.3.5 Reaction of *N*-((4-bromophenyl)(phenyl)methylene)-aniline-*N*-oxide (5a+5a') with Burgess reagent

In this case also the title compound obtained as a mixture of geometrical isomers **5a** and **5a'** was subjected to Burgess reagent mediated rearrangement to give the carbamate **19a** exclusively. Hydrolysis of **19a** gave methyl 4-bromobenzoylcarbamate (**20)** and diphenylamine (**9)**, which indicated that the structure of the precursor carbamate is **19a**.



Scheme 4.11

The complete conversion of mixture of nitrones **5a** and **5a'** to a single carbamate **19a** (Scheme 4.11) in this reaction was fully consistent with the previous observations – the more electron rich aryl group migrates preferentially.

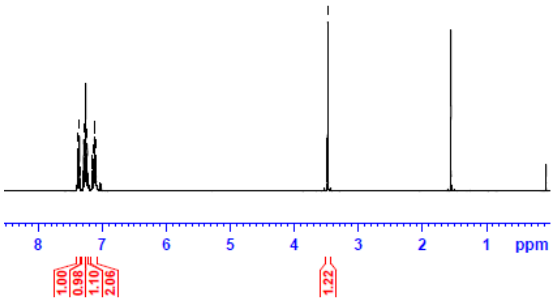


Figure 4.9. ^{1}H NMR spectrum of **19a**.

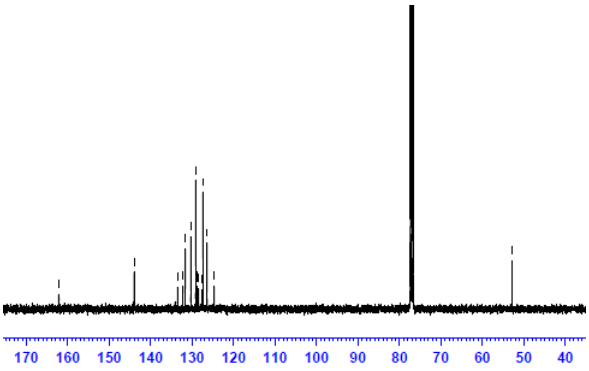


Figure 4.10. ^{13}C NMR spectrum of **19a**.

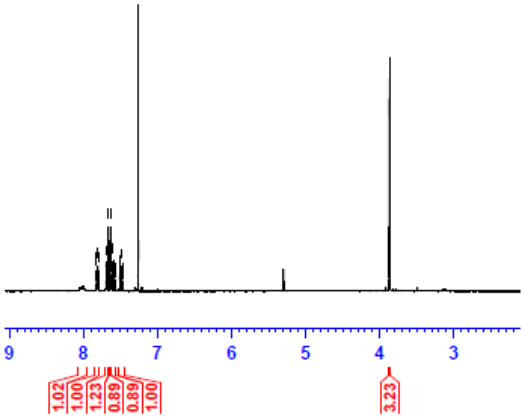
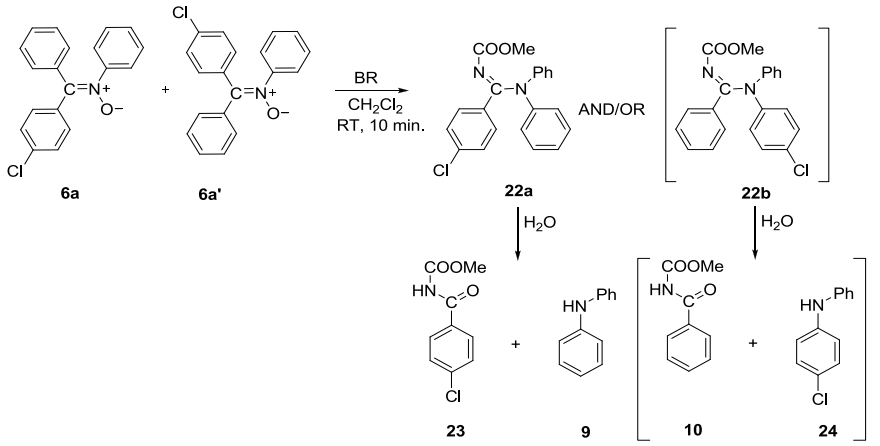


Figure 4.11. ^{1}H NMR spectrum of **20**.

4.3.6 Reaction of *N*-((4-chlorophenyl)(phenyl)methylene)-aniline-*N*-oxide (6a+6a') with Burgess reagent

Here also, starting with a geometrically isomeric mixture of nitrones **6a** and **6a'**, carbamate **22a** was obtained as the single product which could be hydrolysed to methyl 4-chlorobenzoylcarbamate (**23)** and diphenylamine (**9)**.



Scheme 4.12

The complete conversion of isomeric mixture of nitrones **6a** and **6a'** to a single carbamate **22a** (Scheme 4.12) in the reaction was also fully consistent with the previous observations on electronic *vs* geometrical requirements of this reaction.

Compound **22a** had the following spectral features. In the ^{1}H NMR spectrum, the characteristic signal of ester methyl protons was observed at δ 3.51 ppm and ^{13}C NMR spectrum exhibited characteristic carbon signal at 52.8 ppm for ester methyl group and signals at 163.4 ppm and 162.5 ppm for carbonyl carbon and C=N carbon respectively. IR spectrum exhibited characteristic carbonyl absorption at 1716 cm^{-1} and C=N absorption peak at 1609 cm^{-1}. MS (ESI) analysis gave molecular ion peak at 365 corresponding to the molecular formula $C_{21}H_{17}ClN_2O_2$. All data were consistent with that for structure **22a**.

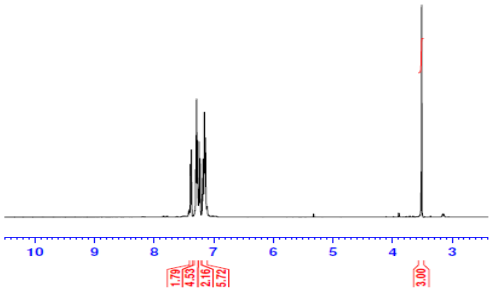


Figure 4.12. ^{1}H NMR spectrum of **22a**.

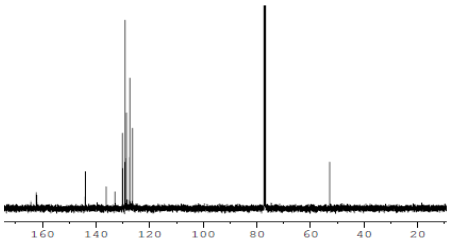


Figure 4.13. ^{13}C NMR spectrum of **22a**.

The following are the spectral details of compound **23**. ^{1}H NMR spectrum exhibited a characteristic signal of ester methyl proton at δ 3.87 ppm and ^{13}C NMR spectrum exhibited characteristic carbon signal at 53.3 ppm for ester methyl group. IR spectrum exhibited characteristic carbonyl absorption at 1716 cm^{-1} and 1748 cm^{-1} indicating the existence of two carbonyl groups. A significant peak at 3256 cm^{-1} in the IR spectrum provided further evidence for the presence of NH group in the molecule. All these spectral data support the presence of ester group, NH group, and two carbonyl groups in compound **23**. MS (ESI) analysis gives molecular ion peak at 214.1 corresponding to the molecular formula $C_9H_8ClNO_3$. All data were consistent with structure **23** (Scheme 4.12).

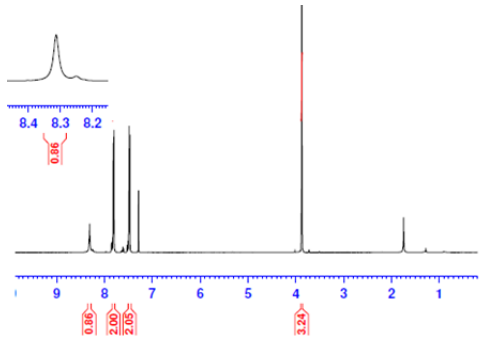


Figure 4.14. ^{1}H NMR spectrum of **23**.

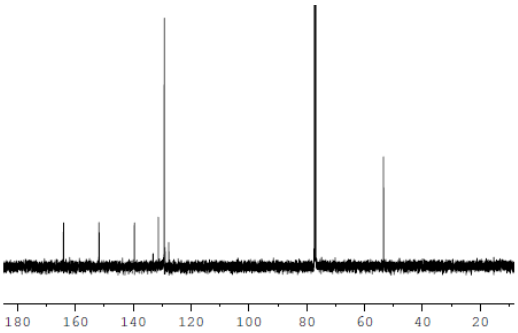


Figure 4.15. ^{13}C NMR spectrum of **23**.

In conclusion, the study of migratory aptitude in Burgess reagent mediated rearrangement of nitrones reveals that migratory aptitude is decided by electronic factors and geometry of the substrate has apparently no influence on the course of rearrangement. This observation is more consistent with the mechanism involving a cyclic intermediate (Scheme 4.6). Beckmann type rearrangement involving an open chain intermediate (Figure 4.16) cannot account for the observed migratory aptitude.

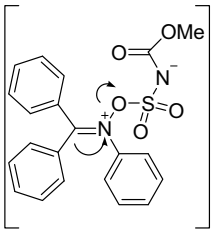


Figure 4.16

The general trend in migratory aptitude as observed in our experiments is given in Figure 4.17 where the encircled group migrates preferentially.

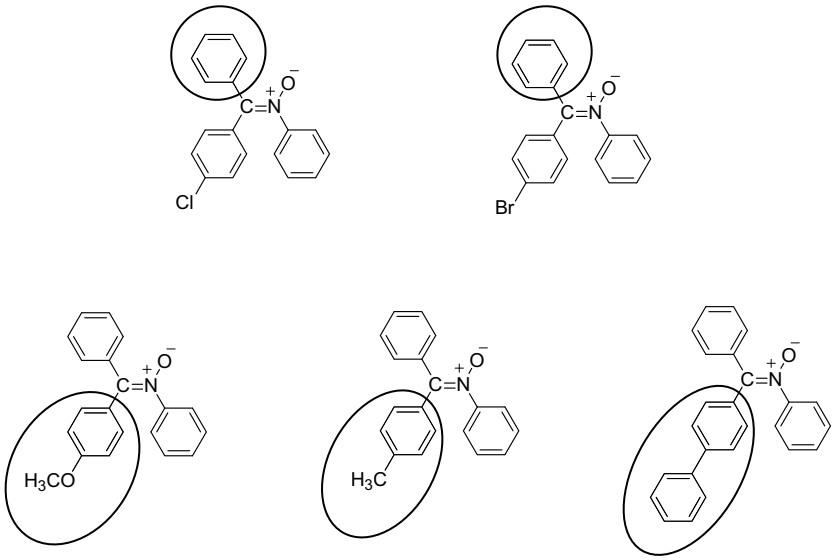


Figure 4.17. Encircled groups undergo preferential migration.

4.4 Experimental

4.4.1 General Techniques

Details of general experimental techniques and instruments used are presented in previous chapters.

4.4.2 General Procedure for Reaction of Triarylnitrones with Burgess Reagent

Burgess reagent (3 eqiv.) was added under nitrogen to a well stirred solution of nitrone in dry dichloromethane at room temperature and stirring was continued for 3h. Progress of the reaction was monitored by thin layer chromatography (ethyl acetate: hexane). The intermediate carbamate product was isolated - in cases where it is possible - from the reaction mixture on precipitation by adding hexane. The upper layer containing white precipitate of carbamate was carefully decanted. The filtrate was allowed to settle and washed repeatedly with hexane to get the colorless precipitate of carbamate and the product was further purified by column chromatography.

4.4.3 General Procedure for Hydrolysis of Carbamates

Dilute HCl (10%) was added to a solution of carbamate in minimum quantity of dichloromethane and stirred for 20 min. at room temperature. It was neutralized with sodium bicarbonate solution and diphenylamine was completely separated by extracting with hexane. The aqueous layer was further extracted with ether. The product which crystallized out on evaporating the solvent was purified by recrystallization (dichloromethane: hexane) mixture and characterized by ^{1}H NMR,^{13}C NMR, MS(ESI) analysis.

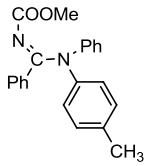
4.4.4 Spectral and Analytical Data of Novel Compounds

4.4.4.1 Compound 11a

Yield 2.68 g, 78%; mp 98 °C

IR (KBr): 1712, 1690, 1587, 1490, 1397, 1238, 1198, 1120 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.42 (d, 2H), 7.32-7.24 (m,7H), 7.16-7.13 (m,5H), 3.50 (s,3H), 2.30 (s,3H)



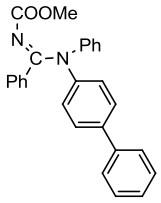
^{13}C NMR (125 MHz, $CDCl_3$): δ 163.57, 162.64, 144.48, 144.38, 141.71, 136.09, 134.58, 130.03, 129.74, 129.08, 129.04, 128.99, 128.82, 128.76, 128.28, 127.47, 127.40, 127.36, 126.05, 52.73, 21.01

MS (**ESI**): *m/z* calculated for $C_{22}H_{20}N_2O_2$: 344.36 (M^+); found: *m/z* 345.30 (M^++1)

Elemental analysis calculated for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; found: C, 77.92; H, 6.01; N, 7.32.

4.4.4.2 Compound 14a

Yield 3.04 g, 75%; mp 92 °C



IR (KBr): 1712, 1692, 1588, 1490, 1372, 1242, 1200, 1119 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.42 (m ,9H), 7.37-7.35 (d, 1H), 7.31-7.29 (t, 5H), 7.27-7.23 (t, 1H), 7.20-7.16 (t ,4H), 3.54 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.12, 160.32, 140.11, 138.89, 134.45, 133.04, 130.22, 129.42,

129.35, 129.12, 129.04, 128.91, 128.84, 128.81, 128.75, 128.38, 127.93, 127.67, 127.64, 127.60, 127.47, 127.28, 127.08, 126.98, 126.90, 126.55, 126.29, 126.21, 117.85, 52.80

MS (**ESI**): *m/z* calculated for $C_{27}H_{22}N_2O_2$: 406 (M^+); found: *m/z* 407 (M^++1)

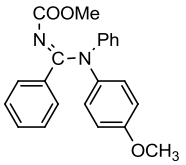
Elemental analysis calculated for $C_{27}H_{22}N_2O_2$: C, 79.78; H, 5.46; N, 6.89; found: C, 78.02; H, 6.01; N, 5.32.

4.4.4.3 Compound 17a

Yield 2.59 g, 72%; mp 84 ^oC

IR (KBr): 1703, 1615, 1588, 1508, 1372, 1244, 1199, 1119 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) 7.42-7.4 (m, 2H), 7.29-7.23 (q, 5H), 7.15-7.09 (m, 5H), 6.80-6.79 (m, 2H), 3.77 (s, 3H), 3.50 (s, 3H)

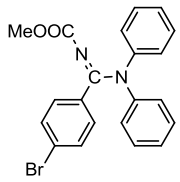


^{13}C NMR (125 MHz, $CDCl_3$): δ 163.67, 162.28, 157.77, 144.64, 144.41, 137.30, 134.56, 130.79, 129.98, 129.33, 129.07, 128.97, 128.86, 128.77, 128.70, 128.28, 127.69, 127.37, 127.23, 125.98, 114.36, 113.77, 55.38, 52.73

MS (**ESI**): *m/z* calculated for $C_{22}H_{20}N_2O_3$: 360 (M^+); found: *m/z* 361 (M^++1)

Elemental analysis calculated for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77; found: C, 71.98; H, 4.07; N, 7.11-

4.4.4.4 Compound 19a



Yield 3.22 g, 81%; mp 136 ^{o}C

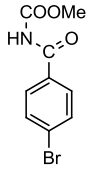
IR (KBr): 1712, 1623, 1582, 1489, 1235, 1193, 1115 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (dt, 1H), 7.29-7.26 (m, 1H), 7.25-7.23 (m, 1H), 7.15-7.09 (m, 2H), 3.47 (s, 1H)

^{13}C NMR (125 MHz, $CDCl_3$): δ, 162.25, 144.02, 133.53, 132.20, 131.63, 130.35, 129.19, 128.86, 128.43, 127.57, 126.38, 52.81.

MS (**ESI**): *m/z* calculated for $C_{21}H_{17}BrN_2O_2$: 408 (M^+); found: *m/z* 410 (M^++2)

4.4.4.5 Compound 20



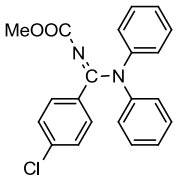
Yield 1.44 g., 56%; mp 124 ^{o}C

IR (KBr): 3247, 1779, 1749, 1592, 1525, 1209, 1006 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.82 (d, 1H), 7.69-7.68 (d, 1H), 7.64-7.63 (t, 1H), 7.47-7.46 (t, 1H), 7.57 (t, 1H), 3.86 (s, 3H)

MS(**ESI**): *m/z* calculated for $C_9H_8ClNO_3$ 258 (M^+); found: *m/z* 260 (M^++2)

4.4.4.6 Compound 22a



Yield 2.88 g, 79%; mp 122 ^{o}C

IR (KBr): 1716, 1609, 1589, 1489, 1372, 1236, 1198, 1119 cm^{-1}

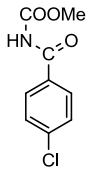
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (d, 2H), 7.30-7.27 (t, 4H), 7.24-7.22 (d, 2H), 7.18-7.14 (m, 6H), 3.51 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ, 163.42, 144.01, 136.26, 132.99, 130.16, 129.25, 129.19, 128.71, 127.42, 126.40, 52.85.

MS (**ESI**): *m/z* calculated for $C_{21}H_{17}ClN_2O_2$: 364 (M^+); found: *m/z* 365 (M^++1)

Elemental analysis calculated for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; N, 7.68; found: C, 67.32; H, 3.23; N, 5.90.

4.4.4.7 Compound 23



Yield 1.32 g., 62%; mp 128 ^{o}C

IR (KBr): 3256, 1779, 1748, 1596, 1490, 1304, 1201, 1011 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.82-7.80 (d, 2H), 7.48-7.47 (d, 2H), 3.87 (s, 3H)

^{13}C NMR (125 MHz, $CDCl_3$): δ164.06, 151.73, 139.54, 131.26, 129.20, 53.35

MS(**ESI**): *m/z* calculated for $C_9H_8ClNO_3$: 213 (M^+); found: *m/z* 214 (M^++1)

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CHAPTER 5

REACTIONS OF NITRONES WITH CYANURIC CHLORIDE

5.1 Abstract

Cyanuric chloride is a mild reagent for various transformations of synthetic importance. Guided by the range of reactivity of cyanuric chloride and the nucleophilic character of nitrones, we were fascinated in the reaction of nitrones with cyanuric chloride. This chapter deals with the present study of reactions of various nitrones with cyanuric chloride which provides additional evidence for the nucleophilic character of nitrones.

5.2 Introduction

Cyanuric chloride (**1**), also known as TCT reminding its name 2,4,6-trichloro-1,3,5-triazine (Figure 5.1) and its derivatives are mild and less expensive reagents for various organic transformations of synthetic importance and are being used as dehydrating agents in organic synthesis; as coupling agents[1-4] in the synthesis of peptides; in the preparation of esters, amides, alkyl chlorides, acyl azides; in the selective protection of hydroxyl groups; conversion of amides to nitriles and so on. [1,3,5]-Triazine compounds have been employed as reagents and intermediates in

the synthesis of several heterocycles and even as "combinatorial core" in the design of new therapeutics.

Being a potential multifunctional intermediate TCT is used in the industrial synthesis of a large number of products like herbicides, reactive dyes, optical brightners and many other specialty chemicals.[5,6] TCT is the main precursor for the herbicide atrazine and 1,3,5-triazine derivatives have widespread applications in pharmaceutical, material, and agrochemical industries also. A potent variant of TCT is prepared by complexing it with three equivalents of DMF {TCT-$(DMF)_3$, **2**} (Figure 5.1).

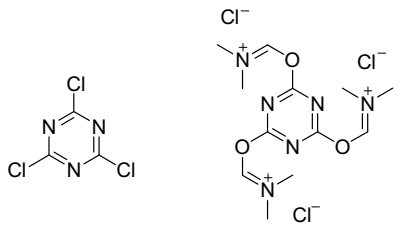
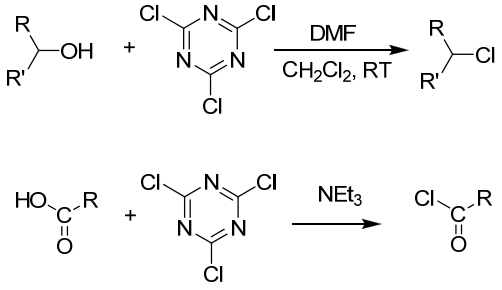


Figure 5.1

5.2.1 Reaction of alcohols with TCT

The transformation of alcohols into the corresponding alkyl halides is one of the most important reactions in organic syntheses. While commonly used reagents for this transformation like thionyl chloride,[7] phosphorus halides[8] etc. requires quite drastic reaction conditions, quantitative conversion of alcohols[9] and acids to corresponding chlorides can be achieved using TCT in very mild, efficient, and chemoselective procedures (Scheme 5.1).[10-12] Here a tertiary amine is often employed as the second reagent. Similarly

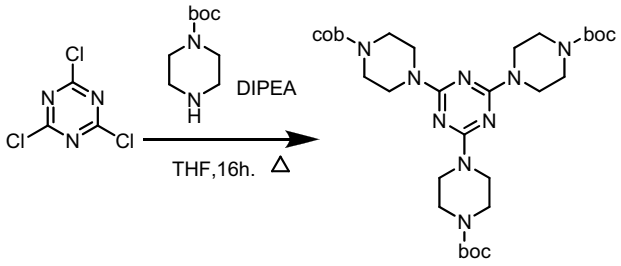
acids can be converted to acid chlorides using TCT in the presence of tertiary amines such as triethylamine and pyridine.[13]



Scheme 5.1

5.2.3 Synthesis of Dendrimers using TCT

TCT and aliphatic diamines can be used as primary raw materials for the synthesize dendrimers containing 1,3,5-triazine (Scheme 5.2). 1,3,5-Triazine ring is important in dendrimer synthesis because of its high solubility and ability to withstand harsh reaction conditions. Furthermore, TCT possesses good chemoselectivity and reaction controllability of three chlorine atoms so that several steps in the synthesis of dendrimers, like structure protection-deprotection or deactivation-activation can be avoided. Dendrimers of 1,3,5-triazine functionalized with 1,8-naphthalimide14 exhibit excellent fluorescent properties.

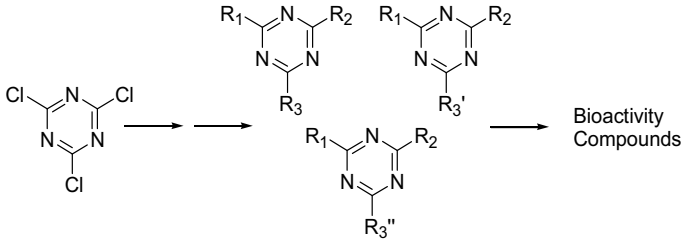


Scheme 5.2

Poly(ethyleneglycol)-supported dendrimers have been synthesized using TCT as dendrons and tris(hydroxymethyl)-aminomethane as linkers with high loading capacity, excellent solubility and thermal stability.[15]

5.2.4 Synthesis of Bioactive 2,4,6-Trisubstituted 1,3,5-Triazines Using TCT

The structural symmetry and ease of functionalization of the 1,3,5-triazine core makes it a powerful scaffold for the rapid generation of diverse molecular libraries. Both solid-phase and solution-phase, methods are available for the synthesis of alkyl/aryl amino- and oxy-substituted triazine libraries. 2,4,6-Trisubstituted 1,3,5-triazines are biologically active compounds[15] (Scheme 5.3).

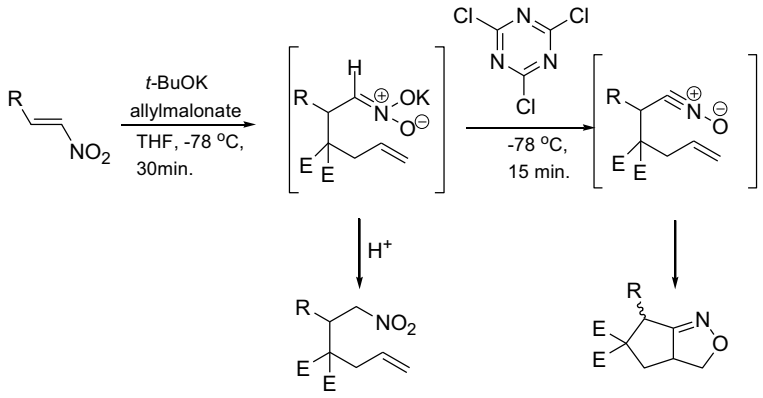


Scheme 5.3

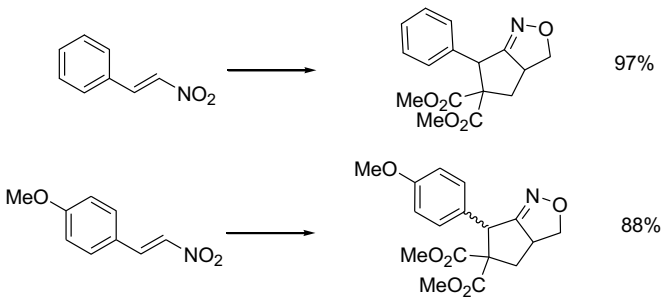
5.2.5 Conversion of Nitronate into Nitrile Oxide using TCT

Nitroalkene can be converted to the corresponding nitronate by reaction with allylmalonate anion in THF. The nitronate generated can be easily transformed into the corresponding nitrile oxide by adding TCT, as the dehydrating agent, directly to the mixture without isolation (Scheme 5.4). The nitrile oxide generated *in situ* undergoes a tandem 1,3-dipolar

cycloaddition with the dipolarophile, giving the bicyclic isoxazoline within 15 minutes at the same temperature.[16] TCT can be used as a mild reagent for the one-pot synthesis of isoxazoline from nitroalkane (Scheme 5.5).



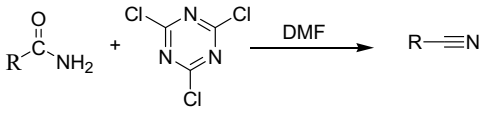
Scheme 5.4



Scheme 5.5

5.2.6 Dehydration of Primary Amides to Nitriles with TCT-DMF Complex

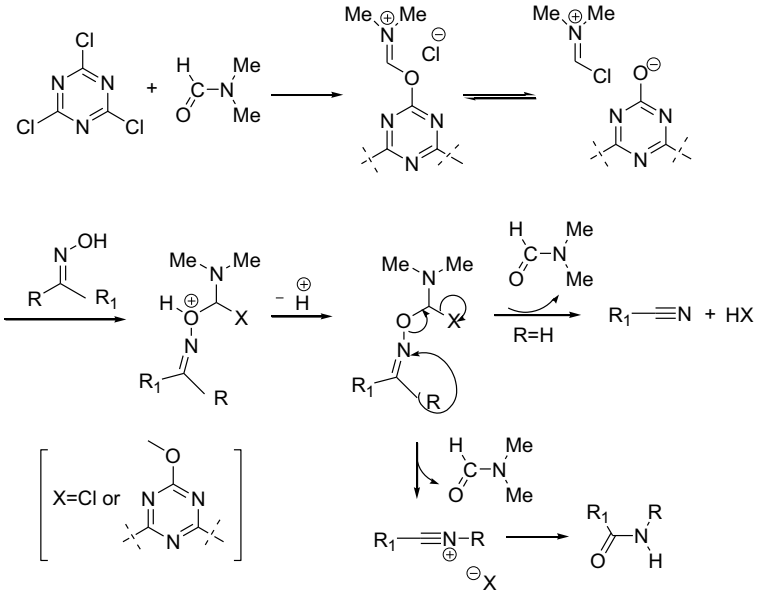
TCT can also be used for the mild conversion of amides to nitriles at room temperature (Scheme 5.6). The reaction is compatible with several sensitive functionalities.[17,18]



Scheme 5.6

5.2.7 Beckmann Rearrangement of Oximes using TCT

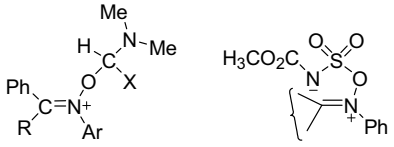
Ketoximes on treatment with TCT in *N,N*-dimethyl-formamide at room temperature give amides[19] in excellent yields. Aldoximes, on the other hand, give the corresponding nitriles.[10] TCT-$(DMF)_3$ complex is the active reagent in this reaction.[20,21] Carbon to nitrogen migration is the key step in the amide formation (Scheme 5.7). As with Beckmann rearrangement, the *anti* group migrates (Scheme 5.7).



Scheme 5.7

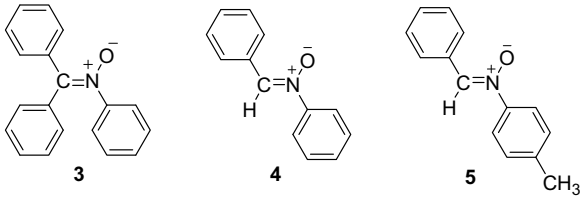
5.2.8 Reaction of Nitrones with TCT-$(DMF)_3$ Complex and Burgess Reagent: A Comparative Study

Burgess reagent and TCT exhibit conspicuous commonality in their reaction with amides, oximes etc. In Chapters 3 and 4 of this thesis, we have described a novel Burgess reagent mediated C to N migration. Guided by our results on the study of the reaction of nitrones with Burgess reagent, observations on the 1,3-dipolar nature of nitrones and the comparable role of TCT in several reactions that are brought about by Burgess reagent on appropriate compounds, we became interested in a comparison study of the reactions of nitrones with TCT and Burgess reagent. On the basis of migratory aptitude studies, we proposed the involvement of a cyclic intermediate in Burgess reagent mediated rearrangement of nitrones. In contrast, in the oxime-{TCT-$(DMF)_3$} reactions, the *anti* group that migrates. Based on the nucleophilic character of nitrones, we reasoned that nitrones can also react with TCT-$(DMF)_3$ with the elimination of triazine component and accompanying C to N migration as observed with the oxime-{TCT-$(DMF)_3$} reaction. Possible intermediates involved in the nitrone-{TCT-$(DMF)_3$} complex reaction and nitrone- Burgess reagent reaction are shown in Figure 5.2. In the present work, we have examined the reaction of TCT with nitrones in DMF with a view to exploit the nucleophilicty of nitrones and to unravel the migratory aptitude, if any, observed in this reaction. We selected nitrones **3-8** having different structural features for the present study (Figure 5.3, give the structure of nitrones).

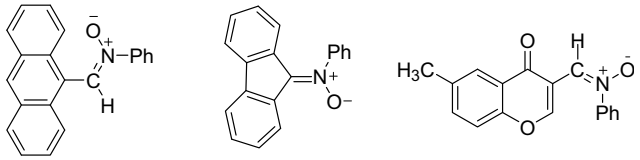


A **B**

Figure 5.2



3 **4** **5**



6 **7** **8**

Figure 5.3

5.3 Results and discussion

5.3.1 Reaction of *N*-(diphenylmethylene)aniline-*N*-oxide (3a) with TCT

It is known that TCT can form a 1:3 complex with DMF (**2**) (Scheme 5.8). In our experiments TCT was first allowed to react with DMF and the TCT-$(DMF)_3$ complex formed thereof was then treated with nitrone **3**. The product formed was identified as *N,N*-diphenylbenzamide (**9**). It was noted that the reaction proceeds reasonably fast in DMF while practically no reaction was observed in other solvents such as dichloromethane or THF suggesting a

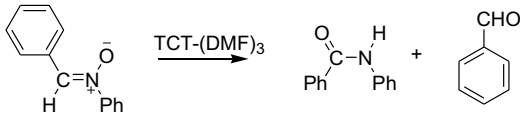
definite role for TCT-$(DMF)_3$ complex. Also, the reaction rate reduced drastically when the amount of TCT with respect to the nitrone was reduced.

3 **9**

Scheme 5.8

5.3.2 Reaction of *N*-(benzylidene)aniline-*N*-oxide (4) with TCT

Reaction of *N*-(benzylidene)aniline-*N*-oxide (**4**) with TCT-$(DMF)_3$ complex gave *N*-phenylbenzamide (**10**), in a reaction involving the migration of hydrogen. GC-MS analysis of the reaction mixture indicated the generation of benzaldehyde (**11**) in this reaction (Scheme 5.9).

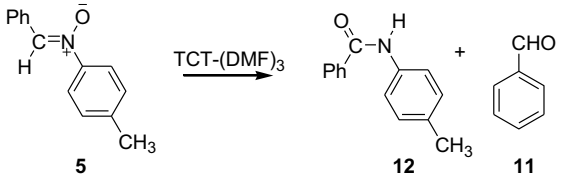


4 **10** 11

Scheme 5.9

5.3.3 Reaction of *N*-benzylidene-4-methylaniline-*N*-oxide (4) with TCT

Reaction of TCT-$(DMF)_3$ complex with *N*-benzylidene-4-methylaniline-*N*-oxide (**5**) gave *N*-*p*-tolylbenzamide (**12**) (Scheme 5.10). Further, the formation of **12** indicated that hydrogen is migrating in this case as well. As in the previous case, GC-MS analysis of the reaction mixture indicated generation of benzaldehyde in this reaction.



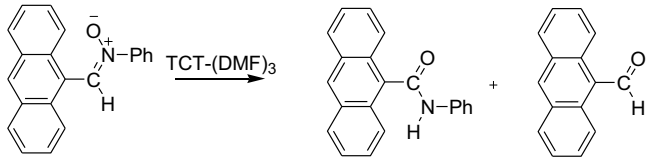
5 12 11

Scheme 5.10

From the results of the above two experiments involving the rearrangement of nitrones **4** and **5**, we were inclined to believe that it is the group *anti* to the leaving group that migrates preferentially in this reaction similar to that in Beckmann rearrangement. We carried out few more experiments to verify this aspect of the mechanism.

5.3.4 Reaction of *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide (6) with TCT

Reaction of *N*-(anthracen-9-ylmethylene)aniline-*N*-oxide (**6**) with TCT-DMF complex gave *N*-phenyl-9-anthracenecarboxamide (**13**) with the migration of *anti* hydrogen. Anthraldehyde (**14**, 20%) was also formed in this reaction (Scheme 5.11).

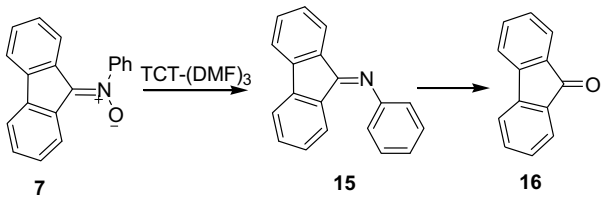


6 13 14

Scheme 5.11.

5.3.5 Reaction of *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide (7) with TCT

In the reaction of *N*-(9H-fluoren-9-ylidene)aniline-*N*-oxide (**7**) with TCT, deoxygenation of nitrone to the corresponding imine was observed. Initially formed imine **15** underwent gradual conversion to fluorenone (**16**) (Scheme 5.12).

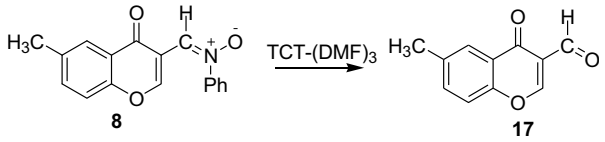


7 15 16

Scheme 5.12

5.3.6 Reaction of *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenyl-nitrone (8) with TCT

C-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**8**) on reaction with TCT gave 6-methyl-3-formylchromone (**17**) through a simple hydrolysis reaction (Scheme 5.13).

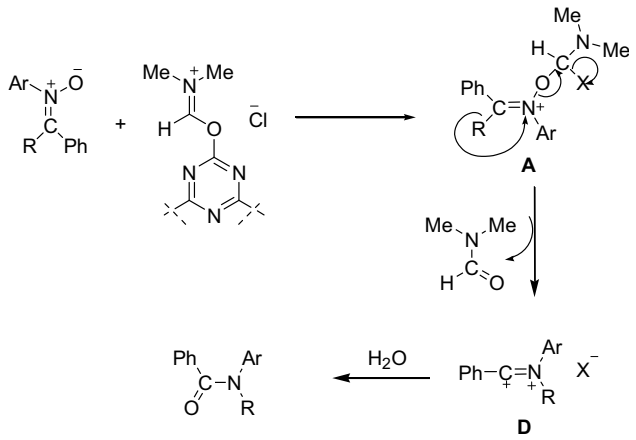


8 17

Scheme 5.13

Our studies on TCT mediated transformations of nitrones revealed three distinct reaction possibilities: *i*) C to N migration of *anti* group reminiscent of classical Beckmann rearrangement and *ii*) deoxygenation followed by hydrolysis to give the corresponding carbonyl compounds as the final products. Possible mechanism for C-to-N aryl migration can be visualized as shown in Scheme 5.9.

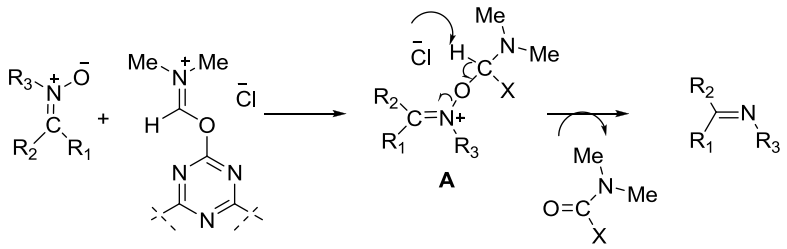
Nucleophilic attack by nitrone-oxygen on TCT-DMF complex **2** can result in intermediate **A** where C to N migration (similar to Beckmann rearrangement) give **D** which on reaction with water gives the corresponding amide as shown in Scheme 5.14. It is also possible that, on intermediate **A**, attack by water on α-carbon, C to N migration and N-O bond cleavage take place in quick succession. In the latter scenario, it is not necessary that **D** is involved as a discrete intermediate in this reaction.



Scheme 5.14

In the case of aldonitrones, the corresponding aldehydes were also formed. This is not surprising since it is well known that aldonitrones undergo slow decomposition to give the corresponding aldehydes. With *C*-(4-oxo-4*H*[1]benzopyran-3-yl)-*N*-phenylnitrone (**8**), the corresponding hydrolysis product *viz.* 6-methyl-3-formylchromone (**17**) was generated as the only product. Fluorenylnitrone behaved anomalously: no C to N migration was observed in this case. This observation is in contrast with the facile C to N migration observed in the reaction of fluorenylnitrone with

Burgess reagent as well as efficient TCT mediated aryl group migration observed with nitrones **3-6**. In the light of the experimental results on the reaction with fluorenylnitrone, we propose that alternate mechanism involving imine generation and subsequent hydrolysis (in addition to obvious simple hydrolysis) for aldehyde generation should be considered for aldonitrones **4-6** as well. A plausible mechanism for deoxygenation is presented in Scheme 5.15.



Scheme 5.15

Comparision of our results presented in this chapter those presentd in Chapter 3 provides insightful information on migratory aptitudes observed with nitrone-TCT and nitrone-Burgess reagent reactions. Based on results presented in Chapter 3 and in this chapter, it is evident that both TCT and Burgess reagent initiate interesting reactions of nitrones. With several nitrones, both reagents initiate C to N aryl migration. However, the migratory aptitude in TCT-mediated and Burgess reagent-mediated rearrangements are different. In cases where applicable, TCT initiated migration of anti group while Burgess reagent initiated migration of the more electron rich substituent. In other words, TCT initiated rearrangements are stereocontrolled while Burgess

reagent initiated rearrangements are controlled by electronic factors. A comprehensive list of nitrones, and the primary products formed under the influence of TCT and Burgess reagent is presented in Table 5.1.

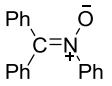
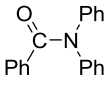
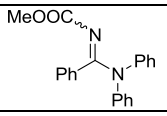
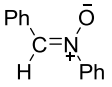
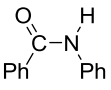
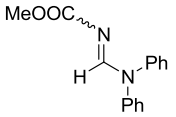
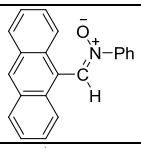
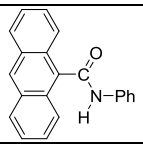
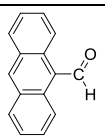
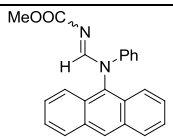
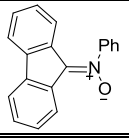
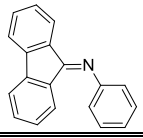
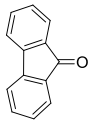
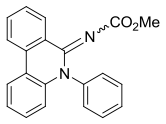
Sl. No.	Nitrones	Products formed		
		With TCT		With BR
1				
2				
4				
5				

Table 5.1. Primary products formed in the reaction of nitrones with TCT and BR.

5.3.7 Conclusions

We have studied the reactions of nitrones with Burgess reagent and cyanuric chloride and characterized various products obtained. Comparison of the reaction of nitrones with these reagents is interesting. With both these reagents, C to N migration is observed. But the identity of migrating groups and products generated are different. In the case of *N*-(diphenylmethylene)aniline-*N*-oxide and

N-(benzylidene)-aniline-*N*-oxide cyanuric chloride promotes C-N migration of the *anti* group leading to amide as product. Here, as with Beckmann rearrangement, C-N migration is governed by geometrical factors. On the other hand, in all cases investigated by us, Burgess reagent promoted migrations are controlled by electronic factors. Hence it is logical to conclude that the significant intermediate where C to N migration takes place is quite different for these two reagents. In summary, both Burgess reagent and cyanuric chloride promotes C-N migration but the reactivity of Burgess reagent is entirely different, and can lead to the formation of interesting new molecules like unsymmetrical diarylamines.

5.4 Experimental Section

5.4.1 General Techniques

General experimental techniques and instruments used are described in the experimental section of Chapter 2.

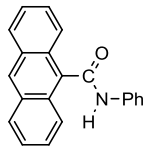
All the required nitrones were prepared using the reported procedure. All known compounds were characterised by comparison with the physical data of authentic samples and/or spectral characteristics.

5.4.2 General procedure for the reaction of nitrones with TCT

TCT (2 mmol) was dissolved in DMF (0.4 mL) with stirring, to get a white precipitate of TCT-DMF complex. The nitrone (1 mmol) dissolved in dichloromethane (3 mL) was added to the above and stirred for 20 minutes. Formation of an yellow precipitate which

was insoluble in most of the organic solvents was noted which was attributed to the formation of TCT derivatives as indicated by the IR spectrum. The filtrate was concentrated and analysed by TLC {EtOAc:hexane (1:4)}. Solvent was removed under reduced pressure and the crude product was chromatographed over silica gel (60-120 mesh) (hexane:EtOAc).

5.4.2.1 Spectral and analytical data for compound 11



Yield 0.16 g., 56%

IR ν_{max} (KBr): 3309, 3067, 2949, 1685 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.53 (s, 1H), 8.17-8.16 (d, 2H), 8.05-8.04 (d, 2H), 7.77-7.74 (t, 3H), 7.55-7.49 (m, 4H), 7.45-7.42 (t, 2H), 7.26 (s, 1H) ;

^{13}C NMR (125 MHz, CDCl3): δ 167.7, 131.5, 131.11, 129.28, 128.73, 128.61, 128.09, 127.05, 125.65, 124.92, 124.89, 119.89 ;

LCMS-ESI: *m/z* calculated. for $C_{21}H_{15}NO$: 297 (M^+); found: *m/z* 298(M^++1)

5.5 References

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CHAPTER 6

Synthetic Application of Reaction of Nitrones with Burgess Reagent: Synthesis of Unsymmetrical Diarylamines

6.1 Abstract

Our studies on Burgess reagent mediated rearrangement of nitrones revealed the potential of the reaction for the synthesis of diarylamines. Considering the very few methods reported and also the very harsh experimental conditions employed therein, our procedure seems very attractive, especially for the synthesis of unsymmetrically substituted diarylamines. The necessity of a facile route to these compounds is obvious with increasing applications of these compounds. This chapter deals with our studies on the synthesis of unsymmetrical diarylamines utilizing a novel reaction discovered by us.

6.2 Introduction

Diaryl heteroatom moieties, particularly the diarylamines are found widely distributed in natural products agrochemicals, pharmaceuticals, HIV-1 protease inhibitors, dyes and optical materials.[1-7] They are also widely used as stabilizers and antioxidants for rubber and polymers, stabilizers for explosives, and as polymerization and corrosion inhibitors.[8] Several diphenylamine

derivatives are useful organic intermediates for manufacturing dyes, agrichemicals, medicines, and compounding agents for rubber.[9] For example, 2-methyl-4-alkoxy-diphenylamines, are valuable raw-materials for fluoran dyes used in heat- or pressure-sensitive recording paper.[10,11] Also, 2-methyl-3'-hydroxy-diphenylamine is the useful intermediate for acid-black 94 dye. Electrochemically initiated reactions of diphenylamines with sulphide can be applied to the voltammetric detection of hydrogen sulphide.[12]

Apart from being highly effective and active antioxidants in natural and many types of synthetic rubbers, diphenylamine derivatives also impart heat-resistance and flex-fatigue resistance to rubber articles used in high-temperature and dynamic applications. They can retain their properties in high-speed, high-temperature and/or high-load applications. Another important use of diphenyl amines is as fungicides in preservation of apple. Diphenylamine based donor acceptor type conjugated polymers are considered to be potential candidates for photonic applications.[13,14] Examples of some useful disubstituted diphenylamines are given in Figure 6.1.

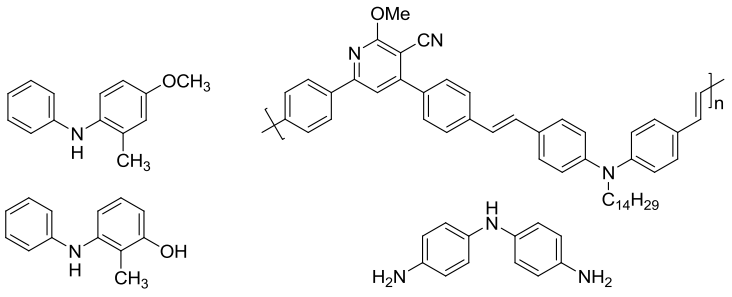


Figure 6.1

6.2.1 Synthesis of Diarylamines

Diphenylamine has been synthesized from aniline and phenol (1:3) in the presence of a phosphoric acid catalyst at high temperature and pressure[15] and also by self-condensation of aniline in the presence of acid catalysts, with the release of ammonia,[16] or by dehydration–condensation of phenol and aniline in the presence of Pd/C as hydrogen transfer catalyst. Soluble trifluoroboric acid-anilinium salts have been used as active acid catalysts used for the synthesis of diphenylamine from aniline[17] in liquid phase under higher pressure. Zeolite Beta with the Si/Al atomic ratio of 12:5 is a suitable catalyst for the condensation of aniline to diphenyl amine.[18]

Of late, synthesis of diphenylamines have been reported by microwave assisted technique using an inorganic solid support, like bentonite and mixtures of alumina, silica, ferric oxide, calcium oxide, magnesium oxide and titanium oxide, in a simple, efficient and environmental friendly method.[19] In a typical reaction, aniline was absorbed on the solid support and then irradiated with microwave in an open quartz vessel, at 850 W power output (2.45 GHz) to get diphenylamine.

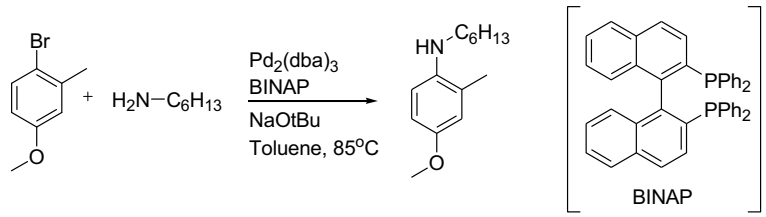
Diphenylamines have also been synthesized by the liquid phase condensation of aniline and phenol in the presence of Pd/C catalyst. 2-Methyl-4-methoxydiphenylamine has been prepared from 3-methyl-4-nitroanisole and cyclohexanone in the presence of Pd/C catalyst.[20]

In a recent report on the synthesis of diarylamines from aryl azides and aryl bromides via an organometallic approach, a reaction of aryl and benzyl azides with aryl cuprates, generated in situ from aryl magnesium bromide and CuCN in THF to furnish a variety of unsymmetrical diarylamines in good yields was described.[21]

Synthesis of unsymmetrical diarylamines and triaryl-methanes via a copper(II)-catalyzed aza-Friedel-Crafts reaction of *N*-(2-pyridyl)sulphonylaldimines was also reported.[22]

Recently, a microwave assisted route to a series of diarylamines, was reported in presence of KF/Al_2O_3 in solvent free conditions. The salient features of this method are short reaction time, high yields, general applicability to substrates and simple workup.[23]

Buchwald–Hartwig amination is another important method for the synthesis of diamines, using diphenylphosphinobinapthyl (BINAP)[24-26] and diphenylphosphinoferrocene (DPPF) as ligands (Scheme 6.1).



Scheme 6.1

6.2.1.1 Present work

Conventional preparative strategies for diarylamines involve *N*-arylation of amines under copper-mediated Ullmann-type conditions involving the coupling of amines with aryl halides.

However, the major concerns of the available reaction are harsh conditions, requirement of stoichiometric amounts of copper, chemical wastage and occurrence of undesirable metal or metal residue, especially in the case of diarylamines required for biological, electronic and optical applications. In spite of improved procedures like palladium-catalyzed cross-coupling reactions of amines with aryl halides;[27-29] oxidative coupling procedures between arylboronic acids and aromatic or heterocyclic amines mediated by Cu(II) salts;[30-33] addition of aromatic Grignard reagents to nitroarenes,[34] it is felt that the existing methods for the preparation of these compounds are tedious and laborious and there is still a need for innovation in such a general chemical transformation in order to provide corresponding structures effectively and on a feasible scale. Our studies on Burgess reagent mediated rearrangement of nitrones have opened a new avenue to the synthesis of diarylamines, especially the unsymmetrical diarylamines using predominantly organic reagents. The reaction is highly selective, effective and reaction conditions are rather mild. Further, this is the first report of synthesis of diarylamines by a rearrangement of appropriate nitrones.

6.3 Results and Discussion

From our studies on the Burgess reagent mediated rearrangement of nitrones, we deduce that nitrones with appropriate substituents on rearrangement can give diarylamines with required substituents. This reaction constitute a reasonably facile synthetic strategy to get desired diarylamines by choosing appropriate

nitrones in which predetermined group can be made to undergo a C to N migration. Facile access to the required nitrones makes the strategy more attractive. The whole procedure can be completed in one-pot. This strategy is particularly useful for getting unsymmetrical diarylamines, for which only limited options are available.

We have demonstrated the application of the above strategy for the synthesis of the following diarylamines (Table 6.1). Selection criteria for the substrate nitrone was that, the group intended to undergo migration is comparatively more electron rich than the other so that the required diamine is resulted. Preparations of the respective nitrones have been detailed in the Chapter 2 of this thesis.

6.4 Experimental Section

6.4.1 General Techniques

Details of general experimental conditions are given in the experimental section of Chapter 2. The nitrones and Burgess reagent were prepared using the reported procedure and detailed in Chapter 2. All the diamine products were characterized by comparing with authentic standards.

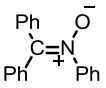
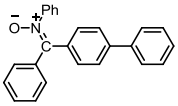
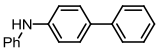
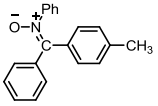
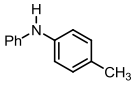
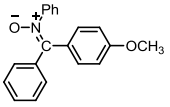
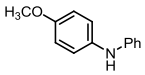
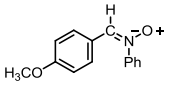
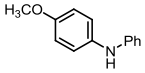
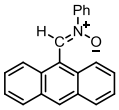
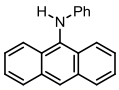
Sl. No.	*Substrate (nitrone)*	*Product (diamine)*	*Yield*
1			68%
2			62%
3			64%
4			64%
5			63%
6			66%
7			58%

Table 6.1. Unsymmetrical diarylamines prepared by Burgess reagent mediated rearrangement of appropriate nitrone.

6.4.2 General Procedure for the Preparation of Diarylamines

Burgess reagent (3 eqiv.) was added under nitrogen to a well stirred solution of nitrone in dry dichloromethane at room temperature and stirring was continued for 3h. The reaction progress was monitored by TLC (ethyl acetate: hexane). The intermediate carbamate products were hydrolysed by aqueous HCl (10%) followed by stirring for 20 min. at room temperature. Diarylamines formed on neutralization with sodium bicarbonate solution were isolated by extracting with hexane and further purified by column chromatography.

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