NOVEL SYNTHETIC TRANSFORMATIONS MEDIATED BY CERIUM (IV) AMMONIUM NITRATE

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BY

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CERTIFICATE

This is to certify that the work contained in the thesis entitled "***NOVEL SYNTHETIC TRANSFORMATIONS MEDIATED BY CERIUM (IV) AMMONIUM NITRATE*** " has been carried out by **V. Sheeba** under my supervision at the Organic Chemistry Division of Regional Research Laboratory [CSIR], Trivandrum and the same has not been submitted elsewhere for any other degree.

G. Vijay Nair
Thesis Supervisor

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PREFACE

Among the various methods employed for carbon-carbon bond formation radical methodology has come to the fore recently. Many of these free radical reactions are initiated by electron transfer and can proceed via the intermediacy of radical ions. The electron transfer can be accomplished electrochemically, photochemically or chemically. Chemically, transition metal salts can promote electron transfer efficiently and this method has found numerous applications in organic synthesis. Among these Mn(III) and Ce(IV) have emerged as powerful one electron oxidants. Especially, oxidative processes mediated by Manganese (III) acetate have received considerable attention, in syntheses of various organic molecules. Eventhough CAN has been shown to offer many advantages over Manganese (III) acetate, its potential has not been tapped adequately. In view of this, a detailed investigation was carried out to explore the synthetic utility of CAN and the details and the results of the study are embodied in the thesis entitled "**Novel Synthetic Transformations Mediated by Cerium (IV) Ammonium Nitrate** "

The thesis is divided into four chapters and appropriate references are given towards the end of each chapter. The first chapter includes a selective literature coverage of appropriate CAN mediated reactions, begining with

developments in the area of radical methodology and converging on electron transfer reactions.

The second chapter is divided into three parts. The first part deals with the dimerization reactions of alkoxystyrenes with CAN in methanol and ethanol. A similar investigation conducted on alkoxystyrenes using acetonitrile as the solvent is detailed in Part II. Part III describes the effect of substitution on the styrenic double bond in the reaction of alkoxystyrenes with CAN.

An experimentally simple, facile and efficient CAN mediated synthesis of oxamates from acetoacetamides is discribed in chapter 3.

Chapter 4 concerns itself with some attempts towards intramolecular cyclization of suitable systems mediated by CAN.

At the end, a summary of the work presented in this thesis is given.

ABBREVIATIONS

AIBN	: Azobisisobutyronitrile
Ac	: Acetyl
brs	: broad singlet
CAN	: Cerium (IV) Ammonium Nitrate
CET	: Chemical Electron Transfer
d	: doublet
dd	: doublet of doublet
DCB	: Dicyanobenzene
DCM	: Dichloromethane
DEPT	: Distortionless Enhancement by Polarization Transfer
DME	: Dimethoxy Ethane
DMF	: Dimethyl Formamide
Et	: Ethyl
ET	: Electron transfer
EWG	: Electron withdrawing group
HOMO	: Highest Occupied Molecular Orbital
HRMS	: High resolution mass spectrum
J	: Coupling constant
LDA	: Lithium diisipropylamide
LUMO	: Lowest Unoccupied Molecular Orbital
m	: multiplet
Me	: Methyl
MNDO	: Maximum Neglect of Differential Overlap
NVC	: N-Vinyl carbazole
o	: ortho
p	: para
PET	: Photoinduced Electron Transfer
PIFA	: Phenyl iodine (III) bis(trifluoroacetate)
r. t.	: Room temperature
s	: singlet
SET	: Single electron transfer
SOMO	: Singly Occupied Molecular Orbital
S. T.	: Sealed tube
t	: triplet
THF	: Tetrahydrofuran
TLC	: Thin layer chromatography
TMS	: Tetramethylsilane
TMSOTf	: Trimethylsilyl trifluoromethanesulfonate

CHAPTER 1

CERIUM (IV) AMMONIUM NITRATE MEDIATED NOVEL SYNTHETIC TRANSFORMATIONS

1.1. INTRODUCTION

The work presented in this thesis is mainly concerned with radicals and radical cations generated by cerium (IV) ammonium nitrate (CAN) which is a very powerful one electron oxidant. In order to put the work in perspective, a brief introduction to radical methodology with some emphasis on the appropriate CAN mediated reactions is given in this chapter. Of necessity, the literature coverage is selective and not intended to be exhaustive. It is worthy of note that there are a number of excellent reviews available on the various aspects of radical methodology and these are cited.

Carbon-carbon bond formation constitutes the fundamental process in organic synthesis. The past few decades have seen an upsurge of

developments in synthetic protocols for the construction of C-C bonds. The earlier methods relied largely on ionic and pericyclic reactions; the use of radical methodology was negligible before 1980's. However, during the past two decades, radical carbon-carbon bond forming reactions have become very popular to the point that they are now routinely considered for the synthesis of complex molecules.

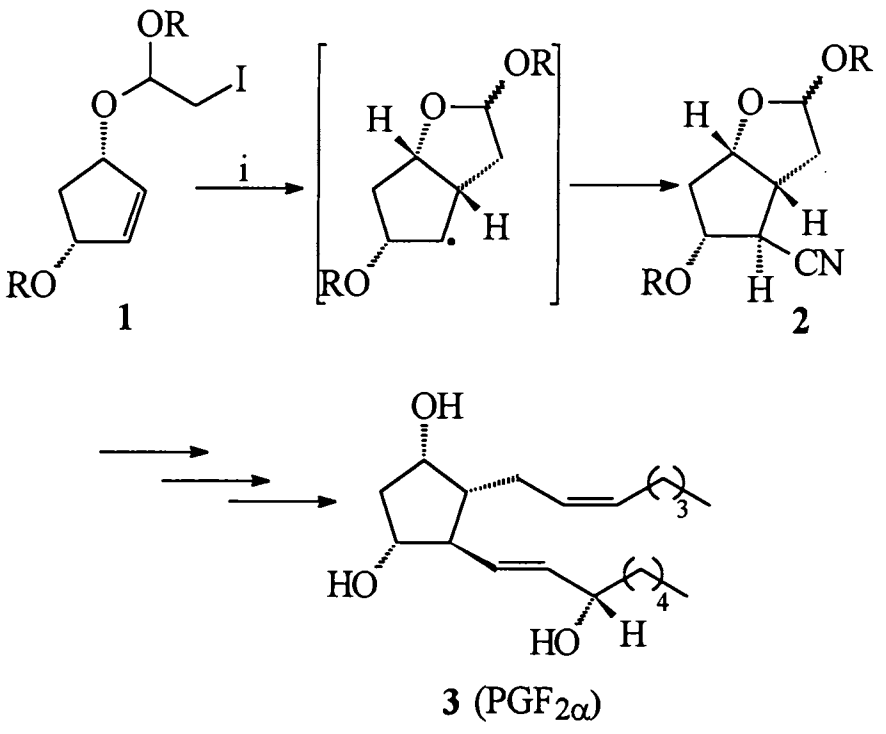
Radicals are essentially neutral species with one unpaired electron. Gomberg[1] isolated the first stable radical (trityl radical) in 1900 and since then free radical species have been recognized as the reactive intermediates in a large number of chemical reactions. Many classical reactions such as Kolbe electrolysis[2], Barton reaction[3] and Hoffmann-Löffler-Freytag[4] reaction have been shown to involve radical intermediates.

Although polymer chemists have routinely used radical reactions for a long time, mainstream organic chemists have avoided radical reactions in their synthetic schemes until recently. This may be due to an erroneous but longstanding notion that radical reactions are too fast, they lack selectivity and hence are prone to give intractable mixtures. This notion was dispelled mainly by the work of Stork,[5] who demonstrated that the controlled generation of carbon centered radicals as well as their subsequent addition to alkenes offers a unique and powerful method for the construction of complex carbocyclic compounds. This work along with the contributions of Beckwith,[6] Ingold,[7] Giese[8] and Julia[9] have led to a better understanding of the structure and reactivity of radicals resulting in a dramatic increase in their use in a number of syntheses. Radical reactions offer a number of advantages over their ionic counterparts, the most important of these being

the chemoselectivity of radicals and the mild and neutral conditions under which these reactions occur.

1.2. FREE RADICAL REACTIONS

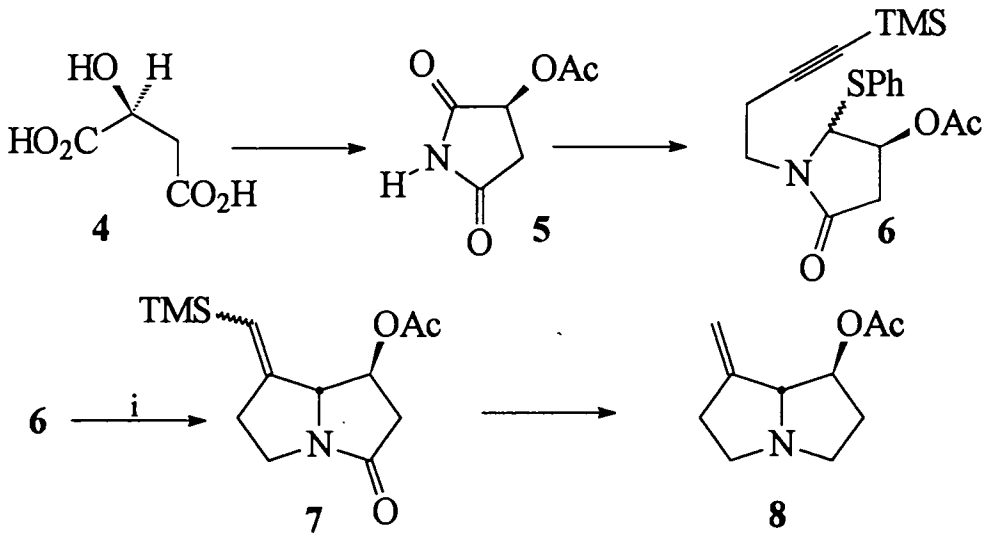
As already mentioned, in the last two decades, free radical addition reactions have gained popularity and their use in the construction of complex organic molecules has been evaluated by a number of research groups. The elegance and efficiency of free radical methodology may be best exemplified by Stork's[10] brilliant prostoglandin synthesis in six steps from the readily available iodoacetal **1**, where the key step is the radical cyclization. The induction of the cyanide group by *tert*-butylisocyanide, through the radical cyclization helps to introduce the side chain (Scheme 1).



i) Bu_3SnH, AIBN, *t*-BuNC

Scheme 1

Another application of radical cyclization, developed by Hart,[11] is in the synthesis of pyrrolidine alkaloids. The synthesis of (-)-dehydrohastanecine starts with malic acid, which is converted to the radical precursor **6**. The radical cyclization affords the product **7** and the latter is converted to the alkaloid **8** in subsequent steps (Scheme 2).



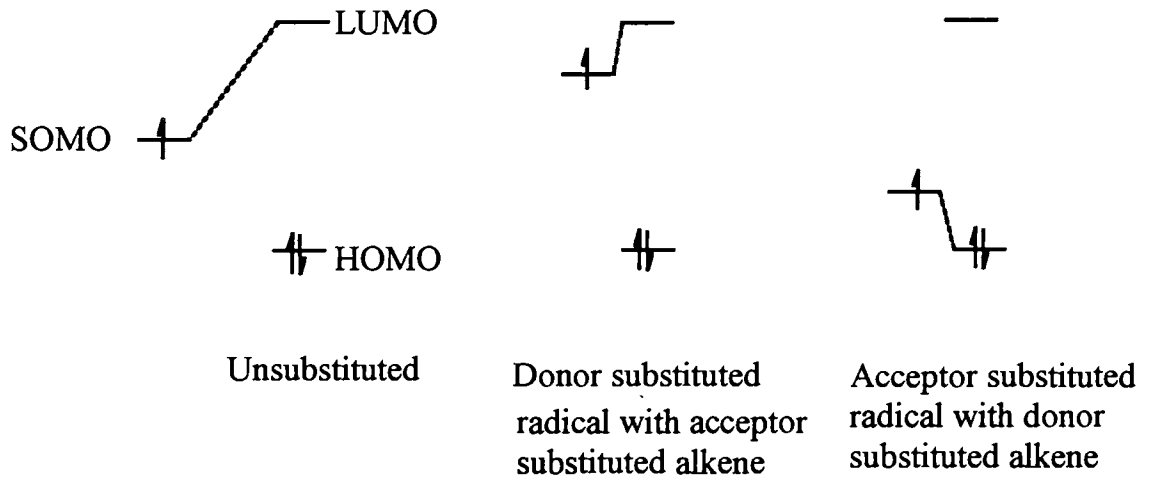
i) Bu_3SnH, 71%

Scheme 2

For the above *5-exo-dig* cyclization, the presence of a bulky trimethylsilyl group at the terminal position of alkyne **6** is important. A less bulky substituent leads to considerable amount of the 6-membered side product.

Free radical reactions, written in the simplest way, imply no separation of charge. Despite their overall electrical neutrality, carbon centered radicals show pronounced electrophilic or nucleophilic character, depending on the substituents present. This dependence is then reflected in the rates of reaction with non-radical species, for example, in their addition to substituted alkenes. Alkyl and alkoxy groups are electron releasing in character; and hence radicals containing these groups react rapidly with alkenes having electron-withdrawing groups (EWG). Electron attracting

radicals like those derived from malonate ester react preferentially with double bonds having electron-releasing substituents. These reactivity trends are in line with Frontier Molecular Orbital interpretation.[12]



Frontier Orbital interactions between different combinations of radicals and alkenes

Figure 1

The singly occupied molecular orbital (SOMO) of the radicals containing electron donating substituents interact very strongly with the low lying LUMO (Lowest Unoccupied Molecular Orbital) of the alkenes having EWG. The radical site having electron accepting substituents lowers the SOMO sufficiently for it to interact strongly with the high lying HOMO (Highest Occupied Molecular Orbital) of the alkenes having electron donating substituents (Fig.1).

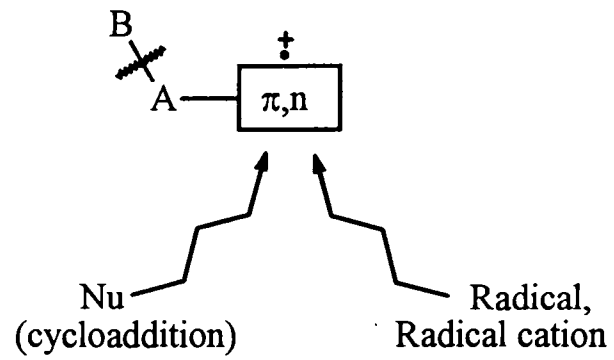
1.3. ELECTRON TRANSFER REACTIONS

Many free radical reactions are initiated by electron transfer (ET) and proceed via the intermediacy of radical ions. A radical ion is essentially a charged species with an unpaired electron. Addition to or removal of one electron from a neutral organic molecule generates a radical ion. This can be done electrochemically, photochemically or chemically. In the last decade many reviews and reports have appeared on this topic covering a broad range of chemistry.[13-15] Surprisingly, little attention has been paid to the one electron transfer mediated C-C bond forming reactions involving radical ions. Evidently, these reactions can significantly influence the chemo- and stereoselective processes used in synthesis and their utility in synthetic strategies is just beginning to be exploited.

Addition of one electron to a molecule usually results in an increase in its reactivity because the bond dissociation energies in radical anions are much smaller than those in the corresponding neutral species.[16] Similarly, many radical cation processes were found to proceed on a flat activation energy hypersurface allowing fast and selective reactions. In radical ions, the unpaired spin and the charged site can be located on the same atom or spatially separated (distonic species). Carbon centered radical ions are generally reactive, with a short half life and according to some reports they cannot be treated either as the conventional radical or as their ionic counterparts.[17] They are characterized by their own unique chemical behavior.

To study the reactivity patterns of radical cations in depth, Schmittel[18] has classified the electrophoric systems involved in one-electron oxidations

into π, n and σ donors. The atom or group of atoms exhibiting the largest HOMO coefficient defines the electrophore of the substrate to be oxidized. The chemistry of radical cations in solution is mainly determined by their primary reaction, which in turn is influenced by the electrophoric system present in the substrate.



Schematic representation of the most important primary reaction pathways for π and n radical cations [18]

Figure 2

The reaction modes usually observed in $\pi^{+\cdot}$ and $n^{+\cdot}$ are the following (See figure 2, above).

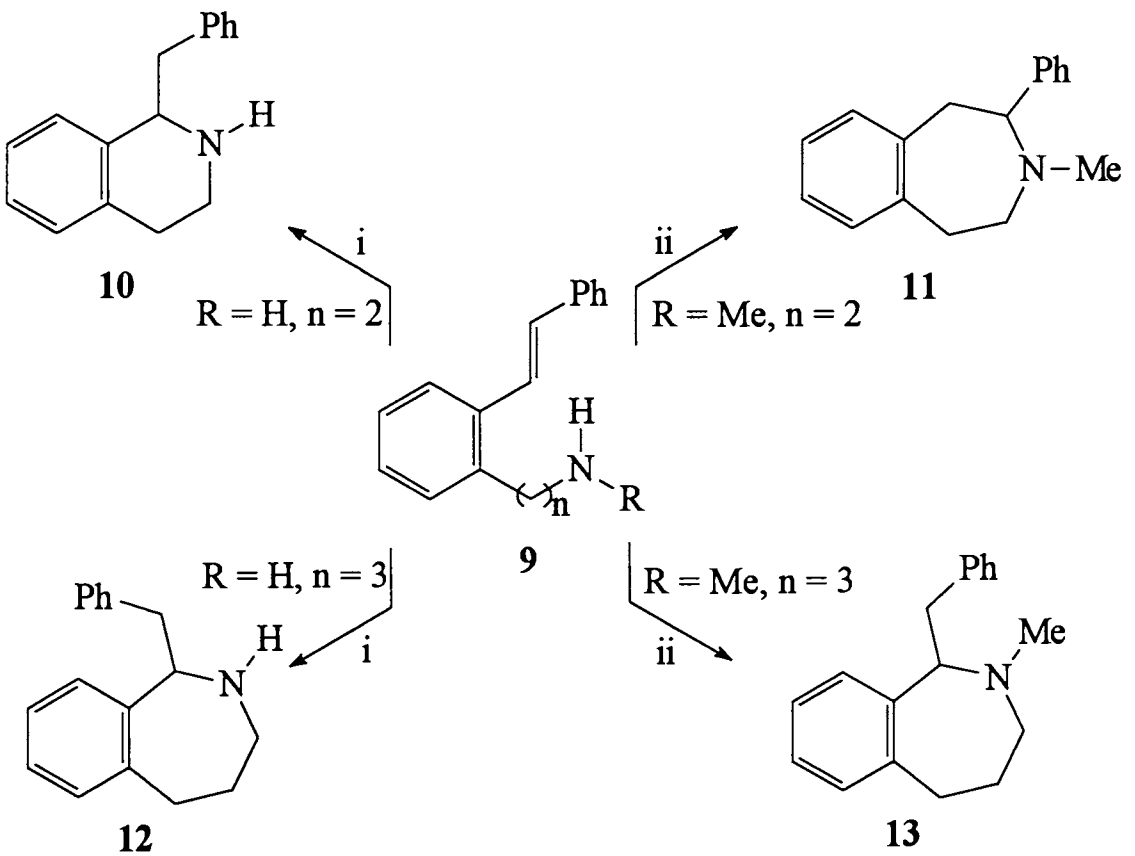
1. A-B bond cleavage at the periphery of the electrophore (A-B = C-H, Ar-H, C-X, C-C, X-Y).
2. Reactions initiated by attack of nucleophiles (including rearrangement and cycloaddition) and
3. Radical based processes (ET, dimerization, hydrogen transfer and reaction with radicals).

The secondary reaction and thus the fate of the primary reaction product (primary intermediate) may be controlled by the appropriate choice of the initial one electron transfer oxidation system. Hence, it makes a

significant difference if we carry out the reaction under photochemical or chemical conditions.

As already stated, electron transfer can be accomplished by electrochemical, photochemical or chemical means. Among these, electrochemical and photoinduced electron transfer reactions (PET) have received considerable attention. Some representative examples from these two fields are given below.

Both tertiary as well as secondary amines add to stilbenes *via* a photoinduced electron transfer (Scheme 3).[19]

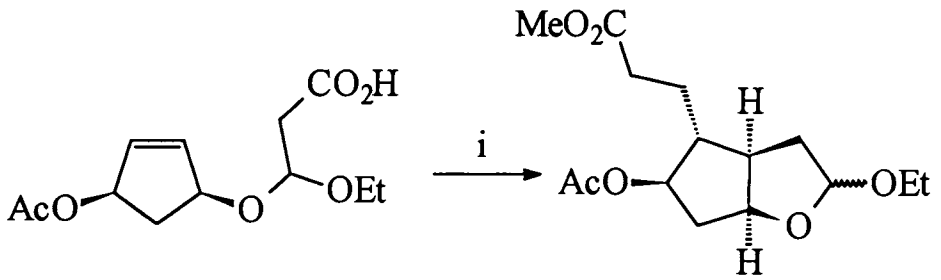


i) hv, DCB

ii) hv

Scheme 3

In the area of electrochemical electron transfer, Kolbe electrolysis is the oldest known reaction and it involves the decarboxylation of a carboxylate salt and dimerization of the radical thus produced. Variations of this reaction have been employed in the synthesis of several natural products. Schäfer and Becking[20] have applied the Kolbe protocol for the synthesis of **15,** a viable precursor of $PGF_{2\alpha}$ (Scheme 4).



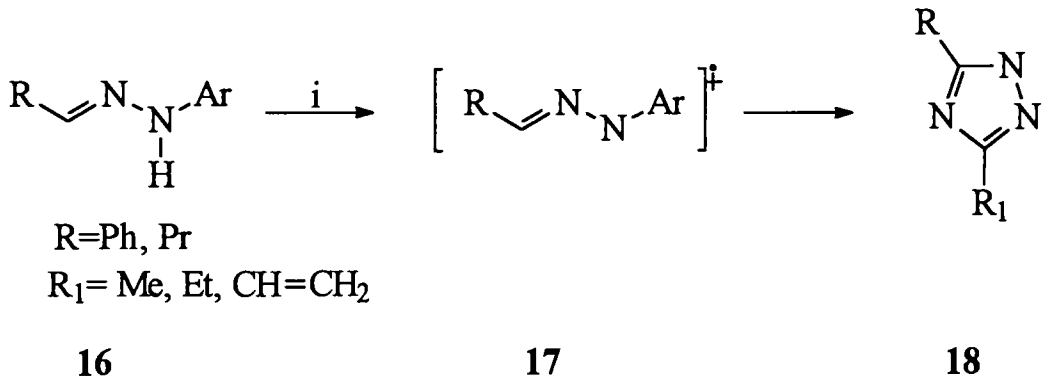
14 **15**

i) 4 eq $MeO_2C(CH_2)_2CO_2H$, 5% neutralization, MeOH, 40 - 45 °C, 1.5 eq current

Scheme 4

In contrast to photochemical (PET) and electrochemical electron transfer, chemical electron transfer (CET) reactions have come to the fore only recently.

Both the scope and synthetic utility of chemically generated radical cation mediated reactions were enhanced by the observation that the shelf stable reagents, triarylaminium salts in catalytic amounts, promote such reactions under extremely mild conditions. A representative example is given in scheme 5, where Shine *et al.* have added arylhydrazones to nitriles to produce 1,2,4-triazoles.[21]



R=Ph, Pr

R_1= Me, Et, CH=CH_2

16 **17** **18**

i) $Ar_3N^{+\cdot}$ $SbCl_6^-$, DCM, 0 °C, R_1CN

Scheme 5

Transition metal salts promoted generation of carbon centered radical by an electron transfer process can be achieved efficiently and this process has found numerous applications in the synthesis of a wide variety of organic molecules. It is often easy to predict the nature of the electron transfer mechanism (one or two electron transfer), by knowing the initial and final degree of oxidation level of the electron transfer agent. Generally high valent metals with stable adjacent oxidation states such as Ti, V, Mn, Fe, Co and Cu are used for single electron transfer.

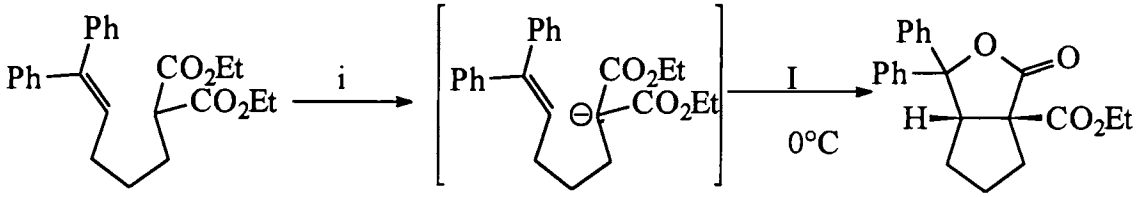
By choosing a suitable oxidizing system, selective electron removal can be accomplished in a multifunctional molecule. Tertiary amines are the most easily oxidized neutral organic substances. These can undergo electron removal and α-CH deprotonation to produce α-amino radicals. Other electrofugal groups (R_3M where M = Si, Sn or Ge) at the α-position may also undergo heterolytic fragmentation. Silane radical cation fragmentations are exceptionally fast. Enolates are moderately easy to oxidize. Enolisable dicarbonyl compounds, enol ethers and substituted cyclopropanes also can be oxidized. Olefins and arenes cannot be oxidized unless activated by electrofugal substituents.[22]

1.4. METAL ION OXIDATION

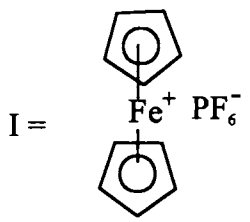
Among the metal salts, Manganese (III) acetate [$Mn(OAc)_3.2H_2O$] and Cerium (IV) Ammonium Nitrate [$Ce(NH_4)_2(NO_3)_6$] have emerged as powerful one electron oxidants. The use of peroxy disulfate ion in the presence of Ag^{2+} is particularly effective for substrates having high oxidation potential. Vanadium (V), Lead (IV), Thallium (III), Iron (III) and Iridium (VI) salts have also been used. Oxidative electron transfer can also be achieved by hypervalent iodine reagents such as $PhI(OAc)_2$.

A few examples of single electron oxidation mediated by some of the metal ions other than Ce (IV) are given below. Examples of Ce(IV) mediated reactions will be treated separately in section 1.5.

Malonate anions undergo single electron oxidation with the ferrocenium ion followed by radical cyclization (Scheme 6).[23]



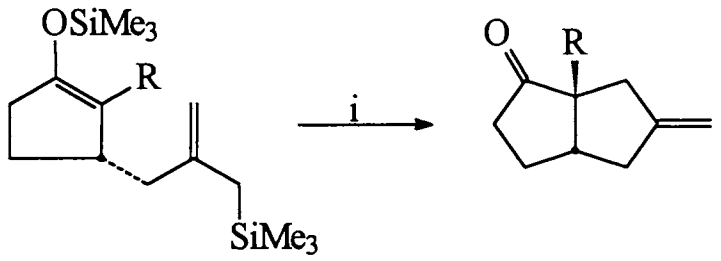
19 **20**



i) LDA or $(Me_3Si)_2NLi$, -78° C, DMF

Scheme 6

A new Vanadium (V) ester has been reported[24] to be useful in the oxidative activation of silyl enol ethers and methylene cyclopentaannulation (Scheme 7).

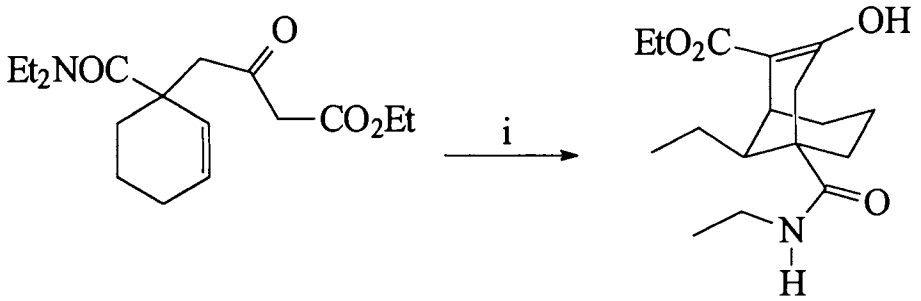


21 **22**

i) $(CF_3CH_2O)VOCl_2$, -78 °C, < 30 min., 82 %

Scheme 7

White[25] has carried out the synthesis of bicyclo[3.3.1]nonane system by an oxidative cyclization mediated by manganese (III) acetate (Scheme 8).

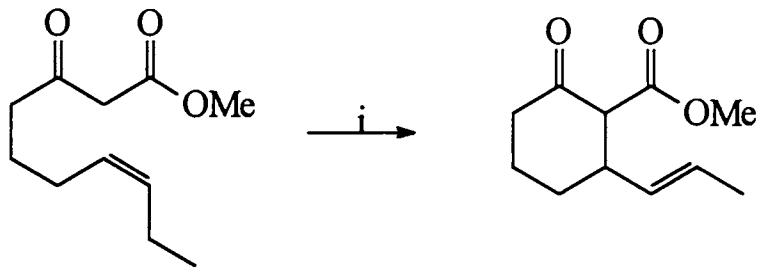


23 **24**

i) $Mn(OAc)_3.3H_2O$, $Cu(OAc)_2.2H_2O$, HOAc, 33 %

Scheme 8

Oxidative cyclization of **25** by $Mn(OAc)_3/Cu(OAc)_2$ has been shown to produce 2,3-disubstituted cyclohexanone **26** with both regio- and stereoselectivity (Scheme 9).[26]

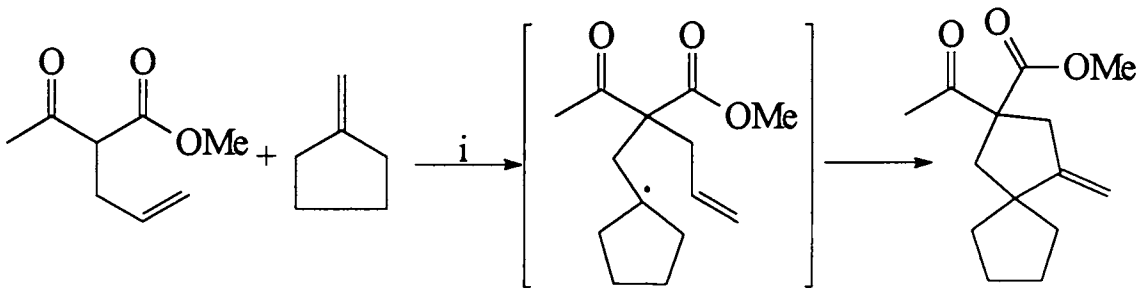


25 **26**

i) $Mn(OAc)_3$, $Cu(OAc)_2$, 50 °C, 1h, 71%

Scheme 9

An elegant spiro cyclization designed by Snider[27] involves the $Mn(OAc)_3$ mediated reaction of allyl acetoacetate with exocyclic alkenes as exemplified by the synthesis of **30** (Scheme 10).



27 **28** **29** **30**

i) $Mn(OAc)_3$, $Cu(OAc)_2$, AcOH, 25 °C, 16 h, 75 %

Scheme 10

It is evident from the literature that Manganese (III) acetate occupies an important position among the one-electron oxidants due to its mediation in a number of novel approaches to the synthesis of different classes of organic compounds. Despite its growing popularity, especially in natural product synthesis, the formation of side products often limits its use.

Cerium (IV) ammonium nitrate (CAN) is slowly emerging as a reagent of choice. The advantages of CAN over Manganese (III) acetate are the enhanced reactivity, low cost, non toxicity and its solubility in organic solvents like methanol, ethanol, isopropanol and acetonitrile. These advantages combined with the experimental simplicity and ease of handling makes CAN an attractive one-electron oxidant.

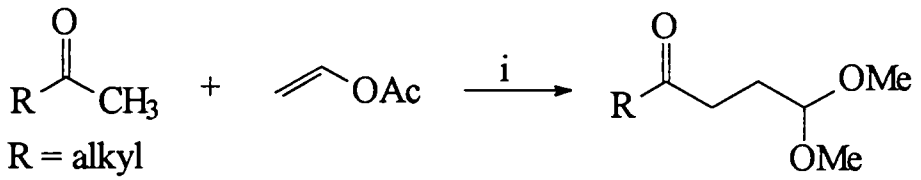
1.5. REACTIONS MEDIATED BY CAN

The pioneering work of Heiba and Dessau[28] has shown that radicals generated by Ce(IV) can be added to alkenes. Subsequent investigations have shown that among the various Ce(IV) reagents CAN is the acceptable reagent in terms of its stability and solubility in organic solvents. It can bring about many useful transformations other than the usual functional group transformations attributed to it.[15, 49] As it is expected of all one-electron oxidants, the chemistry of CAN oxidation is predominantly that of radicals and radical cations. These intermediates can undergo a variety of reactions namely ligand transfer fragmentation, hydrogen atom transfer, C-H bond cleavage, nucleophilic addition etc. A brief review of the CAN mediated reactions is given in the following sections.

A complete description of CAN mediated reactions is beyond the scope of this review; however, some important and useful highlights of its reactivity with various systems are outlined. For the sake of simplicity, the reactions have been classified as carbon-carbon and carbon-heteroatom bond forming reactions and miscellaneous reactions.

1.5.1. Carbon-carbon bond forming reactions

CAN mediated addition of 1,3-dicarbonyl compounds has been extensively studied by Baciocchi.[29] He has also added alkyl radicals to vinyl acetate **32** to afford the acetal **33** in moderate yields (Scheme 11).

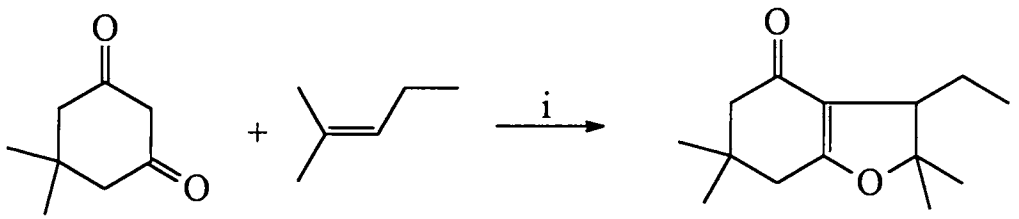


31 **32** **33**

i) CAN, MeOH

Scheme 11

Oxidation of 1,3-dicarbonyl compounds by CAN gives rise to the corresponding methine radicals. These intermediates can add to alkenes to forge carbon-carbon bonds. Extensive work has been carried out in our laboratory in this area.[30, 31] It is noteworthy that active methylene compounds add to cyclic and acyclic alkenes including unactivated ones by the mediation of CAN to afford dihydrofurans in good yields. (Scheme 12).[32]



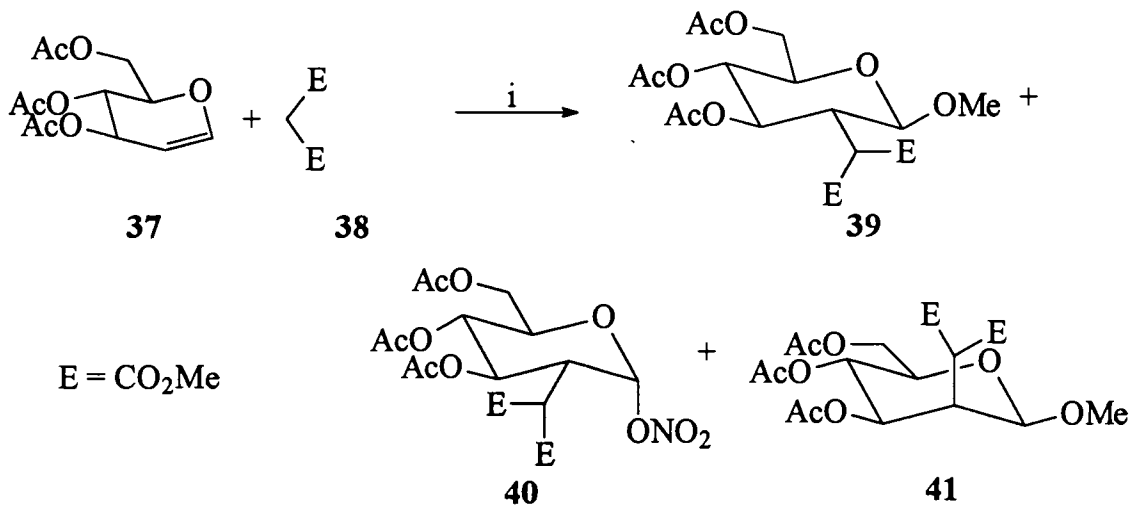
34 **35** **36**

i) CAN, MeOH, 5 min., 5 °C, 60 %

Scheme 12

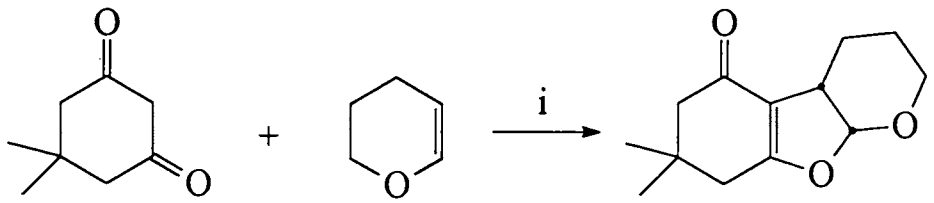
Malonate radical has been shown to add to styrenes to afford a keto derivative and a lactone as the major products (details are given in chapter 2, scheme 9 of section 2.1.4.).[33]

Linker[34] has added radicals generated from dimethyl malonate by CAN to tri-O-acetyl-D-glucal **37** as shown in scheme 13. It is noteworthy that no rearranged product (Ferrier Rearrangement) was formed under these reaction conditions.



Scheme 13

Similarly, CAN mediated addition of 1,3-diketones and 1,3-ketoesters to cyclic enol ethers leading to fused acetals in good yields has been reported (Scheme 14).[35]

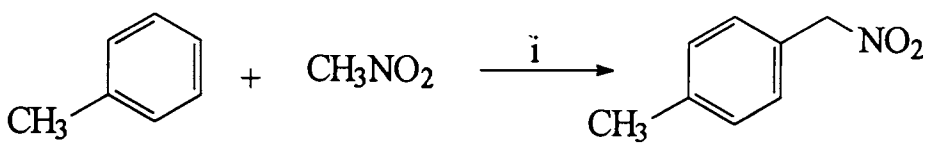


42 **43** **44**

i) CAN, MeCN, 0 °C, 2h, 68 %

Scheme 14

Nitromethylene radical generated by CAN adds to aromatic rings as shown in scheme 15.[36]

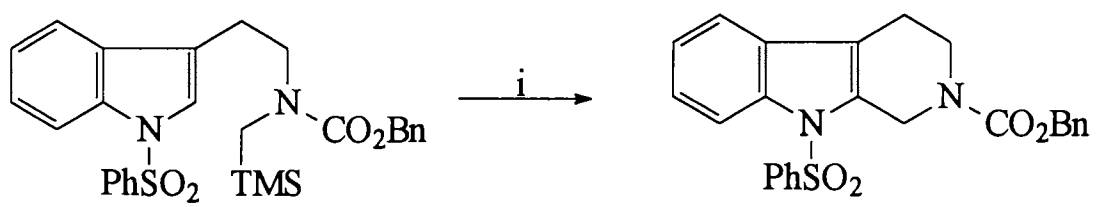


45 **46** **47**

i) CAN, HOAc, N_2 atm., reflux, 24 h, 100 %

Scheme 15

Mariano[37] has demonstrated the feasibility of an oxidative Pictet-Spengler cyclization process mediated by CAN. This involves α-desilylation of a tertiary aminium radical cation to form an N-alkyl iminium cation (Scheme 16).

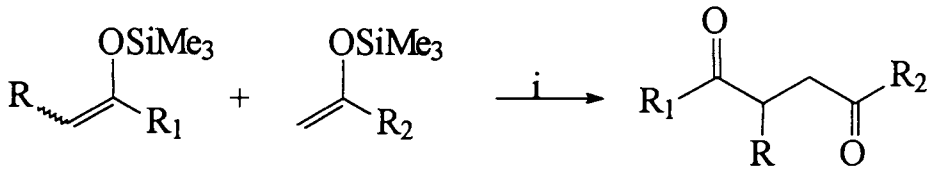


48 **49**

i) CAN, MeCN, r. t., 6 h, 86 %

Scheme 16

Cross coupling reactions of silyl enol ethers resulting in 1,4-dicarbonyl compounds has been reported by Baciocchi (Scheme 17).[38]

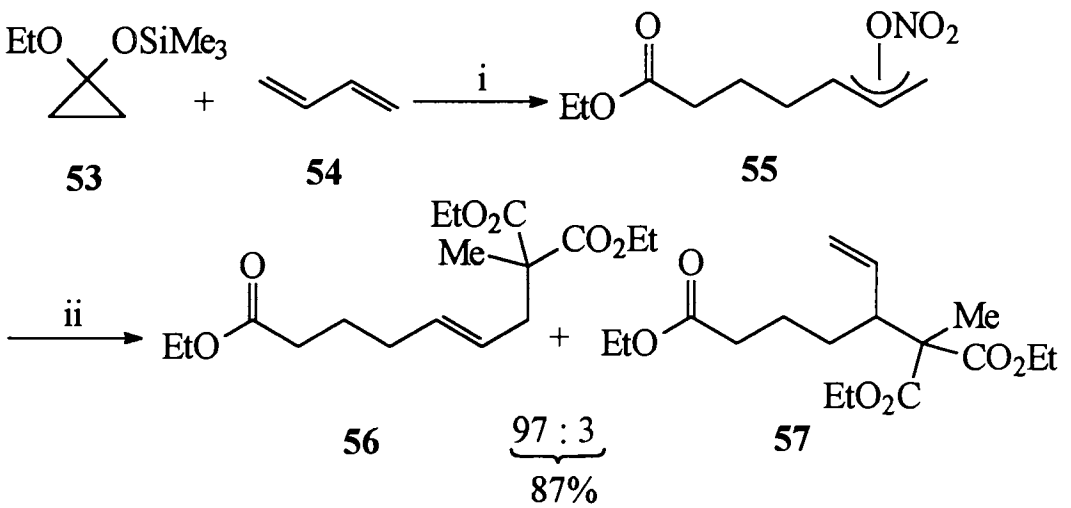


50 **51** **52**

i) CAN, MeOH

Scheme 17

When a mixture of trimethylsilyloxycyclopropane **53** and 1,3-butadiene is treated with CAN in acetonitrile at room temperature, a rapid reaction occurs to give a mixture of products, in nearly equimolar amounts (Scheme 18).[39] The crude product can be further transformed to **56** and **57** by reaction with methyl malonate in the presence of Pd(0).



53 **54** **55**

56 97 : 3 **57**

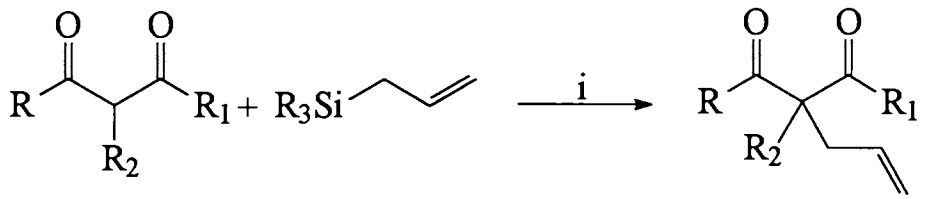
87%

i) **CAN, $CaCO_3$, MeCN, r. t.**

ii) **$MeC^-(CO_2Et)_2$, $Pd(PPh_3)_4$**

Scheme 18

Allylation of 1,3-dicarbonyl compounds with allylsilanes in the presence of CAN has also been reported (Scheme 19).[40]



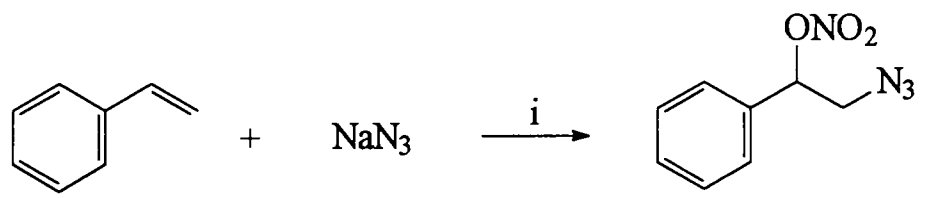
58 **59** **60**

i) CAN, MeOH, r. t., 25 °C

Scheme 19

1.5.2. Carbon-Hetero atom bond forming reactions

Anions like thiocyanate, azide or bromide undergo oxidation by CAN to the corresponding radical, which can be trapped by alkenes. One of the initial reports in this area is the azidonitration of styrenes with sodium azide in the presence of CAN as observed by Trahanovsky[41] (Scheme 20).

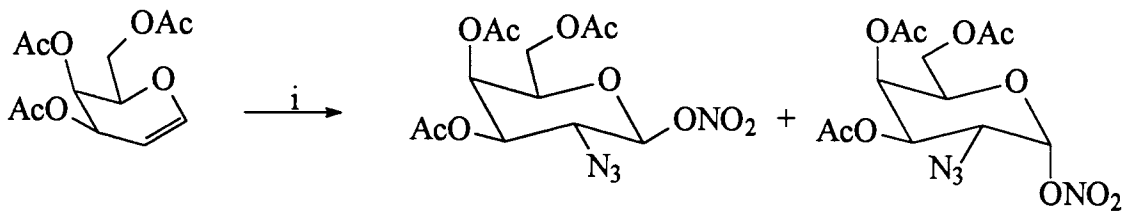


61 **62**

i) CAN, MeCN, r. t., 73 %

Scheme 20

Reaction of 3,4,6-tri-o-acetyl-D-galactal **63** with excess of CAN and sodium azide in acetonitrile afforded two major products **64** and **65** in 53 % and 22 % yields, respectively (Scheme 21).[42]

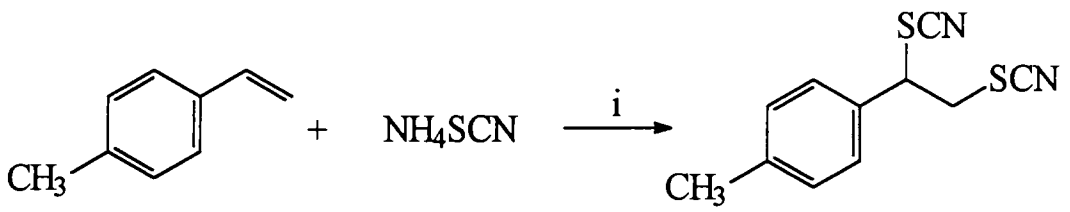


63 **64** **65**

i) CAN, NaN_3, MeCN / H_2O

Scheme 21

Work carried out in our laboratory has shown that a CAN mediated facile dithiocyanation of arylalkenes occurs.[43] A representative example is given in scheme 22.

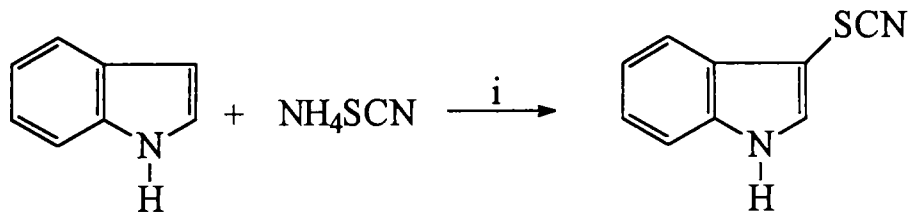


66 **67**

i) CAN, MeCN, r. t., 15 min., 75 %

Scheme 22

Similarly, thiocyanation of indole **68** occurred quantitatively to afford 3-thiocyanatoindole **69** (Scheme 23).[44]



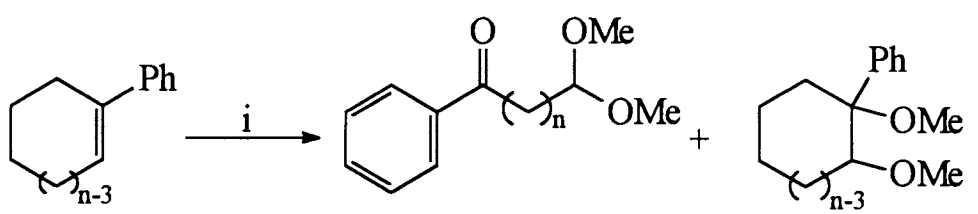
68 **69**

i) CAN, MeOH, r. t., 15 min., 100%

Scheme 23

1.5.3. Miscellaneous Reactions

In addition to the reactions described above, CAN has also been used effectively in a large number of other oxidation reactions. A very interesting CAN mediated oxidative fragmentation of phenyl cycloalkenes **70** in methanol leading to the 1,n-dicarbonyl compounds **71** along with the bis-methoxy compound **72** was observed in our laboratory (Scheme 24).[45]



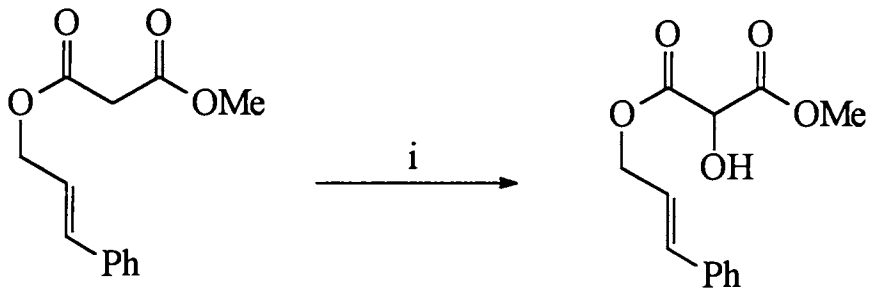
70 **71** **72**

i) CAN, MeOH, 0 °C-r. t.

Scheme 24

CAN mediated oxygenation of alkyl malonates gave rise to tartronic acid derivatives.[46] Presumably, oxygen present in the reaction mixture adds to the

1,3-dicarbonyl alkyl radical to form a peroxy radical which then undergoes further transformation to afford the tartronate **74** (Scheme 25).

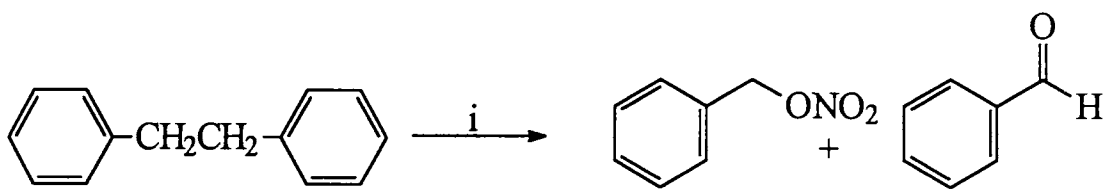


73 **74**

i) CAN, O_2, MeOH, 0 °C - r. t., 6 h, 62 %

Scheme 25

Baciocchi[47] has observed the fragmentation of bibenzyl **75** *via* the intermediacy of a radical cation (Scheme 26).

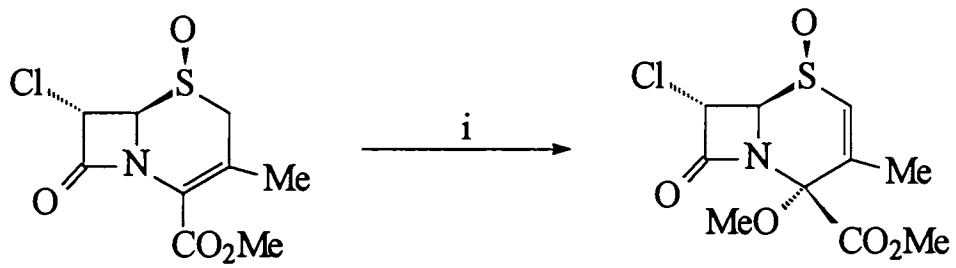


75 **76** (40%) **77** (60%)

i) CAN, MeCN - H_2O, HNO_3, Reflux

Scheme 26

CAN mediated methoxylation of cephem sulphoxides has been reported (Scheme 27).[48]



78 79

i) CAN, MeOH, 5h, r. t.

Scheme 27

1.6. CONCLUSIONS

It is evident from the foregoing discussion that CAN is useful in accomplishing a wide variety of synthetic transformations.[49] But its usefulness has not been tapped sufficiently in some areas such as intramolecular cyclizations (CAN mediated intramolecular cyclizations are reviewed in chapter 3, section 3.1.1.2.) and radical cation chemistry. Hence, it was of interest to carry out some indepth investigations in these areas.

1.7. STATEMENT OF THE PROBLEM

The chemistry of one electron oxidants, especially CAN is of considerable topical interest. It is clear from the literature survey that many facets of this reagent has remained uninvestigated. Of special interests to us have been

i) the chemistry of radical cations generated by CAN and

ii) the potential use of CAN as a reagent to induce intramolecular cyclizations.

With the focal themes identified above, and on the basis of the earlier investigations in our laboratory, it was decided to carry out an in-depth study of the radical cation mediated dimerization of alkoxystyrenes.

The CAN mediated intramolecular cyclization reactions is virtually an unexplored area with only a few isolated examples known so far. Therefore, as the second phase of our investigations, it was decided to probe the ability of CAN to effect intramolecular cyclization of acetoacetanilides.

The final part of the work is concerned with attempts at the CAN mediated intramolecular cyclization of selected 1,n-diene systems.

During the course of the above investigations, many fascinating results were obtained and the details are given in the succeeding chapters.

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CHAPTER 2

CERIUM (IV) AMMONIUM NITRATE INDUCED DIMERIZATION OF ALKOXYSTYRENES

Part I of this chapter deals with the reactions of alkoxystyrenes with CAN in methanol and ethanol. Part II concerns itself with the same reactions carried out in acetonitrile. The results of an investigation on the effect of substitution on the styrenic double bond on the reaction of alkoxystyrenes with CAN are presented in Part III.

PART I

CERIUM (IV) AMMONIUM NITRATE INDUCED DIMERIZATION OF ALKOXYSTYRENES IN ALCOHOL

2.1. INTRODUCTION

Our current knowledge of the chemistry of organic compounds is largely based on our understanding of the reactive intermediates, which are involved in the transformation of starting materials to products. The reactive intermediate from a given compound may vary with the operating mechanism and the conditions under which the reaction is carried out.

Electron transfer is one of the events in chemistry for which mechanistic details have been unraveled only recently. Single electron transfer (SET) to or from electronically neutral molecules results in the formation of radical ions: radical anions or radical cations respectively. Chemically, single electron transfer can be achieved through metal ions such as Ce (IV) and Mn (III).

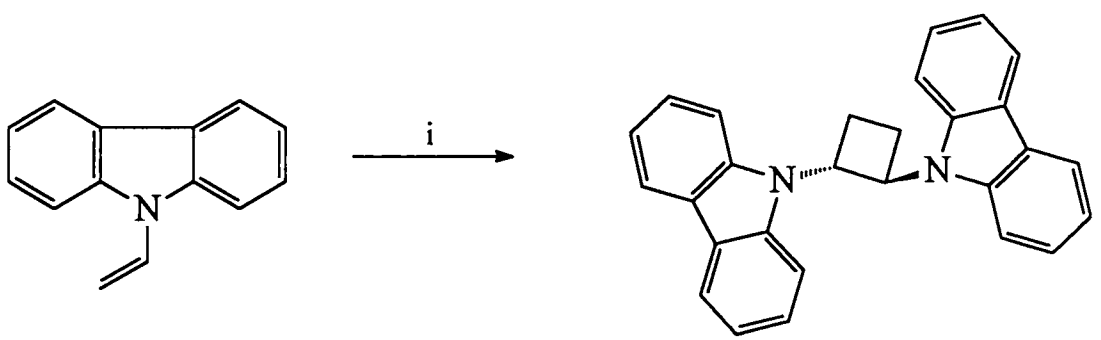
2.1.1. CAN mediated electron transfer reactions

Oxidative electron transfer reactions mediated by Cerium (IV) ammonium nitrate (CAN) have come to the fore recently due to the

advantages of the latter over other metal oxidants (Chapter 1 Section 1.4). A brief overview of the single electron transfer (SET) mediated dimerizations achieved by chemical and photochemical methods, followed by CAN mediated C-C bond forming reactions involving radical cations is given in the following sections.

2.1.2. SET mediated dimerizations achieved by other means

The very first example of a reaction involving cation radicals is the dimerization of N-vinylcarbazole (NVC) **1** catalyzed by ferric, ceric or cupric salts in methanol.[1] This reaction was observed in 1969 and later PET initiated version of the reaction was developed (Scheme 1).[2]

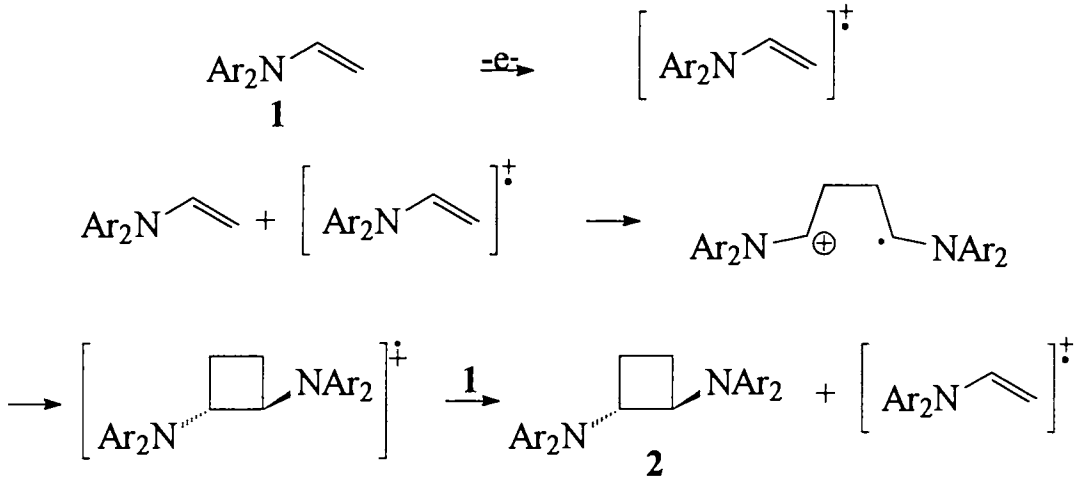


1 **2**

i) Fe^{3+} or Ce^{4+} or Cu^{2+}/ MeOH or hν, Sensitizer

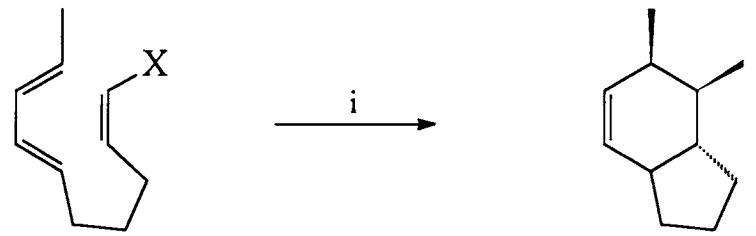
Scheme 1

Finally, the radical cation chain nature of the reaction was established as a result of careful studies by Crellin *et al.* (Scheme 2).[3]



Scheme 2

Triarylaminium salts are known to be powerful one electron oxidants. The construction of a hydrindane ring system with excellent *endo* selectivity using aminium salt is illustrative (Scheme 3).[4]



X=4-MeOPh
X=SPh

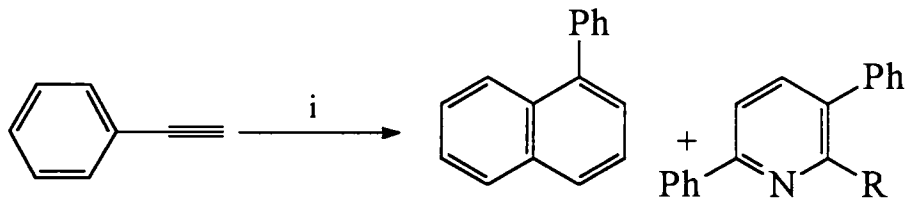
78-100% { 83%
Stereoselectivity { 38%

3 **4**

i) $Ar_3N^{+}SbCl_6^{-}$, -78 °C

Scheme 3

Farid and Mattes[4] have reported the dimerization of phenyl acetylene under photochemical conditions (Scheme 4).



R= Me, R=Et, R=Pr, R=Ph

5 **6** **7**

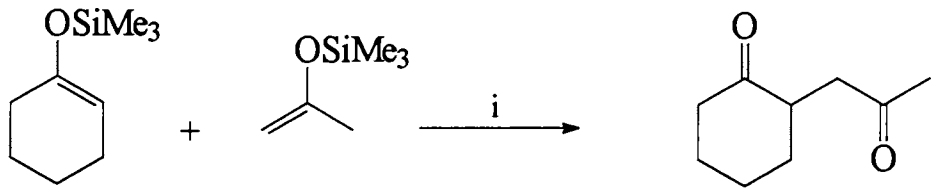
i) hv, Sensitizer, RCN

Scheme 4

2.1.3. CAN mediated C-C bond formation *via* radical cations

Among the many C-C bond forming reactions mediated by CAN, only a few are known to involve radical cations; representative examples are given below.

Trimethylsilylenol ethers are much more easily oxidised than the parent ketones. Baciocchi[5] has observed that CAN induces a very efficient cross coupling between 1,2-disubstituted and 1-substituted trimethylsilylenol ethers to give 1,4-dicarbonyl compounds in good yields (Scheme 5).

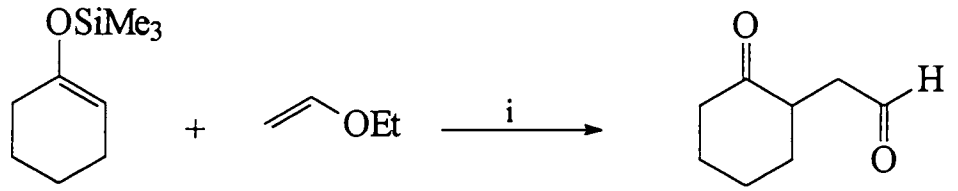


8 **9** **10**

i) CAN / MeCN, $NaHCO_3$, 80%

Scheme 5

As expected, **8** on reaction with ethyl vinyl ether, afforded the corresponding 4-oxaldehyde in good yield (Scheme 6).[6]

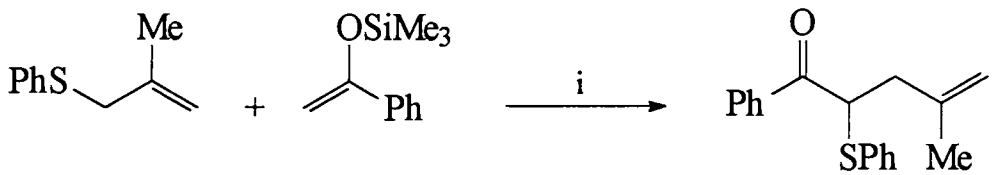


8 **11** **12**

i) CAN / MeOH, 80%

Scheme 6

Similarly, allyl sulfides on reaction with silyl enol ethers in presence of CAN, afforded 1,4-dicarbonyl compounds by a process presumably mediated by radical cations (Scheme 7).[7]



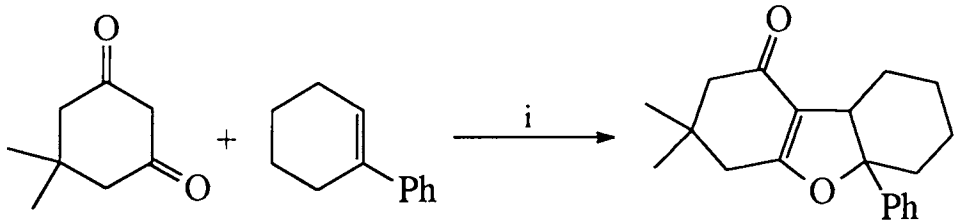
13 **14** **15**

i) CAN / MeCN, Molecular Sieves, 4Å

Scheme 7

2.1.4. Investigations in our own laboratory

Extensive work has been carried out in our own laboratory on the oxidative addition of 1,3-dicarbonyl compounds to alkenes. A representative example is given in scheme 8.[8a]

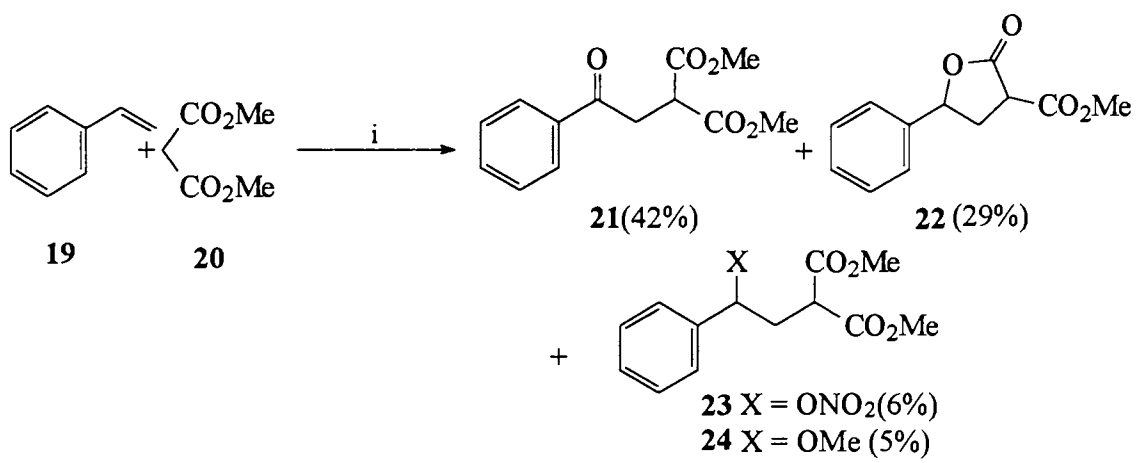


16 **17** **18**

i) CAN / MeOH, 0 °C, 15 min., 98 %

Scheme 8

During these investigations we encountered a mechanistically interesting reaction between dimethyl malonate and styrene in presence of CAN (Scheme 9).[8b]



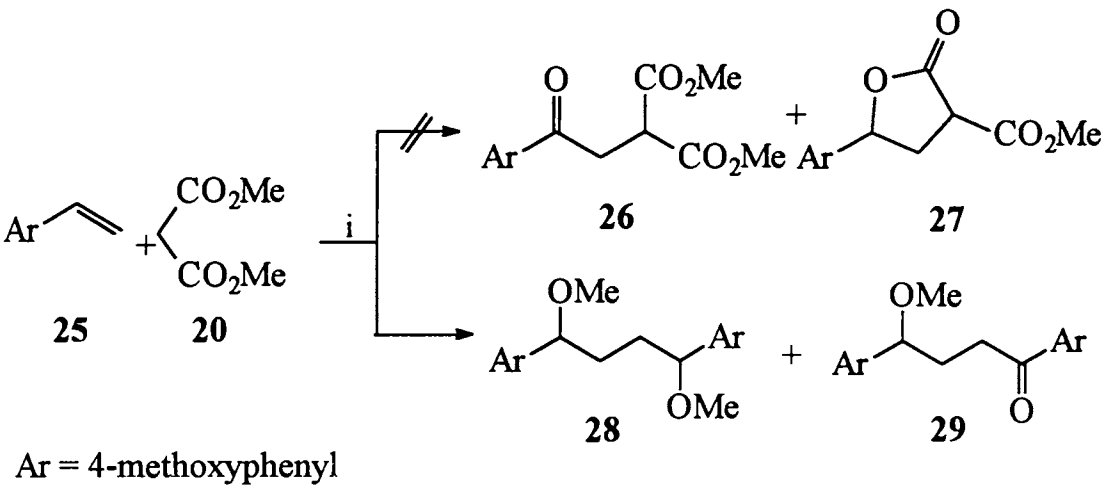
19 **20** **21**(42%) **22** (29%)

23 X = ONO_2(6%)
24 X = OMe (5%)

i) CAN / MeOH, 20 °C

Scheme 9

The reaction was found to occur with various substituted styrenes. However, 4-methoxystyrene **25**, when exposed to CAN and malonate did not afford the expected products. Instead, products arising from the dimerization of **25** and further transformation of the dimer were obtained (Scheme 10).[9] There was no evidence for the participation of malonate in this reaction.



Ar = 4-methoxyphenyl

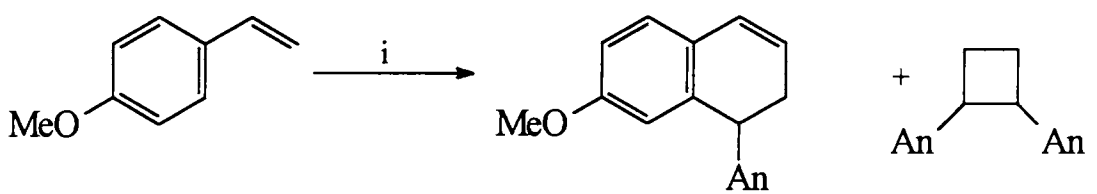
i) CAN / MeOH, 0 °C, 15 min.

Scheme 10

Intrigued by the ease and novelty of this process, we have carried out a detailed investigation of this reaction.

2.1.5. Dimerization of methoxystyrenes

It is noteworthy that 4-methoxystyrene has been known to undergo dimerization under photoinduced electron transfer (PET) conditions (Scheme 11).[10]



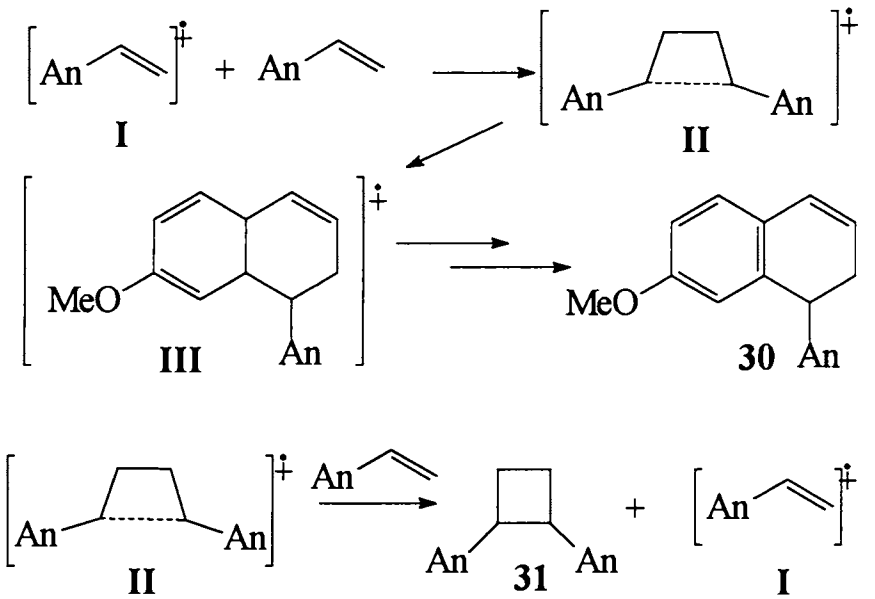
An = 4-methoxyphenyl

25 **30** **31**

i) hv, DCB

Scheme 11

The mechanism of this reaction was established by Bauld *et al.* (Scheme 12).[11] Mechanistically, it is the cycloaddition of the 4-methoxystyrene radical cation **I** to neutral 4-methoxystyrene to form a 1,4-radical cation or a long bond cyclobutane radical cation **II**. This intermediate can either get converted to a hexatriene radical cation **III** (which can subsequently give rise to the dihydronaphthalene **30**) or can form the cyclobutane derivative **31**.



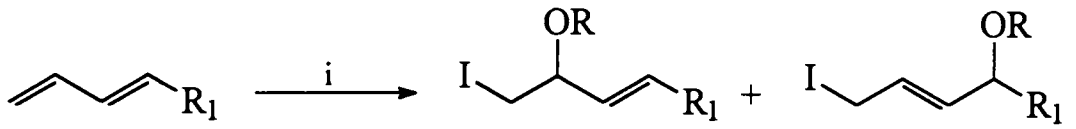
An = 4-methoxyphenyl

Scheme 12

2.1.6. Effect of solvent on CAN mediated reactions

Solvent plays the role of a nucleophile in the CAN mediated dimerization of methoxystyrenes. There are a number of reports on CAN mediated reactions where the solvent determines the course of the reaction.

CAN mediated alkoxy iodination is one of them, where alcohol acts as a nucleophile (Scheme 13).[12]

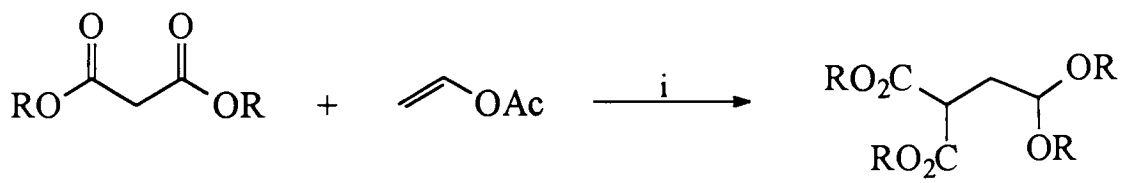


32 **33** **34**

i) CAN / I_2, ROH

Scheme 13

Another example is the acetal formation in presence of CAN (Scheme 14).[13]



35 **36** **37**

i) CAN / ROH, 40 °C, 1h, 75%

Scheme 14

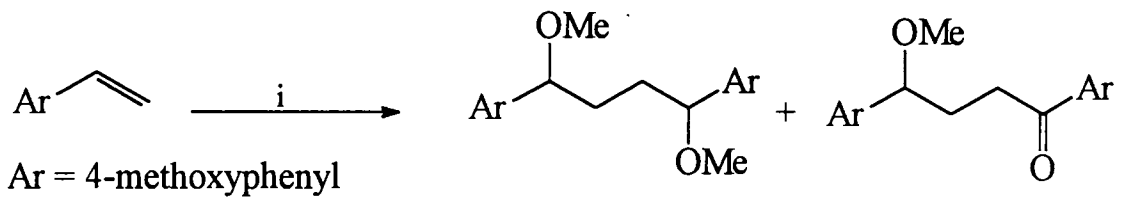
2.1.7. Definition of the problem

The dimerization of 4-methoxystyrene appeared interesting both from the mechanistic and synthetic standpoints. In order to assess the synthetic potential of the reaction, we have carried out a systematic study involving some alkoxystyrenes (Part I). The study was also carried out in different solvents as the solvent plays a major role in determining the reaction course. The solvents in which the reactions were carried out are methanol, ethanol and acetonitrile (Part II). The effect of substitution on the styrenic double bond was also studied (Part III).

2.2. RESULTS AND DISCUSSION

2.2.1. Reactions in Methanol

Against the literature background given in the previous sections, we initiated our investigations on the dimerization reaction of methoxystyrenes induced by CAN. The starting point of our investigations was the reaction of 4-methoxystyrene with CAN in methanol resulting in two products **28** and **29** (Scheme 15. See also scheme 10, page 35). The reaction was carried out under different conditions and the results are summarized in table 1



Ar = 4-methoxyphenyl

25 **28** **29**

i) CAN / MeOH, 0 °C, 30 min.

Scheme 15

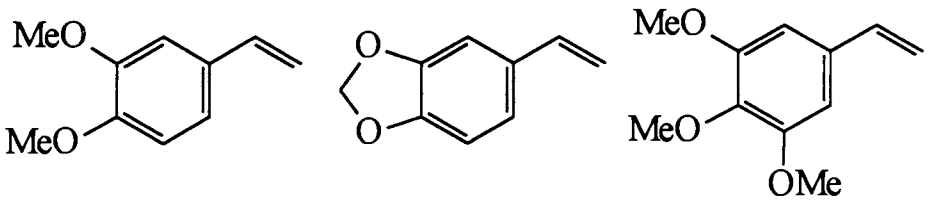
Entry	Reaction Conditions	28	29
1	CAN / MeOH, air, 0 °C	10 %	53 %
2	CAN / MeOH, oxygen, 0 °C	16 %	62 %
3	CAN / MeOH, argon, 0 °C	60 %	8 %

Table 1

Presumably the products **28** and **29** arise *via* dimerization of the methoxystyrene radical cation followed by the incorporation of methanol. The keto group in **29** can be considered to originate from the oxygen in the air as evinced from the predominance of this product when the experiment was carried out in an atmosphere of O_2. Under deoxygenated conditions, **28** was found to be the predominant product (Table 1).

The two products were characterized by the usual analytical and spectroscopic methods. The two aliphatic methoxy groups of **28** appeared as a sharp singlet at δ 3.03 (for 6 protons), and the aryl methoxy groups appeared as a single signal at δ 3.69 in the proton NMR spectrum. The methoxy carbons resonated at δ 55.47 and 56.59 in the ^{13}C NMR spectrum. The IR spectrum of the keto methoxybutane **29** displayed a strong carbonyl band at 1668 cm^{-1}. The carbonyl carbon appeared at δ 198.83 in the ^{13}C NMR spectrum and the aliphatic methoxy group appeared as a sharp singlet at δ 3.19 (3H) in the ^{1}H NMR of **29**. Both the structures were further confirmed by satisfactory elemental analysis.

To probe the generality of the reaction, the following styrenes were included in the study (Figure 1).

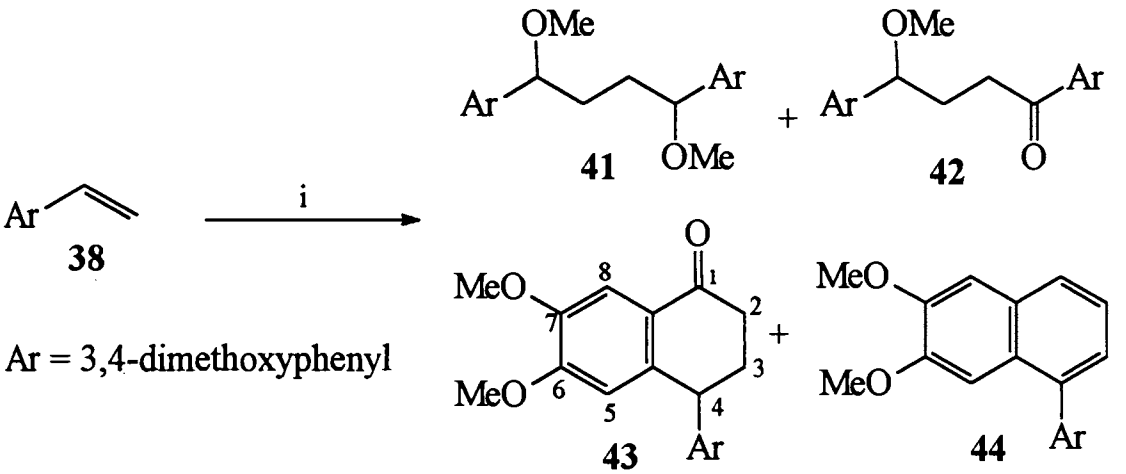


38 **39** **40**

Figure 1

3,4-dimethoxystyrene **38**, when treated with CAN in methanol afforded the products **41**, **42**, **43** and **44**. This reaction too was studied under different conditions. And the results are summarized in table 2. The tetralone derivative **43** was found to predominate when the reaction was carried out under oxygen atmosphere. The dimethoxybutane derivative **41** and the naphthalene derivative **44** were found to be the exclusive products under argon atmosphere. The enhanced reactivity of the dimethoxy benzene ring

predisposes it to electrophilic closure and this may account for the formation of the tetralone and the naphthalene derivative.



i) CAN / MeOH, 0 °C, 30 min.

Scheme 16

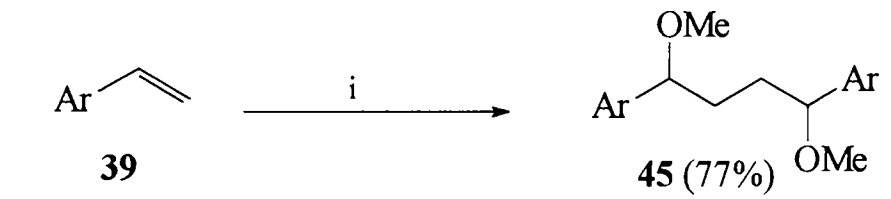
Entry	Reaction Conditions	41	42	43	44
1	CAN / MeOH, air, 0 °C	15 %	12 %	59 %	8 %
2	CAN / MeOH, oxygen, 0 °C	-	-	65 %	10 %
3	CAN / MeOH, argon, 0 °C	36 %	-	-	37 %

Table 2

All the four products were characterized by the usual spectroscopic methods. The proton NMR of the compound **41** showed a multiplet at δ 3.93 for the two methine protons, each geminal to the methoxy groups. The methoxy groups themselves were discernible at δ 3.71 as superimposed singlets accounting for six protons. The methoxy carbon appeared at δ 55.23 in the ^{13}C NMR of **41**. The keto group of **42** was visible as a strong band at 1707 cm^{-1} in the IR spectrum. The proton geminal to the methoxy group was discernible as a multiplet at δ 4.19 and the methoxy protons resonated as a sharp singlet at δ 3.76 in the ^{1}H NMR. The carbonyl carbon was seen at δ 197.06 in the ^{13}C NMR of **42**. The tetralone **43** displayed a sharp band at

1681 cm^{-1} in the IR spectrum. The proton at the benzylic position (i.e. C-4) appeared as a doublet of doublet at δ 4.19 (J = 4.5 Hz and 7 Hz) in the ^1H NMR spectrum. In the ^{13}C NMR, the carbonyl carbon was visible at δ 196.64. The GCMS displayed the M^+ peak at 342 corresponding to the mass of **43**. As expected, the ^1H NMR spectrum of naphthalene derivative **44** showed peaks only in the aromatic region except for the four methoxy groups, which resonated at δ 4.01, 3.96, 3.89 and 3.82 as sharp singlets. The GCMS exhibited the M^+ peak at 324.

3,4-Methylenedioxystyrene **39**, when subjected to CAN in methanol at 0°C afforded a complex mixture of products. However, under deoxygenated conditions it afforded the dimethoxybutane derivative **45** in 77% yield.



39 **45** (77%)

Ar = 3,4-methylenedioxyphenyl

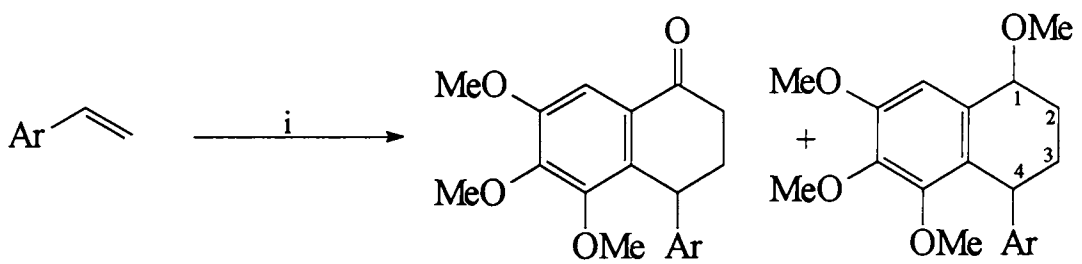
i) CAN / MeOH, argon, 0 °C, 30 min.

Scheme 17

In the proton NMR spectrum of **45**, the four protons of the methylenedioxy group were visible at δ 5.94 as a singlet and the two methoxy groups resonated as overlapping singlets at δ 3.14. The methine protons geminal to the methoxy groups were visible as a broad singlet at δ 3.94. The methoxy carbons appeared together in ^{13}C NMR at δ 56.39. The structure of the compound **45** was further confirmed by HRMS data.

The complexity of the reaction may be attributed to the presence of the methylenedioxy group on the substrate. This group may be undergoing oxidative cleavage in presence of CAN.

When 3,4,5-trimethoxystyrene **40** was treated with CAN in methanol, the reaction afforded **46** and **47** in 20% and 25% yields respectively (Scheme 18). The reaction was studied under different conditions. When the experiment was performed in methanol saturated with oxygen, the tetralone derivative **46** was obtained in 60% yield and the reaction under deoxygenated conditions afforded the methoxytetralin derivative **47** in 78% yield. The results are summarized in table 3.



Ar = 3,4,5-trimethoxyphenyl

40 **46** **47**

i) CAN / MeOH, 0 °C, 30 min.

Scheme 18

Entry	Reaction Conditions	46	47
1	CAN / MeOH, air, 0 °C	20 %	25 %
2	CAN / MeOH, oxygen, 0 °C	60 %	12 %
3	CAN / MeOH, argon, 0 °C	-	78 %

Table 3

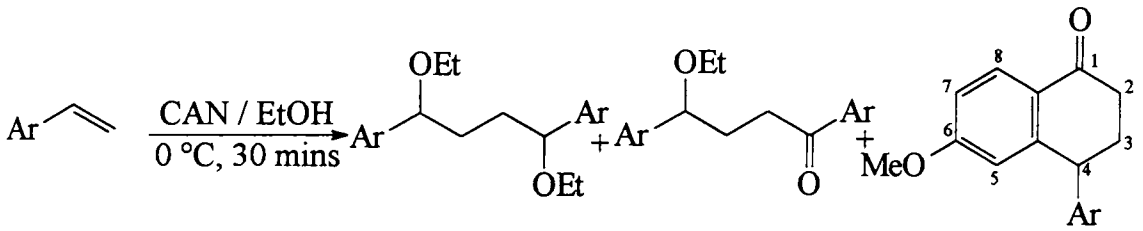
The compounds **46** and **47** were characterized by analytical and spectral data. The tetralone **46** showed the carbonyl stretching at 1683 cm^{-1} in the IR spectrum. The benzylic proton appeared as a multiplet at δ 4.57 in

the ^{1}H NMR. In the ^{13}C NMR of **46,** the carbonyl carbon appeared at δ 197.61. The structure of **46** was further confirmed by the HOMO-COSY and mass data. In the ^{1}H NMR spectrum of **47,** the methine proton geminal to the methoxy group and the methine proton at the benzylic (C-4) position appeared together as a multiplet at δ 4.24. The methoxy protons were seen at δ 3.38 as a sharp singlet. The methoxy carbon was visible at δ 55.75 in ^{13}C NMR. The structure of **47** was further confirmed by the mass data. According to ^{13}C NMR, this compound appears to be an isomeric mixture. It is noteworthy that none of the products obtained are acyclic dimers. This may be attributed to the increase in reactivity (of the cation radical formed) due to the presence of three methoxy groups on the benzene nucleus.

2.2.2. Reactions in Ethanol

In view of the participation of methanol in the reaction, it was of interest to see the effect of a less polar solvent such as ethanol on the reaction. The results of experiments conducted in ethanol are presented below (Scheme 19 and table 4).

4-methoxystyrene **25** when subjected to CAN in ethanol, the reaction took a course markedly different from the one in methanol, leading to **48**, **49** and **50**. The reaction was studied under different conditions and the results are summarized in table 4.



Ar = 4-methoxyphenyl

25 **48** **49** **50**

i) CAN / EtOH, 0 °C, 30 min.

Scheme 19

Entry	Reaction Conditions	48	49	50
1	CAN / EtOH, air, 0 °C	48 %	-	26 %
2	CAN / EtOH, oxygen, 0 °C	10 %	13%	70 %
3	CAN / EtOH, argon, 0 °C	74 %	-	8 %

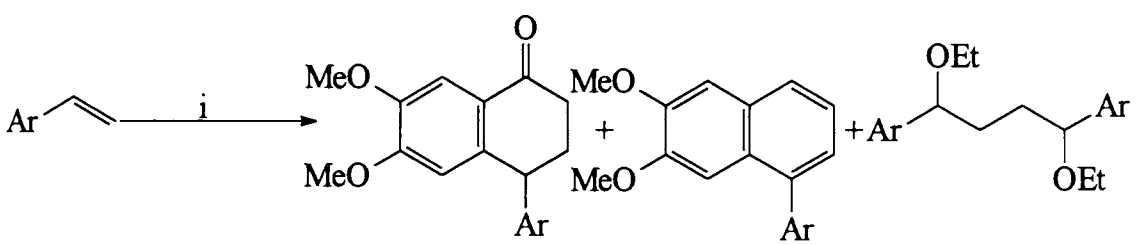
Table 4

Under normal and deoxygenated conditions (Table 4, Entries 1 & 3) the ethoxybutanone derivative **49** was not formed. But under oxygenated conditions this product and the diethoxybutane **48** were obtained in low yields; the major product was the tetralone **50**. Under deoxygenated conditions the diethoxybutane **48** was the major product and the tetralone **50** was formed in trace amounts only.

All the three products were characterized by the usual spectral methods. In the ^{1}H NMR spectrum of **48**, the protons geminal to the ethoxy groups were discernible at δ 4.07 as a broad singlet. The signals due to ethoxy groups at δ 3.25 (m, 4H) and at δ 1.11 (t, J = 6.98 Hz, 6H) were easily identifiable. The ^{13}C NMR spectrum showed the presence of the ethoxy carbons at δ 35.69 and 15.49. The structure was further confirmed by

HRMS. The IR spectrum of the butanone **49** displayed a strong carbonyl stretching at 1674 cm^{-1}. In the ^1H NMR of **49**, the proton geminal to the ethoxy group was visible at δ 4.27 (dd, J = 5.6 and 7.5 Hz). ^{13}C NMR showed the carbonyl carbon at δ 198.35. The tetralone **50** was also characterized by the usual spectral analysis; carbonyl group appeared as a strong band at 1667 cm^{-1} in the IR spectrum and the carbonyl carbon was visible as a signal at δ 196.39 in the ^{13}C NMR.

Similarly, when the reaction was carried out with 3,4-dimethoxystyrene, **43**, **44**, and **51** were obtained (Scheme 20). No ethoxybutanone was detected in the reaction mixture. Studies under different conditions gave similar results, with the tetralone predominating under oxygenated conditions. The naphthalene **44** and the diethoxybutane derivative **51** were obtained in higher yields under deoxygenated conditions (Table 5).



Ar = 3,4-dimethoxyphenyl

38 **43** **44** **51**

i) CAN / EtOH, 0 °C, 30 min.

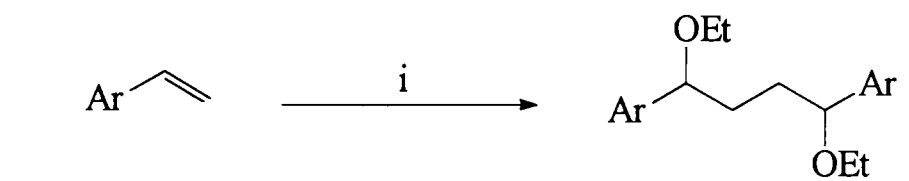
Scheme 20

Entry	Reaction Conditions	43	44	51
1	CAN / EtOH, air, 0 °C	20 %	10 %	15 %
2	CAN / EtOH, oxygen, 0 °C	63 %	8 %	10 %
3	CAN / EtOH, argon, 0 °C	13 %	27 %	40 %

Table 5

The characterization of tetralone **43** and the naphthalene derivative **44** has been described previously (Page 40). The diethoxy butane derivative **51** was characterized as follows. The protons geminal to the ethoxy groups were visible at δ 4.4 and 4.32 as multiplets and the ethoxy protons were visible at δ 3.59 (m, 4H) and at δ 1.22 (t, J = 6.9 Hz). The ethoxy carbons were discernible at δ 29.68 and 15.86 in the ^{13}C NMR of **51**. The GC-mass spectrum displayed the [M^+-2OEt] peak at 326.

3,4-Methylenedioxystyrene, **39** when treated with CAN in ethanol at 0 °C afforded a complex mixture of products reminiscent of the reaction in methanol. Under deoxygenated conditions, **39** afforded the diethoxy butane **52** in 60% yield (Scheme 21).



Ar = 3,4-methylenedioxyphenyl

39 **52**

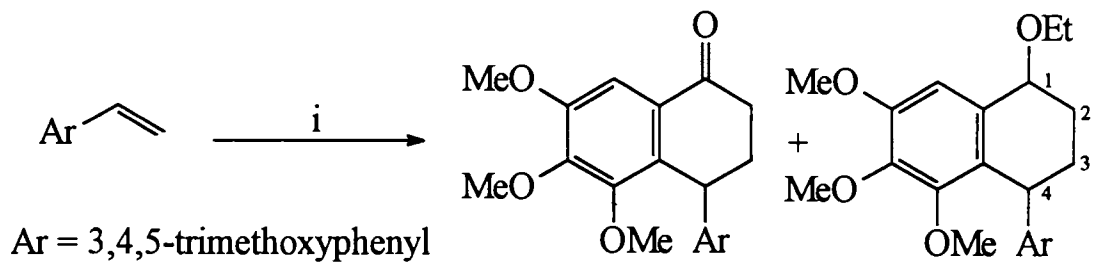
i) CAN / EtOH, Argon, 0 °C, 30 min.

Scheme 21

In the ^{1}H NMR spectrum of **52**, the protons geminal to the ethoxy groups appeared at δ 4.04 and 3.96 as multiplets and the ethoxy protons themselves were located at their usual positions. The ethoxy carbons were visible at δ 32.57 and 15.93 in the ^{13}C NMR of **52**.

Under oxygenated conditions the reaction led to an intractable mixture of products.

The reactivity of 3,4,5-trimethoxystyrene **40** with CAN in ethanol was comparable to that in methanol, thus leading to the tetralone **46** and the ethoxytetralin **53** in 15% and 29% yields respectively (Scheme 22). Similarly, the tetralone derivative predominated under oxygenated conditions (table 6, entry 2) while the tetralin derivative was the major product under deoxygenated conditions (table 6, entry 3).



Ar = 3,4,5-trimethoxyphenyl

40 **46** **53**

i) CAN / EtOH, 0 °C, 30 min.

Scheme 22

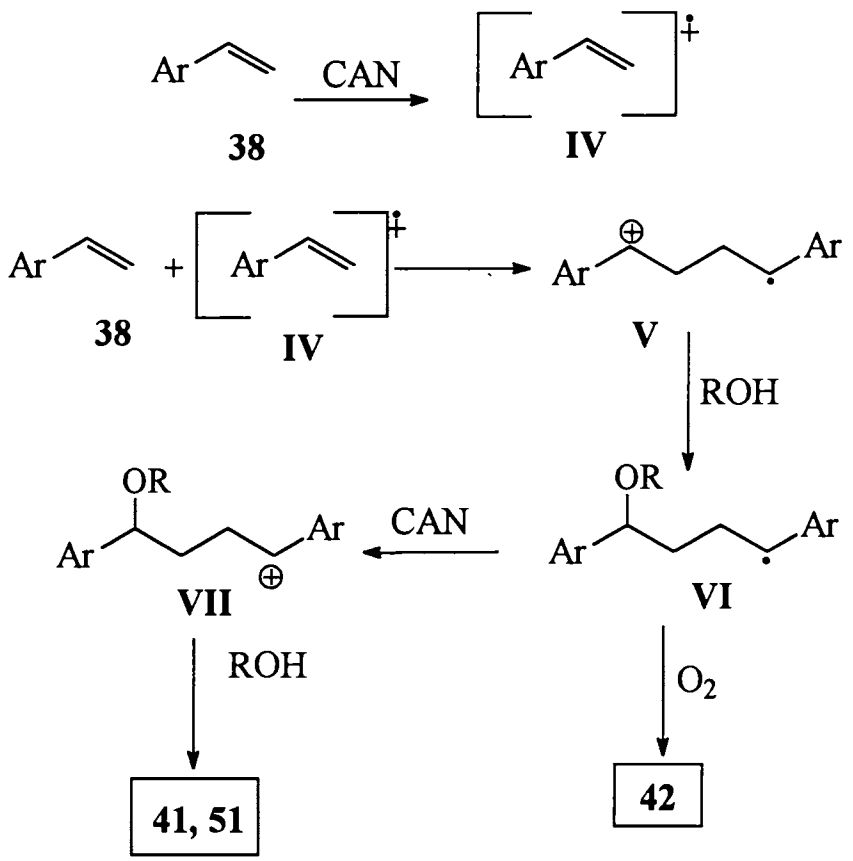
Entry	Reaction Conditions	47	53
1	CAN / EtOH, air, 0 °C	15 %	29 %
2	CAN / EtOH, oxygen, 0 °C	55 %	15 %
3	CAN / EtOH, argon, 0 °C	-	70 %

Table 6

The product **53** was obtained as an isomeric mixture (presumably *cis* and *trans*) as discerned from the ^{13}C NMR spectrum. The tetralin was characterized by the usual spectral methods. The proton on the C-4 carbon displayed a broad singlet at δ 4.34 and the proton geminal to the ethoxy group was visible at δ 4.25 as a multiplet in the ^{1}H NMR of **53**. The ethoxy carbons resonated at δ 14.52 and 22.68 in the ^{13}C NMR. The [M^{+}-OEt] peak

at 386 in the mass spectrum further confirmed the structure. The structure of **46** was established as described earlier in scheme 18.

Eventhough the mechanistic details of the reactions described herein are not known, a rationalization along the following lines may be made. The reaction of 3,4-dimethoxystyrene **38** can be taken as a representative example (Scheme 23). Styrene **38** in presence of Ce(IV) undergoes oxidative



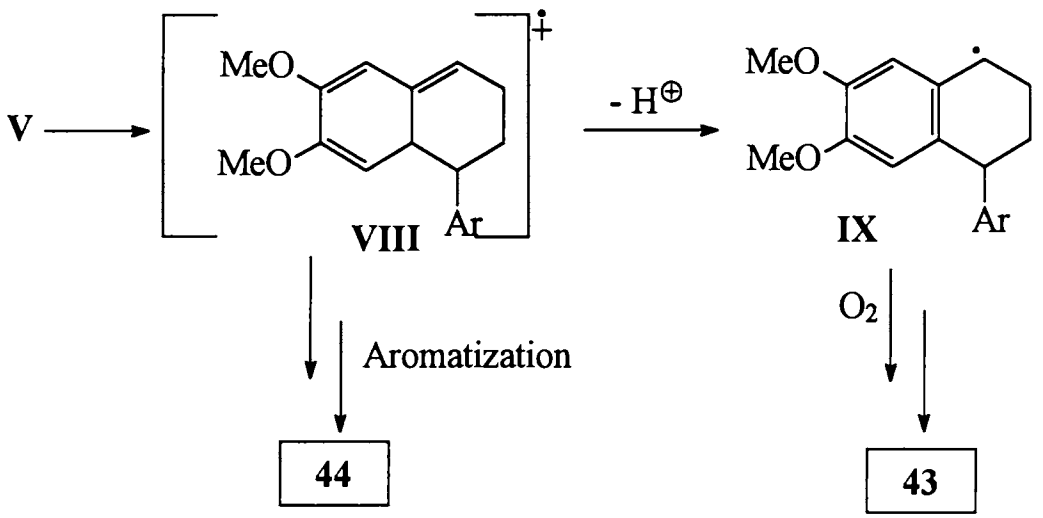
Ar = 3,4-Dimethoxyphenyl

Scheme 23

electron transfer to afford the radical cation **IV**. This in turn would add to another styrene molecule to generate a distonic radical cation **V**. Nucleophilic solvents such as methanol and ethanol can trap this radical cation **V** to generate the radical intermediate **VI.** The latter can react with oxygen from the atmosphere[14] to afford the product **42**. The radical **VI**, on further oxidation by

Ce (IV) to a cation **VII** and subsequent trapping of the latter by solvents, affords the products **41** and **51**.

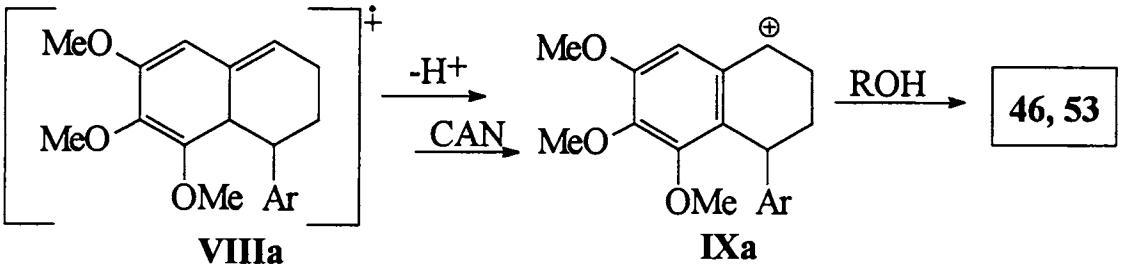
The 1,4-radical cation **V** can also undergo 1,6-cyclization to give a substituted hexatriene radical cation **VIII**, which on losing a proton yields the radical intermediate **IX** that can eventually transform to the tetralone **43** (Scheme 16). The hexatriene radical cation **VIII** can also aromatize to afford the naphthalene derivative **44** (Scheme 24).



Ar = 3,4-Dimethoxyphenyl

Scheme 24

The tetralin derivatives **46** and **53** obtained in the case of 3,4,5-trimethoxystyrene can presumably arise from the radical cation **VIIIa,** which is analogous to **VI**. This on losing a proton and subsequent electron transfer of the resulting radical intermediate generates a cation **IXa**, which is then quenched by the solvent methanol or ethanol to afford the tetralin derivatives **46** and **53** respectively (Scheme 25).



VIIIa **IXa**

Ar = 3,4,5-Trimethoxyphenyl

Scheme 25

It may be noted that an analogous mechanistic postulation has been made for the PET mediated dimerization of 4-methoxystyrene.[15] Bauld [16] and Lewis [17] have given evidence for the formation of a long bond cyclobutane radical cation. This long bond cyclobutane radical cation can undergo a 1,3-sigmatropic shift to give the hexatriene radical cation **VIII**. Also Bauld *et al.* [16] have concluded on the basis of MNDO calculations that the cyclic dimer of the ethylene radical is *ca.* 5 kcal/mol more stable than the acyclic dimer. As shown, our results here are consistent with the mechanism proposed and proven for the PET process.

2.3. EXPERIMENTAL

2.3.1. General

Melting points were recorded on Toshniwal and Büchi melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Perkin-Elmer-882 and Nicolet Impact 400D FT-IR spectrophotometers. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz with $CDCl_3$ as the solvent, unless otherwise mentioned. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Mass spectra

were recorded under EI/HRMS (at 5000 resolution) using Auto Spec. M mass spectrometer. Gravity column chromatography was performed on silica gel (100-200 mesh) in hexane - ethylacetate mixtures as the eluent. Solvents were distilled prior to use. The CAN used for the reactions was purchased from Aldrich Co. and was used without purification. The styrenes used were prepared from the corresponding aldehydes using the Wittig procedure. Commercially available ethanol and methanol were distilled prior to use.

2.3.2. CAN mediated oxidation of alkoxystyrenes

General Procedure: A solution of CAN (1.5 mmols) in alcohol (20 mL) was added dropwise to an ice cold solution of alkoxystyrene (1 mmol) in the alcohol (20 mL). When the starting material was fully consumed (15 min.), as observed by tlc, the reaction mixture was diluted with water (150 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were pooled, washed with water, brine and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with an appropriate mixture of ethyl acetate and petroleum ether afforded the products.

2.3.3. CAN mediated oxidation of alkoxystyrenes in presence of oxygen

General Procedure: To an ice cooled solution of alkoxystyrene (1 mmol) in the appropriate solvent (20 mL) saturated with oxygen, an oxygenated solution of CAN (1.5 mmols) in the same solvent (20 mL) was added dropwise while the reaction mixture was continuously being purged with

oxygen. The reaction mixture, on completion of the reaction, was processed as described in the general procedure given above.

2.3.4. CAN mediated oxidation of alkoxystyrenes in the absence of oxygen

General Procedure: To an ice-cooled deoxygenated (purged with argon) solution of alkoxystyrene (1 mmol) in the alcohol (20 mL), a deoxygenated solution of CAN (1.5 mmols) in the alcohol (20 mL) was added dropwise while the reaction mixture was continuously being purged with argon. The reaction mixture, on completion of the reaction, was processed as described in the general procedure given above.

1,4-Bis(4'-methoxyphenyl)-1,4-dimethoxybutane (28) and 1,4-Bis(4-methoxyphenyl)-4-methoxybutan-1-one (29)

To an ice-cooled solution of **25** (300 mg, 2.24 mmols) in methanol (20 mL), a solution of CAN (1.5 g, 2.69 mmols) in methanol (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 37 mg of **28** (10%).

Product 28

Colorless crystals; recrystallised from hexane - DCM.

m. p. : 98 - 100 °C

IR (KBr) ν_{max} : 2957, 1611, 1512, 1250, 1172, 1094, 1033 cm^{-1}.

^{1}HNMR : δ 7.05 (d, 4H, *J* = 8.6 Hz, ArH), 6.74 (d, 4H, *J* = 8.6 Hz, ArH), 3.88 (m, 2H, CH), 3.69 (s, 6H, ArOMe), 3.03 (s, 6H, CHOMe), 1.61 (m, 4H, CH_2).

^{13}CNMR : δ 159.28, 134.53, 128.12, 113.99, 83.83, 56.59, 55.47, 34.83.

GCMS m/z (%) : [M^+-MeOH] 298 (5), 266 (4), 227 (5), 166 (25), 151 (100), 135(15);

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.7; H, 7.93%. Found: C, 72.64; H, 8.15%.

On further elution of the column using hexane : ethylacetate (90 : 10) afforded 185 mg of **29** in 53% yield.

Product 29

Pale yellow crystals; recrystallised from hexane - DCM.

m. p. : 107 - 108 °C

IR (KBr) ν_{max} : 2954, 1668, 1611, 1593, 1257, 1167, 1027, 835 cm^{-1}

^{1}HNMR : δ 7.92 (d, *J* = 8.2 Hz, 2H, ArH), 7.23 (m, *J* = 8. Hz 2H, ArH), 6.9 (m, 4H, ArH), 4.18 (t, *J* = 6 Hz, 1H, -CHOMe), 3.86 (s, 3H, ArOMe), 3.81 (s, 3H, $ArOCH_3$), 3.19 (s, 3H, OMe), 2.98 (t, J = 7 Hz, 2H, -CH_2), 2.10 (m, 2H, -CH_2).

^{13}CNMR : δ 198.83, 163.6, 159.39, 134.14, 130.52, 130.47, 128.06, 114.09, 113.89, 82.74, 56.68, 55.66, 55.49, 34.55, 32.82;

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05%. Found: C, 72.38; H, 7.02%.

1,4-Bis(3',4'-dimethoxyphenyl)-1,4-dimethoxybutane (41), 1,4-Bis(3',4'-dimethoxyphenyl)-4-methoxybutan-1-one (42), 4-(3',4'-Dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (43), and 1-(3',4'-Dimethoxyphenyl)-6,7-dimethoxynaphthalene (44)

To an ice-cooled solution of **38** (300 mg, 1.83 mmols) in methanol (20 mL), a solution of CAN (1.2 g, 2.19 mmols) in methanol (20 mL) was added dropwise. The reaction mixture, on completion was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 25 mg of **44** (10%).

Product 44

Amorphous powder

m. p. : 135 - 140 °C.

IR (KBr) ν_{max} : 2937, 2834, 1601 1510, 1490, 1257, 1159, 1023, 3854 cm^{-1}.

^1H NMR : δ 7.69 (d, 1H, *J* = 7.98 Hz, ArH), 7.35 (t, 1H, *J* = 7.5 Hz, ArH), 7.25 (m, 2H, ArH), 7.15 (s, 1H, ArH), 7.01 (m, 3H, ArH), 4.01 (s, 3H, -OMe), 3.96 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.82 (s, 3H, OMe).

^{13}C NMR : δ 149.498, 149.370, 138.637, 133.977, 129.812, 125.847, 125.356, 123.900, 122.016, 113.241, 111.256, 106.716, 104.891, 55.981, 55.879, 55.744.

GCMS m/z (%) : M^+ 324 (100), 263 (20), 235 (48), 223 (30), 209 (51), 189 (24), 176 (25), 165 (37), 152 (42), 151 (27), 115 (39), 94 (44), 91 (26), 65 (85).

On further elution of the column using hexane : ethylacetate (90 : 10) afforded 185 mg of **41** in 15% yield.

Product 41

Colorless oil

IR (neat) ν_{max} : 2935, 2837, 1509, 1457, 1260, 1022 cm^{-1}.

^1H NMR : δ 6.72 (m, 4H, ArH), 6.30 (s, 2H, ArH), 3.93 (m, 2H, CHOMe), 3.7 (s, 6H, ArOMe), 3.71 (s, 6H, ArOMe), 3.11 (s, 6H, OMe), 1.65 (m, 4H, CH_2).

^{13}C NMR : δ 148.55, 148.89, 146.69, 146.55, 138.78, 120.13, 111.74, 111.01, 82.45, 56.72, 55.23, 35.93.

GCMS m/z (%) : [M+-2OMe] 326 (100), 295 (25), 165 (52).

On further elution of the column using hexane : ethylacetate (85 : 15) afforded 185 mg of **43** in 59% yield.

Product 43

Colorless oil

IR (neat) ν_{max} : 2942, 2847, 1681, 1607, 1526, 1465, 1270, 1040 cm^{-1}

^1H NMR : δ 7.59 (s, 1H, ArH), 6.82 (d, 1H, J = 8.1 Hz, ArH), 6.66 (s, 1H, ArH), 6.63 (d, 1H, J = 8.2 Hz, ArH), 6.44 (s, 1H, ArH), 4.19 (dd, 1H, J = 4.5 Hz, J = 7 Hz, $CHCH_2$), 3.95 (s, 3H, ArOMe), 3.88 (s, 3H, ArOMe), 3.83 (s, 3H, ArOMe), 3.76 (s, 3H, ArOMe), 2.63 (m, 2H, $COCH_3$), 2.47 (m, 1H, $CHCH_2$), 2.24 (m, 1H, $CHCH_2$).

^{13}C NMR : δ 196.644, 153.607, 149.152, 148.217, 147.925, 140.997, 136.195, 126.213, 120.726, 111.554, 111.162,

110.902, 108.308, 55.908, 55.864, 55.820, 44.753, 36.083, 32.421.

GCMS m/z (%) : M^+ 342(42), 283(25), 271(15), 213(30), 211(30), 197(45), 185(30), 115(32), 91(30), 77(45), 55(100).

On further elution of the column using hexane : ethylacetate (80 : 20) afforded 40 mg of **42** in 12% yield.

Product 42

Colorless oil

IR (neat) ν_{max} : 2371, 1707, 1613, 1526, 1446, 1305, 1171 cm^{-1}.

^1H NMR : δ 7.52 (d, 1H, J = 8.2 Hz, ArH), 7.18 (d, 1H, J = 8 Hz, ArH), 6.82 (d, 1H, J = 8.1 Hz, ArH), 6.66 (s, 1H, ArH), 6.63 (d, 1H, J = 8.3 Hz, ArH), 6.44 (s, 1H, ArH), 4.19 (m, 1H, CHOCH$_3$), 3.97 (s, 3H, ArOMe), 3.95 (s, 3H, ArOMe), 3.88 (s, 3H, ArOMe), 3.82 (s, 3H, ArOMe), 3.76 (s, 3H, -OMe), 2.62 (m, 2H, -COCH$_2$-), 2.44 (m, 1H, -CHCH$_2$-), 2.25 (m, 1H, -CHCH$_2$-).

^3C NMR : δ 197.06, 161.62, 153.71, 153.48, 147.97, 141.20, 135.44, 133.76, 129.77, 119.87, 111.07, 56.07, 56.02, 55.96, 53.99, 44.78, 36.19, 32.44.

GCMS m/z (%) : M^+ 374(26), 342(100), 343(30), 329(32), 315(65), 314(30), 283(35), 255(100), 205(32), 165(32), 115(15), 77(12), 59(15).

1,4-Bis(3',4'-methylenedioxyphenyl)-1,4-dimethoxybutane (45)

To an ice-cooled deoxygenated solution of **39** (300 mg, 2.03 mmols) in methanol (20mL), a deoxygenated solution of CAN (1.33 g, 2.43 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously being purged with argon. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (93 : 7) afforded 279 mg of **45** (77%).

Product 45

Colorless crystals; recrystallised from hexane - DCM

m. p. : 154 - 156 °C

IR (KBr) ν_{max} : 2922, 1483, 1432, 1242, 1097, 1026, 936, 816 cm^{-1}.

^1H NMR : δ 6.69 (m, 6H, ArH), 5.94 (s, 4H, -OCH_2O-), 3.94 (brs, 2H, CHOMe), 3.14 (s, 6H, OCH_3), 1.68 (brs, 4H, CH_2CH_2).

^{13}C NMR : δ 147.835, 146.905, 136.192, 120.240, 107.894, 106.632, 100.906, 83.766, 83.578, 56.389, 34.583, 34.096.

LRMS m/z (%) [M^++1] 359 (0.6), 358 (3), 327 (1), 326 (1.3), 294 (2), 178 (47), 165 (100), 148 (15), 77 (4)

HRMS Calcd for $C_{20}H_{22}O_6$: 358.141639. Found: 358.141282.

4-(3',4',5'-Trimethoxyphenyl)-5,6,7-trimethoxy-1-tetralone (46) and 4-(3',4',5'-Trimethoxyphenyl)-5,6,7-trimethoxy-1-methyoxytetralin (47)

To an ice-cooled solution of **40** (300 mg, 1.55 mmols) in methanol (20 mL), a solution of CAN (1.02 g, 1.85 mmols) in methanol (20 mL) was added dropwise. The mixture, on completion of the reaction was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (93 : 7) afforded 80 mg of **47** (25%).

Product 47

Colorless crystalline solid; recrystallised from hexane - DCM

m. p. : 126 - 127 °C

IR (KBr) ν_{max} : 2929, 1578, 1493, 1458, 1233 1118, 1078, 998 cm^{-1}.

^1H NMR : δ 6.69 (s, 1H, ArH), 6.15 (s, 2H, ArH), 4.24 (m, 2H, -CHOMe and -CHAr), 3.91 (s, 3H, ArOMe), 3.80 (s, 3H, ArOMe), 3.78 (s, 3H, ArOMe), 3.74 (s, 3H, ArOMe), 3.46 (s, 3H, ArOMe), 3.38 (s, 3H, CHOMe), 1.76 (m, 4H, $-CH_2CH_2-$).

^{13}C NMR δ 152.727, 152.284, 151.466, 142.821, 142.117, 136.149, 132.317, 125.287, 107.956, 105.281, 76.272, 60.716, 60.358, 60.043, 56.420, 56.019, 55.754, 38.800, 26.456, 21.946.

LRMS m/z (%) :M^+ 418 (28), 387 (25), 386 (100), 371 (17), 355 (37), 250 (19), 235 (34), 219 (12), 218 (15), 181 (25).

HRMS Calcd for $C_{23}H_{30}O_7$: 418.199154. Found: 418.202779.

On further elution of the column using hexane: ethylacetate (90 : 10) afforded 62 mg of **46** in 20% yield.

Product 46

Colorless crystalline solid; recrystallised from hexane - DCM

m. p. : 114 - 115 °C

IR (KBr) ν_{max} : 2937, 2834, 1683, 1587, 1409, 1345, 1233, 1108, 1020, 895, 864, 772 cm^{-1}.

^1H NMR : δ 2.2 (m, 1H, C<u>H</u>$_2$), 2.53 (m, 3H, C<u>H</u>$_2$), 3.53 (s, 3H, O<u>Me</u>), 3.75 (s, 6H, O<u>Me</u>), 3.81 (s, 3H, O<u>Me</u>), 3.92 (s, 3H, O<u>Me</u>), 3.95 (s, 3H, O<u>Me</u>). 4.57 (m, 1H, C<u>H</u>OMe), 6.23 (s, 2H, Ar<u>H</u>), 7.47 (s, 1H, Ar<u>H</u>).

^{13}C NMR δ 197.617, 153.110, 152.759, 150.731, 147.554, 138.988, 136.602, 132.722, 128.325, 105.322, 104.878, 60.871, 60.796, 56.140, 56.043, 38.001, 33.693, 30.862.

LRMS m/z (%) : $[M^+ +2]$ 404 (4), $[M^+ +1]$ 403 (15), M^+ 402 (100), 371 (10), 177 (9), 176 (10), 175 (6), 77(4), 55 (4).

1,4-Bis(4'-methoxyphenyl)-1,4-diethoxybutane (48) and **4-(4'-Methoxyphenyl)-6-methoxy-1-tetralone (50)**

To an ice-cooled solution of **25** (300 mg, 2.24 mmols) in ethanol (20 mL), a solution of CAN (1.5 g, 2.69 mmols) in ethanol (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (98 : 2) afforded 192 mg of **48** (48%).

Product 48

Colorless oil

IR (neat) ν_{max} : 2971, 2931, 1611, 1511, 1247, 1173, 1092, 832 cm^{-1}.

^1H NMR : δ 7.16 (d, 4H, *J* = 8.54 Hz, ArH), 6.83 (d, 4H, *J* = 8.58 Hz, ArH), 4.07 (brs, 2H, CHOEt), 3.79 (s, 6H, ArOMe), 3.25 (m, 4H, OCH_2CH_3), 1.70 (m, 4H, $CHCH_2$), 1.11 (t, 6H, *J* = 6.98 Hz, CH_2CH_3).

^{13}C NMR : δ 159.010, 135.239, 127.792, 113.808, 81.912, 63.903, 55.232, 35.169, 15.479.

LRMS m/z (%) : $[M^+ + 1]$ 313 (0.4), M^+ 312 (1.1), 266 (2.7), 227 (4.1), 178 (38), 166 (11), 165 (100), 150 (5), 137 (35), 135 (5), 134 (8), 121 (7), 109 (7), 77 (5).

HRMS Calcd for $C_{22}H_{30}O_4$: $[M^+$-OEt] 312.174234. Found : $[M^+$-OEt] 312.172545.

On further elution of the column using hexane : ethylacetate (95 : 5) afforded 82 mg (26%) of **50**.

Product 50

Colorless crystals; recrystallised from hexane - DCM

m. p. :116 - 117 °C

IR (KBr) ν_{max}: : 2953, 1667, 1596, 1513, 1262, 1247, 1230, 1182, 1029, 833 cm^{-1}.

^1H NMR : δ 8.06 (d, 1H, *J* = 8.7 Hz, ArH), 7.01 (d, 2H, *J* = 8.55 Hz, ArH), 6.84 (d, 3H, *J* = 8.66 Hz, ArH), 6.41 (d, 1H, *J* = 1.66 Hz, ArH), 4.11 (dd, 1H, *J* = 4.36 Hz, *J* = 7.44 Hz, $CHCH_2$), 3.79 (s, 3H, ArOMe), 3.73 (s, 3H,

ArOMe), 2.61 (m, 2H, -COCH$_2$), 2.41 (m, 1H, CHCH$_2$), 2.29 (m, 1H, CHCH$_2$).

^{13}C NMR : δ 196.387, 163.584, 158.362, 148.925, 135.392, 129.560, 129.369, 126.491, 113.962, 113.494, 113.181, 55.127, 55.038, 44.825, 36.330, 31.954.

LRMS m/z (%) : [M^++1] 283 (19), M^+ 282 (100), 267 (20), 255 (10), 254 (57), 239 (20), 211 (30), 152 (10), 137(21), 135 (15).

HRMS Calcd for $C_{18}H_{18}O_3$: 282.125595. Found: 282.126726.

1,4-Bis(4-methoxyphenyl)-4-ethoxybutan-1-one (49)

The same reaction when carried out in an atmosphere of oxygen afforded 83 mg of **49** (13%) on elution of the silica gel column with hexane:ethylacetate (93 : 7) along with **48** and **50**, which were obtained in 10% and 70% yields respectively.

Product 49

Colorless oil

IR (neat) ν_{max} : 2959, 2835, 1674, 1607, 1514, 1260, 1161, 1032, 830 cm^{-1}.

^{1}H NMR : δ 7.91 (d, 2H, *J* = 8.72 Hz, ArH), 7.22 (d, 2H, *J* = 8.5 Hz, ArH), 6.90 (d, 2H, *J* = 8.8 Hz, ArH), 6.85 (d, 2H, *J* = 8.5 Hz, ArH), 4.27 (dd, 1H, *J* = 5.6 Hz, 7.5 Hz, CHOEt), 3.86 (s, 3H, ArOMe), 3.80 (s, 3H, ArOMe), 3.30 (m, 2H, -OCH$_2$CH$_3$), 2.96 (t, 2H, J = 7 Hz, -CH$_2$CH$_2$-), 2.09 (m, 2H, -CH$_2$CH$_2$-), 1.14 (t, 3H, J = 7 Hz, -OCH$_2$CH$_3$)

^{13}C NMR δ 198.354, 163.215, 158.932, 134.611, 130.212, 127.568, 113.703, 113.533, 80.421, 63.817, 55.245, 55.061, 34.224, 32.817, 15.284.

GCMS m/z (%) : M^+ 284 (2), 282 (20), 265 (15), 178 (10), 165 (8), 147 (10), 135 (100), 107 (8), 92 (5), 77 (10).

4-(3',4'-Dimethoxyphenyl)-6,7-dimethoxy-1-tetralone (43), 1-(3',4'-Dimethoxyphenyl)-6,7-dimethoxynaphthalene (44) and **1,4-Bis(3',4'-dimethoxyphenyl)-1,4-diethoxybutane (51)**

To an ice-cooled solution of **38** (300 mg, 1.83 mmols) in ethanol (20 mL), a solution of CAN (1.2 g, 2.19 mmols) in ethanol (20 mL) was added dropwise. The mixture, on completion of the reaction was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 30 mg of **44** (10%). On further elution of the column using hexane: ethylacetate (92:8) afforded 60 mg of **51** in 15% yield.

Product 51

Colorless oil.

IR (neat) ν_{max} : 2943, 1601, 1513, 1251, 1026, 864 cm^{-1}.

^{1}H NMR : δ 6.69 (m, 4H, ArH), 6.24 (s, 2H, ArH), 4.40 (m, 1H, -CHOEt), 4.32 (m, 1H, CHOEt), 3.82 (s, 3H, ArOMe), 3.80 (s, 3H, ArOMe), 3.78 (s, 3H, ArOMe), 3.72 (s, 3H, ArOMe), 3.59 (m, 4H, OCH_2CH_3), 1.96 (m, 2H, -CH_2CH_2), 1.72 (m, 1H, -CH_2CH_2), 1.63 (m, 1H, -CH_2CH_2-), 1.22 (t, 3H, J = 6.9 Hz, -OCH_2CH_3)

^{13}C NMR : δ 148.350, 148.650, 147.680, 147.450, 139.450, 121.020, 111.540, 111.000, 75.290, 75.160, 63.490, 55.770, 55.650, 29.680, 26.140, 15.860.

GCMS m/z (%) : [M^+-2OEt] 326 (100), 295 (25), 165 (52).

On further elution of the column using hexane: ethylacetate (85:15) afforded 62 mg of **43** in 20% yield.

1,4-Bis(3',4'-dioxymethylenephenyl)-1,4-diethoxybutane(52)

To an ice-cooled deoxygenated solution of **39** (300 mg, 2.03 mmols) in ethanol (20mL), a deoxygenated solution of CAN (1.33 g, 2.43 mmols) in ethanol (20 mL) was added dropwise while the reaction mixture was continuously being purged with argon. The mixture, on completion of the reaction was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (98 : 2) afforded 235 mg of **52** (60%).

Product 52

Colorless oil

IR (neat) ν_{max} : 2978, 2872, 1487, 1442, 1244, 1097, 1037, 935, 808 cm^{-1}.

^{1}H NMR : δ 6.69 (m, 6H, Ar<u>H</u>), 5.91 (s, 4H, -OC<u>H</u>$_2$O-), 4.04 (m, 1H, -C<u>H</u>OEt), 3.96 (m, 1H, -C<u>H</u>OEt), 3.66 (m, 4H, -OC<u>H</u>$_2$CH$_3$), 2.05 (m, 2H, -C<u>H</u>$_2$CH$_2$), 1.83 (m, 1H, -C<u>H</u>$_2$CH$_2$), 1.69 (m, 1H, -C<u>H</u>$_2$CH$_2$), 1.27 (m, 6H, -OCH$_2$C<u>H</u>$_3$).

^{13}C NMR : δ 148.950, 146.490, 136.280, 121.520, 107.980, 106.720, 100.770, 80.350, 63.570, 32.570, 15.930.

GCMS m/z (%) : [M^+-2OEt] 296 (2), 294 (100), 267 (15), 172 (20), 135 (50), 115 (12), 89 (8)

4-(3',4',5'-Trimethoxyphenyl)-5,6,7-trimethoxy-1-ethyoxytetralin (53)

To an ice-cooled solution of **40** (300 mg, 1.55 mmols) in ethanol (20 mL), a solution of CAN (1.02 g, 1.85 mmols) in ethanol (20 mL) was added dropwise. The mixture, on completion of the reaction was processed as described in the general procedure. Column chromatography on silica gel using hexane: ethylacetate (95:5) afforded 65 mg of **53** (20%).

Product 53

Colorless oil

IR (neat) ν_{max} : 2942, 2833, 1596, 1507, 1458, 1408, 1344, 1235, 1116, 1012 cm^{-1}.

^{1}H NMR : δ 6.69 (s, 2H, ArH), 6.16 (s, 1H, ArH), 4.34 (brs, 1H, CHAr), 4.25 (m, 1H, $CHOCH_2CH_3$), 3.90 (s, 3H, ArOMe), 3.79 (s, 3H, ArOMe), 3.77 (s, 3H, ArOMe), 3.75 (s, 3H, ArOMe), 3.37 (s, 3H, ArOMe), 2.33 (m, 1H, $-CH_2CH_2$), 1.79 (m, 3H, $-CH_2CH_2$), 1.27 (m, 3H, OCH_2CH_3).

^{13}C NMR δ 152.820, 152.394, 151.515, 142.980, 142.110, 136.259, 132.777, 125.483, 108.052, 105.413, 74.664, 64.191, 60.783, 60.406, 60.076, 56.109, 55.818, 39.009, 26.784, 22.938, 15.850.

GCMS m/z (%) : [M^+-OEt] 386 (100), 355 (20), 218 (50), 181 (45), 153 (10).

On further elution of the column using hexane: ethylacetate (90:10) afforded 78 mg of **46** (explained before) in 25% yield.

PART II

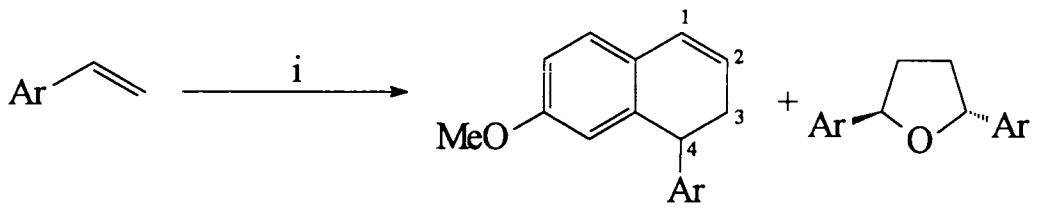
CERIUM (IV) AMMONIUM NITRATE INDUCED DIMERIZATION OF ALKOXYSTYRENES IN ACETONITRILE

2.4. INTRODUCTION

It is evident from the observations presented in Part I that the solvent plays a major role in determining the course of reaction; it stabilizes the radical cation as well as acts as a nucleophile. Since the secondary reactions are determined by the reaction medium, it was decided to carry out some experiments on the dimerization of alkoxystyrenes in acetonitrile, which is less polar and less nucleophilic than methanol or ethanol. It is also noteworthy that almost all the reported PET mediated reactions on methoxystyrenes have been carried out in acetonitrile (Scheme 11).

2.5. RESULTS AND DISCUSSION

The initial experiment involved the reaction of *p*-methoxystyrene with CAN in acetonitrile. The reaction afforded two products **54** and **31** in 22% and 41% yields respectively (Scheme 26).



Ar = 4-methoxyphenyl

25 **31** **54**

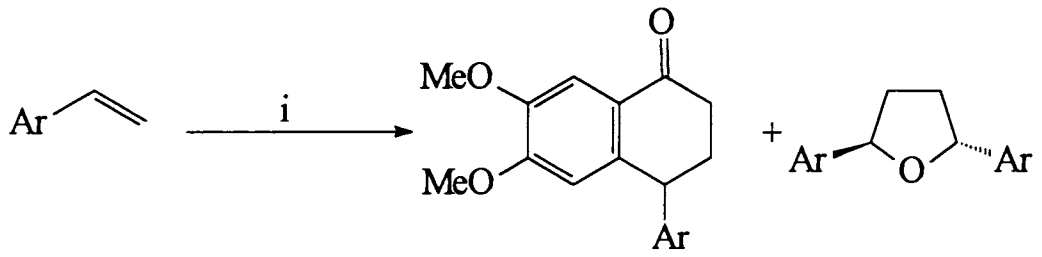
i) CAN / MeCN, 0 °C, 15 min.

Scheme 26

The structure of the dihydronaphthalene derivative **31** was confirmed by comparing its spectral data with that reported in the literature.[11] The ^{1}H NMR spectrum of **31** displayed signals for two olefinic protons at δ 5.36 (d, 1H) and 5.034 (m, 1H). The two allylic protons appeared as multiplets at δ 2.669 and 2.034. The C-4 benzylic carbon was discernible at δ 80.388 and the allylic carbon was visible at δ 33.885 in the ^{13}C NMR of **31**.

The ^{1}H NMR spectrum of the tetrahydrofuran derivative **54** displayed two benzylic protons as a multiplet at δ 5.166 and 4.954. The four methylene protons appeared at δ 2.55 and 1.80 as multiplets. The benzylic carbons were discernible at δ 80.75 and the two methylene carbons appeared together at δ 33.88 in the ^{13}C NMR of **54**. The structure was further confirmed by analytical data.

When the reaction was carried out with 3,4-dimethoxystyrene **38**, it afforded a complex mixture with **43** (22%) and **55** (8%) as the only isolable products (Scheme 27).



Ar = 3,4-dimethoxyphenyl

38 **43** **55**

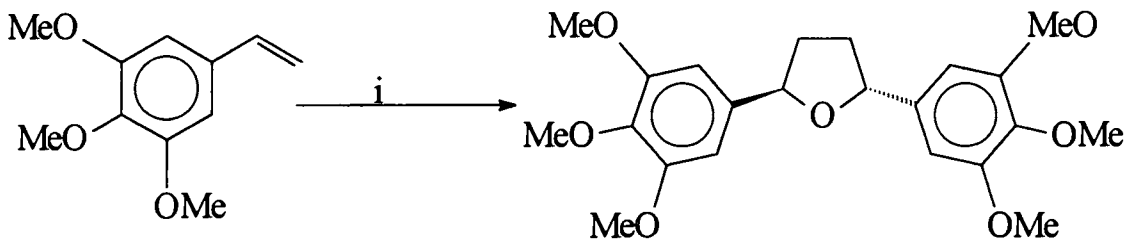
i) CAN, MeCN, 0 °C, 15 min.

Scheme 27

The characteristic details of the product **43** have already been described in section 2.2.1 (Page 40).

The product **55** was characterized by the usual spectroscopic methods. The ^{1}H NMR spectrum of **55** displayed the two benzylic protons as multiplets at δ 5.13 and 4.80. The four methylene protons appeared at δ 1.55 and 1.29 as multiplets. The benzylic carbons were discernible at δ 80.58 and the two methylene carbons appeared together at δ 34.33 in ^{13}C NMR of **55**.

The reaction of 3,4,5-trimethoxystyrene **40** with CAN was very complex, presumably due to the high reactivity of the 3,4,5-trimethoxybenzene nucleus. The tetrahydrofuran derivative **56** was the only isolable product in this case (Scheme 28).



40 **56**

i) CAN / MeCN, 0 °C, 15 min, 10%

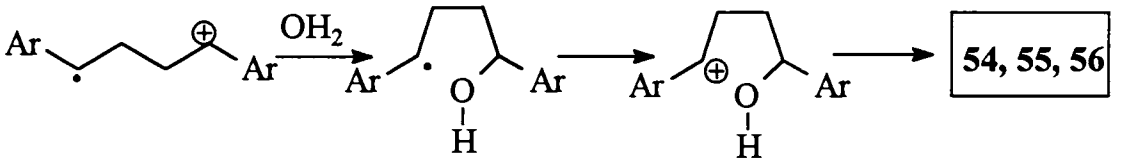
Scheme 28

The product **56** was characterized by the usual spectroscopic methods. The ^{1}H NMR spectrum of **56** displayed the two benzylic protons as a multiplet at δ 4.655 and 4.637. The four methylene protons appeared at δ 1.589 and 1.182 as multiplets. The benzylic carbons were discernible at δ 80.57 and the two methylene carbons appeared together at δ 29.7 in ^{13}C NMR of **56**.

It is worthy to note that the reactions of all the styrenes with CAN in acetonitrile led to the cyclized products exclusively. This may be a consequence of the lower polarity and reactivity of acetonitrile *vis a vis* methanol or ethanol.

3,4-methylenedioxy styrene **39** was found to be too reactive; even at low temperatures **39** reacted with CAN in acetonitrile to afford a complex mixture of products.

Mechanistically the tetrahydrofuran derivatives may be considered to arise from the acyclic 1,4-radical cation (see page 48 for a description of its formation) as shown in scheme 29.



Scheme 29

2.6. EXPERIMENTAL

General experimental details are given in section 2.3.1.

2.6.1. General procedure for acetonitrile reactions

General Procedure: A solution of CAN (1.5 mmols) in acetonitrile (20 mL) was added dropwise to an ice-cooled solution of alkoxystyrene (1 mmol) in acetonitrile (20 mL). When the starting material was fully consumed (15 min.), as observed by TLC, the reaction mixture was diluted with water (150 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were pooled, washed with water, brine and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel (100-200 Mesh). Elution with an appropriate mixture of ethyl acetate and petroleum ether afforded the products.

2,3-Bis(4'-methoxyphenyl)tetrahydrofuran (54) and **7-methoxy-1-(4'-methoxyphenyl)-1,2-dihydronaphthalene (31)**

To an ice-cold solution of **25** (300 mg, 2.24 mmols) in acetonitrile (20 mL), a solution of CAN (1.5 g, 2.69 mmols) in acetonitrile (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (98 : 2) afforded 65 mg of **31** (22%).

Product 31[10]

Colorless oil.

IR (neat) ν_{max} : 2955, 1627, 1512, 1290, 1256, 1034, 879, 831 cm^{-1}.

^1H NMR : δ 7.399 (d, 1H, J = 8.5 Hz, ArH), 6.910 (d, 2H, J = 8.5 Hz, ArH), 6.792 (d, 3H, J = 8.6 Hz, ArH), 6.401 (d, 1H, J = 1.9Hz, ArH), 5.360 (dd, 1H, J = 6 Hz, J = 2.9 Hz, ArCH=CH-), 5.034 (d, 1H, J = 3 Hz, ArCH=CH-), 4.310 (t, 1H, J = 6 Hz, -CHCH$_2$), 3.775 (s, 3H, ArOMe), 3.675 (s, 3H, ArOMe), 2.669 (m, 1H, -C=CHCH$_2$), 2.034 (m, 1H, -C=CHCH$_2$).

^{13}C NMR : δ 159.843, 158.463, 139.371, 136.886, 130.131, 129.385, 128.390, 114.370, 114.142, 113.933, 79.686, 67.485, 55.168, 42.445, 31.618.

On further elution of the column using hexane : ethylacetate (96 : 2) afforded 130 mg of **54** in 41% yield.

Product 54

Colorless Needles; recrystallised from hexane - DCM.

m. p. : 79 - 80°C

IR (KBr) ν_{max} : 2962, 1620, 1526, 1256, 1047, 825 cm^{-1}.

^1H NMR : δ 7.32 (d, 4H, *J* = 8 Hz, ArH), 6.86 (d, 4H, *J*=8.1Hz, ArH), 5.16 (t, 1H, *J* = 6.2 Hz, -OCHAr), 4.95 (t, 1H, *J* = 4.9 Hz, -OCHAr), 3.76 (s, 6H, OMe), 2.33 (m, 4H, CH_2), 1.92 (m, 2H, CH_2).

^{13}C NMR δ 158.853, 135.647, 134.999, 127.161, 126.772, 113.655, 80.750, 55. 064, 35.502, 34.323.

GCMS m/z (%) : M^+ 284 (0.2), 280 (5), 227 (6), 176 (17), 148 (90), 135 (65), 134 (50), 117 (39), 91 (71), 77 (100), 65 (40).

2,3-Bis(3',4'-dimethoxyphenyl) tetrahydrofuran (55)

To an ice-cold solution of **38** (300 mg, 1.83 mmols) in acetonitrile (20 mL), a solution of CAN (1.2 g, 2.19 mmols) in acetonitrile (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 25 mg of **55** (8 %).

Product 55

Colorless oil.

IR (neat) ν_{max} : 2938, 1595, 1508, 1266 cm^{-1}.

^1H NMR : δ 6.45 (m, 3H, ArH), 6.69 (s, 1H, ArH), 6.75 (m, 2H, ArH), 5.85 (m, 1H, OCH), 5.24 (m, 1H, OCH), 2.59 (m, 4H, CH_2).

^{13}C NMR δ 148.634, 147.768, 147.381, 137.028, 130.315, 127.182, 126.944, 124.885, 120.201, 111.579, 111.280, 110.893, 109.639, 55.698, 55.608, 42.988, 32.158.

2,3-Bis(3',4',5'-trimethoxyphenyl) tetrahydrofuran (56)

To an ice-cold solution of **40** (300 mg, 1.55 mmols) in acetonitrile (20 mL), a solution of CAN (1.02 g, 1.85 mmols) in acetonitrile (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (85 : 15) afforded 30 mg of **56** (10%).

Product 56

Colorless oil.

IR (neat) ν_{max} : 2958, 1621, 1514 cm^{-1}.

^{1}H NMR : δ 6.686 (s, 2H, ArH), 6.513 (s, 2H, ArH), 5.97 (t, 1H, J = 6 Hz, OCH), 4.63 (t, 1H, J = 6 Hz, OCH), 3.83 (s, 18H, OMe), 1.58 (m, 2H, CH_2), 1.12 (m, 2H, CH_2).

^{13}C NMR δ 154.014, 153.749, 139.124, 136.411, 128.167, 125.293, 106.516, 103.753, 80.578, 60.979, 60.771, 56.262, 29.708.

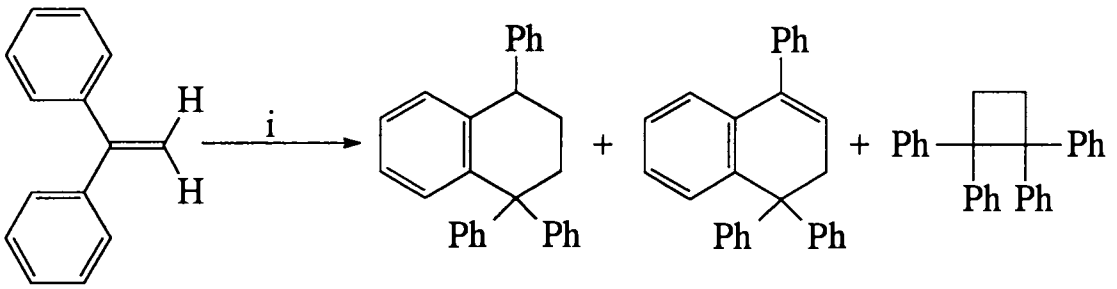
LRMS m/z (%) : [M^+ - 2MeOH, -OH] 392 (0.05), 273 (4), 239 (100), 196 (50), 177 (48), 149 (30)

PART III

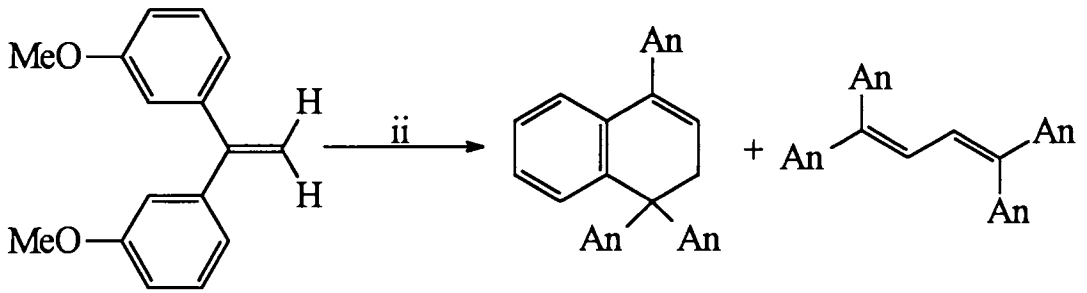
CERIUM (IV) AMMONIUM NITRATE MEDIATED REACTIONS OF α- AND β- SUBSTITUTED STYRENES

2.7. INTRODUCTION

A brief survey of the literature on the one electron oxidation of styrenes with substitution on the double bond is given below. Mattes and Farid[18] have reported the photoinduced electron transfer reactions of α-phenyl styrene **57** and α-anisyl-4-methoxystyrene **61** and their results are as shown in Scheme 30.



57 **58** **59** **60**



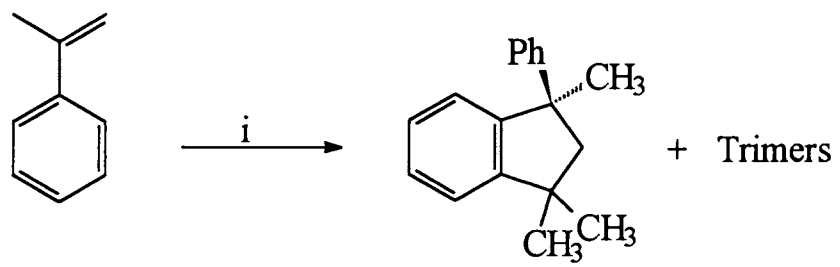
61 **62** **63**

i) hν, sensitizer

ii) hν / MeCN, sensitizer

Scheme 30

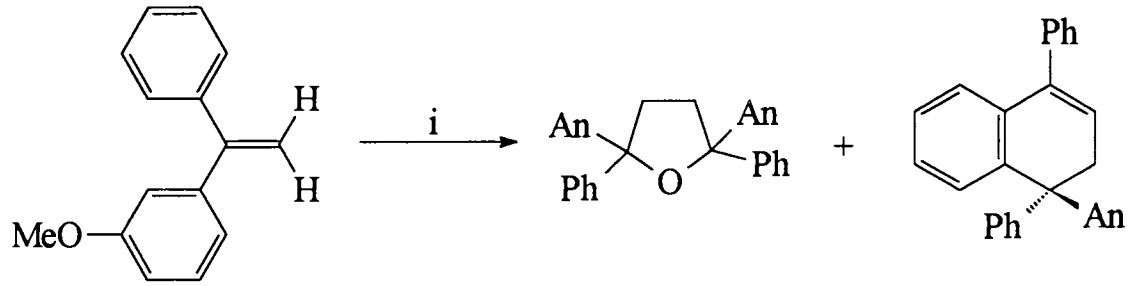
There are also reports of cyclodimerization of α-methylstyrene **64** (Scheme 31) and 1-phenyl-4-methoxystyrene **66** mediated by triaryl aminium salt (Scheme 32) [19].



64 **65**

i) $Ar_3N^{+\cdot}SbCl_6^-$

Scheme 31

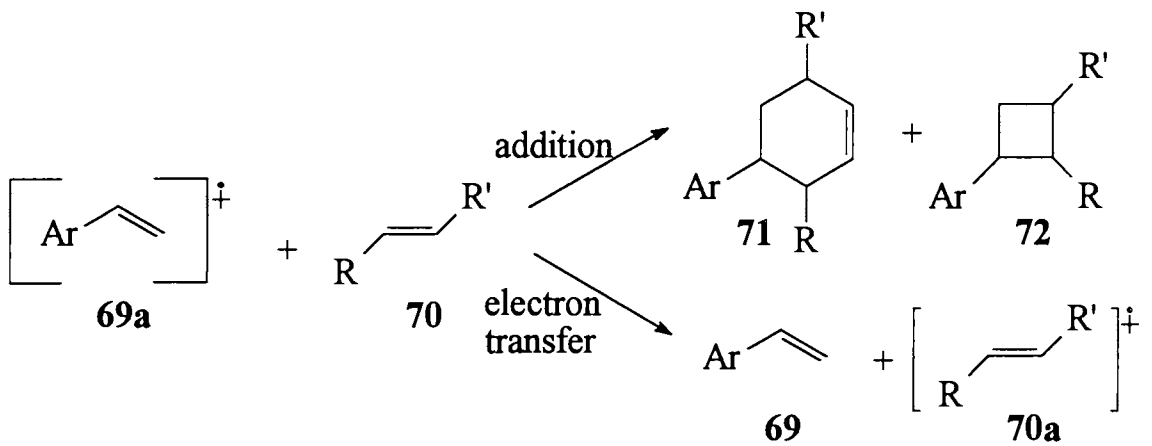


66 **67** **68**

i) $Ar_3N^{+\cdot}SbCl_6^-$

Scheme 32

Johnston and Schepp have studied the reactivity of radical cations derived from various styrenes.[20] They have measured the absolute rate constants for the reactions of various styrene radical cations with a series of alkenes, dienes and enol ethers by laser flash photolysis (Scheme 33).



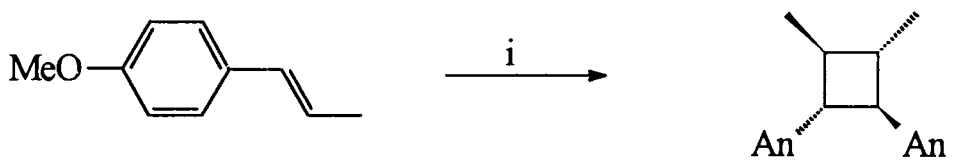
69a **70** **71** **72** **69** **70a**

Scheme 33

On introducing a methyl group to the *β*-position of **69a**, they observed a 140 fold decrease in the rate constant for the reaction with ethyl vinyl ether. However, the rate constant for the reaction of the *α*-methyl-*p*-methoxystyrene radical cation with ethyl vinyl ether is almost identical to that for the reaction of *p*-methoxystyrene radical cation. Thus, while a single

methyl group in the β-position has a strong influence on the kinetics of the addition reaction, the presence of a methyl group in the α-position has no effect.

Bauld and coworkers have reported the cyclodimerization of β-methyl-*p*-methoxystyrene using triarylaminium salt to afford the cyclobutane derivative **74** (Scheme 34)[21]. The same product was obtained when the reaction was done under photochemical conditions.



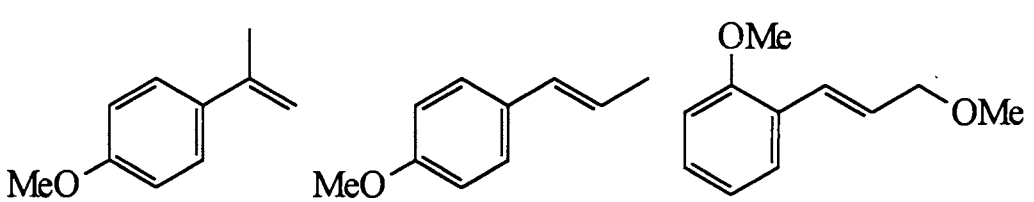
73 **74**

i) $Ar_3N^{+\cdot}SbCl_6^-$

Scheme 34

2.8. RESULTS AND DISCUSSION

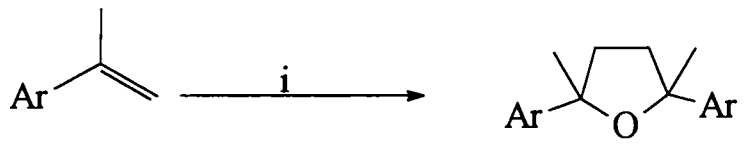
In order to gain more insight into the dimerization reaction of alkoxystyrenes and to study the effect of substitution on the styrenic double bond, we have investigated the CAN induced reactions of the following styrenes.



75 **76** **77**

Figure 2

α-Methyl-*p*-methoxystyrene **75,** on reaction with CAN in methanol afforded the tetrahydrofuran derivative **78** in 50% yield (Scheme 35).



Ar = 4-methoxyphenyl

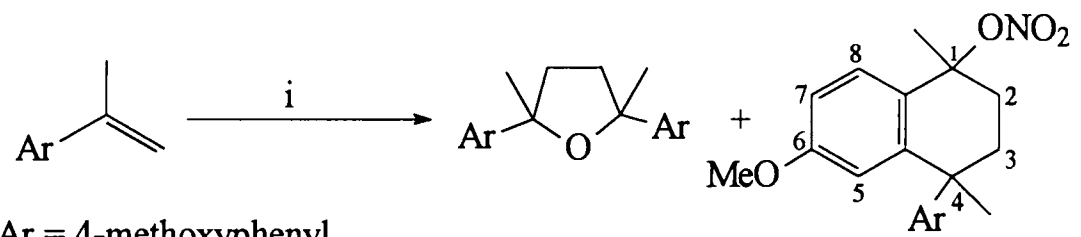
75 **78**

i) CAN / MeOH, 0 °C, 15 min., 50 %

Scheme 35

In the ^{1}H NMR spectrum, the tetrahydrofuran derivative **78** showed two triplets at δ 2.23 and 1.99 corresponding to the two methylene groups. The methyl groups resonated at δ 1.52 as a singlet. In the ^{13}C NMR the two quaternary carbons bonded to the THF oxygen were visible at δ 84.89 and the methylene carbons were discernible at δ 39.5 and 30.82. The structure was further confirmed by satisfactory elemental analysis.

The same reaction, when carried out in acetonitrile afforded the tetralin **79** along with the tetrahydrofuran **78** (Scheme 36).



Ar = 4-methoxyphenyl

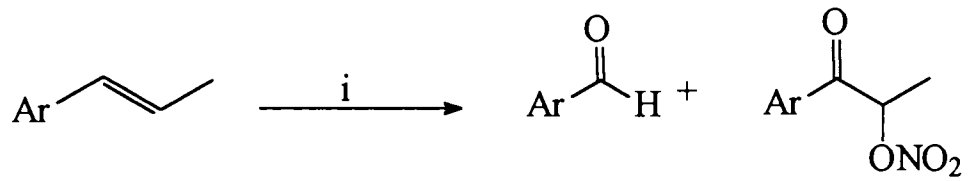
75 **78** (35 %) **79** (13 %)

i) CAN / MeCN, 0 °C, 15 min.

Scheme 36

The tetralin **79** was characterized by the usual spectral and analytical methods. The IR spectrum showed the characteristic C-ONO_2 stretching at 1640 cm^{-1}. In the ^1H NMR spectrum, the C-8 proton signal was visible at δ 7.96, the latter being deshielded by the -ONO_2 group. The two methyl groups resonated together as two overlapping singlets at δ 1.52. The structure was further confirmed by satisfactory elemental analysis.

When *β*-methyl-*p*-methoxystyrene **76** was treated with CAN in methanol, anisaldehyde was obtained in 40% yield. The same reaction when carried out in acetonitrile afforded phenacylnitrate **81** in 5% yield along with anisaldehyde (22 %) (Scheme 37).



Ar = 4-methoxyphenyl

76 **80** **81**

i) CAN / MeCN, 0 °C, 30 min.

Scheme 37

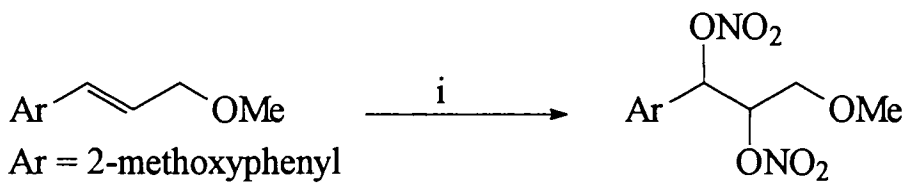
Entry	Conditions	80	81
1	CAN / MeOH, 0°C, 30 min.	40%	-
2	CAN / MeCN, 0°C, 30 min.	22%	5%

Table 7

The product **81** was characterized by the usual spectroscopic methods. The IR spectrum of **81** had the carbonyl stretching at 1683 cm^{-1} and the characteristic C-ONO_2 band at 1642 cm^{-1}. In the ^1H NMR, the proton geminal to the nitrate group resonated at δ 6.09 (q, 1H) and the methyl group appeared at δ 1.68 (d 3H). In the ^{13}C NMR spectrum, the carbon bonded to

the -ONO_2 group resonated at δ 78.74, the methyl was visible at δ 15.318 and the carbonyl carbon was seen at δ 192.708.

The 2-methoxycinnamyl methyl ether **77,** when treated with CAN in acetonitrile afforded the dinitrate **82** in 25% yield (Scheme 38). Similar dinitrates have been prepared by Baciocchi *et al.*[22]



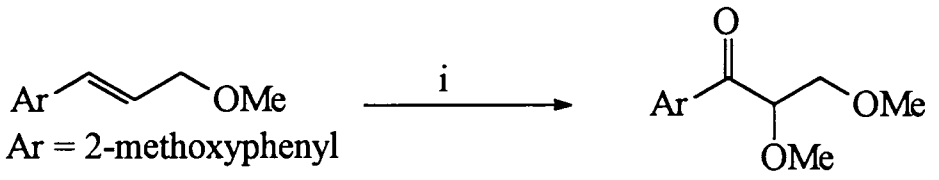
77 **82**(25%)

i) CAN / MeCN, 0 °C, 15 min.

Scheme 38

The IR spectrum of **82** displayed a strong band at 1640 cm^{-1}that can be attributed to the -ONO_2 group. In the ^1H NMR spectrum, the two protons geminal to the two -ONO_2 groups (one of which is also a benzylic proton) resonated at δ 6.48 (d , J = 6.4 Hz) and δ 5.74 as a multiplet. The two methylene protons appeared as multiplets at δ 3.47 and 3.60 in the ^1H NMR of **82.** In ^{13}C NMR, the two carbons bonded to the nitrate groups were visible at δ 79.719 and 77.098 and the methylene carbon appeared at δ 69.392. The structure of the dinitrate was further confirmed by the HRMS data.

The compound **77** on treatment with CAN in methanol afforded a ketomethoxy product **83** in 16% yield (Scheme 39).



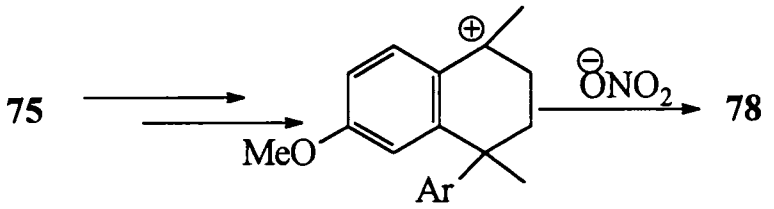
77 **83** (16%)

i) CAN / MeOH, 0 °C, 15 min.

Scheme 39

The compound **83** was characterized by the usual spectral methods. The IR spectrum of **83** displayed the band characteristic to the carbonyl group at 1694 cm^{-1}. In the ^{1}H NMR spectrum, the proton geminal to the methoxy group and the carbonyl carbon resonated at δ 4.93 as a doublet of doublet. The two methylene protons were visible as two multiplets at δ 3.69 and 3.56. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 199.622 and the carbon bonded to the methoxy group adjacent to the carbonyl group was seen at δ 85.831 and the methylene carbon appeared at δ 72.346.

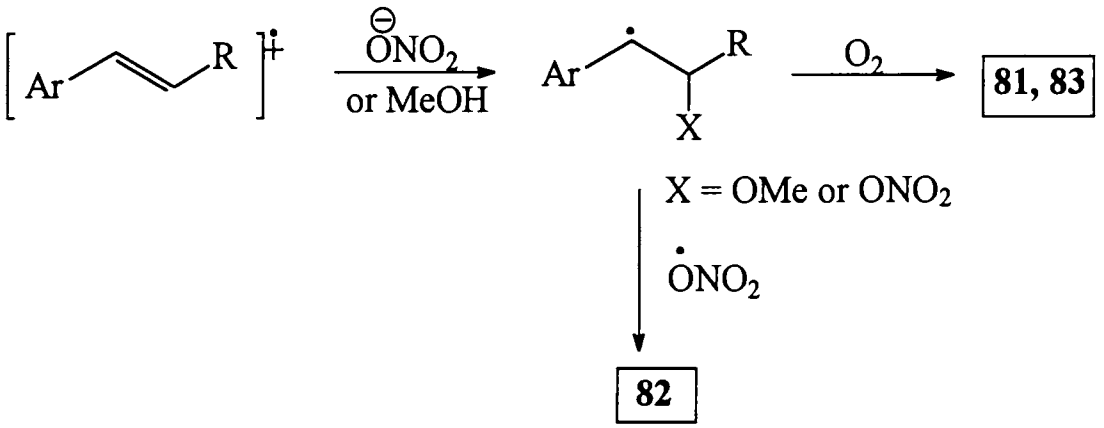
Mechanistically, the reactions described above can be rationalized by invoking a radical cation intermediate as discussed earlier (Section 2.2.2, Page 48). CAN on reaction with **75** can conceivably lead to an intermediate similar to **IX**, which can get transformed to **78**, by reaction with a nitrate anion from the solution.



Ar = 4-methoxyphenyl

Scheme 40

Similarly, an intermediate analogous to **V** derived from **75** can give rise to **79**. The products **80**, **81**, **82** and **83** can arise from an intermediate radical cation **IV** as shown earlier (Section 2.2.2, Page 48).



Scheme 41

The styrenes with β- substitution were not found to dimerize in presence of CAN. It may be due to the low reactivity of radical cations derived from the β-substituted methoxystyrene as shown by Johnston and Schepp.[20]

2.9. EXPERIMENTAL

2.9.1. General Procedure: A solution of CAN (1.5 mmols) in appropriate solvent (20 mL) was added dropwise to an ice cold solution of alkoxystyrene

(1 mmol) in the same solvent (20 mL). When the starting material was fully consumed (15 min.), as observed by tlc, the reaction mixture was diluted with water (150 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were pooled, washed with water, brine and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with an appropriate mixture of ethyl acetate and petroleum ether afforded the products.

2,5-Bis(4'-methoxyphenyl)-2,5-dimethyltetrahydrofuran (78)

To a solution of **75** (300 mg, 2.027 mmols) in methanol (20 mL), a solution of CAN (1.667g, 3.04 mmols) in methanol (20 mL) was added dropwise. On completion of the reaction, the reaction mixture was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 41 mg of **78** (13%).

Product 78

Colorless crystals; recrystallised from hexane - DCM.

m. p. : 135 - 137 °C

IR (KBr) ν_{max} : 2972, 1511, 1243, 1173, 1080, 1031, 830 cm^{-1}.

^1H NMR : δ 7.40 (d, J = 8.6 Hz, 4H, Ar<u>H</u>), 6.84 (d, J = 8.7 Hz, 4H, Ar<u>H</u>), 3.80 (s, 6H, O<u>Me</u>), 2.23 (m, 2H, C<u>H</u>$_2$), 1.99 (m, 2H, CH_2), 1.52 (s, 6H, C<u>H</u>$_3$).

^{13}C NMR : δ 157.951, 141.529, 125.852, 113.164, 96.074, 84.890, 55.024, 39.578, 30.824.

LRMS m/z (%) : M^+ 312.17 (3), 298.15 (20), 297.15 (100), 161.10 (9), 147.08 (14), 135.04 (51).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.88; H, 7.75. Found : C, 76.79; H, 8.41.

2,5-Bis(4'-methoxyphenyl)-2,5-dimethyltetrahydrofuran (78) and **4-(4'-Methoxyphenyl)-6-methoxy-1,4-dimethyltetralin-1-nitrate (79)**

To a solution of **75** (300 mg, 2.027 mmols) in acetonitrile (20 mL), a solution of CAN (1.667g, 3.04 mmols) in acetonitrile (20 mL) was added dropwise. On completion of the reaction, the reaction mixture was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 41 mg of **78** (13%). On further elution of the column using hexane : ethylacetate (90 : 10) afforded 127 mg of **79** in 35% yield.

Product 79

Colorless crystals; recrystallised from hexane - DCM.

m. p. : 143 -145 °C

IR (neat) ν_{max} : 2975, 2837, 1651, 1607, 1507, 1457, 1245, 1033, 827, 727 cm^{-1}.

^1H NMR : δ 7.956 (d, J = 1.7 Hz, 1H, ArH), 7.679 (dd, J = 2 Hz, 8.6 Hz, 1H, ArH), 7.37 (d, J = 8.5 Hz, 2H, ArH), 7.03 (d, J = 8.7 Hz, 1H, ArH), 6.83 (d, J = 8.58 Hz, 2H, ArH), 3.94 (s, 3H, OMe), 3.79 (s, 3H, OMe), 2.24 (m, 2H, CH_2), 2.035 (m, 2H, CH_2), 1.519 (s, 6H, CH_3).

^{13}C NMR 158.148, 151.305, 142.242, 140.838, 139.326, 130.446, 125.784, 122.147, 113.312, 113.058, 85.499, 84.156, 56.437, 55.080, 39.540, 39.359, 30.808, 30.558.

Anal. Calcd for $C_{20}H_{23}O_5$: C, 67.21; H, 6.49; N, 3.92. Found : C, 67.30; H, 6.52; N, 3.95.

4-methoxybenzaldehyde (80) and **1-(4-methoxyphenyl)-2-nitratepropan-1-one (81)**

To a solution of **76** (300 mg, 2.027 mmols) in acetonitrile (20 mL), a solution of CAN (1.667g, 3.04 mmols) in acetonitrile (20 mL) was added dropwise. The mixture, on completion of the reaction, was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 23 mg of **81** (5%).

Product 81

Colorless oil

IR (neat) ν_{max} : 2937, 1688, 1640, 1599, 1266, 1236 cm^{-1}.

^1H NMR : δ 7.969-7.939 (d, 2H; ArH), 7.006-6.976 (d, 2H, ArH), 6.132-6.061 (q, 1H, CHONO$_2$), 3.841 (s, 3H, OMe), 1.607-1.583 (d, 3H, CHCH$_3$).

^{13}C NMR : δ 192.708, 164.38, 130.764, 126.205, 114.262, 78.74, 55.541, 15.318.

On further elution of the column using hexane : ethylacetate (90 : 10) afforded 60 mg of **80** in 22 % yield.

Methyl-3-(2'-methoxyphenyl)-2,3-dinitratepropylether (82)

To a solution of **77** (300 mg, 1.68 mmols) in acetonitrile (20 mL), a solution of CAN (1.4 g, 2.52 mmols) in acetonitrile (20 mL) was added dropwise. The reaction mixture, on completion was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (95 : 5) afforded 126 mg of **82** (25%).

Product 82

Colorless oil.

IR (neat) ν_{max} : 2935, 1640, 1276, 845, 757 cm^{-1}.

^1H NMR : δ 7.355 (m, 2H, ArH), 6.97 (m, 2H, ArH), 6.48 (d, 1H, $CHONO_2$), 5.74 (m, 1H, $CHONO_2$), 3.896 (s, 1H, ArOMe), 3.60 (m, 1H, CH_2OMe), 3.47 (m, 1H, CH_2OMe), 3.30 (s, 3H, CH_2OMe).

^{13}C NMR : δ 156.793, 131.085, 128.001, 121.125, 111.144, 79.719, 77.098, 69.392, 59.354, 55.800.

LRMS : M^+ 302 (8), 182.045 (10), 151.076 (12), 137.057 (15), 136.052 (100), 135.044 (36), 119.49 (30), 118.041 (35), 107.05 (14).

HRMS Calcd for $C_{11}H_{14}N_2O_8$: 302.07501. Found : 302.07488.

Methyl-3-(2'-methoxyphenyl)-2-methoxy-3-oxopropylether (83)

To a solution of **77** (300 mg, 1.68 mmols) in methanol (20 mL), a solution of CAN (1.4 g, 2.52 mmols) in methanol (20 mL) was added dropwise. The reaction mixture, on completion was processed as described in the general procedure. Column chromatography on silica gel using hexane : ethylacetate (90 : 10) afforded 60 mg of **83** (16%).

Product 83

Colorless oil.

IR (neat) ν_{max} : 2942, 1694, 1479, 1249, 1128, 778 cm^{-1}.

^1H NMR : δ 7.702-7.672 (m, 1H, ArH), 7.514-7.462 (m, 1H, ArH), 7.056-6.961 (m, 2H, ArH), 4.945-4.917 (dd, 1H, CHOMe), 3.927 (s, 3H, ArOMe), 3.716-3.673 (m, 1H, CH_2OMe), 3.596-3.532 (m, 1H, CH_2OMe).

^{13}C NMR : δ 199.622, 157.793, 133.507, 130.106, 20.708, 111.191, 85.831, 72.346, 58.950, 58.055, 55.220.

2.10. REFERENCES

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CHAPTER 3

A FACILE CAN MEDIATED TRANSFORMATION OF ACETOACETAMIDES TO OXAMATES

3.1. INTRODUCTION

As described in chapter 1, carbon-carbon bond forming reactions involving radicals generated by one electron oxidants are of topical interest. It has already been pointed out that among the one electron oxidants, cerium (IV) ammonium nitrate (CAN) holds considerable synthetic potential for the future as it has been shown to be an exceptionally useful reagent for accomplishing intermolecular C-C bond formation.[1 - 4.] Naturally it was of interest to probe the effectiveness of CAN in intramolecular reactions. It may be recalled that other one electron oxidants have been used for carrying out intramolecular reactions for constructing a variety of interesting carbocycles and heterocycles[5].

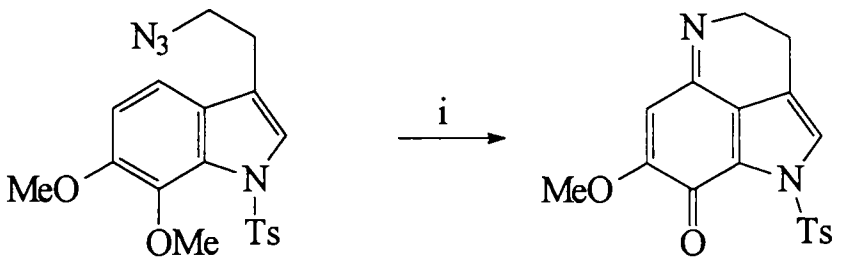
3.1.1. Intramolecular cyclization reactions

To put the work presented in this chapter in perspective, a brief and selective account of the literature concerning intramolecular cyclization reactions mediated by commonly used one electron oxidants is given along with a comprehensive survey of CAN mediated cyclizations. It is noteworthy that there are only a few literature reports on the latter.

3.1.1.1. Intramolecular reactions mediated by common one-electron oxidants

One electron oxidants such as Mn(III), Fe(III), Cu(II) and V(V) salts have been used in the construction of organic molecules by intramolecular reactions. Representative examples are given below.

A direct synthesis of pyrroloiminoquinones from indoles has been developed by Kita by intramolecular cyclization using phenyl iodine (III) bis(trifluoroacetate) (PIFA) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 1)[6].

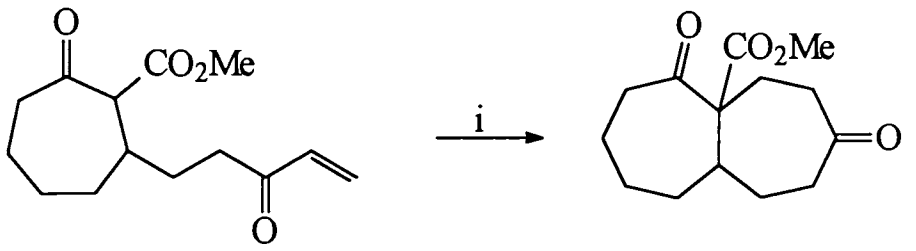


1 **2**

i) PIFA-TMSOTf, $(CF_3)_2CHOH$ - H_2O (50 : 1), 61%

Scheme 1

Intramolecular Michael reaction under mild conditions catalyzed by Fe (III) has been reported (Scheme 2).[7]



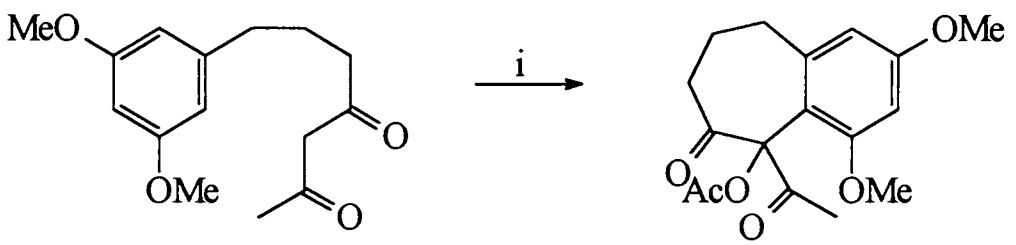
3 **4**

i) 5 mol% $FeCl_3.6H_2O$, r. t., 12h, DCM, 80%

Scheme 2

Manganese (III) acetate has been used in a number of annulation reactions. Two such oxidative cyclizations are given below as representative examples.

ε-(3,5-dialkoxy substituted) aryl-β-diketone **5** on treatment with anhydrous Mn (III) acetate in acetic acid at 60 °C afforded acetoxylated tetrahydrobenzocycloheptanone **6** (Scheme 3).[8]



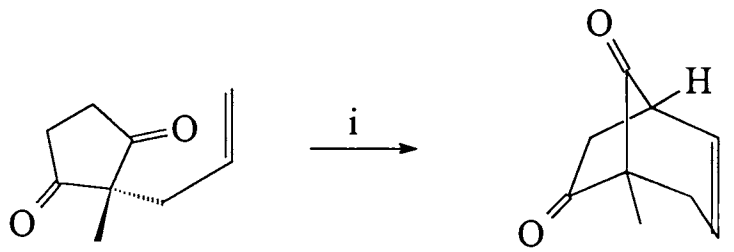
5 **6**

i) $Mn(OAc)_3$, AcOH, 22h, argon, 60 °C, 66%

Scheme 3

Snider[9] has reported the oxidative cyclization of 2-allyl-1,3-cycloalkanediones mediated by $Mn(OAc)_3$ in presence of $Cu(OAc)_2$. For

example oxidative cyclization of 2-allyl-2-methylcyclopentane-1,3-dione **7** in acetic acid at 80° C provides 75% of **8** as the major product (Scheme 4).

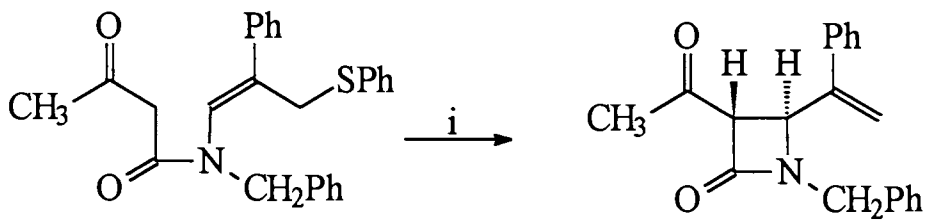


7 **8**

i) 2 $Mn(OAc)_3$, $Cu(OAc)_2$, AcOH, 80° C, 75%.

Scheme 4

Annibale and coworkers[10] have reported a Mn(III) promoted sulfur directed 4-*exo-trig* radical cyclization of enamides to *β*-lactams (Scheme 5).

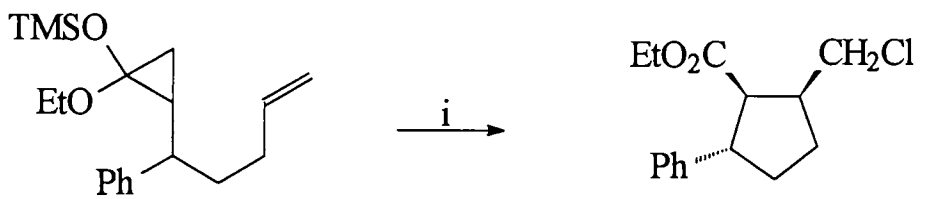


9 **10**

i) $Mn(OAc)_3$, AcOH, 70 ° C, 30 min., 58%.

Scheme 5

A representative example[11] involving Fe(III) is given in scheme 6.



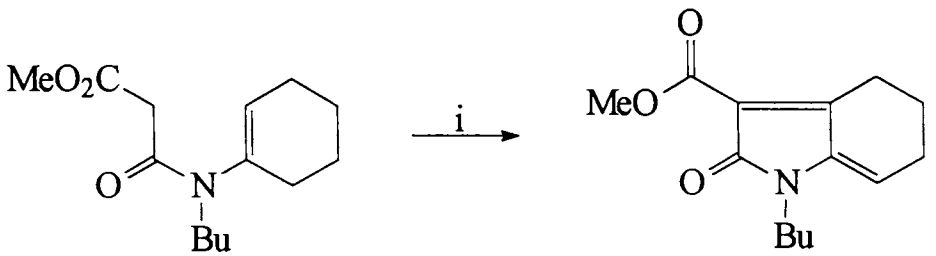
17:1 diastereoselectivity

11 **12**

i) $FeCl_3$, DMF, 0 °C, 57%

Scheme 6

Parsons[12] has shown that when N-acylenamine **13** was treated with $Mn(OAc)_3$, oxidative cyclization occurred in 52% yield to afford the pyrrolidinone **14** (Scheme 7).



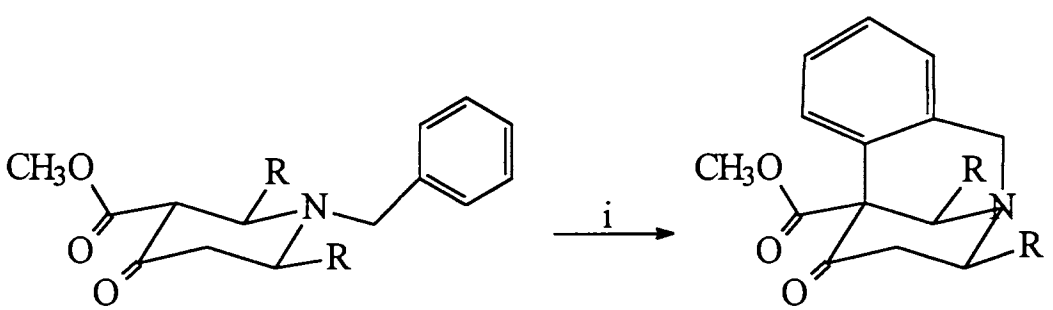
13 **14**

i) $Mn(OAc)_3.2H_2O$, MeOH, reflux, 52%

Scheme 7

3.1.1.2. Reactions mediated by Ce (IV) Reagents

In contrast to the widespread use of Mn(III) in intramolecular reactions, there are only a few examples involving Ce (IV) reagents. The available reports are briefly discussed here. The earliest report on Ce (IV) promoted intramolecular reaction is the cyclization of 1-benzyl-2,6-bis[2'-*pyridyl]-4-piperidone-3-carboxylic acid methyl ester* **15** *by* $Ce(SO_4)_2$ *in 20 % yield (Scheme 8).*[13]



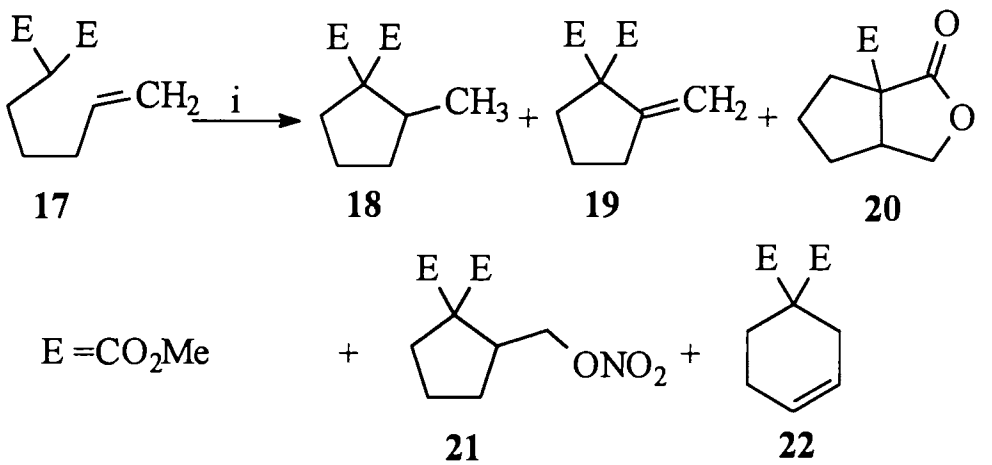
R=2-pyridyl R=2-pyridyl

15 **16**

i) $Ce(SO_4)_2$, 20%

Scheme 8

Baciocchi has reported a study of CAN induced cyclization of dimethyl-4-pentenyl malonate leading to a mixture of products (Scheme 9).[14]

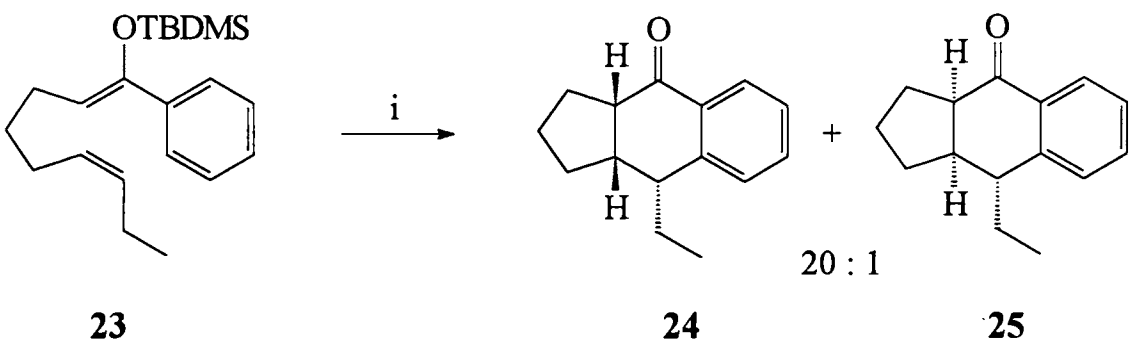


17 18 19 20 21 22

i) CAN, MeOH

Scheme 9

Oxidative cyclization of δ,ε- and ε,ζ-unsaturated enolsilylethers by CAN resulting in tricyclic ketones **24** and **25** in good yields and excellent stereocontrol has been reported by Snider (Scheme 10).[15]

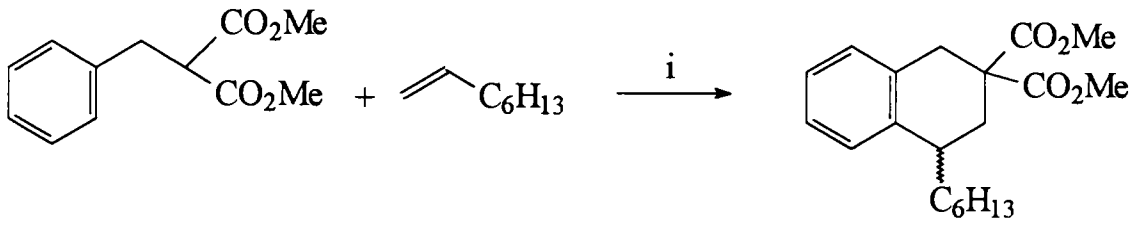


23 24 25

i) CAN, $NaHCO_3$, CH_3CN, 25 °C, 73%

Scheme 10

Citterio[16] has reported CAN mediated tandem annulation reactions. A representative example is given in scheme 11.

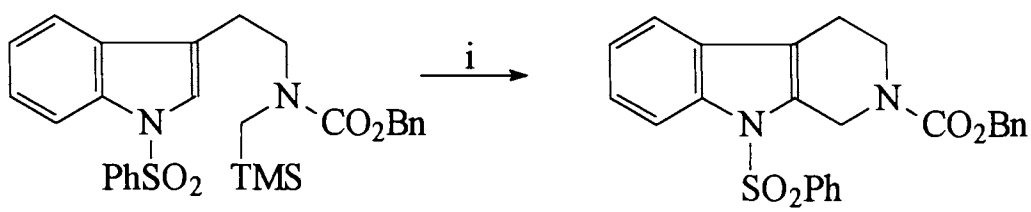


26 **27** **28**

i) CAN, MeOH, 90%

Scheme 11

A CAN mediated Pictet - Spengler type cyclization of N-blocked tryptamine derivative **29** leading to the indolopiperidine **30** in 86% yield has been reported (Scheme 12).[17]

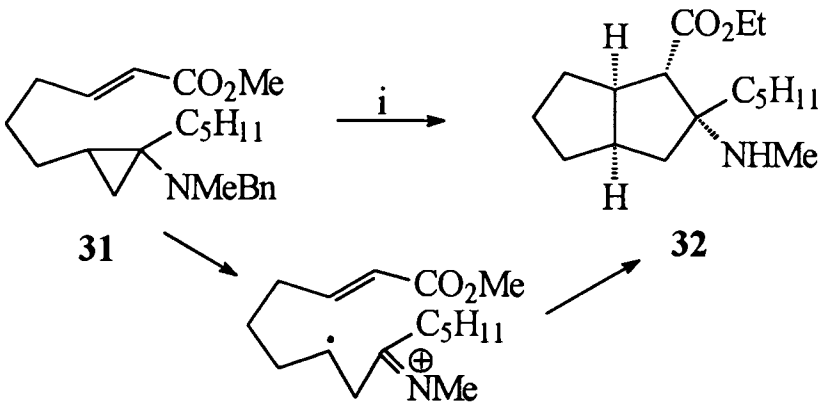


29 **30**

i) CAN, MeOH, 86%

Scheme 12

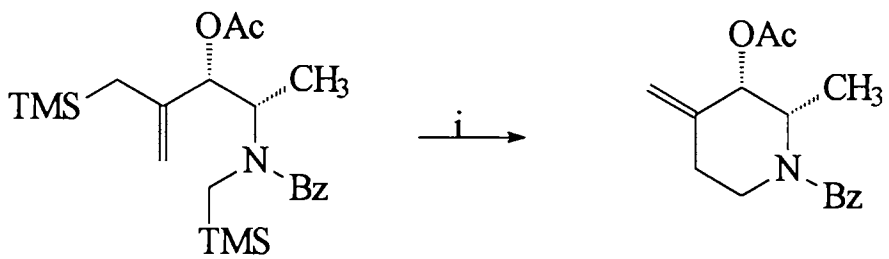
CAN mediated tandem *5-exo*-cyclization of tertiary aminocyclopropanes with an internal alkene has been reported. Single electron oxidation of the tertiary aminocyclopropane **31** generates the distonic iminium radical cation, which is trapped by the α,β-unsaturated ester resulting in a [3+2] cycloaddition (Scheme 13).[18]



i) CAN, $NaHCO_3$, DMF, r. t., 77%

Scheme 13

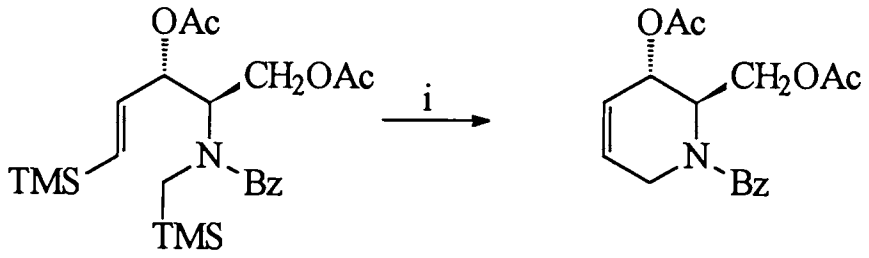
CAN mediated Mannich cyclization of iminium salts which contain N-linked 1-(trimethylsilyl)buten-4-yl and 2-[(trimethylsilyl)methyl]buten-4-yl groups affords piperidine rings. As shown in schemes 14 and 15, reactions of these substrates led to regiocontrolled production of piperidines possessing either *exo* (**34**) or *endo* (**36**) cyclic unsaturation.[19]



33 **34**

i) CAN, MeCN, 67%

Scheme 14

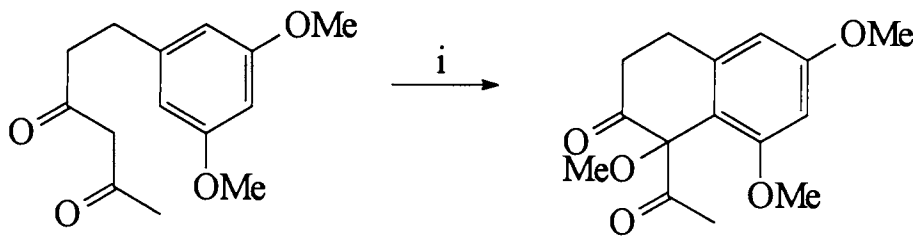


35 **36**

i) CAN, MeCN, 46%

Scheme 15

Rickards has shown that 6-aryl-β-dicarbonyl compounds carrying electron releasing groups on the aromatic ring undergo efficient radical mediated oxidative cyclization to α-methoxylated-β-tetralones in presence of CAN in methanol (Scheme 16).[20]



37 **38**

i) CAN, MeOH, 80%

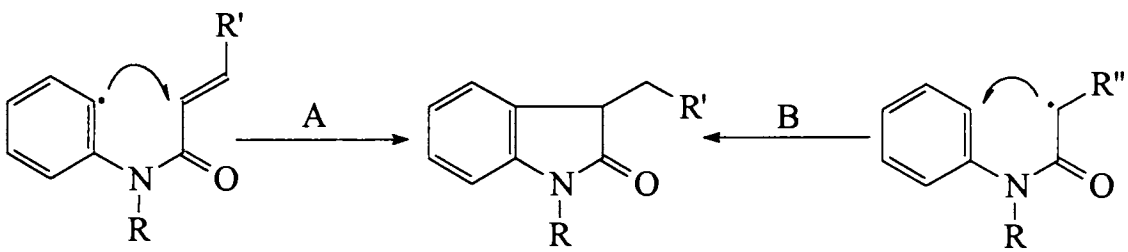
Scheme 16

In view of the limited amount of work in this area and in the context of our general interest in the synthetic utility of CAN, it was decided to explore the reactivity of CAN in intramolecular cyclization.

The reaction of acetoacetanilide with CAN offers the possibility of a facile oxindole synthesis and therefore we decided to study this system.

3.1.2. Introduction to Indolones (Oxindoles)

Interest in indolones (oxindoles) derives not only from the biological activity displayed by some members of the family[21] but also from the fact that they are immediate precursors to important indole derivatives. Most synthetic routes to indolones rely on ionic processes, especially variants of the Friedel Crafts reaction.[22] Radical reactions in this area have had a relatively limited impact, since practically all such approaches involve the use of *o*-bromo(or *o*-iodo)phenylacrylamides,[23] as depicted in scheme 17 (path A).



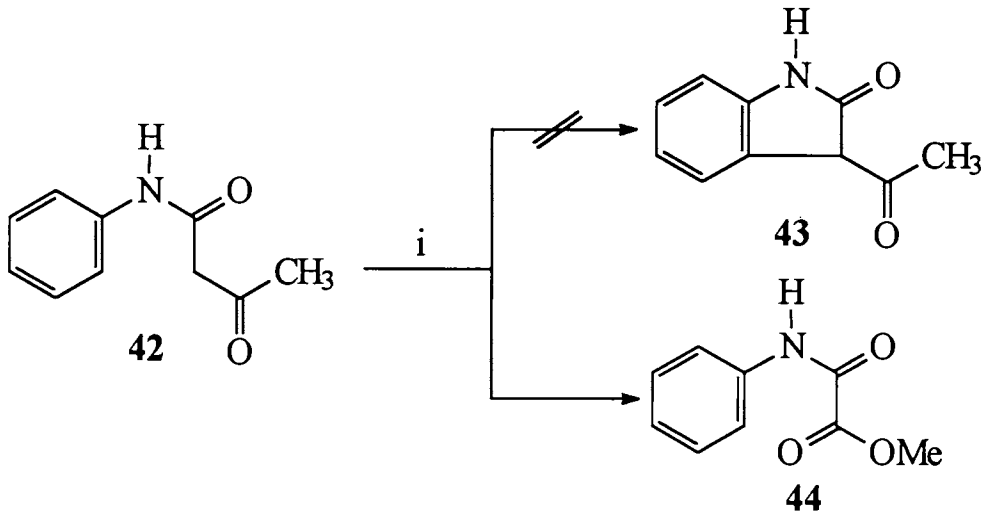
39 **40** **41**

Scheme 17

Except for the simplest members, these starting materials are of limited access. The potentially more flexible route through radical cyclization onto the aromatic ring (Scheme 17, path B) turns out to be quite difficult to accomplish in practice by the usual methods (e.g. stannane chemistry) because the cyclization[24] step is relatively slow as compared with other reactions open to the radical species.

Against the background presented and with the expectation that an oxindole **43** would be the product, acetoacetanilide **42** was treated with CAN in methanol. In the event, no cyclization occurred and an oxidative

transformation of **42** leading to the oxamate **44** was the only discernible reaction (Scheme 18).



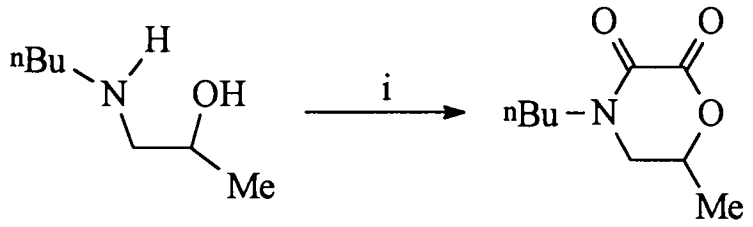
i) CAN, MeOH, r. t., 15 min., 51%

Scheme 18

3.1.3. Introduction to Oxamates

Although the expected reaction did not occur, the facility with which the oxamate was formed was impressive. Therefore we decided to study this reaction in detail. To put the present work in perspective, the existing methods for the synthesis of oxamates are outlined below.

Carbonylation of aminoalcohols using Pd (II) catalyst has been reported (Scheme 19).[25] These catalytic carbonylation reactions require the use of carbon monoxide and most of them are not suitable since monocarbonylation seriously inhibits the desired reaction.

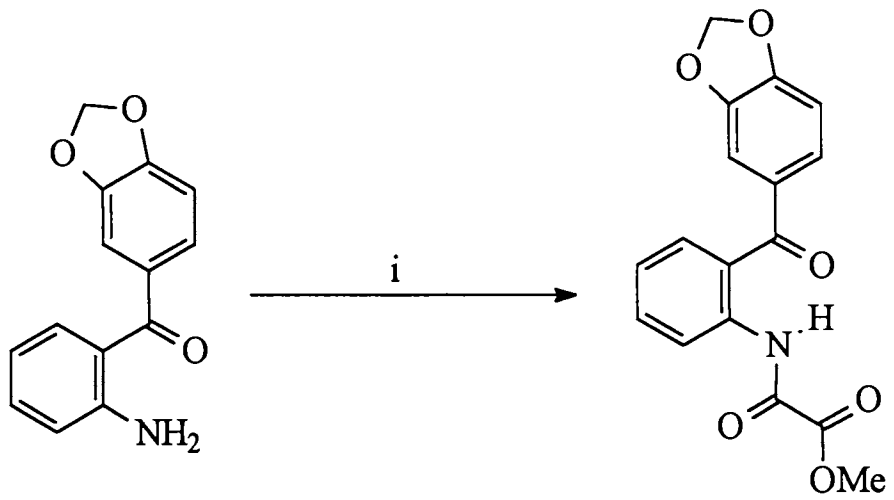


45 **46**

i) CO, $PdCl_2$, DME, NaOAc, r. t., overnight

Scheme 19

In view of the lack of selectivity of direct carbonylation methods, reaction between amines and oxalyl chloride is widely used[26, 27] and this allows access to a variety of dicarbonyl compounds. A representative example is given in scheme 20.



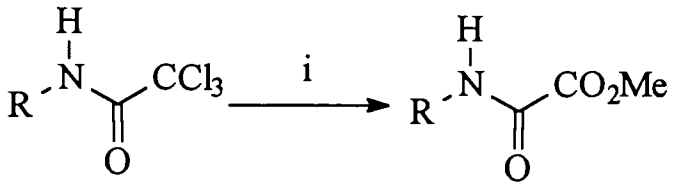
47 **48**

i) $CH_3OCOCOCl$, DCM, Py, r. t., 77%

Scheme 20

The use of oxalyl chloride produces hydrochloric acid and its trapping requires bases, which are not compatible with some pharmaceutical

syntheses. Oxamates can also be obtained in low yields by photoinduced alcoholysis of trichloroacetoanilides (Scheme 21).[28]

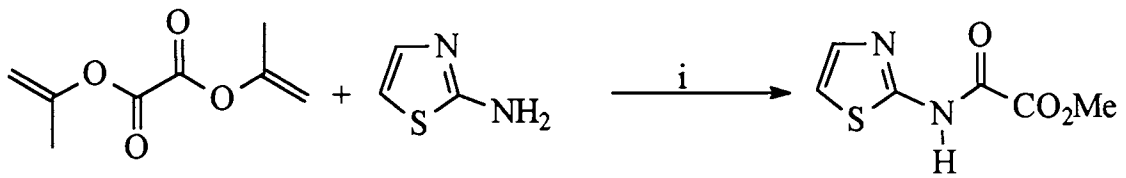


49 **50**

i) hν, MeOH

Scheme 21

A general synthesis of oxamates involves the reaction of amines and diisopropenyl oxalate in methanol (Scheme 22).[29]



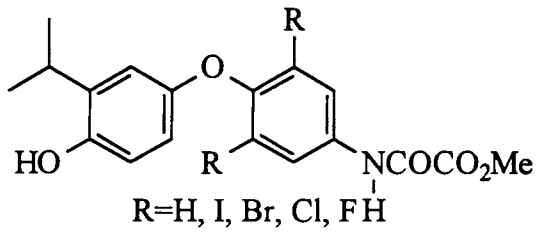
51 **52** **53**

i) MeOH, r. t., 5h, 87%

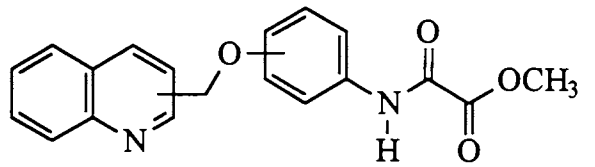
Scheme 22

The major disadvantage of this method is that the starting material, diisopropenyloxalate **51** is not easily accessible.

It is clear from the above discussion that there is scope for newer methods of oxamate synthesis. It is noteworthy that oxamate functionality is present in a number of therapeutically important compounds like **54** and **55** (Figure 1).[30, 31]



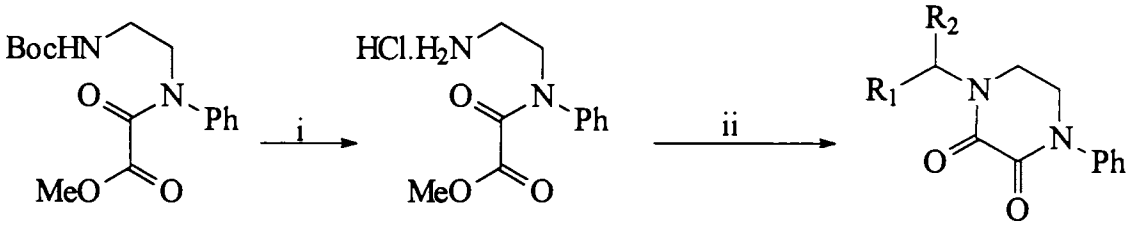
54



55

Figure 1

In addition they serve as key intermediates in the synthesis of bioactive 2,3-diketopiperazines (Scheme 23).[32]



56 57 58

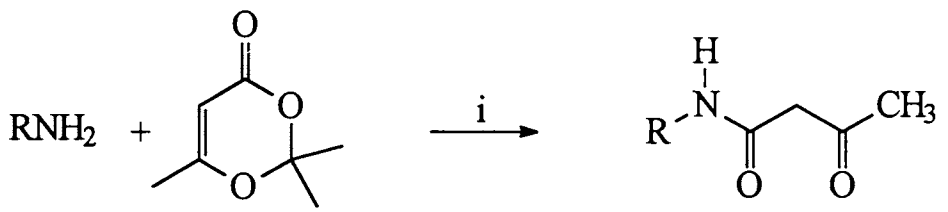
i) HCl ii) R_1COR_2, $Na(AcO)_3BH$

Scheme 23

As already alluded, the facility of formation of the oxamate in the reaction of acetoacetanilide with CAN prompted us to examine the generality of the reaction from the vantage point of using it as a synthetic method for oxamates and the results are presented in the following section.

3.2. RESULTS AND DISCUSSION

The starting materials for the study *viz.*, the acetoacetamides **61,** were obtained in good yields by reacting 2,2,6-trimethyl-1,3-dioxin-4-one **60** and the corresponding amine **59** in refluxing xylene[33] (Scheme 24).



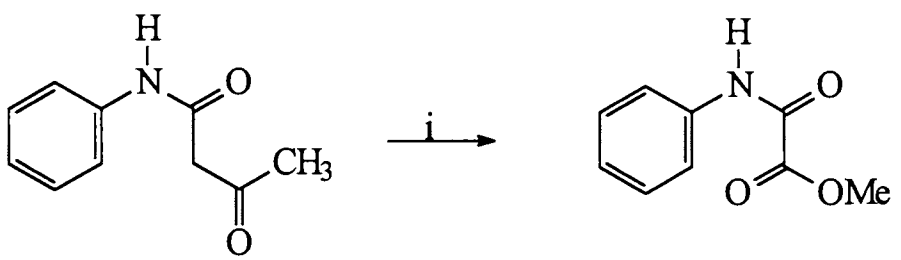
59 **60** **61**

i) Xylene, reflux, 3 - 4 h

Entry	Amine	Acetoacetamide (Yield %)
1.	59a R= *p*-methylphenyl	61a (83)
2.	59b R= *o*-carbomethoxyphenyl	61b (85)
3.	59c R = benzyl	61c (92)
4.	59d R= cyclohexyl	61d (89)
5.	59e R= *p*-methoxyphenyl	61e (73)
6.	59f R= *m*-bromophenyl	61f (95)
7.	59g R= *p*-chlorophenyl	61g (83)
8.	59h R= *o*-methylphenyl	61h (80)

Scheme 24

Our studies were initiated by treating acetoacetanilide **42** in methanol with a methanolic solution of CAN. This reaction afforded the oxamate **44** in 51% yield (Scheme 25).



42 **44**

i) CAN, MeOH, 15 min., r. t., 51%

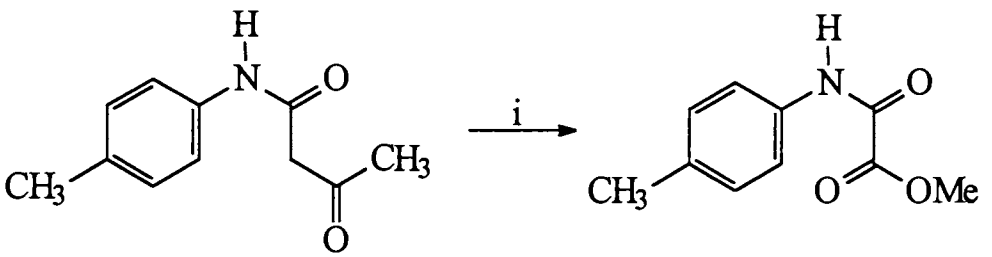
Scheme 25

The product **44** was purified by column chromatography and characterized by spectral analysis. The IR spectrum of **44** showed the

absorptions characteristic to -NH, -CO_2Me and -CONH at 3346, 1728 and 1701 cm^{-1} respectively. In the ^{1}H NMR spectrum, the NH proton appeared at δ 8.889 as a broad singlet (exchangeable with D_2O). The aromatic protons were visible as a doublet for two protons at δ 7.64, as a multiplet for two protons at δ 7.38 and as a multiplet at δ 7.21 for one proton. The methyl protons of ester appeared as a singlet at δ 3.98. In the ^{13}C NMR spectrum, the two carbonyl carbons were discernible at δ 161.449 and 153.779 and the methoxy carbon was seen at δ 53.953. The EIMS data was also in agreement with the assigned structure.

The yield of the oxamate **44** was found to increase to 70% when the addition of CAN to acetoacetanilide **42** was done in an atmosphere of oxygen. Mechanistically, this observation can be rationalized by assuming that the methine radical formed by the action of Ce(IV) on **42,** is being trapped by molecular oxygen and the resulting peroxy radical undergoes further transformation leading to the oxamate **44**. (See page 109 for a detailed discussion on the mechanism of the reaction).

Treatment of *p*-methylacetoacetanilide **61a** with CAN in methanol afforded the oxamate **62** in 40% yield. The reaction when carried out in presence of oxygen afforded the oxamate in 84% yield (Scheme 26).



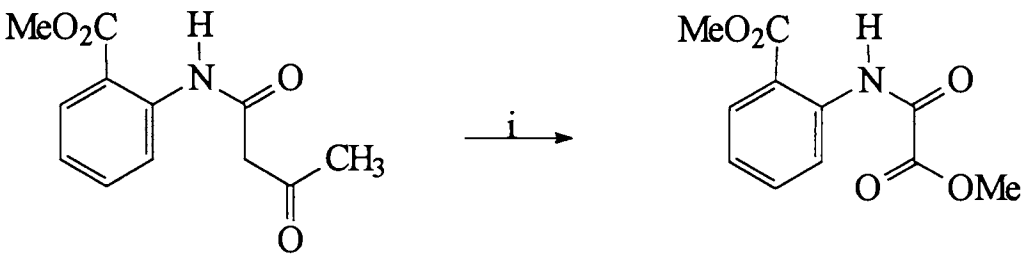
61a **62**

i) CAN, MeOH, O_2, 15 min., r. t., 84%

Scheme 26

The product **62** was characterized on the basis of spectral and analytical data. The IR spectrum of **62** showed the NH stretching at 3337, the ester carbonyl at 1729 and the amide carbonyl at 1700 cm^{-1} respectively. In the ^1H NMR, the methoxy protons appeared as a sharp singlet at δ 3.954 and the NH proton was visible at δ 8.874 (exchangeable with D_2O). In the ^{13}C NMR spectrum, carbonyl carbons appeared at δ 161.523 and 153.348. The elemental analysis was in agreement with the assigned structure.

The reaction appeared general for *para*- as well as *ortho*-substituted acetoacetanilides. A representative example is *o*-carbomethoxy acetoacetanilide **61b**. This on treatment with CAN in methanol afforded the oxamate **63** in 45% yield. When the reaction was done in oxygen atmosphere the corresponding oxamate **63** was obtained in 70% yield (Scheme 27).



61b **63**

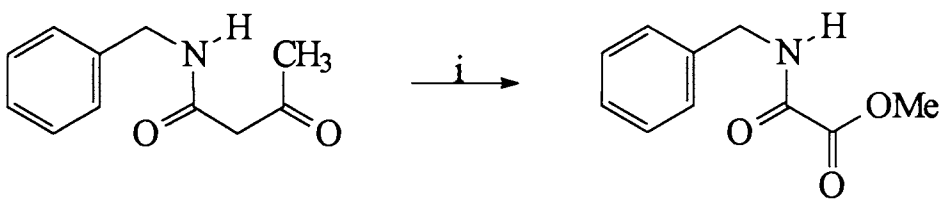
i) CAN, MeOH, O_2, 15 min, r. t., 70%

Scheme 27

The product **63** was characterized by the usual spectral and analytical methods. The NH stretching appeared as a sharp band at 3259 cm^{-1} and the ester and the amide carbonyls appeared as two sharp signals at 1729 and 1702 cm^{-1} respectively in the IR spectrum. In the ^1H NMR, spectrum the -NH proton was visible as a broad singlet at δ 12.59 (exchangeable with

D_2O). The two methoxy groups were discernible as two sharp singlets at δ 4.00 and 3.985. In the ^{13}C NMR, the three carbonyls resonated at δ 168.067, 161.060 and 154.335 respectively. The elemental analysis data was also in agreement with the proposed structure.

This reaction was found to work well with aliphatic systems also. For instance, benzylacetoacetamide **61c** when treated with CAN in methanol in presence of oxygen transformed smoothly into the corresponding oxamate **64** in 83% yield (Scheme 28).



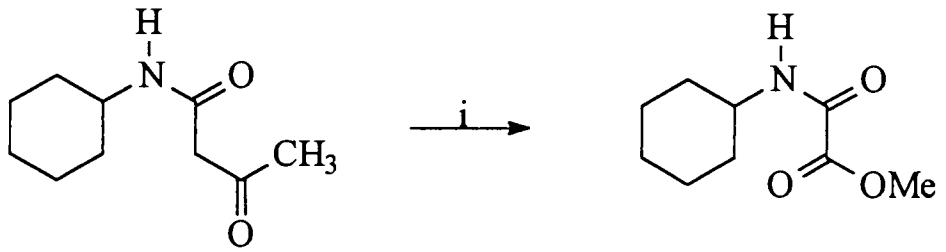
61c **64**

i) CAN, MeOH, O_2, 15 min., r. t., 83%

Scheme 28

The characterization of the product **64** was done by the usual spectral methods. In the IR spectrum of **64,** the NH stretching appeared at 3270 and the carbonyls were visible at 1738 and 1682 cm^{-1}. The ^1H NMR spectrum of **64** showed the -NH protons at δ 7.395 (exchangeable with D_2O) as a broad singlet and the benzylic protons were observed at δ 4.5 as a doublet with a *J* value of 6 Hz. The methyl ester protons were discernible as a singlet at δ 3.89. ^{13}C NMR showed the amide and the ester carbonyls at δ 161.120 and 156.07 respectively.

Similar reactivity was shown by cyclohexyl acetoacetamide **61d**. This when treated with CAN in methanol in an atmosphere of oxygen, efficiently transformed into the corresponding oxamate **65** in 88% yield (Scheme 29).



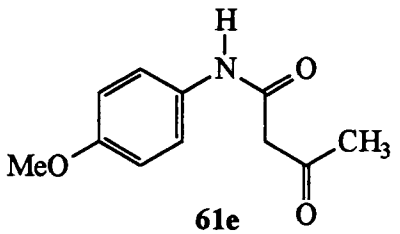
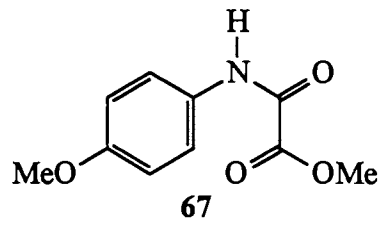
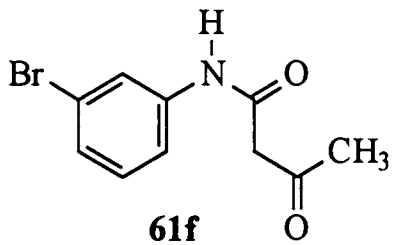
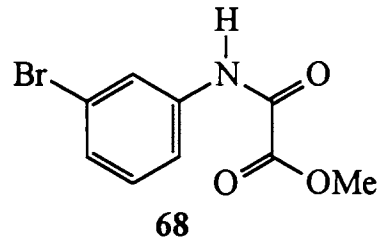
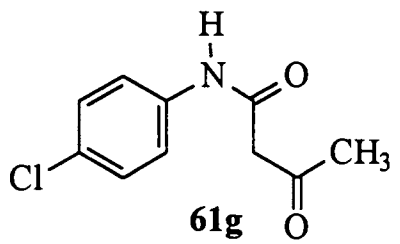
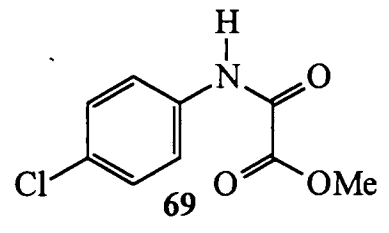
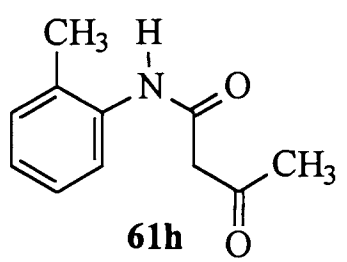
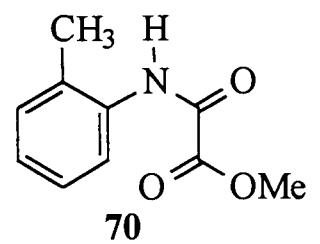
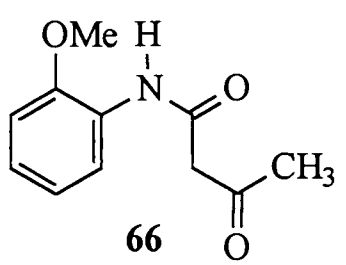
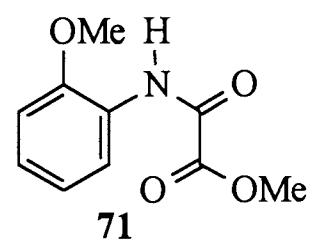
61d **65**

i) CAN, MeOH, O_2, 15 min., r. t., 88%

Scheme 29

The product **65** was characterized by the usual spectral and analytical data. The band characteristic to -NH was observed at 3267 cm^{-1} in the IR spectrum. A broad band was observed at 1742 cm^{-1} in the IR spectrum due to the overlapping of the ester and amide carbonyls. In the ^1H NMR, the -NH proton resonated at δ 6.963 as a broad singlet and the protons on the methyl ester were visible at δ 3.89 as a singlet. In the ^{13}C NMR spectrum, the amide and ester carbonyls resonated at δ 161.555 and 155.211 respectively. The structure was further supported by HRMS.

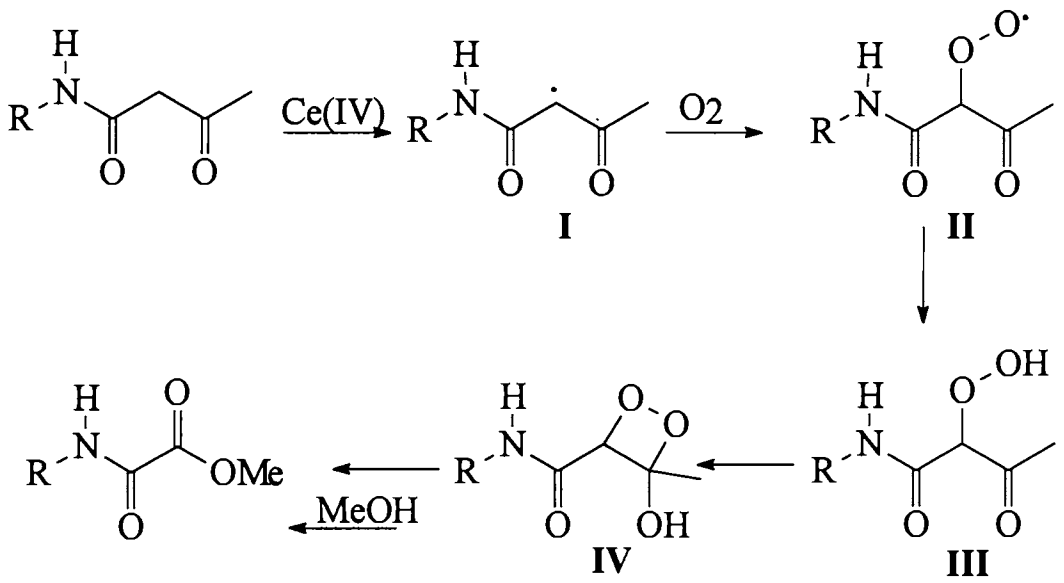
Along with the representative examples discussed, a number of acetoacetamides (**61e - h, 66**) were subjected to similar conditions and the corresponding oxamates (**67 - 71**) were obtained in good yields and are characterized by the usual spectral and analytical methods. The results are summarized in Table 1.

Entry	Acetoacetanilide	Oxamate	Yield %
1.	 **61e**	 **67**	78 (52)
2.	 **61f**	 **68**	77 (40)
3	 **61g**	 **69**	74 (45)
4.	 **61h**	 **70**	85 (50)
5.	 **66**	 **71**	83 (55)

a) CAN / MeOH / O_2, r. t., 15 min. Yields in brackets are those obtained without purging oxygen.

Table 1

Mechanistically this reaction can be rationalized along the following lines (Scheme 30). Oxidation of the 1,3-dicarbonyl system by CAN would conceivably lead to the radical **I**. The latter can trap oxygen[34] leading to the hydroperoxide **III**, which can lead to the dioxetane **IV**. Fragmentation of the dioxetane to the aldehyde and oxidation of the latter in methanol can ultimately lead to the oxamate. Brimble[5c] and others[35] have invoked similar mechanistic rationale to account for the oxidation of 1,3-dicarbonyl systems.



Scheme 30

The peroxy radical **II**, in principle, can abstract a hydrogen from the substrate thus allowing a catalytic cycle to operate. However, there is no evidence for a catalytic process and it has been confirmed that two equivalents of CAN are required for the completion of the reaction. In experiments using less than two equivalents of CAN, a proportionate amount of substrate remains unchanged. This may be rationalized by invoking the possibility that the peroxy radical is more likely to abstract the C-H proton

from methanol, in a process assisted by CAN which is known to form a complex with methanol.

It is noteworthy that when the experiment was performed in the absence of oxygen, oxamate formation was not observed; instead, a product identified as the dimer of the starting material was isolated.

In conclusion, we have encountered a very facile route to the synthesis of oxamates which may be of potential value in the synthesis of bioactive compounds.

3.3. EXPERIMENTAL

General information about the experimental is given in Chapter 2 (Section 2.3.1.). 2,2,6-Trimethyl-1,3-dioxin-4-one used for the reactions was purchased from Aldrich Co. and was used without purification. Substituted acetoacetamides except **42** and **66** were prepared from substituted amines.[33] **42** and **66** were purchased from É. Merck. Co.

3.3.1. Synthesis of Acetoacetamides from Amines[33] : General Procedure

A solution of amine (1 mmol) (1.2 mmols) in 3 mL dry xylene was heated at 140° C for 3 h. The crude product was chromatographed on silica gel using hexane - ethylacetate as the eluent to afford the acetoacetamides in 73 - 95% yields as colorless solids. These were crystallized from CH_2Cl_2 – hexane mixture.

3.3.2. Synthesis of Oxamates from acetoacetamides: General Procedure

A solution of CAN (2.3 mmols) in methanol (20 mL) was added dropwise to a stirred solution of acetoacetamide (1 mmol) in methanol (20 mL). When the starting material was fully consumed (15 min.), as observed by tlc, the reaction mixture was diluted with water (150 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic extracts were pooled, washed with water, brine and dried over sodium sulfate. The solvent was removed on a rotary evaporator and the residue was subjected to column chromatography on silica gel. Elution with an appropriate mixture of ethyl acetate and petroleum ether afforded the oxamate in moderate yields (45-55%) as colorless solids and these were crystallized from DCM – hexane mixtures.

3.3.3. Synthesis of oxamates from acetoacetamides in presence of oxygen : General procedure

To a solution of acetoacetamide (1 mmol) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.3 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously being purged with oxygen. The reaction mixture, on completion of the reaction, was processed as described in the general procedure given above. The oxamates were obtained in high yields (70 – 88 %).

Methyl-N-phenyloxamate (44)[36]

To a solution of **42** (500 mg, 2.82 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (3.8 g, 6.9 mmols) in

methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 350 mg (70 %) of the oxamate **44**.

Product 44

White crystals; recrystallised from hexane - DCM.

m. p. : 111-113 °C

IR (KBr)ν_{max} : 3346, 1728, 1701, 1600, 1539, 1444, 1294, 760 cm^{-1}.

^1H NMR : δ 8.889 (brs, 1H, NH, exchangeable with D_2O), 7.64 (d, 2H, J = 8.1 Hz, ArH), 7.38, (m, 2H, ArH), 7.21 (m, 1H, ArH), 3.981 (s, 3H, OMe).

^{13}C NMR :δ 161.449, 153.779, 136.355, 129.166, 125.546, 119.983, 53.953.

EIMS m/z (%) : M^+ 179.17 (100), 178 (9.7), 118 (7.5), 65(7.4), 39 (19).

Methyl-N-(4-methylphenyl)oxamate (62)

To a solution of **61a** (280 mg, 1.46 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2 g, 3.65 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 238 mg (84%) of the oxamate **62**.

Product 62

White crystals; recrystallised from hexane - DCM.

m. p. : 145 - 147 °C

IR (KBr) ν_{max} : 3337, 1729, 1700 1535, 1299, 1288, 1166, 820, 718, 489 cm^{-1}.

^{1}H NMR : δ 8.87 (brs, 1H, NH, exchangeable with D_2O), 7.52 (d, 2H, J = 8.3 Hz, ArH), 7.17 (d, 2H, J = 8 Hz, ArH), 3.95 (s, 3H, OMe), 2.33 (s, 3H, $ArCH_3$).

^{13}C NMR : δ 161.523, 153.348, 135.123, 133.817, 129.620, 119.789, 53.753, 20.920.

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.15; H, 5.74; N, 7.25 %. Found : C, 62.17; H, 5.49; N, 7.2 %.

Methyl-N-(2-carbomethoxyphenyl)oxamate (63)

To a solution of **61b** (511 mg, 2.17 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.98 g, 5.43 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2 to afford 355 mg (70%) of the oxamate **63**.

Product 63

White crystals; recrystallised from hexane - DCM.

m. p. : 150 - 152 °C

IR (KBr) ν_{max} : 3259, 1729, 1702, 1537, 1272, 1170, 750 cm^{-1}.

^{1}H NMR : δ 12.59 (brs, 1H, NH, exchangeable with D_2O), 8.75 (d, 1H, J = 8.25 Hz, ArH), 8.08 (dd, 1H, J = 1.2 Hz, 7.9 Hz, ArH), 7.61 (m, 1H, ArH), 7.19 (m, 1H, ArH), 4.00 (s, 3H, OMe), 3.98 (s, 3H, OMe).

^{13}C NMR : δ 168.067, 161.060, 154.335, 139.638, 134.708, 131.086, 123.993, 120.593, 116.221, 53.858, 52.592.

Anal. Calcd for $C_9H_8NO_5$: C, 55.7; H, 4.67; N, 5.9 %. Found : C, 55.69; H, 4.71; N, 6.04 %.

Methyl-N-benzyl oxamate (64)

To a solution of **61c** (300 mg, 1.56 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.15 g, 3.92 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 250 mg (83%) of the oxamate **64**.

Product 64

White crystals ; recrystallised from hexane - DCM.

m. p. : 116 - 118 °C

IR (KBr) ν_{max} : 3270, 2952, 1738, 1682, 1532, 1434, 1251, 1013, 775, 737 cm^{-1}.

^1H NMR : δ 7.39 (brs, 1H, NH, exchangeable with D_2O), 7.37 (m, 5H, ArH), 4.51 (d, 2H, J = 6 Hz, CH_2NH), 3.89 (s, 3H, OMe).

^{13}C NMR : δ 161.120, 156.070, 136.728, 128.874, 127.960, 53.409, 43.956.

Methyl-N-cyclohexyl oxamate (65)

To a solution of **61d** (300 mg, 1.63 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.24 g, 4.09 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was

processed as described in section 3.3.2. to afford 265 mg (88%) of the oxamate **65**.

Product 65

White crystals; recrystallised from hexane - DCM.

m. p. : 77 - 79 °C

IR (KBr) ν_{max} : 3267, 2935, 2854, 1742, 1536, 1290, 1246, 1215, 988, 767 cm^{-1}.

^1H NMR : δ 6.96 (brs,1H, NH, exchangeable with D_2O), 3.894 (s, 3H, OCH_3), 3.78 (m, 1H, >CHNH), 1.945 (m, 2H, CH_2), 1.75 (m, 3H, CH_2), 1.41 (m, 2H, CH_2), 1.2 (m, 3H, CH_2).

^{13}C NMR : δ 161.555, 155.211, 53.491, 48.901, 32.657, 25.447, 24.720.

LRMS m/z (%) : M^+ 185 (2), 142 (10), 127 (1.1), 126 (13), 114 (1.3), 104 (83), 83 (100), 55 (56).

HRMS Calcd for $C_9H_{15}NO_3$: 185.105194. Found : 185.106430.

Methyl-N-(4-methoxyphenyl)oxamate (67)

To a solution of **61e** (500 mg, 2.4 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (3.3 g, 6.03 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 390 mg (78%) of the oxamate **67.**

Product 67

White crystals; recrystallised from hexane - DCM.

m. p. : 145 - 147 °C

IR (KBr) ν_{max} : 3353, 3332, 1729, 1697, 1547, 1510, 1293, 1248, 1032, 828 cm^{-1}.

^1H NMR : δ 8.86 (brs, 1H, NH, exchangeable with D_2O), 7.56 (d, 2H, J = 8.88 Hz, ArH), 6.85 (d, 2H, J = 8.9 Hz, ArH), 3.94 (s, 3H, OMe), 3.80 (s, 3H, ArOMe).

^{13}C NMR : δ 161.623, 157.184, 153.242, 129.474, 121.369, 114.303, 55.349, 53.827.

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.3; N, 6.7 %. Found : C, 57.51; H, 5.1; N,6.68 %.

Methyl-N-(3-bromophenyl)oxamate (68)

To a solution of **61f** (500 mg, 1.95 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.67 g, 4.88 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 385 mg (77%) of the oxamate **68**.

Product 68

White crystals; recrystallised from hexane - DCM.

m. p. : 110 - 111 °C.

IR (KBr) ν_{max} : 3337, 1729, 1706, 1590, 1293, 1164, 797, 703 cm^{-1}.

^{1}H NMR : δ 8.88 (brs, 1H, NH, exchangeable with D_2O), 7.85 (s, 1H, ArH), 7.60 (d, 1H, J = 7.7 Hz, ArH), 7.27 (m, 2H, ArH), 3.79 (s, 3H, OMe).

^{13}C NMR : δ 161.319, 153.591, 137.640, 130.643, 128.729, 123.008, 122.895, 118.420, 104.907,54.205.

LRMS m/z (%) : [M^++2] 259 (75), M^+ 257 (80), 200 (98), 199 (43), 198 (100), 197 (35), 172 (26), 170 (25).

HRMS Calcd for $C_9H_8NO_3Br$: 258.966708. Found : 258.966958.

Methyl-N-(4-chlorophenyl)oxamate (69)

To a solution of **61g** (500 mg, 2.3 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (3.24 g, 5.91 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 365 mg (74%) of the oxamate **69**.

White crystals; recrystallised from hexane - DCM.

m. p. : 164 - 166 °C.

IR (KBr) ν_{max} : 3349, 1745, 1690, 1599, 1546, 1298, 840 cm^{-1}.

^{1}H NMR : δ 8.88 (brs, 1H, NH, exchangeable with D_2O), 7.61 (d, 2H, J = 8.8 Hz, ArH), 7.33 (d, 2H, J = 8.8 Hz, ArH), 3.97 (s, 3H, OMe).

^{13}C NMR : δ 161.303, 153.455, 134.862, 130.794, 129.349, 121.041, 54.068.

Anal. Calcd for $C_9H_8NO_3Cl$: C, 50.6; H, 3.77; N, 6.56 %. Found : C, 50.77; H, 3.56; N, 6.53 %.

Methyl-N-(2-methylphenyl)oxamate (70)

To a solution of **61h** (295 mg, 1.54 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (2.11g, 3.857 mmols) in methanol (20 mL) was added dropwise while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 254 mg (85%) of the oxamate **70**.

Product 70

White crystals; recrystallised from hexane - DCM.

m. p. : 76-78 °C.

IR (KBr) ν_{max} : 3382, 1716, 1535, 1294, 1167, 973, 757 cm^{-1}.

^1H NMR : δ 8.83 (brs, 1H, NH, exchangeable with D_2O), 8.01 (d, 1H, J = 7.86 Hz, ArH), 7.24 (m, 2H, ArH), 7.14 (d, 1H, J = 7.05 Hz, ArH), 3.98 (s, 3H, OMe), 2.33 (s, 3H, ArOMe).

^{13}C NMR : δ 161.765, 153.565, 134.427, 130.690, 128.307, 127.182, 126.000, 121.792, 54.036, 17.596.

EIMS m/z (%) :[M^++1] 194 (5), M^+ 193 (69), 134 (100), 106 (33), 91 (56).

HRMS Calcd for $C_{10}H_{11}NO_3$: 193.073893. Found : 193.075254.

Methyl-N-(2-methoxyphenyl)oxamate (71)

To a solution of **66** (500 mg, 2.4 mmols) in methanol (20 mL) saturated with oxygen, an oxygenated solution of CAN (3.3 g, 6.03 mmols) in methanol (20 mL) was added while the reaction mixture was continuously purged with oxygen. On completion of the reaction, it was processed as described in section 3.3.2. to afford 420 mg (83%) of the oxamate **71**.

Product 71

White crystals; recrystallised from hexane - DCM.

m. p. : 72 - 74 °C.

IR (KBr) ν_{max} : 3391, 1785, 1713,1533, 1303, 1163, 1023, 753 cm^{-1}.

^1H NMR : δ 9.48 (brs, 1H, NH, exchangeable with D_2O), 8.40 (dd, 1H, J = 7.9, 1.1 Hz ArH), 7.12 (m, 1H, ArH), 7.01 (m, 1H, ArH), 6.92 (d, 1H, J = 8 Hz, ArH), 3.97 (s, 3H, OMe), 3.923 (s, 3H, OMe).

^{13}C NMR : δ 161.352, 153.429, 148.490, 126.037, 125.374, 121.107, 119.973, 110.146, 55.813, 53.925.

EIMS m/z (%) : $[M^+ + 1]$ 210 (38) M^+ 209 (100), 150 (24), 135 (11), 120 (10), 94 (16), 65 (12), 52 (16), 51 (14).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7 %. Found : C, 56.99; H, 5.32; N, 6.08 %.

3.4. REFERENCES

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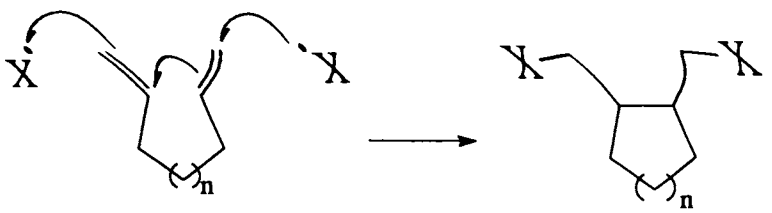
CHAPTER 4

SOME ATTEMPTS AT INTRAMOLECULAR CYCLIZATION MEDIATED BY CAN

4.1. INTRODUCTION

During the past few years, oxidative free radical cyclizations mediated by high valent metal salts have been developed into a general procedure for constructing highly complex and functionalized molecules from simple precursors. These cyclizations are initiated by the metal ion, which induces oxidative electron transfer to produce a radical or a radical cation. A tandem sequence of radical addition-cyclization reaction is a direct and useful annulation methodology for the synthesis of polysubstituted rings (Scheme 1).

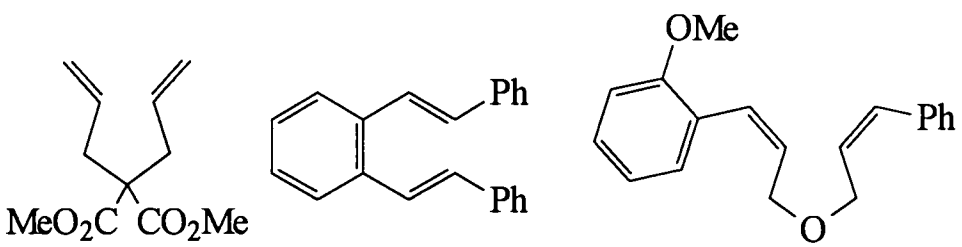


Scheme 1

The metal ions commonly used are Mn (III), Co (III), Cu (II), Fe (III), Ag (II) and V (V). In comparison with these metals, there are only a few reports on the intramolecular cyclization reactions mediated by Ce (IV) reagents. It is noteworthy that $Mn(OAc)_3$ has been used effectively in the intramolecular reactions by Snider[1] and others. A comprehensive survey of literature on CAN mediated intramolecular cyclizations is given in section 3.1.1.2 of chapter 3.

In view of our persistent interest in the mechanistic and synthetic aspects of CAN promoted reactions and the unsuccessful attempt at intramolecular cyclization of acetoacetanilide with CAN, it was decided to attempt cyclization on some other suitable systems. This chapter deals with some preliminary efforts in this arena.

The following systems were included in the study (Figure 1).

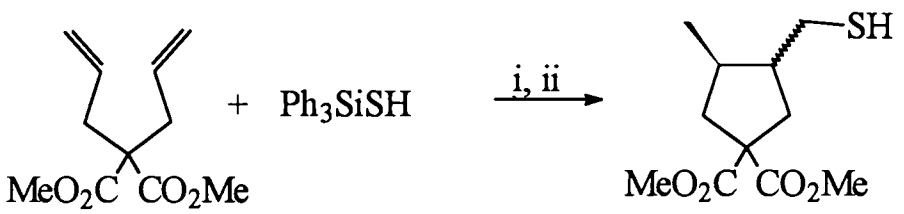


1 **2** **3**

Figure 1

A variety of intramolecular reactions have been reported for these and related systems. The addition-cyclization sequence shown in scheme 1 has been adapted by a number of research groups. A brief overview of these reactions is given below.

The cyclization of diallyl malonate to the carbocyclic thiol **6** in nearly quantitative yield is brought about by the triphenylsilylthiyl radical generated thermally or photochemically.[2] Here the radical formed from the addition of triphenylsilylthiyl radical to **1** was trapped in a *5-exo-trig* fashion yielding the expected carbocyclic thiol **5** (Scheme 2).

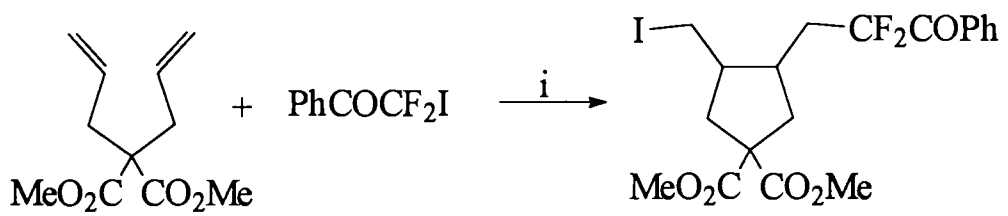


1 **4** **5**

i) UV light
ii) TFA, 99 %

Scheme 2

Qiu *et al.* have used the same strategy to synthesize difluoroketones from diallyl malonate **1** in 95% yield (Scheme 3).[3]

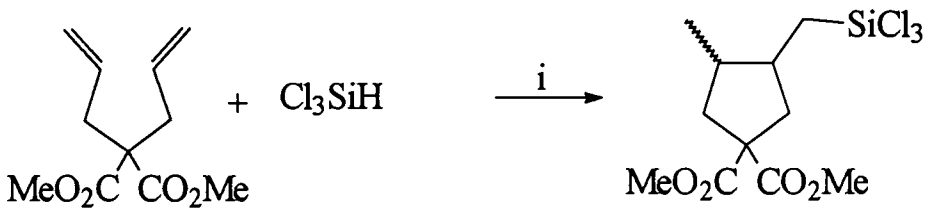


1 **6** **7**

i) $Pd(PPh_3)_4$, r. t., 95%

Scheme 3

Organosilicon radical induced cyclization reactions have been reported. The trichlorosilyl radical generates the 5-hexenyl radical, which in turn undergoes cyclization to afford **9** in high yield (Scheme 4).[4]

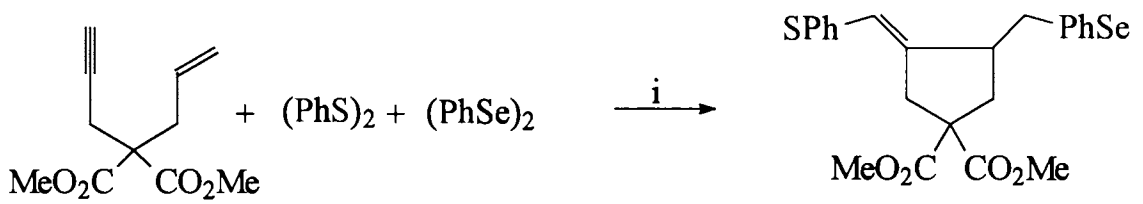


1 **8** **9**

i) Di-*t*-butyl peroxide, Dry benzene, 140 °C, S. T., Argon, 84%

Scheme 4

Highly regioselective thioselenation has been achieved using a $(PhS)_2$-$(PhSe)_2$ binary system. The reaction is triggered by the selective addition of phenylthiyl radical to the triple bond (Scheme 5).[5]



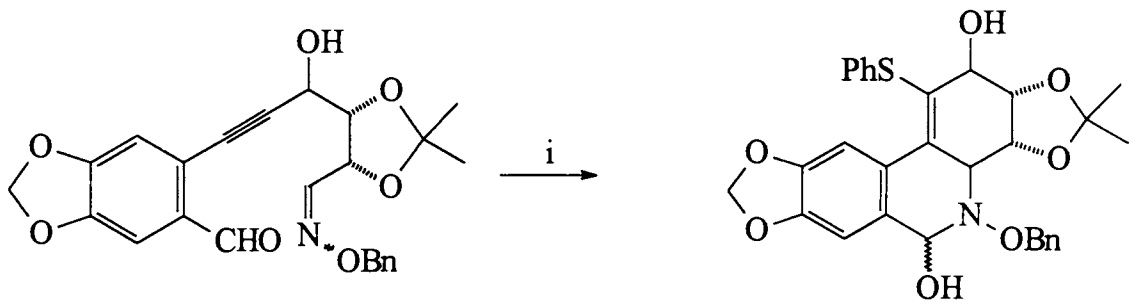
10 **11** **12** **13**

i) hν, 40 °C, 18 h, 61 %

Scheme 5

Many natural products have been synthesized *via* radical cyclization based strategy. For example, in the synthesis of Lycoricidine, the necessary

framework was constructed in a single operation by sequential cyclization processes (Scheme 6).[6]

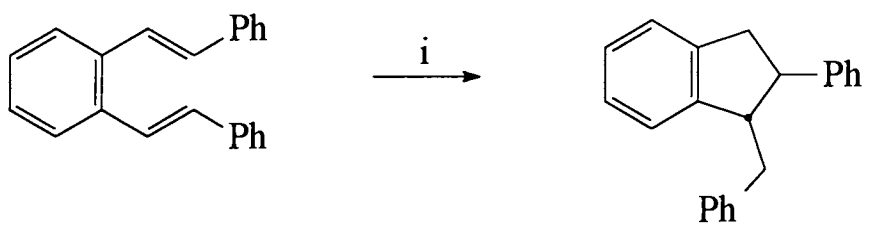


14 **15**

i) PhSH, Toluene, hv, 73%

Scheme 6

Similarly, Müllen[7] has reported that upon electron transfer, 1,2-distyrylbenzene **2,** underwent conversion to an indane derivative. The reduction of **2** with potassium in THF/NH_3 (1:1) on a preparative scale yields 78 % of the indane derivative **16** (Scheme 7).

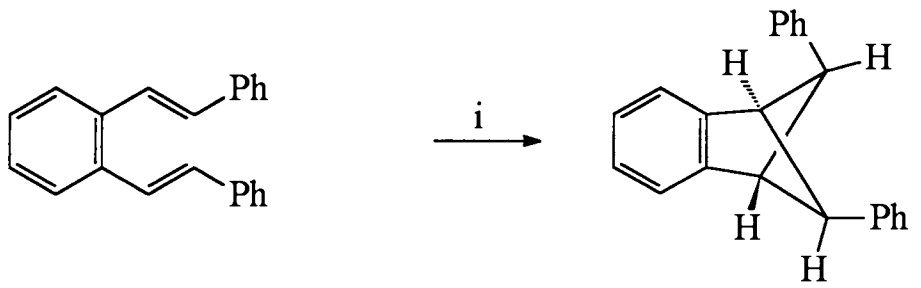


2 **16**

i) Potassium (2.2 eq.), THF /NH_3 (1 : 1), -80°C→-20°C, 78 %

Scheme 7

However, irradiation of a microcrystalline suspension of **2** in water at room temperature led to a bicyclic product **17** in 30% yield (Scheme 8).[8]

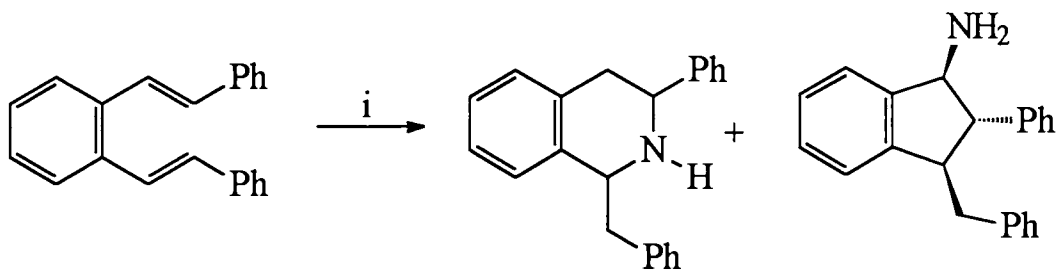


2 **17**

i) hν, 300 nm, Pyrex, r. t., 3 d, 30 %

Scheme 8

Furthermore, intramolecular cyclization of 1,2-distyrylbenzene *via* radical cation generated under PET conditions has been reported. The scheme 9 shows nucleophilic addition of ammonia to the radical cation of **2** leading to the cyclic products **18** and **19**.[9]

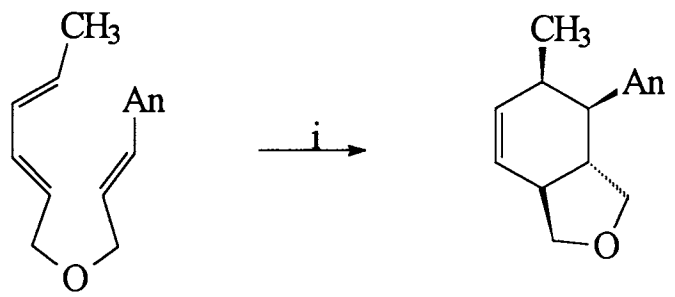


2 **18** **19**

i) hν /NH_3, *p*-DCB, 20 h, r. t., MeCN-C_6H_6-H_2O

Scheme 9

Efficient intramolecular cyclizations of suitable substrates have been reported to occur under the influence of triarylaminium salts. Schemes 10 and 11 show two of the representative examples of this method.[10]

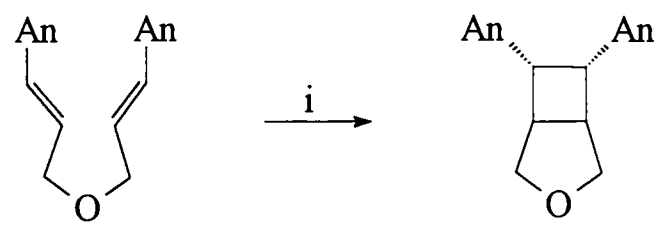


An = 4-methoxyphenyl

20 **21**

i) $Ar_3N^{+\cdot}$ $SbCl_6^-$, DCM, 0 °C, 1 min., 80 %

Scheme 10



An = 4-methoxyphenyl

22 **23**

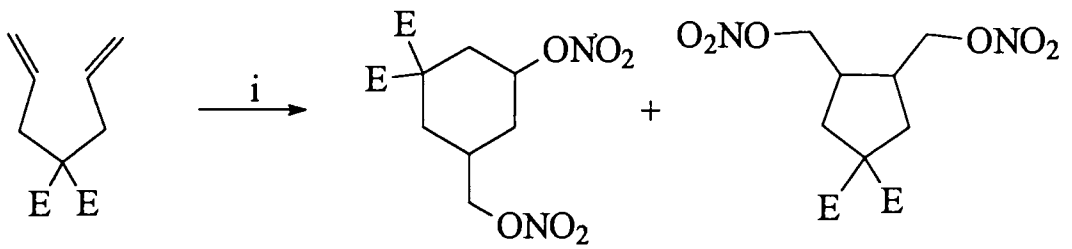
i) $Ar_3N^{+\cdot}$ $SbCl_6^-$, DCM, 0 °C, 15 sec. 80 %

Scheme 11

4.2. RESULTS AND DISCUSSION

Against the backdrop of the above literature precedents, we have carried out some preliminary investigations in the area of intramolecular cyclizations mediated by CAN and the results are presented below.

The initial experiment involved the reaction of 2,2-diallyl dimethyl malonate **1** with CAN in acetonitrile at reflux temperature, which afforded the products **24** and **25** (Scheme 12). The yields of **24** and **25** were found to increase when the reaction was carried out in the presence of light (Table 1).



E = CO_2Me

1 **24** **25**

i) CAN, CH_3CN, reflux, 2 h

Scheme 12

Entry	Conditions	24	25
1.	CAN, CH_3CN, reflux, 2h	10 % (30 %)[a]	15 % (50 %)
2.	CAN, CH_3CN, hv, Argon, 1h	20 % (40 %)	25 % (55 %)

[a] Yields given in brackets are calculated on the basis of the recovered starting material

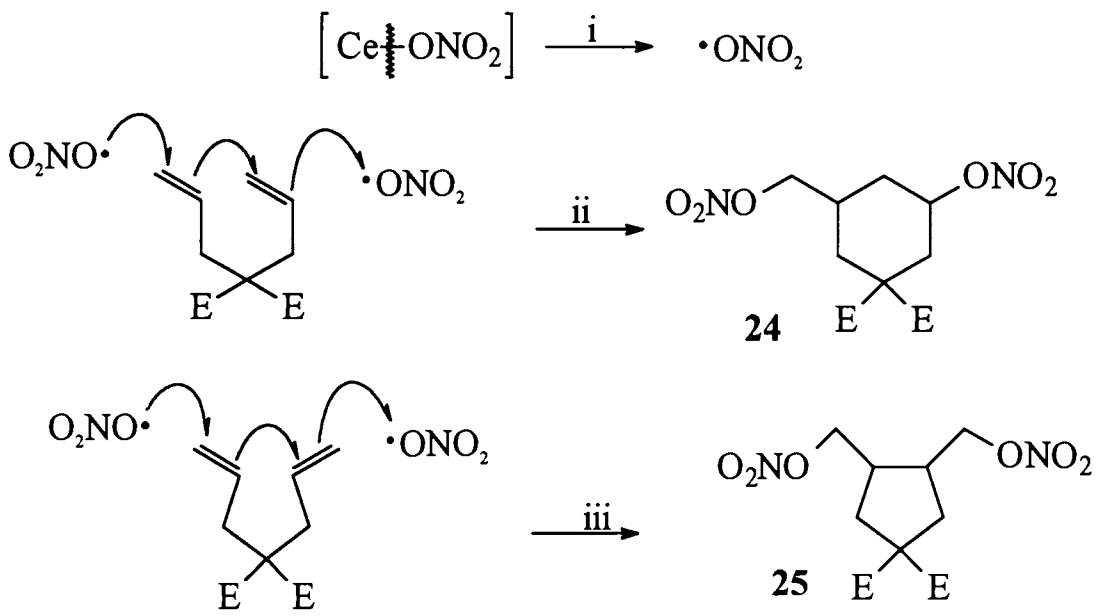
Table 1

The product **24** was characterized by the usual spectral methods. In the IR spectrum of **24** the ester carbonyls displayed a strong sharp band at 1735cm^{-1} and the C-ONO_2 stretching was seen at 1640 $cm.^{-1}$ In the ^1H NMR

spectrum of **24,** the proton geminal to the secondary -ONO_2 group was seen at δ 4.52 as a multiplet and the methylene protons adjacent to the -ONO_2 group appeared as a doublet at δ 4.43. The three methylene protons were seen at δ 2.19 (m, 2H), 2.71 (m, 1H) and 3.00 (m, 1H). The methoxy protons appeared at δ 3.76. In the ^{13}C NMR spectrum, the ester carbonyls were visible at δ 171.716 and 171.546 and the carbon bearing the nitrate groups were seen at δ 75.124 and 71.397. The quaternary carbon resonated at δ 57.967.

The product **25** also was characterized by the routinely used spectroscopic methods. The IR spectrum of **25** displayed the ester carbonyl at 1748 cm^{-1} and the C-ONO_2 stretching was visible at 1640 cm^{-1} as a weak band. The ^1H NMR spectrum of **25** contained a multiplet at δ 4.45 for four protons, corresponding to the protons adjacent to the -ONO_2 groups. The protons on the tertiary carbons appeared at δ 3.07 as a multiplet. The four methylene protons on the ring appeared as doublets for two protons each at δ 2.63 and 2.22. The two methoxy groups were observed at δ 3.768 and 3.764. In the ^{13}C NMR, the ester carbonyls were seen at δ 172.057 and 171.418 and the carbons attached to the -ONO_2 groups appeared at δ 74.748.

A radical-addition-cyclization sequence can rationalize the formation of these products. The ONO_2 radical generated photochemically or thermally from CAN adds to the alkene to produce a hex-5-enyl radical, which is subsequently trapped by another ONO_2 radical to afford the products. If the cyclization occurs in *6-endo-trig* fashion, product **24** is obtained and if *5-exo-trig* is the mode of cyclization, product **25** results (Scheme 13).[11]



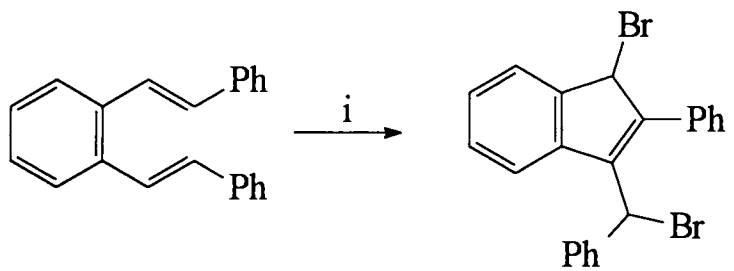
i) hv / Δ

ii) *6-endo-trig*

iii) *5-exo-trig*

Scheme 13

1,2-Distyrylbenzene **2**, the second substrate used in our study, when treated with CAN in the presence of KBr in a biphasic system of dichloromethane and water afforded a product in 80 % yield and this is tentatively identified as **26** (Scheme 14).



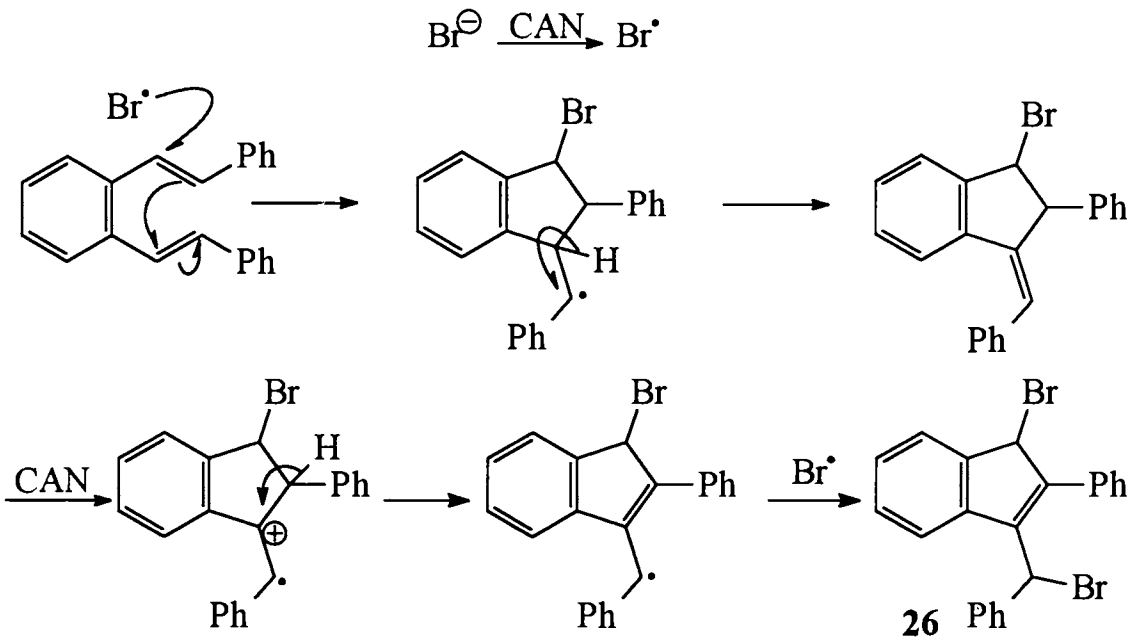
2 **26**

i) CAN, KBr, H_2O : DCM (1 : 1), r. t., 2 h, 80 %

Scheme 14

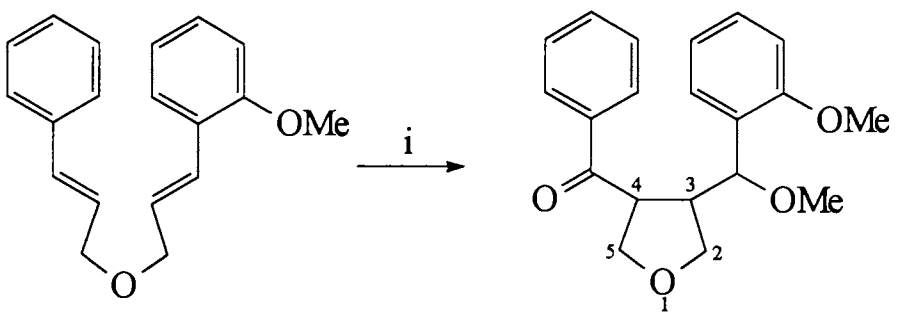
The product **26** was characterized by routine spectral methods. In the proton NMR spectrum, the protons geminal to the bromine atoms were visible at δ 5.92 (brs, 1H) and 5.55 (brs, 1H). The ^{13}C NMR spectrum, exhibited the two carbons attached to the bromine atoms at δ 55.671 and 51.457. The presence of two bromine atoms was ascertained from the mass spectrum which displayed the [M + 4] peak at 444. The structure was further confirmed by HRMS.

A mechanistic rationalization for the formation of **26** may be presented as follows. Addition of bromine radical (generated by the action of CAN on bromide ion) to **2** is followed by cyclization in the *5-exo-trig* fashion. The cyclic intermediate thus generated, after a series of steps gets transformed into the product (Scheme 15).[12]



Scheme 15

The ether **3** when reacted with CAN in methanol at ice temperature underwent oxidative cyclization to afford a product tentatively identified as the tetrahydrofuran derivative **27** in 40.75 % yield (Scheme 16).



3 **27**

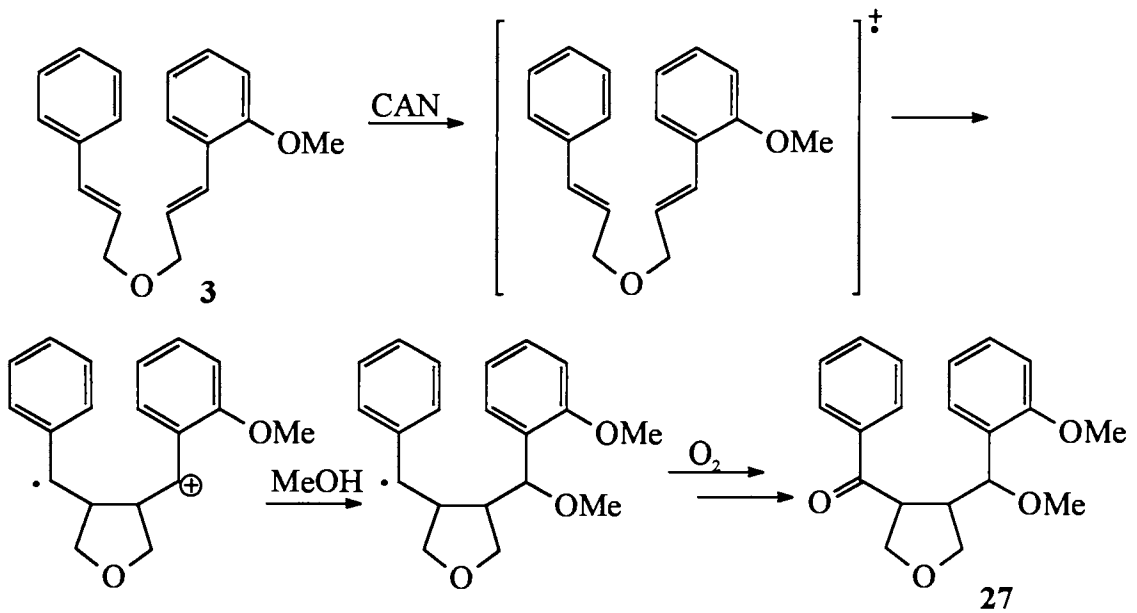
i) **CAN, MeOH, 0 °C, 5 min., 40.75 %**

Scheme 16

The product **27** was characterized by spectral analysis. The IR spectrum of **27** displayed the carbonyl stretching at 1680 cm^{-1}. In the ^{1}H NMR spectrum, the three aliphatic methoxy protons appeared at δ 3.189 as a singlet while the aromatic methoxy protons resonated at δ 3.703. The four methylene protons bonded to C-2 and C-5 appeared at δ 3.07 (m, 1H) and 3.86 (m, 3H). The two methine protons on C-3 and C-4 appeared at δ 4.02 (m, 1H) and 4.149 (t, 1H, J = 6.8 Hz). The proton geminal to the methoxy group resonated as a doublet at δ 4.64 (1H, J = 8 Hz). The ^{13}C NMR spectrum of **27** displayed the carbonyl carbon at δ 199.061. The methine carbons were discernible at δ 49.749 and 48.669. The methoxy carbons resonated at δ 56.750 and 55.038. The methylene carbons bonded to the ether oxygen appeared at δ 71.181and 70.852. The methine carbon carrying

the methoxy group appeared at δ 77.409. The structure was further confirmed by mass spectral data, which showed the M^+ peak at 326.

Formation of the product can be rationalized by invoking a radical cation of the ether **3**. The methoxystyryl radical cation can intramolecularly add to the other styrene moiety to form a distonic radical cation, which further gets converted to the product as depicted in scheme 17.



Scheme 17

In conclusion CAN appears to be useful reagent in intramolecular cyclization.

4.3. EXPERIMENTAL

General information about the experimental is given in section 2.3.1 of chapter 2.

1,1-bis(carbomethoxy)-3-nitrate-5-methylnitratecyclohexane (24)

1,1-bis(carbomethoxy)-3,4-bis(methylnitrate)cyclopentane (25)

Procedure for reaction under thermal conditions: To a solution of **1** (500 mg, 2.36 mmols) in acetonitrile (50 mL) a solution of CAN (2.97g, 5.43 mmols) in acetonitrile was added and the reaction mixture was refluxed. On completion of the reaction, it was processed as described in section 3.3.2. to afford **24** and **25** in 10 % and 15 % yields respectively. Based on recovered starting material, the yields of **24** and **25** were found to be 30 % and 50% respectively.

Procedure for reaction under photochemical conditions: To a solution of **1** (500 mg, 2.36 mmols) in acetonitrile (50 mL) saturated with argon a solution of CAN (2.97g, 5.43 mmols) in acetonitrile was added and the reaction mixture was irradiated under UV light (350 nm). On completion of the reaction, it was processed as described in section 3.3.2. Column chromatography on silica gel using hexane : ethylacetate (90 : 10) afforded 158 mg of **24** (20%).

Product 24

Pale yellow viscous liquid

IR (neat) ν_{max} : 2955, 1735, 1640, 1553 1452, 1276, 980, 858 cm^{-1}.

^{1}H NMR : δ 4.42 (m, 4H, C<u>H</u>ONO$_2$, C<u>H$_2$</u>ONO$_2$, C<u>H</u>CH$_2$), 3.75 (s, 6H, O<u>Me</u>), 3.00 (m, 1H, C<u>H$_2$</u>), 2.71 (m, 1H, C<u>H$_2$</u>), 2.572 (m, 2H, C<u>H$_2$</u>), 2.19 (m, 2H, C<u>H$_2$</u>),

^{13}C NMR : δ 171.716, 171.546, 75.124, 71.397, 57.967, 53.084, 39.161, 38.202, 36.964, 36.193.

LRMS m/z (%) : [M$^+$- 2ONO$_2$ - OMe] 171 (20), 145 (95), 139 (71), 123 (45), 113 (100), 95 (50).

On further elution of the column using hexane : ethylacetate (85 : 15) afforded 190 mg of **25** (25%).

Product 25

Pale yellow viscous liquid

IR (neat) ν_{max} : 2955, 1748, 1640, 1560, 1445, 1378, 1297, 1222, 1175 cm^{-1}.

^{1}H NMR : δ 4.44 (m, 4H, C<u>H$_2$</u>ONO$_2$), 3.768 (s, 3H, O<u>Me</u>), 3.764 (s, 3H, O<u>Me</u>), 3.078 (m, 2H, -C<u>H</u>), 2.63 (d, 1H, J = 7.33 Hz, C<u>H$_2$</u>), 2.58 (d, 1H, *J* = 6.9 Hz, C<u>H$_2$</u>), 2.22 (d, 1H, *J* = 7 Hz, C<u>H$_2$</u>), 2.17 (d, 1H, *J* = 7 Hz, C<u>H$_2$</u>).

^{13}C NMR : δ 172.057, 171.418, 77.692, 74.748, 57.709, 53.278, 53.199, 39.369, 36.832.

GCMS m/z (%) : [M$^+$-HNO$_3$] 273 (98), 226 (45), 166(100), 151(100), 137 (75), 119 (40), 91 (80).

Based on recovered starting material, the yields of **24** and **25** were found to be 40 % and 55% respectively.

1-[1-Bromo-1-phenylmethyl]-2-phenyl-3-bromoindene (26)

To a solution of **2** (500 mg, 1.77 mmols) and KBr (450 mg, 3.8 mmols) in dichloromethane (50 mL), a solution of CAN (2.23 g, 4.08 mmols) in water was added and the reaction mixture stirred for 2 h at room temperature. On completion of the reaction, it was worked up and the residue was recrystallised from hexane to afford **26** in 80 % yield.

Product 26

Colorless crystals; recrystallised from hexane.

m. p. : 124 - 125 °C

IR (KBr) ν_{max} : 3030, 1492, 1443, 1124, 685 cm^{-1}.

^1H NMR : δ 7.484 (m, 13H, ArH), 7.03 (m, 1H, ArH), 5.92 (brs, 1H, CHBr), 5.55 (brs, 1H, CHBr).

^{13}C NMR : δ 139.937, 137.159, 129.336, 129.139, 129.001, 128.842, 128.757, 128.101, 128.026, 127.575, 127.409, 126.817, 125.280, 104.753, 55.671, 51.457.

LRMS m/z (%) : $[M^+ + 4]$ 444 (0.5), 442 (0.8), 440 (0.4), 363 (15), 282 (36), 281 (100), 280 (24), 204 (21), 203 (37), 192 (60), 191 (81), 189 (16), 178 (87).

HRMS Calcd for $C_{22}H_{18}Br_2$: M^+ 439.977523. Found 439.976392.

(2-methoxycinnamyl)cinnamylether (3)

To a solution of *o*-methoxycinnamyl alcohol (500 mg, 3 mmols) in dichloromethane (50 mL) a solution of cinnamyl bromide (662 mg, 3.36 mmols) in dichloromethane was added. To the above tetrabutyl ammonium bromide (29.9 mg, 0.093 mmols) followed by 50 % sodium hydroxide (5 mL) were added and stirred for 3 h. The reaction mixture after

work up and column chromatography (silica gel) using hexane : ethyl acetate (90 : 10) as the eluent afforded 746 mg (87.39 %) of the ether **3**.

Product 3

Colorless liquid

IR (neat) ν_{max} : 3024, 2943, 2837, 1595, 1489, 1457, 1351, 1295, 1114, 739 cm^{-1}.

^1H NMR : δ 7.295 (m, 7H, ArH), 6.895 (m, 3H, ArH, =CH), 6.57 (d, 1H, J = 15 Hz, =CH), 6.30 (m, 2H, =CH), 4.191 (m, 4H, CH_2), 3.825 (s, 3H, OMe).

^{13}C NMR : δ 156.694, 136.737, 132.345, 128.598, 128.419, 127.652, 127.494, 126.950, 126.509, 126.403, 126.141, 125.706, 120.565, 110.689, 71.179, 70.418, 55.239.

GCMS m/z (%) : M^+ 280 (10), 262 (15), 250 (50), 249 (100), 147 (70), 117 (85).

3-[1-Methoxy-1-(2'-methoxyphenyl)methyl]-4-benzoyltetrahydrofuran (27)

To a solution of **3** (550 mg, 1.96 mmols) in methanol (30 mL) a solution of CAN (2.05 g, 3.74 mmols) also in the same solvent (30 mL) was added and the reaction mixture was stirred for 5 min. On completion of the reaction, it was processed as described in section 3.3.2. to afford 260 mg (40.75 %) of the product **27**.

Product 27

Colorless liquid

IR (KBr) ν_{max} : 2943, 1680, 1593, 1486, 1237 cm^{-1}

^{1}H NMR : δ 7.565 (m, 2H, ArH), 7.295 (m, 3H, ArH), 7.149 (m, 1H, ArH), 6.919 (t, 1H, *J* = 7.35 Hz, ArH), 6.68 (d, 1H, *J* = 8.3 Hz, ArH), 4.64 (d, 1H, *J* = 8 Hz, CHOMe), 4.149 (t, 1H, *J* = 6.8 Hz, CH), 4.02 (m, 1H, CH), 3.86 (m, 3H, CH_2), 3.703 (s, 3H, OMe), 3.189 (s, 3H, OMe), 3.07 (m, 1H, CH_2).

^{13}C NMR : δ 199.061, 157.110, 136.660, 132.680, 128.630, 128.254, 128.091, 127.389, 127.080, 120.901, 110.162, 77.409, 71.181, 70.852, 56.750, 55.038, 49.749, 48.669.

DEPT-135 (CH_2, negative) 71.181, 70.852.

GCMS m/z (%) : M^+ 326 (0.8), 294 (1), 177 (25), 151 (100), 121 (9), 105 (11), 91 (5), 77 (10).

4.4. REFERENCES

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SUMMARY

The thesis entitled "**Novel Synthetic Transformations Mediated by Cerium (IV) Ammonium Nitrate**" contains the results of a wide ranging study carried out to probe the usefulness of CAN in generating carbon centered radicals and radical cations to bring about interesting synthetic transformations.

A brief account of the development of radical reactions followed by a survey of literature excerpts of CAN mediated synthetic transformations form the subject matter of chapter 1.

Chapter 2 deals with the dimerization reactions of radical cations of alkoxystyrenes generated by CAN. The alkoxystyrenes (**25**, **39** - **40**) dimerize in presence of CAN *via* a radical cation intermediate. The solvent was found to play an important role in determining the course of the reaction. When methanol or ethanol was used as the solvent, dimers incorporating -OR (R = Me or Et) (**28**, **29**, **41**, **42**, **45**, **47** - **49**, **51** - **53**) were obtained along with other products. The reaction took a different course in acetonitrile, affording mainly tetrahydrofuran derivatives (**54** - **56**).

The α-substituted alkoxystyrene (**75**) was found to dimerize readily to afford the tetrahydrofuran derivative (**78**) and the tetralin (**79**), whereas, the β-substituted alkoxystyrenes did not undergo facile dimerization.

The study of CAN mediated dimerization of alkoxystyrenes has been shown to be an interesting carbon-carbon bond forming reaction both from the mechanistic and synthetic standpoints. In most cases, the products obtained contain structural framework similar to those of lignans, which are biologically active molecules. Hence, it is anticipated that this method will find some use in the synthesis of lignans.

Chapter 3 describes a novel synthesis of oxamates from acetoacetanilides (**42**, **61a - b**, **61e - h**, **66**) mediated by CAN. This reaction was found to give good yields of oxamate when carried out in an oxygenated atmosphere. This method was also extended to aliphatic acetoacetamides (**61c - d**) to afford the corresponding oxamates. The CAN mediated transformation of acetoacetamides to oxamates is very facile and may serve as a convenient alternative to the conventional procedures.

In chapter 4, intramolecular cyclizations involving certain preliminary investigations of 1,n-diene systems (**1 - 3**) by the radical-addition-cyclization strategy, mediated by CAN have been described. It is noteworthy that there are very few examples of CAN mediated intramolecular reactions in the literature and the present study has opened up interesting possibilities in this area.

In conclusion, the work embodied in the thesis has served to enhance the versatility of CAN as a powerful one-electron oxidant useful in effecting transformations of importance in organic synthesis.

LIST OF PUBLICATIONS

1. Nair, V.; Mathew, J.; Kanakamma, P. P.; Panicker, S. B.; **Sheeba V.;** Zeena, S. and Eigendorf, G. K. *" Novel Cerium (IV) ammonium Nitrate Induced dimerization of Methoxystyrenes."* **Tetrahedron Lett. 1997,** *38,* 2191.
2. Nair, V. and **Sheeba, V.** *" A Facile CAN mediated transformation of Acetoacetanilides to Oxamates."* **J. Org. Chem. 1999.** (Accepted).
3. Nair, V.; **Sheeba, V.** and Panicker, S. B. *"Cerium (IV) ammonium Nitrate Induced dimerization of Methoxystyrenes"* **Tetrahedron** (Accepted).
4. Nair, V.; **Sheeba, V.** and Panicker, S. B. *"CAN Mediated Reactions of α- and β- Substituted alkoxystyrenes."* **Synth. Commun.** (To be communicated).

POSTERS PRESENTED AT VARIOUS SYMPOSIA

1. "Chemical Electron Transfer Induced reaction mediated by Cerium (IV) Ammonium Nitrate (CAN)". Kanakamma, P. P.; Mathew, J.; Nair, L. G.; **Sheeba, V.;** Mathen, J. S.; Zeena, S.; Panicker S. B. and Nair, V. National Symposium on emerging trends in Organic Synthesis, Trivandrum, November, 1996. Abstract, p-20.
2. "Carbon-Carbon Bond Forming Reactions Mediated by Cerium (IV) Reagents." Nair, V., Mathew, J.; Nair, L. G.; Panicker, S. B.; **Sheeba, V.** and Tesmol G. George. National Symposium on Newer Vistas in synthetic protocols and Structural Elucidation in Chemistry, Madurai, April, 1998, IL#10.