NOVEL SYNTHETIC TRANSFORMATIONS INVOLVING ELECTRON TRANSFER MEDIATED BY CERIUM(IV) AMMONIUM NITRATE (CAN)

THESIS SUBMITTED TO
THE UNIVERSITY OF KERALA
IN FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY
UNDER THE FACULTY OF SCIENCE

BY

SREELETHA B. PANICKER

ORGANIC CHEMISTRY DIVISION
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, KERALA, INDIA

DECEMBER, 2000

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Dedicated to

My Parents and Teachers

DECLARATION

I hereby declare that, the thesis entitled **"Novel Synthetic Transformations Involving Electron Transfer Mediated by Cerium(IV) Ammonium Nitrate (CAN)"** embodies the results of the investigations carried out by me at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum, under the supervision of **Dr. G. Vijay Nair** and the same has not been submitted elsewhere for a degree.

Sreeletha B. Panicker

December, 2000

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Director

December, 2000

CERTIFICATE

This is to certify that the work embodied in the thesis entitled "**Novel Synthetic Transformations Involving Electron Transfer Mediated by Cerium(IV) Ammonium Nitrate (CAN)**" has been carried out by **Ms. Sreeletha B. Panicker** 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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I take this opportunity to express my deep sense of gratitude, obligation, and admiration to my research supervisor ***Dr. G. Vijay Nair*** *for suggesting this interesting research topic, his constant encouragement, valuable criticism and inspiration.*

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Finally I would like to express my deepest sense of gratitude to my family members, who remain the constant source of encouragement and inspiration throughout my academic career.

Sreelatha B. Panicker *December, 2000*

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PREFACE

Although the discovery of radicals by Gomberg dates back to 1900, only recently radical methodology found a place in the arena of organic synthesis. This may be due to an erroneous but persistent notion that radical reactions lack selectivity and are uncontrollable. However, a remarkable paradigm shift in organic synthesis occurred during the last two decades, which has resulted in the acceptance of radical methodology. This can be attributed in large measure to the demonstration by Stork that the controlled formation as well as addition of vinyl radicals to sp^2 centers constitutes a unique and powerful method for complex carbocyclic construction. Today radical methodology is much appreciated and widely accepted as one of the best methods applicable not only for the construction of carbon-carbon bonds but also for the formation of carbon-heteroatom bonds.

Many of the radical reactions are initiated by electron transfer and proceed *via* the intermediacy of radical ions. Of the various methods available for electron transfer, *viz.* electrochemical, photochemical and chemical reactions, chemical electron transfer reactions are of current interest. Chemically electron transfer oxidation can be accomplished using a number of metal salts and Mn(III) and Ce(IV) have emerged as powerful one-electron oxidants. Although cerium (IV) ammonium nitrate (CAN) has been shown to offer many advantages over Mn(III) acetate, its potential has remained largely untapped. Therefore, a detailed investigation aimed at exploring the synthetic utility of CAN in certain areas of organic synthesis was carried out. The present thesis, entitled **"Novel Synthetic Transformations Involving Electron Transfer Mediated by Cerium(IV) Ammonium Nitrate (CAN)"** contains the results of the study.

The thesis is divided into four chapters. Relevant references are given towards the end of each chapter. Since all these four chapters are presented as independent units, structural formulae, schemes, tables and references are numbered accordingly.

The first chapter includes a brief and selective discussion on radical reactions and electron transfer reactions. A brief account of various synthetic transformations utilizing CAN is also presented.

The second chapter concerns itself with the facile formation of 1,n-dicarbonyl compounds by the CAN mediated fragmentation of 1-Arylcycloalkenes in methanol.

Chapter 3 provides a detailed coverage of the bromination of alkenes using potassium bromide and CAN. The reaction has been studied under various conditions and further transformations of the dibromides are also discussed.

The last chapter contains the preliminary results of the CAN mediated transformations of arylcyclopropanes. These include the bromination of cyclopropanes using potassium bromide and CAN and the ring opening reactions of cyclopropanes in methanol.

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

ABBREVIATIONS

brs	:	broad singlet
CAN	:	cerium(IV) ammonium nitrate
CAS	:	cerium(IV) ammonium sulfate
CCE	:	constant current electrolysis
d	:	doublet
dd	:	double doublet
DMF	:	dimethylformamide
EIMS	:	electron impact mass spectrum
Eq.	:	equivalents
Et	:	ethyl
GC-MS	:	gas chromatography-mass spectrum
h	:	hour
HOMO	:	highest occupied molecular orbital
HRMS	:	high resolution mass spectrum
Hz	:	hertz
IR	:	infrared
J	:	coupling constant
m	:	multiplet
M^+	:	molecular ion
mA	:	milli ampere
Me	:	methyl
min	:	minutes
MS	:	mass spectrum
m/z	:	mass charge ratio
NMR	:	nuclear magnetic resonance
o	:	ortho
p	:	para
Ph	:	phenyl
PPTS	:	pyridinium *p*-toluene sulfonate
rt	:	room temperature
s	:	singlet
t	:	triplet
t-Boc	:	*tert*-butoxycarbonyl
TBACN	:	tetrabutyl ammonium cerium(IV) nitrate
TBDMS	:	*tert*-butyldimethylsilyl
THP	:	tetrahydropyranyl
TLC	:	thin layer chromatography
TMS	:	tetramethylsilane
THF	:	tetrahydrofuran

CHAPTER 1

SYNTHETIC TRANSFORMATIONS MEDIATED BY CERIUM(IV) AMMONIUM NITRATE [CAN]: A REVIEW

1.1. INTRODUCTION

1.1.1. General

The thesis embodies the results of a series of investigations using CAN leading to some novel chemical transformations. These involve the intermediacy of radicals and radical cations generated by oxidative electron transfer mediated by CAN. Before going into a comprehensive review of CAN mediated reactions, to put things in perspective, a brief introduction to the properties of radicals and radical cations, radical reactions and electron transfer oxidation is given.

1.1.2. Radicals in organic synthesis

Radicals are species that contain at least one unpaired electron. In the case of carbon centered radicals, the concept of species with seven valence electrons was established by the work of Gomberg and Paneth. Gomberg first explored and investigated the existence of the stable triphenylmethyl radical.[1] The existence of the less stable methyl radicals in gas phase over a short period of time was confirmed by Paneth in his studies on tetramethyl lead.[2]

In spite of the pioneering work of Gomberg and the more elaborate investigations by Hey and Waters[3] and Kharasch,[4] radical chemistry did not find much application in organic synthesis for a long time. This may be due to an erroneous, but persistent notion that, radical reactions lack selectivity

and are uncontrollable. The situation changed dramatically during the last twenty years and this may be attributed, in large measure, to a new conceptual frame-work and the demonstration by Stork that the controlled formation as well as the addition of vinyl radicals to π-bonds constitutes a unique and powerful method for complex carbocyclic construction.[5] In-depth investigations on the rates of radical reactions by Ingold and Beckwith and their applications in synthesis by Julia, Giese and a number of others have also contributed significantly to the acceptance of radical methodology as a synthetic tool.[6,7] Today radical reactions occupy a pivotal place in organic synthesis comparable to those of ionic and pericyclic reactions. Interestingly, a number of organic reactions, previously believed to occur *via* ionic intermediates are now being recognized to involve radical species. A number of chemical reactions in biological systems are also perceived to proceed *via* radical intermediates.

1.1.3. Properties of radicals

The presence of an odd electron makes radicals very reactive and transient in nature. They are produced by the homolytic cleavage of bonds. The homolytic cleavage can occur either by photochemical or thermal processes. Normally radical reactions are very fast and hence side reactions such as rearrangements are not a serious problem. Also, most of the radical reactions are chemoselective in nature. Solvent effects on radicals are usually very small and can be neglected in most of the cases. The conditions for *almost all radical reactions are neutral and therefore protection of functional* groups such as -OH, -NH_2 etc., is not necessary. A unique property of radicals, which differentiates them from carbocations and carbanions, is the tendency of recombination, which is unlikely with other species.[8]

1.1.4. Electron transfer oxidation

Most of the radical reactions are initiated by electron transfer process and proceed *via* radical ions. Electron transfer is one of the most elementary processes in organic chemistry. In an electron transfer process, the two species involved are a donor and an acceptor. The electron transfer can be effected at an electrode, or by an oxidant or by photochemical methods.

The electron transfer process can be represented by the following equilibrium.

$$R + A \rightleftharpoons [R^{+\cdot}\ A^{-\cdot}]$$

It is the fate of the ion pair $[R^{+\cdot}\ A^{-\cdot}]$, which decides the course of the reaction. Invariably most organic reactions proceed *via* an inner sphere electron transfer in which the intermolecular interaction of the ion pairs formed play an important role. Even though the deciding factor in the formation of the ion pair is the oxidation/reduction potential of the donor/acceptor, knowledge of the potential is not sufficient to predict the feasibility of an electron transfer reaction. The driving force $E_{0\ ox} + E_{0\ red}$ only relates to the electron transfer oxidation and the most important factor is the behavior of the contact ion pair, its further reactions, *viz.*, conversion to the products or back electron transfer to generate the reactants. Although the reactivity cannot be predicted from knowledge of the redox potentials of the species involved, whether the ion pair is formed or not depends on the potentials of the reacting species.[9]

1.1.5. Radical cations

Radical cations, as the term indicates, are charged radicals; that is species having both a cationic and a radical center. They are generated by removing an electron from a neutral molecule. The activation energy for most

of the reactions involving radical cations is zero or nearly zero, thus allowing fast and selective reactions. The unpaired spin and the charge site may be on the same atom or on distal atoms, the latter being called distonic species.[9]

Schmittel has classified organic molecules into three categories as π donors, σ donors, and n donors, considering the atom or group of atoms exhibiting the largest HOMO coefficient. Thus according to his classification, toluene is a π donor, triethylamine an n donor and cyclopropane a σ donor.[10]

Electron transfer oxidation by chemical methods normally involves the use of metal ions as the oxidant. Salts of metal ions such as Mn(III), V(V), Co(II), Cu(II), Fe(III), Ag(II), Ir(VI) and Ce(IV) are useful for chemical electron transfer oxidation. Although Mn(III) acetate occupies a unique position among all one electron oxidants in bringing out certain synthetic transformations such as intramolecular cyclizations, the formation of side products and procedural problems associated with this reagent are serious disadvantages. Very recently, Cerium(IV) ammonium nitrate (CAN) has emerged as a suitable one-electron oxidant for many substrates. The low cost, non-toxicity, solubility in a number of organic solvents and the experimental simplicity make CAN an excellent reagent in organic synthesis.

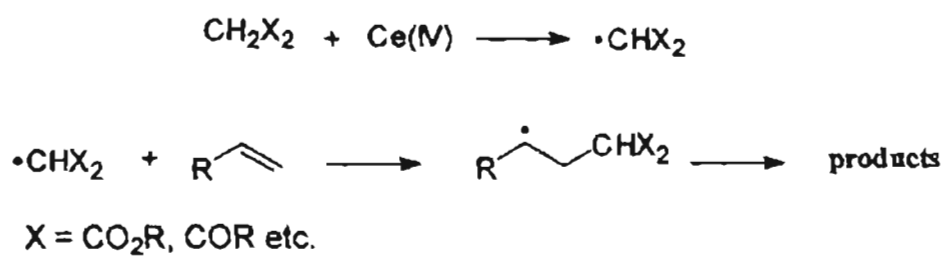
1.1.6. CAN as a one-electron oxidant

It is now generally recognized that CAN is superior to other one-electron oxidants.[11] Electron transfer oxidation using Ce(IV) operates by a borderline mechanism and it cannot be classified as involving either inner sphere or outer sphere.[10] Interaction of CAN with a neutral organic molecule results in the formation of a radical cation, the properties of which have been described earlier. The radical cation formed can undergo a variety of reactions involving fragmentation, deprotonation, or rearrangement. Many of these reactions are of synthetic value.

A number of synthetic transformations are possible with CAN and other Ce(IV) reagents, CAN being the reagent of choice.

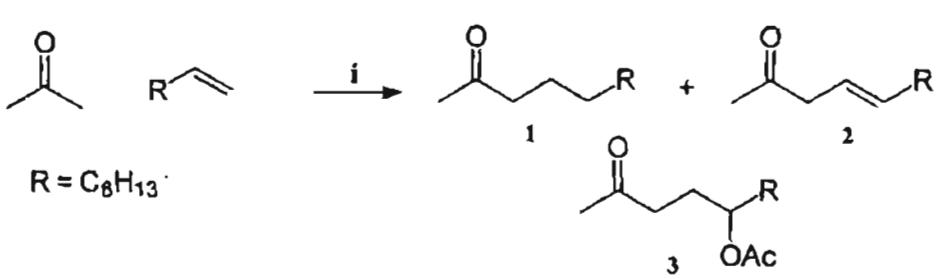
1.2. SYNTHETIC TRANSFORMATIONS USING CAN

The generation of carbon centered radicals using Ce(IV) reagents and addition of these to alkenes go back to the pioneering work of Heiba and Dessau in 1971.[12] Investigations in this area have shown that electrophilic carbon centered radicals generated using Cerium(IV) reagents can react with alkenes producing a number of interesting products. The first example of the Ce(IV) mediated generation of carbon centered radicals involves the oxidation of CH_2X_2 to produce an electrophilic carbon radical $\cdot CHX_2$. Addition of this radical to alkenes gives different products (Scheme 1).



Scheme 1

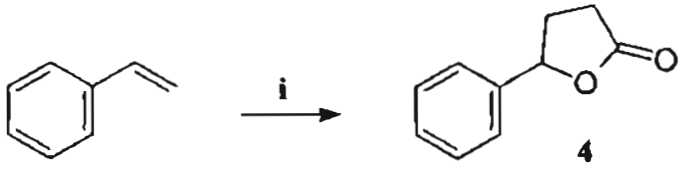
The reaction between acetone and 1-octene is an example. The radical generated from acetone adds to octene giving ketone **1**, the unsaturated ketone **2** and the keto acetate **3** (Scheme 2).[12]



i. $Ce(OAc)_4$, AcOH

Scheme 2

By using a related procedure, γ–lactones have been synthesized by the reaction of cerium(IV) acetate with olefins and carboxylic acids (Scheme 3).[13]



i. $Ce(OAc)_4$, AcOH, 120 °C, 75%

Scheme 3

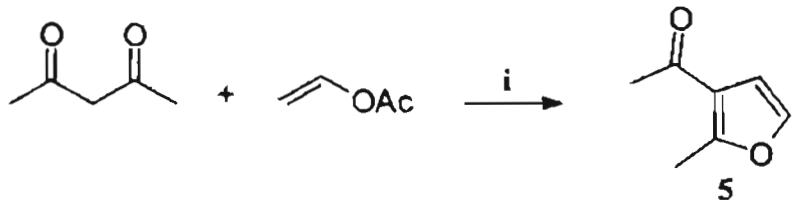
Subsequently, Ce(IV) reagents have been used for various synthetic transformations. It may be pointed out that, in most of the earlier experiments, the Ce(IV) reagent used was the unstable $Ce(OAc)_4$ in acetic acid. A significant advance in this area was made by Baciocchi *et al.* They have shown that a number of synthetic transformations can be performed in methanol or acetonitrile using CAN.

1.2.1. Review of CAN mediated transformations

From the vantage point of the present work, CAN mediated reactions can be broadly classified as carbon-carbon bond forming reactions, carbon-heteroatom bond forming reactions and miscellaneous transformations. Representative examples are presented in the following sections.

1.2.1.1. Carbon-carbon bond forming reactions mediated by CAN

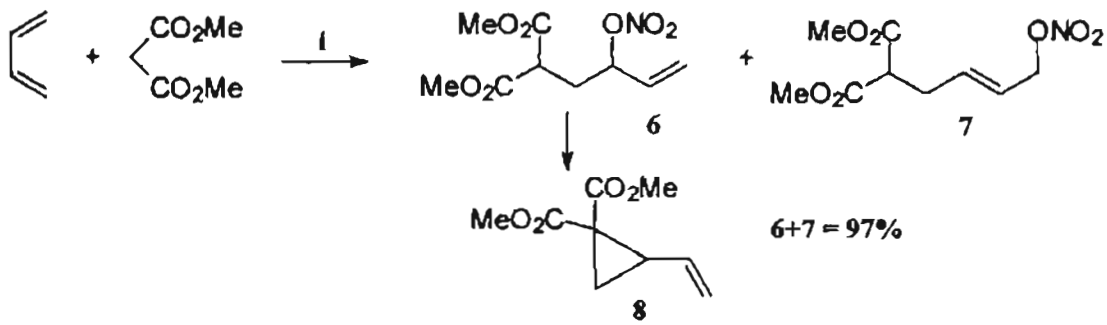
Baciocchi *et al.* have studied the CAN mediated addition of 1,3-dicarbonyl compounds to activated alkenes. The oxidative addition of acetyl acetone and ethyl acetoacetate in presence of CAN to activated alkenes such as vinyl acetates producing furan derivatives is illustrative (Scheme 4).[14]



i. CAN ii. PPTS, 56%

Scheme 4

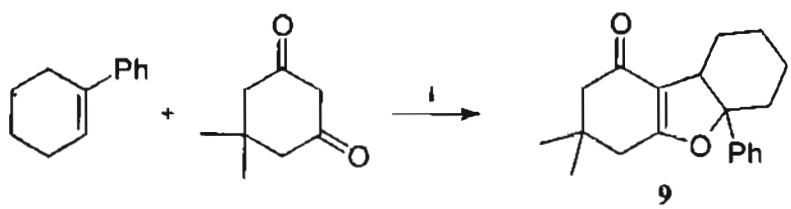
The oxidative addition of dimethyl malonate to 1,3-butadiene leading to different products including a cyclopropane derivative has also been reported by Baciocchi (Scheme 5).[15]



i. CAN

Scheme 5

Extensive studies in this area have been carried out in our own laboratory. It has been shown that the oxidative addition of dicarbonyl compounds such as dimedone, acetyl acetone and ethyl acetoacetate to alkenes constitutes a convenient and efficient method for the preparation of dihydrofurans. The following example is illustrative (Scheme 6).[16]

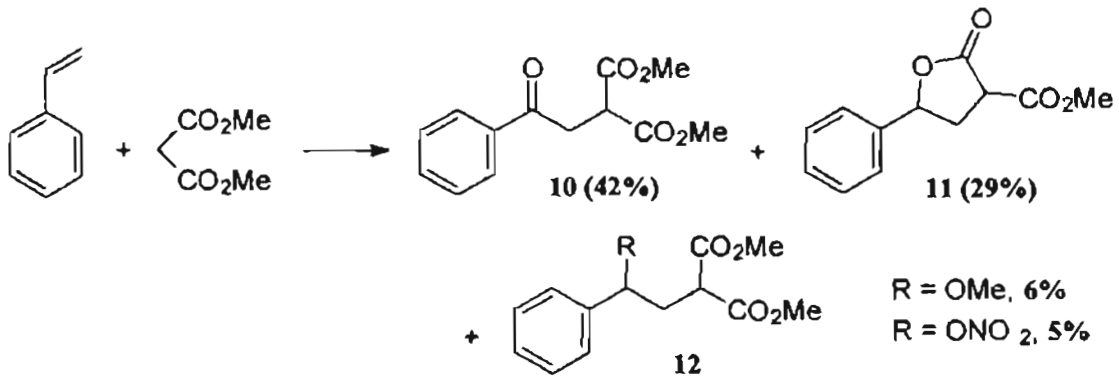


i. CAN, MeOH, 5 °C, 98%

Scheme 6

In a comparative study of the oxidative addition of 1,3-dicarbonyl compounds to alkenes using CAN and Mn(III) acetate, it was found that CAN is superior to the latter in terms of yields of the products, experimental simplicity and rate of the reaction.[16a]

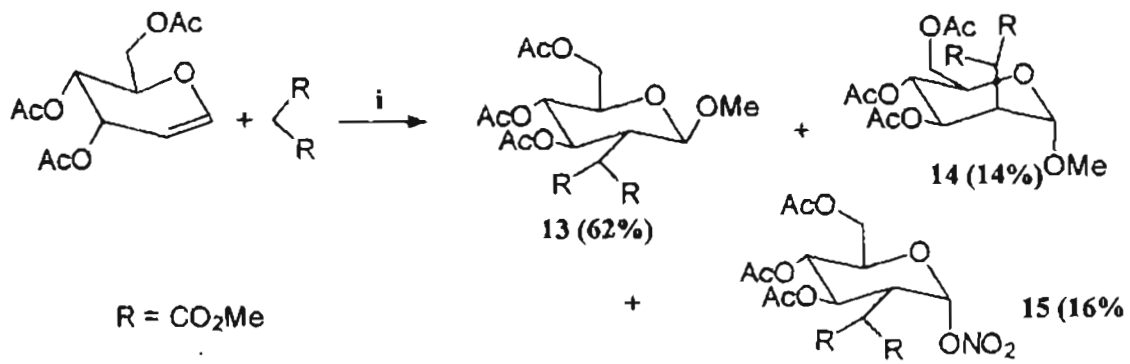
An interesting and mechanistically fascinating reaction was observed in the oxidative addition of dimethyl malonate to styrene in presence of CAN (Scheme 7).[17]



i. CAN, MeOH, 20 °C

Scheme 7

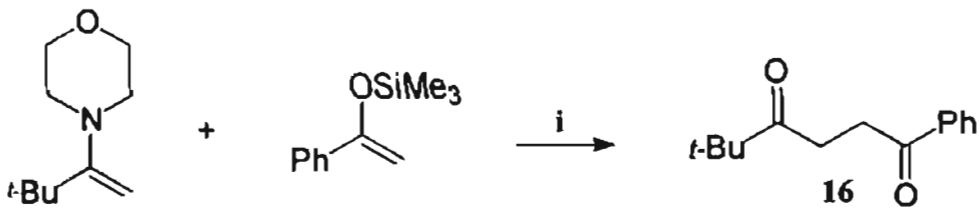
Linker has reported the addition of dimethyl malonate to tri-O-acetyl-D-glucal in methanol in presence of CAN (Scheme 8).[18]



i. CAN, MeOH, 0 °C

Scheme 8

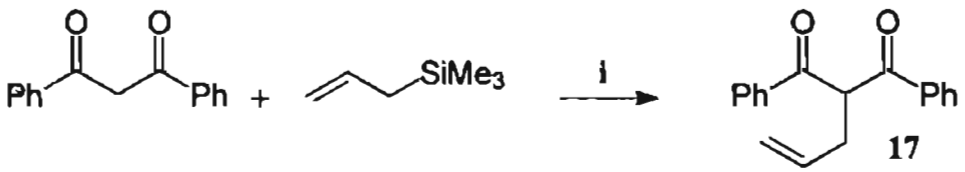
Enamines undergo oxidation by CAN to the radical cation and the subsequent addition of the latter to electron-rich olefins such as silyl enol ethers leads to the formation of diketones (Scheme 9).[19]



i. CAN, MeCN, 0.5 h, rt, 63%

Scheme 9

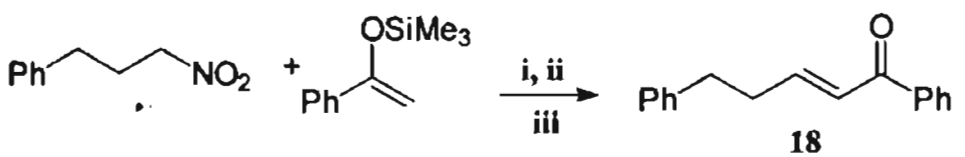
1,3-Dicarbonyl compounds can be allylated using allyltrimethyl silane and CAN in methanol (Scheme 10).[20]



i. CAN, MeOH, rt, 91%

Scheme 10

Potassium salts of nitroalkanes undergo oxidation by CAN to generate the nitro alkyl radicals and these have been added to silyl enol ethers affording β-nitro ketones which are further transformed to α,β-unsaturated ketones (Scheme 11).[21]

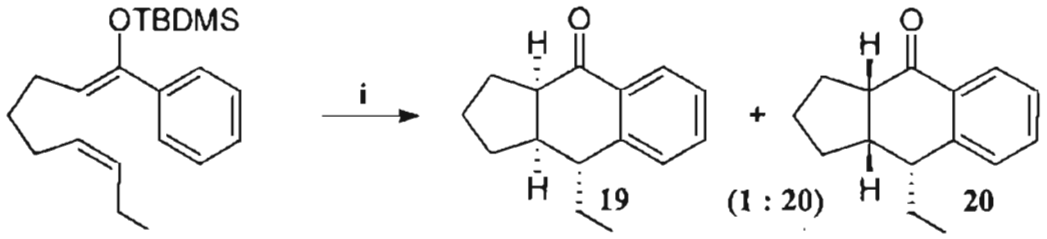


i. KOH, MeOH, rt. ii. CAN, MeOH, -78 °C iii. Et_3N, MeOH, rt.

Scheme 11

Although intermolecular C-C bond formation mediated by CAN has been studied in detail, there are very few reports on the intramolecular

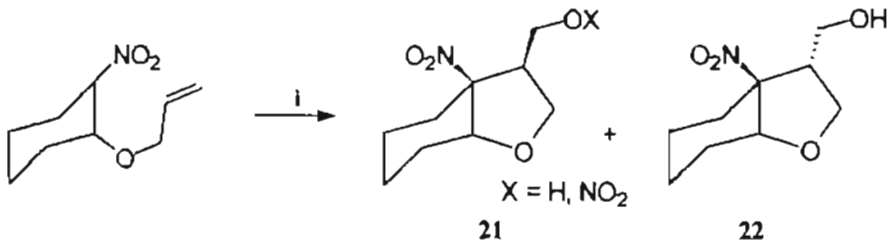
reactions. An interesting example reported by Snider *et al.* involves the intramolecular oxidative cyclization of δ,ε-and ε,ζ-unsaturated silyl enol ethers resulting in tricyclic ketones with excellent stereo control and in good yields (Scheme 12).[22]



i. CAN, $NaHCO_3$, MeCN, 25 °C, 73%

Scheme 12

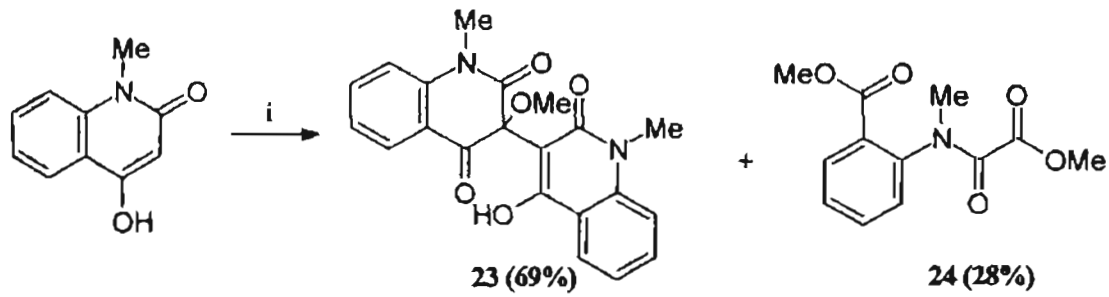
Intramolecular cyclization using nitroalkenyl radicals generated from nitroacyl anions forming tetrahydrofurans and tetrahydropyrans has been reported very recently (Scheme 13).[23, 24]



i. CAN, THF, -78 °C, 0.1N $Na_2S_2O_3$

Scheme 13

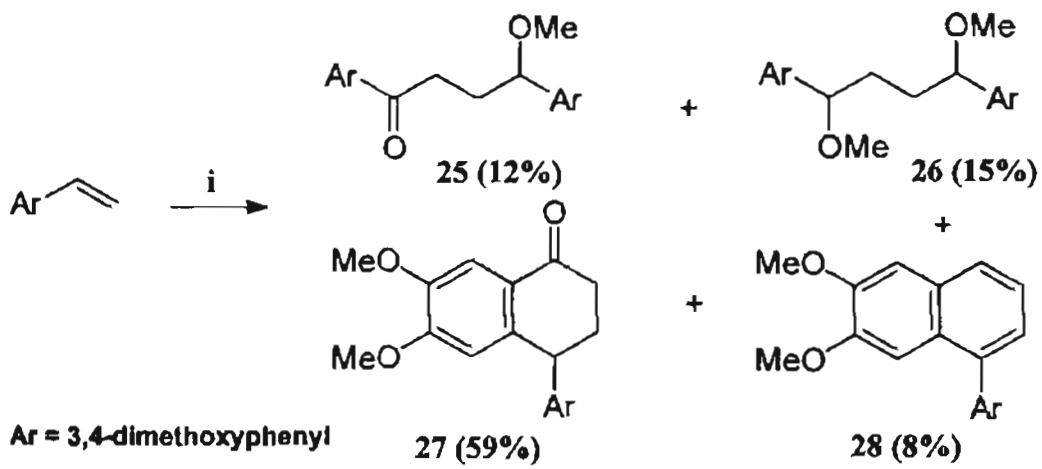
CAN mediated dimerization reactions have also been reported. Dimerization of hydroxy quinolin-2[1H]-ones in presence of CAN in methanol has been reported very recently (Scheme 14).[25]



i. CAN, MeOH, rt

Scheme 14

A facile dimerization reaction of methoxystyrenes in presence of CAN in different solvents has been studied in detail. The following example is illustrative of this very interesting reaction (Scheme 15).[26]



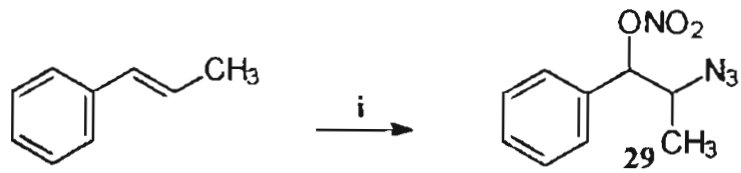
i. CAN, MeOH, 20 °C

Scheme 15

1.2.1.2. Carbon-heteroatom bond forming reactions

In comparison to its use in carbon-carbon bond forming reactions, carbon-heteroatom bond forming reactions mediated by CAN had not received much attention until recently.

The first example of a carbon-heteroatom bond forming reaction by CAN involves the addition of azide to styrenes leading to azidonitrates reported by Trahanovsky as early as 1971 (Scheme 16).[27]

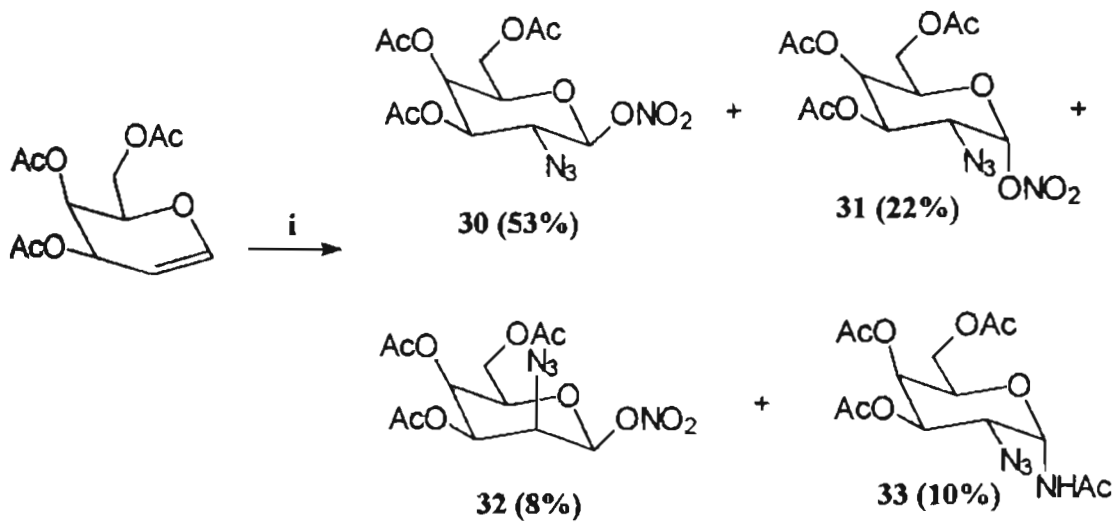


29

i. CAN, NaN_3, MeCN, 73%

Scheme 16

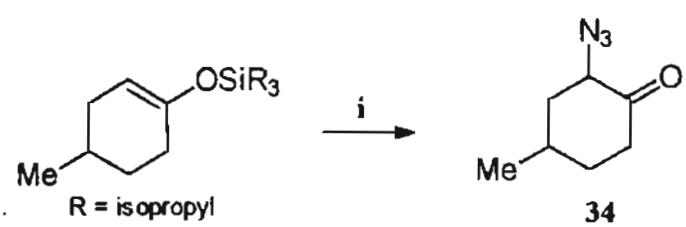
This reaction has been exploited by Lemieux in the synthesis of azidosugars which are important intermediates in the synthesis of aminosugars (Scheme 17).[28]



i. CAN, NaN_3, MeCN, 0 °C-rt, Argon

Scheme 17

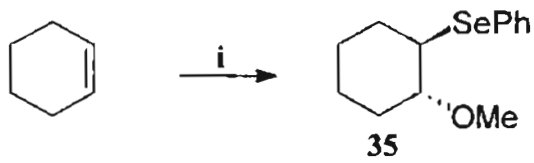
Magnus has synthesized α-azidoketones in average to good yields by the oxidative addition of azide to triisopropylsilyl enol ethers (Scheme 18).[29]



i. CAN, NaN_3, MeCN, -20 °C, Argon, 81%

Scheme 18

Alkenes on reaction with diphenyldiselenide in presence of CAN afforded the corresponding methoxy phenylselenides in excellent yields (Scheme 19).[30]

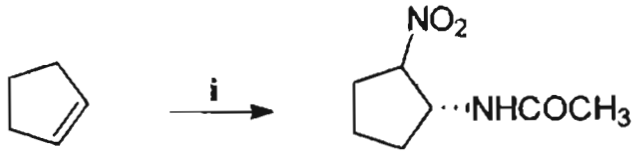


35

i. CAN, PhSeSePh, MeOH, rt, Argon, 93%

Scheme 19

Nitroacetamidation of olefins using CAN and sodium nitrite in acetonitrile has been reported. The product arises *via* the Ritter reaction of the intermediate cation formed (Scheme 20).[31]

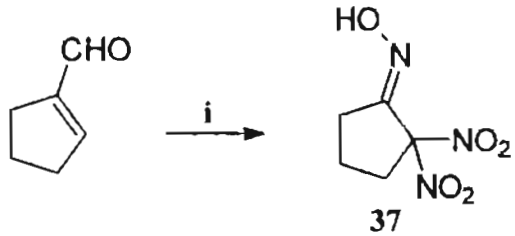


36

i. CAN, $NaNO_2$, MeCN, 64%

Scheme 20

Interestingly, with the same combination of reagents, cyclopentene carboxaldehyde is converted to the dinitrooxime (Scheme 21).[32]

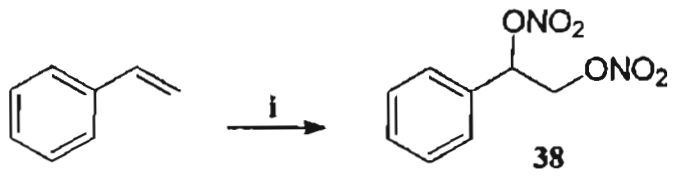


37

i. CAN, $NaNO_2$, MeCN, 21%

Scheme 21

Formation of dinitrates from styrene under photochemical or thermal conditions using CAN in acetonitrile has been reported by Baciocchi *et al.* (Scheme 22). [33]

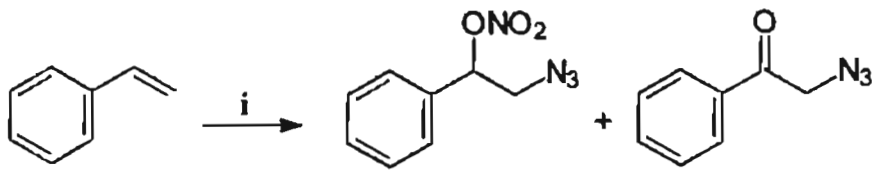


38

i. CAN, MeCN, 86%

Scheme 22

Recent work from our own laboratory has demonstrated the use of CAN in a variety of carbon-heteroatom bond forming reactions.[34-37] A facile synthesis of phenacyl azide and nitratoazide from styrenes has been achieved using sodium azide and CAN in acetonitrile (Scheme 23).[34]

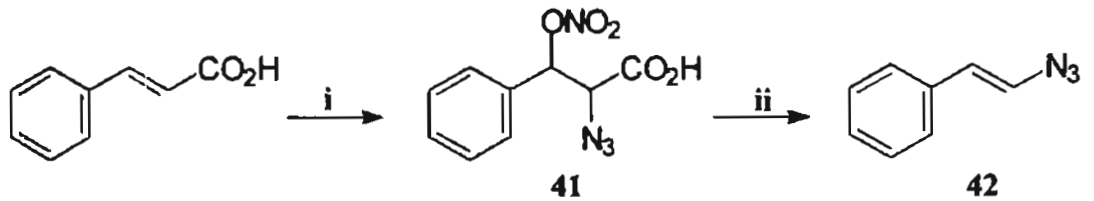


39 (50%) 40 (25%)

i. CAN, NaN_3, MeCN, 0 °C

Scheme 23

The reaction of cinnamic acid with sodium azide and CAN in acetonitrile under deoxygenated atmosphere afforded the azidonitrate (**41**); the latter on treatment with sodium acetate in acetone yielded the β–azido styrene **42** in a one-pot operation (Scheme 24).[35]

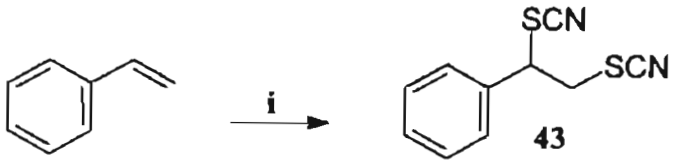


41 42

i. CAN, NaN_3, MeCN, 0 °C, Argon, 70% ii. CH_3CO_2Na, Acetone, reflux, 66%

Scheme 24

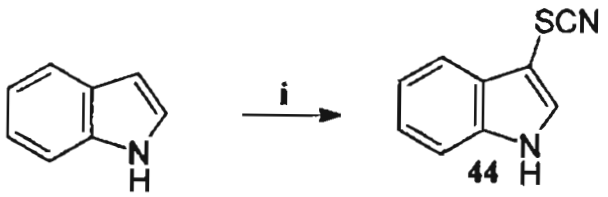
A method for synthesizing 1,2-dithiocyanates in high yields using ammonium thiocyanate and CAN with alkenes in acetonitrile has been reported recently (Scheme 25).[36]



CAN, NH_4SCN, MeCN, rt, 95%

Scheme 25

A direct conversion of indoles to 3-thiocyanato indoles has been achieved by treating them with ammonium thiocyanate and CAN (Scheme 26).[37]

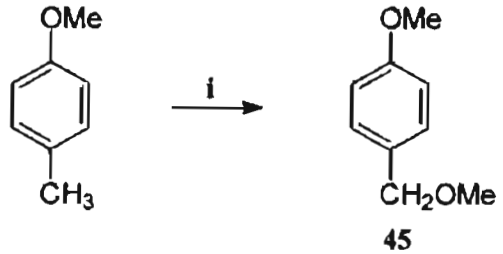


i. CAN, NH_4SCN, MeOH, rt, 100%

Scheme 26

1.2.1.3. Miscellaneous oxidative transformations using CAN

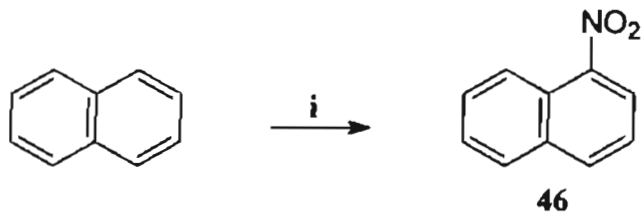
The side chain oxidation of alkyl aromatic compounds has been studied in detail. The methoxylation of 4-methyl anisole by the reaction of CAN with methanol as the solvent has been reported (Scheme 27).[38]



i. CAN, MeOH, reflux, 2 min, 66%

Scheme 27

Nitration of naphthalene using CAN under heterogeneous conditions afforded 1-nitro naphthalene in very good yield (Scheme 28).[39]

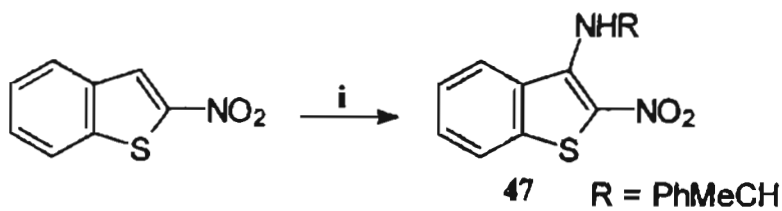


46

i. CAN, silica gel, H_2SO_4, Bu_4NNO_2, CH_2Cl_2, rt, 81%

Scheme 28

2-Nitrobenzothiophenes on treatment with CAN and a primary amine underwent oxidative nucleophilic substitution to give 2-nitro-3-aminobenzothiophene (Scheme 29).[40]

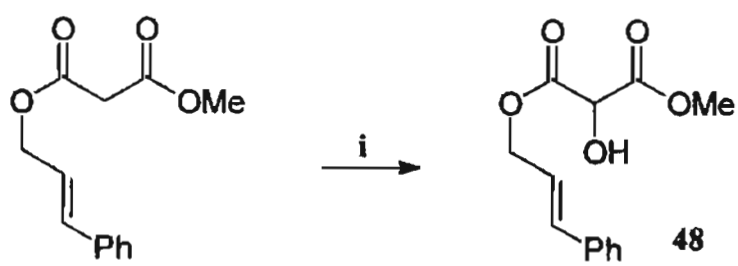


47 R = PhMeCH

i. CAN, $PhMeCHNH_2$, aq.MeCN, 66%

Scheme 29

In an attempted CAN mediated cyclization of cinnamyl malonate, a very interesting reaction leading to tartronic acid derivative was observed (Scheme 30).[41]

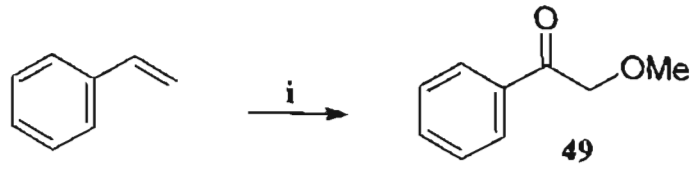


48

i. CAN, MeOH, 0 °C, 62%

Scheme 30

A facile conversion of styrenes and stilbenes to α–methoxy acetophenones has been achieved by using CAN in methanol (Scheme 31).[42]

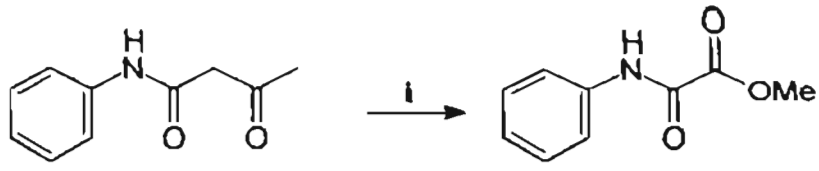


49

i. CAN, MeOH, 0 °C, 55%

Scheme 31

CAN mediated transformation of acetoacetamides to oxamates has been reported recently (Scheme 32).[43]



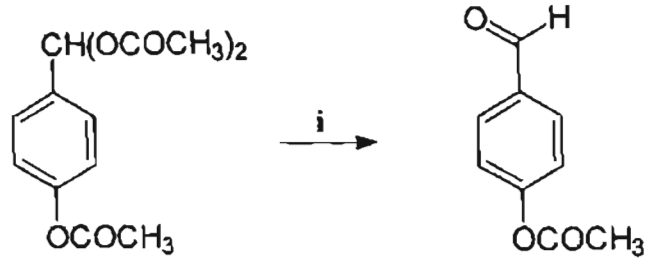
50

i. CAN, MeOH, 0 °C, 80%

Scheme 32

CAN has been used as an efficient reagent for the removal of various protecting groups. The following are some examples.

Benzaldehyde diacetates were selectively converted to the corresponding benzaldehydes by CAN coated on silica gel (Scheme 33). [44]

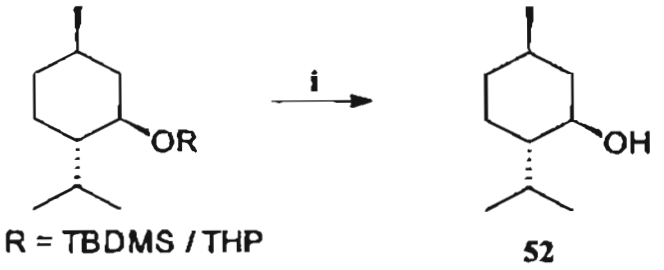


51

i. CAN, SiO_2, CH_2Cl_2, 98%

Scheme 33

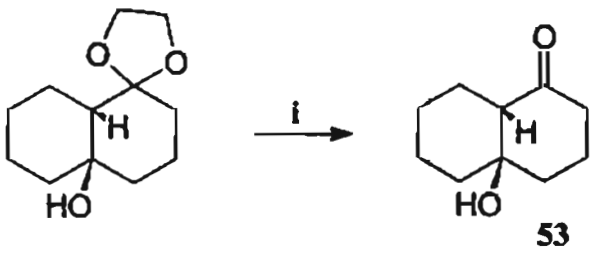
An efficient method for the deprotection of *tert*-butyldimethylsilyl (TBDMS) and tetrahydropyranyl (THP) ethers using CAN has been reported (Scheme 34).[45]



i. CAN, MeOH, 0 °C, 90%

Scheme 34

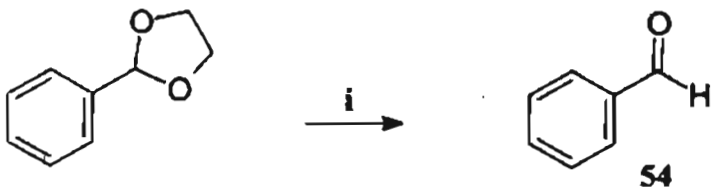
Cyclic acetals and ketals have been deprotected using excess of CAN in aqueous methanol (Scheme 35).[46]



i. 2.5 eq.CAN, aq.MeCN, 70 °C, 90%

Scheme 35

A facile method for the deprotection of acetal using CAN has been reported from our laboratory very recently (Scheme36).[47]



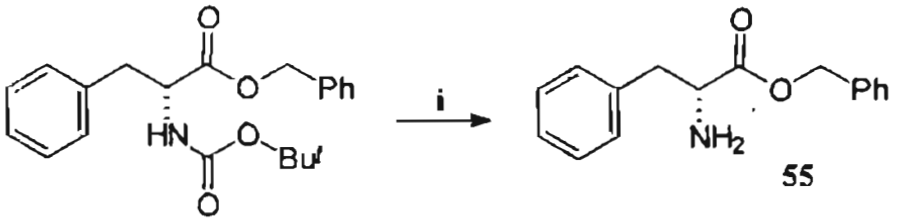
i. CAN, MeOH, 0 °C, 80%

Scheme 36

1.3. CAN AS A CATALYTIC OXIDANT

Although CAN is far superior to many other one-electron oxidants, the large quantities required for the reactions preclude its use in large scale applications. Some reactions of CAN, however, are autocatalytic in nature.

For example, the deprotection of Boc group using CAN operates through a mechanism in which CAN is made autocatalytic (Scheme 37).[48]



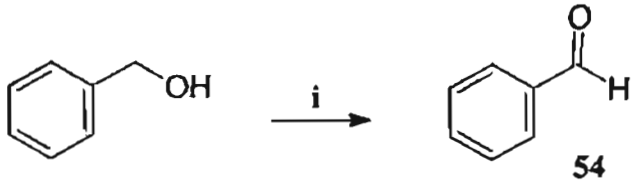
55

i. CAN, MeCN, 80 °C, 95%

Scheme 37

There are a number of reports on the catalytic use of CAN in oxidations, with bromate serving as the co-oxidant. Some representative examples are given below.

Oxidation of benzyl alcohols to the corresponding carbonyl compounds using CAN and sodium bromate as the dual oxidant has been reported (Scheme 38).[49]



54

i. CAN, $NaBrO_3$, aq.MeCN, 80 °C, 90%

Scheme 38

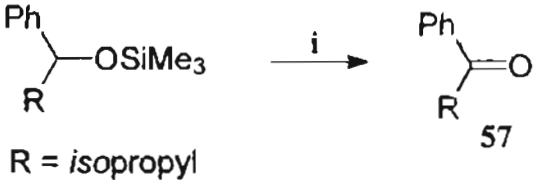
CAN catalyzed oxidation of alkyl aromatics with $KBrO_3$ affords aldehydes or ketones in very good yields (Scheme 39).[50]

56

i. CAN, $KBrO_3$, aq.MeCN, 80 °C, 95%

Scheme 39

Alkyl ethers and trialkyl silyl ethers can be cleaved oxidatively by sodium bromate in presence of catalytic amounts of CAN (Scheme 40).[51]



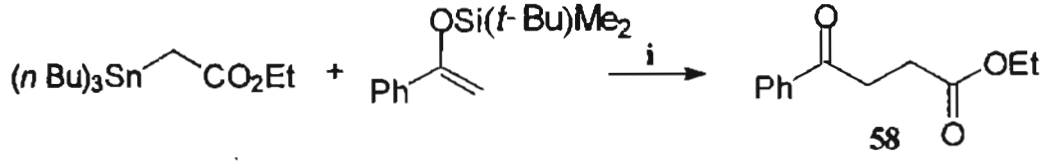
i. CAN, $NaBrO_3$, aq.MeCN, 80 °C, 84%

Scheme 40

1.4. OXIDATION WITH OTHER Ce(IV) REAGENTS

Although CAN is the most widely used Ce(IV) reagent, other reagents like tetrabutylammonium Ce(IV) nitrate, Ce(IV) acetate, Ce(IV) trifluoroacetate, Ce(IV) methanesulfonate, Ce(IV) sulfate, and Ce(IV) ammonium sulfate have also found some use in various synthetic transformations. Since many of them are unstable, only limited reports are available. Representative examples are presented in the following passage.

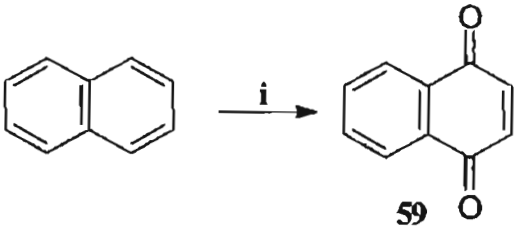
Tetrabutylammonium Ce(IV) nitrate (TBACN) mediated oxidative addition of α-tributyl stannyl alkanoates to olefins like enol ethers giving the ketoester has been reported (Scheme 41).[52]



i. TBACN, K_2CO_3, MeCN, 0 °C, 96%

Scheme 41

Polynuclear hydrocarbons have been oxidized to the corresponding quinones by using Cerium(IV) ammonium sulfate (Scheme 42).[53] Similar results were obtained using $Ce(MeOSO_2)_4$ also.[54]

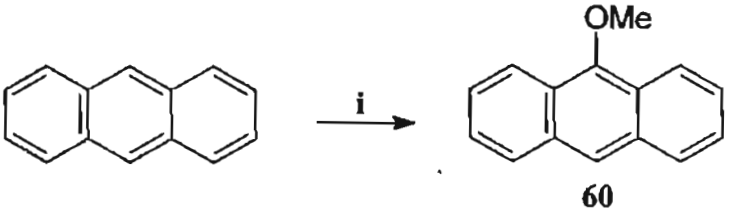


59

i. CAS, MeCN-H_2O-H_2SO_4, 25 °C, 6h, 96%

Scheme 42

Cerium(IV) trifluoroacetate mediated alkoxylation of anthracene has been reported (Scheme 43).[55]



60

i. $Ce(OCOCF_3)_4$, MeOH, 25 °C, 72h, 75%

Scheme 43

Vicinal diols undergo oxidative cleavage with Cerium(IV) perchlorate (Scheme 44).[56]

61

i. $Ce(ClO_4)_4$, H_2O, 25 °C, 91%

Scheme 44

1.5. CONCLUSION

It is clear from the literature survey presented above that CAN is an excellent one electron oxidant useful in bringing about various synthetic transformations. It is also evident that, much of the potential of CAN remains

untapped. The present study is aimed at exploring the synthetic potential of CAN with a view to uncover novel reactions.

1.6. DEFINITION OF THE PROBLEM

Three areas of CAN mediated reactions appeared very interesting for exploration.

In the first instance we decided to investigate a novel CAN mediated fragmentation of arylcycloalkenes both from the mechanistic and synthetic standpoints.

In contrast to the extensive work on C-C bond forming reactions mediated by CAN, C-heteroatom bond formation has received only limited attention. In this context, it was of interest to explore the oxidative addition of bromide to alkenes as an alternative to the conventional use of bromine.

The third area that attracted our attention was the CAN mediated transformations of cyclopropanes.

The results of the studies in the areas outlined above are presented in the following chapters of the thesis.

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CHAPTER 2

OXIDATIVE FRAGMENTATION OF ARYLCYCLOALKENES BY CAN: FACILE SYNTHESIS OF 1,n-DICARBONYL COMPOUNDS

2.1. INTRODUCTION

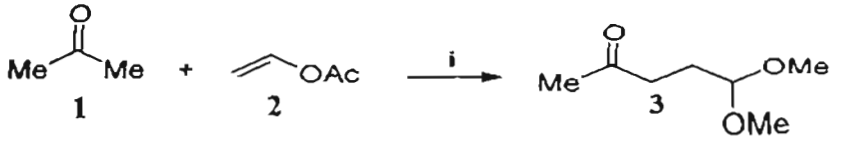
2.1.1. General

Synthesis of an organic compound essentially involves the formation of new carbon-carbon and carbon-heteroatom bonds. The existing methods for such bond formation involve ionic reactions, pericyclic reactions and radical reactions. As mentioned in the introductory chapter, compared to ionic and pericyclic reactions, radical reactions received only limited attention until recently, due to the assumption that they are uncontrollable and less selective. As a consequence of the extensive and systematic investigations carried out by a number of synthetic organic chemists, radical methodology now has been widely accepted. The realization that radical reactions possess many advantages over ionic or pericyclic reactions has continued to invoke enormous interest in this area. Even though photochemical and electrochemical methods have been used for the generation of radicals, methods using electron transfer reagents is the subject of current interest and recently cerium(IV) ammonium nitrate (CAN) has emerged as a powerful one-electron oxidant.

The formation of carbon centered radicals using Ce(IV) reagents and subsequent addition of these radicals to alkenes have been first reported by Heiba and Dessau.[1] Subsequent investigations carried out by a number of

synthetic organic chemists showed that CAN is an excellent one electron oxidant for various synthetic transformations. (For a complete introduction to radical reactions and reactions mediated by CAN (see General Introduction, Chapter 1).

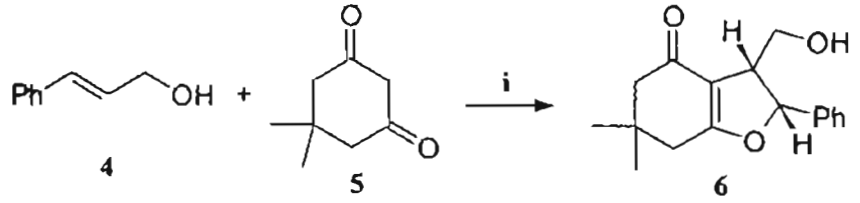
Baciocchi has extensively studied the addition of carbon centered radicals generated by CAN to electron rich alkenes. 1,4-Diketones and 4-keto aldehyde dimethylacetals have been synthesized in good yields by the CAN mediated addition of ketones to isopropenyl and vinyl acetates. The formation of the keto acetal **3** from acetone and vinyl acetate is an example (Scheme 1).[2]



i. CAN, MeOH

Scheme 1

Our research group has been interested in the addition of carbon centered radicals generated using CAN to various alkenes. A detailed investigation carried out in this area has shown that the addition of radicals generated from various 1,3-dicarbonyl compounds such as dimedone, acetylacetone and ethylacetoacetate to alkenes offers a convenient method for the synthesis of dihydrofuran derivatives. For example, the reaction of cinnamyl alcohol and dimedone in methanol with CAN afforded the dihydrofuran derivative **6** in good yield (Scheme 2).[3]

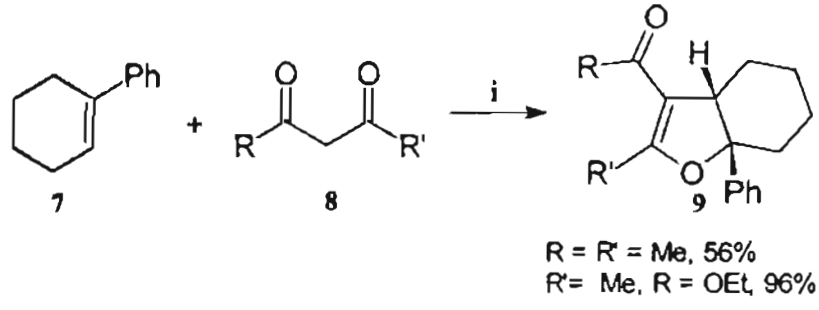


i. CAN, MeOH, rt, 55%

Scheme 2

This reaction has been studied in detail using various alkenes and dicarbonyl compounds.

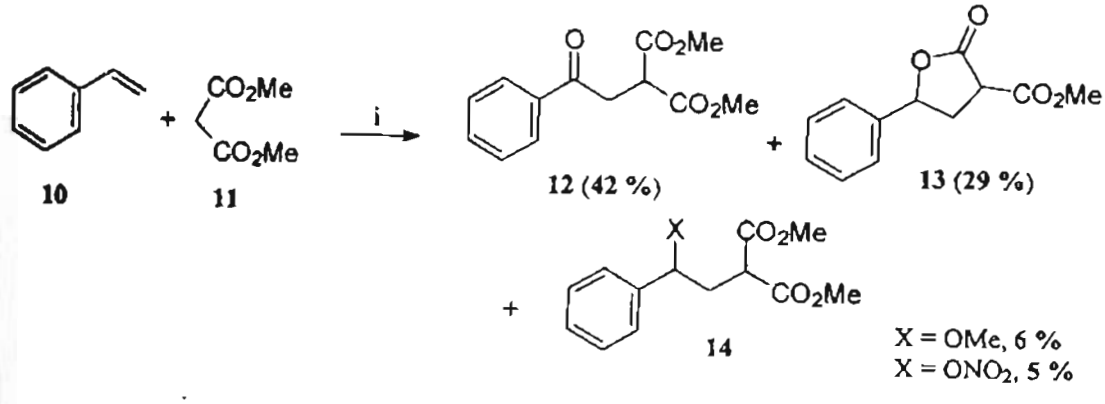
CAN mediated addition of acetylacetone and ethylacetoacetate to phenylcyclohexene leads to the dihydrofuran derivatives as shown in Scheme 3.[4]



i. CAN, MeOH, rt

Scheme 3

The CAN mediated addition of dimethylmalonate to styrene in methanol led to a mechanistically fascinating reaction yielding several products, with 2-oxo-2-phenylethylpropanedioic acid dimethylester **12** as the major product (Scheme 4).[5]

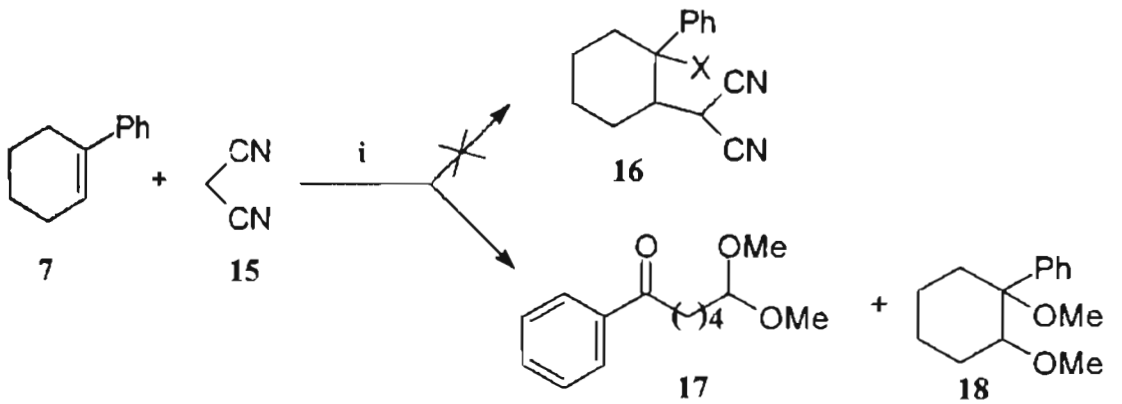


i. CAN, MeOH, 20 °C

Scheme 4

Presumably, these reactions involve the oxidation of the active methylene compound to generate the carbon centered radical and addition of the latter to the alkene, followed by further transformations.

Although the generation of carbon centered radicals from various dicarbonyl compounds has been well studied, the possibility of generating radicals from malononitrile (dicyanomethane) has not been explored. Malononitrile is an active methylene compound (pK_a 11.2) comparable to diethyl malonate (pK_a 12.7) and we were intrigued by the possibility of its oxidative addition to alkenes mediated by CAN. With this objective, a methanolic solution of 1-phenyl-1-cyclohexene and malononitrile was treated with a solution of CAN in the same solvent. However, no addition product was formed; the only products obtained were the monoacetal of 5-benzoylpentanal **17** and 1,2-dimethoxy-1-phenylcyclohexane **18** (Scheme 5).[6]



i. CAN, MeOH, 0 °C

Scheme 5

Although the expected reaction did not occur, the fragmentation of the alkene was quite interesting and therefore we decided to explore the synthetic potential of this novel reaction. In particular, the reaction appeared very useful for generating 1,n-dicarbonyl compounds.

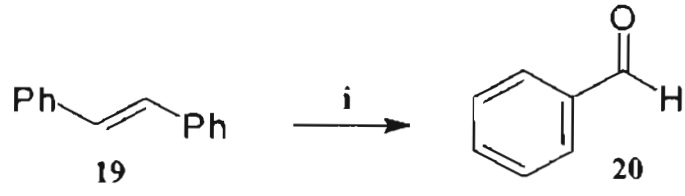
Before discussing the reaction in detail, in order to put the things in perspective, the general methods used for the cleavage of carbon-carbon double bonds and a brief description of the available methods for generating

1,n-dicarbonyl compounds are presented. Only very few reactions have been reported in which CAN has been used for oxidative cleavage. Those reactions are also discussed.

2.1.2. Oxidative cleavage of carbon-carbon double bonds

The oxidative cleavage of carbon-carbon double bonds is a general procedure in organic synthesis for generating carbonyl compounds and a number of methods are available to achieve this. Reactions mediated by metal oxidants are widely accepted. The following are a few examples in which metal oxidants have been used for the oxidative cleavage of carbon-carbon double bonds.

Alkenes are known to undergo oxidative fragmentation to the dicarbonyl compounds when exposed to $KMnO_4$ in aqueous THF. The reaction occurs *via* a glycol intermediate (Scheme 6).[7]

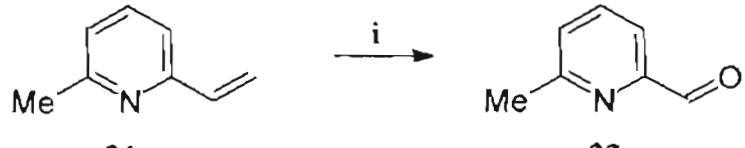


19 20

i. $KMnO_4$, THF, H_2O, 71%

Scheme 6

Ozonolysis is one of the most commonly used methods for the oxidative cleavage of alkenes. An example is the conversion of 2-vinyl-6-methyl pyridine to the corresponding aldehyde (Scheme 7).[8]

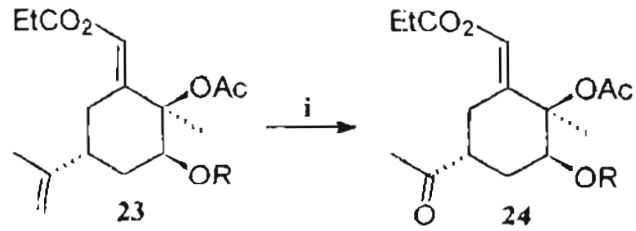


21 22

i. O_3, Na_2SO_3, 80%

Scheme 7

Osmium tetroxide, in presence of periodate has been used for the oxidative cleavage of double bonds. The reaction involves the formation of a vicinal diol and oxidative cleavage of the latter. The following is a representative example (Scheme 8).[9]

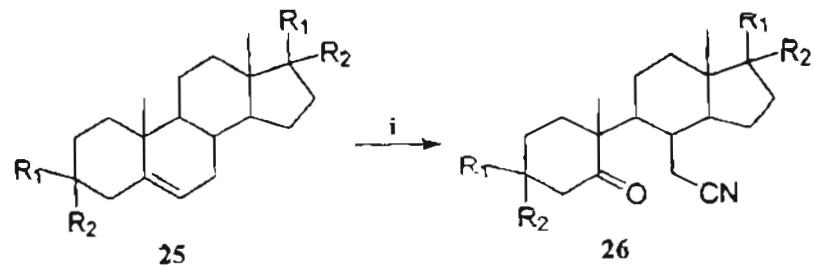


23 24

i. OsO_4, KIO_4, THF, H_2O, 97%

Scheme 8

Another method employed for the oxidative cleavage of carbon-carbon double bonds consists of the reaction of trimethylsilyl azide and lead tetraacetate (Scheme 9).[10]



25 26

i. Me_3SiN_3, $Pb(OAc)_4$, CH_2Cl_2, 30%

Scheme 9

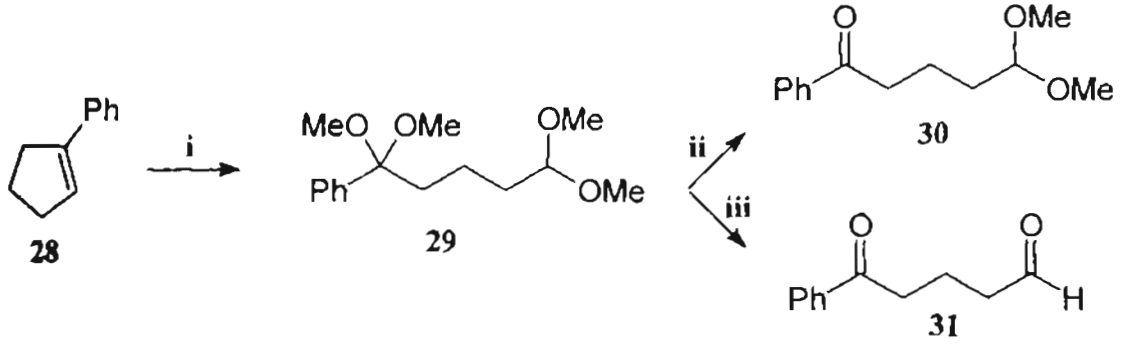
Oxidative cleavage of carbon-carbon double bonds by electrochemical reactions is also well known. Poor selectivity is a disadvantage of this method. An example is the fragmentation of styrenes under electrolytic conditions reported by Maki *et al.* (Scheme 10).[11]

27 20

i. CCE, 20mA, $LiClO_4$, MeCN-H_2O, 78%

Scheme 10

Anodic oxidation of 1-phenyl-1-cyclopentene afforded the diacetal of 4-benzoylbutanal. The product on hydrolysis under different conditions afforded either the monoacetal **30** or the ketoaldehyde **31** (Scheme 11).[12]



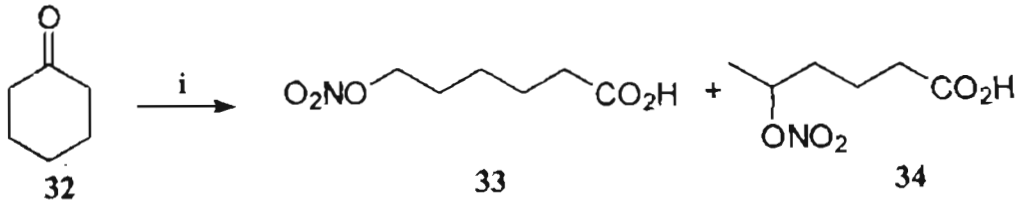
i. 6F mol^{-1}, MeOH, Bu_4NBF_4, 60 °C ii. 10% H_2SO_4, 20 °C iii. 10% H_2SO_4, 50 °C

Scheme 11

2.1.3. Oxidative fragmentation reactions mediated by CAN

There are only a few reports in which CAN has been shown to bring about cleavage of carbon-carbon bonds. The following is a brief discussion of such reactions.

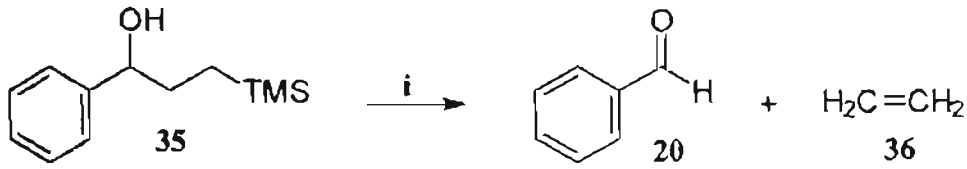
Cycloalkanones have been shown to undergo oxidative fragmentation by CAN in acetonitrile. The reaction presumably occurs *via* the intermediacy of a cation radical (Scheme 12).[13]



i. CAN, MeCN

Scheme 12

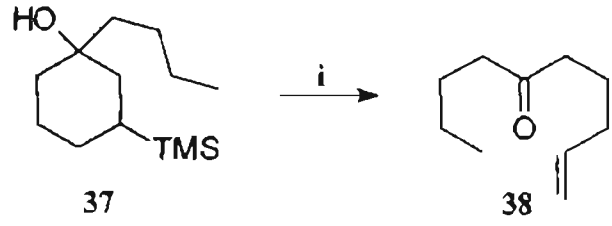
Trahanovsky has reported the oxidative fragmentation of γ-hydroxy silanes by CAN (Scheme 13).[14]



i. CAN

Scheme 13

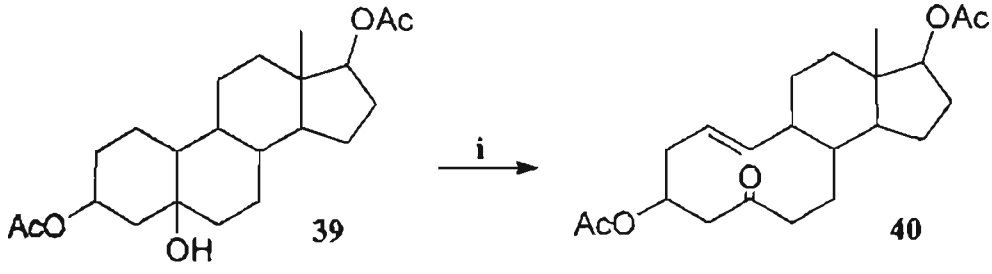
Wilson *et al.* have extended the same reaction to cyclic substrates (Scheme 14).[15]



i. CAN, AcOH, 66%

Scheme 14

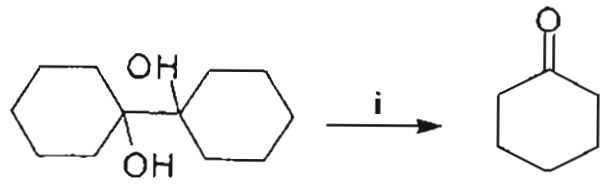
The steroidal alcohol **39** has been shown to undergo oxidative fragmentation in presence of CAN in aqueous acetonitrile (Scheme 15).[16]



i. CAN, MeCN, H_2O, 80 °C, 60%

Scheme 15

Oxidative cleavage of bicyclohexyl-1,1'-diols using CAN has also been reported (Scheme 16).[17]



41 32

i. CAN, AcOH, rt, 94%

Scheme 16

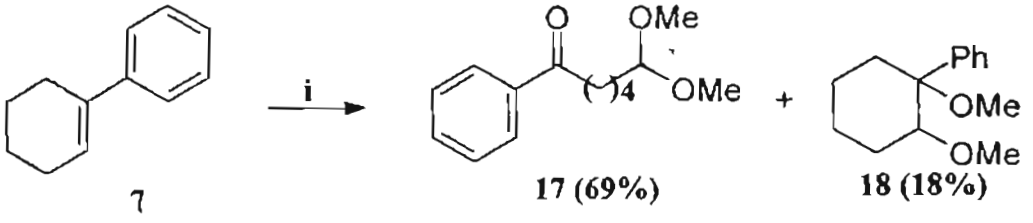
2.1.4. The present work

1,n-dicarbonyl compounds are important intermediates in organic synthesis. Conventional methods for their synthesis involve mainly the ozonolysis of cycloalkenes. It is evident from the literature survey that there is a need for newer and milder reactions for the synthesis of dicarbonyl compounds. In this context, the CAN mediated fragmentation of 1-phenylcyclohexene leading to 5-benzoylpentanal dimethylacetal appeared interesting and a detailed study aimed at exploring the scope of this reaction was undertaken. The results of the investigation are presented in the following section.

2.2. RESULTS AND DISCUSSION

2.2.1. Reaction of phenylcycloalkenes with CAN in methanol

Our studies were initiated by treating a methanolic solution of 1-phenyl-1-cyclohexene with a solution of CAN in methanol at 0 °C. A facile reaction occurred and the absence of the starting material after 30 minutes indicated the completion of the reaction. The products **17** and **18** were isolated in 69% and 18% yields respectively (Scheme 17).



7 **17 (69%)** **18 (18%)**

i. **CAN, MeOH, 0 °C-rt**

Scheme 17

The products were characterized by spectral analysis. The IR spectrum of the product **17** displayed the carbonyl absorption at 1681 cm^{-1}, characteristic of the benzoyl group. In the ^1H NMR spectrum, the aromatic protons resonated as two multiplets centered at δ 7.9 and 7.4. The acetal proton displayed a triplet at δ 4.3 (J = 5.4 Hz). The six methoxy protons presented a singlet at δ 3.2. The two methylene protons adjacent to the carbonyl resonated as a triplet at δ 2.9 (J = 7.2 Hz). The other six aliphatic protons resonated as a multiplet centered at δ 1.7. In the ^{13}C NMR spectrum, the signal due to the carbonyl carbon was seen at δ 200.1. The acetal carbon was discernible at δ 104.4. The signal corresponding to the two methoxy carbons appeared at δ 52.7.

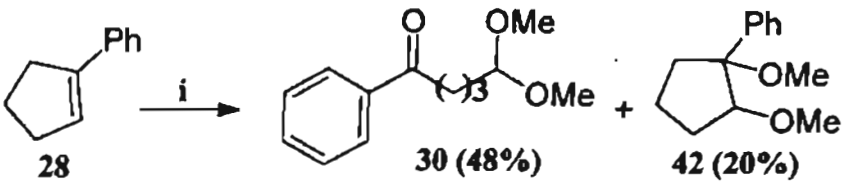
The structure was further confirmed by comparing the spectral data of **17** with those of the authentic compound reported in the literature.[12]

The structure of the dimethyl ether **18** was also confirmed on the basis of spectral analysis. In the ^1H NMR spectrum of the compound, the signal due to the aromatic protons appeared as a multiplet centered at δ 7.3 (5H). The signal corresponding to the methoxy protons appeared as two separate singlets at δ 3.1 and 2.9. The methine proton appeared as a multiplet centered at δ 3.0. The aliphatic protons resonated as a multiplet centered at δ 1.6. In the ^{13}C NMR spectrum of the compound, methoxy carbons appeared at δ 57.8

and 50.1. The carbons bearing the methoxy groups showed signals at δ 85.9 and 80.0. Satisfactory elemental analysis was also obtained.

In order to explore the scope of the reaction, a number of aryl cycloalkenes were treated with CAN in methanol.

1-Phenyl-1-cyclopentene on treatment with a methanolic solution of CAN, afforded the products **30** and **42** in 48% and 20% yields respectively (Scheme 18).



28 **30 (48%)** **42 (20%)**

i. CAN, MeOH, 0 °C-rt, 30 min

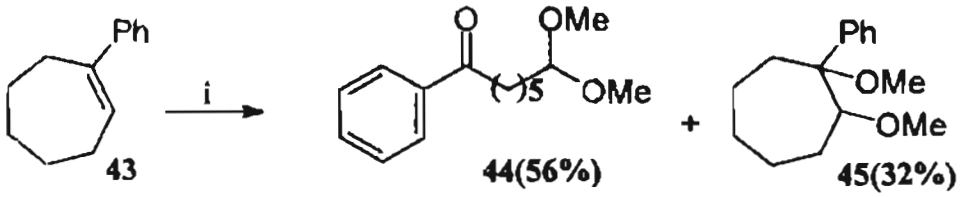
Scheme 18

The structure of the mono acetal **30** was confirmed by spectral analysis and by comparing the data with those reported in the literature.[12] The IR spectrum of the product **30** displayed the carbonyl absorption at 1684 cm^{-1}, characteristic of the benzoyl group. In the ^1H NMR spectrum of **30**, the signal due to the aromatic protons appeared as two multiplets centered at δ 7.9 and 7.4. The characteristic acetal proton was discernible at δ 4.3 as a triplet (J = 5.6 Hz). The methylene protons adjacent to the carbonyl displayed a triplet at δ 3.0 (J = 7.0 Hz). The four aliphatic protons were seen as a multiplet at δ 1.7. In the ^{13}C NMR spectrum of the product, carbonyl carbon resonated at δ 200.5. The acetal carbon was seen at δ 104.6. The two methoxy carbons were discernible at δ 52. 5.

The structure of **42** was assigned on the basis of ^1H and ^{13}C NMR spectra. The aromatic protons resonated as a multiplet centered at δ 7.4 in the ^1H NMR spectrum of **42**. The signals corresponding to the two methoxy

groups appeared as two singlets at δ 3.3 and δ 3.0. The methine proton was discernible as a multiplet at δ 3.1. The ^{13}C NMR spectral values were also in agreement with the assigned structure.

When 1-phenyl-1-cycloheptene was subjected to the reaction conditions described previously, the keto acetal **44** and the dimethylether **45** were obtained in 56% and 32% yields respectively (Scheme 19).



43 **44(56%)** **45(32%)**

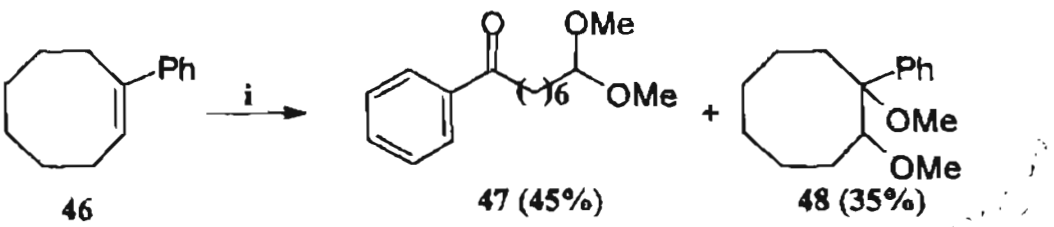
i. CAN, MeOH, 0 °C-rt, 30 min

Scheme 19

As usual, the products were characterized on the basis of spectral data. The IR spectrum of the product **44** displayed the carbonyl absorption at 1681 cm^{-1}, characteristic of the benzoyl group. In the ^1H NMR spectrum, signals due to the aromatic protons were seen as two multiplets centered at δ 7.9 and 7.4. The acetal proton resonated as a triplet at δ 4.3 (J = 5.5 Hz). The methoxy protons displayed a singlet at δ 3.3. The ^{13}C NMR spectrum of **44** showed a signal at δ 200.5 due to the carbonyl carbon. The acetal carbon was seen at δ 104. 6. All the other signals were in complete agreement with the assigned structure.

In the ^1H NMR spectrum of **45**, the signal due to the aromatic protons was seen as a multiplet at δ 7.3. The methoxy protons displayed singlets at δ 3.1 and 2.9. ^{13}C NMR spectrum of **45** showed the signals due to methoxy carbons at δ 57.7 and 50.9. The carbons attached to the methoxy groups displayed signals at δ 89.5 and 82.2. All the other signals were also in agreement with the assigned structure.

When 1-phenyl-1-cyclooctene was treated with a methanolic solution of CAN at ice temperature, the products **47** and **48** were obtained in 45% and 35% yields respectively (Scheme 20).



46 **47 (45%)** **48 (35%)**

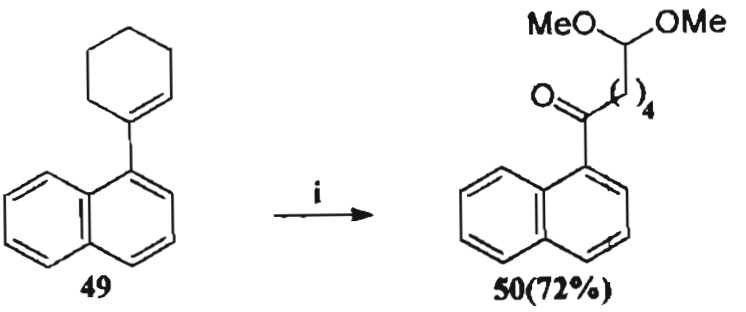
i. CAN, MeOH, 0 °C-rt, 30 min

Scheme 20

The IR spectrum of the product **47** displayed the carbonyl absorption at 1681 cm^{-1}, characteristic of the benzoyl group. In the ^1H NMR spectrum the signals due to the aromatic protons were seen as two multiplets at δ 7.9 and 7.4. The acetal proton was discernible at δ 4.3 as a triplet (J = 5.4 Hz). In the ^{13}C NMR spectrum, the acetal carbon was seen at δ 104. 2. All other signals were also in agreement with the assigned structure. It was further confirmed by comparing the spectral data with those of authentic compounds reported in the literature.[12]

In the ^1H NMR spectrum of **48**, the methoxy protons displayed signals at δ 3.1 and 2.9 as singlets. All the other signals were also in agreement with the assigned structure.

When 1-naphthyl-1-cyclohexene **49**, was treated with a methanolic solution of CAN, the expected fragmentation occurred and the product **50** was obtained in 72% yield. It may be noted that no dimethylether formation was observed in this case.



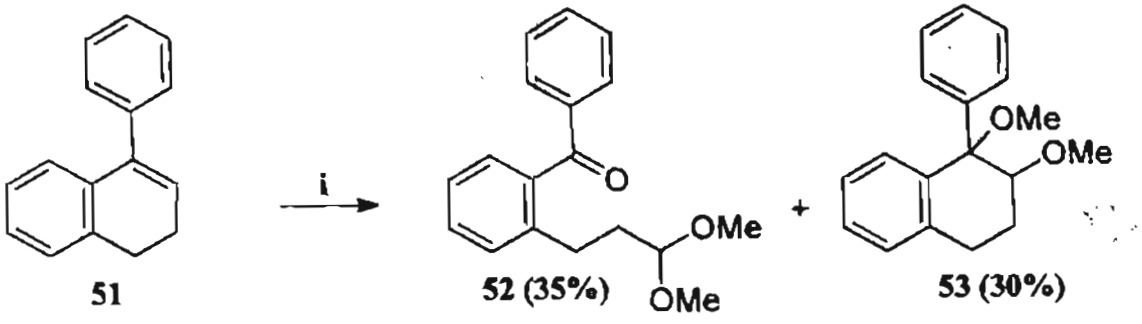
49 50(72%)

i. CAN, MeOH, 0 °C-rt, 30 min

Scheme 21

The structure of **50** was assigned on the basis of spectral data. The IR spectrum of the product displayed the carbonyl absorption at 1681 cm^{-1}, characteristic of the benzoyl group. In the ^1H NMR spectrum of the product, the aromatic protons displayed two doublets at δ 8.5 and 7.9 (J = 8.2 Hz), one triplet at δ 7.8 (J = 8.1 Hz) and a multiplet at δ 7.5. The acetal proton was seen at δ 4.3 as a triplet (J = 5.6 Hz). The signal due to the two methoxy groups appeared as a singlet at δ 3.3. The methylene protons adjacent to the carbonyl appeared as a triplet at δ 3.0 (J = 7.3 Hz). The six aliphatic protons resonated as three multiplets centered at δ 1.8, 1.6 and 1.4. The ^{13}C NMR spectral data was also in agreement with the assigned structure. The carbonyl carbon displayed signal at δ 200.1. The acetal carbon resonated at δ 104.4.

1-Phenyl-3,4-dihydronaphthalene on treatment with a methanolic solution of CAN, afforded the keto acetal **52** and the dimethylether **53** in 35% and 30% yields respectively (Scheme 22).



51 52 (35%) 53 (30%)

i. CAN, MeOH, 0 °C-rt, 30 min

Scheme 22

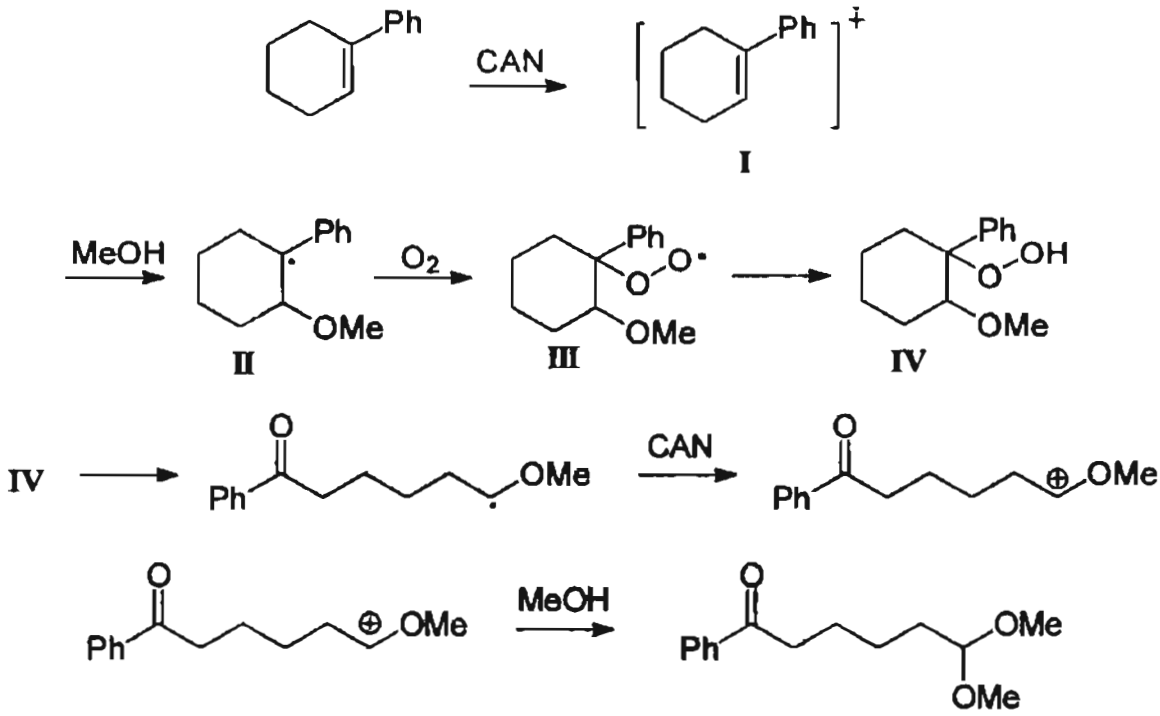
The products **52** and **53** were also fully characterized by spectral analysis. The IR spectrum of the product **52** showed the carbonyl absorption at 1668 cm^{-1} due to the benzoyl carbonyl. In the ^1H NMR spectrum, the signal due to the acetal proton was visible at δ 4.4. The other signals were also in agreement with the assigned structure.

In the ^1H NMR spectrum of product **53**, the aromatic protons were discernible as a multiplet at δ 7.1. Two methoxy groups displayed separate singlets at δ 3.1 and 3.0. The other signals were also in agreement with the assigned structure.

2.2.2. Mechanistic rationalization

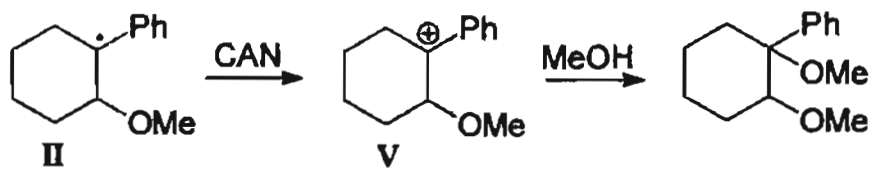
Although the mechanistic details of the reaction are unclear, the following rationalization illustrated by the reaction of phenylcyclohexene with CAN may be invoked to account for the formation of the products.

Oxidation of phenyl cycloalkene by CAN produces the radical cation **I**. Reaction of **I** with methanol can lead to the benzylic radical **II**. This benzylic radical **II** can trap molecular oxygen leading to a peroxyradical **III** and the latter can abstract hydrogen from the solvent to form the hydroperoxide **IV**. The hydroperoxide can undergo fragmentation and ultimately lead to the keto acetal as outlined in Scheme 23.



Scheme 23

Alternatively, the benzylic radical **II** can undergo oxidation to the cation, and the latter on quenching by methanol will result in the formation of the dimethyl ether (Scheme 24).

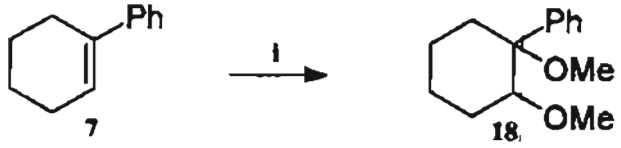


Scheme 24

2.2.3. Reaction of phenylcycloalkenes under deoxygenated conditions

The mechanism proposed for the fragmentation of phenyl cycloalkenes invokes the participation of oxygen in the reaction (Scheme 23). It is reasonable to assume that in the absence of oxygen in the reaction medium, the benzylic radical **II** will undergo further oxidation to the cation which in turn will be quenched by methanol leading to the dimethyl ether (Scheme 24). In order to verify these assumptions, the reactions were done under deoxygenated conditions.

Interestingly, when phenylcyclohexene was treated with CAN in dry methanol under deoxygenated conditions, **18** was formed as the major product in 72% yield (Scheme 25). Only a trace amount of the fragmentation product was observed.

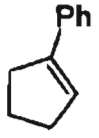
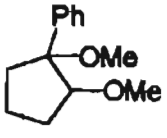
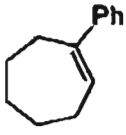
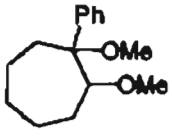
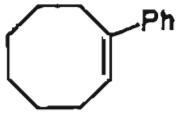
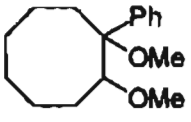
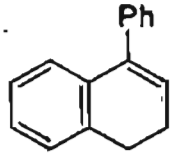
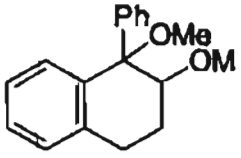


i. CAN, dry MeOH, 0 °C-rt, Argon, 1 h, 72%

Scheme 25

The reaction under deoxygenated conditions was studied with other phenylcycloalkenes also and the results are presented in the following table (Table 1). All the products were characterized as usual by spectral analysis.

Table 1:Reaction of phenylcycloalkenes with CAN in methanol under deoxygenated conditions

Entry	Alkene	Dimethylether	Yield (%)
1			72
2			80
3			69
4			65

Reaction conditions: CAN, dry MeOH, Argon, 1h, 0 °C

Alkyl substituted cycloalkenes were also subjected to the same reaction conditions. The alkenes, **54, 55, 56** and **57 (Figure 1)** were treated with CAN in methanol. In each case, even after 24 hours, most of the starting material remained unreacted.

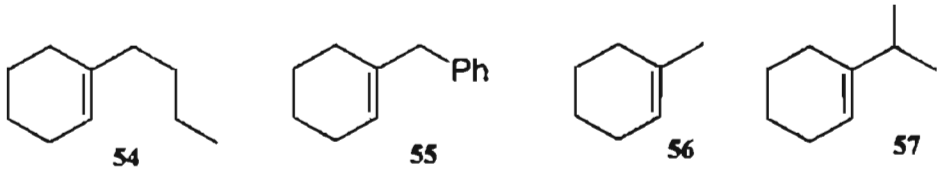


Figure 1

Although the exact reason for the failure of the alkyl substituted cycloalkenes to undergo oxidative fragmentation by CAN is not know[illegible] may be surmised that, the oxidation potential of these compounds [illegible] low enough to let them undergo oxidation by CAN, thus precluding the radical cation formation, which is the initial event in the fragmentation.

2.2.4. Conclusion

In conclusion, we have uncovered a novel Cerium(IV) mediated oxidative fragmentation of phenyl cycloalkenes* resulting in an efficient and direct synthesis of monoacetals of 1,n-dicarbonyl compounds which are otherwise difficult to obtain. The bismethoxylation observed under anaerobic conditions is also an interesting reaction, which may be of potential value in organic synthesis.

2.3. EXPERIMENTAL

General experimental procedure

All reactions were carried out in oven dried glassware. Melting points were recorded on Toshniwal or Buchi-530 melting point apparatus and are uncorrected. The IR spectra were recorded on Nicolet Impact 400D FT-IR

*While our work was in progress, fragmentation of cyclic olefins to ketonitriles by a photooxidative process was reported[18]

and Bomem MB series FT-IR spectrophotometers. The NMR spectra were recorded at 300 MHz on a Bruker 300 MHz FT-NMR spectrometer using chloroform-d as the solvent. Chemical shifts are reported on δ scale with TMS as the internal standard. Mass spectra were recorded on EI/HRMS using MD 800 or Hewlett-Packard 5890 mass spectrometers. Analytical thin layer chromatography was performed on glass plates coated with silica containing 13% calcium sulfate as the binder. Products were purified by gravity column chromatography using silica gel (100-200 mesh) in hexane or hexane-ethyl acetate mixtures as eluent. All the solvents were distilled prior to use. CAN used for the reaction was purchased from Aldrich Co. and was used without purification.

Synthesis of phenylcycloalkenes: General Procedure

All the cycloalkenes were prepared from the corresponding cycloalkanones and bromobenzene or bromonaphthalene by Grignard reaction, followed by acid catalyzed dehydration.

Synthesis of monoacetals of 1,n-dicarbonyl compounds from phenyl cycloalkenes: General procedure

To a solution of the phenylcycloalkene (1 mmol) in methanol (10 mL) was added dropwise a solution of CAN (2.3 mmol) in methanol (15 mL) at ice temperature. When the starting material was fully consumed as shown by tlc, the reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (3 X 30 mL). The combined organic extracts were washed with 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 hexane and ethyl acetate afforded the products

Synthesis of dimethylethers under deoxygenated conditions: General procedure

To a deoxygenated solution of the phenylcycloalkene (1 mmol) in methanol (10 mL), a deoxygenated solution of CAN (2.3 mmol) in methanol (15 mL) was added dropwise at ice temperature. When the starting material was fully consumed as shown by TLC, the reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (3 X 30 mL). The combined organic extracts were washed with 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 hexane and ethyl acetate afforded the products.

5-Benzoylpentanaldimethylacetal (17) and
1,2-Dimethoxy-1-phenylcyclohexane (18)

To a solution of 1-phenyl-1-cyclohexene 7 (156 mg, 1 mmol) in methanol (10 mL) a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) was added at ice temperature and stirred for about 30 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using hexane-ethylacetate mixture(98:2) afforded 39 mg of **18** (18%) and on further elution using hexane-ethylacetate mixture(95:5) afforded 162 mg of **17** (69%).

5-Benzoylpentanaldimethylacetal (17)

IR (neat) ν_{max} : 2959, 1681, 1593, 1482, 1202, 1128, 1067, 960, 703 cm^{-1}.

^1H NMR : 7.94-7.91 (m, 2H, ArH), 7.53-7.43 (m, 3H, ArH), 4.36 (t, 1H, CH $(OMe)_2$, J = 5.4 Hz), 3.29 (s, 6H, OMe), 2.90 (t, 2H, CH_2, J = 7.2 Hz), 1.99-1.39 (m, 6H, CH_2).

^{13}C NMR : 200.15, 137.01, 132.90, 128.55, 127.93, 104.43, 52.75, 38.42, 32.41, 24.34, 24.07.

1,2-Dimethoxy-1-phenylcyclohexane (18)

IR (neat) ν_{max} : 2897, 1647, 1448, 1108, 1202, 1074, 966, 717 cm^{-1}.

^{1}H NMR : 7.46-7.26 (m, 5H, ArH), 3.15 (s, 3H, OMe), 3.06-3.01 (m, 1H, CHOMe), 2.98 (s, 3H, OMe), 2.10-1.25 (m, 8H, CH_2).

^{13}C NMR : 142.35, 127.73, 127.14, 126.67, 85.92, 80.03, 57.82, 50.12, 31.86, 26.86, 26.52, 24.69, 20.92.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33 H, 9.15; Found C, 76.12, H, 8.97.

4-Benzoylbutanal dimethylacetal (30) and

1,2-Dimethoxy-1-phenylcyclopentane (42)

To a solution of 1-phenyl-1-cyclopentene **28** (144 mg, 1 mmol) in methanol (10 mL) was added a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) at ice temperature and stirred for about 30 minutes. On completion of the reaction, it was processed as described as in the general procedure. The residue on column chromatography on silica gel using a mixture of hexane-ethyl acetate (98:2) as eluent afforded 41 mg of **42** (20%) and on further elution with hexane-ethyl acetate (95:5) afforded 106 mg of **30** (48%).

4-Benzoylpentanaldimethylacetal (30)

IR (neat) ν_{max} : 2978, 1684, 1742, 1607, 1364, 1128, 1074, 960 cm^{-1}.

^{1}H NMR : 7.93-7.90 (m, 2H, ArH), 7.52-7.40 (m, 3H, ArH), 4.38 (t, 1H, CH $(OMe)_2$, J = 5.6 Hz), 3.30 (s, 6H, OMe), 3.01 (t, 2H, CH_2, J = 7 Hz), 1.82-1.63 (m, 4H, CH_2).

^{13}C NMR : 200.51, 136.85, 132.90, 128.51, 127.93, 104.67, 52.51, 38.01, 32.26, 23.53, 21.67.

1,2-Dimethoxy1-phenylcyclopentane (42)

IR (neat) ν_{max} : 1621, 1508, 1206, 1169, 721 cm^{-1}.

^{1}H NMR : 7.69-7.28 (m, 5H, ArH), 3.30 (s, 3H, OMe), 3.14 (m, 1H, CHOMe), 3.09 (s, 3H, OMe), 1.67-1.01 (m, 6H, CH_2).

^{13}C NMR 142.81, 128.14, 127.88, 127.04, 126.69, 86.24, 80.58, 59.18, 49.04, 36.64, 29.99, 23.16.

6-Benzoylhexanal dimethylacetal (44) and

1,2-Dimethoxy-1-phenylcycloheptane (45)

To a solution of 1-phenyl-1-cycloheptene **43** (172 mg, 1 mmol) in methanol (10 mL) was added a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) at ice temperature and stirred for about 30 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using a mixture of hexane-ethyl acetate (98:2) as eluent afforded 75 mg of **45** (32%) and on further elution with a mixture of hexane-ethyl acetate (95:5) afforded 140 mg of **44** (56%).

6-Benzoylhexanal dimethylacetal (44)

IR (neat) ν_{max} : 2956, 1681, 1593, 1482, 1450, 1359, 1273, 1091 cm^{-1}.

^1H NMR : 7.96-7.94 (m, 2H, ArH), 7.54-7.42 (m, 3H, ArH), 4.36 (t, 1H, $CH(OMe)_2$, J = 5.5 Hz), 3.31 (s, 6H, OMe), 2.97 (t, 2H, CH_2, J = 7.1 Hz), 1.76-1.25 (m, 8H, CH_2).

^{13}C NMR : 200.51, 137.15, 133.90, 128.67, 128.15, 104.61, 52.79, 38.56, 32.48, 29.29, 24.57, 24.35.

1,2-Dimethoxy-1-phenylcycloheptane (45)

IR (neat) ν_{max} : 2989, 1730, 1632, 1272, 1074, 766, 696 cm^{-1}.

^1H NMR : 7.44-7.23 (m, 5H, ArH), 3.14 (s, 3H, OMe), 3.08-3.01 (m, 1H, CHOMe), 2.99 (s, 3H, OMe), 2.07-1.42 (m, 12H, 6xCH_2).

^{13}C NMR : 144.15, 128.02, 127.62, 127.33, 126.54, 89.57, 82.23, 57.78, 50.91, 33.75, 27.00, 26.21, 23.67, 20.47.

7-Benzoylheptanal dimethylacetal (47) and

1,2-Dimethoxy-1-phenylcyclooctane (48)

To a solution of 1-phenyl-1-cyclooctene **46** (196 mg, 1 mmol) in methanol (10 mL) was added a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) at ice temperature and stirred for about 30 minutes. On

completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using a mixture of hexane-ethyl acetate (98:2) as eluent afforded 84 mg of **48** (35%) and on further elution with a mixture of hexane-ethyl acetate (95:5) afforded 118 mg of **47** (45%).

7-Benzoylheptanal dimethylacetal (47)

IR (neat) ν_{max} : 2987, 1681, 1596, 1442, 1202, 1181, 715 cm^{-1}.

^1H NMR : 7.95-7.92 (m, 2H, ArH), 7.53-7.41 (m, 3H, ArH), 4.34 (t, 1H, CH $(OMe)_2$, J = 5.4 Hz), 3.28 (s, 6H, OMe), 2.95 (t, 2H, CH_2, J = 7.2 Hz), 1.73-1.22 (m, 10H, CH_2).

^{13}C NMR : 199.81, 136.95, 132.63, 128.35, 128.10, 104.25, 52.25, 42.29, 32.21, 29.15, 24.31, 24.05, 20.74.

1,2-Dimethoxy-1-phenylcyclooctane (48)

IR (neat) ν_{max} : 1647, 1448, 1108, 1202, 1074, 966, 717 cm^{-1}.

^1H NMR : 7.46-7.26 (m, 5H, ArH), 3.15 (s, 3H, OMe), 3.06-3.01 (m, 1H, CHOMe), 2.98 (s, 3H, OMe), 2.10-1.25 (m,12H, CH_2).

^{13}C NMR : 142.35, 127.73, 127.14, 126.67, 85.92, 80.03, 57.82, 50.12, 31.86, 26.86, 26.52, 24.69, 20.92.

5-Naphthoylpentanaldimethylacetal (50)

To a solution of 1-naphthyl-1-cyclohexene **49** (208 mg, 1 mmol) in methanol (10 mL) was added a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) at ice temperature and stirred for about 30 minutes. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using a mixture of hexane-ethyl acetate (95:5) as eluent afforded 205 mg of **50** (72%).

IR (neat) ν_{max} : 2942, 1681, 1593, 1482, 1128, 1067, 960, 703 cm^{-1}.

^1H NMR : 8.53 (d, 1H, ArH, J = 8.2 Hz), 7.94 (d, 1H, ArH, J = 8.2 Hz), 7.84 (t, 1H, ArH, J = 8.1 Hz), 7.59-7.45 (m, 4H, ArH),

4.36 (t, 1H, CH $(OMe)_2$, J = 75.6 Hz), 3.30 (s, 6H, OCH_3), 3.05 (t, 2H, CH_2, J = 7.3 Hz), 2.03-1.42 (m, 6H, CH_2)

^{13}C NMR : 200.15, 137.01, 132.90, 128.55, 127.93, 104.43, 52.75, 38.42, 32.41, 24.34, 24.07.

2-(3,3-Dimethoxy) propyl)benzophenone (52) and

1,2-Dimethoxy-1-phenyl tetralin (53)

To a solution of 1-phenyl-3,4-dihydro naphthalene **51** (208 mg, 1 mmol) in methanol (10 mL) was added a solution of CAN (1.26 g, 2.3 mmol) in methanol (15 mL) at ice temperature and stirred. On completion of the reaction, it was processed as described in the general procedure. The residue on column chromatography on silica gel using a mixture of hexane-ethyl acetate (98:2) as eluent afforded 30% of **53** and on further elution using a mixture of hexane-ethyl acetate (95:5) afforded 99 mg of **52** (35%).

2-(3,3-dimethoxy) propyl)benzophenone (52)

IR (neat) ν_{max} : 2976, 1667, 1596, 1470, 1289, 798 cm^{-1}.

^{1}H NMR : 7.22-7.17 (m, 9H, ArH), 4.43 (t, 1H, CH $(OMe)_2$, J = 5.5 Hz), 3.16 (s, 6H, OMe), 2.65(m, 2H, CH_2), 1.77 (brs, 2H, CH_2).

^{13}C NMR : 198.07, 140.88, 138.30, 137.88, 130.28, 130.18, 128.70, 128.38, 127.51, 125.34, 103.64, 52.47, 34.27, 28.50.

1,2-Dimethoxy-1-phenyl tetralin (53)

IR (neat) ν_{max} : 1632, 1486, 1438, 1280, 1115 cm^{-1}.

^{1}H NMR : 7.17-7.04 (m, ArH, 9H), 3.59 (m, CH_2, $PhCH_2$), 3.09 (s, 3H, OMe), 3.03 (s, 3H, OMe), 2.78 (t, 2H, CH_2), 2.12 (brs, 2H, CH_2).

^{13}C NMR : 142.80, 138.73, 136.09, 129.39, 128.78, 127.04, 126.97, 83.49, 80.49, 57.77, 50.83, 26.91, 23.69.

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CHAPTER 3

BROMINATION OF ALKENES USING POTASSIUM BROMIDE AND CAN

3.1. INTRODUCTION

3.1.1. General

The present chapter covers an in depth study on the cerium(IV) ammonium nitrate (CAN) mediated halogenation of various substrates giving special emphasis to bromination of alkenes under different conditions. In the context of our general interest in the oxidative transformations using CAN, especially the oxidative addition of soft anions such as thiocyanate and azide to alkenes, it was of interest to explore the reaction with bromide ions. We undertook a systematic study of the reaction, which forms the subject matter of this chapter.

As an introduction to the work, general methods available for the synthesis of vicinal dibromides and their uses are briefly outlined. This is followed by an account of the role of CAN in carbon-heteroatom bond forming reactions, especially carbon-halogen bond forming reactions.

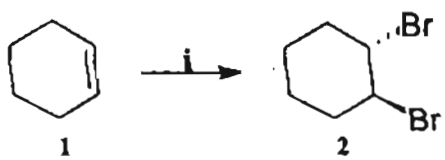
Vicinal dibromoalkanes form an important class of intermediates in organic synthesis, since bromination and debromination reaction has emerged as an efficient protocol for the protection and deprotection of double bonds.[1] For example, the bromination-debromination reaction was used as a protection-deprotection strategy by Windaus to protect the 5,6 double bond of cholesterol during an oxidation step.[2] The same strategy also found application in the synthesis of jasmine constituents and in masking the double bond of cyclobutene.[3] A number of similar approaches involving the

intermediacy of dibromides have been reported. In this context, any method effective in converting olefinic compounds to the corresponding dibromides assumes importance. A brief account of the existing methods for bromination is given in the following section.

3.1.2. General methods for the formation of dibromides

A number of methods are available for the conversion of alkenes to the corresponding dibromides. A complete coverage of these reactions is beyond the scope of this chapter. Only the commonly used methods for the bromination of double bonds, with some emphasis on the recent developments in this area, are presented here.

Molecular bromine in different solvents is the commonly used reagent for bromination of alkenes. On exposure to a solution of bromine in carbontetrachloride, chloroform, carbondisufide, acetic acid, ether or ethyl acetate alkenes yield the corresponding dibromides (Scheme 1).[4]

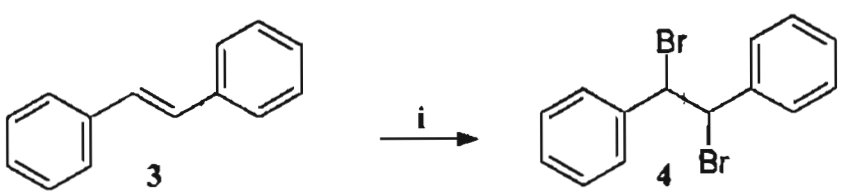


1 2

i. Br_2, CCl_4, -5 °C, 95%

Scheme 1

Pyridinium bromide perbromide is a convenient alternative for the bromination of double bonds (Scheme 2).[5]

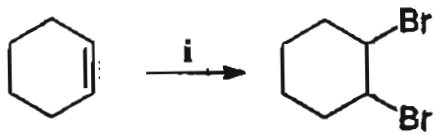


3 4

i. $C_5H_6N^+Br_3^-$, Acetic acid, 93%

Scheme 2

Vicinal dibromides are easily formed by the reaction of copper(II) bromide in acetonitrile, methanol or chloroform (Scheme 3).[6]

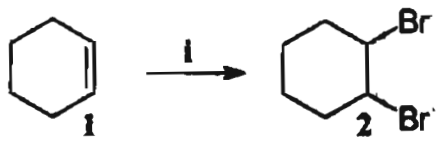


1 2

i. $CuBr_2$, MeCN, 87%

Scheme 3

Halogenation using electrochemical methods are known, but generally the yields are low. Presumably the reaction involves the oxidation of halide ion to the positive halogen species and subsequent addition of the latter to the double bond (Scheme 4).[7]

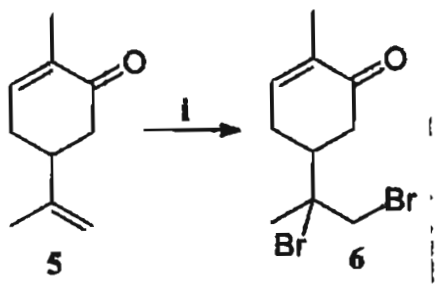


1 2

i. MeOH, NH_4Br, 30%

Scheme 4

A chemoselective bromination using tetradecyl trimethylammonium permanganate and trimethyl bromosilane has been reported in 1994 (Scheme 5).[8]

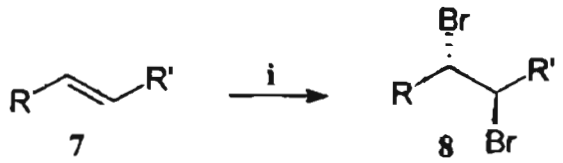


5 6

i. $[N(Me)_3C_{14}H_{29}][MnO_4]$, Me_3SiBr, 73%

Scheme 5

Sonochemical bromination of alkenes using tetrabutylammonium tribromide has also been reported (Scheme 6).[9]



7 8

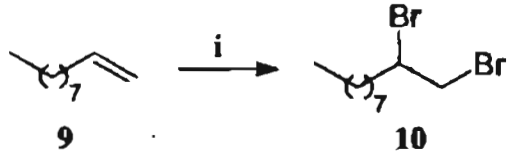
R, R' = Alkyl, Aryl etc.

i. $TBABr_3$, us.

Scheme 6

Very recently while the present work on bromination reactions was in progress, reports of a number of newer methods of bromination of alkenes appeared. The following are some examples.

The bromination of alkenes using hydrobromic acid and *tert*-butyl hydroperoxide has been reported. For this reaction, a mechanism involving the *in situ* generated halonium species has been invoked (Scheme 7).[10]

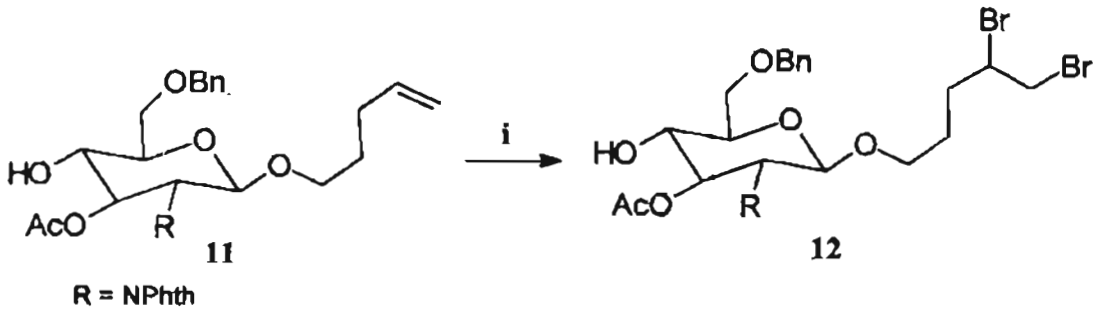


9 10

i. HBr, H_2O_2, TBHP, 95%

Scheme 7

An excellent method for the bromination of alkenyl glycosides has been reported by Fraser-Reid using copper(II) bromide and lithium bromide in acetonitrile (Scheme 8).[11]



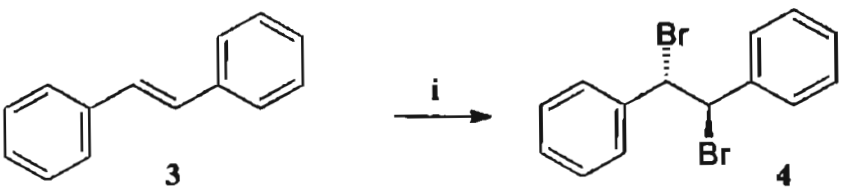
11 12

R = NPhth

i. $CuBr_2$, LiBr, MeCN, THF, 99%

Scheme 8

Stereoselective dibromination of stilbenes and chalcones has been reported very recently by Toda *et al.* using pyridinium bromide suspension in water (Scheme 9).[12]

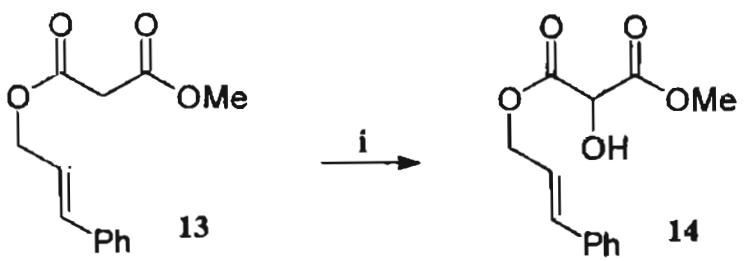


i. $C_5H_6N^+Br_3^-$, H_2O, 15h, 90%

Scheme 9

3.1.3. Role of CAN in C-heteroatom bond forming reactions

CAN has been known to play a vital role in C-C bond forming reactions (See Chapter 1-General Introduction). Recently there has been interest in the use of CAN in C-heteroatom bond forming reactions also. Investigations in our own laboratory have demonstrated that CAN is an excellent reagent in C-heteroatom bond forming reactions. For example, oxidation of dialkylmalonates using CAN in methanol to produce tartronic acid derivatives in good yields was reported recently (Scheme 10).[13]



i. CAN, MeOH, 0 °C, rt, 62%

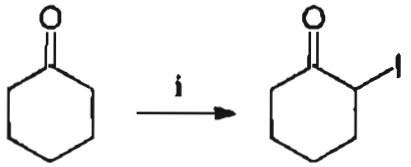
Scheme 10

An efficient thiocyanation of alkenes and electron rich aromatic systems leading to the corresponding dithiocyanates and aryl thiocyanates respectively using ammonium thiocyanate and CAN was reported[14,15] (See **Section 1.2.1.2.**).

3.1.3.1. Carbon-halogen bond forming reactions mediated by CAN

Halogenation reaction using CAN and metal halides or elemental halogen have been reported.

A facile α-iodination of ketones using iodine and CAN in acetic acid or alcohol was reported by Horiuchi *et al.* (Scheme 11).[16]

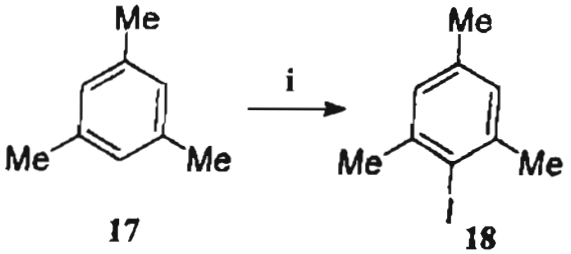


15 **16**

i. I_2, CAN, AcOH, H_2O, 7h, 94%

Scheme 11

Polymethylbenzenes, polymethoxybenzenes and naphthalene were iodinated using alkali metal iodides or elemental iodine with CAN in acetonitrile (Scheme 12).[17]

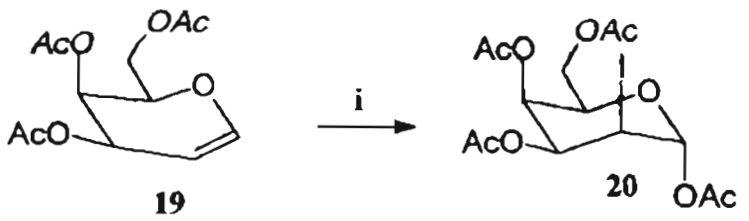


17 **18**

i. NaI, CAN, MeCN, 83%

Scheme 12

Very recently, while our work was nearing completion, stereoselective iodo-acetoxylation of glycals with cerium(IV) ammonium nitrate and sodium iodide in the presence of acetic acid was reported by Roush *et al.* (Scheme 13).[18]

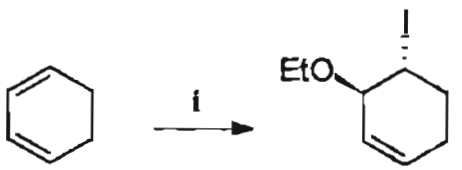


19

i. NaI, CAN, AcOH, MeCN, 75%

Scheme 13

Reaction of 1,3-cyclohexadiene with iodine and CAN in ethanol has been reported to give the *trans*-2-ethoxy-1-iodo-3-cyclohexene as the major product (Scheme 14).[19]

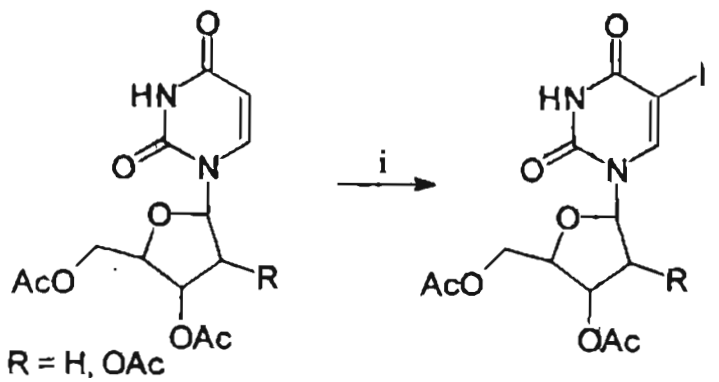


21 22

i. CAN, I_2, EtOH, rt, 8 h, 66%

Scheme 14

Iodination at C-5 of uracilnucleosides using elemental iodine and catalytic amounts of CAN has been reported by Asakura *et al.*(Scheme 15).[20]

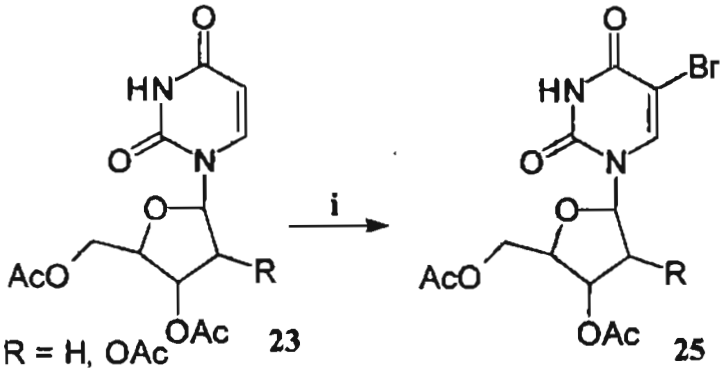


23 24

i. CAN, I_2, MeCN, 80 °C, 97%

Scheme 15

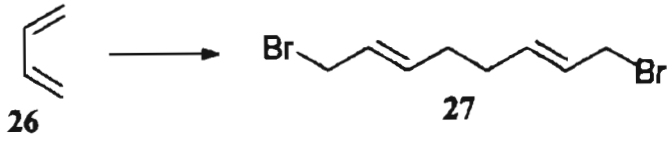
The same authors have reported the bromination of C-5 of uracil nucleosides using CAN and lithium bromide in acetonitrile. In this reaction they have used stoichiometric amounts of CAN and lithium bromide. A mechanism involving the intermediacy of a bromonium ion has been postulated for this reaction (Scheme 16).[21]



i. LiBr, CAN, MeCN, 80 °C, 90%

Scheme 16

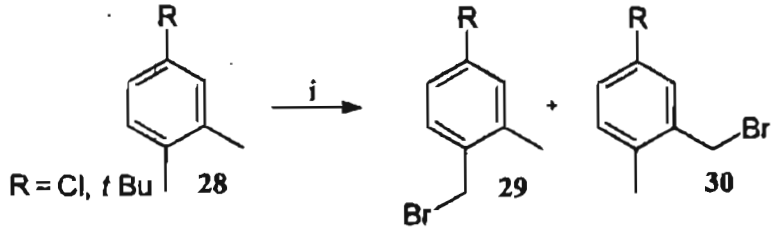
As early as 1960, the additive dimerization of butadiene using Ce(IV) and hydrogen bromide was reported by Langkammerer (Scheme 17).[22]



i. Ce $(HSO_4)_4$, HBr, H_2O, *t*-BuOH, 4 °C, 30%

Scheme 17

Side chain bromination of alkyl aromatics was reported by Baciocchi *et al.* using sodium bromide and CAN (Scheme 18).[23]



i. NaBr, CAN, AcOH

Scheme 18

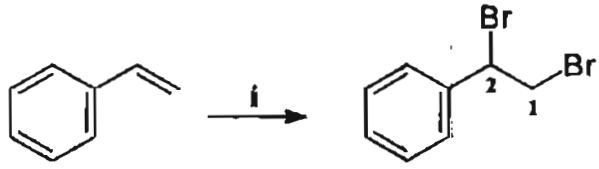
3.1.4. The present work

It is evident from the literature survey given above that although there are a few reports on Ce(IV) mediated bromination, there has been no systematic work in this area. In view of this and in the context of our general interest in exploring the synthetic potential of CAN, we undertook a thorough study of the CAN mediated oxidative addition of bromide to alkenes in various solvents. The results are presented in the following section.

3.2. RESULTS AND DISCUSSION

3.2.1. Bromination of styrenes

Our studies were initiated with experiments involving the bromination of styrene. Treatment of the latter with potassium bromide and CAN in a two phase system of water-dichloromethane at room temperature for 30 minutes, resulted in the formation of the dibromide **32** in 91% yield (Scheme 19).



31 **32**

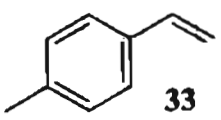
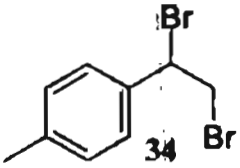
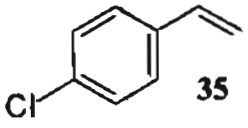
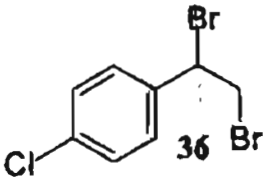
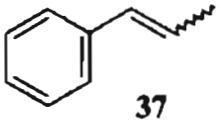
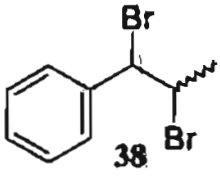
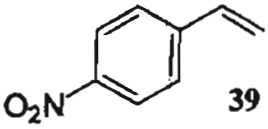
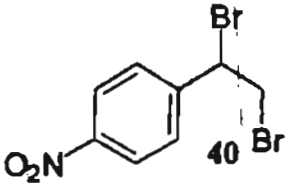
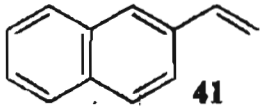
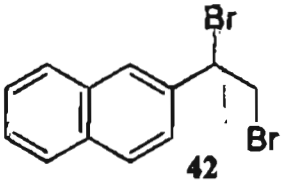
i. CAN, KBr, H_2O, CH_2Cl_2, rt, 30 min, 91%

Scheme 19

The product was characterized by ^1H and ^{13}C NMR spectral data. The aromatic protons resonated as a multiplet at δ 7.3 and the benzylic proton was discernable at δ 5.1 as a doublet of doublet. The signal due to the methylene protons was seen at δ 4.0 as a multiplet. In the ^{13}C NMR spectrum of the product, the two bromine bearing carbons, C_1 and C_2 displayed signals at δ 34.9 and 50.8 respectively. The IR and NMR spectral data were completely identical with those reported for the authentic dibromide.[8]

Subsequently the reaction was studied with a number of styrenes. In every case, the corresponding dibromide was obtained under similar conditions and the results are presented in Table 1.

Table 1: Bromination of styrenes

Entry	Styrene	Dibromide	Yield (%)
1	 33	 34	67
2	 35	 36	85
3	 37	 38	90
4	 39	 40	62
5	 41	 42	95

Reaction conditions: KBr, CAN, CH_2Cl_2, H_2O, rt, 30-45 min

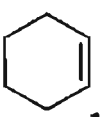
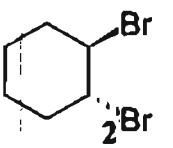
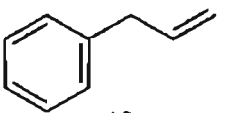
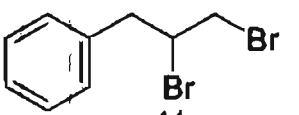
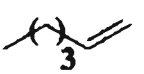
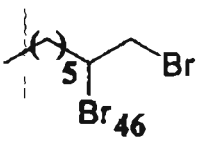
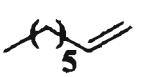
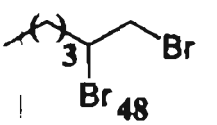
In all the cases, the products were characterized by ^1H and ^{13}C NMR spectra. The data were compared with either those reported in the literature or with those of authentic samples prepared.

3.2.2. Bromination of alkenes

In order to assess the generality of the reaction, CAN mediated bromination was carried out with a few representative alkenes. The results are presented in Table 2. The alkenes selected for our study include cyclohexene **1**, allylbenzene **43**, 1-hexene **45** and 1-octene **47**.

In all these cases, the products were characterized by ^{1}H and ^{13}C NMR spectra and by comparison of the data with those reported in the literature.

Table 2: Bromination of alkenes

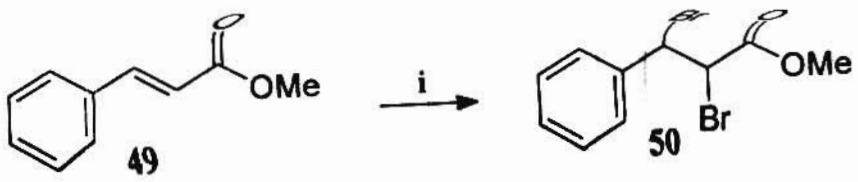
Entry	Alkene	Dibromide	Yield (%)
1	 **1**	 **2**	65
2	 **43**	 **44**	65
3	 **45**	 **46**	82
4	 **47**	 **48**	51

Reaction conditions: KBr, CAN, CH_2Cl_2, H_2O, rt, 20-30 min

The results obtained suggest that the reaction may be of general application.

3.2.3. Bromination of α,β-unsaturated carbonyl compounds

With a view to extend the reaction to α,β-unsaturated carbonyl compounds, a prototype experiment was carried out with methylcinnamate. The reaction proceeded well to afford the dibromide in 78% yield *(Scheme 20).*



49 50

(i) CAN, KBr, H_2O, CH_2Cl_2, rt, 30 min, 78%

Scheme 20

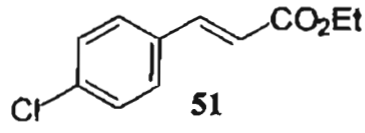
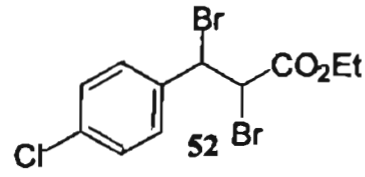
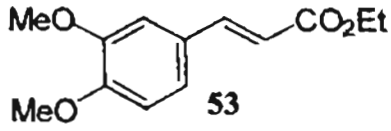
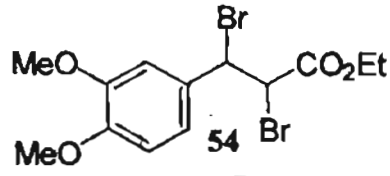
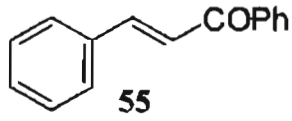
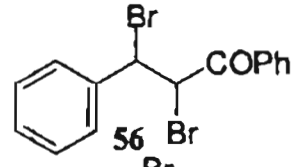
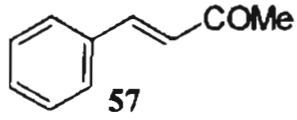
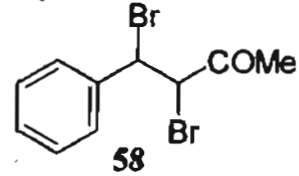
The product was characterized as usual by spectral analysis and by comparison of the spectral data with those reported for the authentic compound.

The IR spectrum of the product showed the carbonyl absorption at *1720 cm^{-1}. In the ^1H NMR spectrum* of the product, the aromatic protons *resonated as a broad singlet centered at δ 7.3. The signal corresponding to the* benzylic proton appeared as doublet at δ 5.3. The proton α to the ester carbonyl appeared as a doublet at δ 4.8. The methoxy protons were seen as a singlet at δ 3.8. In the ^{13}CNMR spectrum, the ester carbonyl was seen at δ 168.0. The bromine bearing carbon atoms gave signals at δ 46.6 and 50.5 corresponding to the benzylic carbon and the carbon adjacent to the ester group respectively. The methoxy carbon was discernible at δ 53.2.

Similar reaction was observed with substituted cinnamates and chalcones and the results are summarized in Table 3. In these cases also the products were characterized by spectral analysis.

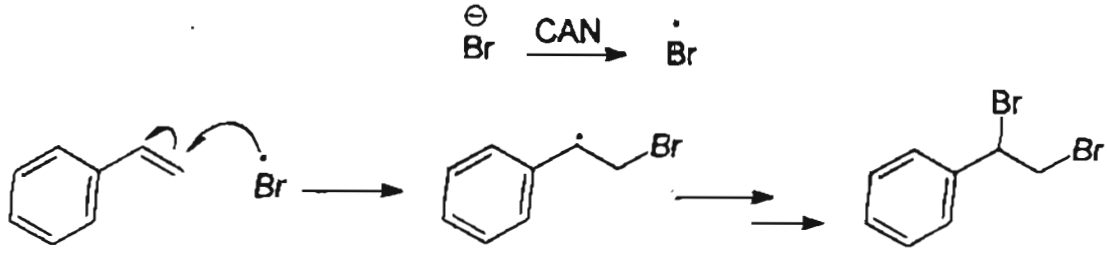
Table 3

Bromination of α,β-unsaturated carbonyl compounds

Entry	Alkene	Dibromide	Yield (%)
1	 51	 52	80
2	 53	 54	80
3	 55	 56	95
4	 57	 58	81

Reaction conditions: KBr, CAN, H_2O, CH_2Cl_2, rt, 20-30 min

Although the mechanistic details of the reaction are far from clear, a rationalization of the results may be made by invoking the initial oxidation of the bromide to the bromine radical and its addition to the styrene leading to a benzylic radical. Conceivably, the latter can be transformed to the dibromide by a number of pathways (Scheme 21).



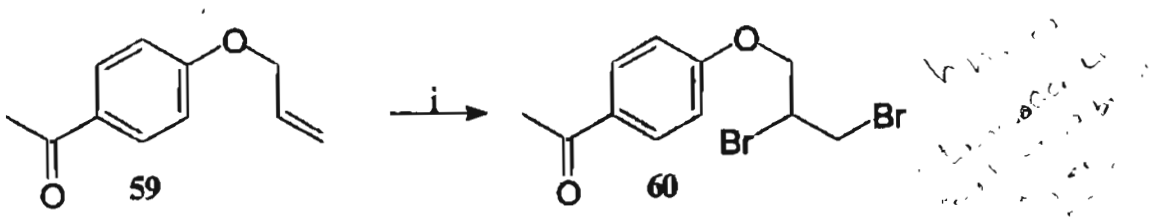
Scheme 21

A detailed description of the probable mechanism of the reaction is presented in section 3.2.7.

3.2.4. Chemoselective bromination

Since radical reactions are chemoselective in nature, it was of interest to probe the chemoselectivity of the CAN mediated bromination. Investigations carried out with this objective are discussed in this section.

The first experiment involved the treatment of the allylphenylether **59** with KBr and CAN in a two phase system of water and dichloromethane under the reaction conditions described previously. The reaction afforded the dibromide **60** in 75% yield (Scheme 22).



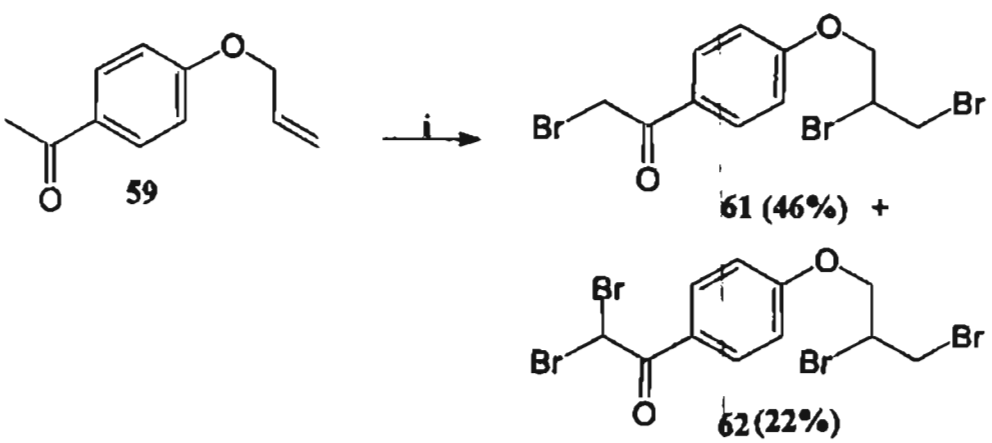
i. CAN, KBr, H_2O, CH_2Cl_2, rt, 30 min, 75%

Scheme 22

The structure of the product was confirmed by spectral analysis. The IR spectrum showed the carbonyl absorption at 1680 cm^{-1}. The acetyl group protons appeared as a singlet at δ 2.54 in the ^1H NMR spectrum. The terminal methylene protons (-C$\underline{H_2}$Br) resonated as a broad doublet at δ 3.9. The methine proton resonated along with the two oxymethylene (-OC$\underline{H_2}$-) protons as a broad triplet at δ 4.4. The aromatic protons resonated as two doublets at δ 7.9 and 6.9 (J = 8.2 Hz). In the ^{13}C NMR spectrum, the two bromine bearing carbon atoms were discernible at δ 46.9 and 32.3, corresponding to methine and the methylene carbons respectively. The signal due to the methylene carbon attached to oxygen was seen at δ 69.0. The

carbonyl carbon resonated at δ 195.9. The methyl carbon of the *acetyl group* displayed a signal at δ 26.2.

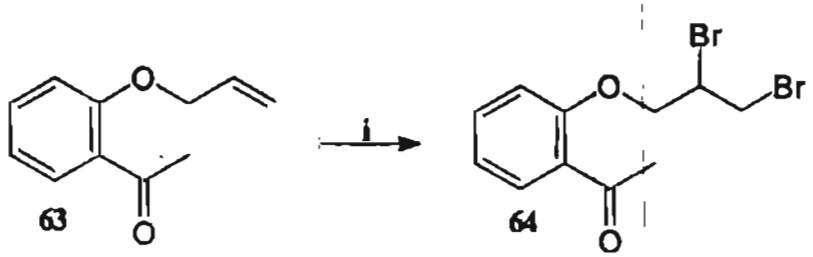
For the purpose of comparison, it was of interest to study the bromination of the above system with molecular bromine. When the allylphenylether **59** was treated with a solution of bromine in CCl_4, two products resulted. They were identified as **61** and **62** (Scheme 23).



i. Br_2, CCl_4, rt

Scheme 23

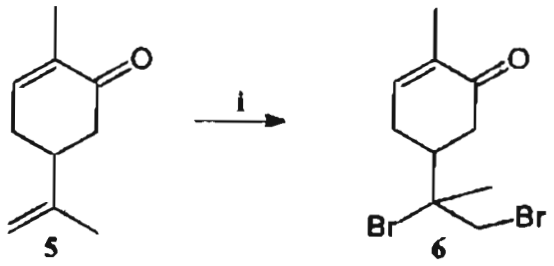
Evidently there is no selectivity in this reaction. The isomeric compound **63** also on treatment with KBr and CAN underwent selective bromination yielding the dibromide **64** (Scheme 24). As usual, the product was characterized on the basis of spectral analysis.



i. CAN, KBr, H_2O, CH_2Cl_2, rt, 30 min, 79%

Scheme 24

Since Carvone **5**, appeared to be an excellent substrate to test chemoselectivity, it was treated with KBr and CAN under the usual reaction conditions. As expected, no bromination of the enone moiety or the methylene α to the carbonyl group occured. The isolated double bond alone gets brominated resulting in the formation of a diastereomeric mixture (Scheme 25).



i. CAN, KBr, H_2O, CH_2Cl_2, rt, 30 min, 70%

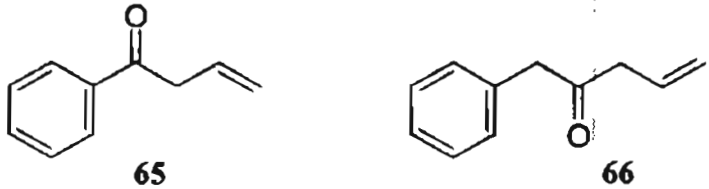
Scheme 25

In this case also the product was characterized on the basis of IR, ^1H and ^{13}C NMR spectra. In the IR spectrum of the product absorption corresponding to the enone carbonyl was seen at 1676 cm^{-1}. In the ^1H NMR spectrum, the olefinic proton resonated as a broad singlet at δ 6.7. The bromomethyl protons resonated as a double doublet centered at δ 3.9 and an uneven triplet at δ 3.8. The spectral data was in complete agreement with those reported.

When carvone was treated with a solution of bromine in carbontetrachloride, a complex reaction mixture was obtained.

From the comparative study presented above, it is well clear that the combination of potassium bromide and CAN in a biphasic system consisting of water and dichloromethane exhibits excellent chemoselectivity. In addition to the chemoselectivity, the present method offers a number of advantages over the conventional procedure. These include the mild experimental conditions, easy work up of the reaction mixture and high yields of products.

In our subsequent experiments it was found that, **65** and **66** also underwent chemoselective bromination. However, the instability of the products precluded their isolation and purification.



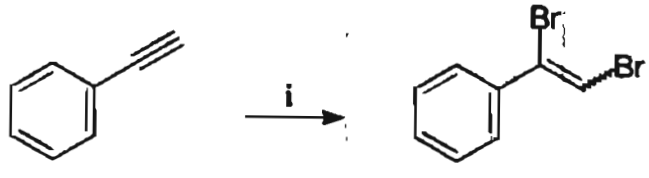
65 **66**

Figure 1

3.2.5. Bromination of alkynes

In view of the facility and ease with which alkenes underwent CAN mediated bromination, it was of interest to explore the applicability of this reaction to acetylenes. With this objective, a number of acetylenes were treated under the reaction conditions used for the bromination of alkenes.

Our experiments started with the reaction of phenyl acetylene with CAN and potassium bromide in a two phase system of water and dichloromethane. Interestingly, as expected, the dibromostyrene was isolated in very good yield (Scheme 26)



67 **68**

i. CAN, KBr, H_2O, CH_2Cl_2, rt, 45 min, 80%, (E/Z ratio 2:3)

Scheme 26

As usual the product was characterized by ^1H and ^{13}C NMR spectra. Two signals corresponding to the olefinic proton in the ratio 2:3 indicate the presence of two isomers. The structure of the product was confirmed by comparing the spectral data with those reported. The ratio of the isomers was determined by GC-MS and ^1H NMR.

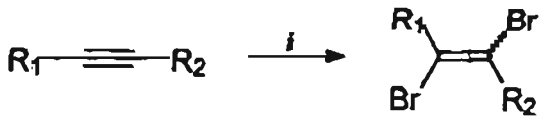
The bromination was extended to a number of acetylenes and the results are presented in table 4.

From the results it appears that the E/Z selectivity of the present method is limited. In spite of this, the reaction will be of some synthetic value due to the experimental simplicity and excellent yields.

In all the cases the ratio of the isomers was determined by GC-MS.

Table 4

Bromination of Acetylenes



69-72 73-76

Entry		R_1	R_2	E/Z	Yield (%)
1	73	Ph	Ph	100/0	94
2	74c	H	$(CH_2)_5CH_3$	80/20	79
3	75	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	100/0	75
4	76	Ph	$Si(Me)_3$	100/0	90

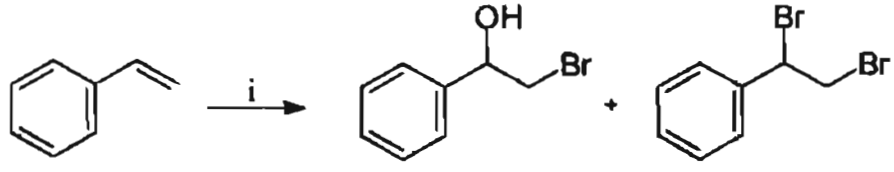
Reaction conditions: KBr, CAN, H_2O, CH_2Cl_2, rt. 30 min

A mechanistic rationalization similar to the one suggested for the CAN mediated bromination of alkenes may be invoked for the bromination of acetylenes also. The initial event will be the oxidation of bromide ions by CAN to generate bromine radical. Addition of the latter to the triple bond can produce the vinyl radical and this on reaction with another bromine radical will lead to the product.

It is evident from the above results that the present method offers significant advantages over the existing methods for the bromination of alkenes. The two phase system consisting of water and dichloromethane is a

particularly efficient solvent system. Under these conditions, bromination of double bond occurs, without affecting other functionalities of the molecule. This may be attributed at least in part to the separation of the oxidant and the organic moiety in two different phases.

In all the above experiments, we have used two-fold excess of bromide relative to the alkene along with a slight excess of the oxidant (For details see the experimental section). In an experiment designed to see if the amount of bromide ion has any bearing on the reactivity pattern, the reaction was carried out with one equivalent of the bromide and two equivalents of the oxidant. Interestingly, in this case along with the dibromide, bromohydrin was also formed (Scheme 27).

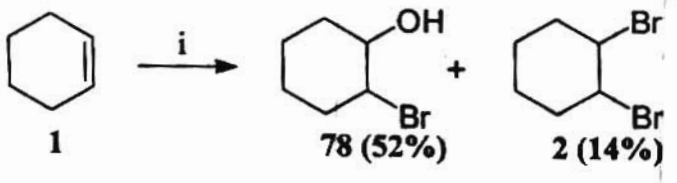


31 77 (26 %) 32 (22%)

i. CAN, KBr, H_2O, CH_2Cl_2, rt, 15 min

Scheme 27

It was speculated that, in the above reaction if the bromide ion concentration was kept low, the dibromide formation would be suppressed and the bromohydrin would emerge as the major product. With this objective a reaction with cyclohexene was done under very dilute conditions. In a typical experiment, to a solution of the cyclohexene in dichloromethane was added a solution of CAN and a solution of potassium bromide in acetone over a period of 2 hours making the consumption of the bromine radical more competitive with its formation. As expected, the reaction yielded the 2-bromocyclohexanol as the major product, along with a small amount of the dibromide (Scheme 28).



1 78 (52%) 2 (14%)

i. CAN, KBr, H_2O, CH_2Cl_2, rt, 2h

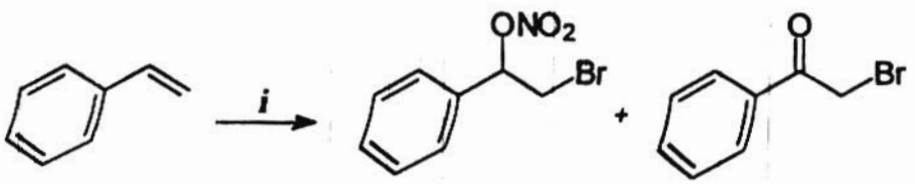
Scheme 28

When the bromination of alkenes was carried out in water instead of the two phase system, in all cases complex reaction mixtures resulted, thus suggesting that the solvent system plays a crucial role in these reactions. In view of this, it was decided to study the effect of solvents in the bromination of alkenes in some detail and the results are presented in the following section.

3.2.6. Effect of solvent on CAN mediated bromination

3.2.6.1. Reaction in aqueous methanol

When styrene was treated with CAN in aqueous methanol, the phenacyl bromide was the major product, along with nitratobromide (Scheme 29).



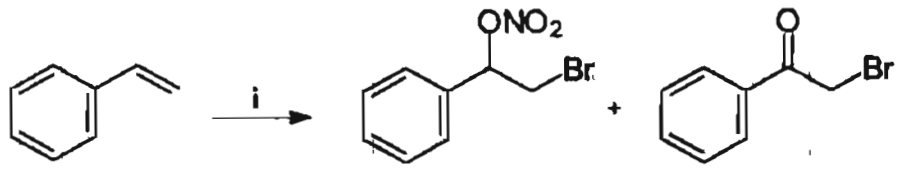
31 *79 (35%)* *80(42 %)*

i. CAN, KBr, H_2O, MeOH, rt

Scheme 29

3.2.6.2. Reaction in aqueous acetonitrile

In aqueous acetonitrile also, the reaction took a similar course giving the phenacyl bromide as the major product along with nitratobromide (Scheme 30).

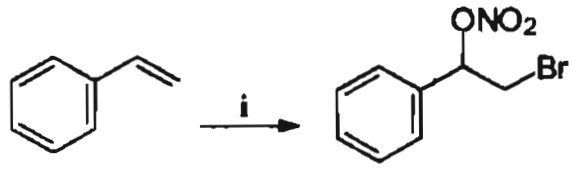


31 79(48%) 80(28%)

i. CAN, KBr, H_2O, MeCN, rt

Scheme 30

When the reaction was carried out in a deoxygenated atmosphere, as expected, no keto product was formed; instead the nitratobromide **79** was formed exclusively (Scheme 31).



31 79 (79 %)

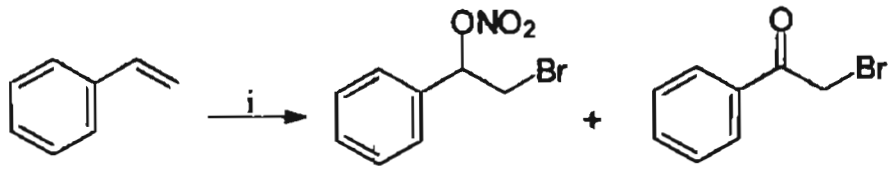
i. CAN, LiBr, MeCN, Argon, rt, 2h

Scheme 31

With cyclohexene and *n*-octene under the same conditions the reactions were found to be highly complex. Thus it appears that the above reactions are limited only to styrenic systems.

3.2.6.3. Reaction in acetic acid/acetonitrile mixture

When a mixture of acetic acid and acetonitrile was used as the solvent, the nitrato bromide **79** was the major product; only a small amount of the phenacyl bromide was formed (Scheme 32).



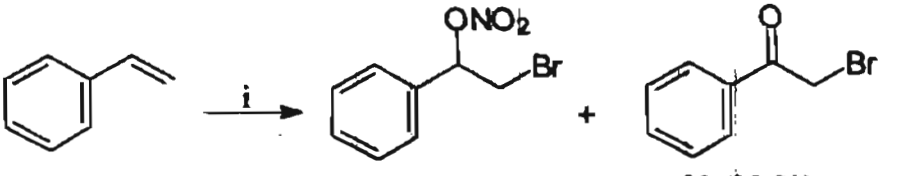
31 79 (61 %) 80 (12 %)

i. CAN, LiBr, MeCN, AcOH

Scheme 32

3.2.6.4. Reaction in *tert*-butanol

In *tert*-butanol also the reaction of styrene with CAN and lithium bromide afforded the nitrato bromide as the major product. Small amount of phenacyl bromide was also formed (Scheme 33).



15 79 (53 %) 80 (20 %)

i. CAN, LiBr, *t*-BuOH, rt

Scheme 33

3.2.7. Mechanistic rationalization of CAN mediated bromination

As stated earlier (see Section page 59) in 1960 Langkammerer *et al.* have reported the additive dimerization of butadienes with bromine atoms generated by Ce(IV) salts and bromide ions.[22] It is conceivable that the bromine radical initially adds to the diene and the radical intermediate thus formed adds to a second molecule of the diene leading to the dimer. In 1988 Baciocchi *et al.* have shown that side chain bromination can be effected either by CAN or Co(III) salts, with bromide ions.[23] A radical mechanism proposed for this reaction is outlined in the following Scheme.

$$Ce(IV)ONO_2 \xrightarrow{Br^-} Ce(IV)Br \quad ONO_2^-$$

$$Ce(IV)Br \longrightarrow Ce(III) + Br^{\bullet}$$

$$ArCH_3 + Br^{\bullet} \longrightarrow ArCH_2^{\bullet} + HBr$$

$$ArCH_2^{\bullet} + Ce(IV)Br \longrightarrow ArCH_2Br + Ce(III)$$

Scheme 34

The mechanism suggested by Asakura *et al.* for the bromination at C-5 of uracil nucleosides using CAN and lithium bromide invokes the

intermediacy of a positive halogen species formed by the further oxidation of the initially formed bromine radical by CAN (Scheme 35).[21]

$$Ce(IV) + MX \longrightarrow Ce(III) + X$$

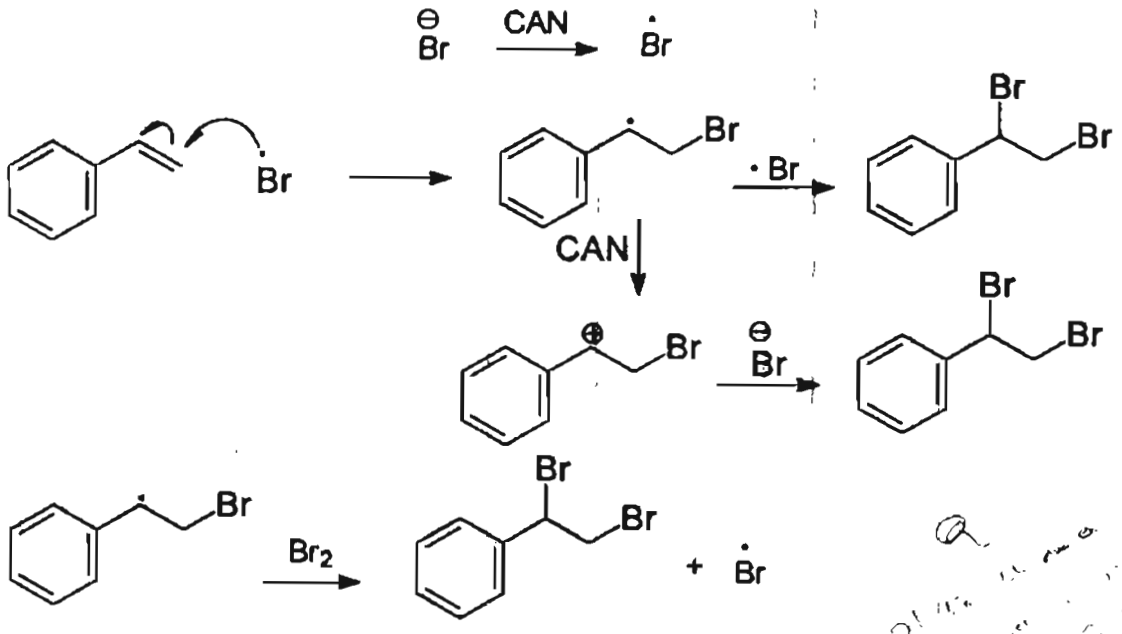
$$X + Ce(IV) \longrightarrow Ce(III) + X^{+}$$

Scheme 35

Thus there is enough circumstantial evidence to suggest that bromide ion can be oxidized to bromine radical by CAN. A comparison of the oxidation/reduction potential of Br^{-}/Br and Ce(IV)/Ce(III) systems (1.6 V for Ce(III)/Ce(IV) and 1.03 for Br/Br-) also lends credence to this postulate.[24]

3.2.7.1. Mechanism for the formation of dibromides

In view of the above discussion, it is reasonable to assume that the bromination reported herein proceeds *via* a similar mechanistic pathway involving bromine radical. Conceivably bromine radical generated by the oxidation of bromide ions can add to the alkene to give a secondary radical. The latter can undergo oxidation to produce the cation which on attack by another bromide ion can give the product; alternatively the radical can be trapped by a bromine radical itself. A third possibility that needs to be considered is the reaction of the secondary radical with molecular bromine, that may be formed by the radical combination, leading to the dibromide (Scheme 36).



Scheme 36

The reddish color that develops in the organic layer during the reaction may be attributed to the Ce(IV)-bromide complex which can decompose to Ce(III) and bromine radical.

It may be pointed out that a mechanistic postulate involving the intermediacy of bromine radical may be preferred over the one involving the halonium ion proposed by Asakura *et al.* Indirect support for a radical mechanism is rendered by the lack of solvent incorporation in the case of reactions carried out in methanol and acetonitrile. A cationic species resulting from the addition of bromonium ion is likely to be quenched by the solvent under these conditions.

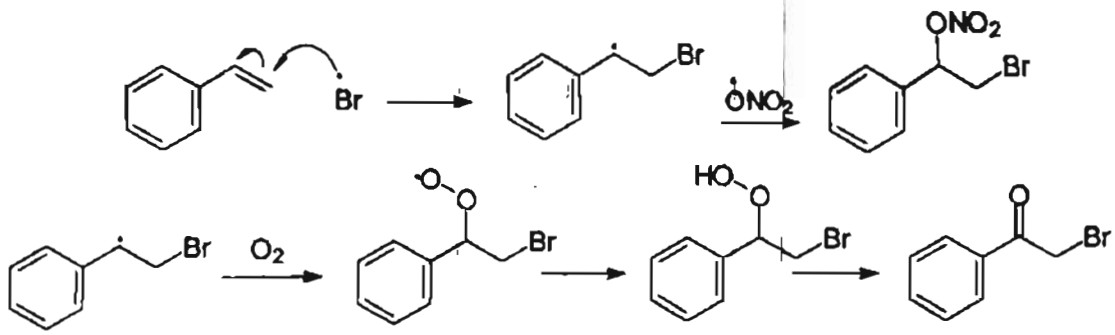
3.2.7.2. Mechanism for the formation of nitrato bromide and phenacyl bromide

The formation of the nitrato bromide and/or the phenacyl bromide in methanol and in acetonitrile can also be explained by invoking the transformations of the benzylic radical. The benzylic radical can either procure a nitrate radical by ligand transfer giving rise to the nitrato bromide

or it can be trapped by molecular oxygen producing a peroxy radical, which is further transformed to the hydroperoxide. The hydroperoxide can undergo fragmentation giving the keto bromide.

The exclusive formation of the nitrato bromide in a deoxygenated atmosphere lends support to the postulate that the genesis of the keto product involves the incorporation of molecular oxygen.

A schematic presentation of the mechanistic pathway is given below.



Scheme 37

3.2.7.3. Mechanism for the formation of bromohydrin

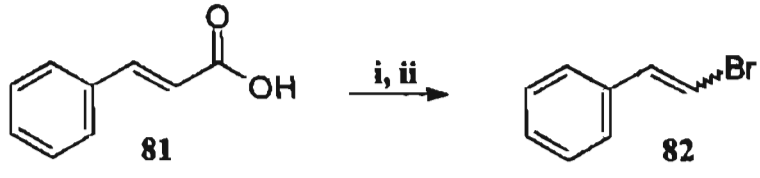
The formation of bromohydrin is observed only in the case of reactions in which a low concentration of the bromide ion is present. Though the mechanism for the formation of the bromohydrin under these conditions is not clear, the intermediacy of HOBr at lower concentrations of the bromide can be postulated.

3.2.8. Transformations of the dibromides

3.2.8.1. Synthesis of β-bromo styrenes from dibromo cinnamic acids

The general methods employed for the preparation of β–bromostyrenes involves the decarboxylative-debromination of dibromocinnamic acids. The reaction is usually accomplished by the treatment of dibromo cinnamic acids with aqueous sodium carbonate under reflux conditions. Various other methods are available for the conversion of alkenes to vinyl bromides.[25,26] In all these cases the dibromides themselves are prepared using either NBS or

molecular bromine. Since the combination of potassium bromide and CAN has been shown to be an excellent brominating agent for various alkenes, we extended the reaction to cinnamic acids. Here we examined the possibility of a one-pot conversion of the latter to the β-bromo styrenes. In a typical experiment the cinnamic acid was treated with potassium bromide and CAN in a solvent system of water and dichloromethane. The reaction took place very efficiently. The crude product thus obtained was subjected to decarboxylative-debromination, using triethylamine and DMF for about 6 hours to afford the vinyl bromide in about 55% yield (Scheme 38)



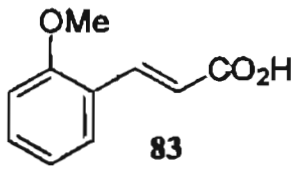
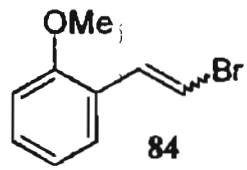
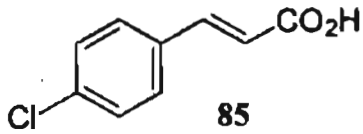
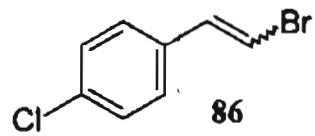
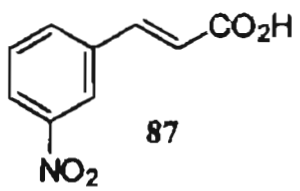
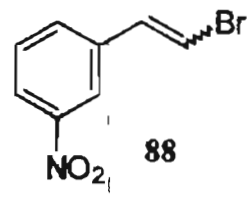
81 82

i. CAN, KBr, H_2O, CH_2Cl_2, 45 min ii. Et_3N, DMF, rt, 55%

Scheme 38

The structure of the product was confirmed on the basis of ^1H and ^{13}C NMR spectra and comparison of the data with those reported for the authentic compound. Different substituted cinnamic acids were converted to the corresponding bromostyrenes. In all these cases, mixtures of ***E*** and ***Z*** isomers, except for 3-nitro cinnamic acid, were obtained. For 3-nitro cinnamic acid, only the *Z* isomer is formed (Table 5).

Table 5: Cinnamic acids to vinyl bromides

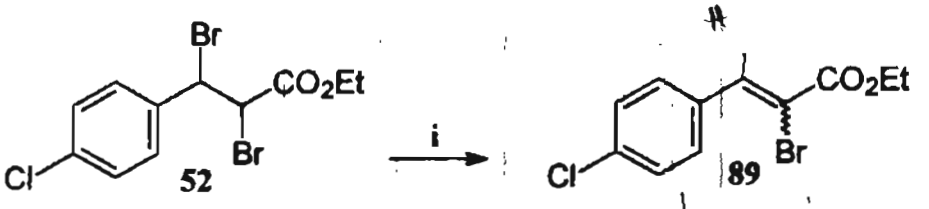
Entry	Cinnamic acid	Vinyl bromide	Yield (%)
1	 **83**	 **84**	55
2	 **85**	 **86**	70
3	 **87**	 **88**	58

Reaction conditions: i. CAN, KBr, H_2O, CH_2Cl_2, 30-45 min
ii. Et_3N, DMF, rt, 6h

3.2.8.2. Conversion of cinnamic esters to α-bromo cinnamates

Since the conversion of cinnamic acids to the corresponding bromostyrenes utilizing the above method appeared efficient, it was of interest to examine the viability of this method for cinnamic esters also. It may be recalled that we have observed the conversion of cinnamic esters and chalcones to their corresponding dibromides in very good yield by using a combination of potassium bromide and CAN. It has been reported from our own group that cinnamic esters can be converted to the corresponding α-azido α-β unsaturated esters.[27] The dibromo cinnamic esters were subjected to base induced dehydrobromination.

In a typical experiment, when 2,3-dibromo-3-(4-chloro)phenylethyl propanoate **52**, was treated with potassium carbonate in dry acetone under reflux conditions, the α-bromo cinnamate was obtained in 67% yield (Scheme 39).



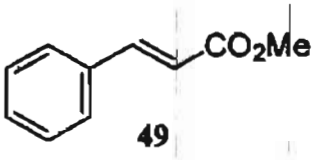
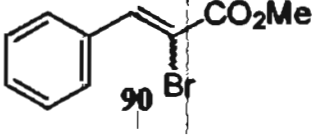
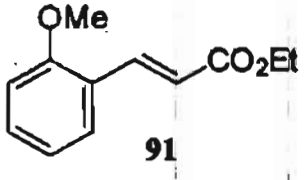
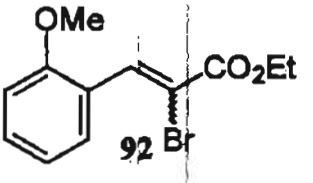
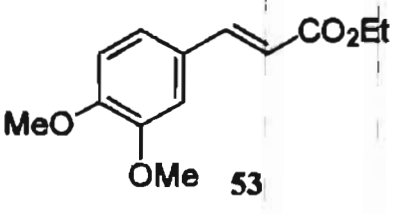
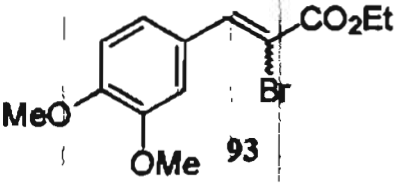
i. K_2CO_3, dry acetone, reflux, 67%

Scheme 39

The product was characterized on the basis of IR, ^1H and ^{13}C NMR spectral analysis, as usual.

The base used was potassium carbonate in the case of cinnamate and 4-chloro cinnamate. With 2,3 dimethoxy cinnamate and 2-methoxy cinnamate potassium *t*-butoxide in presence of crown ether in dry THF was found to give the best results. The results are given in the following table (Table 6).

Table 6: Cinnamic esters to α-bromocianamtes

Entry	Cinnamic ester	α-bromo cinnamate	Yield (%)
1	 49	 90	70
2	 91	 92	62
3	 53	 93	34

Reaction conditions: a. CAN, KBr, H_2O, CH_2Cl_2, 45 min ii. K_2CO_3, dry acetone, reflux
b. CAN, KBr, H_2O, CH_2Cl_2, 45 min ii. KOBu^t, 18-crown-6, dry THF

The products were characterized on the basis of ^1H and ^{13}C NMR spectra.

3.2.9. Attempted iodination of alkenes

Since the bromination of alkenes using potassium bromide and CAN was found to be an efficient method for the dibromination of olefins, the same reaction conditions were applied for iodination reactions also. Styrene was treated with potassium iodide and CAN in a two phase system of water and dichloromethane. The reaction took place efficiently, however, the instability of the products precluded their isolation. Due to the procedural problems associated with the reaction, it was not pursued further.

3.2.10. Attempted chlorination of alkenes

The attempted chlorination of alkenes using potassium chloride and CAN was not successful under the conditions used for the bromination of alkenes.

3.2.11. Conclusion

In conclusion it has been shown that the bromination of olefins can be achieved using CAN and KBr in a two phase system consisting of water and dichloromethane. The present procedure offers a convenient alternative to the use of bromine and a variety of other brominating agents like NBS, pyridiniumbromide perbromide which are either toxic or are costly. The chemoselectivity exhibited by systems such as **59**, **63**, and carvone, **5** is noteworthy. It is important to note that the bromination of these systems under the usual conditions is not chemoselective at all. Since the solvent plays an important role in these reactions, suitable selection of the solvent leads to a desired product. The key point is that by simply using the combination of potassium bromide and CAN, it is possible to convert styrene into a variety of products such as dibromoalkane, bromohydrin, phenacyl bromide and also the nitratobromide. By a suitable selection of the system we

can arrive at a desired product. Moreover, the reaction conditions are mild and simple.

3.3. EXPERIMENTAL

For general information, see section **2.3.** of **Chapter 2**

General procedure for the bromination of alkenes in water-dichloromethane solvent system

To a solution of the alkene (1 mmol) in dichloromethane (10 mL) was added KBr (2.2 mmol) and a solution of CAN (2.3 mmol) in water (10 mL) at room temperature and stirred. After the completion of the reaction the dichloromethane layer was separated, washed with brine and dried over sodium sulfate. The solvent was removed and the residue was purified either by crystallization or by chromatographiy.

General procedure for the bromination of styrene in aqueous methanol

To a solution of the styrene (1 mmol) and potassium bromide (2.2 mmol) in methanol (10 mL), was added a solution of CAN (2.3 mmol) in methanol (15 mL) at room temperature. When the starting material was completely consumed as observed by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine and then dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography on *silica gel* using hexane-ethyl acetate as the eluent to afford the product.

General procedure for the bromination of styrene in aqueous acetonitrile

To a solution of the styrene (1 mml) and potassium bromide (2.2 mmol) in acetonitrile (10 mL), was added a solution of CAN (2.3 mmol) in

acetonitrtile (15 mL) at room temperature. When the starting material was completely consumed as observed by tlc, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine and then dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography on silica gel using hexane-ethyl acetate as the eluent to afford the product.

General procedure for the bromination of styrene under argon atmosphere

To a deoxygenated solution of the styrene and lithium bromide in the solvent (methanol/acetonitrile) was added a deoxygenated solution of CAN, in the same solvent under an atmosphere of argon. On completion, the reaction mixture was processed as described in the general procedure.

General procedure for the bromination of styrene in *tert*-butanol

Styrene (1 mmol), lithium bromide and CAN were taken in 15 mL *tert*-butanol and stirred overnight and processed as described in the general procedure.

General procedure for the formation of β-bromostyrenes from cinnamic acids

α,β-Unsaturated acid (1 mmol), and potassium bromide (2.1 mmol) were taken together in dichloromethane (10 mL), CAN (2.3 mmol) dissolved in water (10 mL) was added to it with stirring. After completion of the reaction, the dichloromethane layer was separated and concentrated. The crude product was taken in DMF (4 mL), triethyl amine (2 mmol) was added to it with stirring. The reaction mixture was stirred overnight. Then it was extracted with ethyl acetate (3x15 mL). The ethyl acetate layer was separated and washed three times with water, then with brine and dried over sodium sulfate.

The crude product obtained after concentrating the solvent was purified by column chromatography on silica using hexane as eluent to afford the vinyl bromide.

General procedure for the formation of α-bromocinnamtes from *cinnamic esters*

(i) *Using Potassium carbonate*

To a mixture of the α,β-unsaturated ester (1 mmol), and potassium bromide in dichloromethane was added an aqueous solution of CAN. After the completion of the reaction, the dichloromethane layer was separated, washed with brine and dried over sodium sulfate. The residue after removing the solvent was refluxed with potassium carbonate (2 mmol) and dry acetone (5 mL) for about 8 hours. After the completion of the reaction, the reaction mixture was washed with water and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated off and the residue on column chromatography using hexane-ethyl acetate mixture as the eluent afforded the product.

(ii) Using Potassium *tert*-butoxide

To a mixture of the α,β-unsaturated ester (1 mmol), and potassium bromide in dichloromethane was added an aqueous solution of CAN. After the completion of the reaction, the dichloromethane layer was separated, washed with brine and dried over sodium sulfate. The residue, after removing the solvent was treated with potassium *tert*-butoxide (2 mmol) and 18-crown-6 in dry THF (5 mL). After the completion of the reaction, the reaction mixture washed with water and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated off and the residue on column

chromatography using hexane-ethyl acetate mixture as the eluent afforded the product.

1,2-Dibromo-1-phenyl ethane (32)

Styrene 31 (500 mg, 4.8 mmol) on treatment with potassium bromide (1.20 g, 10.08 mmol) and CAN (6.05 g, 11.04 mmol) in a two phase system of water and dichloromethane afforded 1.1 g (91%) of the dibromide (32) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 74-76 °C.

IR (KBr) ν_{max} : 3011, 1452, 1243, 1196, 1135, 919, 778, 697 cm^{-1}

^1H NMR : 7.35-7.31 (m, 5H, ArH), 5.11 (dd, 1H, CHBr, J = 5.7 Hz, J = 9.9 Hz), 4.06-3.93 (m, 2H, CH_2Br).

^{13}C NMR : 138.44, 128.99, 128.68, 127.51, 50.82, 34.98.

EIMS m/z (%) : (M^++2) 266 (2), 264 (5), 262 (2), 186 (10), 185 (85), 183 (100), 104 (95), 77 (70), 51 (60).

1,2-Dibromo-1-(4-methyl)-phenyl ethane (34)

4-Methyl styrene 33 (236 mg, 2 mmol) on treatment with potassium bromide (500 mg, 4.2 mmol) and CAN (2.56 g, 4.6 mmol) in a two phase system of water and dichloromethane afforded 372 mg (67%) of the dibromide (34) as viscous liquid.

IR (neat) ν_{max} : 1613, 1512, 1438, 1135, 818 cm^{-1}.

^1H NMR : 7.25 (d, 2H, ArH, J = 8 Hz), 7.15 (d, 2H, ArH, J = 7.8 Hz), 5.09 (dd, 1H, CHBr, J = 5.5 Hz, J = 10.4 Hz), 4.05-3.95 (m, 2H, CH_2Br), 2.35 (s, 3H, CH_3).

^{13}C NMR : 138.94, 135.57, 129.43, 127.45, 50.84, 34.86, 21.22.

EIMS m/z (%) : (M+4) 282 (2), 280 (70), 278 (100), 199 (70), 197 (80), 118 (100), 115 (50).

1,2-Dibromo-1-(4-chloro)-phenyl ethane (36)

4-Chloro styrene **35** (138 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 254 mg (85%) of the dibromide (**36**) as low melting, pale yellow solid.

IR (neat) ν_{max} : 1484, 1091, 1023, 890 cm^{-1}.

^1H NMR : 7.30 (s, 4H, ArH), 5.08-5.03 (m, 1H, CHBr), 4.03-3.87 (m, 2H, CH_2Br).

^{13}C NMR : 137.02, 134.86, 128. 99, 128.96, 49.44, 34.57.

EIMS m/z (%) : 298 (M^+)(2), 219 (60), 217 (50), 138 (100), 103 (40), 77 (30), 51 (30).

1,2-Dibromo-1-phenyl propane (38) (mixture of isomers)

β-Methyl styrene **37** (118 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 250 mg (90%) of the dibromide (**38**) as a viscous liquid.

IR (neat) ν_{max} : 1452, 1371, 1141, 998, 761, 687 cm^{-1}.

^1H NMR : 7.41-7.24 (m, ArH,), 5.22 (d, J = 5.6 Hz), 5.02 (d, 1H, 9.3 Hz), 4.60-4.58 (m, CH_2), 2.11(d, J = 6.2 Hz), 1.70 (d, J = 7.4 Hz).

^{13}C NMR: : 140.61, 137.13, 129.13, 128.78, 128.64, 127.75, 59.14, 58.76, 52.75, 51.02, 29.76, 25.90, 25.23, 22.30.

EIMS m/z (%) : 278 (M^+) (2), 199 (80), 197 (85), 117 (100), 118 (92), 116 (70), 91 (50), 51 (30).

1,2-Dibromo-(4-nitro)-phenyl ethane (40)

4-Nitro styrene **39** (150 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.2 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase

system of water and dichloromethane afforded 191 mg (62%) of the dibromide (40) as light yellow viscous liquid.

IR (neat) ν_{max} : 1613, 1519, 1344, 1231, 893, 812 cm^{-1}.

^1H NMR : 8.27-8.21 (m, 2H, ArH), 7.72 (d, 1H, ArH, J = 7.7 Hz), 7.58 (t, 1H, ArH, J = 7.9 Hz), 5.17 (dd, 1H, CHBr, J = 11.1 Hz, 4.8 Hz), 4.13-3.96 (m, 2H, CH_2Br).

^{13}C NMR : 140.85, 133.66, 129.94, 124.03, 122.91, 47.94, 34.04.

1,2-Dibromo-1-naphthyl ethane (42)

Vinyl naphthalene 41 (154 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 298 mg (95%) of the dibromide (42) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 66-68 °C.

IR (CH_2Cl_2)ν_{max} : 1452, 1371, 1141, 996, 761 cm^{-1}.

^1H NMR : 7.88-7.81 (m, 4H, ArH), 7.51-7.48 (m, 3H, ArH), 5.30 (dd, 1H, CHBr, J = 7 Hz, 9.3 Hz), 4.14-4.08 (m, 2H, CH_2Br).

^{13}C NMR : 135.74, 133.59, 132.98, 129.11, 128.25, 127.83, 127.48, 126.90, 126.69, 124.41, 51.29, 34.72.

EIMS m/z (%) : 314 (M^+)(5), 234 (100), 232 (80), 154 (20), 152 (90), 126 910), 76 (15), 51 (2).

1,2-Dibromo cyclohexane (2)

Cyclohexene 1 (410 mg, 5 mmol) on treatment with potassium bromide (1.0 g, 10.1 mmol) and CAN (6.3 gm, 11.5 mmol) in a two phase system of water and dichloromethane afforded 786 mg (65%) of the dibromide (2) as a viscous liquid.

IR (neat) ν_{max} : 2948, 1445, 1344, 1175, 697, 548 cm^{-1}

^{1}H NMR : 4.47 (s, 2H, CHBr), 2.47-2.43 (m, 2H, CH_2), 1.92-1.80 (m, 4H, CH_2), 1.55-1.52 (m, 2H, CH_2).

^{13}C NMR : 54.72, 31.46, 22.06.

EIMS m/z (%) : 244 (M^++4) (50), 242 (67), 240 (50), 86 (40), 84 (55), 81 (100), 79 (55), 49 (80), 41 (30).

1,2-Dibromo-3-phenyl propane (44)

Allyl benzene **43** (118 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 180 mg (65%) of the dibromide (**44**) as colorless oil.

IR (neat) ν_{max} : 2995, 1809, 1600, 1494, 1580, 1445 cm^{-1}.

^{1}H NMR : 7.33-7.27 (m, 5H, ArH), 4.36-4.30 (m, 1H, CH_2Br), 3.83-3.78 (m, 1H, CH_2Br), 3.63-3.45 (m, 2H, CH_2), 3.11 (dd, 1H, J = 7.7 Hz, J = 14.4 Hz).

^{13}C NMR : 136.74, 129.52, 128.49, 127.20, 52.24, 41.92, 35.89.

1,2-Dibromo hexane (46)

1-Hexene **45** (170 mg, 2 mmol) on treatment with potassium bromide (500 mg, 4.2 mmol) and CAN (2.5 g, 4.6 mmol) in a two phase system of water and dichloromethane afforded 450 mg (82%) of the dibromide (**46**) as colorless viscous liquid.

IR (neat) ν_{max} : *1438, 1244, 1085, 677, 654 cm^{-1}.*

^{1}H NMR : 4.16-4.10 (m, 1H, CHBr), 3.84 (dd, 1H, CHBr, *J = 10.1 Hz, 4.3 Hz), 3.61 (t, 1H, CHBr, J* = 10.1 Hz), 2.16-2.09 (m, 1H, CH_2), 1.80-1.74 (m, 1H, CH_2), 1.52-1.31 (m, 4H, CH_2), 0.94 (t, 3H, CH_3, J = 7.1 Hz).

^{13}C NMR : 52.73, 36.07, 35.56, 28.76, 21.89, 13.88.

1,2-Dibromo octane (48)

1-Octene **47** (500 mg, 4.5 mmol) on treatment with potassium bromide (1.1 gm, 9.3 mmol) and CAN (5.7 gm, 10.35 mmol) in a two phase system of water and dichloromethane afforded 624 mg (51%) of the dibromide (**48**) as viscous liquid.

IR (neat) ν_{max} : 1465, 1452, 1378, 1148, 582 cm^{-1}.

^1H NMR : 4.17-4.09 (m, 1H, CHBr), 3.83 (dd, 1H, CHBr, J = 4.3 Hz, J = 10.1 Hz), 3.59 (t, CH_2, 1H, J = 10 Hz), 2.18-2.08 (m, CH_2, 1H), 1.81-1.70 (m, CH_2, 1H), 1.57-1.25 (m, CH_2, 8H), 0.89-0.87 (brs, CH_2, 3H).

^{13}C NMR : 52.83, 36.08, 35.96, 31.60, 29.71, 28.50, 26.69, 22.57.

2,3-Dibromo-3-phenylmethyl propanoate (50)

Methyl cinnamate **49** (162 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 250 mg (78%) of the dibromide (**50**) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 114-116 °C.

IR (KBr) ν_{max} : 1720, 1614, 1538, 1440, 1120, 881 cm^{-1}.

^1H NMR : 7.35 (brs, 5H, ArH), 5.32 (d, 1H, CHBr, J = 11.7 Hz), 4.83 (d, 1H, CHBr, J = 11.7 Hz), 3.87 (s, 3H, OCH_3).

^{13}C NMR : 168.09, 137.50, 129.30, 128.82, 128.02, 53.29, 50.59, 46.60

2,3-Dibromo-3-(4-chloro) phenylethyl propanoate (52)

4-Chloroethyl cinnamate **51** (210 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 gm, 2.3 mmol) in a two phase system of water and dichloromethane afforded 296 mg (80%) of

the dibromide (**52**) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 86-89 °C

IR (neat) ν_{max} : 1743, 1598, 1490, 1320, 1196, 784 cm^{-1}.

^1H NMR : 7.35 (brs, 5H, ArH), 5.29 (d, 1H, CHBr, J = 11.7 Hz), 4.73 (d, 1H, CHBr, J = 11.7 Hz), 4.36 (q, 2H, OCH_2, J = 7.1 Hz), 1.38 (t, 3H, CH_3, J = 7.1 Hz).

^{13}C NMR : 167.45, 136.34, 135.33, 129.46, 129.21, 62.67, 49.65 46.85, 13.98.

2,3-Dibromo-3-(3,4-dimethoxy)-phenylethyl propanoate (54)

Cinnamyl ester **53** (270 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 382 mg (80%) of the dibromide (**54**) as light yellow crystals, recrystallized from dichloromethane-hexane mixture, mp: 112-114 °C.

IR (neat) ν_{max} : 1738, 1600, 1513, 1463, 1369, 1331, 849, 801 cm^{-1}.

^1H NMR : 6.99-6.81 (m, 3H, ArH), 5.31 (d, 1H, CHBr, J = 11.7 Hz), 4.79 (d, 1H, CHBr, J = 11.7 Hz), 4.36 (q, 2H, OCH_2, J = 7 Hz), 3.92 (*s*, 3H, OCH_3), 3.90 (*s*, 3H, OCH_3), 1.39 (*t*, 3H, CH_3, J = 7.1 Hz).

^{13}C NMR : 167.70, 149.91, 149.27, 129.98, 120.98, 110.89, 110.69, 62.53, 55.95, 55.86, 51.57, 47.37, 13.98.

2,3-Dibromo-1,3-diphenylpropan-1-one (56)

Chalcone **55** (208 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 351 mg (95%) of the dibromide (**56**) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 156-158 °C.

IR (KBr) ν_{max} : 1726, 1452, 1427, 1359, 1197, 1141, 761 cm^{-1}.

^1H NMR : 7.51-7.24 (m, 10H, ArH), 5.81 (d, 1H, CHBr, J = 11.2 Hz), 5.63 (d, 1H, CHBr, J = 11.2 Hz).

^{13}C NMR : 190.89, 138.31, 134.09, 129.00, 128.86, 128.86, 49.75, 46.85.

3,4-Dibromo 4-phenyl butan-2 one (58)

Benzylidene acetone **57** (146 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.3 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 252 mg (81%) of the dibromide (**58**) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 126-128°C.

IR (KBr) ν_{max} : 1726, 1452, 1427, 1359, 1197, 1141, 761 cm^{-1}.

^1H NMR : 7.38-7.35 (m, 5H, ArH), 5.30 (d, 1H, CHBr, J = 11.6 Hz), 4.91 (d, 1H, CHBr, J = 11.6 Hz), 2.47 (s, 3H, CH_3).

^{13}C NMR : 197.85, 137.81, 129.32, 128.87, 128.47, 128.15, 52.82, 49.49, 26.86.

EIMS m/z (%) : 225, 223 (88), 209, 145 (100), 102, 82.

(2,3-Dibromo)allyl(4-acetoxy)phenyl ether (60)

Allyl phenyl ether **59** (176 mg, 1mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 250 mg (75%) of the dibromide (**60**) as colorless crystals, recrystallized from dichloromethane-hexane mixture, mp: 48-50 °C.

IR (neat)ν_{max} : 1680, 1604, 1506, 1363, 1251, 1174, 831, 581 cm^{-1}.

^1H NMR : 7.92 (d, 2H ArH, J = 8.2 Hz), 6.95 (d, 2H, ArH, J = 8.2 Hz), 4.43 (brt, 3H, OCH_2, CHBr), 3.89 (brd, 2H, CH_2Br), 2.54 (s, 3H, CH_3).

^{13}C NMR: : 195.97, 161.58, 131.09, 130.52, 114.33, 69.04, 46.99, 32.99, 26.24.

HRMS Calcd for $C_{11}H_{12}O_2Br_2$, 333.9204; Found, 333.9194.

Tribromide (61)

A solution of the allylphenylether **59** (174 mg, 1mmol) in CCl_4 on treatment with a solution of bromine in the same solvent, (the bromine solution was added till the color persists) followed by removing the solvent in vacuo and purification using a silica column afforded (46%) of the dibromide **61** and 22% of the dibromide **62.**

IR (neat)ν_{max} : 2852, 1688, 1594, 1507, 1451, 1261, 1174, 831 cm^{-1}.

^{1}H NMR : 7.97 (d, 2H ArH, J = 8.4 Hz), 6.99 (d, 2H, ArH, J = 8.4 Hz), 4.45-4.36 (m, 5H, OCH_2, CH_2Br), 3.91 (s, 3H, CH_3).

^{13}C NMR : 189.57, 161.19, 131.35, 130.54, 127.71, 114.63, 69.04, 46.02, 32.01, 30.15.

Tetrabromide (62)

IR (neat)ν_{max} : 1671, 1597, 1509, 1454, 1250, 1114, 837, 611 cm^{-1}.

^{1}H NMR : 8.11 (d, 2H, ArH, J = 8.2 Hz), 7.01 (d, 2H, ArH, J = 8.2 Hz), 6.61 (s, 1H, $CHBr_2$), 3.91-3.89 (m, 2H, CH_2Br).

^{13}C NMR : 184.21, 162.21, 132.26 124.18, 114.71, 69.09, 46.82, 39.61, 31.96.

(2,3-Dibromo)allyl(2-acetoxy)phenyl ether (64)

Allylphenyl ether **63** (174 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 267 mg (79%) of the dibromide (**64**) as colorless viscous liquid.

IR (neat)$_{\nu\ max}$: 1676, 1595, 1483, 1452, 1290, 1159 cm^{-1}.

^{1}H NMR : 7.73 (d, 1H, ArH, J = 7.5 Hz), 7.43 (m, 1H, ArH), 7.03 (t, 1H, ArH, J = 7.4 Hz), 6.93 (d, 1H, ArH, J = 8.3 Hz), 4.49 (broad triplet, 3H, OCH_2, C<u>H</u>Br), 3.90 (broad triplet, 2H, CH_2), 2.67 (s, 3H, CH_3).

^{13}C NMR : 190.70, 156.92, 133.52, 130.69, 128.70, 121.57, 112.51, 69.71, 46.98, 32.15, 32.06.

Dibromo carvone (6)

Carvone **5** (150 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 217 mg (70%) of the dibromide (**6**) as colorless viscous liquid.

IR (neat) ν_{max} : 1676, 1440, 1384, 1216, 1079, 1048, 898 cm^{-1}.

^{1}H NMR : 6.74 (s, 1H, oefinic CH), 3.96 (dd, 1H, CH_2Br, J = 3.5 Hz, J = 10.2 Hz), 3.83, (uneven triplet, 1H), 2.62-2.34 (m, 5H, CH_2), 1.90 (s, 3H, CH_3), 1.79 (s, 3H, CH_3).

^{13}C NMR : 197.81, 197.36, 143.14, 142.91, 135.33, 135.26, 70.93, 70.82, 42.16, 41.93, 40.52, 40.43, 39.79, 28.66, 28.24, 27.73, 15.53.

EIMS m/z (%) : 310 (M^+) (10), 307 (10), 230 (40), 228 (45), 148 (50), 121 (20), 107 (30), 82 (100), 77 (32), 54 (25).

1,2-Dibromo-1-phenyl ethene (68)

Phenylacetylene **68** (102 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 210 mg (80%) of the dibromoethene (**69**) as a 2:3 mixture of E and Z isomers.

IR (neat)ν_{max} : 3064, 1701, 1589, 1483, 1440, 867, 693 cm^{-1}.

^{1}H NMR: : 7.48 (m, 5H, ArH), 6.78 (s, 1H, CHBr).

^{13}C NMR: : 138.40, 136.94, 131.07, 129.26, 129.07, 128.61, 128.44, 128.14, 127.61, 121.28, 108.68, 102.85.

1,2-Dibromo-1,2-diphenylethene (73)

Diphenylacetylene **70** (178 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.3 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 317 mg (94%) of the dibromoethene (**73**) as colorless solid, mp; 210 °C.

IR (neat)ν_{max} : 3058, 1602, 1489, 1440, 1234, 1066, 693, 562 cm^{-1}.

^{1}H NMR: : 7.51 (m, 4H, ArH), 7.41 (m, 6H, ArH).

^{13}C NMR: : 140.83, 129.15, 128.91, 128.38, 118.10.

1,2-Dibromo-hex-1-ene (74)

1-Hexyne **71** (85 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 194 mg (79%) of the dibromoethene **74** as a 5:1 mixture of ***E*** and ***Z*** isomers.

IR (neat)ν_{max} : 2921, 1738, 1465, 1259, 736, 705 cm^{-1}.

^{1}H NMR: : 6.39 (s, 1H, olefinic H), 2.59 (t, 2H, CH_2, J = 7.3 Hz), 1.56 (m, 2H, CH_2), 1.31 (m, 6H, CH_3). 0.89 (m, 3H,CH_3).

^{13}C NMR: : 126.88, 105.32, 102.00, 41.12, 36.81, 31.48, 28.00, 26.93, 22.48, 14.01.

3,4-Dibromo-4-octene (75)

4-Octyne **72** (100 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 202 mg (75%) of the dibromide as colorless liquid.

IR (neat)ν_{max} : 2921, 1726, 1626, 1465, 1259, 1178, 742, 705 cm^{-1}.

^{1}H NMR: : 2.65 (t, 4H, CH_2, J = 7.2 Hz), 1.61 (m, 4H, CH_2), 0.94 (t, 6H, CH_2, J = 7.3 Hz).

^{13}C NMR: : 121.66, 56.45, 42.78, 42.55, 32.10, 20.85, 20.74, 13.01, 11.97.

1,2-Dibromo-1-phenyl-1-trimethylsilyl acetylene (76)

1-Phenyl-1-trimethylsilyl acetylene **73** (98 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 224 mg (90%) of the dibromide (**76**) as colorless liquid.

IR (neat)ν_{max} : 2959, 1564, 1489, 1247, 904, 842, 761, 693, 568 cm^{-1}.

^{1}H NMR: : 7.36 (m, 5H, ArH), 0.0005 (s, 9H).

^{13}C NMR: : 141.51, 133.63, 131.26, 129.18, 128.93, 128.25, 0.59.

2-Bromo-1-phenyl ethanol (77)

Styrene **31** (104 mg, 1 mmol) on treatment with potassium bromide (120 mg, 1 mmol) and CAN (1.26 gm, 2.3 mmol) in a two phase system of water and dichloromethane afforded 58 mg (22%) of the dibromide (**32**) as colorless crystals and 52 mg (26%) of the bromohydrin (**77**) as a colorless oil.

IR (neat)$_{\nu\ max}$: 3400, 1883, 1647, 1600, 1458, 1425, 1061, 1209 cm^{-1}.

^{1}H NMR : 7.33 (m, 5H, ArH), 4.88 (m, 1H, CHOH), 3.55 (m, 2H, CH_2Br), 2.66 (s, 1H, OH, exchangeable with D_2O).

1-Bromo-2-hydroxycyclohexane (78)

Cyclohexene **1** (410 mg, 5 mmol) on treatment with potassium bromide (600 mg, 5.5 mmol) and CAN (6.25 g, 11.5 mmol) in a two phase system of water and dichloromethane afforded 169 mg (14%) of the dibromocyclohexane (**2**) and 465 mg (52%) of the bromohydrin (**78**)

IR (neat)$_{\nu\ max}$: 3405, 2862, 1444, 1357, 1182, 1070, 951, 689.

^{1}H NMR : 3.88 (m, 1H, CHOH), 3.59 (m, 1H, CHBr), 2.35-2.12 (m, 3H, CH_2 and OH), 1.86-1.67 (m, 3H, CH_2), 1.40-1.25 (m, 3H, CH_2).

^{13}C NMR : 75.30, 61.73, 36.21, 33.48, 26.71, 24.16.

1-Bromo1-phenyl-2-nitrato ethane (79) and 1-Bromo acetopheneone (80)

Styrene **31** (118 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in aqueous methanol, after work up and purification as described in the general procedure afforded 88 mg (35%) of the nitrato bromide **79** and 85 mg (42%) of the phenacyl bromide **80** as colorless crystals, recrystallized from dichloromethane-hexane mixture.

Styrene **31** (104 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in aqueous acetonitrile (20 mL), after work up and purification as described in the general procedure afforded 126 mg (28%) of the nitrato bromide **79** and 96 mg (48%) of the phenacylbromide **80** as colorless crystals, recrystallized from dichloromethane-hexane mixture.

Styrene 31(104 mg, 1 mmol) on treatment with lithium bromide (87 mg, 1 mmol) and CAN (1.26 g, 2.3 mmol) in dry acetonitrile under an atmosphere of argon, for one hour afforded, after usual work up and procedure as described in the general experimental procedure, 194 mg (79%) of the nitrato bromide (**79**) as pale yellow liquid.

Styrene 31 (104 mg, 1 mmol) on treatment with lithium bromide (87 mg, 1 mmol) and CAN (1.26 g, 2.3 mmol) in a 1:1 mixture of acetic acid and acetonitrile (20 mL), after processing as described in the general procedure afforded 150 mg (61%) of the nitrato bromide **79** yield and 24 mg (12%) of the phenacyl bromide **80** as colorless crystals recrystallized from dichloromethane-hexane mixture.

Styrene **31** (104 mg, 1 mmol) on treatment with lithium bromide (87 mg, 1 mmol) and CAN (1.26 g, 2.3 mmol) in *t*-butanol, for 10h and after processing as described in the general procedure afforded 138 mg (53%) of the nitrato bromide **79** and 40 mg (20%) of the phenacyl bromide **80** as colorless crystals, recrystallized from dichloromethane-hexane mixture.

1-Bromo1-phenyl-2-nitrato ethane (79)

IR (neat)$_{\nu\ max}$: 1645, 1489, 1452, 1278, 1209, 855, 693 cm^{-1}.

^{1}H NMR : 7.39 (brs, 5H, ArH), 5.97 (q, 1H, $CHONO_2$, J = 5.1 Hz), 3.69-3.53 (m, 2H, CH_2Br).

^{13}C NMR : 135.21, 129.82, 129.07, 126.60, 83.82, 30.41.

1-Bromo acetopheneone (80)

mp: 48-51 °C.

IR (neat)$_{\nu\ max}$: 1682, 1451, 1276, 1195, 1108, 997, 752 cm^{-1}.

^{1}H NMR : 8.01 (t, 2H, ArH, J = 7.2 Hz), 7.61 (d, 1H, ArH, J = 7.3 Hz), 7.69 (t, 2H, ArH, J = 7.6 Hz), 4.44 (s, 2H, CH_2).

^{13}C NMR : 190.77, 135.75, 131.61, 129.61, 30.74.

1-Bromo-2-phenylethene (82)

Cinnamic acid **81** (148 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromocinnamic acid. The crude product on treatment with triethylamine (200 mg, 2 mmol) in DMF (2 mL) at room temperature for 6h followed by usual workup as described in the general procedure afforded 100 mg (55%) of the vinyl bromide **82**, as a viscous oil.

IR (neat)ν_{max} : 2915, 1613, 1525, 1337, 1089, 805, 668 cm^{-1}.

^{1}H NMR : 7.65-7.25 (m, 5H, ArH), 7.01 (d, 1H, olefinic, J = 8.1 Hz), 6.36 (d, 1H, olefinic, J = 8.1 Hz).

^{13}C NMR : 135.85, 132.30, 128.95, 128.26, 128.17, 106.27.

1-Bromo(2-methoxy)phenyl ethene (84)

2-Methoxy cinnamic acid **83** (178 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The crude product was treated with triethyl amine (202 mg, 2 mmol) in DMF (4mL) at room temperature. On completion, the reaction mixture was worked up as described in the general procedure to afford 117 mg (55%) of the vinyl bromide **84** as a 1:1 mixture of ***E*** and ***Z*** isomers.

IR (neat)ν_{max} : 2935, 1595, 1457, 1289, 1233, 1045, 858 cm^{-1}.

^{1}H NMR : 7.47-7.15 (m, 8H,), 7.03 (d, 1H, J = 8.1 Hz), 6.87 (d, 1H, J = 6.9 Hz), 6.75 (dd, 1H, J = 2.8 Hz, J = 8.8 Hz), 6.57 (d, 1H, J = 8.1 Hz), 6.44 (d, 1H, J = 8.1 Hz), 3.82 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3).

^{13}C NMR : 159.31, 158. 30, 136.04, 135.56, 133.11, 132.21, 132.18, 129.14, 12.64, 115.86, 115.59, 114.15, 114.03, 109.18, 106.41, 55.38, 55.03.

1-Bromo-(4-chloro)phenylethene (86)

4-Chlorocinnamic acid **85** (187 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The crude product on treatment with triethylamine (200 mg, 2 mmol) and DMF (2 ml) at room temperature afforded, after usual work up, as described in the general procedure to afford 151 mg (70%) of the vinyl bromide **83** as a 1:1mixture of ***E*** and ***Z*** isomers.

IR (neat)ν_{max} : 2192, 1495, 1387, 1285, 858 cm^{-1}.

^{1}H NMR : 7.82-7.14 (5H, ArH and olefinic H), 6.54 (1H, olefinic H, dd, J = 8 Hz).

^{13}C NMR: : 133.58, 133.46, 133.17, 130.15, 129.79, 129.31, 129.24, 129.15, 126.85, 126.75, 126.10, 109.23, 109.14.

EIMS m/z (%) : 220 (M+) (2), 218 (10), 137 (80), 101 (90), 75 (100), 63 (30), 51 (70).

1-Bromo(3-nitro)phenylethene (88)

3-Nitrocinnamate **87** (193 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The crude product was treated with triethylamine (202 mg, 2 mmol) in DMF (4 mL) at room temperature. The reaction mixture, after completion of the reaction was processed as described in the general procedure to afford 132 mg of the vinyl bromide **88** (58%) as a single isomer.

IR (neat) ν_{max} : 3012, 1692, 1487, 1287, 959 cm^{-1}.

^{1}H NMR : 7.82-7.14 (m, 5H, ArH and olefinic), 6.54 (d, 1H, olefinic, J = 8 Hz).

^{13}C NMR : 148.14, 136.43, 134.60, 130.28, 129.14, 123.61, 122.86, 109.75.

EIMS m/z (%) : 229 (M+) (22), 227 (20), 210 (5), 181 (10), 169 (5), 118 (5), 102 (100), 90 (10), 75 (25), 63 (18), 51 (24).

Ethyl-1-bromo-(4-chloro)phenyl prop-2-enoate (89)

4-Chloro cinnamate **51** (210 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.2 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The dibromide was refluxed with potassium carbonate (2 mmol) in dry acetone (10 mL) for

about 8 hours. The reaction mixture after work up and purification afforded the α-bromo ester as a 1:1 mixture of ***E*** and ***Z*** isomers (193 mg, 67%).

IR (neat)ν_{max} : 2990, 1719, 1613, 1588, 1487, 1406, 1262, 1087, 1018, 807 cm^{-1}.

^{1}H NMR : 8.1 (s, olefinic), 7.79 (d, ArH), 7.38 (d, ArH), 7.36-7.21(m, ArH), 4.34 (q, OCH_2, J = 7.1 Hz), 4.22 (q, OCH_2, J = 7.1 Hz), 1.39 (t, CH_3, J = 7.1 Hz), 1.22 (t, CH_3, J = 7.1 Hz).

^{13}C NMR :163.78, 162.85, 139.23, 138.29, 136.05, 132.11, 131.41, 129.46, 129.33, 129.07, 128.64, 128.54, 113.75, 112.50, 62.69, 62.24.

Methyl-2-bromo-3-phenylprop-2-enoate (90)

Methyl cinnamate **49** (162 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The dibromide was refluxed with potassium carbonate (2 mmol) in dry acetone (10 mL) for about 8 hours. The reaction mixture after work up and purification afforded (70%) of the α-bromo ester as a 1:1 mixture of *E* and *Z* isomers.

IR (neat) ν_{max} : 1738, 1613, 1570, 1225, 1350, 999, 918 cm^{-1}.

^{1}H NMR : 7.22-7.15 (m, 6H, ArH,+ olefinic), 3.61 (s, 3H, OCH_3).

^{13}C NMR : 163.70, 139.68, 134.59, 128.80, 128.29, 128.01, 110.89, 52.68.

Ethyl-1-bromo-(2-methoxy)phenyl prop-2-enoate (92)

Ethyl cinnamate **91** (206 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.2 mmol) and CAN (1.26 g 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The dibromide was treated with potassium *t*-butoxide (1.2 mmol) in presence of catalytic

amount of 18-crown-6 in dry THF (5 mL). The product after workup and purification afforded 173 mg (62%) of the vinylbromoester as a 1:1 mixture of *E* and *Z* isomers.

IR (neat) ν_{max} : 2984, 1719, 1600, 1475, 1250, 1025, 843, 749 cm^{-1}

^1H NMR : 8.42 (1H, olefinic), 8.02 (d, ArH, J = 7.1 Hz), 7.48 1H, olefinic), 7.39-6.83 (m, ArH), 4.35 (q, OCH_2, J = 6.9 Hz), 4.16 (q, OCH_2, J = 7.0 Hz), 3.88 (s, OCH_3), 1.39 (t, CH_3, J = 7.0 Hz), 1.15 (t, CH_3, J = 6.8 Hz).

^{13}C NMR : 163.31, 164.10, 157.83, 156.55, 136.55, 136.29, 131.38, 130.35, 129.91, 129.50, 128.94, 120.26, 120.08, 113.88, 110.47, 62.53, 61.93, 55.54, 55.39, 14.33, 13.79.

Ethyl-2-bromo-(3,4-dimethoxy)phenylprop-2-enoate (93)

3,4-Dimethoxy cinnamate **53** (236 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded the dibromide. The dibromide on treatment with potassium-*tert*-butoxide (1.2 mmol) in presence of catalytic amount of 18-crown-6 afforded 107 mg (34%) of the vinylbromoester as a 1:1 mixture of E and Z isomers as a yellow oily liquid.

IR (neat)ν_{max} : 1711, 1590, 1505, 1456, 1243, 1140, 1018, 799 cm^{-1}.

^1H NMR: : 8.14 (s, olefinic), 7.64 (d, ArH, J = 7.0 Hz), 7.43 (d, ArH), 7.26 (d, ArH, J = 7.1 Hz), 6.93-6.78 (m, ArH), 4.32, (q, OCH_2, J = 7.1 Hz), 4.24 (q, OCH_2, J = 7.0 Hz), 3.92 (s, OCH_3), 3.90 (s, OCH_3,) 3.88 (s, OCH_3,) 3.85 (s, OCH_3), 1.39 (t, CH_3, J = 7.0 Hz), 1.26 (t, CH_3, J = 7.0 Hz).

^{13}C NMR: : 164.51, 163.41, 150.92, 149.86, 148.65, 148.55, 140.30, 139.44, 127.50, 127.80, 126.40, 125.29, 122.13, 112.74, 111.35, 110.72, 110.64, 62.52, 62.11, 55.84, 55.78.

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CHAPTER 4

CAN MEDIATED TRANSFORMATIONS OF CYCLOPROPANES

4.1. INTRODUCTION

4.1.1. General

The results of the work on CAN mediated transformations of 1-arylcycloalkenes, and the addition of radicals to alkenes have been described in Chapters 2 and 3 respectively. During the course of this work, we were intrigued by the possibility of such reactions involving cyclopropanes, this in view of the special bonding characteristics of cyclopropanes.

Cyclopropane ring opening reactions, both electrophilic and nucleophilic, have been well studied. These fall outside the scope of our *studies and only those reports on the generation of radical cations from* cyclopropane ring systems are reviewed here. These include photochemical and *electrochemical oxidation and oxidation by metal ions. Prior to the* description of these reactions, the bonding characteristics of cyclopropanes are briefly reviewed.

4.1.2. Bonding in cyclopropanes

The C-C-C bond angle of cyclopropane is 60°, which is at a large distortion from the normal tetrahedral angle of 109° and hence the ring is under strain. The four sp^3-hybridized orbitals in cyclopropane are not equivalent so that the ring strain will be minimum. The two orbitals used for the C-C bond in the ring have more π-character than the normal sp^3 hybrid

orbital and the two orbitals directed outwards have more *s* character. The internal bonds have more *p* character and molecular orbital calculations show that the bond in cyclopropane is not completely σ in character. Since the so called *bent bonds* in cyclopropane are intermediate between σ and π bonds, cyclopropane behaves more like an alkene. Moreover, since the outside bonds have more *s* character, the electron density is away from the ring.[1]

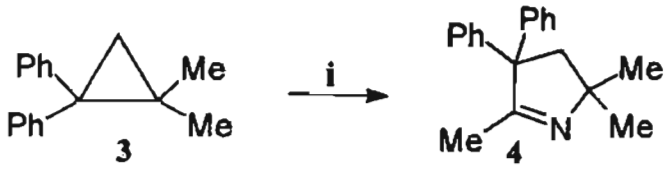
4.1.3. Photochemical ring opening reactions of cyclopropanes

Ring opening reactions of cyclopropanes by photochemical methods have been studied. Phenylcyclopropane under photochemical conditions in acetonitrile-methanol mixture yields 1,3-dimethoxy-1-phenylpropane **2** (Scheme 1).[2]

i. MeOH, MeCN, hν, DCA, $Cu(BF_4)_2$, 84%

Scheme 1

An interesting example involving nucleophilic ring opening is the formation of cyclic imine **4** by the reaction of acetonitrile with the radical cation of **3** generated photochemically (Scheme 2).[3]



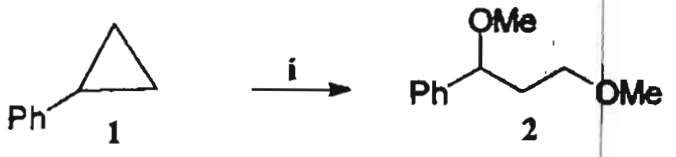
i. 1-Cyanonaphthalene, hν, MeCN, 94%

Scheme 2

4.1.4. Electrochemical reactions of cyclopropanes

The ring opening of cyclopropanes *via* radical cations, under electrochemical conditions have been well studied. Some representative examples are given in the following schemes.

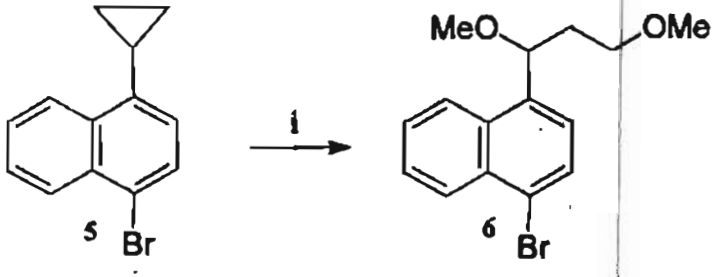
Shono *et al.* have shown that cyclopropane ring can be opened electrochemically in methanol to afford the 1,3-dimethoxy product (Scheme 3).[4]



i. 0.08A/m^2, 1.7 v, -30 - -40 °C, 72%

Scheme 3

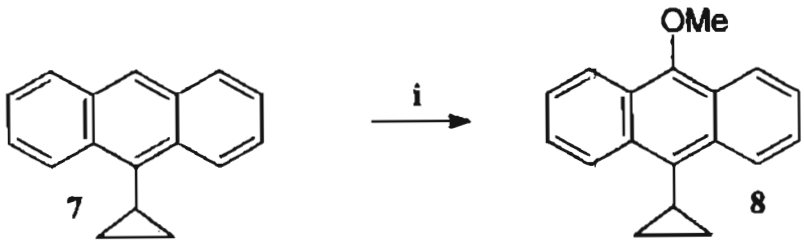
1-Bromo-4-cyclopropylnaphthalene under electrochemical conditions undergoes similar ring opening to afford the 1,3-dimethoxy derivative (Scheme 4).[5]



i. -40 mA, MeOH, $LiClO_4$, 50%

Scheme 4

Electrochemical oxidation of 9-cyclopropylanthracene in methanol has been studied in detail. In this case no ring opening occurs; instead substitution on the aromatic ring is observed (Scheme 5).[6]

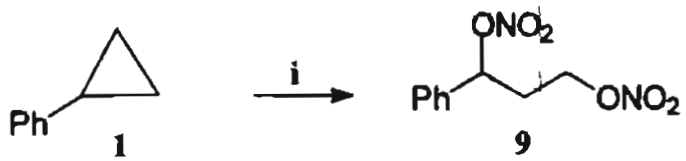


i. CCE, -30 mA, MeOH-MeCN, 37%

Scheme 5

4.1.5. Metal ion mediated oxidation of cyclopropanes

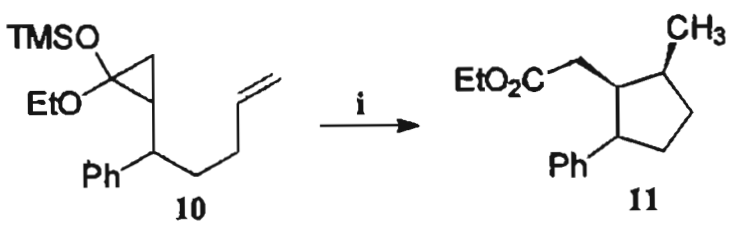
The ring opening reaction of arylcyclopropanes using thallium trinitrate has been reported by Ouellette *et al.* (Scheme 6).[7]



i. $Tl(ONO_3)_3$, pentane

Scheme 6

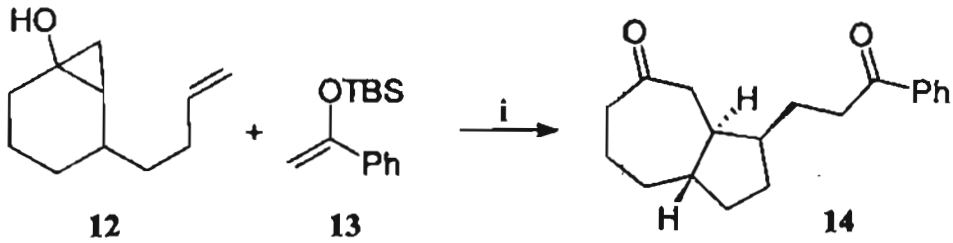
An interesting iron(III) mediated oxidative cyclization of substituted cyclopropane acetal to the cyclopentane derivative has been reported recently (Scheme 7).[8]



i. $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 50 °C, 57%

Scheme 7

Narasaka has reported the ring expansion and concomitant cyclization of bicyclic cyclopropanols with an olefinic side chain in presence of Mn(III) (Scheme 8).[9]



12 13 14

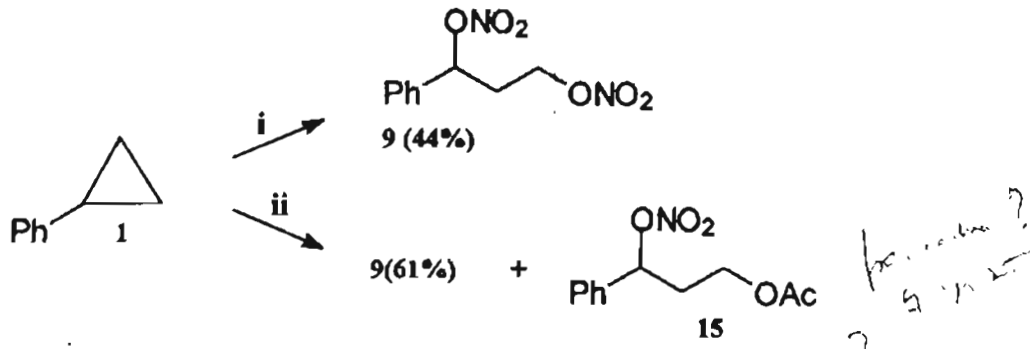
i. $Mn(Pic)_3$, DMF, 0 °C

Scheme 8

4.1.6. Oxidative transformations of arylcyclopropanes with CAN

Although, there are a number of reports on the generation of radical cations from cyclopropanes under a variety of conditions, very little information is available on such reactions involving CAN.

The ring opening reactions of phenyl and diphenylcyclopropane with CAN in acetic acid and acetonitrile have been studied by Young (Scheme 9).[10]

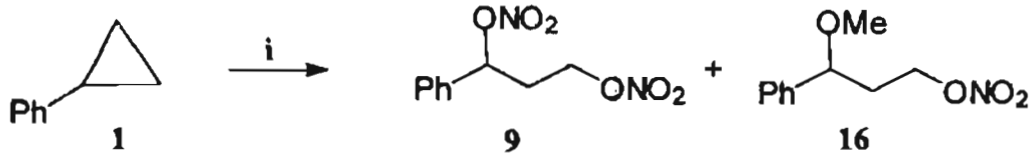


i. CAN, MeCN, rt, 48h

ii. CAN, AcOH, rt, 48h

Scheme 9

A more detailed investigation of various aryl cyclopropanes with CAN has been reported recently (Scheme 10).[11]



1 9 16

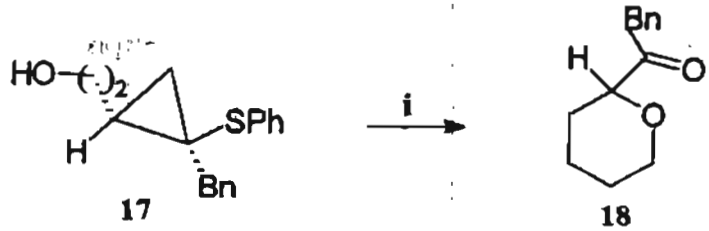
i. CAN, MeOH, MeCN, 80 °C

Scheme 10

4.1.7. Reaction of cyclopropyl sulfides, cyclopropyl amines and cyclopropyl ethers with CAN and other one electron oxidants

Cyclopropyl sulfides are easily oxidized to the radical cations. The latter undergo a variety of interesting transformations depending on the various functionalities present in the molecule.

Cyclopropyl sulfides having a hydroxy group on the side chain undergo CAN mediated tandem ring cleavage and cyclization giving cyclic ethers, *via* the intermediacy of the radical cation (Scheme 11).[12]

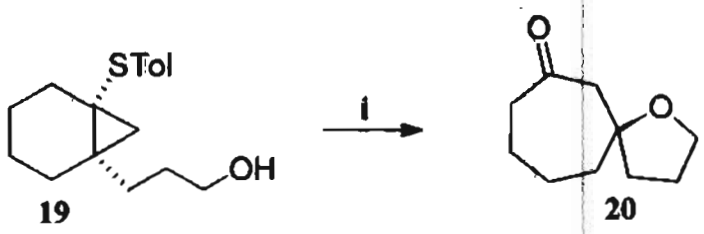


17 18

i. CAN, dry MeOH, K_2CO_3, MS 3A, 0 °C, 73%

Scheme 11

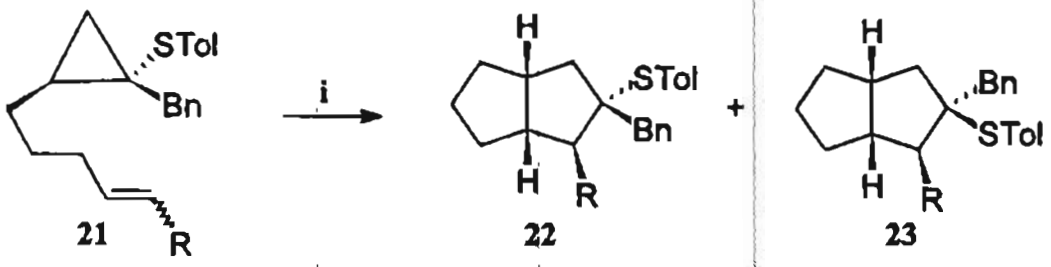
Asymmetric synthesis of oxaspiroundecanone has been achieved by the oxidative ring expansion and cyclization of optically active bicyclo [4.1.0] heptylsulfides having a hydroxy substituent on the side chain. In this case also the reaction occurs through the intermediacy of radical cation (Scheme 12).[13]



i. CAN, K_2CO_3, aq. MeOH, 0 °C

Scheme 12

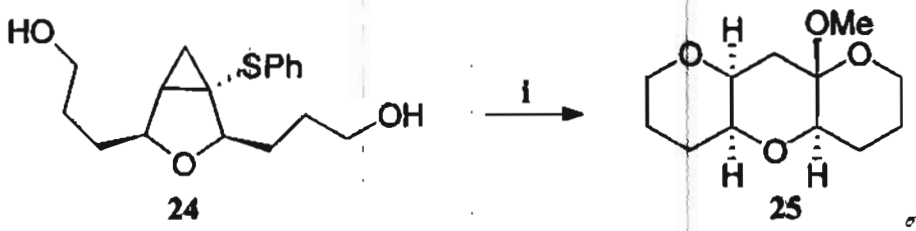
Intramolecular [3+2] cycloaddition of cyclopropyl sulfides with alkenes mediated by CAN has been studied. The reaction appears to be of negligible synthetic value due to the low yield and poor stereoselectivity (Scheme 13).[14]



i. CAN, K_2CO_3, CF_3CO_2H, rt, 8h, 41%

Scheme 13

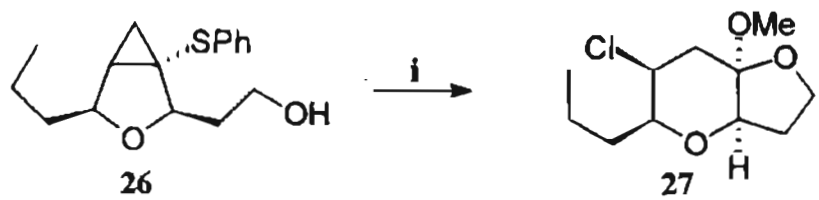
Synthesis of *trans* and *cis* fused tricyclic ethers from 3-oxabicyclo [3.1.0] hexyl systems using CAN has been reported very recently (Scheme 14)[15].



i. CAN, MeOH, MS 3A, rt, 70%

Scheme 14

The same group has reported a method for synthesizing 3β-chlorinated 2,6-disubstituted tetrahydropyrans by CAN mediated oxidation (Scheme 15).[16]

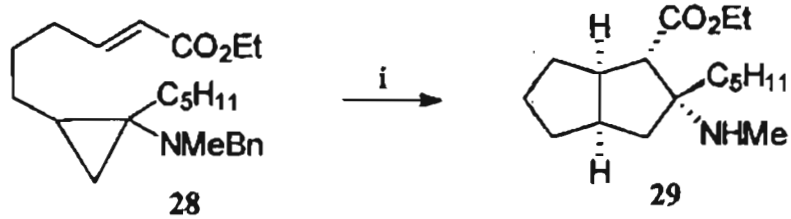


26 27

i. CAN, MeOH, Me_4NCl, MS 3A, rt, 51%

Scheme 15

The ring opening reactions of cyclopropyl amines have received only limited attention. A recent report involves the tandem ring opening-cyclization of cyclopropyl amines using CAN (Scheme 16).[17]



28 29

i. CAN, $NaHCO_3$, DMF, rt, 77%

Scheme 16

4.1.8. The present work

It is evident from the literature survey that radical cations can be generated readily from cyclopropanes. However, not much work has been done in exploring the synthetic potential of cyclopropane radical cations. In the context of our interest in novel synthetic transformations using CAN, we undertook a study aimed at gaining more insight into the chemistry of radical cations derived from cyclopropanes using CAN.

The objectives of the present work are as follows:

(i) To study the ring opening of cyclopropanes with radicals generated using CAN

(ii) To trap the cyclopropane radical cations with alkenes such as cyclohexene and styrene

The results of our preliminary investigations are presented in the following section.

4.2. RESULTS AND DISCUSSION

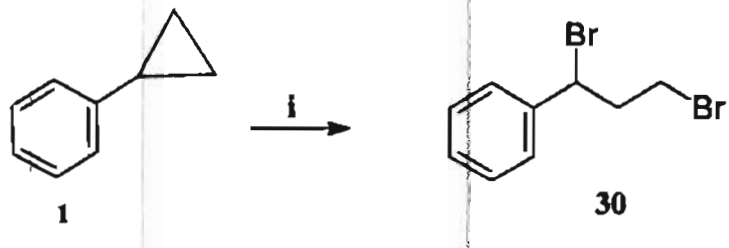
4.2.1. Addition of radicals generated from soft anions

Soft anions have been known to undergo facile oxidation to the corresponding radicals by CAN and the addition of these radicals to alkenes have been studied recently. It has been shown that thiocyanate and azide can be oxidized to the corresponding radicals using CAN and these radicals add to alkenes to give dithiocyanates and phenacyl azides respectively.[18,19] As a part of our general interest in the CAN mediated addition of soft anions to alkenes, and with the perception that, cyclopropanes can be viewed as strained alkenes, it was of interest to examine such reactions with cyclopropanes also.

4.2.1.1. Bromination of cyclopropanes using KBr and CAN

We have observed the facile formation of vicinal dibromides from alkenes using potassium bromide and CAN in a two phase system of water and dichloromethane and this is discussed in **Chapter 3** of this thesis. Literature survey revealed that there are only limited reports on the bromination of cyclopropanes.[20] An investigation of the CAN mediated bromination of cyclopropanes was undertaken and our preliminary results are presented in the following passage.

In a typical experiment, phenylcyclopropane was treated with KBr and CAN in a two phase system of water and dichloromethane to afford the ring opened 1,3-dibromide **30** in 81% yield (Scheme 17).



1 **30**

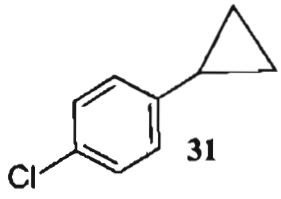
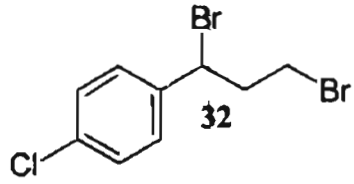
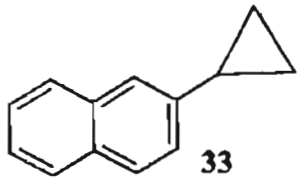
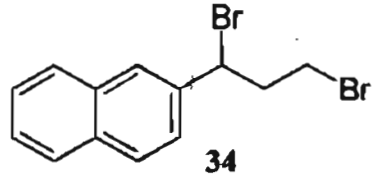
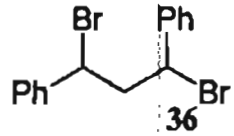
i. CAN, KBr, H_2O, CH_2Cl_2, rt, 81%

Scheme 17

The structure of **30** was assigned on the basis of ^1H and ^{13}C NMR spectra. The aromatic protons resonated as a multiplet centered at δ 7.3. The benzylic proton appeared as a multiplet, centered at δ 5.1. The two other protons geminal to the bromine atom were seen as two multiplets centered at δ 3.5 and 3.3. In the ^{13}C NMR spectrum of the product, the bromine-bearing benzylic carbon atom displayed a signal at δ 52.2 and the terminal carbon was discernible at δ 42.1. All the other signals were also in agreement with the proposed structure.

The bromination using potassium bromide and CAN in water-dichloromethane system was carried out with other cyclopropanes also. In all cases the cyclopropanes were converted to the corresponding open-chain 1,3-dibromides in very good yields. The results are presented in the following table (Table 1). In all cases, the products were characterized by spectral analysis.

Table 1: Bromination of Cyclopropanes

Entry	Cyclopropane	1,3-Dibromide	Yield (%)
1	 31	 32	76
2	 33	 34	72
3	 35	 36	80

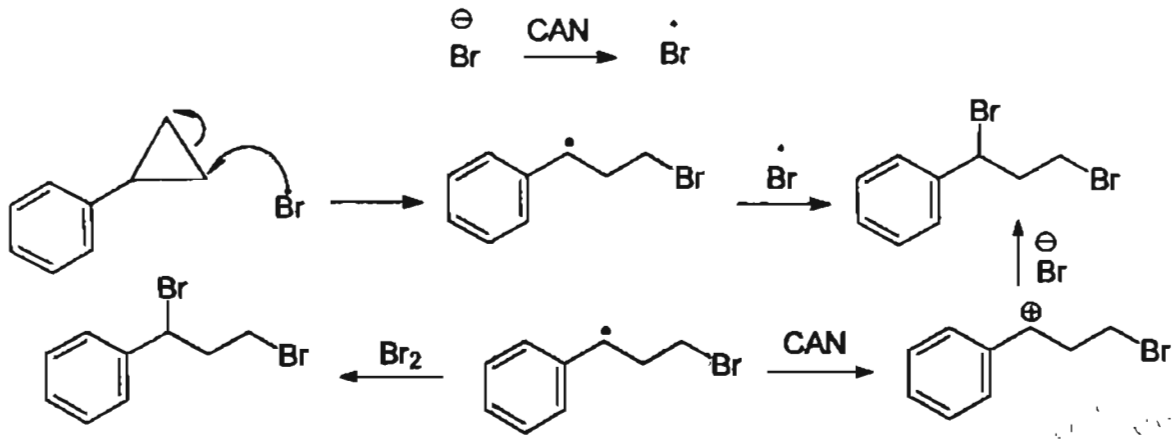
Reaction conditions: CAN, KBr, CH_2Cl_2, H_2O, rt., 30-45 min

It may be noted that the reaction of (4-methoxy)-phenylcyclopropane and 1-phenyl-2-methoxy cyclopropane under the same reaction conditions led to a complex mixture of products.

4.2.1.2. Mechanistic rationalization

A mechanistic rationale for the formation of the 1,3-dibromides may be provided by invoking the initial oxidation of the bromide to the bromine radical and its addition to cyclopropane leading to the benzylic radical. The latter can react with another bromine radical to afford the product. Alternatively, the benzylic radical can be oxidized further to give the cation and that in turn can react with bromide ion to give the dibromide. The involvement of molecular bromine formed by the combination of bromine radicals can also be invoked. Quenching of the benzylic radical with molecular bromine to afford the dibromide and a second bromine radical can

also account for the formation of the dibromide. A schematic representation is as shown below (Scheme 18).

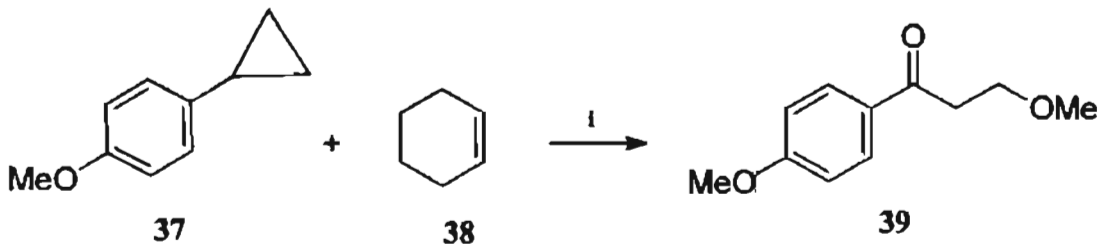


Scheme 18

4.2.2. Attempted reaction of cyclopropane with alkenes

The ring opening reaction of cyclopropane *via* radical cations is well known. However, intermolecular or intramolecular trapping of these radical cations has not been studied so far, although trapping of such species derived from cyclopropyl sulfides and cyclopropylamines has been reported. If the radical cation adds to an alkene, it can produce a distonic species, and this can undergo a number of interesting reactions. In view of this, we attempted the CAN mediated addition of alkenes such as cyclohexene and styrene to (4-methoxy)phenylcyclopropane.

Our experiments started with the reaction of (4-methoxy) phenylcyclopropane **37** and cyclohexene **38**. When the latter was treated with **37** in presence of CAN in methanol, the only product obtained was the ketone **39**. No addition product was isolated (Scheme 19).



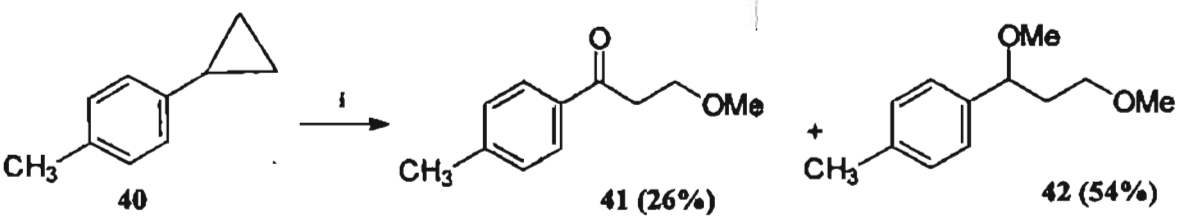
37 38 39

i. CAN, MeOH, 0° C, 39%

Scheme 19

The IR spectrum of the product shows absorption at 1675 cm^{-1} corresponding to the benzoyl carbonyl. In the ^1H NMR spectrum, the aromatic protons were seen as two doublets at δ 7.9 and 6.9 (J = 8.8 Hz). The protons of the two methoxy groups were seen as two singlets at δ 3.8 and 3.3. The four methylene protons resonated as two triplets centered at δ 3.79 and 3.1 (J = 6.5 Hz). In the ^{13}C NMR spectrum, the carbonyl carbon was discernible at δ 196.5. It has been reported that phenyl and naphthyl cyclopropanes with CAN in methanol under reflux conditions afford the corresponding 1,3-dimethylether.[11] The formation of the keto methylether under these conditions is hitherto unknown. Hence we studied the reaction in some detail.

A solution of *p*-tolylcyclopropane when treated with a solution of CAN in methanol at ice temperature afforded the products **41** and **42** in 26% and 54% yields respectively (Scheme 20).



40 41 (26%) 42 (54%)

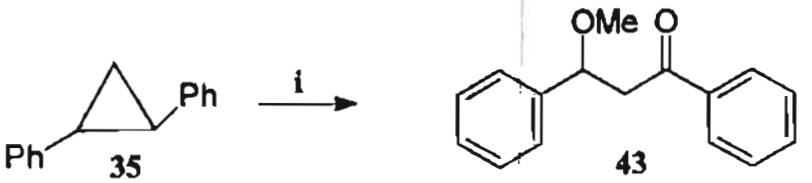
i. CAN, MeOH, 0 ° C

Scheme 20

The products were characterized on the basis of IR, ^{1}H and ^{13}C NMR spectral analysis. The IR spectrum of the product **41** gave absorption at 1682 cm^{-1}, corresponding to the benzoyl carbonyl. In the ^{1}H NMR spectrum, the aromatic protons resonated as two doublets at δ 7.8 and 7.2 (J = 8 Hz). The signal due to the methoxy protons appeared as singlet at δ 3.3. The protons of the methyl group resonated as a singlet at δ 2.41. In the ^{13}C NMR spectrum, the carbonyl carbon gave signal at δ 197.6. All the other signals were in complete agreement with the assigned structure.

In the ^{1}H NMR spectrum of **42**, the aromatic protons resonated as a multiplet centered at δ 7.16. The benzylic proton resonated as a triplet at δ 4.21 (J = 5.4 Hz). The two methoxy groups displayed singlets at δ 3.3 and 3.46. The ^{13}C NMR spectrum of the product displayed signals at δ 80.4 and δ 69.1 corresponding to the benzylic and the terminal carbon respectively.

Interestingly, when 1,2-diphenyl cyclopropane was treated with a solution of CAN in methanol, the only product formed was the keto methylether in 65% yield. No dimethoxy product was detected in this case (Scheme 21).



35 43

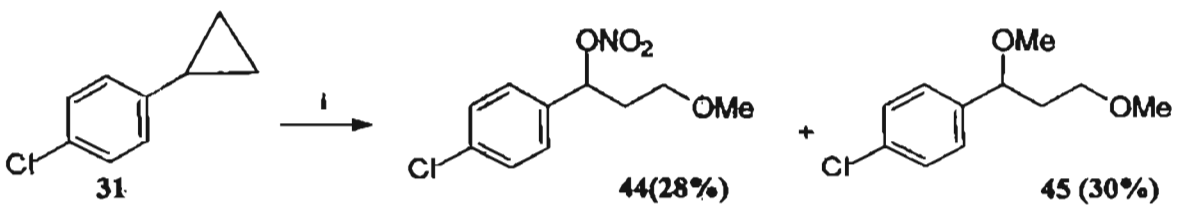
i. CAN, MeOH, 0 °C, 65 %

Scheme 21

In this case also, the product was characterized on the basis of spectral data. In the IR spectrum of **43**, absorption corresponding the benzoyl carbonyl was seen at 1686 cm^{-1}. In the ^{1}H NMR spectrum, the aromatic protons resonated as a multiplet at δ 7.6. The methoxy protons were

discernible at δ 3.2 as a singlet. In the ^{13}C NMR spectrum of the product, the carbonyl carbon displayed a signal at δ 197.3.

When (4-chloro)phenyl)cyclopropane was treated with CAN under the usual reaction conditions, the products **44** and **45** were isolated in 28% and 30% yields respectively (Scheme 22).



31 **44(28%)** **45 (30%)**

i. **CAN, MeOH, 0 °C**

Scheme 22

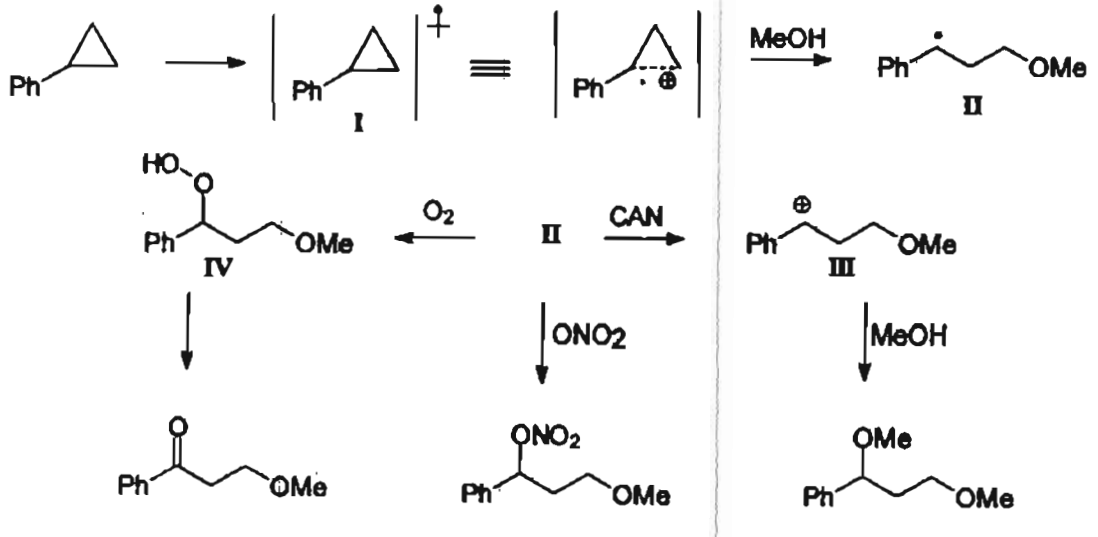
The products were characterized as usual by spectral analysis. In the IR spectrum of **44**, absorption at 1632 cm^{-1} indicated the presence of a benzylic nitrato group. In the ^1H NMR spectrum of the product, the benzylic proton displayed a triplet at δ 5.9 (J = 7.7 Hz). The signal due to the methoxy protons appeared as a singlet at δ 3.3. In the ^{13}C NMR spectrum of **44**, the benzylic carbon was seen at δ 81.52 The methoxy carbon displayed signal at δ 58.79 and the carbon bearing the methoxy group was visible at δ 67.65.

The structure of **45** was also confirmed by spectral analysis.

4.2.3. Mechanistic rationalization

Although the mechanistic details of the reaction remain unclear, a reaction pathway involving the radical cation from phenylcyclopropane may be invoked. Presumably, CAN oxidizes the cyclopropane to the radical cation **I**. The cationic center can be quenched by solvent methanol giving the benzylic radical **II**. The latter can be quenched by molecular oxygen leading to a peroxy radical, which is then transformed to the hydroperoxide **IV**. The hydroperoxide can undergo further transformations ultimately leading to the

keto product. Alternatively, the benzylic radical can be converted to a nitrate by ligand transfer. The benzylic radical on further oxidation to the cation and quenching by methanol affords the dimethyl ether (Scheme 23).
(For similar discussion, see Chapter 3)



Scheme 23

4.2.4. Conclusion

In conclusion, the preliminary results presented above suggests that the chemistry of cyclopropane radical cation, generated using one electron oxidants such as CAN, is worthy of further exploration. It is quite likely that much interesting chemistry will emerge from such studies.

4.3. EXPERIMENTAL

For general information, see section **2.3.** of **Chapter 2.**

Preparation of cyclopropanes

The cyclopropanes used in our studies were prepared by reported procedure[21] from the corresponding alkene.

A solution of the alkene (3 mmol) and diazomethane (prepared from 2 g of N-methyl-N-nitrosourea) in ether (20 mL) is treated with catalytic amount (10 mg) of palladium(II) acetate at ice temperature. The solvent is

removed on a rotary evaporator and the product purified on a silica column using hexane as the eluent.

Bromination of cyclopropanes using potassium bromide and CAN

To a solution of the cyclopropane (1 mmol) in dichloromethane (10 mL) was added KBr (2.2 mmol) and a solution of CAN (2.3 mmol) in water (10 mL) at room temperature and stirred. After 30 minutes, when the reaction was complete as determined by TLC., the dichloromethane layer was separated, washed with brine and the solvent was removed using a rotary evaporator. The residue, on purification by column chromatography using hexane/hexane-ethyl acetate mixture as the eluent afforded the dibromide.

1,3-Dibromo-1-phenylpropane (30)

Phenyl cyclopropane **1** (118 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane for about 30 minutes afforded 234 mg (81%) of the dibromide (**30**) as colorless viscous liquid.

IR (neat) ν_{max} : 2967, 1949, 1876, 1480, 1493, 1249, 1213 cm^{-1}.

^1H NMR : 7.48-7.03 (m, 5H, ArH), 5.19-5.14 (m, 1H, CHBr), 3.56-3.49 (m, 1H, CHBr), 3.43-3.36 (m, 1H, CH_2), 2.79-2.72 (m, 1H, CH_2), 2.57-2.49 (m, 1H, CH_2).

^{13}C NMR : 129.05, 128.78, 128.60, 128.16, 127.29, 52.24, 42.15, 30.73.

EIMS(m/z%) : 278(M^+) (2), 197 (50), 117 (60), 91 (10), 63 (10), 51 (15).

1,3-Dibromo-1-(4-chloro)-phenylpropane (32)

4-Chlorophenyl cyclopropane **31** (76 mg, 0.5 mmol) on treatment with potassium bromide (126 mg, 1.1 mmol) and CAN (630 mg, 1.15 mmol) in a two phase system of water and dichloromethane for about 30 minutes afforded 116 mg (76%) of the dibromide (**32**) as viscous liquid.

IR (neat) ν_{max} : 2978, 1489, 1414, 1220, 1089, 1176, 821 cm^{-1}.

^1H NMR : 7.35-7.31(m, 4H, ArH), 5.12 (dd, 1H, ArCHBr, J = 5.8 Hz, 10.5 Hz), 3.53-3.47 (m, 1H, CH_2Br), 3.41-3.35 (m, 1H, CH_2Br), 2.72-2.68 (m, 1H, CH_2), 2.52-2.47(m, 1H, CH_2).

^{13}C NMR : 139.30, 134.49, 129.08, 128.76, 51.14, 42.09, 30.61.

1,3-Dibromo-1-naphthylpropane (34)

Naphthylcyclopropane **33** (168 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane for 30 minutes afforded 235 mg (72%) of the dibromide (**34**) as yellow amorphous solid.

IR (KBr) ν_{max} : 2932, 1595, 1551, 1495, 1426, 1326, 1264, 964 cm^{-1}.

^1H NMR : 8.31-7.50 (m, 7H, ArH), 6.05-6.00 (m, 1H, ArCHBr), 3.56-3.50 (m, 2H, CH_2Br), 2.86-2.64 (m, 1H, CH_2), 2.76-2.57 (m, 1H, CH_2).

^{13}C NMR : 137.37, 134.22, 128.69, 128.15, 128.02, 127.84, 127.35, 126.91, 125.29, 124.07, 123.37, 57.08, 41.84, 29.99.

1,3-Dibromo-1,3-diphenylpropane (36)

Diphenylcyclopropane **35** (195 mg, 1 mmol) on treatment with potassium bromide (250 mg, 2.1 mmol) and CAN (1.26 g, 2.3 mmol) in a two phase system of water and dichloromethane afforded 290 mg (80%) of the dibromide (**36**) as a colorless low melting solid.

IR (neat) ν_{max} : 2989, 1949, 1693, 1590, 1493, 1450, 1176, 1073, 1018, 909, 751, 690 cm^{-1}.

^1H NMR : 7.34-7.14 (m, 10H, ArH), 5.16 (t, 1H, CHBr, J = 7.1 Hz), 4.84 (t, 1H, CHBr, J = 7.5 Hz), 3.24-2.83 (m, 2H, CH_2).

^{13}C NMR : 141.05, 140.47, 128.95, 128.77, 127.52, 127.48, 52.86, 51.70, 49.50.

EIMS: : 275(M^+-79)(8), 193(100), 171(80), 115(20), 91(10), 80(8).

Reaction of cyclopropane with CAN in methanol

A solution of the cyclopropane (1 mmol) and alkene (1 mmol) in methanol (10 mL) at ice temperature was treated with a solution of CAN (2.3 mmol) in methanol (15 mL) at ice temperature with stirring. After completion of the reaction (2-4 h), as determined by TLC., the reaction mixture was diluted with water and extracted with dichloromethane (3X15 mL) The organic extracts were pooled, washed with brine and dried over sodium sulfate. After removing the solvent in vacuo, the residue was purified by chromatography on a silica gel column with hexane-ethyl acetate mixture as the eluent.

3-Methoxy-1-(4'-methoxy)-phenylpropan-1-one (39)

To a solution of 4-methoxyphenylcyclopropane **37** (148 mg, 1 mmol) in methanol was added a solution of CAN (1.26 g, 2.3 mmol) in methanol at ice temperature with stirring. After completion of the reaction, (2 h), as determined by TLC., the reaction mixture was processed as described in the general procedure. Purification of the product by chromatography on a silica gel column using hexane-ethyl acetate mixture (98:2) as eluent afforded 72 mg (39%) of the ketone **38.**

IR (neat) ν_{max} : 2934, 1675, 1595, 1505, 1304, 1255, 1170, 1109 cm^{-1}.

^{1}H NMR : 7.93 (d, 2H, ArH, J = 8.8 Hz), 6.92 (d, 2H, ArH, J = 8.8 Hz), 3.86 (s, 3H, OMe), 3.79 (t, 2H, CH_2, J = 6.5 Hz), 3.37 (s, 3H, OMe), 3.18 (t, 2H, CH_2, J = 6.5 Hz).

^{13}C NMR : 196.52, 163.53, 130.44, 130.32, 130.25, 127.80, 113.85, 68.15, 58.91, 55. 37, 38.35.

3-Methoxy-1-(4-methyl)-phenyl propan-1-one (41) and 1,3-Dimethoxy-1-(4-methyl)-phenyl propane (42)

To a solution of 4-methylphenyl cyclopropane **40** (132 mg, 1 mmol) in methanol was added a solution of CAN (1.26 g, 2.3 mmol) in methanol at ice temperature with stirring. After completion of the reaction (2h), the reaction mixture was processed as described in the general procedure. Purification of the product by chromatography on a silica gel column using hexane-ethyl acetate mixture (98:2) as the eluent, afforded 46 mg (26%) of the ketone **41** and on further elution afforded 111 mg (54%) of the dimethyl ether **42**.

3-Methoxy-1-(4-methyl)-phenyl propan-1-one (41)

IR (neat) ν_{max} : 1682, 1607, 1445, 1382, 1270, 1114, 983 cm $^{-1}$.

^{1}H NMR : 7.85 (d, 2H, ArH, J = 8.0 Hz), 7.24 (d, 2H, ArH, J = 8.0 Hz), 3.79 (t, 2H, CH_2OMe, J = 6.5 Hz), 3.36 (s, 3H, OMe), 3.20 (t, 2H, CH_2, J = 6.5 Hz), 2.41 (s, 3H, CH_3).

^{13}C NMR : 197.61, 143.76, 134.69, 129.27, 128.31, 68.06, 58.89, 38.59, 21.17.

1,3-Dimethoxy-1-(4-methyl)-phenyl propane (42)

IR (neat) ν_{max} : 2896, 1634, 1279, 1190, 829, 728 cm^{-1}.

^{1}H NMR : 7.22-7.11 (m, 4H, ArH), 4.21 (t, 1H, ArCHOMe, J = 5.4 Hz), 3.46 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.26-3.23 (m, 1H, CH_2OMe), 2.34 (s, 3H, CH_3), 2.09-1.98 (m,2H,CH_2), 1.83-1.75 (m, 1H, CH_2).

^{13}C NMR : 138.98, 136.99, 129.43, 126.38, 80.46, 69.19, 58.48, 56.42, 38.17, 21.11.

3-Methoxy-1,3-diphenylpropan-1-one (43)

To a solution of 1,2-diphenylcyclopropane **35** (195 mg, 1 mmol) in methanol was added a solution of CAN (1.26 g, 2.3 mmol) in methanol at ice temperature with stirring. After completion of the reaction, (4h), as determined by the TLC., the reaction mixture was processed as described in the general procedure. Purification of the product by chromatography on a silica gel column using hexane-ethyl acetate mixture (95:5) as the eluent afforded 156 mg (65%) of the ketone **43** as colorless viscous liquid.

IR (neat) ν_{max} : 2983, 1686, 1449, 1102, 749, 702 cm $^{-1}$.

^{1}H NMR : 7.93-7.26 (m, 10H, ArH), 4.86 (dd, 1H, CHArOMe, J = 8.3 Hz, 4.3 Hz), 3.85 (t, 1H, CH_2, J = 8.4 Hz), 3.22 (s, 3H, OMe), 3.02 (dd, 1H, CH_2, J = 4.2 Hz, 16.4 Hz).

^{13}C NMR : 197.32, 141.50, 137.25, 132.94, 128.54, 128.46, 128.22, 126.59, 79.57, 56.82, 47.15, 42.98.

3-Methoxy-1-nitrato-1-(4-chloro)-phenylpropane (44) and 1,3-Dimethoxy-1-(4-chloro)-phenylpropane (45)

To a solution of 4-chlorophenyl cyclopropane **31** (74 mg, 0.5 mmol) in methanol was added a solution of CAN (630 mg, 1.15 mmol) in methanol at ice temperature and stirred for about 2 hours. Purification of the product by chromatography on a silica gel column using hexane-ethyl acetate mixture (98:5) as the eluent afforded 29 mg (28%) of **44** along with 36 mg (30%) of the dimethyl ether **45**.

3-Methoxy-1-nitrato-1-(4-chloro)-phenylpropane (44)

IR (neat) ν_{max} : 2896, 1632, 1495, 1276, 1089, 1008, 858 cm $^{-1}$.

^{1}H NMR : 7.38-7.26 (m, 4H, ArH), 5.93 (t, 1H, $ArCHONO_2$, J = 7.7 Hz), 3.48-3.44 (m, 1H, CHOMe), 3.31 (s, 3H, OMe), 3.27-3.21 (m, 1H, CH_2), 2.00-1.89 (m, 1H, CH_2).

^{13}C NMR : 136.40, 129.13, 127.95, 127.76, 81.52, 67.65, 58.79, 34.61.

1,3-Dimethoxy-1-(4-chloro)-phenylpropane (45)

IR (neat) ν_{max} : 2946, 1588, 1482, 1276, 1115, 1002, 821 cm $^{-1}$.

^{1}H NMR : 7.49-7.20 (m, 4H, ArH,), 4.25 (t, 1H, CHOMe, J = 5.8 Hz), 3.79-3.43 (m, 1H, CHOMe), 3.31 (s, 3H, OMe), 3.19-3.21 (m, 1H, CHOMe), 2.02-2.00 (m, 1H, CH_2), 1.98-1.55 (m, 1H, CH_2).

^{13}C NMR : 140.67, 133.33, 129.62, 128.96, 128.68, 128.01, 80.03, 68.94, 58.54, 56.74, 38.69.

4.4. REFERENCES

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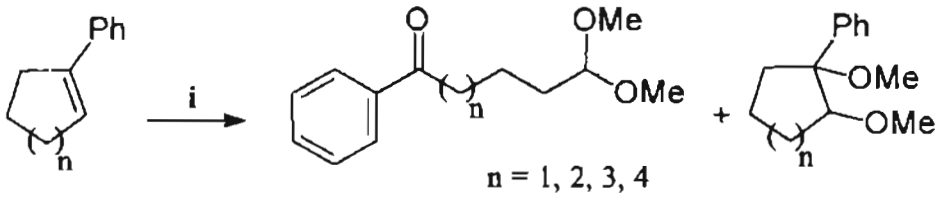
SUMMARY

The present thesis entitled **"Novel Synthetic Transformations Involving Electron Transfer Mediated by Cerium(IV) Ammonium Nitrate (CAN)"** embodies the results of a series of investigations involving CAN mediated transformations of potential application in organic synthesis.

The thesis is divided into four chapters, and the contents are summarized in the following passages

Chapter 1 presents a general introduction to radical reactions, electron transfer reactions, radical cations etc. followed by a review of CAN mediated transformations. A very brief account of catalytic use of CAN and some representative examples of oxidative transformations using other Ce(IV) reagents are also presented.

Chapter 2 comprises the results of CAN mediated reactions of phenylcycloalkenes. 1-phenyl-1-cycloalkenes undergo facile fragmentation to give the monoacetals of 1,n-dicarbonyl compounds along with the dimethyl ether (Scheme1).



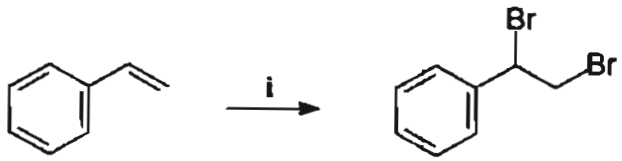
i CAN, MeOH, 0 °C-rt, 48-69%

Scheme 1

The role of oxygen in the above reaction leading to the formation of the fragmentation product was confirmed by its absence under deoxygenated conditions. Under these conditions, the dimethylether is formed exclusively.

Chapter 3 deals with the detailed study on the bromination of alkenes using bromide ions and CAN under a variety of conditions.

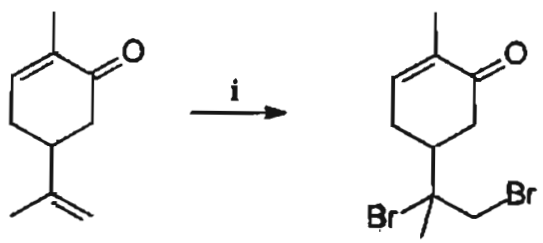
A facile conversion of alkenes to the corresponding dibromides was achieved by treating the alkene with KBr and CAN in a two phase system of water and dichloromethane (Scheme 2).



i. CAN, KBr, H_2O, CH_2Cl_2, rt, 90%

Scheme 2

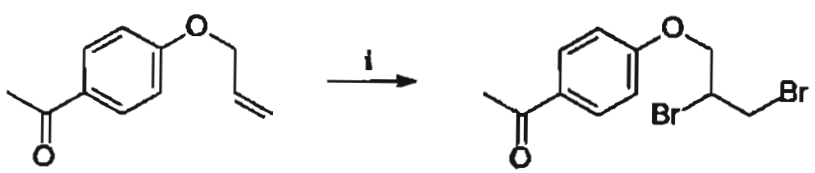
The reaction is very general and applicable to a variety of alkenes including arylalkenes, cycloalkenes, α,β-unsaturated ketones, esters etc. With systems such as carvone, chemoselective bromination occurs (Scheme 3).



i. CAN, KBr, H_2O, CH_2Cl_2, rt, 90%

Scheme 3

Chemoselectivity was observed in other systems also (Scheme 4).

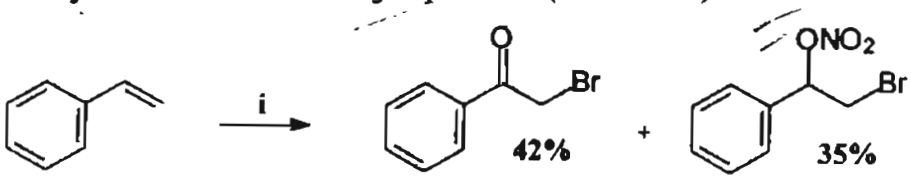


i. CAN, KBr, H_2O, CH_2Cl_2, rt, 90%

Scheme 4

In order to study the effect of solvents in these reactions, the reactions have been carried out in various solvents such as methanol, acetonitrile, acetic acid-acetonitrile mixture and *tert*-butanol.

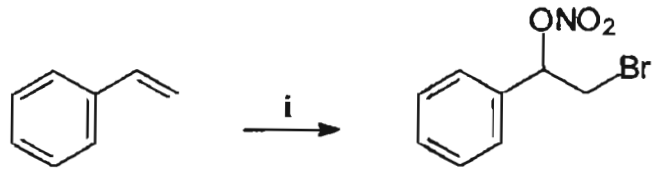
With aqueous methanol and aqueous acetonitrile as solvent, styrene gave phenacyl bromide as the major product (Scheme 5).



i. CAN, KBr, aq.MeOH, rt

Scheme 5

The reaction under deoxygenated conditions afforded the nitratobromide as the only product (Scheme 6).



i. CAN, LiBr, rt, MeCN, Argon, 79%

Scheme 6

A facile conversion of cinnamic acids to β-bromostyrenes was achieved in a one-pot reaction as shown in Scheme 7.

i. CAN, KBr, H_2O, CH_2Cl_2, rt ii. Et_3N, DMF, rt, 6h

Scheme 7

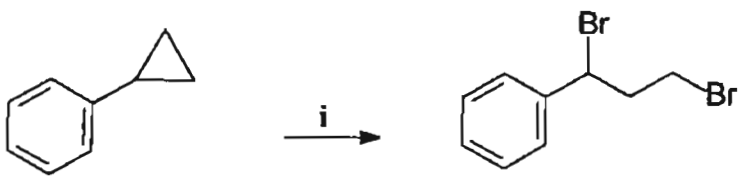
Cinnamic esters were converted to α-bromo cinnamates by bromination-dehydrobromination in a one-pot procedure. In the first step bromination was accomplished by using KBr and CAN in a two phase system of water and dichloromethane. The crude product on treatment with K_2CO_3 in acetone affords the α-bromo cinnamates (Scheme 8).

i CAN, KBr, H_2O, CH_2Cl_2, rt ii. K_2CO_3, acetone, reflux

Scheme 8

The results of some preliminary studies on radical cations of cyclopropanes are presented in **Chapter 4**.

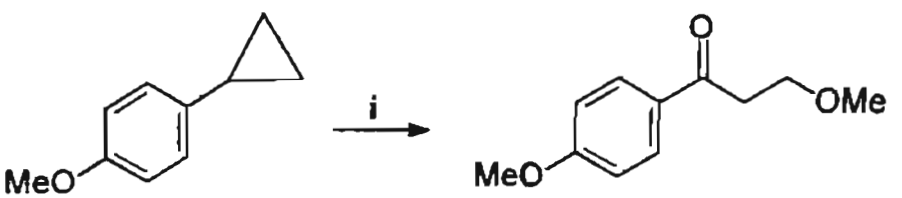
Bromine radical generated by using potassium bromide and CAN adds to cyclopropane affording the ring opened 1,3-dibromide in very good yields A typical example is as shown in the following scheme (Scheme 9).



i. CAN, KBr, H_2O, CH_2Cl_2, rt, 81%

Scheme 9

4-Methoxyphenyl cyclopropane on reaction with CAN in methanol afforded the keto methoxy product (Scheme 10).



i. CAN, MeOH, 0 °C, 2h, 58%

Scheme 10

The reaction has been studied with a number of cyclopropanes.

In conclusion, we have uncovered some novel synthetic transformations using CAN, especially the C=C bond fragmentation and bromination of alkenes and alkynes. Some insight into the CAN mediated reactions of cyclopropanes was also obtained.

List of Publications

1 Nair, V.; Mathew, J.; Kanakamma, P. P.; **Panicker, S. B.**; Zeena, S.; Sheeba, V.; Eigendorf, G. K. "Novel Cerium(IV) Ammonium Nitrate Induced Dimerisation of Methoxy Styrenes." *Tetrahedron Lett.* **1997**, *38*, 2191.

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Posters presented at various symposia

1 "Chemical Electron Transfer Induced Reactions 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.

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