Some Aspects of the Chemistry of Sulfur and Halogenated Organic Compounds

A thesis submitted to the

Indian Institute of Technology Guwahati

as Partial Fulfillment for the Degree of

DOCTOR OF PHILISOPHY in Chemistry

Submitted by

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October 2007

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October 2007

Dedicated to

My Parents,
brother and sisters

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the supervision of Dr. Anil K. Saikia.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

October, 2007
IIT Guwahati

Bachu Rama Raju

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CERTIFICATE

It is certified that the work described in this thesis entitled "Some Aspects of the Chemistry of Sulfur and Halogenated Organic Compounds" by Mr. Bachu Rama Raju for the award of degree of Doctor of Philosophy is an authentic record of the results obtained from the research work carried out under my supervision in the Department of Chemistry, Indian Institute of Technology Guwahati, India and this work has not been submitted elsewhere for a degree.

October, 2007
IIT Guwahati

Dr. Anil K. Saikia
Supervisor

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE OF COURSE WORK

This is to certify that Bachu Rama Raju has satisfactorily completed all the courses required for the Ph.D. degree program. These courses include

CH 603	Supramolecules: Concepts and Applications
CH 611	Bioinorganic Chemistry
CH 627	New Reagents in Organic Chemistry
CH 630	A molecular Approach to physical Chemistry

Bachu Rama Raju has successfully completed his Ph.D. qualifying examination in April 2004.

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Ph.D. GRADE CARD

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Course	Course Name	Credit	Grade
CH 603	Supra Molecules: Concept and Applications	6	BC
CH 627	New Reagents in Organic Synthesis	6	BC
CH 630	A Molecular Approach to Physical Chemistry	6	BC
CH 632	Group Theory	6	BC

Semester Performance Index: (S. P. I): 7.00

Cumulative Performance Index: (C. P. I): 7.00

October, 2007

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(Academic)

Acknowledgements

I express my profound gratitude and indebtness to my research supervisor Dr. Anil K. Saikia who initiated me to the science. His suggestions, criticisms and constant encouragement helped me immensely to achieve this target. His true scientific spirit has helped me a lot during my research work. My everlasting gratitude goes towards him.

I express my sincere thanks to Prof. J. B. Baruah, Prof. A. T. Khan and Dr. P. K. Iyer for their earnest suggestions and corrections for nourishment of the work. My honest regard to faculty of the Department of Chemistry for their motivation and encouragement. I acknowledge the Indian Institute of Technology Guwahati for supporting me with the fellowship and the Department of Chemistry for offering me the state of art facilities. I also thank Central Instrument Facility, IIT Guwahati for providing the NMR facility.

I am thankful to my lab mates Bosco, Pramod, Chandra mouli, Nilu, Anirban, Marjit, Rupam and Abhilasha for the cheerful atmosphere in lab and help in every aspect through out the research work.

I thank my all time friends Shashi, Subendhu, Shankar, Santosh, Babu, Vishnu, Prasad, Vijay, Ravi and Anji for their support and unreserved help during my stay at IIT Guwahati. I thank my friends Siva, Sahid, Panda, Ballav, Sonit, Prasant, Gunin, Chandanda, Kula, Babulal, Suribabu, Avishek, parikshit, Jagannath and all other juniors.

I am grateful to Dr. Monali Dutta Saikia for her help and moral support during my stay at IIT Guwahati.

Words are not enough to express my gratitude to my parents for encouraging and inspiring me to have a successful academic career. The values I imbibed from them stood me in good stead under challenging circumstances. I thank my family members Ramdash, Rajeswari, Sitaratnam, Simhadri, Kamaraju and Subhadra for their affection and deep concern for career.

Finally, thanks are due to DST for providing the X-ray facility under the FIST programme.

Abbreviations

Ac	acetyl
Acac	acetylacetonate
AIBN	azobisisobutylonitrile
Anhy	anhydrous
Ar	aryl
Br	broad
iBu	isobutyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzyl
^{0}C	degree Celsius
Calcd	calculated
CAN	cerium(IV) ammonium nitrate
Cbz	carbobenzyloxy
CTAB	cetyl trimethyl ammonium bromide
CTMATB	cetyl trimethylammonium tribromide
δ	chemical shifts
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undecene-7
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ee	enantiomeric excess
EIMS	electron spray ionization mass spectroscopy
Et	ethyl
FID	flame ionization detection
FT	fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
Hz	hertz
IR	infrared
LDA	lithium di-isoprpylamide
L	liter(s)
µL	microliter(s)
m	multiplet (spectral)
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	megahertz
mol	mole(s)
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMPO	*N*-methylpyrolidineoxide
Ph	phenyl
ppm	parts permillion
PTSA	p-toulenesulfonic acid
Py	pyridine
q	quartet (spectral)
Red-Al	sodium bis(2-methoxyethoxy) aluminium hydride
rt	room temperature
s	singlet (spectral)
TEMPO	tetramethylpiperidine *N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
t	triplet (spectral)
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsily chloride
Ts	tosyl (*p*-toluenesulfonyl)
UV	ultraviolet

Contents

PART I

Organosulfur Compounds

CHAPTER I

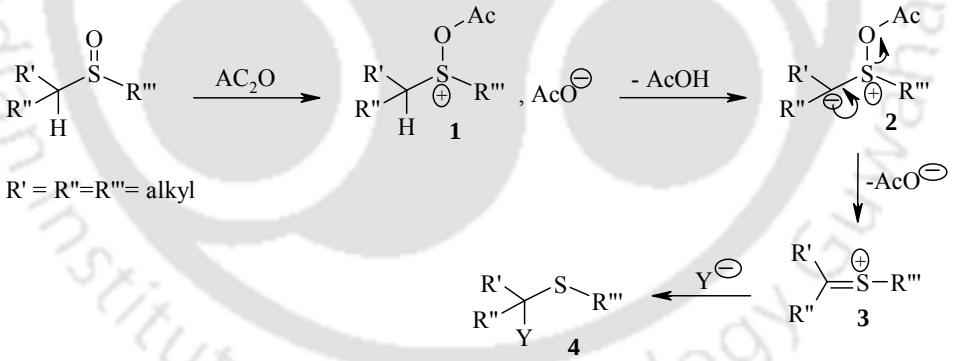
Introduction

1.1 Introduction

Organosulfur compounds play an important role in organic synthesis. The desire to prepare these compounds and their analogs has lead to many impressive advances in synthetic technology. These compounds are useful as synthons for molecular rearrangements and functional group transformations. Many of the natural products of biological interest contain the carbon-sulphur framework. Within the realm of synthetic environment, organic sulfur compounds represent an important family of intermediates widely employed in the synthesis of agrochemicals, cosmetics, drugs, food industries and chiral auxiliaries.

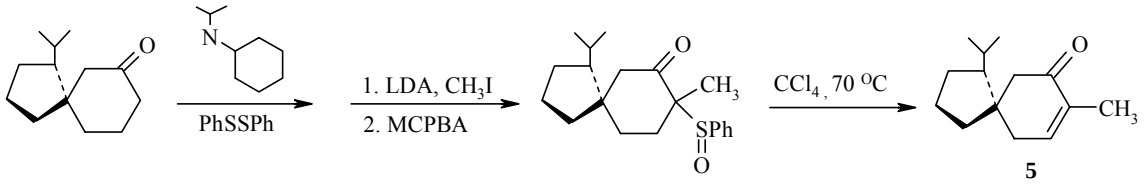
1.2 Applications of Organosulphur compounds: Sulfoxides, Sulfones and Sulfides

Sulfoxides are versatile intermediates for carbon-carbon bond forming reactions. One of the well-known reactions is Pummerer reaction which involves the formation of an α-functionalized sulfide from a sulfoxide.[1] Acetic anhydride is commonly used as the electrophile, which adds to the sulfoxide forming a sulfonium salt **1**. The rearrangement occurs through successive formation of an ylide **2** and an alkylidine sulfonium **3**, further trapped by a nucleophile to afford the α-alkylated sulfide **4** (Scheme 1.1).



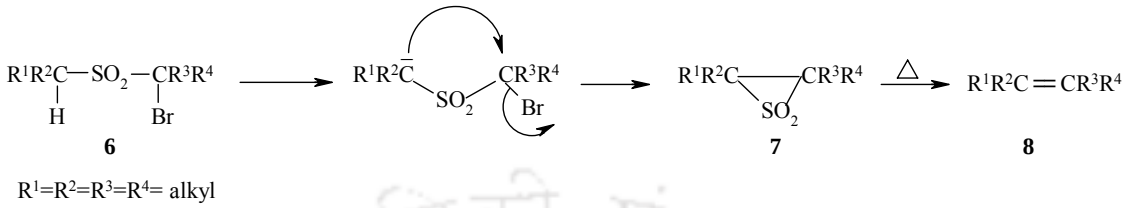
Scheme 1.1

The selective sulfinylation of carbonyl compounds followed by thermolytic extrusion constitutes a general route for converting a saturated carbonyl compound to its α, β-unsaturated derivative.[2] The synthesis of acorenone **5** employed such a sequence[3] as shown in Scheme 1.2.



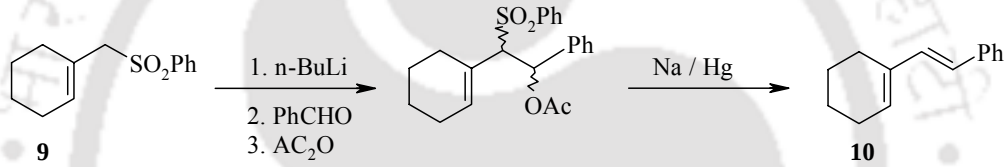
Scheme 1.2

Sulfones are useful intermediates for the formation of carbon-carbon double bonds.[4] The best known route is Ramberg-Backlund reaction. The α-halosulfone **6** upon treatment with an appropriate base forms an intermediate episulfone **7**, which upon heating gives the desired olefin **8** (Scheme 1.3).



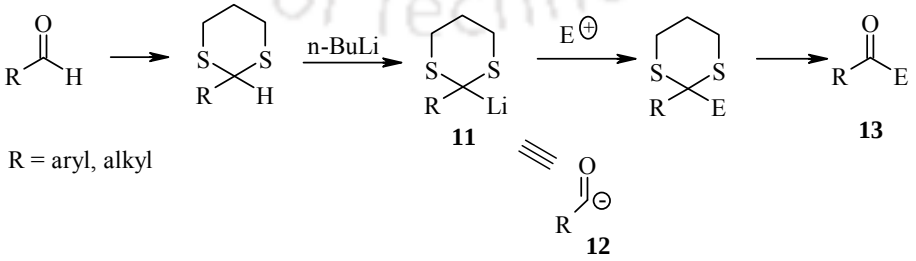
Scheme 1.3

The other sulfone-based elimination of large applicability is the Julia reaction.[5] Condensation of a metallated phenyl alkyl sulfone **9** with a carbonyl compound, functionalization of the alkoxide and upon the reductive elimination leads to an olefin **10** (Scheme 1.4).



Scheme 1.4

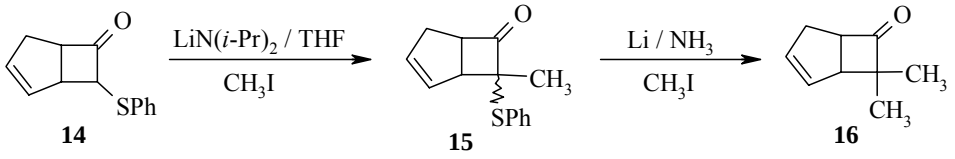
Synthesis of 1,3-dithiane is of great utility for the synthesis of mono and poly functional molecules. The sulfur atom of 1,3-dithiane moieties can stabilize the generated carbanion thereby reversing the normal reactivity pattern of the carbonyl compound. Such a reversal in reactivity is termed as umplong.[6] The sulphur stabilized anion **11** is generated by a base which acts as an acyl anion equivalent **12**. After reaction with an electrophile the dithioacetal moiety can be hydrolyzed to provide the corresponding ketone **13** (Scheme1.5).



Scheme 1.5

Sulfides allow regiosepecific alkylation as a result of strong acidifying influence of the sulfur. In a representative example, the α-phenylthio ketone **14** can be alkylated at carbon bearing

sulfur and further the sulfide function of the alkylated phenylthio ketone **15** was regiospecifically replaced by an alkyl substituent through reductive alkylation forming a quaternary carbon center[7] **16** (Scheme 1.6).

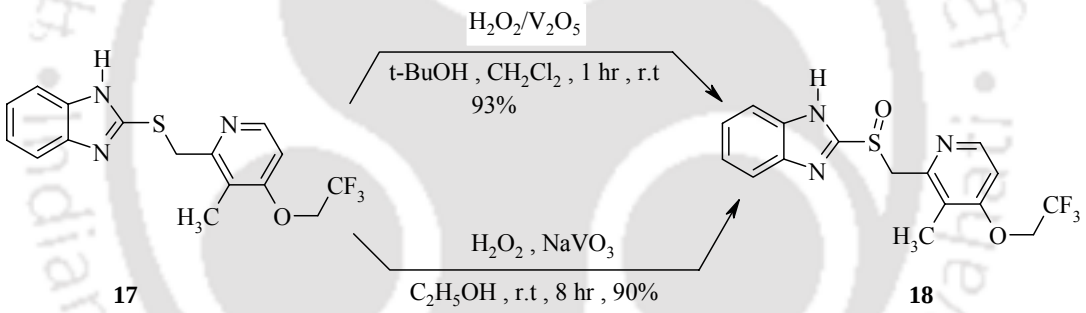


14 **15** **16**

Scheme 1.6

1.3 Literature Methods of Sulfoxidation

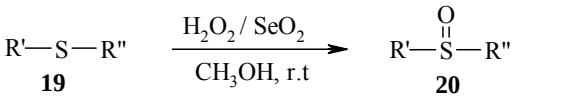
Sulfoxidation can be obtained by the oxidation of sulfide with vanadium compounds like VCl_3,[8] ammonium metavanadate[9] and vanadium(IV) acetylacetonate.[10,11] In a representative example vanadium pentoxide[12,13] and sodium metavanadate[14] were employed for the oxidation of sulfide **17** to sulfoxide **18** in excellent yields (Scheme 1.7).



17 **18**

Scheme 1.7

Drabowicz *et al*. reported selenium dioxide as a catalyst for the selective oxidation of sulfides **19** to sulfoxides **20** by hydrogen peroxide in methanol as a solvent[15] (Scheme 1.8).

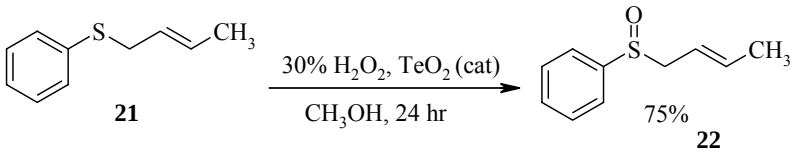


19 **20**

R' = R" = alkyl, aryl 85 - 90 %

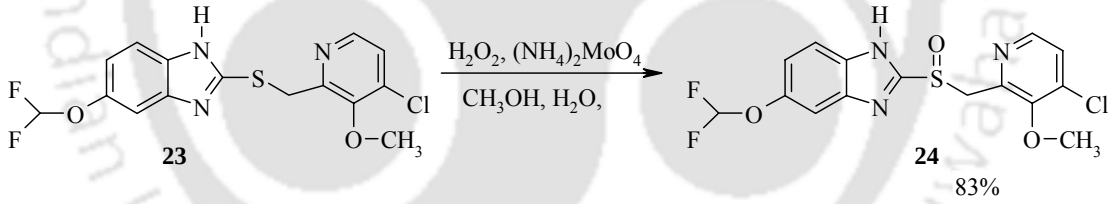
Scheme 1.8

Kim *et al*. used the combination of TeO_2 and H_2O_2 as an efficient system for the selective oxidation of β,γ-unsaturated sulfide **21** to sulfoxide **22** with excellent yields at room temperature[16] (Scheme 1.9).



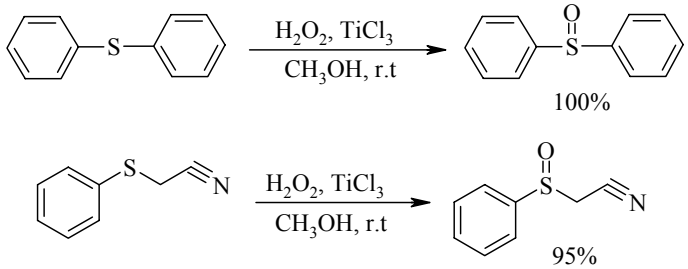
Scheme 1.9

Tungsten catalysts like the tungstic oxide,[17] tungstic acid,[18] hexacarbonyl-tungsten,[19] phosphotungstenic acid,[20] $[C_5H_5N(n\text{-}C_{16}H_{33})]_3PO_4[W(O)(O_2)_2]_4$,[21] peroxo-tungsten complex $[WO(O_2)_2$, HMPT-$H_2O]$,[22] Na_2WO_4[23] and phosphotungstic acid[24] in presence of phase transfer agent tetraoctylammonium bromide was used for the oxidation of sulfides to their corresponding sulfoxides. The salts of molybdenum such as molybdyldiacetylacetonate,[25] Na_2MoO_4[26] in presence of *β*-cyclodextrin and molybdenum peroxide[27] were employed for the oxidation of sulfides with aqueous hydrogen peroxide. Raghavan and coworkers[28] have reported the selective oxidation of thioethers to their corresponding sulfoxides without the generation of sulfones, using 30% aqueous H_2O_2 as oxidant catalyzed by Molybdenum-silicalite-1 (MoS-1). Palomo and his coworkers[29] reported the sulfoxide **24**, which was one of the main intermediate in Pantoprazole (anti-ulcer agent) synthesis, *via* the oxidation of sulfide **23** [5-(difluoromethoxy)-2-{[(3-methoxy-4-chloro-2-pyridinyl)-methyl]thio}-*1H*-benzimidazole] with aqueous hydrogen peroxide in the presence of ammonium molybdate (Scheme 1.10).



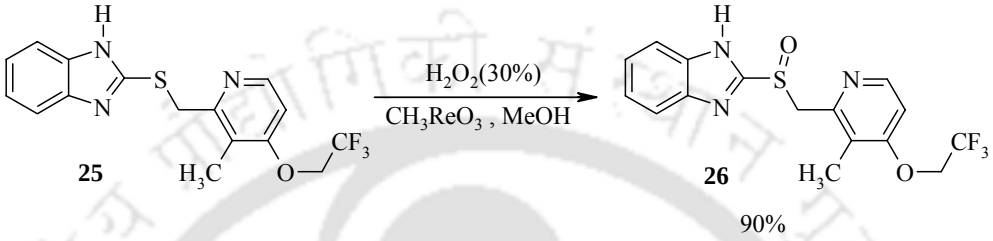
Scheme 1.10

Watanabe *et al*. reported that titanium trichloride efficiently catalyze the oxidation of sulfides to sulfoxides with hydrogen peroxide using methanol as solvent. The reaction proceeded well within short reaction time in excellent yields[30] (Scheme 1.11).



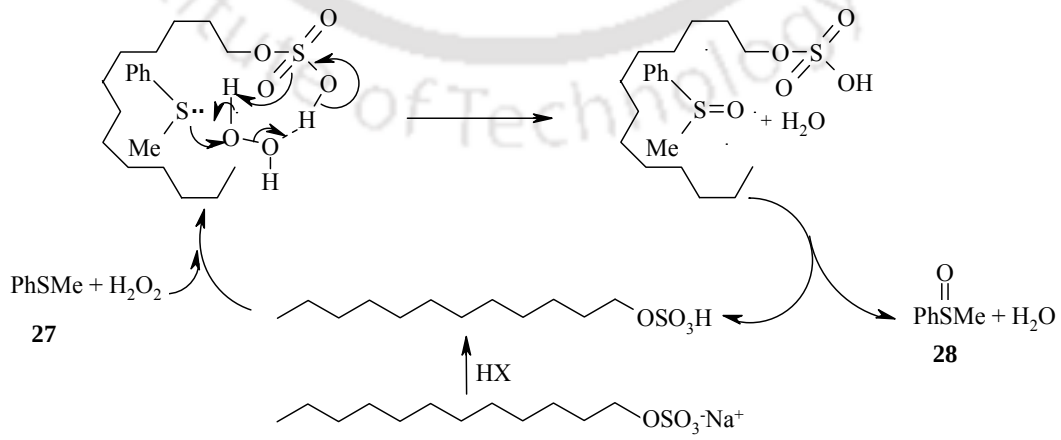
Scheme 1.11

De Rosa *et al*. reported the titanium binaphthyl-bridged Schiff base complex to be an efficient catalyst for the hydrogen peroxide oxidation of sulfides to corresponding sulfoxides under solvent-free conditions.[31] Rhenium compound such as methyltrioxorhenium (MTO) is known as a versatile oxygen-transfer catalyst for the oxidation of various sulfides by hydrogen peroxide. [32-37] One of the main applications of the above catalyst (MTO) is the synthesis of Lansoprazole **26** an anti-ulcer drug from the corresponding sulfide **25** in methanol as solvent (Scheme 1.12).



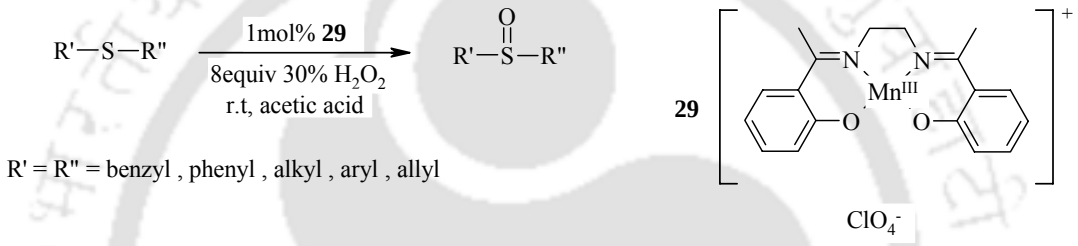
Scheme 1.12

Kagan *et al*.[38] reported the use of titanium tetra-isopropoxide and diethyltartrate as catalysts in asymmetric oxidation of sulfides by hydrogen peroxide. Quideau and his coworkers[39] reported the oxidation of thioethers to sulfoxides catalyzed by SIBX, (a stabilized formulation of λ^5-iodane 2-iodoxybenzoic acid IBX) which can be used as a suspension in CTAB-induced reversed micellar conditions in dichloromethane-water (50:1). Firouzabadi and his co-workers[40] employed a green process for the oxidation of sulfides with an aqueous solution of 35% H_2O_2 catalyzed by *in situ* generated dodecyl hydrogen sulfate as Bronsted acid surfactant under metal-free conditions. As for example phenyl methyl sulfide **27** was oxidized to phenyl methyl sulfoxide **28** in good yields (Scheme 1.13).



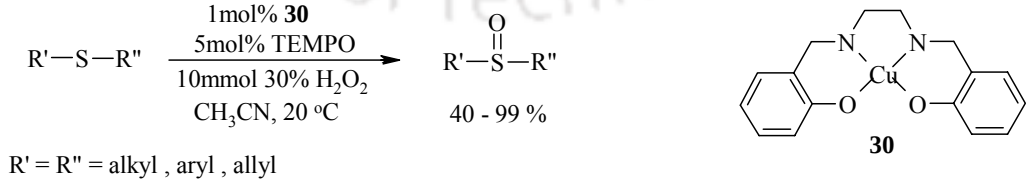
Scheme 1.13

Pei *et al*.[41] reported the selective oxidation of sulfides to sulfoxides in presence of an ionic liquid $[dibmim]^+[BF_4]^-$ containing hypervalent iodine. Various functional groups like the hydroxyl, nitrile, methoxy, olefinic double bonds, and ester remain unaffected. Aqueous mediated selective sulfoxidation of sulfides was achieved with *N*-bromosuccinimide (NBS) catalyzed by *β*-cyclodextrin. The reaction conditions were mild and neutral at room temperature with recycling of cyclodextrin and regeneration of NBS.[42] Reddy *et al*. have reported the selective oxidation of thioethers to sulfoxides with L-proline-H_2O_2 system for structurally divergent sulfides with excellent yields at ambient conditions.[43] Golchoubian and his coworkers[44] achieved the oxidation of sulfides to sulfoxides with hydrogen peroxide catalyzed by a manganese (III) Schiff-base complex **29** in glacial acetic acid as solvent (Scheme 1.14).



Scheme 1.14

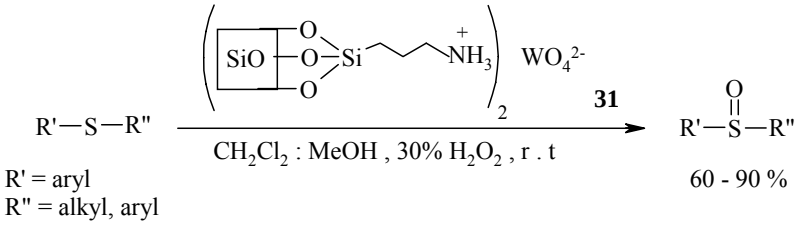
Shen *et al*.[45] demonstrated that activation of potassium superoxide with boron trifluoride in dry acetonitrile facilitates the oxidation of sulfides to corresponding sulfoxides in ice cold conditions without any interference of ketone, olefin, ether, and hydroxyl functionalities under mild conditions. Punniyamurthy and his coworkers[46] reported the oxidation of sulfides with 30% aqueous hydrogen peroxide catalyzed by the copper (II) complex **30**, addition of a catalytic amount of TEMPO to the reaction mixture enhances the conversion and selectivity (Scheme 1.15).



Scheme 1.15

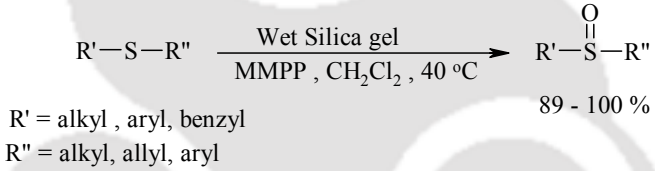
Oxidation of thioethers to corresponding sulfoxides can be achieved with 3-carboxypyridinium chlorochromate[47] in the presence of aluminum chloride. Nezhad *et al*.[48] reported the oxidation of sulfides to sulfoxides in presence of catalytic amounts of a recoverable silica-based

tungstate interphase catalyst **31** using 30% H_2O_2. The recovered catalyst can be reused without any loss in its activity (Scheme 1.16).



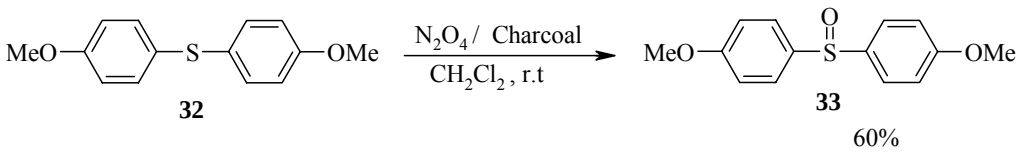
Scheme 1.16

Sulfoxidation can be obtained with ceric ammonium nitrate[49] mediated by hydrated silica gel in dichloromethane. Ali and his coworkers[50] have reported the oxidation of sulfides to sulfoxides with magnesium monoperoxypthalate (MMPP) on hydrated silica gel as a solid support. Functional groups on the sulfides, including carbonyl and olefinic bonds that generally undergo Baeyer-Villiger oxidation and epoxidation respectively were not affected (Scheme 1.17).



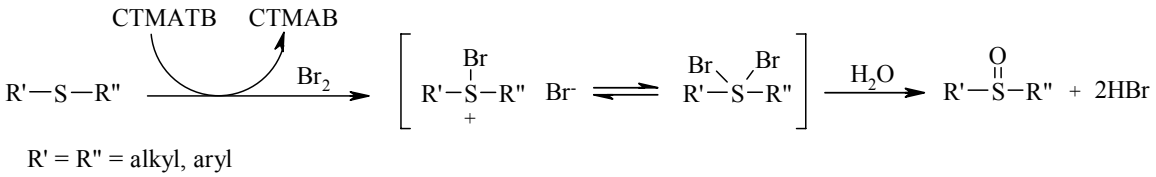
Scheme 1.17

Molecular bromine[51] supported on solid silica gel can be used as a reagent for the oxidation of sulfides to corresponding suulfoxides in dichloromethane as a solvent. This method does not require any additional base or reagent to scavenge the by-product HBr formed in the reaction. Iranpoor and his coworkers[52] reported the stable heterogeneous reagent (N_2O_4-charcoal) by impregnating dinitrogen tetroxide on activated charcoal, which can be employed for the oxidation of thioether **32** to the sulfoxide **33** in dichloromethane at room temperature (Scheme 1.18).



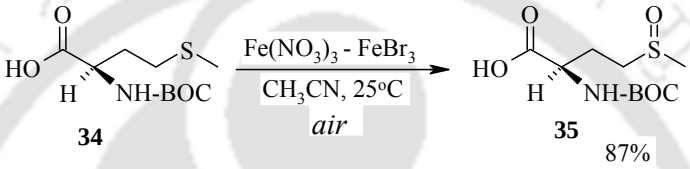
Scheme 1.18

Saikia and his coworkers[53] reported the selective oxidation of sulfides to their corresponding sulfoxides in high yields with cetyltrimethylammonium tribromide (CTMATB) in acetonitrile and water (2:1) (Scheme 1.19).



Scheme 1.19

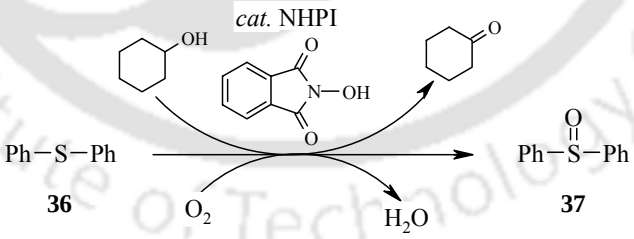
Selective aerial sulfoxidation was accomplished with the binary catalytic system, BiBr-$Bi(NO_3)_3$[54] in high yields under ambient conditions. Rossi *et al*.[55] reported the binary system $Fe(NO_3)_3$-$FeBr_3$ to be an efficient catalyst for the selective *air*-oxidation of sulfides to sulfoxides. The above system was utilized for the sulfoxidation of *Boc* protected amino acid **34** to the corresponding product **35** (Scheme 1.20).



34 **35**

Scheme 1.20

Ishi and his co-workers[56] reported an aerobic oxidation of sulfides using *N*-hydroxypthalimide (NHPI) in presence of cyclohexanol. For instance, the oxidation of diphenyl sulfide **36** in presence of cyclohexanol and a catalytic amount of NHPI in benzonitrile gave diphenyl sulfoxide **37**. The actual oxidant in this oxidation is considered to be α-hydroperoxide generated by the autooxidation of alcohol assisted by the NHPI, which serves as the radical catalyst (Scheme 1.21).

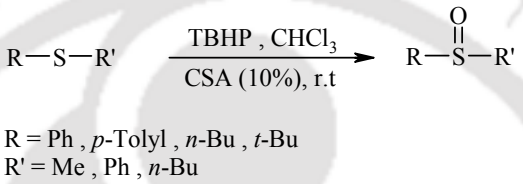


36 **37**

Scheme 1.21

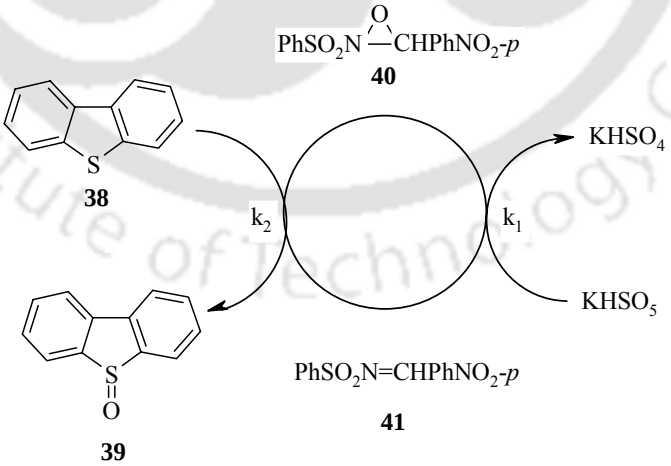
Chemoselective and efficient oxidation of sulfides were carried out by trimethylsilylchloride and K_2O[57] in dry acetonitrile at -15 °C to afford corresponding sulfoxides without any interference in presence of ketone, olefin, ether and hydroxyl functionalities also without further oxidation to sulfones. Oxidation of sulfides to corresponding sulfoxides was achieved by 4,4-dibromo-3-methylpyrazol-5-one,[58] $Bi(NO_3)_3.5H_2O$[59] in acetic acid, trichloroisocyanuric acid in acetonitrile,[60] microwave thermolysis with iron(III) nitrate impregnated on clay

(clayfen) under solvent-free conditions,[61] tetrabutylammonium peroxydisulfate in methylene chloride, [62] manganese dioxide in methanol,[63] phenyltri-methylammonium tribromide in aqueous pyridine solution,[64] and benzyltrimethyl-ammonium tribromide in aqueous sodium hydroxide dichloromethane[65] at room temperature in good yields. Roh *et al*. reported the oxidation of sulfides to sulfoxides with iodosobenzene in presence of catalytic amount of benzene-seleninic acid through ligand coupling on the iodine atom in acetonitrile as solvent in mild conditions.[66] Orito and his coworkers reported the oxidation of sulfides to sulfoxides with mercury(II) oxide-iodine[67] as a reagent. An efficient synthesis of sulfoxides was achieved by oxidation of sulfides with *t*-butyl hydroperoxide catalyzed by camphorsulfonic acid (CSA)[68] (Scheme 1.22).



Scheme 1.22

Misiti *et al*. achieved the oxidation of sulfides to sulfoxides by nitric acid in a biphasic system (nitromethane-water) catalyzed by tetrabromoaurate(III).[69] Davis and his coworkers[70] reported the oxidation of sulfide **38** to the corresponding sulfoxide **39** with *N*-sulfonyloxaziridine **40** prepared by biphasic oxidation of sulfonimine **41** generated by using a buffered potassium peroxymono- sulfate (Oxone) (Scheme 1.23).



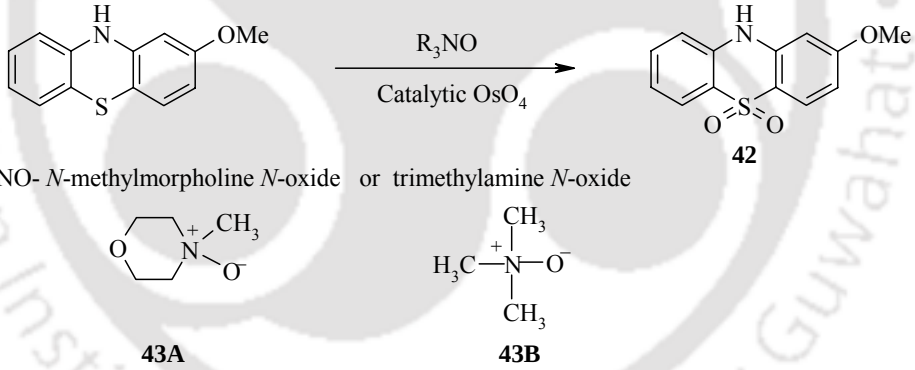
Scheme 1.23

Oxidation of thioethers to the corresponding sulfoxides using molecular oxygen (P_{O2} = 5 - 15 bar) as oxidant catalyzed by ceric ammonium nitrate[71] was reported. Oxidation of sulfides can

be accomplished by using *o*-iodosylbenzoic acid,[72] [hydroxy(tosyloxy)iodo] benzene,[73] esters of 2-iodoxybenzoic acid,[74] iodosobenzene in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetonitrile,[75] periodic acid catalyzed by $FeCl_3$ in acteonitrile,[76] iodosobenzene or phenyliodine-diacetate in water,[77] *o*-iodoxybenzoic acid (IBX) and tetraethylammonium bromide,[78] *N*-tert-butyl-*N*-chlorocyanamide,[79] urea-hydrogen peroxide adduct as oxidant catalyzed by titanium-beta zeolite[80] and aqueous hydrogen peroxide in Chloroform in the presence of catalytic amounts of 1,1,1-trifluoroacetone.[81]

1.4 Literature Methods for Sulfone Synthesis

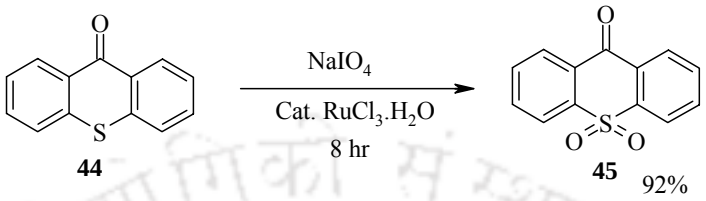
Sulfones can be obtained by the over oxidation of sulfides. Iqbal and his coworkers described the synthesis of sulfones by using a combination of molecular oxygen, 2-methylpropanal and catalytic amount of cobalt salophen. They also demonstrated that in absence of cobalt salophen a five fold excess of 2-methylpropanal was necessary along with molecular oxygen for the same conversion.[82] Friebe *et al*.[83] achieved the synthesis of sulfone **42** under mild conditions using a catalytic amount of osmium tetroxide and tertiary amine *N*-oxides **43A** and **43B** (Scheme 1.24).



Scheme 1.24

Jeyakumar *et al*.[84] reported the oxidation of sulfides to sulfones by hydrogen peroxide using MoO_2Cl_2 as the catalyst. Substituted sulfides were selectively oxidized without affecting the sensitive functional groups such as methyl, methoxy, bromo, nitro, alkene, alkyne, alcohol, ester, aldehyde and an oxime. Hydrogen peroxide in presence of zirconium tetrachloride is an efficient reagent for the oxidation of sulfides to sulfones in methanol at room temperature. It is noteworthy that under such conditions, the sulfide function is highly reactive and various other functional groups such as alkenes and a ketone are tolerated.[85] Synthesis of sulfones was achieved by employing the fluorine complex $HOF{\cdot}CH_3CN$[86], wet silica-supported sodium periodate under microwave thermolysis[87] and potassium hydrogen persulfate in aqueous

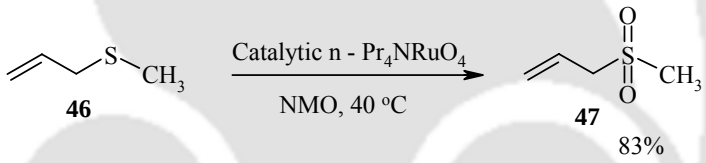
methanol.[88] Des Marteau and his coworkers[64] reported the oxidation of thioethers to sulfones by using stochiometric amounts of perfluoro-*cis*-2,3-dialkyloxaziridines in trifluoroethanol.[89] Ruthenium trichloride-sodium periodate combination was an efficient system for the oxidation of sulfides to sulfones. In a representative example electron withdrawing substrates such as thioxanthen-9-one **44** was oxidized to sulfone **45** at room temperature[90] (Scheme 1.25).



44 **45** 92%

Scheme 1.25

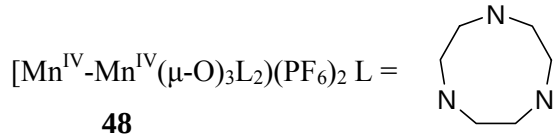
Cuertin *et al*. described the chemoselective oxidation of thioethers to sulfones catalyzed by tetrapropylammonium perruthunate in presence of the co-oxidant N-methylmorpholine-N-oxide (NMO). For example sulfide **46** was oxidized to the corresponding sulfone **47** without affecting the double bond under these reaction conditions[91] (Scheme 1.26).



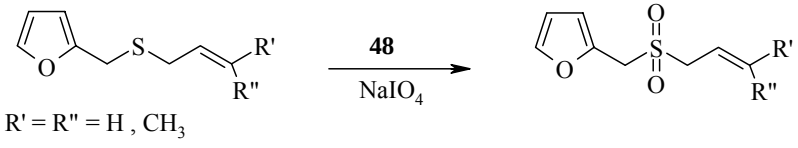
46 **47** 83%

Scheme 1.26

Smith and his coworkers reported the oxidation of sulfides to sulfones using periodic acid catalyzed by a binuclear Mn ^{IV} - Mn ^{IV} manganese complex **48** under mild conditions. The reaction was selective giving almost quantitative yields in the presence other easily oxidizable groups. Only amines were found to hinder the reaction[92] (Scheme 1.27).



48

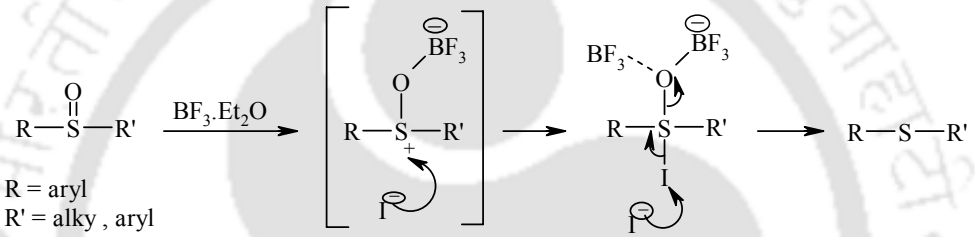


R' = R" = H , CH_3

Scheme 1.27

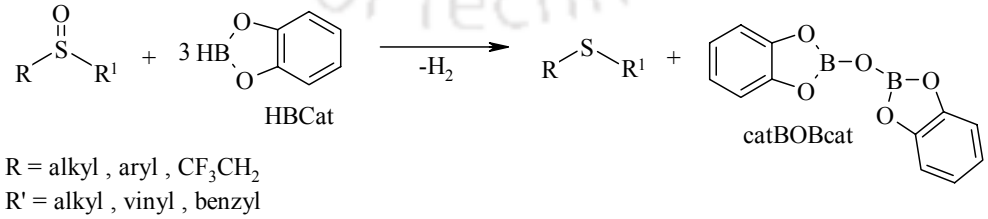
1.5 Literature Methods for the Reduction of Sulfoxides

In general sulfides can be achieved by the reduction of sulfoxides with various boron reagents such as $HBCl_2$,[93] 9-BBN-Br, Me_2BBr and BBr_3.[94] Similarly complexes of boron such as boron triiodide-N,N-diethylaniline was used to reduce sulfoxides to sulfides, in good yield under mild conditions.[95] Aromatic and aliphatic sulfoxides were reduced by thexylchloroborane-methyl sulfide complex [96] to sulfides at 0 °C in a highly selective manner and leaves intact other reducible groups such as epoxides, quinones, esters, amides, disulfides and sulfones. Other boron compounds like catecholborane,[97, 98] diborane-THF,[99, 100] disiamylborane-THF,[101] thexylborane-DMS,[102] and 9-borabicyclo[3.3.1]nonane-THF[103] were used exclusively for the reduction of dimethysulfoxide to dimethylsulfide. Vankar *et al*. obtained aromatic sulfides by boron trifluoride etherate-sodium iodide system[104] (Scheme 1.28).



Scheme 1.28

Clive *et al*. reported the selective reduction of sulfoxides by selenoboron compounds like $[(C_6H_5Se)_3B]$ and $[(CH_3Se)_3B]$ in chloroform at -30 °C. Ketones, carbon-carbon double bonds, lactams, and amides remained intact under these reaction conditions.[105] Harrison *et al*. reported the addition of catecholborane to sulfoxides affording sulfide, dihydrogen, and catBOBcat. The diboron compound catBOBcat acts as a Lewis acid, which coordinates with the sulfoxide. The reaction can be accelerated by using excess HBcat or by employing a rhodium catalyst[106] (Scheme 1.29).

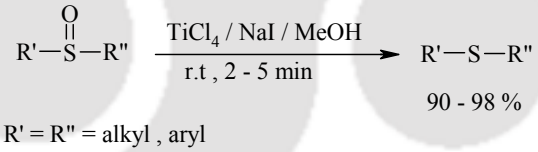


Scheme 1.29

Deoxygenation of sulfoxides can be achieved by lithium aluminum hydride[107] and Red-Al.[108] The reduction of dimethylsulfoxide to dimethylsulfide with aluminum hydride[109] is described.

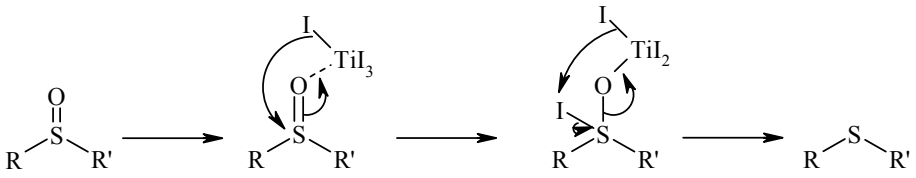
Thiolane-l-oxide was rapidly reduced by diisobutylaluminium hydride in toluene at 0 °C to the corresponding thiolane.[110] Similarly, Anastassiou *et al*. achieved the deoxygenation of systems such as 9-thial[4.2.1.]nonabicyclic S-oxides with $LiAlH_4$ in good yields.[111] Sodium borohydride was found to be a versatile reducing agent when used in combination with metal salts like cobalt chloride hexahydrate,[112] $TiC1_4$,[113] $FeCl_3$ in aqueous EtOH[114]and $CoCl_2$ in EtOH under N_2 at room temperature.[115] Karimi and his coworkers reported the chemoselective deoxygenation of structurally divergent sulfoxides to their thioethers with sodium borohyride in presence of I_2.[116] Other functional groups such as esters, nitriles and double bonds remain unaffected.

Sodium borohydride in association with co-reagents such as boron trifluoride etherate[117] and sodium hydroxide,[118] readily reduces sulfoxides to their sulfides. Durst *et al*. achieved the selective deoxygenation of various sulfoxides under mild conditions using cyanohydridoborate crown ether.[119] Khurana *et al*. obtained the deoxygenation of acyclic sulfoxides with anhydrous nickel chloride and sodium borohydride in tertahydrofuran at 0-5 ^oC. The reaction was proposed to proceed by an oxidative-addition and reductive-elimination mechanism.[120] $TiCl_4$ in combination with metals like In,[121] Sm,[122] and Zn[123] reduced sulfoxides to their corresponding thioethers. Similarly, the aromatic and aliphatic sulfoxides were converted to sulfides with $TiCl_4$-NaI,[124] in good yields at room temperature (Scheme 1.30).



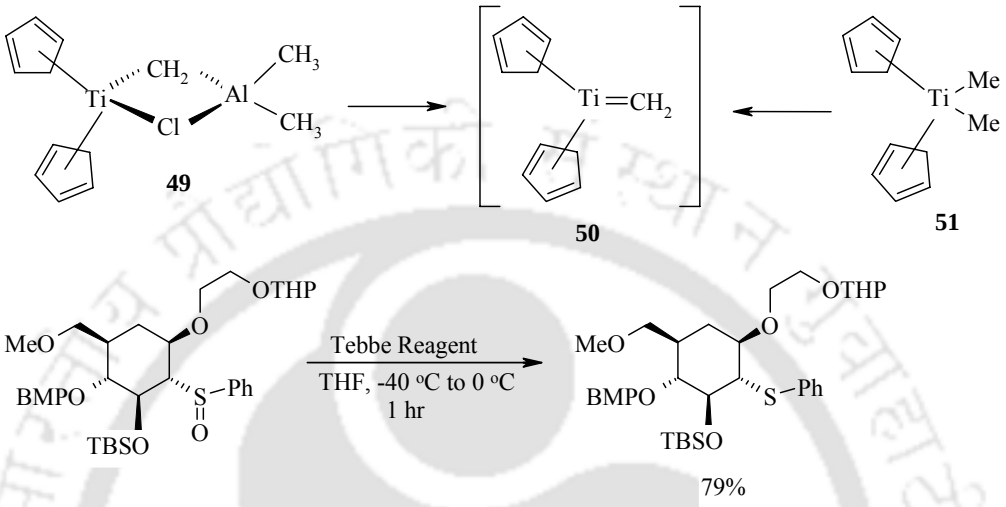
Scheme 1.30

Chemoselective deoxygenation of sulfoxides was obtained using TiI_4 as a reducing agent in excellent yields[125] (Scheme 1.31). Kikuchi *et al*. reported the $TiCl_4$-Ph_3P combination to be an effective promoter for reduction of sulfoxides under mild conditions.[126]



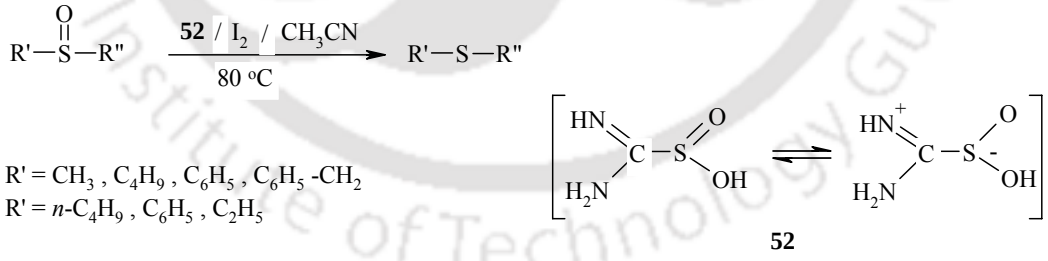
Scheme 1.31

Similarly, the complexes of titanium such as Cp_2TiCl_2 in combination with metals In[127] and Sm[128] were effective for the reduction of sulfoxides to their corresponding thioethers in excellent yields. Nicolaou and his coworkers[129] reported that the deoxygenation of sulfoxides could be accomplished with titanocene methylidene **50**, generated either from the Tebbe reagent **49** or Cp_2TiMe_2 **51** (Scheme 1.32).



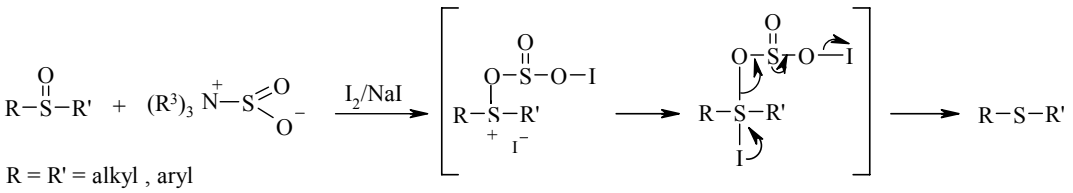
Scheme 1.32

Deoxygenation of dialkyl, diaryl, and alkyl aryl sulfoxides to the corresponding sulfides were obtained with NaI in combination with sulfonic acid,[130] $AlCl_3$,[131] $P(OEt)_3$-iodine,[132] and BF_3-Et_2O.[133] Drabowicz *et al*. reported the reduction of sulfoxides to sulfides by formamidine-sulphinic acid **52** in combination with iodine as a catalyst[134] (Scheme 1.33).



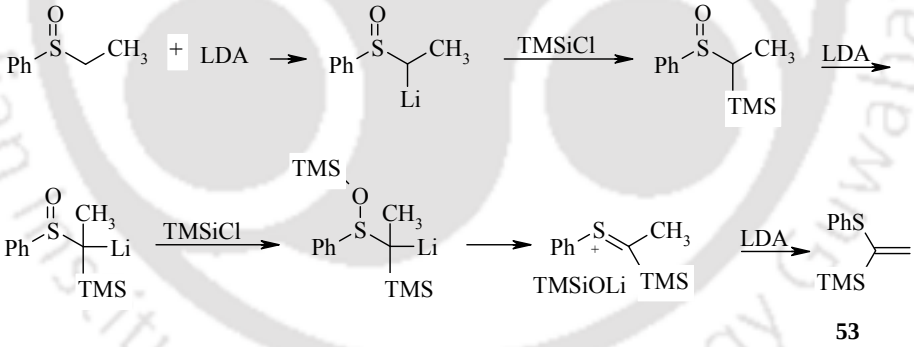
Scheme 1.33

Similarly, systems like $ClSO_2NCO$-NaI in MeCN,[135] $(ClCO)_2$-NaI in MeCN,[136] WCl_6-NaI in anhydrous MeCN,[137] and pyridine-SO_3 in presence of iodine were effective for the reduction of sulfoxides. Olah and his coworkers[138] reported that trimethyl(ethyl)amine-sulfurdioxide complexes along with iodine and sodium iodide in acetonitrile reduce aliphatic sulfoxides to the corresponding thioethers in good yields (Scheme 1.34).



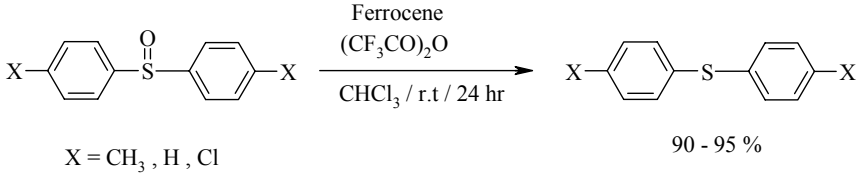
Scheme 1.34

Fernandes *et al*. developed in water, an air stable catalytic system PMHS-MoO_2Cl_2-$(H_2O)_2$[139] for the reduction of sulfoxides with a wide functional group tolerance. 3-Mercapto-propionic acid[140] in association with a catalytic amount of trimethylchlorosilane (10-20 mol%) in CH_3CN at ambient temperature was used for the reduction. Phase transfer catalyst $Bu_4N^+.Br^-$ at room temperature in an argon atmosphere with $PhSSiMe_3$ reduces the sulfoxides in good yields.[141] Sulphur analogues of silane such as hexamethylcyclotrisilthiane at room temperature reduces sulfoxides.[142] Thiopyran S-oxides and benzothiopyran derivatives were converted to their respective sulfides by Zn-Me_2SiCl_2.[143] Eliminative deoxygenation of sulfoxides was achieved with Me_3SiI[144] in the presence of a teritiary amine like $(Me_2CH)_2NEt$ at 25 °C. α-Trimethylsilylvinyl sulfides **53** were also obtained in good yields with LDA in combination with Me_3SiCl[145] (Scheme 1.35).



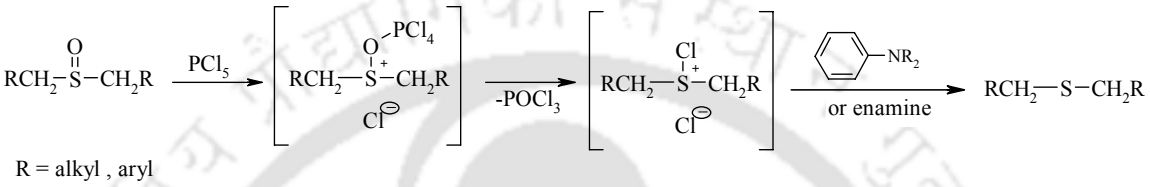
Scheme 1.35

Kobayashi and his coworkers reported the reduction of diaryl sulfoxides with trifluoroacetic anhydride in presence of ferrocene to their corresponding sulfides. The reduction was composed of the ferrocene-spacer-methylsulfinyl triad system, which would proceed via a through-bond electron transfer rather than a through-space process[146] (Scheme 1.36).



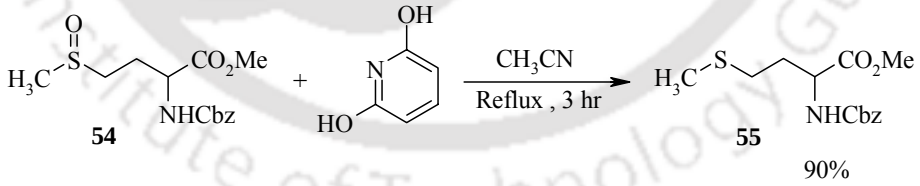
Scheme 1.36

Deoxygenation of sulfoxides can be achieved by various phosphorous reagents like $PSBr_3$,[147] PI_3[148]and P_2I_4.[149] Still *et al*. achieved the reduction of sulfoxides to sulfides in presence of P_4S_{10}. Reducible functional groups such as ketone, ester, amide, nitro, and halogen remain unaffected. P_4S_{10} is ineffective for reducing sulfones. The mechanistic evidence indicates a probable four-center (Wittig-like) intermediate or transition state for the reduction of sulfoxides by P_4S_{10}.[150] Similarly, phosphorous pentachloride was also an effective reductant in the presence of an enamine at 0 ^oC[151] (Scheme 1.37).



Scheme 1.37

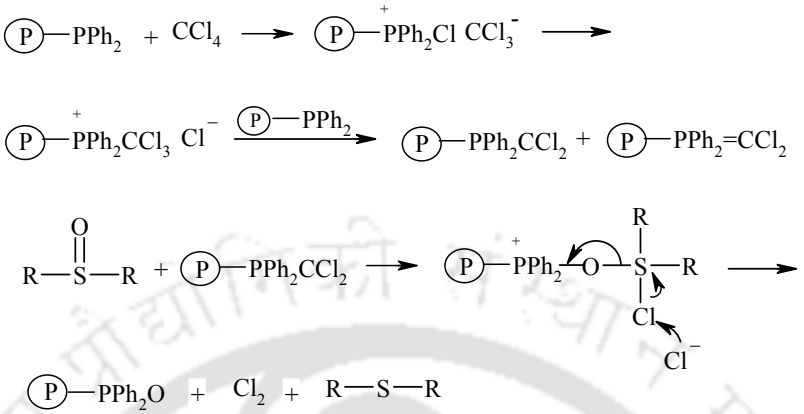
Yadav and his coworkers reported that several aromatic and aliphatic sulfoxides were selectively deoxygenated to the corresponding thioethers by samarium metal in methanolic ammonium chloride under sonication. Other functional groups such as halides, esters, ethers, nitriles, olefins and ketones were unaffected.[152] Sulfoxide **54** bearing protecting group was deoxygenated to the corresponding sulfide **55** with 2,6-dihydroxypyridine under mild reaction conditions in good yileds[153] (Scheme 1.38).



Scheme 1.38

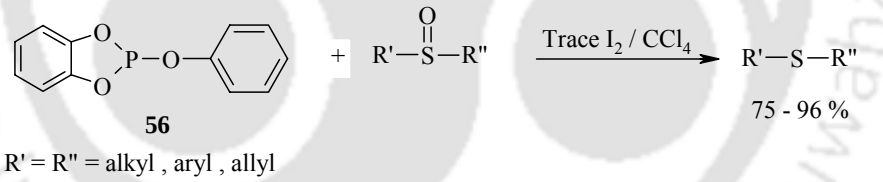
Shaterian *et al*. reported the deoxygenation of sulfoxides to their corresponding sulfides with 1,3-dithiane at room temperature in presence of catalytic amounts of *N*-bromosuccinimide, 2,4, 4,6-tetrabromo-2,5 cyclohexadienone or Br_2 as the source of electrophilic bromine.[154] Other functionalized sulfoxides, e.g., Ph_2SO, can be selectively deoxygenated to sulfides, e.g., Ph_2S, in high yields by Lawesson reagent.[155] Solvent free reduction was achieved by NaBr in DMF. Hydrogen bromide formed in the reaction, acts as a catalyst.[156] Polystyryldiphenyl - phosphine with CCl_4 in THF in refluxing conditions reduces various dialkyl, arylalkyl, and diaryl

sulfoxides to the corresponding sulfides. The reaction was compatible with a variety of functional groups particularly the easily reducible nitro and then olefinic bonds[157] (Scheme 1.39).



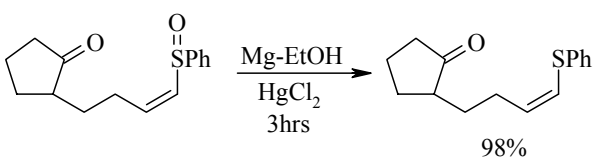
Scheme 1.39

Aryl and aliphatic sulfoxides underwent facile phase-transfer-catalyzed deoxygenation with dicholorcarbene[158] at 25 ^{o}C to give sulfides in excellent yield. Dreux *et al*. reported that 2-phenoxy-1,3,2-benzodioxaphosphole **56** as a mild reducing agent in presence of a catalytic amount of iodine to variety of sulfoxides. Sulfones remain unaffected under this conditions[159] (Scheme 1.40).



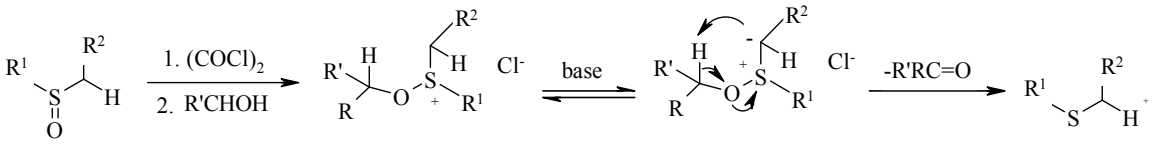
Scheme 1.40

Sulfoxides were reduced by $SnCl_2$-HCl system to their corresponding sulfides.[160] Lee *et al*. reported an extremely convenient deoxygenating reagent for the reduction of 1-alkenyl, alkyl, and aryl phenyl sulfoxides with magnesium powder in absolute methanol or ethanol in presence of a catalytic amount of mercuric chloride[161] (Scheme 1.41).



Scheme 1.41

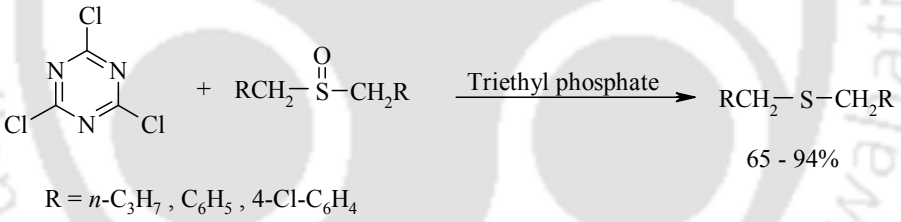
Bhatia *et al*. reported the deoxygenation of α-hydrogen-containing sulfoxides with oxalyl chloride at −78 °C. This method is in accordance with Swern oxidation where the alcohol implemented was oxidized to ketone and the sulfoxide was reduced to its thioether[162] (Scheme 1.42).



R^1 = Ph , $PhCH_2$, *n*-C_4H_9
R^2 = Me , n -Pr

Scheme 1.42

Various other reducing agents for deoxygenation of sulfoxides to their sulfides such as 3-mercaptopropionic acid with a catalytic amount of iodine,[163] silica gel,[164] Mg-MeOH[165] indium and pivaloyl chloride[166] at room temperature were reported. Narang *et al*. reported the reduction of sulfoxides with cyanuric chloride in triethyl phosphate. No chlorinated products were obtained[167] (Scheme 1.43).



R = *n*-C_3H_7 , C_6H_5 , 4-Cl-C_6H_4

Scheme 1.4

1.6 References

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CHAPTER II

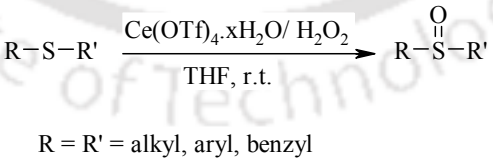
Cerium(IV) triflate Catalyzed Selective Oxidation of Sulfides to Sulfoxides and Sulfones with Aqueous Hydrogen Peroxide

2.1 Objective

Sulfoxides and sulfones are useful intermediates in various organic transformations. Moreover, they are present in sulfur substituted natural compounds such as aminoacids, vitamins, drugs and other xenobiotics. Both sulfoxides and sulfones are commonly prepared by the oxidation of corresponding sulfides. The main objective of this work was to develop a synthetic method for the selective oxidation of sulfides to sulfoxides without over-oxidation to sulfones in presence of other functional groups. The same catalyst was utilized for the synthesis of sulfones.

2.2 Present work

In view of the importance of sulfoxides, several catalysts along with oxidants have been employed for this key transformation. There are a number of oxygen donors in the literature, but the use of H_2O_2, O_2, and ^tBuOOH have become increasingly more important under green context.[1] Of these, aqueous H_2O_2 is most attractive from the environmental viewpoint. It is an ideal oxidant, since water is the only by-product, and is suitable for liquid-phase reactions, due to its solubility in water and many organic solvents.[2,3] Though different approaches for sulfoxidation have been reported, there are various limitations such as the use of strong acidic conditions,[4,5] elevated temperatures,[6] long reaction times,[7] hazardous organic solvents and reagents.[8-10] Many of the existing methods give sufficient amount of over oxidised product sulfone.[11,12] In the present work we report an efficient and a synthetic protocol in which aqueous hydrogen peroxide has been used as the oxidising agent catalyzed by cerium(IV) triflate for the chemoselective oxidation of structurally divergent sulfides to sulfoxides at room temperature as shown in Scheme 2.1.

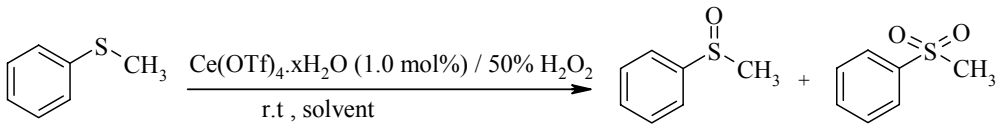


Scheme 2.1

2.3 Results and Discussion

Initially we performed a set of preliminary experiments considering phenyl methyl sulfide as a model substrate. The oxidation was investigated in various solvents such as toluene, THF, CH_3CN, CH_3NO_2, CH_3OH, CH_3COOH and CH_2Cl_2 using 1 mol% of catalyst. The results are formulated in Table 2.1.

Table 2.1: **Oxidation of Phenyl methyl sulfide in various solvents**



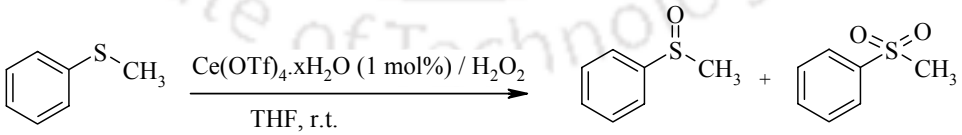
Entry	Solvent	H_2O_2[a] (equiv)	Time (min)	Sulfoxide (Yield)[b]	Sulfone (Yield)[b]
1	Toluene	3	60	97	3
2	THF	3	40	97	3
3	CH_3CN	3	30	89	11
4	CH_3NO_2	3	30	92	8
5	CH_3OH	3	30	53	47
6	CH_3COOH	3	30	76	24
7	CH_2Cl_2	3	12 hr	0	0

a. 50% aqueous hydrogen peroxide was used
b. Determined by GC-MS and ^{1}H NMR

The efficiency of toluene and THF as a solvent were found to be similar with a minimum amount of sulfone formation. The drawback of toluene is that some of the substrates were not completely soluble in this solvent. The reaction proceeded well in CH_3NO_2, CH_3CN, and CH_3COOH with the formation of sulfone, 8%, 11% and 24% respectively. In methanol almost equal amounts of sulfoxide and sulfone were formed. There was no reaction in CH_2Cl_2. Therefore, based on the results obtained we found that THF could be an appropriate solvent for the selective oxidation and was further used in subsequent optimization studies.

Further the reaction was monitored with different oxidant levels in THF using 1 mol% of cerium(IV) triflate (Table 2.2).

Table 2.2: **Oxidation performed at different amounts of 50% H_2O_2 in THF**



Entry	H_2O_2[a] (equiv)	Time (min)	Sulfoxide (Yield)[b]	Sulfone (Yield)[b]
1	2	60	93	7
2	3	40	97	3
3	4	30	87	13
4	5	30	80	20

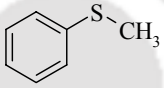
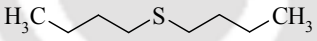
a. 50% aqueous hydrogen peroxide was used.
b. Determined by GC-MS and ^{1}H NMR

It was observed that at lower concentration of hydrogen peroxide (2 equiv) the reaction time got increased to 60 min with 7% of sulfone. Similarly, increasing the concentration of hydrogen peroxide to 4 and 5 equivalents decreases the reaction time (30 min) but increases the amount of sulfone to 13% and 20% respectively. At 3 equivalents of hydrogen peroxide, the over oxidation to sulfone was minimal (3%).

Similarly, the reaction was carried out in different catalyst loadings. At a lower catalyst loading (0.1 mol%) the reaction took longer time and was not completed even after stirring for 4 hours, with 0.5 mol% of catalyst the reaction was completed in 2 hrs, yielding 97% of sulfoxide with a small amount of sulfone (3% yield). It was also observed that increasing the amount of catalyst to 5 mol%, the reaction leads to more sulfone (15%) formation.

The oxidation reaction was carried out with cerium(III) chloride heptahydrate in tetrahydrofuran. Although it gives sulfoxides but it takes longer time with the formation of more sulfones. As a representative example the reaction of methyl phenyl sulfide with $CeCl_3.7H_2O$ in THF gave sulfoxide 71% and sulfone 29% respectively. Similarly dibutylsulfide gave sulfoxide 78% and sulfone 22% as shown in Table 2.3.

Table 2.3: **Oxidation of sulfides to sulfoxides catalyzed by $CeCl_3.7H_2O$**

Entry	Substrates	Time (hr)	sulfoxide (Yield)[a]	sulfone (Yield)[a]
1		48	71	29
2		46	78	22

a. Determined by ^{1}H NMR

Therefore, an optimum amount of catalyst and oxidant with a suitable solvent is essential for the oxidation and based on the above observations we could conclude that 1 mol% of cerium(IV) triflate, 3 equivalents of 50% hydrogen peroxide and THF as a solvent is the best combination for the oxidation of sulfides to sulfoxides. The reaction is generalized through entries 1 - 19 (Table 2.4).

Table 2.4: Oxidation of sulfides to sulfoxides catalyzed by $Ce(OTf)_4.xH_2O$

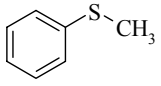
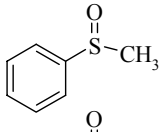
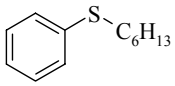
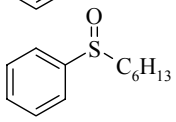
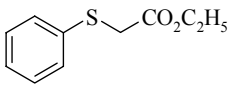
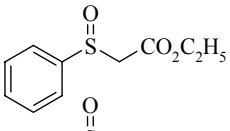
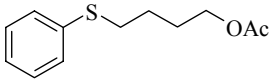
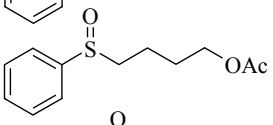
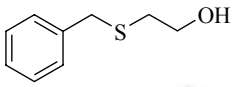
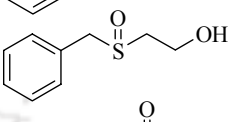
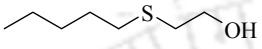
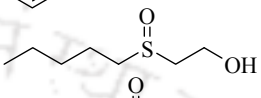
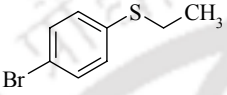
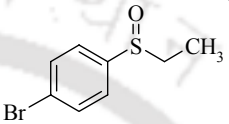
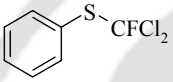
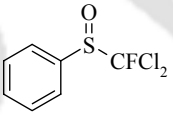
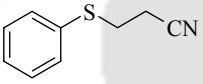
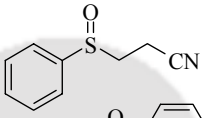
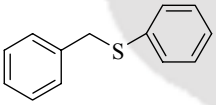
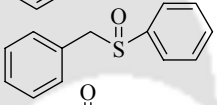
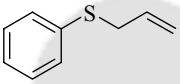
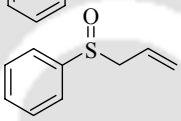
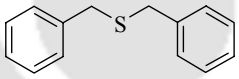
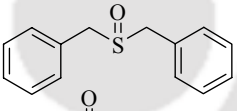
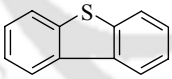
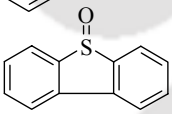
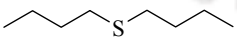
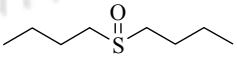
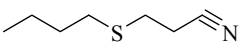
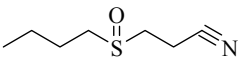
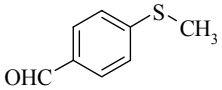
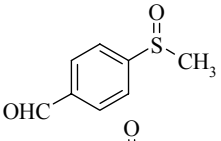
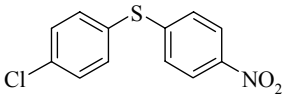
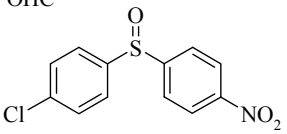
Entry	Substrates	Time (hr)	Products	Yield (%)[a]
1		0.7		93
2		3		96

Table 2.4: Oxidation of sulfides to sulfoxides catalyzed by $Ce(OTf)_4.xH_2O$

Entry	Substrates	Time (hr)	Products	Yield (%)[a]
3		6		93
4		5		94
5		3		95
6		3		92
7		10		92
8		11		91
9		6		95
10		6		94
11		6		92
12		6		93
13		13		91
14	$C_{16}H_{33}SC_6H_{13}$	5	$C_{16}H_{33}SC_6H_{13}$	89
15	$C_{12}H_{25}SC_6H_{13}$	4	$C_{12}H_{25}SC_6H_{13}$	94
16		0.5		91
17		2		92
18		12		90
19		65		73

(a) Isolated yields. The compounds are characterized by GC-MS, ^{1}HNMR, ^{13}CNMR and IR spectroscopy.

It was observed that the reaction is extremely mild and equally good for alkyl aryl, dialkyl and cyclic sulfides. Inert cyclic sulfide dibenzothiophene (entry 13) was efficiently oxidized to sulfoxide. In these reaction conditions functional groups like esters, hydroxyls, nitrile and olefin remain intact. This was confirmed by spectroscopic methods. For example the IR spectrum of the product ethyl 2-(phenylsulfinyl) acetate (entry 4) showed sharp peaks at 1050 and 1742 cm^{-1} corresponding to sulfoxide (S=O) and carbonyl (C=O) groups respectively. ^{1}H NMR spectrum displayed two doublets at δ 3.66 and 3.85 with a coupling constant J = 13.6 Hz corresponding to the protons adjacent to the sulphoxide group (PhSO-$\underline{CH_2}$-). ^{13}C NMR showed a peak at δ 164.4 indicating the presence of carbonyl carbon of the acetate group. Hence from the above spectral data it can be confirmed that acetate functionality remained intact along with the formation of sulfoxide.

Similarly the IR spectrum of 2-(benzylsulfinyl) ethanol (entry 5) showed a broad peak at 3498 and a sharp peak at 1081 cm^{-1} indicating the presence of (OH) and (S=O) groups respectively. The ^{1}H NMR spectrum displayed a broad singlet at δ 3.50 for the O-H protons. Thus from the above spectral values the presence of hydroxyl group was confirmed.

The IR spectrum of 1-(dichlorofluoromethylsulfinyl)benzene (entry 8) displayed a sharp peak at 1076 cm^{-1} for the (S=O) group. The ^{13}C NMR spectrum showed a doublet at δ 127.1 with coupling constant J = 339.4 Hz corresponding to the carbon attached to the fluorine atom. The ^{19}F NMR spectrum showed a singlet at δ 98.61 for the fluorine atom (-C$\underline{F}Cl_2$-). The mass spectrum (EIMS (m/z)) showing a peak at (M^{+}+1) 141 confirms its molecular mass.

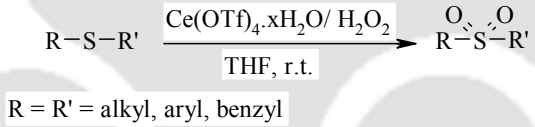
The IR spectrum of 3-(phenylsulfinyl)propanenitrile (entry 9) showed a sharp peak at 2250 cm^{-1} confirming the presence of nitrile group. ^{1}H NMR spectrum displayed two multiplets at δ 2.48 - 2.56 and δ 3.20 - 3.27 corresponding to the protons adjacent to the sulphoxide group (PhSO-$\underline{CH_2}$-) and a multiplet at δ 7.56 - 7.60 indicating the presence of aromatic protons. Mass spectra (EIMS (m/z)) showed a peak at (M^{+}+1) 180, which indicates the presence of nitrile group.

The IR spectrum of 1-(allylsulfinyl)benzene (entry 11) displayed sharp peaks at 1644 cm^{-1} and 1086 cm^{-1} corresponding to (C=C) and sulfoxide (S=O) groups respectively. The ^{1}H NMR showed two doublets at δ 5.14 (J = 17.2 Hz) and δ 5.31 (J = 10.4 Hz) which can be assigned to the terminal protons and a multiplet at δ 5.72 -5.82 to the internal proton of the olefin. A doublet was observed at δ 3.81 for the methylene protons adjacent to the sulphoxide group (PhSO-$\underline{CH_2}$-). ^{13}C NMR displayed peaks at δ 124.6 and δ 125.7 corresponding to the carbons of the double bond. Hence from the above spectral data it can be confirmed that olefin remained intact along with the formation of sulfoxide.

The IR spectrum of the product 4-(methylsulfinyl)benzaldehyde (entry 18) showed sharp peaks at 1040 and 1711 cm^{-1} indicating the sulfoxide (S=O) and carbonyl (C=O) groups respectively. The ^1H NMR spectrum displayed a singlet at δ 10.10 due to the presence of aldehyde proton. A singlet appeared at δ 2.80 corresponding to protons of the methyl group and two doublets at δ 7.81 and 8.00 were assigned for the aromatic protons of A_2B_2 pattern. Thus from above spectral data the presence of aldehyde group was confirmed.

The IR spectrum of 4-chlorophenyl-4-nitrophenyl sulfoxide (entry 19) showed sharp peaks at 1060 cm^{-1} for (S=O) group, 1342 and 1521 cm^{-1} for the NO_2 group. The ^1H NMR spectrum displayed four doublets at δ 7.45, 7.59, 7.79 and 8.29 corresponding to four aromatic protons of A_2B_2 pattern. The mass spectrum EIMS (m/z) showing a peak at $(M^+ + 1)$ 283 confirms the product.

Further this methodology was extended for synthesis of sulfones. As it was evident from Table 2.1 that the reaction in methanol gives almost 50 % sulfone. Therefore, the reaction was carried out by increasing the amount of catalyst $Ce(OTf)_4.xH_2O$ (10 mol%) and oxidant (10 equivalent; 50% aqueous H_2O_2) in methanol (Scheme 2.2). The reaction is generalized through entries 1- 18 (Table 2.5).



Scheme 2.2

Table 2.5: Oxidation of sulfides to sulfones catalyzed by $Ce(OTf)_4.xH_2O$

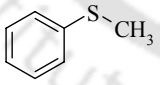
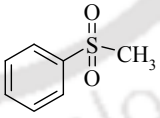
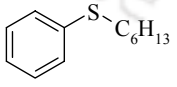
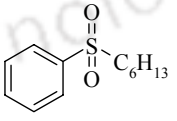
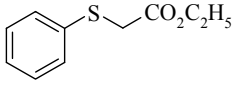
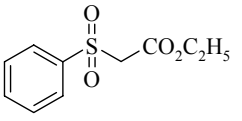
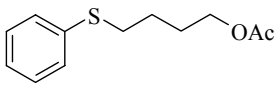
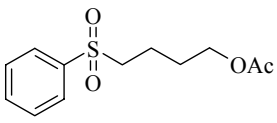
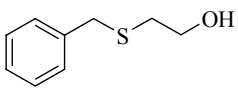
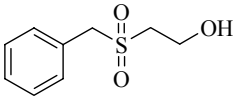
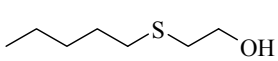
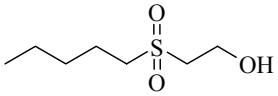
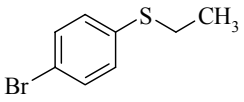
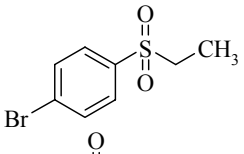
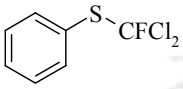
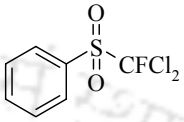
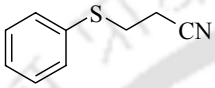
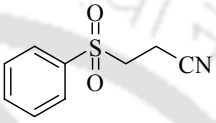
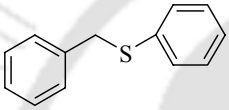
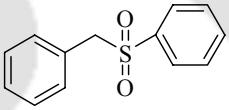
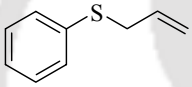
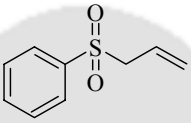
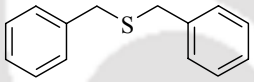
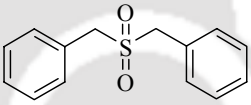
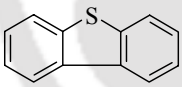
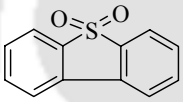
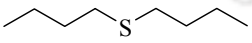
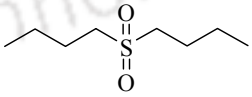
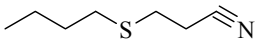
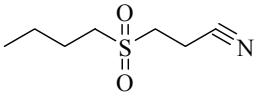
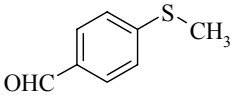
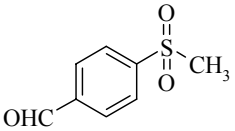
Entry	Substrates	Time (hr)	Products	Yield (%)[a]
1		3		94
2		10		90
3		17		88
4		10		86
5		8		87

Table 2.5: Oxidation of sulfides to sulfones catalyzed by $Ce(OTf)_4.xH_2O$

Entry	Substrates	Time (hr)	Products	Yield (%)[a]
6		6		90
7		17		87
8		48		45
9		11		91
10		12		96
11		12		88
12		14		61
13		40		82
14	$C_{16}H_{33}SC_6H_{13}$	15	$C_{16}H_{33}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}C_6H_{13}$	80
15	$C_{12}H_{25}SC_6H_{13}$	11	$C_{12}H_{25}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}C_6H_{13}$	84
16		2.5		84
17		5		92
18		32		57

(a) The yields are isolated yield. The compounds are characterized by GC-MS, ^{1}H NMR, ^{13}C NMR and IR spectroscopy and by comparison with the literature.

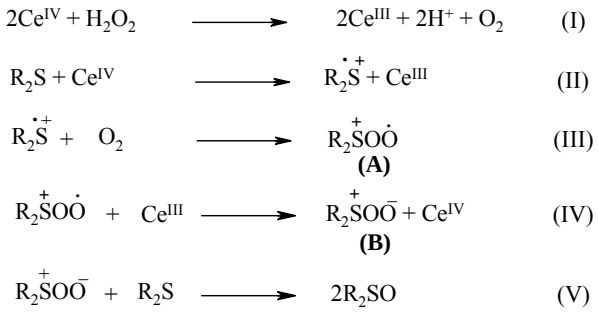
In these reaction conditions functional groups such as esters, hydroxyls and aldehyde remain intact. This was confirmed by spectroscopic methods. The IR spectrum of the product 4-(Phenylsulfonyl)butylacetate (entry 4) showed sharp peaks at 1141 and 1725 cm^{-1}corresponding to (SO_2) and carbonyl (C=O) groups respectively. ^1H NMR spectrum displayed a multiplet at δ 1.67 - 1.80 for four methylene protons, a sharp singlet at δ 2.00 for the acetate group and multiplets at δ 7.52 - 7.66 corresponding to the aromatic protons. ^{13}C NMR showed a peak at δ 171.1, which can be assigned to carbonyl carbon of the acetate group. Hence it was confirmed from above spectral values that the acetate group remained intact along with the sulfone formation.

The IR spectrum of 2-(butylsulfonyl)ethanol (entry 6) showed a broad peak at 3472 cm^{-1} and a sharp peak at 1124 cm^{-1} indicating the presence of (OH) and (SO_2) groups respectively. The ^1H NMR spectrum displayed a broad singlet at δ 3.08 could be assigned to O-H protons. The mass spectrum EIMS (m/z) showed a peak at (M^++1) 167 for the expected product.

The IR spectrum of the product 4-(methylsulfonyl)benzaldehyde (entry 18) showed sharp peaks at 1152 and 1698 cm^{-1} corresponding to the (SO_2) and carbonyl (C=O) groups respectively. The ^1H NMR spectrum displayed a singlet at δ 10.0 indicating the presence of aldehyde proton. A singlet appeared at δ 2.96 corresponding to the protons of the methyl group and two doublets at δ 7.97 and 8.09 were assigned for the aromatic protons of A_2B_2 pattern. Thus from above spectral values the presence of aldehyde can be confirmed along with the sulfone formation.

The advantage of this method is that sulfides having irrespective of electron-withdrawing or electron-donating substituents give sulfoxides and sulfones in good to excellent yields although electron-withdrawing groups takes longer time. This is possible only if the reaction proceed via free radical as both electron-withdrawing and releasing groups stabilize a free radical.

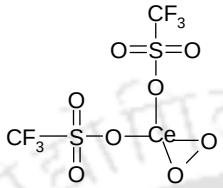
The mechanism of Ce(IV) oxidation is well established.[13-15] Cerium (IV) oxidizes hydrogen peroxide and itself gets reduced to cerium(III) (Scheme 2.3 eq I). Ce(IV) also oxidizes sulfide



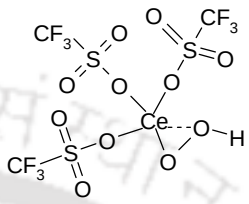
Scheme 2.3

to its radical cation (eq 2). This radical cation captures the oxygen generated by the oxidation of Ce(IV) with H_2O_2, to give oxygenated sulfur radical cation (A), which oxidizes Ce(III) to Ce(IV) species to complete the catalytic cycle. The species (B) formed in this process is known to give sulfoxide by reaction with additional sulfide.[13,16]

The formation of peroxo **C** or hydroperoxide **D** species may also be possible, which could be responsible for the rate acceleration and chemoselectivity of the reaction.



C



D

2.4 Conclusion

In conclusion, we have demonstrated the catalytic role of cerium(IV) triflate towards activation of H_2O_2 for the selective oxidation of sulfides to sulfoxides and sulfones. The reaction proceeds well under neutral and mild conditions. Sulfides with divergent functional groups were tolerated under these reaction conditions. The yields were excellent. The reagent and catalyst are commercially available and the experimental procedure is convenient, safe and easy to handle.

2.5 Experimental Section

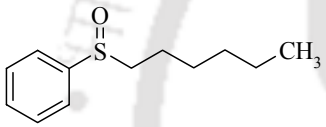
General: All the solvents and reagents employed were of reagent grade (AR grade) and used as purchased without further purification, unless otherwise stated and obtained from E. Merck, Sigma-Aldrich, SRL, CDH and Qualigens. Organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60 - 120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25mm).

Characterization of Organic Substrates

Fourier transform-infra red (IR) spectra were recorded on Nicolet Impact - 410 instrument either as neat or KBr pellets. Elemental analysis was carried out in automatic C, H and N analyzer on 2400 Perkin Elmer Series II/CNO. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (Varian AS 400; 400 MHz) or $CDCl_3$ as the internal standard for ^{13}C (100MHz). Gas chromatography-mass spectra was performed using Perkin Elmer Clarus 500 MS.

Experimental procedure for the oxidation of sulfide to sulfoxide:

In a typical experiment the mixture of methyl phenyl sulfide (124 mg, 1mmol,), $Ce(OTf)_4.xH_2O$ (5 mg, 1 mol%) and 50% (aqueous) H_2O_2 (0.16 ml, 3mmol,) in THF (2 ml) was stirred for 40 min at room temperature. The progress of the reaction was monitored by thin layer chromatography (silica gel; EtOAc: Hexane; 3:7). After completion of the reaction, solvent was evaporated and the reaction mixture was extracted with ethyl acetate (10 ml × 2) and dried over anhydrous Na_2SO_4; filtered and evaporated to afford the corresponding crude product. Finally the product was purified by column chromatography (silica gel; EtOAc: Hexane; 1:9) to give methyl phenyl sulfoxide as colourless oil in 93% yield. The product was characterized by spectroscopic methods. **IR** (Neat): 3012, 2925, 1650, 1450, 1091, 1040, 753 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.72 (s, 3 H, -SO-CH_3), 7.46 - 7.56 (m, 3 H, ArH), 7.62 - 7.64 (m, 2 H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 43.8, 123.2, 129.1, 130.8, 145.2; **EIMS (m/z)**: (M^++1) 141; **Anal. Calcd for C_7H_8OS**: C, 59.97; H, 5.75. Found: C, 59.76; H, 5.90.



(1-Hexylsulfinyl)benzene

State: Liquid

Colour: Pale yellow

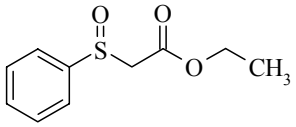
IR (Neat): 2966, 2868, 1450, 1096, 1045, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 3 H, -CH_3), 1.24 - 1.30 (m, 4 H, 2 × -CH_2-), 1.33 - 1.45 (m, 2 H, -CH_2-), 1.55 - 1.66 (m, 1 H), 1.70 - 1.80 (m, 1 H), 2.80 (t, *J* = 5.2 Hz, 2 H, -SO-CH_2-), 7.44 - 7.54 (m, 3 H, ArH), 7.58 - 7.62 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.1, 22.4, 28.3, 31.3, 57.1, 123.8, 128.9, 130.8, 143.4.

EIMS (m/z): (M^++1) 211.

Anal. Calcd for $C_{12}H_{18}OS$: C, 68.52; H, 8.63. Found: C, 68.64; H, 8.51.



Ethyl 2-(phenylsulfinyl)acetate

State: Liquid

Colour: Colourless

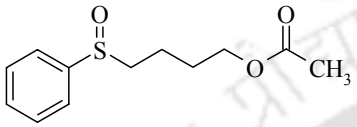
IR (Neat**)**: 2991, 2935, 1742, 1450, 1276, 1096, 1050, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 3 H, -CH_3), 3.66 (d, *J* = 13.6 Hz, 1 H), 3.85 (d, *J* = 13.6 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H, -OCH_2-), 7.51 - 7.53 (m, 3 H, ArH), 7.67 - 7.70 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 61.4, 62.0, 124.1, 129.2, 131.7, 142.6, 164.4.

EIMS (m/z): (M^++1) 213.

Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70. Found: C, 58.64; H, 5.68.



4-(Phenylsulfinyl)butyl acetate

State: Liquid

Colour: Colourless

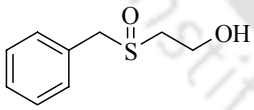
IR (Neat**)**: 2966, 1737, 1455, 1250, 1091, 1040, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 - 1.81 (m, 4 H, 2 × -CH_2-), 2.00 (s, 3 H, -$CO\underline{CH_3}$), 2.80 (t, *J* = 6.4 Hz, 2 H, -$SOCH_2$-), 4.00 (t, *J* = 6 Hz, 2 H, -OCH_2-), 7.45 - 7.50 (m, 3 H, ArH), 7.56 - 7.58 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 21.1, 27.9, 56.6, 63.6, 124.0, 129.2, 131.1, 143.4, 170.9.

EIMS (m/z): (M^++1) 241.

Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 60.12; H, 6.64.



2-(Benzylsulfinyl)ethanol

State: Liquid

Colour: Yellow

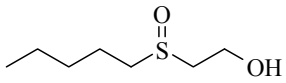
IR (Neat**)**: 3498, 2930, 1301, 1127, 1081, 1025, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (m, 2 H, -$SOCH_2$-), 3.50 (bs, 1 H, -OH), 4.10 - 4.16 (m, 4 H, 2 × -CH_2-), 7.36 - 7.41 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 56.7, 58.6, 128.8, 129.3, 129.6, 130.4.

EIMS (m/z): (M^++1) 185.

Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.83; H, 6.72.



2-(Pentylsulfinyl)ethanol

State: Liquid

Colour: Colourless

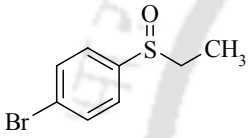
IR (Neat**)**: 3426, 2960, 2935, 2863, 1271, 1127, 1066, 1050, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 6.8 Hz, 3 H, $-CH_3$), 1.25 - 1.46 (m, 4 H, 2 × $-CH_2-$), 1.82 - 1.90 (m, 2 H, $-CH_2-$), 2.70 (bs, 1 H, -OH), 3.05 - 3.10, (t, *J* = 6.8 Hz, 2 H, $-CH_2-$), 3.18 -3.21 (t, *J* = 5.6 Hz, 2 H, $-CH_2-$), 4.10 - 4.13 (t, *J* = 4.4 Hz, 2 H, $-CH_2-$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21.8, 22.5, 30.8, 54.8, 55.0, 56.6.

EIMS (m/z): (M^++1) 165.

Anal. Calcd for $C_7H_{16}O_2S$: C, 51.18; H, 9.82 Found: C, 51.37; H, 9.78.



1-Bromo-4-(ethylsulfinyl)benzene

State: Liquid

Color: Yellow

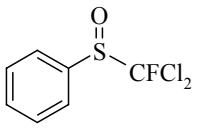
IR (Neat**)**: 2986, 2879, 1470, 1388, 1086, 1045, 830 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.6 Hz, 3 H, $-CH_3$), 2.73 - 2.80 (m, 1 H), 2.87 - 2.94 (m, 1 H), 7.47 (d, *J* = 8.4 Hz, 2 H, ArH), 7.64 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 6.0, 50.2, 125.3, 125.8, 132.3, 142.0.

EIMS (m/z): (M^++1) 234.

Anal. Calcd for C_8H_9BrOS: C, 41.22; H, 3.89. Found: C, 41.55; H, 4.12.



1-(Dichlorofluoromethylsulfinyl)benzene

State: liquid

Colour: colourless

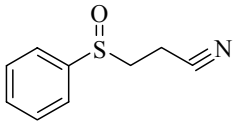
IR (Neat**)**: 3068, 1122, 1076, 866, 805, 748, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 - 7.66 (m, 3 H, ArH), 7.82 - 7.84 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 127.1 (d, *J* = 339.4 Hz), 127.1, 129.1, 133.7, 137.7.

^{19}F NMR (376 Hz, $CDCl_3$ - C_6F_6): δ 98.61 (s, 1 F, -$CFCl_2$-).

EIMS (m/z): (M^++1) 227.



3-(Phenylsulfinyl)propanenitrile

State: Solid

M. P : 57 - 59 ^oC

Color: Colourless

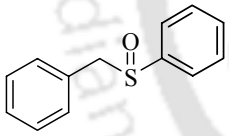
IR (Neat**)**: 2976, 2847, 2250, 1455, 1050, 1025, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.48 - 2.56 (m, 1 H), 2.83 - 3.00 (m, 2 H), 3.20 - 3.27 (m, 1 H), 7.56 (m, 3 H, ArH), 7.60 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 9.8, 50.3, 117.3, 123.9, 129.6, 131.7, 141.0.

EIMS (m/z): (M^++1) 180.

Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.58; H, 5.24; N, 7.90.



1-(Benzylsulfinyl)benzene

State: Solid

M. P : 124 - 126 ^oC

Color: colourless

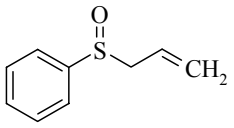
IR (Neat**)**: 3032, 2971, 1455, 1317, 1163, 1096, 1045, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (d, *J* = 12.8 Hz, 1 H), 4.06 (d, *J* = 12.8, 1 H), 6.95 (d, *J* = 6.8 Hz, 2 H, ArH), 7.20 - 7.27 (m, 3 H, ArH), 7.34 - 7.45 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 63.7, 124.4, 128.2, 128.4, 128.8, 129.1, 130.3, 131.1, 142.7.

EIMS (m/z): (M^++1) 217.

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59. Found: C, 72.57; H, 5.22.



1-(Allylsulfinyl)benzene

State: liquid

Color: Colourless

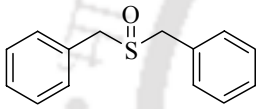
IR (Neat**)**: 3068, 2925, 1644, 1455, 1322, 1148, 1086, 1004, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (d, *J* = 7.2 Hz, 2 H), 5.14 (d, *J* = 17.2 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 5.72 - 5.82 (m, 1 H), 7.52 - 7.56 (m, 2 H, ArH), 7.62 - 7.65 (m, 1 H, ArH), 7.84 -7.87 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 60.9, 124.6, 124.7, 128.4, 129.0, 133.7, 138.2.

EIMS (m/z): (M^++1) 167.

Anal. Calcd for $C_9H_{10}OS$: C, 65.03; H, 6.06. Found: C, 65.14; H, 6.16.



1-((Benzylsulfinyl)methyl)benzene

State: Solid

M. P : 135 - 137 ^{o}C

Colour: Colourless

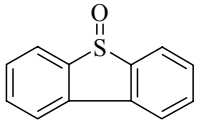
IR (Neat**)**: 3032, 1465, 1224, 1086, 1040, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (d, *J* = 10.4 Hz, 4 H), 7.27 - 7.30 (m, 5 H, ArH), 7.34 - 7.39 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 57.4, 128.4, 128.9, 130.1, 130.9.

EIMS (m/z): (M^++1) 231.

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 73.38; H, 6.24.



9-Sulfinyl fluorine

State: Solid

M. P : 186 - 188 ^{o}C

Colour: Colourless

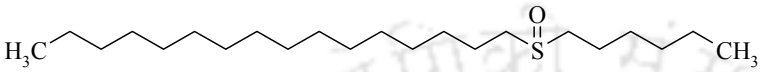
IR (Neat**)**: 2935, 2863, 1650, 1465, 1224, 10876, 1025, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 - 7.48 (m, 2 H, ArH), 7.53 - 7.57 (m, 2 H, ArH), 7.76 (d, *J* = 7.6 Hz, 2 H, ArH), 7.94 (d, *J* = 7.6 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 122.0, 127.5, 129.6, 132.6, 137.1, 144.9.

EIMS (m/z): (M^++1) 201.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.03. Found: C, 80.13; H, 4.18.



1-(Hexylsulfinyl)hexadecane

State: Powder

M. P : 67 - 68 ^oC

Colour: Colourless

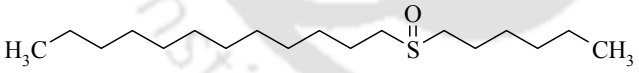
IR (Neat**)**: 2919, 2848, 1470, 1096, 1025, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 - 0.82 (m, 6 H, 2 × -CH_3), 1.18 - 1.25 (m, 28 H, 14 × -CH_2-), 1.35 - 1.38 (m, 4 H, 2 × -CH_2-), 1.66 - 1.70 (m, 4 H, 2 × -CH_2-), 2.51 - 2.65 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.4, 22.7, 22.8, 22.9, 28.8, 29.1, 29.5, 29.6 (2c), 29.7, 29.8 (2C), 29.90 (3c), 29.92 (3C), 31.6, 32.2, 52.6.

EIMS (m/z): (M^++1) 359.

Anal. Calcd for $C_{22}H_{46}OS$: C, 73.67; H, 12.93. Found: C, 73.78; H, 12.80.



1-(Hexylsulfinyl)dodecane

State: Powder

M. P: 75 - 76 ^oC

Colour: Colourless

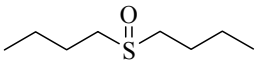
IR (Neat**)**: 2960, 2858, 1475, 1015, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 - 0.91 (m, 6 H, 2 × -CH_3), 1.26 - 1.34 (m, 20 H, 10 × -CH_2-), 1.40 - 1.50 (m, 4 H, 2 × -CH_2-), 1.70 - 1.80 (m, 4 H, 2 × -CH_2-), 2.60 - 2.71 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.3, 22.6, 22.7, 22.8, 22.9, 28.8, 29.1, 29.4, 29.5, 29.6, 29.7, 29.8 (2C), 31.6, 32.1, 52.6 (2C).

EIMS (m/z): (M^++1) 303.

Anal. Calcd for $C_{18}H_{38}OS$: C, 71.46; H, 12.66. Found: C, 71.35; H, 12.83.



1-(Butylsulfinyl)butane

State: Liquid

Colour: Yellow

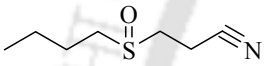
IR (Neat**)**: 2966, 2879, 1470, 1081, 1035, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.2 Hz, 6 H, 2 × -CH_3), 1.45- 1.55 (m, 4 H, 2 ×-CH_2-), 1.71 - 1.80 (m, 4 H, 2 × -CH_2-), 2.60 - 2.72 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.1, 24.7, 52.1.

EIMS (m/z): (M^++1) 163.

Anal. Calcd for $C_8H_{18}OS$: C, 59.21; H, 11.18. Found: C, 59.52; H, 11.04.



3-(Butylsulfinyl)propanenitrile

State: Liquid

Colour: Colourless

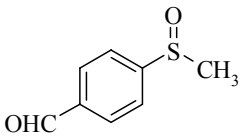
IR (KBr**)**: 2971, 2884, 1650, 1429, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.2 Hz, 3 H, -CH_3), 1.44 - 1.52 (m, 2 H, -CH_2-), 1.70 -1.77 (m, 2 H, -CH_2-), 2.66 - 3.00 (m, 6 H, 3 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.3, 13.8, 22.4, 24.7, 46.4, 52.2, 117.6.

EIMS (m/z): (M^++1) 160.

Anal. Calcd for $C_7H_{13}NOS$: C, 52.80; H, 8.23; N, 7.99. Found: C, 52.93; H, 8.42; N, 8.15.



4-(Methylsulfinyl)benzaldehyde

State: Solid

M. P : 85 - 86 ^oC

Color: Colourless

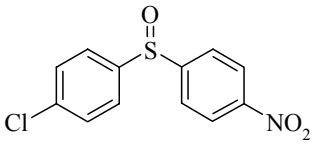
IR (Neat**)**: 2930, 2858, 1711, 1424, 1209, 1096, 1040, 835, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.80 (s, 3 H, $-CH_3$), 7.81 (d, *J* = 8.0 Hz, 2 H, ArH), 8.00 (d, *J* = 8.4 Hz, 2 H, ArH), 10.10 (s, 1 H, -CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ 43.9, 124.2, 130.4, 138.1, 152.4, 191.0.

EIMS (m/z): (M^++1) 169.

Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79. Found: C, 57.32; H, 4.57.



4-chlorophenyl-4-nitrophenyl sulfoxide

State: Solid

M. P : 123 - 125 °C

Colour: Yellow

IR (Neat): 3038, 2914, 1521, 1465, 1342, 1086, 1061, 1004, 820, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2 H, ArH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.79 (d, *J* = 8.4 Hz, 2 H, ArH), 8.29 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 124.8, 125.5, 126.4, 130.4, 138.6, 143.1, 149.6, 152.7.

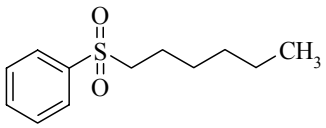
EIMS (m/z): (M^++1) 283.

Anal. Calcd for $C_{12}H_8ClNO_3S$: C, 51.16; H, 2.86; N, 4.97. Found: C, 51.34; H, 2.52; N, 5.12.

Experimental procedure for the oxidation of sulfide to sulfone

A mixture of methyl phenyl sulfide (124 mg, 1mmol), $Ce(OTf)_4.xH_2O$ (64 mg, 10 mol%) and 50% (aqueous) H_2O_2 (0.68 ml, 10 mmol) in methanol (2 ml) was stirred for 3 hours at room temperature. The reaction progress was monitored with thin layer chromatography (silica gel; EtOAc: Hexane; 3:7), after completion of the reaction, solvent was evaporated and the reaction mixture was extracted with ethyl acetate (10 ml × 3) and dried over anhydrous Na_2SO_4, filtered and evaporated to afford the corresponding crude product. Further the product was purified by column chromatography over (silica gel; EtOAc: Hexane; 1: 9) to give 1-(Methylsulfonyl) benzene as a colorless solid **M. P**: 99 - 100°C in 94% yield. The product obtained was characterized by spectroscopic methods.

IR (Neat): 3021, 2923, 1632, 1410, 1305, 1152, 1086, 957, 740 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.0 (s, 3H, $-SO_2-CH_3$), 7.52 - 7.61(m, 3H, ArH), 7.88 (m, 2H, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 44.5, 127.4, 129.4, 133.8, 140.6; **EIMS (m/z)** : (M^+) 156, 141, 94, 77; **Anal. Calcd for $C_7H_8O_2S$**: C, 53.83; H, 5.16. Found: C, 53.66; H, 5.35.



1-(Hexylsulfonyl)benzene

State: Liquid

Colour: Yellow

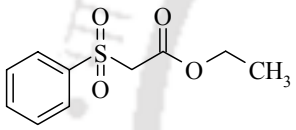
IR (Neat): 2934, 2857, 1445, 1303, 1146, 1083, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 6.0 Hz, 3 H, $-CH_3$), 1.14 - 1.20 (m, 4 H, 2 × $-CH_2-$), 1.24 - 1.30 (m, 2 H, $-CH_2-$), 1.57 - 1.65 (m, 2 H), 3.00 (dd, *J* = 7.6 and 5.6 Hz, 2 H, $-SO_2-CH_2-$), 7.46 - 7.50 (m, 2 H, ArH), 7.54 - 7.60 (m, 1 H, ArH), 7.80 - 7.83 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.3, 22.6, 28.0, 31.1, 56.3, 128.0, 129.3, 133.7, 139.2.

EIMS (m/z): (M^+) 226, 143, 91, 77.

Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 68.34; H, 8.38.



Ethyl 2-(Phenylsulfonyl)acetate

State: Solid

M. P : 41- 42 ^oC

Colour: Colourless

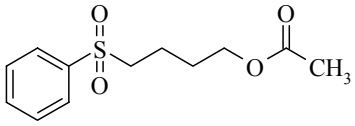
IR (Neat): 2989, 2939, 1733, 1445, 1322, 1270, 1149, 1080, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 6.8 Hz, 3 H, $-CH_3$), 4.10 - 4.15 (m, 4 H, $-OCH_2-$, $-SO_2-CH_2-$), 7.55 - 7.68 (m, 3 H, ArH), 7.90 - 7.95 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 61.2, 62.5, 128.7, 129.4, 134.5, 138.8, 162.5.

EIMS (m/z): (M^++1) 229, 164, 141, 91, 77.

Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30. Found: C, 52.80; H, 5.16.



4-(Phenylsulfonyl)butyl acetate

State: Liquid

Colour: Colourless

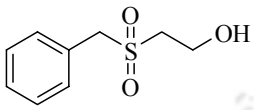
IR (Neat): 2956, 1725, 1445, 1256, 1141, 1083, 751cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 - 1.80 (m, 4 H, 2 × $-CH_2-$), 2.00 (s, 3 H, $-COCH_3$), 3.08 (t, *J* = 7.6 Hz, 2 H, $-SOCH_2-$), 4.0 (t, *J* = 6.0 Hz, 2 H, $-OCH_2-$), 7.52 - 7.57 (m, 2 H, ArH), 7.61 - 7.66 (m, 1 H, ArH), 7.86 - 7.90 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 21.0, 27.4, 55.9, 63.4, 128.2, 129.5, 134.0, 139.1, 171.1.

EIMS (m/z): (M^+) 256, 213, 115, 77.

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29. Found: C, 56.54; H, 6.48.



2-(Benzylsulfonyl) ethanol

State: Solid

M. P : 68 - 71°C

Colour: Colourless

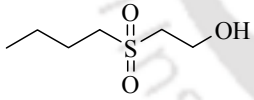
IR (Neat): 3472, 2928, 1393, 1278, 1116, 1028, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.6 (brs, 1 H, -OH), 3.10 (t, *J* = 4.8 Hz, 2 H, $-SO_2\underline{CH_2}CH_2-$), 4.02 (t, *J* = 5.2 Hz, 2 H, $-\underline{CH_2}OH-$), 4.35 (s, 2 H, Ph-$\underline{CH_2}-$), 7.40 - 7.45 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 53.2, 56.6, 61.2, 128.0, 129.2, 129.3, 131.1.

EIMS (m/z): (M^+) 200, 108, 91, 65.

Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04. Found: C, 53.25; H, 6.33.



2-(Butylsulfonyl)ethanol

State: Liquid

Colour: Yellow

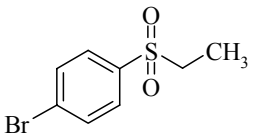
IR (Neat): 3472, 2967, 2873, 1643, 1270, 1124, 1061, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (*t*, *J* = 7.2 Hz, 3 H, $-CH_3$), 1.35 - 1.45 (m, 2 H, $-CH_2-$), 1.70 -1.78 (m, 2 H, $-CH_2-$), 3.05 (t, *J* = 8.4 Hz, 2 H, $-CH_2-$), 3.08 (bs, 1 H, -OH), 3.14 (t, *J* = 5.2 Hz, 2 H, $-CH_2-$), 4.00 (*t*, *J* = 5.2 Hz, 2 H, $-CH_2-$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 21.7, 23.7, 54.4, 55.0, 56.2.

EIMS (m/z): (M^++1) 167, 119, 105, 91.

Anal. Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49 Found: C, 43.14; H, 8.67.



1-Bromo-4-(ethylsulfonyl)benzene

State: Solid

M. P : 56 - 57^{o}C

Color: Colourless

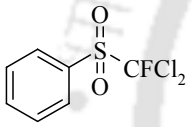
IR (Neat): 3093, 2939, 1574, 1388, 1146, 1083, 823 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.6 Hz, 3 H, -CH_3), 3.14 (q, *J* = 7.6 Hz, 2 H), 7.74 (d, *J* = 8.4 Hz, 2 H, ArH), 7.78 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 7.5, 50.6, 129.0, 130.0, 132.6, 137.5.

EIMS (m/z): (M^+) 249, 219, 172, 155, 141, 75.

Anal. Calcd for $C_8H_9BrO_2S$: C, 38.57; H, 3.64. Found: C, 38.15; H, 3.87.



1-(Dichlorofluoromethylsulfonyl)benzene

State: Solid

M. P : 53 - 54 ^{o}C

Colour: Colourless

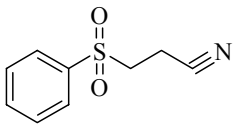
IR (Neat): 3065, 1358, 1166, 1089, 858, 751, 713, 683 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (t, *J* = 8 Hz, 2 H, ArH), 7.80 (t, *J* = 7.6 Hz, 1 H, ArH), 8.04 (d, *J* = 8 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 121.9 (d, *J* = 335.0 Hz), 129.7, 130.4, 132.0, 136.4.

^{19} F NMR (376 Hz, $CDCl_3$ - C_6F_6): δ 99.33 (s, 1 F, -$CFCl_2$-).

EIMS (m/z): (M^+) 242, 141, 125, 77.



3-(Phenylsulfonyl)propanenitrile

State: Solid

M. P : 96 - 97 ^{o}C

Colour: Colorless

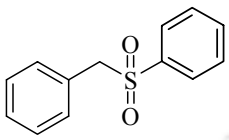
IR (Neat): 3060, 2956, 2252, 1445, 1311, 1155, 1083, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (t, *J* = 7.2 Hz, 2 H), 3.36 (t, *J* = 7.2 Hz, 2 H), 7.55 - 7.60 (m, 3 H, ArH), 7.88 - 7.90 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 51.1, 116.3, 128.3, 130.0, 134.8, 137.6.

EIMS (m/z) : (M^+) 195, 141, 77.

Anal. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 6.63. Found: C, 55.67; H, 4.32, N, 6.94.



1-(Benzylsulfonyl)benzene

State: Solid

M. P : 148 ^oC

Color: Colourless

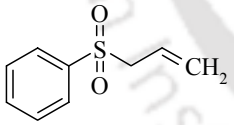
IR (Neat): 3065, 2923, 1445, 1308, 1141, 1045, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (s, 2 H), 7.08 (d, *J* = 7.2 Hz, 2 H, ArH), 7.24 - 7.34 (m, 3 H, ArH), 7.45 (t, *J* = 7.2 Hz, 2 H, ArH), 7.58 - 7.64 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 63.1, 128.3, 128.7, 128.8, 128.9, 129.0, 131.0, 133.9, 138.1.

EIMS (m/z): (M^+) 232, 141, 125, 91, 77.

Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.53; H, 5.10.



1-(Allylsulfonyl)benzene

State: Liquid

Colour: Colorless

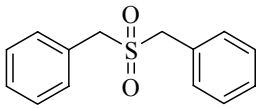
IR (Neat): 2961, 2923, 1637, 1443, 1305, 1144, 1083, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (d, *J* = 7.2 Hz, 2 H), 5.07 (d, *J* = 16.0 Hz, 1 H), 5.23 (d, *J* = 10.4 Hz, 1 H), 5.62 - 5.74 (m, 1 H), 7.42 - 7.48 (m, 2 H, ArH), 7.53 - 7.58 (m, 1 H, ArH), 7.78 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 60.7, 124.5, 124.7, 128.4, 129.0, 133.8, 138.2.

EIMS (m/z) : (M^+) 182, 141, 117, 77.

Anal. Calcd for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.56; H, 5.87.



1-((Benzylsulfonyl)methyl)benzene

State: Solid

M. P : 152 ^{o}C

Color: Colourless

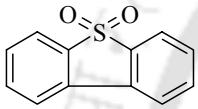
IR (Neat): 2923, 1495, 1297, 1111, 691cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.1 (s, 4 H, -$(CH_2)_2$-Ph), 7.38 (s, 10 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 58.2, 127.7, 129.2, 129.3, 131.1.

EIMS (m/z) : (M^+) 246, 182, 91.

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73. Found: C, 68.63; H, 6.02.



9-Sulfonyl fluorine

State: Solid

M. P : 246 ^{o}C

Color: Colourless

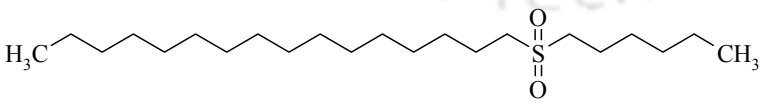
IR (Neat): 2956, 2868, 1643, 1432, 1294, 1124, 1061, 751cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, *J* = 7.6 Hz, 1 H, ArH), 7.64 (t, *J* = 7.6 Hz, 1 H, ArH), 7.79 (d, *J* = 7.6 Hz, 1 H, ArH), 7.82 (d, *J* = 7.6 Hz, 1 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 121.6, 121.9, 130.3, 131.4, 133.9, 137.4.

EIMS (m/z): (M^+) 216, 200, 184, 171, 139.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.36; H, 3.80.



1-(Hexylsulfonyl)hexadecane

State: Powder

M. P : 96 - 97 ^{o}C

Colour: Colourless

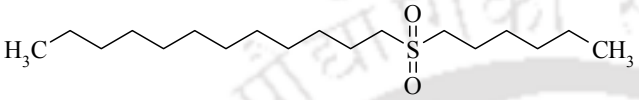
IR (Neat): 2923, 2851, 1451, 1275, 1122, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85- 0.90 (m, 6 H, 2 × -CH_3), 1.20- 1.31 (m, 28 H, 14 × -CH_2-), 1.37- 1.45 (m, 4 H, 2 × -CH_2-), 1.61- 1.84 (m, 4 H, 2 × -CH_2-), 2.90- 2.94 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.3, 22.2 (2C), 22.5, 23.0, 28.4, 28.7, 29.3, 29.5, 29.6, 29.7, 29.8 (3C), 29.9 (3C), 31.4, 32.2, 53.0 (2C).

EIMS (m/z): (M^+) 374, 291, 151, 85, 57, 43.

Anal. Calcd for $C_{22}H_{46}O_2S$: C, 70.53; H, 12.38. Found: C, 70.68; H, 12.20.



1-(Hexylsulfonyl)dodecane

State: Powder

M. P : 101 - 103 ^oC

Colour: Colourless

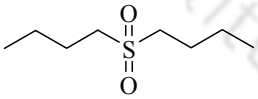
IR (Neat): 2917, 2851, 1467, 1264, 1135, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 - 0.88 (m, 6 H, 2 × -CH_3), 1.22 - 1.30 (m, 20 H, 10 × -CH_2-), 1.35 - 1.45 (m, 4 H, 2 × -CH_2-), 1.75 - 1.84 (m, 4 H, 2 × -CH_2-), 2.89 - 2.93 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 22.1, 22.2, 22.5, 23.0, 28.4, 28.7, 29.2, 29.4, 29.5, 29.7, 29.8 (2C), 31.4, 32.1, 52.9 (2C).

EIMS (m/z): (M^++1) 319, 235, 151, 85, 71, 57, 43.

Anal. Calcd for $C_{18}H_{38}O_2S$: C, 67.87; H, 12.02. Found: C, 67.90; H, 12.12.



1-(Butylsulfonyl) butane

State: Liquid

Color: Colourless

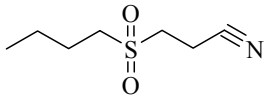
IR (Neat): 2956, 2868, 1473, 1311, 1127, 1094, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 6 H, 2 × -CH_3), 1.34 - 1.44 (m, 4 H, 2 × -CH_2-), 1.68 - 1.77 (m, 4 H, 2 × -CH_2-), 2.85 - 2.90 (m, 4 H, 2 × -CH_2-).

^{13}C NMR (100 MHz, CDCl3): δ 13.6, 21.7, 23.9, 52.4.

EIMS (m/z): (M^++1) 179, 149, 123, 81, 57.

Anal. Calcd for $C_8H_{18}O_2S$: C, 53.89; H, 10.18. Found: C, 54.04; H, 10.12.



3-(Butylsulfonyl)propanenitrile

State: Liquid

Colour: Colourless

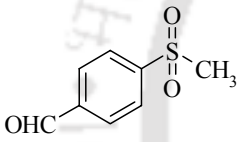
IR (Neat): 3065, 2961, 1626, 1445, 1146, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, *J* = 6.8 Hz, 3 H, $-CH_3$), 1.33 - 1.40 (m, 2 H, $-CH_2-$), 1.67 -1.70 (m, 2 H, $-CH_2-$), 2.80 (t, *J* = 6.8 Hz, 2 H, $-CH_2-$), 2.96 (t, *J* = 6.8 Hz, 2 H, $-CH_2-$), 3.18 (t, *J* = 6.8 Hz, 2 H, $-CH_2-$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 13.4, 21.5, 23.6, 47.4, 53.1, 117.1.

EIMS (m/z): (M^+) 175, 155, 141, 93, 75, 50.

Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48; N, 7.99. Found: C, 47.67; H, 7.87; N, 8.15.



4-(methylsulfonyl)benzaldehyde

State: Solid

M. P : 156 - 158 ^oC

Color: Colourless

IR (Neat): 3000, 2923, 1698, 1426, 1294, 1152, 963, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$ - DMSO-d_6): δ 2.96 (s, 3 H, $-CH_3$), 7.97 (d, *J* = 8.0 Hz, 2 H, ArH), 8.09 (d, *J* = 8.0 Hz, 2 H, ArH), 10.0 (s, 1 H, -CHO).

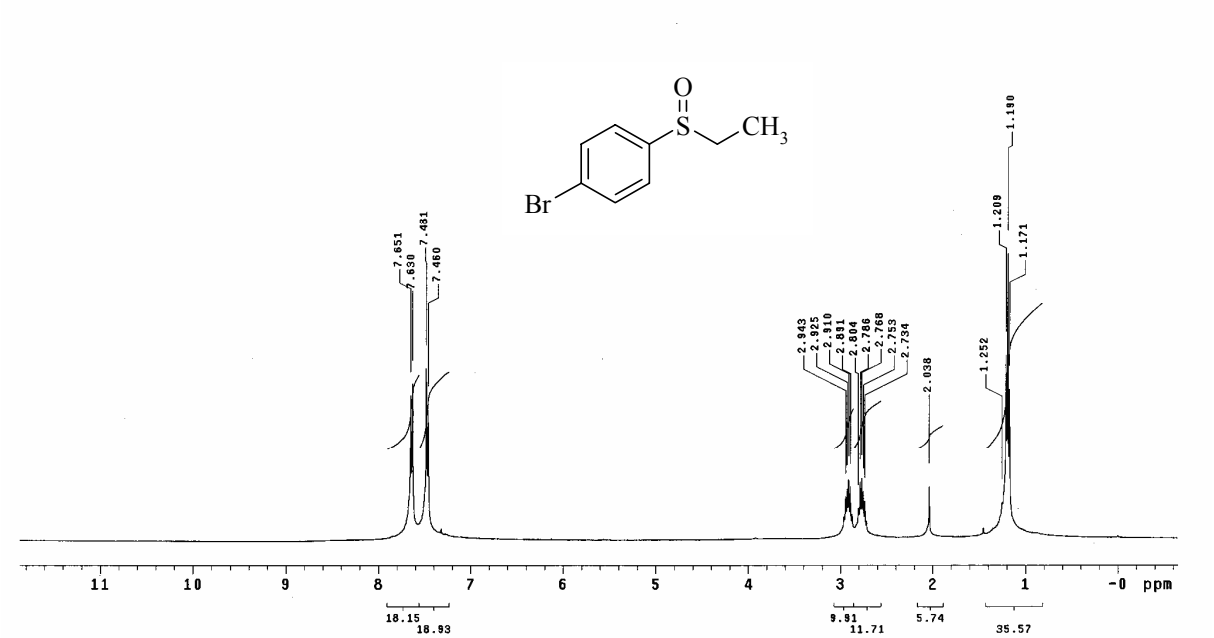
^{13}C NMR (100 MHz, $CDCl_3$-DMSO-d_6): δ 44.2, 127.2, 128.1, 130.3, 130.6, 190.8.

EIMS (m/z) : (M^++1) 185, 169, 122, 105, 77.

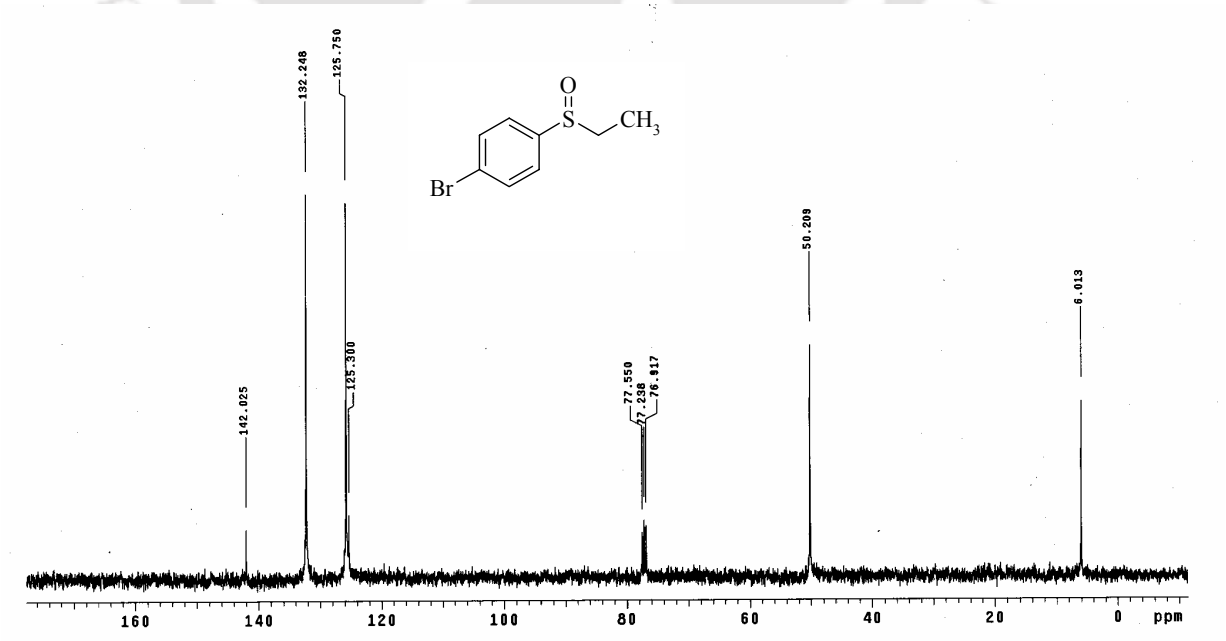
Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.35; H, 4.40.

2.6 Selected Spectra of Sulfoxides

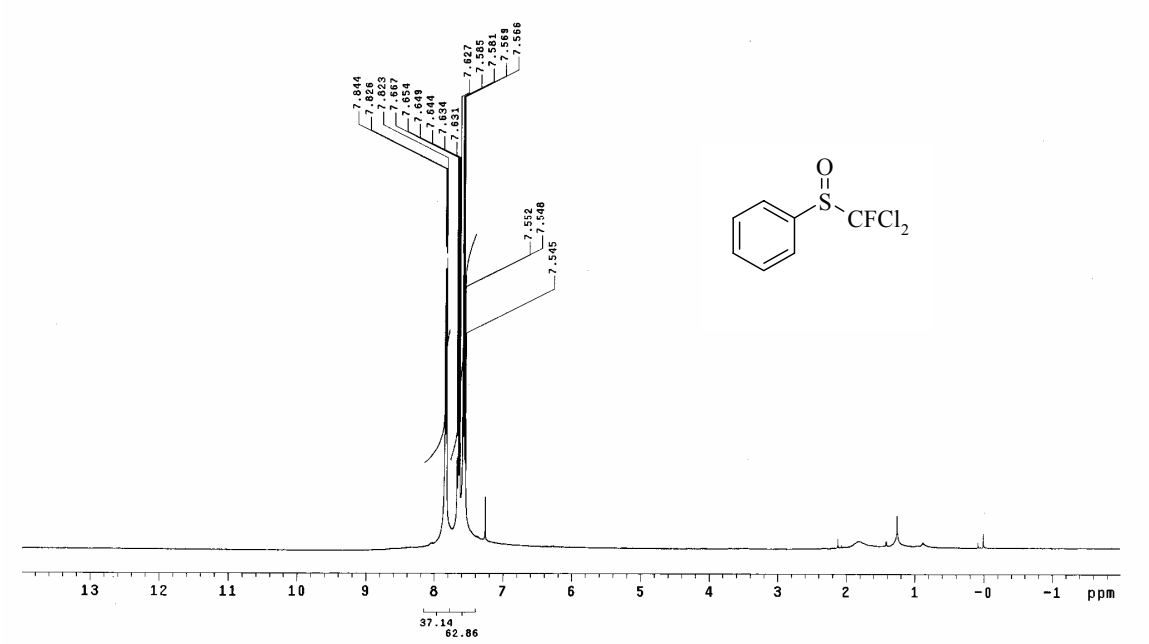
^{1}H NMR (400MHz, $CDCl_3$): 1-Bromo-4-(ethylsulfinyl)benzene



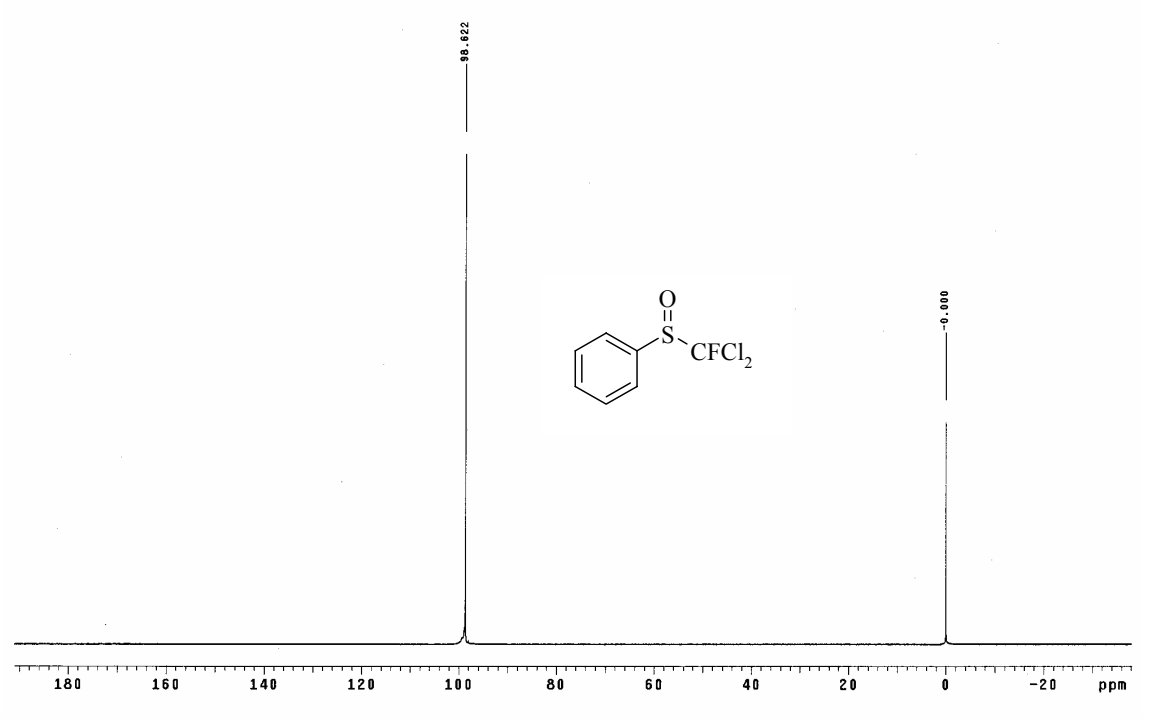
^{13}C NMR (100MHz, $CDCl_3$): 1-Bromo-4-(ethylsulfinyl)benzene



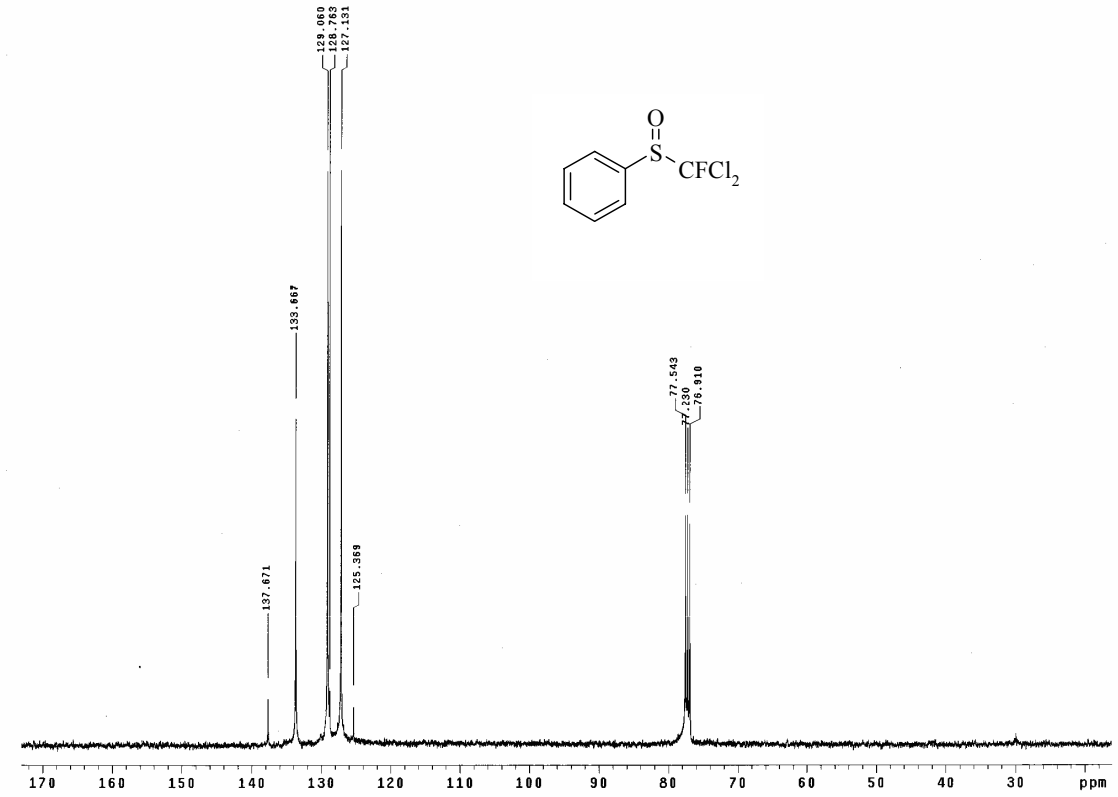
^{1}H NMR (400MHz, $CDCl_3$): 1-(Dichlorofluoromethylsulfinyl)benzene



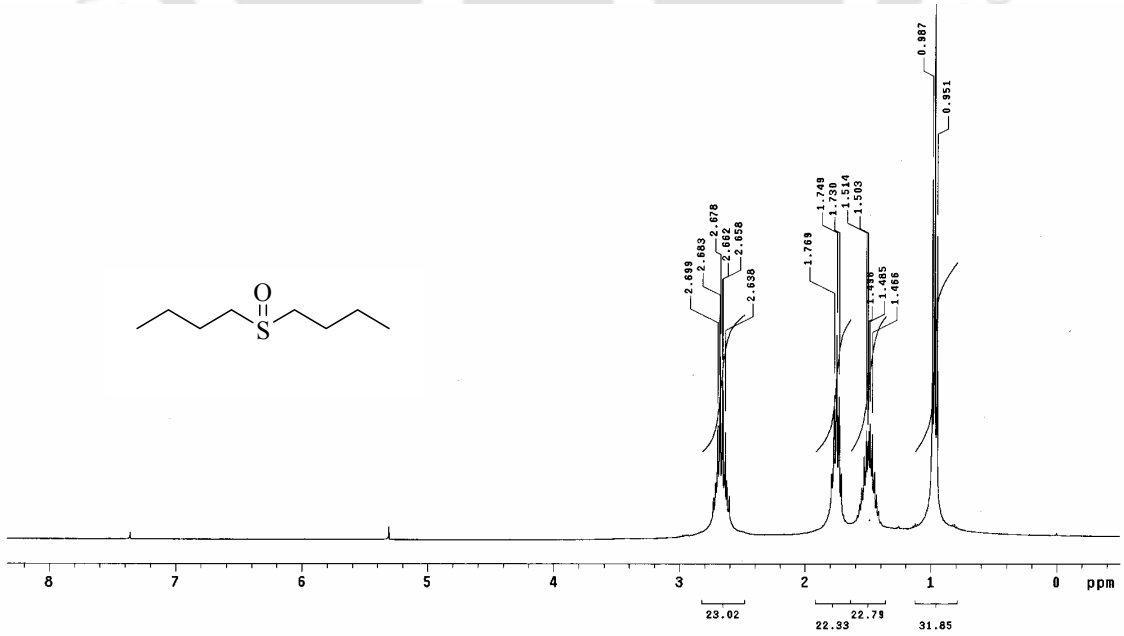
^{19}F NMR (376 MHz, $CDCl_3$- C_6F_6): 1-(Dichlorofluoromethylsulfinyl)benzene



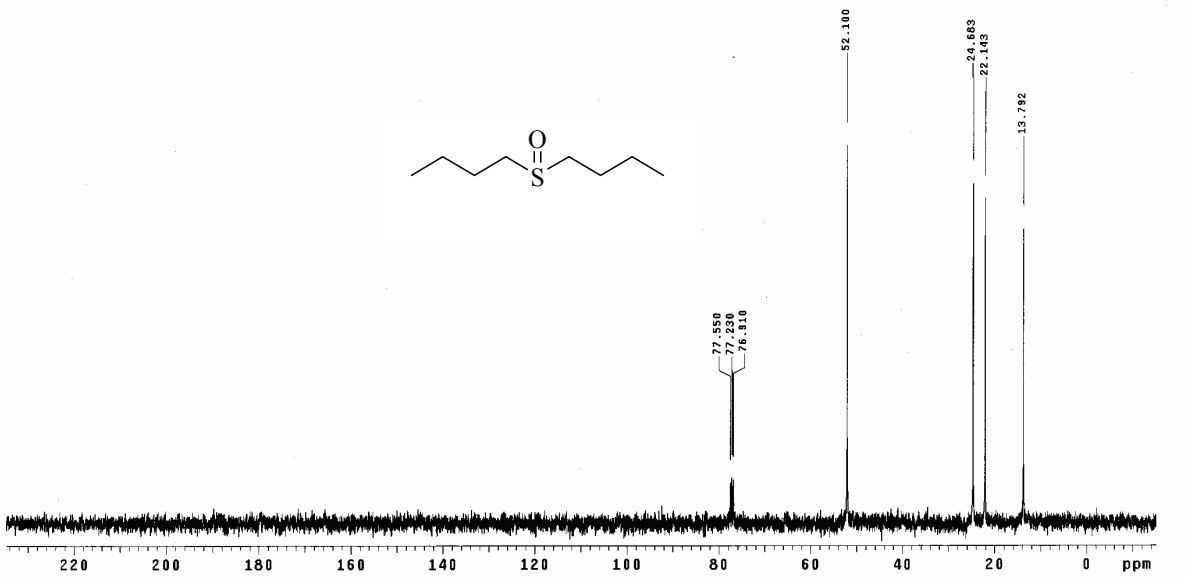
^{13}C NMR (100MHz, $CDCl_3$): 1-(Dichlorofluoromethylsulfinyl)benzene



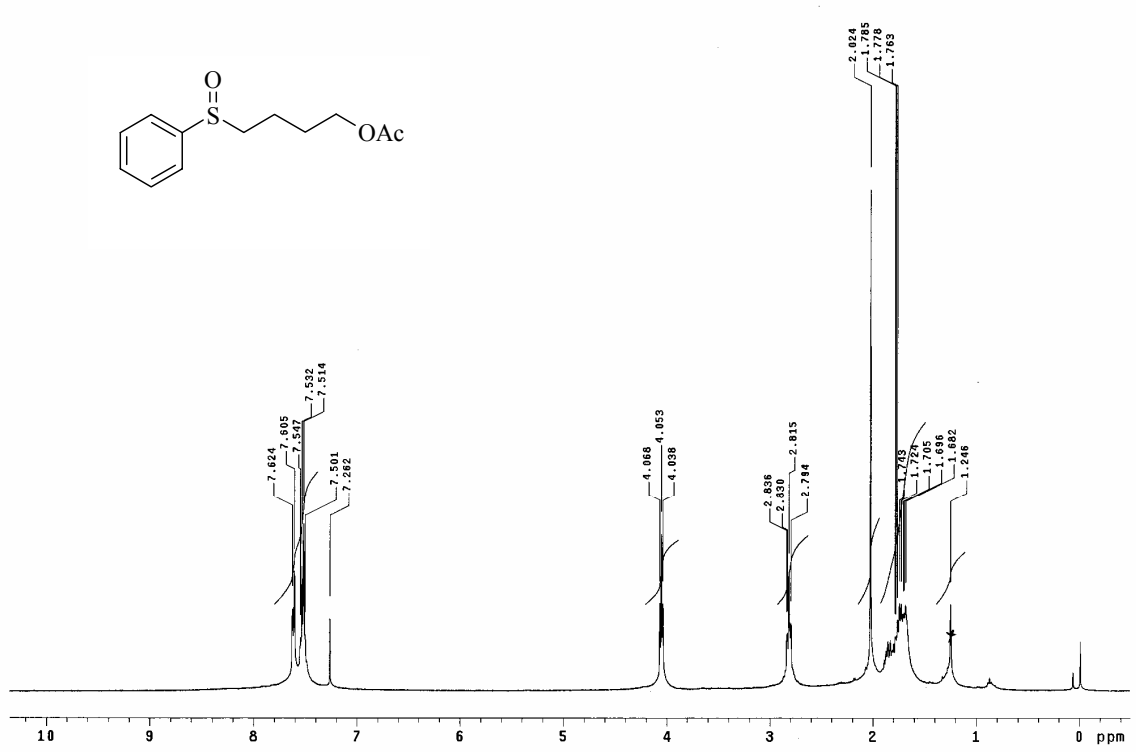
^{1}H NMR (400MHz, $CDCl_3$): 1-(Butylsulfinyl)butane



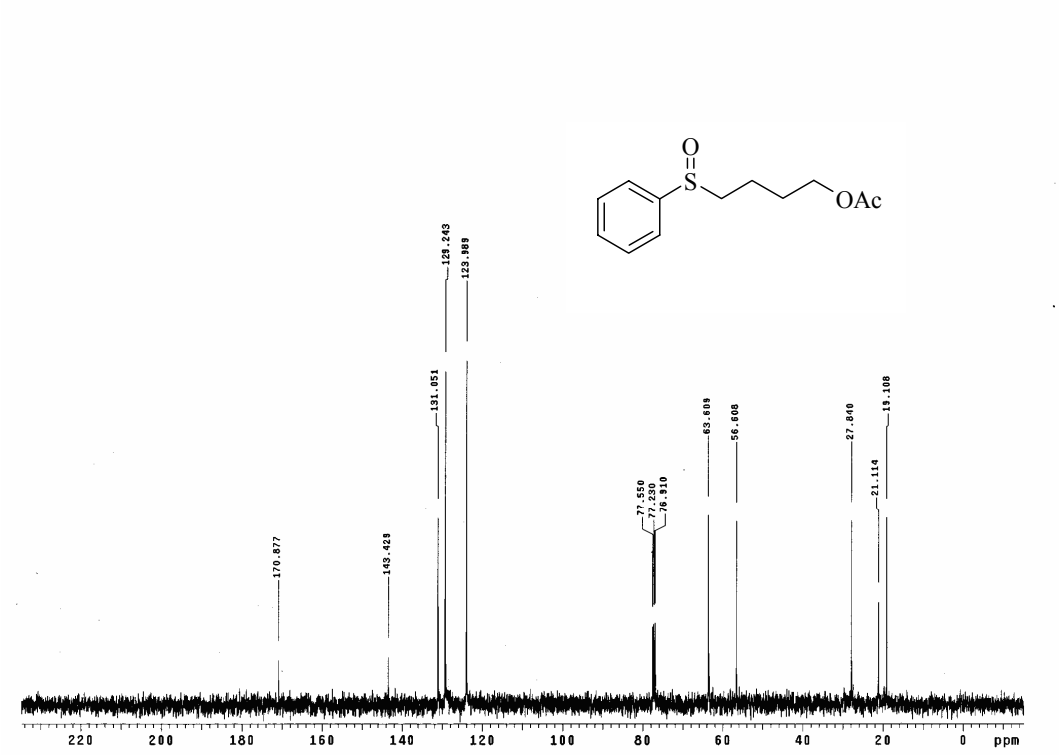
^{13}C NMR (100MHz, $CDCl_3$): 1-(Butylsulfinyl)butane



^{1}H NMR (400MHz, $CDCl_3$): 4-(Phenylsulfinyl)butyl acetate

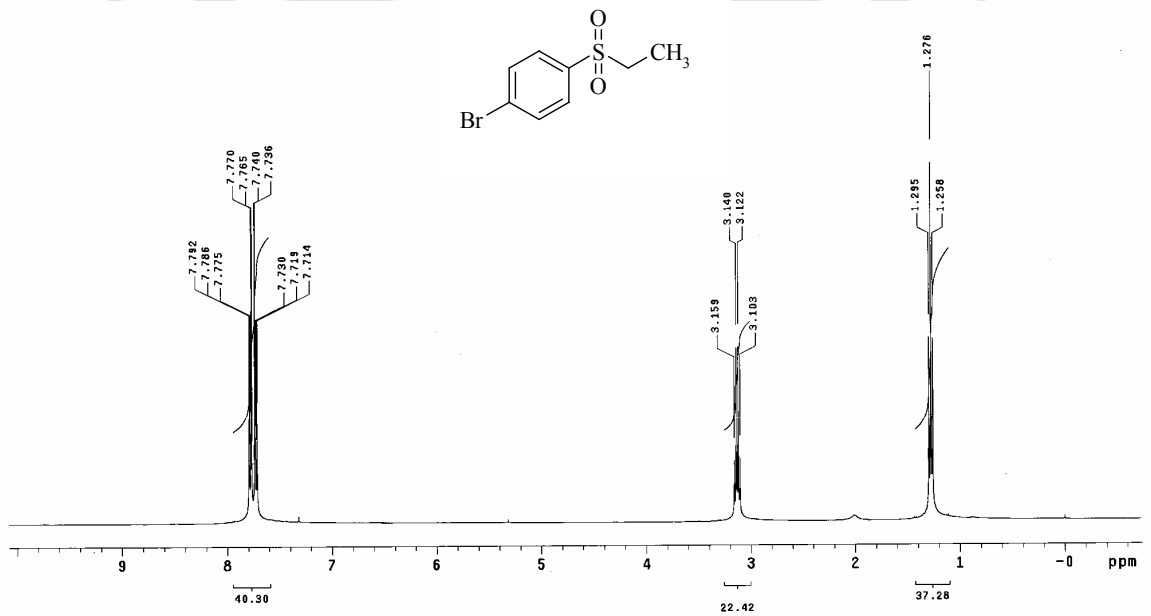


^{13}C NMR (100MHz, $CDCl_3$): 4-(Phenylsulfinyl)butyl acetate

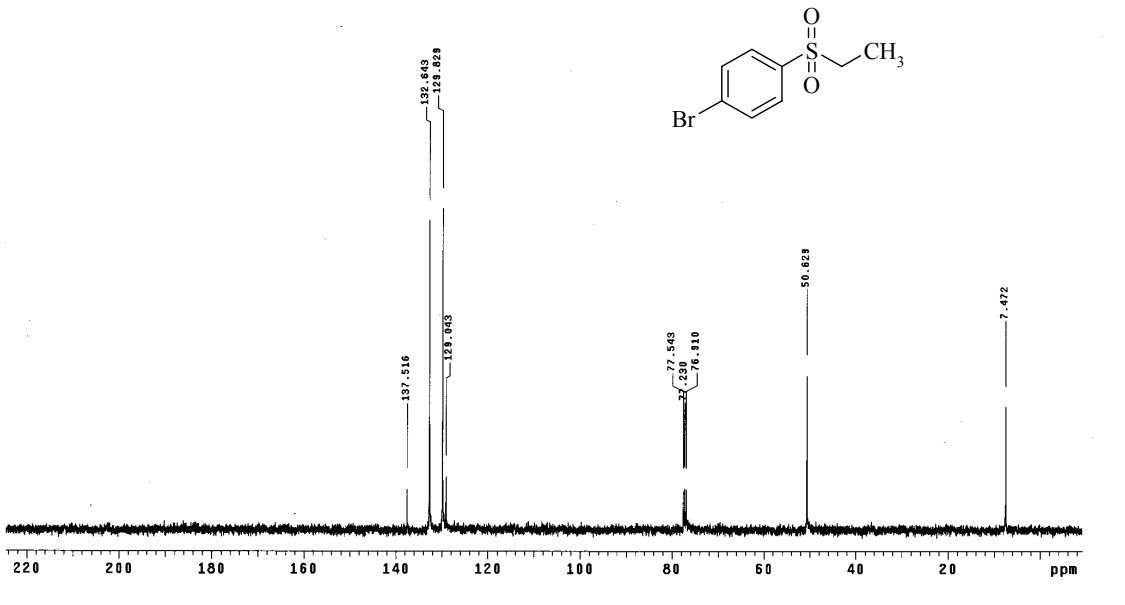


2.7 Selected Spectra of Sulfones

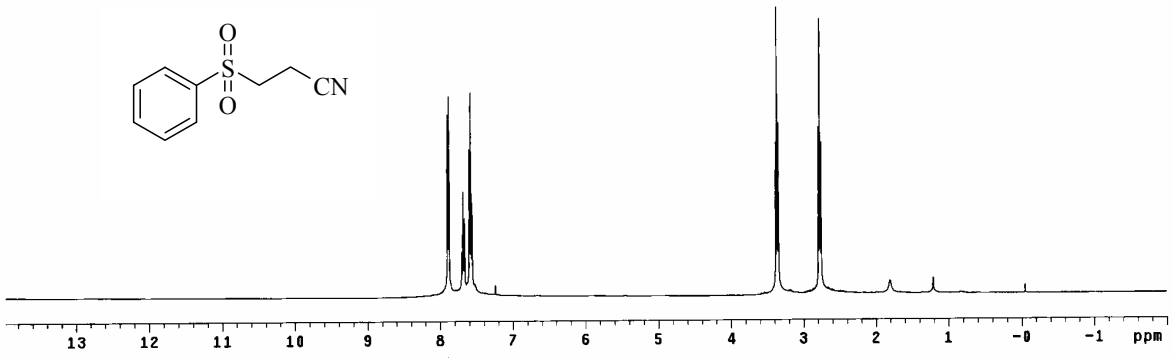
^{1}H NMR (400MHz, $CDCl_3$): 1-Bromo-4-(ethylsulfonyl)benzene



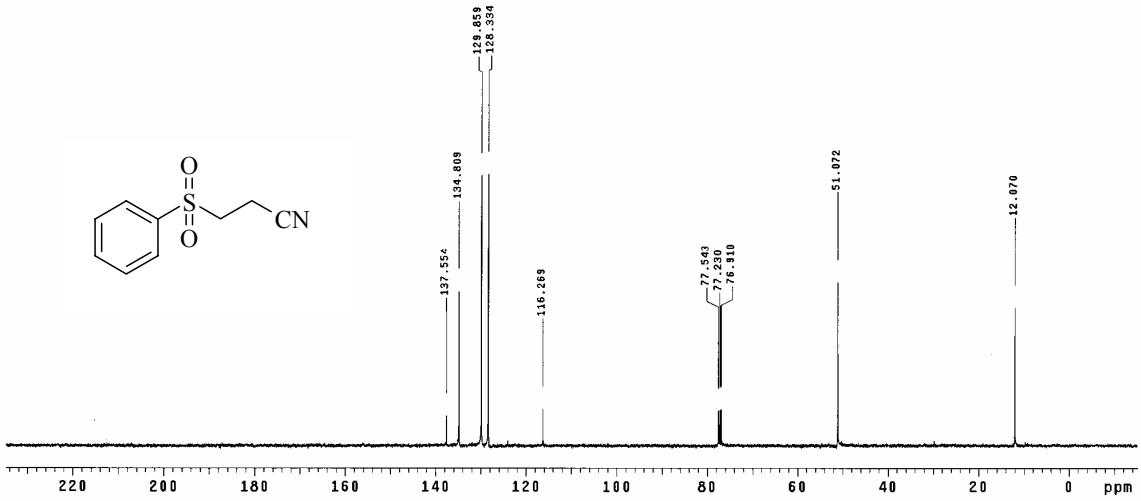
^{13}C NMR (100MHz, $CDCl_3$): 1-Bromo-4-(ethylsulfonyl)benzene



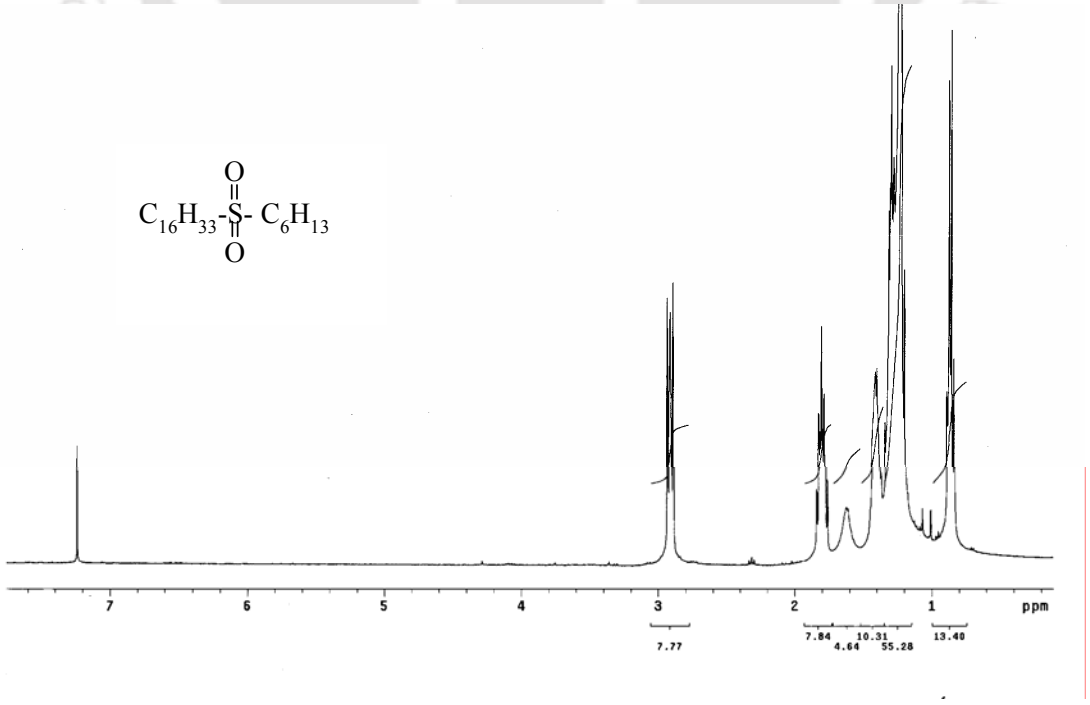
^{1}H NMR (400MHz, $CDCl_3$): 3-(Phenylsulfonyl)propanenitrile



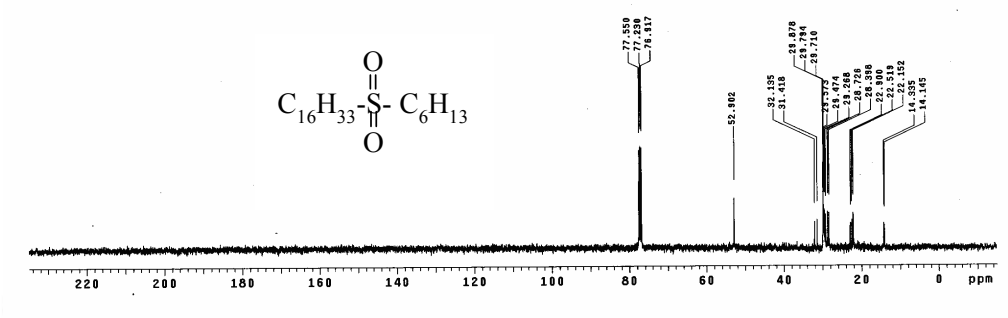
^{13}C NMR (100MHz, $CDCl_3$): 3-(Phenylsulfonyl)propanenitrile



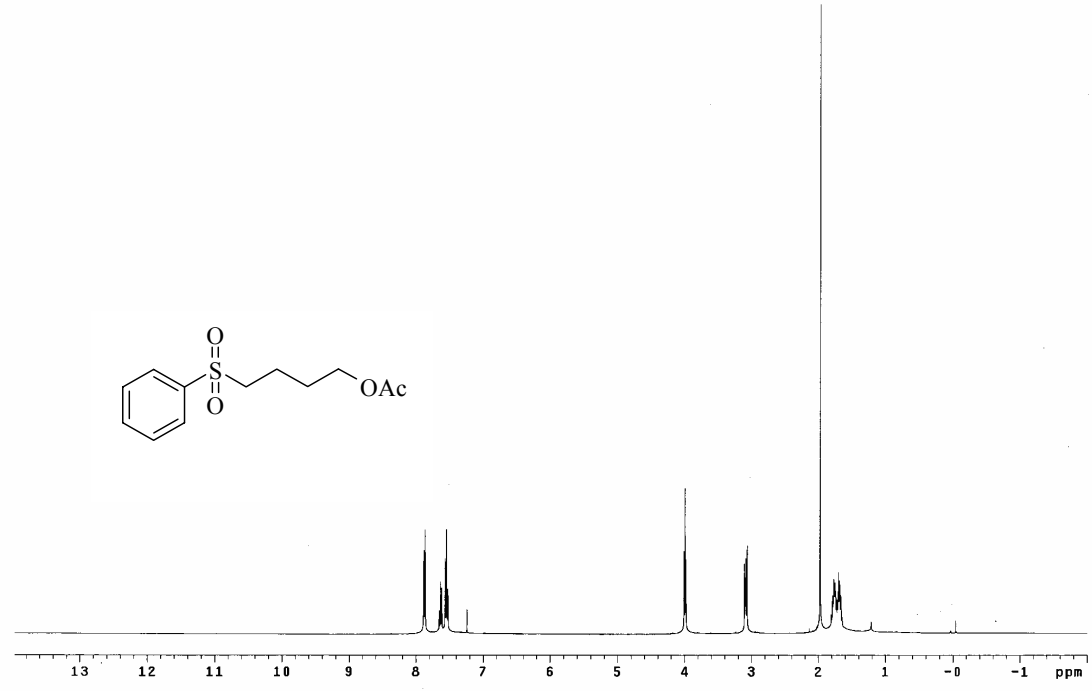
^{1}H NMR (400MHz, $CDCl_3$): 1-(Hexylsulfonyl)hexadecane



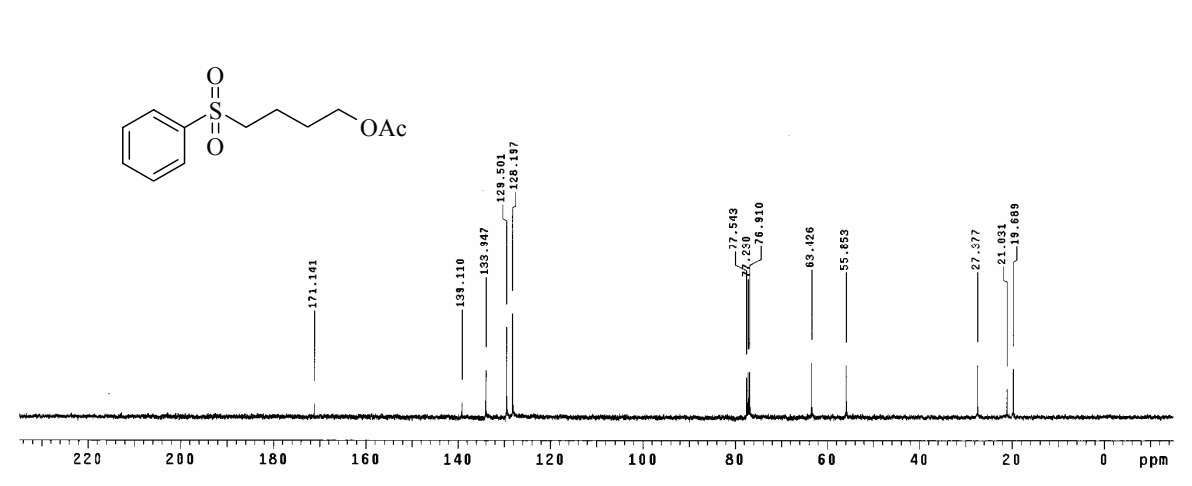
^{13}C NMR (100MHz, $CDCl_3$): 1-(Hexylsulfonyl)hexadecane



^{1}H NMR (400MHz, $CDCl_3$): 4-(Phenylsulfonyl)butyl acetate



^{13}C NMR (100MHz, $CDCl_3$): 4-(Phenylsulfonyl)butyl acetate



2.8 References

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CHAPTER III

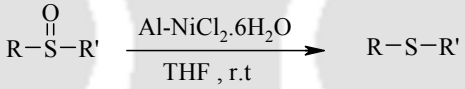
Reduction of Sulfoxides to Sulfides with Al-$NiCl_2.6H_2O$-THF system

3.1 Objective

The main aim was to develop an efficient and selective reduction method for the conversion of sulfoxides to their corresponding sulfides using aluminium and nickel(II)chloride combination.

3.2 Present Work

Reduction of sulfoxides to sulfides is one of the transformations that are of increasing importance in organic and biological reactions. Numerous methods have been reported for the conversion of sulfoxides to sulfides.[1] However, many of these transformations require expensive reagent,[2] difficult work up procedures,[3] dry reaction conditions,[4] harsh acidic[5] or basic[6] conditions, low yields,[7] very high reaction temperatures,[8] side products[9] and long reaction times.[10] Metal- metal salt binary systems such as Al-$NiCl_2.6H_2O$-THF,[11] Al-$SbCl_3$ or Zn-$SbCl_3$,[12] Fe-$NiCl_2.6H_2O$-THF[13] and Mg-$CdCl_2$[14] have long been used as reducing agents for many functional groups. Al-$NiCl_2.6H_2O$-THF system was found to reduce α,β-unsaturated carbonyl compounds to saturated ketones,[15] nitroarenes to amines,[16] nitroolefins to saturated ketones,[17] and epoxides to alcohols.[11] In light of this information, we sought to explore the utility of Al-$NiCl_2.6H_2O$-THF system for deoxygenation of sulfoxide to sulfide and we found that this system was quite effective for the reduction of sulfoxides to their corresponding thioethers as shown below (Scheme 3.1).



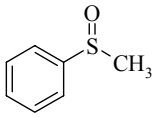
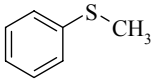
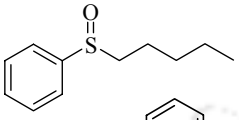
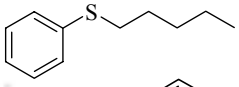
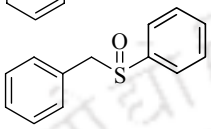
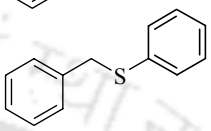
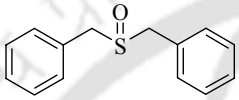
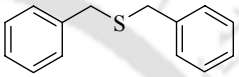
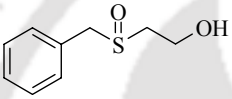
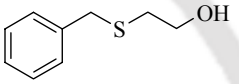
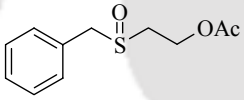
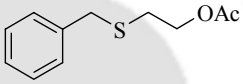
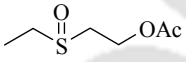
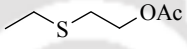
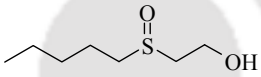
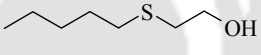
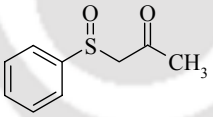
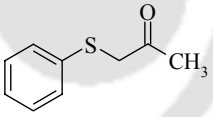
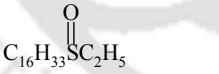
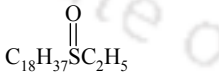
Where R = alkyl,aryl

Scheme 3.1

3.3 Results and discussions

To establish the efficiency of the reagent a wide range of sulfoxides were examined under these reaction conditions. It was found that diaryl, aryl-alkyl, and dialkyl sulfoxides are readily and rapidly reduced in good yields at room temperature. The reaction is compatible to groups such as ester, alcohol and ketone. The selectivity in reduction of 1-(phenylsulphenyl)propan-2-one (entry 9) to 1-(phenylthio)propan-2-one has added advantage of this methodology. Long chain aliphatic sulfoxides (entry 10 and 12) were deoxygenated readily in high yields. The reduction of dibenzyl sulfoxide (entry 4) serves as a diagnostic measure for the utility of the reaction. Since most methods either fail completely with this substrate or provide poor yields of dibenzylsulfide.[18] The reaction is generalized through entries 1-12 as shown below in Table 3.1.

Table 3.1: Reduction of sulfoxides to sulfides with Al-$NiCl_2.6H_2O$-THF system.

Entry	Substrates	Time (min)	Products	Yield (%)[a]
1		45		92
2		50		94
3		45		84
4		60		86
5		40		90
6		50		84
7		50		87
8		45		93
9		40		86
10		45		94
11		50		91
12		45		93

(a) Isolated yields. The compounds are characterized by GC-MS, ^{1}H NMR, ^{13}C NMR and IR spectroscopy and by comparison with the literature.

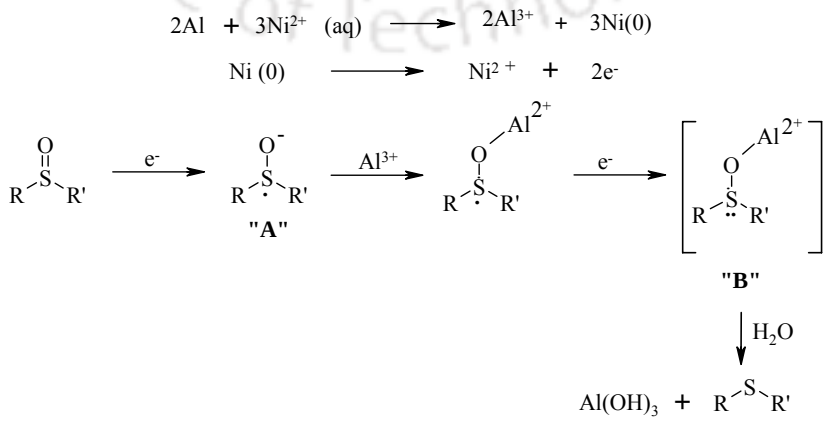
The selective reduction of the substrates was confirmed by spectroscopic methods. Thus the IR spectrum of 2-(benzylthio)ethanol (entry 5) showed a broad peak at 3384 cm^{-1} indicating the presence of hydroxyl (OH) group. The ^{1}H NMR spectrum displayed a triplet at δ 2.58 with a coupling constant J = 6 Hz for -S$\underline{CH_2}$-, a broad singlet at δ 3.0 could be assigned to O-H proton, triplet at δ 3.63 (J = 6 Hz) for –$\underline{CH_2}$OH, δ 3.69 to the benzylic protons and a multliplet

at δ 7.30 corresponds to the aromatic protons. The mass spectrum EIMS (m/z) showed a peak at (M^+) 168 for the expected product.

The IR spectrum of 2-(ethylthio)ethyl acetate (entry 7) displayed a sharp peak at 1739 cm^{-1} indicating the presence of C=O group of the ester functionality. The ^1H NMR spectrum displayed a triplet at δ 1.21 with coupling constant J = 7.2 Hz for the methyl group (-CH_3), a sharp singlet at δ 2.0 for carbonyl methyl protons of -OCO$\underline{CH_3}$, a quartet at δ 2.54 corresponding to the -$\underline{CH_2}$S- protons, a triplet at δ 2.69 for the methylene protons -S$\underline{CH_2}$- and a triplet at δ 4.16 with coupling constant J = 7.2 Hz corresponding to the methylene protons adjacent to the acetate group (-$\underline{CH_2}$OCO-). ^{13}C NMR showed a peak at δ 170.98 indicating the presence of carbonyl carbon of the acetate group. Hence from the above spectral data it can be confirmed that acetate functionality remained intact along with the formation of sulfide.

The IR spectrum of 1-(phenylthio)propan-2-one (entry 9) shows a sharp peak at 1711 cm^{-1} indicating the presence of C=O group of the ketone. The ^1H NMR spectrum displayed a singlet at δ 2.27 to the methyl protons, at δ 3.66 corresponding to the methylene protons adjacent to the C=O group, multliplets at δ 7.21 and 7.32 corresponding to the aromatic protons. ^{13}C NMR showed a peak at δ 203.56 indicating the presence of carbonyl carbon of the keto group. Thus from the above spectral data it was confirmed that the C=O group of the ketone remained intact.

It was observed that anhydrous $NiCl_2$ does not react with aluminum powder even after long exposure, but upon addition of few drops of water to this system initiates a vigorous exothermic reaction with evolution of hydrogen and subsides after a few minutes along with the formation of a black spongy mass which could be probably Ni(0).[19] The hydrogen might be produced by aluminum with HCl generated from hydrolysis of $NiCl_2$.[20] This can be attributed to the reducing property exhibited by these metal-metal salt combinations proceeds through transfer of electron from the metal surface or the metal in solution to the substrate. The



Scheme 3.2

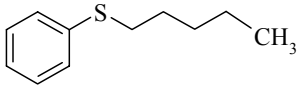
probable mechanism for the reduction of sulfoxide to sulfide is shown in Scheme 3.2. The sulfoxide accepts electrons released during the oxidation of Ni(0), formed in the reaction of aluminium and $NiCl_2.6H_2O$[21] to Ni^{2+}. The radical anion '**A**' reacts with aluminum chloride, which accepts another electron to give the species '**B**'. The species '**B**' then decomposes to give the corresponding sulfide.

3.4 Conclusion

In conclusion we have developed a simple, high yielding and selective methodology for the reduction of sulfoxides to their corresponding sulfides with Al-$NiCl_2.6H_2O$-THF system. Low cost of the reagents, short reaction times and easy isolation process makes this method an alternative to the existing methods.

3.5 Experimental Section

General procedure for the reduction of sulfoxides: $NiCl_2.6H_2O$ (2.38gm, 10 mmol) was added to an ice-cold solution of 1-methylsulfinyl benzene (140 mg, 1mmol) in 2 ml of distilled THF. Aluminum powder (270 mg, 10 mmol) was added pinch wise to the reaction mixture. A vigorous exothermic reaction took place, which subsided after few minutes. Stirring of the reaction mixture was continued for 45 minutes. The reaction was monitored by TLC (silica gel) using ethyl acetate and hexane (7:3) as eluent. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered. The residue (black precipitate) was washed with ethyl acetate (3 × 5 ml) and the combined filtrate and washings were dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and evaporated to dryness. Finally, the crude product was purified by column chromatography (silica gel, ethylacetate: hexane 1:9) to give 114 mg of pure methyl phenyl sulfide as a colorless liquid in 92% yield. The product was characterized by spectroscopic methods. IR (neat): 3060, 2912, 2829, 1577, 1478, 1434, 1089, 1023, 965, 735, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3 H, $-SCH_3$), 7.10 (m, 1 H, ArH), 7.25 (m, 4 H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 125.3, 126.9, 129.1, 138.7; EIMS (m/z): (M^+) 124, 109, 91, 78. Anal. Calcd for C_8H_8S: C, 68.51; H, 8.62; S, 22.86. Found C, 68.39; H, 8.53; S, 23.01.



Pentyl(phenyl)sulfide

State: Liquid

Colour: Colourless

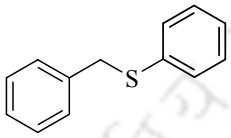
IR (Neat): 2930, 2858, 1588, 1486, 1107, 1025, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3), 1.26 - 1.43 (m, 4 H, 2 × -CH_2-), 1.63 (m, 2 H, CH_2), 2.89 (t, 2 H, *J* = 7.2 Hz, -SCH_2), 7.12 (m, 1 H, ArH), 7.25 (m, 2 H, ArH), 7.30 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ14.1, 22.4, 28.9, 31.2, 33.6, 125.7, 126.8, 128.9, 137.2.

EIMS (m/z): (M^+) 180, 77.

Anal. Calcd for $C_{11}H_{16}S$: C, 73.27; H, 8.94; S, 17.78. Found C, 73.33; H, 9.18; S, 17.32.



Benzyl(phenyl)sulfide

State: Liquid

Colour: Colourless

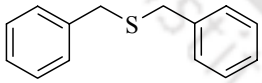
IR (Neat): 3054, 2912, 2840, 1580, 1476, 1437, 1064, 1023, 716, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 2 H, CH_2), 7.16 - 7.20 (m, 1 H, ArH), 7.23 - 7.25 (m, 3 H, ArH), 7.26 - 7.27 (m, 3 H, ArH), 7.28 - 7.32 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 39.2, 126.5, 127.4, 128.7, 129.0, 130.0, 131.4, 136.5, 137.6.

EIMS (m/z): (M^+) 200, 165, 109, 91, 77.

Anal. Calcd for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01. Found C, 77. 89; H, 6.14, S,15.89.



Dibenzylsulfide

State: Solid

Colour: Colourless

M. P : 49 - 50 ^oC

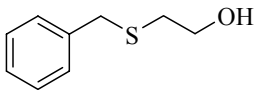
IR (KBr): 3032, 2917, 2851, 1602, 1495, 1454, 1412, 1264, 1231, 1070, 1023, 910, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.59 (s, 2 H, CH_2), 7.24 - 7.27 (m, 4 H, ArH), 7.29 (m, 4 H, ArH), 7.31 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 127.2, 128.7, 29.2, 138.3.

EIMS (m/z): (M^+) 214, 123, 91, 77.

Anal. Calcd for $C_{14}H_{14}S$: C, 78.46; H, 6.58; S, 14.96. Found C, 78.51; H, 6.52; S, 14.90.



2-(Benzylthio)ethanol

State: Liquid

Colour: Colourless

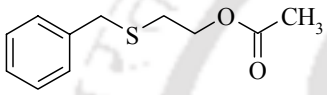
IR (Neat): 3384, 2923, 2873, 1492, 1451, 1050, 1012, 757, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (t, 2 H, *J* = 6 Hz, -SCH_2-), 3.0 (brs, 1 H, -OH), 3.63 (t, 2 H, *J* = 6 Hz, -CH_2OH), 3.69 (s, 2 H, $ArCH_2$-), 7.30 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 34.1, 35.8, 60.4, 127.1, 128.6, 128.8, 138.1.

EIMS (m/z): (M^+) 168, 123, 91, 77.

Anal. Calcd for $C_9H_{12}OS$: C, 64.25; H, 7.19; S, 19.06. Found C, 64.19; H, 7.10; S, 19.11.



2-(Benzylthio)ethyl propionate

State: Liquid

Colour: Colourless

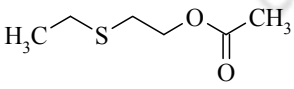
IR (Neat): 3060, 2917, 1739, 1495, 1451, 1377, 1231, 1061, 1023, 968, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04 (s, 3 H, CH_3), 2.62 (t, 2 H, *J* = 6.8 Hz, -SCH_2-), 3.73 (s, 2 H, $ArCH_2$), 4.16 (t, 2 H, *J* = 6.8 Hz, -CH_2OCO-), 7.31 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 29.6, 36.3, 63.2, 127.3, 128.7, 128.8, 138.0, 170.9.

EIMS (m/z): (M^+) 210, 150, 122, 91, 77.

Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.25. Found C, 62.78; H, 6.71; S, 15.31.



2-(Ethylthio)ethyl acetate

State: Liquid

Colour: Colourless

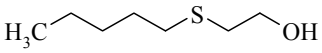
IR (Neat): 2965, 2928, 1739, 1448, 1377, 1231, 1048, 968, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.0 (s, 3 H, -$OCOCH_3$), 2.54 (q, 2 H, -CH_2S-), 2.69 (t, 2 H, *J* = 7.2 Hz, -SCH_2-), 4.16 (t, 2 H, *J* = 7.2 Hz, -CH_2OCO-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 21.0, 26.3, 30.1, 63.6, 171.0.

EIMS (m/z): (M^+) 148, 105, 88, 75, 60, 43.

Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63. Found C, 62.78; H, 6.71; S, 15.31.



2-(Pentylthio)ethanol

State: Liquid

Colour: Colourless

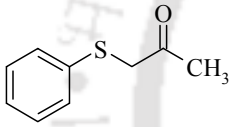
IR (Neat): 3391, 2960, 2935, 2858, 1465, 1050, 1015, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3 H, *J* = 6.8 Hz, CH_3), 1.33 (m, 4 H, -$\underline{CH_2CH_2}CH_3$), 1.54 (m, 2 H, -CH_2), 2.26 (brs, 1 H, -OH), 2.49 (m, 2 H), 2.71 (m, 2 H, -CH_2S-), 3.70 (s, 2 H, -CH_2OH)

^{13}C NMR (100 MHz, $CDCl_3$): δ14.2, 22.5, 29.6, 31.2, 31.8, 35.5, 60.3.

EIMS (m/z): (M^++1) 149, 117, 103, 91, 69, 61.

Anal. Calcd for $C_7H_{16}OS$: C, 56.80; H, 9.53; S, 16.85. Found C, 57.12; H, 9.36; S, 17.14.



1-(Phenylthio)propan-2-one

State: Liquid

Colour: Colourless

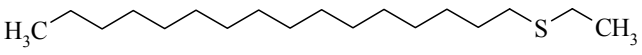
IR (Neat): 3073, 2935, 1711, 1358, 1235, 1163, 1025, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3 H, -CH_3), 3.66 (s, 2 H, -$SOCH_2CO$-), 7.21 (m, 2 H, ArH), 7.32 (m, 3 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4, 45.1, 127.1, 129.4, 129.7, 134.8, 203.6.

EIMS (m/z): (M^+) 166, 77, 43.

Anal. Calcd for $C_9H_{10}OS$: C, 65.03; H, 6.06; S, 19.29. Found C, 64.93; H, 6.14; S, 19.35.



Ethyl(hexadecyl)sulfide

State: Liquid

Colour: Yellow

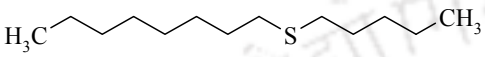
IR (KBr): 2923, 2857, 1465, 1374, 1262, 718 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3 H, *J* = 6.8 Hz, CH_3), 1.20 (t, 3 H, *J* = 6.8Hz, CH_3), 1.29 -1.33 (m, 26 H, -$(CH_2)_{13}$-), 1.54 (q, 2 H, -$\underline{CH_2}CH_2S$), 2.46 (t, 2 H, *J* = 7.2 Hz, -CH_2S-), 2.65 (t, 2 H, *J* = 7.2 Hz, -SCH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 14.3, 22.8, 22.9, 28.7, 28.8, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 30.0, 31.7, 32.1, 32.4, 39.3.

EIMS (m/z): (M^+) 286, 257, 117, 97, 83, 75, 69, 55.

Anal. Calcd for $C_{18}H_{38}S$: C, 75.44; H,13.37; S, 11.19. Found C, 75.57; H, 13.26; S, 11.10.



Octyl(pentyl)sulfide

State: Liquid

Colour: Colourless

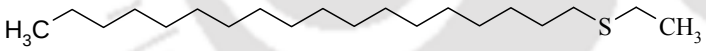
IR (KBr): 2928, 2857, 1459, 1374, 1325, 1127, 1039, 718 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (m, 6 H, 2 CH_3), 1.29 - 1.33 (m, 14 H, 7 × -CH_2-), 1.56 (m, 4 H, 2 × -CH_2-), 2.52 (m, 4 H, -CH_2-S-CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8 (2C), 29.1, 29.4, 29.9(2C), 32.0, 32.4(3C), 32.5(2C).

EIMS (m/z): (M^++1) 217, 157, 86, 72, 56.

Anal. Calcd for $C_{13}H_{28}S$: C, 72.15; H, 13.04; S, 14.81. Found C, 72.06; H, 13.11; S, 14.72.



Ethyl(octadecyl)sulfide

State: Liquid

Colour: Colourless

IR (KBr): 2925, 2863, 1465, 723 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3 H, *J* = 6.0 Hz, -CH_3), 1.35 (m, 33 H, $(CH_2)_{15}$, -CH_3), 1.55 (m, 2 H, -CH_2-), 2.53 (m, 4 H, -CH_2SCH_2-).

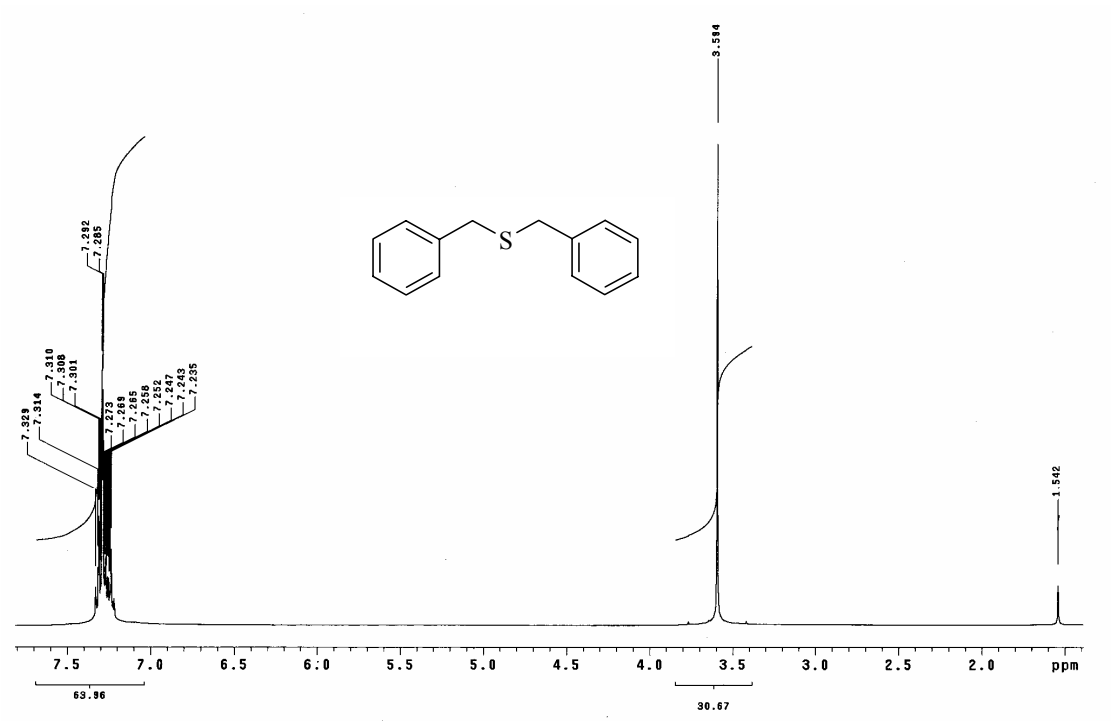
^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.0(2C), 22.9, 26.1, 29.2(3C), 29.5, 29.6(3C), 29.7, 29.8(2C), 29.9, 30.0, 31.9(2C), 32.1.

EIMS (m/z): (M^+) 314, 253, 113, 69, 55.

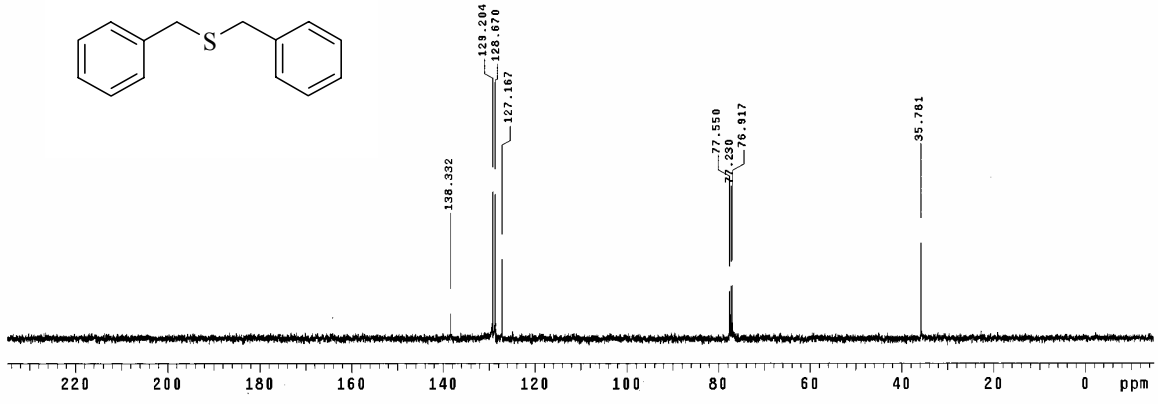
Anal. Calcd for $C_{20}H_{42}S$: C, 76.35; H, 13.46; S, 10.19. Found C, 76.52; H, 13.17; S, 10.38.

3.6 Selected Spectra of Sulfides

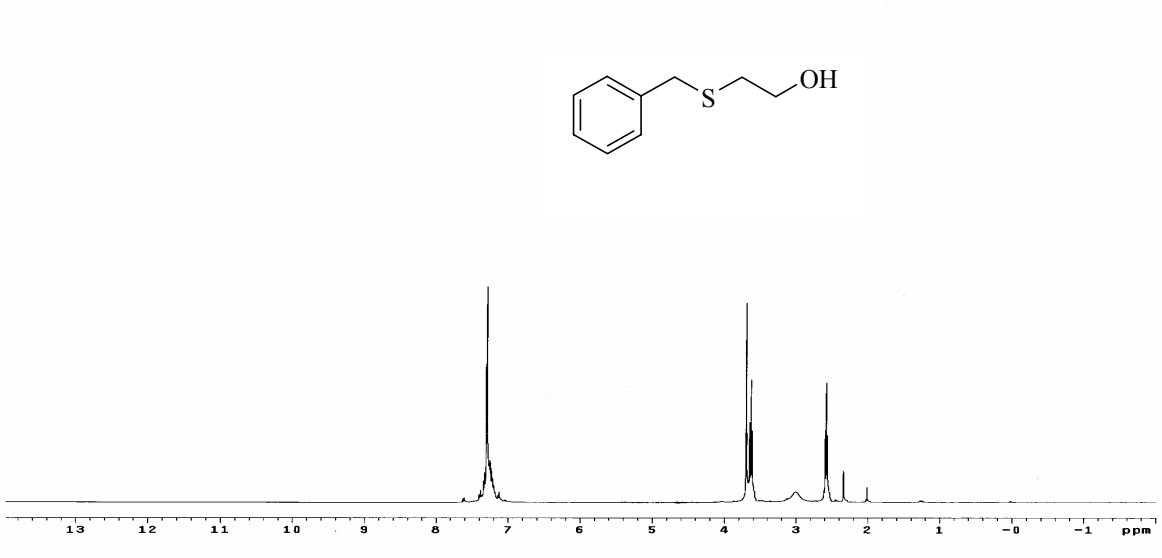
^{1}H NMR (400MHz, $CDCl_3$): Dibenzylsulfide



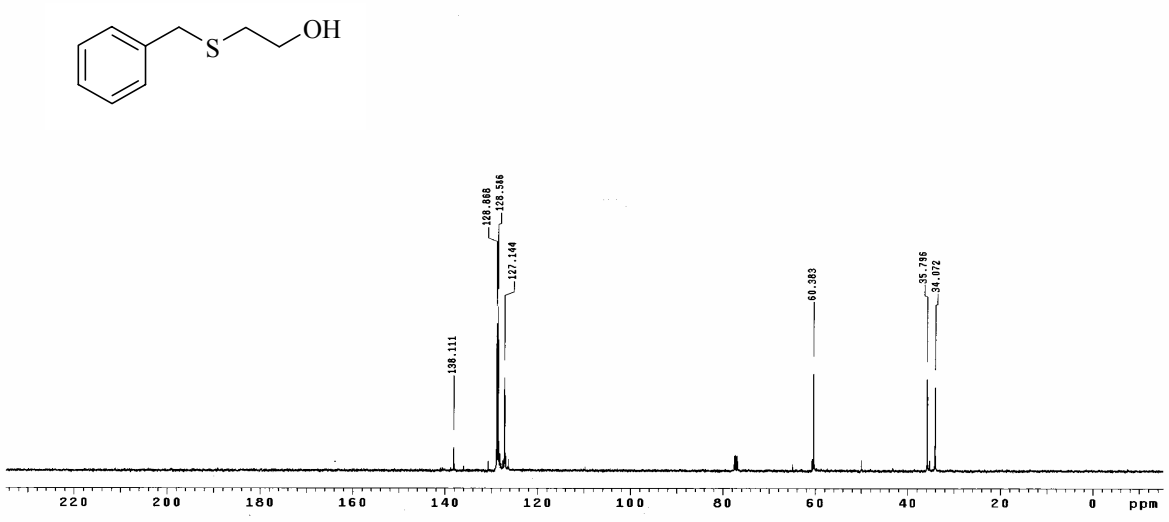
^{13}C NMR (100MHz, $CDCl_3$): Dibenzylsulfide



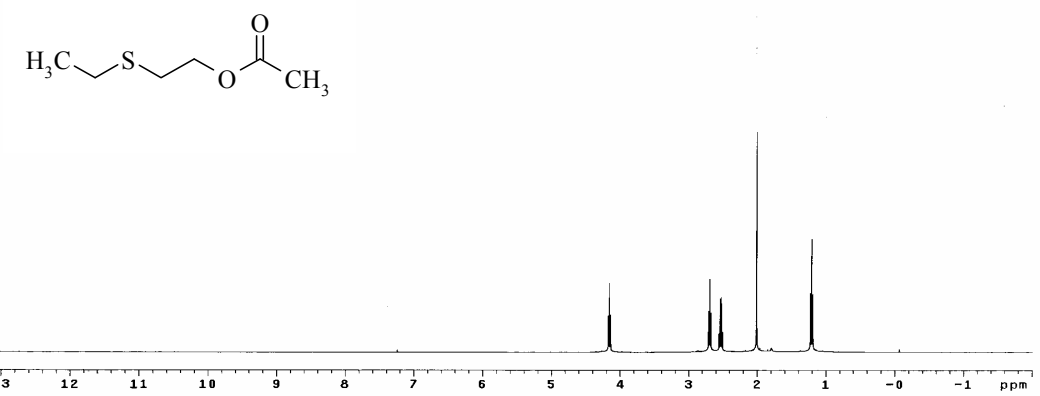
^{1}H NMR (400MHz, $CDCl_3$): 2-(Benzylthio)ethanol



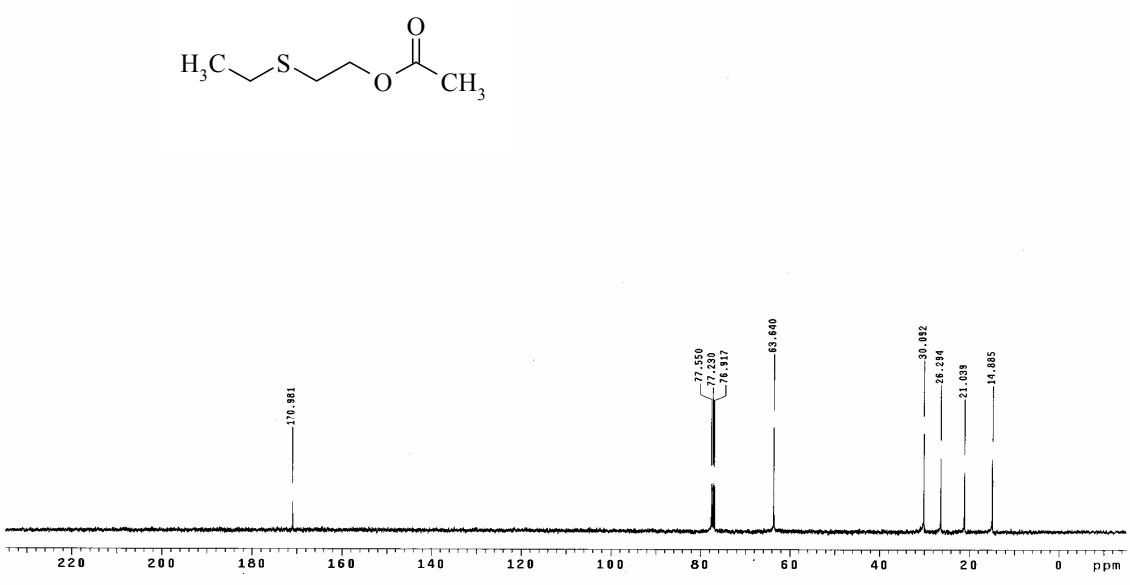
^{13}C NMR (100MHz, $CDCl_3$): 2-(Benzylthio)ethanol



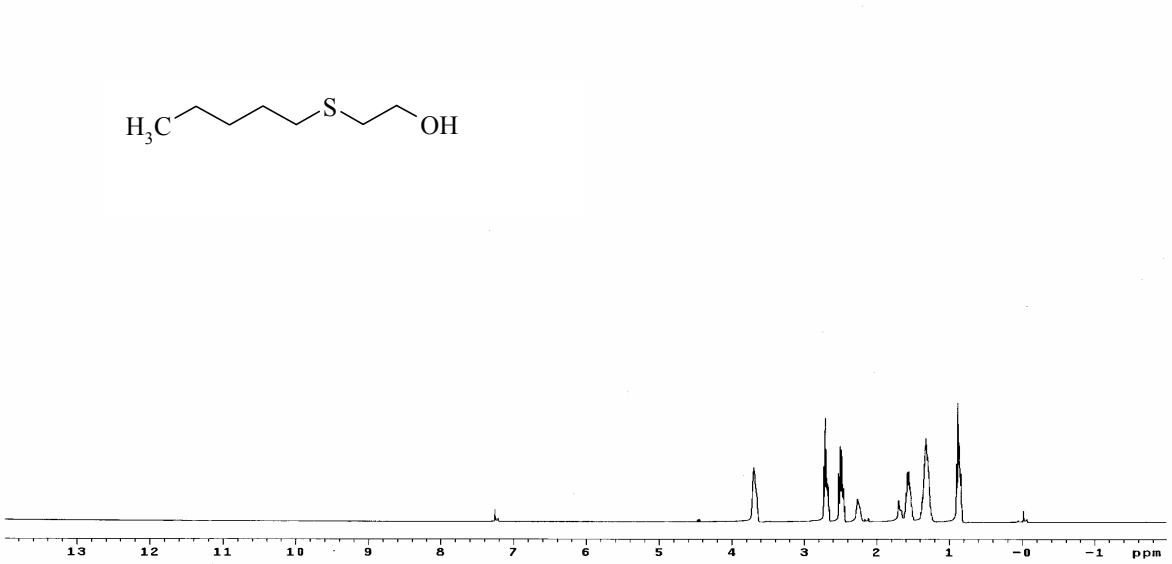
^{1}H NMR (400MHz, $CDCl_3$): 2-(Ethylthio)ethyl acetate



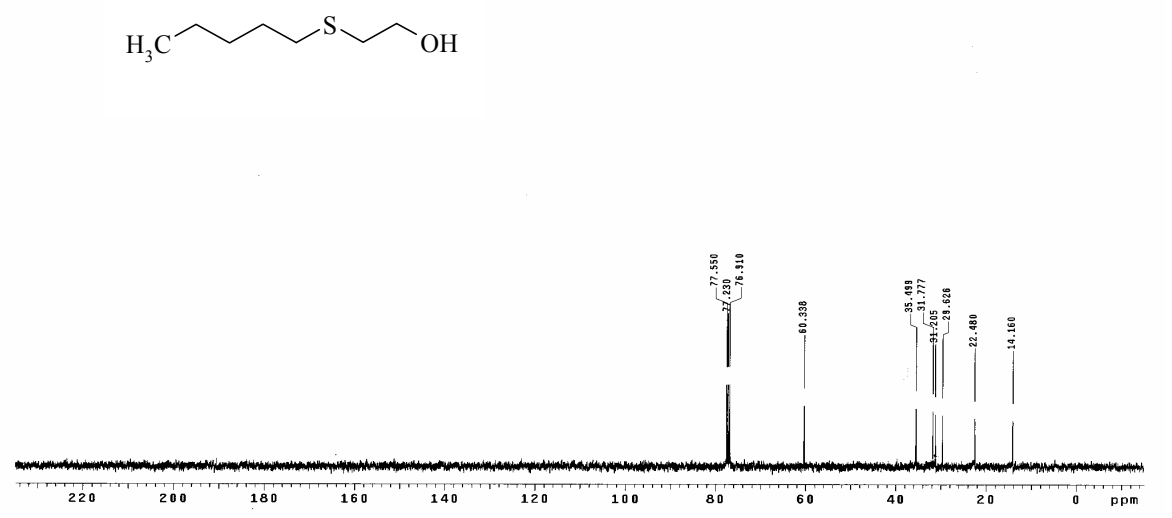
^{13}C NMR (100MHz, $CDCl_3$): 2-(Ethylthio)ethyl acetate



^{1}H NMR (400MHz, $CDCl_3$): 2-(Pentylthio)ethanol



^{13}C NMR (100MHz, $CDCl_3$): 2-(Pentylthio)ethanol



3.7 References

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PART II

Organofluorine Compounds

Chapter I

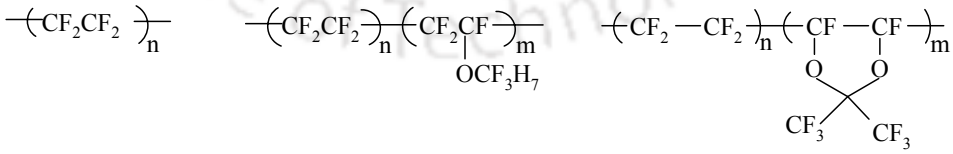
Introduction

1.1 Introduction

Incorporation of fluorine selectively into organic compounds remains a great challenge in the present days of research. Many approaches have been devised to cover the needs of academic and industrial chemists interested in organofluorine derivatives.[1] Fluorine is unique in that it is possible to replace hydrogen by fluorine in organic compounds without gross distortion in geometry of the system.[2] The introduction of fluorine into organic compounds increases thermal and oxidative stability, increases lipophilicity and alters electronic effects.[3] Thus the fluorinated molecules find a wide application in fine-tuning of technical and biological properties. There has also been an enormous increase in the use of fluorine containing compounds in the medicinal field.

1.2 Applications of organofluoro compounds

Fluoropolymers are one of the largest scale applications of fluororganic compounds. These polymeric materials are thermal and chemically stable due to the greater strength of carbon-fluorine bonds. The widely used polymers are polytetrafluoroethylene (PTFE), poly-(chlorotrifluoroethylene) (PCTFE), polyvinylidine difluoride (PVDF) and other perfluorinated polyethers. PTFE is chemically stable against the aggressive reagents and possess anti-sticking properties. PCTFE has applications as a thermoplastic or a lubricant. PVDF is used to prepare thin films with very good light transmittance. This and its high UV resistance makes it excellently stable as a cover for solar collectors as components for formulation of high performance paints and other coatings. Other types of perfluorinated polymer include ether structures. The monomers of these materials are trifluoroenol ethers **2** and cyclic difluoroendiol ethers **3** (Scheme 1.1). Perfluorinated polyethers are used for labware in analytical chemistry due to its anti corrosive nature and also have special applications in the manufacture of electronic circuits.

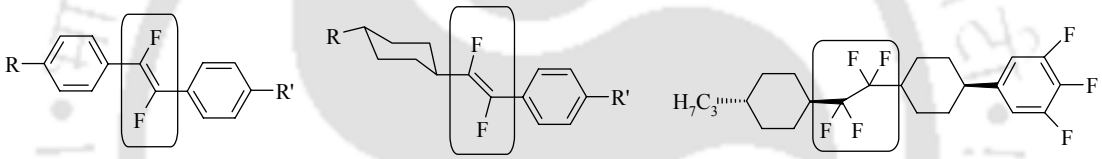


1 **2** **3**

Scheme 1.1

There are many good reasons to make use of the unique properties of fluorinated substructures for design of liquid crystals as these far out weigh the economic and synthetic disadvantages. Liquid crystals find wide use in liquid crystal displays, which rely on the optical properties of certain liquid crystalline substances in the presence or absence of an electric field. Of these, a

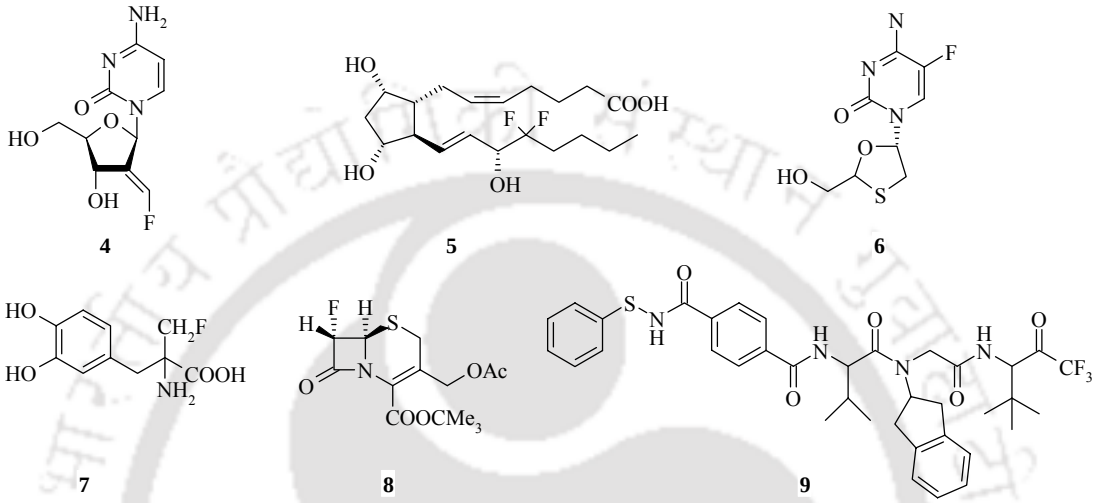
display device using twisted nematic (TN) liquid crystals appeared in 1970.[4] Liquid crystals used for a TN display device are rod-like molecules comprising a six memebred ring unit (mesogen) like benzene and cyclohexane, a connecting group like the -COO-, an alkylsubstitutent and a polar group like CN.[5,6] Compounds such as 4-butyloxy-2,3-dicyanophenyl-4-pentylcyclohexane- carboxylate was added to nematic liquid crystals to improve the quality of display. However the miscibility of the compounds is limited mainly due to the steric perturbation by a cyano group. The replacement of cyano by fluorine was shown to improve this limitation.[7-9] Since fluorine is similar to hydrogen in size and induces a large dipole, the fluorine containing liquid crystals retain liquid crystallinity with much reduced viscosity. Fluorine introduced at an alkyl or alkoxy substituent of nematic liquid crystals raises the viscosity slightly as compared to the parent compound. In contrast, fluorine introduced at a connecting group appears to stabilize the nematic phase lowering the viscosity and exemplified by the difluoro-*trans*-stilbene type compounds[10] (Scheme 1.2).



Scheme 1.2

The physiological properties of many biologically significant drugs can be modulated if fluorinated groups are incorporated into their structures.[11] Fluorine or trifluoromethyl substituents generally enhance the lipophilicity of an aromatic substrate and increase the rate of transport of the drug to the active site. Another contributing factor could be, for example the change in the acidity of the drug upon fluorination, thus increases the solubility. A further significant effect of introducing fluorine is the resulting enhanced resistance to metabolic oxidation and therefore to potentially toxic byproducts, thus increasing both the effective lifetime and the safety of a drug. Some examples of fluorinated pharmaceuticals are the fluoroolefin analog of cytidine nucleoside, **4** that inhibits a ribonucleotide diphosphate reductase for the treatment of tumors. Fluorinated prostaglandin's like 16,16-difluoro-$PGF_{2\alpha}$ **5** are used as antifertility compounds. Fluorinated pyrimidime and purine nucleosides have been prepared in order to find an alternative to 3'-azidothymidine (AZT) an inhibitor of HIV-1. The potent therapeutic agent against HIV is (-)-2',3'-dideoxy-5-fluoro-3-thiacytidine (FTC) **6** that serves as an extremely potent and selective inhibitor of HIV replication in vitro and vivo. The

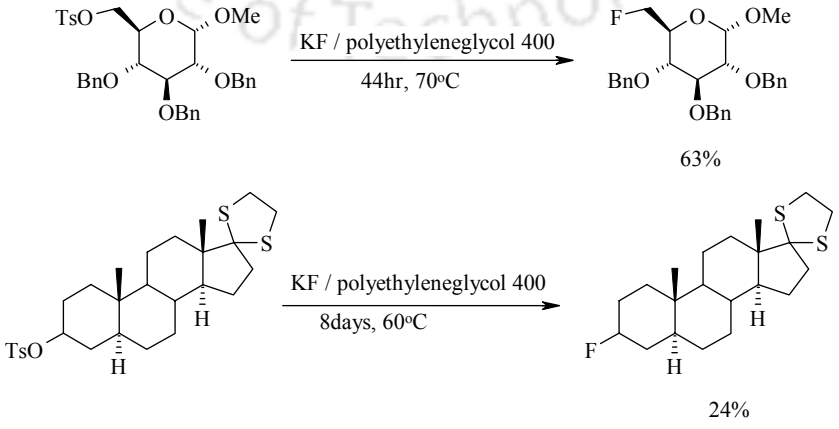
introduction of fluoromethyl group at a α-position enhances the potency and efficiency of α-amino acids. α-Monofluoromethyl-dopa, **7** for example has selective peripheral activity as anti-gestinal agent. The β-lactam antibiotic Fluorocephalosporin derivative **8** is used as an antibacterial agent. Protease inhibitors are effective for the treatment of several diseases such as malaria, arthritis sleeping sickness etc. A typical example is an inhibitor of human leukocyte elastase (HLE) **9** is used for rheumatoid arthritis (Scheme 1.3).



Scheme 1.3

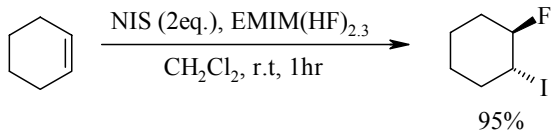
1.3 Literature Methods for synthesis of organofluorine compounds

Several methodologies have been developed for the synthesis of fluorinated molecules. Tavecchia *et al.*[12] achieved the synthesis of monoflourinated organic compounds, in reaction with potassium fluoride from the corresponding mesylates and tosylates of alcohols when polyethylene glycol 400 was used as solvent. The limitation of this reaction is solvolysis of the leaving group by the solvent; this phenomenon was controlled by the degree of steric hindrance around the reaction centre (Scheme 1.4).



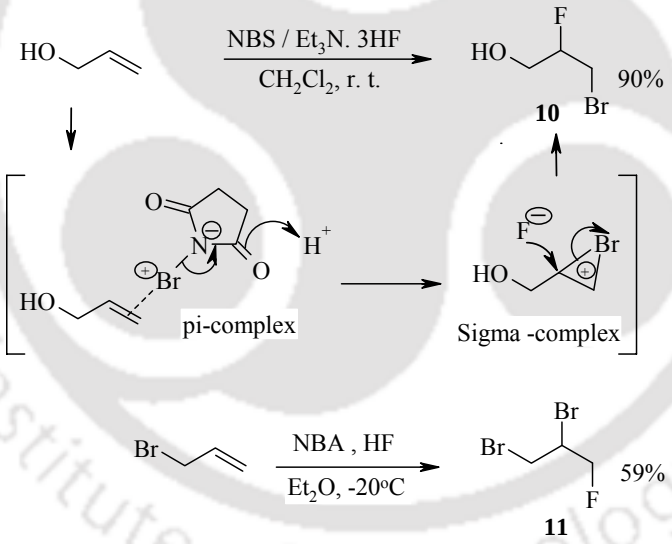
Scheme 1.4

Matsubura and his coworkers[13] achieved the halofluorination of alkenes with *N*-iodosuccinimide and ionic liquid, 3-ethyl-1-methyl-imidazorium oligo hydrogen fluoride ($EMIM(HF)_{2.3}$) as the source of HF (Scheme 1.5).



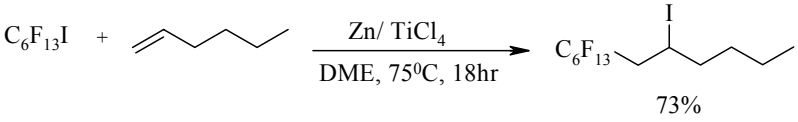
Scheme 1.5

Haufe and his coworkers reported the bromofluorinations[14] of 1-alkenes with combinations of *N*-bronosuccinimide and $Et_3N.3HF$ depending on the functional groups in the neighborhood of the double bond. Mono-substituted terminal alkene mainly yield Markonikov-oriented product **10**, electron-withdrawing groups in allylic or homoallylic position to the double bond yield mainly the anti-Markonikov-oriented bromofluoride **11** (Scheme 1.6).



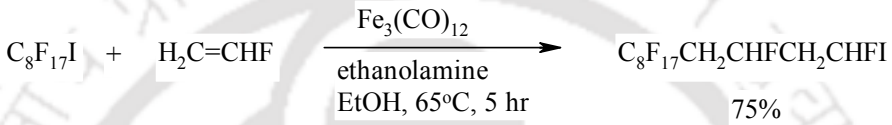
Scheme 1.6

Davis *et al*. reported that the perfluoroalkyl iodides can be added to alkenes in presence of a catalytic amount of Ti^0 generated *in situ* in dimethoxyethane as a solvent in good yields[15] (Scheme 1.7).



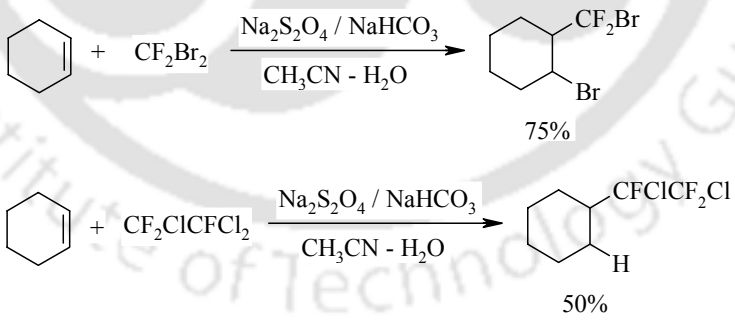
Scheme 1.7

Kesse and his coworkers[16] achieved the synthesis of organofluorine compounds containing perfluoroalkyl groups from alkenes or alkynes by the addition of perfluorinated alkyl iodides with sodium dithionate under ultrasonic irradiation or phase transfer conditions. Zhang *et al*.[17] reported that the perfluoroalkyl iodides reacted with alkenes in acetonitrile solution containing catalytic amounts of triphenylphosphine under mild conditions to give the corresponding adducts in good yields. Ojima and his coworkers achieved the addition of polyfluoroalkyl halides to alkynes and alkenes bearing a variety of substituents catalyzed by ironpentacarbonyl[18] in good yields. The addition of catalytic amounts of amine such as ethanolamine, diethylamine, triethylamine and pyridine accelerates the reaction (Scheme 1.8).



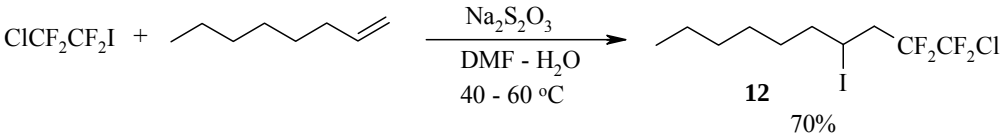
Scheme 1.8

Low valent metal complexes of ruthenium and platinum catalyzed the addition of perfluoroalkyl iodides to 1-alkenes in good yields.[19] Wu *et al*.[20] reported that the addition of halocarbons such as CF_2Br_2, $BrCF_2CFClBr$, $BrCF_2CF_2Br$, CF_3CCl_3, and CCl_3Br to olefins in presence of sulfinatodehalogenation reagent sodium dithionate under mild conditions to give the corresponding polyfluoroalkylation products in good yields (Scheme 1.9).

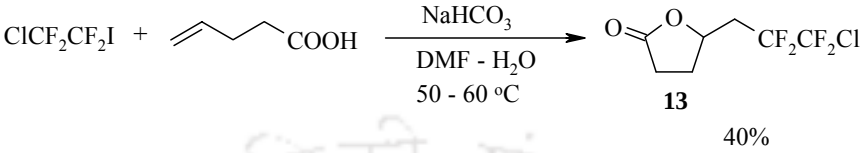


Scheme 1.9

Wu and his coworkers[21] reported that the addition of polyfluoroalkyl iodides with alkenes can be promoted by sodium bisulfite and sodium sulfite in aqueous DMF solution to give the corresponding adduct **12** in good yields. (Scheme 1.10) In case of 4-pentanoic acids the addition product obtained further cyclizes to give the γ-lactones **13** (Scheme1.11).

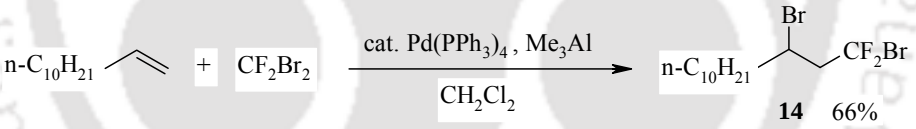


Scheme 1.10

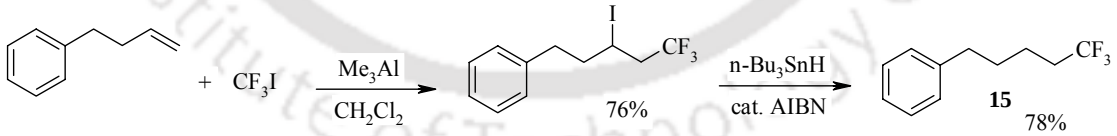


Scheme 1.11

Yamamoto and his coworkers reported the polyfluoromethylation of olefins induced by organoaluminium.[22] In a representative example, the treatment of 1-dodecane with dibromo-difluoromethane in presence of trimethylaluminium and catalytic amounts of $Pd(PPh_3)_4$ at room temperature gives the 1,3-dibromo-1,1,difluorotridecane **14** as the addition product shown in (Scheme 1.12). More significant are the facile addition of iodotrifluoromethane to 3-phenyl- propene at -25 °C and the removal of iodo moiety with tributyltinhydride in the presence of catalytic azobisisobutyronitrile in refluxing benzene to give the 1,1,1-trifluoro-3-phenylpropane **15** in good yield (Scheme 1.13).



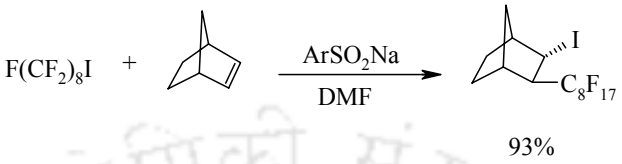
Scheme 1.12



Scheme 1.13

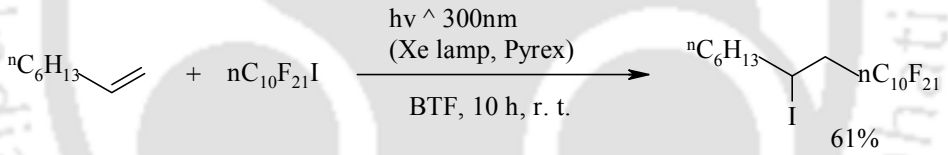
The fluoroalkyl iodides can be conveniently added to alkenes mediated by 2-amino ethanol and diethylammonium hydrochloride[23] as an initiator in acetonitrile at 120-140 °C *via* a free radical process. A facile photo-induced[24] addition of perfluoroalkyl iodides to dienes was described. Qiu *et al*.[25] reported the addition of fluoroalkyl iodides to alkenes by the addition of catalytic amounts of tetrakis(triphenylphosphine)palladium. They have proposed that a radical-chain process initiated by single electron transfer from palladium(0) to iodide might be involved. Further, the formation of fluoroalkylbis(triphenylphosphine)palladium iodide was proved to

proceed through a radical intermediate by e.s.r. trapping techniques. The addition of iodoperfluoroalkanes to cyclohexene or cyclopentene initiated by peroxides, azonitriles or radiant energy[26] was described. The radical chain addition of primary and secondary perfluoroalkyl iodides to olefins initiated by sodiumarene and alkanesulfinates[27] at room temperature in dipolar aprotic solvents such as DMF or DMSO was described (Scheme 1.14).



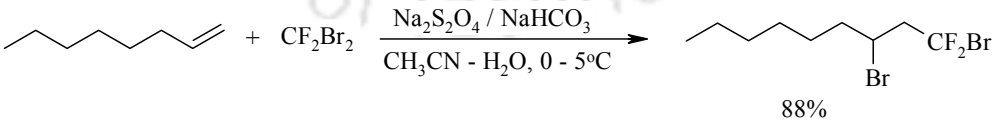
Scheme 1.14

Burton and his coworkers[28] reported the addition of iododifluoroacetates to alkenes mediated by zinc-nickeldichloride hexahydrate couple in THF at 60 °C to the corresponding α, α-difluoroesters in good yields. The reaction also proceeded well with alkenes containing functional groups such as trimethylsilyl, hydroxyl, ketone and ester moieties. Tsuchii *et al*.[29] reported the iodoper- fluoroalkylation to the terminal double bonds upon irradiation with a xenon lamp through pyrex (*hv* >300nm) (Scheme 1.15).



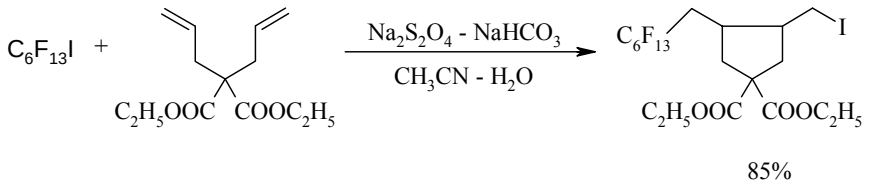
Scheme 1.15

Wu *et al*.[30] reported the addition of dibromodifluoromethane to terminal alkenes in presence of sodium dithionate, rongalite or thiourea at room temperature or with cooling in an ice bath to give the corresponding adducts in good yields (Scheme 1.16).



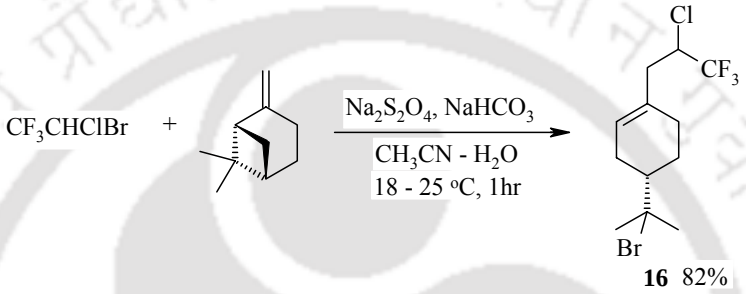
Scheme 1.16

Zhao *et al*.[31] achieved the carbocyclic and heterocyclic five membered ring compounds bearing polyfluoroalkyl groups using sodiumdithionate-sodiumbicarbonate, promoted addition-cyclization of per(poly)fluoroalkyl iodides or perhaloalkanes with 1,6-heptadienes (Scheme 1.17).



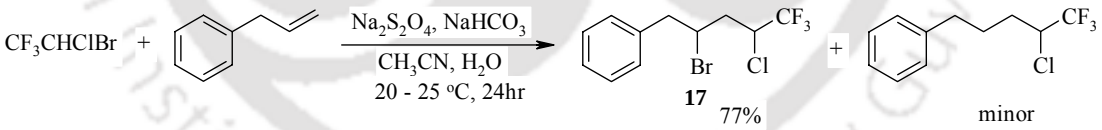
Scheme 1.17

Dmowski and his coworkers[32] reported that sodium dithionate effectively promotes the addition of 1-bromo-1-chloro-2, 2, 2-trifluoroethane to the exocyclic double bond of β-pinene in acetonitrile-water system to give a 1:1 mixture of diastereoisomers of 4-(2-bromoisopropyl)-1- (2-chloro-3,3,3-trifluoropropyl)-cyclohexene **16** in quantitative yield (Scheme 1.18).



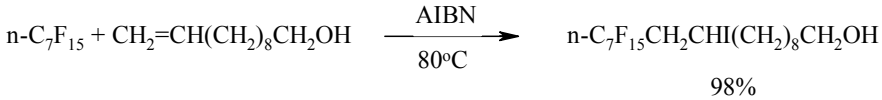
Scheme 1.18

Ignatowska *et al*.[33] reported that the addition of 1-bromo-1-chloro-2,2,2-trifluoroethane to the terminal double bond of allylbenzene mediated by sodium dithionite in acteonitrile-water medium to give the corresponding 1-(2-bromo-4-chloro-5,5,5-trifluoropentyl-) benzene **17** as the major product (Scheme 1.19).



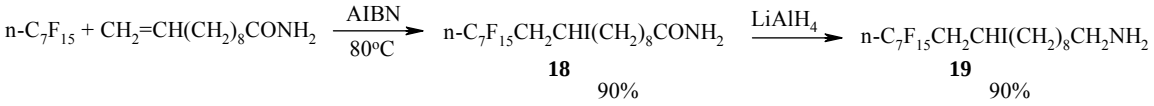
Scheme 1.19

AIBN initiated regioselective addition of perfluoroalkyl iodides to long chain alcohols containing terminal double bonds is described. The perfluoroalkyl group is added to the end of the double bond as in the Markonikov addition[34-36] (Scheme 1.20).



Scheme 1.20

Similarly amides containing terminal double bonds also effectively add the perfluoroalkyl group to give the addition product **18**, which was further reduced by lithium aluminum hydride to give the corresponding perfluorinated alkyl amine **19** in excellent yields [37,38] (Scheme 1.21).

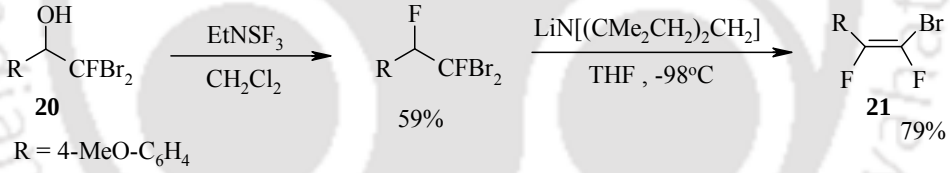


Scheme 1.21

Burton and his coworkers obtained the synthesis of perfluoroalkanes using copper(I) chloride, ethanol amine and t-butyl alcohol as the solvent under refluxing conditions.[39] Ignatowska *et al*. reported the addition of CF_2Br_2, CF_3I and $(CF_3)_2CFI$ to the terminal double bond of allylbenzenes and of $(CF_3)_2CFI$ to allylpyridines initiated by sodium dithionite in MeCN-H_2O system.[40]

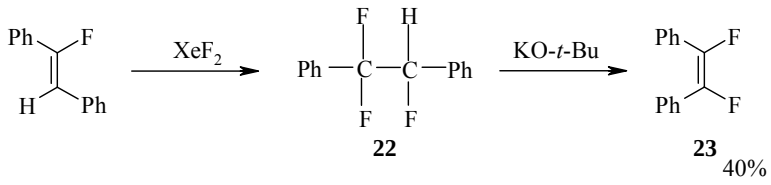
1.4 Literature Methods for the Preparation of 1, 2-Difluoroolefins

Very few methods are known for the synthesis of 1,2-difluoroolefins. Hiyama *et al*.[41] achieved the synthesis of *cis* 1,2-difluorolefins in two successive steps. The first is fluorination of an alcohol **20** to $RCHFCFBr_2$, and the second step is the dehydrobromination to the required olefin **21** (Scheme 1.22).



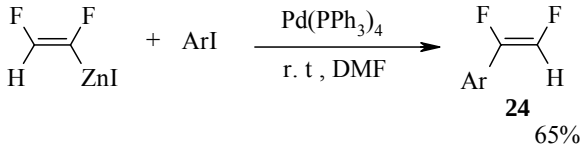
Scheme 1.22

1,1,2-trifluoro-1,2-diphenyl- ethane **22** was achieved by fluorination of *trans*-fluorostilbene with xenon difluoride. Under basic conditions (KO-*t*-Bu), convenient elimination resulted in the formation of *cis*-1,2-difluoro-1,2-diphenylethylene **23** (Scheme 1.23).[42]



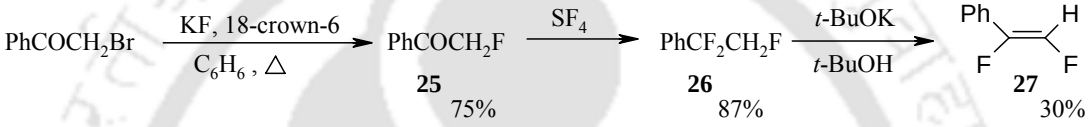
Scheme 1.23

Substituted aromatic iodides couple smoothly under mild conditions with (*E*)-HFC=CFZnI in the presence of catalytic $Pd(PPh_3)_4$ to give (*Z*)-α,β-difluorostyrenes **24** in good yields (Scheme 1.24).[43]



Scheme 1.24

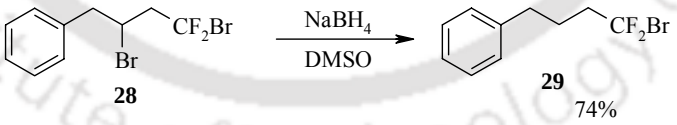
The synthesis of *cis*-1,2-difluoroalkenes can be achieved from bromomethyl ketones. [44] The first step involves the conversion of bromomethyl ketones to fluoromethyl ketones. The fluorinated ketone **25** upon treatment with sulfur tetrafluoride gave 1,2,2-trifluorothane **26**which undergoes dehydrofluorination in presence of potassium *tert*-butoxide to give the corresponding olefin **27** in moderate yields (Scheme 1.25).



Scheme 1.25

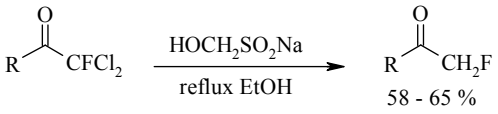
1.5 Literature Methods for selective reduction of halofluoro to fluoro compounds

Selective reduction of bromofluoroalkanes to fluoroalkanes is an important transformation in organic synthesis. Gonzalez *et al*. reported the selective reduction of 1,3-dibromo-1,1-difluoro-alkane **28** to 1-bromo-1,1-difluoroalkane **29** upon treatment with sodium borohydride in DMSO under anhydrous conditions (Scheme 1.26).[45]



Scheme 1.26

Tsuboi and his coworkers[46] reported the selective dechlorination of dichlorofluoromethyl aryl ketones to fluoromethyl phenyl ketones using sodium hydroxymethane sulfinate in refluxing ethanol (Scheme 1.27).



R = C_6H_5 , 4-$MeOC_6H_4$, 4-BrC_6H_4

Scheme 1.27

1.6 References

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CHAPTER II

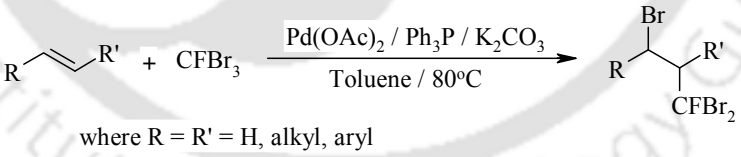
Palladium Catalyzed Addition of $CFBr_3$ to Olefins: Synthesis of 1,1,3-tribromo-1-fluoroalkanes

2.1 Objective

Halofluorination of unsaturated hydrocarbon has been a useful method to incorporate fluorine in organic molecules. The main objective of this work was to develop a synthetic method for the synthesis of 1,1,3-tribromofluoroalkanes catalyzed by *insitu* generated palladium (0).

2.2 Present work

The incorporation of Fluorine into organic materials is prevalent in fields of pharmacology or functionalized materials because of the unique biological and physical properties of the resulting compounds.[1] Several β-fluorophenethylamines,[2] 3-fluoroalkylamines,[3] and vinyl fluorides[4] have been shown to be irreversible inhibitors of certain enzymes. In particular, reactions using fluoroorganometallic reagents derived from fluorohalohydrocarbons are versatile for constructing fluorinated target molecules.[5] Therefore, the development of new methodologies for selective introduction of fluorinated functions into organic molecules is of great importance.[6] The addition of perfluoroalkyl iodides or bromides to unsaturated compounds continues to be among the most useful methods for incorporation of fluorinated groups into organic molecules. This transformation can be achieved by photochemical,[7] redoxsystems,[8] especially sulfur oxy-acid salts, such as sodium dithionate,[9] sodium hydroxymethane sulfinate,[10] thioureadioxide[11] and a variety of metals.[12-15] In this chapter,[16] the addition of tribromofluoromethane to alkenes in the presence of palladium acetate, triphenylphosphine and anhydrous potassium carbonate in distilled toluene under nitrogen atmosphere to afford 1,1,3-tribromofluoro-1-fluoroalkanes is described (Scheme 2.1).



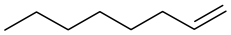
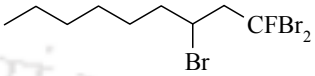
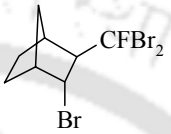
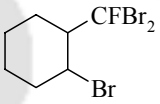
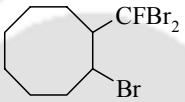
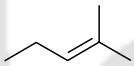
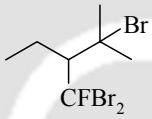
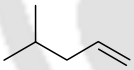
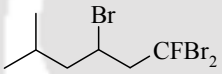
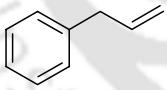
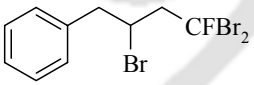
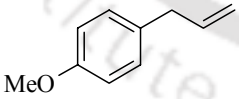
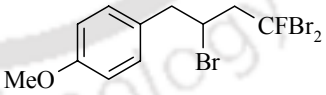
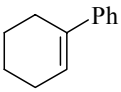
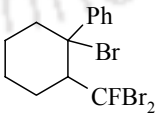
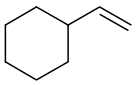
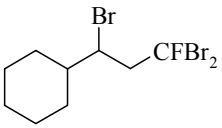
Scheme 2.1

2.3 Results and discussions

Following a literature procedure for the addition of perfluoroalkyl monobromide under free radical conditions,[17] where $CFBr_3$ was treated with olefin in the presence of sodium dithionate, the reaction resulted in a complex mixture. A variety of addition reactions of organic halides to alkenes catalyzed by palladium (0) have been reported.[18] Klabunde and Low have studied the stabilities and properties of some oxidative addition products of palladium and perfluoroalkyl halides.[19] They studied various fluorohaloalkanes, however there was no mention of $CFBr_3$.

Taking cues from this it was envisaged that palladium (0) might be a suitable reagent for the addition of $CFBr_3$ to olefins. The scope of this reaction was explored with various olefinic substrates. The reaction is generalized as through entries 1-10 (Table 2.1).

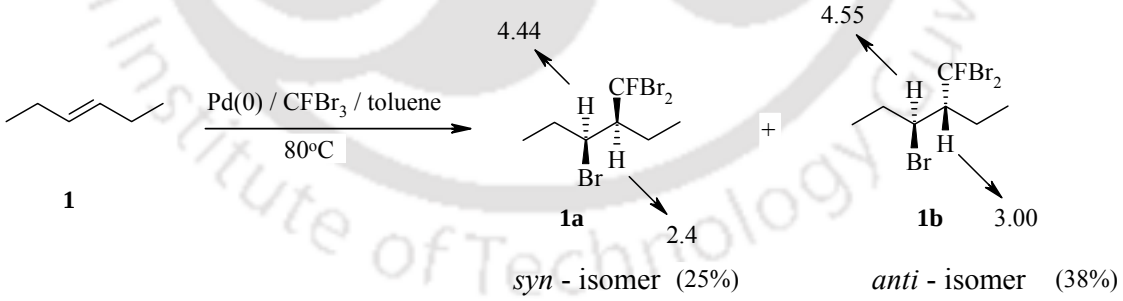
Table 2.1: Synthesis of 1,1,3-tribromo-1-fluoroalkanes catalyzed by Palladium(0)

Entry	Substrates	Time (h)	Products	Yield[a] (%)
1		30		79
2		16		79
3		31		78
4		49		96
5		27		63[b]
6		21		79
7		15		81
8		17		75
9		71		33
10		18		85

(b) Determined by ^{1}H NMR.

(a) Isolated yields. The compounds are characterized by GC-MS, ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectroscopy.

Excellent yields were obtained with both terminal and internal olefins to the corresponding fluorobrominated products. Initially we performed an experiment with 1-octene as a model substrate with $CFBr_3$ in presence of catalytic amount of palladium(II) acetate and triphenyl-phosphine, K_2CO_3, in dry toluene under nitrogen atmosphere at room temperature. The product formation was very less even after long time. Therefore starting material was isolated as the major product. When the reaction was carried out at an elevated temperature of 80 ^oC in an oil bath, we found an increment of product formation. The reaction proceeded well with aliphatic terminal alkenes, internal cyclic olefins like the norbornene, cyclohexene and cyclooctene. Aromatic substrates such as allyl benzene and allyl anisole also reacted well under the similar reaction conditions (Table 2.1). The relatively low yield and long reaction time of 1-cyclohexenylbenzene (entry 9) may be due to the steric reason. Under similar reaction conditions we checked the reactivity of dibromodifluoromethane with the olefins and the reaction did not proceed. It may be due to the formation of an unstable $CFBr_2PdBr$ species,[19] as reported earlier. With unfunctionalized olefins such as 1-octene, 4-methyl-1-pentene, the insertion occurs in such a way that the bromine is added at highly substituted position and the $CFBr_2$ group at least substituted end of the olefin. For example, the ^1H NMR of 1,1,3-tribromo-1-fluorononane showed a multiplet at δ 4.20 integrating to one proton. This indicates that the bromine is attached to the more substituted end of the olefin. Internal olefins such as *trans*-3-hexene **1** gave a mixture of diastereomers **1a** and **1b**, which was separated by preparative thin layer chromatographic technique using hexane as eluent to give *cis* (25%) and *trans* (38%) product (Scheme 2.2).

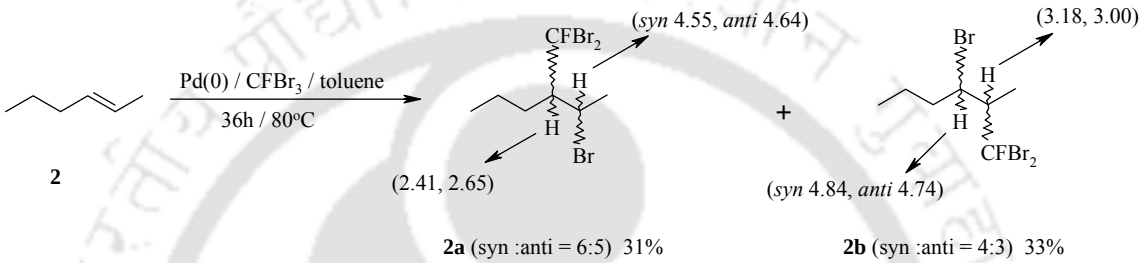


Scheme 2.2

The ^1H NMR of (3S, 4S)-3-bromo-4-(dibromofluoromethyl)hexane **1a** showed a multiplet at δ 4.44 corresponding to the proton, -C<u>H</u>Br- with a coupling constant J = 6.8 Hz and δ 2.40 to the proton attached to -$CFBr_2$- group. Hence from the coupling constant values the stereochemistry of the product was confirmed to be the *cis* isomer. The ^1H NMR of (3S, 4R)-3-bromo-4-(dibromofluoromethyl)hexane **1b** displayed multiplets at δ 4.55 indicating the proton, -C<u>H</u>Br-

with a coupling constant J = 10.8 Hz and δ 3.00 to the proton attached to -$CFBr_2$- group. In accordance with the standard ^{1}H NMR values the product was confirmed to be the *trans* isomer.

In case of unsymmetrical olefin the addition of $CFBr_3$ is not regioselective. Bromine was added either at 2 or 3 position of the double bond. Thus the reaction of unsymmetrical olefin *trans*-2-hexene **2** with $CFBr_3$ gave two inseparable mixtures *syn-anti*-2-Bromo-3-dibromofluoro- methylhexane **2a** and *syn-anti*-3-Bromo-2-dibromofluoromethylhexane **2b** in 31% and 33% yields respectively (Scheme.2.3).



Scheme 2.3

*c*is-*trans*-2-Bromo-3-dibromofluoromethylhexane displayed a multiplet at δ 4.55 with a coupling constant J = 6.8 Hz and another multiplet at δ 4.64 with J = 10.8 Hz corresponding to the proton (-CHBr-). Similarly *cis-trans*-3-bromo-2-dibromofluoro methylhexane showed two multiplets one at δ 4.74 with coupling constantr J = 10.8 Hz and another at δ 4.84 with coupling constant J = 6.8 Hz corresponding to the proton (-CHBr-). From the above coupling constants the presence of *cis* and *trans* isomers were confirmed.

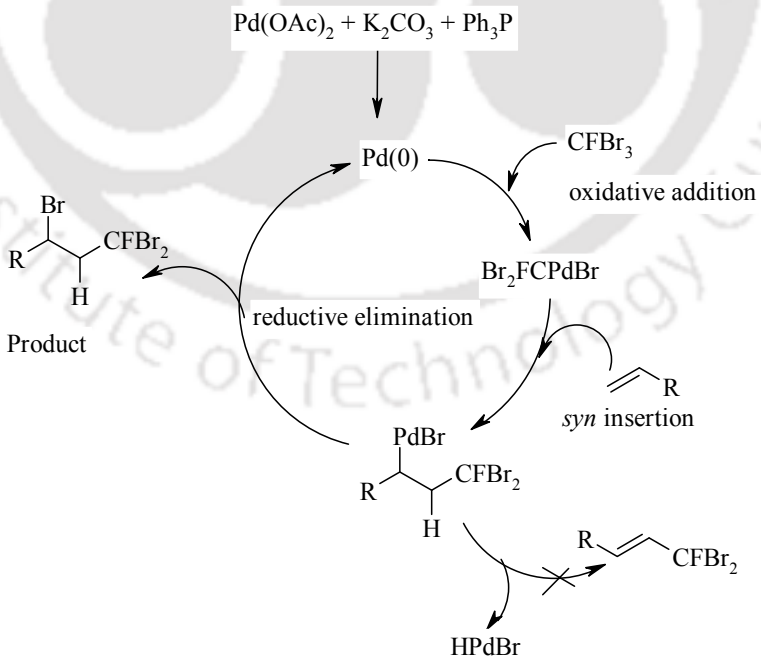
The ^{1}H NMR of *cis-trans*-1-Bromo-2-dibromofluoromethylcyclohexane showed multiplet at δ 2.04 corresponding to the -CH_2- group adjacent to -CHBr, another multiplet at δ 2.65 was assigned to the proton attached to -$CFBr_2$, the methine proton -CHBr- showed a multiplet at δ 4.17 with a coupling constant $^3J_{H,H}$ = 9.2 Hz for the *trans* isomer and a broad singlet at δ 4.96 for the *cis* compound. ^{19} F NMR displayed a doublet at δ 108.43 with coupling constant J = 18.4 Hz for the *trans* and at δ 122.35 with J = 11.65 Hz for the *cis* isomer. Hence from the above coupling constants the presence of isomers were confirmed and the ratio was determined based on the integration of -CHBr- proton (*cis*: *trans* 45:55).

The product 2-Bromo-3-(dibromofluoromethyl)-2-methylpentane was obtained by the addition of $CFBr_3$ to 2-methyl-2-pentene. ^{1}H NMR displayed a triplet for the terminal methyl group at δ 1.35 with coupling constant J = 7.2 Hz, the methylene group adjacent to the methyl shows a multiplet at δ 1.78, the methine proton to which -$CFBr_2$ group is attached shows a multiplet at δ

2.74 and a broad singlet for the two methyl groups at δ 1.99. The absence of peak at δ 4.5 indicates that the bromine is attached to the tertiary carbon. ^{19}F NMR displayed a doublet at δ 111.85 with J = 18.42 Hz indicating that a single proton is present adjacent to the -$CFBr_2$- group. ^{13}C NMR showed a doublet at δ 100.10 with coupling constant J = 322.6 Hz corresponding to the carbon attached to the fluorine atom and a doublet at δ 68.80 with J = 12.2 Hz corresponding to the carbon adjacent to the $CFBr_2$ group. Hence from the spectral values it is confirmed that bromine is added at highly substituted end of the olefin.

The ^{1}H NMR of 1-(2,4,4-tribromo-4-fluorobutyl) benzene showed multilplets at δ 4.45 for the proton -C<u>H</u>Br-, δ 3.45 indicating the (PhC<u>H_2</u>-) protons, δ 3.11- 3.33 for the methylene group adjacent to -$CFBr_2$-, and δ 7.21- 7.35 for the aromatic protons. ^{19}F NMR displayed a triplet at δ 115.27 with a coupling constant J = 17.30 Hz indicating the presence of the methylene group adjacent to -$CFBr_2$-. ^{13}C NMR showed a doublet at δ 93.10 with coupling constant J = 319.6 Hz corresponding to the carbon directly attached to the fluorine atom, another doublet was shown at δ 59.52 with J = 12.2 Hz indicates the carbon adjacent to the attached $CFBr_2$ group. The product is confirmed from the above spectral values.

The probable mechanism is shown below in Scheme 2.4. Palladium (II) acetate in combination with triphenylphosphine as ligand and the base anhydrous potassium carbonate resulted in palladium(0) species.



No β - hydrogen elimination product

Scheme 2.4

The first step is the oxidative addition of Pd(0) to $CFBr_3$ to form $Br_2FCPdBr$ species which in turn undergoes a syn insertion to the olefin. Reductive elimination of palladium(II) to palladium(0) with consequent addition of bromine gives the product. Thus, the regioselectivity of insertion was controlled by steric and not by any electronic factors with these substrates. β-Hydrogen elimination, which generally occurs in the Heck reaction, does not take place in this case.

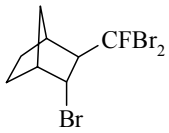
2.4 Conclusion

In conclusion we have devised an efficient method for the synthesis of 1,1,3-tribromo-1-fluoroalkanes catalyzed by *in situ* generated palladium(0). Since bromine being at 1 and 3 positions further methodologies can be developed for C-C bond formation. The mild reaction conditions and good yields without any side products make this method an attractive and practical entry to partially fluorobrominated compounds.

2.5 Experimental Section

General procedure for the addition of $CFBr_3$ to olefins: A mixture of 1-octene (100mg, 0.89mmol) and $CFBr_3$ (300mg, 1.12mmol) was added to a reaction flask containing $Pd(OAc)_2$ (4.00mg, 0.018mmol), Ph_3P (9.35mg, 0.036mmol) in 2 ml of distilled toluene. The reaction flask was evacuated and flushed with dry nitrogen gas, two such cycles were repeated. The reaction mixture was heated with stirring at 80 ^oC in an oil bath under nitrogen atmosphere for 30 hours. The progress of the reaction was monitored by TLC (silica gel) using hexane as the eluent. After completion, the reaction mixture was neutralized with 5% HCl. The product was extracted with (2 × 10ml) of ethyl acetate and the organic fraction was washed with saturated brine solution and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to give the crude product, which was purified by a short column chromatography over silica gel using hexane as eluent to give 269 mg (79%) of the pure 1,1,3- tribromo-1–fluorononane as a colorless oil. The compound was characterized by spectroscopic methods. **IR** (Neat): 2927, 2860, 1459, 1122, 997, 766 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3 H, -CH_3), 1.25 -1.38 (m, 6 H, 3 ×-CH_2-), 1.46 -1.59 (m, 2 H, -CH_2-), 1.85- 1.93 (m, 2 H, -CH_2-), 3.27 -3.47 (m, 2 H, -CH_2-), 4.20 (m, 1 H, -CH-); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 22.7, 27.2, 28.5, 31.7, 38.6, 49.7, 60.5,(d, J = 17.6 Hz), 93.2 (d, J = 319.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$ - C_6F_6): δ 114.97 (t, J = 17.29 Hz, 1 F, -$CFBr_2$).

Spectral data



2-Bromo-3 -(dibromofluoromethyl)bicyclo [2.2.1] heptane

State: liquid

Colour: colourless

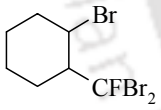
IR (Neat): 2971, 2884, 1465, 1235, 1153, 979, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35- 1.42 (m, 2 H), 1.56-1.67 (m, 2 H), 1.82 (d, *J* = 10.8 Hz, 1 H), 2.00 (m, 1 H), 2.60- 2.70 (m, 3 H), 4.17 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 29.7, 35.6, 42.0, 45.3, 54.5, 70.9 (d, *J* = 18.3 Hz), 97.3 (d, *J* = 321.10 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 105.86 (d, *J* = 23.69 Hz, 1 F, -$CFBr_2$).

EIMs (m/z): 361 (M^+-1), 363 ((M^+-1) + 2), 365 ((M^+-1) + 4), 367 ((M^+-1) + 6), 285, 283, 281, 203, 201, 123.



***cis-trans*-1-Bromo-2-dibromofluoromethylcyclohexane** (*cis: trans*; 45: 55)

State: liquid

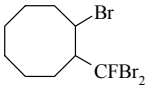
Colour: colourless

IR (Neat): 2941, 2862, 1448, 1299, 1250, 1190, 1017, 941, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (m, 2 H, -CH_2-), 1.65 (m, 2 H), 1.85 (m, 1 H), 2.04 (m, 1 H), 2.65 (m, 3 H), 4.17 (*trans*, m, 0.5 H), 4.96 (*cis*, bs, 0.5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 23.4, 23.8, 25.1, 25.4, 29.9, 36.0, 37.0, 50.4, 52.3, 60.1 (d, *J* = 18.3 Hz), 60.7 (d, *J* = 13.8 Hz), 100.5 (d, *J* = 324.9 Hz), 103.1 (d, *J* = 324.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 108.43 (d, *J* = 18.42 Hz, 0.5 F, -$CFBr_2$), 122.35 (d, *J* = 11.65 Hz, 0.5 F, - $CFBr_2$).



***cis-trans*-1-Bromo-2-dibromofluoromethylcyclooctane** (*cis*: *trans*; 47: 53)

State: liquid

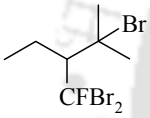
Colour: colourless

IR (Neat): 2930, 2858, 1465, 1239, 1169, 1104, 958, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 - 1.56 (m, 4 H, 2 ×-CH_2-), 1.70 (m, 1 H), 1.73 - 2.15 (m, 5 H), 2.29 - 2.43 (m, 2 H), 2.58 (m, 1 H), 4.40 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 25.4, 27.1, 27.6, 27.7, 28.6, 29.4, 29.5, 32.8, 34.1, 36.2 (2C), 37.4 (2C), 55.1 (d, J = 29 Hz), 56.6 (t, J = 18.3 Hz), 105.7 (d, J = 318.8 Hz), 105.9 (d, J = 319.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ114.65 (d, J = 18.4 Hz, 1 F, - $CFBr_2$), 119.00.



2-Bromo-3-(dibromofluoromethyl)-2-methylpentane

State: liquid

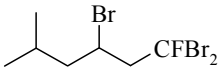
Colour: colourless

IR (Neat): 2981, 2879, 1465, 1388, 1214, 1112, 963, 779 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3 H, -CH_3), 1.78 (m, 2 H, -CH_2-), 1.99 (bs, 6 H, 2×-CH_3), 2.74 (m, 1 H, -CH-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 27.5, 31.8, 36.4, 68.8 (d, J = 12.2 Hz), 69.0, 100.1 (d, J = 322.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 111.85 (d, J = 18.42 Hz, 1 F, -$CFBr_2$).



1,1,3-tribromo-1-fluoro- 5-methylhexane

State: liquid

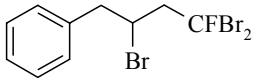
Colour: colourless

IR (Neat): 2959, 2874, 1463, 1378, 1182, 1126, 986, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.8 Hz, 3 H, -CH_3), 0.98 (d, *J* = 6.8 Hz, 3 H, -CH_3), 1.68 (m, 1 H, -CH-), 1.79 - 1.95 (m, 2 H), 3.26 (m, 1 H), 3.45 (m, 1 H), 4.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 23.1, 26.6, 47.7, 48.2, 61.0 (d, *J* = 18.3 Hz), 93.2 (d, *J* = 320.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 115.61 (t, *J* = 17.30 Hz, 1F, -$CFBr_2$).



1-(2, 4, 4-tribromo -4-fluorobutyl) benzene

State: liquid

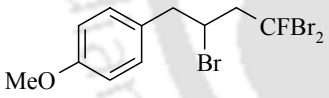
Colour: colourless

IR (Neat): 2930, 1455, 1194, 1122, 999, 769, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14 (dd, *J* = 14.4 and 8.0 Hz, 1 H), 3.25 - 3.45 (m, 3 H), 4.45 (m, 1 H, -CH-), 7.21 - 7.35 (m, 5 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 45.0, 48.8, 59.5 (d, *J* = 18.3 Hz), 93.1 (d, *J* = 319.6 Hz), 127.2, 129.3, 130.2, 158.6.

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 115.27 (t, *J* = 17.30 Hz, 1 F, -$CFBr_2$).



1-(2, 4, 4-tribromo-4-fluorobutyl) -4-methoxybenzene

State: liquid

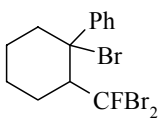
Colour: colourless

IR (Neat): 2940, 2843, 1619, 1511, 1460, 1260, 1199, 1122, 1035, 830, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.12 (dd, *J* = 14.4 and 8.4 Hz, 1H), 3.22- 3.38 (m, 3 H), 3.80 (s, 3 H, -CH_3), 4.42 (m, 1 H, -CH-), 6.85 (m 2 H, ArH), 7.12 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 44.2, 49.3, 55.3, 59.4 (d, *J* = 18.3 Hz), 93.2 (d, *J* = 319.5 Hz), 113.9, 128.5, 129.2, 137.1.

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 115.33 (t, *J* = 18.00 Hz, 1 F, -$CFBr_2$).



1-(1-bromo-2-(dibromofluoromethyl)cyclohexyl)benzene

State: liquid

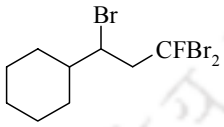
Colour: colourless

IR (Neat): 2935, 2863, 1445, 1265, 1096, 1025, 799, 712 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (m, 3 H), 1.77 (m, 3 H), 2.06 (m, 1 H), 2.16 (m, 1 H), 2.98 (m, 1 H), 7.33- 7.56 (m, 3 H, ArH), 7.93 (m, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.6, 25.7, 28.6, 33.6, 54.8 (d, J = 12.2 Hz), 104.6 (d, J = 323.3 Hz), 126.5, 126.9, 127.8, 143.1.

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 125.95 (d, J = 9.00 Hz, 1 F, -$CFBr_2$).



(1, 3, 3-tribromo-3-fluoropropyl)cyclohexane

State: liquid

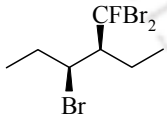
Colour: colourless

IR (Neat): 2925, 2858, 1450, 1189, 1117, 999, 764 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (m, 6 H, 3 ×-CH_2-), 1.60-1.78 (m, 5 H), 3.30 (m, 2 H, -CH_2-), 4.22 (m, 1 H, -CHBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 26.1, 26.2, 28.1, 31.2, 43.9, 56.1, 58.2 (d, J = 18.3 Hz), 93.7 (d, J = 320.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 114.68 (t, J = 18.42 Hz, 1 F, -$CFBr_2$).



Syn-(3S, 4S) -3-bromo-4-(dibromofluoromethyl)hexane

State: liquid

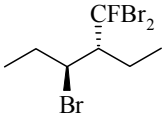
Colour: colourless

IR (Neat): 2971, 2884, 1460, 1388, 1286, 1132, 1066, 989, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.2 Hz, 3 H, -CH_3), 1.18 (t, J = 7.2 Hz, 3 H, -CH_3), 1.91- 2.00 (m, 4 H, 2 ×-CH_2-), 2.40 (m, 1 H, -CHCFBr_2), 4.44 (m, J = 6.8 Hz, 1 H, -CHBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.9, 14.2, 24.6, 32.6, 58.1, 62.7 (d, J = 15.2 Hz), 101.4 (d, J = 321.10 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 115.28 (d, J = 11.66 Hz, 1 F, -$CFBr_2$).



Anti-(3S, 4R)-3-bromo-4-(dibromofluoromethyl)hexane

State: liquid

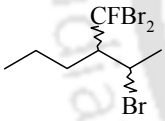
Colour: colourless

IR (Neat): 2971, 2879, 1460, 1388, 1281, 1204, 1122, 1061, 974, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, *J* = 6.8 Hz, 3 H, $-CH_3$), 1.26 (t, *J* = 7.2 Hz, 3 H, $-CH_3$), 1.80 (m, 1 H), 1.95 (m, 2 H), 2.14 (m, 1 H), 3.00 (m, 1 H, $-CHCFBr_2$), 4.55 (m, *J* = 10.8 Hz, 1 H, -CHBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 14.5, 21.8, 27.0, 57.8, 65.4 (d, *J* = 16.00 Hz), 99.9 (d, *J* = 321.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 115.24 (d, *J* = 14.30 Hz, 1 F, $-CFBr_2$).



***cis-trans*-2-Bromo-3-dibromofluoromethylhexane**

State: liquid

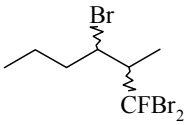
Colour: colourless

IR (Neat): 2966, 2879, 1465, 1250, 1132, 1055, 933, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 (m, 3 H, $-CH_3$), 1.40 (m, 3 H, $-CH_3$), 1.65 (m, 1 H), 1.82 (m, 2 H), 1.98 (m, 1 H), 2.41 (m, 0.6 H, *cis*), 2.65 (m, 0.4 H, *trans*), 4.55 (m, 0.6 H, *cis*), 4.64 (m, 0.4 H, *trans*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 14.2, 14.3, 20.9, 22.9, 26.8, 33.6, 40.8, 49.9, 54.8, 56.5 (d, *J* = 16.8 Hz, *cis*), 62.5 (d, *J* = 15.2 Hz, *trans*), 100.0 (d, *J* = 322.00 Hz, *cis*), 101.2 (d, *J* = 321.80 Hz, *trans*).

^{19}F NMR (376 MHz, $CDCl_3$ - C_6F_6): δ 111.36 (d, *J* = 14.66 Hz, 0.6 F, $-CFBr_2$, *cis*), 115.33 (d, *J* = 11.66 Hz, 0.44 F, $-CFBr_2$, *trans*).



***cis-trans*-3-Bromo -2-dibromofluoromethylhexane**

State: liquid

Colour: colourless

IR (Neat): 2960, 2873, 1460, 1383, 1255, 1204, 1122, 1055, 933, 769 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (m, 3 H, -CH_3), 1.48 (m, 3 H, -CH_3), 1.66-1.94 (m, 4 H), 3.00 (m, 0.4 H, *trans*), 3.18 (m, 0.6 H, *cis*), 4.74 (m, 0.4 H, *trans*), 4.84 (m, 0.6 H, *cis*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 13.3, 14.3, 21.3, 21.7, 23.0, 30.1, 35.0, 47.7, 55.4, 59.7 (d, J = 16.8 Hz, *cis*), 63.2 (d, J = 16.0 Hz, *trans*), 99.4 (d, J = 322.6 Hz, *cis*), 99.8 (d, J = 321.80 Hz, *trans*).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 111.76 (d, J = 18.4 Hz, 0.6 F, -$CFBr_2$, *cis*), 115.32 (d, J = 15.80 Hz, 0.4 F, -$CFBr_2$, *trans*).

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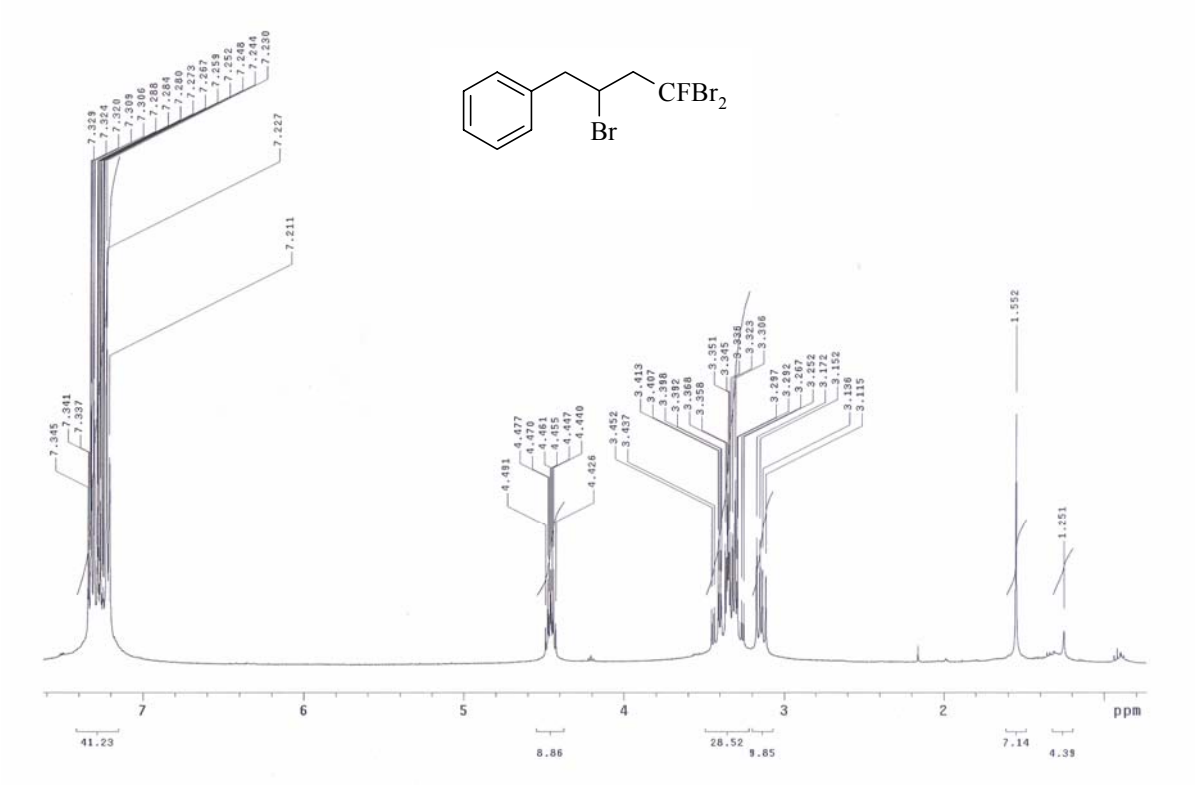
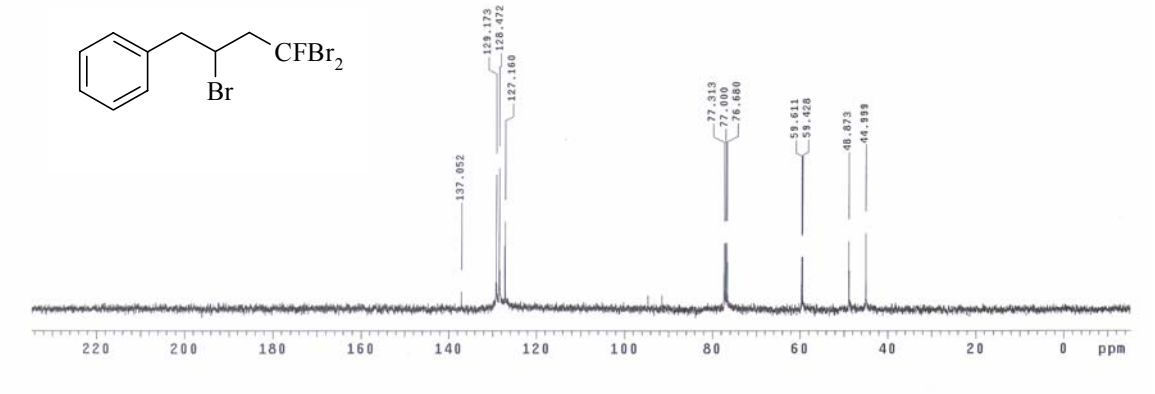
2.6 Selected Spectra of 1,1,3-tribromofluoroalkanes

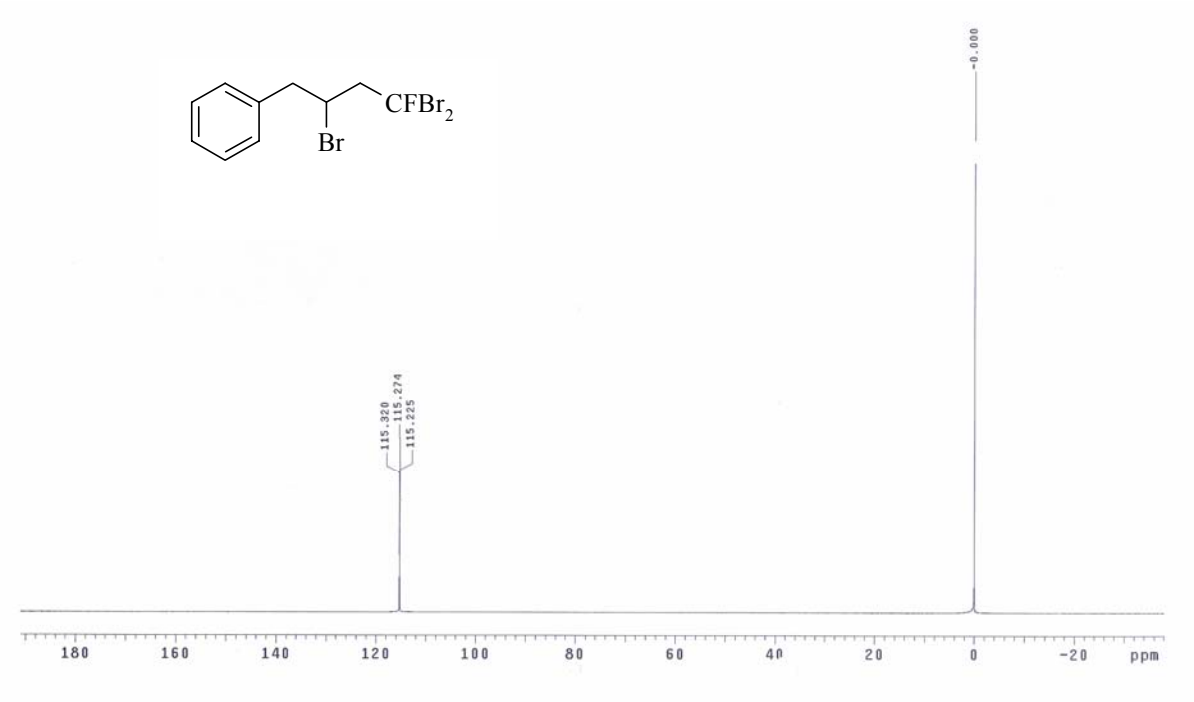
^{1}H NMR (400MHz, $CDCl_3$): 1-(2,4,4-tribromo-4-fluorobutyl)benzene



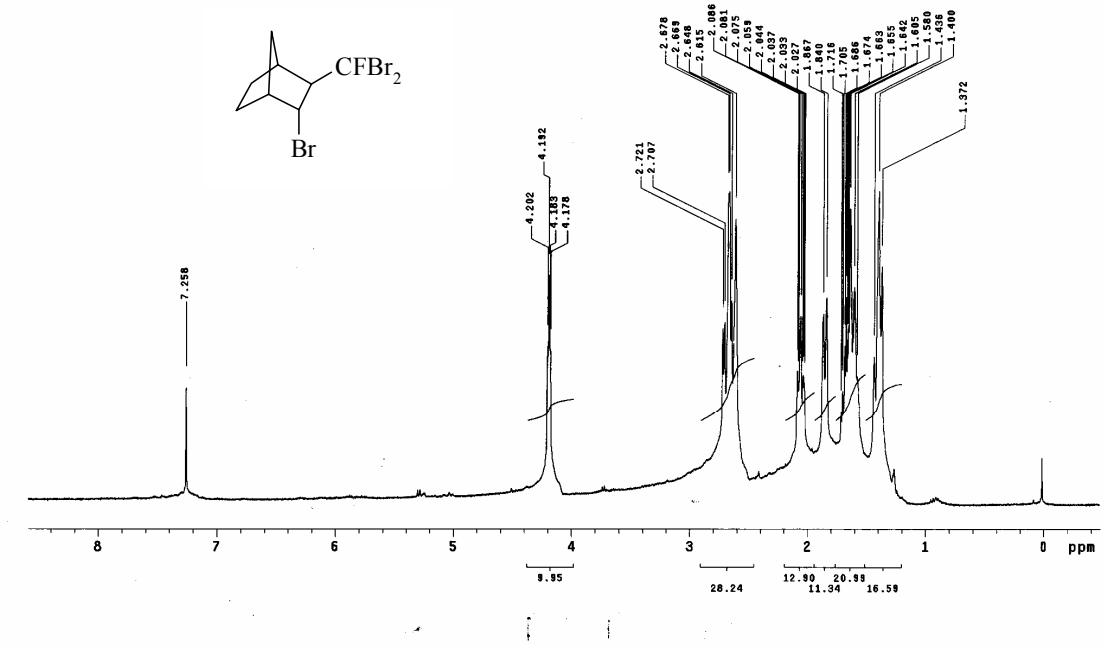
^{13}C NMR (100MHz, $CDCl_3$): 1-(2,4,4-tribromo-4-fluorobutyl)benzene



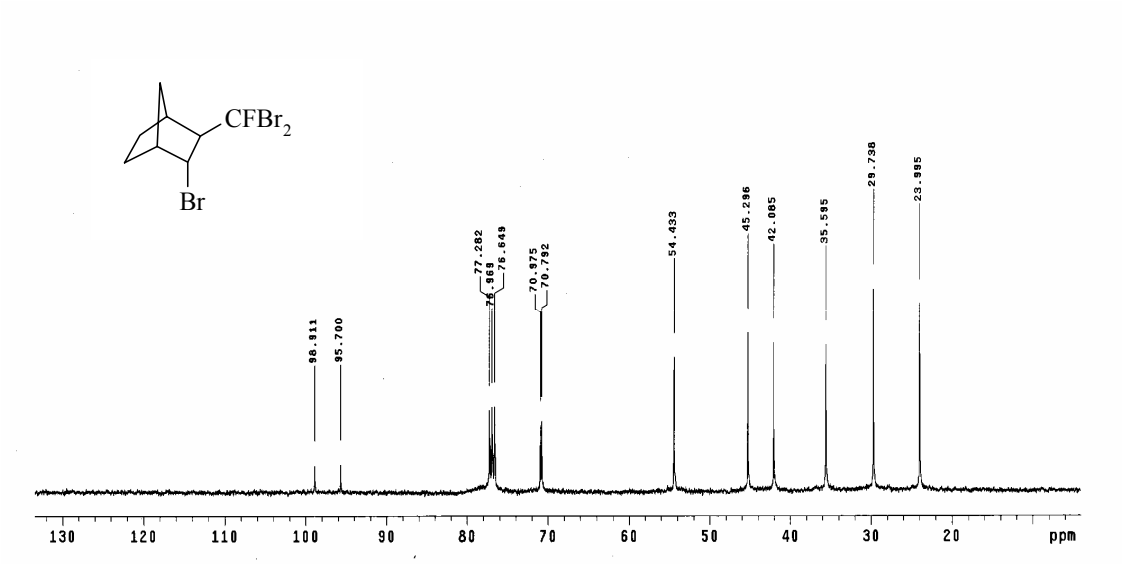
^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): 1-(2,4,4-tribromo-4-fluorobutyl)benzene



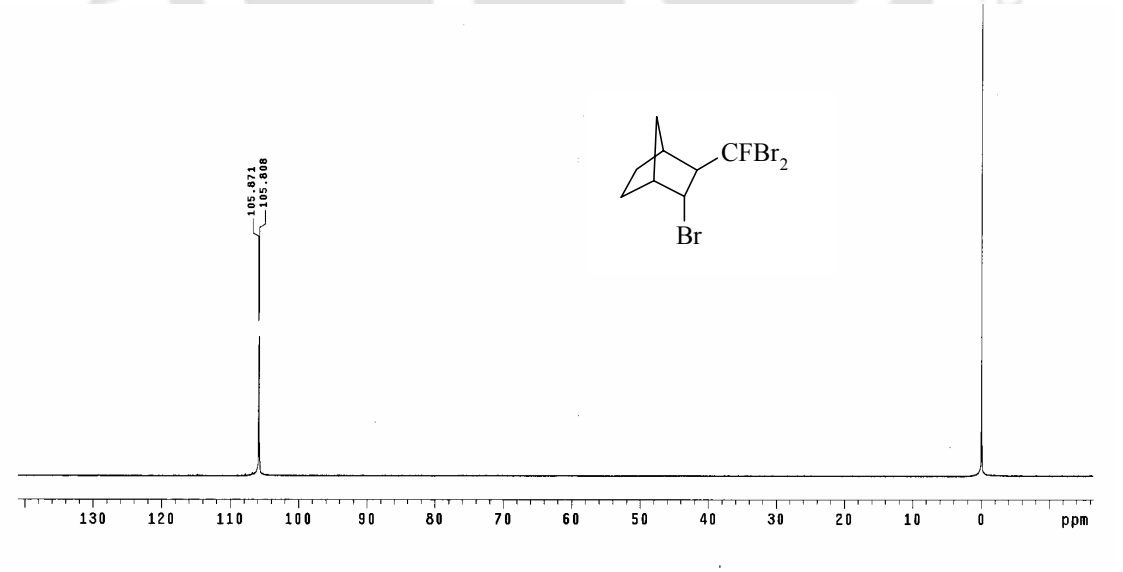
^{1}H NMR (400MHz, $CDCl_3$): 2-Bromo-3 -(dibromofluoromethyl)bicyclo [2.2.1] heptane



^{13}C NMR (100MHz, $CDCl_3$): 2-Bromo-3 -(dibromofluoromethyl)bicyclo [2.2.1] heptane



^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): 2-Bromo-3 -(dibromofluoromethyl)bicyclo [2.2.1] heptane



2.7 References

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CHAPTER III

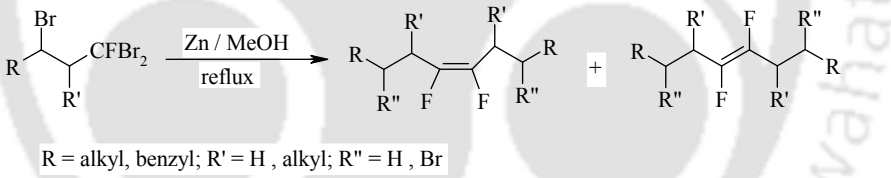
Reductive Coupling of 1,1,3-tribromo-1-fluoroalkanes: Synthesis of 1,2-difluoroalkenes

3.1 Objective

The main objective was to develop a simple method for the synthesis of 1,2-difluoroolefins from 1,1,3-tribromofluoroalkanes in presence of zinc and methanol.

3.2 Present work

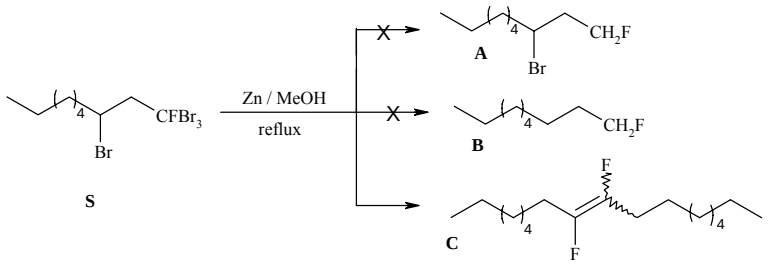
1,2-Difluoroethylenes are useful building blocks in organofluorine chemistry and have found wide applications as monomers[1] and as precursors for the synthesis of biologically active agents like peptide isosteres[2] and enzyme inhibitors.[3] The ease of structural modification of the fluorinated olefins makes them an interesting scaffold for design of functional materials such as the liquid crystals,[4] compounds for non-linear optics[5] or media for holographic data storage.[6] The use of zinc has gained popularity in effecting synthetically useful transformations like the ene cyclization,[7] the Diels-Alder reaction,[8] the synthesis of benzhydrols,[9] homoallylic alcohols,[10] selective reduction of alkynes to *cis*-alkenes,[11] reductive coupling of carbonyl compounds[12] and dehalogenation reactions.[13] In this chapter we describe the utilization of zinc for the synthesis of *cis*-and *trans*-1,2-difluoroolefins in refluxing methanol under nitrogen atmosphere from the corresponding tribromofluoro compounds shown in Scheme 3.1.



Scheme 3.1

3.3 Results and discussions

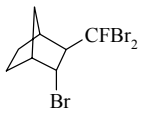
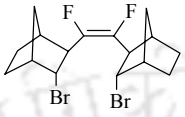
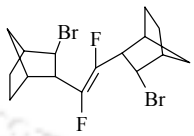
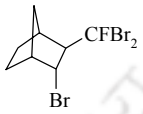
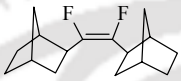
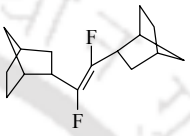
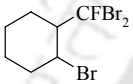
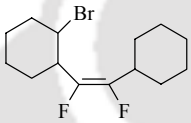
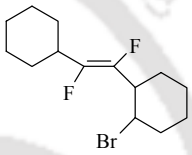
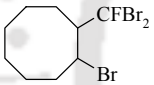
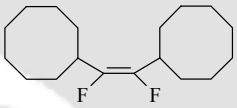
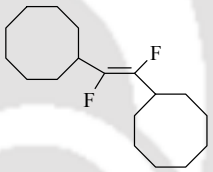
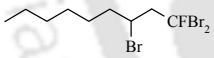
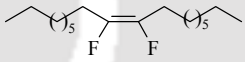
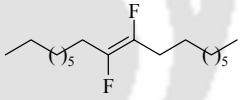
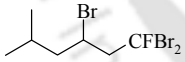
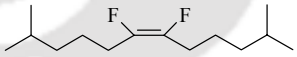
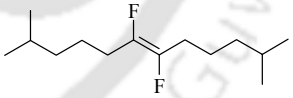
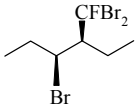
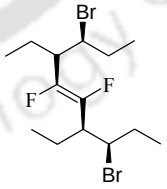
Zinc dust in methanol or acetic acid has long been used to replace halogen by hydrogen.[13] To utilize its reducing property towards 1,1,3-tribromo-1-fluoroalkanes, when 1,1,3-tribromo-1-fluorononane was treated with activated zinc dust in methanol the usual debromination product **A** or **B** was not observed but reductive coupling product **C** was obtained (Scheme 3.2).



Scheme 3.2

The same reaction proceeded well for cyclic and acyclic substrates with moderate yields as shown in Table 3.1.

Table 3.1: Synthesis of 1, 2-Difluoroolefins with Zn / MeOH

Entry	Substrates	Time (hr)	Products		Yield (%)[a]	
			Cis (c)	Trans (d)	Cis	Trans
1		18			23	44
2		52			21	48
3		22			18	36
4		20			24	43
5		14			28[b]	44[b]
6		28			26	38
7		8	—		—	62

(a) Isolated yields. The compounds are characterized by GC-MS, ^{1}H NMR, ^{19}F NMR and ^{13}C NMR.

(b) Determined by ^{1}H NMR.

2-Bromo-3-(dibromofluoromethyl)bicyclo[2.2.1]heptane on treatment with zinc in refluxing methanol for 18 hours gave two isomeric cis and trans compounds. The cis and trans isomers were isolated by preparative thin layer chromatographic technique yielding 23% and 44% respectively. The ^{1}H NMR of *cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoro-ethene showed a multiplet at δ 4.26 corresponding to the proton attached to bromine atom (-

CHBr-), and a multiplet at δ 2.63 for –CHCF=CFCH- proton. ^{13}C NMR displayed a doublet at δ 138.3 with a coupling constant J = 231.1 Hz corresponding to the carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 51.1 with J = 21.4 Hz indicates the carbon adjacent to the -CF=CF- group. ^{19}F NMR spectrum displayed a doublet at δ 15.75 with coupling constant J = 36.85 Hz indicating the presence of a proton adjacent to the olefinic fluorine, (-CHCF=CF-). The *cis* conformation of the product was determined by single crystal X-ray crystallography technique. The ORTEP diagram is shown in Figure 1.

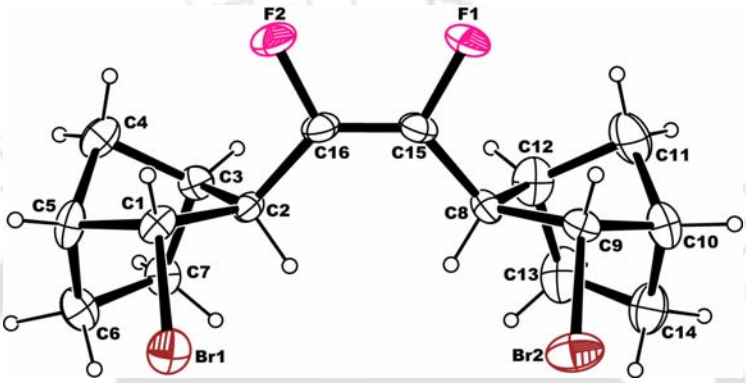


Fig 1. *cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene.

The ^{1}H NMR of *trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene showed a multiplet at δ 4.24 corresponding to the protons attached to the bromine atom (-CHBr-) and a multiplet at δ 2.72 for –CHCF=CFCH- proton. ^{13}C NMR displayed a doublet at δ 138.3 with a coupling constant J = 231.1 Hz corresponding to the carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 51.1 with J = 21.4 Hz indicates the carbon adjacent to the -CF=CF- group. ^{19}F NMR spectrum displayed a doublet at δ 13.43 with $^{3}J_{H\text{-}F}$ = 31.59 Hz, indicating the presence of a proton adjacent to olefinic fluorine, (-CHCF=CF-), the high resolution mass spectrum showed an exact mass peak at 410.00489 as compared with the calculated mass 410.1340. The ORTEP diagram of the *trans* isomer is shown in Figure 2.

2-Bromo-3-(dibromofluoromethyl)bicyclo[2.2.1]heptane on treatment with zinc in refluxing methanol for 52 hours gave *cis* and *trans*-1,2-*bis*(Bicyclo[2.2.1]heptan-2-yl)-1,2-difluoro-ethene in 21 % and 48 % respectively as isolated yields. In ^{1}H NMR the disappearance of peak at δ 4.26 indicates the absence of both the bromine atoms at C-1 and C-1'. The ^{19}F NMR of *cis*-1,2-*bis*(Bicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene displayed a doublet at δ 12.00 with coupling constant J = 30.45 Hz for the proton adjacent to olefinic fluorine -CHCF=CF-. ^{13}C NMR showed a doublet at δ 147.00 with coupling constant J = 250.0 Hz for carbon directly

attached to the fluorine atom (=C-F), another doublet was shown at δ 42.26 with J = 6.1 Hz indicated the carbon adjacent to the –CF=CF-group. Thus from the above spectral values the presence of *cis* isomer was confirmed.

The ^{19}F NMR of *trans*-1,2-*bis*(bicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene displayed a doublet at δ -1.10 with coupling constant J = 19.5 Hz for the proton adjacent to olefinic fluorine -CHCF=CF-. ^{13}C NMR showed a doublet at δ 130.00 with coupling constant J = 203.6 Hz for carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 41.92 with J = 13.7 Hz indicating the carbon adjacent to the –CF=CF- group. Hence from the above spectral data the trans isomer was confirmed.

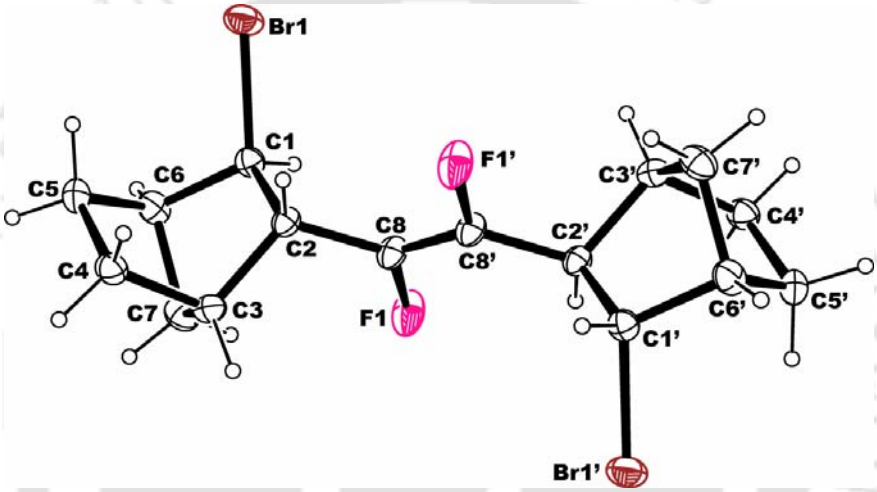


Fig 2. *trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene

1-Bromo-2-(dibromofluoromethyl)cyclohexane upon treatment with zinc in refluxing methanol for 22 hours gave *cis- and trans*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)-cyclohexane in 21 % and 48% yields respectively. The ^{1}H NMR of *cis*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)cyclohexane showed a multiplet at δ 4.10 for the proton attached to the bromine atom (-CHBr-), ^{19}F NMR showed a doublet of doublet (dd) at δ 12.24 with a coupling constant $^{3}J_{F,F(cis)}$ = 31.58 Hz and $^{3}J_{H\text{-}F}$ = 9.4 Hz, for C_7-F, and another dd at δ 5.20 with $^{3}J_{F,F(cis)}$ = 34.21 Hz and $^{3}J_{H\text{-}F}$ = 17.30 Hz, for C_8-F. Thus the cis isomer was confirmed with the standard NMR values and further confirmed by single crystal X-ray diffraction technique. The ORTEP diagram of *cis*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)cyclohexane is shown in Figure 3.

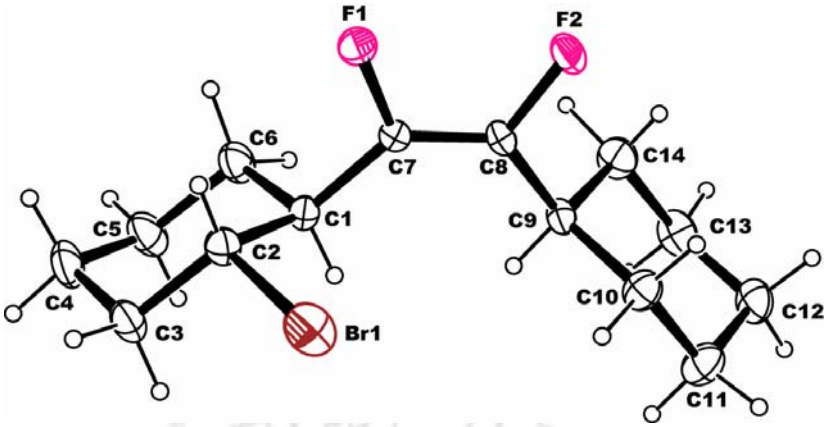


***Fig 3. cis*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)cyclohexane**

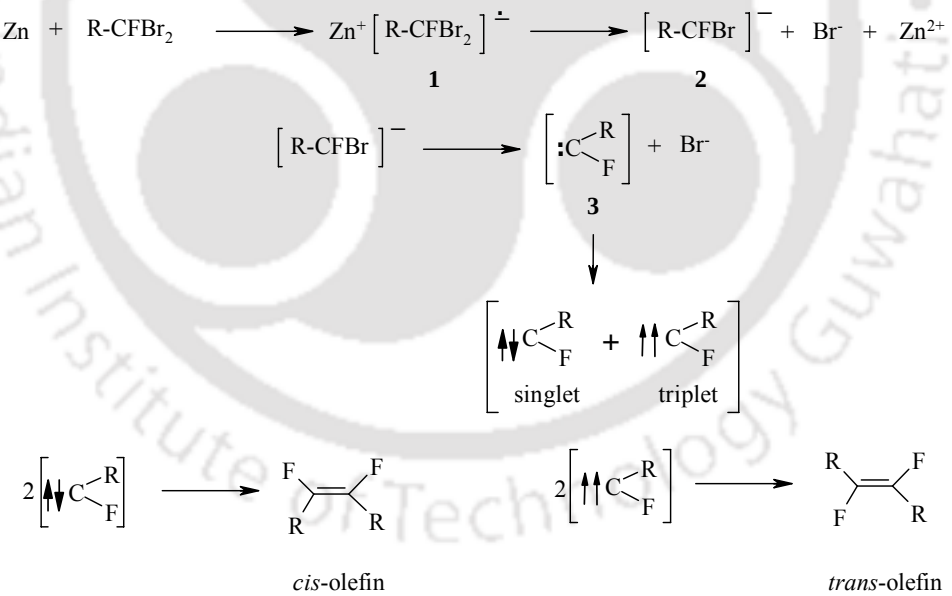
The ^{19}F NMR of *trans*-2-(2-bromocyclohexyl)-1,2-difluorovinyl)cyclohexane showed a (dd) doublet of doublet at δ -1.21 with coupling constant $^{3}J_{F,F(trans)}$ = 122.2 Hz and 30.46 Hz another dd at δ -8.00 with coupling constants $^{3}J_{F,F(trans)}$ = 122.57 Hz and $^{3}J_{H\text{-}F}$ = 30.46 Hz for the other fluorine atom. Hence in comparison with the standard values of coupling constants the *trans* isomer was confirmed. The mass spectrum EIMS (m/z) shows a peak at (M^+) 308 for the expected product.

In these reaction conditions cyclic substrate such as 1-bromo-2-dibromofluoro methylcyclooctane gave *cis*- and *trans*-1,2-dicyclooctyl-1,2-difluoroethene in 24 % and 43 % respectively as isolated yields. The ^{1}H NMR of the products did not show any peak in the region δ 3-5. Thus from the above spectral values the absence of bromine is confirmed. The ^{19}F NMR of *cis*-1,2-dicyclooctyl-1,2-difluoroethene displayed a doublet at δ 8.32 with coupling constant J = 30 Hz indicating the presence of proton adjacent to olefinic fluorine, -CHCF=CF-. ^{13}C NMR showed a doublet at δ 130.00 with coupling constant J = 221.2 Hz corresponding to the carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 36.89 with J = 25.9 Hz indicating the carbon adjacent to the –CF=CF-group. The mass spectrum EIMS (m/z) shows a peak at (M^+) 284 for the expected product.

Similarly the ^{19}F NMR of *trans*-1,2-dicyclooctyl-1,2-difluoroethene displayed a doublet of doublet (dd) at δ -3.65 with coupling constant J = 37.9 and 18.42 Hz indicates the presence of proton adjacent to olefinic fluorine, -CHCF=CF-. ^{13}C NMR showed a doublet at δ 153.2 with coupling constant J = 183.10 Hz corresponding to the carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 34.00 with J = 11.1 Hz indicating the carbon adjacent to the –CF=CF-group.

Aliphatic substrate *syn*-(3S, 4S)-3-bromo-4-(dibromofluoromethyl)hexane upon treatment with zinc in refluxing methanol for 8 hours gave only one isomer (*E*)-3-bromo-7-(1-bromoethyl)-4-ethyl-5,6-difluorodec-5-ene (62 %) as isolated yield. The ^{1}H NMR showed a multiplet at δ 4.04 for the proton attached to the bromine atom (-CHBr-), ^{19}F NMR showed a doublet at δ 16.24 with a coupling constant $^{3}J_{H\text{-}F}$ = 31.5 Hz indicating the presence of a proton adjacent to the olefinic fluorine, -CHCF=CF-. ^{13}C NMR displayed a doublet at δ 139.48 with a coupling constant J = 273 Hz corresponding to the carbon directly attached to the fluorine atom (=C-F), another doublet was shown at δ 59.49 with J = 49.6 Hz indicating the carbon adjacent to the –CF=CF- group. Hence from the above spectral values it was confirmed that the bromine remained intact in the molecule.

The probable mechanism of the reaction is shown below (Scheme 3.3). Electron transfer between the zinc and the dibromoflouro moiety produces a radical anion **1**. A second electron-transfer produces the Zn^{2+} ion and the bromofluoromethide ion **2**, which subsequently loses halide ion to give difluorocarbene **3**. This reactive species (carbene) can exist in singlet and triplet forms, the singlet difluorocarbene dimerize to give the cis olefin and triplet difluorocarbene to the corresponding trans olefin.



Scheme 3.3

3.4 Conclusion

In conclusion we have devised a simple method for the synthesis of 1,2-difluoroolefins from 1,1,3-tribromo-1-fluoroalkanes mediated by zinc in refluxing methanol. Easy availability, low cost of the reagents and easy isolation procedure makes this protocol synthetically important.

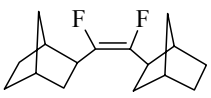
3.5 Experimental Section

General procedure for the synthesis of 1,2-difluoroolefins: 2-Bromo-3-(dibromofluoro-methyl)- bicyclo[2.2.1]heptane (100mg, 0.27mmol) diluted with dry methanol 5 ml was added to a reaction flask containing powdered zinc (27mg, 0.41mmol). The reaction mixture was heated to reflux in an oil bath under nitrogen atmosphere. The progress of the reaction was monitored by TLC (silica gel) using hexane as the eluent. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered. The solid material (white precipitate) was washed with (3 × 10 ml) ethyl acetate and the combined filtrate was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and evaporated to dryness. The crude mixture thus obtained was purified by preparative thin layer chromatographic plates to give 25mg and 49mg of c*is and trans*-1,2-*bis*(3-bromobicyclo-[2.2.1]heptan-2-yl)-1,2-difluoro-ethene as colourless crystals in 23% and 44% of yields respectively. The obtained products were characterized by spectroscopic methods.

***cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene**: **M. P** : 79 - 80 ^oC ; **IR** (Neat): 2961, 2923, 2873, 1722, 1454, 1299, 1223, 1193, 1064, 1020, 938, 762, 691cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35-1.47 (m, 3 H), 1.50-1.76 (m, 6 H), 1.89-2.00 (m, 2 H), 2.22 (m, 4 H), 2.48 (m, 2 H), 2.54-2.73 (m, 1 H), 4.26 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.6, 30.0, 30.9, 36.7, 43.2, 44.1, 53.4 (d, *J*= 9.1 Hz), 138.2 (d, *J*= 247.8 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$-C_6F_6): δ 15.75 (d, *J*= 36.85 Hz, 1 F, -CF=CF-).

***trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene**: **M.P**: 85 - 86 ^oC ; **IR** (Neat): 2961, 2879, 1725, 1456, 1297, 1264, 1220, 1193, 1070, 1015, 965, 760, 694 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.46 (m, 3 H), 1.56-1.76 (m, 5 H), 1.91-2.00 (m, 2 H), 2.28 (m, 4 H), 2.48 (m, 2 H), 2.67-2.78 (m, 2 H), 4.24 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$-C_6F_6): δ 23.5, 30.0, 30.7, 36.8, 42.3, 44.1, 50.1 (d, *J*= 14.5 Hz), 150.53 (d, *J*= 289.00 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$): δ 13.43 (d, *J*= 31.59 Hz, 1 F, -CF=CF-). **EIMS (m/z)**: 408 (M^+), 410 (M^++2), 412 (M^++4), 329, 331, 249, 229, 207, 93, 67.

Spectral data



***cis*-1,2-*bis*(Bicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene**

State: liquid

Colour: colourless

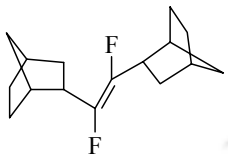
IR (Neat): 2961, 2880, 2804, 1711, 1448, 1367, 1286, 1190, 963 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 - 1.26 (m, 6 H), 1.44 - 1.58 (m, 10 H), 2.25 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 30.8, 35.4 (d, *J* = 9.1 Hz), 36.3, 37.5, 39.6 (d, *J* = 21.3 Hz), 42.3 (d, *J* = 6.1 Hz), 147.0 (d, *J* = 250.20 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 12.00 (d, *J* = 30.45 Hz, 1 F, -CF=CF-).

EIMS (m/z): 252 (M^+), 172, 123, 95, 80, 67.



***trans*-1,2-*bis*(Bicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene**

State: liquid

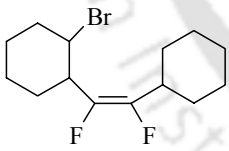
Colour: colourless

IR (Neat): 2956, 2873, 2813, 1703, 1451, 1369, 1344, 1294, 1185, 1089, 984, 919, 883 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 - 1.27 (m, 8 H), 1.48 - 1.58 (m, 8 H), 2.24 (m, 4 H), 2.55 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 30.7, 35.00 (d, *J* = 15.3 Hz), 36.4, 37.6, 38.5 (t, *J* = 10.7 Hz), 41.9 (d, *J* = 13.7 Hz), 130.0 (d, *J* = 203.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ -1.10 (d, *J* = 19.55 Hz, 1 F, -CF=CF-).



***cis*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)cyclohexane**

State: Solid

Colour: colourless

M. P : 66 - 67 ^{o}C

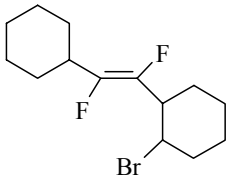
IR (Neat): 2923, 2846, 1717, 1448, 1347, 1262, 1187, 1075, 894, 738, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42- 1.68 (m, 9 H), 1.74- 1.95 (m, 10 H), 2.45 (m, 1 H), 4.10 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 25.4, 25.9, 26.3 (2C), 26.4 (2C), 27.4, 36.9 (d, *J* = 22.20 Hz), 38.5, 46.4 (d, *J* = 22.10 Hz), 52.2, 129.9 (d, *J* = 202.9 Hz), 138.1 (d, *J* = 265 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 12.24 (dd, *J* = 31.58 and 9.4 Hz, 1 F, -CF=CF-), 5.20 (dd, *J* = 34.21 and 17.30 Hz, 1 F, -CF=CF-).

EIMs (m/z): 306 (M^+), 308 (M^++2), 226, 207, 187, 82.



***trans*-2-(2-Bromocyclohexyl)-1,2-difluorovinyl)cyclohexane**

State: Solid

Colour: colourless

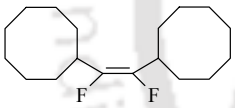
M. P : 73 - 74 ^oC

IR (Neat): 2928, 2851, 1725, 1604, 1492, 1451, 1371, 1256, 1185, 1086, 1028, 888, 801 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 - 1.60 (m, 8 H), 1.65 - 1.87 (m, 9 H), 2.44 (m, 1 H), 2.55 (m, 1 H), 2.85 (m, 1 H), 4.00 (m, 1 H, -CHBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.9, 26.1, 26.3 (2C), 26.4 (2C), 27.5, 35.9 (d, J = 22.2 Hz), 38.4, 45.1 (d, J = 22.1 Hz), 52.0, 129.7 (d, J = 255.7 Hz), 138.2 (d, J = 239.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ -1.21(dd, J = 122.2 and 30.46 Hz, 1 F, -CF=CF-), -8.00 (dd, J = 122.57 and 30.46 Hz, 1 F, -CF=CF-).



***cis*-1,2-Dicyclooctyl-1,2-difluoroethene**

State: liquid

Colour: colourless

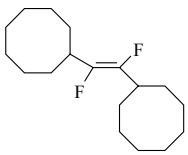
IR (Neat): 2916, 2860, 1732, 1440, 1371, 1255, 1190, 1066, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 - 1.64 (m, 20 H), 1.66 - 1.78 (m, 8 H), 2.36-2.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.5, 26.6, 30.0, 36.9 (d, J = 25.9 Hz), 130.3 (d, J = 221.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 8.32 (d, J = 30.00 Hz, 1F, -CF=CF-).

EIMS (m/z): 284 (M^+), 142, 123, 111, 55.



***trans*-1,2-Dicyclooctyl-1,2-difluoroethene**

State: liquid

Colour: colourless

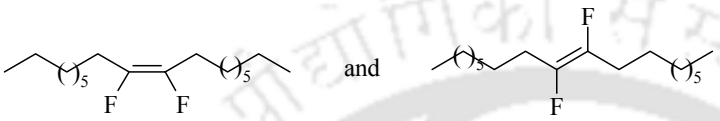
IR (Neat): 2923, 2851, 1728, 1465, 1448, 1374, 1259, 1182, 1116, 1072, 1051, 963, 809 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 - 1.62 (m, 20 H), 1.66 (m, 8 H), 2.75 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9, 26.6, 26.9, 29.8, 34.0 (t, *J* = 11.1 Hz), 153.2 (d, *J* = 183.10 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ -3.65 (dd, *J* = 37.98 and 18.42 Hz, 1 F, -CF=CF-).

EIMS (m/z): 284 (M^+), 142, 123, 111, 55.



***cis-trans*-9,10-difluorooctadec-9-ene**

State: liquid

Colour: colourless

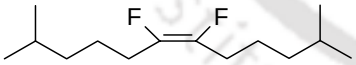
IR (Neat): 2961, 2923, 2851, 1462, 1377, 1196, 1059, 1012, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (m, 6 H, 2 × -CH_3), 1.25 - 1.33 (m, 20 H, 10 × -CH_2-), 1.50 (m, 4 H, 2 ×-CH_2-), 2.16 (m, 2 H, -CH_2-), 2.34 (m, 2 H, -CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.9, 26.1, 26.2, 26.4, 26.5, 26.6, 27.7, 27.9, 29.0, 29.06, 29.10, 29.3, 29.4, 29.5, 29.9, 32.1, 145.2 (d, *J* = 243.30 Hz, *trans*); 150.6 (d, *J* = 179.2 Hz, *cis*).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 5.78 (m, 1 F, -CF=CF-, *trans*); 20.70 (m, 1 F, -CF=CF-, *cis*).

EIMS (m/z): 288 (M^+),123, 70, 57.



***cis*-6,7-Difluoro-2-11-dimethyldodec-6-ene**

State: liquid

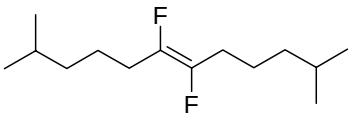
Colour: colourless

IR (Neat): 2956, 2912, 2851, 1728, 1459, 1374, 1273, 1119, 1075, 979, 910, 803, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 6 H, 2 × -CH_3), 0.90 (s, 6 H, 2 × -CH_3), 1.18 - 1.26 (m, 4 H, 2 ×-CH_2-), 1.49- 1.59 (m, 6 H, 2 ×-CH_2-, 2 ×-CH-), 2.15 (dt, *J* = 7.6 and 7.2 Hz, 4 H, 2 ×-CH-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 24.6, 28.1 (d, *J* = 24.00 Hz), 28.2, 38.5, 130.0 (d, *J* = 206.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 20.72 (m, 1 F, -CF=CF-).



***trans*-6,7-Difluoro-2-11-dimethyldodec-6-ene**

State: liquid

Colour: colourless

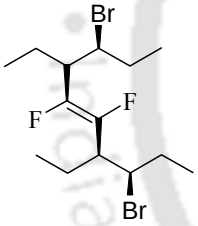
IR (Neat): 2956, 2928, 2868, 1731, 1462, 1382, 1363, 1278, 1201, 1179, 1127, 1070, 1028, 968, 814, 773, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (s, 6 H, 2 ×-CH_3), 0.90 (s, 6 H, 2 ×-CH_3), 1.27 (m, 4 H, 2 ×-CH_2-), 1.47 - 1.58 (m, 6 H, 2 ×-CH_2-, 2 ×-CH-), 2.32 (m, 4 H, 2 ×-CH_2-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 22.9, 24.0, 26.7 (t, J = 12.3 Hz), 28.0, 38.4, 129.9 (d, J = 202.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 5.77 (m, 1 F, -CF=CF-).

EIMS (m/z): 232 (M^+), 80, 69.



(*E*)-3-bromo-7-(1-bromoethyl)-4-ethyl-5,6-difluorodec-5-ene

State: liquid

Colour: colourless

IR (Neat): 2943, 2860, 1729, 1368, 1272, 1062, 907, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (m, 12 H, 4 ×-CH_3), 1.8 (m, 4 H, 2 ×-CH_2), 1.96 (m, 4 H, 2 × -$\underline{CH_2}$-CH_2Br-), 2.99 (m, 2 H), 4.04 (m, 2 H, 2 ×C$\underline{H}$Br).

^{13}C NMR (100 MHz, $CDCl_3$): 12.3, 22.3, 29.7, 30.0, 45.8, 59.5 (d, J = 49.6 Hz), 139.5 (d, J = 273 Hz).

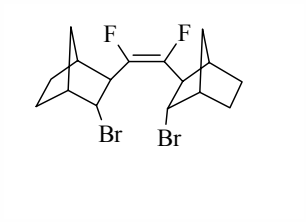
^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): 16.24 (d, J = 31.5 Hz, 1 F, -CF=CF-).

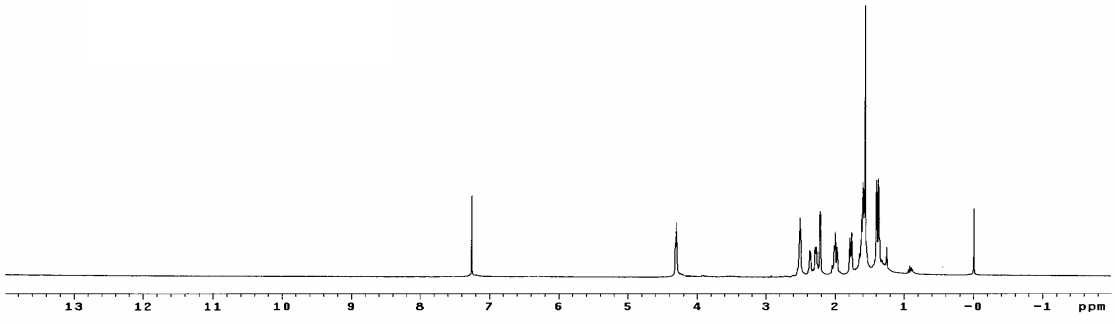
The crystal parameters of compounds 1c, 1d and 3c.

	1c	**1d**	**3c**
Formula	$C_{16}H_{20}Br_2F_2$	$C_{16}H_{20}Br_2F_2$	$C_{14}H_{21}BrF_2$
Formula weight	410.14	410.14	307.22
T/K	296(2)	296(2)	296(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/n$
a/Å	5.9501(3)	10.8164(4)	12.1607(7)
b/Å	10.0784(5)	13.5908(6)	6.4333(3)
c/Å	13.0385(7)	11.6064(4)	17.9735(10)
α/º	90.00	90.00	90.00
β/º	93.220(4)	109.161(2)	90.699(4)
γ/º	90.00	90.00	90.00
V/Å^3	780.65(7)	1611.66(11)	1406.02(13)
Z	2	2	4
Abs. Coeff./mm^{-1}	5.201	5.038	2.924
Abs. Correction	None	None	None
GOF on F^2	0.860	1.011	0.968
Final *R* indices	*R*1 = 0.0360	*R*1 = 0.0495	*R*1 = 0.0511
[$I > 2\sigma(I)$]	*wR2* = 0.1089	*wR2* = 0.1150	*wR2* = 0.1329
R indices [all data]	*R*1 = 0.0560	*R*1 = 0.1067	*R*1 = 0.1139
	wR2 = 0.1273	*wR2* = 0.1628	*wR2* = 0.1379

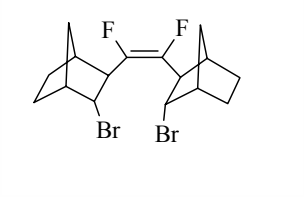
3.6 Selected Spectra of 1,2-difluoroalkanes

^{1}H NMR (400MHz, $CDCl_3$): *cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene

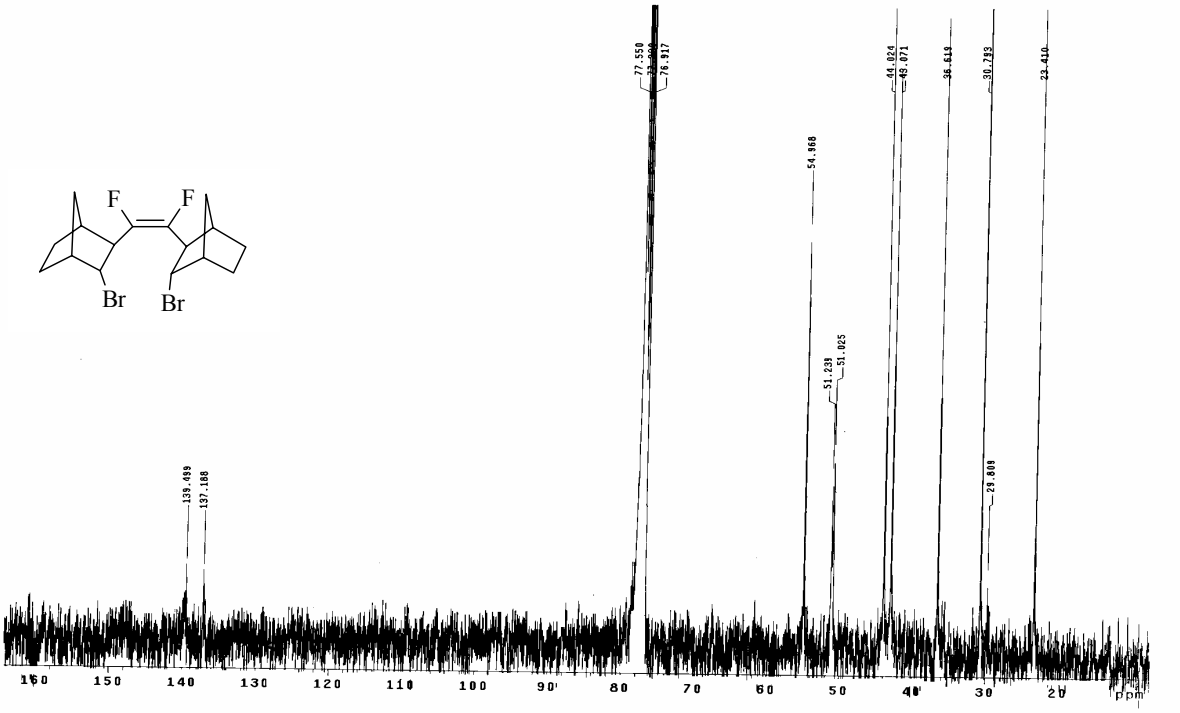




^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): *cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene



^{13}C NMR (100MHz, $CDCl_3$): *cis*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoro-ethene



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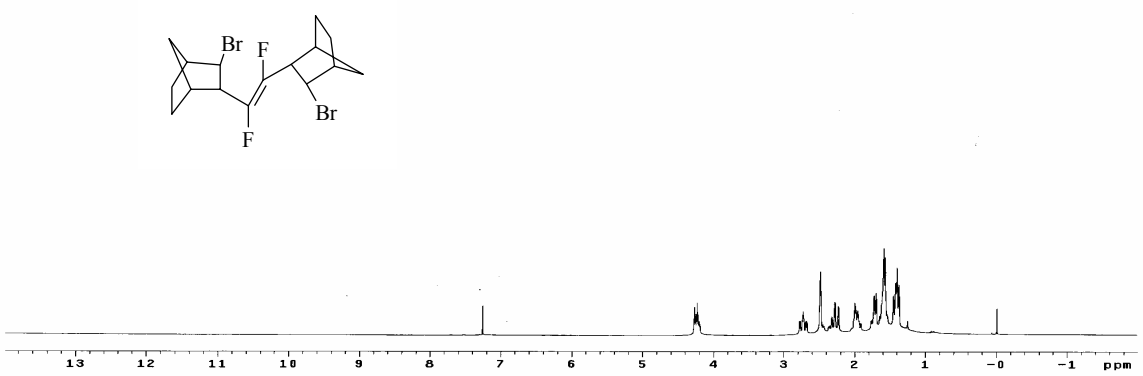
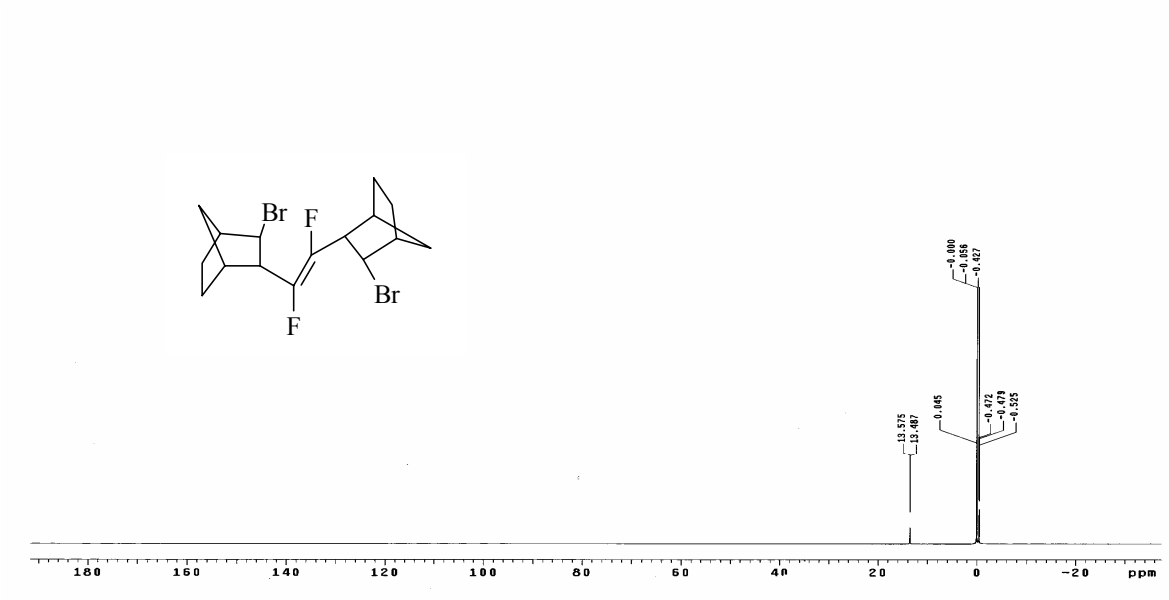
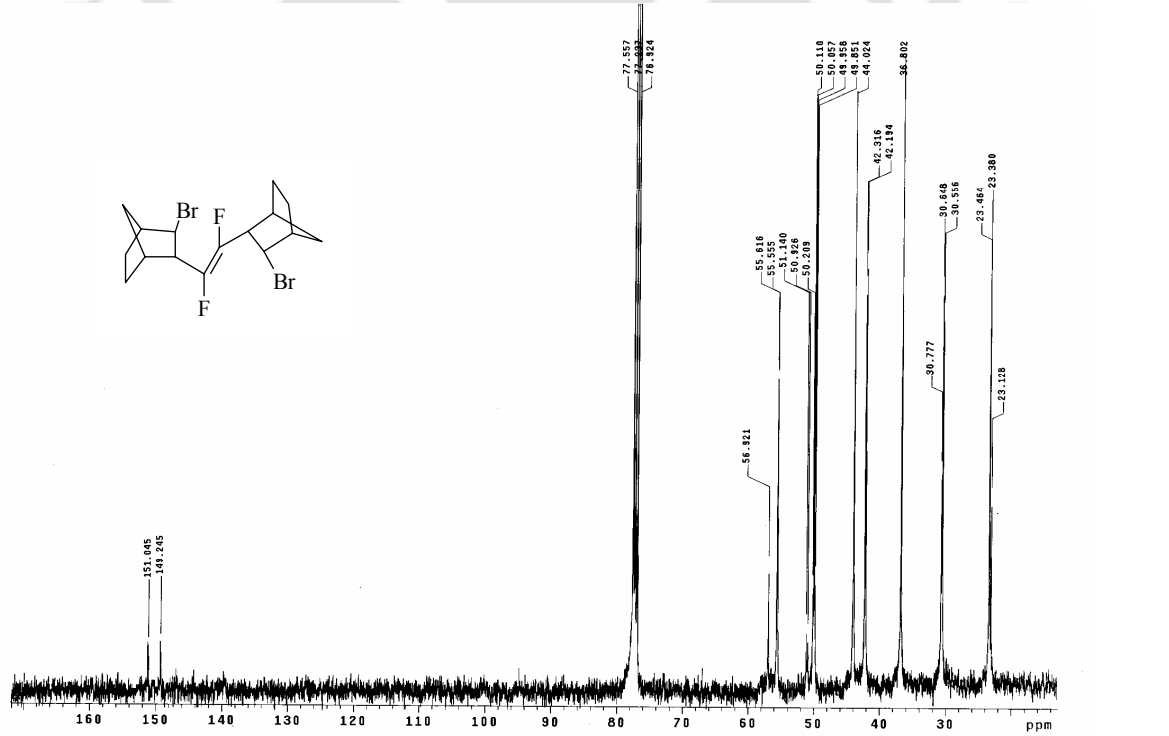


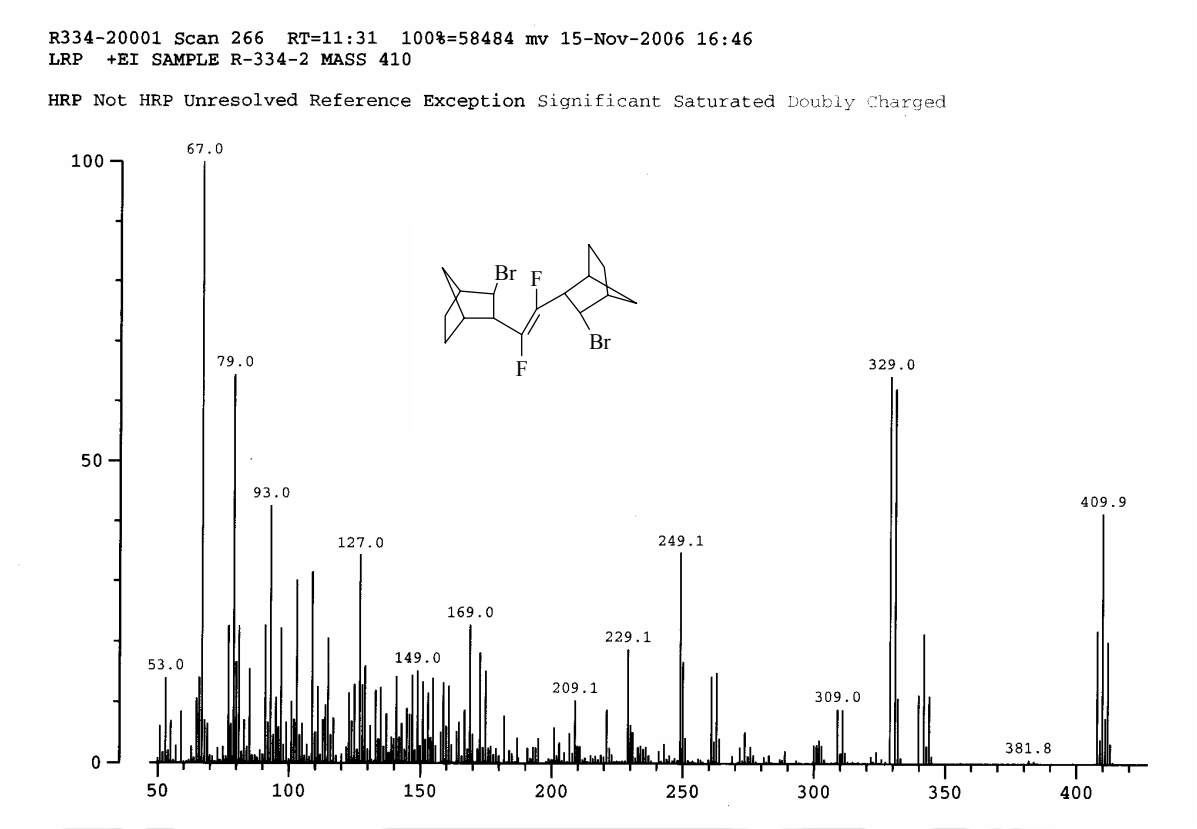
^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): *trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene



^{13}C NMR (100MHz, $CDCl_3$): *trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethane



EIMS: *trans*-1,2-*bis*(3-Bromobicyclo[2.2.1]heptan-2-yl)-1,2-difluoroethene



3.7 References

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CHAPTER IV

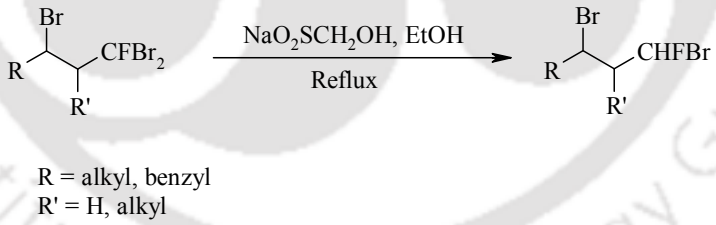
Selective reduction of 1,1,3-tribromo-1-fluoroalkanes: Synthesis of 1,3-dibromo-1-fluoroalkanes

4.1 Objective

The main aim of this work was to develop a selective debromination method for the synthesis of 1,3-dibromo-1-fluoroalkanes from their corresponding 1,1,3-tribromo-1-fluoroalkanes using sodium hydroxymethane sulfinate (Rongalite).

4.2 Present work

The synthesis of bromofluoromethyl-substituted compounds (-CHFBr-) has been an area of interest, as these compounds can be used as building block for the synthesis of fluorinated compounds.[1] The active hydrogen present can be deprotonated to generate a carbanion by a suitable base or the bromine present can be manipulated to give different types of fluorinated molecules. Sodium hydroxylmethane sulfinate (rongalite) has been mostly used in reductive halogenation reactions of various halogenated ketones,[2] and formation of R-CH_2F or $RCOCF_2H$ moieties.[3] The synthetic utility of this reagent is not fully explored and have been limited only to few examples such as the free radical addition or cyclization reactions with perfluoro-alkyl halides as starting materials.[4] In light of this information we investigated the utility of this reducing agent for the selective monodebromination, and we found that using rongalite in refluxing ethanol was quite effective for the conversion of 1,1,3-tribromo-1-fluoroalkanes to 1,3-dibromo-1-fluoroalkanes as shown below (Scheme 4.1).



Scheme 4.1

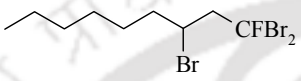
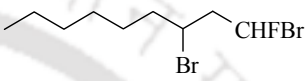
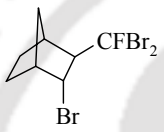
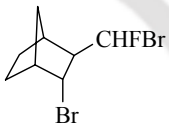
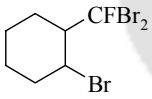
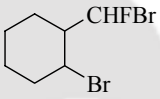
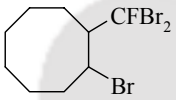
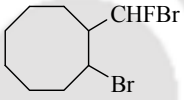
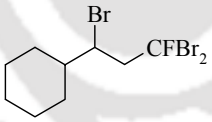
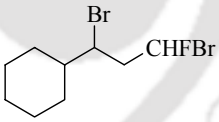
4.3 Results and discussions

Initially we investigated a number of methods for the selective debromination reaction. For example reaction with $NaBH_4$ yielded a mixture of products while the other reducing systems like Al/$SnCl_2$, Al/$NiCl_2.6H_2O$, Sn/HCl and 10% Pd/C also failed to give the required conversion. It was observed that the same transformation could be achieved with sodiumhydroxymethane sulfinate in refluxing ethanol to give the corresponding 1,3-dibromo-1-fluoroalkanes as inseperable diastereomeric mixture. However, no over reduction product

was detected even after prolonged reaction time, which was confirmed by ^{1}H NMR spectum of the crude product.

The scope of the reaction was explored with aliphatic cyclic and acyclic substrates. Moderate yields with selective debromination were obtained in all the cases. The reaction is generalized through entries 1-5 (Table 4.1).

Table 4.1: Selective reduction of 1,1,3-dibromo-1-fluoroalkanes by sodium hydroxymethane sulfinate

Entry	Substrates	Time (h)	Products	Yield (%)[a]
1		24		69
2		32		58
3		28		47
4		46		63
5		22		52

(a) Isolated yields. The compounds are characterized by GC-MS, ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectroscopy.

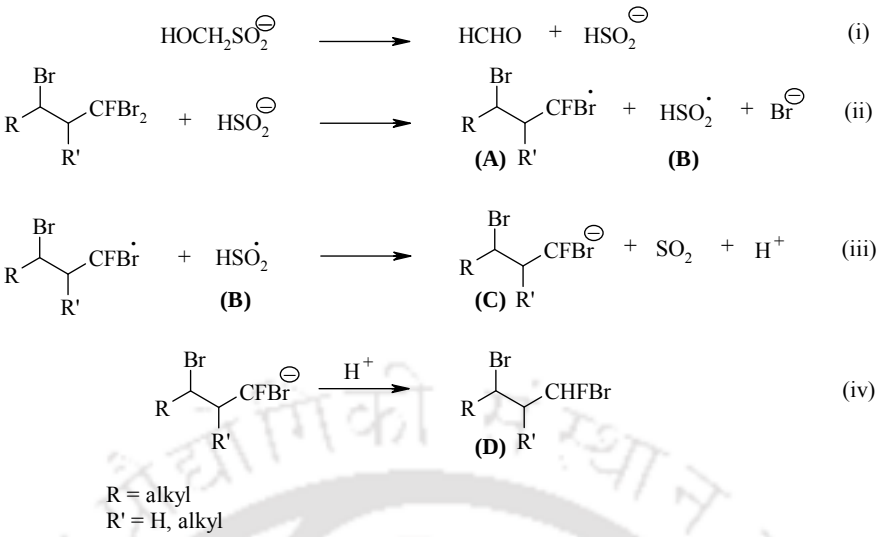
The ^{1}H NMR of 1,3-dibromo-1-fluorononane showed two multiplets at δ 6.64 and δ 6.75 for two diastereoisomeric protons of -CHFBr, and a multiplet at δ 4.05 - 4.14 integrating to one proton indicates the presence of -C<u>H</u>Br proton. Similarly another multiplet appeared at δ 2.45 – 2.84 which can be assigned to the methylene protons adjacent to -CHFBr group (-C<u>H$_2$</u>-CHFBr). ^{13}C NMR displayed a doublet at δ 92.4 with coupling constant J = 251.0 Hz, and another doublet at δ 95.5 with J = 248.6 Hz, corresponding to the carbons directly attached to the fluorine atom. A doublet at δ 48.6 with J = 20.6 Hz and another at δ 50.5 with coupling constant J = 19.8 Hz indicates the carbon adjacent to the –CHFBr group. The ^{19}F NMR displayed a doublet of doublet of doublet (ddd) at δ 23.4 with coupling constants $^{2}J_{F\text{-}H}$ = 51.3

Hz, $^{3}J_{F\text{-}H}$ =35.7 Hz, $^{3}J_{F\text{-}H}$ = 10.5 Hz, and a doublet of triplet at δ 29.2 with $^{2}J_{F\text{-}H}$ = 50 Hz and $^{3}J_{F\text{-}H}$ 10.5 Hz corresponding to two diastereomeric fluorine of the -CHFBr- group. If -CH_2F- could have been present then the -CH_2F- fluorine could have shown a multiplet in up field region. Hence from the difference in chemical shifts the presence of -CHFBr- group was confirmed.

The ^{1}H NMR of 1-bromo-2-(bromofluoromethyl)cyclooctane showed multiplets ranging from δ 1.33-2.34 for six methylene groups, another multiplet at δ 2.36-2.42 corresponding to the proton adjacent to -CHFBr- group (-CH-CHFBr). The proton attached to bromine -CHBr appeared as a multiplet at δ 4.39. The diastereomeric methine proton of -CHFBr- group was identified by a multiplet at δ 6.40 and a doublet of doublet (dd) at δ 6.33 with coupling constants $^{2}J_{H\text{-}F}$ = 50 Hz and $^{3}J_{H\text{-}H}$ = 3.6 Hz. ^{13}C NMR displayed a doublet at δ 100 with coupling constant J = 286.2 Hz, and another doublet at δ 102.5 with J = 256.2 Hz corresponding to the carbons directly attached to the fluorine atom, a doublet at δ 56.0 with J = 7.6 Hz and another at δ 55.9 with coupling constant J = 7.0 Hz indicating the carbon adjacent to the -CHFBr group. ^{19}F NMR showed a doublet of doublet at δ 28.20 with coupling constants $^{2}J_{F\text{-}H}$ = 48.5 Hz and $^{3}J_{F\text{-}H}$ = 14.2 Hz and another doublet of doublet at δ 27.10 with $^{2}J_{F\text{-}H}$ = 50 Hz and $^{3}J_{F\text{-}H}$ = 15.7 indicating that both the fluorine and hydrogen are attached to the same carbon (geminal) -CHFBr.

The ^{1}H NMR of 1,3-dibromo-3-fluoropropylcyclohexane showed two multiplets at δ 6.62 and δ 6.75 for two diastereoisomeric protons of -CHFBr group. Similarly, two multiplets appeared at δ 2.54 and δ 2.73 were assigned to the methylene protons adjacent to –CHFBr group (-CH_2-CHFBr). The methine proton of -CHBr showed multiplets at δ 3.99 and δ 4.06. ^{13}C NMR displayed two doublets at δ 92.9 with a coupling constant J = 249.4 Hz and at δ 96.5 with J = 251.0 Hz corresponding to the carbon directly attached to the fluorine atom. ^{19}F NMR showed a doublet of doublet of doublet (ddd) at δ 23.52 with coupling constants $^{2}J_{F\text{-}H}$ = 51.5 Hz, $^{3}J_{F\text{-}H}$ 35.5 Hz and $^{3}J_{F\text{-}H}$ = 10.5 Hz and another doublet of triplet (dt) at δ 29.25 with $^{2}J_{F\text{-}H}$ = 50 Hz and $^{3}J_{F\text{-}H}$ = 10.5 Hz indicating that both the fluorine and hydrogen are attached to the same carbon (geminal) -CHFBr.

The mechanism of the debromination reaction by this reagent was supposed to be similar as reported earlier.[5] The sulfoxylate anion is formed in the first step. An electron transfer occurs between the starting material and sulfoxylate anion generating the bromofluoroalkyl radical (**A**), which in turn gets reduced by the sulfoxylate radical (**B**) to form bromofluoroalkyl anion (**C**). This bromofluoro anion gets protonated to give the corresponding product (**D**) (Scheme 4.2).



Scheme 4.2

4.4 Conclusion

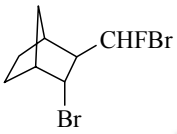
In conclusion we have shown the utilization of sodium hydroxymethane sulfinate as a selective reducing agent for the synthesis of 1,3-dibromo-1-fluoroalkanes from their corresponding 1,1,3-tribromo-1-fluoroalkane compounds. Easy availability, low cost of the reagents and easy isolation procedure makes an alternative for the existing methods.

4.5 Experimental Section

General procedure for the synthesis of 1,3-dibromo-1-fluoroalkanes: A solution of 1,1,3-tribromo-1-fluorononane (200 mg, 0.52 mmol) in 10 ml of dry ethanol was added to a reaction flask containing sodium hydroxymethane sulfinate (247 mg, 2.08 mmol). The reaction mixture was heated to reflux in an oil bath under nitrogen atmosphere. The progress of the reaction mixture was monitored by TLC (silica gel) using hexane as the eluent. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered. The colourless salt was washed with (3 × 10 ml) of ethyl acetate and the combined filterate was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to dryness. The crude product obtained was purified by preparative thin layer chromatography plates to give 110 mg of 1,3-dibromo-1-fluorononane as yellow oil in 69% of yield. The product obtained was characterized by spectroscopic methods. **IR** (Neat): 2989, 2864, 1210, 1137, 981, 740 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, J = 6.4 Hz, 3 H, -CH_3), 1.20 - 1.40 (m, 6 H, 3 ×-CH_2), 1.41 – 1.58 (m, 2 H, -CH_2-), 1.80 - 2.18 (m, 2 H, -CH_2-), 2.45 - 2.84 (m, 2 H, -$\underline{CH_2}$-CHFBr-), 4.05 - 4.14 (m, 1

H, -CHBr-) 6.61 - 6.67 (m, 0.5 H, -CHFBr), 6.74 - 6.80 (m, 0.5 H, -CHFBr); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2 (2C), 22.8 (2C), 27.3, 27.4, 28.72 (2C), 30.0, 31.8, 39.0, 39.2, 48.6 (d, *J* = 20.6 Hz) 50.5 (d, *J* = 19.8 Hz), 51.4, 51.5, 92.4 (d, *J* = 251.0 Hz), 95.5 (d, *J* = 248.6 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$-C_6F_6): δ 23.4 (ddd, *J* = 51.3, 35.7 and 10.5 Hz, 1 F, -CHFBr), 29.2 (dt, *J* = 50 and 10.5 Hz, 1 F, -CHFBr); **EIMS** (m/z): (M^+) 304, 223, 123, 81.

Spectral data



2-bromo-3-(bromofluoromethyl)bicyclo[2.2.1]heptane

State: liquid

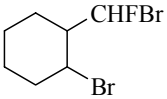
Colour: colourless

IR (Neat): 2862, 2887, 1460, 1228, 1170, 1039, 961, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 - 1.39 (m, 2 H, -CH_2-), 1.48 - 1.67 (m, 3 H), 1.88 - 1.98 (m, 2 H, -CH_2-), 2.14 - 2.26 (m, 1 H), 2.46 (m, 1 H, -CH-CHFBr-), 3.86 (m, 0.5 H, -CHBr), 4.14 (m, 0.5 H, -CHBr), 6.21 (dd, *J* = 50.0 and 6.4 Hz, 0.5 H, -CHFBr-), 6.30 (dd, *J* = 50.4 and 5.6 Hz, 0.5 H, -CHFBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.0, 24.3, 30.3, 30.8, 35.8, 35.9, 40.7, 42.1, 44.7, 44.9, 54.7, 56.4, 61.1 (d, *J* = 21.3 Hz), 61.8 (d, *J* = 18.3 Hz), 118.5 (d, *J* = 258.5 Hz), 119.3 (d, *J* = 262.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 20.60 (dd, *J* = 50.0 Hz and 21.0 Hz, 0.5 F, -CHFBr), 26.33 (dd, *J* = 49.6 and 19.5 Hz, 0.5 F, -CHFBr).



***Cis-trans*-1-bromo-2-(bromofluoromethyl)cyclohexane**

State: liquid

Colour: colourless

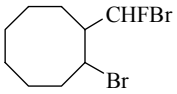
IR (Neat): 2954, 2860, 1442, 1280, 1251, 1176, 940, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 - 1.61 (m, 3 H), 1.64 - 1.96 (m, 3 H), 2.0 - 2.23 (m, 2 H, -CH_2-), 2.34 - 2.44 (m, 1 H, -CH-CHFBr-), 3.80 - 3.86 (m, 0.5 H, -CHBr), 4.0 - 4.10 (m, 0.5 H,

-CHBr), 6.18 - 6.33 (dd, *J* = 50.4 and 8.8 Hz, 0.5 H, -CHFBr), 6.22 - 6.36 (dd, *J* = 50.0 and 8.8 Hz, 0.5 H, -CHFBr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.5, 24.8, 25.10, 25.8, 26.1, 38.2, 38.9, 51.8 (d, *J* = 19.0 Hz), 54.4 (d, *J* = 19.1 Hz), 55.4, 55.5, 99.6 (d, *J* = 330.2 Hz), 100.1 (d, *J* = 253.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 20.52 (dd, *J* = 50.00 and 6.77 Hz, 0.5 F), 21.68 (dd, *J* = 48.8 and 5.26 Hz, 0.5 F).



1-Bromo-2-(bromofluoromethyl)cyclooctane

State: liquid

Colour: colourless

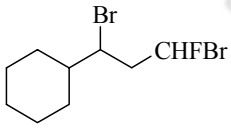
IR (Neat): 2932, 2864, 1460, 1237, 1173, 1041, 968 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 - 1.51 (m, 2 H, -CH_2-), 1.55 - 1.70 (m, 3 H), 1.80 - 1.97 (m, 3 H), 2.00 - 2.12 (m, 2 H, -CH_2-), 2.15 - 2.34 (m, 2 H) 2.36 - 2.42 (m, 1 H, -CH-CHFBr-), 4.39 (m, 1 H, -CHBr), 6.33 (dd, *J* = 50.00 and 3.6 Hz, 0.5 H, -CHFBr-), 6.40 (m, 0.5 H, -CHFBr-).

^{13}C NMR (100 MHz, $CDCl_3$): δ 24.1 (2C), 25.2, 25.23, 26.23, 26.5, 27.3, 27.4, 33.2, 33.5, 36.6, 36.7, 46.2, 46.4, 56.0 (d, *J* = 7.6 Hz), 55.9 (d, *J* = 7.0 Hz), 100.00 (d, *J* = 286.2 Hz), 102.5 (d, *J* = 256.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 27.10 (dd, *J* = 50.00 and 15.7 Hz, 1 F), 28.20 (dd, *J* = 48.5 and 14.2 Hz).

EIMS (m/z): 222, 140, 121, 93, 79.



(1,3-dibromo-3-fluoropropyl)cyclohexane

State: liquid

Colour: colourless

IR (Neat): 2916, 2850, 1444, 1193, 1055, 972, 760 cm^{-1}.

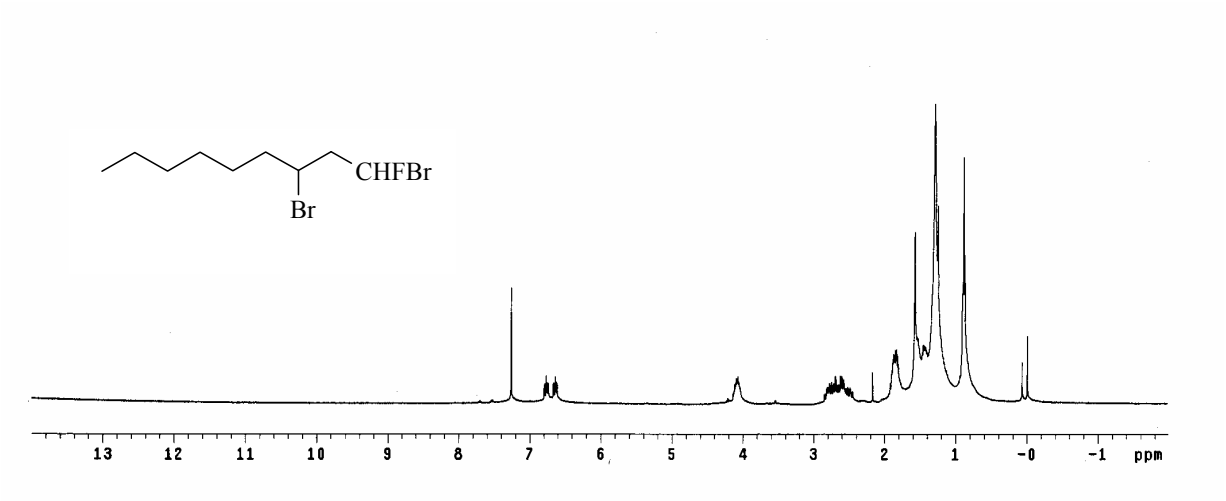
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 - 1.26 (m, 5 H), 1.50 - 1.76 (m, 6 H), 2.45 - 2.61 (m, 1 H), 2.65 - 2.80 (m, 1 H), 3.97 - 4.01 (m, 0.5 H, -CHBr), 4.03 - 4.10 (m, 0.5 H, -CHBr), 6.59 - 6.66 (m, 0.5 H, -CHFBr), 6.71 - 6.78 (m, 0.5 H, -CHFBr).

^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.3, 29.2, 29.6, 30.6, 30.8, 44.4, 44.6, 45.7, 45.9, 47.8 (d, J = 19.8 Hz), 58.0, 58.2, 92.9 (d, J = 249.4 Hz), 96.5 (d, J = 251.0 Hz).

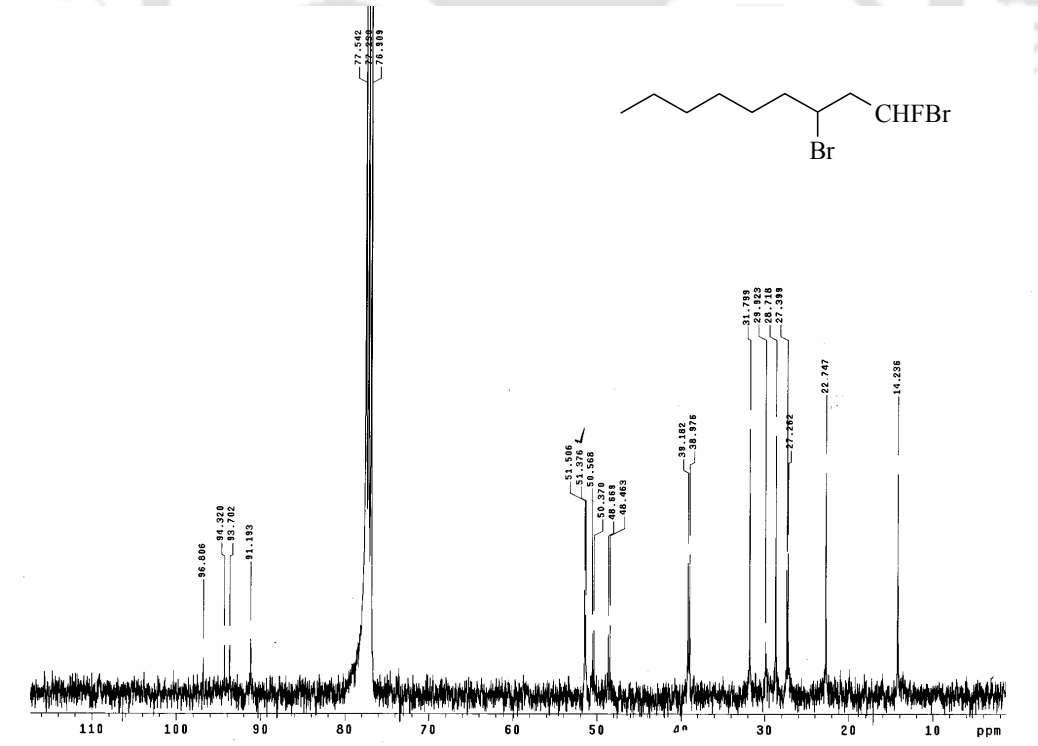
^{19}F NMR (376 MHz, $CDCl_3$-C_6F_6): δ 23.4 (ddd, J = 51.3, 35.5 and 10.5 Hz, 0.5 F), 29.25 (dt, J = 50 Hz and 10.5 Hz, 0.5 F).

4.6 Selected Spectra of 1,3-dibromo-1-fluoroalkanes

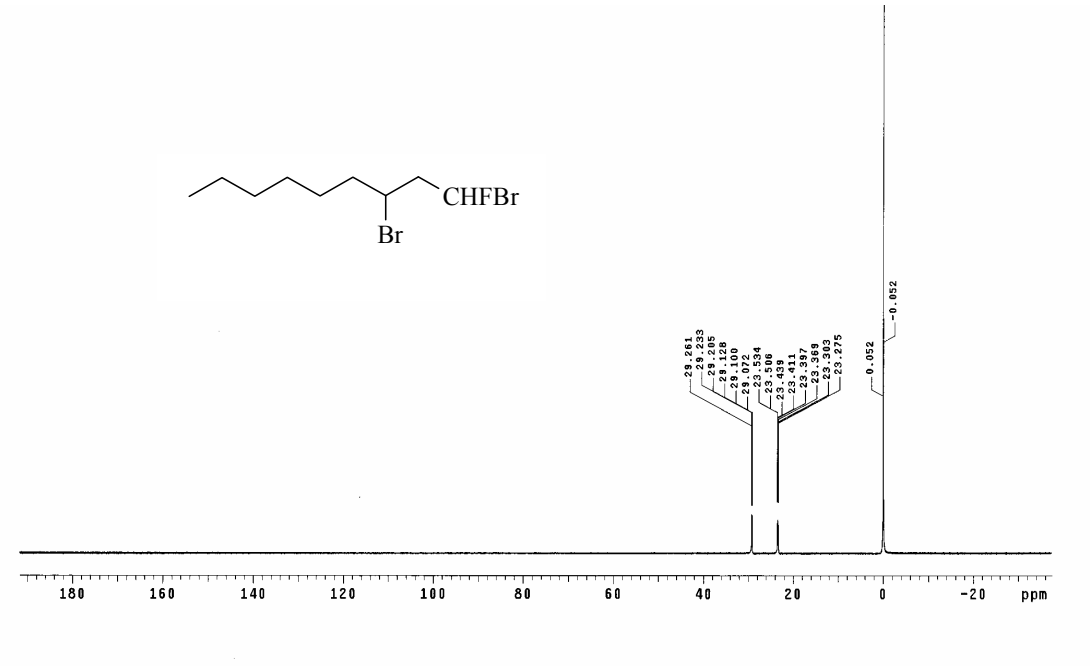
^{1}H NMR (400MHz, $CDCl_3$): 1,3-dibromo-1-fluorononane



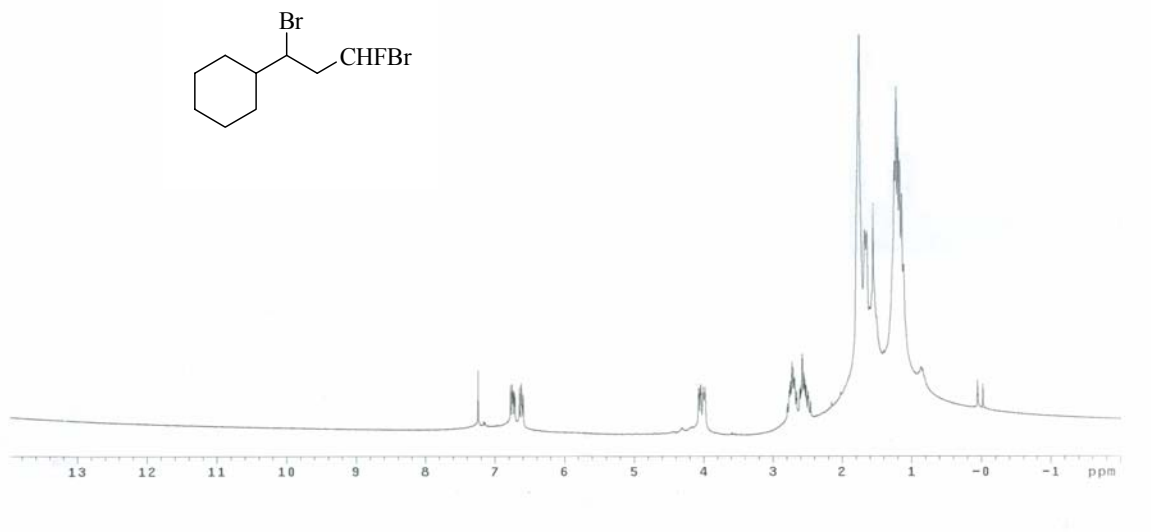
^{13}C NMR (100MHz, $CDCl_3$): 1,3-dibromo-1-fluorononane



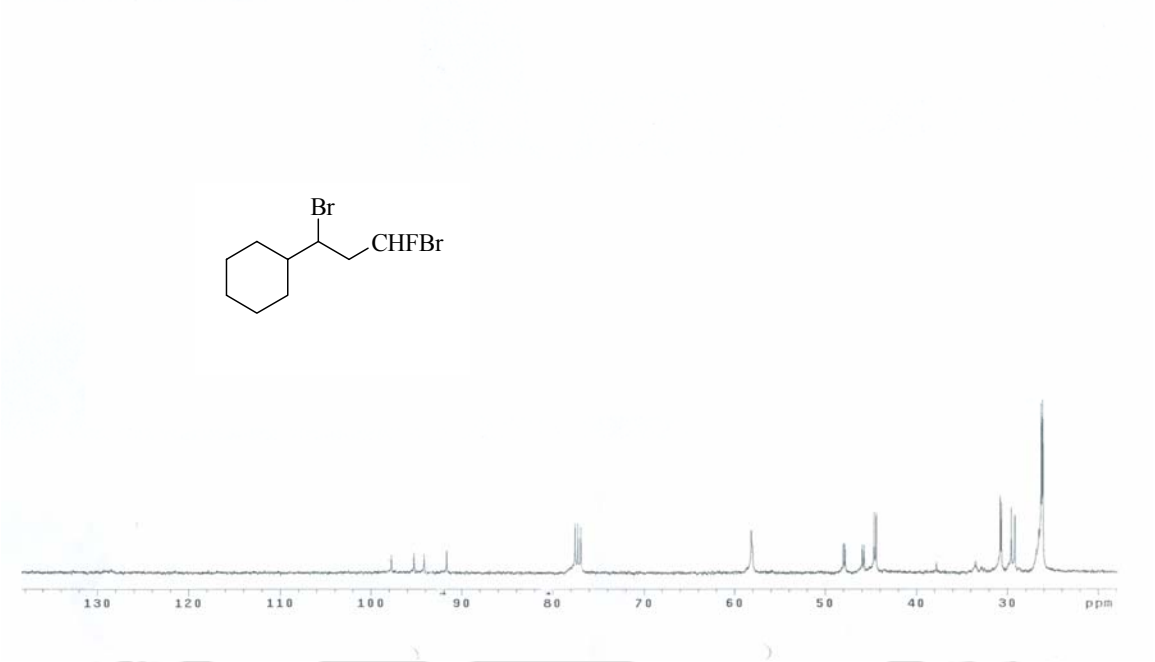
^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): 1,3-dibromo-1-fluorononane



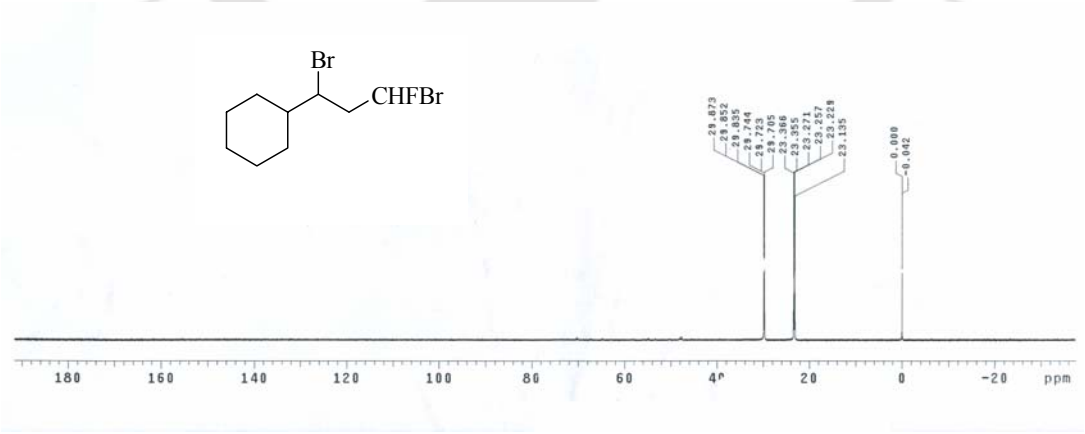
^{1}H NMR (400MHz, $CDCl_3$): (1,3-dibromo-3-fluoropropyl)cyclohexane



^{13}C NMR (100MHz, $CDCl_3$): (1,3-dibromo-3-fluoropropyl)cyclohexane



^{19}F NMR (376MHz, $CDCl_3$- C_6F_6): (1,3-dibromo-3-fluoropropyl)cyclohexane



4.7 References

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