Synthesis And Modification Of Sulfur Based Compounds And Their Application As Anticancer Compounds And Synthetic Applications Of Solid Superacids

A thesis submitted to the

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for the degree of

Doctor of Philosophy

in

CHEMISTRY

By
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January 1996

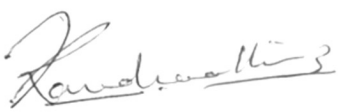
To

My Parents
and
Brother Ashish

CONTENTS

CERTIFICATE

Certified that the work incorporated in the thesis entitled "Synthesis and modification of sulfur based compounds and their application as anticancer compounds and synthetic applications of solid superacids." submitted by **Miss SHUBHADA WASUDEO DANTALE** was carried out by the canditate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.



Dr. T. RAVINDRANATHAN

January, 1996

Preface

The work presented in the thesis represents synthesis and modification of sulfur based anticancer compounds and development of novel synthetic methodologies having practical utility in a multistep total synthesis of biologically active compounds. The theme has been practised in our laboratory for the last decade. Development of the environmentally benign technologies has also been the focus of our current interest. Efforts have been made to develop enviornmentally friendly technologies.

There are two main aspects of synthetic organic chemistry *viz* development of new protocols for functional group transformations and application of these protocols in simple and highly stereospecific total synthesis of natural products and compounds of daily use in human life for health, happiness and comfort. The work described in the thesis is divided into three chapters. The first chapter presents synthesis and study of carcinostatic properties of sulfur compounds on isolated human cell lines. The latter half of this chapter contains a study on the role of sulfur in a new assisted reaction *viz* reduction by sodium borohydride, similar to the participatory mechanism implied in the anticancer action of sulfur mustards.

In the first part of first chapter attempts were made to synthesize mono and bi-functional open chain sulfides and thiophene analogues and were tested for the first time *in vitro* against human chronic myeloid leukemia cells and sarcoma 180 cells derived from mouse fibrosarcoma. This work was based on earlier work where bifunctional sulfides were found to be active against cancer cells. Since these compounds are easy to prepare and water soluble they can find application in cancer treatment.

The second part of the first chapter represents development of a protocol for the sulfur assisted reduction of esters using sodium borohydride in ethanol at room temperature for the first time. Here the role of sulfur in assisted reduction of ester has been clearly established and demonstrated on a wide variety of substrates.

Protection and deprotection methodologies of oxathiolanes is described in second chapter. Interconversion of oxathiolanes and carbonyls has been achieved using TMSOTf as mild, efficient catalyst at room temperature in good yields. This study is the first of its kind where it has been shown that the same reagent was used for the protection as well as deprotection under essentially identical conditions. Also another protocol involving deprotection of oxathiolanes under mild conditions using aq hydrogen peroxide in refluxing acetonitrile was developed as a contribution and awareness to develop enviornmentally benign technologies.

Third chapter describes synthetic applications of solid superacids. One to one exchange of ketoesters was achieved in good to excellent yields using sulfated tin oxide as solid superacid catalyst. This methodology was found to be useful in making even tert butyl esters which were difficult to prepare by other conventional methods. It is catalytic method in which catalyst can be recycled after use.

A facile and efficient catalytic protocol was developed for efficient hydrolysis of allylic esters, using sulfated tin oxide in refluxing toluene to give acids in high yields. Normal esters remain unaffected under the same reaction conditions.

Thus the classical stoichiometric processes has been replaced to a greater extent by catalytic processes in which the use of less amount of catalyst and recycling of the catalyst and efficiency associated with it would make these methodologies more attractive.

Throughout the course of this presentation all the references pertaining to the work from reviews and individual papers have been appropriately quoted and if at all any information is presented without proper accreditation, it may be viewed as unintentional.

Acknowledgements

I am indebted to ***Dr. B.D.TILAK*** former Director National Chemical Laboratory and now Honorary Consultant , for his keen interest, constant encouragement and useful guidance throuout the course of my work.

It gives me great pleasure in acknowledging my deep sense of gratitude to my research guide ***Dr. T.RAVINDRANATHAN*** Deputy Director and Head Organic Chemistry:Technology, National Chemical Laboratory for his inspiring guidance, constant encouragement and moral support which have been indispensable for the completion of this work.

My feelings go beyond the limits of my language in acknowledging ***Dr. SUBHASH P.CHAVAN*** an aspirer of perfection, who indeed helped me in my work with his expertise, and support in the form of useful suggestions. I also take this apportunity to thank him for the help rendered in the preparation of this manuscript.

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Last few years in lab was a period of fun and excitement. It is my pleasure to thank Dr. Rajkumar Tejwani, Dr. P.K.Zubaidha, Dr. Mrs. Kalpana Kulkarni, Dr. Rani Menon and Mrs. Girija Iyer for being an integral part of my student days, from whom I received help, support, fun and excitement in various ways during the research.

I am thankful to all my collegues in this laboratory especially Vijay , Sachin, Keshavaraja and seniors Dr. V.H.Deshpande, Dr. Mrs. R.D.Wakharkar and Dr. Mrs. Bhanu Chanda for their willing assistance.

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Assistance rendered by Spectroscopic (NMR,IR and Mass) section and Micro-anlytical section of this laboratory is greatly acknowledged.Thanks are due to Mrs. Kulkarni, Mr. Kulkarni, Mr. Mane and Mr. Bhujang for the technical assistance in preparing the thesis.

I wish to thank Dr U.V. Wagh and Dr. Sujata of National Facility for Animal Tissue and Cell Culture for providing testing facility.

Financial assistance from Council of Scientific and Indusrial Research, New Delhi is grately acknowledged.

I wish to thank Director,National Chemical Laboratory ,Pune for allowing me to submit this work in the form of a thesis.

The completion of this work would not have been possible without the encouragement and wholehearted support of ***MY PARENTS AND BROTHER ASHISH***.I adore you all very much.

JANUARY 1996
NCL, Pune

Shubhada W. Dantale

Abbrevations

BP	Boiling point
$BF_3.Et_3O$	Boron trifluoride etherate
CAN	Cerric ammonium nitrate
DMAP	4-Dimethylamino pyridine
EtOH	Ethyl alcohol
Et_3N	Triethyl amine
E	Electrophile
^{1}H-NMR	Nuclear magnetic resonace
IR	Infrared spectrum
KSCN	Potassium thiocyanate
LAH	Lithium aluminium hydride
M^+	Molecular ion
MP	Melting point
NCS	N-chlorosuccinimide
Nu	Nucleophile
$NaBH_4$	Sodium borohydride
Ph	Phenyl
RT	Room temperature
SiO_2	Silica gel
$S.SnO_2$	Sulphated tinoxide
$SOCl_2$	Thionyl chloride
TLC	Thin layer chromatography
TMSOTf	Trimethylsilyl trifluoromethane sulfonate
TMSCl	Trimethylsilyl chloride
THF	Tetrahydrofuran

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in centrigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular chapter only.
3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.
4. Organic layers were dried over anhydrous sodium sulfate.(Na_2SO_4)
5. TLC analyses were carried out on glass plates using silica gel: GF-254 and the plates were analysed by keeping in iodine chamber.
6. In cases where chromatographic purifications were done, SiO_2 was used as a stationary phase.
7. The IR spectra were recorded on Perkin-Elmer infrared spectra-photometer model 683B or 1605 FTIR and IR, absorptions are expressed in cm^{-1}.
8. The ^1H and ^{13}C NMR spectra were recorded on varian FT 80A (20 MHz) or Brucker WH 90 (22.63 MHz) or Brucker AC 200 (50 MHz) instrument. Figures in the parentheses correspond to ^{13}C frequencies. ^1H NMR & ^{13}C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on δ scale.
9. Mass spectra were recorded at an ionisation energy or & mass values are expressed as (m/e).

ABSTRACT

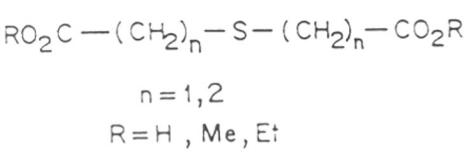
The thesis **"Synthesis and modification of sulfur based compounds and their application as anticancer compounds and synthetic applications of solid superacids"** has been divided into three chapters.

CHAPTER 1: CARCINOSTATIC PROPERTIES OF SULFUR COMPOUNDS ON HUMAN CELL LINES AND THEIR STUDY IN ASSISTED REDUCTION OF ESTERS.

This chapter consists of two parts.

Part I: ***Carcinostatic properties of sulfur compounds on human cell lines.***

Carcinostatic activity of mono and bi-functional open chain sulfides and thiophene derivatives was tested in vitro against human chronic myeloid leukemia cells and sarcoma 180 cells derived from mouse fibrosarcoma. Of all the compounds tested, bis-2,5-dimethylenyl thiouronium dichloride (**3**) and Dicetol disodium salt (**4**) showed significant carcinostatic activity.



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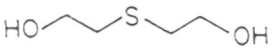

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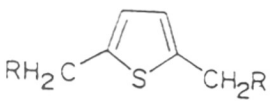

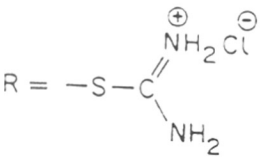

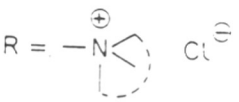

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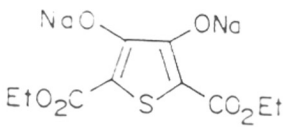


4

Several quaternary ammonium salts and thiouronium salts were tested for anticancer activity.

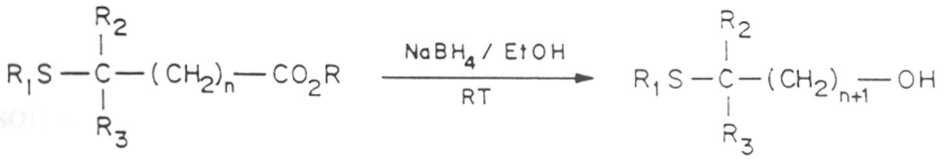
These compounds are water soluble (as sodium salts or chlorides) and thus easy to administer. It is evident that the active compounds are bi-functional derivatives as indeed many cancer chemotherapeuticals are.[1,2]

Part II: ***Sulfur assisted $NaBH_4$ reduction of esters in ethanol.***

Normally esters are not reduced to alcohols in alcoholic solvents at room temperature.[3] However, under certain circumstances esters (bearing α halo or N,O atom) can be smoothly reduced to the corresponding alcohols at room temperature.[4] Present study details the role of sulfur in reduction of esters.

Esters (**5**) were reduced to alcohols (**6**) with $NaBH_4$ in ethanol at room temperature when sulfur was adjacent to the ester (α,ß or γ position). Thus a variety of α,ß & γ substituted mercapto esters were reduced with $NaBH_4$ in ethanol at room temperature to the corresponding alcohols in high yields.

SCHEME-1



5 6

n = 0, 1, 2

R = —Me, —Et, —i-Pr, —t-bu

R_2 = —H, —Me, —Ph, —SPh

R_1 = —Ph, $—CH_2—CH_2S—$

R_3 = —H, —Me

It was found that methyl, ethyl, isopropyl esters undergo facile reduction, whereas t-butyl ester was resistant to reduction. Also normal esters were not reduced with $NaBH_4$ confirming sulfur assistance in reduction.

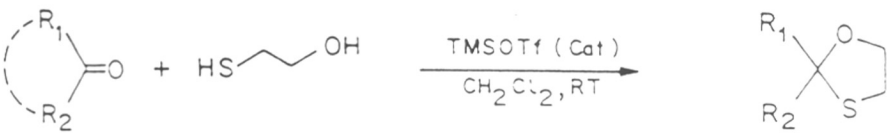
CHAPTER-2: PROTECTION AND DEPROTECTION METHODOLOGIES OF OXATHIOLANES.

This chapter consists of two parts.

Part I: ***Interconversion of oxathiolanes and carbonyls under essentially identical conditions.***

Protection of carbonyls (7) to oxathiolanes (8) was achieved using TMSOTf as mild, efficient catalyst at room temperature in good yields[5]. (Scheme-2)

SCHEME-2



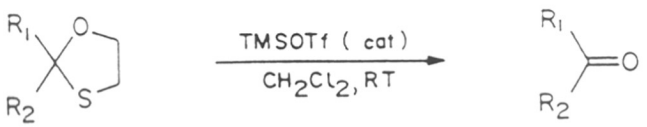
7 8

R_1 = Alkyl , Aryl.

R = H , Alkyl , Aryl.

Also "activated" oxathiolanes were deprotected to carbonyls in presence of cat TMSOTf in high yields. Presence of aryl ring seems to be an essential factor for the deprotection. According to this methodology, selectively oxathiolanes can be deprotected in presence of thioacetals. (Scheme-3)

SCHEME-3

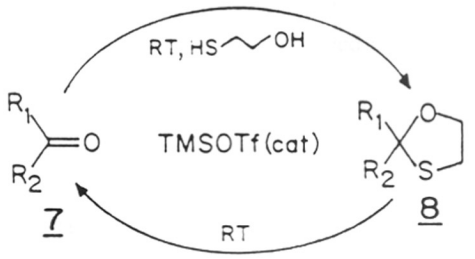


8 7

R = Aryl

R = H , Alkyl , Aryl

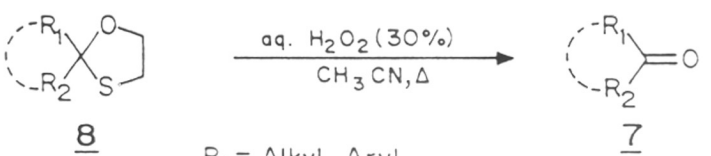
Thus TMSOTf can be used as mild, efficient and versatile catalyst for the conversion of carbonyls to oxathiolanes and vice-versa under essentially identical conditions. (Scheme-4)



Scheme - 4

Part II: ***Deprotection of oxathiolanes under mild conditions using aqueous H_2O_2.***

Oxathiolanes were deprotected to carbonyls using aqueous H_2O_2 in refluxing acetonitrile in high yields. (Scheme-5)



R_1 = Alkyl, Aryl

R_2 = H, Alkyl, Aryl

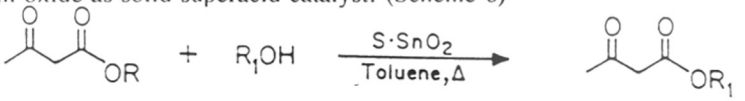
Scheme - 5

CHAPTER 3: SYNTHETIC APPLICATIONS OF SOLID SUPERACIDS.

This chapter consists of two parts.

Part I: ***Transesterification of ß-ketoesters.***[6]

One to one exchange of keto ester was achieved in good to excellent yields using sulfated tin oxide as solid superacid catalyst. (Scheme-6)



9 10 11

R = $-CH_3$, $-C_2H_5$

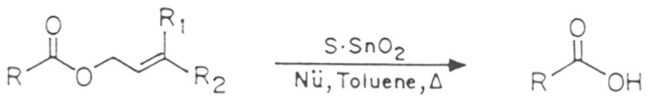
R_1= pri , sec , tert and allyl alcohol

Scheme-6

This methodology was found to be useful in making tert butyl esters which were difficult to prepare by conventional methods. It is mild and catalytic method for transesterification wherein the catalyst is recycled after use.

Part II: ***Deprotection of allyl esters.***[7]

A facile and efficient catalytic protocol was developed for efficient hydrolysis of allylic esters, using sulfated tin oxide in refluxing toluene to give acids in high yields. (Scheme-7)

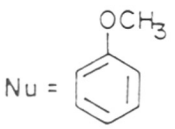


12 13

R = $-Ph$, $-CH_2Ph$, $-OPh$

R_1= $-H$, $-CH_3$

R_2= $-CH_3$, $-Ph$

Nu = 

Scheme-7

Allyl esters were easily and selectively deprotected in the presence of normal (ethyl, methyl) esters.

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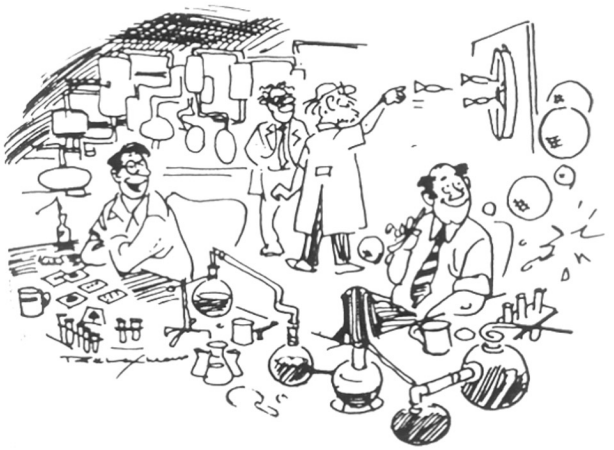
CHAPTER-1

Carcinostatic Properties Of Sulfur Compounds On Human Cell Lines And Their Study In Assisted Reduction Of Esters



I'm glad you like it here — they give a lot of funds and equipment and leave you alone to do what you like!

Part - I: Carcinostatic Properties Of Sulfur Compounds On Human Cell Lines

1.1.0 *Introduction : Cancer Therapeuticals*

Success lends wings to hope is the motto for the search of new and effective drugs for the treatment of cancer. References of cancer have been found in early Greek and Sanskrit writings. Through the ages, man has attempted to find alleviation from this disease by means of plant and herbal preparations. Only recently however, a determined effort is mounted to control this disease, thus bringing hope to those sufferings from cancer.

Although radiation and surgery are the most successful treatments of cancer today, they have their own limitations. Besides curing cancer, radiation is accompanied by toxic side-reactions. Surgery on the other hand becomes extremely difficult in disseminated cancers. Under such circumstances cancer chemotherapy is the only method of choice.

Cancer chemotherapy involves the use of chemicals ordinarily foreign to the body, which when administered to the host bearing tumour, will adversely affect the tumour without destroying the host. This treatment is mostly resorted to after all other methods of therapy have failed. The main disadvantage of cancer chemotherapy is the toxicity of the drugs used.

The development of ideal chemotherapeutic agent for cancer is extremely difficult, because there is little difference between the normal cells and the malignant cells which proliferate spontaneously. The cancer cells are not really foreign to the host and they are therefore unable to elicit immunological response. Unlike antibacterial drugs which may be bacteriostatic, an anti-cancer agent has to be administered until every single cancer cell is completely destroyed. Such an agent has, therefore, to be non-toxic to the host cell during its prolonged administration and at the same time it has to be sufficiently toxic to the cancer cell.

Broadly cancer chemotherapeutic agents can be divided as (a) Alkylating agents (b) Antimetabolites and (c) Hormones (d) Anthracyclines (e) Natural products and (f) Miscellaneous agents.

A) *Alkylating Agents*:

The term alkylating agents refers to alkylation of substrate by a variety of chemical agents. The substrate may be any electron-rich biological system, such as amino, sulfhydryl, organic and inorganic anions[1,2]. As the alkylating agents are electrophilic, they react with a variety of nucleophiles. The alkylating agents react irreversibly with the biological substrate system through formation of covalent bonds. The toxicity of alkylating agents is obviously due to such a reaction.

Bifunctionality appears to be essential for the cytotoxic activity of alkylating agents. This requirement of bi-functionality is the basis of cross-linking hypothesis which states that the alkylating agent reacts with two nucleophilic centres of biological macromolecules such as deoxyribonucleic acid and that the resulting bridges alter the chromosomes, causing cytotoxicity.

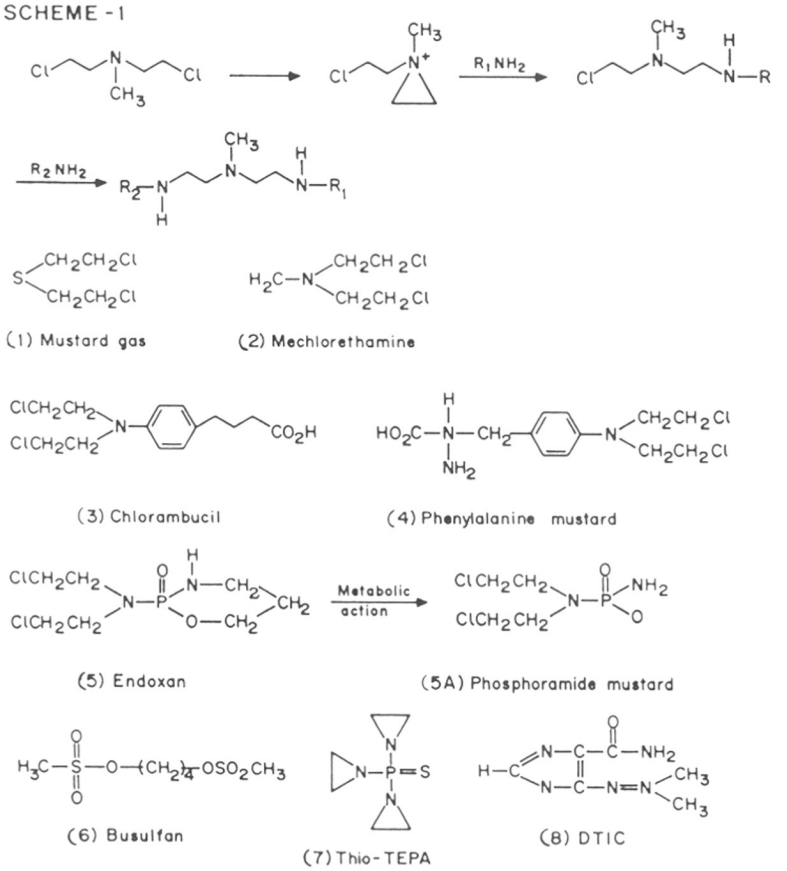
Common alkylating agents are nitrogen mustards, aziridines, nitrosoureas, triazine derivatives[1], epoxides and sulfonic acid esters.

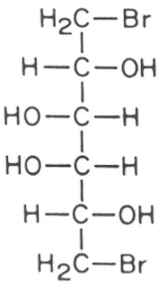
Compounds belonging to the 2-chloroethylamine class are commonly known as the "classical alkylating agents" or as nitrogen mustards. Due to its cytotoxic property they are used as possible anticancer compounds. During the world war (I) Germans had used, mustard gas bis-(2-chloroethyl)sulfide (**1**) as a chemical weapon resulting in tremendous casualties.

The first nitrogen mustard derivative to be used extensively clinically was mechlorethamine (**2**). The lone pair of electrons in the nitrogen atom provides an electron-rich target for the electrophilic carbon atom to produce an aziridine intermediate.

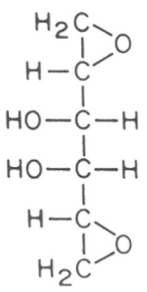
(Scheme-1) Mechlorethamine shows good activity against lymphomas ,but the extreme reactivity of this reagent makes it somewhat difficult to administer in that it cannot be given orally. Effective nitrogen mustards which are widespread in clinical use against tumors are chlorambucil (**3**), phenylalanine mustard (**4**) and cyclophsophamide (Endoxan) (**5**).

SCHEME - 1





(9) Dibromomannitol



(9A) Dibromodulcitol

Busulfan[3] (Myleran)(6) which is an alkyl alkanesulfonate, thio-TEPA (triethylenetriphosphoramide)(7) which is an aziridine, dacarbazine (8) (DTIC[4])[5- (3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide] which is a triazine and dibromomannitol(**9**) and dibromodulcitol as epoxide (**9A**) are commercially available for clinical use. They show good antitumor activity.

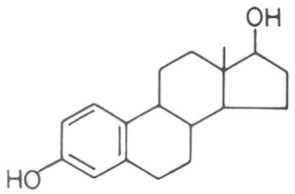
Nitrogen mustards are administered as water soluble hydrochlorides in the treatment of lymphosarcoma, leukemia, bronchogenic carcinoma, ovarian carcinoma and other types of disseminated cancers.

B) Antimetabolites:

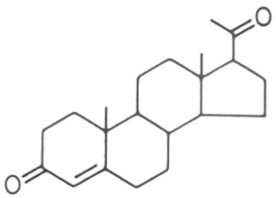
An antimetabolite is a compound whose biological activity depends on interference in utilization of a normal metabolite in the body.[6] They are slight structural variants of compounds essential to cell metabolism. Since cancer cells follow more or less the same metabolic process as the normal cells, blocking of any pathway by such an agent would result in toxicity to the host. Of these metabolites emphasis has been placed on the analogs of metabolites involved in "de novo" synthesis of nucleic acid and of purine and pyrimidine containing cofactors.

C) Hormones:

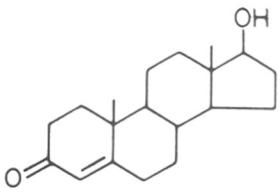
Tumours of reproductive organs are known to be hormone dependent. Estrogens [estradiol(**10**)] are used in the treatment of cancer of prostate glands. Similarly androgens are used in the treatment of breast cancer.



(10) Estradiol



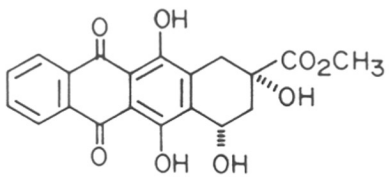
Progesterone



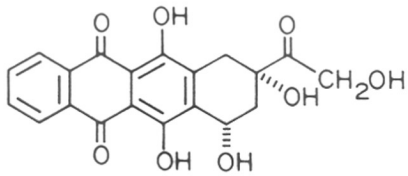
Testosterone

D) Anthracyclins:

The anthracyclins are a group of structurally related antitumor antibiotics [7]. The two protype anthracyclins are daunomycin (**11**) and adriamycin (**12**) produced from streptomyces species[8].



(11) Daunomycin



(12) Adriamycin

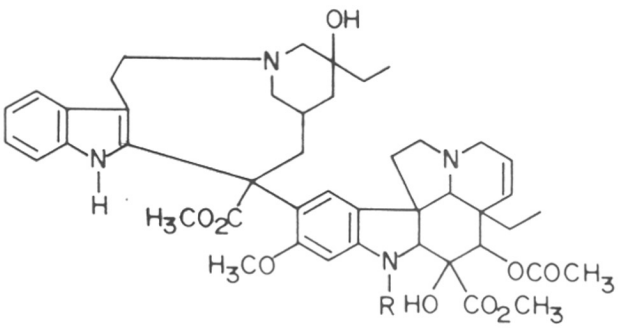
Daunomycin is effective in treatment of acute lymphocytic and myelocytic leukemia. Adriamycin has proved to be effective in the treatment of oesteogenic sarcoma, carcinomas of breast, thyroid, leukemias as well as solid tumors.

E) ***Natural Products*: *Drugs derived from plant sources.***

Prominent drugs derived from plants which are clinically used as anti-cancer drugs are vinca alkaloids, taxol, podophyllotoxin and camptothecin.

(1) Vinca alkaloids: Vincristin and Vinblastin

The vinca alkaloids, vincristine (**13**) and vinblastine(**14**) derived from the shrub *vinca rosea* are widely used in chemotherapy[9,10].

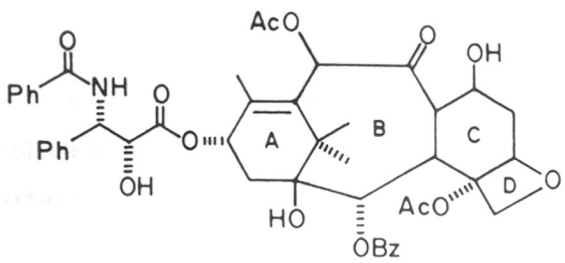


(13) R = — CHO Vincristine

(14) R = — CH_3 Vinblastine

(2) Taxol:

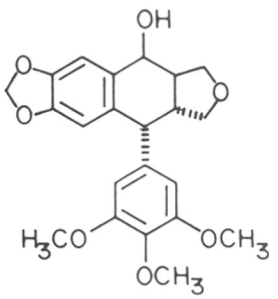
Taxol[11] (**15**) a complex polyoxygenated diterpene isolated from the Pacific Yew, *Taxus brevifolia* was discovered by Wani and co-workwrs[12]. Taxol has proven to be effective against a number of leukemias, solid tumors including those of breast, lung, ovary and brain. Till date, taxol is the most effective drug in cancer chemotherapy. The mechanism of action is unique among anticancer agents, functioning as a mitotic inhibitor and blocking cells in cell cycle and preventing microtubule depolymerization[11].



(15) Taxol

(3) Podophyllotoxin:

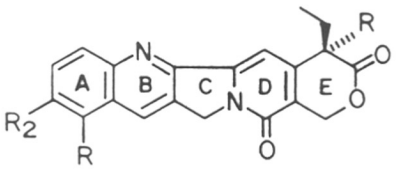
Podophyllotoxin (**16**) was isolated from the *May Apple* or *Podophyllum pellatum* and found to be active against wide range of tumors, lymphoblastic leukemias[7,13,14]. Similarly water soluble derivatives of podophyllotoxin *viz* etoposide, tenoposide are available in market as anticancer agents.



(16) Podophyllotoxin

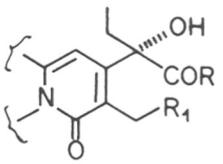
(4) Camptothecin:

Camptothecin (**17**) was isolated by Wall and co-workers[15] from *Camptothecia acuminata*. Camptothecin has broad spectrum of activity in a variety of leukemia and solid tumor systems[7,16].Camptothecin is a high melting compound (M.P.264-267 dec) which is insoluble in water and has only limited solubility in most organic solvents. Two water soluble analogues of camptothecin,10-Hydroxycamptothecin (**17A**)and sodium salt (**17B**) have high activity against leukemia and solid tumor.



(17) R = OH $R_1 = R_2 = H$ Camptothecin

(17A) R = R_2 = OH R_1 = H 10- Hydroxycamptothecin



(17B) R = ONa ; R_1 = OH

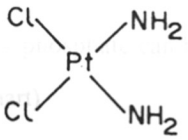
Sodium salt of Camptothecin

Similarly, other water soluble derivatives of camptothecin *viz* topotecan and irinotecan have been introduced in market by Smith Kline and Beecham USA and Diichi Japan respectively.

(5) Miscellaneous Agents:

Cis(II) platinum diamine dichloride (**18**) (cisplatin) is the only heavy metal compound used as a cancer chemotherapeutic drug for the treatment of testicular and ovarian carcinomas[17]. It has also demonstrated significant activity in carcinomas of the

urinary bladder, prostate, and head and neck and in oesteogenic sarcomas in children[18].



(18) Cisplatin

1.1.1 *An Attempt At Rationalization Of Development Of Cancer Chemotherapeuticals (by M.B.Sahasrabudhe[19]).*

In a growing tissue, irrespective of whether it is neoplastic or normal, there is a rapid nucleic acid synthesis as well as pyridine nucleotide synthesis. It was shown by Sahasrabudhe[19] that nucleic acid synthesis takes up major portion of adenine precursor and very little is left for pyridine nucleotide synthesis. It was further shown that this is the time for the nucleic acid synthesis in both the types of growing tissues[20,21] Pyridine nucleotides have an important role in the hydrogen transport system and thus indirectly participate in the production of energy *via* tricarboxylic acid cycle. So it was suggested that low level of pyridine nucleotide automatically slows down all the synthetic and proliferative activities by controlling energy production. Since nucleic acid synthesis requires energy, the appropriation of adenine will itself act as a self-regulatory feed back mechanism by limiting the pyridine nucleotide levels. The fact that tumour continues to grow indefinitely indicates that it finds some alternative source for its energy requirements independently of tricarboxylic acid cycle and pyridine nucleotide. Thus, through HMP (hexosemono phosphate shunt) or oxidative pathway tumour derives major portion of energy[22].

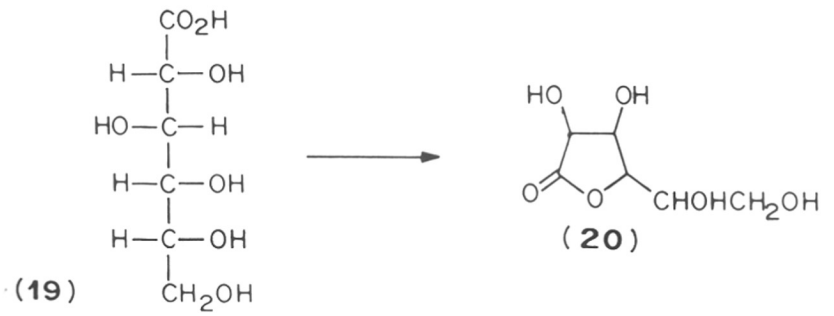
In Embden-Meyerhoff pathway (EMP) glycolysis occurs whereby glucose was

metabolised through the formation of glucose-6-phosphate, fructose-6-phosphate, fructose-1,6-diphosphate and triose phosphate. In HMP pathway sedoheptulose-7-phosphate and erythrose-4-phosphate can be converted to triose phosphate and thus meet EMP pathway. (see chart)

Sahasrabudhe[19], suggested for the first time the usefulness of preparing antimetabolites against, glucose-6-phosphate, 6-phosphogluconic acid and ribulose-5-phosphate. Glucose-6-phosphate takes part in EMP path also.

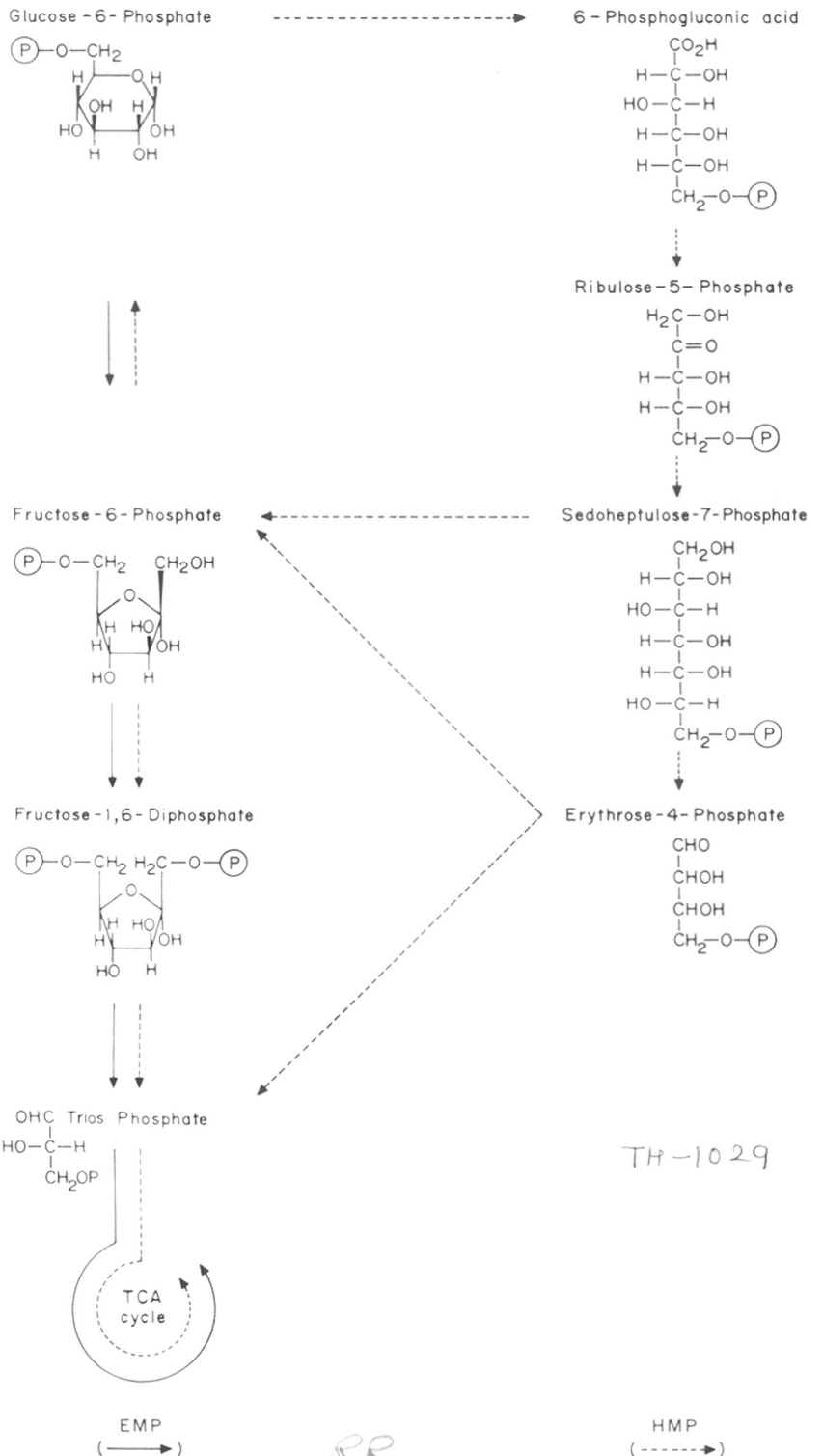
The antimetabolites of 6-phosphogluconic acid should have (1) a free carbonyl group at one end and (2) a free or phosphorylated hydroxymethyl or carboxyl group at the other end[22].

Any deliberate departure, in the structural configuration of central $(CHOH)_4$ grouping of 6-phosphogluconic acid may be expected to result in a substance having antimetabolite properties. These considerations and the fact that gluconic acid(**19**) is readily converted to 5-membered -lactone structure(**20**) suggested that compounds containing the following moieties furan (**21**) , tetrahydrofuran (**22**), thiophene (**23**) and tetrahydrothiophene (**24**) might inhibit malignant growth through interference in the HMP pathway. Consequently Tilak and Sahasrabudhe *et al* synthesised a large number of derivatives of furan, thiophene and their tetrahydro derivatives and tested their anticancer properties. (Ref Para 1.1.2)



(**19**) (**20**)

CHART



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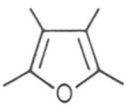

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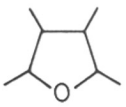

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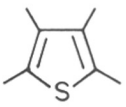

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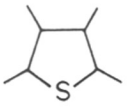
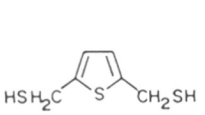


(24)

1.1.2 *Anticancer Activity Based On Interference In HMP And EMP Pathway (by B.D.Tilak and M.B.Sahasrabudhe et al[22])*

The anticancer action of the heterocyclic compounds was studied against transplantable *Yoshida sarcoma* (acsites) in rats and solid fibrosarcoma in Swiss mice. *Yoshida sarcoma* is a very rapidly growing tumor whereas solid fibrosarcoma is a comparatively slow growing tumor. The compounds to be tested were injected intraperitoneally 24 hours after the transplantation.

Reduced heterocyclic compounds were found to be inactive, whereas aromatic bi-functional compounds proved to be active. Among the large number of heterocyclic compounds tested, the following compounds showed significant activity: 2,5-Dimercaptomethylthiophene (**25**), 2,5-Dicarbethoxy-3,4-dihydroxythiophene disodium salt (Dicetol)(**26**), Thiophene-2,5 bisdimethylenylthiouronium dichloride (**27**)[22].



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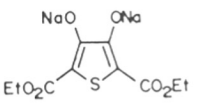
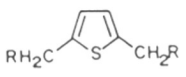
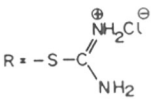


(26)



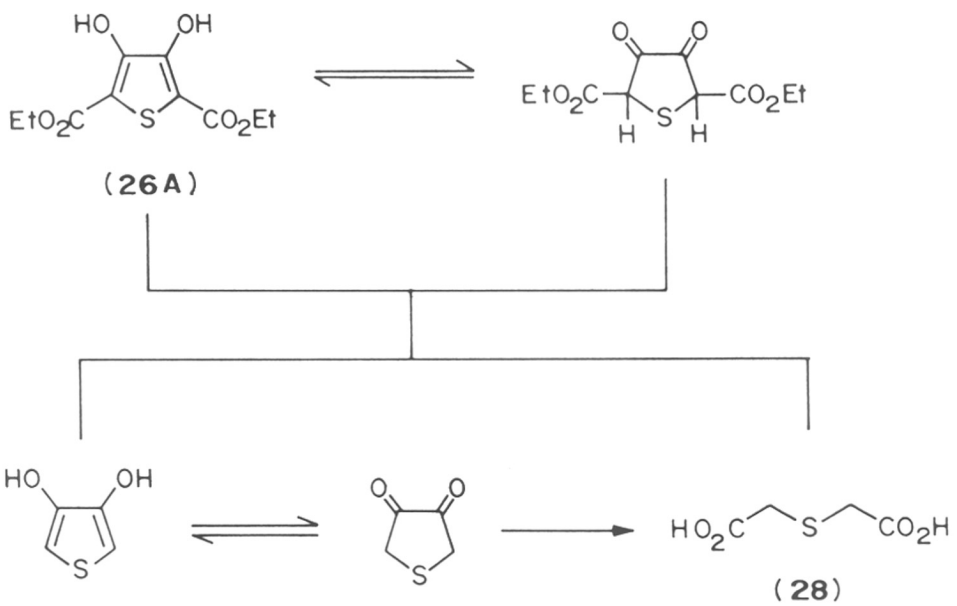
(27)



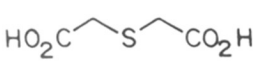
With bisthiouronium dichloride (**27**) treatment for ten days only, the Yoshida sarcoma transplanted animals survived for more than six months without any trace of malignancy. These animals lived their natural life span of two years. The corresponding controls died by the 5th day after transplantation.Dicetol (**26**) disodium salt gave best results with solid fibrosarcoma.Thus all the active compounds were bifunctional as indeed many cancer chemotherapeuticals are.

While considering the possible routes by which Dicetol (**26A**) may be metabolised, Dicetol may be degraded *in vivo* to thiodiglycollic acid (**28**)if Dicetol is considered in its bis keto-enol form. (Scheme-2)

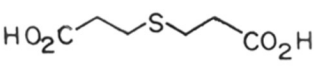
SCHEME - 2



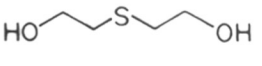
The activity of thiodiglycollic acid (**28**) was examined and the compound indeed proved active. Several analogues of open chain bisulfides were tested of which thiodiglycollic acid (**28**), thiodipropionic acid (**29**) and thiodiglycol (**30**) showed good anticancer activity[23,24].



(28)



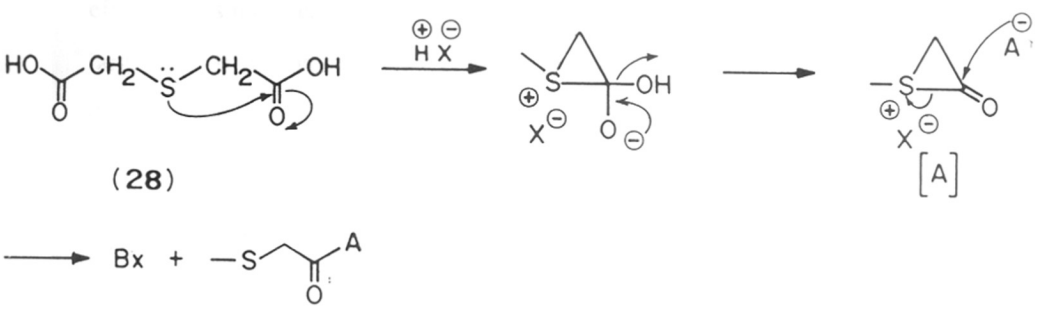
(29)



(30)

Thiodiglycollic acid (28) may be acting as a cross-linking agent through neighbouring group participation by sulfur to give a episulfonium cation(A) as a reactive intermediate which cross-links on cellular molecules. (Scheme-3) However in the case of dicarboxyllic acids (28) and (29); the cross-linking, if it occurs, will be through bis-ester and not through covalent bis-alkyl linkages. Consequently the former cross-linking is likely to be reversible as against bis-alkylation. Hence in order to maintain adequate drug level *in vivo* such compounds (27, 28,29) will have to be adnimistered in repeated doses, since they may be acting as carcinostatic agents not carcinocidal alkylating agents. One would therefore expect such compounds to be less toxic.

SCHEME - 3



The activity of the anticancer compounds was based on inhibitory action on Embden-Meyerhoff and HMP glycolysis pathway.The test employed for judging such competitive inhibition of EM and HMP pathways consisted in carrying out *in vitro* studies by incubating the tumor tissue with glucose-1^{14}C and glucose-6^{14}C with and without the presence of the drug under examination[25]. The liberation of radioactive $^{14}CO_2$ from glucose-1-^{14}C was expected to diminish in presence of the drug if it inhibits the HMP pathways and was expected to be active anticancer drug. Whereas $^{14}CO_2$ evolution from glucose-6-^{14}C should result from interference in normal EM pathway. It was found that several of the more active compounds did not preferably inhibit the HMP pathway as expected, whereas some compounds which showed preferential inhibition were found to have no anticancer activity. Thus the rationale of the synthesis of above anticancer compounds based on HMP pathway interference[19] did not prove to be valid.

1.1.3 *Present Work*:

Despite considerable advances in cancer treatment, chemotherapy remains a major clinical choice. An ideal chemotherapeutic drug should have maximum action on the diseased tissue and no or minimum action on the host tissue. Inspite of the best efforts it has not been possible to obtain a completely safe chemotherapeutic drug. A large number of potent anticancer drugs such as cross linking bis-alkylating agents discovered over the years damage the normal cells and are therefore toxic. The margin between effectiveness and toxicity of anticancer drugs is extremely narrow. Consequently most effective anticancer drugs are also toxic causing painful side reactions.

In the use of carcinostatic drugs, the drug has to be administered in repeated dosages over a prolonged period to control proliferation of cancerous cells.Thus such drugs should be non-toxic, less harmful and should not have side effects even after

prolonged administration.

Earlier Tilak *et al*[23-29] synthesised a large number of compounds with the view to devlop anticancer agents which would be specific in their action on malignant cells. Of the large number compounds tested the following lead compounds showed significant anticancer activity: thiodiglycollic acid (**28**), thiodipropionic acid (**29**), thiodiglycol (**30**), 2,5-Dicarbethoxy-3,4-dihydroxythiophene disodium salt (**26**) and Thiophene-2,5-bis dimethylenylthiouronium dichloride (**27**). Anticancer action of these compounds was studied against transplantable *Yoshida Sarcoma* (ascites) in rats and solid fibrosarcoma in Swiss mice. All these compounds were found to be carcinostatic in nature and thus were taken as lead compounds for present work.

The carcinostatic property of compounds **26,27,28,29,30** was studied earlier *in vivo* against transplantable *Yoshida sarcoma* (ascites) and solid fibrosarcoma in Swiss mice. These compounds proved to be satisfactory in arresting growth of cancerous cell.

Encouraged by these results, carcinostatic activity of mono and bifunctional open chain sulfides and thiophene derivatives was tested *in vitro* against human chronic myeloid leukemia cells and sarcoma 180 cells derived from mouse fibrosarcoma. Of all the compounds tested Thiophene-2,5-bisdimethylenylthiouronium dichloride(**27**) showed significant carcinostatic activity.

1.1.4 *Results & Discussion*:

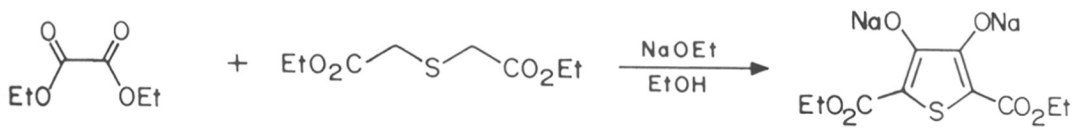
The area of anticancer drug discovery is developing rapidly. New drugs are being screened for their suitability for clinical use. The National Cancer Institute (NCI), Division of Cancer Treatment NIH, Bethesda, USA has relied on *in vivo* tests on animals. However, the drug discovery programmes have shifted to *in vitro* systems involving isolated cells.[30] This shift was due to the disappointing correlation in clinical

treatment of solid tumours, the rising cost, the long time required for the tests and the controversies over the use of animals in drug testing.

The NCI uses a panel of sixty established cell lines[31] for screening anticancer drugs, due to which inactive compounds can be eliminated from further consideration and active compounds can be selected and in depth studies can be done on priority basis.

Thiodiglycollic acid (**28**) was prepared by the interaction of mono chloroacetic acid with sodium sulfide.[32] Similarly thiodipropionic acid(**29**) was prepared[33] by using monochloropropionic acid and sodium sulfide. Thiodiglycol (**30**) was prepared from chlorohydrin and sodium sulfide.[34] The sulfoxide(**28B**) and sulfone(**28C**) of dimethyl thiodiglycollate were prepared by reaction with $NaIO_4$ and H_2O_2/AcOH respectively[37]. 2,5-Dicarbethoxy-3,4-dihydroxythiophene was prepared by Hisenberg condensation methods[35] using diester of thiodiglycollic acid and diethyloxalate in NaOEt (Scheme-4) and isolated as disodium salt which is highly water soluble; a highly desired property for the carcinostatic compounds.

SCHEME - 4



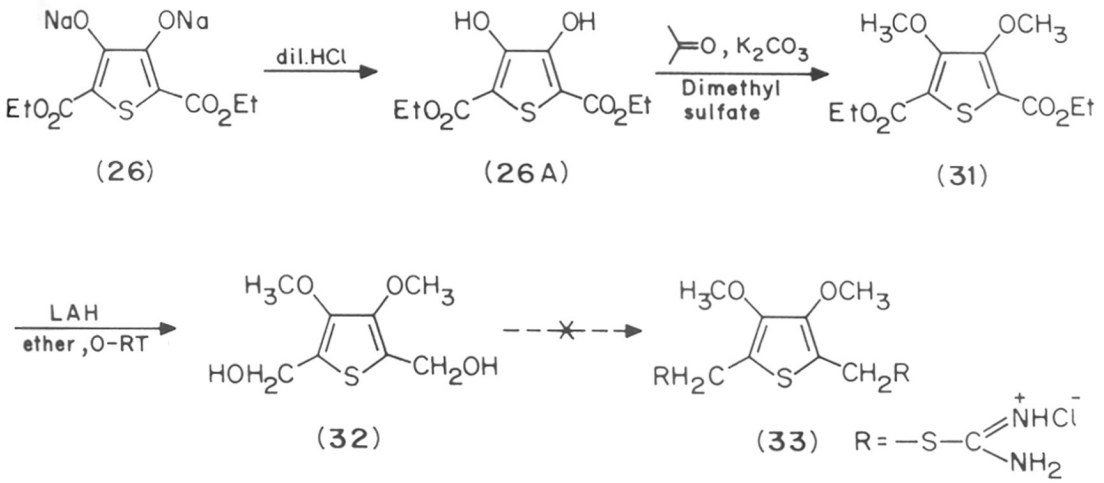
(28A) (26)

This disodium salt on acidification gave 3,4-Dihydroxy-2,5-dicarbethoxy thiophene which was methylated to give (**31**). The latter on reduction of diesters gave 2,5-Dihydroxymethyl-3,4-dimethoxythiophene (**32**) (Scheme-5).

Attempted conversion of alcohol (**32**) to its thiouronium salt (**33**) *via* chloro or

mesyl derivative or direct conversion was unsucessful and led to formation of intractable mixtures. This may be attributed to the presence of methoxy groups. Presence of methoxy groups makes the chloro or mesyl derivatives highly reactive which results in polymerisation. Thus attempts at preparing hydroxylated or methoxy derivatives of the bis-thiouronium salt (33) which were expected to be less toxic than (27) proved unsuccesful.

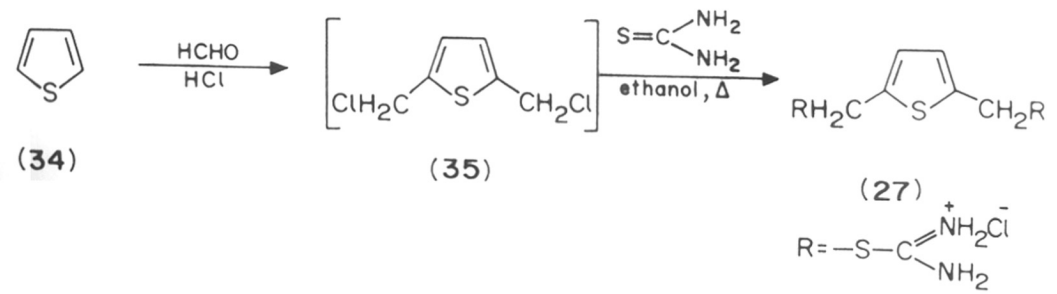
SCHEME-5



(26) (26A) (31) (32) (33)

2,5-bis-Chloromethylthiophene was prepared by the procedure described by Griffing and Salisburg[36] by chloromethylation of thiophene. This was immediately converted to its bis-thiouronium salt by reacting with thiourea in ethanol (Scheme-6).

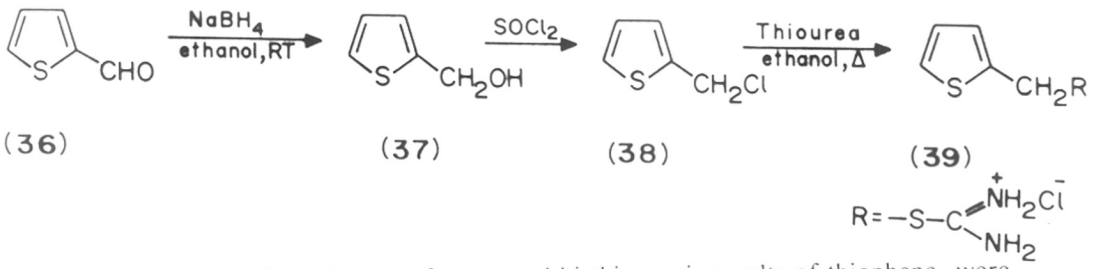
SCHEME-6



(34) (35) (27)

Similarly monothiouronium salt of thiophene(**39**) was prepared from thiophene-2-aldehyde(**36**) (Scheme-7).

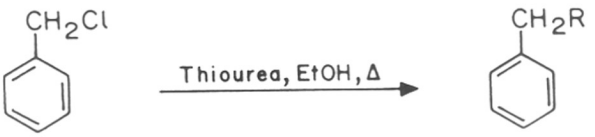
SCHEME - 7



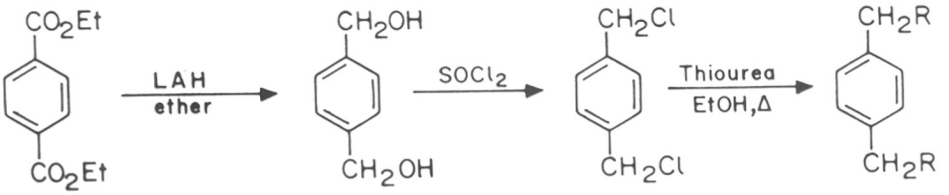
(**36**) (**37**) (**38**) (**39**)

Isoelectronic analogues of mono and bisthiouronium salts of thiophene were prepared. Treatment of benzyl chloride with thiourea gave mono thiouronium salt(**41**). 1,4-bis-Chloromethylbenzene (**44**) was obtained from diethyl terephthalate(**42**). (Scheme-8)Compound (**44**) was then converted to the bis-thiouronium salt(**45**) by reacting with thiourea in ethanol.

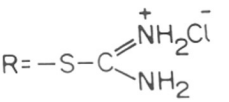
SCHEME - 8



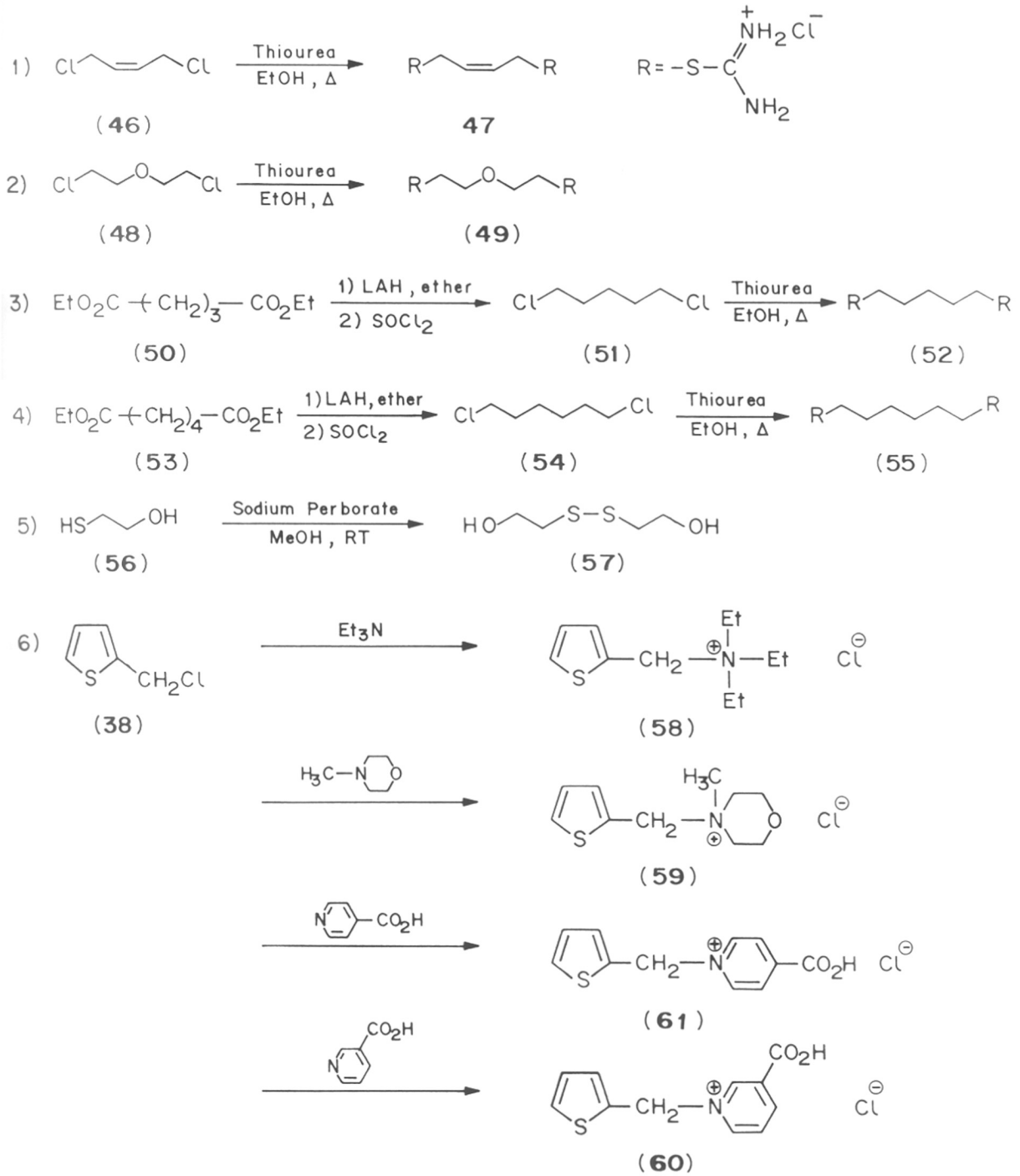
(**40**) (**41**)



(**42**) (**43**) (**44**) (**45**)



SCHEME - 9


1)
Thiourea
EtOH , Δ
(46)
47
R= -S-C
NH2 Cl
NH2
2)
Thiourea
EtOH , Δ
(48)
(49)
3)
1) LAH , ether
2) SOCl2
Thiourea
EtOH , Δ
(50)
(51)
(52)
4)
1) LAH, ether
2) SOCl2
Thiourea
EtOH , Δ
(53)
(54)
(55)
5)
Sodium Perborate
MeOH , RT
(56)
(57)
6)
Et3N
(38)
(58)
(59)
(61)
(60)

All these compounds were characterised by IR, ^{1}H-NMR and mass analysis. Few more bis-thiouronium salts listed in(Scheme-9) were prepared and tested for their anticancer properties.

1.1.5 *Biological Testing Of Compounds*:

All the above bis-thiouronium salts were water soluble having a desirable property for good drug penetration.The carcinostatic effect of anticancer compounds derived from open chain and cyclic sulfur compounds was examined *in vitro*.

Human cell lines used to ascertain anticancer properties of the above compounds were

1) **K562**: Derived from human chronic myeloid leukemia origin. They are malignant, and multipotential in nature.

2) **Sarcoma 180**: Derived from mouse fibrosarcoma. It is extremely tumorigenic and fibroblast like in morphology.

3) **KGI**: Leukemic origin cells.

4) **WI38**: Lung fibroblast cells.

Different doses were added to the cell cultures. and the effect was assessed by cell counts, viability and ^{3}H Thymidine uptake cell counts were taken on haemocytometer. Viability was assessed by dye exclusion method using Erthromycin B and MTT (3,4,5-dimethyl thiazl-2-yl) 2,5-diphenyltetrazolium bromide.

Increase in population doubling time was used as the parameter to assay the effect of carcinostatic drugs. An increase in the doubling time can be regarded as an indication of cytotoxicity. Growth kinetics of treated cells was compared to that of untreated and the cells that were treated only once and allowed to recover in the absence of the drug. Cell counts were taken every 24 hrs and followed up for 96 hr. The results showed that Dicetol disodium salt (**26**) and thiouronium salt (**27**) are carcinostat-

ic in nature. The other two drugs (**28**) and(**29**) did not suppress the cell proliferation. In fact thiodipropionic acid (**29**) actually increased the proliferation of cells.This observation is in contrast to what was observed *in vitro* animal tests.

In MTT assay[30,31], MTT solution was added to the culture at a final conc. of 500 μg/ml. After 4 hr. incubation, the formazan crystals formed were dissolved in acidic isopropanol and the absorption was read on a Dynatech Elisa Plate reader at 570 nm (reference wavelength 630 nm, calibration factor 1.00). MTT assay is a colorimetric procedure for estimation of the cell viability. There is a good correlation between the number of cells and level of absorbance. MTT assay on treated versus untreated controls showed that the treated cells were not proliferating over a period of 4 days. Thus MTT assay also showed comparable results.

^{3}H-Thymidine uptake assay was performed on cells plated at a density of 10^{4} per wall in 96 wall plates. After 24 hrs. different doses of the compounds were added in quadruplicates. After further 24 hrs incubation, ^{3}H-Thymidine was added for 16-18 hr. Cells were harvested using a PHD cell harvester and the radioactivity counted on a Beckman beta counter. The effect of the compounds was expressed as % (^{3}H-Thymidine uptake) of control.

All the sulfur-containing compounds which showed carcinostatic activity had two reactive groups such as hydroxy, carboxy and thiouronium chloride. Thus, the monofunctional TU (**39**) was inactive against K562 cells. Also the hydrocarbon isoesters of thiouronium salts(**41**) and (**45**) were also inactive against K502. Dicetol disodium salt (**26**) was found to be active against K562. In order to reduce its toxicity, it was methylated and ester was reduced to give the alcohol (**32**), which was also inactive against K562. Also thiodiglycol (**30**) was also found to be inactive against K562 cells. (Earlier it was found to be active *in vivo*). Thiodipropionic acid (**29**) found earlier to be active anticancer agent in experimental animals was ineffective on K562 cells, in fact

cell proliferation was observed. Sulfone and sulfoxide of dimethyl thiodiglycollate were also found to be inactive.

1.1.6 Conclusion:

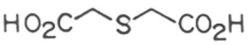
Carcinostatic effect of various open chain sulfides and thiophene derivatives is as follows:

Drug	Cell lines used	Carcinostatic
Dicetol(26)	K562	Yes
Dicetol alcohol (32)	KG-I	No
	WI 38	No
Thiodipropionic acid(29)	K562	No
		cells proliferate
Thiodiglycollic acid(28)	K562	No
Thiodiglycol(30)	K562	No
Thiodiglycol sulfone(28C)	WI 38	No
Thiodiglycol sulfoxide(28B)	WI 38	No
Bis-thiouronium salt(27)	K562	Yes
	WI 38	Yes
	VA 13	Yes
Mono TU salt(37)	K562 & WI 38	No
Mono Bz TU salt(41)	K562 & WI 38	No
Bis-Bz TU salt(45)	K562 & WI 38	No

The sulfur compounds have been tested for the first time on the human cell lines and have shown promising results.Thus Dicetol disodium salt and bis thiouronium salts have proved to be effective drugs against cancer cells. Since all these compounds are water soluble, they are easy to administer. A quick biological screen of the above compounds has been established which in turn would allow rapid screening of other compounds for their carcinostatic activity. The *in vitro* carcinostatic activity of the bis-thiouronium salts and thiophene quaternary salts newly synthesised in the present work *viz* **47,49,51,53,55,56,57, 58,59** on human cancerous cell lines has yet to be examined.

1.1.7 *Experimental*

Thiodiglycollic acid (28)

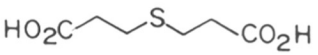


Thiodiglycollic acid was prepared from mono-chloroacetic acid an sodium sulfide according to reported procedure[19].

$C_4H_6O_4S$

M.P. 128° (Lit. 128-131°) White solid.

Thiodipropionic acid (29)

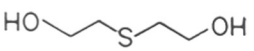


Thiodipropionic acid was prepared from monochloro propionic acid and sodium sulfide according to literature procedure[20].

$C_6H_{10}O_4S$

M.P. 132° (Lit. 131-134°)

Thiodiglycol (30)

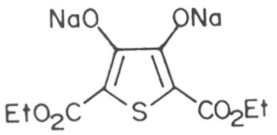


Thiodiglycol was prepared from chlorohydrin and sodium sulfide as described in the literature[21].

$C_4H_{10}O_2S$

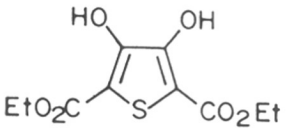
BP 164/20 mm (Lit. 166/20 mm)

Dicetol disodium salt[22] (26)



To a sodium ethoxide solution (3 gm of sodium in 40 ml of absolute alcohol), diethyl thiodiglycollate (0.01 mol) and diethyl oxalate (0.01 mol) was added at 0°C. The reaction mixture was stirred for 2 hrs at 0°C and then brought to room temperature and stirred for another two hrs. The precipitated yellow sodium salt was removed by filtration. Yield 80% M.P. >250°C.

Dicetol 3,4-dihydroxy-2,5-dicarbethoxy thiophene (26A)



Disodium salt of 3,4-dihydroxy-2,5-dicarbethoxythiophene was dissolved in minimum water and dil. HCl (10N) was added slowly and stirred at room temperature for 2 hrs. The white ppt formed was filtered and recrystallized from aq. ethanol.

$C_{10}H_{12}O_6S$

M.P. 178°C White solid

IR ($CHCl_3$, cm^{-1}): 580, 750, 920, 1020, 1220, 1320, 1380, 1500, 1740, 3400, 3500.

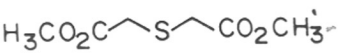
^1H NMR (80MHz, $CDCl_3$, δ): 1.1 (t, 6H, CH_3; 4.2 (q, 4H, $-OCH_2$); 9.1 (bs, 2H, exchangeable protons)

Mass (m/e): 232 (M^+, 45), 200 (100), 168 (75), 132 (15), 100 (70), 89 (10), 85 (30), 72 (18).

Analysis: Cal. C 51.72; H 5.17; S 13.79

Obs. C 51.58; H 5.58; S 13.51

Dimethyl thiodiglycollate (28A)



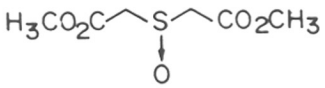
Dimethyl thiodiglycollate was prepared by refluxing thiodiglycollic acid in methanol in presence of concentrated sulphuric acid.[25]

$C_6H_{10}O_4S$ colourless liq.

IR (neat, cm^{-1}): 1020, 1180, 1320, 1450, 1740

^1H NMR (80MHz, $CDCl_3$, δ): 3.2 (s, 4H, CH_3); 3.8 (s, 6H, CH_3)

Dimethyl thiodiglycollate sulfoxide (28B)



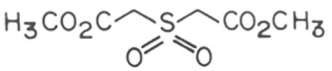
Dimethyl thiodiglycollate sulfoxide was prepared by reacting dimethyl thiodiglycollate and sodium metaperiodate(equivalent amount) in methanol at 0°C.[24]

$C_6H_{10}O_5S$ Colourless liq.

IR (neat, cm^{-1}): 780, 920, 980, 1060.

^1H NMR (80MHz, $CDCl_3$, δ): 3.7 (s, 6H, CH_3); 3.8 (s, 2H, CH_2); 3.9 (s, 2H, CH_2)

Dimethyl thiodiglycollate sulfone (28C)



Dimethyl thiodiglycollate sulfone was prepared by refluxing dimethyl thiodigly-

collate with aqueous hydrogenperoxide (excess) in acetic acid.[24]

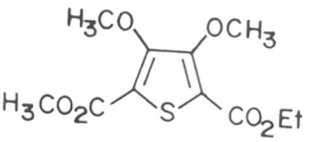
$C_6H_{10}O_6S$

M.P. 105° White solid

IR (nujol, cm^{-1}): 720, 880, 1020, 1060, 1120, 1150, 1280, 1310, 1450, 1740

^1H NMR(80MHz, $CDCl_3$, δ): 3.8 (s, 6H, CH_3); 4.2 (s, 4H, CH_2).

3,4-dimethoxy-2,5-dicarbethoxy thiophene (31)



A mix of 3,4-dihydroxy-2,5-dicarbethoxy thiophene (**26A**) (1 eq), dimethyl sulfate (2.1 eq) and anhydrous potassium carbonate (4 eq) was refluxed in acetone with vigorous stirring; for 6 hrs. After completion of reaction solid was filtered off and solvent removed under reduced pressure. The crude solid was recrystallised from alcohol. 75% yield

M.P. 98° Pale yellow solid

IR (nujol, cm^{-1}): 580, 780, 850, 920, 950, 1020, 1080, 1120, 1180, 1220, 1350, 1420, 1450, 1500, 1740, 2850.

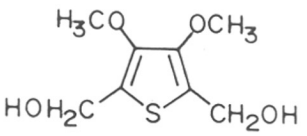
^1H NMR (80MHz, $CDCl_3$, δ): 1.2 (t, 6H, CH_3); 3.6 (s, 6H, $-OCH_3$); 4.1 (q, 4H, $-OCH_2$)

Mass (m/e): 288 (M^+, 28), 241 (35), 213 (38), 185 (10), 169 (15), 88 (30), 60 (100).

3,4-dimethoxy-2,5-bis hydroxymethyl thiophene (32)

3,4-dimethoxy-2,5-bis hydroxymethyl thiophene (**32**) was prepared by reduction of 3,4-methoxy-2,5-dicarbethoxy thiophene (**31**) with lithium aluminium hydride

in dry ether. A solution of 3,4-dimethoxy-2,5-dicarbethoxy thiophene (3.5 gms, 0.013 mmol) in dry ether was added at 0°C under nitrogen atmosphere to a suspension of lithium aluminium hydride (2.4 gms, 3 eqs) in dry ether. Reaction mixture was stirred at 0°C for 3 hrs and then slowly brought to room temperature at stirred for 5 hrs. On completion of the reaction, the reaction mixture was cooled to 0°C and quenched with saturated sodium sulphate solution. After filtration, extracted with dichloromethane and column purification gave (**32**) in 65% yield.



$C_8H_{12}O_4S$ Pale yellow viscous liq (unstable), Yield 65%

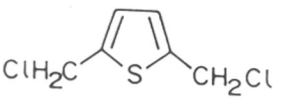
IR ($CHCl_3$, cm^{-1}): 780, 1020, 1080, 1250, 1280, 1400,1450, 1500, 3400, 3500.

^1H NMR (80MHz, $CDCl_3$, δ): 2.1 (bs, 2H, exchangeable proton); 3.8 (s, 6H, $-OCH_3$); 4.6 (s, 4H, $-CH_2$).

Analysis Cal. C 47.05; H 5.88; S 15.68

Obs. C 47.30; H 5.89; S 15.83

2,5-bis-Chloromethyl thiophene (35) was prepared by chromomethylation of thiophene[23]

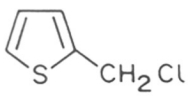


B.P. 106-108°/5 mm.

2-Chloromethyl thiophene[21] (38)

Thiophene-2-aldehyde (36) 5 gm (0.044 mmol) was reduced with sodium

borohydride (3.3 gm, 2 eq, 0.088 mmol) in ethanol (50 ml) to give alcohol (**37**) 4.1 gm in 80%. To the solution of alcohol 4 gm (0.035 mmol) (**24**) in benzene (25 ml) at 0°C was added thionyl chloride 2.8 ml (0.038 mmol) slowly with stirring; and then refluxed for 8 hrs. Removal of solvent gave crude product, which on distillation gave pure 2-chloromethyl thiophene(**38**) in 3.5 gms 75% yield.



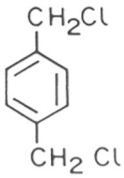
C_5H_5ClS

B.P. 73-75/17 mm.

IR (neat cm^{-1}): 780, 820, 970, 1020, 1280, 1380, 1480, 1610.

^1H NMR (80MHz, $CDCl_3$, δ): 4.6 (s, 2H, CH_2); 7.1-7.5 (m, 3H, aromatic).

1,4 bis chloromethyl benzene (44)



A solution of diethyl terephthalate (**42**) (2.2 gm, 0.01 mmol) in dry ether was added to a suspension of lithium aluminium hydride (1 gm, 0.025 mmol) in dry ether at 0°C, slowly with stirring. The reaction mixture was stirred at 0°C for 2 hrs and then at room temperature for 2 hrs. Reaction mix was quenched with saturated Na_2SO_4 solution. Extraction with CH_2Cl_2 gave the diol (**43**) 0.68 gm in 50% yield. Reacting with thionyl chloride (0°C-reflux), 1,4-bis-chloromethyl benzene (**31**) was obtained 0.445 gm in 70% yield. To the Diol (0.500 gm, 0.0036 mmol) in benzene was added $SOCl_2$(0.60 gm, 2.2 eq) at 0°C and later

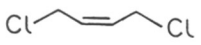
refluxed for 3 hrs. Removal of solvent under reduced pressure gave dichloro (**44**) which was purified by flash chromatography.

$C_8H_8Cl_2$

IR ($CHCl_3$ cm^{-1}): 700, 750, 860, 1120, 1220, 1260, 1420, 1450, 1600.

^1H NMR(80MHz, $CDCl_3$ δ): 4.6 (s, 4H, CH_2); 7.5 (m, 4H, aromatic)

Cis-1,4-dichloro-2-butene (46)



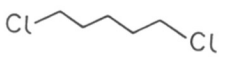
Cis-1,4-dichloro-2-butene was prepared from cis, 1,4-butene diol and thionyl chloride according to the literature procedure.[26]

B.P. 150°C (Reported 152°C)

IR (neat, cm^{-1}):780, 820, 970, 1020, 1080

^1H NMR (80MHz, $CDCl_3$, δ): 4.1 (d, 4H, $-CH_2$); 5.5 (m, 2H, olefinic).

1,5-Pentane dichloride[28] (51)

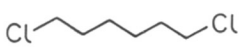


B.P. 63/10mm

IR (neat cm^{-1}): 580, 650, 780, 1050, 1250, 1320, 1450, 2850

^1H NMR(80MHz, $CDCl_3$ δ): 1.9 (m, 6H, $-CH_2$); 3.4 (t, 4H, $-CH_2Cl$)

1,6-Dichlorohexane[29] (54)



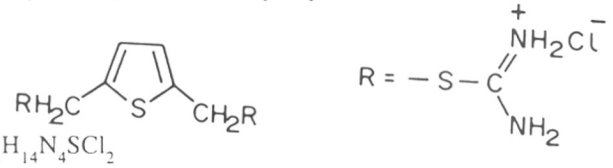
B.P. 87-90°/15 mm

General procedure for thiouronium salts.

(27, 39, 41, 45, 47, 49, 52, 55)

A solution of thiourea (0.02 mol) in 20 ml ethanol was added dropwise to a stirred solution of halomethyl compounds 0.01 mol in case of **(38,40)** **(35,44,46,48,51,54)** (0.01 mol) in 20 ml of ethanol at 0-5°C. The reaction mixture was heated under reflux for 6 hrs. After removal of ethanol, residue was treated with ether and crude salt was filtered and recrystallised from aq. alcohol to give colourless thiouronium salts.

Thiophene 2,5-bis dimethylenyl thiouronium dichloride (27)



$C_8H_{14}N_4SCl_2$

M.P. 218° (literature[5] 220 dec) White crystals

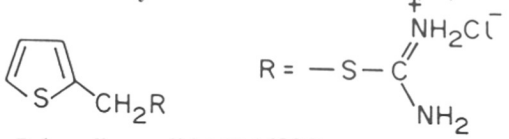
IR ($CHCl_3$, cm^{-1}): 580, 750, 1020, 1250, 1380, 1450, 1640, 1650, 2880, 2980, 3040

^1H NMR (80MHz, DMSO-d_6, δ): 4.7 (s, 4H, CH_2); 7.1 (s, 2H, Aromatic); 9.2 (bs, exchangeable proton.

Analysis Cal C 35.68; H 5.20; N 20.81; S 11.89;Cl 26.39

Obs C 35.39; H 5.41; N 20.71; S 11.71;Cl 25.99

Thiophene-2-chloromethyl thiouronium chloride (39)



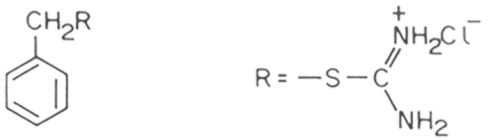
$C_6H_9N_2SCl$ Pale yellow solid MP 168°C

^{1}H NMR(DMSO-d_6): 4.8 (s, 2H, -CH_2); 7-7.5 (m, 3H, aromatic); 9.5 (bs exchangeable proton).

Analysis Cal C 40.79; H 5.09; S 18.13; Cl 20.11;N 15.86

Obs C 40.51; H 5.36; S 17.98; Cl 20.32;N 15.61

Benzene-chloromethyl thiouronium chloride (41)



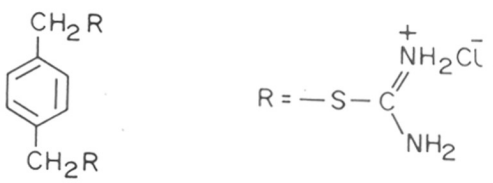
$C_8H_{11}N_2SCl$

M.P. 146°C

Analysis Cal. C 56.02; H 6.71; N 16.13; Cl 20.65

Obs. C 56.03' H 6.54; N 16.42; Cl 20.82

Benzene-1,4-bis-chloromethylenyl thiouronium dichloride (45)



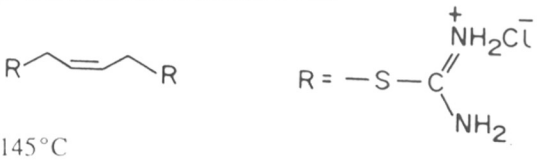
$C_{10}H_{16}N_4S_2Cl_2$

M.P. 250°C

Analysis Cal. C 45.62; H 6.03; N 21.29; Cl 26.99

Obs. C 45.30; H 6.08; N 21.45; Cl 26.05

Cis-1,4-thiouronium dichloride (47)

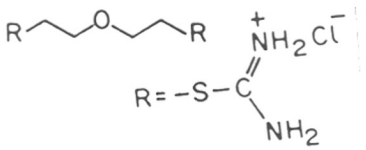


M.P. 145°C

Analysis Cal C 25.69; H 4.91; N 20.48; S 23.48;Cl 25.52

Obs C 25.99; H 5.05; N 20.21; S 23.10;Cl 25.63

Digol bis thiouronium dichloride (49)

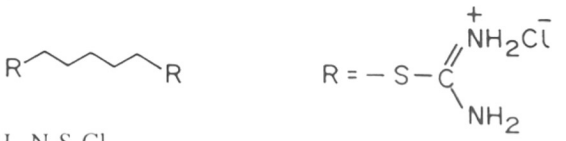


M.P. 120°

Analysis Cal. C 24.40; H 5.42; S 21.69; N 18.98;

Obs. C 24.61; H 5.21;

1,5-pentane thiouronium dichloride (52)



$C_7H_{18}N_4S_2Cl_2$

M.P.: 191°C

Analysis Cal C 28.66; H 6.14; N 19.11; S 21.84;Cl 24.23

Obs C 28.81; H 6.01;

1,6-Hexane thiouronium dichloride (55)

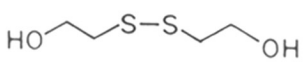
$C_8H_{20}N_4S_2Cl_2$

M.P. 110°C, white solid.

Analysis Cal C 31.27; H 6.51; N 18.24; S 20.84;Cl 23.12

Obs C 31.41; H 6.72;

2-Hydroxyethyl disulfide (57)



To a solution of mercaptoethanol (2 gm, 1 eq) in methanol 20 ml was added sodium perborate (7.8 gm, 2 eq) at room temperature and stirred for 10 hrs. Methanol was removed under reduced pressure and the residue extracted in ethyl acetate to furnish 2.96 gm of disulphide (**57**).

$C_4H_{10}O_2S_2$

Yield: 75%

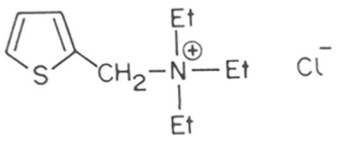
B.P. 158-163/3.5 mm Colourless liq.

^1H NMR (80MHz, $CDCl_3$, δ): 2.9 (t, 4H); 3.5 (t, 4H); 4.2 (s, 2H)

General procedure for preparation of Quarternary ammonium salts

Quarternary ammonium salts (**58,59,60,61**) were prepared by refluxing equivalent mix of 2-chloromethyl thiophene and base in benzene for 8-10 hrs upon which the quarternary ammonium salt separates. The salt was filtered and recrystallised from ethanol.

2-methylenyl thiophene-triethyl ammonium chloride (58)

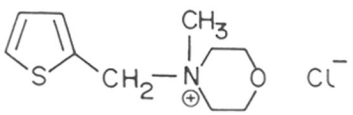


M.P. 91°C

Analysis Cal C 31.27; H 6.51; N 18.24; S 20.84;Cl 23.12

Obs C 56.71; H 8.48; N 5.22

2-methyl thiophene-N-methylmopholine chloride (59)

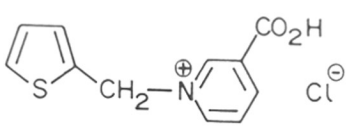


M.P. 210° White solid

Analysis Cal C 51.39; H 6.85; N 5.99; S 13.70;Cl 15.20

Obs C 50.65; H 6.61; N 6.08

2-methyl thiophene-nicotinic acid chloride (60)

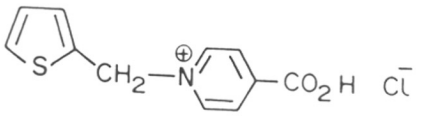


M.P. 246°C White solid

Analysis Cal C 51.66; H 3.91; N 5.47; S 12.52; Cl 13.89

Obs C 51.41; H 3.73; N 5.71;

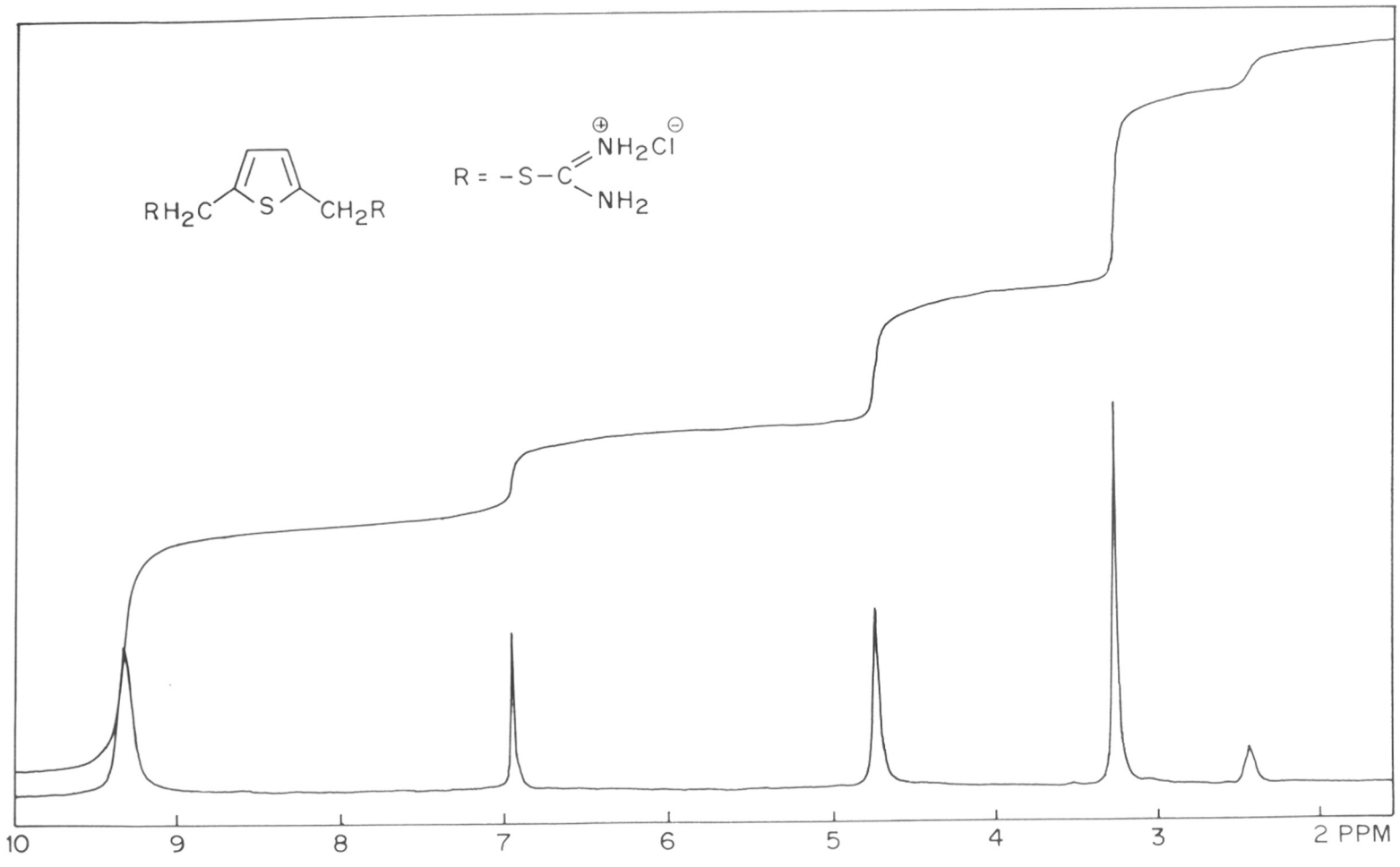
2-methyl thiophene-isonicotinic acid chloride (61)



M.P. 260°C

Analysis Cal C 51.66; H 3.91; N 5.47

Obs C 51.88, H 3.80; N 5.31



^{1}H-NMR SPECTRUM OF **27** (80 MHz, DMSO-d_6)

1.1.8 *References*

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This is actually the research lab. But we have such a load of administrative work to do that we can't conduct any experiments!

Part-II : Sulfur Assisted $NaBH_4$ Reduction Of Esters In Ethanol At Room Temperature

1.2.0 *Introduction*:

The discovery of $NaBH_4$[1] in 1942 by Schlesinger, Brown and co-workers has brought about a revolutionary change in procedures for the reduction of functional groups in organic molecules. This complex hydride provides a simple and convenient route for the reduction of functional groups and they are invariably used in laboratory synthesis involving such transformations. $NaBH_4$ is presently one of the most easily available among many complex metal hydrides; it is easier to manipulate than lithium aluminium hydride ($LiAlH_4$) and lithium borohydride because of its lower sensitivity towards moisture.[2]

The reactivity of these complex metal hydrides is strongly influenced by the following factors:

1. The influence of solvents on the reducing power of the complex hydride.
2. Variations of the cation in the complex hydride that might alter the reducing power.
3. Introduction of the substituents in the complex ion that exert steric and electronic influences upon the reactivity of substituted complex ion.
4. Presence of catalysts such as $B(OMe)_3$, halides of Co, Ni, Ir, Os, Cu, Ti.
5. Presence of activating substituents.

Sodium borohydride is highly soluble in water as well as in various alcoholic solvents. Although it reacts rapidly with methanol liberating hydrogen, the corresponding reaction in ethanol is much slower.[3] Hence ethanol is the most commonly used solvent in borohydride reduction. Sodium borohydride is a relatively mild reducing agent which is practically specific for the carbonyl groups in aldehydes and ketones. Sodium borohydride has advantages over lithium aluminium hydride. Since it can be used in a much wider range of solvents, such as ethanol, tetrahydrofuran, diglyme (dimethyl ether of diethylene glycol), triglyme (dimethyl ether of triethylene glycol),

dipolar aprotic solvents such as dimethyl sulfoxide, hexamethyl phosphoroustriamide.

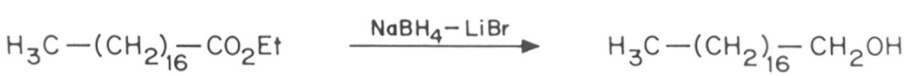
1.2.1 *"Assisted" Reduction Of Esters:*

Though selective reduction of esters is an important method in organic synthesis, $LiAlH_4$ cannot be used for the purpose because of its excessive reducing power.[2] On the other hand $NaBH_4$ is a mild reducing agent, used only for the selective reduction of carbonyl group. $NaBH_4$ does not normally reduce carboxylic esters as the reactivity of esters towards it is very less. However, it is known that the reducing property of $NaBH_4$ can be increased by use of the catalysts, varying the solvents or refluxing at elevated temperatures and presence of activating substituents near ester function.[2]

1.2.2 *Use Of Catalyst:*

The reduction of esters of sodium borohydride was achieved by addition of metal hydrides,[4] Lewis acids[5] or acids.[6] The addition of an equivalent quantity of (lithium halides) lithium bromide to a one molar solution of sodium borohydride in diglyme results in the formation of a precipitate of sodium halide and the formation of *in situ* of lithium borohydride,[4] which reduces esters to corresponding alcohols. The reagent can be used directly without removing the precipitated salt. Similarly lithium chloride-sodium borohydride, calcium chloride - sodium borohydride[4b] and Barium and Strontium salts in presence of $NaBH_4$ were used for ester reduction. (Scheme-1)

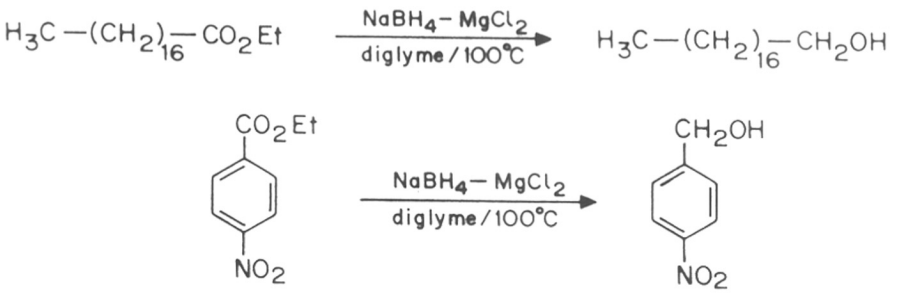
SCHEME - 1



Ref. : Nature (1955), 175 , 346

Ions of higher ionic potential were expected to be more effective. Addition of equivalent amount of solid magnesium halide[5&7] ($MgCl_2$ and $MgBr_2$) to diglyme solutions of sodium borohydride brings about the reduction of esters. (Scheme-2)

SCHEME - 2



Ref. : J. Am. Chem. Soc. (1955), 77, 6209

Addition of one equivalent of aluminium chloride to three equivalents of sodium borohydride solution in diglyme provides a clear solution.[5] The resulting solution exhibit markedly enhanced reducing power, approaching that of lithium aluminium hydride itself.

$$AlCl_3 + 3NaBH_4 \longrightarrow Al(BH_4)_3 + 3\ NaCl$$

The failure to obtain a precipitate of sodium chloride suggests that the reaction proceeds to produce an equilibrium amount of aluminium borohydride with the equilibrium being shifted to completion as the aluminium borohydride reacts with the organic compound.

Sodium borohydride and the trimethyl silyl chloride[6a] in tetrahydrofuran was also used for reduction of esters.

$$NaBH_4 + Me_3SiCl \xrightarrow{THF} NaCl + Me_3SiH + BH_3THF$$

In tetrahydrofuran, a borane-THF complex is formed which with the assistance of excess trimethyl silyl chloride acts as reducing agent.

Sodium borohydride and methane sulfonic acid[6b] in equimolar ratio in dimethyl sulfoxide as solvent bring about ester reduction. Acid used can protonate the carbonyl group, activating it for attack by the hydridic reducing agent or can react with BH_4 liberating a solvated BH_3 which brings about the reduction.

Thus in most of the reductions of sodium borohydride and catalyst, the reducing agent could be the metal borohydride formed *in situ*.

1.2.3 *Effect Of Solvent:*

The reactivity of $NaBH_4$ is enhanced in protic solvents. Reduction of esters with $NaBH_4$ in ethanol[8] or methanol[9] results in the formation of alcohols only in low yields. Polyethylene glycol[10] has also been used. Mixed solvents of t-butyl alcohol-methanol or tetrahydrofuran-methanol[11,12] were used, wherein slow addition of methanol to the refluxing mixture of ester and sodium borohydride in t-butyl alcohol or borohydride and iodine[13] has been used in THF for reduction of carboxylic esters to alcohols. Bianco *et al*[12b] have used THF/Dioxane -H_2O for reduction of esters to alcohols. The mixture of $NaBH_4$ and sodium hydroxyborohydrides so formed were found to be efficient agent for reducing esters.

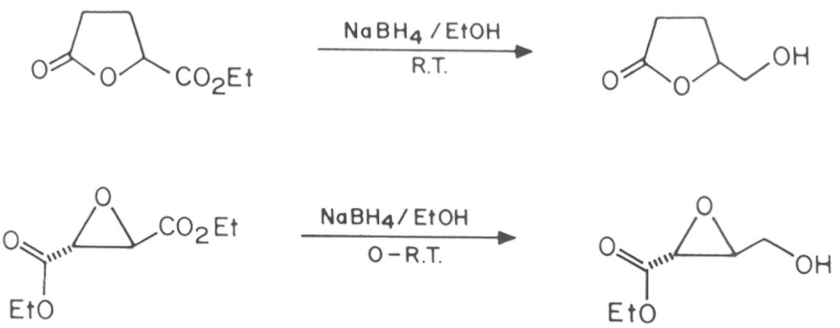
1.2.4 *Presence Of Activating Substituents:*

The presence of activating substituents near the ester group could modify their reactivity towards $NaBH_4$. Electron withdrawing nitro group[2a] or nitrile function[14] are known to increase the suseptibility of the ester carbonyl to nucleophilic attack.

Esters bearing α-oxygen, nitrogen or chloro substituents are rapidly reduced by sodium borohydride at room temperature.[15] (Scheme-3A) Probably chelation and/or inductive activation accelerates the reaction.

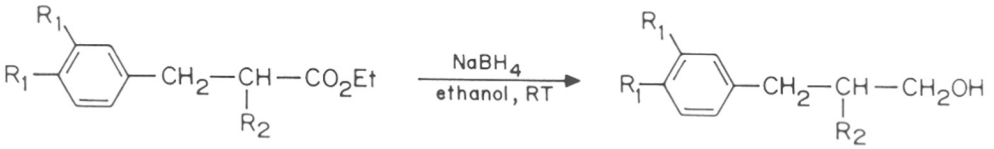
A recent article[16] shows reduction of esters by sodium borohydride at room temperature, taking the advantage of electronegativity of nitrogen at α-position to the ester. (Scheme-3A) Similarly, esters having N-alkyl, N-acyl functionality at the α-position are reduced with $NaBH_4$-MeOH at 0-5°C.[17]. (Scheme-3B) Esters bearing oxygen functionality at α-position are reduced to alcohols with $NaBH_4$ and ethanol.[18]. (Scheme-3C)

SCHEME - 3C



Ref. : Chem. Pharm. Bull. (1967), 15, 1948

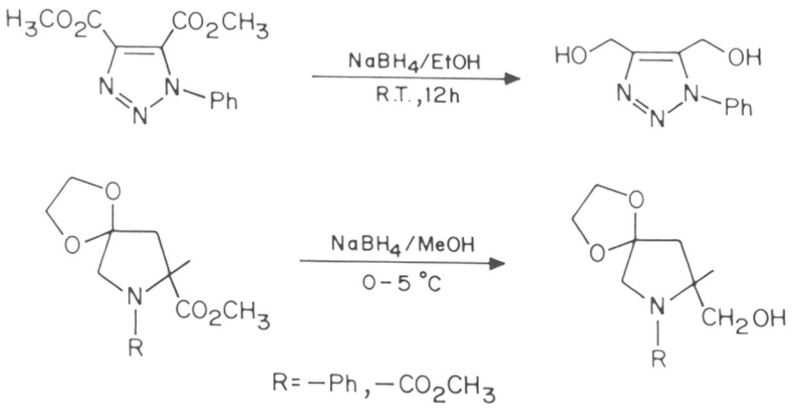
SCHEME – 3A



R_2= —NH_2 , —$NHCH_3$, —$NHCH_2Ph$, —NMe_2 , —OH , —Cl

Ref. : Chem. Pharm. Bull. (1967), 15, 1948

SCHEME – 3B



R= —Ph , —CO_2CH_3

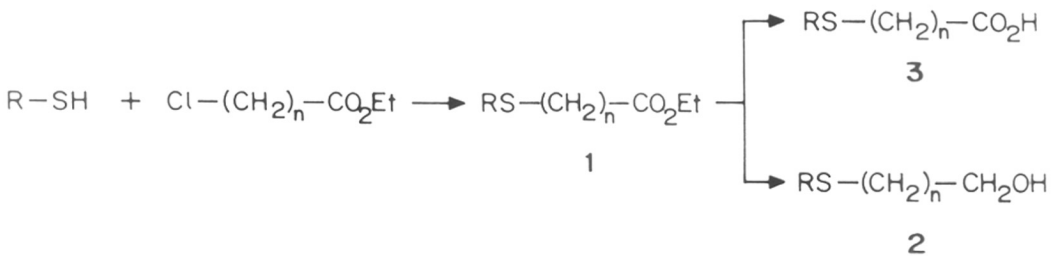
Ref. : Chem. Pharm. Bull. (1967), 15, 1948

1.2.5 *Present Work:*

In connection with our interest in carcinostatic compounds, where thiodiglycols and thiodiglycollic acid[19] were shown to exhibit carcinostatic properties, a variety of thioglycols were required. Thioglycols are conveniently prepared by the reaction of appropriate sulfide with chloroethanol.[20] Other alternative would be by reduction of α-mercapto esters with mild reducing agents like sodium borohydride.

Since α-mercaptoesters were available a mild and convenient method for the interconversion of mercaptoesters (1) to mercaptoalcohols (2) (Scheme-4) was required.

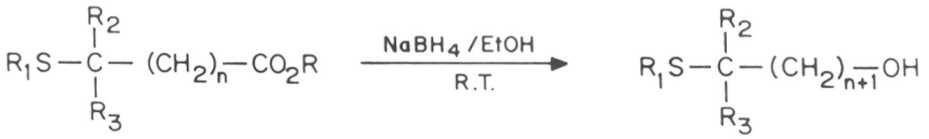
SCHEME - 4



Normally sodium borohydride does not reduce esters. However, there are few examples of reduction by sodium borohydride in presensce of hetero atom (O,N, chloro) in vicinity to the esters. However, there is no account of such kind of reductions in case of sulfur. A recent article by Rajappa *et al*[21] shows evidence of non-bonded sulfur and oxygen interactions in solutions. Besides this, there have been several revelations (X-ray) about attraction between S and O in solid state.[21] Encouraged by this, it was reasoned that the thro' space affinity of sulfur towards oxygen should enhance the reactivity of the carbonyl carbon. In order to see its synthetic applicability, a variety of α,ß, and ϒ-substituted mercaptoesters of general formula (I)

were subjected to borohydride reduction in ethanol at room temperature. The α,ß, and ϒ mercaptoesters underwent smooth reductions to the corresponding alcohols (II) at room temperature in high yields confirming sulfur assistance in borohydride reduction (Scheme-5).

SCHEME - 5



1 2

n = 0, 1, 2

R = −Me, −Et, −i-Pr ; R_1 = −Et, −Ph, $-CH_2-CH_2S-$

R_2 = −H , −Me, −Ph, −SPh ; R_3 = −H , −Me

The generality and scope of the method is discussed below.

1.2.6 *Results And Discussions*:

A variety of α,ß and ϒ substituted mercaptoesters were smoothly reduced by sodium borohydride in ethanol at room temperature to furnish mercaptoalcohols in high yields. The results are summarized in Table I.

α,ß and ϒ mercaptoesters were prepared by the literature procedures. Esterification and treatment with thiol[22] of α-bromoacetic acid, α-bromophenylacetic acid, 2-bromopropionic acid and 3-bromopropionic acid resulted in corresponding α-mercaptoesters (entry 1,4,5,6 and 14). Diazomethane esterification and then protection of the carbonyl with thiophenol and 1,2-ethanedithiol of pyruvic acid and glyoxyllic acid gave α,α disubstituted mercapto esters[23] (entry 7,8,9 and 10). Entry 11 to 13 were synthetic

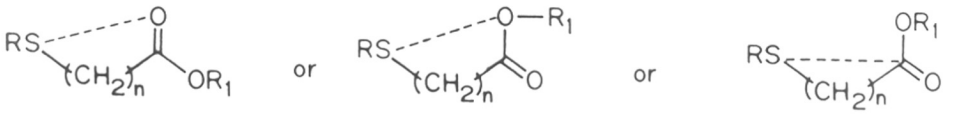
intermediates of biotin synthesis. Ketocarbonyl protection of ethyl levulinate gave mercaptoester (entry 15).

Initially when α-mercaptoester (entry 1A) was treated with sodium borohydride in ethanol at room temperature, it furnished the pure corresponding mercaptoalcohol (2A) in 77% yield. The mercapto alcohol was characterised by its IR, ^{1}H-NMR and mass spectral analysis. IR spectra showed the disappearance of estercarbonyl function at 1720 cm^1 and showed peak at 3500 cm^{-1} characteristic of alcohol. Also ^{1}H-NMR showed disappearance of ethyl ester peaks at 1.2 δ triplet for -CH_3 and 4.1 δ quartet for -CH_2 group and presence of -CH_2-CH_2OH triplet at 3.7 δ for -CH_2OH.

It is evident from the Table-I that methyl, ethyl, isopropyl esters undergo facile reduction whereas tertiary butyl ester (entry 3) is resistant to the above conditions. It is noteworthy that increasing the steric bulk at α to the ester doesnot have any adverse effect on the ease of reduction (entries 4,5 & 6). This observation is in stark contrast to α-dialkyl amino esters which are resistant to reduction by sodium borohydride at ambient temperature. Also α,α-thiosubstitution (entry 7-10) on the ester enhanced the ease of the reduction as evidenced by higher yields and shorter time required for the substrates. Preferential reduction of α-mercaptoester in the presence of susceptible carbonyl group of the hydantoin (entry 11) could be used to advantage in the selective transformation of such systems.

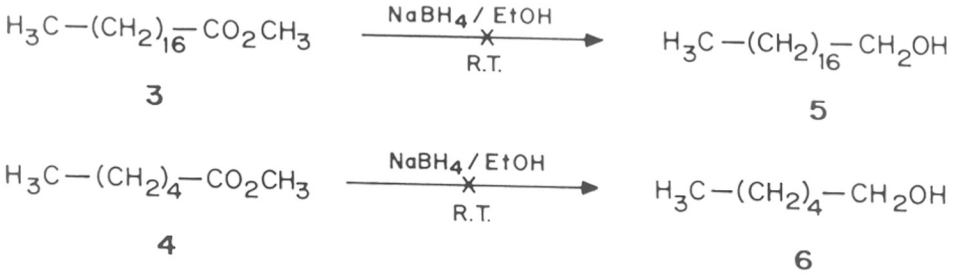
Even ß (two carbon atoms) and (three carbon atoms) mercaptoesters (entry 14, 15) were smoothly reduced with sodium borohydride which can be explained by sulfur assisted activation of ester group besides the inductive effect. Although it can be postulated that the non-bonded S-O interaction as the activating force, the anchimeric assistance of sulfur by attack on carbonyl carbon of the ester cannot be ruled out.

SCHEME - 6



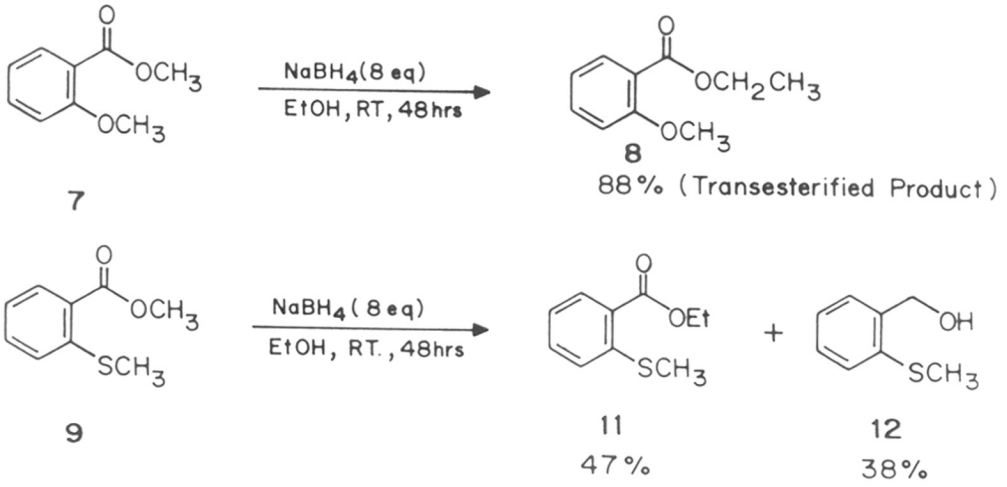
In order to confirm the participation of sulfur on even firmer grounds, ester (**3**) and (**4**) (Scheme-6) were subjected to reductions under identical conditions and as anticipated, these esters were not reduced to the corresponding alcohols (**5**) & (**6**) respectively, but were recovered unchanged. (85% recovered)

SCHEME - 6

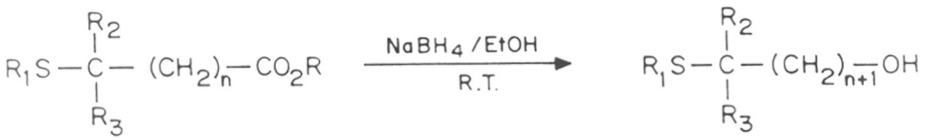


Additionally the role of sulfur in "assisted" reduction of esters becomes even more apparent by comparison of reactivity profile of thiosalicylate (**9**) and salicylate (**7**) towards sodium borohydride reduction. (Scheme-7) Methyl salicylate (**7**) on treatment with $NaBH_4$ in ethanol doesnot yield any reduced product, whereas the corresponding mercapto ester (**9**) undergoes reduction to the corresponding alcohol (**10**) in 38% yield.

SCHEME - 7



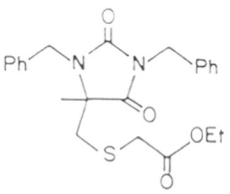
All the mercaptoalcohols were characterised by IR, ^{1}H-NMR and mass spectroscopic data and they were in agreement with the reported values.



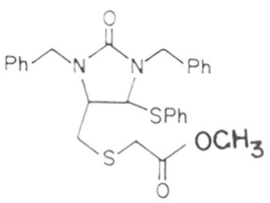
1 2

Table-I

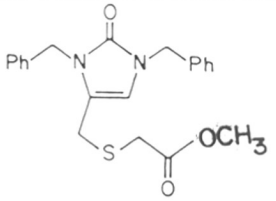
Entry		n	R	R^1	R^2	R^3	Yield(%)	Time(h)	$NaBH_4$
1	A	0	Et	Ph	H	H	77	24	2
2	B	0	i-Pr	Ph	H	H	80	20	2.5
3	C	0	t-Bu	Ph	H	H	0	84	3
4	D	0	Et	Ph	Ph	H	82	18	3
5	E	0	CH(Me)COOEt	Ph	Me	H	80	18	3
6	F	0	Et	Et	Me	H	65	20	3
7	G	0	Me	Ph	SPh	Me	82	20	3
8	H	0	Me	$-CH_2CH_2$	S-	Me	84	4	3
9	I	0	Me	Ph	SPh	H	88	8	3
10	J	0	Me	$-CH_2CH_2$	S-	H	88	17	3
11	K	0	Et	X	H	H	65	8	3
12	L	0	Me	Y	H	H	60	24	2.5
13	M	0	Me	Z	H	H	77	6	2.5
14	N	1	Et	Ph	H	H	63	8	2.5
15	O	1	Me	Ph	Me	SPh	78	36	6



X



Y



Z

1.2.7 *Conclusion:*

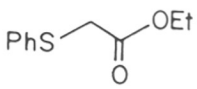
1. This methodology demonstrates the utility of sodium borohydride for the first time as mild reducing agent for the selective reduction of α,ß, and ϒ mercapto esters in ethanol at room temperature in high yields.
2. Increasing steric bulk at α-position does not inhibit the ease of ester reduction.
3. α,α thiosubstitution enhances borohydride reduction in terms of yield.
4. Preferential reduction of α-mercaptoesters in presence of other carbonyl functionality like ureide esters can be performed.
5. Sulfur assistance in borohydride reduction is observed even if it is two carbons or three carbons away from the ester group.
6. Normal esters are not reduced with borohydride in ethanol confirming sulfur assistance in reduction.

1.2.8 *Experimental*

α & ß mercapto esters : (Table entries 1-6 & 14): Usual esterification of α-bromo acetic acid α-bromophenyl acetic acid, 2-bromo propionic acid and 3-bromopropionic acid in refluxing alcohol and acid (H_2SO_4) gave the corresponding esters.

A mixture of bromo ester (10 mmol) and thiophenol (10 mmol) in acetone (50 ml) and anhydrous potassium carbonate (30 mmol, 3 eq) was refluxed with vigorous stirring. The reaction was monitored by TLC (5-8 hrs). After completion of the reaction, solid was filtered off and acetone was removed under reduced pressure. The residue was extracted in ethyl acetate and washed with water, brine and dried over anhydrous Na_2SO_4. Solvent evaporation gave the crude α-mercapto ester which was purified on column (SiO_2) using pet ether-ethylacetate as eluant to give the pure α & ß-mercapto esters in good yields.

1A Phenyl thio ethylacetate



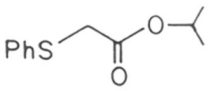
Mol. formula: $C_{10}H_{12}O\,S$. Colourless liquid.

Yield : 85%

IR (neat, cm^{-1}): 780, 850, 920, 1080, 1120, 1340, 1500, 1609, 1740, 2850.

^1H NMR (80MHz, $CDCl_3$, δ): 1.2 (t, 3H $-CH_3$); 3.8 (s, 2H, $-CH_2-$); 4.1 (q, 2H, $-OCH_2-$); 7.5 (m, 5H, Aromatic).

1B Phenylthio isopropyl acetate



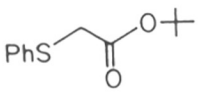
Mol. formula: $C_{11}H_{14}O_2S$. Colourless liquid

Yield : 78%

IR (neat, cm^{-1}): 720, 780, 950, 1120, 1230, 1450, 1500, 1600, 1740, 2880.

^1H NMR (80MHz, $CDCl_3$, δ): 1.2 (d, 6H, $-CH_3$); 3.5 (s, 2H, $-CH_2-$); 4.8 (m, 1H, -CH-); 7.6 (m, 5H, aromatic).

1C Phenylthio tert-butyl acetate



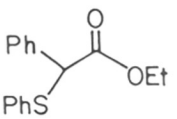
Mol. formula: $C_{12}H_{16}O_2S$. Colourless liq.

Yield: 75%

IR (neat, cm^{-1}):850, 920, 1120, 1180, 1280, 1350, 1420, 1500, 1600, 1740.

^1H NMR (90MHz, $CDCl_3$, δ): 1.2 (s, 9H,$-CH_3$); 3.5 (s, 2H, $-CH_2$); 7.5 (m, 5H, aromatic).

1D α-Phenyl-α-phenylthio ethyl acetate



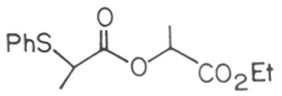
Mol. formula $C_{16}H_{16}O_2S$. Pale yellow liq.

Yield: 75%

IR (neat, cm^{-1}): 580, 720, 780, 1150, 1380, 1420, 1480, 1500, 1600, 1750, 2820.

^{1}H NMR (80MHz, $CDCl_3$, δ): 1.1 (t, 3H, $-CH_3$); 4.1 (q, 2H, $-OCH_2$); 4.7 (s, 1H, -CH); 7.5 (m, 5H, aromatic).

1E O-(2-ethyl propionate)-α-phenylthio propionate



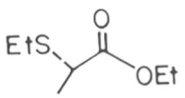
Mol. formula $C_{14}H_{18}O_4S$. Colourless liq.

Yield : 68%

IR (neat, cm^{-1}): 580, 620, 780, 850, 950, 1050, 1230, 1380, 1420, 1500, 1600, 1710, 1730, 2850, 2950.

^{1}H NMR (80MHz, $CDCl_3$, δ): 1.1 (t, 3H, $-CH_3$); 1.5 (d, 6H, $-CH_3$); 3.8 (m, 2H, -CH); 4.1 (q, 2H, $-OCH_2$-); 7.5 (m, 5H, aromatic).

1F α-Ethylthio-α-methyl ethyl acetate



Mol. formula: $C_7H_{14}O_2S$. Colourless liq.

Yield: 78%

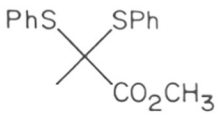
IR (neat, cm^{-1}): 750, 860, 920, 1020, 1180, 1350, 1420, 1730, 2850.

^{1}H NMR (90MHz, $CDCl_3$, δ): 1.5 (t, 6H, $-CH_3$); 1.6 (d, 3H, $-CH_3$); 2.7 (q, 2H, $-SCH_2$-); 3.1 (m, 1H, -CH-); 4.1 (q, 2H, $-OCH_2$-).

α,α-Mercapto esters (Table entries 7-10)

Pyruvic and Glyoxylic acid were esterified with diazamethane CH_2N_2 in ether as the solvent. To the stirred mixture of ester (10 mmol) and thiophenol (20 mmol) or ethane dithiol (10 mmol) in dichloromethane (20 ml) at 0°C was added $BF_3.Et_2O$ (15 mmol). The reaction mixture was stirred at 0°C for 2 hrs and then slowly allowed to come to room temperature and stirred for another two hours. Reaction was quenched with aq. $NaHCO_3$, washed once with water and thrice with brine, dried over anhydrous Na_2SO_4. Solvent evaporation and column purification gave pure α,α thioesters in good yields.

1G α,α-bis (phenyl thio) methyl propanoate



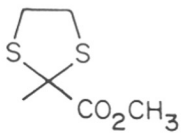
Mol. formula: $C_{16}H_{16}O_2S_2$. Pale yellow liq.

Yield: 82%

IR (neat, cm^{-1}): 650, 700, 750, 1020, 1050, 1150, 1280, 1450, 1500, 1600, 1730.

^1H NMR (80MHz, $CDCl_3$, δ):1.1 (s, 3H,-CH_3); 3.7 (s, 3H, -OCH_3); 7.5-7.8 (s, 10H, aromatic).

1H 1,2-dithiolane- methyl propanoate



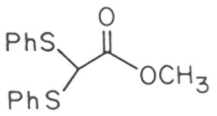
Mol. formula $C_6H_{10}O_2S_2$. Pale yellow liq.

Yield: 82%

IR (neat, cm^{-1}): 650, 780, 1020, 1180, 1250, 1300, 1450, 1750.

^1H NMR (80MHz, $CDCl_3$, δ): 1.6 (s, 3H, $-CH_3$); 3.1 (s, 4H, $-SCH_2CH_2S-$); 3.8 (s, 3H, $-OCH_3$).

1I 2-(bis phenyl thio) methyl acetate



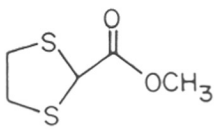
Mol. formula: $C_{15}H_{14}O_2S_2$. Pale yellow liq.

Yield: 85%

IR (neat, cm^{-1}): 780, 820, 950, 1020, 1050, 1180, 1250, 1380, 1450, 1500, 1600, 1750.

^1H NMR (80 MHz, $CDCl_3$, δ): 3.8 (s, 3H,$-CH_3$); 4.8 (s, 1H, -CH-); 7.5 (m, 10H, aromatic).

1J 1,2 Dithiolane methyl acetate



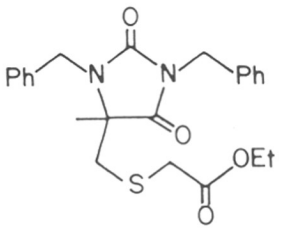
Mol formula: $C_5H_8O_2S_2$. Pale yellow liq.

Yield: 83%

IR (neat, cm^{-1}): 620, 680, 780, 1020, 1180, 1250, 1380, 1420, 1740.

^{1}H NMR (80MHz, $CDCl_3$, δ): 3.2 (s, 4H, $-SCH_2CH_2S-$); 3.7 (s, 3H, $-OCH_3$); 4.5 (t, 1H, -CH-).

1K 1,3-Dibenzyl-5(3-ethoxycarbonyl-2-thiapropyl) 5-methyl-hydantoin

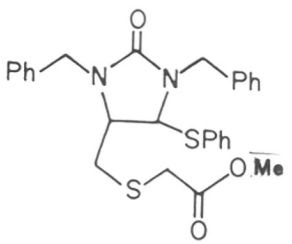


Mol. formula: $C_{23}H_{26}N_2O_4S$

IR (neat, cm^{-1}): 650, 720, 780, 1050, 1080, 1150, 1180, 1300, 1380, 1420, 1450, 1500, 1600, 1730, 1780, 2820.

^{1}H NMR (80MHz, $CDCl_3$, δ): 1.2 (t, 3H, $-CH_3$); 1.3 (s, 3H, $-CH_3$); 1.9 (s, 2H, $-CH_2-S$); 2.8 (q, 2H, $-SCH_2-$); 4.0 (q, 2H, $-OCH_2-$); 4.6 (s, 4H, $-CH_2Ph$); 4.5 (m, 10H, aromatic).

1L 1,3-Dibenzyl-2-oxo-5(3-carbmethoxycarbonyl-2-thiopro-pyl)-4-phenylthio-imidazolidine



Mol. formula: $C_{27}H_{28}N_2O_3S_2$.

IR (neat, cm^{-1}): 1064, 1365, 1465, 1583, 1695, 1725, 2920, 3030.

^1H NMR (200MHz, $CDCl_3$, δ): 2.53 (1H, dd, J=14, 7.5 Hz); 2.7 (1H, dd, J=14, 3.7 Hz); 2.9 (2H, s); 3.6 (1H, ddd, J=7.5, 3.7 Hz); 3.65 (3H, s); 4.0 (1H, d, J= 15.5 Hz); 4.3 (1H, d, J= 15.5 Hz); 4.53 (1H, d, J=15 Hz); 4.57 (1H, d, J=3.7 Hz); 5.1 (1H, d, J=15 Hz); 7.05 (3H, m, aromatic); 7.25 (12H, m, aromatic).

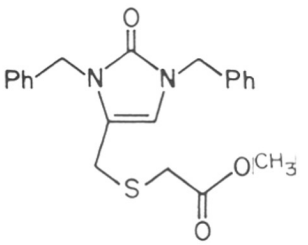
^{13}C NMR (200MHz): 32.72 (t), 33.48 (t), 44.64 (t), 45.67 (t), 52.19 (q), 58.09 (d), 66.55 (d), 127.24 (d), 127.39 (d), 127.90 (d), 128.24 (d), 128.48 (d), 128.63 (d), 129.07 (d), 130.16 (d), 134.82 (s), 136.15 (d), 136.21 (s), 157.71 (s), 169.93 (s).

Mass (m/e): 383 (M^+, 18): 277 (100), 264 (7), 187 (7), 110 (7), 91 (54).

Analysis Cal C 65.78; H 5.73; N 5.69; S 13.01

Obs C 65.56; H 5.69; N 5.31; S 13.21

1M 1,3-Dibenzyl-2-oxo-4(3-methoxycarbonyl-2-thiapropyl) imidazolidin-4-ene



Mol. formula: $C_{21}H_{22}N_2O_3S$.

IR (neat, cm^{-1}): 940, 1020, 1460, 1595, 1600, 1700, 1730, 2910, 3000.

^1H NMR (200MHz, $CDCl_3$, δ): 3.07 (2H, s); 3.35 (2H, s); 3.60 (3H, s); 4.82 (2H, s); 5.04 (2H, s); 5.04 (2H, s); 6.10 (1H, d, J=0.7 Hz); 7.25 (10H, m).

^{13}C NMR: 26.14 (t), 31.17 (t), 44.37 (t), 46.89 (t), 52.01 (d), 107.79 (d), 114.74 (s),

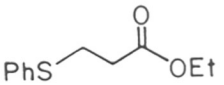
126.69 (d), 126.86 (d), 127.24 (d), 127.75 (d), 127.9 (d), 128.30 (d), 128.47 (d), 136.49 (s), 137.06 (s), 153.67 (s), 170.06 (s).

Mass (m/e): 382 (M^+, 15), 277 (100), 264 (8), 187 (7), 91 (60).

Analysis Cal C 65.95; H 5.80; N 7.32; S 8.38

Obs C 65.82; H 5.72; N 7.15; S 8.20

1N Phenylthio ethyl propionate



Mol. formula: $C_{11}H_{14}O_2S$. Colourless liq.

Yield: 88%

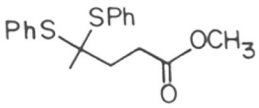
IR (neat, cm^{-1}): 680, 780, 1020, 1050, 1120, 1280, 1350, 1450, 1500, 1600, 1740

^1H NMR (80MHz, $CDCl_3$, δ): 1.1 (t, 3H, $-CH_3$); 2.5 (t, 2H, $-CH_2$); 3.1 (t, 2H, $-SCH_2$); 4.1 (q, 2H, $-OCH_2$); 7.6 (m, 5H, aromatic).

γ-Mercapto ester (entry 15)

To a mix of ethyl levulinate (2 gm, 0.015, 1 mmol) & thiophenol (2 mmol) 0°C in CH_2Cl_2 solvent was added BF_3-Et_2O (2.8 ml, 1.5 mmol). The reaction was allowed to come to room temperature and stirred at room temperature for 4 hrs. The reaction mixture was quenched with aq. $NaHCO_3$, washed once with water, brine and dried over Na_2SO_4. Solvent evaporation under reduced pressure and column purification (SiO_2) gave pure α-mercapto ester in 80% yield (4.05 gms).

10 4-(bis phenyl thio) methyl pentanoate



Mol. formula: $C_{18}H_{20}O_2S_2$. Colourless liq.

Yield: 78%

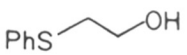
IR (neat, cm^{-1}):

^1H NMR ($CDCl_3$, δ): 1.1 (s, 3H, $-CH_3$); 1.9 (t, 2H, $-CH_2-$); 2.8 (t, 2H, $-CH_2-$); 3.7 (s, 3H, $-OCH_3$); 7.5-7.8 (m, 10 H aromatic)

General Procedure for reduction of mercaptoesters with $NaBH_4$

To a stirred solution of mercapto ester (10 mmol) in ethanol at room temperature was added $NaBH_4$ (20 mmol 2-3 eq) in portions. The reaction mixture was stirred at room temperature (6-20 hrs) and was monitored by TLC. After completion of the reaction, solvent was evaporated under reduced pressure and water (5 ml) was added and residue extracted in ethyl acetate. Organic layer washed once with brine (10 ml), dried over sodium sulfate, concentrated under vacuo to give the crude alcohol in good yields. Further purification by chromatography (SiO_2) afforded pure alcohol.

2A 2-(Phenylthio)-ethanol[24]



Mol. formula: $C_8H_{10}OS$. Colourless liq

Yield: 77%

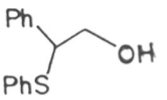
BP: 115-116°/2mm

IR (neat, cm^{-1}): 780, 820, 840, 920, 1020, 1060, 1380, 1440, 1450, 1480, 1600, 2850, 3020, 3120, 3440, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 2.8 (1H, s, exchangeable proton); 3.1 (t, 2H, $-SCH_2-$); 3.8 (t, 2H, $-OCH_2-$); 7.5 (m, 5H, aromatic).

^{13}C NMR (200MHz): 37.25 (d); 60.56 (d); 126.75 (d); 129.21 (d); 130.22 (d), 135.66 (s).

2D α-Phenyl-α-phenyl thio ethanol[25]



Mol. formula: $C_{14}H_{14}OS$. Viscous liq.

Yield: 82%

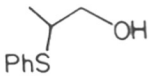
IR (neat, cm^{-1}): 700, 750, 1020, 1050, 1180, 1450, 1480, 1600, 2850, 3020, 3400, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 2.0 (bs, 1H, exchangeable proton); 3.8 (d, 2H, $-CH_2-$); 4.1 (t, 1H, -CH-); 7.4 (m, 10H, aromatic).

^{13}C NMR (200MHz): 56.00 (d); 65.38 (t), 127.60 (d), 127.85 (d); 128.24 (d); 128.79 (d); 129. 03 (d); 132.58 (d); 134.00 (s); 139.16 (s).

Mass (m/e): M^+ (230), 197, 163, 120, 102 (100), 90, 76, 64.

2E 1-Propanol-2(phenylthio)[26]



Mol. formula: $C_9H_{12}OS$. Viscous liq.

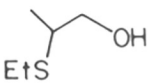
Yield: 80%

IR (neat, cm^{-1}): 700, 750, 1020, 1050, 1220, 1440, 1450, 1500, 1600, 1680, 3020, 3400, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 1.1 (d, 3H, $-CH_3$); 2.1 (bs, 1H, exchangeable proton); 3.4 (m, 1H, -CH-); 3.6 (d, 2H, $-OCH_2-$); 7.6 (m, 5H, aromatic).

^{13}C NMR (200MHz): 17.71 (q); 46.25 (d); 65.66 (t), 127.46 (d); 129.03 (d); 132.78 (d); 133.62 (d).

2F 1-propanol-2-(ethyl thio)[27]



Mol. formula: $C_5H_{12}OS$. Colourless liq.

Yield: 65%

IR (neat, cm^{-1}):550, 680, 780, 1020, 1080, 1250, 1410, 2850, 3000, 3400, 3540.

^1H NMR (200MHz, $CDCl_3$, δ): 1.5 (t, 3H, $-CH_3$); 1.6 (t, 3H, $-CH_3$); 2.6 (q, 2H, $-SCH_2-$); 3.2 (m, 1H, -CH-); 3.8 (dd, 2H $-OCH_2-$); 4.1 (bd, 1H exchangeable proton).

2G 1-Propanol-2,2-bis (phenylthio)

Mol. formula: $C_{15}H_{16}OS_2$. Colourless liq.

Yield: 82%

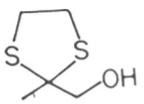
IR (neat, cm^{-1}): 650, 760, 1020, 1050, 1180, 1250, 1380, 1450, 1500, 1600, 2850, 3020, 3450, 3520.

^1H NMR (200MHz, $CDCl_3$, δ): 1.1 (s, 3H, $-CH_3$); 2.5 (bs, 1H, exchangeable proton); 3.5 (s, 2H $-CH_2-$); 7.5-7.8 (m, 10H, aromatic).

^{13}C NMR (200MHz): 24.62 (q); 65.14 (s), 67.87 (t), 128.92 (d), 129.59 (d), 130.57 (d), 137.27 (d).

Mass (m/e): 276 (M^+) 258, 217, 204, 191, 166, 148 (100), 136, 108.

2H 1,3-dithiolane-2-methanol-α-methyl[28]



Mol. formula: $C_5H_{10}OS_2$. Pale yellow liq.

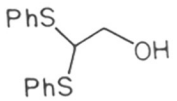
Yield : 84%

IR (neat, cm^{-1}): 620, 780, 920, 1050, 1180, 1280, 1320, 2850, 3020, 3400, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 1.6 (s, 3H, $-CH_3$); 3.1 (s, 4H, $-SCH_2CH_2S-$); 3.5 (s, 2H, $-CH_2OH$).

Mass (m/e): 150 (75, M^+), 105 (100), 77 (15), 61 (35).

2I 2-(bis phenyl thio) ethanol[29]



Mol. formula: $C_{14}H_{14}OS_2$. Colourless liq.

Yield : 88%

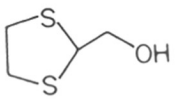
IR (neat, cm^{-1}): 680, 750, 1020, 1050, 1380, 1450, 1500, 1600, 2950, 3020, 3400, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 3.7 (d, 2H, $-CH_2OH$); 3.6 (bs, 1H, exchangeable proton); 4.8 (1H, t, -CH); 7.5-7.8 (m, 10H, aromatic).

^{13}C NMR (200MHz): 60.68 (d); 64.06 (t), 128.21 (d); 129.18 (d); 133.03 (d).

Mass (m/e): 262 (M^+), 152, 134 (100), 108, 44.

2J 1,3-dithiolane-2-ethanol[30]



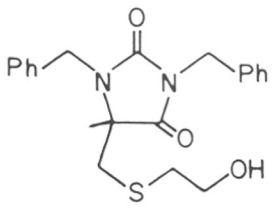
Mol. formula: $C_4H_8OS_2$. Colourless liq.

Yield : 85%

IR (neat, cm^{-1}): 580, 620, 780, 1020, 1050, 1250, 1280, 1320, 2850, 2950, 3000, 3250, 3400, 3500.

^1H NMR (200MHz, $CDCl_3$, δ): 3.2 (s, 4H, $-SCH_2CH_2S-$); 3.5 (t, 2H, $-CH_2OH$); 4.5 (t, 1H, -CH-); 4.6 (bs, 1H, exchangeable proton).

2K 1,3-Dibenzyl-5-(3-thiobutan-1-ol)-5-methyl hydantoin



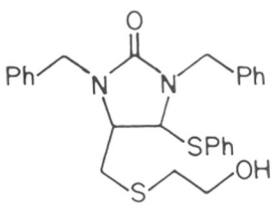
Mol. formula:$C_{21}H_{24}N_2O_3S$

Yield : 65%

IR (neat, cm^{-1}): 780, 1050, 1180, 1320, 1380, 1450, 1500, 1600, 1730, 3300, 3400.

^1H NMR (200MHz, $CDCl_3$, δ): 1.3 (s, 3H, $-CH_3$); 1.9 (s, 2H,); 2.8 (t, 2H, $-SCH_2-$); 3.7 (t, 2H, $-CH_2OH$); 4.6 (s, 4H, $-CH_2Ph$); 5.5 (bs, 1H, exchangeable proton); 7.5 (m, 10H, aromatic).

2L 1,3-Dibenzyl-2-oxo-5-(3-thiobutan-1-ol)-4-phenylthio-imidazolidine



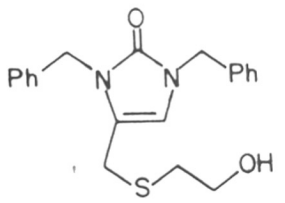
Mol. formula: $C_{26}H_{28}N_2O_2S_2$.

Yield : 60%

IR (neat, cm^{-1}):750, 1050, 1150, 1220, 1280, 1450, 1500, 1600, 1700, 3400, 3500.

^{1}H NMR (200MHz, $CDCl_3$, δ): 2.3 (dd, 1H); 2.5 (dd, 1H); 3.4 (t, 2H); 3.5 (t, 2H); 4.0 (d, 1H); 4.2 (d, 1H); 4.3 (d, 1H); 4.4 (d, 1H); 4.5 (d, 1H); 5.1 (d, 1H); 6.9 (m, 3H, aromatic); 7.2 (m, 12H, aromatic).

2M 1,3-Dibenzyl-2-oxo-4-(3-thiabutan-1-ol)-imidazolidin-4-ene



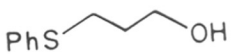
Mol. formula: $C_{20}H_{22}N_2O_2S$.

Yield : 70%

IR ($CHCl_3$, cm^{-1}): 550, 680, 720, 780, 1220, 1350, 1450, 1500, 1680, 3350, 3500.

^{1}H NMR (200MHz, $CDCl_3$, δ): 3.1 (2H, s); 3.4 (2H, t); 3.7 (2H, t); 4.8 (2H, s); 5.0 (2H, s);6.1 (1H, d); 7.25 (10 H, m).

2N 1-propanol-3 (phenylthio)[31]



Mol. formula: $C_9H_{12}OS$. Colourless liq.

Yield : 63%

IR (neat, cm^{-1}): 780, 850, 920, 1020, 1050, 1450, 1500, 1600, 2950, 3000, 3400,

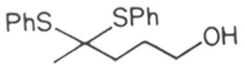
3500.

^{1}H NMR (200MHz, $CDCl_3$, δ): 2.0 (m, 2H, -CH_2-); 2.9 (t, 2H, -SCH_2-); 3.8 (t, 2H, -OCH_2-); 7.8 (m, 5H, aromatic).

^{13}C NMR (200MHz): 30.21 (t); 31.79 (t), 61.14 (t); 126.0 (d); 128.97 (d); 129.18 (d); 136.4 (s).

Mass (m/e): 168 (M^+), 109 (100), 43.

2O 4-bis (phenylthio) pentanol



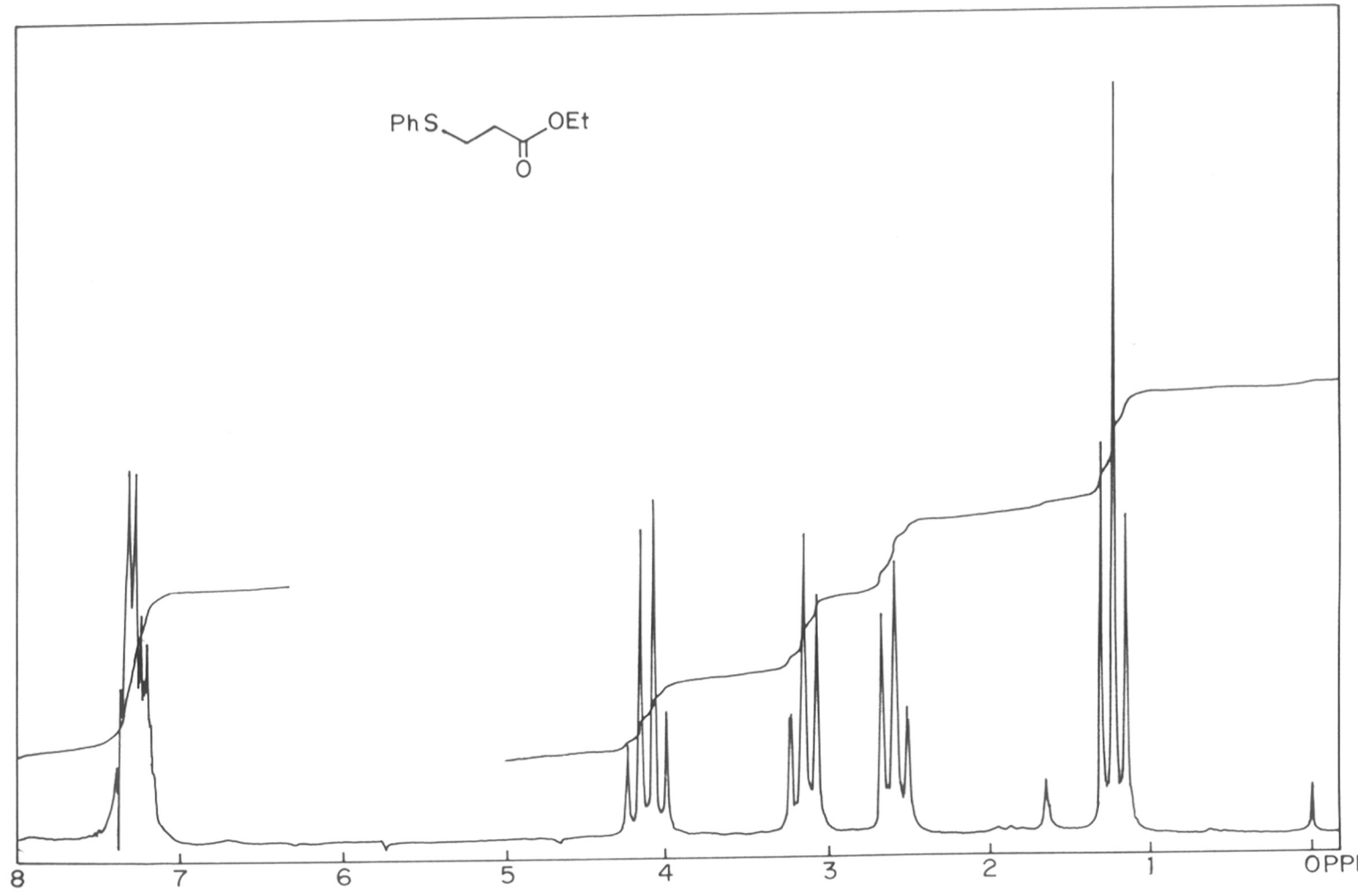
Mol. formula: $C_{17}H_{20}OS_2$. Colourless liq.

Yield : 78%

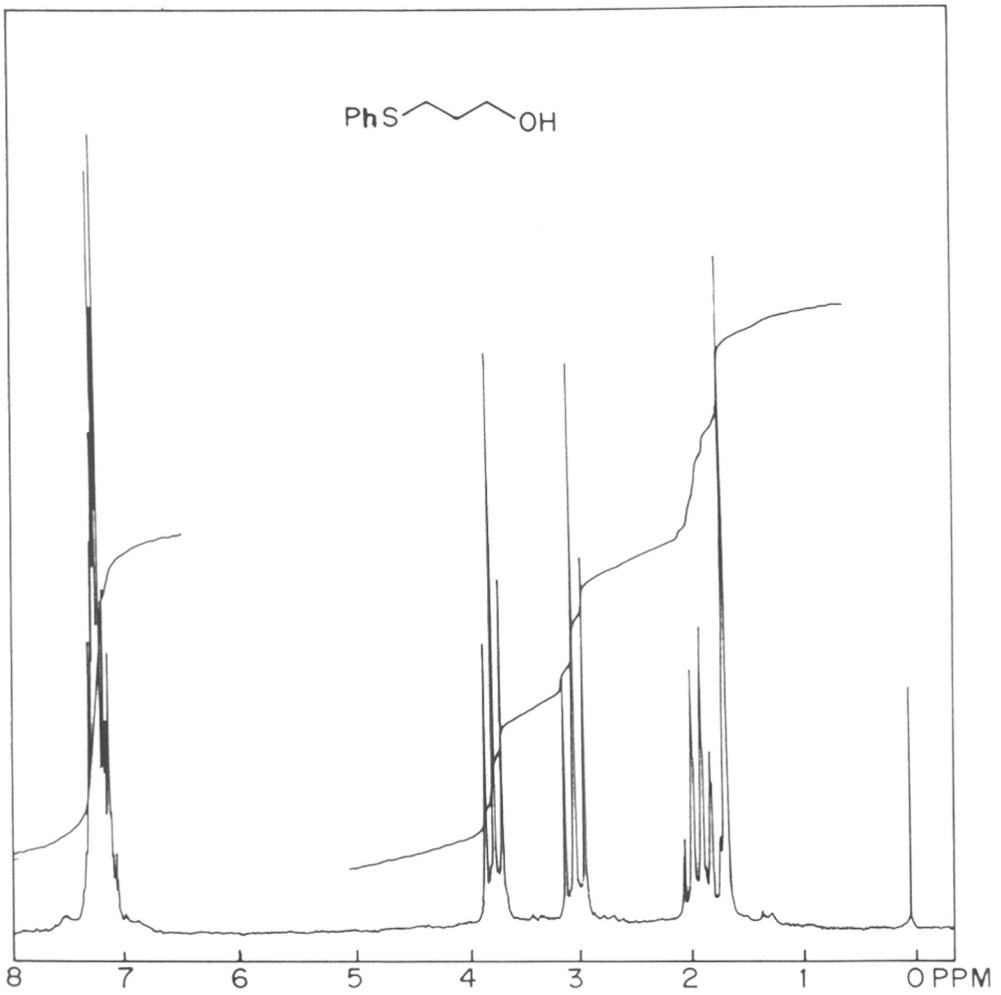
IR (neat, cm^{-1}): 680, 720, 920, 1050, 1250, 1450, 1500, 1600, 2820, 3000, 3400

^{1}H NMR (200MHz, $CDCl_3$, δ): 1.1 (s, 3H, -CH_3); 1.9 (m, 2H, -CH_2-); 2.7 (bs, 1H, exchangeable proton); 2.8 (t, 2H, -SCH_2-); 3.7 (t, 2H, -CH_2OH); 7.5-7.8 (m, 10H, aromatic).

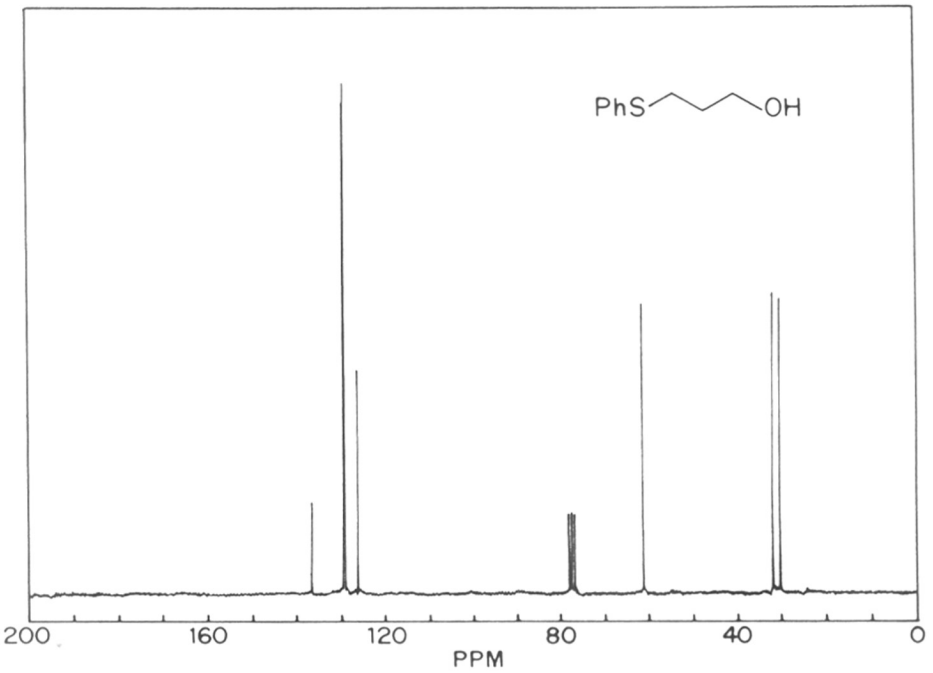
^{13}C NMR (200MHz): 28.40 (q); 30.33 (t); 36.26 (t); 38.08 (t); 62.84 (t); 63.92 (s); 128.79 (d); 128.91 (d); 129.27 (d); 129.51 (d); 131.58 (d); 132.18 (d); 137.13 (s), 137.24 (s).

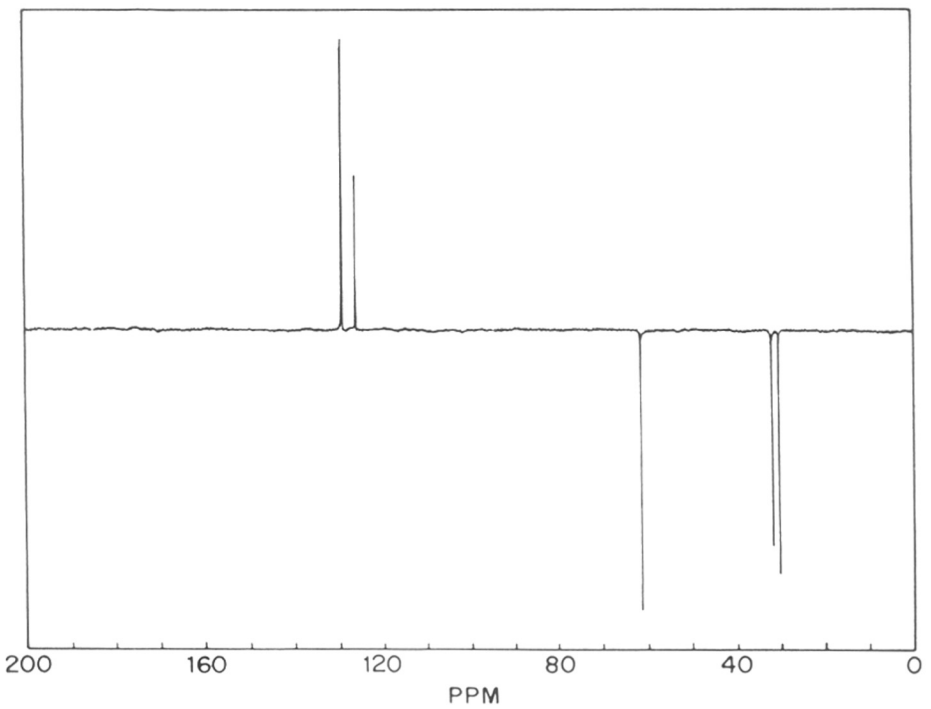


^{1}H-NMR SPECTRUM OF **1N** (80 MHz, $CDCl_3$)



^{1}H-NMR SPECTRUM OF **2N** (200 MHz, $CDCl_3$)





^{13}C-NMR SPECTRUM OF **2N** (200MHz, $CDCl_3$)

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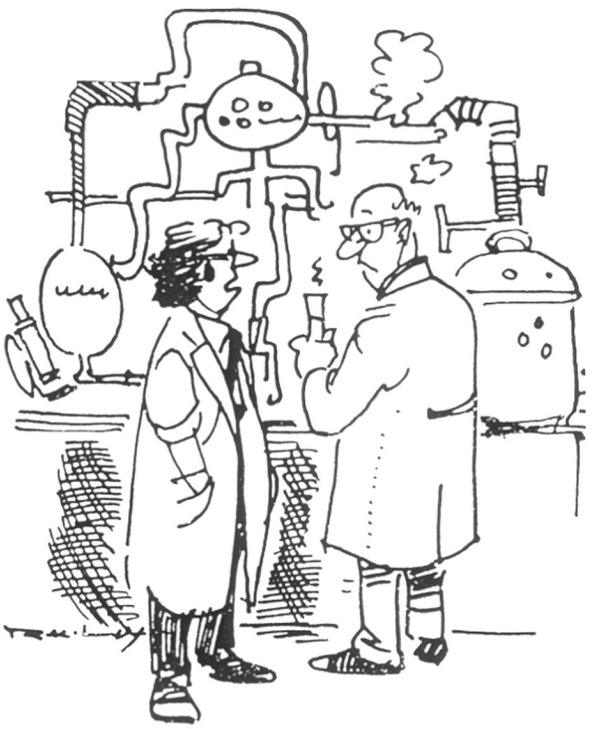
CHAPTER-2

Protection And Deprotection Methodologies

Of oxathiolanes



I'm leaving. I don't have any job satisfaction I haven't been to a single seminar since I joined last week, sir.

Part-I : Interconversion Of Oxathiolanes And Carbonyls Under Essentially Identical Conditions

2.1.0 *Protecting Groups In Organic Chemistry: Introduction*

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound other reactive sites must be temporarily blocked. For this reason such blocking functions have been developed for nearly hundred years by numerous researchers of the disciplines of organic chemistry and consequently solutions to the existing problems were devised; making use of various synthetic transformations. It was Fischer, who among his many important contributions to chemistry, first realized that the application of protecting functions is often a necessity for a successful synthesis. Thus he introduced the isopropylidene acetal in carbohydrate chemistry[1] and for the first time used both the chloroacetyl moiety and a urethane, namely the ethoxycarbonyl group as N-terminal protecting group in the selective synthesis of peptides.[2]

It was not until 1932, that the decisive break-through for the invention of easily and selectively removable protecting groups was achieved by the use of benzoyloxycarbonyl (Z, Cbz) group in peptide synthesis[3] and thereby opened up this new field of organic chemistry which has resulted in highly selective construction of polyfunctional molecules through the extensive use of protecting groups. The studies aiming at the successful total synthesis of pallytoxin[4] the most complex acyclic compound known to date, provide an impressive example of this. Today therefore, protecting group chemistry is more important than ever.[5]

2.1.1 *Carbonyl Protecting Groups*:

The carbonyl function as present in aldehydes and ketones is probably the most versatile functional group in organic chemistry and a great deal of work has been done on the protection and deprotection of aldehyde and ketone groups. In the course of complex syntheses, for instance in the total syntheses of natural products carbonyl groups often must be protected against nucleophilic attack e.g. by organometallic

compounds, reduction, oxidation and also deprotonation by strong bases. To achieve this aim, the carbonyl functions generally are transformed into suitable acetals, thioacetals, hydrazones, oximes and cyanohydrins. In addition they can be converted to enamines, enol ethers and silylenol ethers. Most of the protecting groups can be removed by treatment with acids or Lewis acids. In particular, the oxygen acetals and ketals are readily cleaved by acidic hydrolysis and are stable to oxidants and heavy metal ions. In contrast, thioacetals are cleaved by a wide range of oxidants and under neutral conditions by mercury (II), silver (I) or copper (II) salts. Due to the pronounced differences in reactivity between the different carbonyl groups, in many cases a reactive carbonyl group may be protected selectively in the presence of less reactive one.

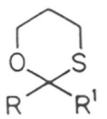
The order of reactivity of the carbonyl group in general is aldehydes (aliphatic > aromatic) > acylic ketones and cyclohexanones > cyclopentanones > α,ß unsaturated ketones > > aromatic ketones.

The most commonly used protecting groups are the acyclic and cyclic acetals and the acyclic or cyclic thio acetals. These protecting groups have opened a field in the electrophilic substitution at the carbonyl carbon, "Umpolung of the reactivity" introduced by Corey and Seebach.[6]

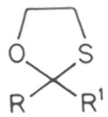
The carbonyl compounds are protected in presence of acids with an alcohol, diol, thiol, or dithiol. The acetals are of O,O, O,S and S,S type namely 1,3-dioxolanes, 1,3-oxathiolanes and 1,3-dithiolanes of cyclic and acyclic form.

2.1.2 *Oxathiolanes*:

The properties of oxygen and sulfur compounds are combined in the cyclic 1,3-oxathianes (A) and 1,3-oxathiolanes (B).



(A)



(B)

R = H , alkyl , aryl

R^1 = alkyl , aryl

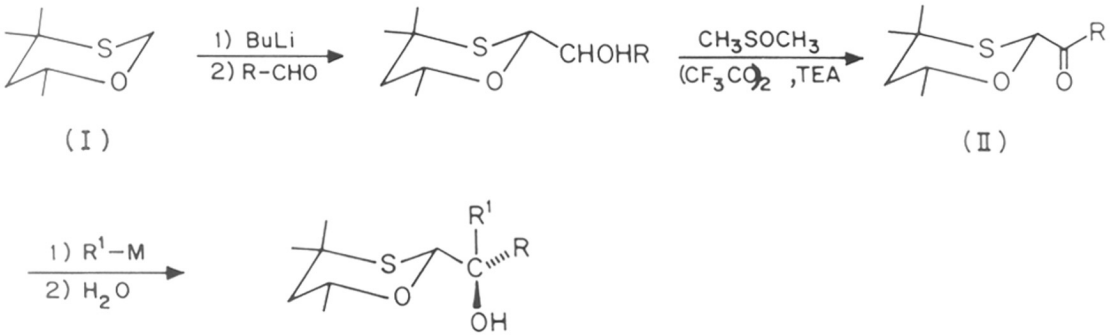
These are formed by acid catalyzed reaction of carbonyl compounds with mercaptopropanol and mercaptoethanol respectively to give the corresponding 1,3-oxathianes and 1,3-oxathiolanes. Due to combined properties of oxygen and sulfur acetals, they can be cleaved with mercury salts and are also more labile towards acids than the sulfur analogs. (ease of deprotection O,O acetals > O,S acetals > S,S acetals).

Oxathioacetals have gained prominence as protective group[5] in functional group transformations, carbon-carbon bond formation by vitrue of their stability and ability to act as a acyl anion equivalent.[7] Eliel has established the use of oxathioacetals as acyl anion equivalent for the synthesis of chiral alcohols (Scheme-1).

A highly stereoselective synthesis of oxathiane carbinol was achieved in two steps. The first one involving a highly stereoselective electrophilic substitution in a conformationally locked 1,3-oxathiane (**I**) to an equatorially substituted ketone (**II**) and the second step involving a highly stereoselective Grignard addition to the ketone to give essentially a single diastereomeric tertiary carbinol (**III**) the diastereomeric excess

generally above 90%.

SCHEME-1



(I) (II) (III)

Ref. : J. Am. Chem. Soc. (1984) , 106 , 2937

The electronegativity of oxygen naturally polarizes the carbonyl group so that the carbon atom is electrophilic and provide acylcation (C) , however getting the subsequent counterpart (D) is difficult under normal circumstances.

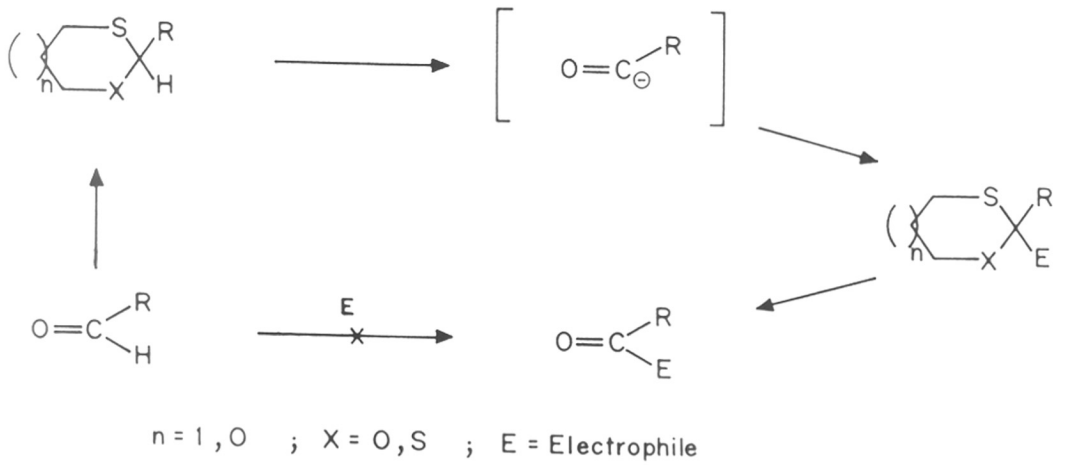
(C) (D)

But reversal of this natural polarity of masked carbonyl groups lead to formyl (CH=O) and acyl (RC = O) anions. As indicated in (Scheme-2), the sulfur stabilized anionic reagents are equivalent to acyl anions which implies that they can be used effectively to reverse the characteristic electrophilicity of a carbonyl carbon (Symmetrization of reactivity, reversible umpolung).

As shown in (Scheme-2), protected-carbonyl group (dithiolanes, dithianes, oxathiolanes, oxathianes) are acyl anion equivalent or metalated masked carbonyls, which can

react with various electrophiles. These acyl anion equivalents are responsible for the formation of additional asymmetric centre in the molecule.

SCHEME - 2



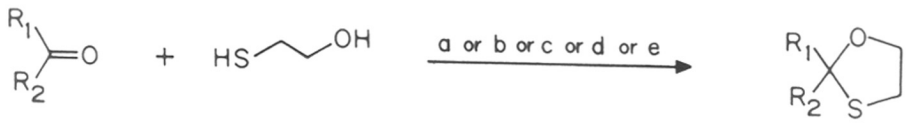
n = 1 , O ; X = O , S ; E = Electrophile

2.1.3 *Preparation Of Oxathiolanes*:

Oxathiolanes can be prepared by various different methods for example,by treating aldehydes or ketones with 2-mercaptoethanol in the presence of mild catalyst, anhydrous zinc chloride and sodium sulphate as water scavenger in dioxane at room temperature.[8] The main disadvantage of this method is the longer time required for the product formation. Other method is using hydrochloric acid (gas) in ether[9] and also by the usual method of refluxing carbonyl compound with mercaptoethanol in benzene with p-toluene sulfonic acid[10]. Oxathiolanes can also be prepared using TMSCl-NaI[11], SO_2[12] and trimethylsilyl triflate, silyl ethers and phenyl sulfide[14]. Most commonly used method is use of one equivalent of boron trifluoride to equimolar mixture of carbonyl compound and 2-mercaptoethanol in ether.[13] Yields obtained in this method are better than other conventional ones. The boron trifluoride scavenges the water formed and is

converted to its mono or dihydrate. (Scheme-3).

SCHEME - 3



a : TMSCl–NaI Ref. : J. Am. Chem. Soc. (1953), 75, 3704

b : BF_3–Et_2O, Δ Ref. : J. Org. Chem. (1968), 33, 2133

c : SO_2 Ref. : Synthesis (1982), 831

d : HCl (g) Ref.: J. Am. Chem. Soc. (1949), 71, 3320

e : $ZnCl_2$–Na_2SO_4, dioxane, R.T. Ref.: J. Am. Chem. Soc. (1951), 73, 4961

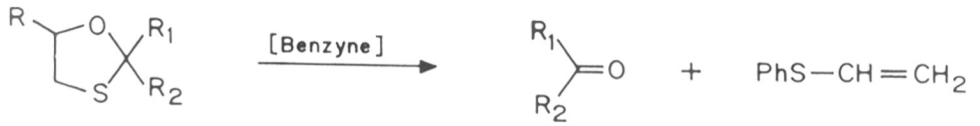
Most of these reported methods employ harsh reaction conditions and yields obtained are generally low thus limiting their usage in a synthetic strategy.

2.1.4 *Deprotection Of Oxathiolanes*:

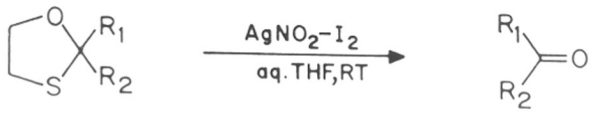
The standard method for the deprotection of oxathiolanes is the acid-catalysed hydrolysis. Deprotection of 1,3 oxathiolanes using Raney Nickel[15] needs harsh conditions and is contaminated with byproducts in some cases because of radical reaction pathway. Hydrolysis by mineral acids requires drastic conditions to give the ketones in moderate yields.[16] Reactions using isoamyl nitrite[17] or chloramine T[18] afford the parent carbonyl compound under mild reaction conditions. The Corey's method (NCS-$AgNO_3$)[19] was applied for deprotection of 2-hydroxy-alkyl-1,3-oxathianes in moderate yields of desired α-hydroxy aldehydes. (62-65%) The use of conventional mercuric chloride for the deprotection of the same type of 1,3-oxathiane gave the corresponding aldehyde in 54% yield.[20] A variety of 2-substituted 1,3-oxathiolanes were deprotected to carbonyl groups and phenylvinyl sulfides with benzyne induced fragmentation.[21]

Benzyne was generated by decomposing 2-carboxybenzene diazonium chloride in the presence of propylene oxide (HCl scavanger). A recent method uses silvernitrite-iodine system for the deprotection of oxathiolanes.[22] (Scheme-4)

SCHEME-4



Ref.: Tet. Lett. (1985), 26, 2195



Ref.: Tet. Lett. (1993), 34, 3425

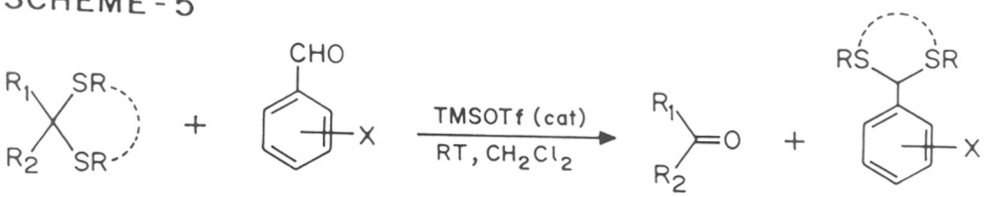
2.1.5 *Present Work*:

Oxathioacetals constitute important class of compounds as acylanion equivalent in C-C bond formation and as protecting groups of carbonyl compounds. Although a variety of methods for their formation are reported using HCl (gaseous), refluxing with p-toluenesulfonic acid, TMSCl-NaI, $BF_3{\cdot}Et_2O$, these methods of deprotection employ rather harsh conditions, many times low yielding and thus are inconvenient to use. As compared to this, the conventional methods of deprotection employ even harsher conditions, involving stoichiometric amounts of oxidants, refluxing with Raney Nickel, thus limiting their usage in synthetic strategy and especially on a large scale.

Search for effective and mild protocol for deprotection of oxathiolanes is the

focus of current interest. In connection with the interest in the synthesis of vitamin H, (D(+)Biotin), a novel, catalytic, mild and efficient transthioacetalization protocol was developed in our group.[23] (Scheme-5) Subsequently a highly convenient transoxathioacetalization protocol was developed using TMSOTf as catalyst in presence of p-nitrobenzaldehyde[24] (Scheme-6). Also oxathiolanes were smoothly deprotected to carbonyl compounds by polymer supported nitrobenzaldehyde and TMSOTf (cat.)[25]. (Scheme-7).

SCHEME-5



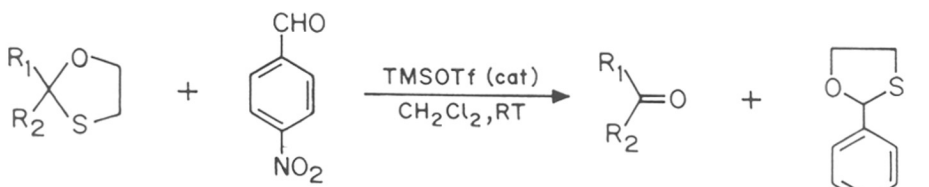
1b 3 2 3b

R= $-CH_2-CH_2-$
R_1= H, alkyl, aryl
R_2= alkyl, aryl

i) X = H
ii) X = 2-NO_2
iii) X = 3-NO_2
iv) X = 4-NO_2

Ref. : J. Chem. Soc. Chem. Commun. (1991), 1750

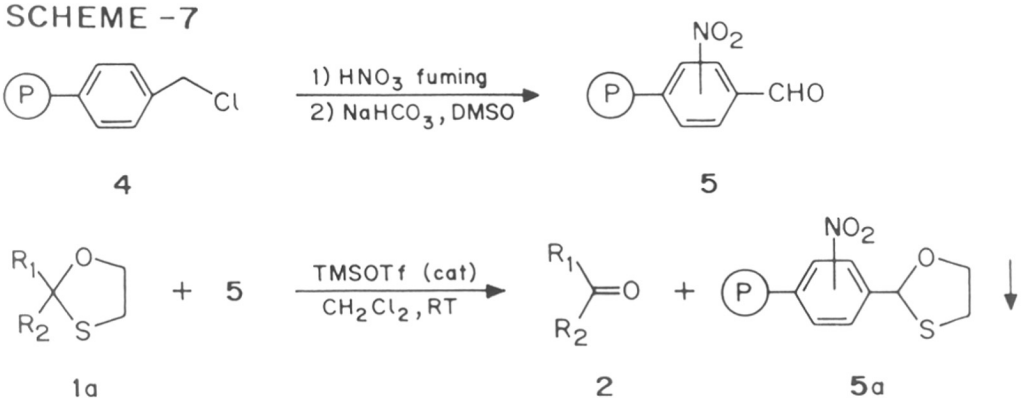
SCHEME-6



1a 3 2 3a

Ref. : J. Chem. Soc. Chem. Commun. (1994), 1937

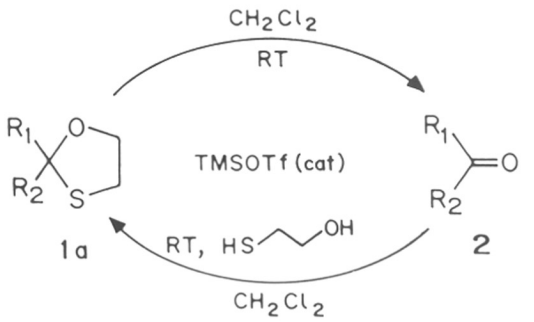
SCHEME -7



Ref. : Tet. Lett. (1994), 35, 8895

It is obvious from the above discussion that the preparation of oxathiolanes as well as deprotection require drastically different conditions. In this connection a novel, mild, catalytic method for the interconversion of oxathiolanes and carbonyls under anhydrous and essentially identical conditions[26] has been developed which is summarised in (Scheme-8).

SCHEME - 8 "MERRY-GO-ROUND" Interconversion of oxathiolanes & carbonyls



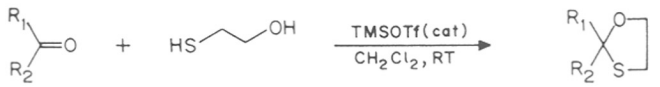
Ref. : Tet. Lett. (1995), 36, 2285

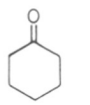
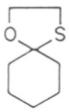
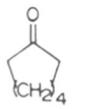
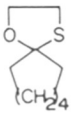
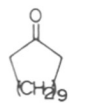
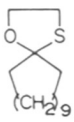
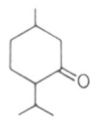
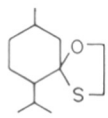
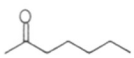
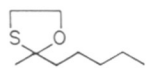
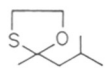
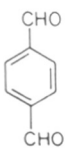
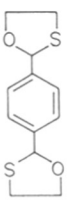
2.1.6 *Results And Discussions*:

A catalytic, non-aqueous protocol for the interconversion of oxathiolanes and carbonyl compounds at room temperature in the presence of TMSOTf as the catalyst has been developed. Although a variety of functional group transformation can be performed by the same catalyst, the conditions employed for their interconversions are drastically different. Most of these reactions, i.e. protection and deprotection of carbonyl compounds are equilibrium driven reactions, where water generated during the reaction has to be removed either azeotropically or otherwise from reaction mixture or added for their efficient deprotection.

Oxathiolanes (**1a**) were prepared by stirring equimolar mixture of the carbonyl compound (**2**) and mercaptoethanol in dichloromethane under nitrogen atmosphere in presence of TMSOTf (cat) at room temperature. Reaction was monitored by TLC and usually completed in 10 min- 3 hr. Reaction mixture was quenched with $NaHCO_3$ and extraction with appropriate solvent gave the crude oxathiolane which was further purified by column chromatography. A variety of carbonyl compounds including cyclic ketones such as cyclohexanone, cycloheptanone, cyclododecanone, natural terpenes like menthone, acyclic ketones as 2-heptanone, methylisobutyl ketone, aromatic aldehydes like benzaldehyde, terephthaldehyde and aromatic ketones were efficiently converted to their corresponding oxathiolanes in high yields (Table-I). The oxathiolanes formed were characterized by IR, H^1-NMR and mass spectroscopy and values were in agreement with the reported ones. The IR spectra indicated the absence of carbonyl absorption and H^1-NMR spectra showed peaks at 3.8-4.1δ and 2.3-2.9δ characteristics of methylene groups adjacent to oxygen and sulfur group respectively.

TABLE - I



Entry	Carbonyl	Oxathiolane	Time(min)	% Yield
1	 (6)	 (6a)	10	76
2	 (7)	 (7a)	10	69
3	 (8)	 (8a)	10	76
4	 (9)	 (9a)	10	68
5	 (10)	 (10a)	10	65
6	 (11)	 (11a)	10	63
7	 (12)	 (12a)	10	50
8	 (13)	 (13a)	10	68
9	 (14)	 (14a)	3hrs	61
10	 (15)	 (15a)	10	72
11	 (16)	 (16a)	10	78

SCHEME - 9

2

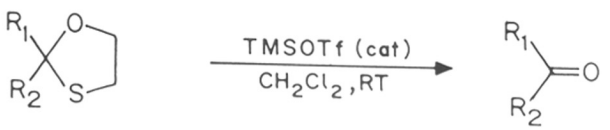
R_1 = H, alkyl, aryl

R_2 = alkyl, aryl

1a

Deprotection of oxathiolanes using cat. TMSOTf and in presence of p-nitrobenzaldehyde[24] and polymer-supported nitrobenzaldehyde[25] to carbonyl group in high yields has been already reported in our group. In both the cases equivalent amount of oxathiolane of p-nitrobenzaldehyde is formed as a byproduct, which was then separated by column chromatography. To see whether one can avoid the use of p-nitrobenzaldehyde at all and few "activated" oxathiolanes when subjected to the treatment of same catalyst (TMSOTf) and it was interestingly observed that they were converted to carbonyl compounds in high yields! It was obvious that the presence of an aryl ring seems to be an essential factor for successful transformation of (1a) to (2). (Scheme-10)

SCHEME - 10



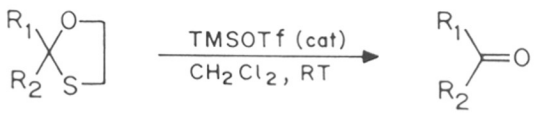
1a

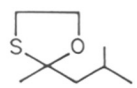
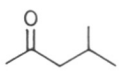
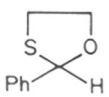
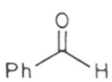
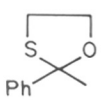
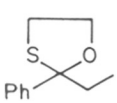
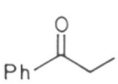
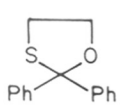
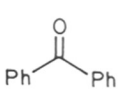
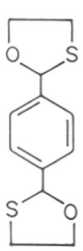
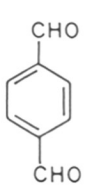
2

R_1 = alkyl, aryl, H

R_2 = aryl

TABLE - 2



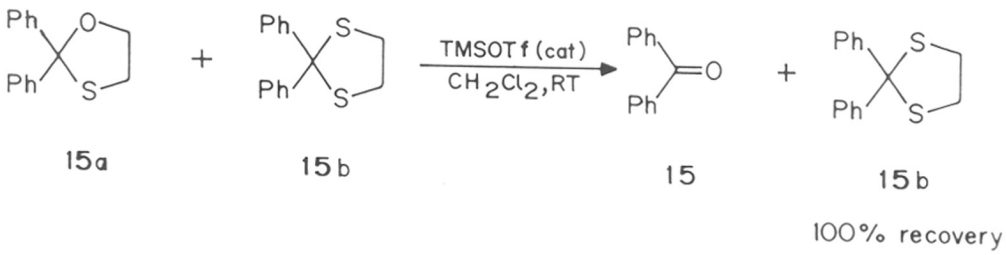
Entry	Oxathiolane	Carbonyl	Time	% Yield
1	 (11a)	 (11)	12 hr	60
2	 (12a)	 (12)	12 hr	50
3	 (13a)	 (13)	10 min	72
4	 (14a)	 (14)	15 min	69
5	 (15a)	 (15)	10 min	82
6	 (16a)	 (16)	12 hr	50

Oxathiolanes lacking aryl groups were resistant to TMSOTf and recovered unchanged. This may be attributed to the ease of formation of stable benzyl carbocation on treatment with TMSOTf (Table-2). The mildness of the methodology developed is manifested in its selectivity.

Selectivity:

When an equimolar mixture of benzophenone oxathiolane (**15a**) and benzophenone dithiolane (**15b**) were treated with TMSOTf, selective and clean conversion of oxathiolane (**15a**) to benzophenone (**15**) was observed, (Benzophenone was isolated as its corresponding alcohol after $NaBH_4$ reduction in 85% yield) whereas benzophenone dithiolane (**15b**) was quantitatively recovered unchanged (Scheme-11).

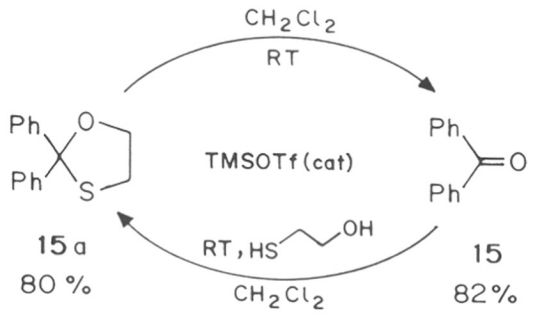
SCHEME - 11



An interesting point which emerged from the above study was that oxathiolanes (**1a**) and carbonyls (**2**) could be interconverted under essentially identical conditions in a "merry-go-round" fashion. An illustrative example to highlight the above point was on treatment of benzophenone oxathiolane (**15a**) with TMSOTf (cat.), complete and clean conversion to the benzophenone (**15**) was obtained. (TLC) (On quenching the reaction ketone **15** was isolated in 82% yield). However addition of mercaptoethanol to the same reaction mixture and TMSOTf (cat.) and overnight stirring at room temperature

gave benzophenone oxathiolane (**15a**) in 80% isolated yield (Scheme-12).

SCHEME-12



Thus TMSOTf can be used as versatile catalyst for interconversion of oxathiolanes & carbonyls under essentially identical conditions.

2.1.7 *Conclusion*:

Facile protection of carbonyl compounds was achieved in the presence of TMSOTf as the catalyst at room temperature. This would probably be the mildest method for the protection of carbonyl group to oxathiolanes in good yields. Also the interconversion of oxathiolanes and carbonyls can be performed catalytically at room temperature and under essentially identical, anhydrous conditions. This observation in this regard is novel and unique and does not seem to have any parallel in the field of synthetic functional group transformations.

More exciting feature of the methodology is that oxathiolanes bearing aryl group could be selectively deprotected to carbonyl compounds using catalytic TMSOTf under mild conditions. Additionally oxathiolanes can be selectively deprotected in presence of thiolanes. Althogh the exact mechanism of the above protocol is not known, it should find wide applications in selective functional group transformation to the synthetic chemists by virtue of its high degree of selectivity, mildness and ease of operation and superiority over existing methods.

2.1.8 *Experimental*

TMSOTf preparation

TMSOTf was prepared by the literature procedure[27] using trimethyl silyl chloride and triflic acid.

Trimethyl silyl chloride (1.1 mol) was added with vigorous stirring to trifluoromethane sulfonic acid (1 mol) at 5°C, and allowed to stir at room temperature for 2 hrs after completion of addition. The mixture was then heated at 80°C for 6 hrs until hydrogen chloride evolution ceases, the product trifluoromethane trimethyl silyl triflate was isolated by fractional distillation.

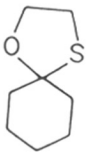
Yield: 92%

B.P. 71/80 mm.(lit[27] B.P.32/12torr)

General procedure for the preparation of oxathiolanes

To a stirred mixture of the carbonyl compound (10 mmol) and mercaptoethanol (10 mmol) in dry dichloromethane under nitrogen atmosphere was added cat. TMSOTf (0.02 ml,) at room temperature. The reaction was monitored by TLC and usually completed in 10 min- 3 hr. After completion of the reaction, the reaction mixture was quenched with aq. $NaHCO_3$ and extracted with dichloromethane (3 x 20 ml), washed with $NaHCO_3$ solution (1 x 10 ml) and brine (10 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave the crude oxathiolane which was further purified by flash chromatography using (95% pet.ether : 5% ethyl acetate) as eluant to furnish oxathiolanes in good yields.

6a Cyclohexanone oxathiolane[13]



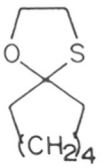
Mol. formula: $C_8H_{14}OS$. Pale yellow liq.

Yield: 76%

IR (neat, cm^{-1}): 580, 620, 780, 1080, 1180, 1250, 1280, 1350, 1450, 2980.

^1H NMR (80MHz, $CDCl_3$, δ): 1.3-1.8 (m, 6H, $-CH_2-CH_2-$); 2.1 (m, 4H) ; 3.1 (t, 2H, $-SCH_2-$); 4.25 (t, 2H, $-OCH_2-$).

7a Cycloheptanone oxathiolane[13]



Mol. formula: $C_9H_{16}OS$. Colourless liq.

BP: 77°C/1.2 mm (lit. 77-78/1.2 mm)

Yield: 69%

IR (neat, cm^{-1}): 540, 760, 860, 950, 1030, 1070, 1160, 1200, 1230, 1270, 1360, 1460, 2850, 2920.

^1H NMR (200MHz, $CDCl_3$, δ): 1.5 (m, 8H, $-CH_2-CH_2-$); 2.02 (t, 4H); 3.01 (t, 2H, $-SCH_2-$); 4.8 (t, 2H, $-OCH_2$).

Mass (m/e):172 (M^+, 79), 165 (1), 157 (2), 144 (10), 129 (31), 115 (100), 102 (9), 95 (26), 89 (6), 84 (48), 79 (6), 68 (47), 60 (94), 55 (86), 45 (23), 41 (46).

8a Cyclodadecanone oxathiolane

Mol. formula:$C_{14}H_{26}OS$. Colourless liq.

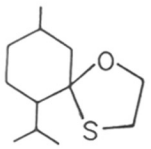
Yield: 76%

IR (neat, cm^{-1}): 760, 850, 950, 1080, 1120, 1160, 1220, 1250, 1330, 1350, 1450, 1480, 2960.

^1H NMR (80MHz, $CDCl_3$, δ): 1.2 (m, 18H, $-CH_2-CH_2-$); 2.43 (t, 4H); 3.1 (t, 2H $-SCH_2-$); 4.2 (t, 2H $-OCH_2$)

Mass (m/e): 242 (M^+, 33); 213 (4); 199 (9); 182 (21); 171 (11); 157 (6); 125 (13); 115 (100); 111 (28); 102 (16); 98 (86); 84 (58); 71 (39); 60 (29); 55 (60); 41 (13).

9a Menthone oxathiolane[22]



Mol. formula:$C_{12}H_{22}OS$ colourless liq.

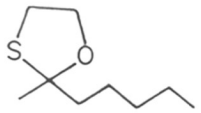
Yield: 68%

IR (neat, cm^{-1}): 550, 640, 820, 840, 860, 920, 1020, 1060, 1080, 1150, 1200, 1220, 1270, 1300, 1370, 1390, 1450, 2840, 2920.

^1H NMR (80MHz, $CDCl_3$, δ): 0.77-2.66 (multiplate 18H); 2.84-3.04 (multiplate 2H, $-SCH_2-$); 3.71-4.46 (multiplate 2H, $-OCH_2$).

Mass (m/e): 214 (M^+, 41), 199 (9), 157 (19), 139 (33), 129 (100), 112 (37), 98 (18), 83 (15), 69 (45), 60 (45), 55 (40), 41 (34).

10a 2-heptanone oxathiolane



Mol. formula: $C_9H_{18}OS$. Colourless liq.

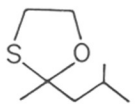
Yield: 65%

IR (neat, cm^{-1}): 550, 650, 820, 870, 960, 1030, 1080, 1100, 1140, 1170, 1200, 1230, 1380, 1480, 2860, 2930.

^1H NMR (80MHz, $CDCl_3$, δ): 0.88 (t, 3H, $-CH_3$); 1.28 (m, 6H, $-(CH_2)_3-$); 1.55 (s, 3H, H_3C-C-); 1.73 (m, 2H, $-CH_2-$); 3.04 (dd, 2H, (J=6Hz), $-SCH_2-$); 4.13 (dt, 2H, (J=6,2Hz) $-OCH_2-$).

Mass (m/e): 174 (M^+, 11), 114 (15), 103 (100), 71 (22), 58 (55), 42 (50), 39 (15).

11a Methyl isobutyl ketone oxathiolane



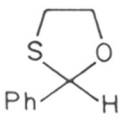
Mol. formula: $C_8H_{16}OS$. Colourless liq.

Yield: 63%

IR (neat, cm^{-1}): 580, 650, 820, 900, 1020, 1050, 1120, 1180, 1250, 1300, 2860.

^1H NMR (80MHz, $CDCl_3$, δ): 0.90 (d, 6H); 1.5 (s, 3H, $-CH_3$); 1.7 (d, 2H, $-CH_2-$); 1.8 (t, 1H, -CH-); 3.0 (t, 2H; $-SCH_2-$); 4.1 (m, 2H, $-OCH_2-$).

12a Benzaldehyde oxathiolane[13]



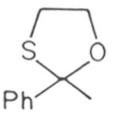
Mol. formula:$C_9H_{10}OS$ colourless liq.

Yield: 50%

IR (neat, cm^{-1}): 720, 780, 820, 980, 1020, 1050, 1120, 1250, 1380, 1500, 1600, 2950.

^1H NMR (80MHz, $CDCl_3$, δ): 3.3 (m, 2H, $-SCH_2$); 4.1-4.5 (m, 2H, $-OCH_2-$); 6.1 (s, 1H, -CH); 7.57.8 (m, 5H, aromatic).

13a Acetophenone oxathiolane[13]



Mol. formula:$C_{10}H_{12}OS$. Colourless liq.

BP 85°/1.2 mm (lit. 85/1.2 mm).

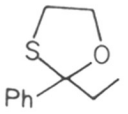
Yield: 68%

IR (neat, cm^{-1}): 650, 700, 760, 800, 870, 920, 950, 1030, 1050, 1070, 1100, 1130, 1220, 1270, 1310, 1360, 1380, 1440, 1500, 1600, 2860, 2920, 2960.

^1H NMR (80MHz, $CDCl_3$, δ): 1.88 (s, 3H, $-CH_3$); 2.88 - 3.3 (m, 2H, $-SCH_2-$); 3.8-4.4 (m, 2H, $-OCH_2-$); 7.15 - 7.55 (m, 5H, aromatic).

Mass (m/e): 180 (M^+, 83); 165 (94); 149 (17); 133 (17); 121 (89); 115 (10); 105 (100); 91 (43); 77 (88); 69 (10); 65 (27); 60 (87); 51 (70); 43 (77); 39 (23).

14a Propiophenone oxathiolane



Mol. formula: $C_{11}H_{14}OS$. Pale yellow liq.

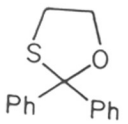
Yield: 61%

IR (neat, cm^{-1}): 650, 705, 760, 850, 890, 930, 960, 1020, 1060, 1080, 1130, 1170, 1210, 1270, 1300, 1385, 1450, 1500, 1600, 2880.

^1H NMR (80MHz, $CDCl_3$, δ): 1.1 (t, 3H, $-CH_3$); 2.8 (q, 2H, $-CH_2$); 3.1 (m, 2H, $-SCH_2-$); 3.8 (m, 2H, $-OCH_2-$); 7.5-7.8 (m, 5H, aromatic).

Mass (m/e): 194 (M^+ 5), 165 (77), 135 (12), 105 (100), 91 (5), 77 (43), 66 (23), 57 (5).

15a Benzophenone oxathiolane[13]



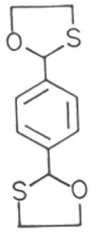
Mol. formula:$C_{15}H_{14}OS$ pale yellow solid (low melting)

Yield: 72%

IR (neat, cm^{-1}): 700, 750, 880, 980, 1020, 1050, 1180, 1220, 1250, 1320, 1450, 1500, 1600, 2880, 2950.

^1H NMR ($CDCl_3$, δ): 3.1 (t, 2H, $-SCH_2-$); 4.1 (t, 2H, $-OCH_2-$); 7.2-7.6 (m, 10 H, aromatic).

16a Terephthaldehyde oxathiolane



Mol. formula: $C_{12}H_{14}OS$ pale yellow solid

MP: 125°C

Yield: 78%

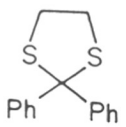
IR (neat, cm^{-1}):700, 750, 800, 950, 1050, 1080, 1120, 1250, 1300, 1410, 1500, 1600, 2950.

^1H NMR (80MHz, $CDCl_3$, δ): 3.1 (m, 4H, $-SCH_2-$); 4.1-4.4 (m, 4H, $-OCH_2-$); 6.1 (s, 2H); 7.5-7.8 (m, 4H, aromatic).

Preparation of benzophenone thioacetal (15b)

Thioacetal was prepared according to the reported procedure by Corey and Seebach[28].

To a stirred mixture of benzophenone (1.82g, 10 mmol) and ethanedithiol (0.95g, 10 mmol) in 10 ml of dry dichloromethane at 0°C was added BF_3 etherate (1.25ml, 10 mmol). The mixture was slowly allowed to come to room temperature and stirred overnight. Organic layer washed with aq. $NaHCO_3$ solution (1x10 ml) and brine (2 x 10 ml) and dried over sodium sulphate. On solvent evaporation gave crude thioacetal which was further purified by flash column chromatography.



Mol.formula:$C_{15}H_{14}S_2$

Pale yellow crystals

Yield: 80%

IR (neat, cm^{-1}): 780, 820, 860, 990, 1050, 1080, 1120, 1160, 1220, 1280, 1320, 1480, 1500, 1600, 2860, 2910.

H^1 NMR (80MHz, $CDCl_3$, δ): 3.35 (s, 4H, $-SCH_2CH_2-S-$); 7.5-7.8 (m, 10H, aromatic).

Selectivity experiment between oxathiolanes and dithiolanes

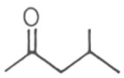
To a stirred mixture of benzophenone oxathiolane (**15a**) (0.240g, 10 mmol) and benzophenone dithiolane (**15b**) (0.258g, 10 mmol) in dry dichloromethane (10 ml) under nitrogen atmosphere at room temperature was added TMSOTf (0.02 ml,) TLC showed disappearance of benzophenone oxathiolane (**15a**) immediately. The reaction mixture was stirred for some more time at room temperature (0.5 hr) and quenched with aq. sodium bicarbonate. The organic layer was washed once with water and brine and dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure furnished a residue which consisted of benzophenone (**15**) and benzophenone dithiolane (**15b**). Benzophenone (**15**) was isolated as its alcohol (0.155g 85% yield) after borohydride reduction in ethanol (solvent) and (**15b**) benzophenone dithiolane was recovered quantitatively.

General procedure for deprotection of "Activated" oxathiolanes"

To a stirred mixture of "activated" oxathiolanes (10 mmole) in dry CH_2Cl_2 (15 ml) under nitrogen atmosphere at room temperature was added TMSOTf. (0.02 ml) The reaction was monitored by TLC, disappearance of oxathiolane; usually completed in 10 min - 10 hr. After completion of reaction (TLC) aqueous sodium bicarbonate

was added, the organic layer was washed once with water, brine and dried over Na_2SO_4. Removal of organic solvent under reduced pressure furnished the crude product which was purified by column chromatography using pet.ether-ethyl acetate as the eluant to furnish the carbonyl compounds in good yields.

11 Methyl isobutyl ketone



Mol. formula: $C_6H_{12}O$.

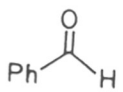
Yield: 68%

IR (neat, cm^{-1}): 550, 680, 850, 890, 1020, 1150, 1130, 1280, 1300, 1450, 1700, 2870. 1470, 1720, 2850, 2920.

^1H NMR (80MHz, $CDCl_3$, δ): 1.0 (d, 6H, $-CH_2$); 1.6 (s, 3H, $-CH_3$); 1.8 (d, 2H, -CH-); 2.0 (t, 1H,$-CH_3$); 2.4 (t, 2H)

Mass (m/e):114 (M^+, 100), 99 (50), 95 (93), 91 (30), 88 (35), 80 (45), 71 (93), 58 (80), 55 (15), 43 (48).

12 Benzaldehyde



Mol. formula:C_7H_6O.

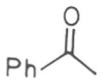
BP: 178°C (Lit. 178-179°C)

Yield: 50%

IR (neat, cm^{-1}): 780, 850, 880, 920, 1200, 1480, 1500, 1600, 1700, 2950

^1H NMR (80MHz, $CDCl_3$, δ): 7.5-7.8 (m, 5H, aromatic); 9.8 (s, 1H, -C-H).

13 Acetophenone



Mol. formula:C_8H_8O.

BP: 200°C (Lit. 202°C)

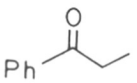
Yield: 72%

IR (neat, cm^{-1}): 580, 740, 820, 880, 1050, 1150, 1200, 1280, 1360, 1380, 1450, 1570, 1650, 1675, 1775, 3000, 3060.

^1H NMR (80MHz, $CDCl_3$, δ): 2.57 (S, 3H, $-CH_3$); 7.26 (m, 5H, aromatic)

Mass (m/e):120 (M^+, 5); 105 (35); 77 (100); 51 (15).

14 Propiophenone



Mol. formula: $C_9H_{10}O$.

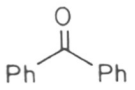
BP: 218° (Lit. 218°C)

Yield: 69%

IR (neat, cm^{-1}): 710, 760, 970, 1030, 1100, 1200, 1340, 1360, 1390, 1430, 1460, 1590, 1610, 1700, 2950, 2990.

^1H NMR (80MHz, $CDCl_3$, δ): 1.25 (t, 3H, $-CH_3$); 2.8 (q, 2H $-CH_2$); 7.5 (m, 3H, aromatic); 8.0 (m, 2H, aromatic).

15 Benzophenone



Mol. formula: $C_{13}H_{10}O$.

MP: 49°C (Lit. 49-50°C)

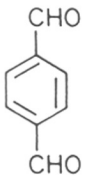
Yield: 82%

IR (neat, cm^{-1}): 650, 700, 780, 820, 920, 1050, 1080, 1180, 1280, 1320, 1450, 1500, 1550, 1600, 1700, 2880.

^1H NMR (80MHz, $CDCl_3$, δ): 7.5 -7.8 (m, 10H, aromatic).

Mass (m/e): 182 (M^+, 30), 105 (100), 77 (65), 51 (15).

16 Terephthaldehyde



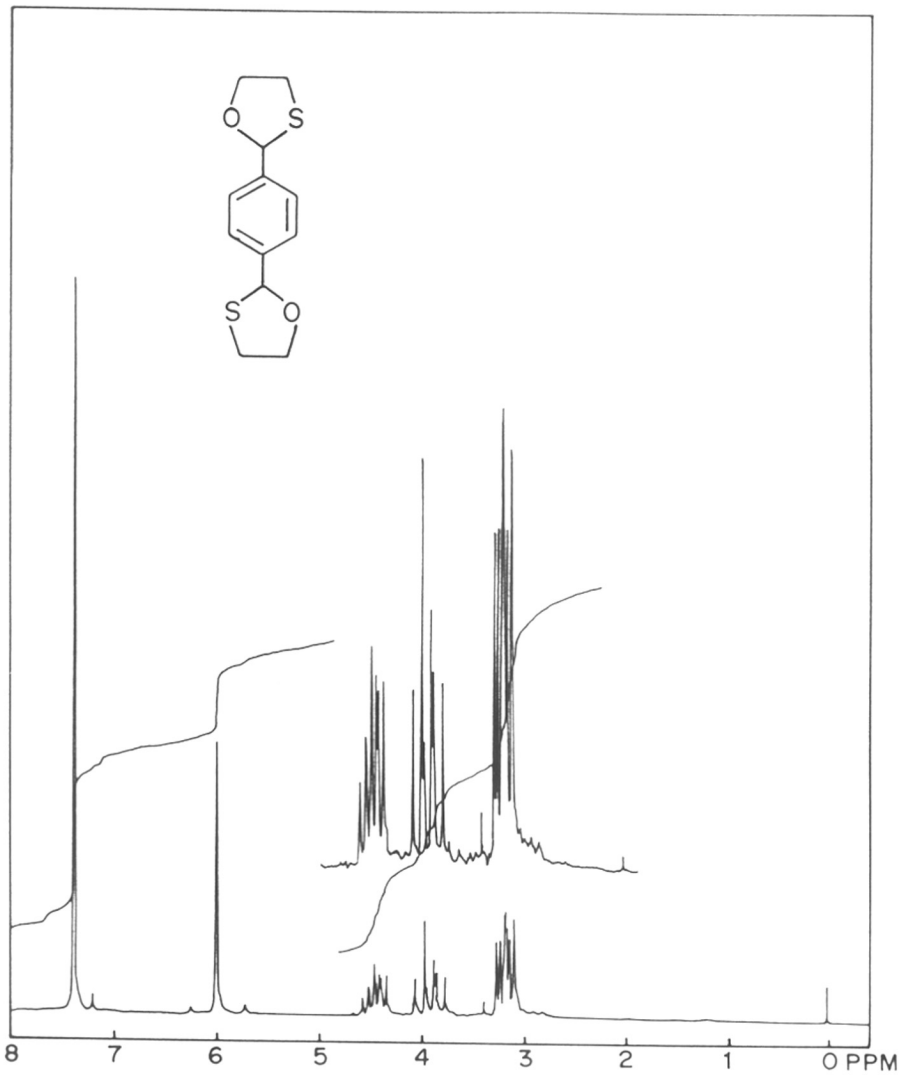
Mol. formula:$C_8H_6O_2$

MP: 115 (Lit. 115-116°)

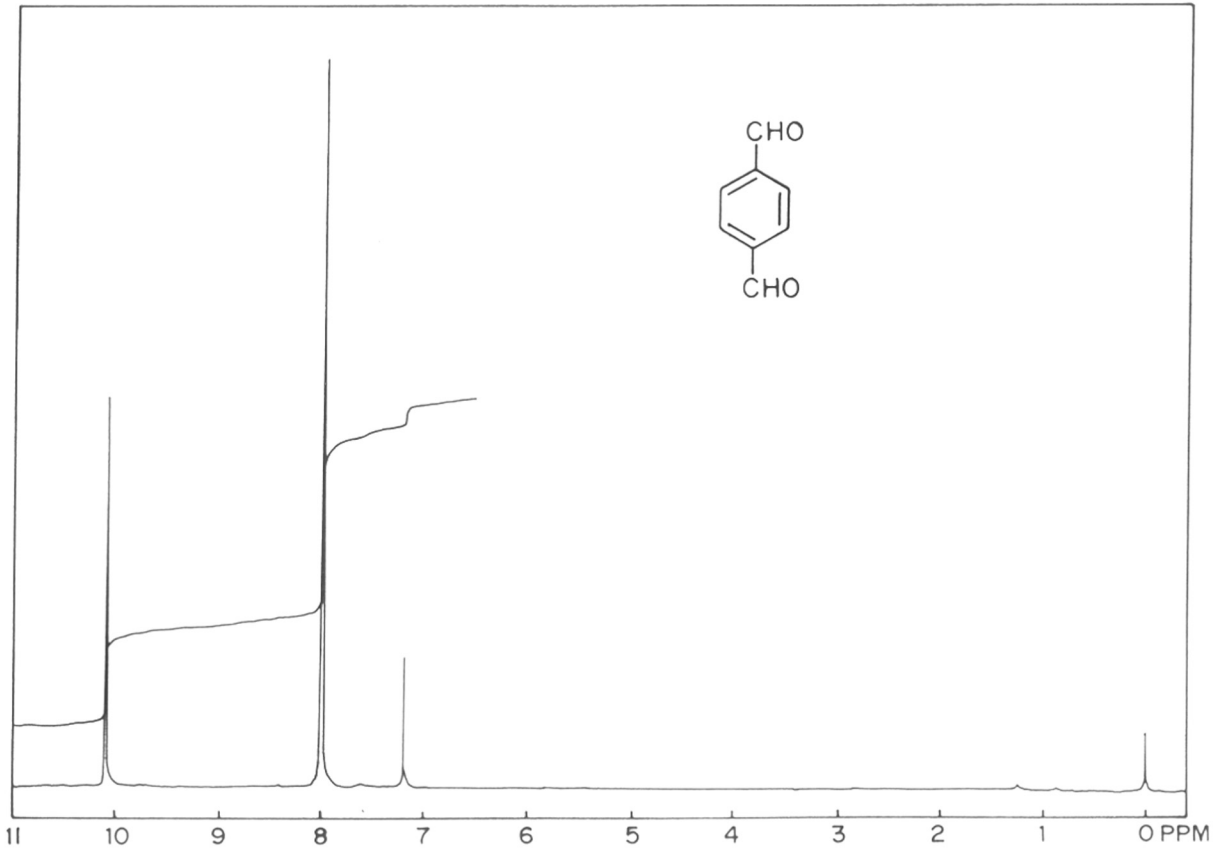
Yield: 50%

IR (neat, cm^{-1}): 780, 820, 1200, 1320, 1400, 1450, 1500, 1620, 1700, 2950.

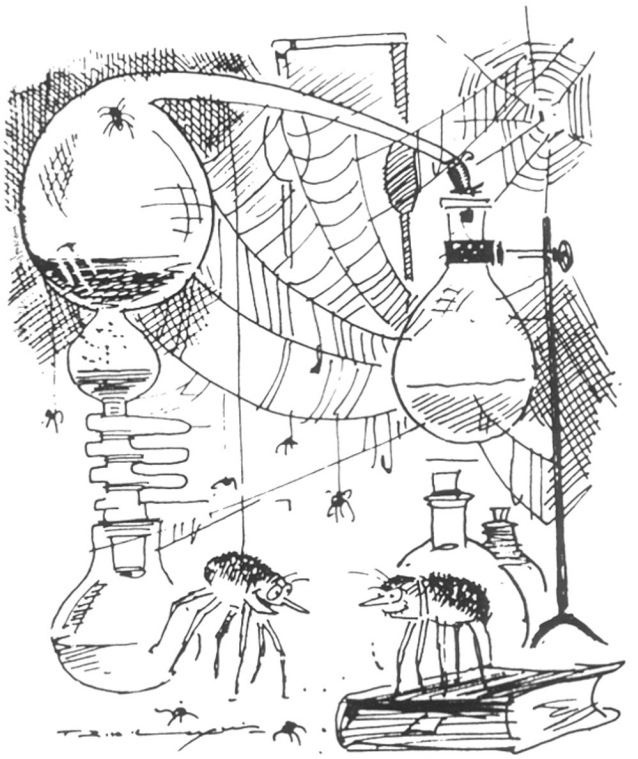
^1H NMR (80MHz, $CDCl_3$, δ): 7.8 (m, 4H, aromatic); 9.8 (s, 2H, -C-H).



^{1}H-NMR SPECTRUM OF **16a** (80 MHz, $CDCl_3$)



^{1}H-NMR SPECTRUM OF **16** (80 MHz, $CDCl_3$)



The nice thing about this research lab is that the scientists are always out attending seminars, leaving you completely undisturbed!

Part-II : Deprotection Of Oxathiolanes Under Mild Conditions Using Aq. H_2O_2

2.2.0 *Introduction*:

Development of a catalytic, mild and efficient protocol for deprotection of carbonyl compounds has been the focus of our group in connection with synthesis of bioactive compounds like Biotin.

In this connection, a catalytic, efficient and mild protocol for deprotection of oxathiolanes and dithiolanes using p-nitrobenzaldehyde[23,24] and polymer supported nitrobenzaldehyde[25] was developed. Practically irreversible and one to one exchange of oxathiolanes was demonstrated to furnish carbonyl compounds in excellent yield. Oxathiolanes and p-nitrobenzaldehyde were used in equimolar mixture in presence of TMSOTf (cat) to give the carbonyl compounds and oxathiolane of p-nitrobenzaldehyde which were separated by column chromatography. Oxathiolane of p-nitrobenzaldehyde was formed as a byproduct in equivalent amounts.

2.2.1 *Present Work*:

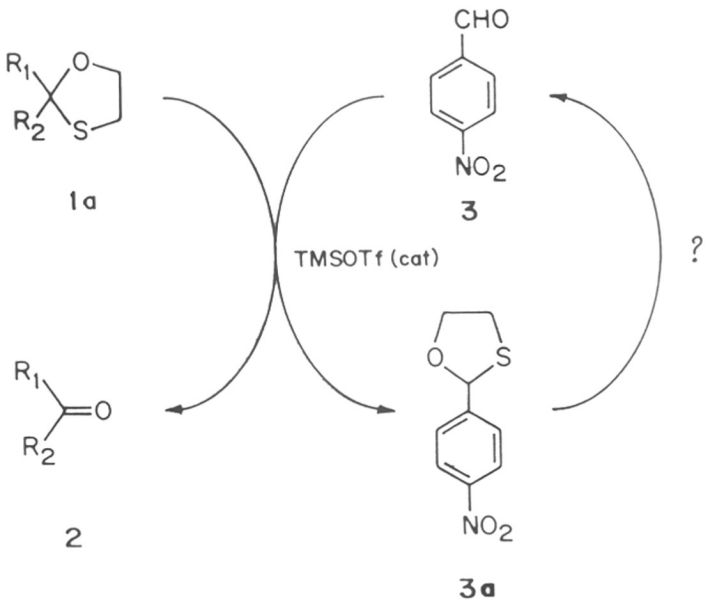
In connection with deprotection protocol of oxathiolanes to furnish carbonyl compounds, p-nitrobenzaldehyde was used as oxathiol acceptor which resulted in equivalent amount of oxathiolane of p-nitrobenzaldehyde as a byproduct (Scheme-1). p-Nitrobenzaldehyde was prepared by a tedious procedure using p-nitrotoluene[24B].

Since one equivalent of p-nitrobenzaldehyde was sacrificed for converting one equivalent of oxathiolane, it was felt necessary to devise a protocol for regeneration of p-nitrobenzaldehyde from its oxathiolane efficiently without the use of heavy metals as oxidants.

It was evident that the choice of the reagent should be such that it should be commercially available, non-polluting and nonhazardous. For this purpose hydrogen peroxide was chosen as an oxidant, as any reagent whose byproduct is water assumes utmost importance and priority in this age of heightened enviornmental awareness and

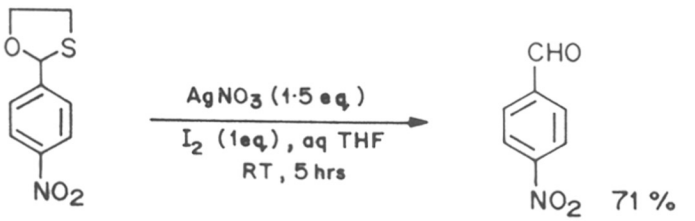
development of environmental friendly technologies.

SCHEME - 1



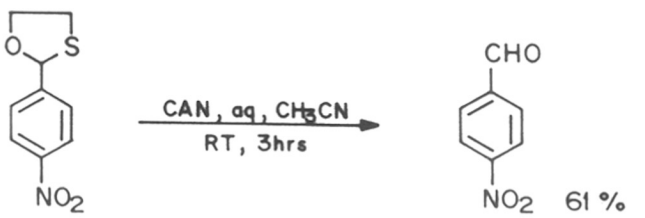
A mild, efficient protocol for the deprotection of oxathiolanes in refluxing acetonitrile in presence of aqueous hydrogen peroxide has been developed. In order to compare the utility of our method we decided to convert **3a** to **3** by the reported procedure.(Scheme-2) Nishida *et al*[22] have recently described a very mild reagent *viz* Ag^+/I_2 combination for deprotection of oxathiolanes. In order to compare our methodology we chose to deprotect **3a** employing the above $AgNO_3/I_2$ combination.Our method compared well with Nishida's in terms of yields (70%); moreover it does not involve the use of stoichiometric amount of expensive reagents. Our method also compared well with CAN oxidation or Raney Ni procedure which led to poorer yields. CAN oxidative deprotection of p-nitrobenzaldehyde oxathiolane gave 60% yield of p-nitrobenzaldehyde, where as Raney Ni procedure resulted in the formation of complex mixtures. This comparision of our method with the conventional CAN mediated oxidative depro

SCHEME - 2A



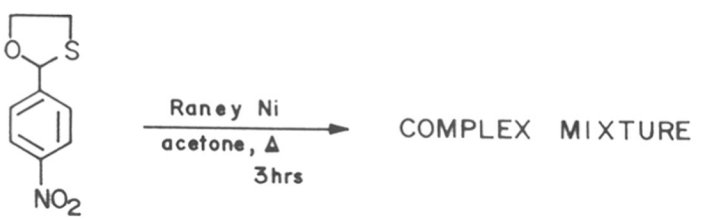
According to Ref : Tet Lett (1993), 34, 3425

SCHEME-2B



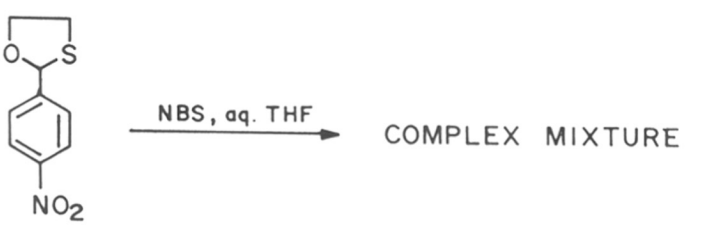
According to Ref : J.C.S. chem. Commun. (1972), 791

SCHEME-2C



According to Ref : J. Am. chem. soc. (1958), 80, 4723

SCHEME-2D



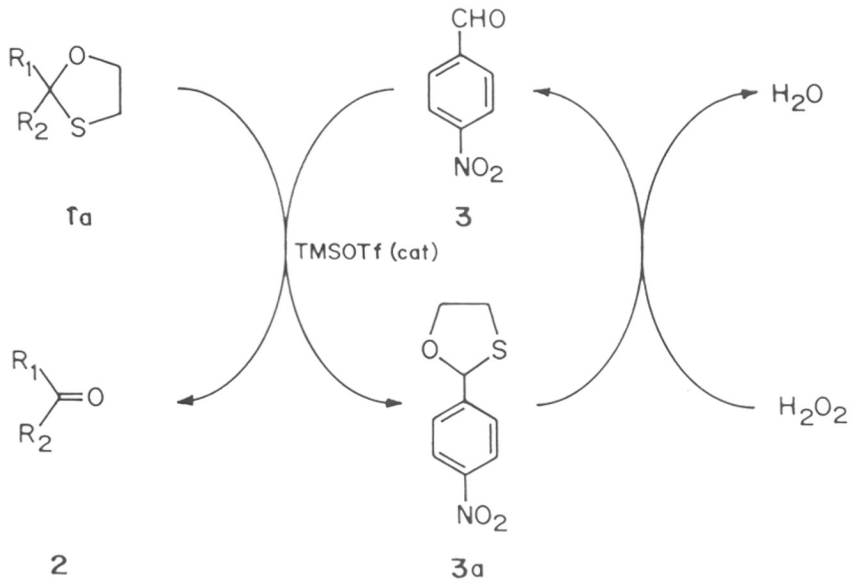
According to Ref : J. O. Chem. (1971), 36, 3553

tection as well as Raney Ni mediated removal of oxathiol, established the superiority of our method over the existing methods.

2.2.2 *Results And Discussion*:

In order to recycle the oxathiolane of p-nitrobenzaldehyde it was refluxed with H_2O_2 in CH_3CN to furnish p-nitrobenzaldehyde in good yields (Scheme-3).

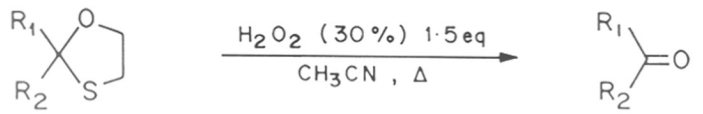
SCHEME - 3

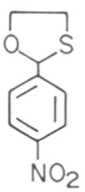
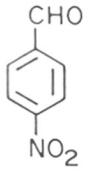
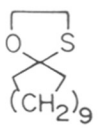
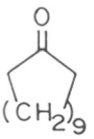
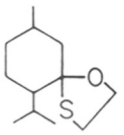
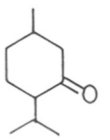
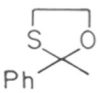
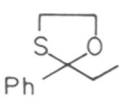
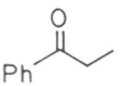
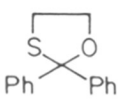
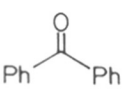
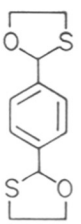
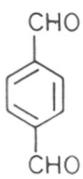
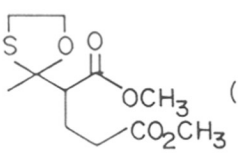
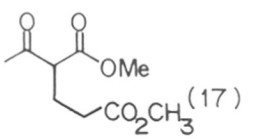
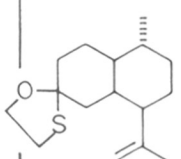
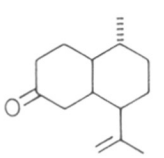


In order to test the generality and scope of this method it was extended to other oxathiolanes as well. Thus a mild and efficient method has been developed.

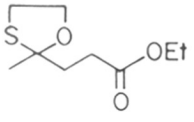
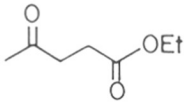
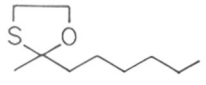
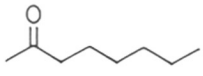
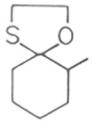
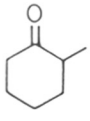
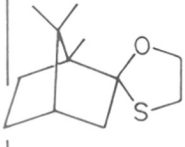
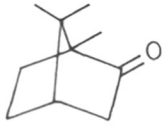
A variety of oxathiolanes (**1a**) were prepared from the carbonyls (**2**) by using TMSOTf as the catalyst as described in the previous section and mercaptoethanol in dichloromethane at room temperature.[26] (Scheme-4)

TABLE-1

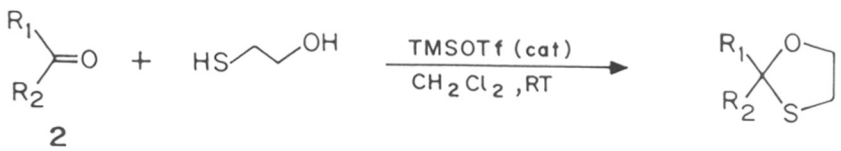


ENTRY	OXATHIOLANE	CARBONYL	TIME (hr)	% YIELD
1	 (3a)	 (3)	2·5	70
2	 (7a)	 (7)	4	89
3	 (9a)	 (9)	2	92
4	 (13a)	 (13)	3	84
5	 (14a)	 (14)	6	80
6	 (15a)	 (15)	3	100
7	 (16a)	 (16)	4	78
8	 (17a)	 (17)	3	56
9	 (18a)	 (18)	1·5	81

Contd

Entry	Oxathiolane		Carbonyl		Time (hr)	% Yield
10		(19a)		(19)	1·5	80
11		(20a)		(20)	1·5	52
12		(21a)		(21)	1·5	66
13		(22a)		(22)	1·5	71

SCHEME - 4



R_1 = H , alkyl , aryl

R_2= alkyl , aryl

The carbonyls used were aromatic compounds such as p-nitrobenzaldehyde, benzophenone, acetophenone, propiophenone, terephthaldehyde (dialdehyde), natural terpene compounds as menthone, camphor, open chain ethyl levulinate. The oxathiolanes were characterised by IR, ^{1}H-NMR and mass spectroscopy.

Deprotection of oxathiolane of p-nitrobenzaldehyde was done by using 1.5 eq. of 30% aq. H_2O_2 and refluxing in acetonitrile. Reaction was monitored by TLC. After completion of reaction, solvent was evaporated under reduced pressure and directly purified by column chromatography to give the pure p-nitrobenzaldehyde. It was characterised by IR & ^{1}H-NMR. The generality and the effiency of this methodology was demonstrated by deprotection of other oxathiolones to give the corresponding carbonyls in high yields. (Table-I).

2.2.3 *Conclusion*:

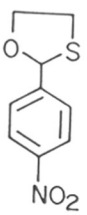
Deprotection of oxathiolanes to carbonyls has been achieved using aq. H_2O_2 in high yields. This is a mild non-polluting method with clean transformation of oxathiolanes to carbonyls without any elaborate work up procedures.

2.2.4 *Experimental*

Preparation of oxathiolanes

Oxathiolanes were prepared by the TMSOTf method as described is previous section (2.1.8), for **7a, 9a, 13a, 14a, 15a, 16a**.

3a p-Nitrobenzaldehyde oxathiolane



Mol. formula:$C_9H_9NO_3S$. Pale yellow crystals

MP: 72° (Lit.[29] 72-73°)

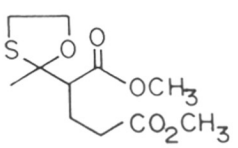
Yield: 65%

IR (nujol, cm^{-1}): 720, 820, 850, 980, 1080, 1200, 1250, 1350, 1450, 1500, 1600, 2920, 2950.

^1H NMR (200MHz, $CDCl_3$, δ): 3.15 (t, 2H, $-CH_2-$); 4.5 (m, 2H, $-OCH_2$); 6.0 (s, 1H); 7.5-8.0 (m, 4H, aromatic).

Mass (m/e): 211 (M^+, 15), 89 (5), 77 (11), 60 (100).

17a 3-(methyl propionate)-methyl acetoacetate oxathiolane



Mol. formula: $C_{11}H_{18}O_5S$. colourless liq.

Yield: 65%

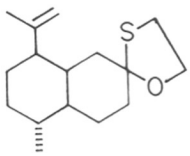
IR (neat, cm^{-1}): 720, 750, 900, 1020, 1050, 1180, 1250, 1280, 1320, 1450, 1720, 2850.

^1H NMR (200MHz, $CDCl_3$, δ)Diastereomeric mixture (1:1) : 1.5 (s, 3H, $-CH_3$); 2.1-2.25 (m, 4H); 2.8 (m, 1H, -CH-); 3.0 (t, 2H, $-SCH_2-$); 3.7 (s, 6H, $-OCH_3$); 4.1 (m, 2H, $-OCH_2-$).

^{13}C NMR(200MHz) : 22.54 (t), 23.75 (t), 24.19 (t), 25.73 (q), 25.78 (q), 25.58 (t), 30.73 (t), 31.67 (t), 31.78 (t), 33.26 (t), 51.04 (), 51.16 (d), 51.94 (d), 55.39 (q), 55.70 (q), 57.57 (q), 70.06 (t), 70.38 (t), 94.10 (s), 95 (s), 172.34 (s), 172.44 (s).

Mass (m/e) : 171 (10), 139 (15), 128 (15), 103 (100), 87 (10), 69 (20), 60 (90), 55 (50)

18a 1-methyl-4-propenyl-6-one decahydronaphthalene oxathiolane



Mol. formula:$C_{16}H_{26}OS$. Colourless liq.

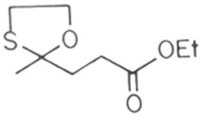
Yield: 82%

IR (neat, cm^{-1}):900, 920, 1020, 1080, 1120, 1280, 1380, 1450, 2950

^1H NMR (200MHz, $CDCl_3$, δ): 0.99 (d, 3H); 1.6 (s, 3H); 1.8-2.4 (m, 14H); 3.0 (m, 2H, $-SCH_2-$); 4.1 (m, 2H, $-OCH_2-$); 4.8 (d, 2H, olefinic).

Mass (m/e): 266 (M^+), 188, 163, 148, 115 (100), 91,79,67,55,41.

19a Ethyl levulinate oxathiolane



Mol. formula:$C_9H_{16}O_3S$. Colourless liq.

Yield: 80%

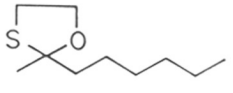
IR (neat, cm^{-1}): 720, 820, 850, 950, 1080, 1100, 1180, 1210, 1280, 1380, 1450, 1720, 2950, 3020.

^1H NMR (200MHz, $CDCl_3$, δ): 1.35 (t, 3H, $-CH_3$); 1.6 (s, 3H, $-CH_3$); 2.15 (t, 2H, $-CH_2-$); 2.4 (m, 2H, $-CH_2-$); 3.0 (m, 2H, $-SCH_2-$); 4.1 (m, 4H, $-OCH_2-$)

^{13}C NMR (200MHz) : 13.8 (q); 29 (q); 29.9 (t); 33.99 (t); 37.27 (t); 59.84 (t); 70.33 (t); 93.85 (s); 172.84 (s).

Mass (m/e): 204 (M^+), 160, 145, 103 (100), 60, 40.

20a 2-Octanone oxathiolane



Mol. formula: $C_{10}H_{20}OS$. Colourless liq.

Yield: 66%

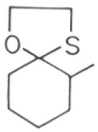
IR (neat, cm^{-1}):750, 820, 950, 1080, 1150, 1200, 1250, 1380, 1450, 2830, 2850.

^1H NMR (200MHz, $CDCl_3$, δ): 0.9 (t, 3H, $-CH_3$); 1.4 (m, 8H, $-CH_2-CH_2-$); 1.5 (s, 3H, $-CH_3$); 1.7 (t, 2H, $-CH_2-$); 3.0 (t, 2H, $-SCH_2-$); 4.1 (m, 2H, $-OCH_2-$).

^{13}C NMR(200MHz) : 13.95 (q), 22.56 (t), 25.42 (t), 28.83 (q), 29.48 (t), 31.76 (t), 33.83 (t), 43.41 (t), 70.14 (t), 95.13 (s).

Mass (m/e): 188 (M^+), 130, 103 (100), 60, 40.

21a 2-Methyl cyclohexanone oxathiolane



Mol. formula:$C_9H_{16}OS$. Colourless liq.

Yield: 52%

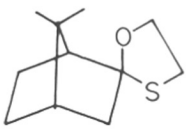
IR (neat, cm^{-1}): 850, 880, 1020, 1080, 1150, 1250, 1280, 1450, 2960, 2980.

^1H NMR (80MHz, $CDCl_3$, δ)Diastereometric mixture (1:1): 0.99 (d, 3H, $-CH_3$); 1.5 (multiplate 9H); 3.0 (m, 2H, $-SCH_2-$); 3.9-4.1 (m, 2H, $-OCH_2-$).

^{13}C NMR (200MHz): 15.40 (q), 15.81 (q), 23.98 (t), 24.30 (t), 24.69 (t), 24.85 (t), 31.84 (t), 33.06 (t), 33.33 (t), 34.01 (t), 38.82 (t), 40.40 (t), 41.28 (t), 41.58 (d), 70.03 (t), 70.35 (t), 98.17 (s), 101.26 (s).

Mass (m/e): 172 (M^+, 30), 144 (8), 129 (50), 115 (90), 112 (48), 102 (15), 97 (15), 84 (30), 68 (45), 60 (52), 55 (100), 53 (18).

22a Camphor oxathiolane[13]



Mol. formula: $C_{12}H_{20}OS$. White solid

MP: 135°C

Yield: 72%

IR (neat, cm^{-1}): 550, 815, 850, 900, 1030, 1050, 1090, 1170, 1220, 1270, 1310, 1380, 1400, 1450, 2880, 2940.

^{1}H NMR (80MHz, $CDCl_3$, δ): 0.88 (s, 3H,- CH_3); 0.95 (s, 3H, -CH_3); 1.04 (s, 3H, -CH_3); 2.3 (m, 2H, -SCH_2-); 4.2 (m, 2H, -OCH_2-); 2.9 (m, 4H); 3.95 (m, 1H); 3.7 (m, 1H); 2.1 (m, 1H).

General procedure for the deprotection of oxathiolanes

To a solution of oxathiolane (1 eq, 10 mmol) in distilled acetonitrile was added 30% aq. H_2O_2 (1.5 eq) and the mix was heated at 80°-100° (bath temp) with stirring. Reaction was monitored by TLC by disappearance of starting oxathiolane (3-8 hrs). After completion of the reaction, solvent was evaporated under reduced pressure and the crude product ketone was purified by flash chromatography using pet ether-ethyl acetate as eluant to give the pure ketone in good yield.

Comparative study for deprotection of 3a p-nitrobenzaldehyde oxathiolane

(1) **$AgNO_3/I_2$ method** : A suspention of silver nitrate (0.160g,1.5eq) and iodine (0.170g,1eq) in aqueous tetrahydrofuran was stirred for half hour at room temperature. p-Nitrobenzaldehyde oxathiolane **(3a)** (0.138g) was added and the resulting mixture was stirred for additional 5hours at room temperature. A dilute sodium thiosulphate solution was added to the mixture at 0 C, followed by extraction with dichloromethane, washing with brine ,drying over anhydrous sodium sulphate , concetration in vacuo. Purification of the crude product by column chromatography (90 pet ether-10 ethyl acetate) gave **(3)** p-nitrobenzaldahyde in 70% yield.(0.70mg).

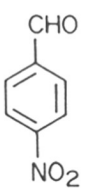
(2) **Cerric ammonium nitrate method** : To a suspention of **(3a)** p-nitrobenzaldehyde oxathiolane (0.100g) in aqueous acetonitrile was added cerric ammonium nitrate (CAN, 0.570g,2eq) at room temperature. Reaction mixture was stirred at room

temperature for 3 hours upon which decolorization was observed ,reaction was monitored by TLC. On completion of the reaction ,reaction mixture was passed thro' celite, concetrated in vacuo and the product was chromatographed to give (3) in 60% yield.(0.61mg).

(3) **Raney Nickel method** : A mixture of (3a) (0.110g) and Raney Nickel was refluxed in acetone. Progress of the reaction was monitored by TLC. After 3hours catalyst was filtered and solvent evaporation gave a mixture which contained very little p-nitrobenzaldehyde accompanied by other side products.

(4) **H_2O_2 method** : A mixture of **3a** p-nitrobenzaldehyde oxathiolane (0.130g 1eq) and 30% aqueous hydrogen peroxide(1.5eq) was refluxed in acetonitrile (5ml) for 2.5 hours. Reaction was monitored by TLC. After completion of the reaction solvent was removed under reduced pressure and product thus obtained was purified by column chromatography (90% pet ether-10%ethyl acetate) to furnish **3** p-nitrobenzaldehyde in 70%yield.(0.70mg)

3 **p-nitrobenzaldehyde**



Mol. formula: $C_7H_5NO_3$.

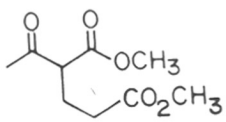
Yield: 70%

MP: 105 (Lit. 105-108°)

IR (nujol, cm^{-1}): 740, 820, 850, 1100, 1200, 1350, 1450, 1520, 1600, 1710, 2850, 3020.

^{1}H NMR (80MHz,$CDCl_3$, δ): 7.8 (m, 4H, aromatic); 9.8 (s, 1H, -CHO).

17 3-(methyl propionate)-methyl acetoacetate



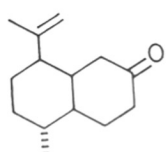
Mol. formula: $C_9H_{14}O_4$. colourless liq.

Yield: 56%

IR (neat, cm^{-1}): 550, 750, 980, 1020, 1050, 1180, 1200, 1250, 1350, 1450, 1720, 2850, 2960.

^{1}H NMR (200z,$CDCl_3$, δ): 2.0 (m, 2H, $-CH_2-$); 2.1 (s, 3H, $-CH_3$); 2.4 (t, 2H, $-CH_2-$); 3.5 (t, 1H, -CH-); 3.7 (s, 6H, $-OCH_3$).

18 1-methyl-4-propenyl-6-one decahydronaphthalene



Mol. formula: $C_{14}H_{22}O$. Colourless liq.

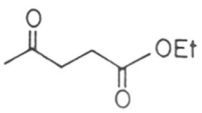
Yield: 81%

IR (neat, cm^{-1}): 900, 950, 1050, 1180, 1200, 1250, 150, 1450, 1650, 1710, 2850, 2980, 3020.

^{1}H NMR (200MHz,$CDCl_3$, δ): 1.0 (d, 3H,- CH_3); 1.5 (s, 3H, $-CH_3$); 1.7-2.5 (m, 14H); 4.8 (d, 2H, olefinic)

Mass (m/e): 206 (M^+, 15), 123 (30), 107 (35), 95 (18), 91 (25), 82 (20), 77 (50), 67 (47), 55 (100).

19 Ethyl levulinate



Mol. formula: $C_7H_{12}O_3$.

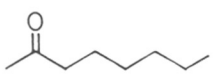
BP: 93-94/18 mm. (Lit. 94/18 mm)

Yield: 80%

IR (neat, cm^{-1}): 680, 750, 1220, 1420, 1710, 2890, 3020.

^1H NMR (80MHz,$CDCl_3$, δ): 1.0 (t, 3H, $-CH_3$); 2.0 (s, 3H, $-CH_3$); 2.4 (m, 4H, $-CH_2-CH_2-$); 3.7 (q, 2H, $-OCH_2$).

20 2-Octanone



Mol. formula: $C_8H_{16}O$.

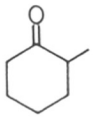
BP: 173° (Lit. 173°)

Yield: 52%

IR (neat, cm^{-1}): 780, 1180, 1220, 1380, 1450, 1700, 2800, 2850, 3020.

^1H NMR (80MHz,$CDCl_3$, δ): 0.99 (t, 3H, $-CH_3$); 1.5 (m, 8H, $-CH_2-CH_2-$); 2.0 (s, 3H, $-CH_3$); 2.2 (t, 2H, $-CH_2-$).

21 2-Methyl cyclohexanone



Mol. formula: $C_7H_{12}O$.

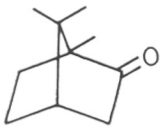
BP: 160° (Lit. 162-163°)

Yield: 66%

IR (neat, cm^{-1}): 720, 820, 860, 900, 980, 1000, 1060, 1080, 1125, 1220, 1320, 1420, 1450, 1710, 2850, 2980.

^1H NMR (80MHz,$CDCl_3$, δ): 1.1 (d, 3H, $-CH_3$); 1.3-1.8 (m, 9H).

22 Camphor



Mol. formula: $C_{10}H_{16}O$.

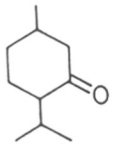
MP 176° (Lit. 178-180°)

Yield: 71%

IR (neat, cm^{-1}): 800, 1030, 1050, 1100, 1180, 1290, 1330, 1390, 1400, 1420, 1450, 1750, 2880, 2960.

^1H NMR (80MHz,$CDCl_3$, δ): 0.85 (s, 3H, $-CH_3$); 0.95 (s, 3H, $-CH_3$); 1.0 (s, 3H,-CH_3); 1.1-3.1 (multiplet 7H).

9 Menthone



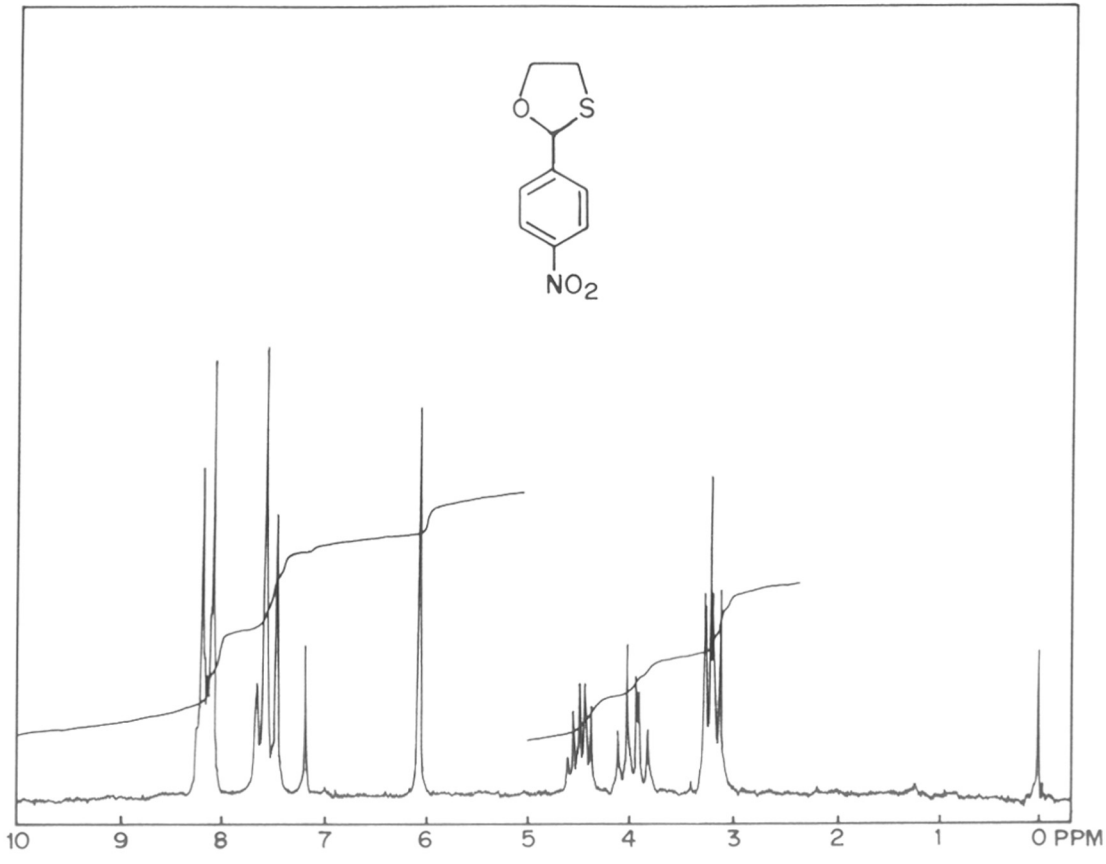
$C_8H_{18}O$

BP 208°C

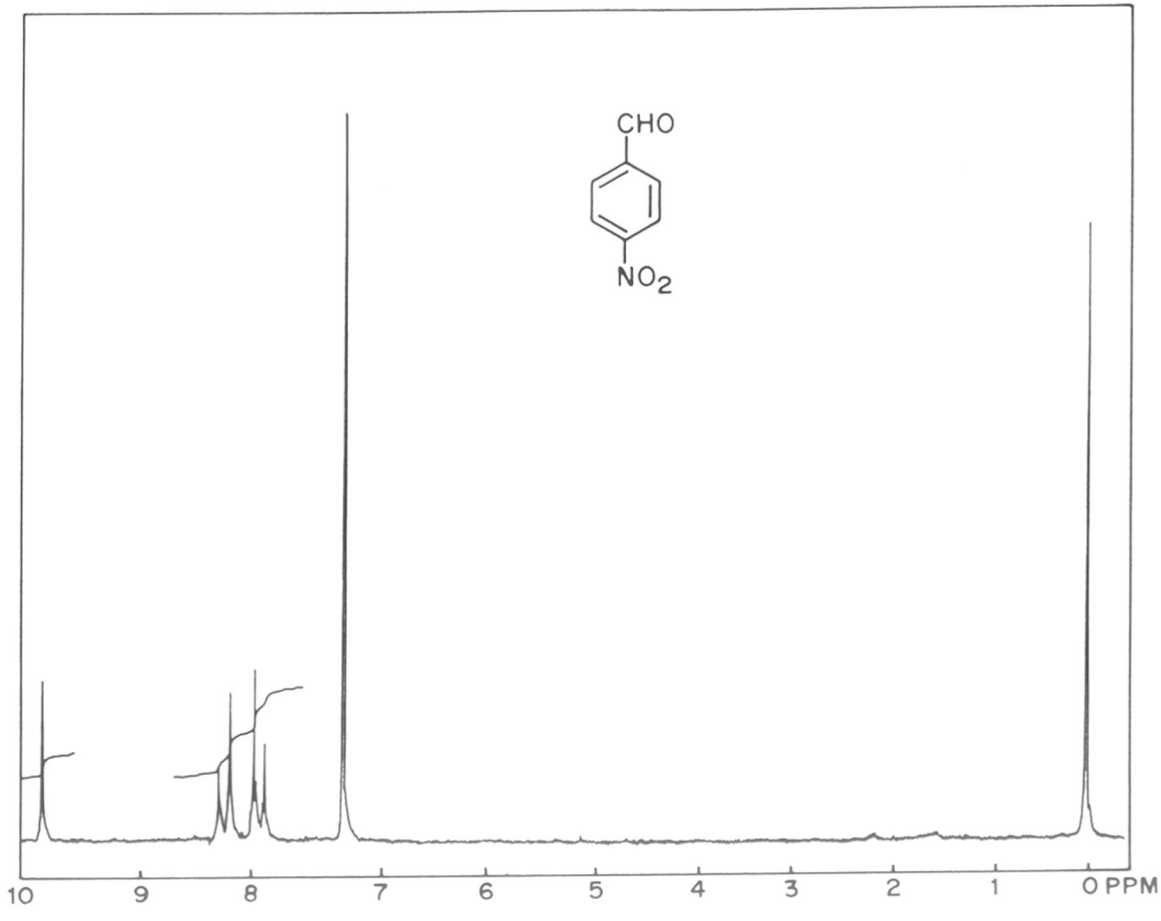
IR (smear, cm^{-1}): 600, 1220, 1370, 1470, 1720, 2880, 2960.

^1H NMR ($CDCl_3$, δ): 0.66 - 2.44 complex (18H)

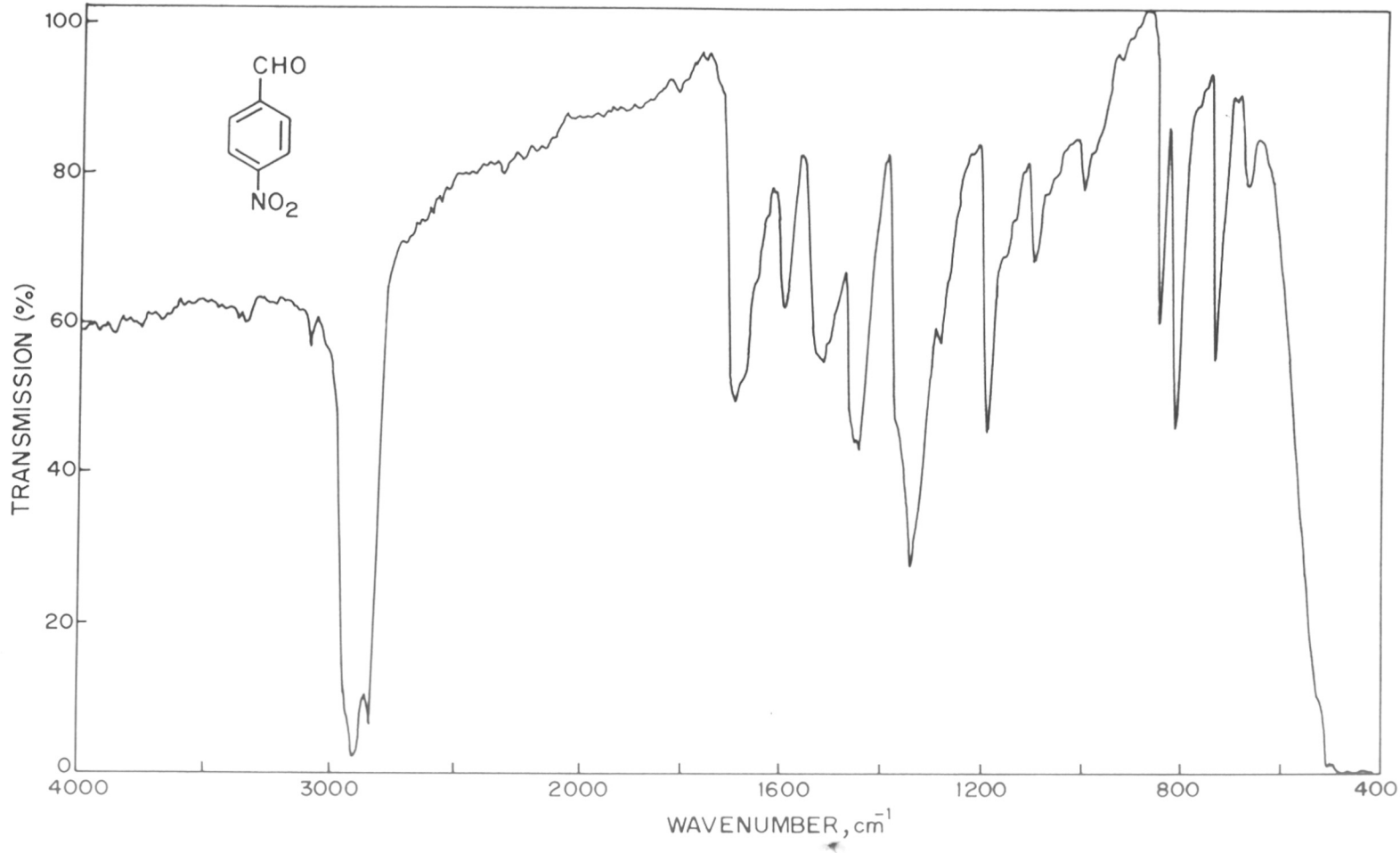
Mass (m/e): 154 (M^+, 46), 139 (68), 125 (16), 121 (5), 122 (100), 97 (15), 83 (8), 69 (5).



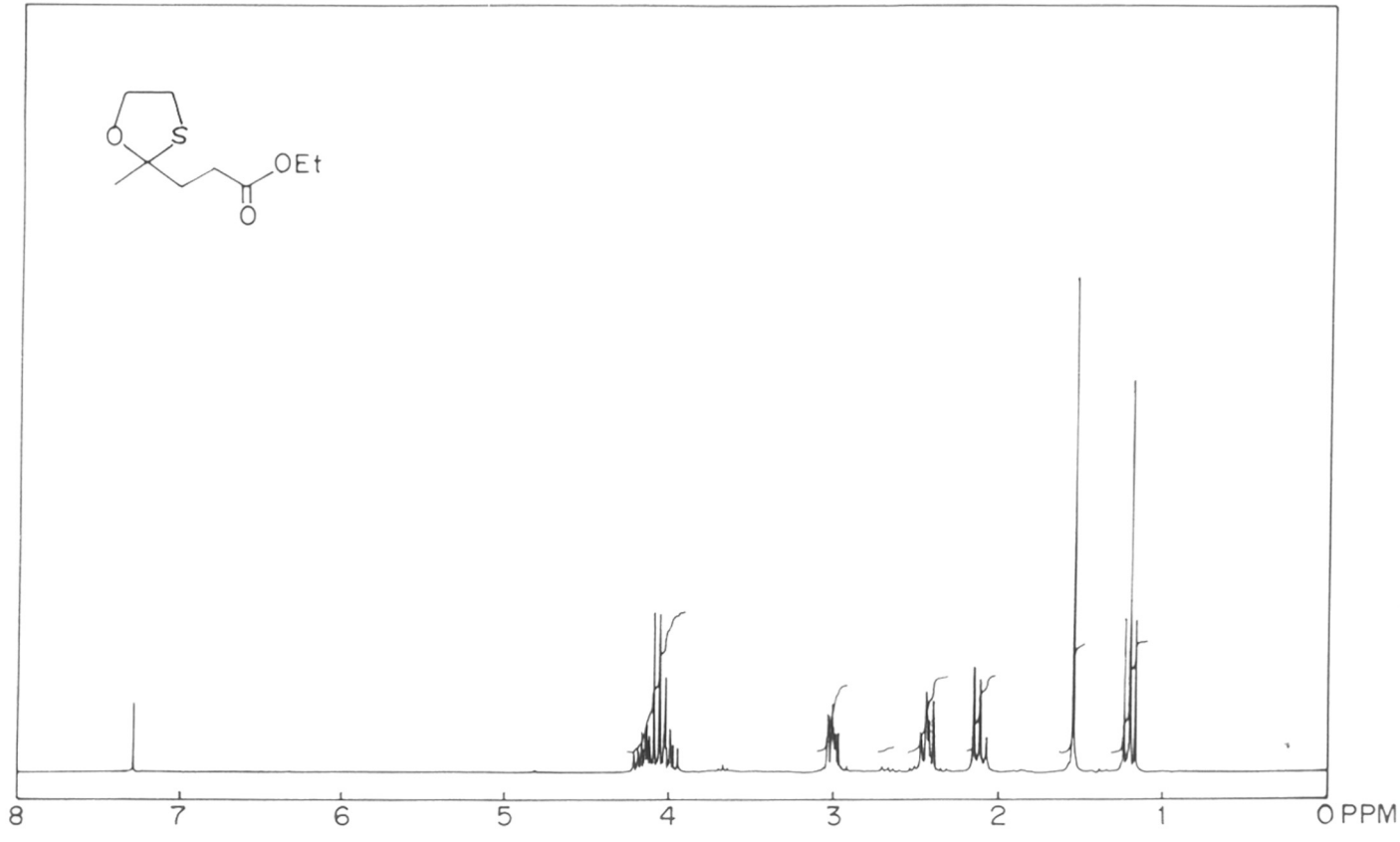
^{1}H-NMR SPECTRUM OF **3a** (80 MHz, $CDCl_3$)



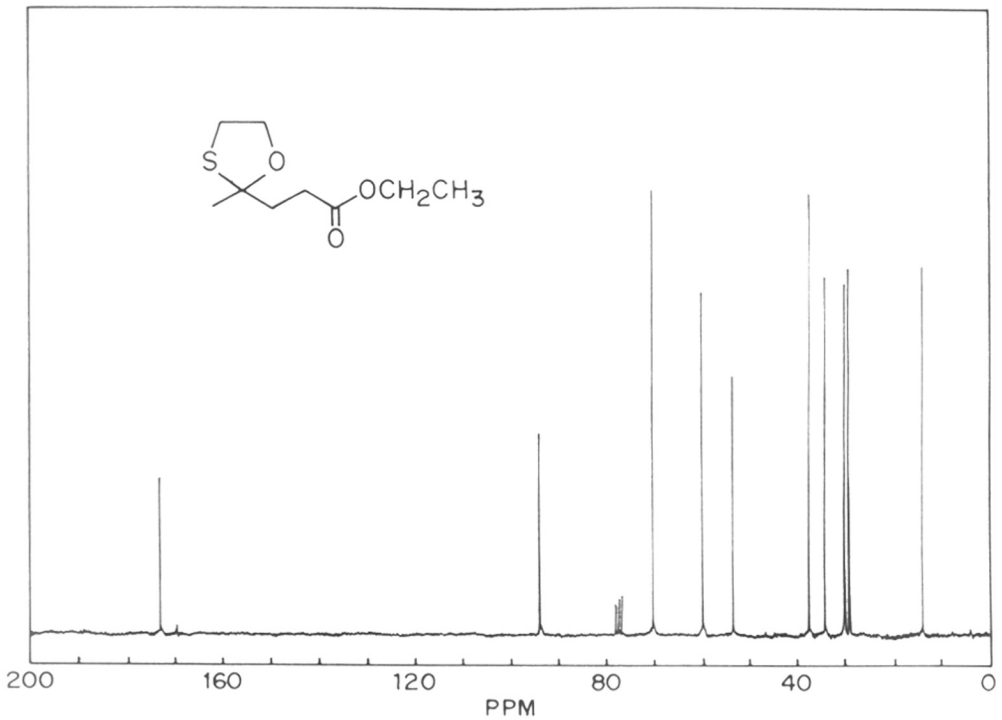
^{1}H-NMR SPECTRUM OF **3** (80 MHz, $CDCl_3$)

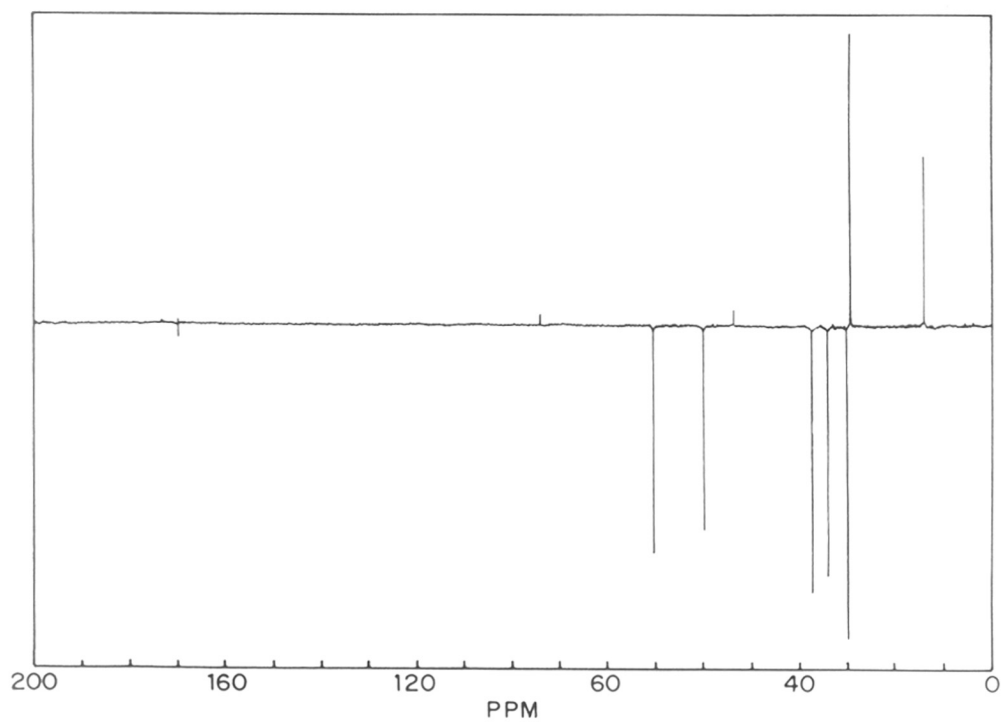


IR SPECTRA OF 3 (NUJOL)

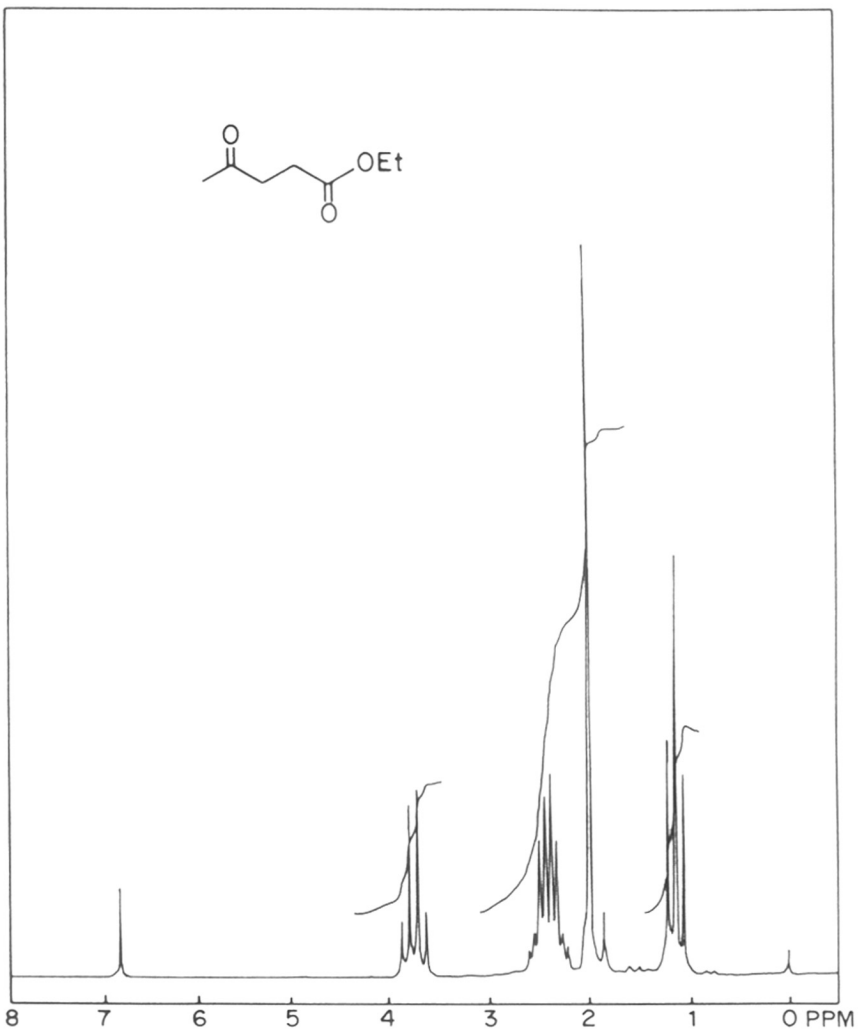


^{1}H-NMR SPECTRUM OF **19a** (200 MHz, $CDCl_3$)





^{13}C-NMR SPECTRUM OF **19a** (200 MHz, $CDCl_3$)



^{1}H-NMR SPECTRUM OF **19** (80 MHz, $CDCl_3$)

2.2.5 *References*

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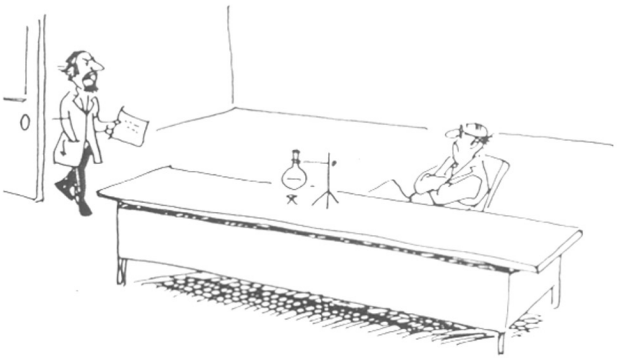
CHAPTER - 3

Synthetic Applications Of Solid Superacids



A further cut in the research funds, Professor; because we have not shown much in the way of results.

Part - I Transesterification Of Ketoesters

3.1.0 *Solid Superacid Catalysts : Introduction*

Solid acids have been extensively studied and used as catalysts or catalyst carriers in chemical industry, particularly in the petroleum field for many years. Many kinds of solid acids, have been found, their acidic properties on catalyst surfaces and their catalytic action and the structure of acid sites have been elucidated for last 30 yrs.[1] Among a large number of solid acids, catalysts with fairly high surface acidity, stronger than Ho = -8.2, are the binary oxides of SiO_2-Al_2O_3, TiO_2-ZrO_2, SiO_2-TiO_2 and SiO_2-ZrO_2; in particular SiO_2-Al_2O_3 bears strong acid sites on its surface and has been used in various organic reactions.

The preparation and use of strong solid acids and superacids are active areas of research for isomerization, cracking, hydrocracking, dehydration, alkylation, acylation, converting methanol to gasoline etc. Because of the reported advantages of solid catalysts, recent research has focused on the preparation and characterization of stronger solid acids. Replacement of homogeneous liquid acids by heterogeneous solid acids as catalysts in the chemical industry is expected to bring about the ease of separation from the reaction mixture, which allowed continuous operation, as well as regeneration and reutilization of the catalyst. Furthermore, use of heterogeneous solid catalysts can lead to additional advantages e.g. no corrosion of the reactor, and no environmental problem in the disposal of the used catalyst.

According to Gillespie's definition any acid may be termed as superacid, when its acidity is stronger than that of 100% H_2SO_4 i.e, Ho $\leq$ -12. Such a superacidity has been reached by a number of systems which are generally made up by mixing a fluorine containing Bronsted acid (HF, HSO_3F, CF_3SO_3H etc) and a fluorinated Lewis acid. (BF_3, SbF_5, TaF_5 etc). The acid strength of a solid is defined as the ability of the surface to convert an adsorbed neutral base into its conjugate acid. The most simple and useful way to estimate the acidity of a solid catalyst is to test its catalytic activity in

well-known acid-catalyzed reactions, usually comparing the activity with that of SiO_2-Al_2O_3.

Novel organic synthesis that are not possible in the usual acidic media can be accomplished in superacids, including syntheses of economically important hydrocarbons. The remarkable ability of superacids to bring about hydrocarbon transformations has opened up a new field in chemistry. Homogeneous acidic media are widely used for organic reactions for instance the acylation reaction using $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, CF_3SO_3H, H_2SO_4. However, they have several disadvantages if applied to industrial processes, wasting large amounts of catalysts, corrosion of reactors, water pollution by acidic waste and difficulty in catalyst recovery. In order to overcome these difficulties of the homogeneous systems, the development and utilization of a solid acid catalyst, specifically a "Solid Superacid Catalyst" is quite appropriate to replace homogeneous acid catalysts.[2,3]

3.1.1 *Types Of Solid Superacids*:

In the last decade, several types of solid superacids were developed and applied to catalytic reactions. They are

1. *Mounted Acid*: A mounted acid which was obtained by the fixation of a liquid acid such as SbF_3, BF_3, SbF_5-CF_3SO_3H on supports of high surface area such as porous oxides (SiO_2, SiO_2-Al_2O_3), graphite ion exchange resin. Mounted acid type catalyst is the first generation of solid superacid.

   Catalytic reactions attempted are isomerization of alkane, alkylation and transalkylation, oligomerization, and polymerization, carbonylation.[4]

   The major drawback in the extended use of this catalyst system is its relatively short lifetime and ease of deactivation.

2. *Combined acid*: This acid includes the combined system of aluminium halide with metal salts such as $CuCl_2$, $CuSO_4$ etc and with sulfonic acid and resin and is used for the isomerization of alkanes.[5] Mixtures of aluminium halides with metal salts such as $AlCl_3$ -$Ti(SO_4)_3$, $AlCl_3$-$CuSO_4$, $AlCl_3$-$CuCl_2$ are active for the isomerization of paraffins at room temperature.[5]

3. *Sulfate promoted metal oxides*: A new type of solid acid that is promoted by a sulfate ion, such as SO_4^{2-}/ZnO_2, SO_4^{2-}/TiO_2 and SO_4^{2-}/SnO_2, SO_4^{2-}/Fe_2O_3 are used as powerful catalyst for various acid-catalysed reactions such as the skeletal isomerization of butane to isobutane, acylation of benzene derivatives by acyl chloride and the ring opening isomerization of cyclopropane.[6] It was pointed out that the existence of covalent S=O bonds in sulfur complexes formed on metal oxides was necessary for the generation of acidity.

4. *Nafion-H*: Nafion-H is shown to be useful and versatile catalyst for organic reactions.[7] Nafion resins are co-polymers of tetra-fluoro-ethylene and monomers such as perfluoro-3,6-dioxo-4 methyl-7-octensulfonic acid and were first synthesised by DuPont chemists. It is effective in a wide range of liquid and gas-phase reactions including dehydration of alcohols, rearrangements, electrophilic substitutions on aromatic nuclei, polymerization, esterification, disproportionation. It had been found that no reactivation of the catalyst was needed because the catalytic activity of the Nafion remained unchanged for prolonged periods of operation.

5. *Zeolites (e.g. ZSM-5)*: Zeolites are porous crystalline aluminosilicates with Si^{IV} and Al^{III} tetrahedrally surrounded by oxygen.[8] The unique characteristics of their aluminosilicate frame work and the present well defined channel systems in the zeolites have made possible a variety of industrial application in adsorption, ion exchange and catalysis. The combination of the acidity and the shape selec-

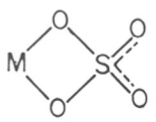
tivity in zeolite catalysts can be advantageously used in the synthesis of organic intermediates[9]. Present day main applications of synthetic zeolites include their use as cation exchangers in detergent formulations, as selective adsorbents in drying and separations and as catalysts in the process industry.

3.1.2 *Sulfate Promoted Metal Oxides : $SO_4^{=}/SnO_2$.*

Sulfated tin oxide: It is known that sulfur treatment of catalysts changes the catalytic behaviour significantly.[10] Arata[11] and Wang *et al* have reported that solid superacid catalysts with an acid strength of upto $H_O \leq -16.04$ were obtained by exposing hydroxides or oxides of iron, titanium, zirconium,. hafnium, tin, prior to the crystallization to sulfate ion followed by calcination in air at over 773K. Tanabe *et al*[12] studied in detail the catalytic action and properties of metal sulfates, most of the sulfates showed the maximum acidity and activity by calcination at temperatures below 500°C, with respect to the surface acidity and the acid catalysed reaction. The sulfate ion can be introduced from H_2SO_4, ammonium sulfate $[(NH_4)_2SO_4]$, SO_2, SO_3 and H_2S. The covalent S=O bonds in sulfur complexes formed on metal oxides are necessary for the acidity.

The sulfate ion treatment was effective for increasing the catalytic activity of SnO_2.

Infrared spectra showed the SO_4^{2-}/SnO_2 catalysts to possess a bidentate sulfate ion co-ordinated to the metal 987, 1041, 1153 and 1211 cm^{-1}.



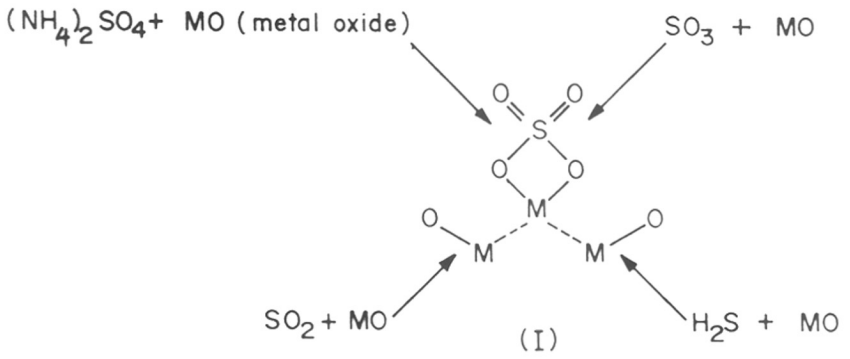
1230-1240 cm^{-1}

1090-1125 cm^{-1}

995-1035 cm^{-1}

940- 960 cm^{-1}

A comparison of experimentally obtained spectra of sulfur promoted oxides with the reported S-O stretching frequencies shows that the structure of the catalytically active species or of the species responsible for giving highly acidic properties involves inorganic sulfate structure with a metal cation which acts as a Lewis acid.



(I)

The surface sulfur complex in highly acidic catalyst has a strong tendency to reduce the bond order of S-O from a highly covalent double-bond character to a lesser double bond character when a basic molecule is adsorbed on its central metal cation. The strong ability of the sulfur complex with structure (I) to accomodate electrons from a basic molecule is a driving force in the generation of highly acidic properties.

Sulfated tin oxide can be prepared by treating tin oxide with H_2SO_4, ammonium sulfate or H_2S and then calcinating in air at about 500K. The catalyst thus formed is found to be active for various reactions, such as skeletal isomerization of butane to isobutane at room temperature,[13] and catalysed hydration of ethane, the decomposition of cyclohexanol, Friedel Crafts alkylation acylation etc.

3.1.3 *Transesterification: Introduction*

Transesterification is one of the classic organic reaction of wide industrial application and synthetic utility in a particular reaction sequence. Organic chemists very often use this reaction for preparation of esters.

Transterification is a process where an ester is transformed into another through interchange of the alkoxy moiety. Since the reaction is an equilibrium process, the transformation occurs essentially by mixing the two components.[14] However, the reaction is accelerated by acid or base catalysts.

Many times, transesterification is more advantageous than the ester synthesis from carboxylic acids and alcohols. For instance, some carboxylic acids are sparingly soluble in organic solvents and accordingly difficult to subject to homogeneous esterification whereas esters are commonly soluble in most of organic solvents. The ester to ester transformation is particularly useful when the parent carboxylic acids are labile and difficult to isolate. Some esters, especially methyl and ethyl esters are readily or commercially available and thus they serve conveniently as starting materials in transesterification. Transesterification can be conducted under anhydrous conditions to allow use of moisture-sensitive materials.

Transesterification is applicable not only to pure organic synthesis, but also to polymerization. Besides the laboratory utilization transesterification has a long history in industry as well as production of esters of oils and fats, in paint industry. Due to the wide applicability of this reaction there are constant efforts made for discovery of new catalyst. More emphasis is focused on those catalysts which have enabled transesterification to be highly efficient, chemo-, stereo- and regioselective.

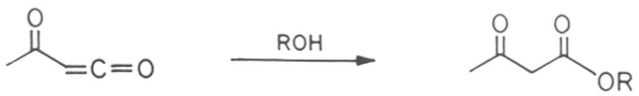
3.1.4 *Transesterification Of ß-Ketoesters*:

ß-Ketoesters serve as important synthons in organic chemistry. They can be easily transformed to chiral building blocks by chemical and enzymatic transformations. These acetoacetylated materials are of interest as chemical intermediates in the pharmaceutical, agrochemical, chemical and polymer industries.

Transesterification reaction is of great importance in producing a variety of ß-ketoester/acetoacetate, useful chemical intermediates, which can be obtained from storable and easily available materials.

The alternative process of getting ß-ketoesters is alcoholysis of acetylketenes, the use of which is avoided due to their lachrymatory and toxic properties as well as shipping problem (Scheme-1).

SCHEME-1



Ref : Chem. Rev. (1986),86, 241

Diketene (4-methyleneoxetan-2-one) is a reactive and versatile compound which is used for the introduction of functionalized C_2, C_3 and C_4 units into organic compounds, although it is best known as a reagent for the preparation of acetoacetic acid derivatives.[15] Diketene is most commonly used for the preparation of acetoacetate esters and acetoacetamides, which are important synthetic intermediates used in the agrochemical, pharmaceutical and dyestuff industries. Because it is inexpensive and highly reactive, diketene is frequently the reagent of choice for acetoacetylations on both laboratory and industrial scale.

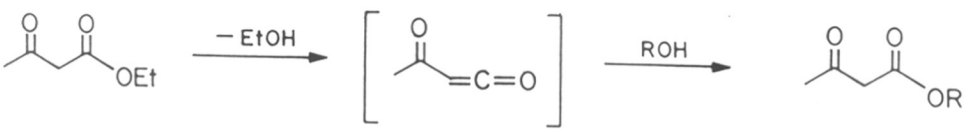
However, use of diketene is avoided due to its lacrymatroy and toxic properties

and shipping problems. Diketene can cause eye injury or burns to the skin or respiratory tract. In liquid state diketene undergoes gradual discoloration and decomposition. Because diketene liberates carbon dioxide during its decomposition, it should not be stored in glass bottles. Reactions of diketene are often extremely exothermic, and diketene rapidly self condenses in presence of both acidic and basic catalysts thus making it unattractive as starting material for the preparation of ß-keto esters on a laboratory scale.

The "diketene-free" approach to the preparation of acetoacetates involves the transesterification of the corresponding nucleophile with an appropriate acetoacetate (transesterification). This approach appeared worthy of attention since it should be readily amenable to industrial application.

Carroll[16a] and Bader *et al*[16b] independently found that ß-ketoesters were transesterified by heating the esters and alcohols in the absence of catalysts. However ß-ketoester was used in large excess and also reaction time was more. The proposed reaction mechanism assumed to have acyl ketone intermediate (Scheme-2). The dialkylation at the 2-position of acetoacetates retarded the reaction, while the reaction occurred with monoalkylated acetoacetates, implicating an active hydrogen to be a prerequisite for the reaction. These problems have been partially solved by Otera *et al*[17], who were able to achive transesterification of non-enolizable ß-ketoesters under practically neutral conditions under the catalysis of 1,3-disubsituted tetrabutylstannoxanes. (Scheme-3)

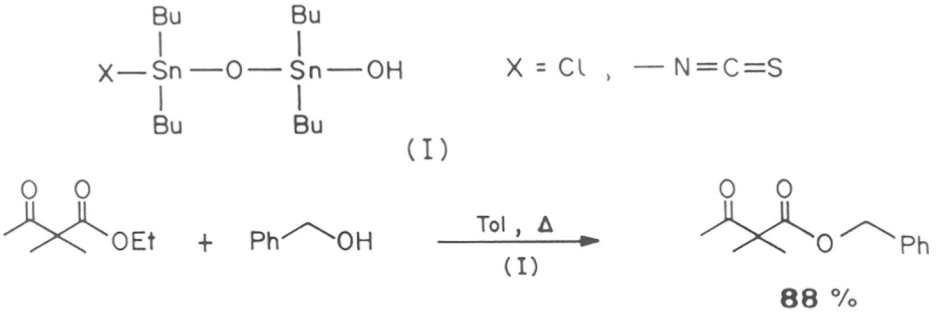
SCHEME-2



acyl ketene

Ref : J. Am chem. soc. (1951), 73 , 4195

SCHEME-3



Ref : Tet Lett (1986), 27, 2383

Recently Witzeman *et al*[18] have reported a very convenient and efficient method for transesterifiction. The tert-butyl and tert-amylacetoacetates reacted 15-20 fold faster than other less sterically hindered esters. These findings allowed to utilize commercially available tert-butyl acetoacetate as versatile acetoacetylating reagent[18]. In a typical reaction (Scheme-4), the tert-butyl acetoacetate and equimolar amount of alcohol were heated at 100-150°C in toluene or xylene in absence of catalyst to yield a variety of acetoacetates.

SCHEME-4

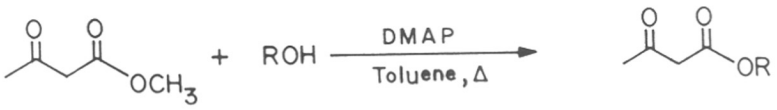
Ref : J. Org. chem (1991) 56, 1713

This methodology being mild allowed the usage of allyl alcohols which were not previously possible.

However, this reaction is limited to the use of tert butyl acetoacetate as starting material and hence lacks generality.

Taber[19] *et al* found that methylacetoacetate (excess) were more smoothly transesterified with primary or secondary alcohols in the presence of 4-dimethylamino pyridine (DMAP) in toluene at reflux. (Scheme-5).

SCHEME-5

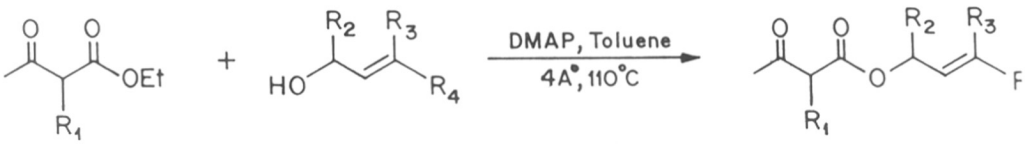


Ref : J. Org. Chem (1985), 50, 3612

The reaction eventhough workable for a variety of alcohols was inert for unenolizable ß-ketoacetoacetate. Also tertiary alcohols were not effective for transesterification.

Gilbert[20] used DMAP for the preparation of allylacetoacetates which are rather difficult to prepare because of facile decarboxylative rearrangement. The modified DMAP method was used for transesterification (Scheme-6).

SCHEME-6



Ref : J. Org. Chem. (1988), 53, 449

Ethanol formed was removed by molecular sieves (4A°) and the equilibrium thus shifted in favour of the allylic ester. Allylalcohol itself did not react, because it was small enough to be absorbed by the molecular sieves. However, this problem was solved by using methylacetoacetate and (3Å) molecular sieves. Secondary and tertiary

alcohols were unreactive and nonenolizable ketoesters failed to react.

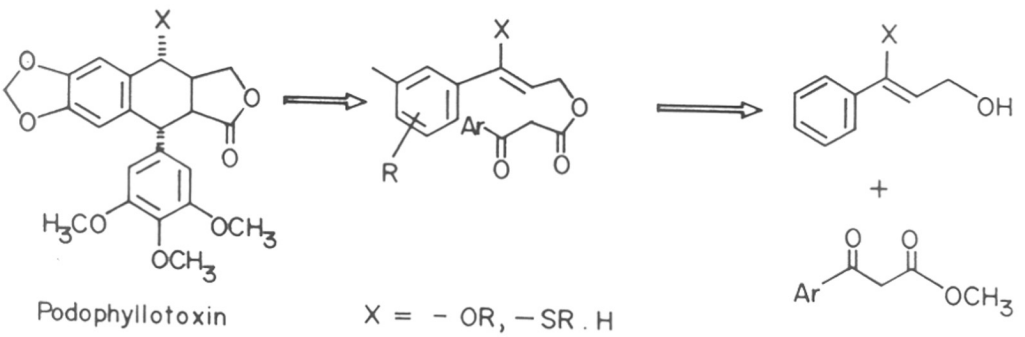
Present literature search reveals that the utility of transesterification in large scale and/or industrial processes has been limited by the long reaction times, excess reagents, dilute solutions, large amount of toxic & expensive DMAP catalyst required.

3.1.5 *Present Work*:

ß-Ketoesters serve as important synthons by virtue of the ease with which they can be transformed to chiral building blocks by chemical and enzymatic transformations as well as tool for chain extension reactions. As a consequence of their importance, interconversion to different esters has received considerable attention.[14, 17c]

In connection with total synthesis of biologically active compounds, podophyllotoxin, we wanted to effect transesterification of ß-ketoester as indicated in Scheme-7.

SCHEME -7



Although quite a few methods are reported for transesterification they are not general as far as ß-ketoesters are concerned. Normal methods of transesterification are equilibrium driven reactions, wherein excess of reactants is required. Although, DMAP catalysed transesterification of ß-ketoesters has been reported recently, this method makes

use of toxic and expensive DMAP in relatively large amounts (30 mole %) in addition to excess usage of ß-keto ester and the reaction is performed at elevated temperature for extended period of time.

It was, therefore, felt necessary to develop a suitable methodology for interconversion of readily available esters by transesterification. Solid superacids by virtue of heterogeneous catalysis are widely employed in petrochemical industries, however, their potential has not been fully exploited by the synthetic organic chemists.

It was therefore, felt necessary to explore solid superacids as the catalyst in transesterification reactions. It may be pointed out that solid superacids have not been employed to effect transesterification.

One to one exchange of ß-ketoesters was achieved in good to excellent yields using sulfated tin oxide ($S.SnO_2$) as solid superacid catalyst (Scheme-8).

SCHEME-8

R = Et , Me

R = Primary , secendary , tertiary , allyl alcohol.

The generality and scope of the reaction is discussed.

3.1.6 *Results And Discussion*:

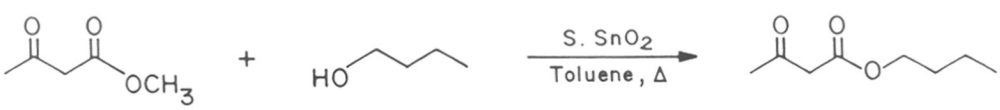
A variety of ß-ketoesters when treated with an equivalent amount of alcohol in presence of catalytic (10% by wt.) sulfated tin oxide in refluxing toluene gave the

corresponding transesterified esters in good to excellent yield. Thus one to one exchange of ß-ketoesters can be achieved in good to excellent yields using solid superacid namely sulfated tin oxide. This aspect is very important when either the ketoester or alcohol is precious.

It is well established[11] that the sulfate treatment of metal oxides is necessary in the making of solid superacids which are found to be effective for a number of reactions. A solid superacid catalyst with an acid strength of Ho $\leq$ -16.04 was synthesized from tin hydroxide which was obtained from the solution of pH 10, by exposing to 3M H_2SO_4, followed by calcination at air at 623K to give the catalyst SO_4^{--}/SnO_2. IR spectra showed the catalyst to possess a bidentate sulfate ion coordinated to the metal.

Sulfated tin oxide was found to be an efficient catalyst for transesterification of ß-ketoesters. In a typical reaction equivalent amount of methylacetoacetate and n-butyl alcohol (Scheme-9) and sulfated tin oxide (10% by wt.) were refluxed in toluene with stirring. The low boiling alcohol (methanol) thus formed was removed by distillation, to give the transesterified ester in 97% yield, as viscous oil.

SCHEME - 9



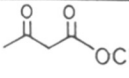
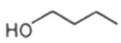
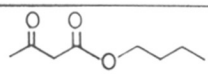
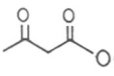
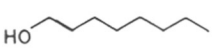
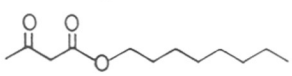
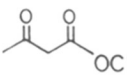
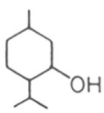
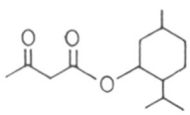
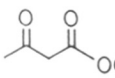
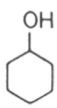
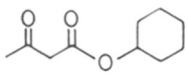
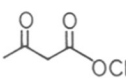
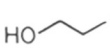
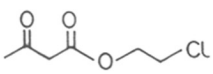
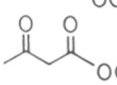
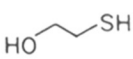
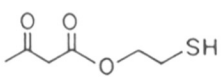
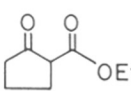
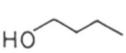
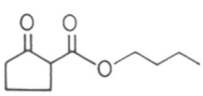
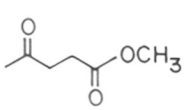
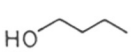
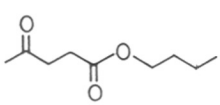
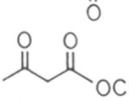
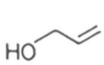
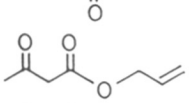
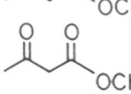
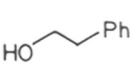
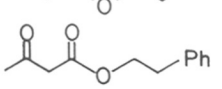
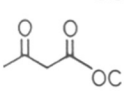
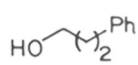
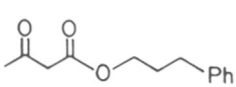
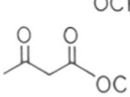
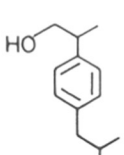
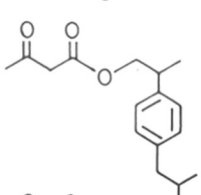
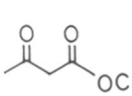
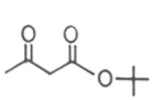
The transesterified ester thus formed was characterized by IR, ^{1}H-NMR and mass spectroscopy. ^{1}H-NMR showed absence of singlet at 3.8 δ for -OCH_3 and presence of triplet at 4.1 δ for -OCH_2, multiplet at 1.3 - 1.5 δ for -CH_2-CH_2 and triplet

at 0.93 δ for $-CH_3$.

This methodology of transesterification was found to be effective for various alcohols which included primary, secondary, tertiary and allyl alcohols. The most important point of this methodology is that even tertiary butylesters can be prepared which are otherwise difficult to prepare, where other known methods of transesterification fail.

The starting ß-ketoester used was the commercially and easily available methylacetoacetate or ethylacetoacetate. Even γ-keto ester *viz.* methyl levulinate was also used for transesterification. However, the yields obtained in the transesterification were much lower as compared to ß-ketoester. Transesterification of -ketoesters in addition to efficient transformation of ketoester such as that the role of a carbonyl group in enhancing the reactivity of the ester by chelation with the metal oxide in crucial for the success of the reaction. The alcohols used were primary, secondary alcohols such as n-butyl alcohol, n-octyl alcohol, cyclohexanol, chlorohydrin, tertiary alcohol and allyl alcohol. Even chiral alcohol such as menthol was also used. All the transesterified esters thus formed were purified either by distillation or flash column chromatography. The esters were characterized by spectral analysis such as IR, ^{1}H-NMR and mass spectroscopy. Results are summarized in table-I.

TABLE - I

ENTRY	KETOESTER	ALCOHOL	TIME (hr)	PRODUCT	% YIELD
1			6		97
2			7		89
3			6		91
4			7		84
5			6		92
6			8		82
7			7		63
8			10		45
9			8		65
10			6		97
11			6		100
12			8		65
13			12		50

3.1.7 *Conclusion:*

1. One to one exchange of ß-ketoesters and alcohols was achieved in the presence of catalytic amount of solid superacid namely sulfated tin oxide. This aspect is important when either the ß-ketoester or alcohol is precious. It is in sharp contrast with the conventional transesterification reaction which is equilibrium driven reaction where excess of either of the reactants is required to shift the equilibrium to the desired direction.
2. A variety of primary, secondary and even tertiary and allyl alcohols were used for transesterification. Even tertiary esters can be formed which are otherwise difficult to make by other methods. Similarly, allyl alcohols were also used for facile transesterification.
3. First time solid superacids were used for the trans-esterification of ß-ketoesters; as heterogeneous catalyst, which can be recovered and recycled after use.
4. The ß-ketoesters used were commercially available methylacetoacetate; even other ketoesters can be transesterified. The mildness of the present methodology manifests in selective transesterification of keto esters where as normal esters remains unaffected. Superiority of the current protocol over the existing methods is evident by short reaction time and high yields.

3.1.8 *Experimental*

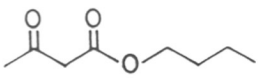
General Procedure for the preparation of catalyst (Sulfated SnO_2)

22.56 gm of stannous chloride was dissolved in 200 ml deionised water to get a clear solution. 25 ml of aqueous ammonium hydroxide solution was added to this solution under constant stirring until pH of 8. The yellowish precipitate thus obtained was washed well with deionised water, dried at 110° for 12 hours to get stannous hydroxide (18gm). 5gm of the dry hydroxide powder was then equilibrated with 25 ml of 2N H_2SO_4 for 2 hour and then it was evaporated to dryness, calcinated at 500° for 4 hour to get the catalyst of the final form.

General Procedure for transesterification

A mixture of keto ester (1 eq), alcohol (1 eq), and the catalyst (100 mg, 10% by weight) in toluene (20 ml) was heated to 110°C in a two-necked round bottom flask provided with a distillation condensor to remove the methanol. The reaction was followed by T.L.C. After completion of the reaction (ca 6 hr), the catalyst was filtered and the filtrate was concentrated and chromatographed (SiO_2) using pet ether-ethyl acetate (95:5) to afford the ester as a viscous colourless liquid in excellent yields.

(1) n-butyl acetoacetate[31]



Mol. formula: $C_8H_{14}O_3$ (158). Colourless liq.

BP: 55/01. mm (Lit [31] 55/0.1 mm)

Yield: 97%

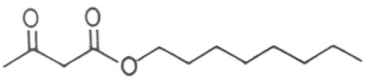
IR (neat, cm^{-1}): 750, 820, 950, 1020, 1050, 1150, 1180, 1250, 1320, 1350, 1420, 1650, 1730, 1750, 2950, 2980

^1H NMR (200MHz,$CDCl_3$, δ): 0.9 (t, 3H, $-CH_3$); 1.35 (m, 2H, $-CH_2-$); 1.6 (m, 2H, $-CH_2-$); 2.25 (s, 3H,$-CH_3$); 3.4 (s, 2H, $-CH_2-$); 4.1 (t, 2H, $-OCH_2-$).

^{13}C NMR (200MHz): 13.54 (q), 18.99 (t), 21.00 (t), 29.96 (q), 30.6 (t), 50.00 (t), 65.09 (t), 167.1 (s), 200.5 (s).

Mass (m/e): 158 (M^+), 103 (100), 85, 70, 56, 43.

(2) n-octyl acetoacetate[15b]



Mol. formula: $C_{12}H_{22}O_2$ (214). Colourless liq.

BP: 102/0.9 mm (Lit[15b] 100/0.9 mm).

Yield: 89%

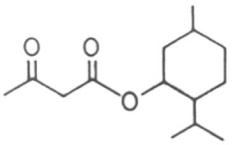
IR (neat, cm^{-1}): 1020, 1150, 1220, 1300, 1350, 1400, 1450, 1650, 1720, 1750, 2850, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 0.90 (t, 3H, $-CH_3$); 1.3 (m, 10H, $-CH_2-$); 1.6 (t, 2H, $-CH_2-$); 2.6 (s, 2H,$-CH_3$); 3.4 (s, 2H, $-CH_2-$); 4.1 (t, 2H, $-OCH_2-$).

^{13}C NMR(200MHz): 13.71 (q), 22.36 (t), 25.59 (t), 28.29 (t), 28.92 (t), 29.51 (q), 31.53 (t), 49.63 (t), 63.66 (t), 64.94 (t), 166.87 (s), 199.98 (s).

Mass (m/e): 214 (M^+), 149, 131, 107, 91, 57, 43 (100).

(3) Menthyl acetoacetate[17]



Mol. formula: $C_{14}H_{24}O_3$ (240). Viscous liq.

Yield: 91%

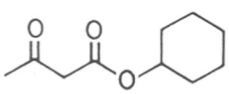
IR (neat, cm^{-1}): 850, 900, 950, 980, 1020, 1080, 1120, 1240, 1300, 1350, 1400, 1450, 1650, 1700, 1740, 2820, 2980.

^1H NMR (200MHz,$CDCl_3$, δ): 0.80 (d, 3H,- CH_3); 1.1 (d, 6H, -CH_3); 1.2 (m, 4H, -CH_2-); 1.35 (m, 2H, -CH_2-); 1.55-1.85 (m, 3H); 2.3 (s, 3H,); 3.5 (s, 2H, -CH_2-); 4.7 (dt,J= 4.4 & 10.9 1H, -OCH-).

^{13}C NMR (200MHz): 16.16 (q), 16.44 (q), 20.69 (q), 21.07 (q), 21.94 (q), 23.35 (t), 23.60 (t), 26.12 (t), 26.32 (t), 29.91 (q), 31.38 (q), 34.18 (t), 40.11 (t), 41.0 (t), 46.87 (d), 47.07 (d), 50.41 (t), 73.60 (d), 75.31 (d), 89.98 (d), 166.66 (s), 200.4 (s).

Mass (m/e): 240 (M^+), 138, 123, 103, 95, 85, 43.

(4) Cyclohexyl acetoacetate[15b]



Mol. formula: $C_{10}H_{16}O_3$. Colourless liq.

BP: 133/16 mm (lit. 131°C/16 mm)

Yield: 84%

IR (neat, cm^{-1}): 650, 700, 780, 850, 920, 1020, 1050, 1180, 1250, 1350, 1420, 1560,

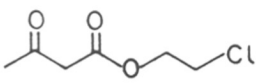
1650, 1720, 1750, 2980, 3010.

^{1}H NMR (200MHz,$CDCl_3$, δ): 1.35 (m, 6H, $-CH_2-$); 1.70 (m, 2H, $-CH_2-CH$); 1.8 (m, 2H, $-CH_2-CH$); 2.4 (s, 3H, $-CH_3$); 3.4 (s, 2H, $-OCH_2-$); 4.8 (m, 1H, -CH-O).

^{13}C NMR (200MHz): 23.20 (t), 24.94 (t), 29.41 (q), 31.03 (t), 31.27 (t), 49.91 (t), 71.70 (t), 73.06 (d), 166.17 (2), 200.13 (s).

Mass (m/e): 184 (M^+),103 (100), 99(30), 85(50), 67(55), 55(50), 43(80).

(5) 2-Chloroethyl acetoacetate[32]



Mol. formula: $C_6H_9O_3Cl$. Colourless liq.

Yield: 92%

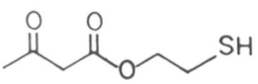
IR (neat, cm^{-1}): 650, 780, 1020, 1150, 1250, 1320, 1350, 1420, 1450, 1650, 1720, 1750, 2950.

^{1}H NMR (200MHz,$CDCl_3$, δ): 2.1 (s, 3H,$-CH_3$); 3.4 (s, 2H, $-CH_2Cl$); 3.6 (t, 2H, $-CH_2-$); 4.3 (t, 2H, $-OCH_2-$).

^{13}C NMR(200 MHz): 30.1 (q), 41.44 (t), 49.80 (t), 52.34 (t), 64.82 (t), 166.85 (s), 200.22 (s).

Mass (m/e): 200, 164 (10), 129, 115, 102(25), 85 (100), 69(60), 63(80).

(6) 2-Mercaptoethyl acetoacetate[33]



Mol. formula: $C_6H_{10}O_3S$ (162). Colourless liq.

Yield: 85%

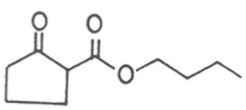
IR (neat, cm^{-1}): 1020, 1150, 1250, 1300, 1350, 1400, 1600, 1710, 1740

^1H NMR (200MHz,$CDCl_3$, δ): 1.5 (t, -SH); 2.25 (s, 3H, $-CH_3$); 2.7 (dt, 2H, $-CH_2SH$); 3.5 (s, 2H, $-CH_2-$); 4.3 (t, 2H, $-OCH_2-$).

^{13}C NMR(200MHz): 21.02 (t), 22.09 (t), 23.11 (t), 30.32 (q), 49.65 (t), 65.03 (t), 66.26 (t), 166.68 (s), 200.38 (s).

Mass (m/e): 162 (M^+), 139, 103, 85, 60, 43.

(7) Cyclopentanone-2-oxobutyl ester



Mol. formula: $C_{10}H_{16}O_3$. Viscous liq.

Yield: 63%

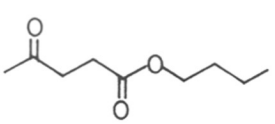
IR (neat, cm^{-1}): 840, 920, 1020, 1050, 1100, 1180, 1250, 1300, 1350, 1450, 1610, 1640, 1720, 1750, 2850, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 0.90 (t, 3H,$-CH_3$); 1.3 (m, 2H); 1.6 (m, 2H); 2.1 (m, 2H); 2.3 (m, 4H); 3.15 (t, 1H); 4.2 (t, 2H, $-OCH_2-$).

^{13}C NMR(200MHz):14.4 (q), 19.21 (t), 21.1 (t), 27.6 (t), 30.79 (t), 38.2 (t), 54.94 (d), 65.38 (t), 169.65 (s), 212.39 (s).

Mass (m/e): 184 (M^+), 103 (100), 85, 67, 55, 43.

(8) Butyl levulinate[34]



Mol. formula: $C_9H_{16}O_3$. Viscous liq.

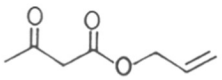
Yield: 45%

IR (neat, cm^{-1}): 650, 780, 950, 1020, 1050, 1150, 1180, 1350, 1450, 1620, 1720, 1740, 2800, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 0.90 (t, 3H,-CH_3); 1.5 (m, 4H, -CH_2); 2.1 (s, 3H, -CH_3); 2.5 (t, 2H, -CH_2-); 2.7 (t, 2H, -CH_2-); 4.1 (t, 2H, -OCH_2-).

^{13}C NMR (200MHz): 13.55 (q), 19.03 (t), 27.98 (t), 29.61 (q), 30.6 (t), 37.88 (t), 64.37 (t), 172.69 (s), 206.53 (s).

(9) Allyl acetoacetate[16]



Mol. formula: $C_7H_{10}O_3$. Pale yellow liq.

Yield: 65%

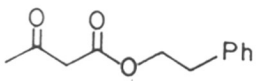
IR (neat, cm^{-1}): 550, 780, 950, 1000, 1020, 1150, 1280, 1320, 1380, 1420, 1640, 1720, 1750, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 2.2 (s,. 3H, -CH_3); 3.4 (s, 2H, -CH_2-); 4.6 (d, 2H, -OCH_2-); 5.25 (d, 2H); 5.8 (m, 1H).

^{13}C NMR(200MHz): 29.65 (q), 49.48 (t), 65.36 (t), 118.0 (t), 131.5 (d), 132.06 (d), 166.54 (s), 200.23 (s).

Mass(m/e): 142(M^+, 15), 124 (10), 114 (15), 100 (35), 85 (100), 69.(20), 58 (90).

(10) 2-phenylethyl acetoacetate



Mol. formula: $C_{12}H_{14}O_3$. Pale yellow liq.

Yield: 97%

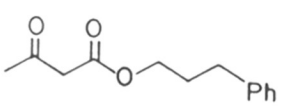
IR (neat, cm^{-1}): 550, 580, 720, 810, 920, 1020, 1050, 1200, 1250, 1300, 1400, 1620, 1720, 1750, 2900, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 2.15 (s, 3H, $-CH_3$); 3.0 (t, 2H, $-CH_2-CH_2O-$); 3.4 (s, 2H, $-CH_2-$); 4.4 (t, 2H, $-OCH_2-$); 7.5 (m, 5H, aromatic)

^{13}C NMR(200MHz): 29.97 (q), 34.92 (t), 49.72 (t), 49.95 (t), 52.24 (t), 65.69 (t), 126.33 (d), 126.67 (d), 128.58 (d), 128.8 (d), 129.01 (d), 167.06 (s), 200.5 (s).

Mass(m/e): 122 925), 108 (15), 91 (100), 81 (45), 77 (10), 67 (30), 58 (90).

(11) 3-Phenyl propyl acetoacetate[35]



Mol. formula: $C_{13}H_{16}O_3$. Pale yellow viscous liq.

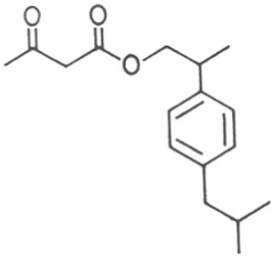
Yield: 98%

IR (neat, cm^{-1}): 700, 750, 1030, 1150, 1170, 1260, 1360, 1455, 1500, 1600, 1650, 1720, 1740, 2860, 3030.

^1H NMR (200MHz,$CDCl_3$, δ): 2.0 (m, 2H); 2.2 (s, 3H); 2.7 (t, 2H); 3.5 (s, 2H); 4.2 (t, 2H); 7.25 (m, 5H).

^{13}C NMR(200MHz): 30.15 (q), 30.15 (t), 32.1 (t), 50.1 (t), 64.7 (d), 126.1 (d),128.49 (d), 128.53 (d), 141.1 (s), 162.2 (s), 200.6 (s)

(12) Ibuprophyl acetoacetate



Mol. formula: $C_{17}H_{24}O_3$. Pale yellow liq.

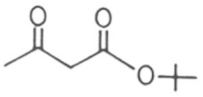
Yield: 63%

IR (neat, cm^{-1}): 580, 760, 820, 1020, 1050, 1200, 1340, 1500, 1600, 1650, 1720, 1750, 2920, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 0.90 (d, 6H); 1.0 (d, 3H); 2.1 (s, 3H); 2.3 (d, 4H, $-CH_2-$); 3.4 (s, 2H, $-CH_2-$); 4.2 (dd, 2H, $-OCH_2-$); 7.5 (m, 4H, aromatic).

^{13}C NMR(200MHz): 17.99 (q), 22.36 (q), 29.84 (q), 30.16 (d), 38.44 (d), 45.00 (t), 49.94 (t), 70.18 (t), 126.95 (d), 129.24 (d), 140.0 (s), 166.94 (s), 200.27 (s).

(13) Tert butyl acetoacetate[16]



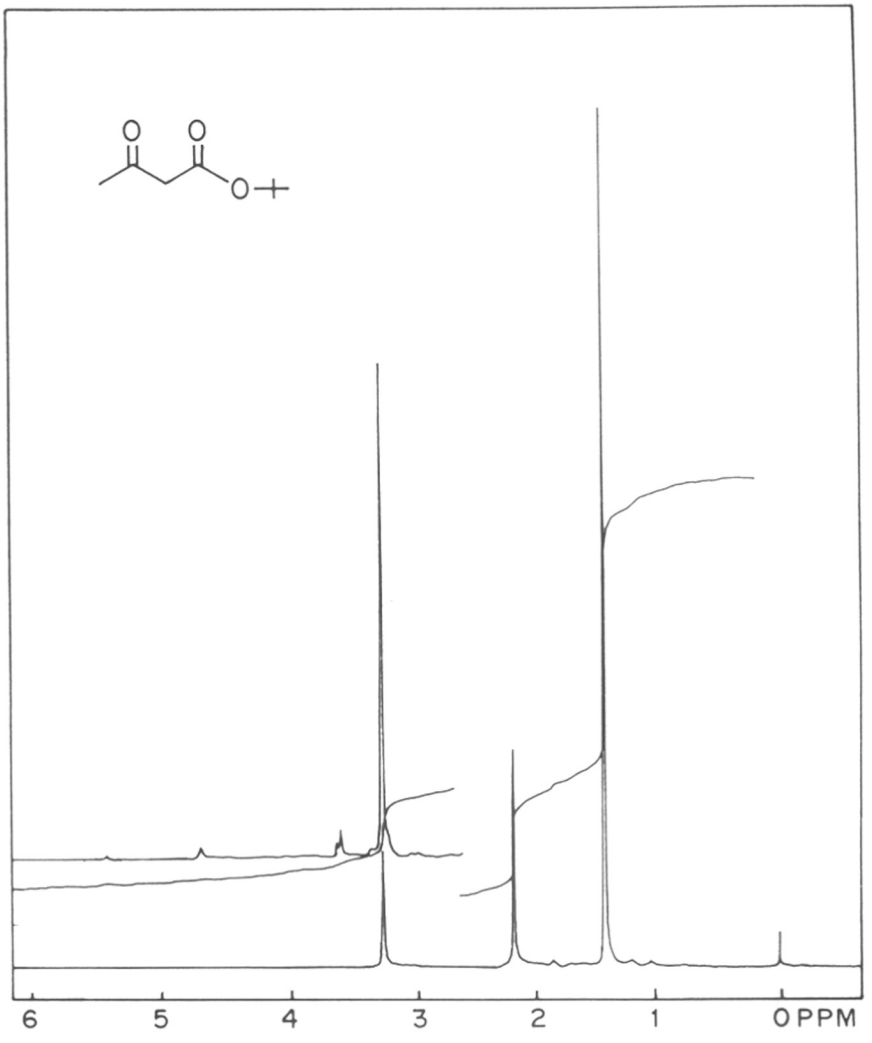
Mol. formula: $C_8H_{15}O_3$. Colourless liq.

Yield: 50%

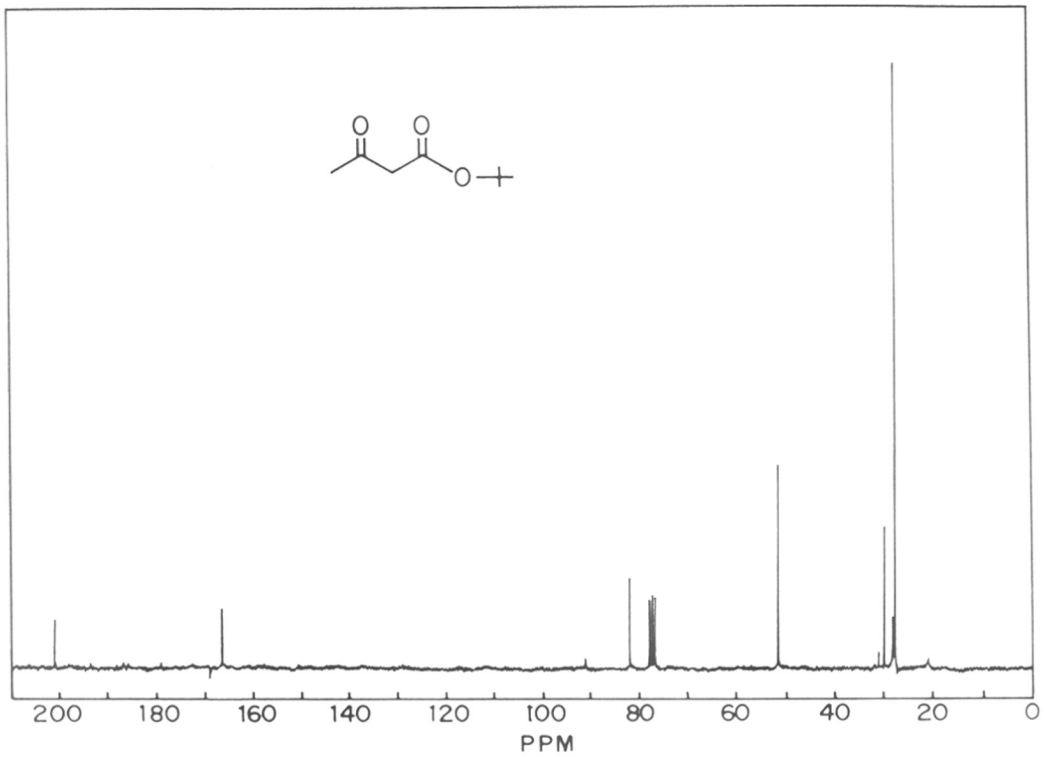
IR (neat, cm^{-1}): 650, 720, 850, 900, 920, 1020, 1150, 1250, 1310, 1360, 1400, 1650, 1720, 2950, 3000.

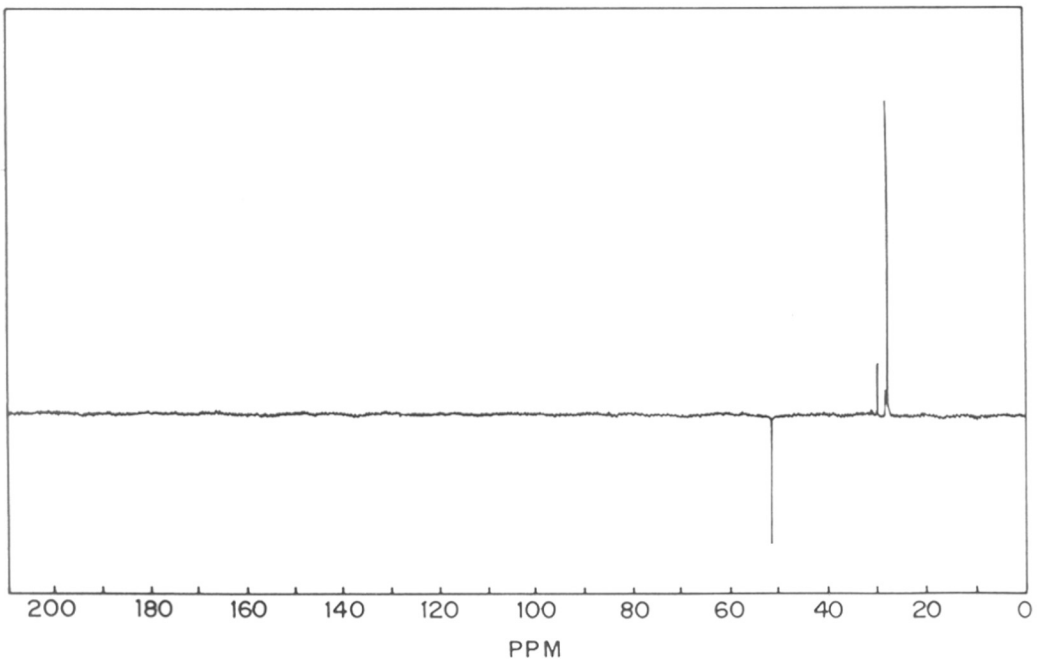
^{1}H NMR (80MHz, $CDCl_3$, δ): 0.9 (s, 9H, $-CH_3$); 2.1 (s, 3H, $-CH_3$); 3.4 (s, 2H, $-CH_2-$).

^{13}C NMR(200MHz): 27.99 (q), 28.35 (q), 30.00 (q), 31.22 (q), 51.5 (t), 81.90 (s), 166.44 (s), 201.11 (s).

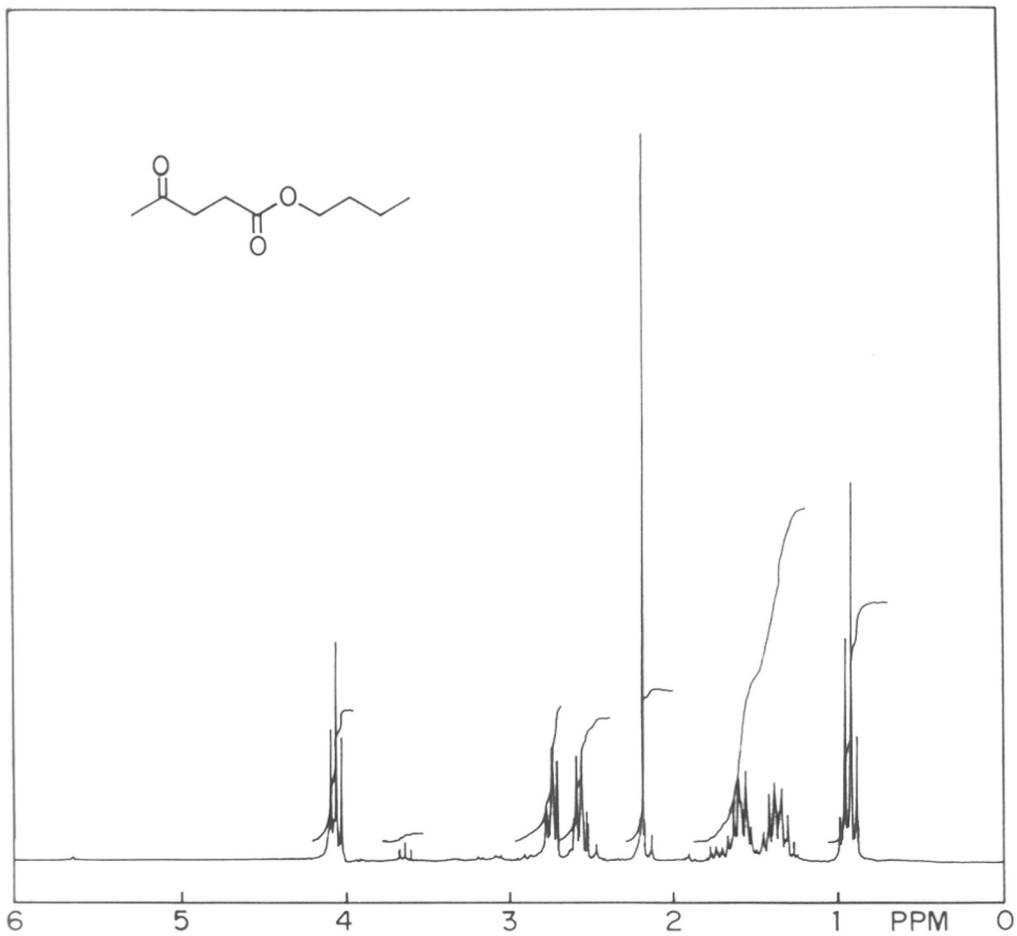


^{1}H-NMR SPECTRUM OF **13** (200 MHz, $CDCl_3$)

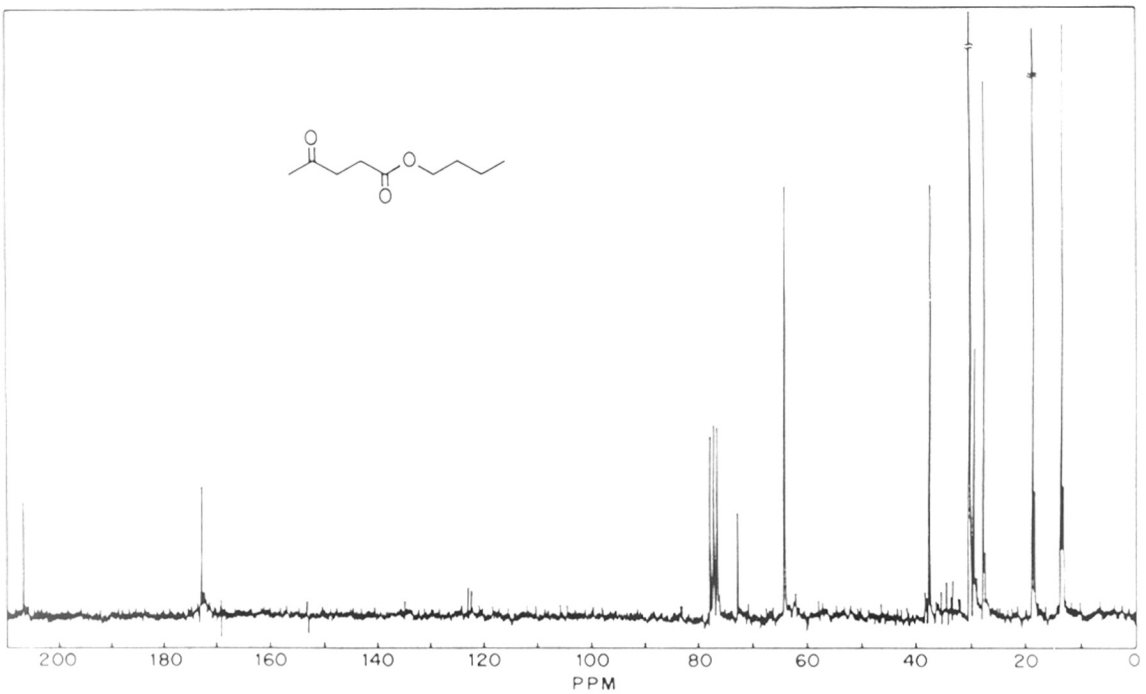


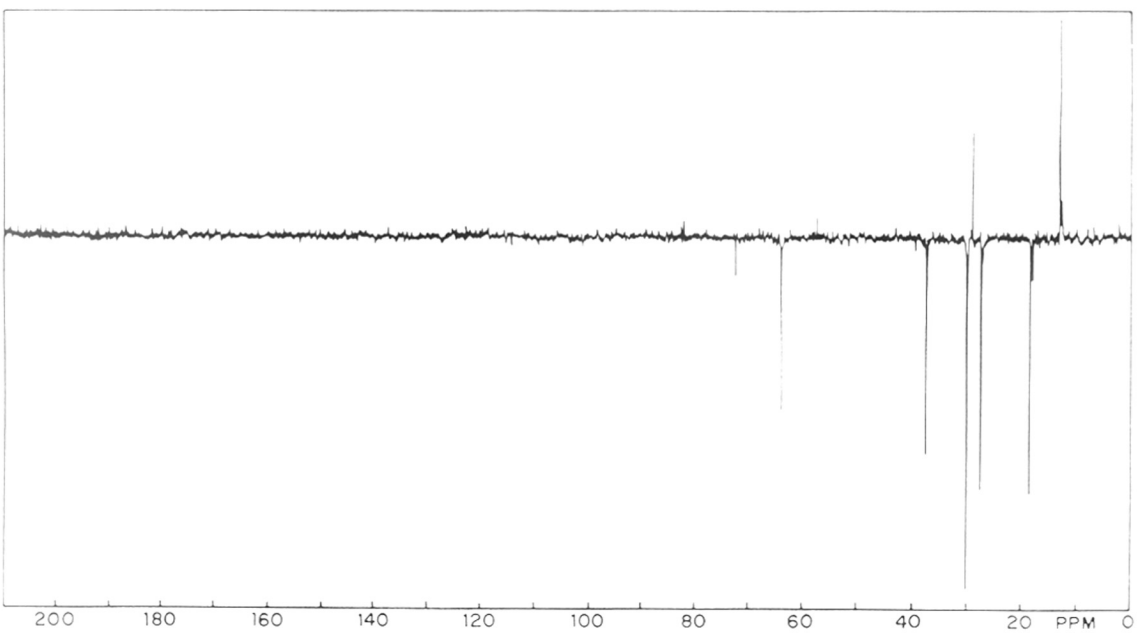


^{13}C-NMR SPECTRUM OF **13** (200 MHz, $CDCl_3$)



^{1}H-NMR SPECTRUM OF **8** (200 MHz , $CDCl_3$)





^{13}C-NMR SPECTRUM OF **8** (200 MHz, $CDCl_3$)

Conditions are excellent here, young man. He was brought here for experimental purposes and today he heads the Department!

Part-II *Allyl Ester Deprotection*

3.2.0 *Solid Superacids : Organic Transformations.*

Novel organic syntheses that are not possible in the usual acidic media can be worked out using solid superacids and zeolites including syntheses of economically important hydrocarbons. Any acid may be termed as superacid when its acidity is stronger than that of 100% H_2SO_4.

The preparation and use of solid superacids are active areas of research for isomerization, cracking, polymerization, alkylation, acylation, esterification etc. Replacement of homogeneous liquid acids by heterogeneous solid acids as catalysts in the chemical industry brings about the ease of separation from the regeneration and reutilisation of the catalyst.

Sulfate promoted metal oxides are the new type of solid acids such as SO_4^{--}/ZnO_2, SO_4^{--}/SnO_2, SO_4^{--}/Fe_2O_3. They are used as powerful catalysts for various acid-catalysed reactions such as skeletal isomerization of butane to isobutane at room temperature, acylation of benzene derivatives by acyl chlorides, ring opening isomerization of cyclopropane etc. Previous section (Part-I) of this chapter describes the utility of solid superacids as efficient catalyst for transesterification of ß-ketoesters. The sulfate ion can be introduced from H_2SO_4, ammonium sulfate or H_2S. The existence of the covalent S=O bonds in sulfur complexes formed on metal oxides is necessary for the generation of acidity.

3.2.1 *Allyl Ester Deprotection*:

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been and are being developed for this purpose. The protective group must react selectively in good yields to give a protected substrate that is stable to the projected reactions. Also the protective group must be selectively removed in good

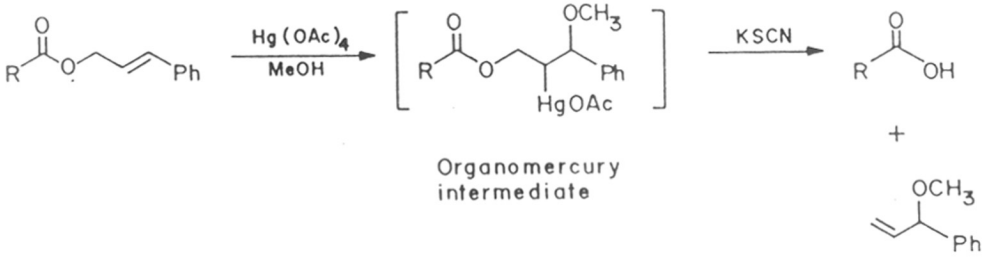
yield by readily available preferably nontoxic reagents that do not attack the regenerated functional group.

Carboxylic acid can be protected as anhydrides,[21] amides[22] or esters[23]. Unsaturated esters are particularly used as protecting groups. Allyl esters are formed by the reaction of corresponding alcohols with acid chlorides or alkylation of the corresponding halide under base-catalysed conditions.

Allyl esters can be deprotected using $Pd(OAc)_2$[24], $Pd(Ph_3P)_4$[25], $PdCl_3(Ph_3)_3$[26], $(Ph_3P)_3RhCl$[27], and Me_2CuLi[28]. In all these cases the regeneration of acid from the unsaturated ester involves metals, acidic or basic conditions.

Earlier a two step protocol for deprotection of cinnamyl esters has been described by E.J. Corey[29] (Scheme-1). Eventhough yields were good it is limited for cinnamyl ester and also expensive and toxic mercuric acetate was used.

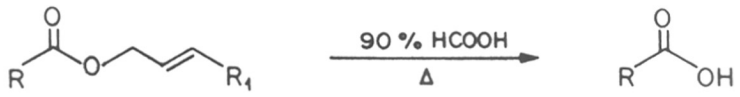
SCHEME - 1



Ref : Tet Lett (1977), 24, 2080

In a recent report substituted allylic esters were cleaved in refluxing 90% formic acid to afford carboxylic acids[30]. Methallyl, crotyl, cinnamyl esters were also completely removed under these conditions (Scheme-2).

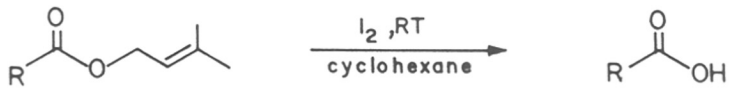
SCHEME-2



Ref : Tet Lett (1992), 33, 757

Another recent publication[31] utilises excess iodine for deprotection of allyl esters (Scheme-3), in mild and neutral conditions.

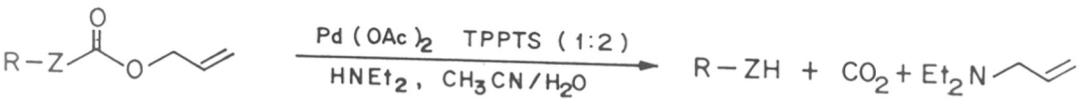
SCHEME-3



Ref : Tet. Lett (1994), 35, 1539

Allyloxycarbonyl and allylcarboxy groups can be removed without affecting dimethylallylcarboxy and cinnamylcarboxy groups in the same molecule, using Pd(O) water soluble catalyst prepared *in situ* with diethylamine as allyl scavenger.[32] (Scheme-4).(TPPTS: m-sulfonated triphenylphosphine)

SCHEME-4



Ref : Tet Lett (1994), 35, 8783

However, all these methods for deprotection of allyl esters employ harsh conditions, use of excess oxidising agents, or employ expensive reagents like Pd, Mercuric acetate.

3.2.2 *Present Work*:

Solid superacids are widely used in petroleum industry however they remain relatively unexplored in synthetic organic chemistry. Since allyl esters are easily formed under basic conditions using Corey's protocol[29], this gives an opportunity for easy and selective deprotection using the solid superacid.It was reasoned that allyl esters when treated with solid superacid in the presence of a nucleophile (solvent or additional nucleophile) would lead to alkylation and hence would generate acid. Thus this method could be employed as a protocol for deprotection of allyl esters. In connection with the use of solid superacids in organic chemistry, a variety of allyl esters were deprotected to corresponding carboxylic acid in good yields using sulfated tin oxide (Scheme-5).

SCHEME-5

$R_1 = -H, -CH_3$

$R_2 = -CH_3, -Ph$

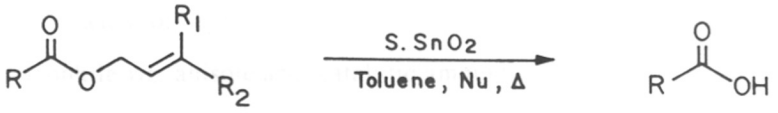
The hydrolysis of allyl esters was achieved using catalytic amount of sulfated SnO_2, under "anhydrous" conditions. A variety of allyl esters were deprotected to acids in high yields.

3.2.3 *Results And Discussion*:

Allyl esters were smoothly deprotected with sulfated tin oxide in refluxing toluene to carboxylic esters in high yields.

Allyl esters were prepared by treating the corresponding acid chlorides with allyl alcohols in basic media. Acid chlorides of phenylacetic acid, benzoic acid, p-nitrobenzoic acid, phenoxyacetic acid and 5-phenylvaleric acid were prepared and treated with dimethylallyl alcohol, crotyl alcohol and cinnamyl alcohol to give the corresponding substituted allyl alcohols. Phthalic anhydride and succinic anhydride when opened up with allyl alcohol in basic media gave monoester which on treatment with dimethyl sulphate and K_2CO_3 in refluxing acetone gave diester (entry 2&3).

SCHEME-6

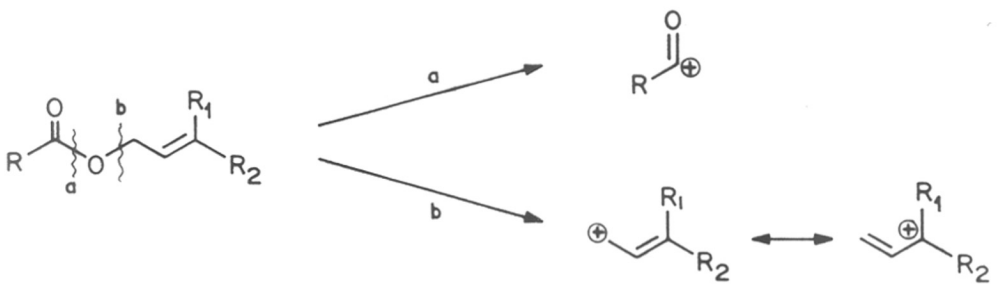


The allyl esters thus prepared were characterised by IR and ^{1}H-NMR, which were in agreement with the reported values.

Allyl esters were deprotected with cat.sulfated tin oxide($S.SnO_2$) in refluxing toluene to give carboxylic acid in good high yields (scheme-6). (Table I) It is evident from the table that prenyl esters were easily deprotected whereas cinnamyl and crotyl esters require the additional presence of more nucleophilic species i.e. anisole. The hydrolysis of allyl esters were performed under anhydrous conditions.

Although exact mechanism is not known, there can be two possibilities of cleavage of allyl ester (Scheme-7) considering the pattern of reactivity of various allylic esters dimethyl allyl > crotyl > cinnamyl esters, path `b' seems to be operative. The propensity for reaction of substituted allylic systems over simple allyl can be explained by the increased allylic cation stability provided by alkyl substitution or conjugation.

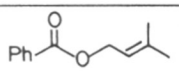
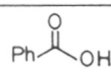
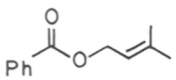
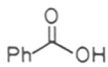
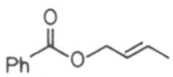
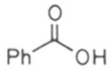
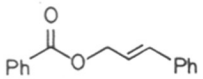
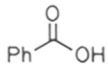
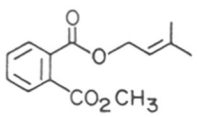
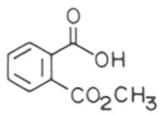
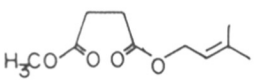
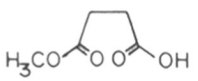
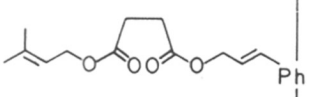
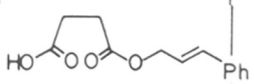
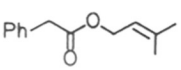
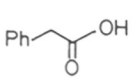
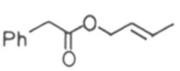
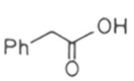
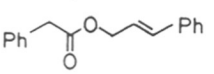
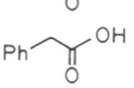
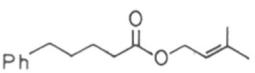
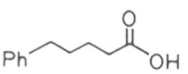
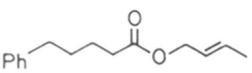
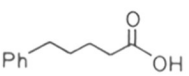
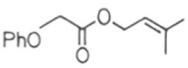
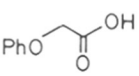
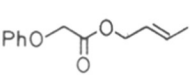
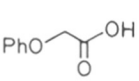
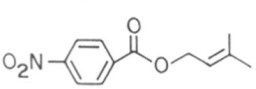
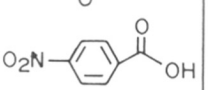
SCHEME-7



In a typical reaction of deprotection of allyl esters, when refluxed in toluene in presence of nucleophile *viz.* anisole and catalytic amount of sulfated tin oxide the corresponding carboxylic acid was obtained. The reaction was monitored by TLC. After evaporating the solvent, aq. NaOH was added and aq. solution was extracted with ethyl acetate. The aq. layer on neutralisation with dil. HCl and extraction gave the acid in high yields, which was characterised by IR, ^{1}H-NMR & M.P. (if solid) which matched with the authentic ones.

A striking feature of the above protocol is normal esters remain unaffected under the reaction conditions; as evident from diesters of phthalic and succinic esters where only allylic esters were deprotected over methyl ester (entries 2,3 table). Also dimethylallyl esters can be selectively deprotected in presence of cinnamyl esters. (entry 4).

TABLE

ENTRY	ALLYL ESTER	Nu (eq)	TIME (hr)	PRODUCT	%YIELD
1	(A) 	–	7		82
		2	5		92
	(B) 	2	8		50
	(C) 	2	6		81
2		–	2		72
3		–	5		60
4		–	6		50
5	(A) 	–	5		68
	(B) 	2	5		70
	(C) 	2	12		80
6	(A) 	2	10		85
	(B) 	2	10		78
7	(A) 	2	10		89
	(B) 	2	4		85
8		2	2		80

The solid superacid being heterogeneous in nature, involve easy work up and recycle of the catalyst.

Acidic resin can also be used for the deprotection of allyl esters.

3.2.4 *Conclusion*:

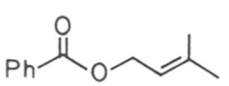
1. A catalytic, efficient deprotection of allyl esters has been achieved in presence of sulfated tin oxide and resin under anhydrous conditons. This is in contrast with the earlier reported procedures which employ harsh conditions, excess oxidising agents or employ expensive reagents.
2. The present method is non-oxidative, catalytic and practically irreversible.
3. Since the ease of formation of allyl cations govern the ease of deprotection of allyl esters, normal esters are resistant to the above conditions.
4. Dimethyl allyl esters could be deprotected selectively over crotyl and cinnamyl esters.
5. Being a heterogeneous reaction the catalyst can be reused and recycled.

3.2.5 *Experimental*

General Procedure for the preparation of allyl esters

To a stirred solution of allyl alcohol (10 mmol) in dichloromethane (15 ml) at 0°C was added triethylamine (10 mmol) dropwise and stirred for 10-15 min. Acid chloride (10 mmol) was added slowly with vigorous stirring at low temperature for 10 min. The reaction mixture was stirred at 0°C for 2 hrs and the reaction mixture was allowed to stir at room temperature for another 2 hrs. After the completion of reaction (TLC), dil HCl was added and the aqueous layer was extracted with dichloromethane. Organic layer was washed once with water (10 ml) and brine (2 x 10 ml), dried over anhydrous sodium sulphate. Solvent evaporation under reduced pressure gave the crude allyl ester, which was further purified by flash chromatography using pet-ether - ethyl acetate as eluant.

1A Dimethyl allyl benzoate[28]



Mol. formula: $C_{12}H_{14}O_2$. Viscous liq.

Yield: 85%

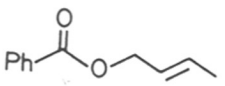
IR (neat, cm^{-1}): 450, 580, 680, 750, 920, 1020, 1080, 1120, 1200, 1280, 1320, 1380, 1450, 1600, 1620, 1720, 2350, 3000.

^1H NMR (200MHz,$CDCl_3$, δ): 1.5 (s, 6H, $-CH_3$); 4.8 (d, 2H, $-CH_2-$ [J=9.75 Hz]); 5.5 (t, 1H, olefinic [J=9.75 Hz]); 7.5 (m, 3H, aromatic); 8.1 (m, 2H, aromatic).

^{13}C NMR(200MHz): 17.77 (q), 25.48 (q), 61.64 (t), 118.75 (d), 128.10 (d), 129.40 (d), 129.90 (d), 130.30 (d), 132.58 (d), 132.79 (s), 138.65 (s), 166.36 (s).

Mass (m/e): 190 (M^+), 105 (100), 85 (8), 77 (55), 68 (80), 53 (22), 51 (48).

1B Crotyl benzoate[28]



Mol. formula: $C_{11}H_{12}O_2$. Viscous liq.

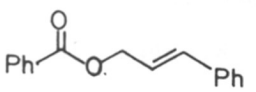
Yield: 88%

IR (neat, cm^{-1}):

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (d, 3H); 4.8 (d, 2H, $-OCH_2$ [J=7.3 Hz]); 5.8 (dt, 1H, [J=7.3, 12Hz]); 5.9 (dq, 1H, [J=7.3, 19.5 Hz])

^{13}C NMR(200MHz): 18.00 (q), 65.87 (t), 125.45 (d), 128.5 (d), 128.65 (d), 129.83 (d), 130.41 (d), 130.67 (d), 131.57 (d), 133.00 (d), 133.9 (s), 166.7 (s).

1C Cinnamyl benzoate[28]



Mol. formula: $C_{16}H_{14}O_2$. Pale yellow viscous liq.

Yield: 82%

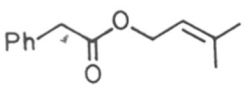
IR (neat, cm^{-1}): 580, 680, 750, 920, 980, 1000, 1080, 1150, 1180, 1280, 1380, 1450, 1500, 1600, 1720, 1800, 2350, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 4.8 (d, 2H, $-CH_2-$ [J=6.5 Hz]); 6.5 (dt, 1H, olefinic [J=6.5, 16.1 Hz]); 6.8 (d, 1H, olefinic [J=16 Hz]); 7.5-8.0 (m, 10H, aromatic)

^{13}C NMR(200MHz): 65.46 (t), 123.25 (d), 126.63 (d), 128.03 (d), 128.34 (d), 128.57 (d), 128.77 (d), 129.63 (d), 130.12 (d), 130.22 (d), 130.55 (d), 132.95 (d), 133.5 (d), 134.17 (s), 136.22 (s), 166.25 (s)

Mass (m/e): (M) 238, 159 (18), 131 (15), 122 (25), 105 (60), 89 (10), 77 (75), 74 (12), 63 (20), 69 (10), 50 (100).

5A Dimethyl allyl phenyl acetate



Mol. formula: $C_{13}H_{16}O_2$. Colourless liq.

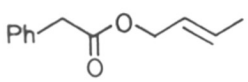
Yield: 85%

IR (neat, cm^{-1}): 550, 720, 750, 980, 1150, 1250, 1380, 1450, 1500, 1600, 1730, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (s, 6H,- CH_3); 3.7 (s, 2H, -CH_2Ph); 4.7 (d, 2H, -CH_2 olefin [J=9.75 Hz]); 5.4 (t, 1H olefine [J=9.75 Hz]); 7.4 (m, 5H, aromatic).

^{13}C NMR(200MHz): 17.69 (q), 25.40 (q), 41.1 (t), 61.47 (t), 118.62 (d), 126.77 (d), 128.28 (d), 128.54 (d), 128.79 (d), 129.05 (d), 134.05 (s), 138.57 (s), 171.21 (s).

5B Crotyl phenyl acetate



Mol. formula: $C_{12}H_{14}O_2$. Colourless liq.

Yield: 84%

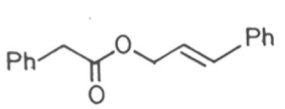
IR (neat, cm^{-1}): 620, 680, 720, 750, 980, 1150, 1250, 1320, 1380, 1450, 1500, 1610, 1730, 2950, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (d, 3H, $-CH_3$); 3.5 (s, 2H, $-CH_2Ph$); 4.5 (d, 2H, $-OCH_2-$ [J=8 Hz); 5.0 (dt, 1H olefin [J=8, 12 Hz]); 5.1 (dq, 1H, olefin [J=8, 18 Hz]).

^{13}C NMR(200MHz): 17.54 (q), 41.17 (t), 65.21 (t), 125.12 (d), 126.88 (d), 128.39 (d), 129.15 (d), 129.38 (d), 130.96 (d), 134.06 (s), 170.96 (s).

Mass (m/e): 190 (M^+), 118, 91 (100), 89, 65, 55.

5C Cinnamyl phenylacetate



Mol. formula: $C_{17}H_{16}O_2$. Pale yellow liq.

Yield: 87%

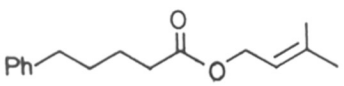
IR (neat, cm^{-1}): 550, 720, 750, 980, 1150, 1250, 1320, 1350, 1450, 1500, 1600, 1740, 2850, 3010.

^1H NMR (200MHz,$CDCl_3$, δ): 3.8 (s, 2H, $-CH_2Ph$); 4.8 (d, 2H, $-CH_2-$ olefin [J=9.75 Hz]); 6.3 (dt, 1H, Olefin [J=9.75, 16.3 Hz]); 6.7 (d, 1H, Olefin [J=16.1 Hz]); 7.4 (m, 10H, aromatic).

^{13}C NMR(200MHz): 41.14 (t), 65.08 (t), 123.01 (d), 126.5 (d), 126.95 (d), 127.88 (d), 128.44 (d), 128.83 (d), 129.19 (d), 133.79 (s), 133.94 (s), 136.11 (s), 170.99 (s).

Mass (m/e): 206, 164, 131 (30), 103 (25), 91 (100), 77 (55), 65 (28), 55 (30).

6A Dimethyl allyl-5-phenyl valerate



Mol. formula: $C_{16}H_{12}O_2$. Pale yellow liq.

Yield: 86%

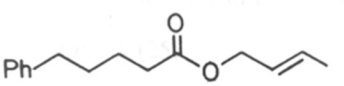
IR (neat, cm^{-1}): 500, 700, 740, 1180, 1220, 1380, 1450, 1600, 1720, 2950, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (s, 6H,-CH_3); 1.9 (m, 4H, -CH_2-); 2.4 (t, 2H, -CH_2-, [J = 14.63 Hz]); 2.7 (t, 2H, -CH_2-, [J = 14.63 Hz]); 4.8 (d, 2H, -OCH_2-[J=9.75 Hz]); 5.5 (t, 1H, Olefin [J=9.75 Hz]); 7.4 (m, 5H, aromatic).

^{13}C NMR(200MHz): 17.96 (q), 24.66 (t), 25.71 (q), 30.92 (t), 34.16 (t), 35.60 (t), 61.14 (t), 118.94 (d), 125.77 (d), 128.34 (d), 138.65 (s), 142.13 (s), 173.42 (s).

Mass(m/e): 177 (25), 159 (22), 131(10), 117 (80), 104 (20), 91 (100), 77 (10), 69 (60), 53 (18).

6B Crotyl-5-phenyl valerate



Mol. formula: $C_{15}H_{20}O_2$. Colourless liq.

Yield: 82%

IR (neat, cm^{-1}): 500, 700, 750, 980, 1080, 1150, 1380, 1450, 1720, 2850, 2950.

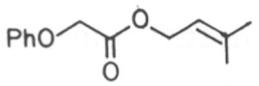
^1H NMR (200MHz,$CDCl_3$, δ): 1.7 (d, 3H,-CH_3); 1.7 (m, 4H, -CH_2-); 2.7 (t, 2H, J=14.7Hz, -CH_2Ph); 4.6 (t, 2H, -CH_2 - [J=7.3 Hz]); 5.6 (dt, 1H, Olefin [J=7.3, 14.63 Hz]); 5.8 (dq, 1H, Olefin [J=7.3, 19.4 Hz]); 7.25 (m, 5H, aromatic).

^{13}C NMR(200MHz): 17.70 (q), 24.63 (t), 30.92 (t), 34.4 (t), 35.6 (t), 64.99 (t),

115.64 (d), 125.38 (d), 125.79 (d), 128.39 (d), 129.42 (d), 131.09 (d), 142.14 (s), 173.24 (s).

Mass (m/e): 177 (20), 159 (15), 117 (70), 104 (10), 91 (100), 77 (10) 65 (15), 55 (50)

7A Dimethylallyl phenoxy acetate



Mol. formula: $C_{13}H_{16}O_4$. Colourless liq.

Yield: 81%

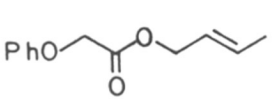
IR (neat, cm^{-1}): 780, 980, 1080, 1200, 1280, 1450, 1510, 1620, 1750, 1780, 2920, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (s, 6H,- CH_3); 4.6 (s, 2H, -CH_2-OPh); 4.8 (d, 2H, -OCH_2- Olefin [J=9.75 Hz]); 5.5 (t, 1H, Olefin [J=9.75 Hz]); 7-7.5 (m, 5H, aromatic])

^{13}C NMR(200MHz): 17.65 (q), 25.38 (q), 61.63 (t), 65.07 (t), 114.46 (d), 118.06 (d), 121.34 (d), 129.24 (d), 139.46 (s), 157.75 (s), 168.57 (s).

Mass (m/e): 220 (M^+), 180 (15), 139 (10), 107 (50), 94 (30), 85 (15), 77 (60), 69 (100), 65 (20), 55 (25).

7B Crotyl phenoxyacetate



Mol. formula: $C_{12}H_{14}O_3$. Pale yellow liq.

Yield: 79%

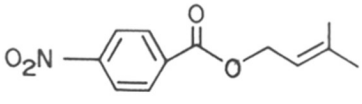
IR (neat, cm^{-1}): 780, 880, 1080, 1200, 1280, 1400, 1450, 1500, 1600, 1750, 1780, 2980.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (d, 3H,-CH_3); 4.7 (d, 4H,-CH_2-); 5.6 (dt, 1H, Olefin [J=9.75, 14.63 Hz]); 5.8 (dq, 1H, Olefin [J=9.7, 19.57 Hz]); 7-7.5 (m, 5H, aromatic).

^{13}C NMR(200MHz): 17.22 (q), 64.82 (t), 65.22 (t), 114.30 (d), 121.17 (d), 124.35 (d), 129.09 (d), 131.47 (d), 157.60 (s), 168.19 (s).

Mass (m/e): 206 (M^+,5), 107 (20), 77 (22), 55 (100).

8 Dimethyl allyl p-nitrobenzoate



Mol. formula: $C_{12}H_{13}O_4N$. Pale yellow solid

MP: 63°C

Yield: 88%

IR (neat, cm^{-1}): 580, 680, 780, 920, 1020, 1120, 1280, 1350, 1400, 1450, 1550, 1620, 1720, 2950, 3020.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (s, 6H, -CH_3); 4.8 (d, 2H, CH_2 [J=9.75 Hz]); 5.5 (t, 1H, Olefin [J=9.75 Hz]); 8.4 (m, 4H, aromatic).

^{13}C NMR(200MHz): 18.10 (q), 25.77 (q), 62.75 (t), 118.21 (d), 123.47 (d), 130.71 (d), 135.99 (s), 140.03 (s), 150.53 (s), 164.67 (s).

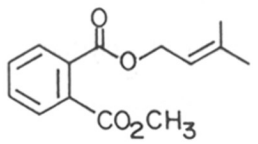
Mass (m/e): 235 (M^+), 150 (88), 134 (18), 120 (12), 104 (30), 92 (15), 85 (8), 76 (35), 68 (100), 57 (10), 53 (35).

General procedure for preparation of Diesters

To a stirred solution of allyl alcohol (10 mmol) and triethyl amine (10 mmol) at 0°C in CH_2Cl_2 was added phthallic anhydride (10 mmol) or succinic anhydride (10 mmol). The reaction mixture was stirred at 0°C for 2 hrs during which the anhydride dissolves as the reaction proceeds towards completion. The reaction mixture was stirred at room temperature for one hr and reaction was quenched with dil HCl (10 ml) and organic layer was washed once with water (10 ml) and brine (2 x 10 ml), dried over sodium sulfate. Solvent evaporation under reduced pressure gave crude half ester. The half ester was purified by column chromatography using pet·ether-ethyl acetate as eluant.

A mixture of half ester (10 mmol 1eq.), dimethyl sulfate (10 mmol) and anhydrous potassium carbonate (4 eq) in acetone (50 ml) was refluxed with stirring for 5-8 hrs. After filtration and concentration under reduced pressure, the residue (diester) was purified by flash chromatography to give pure diester.

2 Dimethyl allyl methyl phthallate



Mol. formula: $C_{14}H_{16}O_4$ Viscous liq.

Yield: 63% (over two steps)

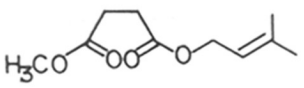
IR (neat, cm^{-1}): 550, 700, 720, 820, 880, 1080, 1120, 1200, 1280, 1380, 1420, 1580, 1600, 1700, 2920, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 1.8 (s, 6H, $-CH_3$); 3.9 (s, 3H, $-OCH_3$); 4.8 (d, 2H, $-OCH_2-$ [J=9.75 Hz]); 5.4 (t, 1H, Olefinic [J=9.75 Hz]); 7.5-7.8 (m, 5H, aromatic).

^{13}C NMR(200MHz): 17.10 (q), 24.88 (q), 51.67 (q), 57.98 (d), 61.72 (t), 118.00 (s), 128.21 (d), 128.35 (d), 133.55 (s), 131.55 (d), 131.70 (d), 138.68 (s), 166.67 (s), 167.32 (s).

Mass (m/e): 194 (10), 163 (100), 149 (65), 136 (25), 121 (15), 105 (35), 92 (40), 77 (60), 69 (10), 65 (43), 59 (15), 55 (12).

3 Dimethyl allyl methyl succinate



Mol. formula: $C_{10}H_{16}O_4$. colourless liq.

Yield: 62%

IR (neat, cm^{-1}): 550, 580, 720, 850, 1020, 1120, 1250, 1350, 1380, 1450, 1720, 1750, 2950.

^1H NMR (200MHz,$CDCl_3$, δ): 1.7 (s, 6H); 2.65 (s, 4H, $-CH_2-$); 3.7 (s, 3H, $-OCH_3$); 4.5 (d, 2H, $-CH_2-$ [J=8.1 Hz]); 5.3 (t, 1H, Olefinic [J=8.1 Hz]).

^{13}C NMR(200MHz): 17.11 (q), 24.86 (q), 28.17 (t), 28.23 (t), 28.46 (t), 50.89 (q), 60.76 (t), 11.35 (d), 138.06 (s), 171.51 (s), 172.0 (s).

Mass (m/e): 121 (15), 105 (9), 100 (12), 93 (18), 81 (20), 74 (35), 69 (45), 59 (22), 55 (100).

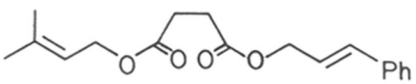
Preparation of allyl-diester

To a stirred solution of cinnamyl alcohol (10 mmol) and triethylamine (10 mmol) at 0°C in CH_2Cl_2 (20 ml) was added, succinic anhydride (10 mmol) and stirred for 2 hrs. The reaction mixture was stirred at room temperature for one hr. The reac-

tion was quenched with dil. HCl (10 ml), washed once with water (10 ml), brine (2 x 10 ml), dried over anhydrous Na_2SO_4. Solvent evaporation under reduced pressure gave the half ester.

A mixture of half ester (5 mmol), dimethyl allyl bromide (5 mmol), potassium carbonate (20 mmol) in acetone (50 ml) was refluxed with stirring for 2 hrs. Filtration and concentration of the reaction mixture gave crude diester, which was purified by flash chromatography using pet. ether-ethyl acetate as eluant.

4 Cinnamyl dimethylallyl succinate



Mol. formula: $C_{18}H_{22}O_4$. Pale yellow viscous liq.

Yield: 70%

IR (neat, cm^{-1}): 550, 580, 720, 780, 950, 980, 1180, 1220, 1380, 1480, 1600, 1720, 1730, 2850, 2980.

^1H NMR (200MHz,$CDCl_3$, δ): 1.7 (s, 6H); 2.7 (s, 4H, $-CH_2-$); 4.65 (d, 2H, $-CH_2-$ [J=9.75 Hz]); 4.8 (d, 2H, $-CH_2-$ [J=7.3 Hz]); 5.4 (t, 1H, Olefin [J=9.75 Hz]); 6.25 (dt, 1H, Olefin [J=7.3, 14.63 Hz]); 6.7 (d, 1H, Olefin [J=14.63 Hz]); 7.4 (m, 5H, aromatic).

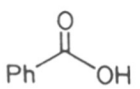
^{13}C NMR(200MHz): 17.74 (q), 25.47 (q), 28.96 (t), 61.35 (t), 64.96 (t), 118.55 (d), 122.99 (d), 126.45 (d), 127.85 (d), 128.41 (d), 133.84 (d), 136.09 (s), 138.61 (s), 171.75 (s), 171.91 (s).

Mass (m/e): 302 (M^+), 143 (10), 133 (48), 122 (8), 117 (30), 105 (30), 91 (20), 85 (50), 77 (38), 69 (100), 55 (70).

General procedure for the deprotection of allyl esters (using catalyst)

A mixture of allyl ester (1 eq), anisole (2 eq) and the catalyst (100 mg, 10% by weight) in toluene (20 ml) was heated with stirring at 110°C in oil bath. The reaction was monitored by T.L.C. After completion of the reaction, the catalyst was filtered and aq. NaOH was added to the filtrate, and extracted once with ethyl acetate. The aq. layer was neutralised with dil. HCl, saturated with NaCl and extracted (3 x 20) with ethyl acetate. Dried over Na_2SO_4 and concentrated to give the corresponding acid in high yields.

Benzoic acid



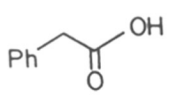
Mol. formula: $C_7H_6O_2$. White solid

M.P.: 122 (lit. 122-123°)

IR (nujol, cm^{-1}): 720, 820, 950, 1080, 1150, 1200, 1300, 1340, 1380, 1450, 1480, 1600, 1700, 1710, 2820, 2950

^1H NMR (80MHz,$CDCl_3$, δ): 3.2 (bs, -OH, exchangeable proton); 7.5 (m, 5H, aromatic).

Phenyl acetic acid



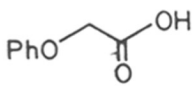
Mol. formula: $C_8H_8O_2$. White crystals

M.P.: 77°C (Lit. 77-78°C)

IR ($CHCl_3$, cm^{-1}): 550, 710, 780, 850, 1250, 1420, 1480, 1600, 1710, 2850, 2980, 3020.

^1H NMR (80MHz,$CDCl_3$, δ): 3.6 (s, 2H, $-CH_2Ph$); 4.2 (bs, 1H, exchangeable proton); 7.4 (m, 5H, aromatic).

Phenoxy acetic acid



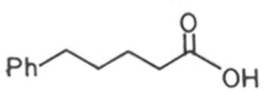
Mol. formula: $C_8H_8O_3$. Light pink crystals

M.P.: 98° (Lit. 98-100°)

IR ($CHCl_3$, cm^{-1}): 650, 780, 820, 950, 980, 1100, 1250, 1280, 1380, 1450, 1490, 1600, 1620, 1710, 1740, 2850, 2900, 3020.

^1H NMR (80 MHz,$CDCl_3$, δ): 4.4 (s, 2H, $-CH_2$); 7.4 (m, 5H, aromatic).

5-Phenyl valeric acid



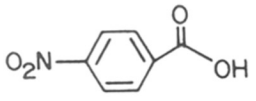
Mol. formula: $C_{11}H_{14}O_2$. White solid

M.P.: 58° (lit. 58-60°C)

IR ($CHCl_3$, cm^{-1}): 650, 780, 820, 980, 1020, 1080, 1250, 1380. 1450, 1500, 1600, 1710, 2850, 2980, 3020.

^1H NMR (80MHz,$CDCl_3$, δ): 1.5 (m, 4H); 2.3-2.5 (m, 4H); 7.5 (m, 5H, aromatic).

p-Nitrobenzoic acid



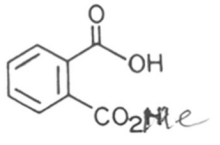
Mol. formula: $C_7H_5NO_4$. Pale yellow solid.

M.P.: 240°C (Lit. 239-241°C)

IR ($CHCl_3$, cm^{-1}): 550, 720, 820, 880, 920, 1020, 1280, 1320, 1450, 1500, 1600, 1620, 1710, 2920, 2980, 3000

^1H NMR (80MHz,$CDCl_3$, δ): 7.5 (m, 4H, aromatic)

Monomethyl phthalic acid (half ester)



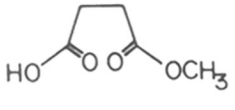
Mol. formula: $C_9H_8O_4$. Viscous liq.

Yield: 72%

IR (neat, cm^{-1}): 750, 780, 980, 1080, 1140, 1280, 1450, 1580, 1620, 1710, 1720, 2650, 3000, 3400, 3500.

^1H NMR (80MHz,$CDCl_3$, δ): 3.7 (s, 3H); 7.5-7.8 (m, 5H)

Monomethyl succinate



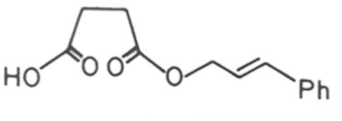
Mol. formula: $C_5H_8O_4$. Viscous liq.

Yield: 60%

IR (neat, cm^{-1}): 750, 920, 1180, 1450, 1720, 2850, 3000, 3400.

^1H NMR (80MHz,$CDCl_3$, δ): 2.6 (s, 4H, $-CH_2-$); 3.7 (s, 3H, $-OCH_2-$); 4.2 (bs, 1H, exchangeable protons)

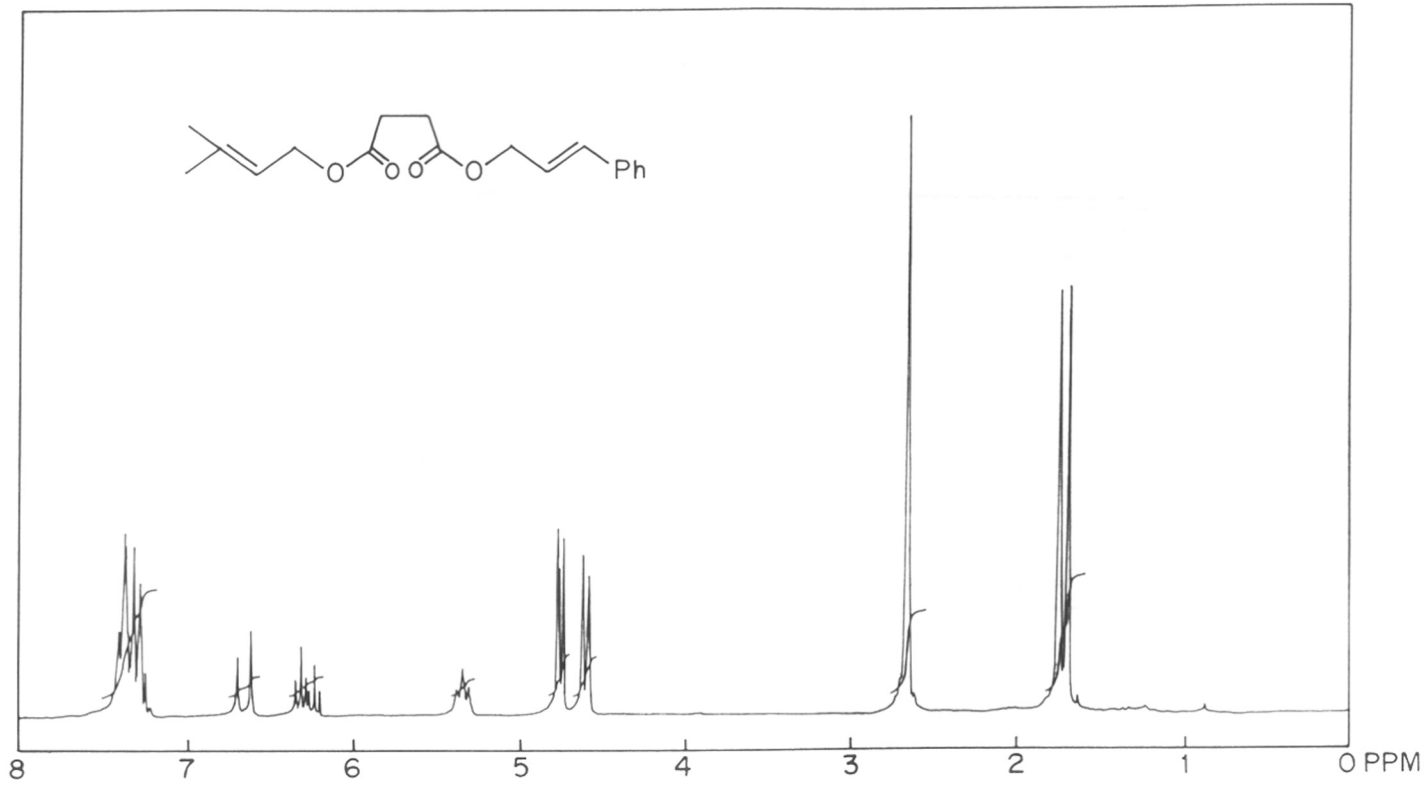
Cinnamyl succinate (Half ester)



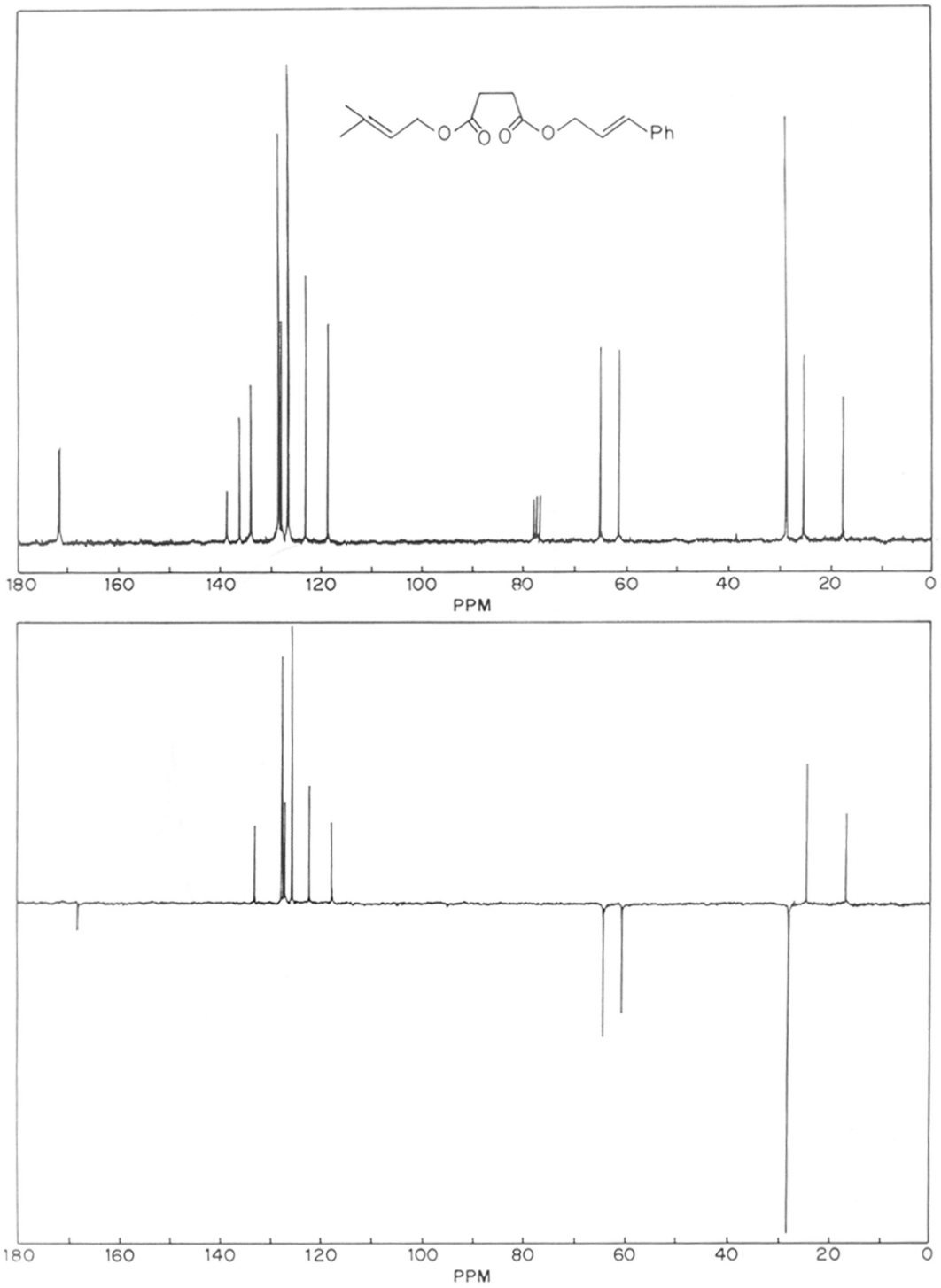
Mol. formula: $C_{13}H_{14}O_4$. Pale yellow solid

Yield: 50%

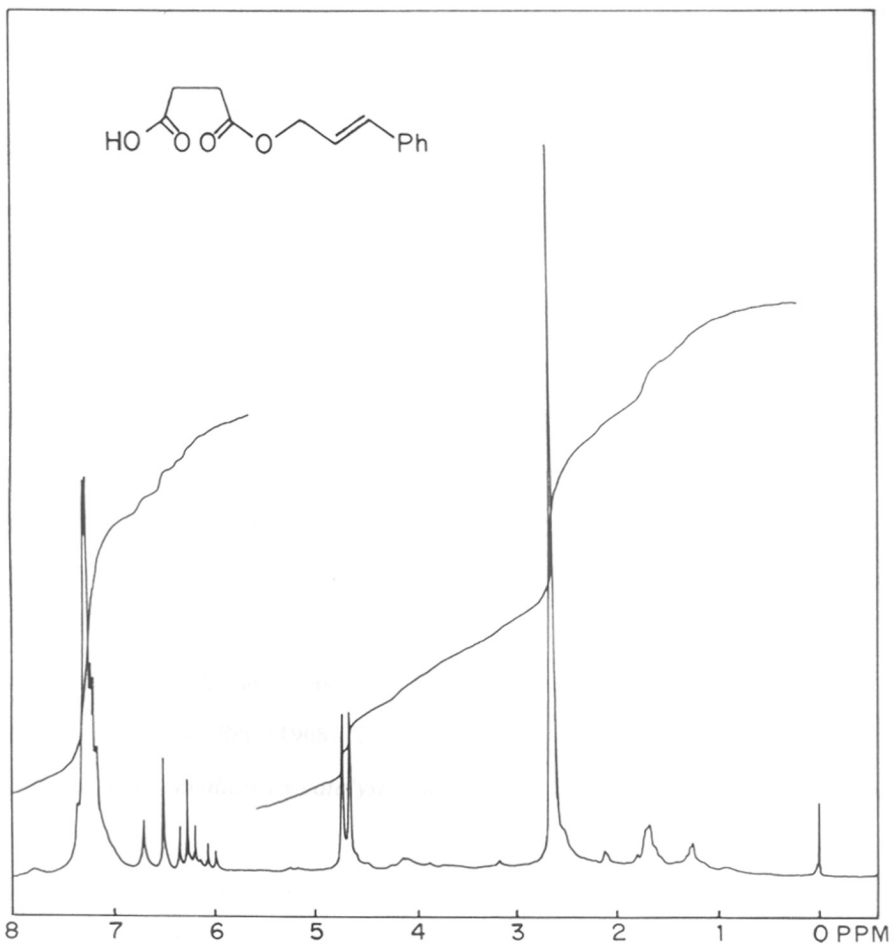
^1H NMR (80MHz,$CDCl_3$, δ): 2.6 (s, 4H, $-CH_2-$); 4.7 (d, 2H, $-CH_2-$ [J=6.5 Hz]); 6.25 (m, 1H, Olefin [J=6.5, 16.2 Hz]); 6.7 (d, 1H, Olefin [J=16.2 Hz]); 7.5 (m, 5H, aromatic)



^{1}H-NMR SPECTRUM OF 4 (Ester) (200 MHz, $CDCl_3$)



^{13}C-NMR SPECTRUM OF **4** (ESTER) (200 MHz, $CDCl_3$)



^{1}H-NMR SPECTRUM OF **4** (ACID) (200MHz, $CDCl_3$)

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List of Publications

1. Unusually facile oxathioacetal transfer reaction : an efficient, highly selective catalytic deprotection protocol.
   T.Ravindranathan, Subhash P.Chavan, Jos P.Varghese, Rajkumar B.Tejwani and Shubhada W.Dantale.
   Journal of Chemical Society Chemical Communication, **1994**,1937.

2. Interconversion of oxathiolanes and carbonyls under essentially identical conditions.
   T.Ravindranathan, Subhash P.Chavan and Shubhada W.Dantale.
   Tetrahedron Letters, **1995**,36,2285.

3. Use of solid superacids (sulphated SnO_2) as efficient catalyst in facile transesterification of ketoesters.
   T.Ravindranathan, Subhash P.Chavan, Shubhada W.Dantale, P.K.Zubaidha, A. Keshavaraja and A.V.Ramaswamy.
   Tetrahedron Letters(In Press)

4. Facile deprotection fo allyl esters mediated by solid superacids (Sulphated SnO_2).
   T.Ravindranathan, Subhash P.Chavan, Shubhada W.Dantale, P.K.Zubaidha, A. Keshavaraja and A.V.Ramaswamy.
   Tetrahedron Letters (In Press)

5. A non catalytic oxidative deprotection of oxathioacetals.
   T.Ravindranathan, Subhash P.Chavan, Shubhada W.Dantale, Sachin S.Patil and Vijay D.Dhondge.(communicated)

6. Facile deprotection of allyl esters mediated by acidic resin : Amberlyst-15. (communicated)
   T.Ravindranathan, Subhash P.Chavan, Shubhada W.Dantale, P.K.Zubaidha, Sachin S.Patil and Vijay D.Dhondge.

7. Sulfur assisted reduction of esters using $NaBH_4$/EtOH. (To be communicated)
   Subhash P.Chavan, Shubhada W.Dantale and Rajkumar B.Tejwani.

Papers Presented

1. Solid superacids as efficient catalyst in facile transesterification of ketoesters.
   S.P.Chavan, P.K.Zubaidha, S. W. Dantale, A. Keshavaraja and T.Ravindranathan.
   International IUPAC symposium on organic synthesis, I.I. Sc., Bangalore, India, Dec.11-16, **1994**.
2. Solid superacids (Sulphated Tinoxide) for facile deprotection of allyl esters.
   S.P.Chavan, P.K.Zubaidha, S.W.Dantale, A. Keshavaraja, A.V.Ramaswamy and T.Ravindranathan.
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