SYNTHESIS OF THIAPROSTAGLANDINS AND SOME ORGANIC TRANSFORMATIONS LIKE OXIDATIVE HALOGENATION, PROTECTION- DEPROTECTION AND MULTICOMPONENT REACTIONS

A THESIS

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CHEMISTRY

BY

VASUDHA H. TILLU

DIVISION OF ORGANIC CHEMISTRY : TECHNOLOGY

NATIONAL CHEMICAL LABORATORY

PUNE - 411 008, INDIA

JULY 2006

CERTIFICATE

This is to certify that the work presented in the thesis entitled "Synthesis of thiaprostaglandins and some organic transformations like oxidative halogenation, protection- deprotection and multicomponent reactions" submitted by Vasudha H. Tillu was carried out by the candidate at the National Chemical Laboratory, Pune, under my supervision. Such materials as obtained from other sources have been duly acknowledged in the thesis.

(Dr. R. D. Wakharkar) Date :

Research Supervisor

DECLARATION

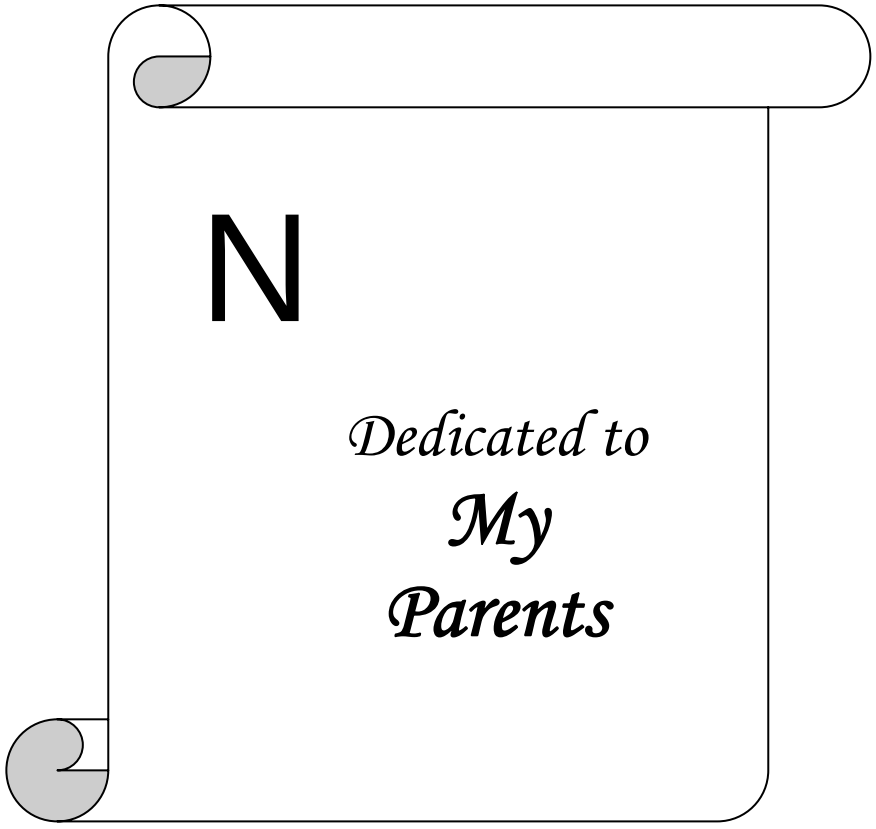
I hereby declare that the work presented in the thesis entitled “Synthesis of thiaprostaglandins and some organic transformations like oxidative halogenation, protection-deprotection and multicomponent reactions” submitted for Ph.D. degree to the University of Pune has been carried out at National Chemical Laboratory (Pune), under the supervision of Dr. R. D. Wakharkar. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Vasudha H. Tillu **Date:**

Division of Orgnaic Chemistry : Technology

National Chemical Laboratory

Pune - 411008.


N
Dedicated to
My
Parents

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Vasudha Tillu
Division of Organic Chemistry : Technology
National Chemical Laboratory,
Pune 411 008.

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
$AlCl_3$	Aluminium chloride
B.p.	Boiling Point
$BF_3.OEt_2$	Boron trifluoride diethyl etherate
Boc	*tert*-Butoxycarbonyl
br	Broad (signal)
d	Doublet
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EDC	Ethylene dichloride
ESI	Electrospray ionization
g	Grams
GC	Gas chromatography
h	Hours
HRMS	High resolution mass spectrum
IR	Infra red
KO t-Bu	Potassium *tert*-butoxide
m	Multiplet
M.p.	Melting point
M^+	Molecular ion
Me	Methyl
mg	Milligrams
min	Minutes
ml	Millilitre

mmol	Millimole
Mont/mont	Montmorillonite
MS	Mass spectrum
MW	Microwave
NaH	Sodium hydride
n-BuLi	*n*-Butyllithium
NMR	Nuclear magnetic resonance
Pet.ether	Petroleum ether
Ph	Phenyl
PPA	Polyphosphoric acid
p-TSOH	*p*-Toluene sulfonic acid
q	Quartet
r.t.	Room temperature
RBF or rbf	Round bottom flask
s	Singlet
t	Triplet
THF	Tetrahydrofuran
$TiCl_4$	Titanium (IV) chloride
TLC	Thin layer chromatography
TMEDA	Tetramethyl ethylenediamine
w/w	By weight (quantity by weight)
$ZnCl_2$	Zinc chloride

GENERAL REMARKS

- All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 º C).
- Unless otherwise stated, all commercial reagents were obtained from Aldrich Chemical. Co. and others. Progress of the reaction was monitored by TLC and was visualized by UV absorption by florescence quenching or I_2 staining or by both.
- Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi rotary evaporator. Silica gel for column chromatography was 60-120 mesh.
- Microwave irradiations were carried out in a Batliboi Eddy domestic microwave oven model No. ER 5054D operating at 2450 MHz and reactions were performed at 30% of its full power.
- All the temperatures are in º C. All the melting points and boiling points are in º C and are uncorrected and were recorded on a Buchi B-540 melting point apparatus.
- IR spectra were recorded on a Perkin-Elmer infra-red spectrometer model 599-B and model 1620 FT-IR (γ-max in cm^{-1}).
- Unless otherwise stated, ^{1}H-NMR spectra were recorded using TMS as internal reference on Bruker AC 200, MSL-300 and 400 instruments using $CDCl_3$ as solvent. All chemical shifts are reported in parts per million down field from TMS. The coupling constants (J values) are reported in Hertz.
- ^{13}C-NMR spectra were recorded on Bruker AC 200, MSL-300 or 400 instruments operating at 50 MHz, 75 MHz and 100 MHz respectively.
- ^{31}P-NMR was recorded on Bruker-400 instrument.
- Mass spectra were recorded on Finnigan-Mat 1020C mass spectrometer and were obtained at an ionization potential of 70 eV.
- GC analysis was carried out on Hewlett Packard 5890 unless otherwise stated.
- Microanalysis was carried out in the microanalytical section of NCL.
- Scheme numbers, figure numbers and reference numbers given in each section refer to the particular section only.

Title of the thesis

"Synthesis of thiaprostaglandins and some organic transformations like oxidative halogenation, protection-deprotection and multicomponent reactions."

The thesis is divided in to three chapters.

Chapter 1: Synthesis of thiaprostaglandins

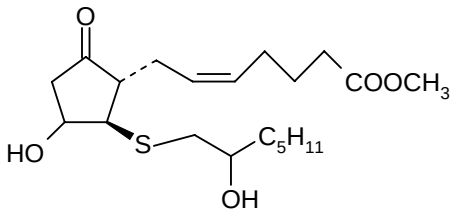
Chapter 2: Development of new methodologies for organic transformations

Chapter 3: Multicomponent reactions

CHAPTER 1 : SYNTHESIS OF 13-THIAPROSTAGLANDINS

The interest in novel prostaglandins exhibiting pharmacological specificity and increased metabolic stability has led to the synthesis of analogs possessing diverse structural modifications. One approach which has recently recieved considerable attention has been the introduction of N, O and S heteroatoms in to the prostanoic acid skeleton.[1,2] Principal efforts in this area have focused on replacement of 13-14 double bond which is known to be connected with biological activity.

Recently Orth and Radunz[3] reported the synthesis of 13-thiaprostanoids and the remarkable blood pressure lowering activity of its E type analog **1**. Luprostiol or prosolvin **2** is known to be a good leuteolytic agent in veterinary medicine.[4]



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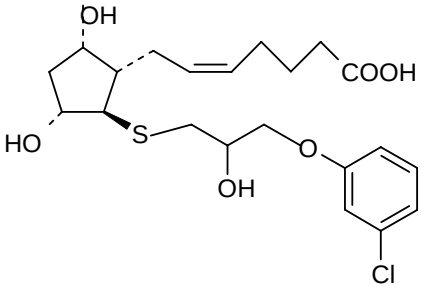

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The increased metabolic stability of these analogs prompted us to design and synthesize a number of novel 13-thiaprostaglandin analogs.

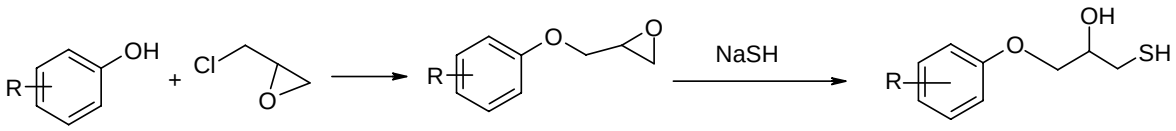
Section A : Review of literature of thiaprostaglandin synthesis and activity

Section B : Michael addition of thiols

Conjugate addition of thiols to enone acceptor is the key step for synthesis of prostaglandin molecules by two component coupling.

Synthesis of thiols

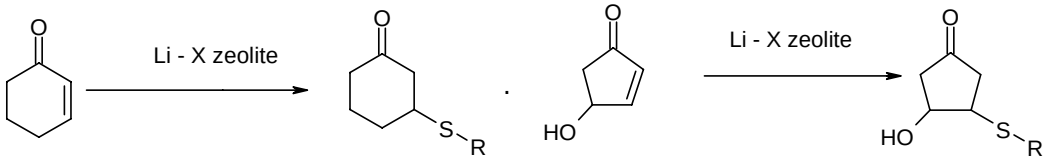
The thiols required were prepared by reacting substituted phenols with epichlorohydrin and opening of the resultant epoxy ether with NaSH to afford the desired product in good yield (Scheme 1).



Scheme 1

Conjugate addition of thiol

The Michael reaction of thiols is traditionally catalyzed by strong bases such as alkali metal alkoxides and hydroxides, triethylamine etc. The limitations of these strong bases in these reactions are mainly the formation of undesirable side products by polymerization, bis-addition and self-condensations. In order to find a solution to this problem, we prepared a series of basic zeolite catalysts and carried out Michael addition using cyclohexenone and 4-hydroxy cyclopentenone as model Michael acceptors (Scheme 2).



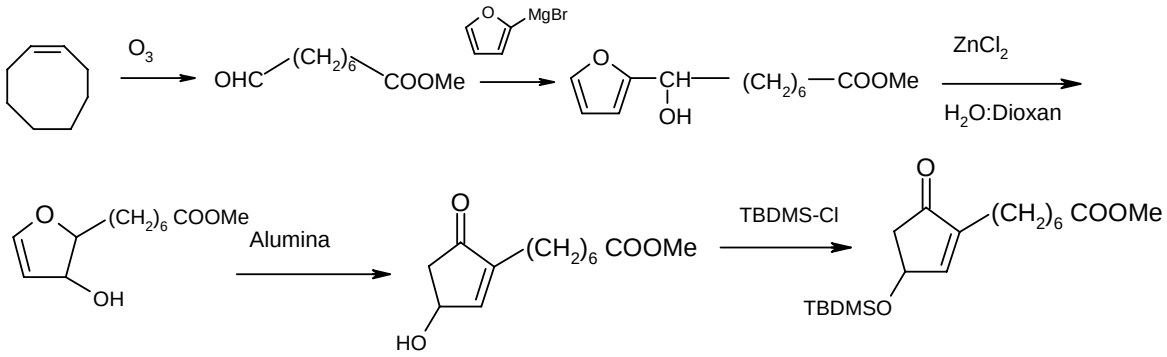
Scheme 2

Using Li incorporated X type zeolite only Michael adduct was formed in good yield without formation of undesirable dimer of thiol. The methodology was substantiated by several examples.

Section C

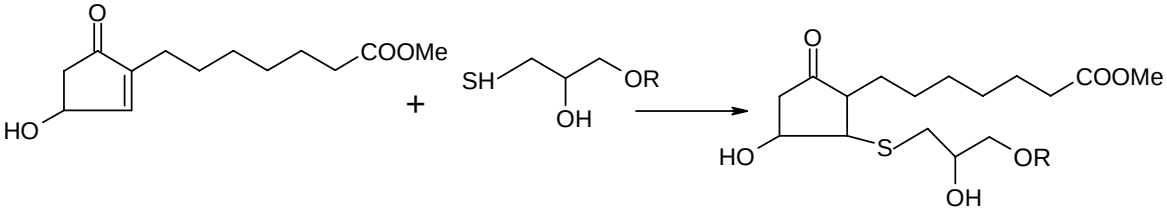
Synthesis of 13-thiaprostaglandins

After standardizing the Michael addition catalyzed by Li-X zeolite, we applied this method for synthesis of 13-thiaproslaglandins. The intermediate enone **3** required for this reaction was synthesized by ozonolysis of cyclooctene to form aldehyde-ester which on Grignard reaction with furylmagnesium bromide gave the addition product. Rearrangement of this product with $ZnCl_2$ in H_2O, dioxan and subsequently on alumina gave the desired intermediate **3** (Scheme 3).



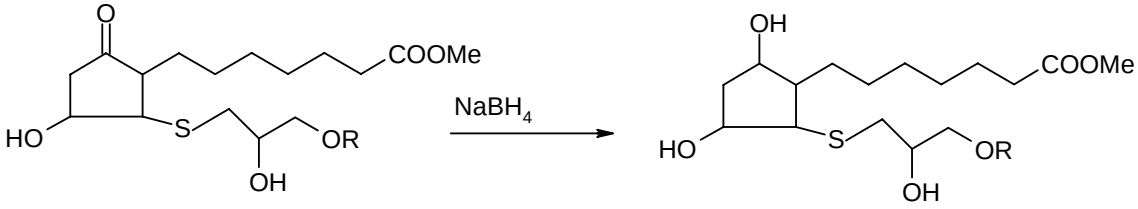
Scheme 3

The intermediate **3** was then subjected to Michael addition of various thiols using LiX zeolite to afford novel 13-thiaprostaglandins (Scheme 4).



Scheme 4

The ketone functionality in these thiaprostaglandin E analogs was reduced with $NaBH_4$ to yield corresponding hydroxyl derivatives i.e. PGF analogs in almost quantitative yield (Scheme 5).



Scheme 5

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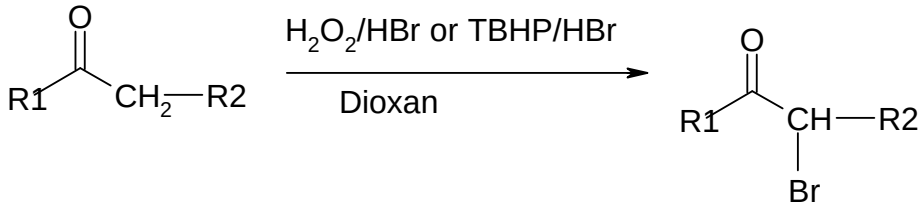
CHAPTER 2 : ORGANIC TRANSFORMATIONS

Section A : Bromination of active methylene by a mixture of hydrobromic acid and hydrogen peroxide (or TBHP)

α-Bromoketones form an important class of intermediates as they can be converted efficiently in to several compounds by simple chemical transformations. Bromination of such compounds have been carried out with molecular bromine[1] as such or generated *in situ* or with reagents such as dibromobarbituric acid,[2] dioxanedibromide,[3] pyridinium hydrobromide perbromide,[4] polymeric reagents[5] . The reagents listed above are not easy to prepare and they are expensive or generate byproducts after bromination which are difficult to separate from the reaction mixture. Bromination with elemental bromine utilizes only 50% of bromine with other half forming HBr waste.

We have explored an effecient reagent system comprising a mixture of hydrohalic acid and hydrogen peroxide or *tert*-butylhydroperoxide (TBHP) for the bromination of compounds having active methylene group (Scheme 6).



Scheme 6

When a ketone was added to a solution of halogenation reagent formed by adding TBHP/H_2O_2 to a cooled mixture of HBr (48% aq) in dioxan (5 ml) at 10°C and heated to completion of reaction, α-brominated ketone was obtained in good yield whereas acetophenones with strong activating substituents like hydroxyl resulted into aromatic bromination. In conclusion, we have presented selective bromination of active methylene in high yields by applying our halogenation system using a combination of hydrobromic acid and H_2O_2 or TBHP.

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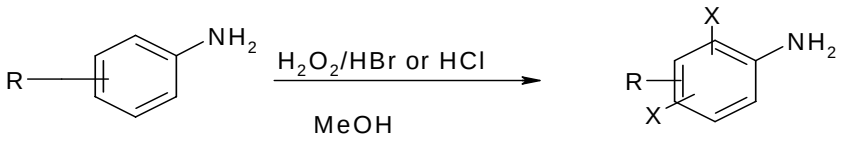
Section B : Regioselective halogenation of anilines

Aromatic primary amines have been converted to the corresponding anilides prior to halogenation if monosubstitution was desired.[1] Preparation of halogenated compounds using molecular halogen with or without transition metal based catalysts has several environmental drawbacks arising out of the toxic nature of the reagents and catalysts. However new methods allowing good control over selectivity and polybromination of unprotected anilines have been reported of which oxidative bromination using a combination of KBr, H_2O_2 and various metal-oxide catalysts have gained much interest.[2,3] We have presented our results towards an environmentally safe and efficient bromination of aromatic amines by *in situ* oxidation of HCl/ HBr with hydrogen peroxide.We have found that when aromatic amine was treated with aqueous mixture of H_2O_2 and HBr in refluxing MeOH, selectively mono or di- halogenated products could be obtained depending on the stoichiometry of the reagents used (Scheme 7).



X=Br or Cl

Scheme 7

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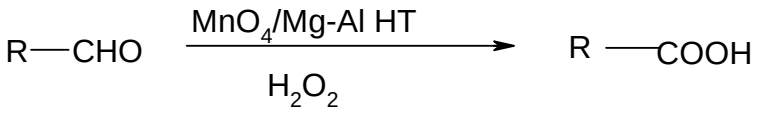
Section C : Selective oxidation of aldehydes to carboxylic acids

Although several oxidising agents have been used for oxidation of aldehydes to carboxylic acid, the problem of the efficient conversion of aromatic aldehydes to arene carboxylic acids remains still open.[1] The most common oxidants such as chromic acid, potassium permanganate in acid, basic and neutral solution, bromine, nitric acid, silver oxide and others are not attractive because they do not fulfill the requirements of modern practical organic synthesis and environmental restrictions. On the other hand, oxidation with environmentally friendly reagents such as dioxygen gives poor results. Using peroxyacids or hydrogen peroxide in the presence of various catalysts lead to phenols since competitive Baeyer- Villiger rearrangement takes place [2] especially for aromatic aldehydes with electron-donating substituents.[3] Several transition metal catalysts have been reported to be effective for this oxidation but the toxic waste arising from the used catalysts make the method environmentally undesirable. Reusable heterogeneous catalytic oxidation with H_2O_2 would be a eco-friendly method for oxidation of aldehydes. Hence a series of MnO_4 incorporated Mg-Al hydrotalcites were prepared and used as a catalyst for oxidation of benzaldehyde to benzoic acid. Out of the 11 catalysts tested, MnO_4/Mg-Al HT was found to be most effective. In this work we provide the evidence that oxidation of aromatic aldehydes having electron withdrawing or electron donating

substituents with H_2O_2 leads almost exclusively to carboxylic acids when MnO_4/Mg-Al HT is used as an oxygen transfer catalyst (Scheme 8).



R = aromatic with electron withdrawing or electron donating substituents, heterocyclic or aliphatic group.

Scheme 8

These new catalysts will add to the rapidly expanding repertoire of heterogeneous catalysts used in organic synthesis.

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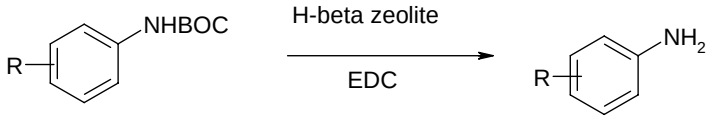
SECTION D

Selective removal of the N-(*tert*-butoxycarbonyl) protecting group using H-β zeolite

The *tert*-butoxy carbonyl (BOC) group is extensively used as a convenient group for protecting a variety of amino compounds due to its stability towards mild acidic or basic conditions. In general the deprotection of N-BOC group is performed by using strong acids like trifluoroacetic acid (TFA) [1]or HNO_3, [2] $Yb(OTF)_3$ supported on silica gel, Mont K-10. However the incompatibility of some functional groups with strong acid, large amount of adsorbent required for heterogenous reaction and limited reusability of catalysts are some of the limitations of reported procedures. We found that when N-aromatic N-BOC compounds were refluxed in EDC in the presence of catalytic amount of H - β zeolite, the corresponding amines were obtained in excellent yields; where as aliphatic amines, t-butyl ester and acetal group remains unaffected under the reaction conditions (Scheme 9).



Scheme 9

This difference in the reactivity pattern of N-BOC derivative could probably be utilized in selective manipulation of N-BOC deprotection in a synthetic sequence.

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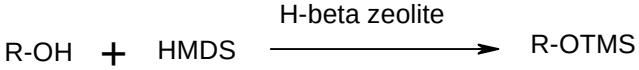
SECTION E

Selective silylation of alcohols, phenols and naphthols with HMDS catalyzed by H-β zeolite

Trimethyl silylation of organic compounds having labile hydrogen atom is frequently used protection method in multistep synthesis of natural products. Out of several silylating agents reported, silylation using commercial HMDS is a method of choice as the reaction is nearly neutral, does not need special precaution and products are separated from excess HMDS easily. However, the low silylating power of HMDS has necessisated the use of catalysts like trimethylsilylchloride,[1] sulfonic acid,[2] $ZnCl_2$,[3] montmorillonite K-10[4] etc. To make the methodology eco friendly, we carried out the reaction without using solvent. Use of H-β zeolite as a catalyst increased the yield of product and shortened the reaction time remarkably. When an alcohol, phenol or naphthol, HMDS and 10% (w/w) H-β zeolite was heated at 80ºC, the corresponding TMS ethers were obtained in excellent yield, whereas amines and thiols remained unaffected under the reaction conditions (Scheme 10).



R = primary, secondary and tertiary alkyl, aryl or cyclohexyl

Scheme 10

This methodology has the advantage of enhanced yield and good selectivity. The reusability of the catalyst makes this method ecofriendly.

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CHAPTER 3 : MULTICOMPONENT REACTIONS

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of structural complexity and diversity with a minimum number of synthetic steps. Multicomponent reactions have several advantages like atom economy, simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules as well as very large number of accessible compounds.

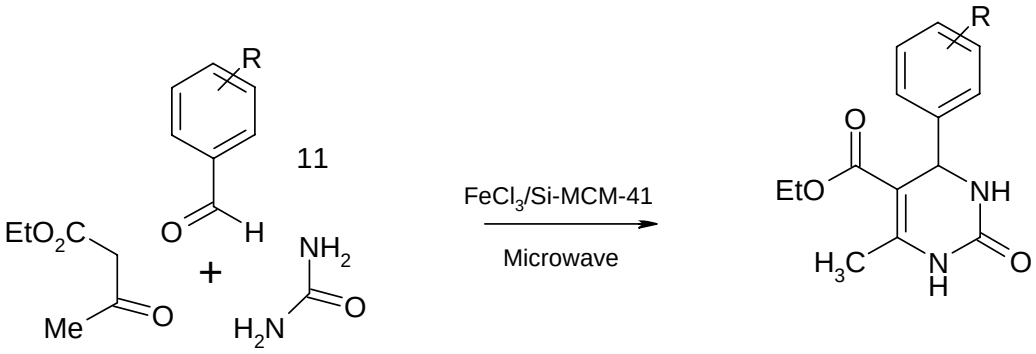
The outcome of a MCR is crucially dependent on the nature of solvents, catalyst concentrations and excess of reagents used; making the optimization of ideal reaction conditions more demanding when compared with sequential reaction schemes. The unparalleled atom efficiency of this diversity oriented synthesis prompted us to undertake work by introducing novel catalysts and reaction conditions.

Section A : Si-MCM –41 supported $FeCl_3$ catalyzed synthesis of dihydropyrimidinones

Dihydropyrimidinones are known to exhibit pharmacological and therapeutic activities like anti- hypertensive agent, calcium channel blockers etc.[1, 2] The classical synthesis of DHPM's by Biginelli reaction involving the one-pot multicomponent condensation of β-ketoesters, aldehydes and urea in refluxing ethanol containing a catalytic amount of HCl[3] gives low yields of product for substituted aldehydes. Several homogeneous catalysts

such as polyphosphate esters, HCl – $FeCl_3$, $SnCl_2$, $ZnCl_2$ or $CuCl_2$, $InCl_3$, $InBr_3$ have been used to circumvent the problem of low yield.

It is of practical importance to synthesize DHPMs under solvent free conditions using easily separable and reusable solid catalysts so that the synthesis is environ-friendly producing little or no waste. Hence several metal chlorides supported on Si-MCM-41 and Mont K-10 were tested for this reaction. Out of the several catalyst tried, $FeCl_3$ supported Si-MCM-41 was found to catalyze formation of DHPMs with substituted benzaldehydes or other aromatic aldehydes without any solvent under microwave irradiation for a short period (Scheme 11).



Scheme 11

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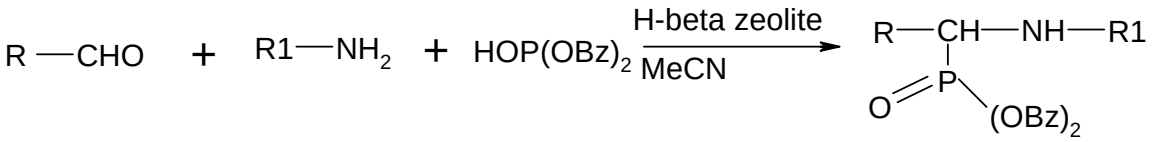
Section B : H-β catalysed Kabachnik – Field synthesis of α-aminophosphonates

The potential of α-aminophosphonates and α-aminophosphonic acids as peptide mimetics[1] enzyme inhibitors,[2] antibiotics and pharmacologic agents[3] has been well established. A number of synthetic methods for α-aminophosphonates synthesis have been developed. Of these methods, the nucleophilic addition of an amine to a carbonyl

compound followed by addition of dialkyl phosphites to the resulting imines catalyzed by a base or an acid is most convenient. Benzyl phosphonates were designed as hydrolysis of benzyl group is relatively easy. The reaction of benzaldehyde, aniline and dibenzyl phosphite did not yield the product with good yield and selectivity. Hence a method was developed wherein H-β was used as a catalyst to obtain the desired product in good yield.

A solution of aliphatic or aromatic aldehyde or ketone, aliphatic or aromatic amine and dibenzyl phosphite (1.2 mmol) containing10% H-β in refluxing MeCN yielded exclusively the corresponding aminophosphonates in excellent yield (Scheme 12).



Scheme 12

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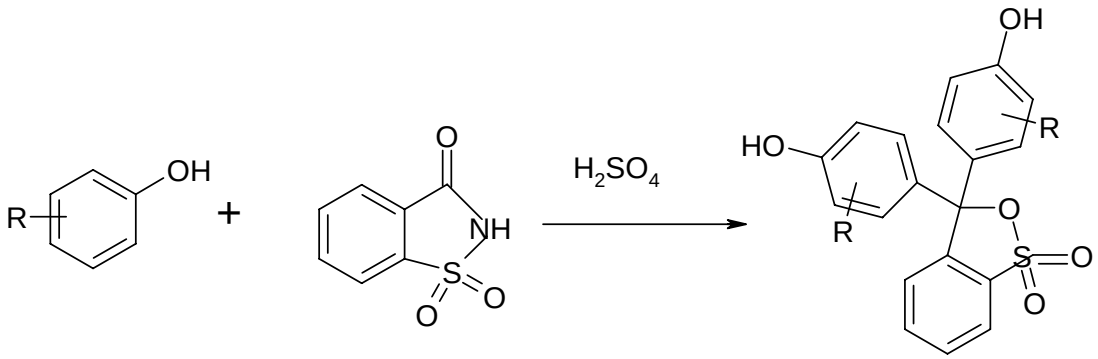
Section C : Synthesis of sulfonephthalein dyes

The sulfonephthaleins constitute a group of compounds that have been extensively used both as indicators and as diagnostic aids in clinical and experimental medicine.[1]

The synthesis of these compounds is reported by condensation of substituted phenol with anhydride or chloride of acid [2] for 8 to 20 hours. However, the o-sulfobenzoic anhydride is expensive. We have developed a methodology wherein sulfonephthalein were obtained directly from the more economical saccaharin in one step in few hours (Scheme 13).



Scheme 13

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LIST OF PUBLICATIONS

1. Li-X type zeolite mediated Michael addition of thiols to cyclic enones and its application in the synthesis of 13-thiaprostaglandins;
   Popat D. Shinde, Vishal A. Mahajan, Hanumant B. Borate, **Vasudha H. Tillu,** Rajaram Bal, Asha Chandwadkar, Radhika D. Wakharkar; *Journal of Molecular Catalysis A : Chemical* **216 (1)** 115-119, 2004.

2. Selective removal of the N- (*tert*- butoxy carbonyl) protecting group using H-β zeolite;
   Vasudha H. Tillu, Radhika D. Wakharkar, Rajesh K. Pandey and Pradeep Kumar;
   Indian Journal of Chemistry Section B, **43**, 1004-1007, 2004.

3. Studies on bromination of active methylene by a mixture of hydrobromic acid and hydrogen peroxide (or TBHP);
   Vasudha H. Tillu, Popat D. Shinde, Ashutosh V. Bedekar, and Radhika D. Wakharkar
   Synthetic Communications, **33(8)**, 1399-1403, 2003.

4. Solvent free selective silylation of alcohols, phenols and naphthols with HMDS catalyzed by H-β zeolite;
   Vasudha H. Tillu, Vinod H. Jadhav, Hanumant B. Borate and Radhika D. Wakharkar;
   ARKIVOC (xiv) 83-88, 2004.

5. Microwave assisted solvent-free synthesis of dihydropyrimidinones by Biginelli reaction over Si-MCM-41 supported $FeCl_3$ catalyst;
   V. R. Choudhary, **V. H. Tillu,** V. S. Narkhede, H. B. Borate, R. D. Wakharkar.
   Catalysis Communications, **4**, 449-453, 2003.

6. Natural Kaolinitic clay and EPZG : Efficient solid catalysts for selective regeneration of carboxylic acids from their corresponding allyl or cinnamyl esters; A. S. Gajare, **V.R.Kulkarni**, N. B. Barhate, M. S. Shingare and R. D. Wakharkar, *Synthetic Communications*, **28**, 25-33, 1998.

7. A process for the preparation of 3-sulfanyl cyclic ketones.
T. Ravindranathan, R. D. Wakharkar, H.B.Borate, P. D. Shinde, V.A.Mahajan, **V.H. Tillu**, S.Ghumre and H.S.Jagtap. Indian patent. NF-374/99 (Submitted Dec 1999, filed 17.2.2000.

8. MnO_4 /Mg-Al hydrotalcite catalyzed selective oxidation of aldehydes to carboxylic acids
V. H. Tillu, D.A.Dumbre, V.R.Choudhari, R. D. Wakharkar. (Manuscript under preparation).

Chapter 1

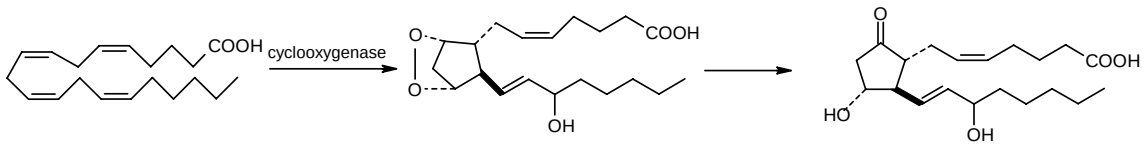
Synthesis of thiaprostaglandins

CHAPTER 1

(section A)

Review on thiaprostaglandins : Synthesis and activity

Prostaglandins (PGs) are naturally occurring substances found in animals and playing important regulatory roles in many normal cellular functions in human beings. They are biosynthesized from C_{20} polyunsaturated fatty acids *via* a cyclooxygenase enzyme system widely distributed in mammalian tissues.



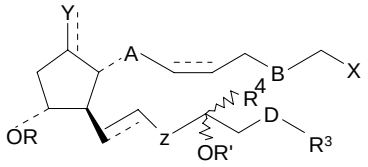
1 **2** **3**

Arachidonic acid **PGH_2** **PGE_2**

Scheme 1: Biosynthesis of prostaglandins

In contrast to hormones PGs do not circulate nor are they stored in tissues, but are synthesized locally on demand, perform a tissue specific function and are rapidly inactivated by metabolic enzymes. Given extrinsically, they can exert a host of pharmacological effects and have been the subject of extensive research and chemical modification by pharmaceutical companies in the quest for drug candidates. The road to therapeutic utility however is impeded by three major problems with natural PGs : 1) chemical instability, 2) rapid metabolism and 3) incidence of numerous side effects. To overcome these problems, several PG analogues with modified structure were synthesized and studied for their activities. Among the several modifications carried out in the structure of prostaglandins, the introduction of heteroatom like N, O or S have reported to effect the biological activity of PGs. Numerous sulfur containing PGs or thiaprostaglandins have been therefore synthesized and studied for their biological activity.

In 2002 Burk *et al.*[1] prepared thia and oxa prostanoic acid derivatives as agents for lowering intraocular pressure. They found that a method of treating ocular hypertension or glaucoma comprises administering therapeutically effective thia or oxa prostanoic acid derivatives such as **4** and **4A**.



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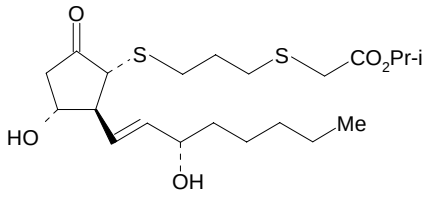
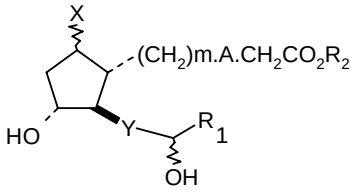


4A

Where wavy lines = α or β configuration; dashed lines = single or double bonds; A = O, S, CH_2, B=CH_2, O, S, NH; X = CO_2R, $CONR^2$, CH_2OR, P(O) $(OR)_2$, CO, $NRSO_2R$, $SONR^2$, Y = O, OH, $OCOR^2$, halogen, CN; Z = CH_2, bond; R = H, R^2; R^1 - H, R^2 Ph, COR_2, R^2 = alkyl, alkenyl, R^3 = benzothienyl, benzofuranyl, naphthyl, R^4 = alkyl.

Fig 1: Thiaprostanoic acid derivatives for lowering intraocular pressure

Prostaglandin derivatives with structure **5** were found to have prostaglandin D_2-like agonist activity.[2]



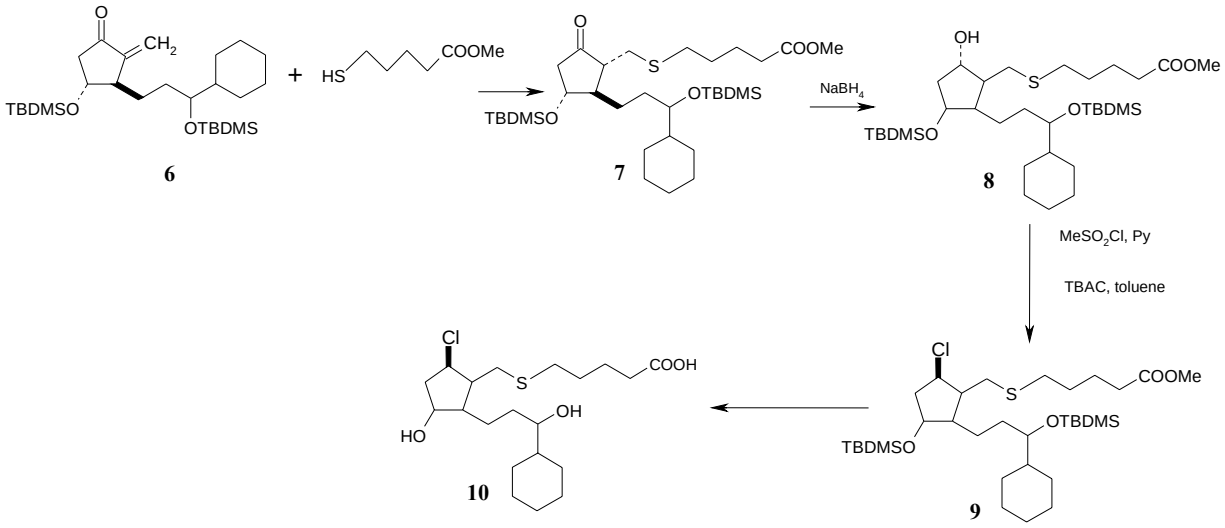
5

Where X=halogeno, Y= ethylene, vinylene or ethynylene; A=$O(CH_2)_n$, $S(O)_p(CH_2)_n$, $S(O)_p(CH_2)_q$, $S(O)p(CH_2)_r$ or $S(O)_p$ $(CH_2)_qO(CH_2)_r$ (n=1, 2 or 3, p=0, 1 or 2, q=1, 2 or 3 and r=0 or 1)R^1=C_{3-10} cycloalkyl, C_{1-4} alkyl; R^2= H,C_{1-10} alkyl and m is 0, 1 or 2.

Fig 2: 6-Thiaprostaglandins having prostaglandin D_2-like agonist activity

These compounds were prepared e.g. by addition reaction of 5-mercaptopentanoic acid methyl ester with (3R, 4R)-2-methylene-3- [(3S)-3-(tert-butyldimethylsilyloxy)-3-cyclohexylpropan-1-yl]- 4-(tert-butyldimethylsilyloxy) cyclopentan-1-one (**6**, scheme 2) in the presence of triethyl borane in toluene at 0º C overnight. The 6-thia-16, 17, 18, 19, 20-pentanor - 15 - cyclohexyl - 13, 14 - dihydroprostaglandin $F_{1\beta}$ Me ester 11, 15 - bis (tert - butyldimethylsilyl) ether **7** obtained, underwent reduction with $NaBH_4$ in MeOH at 0ºC to give the corresponding $F_{1\alpha}$ and $F_{1\beta}$ analogues **8**. Mesylation of these PGF

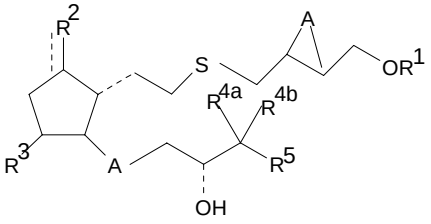
analogues by $MeSO_2Cl$ in pyridine at room temperature for 2 hours followed by chlorination with tetrabutylammonium chloride in toluene at 45º C overnight gave 6-thia-9- deoxy - 9 β -chloro - 16, 17, 18, 19, 20 - pentanor - 15 - cyclohexyl - 13, 14 - dihydro - prostaglandin F_1 Me ester 11, 15 - bis (tert-butyldimethylsilyl) ether **9** which underwent desilylation with methanolic HCl at room temperature for 2 hours followed by saponification and acidification to give 6 - thia - 9 - deoxy - 9β - chloro - 16, 17, 18, 19, 20 - pentanor - 15 - cyclohexyl - 13, 14 - didehydro - prostaglandin $F_{1\,\beta}$ (**10**).



Scheme 2 : Synthesis of thia analog of $PGF_{1\alpha}$ for production of cyclic adenosine monophosphate in bovine trachea.

This compound *in vitro* promoted the production of cyclic adenosine monophosphate in bovine trachea. The compounds with structure shown in Fig. 3 exhibit excellent prostaglandin D_2 - like agonism and a sleep - inducing effect with excellent stability and intracerebral transferability. They are useful for the treatment of cardiovascular diseases such as kidney diseases, ischemic heart diseases, heart failure and hypertension and glaucoma.

The carboxylic acids formed *in vivo* from 5 -thia - ω - (substituted phenyl) - prostaglandin E alcohols (Fig. **3**, **11**) strongly bind to PGE_2 receptors, so that the alcohols **11** are expected to be useful in the prevention and treatment of immunopathy, asthma, bone dysplasia, nerve cellular death, lung failure, hepatopathy, acute hepatitis, nephritis, renal failure, hypertension, myocardial ischemia, systemic inflammatory reaction syndrome, septicemia, hemophagocytosis syndrom, sleep disorder and platelet aggregation.[3]



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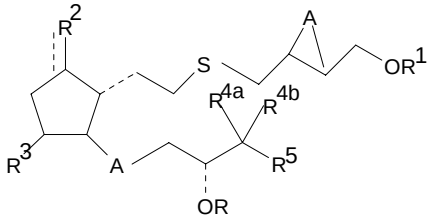
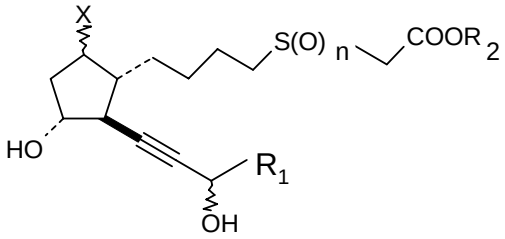


12

A is CH_2 or CH_2CH_2, R^1=H, C_{1-6} alkyl, phenyl-C_{1-6} alkyl, C_{2-6} alkanoyl, phenyl-C_{2-6} alkanoyl, R^2=oxo, halo; R^3 = H, OH, R^4 = H, C_{1-4} alkyl; R^5=subst Ph.

Fig 3: 5-Thia-ω-substituted phenyl PGE alcohols which strongly bind to PGE_2 receptors

Prostaglandins like 3 - thia - 9 - deoxy - 9β - chloro - 16, 17, 18, 19, 20 - pentanor - 15 - cyclohexyl - 13,14 - didehydro $PGF_{1\alpha}$ methyl ester 3-oxide (**13**) were found to strongly bind to PGE_2 receptors in particular subtype EP4, so that they are useful in preventing and/or treating immunological diseases, asthama, bone dysplasia etc. Since PGE_2 receptors participate in sleep disorders and platelet aggregation, these compounds are expected to be useful in prevention or treatment of these disesases.



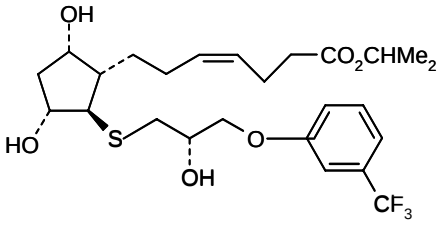
13

where X = halo; n = 1 - 2; R_1 = (un) substituted C_{3-10} Cycloalkyl, C_{4-13} cycloalkyl/alkyl, C_{5-10} alkyl hydrates or salts, R_2=alkyl.

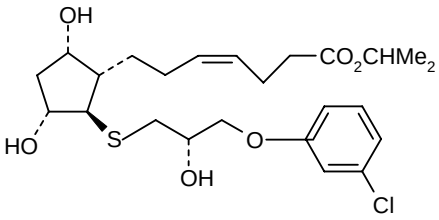
Fig 4: $PGF_{2\alpha}$ analogues for preventing immunological diseases

Such compounds have been prepared by reacting the corresponding thiaprostaglandin methyl esters with sodium metaperiodate in MeOH - H_2O at O^oC to room temperature for two to five hours[4] and were found to be useful for treatment of renal disease, ischemic heart disease, heart failure, hypertension etc.

In 1998 Zinke and Hellberg[5] prepared the 13-thiaprostaglandins **14a** and **14b** and found them effective for treatment of glaucoma and ocular hypertension.



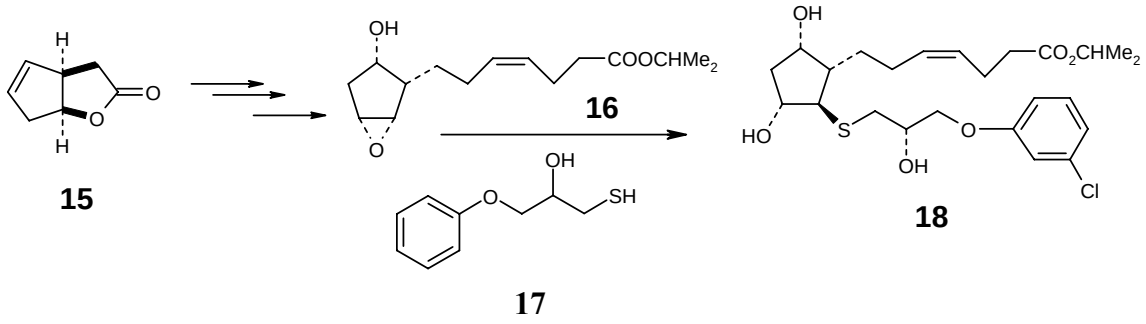
14a



14b

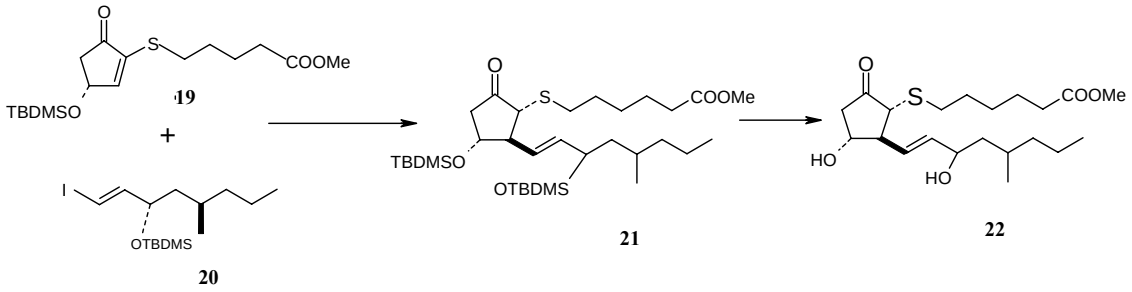
Fig 5: 13-Thiaprostanoic acid esters for treatment of glaucoma and ocular hypertension.

The 13-thiaprostaglandins were synthesized from the epoxy cyclopentyl heptenoic acid derivative, which was prepared in four steps from (–) – cis-oxabicyclo [3.3.0] oct-6-en-3-one, was treated with 2-hydroxy - 3 - (3 - trifluoromethylphenoxy) propanethiol to give the thiatetranor - 4 – prostenoic acid derivatives **14a** and **14b**. They found that the thiatetranor 5 – prostenoic acid derivatives **14a** and **14b** with a low incidence of side effects, exhibit a significantly improved therapeutic profile of $PGF_{2\alpha}$ iso-propyl ester (Scheme 3).



Scheme 3: Synthesis of 13-Thiaprostanoic acid.

7-Thiaprostaglandins. (**22**) were reported to inhibit cell migration caused by chemokives such as monocyte migration factor MCP - 1 / MCAI and thus they are useful for the treatment of arteriosclerosis, diabetic angiopathy etc.



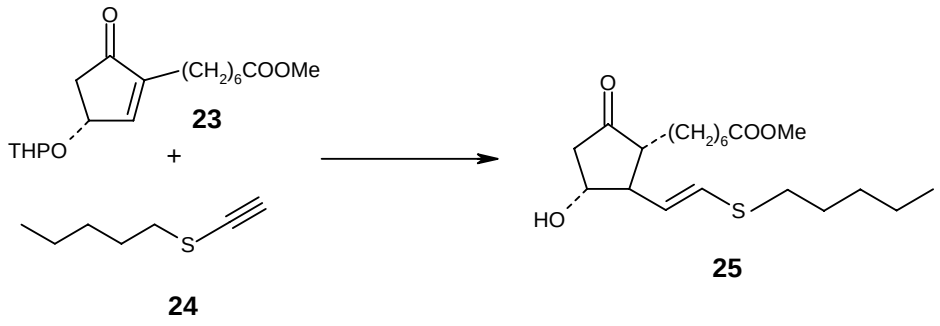
Scheme 4 : Synthesis of 7-thiaprostaglandins

Thus the reaction of (1E, 3S, 5R) - 1 - iodo – 3- (tert-butyldimethylsilyloxy) - 5 - methyl - 1 - octene **20** with (4R) - 4 – tert- butyldimethylsilyloxy -2 - (5 - methoxycarbonyl pentylthio) -2 -cyclopenten - 1 – one **19** and butyric anhydride was found to yield **21** which was desilylated to give the corresponding diol **22** (Scheme 4)[6].

Golubeva *et al.*[7] studied the influence of six endoperoxide 13-thia analogs on the primary immune response, the reaction of delayed hyper sensitivity on the function of mononuclear phagocyte system cells and radiosensitivity of CBA mice. They found that the compound containing a fragment of thiolacetic acid depressed the humoral immunity.

One compound decreased the reaction of delayed hypersensitivity by 35% and three prostanoids stimulated it by 19-46% . Two of these stimulators increased the number of antibody - forming cells by 37 – 65% and hem agglutinin titer by 25-45%. One compound increased the functional activity of mononuclear phagocytes. Three compounds with immunostimulating properties administered before and after gamma irradiation, increased 15 - day survival by 47 - 53%. Two of them administered before and after irradiation increased 30 - day survival by 50% and average life of mice by 35 – 85%. Thus, 13 - thia analogs of endoperoxide are perspective for creating new immuno-stimulating and radio- protective compounds.

The compound **25** has been prepared by the zirconocene chloride mediated conjugate addition of an n - pentyl ethynyl sulfide - derived anion to the cyclopentenone (**23**). Similar methodology has been used to prepare other 3- (3' - thia – 1' - octenyl) cyclopentanones (Scheme 6).[8]



Scheme 6: Zirconocene chloride mediated conjugate addition for the preparation of 15 - thia - 15 - deoxy analogue of prostaglandin E_1 methyl ester

Thus, thiaprostaglandins have a potential in the treatment of various ailments and improved methods for their synthesis would be useful to make more number of thiaprostaglandins for further study.

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8. Holland, H.;Ratemi, E.;Contreras, L. *Can. J. Chem*. 1994, **7**,1-5.

CHAPTER 1
(Section B)

Michael addition of thiols

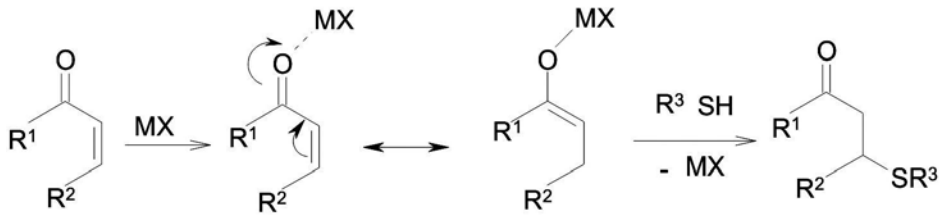
1.2.1 Introduction

The Michael addition reaction, a base promoted 1, 4 - addition of nucleophile to α, β - unsaturated esters, ketones, nitriles, sulfones, nitro-compounds etc, is one of the effective and versatile method for C-C, C-N and C-S bond formation. The Michael addition of thiols to α, β-unsaturated carbonyl compounds constitutes a key step in biosynthesis[1] and in synthesis of bioactive compounds such as calcium antagonist diltiazem.[2a] The reaction gains further importance in synthetic organic chemistry as: i) it provides a means to protect the olefinic double bond of α, β-unsaturated carbonyl substrates[2b] due to the ease of regeneration by removal of the sulfur group either by copper (I) induced elimination[3] or by oxidation followed by thermolytic elimination,[2b] and ii) the resultant β-sulfidocarbonyl compounds serve as starting materials for the generation of β-acylvinyl cation equivalents[4] and homoenolate equivalents.[5]

Traditionally 1, 4-addition of mercaptans is catalyzed by strong amine bases.[6] Though these strong bases are effective for unfunctionalised thiophenols, some functionalized thiols and enones are susceptible to basic conditions. Use of these strong bases leads to the formation of undesirable side products due to competing reactions like polymerization, self-condensation and rearrangement.[7] The importance of this reaction has led to several reports and the modifications resulted in use of stoichiometric to catalytic amount of base. Several methodologies based on addition of thiols by activation of acceptors with Lewis acids or activation of thiol nucleophile by bases have been reported to generate Michael adducts with increased efficiency.

A large number of methods have been reported for the 1, 4-addition of thiols to electron deficient olefins through the activation of thiols by bases.[8-13]

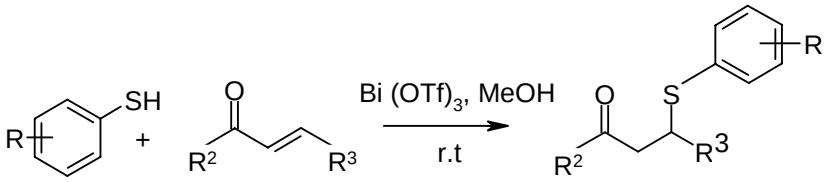
The role of Lewis acid catalyst in the thia-Michael addition reaction can be envisaged as an electrophilic activation process during which coordination of the Lewis acid with the carbonyl oxygen of the α, β-unsaturated carbonyl compounds renders it more susceptible to nucleophilic attack at the β-carbon (Scheme 1).



26 **27** **28** **29**

Scheme 1 : Role of Lewis acid in the Michael addition

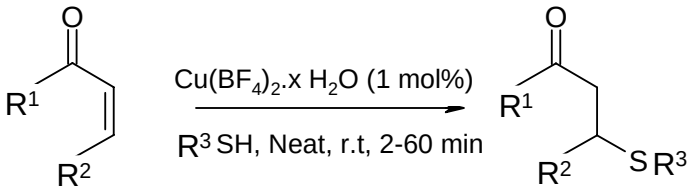
The 1, 4-addition of sulfur nucleophile to electron deficient olefins to form a carbon - sulfur bond was carried out using $Bi(OTf)_3$.[14] Substituted and unsubstituted aromatic thiols were used with numerous cyclic and acyclic ketones.



30 **31** **32**

Scheme 2 : Michael additions of thiols with various conjugate acceptors

Garg *et al.*[16] found that copper (II) tetrafluoroborate $Cu(BF_4)_2.xH_2O$ is an efficient electrophilic activation catalyst of enones for Michael addition reactions with thiols.

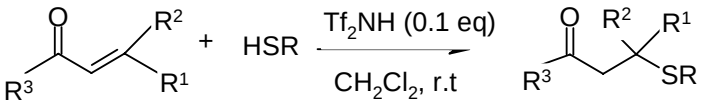


33 **34**

Scheme 3 : $Cu(BF_4)_2.xH_2O$ catalyzed Michael addition of thiols to enones

The reaction was carried out at room temperature and non-anhydrous conditions. This catalyst gives improved yields in shorter reaction period compared to other Lewis acids like $InBr_3$, $BiNO_3$, $Bi(OTf)_3$.

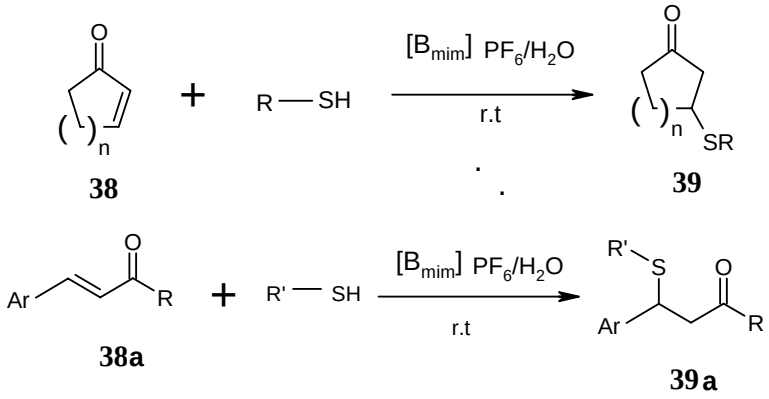
Since thiols have tendency to poison Lewis acid, strong Bronsted acids such as bis (trifluoromethanesulfon) imides (Scheme 4) were used to catalyze the hetero-Michael addition of thiols to α, β-unsaturated ketones, alkylidene malonates and acrylimides.[15]



35 **36** **37**

Scheme 4 : Tf_2NH catalyzed Hetero-Michael addition with sulfur nucleophile

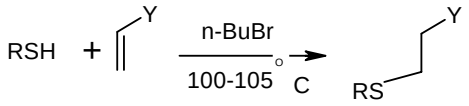
onic liquid $[B_{mim}]$ PF_6/H_2O system (2:1)[16] was found to be an effective alternative reaction medium for the conjugate addition of thiols to α, β-unsaturated ketones in absence of any acid catalyst to afford the corresponding Michael adducts with excellent 1,4 - selectivity under mild and neutral conditions (Scheme 5).



Scheme 5 : Michael addition in ionic liquid

The enones show enhanced reactivity in ionic liquids thereby reducing reaction times and improving the yield significantly. The use of ionic liquids helps to avoid the use of either acid or base catalysts for this conversion. The recovered ionic liquid was reused four to five times with consistent activity.[16]

Though use of ionic liquid as solvent and catalyst is known to be useful in the context of green synthesis, the high cost of most of the conventional room temperature ionic liquids and apprehension regarding the toxicity of some of them has led to the use of more benign salts in molten state as practical alternatives. Molten tetrabutylammonium bromide was found to efficiently catalyze the conjugate addition of thiols to α, β-unsaturated nitriles, carboxylic esters, ketones and aldehydes as well as nitroolefins (Scheme 6) .[17]



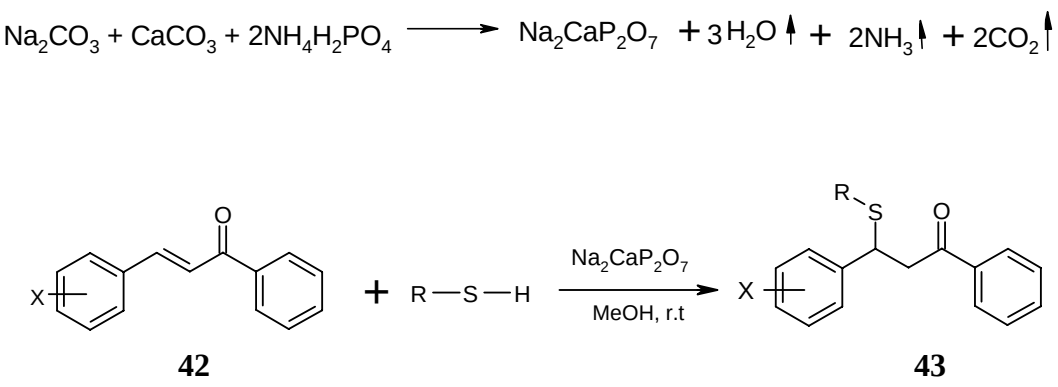
40 **41**

Scheme 6: Michael addition of thiols catalyzed by n-BuBr

In recent years, there has been increasing emphasis on the design and development of environment-friendly solid base catalysts to replace soluble bases.[18] The objective to eliminate undesirable side products and reduce salt formation consequent to the neutralization of soluble bases with acids is prompted by more stringent laws laid down for the protection of environment.

Various heterogeneous catalysts have been employed to accelerate hetero-Michael reaction. These include lanthanides,[3] heteropolyacids,[18] aluminium oxide,[19a,b] Al_2O_3 / KF,[2a] $Al_2O_3/ZnCl_2$,[2b] montmorillonite / $NiBr_2$,[20] Mg - Al hydrotalcite,[21] natural phosphate doped by potassium fluoride,[19c] various fluorides,[7] SiO_2[8] and functionalized silica.[8]

Mohamed Zahouily *et al.*[11] found that a synthetic phosphate $Na_2CaP_2O_7$ catalyzes Michael addition between chalcone derivatives and mercaptans.
This heterogeneous catalyst was prepared from Na_2CO_3, $CaCO_3$ and $NH_4H_2PO_4$ in proportions 1:1:2 respectively as shown in scheme 7.



42 **43**

Scheme 7: Michael addition catalyzed by synthetic phosphate $Na_2CaP_2O_7$

The use of this heterogeneous catalyst prevents the formation of products of undesirable side reactions resulting from 1, 2-addition, polymerization and bis-addition.

Use of zeolite catalysts due to their characteristic properties such as shape selectivity, thermal stability, acidic and basic nature and reusability has gained considerable attention for last decade. Zeolites are aluminosilicates that are constructed from TO_4 tetrahedra (T = tetrahedral atom, e.g. Si, Al) with each apical oxygen atom shared with an adjacent tetrahedron. When tetrahedra containing Si^{4+} and Al^{3+} are connected to form a three dimensional zeolite framework, there is a negative charge associated with each Al^{3+} atom. The negative framework charge is balanced by an exchangeable cation, yielding electrical neutrality. Zeolite X is a faujasite type zeolite with a silicon - to - aluminium ratio ranging from 1 to 1.5. The highly porous nature and the need for charge balancing cations of faujasite, a type of zeolite, is illustrated in fig 1.

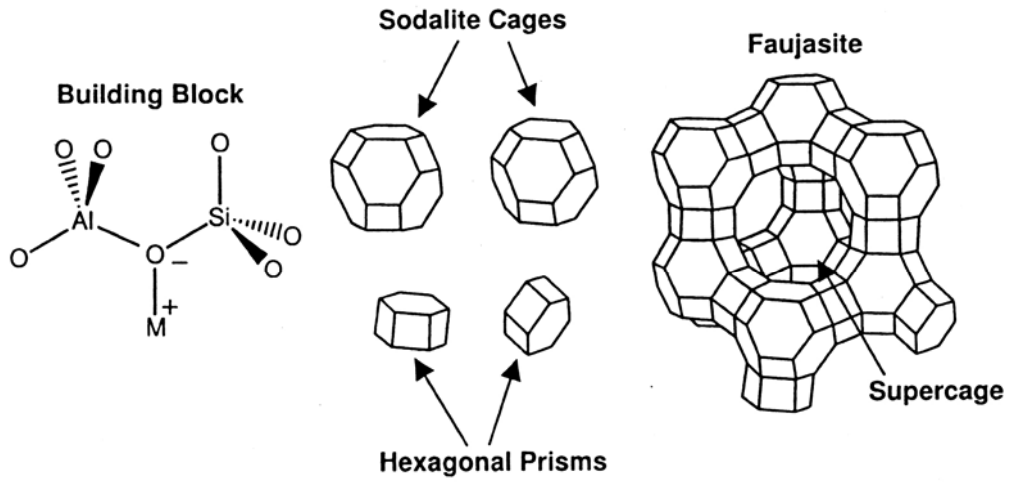


Fig 1 : Schematic diagram of a Faujasite-type zeolite. M^+ is a charge balancing cation

The basicity of ion - exchanged zeolites arises from the framework negative charge. Thus the relatively high aluminium content of zeolite X results in a substantial framework negative charge, which makes zeolite X one of the most basic zeolites when in the alkali - exchanged form.[23] Over the past few decades, zeolites X have shown great potential for a number of applications in various fields such as adsorption, separation, ion exchange and catalysis due to their peculiar structural characteristics like: (1) three- dimensional lattice having uniform pores of molecular dimensions, (2) high internal surface area, (3) high ion - exchange capacity and (4) remarkable thermal and hydrothermal stability.[25] The post-synthesis modification of zeolite by ion exchange is one of the approaches to tune the physico-chemical properties that are favourable for a particular application.

Ion-exchanged zeolites are used recently as catalyst for base catalyzed reactions. One of the interesting reaction is the side - chain alkylation of toluene with methanol to form styrene and / or ethylbenzene, with alkali - exchanged zeolite. Fig 2 summarizes the activity and selectivity of the reaction over a range of alkali - exchanged faujasites.

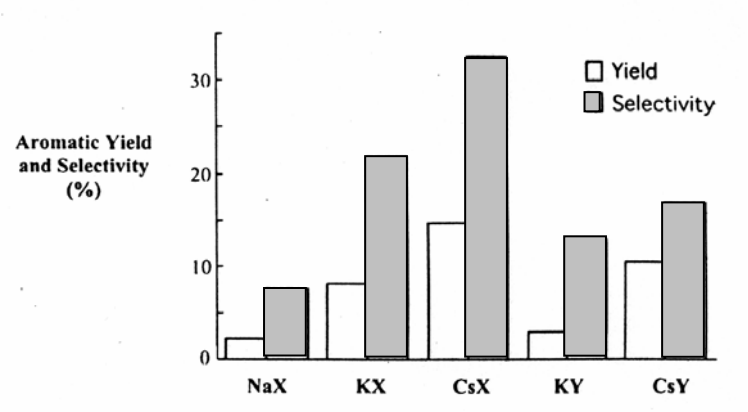


Fig 2: Alkali - exchanged zeolite catalyzed side - chain alkylation of toluene with methanol to form styrene and / or ethylbenzene

Cs-exchanged X zeolite was found to be most effective catalyst, no activity for the reaction was observed over a Cs-doped alumina. The unique environment inside the microporous zeolite is important for this base catalyzed reaction.

Transition metal (Co^{2+}, Mn^{2+}, Fe^{3+}) - modified zeolites NaX prepared by ion exchange were found to catalyze combustion of hexane, a typical VOC encountered in many industrial emissions.[24]

The heterogeneous vapor phase alkylation of pyridine and 2-, 3-, 4- picolines with methanol as alkylating agent over alkali metal Na^+, Cs^+ ion exchanged X and Y zeolites in an atmosphere of N_2 resulted in the formation of side - chain alkylated products : ethylpyridines and vinylpyridines. Though alkali metal ion-exchanged faujasite zeolites were found to be effective for side chain alkylation of picolines, the selectivity towards ethylpyridines was more than vinyl pyridines.[26]

Rare earth exchanged faujasites have been shown to have a good ability to catalyze isobutane/butene alkylation, an important refining process in which isobutanes and butene are converted in to a complex mixture of branched alkanes (alkylate), which is an excellent blending component in the gasoline pool. The overall cycle in the alkylation reaction comprises the addition of linear butene (1- or 2-butene) to a tert-butyl carbenium

ion to form a secondary octyl carbenium ion, which can undergo isomerization to a *tert*-octyl carbenium ion (Fig 3). Finally, the octyl carbenium ion is removed from the acid site by hydride transfer from isobutane leading to a *tert*-butyl carbenium ion. Competition between hydride transfer and addition of butene to a carbenium ion determines the lifetime of the catalyst. A high ratio of hydride transfer vs. olefin addition leads to enhanced trimethylpentane formation and reduction of catalyst deactivation. The high concentration of aluminium in the frame-work leads to an optimum strength of the bond between the zeolite oxygen and the secondary or tertiary carbon atom of the alkoxy groups being the ground state for the carbenium ions in the transition state of olefin addition or hydride transfer and the resulting high concentration of strong Bronsted acid sites allows to generate a (relatively) high concentration of alkoxy groups / carbenium ions increasing the probability of hydride transfer over olefin addition for the individual alkoxy group.[27]

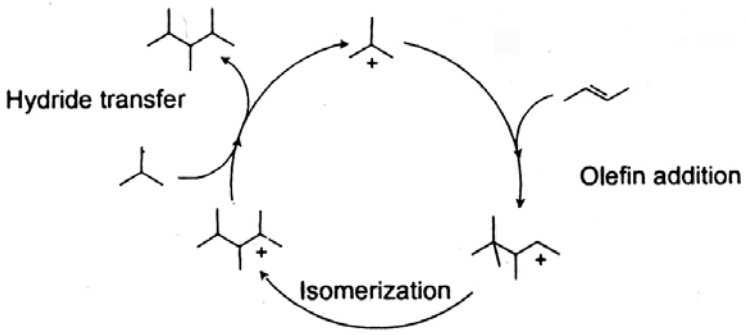


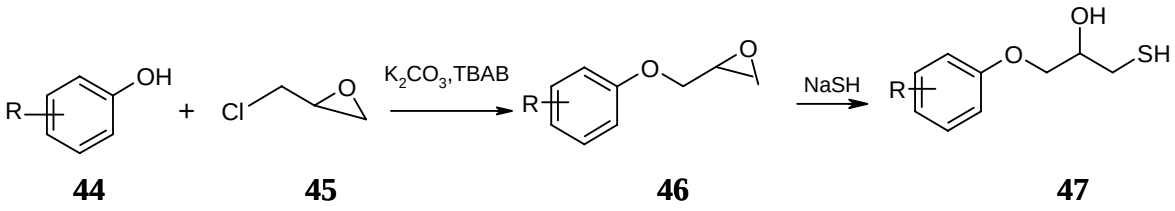
Fig 3: Simplified alkylation mechanism

R. Sreekumar *et al.*[22] synthesized Y type zeolite for conjugate addition. It was observed that the incorporation of alkali metals[9] such as Cs^+ in this zeolite[10] and mesoporous molecular sieve by cationic exchange provides low basicity useful for a small range of organic reactions. Na clusters introduced in the zeolites afford strong basic sites which even catalyze side chain alkylations but are easily deactivated by moisture.[11]

1.2.2 Present work

Though there are several reports regarding the conjugate addition of mercaptans to α, β - unsaturated esters and amides with thiols, many of these methods often involve the use of an acid or a base catalyst which demand aqueous work-up for the catalyst seperation, recycling and disposal. Furthermore, some of them involve the use of harsh conditions and expensive reagents. In many cases the yields and selectivities are far from satisfactory due to the occurrence of several side reactions. Since organosulfur compounds have become increasingly useful and important imtermediates in the synthesis of biologically active compounds such as calcium antagonist diltiazem, the development of simple, convenient and environmentally benign approaches are desirable.[28] The zeolite mediated Michael addition of acceptors like enones susceptible to dehydration, rearrangement etc under basic conditions is not reported. Conventional bases like triethylamine have been reported to yield undesirable side products. In order to carry out the reaction under neutral conditions, X type zeolites incorporated with Li, K and Cs were prepared and tested for the preparation of 3-sulfanyl cyclic ketones from the corresponding enones by 1, 4 - addition of thiols and the results are described in this section.

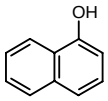
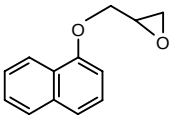
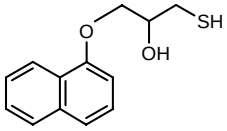
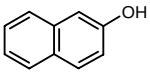
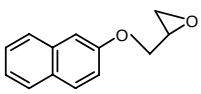
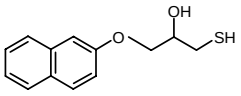
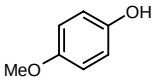
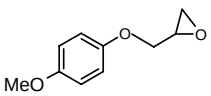
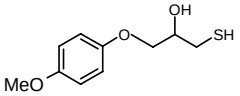
Substituted 3-aryloxy - 2 - hydroxy - 1- propane thiols (compounds **47**) were prepared from the corresponding phenols or naphthols. The phenols or naphthols were treated with epichlorohydrin in presence of potassium carbonate and tetra-n-butylammonium bromide to obtain epoxy ethers which on nucleophilic opening with sodium hydrosulfide in methanolic carbon disulfide, followed by acidification provided the corresponding thiols **47** in 70 - 85% yields (Scheme 8).



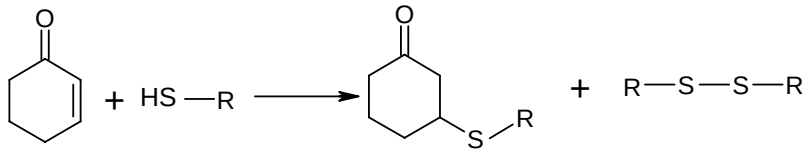
44 **45** **46** **47**

Scheme 8: Synthesis of thiols for Michael addition

Table 1 : Synthesis of thiols

Sr No	Synthesis of epoxy ether				Synthesis of thiols from epoxyethers		
	Phenol Used	**Reaction time (hr)**	**Product Formed**	**Yield %**	**Reaction time (hr)**	**Product Formed**	**Yield %**
1.		2		68	15		71
2.		2.5		54	12		69
3.		2		61	12		73

To optimize the Michael reaction conditions, cyclohexenone was used as model Michael acceptor and simple 4-methyl thiophenol as Michael donor. When the reactants and zeolites (20% by wt. of enone) were stirred in dry chloroform at 0º C for 1 hour and at room temperature till completion of reaction, good yields of Michael adducts were obtained on work up and purification. However, when 1-(l-naphthyloxy)-3-sulfanyl - 2 - propanol was used, Li - X zeolite resulted into cleaner and efficient Michael addition product whereas the other two catalysts resulted into simultaneous dimerisation of thiol along with lower yield of product as shown in Scheme 9.



A **B**

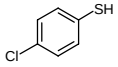
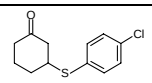
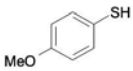
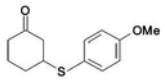
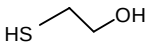
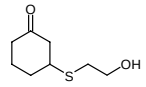
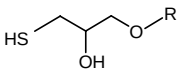
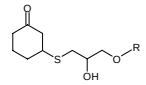
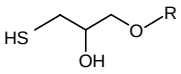
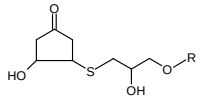
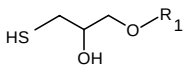
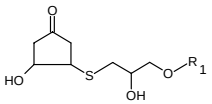
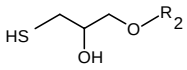
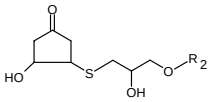
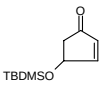
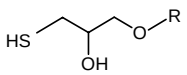
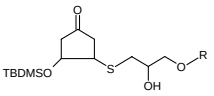
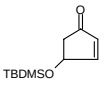
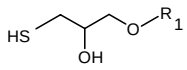
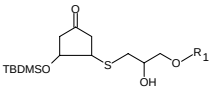
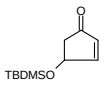
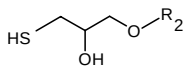
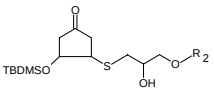
Scheme 9: Effect of catalyst on Michael addition

Table 2 : Effect of catalyst on Michael addition

Catalyst	**Yield of Product A (%)**	**Yield of Dimer B (%)**
Li -X	75	-
K- X	69	11
Cs -X	71	7

In most of the substrates used, the disulfides and Michael addition products had very close R_f values and the separation was tedious. Therefore it was necessary to avoid the formation of disulfide. Consequently Li-X zeolite was selected as the catalyst of choice for further studies. Several thiols and enones were subjected to Michael addition reaction under the optimized reaction conditions and the results are depicted in Table 3.

Table 3 : Li-X-zeolite mediated 1, 4-addition of thiols to cyclic enones

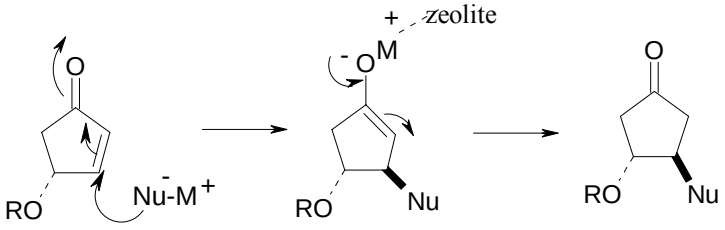
Entry	Enone	Thiol	Product[a]	Yield [b,c]
1				82
2				81
3				71
4				75
5				80
6				79
7				78
8				65
9				65
10				63

R=1-Naphthyl, R_1=2-Naphthyl, R_2=4-Methoxyphenyl a= All products were characterized by IR, ^{1}H NMR and Mass spectra. b=Isolated pure products, c = Reaction time was 20-24 h.; for entries 1-4 solvent was methanol and for entries 5-10 solvent was chloroform.

1.2.3 Results and Discussion

As can be seen from the results in Table 2, reaction using Li-X zeolite resulted in to cleaner and efficient Michael addition products. Michael addition of 2-substituted 4-hydroxycyclopentenone is known to lead to rearranged product [15] (enolate induced [1, 5] - sigmatropic shift) under basic conditions. However Li-X type catalyst gave Michael addition product and formation of such rearranged product could be avoided. The reaction proceeds with selectivity for thioether formation in the presence of free hydroxyl group in the thiols used (entries 3-10, Table 3). All the experiments were conducted in methanol and chloroform as solvent and it was observed that cyclohexenone was more selective with methanol whereas 4-hydroxy- and 4-tert-butyl- dimethylsilyloxy cyclopentenone reacted better in chloroform. Conjugate addition of 4-hydroxy cyclopentenone (examples 5 to 10) finds applications in the synthesis of prostaglandins by two-component or three- component coupling methodology wherein the asymmetry at C-4 decides the asymmetry at C-2 and C-3 (of the enones) in the products due to favoured *trans* addition of nucleophile. We used racemic enones (entries 5-10) for our experiments which resulted in to the Michael adducts as mixture of diastereoisomers.

Presumably the basic oxygen of zeolite abstracts proton from the thiol and the resultant anion adds in 1, 4 fashion to the enone which acts as the Michael acceptor. The enolate thus formed (scheme 10) is stabilized by the metal incorporated in the zeolite.



48 **49** **50**

Scheme 10: Mechanism of conjugate addition

It was observed that the selectivity for 1, 4 - addition and minimization of competing reactions (e.g. disulfide formation) were best achieved with lithium incorporated zeolite.

1.2.4 Conclusion

Thus in conclusion, we have demonstrated that lithium incorporated X-type zeolite catalyst (basic in nature) provides mild condition for Michael addition of cyclic enones with variety of substituted thiols; which minimizes the side reactions such as dimerization of thiols or rearrangement. This methodology finds interesting applications in the synthesis of 13-thiaprostaglandin analogues. It has all the advantages of heterogeneous catalysis such as mild conditions, ease of work-up and separation, recycling of the catalyst as well as non-toxic, inexpensive and environmentally - friendly conditions. This protocol offers an alternative to routine basic reaction conditions.

1.2.5 Experimental

Synthesis of zeolite catalyst:

Zeolite - X was synthesized using the gel composition in terms of oxides 4.54 Na_2O : 3.44 SiO_2 : Al_2O_3 : 180 H_2O. Sodium silicate (28.6% SiO_2, 8.88% Na_2O and 62.6% H_2O) was used as the silicon (SiO_2) source and $NaAlO_2$ was used as the alumina (Al_2O_3) source. In a typical synthesis 18.6 g of sodium silicate was taken in a beaker and a mixture of 5.9 g sodium aluminate, 3.9 g sodium hydroxide and 70 g water was added to it. The mixture was stirred for 1h and transferred in to an autoclave, aged for 24 h at room temperature and then heated at 373 K for 6 h. The product was filtered, washed with distilled water and dried at ambient temperature.

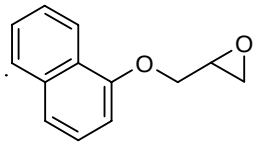
Ion exchange of zeolite-X was carried out using the hydroxide and chloride solutions (1M) of cesium, potassium and lithium. Ion exchange was carried out at 353 K using 50 ml of solution per g of sample (6 hr elution). The exchange procedure was repeated six times. The ion-exchanged zeolites were washed with deionized water and dried at 383 K for 12 h. The degree of ion exchange was estimated by flame photometry and atomic absorption spectroscopy and the percentage of exchange was found to be Cs 52%, K 88% and Li 75%.

Preparation of 1- mercapto -3 - (aryloxy) - propan -2-ol

a) Preparation of 2-(aryloxymethyl)-oxirane :

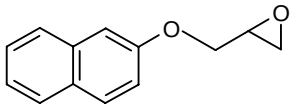
A mixture of phenol or naphthol (0.1 mol), epichlorohydrin (100 ml) and potassium carbonate (27.6 g, 0.2 mol) in the presence of catalytic amount of tetra-butylammonium bromide (0.312 g, 0.001 mol) was refluxed till completion of reaction (TLC). The excess of epichlorohydrin was removed under reduced pressure, the residue was cooled to room temperature, diluted with water and extracted with ethyl acetate (3 × 100 ml). The organic layer was washed with dilute sodium hydroxide solution followed by water and brine, dried over sodium sulfate and concentrated under reduced pressure to give the 2-(aryloxymethyl)-oxirane.

2-(1-Naphthyloxymethyl)-oxirane [Table 1, entry 1]



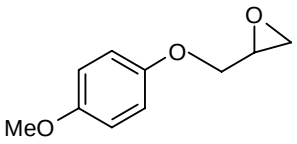
^{1}H NMR (200 MHz, $CDCl_3$): δ 2.75-2.85 (m, 2H), 2.90 (t, J= 6Hz, 1H), 4.02- 4.11 (m, 2H), 6.80-6.90 (m, 1H), 7.40-7.60 (m, 4H), 7.80- 7.90 (m, 1H), 8.20-8.30 (m, 1H).

2-(2-Naphthyloxymethyl)-oxirane [Table 1, entry 2]



^{1}H NMR (200 MHz, $CDCl_3$): δ 2.70-2.80 (m, 2H), 3.00 (t, J= 6Hz, 1H), 4.02 - 4.11 (m, 2H), 6.89-7.00 (m, 1H), 7.30- 7.60 (m, 6H).

2-(4-Methoxyphenoxymethyl)-oxirane [Table 1, entry 3]



^{1}H NMR (200 MHz, $CDCl_3$): δ 2.81-2.91 (m, 2H), 3.00 (t, J= 6 Hz, 1H), 3.80 (s, 3H), 3.92- 4.05 (m, 2H), 6.90 (s, 4H).

b) Preparation of 1- mercapto -3 - (aryloxy) - propan -2-ol

A mixture of 2- (aryloxymethyl)-oxirane (0.015 mol) and sodium hydrosulfide (0.027 mol) in methanolic carbon disulfide (10 ml) was stirred at room temperature till

completion of reaction (TLC). The reaction mixture was then acidified and extracted with ethyl acetate (3 × 25 ml), organic layer washed with water followed by brine, dried over sodium sulfate, concentrated under reduced pressure and purified by column chromatography to give the product.

1-Mercapto-3-(naphthalen-1-yloxy) propan- 2-ol [Table 1, entry 1]

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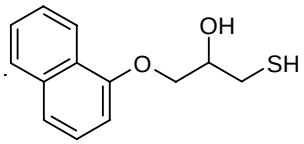
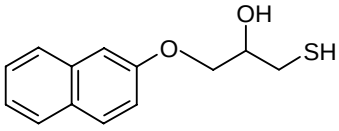


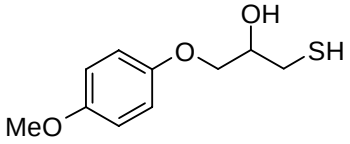
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (t, J = 8Hz, 1H), 1.86-1.91 (m, 2H), 2.65-2.75 (m, 1H), 3.53 (brs, 1H), 4.05-4.25 (m, 2H), 6.75-6.85(m, 1H), 7.35-7.60 (m, 4H), 7.75- 7.90 (m, 1H), 8.24- 8.35 (m, 1H).

1-Mercapto-3-(naphthalen-2-yloxy) propan- 2-ol [Table 1, entry 2]



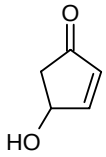
^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (t, J=8 Hz, 1H), 1.86-2.01 (m, 2H), 2.50 (brs, 1H), 3.63-3.70 (m, 1H), 3.90-3.95 (m, 2H),6.97-7.01 (m, 2H), 7.29-7.70 (m, 5H).

1-Mercapto-3-(4-methoxyphenoxy) propan- 2-ol [Table 1, entry 3]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.55 (t, J= 8Hz, 1H), 1.86-1.95 (m, 2H), 2.50 (brs, 1H), 3.50-3.60 (m,1H), 3.94 - 4.15 (m, 2H), 6.85 (s, 4H), 3.80 (s, 3H).

Synthesis of 4-hydroxycyclopent-2-en-1-one

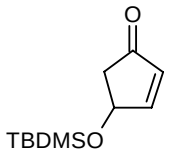


A 3 L three-necked round bottomed flask equipped with long air condensor, thermometer pocket and a bubbler; was charged with furfuryl alcohol (25 g, 0.255 mol), potassium dihydrogen orthophosphate (6.3 g, 0.022 mol) and distilled water (1.5 L). The reaction mixture was purged with a slow stream of nitrogen along with magnetic stirring. It was heated to 95^{o}C for 48 hr while maintaining effective stirring and nitrogen purge. The solution developed brownish insoluble impurities during reaction. It was cooled to room temperature and then washed twice with ethyl acetate. The aqueous layer was concentrated almost to dryness under reduced pressure. The residue was then thoroughly extracted with ethyl acetate. The combined organic extracts were then dried on anhydrous sodium sulfate and concentrated under vacuum. The residue was distilled under high vacuum using a fractionating column to afford the product as a lemon yellow coloured liquid distilling at 95-100^{o}C at 0.5 mm vacuum.

Yield (%) : 10 g (40%) .

^{1}H NMR (200 MHz, $CDCl_3$): δ 2.30 (brs, 1H), 3.01 (d, J= 6Hz, 2 H), 4.91 (d, J = 8Hz, 1H), 6.19 (d, J = 4Hz, 1H)) 7.14 (d, J = 8 Hz, 1H).

Protection of 4-hydroxycyclopentenone



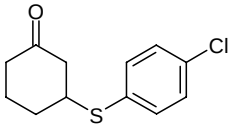
A solution of 4-hydroxycyclopent-2-en-1-one (196 mg, 2 mmol) in dry CH_2Cl_2 (5 ml) was taken in a 25 ml 2-necked R B flask with magnetic stirrer, septum and condensor equipped with 3-way stopcock which was evacuated and flushed with N_2. The solution was cooled with ice and a solution of TBDMS-Cl (331 mg, 2.2 mmol) and DMAP (24.0 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) was added with the aid of cannula. The reaction mixture was stirred for 5 min., Et_3N (262 mg, 2.6 mmol, 0.3 ml) added, again stirred for 5 min, brought to r.t. and stirred at r.t. for 3 hrs till TLC indicated completion of reaction. After completion of the reaction, the reaction mixture was filtered, concentrated and purified by column chromatography.

^{1}H NMR (200 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.85 (s, 9H), 2.16 (dd, J_1= 16 Hz, J_2= 2 Hz, 1H), 2.63(dd, J_1=16 Hz, J_2=6 Hz, 1H), 4.85-5.01(m, 1H), 6.10 (d, J = 4Hz , 1H)) 7.39 (bd, 1H).

Michael addition of thiols:

A mixture of cyclohexenone/4-hydroxy cyclopentenone or its silyl ether (1 mmol), 2-hydroxy-3-(1-aryloxy)-1-propanethiol (2 mmol) and Li-X zeolite (20 mg, 20% by wt of enone) in dry chloroform was stirred at 0^{o}C under inert atmosphere for 1 hr. Stirring was continued further at room temperature until the completion of the reaction (monitored by TLC). The zeolite was filtered off and washed with chloroform (5 ml). Removal of the solvent followed by chromatographic purification on a column of silica gel using petroleum ether-ethyl acetate as eluent afforded the pure product.

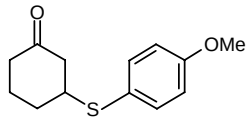
3-[4'-Chlorophenylsulfanyl]-1-cyclohexanone [Table 3, entry 1]



IR ($CHCl_3$) **:** 3009.44, 2939.95, 1706.48, 1464.32, 1215.03 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) **:** δ 2.15 (t, J=9 Hz, 2H), 2.20-2.55 (m, 4H), 2.65 (d, J=6Hz, 2H), 3.25-3.45 (m, 1H), 7.21 – 7.45 (m, 4H).

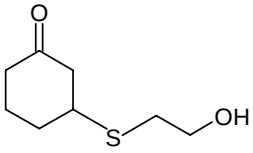
3-(4-Methoxyphenyl)sulfanyl -1-cyclohexanone [Table 3, entry 2]



^1H NMR (200 MHz, $CDCl_3$) **:** δ 3.25 – 3.59 (m, 9H), 3.76 (s, 3H), 6.84 (s, 4H).

MS **:** 236 (M^+), 205.97.

3-[2-Hydroxyethylsulfanyl]-1-cyclohexanone [Table 3, entry 3]

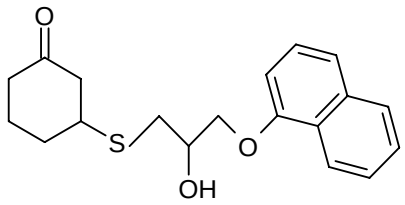


IR($CHCl_3$) : 3394.70, 2934.7, 1701.88, 1410.57 cm^{-1}.

NMR (200MHz, $CDCl_3$) : δ 1.26 (t, J=6 Hz, 2H), 1.74 (t, J=6 Hz, 2H), 2.15-2.21 (m, 2H), 2.30-2.39 (m, 2H), 2.56 -2.61 (m, 1H), 2.75- 2.81 (m, 2H), 3.13 (brs, 1H), 3.74 (t, J = 6Hz, 2H).

MS : 174 (M^+), 144, 96, 69.

3-[2-Hydroxy-3-(1-naphthyloxy)propylsulfanyl]-1-cyclohexanone [Table 3, entry 4]



IR (neat) **:** 1709, 3410 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.52 -1.75 (m, 1H), 2.19-2.42 (m, 7H), 2.60-3.05 (m, 2H), 3.07 – 3.25 (m, 1H), 4.10 - 4.35 (m, 3H), 6.82 (d, J = 8 Hz, 1H), 7.25-7.57 (m, 4H), 7.75 - 7.85 (m, 1H), 8.15 - 8.30 (m, 1H).

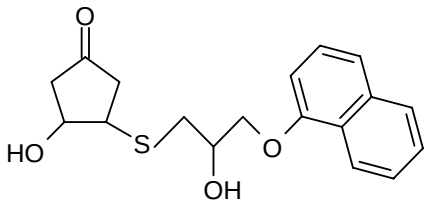
MS **:** 330 (M^+), 234, 187, 144, 115, 97.

C, H, N Analysis

Calculated for $C_{19}H_{22}O_3S$	**:**	C 69.09	H 6.66	S 9.69
Found	**:**	C 68.81	H 6.78	S 9.54 %.

3-Hydroxy-4-[2-hydroxy-3-(1-naphthyloxy) propyl sulfanyl]1-cyclopentanone

[Table 3, entry 5]



^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 2.30 - 3.15 (m, 4H), 3.25 - 3.56 (m, 2H), 4.00 - 4.44 (m, 5H), 6.78 (d, J = 9 Hz, 1H), 7.16 – 7.56 (m, 4H), 7.65 –7.87 (m, 1H), 8.05 - 8.30 (m, 1H).

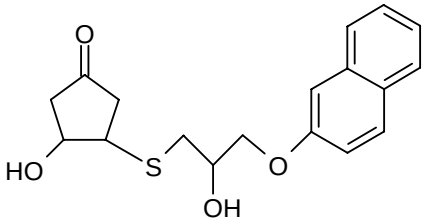
MS **:** 332 (M^+), 314, 234, 189, 144, 115.

C, H, N Analysis

Calculated for $C_{18}H_{20}O_4S$	**:**	C 65.06	H 6.02	S 9.64
Found	**:**	C 64.81	H 6.33	S 9.85 %

3-Hydroxy-4-[2-hydroxy-3-(2-naphthyloxy) propyl sulfanyl]-1-cyclopentanone

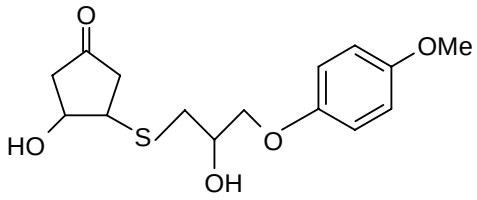
[Table 3, entry 6]



^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 2.02 - 2.53 (m, 4H), 2.70 - 3.30 (m, 3H), 3.50 - 3.62 (m, 2H), 4.08 - 4.52 (m, 4H), 7.06 – 7.20 (m, 2H), 7.35 -7.55 (m, 2H), 7.65 – 7.90 (m, 3H).		
MS	**:**	332 (M^+), 314, 234 , 189 , 144, 115.		
C, H, N Analysis				
Calculated for $C_{18}H_{20}O_4S$	**:**	C 65.06	H 6.02	S 9.64
Found				
	:	C 65.32	H 6.11	S 9.48 %

3-Hydroxy-4-[2-hydroxy-3-(4-methoxyphenoxy) propylsulfanyl]-1-cyclopentanone

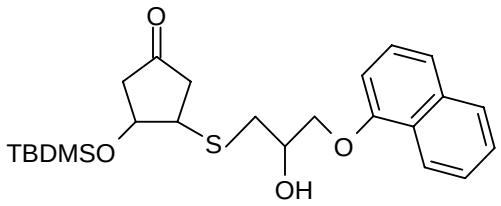
[Table 3, entry 7]



^{1}H NMR (200 MHz, $CDCl_3$)	**:**	δ 2.12 - 2.67 (m, 4H), 2.70 - 3.05 (m, 2H), 3.31 -3.63 (m, 1H), 3.79 (s, 3H), 3.93 – 4.09 (m, 2H), 4.10 - 4.28 (m, 1H), 4.37 - 4.50 (m, 1H), 6.86 (brs, 4H).		
MS	**:**	312 (M^+), 294 , 214, 189, 171 , 124 , 109 .		
C, H, N Analysis				
Calculated for $C_{15}H_{20}O_5S$	**:**	C 57.69	H 6.41	S 10.26

Found **:** C 57.37 H 6.38 S 10.58 %.

3-*tert*-Butyldimethylsilyloxy-4-[2-hydroxy-3-(1-naphthyloxy)propylsulfanyl] 1-cyclopentanone [Table 3, entry 8]



^{1}H NMR ($CDCl_3$) **:** δ 0.10 (s, 3H), 0.15 (s, 3H), 0.85 (s, 9H), 1.55-1.80 (brs, 1H), 2.12- 2.29 (m, 2H), 2.67 - 3.17 (m, 4H), 3.40 - 3.51 (m, 1H), 4.18 - 4.45 (m, 4H), 6.85 (d, J = 7 Hz, 1H), 7.38 (t, J = 7 Hz, 1H), 7.43 - 7.58 (m, 3H), 7.72 - 7.90 (m, 1H), 8.12- 8.28 (m, 1H).

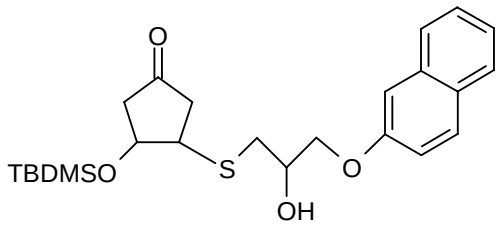
MS **:** 446 (M^+), 257, 183, 155, 144, 115 .

C, H, N Analysis

Calculated for $C_{24}H_{34}O_4SSi$ **:** C 64.57 H 7.62 S 7.17

Found **:** C 64.29 H 7.35 S 7.28 %.

3-*tert*-Butyldimethylsilyloxy-4-[2-hydroxy-3-(2-naphthyloxy)propylsulfanyl] 1-cyclopentanone [Table 3, entry 9]



IR **:** 1739, 3446 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CCl_4) **:** δ 0.07 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 2.12-

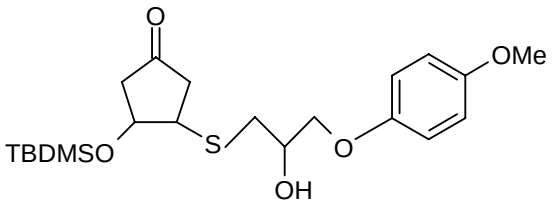
2.25 (m, 2H), 2.65 - 3.11 (m, 4H), 3.39 - 3.49 (m, 1H), 4.05- 4.27 (m, 3H), 4.34 - 4.45 (m, 1H), 7.05 - 7.43 (m, 4H), 7.65 - 7.85 (m, 3H).

MS : 446 (M^+), 389, 357, 183, 155, 144, 137, 115.

C, H, N Analysis

Calculated for $C_{24}H_{34}O_4S$ Si	:	C 64.57	H 7.62	S 7.17
Found	:	C 64.89	H 7.51	S 7.43 %.

3-*tert*-Butyldimethylsilyloxy-4-[2-hydroxy-3-(4-methoxyphenyloxy)propylsulfanyl]1-cyclopentanone [Table 3, entry 10]



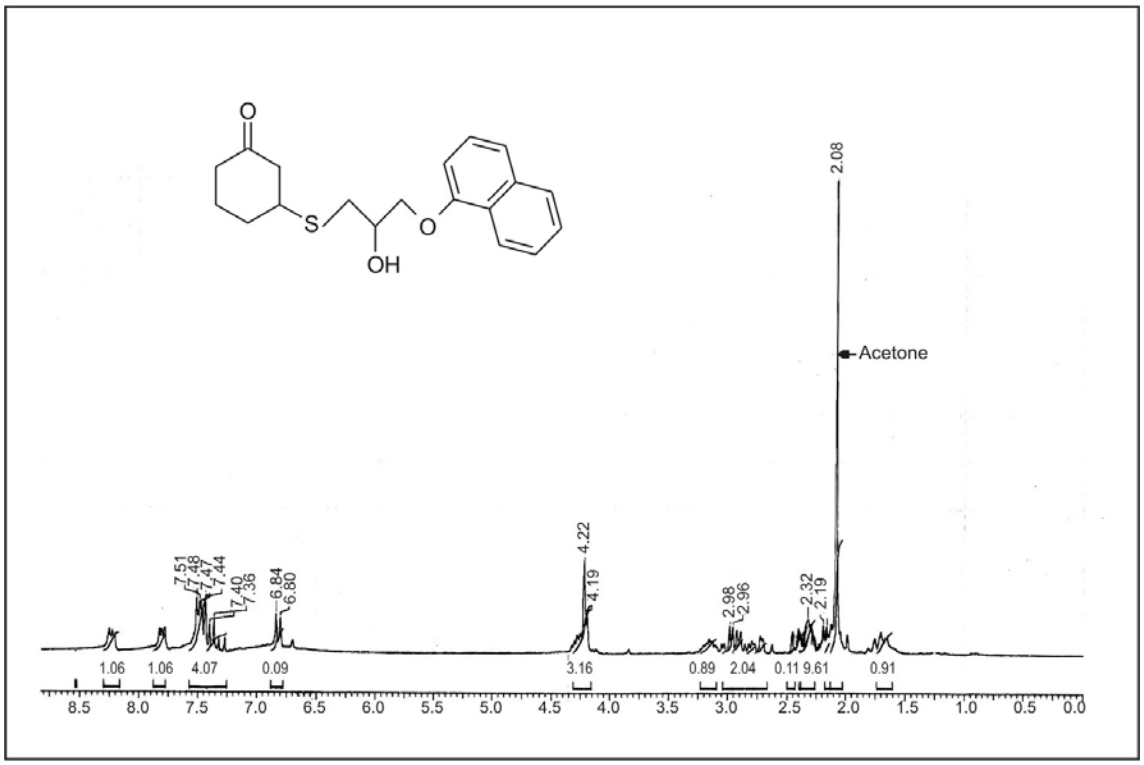
^{1}H NMR ($CDCl_3$) : δ 0.08 (s, 3H), 0.13 (s, 3H), 0.87 (s, 9H), 2.12-2.24 (m, 2H), 2.60 - 3.02 (m, 5H), 3.36-3.46 (m, 1H), 3.77 (s, 3H), 3.90 - 4.05 (m, 2H), 4.05 – 4.18 (m, 1H), 4.34 - 4.43 (m,1H), 6.82 (brs, 4H).

MS : 426 (M^+), 369, 237, 163, 155, 123 , 109.

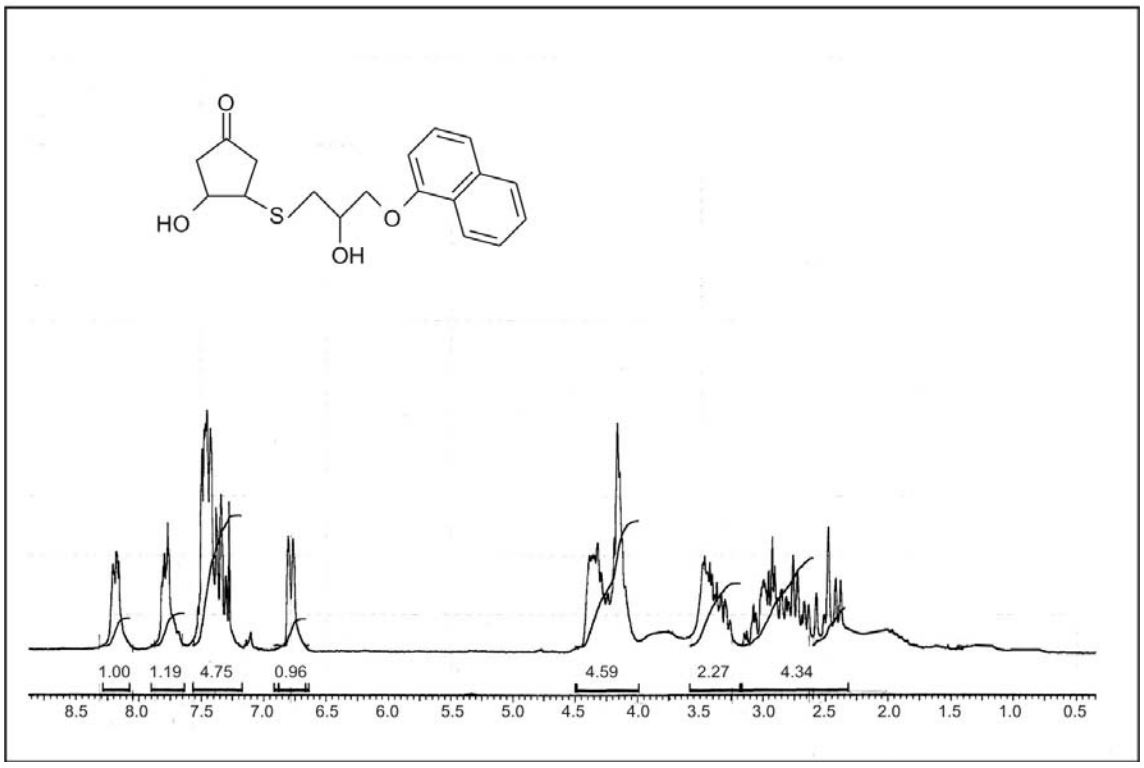
C, H, N Analysis

Calculated for $C_{21}H_{34}O_5S$ Si	:	C 59.15	H 7.98	S 7.51
Found	:	C 59.23	H 8.08	S 7.26 %.

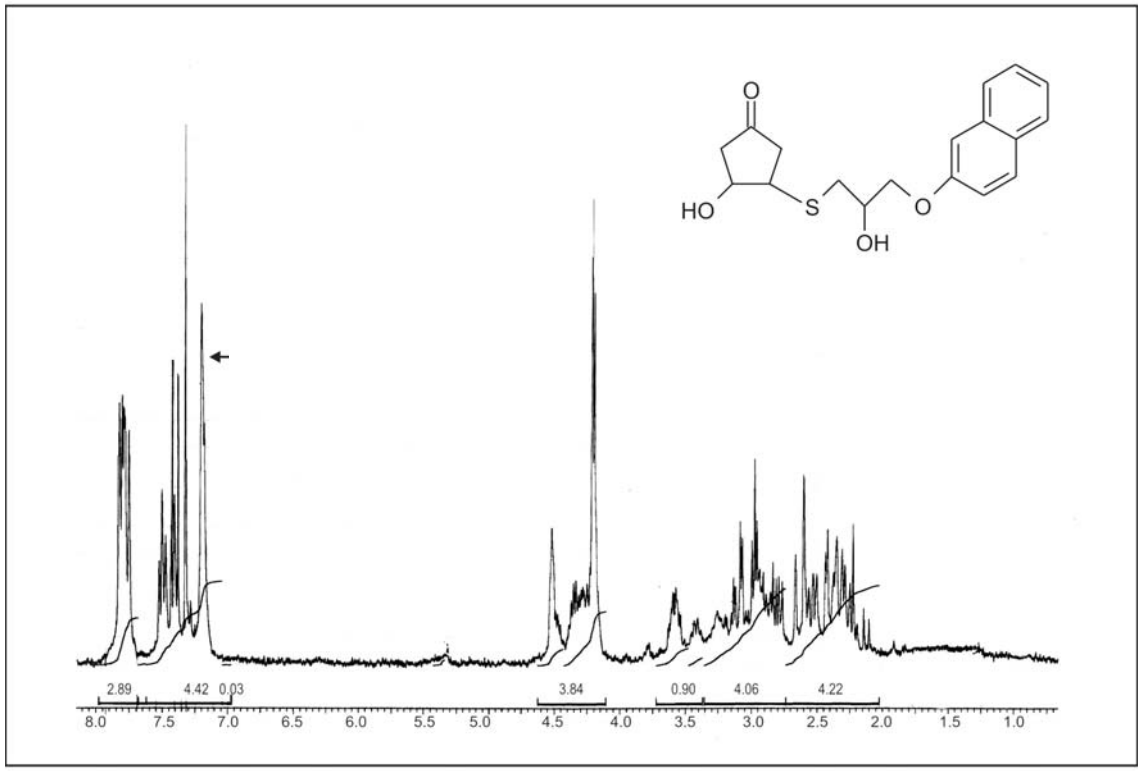
^{1}H NMR 3-[2-hydroxy-3-(1-naphthyloxy)propylsulfanyl]-1-cyclohexanone



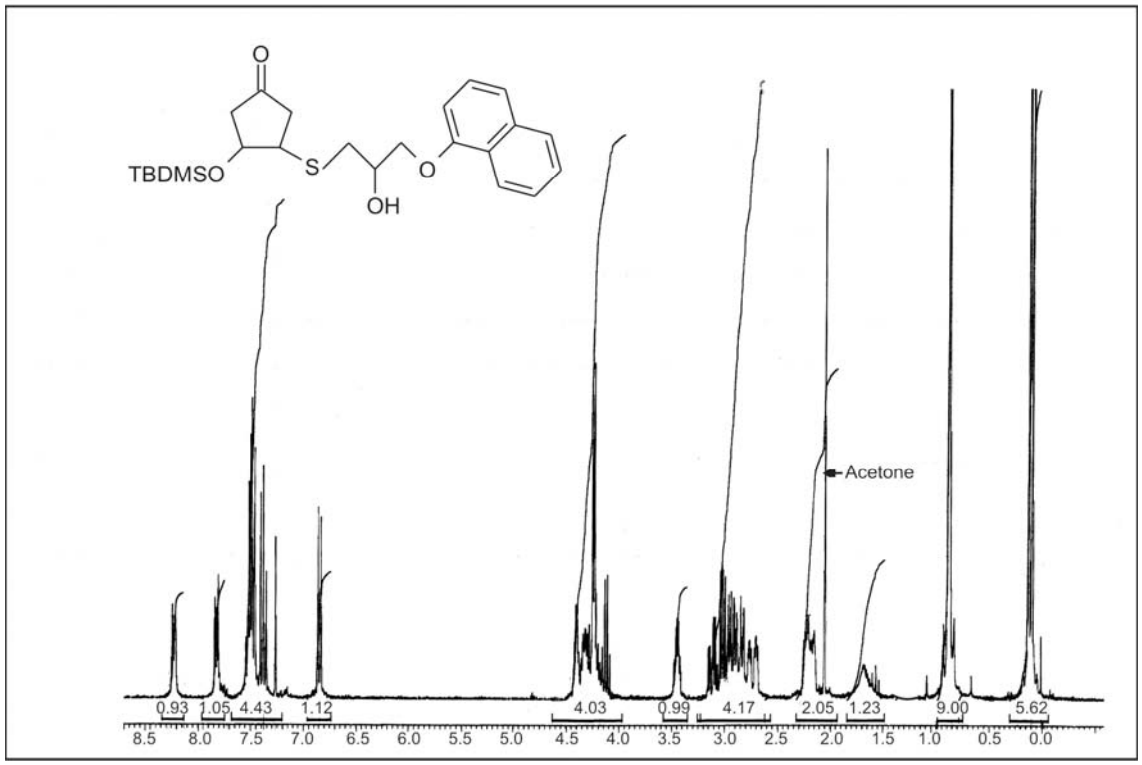
^{1}H NMR of 3-hydroxy-4-[2-hydroxy-3-(1-naphthyloxy) propyl sulfanyl]1-cyclopentanone



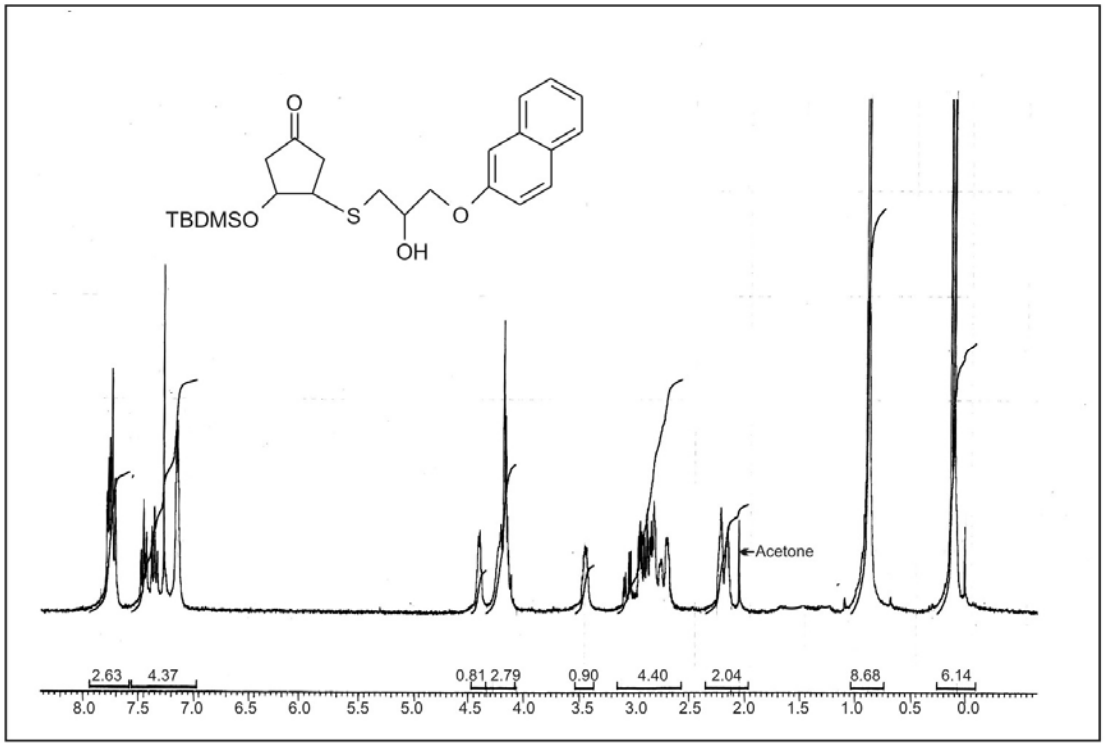
^{1}H NMR of 3-hydroxy-4-[2-hydroxy-3-(2-naphthyloxy) propyl sulfanyl]1-cyclopentanone



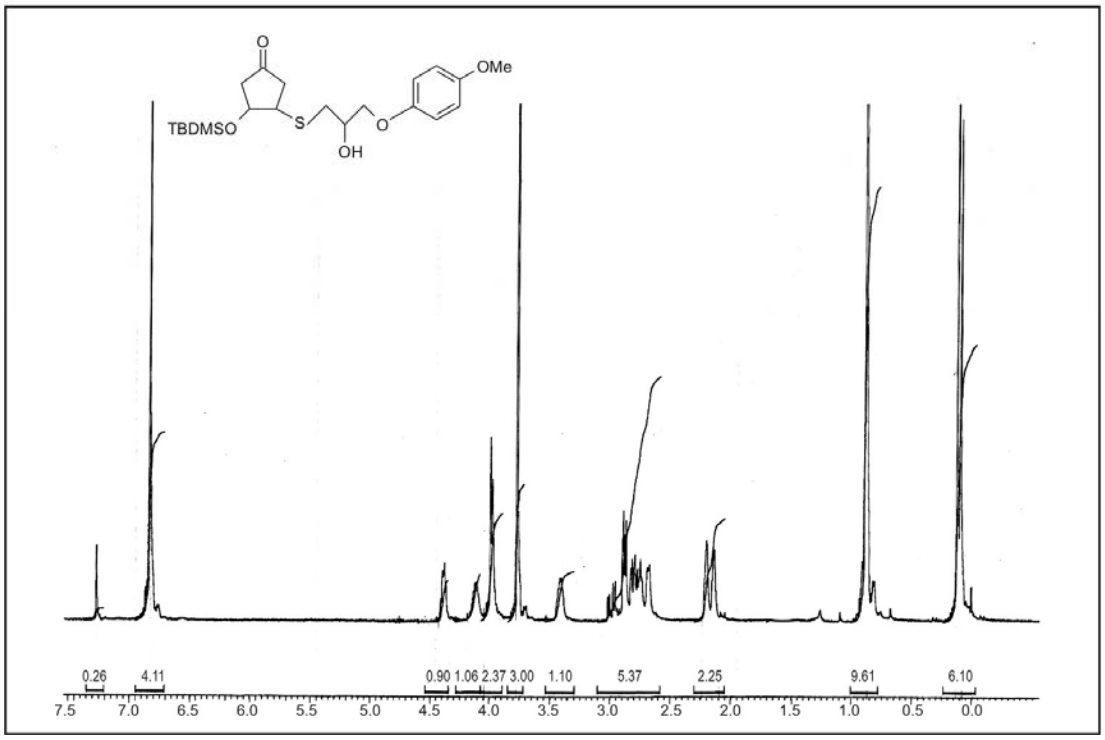
^{1}H NMR of 3-tertbutyl dimethylsilyloxy-4-[2-hydroxy-3-(1-naphthyloxy)propyl sulfanyl] 1-cyclopentanone



^{1}H NMR of 3-tertbutyl dimethylsilyloxy-4-[2-hydroxy-3-(2-naphthyloxy)propyl sulfanyl] 1-cyclopentanone



^{1}H NMR of 3-tertbutyldimethylsilyloxy-4-[2-hydroxy-3-(4-methoxyphenyloxy) propyl sulfanyl]1-cyclopentanone



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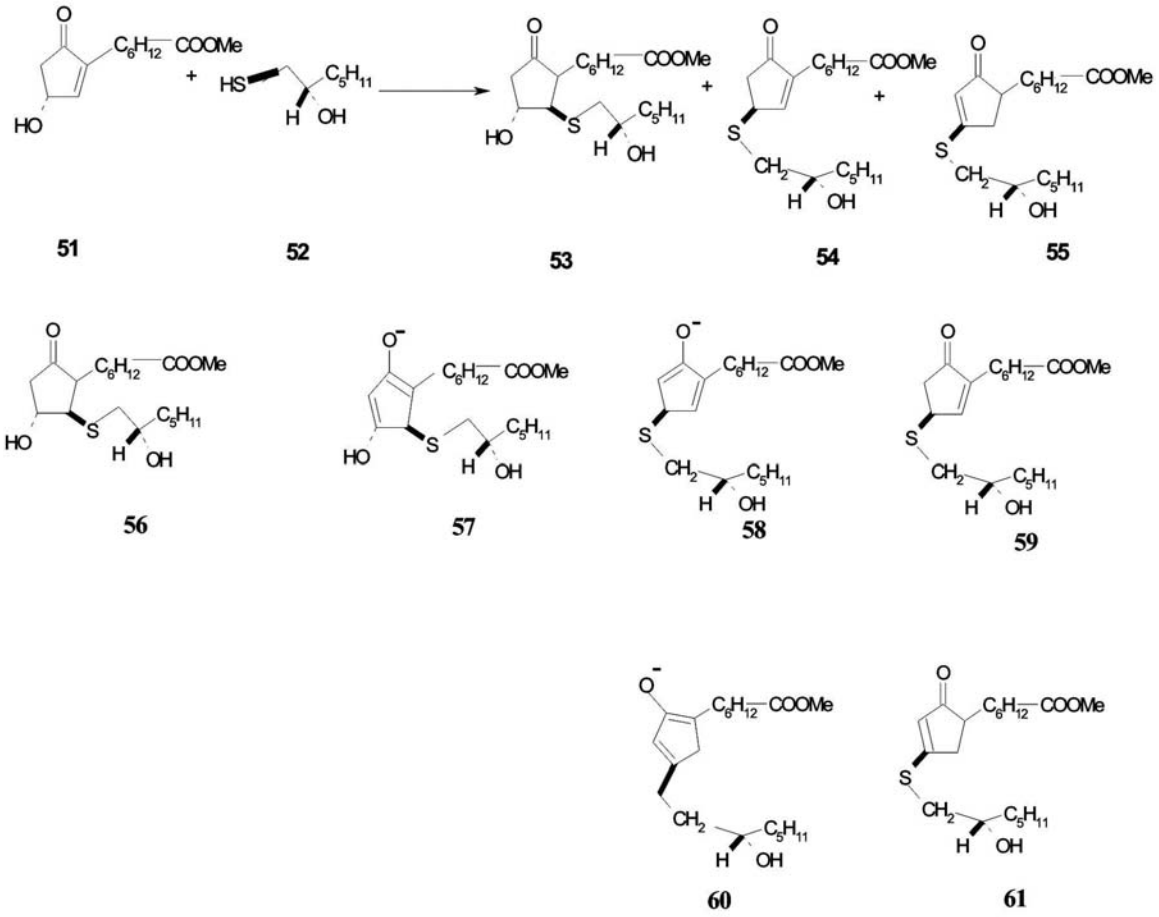
CHAPTER 1
(Section C)

Synthesis of 13-thiaprostaglandins

1.2.1 Introduction

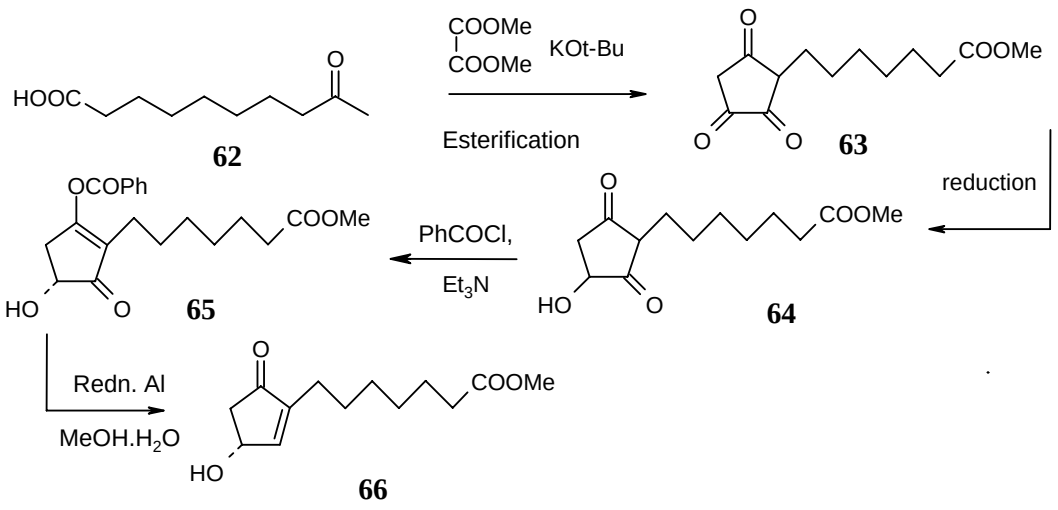
Prostaglandins are the local hormones which control a multitude of physiological processes. In lieu of the various activities displayed by the prostaglandins and the instability of naturally occurring prostaglandins, several analogs have been synthesized and studied extensively for structure - activity relationship. Among the numerous analogues reported the 13 - thiaprostaglandins are known to possess valuable pharmacological properties.[1-6] The PGE analog of 13-thiaprostanoic acid possesses blood pressure - lowering activity. In contrast to the acid form of these prostaglandins, the esters have an outstandingly high gastric tolerance in oral administration. The 13-thiaprostanoic acid derivatives have also exhibited other pharmaceutical activities such as vasodilatory, antiphlogistic, diuretic and bronchial relaxing, inhibiting gastric juice secretion, thrombocyte aggregation, nasal mucosal decongestant lipid breakdown and non adrenaline liberation. They also influence the function of the corpus luteum, the ova transport through the fallopian tubes and fertility. Some derivatives exhibit an oestrus - synchronizing action in cattle.

One of the methods for synthesis of prostaglandin involves two component coupling where-in the key step is the Michael addition to the appropriately substituted enones. The synthesis of 13 - thiaprostaglandin by this method involves conjugate addition of thiols to cyclic enones. Basic catalyst like triethylamine[7] has been reported for this purpose. Scheme 1 depicts the synthetic strategy reported, wherein the 1, 4-addition of thiol resulted in a mixture of three compounds. The base present during the reaction effects the dehydration of thiaprostaglandin formed producing PGA analogue. Base - catalyzed enolization of the latter, followed by simultaneous migration of the lower side chain and rearrangement of double bonds yield the intermediate anion, which can give rise to two different products. Protonation of anion results in thioether. Double bond migration followed by the protonation of the resultant anion, eventuates in the formation of the thermodynamically more stable enol ether .



Scheme 1 : By-products formed in the synthesis of 13-thiaprostaglandins using triethylamine

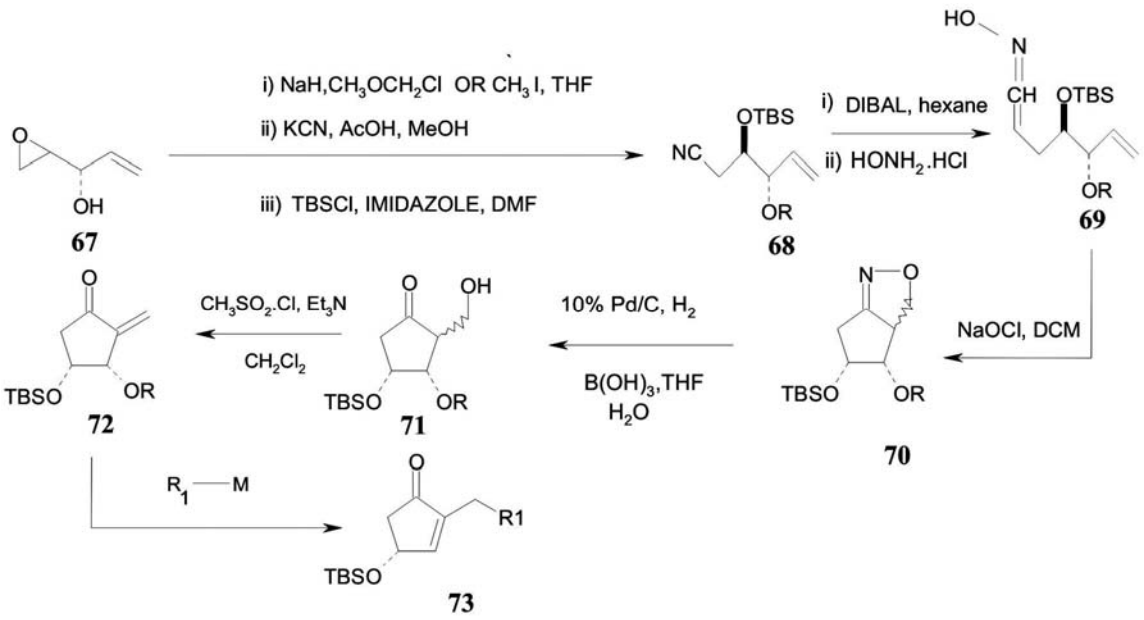
The synthesis of the key intermediate 2-substituted 4-hydroxy cyclopentenone has been reported by several methods as described below:



Scheme 2 : Synthesis of 2-substituted-4-hydroxy cyclopentenone from 9-oxo-decanoic acid.

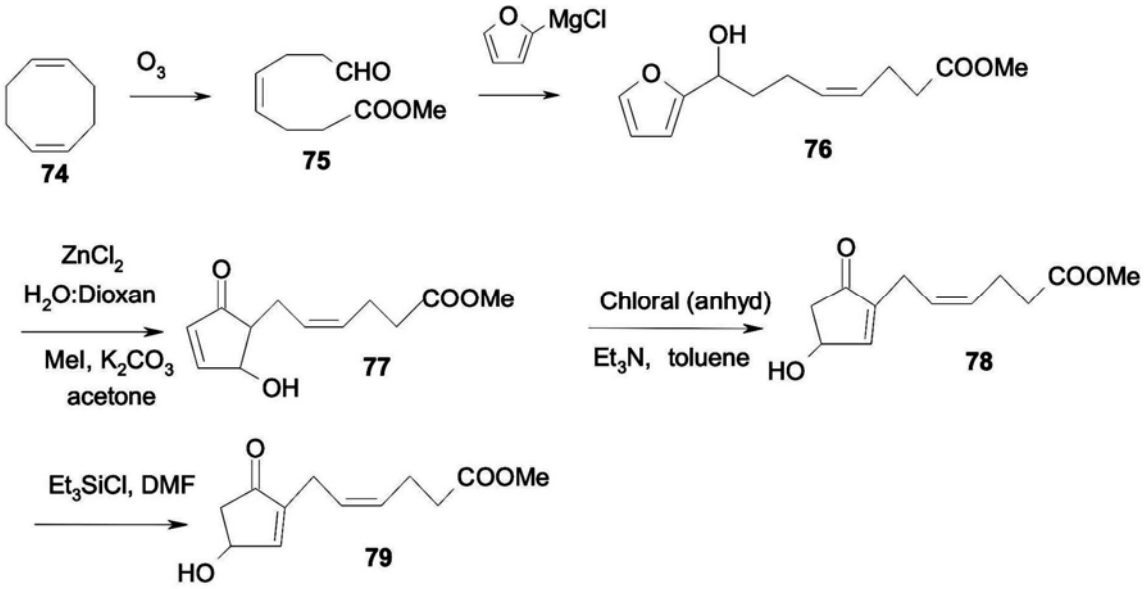
The asymmetric hydrogenation of 2-(6-carbomethoxyhexyl) cyclopentane- 1, 3, 4-trione (**63**), obtained from 9-oxo-decanoic acid, using $L_2RhCODBF_4$ in methanol yielded the corresponding 3-hydroxy derivative **64** which was converted to enolate. Subsequent reduction of the 3-carbonyl group followed by acidic allylic rearrangement yielded the desired intermediate **66** (Scheme 2).[8-10]

An alternate approach for 2- substituted-4-hydroxycyclopent-2-en-1-ones was reported by Zhang *et al*[11] wherein the protection of the hydroxyl group of the readily available chiral epoxy- (2R, 3S)-1, 2-epoxy pent-4-en-3-ol (**67**), followed by epoxide ring opening with cyanide ion and silylation with TBS-Cl afforded the product **68** which on reduction with DIBAL followed by the reaction of the resulting aldehyde with hydroxylamine gave the oxime **69**. Oxidation of this oxime with aqueous NaOCl resulted in the nitrile oxide cycloaddition to give the product **70** which on hydrogenolysis / hydrolysis with H_2 and 10% Pd/C in aqueous THF containing $B(OH)_3$ gave the corresponding mixture of ketones **71**. Mesylation of mixture of these ketones **71** accompanied by direct elimination gave the enone **72** which on reaction with mixed organocuperate resulted in desired α-substituted 4-tert-butyl dimethylsilyloxy-2-cyclopent-1-enone **73** (Scheme 3).[11]



Scheme 3 : Synthesis of 2-substituted-4-hydroxy cyclopentenone from chiral epoxy-(2R, 3S)-1, 2-epoxy pent-4-en-3-ol

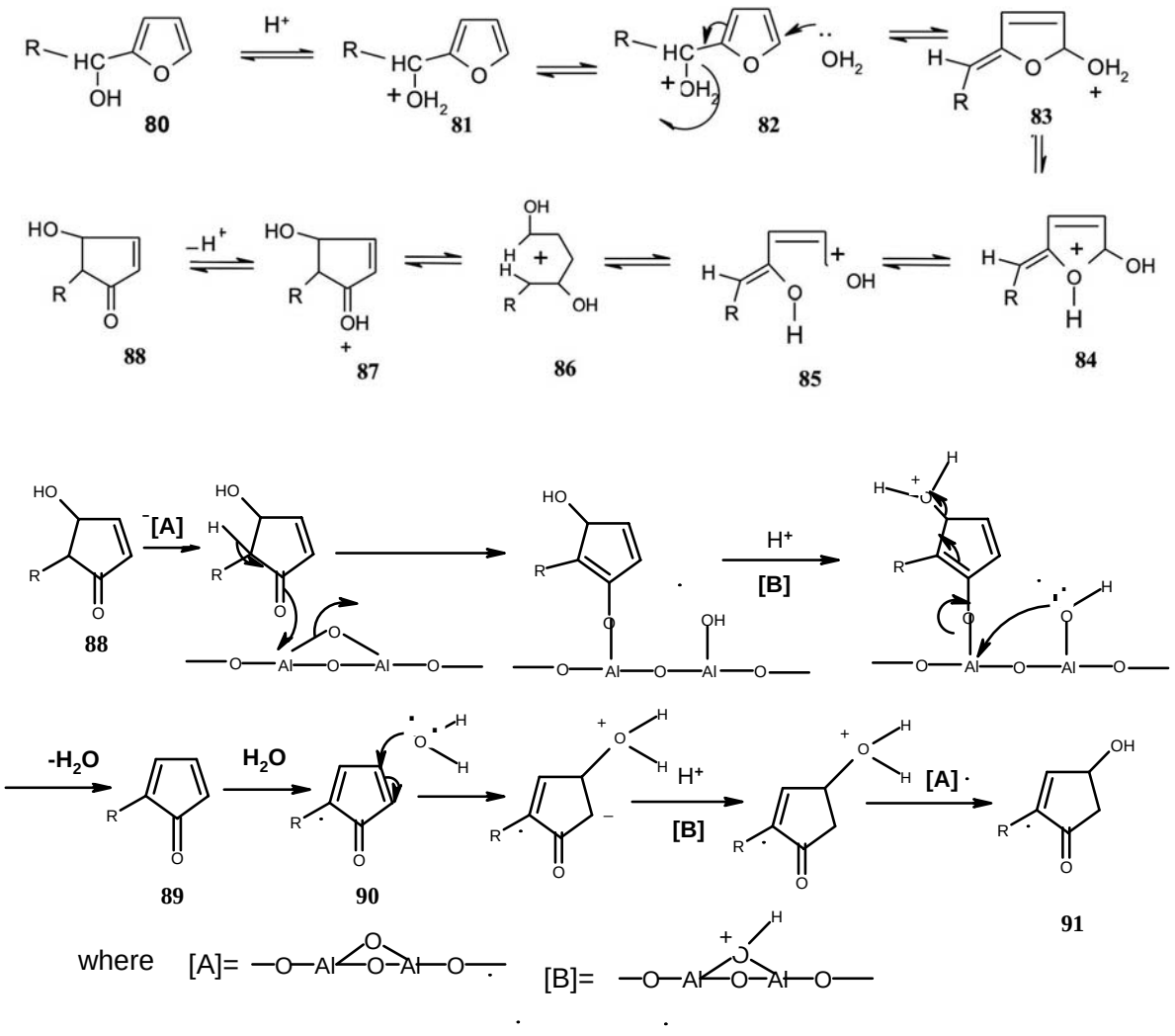
One more approach employing cyclooctadiene as a starting material was reported by groups of Piancatelli[12] and Dygos[13] wherein the ozonylysis of (z, z)-1, 5-cyclooctadiene yielded half ester-half aldehyde **75.** This on reaction with 2-furanylmagnesium chloride gave the substituted furanyl carbinol **76**. Rearrangement of this furanyl carbinol with $ZnCl_2$ followed by chloral in toluene gave the desired substituted 4-hydroxy cyclopentenone **78** which on protection with triethylsilyl chloride in DMF gave the corresponding triethylsilyl ether **79** (Scheme 4).



Scheme 4: Synthesis of 2-substituted-4-hydroxy cyclopentenone from (z, z)-1, 5-cyclooctadiene

The mechanism of this acid catalyzed hydrolysis has been explained in terms of a thermal electrocyclic reaction of a 4 π electron system, that is conrotatory. [14]

The conversion of intermediate **88** to the 2-substituted 4-hydroxycyclopentenone **91** proceeds via dehydration-hydration sequence involving heterogeneous catalysis. The unstable cyclpentadienone intermediate formed immediately changes to more stable α, β-unsaturated ketone.

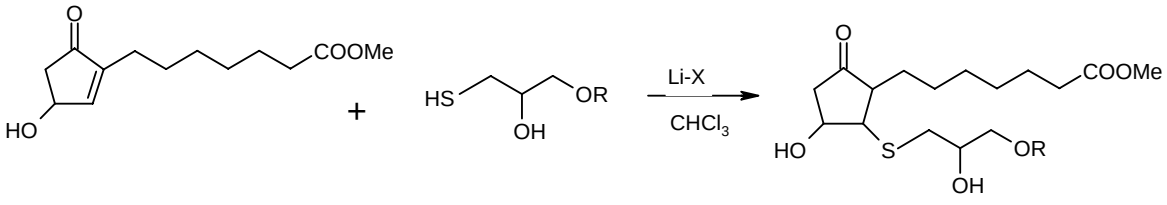


Scheme 5 : Mechanism of formation of 2-substituted-4-hydroxy cyclopentenone

1.3.2 Present work

Taking in to consideration the problems associated with use of soluble bases, the development of efficient and selective solid acid base catalysts for key step in synthesis of prostaglandins has been and continues to be a challenging and active exploration in organic synthesis. The characteristic properties of zeolites such as thermal stability, shape selectivity, simplicity of reaction, ease of workup due to heterogeneous nature and reusability made them the reagent of choice. Our effort in this direction resulted in a novel application of X-type zeolite for the aforementioned goal. The synthesis of various 13-thiaprostaglandins by using X-type zeolite has been developed to suit the requirements by more stringent laws laid down all over the world for the protection of environment.

The methodology for this reaction was standardized using cyclohexenone and various thiols for Michael addition using X-type zeolite incorporated with Li, Cs and K as shown in section B of this chapter. Out of the three catalysts used, Li-X zeolite yielded cleaner and efficient Michael addition product for cyclohexenone as well as 4-hydroxy and 4-*tert*-butyldimethylsilyloxy cyclopentenone. The enone was treated with aryloxythiols as nucleophiles in the synthesis of 13-thiaprostaglandins. Applying this methodology, PGE analoges were synthesized as shown in scheme 6.

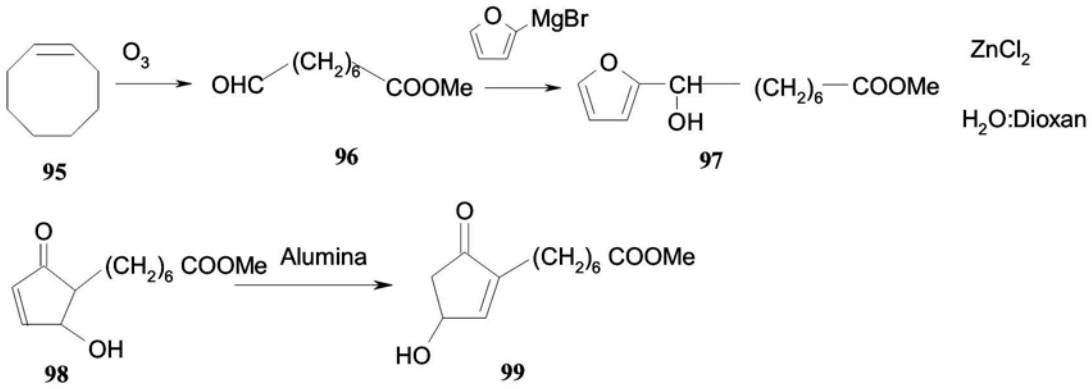


92 **93** **94**

R = 4-methoxyphenyl, 1-naphthyl, 2-naphthyl

Scheme 6 : Synthesis of 13-thiaprostaglandins using Li-X zeolite as catalyst

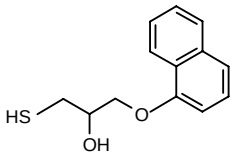
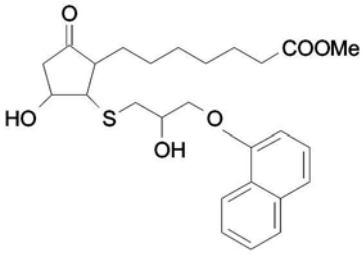
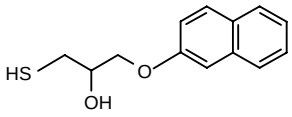
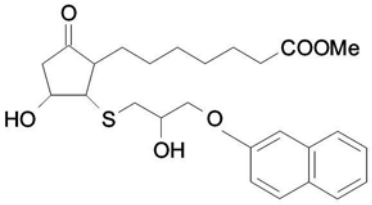
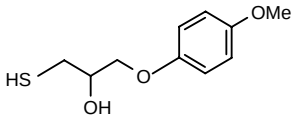
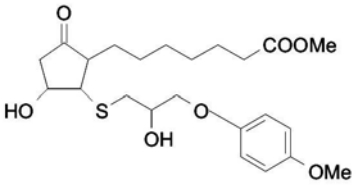
The required enone was prepared from cyclooctene as shown in scheme 7.



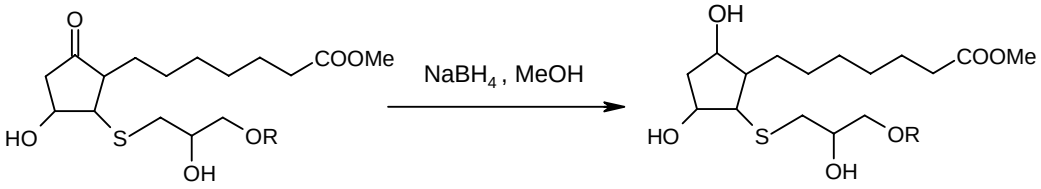
Scheme 7: Synthesis of enone intermediate for prostaglandin synthesis by two component coupling

The ozonolysis of cyclooctene yielded methyl-8-oxooctanoate (**96**). The reaction of methyl 8-oxooctanoate with 2-furylmagnesium bromide afforded the corresponding substituted 2-furanmethanol **97** which was sequentially rearranged with zinc chloride followed by second rearrangement with basic alumina to afford the desired enone **99**. This enone **99** was subjected to Michael addition as shown in scheme 6 to afford the PGE analogues.

Table 1 : Li-X-zeolite mediated 1, 4-addition of thiols to enone 92

Entry No.	Thiol	Product	Yield %
1			48
2			53
3			65

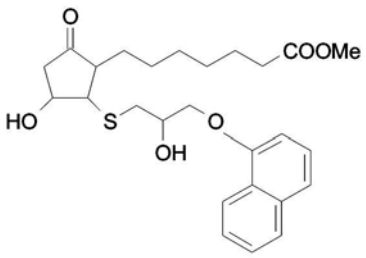
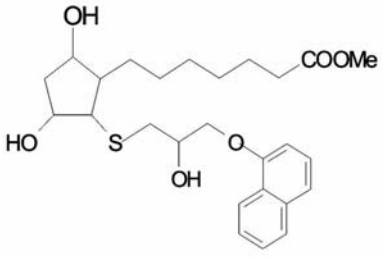
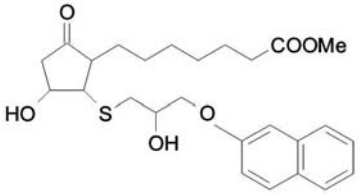
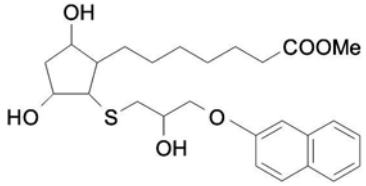
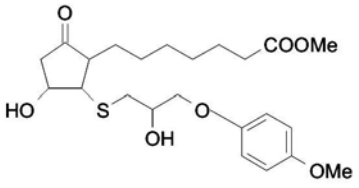
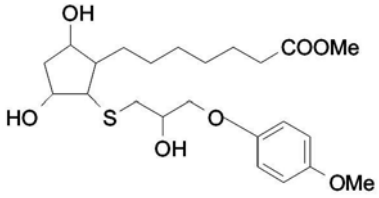
The ketone functionality in the thiaprostaglandins was reduced with sodium borohydride to yield the corresponding hydroxy derivatives in almost quantitative yields as shown in scheme 8.



101 **102**

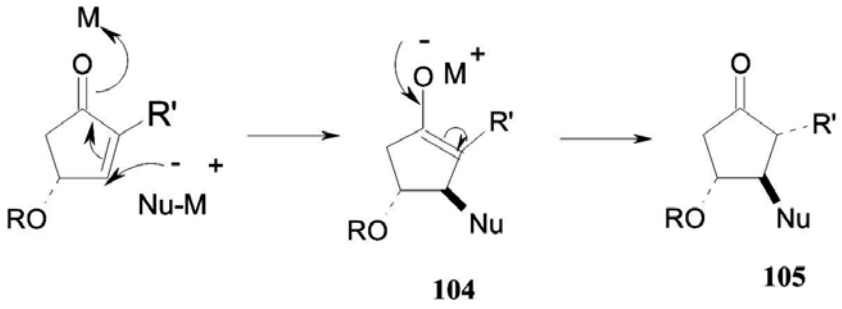
Scheme 8 : Reduction of PGE analogue to form PGF analogue

Table 2 : Synthesis of PGF analogues

Sr. No.	PGE analogue used	Reaction time (hr)	Product	Yield %
1.		2		94
2.		2		97
3.		2		96

1. 3. 3 Results and Discussion

The desired Michael donors i.e. the thiols corresponding to the β-side chains for the synthesis of 13-thiaprostaglandins were obtained as described in the Section B of this chapter. Michael addition of thiols on the cyclopentenone intermediate **99** which acted as Michael acceptor in the presence of Li-X-zeolite provided the Michael adducts with the basic skeleton of 13-thiaprostaglandins. The products were characterized by spectroscopic methods.



Scheme 9 : Mechanism for the formation of 13-thiaprostaglandins

It was noteworthy to observe the versatile nature of the catalyst to perform 1, 4-addition reaction on cyclic enones. The basicity of lithium incorporated in the X-type zeolite catalyst was sufficient for 1, 4-addition of thiol (Scheme 6), thus providing neutral reaction conditions. The catalyst could be then recovered by filtration and recycled. The reaction proceeded to give 1, 4-addition products selectively and side products formation like elimination reaction and rearranged product could be totally avoided which are favored by basic reaction conditions.

It is well established that the stereochemistry of the 4-hydroxy group in the cyclopentenone intermediate in the two-component coupling synthetic strategy directs the in-coming side chain at C-3 position followed by the stereochemistry at C-2 position which is eventually trans / trans addition reaction. We performed the Michael addition

reaction using racemic 4-hydroxy-2-substituted-cyclopent-2-en-1-one therefore the product was expected to be a mixture of diastereomers. During the application of our methodology using Li-X-zeolite for 1, 4-addition of thiols as described in Section A of this chapter for the synthesis of 13-thiaprostaglandin, use of chiral 4-hydroxy-cyclopentenone was out of the scope.

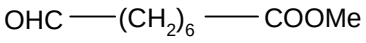
The Michael adduct (**101**) thus obtained was further converted (scheme 8) to the PGF series by reduction of the ketone at C-9 position. Selective reduction using L/K-selectride on the chiral prostaglandins taking care of all the asymmetric centers is well documented in the literature.

1. 3. 4 Conclusion

Novel 13-thiaprostaglandin analogues were synthesized by Li-X zeolite catalyzed Michael addition of thiols to appropriately functionalized 4-hydroxy cyclopenteone. Reported methods for synthesis of 13-thiaprostaglandins use organic or inorganic bases as catalysts which in case of cyclic hydroxy enones lead to rearrangement products. 4-Hydroxy cyclopentenone, an intermediate for the synthesis of prostaglandins is sensitive to basic conditions and results in H_2O eliminated product. However when Li-X zeolite was used as catalyst, almost exclusively the desired Michael adduct was formed. This methodology has all the advantages of heterogeneous catalysis such as mild condition, ease of work-up as well as separation, recoverability of catalyst, inexpensive and environmentally friendly conditions. Various optically active 13-thiaprostaglandin analogues could be prepared by employing heterogeneous catalyst Li-X zeolite from optically active 4-hydroxy cyclopentenone and substituted thiols, wherein the Michael addition is expected to proceed in trans manner.

1.3.5 Experimental

Synthesis of methyl 8-oxo octanoate:

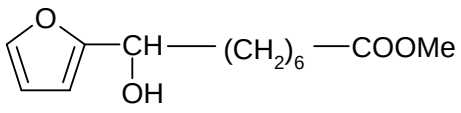


A slurry of cyclooctene (1.10 g, 10 mmol) and $NaHCO_3$ (2.11 g, 25. 1 mmol) in CH_3OH (185 ml) and CH_2Cl_2 (12 ml) was ozonized at –40°C for 8 hrs. The progress of the reaction was monitored by quenching the aliquots with Et_3N and Ac_2O and analyzing toluene layer by TLC. After the reaction was ~ 65% complete, the reaction mixture was purged with N_2 for 30 min and Et_3N was added over a 30 min period below –20°C. The reaction mixture was allowed to warm to 25°C and stirred overnight under N_2. The mixture was then filtered, and the inorganic salts were washed with toluene. The organic phase was then treated with a solution of $FeSO_4.7H_2O$ (50 g, 18.0 mmol) and 12 N HCl in water until the absence of peroxides was indicated by a negative starch-iodide test. The phases were separated, organic phase washed twice with water and filtered through a mixture of silica gel and diatomaceous earth. The filtrate was concentrated in vacuum to give the desired product.

Yield : 67 %.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.50-1.70 (m, 6H), 2.35-2.50 (m, 6H), 4.35 (s, 3H), 9.70 (s, 1H).

Synthesis of methyl-8-(2-furanyl)-8-hydroxy octanoate



Step A] Preparation of anhydrous $MgBr_2$:

Mg turnings (768 mg) were taken in a 3-necked r. b flask, dried, evacuated and flushed with argon. Dry ether (30 ml) was then added followed by dropwise addition of a solution of dibromoethane (5.64 ml) in dry ether (25 ml) at r.t . The reaction was stirred at r.t. for 1 hr and concentrated with industrial vacuum to get buff white solid.

Step B] Preparation of furyl magnesium bromide:

Furan (8.72 g, 40 mmol) in dry diethyl ether (10 ml) was cooled with ice-salt mixture, 15% n-BuLi (12.5 ml, 30 mmol) was added dropwise to it and the mixture stirred at 0ºC for ½ hour. The resulting solution was added to $MgBr_2$ and mixture stirred at r.t for 1½ hr. Two layers, one dark brown and other pale yellow (similar to Mg Br_2 in ether) were seen.

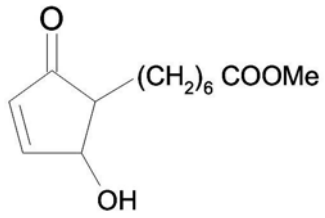
Step C] Preparation of methyl – 8- (2'-furanyl)-8-hydroxy octanoate.

The above solution was cooled to -25º C and 5.16 g (30 mmol) methyl-8-oxo-octanoate in dry ether (10 ml) was added dropwise (immediate precipitation of white solid was observed and solid product separated from ether, making stirring impossible). The reaction mixture was kept at 0ºC for 2 hrs, quenched with sat. NH_4Cl solution, extracted with EtOAc, dried and concentrated.

Yield : 71%

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.50-1.70 (m, 4H), 1.75-1.90 (m, 4H), 2.35 (t, J=15 Hz, 2H), 3.65 (s, 3H), 4.65 (t, J=6.7 Hz, 1H), 6.22 (dd, J_1=3.2 Hz,J_2=1.0 Hz, 4H), 6.32 (dd, J_1=3.2 Hz, J_2=1.9 Hz, 1H), 7.35-7.38 (m, 1H).

Synthesis of methyl-7-(2-hydroxy-5-oxo-3-cyclopenten-1-yl) heptanoate



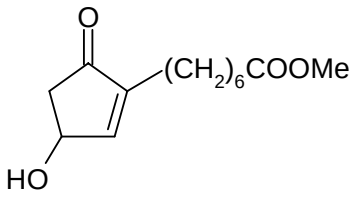
A] $ZnCl_2$ (0.6 g, 44 mmol) was added to a mixture of the product from above experiment in dioxan (36.0 ml) and H_2O (24.0 ml). The reaction mixture was stirred to ensure complete dissolution in a 2-necked 1 litre round bottomed flask with magnetic stirrer condensor and stopper. The reaction mixture was refluxed over a period of two days (bath temp. 95ºC - 100ºC) and kept at room temperature for one day (reaction monitored by TLC). The mixture was then acidified with HCl to pH 4 and extracted with EtOAc. The organic layer was washed with water, saturated brine, dried with Na_2SO_4 and concentrated. The crude product obtained was methylated directly.

B] Methylation of above crude product:

The product from previous step and MeI (3.124 g , 50 mmole) in 40.0 ml dry acetone were taken in a single necked 1 litre r.b. with condensor and refluxed on a water bath along with anhydrous K_2CO_3 (3.12 g, 44 mmol). The reaction was monitored by TLC for disappearance of white spot of acid. After completion of reaction, the solution was filtered to remove K_2CO_3, washed with acetone and concentrated. The column purification of the crude residue afforded 7.47 g (27.8%) of the pure product.

^1H NMR (200 MH_2, $CDCl_3$) : δ 1.33-1.60 (m, 8H), 2.25-2.33 (m, 4H), 2.85 (d, J=3.0 Hz,1H), 3.65 (s, 3H), 4.65 (s, 1H), 6.16 (d, J=3.2 Hz,1H), 7.45 (dd, J_1=3.2 Hz, J_2=1.0 Hz, 1H).

Synthesis of Methyl-7-(3-hydroxy-5-oxo-2-cyclopenten-1-yl) heptanoate



The above product (7.47 g) was dissolved in minimum amount of dry methylene dichloride and adsorbed on alumina (115 g). Methylene dichloride was allowed to evaporate at ambient conditions and reaction mass kept at room temperature for 40 hrs. It was then poured in a column and eluted with methanol. Methanol was then evaporated, residue dissolved in ethyl acetate, dried over Na_2SO_4, filtered and concentrated to give a solid product.

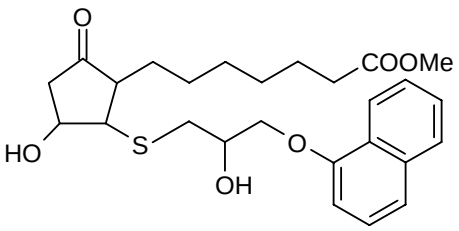
Yield : 6.34 g (85%).

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.30-1.60 (m, 8H), 2.10-2.30 (m, 5H), 2.85 (d, J=6.0 Hz, 1H), 3.65 (s, 3H), 4.20 (brs, 1H), 4.85 -4.90 (m, 1H), 7.05 (s, 1H).

General procedure for the synthesis of 13-thiaprostaglandins by Michael addition

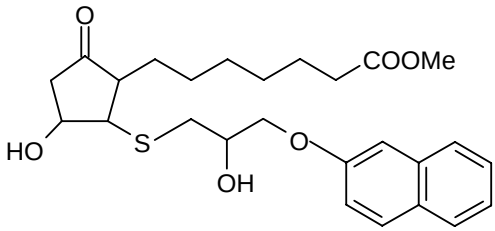
To a mixture of enone (0.5 mmol) and thiol (0.5 mmol) in dry chloroform (1 ml) at 0^{o}C under argon atmosphere was added lithium-X-zeolite (24 mg, 20% by wt of enone) and stirred at 0^{o}C for 2 hrs. The reaction mixture was then brought to room temperature and stirred for 24 hours. After completion of reaction (TLC), the catalyst was filtered off and washed with water followed by brine, dried and concentrated under reduced pressure. Column chromatography on silica gel afforded the novel prostaglandin E analogues as shown in Table 1.

Methyl 11, 15-dihydroxy-16-(1-naphthyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate [Table 1, entry1]



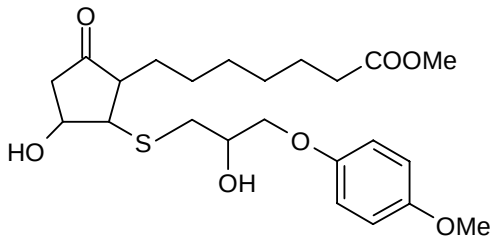
^{1} H NMR ($CDCl_3$)	**:**	δ	1.28 –1.44 (m, 6H), 1.50 – 1.82 (m, 4H), 2.16 -2.38 (m, 4H), 2.51 - 3.42 (m, 4H), 3.65 (s, 3H), 4.12 - 4.55 (m, 4H), 6.80 (d, J = 6.0 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.40- 7.55 (m, 3H), 7.75 - 7.86 (m, 1H), 8.18 – 8.27 (m, 1H).
MS	**:**		474 (M^+), 456, 331, 313, 234, 191, 144, 115 .
Anal calc. for $C_{26}H_{34}O_6S$	**:**		C 65.82, H 7.17, S 6.75
found			C 66.11 H 7.08, S 6.69.

Methyl 11,15-dihydroxy-16-(2-naphthyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate [Table 1, entry 2]



^{1}H NMR ($CDCl_3$)	**:**	δ 1.05 - 1.38 (m, 6H), 1. 48 - 1. 80 (m, 4H), 2.07 - 2. 40 (m, 5H), 2. 49 - 3.13 (m, 2H), 3.13 -3. 40 (m, 1H), 3.66 (s, 3H), 4.00 - 4.64 (m, 4H), 7.02 - 7.21 (m, 2H), 7. 29 - 7.53 (m, 2H), 7.63 - 7.85 (m, 3H).
MS	**:**	474 (M^+), 456, 331, 313, 234, 144, 127, 115
Anal calc. for $C_{26}H_{34}O_6S$	**:**	C 65.82 H 7.17 S 6.75
found		C 65.56 H 7.28 S 6.61

Methyl 11, 15-dihydroxy-16-(4-methoxyphenyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate [Table1, entry 3]

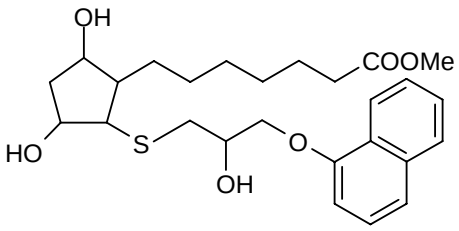


^{1}H NMR ($CDCl_3$)	**:**	δ 1.23 - 1.45 (m, 6H), 1.54 - 1.77 (m, 4H), 1.80 -2.10 (m, 1H), 2.19 - 2.39 (m, 4H), 2.65 - 3.25 (m, 3H), 3.65 (s, 3H), 3.75 (s, 3H), 3.89 – 4.07 (m, 2H), 4.07 - 4.40 (m, 2H), 6.80 (brs, 4H).
MS	**:**	454 (M^+), 436, 331, 313, 191, 163, 124, 109, 95.
Anal calc. for $C_{23}H_{34}O_7S$	**:**	C 60.71 H 7.49 S 7.05
found		C 60.72 H 7.84 S 6.87.

Synthesis of PGF analogues

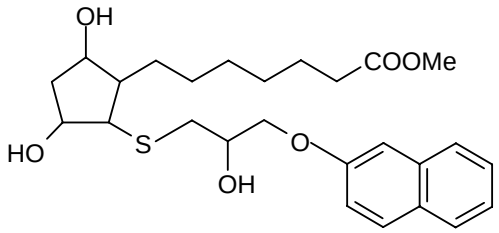
13-Thiaprostaglandins E (0.25 mmol) in dry methanol (10 ml) were treated with excess sodium borohydride (2.5 mmol) at – 20°C for 2 hrs after which the reaction was quenched with water and the product was extracted with ethyl acetate. Chromatographic purification afforded the novel thiaprostaglandins F in almost quantitative yield (Table 2).

Methyl 9,11,15-trihydroxy-16-(1-naphthyloxy)-13-thia-17, 18, 19, 20 –tetranorprostanoate [Table 2, entry 1]



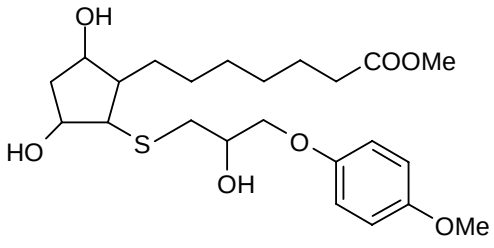
^{1}H NMR ($CDCl_3$)	**:**	δ 1.50 - 1.49 (m, 6H), 1.49 - 1.88 (m, 6H), 1.97-2.15 (m, 1H), 2.30 (t, J = 6.5 Hz, 2H), 2.48 - 3.27 (m, 3H), 3.65 (s, 3H), 3.80 - 4.50 (m, 5H), 6.85 (d, J = 6.5 Hz, 1H), 7.38 (t, J = 6.5 Hz, 1H), 7.45 - 7.60 (m, 3H), 7.82 (d, J = 6.5 Hz, 1H), 8.15 – 8.30 (m, 1H).
MS	**:**	476 (M^+), 333, 315, 144, 115.
Anal calc. for $C_{26}H_{36}O_6S$	**:**	C65.55 H 7.56 S 6.72
found		C 65. 23 H 7.39 S 6.64

Methyl 9, 11, 15-trihydroxy-16-(2-naphthyloxy)-13-thia-17, 18, 19, 20-tetranor-prostanoate [Table 4, entry 2]



^{1}H NMR ($CDCl_3$)	**:**	δ 1. 25 - 1. 52 (m, 6H), 1. 52 - 1.70 (m, 4H), 1.70 – 2. 23 (m, 3H), 2. 30 (t, J = 6.5 Hz, 2H), 2.62 - 3. 43 (m, 3H), 3. 62 (s, 3H), 3. 84 - 4.42 (m, 5H), 7.07 - 7. 20 (m, 2H), 7. 29 - 7. 51 (m, 2H), 7.62 - 7. 84 (m, 3H).
MS	**:**	476 (M^+), 333, 315, 144, 115.
Anal calc. for $C_{26}H_{36}O_6S$	**:**	C 65.55 H 7.56 S 6.72
found		C 65.83 H 7.39 S 6.66.

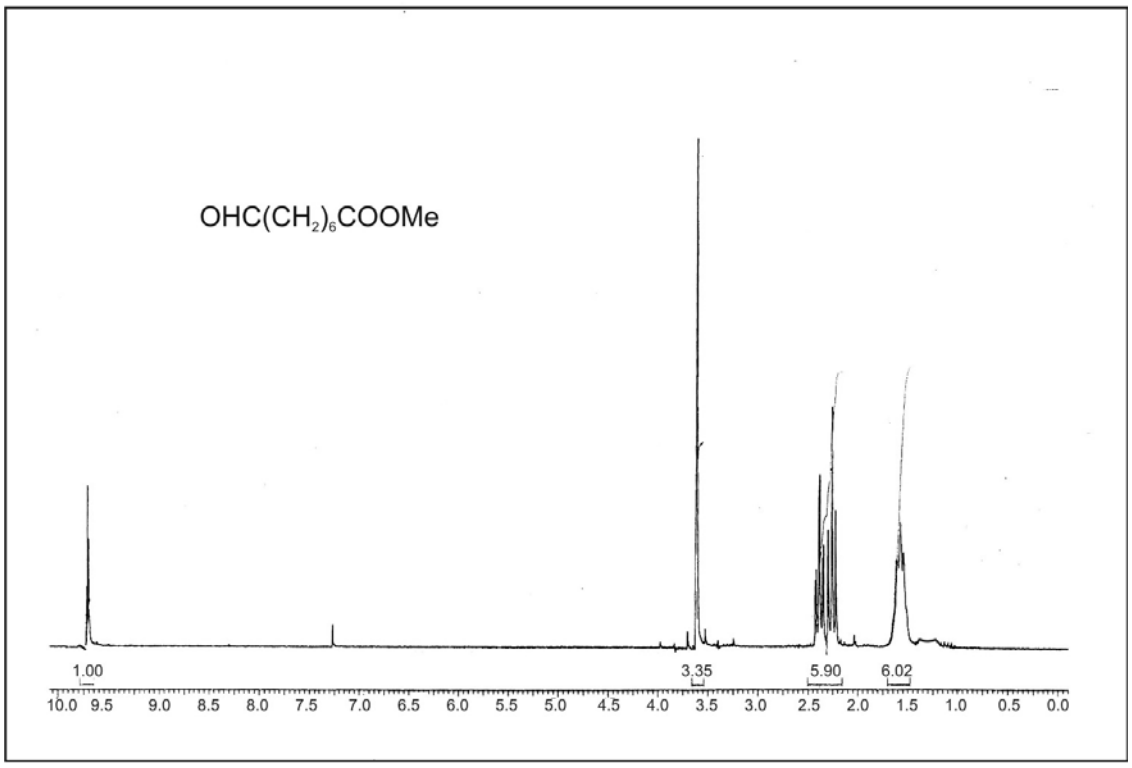
Methyl 9,11,15-trihydroxy-16-(4-methoxyphenyloxy)-13-thia-17, 18, 19, 20-tetranorprostanoate [Table 2, entry 3]



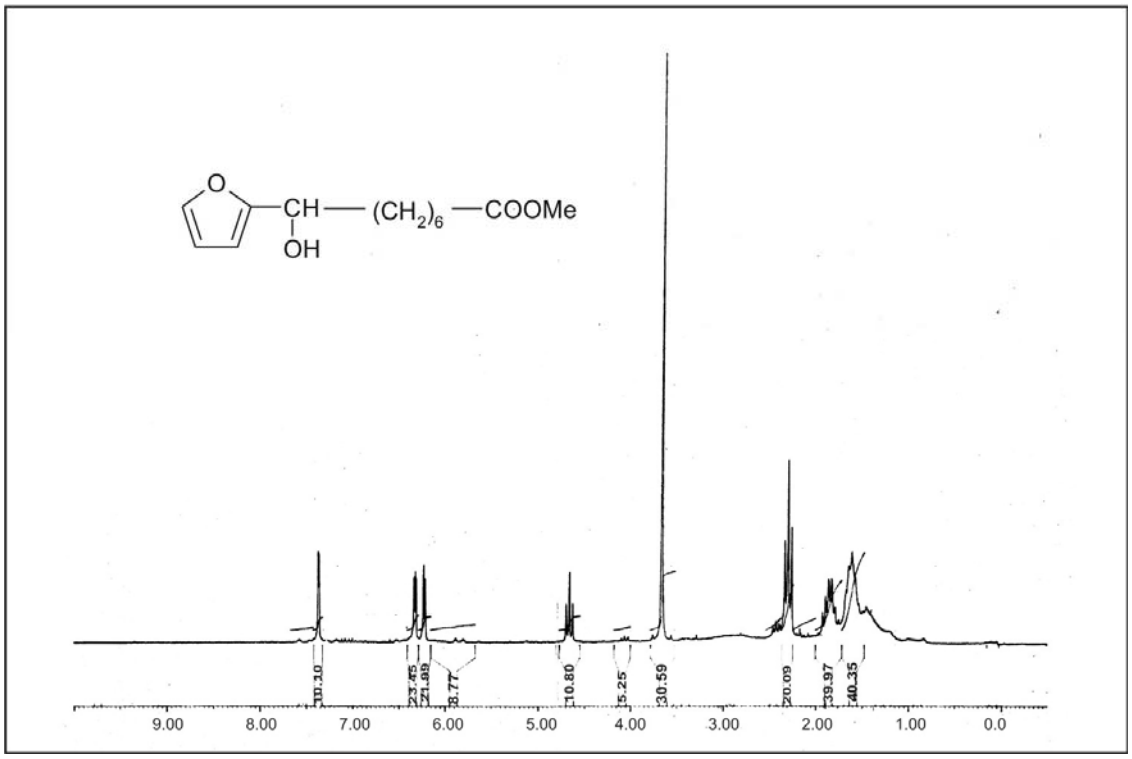
^{1}H NMR ($CDCl_3$)	**:**	δ 1.15 - 1.50 (m, 6H), 1.50 - 1.72 (m, 4H), 1.78 – 2.15 (m, 3H), 2. 27 (t, J = 6.5 Hz, 2H), 2.45 - 3.08 (m, 3H), 3. 67 (s, 3H), 3.77 (s, 3H), 3. 90 - 4.05 (m, 2H), 4.05 - 4.40 (m, 3H), 6. 84 (brs, 4H).
MS	**:**	456 (M^+), 333, 315, 193, 163, 124, 109.

Anal calc. for $C_{23}H_{36}O_7S$	**:**	C 60.53	H 7.89	S 7.02
found		C 60.59	H 8.06	S 6.89.

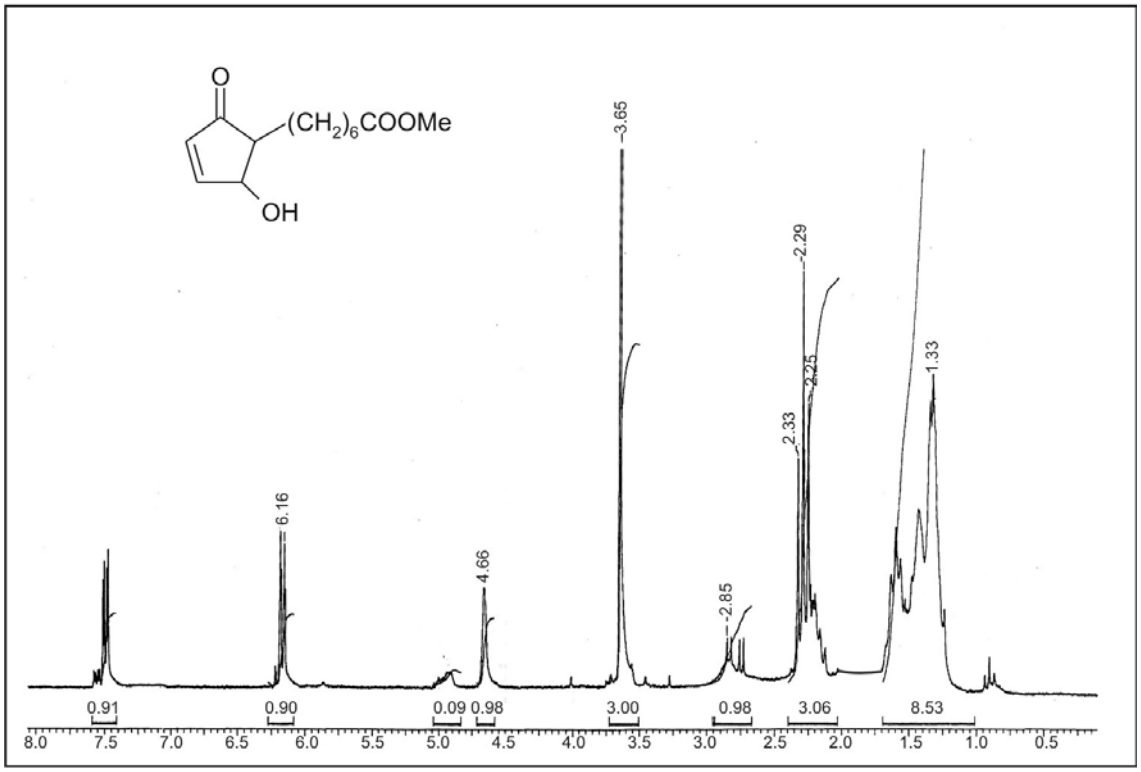
^{1}H NMR of methyl-8-oxooctanoate



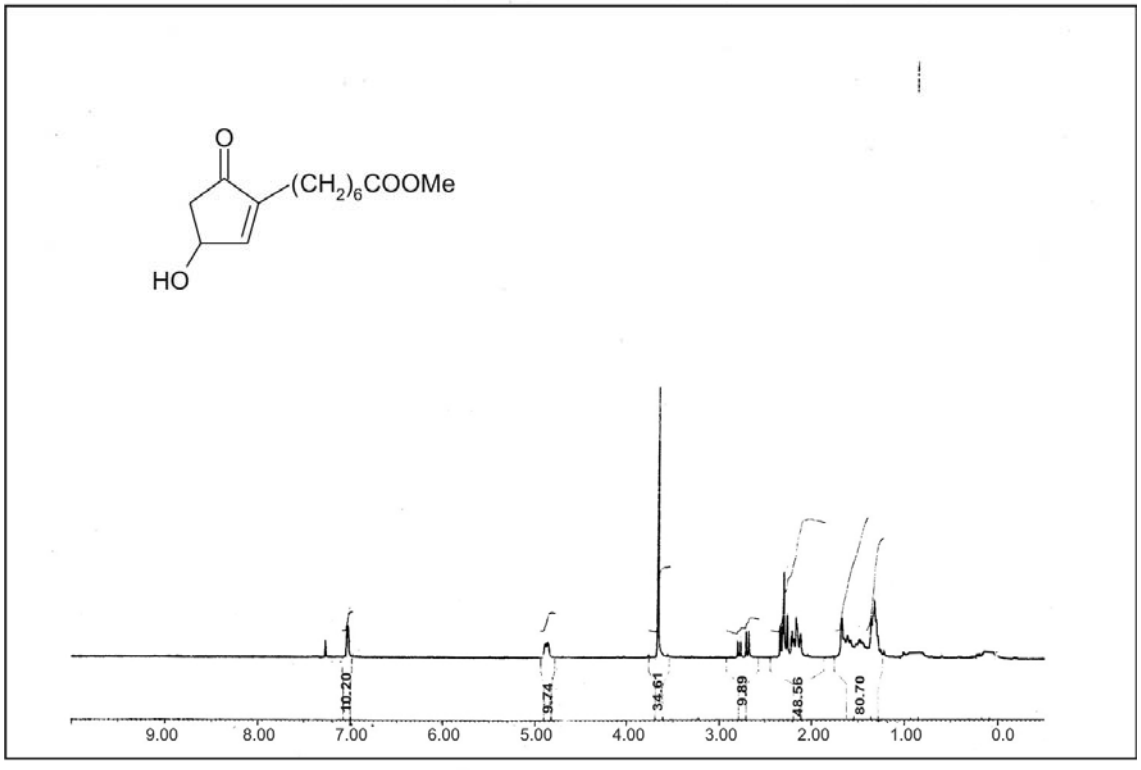
^{1}H NMR of methyl 8- (2'-furanyl) - 8 - hydroxy octanoate



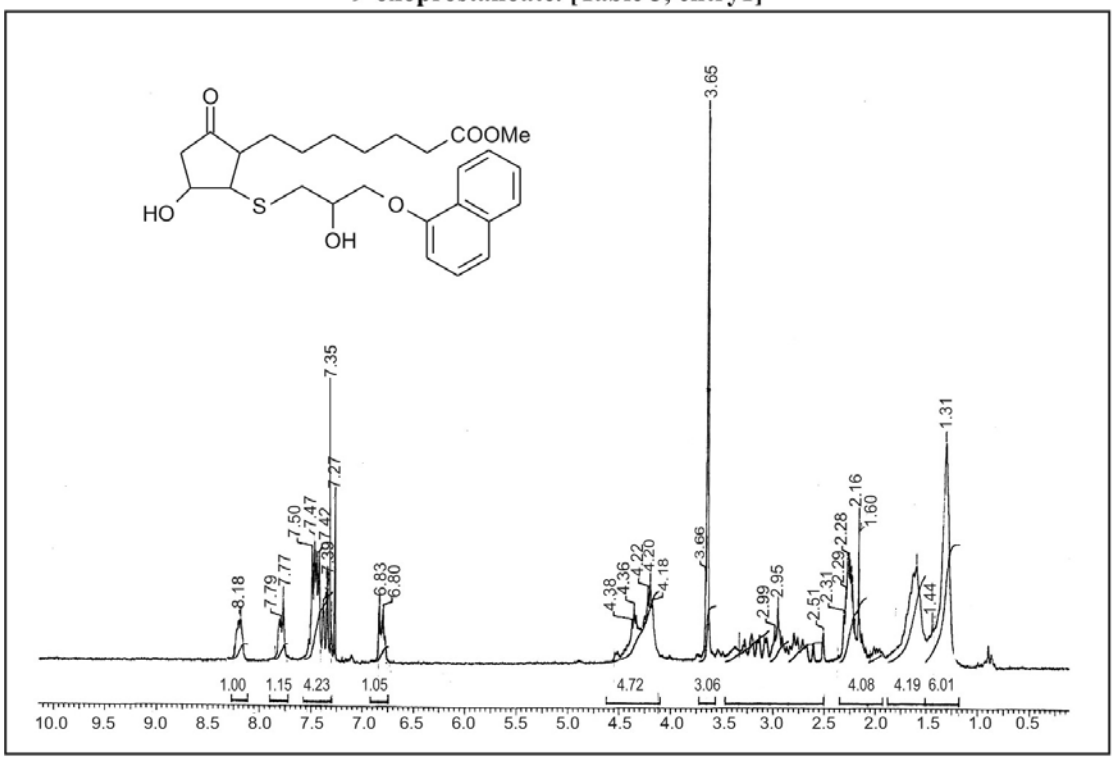
^{1}H NMR of methyl-7-(2-hydroxy-5-oxo-3-cyclopenten-1-yl) heptanoate



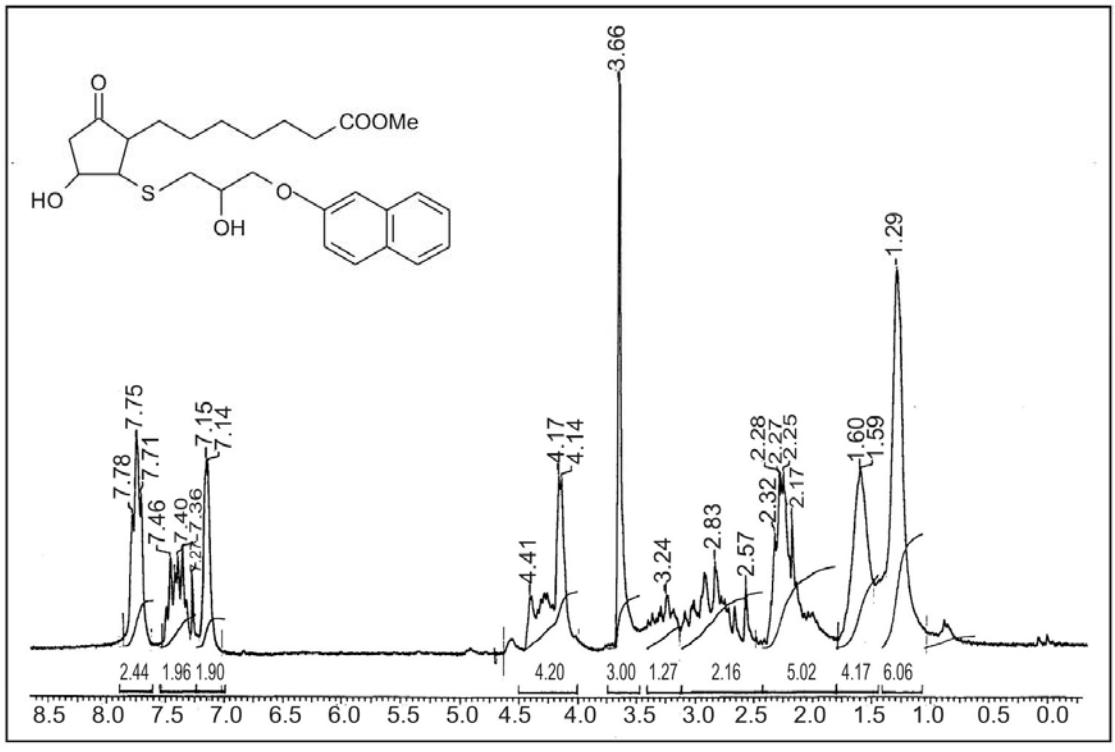
^{1}H NMR of methyl-7-(3-hydroxy-5-oxo-2-cyclopenten-1-yl) heptanoate



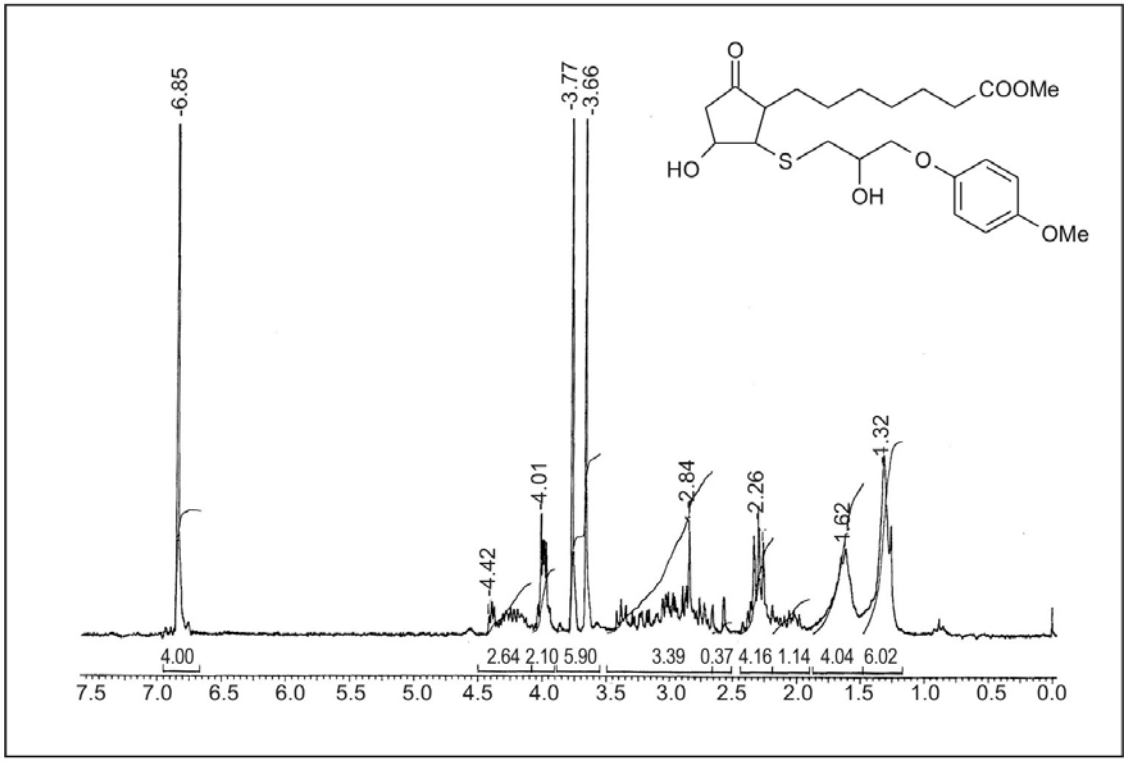
^{1}H NMR of methyl 11,15-dihydroxy-16-(1-naphthyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate. [Table 3, entry1]



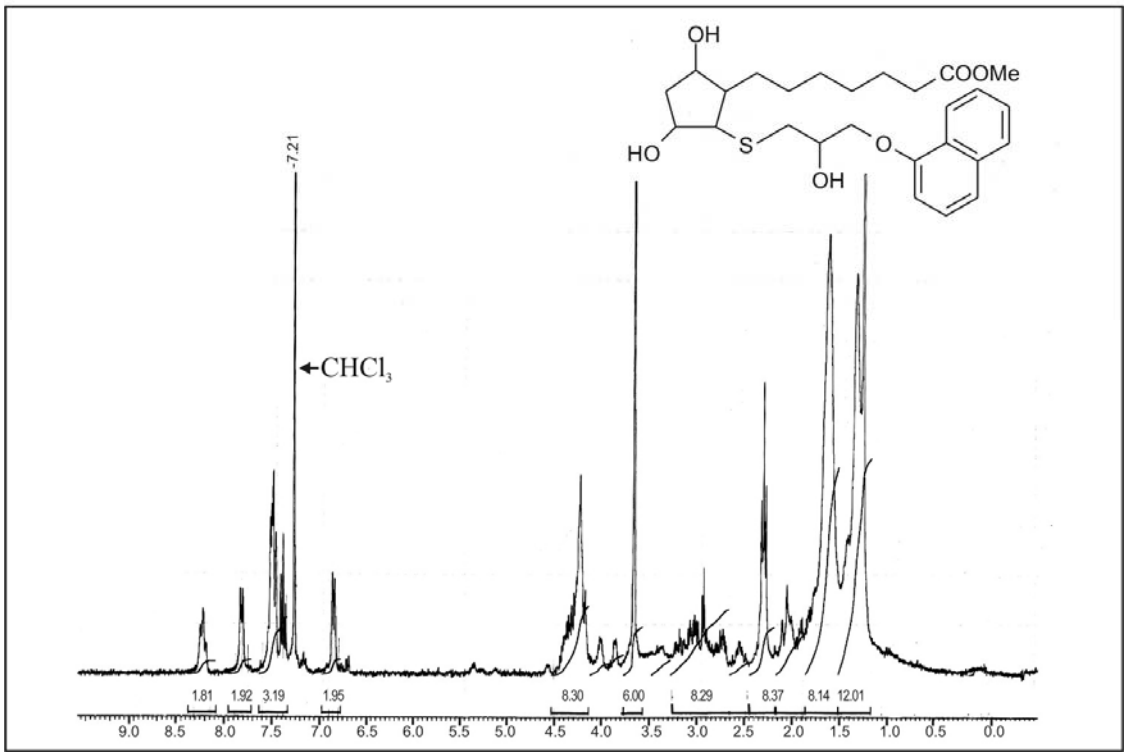
^{1}H NMR of methyl 11,15-dihydroxy-16-(2-naphthyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate



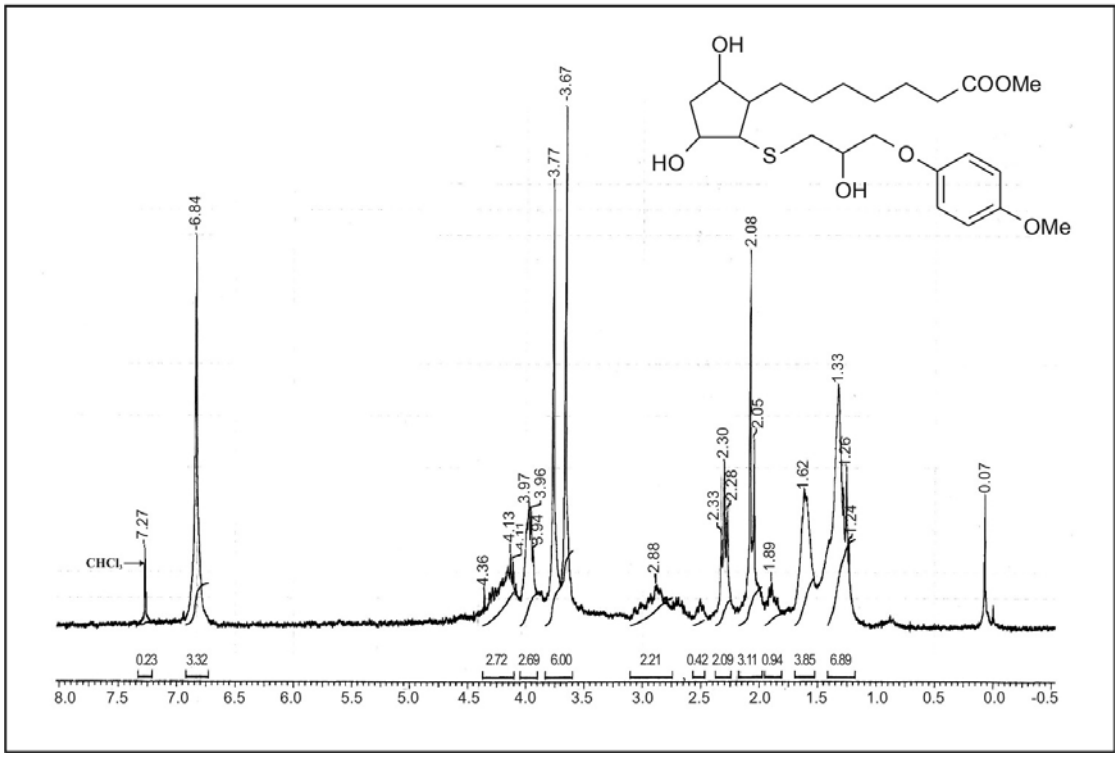
^{1}H NMR of methyl 11,15-dihydroxy-16-(4-methoxyphenyloxy)-13-thia-17, 18, 19, 20-tetranor-9-oxoprostanoate



^{1}H NMR methyl of 9,11,15-trihydroxy-16-(1-naphthyloxy)-13-thia-17, 18, 19, 20 -tetranorprostanoate



^{1}H NMR of methyl 9,11,15-trihydroxy-16-(4-methoxyphenyloxy)-13-thia-17, 18, 19, 20-tetranor prostanoate.



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CHAPTER 2

ORGANIC TRANFORMATIONS

CHAPTER 2
(Section A)

Bromination of active methylene by a mixture of hydrobromic acid and hydrogen peroxide (or TBHP)

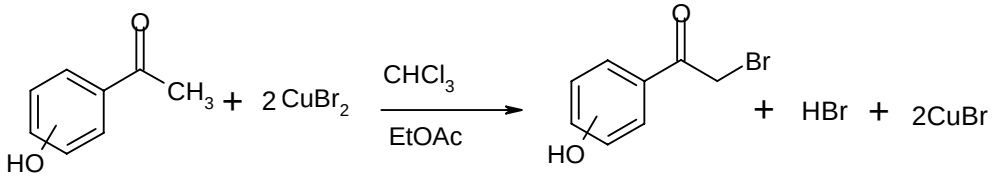
2.1.1 Introduction

Halogenated,[1] particularly brominated carbonyl compounds; due to their higher reactivity find a unique place in the synthetic schemes towards important organic molecules. α-Haloketones are known to be versatile intermediates in Cornforth olefin synthesis, Favorskii rearrangement etc. In the field of halogen containing alkylating reagents organic bromine compounds activated by electron withdrawing carbonyl group at α-position have been reported to possess a particularly high alkylating reactivity.

Several methods have emerged for efficient synthesis of α-haloketones, which include direct side chain bromination by electrophilic substitution of α-hydrogen of ketones with bromine.[4] But this protocol is not reliable for activated aromatic substrates such as hydroxy acetophenones or with electron rich heterocyclic systems where concurrent nuclear bromination is facile.[1] The hydrobromic acid as a by-product brings about demethylation or deacetylation in the substituted aromatic nucleus such as methylated and acetylated phenols and also adds on to the double bond, if present in the molecule, thus making the method incompatible with acid sensitive functionalities. It has been observed that during direct α-halogenation, polyhalogenation, low yields and/or difficultly separable mixtures are common experimental outcomes. On the other hand there are certain disadvantages for the indirect procedures (enol derivatives, acetates, ethers etc) unless some thermodynamic or steric factors predominate.[2] To overcome these problems, several reagents like dibromobarbituric acid,[5] dioxanedibromide,[6] trimethylbromosilane-dimethyl sulfoxide,[7] bromine-trimethyl borate,[8] pyridinium hydrobromide perbromide,[11] phenyltrimethyl-ammonium perbromide[12] and polymeric reagents[13] have been used for bromination of compounds with active α-hydrogen.

Cu (II) halides in water, alcohol, DMF or dioxane have been used to halogenate a variety of ketones. However low selectivity along with difficulty in isolation of the products is a disadvantage of this method. In order to improve efficiency of the reaction L. Carrol King and G. K. Ostrum[3] reported that a heterogeneous system consisting of copper (II) bromide

in chloroform-ethyl acetate reacts with ketones to give the corresponding α-bromoketone in high yields. The by-product HBr being slightly soluble in the solvent system escapes from the reaction vessel. The copper (I) bromide is insoluble and is easily removed by filtration.

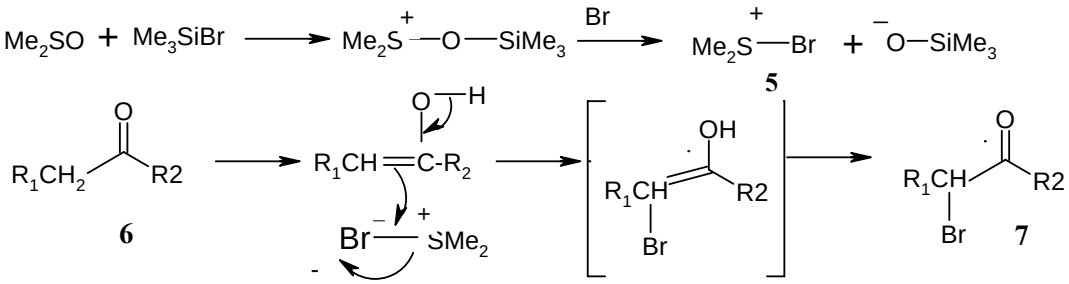


1 **2** **3** **4**

Scheme 1 : Bromination of ketones with suspended Cu(II)Br

However, the high cost of copper (II) bromide along with disposal of Cu (I) Br and HBr limits the use of this method for large scale bromination.

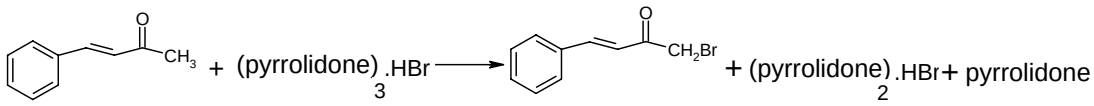
In 1986, Franco Bellesia *et al.* [7] reported that trimethyl bromosilane-dimethyl sulphoxide (TMBS-DMSO) reagent system in acetonitrile brominates efficiently and regiospecifically at the more substituted α-position of the carbonyl compounds in 0.5 to 2 hrs.



Scheme 2: α-Bromination of carbonyl compounds by TMBS-DMSO reagent

To achieve selective bromination of ketone in the presence of a double bond, pyrrolidino hydrotribromide[10] has been used in a solvent of low dielectric constant like THF. The

hydrogen bromide liberated as a result of bromoketone formation can be trapped effectively as the insoluble compound pyrrolidone hydrobromide by prior addition of equimolar amount of pyrrolidone to the reaction mixture. The ketone was thus brominated in the presence of both a double bond and an acid sensitive group. Under the reaction conditions, the relative susceptibilities towards bromination are ketone >> olefin >> enol acetate.

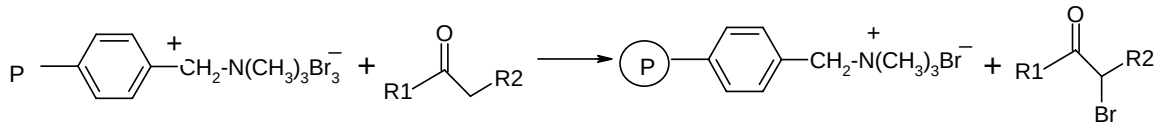


8 **9** **10** **11**

Scheme 3: Selective bromination of ketone with pyrrolidone

The selective monobromination at methyl group of benzylideneacetone has also been reported by using 2-bromo-2-cyano-N, N-dimethylacetamide as the brominating agent. 2-Bromo-2-cyano-N, N-dimethylacetamide and 2, 2-dibromo-2-cyano-N, N-dimethyl acetamide[9] were found to be effective brominating agent for monobromination at α-carbon atom of the ketone. Since hydrobromic acid is not liberated in this reaction formation of byproducts is prevented. Nuclear bromination of substituted reactive aromatic compounds does not take place under the reaction conditions.

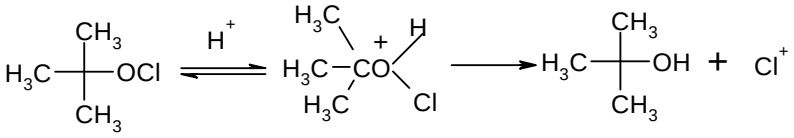
Sandro Cacchi and Luciano Caglioti[13d] reported the use of Amberlyst-A 26Br_3^- for α-bromination of carbonyl compounds. The polymer was prepared by washing commercially available Amberlyst-A 26-Cl^- with 1 N aqueous NaOH to remove all Cl^- and then with distilled water until neutral and stirred overnight at room temperature with 1 N aqueous HBr. The polymer so prepared was reported to brominate the carbonyl compounds in 55-76% yield as shown in the scheme 4.



12 **13** **14** **15**

Scheme 4: Bromination with Amberlyst-A $26Br_3^-$

Some of the reagents listed above are not easy to prepare, slightly costly or give byproducts after bromination which are difficult to separate from the reaction mixture. Looking at the serious drawbacks of the use of molecular halogen for halogenation of organic compounds, many researchers have used system which *in situ* generates halogen or positive species responsible for the halogenation reaction. Harway and Norman[14] demonstrated that tert-butyl hypochlorite (TBHC) gives Cl^+ in the acidic medium. The kinetic study of the reaction of TBHC with mineral acid suggested the formation of chloronium ion. Further it was observed that chlorination in acid solution occurs rapidly as is consistent with the expected rapid production of the Cl^+ by the mechanism shown below (Scheme 5). In the acidic medium protonation of the oxygen of TBHC should release the chloronium ion faster to react further.



16 **17** **18**

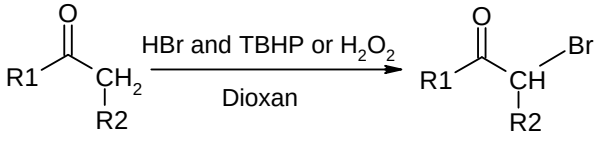
Scheme 5: Formation of chloronium ion from TBHC in acidic medium

In 1962, Walling and Mintz [15] reported the preparation of *tert*-butyl hypobromite (TBHB) and its utility for the bromination of hydrocarbons. TBHB was prepared by the reaction of *tert*-butyl alcohol with bromide from free aqueous hypobromous acid (HOBr) and extraction of the product with trifluoromethane to give the dibromide in 42% yield. The reddish orange coloured liquid was light sensitive and had to be stored in cool and dark place. The product was highly explosive at high temperature (>80^{o}C). Due to the tedious preparation and low stability under normal conditions, use of TBHB was very limited for the brominations and other reactions.

2.2.2. Present work

Though there are several methods reported for the halogenation of the carbonyl compounds, most of them have limitations like toxic nature of the reagent/catalysts, handling problems of the highly corrosive molecular halogen and disposal of the side products making the process environmentally hazardous and operationally costly. In view of these many researchers have paid attention to use *tert*-butyl hypohalite and hypohalous acid for the halogenation of organic compounds. The preparation of the *tert*-butyl hypohalite and hypohalous acid is known in the literature but it is tedious and dangerous as great care should be taken for the preparation of *tert*-butyl hypohalite due to its explosive nature and low stability. In this context it would be very advantageous if the reagent is generated *in situ* and used up in the reaction.

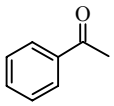
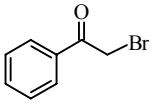
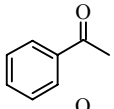
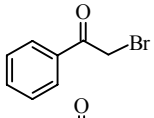
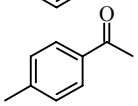
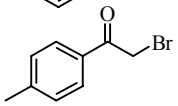
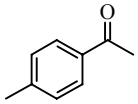
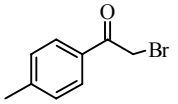
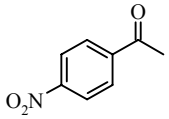
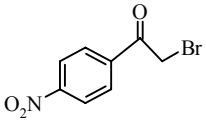
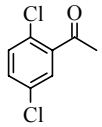
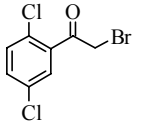
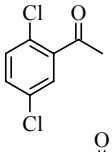
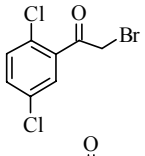
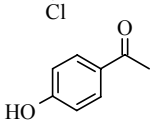
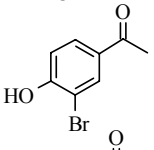
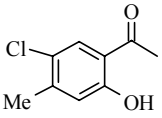
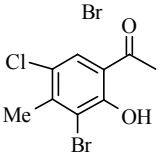
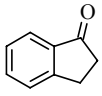
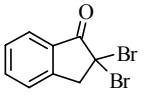
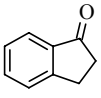
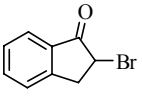
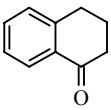
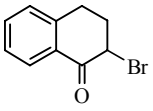
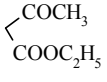
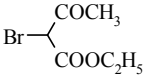
We have explored an effective reagent system in a mixture of hydrohalic acid and hydrogen peroxide or *tert*-butylhydroperoxide (TBHP) for the halogenation of organic substrates.[2] This oxyhalogenation method with these reagents yields vicinal *trans*-dihalogenated alkanes and 1,2-dihaloalkenes selectively from alkenes and alkynes respectively. 1-Bromo-2-chloroalkanes from alkenes could be obtained in good yields when a mixture of hydrobromic acid and hydrochloric acid along with H_2O_2 was used. After successful implementation of this methodology for the synthesis of halogenated arenes, halogenated alkanes and alkenes; we have extended it to α-bromination of carbonyl compounds. The study on the oxyhalogenation of the compounds having active methylenes with the *in situ* generated positive halogen using the combination of the hydrohalic acid and a suitable oxidant such as *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide is presented in this section. Several ketones were subjected to the bromination reaction as shown in scheme 6.



19 **20**

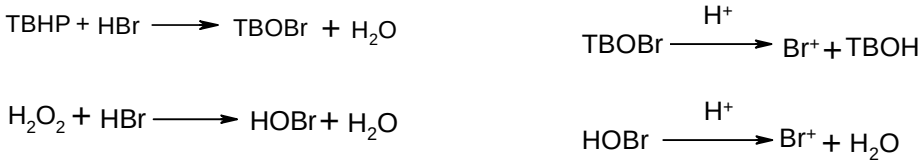
Scheme 6 : α-Bromination of active methylenes

TABLE

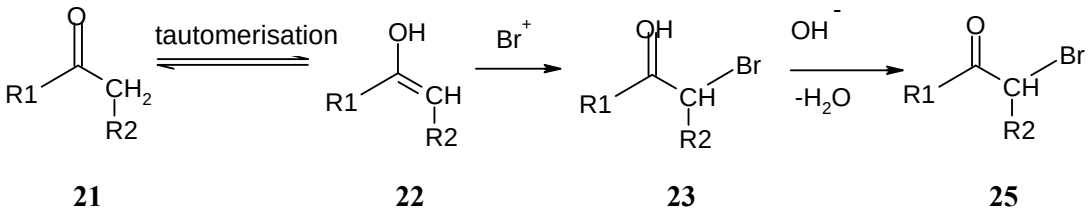
Entry	Substrate	Reaction condition	Product	% Yield (a)
1		Dioxan HBr(1.5) H_2O_2(1.1)		95
2		Dioxan HBr(1.1) TBHP(1.1)		85
3		Dioxan HBr(1.1) H_2O_2(.1.1)		93
4		Dioxan HBr(1.1) TBHP (1.1)		87
5		Dioxan HBr(1.5) H_2O_2(1.1)		75
6		Dioxane HBr (1.1) H_2O_2 (1.1)		94
7		Dioxane HBr (1.1) TBHP(1.1))		90
8		Dioxan HBr(1.5) H_2O_2(1.1)		90
9		Dioxane HBr (1.2) H_2O_2 (1.1)		98
10		Methanol HBr (4.0) H_2O_2 (4.0)		89
11		Dioxan HBr(1.1) TBHP(1.1)		65
12		Dioxan HBr(1.1) TBHP(1.1)		64
13		CH_2Cl_2 HBr (1.5) H_2O_2 (1.1)		99

a, isolated yield, characterised by usual spectral analysis

It is believed that bromination proceeds *via* the formation of *tert*-butyl hypobromite when the combination of TBHP/ HBr was used while *via* hypobromous acid when H_2O_2/HBr was used. The hypobromous acid has higher instability due to pronounced ionic nature compared to *tert*-butyl hypobromite and hence exhibits high reactivity and lower selectivity.



The acidic conditions ensures that the necessary enolisation takes place. The reaction is likely to proceed through the oxonium ion formed by using electrons of the oxygen thus enhancing the nucleophilicity of the alkene formed. The hydroxide ion then deprotonates the oxonium ion to get the corresponding α-bromoketone and water (Scheme 7).



21 **22** **23** **25**

Scheme 7: Mechanism for α-bromination of ketones

2.1.3 Results and discussion

Results of the application of our system for bromination of active methylene are summarized in Table 1. When the bromination of acetophenone is carried out with hydrobromic acid and H_2O_2 or TBHP, the methyl group α to the carbonyl was brominated selectively to give 2-bromoacetophenone without the impurity of aromatic bromination. This is confirmed from NMR where a singlet at δ 4.44 ppm corresponding to CH_2Br is observed. This reaction was performed in dioxan as an impurity of 2-methoxy acetophenone was detected in methanol. It was observed that acetophenones with electron withdrawing substituents on aromatic ring like NO_2, Cl undergo bromination at α-position to carbonyl group whereas acetophenones with electron donating substituents like phenolic group undergo nuclear bromination as evident from NMR singlet peak at δ 2.56 ppm corresponding to the three hydrogens of $COCH_3$ and absence of peak corresponding to one aromatic proton. Various acetophenones (entries-1 to 7) and cyclic, acyclic ketones (entries 10 to 13) undergo α-bromination in high yields using hydrogen peroxide or TBHP as oxidants. Acetophenone, indanone and α-tetralone afforded only the corresponding α-bromo substituted product without any trace of nuclear bromination on aromatic ring.

When indanone was subjected to bromination using 1.2 equiv HBr and 1.1 equiv H_2O_2, a mixture of monobrominated and dibrominated product was obtained along with unreacted indanone. The optimum yield of the dibrominated product as the single product in 89 % yield was obtained when 4 equivalents of H_2O_2 and HBr were used (entry-10). This was confirmed from the absence of CH peak at δ 4.73 ppm α to the carbonyl carbon. When TBHP was used as an oxidant, selectively monobrominated product was obtained as evident from CH peak at δ 4.73 ppm α to carbonyl group. This selectivity for monobromination was also observed in the case of tetralone where a NMR peak at δ 4.75 ppm corresponding to H α to the carbonyl is observed (entries-11 and 12). The reagent was found to be selective for bromination of active methylene as no bromination of benzylic positions was observed. It is note-worthy that bromination of ethyl acetoacetate could be controlled (entry-13) to obtain only monobrominated product in 99% yield. The spectral characteristics of the products were well in accordance with the expected values.

2.1.4 Conclusion

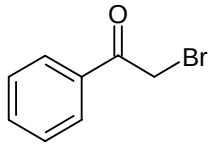
Selective bromination of active methylene in high yields can be achieved by applying halogenation system using a combination of hydrobromic acid and H_2O_2 or TBHP. TBHP exhibited excellent selectivity for monobromination in case of cyclic ketones where as H_2O_2 yielded dibrominated product exclusively. Various acetophenones (unsubstituted and with electron-withdrawing groups) and cyclic and acyclic ketones could be brominated in the α-position selectively without affecting the benzylic position or without any trace of nuclear bromination on aromatic ring.

2.1.5 Experimental

Preparation of α-bromo ketone

A solution of TBHP (70%aq. 0.25 ml, 2 mmol) or H_2O_2 (30% aq., 2mmol) was added to a cooled mixture of HBr (48% aq 0.34ml, 2 mmol) in dioxan (5 ml) and the mixture stirred for 5 minutes. To this cold solution, ketone (2 mmol) was added, stirred at same temperature for 30 minutes and then refluxed till completion of the reaction. On completion of reaction (TLC) the solvent was evaporated and the product was taken in 5 ml water, extracted with EtOAc (3 ×10 ml), washed with water and brine, dried on sodium sulphate and concentrated on rotary evaporator to afford a crude product. The product was purified by flash column chromatography over silica gel to afford pure product.

Bromomethyl phenyl ketone [Table 1, entries 1 and 2]

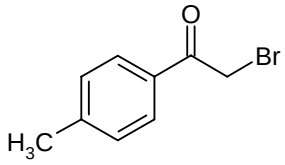


IR ($CHCl_3$) : 2928.83, 1693.22, 1590.25, 1445.96, 1396.64, 1273.19, 1191.31 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 4.44 (s, 2H), 7.42 – 7.59 (m, 3H), 7.93 (d, J= 8Hz, 2H).

MS (m/e, %) : 198 ($M^+ + 1$) (11), 120 (9), 105 (100), 77 (98).

Bromomethyl (4-methylphenyl) ketone [Table 1, entries 3 and 4]

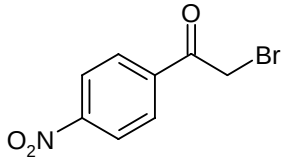


IR ($CHCl_3$) : 3001.83, 2932.10, 1669.80, 1593.11, 1406.74, 1267.90, 1181.54 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 4.40 (s, 2H), 2.41 (s, 3H), 7.27–7.30 (m, 2H), 7.87–7.89 (m, 2H).

MS (m/e,%) : 214 ($M^+ + 1$), 119 (100), 91 (100), 65 (52).

Bromomethyl (4'-nitrophenyl) ketone [Table 1, entry 5]

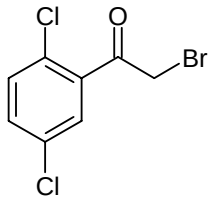


IR ($CHCl_3$) : 2966.92, 1692.79, 1603.04, 1401.16, 1269.98, 760.41, 667.97 cm^{-1}.

^1H NMR ($CDCl_3$) : δ 4.46 (s, 2H), 8.34 (d, J = 8Hz, 2H), 8.15 (d, J = 8Hz, 2H).

MS (m/e, %) : 165 (M^+–Br) (5), 150 (100), 120 (10), 104 (42), 92 (23).

Bromomethyl (2', 5'-dichloro) phenyl ketone [Table 1, entry 6 and 7]

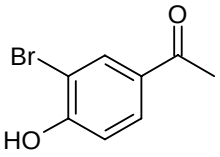


IR ($CHCl_3$) **:** 2926.33, 1687.15, 1439.37, 1366.39, 1256.39, 1173.82 cm^{-1}.

^1H NMR ($CDCl_3$) **:** δ 4.50 (s, 2H), 7.37 (d, J = 6Hz, 2H), 7.53 (d, J = 2Hz, 1H).

MS (m/e,%) **:** 268 (M^+, 5), 187 (4), 173 (100), 145 (50), 109 (65), 74 (57).

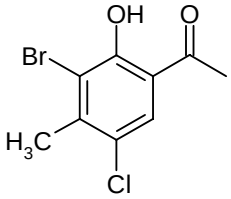
(3'-Bromo-4-hydroxyl) phenyl methyl ketone [Table 1, entry 8]



^1H NMR ($CDCl_3$, 200 MHz) : δ 2.56 (s, 3H), 6.35 (brs, 1H), 8.08-8.10 (m, 2H), 8.12 (s, 1H).

MS (m/e, %) **:** 215 (M^+, 50), 199 (100), 171 (21), 92 (47), 63 (90).

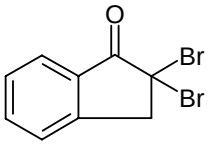
(3'-Bromo-5'-chloro-2'hydroxy-4'-methyl) phenyl methyl ketone [Table 1, entry 9]



^1H NMR ($CDCl_3$, 200 MHz) : δ 2.60 (s, 3H), 2.65 (s, 3H), 7.73 (s, 1H).

MS (m/e, %) **:** 264 (M^+ +1, 31), 249 (100), 169 (80), 139 (10), 77 (39).

2,2–Dibromo indanone [Table 1, entry 10]

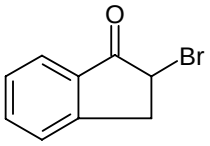


M.P. **:** 134ºC.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 4.30 (s, 2H), 7.40–7.55 (m, 2H), 7.75-7.80 (m, 1H), 7.95 (d, J=4 Hz, 1H).

MS **:** 290 (M^+, 25), 211 (84), 130 (31), 102 (100), 75(45).

2-Bromo Indanone [Table 1, entry 11]



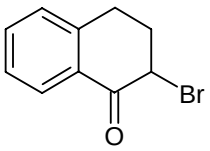
M.P. **:** 38º C .

IR ($CHCl_3$) **:** 3008.00, 2913.76, 1709.08, 1202.28, 745.82, 657.32 cm^{-1}.

^{1}H NMR($CDCl_3$, 200 MHz) : δ 3.90–3.96 (m, 2H), 4.73 (dd, J = 7.5, 3Hz 1H), 7.52-7.56 (m, 2H), 7.75-7.79 (m,1H), 7.91-8.01 (m, 1H).

MS **:** 210 (M^+, 30), 131 (100), 103 (70), 77 (48).

2-Bromo-1- tetralone [Table 1, entry 12]

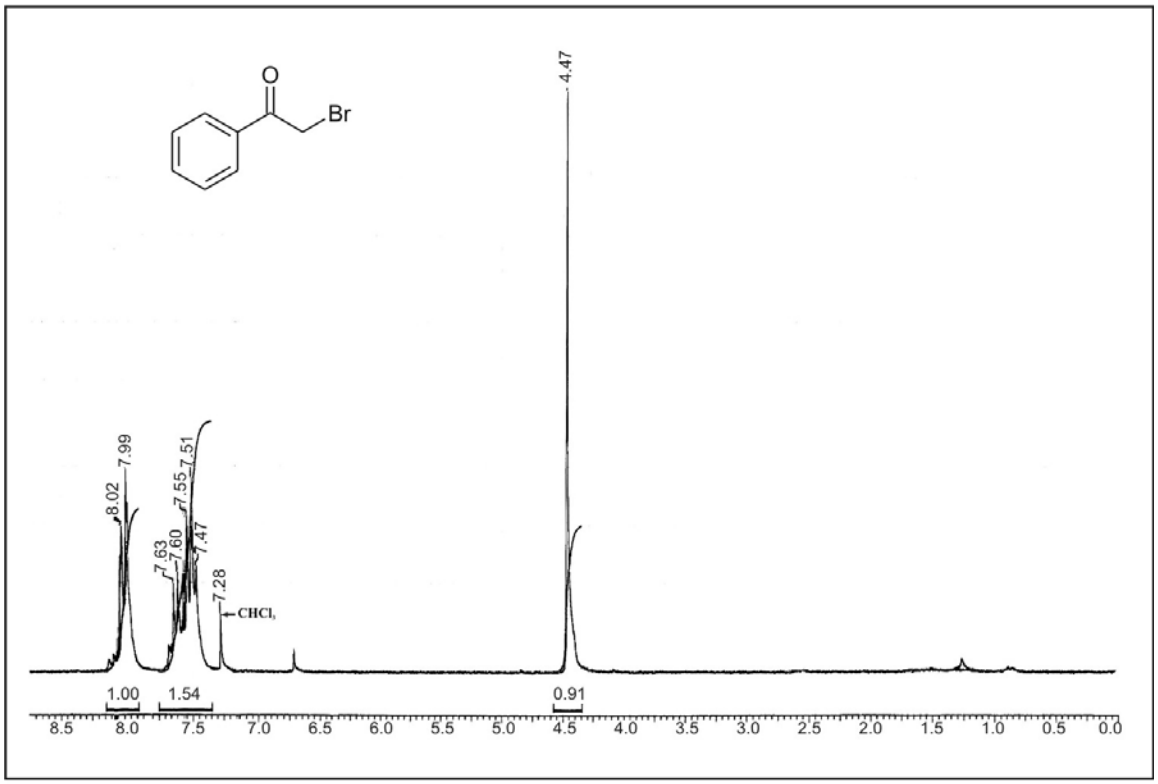


M.P. **:** 38 – 39ºC .

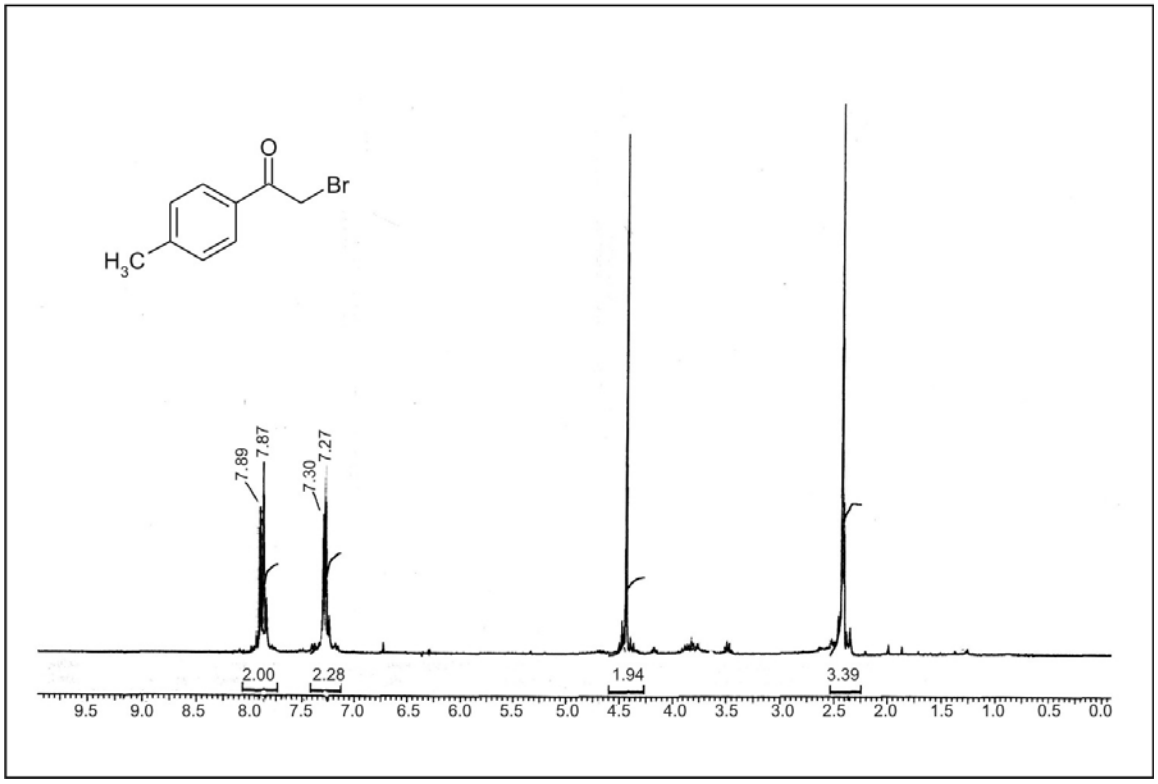
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 2.41–2.62 (m, 2H), 2.92–3.01 (m, 1H), 3.22–3.26 1 (m, 1H), 4.75 (dd, J_1 = 7.7 Hz, J_2=3.9 Hz, 1H), 7.21–7.34 (m, 2H), 7.46–7.52 (m, 1H), 8.04 (d, J = 7.9Hz, 1H).

MS **:** 224 (M^+, 25), 144 (51), 118 (100), 90 (45).

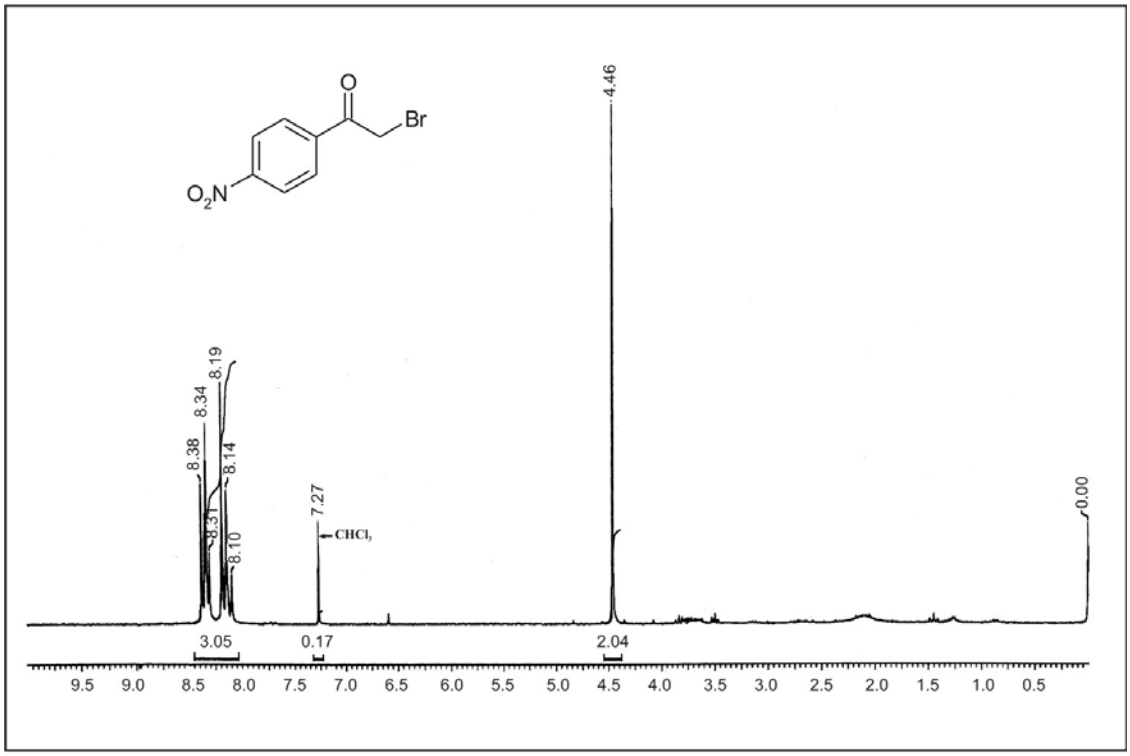
^{1}H NMR of bromomethyl phenyl ketone



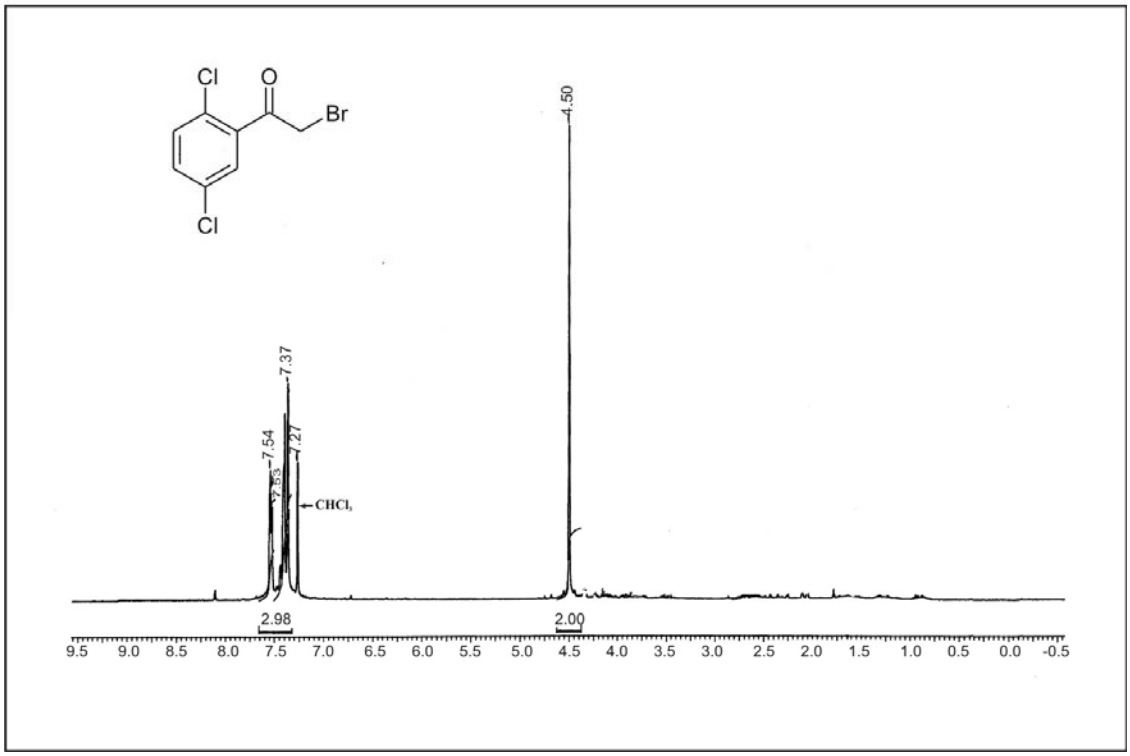
^{1}H NMR of bromomethyl (4-methylphenyl) ketone



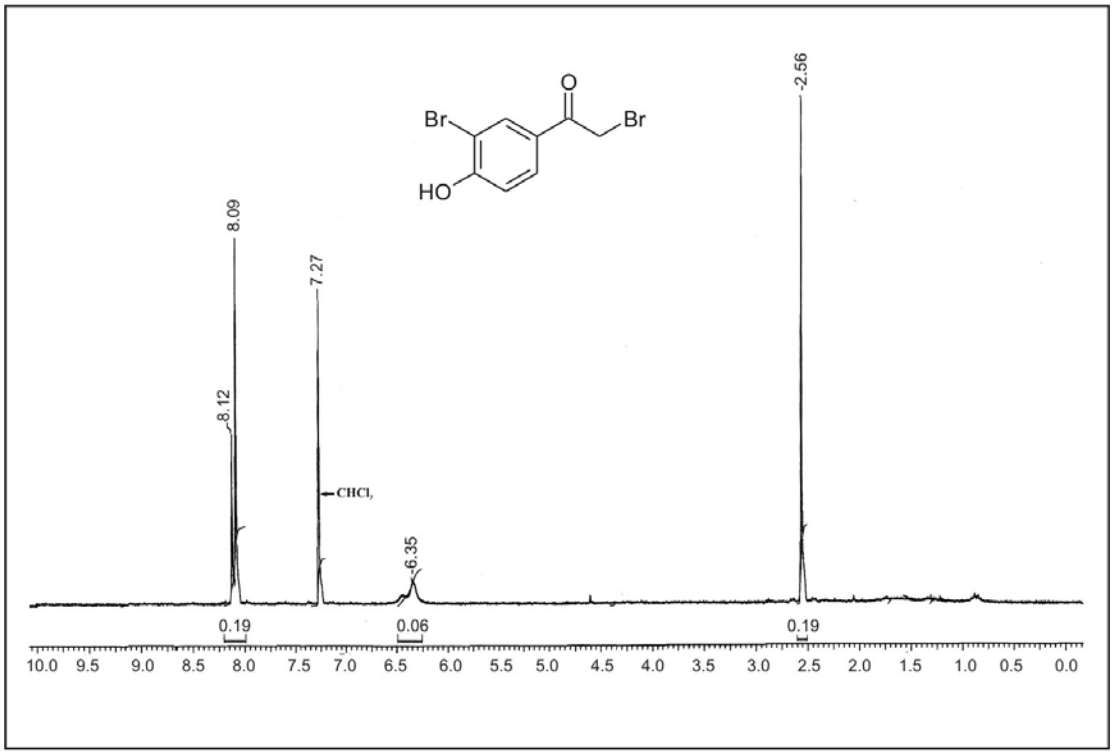
^{1}H NMR of bromomethyl (4'-nitrophenyl) ketone



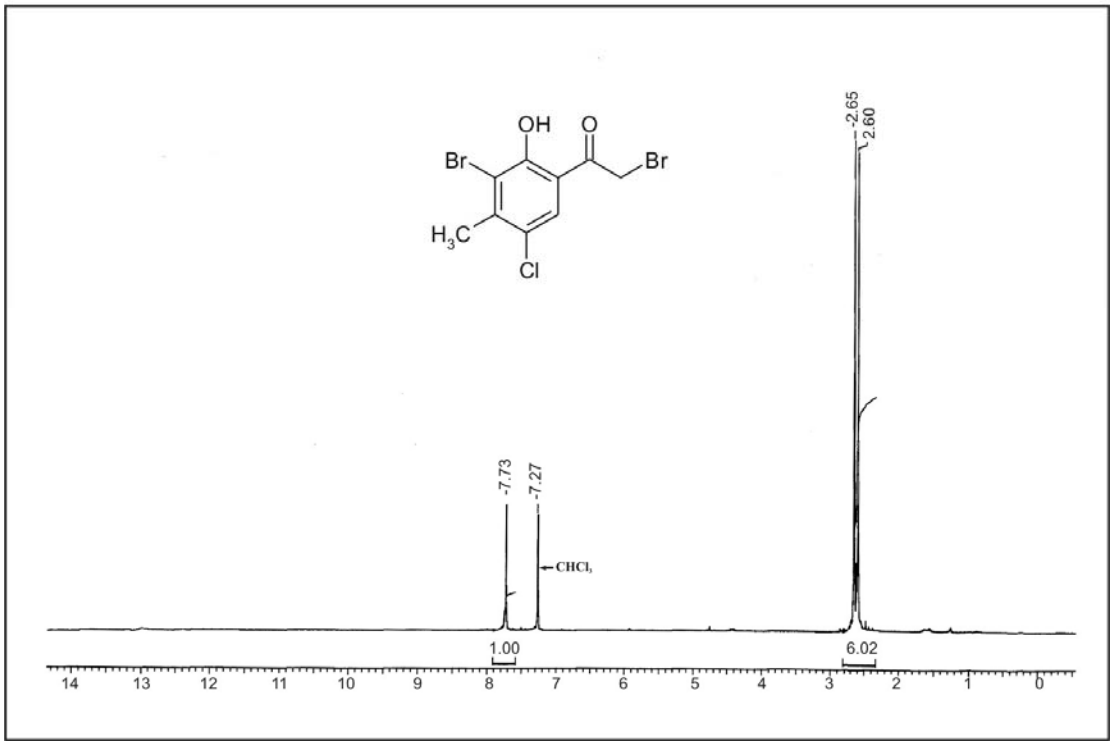
^{1}H NMR of bromomethyl (2', 5'-dichloro) phenyl ketone



^{1}H NMR of (3'-bromo-4-hydroxyl) phenyl methyl ketone



^{1}H NMR of 3'-bromo-5'-chloro-2'hydroxy-4'-methyl) phenyl methyl ketone



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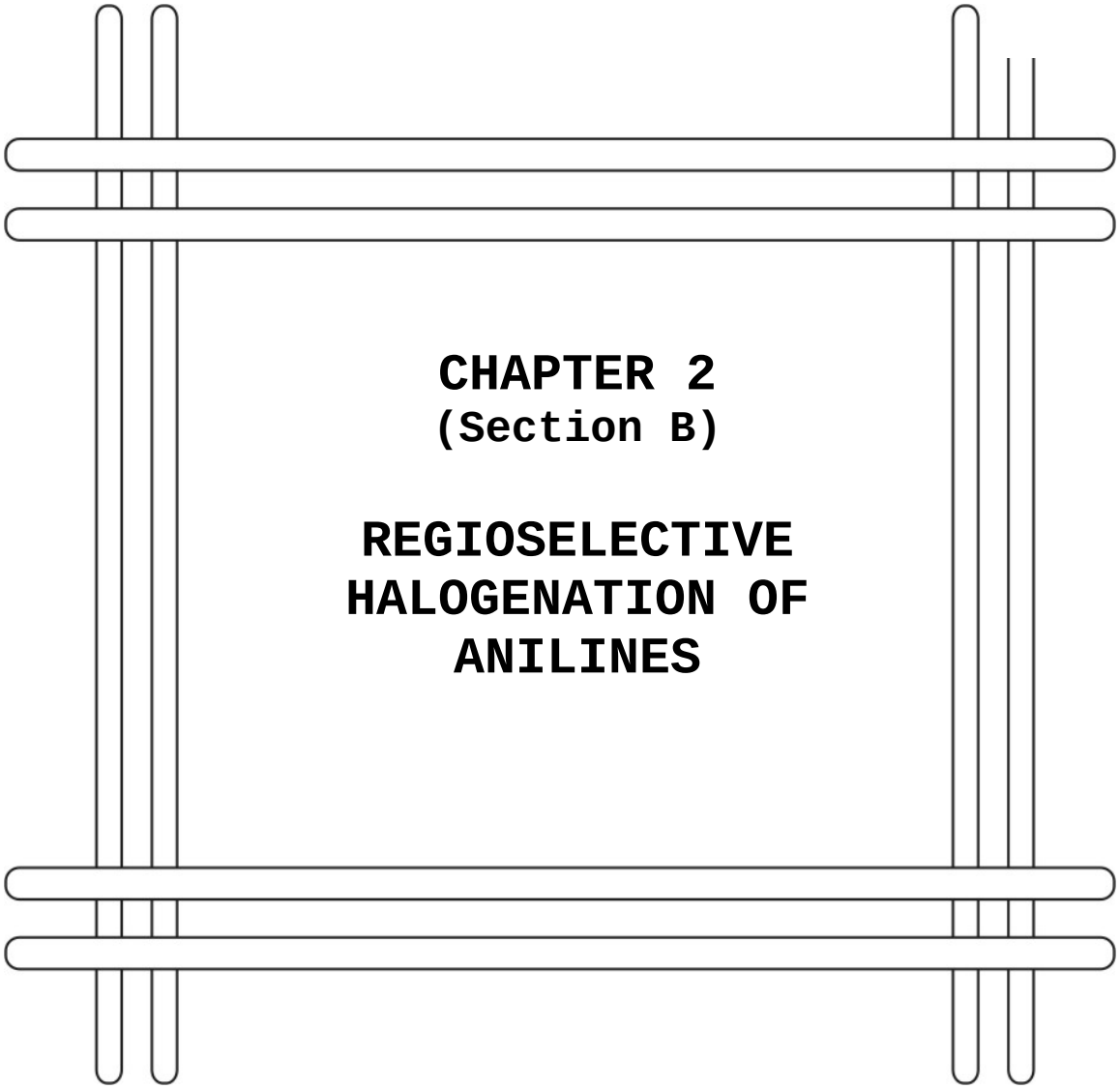


CHAPTER 2
(Section B)

REGIOSELECTIVE HALOGENATION OF ANILINES

2.2.1 Introduction

Halogenated anilines form an important class of intermediates as they can be converted efficiently into several compounds by simple chemical transformations.[1] The majority of the reactions for introducing halogen in an aromatic nucleus can be classified into three categories depending upon the nature of the halogen source employed as follows:

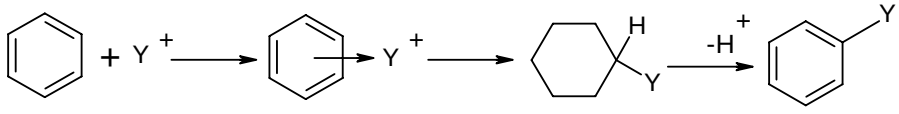
a) molecular halogen as such or generated *in situ*,

b) molecular halogen activated by a catalyst or

c) a positive halogen source.

The general trend in the electrophilicity in this series is a < b < c.

In aromatic electrophilic substitution reaction, the attacking species is an electrophile X^+ or positive end of the dipole which gets attracted to the aromatic ring because of the high electron density of aromatic ring. The leaving group is essentially without lone pair of electrons i.e. proton in most of the cases. Aromatic electrophilic halogenation reaction generally proceeds *via* arenium ion mechanism (the two step mechanism). The electrophile attacks in the first step giving rise to arenium ion intermediate and the leaving group departs in the second step. The electrophile i.e. +ve halogen or dipole, attacks the ring followed by removal of the pair of electrons from the sextet to give carbocation which is stabilized by the different resonance structures as shown in Scheme 1. The formation of arenium ion intermediate in the first step is slow and removal of proton in the second step is fast.



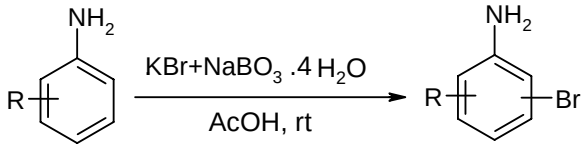
26 **27** **28** **29**

Scheme 1: Mechanism of electrophilic halogenation

Bromination of aromatic amines with molecular bromine, when carried out on the free amine, usually yields polybrominated derivatives together with oxidation products. Hence, aromatic primary amines have been converted to the corresponding anilides prior to

bromination if monosubstitution was desired.[1] In some cases, e.g. the reaction of aniline with bromine in acetic acid, good yields of p-bromo derivatives can be obtained,[2] but β-naphthylamine and diphenyl amine in acetic acid yield only polybrominated products.

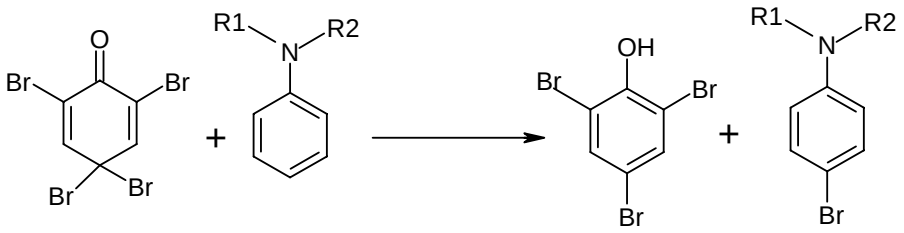
The effects of mild brominating agents such as dioxan perbromide,[3] N-bromosuccinimide (NBS) or alkyl bromides in dimethyl sulphoxide (DMSO) cannot be generalized for all aromatic amines. Dioxan perbromide is a monobrominating agent for some N, N-dialkyl anilines, but for primary and secondary anilines the reported yields are low. Bromination with NBS in some cases is accompanied by decomposition.[4] Use of alkyl bromides in DMSO can lead to N-alkylated products from primary or secondary anilines.[5, 6] However, new methods allowing good control over selectivity and polybromination of unprotected anilines have been reported in the past decade.[7] D. Roche *et al.*[8a] achieved the selective monobromination of deactivated anilines using potassium bromide and sodium perborate as oxidant. They found that the use of ammonium molybdate as a catalyst accelerates the rate of reaction but is not essential to obtain good yields and high selectivities.



30 **31**

Scheme 2: Selective monobromination using potassium bromide and sodium perborate

V. Calo *et al.*[8b] developed a method for monobromination of aromatic amines predominantly or exclusively at *p*-position using 2, 4, 4, 6-tetrabromocyclohexa-2, 5-dienone as the halogenating agent in dichloromethane or chloroform (Scheme 3).

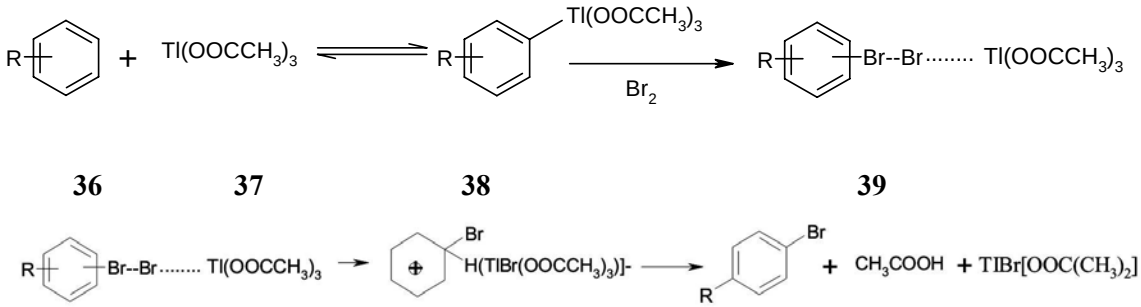


32 **33** **34** **35**

R_1=R_2=H; R_1=H, R_2=Et, Ph; R_1=R_2=Et

Scheme 3 : Monobromination with 2, 4, 4, 6-tetrabromocyclohexa-2, 5-dienone

Gadi and Clark[9] reported the use of vanadium pentoxide catalyzed two electron oxidation of Br^- to Br^+ using aqueous hydrogen peroxide under dilute acidic condition. The salt / acid / peroxide system was used for *in situ* or *ex situ* oxidation of various aromatic compounds. Gowda *et al*. [10] reported the use of dichloroamine B (N, N–dichlorobenzene sulfonamide) in aqueous acetic acid for chlorination of anilines and substituted anilines. Mckillop and Bromley[13] showed that a combination of thallium (III) acetate and bromine is a very effective reagent for electrophilic bromination of activated aromatic substrates like amines, phenols etc (Scheme 4).



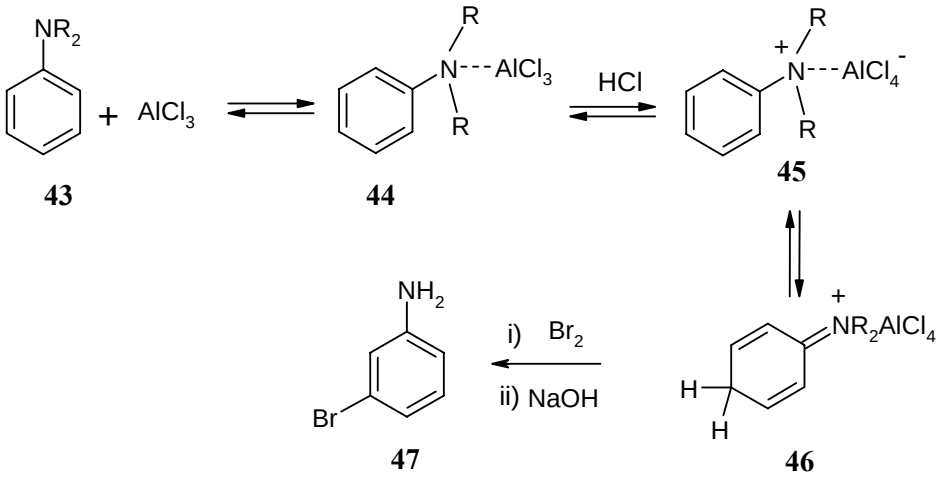
36 **37** **38** **39**

39 **40** **41** **42**

Scheme 4: Bromination with thallium (III) acetate and bromine

Mechanistically, thallium (III) acetate forms the complex **38** with aromatic compound and then bromine molecule attacks on the complex **38**, which removes the proton to give *para* bromo product **41** with acetic acid and thallium bromoacetate as side products.

While investigating the means of obtaining *meta* halo anilines by changing the orientation of the powerfully *ortho* and *para* directing amino groups in anilines, Suther *et al.*[11] found that the halogenation of the aluminium chloride-hydrogen chloride complexes of *p*-alkyl and *p*-haloanilines gave good yields of 3-halo-4-alkyl (or halo) anilines and it is the method of choice for preparation of these compounds (Scheme 5).

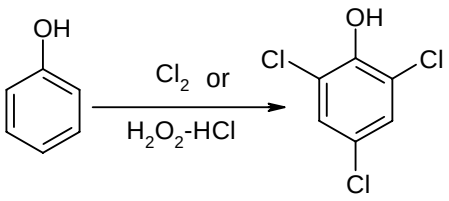


Scheme 5 : Meta-halogenation of anilines

Chaudhari and coworkers[12] reported the use of ammonium molybdate as a catalyst with potassium bromide and oxidant hydrogen peroxide as the bromine source for the halogenation of protected and non protected anilines. The reagent is regioselective giving only *para* brominated product in high yields.

Taking in to consideration the hazards in the use of molecular halogen for halogenation of organic compounds, many researchers have used system which *in situ* generates halogen or positive species responsible for halogenation. Labbecke and Boldt[14] have reported that when phenol was treated with chlorine, 2, 4, 6-trichlorophenol was obtained

(87% yield) along with hydrochloric acid as a side product, but when phenol was treated with H_2O_2 – HCl same product was obtained with better yield (94%) and only water as a side product (Scheme 6).

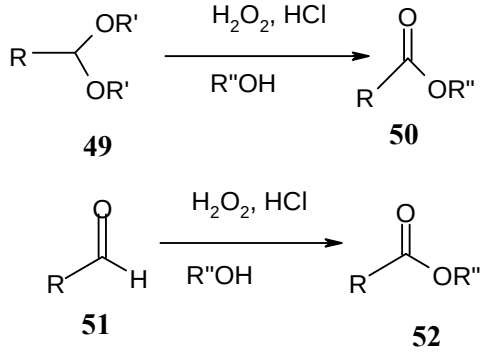


47 **48**

Scheme 6: Chlorination of phenolic compounds

This fact attracted the attention of the environmental chemists to employ the combination of hydrogen peroxide and hydrohalic acid (which *in situ* generates hypohalous acid) for the oxidation and halogenation reactions. Some of the methods are discussed below.

T. Takeda and coworkers[15] have recently demonstrated the H_2O_2 / HCl system to be a good reagent for the direct oxidation of acetals and aldehydes to esters as shown in Scheme 7.



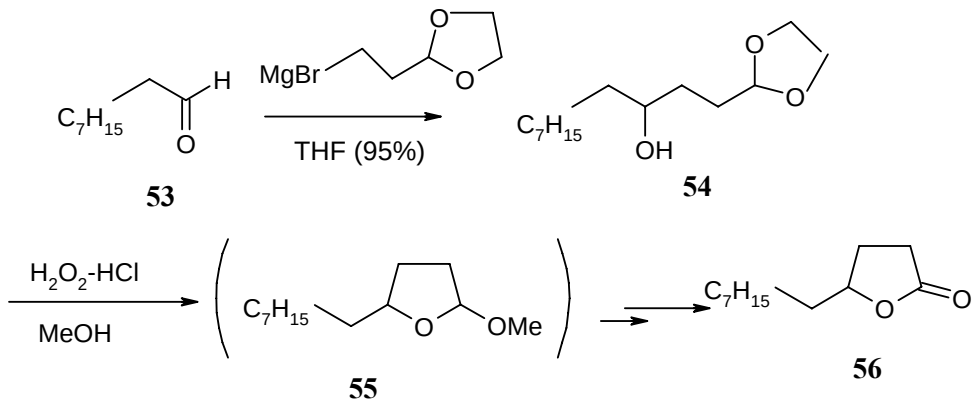
49 **50**

51 **52**

Scheme 7: Oxidation of acetals and aldehydes to esters using H_2O_2 + HCl

When HCl was replaced with H_2SO_4, it was observed that the reaction was very slow. This again indicated[16] that HCl played role of protonation of carbonyl oxygen of the acetals. The present H_2O_2-HCl system was successfully applied for the synthesis of γ-

dodecalactone which is a flavor and a pheromone component[17] as shown below. Reaction of nonanal **53** with acetal Grignard gave hydroxyl acetal **54**, which was oxidized *via* protected lactol with H_2O_2-HCl in methanol to give title compound γ-dodecalactone **56** in very good yield (86%) (Scheme 8).

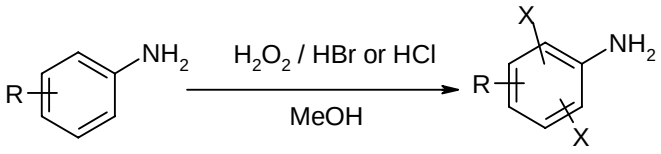


Scheme 8: Synthesis of γ-dodecalactone

2.2.2 Present work

Though there are several methods reported for the halogenation of anilines, the drawbacks like the toxic nature of the reagents / catalyst, the increase in cost due to preparation of halogenating agent, disposal of side products in case of large scale preparation of halogenated compounds and handling problem of the molecular halogen limits the application of these methods. The most economical method of halogenation with molecular halogen is environmentally hazardous due to the corrosive nature of molecular halogen and disposal of the hydrohalic acid formed in the reaction. This low atom efficiency using molecular halogen has led to publication of several reports regarding the use of hypohalous acid for the halogenation.[18] The preparation of hypohalous acid is known in the literature but it is tedious and dangerous due to its explosive nature and low stability at normal conditions. It would be very advantageous if the reagent is generated *in situ* and used up in the reaction.[19]

Oxyhalogenation of anilines with *in situ* generated positive halogen using combination of hydrohalic acid and an oxidant such as hydrogen peroxide is reported in this section (Scheme 9).



X=H, Br, Cl

57 **58**

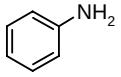
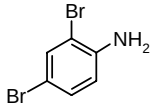
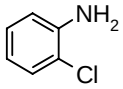
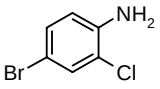
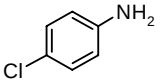
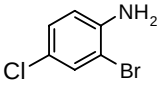
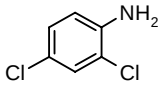
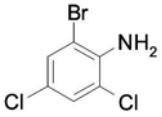
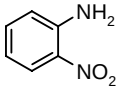
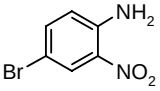
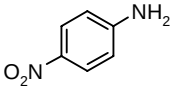
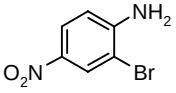
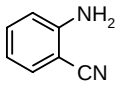
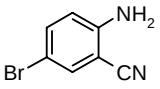
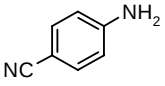
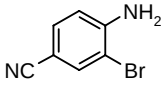
Scheme 9 : Halogenation of anilines

2.2.3 Results and Discussion

Chlorination as well as bromination of different anilines containing both electron donating and electron withdrawing groups was carried out in high yields using H_2O_2-HCl or H_2O_2- HBr which generates *in situ* Cl^+ or Br^+ which attacks on aromatic ring of aniline to give corresponding chloro or bromo anilines. Methanol was used as a solvent because of the good solubility of the reagent as well as its suitable polarity.

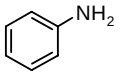
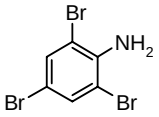
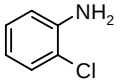
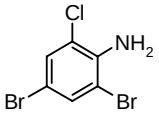
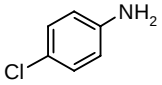
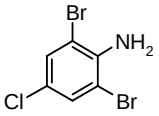
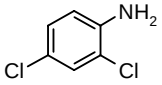
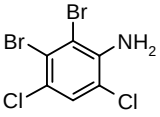
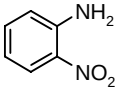
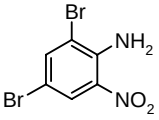
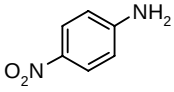
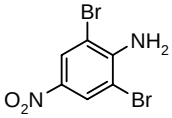
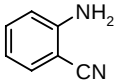
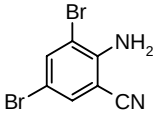
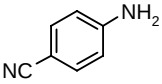
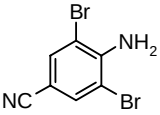
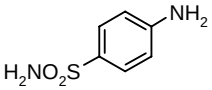
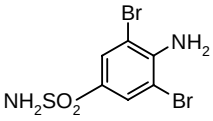
As shown in Table 1, when substituted anilines were added to a 1 equivalent preformed mixture of H_2O_2 and HBr in methanol at 10ºC and refluxed till completion of reaction, monobrominated products were formed in good to excellent yields. Unsubstituted aniline however yielded a mixture of 2, 4 dibromoaniline (48%) along with unreacted aniline (40%) under the reaction conditions (entry 1).

Table 1 :Monobromination of anilines using 1 equivalent of H_2O_2 and 1 equivalent of HBr

ENTRY NO	SUBSTRATE	REACTION TIME (hr)	PRODUCT	YIELD (%).
1		8		48 (+40 % unreacted aniline)
2		8		69
3		8		65
4		8		62
5		7		84
6		7		91
7		6		81
8		5		90

When 2 equivalents of the preformed mixture of H_2O_2 and HBr in methanol was reacted with substituted anilines, the corresponding dibromo compounds were obtained in excellent yields (Table 2). However, when aniline was subjected to above reaction conditions, 71% 2, 4, 6-tribromoaniline was obtained along with unreacted (28%) aniline (Table 2, Entry 1).

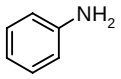
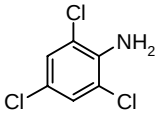
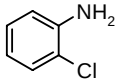
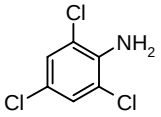
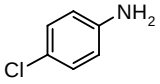
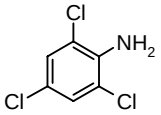
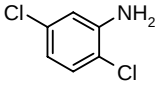
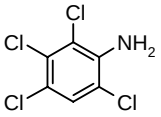
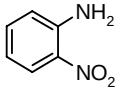
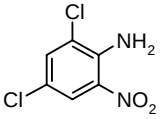
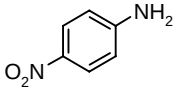
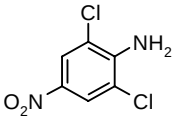
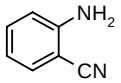
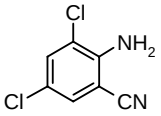
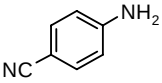
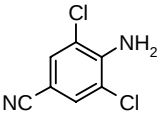
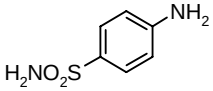
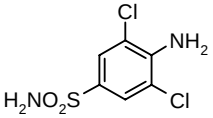
Table 2 : Dibromination of anilines using 2 equivalent of H_2O_2 and HBr

ENTRY NO	SUBSTRATE	REACTION TIME (hr)	PRODUCT	YIELD (%)
1		4		71 +28 Aniline
2		1.5		99
3		3		72
4		1.5		80
5		1		91
6		3		89
7		1		71
8		4		81
9		3		68

Chlorination however required the use of excess reagent (4 equivalent). The reaction did not take place when one equivalent of reagent was used and almost all the starting

material was observed along with mono chlorinated and traces of dichlorinated product. When two equivalents of preformed mixture of H_2O_2 and HCl was used for chlorination of substituted aniline, a mixture of monochloro, dichloro and unreacted aniline was obtained. The optimum yield was obtained when 4 equivalents of the reagent was used (Table 3).

Table 3: Dichlorination of anilines using 4 equivalents of H_2O_2 and HCl

Entry No	Substrate	Reaction time (hr)	Product	Yield (%)
1		7		69
2		7		95
3		5.5		70
4		10		86
5		5		90
6		8		87
7		3		73
8		3		79
9		10		65

2.2.4 Conclusion

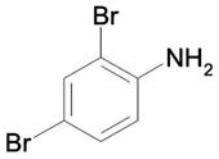
Chlorination and bromination of substituted anilines can be carried out using a mixture of HCl, H_2O_2 and HBr, H_2O_2 respectively. This reagent gives enhanced yield and selectivity of the products compared with the conventional methods. Depending on the stoichiometry of the reagent used, mono or dibrominated product can be obtained selectively. The reagent yields nuclear brominated product exclusively without the traces of N-bromo or N-chloro impurity. This methodology is simple, high yielding and environmentally friendly as side product is only water.

2.2.5 Experimental

General procedure for monobromination of anilines:

A solution of H_2O_2 (50% aq., 100 mmol) was added to a cooled mixture of HBr (48% aq., 100 mmol) and methanol (20-25 ml) and the mixture was stirred for 5 minutes. To this cold solution, substituted aniline (100 mmol) was added and the mixture stirred for 30 minutes and then refluxed till the reaction was complete. On completion of reaction (TLC), the solvent was evaporated and the product was made alkaline with Na_2CO_3, extracted with dichloromethane (3 x 25 ml) and concentrated. The residue was purified by flash column chromatography over silica gel to afford pure product in yields as shown in Table-1.

2, 4-Dibromoaniline [Table 1, entry 1]

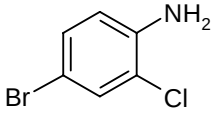


IR (Nujol) : 3477.42, 3329.55, 3019.77, 1614.69, 1215.85, 1148.59, 1100.09, 766.85, 669.62 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.76 (brs, 2H), 6.39 (d, J=9 Hz, 2H), 6.91 (d, J=6 Hz, 1H).

Mass m/z (%) : 251 (M^+, 100), 172 (15), 145 (5), 90 (10), 63 (10).

4-Bromo-2-chloroaniline [Table 1, entry 2]

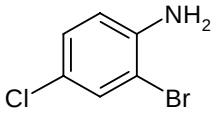


IR (Nujol) : 3405. 98, 3300. 46, 3178. 77, 2924. 74, 1616. 12, 1459. 34, 1376.32, 809.08 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1. 82 (brs, 2H), 6. 50 (d, J =9 Hz, 1H), 7. 20 (dd, J_1=8 Hz, J_2= 3 Hz, 1H), 7. 37 (d, J= 3 Hz, 1H).

Mass m/z (%) : 207 (M^+, 100), 126 (10), 90 (52), 63 (41).

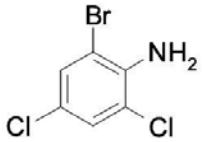
2-Bromo – 4-chloroaniline [Table 1, entry 3]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 4. 61 (brs, 2H), 6. 70 (d, J=6 Hz, 1H), 7. 09 (d, J = 6 Hz, 1H), 7. 40 (s, 1H).

Mass m/z (%) : 207 (M^+, 100), 126 (27), 90 (37), 63 (33).

6-Bromo-2, 4-dichloroaniline [Table 1, entry 4]

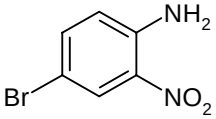


IR (Nujol) : 3409. 64, 3303. 67, 3185. 95, 2955. 26, 1613. 37, 1466. 59, 1377. 51, 865. 31, 711. 33, 697. 37, 664. 46, 637. 57, 542. 85, 434. 28 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6.13 (brs, 2H), 8.52 (d, J = 3 Hz, 1H), 9.25 (d, J = 3 Hz, 1H).

Mass m/z (%) : 241 (M^+, 100), 160 (8), 124 (15), 89 (9).

4-Bromo – 2-nitroaniline [Table 1, entry 5]

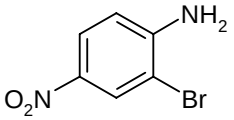


IR (Nujol) : 3464.56, 3353.16, 2924.13, 1624.95, 1462.47, 1377.47, 1256.63 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6. 12 (brs, 2H), 6. 74 (d, J=7Hz, 1H), 7. 44 (d, J=7Hz, 1H), 8. 27 (s, 1H).

Mass m/z (%) : 218 (M^+ + 1), 170 (44), 91 (85), 63 (100).

2-Bromo- 4-nitroaniline [Table 1, entry 6]

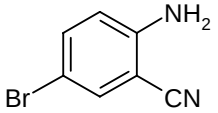


IR (Nujol) : 3466.75, 3371.32, 2923.74, 1622.91, 1585.91, 1485.66, 1311.94, 894.12, 746.33, 698.28 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.86 (brs, 2H), 6.76 (d, J = 8 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 8.37 (s, 1H).

Mass m/z (%) : 218 (M^+ + 1, 44), 170 (15), 90 (100), 63 (63).

2-Cyano -4-bromoaniline [Table 1, entry 7]

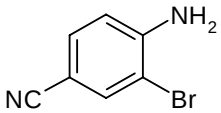


IR (Nujol) : 3430.03, 3347.95, 2922.46, 2854.95, 2213.31, 1628.67, 1458.97, 1250.61, 1172.12, 1150.56, 822.91, 487.59 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.50 (brs, 2H), 6.70 (d, J = 8 Hz, 1H), 7.40 (d, J= 8 Hz, 1H), 7.50 (s, 1H).

Mass m/z (%) : 196 (M^+, 100), 117 (7), 90 (91), 63 (100).

2-Bromo – 4-cyanoaniline [Table 1, entry 8]



IR (Nujol) : 3471.71, 3365.17, 2924.57, 2338.18, 2216.30, 1622.81, 1503.54, 1165.83, 883.31, 815.00, 579.77 cm^{-1}.

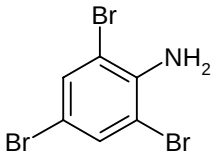
^{1}H NMR (200 MHz, $CDCl_3$) : δ 4. 61 (brs, 2H), 6.77(d, J=8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7. 69 (s, 1H).

Mass m/z (%) : 196 (M^+, 100), 117 (47), 90 (73), 63 (53).

General procedure for dibromination of anilines:

A solution of H_2O_2 (50% aq., 200 mmol) was added to a cooled mixture of HBr (48% aq.; 200 mmol) and methanol (20-25 ml) and the mixture was stirred for 5 minutes. To this cold solution, substituted aniline (100 mmol) was added and the mixture stirred for 30 minutes and then refluxed till the reaction was complete. On completion of reaction (TLC), the solvent was evaporated and the product was made alkaline with Na_2CO_3, extracted with dichloromethane (3 X 25 ml) and concentrated. The residue was purified by flash column chromatography over silica gel to afford pure product in yields as shown in Table 2.

2, 4, 6-Tribromoaniline [Table 2, entry 1]

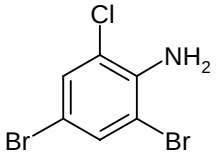


IR (Nujol) : 3401.32, 3292.61, 2952.02, 2923.90, 1614.80, 1464.62 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.58 (brs, 2H), 7.52 (s, 2H), .

Mass m/z (%) : 329 (M^+, 100), 250 (20.5), 223 (7), 170 (23), 90 (35).

2, 4-Dibromo -6-chloroaniline [Table 2, entry 2]



IR (Nujol) : 3414. 32, 3288. 98, 2923. 05, 1611. 18, 1558. 42 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.44 (brs, 2H), 7.37 (s, 1H), 7.47 (s, 1H).

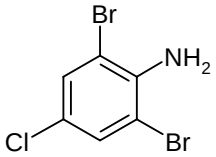
Mass m/z (%) : 285 (M^+, 100), 206 (10), 124 (8), 90 (5).

Microanalysis calculated for

C_6H_4N Br Cl : C – 25.04, H – 1.39, N – 4.86, Cl – 12.34, Br – 55.65 %.

Found : C – 25.05, H – 1.29, N – 4.94, Cl – 12.37, Br - 55.71 %.

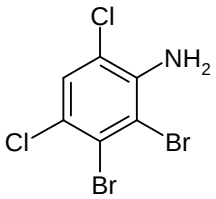
2, 6-Dibromo-4-chloroaniline [Table 2, entry 3]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.55 (brs, 2H), 7.39 (s, 2H).

Mass m/z (%) : 285 (M^+, 100), 206 (11), 124 (30), 90 (2), 62.

2, 3-Dibromo-4, 6-dichloroaniline [Table 2, entry 4]

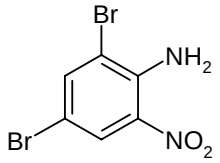


IR (Nujol) : 3478. 22, 3381. 36, 2953. 48, 1602. 07, 1462. 44 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 4. 67 (brs, 2H), 7.62 (s, 1H).

Mass m/z (%) : 319 (M^+), 239 (14), 204 (14), 177 (5).

4, 6–Dibromo-2-nitroaniline [Table 2, entry 5]



IR (Nujol) : 3460. 00, 3348. 80, 2922. 72, 1620. 84, 1494. 26 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 6. 65 (brs, 2H), 7. 81 (s, 1H), 8. 30 (s, 1H).

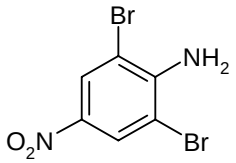
Mass m/z (%) : 296 (M^+, 100), 250 (35), 170 (21), 90 (9).

Microanalysis calculated for

$C_6H_4Br_2N_2O_2$: C – 24.10, H – 1.34, N – 9.39, Br – 53.69 %.

Found : C – 24.09, H – 1.35, N – 9.38, Br – 53.40%.

2, 6-Dibromo-4-nitroaniline [Table 2, entry 6]



M.P. : 202 – 203 ºC.

IR (Nujol) : 3479.03, 3370.20, 2928.29, 1603.61, 1464.57, 1298.88, 900.00 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 5.60 (brs, 2H), 7.90 (s, 2H).

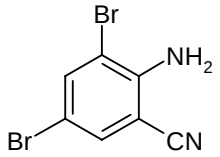
Mass m/z (%) : 296 (M^+, 100), 250 (37), 170 (66.6), 90 (63.1).

Microanalysis calculated for

$C_6H_4N_2O_2Br_2$: C – 24.1; H – 1.34, N – 9.39; Br – 53.69 %.

Found : C – 24.0; H – 1.39, N – 9.21; Br – 53.47 %.

2, 4-Dibromo- 6-cyanoaniline [Table 2, entry 7]



M.P. **:** 147ºC.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 4. 92 (brs, 2H), 7. 49 (s, 1H), 7. 78 (s, 1H).

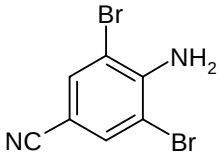
Mass m/z (%) **:** 276 (M^+, 100), 195 (21), 116 (19.4).

Microanalysis calculated for

$C_7H_4N_2Br_2$ **:** C– 30. 43, H – 1. 45, N – 10. 14, Br – 57. 97 %.

Found **:** C – 30. 33, H – 1. 46, N – 10. 04, Br – 57. 64 %.

2, 6-Dibromo-4-cyanoaniline [Table 2, entry 8]



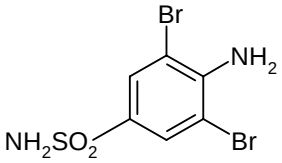
M.P. **:** 108°C.

IR (Nujol) **:** 3470. 18, 3358. 79, 2926. 36, 2856. 85, 2224. 36, 1636. 46, 1466. 32, 1377. 34, 870. 72, 539. 02 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 5. 13 (brs, 2H), 7. 66 (s, 2H).

Mass m/z (%) **:** 276 (M^+, 100), 195 (8.3), 115 (25), 88 (23), 63 (15).

3, 5-Dibromo -4-aminophenylsulfonamide [Table 2, entry 9]



IR (Nujol) **:** 3440.34, 3338.45, 3233.65, 2919.12, 2856.95, 1611.36, 1462.50 cm^{-1}.

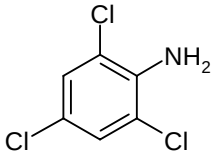
^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 4.97 (brs, 2H), 6.49 (brs, 2H), 7.53 (s, 2H).

Mass m/z (%) **:** 330 (M^+, 100), 314 (68. 4), 250 (31. 5), 223 (5), 90 (26), 64 (26).

General procedure for chlorination of anilines:

A solution of 400 mmol H_2O_2 (50% aq.) was added to a cooled mixture of 400 mmol HCl (36% aq.) and methanol (20-25 ml) and the mixture was stirred for 5 minutes. To this cold solution, substituted aniline (100 mmol) was added and the mixture stirred for 30 minutes and then refluxed till the reaction was complete. On completion of reaction (TLC), the solvent was evaporated and the product was made alkaline with Na_2CO_3, extracted with dichloromethane (3 x 25 ml) and concentrated. The residue was purified by flash column chromatography over silica gel to afford pure product in yields as shown in Table-3.

2, 4, 6-Trichloroaniline [Table 3, entry 1, 2, 3]

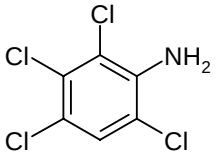


IR ($CHCl_3$) **:** 3497.89, 3399.43, 3018.94, 1613.16, 1586.29, 1396.49, 1215.64, 864.25, 757.60, 669.38 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 4.44 (brs, 2H), 7.21 (s, 2H).

Mass m/z (%) **:** 195 (M^+, 100), 159 (11), 133 (12), 107 (7), 62 (28.5).

2, 3, 4, 6 – Tetrachloroaniline [Table 3, entry 4]

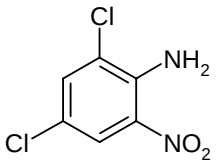


IR ($CHCl_3$) **:** 3499.64, 3402.28, 3019.39, 1607.21, 1451.15, 1383.65, 1215.68, 765.42, 669.59 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) **:** δ 4. 60 (brs, 2H), 7. 34 (s, 1H).

Mass m/z (%) **:** 231 (M^+, 100), 196 (11), 169 (13.1), 133 (14), 96 (13), 61 (22).

2,4-Dichloro-6-nitroaniline [Table 3, entry 5]

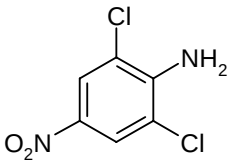


IR (Nujol) **:** 3508.75, 3391.45, 3019.76, 1620.96, 1513.33 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$) **:** δ 6.58 (brs, 2H), 7.54 (s, 1H), 8.11 (s, 1H).

Mass m/z (%) **:** 206 (M^+, 94), 160 (82), 148 (19), 124 (100), 90 (23.5), 62 (52.9).

2, 6-Dichloro-4-nitroaniline [Table 3, entry 6]

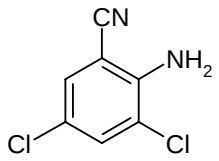


IR ($CHCl_3$) **:** 3475.49, 3363.71, 1619.18, 1504.43, 1048.06, 668.47 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) **:** δ 1.99 (brs, 2H), 8.17 (s, 2H).

Mass m/z (%) **:** 206 (M^+, 83), 176 (77), 160 (43), 148 (16), 124 (100), 90 (36).

2, 4-Dichloro-6-cyanoaniline [Table 3, entry 7]

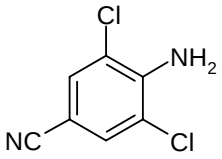


IR ($CHCl_3$) **:** 3464. 29, 3345. 84, 2225.01 1638. 68, 1476. 08 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz) **:** δ 4. 87 (brs, 2H), 7. 33 (s, 1H), 7. 46 (s, 1H).

Mass m/z (%) **:** 186 (M^+, 100), 151 (16), 124 (18), 97 (6), 61 (6).

2, 6-Dichloro-4-cyanoaniline [Table 3, entry 8]

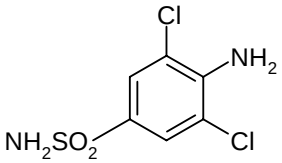


IR (Nujol) **:** 3487. 92, 3376. 17, 2225. 26, 1616. 07, 1491. 66 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 5. 02 (brs, 2H), 7. 49 (s, 2H) .

Mass m/z (%) **:** 186 (M^+, 100), 151 (9), 124 (13).

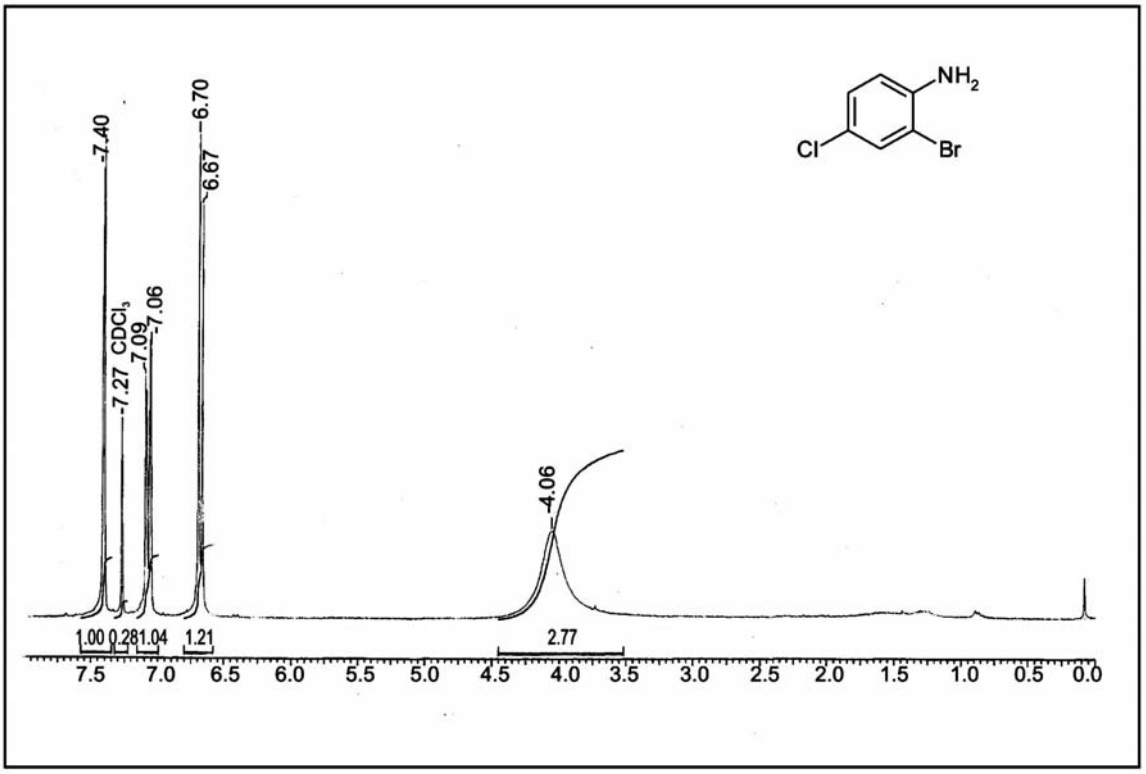
3, 5–Dichloro–4–aminophenylsulphonamide [Table 3, entry 9]



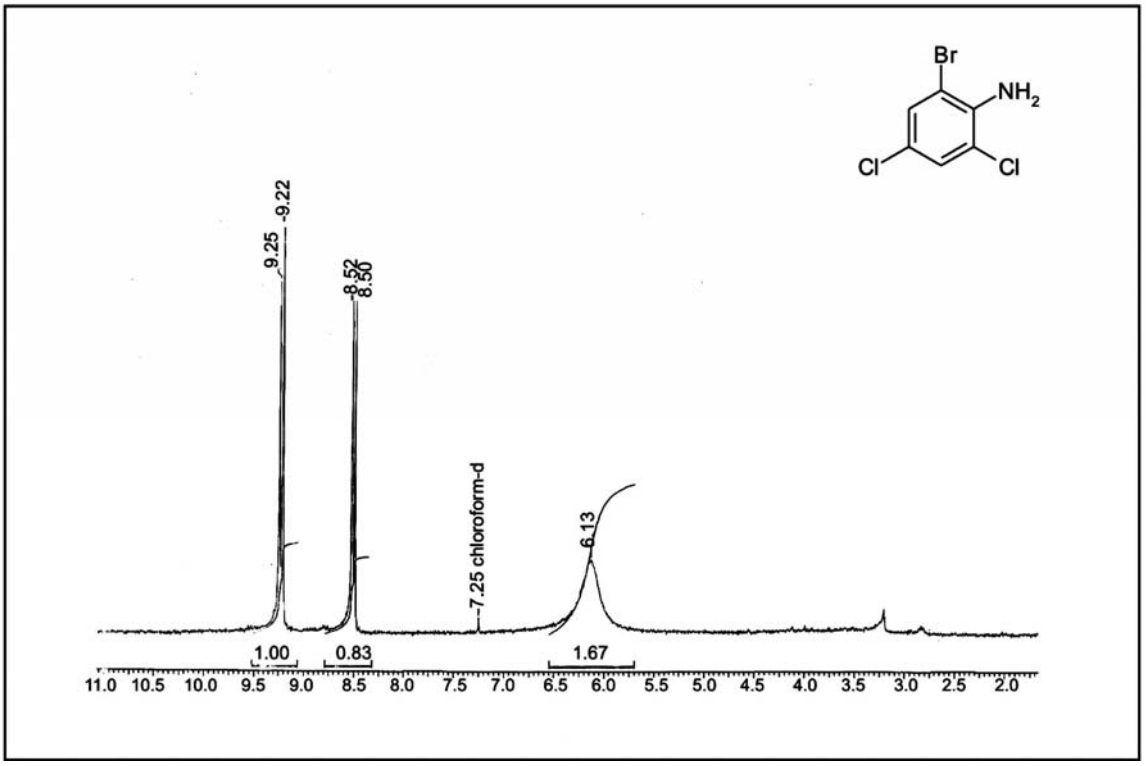
^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 4.99 (brs, 2H), 6.47 (brs, 2H), 7.14 (s, 2H).

Mass m/z (%) **:** 240 (M^+, 95), 224 (82), 160 (60), 124 (100), 97 (38).

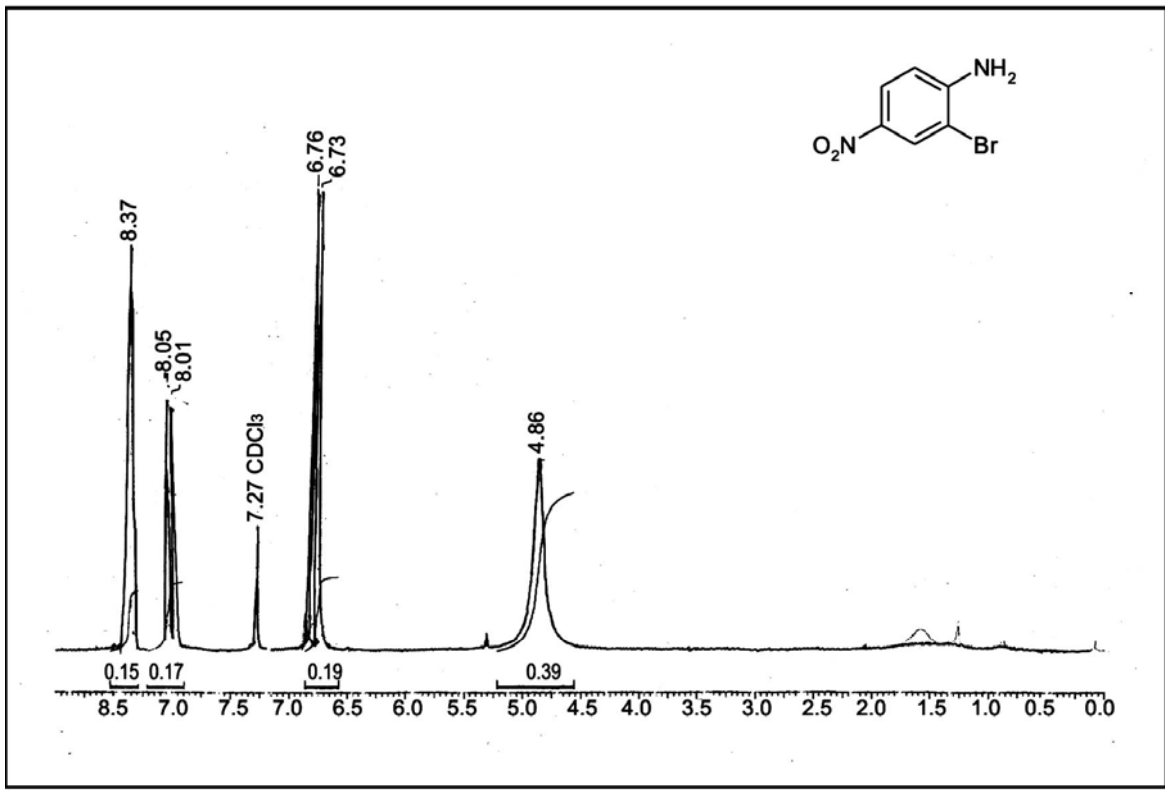
^{1}H NMR of 2-bromo-4-chloroaniline [Table 1, Entry 3]



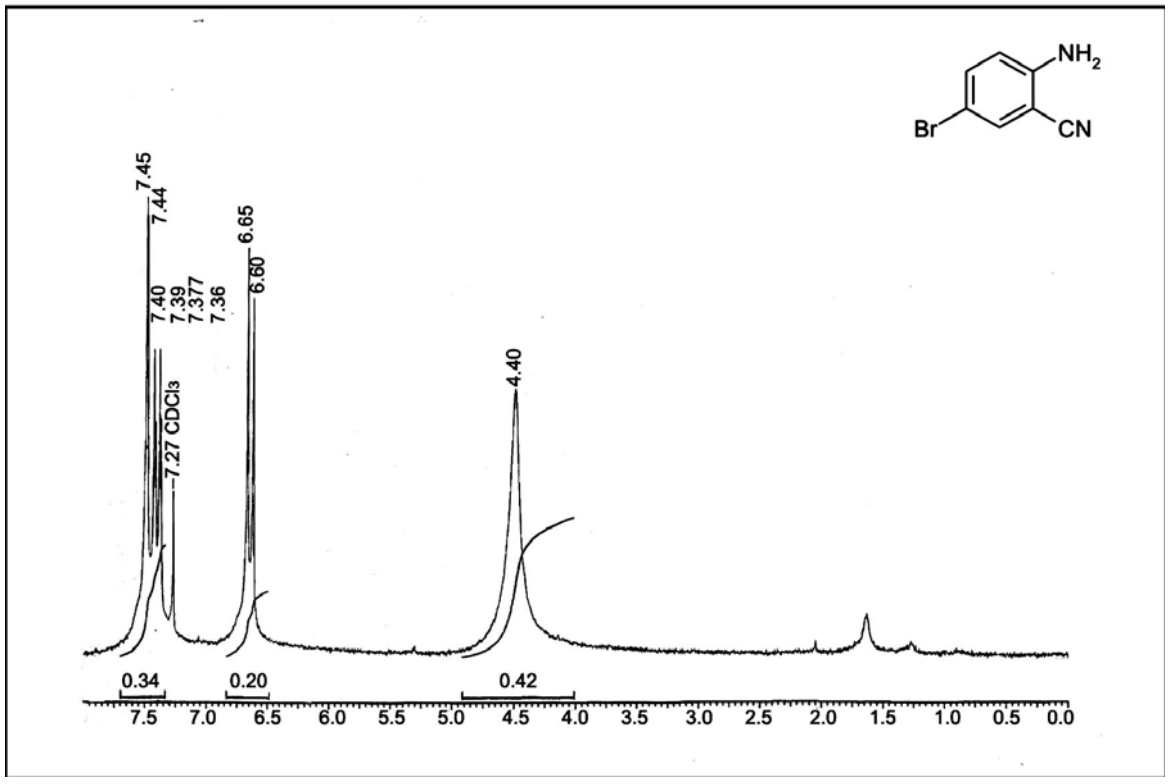
^{1}H NMR of 2-bromo-2, 4-dichloroaniline [Table 1, Entry 4]



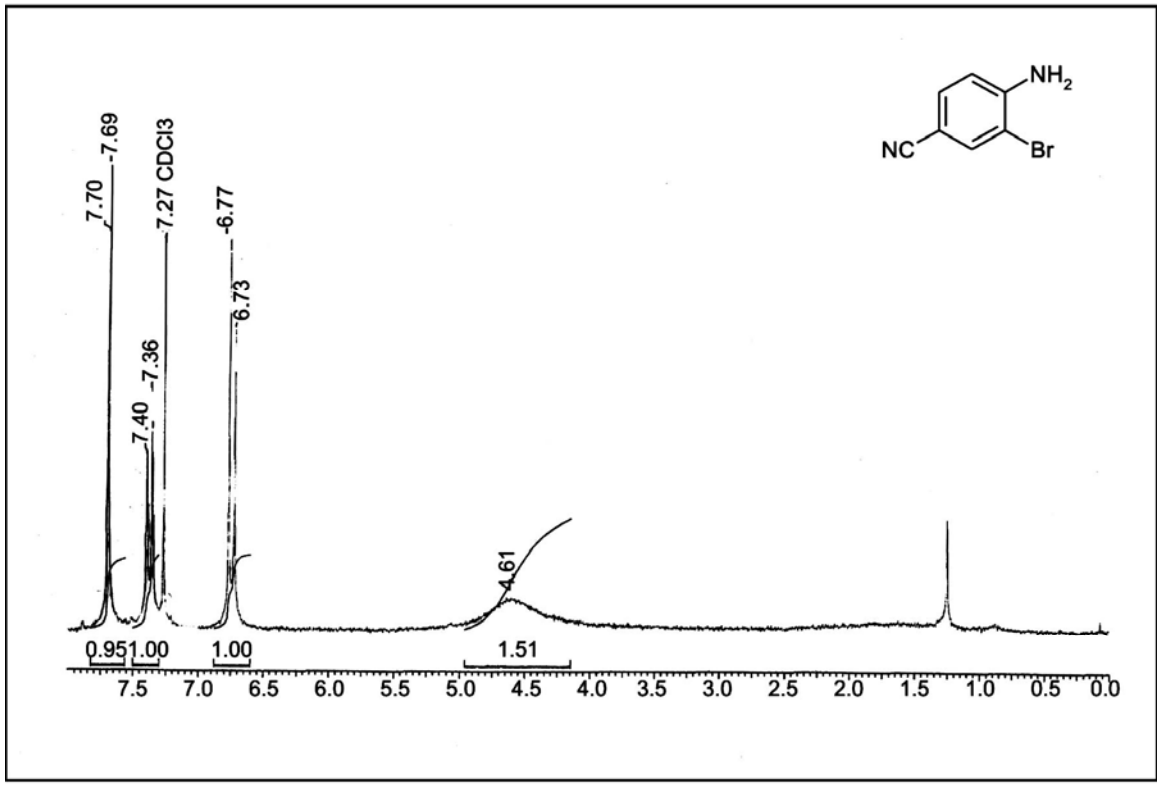
^{1}H NMR of 2-bromo-4-nitro aniline [Table 1, Entry 6]



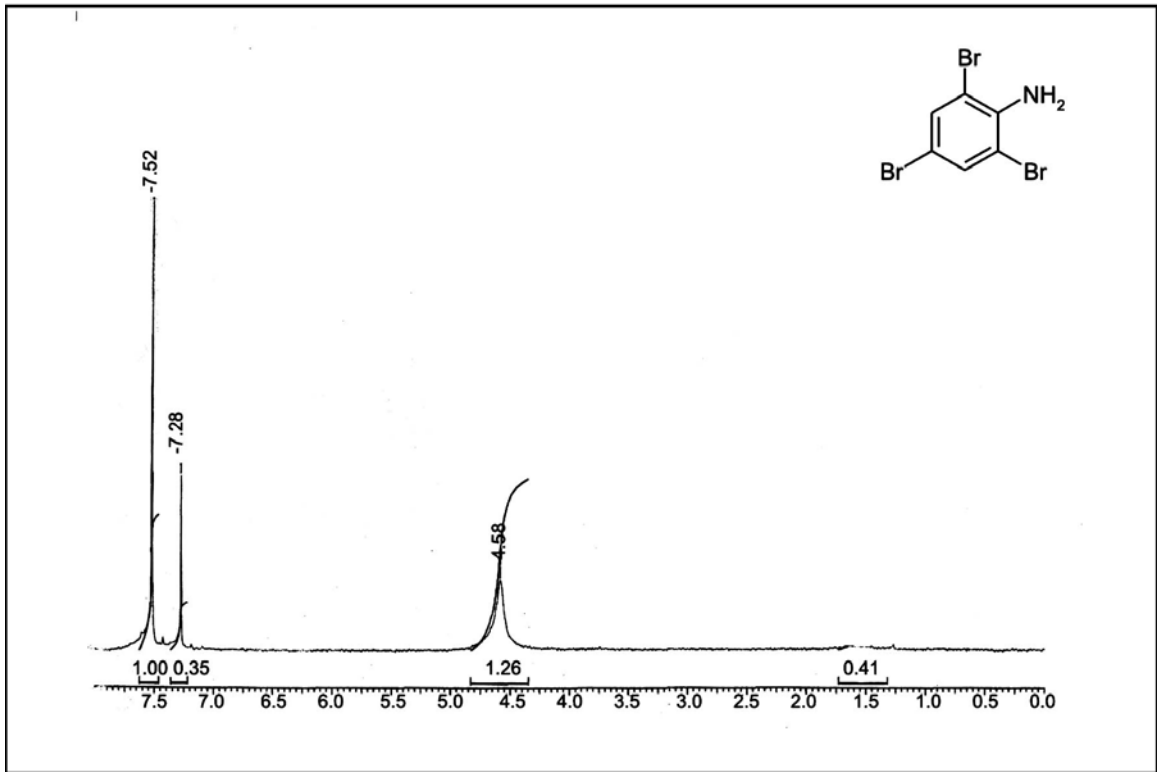
^{1}H NMR of 4-bromo-2-cyano aniline [Table 1, Entry 7]



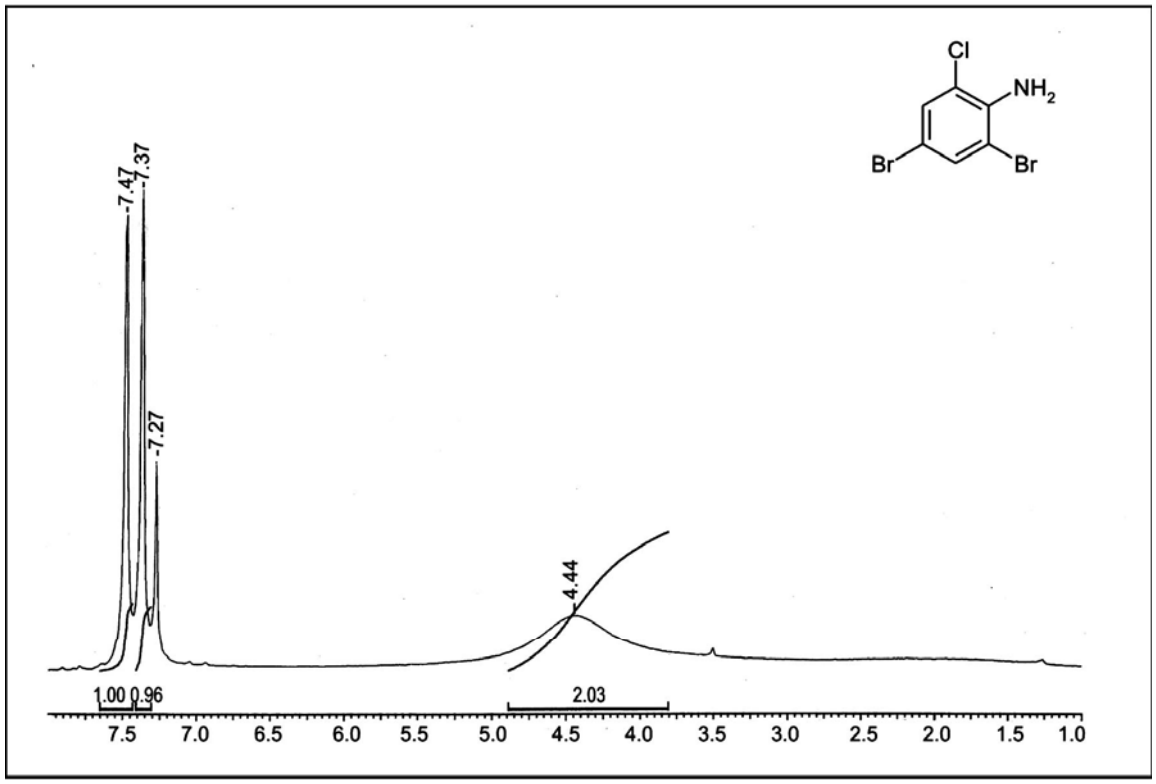
^{1}H NMR of 2-bromo-4-cyanoaniline [Table 1, Entry 8]



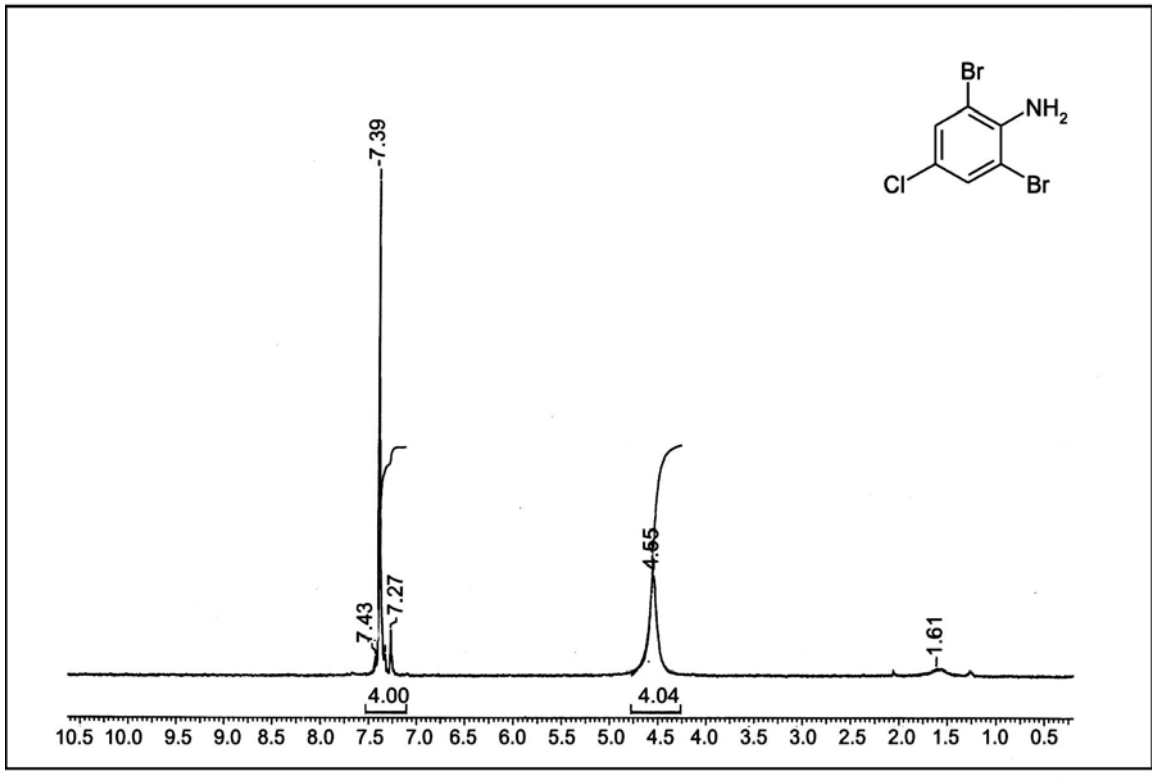
2, 4, 6 - tribromoaniline [Table 2, entry 1]



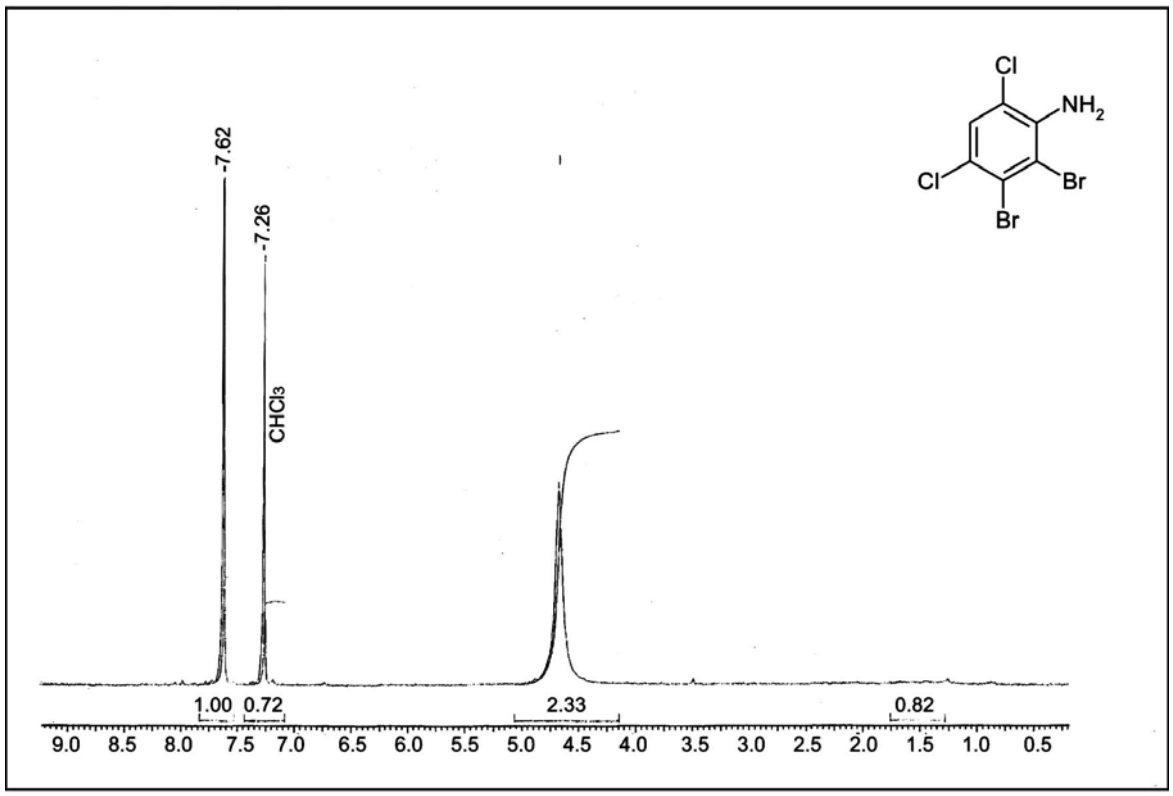
^{1}H NMR of 2-chloro-4, 6-dibromoaninline [Table 2, Entry 2]



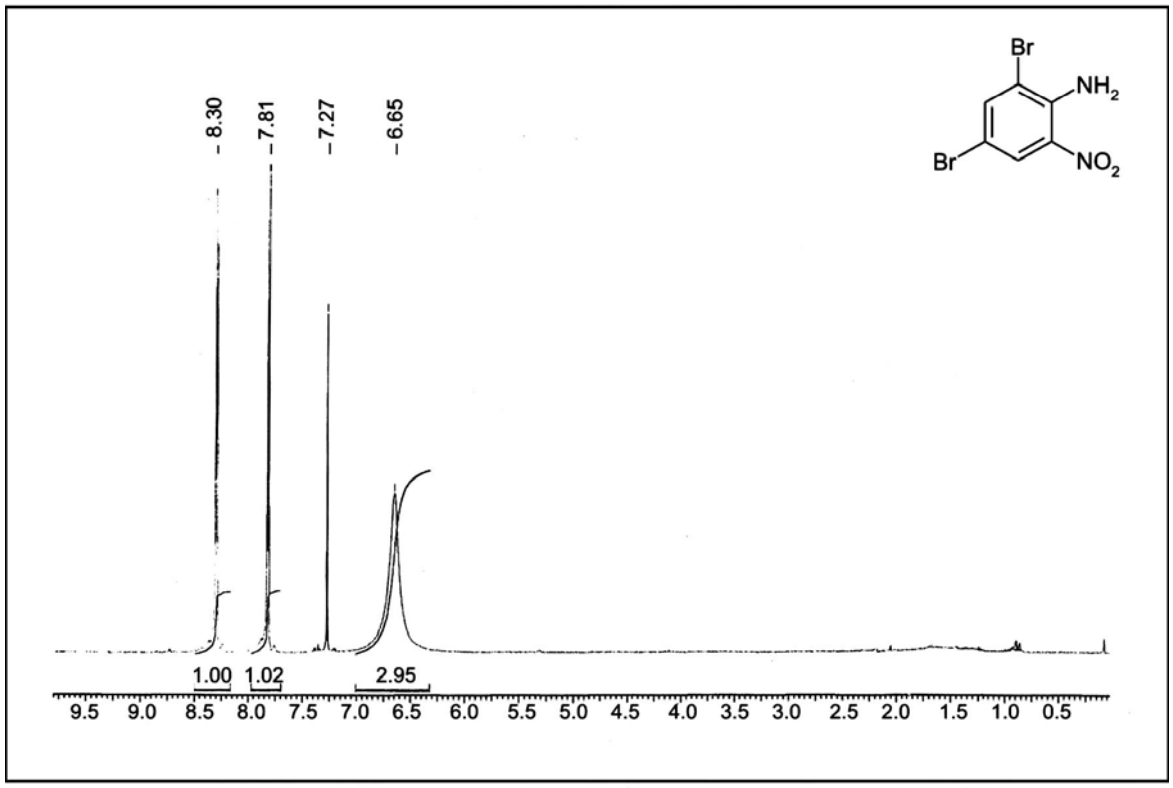
^{1}H NMR of 4-chloro-2, 6-dibromo aniline [Table 2, Entry 3]



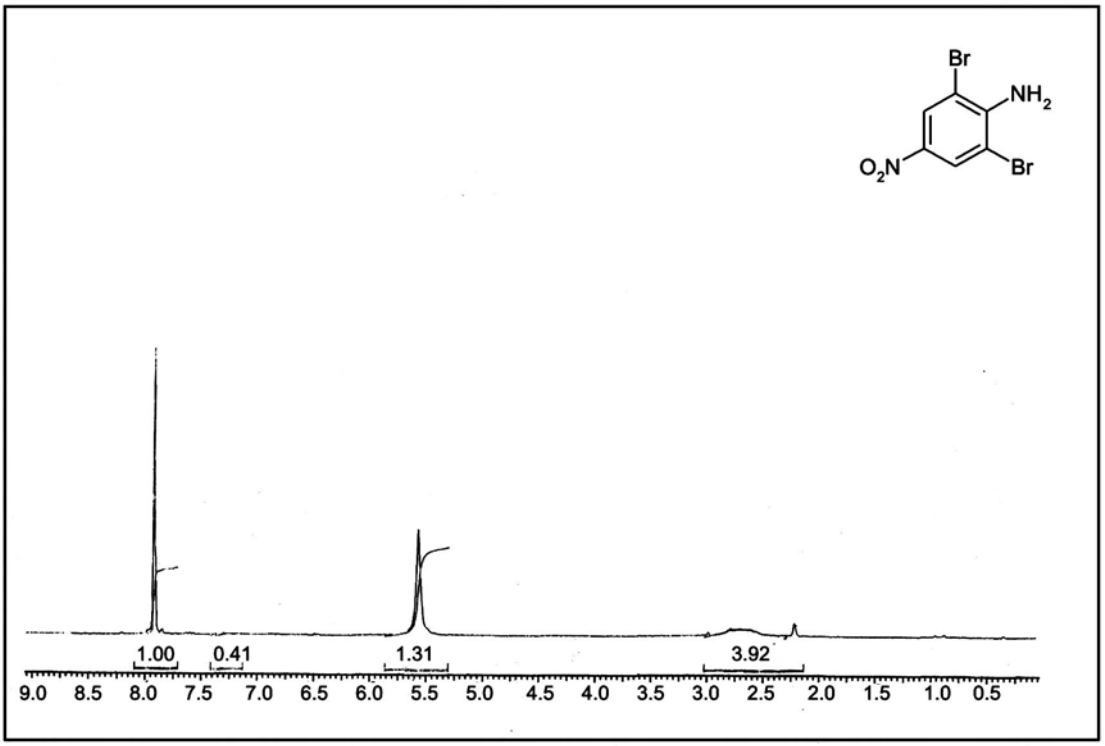
^{1}H NMR of 2, 3 -dibromo-4, 6-dichloroaniline [Table 2, Entry 4]



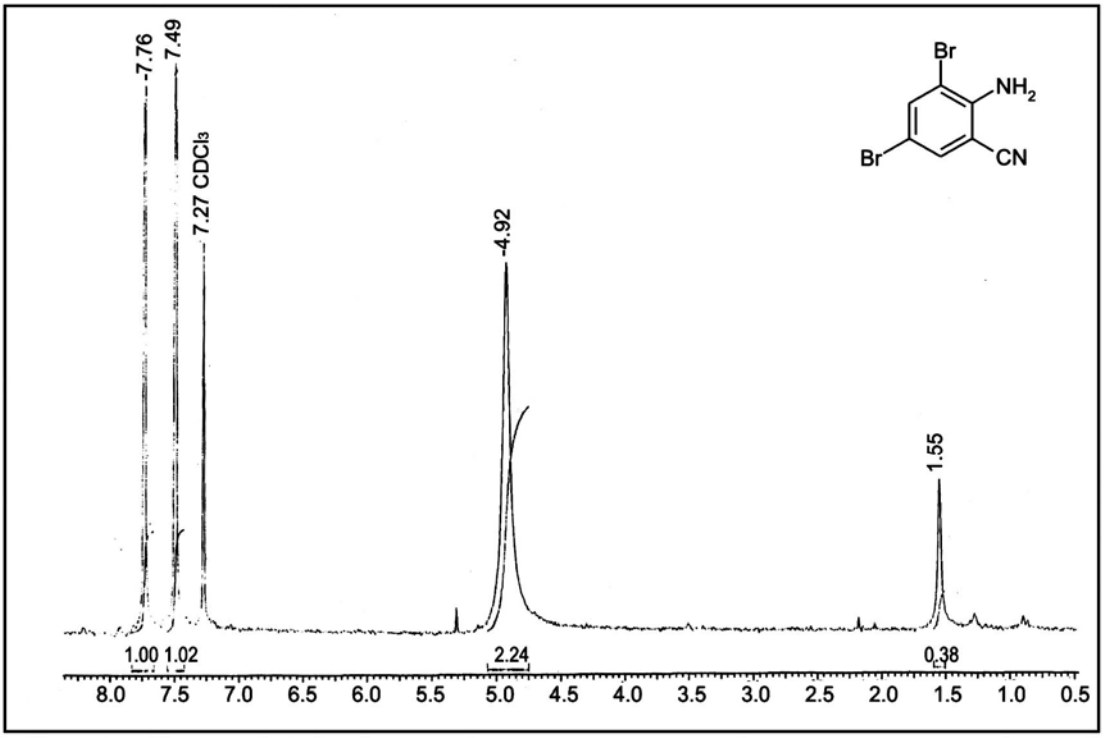
^{1}H NMR of 2, 4-dibromo-6-nitro aniline [Table 2, Entry 5]



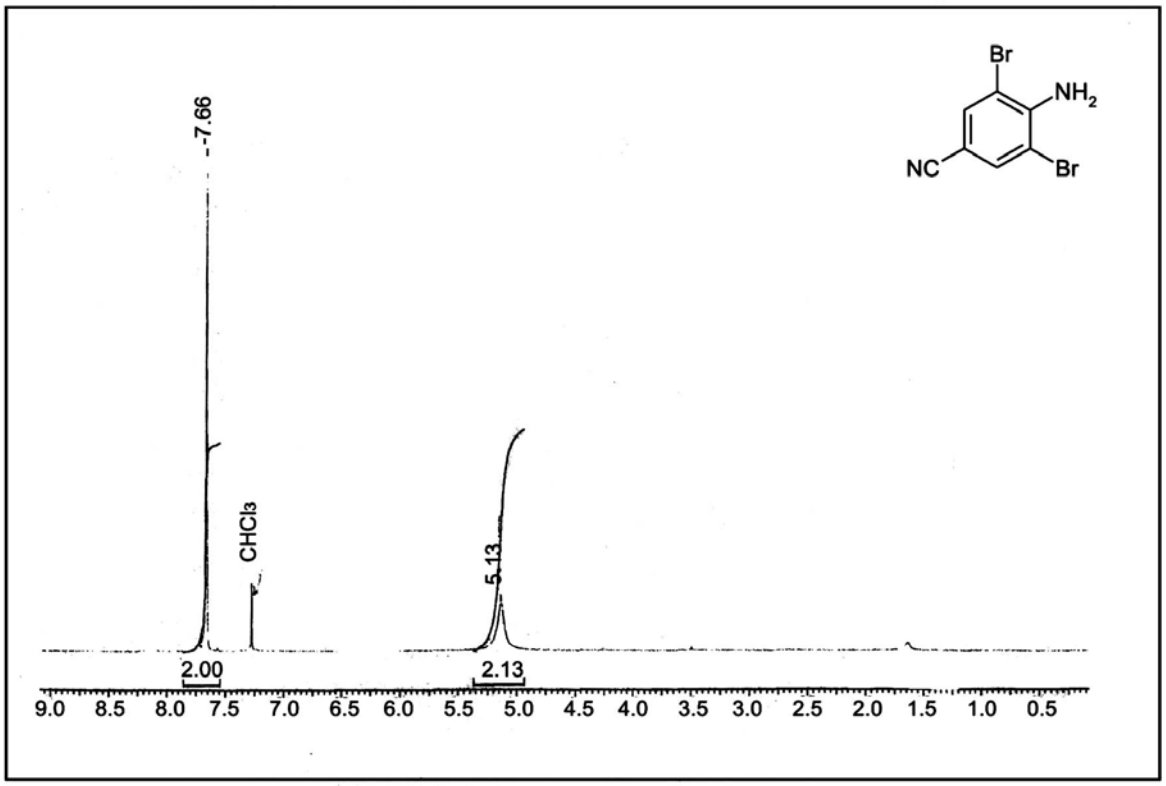
^{1}H NMR of 2, 6-dibromo-4-nitro aniline [Table 2, Entry 6]



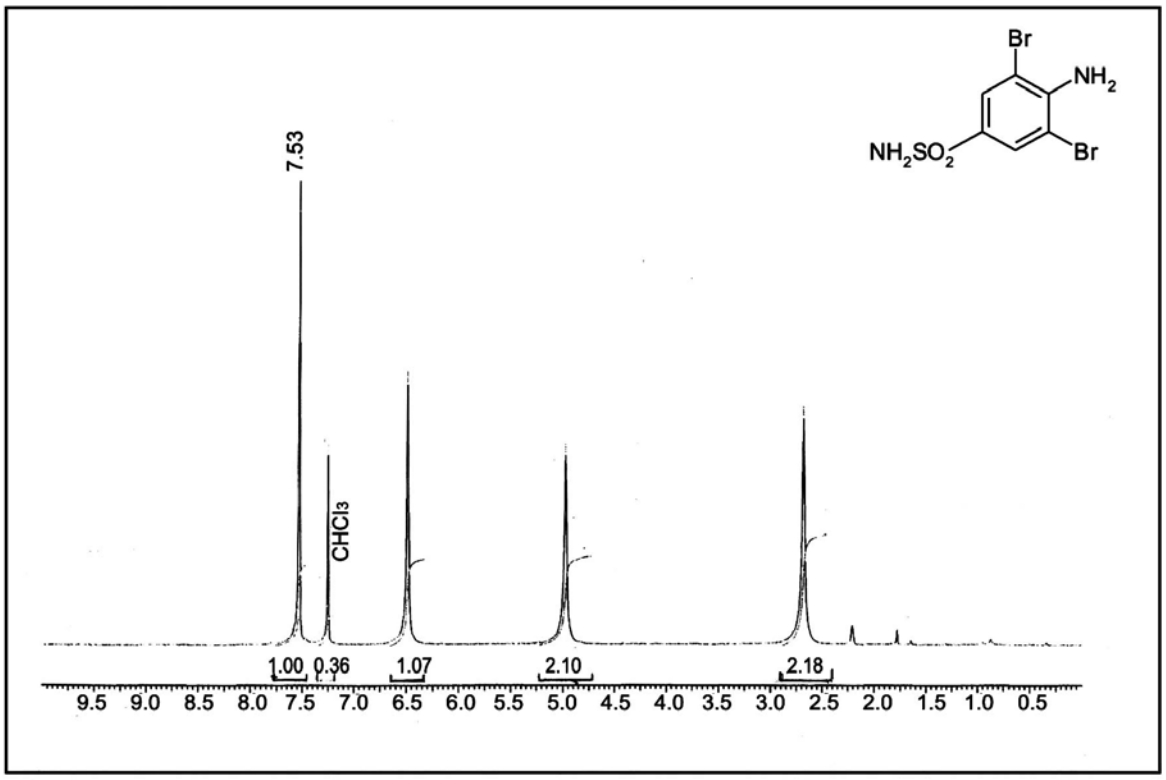
^{1}H NMR of 2-cyano-4, 6-dibromoaniline [Table 2, Entry 7]



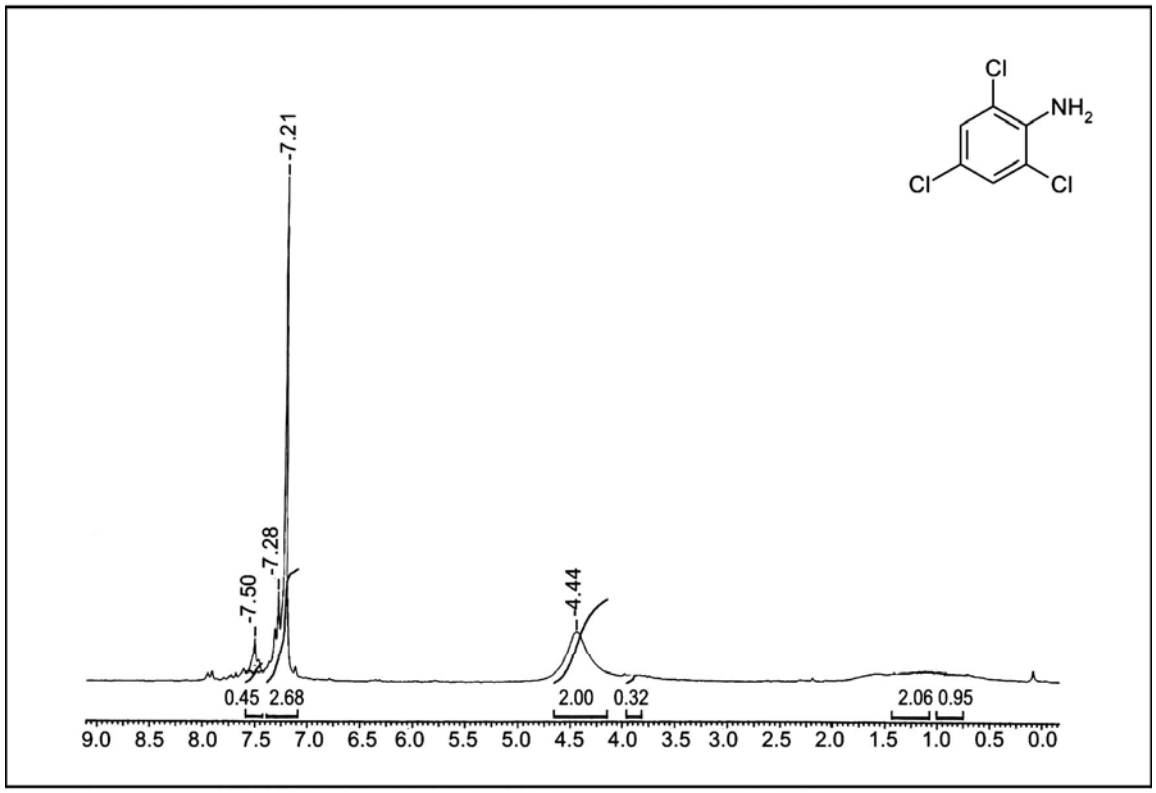
^{1}H NMR of 4-cyano-2, 6-dibromoaniline [Table 2, Entry 8]



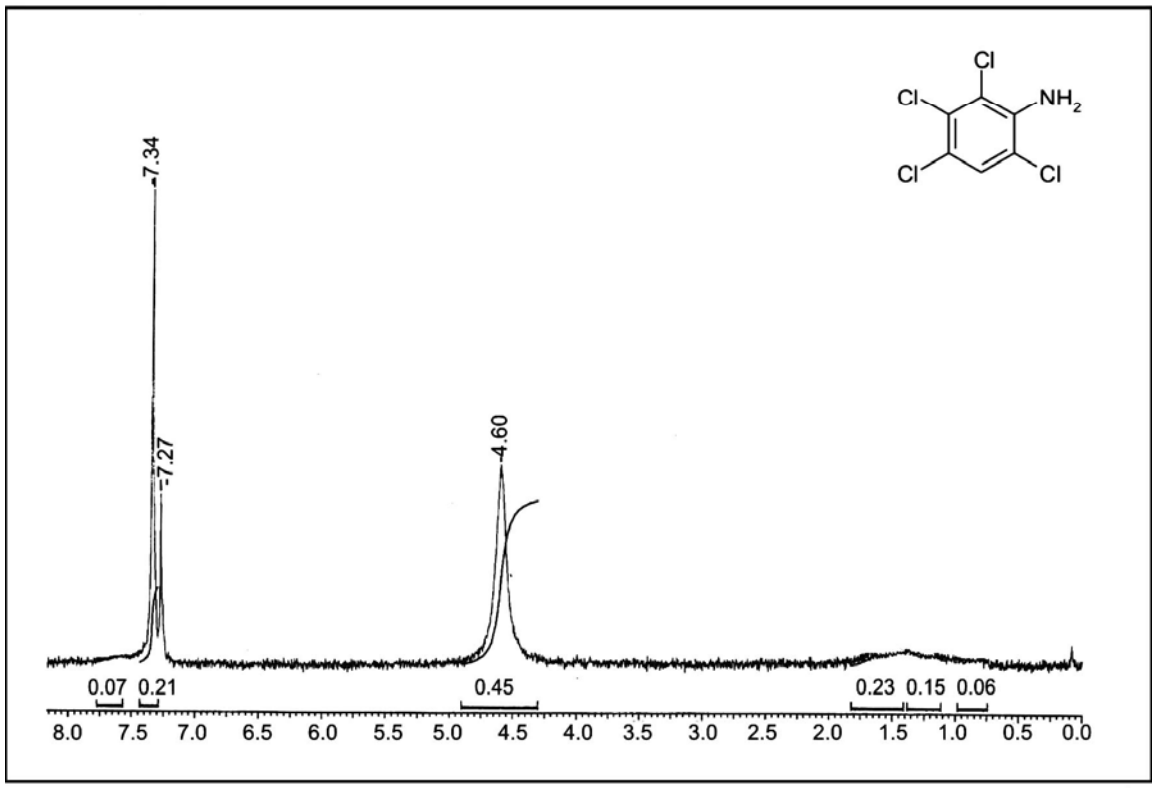
^{1}H NMR of 4-amino-2, 6-dibromophenylsulfonamide [Table 2, Entry 9]



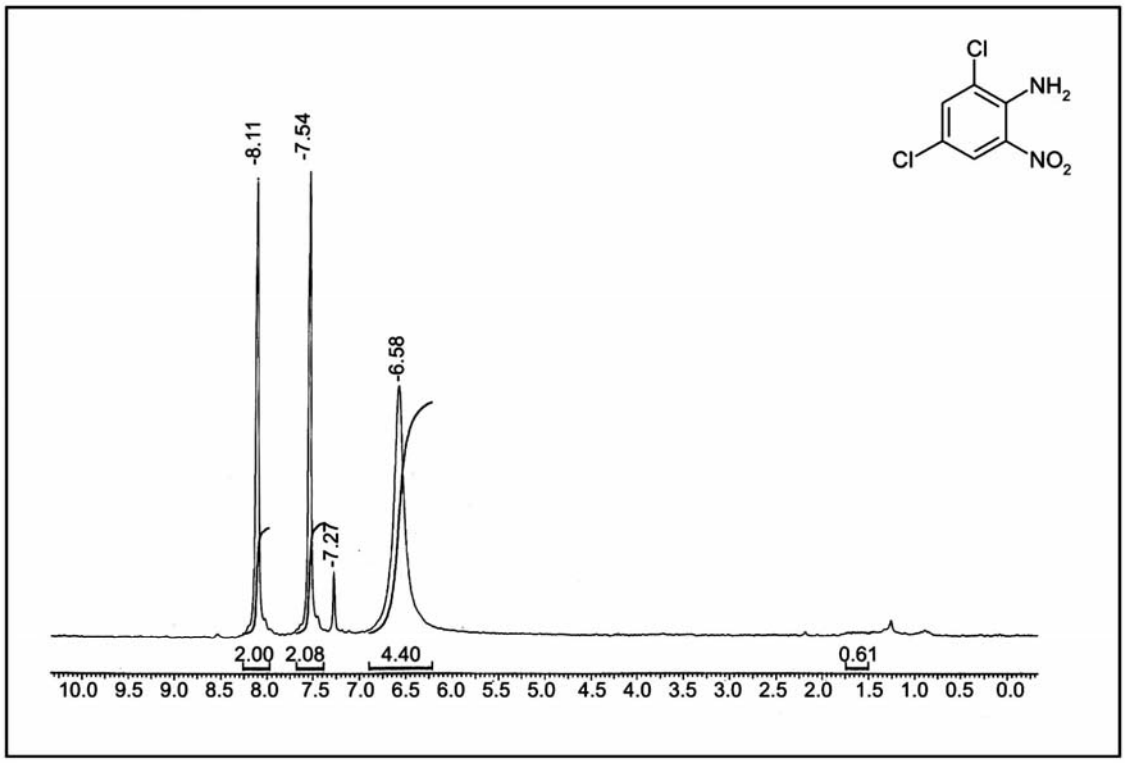
^{1}H NMR of 2, 4, 6-trichloroamiline [Table 3, Entry 1]



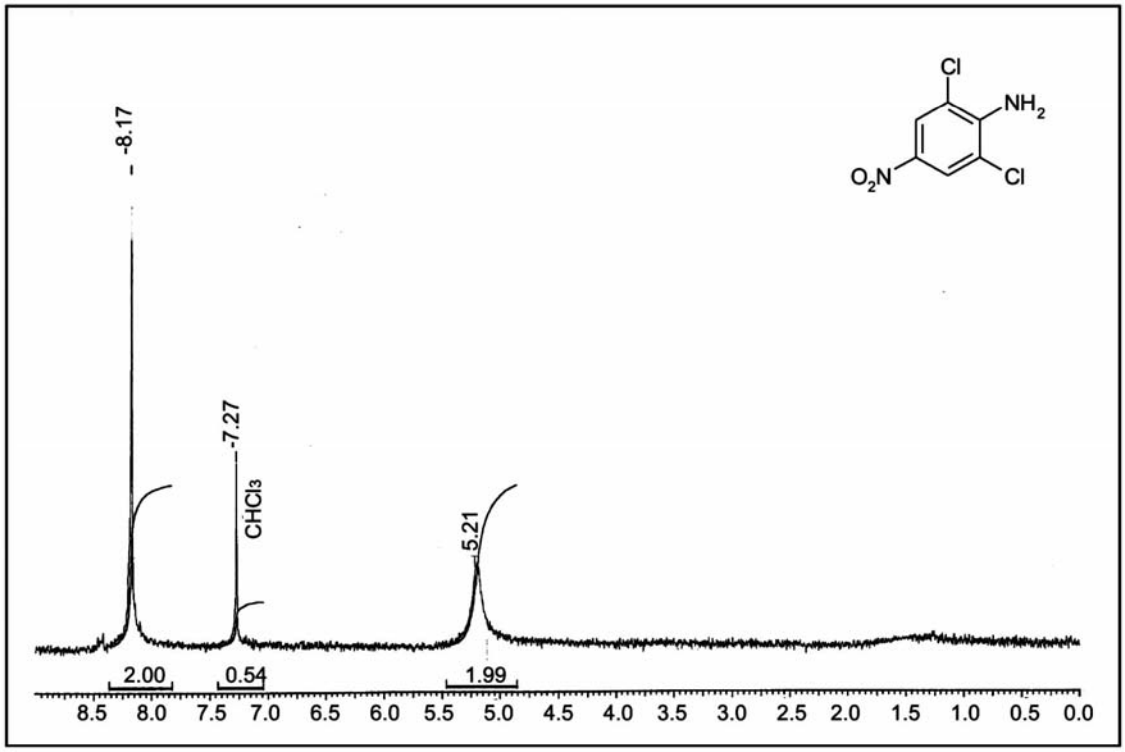
2, 3, 5, 6 - tetrachloroamiline [Table 3, entry 4]



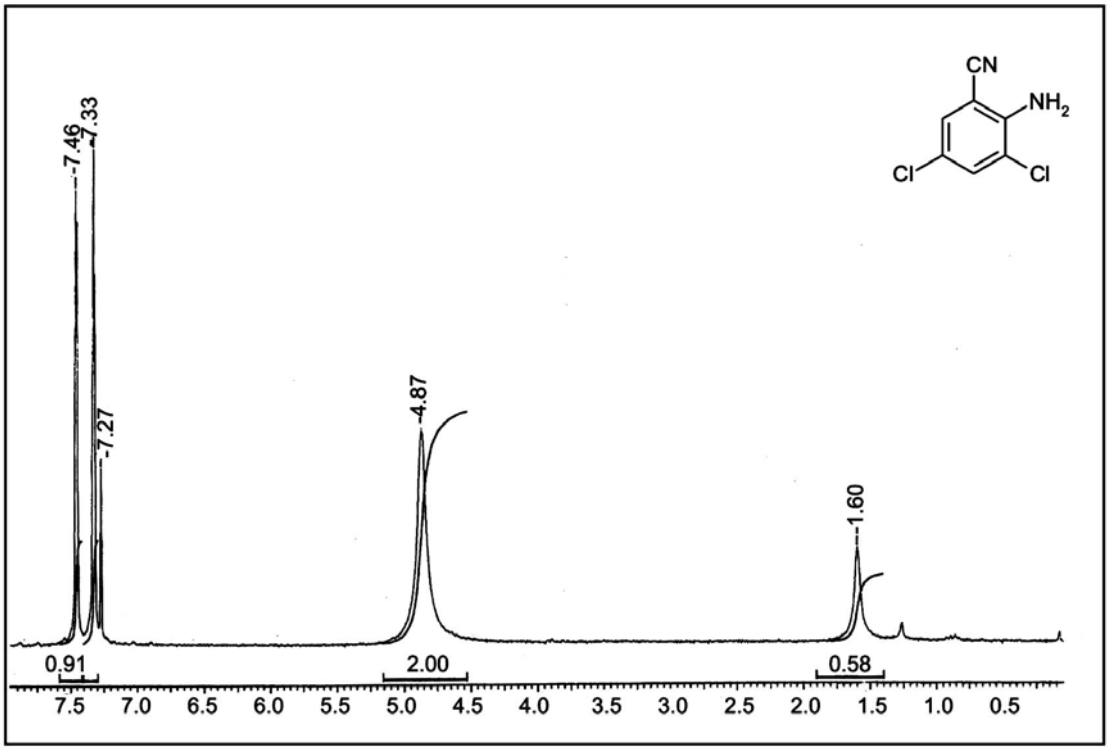
^{1}H NMR of 2, 4-dichloro-6-nitroaniline [Table 3, Entry 5]



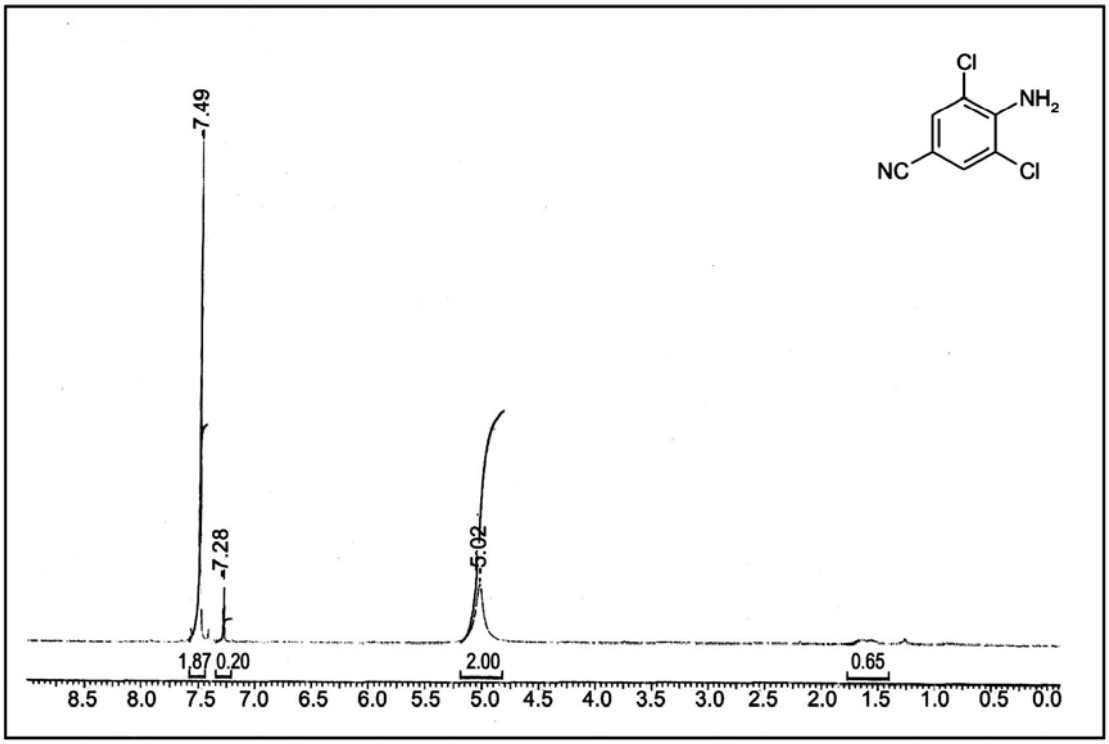
^{1}H NMR of 2, 6-dichloro-4-nitro aniline [Table 3, Entry 6]



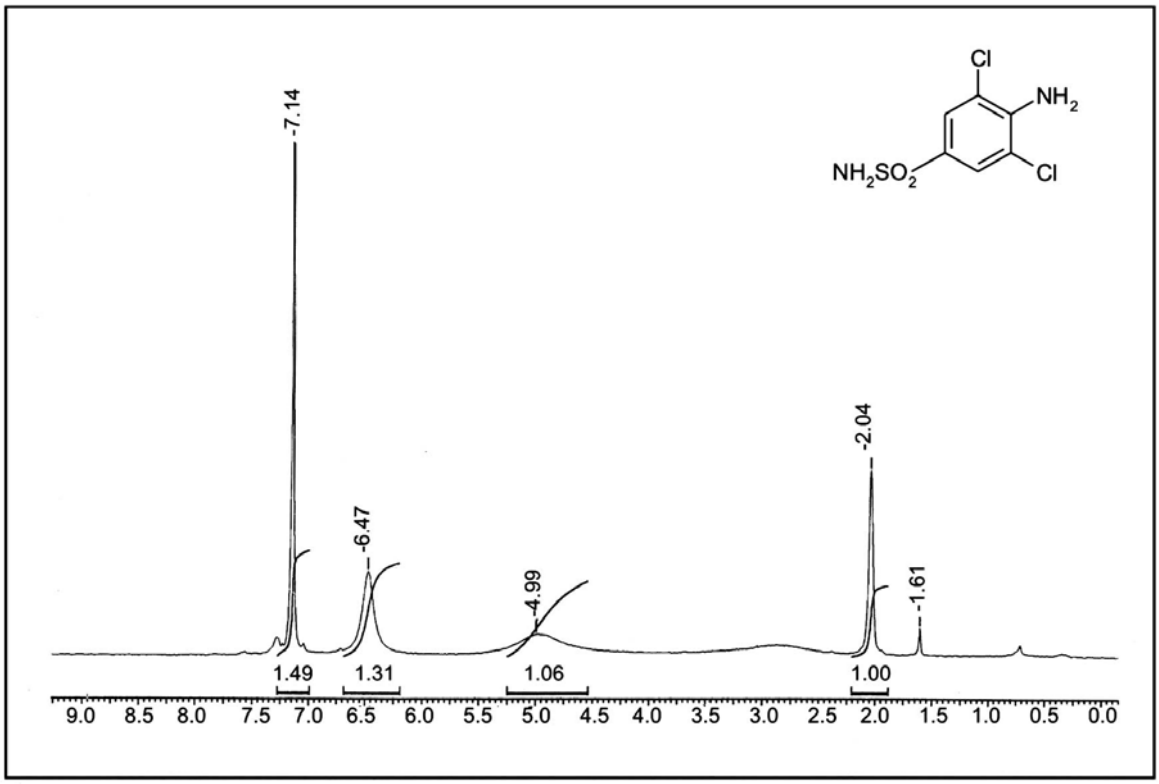
^{1}H NMR of 2-cyano-4, 6-dichloroaniline [Table 3, Entry 7]



^{1}H NMR of 4-cyano-2, 5-dichloroaniline [Table 3, Entry 8]



^{1}H NMR of 4-amino - 2, 6 - dichlorophenylsulfonomide [Table 3, entry 9]



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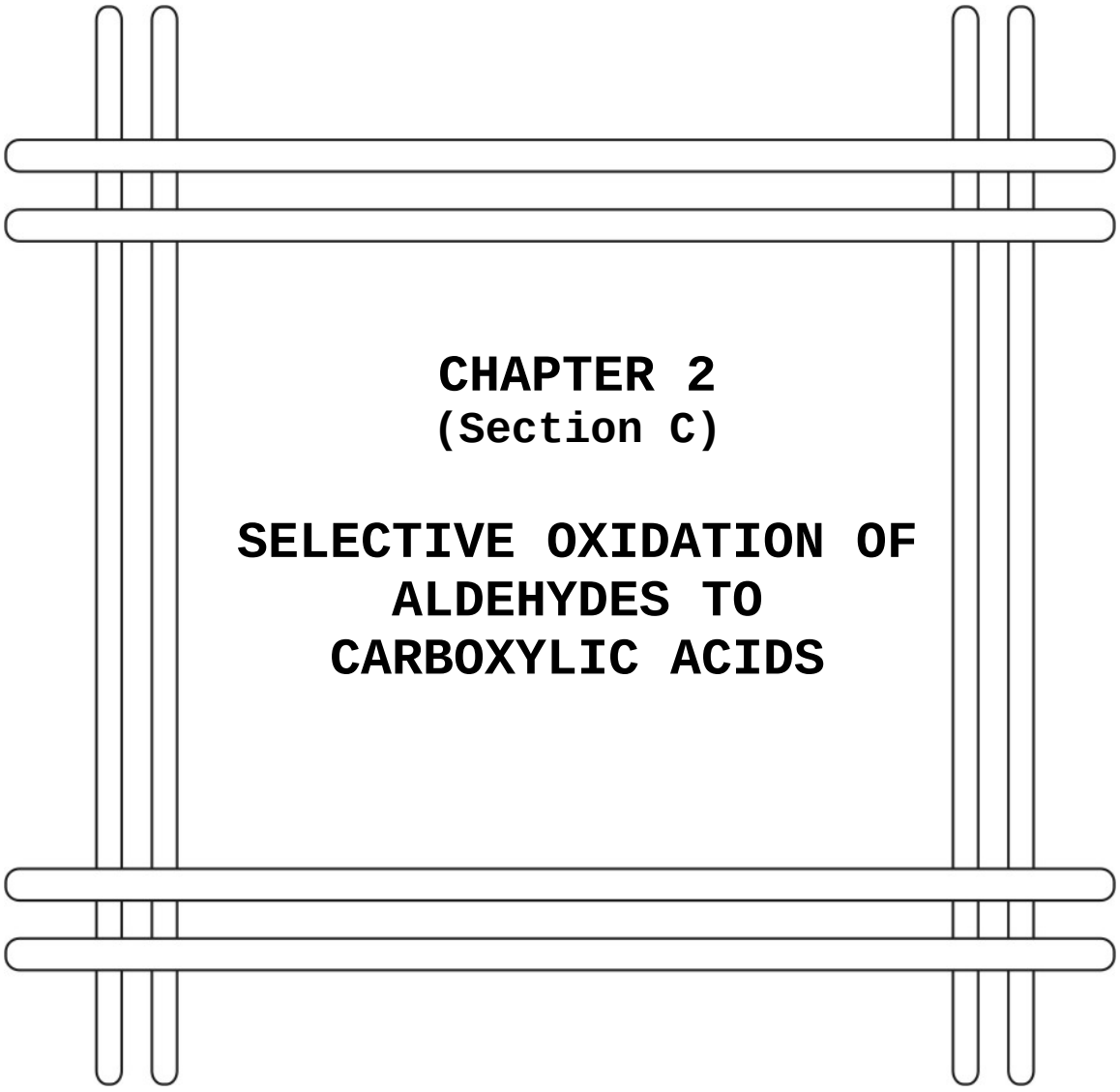


CHAPTER 2
(Section C)

SELECTIVE OXIDATION OF ALDEHYDES TO CARBOXYLIC ACIDS

2.3.1 Introduction

Oxidation of aldehydes is one of the frequently used transformations in organic synthesis. It is one of the most important step in the synthesis of pharmaceutically important compounds like α-arylpropionic acids e.g. ibuprofen, flurbiprofen etc. which are known to be good antiinflammatory agents.[1] Aldehydes are oxidized to carboxylic acids by atmospheric oxygen, but the actual direct oxidation product in this case is the peroxy acid RCO_3H, which with another molecule of aldehyde disproportionates to give two molecules of acid in very low yield.[2]

Several reagents have been reported in the literature for oxidation of aldehydes. However the common oxidants like chromic acid, potassium permanganate in acidic, basic and neutral solution, bromine and nitric acid are not suitable for large scale preparation of carboxylic acid because of the hazard they cause to the environment. Environmentally friendly reagents such as dioxygen gives poor results.[3] Hence several reagents have been reported for this reaction. Pyridinium chlorochromate is known to oxidize aromatic and cinnamyl aldehydes to the corresponding acids under solvent free conditions. Chinkai Seiji *et al.*[4] reported the oxidation of aldehydes and α-ketoacids to carboxylic acids in the presence of 0.2 equivalent of N-hexadecylthiazolium bromide and 1 equivalent 3-methyl tetra-*o*-acetyl riboflavin along with a cationic micelle. Tetrabutylammonium tribromide (TBATB) in aqueous acetic acid oxidizes aliphatic aldehydes to the corresponding carboxylic acids.[5] Balicki Roman[6] achieved mild and safe oxidation of aromatic and heteroaromatic aldehydes to the corresponding acids using urea hydrogen peroxide in formic acid. $KBrO_3$ oxidises aromatic aldehydes having general formula RC_6H_4CHO where R = NO_2, Cl or MeO group in *ortho*, *meta* or *para* position.[7] Some microbiological agents have also been employed for this purpose. In 1999, Perez Herminia and others[8] reported the preparation of cinnamic acid, m-nitrocinnamic acid, veratric acid and 2-naphthoic acid from the corresponding alcohols or aldehydes with whole cells of Nocardia Corallina B-276 in yields from 19 to 71%. However, similar microbiological oxidations gave poor yields for obtaining heterocyclic acids like 4-chromanic acid or 3-pyridylcarboxylic acid from the corresponding alcohol or aldehyde. It was observed that

Burkholderia Cepacia TM 1 isolated from humus was able to oxidize aromatic aldehydes to the corresponding aromatic carboxylic acids with an extreme high yield in distilled water containing only the aromatic aldehyde as the substrate. By following this procedure, the molar yields of vanillic acid from vanillin, p-hydroxy benzoic acid from p-hydroxybenzaldehyde and syringic acid from syringaldehyde were approximately 94%, 92% and 72% respectively. Until the added aromatic aldehyde was significantly consumed, the consumption of the produced acid hardly occurred. The appropriate reactor residence time for continuous production can be set and that aromatic carboxylic acid can be produced efficiently and continuously from the corresponding aldehyde.[9]

Several metal catalysts are known to catalyze the oxidation of aldehydes using different oxidants. Howarth[10] reported the oxidation of aromatic aldehydes containing both electron donating and electron withdrawing substituents at *para* position using the catalyst [$Ni(acac)_2$] and dioxygen at atmospheric pressure as the oxidant in the ionic liquid N-butyl-N-methyl imidazolium hexafluorophosphate, [b_{mim}] × PF_6. The catalyst and ionic liquid could be recycled after extraction of the carboxylic acid product.

Scholz Dieter[11] reported the use of $PhCH_2N^+$ Et_3 MnO_4^- in CH_2Cl_2 / AcOH at room temperature to get good yields of aliphatic and aromatic aldehydes except salicylaldehyde which could not be oxidized to the acid.

In 1981 Hobbs and Thigpen[12] obtained a patent for the process of oxidation of aliphatic aldehydes to carboxylic acids in carboxylic acid solvents catalyzed by combination of Mn salts and Cu salts which are soluble in the solvents. They found that Mn $(OAc)_2$ - $Cu(OAc)_2$ mixtures are more effective catalysts than either alone or the insoluble elements. Aldehydes oxidized include acetaldehyde, propionaldehyde, valeraldehyde, heptanal and nonanal. An European patent[13] was granted for obtaining unsaturated carboxylic acids in high yield and selectivity by oxidizing the corresponding unsatuarated aldehyde with an oxidizing agent selected from alkali metal hypohalites, hypohalous acids, peroxides (e.g. benzoyl peroxide), pyridine N-oxide or peracids in the presence of a transition metal oxide (eg cupric oxide) or hydroxide catalyst. Iron (III) porphyrin

complex – m- chloroperbenzoic acid system gives good yields of carboxylic acid. The aldehydes are oxidized with Fe (III) LCl [L=5,10,15, 20 – tetrakis (penta fluorophenyl) porphyrin] and 3-Cl $C_6H_4CO_3H$.[14]

In another patented process, aromatic aldehydes with halo, CHO, cyano, CO_2H, NO_2, alkyl, alkoxy and alkylthio substituents were oxidized with an 1.2 equivalent alkali metal perborate in acetic acid to give the corresponding carboxylic acid.[15] It was also observed that aqueous hydrogen peroxide oxidizes aldehydes to carboxylic acids without affecting olefinic or alcoholic functions under aqueous / organic biphasic conditions in the presence of a quaternary ammonium salt.

Though several homogenous catalysts are reported for the oxidation of aldehydes, only two heterogeneous catalysts are reported for this reaction. Toshiyasu[16] prepared phosphate buffered silica gel (SiO_2) supported $KMnO_4$ and polymer supported chlorite and used them for conversion of aldehydes to carboxylic acids. In 2001 Kaneda Kiyoomi and Ogawa Hiroo[17] prepared hydrotalcites having a general formula $(M^{2+})_a (M^{3+})_b (OH^-)_c \times d. nH_2O$ where M^{2+} is a metal of valence two selected from Mn, Fe, Zn and Mg, M^{3+} is metal of valence 3 selected form Al and Ru, X is an anion other than OH and used as an oxidation catalyst in manufacture of aldehydes, ketone and carboxylic acids. In a recent report MnO_4^- exchanged Mg-Al-hydrotalcite was reported to be effective in catalyzing the selective oxidation of benzylalcohol to benzaldehyde.[20]

Hydrotalcites are synthetic or natural crystalline materials containing positively charged two dimensional sheets with water and exchangeable charge compensating anions in the interlayer region (Fig 1). Their general structure is as shown in figure 1 where M^{2+} and M^{3+} represent divalent and trivalent cations in the brucite-type layers, A is the inter layer anion with charge n, x is the fraction of the trivalent cation (x values in the general formula are in the range of 0.20-0.5) and m is the water of crystallization.

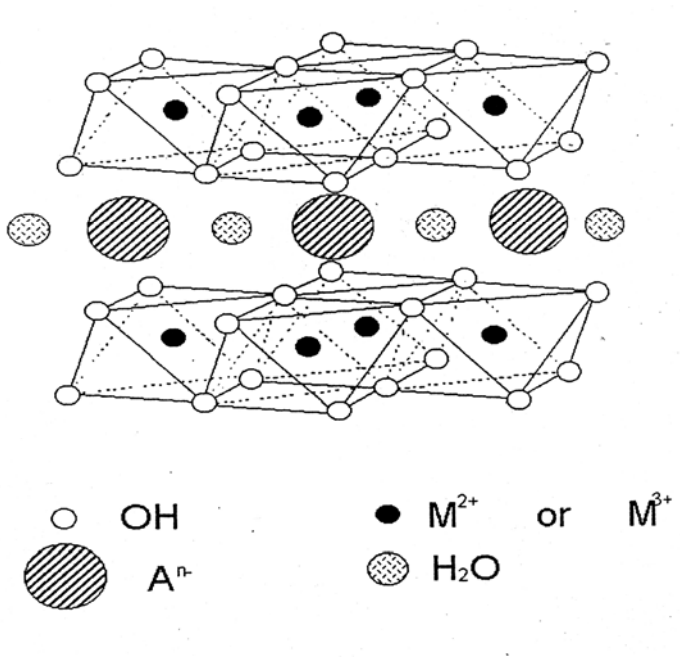


Fig 1: Hydrotalcite-like compound

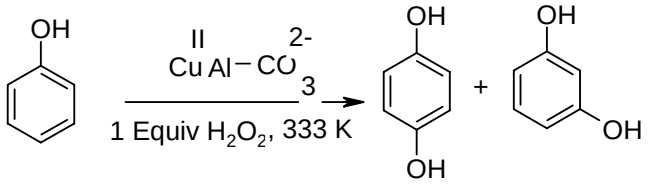
M^{2+} M^{3+} $(OH)_2$ (A^{n-}) • mH_2O

0.20 < x < 0.33 (Mg – Al System)

The mineral hydrotalcite itself is a magnesium – aluminium hydroxycarbonate; the class of HTs comprising many isostructural and polytype forms. HTs may be used as such or they may be calcined to form mixed oxides that are useful catalysts. HTs in the uncalcined form can be used as catalyst supports but they are mainly applied because of their basic properties or as redox catalyst.

As is evident from the structural formula, HTs have a considerable anion-exchange capacity. Under proper conditions, small exchanged ions such as NO_3^- or Cl^- can be replaced completely with large anions, and an expanded layered structure with intercalated guest species is obtained. Hydrotalcites are reported to catalyze some redox reactions very effectively.

Copper (II) containing HTs were tested for the liquid-phase hydroxylation of phenol using H_2O_2 as the oxygen source.[18a]

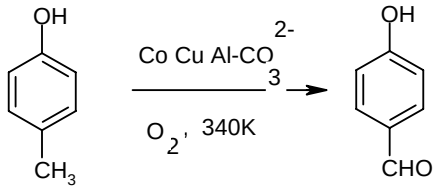


Hydroquinone 32% yield Catechol 22% yield

59 **60** **61**

Scheme 1 : Copper (II) containing HTs catalyzed liquid-phase hydroxylation of phenol

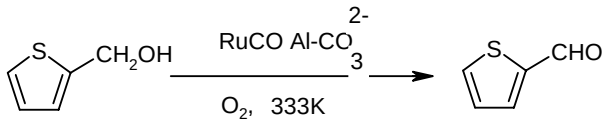
Copper (II) containing HTs catalyzed liquid-phase hydroxylation of phenol can yield *p*-hydroxybenzaldehyde, which is an important chemical for the pharmaceutical and perfume industries.



62 **63**

Scheme 2 : Liquid phase oxidation of *p*-cresol with Co and Cu containing HTs

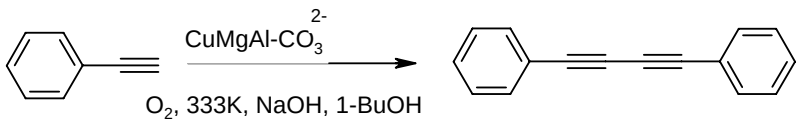
Ru CO Al-CO_3^{2-} and Ru Al Mg-CO_3^{2-} hydrotalcites were used as catalyst for the oxidation of allylic and benzylic alcohols with molecular oxygen. The reaction is chemoselective as primary allylic and benzylic alcohol groups are converted in to the corresponding aldehydes, with negligible formation of the acids. Even oxidation – sensitive functions such as thiophene are not attacked during alcohol oxidation.[19]



63 **65**

Scheme 3: Ru CO Al-CO_3^{2-} and Ru Al Mg-CO_3^{2-} hydrotalcites as catalyst for the oxidation of allylic and benzylic alcohols with molecular oxygen

The synthesis of substituted conjugated alkynes, valuable components for liquid-crystal applications was reported[18b] by oxidative coupling of phenylethyne, leading to 1,4-diphenyl buta-1,3-diyne, with a calcined Cu containing Mg-Al-HT as the catalyst.



66 **67**

Scheme 4 : Oxidative coupling of phenylethyne with a calcined Cu containing Mg-Al-HT as the catalyst

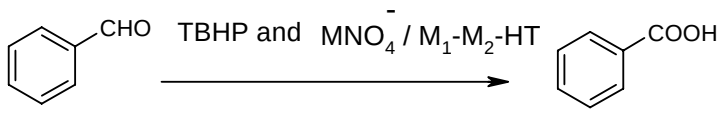
2.3.2 Present work

Though several methods for oxidation of aldehyde to carboxylic acid are reported, many reagents oxidize aromatic aldehydes with electron-donating substituents to phenol formates which are easily hydrolyzed to phenols. Hence the problem of efficient conversion of aromatic aldehydes to arene carboxylic acids remains still open. Due to growing awareness about the ecofriendliness of any method developed, solid catalysts are becoming popular in chemical industry.

Corma *et al.*[19] reported the oxidation of benzyl alcohol to benzaldehyde and benzoic acid using stoichiometric or excess amounts of potassium permanganate in aqueous acidic medium. These stoichiometric reactions have severe limitations such as the formation of large amounts of liquid and solid wastes and the corrosive nature of the acidic reaction medium. Hence a series of metal incorporated hydrotalcites were prepared and were tested as catalyst for oxidation of benzaldehyde to benzoic acid using TBHP as oxidizing agent. The hydrotalcite catalysts were synthesized according to the procedure reported by V.R. Chaudhary *et al.*[20] Two aqueous solutions, one containing the two metal salts with the required ratio and the other containing potassium hydroxide and potassium carbonate were added drop wise into a flask containing deinoized water under vigorous stirring at 40ºC, while maintaining a constant pH of 11 – 12. The resulting white gel was aged for 0.5 hours and then filtered, thoroughly washed and dried at 80ºC in a vacuum oven for 12 hours. The resulting hydrotalcites were powdered and calcined at 600ºC for 4 hours. The calcined mass was then treated under stirring with an aqueous solution of $KMnO_4$ (1.58 g in 100 ml of water) at 80ºC for 2 hours. The resulting MnO_4^- exchanged hydrotalcites were filtered and washed with hot deionized water and then dried at 80ºC in a vacuum oven. The amount of MnO_4^- exchanged was determined by measuring the amount of $KMnO_4$ present in the filtrate and washings. Before use, the MnO_4^- exchanged hydrotalcite catalysts were heated in an air oven at 200ºC for 2 hours.

The MnO_4^- exchanged Mg-Al-hydrotalcites [with Mg/Al ratios of 2, 3, 5 and 10 but same MnO_4^- loading (0.42 ± 0.01 mmol/g)] were prepared by adding two aqueous solutions, one containing magnesium nitrate and aluminium nitrate with the required Mg/Al ratio and the other containing potassium hydroxide and potassium carbonate as stated above. They were characterized for their crystalline structure by XRD (using a Philips 1730 series) diffractometer and $CuK_\propto$ radiation, for their surface area by the single point N_2 adsorption method (using a surface area analyzer, Quanta Chrome USA) and for their basicity by measuring the pH of their suspension in water (6.15 g of catalyst in 10 ml of deionized water at room temperature) and also for their concentration of carbonate anions (by treating the catalyst with 4 N HNO_3 and measuring quantitatively the CO_2 evolved).

The effect of catalyst was determined by stirring a mixture of benzaldehyde, 70% TBHP and catalyst at 100ºC for five hours. The products were analyzed by GC. [Column:10% SE-30, Column initial temperature :250^{o}C, Column final temperature : 270^{o}C,Column injector temperature :250^{o}C, Column detector temperature :250^{o}C]
The results of these experiments are presented in Table 1.



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Scheme 5: Catalytic effect of MnO_4^- exchanged metal hydrotalcites on oxidation of benzaldehyde to benzoic acid

Table 1: Effect of catalysts on oxidation of benzaldehyde to benzoic acid

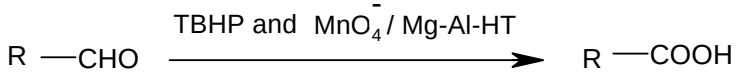
No.	CATALYST	Conversion of benzaldehyde (%)	Selectivity for benzoic acid %
1.	MnO_4 (1.55 mmol/g) / Ni-Al HT (Ni/Al = 3)	90.54	100
2.	MnO_4 (0.947 mmol/g) / Ni-Al HT (Ni/Al = 10)	92.72	100
3.	MnO_4 (0.422 mmol/g) / Cu-Al HT (Cu/Al = 3)	11.01	100
4.	MnO_4 (0.772 mmol/g) / Mn-Al HT (Mn/Al = 3)	95.44	100
5.	MnO_4 (0.233 mmol/g) / Co-Al HT (Co/Al = 3)	95.62	100
6.	MnO_4 (0.148 mmol/g) / Co-Al HT (Co/Al = 10)	98.59	100
7.	MnO_4 (2.11 mmol/g) / Mg-Cr HT (Mg/Cr = 3)	86.90	100
8.	MnO_4 (0.674 mmol/g) / Mg-Fe HT (Mg/Fe = 3)	87.84	100
9.	MnO_4 (0.700 mmol/g) / Mg-Fe HT (Mg/Fe = 10)	99.02	100
10.	MnO_4 (0.700 mmol/g) / Mg-Al HT (Mg/Al = 10)	99.37	100
11.	Mg – Al – HT	11	100
12.	5 ml Benzaldehyde + 10 ml TBHP	11.29	

As shown in Table 1, MnO_4^- exchanged Mg/Al-HT with Mg/Al ratio 10 showed the best activity for oxidation of benzaldehyde with TBHP. To study the effect of Mg/Al ratio on the activity of the catalyst, MNO_4^- exchanged hydrotalcites with different Mg/Al ratio were prepared and tested for their efficiency for the oxidation reaction. Results showing the selective oxidation of benzaldehyde to benzoic acid by TBHP over the MnO_4^- exchanged hydrotalcites with different Mg/Al ratios are presented in table 2.

Table 2: Oxidation of benzaldehyde to benzoic acid by TBHP over MNO_4^- exchanged Mg-Al-hydrotalcite with different Mg/Al ratio

Mg/Al ratio	Conversion of benzaldehyde (%)	Selectivity for benzoic acid (%)
2	84.2	100
3	92.7	100
5	94.5	100
10	99.4	100

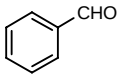
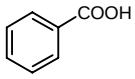
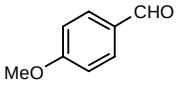
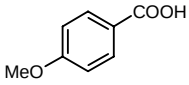
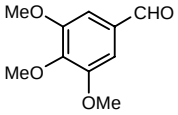
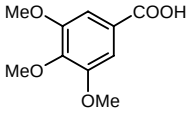
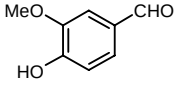
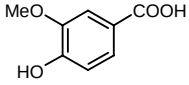
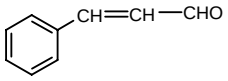
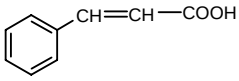
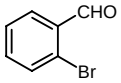
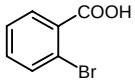
Several aldehydes were subjected to oxidation reaction using MnO_4 (0.7 mmol/g) /Mg – Al- HT(Mg /Al=10) and the results are presented in Table 3.



70 **71**

Scheme 6 : Selective oxidation of aldehydes to the corresponding acids using MnO_4^- exchanged Mg-Al-hydrotalcites and TBHP

Table 3 : Selective oxidation of aldehydes to the corresponding acids using MnO_4-exchanged Mg-Al-hydrotalcites and TBHP

	Aldehydes	Ald:TBHP	Rea. Time	Acid	M.P.	Yield(%)
1.		1 : 2	5		121ºC	91
2.		1 : 2	7		183ºC	77
3.		1 : 2	7		170ºC	71
4.		1 : 2	10		212ºC	63
5.		1 : 2	10		133ºC	59
6.		1 : 2	7		150ºC	87
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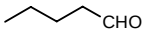
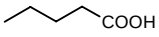
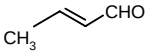
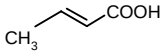
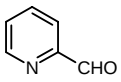
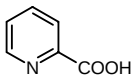
8.		1 : 2	7		Liq	63
9.		1 : 2	10		73ºC	56
10.		1 : 2	7		192ºC	81

2.3.3 Results and Discussion

Catalyst Characterization:

Data on the characterization of the MnO_4^- exchanged Mg-A1-hydrotalcite catalysts with different Mg/Al ratios are presented in Table 4.

Table 4 : Characterization of MnO^-_4 exchanged Mg-Al-hydrotalcite catalyst with different Mg/Al ratios

Mg / Al ratio	Concentration of MnO_4^- anions (mmol/g)	XRD phase	Surface area m^2 / g	CO_2 evolved in the acid treatment (mmol/g)	pH of the suspension of catalyst in water
2.0	0.42	H T	36.3	2.15	9.3
3.0	0.40	H T	31.5	1.74	9.8
5.0	0.41	H T	29.1	1.29	10.0
10.0	0.6	H T	25.9	0.84	10.4

The large amount of CO_2 evolved in the acidification of the catalysts indicates that the anions present in the hydrotalcite catalysts other than MnO_4^- anions are carbonated anions. The pH (>7.0) of the catalyst water suspension is indicative of the basic nature of the catalysts. The increase in pH with increasing Mg/Al ratio suggests that the basicity of the catalyst is increased with increase in Mg/Al ratio. The surface area of the catalyst, however decreases with increasing Mg/Al ratio.

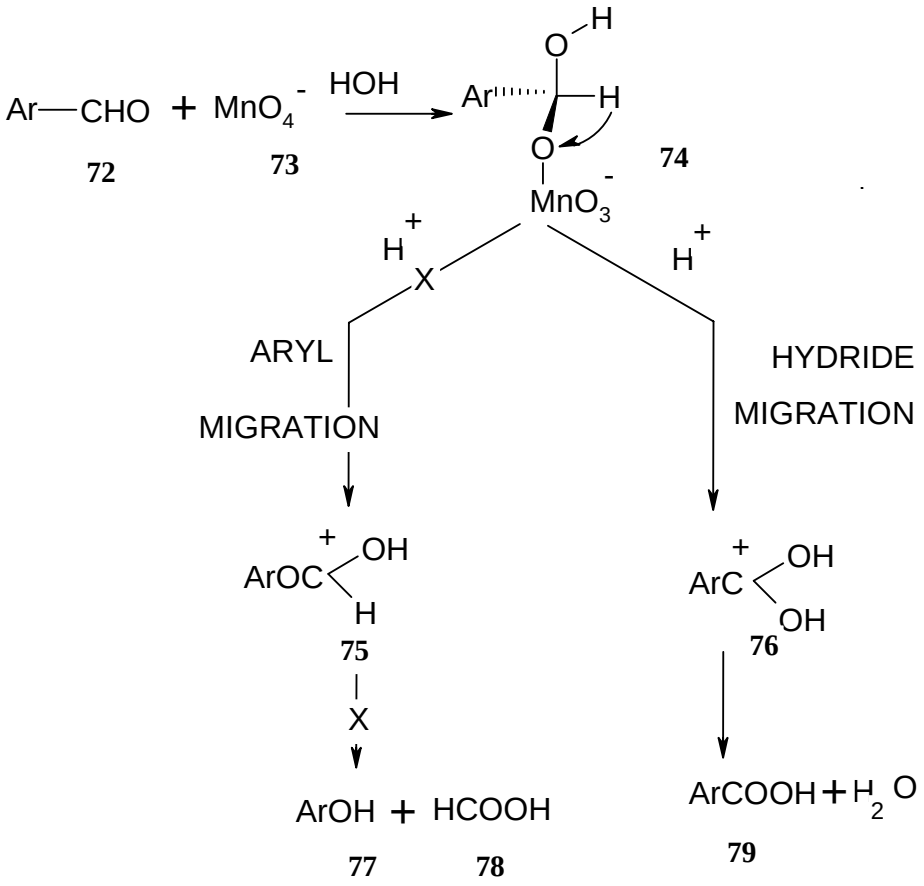
Oxidation of benzaldehyde

As can be seen from Table 1, MnO_4^- exchanged Mg-Al-Hydrotalcite is most active catalyst for the selective oxidation of benzaldehyde in the absence of solvent. It is interesting that although the concentrations of MnO_4^- anions in the hydrotalcite catalysts are nearly the same, the activity of the catalyst showed a strong dependence upon its Mg/Al ratio: the activity increased with increasing Mg/Al ratio. This may be attributed to the different basicities of the hydrotalcite catalysts; the higher the basicity, the higher is the catalytic activity (Table 2).

Results showing the performance of the MnO_4^- exchanged Mg-Al-hydrotalcite catalyst in the oxidation of aldehydes to the corresponding carboxylic acid are presented in Table 3. As shown in Table 3, a wide range of heterocyclic, aliphatic as well as aromatic aldehydes with both electron-withdrawing as well as electron donating substituents are selectively oxidized to the corresponding carboxylic acids in good yields. Olefinic or alcoholic functionalities remain unaffected under the reaction conditions.

As seen in Table 1, only 11.29% of the product was obtained when the reaction was carried out without catalyst (entry 12). Maximum yield and selectivity was obtained when MnO_4^- (0.700 mmol/g) Mg-Al-HT with Mg/Al ratio 10 was used. Mg-Al-HT without incorporation of MNO_4^- yielded only 11% benzoic acid (entry 11). The results presented above explain the significant role played by the catalyst MnO_4^-/Mg-Al-HT along with TBHP in the chemoselective oxidation of aromatic aldehydes into arene carboxylic acid.

In the light of the widely accepted mechanism for the reaction of carbonyl compounds with permanganate in homogeneous medium,[18] the first step is addition of MnO_4^- to the corresponding carbonyl compound resulting in the formation of tetrahedral intermediate [A, Scheme 7]. The subsequent step of the Baeyer-Villiger rearrangement, which is rate determining; should be migration of the aryl group to the electrophilic oxygen atom of the peroxide bridge and simultaneously, cleavage of the O-O-bond along with release of $HMnO_4^-$ to give phenol as the final product. However, the bulky group MnO_4^- in the vicinity of the electrophilic oxygen atom in the peroxy bridge hinders aryl migration and competitive hydride ion migration predominates. This pathway leads to the acid.



Scheme 7: Mechanism for MnO_4^- /Mg-Al-HT for oxidation of aldehydes to the corresponding acids

The $Mn(VII)O_4^-$ necessary for the reaction is likely to be regenerated from TBHP involving the following redox mechanism.

$$\underset{\mathbf{80}}{Mn\,(V)\,O^{-}_{3}} + \underset{\mathbf{81}}{(CH_3)_3COOH} \rightarrow \underset{\mathbf{82}}{Mn\,(VII)\,O^{-}_{4}} + \underset{\mathbf{83}}{(CH_3)_3\,COH}$$

Scheme 8 : Mechanism for the regeneration of $Mn(VII)O_4^-$ from TBHP

The basic sites of the catalyst may be responsible for the activation of the aldehyde through partial abstraction of H.

2.3.4 Conclusion

MnO_4^- exchanged Mg-Al-hydrotalcites (Mg/Al=10) show high activity and selectivity in the oxidation of aldehydes to the corresponding carboxylic acids. The method is general for a wide range of aldehydes like aliphatic, alicyclic or heterocyclic aldehydes as well as aromatic aldehydes with both electron donating or electron withdrawing groups. No formate or phenolic product was formed. A redox mechanism involving reduction of Mn (VII) to Mn (V) and oxidation of Mn (V) to Mn (VII) by TBHP seems to be operative in this catalytic oxidation process. The solvent free conditions and reusability of catalyst make this methodology environmentally friendly as well as economically viable.

2. 3. 5 Experimental

Preparation of MnO_4^- exchanged hydrotalcites:

Two aqueous solutions, one containing the two metal salts with the required ratio and the other containing potassium hydroxide and potassium carbonate were added drop wise into a flask containing deinoized water under vigorous stirring at 40ºC, while maintaining a constant pH of 11 – 12. The resulting white gel was aged for 0.5 h and then filtered, thoroughly washed and dried at 80ºC in a vacuum oven for 12 h. The resulting hydrotalcites were powdered and calcined at 600ºC for 4 h. The calcined mass was then treated under stirring with an aqueous solution of $KMnO_4$ (1.58 g in 100 ml of water) at 80ºC for 2 h. The resulting MnO_4^- exchanged hydrotalcites were filtered and washed with hot deionized water and then dried at 80ºC in a vacuum oven. The amount of MnO_4^- exchanged was determined by measuring the amount of $KMnO_4$ present in the filtrate and washings. Before use, the MnO_4^- exchanged hydrotalcite catalysts were heated in an air oven at 200ºC for 2 h.

Preparation of MnO_4^- exchanged Mg-Al-hydrotalcites with different Mg/Al ratio:

The MnO^-_4 exchanged Mg-Al-hydrotalcites [with Mg/Al ratios of 2, 3, 5 and 10 but same MnO^-_4 loading (0.42 ± 0.01 mmol/g)] were prepared by adding two aqueous solutions, one containing magnesium nitrate and aluminium nitrate with the required Mg/Al ratio and the other containing potassium hydroxide and potassium carbonate as stated above. They were characterized for their crystalline structure by XRD (using a Philips 1730 series) diffractometer and $CuK_\propto$ radiation, for their surface area by the single point N_2 adsorption method (using a surface area analyzer, Quanta Chrome USA) and for their basicity by measuring the pH of their suspension in water (6.15 g of catalyst in 10 ml of deionized water at room temperature) and also for their concentration of carbonate anions (by treating the catalyst with 4 N HNO_3 and measuring quantitatively the CO_2 evolved).

Selection of catalyst for oxidation of benzaldehyde to benzoic acid (Table 1):

A mixture of benzaldehyde (1mmol), 70% TBHP and 10% by wt. of the MnO_4 exchanged M_1^{2+}-M_2^{3+} HT was stirred at 100^oC for five hours. The products were analyzed by GC.

Column	:	10% SE-30.
Column initial temperature	:	250^oC.
Column final temperature	:	270^oC.
Column injector temperature	:	250^oC
Column detector temperature	:	250^oC

The catalyst with Mg/Al ratio of 10 showed maximum conversion of 99.4%

Oxidation of benzaldehyde over MnO_4^- exchanged Mg-Al-HT with different Mg/Al ratio

A mixture of benzaldehyde (1mmol), 70% TBHP and 10% by wt. of the MnO_4 exchanged M_1^{2+}-M_2^{3+} HT was stirred at 100^oC for five hours. The products were analyzed by GC.

Oxidation of aromatic aldehydes over MnO_4^- exchanged Mg-Al-HT [Table 3, entries 1-4, 6]

10 Mmol of aldehyde was taken in 20 mmol of 70% TBHP and 20% of MnO_4^- /Mg-Al HT and heated at 100ºC with stirring for 7 to 10 hours. After the reaction was complete (TLC), the reaction mixture was concentrated, made alkaline with Na_2CO_3 and the aqueous layer was washed with chloroform. It was then acidified with HCl. The product obtained was extracted in ether, dried over anhydrous Na_2SO_4 and concentrated. The products were crystallized from methanol or purified by column chromatography if necessary. All the products showed melting point and IR identical with those of the authentic samples.

Oxidation of cinnamaldehyde over MnO_4^- exchanged Mg-Al-HT [Table 3, entry 5]

10 Mmol of cinnamaldehyde was taken in 20 mmol of 70% TBHP and 20% of MnO_4^- /Mg-Al HT and heated at 100ºC with stirring for 10 hours. After the reaction was complete (TLC), the reaction mixture was concentrated, made alkaline with Na_2CO_3 and the aqueous layer was washed with chloroform. It was then acidified with HCl. The product obtained was extracted in ether, dried over anhydrous Na_2SO_4 and concentrated. The product was crystallized from methanol. The product showed melting point and IR identical with that of the authentic sample of cinnamic acid.

Oxidation of aliphatic aldehydes over MnO_4^- exchanged Mg-Al-HT [Table 3, entry 7, 8, 9]

10 Mmol of aliphatic aldehyde was taken in 20 mmol of 70% TBHP and 20% of MnO_4 /Mg-Al HT and the mixture was heated at 100ºC with stirring for 7-10 hours. After the reaction was complete (TLC), the reaction mixture was concentrated, made alkaline with Na_2CO_3 and the aqueous layer was washed with chloroform. It was then acidified with HCl. The product obtained was extracted in ether, dried over anhydrous Na_2SO_4 and concentrated. The products were crystallized from methanol or purified by column chromatography if necessary. All the products showed melting points and IR spectra identical with those of the authentic samples.

Oxidation of pyridine-2- aldehyde over MnO_4^- exchanged Mg-Al-HT [Table 3, entry 10]

10 Mmol of pyridine-2-aldehyde was taken in 20 mmol of 70% TBHP and 20% of MnO_4^- /Mg-Al- HT and heated at 100ºC with stirring for 7 hours. After the reaction was complete (TLC), the reaction mixture was concentrated, made alkaline with Na_2CO_3 and the aqueous layer was washed with chloroform. It was then acidified with HCl. The product obtained was extracted in ether, dried over anhyd. Na_2SO_4, concentrated and crystallized from methanol. The product showed melting point and IR spectrum identical with that of the authentic sample of pyridine-2-carboxylic acid.

2.3.6 References

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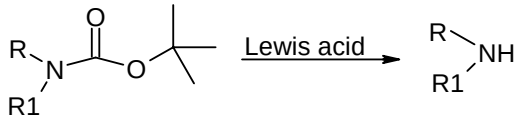
CHAPTER 2
(Section d)

SELECTIVE REMOVAL OF THE N-(*tert*-butoxy-carbonyl) protecting group using h-β zeolite.

2.4.1 Introduction

Protection / deprotection of functional groups is very important when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound; whereas other reactive sites must be temporarily blocked. The amino function is one of the most important groups in organic molecules and its controlled manipulation during the synthesis is of great value in synthetic organic chemistry. The frequently used protective group for the amino groups [1] include carbamates- formed by the reaction of an amine with an azido or chloroformate or a carbonate and amides formed from acid chlorides. The tert-butoxycarbonyl (Boc) group is extensively used as a convenient group for protecting primary and secondary amines[1] and aminoacids in peptide chemistry due to its stability towards mild acidic or basic conditions.[2] The ease of introduction by controlled pH technique[3] and the relatively mild conditions required for the removal of this group are additional advantages resulting in frequent use of this protecting group in amino chemistry.

In general, deprotection of N-Boc group is performed by using strong Lewis acid[4] or protic media (Scheme1).

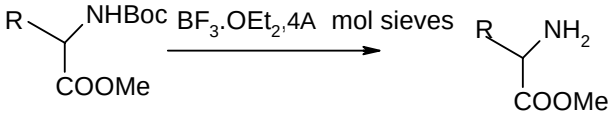


84 **85**

Scheme 1 : Deprotection of Boc group from amines

Acids like trifluoroacetic acid (TFA)[5] either neat or in CH_2Cl_2 solution, mineral acids like nitric acid, ceric ammonium nitrate,[6] tin tetrachloride[7] are generally used for regeneration of amines from their BOC derivatives. Isobutene generated in these acidic conditions was reported to give some electrophilic additions necessitating the use of scavengers like thiophenols. Several organic functions are incompatible with these reaction conditions.

t-Boc removal in case of water insoluble peptide derivatives has been carried out using boron trifluoride etherate (three fold excess) along with 10% glacial acetic acid under anhydrous reaction conditions.[7a] In case of water soluble peptides the similar reagent can cause formation of boric acid salt. A modification of this protocol was reported by Evans *et al.*[7b] wherein they found that boron trifluoride etherate in presence of 4A molecular sieves was good substitute for the glacial acetic acid (Scheme 2).

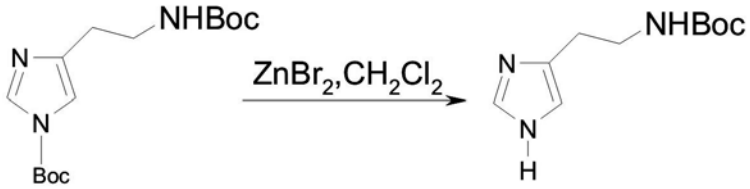


86 **87**

Scheme 2: Boc deprotection using $BF_3.OEt_2$, 4A mol sieves

Five equivalents boron reagent and prolonged duration of the reaction limits the application of this procedure even for simple aromatic amines.

In another report, two equivalents of anhydrous $ZnBr_2$[8] was found to be selective reagent for deprotection of aliphatic N-Boc group (Scheme 3).

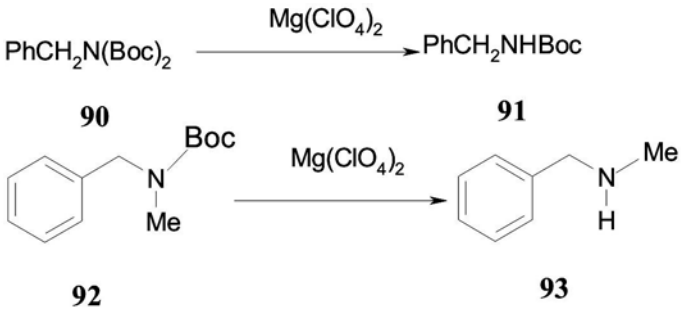


88 **89**

Scheme 3: $ZnBr_2$ mediated removal of Boc group

During the studies on β-lactum antibiotics, Tsuji and coworkers[9] reported that concurrent deprotection of the carboxylester (benzyl) and amino protecting (t-Boc) was observed by using aluminium chloride (3.0 eq.) and anisole (3.0 eq.) in CH_2Cl_2 / $MeNO_2$ at room temperature. This was further generalized using one equivalent amount of aluminium chloride in dichloromethane at room temperature for cleavage of Boc group from aromatic as well as aliphatic protected amines in satisfactory yields within three hours.

Stafford *et al.* [10] have reported the use of catalytic $Mg(ClO_4)_2$ in acetonitrile for Boc deprotection from amide (or carbamate). In case of diprotected (di-Boc) amines only mono deprotection has been observed (Scheme 3). However the duration of the reaction varies from 3 to 72 hours depending upon the substrate to obtain good to excellent yields.



Scheme 4: $Mg(ClO_4)_2$-catalyzed deprotection of Boc amides and carbamates

Routier *et al.*[11] have found that N-Boc group can be removed from the substrates supported on Rink's amide resin by treatment with trimethylsilyltriflate / 2, 6-lutidine. The deprotection conditions were tolerated well by frequently used protecting groups in solid phase synthesis like triisopropylsilyl and 2, 4-dinitro phenyl. However TMSOTf / 2, 6-lutidine causes cleavage of some esters in the solution and therefore is not compatible when fluorenylmethylene or FMOC group is present.

Though several homogeneous catalysts are reported for cleavage of N-Boc group, very few heterogeneous catalysts like Montmorillonite K 10[12] have been used for this reaction. Shiro[13] and others have reported microwave assisted silica gel deprotection of N-Boc derivatives wherein 1mmol of N-Boc derivative when adsorbed on 10 g of silica gel and irradiated in microwave oven for few minutes yielded the corresponding amines. $Yb(OTf)_3$ (9%) supported on silica gel is also known to catalyze the deprotection of N-Boc amines.[13]

Selective removal of Boc group from nitrogen atoms in conjugation with an aromatic or carbonyl group was described by Wensbo and Apelqvist.[14] Simple aromatic N-Boc protected amine when adsorbed on silica gel and heated under reduced pressure (0.2 mm

Hg) for long duration yielded the corresponding amines whereas aliphatic amines remained unaffected. For example p-ansidine and p-nitroaniline were obtained in 83 and 92% yields after 144 and 48 hours repectively from their coresponding Boc compounds. (Scheme 5).

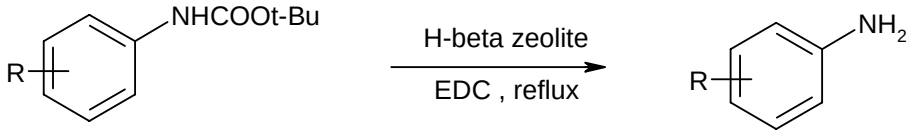
94 **95**

Scheme 5 : Selective removal of the N-Boc group using silica gel at low pressure

2.4. 2 Present work

Though a few heterogeneously catalyzed regenerations of amines from their N-Boc derivatives are reported; the large amount of absorbent required, the limited reusability of the catalyst and long reaction times have limited their applications. These drawbacks of the reported procedures justified the need for a selective and practical method for the deprotection of N-Boc group.

Growing concern for the environment demands the development of eco-friendly and economic processes. As a result, there has been considerable upsurge of interest in the area of developing solid catalysts and their subsequent application for various organic transformations. Zeolites, due to their acidic and shape selective nature have been found to be a suitable replacement for various homogeneous acid catalysts. The use of H-beta zeolite as an unprecedented, convenient and heterogeneous catalyst for deprotection of Boc group has been demonstrated in this section. When N-Boc compounds were refluxed in dichloroethane in the presence of catalytic amount of H-β zeolite, the corresponding amines were obtained in excellent yields (Scheme 6).



96 **97**

Scheme 6 : Boc deprotection using $BF_3.OEt_2$, 4A mol sieves

2. 4. 3 Results and discussion

A series of N-Boc amines were subjected to the deprotection reactions with H-beta zeolite and results are presented in Table 1.

Table 1: Selective removal of N-Boc group using H-β zeolite

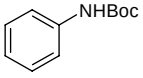
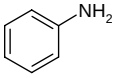
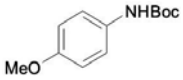
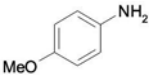
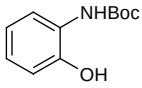
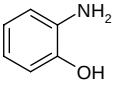
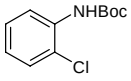
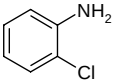
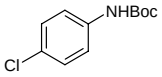
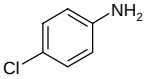
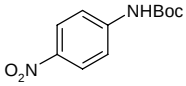
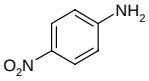
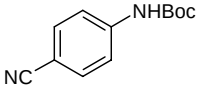
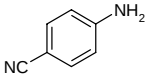
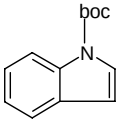
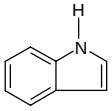
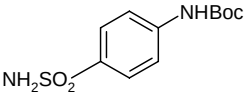
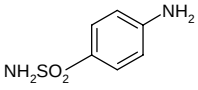
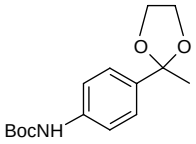
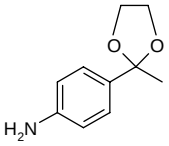
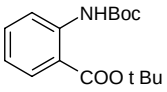
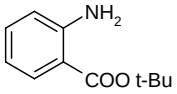
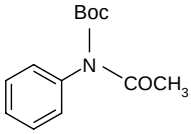
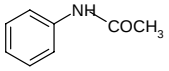
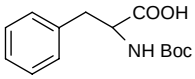
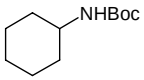
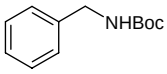
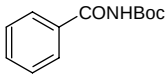
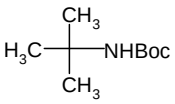
Entry	Reactant	Reaction time (hr)	Product[a]	Yield (%)[b]
1		5		100
2		5		91
3		10		71
4		5		99
5		5		98
6		4		98
7		8		77
8		10		97
9		10		91

Table 1: Selective removal of N-Boc group using H-β zeolite (Contd.)

Entry	Reactant	Reaction time (hr)	Product[a]	Yield(%)[b]
10		7		91
11		10		85[c]
12		10		93
13		10	No reaction	–
14		10	No reaction	–
15		10	No reaction	–
16		10	No reaction	–
17		10	No reaction	–

[a] Products were characterized by spectroscopic data and also by comparison with the authentic sample.[b] Yields refer to isolated pure products.[c] The formation of anthranilic acid (10%) as side product was observed.

The present procedure is quite general as a wide range of structurally varied *N*-Boc compounds underwent deprotection smoothly under the reaction conditions employed while the Boc group attached to nitrogen atoms belonging to an aromatic system could easily be deprotected. Boc-substituents at aliphatic amines were left unaffected. The effectiveness of this protocol is further manifested in its selectivity for the deprotection of *N*-Boc in the presence of ketal group (Table 1, entry 10). Another notable feature of this reaction is that *N*-Boc group is deprotected selectively in the presence of a *t*-butyl ester group (Table 1, entry 11). This is in contrast with recent reports where the deprotection of ester group has been achieved in the presence of *N*-Boc group using $ZnBr_2$ in CH_2Cl_2[14] or $CeCl_3.7H_2O$-NaI system in acetonitrile.[16] Interestingly, the *N*-Boc group of aromatic amines was removed with ease while Boc-group attached to nitrogen atoms in conjugation with a carbonyl group and not being part of an aromatic system failed to undergo cleavage (Table 1, entry 15). The difference in the reactivity pattern of *N*-Boc derivative could probably be utilized in selective manipulation of *N*-Boc deprotection in a synthetic sequence. In an control experiment, with N-Boc aniline using other zeolites such as mordenite yielded 35% aniline, H-Y yielded 30% of the product whereas 4A and 5A molecular sieves failed to accomplish the above transformation. The observed efficient performance of H-β zeolite may be attributed to its large pore opening, three dimensional channel system and higher concentration of acid sites.[17] The recovered catalyst was reactivated for reuse by heating at 100-110°C in the presence of air. The catalyst was reused five times without loss of activity and selectivity.

2. 4. 4 Conclusion

It has been shown that H-β zeolite serves as an efficient catalyst for cleavage of t-butoxy carbonyl protecting group from aromatic amines. A wide range of aromatic N-Boc derivatives with electron donating as well as electron withdrawing substituents yielded the corresponding amines in good to excellent yields within a short period of time. However aliphatic N-Boc derivatives failed to undergo this deprotection. The potential for the selective removal of different *N*-Boc groups has been demonstrated. Since no inorganic wastes are produced, this methodology is eco-friendly. The obvious advantages of heterogeneous catalysis in terms of simple operation coupled with the ease of work-up and reusability of the catalyst are noteworthy. Thus, the present catalytic method should serve as a useful addition to synthetic organic chemistry.

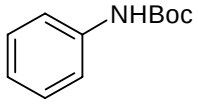
2.4.5 Experimental

H-β zeolite was procured as a gift from United Catalyst India Ltd. (UCIL) Mumbai; SiO_2/Al_2O_3 = 30, Surface area = 700 m^2/g, Pore diameter =7.6x 6.4 A. Prior to use it was calcined at 110^0C for 2h in air.

t - Boc derivatives of amines were prepared by stirring together a solution of the amine (1 eq.) and di-tert-butyl dicarbonate (1.2 eq.) in acetonitrile in the presence of DMAP (0.1 eq.) at room temperature for 6 to 10 h. After completion of reaction, the reaction mixture was concentrated and purified by column chromatography on neutral alumina. These substrates were subjected to deprotection reaction. The compounds obtained after deprotection were compared with authentic samples as a preliminary analysis of the product. All N-Boc-protected amines and products (free-amines) gave satisfactory analytical and spectroscopic data.

Spectral characteristics of the reactants:

Phenycarbamic acid tert-butyl ester [Table 1, entry 1]



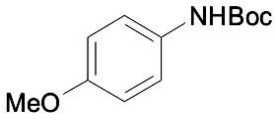
M. P. : 64^0C

IR ($CHCl_3$) : 3019, 1723, 1518, 1215, 1159 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.53 (s, 9H), 6.60 (brs, 1H), 7.15-7.65 (m, 5H).

MS m/z, (%) : M^+ 193 (9), 137 (67), 93 (100), 65 (56), 57 (95).

(4- Methoxy) phenylcarbamic acid tert-butyl ester [Table 1, entry 2]



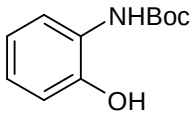
M.P : 105 – 110 ^{0}C.

IR [1] ($CHCl_3$) : 3440, 2981, 1717, 1520, 1368, 1242 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.53 (s, 9H), 3.78 (s, 3H), 6.37 (brs, 1H), 6.84 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 7.5 Hz, 2H).

MS (m/z, %) : 223 ($M^{+\cdot}$,15), 107 (90), 123 (45), 108 (79), 57 (100).

(2-Hydroxyphenyl) carbamic acid tert-butyl ester [Table 1, entry 3]



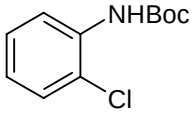
M.P. : 170 ^{0}C.

IR ($CHCl_3$) : 3224, 2921, 1705, 1455, 1231 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.50 (s, 9H), 5.50 (brs, 1H), 6.50 (brs, 1H), 6.90-7.25 (m, 4H).

MS (m/z, %) : 209 (M^+,7), 153 (80), 135 (10), 109 (100), 80 (20), 57 (10).

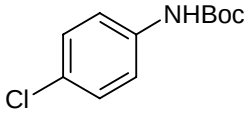
(2 - Chlorophenyl) carbamic acid tert- butyl ester [Table 1,entry 4]



^{1}H NMR (200 MHz, $CDCl_3$) : 1.47 (s, 9H), 6.89 (m, 2H), 7.20 (m, 2H), 8.10 (brs, 1H).

MS (m/z, %) : 227, (M^+), 183 (5), 171 (10), 127 (25), 57 (100).

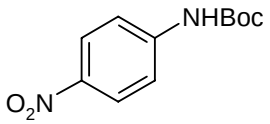
(4 – Chlorophenyl) carbamic acid tert- butyl ester [Table 1, entry 5]



^{1}H NMR (200 MHz, $CDCl_3$) : 1.52 (s, 9H), 6.55 (brs, H), 7.20 - 7.33 (m, 4H)

MS (m/z, %) : 229 (M^++2), 227 (M^+), 171 (58), 127 (89), 57 (100).

(4-Nitrophenyl) carbamic acid tert-butyl ester [Table 1, entry 6]

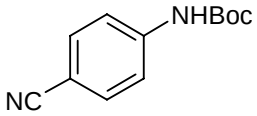


IR ($CHCl_3$) : 3430, 3020, 1731, 1215, 1159 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.55 (s, 9H), 6.56 (brs, 1H), 7.50 (d, J=8.9 Hz, 2 H), 8.20 (d, J = 8.9 Hz, 2H).

MS : m/z (%) : 238 (M^+, 5), 182 (8), 138 (40), 108 (35), 92 (20), 65 (45), 57 (100).

(4-Cyanophenyl) carbamic acid tert-butyl ester [Table 1, entry 7]

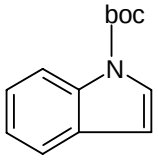


IR ($CHCl_3$) : 3429.37, 3019.74, 7.27.21, 588.35, 1270.96, 1054.09 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.55 (s, 9H), 6.70 (brs, 1H), 7.45 (d, J=8 Hz, 2H),7.60 (d, J=8 Hz, 2H).

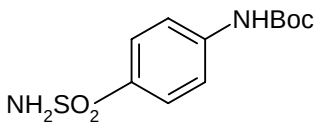
MS m/z (%) : 218 (M^+,3), 162 (18), 118 (27), 57 (100).

Indolyl carbamic acid tert butyl ester [Table 1, entry 8]



^{1}H NMR ($CDCl_3$, 200 MHz) : 1.55 (s, 9H), 6.48 (m, 1H), 7.20-7.40 (m, 4H), 7.64-7.80 (m,1H).

***tert*-Butyl-4-sulfamoylphenyl carbamate** [Table 1, entry 9]

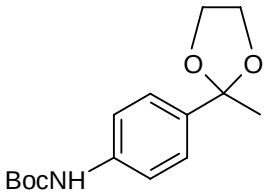


IR (nujol) : 3374.8, 3311.56, 2856.26, 1691.73, 1148 cm^{-1}.

^{1}HNMR ($CDCl_3$, 200 MH_z) : δ 1.35 (s, 9H), 4.85 (brs, 2H), 6.15 (brs,1H), 7.42 (d, J = 6Hz, 2H), 7.62 (d, J = 6 Hz, 2H).

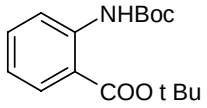
MS (m/z %) : 272 (M^+) (12), 216 (90), 172 (15), 57 (100).

4-(2-Methyl – (1, 3) dioxolan –2-y1)phenylcarbamic acid tert butyl ester [Table 1, entry 10]



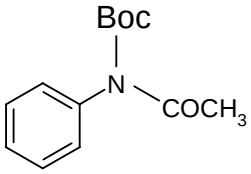
^{1}HNMR (200 MHz, $CDCl_3$) : δ 1.55 (s, 9H), 1.67 (s, 3H), 3.83 (m, 2H), 4.10 (m, 2H), 6.74 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8. 9 Hz, 2H).

(2 tert-Butylcarboxylate) phenyl carbamic acid tert butyl ester [Table 1, entry 11]



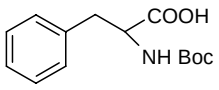
^{1}HNMR (200 MHz, $CDCl_3$) : δ 1.45 (s, 9H), 1.55 (s, 9H), 6.73 (m, 1H), 7.20-7.70 (m, 3H).

***tert*-Butyl acetyl (phenyl) carbamate** [Table 1, entry 12]



^{1}HNMR (200 MHz, $CDCl_3$) : δ 1.57 (s, 9H), 2.50 (s, 3H), 6.60 (brs, 1H), 7.15-7.65 (m, 5H).

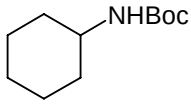
N – Boc phenyl alanine. [Table 1, entry 13]



IR : 3435.87, 3015.35, 2980.7, 1703.77 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.35 (s, 9H), 3.00 (m, 2H), 4.40 (brs, 1H), 7.37-7.48 (m, 5H).

Cyclohexyl carbamic acid tert-butyl ester [Table 1, entry 14]

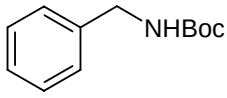


M.P. : 45ºC.

IR ($CHCl_3$) : 3345, 2979, 1705, 1504, 1393, 1169 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.00 – 1.45 (m, 11H), 1.50 (s, 9H), 3.15 (m, 1H).

Benzyl carbamic acid tert -butyl ester [Table 1, entry 15]

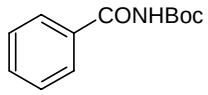


M.P. : 75ºC.

IR γ_{max} : 3348, 2978, 1712, 1525, 1369, 1169 cm^{-1}.

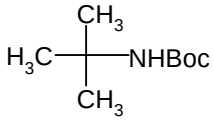
^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.50 (s, 9H), 4.50 (s, 2H), 5.50 (s, 1H), 7.20– 7.50 (m, 5H).

Benzamide carbamic acid tert -butyl ester [Table 1, entry 16]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.50 (s, 9H), 7.20-7.50 (m, 4H), 7.90 (d, J=8 Hz, 2H).

t-butyl carbamic acid tert-butyl ester [Table 1, entry 17]



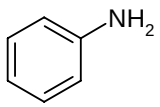
IR (nujol) : 3266.90, 2955.38, 1721.35, 1690.32 cm^{-1}.

^{1}H NMR (200MHz, $CDCl_3$)) : δ 1.27 (s, 9H), 1.41 (s, 9H).

General procedure for deprotection of amines

A mixture of N-Boc protected amine (l0 mmol), and 15% by wt. of catalyst H.β zeolite (preheated at 100^0C for 30 min per activation) in dichloroethane was refluxed till the reaction was complete (by TLC). On completion of the reaction, the catalyst was separated from reaction mixture by filtration, organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was chromatographed on neutral alumina column to afford the pure amine.

Aniline [Table 1, entry 1]



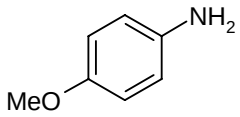
Yield 100%.

Appearance colourless liquid.

IR ($CHCl_3$) : 3515, 3500, 3100, 1640, 1480, 1290,1000,890,760cm^{-1}

^1H NMR (200 MHz, $CDCl_3$) : δ 3.57 (brs, 2H)), 6.62 (m, 2H), 6.73 (m, 1H), 7.08 – 7.20 (m, 2H).

4-Methoxy aniline [Table 1, entry 2]

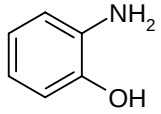


Yield 97%.

M.P. : 58-60ºC (Lit.[16] m.p. 57-60ºC).

IR ($CHCl_3$) : 3520, 3500, 2910, 1575, 1460, 1280, 1050, 820 cm^{-1}.

o-Aminophenol [Table 1, entry 3]



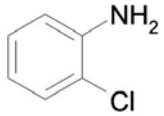
Yield : 71%.

M.P. : 173-175ºC (Lit[16] m.p. 176ºC).

IR (Nujol) : 3505, 3200, 2700, 1620, 1500, 1360, 1120, 900, 780, 670 cm^{-1}.

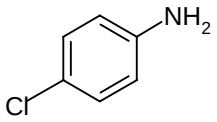
^1H NMR (200 MHz, $CDCl_3$) : δ 4.43 (brs, 2H)), 6.46-6.32 (m, 1H), 6.71-6.52 (m, 3H), 8.91 (brs. 1H).

2-Chloroaniline [Table 1,entry 4]



^1H NMR (200 MHz,$CDCl_3$) : δ 7.12 (s. 1H), 6.89-6.56 (m, 2H), 6.41-6.35 (m, 1H), 4.50 (brs, 2H).

4-Chloroaniline. [Table 1, entry 5]



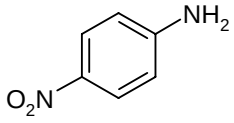
Yield : 98%.

M.P. : 69.5ºC (lit[16] m.p. 70ºC).

IR ($CHCl_3$) : 3612, 3510, 3320, 1570, 1420, 1280, 1120, 1000, 820 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$) : δ 3.62 (brs, 2H), 6.56 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H).

4-Nitroaniline. [Table 1, entry 6]



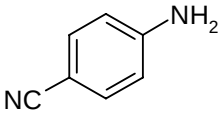
Yield : 94%.

M.P. : 147 – 149ºC (Lit[16] m.p. 150ºC).

IR ($CHCl_3$) : 3510, 3500, 2830, 1625, 1490, 1170, 835, 760 cm^{-1}.

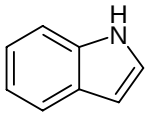
^{1}HNMR (200 MHz, $CDCl_3$) : δ 6.42 (brs, 2H), 6.63 (d, J = 8.9 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H).

4-Cyanoaniline [Table1, entry 7]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 4.00 (brs, 2H), 6.51 (s, 2H), 7.02 (s, 2H).

1H-Indole [Table 1, entry 8]



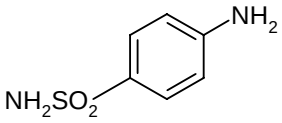
Yield : 97 %.

M.P. : 51-53ºC (Lit.[16] m.p. 53ºC).

IR (Nujol) : 3460, 3000, 1500, 1420, 1320, 1255, 1080, 870, 740 cm^{-1}.

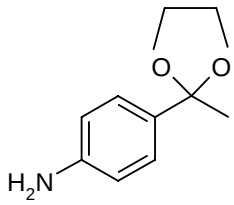
^1H NMR (200 MHz,$CDCl_3$) : δ 6.48-6.52 (m, 1H), 6.92-7.30 (m, 4H), 7.64 (m, 1H), 7.76 (brs, 1H).

4-Aminosulfonamide [Table1, entry 9]



^1H NMR (200MHz,$CDCl_3$) : δ 2.10 (brs, 2H), 4.00 (brs, 2H), 6.94 (d, J=9 Hz, 2H), 7.70 (d, J=8 Hz, 2H) .

4-(2-Methyl-[1, 3] dioxolan-2-yl)-aniline [Table 1, entry 10]

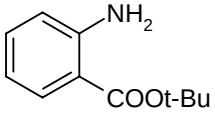


Yield : 64%.

IR (Neat) : 3500, 3363, 2967, 1589, 1043, 860 cm^{-1}.

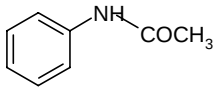
^1H NMR (200 MHz, $CDCl_3$) : δ 1.67 (s, 3H), 3.21 (brs, 2H), 3.83 (m, 2H), 4.10 (m, 2H), 6.74 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.9 Hz, 2H).

2-Aminobenzoic acid, tert-butyl ester [Table 1, entry 11]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.40 (s, 9H), 4.00 (brs, 2H), 6.73-7.79 (m, 4H).

Acetanilide [Table 1, entry 12]



^{1}H NMR (200 MHz, $CDCl_3$) : δ 2.50 (s, 3H), 7.20 (brs 1H), 7.50-8.50 (m, 5H).

2.4.6 References

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CHAPTER 2
(Section e)

SELECTIVE silylation of alcohols, phenols and naphthols with hmds catalyzed by H-β zeolite.

2.5.1 Introduction

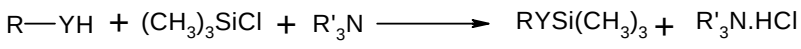
The importance of hydroxyl group functionality in organic chemistry is reflected by the continuous reports of methods for developing complex structures based on the chemical interconversion of this functional group. A limiting factor in some cases is the presence of more than one oxygen function of comparable reactivity in the molecule to be transformed. This difficulty is circumvented by the use of protective group which allows free manipulation of the desired functionality; however the difficulty involved in selectivity of protecting and of regenerating specific hydroxyl groups poses a challenge.

Since the introduction of silyl ethers in early seventies for protection of hydroxy groups, the use of organosilicon compounds as protective groups in organic synthesis has undergone an explosive development. Trimethylsilylation of organic compounds[1,2] having labile hydrogen atoms is a frequently used transformation in analytical and preparative organic chemistry. It is a frequently used protection method in multi-step synthesis of natural products due to the enhanced stability of the product under a variety of conditions, increased solubility in non-polar solvents, thermal stability and the ease of removal which is simply accomplished by acid or base induced hydrolysis giving only unreactive siloxane as byproduct. It is also used extensively for the derivatization of hydroxy compounds to increase their volatility for gas chromatography and mass spectrometry.

It can be advantageous to silylate an active material rendering it inactive and then at a later stage, by reaction with water, regenerate the active species plus the non-interfering hexamethyldisiloxane. For example, the antimicrobial lincomycin is used to treat fabric, paper etc. but has a limited solubility in the chlorinated solvents, ethers and vegetable oil as carriers. Silylation increases its solubility. The activity can be regenerated using aqueous acid.[2] In the development of liquid fuels from coal, TMS derivatives have been found to be useful for identification and analysis as well as separation and purification procedures. For example, it is possible to distill phenolic portions of coal hydrogenation products as TMS derivatives at atmospheric pressure without significant decomposition.

Styrene may be polymerized using peroxide initiators in the presence of silylated phenolic antioxidants thus avoiding the presence of phenolic compounds which would normally interfere with free radical process. The free antioxidant may be liberated in the polystyrene by immersion in hot dilute aqueous acetic acid.

Two general methods are available for silylations: reactions with chlorosilanes and a tertiary amine as acid acceptor and exchange reactions with silicon-nitrogen compounds functioning as silyl donors. The classical chlorosilane method employs a very powerful reagent mixture; the removal of hydrochloric acid in the form of its amine salt provides sufficient driving force to displace any reactive hydrogen on a heteroatom by silyl group (Scheme 1).

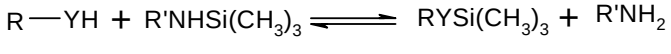


98 **99** **100** **101** **102**

Scheme 1 : Silylation using chlorosilane and tertiary amine

Separation problems stemming from the formation of amine salts and the corrosive nature of the reagents are the drawbacks of this method.

Silyl amines have long been used as alternative silylating agents. This silylation method is based on the relatively slow silyl-proton exchange between the silyl derivative of a low boiling amine or ammonia and mobile protons of the substrate. The reaction equilibria are shifted towards the product side by distillation of the amine (Scheme 2).

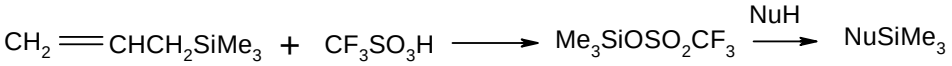


103 **104** **105** **106**

Scheme 2: Silylation using silyl amines

Although the exchange rates are enhanced by the addition of catalytic amounts of ammonium salts or chlorosilanes, silylations by this method require several hours at reflux temperature.

Recently a wide variety of methods using silylating agents such as N-alkyl substituted carbamates[3], bis-(trimethylsilyl)-trifluoroacetamide[4], allyl silanes with acid[5], bistrimethylsilyl ether[6] etc. are reported for silylation. However, these reagents require preparation from the corresponding silyl compound and the difficulty in removal of amine salts formed from the by-produced acid and the base added is frequently encountered. Moreover longer reaction time is an additional disadvantage of these reagents. To enhance the rate of reaction TMSOTf,[7] generated *in situ* from allyltrimethylsilane and trifluoromethanesulfonic acid, is used for silylation in the presence of base (Scheme 3).



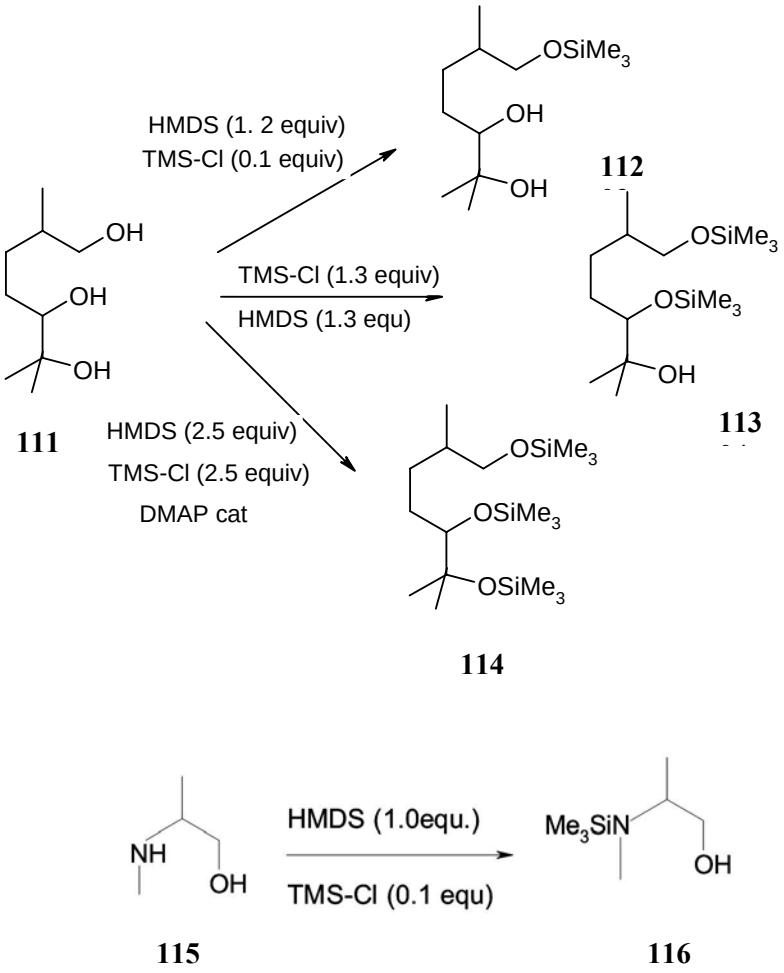
107 **108** **109** **110**

Scheme 3 : Silylation using *in situ* generated TMSOTf

However, the *in situ* preparation of TMSOTf requires the use of triflic acid, thus making the process expensive and environmentally hazardous.

1, 1, 1, 3, 3, 3-Hexamethyldisilazane (HMDS) is a stable commercially available substitute for trimethylsilylation of hydrogen labile substrates giving ammonia as the only byproduct. Silylation using this silazane type reagent is nearly neutral and does not need special precautions and products are separated from excess HMDS using simple techniques. However, the low silylating power of HMDS is a main drawback for its application, which needs forceful conditions and long reaction times in many instances. Hence, a variety of catalysts such as sulfonic acids,[8] nitrogen ligand complexes of metal chloride,[9] zirconium sulfophenyl phosphonate,[10] etc. have been reported for the silylation using HMDS .

J. Cossy and P. Pale[11] reported the use of a mixture of hexamethyldisilazane and chlorotrimethylsilane for the protection of alcohols, amines and acids. Depending on the quantities of these reagents a selectivity is observed for primary, secondary and tertiary alcohols as well as for amino alcohols (Scheme 4).



Scheme 4: Selective silylation with HMDS and TMS-Cl

Special types of catalysts having the general formula X NHY in which at least one of X and Y is an electron withdrawing group containing a CO, SO_2, or OP= moiety directly linked to the nitrogen atom and the other may be hydrogen or X and Y together represent such an electron withdrawing group, forming a cyclic system with the nitrogen atom are reported by Bruynes and Jurriens.[12] These catalysts when added in concentrations of 0.001-10 mol% to the reaction mixture as the sodium or trimethylsilyl derivative were found to effect trimethyl silylation of alcohols, phenols, carboxylic acids, hydroxamic acids, carboxylic amides and thioamides, sulfonamides, phosphoric amides, mono and di-alkylphosphates, mercaptans, hydrazines, amines, NH groups in heteroaromatic rings and enolizable β-diketones.

Firouzabadi and Karimi[9] found that HMDS in presence of catalytic amount of anhydrous zinc chloride silylates selectively different types of alcohols and phenols in refluxing acetonitrile or benzene-acetonitrile, whereas amines and thiols remain unaffected under the reaction conditions. However, $ZnCl_2$ is a very hygroscopic compound and the difficulty in handling restricts its use in reaction. [10]

A report using nitrogen ligand complexes of metal chlorides describes effective use of the catalysts like 2,2'-bipyridyl complexes of $ZnCl_2$, $FeCl_3$ and Fe(tpp)Cl for selective silylation of hydroxy groups with HMDS at room temperature in dry acetonitrile in the presence of other functional groups with replaceable hydrogen atoms.[13]

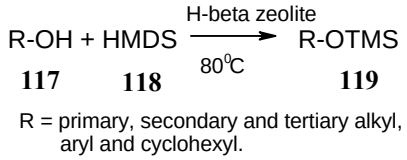
Heterogeneous strong lewis acid catalyst prepared from yttrium nitrate and zirconyl nitrate was reported to catalyze the trimethylsilylation of alcohols and phenols in dichloromethane in moderate to good yields.[14]

Montmorillonite K-10 is known to catalyze formation of trimethylsilyl ethers of a wide range of hydroxy compounds like primary, secondary and benzylic alcohols as well as phenols having electron donating substituents whereas electron withdrawing substituents inhibited the reaction.[15] Envirocat EPZG® a supported catalyst having both Lewis acid and Bronsted acid characteristics has been reported to chemoselectively silylate alcohols in acetonitrile in the presence of phenols, amines and thiols.[16] Most convenient protocol for laboratory scale derivatization accepted as green technology appeared recently[17] using microwave irradiation under solvent free conditions.

2. 5. 2 Present work

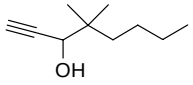
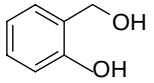
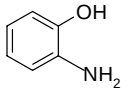
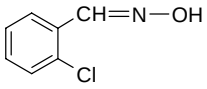
Growing concern for the environment demands the development of eco-friendly and economic processes. As a result, there has been considerable upsurge of interest in the area of developing solid catalysts and their subsequent application for various organic transformations. Zeolites, due to their acidic and shape selective nature, have been found to be a suitable replacement for various homogeneous acid catalysts.

An efficient solvent free silylation of alcohols, phenols and naphthols with HMDS catalyzed by commercially available H-β zeolite providing heterogenous reaction conditions is presented in this section.



Scheme 5: H-β zeolite catalyzed trimethylsilylation of alcohols and phenols

TABLE 1 : H-β zeolite catalyzed selective protection of alcohols and phenols as their silyl ethers

Entry No.	Substrate	Subs./ HMDS ratio	Stirring in toluene at r.t.		Heating at 80^{0}C without solvent	
			Time (h)	Yield[a] %	Time (h)	Yield[a] %
1	n-Octanol	1:0.6	8	96	1.3	98
2	$MeOOC—(CH_2)_6—CH_2OH$	1:0.6	8	96	1.5	95
3	Allyl alcohol	1:0.6	7	97	1.5	98
4		1:0.6	15	85	2.5	96
5	Cyclohexanol	1:1	12	95	2.0	98
6	*tert*-Butanol	1:0.6	30	45	2.5	70
7	Benzyl alcohol	1:0.6	5	95	1.3	97
8		1:0.6	9	91	1.5	95
9	Phenol	1:1.5	10	87	1.5	90
10	Resorcinol	1:0.75	10	76	1.5	89
11	*m*-Cresol	1:1.0	12	76	1.7	91
12	α - Naphthol	1:0.75	12	67	2.5	90
13		1:1	15	92	2.0	92
14		1:0.75	15	80	2.0	91
15	Aniline	1:0.75	5.0	-	30	-
16	Benzylamine	1:0.75	5.0	-	30	-
17	Thiophenol	1:0.75	5.0	-	30	-

[a] Isolated yield, products confirmed by comparision with IR, ^{1}H NMR of authentic samples.

2.5.3 Results and Discussion

Initially we conducted blank experiments without the H-β zeolite as the catalyst and found the reactions to be sluggish (~7-15 h). Silylation of m-cresol without catalyst yielded only 25% of the product in 4 hours. Silylation of phenol and benzyl alcohol using HMDS in toluene at ambient temperature in presence of H-β zeolite (10% w/w) was performed which took about 10 hours and 5 hours for completion respectively. Same experiments were then repeated at 70-80ºC to collect the corresponding products in comparable yield in more or less similar time period. However, neat reaction without any solvent enhanced the yield in much shorter duration and the derivatization was complete in ~1.5 h.

The selectivity and versatility of thermal solvent free recipe was further confirmed by application of the general procedure given below for various examples shown in Table 1. In a typical general procedure, a neat mixture of hydroxy compound, HMDS and 10% (w/w) H-β zeolite was heated at 80ºC till the reaction was complete (TLC). After completion of reaction ethyl acetate was added and catalyst filtered. The filtrate was concentrated and pure product was obtained either by distillation under reduced pressure or by column chromatography on neutral alumina.

A wide range of structurally diverse and functionalized alcohols, phenols and naphthols underwent silylation by this procedure to provide the corresponding TMS ethers in excellent isolated yields as shown in Table 1, whereas amines (Table 1, entries 13, 15, 16) and thiol (Table 1, entry 17) remained unaffected under the reaction conditions. The product of entry 13 in Table 1 was o-silyloxy aniline which indicated that only phenolic OH was silylated and not the NH_2 group. Table 1 also displays a comparison of the results obtained by silylation at room temperature in toluene with those carried out under solvent free conditions at elevated temperature. It is noteworthy from Table 1 that primary alcohols were silylated more easily than secondary alcohols and phenols. Tertiary alcohols however gave low yields (Table 1, entry 6).

Heating increased the rate of reaction reducing the reaction time from several hours to 1 to 2 hours and obviated the need for solvent. The efficacy of H-β zeolite as a catalyst can be clearly visualized in the case of unsaturated alcohols (Entries 3 and 4) where the corresponding silyl ethers were obtained in

excellent yields. After the reaction, the catalyst was recovered with retention of its catalytic activity. It can be further reactivated for reuse by heating at 100ºC for one hour in presence of air.

2.5.4 Conclusion

A facile heterogeneous catalytic method for the selective silylation of a variety of hydroxy compounds in presence of amino and thiol group using H-β zeolite has been developed.

The present solvent free procedure provides a practical and viable green technology of selective, solvent free silylation of hydroxyl group in presence of amines and thiols. This method has the advantage of simplicity in operation and mild reaction conditions tolerable to acid sensitive functionalities, cost efficiency, increased yields and environment friendliness. The observed efficient performance of H-β zeolite may be attributed to its large pore opening, three dimensional channel system and the high concentration of acid sites.[18] The solvent free conditions and the reusability of the catalyst make this method cost effective. The obvious advantages of heterogeneous catalysis in terms of easy separation, consistent yields and recyclability of the catalyst are note worthy. Thus the present catalytic method should prove to be a useful addition to synthetic organic chemistry.

2.5.5 Experimental

Commercially available alcohols, amines and thiols were distilled before use. HMDS was purified by fractional distillation. H-β zeolite was procured as a gift from United Catalyst India Ltd. (UCIL) Mumbai, SiO_2/Al_2O_3 – 30, surface area – 700 m²/g, pore diameter = 7.6 × 6.4 Aº. Prior to use it was calcined at 110ºC for 2 hrs. Infrared spectra were recorded on an ATIMATTSON RS-1 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer.

Silylation in toluene or dichloromethane

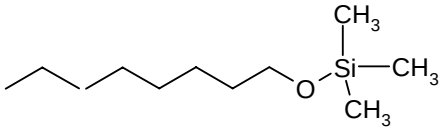
A mixture of alcohol (1 mmol), HMDS (0.6 mmol) and H-β zeolite (10% w/w) in toluene (10 ml) was stirred at room temperature and the reaction progress was monitored by TLC. After complete conversion was observed (TLC), the catalyst was filtered off and the solvent was removed under reduced pressure. The residue obtained was passed through a column of neutral alumina to collect the trimethyl silylether. The products were characterized by IR and NMR spectroscopy.

Preparation of trimethyl silyl ether at 80ºC

A neat mixture of alcohol (1 mmol), HMDS (0.6 mmol) and H-β zeolite (10% w/w) was heated at 80^{0}C till completion of reaction (monitored by TLC). After completion of the reaction, ethyl acetate was added, reaction mixture was filtered and filtrate was concentrated. The product was then purified by column chromatography on neutral alumina to yield trimethyl silyl ether as a colorless liquid (90 - 98%). The products were characterized by IR and NMR spectroscopy.

The same procedure was followed for the preparation of all TMS ethers using H-β zeolite at 80^{0}C as listed in Table 1. All the TMS ethers prepared in the present work are well known compounds and are easily identified by the IR, ^{1}H NMR spectra as well as boiling point comparison with the reported data.

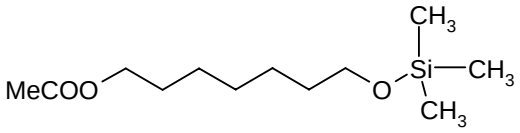
Trimethyl silyloxy octane [Table 1, entry 1]



IR ($CHCl_3$) **:** 2957.18, 2930.26, 2858.35 1252.62, 1215.83, 833.55, 760.18, 581.12, 463.05, 411.73, 422.70, 433.72, 447.87 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.06 (s, 9H), 0.089 (t, J=6Hz, 3H), 1.28 (m, 10H), 1.52 (t, J=6Hz, 2H), 3.56 (t, J=7 Hz, 2H) .

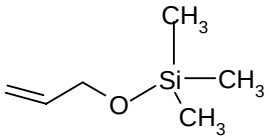
Methyl 8-trimethylsilyloxyoctanoate [Table 1, entry 2]



IR ($CHCl_3$) **:** 2934.0, 2859.0, 2357.3, 1717.5, 1695.8, 1436.9, 1250.8, 843.0, 748.8, 668.3 cm^{-1}.

^{1}HNMR (200 MHz,$CDCl_3$) **:** δ 0.06 (s, 9H), 1.38 (t, J=6 Hz, 4H), 1.59 (m, 4H), 2.31 (t, J=7 Hz, 2H), 3.63-3.55 (m, 4H), 3.66 (s, 3H).

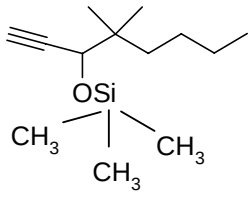
Trimethyl [1-(2-propenyloxy)] silane [Table 1, entry 3]



IR ($CHCl_3$) **:** 2925.3, 2357.3, 2330.3, 1730.0, 1251.7, 843.3, 667.8, 436.4, 419.0 cm^{-1}.

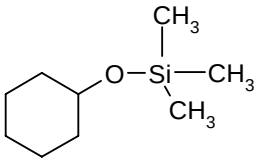
^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.06 (s, 9H), 4.13 (d, J = 6Hz, 2H) , 5.13-5.20 (m, 2H), 5.91-6.08 (m, 1H).

Trimethyl [3-(4, 4-dimethyl-1-octynyloxy)] silane [Table 1, entry 4]



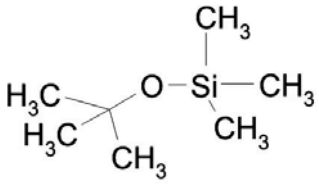
^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.06 (s, 9H), 0.95 (s, 6H),1.05 (t, J=6Hz, 3H), 1.19- 1.28 (m, 6H), 2.42 (s, 1H), 4.06 (s, 1H).

Trimethyl (1-cyclohexyloxy)silane [Table 1, entry 5]



^{1}HNMR (80 MHz) **:** δ 0.01 (s, 9H), 0.70 – 1.05 (m, 4H), 1.70 – 1.90 (m, 4H), 3.50 – 3.70 (m, 3H).

Trimethyl (tert-butyloxy) silane [Table 1, entry 6]

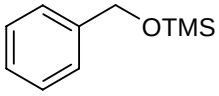


Bp **:** 101ºC .

IR (Neat) **:** 2980, 1380, 1270, 1220, 1170, 940, 870, 770, 540, 410, 380 cm^{-1}.

^{1}HNMR (60 MHz, $CDCl_3$) **:** δ 0.03 (s, 9H), 1.20 (s, 9H).

Trimethyl (benzyloxy) silane [Table 1, entry7]

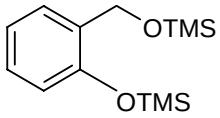


Bp **:** 51ºC / 2mmHg

IR (Neat) **:** 1450, 1380, 1250, 1080, 860, 750, 700, 410, 380 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.09 (s, 9H), 4.70 (s, 2H), 7.20 (m, 5H).

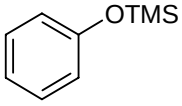
Trimethyl (2'-trimethylsilyloxy benzyloxy) silane [Table 1, entry 8]



IR ($CHCl_3$) **:** 3070, 3040, 2960, 1600, 1582, 1490, 1452, 1380, 1258, 1120, 1080, 928, 848, 760 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.18 (s, 9H), 0.30 (s, 9H), 4.71 (s, 2H), 7.50 – 6.72 (m, 4H).

Trimethyl (phenyloxy) silane [Table 1, entry 9]

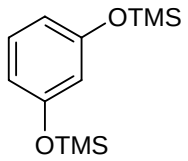


Bp **:** 182ºC / 742 mmHg.

1R (Neat) **:** 3040, 2980, 1600, 1500, 1260, 1180, 1080, 950, 770, 700, 520, 400 cm^{-1}.

^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.26 (s, 9H), 6.64-6.91 (m, 3H), 7.00 – 7.24 (m, 2H).

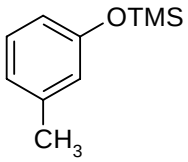
1, 3 – Bis (trimethyl silyloxy) benzene [Table 1, entry 10]



1R (Neat) **:** 2980, 1620, 1250, 1080 cm^{-1}.

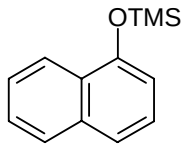
^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.29 (s, 18H), 6.10-6.21 (m, 3H), 6.90-6.93 (m, 1H).

Trimethyl [1-(3-methylphenyloxy)] silane [Table 1, entry 11]



^{1}HNMR (200 MHz, $CDCl_3$) **:** δ0.20 (s, 9H), 2.30 (s, 3H), 6.60-6.69 (m, 2H), 6.75 (d, J=4 Hz, 1H), 7.10-7.19 (m, 1H).

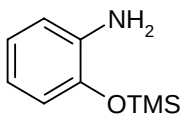
Trimethyl (1-naphthyloxy) silane [Table 1, entry 12]



B p **:** 272ºC / 74 mmHg.

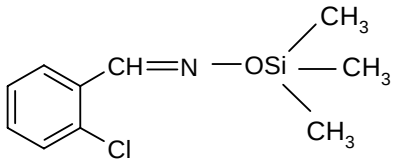
^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.25 (s, 9H), 6.70-6. 78 (m, 1H), 7.20 – 7.30 (m, 1H), 7.40 – 7.50 (m, 3H), 7.80-7. 84 (m, 1H), 8.15-8. 21 (m, 1H).

Trimethyl [1-(2-aminophenyloxy)] silane [Table 1, entry13].



^{1}HNMR (200 MHz,$CDCl_3$) **:** δ 0.33 (s, 9H), 3.70 (brs, 2H), 6.67-6.80 (m, 4H).

2- Chlorobenzaldehyde oxime trimethylsilyl ether [Table 1, entry14]



^{1}HNMR (200 MHz, $CDCl_3$) **:** δ 0.32 (s, 9H), 7.27 -7.37 (m, 3H) ,7.95-8.05 (m, 1H), 8.63 (s, 1H).

2.5.6 References

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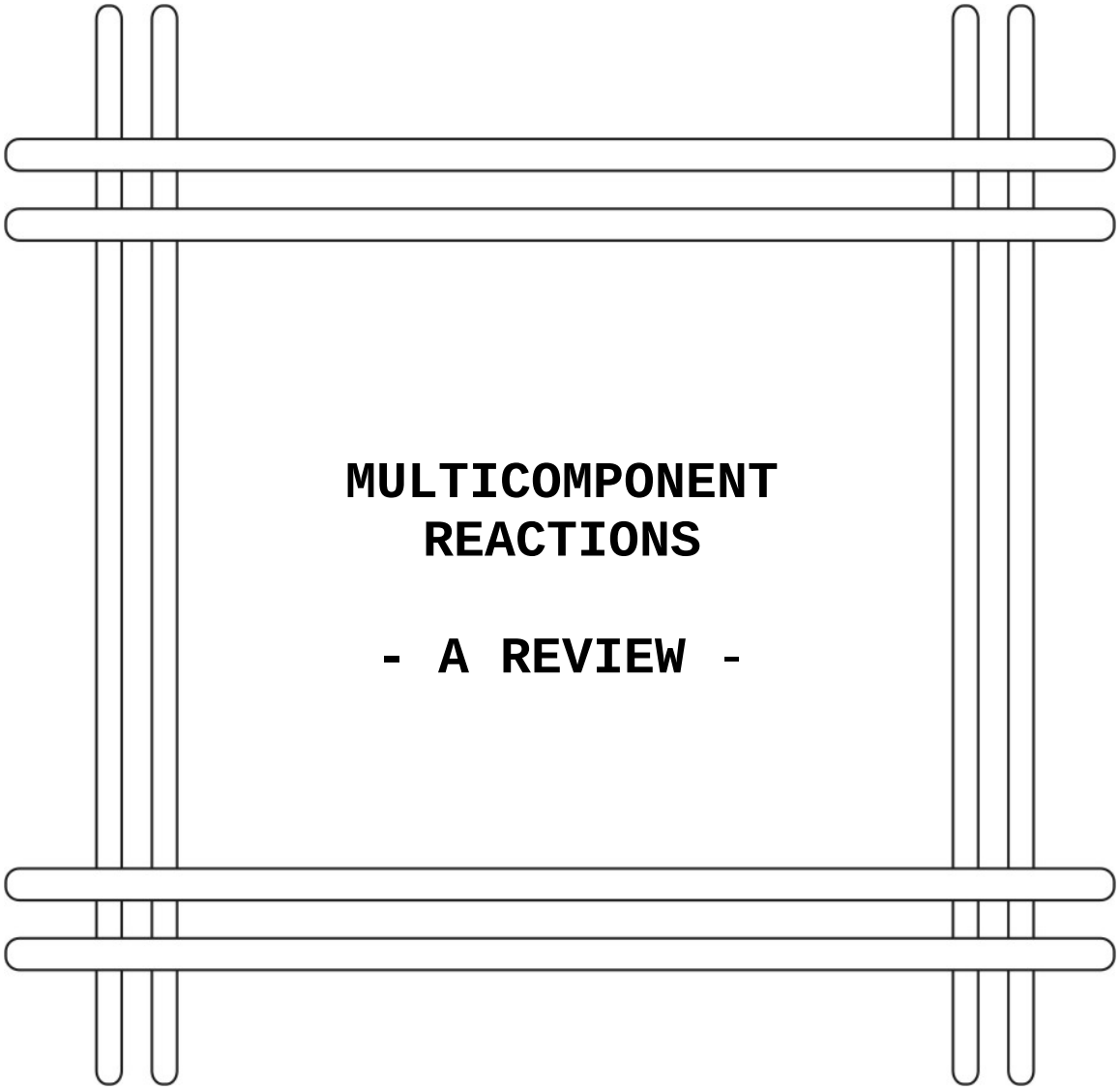
CHAPTER 3

MULTICOMPONENT REACTIONS

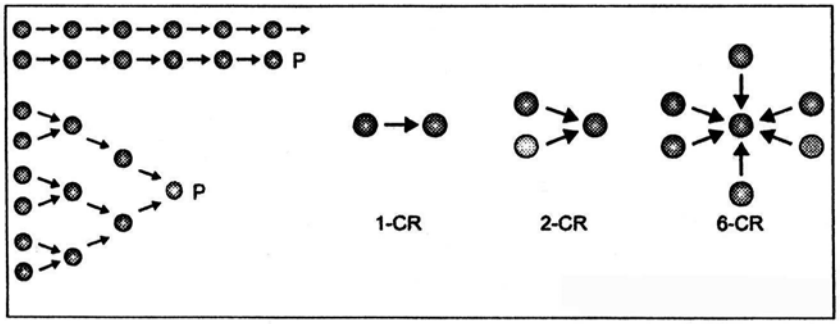


MULTICOMPONENT REACTIONS

- A REVIEW -

MULTICOMPONENT REACTIONS

A major challenge of modern drug discovery is the design of highly efficient chemical reaction sequences which provide a maximum of structural complexity and diversity in the product with a minimum number of synthetic steps. Multicomponent reactions (MCR) - reactions of more than two starting materials, provide a powerful tool towards the one-pot synthesis of diverse and complex molecules as well as small and drug like heterocycles.



Divergent and convergent synthesis

The conventional divergent synthesis where more than two educts are converted into product require a sequence of chemical reactions where the product of last step is the starting material of the next step. The intermediate or final product must be isolated and purified after each step resulting in decrease of overall yield of product. The use of protecting groups in traditional approaches towards the synthesis of complex molecules is hard to avoid, adding additional protection and deprotection steps to the overall synthesis. By using convergent synthesis i.e. multicomponent reactions, the target molecule is built up by the assembly of key intermediates and one may avoid these additional steps, allowing the assembly of complex structures by simple one-pot procedures. In times where a premium is put on speed, diversity and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional synthesis like superior atom economy, simple procedure, one pot character and large number of accessible backbone of target molecules.[1]

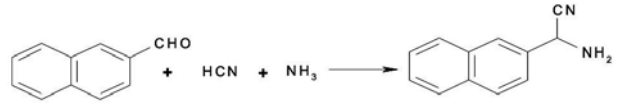
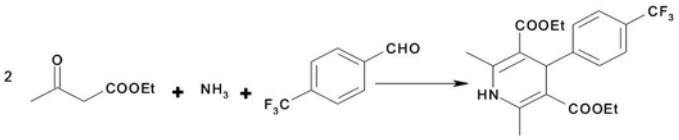
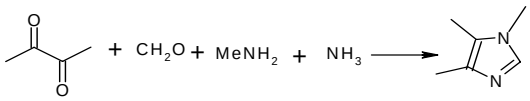
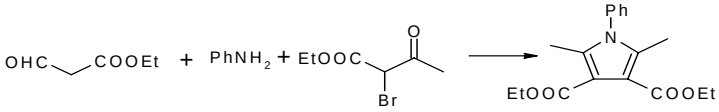
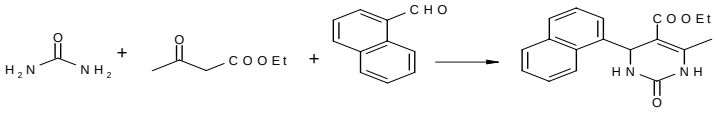
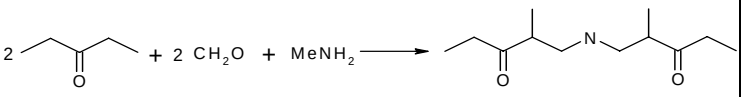
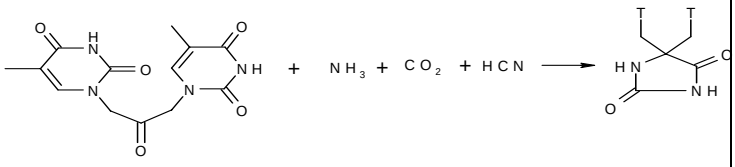
Types of multicomponent reactions

Three different types of MCRs exist. MCRs of type I are collections of equilibria between all participating subreactions, including the last step which forms the final product. MCRs of type I are usually three component reactions (3CRs) that form their products from ammonia or amines, carbonyl compounds and neutral nucleophilic compounds or anions of weak acids. In type II the educts and intermediate products equilibrate, but the final product results from a practically irreversible final reaction step e.g. : Hantzsch or Biginelli reaction for heterocycles. MCRs of type III correspond to sequences of irreversible reactions that all proceed towards the product. Few MCR of type III are known in preparative chemistry whereas in living cells most products are formed by biochemical MCRs of type III.

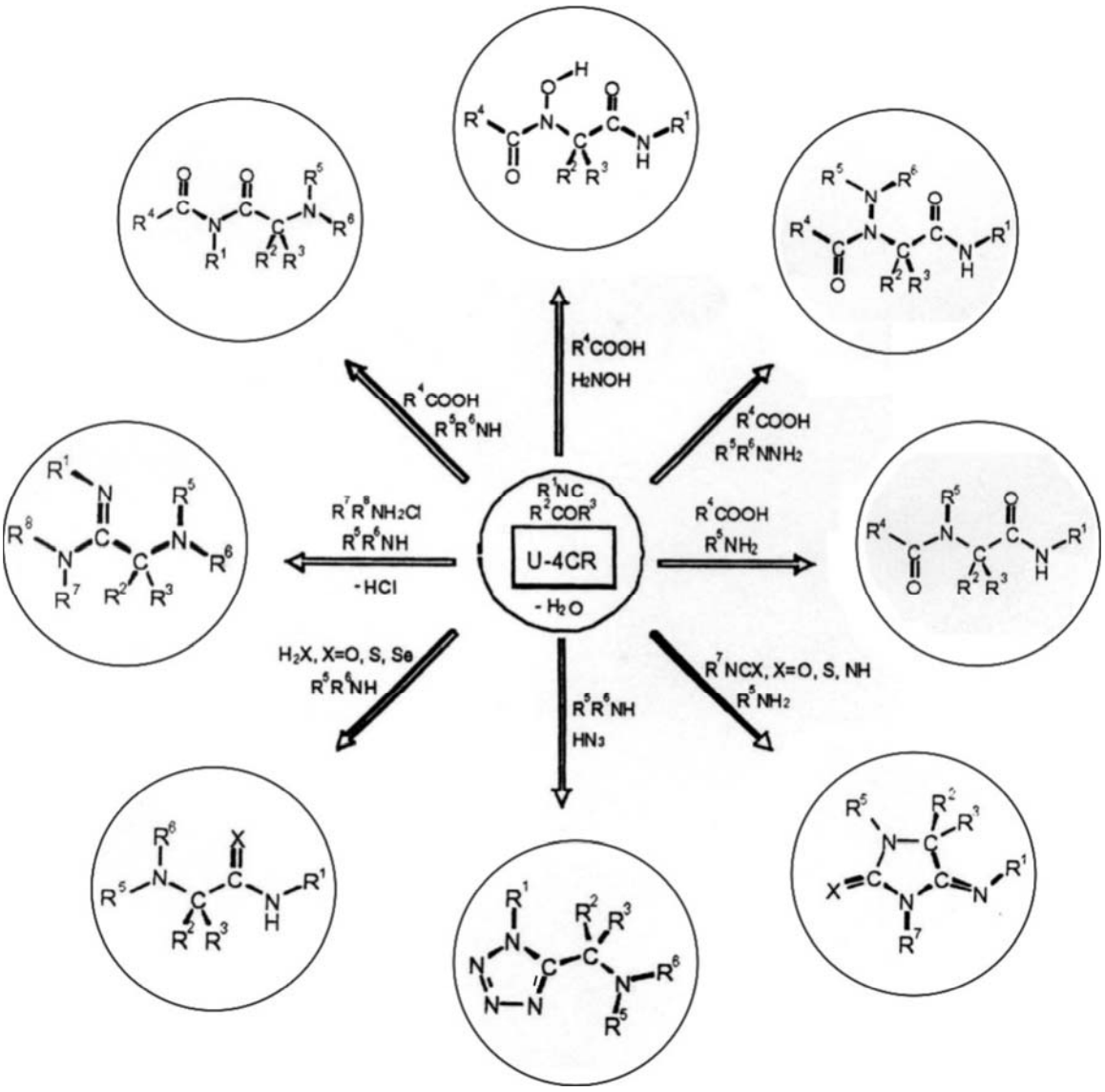
History of MCRs

The first MCRs were accomplished in 1838 when Laurent and Gerhardt[2] formed the benzoylazotide from bitter almond oil and ammonia *via* benzaldehyde and hydrogen cyanide. The chemistry of the MCRs officially began twelve years later when Strecker[3] introduced the general formation of α-aminocyanides from ammonia, carbonyl compound and hydrogen cyanide. The preparation of heterocyclic compounds by MCRs was introduced in early 1880.[4]

Table 1. Historically significant MCRs based on the reactivity of carbonyl or imine groups [5]

Name of the reaction	Year of discovery	Example
Strecker synthesis	(1838) 1850	 **1**
Hantzsch dihydropyridine synthesis	1882	 **2**
Radziszewski imidazole synthesis	1882	 **3**
Hantzsch pyrrole synthesis	1890	 **4**
Biginelli reaction	1891	 **5**
Mannich reaction	1912	 **6**
Bucherer - Bergs hydantoin synthesis	1941	 **7**

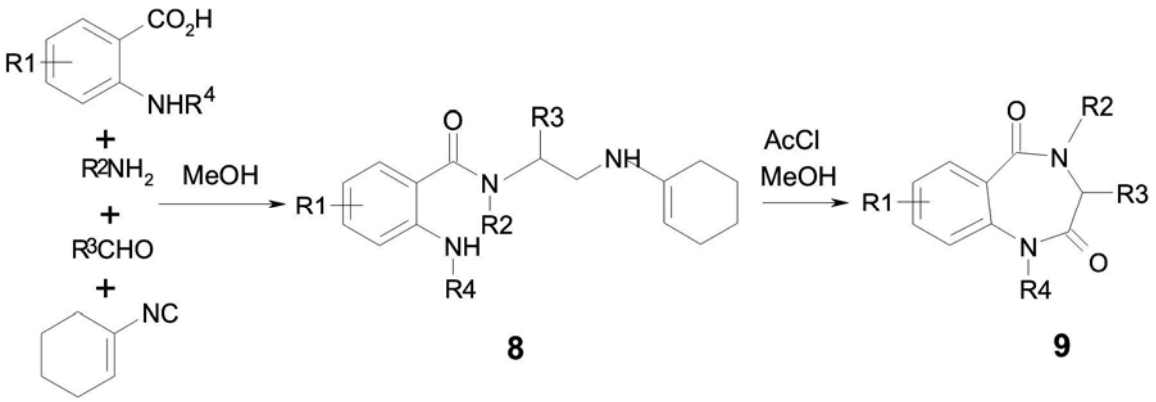
The classic reaction between carboxylic acids, oxo compounds and C-isocyanides described by Passerini in 1921 and later given his name; opens the access to α-acyloxycarboxamide in one step. In 1959 Ugi *et al.* described the most important variants of the four component condensation, the U-4CRs and within few weeks most of the condensation types known today were discovered. In 1960 Hellmann and Opitz[9] introduced their α-Aminoalkylierung book where it was mentioned that majority of the MCR 'name reactions' belong together since they all consist of similar processes. They are α-aminoalkylations of nucleophilic compounds (MCR type I) or they form in related reactions intermediate products that react with further educts in a final ring closure step. The MCRs of the isocyanides are type II reactions whose irreversible step is always an α -addition of a cation and an anion onto the C^{II} of the isocyanides. Subsequently their α-adducts rearrange into their final products. The educts of this Ugi reaction are amine (ammonia, mono and disubstituted amines, hydroxylamine, hydrazine and its suitable derivatives), carbonyl compounds, acid components and related compounds (water, thiol, hydrogen selenide, hydrazoic acid, hydrogen cyanate and thiocyanate, aminocyanic acid, carboxylic acids and thioacids, alkoxycarboxylic acids and amines) and isocyanides. The educts and products of this Ugi reaction abbreviated as the U-4CR, are more variable than those of any other reaction, since not only products with different substituents on a similar skeleton are obtained, like in usual chemical reactions, but also the skeletons of the products can structurally differ. The skeletons of the U-4CR products are essentially determined by their amine and acid components[10] as shown in scheme 1.



Scheme 1 : The variability of U-4CR products

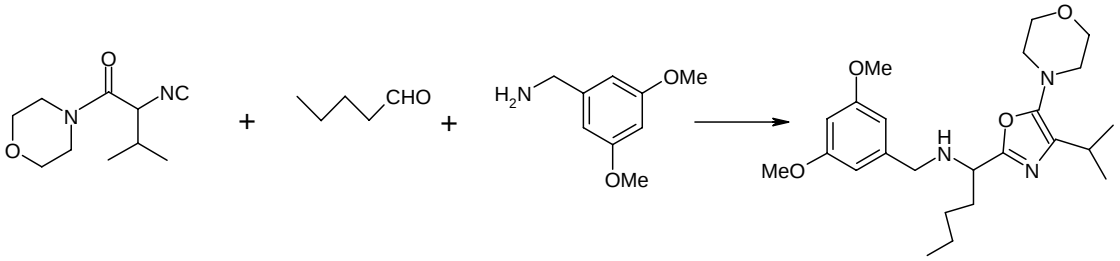
An increasing number of industries began to produce and to investigate the libraries of pharmaceutically active compounds. A series of recently reported multicomponent reactions with a subsequent transformation are used for synthesis of biologically active molecules as shown below:

Ugi MCC–employed a convertible isocyanide to afford a triply variable benzodiazepine in two steps[6](Scheme 2). This condensation was further developed by Armstrong *et al.*[11] for application to combinatorial libraries.



Scheme 2 : Synthesis of benzodiazepines by Ugi multicomponent condensation

Zhu *et al.*[12] introduced a novel MCR of α-substituted isocyanoacetic acid amides, primary amines and aldehydes or ketones to yield polysubstituted 5-amino oxazoles. The intermediate U-3CR product cyclizes under reflux conditions in ethanol to the corresponding oxazole (Scheme 3).

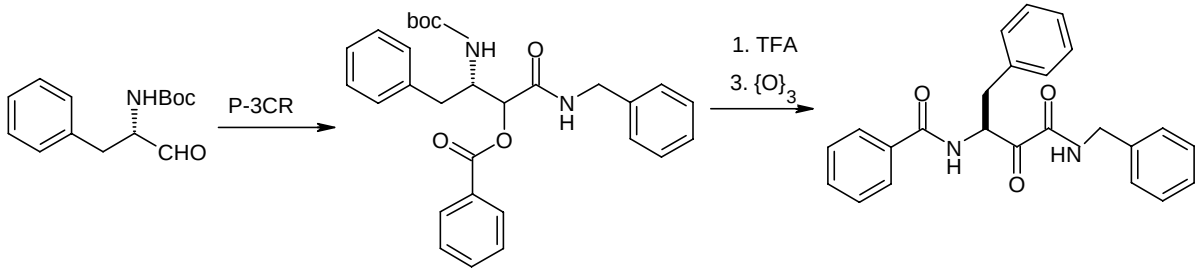


10

Scheme 3 : Synthesis of polysubstituted 5-amino oxazoles

Banfi *et al.*[13] described the use of the Passerini three-component reaction (P- 3CR) (Scheme 4) to get rapid access to α-ketoamides. Protected α-amino acid derived aldehydes react in a classical P-3CR to give the corresponding α-aminoacyl amides. Deprotection of the amine and subsequent acyl migration results in N-(2-hydroxy-3-oxobutyl)- N-methyl acetamides which upon oxidation give N- (2, 3-dioxobutyl)-N-

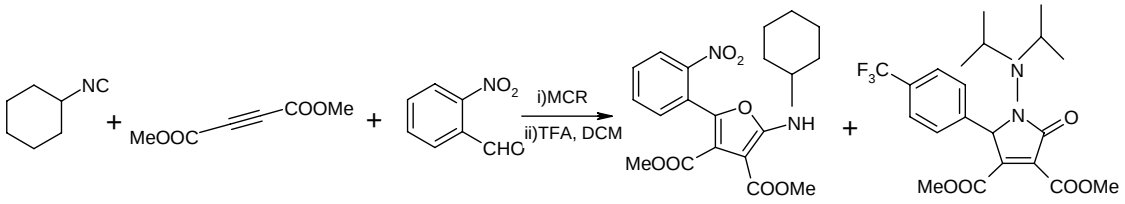
methyl acetamides. Such α-ketoamides are found as ubiquitous fragments in various biologically active natural products and drugs e.g. FK-506 derivatives.[13]



11 **12**

Scheme 4 : Synthesis of α-ketoamides

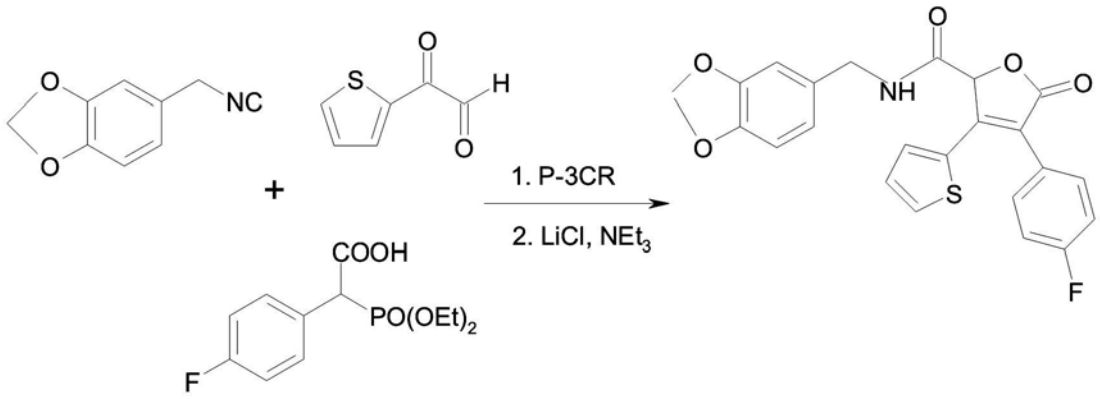
Nair and co-workers[14] exploited the reaction between isocyanide, rarely used N-isocyanides, acetylendicarboxylic acid diesters and aldehydes to yield smooth formation of 2-aminofuranes and 3 (5H) – pyrroline-2-ones (Scheme 5).



13 **14**

Scheme 5 : Synthesis of 2-aminofuranes and 3(5H)-pyrroline-2-ones

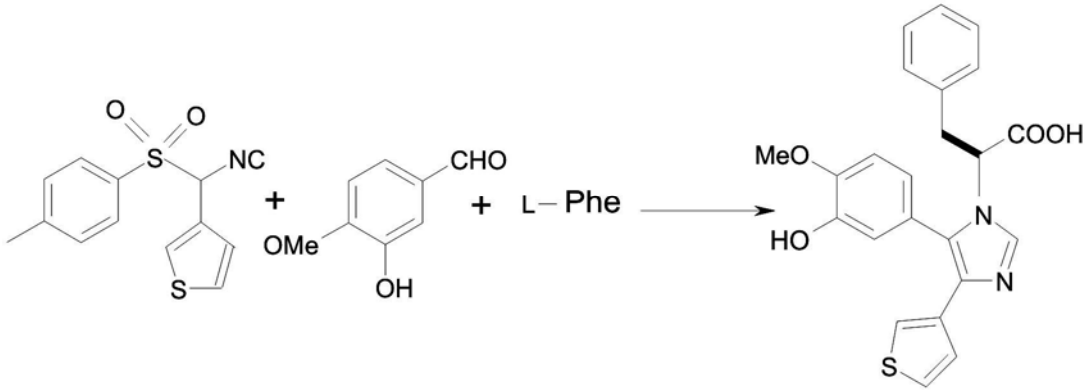
Butenolides are ubiquitous moieties in many natural products. A novel MCR by using α-ketoaldehydes, isocyanides and α-substituted phosphonoacetic acid diethyl esters to yield 5-carboxy amide is shown below (Scheme 6).[15] In this sequence the first reaction is a P-3CR and the second a Wittig reaction.



15

Scheme 6 : Synthesis of butenolides by P-3CR followed by Wittig reaction

The Van Leusen's imidazole synthesis has been used for last 20 years (Scheme 7).



16

Scheme 7 : Van Leusen's imidazole synthesis

However the systematic research performed by this group greatly broadens the scope of this reaction.[16] The unprotected functional groups like alkyl-OH, phenyl – OH, aldehyde, ketone, carboxylic acid, amide, secondary amine, tertiary amine, nitrile are compatible with the reaction.

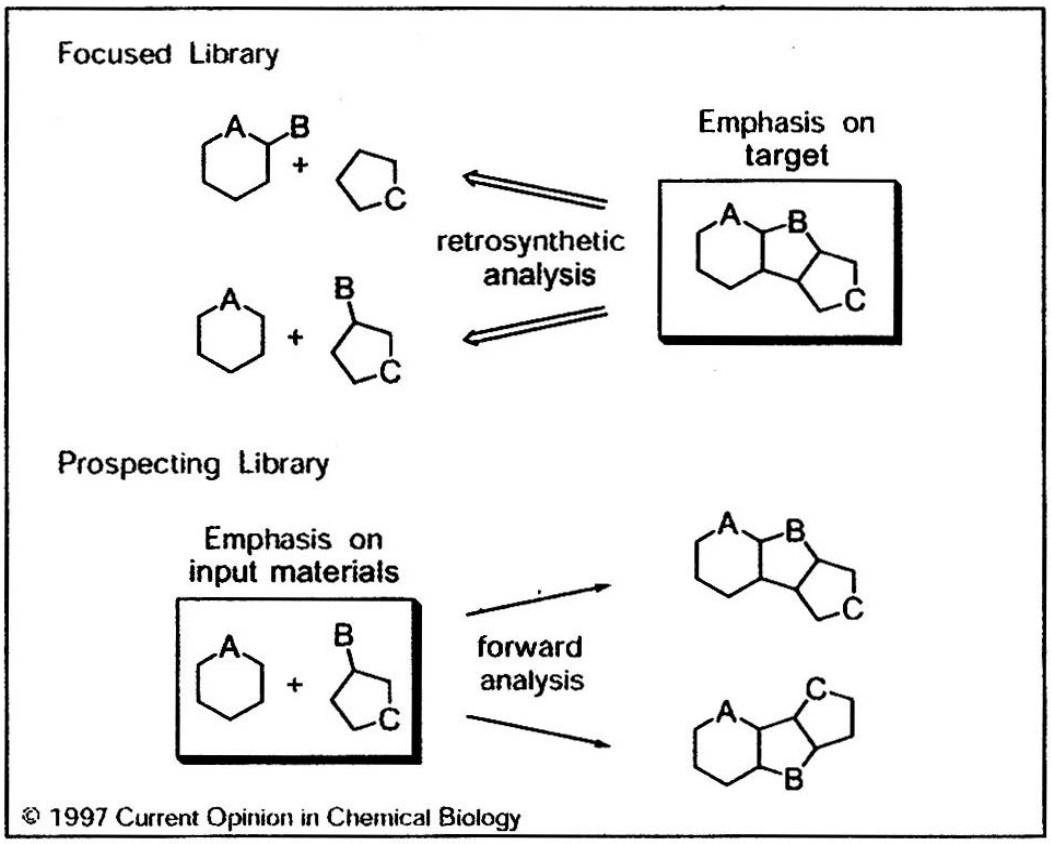
Combining an MCR with a subsequent secondary reaction is a powerful concept. MCR reaction conditions are usually compatible with a number of orthogonal functional groups that do not participate in the primary MCR. These functional groups can then serve as a

starting point for a secondary transformation thus allowing the assembly of complex structures by simple procedures.

The chemical industry recognized the advantages of the U-4CR and related MCRs for the effective synthesis of many compounds compared to conventional multistep syntheses, and subsequently the former were used for the creation of substance libraries. In recent years the industrial search for new desirable compounds from semi-automatically liquid or solid phase libraries of the U-4CR has been developed further. A large number of products i.e. libraries can be synthesized by varying the substituents in these educts.

Multicomponent reactions are very useful in constructing focused as well as prospecting libraries of novel organic structures. The focused library often called targeted, directed or biased libraries are made up of analogs of a compound with known biological activity (a 'lead') and are used to identify alternatives to this structure and to expand structure – activity relationships. Such compounds are typically accessible by known routes which are modified for the library format. Reaction that generates multiple linkages in one transformation are extraordinarily powerful in introducing complexity quickly. Their value is all the greater for prospecting libraries since a premium is placed on reducing the total number of transformations, to ensure adequate yield and purity.

For many biological systems of interest, no lead is known, or an entirely new one is sought; libraries of novel structure that might produce such leads are therefore needed and are sometimes called 'random' or prospecting libraries. Libraries of compounds that are deemed at the outset to be more 'drug-like' are more favored, comprising known pharmacological motifs, as described above or simply exhibiting some intuitively appealing combination of molecular weight, polarity, conformational constraint, novelty, diversity etc. In drug discovery, the prospecting library provides a reservoir of potential leads and subsequent cycles of optimization are handled by appropriately narrowed focused libraries.[6]



Conceptual difference between synthetic strategies for focused and prospecting library

The Libraries of U - 4CR products were described in 1961 by Ugi and steinbrückner[7] but this field was largely ignored for many decades. In 1995, Weber *et al.*[8] published the first industrial libraries of U-4 CR products; from which they found two thrombine inhibitors whereas the search for such products by the then conventional methods was not successful for a decade.

In recent years the industrial search for new desirable compounds by semi-automatically formed libraries has been developed further. When an interesting compound has been found, MCRs also offer the possibility of preparing large quantities of the preferred products. It is usually necessary to find out the optimal reaction conditions in order to obtain a maximal yield of the product.

Conclusion

The enormous potential of MCRs in modern drug discovery has led to the increasing demand for novel MCRs. Though the current emphasis in the library synthesis using MCR is concentrated on translating known chemistries to solid phase and in preparing focused libraries, the need for prospecting libraries is growing rapidly. From examples of their design and synthesis, a specific strategy for combinatorial synthetic design can be discerned : a powerful and general reaction that forms several bonds in one step is employed as the key transformation and a substrate is assembled in an efficient sequence that incorporates a variety of common input materials. The implementation of this strategy promises the same opportunities for creativity and elegance as that of conventional, target-directed organic synthesis.

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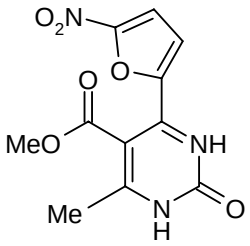
CHAPTER 3
(Section A)

Synthesis of Dihydropyrimidinones by Biginelli reaction

3.1.1 Introduction

In the past decade dihydropyrimidinones have become increasingly significant due to their remarkable pharmacological properties.[1] A broad range of biological effects have been ascribed to these partly reduced pyrimidine derivatives, e.g. Nitractin **17** is known to exhibit both antibacterial as well as antiviral activity against viruses of trachoma group.[2] Recently appropriately functionalized DHPMs have emerged as antitumor[3] compound (e.g. **18)** or anti-inflammatory analgesic,[4] α_{1a} selective antagonists and antihypertensive agents.



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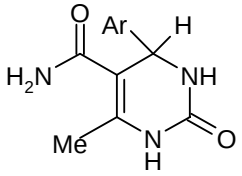
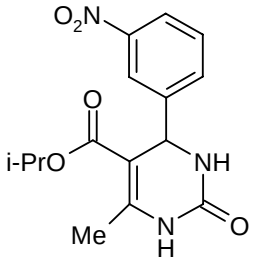
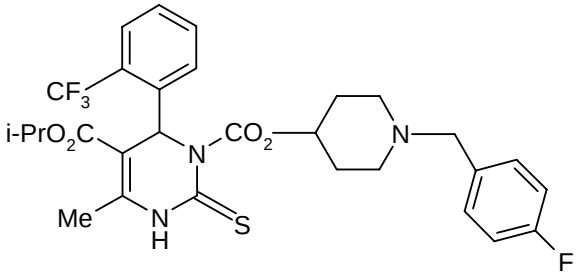


18

This is not surprising since DHPMs may be regarded as aza analogs of dihydropyridines of the Nifedipine type. DHPMs like SQ 32926 (**19)** and SQ 32547 (**20)** are known to be effective Ca channel blockers.[5] Apart from their use as antihypertensive agents, dihydropyrimidine calcium channel blockers are also of interest as agents for treating anxiety[6] and optic nerve dysfunction.[7]

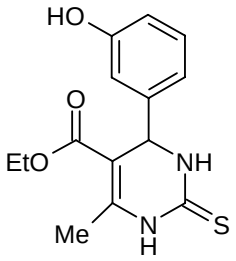


SQ 32926 (19)



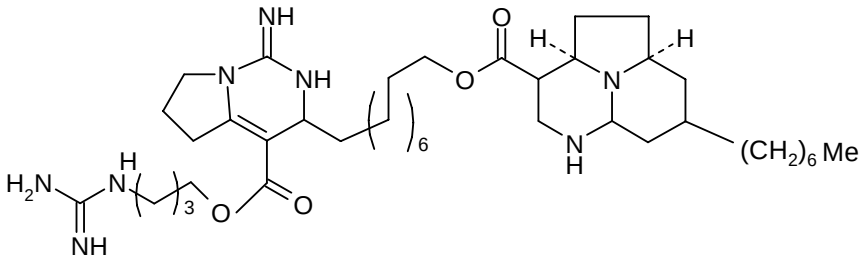
SQ 32547 (20)

A very recent highlight in this context has been the identification of the structurally rather simple DHPM, Monastrol (**21**) as a novel cell permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest. Monastrol specifically inhibits the kinesin motor protein[8] and can be considered as a new lead for the development of anticancer drugs.



21

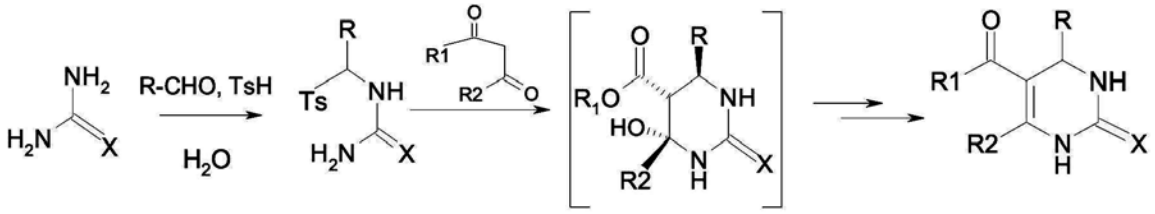
Apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated. Most notable among these are the Batzelladine alkaloids A and B (e.g.**22)** which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and therefore are potential new leads for AIDS therapy.[9]



22

These interesting activities exhibited by DHPM have attracted the attention of researchers for discovery of more and more practical routes for their synthesis. Shutalev *et al.*[10] have described a synthesis of DHPM based on condensation of readily available α–tosyl-substituted-thioureas **23** (X=S) with the (*in situ* prepared) enolates of acetoacetates or 1, 3-dicarbonyl compounds. The resulting hexahydropyrimidines **24** need not be isolated and can be converted directly to DHPMs **25** (Scheme 1). This method works well for aliphatic

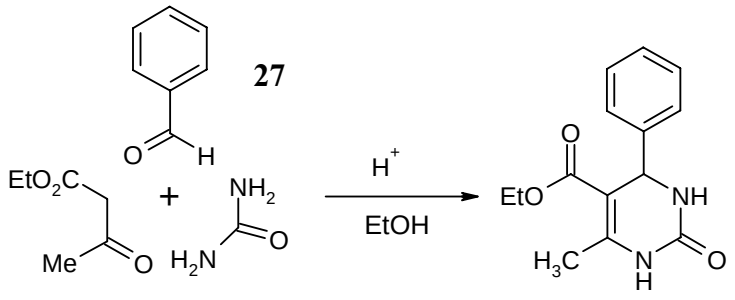
aldehydes as well as thioureas and produces high overall yields of the desired target compounds.



23 **24** **25**

Scheme 1 : Synthesis of DHPMs from α–tosyl- substituted thioureas

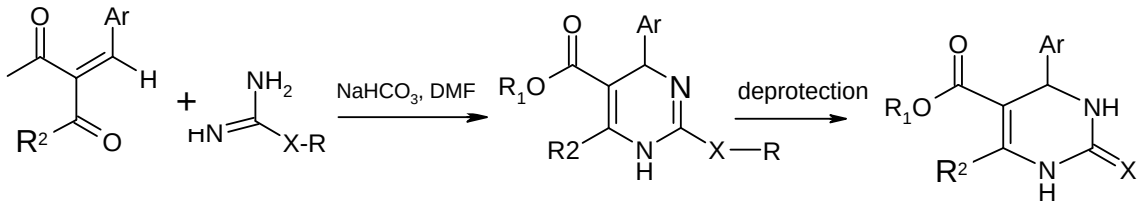
The most simple method for synthesis of DHPMs was reported by Italian chemist Pietro Biginelli[11] in 1893. This method consists of hydrochloric acid catalyzed cyclocondensation reaction of ethyl acetoacetate (**26)**, benzaldehyde (**27)** and urea (**28)** in refluxing ethanol (Scheme 2).



26 **28**

Scheme 2: Biginelli reaction for the synthesis of DHPMs

Unfortunately the original protocol provides only low to moderate yields of desired DHPM targets, in particular when substituted aromatic aldehydes or thioureas are employed. Hence Atwal modified the reaction[12-14] wherein an enone of type **29** is first condensed with a suitably protected ureas or thiourea derivatives **30** under almost neutral conditions (Scheme 3).



29 **30** **31**

a: X=O, R=Me ; b: X=S, R= 4-Methoxy benzyl

Scheme 3 : Atwal modification of the Biginelli reaction

Deprotection of the resulting 1, 4-DHPM with HCl or TFA / EtSH leads to the desired DHPMs **31**. Although this method requires prior synthesis of enones (**29**), its reliability and broad applicability makes it an attractive alternative to the traditional one-step Biginelli condensation. In addition 1, 4-DHPMs **31** can be acylated regiospecifically at N-3 thereby making the pharmacologically important DHPM analogues readily accessible.

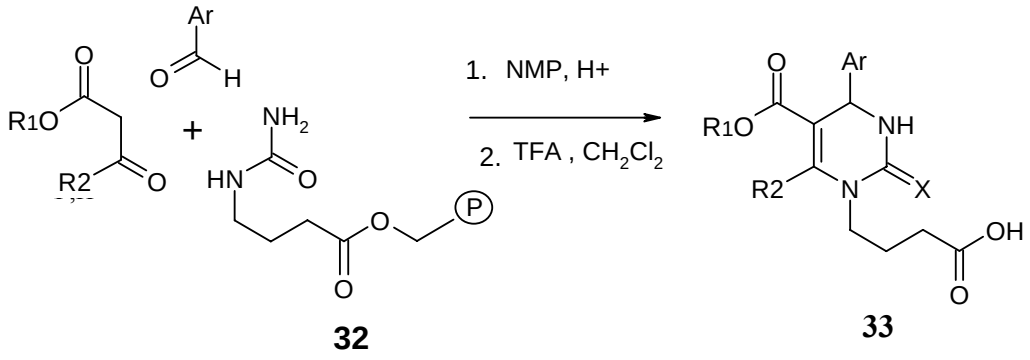
Although high yields of DHPMs can be achieved by following complex multistep procedures,[15] these methods lack the simplicity of the original one-pot Biginelli protocol. Hence the Biginelli reaction continues to attract the attention of researchers for discovery of a milder and more practical route for synthesis of DHPMs. Therefore several modifications and improvements in the original Biginelli protocol have been sought.

Solid phase and combinatorial procedures

Biginelli condensation is very useful for the creation of diverse chemical libraries, since the combination of n>3 small-molecular weight building blocks in a single operation leads to high combinatorial efficacy. Since the experimental conditions for Biginelli reaction are straightforward, small libraries of DHPMs are readily accessible by parallel synthesis.[16] Kappe have shown that small single compound DHPM libraries can be obtained in high yield

by parallel synthesis employing the solventless microwave enhanced variation of the Biginelli reaction. This has given impetus to development of new protocols for this reaction.

The first solid-phase modification of the Biginelli condensation was reported by Wipf and Cunnigham[18] wherein 8-aminobutyric acid - derived urea was attached to Wang resin. The resulting polymer-bound urea **32** was condensed with excess of β-ketoesters and aromatic aldehydes in THF at 55 °C in presence of catalytic amount of HCl to afford the corresponding immobilized DHPMs.

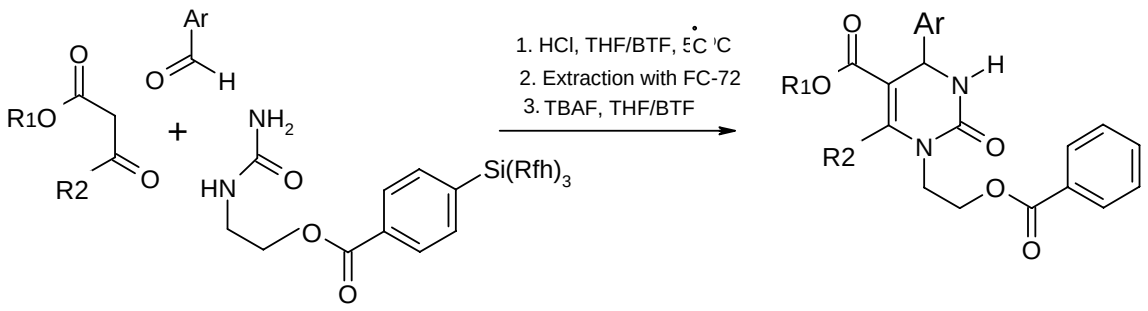


32 **33**

Scheme 4 : Solid phase modification of the Biginelli reaction

Subsequent cleavage of product from the resin by 50% trifluoroacetic acid (TFA) provided DHPMs in high yields and excellent purity.

In an interesting variation of this protocol, the Biginelli reaction was also adapted to fluorous-phase conditions by the Wipf and Curran group.[19] Here the fluorous urea derivative **34** was prepared by attachment of a suitable fluorous tag to hydroxyethyl urea. The fluorous urea was then condensed with 10 equivalent each of the corresponding acetoacetates and aldehydes in THF-benzotrifluoride (BTF) containing HCl. After extraction of fluorous DHMPs with fluorous solvent (perfluorohexanes, FC_72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the "organic" Biginelli products DHMPs **35** in good overall yields. The simplicity of this experimental technique makes automation feasible for preparation of DHPM libraries.

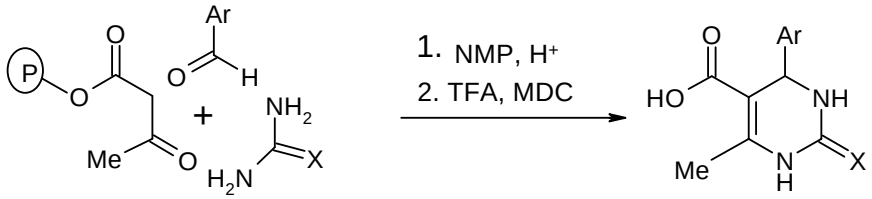


34 **35**

Rfh = $C_{10}F_{21}CH_2CH_2$-

Scheme 5 : The fluorous Biginelli reaction

To access pharmacologically active N_1-unsubstituted DHPMs, Kappe[17] developed an alternative protocol, where the acetoacetate building block was linked to the solid support. This Wang-bound acetoacetate **36** with excess aldehydes and ureas / thioureas in NMP / HCl provided the desired DHPMs on solid support. Subsequent cleavage with 50% TFA furnished the free carboxylic acids **37** in high overall yield (Scheme 6).

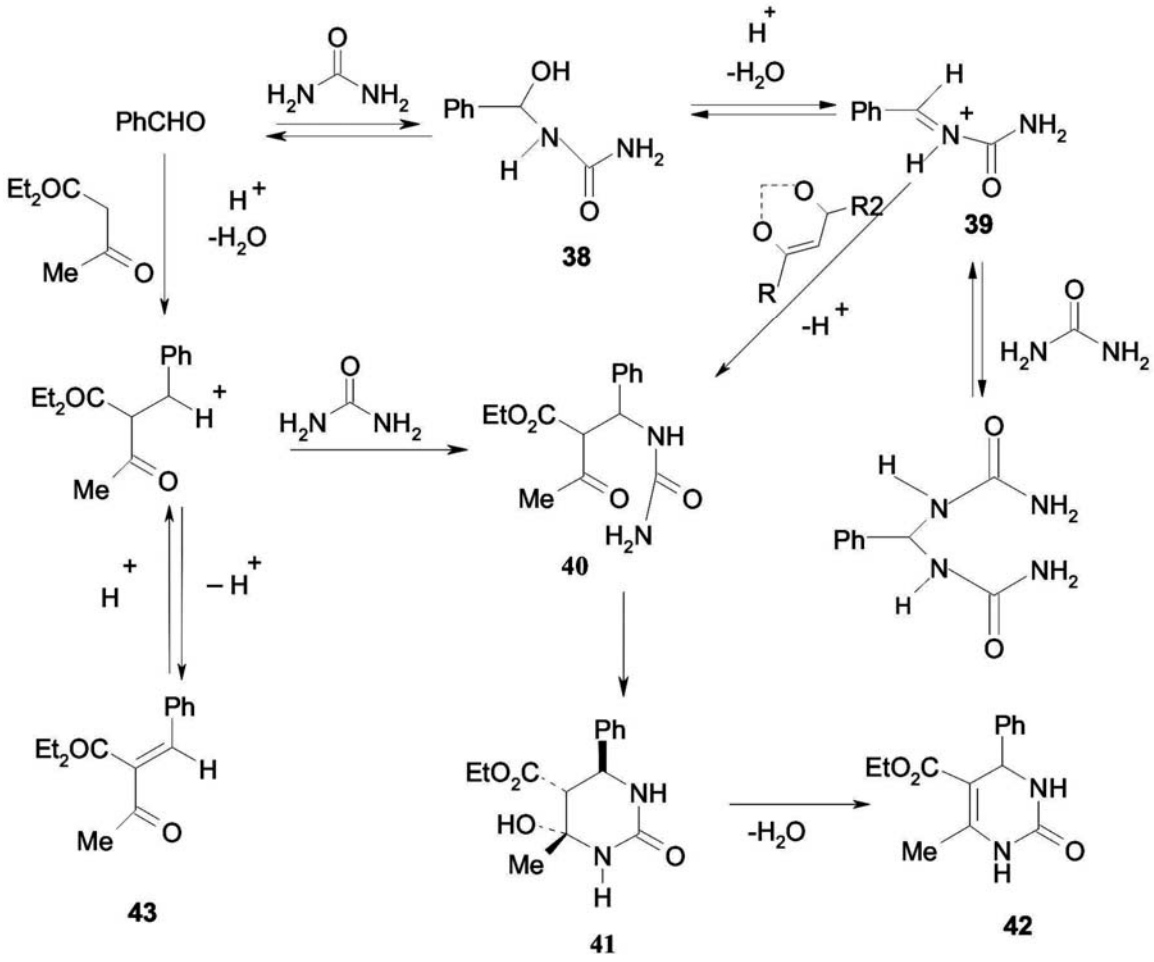


36 **37**

Scheme 6 : Biginelli condensation of Wang-bound acetoacetate

The mechanism of Biginelli reaction was investigated by C. Oliver Kappe[20] in 1997 using ^1H and ^{13}C NMR spectroscopy and trapping experiments. He established that the key step in this sequence involves the acylinium ion intermediate of the type **38** formed from aldehyde and urea precursors; which is converted to iminium ion **39** by protonation and dehydration.

Interception of the iminium ion **39** by ethyl acetoacetate presumably through its enol tautomer produces an open chain ureide **40** which subsequently cyclizes to hexahydropyrimidine **41**. Acid catalyzed elimination of water from **41** ultimately leads to the final DHPM product **42**. The reaction mechanism can therefore be classified as amidoalkylation or more specifically as an α-ureidoalkylation.[21] The alternative mechanism does not constitute a major pathway. However small amount of enone **43** is sometimes observed as a byproduct.



Scheme 7: Mechanism of the Biginelli reaction

3.1.2 Present work

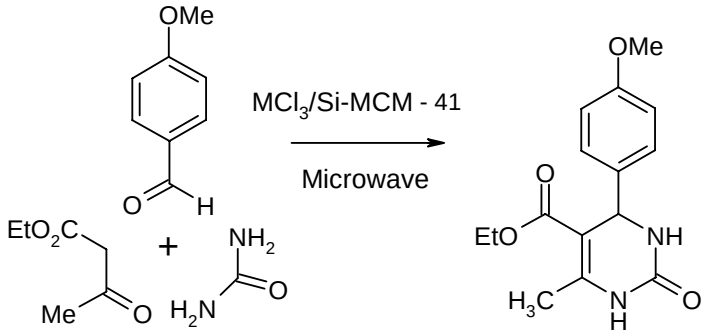
The Lewis acids (metal ions) are known to stabilize the iminium ion **39** and enolate of ethyl acetoacetate and hence catalyze the reaction. Strong Lewis acids like $FeCl_3$ + HCl,[22] $InCl_3$,[23] $InBr_3$,[24] $ZnCl_2$,[25] $AlCl_3$,[26] $LaCl_3.7H_2O$,[27] $Yb(OTf)_3$,[28] $BiCl_3$,[29] and $ZrCl_4$[30] are reported to promote the reaction by favoring the formation and interception of iminium ion intermediates of type **39**. However many of these procedures require high temperature and prolonged reaction time. Since strong protic or Lewis acids are incompatible with some of the functional groups, heterogeneous catalysts such as Mont -K10,[31] HY,[32] KSF,[33] Amberlyst-15 or Nafion–H in refluxing toluene[34] have been used for this reaction. However in spite of their utility, some of the reported methods suffer from drawbacks like unsatisfactory yields and cumbersome isolation procedures. Microwaves have been applied to accelerate this reaction and improve the yields of the product. The rate enhancement under microwave irradiation may be attributed to the effective absorption of microwaves by the polar media. Stefani[35] reported that 4-phenyl-3, 4-dihydropyrimidine-2-one was obtained in 30% yield under microwave irradiation without any additive. Enhancement in yield using ethanol as energy transfer medium or PPE [35] as a reaction mediator is also reported. In 2000 Quan et al. reported that ytterbium triflate[28] was an effective catalyst in the Biginelli condensation under solvent free conditions. Lewis acid or HCl catalysed rapid microwave assisted solvent free Biginelli condensation was reported in 2002 by S. Xue *et al*.[25] Taking in to consideration the limitations of the reported methods, it was felt that there is scope for further improvement towards milder reaction conditions, simple, eco-friendly catalytic process avoiding use of toxic reagents and large amount of solvents, cumbersome work-up and purification techniques. The scope of such reaction methodology can therefore be extended for synthesis of a number of DHPM analogs in a parallel mode in a single microwave irradiation experiment, following the MICROCOS (MICROWAVE ASSISTED COMBINATORIAL SYNTHESIS) approach.

Considering the catalytic activity of Lewis acids, it was propounded to incorporate them on acidic supports and study their catalytic effect on this reaction. Si-MCM-41 is known to effect the Biginelli reaction albeit yielding only 29 % product.[32] Mont-K10 was chosen

owing to its acidic nature. A series of Lewis acids supported on Si-MCM-41 and Mont K-10 were prepared and evaluated for their activity for Biginelli reaction in the present work.

Supported $InCl_3$, $GaCl_3$, $FeCl_3$ and $ZnCl_2$ catalysts (loading of metal chloride = 1.13 mmol / g) were prepared by impregnating Montmorillonite K-10 (procured from Aldrich, U.S.A.) and Si-MCM-41 (high silica mesoporous-MCM-41 having surface area of 1140 m^2g^{-1}) with anhydrous metal chloride (purity 99.99%, Aldrich) from their acetonitrile solution by incipient wetness technique and evaporating the solvent in vacuum oven at 120º C for 8 hours.

A summary of optimization of the process by screening of the catalysts by heating the reaction mixture (scheme 8) in microwave for 3 minutes is provided in Table 1.



44

Scheme 8 : Reaction for screening of catalysts for Biginelli reaction

Anisaldehyde (1 mmol), ethylacetoacetate (1 mmol) and urea (1.3 mmol) were mixed thoroughly. To this mixture 10% (w/w) of catalyst was mixed. The mixture was then irradiated in a domestic microwave oven at 700 W with 30 second pulse and 10 sec interval for 3 minutes. Entries 1-17 show the effect of various catalysts on the reaction. Entries 11-13 show the yields obtained in the three consequent condensations using recycled catalyst leading to the product. In these experiments the product was isolated by filtration. The catalyst was washed with ethanol, dried at 100-105 ºC for 1 hour and reused.

Screening of catalysts for the Biginelli reaction

Comparision of the supported $InCl_3$, $GaCl_3$, $ZnCl_2$, $AlCl_3$ and $FeCl_3$ (metal chloride loading =1.13 mmol/g) catalysts for their performance in the Biginelli reaction was performed as follows: a mixture of anisaldehyde (1.0 mmol), ethyl aetoacetate (1.0 mmol), urea (1.3 mmol) and catalyst (0.037g) in a glass sample vial was subjected to repeated microwave irradiation for a total period of 3 minutes.

Table1: Screening of the catalyst for the Biginelli reaction

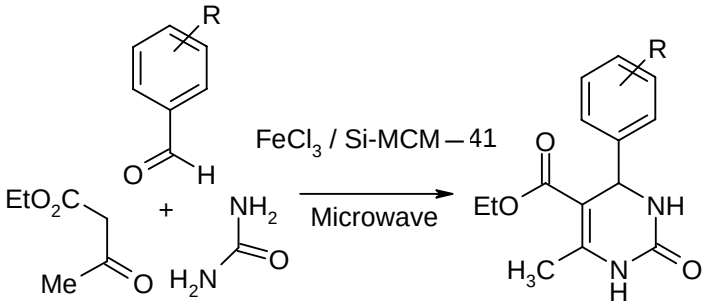
ENTRY	CATALYST	YIELD (%) [e]
1.	$ZnCl_2$/MontK10	79
2.	$GaCl_3$/Mont K10	65
3.	$InCl_3$/Mont K10	67
4.	$AlCl_3$/Mont K10	77
5.	$FeCl_3$/ Mont K10	70
6.	$ZnCl_2$/ SiMCM-41	63
7.	$GaCl_3$/SiMCM-41	48
8.	$InCl_3$/Si-MCM-41	75
9.	$AlCl_3$/ Si-MCM-41	53
10	$FeCl_3$/Si-MCM-41	85
11.	$FeCl_3$/Si- MCM-41[a]	85
12.	$FeCl_3$/Si- MCM-41[b]	85
13	$FeCl_3$/Si- MCM-41[c]	84
14	$FeCl_3$[d]	66
15.	$ZnCl_2$[d]	58
16.	$AlCl_3$[d]	50
17.	Without catalyst	29

[a]First reuse. [b]Second reuse. [c]Third reuse. [d] Amount equivalent to that used in the supported metal chloride catalyst.

[e] Ethyl-6-methyl-2-oxo-4-(4-methoxyphenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate.

All the catalysts examined showed good catalytic effect but Fe-Si-MCM-41 was particularly effective for this reaction (entry 10) and could be reused 3 times without showing any loss of activity (Entries 11-13).

Several substituted aromatic aldehydes were subjected to Biginelli reaction with ethyl acetoacetate and urea under optimized conditions (Scheme 9).

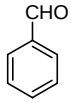
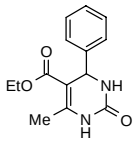
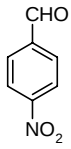
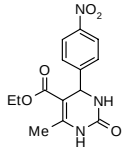
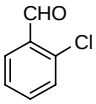
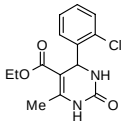
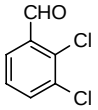
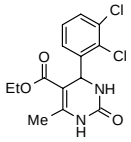
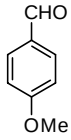
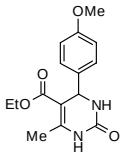
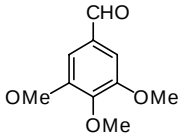
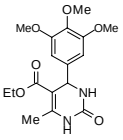
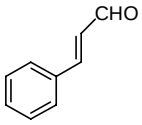
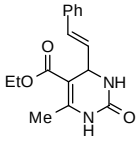
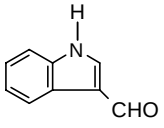
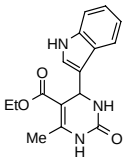


45

Scheme 9 : Dihydropyrimidinones synthesized using $FeCl_3$ supported on Si-MCM 41

Biginelli reaction over the $FeCl_3$ / Si-MCM-41 catalyst using different aldehydes by optimized protocol: A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.3 mmol) and catalyst (10 wt % of the reaction mixture) was subjected to repeated microwave irradiation for a total period ranging from 3 minutes to 5 minutes. The results of these reaction are summarized in Table 2.

Table 2: Dihydropyrimidinones synthesized using $FeCl_3$ supported on Si-MCM-41

ENTRY	ALDEHYDE	REACTION TIME (min)	PRODUCT	YIELD(%)
1.		3.0		84
2.		3.5		72
3.		4.5		90
4.		3.0		75
5.		3.0		80
6.		5.0		66
7.		4.0		69
8.		5.0		68

3.1. 3 Results and discussion

A comparision of the results on the Biginelli reaction over different supported and unsupported metal chloride catalysts under the microwave irradiation shows that maximum yield of the product in the Biginelli reaction was obtained using $FeCl_3$/Si-MCM-41 as catalyst. The catalyst support played an important role for deciding the catalytic activity of a particular metal chloride in the reaction. It is interesting to note that even in the absence of catalyst the reaction occurs but with a much lower product yield (29 %). The product yield also increased in the presence of the homogeneous metal chloride ($ZnCl_2$, $AlCl_3$ and $FeCl_3$) catalyst. However, when the metal chloride is supported on mesoporous Si-MCM-41 or Montmorillonite K-10 the product yield increased very appreciably in all the cases. This also showed that the observed high catalytic activity of the respective supported metal chloride catalyst cannot be only because of a homogeneous reaction catalyzed by the dissolved metal chloride, if any, in the reaction mixture. The reaction over the supported metal chloride catalysts is truly heterogeneous. The observed excellent reusability of the $FeCl_3$ / Si-MCM-41 catalyst further confirms this fact. No significant leaching of $FeCl_3$ from the catalyst was observed during the reaction.

It was observed that the metal chloride catalyst after heterogenization (i.e. after depositing on the Si-MCM-41 or Montmorillonite K-10 clay support) showed a better performance in the Biginelli reaction. The increased activity in the present case may be due to the formation of more active sites as a result of interaction of metal chloride with the support, particularly with surface hydroxyl groups.

The results in Table 2 show that the $FeCl_3$ / Si-MCM- 41 catalyst can be used in the Biginelli reaction with different substituted benzaldehydes or other aromatic aldehydes for the synthesis of corresponding DHPM with a high yield without using any solvent within a very short reaction period (up to 5 minutes). The catalyst is mesoporous (channel diameter~3.0 nm), which allowed non-restricted diffusion of the large size reacting species in the catalyst. Aromatic aldehydes carrying either electron donating or electron

withdrawing substituents, reacted well giving good yields of the expected products. The microwave heating eliminated the use of solvent and shortened the reaction time from several hours to few minutes. In addition to its simplicity and milder reaction conditions, this method is effective with α-β unsaturated aldehydes (entry 7, Table 2) which gave poor yields of product in presence of either protic or Lewis acids due to their decomposition or polymerization under acidic conditions. Another important feature of this procedure is survival of variety of functional groups like NO_2, Cl, olefin, ether under the reaction conditions.

3.1.4 Conclusion

$FeCl_3$ supported on mesoporous Si-MCM-41 was found to be a highly promising environ-friendly catalyst for one-pot synthesis of large size dihydropyrimidinone molecules by the Biginelli reaction without using any solvent. Many pharmacologically relevant substitution patterns on the 4-aryl ring can thus be introduced with high efficiency compared to original protocol. Since all the five variable substituents around DHPM scaffold (R-R, X Z str **9**) can be modified, a significant structural diversity in DHPM analogues can be generated expeditiously. Thus, the procedure not only preserves the simplicity of the BGR but also offers an easy access to pharmaceutically relevant substituted dihydropyrimidinones in good yield in eco-friendly method.

3. 1. 5 Experimental

Preparation of the catalyst Si-MCM-41

Si-MCM-41 was prepared by the following procedure reported by Mokaya and others.[36] A mixture of NaOH (1.79 g in 30 g H_2O) and tetramethylammonium hydroxide (2 ml of 25 wt % TMA-OH) solution was added to an adequate solution of cetyl tetrabutylammonium bromide (14.6 g in 100 g of water) with continuous stirring. Water (210 g) was added to this solution. After allowing the solution to stir for 10 min, tetraethyl orthosilicate (TEOS, Silica source) was combined with resulting solution at room temperature under stirring and kept for 24 hrs. The final gel composition of the mixture was 0.17 TEOS : 0.04 NaOH : 0.02 TMAOH : 0.04 CTAB : 18.9 H_2O. The solid product was obtained by filtration, washed with distilled water, dried in air at room temperature and finally calcined at 550° C for 16 hours.

Preparation of Al-Si-MCM-41

It was prepared by its hydrothermal synthesis as follows- i)10.4 ml (25 wt %) of solution of tetramethylammonium hydroxide was combined with 14.23 g of sodium trisilicate dispersed in 50 g of water with stirring and 29.5 g of CTAB (in 75 g of water) (surfactant / silica mole ratio = 0.5) solution was added and stirred for 30 min.

ii) 2.3 g of Na-aluminate (Si/Al = 5.0) was dispersed or dissolved in 50 g of water and then added slowly to the gel.

iii) The pH was adjusted with dilute sulfuric acid to 11.5. The resulting gel composition was 1.0 SiO_2 : 0.097 Al_2O_3 : 0.298 CTAB : 0.20 TMAOH : 0.41 Na_2O : 75 H_2O. The final gel was transferred into teflon-lined stainless steel autoclave and heated at 120ºC for 120 hr under autogeneous pressure. After cooling to room temperature, the resulting solid product was recovered by filtration on a Buchner funnel, washed with water and dried in air at ambient temperature. Surfactant was removed by calcining the product at 540ºC for 5 hours.

Supported $InCl_3$, $GaCl_3$, $FeCl_3$ and $ZnCl_2$ catalysts (loading of metal chloride = 1.13 mmol/g) were prepared by impregnating Montmorillonite K-10 (procured from Aldrich, U.S.A.) and Si-MCM-41 (high silica mesoporous-MCM-41 having surface area of 1140 m^2g^{-1}) with anhydrous metal chloride (purity 99.99%, Aldrich) from their acetonitrile solution by incipient wetness technique and evaporating the solvent in vacuum oven at 120ºC for 8 h.

Screening of catalysts for Biginelli reaction

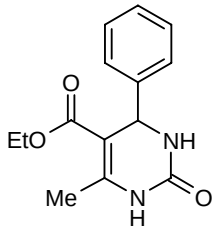
Comparision of the supported $InCl_3$, $GaCl_3$, $ZnCl_2$, $AlCl_3$ and $FeCl_3$ (metal chloride loading =1.13 mmol / g) catalysts for their performance in the Biginelli reaction [a mixture of anisaldehyde (1.0 mmol), ethylacetoacetate (1.0 mmol), urea (1.3 mmol) and catalyst (0.037 g) in a glass sample vial was subjected to repeated microwave irradiation for a total period of 3 minutes.

Biginelli reaction over the $FeCl_3$/Si-MCM-41 catalyst using different aldehydes

General procedure: Ethyl acetoacetate (1 mmol), aldehyde (1 mmol), urea (1.3 mmol) and catalyst (10% w/w) were mixed in a sample vial and subjected to pulsed irradiation of 20 sec at 700 W in a domestic microwave oven. The progress of the reaction was monitored by TLC and after completion of the reaction, the crude product was dissolved in EtOH, catalyst was filtered through Whatman No. 1 filter paper, EtOH removed under reduced pressure, water was added to the residue and the solid product was filtered. It was then recrystallized from hot ethanol. The catalyst was washed thoroughly with ethanol, dried at 100^0C for 1 hr and reused.

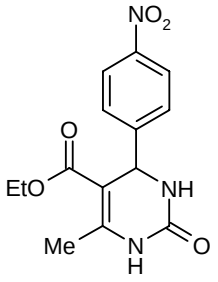
Spectral and physical characteristics of the products

1. **5-Ethoxycarbonyl-6-methyl-4-phenyl –3,4-dihydropyrimidin-2(1H)-one [Table 2, entry 1]**



M.P.	**:**	204˚C; lit.[38] 202-204˚C.
IR ($CHCl_3$)	**:**	3228, 3019.05, 1700.52, 1648cm^{-1}.
^{1}H NMR (200 MHz,$CDCl_3$):	**:**	δ 1.08 (t, J = 6.5 Hz, 3H), 2.24 (s, 3H), 4.02 (q, J = 6.5 Hz, 2H), 5.14 (s, 1H), 7.25-7.40 (m, 5H), 7.78 (s, 1H), 9.23 (s, 1H).
Mass m/z (%)	**:**	260 (M^+, 33.3), 231 (80.7), 183 (100).
C, H, N (%)	**:**	
Calculated for $C_{14}H_{16}N_2O_3$		C-64.60, H 6.15, N 10.76.
Found		C-64.62, H 6.13, N 10.85.

2. **5-Ethoxycarbonyl –6-methyl-4-(4-nitrophenyl)-3, 4-dihydropyrimidin-2(1H)-one [Table 2, entry 2]**



M.P.	**:**	209ºC, lit [37] 208-211ºC.
IR (KBr)	**:**	3240, 3110, 1695, 1665, 1560 cm^{-1}.
^{1}H NM R (200 MHz,$CDCl_3$)	**:**	δ 1.08 (t, J = 7.0 Hz, 3H), 2.50 (s, 3H), 3.97 (q, J

= 7.0 Hz, 2H), 5.27 (s,1H), 7.49 (d, J=8.7 Hz, 2 H) , 7.90 (brs, 1H), 8.23 (d, J=8.76 Hz, 2H), 9.37 (s,1H).

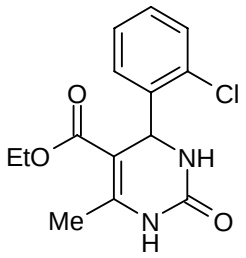
MS m/z (%) **:** 305 (M^+, 12), 276, 183 (100).

C, H, N (%) **:**

Calculated for $C_{14}H_{15}N_3O_6$ C 55.11, H 4.96, N 13.77 .

Found C 55.11, H 4.83, N 13.81.

3. 4-(2-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-2 (1H)-one [Table 2, entry 3]



M.P. **:** 222ºC, lit[24] 222-224ºC.

IR (KBr) **:** 3150, 1688, 1626 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 0.90 (t, J=6.9 Hz, 3H), 2.35 (s, 3H), 3.75 (q, J=6.9 Hz, 2H), 5.47 (s, 1H)**,** 7.29-7.37 (m, 4H), 7.79 (s, 1H), 9.15 (s, 1H) .

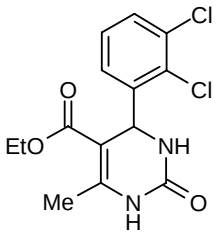
MS *m/z (%)* **:** 294 (M^+, 14), 279 (53), 265 (31), 183 (100), 155 (67.5).

C, H, N (%) **:**

Calculated for $C_{14}H_{15}O_3N_2Cl$ C 57.14, H .5.10**,** N 9.51.

Found C 57.16, H 5.14, N 9.50.

4. 4-(2,3-Dichlorophenyl)-5-ethoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-2(1H)-one [Table 2, entry 4]



M.P. **:** 248ºC.

IR (K Br) **:** 3219, 3104, 2969, 1641 cm^{-1}.

^{1}H NMR (DMSO d_6, 300 MHz) : δ 1.07 (t, J=7.2 Hz, 3H), 2.52 (s, 3H), 3.91 (q, J = 7.2 Hz, 2H), 5.70 (s, 1H), 6.00 (brs, 2H), 7.31-7.50 (m, 3H), 9.37 (brs, 1H).

MS m/z (%) **:** 328 (M^+), 330 (M^++2).

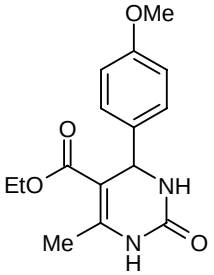
(ESI)

C, H, N (%) **:**

Calculated for $C_{14}H_{14}Cl_2N_2O_3$ C 51.06, H 4.26, N 8.50.

Found C 51.32, H 4.43, N 8.44.

5. 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one [Table 2, entry 5]



M.P. **:** 202-204 º C, lit[29] 201-203 º C.

^{1}H NMR (200 MHz, $CDCl_3$) **:** δ 1.15 (t, J= 6.8 Hz, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 4.01 (q, J = 6.8 Hz, 2H), 5.35 (s, 1H), 6.00 (s, 1H), 6.84 (d, J=8 Hz, 2H), 7.35 (d, J=8 Hz, 2H), 8.50 (s, 1H).

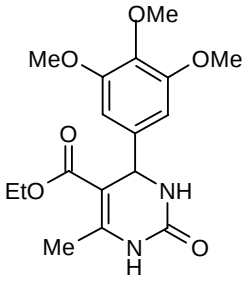
Mass *m/z*(%) **:** 290 (M^+), 275 (6), 261 (100), 217 (88.3), 183 (69.8).

C, H, N (%) **:**

Calculated for $C_{15}H_{18}N_2O_4$: C 62.06, H 6.20, N 9.65.

Found: C 62.10, H 6.11, N 9.67.

6. 5-Ethoxycarbonyl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2-(1H)-one [Table 2, entry 6]



M.P. **:** 179-180 º C, lit[29] 179-180 º C.

IR ($CHCl_3$) **:** 3019, 1695, 1592, 1129, 1092, 840 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6) **:** δ 1.09 (t, J = 6.8 Hz, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 4.01(s, 6H), 4.20 (q, J = 6.8 Hz, 2H) 5.09 (d, J = 2.7 Hz, 1H), 5.80 (brs, 1H), 6.54 (s, 2H), 8.40 (brs, 1H).

MS (m/z) **:** 349 (M^+).

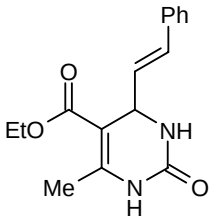
(ESI)

C, H, N (%) **:**

Calculated for $C_{17}H_{22}N_2O_6$ C 58.28, H 6.23, N 8.02.

Found C 58.50, H 6.21, N 8.10.

7. 5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one [Table 2, entry 7]



M.P. **:** 225-227 ºC (dec) lit[38] 225 °C (dec).

^{1}H NMR (200 MHz,$CDCl_3$) **:** δ 1.19 (t, J=7.0 Hz, 3H), 2.52 (s, 3H), 4.05 (q, J=4 Hz, 2H), 4.72 (d, J=5.5 H_Z,1H), 6.21 (dd, J= 12.0 Hz, 5.8 Hz, 1H), 6. 32 (d, J = 12.0 Hz, 1H), 7.21-7. 37 (m, 5H), 8. 85 (s, 1H), 9. 21 (s, 1H).

MS m/z (%) **:** 286 (M^+), 252, 224, 196, 149, 84.

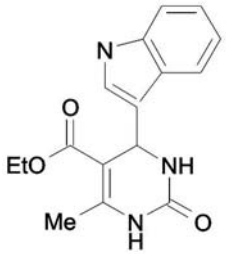
C, H, N(%) **:**

Calculated for $C_{16}H_{18}N_2O_3$ C 67.13, H 6.29, N 9.79.

Found C 67.18, H 6.26, N 9.75.

8.5-Ethoxycarbonyl –4-(3-indolyl)- 6-methyl-3, 4-dihydropyrimidin-2-(1H)-one

[Table 2, entry 8]



^{1}HNMR (DMSO d_6) **:** δ 1.08 (t, J=7 Hz, 3H), 2. 40 (s, 3H), 3.90 (q, J=6 Hz, 2H), 5.97 (d, J=4 Hz,1H), 7.12-7.30 (m, 5H), 8.76 (brs, 1H), 9.15 (brs, 1H).

MS **:** 298.43 (M^+).

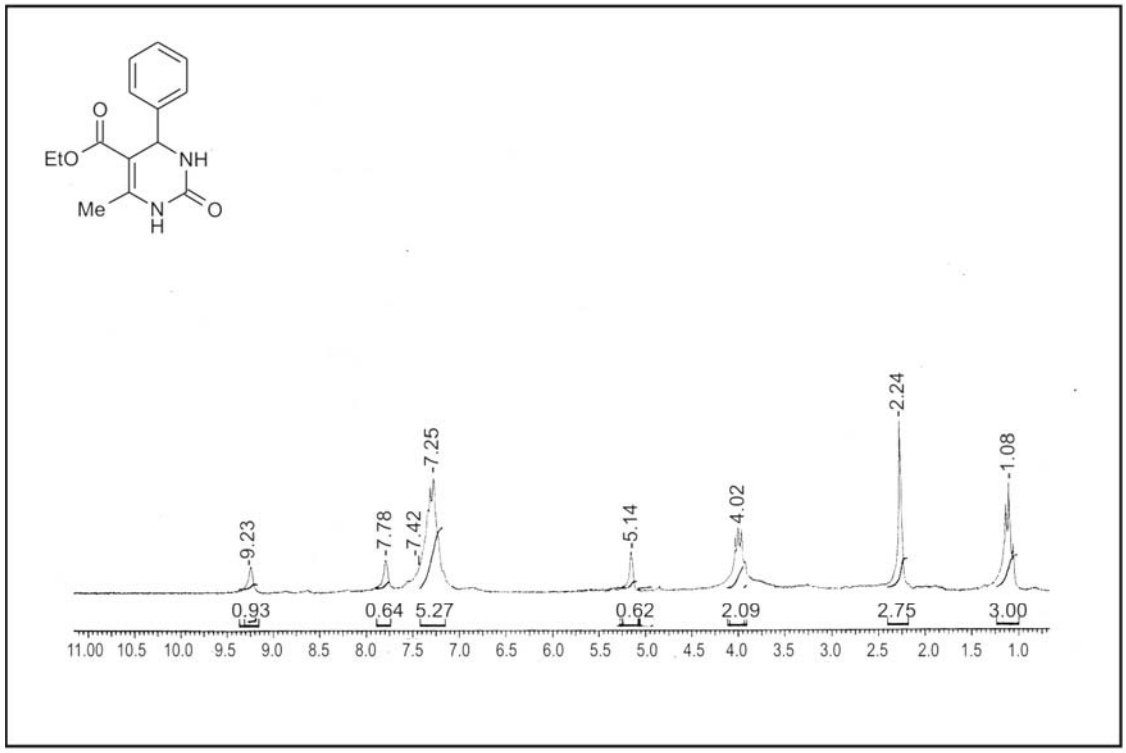
(ESI)

C, H, N (%) **:**

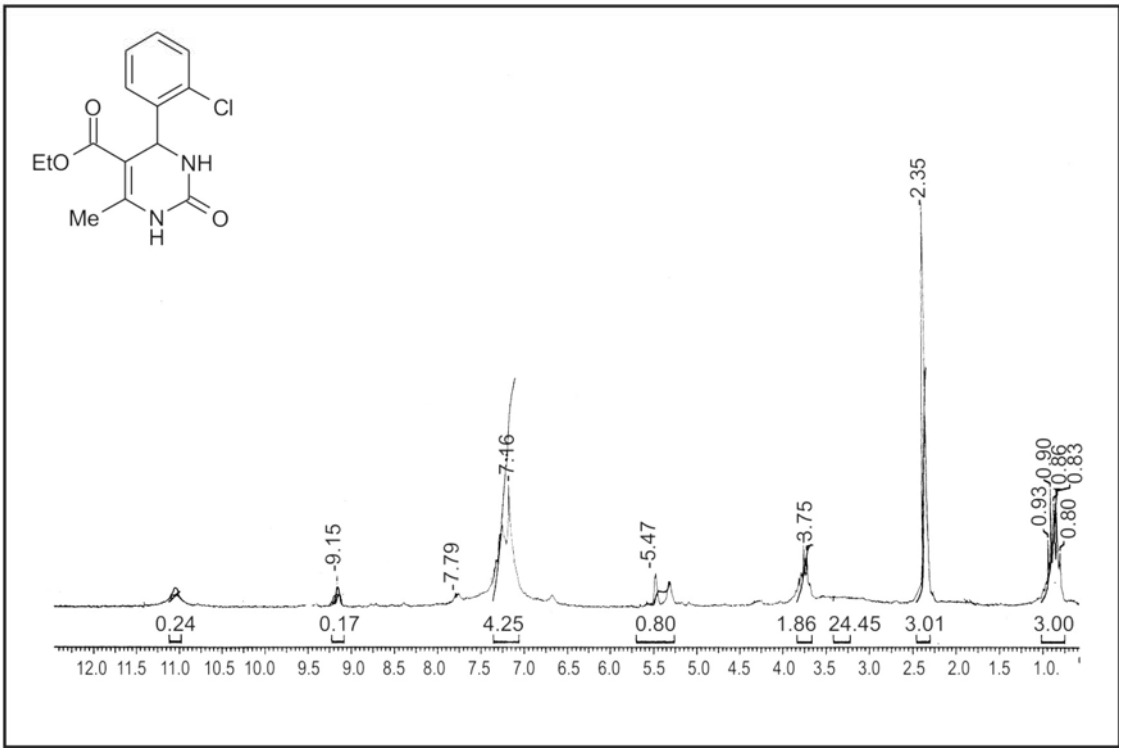
Calculated for $C_{16}H_{17}N_3O_3$ C 64.21, H 5.68, N 14.05.

Found: C 64. 20, H 5.65, N 14.07.

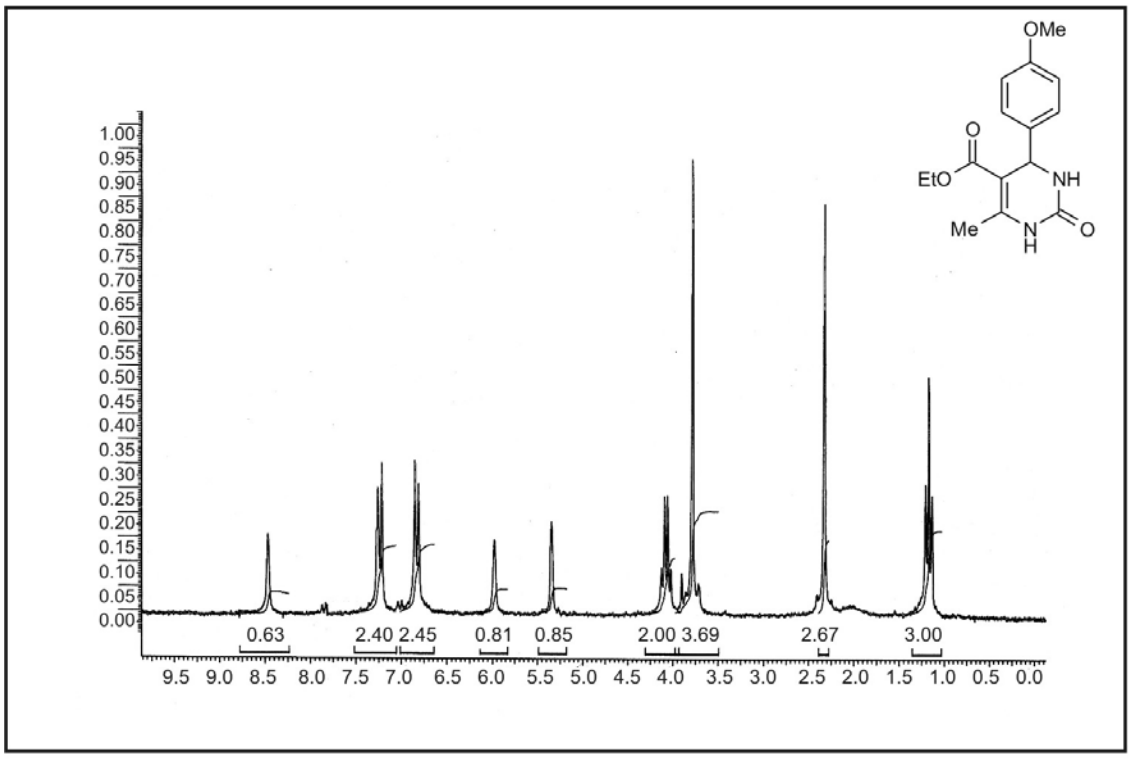
^{1}H NMR of 5-ethoxy carbonyl-6-methyl-4-phenyl 3,4-dihydropyrimidin-2 (1H)-one [Table 2, entry 1].



^{1}H NMR of 4-(2-chlorophenyl)-5-ethoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-2 (1H)-one (Table 2, entry 3).



^{1}H NMR of 5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3, 4-dihydropyrimidine-2(1H)-one [Table 2, entry 5].



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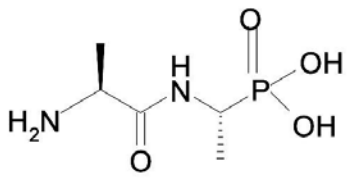
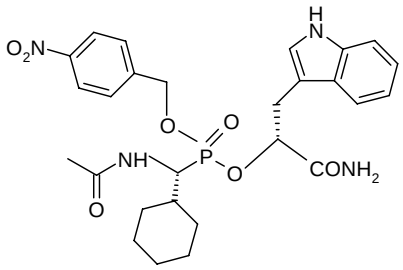
CHAPTER 3
(Section B)

Kabachnik–Field synthesis of α-aminophosphonates

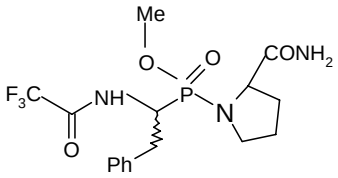
3.2.1 Introduction

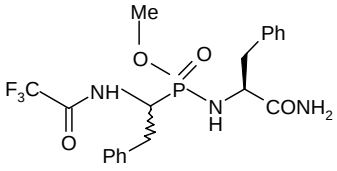
The ∝-aminophosphonic acids and α-aminophosphonates exhibit a wide range of intriguing biological activities. The ∝-aminophosphonic acids are potential antibacterial agents besides exhibiting neuroactive characteristics and have been employed as anticancer drugs and pesticides.[1] Biologically relevant ∝-aminophosphonate derivatives include the antibacterial agent alafosfalin **46**, haptens for the generation of catalytic antibodies **47** and transition-state analogue inhibitors of proteolytic enzymes **48** and **49**. (R)-Phosphotyrosine (**50**) occurs naturally as a component of two hypotensive tripeptides.

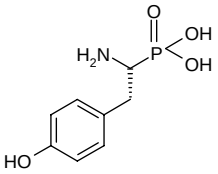




Alafosfalin **46** **47**







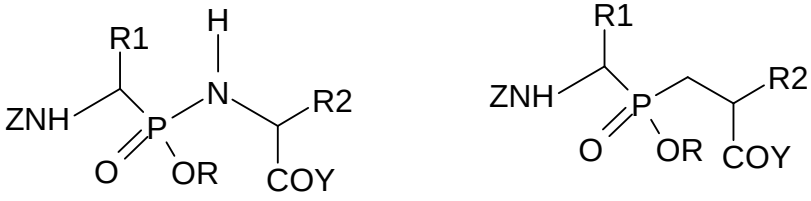
48 **49** **50**

Figure 1 : Biologically active α-aminophosphonates

1-Aminophosphinic acid containing molecules have demonstrated their ability to modulate biochemical processes by enzyme inhibition. Examples of 1-aminophosphinic acid containing enzyme inhibitors include the therapeutic agent fosinopril, inhibitor of

angiotensine converting enzyme[2], D-Ala:D-Ala ligase,[3] HIV-protease,[4] glutamine synthetase[5] and stromelysin-1 (MMP-3) inhibitors.[6] Besides antagonists in the metabolism of amino acids, 1-aminophosphinic acid containing molecules have also found novel drug delivery applications, for example to stabilize peptide drugs during their intranasal absorption.[7]

1-Aminoalkylphosphonic acids and the corresponding peptides (phosphonopeptides) are analogous to α-aminocarboxylic acids and their derived peptides. The phosphonopeptides **51** through their hydroxyphosphonyl design [– P(O)OH–], approximating a presumed enzymatic reactive tetrahedral intermediate, can induce enzyme inhibitor properties. But owing to some sensitivity of the (O)–P–N phosphonamidate bond to hydrolysis, their P–C analogs **52** are better candidates for the elaboration of more stable biologically active compounds. The construction of such phosphinopeptides requires the synthesis of the phosphinodipeptide analogue of type **52** as building blocks.[8]



51 **52**

Z, R = H, Y = OH or protecting groups. R^1, R^2 = alkyl, aryl, heteroatomic groups.

Figure 2: Phosphonodipeptides and their analogous phosphinodipeptides

Compounds **52** are generally prepared in a multistep synthesis from the corresponding adequately protected 1-aminoalkyl phosphonous acids by Michael additions using basic activation or silyl derivatives.

The 1-aminoalkyl phosphonous acids can be synthesized in several ways by the oxime procedure,[9] by Michaelis – Arbuzov reaction with the bis (trimethylsilyl) phosphonite,[10] by alkylation of a suitably protected 1-aminomethylphosphinic acid,[11] by a Mitsunobu reaction on 1-hydroxyalkyl phosphinates,[12] by amination of chloromethylphosphinic

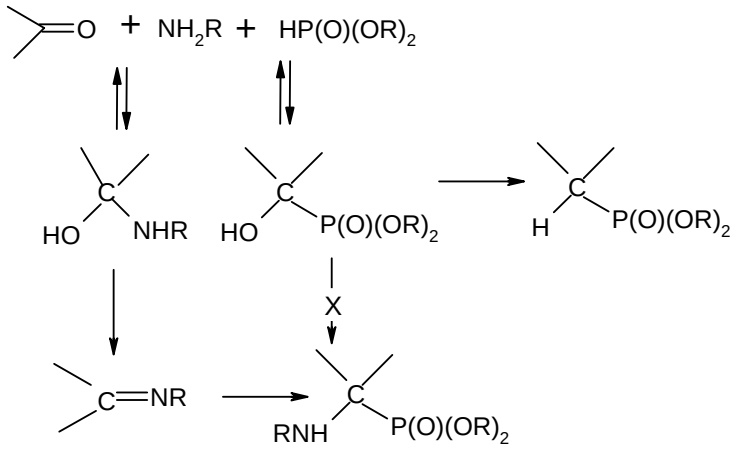
acid,[13] by a Michael reaction of ethyldioxymethyl phosphonite with ethylacetamido methylene malonate[14] or by Kabachnik–Field reactions involving addition of hypophosphorous acid or its derivatives to a C=N double bond. α-Aminophosphonates, the key substrates in the synthesis of aminophosphonic acid, are obtained by nucleophilic addition of dialkyl phosphites to imines and exhibit several interesting activities. They are considered to be transition state mimics of peptide hydrolysis. Some α-aminophosphonates e.g. $(R_1O)_2P(O)CH_2NHCH_2Ph$ (R_1 = 2-ethylhexyl) exhibited remarkable selectivity as carriers for the membrane transport of the biorelevant species such as α-amino and α-hydroxy acids.[15] Calyx [4] arene based α-aminophosphonate exhibited remarkable selectivity as carriers for the membrane transport of zwitterionic form of aromatic amino acids.[16]

In 1989 Lenjezak Barbara and coworkers[17] synthesized more than 30 analogues of α-aminophosphonates with structural changes introduced in to phosphonate analogue of leucine to see their ability to inhibit cytostatic and microsomal aminopeptidases. They found that 1-amino-2-N-(cyclohexylamino) ethyl phosphonic acid was equipotent with bestatin, leucinal and hydroxamic acids, the strongest known nonpeptide inhibitors of microsomal enzymes. Aminophosphonates substituted at α-position by phenol groups were found to have lipoprotein lowering activity. These compounds were also useful in treating thrombosis, restenosis following angioplasty and atherosclerosis.[18]

Wieczorek *et al.* [19] and others studied the structure dependent activity of 37 newly synthesized acyclic aminophosphonic acid derivatives on spirodela oligorrhiza. The phytotoxicity of the compounds studied depended on their hydrophobic parameters and to a smaller extent on the electronic parameters of the substituents of N and P atoms. No phytotoxicity dependence on the steric parameters of compounds was found. The use of α-aminophosphonates as haptens of catalytic antibodies,[20] antibiotics and pharmacological agents[21] are well documented.

A number of synthetic methods for the synthesis of 1-aminoalkyl phosphonates have been developed during past two decades.

One of the very first methods of aminophosphonate synthesis was described by Kabachnik and Medved[22] wherein these compounds were obtained by reaction of ammonia, dialkylphosphite and the corresponding carbonyl compound. A little later Fields[23] presented a method of synthesis of N-mono and N, N-disubstituted aminophosphonates in a similar manner, replacing ammonia with the corresponding amine. These methods have received the common name Kabachnik-Fields reaction and are still important especially for synthesis of N-substituted derivatives. The mechanism of this reaction has been studied extensively. Since Kabachnik and Medved found that hydroxyphosphonates are present in the mixture of ammonia, carbonyl compound and dialkyl phosphite at room temperature, they postulated that the reaction proceeds via hydroxyphosphonates followed by the substitution of hydroxyl group by amino group. Pietrov[24] however presented arguments that aminophosphonates are not formed in a hydroxyl group substitution reaction but rather due to reversibility of the hydroxyphosphonate formation. Based on this idea, Fields[25] postulated that aminophosphonates are formed *via* hydroxyamines or imines. The possible reactions are presented in scheme below.



Scheme 1 : Mechanism for the formation of α-aminophosphonates

Roman Gancarz and Irena Gancarz[26] added the path leading to phosphate and believed that formation of phosphates is a reason of many failures of aminophosphonate synthesis especially when diarylketones are used as a carbonyl substrate.

They studied the reaction progress by NMR and kinetic methods and observed that when aliphatic amines are replaced by aromatic amines, the yield of the corresponding α-aminophosphonates increased. They postulated that aromatic amines as weak basic species do not "activate" the dialkyl phosphates and the reaction proceeds *via* hydroxylamine-imine path. The conditions are dramatically changed when any alkylamine appears. They are much stronger bases and they "activate" the dialkyl phosphate either by path A or path B as shown below.

Scheme 2 : Formation of phosphate by-product in Kabachnik-Field reaction

Such activated dialkyl phosphates react with ketone forming hydroxyphosphonates. Reversibility of this reaction should still allow the formation of aminophosphonate unless in another competing reaction like phosphonate-phosphate rearrangement only phosphate is formed irreversibly as a final product. Further heating the reaction mixture frequently leads to decomposition products.

Despite the implementation of a number of new methods, Kabachnik-Field synthesis of aminophosphonates still remains important and widely used. Several catalysts have been reported to increase the selectivity and yield of α-aminophosphonates in this reaction. Lewis acids [27] such as $SnCl_2$, $SnCl_4$, BF_3. Et_2O, $ZnCl_2$, $MgBr_2$ and $InCl_3$ have been used as catalysts. However these reactions cannot be carried out in a one-step operation with the carbonyl compound, amine and dialkyl phosphite because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids.[28] This disadvantage has been overcome by a recent procedure[29] using a combination of lanthanide triflate and magnesium sulfate. Although this approach is satisfactory for

reactions with aromatic aldehydes and amines, the reaction of ketones has not been reported. In addition, aminophosphonates from aliphatic aldehydes and amines are obtained in low or moderate yields. Recently $InCl_3$ was used to catalyze this reaction in good yields.[30] However, longer reaction time required is the limitation of this method. Kei and Shu, [31] reported facile synthesis of α-aminophosphonates in water using a Lewis acid-surfactant combined catalyst like Sc- tris (dodecyl sulfate).

Some heterogeneous supports like acidic alumina[32] and KSF[33] have been used for solvent free synthesis of aminophosphonates. However, large quantity of support needed and limited reusability are the limitations of these methods. Taking in to consideration the limitations of the reported methods, we feel that there is need for a truly catalytic eco-friendly method for synthesis of aminophosphonates.

3.2.2 Present work

Multicomponent reactions have attracted much attention recently due in part to their potential for the generation of molecular diversity within the context of combinatorial chemical libraries. These libraries have furnished unprecedented numbers of novel entities which can be screened for potential biological activities. Many of the early libraries were peptide based, however to ensure molecular diversity non-natural amino acid derivatives are of increasing interest for incorporation into libraries. In this context, synthetic procedures which enable rapid preparation of structurally diverse 1-aminophosphinic acid analogues are of considerable use and interest.

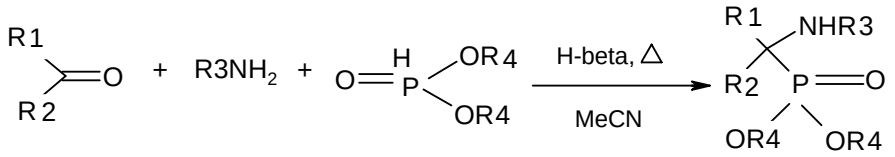
Taking into consideration the importance of α-aminophosphonous acid and α-aminophosphonates, it was decided to undertake preparation of a series of α-aminophosphonates from an aldehyde, amine and dibenzylphosphite. Dibenzylphosphite was used instead of diethylphosphite or dimethyl phosphite as the benzyloxy group can be easily removed using 30% HBr in HOAc from the corresponding α-aminophosphonates.[34] When a mixture of anisaldehyde, p-anisidine and dibenzylphosphite was stirred together at room temperature for 10 hours, only 17% aminophosphonate was obtained along with several impurities and unreacted aldehyde, anisidine and dibenzylphosphite. When these three reactants were heated at 80ºC for 2.5 hour, the yield of desired aminophosphonate increased to 63% and the reaction mixture contained unreacted starting materials along with traces of new impurties. The overall yield of the aminophosphonate could be increased to 76% when the reaction was carried out by heating anisaldehyde and p-anisidine, isolating and purifying the resulting imine and heating it with dibenzylphosphite. However when indole-2-carboxaldehyde, p-anisidine and dibenzylphosphite were heated at 80ºC, a sticky resinous product was obtained from which the purification to get the desired product was difficult. However many imines are hygroscopic, unstable at high temperature and difficult to purify by distillation or column chromatography.[35] Thus it is desirable from a synthetic point of view that imines, generated *in situ* from aldehydes and amines, immediately react with phosphates and afford α-aminophosphonates in one pot. Since Lewis acids are known to

catalyze this reaction, some acidic zeolites having Lewis acid character were used for reaction of indole-3-carboxaldehyde, p-anisidine and dibenzylphosphite in acetonitrile. The results of these experiments are presented in table 1.

Table 1: Effect of catalyst in the preparation of α-aminophosphonates

Expt No.	Catalyst used	Reaction time	Reaction temp.	Yield (%)
1	H β	4	Reflux	84
2	H Y	4	Reflux	81
3	$InCl_3$ / Hβ	4	Reflux	83
4	$FeCl_3$ / Hβ	4	Reflux	79
5	Mordenite	5	Reflux	61

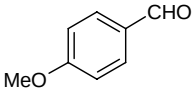
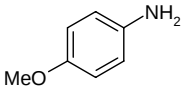
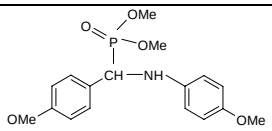
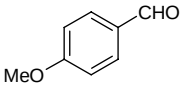
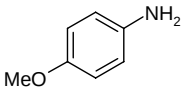
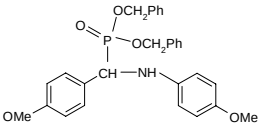
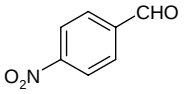
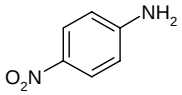
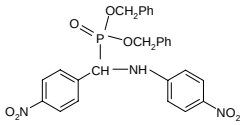
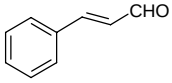
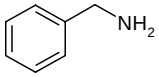
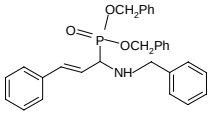
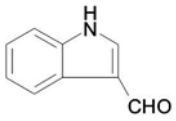
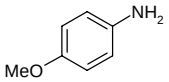
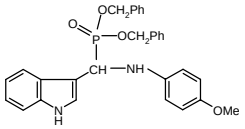
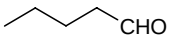
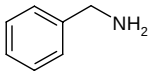
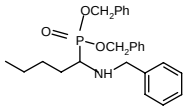
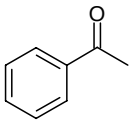
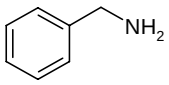
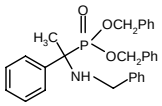
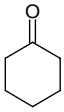
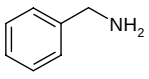
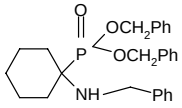
Since H-β catalyzed reaction gave the best yield, different aldehydes, ketones and amines were subjected to above reaction using H-β catalyst as shown in scheme 3 and the results are summarized in Table 2.



53 **54** **55** **56**

Scheme 3: H-beta zeolite catalysed synthesis of α- aminophosphonates

Table 2: H-beta zeolite catalysed Kabachnik–Field synthesis of α-aminophosphonate

Sr. No.	Carbonyl compound	Amine	Product*	Reaction Time Hr	Yield %
1.				1	78
2.				1	89
3.				4	76
4.				5	94
5.				1	84
6.				4	91
7.				2	87
8.				1	93

*Dimethylphosphite is used in entry No.1 whereas dibenzylphosphite is used in entry Nos. 2- 8

3.2.3 Results and discussion :

As shown in Table 1; H-β zeolite was the most effective catalyst for the above reaction. Impregnation of this catalyst with Lewis acids like $InCl_3$, $FeCl_3$ etc. did not show significant increase in selectivity, rate of reaction or yield of product. The observed efficient performance of H - β zeolite may be attributed to its large pore opening, three dimensional channel system and higher concentration of acid sites.[36] As shown in Table 2, a wide range of structurally varied carbonyl compounds and amines were subjected to this procedure and converted to the corresponding α-aminophosphonates in high yields. Both aromatic and aliphatic aldehydes and ketones react with aromatic as well as aliphatic amines equally effectively for conversion to open- chain, cyclic and aromatic imines and then to the respective α-aminophosphonates. No difficulty was encountered with the reaction of conjugated aldehydes (entry 4). Several sensitive functionalities such as OMe, NO_2 and C-C- double bond are unaffected under the present reaction conditions. The reactions are faster and the products obtained are much cleaner. All the products were characterized by usual spectroscopic methods as evident from the data given in the experimental section.

3.2.4 Conclusion

The present procedure using Hβ zeolite as the catalyst provides an efficient one-pot synthesis of α-aminophosphonates from the reaction of a carbonyl compound, amine and dibenzyl phosphite. The carbobenzyloxy group from the phosphonates can be easily removed by treatment with a solution of 30% HBr in HOAc to yield the corresponding α-aminophosphonous acid.[36] The notable advantages of this procedure are a) operational simplicity and requirement of no additive b) general applicability to aldehydes and ketones c) participation of aromatic as well as aliphatic amines d) reaction conditions tolerant to a variety of sensitive functional groups e) reduced reaction time and f) high yields. This will be a more practical alternative to existing methodologies for synthesis of α-aminophosphonous acid from their corresponding dibenzyl α-aminophosphonates.

3.2.5 Experimental

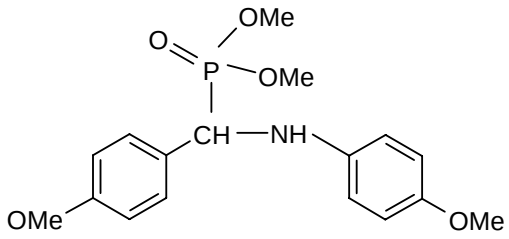
Selection of catalyst for preparation of [(4-methoxy-phenylamino)-(3a, 6, 7, 7a, tetrahydro-1*H*- indol-3-yl)-methyl]-phosphonic acid dibenzyl ester:

A mixture of indole-3-carboxaldehyde (1 mmol), p-anisidine (1 mmol), dibenzyl phosphite and different catalysts (10 % w/w of aldehyde) in acetonitrile was refluxed for four to five hours. The reaction mixture was then cooled to room temperature, catalyst filtered, filtrate concentrated and the crude product purified by column chromatography on silica gel.

Synthesis of different α-aminophosphonates by optimized procedure using H-beta zeolite:

A mixture of aldehyde (1 mmol), amine (1 mmol), dibenzyl/dimethyl phosphite and zeolite Hβ (10% w/w of aldehyde) in acetonitrile was refluxed. After completion of the reaction (TLC), the reaction mixture was cooled to room temperature, catalyst filtered, filtrate concentrated and the crude product purified by column chromatography on silica gel.

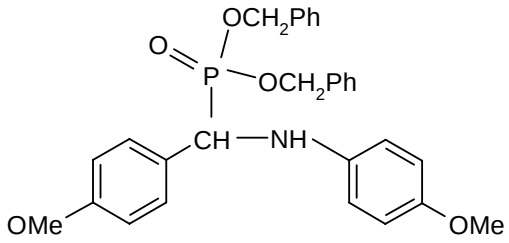
(4-Methoxyphenylamino)-4-methoxyphenylmethyl-phosphonic acid dimethyl ester [Table 2, entry 1]



Yield (%)	:	78.
IR ($CHCl_3$)	:	2947. 51, 1611. 09, 1512. 28, 1235. 31, 1036.99 cm^{-1}.

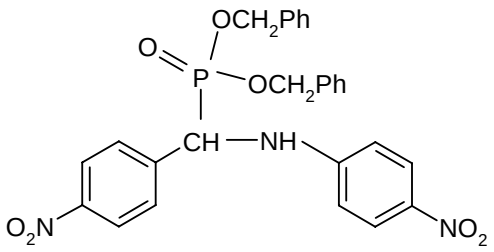
^{1}H NMR (200 MHz, $CDCl_3$)	: δ	3.45 (s, 3H), 3.51(s, 3H), 3.67 (s, 3H), 3.37 (s, 3H), 4.64 (d, J_{P-H} = 24 Hz, 1H), 6.52 (d, J=8 Hz, 2H), 6.67 (d, J=8 Hz, 2H), 6.85 (d, J=8 Hz, 2H), 7.33-7.77 (m, 2H).
MS	:	350. 64 (M^+), 240. 24.

(4-Methoxyphenylamino)-4-methoxyphenylmethyl-phosphonic acid dibenzyl ester [Table 2, entry 2]



Yield (%)	:	89.
IR ($CHCl_3$)	:	3320.09, 2924.45, 2854.52, 1608.46, 1510.28, 1234.8, 1029. 82, 993.24 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 3.67 (s, 3H), 3.77 (s, 3H), 4.57- 4.85 (m, 4H), 4.98 (d, J = 8 Hz, 1H), 6. 47 (d, J= 8 Hz, 2H), 6.65 (d, J = 8 Hz, 2H), 6.82 (d, J=8 Hz, 2H), 7.25-7.35 (m, 12 H).
^{31}P NMR (125 MHz, $CDCl_3$)	:	δ 24.11.
MS (ESI)	:	503.03 (M^+), 240.54.

(4-Nitrophenyl amino)-4-nitrophenylmethyl-phosphonic acid dibenzyl ester [Table 2, entry 3]

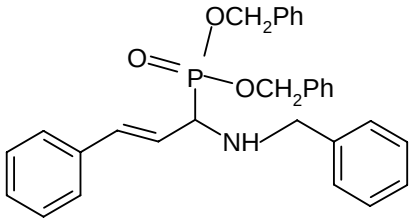


Yield (%) : 76.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.60- 3.77 (m, 4H), 4.45 (d, J= 7 Hz, 1H), 6.50- 6.65 (d, J= 4 Hz, 4H), 7.30-7.45 (m, 10H), 8.10 (d, J = 4 Hz, 4H).

MS (ESI) : 534.05 (M^++1), 318.00, 227.00, 188.05.

(1-Benzylamino)-3-phenylallyl - phosphonic acid dibenzyl ester [Table 2, entry 4]



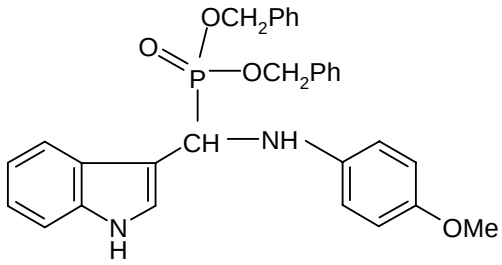
Yield (%) : 94.

IR ($CHCl_3$) : 3016. 48, 1731. 72, 1564. 52, 1245. 09 cm^{-1} .

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.70 (d, J= 8 Hz, 1H), 4. 18 (brs, 1H), 4.25 (s, 2H), 5. 14- 5. 18 (m, 4H), 6.51 (d, J= 12 Hz, 1H), 6.57 (d, J= 12 Hz, 1H), 7. 41-7. 27 (m, 20H).

MS (ESI) : 483.01 (M^+), 220.00

[(4-Methoxyphenylamino)-(3a, 6, 7, 7a- tetrahydro-1*H*- indol-3-yl)-methyl]-phosphonic acid dibenzyl ester [Table 2, entry 5]



Yield (%) : 84.

IR ($CHCl_3$) : 2925. 94, 1509. 88, 1462. 33, 1377. 59, 1233. 85 cm^{-1}.

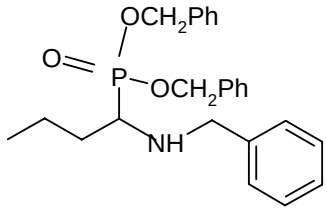
^1H NMR (200 MHz,$CDCl_3$) : δ 2.24 (brs, 1H), 3.79 (s, 3H), 4.09 (d, J=8 Hz, 1H), 4.71-4.83 (m, 4H), 6.00-6.12 (m, 4H), 6.20 (s, 1H), 6.74 (d, J = 8 Hz, 2H), 6.89 (d, J=8 Hz, 2H), 7.30-7.42 (m, 10 H).

^{31} P NMR (300 MHz, $CDCl_3$): δ 24.67.

MS : 512.01 (M^++1), 389.00.

(ESI)

(1-Benzylamino-pentyl)-phosphonic acid dibenzyl ester [Table 2, entry 6]



Yield (%) : 91.

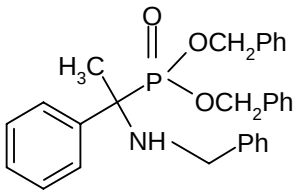
IR ($CHCl_3$) : 3019. 30, 2965. 20, 1714. 52, 1455. 52, 1215. 68 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz) : δ 0.75 (t, J= 5 Hz, 3H), 1.23-1.30 (m, 4H), 2.00-2.25 (m, 2H), 4.14 (d, J= 8 Hz, 1H), 4.56 (d, J=8 Hz, 2H), 4.86-5.10 (m, 4H), 7.27-7.35 (m, 15H).

^{31}P NMR ($CDCl_3$, 200 MHz): δ 28.1.

MS (ESI) : 424.03 (M^++1), 216.05, 162.04.

(1-Benzylamino-1-phenyl-ethyl)-phosphonic acid dibenzyl ester [Table 2, entry 7]

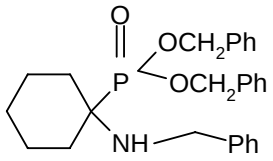


Yield (%) : 87.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 3.78 (s, 3H), 4.69 (d, J=8 Hz, 4H), 5.01 (s, 2H), 7.25-7.45 (m, 20 H).

MS (ESI) : 471.01 (M^+).

(1-Benzylamino-cyclohexyl)-phosphonic acid dibenzyl ester [Table 2, entry 8]



Yield (%) : 93.

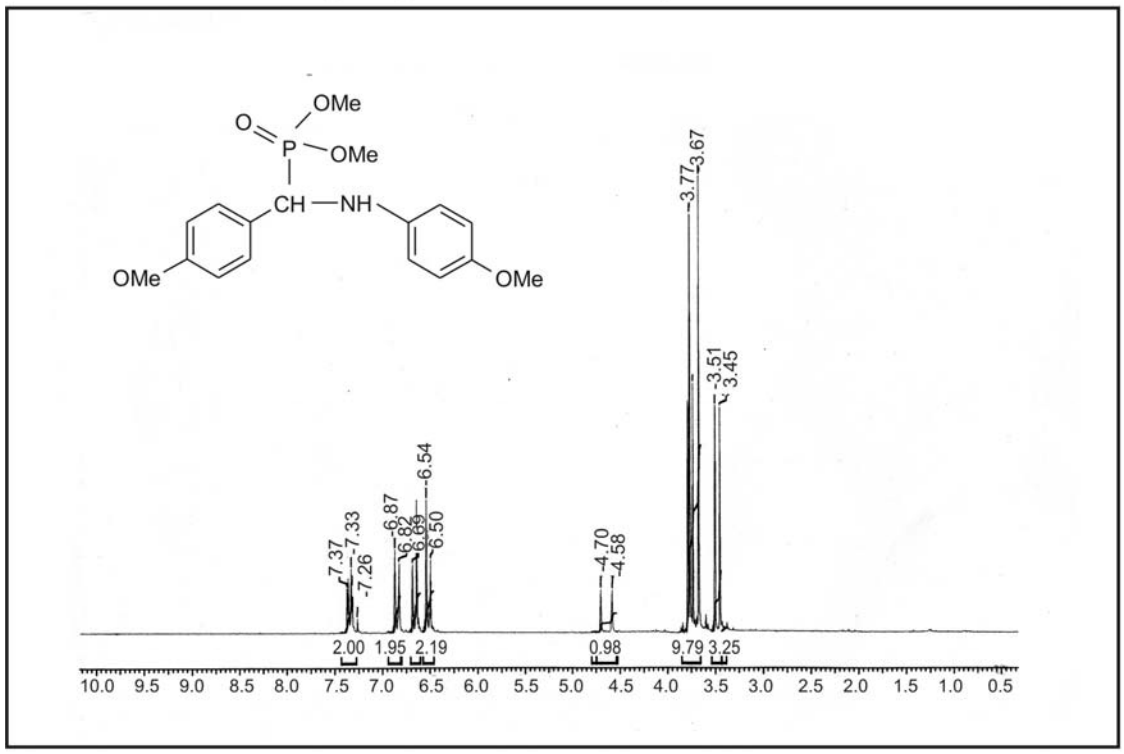
IR ($CHCl_3$) : 3019.07, 1603.75, 1454.17, 1215.90, 757.74 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.56-1.69 (m, 6H), 1.74-1.81 (m, 4H), 4.21-4.40 (m, 2H), 4.91-5.08 (m, 4H), 7.18-7.27 (m, 15H).

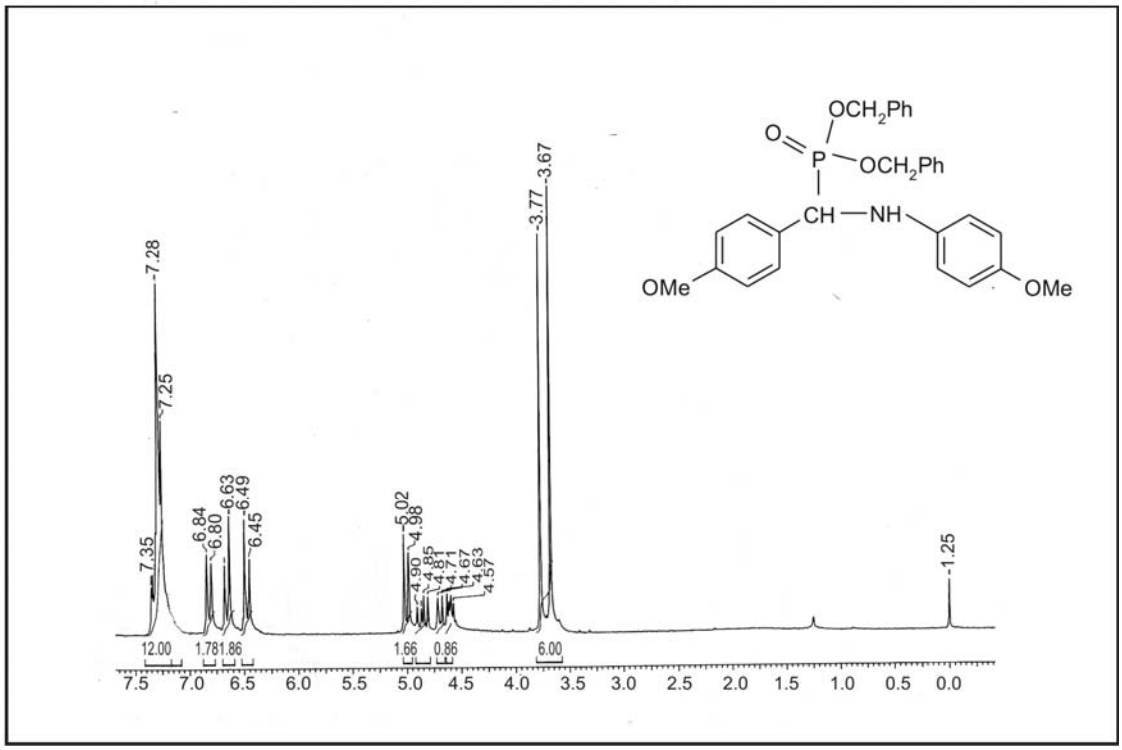
^{31}P NMR (200 MHz, $CDCl_3$) : δ 31.5.

MS (ESI) : 450.01 (M^++1), 314.01.

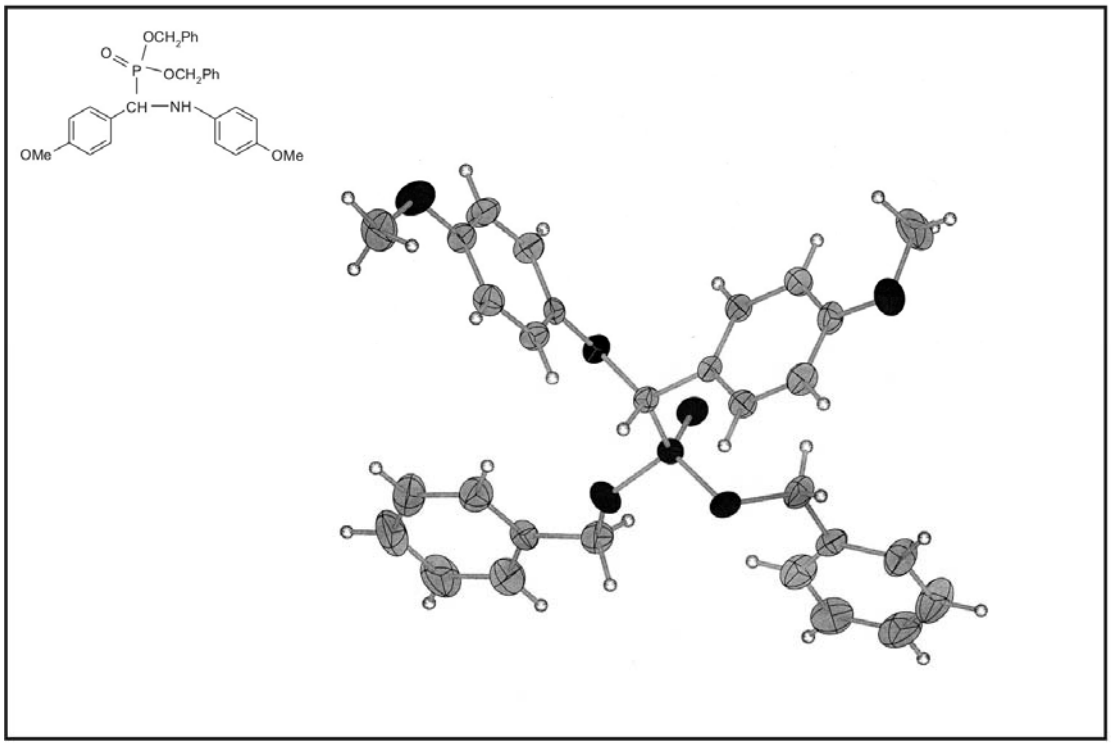
^{1}H NMR of (4-methoxyphenylamino-4-methoxyphenylmethyl) -phosphonic acid dimethyl ester



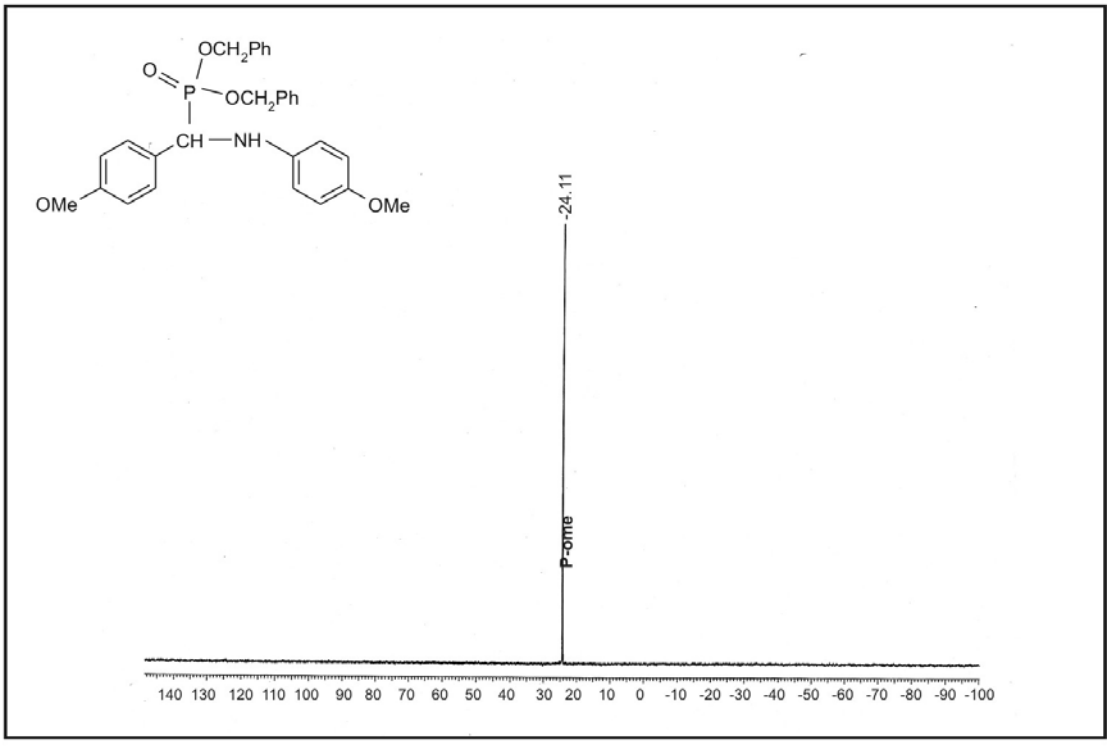
^{1}H NMR of (4-methoxyphenylamino-4-methoxyphenylmethyl)- phosphonic acid dibenzyl ester



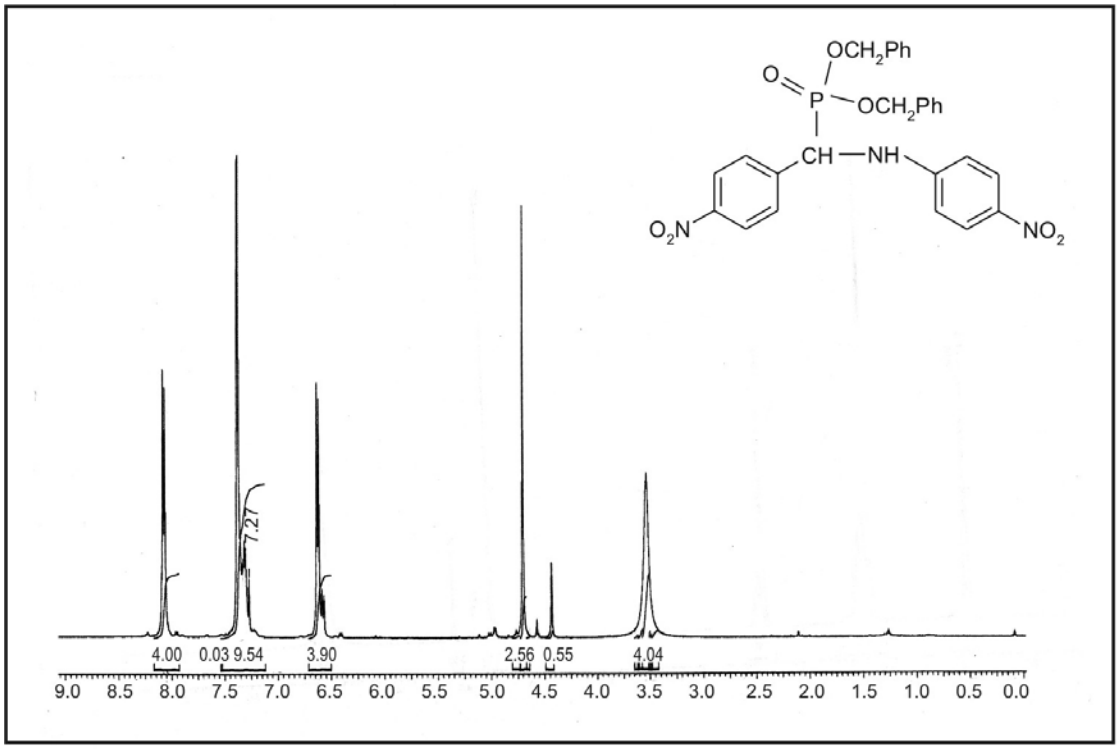
XRD of (4-methoxyphenylamino-4-methoxyphenylmethyl)-phosphonic acid dibenzyl ester



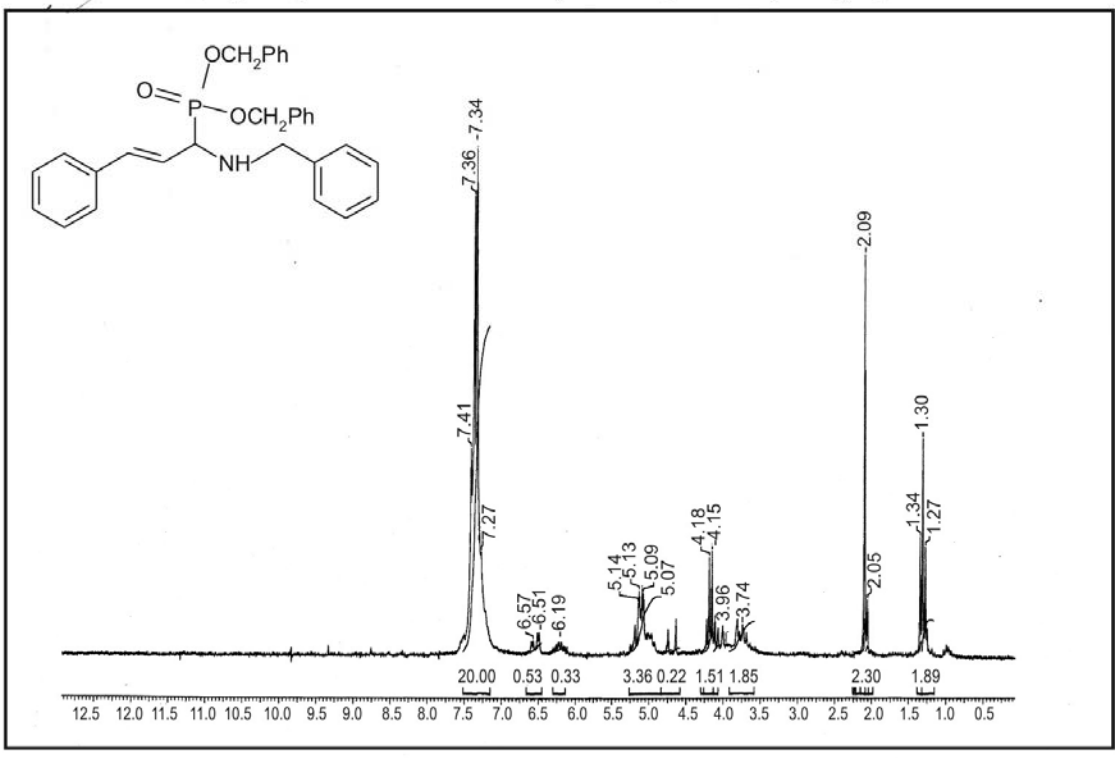
^{31}P NMR of (4-methoxyphenylamino-4-methoxyphenylmethyl)-phosphonic acid dibenzyl ester



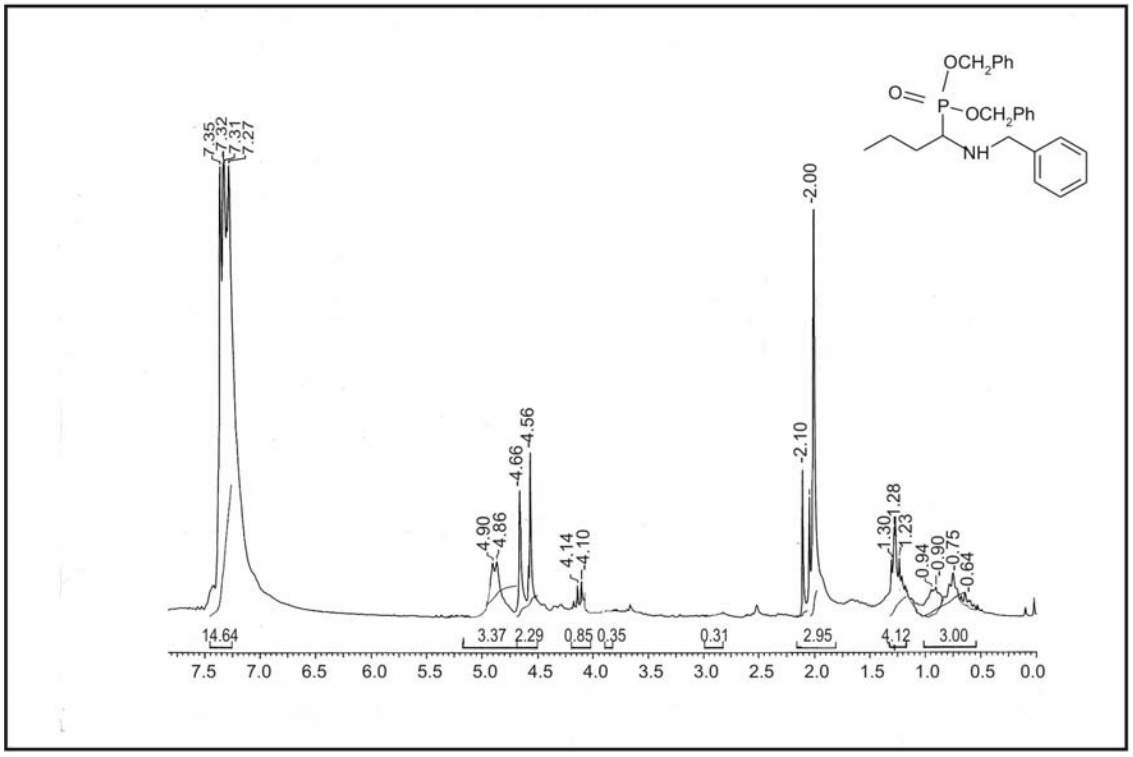
^{1}H NMR of (4-nitrophenylamino-4-nitrophenylmethyl)-phosphonic acid dibenzyl ester



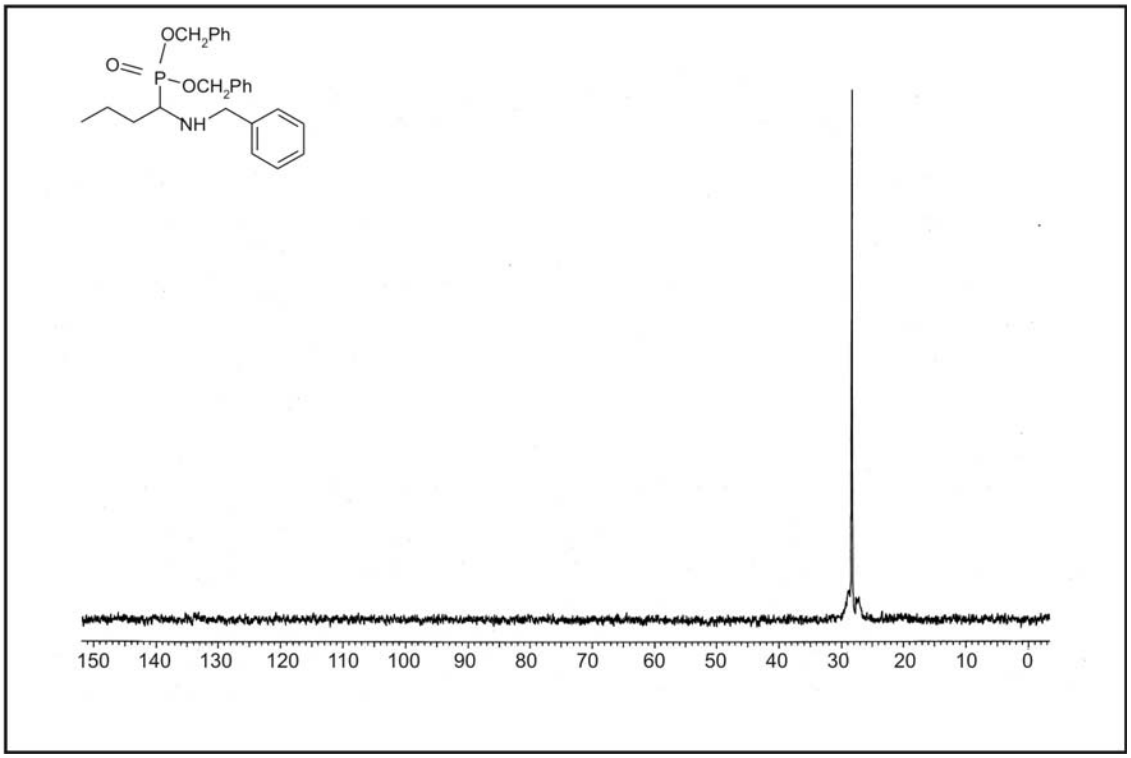
^{1}H NMR of (1-benzylamino-3-phenyl-allyl) - phosphonic acid dibenzyl ester [Table 2,entry 4]



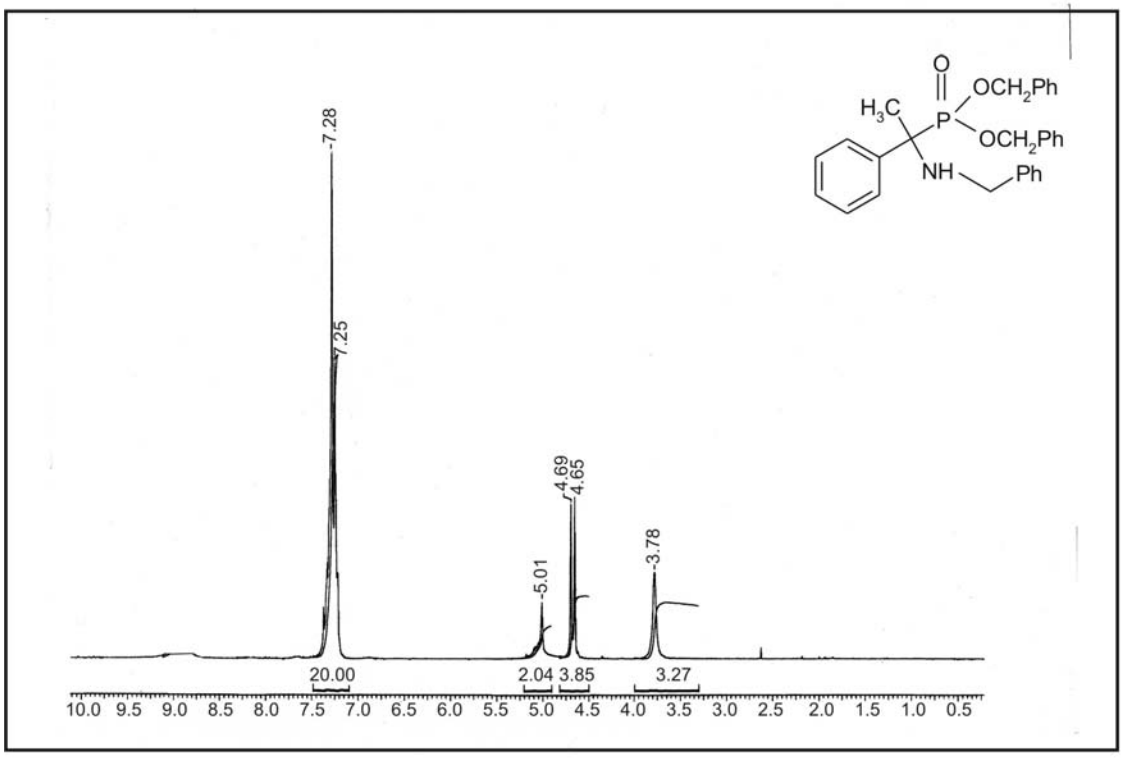
^{1}H NMR of (1-benzylamino-pentyl)-phosphonic acid dibenzyl ester [Table 2, Entry 6]



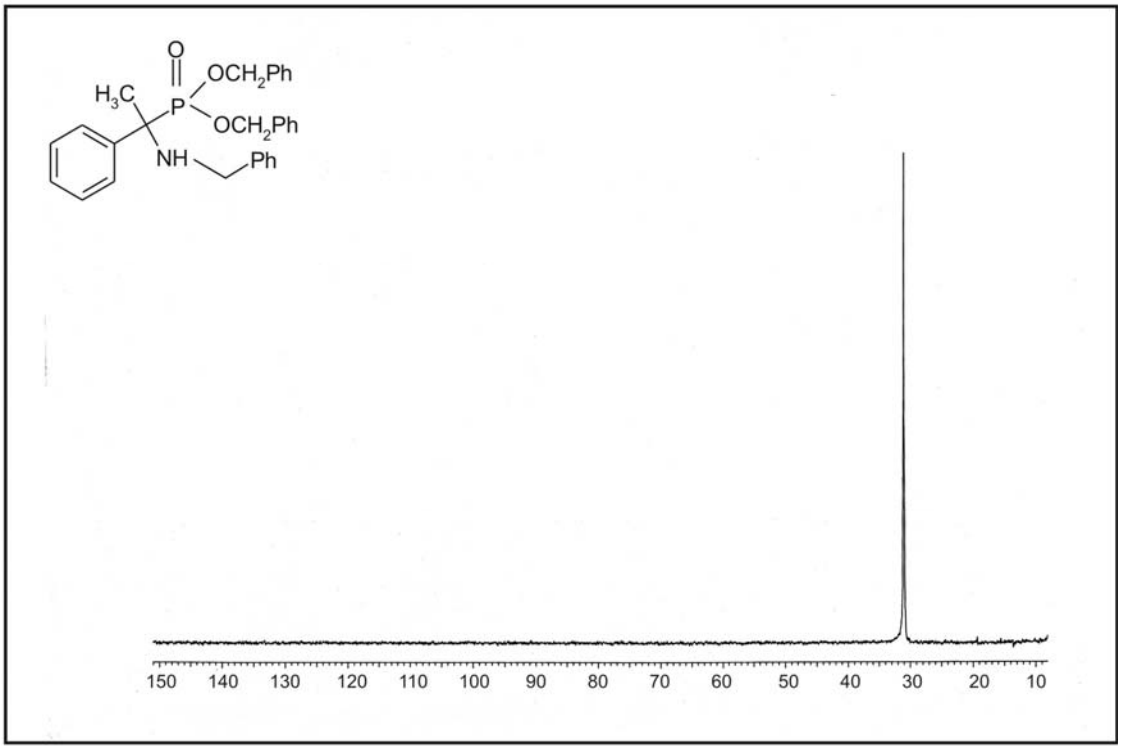
^{31}P NMR of (1-benzylamino-pentyl)-phosphonic acid dibenzyl ester [Table 2, Entry 6]



^{1}H NMR of (1-benzylamino-1-phenyl-ethyl)-phosphonic acid dibenzyl ester [Table 2, entry 7]



^{31}P NMR of (1-benzylamino-1-phenyl-ethyl)-phosphonic acid dibenzyl ester [Table 2, entry 7]



3.2.6 References

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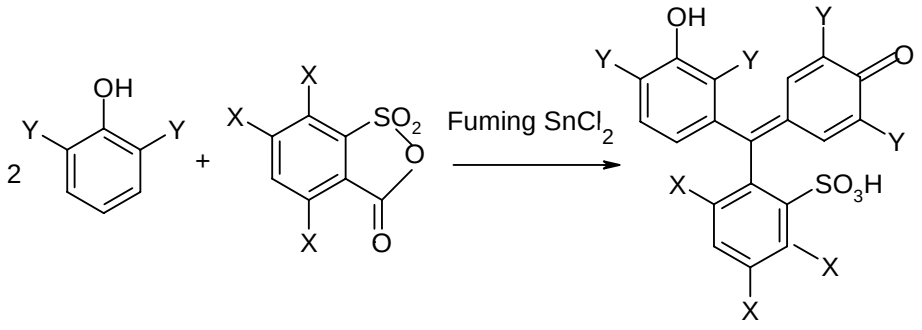
CHAPTER 3
(Section C)

Synthesis of Sulfonephthaleins

3.3.1 Introduction

The sulfonepthaleins constitute an interesting group of compounds. Since the discovery of sulfonefluorescein and the first synthesis of these compounds by Remsen and his co-workers in 1884,[1] they have been extensively used both as indicators and as diagnostic aids in clinical and experimental medicine. The sulfonephthaleins, in general and phenolsulfonephthaleins in particular have been much used as means of testing the renal function, since they are eliminated from the blood stream after intravenous injection almost quantitatively through the kidneys.[2] Sulfonephthaleins like bromophenol blue and bromocresol purple are used for the extractive-spectrophotometric determination of antibiotics like ofloxacin, cinnarazine, enoxacin and cisapride in bulk and dosage form. These methods are based on the formation of yellow ion–pair complexes between the basic nitrogen of the drug and sulfonephthalein dyes which were extracted in chloroform and the absorbance measured spectrophotometrically in the range of 408-412 nm.[3, 4, 5]

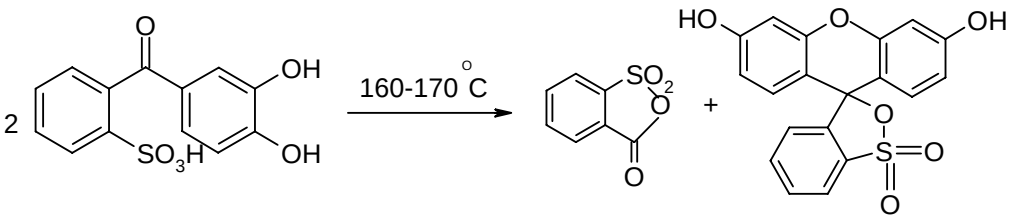
Though the sulfonephthaleins are used widely, there are very few reports about their synthesis. Wilton C. Harden and Nathan L. Drake[6] synthesized a number of sulfonephthaleins having four halogens in the o-sulfobenzoic acid part of the molecules. The sulfonephthaleins were prepared by addition of halogenated o-sulfobenzoic anhydride to phenol heated at 110ºC followed by addition of fuming stannic chloride and heating at 120-140ºC for a period of 4-12 hours. The sulfonephthaleins were obtained in low yields after the work-up of the reaction.



57 **58** **59**

Scheme 1: Synthesis of halogenated sulfonephthaleins using fuming stannic chloride

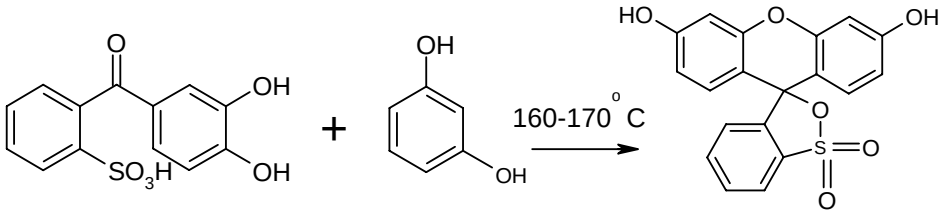
W. R. Ondarff and R. S. Vose[7] reported that sulfonefluorescein is readily formed by heating dihydroxylbenzoyl-benzene-o-sulfonic acid at 160-170ºC for two hours by eliminating o-sulfobenzoic anhydride and water.



60 **61** **62**

Scheme 2 : Synthesis of sulfonefluorescein from dihydroxybenzoyl-benzene-o-sulfonic acid

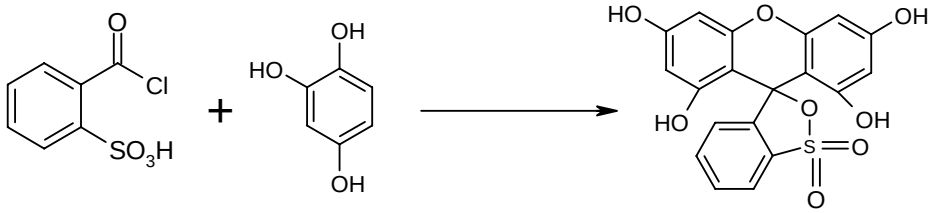
Further modification of the above route by heating the acid with resorcinol at 160-70ºC resulted in the formation of sulfonefluorescien with more efficiency (scheme 3).



60 **63** **62**

Scheme 3: Synthesis of sulfonefluorescein

W.Orndroff and A. Purdy[8] prepared hydroxyhydroquinolsulfonephthalein **66** by heating o-sulfobenzoic acid chloride with hydroxylhydroquinol at 90 – 120ºC to yield 40% of the desired product (scheme 4).

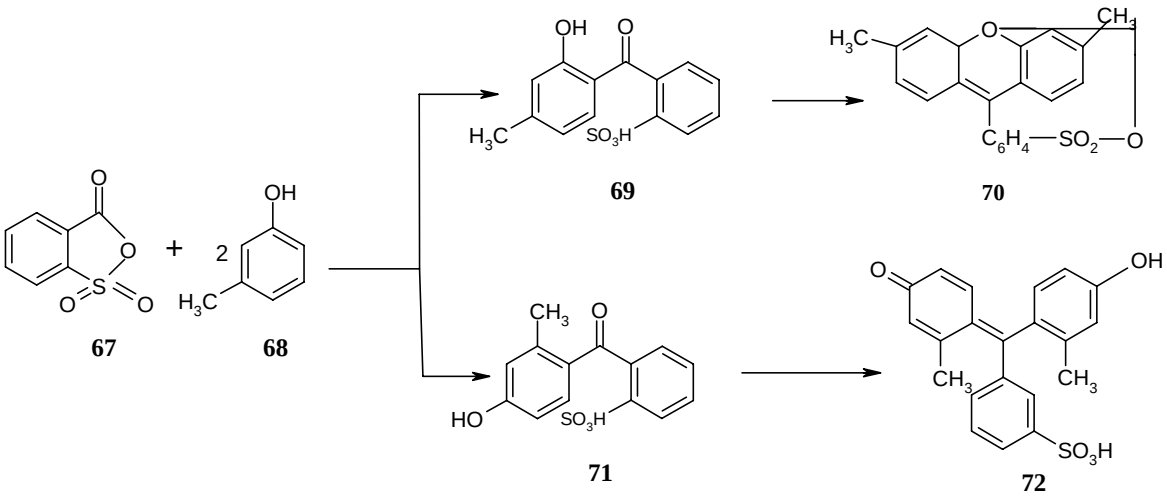


64 **65** **66**

Scheme 4: Synthesis of hydroxyhydroquinolsulfonephthalein

However, better yields were obtained (80%) when hydroxyhydroquinol triacetate was heated with o-sulfobenzoic anhydride for eight hours at 140ºC .

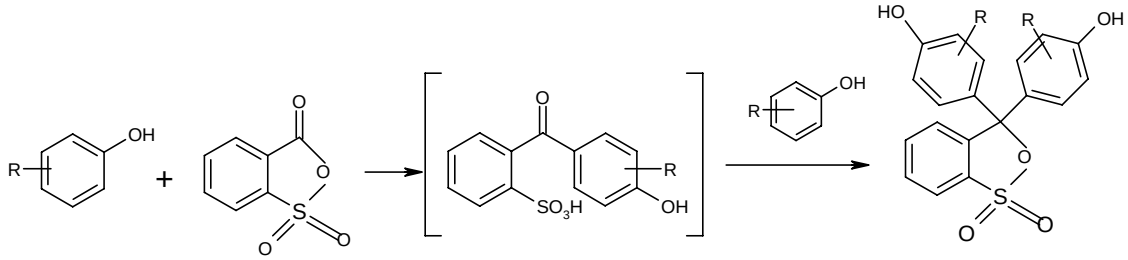
In the detailed study for preparation of meta-cresol sulfonephthalein, Orndorff and Purdy[9] found that the products of the condensation of m-cresol with o-sulfobenzoic acid anhydride depend on the temperature of the reaction. They reported that the m-cresolsulfonephthalein was obtained in 15% yield when one mole of anhydride was dissolved in two moles plus a slight excess of m-cresol and treated with zinc chloride (weight equal to that of m-cresol). This mixture was heated at 105-108ºC until the mass solidified. However when the reaction was carried out at 145ºC without employing any condensing agent, 20% dimethyl sulfone fluoran (**70**) was formed.



Scheme 5: Formation of m-cresolsulfonephthalein/dimethylsulfone fluoran depending on temperature

However under these conditions, a large amount of highly coloured substance insoluble in water and Na_2CO_3 solution was obtained which was difficult to characterize. The meta cresol sulfonephthalein in 20% yield was also prepared by condensing m-cresol with the sulfonechlorides at a temperature of 105 – 110ºC using zinc chloride as a condensing agent.

The formation of sulphonephthalein from substituted phenol and o-sulfobenzoic anhydride has been extensively studied. The formation of the sulfonephthalein takes place in two stages. First a molecule of anhydride combines with a molecule of substituted phenol to form addition compound, a tautomeric substance the intermediate acid **75**. The intermediate acid then reacts with one mole of phenol to give the corresponding sulfonephthalein.



73 **74** **75** **76**

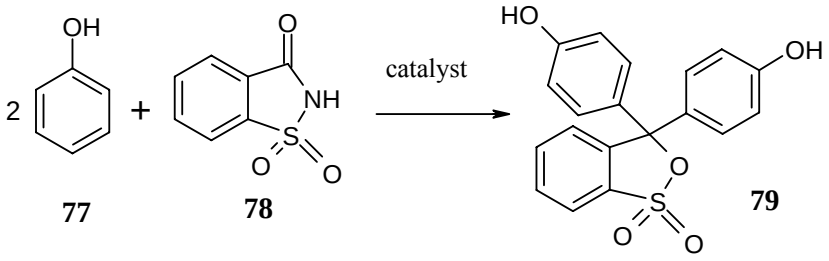
Scheme 5 : Mechanism for formation of sulfonephthalein from sulfobenzoic anhydride and phenol

3.3.2 Present work

Considering the importance of phenolsulfonephthalein group of compounds as indicators and diagnostic aid in clinical field, synthesis of these molecules was undertaken. The main purpose was to use readily available saccharin as the starting material in place of the o-sulfobenzoic acid or anhydride. The reported preparation of phenolsulfonephthalein involved a two step synthesis in which o-sulfobenzoic anhydride has been prepared in first step which on reaction with phenol led to the desired bisphenol. The one-pot synthesis of sulfonephthaleins via the *in situ* prepared o-sulfobenzoic anhydride has many advantages over conventional synthesis like enhancement in yield, simplification, reduced reaction and process time.

It has been reported that saccharin undergoes hydrolysis with agents like H_3PO_4, H_2SO_4 etc. to give o-sulfobenzoic anhydride. It was envisaged that hydrolysis of saccharin would lead to formation of sulfobenzoic anhydride and this should react *in situ* with two moles of phenols to yield phenolsulfonephthalein in one-pot. Our efforts in this direction using different acidic conditions including heterogeneous catalysts to achieve optimum conditions for one-pot preparation have been discussed in this section.

The reaction conditions were optimized for synthesis of phenol sulfonephthalein by condensation of saccharin with phenol (scheme 6).



77 **78** **79**

Scheme 6: Optimization for synthesis of phenlosulfonephthalein

Several homogeneous and heterogeneous catalysts were tested for this reaction and the results are presented in Table 1.

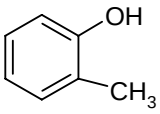
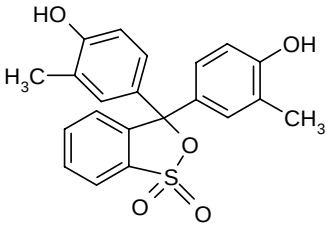
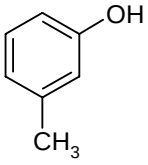
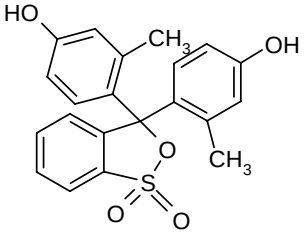
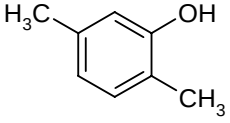
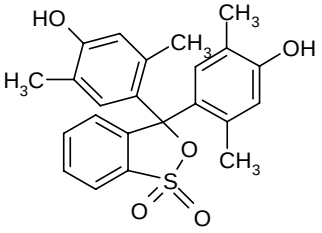
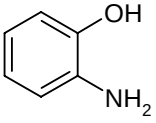
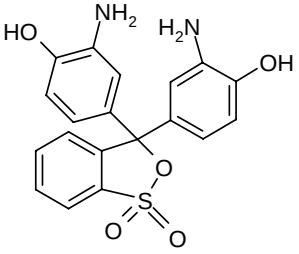
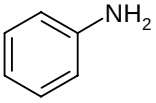
Table 1: Optimization for synthesis of phenlosulfonephthalein

Expt. No.	Saccharin	Phenol	Catalyst	Temp. °C	Time hrs	Yield[a] (%)
1	1 mmol	3 mmol	H_2SO_4, 3 eq	140	3.5	26
2	1 mmol	3 mmol	Oleum, 3 eq	140	3.5	4
3	1 mmol	2 mmol	H_2SO_4, 2 eq	140	3.5	18
4	1 mmol	3 mmol	H_2SO_4, 3 eq	100-110ºC	5	5
5	1 mmol	2.2 mmol	H_2SO_4, 3 eq	140	3.5	27
6	1 mmol	3 mmol	HCl , 3 eq.	140	3.5	-
7	1 mmol	3 mmol	$ZnCl_2$, 10%	140-60	10	-
8	1 mmol	3 mmol	EPZ-10, 20%	140-60	10	-
9	1 mmol	3 mmol	Hβ, 20%	140	5	No reaction
10	1 mmol	3 mmol	Dowex-50 20%	140	5	No reaction

a : Yields indicated here are isolated yields. Phenol red is water soluble and could not be fully recovered after work-up.

Different sulfonephthaleins were synthesized under the optimized reaction conditions using 3 equiv. H_2SO_4; the results of which are presented in Table 2.

Table 2: Synthesis of sulfonephthaleins

Expt No.	Substituted phenol for 1 mmol saccharin	Temp.	Time	Product	Yield (%)
1.		140ºC	4h		33
2.		110ºC	4h		34
3.		110ºC	4h		18
4.		140ºC and 160-170ºC	4h 2h		21
5.		140ºC	4h	-	--

Condensation of saccharin with phenol was also attempted under microwave in an attempt to improve the isolated yield. Other reagents like BF_3-etherate, Dowex-50, Amberlyst-15, HCl, Hβ zeolite, HY zeolite, $ZnCl_2$ were used to replace H_2SO_4, however only sulfuric acid or oleum could give the desired conversion as depicted in Table 3.

Table 3: Reaction of saccharin with phenol in microwave oven at 700W

Expt No.	Saccharin	Phenol	Catalyst	Time	Yield of Phenolsulfonephthalein (%)
1.	1 equiv	2.2 equiv	H_2SO_4 (3eq)	36 sec	21
2.	1 equiv	3 equiv	H_2SO_4 (3eq)	36 sec	22
3.	1 equiv	2.2 equiv	BF_3 etherate	2 min.	No reaction
4.	1 equiv	2.2 equiv	Dowex-50	2 min.	--
5.	1 equiv	2.2 equiv	Amberlyst-15	2 min	--
6.	1 equiv	2.2 equiv	HCl	2 min	--
7.	1 equiv	2.2 equiv	Hβ	2 min	--
8.	1 equiv	2.2 equiv	HY	2 min	--
9.	1 equiv	2.2 equiv	$ZnCl_2$	2 min	--
10.	1 equiv	-	H_2SO_4 drops	2 min	93% 2- sulfobenzoic anhydride

As seen in Table 3, the optimum yield of phenolsulfonephthalein was obtained by irradiating 1 equivalent of saccharin with 2.2 equivalent of phenol and 3 equivalent of H_2SO_4 in domestic microwave for 36 seconds. The synthesis of other sulfonephthaleins

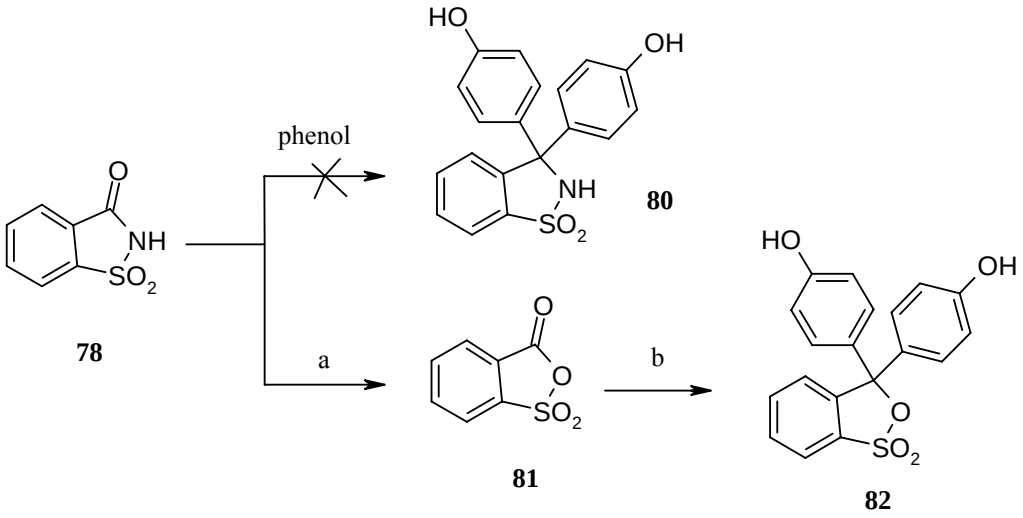
was attempted in microwave and the results of these experiments are presented in Table 4.

Table 4: Microwave mediated synthesis of sulfonephthalein

Expt No.	Saccharin	Phenol	Time	Yield (%)
1.	1 equiv	Phenol 0.5 equiv	32 sec	10
2.	**1 equiv**	**Phenol 2.2 equiv**	**36 sec**	**40**
3.	1 equiv	o- Cresol 2.2 equiv	36 sec – 2.0 min	-
4.	1 equiv	m-Cresol 2.2 equiv	36 sec – 2.0 min	-
5.	1 equiv	2,5-Dimethylphenol 2.2 equiv	36 sec – 2.0 min	-
6.	1 equiv	2-Aminophenol 2.2 equiv	32 sec	-
7.	1 equiv	2-Aminophenol 0.5 equiv	32 sec	41
8.	1 equiv	o-Cresol 0.5 equiv	32 sec	-
9.	1 equiv	m-Cresol 0.5 equiv	32 sec	15
10.	1 equiv	2,5-Dimethylphenol 0.5 equiv	32 sec	-

3.3.3 Results and discussion

As can be seen from Table 1, the optimum yield of phenol sulfonephthalein was obtained when 1 mmol of saccharin and three equivalent of concentrated H_2SO_4 (98%) were heated with 2.2 mmol of phenol at 140ºC for 3.5 hours. The product was identified as phenol red by direct comparison with the commercial sample. All the spectral and analytical data (HPLC) of our product were in full agreement with the commercial sample of phenol red. Elemental analysis showed absence of nitrogen thus ruling out the formation of phenolsulphamphthalein **80**.These results indicated that perhaps saccharin might be getting hydrolyzed to form 2-sulphobenzoic anhydride (**81**, scheme 7) with elimination of ammonia in the form of ammonium sulphate and the resulting 2-sulphobenzoic anhydride reacted with phenol to form phenol red. To confirm this assumption, saccharin was heated with concentrated H_2SO_4 at 140°C for 3 hours. After cooling the reaction mixture and usual work up, a colourless crystalline product obtained was characterized with the help of NMR and mass spectroscopy as 2-sulphobenzoic anhydride **81** (m.p.121°C, Lit. m.p[3]. 120°C). The elemental analysis of **81** showed the absence of nitrogen. When saccharin was heated with 20% oleum at 140°C for 3 hours 2-sulphobenzoic anhydride **81** was obtained after usual work up**.**



a) Conc. H_2SO_4 / oleum, 140°C, 3hr. b) Phenol, conc. H_2SO_4, 140°C, 3 hr.

Scheme 7 : Synthesis of phenolsulfonephthalein from phenol and saccharin

It is noteworthy from Table 2 that the reaction was selective for phenols and the amine functionality (Table 2, entries 4 and 5) did not react under these reaction conditions. All the products were identified by spectral analysis and exhibited different colours e.g. products from o-cresol, m-cresol, xylenol and aminophenol had red, purple, blue and purple colours respectively.

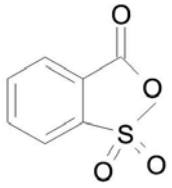
Unfortunately this condensation of saccharin with o-cresol, m-cresol and 2-aminophenol under microwave conditions was not consistent. Although the yields of phenol red and product from 2- aminophenol (Table 4, entries 2 and 7 respectively) were on higher side, o/m-cresols and xylenol did not react to give the corresponding products. The synthesis of sulfonephthaleins could not be achieved in microwave probably due to the lack of control of reaction temperature in the domestic microwave oven.

3.3.4 Conclusion

Synthesis of sulfonephthalein was achieved in one-pot from saccharin and (un) substituted phenol *via* the *in situ* formation of 2-sulfobenzoic anhydride. The synthesis from saccharin instead of the expensive sulfobenzoic anhydride, use of H_2SO_4 as condensing agent and solvent free reaction makes this method more economic and environmentally friendly.

3.3.5 Experimental

Preparation of 2-sulfobenzoic anhydride:



a) In a thick glass vial saccharin (100 mg) and conc. H_2SO_4 (3 drops) were added and the mixture was heated in microwave oven for 32 seconds. A clear colourless solution was obtained which on standing became crystalline solid product.

   Yield: 95 mg (95%) Mp. 121ºC.

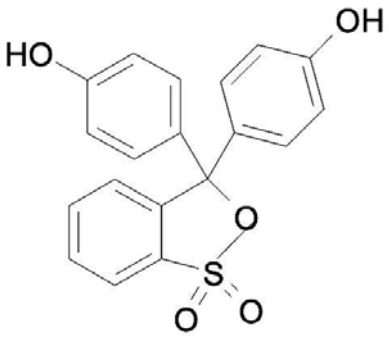
   The same reaction carried out by using oleum (3 drops) for 47 seconds yielded 93 mg (93%) of the product.

b) A mixture of saccharin (100 mg) and conc. H_2SO_4 (3 drops) was heated at 140ºC for 3 h in an oil bath. On cooling, a colourless crystalline solid product was obtained which showed sharp melting point at 121ºC.

   ^{1}H NMR (DMSO d_6 + $CDCl_3$) : δ 8 .10-8.33 (m, 4H, ArH).

   Mass m/e : 184 (M^+), 120, 104, 92, 76 (100), 64.

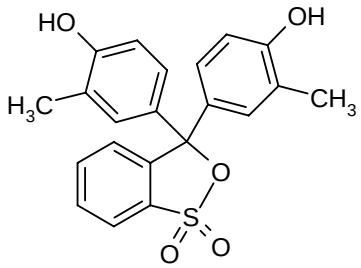
Synthesis of 3, 3-bis (4-hydroxybenzoxathiole 1,1-dioxide (Phenol red) [Table 1, entry 5]



To a three necked round bottom flask with magnetic needle, water condenser and $CaCl_2$ guard tube, saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added. The reaction mixture was heated to 140ºC for 1 hour and 2.2 mmol phenol was added to it. The reaction mixture was then heated under stirring at 140ºC for 4 hours. After completion of reaction (TLC), the reaction mixture was poured in to ice water and steam distillation was carried out to remove phenol. The crude product was washed with benzene and diethylether to remove saccharin. The residue was then dissolved in hot sodium carbonate solution, filtered and filtrate acidified with dil. HCl. The coloured solid product precipitated was filtered, dried and purified by column chromatography on silica gel.

IR (nujol)	:	1583.94, 1553.83, 1460.01, 1366.04 cm^{-1}.
^1H NMR	:	δ 7.52 (d, J = 8 Hz, 4H) 7.83 (dd, J = 8 Hz, 8H),
(DMSO d_6 + $CDCl_3$)		8.08-8.63 (m, 4H).
^{13} C NMR (200 MHz)	:	δ 156.99, 139.84, 131.87, 130.20, 128.55,
(DMSO d_6 + $CDCl_3$)		127.57, 113.65, 9928, 93.88.

Synthesis of 3, 3-bis (4-hydroxy-2-methylphenyl) –3*H* – 2, 1 λ^6 benzoxathiole 1, 1-dioxide (o-Cresol red) [Table 2, entry 1]

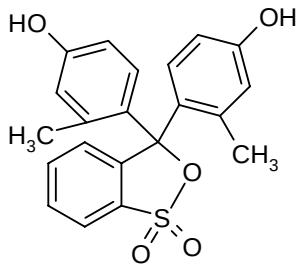


To a three necked round bottom flask with magnetic needle, water condenser and $CaCl_2$ guard tube, saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added. The reaction mixture was heated to 140ºC for 1 hour and 2.2 mmol o-cresol was added to it. The reaction mixture was then heated under stirring at 140ºC for 4 hours. After completion of reaction (TLC), the reaction mixture was poured in to ice water and steam distillation was carried out to remove unreacted o-cresol. The crude product was washed with benzene

and diethylether to remove saccharin. The residue was then dissolved in hot sodium carbonate solution, filtered and filtrate acidified with dil. HCl. The coloured solid product precipitated was filtered, dried and purified by column chromatography on silica gel.

IR (nujol)	:	2924.68, 2854.74, 1625.01, 1459.4 cm^{-1}.
^{1}H NMR (200 MHz) (DMSO d_6 + $CDCl_3$)	:	δ 1.34 (s, 6H), 5.87 (d, J=6 Hz, 2H), 6.34-6.41 (m, 4H), 6.70-6.76 (m, 2H), 7.34 (d, J=6 Hz, 2H).
^{13} C NMR (200 MHz) (DMSO d_6 + $CDCl_3$)	:	δ 168.48, 152.83, 141.63, 136. 66, 134.10, 133. 54, 128.10, 125. 80, 117.74, 77. 20, 14.88.
LCMS	:	405.0 (M^++ Na), 383.1 (M^++ 1).

Synthesis of 3, 3-bis (4-hydroxy-3-methylphenyl) – 3H – 2,1, λ^6 benzoxathiole 1,1-dioxide (m-Cresol purple) [Table 2, entry 2]

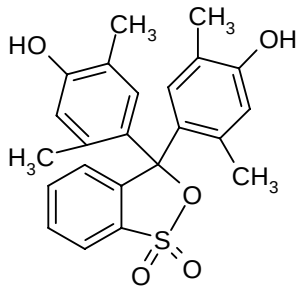


To a three necked round bottom flask with magnetic needle, water condenser and $CaCl_2$ guard tube, saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added. The reaction mixture was heated to 140ºC for 1 hour and m-cresol (2. 2 mmol) was added to it. The reaction mixture was then heated under stirring at 110ºC for 4 hours. After completion of reaction (TLC), the reaction mixture was poured in to ice water and steam distillation was carried out to remove m-cresol. The crude product was washed with benzene and diethylether to remove saccharin. The residue was then dissolved in hot sodium carbonate

solution, filtered and filtrate acidified with dil. HCl. The coloured solid product precipitated was filtered, dried and purified by column chromatography on silica gel.

IR(nujol)	:	2927.47, 2855.46, 1603.00, 1455.75, 1215.76, 757.18, 669.01 cm^{-1}.
^1H NMR (200 MHz, DMSO d_6 + $CDCl_3$)	:	δ 1.05 (s, 6H), 6.10-6.13 (m, 2H), 6.75-6.81 (m, 4H), 6.93 (d, J=6 Hz, 1H), 7.00-7.10 (m, 2H), 7.35 (d, J=6 Hz, 1H).
^{13}C NMR (300 MHz, DMSO d_6 + $CDCl_3$)	:	δ 167.89, 154.79, 142.62, 138.68, 136.24, 133.83, 133.46, 127.82, 127.12, 119.85, 117.93, 77.43, 14.59.
LCMS	:	405.2 (M^++Na), 383.3 (M^++1).

Synthesis of 3, 3-bis (4-hydroxy-2,5 dimethylphenyl)-3H-2, 1 λ^6- benzoxathiole 1,1-dioxide (p-Xylenol blue) [Table 2, entry 3]



To a three necked round bottom flask with magnetic needle, water condenser and $CaCl_2$ guard tube, saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added. The reaction mixture was heated to 140ºC for 1 hour and 2.2 mmol 2,5-dimethyl phenol was added to it. The reaction mixture was then heated under stirring at 110ºC for 4 hours. After completion of reaction (TLC), the reaction mixture was poured in to ice water and steam distillation was carried out to remove 2,5-dimethyl phenol. The crude product was washed with benzene and diethylether to remove saccharin. The residue was then dissolved in hot sodium carbonate solution, filtered and filtrate acidified with dil. HCl.

The coloured solid product precipitated was filtered, dried and purified by column chromatography on silica gel.

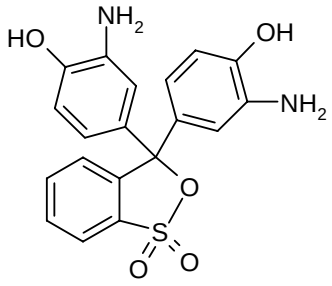
IR (nujol) : 3369.60, 2924.39, 2855.01, 1628.77, 1460.51, 1256.86, 761.76, 659.9 cm^{-1}.

^1H NMR (200 MHz, DMSO d_6 + $CDCl_3$) : δ 1.45 (s, 12H), 5.91-6.03 (m, 2H), 6.45-6.68 (m, 3H), 6.76-6.88 (m, 2H), 7.50-7.61 (m, 1H).

^{13}C NMR (200 MHz, DMSO d_6 + $CDCl_3$) : δ 167.95, 154.37, 142.89,138.37, 131.08, 128.03, 126.81, 126.35, 125.89, 77.46, 19.47, 13.70.

LCMS (m/e) : 411.2 (M^++1), 433.1 (M^++Na).

Synthesis of 3, 3-bis (2-amino-4-hydroxyphenyl)-3H-2, 1 λ^6- benzoxathiole 1, 1-dioxide [Table 2, entry 4].



To a three necked round bottom flask with magnetic needle, water condenser and $CaCl_2$ guard tube, saccharin (2 mmol) and H_2SO_4 (3 equivalent) were added. The reaction mixture was heated to 140ºC for 1 hour and 2-amino phenol (1 mmol) was added to it. The reaction mixture was then heated under stirring at 140 ºC for 4 hours and then 160-170ºC for 2 hours. After completion of reaction (TLC), the reaction mixture was poured in to ice water and steam distillation was carried out to remove 2-aminophenol. The crude product was washed with benzene and diethylether to remove saccharin. The residue was then dissolved in hot sodium carbonate solution, filtered and filtrate acidified with dil.

HCl. The coloured solid product precipitated was filtered, dried and purified by column chromatography on silica gel.

IR (nujol) : 3566.52, 3373.62, 3020.10, 1644.30, 1451.66, 1258.28, 753.14, 606.21 cm^{-1}.

^{1}H NMR (200 MHz, DMSO d_6 + $CDCl_3$) : δ 6.85- 6.92 (m, 6H), 6.99-7.02 (m, 2H), 7.03-7.05 (m, 2H).

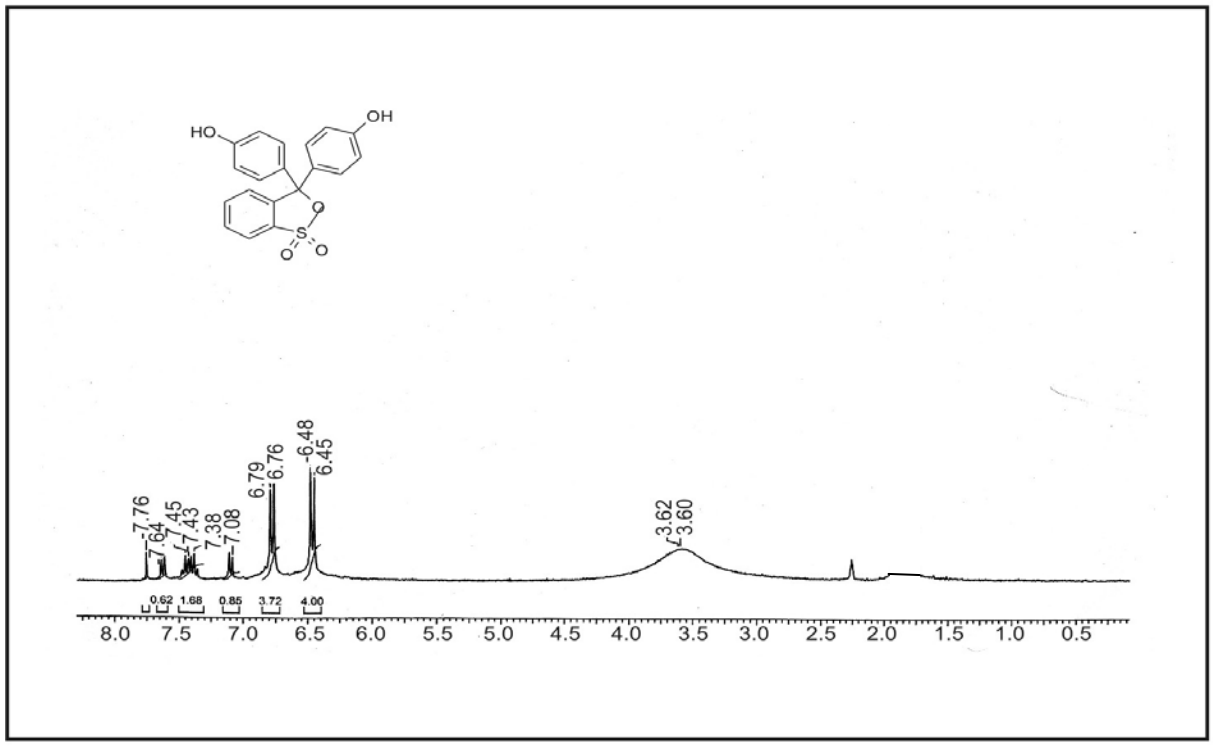
^{13}C NMR (200 MHz, DMSO d_6+$CDCl_3$) : δ 167.72, 143.08, 137.56, 132.43, 130.56, 130.13, 126.91, 124.40, 121.75, 118.05, 77.0.

LCMS : 417.10 (M^{+}+1).

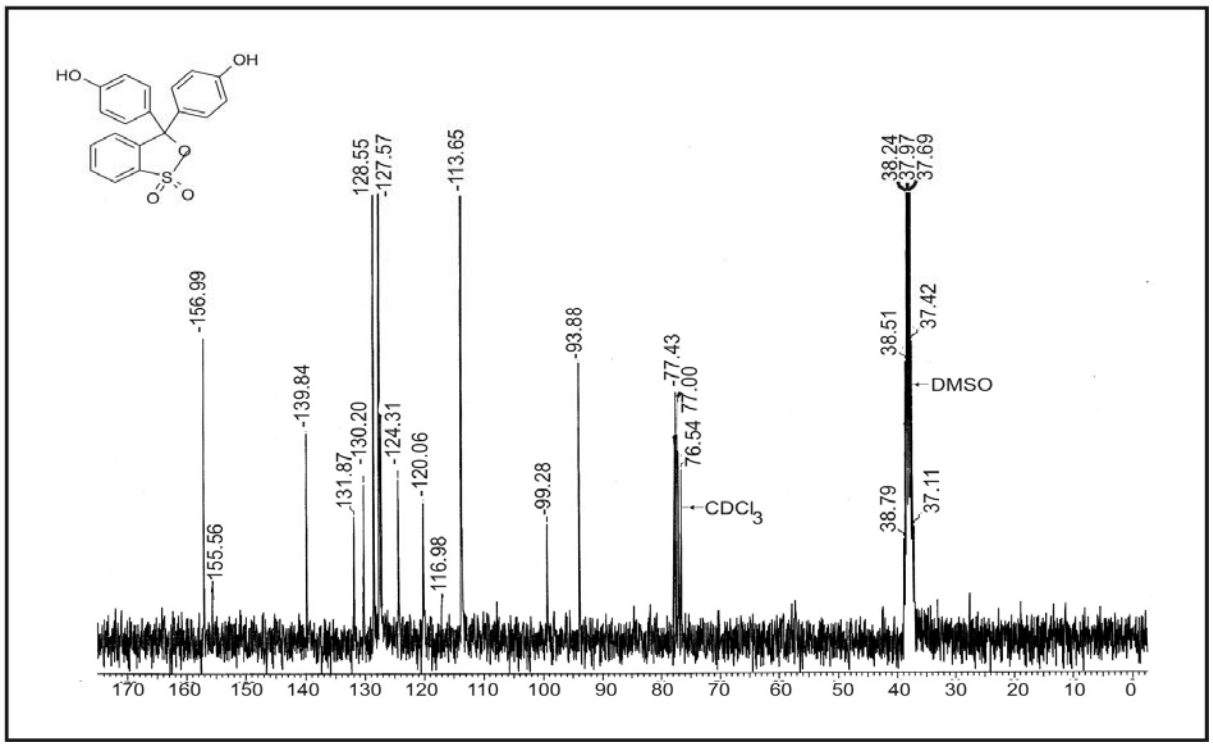
Synthesis of sulfonephthaleins in microwave :

In a thick glass vial saccharin and (un) substituted phenol in ratio 1:2.2 were added followed by addition of H_2SO_4. The vial was kept in a beaker and heated in microwave oven (720 W) for 36 seconds to 5 minutes. The coloured product was cooled and subjected to purification as described in earlier procedure.

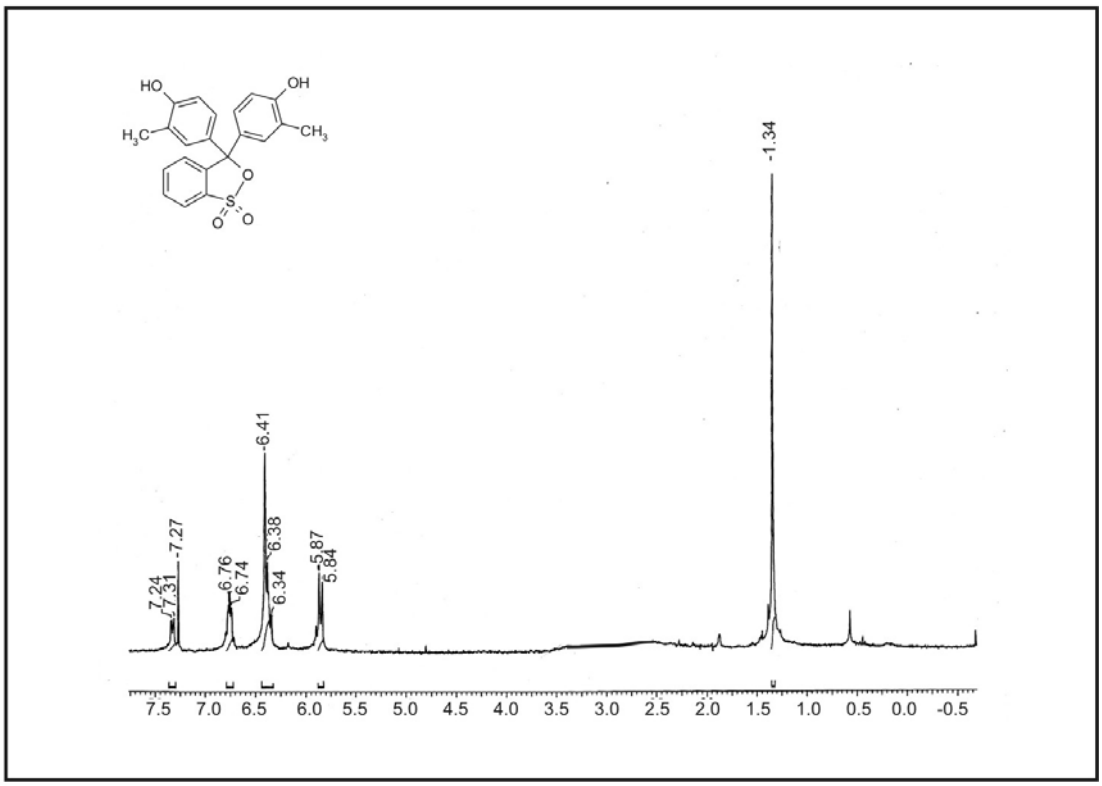
^{1}H NMR of phenol red



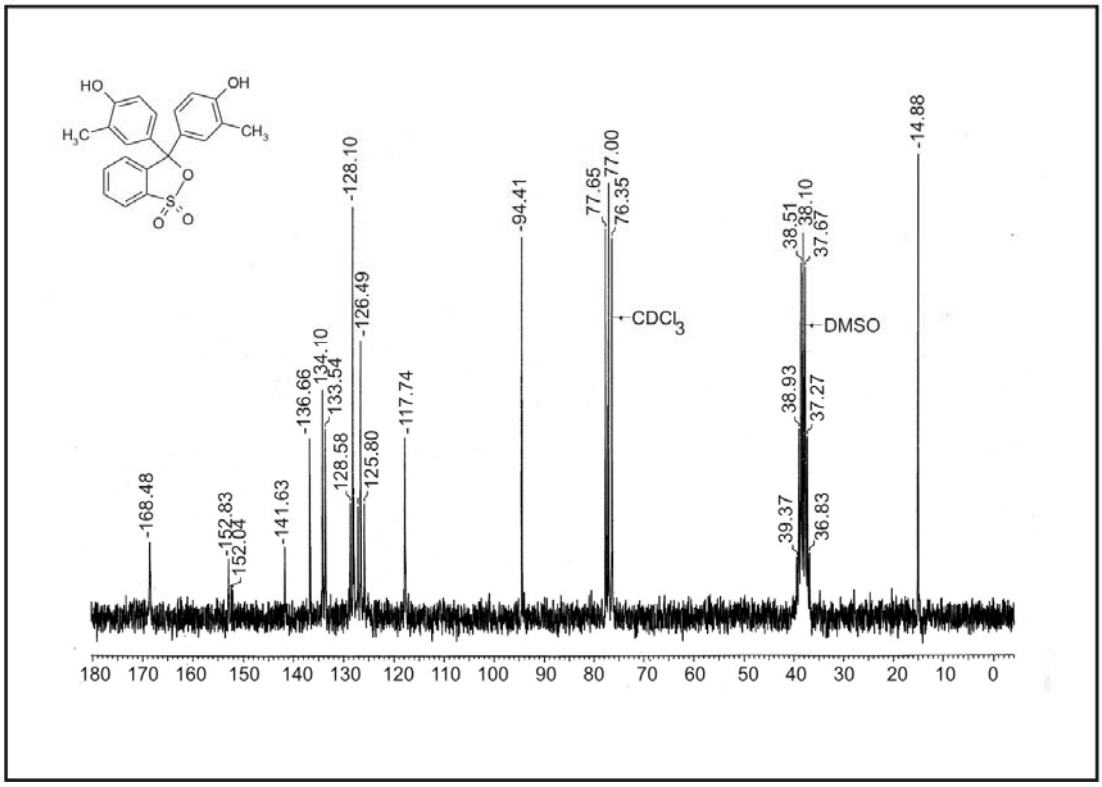
^{13}C NMR of phenol red



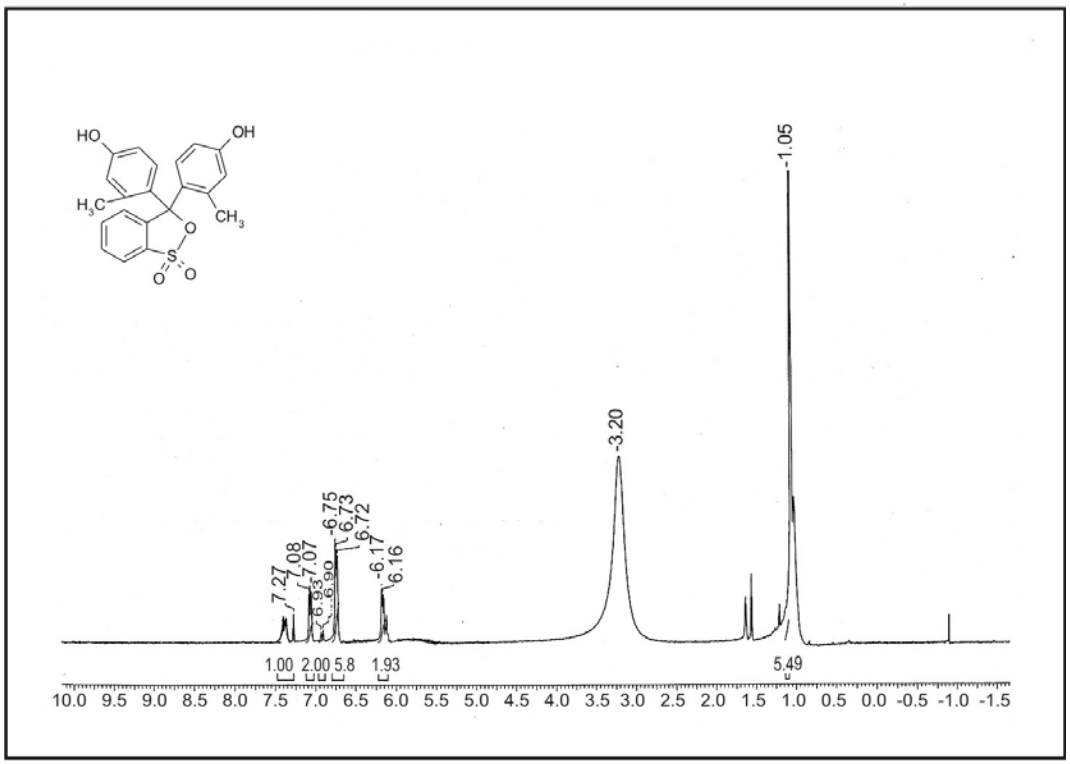
^{1}H NMR of o-cresol red



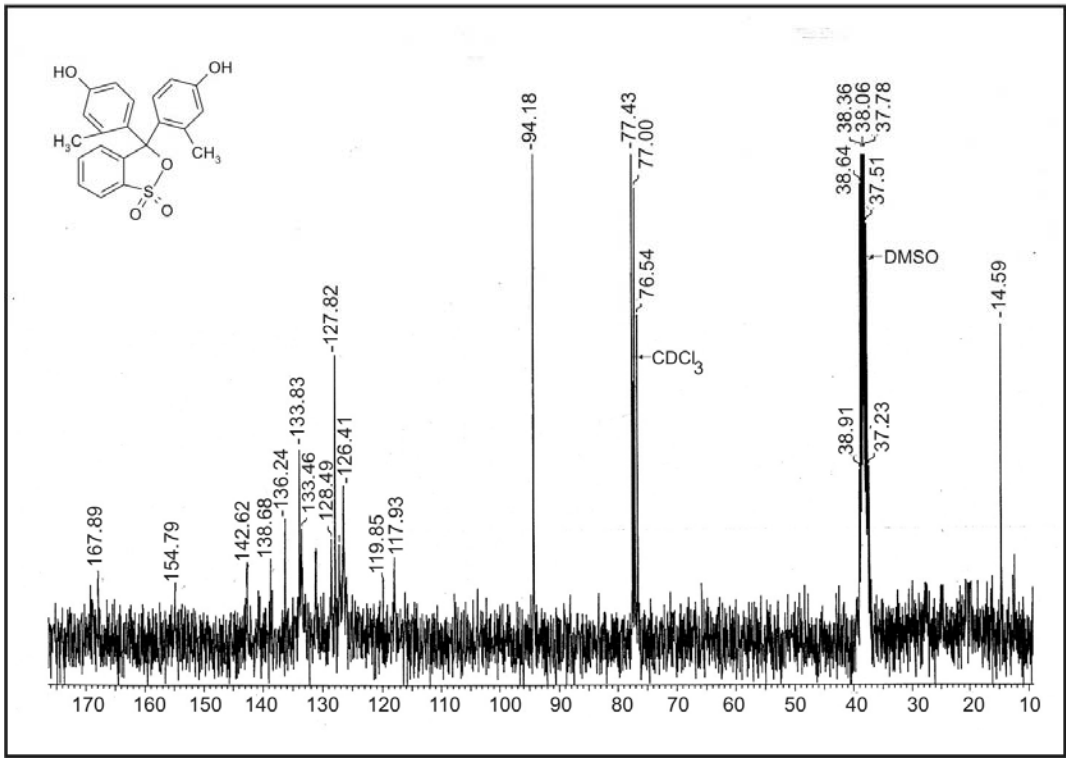
^{13}C NMR of o-cresol red



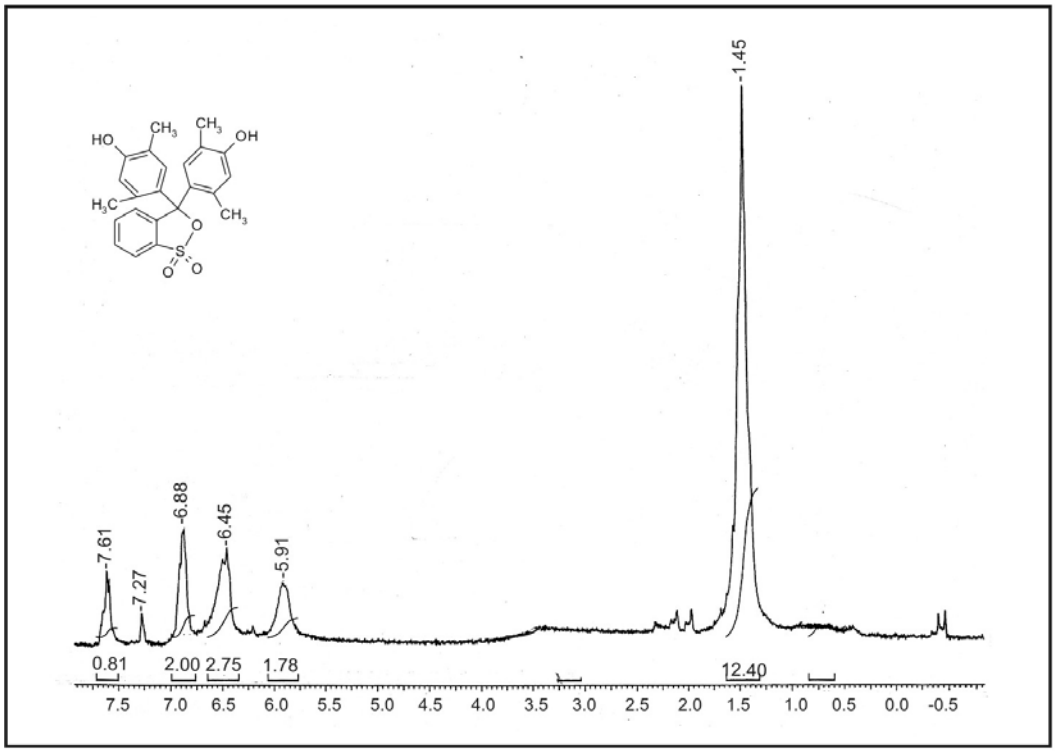
^{1}H NMR of m-cresol purple



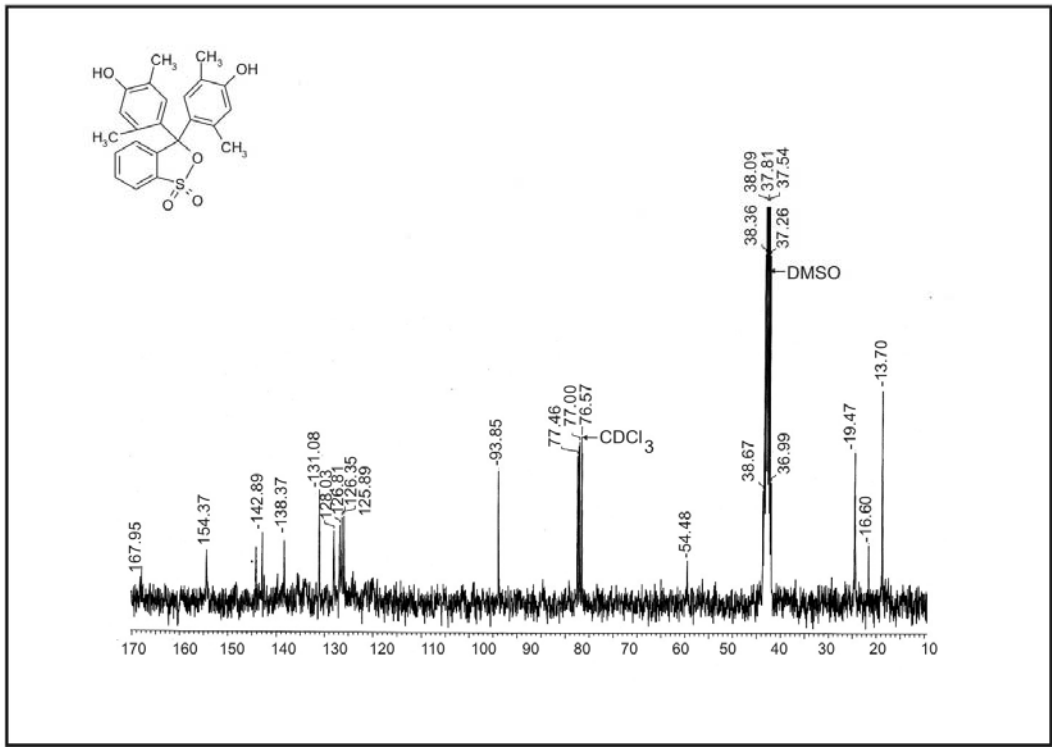
^{13}C NMR of m-cresol purple



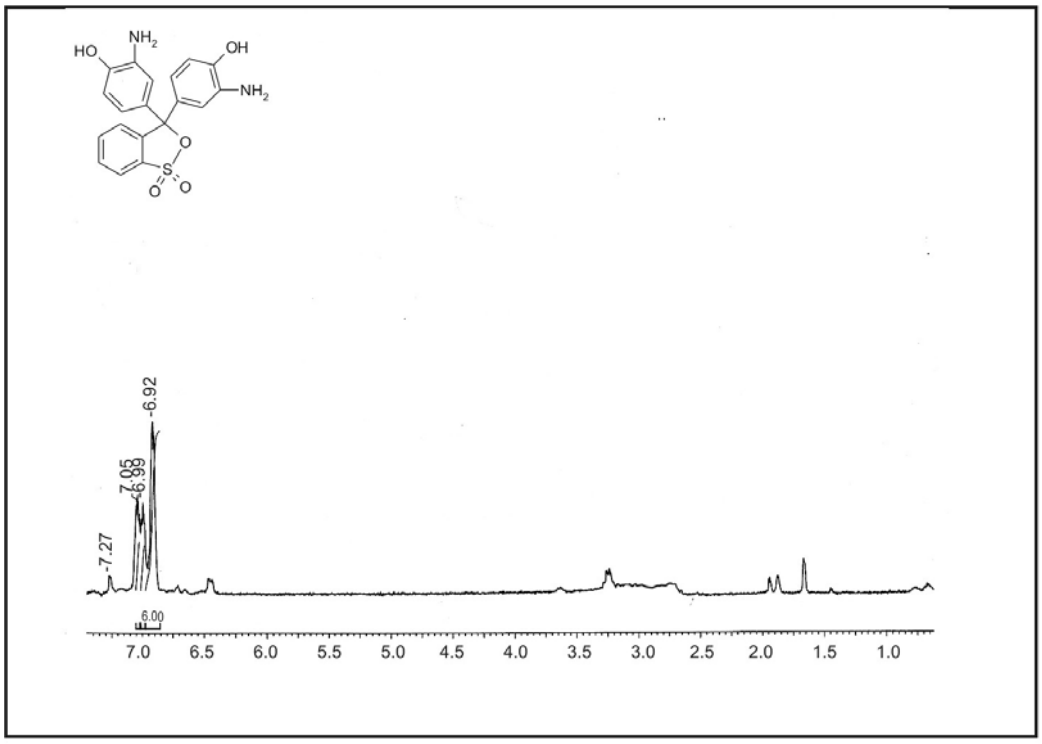
^{1}H NMR of p-xylenol blue



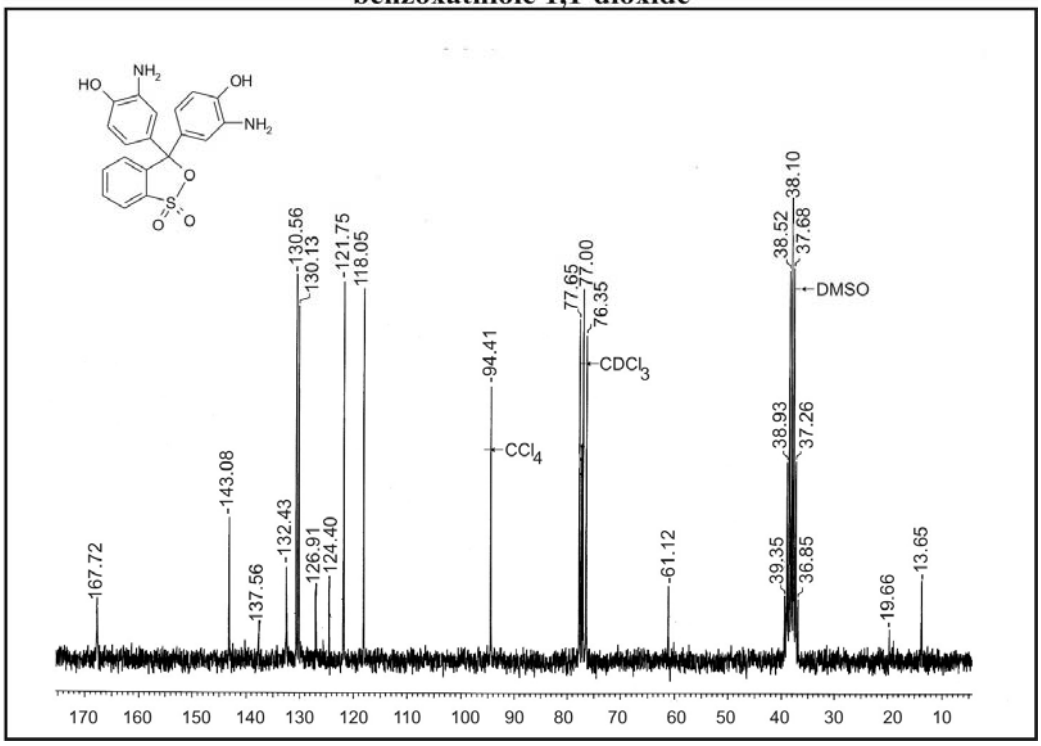
^{13}C NMR of p-xylenol blue



^{1}H NMR of 3,3-bis (2-amino-4-hydroxy phenyl)-3,H-2, 1 ^{6}-benzoxathiole 1,1-dioxide



^{13}C NMR of 3,3-bis (2-amino-4-hydroxy phenyl)-3,H-2, 1 ^{6}-benzoxathiole 1,1-dioxide



3.3.6 References

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