Newer Catalytic Methodologies for C-C, C-N bonds formation and Oxidation of Sulfides, Bromide and Aldehydes with H_2O_2

A thesis submitted in part fulfillment of the requirements
for the degree of
Doctor of Philosophy

By

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Dedicated to

My Parents

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Declaration

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemical Sciences, Tezpur University, India under the guidance of Professor Mihir K. Chaudhuri, FASc., FNA, Vice Chancellor, Tezpur University and Dr. Ashim J. Thakur, Associate Professor, Department of Chemical Sciences, Tezpur University.

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

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CERTIFICATE

This is to certify that the thesis entitled "*Newer Catalytic Methodologies for C-C, C-N bonds fromation and Oxidation of Sulfides, Bromide and Aldehydes with* H_2O_2" submitted to the School of Science, Tezpur University in part fulfillment for the award of the degree of Doctor of Philosophy in Chemical Sciences is a record of research work carried out by Mr. Dhrubajyoti Talukdar under our supervision and guidance.

All help received by him from various sources have been duly acknowledged.
No part of this thesis has been submitted elsewhere for award of any other degree.

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I thank my father for the lessons he taught me when I was a child, and...for his blessings, which are always with me.

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Dhrubajyoti Talukdar.

(Dhrubajyoti Talukdar)

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The aforementioned title of the thesis is based on a few chosen aspects of catalysis for some important reactions *viz.* C-C, C-N bond forming reactions and synthetically consequential oxidation process. The main text has been divided into five chapters. The Chapter 1 includes the introduction of the thesis which gives a brief description of the importance and the current developments in this field. The second chapter provides experimental procedures, sources of reagents and solvents, particulars of the equipments and instruments used. Chapters 3 to 5 present the newer results inferred during the Ph.D. research work.

Chapter 1: Introduction and Scope of the Work

This chapter presents a brief account of prior arts of reactions following green chemistry principles, as well as the peroxometal based oxidation chemistry. Importance of C-C, C-N bonds formation and oxidations of sulfides, bromide and aldehydes with H_2O_2 are highlighted. There is a general interest related to binding, interaction and reactivity of coordination compounds of vanadium(V) centre starting from synthetic inorganic chemistry through biochemistry, theoretical chemistry and catalysis. Participation of vanadium(V) as an intermediate electron carrier in the oxidation of NADH, in stimulating nitrogen fixation and active involvement in oxidizing organics are very exciting contributions to the current knowledge of biochemical and catalytic involvement of metal.

In pursuance of sustained activity of our laboratory on peroxovanadium based oxidation chemistry, catalytic oxidation of organic sulfide selectively to sulfoxide and aldehyde to the corresponding acid and ester were chosen as a part of the present Ph.D. research project. The targeted selective oxidation was achieved by commercially available $VO(acac)_2$, V_2O_5 and newly synthesized $VO_2F(dmpz)_2$. The synthesis method of the complex $VO_2F(dmpz)_2$ has already been disclosed in one of the Ph.D. thesis from our group ; here, in this thesis, a refined and newly solved structure of the complex has been reproduced and its application in the selective oxidation of sulfides to sulfoxides has been studied.

The Carbon-Carbon(C-C) and Carbon-Nitrogen(C-N) coupling are burgeoning areas of synthetic chemistry with the potential to provide a wealth of improved protocols in synthetic organic chemistry. However, to date many challenges remain unsolved that continue to limit its synthetic utility. In consonance with the current trend and appreciating the need for clean chemistry practices, the present thesis has been

framed mainly on the development of newer catalysts for C-C and C-N coupling. The chosen organic transformations include synthesis of *β*-nitroalkanols, bis (indol-3-yl)methanes, *N*-methylamides and *N*-aryl heterocycles. The Chapters 3 and 4 of this thesis describe the C-C and C-N bond forming protocols that have been developed during my Ph.D. research.

Quaternary ammonium tribromide (QATB) is known as the solid bromine and has been used to synthesise various bromoorganics. In this thesis, a comprehensive report on the synthesis, characterization, crystal structure and bromination ability of a series of quaternary ammonium tribromide are described. Both experimental and theoretical tools have been used to study the reactivity of the tribromides for the electrophilic bromination of the organic substrates. The entitled work has been designed to meet the green chemistry principles. The catalyst that has been developed was successfully utilized for some industrially applicable organic conversions. The future scope has also been highlighted in this section.

Chapter 2: Details of General Materials, Methods and Equipments

The sources of chemicals and solvents, methods for quantitative chemical estimations, determination of elements and details of all the equipments used for physico-chemical studies are provided in this chapter. The characterization of samples was done using appropriate physico-chemical techniques.

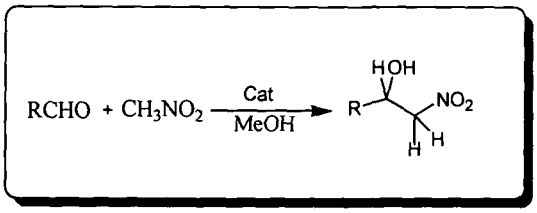
Chapter 3: Carbon-Carbon Bond forming Reactions

Section 3A: Musa balbisiana Colla: a potential renewable base for regioselective nitroaldol reaction

Henry or Nitroaldol reaction is one of the classical C-C bond forming process by which diastereomeric mixture of *β*-nitroalcohols are formed in a base catalyzed reaction between primary or secondary nitroalkanes and carbonyl derivatives. The potential chemical transformations possible from the nitroaldol product *viz.* such as reduction to amines or Nef reaction to carbonyl compounds provide numerous applications of this process. The typical nitroaldol reaction is catalyzed by base. To date, various base catalysts have been reported to catalyze the condensation reaction. Here in this thesis, I have reported a renewable base derived from *M. balbisiana*

Colla a wild variety of banana tree specially found in the south Asia to catalyze the Nitroaldol reaction.

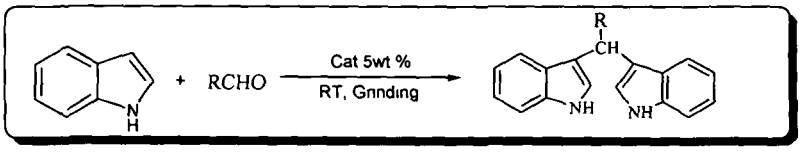
Musa balbisian Colla is a species of wild banana native to south Asia. In the north-east region of India, Assamese community uses the ash of the *M. balbisiana Colla* peal as a medicine for stomach problems especially for acidity. The ash of the *M. balbisiana Colla* peal is found to be basic. To check its activity as a basic catalyst we have used it for the catalysis of Henry reaction. It is interesting to see that the catalyst can effectively and selectively catalyses the Henry reaction affording nitroaldol as the major product. No dehydrated or polymerized product was observed (scheme i).



Scheme i: Henry reaction catalyzed by renewable base

Section 3B: A green synthesis of symmetrical bis(indol-3-yl)methanes (BIMs) using phosphate impregnated titania catalyst under solvent free grinding condition

Naturally occurring or synthetic BIMs and its related structures are important intermediates in organic synthesis and are particularly important in pharmaceutical chemistry as they exhibit various pharmacological activities and are important metabolites.



Scheme ii: Solid acid catalyzed solid phase synthesis of BIM's

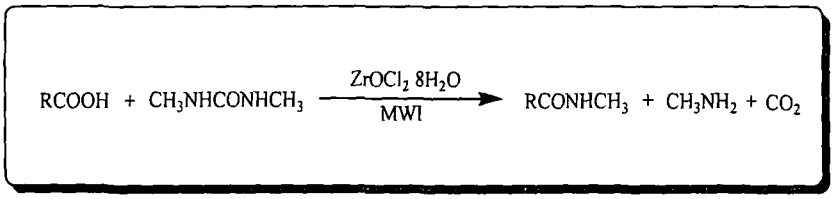
In this chapter we reveal a chemoselective method for the preparation of bis(indol-3-yl)methane from aldehydes and indoles using phosphate impregnated titania as the reusable catalyst under solvent-free grinding condition (scheme ii). The desired

products were obtained in excellent yields with tolerability to functional groups such as -OMe, -Me, -Cl, $-NO_2$ and -OH in a simple and environmentally benign procedure.

Chapter 4: Carbon-Nitrogen bond forming reaction

Section 4A: Zirconyl chloride: an efficient, water-tolerent and reusable catalyst for the synthesis of N-methylamides

The amide functionality is a common feature in small or complex synthetic or natural molecules. Amide bond formations are one of the most important transformations carried out in pharmaceutical synthesis accounting for 65% of all preliminary screening reactions in industrial medicinal chemistry laboratories as recently reported. The American Chemical Society Green Chemistry Institute Pharmaceutical Round table recently identified amide formation as one of the most utilized and problematic synthesis in the pharmaceutical industry and as such has been labeled as a high priority research area.



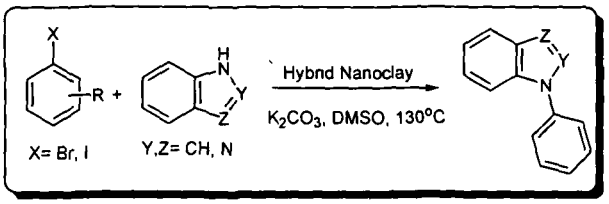
Scheme *iii*: MW enhanced Zirconyl chloride catalyzed condensation of acid and DMU

We found $ZrOCl_2 \cdot 8H_2O$ to be highly effective and reusable heterogeneous catalyst for the direct condensation of carboxylic acids (mono- and di-, aliphatic and aromatic) and *N,N'*- dimethylurea under microwave irradiation to give the corresponding *N*-methylamides in moderate to excellent yields (scheme iii). Notably $ZrOCl_2 \cdot 8H_2O$ is potentially a green catalyst due to their low toxicity, easy availability, low cost, ease of handling and reusability.

Section 4B: Copper nanoparticles decorated Organically Modified montmorillonite (OMMT): an efficient catalyst for the N-arylation of indoles and similar heterocycles

N-aryl heterocycles are very important structural units present in many biologically active and pharmaceutically important compounds. Ullmann type coupling method has often been used to synthesize such *N*-arylheterocycles. In this chapter, a newly synthesized hybrid nanoclay system has been used to catalyze the Ullmann type coupling reaction between NH-heterocycles and arylhalides.

The hybrid copper nanoclay systems have many implications as catalysts for organic synthesis. Nanoclay has been widely used in catalysis as a supporting material. A copper decorated organically modified nanoclay system has been developed to catalyze the coupling between nitrogen containing heterocycle *viz.* indole, imidazole, benzimidazole etc., with the aryl halide to give corresponding *N*-arylheterocycles (scheme iv). The hybrid nanoclay system has been found to be higly active to catalyze the coupling reaction affording high yield of product. The easy recovery and the reusability of the catalyst add advantage to the mentioned protocol.



Scheme iv: *N*-arylation of heterocycles catalyzed by copper clay nano hybrid

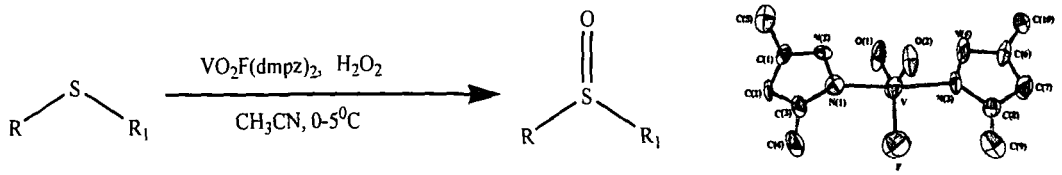
Chapter 5: Development of new catalyst for the selective oxidation of sulfides, aldehydes and bromide with H_2O_2

Section 5A: $VO_2F(dmpz)_2$: a new catalyst for selective oxidation of organic sulfides to sulfoxides with H_2O_2

Sulfoxides and sulfones are of immense interest because of their extensive applications as reagents in organic chemistry as well as synthetic intermediates for

the construction of various chemically and biologically active molecules. For this reason the oxidation of sulfides to sulfoxides or sulfones has been the subject of extensive studies. Generally, it is important to stop the oxidation at the sulfoxide stage by controlling the electrophilic character of the oxidant, but this requirement is often hard to meet and failure results in over oxidation to sulfones. The reported methods rarely offer the ideal combination of simplicity of method, selective reactions and high yields of products and often suffer from a lack of generality and economic viability hence the search for newer methods for the selective oxidation of sulfides to sulfoxides has continued.

A newly synthesized and structurally characterized vanadium complex $[VO_2F(dmpz)_2]$ (dmpz = 3,5 dimethyl pyrazole) is reported as recyclable catalyst for the selective oxidation of organic sulfides with H_2O_2 in CH_3CN at room temperature (scheme v). The $[VO_2F(dmpz)_2]$-H_2O_2 system can chemoselectively oxidize alkyl as well as aryl sulfides in presence of oxidation prone functional groups such as C=C, – CN and –OH.



Scheme v: Selective oxidation of sulfides to sulfoxides

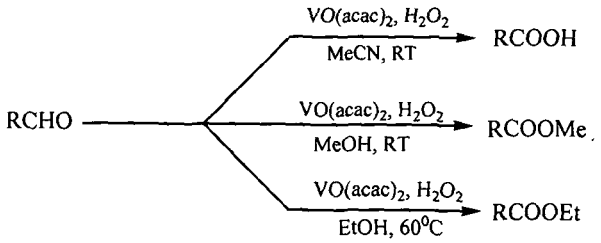
Various aliphatic and aromatic groups attached to sulfur atom and refractory sulfur (e.g. dibenzothiophene (DBT), 4-methyl-DBT and 4,6-dimethyl DBT) compounds were subjected to oxidation with H_2O_2 catalyzed by $VO_2F(dmpz)_2$. The oxidations were selective affording sulfoxides. In case of allylic sulfides oxidation, sulfoxides were formed without the cleavage of carbon-carbon bond.

Section 5B: $VO(acac)_2$: an efficient catalyst for the oxidation of aldehydes to the corresponding acids in presence of aqueous H_2O_2

In the plethora of oxidation processes, aldehyde oxidation occupies a cardinal position, owing to their diversified importance in the industrial manufacturing, and in synthetic chemistry. Despite the growing awareness of the need for "Green Chemistry", many chemists still uses environmentally unacceptable reagents or

sophistication for the oxidation of aldehyde. Consequently, development of industrially applicable method to such oxidation process stimulates the interest of various research groups over the years. The prolonged activity of our group on peroxovanadium and the knowledge obtained from literature informations on vanadium bromoperoxidase (VBrPO) reactivity encouraged us to develop new and cleaner protocols for such oxidations involving peroxometal based chemistry.

In this chapter, we have reported that $VO(acac)_2$ can catalyze the oxidation of aldehydes (aromatic, aliphatic and heterocyclic) to the corresponding acids efficiently and selectively in presence of H_2O_2 as an oxidant (scheme vi). This method possesses functional group compatibility, easy workup procedure and requires reasonably shorter reaction time. The reaction is highly dependent on the solvent used. Performance of *titania* supported $VO(acac)_2$ *in the oxidation of* aldehyde was also investigated.



Scheme vi: $VO(acac)_2$ catalyzed oxidation of aldehydes

Section 5C: A green route to tribromides: an experimental and theoretical insight into reactivity of organic ammonium tribromides(OATBs)

Crystalline quaternary ammonium tribromides namely tetrabutyl ammonium tribromide (TBATB), cetyltrimethyl ammonium tribromide (CTMATB), tetrapropyl ammonium tribromide (TPATB), tetradecyltrimethyl ammonium tribromide (TDTMATB), benzyltriethyl ammonium tribromide (BTEATB) have been synthesized. The chemical reactivity of these tribromides is determined using the density functional theory based reactivity descriptors such as global hardness, global softness and Fukui functions (fig a). Experimental observation is quite consistent with the theoretical prediction.

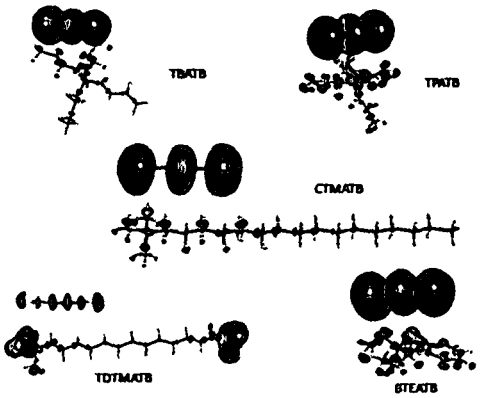


Figure a: Graphical representation of the Fukui function value for nucleophilic attack on the system derived from DFT/GGA/BLYP calculations

1.1 Introduction

To fulfill the demands of growing civilization there is always a need for the development of new compounds, as a consequence of this there is a rise in complexity of the targeted molecule in industrial as well as in academic research [1-4]. To synthesize such complex structures development of new methodology remains an important aspect in organic chemistry [5-7]. Across the different domains of chemistry, efficient synthetic methods are crucial and receiving importance especially in the context of sustainable chemistry [8-16]. Broadly, organic synthetic chemistry can be divided into two major domains [17]. The first domain involves the synthesis of targeted molecule by using sets of existing protocols. Performing such sequence of transformations, modifying and combining various fragments more complex structures can be achieved. Second domain involves discovering new reagents, catalysts and protocols for the organic conversions [18]. Such methodological studies gives us new protocols for construction of various bonds between different atoms and are finding high importance in the modern synthetic organic chemistry [19]. Catalysts play an important role in developing such newer protocols [20, 21].

The term catalysis was coined by J.J. Berzelius in his note to Swedish Academy of Science in 1835: [22]

"*It is given then, that many, both simple and complex compounds, both in solubilized and solid form, have the ability to, without necessarily contributing with its own constituents, produce transformation of other compounds This is a new power, able to produce chemical activity, belonging to both inorganic and organic nature, which is surely more extensive than we have hitherto believed and the nature of which is hidden to us When I call it a new power, I do not mean that it is a force independent of the electrochemical properties of matter. On the contrary, I am unable to suppose that this is anything other than a kind of special manifestation of these, but as long as we are unable to discover their relationship, it will simplify our research to regard it as a separate power It will also make it easier for us to refer to it if it possesses a name of its own I shall therefore, using a derivation well known in chemistry, call it the catalytic power of substances, and decomposition by means of this power catalysis, similar to how we use the word analysis to denote separation of the component parts of bodies by means of ordinary chemical forces. The catalytic power appears to constitute the ability of substances that, just by their mere presence, and not by its reactivity, awaken reactions that otherwise would be slumbering at the observed conditions.*"

Catalysis lies at heart of numerous chemical transformations, form the academic research laboratories to the large industries [23-25]. Catalysis is a necessary and critical tool for achieving socio-economic objectives. Catalysis is not only one of the

principal tenets of "Green Chemistry" but also an integral part of it [26-29]. It is widely acknowledged replacing traditional non-catalytic process by the modern catalytic process. The value of catalysis, in both impact on quality of life and economic terms cannot be underestimated. The importance of the catalytic methods can be seen from the timely publication on the compendium which affirms beyond any scope of imagination. Current information estimates that the value of catalyst market > 20 billion USD, which is remarkable as it has been estimated that for every 1USD spent on a catalyst it can generate up to 1000 USD worth of product [30]. This in itself underscores the need to develop practical catalytic processes. It is always appreciated to have a clean catalytic methodology for chosen chemical conversions. In search of better and efficient catalytic system the domain of catalysis expands crossing the boundary of various sub-disciplines e.g. bio, abio and material chemistry for example. The domain catalysis has been distributed over three sub domain *viz.* homogeneous, biocatalysis and heterogeneous. Heterogeneous catalysis is favorable and widely practiced due to its advantages over the others [31-39]. The first report on heterogeneous catalyst dates back to 1800s, it was Faraday who first used platinum metal for facilitating oxidation process [40]. The principal advantages of heterogeneously catalytic reactions are (a) good dispersion of active sites, (b) constraints of the pores, (c) easier and safer to handle, (d) easier to remove from the reaction mixture and (e) reusability [41, 42]. In this 21st century we cannot imagine our world without the fruit of heterogeneous catalyst.

The 12 principles of green chemistry

1. **Prevent waste**
2. **Atom economy**
3. **Less hazardous synthesis**
4. **Design of benign chemicals**
5. **Benign solvents and auxiliaries**
6. **Design for energy efficiency**
7. **Use of renewable feedstocks**
8. **Reduce derivatives**
9. **Catalysis**
10. **Design for degradation**
11. **Real-time analysis for pollution prevention**
12. **Inherently benign chemistry for accident prevention**

Figure 1.1: 12 principles of green chemistry by P. Anastas

Non-catalytic stoichiometric organic transformations using conventional reagents are still being used for the synthesis of various important compound Despite such unavoidable use of stoichiometric reagents general trend is to replace the traditional stoichiometric chemical processes to the catalytic processes.

In the context so called 'green technology', sustainability is becoming an important issue deáling with science and technology [43-45]. It is an interdisciplinary area of research finding its applications in chemistry, biology, environmental technology, energy technology to name a few [46]. Sustainable technology is important for the socio-economic development of the modern society [47].

We have twelve well set principles proposed (figure-1.1) by Anastas and Warner accepted internationally, which limits and guides to develop chemical technology for the sustainable development of our society [48].

Due to high toxicity of the organic solvents it is always preferred to minimize or if possible remove it in organic synthetic process. Reports using alternative solvents like liquid CO_2, $ScCO_2$, ionic liquid and high boiling solvents like propylene glycol is quite often encountered [49-51].

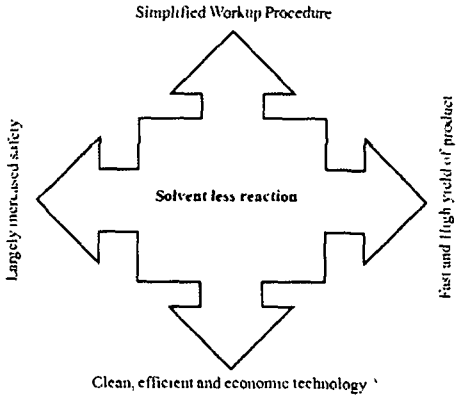


Figure 1.2: Advantages of solvent less process

Although various alternatives of the volatile organic solvents are reported but it is better to find some protocols which can be carried out in absence of any reaction medium [52, 53]. There are some advantages of solvent less organic reactions over the traditional reactions in organic medium (figure 1.2):

1. No medium has to be collected and purified after the completion of the reaction.
2. The compounds formed are often sufficiently pure to skip extensive purification technique.
3. Often gives high yield of products compared to the traditional methods.

4. The reaction can be rapid, often reaching substantial completion in several minutes.
5. No need for special reaction set up.
6. Minimization of energy used.
7. Necessary functional group protection deprotection steps can be avoided.

Inspite of such advantages of the solvent less processes there are some disadvantages also which can be tackled by the development of proper reactor technology. Although solvent less method appears to be reaction between discrete macroscopic organic particles, yet mechanistically the reaction proceeds in liquid or in melt phase [54-57]. When two solid components are mixed together, the melting point of the mixture becomes lower than the melting point of the individual components [58-60]. In some cases, entire mixture can melt upon mixing (figure 1.3). This liquefaction implies the presence of eutectic mixture with temperature of fusion (T_{fusion}) below ambient temperature [61,62]. The reaction then occurs in a viscous liquid state. Solvent less organic conversions are often mediated by microwave irradiation, ultrasound and in some cases by conventional thermal process [63-67]. Use of such (MWI) external energy generally speeds up solvent less reactions giving high yield of product.

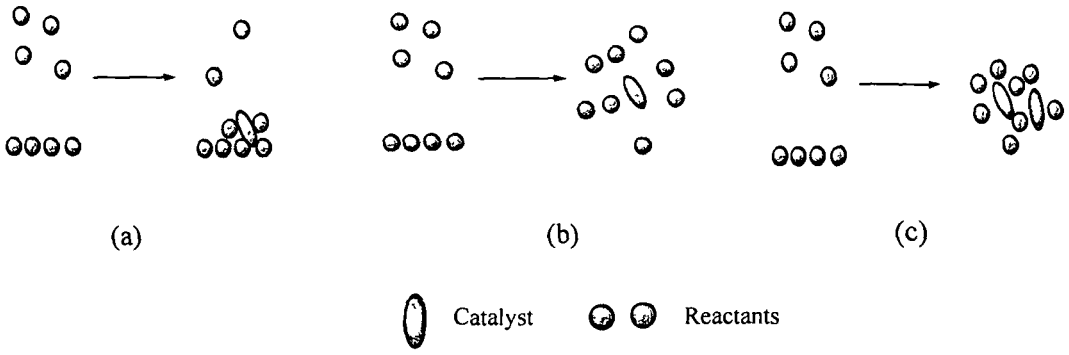
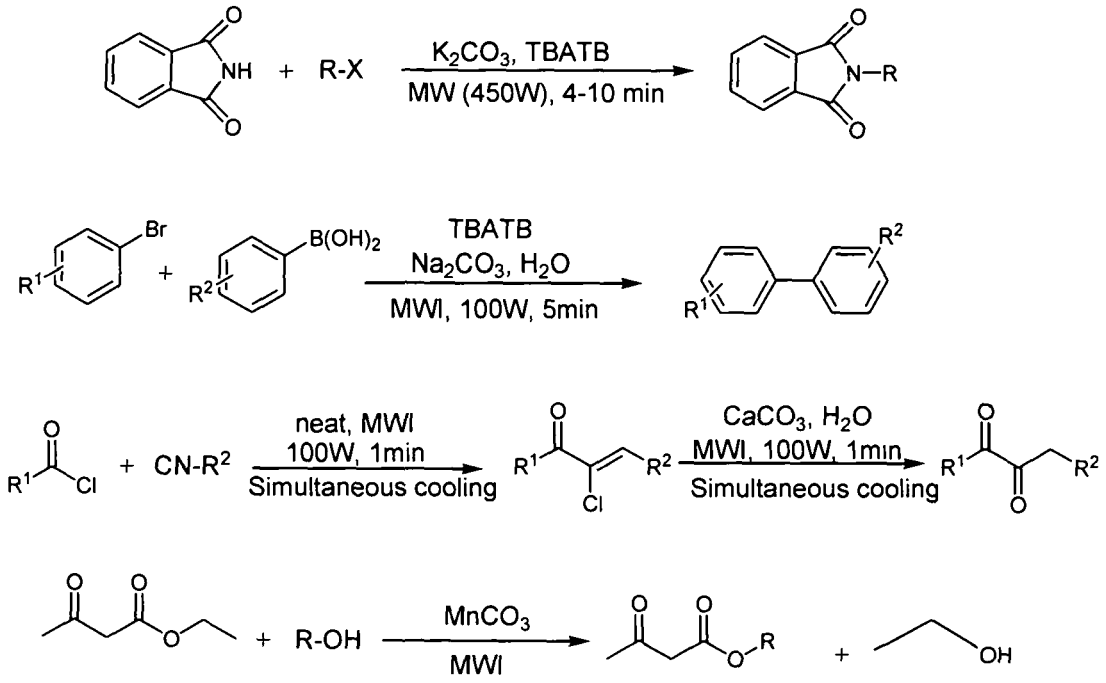


Figure 1.3: Cartoon showing a) Solid phase reaction, b) Solvent free reaction, c) Solid-Solid reaction

Since the first report in 1986 on the use of microwave heating to accelerate the organic reaction, it is emerging as a tool for the sustainable chemistry [68-74]. The main advantage of microwave heating over thermal one is derived from the almost instantaneous "in core" heating of a material, in a homogeneous and selective manner, especially those with poor heat conduction properties [75, 76]. Microwave-

assisted synthesis superior to the traditional heating in many ways. On exposing reactants to the MWI, the thermal effect exhibits by the material increases with subsequent increase in polarity of the substrates. Such thermal effect has been observed both in solid and liquid systems. The resultant advantages of such microwave heating over the classical heating are especially impressive. The ultrafast reaction observed in microwave heating results from both temperature and pressure effects and supposed specific effect of radiation, such as improved homogeneity in temperature, a fast temperature rise and possible modification of activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$. Often high purity of product is observed in the microwave assisted reaction which might be correlated with the fast reaction and absence of local overheating that occurs in conventional heating(scheme 1.1).



Scheme 1.1: Examples of some microwave assisted reactions

Due to safety measures solvent less reaction under microwave activation is always preferred, because, use of organic solvent sometimes leads to explosions. Three types of solvent free reactions can be coupled with the microwave activation [77,78].

a. Reaction between neat reactants *viz.* liquid-liquid, liquid-solid and solid-solid provided at least one of the reactants is sufficiently polar to absorb microwave.

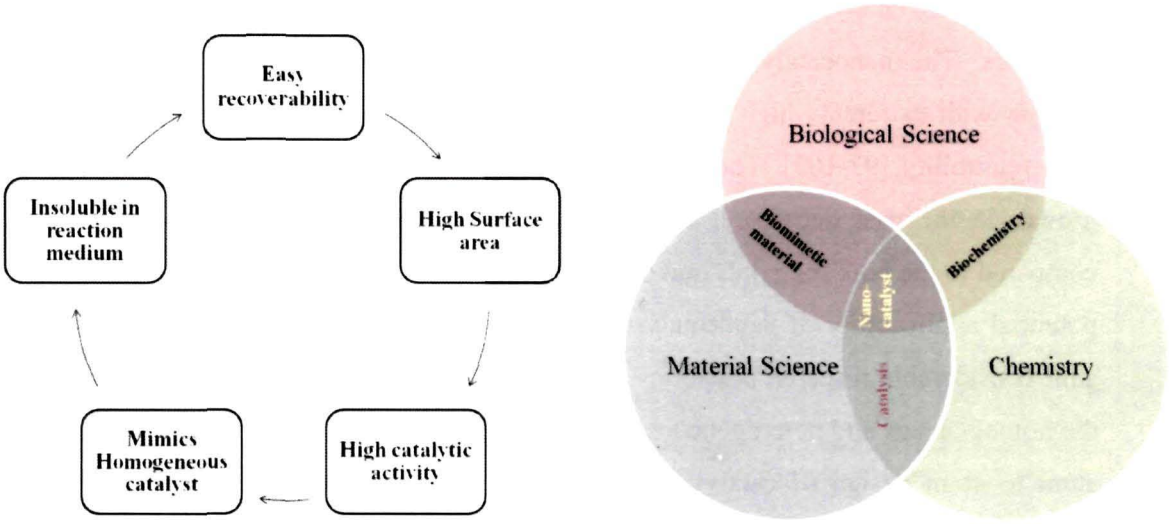
b. Reaction can also be carried out between the supported reagents e.g. Impregnation of the compounds over silica, alumina, zeolites, clay etc.
c. Phase transfer catalysis can also be carried out in absence of organic solvents under MWI.

Homogeneous catalyst finds wide applications on number of industrial processes. Although, such applicability of the homogeneous catalysis, there are some drawbacks associated with the traditional homogeneous processes. The difficulty in the separation of the catalyst from final product limits its application in many cases. Removal of the trace metal from the reaction mixture is important because metal contamination is highly regulated, especially in the pharmaceutical industries. The commonly used techniques such as distillation, chromatographies etc. are unable to remove the trace metal.

The problem of recoverability of the catalyst can be overcome up to some extent by anchoring such homogeneous metal catalysts over the heterogeneous support. The commonly used supports are like silica, clay, zeolite, metal oxide etc. to name a few [79-82].

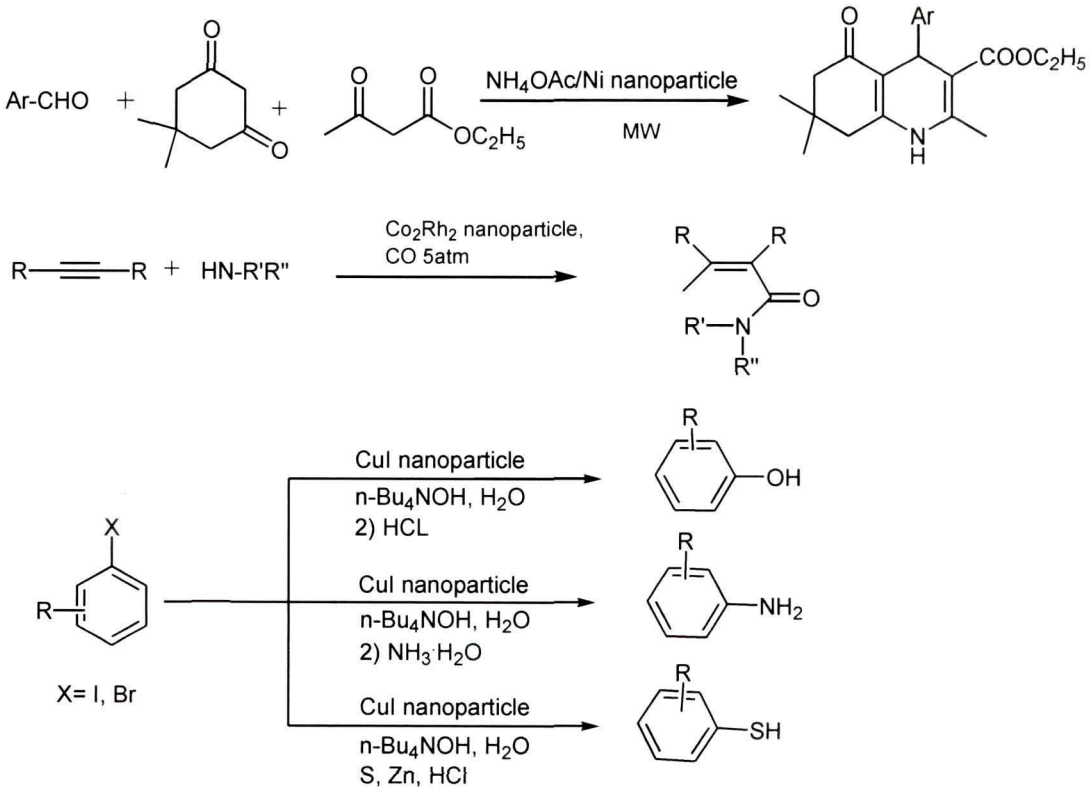
Such heterogenization has many advantages over the homogeneous catalyst viz. high stability, large surface area, porosity, shape selectivity etc. (figure 1.4). Although having such advantages over homogeneous catalyst but in many cases the catalysts get deactivated when supported over such heterogeneous supports [83, 84]. Another problem with such supported catalyst is the leaching of the metal from the surface of the catalyst during the reaction, which again necessitates the removal of trace metal from the final product. Because of such problems with homogeneous and heterogeneous catalyst, there is a need for new catalyst which allows the rapid and selective chemical transformation along with ease of removal and recovery of the catalyst from the final product

Transition metal nanoparticle has emerged as a sustainable alternative for the traditional transition metal catalyst [85-91]. Nanocatalysts are intended to overcome the drawbacks of traditional homogeneous and heterogeneous catalysis. The aim of the nanocatalysis is to control the chemical reaction and kinetics by nanopatterning of the active centers. Nanocatalysts act as a bridge between the homogeneous and heterogeneous catalysts [92].



(a) (b)

Figure 1.4: (a) Advantages of nanocatalyst and (b) Interconnection of various fields with nanocatalyst



Scheme 1.2: Nanoparticle catalyzed organic conversions

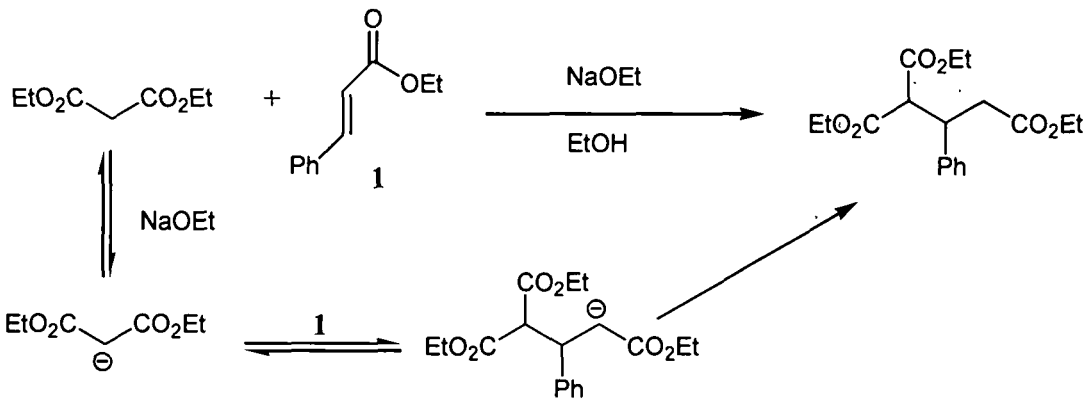
Nanocatalyst has several advantages over both homogeneous catalyst and the heterogeneous catalyst and already finds wide applications in various organic syntheses. The nanocatalytic research is mainly intended to achieve developed catalyst with extremely high activity and selectivity, low energy consumption and high reusability [93-103]. The nanocatalysis research has undergone an explosive growth in the past decades. Large surface to volume ratio of the nanoparticles compared to the bulk materials makes them efficient for the catalysis. In view of the potential applicability of nanocatalysts, nanostructured catalysts have been able to gain considerable research attentions both in academic and industrial field. Unlike the homogeneous and heterogeneous catalysis, nanocatalyst opens an avenue for the atom to atom design of catalyst to achieve better activity and selectivity of the product. The potential application of the nanocatalysts lies in their tunable activity by changing the chemical and physical properties like shape, size chemical composition etc. One classic application of nanocatalyst is the Haber-Bosch process for the preparation of ammonia by combining N_2 and H_2.

The iron catalyst [BASF-S6-10, bulk composition: Fe (40.5%), K (0.35%), Al (2.0%), Ca (1.7%), and O (53.2%)] used in this process contains nanometer-sized particles with a surface area of 20 m^2g^{-1} [104]. Under the reaction conditions, iron oxide undergoes reduction, and the particles formed are protected against agglomeration by a framework of Al_2O_3 and CaO. This shows that nanocatalysis was introduced for the catalytic processes long before they were actually realized. With advancement of modern characterization techniques of materials, the old technology finds new dimensions. Most of the issues associated with sustainable development of chemical technology can be addressed with the help of nanocatalysis (scheme 1.2). The high activity of nanocatalysts eliminates the drastic condition required in a chemical transformation which results less energy consumption. The high selectivity in the nanocatalytic process also increases the atom economy of the reactions.

Carbon-Carbon and the Carbon-Nitrogen bonds formations are most often found in the synthesis of compounds which exhibit important biological and pharmaceutical activity and also important in material chemistry [105-112]. Due to such important applications of the Carbon-Carbon and Caron-Nitrogen bonds it is very important to develop clean and efficient methodologies for such synthesis.

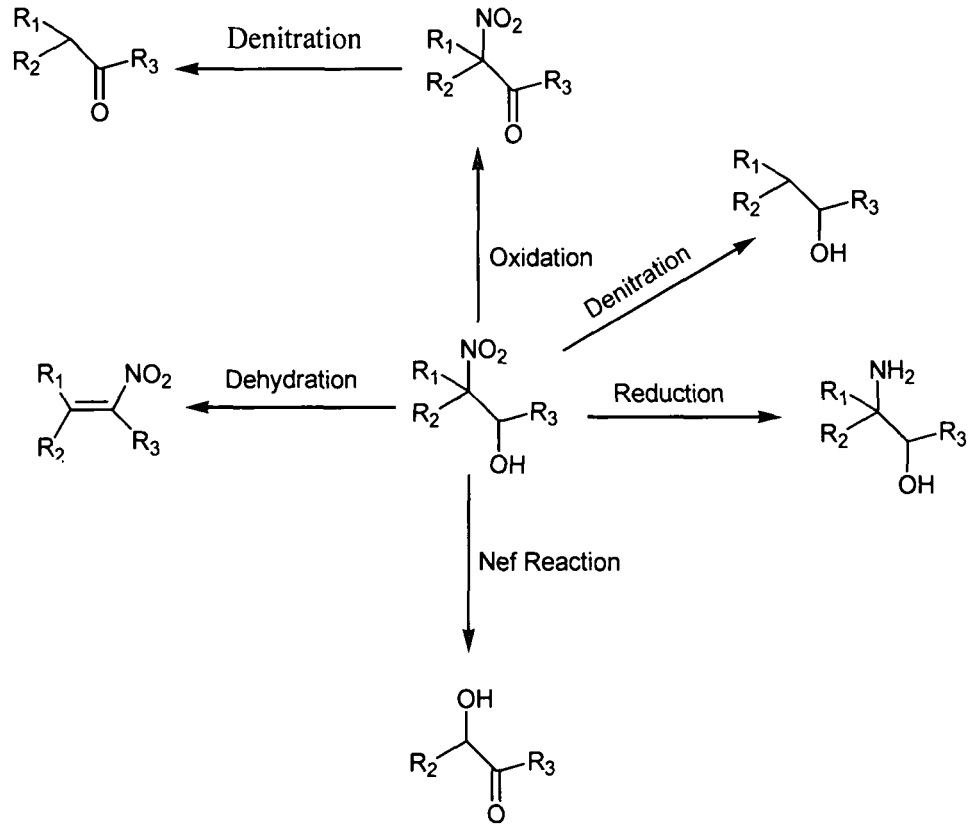
Carbon-Carbon bond formation constitutes cardinal events in the organic transformations. Carbon-carbon coupling is a key transformation in organic synthesis for the construction of structurally diverse compounds. Carbon-Carbon bond forming reaction has become a very efficient method for the production of combinatorial libraries. Consequently the development of methodologies for the carbon-carbon bond formation has been an area of perennial interest, even since the dawn of organic chemistry [113-119]. It is noteworthy to mention here that from about ten petrochemical feedstock's today people have synthesized millions of new compounds. The statistics well estimates the importance of the C-C coupling in organic synthesis.

The majority of C-C coupling is achieved by nucleophilic attack of one carbon to other electrophilic carbon centre (scheme 1.3). The nucleophilic carbon is of two general kinds: (a) The carbanion like group in organomettallic compounds e.g. Grignard reagent, organolithium reagents etc. and (b) The carbanions generated through the abstraction of proton from carbon atom flanked with some electron withdrawing groups like $-NO_2$, carbonyl etc. [120].



Scheme 1.3: "Michael addition" a classic example of C-C bond formation through carbanion formation

Among the plethora of protocols developed over the years, a large number of them take the advantage of active methylene imparted by the effect of adjacent electron withdrawing groups [121-125]. The carbanion stabilizing ability of the nitro group makes nitroalkanes an important reagent for the carbon-carbon bond formation reaction [126,127].

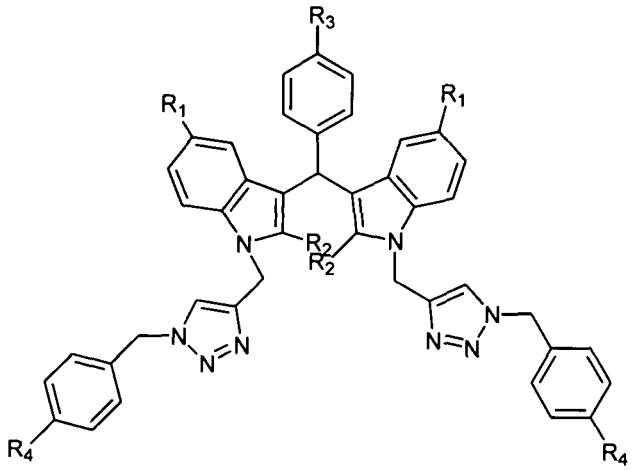


Scheme 1.4: Application of the Henry product

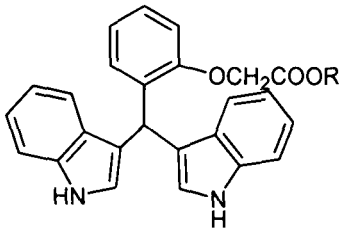
The Henry reaction is a Nitroaldol condensation reaction and represents a classical C-C bond forming reaction. Basically, "Henry reaction" is an important carbonyl addition process that affords products that can be converted to various valuable building blocks [128-130]. Various modifications have been done on the nitroaldol reactions to achieve some important and complex structures. The beauty of the reaction is that the Nitroaldol product is an important intermediate and used to synthesize various important structures [131-133]. Henry reaction is the most atom economic carbon-carbon bond forming reaction and the so called Henry product finds wide applications (scheme 1.4) as an intermediate for the synthesis of many value added compounds [134,135]. Once the nitro alkane has been introduced in a molecular framework, the nitro group is amenable to further transformation including the reduction to the primary amine [136,137].

In recent years selective C-H functionalization has found special attention both in industrial and academic research. The importance of such strategy can be intriguing

for various structural modifications of organic molecules to achieve definite purpose. The application of such strategies in the multiscale level allows the utilization of cheap and environmentally benign starting materials [138,139]. Direct C-H functionalization of the heteroarenes is an important protocol for the synthesis of various compounds which has significant biological activity. In this regards indole represents a system of particular interest. Convergent synthesis of C-3 functionalized indoles becomes an important area of research because of their medicinal and biological applications. In the wide spectrum of the C-3 substituted indole products, bis(indolyl)alkanes gets special attention because of their numerous applications starting from the medicinal to the material science [140,141]. Some specially designed bis(indolyl)alkanes find application as chemical sensors. The significant biological activities of indole derivatives are well acknowledged by synthetic as well as biological chemists. Both symmetrical and asymmetrical bis(indolyl)alkanes find wide applications in the biological and the medicinal fields.



Anti-HIV and antimicrobial activity
Compound a

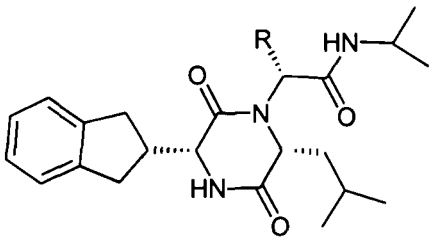


antituberculosis activity
Compound b

The C-3 carbon of the indole moiety is sufficiently activated for the nucleophilic addition reaction; in fact C-3 of indole is 1013 times more reactive than benzene molecule for the nucleophilic addition reaction [142,143]. It is observed that indole and its derivatives react with carbonyl group to give the corresponding bis(3-indolyl)alkane. Generally such reactions are catalyzed by Lewis acids [144-146]. Bis(3-indolyl)alkanes have wide applications in medicinal and the pharmaceutical

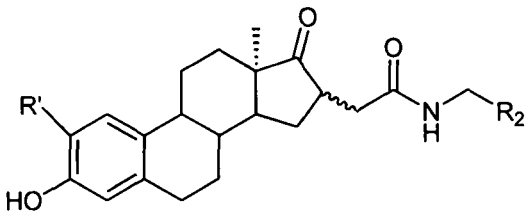
fields. They have various biological activities (*ca.* compound a, compound b) and have been used for the preparation of number of medicines [147,148].

Carbon-Nitrogen bond forming reaction is another primary important reaction in organic synthetic process. Carbon-Nitrogen bonds are present in many biologicaly active molecules (*ca.* Compound c, Copmound d) and are finding special interest in synthetic chemistry. Both carbon-carbon and carbon-nitrogen bonds are extremely important for the construction of diverse molecular stuctures and are considered as the key element in the organic synthesis. In this respect amide bond formation offers a versatile area of research. The amide bond is an important linkage, present in many naturally available molecules including peptide and the protein stucture [149-151].



oxytocin antagonist

Compound c

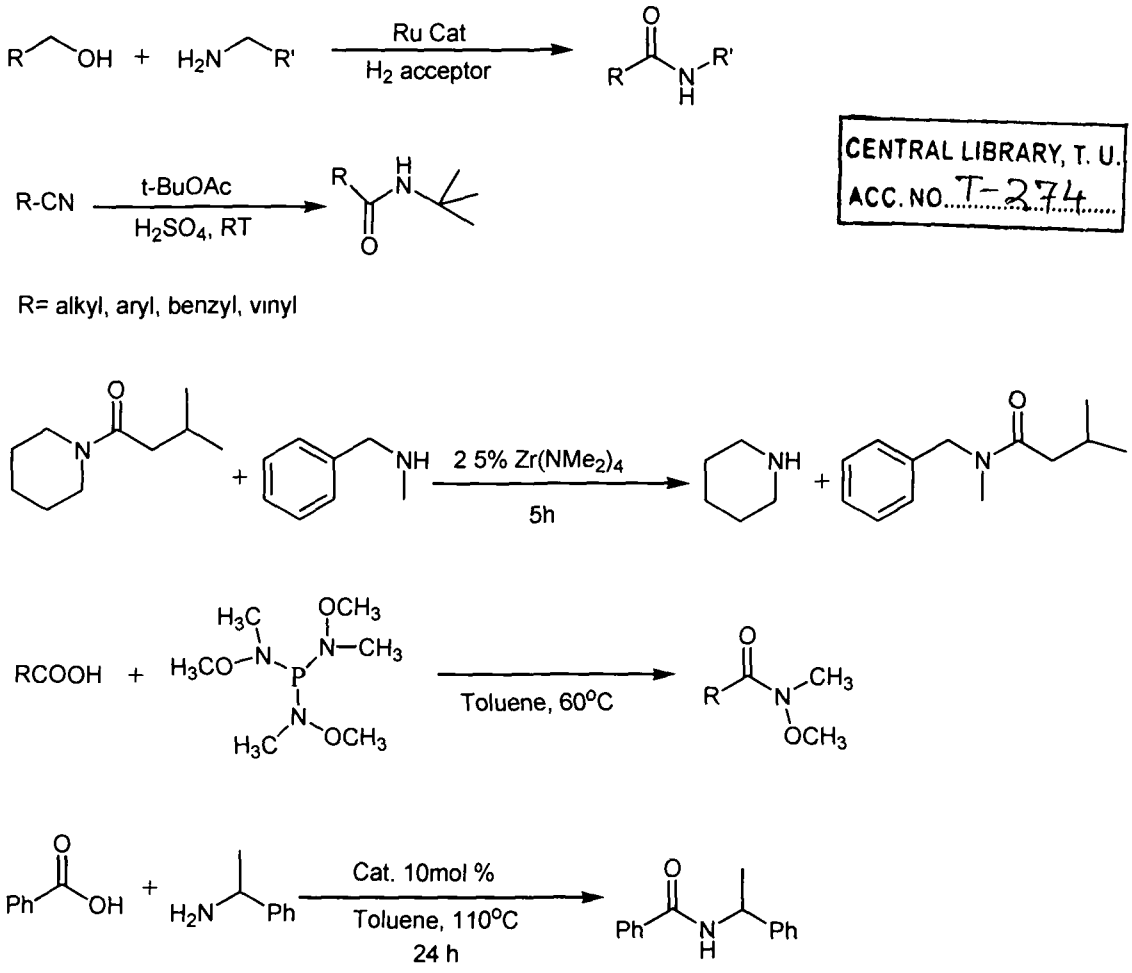


17β Hydroxysteroid
Dehydrogenase Type 1 Inhibitors

Compound d

Amide bond formation is an important C-N bond forming reaction widely applied for the synthesis of various important molecules specially in medicinal industries. Amide bond forming reactions finds special interest in the medicinal and the pharmaceutical industries, because majority of the drug involves the amide linkage. Traditional methods for construction of the amide bond relies mainly on dehydrative approach, although the oxidative and radical-based methods are also available [152-155]. The main problem in dehydrative approach is the generation of water as the by-product which again hydrolyzes amide bonds during the progress of the reaction. Condensation of alcohol and amine under catalytic condition is a straight forward method for the construction of amide bond. A huge number of literature reports are available which basically utilizes this condensation to construct amide bonds. Generally the mechanism of amide bond forming reactions invloves

coupling of electrophilic carbon and nucleophilic nitrogen centre (scheme 1.5). However, umpolung reversibility is also ovserved in the amide bond formation.



Scheme 1.5: Some amide bond forming reations

Development of new catalyst for the direct condensation of the carboxylic acid and the amine is finding special interest because water is the corresponding by-product. Tang and his group reported benzene boronic acid catalyzed direct condensation of carboxylic acids and amines. After his report number of benzene boronic acid based catalyst have been reported which can directly catalyze such condensation at relatively lower temperature [156]. Developing environmentaly benign methodologies are emerging out as an important and challenging area of research. Although numbers of protocols have been reported in the literature for amide bond formation but only a few of them are applicable industrially [157-160].

Palladium and copper catalyzed C-N bond formation and the related cross-coupling is well established in the synthetic organic chemistry. Palladium catalyzed reaction of aryl halide with "soft" nucleophiles e.g amines, indoles, amides etc. is direct method for the construction of the C-N bond and was developed independently by Buchwald and Hartwig in 1995 [161-163]. Since then such methodologies finds wide application for the successful construction of various C-N bonds with amines and NH-heterocycles. The pioneer work by Buchwald and Hartwig on the C-N coupling reaction several group of researchers embarked an investigation on the new methodologies for such C-N coupling reaction based on palladium or the copper based catalysis both in homogeneous and in the heterogeneous medium. *N*-arylated heteroaromatics are important structural motifs and have many biological and the pharmaceutical relevance [164-166]. *N*-arylated indoles occupy a large area in this domain. Due to the significant biological acitivity of the *N*-arylated indoles various methods have been reported for their synthesis over the years. Out of the many methods reported so far in the literature Fischer indole synthesis is a general and efficient way to synthesize such structures [167]. However, Buchwald have reported palladium catalyzed methodology for coupling between NH-heterocycles and aryl halide for the synthesis of *N*-arylheterocycles [168]. Nevertheless, the high cost associated with palladium salts, high oxophilicity associated with phosphine ligands, C-3 arylation through π-complex formation and tedious multistep processes involved in the synthesis of these phosphine ligands have rendered Pd unpopular, particularly for large scale reactions [169-170]. Ullmann type couplings involving the use of copper catalyst in presence of base is an alternative for such C-N coupling to carry out [171,172]. There is a vast literature report for such C-N coupling reactions catalyzed by different copper catalysts. Apart from copper and palladium based catalysts there are reports of cadmium, ruthenium and nickel catalysts for such C-N coupling reactions [173-175]. Even though a number of catalysts have been reported in the literature for C-N coupling reactions, still palladium and copper based catalysts are getting special attention because of the ease of formation of product and efficient catalytic activity.

Nature utilizes enzymes to catalyze chemical coversions which are difficult or impossible to catalyze by the modern chemical catalysis. Generally, such enzymes contain some metal cofactors which act as the active centres for catalysis. One of such widely studied metalloenzymes is the vanadium haloperoxidase (V-HPO)

[176]. Vanadium haloperoxidase is found in some marine seaweeds, lichanes and algae and some terrestrial fungi, catalyzes the halogenation of organic substrates or the halide assisted disproportionation of H_2O_2 [177,178]. V-HPOs utilizes hydrogen peroxide to convert a halide ion (X^-) to the corresponding hypohalite (^-OX) intermediate which is considered as chemically equivalent to an electrophilic "X^+" [179,180]. However, unlike the Fe-heme enzyme, the oxidation state of the V-HPO metal center does not undergoes any change during of the oxidation process (figure 1.5). Consequently, V-HPOs do not suffer from oxidative inactivation during turnover and have received increasing attention as a model for biocatalysts in pharmaceutical applications.

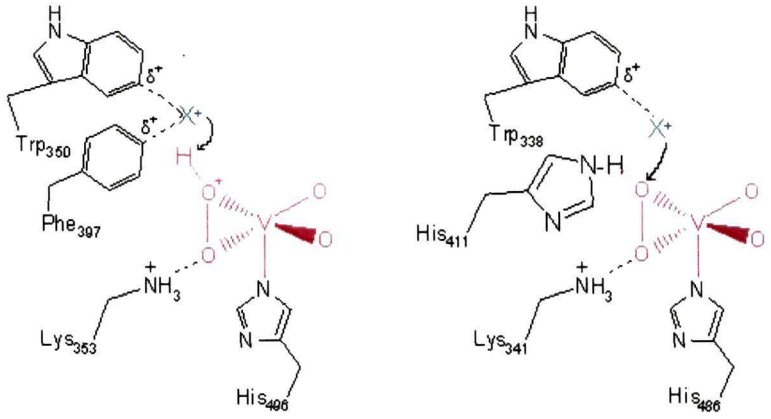


Figure 1.5: Line draw structures of the peroxo-intermediate of VClPO and VBrPO, demonstrating the origin of hydrogen bonding which tunes the activity in oxidation of chloride and bromide, respectively. (Adopted from Saitanya K. Bharadwaj PhD Thesis, IIT Guwahati, India, 2009 with due permission)

Due to tolerance of such catalyst for organic solvents, high temperatures and ability for halogenations of organic compounds in a regio- and stereo specific manner and the ability to oxidize organic sulfides in absence of halides attracts attention of researchers for the V-HPO chemistry [181-184].

Coordination compounds with vanadium(V) centre attracts the attention of both synhtetic, biochemist and theoretical chemists over the years [185-190]. Participation of vanadium(V) as an intermediate electron carrier in the oxidation of NADH for stimulating nitrogen fixation and active involvement in oxidizing

organics are very exciting contributions to the current knowledge of vanadium chemistry [191-193].

The potential activity of d^0 metal complex to catalyze oxygen transfer reaction has received much attention during the last three decades. The d^0 metal system can effectively activate peroxides such as hydrogen peroxide, cumyl or *t*-butyl hydroperoxide for the oxidation of a large variety of substrates and with the addition of proper chiral ligands, high degree of stereoselectivity can be achieved [194-197].

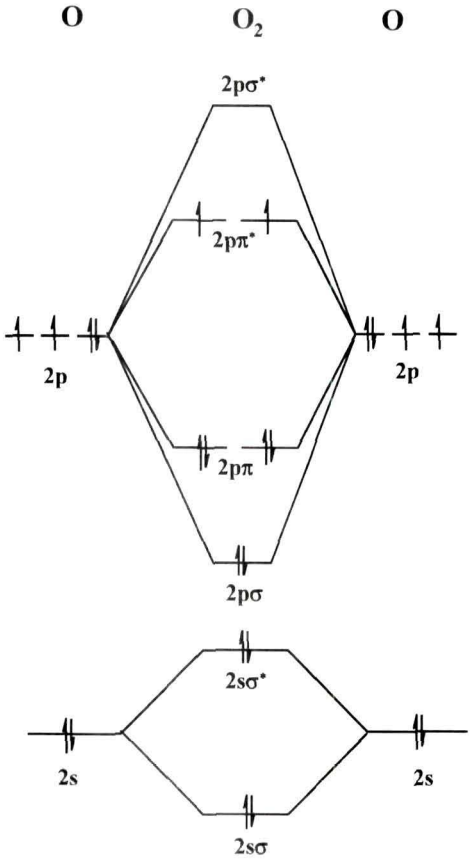


Figure 1.6. Molecular orbital diagram of O_2

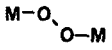
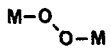
In our group we are highly interested in oxygen transfer reaction involving vanadium based catalyst. Notably, vanadium catalyzed oxidation received attention by virtue of the interesting property to oxidize organics in regio- and stereo selectivity mode [198]. Vanadium complex like V-HPO can activate peroxides to the corresponding peroxovanadium species [199-201]. The activity of the peroxo complex compared to that of molecular oxygen can be described from the molecular orbital theory, that addition of two extra electrons to $2P\pi^*$ orbital of molecular oxygen results in peroxide (O_2^{2-}) formation and decreases the O-O bond order [202].

As a result, reactivity of peroxo compound differs from unreduced dioxygen complex (figure-1.6).

The different possible modes of bonding of peroxide to metals are interesting from the structural viewpoint. Such bonding mode can range from a symmetrical bidentate to a terminal monodentate position including all the possible angles in between [203-206] (table 1.1). The bridging μ-peroxo could vary from *cis*-planar and *trans*-planar to *trans*-nonplanar configurations [207-210].

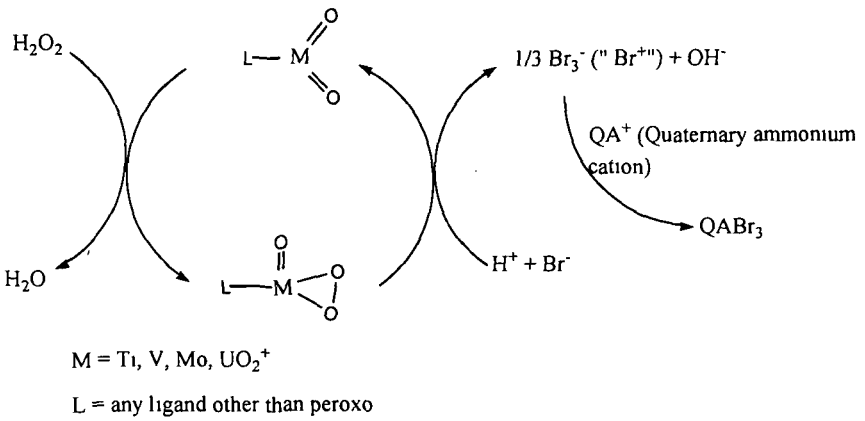
Generally, peroxo compounds are not stable, some of them decompose above 0 °C, and some are sensitive to shock, while several do not even exist as stoichiometric compounds. Proper, heteroligand combinations generally helps to enhance the stability of and isolation of such peroxo species [211-213].

Table 1.1: Vaska's classification of peroxo complexes

Structural type	Structural designation	Vaska classification
	η^1 dioxygen	Type a (superoxo)
	η^2 dioxygen	Type II a (peroxo)
	$\eta^1:\eta^1$ dioxygen	Type I b (superoxo)
	$\eta^1:\eta^1$ dioxygen	Type II b (peroxo)

The enhanced stability of such peroxovanadium compounds can be explained on the basis of electrostatic interaction, steric effect and back donation. Such heteroligand combination brings stability by tailoring the redox potential, electron transfer rate and the magnetic moment of the bound vanadium system. Remarkably, in such peroxocomplexes the O-O bond is much weaker (120-190 $kJmol^{-1}$) than the molecular oxygen and can be easily cleaved [214]. Depending on their mode of cleavage, peroxo complexes can involve in either polar or radical oxidations [215,216]. Due to the presence of weak peroxy bond peroxovanadium complexes find wide applications in various oxidative organic transformations like epoxidation, oxidation of alcohols to aldehydes, oxidation of organic sulfides etc. to name a few.

The most notable application of the peroxovanadium is their application for oxidative bromination of organic substrates. Although bromo-organics take a rather small share of the domain in organic chemistry, but it enjoys a cardinal position in the plethora of organic synthesis because of their application in the manufacture of a range of bulk and fine chemicals including flame-retardants, disinfectants, antibacterial and antiviral drugs [217-223]. The wider applicability of bromo-organics in the synthesis of a large number of natural products as well as the manufacture of pharmaceuticals, agrochemicals and numerous industrially valuable products bromination of organic compounds have received significant attention over the years. Traditional methods involve the use of elemental bromine even though the reagent is extremely toxic and corrosive in both liquid and vapor forms. Moreover, the atom accountability in reactions involving bromine shows maximum of 50% atom-economy and formation of hazardous HBr as waste [224]. As described earlier some marine natural chemicals contain bromometabolites such as halogenated phenols, tarpenes, C-15acetogenins, indoles etc. are generated through enzyme catalyzed bromination. Studies have revealed that vanadium bromoperoxidase (VBrPO) enzyme plays important role as a catalyst for the synthesis of such compounds in marine environment. Structure and reactivity studies showed that enzymes activate H_2O_2 through coordination. The activated peroxide enables Br^- oxidation available in marine natural system which in turn brominates the organics in marine environment [225-229]. Since early eighties, our group has been working on peroxo metal and non-metal chemistry where H_2O_2 is being activated by various metals like V(V), Mo(VI), W(VI), Ti(IV), Cu(II) and non-metals like B, P, etc. The *in vitro* Br^- oxidation reveals that 2 equivalents of KBr and 1 equivalent of tetrabutylammonium bromide (Bu_4NBr) on being reacted with peroxovanadium(V) complexes afforded orange-yellow crystalline product in very high yield which was finally identified to be tetrabutylammonium tribromide (Bu_4NBr_3) (scheme 1.6). Following the same strategy a series of tribormides were synthesized and applied for various organic transformations e.g. oxidation of sulfides and bromination of activated aromatics [230].



Scheme 1.6: Mechanistic pathway for QATB synthesis

Quaternaryammonium tribromide (QATB) is known as the solid bromine and has been used to synthesize various bromo-organics. In this thesis, a comprehensive report on the solution phase synthesis, characterization and reactivity of a series of quaternaryammonium tribromide is described. Their reactivity has been studied for bromination of the organic substrates. Both experimental and theoretical tools have been used to study reactivity of the tribromides for electrophilic bromination of organic substrates.

1.2 Scope of the work

The literature review presented above inspires us to choose four problems for my Ph.D. research work:

(a) Synthesis of vanadium(V) complex containing 3,5-dimethylpyrazole (dmpz), with fluoride as the heteroligand, investigation of their structural motifs and their application in the important oxidations *viz.* bromide and sulfides.

(b) Bromoperoxidase enzyme catalyzes the oxidation of bromide and brominates the organic substrates in marine organism. Therefore, taking clues from this it is worthwhile to prepare new organicammonium tribromides and their subsequent application in the selective bromination of organics.

(c) Solid acid catalysis is also an important area of research. Development of newer solid acid catalysts and their use for specific organic transformations are the order of the day. A solid acid not only replaces mineral acids in fine chemical manufacturing process but also catalyzes the reaction heterogeneously.

(d) Efficient and the green methodologies for the C-C and C-N bond forming reaction.

The problems highlighted above are gaining wide attentions to the research community through the years because of their high applicability in the real world. Accordingly, attempts have been made to address the problems defined above for the present Ph.D. research.

In the thesis we have described the synthesis, characterization and studies of reactivity of newer heterooxovanadates(V) and development of newer solid acid catalysts for some important organic reactions *viz.* oxidation of aldehydes, bromides and organic sulfides.

The main theme of the thesis has been divided into five chapters. **Chapter 1** highlights a detailed background of the chosen aspects of studies. The detailed experimental procedures and instruments used for the characterization are encompassed in **Chapter-2**. The main findings of this research work have been described in **Chapter-3** to **Chaper-5**. Each chapter is anchored with a small introduction of the problem followed by experimental details, results, discussions and finally the conclusions.

The main theme of **Chapter 3** is the carbon-carbon bond forming reaction which is again divided in to two sections *i.e.* Section 3A and Section 3B. The Section 3A describes the use of a new renewable base catalyst for Henry reaction. Section 3B of **Chapter 3** introduces a new solid acid catalyst developed independently by our group and its application in the synthesis of acid catalyzed condensation of indole and aldehyde.

The **Chapter 4** has also been divided into two sections. The basic subject matter of the **Chapter 4** has been distributed over Section 4A and Section 4B. Section 4A demonstrates a new catalytic methodology for the amide bond formation. Section 4B describes the synthesis of a new supported catalyst and its application for the Ullmann type coupling.

Chapter 5 describes the synthesis, characterization and catalytic activity of a newly synthesized heteroligated oxovanadium(V) complex. The reactivities have been studied with respect to oxidation of sulfide. Theoretical and experimental insights

have also been made on the reactivity of various organicammonium tribromides in this section.

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Details of General Materials, Methods and Equipments

A detailed report of the procedures followed for the preparation of different starting materials is described in this chapter. The details of the methods used for quantitative determination of various constituents and the relevant particulars of the instruments/equipment used for the characterization and structural assessment of the newly synthesized compounds are also described herein.

All the chemicals and solvents used for the present work were of analytical grade quality. Following are the sources of the chemicals and solvents: S.D. fine-chem Ltd., Qualigens Fine Chemicals, Merck (India) Limited, Sisco Research Laboratories Pvt. Ltd., Central Drug House (P) Ltd., Bengal Chemicals and Pharmaceuticals Ltd., Loba Chemie Industries, and Sigma-Aldrich (India).

2A. Preparation of starting materials

a) 3,5-dimethylpyrazole (dmpz)[1]

A methanolic solution of 25 mL of hydrazine hydrate, $N_2H_4 \cdot H_2O$, (25.0 g, 499.4 mmol) was added slowly with stirring to a methanolic solution of 25 mL of acetylacetone (25.0 g, 249.7 mmol) in an ice-cold condition. A light yellow solution was obtained. The solution was concentrated to *ca.* 20 mL on a steam-bath and left overnight in a refrigerator. A white crystalline compound was obtained and this was isolated by filtration, washed 4 or 5 times with water and dried in air. The yield of pure 3,5-dimethylpyrazole (dmpz) was 23.5 g (98%) having m.p. 107–108 °C (lit. m.p. 107 – 109 °C).

b) $VO(acac)_2$[2]

To an aqueous suspension of vanadium pentoxide (5 g, 27.49 mmol) in 20 mL of water taken in a 500 mL beaker, 30% hydrogen peroxide (37.37 mL, 329.88mmol) was added drop wise in an ice-cold condition and stirred till a clear dark solution was formed. To the dark brown colored solution, distilled acetylacetone (19.84 mL, 192.5 mmol) was added drop wise very carefully with continuous stirring. Vigorous effervescence took place after 15 min. stirring for a period of 30 min led to a precipitation of a brown colored microcrystalline compound. The reaction mixture was heated at 70 °C for 15 min under stirring. The precipitate turned olive green with shiny crystalline appearance with the solution also turning green. The solution

was concentrated by heating on a steam bath for 30 min and then placed in an ice-water bath for 15 min. The compound was filtered through Whatman No. 42 filter paper, washed with acetone and dried in vacuo over fused $CaCl_2$. Yield: 11.7 g (80%).

2B. Elemental analysis

a) Vanadium [3]

Vanadium was estimated iodometrically.

An accurately weighed amount (*ca.* 0.1 g) of vanadium compound was dissolved in 100 mL of water. To the solution was added 5 mL of 5M H_2SO_4. The solution was boiled for 10 min to remove peroxide. To this solution was added 5 g of potassium persulphate followed by the addition of one drop of silver nitrate, $AgNO_3$, solution. The resultant mixture was boiled for 1 h. After this 15 mL of 5M H_2SO_4 was added and the solution was boiled for a further period of 30 min. The solution was allowed to cool to room temperature and *ca.* 5 g of KI was added with stirring. This was then kept in the dark for 15 min. The liberated iodine was then titrated with standard $Na_2S_2O_3$ solution using starch as an indicator. The end point was detected by the appearance of a light-blue colour.

1 mL of 0.1 M $Na_2S_2O_3$ = 0.00519 g of vanadium

b) Bromide [4]

An accurately weighed amount (*ca.* 0.1 g) of organicammonium tribromide was dissolved in 20 mL of acetonitrile. The solution was treated with 20 mL of a 20% NaOH solution, followed by the addition of 100 mL of water. The solution was boiled for 1 h and acidified with dilute (1:1) HNO_3. The acidified bromide solution was then treated with an excess of 0.1 M silver nitrate solution. The suspension was heated almost to boiling and stirred vigorously. The beaker along with the suspension was kept in the dark for 30 min. The precipitated AgBr was separated out by filtration and washed several times with water. The filtrate and the washings were collected and the unreacted $AgNO_3$ was titrated with standard KSCN solution using $Fe(NO_3)_3$ as indicator. The end point was marked by the appearance of a faint red – brown colour. From the equivalence of standard $AgNO_3$ and standard KSCN

solutions, the volume of excess $AgNO_3$ was calculated and this was subtracted from the volume of $AgNO_3$ initially added. The difference is the volume of $AgNO_3$ solution consumed.

1 mL of 1 M $AgNO_3$ = 0.0799 g of bromide

c) Sodium and Potassium [5]

Sodium and potassium contents were determined by flame photometry. A solution containing sodium or potassium ions was acidified with hydrochloric acid. The acidified solution thus obtained was used for flame photometry.

d) Peroxide

I. Permanganometry [6]

Nearly 1 g of boric acid was dissolved in 100 mL of water taken in a conical flask. To this was added an accurately weighed amount (*ca.* 0.1 g) of peroxo compound followed by the addition of 7 mL of 5M H_2SO_4. The solution was shaken well to dissolve the compound. The peroxide was then estimated by redox titration with standard $KMnO_4$ solution. The end point was marked by the appearance of a permanent faint pink colour.

1 mL of 0.2 M $KMnO_4$ = 0.016 of peroxide

II. Iodometry[7]

To a freshly prepared 2 M sulphuric acid solution, containing an appropriate amount of potassium iodide (~2 g in 100 mL) was added an accurately weighed amount (*ca.* 0.1 g) of a peroxo compound with stirring. The mixture was allowed to stand for *ca.* 15 min in carbon dioxide atmosphere in the dark. The amount of iodine liberated was then titrated with a standard sodium thiosulphate solution, adding 2 mL of freshly prepared starch solution when the colour of the iodine was nearly discharged.

1 mLof 1N $Na_2S_2O_3$ = 0.01701 g of peroxide (O_2^{2-})

[In case of a peroxovanadate(V) complex, this method gives the total amount of peroxide plus vanadium present in the compound. On deduction of the contribution of vanadium(V) from the total amount of iodine liberated, the net peroxide content of the compound is evaluated.]

e) Phosphate [7]

To a neutral or weakly acidic solution (50-100 mL) of the phosphate containing compound, 3 mL of conc. HCl and few drops of methyl red indicator was added. A magnesia mixture** was introduced, followed by addition of conc. NH_3 solution slowly. The solution was then vigorously stirred until the color of indicator turns yellow. At that point precipitate appeared, and allowed the solution to stand for few hours. Then the precipitate was filtered off through sintered glass crucible and washed with 0.8 M aqueous solution of NH_3. The washing continues until a few mL of filtrate, when acidified with dil. HNO_3 and tested with $AgNO_3$ gave no test for Cl^-. Further, it was washed with small portions of alcohol or ether and drained well. The outside of crucible is then wiped with cloth, kept in a desiccator for about 20 minutes and weighed.

** [25g of magnesium chloride, $MgCl_2 \cdot 6H_2O$ and 50 g of NH_4Cl was dissolved in 250 mL water. Slight excess of NH_3 solution was added to that and allowed to stand overnight. Acidified with dil. HCl, further 1 mL of conc. HCl was added and diluted to 500 mL]

f) Carbon, Hydrogen and Nitrogen

The carbon, hydrogen and nitrogen contents were estimated by micro-analytical methods. The results of the analyses were obtained using a 2400 Perkin Elmer Series II CHNS/O Analyzer.

2C. Particulars of Instruments/Equipments Used for the Following Physico-chemical studies

a) pH Measurement

pH values of the reaction solutions were recorded with a Systronics Type 335 digital pH meter and also by using Merck pH indicator paper.

b) Solution Electrical Conductance Measurement

Solution electrical conductance measurements were measured on a Systronics Type 304 direct digital reading conductivity meter. Solution strength was maintained at 10^{-3} M in appropriate solvents.

c) Recording of Melting Point

Melting points of the compounds were recorded using a MP1 V-Scientific melting point apparatus and a Büchi-504 melting point apparatus. The heating rate was maintained at either 5 °C or 10 °C.

d) Infrared Spectroscopy

Infrared spectra of the compounds were recorded as KBr pellets using a Nicolet Impact–410 Fourier Transform Infra-Red Spectrophotometer or on a Perkin-Elmer model 983 Spectrophotometer.

e) Electronic Absorption Spectroscopy

UV-visible spectra were recorded by dissolving a calculated amount of the sample in an appropriate solvent, on a SHIMADZU-2550 Spectrophotometer.

f) ^{1}H Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were recorded either on a JEOL JNM ECS 400 MHz NMR spectrophotometer using tetra methylsilane (TMS) as internal standard.

g) Thermal Studies

Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC) experiments were conducted on a SHIMADZU-TGA50Thermal Analyzer instrument. Experiments were done using either aluminium or platinum crucibles. Pure N_2 gas was used as the flow gas.

h) Mass Spectrometry

Mass spectrometric analysis was done using GC-MS Fission 5000, EI mode (70 eV) instrument (Quadruple Mass Spectrometer).

i) Gas Chromatography

Gas chromatographic analysis was done on a Perkin-Elmer Clarus 600 instrument using a capillary column (30×0.25×0.25 mμ) in EI mode.

j) Surface area measurement

Surface area (BET), pore volume, average pore size and pore size distribution were determined by the nitrogen adsorption-desorption method at liquid N_2 temperature on a BECKMAN COULTER (SA3100 serial no.AJ15007). The samples were degassed at 220 ^{0}C for 3 hours.

k) Powder X-ray diffraction

The powder XRD was recorded on Rigaku X-Ray diffractometer Miniflex, UK CuK_α source (λ = 1.54 Å) on glass surface of air-dried sample.

l) X-ray Crystallography

The X-ray data were collected at 293 K with MoK_α radiation (λ= 0.71073Å) on a Bruker Nonious SMART CCD diffractometer equipped with graphite monochromater. The SMART software was used for data collection, indexing the reflection and determination of the unit cell parameters. Integration of the collected data was made using SAINT XPREP software. Multi-scan empirical absorption corrections were applied to the data using the program SADABS. The structures were solved by direct methods and refined by full-matrix least-square calculations by using SHELXTL software. All non-hydrogen atoms were refined in the anisotropic approximation against F^2 of all reflections. The hydrogen atoms attached were located in difference Fourier maps and refined with isotropic displacement coefficients. The hydrogen atoms were placed in their geometrically generated positions. Crystal parameters for the compounds are presented in the experimental section of the respective chapters.

m) Surface morphology

The surface morphology of the heterogeneous catalyst has been investigated by Scanning Electron Micrograph (SEM image are recorded in JSM-639LV, JEOL,

Japan) and Transmission Electron Micrograph (TEM are recorded in JEOL, 2100X and 200kV).

2D. Computational details

In order to investigate the reactivity of the complexes, we performed density functional theory (DFT) calculations. All calculations were performed with the DMol3 program using BLYP functional and DNP basis set. The size of the DNP basis sets is comparable to that of the Gaussian 6-31G** basis sets, but this numerical basis set is more accurate than a Gaussian basis set of the same size. The integration grid referred to as FINE in the software program has been used for optimization of the complexes.

2E. References

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Carbon-Carbon Bond forming Reactions

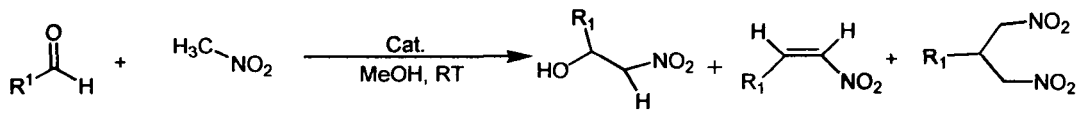
* The work described in this chapter has been published in

1. ***Green Chemistry Letters and Reviews*** **6**(1), 55-61, 2013 [Section 3B]

Section 3A

Musa balbisiana Colla: a potential renewable base for regioselective nitroaldol reaction

Development of efficient base catalyst for the C-C bond formation is a profound area of research [1–6]. Most often Henry, Knoevenagel, Michael addition reactions are employed for C-C bond forming reactions has been intensively sought and many new catalysts for these reactions were recently reported [7–11]. Owing to the significance of nitroaldol product (*β*-nitro alcohol) as a synthetic intermediate for various industrial methods, development of selective base catalyzed Henry reaction is a crucial area of research [12,13]. Since the discovery (1895) [14], various catalysts have been reported to catalyze the Henry reaction [15–17]. Classical Henry reaction involves a homogeneous catalytic condition which suffers from difficulty to separate the catalyst from the reaction mixture [18,19]. The current drift of green chemistry demands the development of environmentally benign methodologies for the organic conversions [20–22]. Heterogeneous solid catalysts like amberlyst [23], hydrotalcite [24], MgO [25] layered silicate [26] modified zeolite [27] etc. have been reported for the Henry reaction. Due to the high applicability of the product formed in the Henry reaction different methodologies such as microwave [28], sonication [29], supercritical fluid [30] have also been employed. Albeit presence of such vast literature reports of various catalysts for Henry reaction, their industrial applicability is hindered by low yield, retro-aldol product, side product formed by Cannizzaro reaction of aldehyde, requirement of quantitative amount of base, purification of the product from the base, use of environmentally hazardous solvents etc. [31].



1 2 3 4 5

R^1= aryl, alkyl, heterocycle

Scheme 3.1: Base catalyzed nitroaldol reaction

Renewability of a catalyst adds additional advantage to the catalyst [32–34]. *Musa balbisiana Colla* is a species of wild banana native to south Asia. In the north-east region of India, the Assamese community uses the ash of the *M. balbisiana Colla* peel as a medicine for stomach problems especially for acidity [35].

The ash of the *M. balbisiana Colla peel* is found to be basic [36]. A fair degree of control over the type of Henry product with desired stoichiometry has been achieved in homogeneous medium by use of the mentioned catalyst in methanol solvent and at room temperature. It is interesting to see that the catalyst effectively and selectively catalyzes the Henry reaction giving *β*-nitroalcohol (**3** in scheme 3.1) as the major product.

3A. 1 Experimental

Preparation of the catalyst

The preparation method of the catalyst is very simple. The yellow peel of ripe *M. balbisiana Colla* fruit is collected and dried under sun light for several days. The dried grey material was ignited and allowed to burn into ash. The ash was collected and grinded into powder and kept inside an airtight vial in a desiccator.

Determination of basic strength of the catalyst

a) Hammett indicator method

The strength of the basic sites was measured qualitatively using Hammett indicator method. In this technique, 25 mg of solid catalyst dried at 120 °C was shaken with 1 mL solution (0.1% in methanol) of the indicator and left to equilibrate for 1h. The colour of the catalyst and the solution were noted. The following Hammett indicators were used: phenolphthalein (pKBH+ = 8.0-9.6) and Tropiline-O (pKBH+ = 11.1-12.7) [37]. The pKBH+ value of the catalyst is found to lie between 8 and 11.1. The base strength is reported as stronger than the weakest indicator and weaker than the strongest indicator which shows no color change.

b) Acid base titration

The soluble basicity of the catalyst has been determined by acid base titration method. In this method, 100 mg of the catalyst was initially taken in 10 mL of Methanol and stirred for 2 hrs. The methanol was separated out from the catalyst and evaporated in the rotary evaporator. A white residue soluble in water was left in the

bottom of the round bottom flask. The residue was solubilized in 10mL distilled water and titrated with standard (0.05 M, HCl). The observed basicity was 1.970 mmol/gm.

c) Henry (Nitroaldol) Reaction

The Henry reaction was performed by using the material mentioned above as the catalyst. Typically, 2 mg of catalyst was added to a mixture of *4*-chlorobenzaldehyde (140 mg, 1 mmol) and nitromethane (0.1 mL, 1.5 mmol) in methanol at room temperature and allowed to stir for 5h. The product was recovered with ethyl acetate and purified using column chromatographic techniques over silica.

d) Flame Photometric estimation of K, Ca, Mg:

The fluid under analysis is sprayed as a fine mist into non-luminous flame, which becomes coloured according to the characteristics of emission of elements (K: 768, Ca: 622nm). A photo detector which views the flame through a selected narrow band optical filter that only passes the wavelengths centered around the characteristic emission of the selected element monitors the flame. The output of the photo detector is fed to an electronic module, which provides digital readout of the concentration of the selected elements. Before analyzing the unknown fluid sample, the system is standardized with solution of known concentrations of elements of interest. The general procedure for the stock solution is given below:

Potassium: 1000 ppm: Dissolve 1.9070 g KCl in 1 lit. distilled water

Calcium: 1000 ppm: Dissolve 2.497 g CaCO3 in 300 mL distilled water and added 10 mL conc. HCl. Dilute to 1 litt.

Magnesium: 1000 ppm: Dissolve 3.9160g. of magnesium chloride ($MgCl_2.6H2O$) in 200ml. of distilled water. Dilute to 1 litre .

3A. 2 Results and Discussion

The role of base is very important in a conventional synthesis of *β*-nitroalkanols from different aldehydes and nitroalkanes. A conventional base catalyst, catalyzes the dehydration of *β*-nitroalkanols to the corresponding nitroalkene which then

readily polymerizes. Thus, choosing a base of proper strength for the selective synthesis of β-nitroalkanols is a challenging task. The catalyst that we have mentioned already (i.e. *Musa balbisiana Colla*) selectively catalyzes Henry reaction giving β-nitroalkanols as the major product. The basic property of the catalyst is attributed due to the presence of various alkali metals in the catalyst.

Table 3.1: Optimization of the reaction condition for *p*-ClC_6H_4CHO and nitromethane as model substrates

Entry	Catalyst (wt %)	4-ClC_6H_4CHO	CH_3NO_2	Yield (%)[a]
1	5	1	1	60
2	5	1	1.5	65
3	6	1	1.5	75
4	8	1	1.5	83
5	10	1	1.5	87
6	15	1	2	90
7	20	1	2	92

[a]Yields are reported on the basis of ^1H NMR data

Initial attempts were carried out using *4*-chlorobenzaldehyde and nitromethane as the model substrate. The reaction gave high yield of product in very short time period at room temperature when methanol was used as the solvent. We have optimized the reaction taking various parameters e.g. solvent, catalyst amount, temperature etc.

Taking *p*-chlorobenzaldehyde and nitromethane as the model substrates we carried out the experiment and the results are tabulated in table-3.1.Our study shows that the catalyst gives high yield of product in methanol medium at room temperature (figure 3.1). The polarities of the solvents have a marked effect on the yield of the product as observed from the figure-3.1. The reaction is favored in the polar solvents and gives high yield of product; however in the non polar solvents the reaction proceeds slowly and gives low yield. The low yield of the product in the non polar solvents might be attributed to the less solubility of the alkali metal present in the catalyst. We also performed some control experiments to demonstrate the specific catalytic effect of the catalyst. We observed that no product was formed between *4*-chlorobenzaldehyde and nitromethane even after 2 days stirring in a round bottom flask, only aldehyde was getting oxidized to the corresponding acid very slowly. At

the elevated temperature the reaction led to the generation of other two Henry reaction products **4** and **5** (scheme-3.1, figure-3.2).

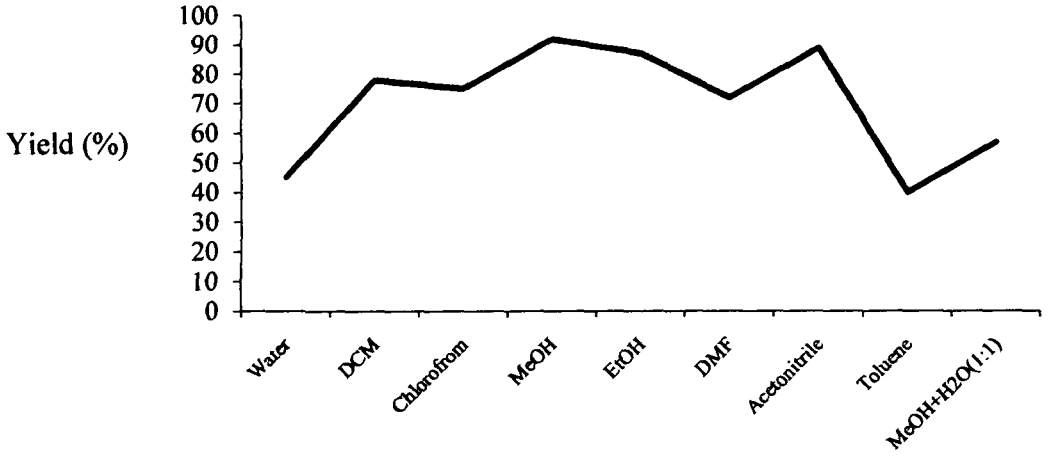


Figure 3.1: Effect of various solvents on the yield of Henry products

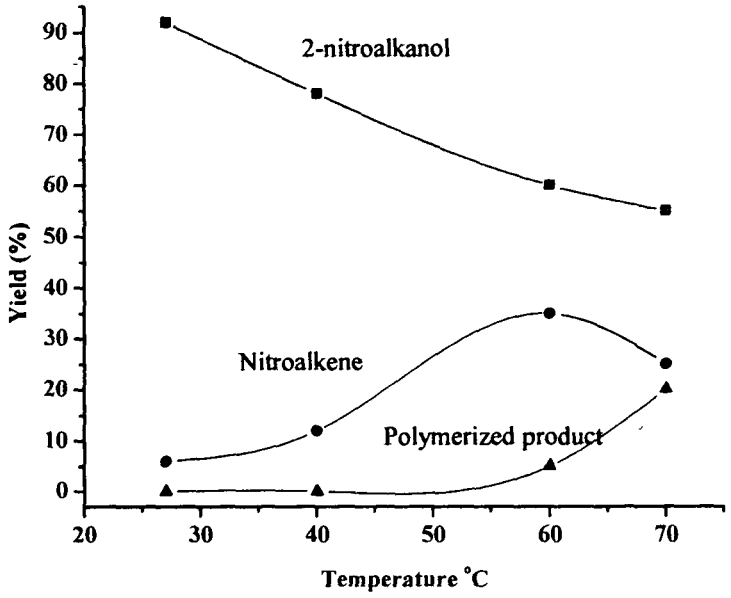
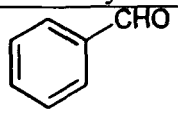
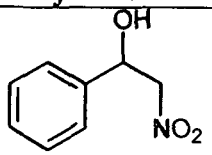
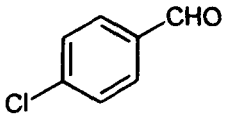
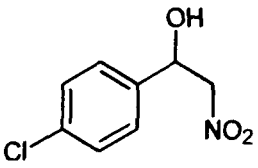
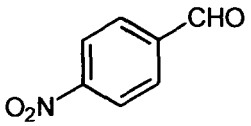
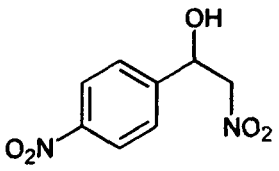
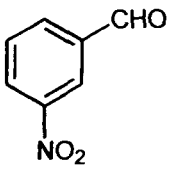
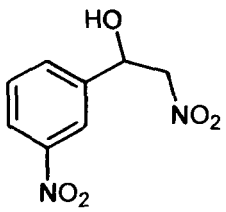
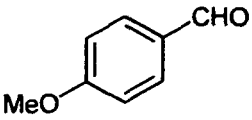
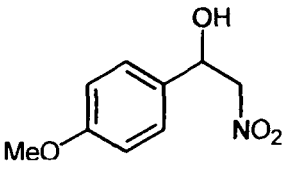
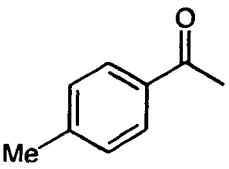
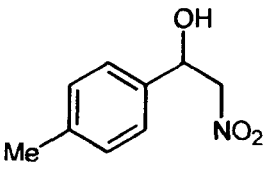
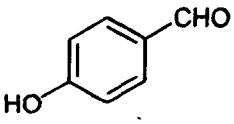
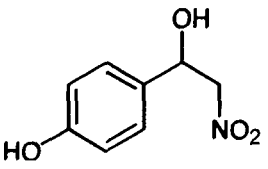
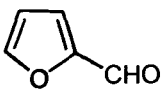
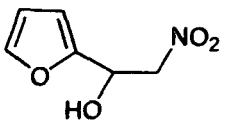
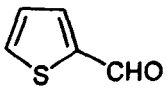
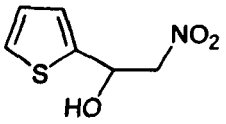
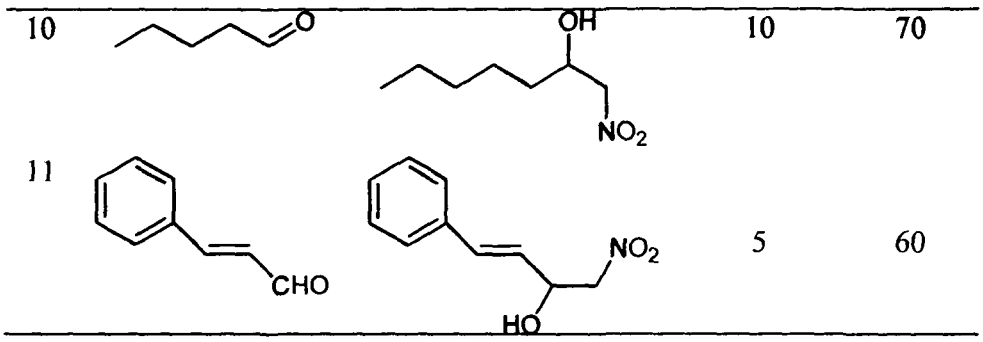


Figure 3.2: Effect of temperature on the yield of various Henry products

Table 3.2: M. balbisiana Colla catalyzed nitroaldol reaction between nitromethane and aldehyde

Entry	Aldehyde	Major Product	Time (h)	Yield (%)
1			5.5	87
2			5	92
3			5	97
4			5	95
5			6	87
6			6	87
7			7	82
8			5	80
9			5	78



After optimizing the reaction condition we proceeded with a range of aliphatic, aromatic & heterocyclic aldehydes (entries 1-11, table 3.2). The catalyst is found to be very effective for the aromatic and heterocyclic aldehydes. Unsaturated aliphatic aldehyde also gives nitroaldol product under the same condition. Aliphatic aldehydes like pentanal reacts slowly giving low yield (entry 10, table 3.2).

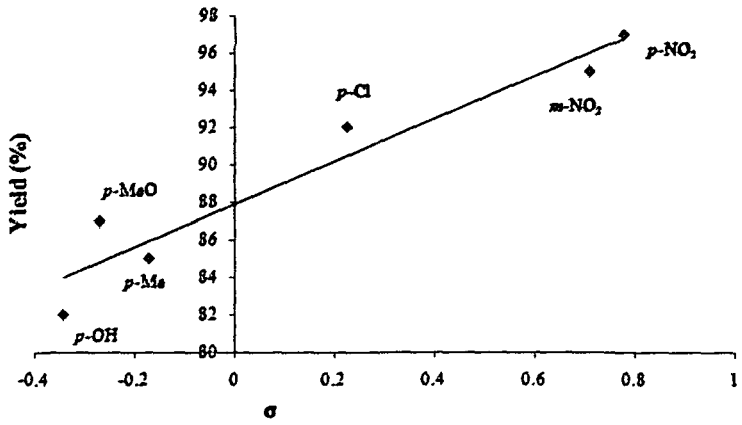


Figure 3.3: Linear relationship between yield and the Hammett sigma constant

The reason might be attributed to the low electrophilicity of aliphatic aldehyde than the aromatic one. Further investigation on the electronic effect of the substituents on the aromatic ring of the aromatic aldehyde was done (entries 2-7, table-3.2). For aryl aldehyde bearing electron withdrawing groups the reaction took place smoothly to afford the desired nitroaldol product in good yield within short time. However the aryl aldehydes bearing electron donating groups such as *p*-tolualdehyde and anisaldehyde the reactions were slow.

A correlation between the Hammett constant (σ) and the corresponding yield of the products have been shown in the figure-3.3; it reveals a linear relationship between

the yields of the product and the substitution constant (σ). Change in reaction rate is also influenced by the chain length of the nitroalkanes. Changing nitromethane by nitroethane the reaction becomes slower (figure-3.4).

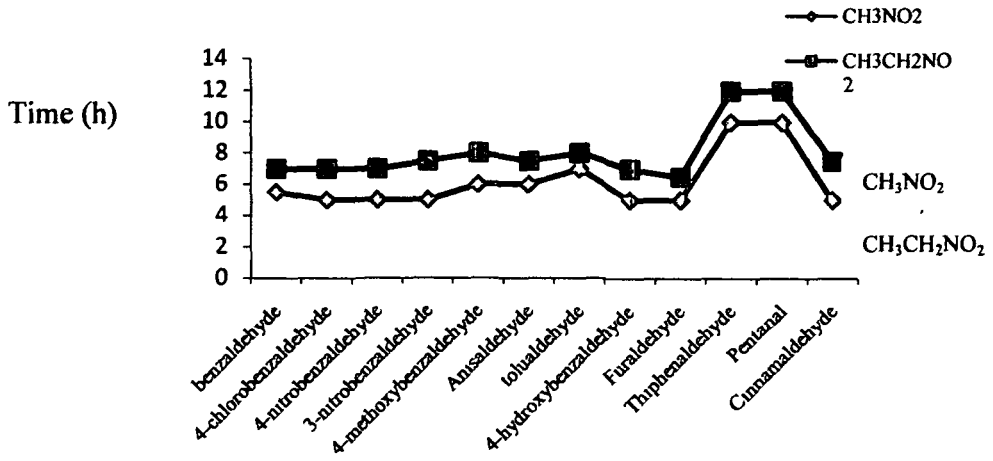
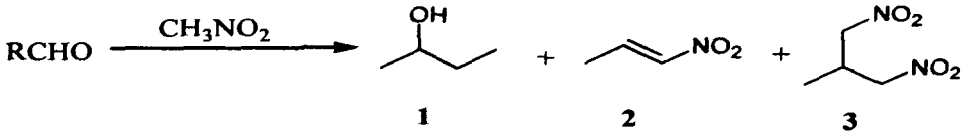
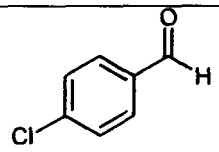
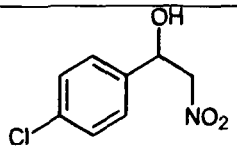
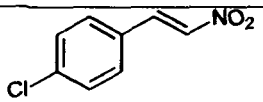
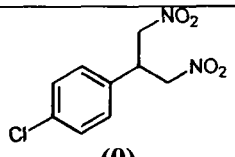
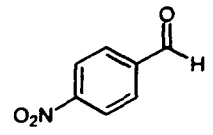
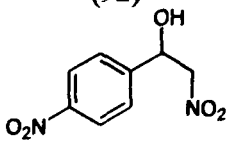
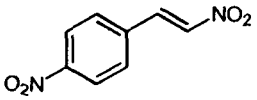
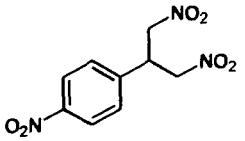
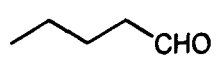
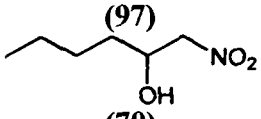
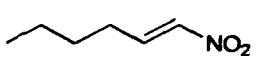
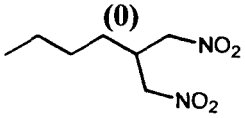


Figure 3.4: Variation of reaction time with change in chain length of nitroalkane

Table 3.3: Percentage of various products formed in the *M balbisiana Colla* catalyzed Henry reaction



Entry	Substrate	Product -1	Product-2	Product-3
1		 (92)	 (6)	 (0)
2			 (3)	
3		 (70)	 (22)	 (8)

The catalyst is found to catalyze the reaction in a regioselective way giving only the β-nitroalkanol as the major products. The percentage of different products formed between some aldehydes and the nitromethane is shown in the table-3.3. The catalyst is efficient and effective for catalyzing the Henry reaction giving β-nitro alcohol as the major product in MeOH.

Although the catalyst used is a heterogeneous one but the reaction is taking place in a homogeneous medium. The alkali metals like K, Ca etc. get solubilized in the reaction medium which is confirmed by the flame photometric experiments shown in table-3.4.

After each reaction the catalyst has been recovered by filtration method, washed with ethyl acetate and stored in a dessicator. The reusability of the catalyst has also been studied and it is found that catalytic activity of the catalyst decreases considerably after the first cycle.

Table 3.4: Flame photometric estimation of K, Ca and Mg in the reaction medium.

Entry	Element	Amount in mmol/gm
1	K	1.023
2	Ca	0.60
3	Mg	0.52

The recycled catalyst is used for the following C-C bond forming reaction without any further modification. The catalyst activity decreases consistently with successive run and ends up with >50% conversion after the 4^{th} run. The decrease in yield of the product with successive reuse may be attributed to the leaching of alkali metals from the catalyst. A relation between the soluble basicity and the yield of the product can be drawn from table-3.5. It is clearly reflected from that the table 3.5 that with decrease in soluble basicity of the catalyst there is a decrease in yield of the product was observed

Table 3.5: The reusability of the catalyst in correlation with the soluble basicity (based on acid base titration) of the catalyst

Catalyst	Amount in mmol/gm	Yield of Product (%)
Fresh	1.926	97
Second run	0.966	82
Third run	0.741	70
Fourth run	0.632	55

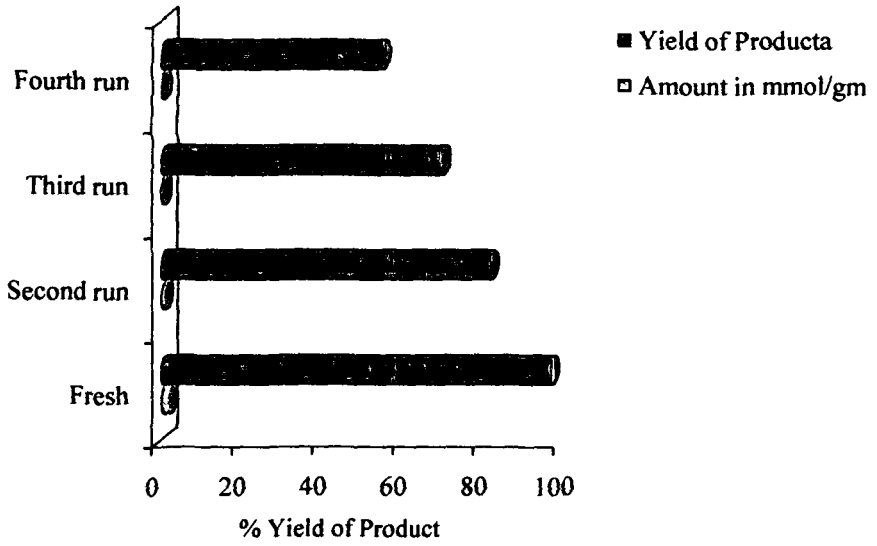


Figure 3.5: Correlation of yield of product and the soluble basicity of the catalyst

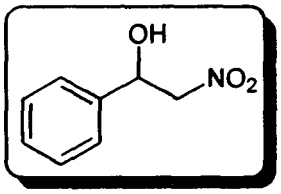
The intrinsic basicity of the catalyst might have potential application as a base catalyst for other base catalyzed organic conversions. The activity of the catalyst may be attributed to the controlled basicity of the catalyst compared to the classical homogeneous base catalyzed reactions.

3A. 3 Conclusion

In summary, we have described an efficient synthesis of β-nitro alcohol using a renewable material as a catalyst. The renewability and the easy preparation method of the catalyst may be appealing for the chemist practicing green synthetic process. The protocol is effective and selective one and is superior to many reported methods of the literature in terms of reactivity and efficiency. Above all the importance of this protocol lies in the avoidance of toxic organic solvents, fast reaction rate, high yield of product, high product selectivity in case of aromatic aldehyde. The controlled basicity of the catalyst might be responsible for the high selectivity of the product by suppressing the competitive reaction usually associated with the Henry reaction.

3A. 4 Physical and Spectral data

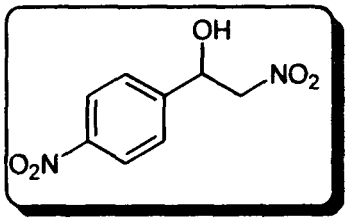
2-Nitro-1-phenyl-ethanol (entry 1, table-3.2)



Colourless oil

FT-IR(KBr): 3545,3042,1690,1553,1497 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ 7.35-7.47(m, 5H), 5.42-5.47(m,1H), 4.55-4.49(m,1H), 4.40-4.43(m,1H), 2.95(brs,1H).

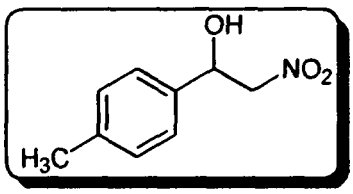
2-Nitro-1-(4-nitro-phenyl)-ethanol (entry 3, table-3.2)



Yellow oil

FT-IR(KBr): 3532, 2930, 1557, 1345 cm^{-1};^1H NMR(400 MHz, $CDCl_3$): δ 8.22-8.24(d, *J*=8 Hz, 2H), 7.62-7.64(d, *J*=8Hz, 2H), 5.57-5.70(m, 1H), 4.56-4.58(m,2H), 3.52(s,1H).

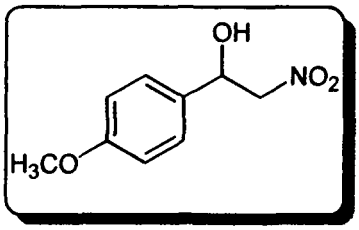
2-Nitro-1-*p*-tolyl-ethanol (entry 6, table-3.2)



Viscous liquid

FT-IR(KBr): 3440, 2930, 1563cm^{-1};^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.35(d, *J*=8.0Hz, 2H), 7.24-7.26(d, *J*=8.0Hz,2H), 5.40-5.45(m,1H),4.58-4.62(m,1H),4.47-4.50(m,1H), 2.64(brs,1H), 2.43(s,3H).

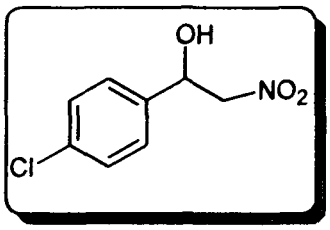
1-(4-Methoxy-phenyl)-2-nitro-ethanol (entry 5, table-3.2)



Viscous liquid

FT-IR(KBr): 3512, 2935, 1678, 1557, 1360 cm^{-1},^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.35(d, *J*=8.0Hz, 2H), 6.72-6.74(d, *J*=8Hz, 2H), 5.33(d, 5.2Hz, 1H),4.90(m, 1H), 4.65-4.78(m,1H), 3.91(s,3H), 1.50(d, *J*=6.7Hz, 3H), 1.42(d, *J*=6.5Hz, 3H).

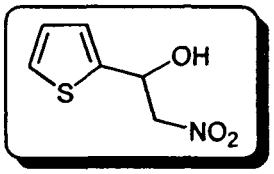
1-(4-Chloro-phenyl)-2-nitro-ethanol (entry 2, table-3.2)



Yellow oil

FT-IR (KBr): 3510, 2935, 1621, 1571, 1495, 1383 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.37(d, *J*=8 Hz, 2H), 7.32-7.34(d, *J*= 8.0Hz, 2H), 5.36-5.46(m, 1H), 4.50-4.55(m, 1H), 4.39-4.44(m, 1H), 3.12(brs, 1H).

2-Nitro-1-thiophen-2-yl-ethanol (entry 9, table-3.2)



Viscous liquid

FT-IR(KBr): 3460, 1553, 1510cm^{-1}; ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.44-7.46(m, 1H), 6.40-6.53 (m, 2H), 5.42-5.46 (m, 1H), 4.77-4.85 (m, 1H), 4.65-4.70 (m, 1H), 2.91(brs, 1H).

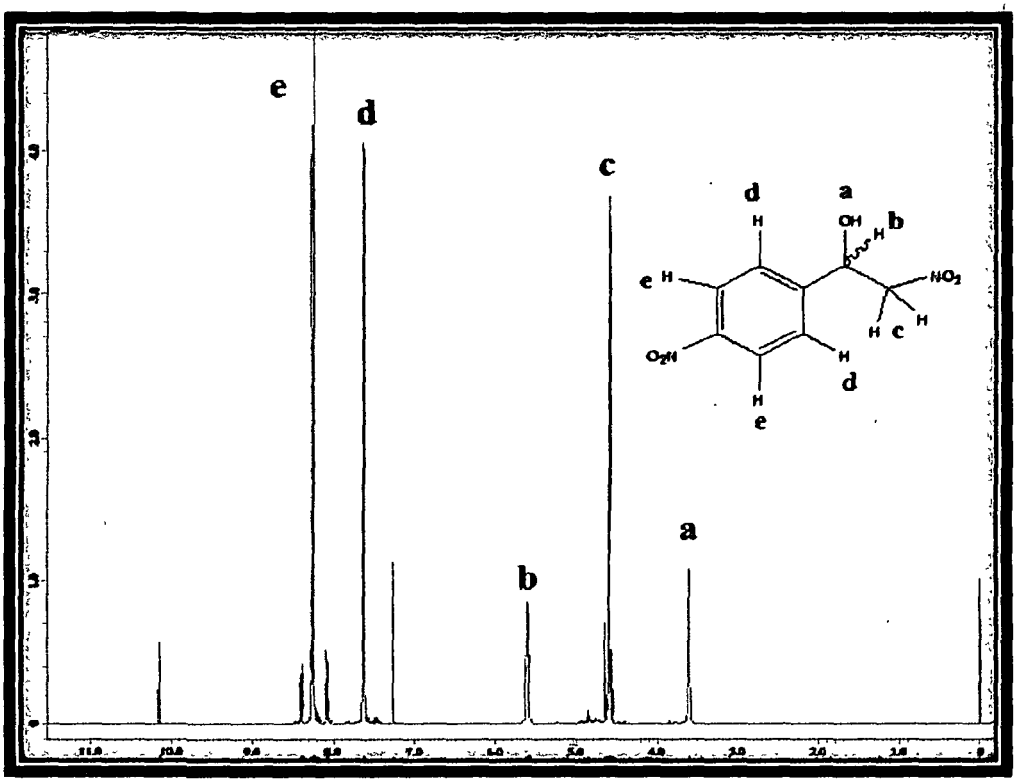


Image 1: ^{1}H NMR spectrum of reaction mixture of *4*-$NO_2C_6H_4CHO$ and $MeNO_2$

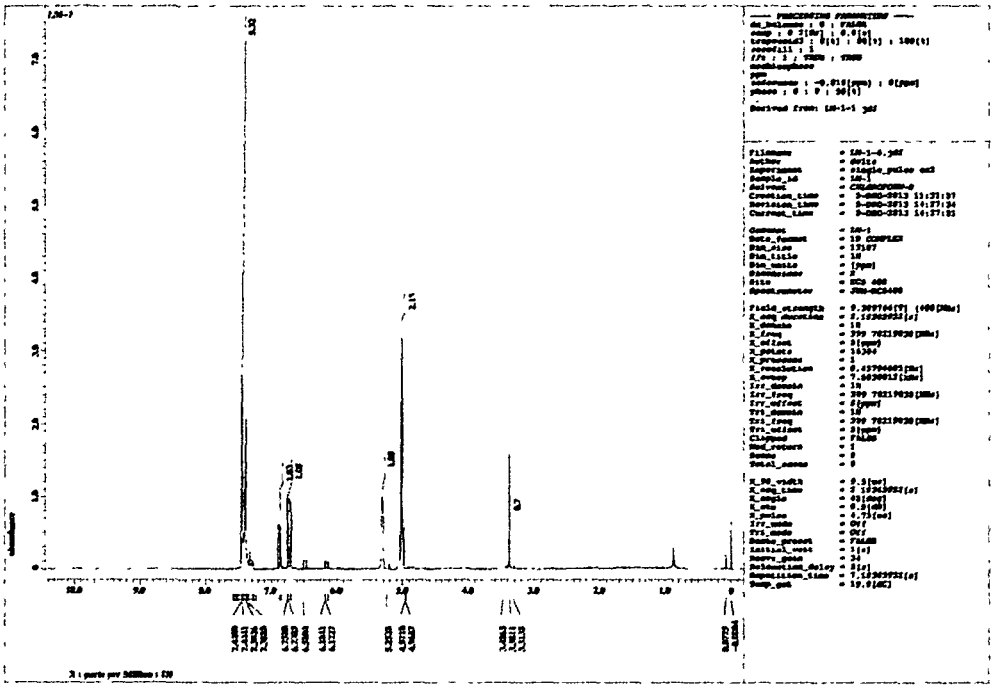


Image 2: 1H NMR Spectrum of 1-Nitro-4-phenyl-but-3-en-2-ol

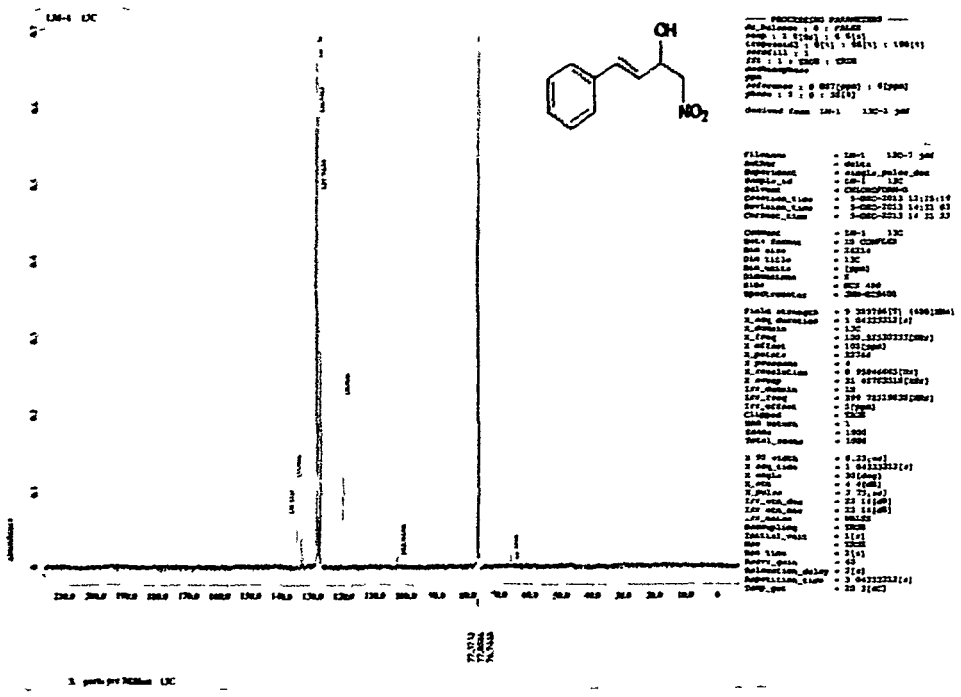


Image 3: 13 C NMR spectra of 1-Nitro-4-phenyl-but-3-en-2-ol

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Section 3B

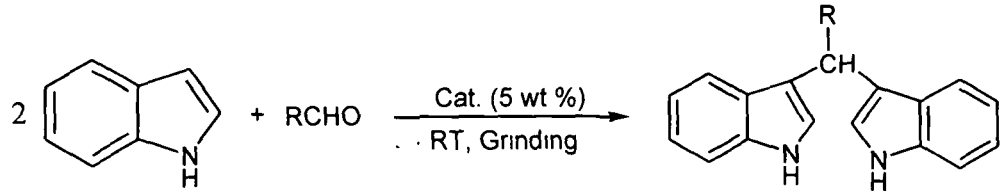
A green synthesis of symmetrical bis(indol-3-yl)methanes (BIMs) using phosphate impregnated titania catalyst under solvent free grinding condition

Indole is one of the most profoundly studied, ubiquitous and π-electron excessive nitrogen heterocyclic systems [1] having interesting biological properties that received particular interest in the mid 1950s, when alkaloid reserpine [2] was introduced as one of the first drugs for the treatment of central nervous system (CNS) disorders such as anxiety and mental disorder. Substituted indoles are referred to as "privileged structures" since they are capable of binding to many receptors with high affinity. Indole containing compounds have been reported to exhibit anti-apoptotic properties [3]. Compared to benzene, indole shows enhanced reactivity in the electrophilic aromatic substitution reaction. The C-3 position of Indole is about 1013 times more reactive than benzene [4,5].

Unsubstituted indoles respond to electrophilic substitution reaction with aldehyde or ketone in the presence of Lewis or Brønsted acids [6,7] via reactive C-3 position resulting bis(indol-3-yl)methanes (BIMs). Various catalysts e.g. FeF_3, $ZrCl_4$, $InCl_3$, $In(OTf)_3$, polyvinylsulfonic acid, [bimim][$MeSO_4$], $Cu_{1.5}PMo_{12}O40(14)$, SiO_2-$AlCl_3$, NH_4Cl, $Zn(OTf)_2$, ultrasound, cellulose sulfuric acid, supported-SO_3H etc. have been reported for the synthesis of BIMs [8-20]. There are reports describing the preparation of BIMs in water [21]. Very recently, new *β*-lactam compounds containing a bis(indol-3-yl) framework were synthesized [22].

Naturally occurring or synthetic BIMs and its privileged structures are important intermediates in organic synthesis [23] and are particularly important in pharmaceutical chemistry as they exhibit various pharmacological activities and are important metabolites [24-27]. BIM derivatives as highly selective colorimetric and fluorescent molecular chemosensors for Cu^{2+} cation has been reported [28]. Although a number of different methods have been reported for the preparation of BIMs, these methods have their merits in some way as claimed, but, on the other hand, they suffer from certain drawbacks e.g. longer reaction time, harsh reaction conditions, expensive use of reagent/catalyst, sensitivity to moisture and air, incompatibility of functional groups, environmental incompatibility, many Lewis acids are prone to undergo decomposition in the presence of nitrogen containing

reactants and this requires the use of excess and sometimes stoichiometric amount of Lewis acid catalyst [29]. Hence, there is still a need to search for better catalysts in terms of toxicity, handling, availability, economic viability, and operational simplicity. In view of the recent trend in catalytic process which comes under the purview of green chemistry, investigations for new and less hazardous catalysts have become a priority in synthetic organic chemistry. The sustained activity of our group for the solid acid catalyzed organic conversions [30-32] inspired us to develop an efficient green methodology for the synthesis of BIMs **3** (scheme 3.2) from indole **1** and aldehydes **2** catalyzed by solid acid (viz. phosphate impregnated titania catalyst). To mention, in recent years, the use of solid acid catalysts have received paramount attention and interest in different areas of organic synthesis because of their several inherent useful properties such as environmental compatibility, reusability, greater selectivity, simplicity of handling, lesser toxicity, non-corrosiveness, cheap and ease of isolation. Furthermore, generation of wastes and by-product can also be minimized or avoided by using solid acid catalyst, thereby developing cleaner synthetic routes [33,34].



1 2 3

Scheme 3.2: Solid acid catalyzed condensation of indole (1) and aldehyde (2)

3B. 1 Experimental

a) Preparation and characterization of the catalyst

We have followed the literature method [30] for the preparation of the catalyst as reported, *viz.* titania and phosphoric acid (88%) were mixed in the molar ratio of 1:1 in a silica boat followed by heating at 200-220 °C on a hot sand bath under stirring until the mass solidified. Heating was then withdrawn and temperature was allowed to come down to *ca.* 100 °C, then the catalyst was transferred to a vacuum desiccator. Finally the catalyst was properly stored in an airtight sample vial. After preparation, the catalyst was characterized by IR spectroscopy and XRD technique and was compared with the reported data [30].

*b) Typical procedure for the synthesis of **BIMs 3***

A mixture of indole **1** (2 mmol, 0.23 gm), 4-chlorobenzaldehyde **2b** (1 mmol,0.14 gm), and catalyst, phosphate impregnated titania (5 wt%, 0.02 gm) under solvent free condition was grounded in a mortar with pestle at room temperature for an appropriate time (1 min). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2×10 mL) and filtered to separate the catalyst. The combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure in a rotary evaporator to furnish a crude product that was further purified by column chromatography on silica gel [Eluent: EtOAc/Pet. Ether (1:2)] to give the pure product (99% yield).

c) Typical procedure for the synthesis of tetra-indolyl(terephthalyl)dimethane 3o

A mixture of indole **1** (4 mmol, 0.47 gm), terephthaldehyde **5** (1 mmol, 0.13 gm), and the catalyst (5 wt%, 0.02 gm) under solvent free condition was grinded in a mortar with pestle at room temperature for an appropriate time (1 min). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2×10 mL) and filtered to separate the catalyst. The combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure in a rotary evaporator to furnish a crude product that was further purified by column chromatography on silica gel [Eluent: EtOAc/Pet. ether (1:2)] to give the pure product (93% yield).

3B. 2 Results and discussion

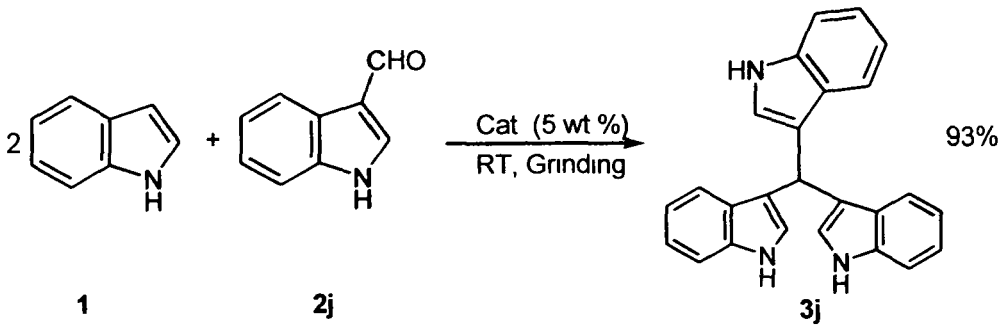
Initially, 4-chlorobenzaldehyde **(2b)** was chosen as a model substrate for the reaction with indole. Compound **2b** (1 mmol, 0.14 gm) was grinded with indole **1** (2 mmol, 0.23 gm) in the presence of 5 wt% (0.02 gm) of the catalyst in a mortar and pestle at room temperature for 1 min without any solvent. When we checked the TLC after 1 min for monitoring the progress of the reaction, interestingly, we were surprised to observe that the reaction was indeed over by that time providing BIM **(3b)**. It has been observed that by changing the catalyst amount from 2-5 wt% the yield of the product changed from 20%-99%, after that there was no change in the yield of the product. Hence, 5 wt% was the optimum catalyst amount for this reaction (table 3.6). Having established the optimum reaction condition, structurally diverse aldehydes were treated with indole **(1)** under the same reaction condition in order to investigate the reaction scope and generality and results are summarized in

table 3.7 (entries **2a-t**). The methodology is found to be quite general as variety of substituted aromatic aldehydes, aliphatic aldehydes and heterocyclic aldehydes (entries **2a-t,** table 3.7) reacted efficiently with indole (**1**) to give the BIMs (**3a-t**) in excellent yields quickly than any other reported methods. The generality of the reaction was also investigated for the substituted indole (table 3.8). Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency using this procedure. Furthermore, the unsaturated aldehyde, cinnamaldehyde (entry 2g, table 3.7) gave the corresponding BIM **3g** without polymerization under the above reaction conditions in 98% yield within 1.5 min. The heterocyclic aldehydes like furaldehyde, which was known as acid-sensitive species, was proved to be applicable under the reaction condition (entry 2i, table 3.7), indicating the usefulness of our methodology. Furthermore, thiophene carboxaldehyde (entry 2h, table 3.7) also worked well without forming any side products. Notably, the reaction condition is mild enough, works nicely without damaging moieties such as -OMe, -Me, -Cl, $-NO_2$ and -OH. No solvent was used for the reaction and it was carried out at room temperature under grinding conditions. In absence of the catalyst the reaction did not proceed, thereby indicating the necessity of a catalyst.

Table 3.6: Effect of catalyst amount investigated for the condensation between indole and 4-ClC_6H_4CHO

Entry	Wt% of the catalyst	Yield (%) after 1 min	Yield (%) after 10 min
1	1	20	22
2	2	40	43
3	3	75	79
4	4	88	90
5	**5**	**99**	**99**
6	6	99	99
7	7	99	99

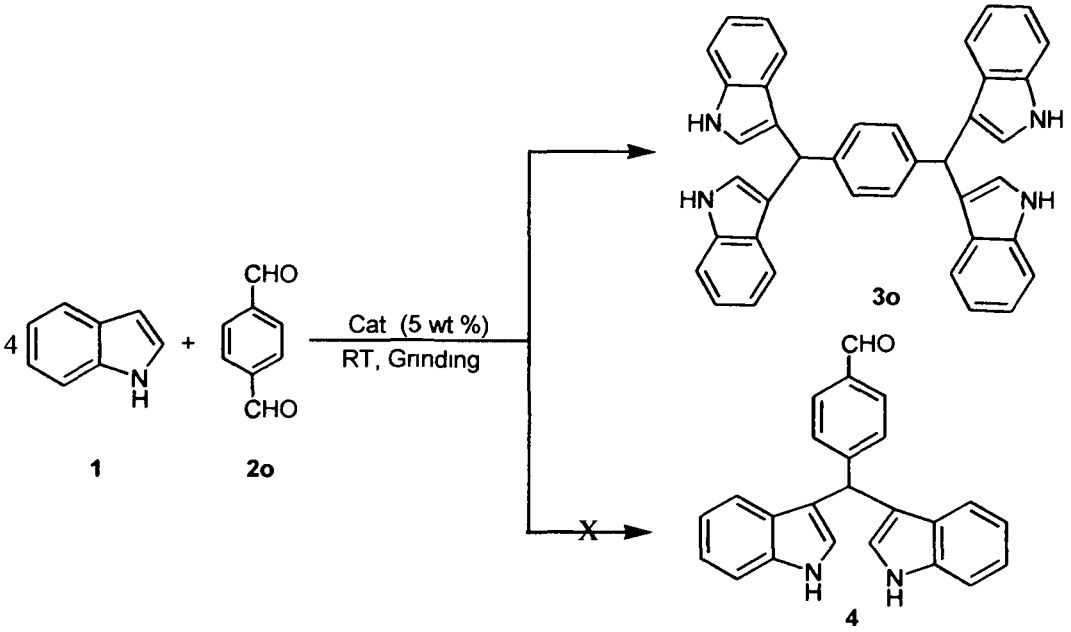
Interestingly, indol-3-carbaldehyde (entry 2j, table 3.7) reacting with two equivalents of indole **1** under similar conditions afforded tri-indolylmethane **3j** in 93% yield (scheme 3.3).



Scheme 3.3: Synthesis of triindolylmethane

To note, aliphatic aldehydes (entries 2k-n, table 3.7) took some what longer time than the aromatic ones. However, ketones (entries 2q-t, table 3.7) did not react at all with indole (**1**) under the reaction condition, demonstrating the chemoselective nature of the methodology. For example, when an equimolar mixture of benzaldehyde (entry 2a, table 3.7) and acetophenone (entry 2q, table 3.7) were allowed to react with indole (**1**) in the presence of the catalyst, only phenyl-3,3′-bis(indolyl)methane was obtained, while acetophenone (**2q**) remained as such and was recovered. When we carried out the reaction with 6-oxo-6-phenylhexanal (**2p**) only the aldehydic group of the molecule takes part in the reaction and the ketonic group remains unreactive, hence demonstrates the chemoselective nature of the method. The electron rich aldehydes is expected to react faster than the aldehydes with electron withdrawing group. However, we did not observe any such difference; this may be due to the short reaction time with the exception of *p*-hydroxybenzaldehyde (entry 2f, table 3.7) that required longer time (9.5 min).

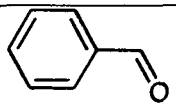
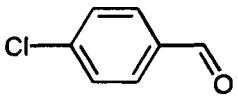
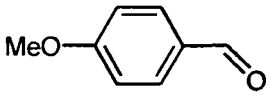
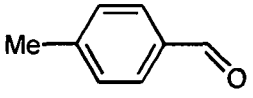
Encouraged by this result, we extended the reaction to dialdehyde. Accordingly, the reaction of terephthaldehyde (entry 2o, table 3.7) with indole **1** was investigated under similar conditions (scheme 3.4). To our delight, terephthaldehyde **2o** (1 mmol) reacted smoothly with indole **1** (4 mmol) to provide 1,4-bis(di-indol-3-yl)methyl)benzene **3o** in 93% yield, which indicated that both the two aldehydic groups of terephthaldehyde reacted. Formation of bis-indolylmethane **4** was not observed (scheme 3.4).

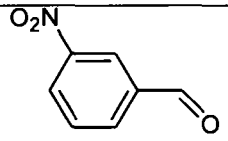
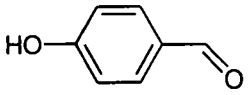
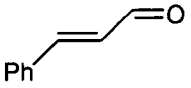
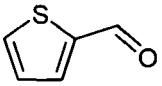
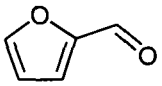
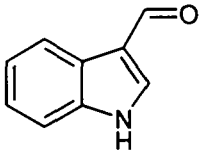
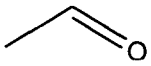
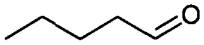
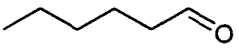
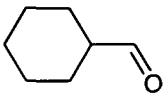
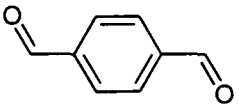
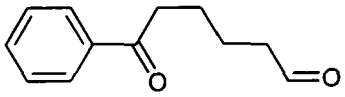
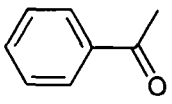


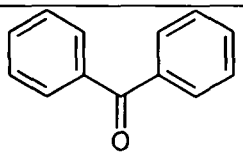
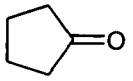
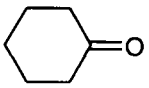
Scheme 3.4: Reaction of indole (1) with dialdehyde (2o) in presence of phosphate impregnated titania ctaalyst

Indole derivatives also react with the aldehyde to give the corresponding bis-indolyl methane (entries 1-4, table-3.8). The above mention method is a general and selective for the synthesis of the bis-indolyl methane.

Table 3.7: Synthesis of BIMs using phosphate impregnated titania catalyst

Entry	Aldehyde 2/ketones	Product 3	Time	Yield (%)[a]
a		3a	1 min	99
b		3b	1 min	99
c		3c	1 min	98
d		3d	1 min	95

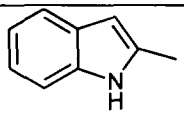
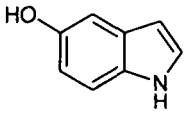
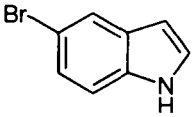
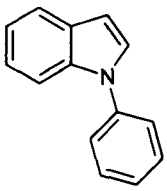
e		3e	1.5 min	95
f		3f	9.5 min	80
g		3g	1.5 min	98
h		3h	1.5 min	95
i		3i	1 min	97
j		3j	4 min	93
k		3k	5.5 min	90
l		3l	6 min	88
m		3m	6 min	88
n		3n	2 min	89
o		3o	1 min	93
p		3p	8 min	45
q		No reaction	3 hr	-

r		-do-	3 hr	-
s		-do-	3 hr	-
t		-do-	3 hr	-

[a] isolated yield

The IR spectra of BIMs **3** show characteristic IR absorptions within 3437–3480 cm^{-1} (N–H). In addition, the ^1H NMR spectrum of **3** display characteristic signals within δ 7–8 ppm (brs, NH, exchangeable with D_2O).

Table 3.8: Synthesis of BIMs from some indole derivatives

Entry	Indole derivatives	Product	Time (min)	Yield (%)
1		3q	1	94
2		3r	3	90
3		3s	2	96
4		3t	6	60

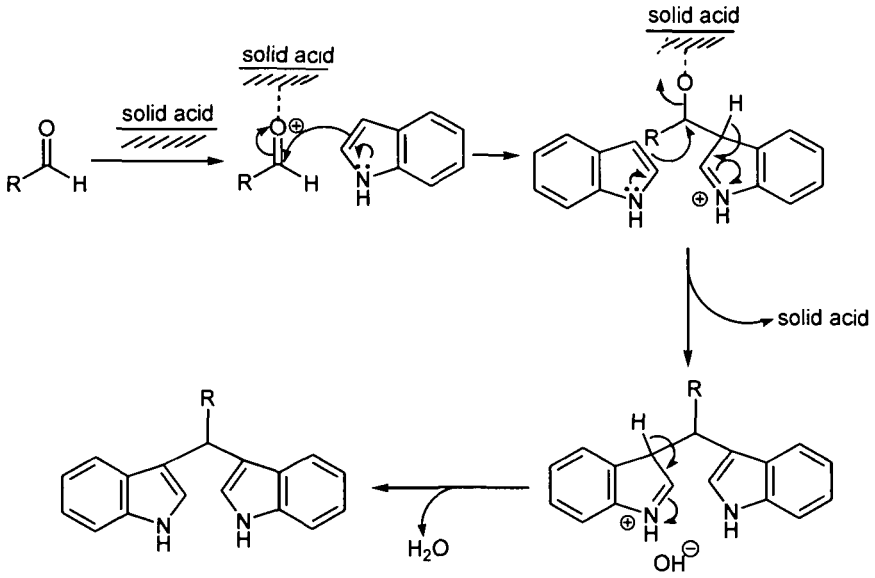
The reusability of the catalyst was examined for the reaction of 4-chlorobenzaldehyde (**2b**) and indole (**1**) as model substrates vide scheme 3.2. The result showed that the solid catalyst, phosphate impregnated titania could be reused for at least four times without reducing the catalytic property of the catalyst

appreciably (table 3.9); thereafter, the yield started decreasing because of the leaching of the catalyst.

Table 3.9: Reusability of the catalyst

Run	Time(min)	Yield (%)
1	1	99
2	4.5	94
3	10	88
4	15	80
5	20	60

A plausible mechanism for the reaction is shown in scheme 3.5. The interaction of the solid catalyst, phosphate impregnated titania with the aldehyde probably occurs, that increases the electrophilicity of the carbonyl carbon and which in turn facilitates the participation of indole molecules. The interaction may also occur via the external acidic sites of the catalyst.



Scheme 3.5: Plausible mechanism of the reaction

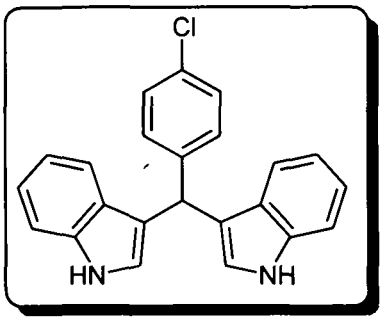
3B. 3 Conclusion

In conclusion, we have developed a highly efficient electrophilic substitution reaction of indole with various aromatic, aliphatic as well as heterocyclic aldehydes using phosphate impregnated titania as a recyclable catalyst. The procedure offers several advantages including improved yield of products with no by-products

formation, simple experimental procedure with an economic and environmentally friendly solvent- free condition, cleaner reaction profile, short reaction time, and use of inexpensive catalyst; hence, it is a useful addition to the existing methods for the synthesis of BIMs. Interestingly, the experimental procedure for these reactions is remarkably simple without requiring dry solvents, inert atmosphere, and reflux conditions, which makes it a useful and attractive process for the rapid synthesis of substituted BIMs.

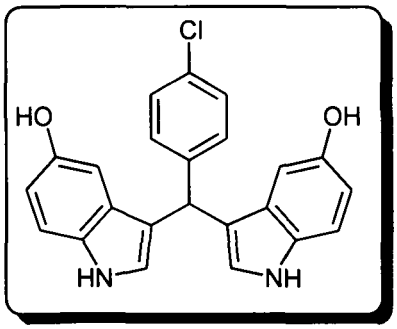
3B. 4 Physical and Spectral data

(3,3′-((4-Chlorophenyl)methylene)bis(1*H*-indole) (3b)



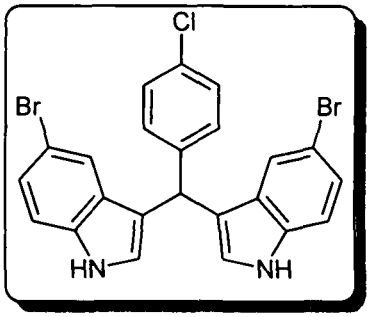
Yield 99%, solid, m.p. 104-105 °C; FT-IR (KBr) 3402, 3050, 2986, 1615, 1600, 1455, 1112 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 6.68 (d, *J*= 2.24 Hz, 2H), 7.10-7.45 (m, ArH, 12H), 7.81 (brs, 2H, NH, exchangeable with D_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2. MS, *m/z* 322 (M^+). Elemental analyses: Calculated, C, 85.72; H, 5.89; N, 8.72%. Found: C, 85.73; H, 5.90; N, 8.74%.

3,3′-((4-chlorolphenyl)methylene)bis(5-hydroxy-1*H*-indole) (3r)



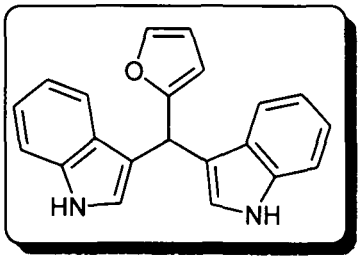
Yield 90%, solid, m.p. 122-124 °C; FT-IR (KBr) 3410, 2927, 1624, 1466, 1176, 1088 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 5.58 (s, 1H), 6.66 (d, *J*= 2.28 Hz, 2H), 7.1-7.3 (m, 10H), 8.51 (s, 2H), 10.4 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 30.3, 103.6, 111.7, 112.2, 117.1, 124.5, 127.6, 128.4, 130.62, 130.69, 131.6, 144.4, 150.47. MS, m/z 386 (M^+). Elemental analyses: Calculated C, 54.76; H, 40.47; N, 4.76%. Found C, 54.74; H, 40.48; N, 4.78%.

3,3'-((4-chlorolphenyl)methylene)bis(5-bromo-1*H*-indole) (3s)



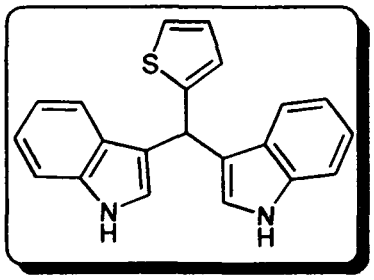
Yield 96%, solid, m.p. 191-192 °C; FT-IR (KBr) 3423, 2926, 1448, 1089 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 5.73 (s, 1H), 6.62 (s, 2H), 7.24-7.25 (m, 10H), 8.11 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.38, 112.74, 112.85, 118.6, 122.21, 124.84, 125.18, 128.56, 128.66, 129.95, 132.29, 135.44, 141.73. MS m/z 514 (M^+). Elemental analyses: Calculated: C, 57.5; N, 5; H, 37.5%. Found: C, 57.6; N, 5.04; H, 37.8%.

3,3'-(Furan-2ylmethylene)bis(1*H*-indole) (3i)



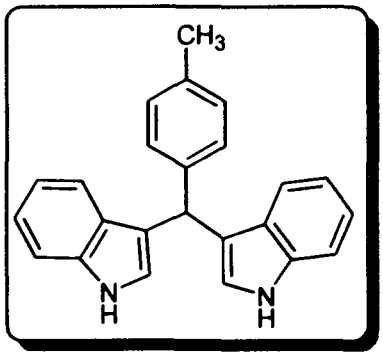
FT-IR(KBr): 3456, 3020, 2398, 1457,1093,758 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 6.06 (d, 1H), 6.30 (t, 1H), 6.89 (d, 1H), 7.04 (t,2H), 7.17 (t, 1H), 7.35-7.37 (d, 2H), 7.47-7.49 (d, 2H), 7.97 (brs, 2H).

3,3′-(Thiophene-2ylmethylene)bis(1*H*-indole) (3h)



FT-IR(KBr): 3410, 3012, 2410, 1098, 7067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 6.86 (s, 2H), 6.06 (d, 1H), 6.30 (t, 1H), 6.89 (d, 1H), 7.04 (t,2H), 7.17 (t, 1H), 7.35-7.37 (d, 2H), 7.47-7.49 (d, 2H), 7.97 (brs, 2H).

3,3′-(p-Tolylmethylene)bis(1*H*-indole) 3d



FT-IR(KBr): 3454, 3120, 2955, 1612, 1520, 1223, 765 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 5.87 (s, 1H), 6.70 (d, *J*= 2.24 Hz, 2H), 7.10-7.45 (m, ArH, 12H), 7.84 (br s, 2H).

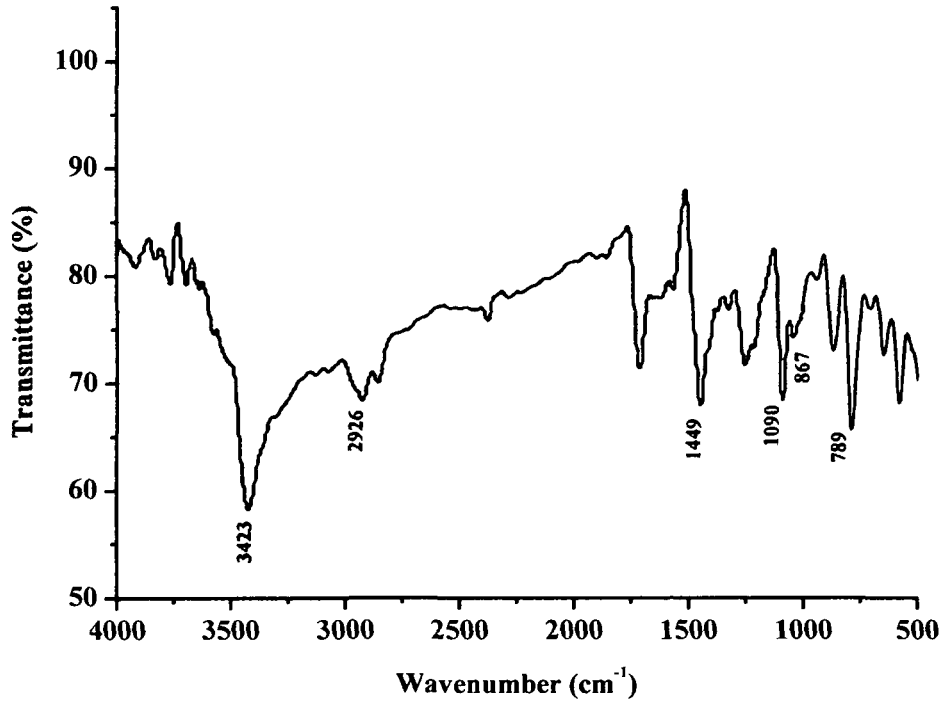


Image 4: FT-IR spectrum of compound **3s**

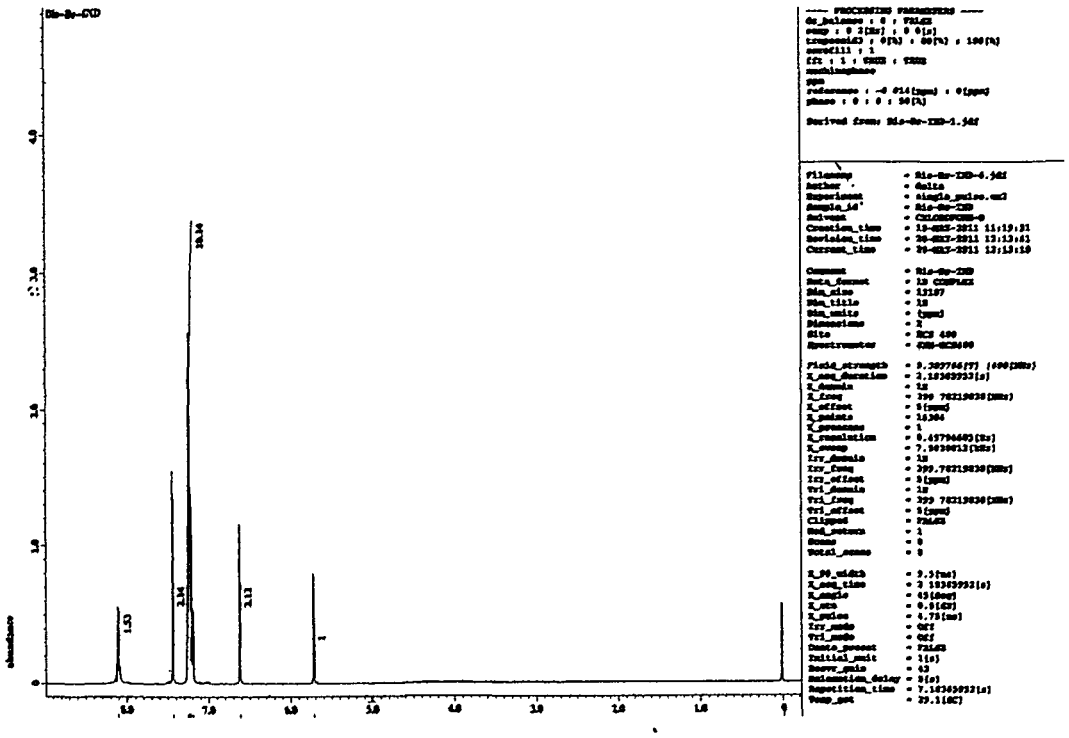


Image 5: ^{1}H NMR spectrum of compound **3s**

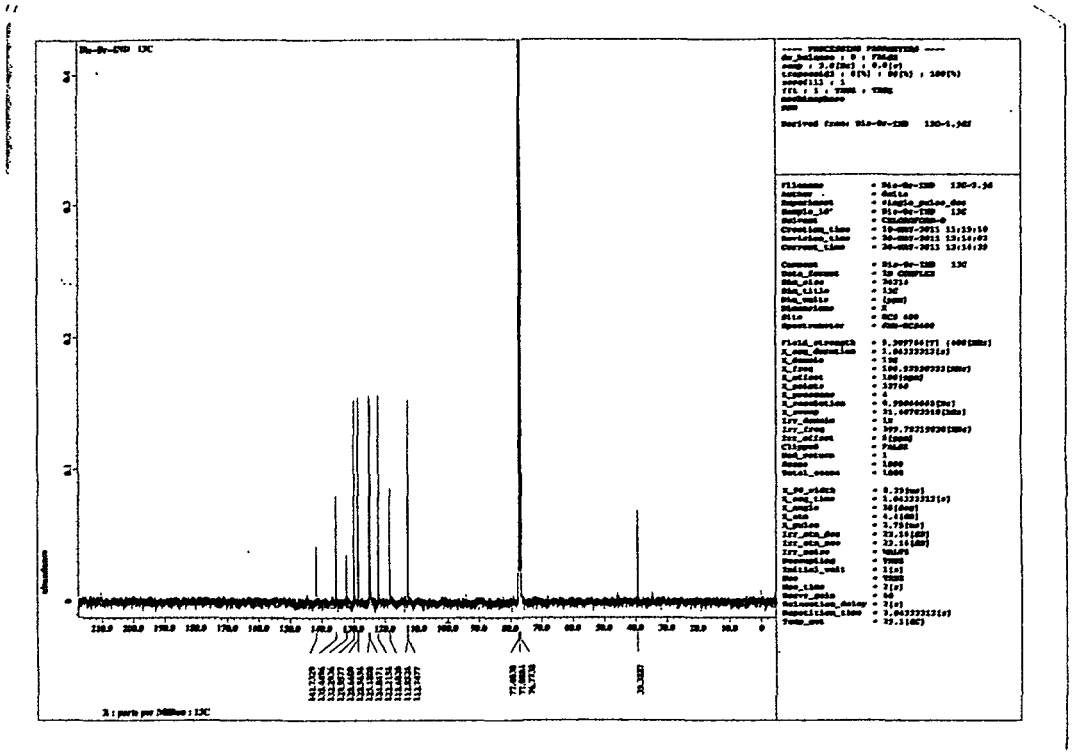


Image 6: ^{13}C NMR spectrum of compound **3s**

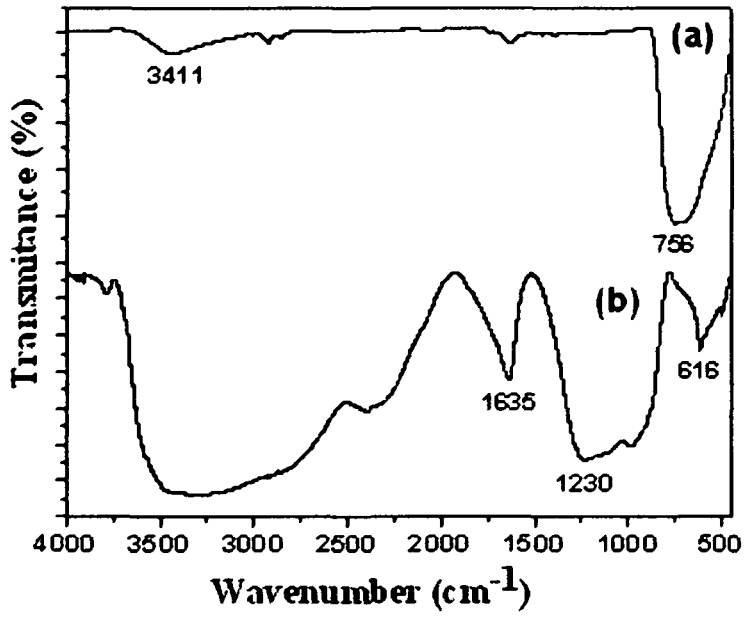


Image 7: FTIR spectra of (a) TiO_2 (blue line) and (b) Catalyst (black line).

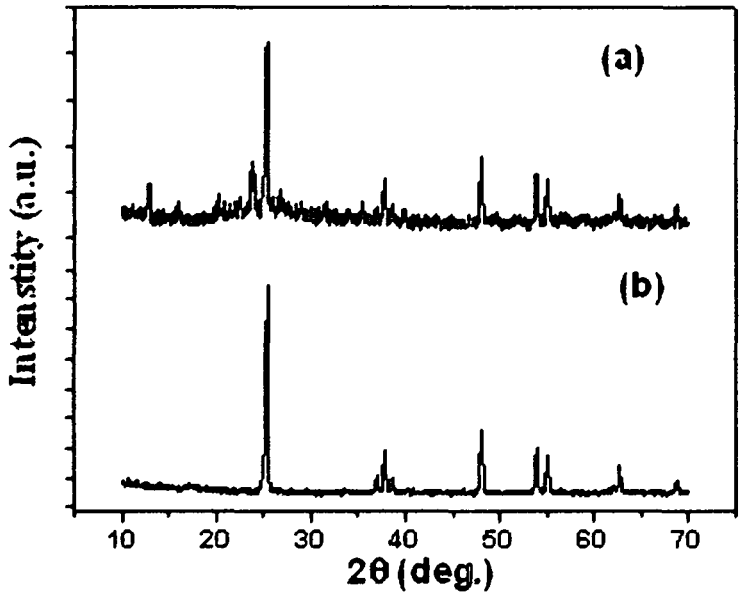


Image 8: XRD patterns of (a) Catalyst and (b) commercial TiO_2.

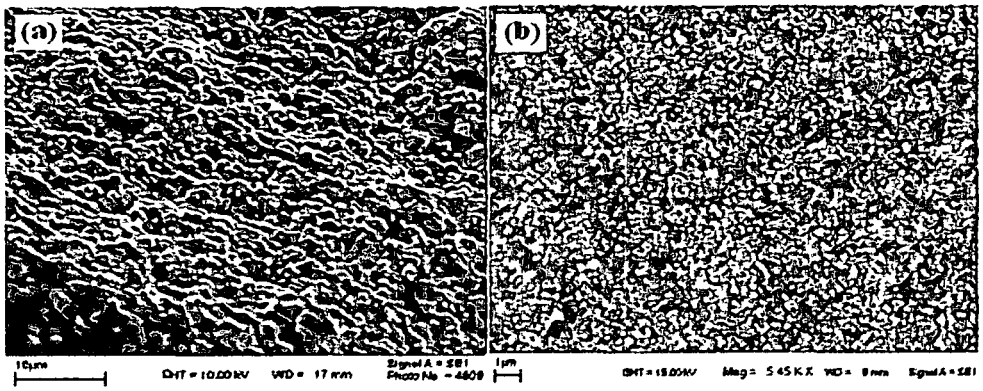


Image 9: Scanning Electron Micrographs of (a) Catalyst with magnification of 10 μm (b) pure TiO_2 with 1 μm magnification.

3B. 5 References

(1) Bandini, M. & Eichholzer, A. *Angew. Chem. Int. Ed.* **48**(51), 9608-9644, 2009.

(2) Chen, F.R. & Huang, J. *Chem. Rev.* **105**(12), 4671-4706, 2005.

(3) Kuo, C.C. et al. *Cancer Res.* **64**(13), 4621-4628, 2004.

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Carbon-Nitrogen Bond forming Reactions

* The work described in this section has been published in

1. ***Synlett.*** **11**, 1597-1601, 2011 [Section 4A]

Section4A

Zirconylchloride: an efficient, water-tolerant and reusable catalyst for the synthesis of N-methylamides

Amide is one of the most important functionalities in organic chemistry and is crucial in the architecture of biological system [1–11].Recently, it has been shown that in pharmaceutical industry, the amide bond formation alone accounts for 65% of all preliminary screening reactions [12].The American Chemical Society Green Chemistry Institute Pharmaceutical Round table recently identified amide formation as one of the most utilized and problematic synthesis in the pharmaceutical industry and as such has been labeled as a high priority research area [13].

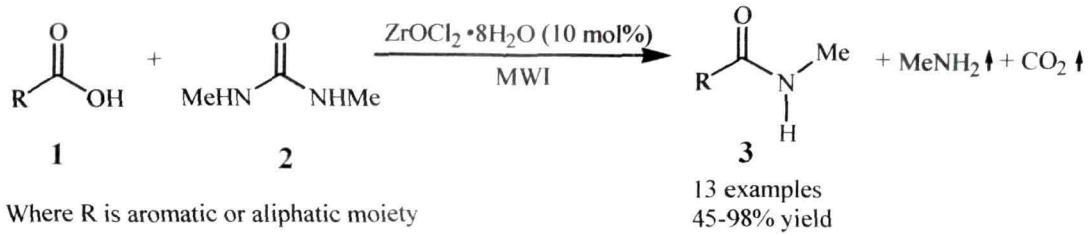
Various methods are reported in the literature for amide synthesis [14–21].The available methods rely mainly on the dehydrative approach, the oxidative and the free radical approaches are the other alternatives [22]. In nature, the structural diversity in the protein synthesis is achieved by straightforward dehydrative condensation of the amino acids. The main advantage of the dehydrative method over the others is the easy availability and the structurally diverse nature of the carboxylic acids. In this regard, the reaction of amines with the carboxylic acid or acid chlorides is the most attractive one [23]. Other methods for the synthesis of amides involves Staudinger ligation [24],aminocarbonylation of aryl halides[25–26],oxidative amidation of aldehydes[27–29],Ritter reaction [30],*N*-acylation of amines [31].

However, the majority of such protocols involve the use of stoichiometric, activated, toxic and corrosive reagents (e.g. acid anhydrides and/or acyl chlorides). Furthermore, an excess of these reagents is normally needed and the reaction being water-sensitive, efficient removal of water being a critical factor in the systems [32–34].Therefore, the development of new procedures for easy, clean and simple synthesis of amides is of topical interest in medicinal chemistry.

As documented, *N*-methylation of peptides is a promising way to rationally improve key pharmacological characteristics of peptidesand Taxanes [35-40].In the literature, synthesis of *N*-methylamides is not well documented. The most generally useful method was to add the acid chloride very slowly drop wise, with constant stirring, into amine in concentrated aqueous solution[41].

We have recently reported an environmentally benign methodology for the synthesis of*N*-methylamides 3 using Zirconyl chloride ($ZrOCl_2 \cdot 8H_2O$) as catalyst to carry out

the condensation between carboxylic acids **1** and*N,N'*-dimethylurea (DMU) **2** (scheme 4.1)under microwave irradiation (MWI) in the solvent free condition [42].



Scheme 4.1: Condensation of carboxylic acid (1) and dimethylurea (2) to give*N*-methylamide (3)

The application of $ZrOCl_2 \cdot 8H_2O$ as a catalyst in organic synthesis has attracted our attention [43] as it is relatively inexpensive, readily available, easy to handle, insensitive to air and moisture [44–52] and importantly less-toxic (LD_{50} for $ZrOCl_2 \cdot 8H_2O$, oral rat= 2950 mg/kg) [53–54].It has been already recognized as a green catalyst for different organic conversions [21, 22&55, 56].

4A.1Experimental

Typical procedure for the synthesis of N-methylamides3

A 1:1 mixture of DMU **2** (0.09 g, 1 mmol), carboxylic acid **1a**(0.12 g, 1 mmol) (R=Ph) and $ZrOCl_2 \cdot 8H_2O$ (0.03 g, 10 mol %) were taken in a mortar and were grinded with a pestle. The grinded mixture was placed in a 50 mL conical flask followed by MWI for 3 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were extracted with ethyl acetate (3×10 mL) and filtered to remove the catalyst. To remove the unreacted acid, organic layer was washed with $NaHCO_3$ followed by water during workup. Evaporating the organic solvent in a rotary evaporator provided the product in pure form. Column chromatography was used when required. Finally, recrystalization from ethanol afforded the pure product *N*-methylbenzamide**3a**.

4A.2Results and Discussion

In order to develop a standard experimental protocol, after screening over a range of microwave power, reaction temperature, time, substrate to catalyst ratio and exploring

scope of various solvents, we have found that $ZrOCl_2 \cdot 8H_2O$ (10 mol%) is an efficient catalyst for the conversion of carboxylic acids **1** to *N*-methylamides**3** reacting with DMU **2** under MWI (560 W), in the absence of any solvents. Dimethyl urea (DMU) is an important and versatile reactant in organicchemistry [57].

The effect of the amount of the catalyst on the yield of the *N*-methylamide**3c** was studied by varying the catalyst amount from 0.01 to 0.15 mmol (table 4.1, figure4.1) for the model reaction between *p*-chlorobenzoic acid **(1c)** (1 mmol) and DMU **(2)**(1 mmol). It was found that the yield increased with increasing the catalyst's amount from 0.01 to 0.15 mmol. However, further increase in catalyst's amount did not provide any improvement on yield. From these observations, 0.1 mmol of the catalyst was found to be the optimum amount for this reaction.

Table 4.1: Effect of amount of$ZrOCl_2 \cdot 8H_2O$ on the yield of *N*-methylamide**3c**[a]

Entry	$ZrOCl_2 \cdot 8H_2O$ (mmol)	Substrate/catalyst (molar ratio)	Yield (%)
1	0.01	100	45
2	0.02	50	70
3	0.1	10	92
4	0.15	6.66	92.3

[a]Reaction condition: *p*-Chlorobenzoic acid (**1c**) : DMU (**2**) were taken in 1:1 molar ratio; MW power: 600 watt, time: 6 min

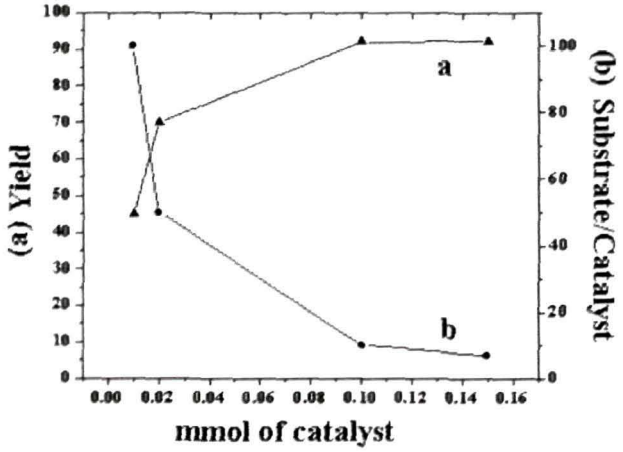


Figure4.1: Effect of amount of $ZrOCl_2 \cdot 8H_2O$ on the yield of *N*-methylamide**3c**

We have also varied the microwave power to see its effect on the yield of *N*-methylamides**3c** (table 4.2, figure4.2) for the aforementioned model reaction. It is

evident from the figure that yield increases with an increase in MW power from 140 to 560 watt. At 700 watt, the reactants decomposed. Hence, 560 watt power was chosen as the optimum power.

Table 4.2: Dependence of conversion with microwave power

Entry	MW power	Yield (%)
1	140	0
2	280	10
3	420	15
4	560	92
5	700	Decomposes

**The reactions were carried out taking 4-ClC_6H_4COOH and DMU as the substrate

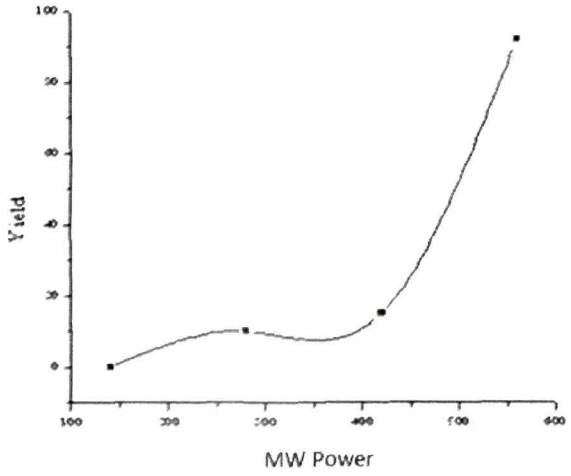
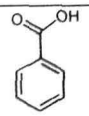
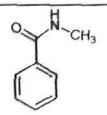
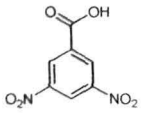
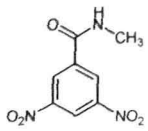
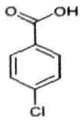
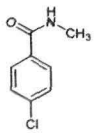
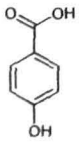
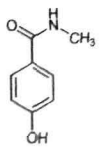
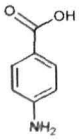
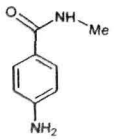
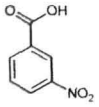
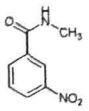
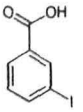
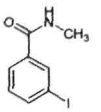
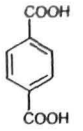
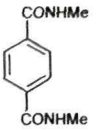
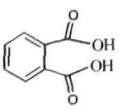
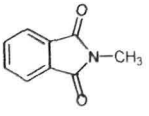
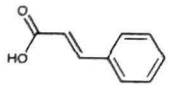
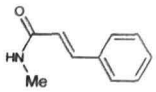
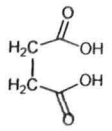
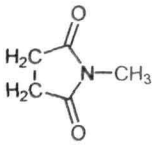
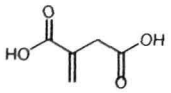
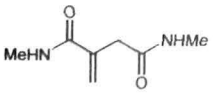
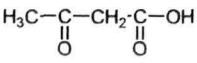
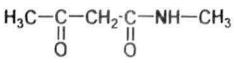


Figure4.2: Effect of the MW power on the conversion of the product **3c**

The efficiency of the catalyst has been studied for the synthesis of various kinds of amides and the optimized results are summarized in the table 4.3(entries a-m).

Table 4.3: $ZrOCl_2 \cdot 8H_2O$ catalyzed conversion of carboxylic acids **1a-m** to the corresponding *N*-methylamides**3a-m**

Entry	Carboxylic acids **1**	Amides **3**	Reaction time		Yield(%)[a,b]	
			MWI (min)	Thermal (hrs)	MWI	Thermal
a			3	8	98	48
b			5	9	90	45
c			6	10	92	47
d			10	12	55	20
e			15	17	50	18
f			18	17	90	44
g			15	15	90	38
h			8	10	75[c]	30[c]
i			9	12	50	15

j			10	15	90	45
k			5	5	45	7
l			30	20	65	33
m			20	20	69	25

[a] Yields referred to isolated yields
[b] Characterized using ^{1}H, ^{13}C NMR and IR spectroscopy, mass spectrometry and elemental analysis.
[c] Acid (**1h**): DMU (**2**)=1:2 (molar ratio) was used

The generality and the scope of the reaction were evaluated for a wide spectrum of carboxylic acids, bearing both electron withdrawing and electron donating substituent at various positions including dicarboxylic acids. As evident from table-4.3, the reaction has a broad scope for aromatic, alkyland α,β-unsaturated carboxylic acids. Various mono- and di-carboxylic acids **1a-m** (aliphatic and aromatic) reacted efficiently with DMU **2** to give the corresponding *N*-methylamides**3a-m** in moderate to excellent yields (45-98%). It is noteworthy to mention that these reactions proceeded efficiently without using any solvent. This may be due to the selective absorption of microwaves by the reactants, intermediates or the catalyst, which accelerates the reaction rate [58].This reaction also proceeded under conventional heating in an oil bath under solvent less condition, but took very longer time (5-20 h) and of course the yield (7-48%) was also not satisfactory. In the absence of the catalyst, the reaction did not provide any product(s) and the reactants were recovered as such.

However, it has been observed that *N,N'*-diphenylurea (DPU) failed to react with carboxylic acids to provide the corresponding *N*-phenylamides under the reaction condition. Hence, our synthetic methodology is specific for the synthesis of *N*-methylamides.The method is advantageous in the sense that the reaction does not generate water. So, the problem of reversibility of the equilibrium and destroying of amide does not arise. The chemoselective nature of the reaction is demonstrated in entry**1d** (table 4.3), where sensitive phenolic –OH remains intact under the reaction

condition, reaction occurring in –OH of the carboxylic acid part selectively. Other groups, such as -NO_2 (entries 1b and1f, table 4.3), -Cl (entry 1c,table 4.3), -NH_2 (entry 1e,table 4.3), -I (entry 1g,table 4.3) and double bonds (entries 1j and 1l,table 4.3) remained intact, thus showing their tolerance to the reaction condition.

Interestingly, 1,2-dicarboxylic acids, succinic acid (entry 1k, table 4.3) and phthalic acid (entry 1i, table 4.3) reacting with 1 equivalent of DMU **2** provided cyclic *N*-methylamides (**3k** and **3i** respectively) instead of dimethylated amides. Using 2 equivalents of DMU **(2)** also did not give the dimethylated product. Interestingly, 1,2-dicarboxylic acid (entry 1l, table 4.3) provided dimethylated amides **3l** only, no cyclic amide was obtained. However, with the 1,4-dicarboxylic acid, terephthalic acid (entry 1h, table 4.3), 2 equivalents of DMU were used to provide *N,N'*-dimethylated terephthalamide **3h**.Neither any additive/activator for the acids nor any amines were required. Moreover, the reaction time was short requiring only 3-30 min, i.e. less than an hour.

To investigate the versatility of the catalyst for reuse, the model reaction of 4-chlorobenzoic acid **1c** with DMU **2** was investigated under the same reaction condition. After the reaction, the product was extracted with ethyl acetate and the catalyst was recovered simply by filtration method. After filtration the catalyst was washed with CH_2Cl_2 or CH_3Cl and dried at 60^0 C (at 75^0C, dehydration from $ZrOCl_2 \cdot 8H_2O$ to $ZrOCl_2 \cdot 6H_2O$ occurs) [59,60], which was subjected to reaction again. The recovered catalyst can be further reused for at least four times without much loss in activity of the catalyst (entries 1-5, table 4.4).

Table 4.4: Coupling of 4-chlorobenzoic acid **(1c)** with DMU **(2)**using fresh and recovered catalyst[a]

Entry	Catalyst	Yield[b]
1	Fresh	92
2	First reuse	89
3	Second reuse	86
4	Third reuse	85
5	Fourth reuse	80

[a] Reaction condition: 1:1 molar mixture of 4-chlorobenzoic acid (**1c**) andDMU (**2**), 10 mol% of catalyst, MW 560W, 6 min.
[b] Isolated yields

Structurally, $ZrOCl2 \cdot 8H_2O$ is known to be an ionic cluster $[Zr_4(OH)_8(H_2O)_{16}]Cl_8 \cdot 12H_2O$ [26]. Generally, the cationic cluster $[Zr_4(OH)_8(H_2O)_{16}]^{8+}$ is regarded as the active species. This cationic cluster may have high coordinating ability to ligands like urea, DMU etc. through ligand exchange process. The comparison of the XRD patterns of the fresh catalyst with the standard one reveals that the catalyst, which we have used is actually a mixture of $ZrOCl_2 \cdot 8H_2O$ and $ZrOCl_2 \cdot 6H_2O$ (figure4.3). The XRD pattern of the recovered catalyst shows that the recovered catalyst is a typical amorphous material (figure4.3) [26].

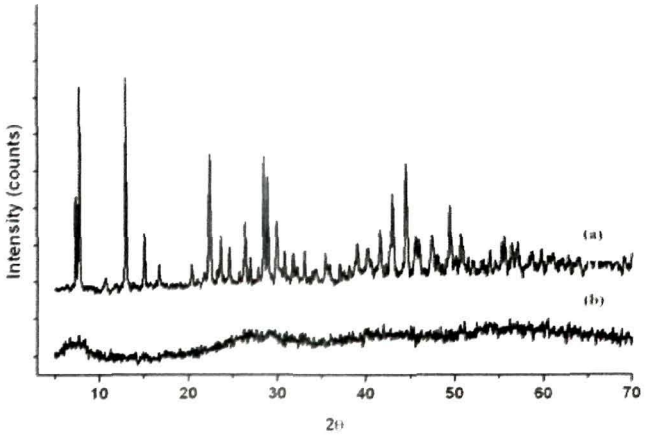


Figure4.3: XRD of (a) the catalyst and (b) the recovered catalyst

The FT-IR spectra of the catalyst and the recovered catalyst were recorded in the range 500 cm^{-1} to 4000 cm^{-1} (figure4.4). The peak at 1621 cm^{-1} is a characteristic peak for the $ZrOCl_2 \cdot 8H_2O$ as per literature [26].

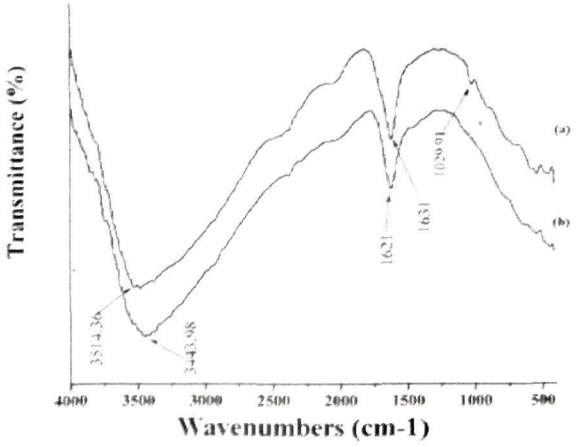
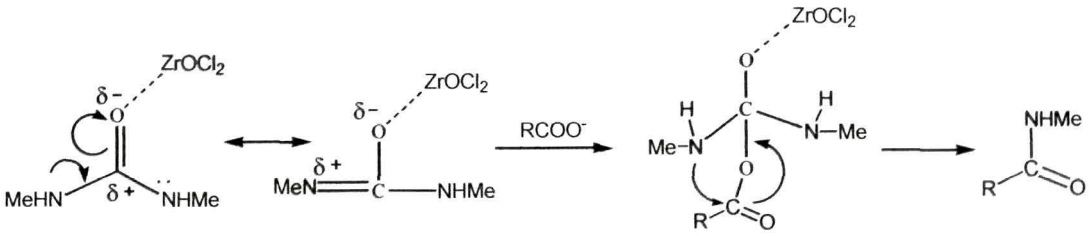


Figure 4.4: FT-IR spectra of (a) the recovered catalyst and (b) the fresh catalyst

There is a broad absorption peak in the range 3400-3520 cm^{-1} which is observed both in the catalyst and in the recovered catalyst. However, a small new peak at 1029.91 cm^{-1} is observed for the recovered catalyst. These are in good agreement with report found in the literature [26].

A plausible mechanism for the reaction is depicted in scheme 4.2.



Scheme 4.2: Plausible mechanism for the synthesis of *N*-methylamides**3**

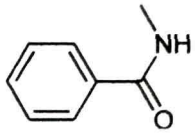
The mechanism is in accordance with the experimental observations. The coordination of the DMU with the zirconylcentre increases the nucleophilic character of the carbonyl centre of DMU and hence nucleophilic attack by $RCOO^-$ is possible at the carbonyl carbon. Any electron withdrawing group attached with urea (e.g. *N,N'*-diphenylurea) may hinder the reaction because the lone pair of electron over the *N*-atom will no longer easily available for sharing.

4A.3Conclusion

In conclusion, the procedure as described above is an efficient, different from traditional approach, fast (3-30 min) and useful greener method for the direct synthesis of *N*-methylamides from carboxylic acids and DMU in the presence of $ZrOCl_2 \cdot 8H_2O$ as a catalyst. The catalyst has the advantage of being readily available, low cost, moisture stable, environmentally benign and reusable, that makes the presented methodology a useful one.

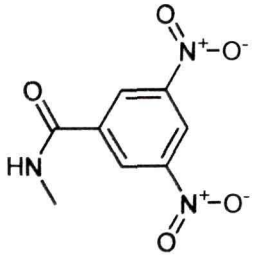
4A.4Physical and Spectral data

***N*-Methylbenzamide (3a)**



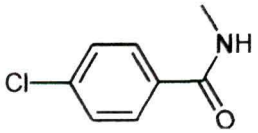
White solid.m.p. 77^{0}C.FT-IR(KBr): 3289, 3105, 1646, 1540, 1411, 715cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (s, 3H, -NMe), 6.85 (bs, 1H, -NH, exchangeable with D_2O), 8.83- 9.03 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27, 127.5, 134.3, 136.4, 149.5, 168.3;MS m/z = 225(M^+);Elemental analyses:Found: C, 71.18; H, 6.68; N, 10.63%. Calculated: C, 71.09; H, 6.71; N, 10.36%.

3,5-Dinitro-*N*-methylbenzamide (3b)



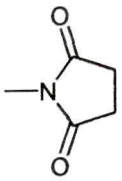
Pale Yellow Solid, m.p. 140^{0}C. FT-IR(KBr): 3292, 3100, 1643, 1538, 713cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (s, 3H), 6.79 (bs, 1H, -NH), 8.97 (s, 2H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.9, 128.3, 135.2, 136.9, 148.9, 168.3; MS m/z = 171(M^+); Elemental analyses:Found: C, 42.60; H, 3.12; N, 18.64%; Calculated: C, 42.67; H, 3.13; N, 18.66%.

***p*-Chloro-*N*-methylbenzamide (3c)**



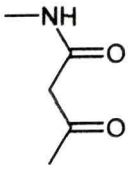
Yellowish solid, m.p. 178^{0}C. FT-IR(KBr): 3297, 1646, 1550, 1405, 767, 694cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 3H), 6.2 (bs, 1H, -NH), 7.3-7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.84, 127.01, 130.59, 130.14, 131.28, 135.08, 167.23; MS m/z = 156.00(M^+); Elemental analyses:Found: C, 56.62; H, 4.74; N, 8.23%; Calculated: C, 56.65; H, 4.75; N, 8.26%.

N-Methylsuccinimide (3h)



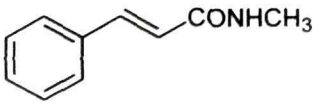
Yellowish solid, mp. 66 ^{0}C. FT-IR(KBr): 1730, 1646, 1550cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.678 (s, 4H), 2.950 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 24.5, 15.8, 45.5, 169.7;MS m/z = 113(M^+); Elemental analyses:Found: C, 53.05; H, 6.22; N, 12.36%; Calculated: C, 53.09; H, 6.24; N, 12.38%.

N-Methylacetoacetamide (3m)



Yellowish liquid, FT-IR(KBr): 3415, 1585, 1520, 1425, 1310cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 2.71, 2.15, 3.5, 6.3; ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ 19.26, 26.97, 32.49, 164.91, 171.09; MS m/z= 115(M^+);Elemental analyses:Found: C, 52.14; H, 7.84; N, 12.13%; Calculated: C, 52.16; H, 7.88; N, 12.17%.

N-Methyl-3-phenyl-acrylamide (3j)



Viscous liquid

1H NMR(400 MHz, $CDCl_3$): δ 2.86(d, 1H), 5.63(brs, 1H), 6.30-6.34(d, J=16Hz, 1H), 7.28-7.42(m, 5H), 7.54-7.58(d, J=16Hz, 1H); 13C NMR(400 MHz, $CDCl_3$): 24.5, 117.4, 122.3, 124.2, 126.5, 135.5, 168.3.

Spectra

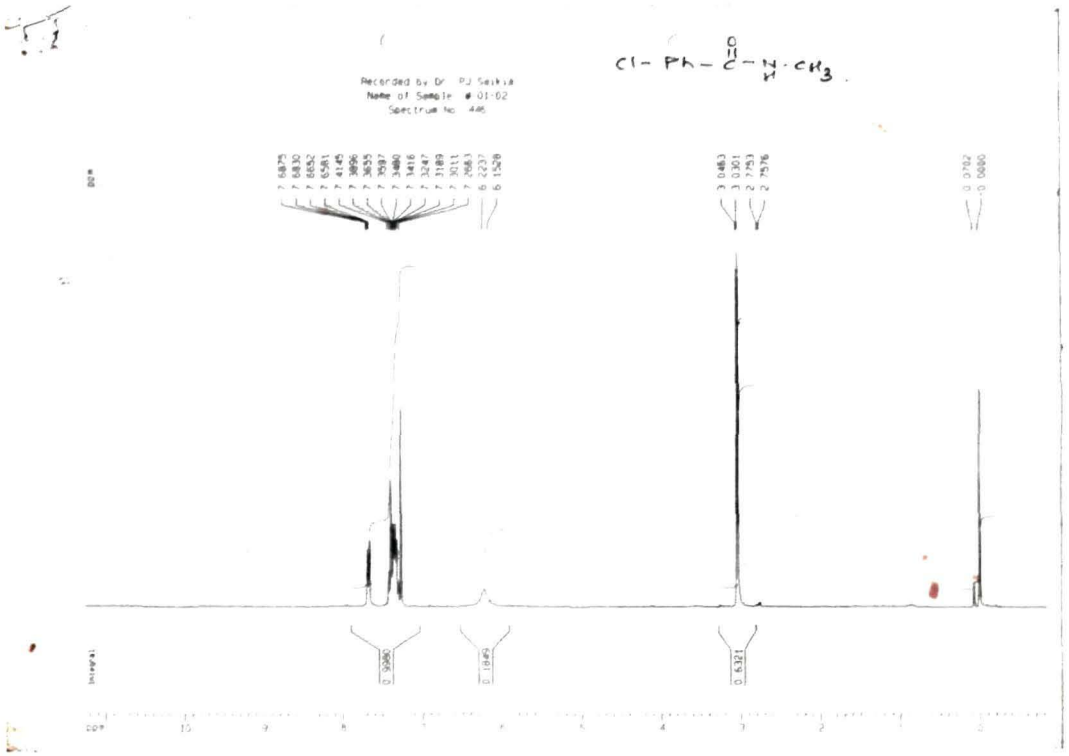


Image 10: ^{1}H NMR spectrum of *p*-Chloro-*N*-methylbenzamide

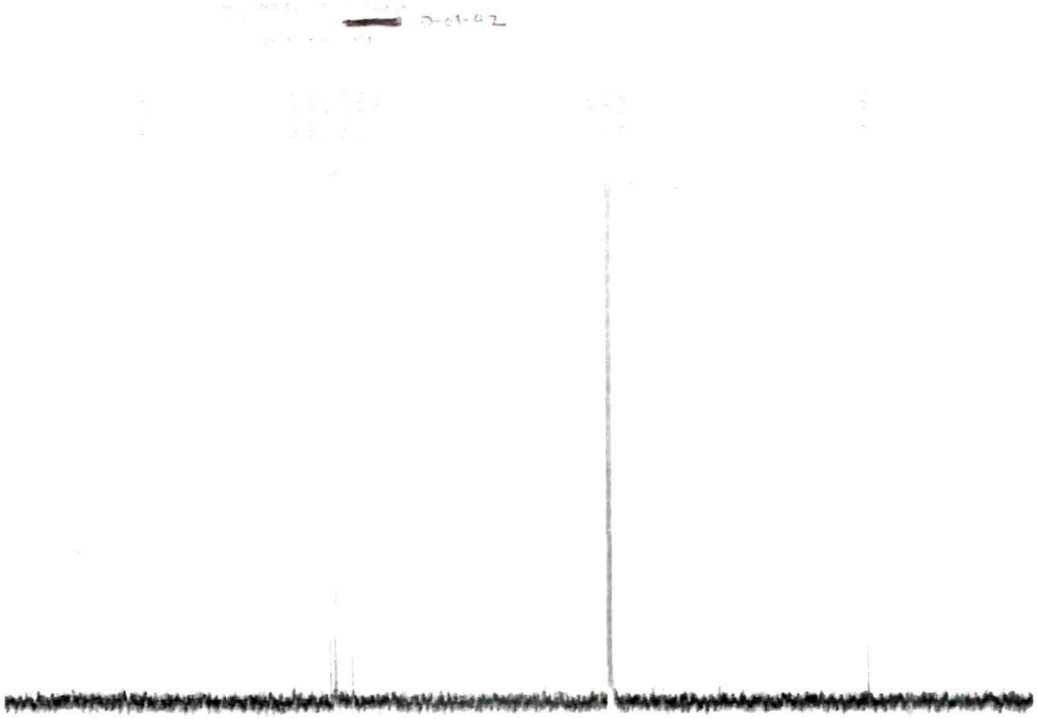


Image 11: ^{13}C NMR spectrum of *p*-Chloro-*N*-methylbenzamide

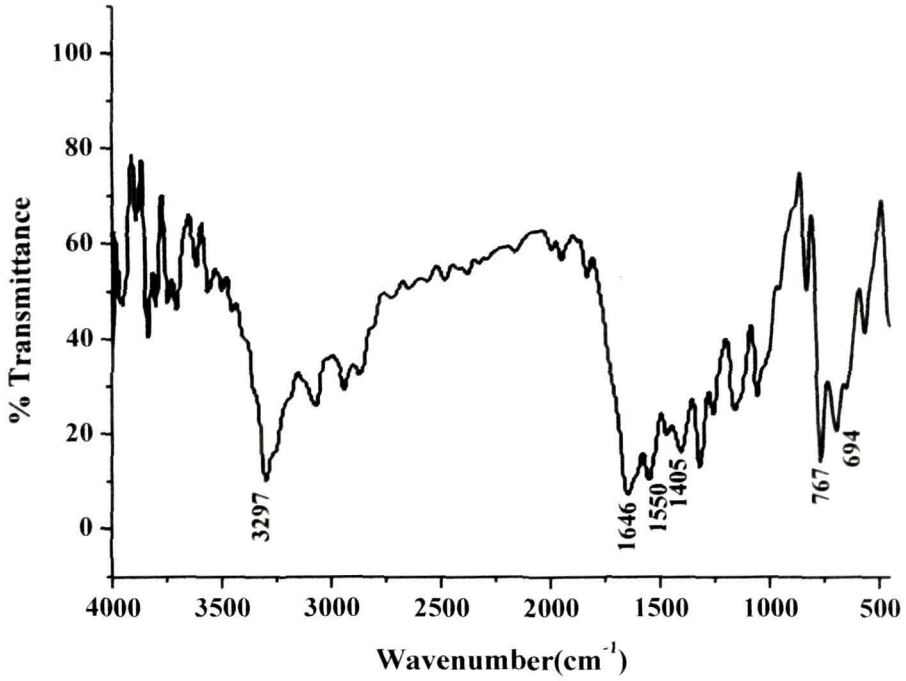


Image 12: FT-IR spectrum of *p*-Chloro-*N*-methylbenzamide

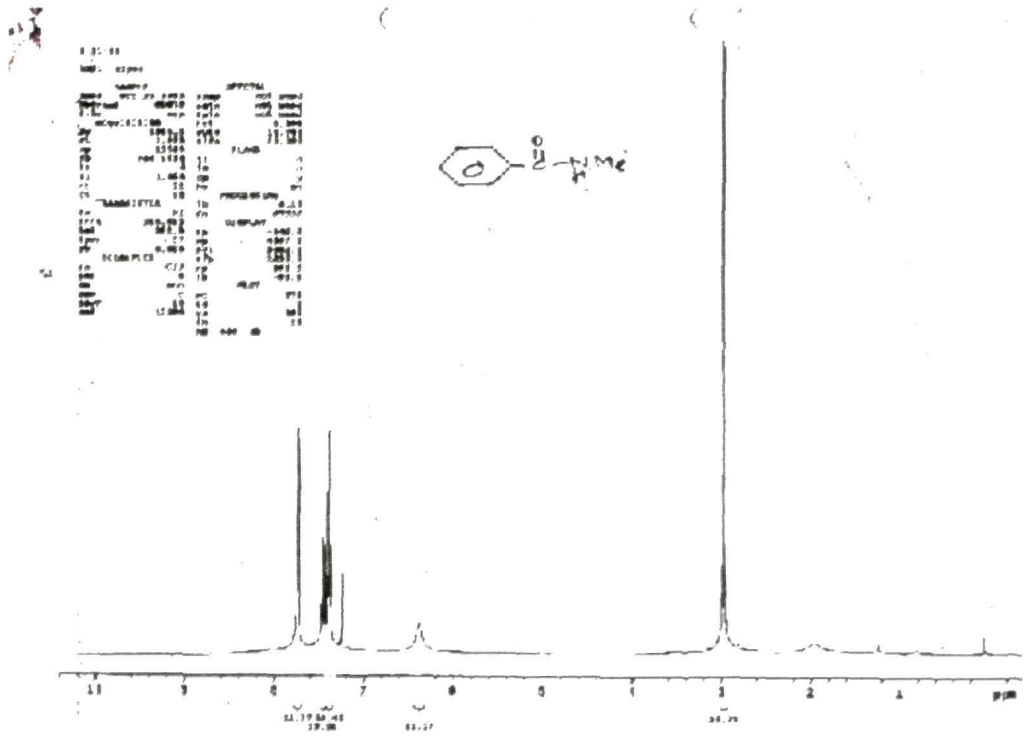


Image 13: ^{1}H NMR spectrum of *N*-methylbenzamide

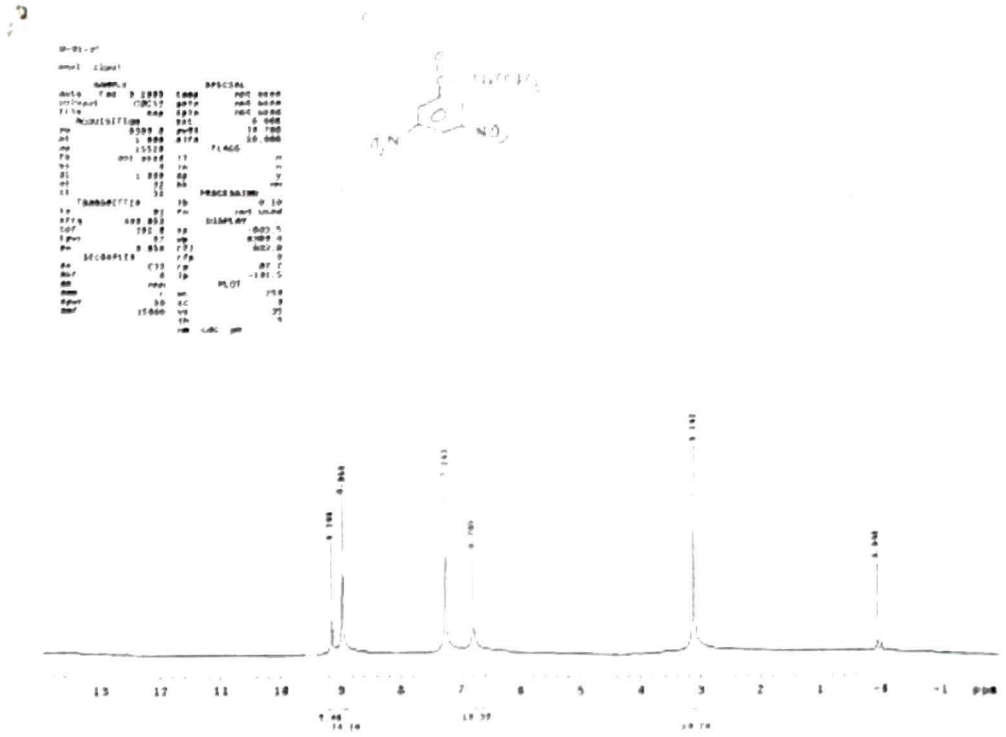


Image 14: ^{1}H NMR spectrum of 3,5-Dinitro-*N*-methylbenzamide

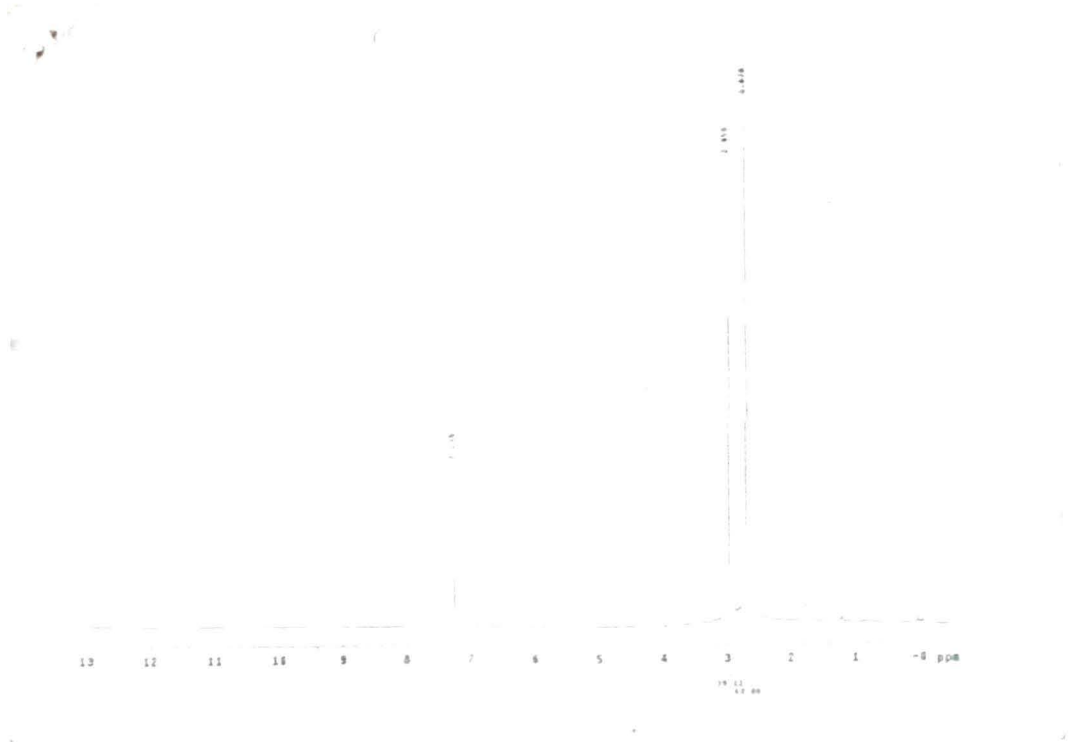


Image 15: ^{1}H NMR spectrum of *N*-Methylsuccinimide

4A. 5 References

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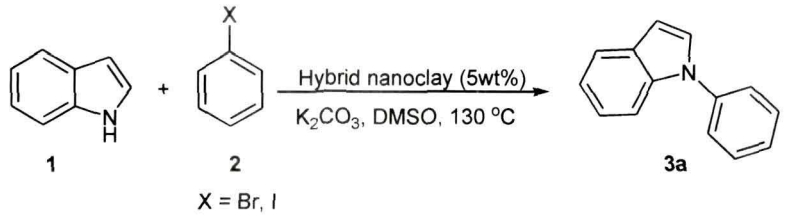
Section 4B

Copper nanoparticles decorated Organically Modified Montmorillonite (OMMT): an efficient catalyst for the N-arylation of indoles and similar heterocycles

N-arylated heterocycles of indole, imidazole, triazole, pyrazole etc. are important building blocks in the organic synthesis as well as in pharmaceutical, agrochemical and synthetic intermediates in many biologically active compounds [1–4]. Transition metal catalyzed *N*-arylation of the heterocycles is an important strategy for the synthesis of various pharmaceuticals, natural products and important compounds [5–8]. Over the past decades, efficient palladium and copper complexes have been introduced for the C-N coupling reactions [9–12]. Nevertheless, further modification for efficient catalytic system is still important. Copper catalyzed C-N coupling is attractive in comparison to the noble metal (often Palladium) catalyzed C-N coupling from the industrial, environmental and the economic point of view[13–16]. However, the traditional methods involve the use of copper catalyst along the added ligands e.g. 2-oxocyclohexanecarboxylate, 2-amino-pyrimidinenes-4,6-diol, amino acids etc. which on scale up leads to the problem of waste disposal [17–19]. Copper(I) oxide and Copper(II) oxide nanoparticles have been reported as catalyst for the C-N coupling reactions affording good to excellent yield of product [20,21]. Buchwald and coworkers have reported bulky copper(I)oxide/4,7-dimethoxy-1,10-phenanthroline to catalyze the coupling of 2 and 4 substituted imidazole with arylbromide [22]. Such process demands the use of harmful solvents (PrCN and NMP) and also the 4,7-dimethoxy-1,10-phenanthroline is very expensive one. According to Punniamurthy and his coworkers nano CuO is found to be highly active catalyst for the N-arylation reaction; however the reaction is still limited to use of the activetd aryl iodide [23]. Li et al. have reported a more general and efficient method for the *N*-arylation of heterocycles using Cu_2O combined with 1,10-phenathroline as a catalyst in solvent free reaction condition [24]. The reported methods were excellent for catalyzing such C-N coupling reaction. Still there is a scope for farther development of such methodologies. The activity of the copper oxide nanoparticles for the C-N coupling inspires us to develop supported copper catalyst for such C-N coupling reaction. Accordingly, we have developed a copper decorated nanoclay system and used it as a catalyst for the C-N coupling of various heterocycles. The nanohybrid system has high activity as a catalyst in comparison to that of the bare copper oxide nanoparticles. The developed catalyst has various

advantages over the bare copper oxide nanoparticles or the other copper reagents like good recoverability, reusability, high activity, short reaction time. Furthermore, imidazole, indoles, carbazoles etc. can be effectively N-arylated under the standard reaction condition (scheme 4.3). The detailed synthesis and the characterization method have been described in the experimental section.



Scheme 4.3: *N*-arylation of indoles catalyzed by copper clay nanohybrid

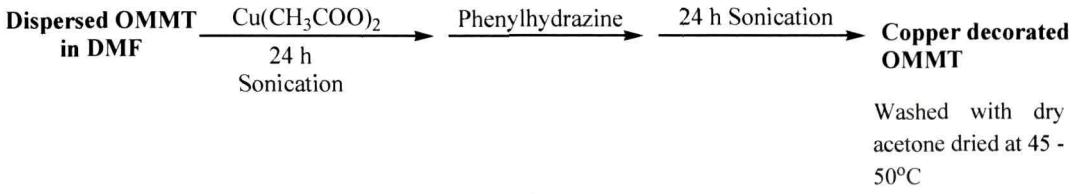
4B.1 Experimental

A. Materials and Methods

Phenyl hydrazine and copper acetate (Merck, Mumbai, India) were used as received. **O**rganically **M**odified **M**ontmorillonite (OMMT), (Nanomer I.30E, octadecylamine modified) was purchased from Nanomer PGV, Aldrich, Germany.

B. Preparation of the catalyst

The clay supported copper nanoparticles were prepared using a novel method developed by us. Briefly, 1 g of OMMT was first dispersed in 50 mL DMF. It was then again dispersed by sonication for 20 minutes. To achieve theoretical copper loading in the clay/copper weight ratio of 1:1, 1:0.5 and 1:0.25 (coded as N1, N0.5 and N0.25, respectively), 3.16 g, 1.58 g and 0.792 g of copper acetate were dissolved in 30 mL, 15 mL and 8 mL respectively. The full copper acetate solutions were then added to the clay suspension and stirred for 24 h under ambient condition, followed by sonications for 10 min. The copper precursor was then reduced in the presence of montmorillonite by adding phenyl hydrazine in the mole ratio of 1:3 (copper acetate/phenyl hydrazine). The whole solution was stirred at room temperature for 48 h until reddish brown coloration appeared. The whole solution was further sonicated for 15 min. The obtained suspension consisting of copper nanoparticles embedded in montmorillonite was centrifuged and washed repeatedly with acetone. The resulting solid phase was dried at 45-50 °C under vacuum (scheme 4.4).



Scheme 4.4: Preparation of copper decorated OMMT

C. Typical Procedure for the N-arylation of the heterocycles

Copper-clay nanohybrid (N1, 5 wt %) was added to a mixture of bromobenzene (1.2 mmol), imidazole (1 mmol) and K_2CO_3 (2 mmol) in DMSO and stirred at 130 °C. The reaction was monitored by thin layered chromatographic technique. The catalyst was separated out from the reaction mixture by centrifugation and washed with distilled ethyl acetate. The recovered catalyst was used for further reaction. The product was extracted with ethyl acetate and purified using column chromatographic technique on silica gel (ethyl acetate/hexane, 30/70). The purified product so obtained was characterized by FT-NMR, FT-IR spectroscopy and ESI-MS techniques.

4B.2 Characterization of the catalyst

A. UV-visible spectroscopy

The formation of copper nanoparticles in clay system was first observed by UV–visible absorption studies (figure-4.5). The UV-visible spectrum matches with the literature value [25–28]. The absorbance UV spectrum shows a broad band from about 588 nm to 612 nm (figure-4.5). This surface-plasmon band may shift depending upon the particle size and shape.

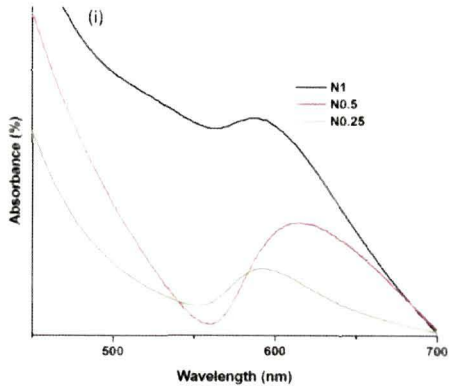


Figure 4.5: UV-visible spectra of N1, N0.5 and N0.25 nanohybrid

The strong surface-plasmon absorption band observed is due to the formation of copper nanoparticles. The broadness of the absorption band (figure. 4.5) probably arises from the wide size distribution of copper nanoparticles.

B. XRD analysis

The X-ray diffractograms (figure 4.6 a,b,c) of the powder sample are well agreed with the literature values [29,30]. The reflection peaks at 2θ values 43.61°, 50.59° and 74.47° represent the [111], [200] and [220] Bragg's reflections respectively of cubic structure of copper. Besides these, the peaks appearing at 35.62° and 61.81° correspond to copper oxide (CuO), though UV-visible spectrum is silent about this. The peaks for the layered silicate were also observed, however the peak at 4.15° corresponding to basal reflection [110] shifts to 3.64° indicating an increase in the gallery spacing with increase in the copper loading, other peaks observed was 20.1°. The observation of low-angle peak suggests the possible coexistence of staked nanostructures made up of copper nanoparticles in layered nanoclay. The intensity of the peak corresponding to copper nanoparticles increases with the increase in the loading of the copper into the layered silicate. The increased intensity of the XRD peak observed might be due to the increase in particle size of the copper nanoparticels. As shown by the sharper and more intense band, the degree of crystallinity increases with copper concentrations. The oxidation of the Cu nanoparticles might be responsible for the presence of reflection peak for copper oxide nanoparticles.

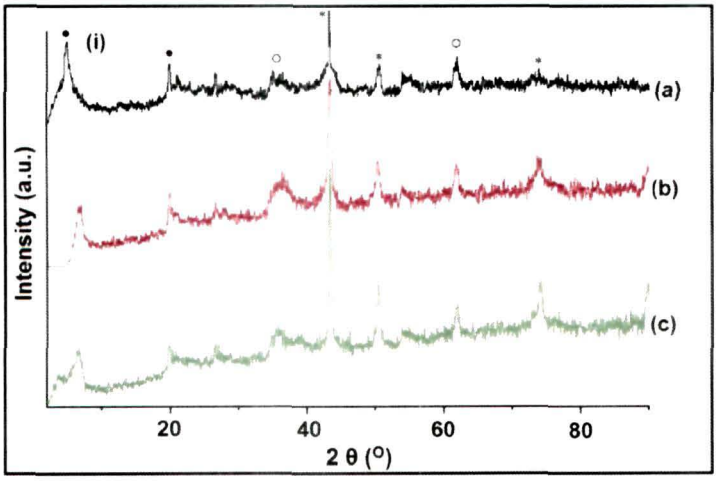
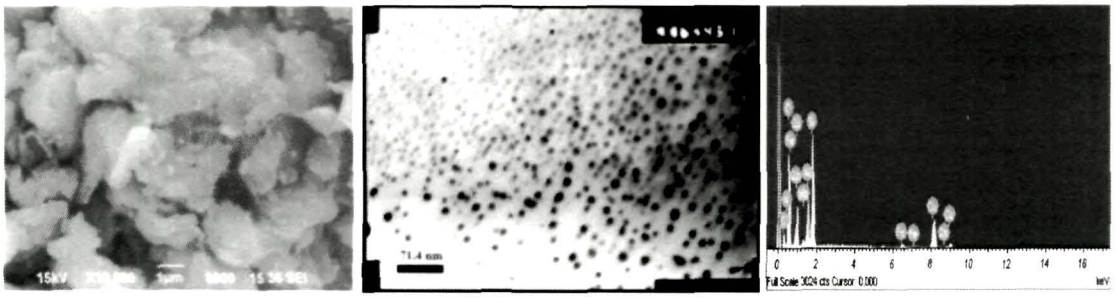


Figure 4.6: XRD of (a) N0.25 (b) N0.5 and (c) N1 catalysts

C. Morphology of the catalyst

The SEM & TEM micrographs of N1 are shown in figure 4.7. It was observed that the treated clay contains heterogeneous particles.



(a) (b) (c)

Figure 4.7: (a) SEM (b) TEM and (c) EDX of the N1

The white nanoparticles in case of N1 were clearly seen (figure 4.7a) to anchor onto the surface of the clay and the well dispersed exhibited no agglomeration. The EDX data (figure 4.7c) further supports the presence of the copper in the clay.TEM image shows uniform distribution of the nanoparticle over the clay. The size of the nanoparticles in N1 is found to be in the range of 5-10 nm. TEM images of the other two catalysts i.e. N0.5 and N0.25 show that the particles size are not uniform and range from 20 nm to 2 nm.

4B.3. Results and Discussion

During our investigation for preparing *N*-arylated indoles by employing this reaction, we found that copper hybrid nanoclay is an effective catalyst for *N*-arylation of the indole. The reaction proceeds smoothly under the aforementioned condition giving high yield of the product (table-4.5). Coupling of indole with bromobenzene taking N1, N0.5 and N0.25, it is observed that N1 has the high activity for catalyzing the coupling reaction giving high yield of *N*-arylindole (figure 4.8).

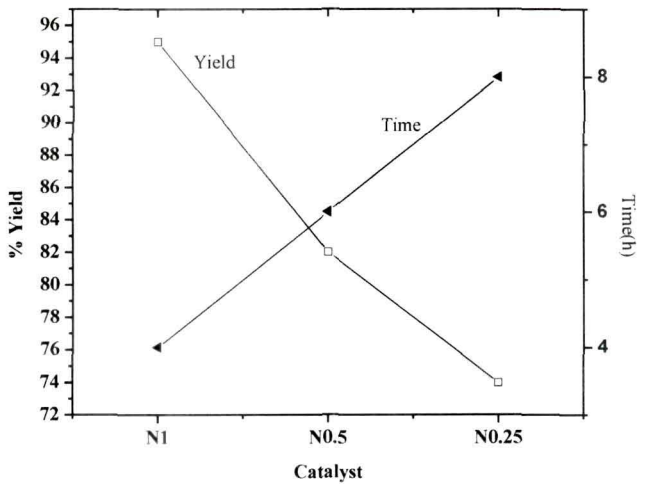
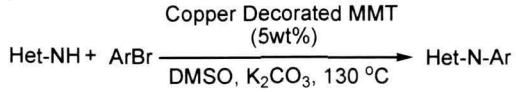


Figure 4.8: Activity of catalysts N1, N0.5 and N0.25

The reaction has been optimized using various parameters (table-4.5) such as reaction time, temperature, solvents, base etc. Initially the coupling reaction was studied with indole and bromobenzene. In the presence of 5 wt% of the catalyst and 2 equiv. K_2CO_3 in DMSO at 130 °C, to our delight, the reaction afforded the desired product with 94% yield. Encouraged by this result we examined the reaction with different solvents, bases, and varying the temperature. Of the solvents tested DMSO was clearly the best choice (table-4.5). The choice of the base is also important for the effective and the selective synthesis of the desired product. The reaction proceeds can be readily perceived that temperature has a significant effect on the present catalytic system. Temperature higher or lower than 130 °C makes the reaction slower (table-4.5). This might be due to the oxidation of the metallic nano copper to copper oxide. The scope of the present catalytic system was extended by reaction of bromobenzenes with various indoles and heterocycles like imidazole, benzimidazole. The catalyst can effectively catalyze the coupling reaction giving very high yield of product in very short period. The scope of the reaction has also been studied for the other haloarenes *viz.*, iodobenzene, chlorobenzene. Except chlorobenzene, iodobenzene effectively couples with the heterocycles under the mentioned condition to give the corresponding *N*-aryl heterocycles.

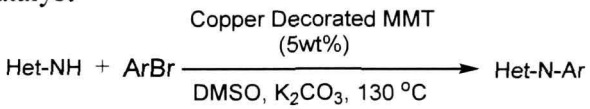
Table 4.5: *N*-arylation of various nitrogen nucleophiles with selective arylhalide catalyzed by N1 catalyst

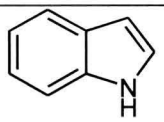
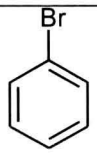
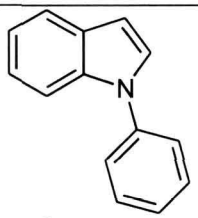
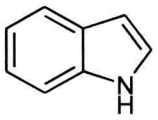
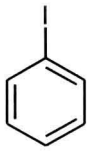
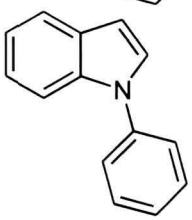
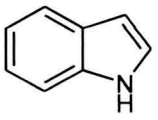
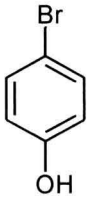
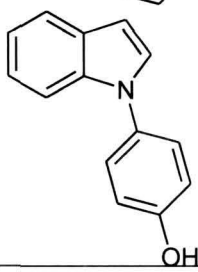


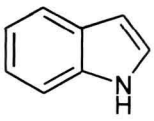
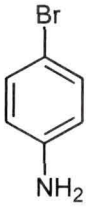
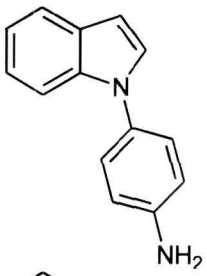
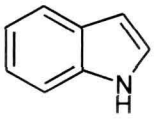
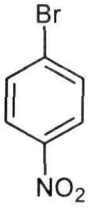
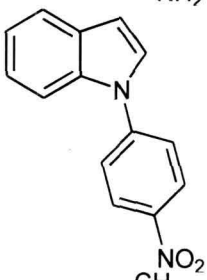
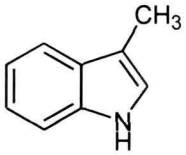
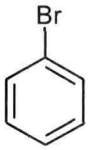
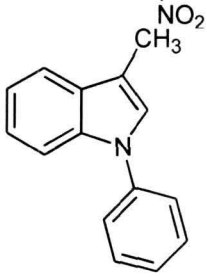
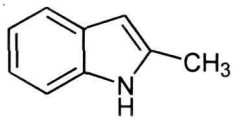
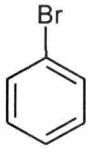
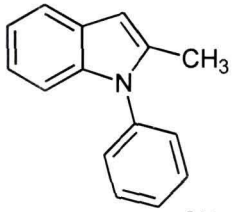
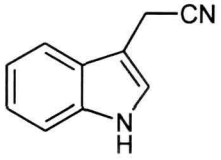
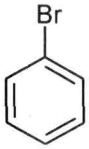
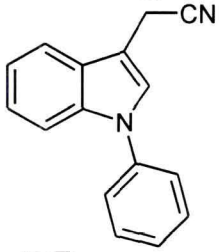
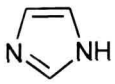
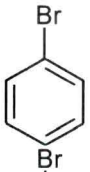
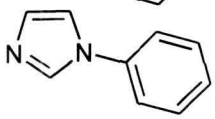
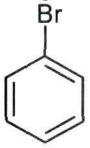
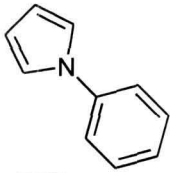
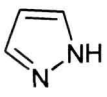
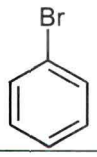
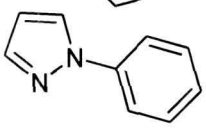
Entry	Solvent	Temperature (°C)	Base	Catalyst (wt %)	Base (mmol)	Time (h)	Yield (%)[a]
1	DMSO	80	K_2CO_3	3	2	6	30
2	DMSO	80	K_2CO_3	5	2	7	52
3	DMSO	100	K_2CO_3	5	2	6	75
4	DMSO	120	K_2CO_3	5	2	5	78
5	DMSO	130	K_2CO_3	5	2	6	94
5	DMSO	130	KOH	5	2	6	77
6	DMSO	130	NaOEt	5	2	6	72
7	DMSO	150	K_2CO_3	5	2	6	85
8	DMF	150	K_2CO_3	5	2	6	80
9	Toluene	reflux	K_2CO_3	5	2	6	40
10	THF	reflux	K_2CO_3	5	2	6	33

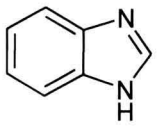
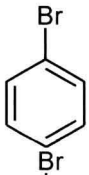
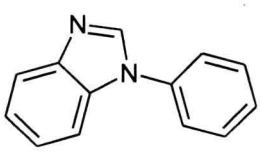
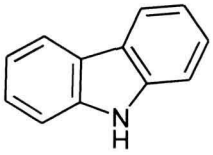
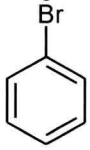
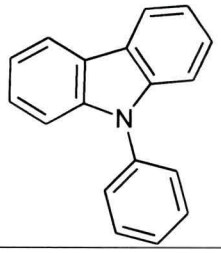
[a] isolated yield

Table 4.6: *N*-arylation of various nitrogen nucleophiles with selective arylhalide catalyzed by N1 catalyst



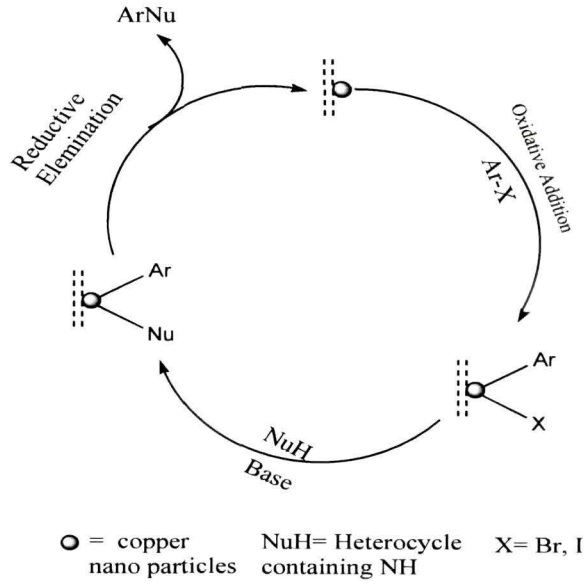
Entry	Het-NH	ArX	Product	Yield (%)[a]	Time (h)
1				95	5
2				97	4.5
3				78	7

4				73	9
5				96	3
6				92	6
7				85	8
8				90	7
9				92	4
10				94	4.5
11				70	10

12				86	7
13				67	9

[a]isolated yields

The reaction proceeds smoothly for the various substituents of indole and aryl halide having different groups (table-4.6). A 5 wt% amount of the catalyst is found to be the optimum amount to catalyze the reaction.



Scheme 4.5: Plausible mechanism of the reaction

To elucidate the obtained results explained above we have proposed a mechanism which based on the previously proposed (scheme 4.5) [3,7-9]. The reaction proceeds with the initial oxidative addition of the aryl hlide over the metallic copper nano particle. Further the N-H heterocycles gets coordinated with the copper atom followed by reductive elimination to give the desired N-arylated heterocycles. The base used in the reaction abstracts the N-H proton from the heterocyclic substrate hereby generates a nucleophile.

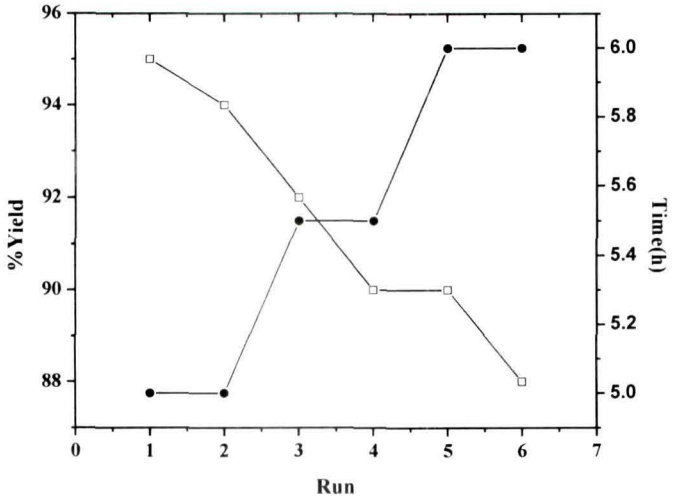


Figure 4.9: Reusability of the catalyst for the *N*-arylation of Indole

The reusability of the catalyst is an important attribute to the industrial application. Therefore the recovery and reusability of our catalyst was initially investigated in the *N*-arylation of indole. Before running another catalytic cycle, the recovered catalyst was washed with dry acetone and then dried in a desiccator over anhydrous $CaCl_2$. The catalyst can be easily separated from the reaction mixture by centrifugation or by simple filtration technique. The catalyst has been reused up to 6^{th} times with almost consistent activity (figure 4.9). Even in the 6^{th} run, the yield of *N*-arylated product is 88%, which indicates excellent reusability of the catalyst

Table 4.7: Results obtained from the XRD pattern of fresh and the recovered catalyst

Sample	Characteristic Planes[a]	Crystal System	Space Group
Fresh Catalyst	111, 200, 220	Cubic	$Fm^{-}3m$
Recovered catalyst[b]	111, 200, 220	Cubic	$Fm^{-}3m$

[a] According to Miller indices
[b] Recovered catalyst after the sixth run

The recovered catalyst retains its stoichiometry as reflected from the powder XRD pattern table-4.7. Although the intensity of the copper oxide peak increases slightly as reflected form the XRD. The oxidation of the metallic copper to copper oxide

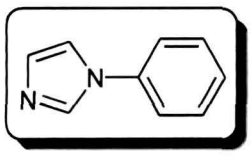
takes place very rapidly at higher temperature and hence increasing the temperature of the reaction above 130 °C decreases the yield of the product as observed in the table-4.5.

4B.4.Conclusion

In conclusion, we have developed a new clay supported copper nanohybrid system. Nanocopper clay hybrid is found to be an effective catalyst for the *N*-arylation of heterocyles. The procedure is simple, general, ligand free, and efficient to afford the corresponding *N*-aryl heterocycles in good to excellent yield. Comparing the various report for the *N*-arylation of the hetrocycles with copper catalyst several features of this modified reaction was established: 1) No need to use any ligand, 2) The high activity of the catalyst system, 3) Considerably good stability of the Nano copper system, 4) High yield of product in very short time, 5) Sacrificial reducing agents used for preparation of Copper nano particle, 6) High recoverability and the reusability of the catalyst and 7) The support i.e. OMMT helps the catalyst to disperse in the reaction mixture which adds the advantage of homogeneous catalyst in the heterogeneous catalyst.

4B. 5 Physical and Spectral Data

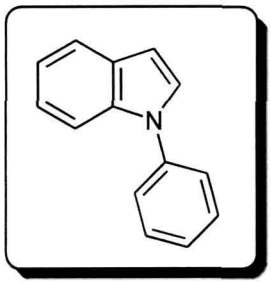
1-Phenyl-1*H*-imidazole (entry 9, table-4.6)



Yellow Oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (brs, 1H), 7.38-7.47 (m, 5H), 7.36 (brs, 1H), 7.25 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.31, 121.53, 127.57, 127.80, 129.66, 129.95, 130.40, 135.64, 137.41.

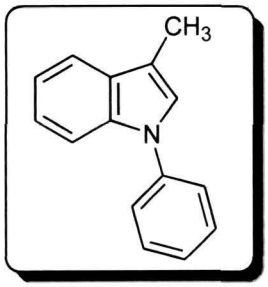
1-Phenyl-1*H*-indole (entry 1, table-4.6)



Oily liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.7 (m, 1H), 7.55-7.60 (m, 1H), 7.50-7.51 (m, 4H), 7.33-7.37 (m, 2H), 7.16-7.24 (m, 2H), 6.67-6.68 (d, *J*=4Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 135.9, 129.6, 129.4, 128.0, 126.5, 124.4, 122.4, 121.2, 121.2, 120.4, 110.5, 103.6.

3-Methyl-1-phenyl-1*H*-indole (entry 6, table 4.6)



Oily liquid

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.64 (m, 1H), 7.54-7.56 (m, 1H), 7.49-7.54 (m, 3H), 7.30-7.37 (m, 2H), 7.13-7.25 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.07, 136.02, 129.84, 129.62, 125.99, 125.55, 124.07, 122.41, 119.83, 119.25, 112.89, 110.44, 9.67.

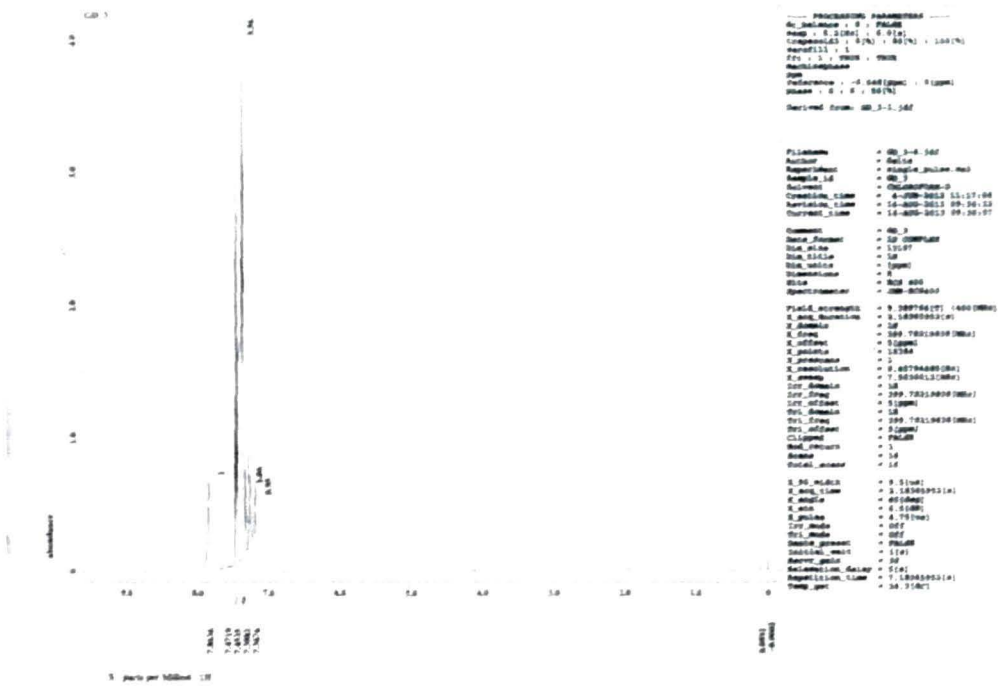


Image 16: ^{1}H NMR spectrum of of 1-Phenyl-1*H*-imidazole

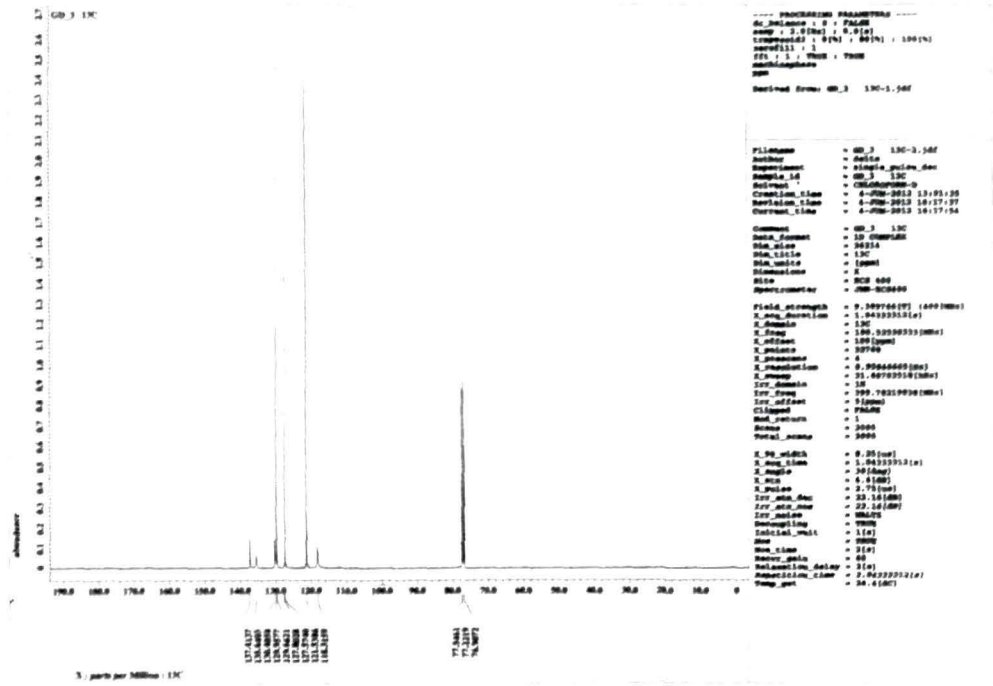


Image 17:^{13}C NMR spectrum of 1-Phenyl-1*H*-imidazole

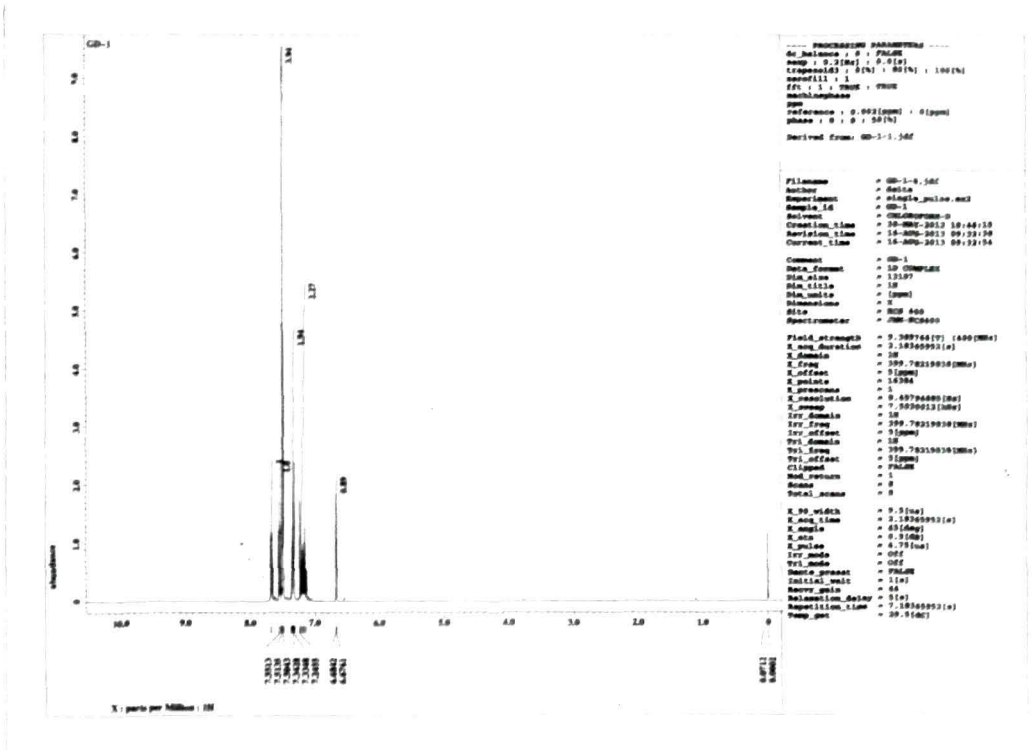


Image 18: ^{1}H NMR spectrum of 1-Phenyl-1*H*-indole

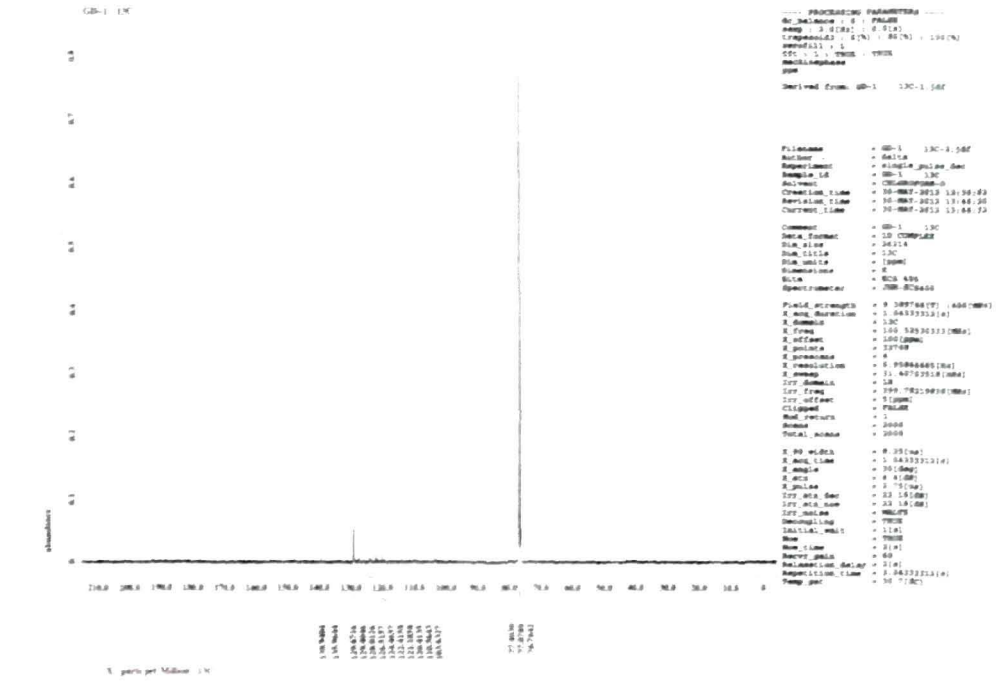


Image 19: ^{13}C NMR spectrum of 1Phenyl-1*H*-Indole

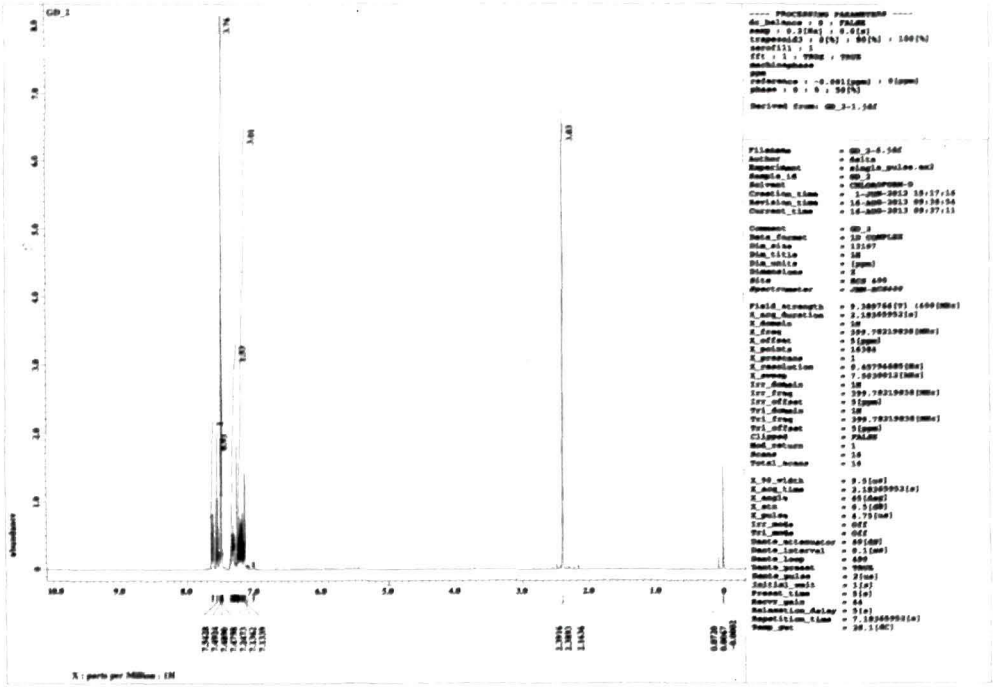


Image 20: ^{1}H NMR spectrum of 3-Methyl-1-phenyl-1*H*-indole

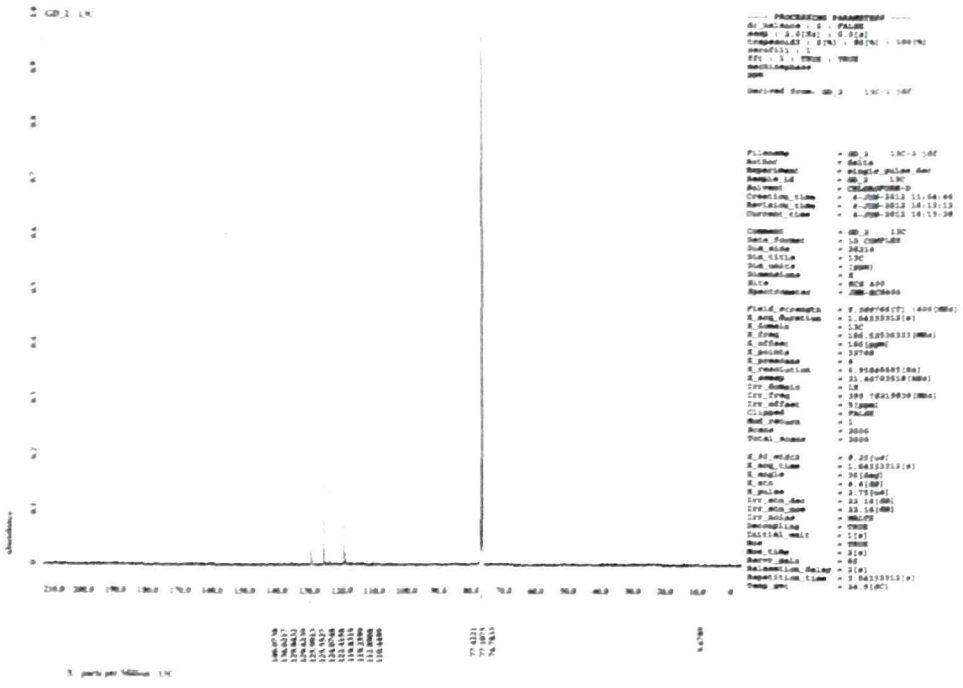


Image 21:^{13}C NMR spectrum of 3-Methyl-1-phenyl-1*H*-indole

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Development of Newer Catalysts for Selective Oxidation of Sulfides, Aldehydes and Bromide with H_2O_2

*The works in this section have been published in

1. ***Tetrahedron Lett.*** **53**, 6512-6515, 2012. [Section 5A]
2. ***Synlett.*** 24, 963-966, 2013. [Section 5B]

Section 5A

$VO_2F(dmpz)_2$: a new catalyst for selective oxidation of organic sulfides to sulfoxides with H_2O_2

There is an increasing interest related to binding interaction and reactivity of heteroligand vanadium(V) compounds starting from synthetic inorganic chemistry through biochemistry, theoretical chemistry and catalysis [1-6]. Participation of vanadium(V) as an intermediate electron carrier in the oxidation of NADH [7] in stimulating nitrogen fixation [8] and active involvement in oxidizing organics [9-15] are very exciting contributions to the current knowledge of biochemical and catalytic involvement of the metal. Dioxovanadium(V) complexes are also studied as biomimetic synthetic models [16-20] and information obtained thereof is valuable in the context of biomodeling and developing practically useful catalytic systems. Penta coordinated complexes of 3,5-dimethylpyrazole (dmpz) vanadium(V) are scanty and incidentally no rational synthesis [21] for the mixed fluorodioxovanadium(V) was known. In view of the above reasons and resemblance of pyrazole with imidazole our attention was drawn towards this synthesis. Yet, another reason was to gain an access to a penta coordinated vanadium complex so as to enable *in situ* generation of an active peroxo complex through its reaction with H_2O_2 and then used for organic sulfur oxidations.

Selective oxidation of organic sulphides to the corresponding sulfoxide and sulfones are of immense interest because of their extensive applications as reagents in organic chemistry as well as synthetic intermediates for the construction of various biologically active molecules [22,23]. For this reason the oxidation of sulphides to sulfoxide or sulfones has been the subject of extensive studies. There are many reagents available for the oxidation of sulphides such as halogen compounds [24-26], nitrates[27], transition metal oxides[28], oxygen and hydrogen peroxide [29-31]. Incidentally, most of these reagents are not satisfactory for the medium to large-scale synthesis for one or the other reasons like low content of effective oxygen, over oxidation, the formation of environmentally unfavourable by-products and cost effectiveness. Generally, it is important to stop the oxidation at the sulfoxide stage by controlling the electrophilic character of the oxidant, but this requirement is often hard to meet and failure results over oxidation to sulfones. This chapter describes a

rational synthesis of $VO_2F(dmpz)_2$, complete characterization and its catalytic efficacy for selective oxidation of organic sulphides at sub ambient temperature.

5A. 1 Experimental Section

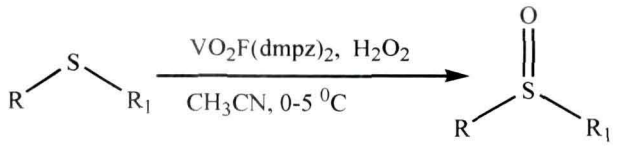
Reagent grade chemicals such as V_2O_5 (E. Merck, India), H_2O_2 (Merck, India) were used as purchased. The strength of H_2O_2 was ascertained by permanganometry before use. Dibenzothiophene (DBT), 4-methyl DBT, 4,6-dimethyl DBT were purchased from Sigma Aldrich, India. Other organic sulfides were prepared by literature procedures.

a) Synthesis of Dioxofluoro(bis-dimethylpyrazole)vanadium(V), $VO_2F(dmpz)_2$

An aqueous suspension (15-20 mL) of 0.5 g (2.75 mmol) V_2O_5 was treated with 0.55 g (9.64 mmol) NH_4HF_2 followed by heating on a steam bath to get a clear solution. An ethanolic solution (15-20 mL) of 1.33 g (13.73 mmol) of 3,5-dimethyl pyrazole was then added to it and the solution was allowed to concentrate (*ca.* 10-12 mL) by heating on a steam bath. The concentrated solution was kept in a freezer until shiny lemon yellow crystals of $VO_2F(dmpz)_2$ were obtained. The compound was separated by decantation and dried *in vacuo* over conc. H_2SO_4. The yield was 1.3 g (81%).

b) Typical procedure for the oxidation of organic sulfide

Alkyl, aryl or allyl sulfide (2 mmol) in acetonitrile (2 mL) solvent was reacted with $VO_2F(dmpz)_2$ (0.006 g, 0.02 mmol) and H_2O_2 (30% aqueous solution, 25 µL, 2.2 mmol) under stirring at ice bath temperature for 5 h. TLC was used to monitor the reaction.



R_1= alkyl, phenyl, benzyl, allyl, alkanol etc.

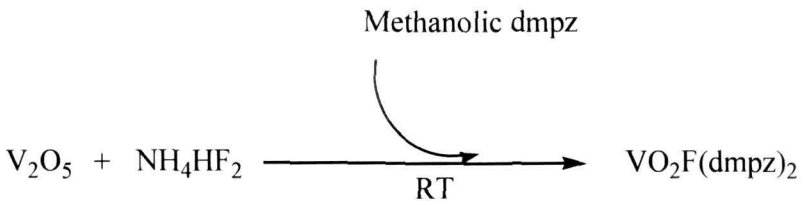
Scheme 5.1: Oxidation of sulfide to sulfoxides

On completion of the reaction, acetonitrile was removed under reduced pressure and 1 mL of water was added. The product was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated to dryness, while the aqueous layer was retained for recovery of the catalyst. The ctalyst can be recoverd from the aqueous layer during

work up procedure and can be reused. In order to remove any traces of $VO_2F(dmpz)_2$, the product was transferred to silica gel (60-120 mesh) column and eluted with ethyl acetate : hexane (1 :7).

5A. 2 Results and Discussion

The strategy of the synthesis was that V_2O_5 would react with NH_4HF_2, a mildly acid fluoridating agent, to produce oxofluorovanadates (V) in solution which would then react with dmpz to afford $VO_2F(dmpz)_2$, as targeted, in a very high yield (scheme-5.2). An ethanolic solution of it was used for the reaction. Ethanol might have also helped in precipitation of the complex out of the reaction solution. Strategically important was also the selection of NH_4HF_2 as an important reagent. The role of NH_4HF_2 was not only to afford fluoridation but also to provide mild acidity (pH~ 4) of the reaction medium. This has facilitated coordination of dmpz through its non-protonated N-donor atom. A higher acidity is not conducive to the synthesis. The targeted product is found to be highly crystalline lemon yellow solid, stable in air, soluble in nearly all-polar solvents and having sharp decomposition point at 156 °C. Its solution electrical conductance value of 26 mho cm^2 mol^{-1} in acetonitrile attests its neutral character [32].



Scheme 5.2: Synthesis of the $VO_2F(dmpz)_2$

Magnetic susceptibility measurement shows that the compound is diamagnetic with Gram susceptibility being $-0.369X10^{-6}$ cgs [33]. The IR spectrum of $VO_2F(dmpz)_2$ showed characteristic absorption bands due to coordinated dmpz [34], fluoride [35], and oxo ligands [36]. A strong band at 446 cm^{-1} is due to ν(V-N) stretching. This is very important in support of the dmpz coordination. The strong bands appearing at 948, 930 cm^{-1} are due to ν(V=O). Splitting of this band is a clear indication of the occurrence of a *cis*-dioxovanadyl center [36]. The Laser Raman (LR) spectrum showed complimentary signals at 547 cm^{-1} due to ν_{V-F}, and at 947 and 930 cm^{-1}

assigned to $\nu_{V=O}$ originating from the *cis*-VO_2 core. The UV-Vis spectrum showed one intense broad band at 245 nm which might be for ligand to metal charge transfer [37]. The X-ray analysis of the compound [38] indicates that it is a penta coordinated mononuclear vanadium (V) species $[VO_2F(dmpz)_2]$ with space group *Cc* (table 5.1). The ORTEP diagram of the compound with the atom-numbering scheme is shown in the figure 5.1. This complex is similar to serendipitously obtained $[(t\text{-Bupz})_2VO_2F]$ [21] showing same trigonal bipyramidal (TBP) geometry with dmpz ligands, as purely strong σ-donor, occupying the apical positions and the oxo and fluoride groups in the equatorial site. The X-ray data shows that the V=O bonds and O=V=O angle are slightly greater (mean V=O bond = 1.722Å and O=V=O angle =122.2°) than the normal (V=O bond 1.604 Å to 1.649Å and O=V=O angle 108.2 to 110.7°) which might be due to the formation of intramolecular hydrogen bonding between N-H hydrogens and *cis*-disposed dioxo groups (table 5.2). The mean O....H is found to be 2.108 Å which is unlike with the reported $[(t\text{-Bupz})_2VO_2F]$ [21].

Table 5.1: Crystal data and structure refinement for compound $VO_2F(dmpz)_2$

Empirical formula	$C_{10}H_{16}FN_4O_2V$
Formula weight (amu)	294.21
Temperature (K)	298
Wavelength (nm)	0.71073
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions, Å and ^{0}	a = 11.2074(4) α= 90
	b = 11.9492(5) β= 94.380
	c = 9.7556(6) γ = 90
V(Å^3)	1302.64
Z	4
Density (mg/m^3) Mg/m^3	1.5
Absorption coeff., μ mm^{-1}	0.77
F(000)	608
Goodness-of-fit on F^2	1.324
R indices (all data) R1, wR2	0.0449, 0.053

Table 5.2: Selected bond distances and bond angles of $VO_2F(dmpz)_2$

Bond distances	(Å)	Bond angles	(°)
V1-F3	1.601(2)	F3-V1-O3	117.5 (3)
V1-O2	1.721(5)	F3-V1-O2	120.3 (3)
V1-O3	1.723 (5)	F3-V1-N2	86.3 (2)
V1-N2	2.056 (5)	F3-V1-N3	92.4 (3)
V1-N3	2.151 (5)	O2-V1-O3	122.2(2)
		O2-V1-N2	86.3 (2)
		O2-V1-N3	91.4 (2)
		O2-V1-N2	86.3 (2)
		O3-V1-N2	90.0(2)
		N2-V1-N3	174.8(2)

It is also interesting to note that the V-F bond is short which might posses more than single bond character to nullify the charge density drawn from vanadium for intramolecular hydrogen bond. The present investigation clearly demonstrates that dmpz complex of vanadium (V) can be synthesized from an aqueous solution in presence of fluoride.

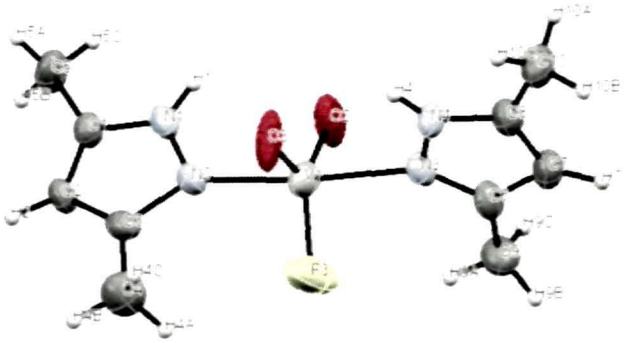


Figure 5.1: ORTEP plot of $VO_2F(dmpz)_2$

From the prior knowledge in the peroxovanadium chemistry [39-43], it is believed that the complex interacts with H_2O_2 to form peroxovanadium intermediate thereby activating the bound peroxide. Sometimes it was found that peroxovanadium species in presence of electron donating ligands (EDL) could not oxidize bromide but even after having EDL it worked well, which might be due to the presence of fluoride.

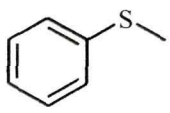
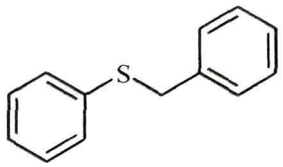
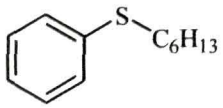
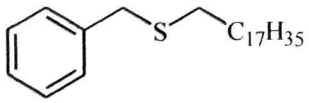
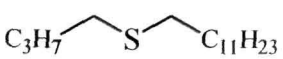
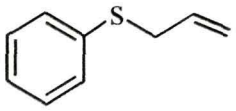
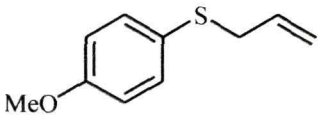
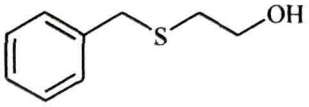
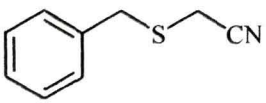
Our interest in peroxovanadium catalyzed oxidation inspired us to use this complex as catalyst for sulfide oxidation.

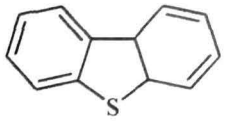
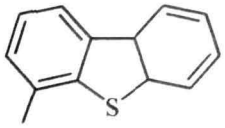
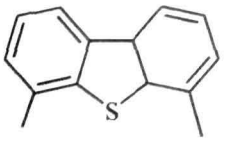
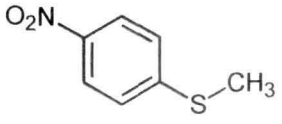
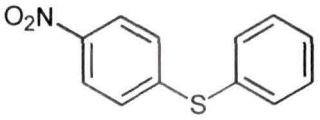
Table 5.3: Optimization of reaction condition for the oxidation of methyl phenyl sulphide

The complex was screened for oxidation of sulfides with aqueous 30% H_2O_2. To optimize the reaction condition, we carried out oxidation of methyl phenyl sulfide in acetonitrile at room temperature (table 5.3). It was found that methyl phenyl sulfide was oxidized to a 3:1 mixture of methyl phenyl sulfoxide and sulfone in the presence of 5 mol% of the catalyst and 2 equiv. of H_2O_2. We also performed the oxidation in different solvents (table 5.3) maintaining the same conditions. Unfortunately, over oxidation could not be averted. The over oxidation could not be overcome even by lowering the amount of H_2O_2 to 1.1 equiv. The attention was then turned on to the temperature of the reaction. Sulfoxide as the sole product was found when the reaction was carried out at ice-bath temperature. To ascertain the efficacy of the catalyst several reactions were carried out with or without catalyst. The reactions took place in each case with the best performance being in acetonitrile with 1 mol% of the catalyst. Accordingly, all the reactions discussed herein after were conducted with this combination. In order to generalize the scope, a series of structurally diverse sulfides were subjected to oxidation under the optimized reaction conditions and the results are presented in table 5.4. The reactions went well affording the products in high yields. It is notable that sulfides were chemoselectively oxidized in presence of some oxidation prone functional groups such as C=C, –CN, –OH (entries 7-11, table 5.4).

Entry	Catalyst mol%	Time (h)	Temp (^{0}C)	H_2O_2 equiv.	Solvent	Sulfoxide (%)	Sulfone (%)
1	5	2.5	27	2	CH_3CN	75	20
2	5	2.5	27	2	C_2H_5OH	70	23
3	5	5	27	2	H_2O	55	20
4	5	3	27	1.1	CH_3CN	65	20
5	5	3.5	0-5	1.1	CH_3CN	95	<1
6	3	4.0	0-5	1.1	CH_3CN	95	<1
7	1	5	0-5	1.1	CH_3CN	95	<1
8	1	12	0-5	0	CH_3CN	0	--
9	0	12	0-5	1.1	CH_3CN	35	--
10	5	5.5	0-5	1.1	C_2H_5OH	92	5

Table 5.4: $VO_2F(dmpz)_2$ catalyzed oxidation of organic sulfide with H_2O_2 in CH_3CN

Entry	Substrate	Time(h)	Sulfoxide[a]
1	$(Me)_2S$	30 min	99
2		5	95,90[b],86[c],97[d]
3		5	93
4		5.5	87
5		6.5	95
6		6	87
7		3	97
8		6.5	86
9		4.5	85
10		4.5	82
11		2	85

12		5	88[e]
13		8	75[e]
14		12	80[e]
15		5	35[a]
16		5	30[a]

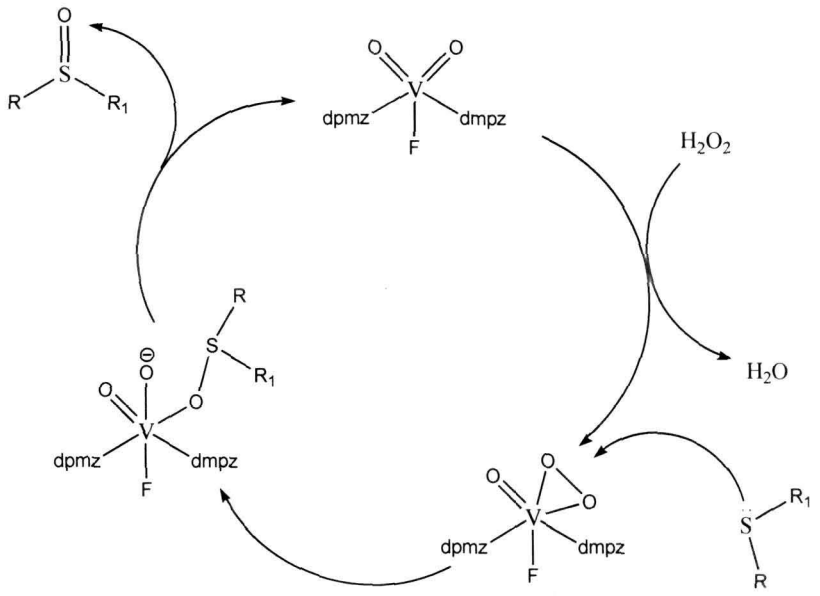
[a] Isolated Yield, [b] Reaction in ethanol, [c] Yield after fifth cycle, [d] Yield at 5g scale, [e] Reaction at room temperature

Dibenzothiophene (DBT) and substituted DBT oxidations are rather difficult with the standard oxidation procedures [44]. However, upon the treatment with $VO_2F(dmpz)_2$-H_2O_2 system these were converted to the corresponding sulfoxides (entries 12-14, table 5.4) in good yields. It is noteworthy to mention that the catalytic conversion of foul smelling toxic gas, i.e. dimethyl sulfide (DMS) generated in many medicinal industries (e.g. during Renitidine HCl synthesis) to the corresponding sulfoxide is important to stop the release of such toxic gas in to the environment.

DMS is found in many industrial waste gas streams and has very low odorous threshold value and toxic for both the environment and the human health. The low vapour density of the gas facilitates its easy diffusion into and rapid mixing of atmospheric air thereby rendering the air stinky. Moreover, methylmarcaptans are health hazard because they cause dizziness, headache, nausea, respiratory arrest and even coma and unconsciousness. A little longer exposure to high concentration of

the gas can be fatal. The sustained contact with the liquid and the gas may cause frostbite as well.

It may be mentioned that with the increase in alkyl chain length of the sulfides, the rate of reaction becomes slower (entries 4, 5 & 6, table 5.4). This may be due to the orientation of hydrophobic alkyl chain around the sulfur atom. Recyclability of the catalyst was examined through a series of reactions with methyl phenyl sulfide by using the aqueous phase containing $VO_2F(dmpz)_2$, obtained after extraction of the reaction mixture with ethylacetate. This was charged with fresh substrate and 1.1 equivalents of H_2O_2. The catalyst could be reused for at least five reaction cycles with consistent activity. Importantly, the reaction can be performed on a relatively larger scale (5 g) to give good yields (entry 2, table 5.4) showing its potential for scaled-up applications. Chu and Trout's report said that the major reaction coordinates of the reaction were the breaking of the O-O of the intermediate and the formation of the S-O bond in the sulfide oxidation to sulfoxide by H_2O_2 [45].



Scheme 5.3: Plausible mechanism of the reaction

The oxidation is expected to progress via metal-oxygen shift mechanism in the present reaction as depicted in scheme 5.3. The ease of the formation of sulfoxide is likely to happen through the nucleophilic attack by the sulfide to the electrophillic O-O bond of peroxometal species thus facilitating the regeneration of the catalyst. It

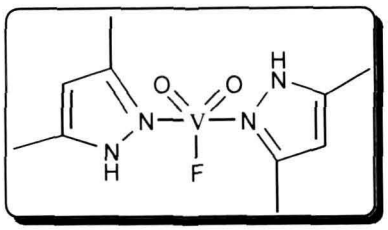
is found that the presence of electron withdrawing group in the substrates hinder the reaction which is expected according to the proposed mechanism of the reaction.

5A. 3 Conclusions

In conclusion, a new penta-coordinated $VO_2F(dmpz)_2$ catalyst has been developed and fully characterized. Its throughput as catalyst for the oxidation of alkyl as well as aryl sulfides in presence of oxidation prone functional groups such as C=C, –CN, –OH and its reusability offers a potentially competitive practicable process. The selective oxidation of DMS to DMSO is industrially important in the context of renitidine hydrochloride. Refractory sulfides are also capable of being oxidized quite effectively. The oxidations of DBTs are especially important in the context of transportation fuel chemistry research targetting desulfurization of diesel and gasolene, for instance.

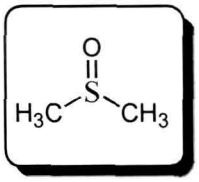
5A. 4 Spectral Data

$VO_2F(dmpz)_2$



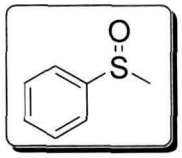
FT-IR(KBr): 3257, 1577, 948, 930 cm^{-1} ; ^{1}HNMR (400MHz, $CDCl_3$) : δ 2.13 (s, 3H), 2.47 (s, 3H), 5.85 (s, 1H), 11.62 (brs, 1H, N-H) ;^{13}C NMR (100 MHz, $CDCl_3$): δ 11.74, 105.04, 145.76.

Demethyl sulfoxide (entry 1, table 5.4)



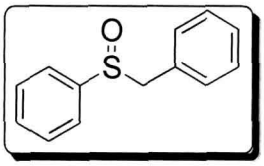
FT-IR(KBr): 950, 1018, 3419 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (s, 6H)
^{13}C NMR (100 MHz, $CDCl_3$): δ 31

Methyl phenyl sulfoxide (entry 2, table-5.4)



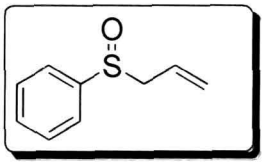
FT-IR(KBr): 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (s, 3H), 7.51-7.53 (m, 3H), 7.64-7.66 (m, 2H); MS : m/z 157 (M^+).

Benzyl phenyl sulfoxide (entry 3, table-5.4)



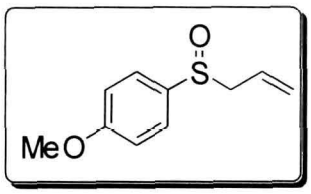
FT-IR (KBr): 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.99 (d, J = 12.8Hz, 1H), 4.16 (d, J = 12.4Hz, 1H), 6.95 (m, 2H), 7.19-7.28 (m, 3H), 7.34-7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.8, 124.5, 128.3, 128.5, 128.9, 129.2, 130.4, 131.2, 142.7.

Allyl phenyl sulfoxide (entry 7, table -5.4)



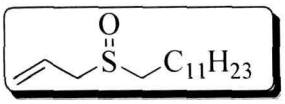
FT-IR (KBr): 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.48-3.60 (m, 2H), 5.18 (d, J = 16.8Hz, lH), 5.33 (d, 1H, J = 10.8Hz, 1H), 5.58-5.68 (m, lH), 7.48-7.53 (m, 3H), 7.55-7.58 (m, 2H).

Allyl 4-methoxyphenyl sulfoxide (entry 9, table-5.4)



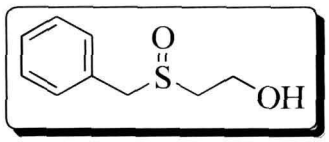
FT-IR (KBr): 1044 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 3.45-3.57 (m, 2H), 3.78 (s, 3H), 5.18 (d, J = 16.8Hz, 1H), 5.31 (d, J = 10.8Hz, 1H), 5.58-5.68 (m, 1H), 7.47-7.51(m, 3H), 7.54-7.57 (m, 2H).

Allyl dodecyl sulfoxide (entry 8, table-5.4)



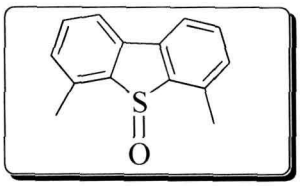
FT-IR (KBr): 1035 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 0.9 (t, J =6.4Hz, 3H), 1.31-1.46 (m, 16H), 1.78-1.88 (m, 2H), 2.93 (t, J = 8.4Hz,2H), 3.69 (d, J = 8.4Hz, 2H), 5.42 (d, J = 16.4Hz, 1H), 5.49 (d, J = 10.8Hz, 1H), 5.85-6.0 (m, 1H)

2-Phenylmethanesulfinyl-ethanol (entry 10, table-5.4)



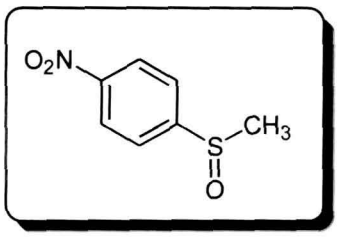
FT-IR (KBr): 1025 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 2.72-2.77 (m, 1H), 2.81-2.87 (m, 1H), 4.05-4.13 (m, 4H), 7.29-7.31 (m, 2H), 7.34-7.38 (m, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 53.34, 55.29, 58.04, 128.60, 129.11, 130.04, 130.52.

4, 6-Dimethyldibenzothiophene sulfoxide (entry 14, table-5.4)



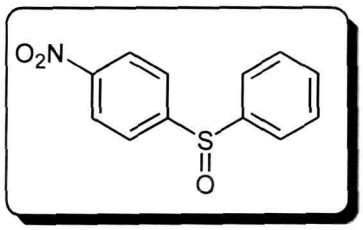
FT-IR (KBr): 1028 cm^{-1} ; ^1H NMR (400MHz, $CDCl_3$): δ 2.52 (s, 6H), 7.14-7.27 (m, 3H), 7.46 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.4Hz, 1H).

4-nitrophenyl methyl sulfoxide (entry 15, table-5.4)



FT-IR (KBr): 3578, 1509, 1338, 1078, 1037, 835, 664; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.39 (d, *J*=8 Hz, 2H), 7.81-7.83 (d, *J*=8 Hz, 2H), 2.78 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 153.34, 149.61, 149.45, 124.74, 43.97.

4-nitrophenyl phenyl sulfoxide (entry 16, table-5.4)



FT-IR (KBr): 3449, 3091, 1516, 1338, 1086, 1037, 843, 730, 680, 526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 8.28-8.30 (d, *J*=8 Hz, 2H), 7.80-7.83 (d, J=12 Hz, 2H), 7.65-7.66 (m, 2H), 7.48-7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 141.31, 128.84, 127.33, 127.25.

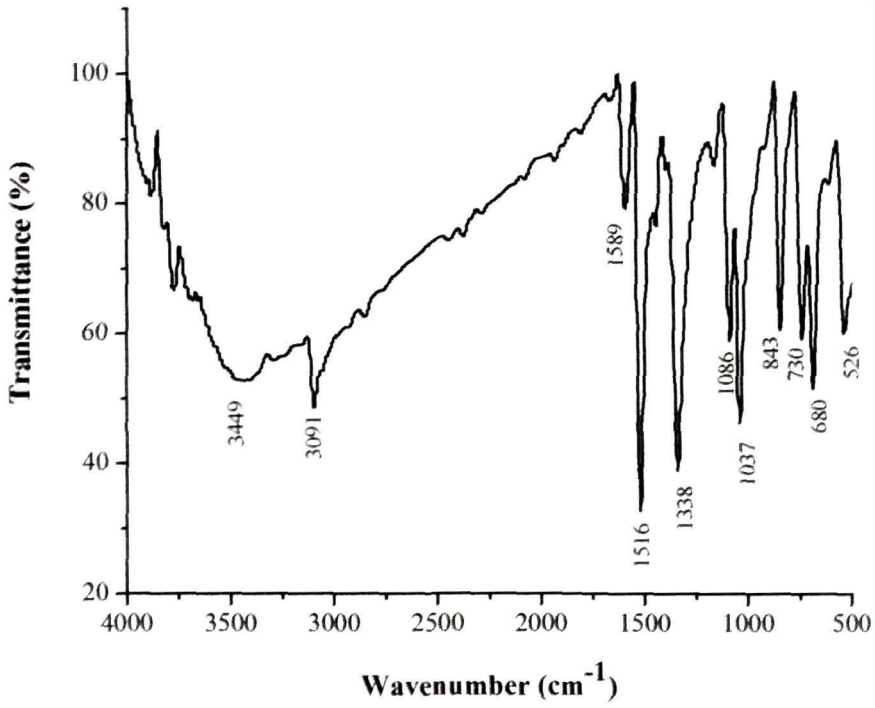


Image 22: FT-IR spectrum of 4-nitrophenyl phenyl sulfoxide

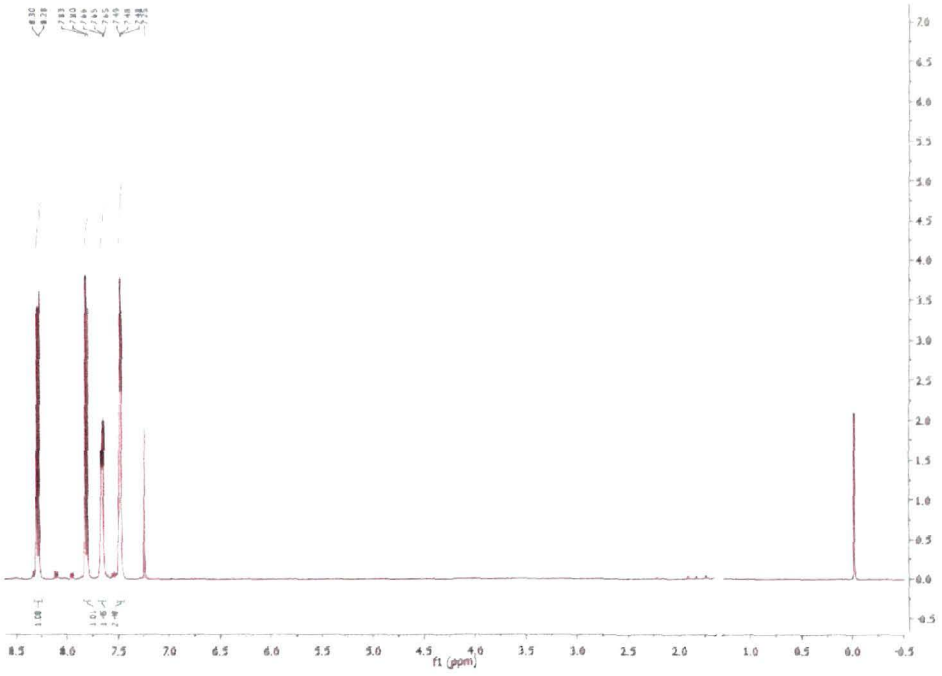


Image 23: ^{1}H NMR spectrum of 4-nitrophenyl phenyl sulfoxide

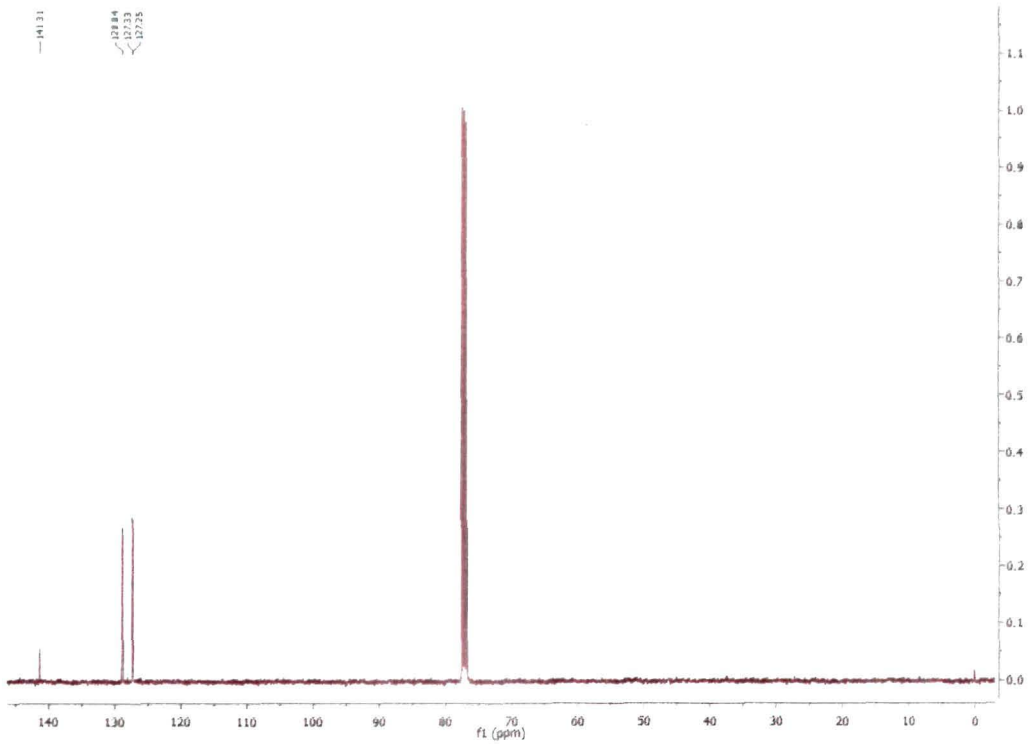


Image 24: ^{13} C NMR spectrum of 4-nitrophenyl phenyl sulfoxide

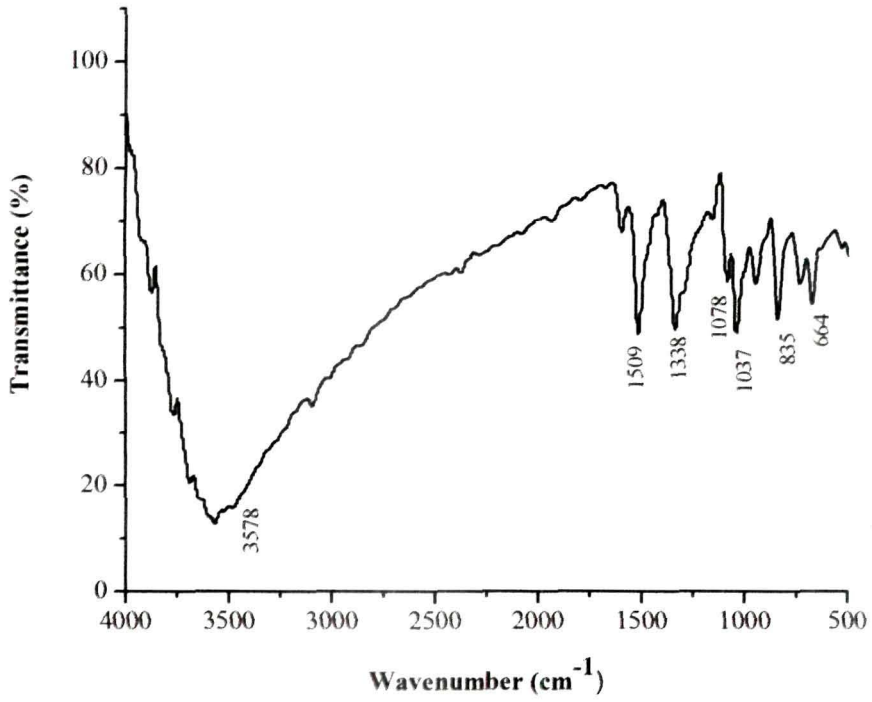


Image 25: FT-IR spectrum of 4-nitrophenyl methyl sulfoxide

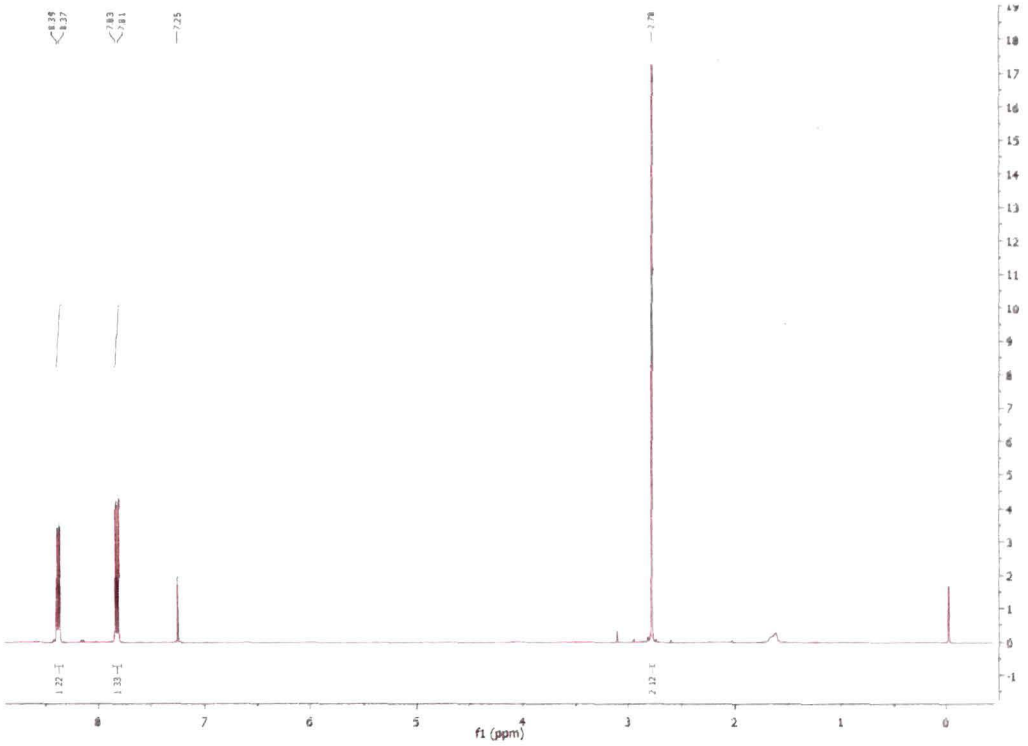


Image 26: ^{1}H NMR spectrum of 4-nitrophenyl methyl sulfoxide

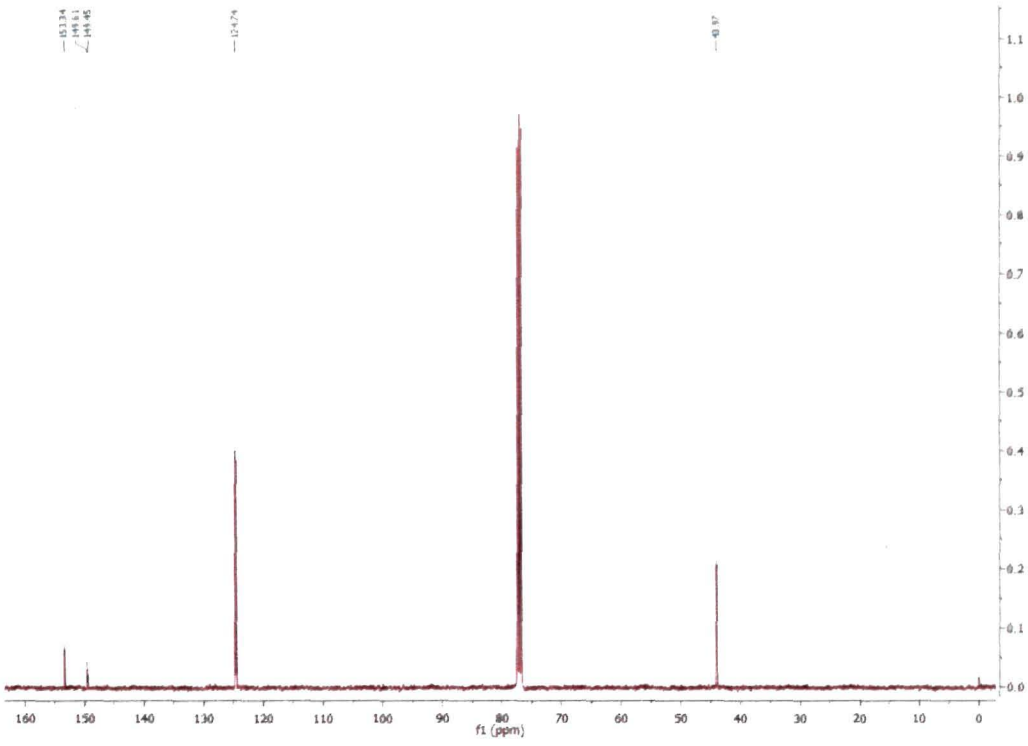


Image 27: ^{13}C spectrum of 4-nitrophenyl methyl sulfoxide

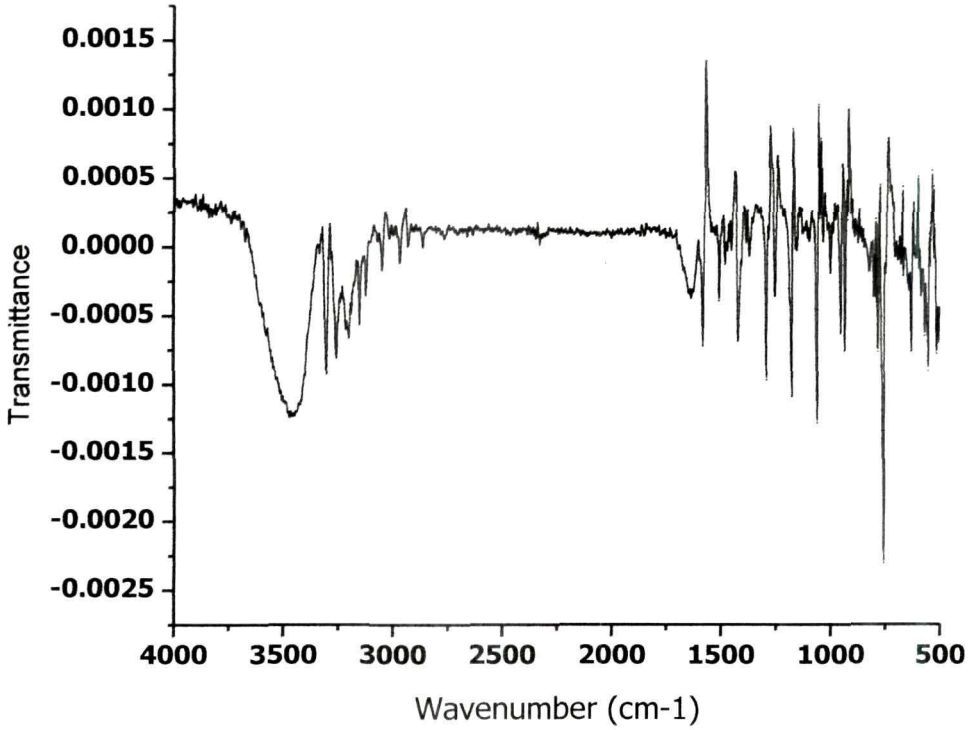


Image 28: FT-IR spectrum of $VO_2F(dmpz)_2$

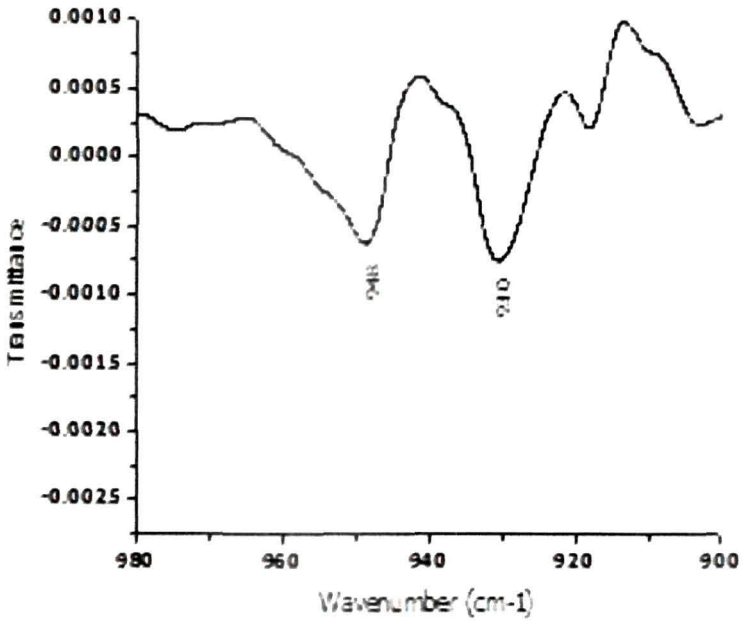


Image 29: FT-IR spectrum of $VO_2F(dmpz)_2$ showing the splited peak due to cis-dioxovanadyl species

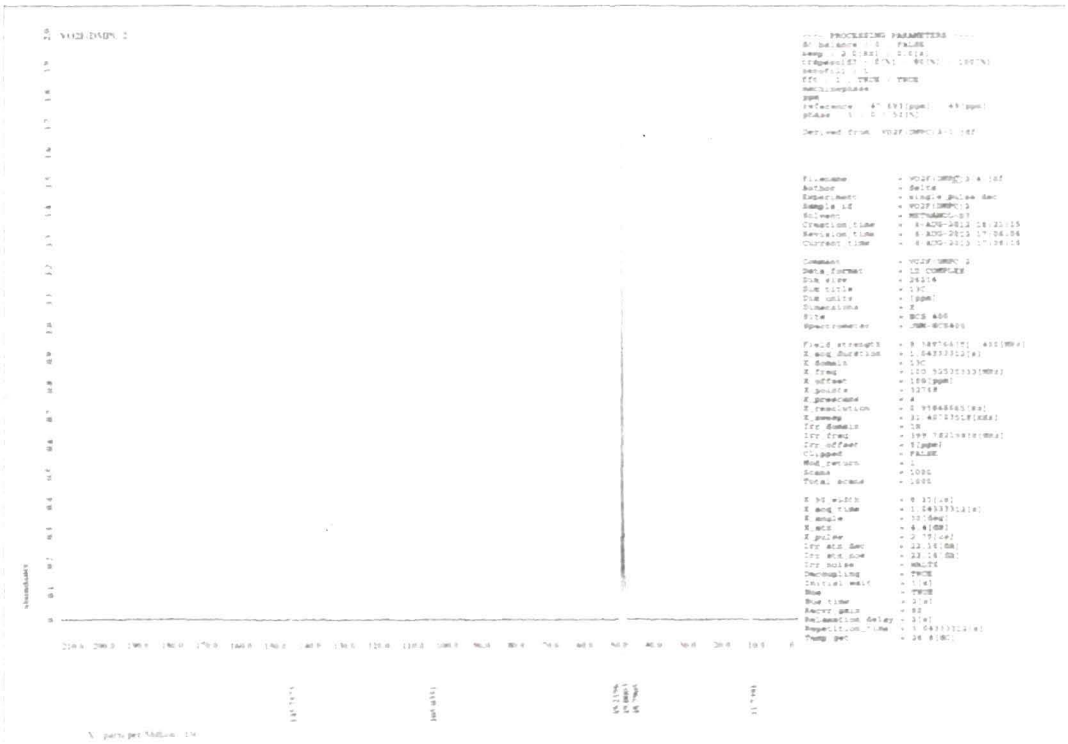


Image 30: ^{13}C NMR spectrum of of $VO_2F(dmpz)_2$

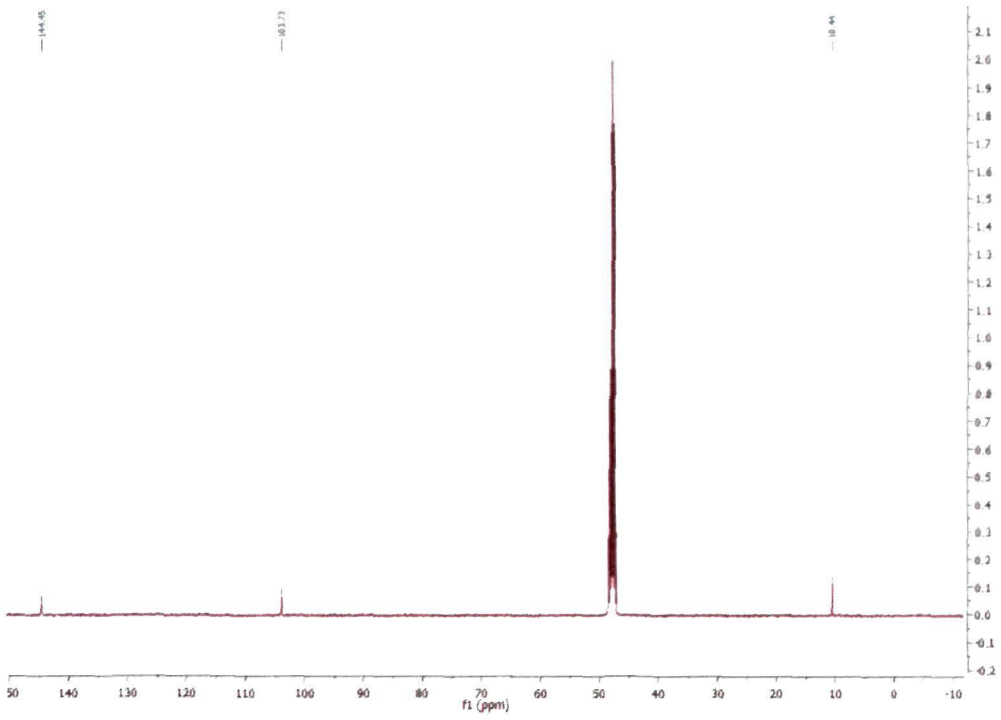


Image 31: ^{13}C NMR spectrum of DMPZ

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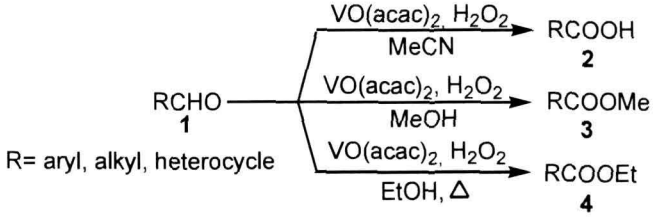
Section 5B

$VO(acac)_2$: an efficient catalyst for the oxidation of aldehydes to the corresponding acids in presence of aqueous H_2O_2

In the plethora of oxidation processes, aldehyde oxidation occupies an important position owing to their diversified importance in the industrial manufacturing, and in synthetic chemistry [1-3]. The classical methods for the oxidation of aldehyde involve the use of oxidising reagents like Jones reagent [4,5], $KMnO_4$[6,7], bromine [8,9], HNO_3 [10] Ag_2O [11] which are not desirable because of the current industrial and environmental demand. In recent times, various catalysts and catalyst systems have been reported for the catalytic oxidation of aldehyde, e.g. CuCl [12], $AgNO_3$ [13], Bi_2O_3 [14] supported metal acetyl acetonate [15] etc. In the domain of green oxidation processes, hydrogen peroxide is considered as the ultimate green oxidizing (active oxygen 47.1%) reagent because the by-product is water. The first report of oxidation of aldehydes using H_2O_2 is almost seven decades old [16]. Noyori *et al.* exploited the ability of H_2O_2 for the oxidation of aldehyde to the corresponding acid [17]. In recent years, H_2O_2 has been extensively used in synthetically important processes like epoxidation [18,19], oxidation of sulphides [20,21], oxidation of alcohols [22,23], Baeyer-Villiger oxidation [24] etc. The oxidizing ability of H_2O_2 can be enhanced by adding a little vanadium compound to the reaction mixture [25]. Such activation of H_2O_2 by vanadium compound leads to the generation of various reactive peroxovanadium species with various co-ordination modes [26–28]. V_2O_5/H_2O_2 has been used to oxidize aldehyde to the corresponding esters [29,30].



Scheme 5.4: $VO(acac)_2$ catalyzed oxidation of aldehyde

The five co-ordinate $VO(acac)_2$ has been proved to be a good oxidation catalyst [31]. It is found that $VO(aacac)_2$ along with H_2O_2 can oxidize aldehydes to the corresponding acids or the esters depending on the solvents used (scheme 5.4) *viz.* methyl ester is formed in the presence of methanol and acid is the product in the

presence of acetonitrile. Activity of various vanadium sources-H_2O_2 systems have been studied for the oxidation of aldehydes to the corresponding acids

5B. 1 Experimental:

a) Procedure for the oxidation of 4-ClC_6H_4CHO with $VO(acac)_2$

In a typical procedure, 0.007 g of $VO(acac)_2$ (4 mol%) was dissolved in 0.34 mL (3 mmol) of 30% H_2O_2; the color of the mixture changed to reddish brown. To this mixture, 0.14 g (1 mmol) of 4-chlorobenzaldehyde dissolved in minimum amount of acetonitrile was added and allowed to stir. Progress of the reaction was monitored by thin layer chromatography (TLC). On completion of the reaction, acetonitrile was removed under reduced pressure and 3 mL of water was added. The product was extracted with ethyl acetate (3×10 mL) and the organic layer was dried over anhydrous Na_2SO_4. Finally, the product was purified by column chromatographic technique.

b) Typical procedure for the preparation of $VO(acac)_2$ catalyst

To an aqueous suspension of vanadium pentoxide (5 g, 27.49 mmol) in 20 mL of water taken in a 500 mL beaker, 30% hydrogen peroxide (37.37 mL, 329.88 mmol) was added dropwise in an ice-cold condition and stirred till a clear dark solution was formed. To the dark brown colored solution, distilled acetylacetone (19.84 mL, 192.5 mmol) was added dropwise very carefully with continuous stirring. Vigorous effervescence took place after 15 min., stirring for a period of 30 min led to a precipitation of a brown colored microcrystalline compound. The reaction mixture was heated at 70 °C for 15 min under stirring. The precipitate turned olive green with shiny crystalline appearance with the solution also turning green. The solution was concentrated by heating on a steam bath for 30 min and then placed in an ice-water bath for 15 min. The compound was filtered through Whatman No. 42 filter paper, washed with acetone and dried in vacuo over fused $CaCl_2$. Yield: 11.7 g (80%).

c) Preparation of $VO(acac)_2$ supported on titania ($VO(acac)_2$–TiO_2) [32]

To a solution of $VO(acac)_2$ (265 mg) in anhydrous THF (50 mL), TiO_2 (1.0 g) was added and stirred at 293 K for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed several times with anhydrous THF, and finally dried in vacuo.

Measurement of the mass increase of the resultant $VO(acac)_2$–TiO_2 indicates that 170 mg of $VO(acac)_2$ is supported, and the vanadium content is 0.64 mmol/g.

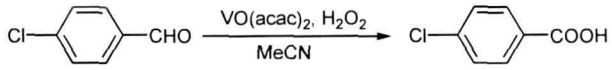
d) Procedure for the oxidation of 4-$NO_2C_6H_4CHO$ with TiO_2-$VO(acac)_2$

In a typical procedure, 0.0075 g of TiO_2-$VO(acac)_2$ (5 wt%) was taken in 0.34 mL (3 mmol) of 30% H_2O_2. To this mixture, 0.15 g (1 mmol) of 4-nitrobenzaldehyde dissolved in minimum amount of acetonitrile was added and allowed to stir. Progress of the reaction was monitored by thin layer chromatography (TLC). On completion of the reaction, the mixture was filtered to recover the catalyst, acetonitrile was removed under reduced pressure. The product was extracted with ethyl acetate (3×10) and dried over anhydrous Na_2SO_4. The recovered catalyst was washed with chilled ethanol and dried at 120 °C for 1 h and then used it for further reaction. Finally, the product was purified by column chromatographic technique.

5B. 2 Results and Discussion

The results of our initial attempts to optimize the reaction condition using 4-chlorobenzaldehyde as the model substrate in the presence of H_2O_2 as the oxidant and $VO(acac)_2$ as the catalyst are elaborated in table 5.5.

Table 5.5: Optimization of the reaction condition[a]



Entry	H_2O_2[b] (mmol)	Solvent	Catalyst	Time (h)	Yield (%)[c]
1	1	MeCN	-	5	4
2	-	MeCN	$VO(acac)_2$ (1 mol%)	8	0
3	1	MeCN	$VO(acac)_2$ (1 mol%)	8	48
4	1.5	MeCN	$VO(acac)_2$ (1 mol%)	8	55

5	2	MeCN	$VO(acac)_2$ (1 mol%)	8	56
6	2	MeCN	$VO(acac)_2$ (2 mol%)	7	65
7	2	MeCN	$VO(acac)_2$ (3 mol%)	6	78
8	2	MeCN	$VO(acac)_2$ (4 mol%)	5	82
9	**3**	**MeCN**	$VO(acac)_2$ (4 mol%)	**4**	**97**
10	3	Toluene	$VO(acac)_2$ (4 mol%)	10	40
11	3	CH_2Cl_2	$VO(acac)_2$ (4 mol%)	8	45
12	3	MeOH	$VO(acac)_2$ (4 mol%)	3	90[d]
13	3	EtOH	$VO(acac)_2$ (4 mol%)	4	45
14	3	CH_3CN	V_2O_5 (4 mol%)	4	45
15	3	CH_3CN	NH_4VO_3 (4 mol%)	4	62

[a] *p*-chlorobenzaldehyde (1 mmol), stirred at room temperature.
[b] 30% H_2O_2.
[c] Yields are referred to as isolated yields.
[d] Ester is the product.

To ascertain the presence and efficacy of the catalyst several reactions were carried out with and without catalyst (entries 1-15, table 5.5). From our study it is found that, in the absence of H_2O_2, only $VO(acac)_2$ cannot catalyze the oxidation of the aldehyde (entry 2). The oxidizing ability of H_2O_2 in the absence of $VO(acac)_2$ was found to be negligible (<5% yield was isolated) (entry 1). 4 mol% of the catalyst and three fold amount of H_2O_2 provided the best result (entry 9). Effect of various solvents and vanadium catalysts on the above model reaction are also studied (entries 1-15, table 5.5). The study revealed that $VO(acac)_2$ and acetonitrile were the best catalyst and solvent respectively for the oxidation of aldehyde to the corresponding acid (entry 9). Interestingly, under the reaction condition, in ethanol corresponding acid was obtained (entry 13) in moderate yield while in methanol corresponding methyl ester was obtained in excellent yield (entry 12). Gas

chromatogram of the reaction mixture does not show any decomposition product; only acid or ester and unreacted aldehyde are present in the reaction mixture.

To demonstrate the generality and scope of the reaction, a series of structurally diverse aldehydes were subjected to oxidation under the optimized condition and the outcome is summarized in table 5.6 (entries 1-12). The reaction went well affording moderate to excellent yields of the product. As can be seen from the table 5.6, the method was equally effective for the oxidation of both aromatic and heterocyclic aldehydes (entries 1-9). However, aliphatic aldehydes (entries 10 and 11) except unsaturated aldehyde (entry 12) reacted slowly to afford moderate yield of product. This might be due to the low electrophilicity of aliphatic carbonyl carbon than the aromatic one. Notably, oxidation prone functional groups such as -OH (entry 3), -OMe (entry 5) and -C=C (entry 6) in aldehydes remain unaffected during the reaction that showed the chemoselectivity of the protocol. Similarly, heterocyclic aldehydes are also prone to oxidation at the hetero atom. Notably, in our protocol oxidation occurs only at the aldehydic group without affecting the hetero atom (entries 7 and 8).

Table 5.6: Oxidation of aldehyde catalyzed by $VO(acac)_2$

Entry	Aldehyde	Catalyst	Time (h)	Yield (%)[a]	
				Acid[b]	Ester[c]
1	*4*-ClC_6H_4CHO	$VO(acac)_2$	4	97	97
		TSV[e]	4	96	95
2	*2*-ClC_6H_4CHO	$VO(acac)_2$	5.30	94	89
		TSV	5.30	93	85
3	*4*-OHC_6H_4CHO	$VO(acac)_2$	5.30	96	96
		TSV	5.30	91	90
4	*4*-$NO_2C_6H_4CHO$	$VO(acac)_2$	6	98	98
		TSV	6	97	95
5	*4*-$MeOC_6H_4$-CHO	$VO(acac)_2$	4	96	96
		TSV	4	94	93
6	*trans*-cinnamaldehyde	$VO(acac)_2$	7	90	72
		TSV	7	87	73

7	Thiophene-2-carbaldehyde	$VO(acac)_2$	6.30	92	72
		TSV	6.30	90	73
8	Pyridine-2-carbaldehyde	$VO(acac)_2$	5.30	91	76
		TSV	5.30	87	73
9	2-Furaldehyde	$VO(acac)_2$	6	89	74
		TSV	6	86	75
10	Pentanal[d]	$VO(acac)_2$	7	65	61
		TSV	7	62	60
11	Gluteraldehyde[d]	$VO(acac)_2$	8	42	40
		TSV	7	42	39
12	Acrylaldehyde	$VO(acac)_2$	6	76	75
		TSV	6	76	74

[a] Yields are referred to as isolated yields. [b] All the reactions are carried out with 4 mol% of $VO(acac)_2$ and 3 mmol of 30% H_2O_2 in MeCN at room temperature under stirring. [c] MeOH was used as solvent. [d] Reactions were carried out at 60 °C. [e] TSV= TiO_2 supported $VO(acac)_2$

Mechanistically, peroxovanadium species is involved in the reaction. The intermediacy of the peroxovanadium species in the catalytic process can be observed from the UV-Visible spectrum of H_2O_2, $VO(acac)_2$ and solvent mixture. The peak at around 414 nm is due to the ligand to metal charge transfer transition, which is a characteristic of peroxovanadium compounds. Accordingly, a plausible mechanism involving peroxovanadium species is described in figure 5.2. $VO(acac)_2$ and H_2O_2 form a reactive peroxovanadium species (II). In the absence of methanol, the metal peroxo oxygen atom in (II) attacks the electrophilic carbonyl carbon of aldehyde affording the corresponding acid (**path b**). The alcoholic proton in methanol is more acidic than ethanol, therefore it is easily abstracted by (II) resulting the methoxide ion which further attacks the carbonyl carbon of aldehyde resulting the ester as the product (**path a**). Interestingly, when the reaction was carried out at elevated temperature, i.e. 50-60 °C in presence of ethanol the product was the corresponding ethyl ester (table 5.7) along with the corresponding acid as the side product and some amount of unreacted starting aldehyde. This observation is supported by the suggested mechanism (**path a**, figure 5.2). Higher temperature facilitates the abstraction of comparatively less acidic alcoholic proton of ethanol.

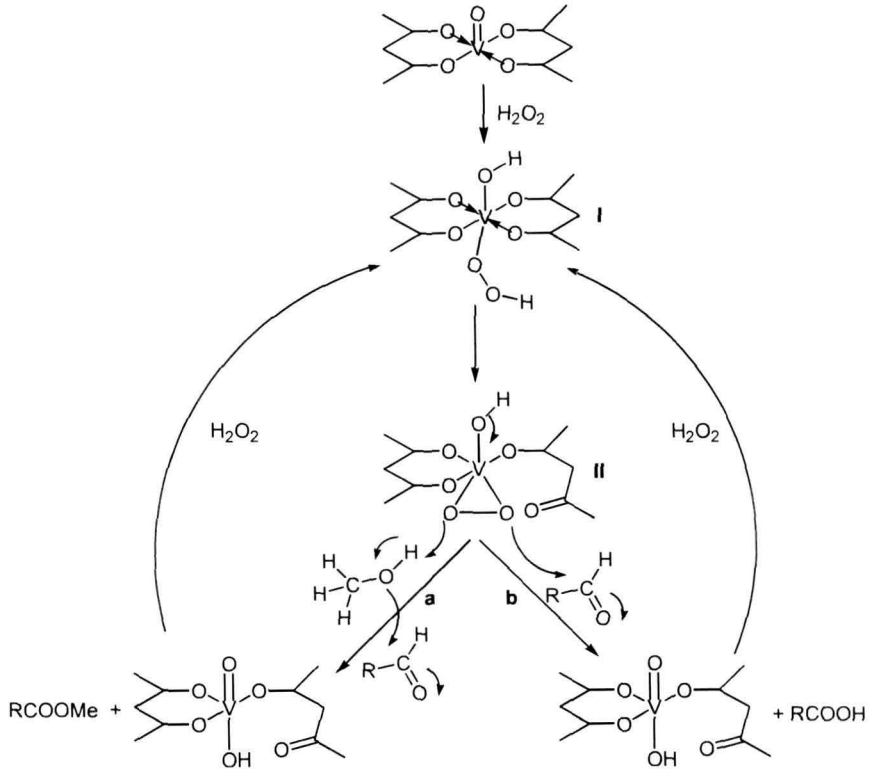
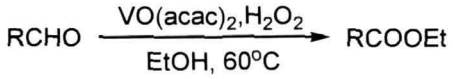


Figure 5.2: Plausible mechanism for the oxidation of aldehyde

Homogeneous catalytic processes produce unwanted waste and hence heterogenization of the homogeneous process is important. TiO_2 supported $VO(acac)_2$ (TSV) has been reported for the oxidation of the organic sulfides to the corresponding sulfoxides [32]. This impregnated catalyst also showed good results as summarized in table 5.8 (entries 1-5).

Table 5.7: Oxidation of aldehyde to ethylester



Entry	Substrate	Time (h)	Yield (%)[a,b]
1	Pentanal	4	60
2	*p*-chlorobenzaldehye	2.5	75
3	*p*-nitrobenzaldehye	3	90
4	*2*-furaldehyde	4	57

[a] Yields are referred to as isolated yields. [b] Trace amount of acid is formed as the corresponding side product

With a change in the catalyst loading, variation in the yield of the product was also observed, which are shown in the table 5.8. Best result was obtained when the

catalyst loading was 5 wt% (entry 5). Vanadium content in the catalyst was found to be approx 0.64 mmol/g. Further increasing the catalyst loading and reaction time did not improve the yield of the reaction.

In catalysis, recyclability is one of the important attributes. For this, we have conducted a series of reactions with the recycled TSV catalyst. The catalyst can be effectively recycled for at least five cycles with reasonably consistent activity.

Table 5.8: Effect of catalyst (TSV) loading on the product yield[a]

Entry	TSV (wt%)	Time (h)	Yield (%)[b]
1	1	6	40
2	2	6	55
3	3	6	70
4	4	6	85
5	5	6	97

[a] The reactions have been carried out considering *p*-nitrobenzaldehyde as the substrate in acetonitrile under stirring at room temperature.
[b] Yields are referred to as isolated yields

The recycled TSV catalyst shows slow deactivation, which may be due to the slow leaching out of vanadium from the surface of the support. The activity of the catalyst can be easily regained simply by treating the recycled catalyst with a solution of $VO(acac)_2$ in THF [33]. The regenerated catalyst has the same activity as the fresh catalyst (table 5.9).

Table 5.9: Yield[a] of product[b] without and after regeneration of the catalyst

Run	Time (h)	Yield without regeneration (%)	Yield after regeneration (%)
Fresh	6	97	-
1st	6.5	94	94
2nd	6.5	92	93
3rd	7	89	93
4th	7	87	92
5th	7.5	87	90

[a] isolated yield of product.
[b] Reactions were carried out using *p*-nitrobenzaldehyde (1 mmol) as the substrate at room temperature in MeCN and H_2O_2 (3 mmol) as the oxidant using 5 wt% of the TSV.

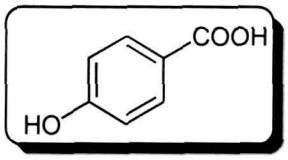
However, calcination (at 450 °C) of the catalyst helps in decreasing the leaching of the vanadium from the surface of the catalyst but the activity of the catalyst for the oxidation of the aldehyde decreases. Gas chromatographic analysis of the product mixture of the oxidation of *p*-nitrobenzaldehyde showed 30% of ester and 7% of acid after 6 hours when calcined catalyst was used.

5B. 3 Conclusions

In summary, we have developed an efficient catalytic process for the oxidation of aldehyde. We anticipate that the simplicity and the catalytic nature of the protocol will make it appealing to the synthetic chemist, particularly those who are practicing the green oxidation process.

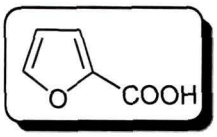
5B. 4 Spectral Data

4-Hydroxybenzoic acid (entry 3, table-5.6)



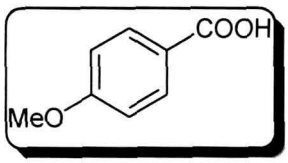
FT-IR (KBr): 3375, 1682, 1592, 1422, 933 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.24, 7.76-7.79 (d, *J*=12 Hz, 2H), 6.80-6.82 (d, *J*= 8Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.64, 121.05, 132.05, 162.09, 167.70.

Furan-2-carboxylic acid (entry 9, table-5.6)



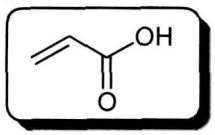
FT-IR (KBr): 1718, 3025; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.50-7.61(m, 2H), 7.62(dd, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): 113.7, 120.4, 145.8, 147.6, 162.14.

4-Methoxybezoic acid (entry 5, table-5.6)



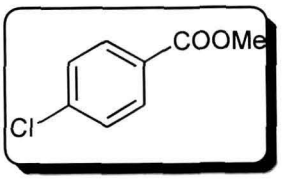
FT-IR (KBr): 1710, 2980; ^{1}H NMR (400 MHz, DMSO-d_6): 3.67 (s, 3H), 6.87-6.89 (d, *J*=8Hz, 2H), 7.92-7.94(d, *J*=8Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): 54.5, 114.3, 132.3, 164.2, 167.4.

Acrylic acid (entry 12, table-5.6)



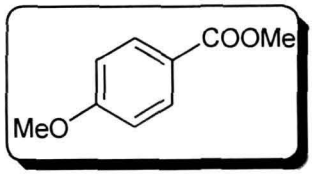
FT-IR (KBr): 3507, 1732, 1406, 1289, 1185, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.40 (s, 1H), 6.48-6.53 (m, 1H), 6.13-6.14 (m, 1H), 5.87-5.97 (m,1H); ^{1}H (100 MHz, $CDCl_3$): δ 33.58,133.10, 166.14.

4-Chloro-benzoic acid methyl ester (entry 1, table-5.6)



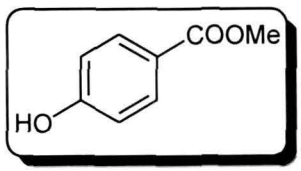
^{1}H NMR (400 MHz, $CDCl_3$): 3.92 (s, 3H), 7.44-7.46 (d, *J*=8Hz, 2H), 8.02-8.04 (d, *J*=8Hz, 2H). ^{13}C NMR (100 MHz, CDl_3): 52.13,129, 131.75, 140.4, 169.4.

4-Methoxy-benzoic acid methyl ester (entry 5, table-5.6)



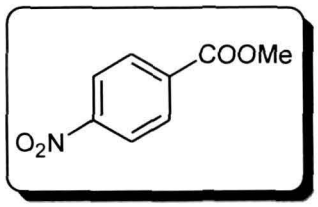
^{1}H NMR (400 MHz, $CDCl_3$): 3.94 (s, 3H), 8.11-8.17 (dd, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): 55.68, 113.8, 121.74, 132.42, 164.11, 171.61.

4-Hydroxy-benzoic acid methyl ester (entry 3, table-5.6)



FT-IR (KBr): 3300, 2910, 1680, 775 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.89-7.91 (d, J=8Hz, 2H), 6.87-6.89 (d, J=8Hz, 2H), 5.44 (brs, 1H), 3.92 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$):δ 51.2, 115.3, 121.5, 132.1, 162.4, 165.7.

4-Nitro-benzoic acid methyl ester (entry 4, table-5.6)



FT-IR (KBr): 3100, 2875, 1720, 1512, 1387, 722cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (dd, 4H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 52.7, 124.2, 131.7, 134.5, 153.4, 166.4.

5B. 5 Reference and Note

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33. Regeneration of the catalyst: To a solution of $VO(acac)_2$ (265 mg) in anhydrous THF (50 mL), the recovered catalyst (1 g) was added stirred at room temperature under nitrogen atmosphere. The solid catalyst was filtered and dried in the vacuum.

Section 5C

A green route to tribromides: an experimental and theoretical insight into reactivity of organicammonium tribromides (OATBs)

Bromoorganics occupy a cardinal position in the domain of organic chemistry [1,2]. They find wide applications in the synthesis of a large number of natural products as well as the manufacture of pharmaceuticals, agrochemicals and numerous industrially valuable chemicals including fire retardants. It is noteworthy that of the various bromoorganics, arylbromides find extensive applications for carbon-carbon and carbon-heteroatom bond forming reactions [3-5]. Electrophilic substitution is the most common method for bromination of organics wherein, the regioselectivity is controlled by the electronic properties of the substituents [6]. For over a century, molecular bromine has been the most commonly and widely used brominating reagent because of being inexpensive and easily available. However, bromine is found to be a very toxic chemical and it is difficult to manipulate it as a brominating reagent [7-10]. Furthermore, substitution reactions involving elemental bromine (Br_2) gives only 50% atom economy and leads to generation of toxic HBr waste [11]. Due to such toxicity associated with elemental bromine, researchers have been searching for alternative brominating reagents and methods for bromination of organics. Apart from such toxicity issues it is very difficult to maintain the stoichiometry of the reagent when elemental bromine is used as a brominating reagent. The concerns expressed above led to the development of a number of new brominating reagents over the years.

Developing greener protocols for the synthesis of commercially important compounds is a major challenge in chemical research. Therefore, revisiting the traditional methods for organic and inorganic synthesis by introducing greener reagents or mild and efficient catalysts are much sought after in academia and industrial research.

To overcome the problems associated with the use of molecular bromine, a number of alternative strategies have been devised. One of such strategies is to generate bromine *in situ* by oxidation of bromide. The oxidizing agents and the bromide sources used for the purpose include HBr-*tert*-bytylhydroperoxide (TBHP) [12], HBr/DMSO [13], BuOBr/Zeolite [14], NaBr/dimethyldioxirane [15], LiBr-$(NH_4)_2S_2O_8$ [16] and LDH-$WO_4/H_2O_2/Br_2$ [17] etc. In spite of such vast literature reports, the industrial applicability of such processes is restricted by the use of toxic

and expensive reagents/catalysts, volatile organic solvents, low yield, lack of regioselectivity and discharge of HBr waste [18-29].

Apart from such *in situ* generation of bromine, there are latent brominating reagents like *N*-bromosuccinimide for allylic bromination, 2,4,4,6-tetrabromo-2,5-hexadiene-1-one (TBCD) for the monobromination with para selectivity, but their preparation still needs use of elemental bromine [30-33].

Since early eighties, our group has been working on peroxo metal and non-metal chemistry where H_2O_2 activated by various metals like V(V), Mo(VI), W(VI), Ti(IV) and non-metals like B, P, etc. are used. While trying to ligate bromide with peroxovanadates, we ended up with the isolation of tribromides (Br_3^-) using organic ammonium cation. Subsequently, environmentally benign synthesis of new solid brominating agents by the reaction of V_2O_5, aqueous H_2O_2 and KBr was reported [34]. In continuation of this work, subsequently we extended the use of this philosophy to the extraction of bromide from sea-water [35]. The versatility of the protocol is demonstrated with different organic counter cations [36] that modulate the properties of the tribromides. Until then, tribromide did not receive much attention, even though it is a greener alternative for hazardous bromine. However, thereafter, scientific workers realized their potentiality and now they find a respectable position in terms of their applicability as reagents as well as catalysts in various organic reactions [37-41].

Following the aforementioned strategy a series of (second generation) brominating reagents has been developed by our group which includes tetramethyl ammonium tribromide (TMATB), tetrabutyl ammonium tribromide (TBATB), tetraethyl ammonium tribromide (TEATB), cetyltrimethyl ammonium tribromide (CTMATB), pyridine hydrobromide perbromide (PHPB) and benzyltriethyl ammonium tribromide (BTEATB) [42]. A variety of brominations have also been carried out by us and others by using these reagents. Significantly, it was observed that less usual bromination, e.g. bromination of imidazoles has not been very successful with many of these tribromides. It was then considered worthwhile to develop newer organic ammonium tribromides with varying counter cations and study their reaction profiles focusing on such less usual bromainations.

Here in this thesis, two new tribromides, namely, terapropyl ammonium tribromide ($C_{12}H_{28}NBr_3$,TPATB) and tetradecyldecyltrimethyl ammonium tribromide ($C_{17}H_{39}NBr_3$,TDTMATB) have been introduced. These two tribromides have been characterized by a variety of physico-chemical analysis. Studies have been done on

the relative reactivity of the different tribromides that have been synthesized by us. Some less usual brominations have been observed with tetrapropylammonium tribromide (TPATB). The observed unusual reactivity of TPATB has been rationalized on the basis of density functional theory (DFT).

5C. 1 Experimental

a. General: All the reactions were conducted in oven-dried glasswares. Reagents and solvents were used as purchased. All the products were recrystallized from acetonitrile. Melting points were recorded in a Büchi B-545 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400 MHz and Varian 400 MHz spectrophotometers. Chemical shifts are reported in (ppm) relative to TMS (^{1}H and ^{13}C) internal standards. IR spectra were recorded in KBr with a Nicolet Impact 410 spectrophotometer. Elemental analyses were carried out on a Perkin-Elmer 2400 automatic carbon, hydrogen, nitrogen and sulfur analyzer. The X-ray data were collected at 293 K with Mo K_α radiation (λ= 0.71073Å) on a Bruker Nonious SMART CCD diffractometer equipped with graphite monochromater.

b. Computational details: All calculations were performed with the DMol3 program using BLYP functional and DNP basis set. The size of the DNP basis sets is comparable to that of the Gaussian 6-31G** basis sets, but this numerical basis set is more accurate than a Gaussian basis set of the same size. The Fukui functions were evaluated using Hirshfeld population analysis (HPA) and Mulliken population analysis (MPA) schemes. The integration grid referred to as FINE in the software program has been used for optimization of the complexes.

5C. 2 Synthesis of Tetrapropylammonium Tribromide (TPATB), $(C_3H_7)_4NBr_3$

Two different methods have been developed for the synthesis of TPATB

a. Method-I

In a typical synthesis, 0.03 g (0.16 mmol) of vanadium pentoxide, V_2O_5 was added to 3 mL (26.50 mmol) of 30% hydrogen peroxide, H_2O_2, taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred

magnetically at 0-5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. A solution of 2.38 g (20 mmol) of potassium bromide, KBr and 2.66 g (10 mmol) of tetrapropylammonium bromide (TPAB) dissolved in 35 mL of water was added. To this, 40 mL of 1M sulphuric acid (H_2SO_4) was added in small portions. Magnetic stirring was continued for a further period of 2h at ice-water temperature. The product thus formed was isolated by suction filtration using Whatman No. 42 filter paper. The compound was then dried in a vacuum desiccator using anhydrous calcium chloride, $CaCl_2$, as desiccant. The product was obtained as bright yellow micro-crystals. The yield of the product was 4.5 g (88.3 %). m.p. 120 °C.

b. Method-II

In a typical example molybdic acid monohydrate, $H_2MoO_4 \cdot H_2O$ (0.16 mmol, 0.03g), potassium bromide, KBr, (20 mmol, 2.38 g) and tetrapropylammonium bromide (TPAB) (10 mmol, 2.66 g) were powdered separately, mixed together smoothly and thoroughly. The whole content was transferred to a boat kept on an ice-water bath and 30% hydrogen peroxide, H_2O_2 (26.50 mmol, 3 mL) was added drop wise with continuous grinding for 15 min, followed by drop wise addition of H_2SO_4 (1.55 mL, 10M). The whole was stirred smoothly with a glass rod for 10 min and then at room temperature for 30 min. An exothermic reaction set in to form orange-yellow crystalline tetrapropylammonium bromide (**TPATB**). The compound was dried over fused $CaCl_2$ and extracted with ethyl acetate by dissolving in a minimum amount of solvent followed by filtration through Whatman No. 42 filter paper. Aqueous phase, if present, could be removed using anhydrous sodium sulphate. The organic layer was concentrated to get yellow-orange **TPATB**, which was recrystallized from acetonitrile. Yield: 4.3 g (85.3%).

5C.3 Synthesis of Tetradecyltrimethylammonium tribromide (TDTMATB), $C_{17}H_{39}NBr_3$

a. Method-I

In a typical synthesis, 0.03 g (0.16 mmol) of vanadium pentoxide, V_2O_5 was added to 3 mL (26.50 mmol) of 30% hydrogen peroxide, H_2O_2, taken in a pre-cooled 250 mL beaker (*Care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic*). The reaction mixture was stirred

magnetically at 0-5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. A solution of 1.85 g (15.5 mmol) of potassium bromide, KBr and 2.10 g (7.5 mmol) of tetradecyltrimethyl bromide (TDTMATB), dissolved in 35 mL of water was added. To this, 40 mL of 1M sulphuric acid (H_2SO_4) was added in small portions. Magnetic stirring was continued for a further period of 2h at ice-water temperature. The product thus formed was isolated by suction filtration using Whatman No. 42 filter paper. The compound was then dried in a vacuum desiccator using anhydrous calcium chloride, $CaCl_2$, as desiccant. The product was obtained as bright yellow micro-crystals. Yield 3.8 g (96.2 %). m.p. 67 °C

b. Method-II

In a typical example molybdic acid monohydrate, $H_2MoO_4 \cdot H_2O$ (0.16 mmol,0.03g), potassium bromide, KBr, (20 mmol, 2.38 g) and tetradecyltrimethylammonium tribromide (10 mmol, 2.80 g) were powdered separately, mixed together smoothly and thoroughly. The whole content was transferred to a boat kept on an ice-water bath and 30% hydrogen peroxide, H_2O_2, (26.5 mmol, 3 mL) was added drop wise with continuous grinding for 15 min, followed by drop wise addition of H_2SO_4 (15.5 mL, 1M). The whole was stirred smoothly with a glass rod for 10 min and then at room temperature for 30 min. An exothermic reaction set in to form orange-yellow crystalline tetradecyltrimethylammonium tribromide **(TDTMATB)**. The compound was dried over fused $CaCl_2$ and extracted with ethyl acetate by dissolving in a minimum amount of solvent followed by filtration through Whatman No.42 filter paper. Aqueous phase, if present, could be removed using anhydrous sodium sulphate. The organic layer was concentrated to get yellow-orange **TDTMATB**, which was recrystallized from acetonitrile. Yield: 3.3 g (64%).

5C.4 Typical Procedure for Bromination of Organic Substrates using TPATB

a. Bromination of Styrene

An amount of 0.10 g (1 mmol) styrene was taken in a rotary bottle, added 6 mL dichloromethane (DCM) and allowed to stir using magnetic stirrer and a magnetic needle. Then 0.46 g (2 mmol) of TPATB was added to the stirring solution. The reaction was allowed to stir at room temperature and the progress of the reaction was monitored by TLC. The reaction was allowed to stir for about 45 min. The product

was extracted with ethyl acetate. The extract was dried using anhydrous Na_2SO_4. Ethyl acetate was removed with the help of rotary evaporator and the residue was purified by column chromatography. The residue was run on silica gel of mesh 60-120 with 1% ethyl acetate-hexane to get the corresponding pure brominated product, 1-(1,2-dibromo)ethyl benzene in solution with the solvent mixture. Then solvent was removed using rotary evaporator to get solid product. The isolated yield of the product was ~100% for this reaction (scheme-5.5).

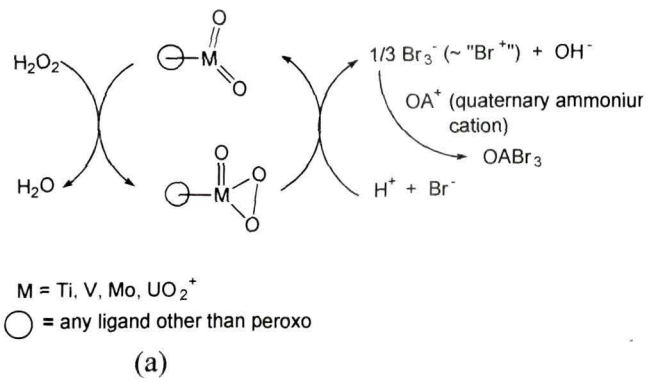
Scheme 5.5: Bromination of styrene by TPATB

70%

Scheme 5.6: Bromination of imidazole with TPATB

5C. 5 Results and Discussion

Peroxometal based (V, Mo, W) oxidation of bromide to tribromide with H_2O_2 has lead to isolation of several tribromides, e.g. TMATB, TEATB, TPATB, TBATB, BTEATB, TDTMATB, and CTMATB [42]. Unlike traditional methods the use of bromine and HBr is completely avoided in their synthesis. Both solid and liquid phase syntheses of tribromides were developed to provide easy access to the commercially important organicammonium tribromides (OATB). The proposed mechanism of the reaction leading to OATB is depicted in scheme 5.7(a).



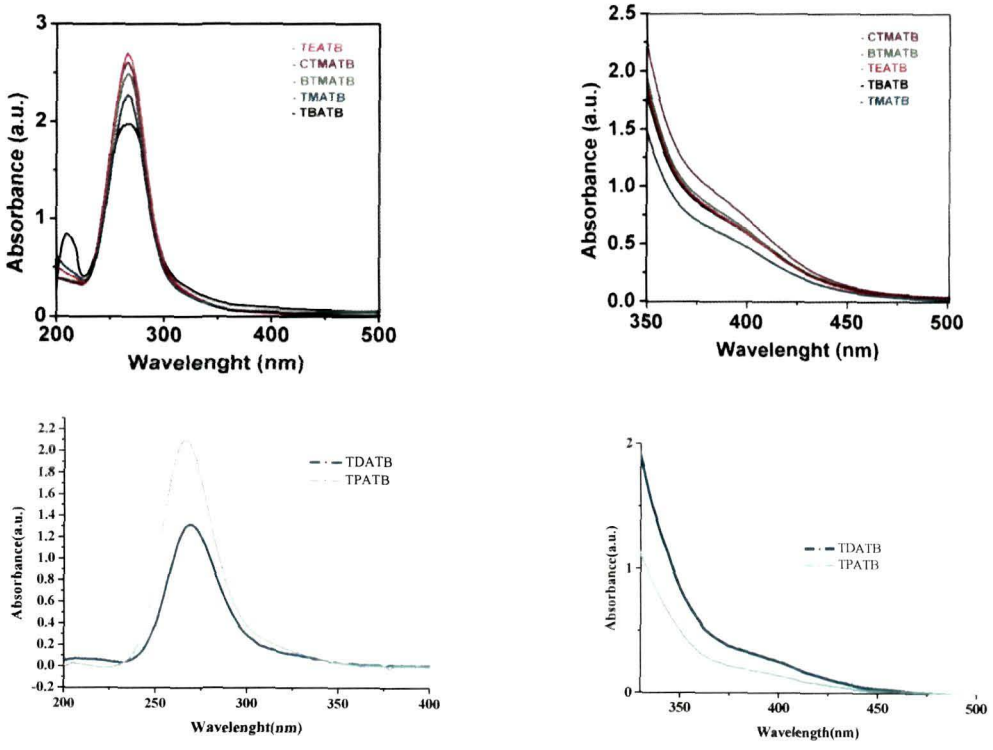
(b)

Scheme 5.7: (a) Peroxo-metal catalyzed synthesis of **OATBs** (b) Crystals of TPATB

According to the proposed mechanism, VO_2^+, for example, serves as a functional mimic of VBrPO (vanadium bromoperoxidase) which coordinates with one or two equivalents of H_2O_2 in solution forming $VO(O_2)^+$ and/or $VO(O_2)_2^-$ species and both of them are capable of oxidizing bromide to HOBr ⇆ Br_2 ⇆ Br_3^-. The Br_3^- thus formed can be isolated as organicammonium tribromide. Alternatively, in presence of an appropriate organic substrate in the reaction the corresponding brominated product is formed.

The tribromides TBATB, BTEATB, CTMATB, TEATB, TMATB, TPATB and TDTMATB are all bright yellow or orange in color. Recrystallization from acetonitrile gives deep orange crystals (scheme-5.7 (b)). All of them have moderate to high solubility in the common organic solvents. The tribromides have a very long shelf life too. They remain stable for months. Organic ammonium tribromides are thus known as the store house of bromine. However, TEATB and TMATB are less stable than other tribromides. Their stability can be monitored by the determination of bromine contents periodically and recording melting points from time to time.

Solution electronic spectra of the tribromides show characteristic signature at *ca.* 265 nm with a shoulder at *ca.* 385 nm due to the transitions σ-σ* and π-π*, respectively. The tribromides give values in the range 267–269 nm and 380–400 nm, (figures 5.3)[43,44].



Figures 5.3: UV-visible absorbtion of QATBs at around 267 nm and 380 nm

For a linear tribromide (Br_3^-), three vibrational modes, ν_{sym} (ν_1), ν_{asym} (ν_3) and bending (ν_2) are expected in the far-IR region [45]. Of the three modes ν_1 and ν_3 occur at *ca.* 165 cm^{-1} and *ca.* 195 cm^{-1}, respectively, while the bending mode ν_2 generally appears at a far low value of *ca.* 50 cm^{-1}. In the present vibrational spectroscopic experiments ν_1 and ν_3 have been observed in the range 145–172 cm^{-1} and 185–192 cm^{-1} in complete agreement with those expected for a linear Br_3^- species (figure 5.4, table 5.10). Unfortunately, owing to the instrumental limitations the region of the peak corresponding to ν_2 mode (at *ca.* 50 cm^{-1}) could not be covered.

Table 5.10: Structurally significant IR and electronic spectral bands of tribromides

Compounds (QATBs)	IR bands (cm^{-1})	UV-visible (λ, nm) (ε, $M^{-1}cm^{-1}$)
TBATB ($C_{16}H_{36}NBr_3$)	171(s), 191(s)	267 (49000),400 (150)
BTEATB ($C_9H_{16}NBr_3$)	156(s), 195(s)	268 (51000),385(152)
CTMATB ($C_{19}H_{42}NBr_3$)	152(s), 203(s)	269 (51500),385(155)
TEATB ($C_8H_{20}NBr_3$)	162(s), 192(s)	269 (52000), 390(150)
TMATB ($C_4H_{12}NBr_3$)	146(s), 188(s)	269 (50500),380(149)
TPATB($C_{12}H_{28}NBr_3$)	170(s), 191(s)	269(51000), 385(155)
TDTMATB($C_{17}H_{39}NBr_3$)	153(s), 195(s)	268(51500), 386(150)

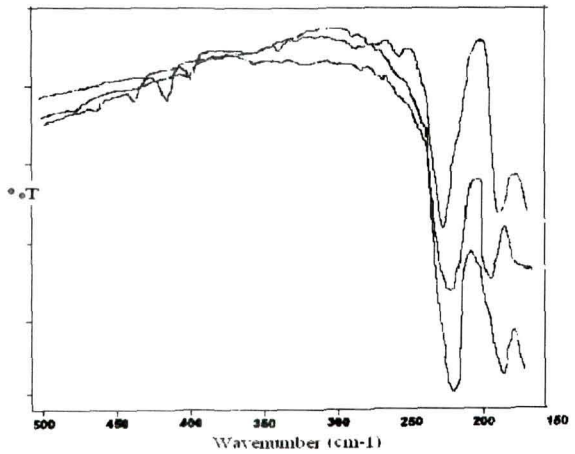


Figure 5.4: Representative far-IR spectra of TBATB, CTMATB and TMATB

Single crystal X-ray structures of TBATB, TPATB, BTEATB, TDTMATB, and CTMATB have been determined. The ORTEP diagrams of these tribromides are shown in figure 5.5. The crystal data and structure refinement results are incorporated in table 5.11. TBATB, TDTMATB and CTMAB crystallize in monoclinic system, whereas TPATB and BTEATB crystallize in triclinic and orthorhombic systems, respectively.

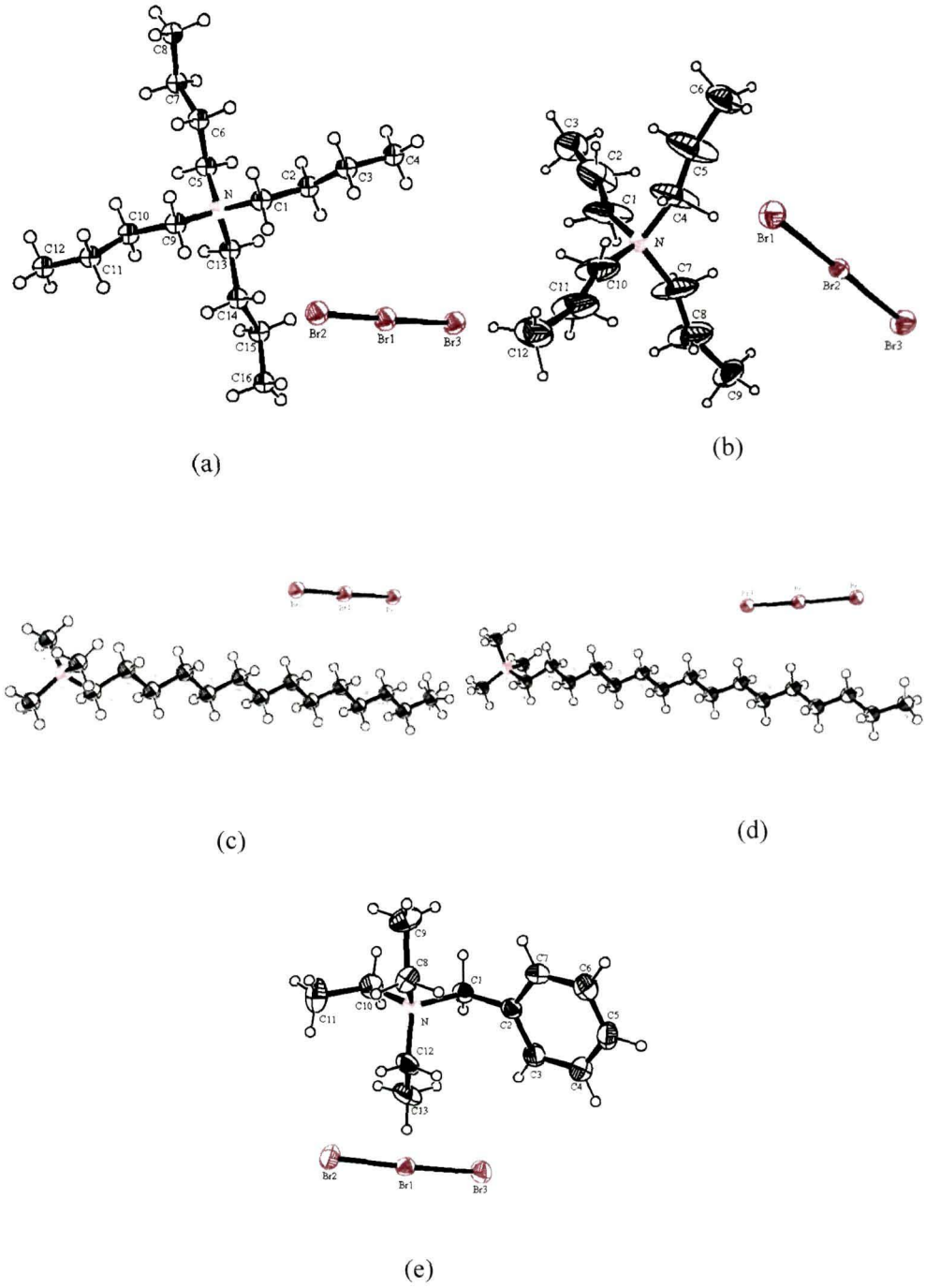


Figure 5.5: ORTEP diagrams of (a) TBATB (b) TPATB (c) TDTMATB (d) CTMATB and (e) BTEATB

Table 5.11: Crystallographic details of TPATB, TBATB, TDTMATB, CTMATB and BTEATB

Crystal data	TBATB(**1**)	TPATB(**2**)	TDTMATB(**3**)	CTMATB(**4**)	BTEATB(**5**)
Formula	$C_{16}H_{36}NBr_3$	$C_{12}H_{28}NBr_3$	$C_{17}H_{39}NBr_3$	$C_{19}H_{42}NBr_3$	$C_{13}H_{22}NBr_3$
Formula weight	482.19	426.08	497.19	524.27	432.00
Temp (K)	296(2)	296(2)	293(2)	273(2)	296(2)
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	C2/c	P-1	P2(1)/m	P2(1)/m	P2(1)2(1)2(1)
Z	4	2	3	2	4
a, Å	12.982(7)	7.825(9)	7.198(3)	7.177(4)	8.422(4)
b, Å	10.382(6)	8.920(12)	7.499(3)	7.495(4)	10.132(4)
c, Å	16.242(8)	13.175(16)	21.255(9)	23.152(15)	19.475(9)
α /°	90.000	90.110(9)	90.000	90.000	90.000
β/°	93.921(3)	98.707(8)	92.354(2)	96.757(4)	90.000
γ /°	90.000	90.018(9)	90.000	90.000	90.000
V, A^3	2184.000(2)	909.00(2)	1146.290(8)	1236.770(12)	1661.900(13)
μ (mm^{-1})	5.536	6.639	5.276	4.894	7.264
R	0.032	0.079	0.033	0.039	0.031
wR2	0.069	0.207	0.077	0.102	0.053
GoF	1.009	0.871	0.981	1.071	0.924

Tribromides are known to be capable of bromination of organic substrates and do most of the job what molecular bromine does. It is expected that the counter cation of tribromide anion might change its reactivity, due to which number of tribromides have been synthesized with different cations (organic as well as inorganic). The variation in reactivity might have some relation with the bond angle (∟Br-Br-Br) and bond length (Br-Br). Moreover, cation like cetylammonium acts as a phase transfer agent in the reaction medium. The bond angles and Br-Br distances of these tribromides are summarized in table 5.12. Notably, TBATB shows equal bond lengths of two Br-Br bonds and a linear structure with ∟Br-Br-Br = 180^0. Although the two

Br-Br bond distances are almost similar, the bond angle of BTEATB is 174.75^0. In case of TPATB, TDTMATB, and CTMATB the bond angles are found to be 179.38^0, 179.07^0 and 179.03^0, respectively, which are close to linearity. The two Br-Br bond distances in TPATB, TDTMATB and CTMATB are not equal.

Table 5.12: Selected bond angles and bond lengths of tribromides

Parameter	TBATB	TPATB	TDTMATB	CTMATB	BTEATB
Br_1-Br_2 (Å)	2.539	2.517	2.625	2.623	2.531
Br_1-Br_3 (Å)	2.539	2.530	2.467	2.462	2.539
Br_2-Br_1-Br_3 (^{0})	180.000	179.380	179.030	179.070	174.750

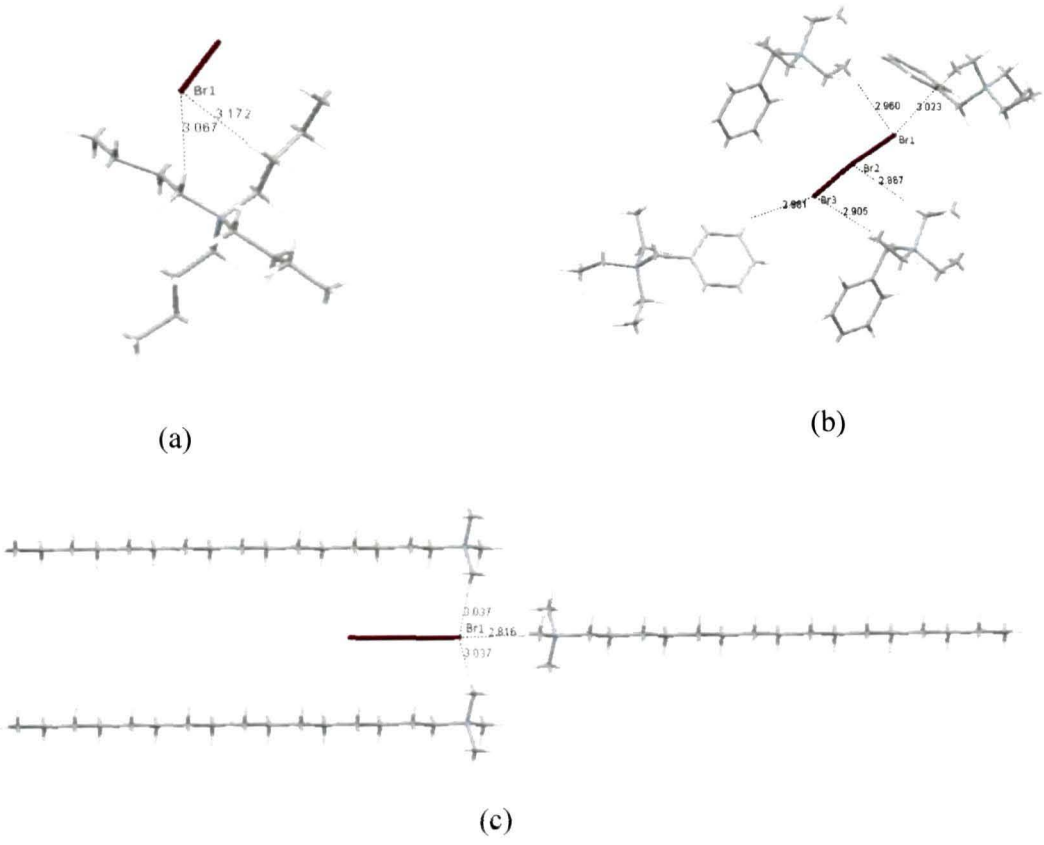


Figure 5.6: Different weak interactions between H and Br in (a) TBATB (b) BTMATB and (c) CTMATB. Numbers of weak interactions and distances are depicted in the figure

Apart from the differences in bond angles (∟Br-Br-Br) and bond distances (Br-Br), several weak H-Br hydrogen bonding are observed from the single crystal structure (figure 5.6). The H-Br distance varies from 2.816Å to 3.017Å. This interaction

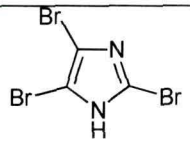
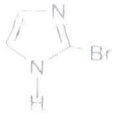
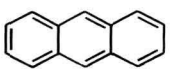
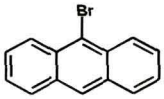
decreases the electron density on the bromine atom. The number of weak interactions in BTEATB is five while TDTMATB and CTMATB have three such weak interactions but TBATB and TPATB possess only two. The H-Br distances are comparatively shorter in BTEATB. Shorter H-Br distance implies a stronger hydrogen bonding interactions in case of BTEATB. From these observations we predict BTEATB to be the most reactive tribromide in the group.

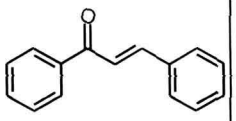
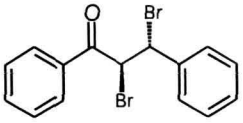
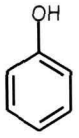
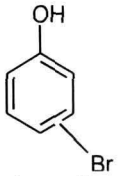
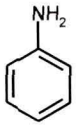
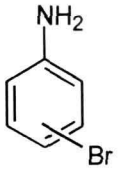
5C. 6 Some representative examples of bromination with organic ammonium tribromide

Tribromide has already been exploited as an alternative to elemental bromine. These reagents have been gaining remarkable popularity in organic transformations not only as reagent but also as catalyst [46-50]. Several reactions other than bromination have also been reported in literature.

As we mentioned earlier that reactivity of tribromides might be tailored by changing the counter cation. Hence, a comparative study of different tribromides has been done in terms of yield towards bromination of organic substrates. The results that we have obtained are shown in table 5.13.

Table 5.13: Comparative study of various tribromides towards bromination of organic substrates

Substrate	Reagent	Sub: TB	Time	Product	Yield (%)
	TMATB TEATB TBATB CTMATB BTEATB TPATB TDTMATB	1:1 1:1 1:1 1:1 1:1 1 1:1	3 h 3 h 4 h 3 h 1 h 1.5 h 1 h	  (Monobrominated imidazole is obtained when TPATB used as brominating reagent)	30 29 31 28 32 70 31
	TMATB* TEATB* TBATB CTMATB BTEATB TPATB TDTMATB	1:1 1:1 1:1 1:1 1:1 1:1 1:1	15 min 45 min 2 h 4.5 h 30 min 1.5 h 45 min		87 68 70 87 90 83 90

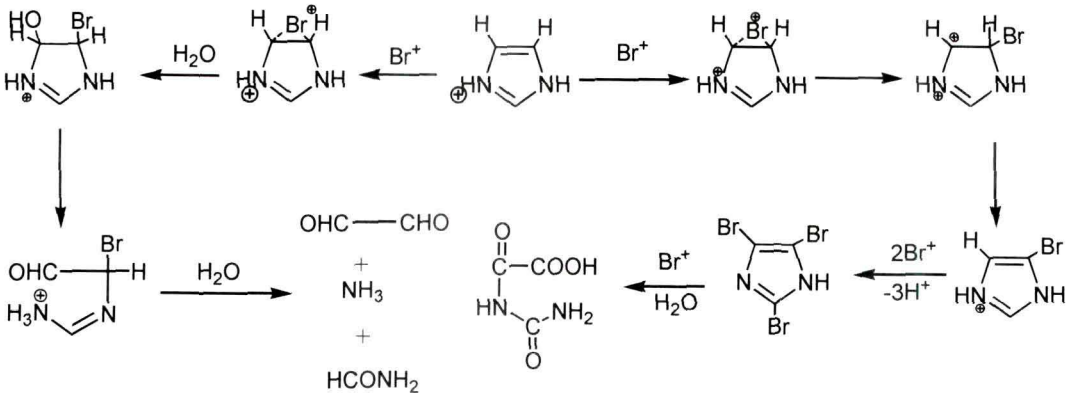
	TMATB TEATB* TBATB CTMATB BTEATB TPATB TDTMATB	1:1 1:1 1:1 1:1 1:1 1:1 1:1	5 h 5 h 5 h 5 h 2 h 5 h 2 h		60 55 65 92 95 90 94
	TMATB* TEATB* TBATB CTMATB BTEATB TPATB TDTMATB	1:1 1:1 1:1 1:1 1:1 1:1 1:1	20 min 5 min 1 h 1.5 h 30 min 45 min 35 min	 (Mixture of *ortho*, *para*, *meta* and di-, tri- bromo phenols are formed) TPATB Gives 85% selectivity for *para* product	70 60 60 70 90 85 89
	TMATB* TEATB* TBATB CTMATB BTETB TPATB DTMATB	1:1 1:1 1:1 1:1 1:1 1:1 1:1	4.5h 3.5h 2.5h 3h 1h 2.5h 1h	 (Mixture of *ortho*, *para*, *meta* and di-, tri- bromo anilines are formed) TPATB Gives 89% selectivity for *para* product	67 65 60 65 92 89 92

*Examples are drawn from U. Borah, PhD thesis, IITG, Sub= Substrate, TB= Tribromide

From the table 5.13 it is interesting to note that unlike other tribromides, TPATB shows some regioselectivity towards the bromination of organics. The most striking result is the monobromination of imidazole.

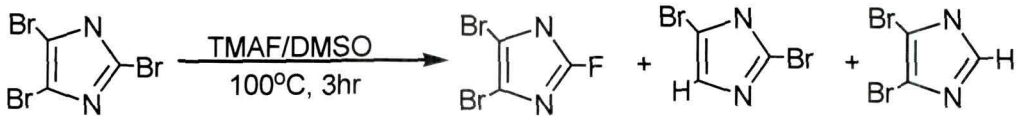
Monobromination of imidazole is a very important and difficult task to achieve because bromination of imidazole by Br_2 gives 2,4,5-tribromo imidazole in presence of chloroform, dichloroethane, etc. as solvent [51]. Monobromination and dibromination of imidazole are very difficult. It has been reported that reaction of imidazole and 4(5)-substituted imidazole with Br_2 or NBS did not give brominated

product and undergo oxidative degradation of heterocyclic ring. The products formed are ammonia, glyoxal (or the corresponding substituted dioxal) (scheme 5.8). The ring degradation of imidazole with bromine is shown below [52].

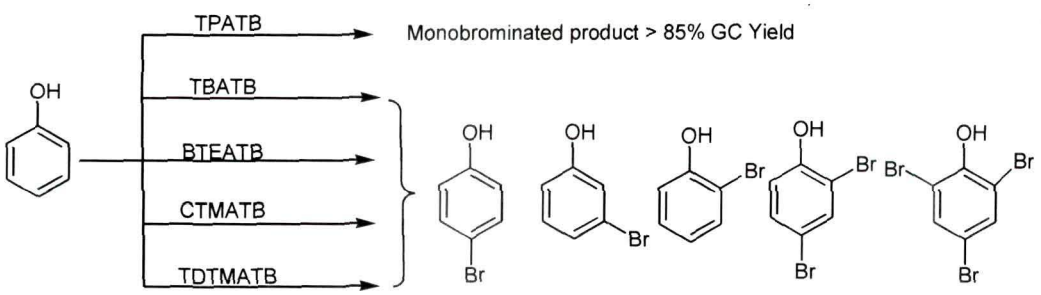


Scheme 5.8: Ring degradation of imidazole in presence of elemental bromine

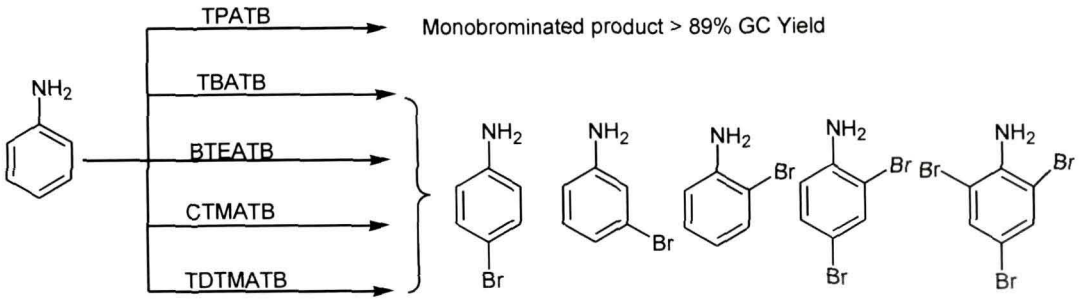
Mono and dibromoimidazole are generally obtained by debromination of tribromo imidazole by tetramethylammonium fluoride (TMAF) in aprotic solvent [53] (scheme 5.9). However, this process is an indirect one and rather lengthy, and the yield is less. Hence direct mono- and dibromination is desirable.



Scheme 5.9: Debromination of tribromo imidazole



Scheme 5.10: Bromination of phenol by various tribromides



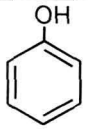
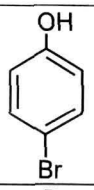
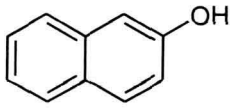
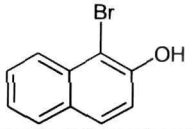
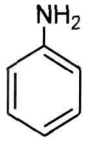
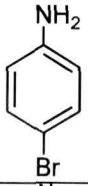
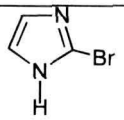
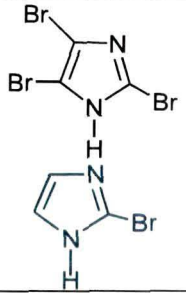
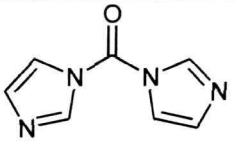
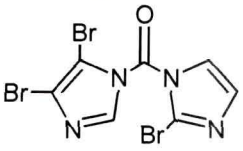
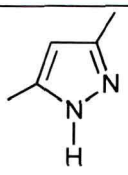
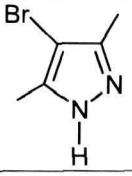
Scheme 5.11: Bromination of aniline by various tribromides

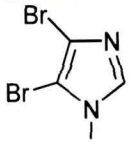
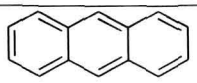
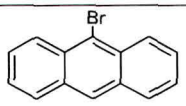
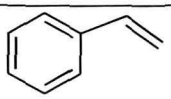
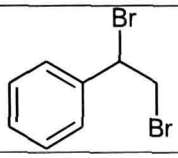
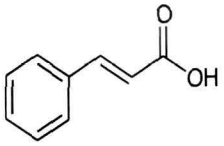
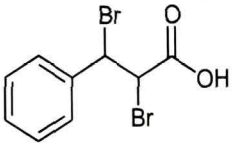
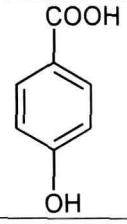
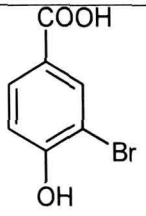
Apart from imidazole, regioselectivity is also observed in the bromination of activated aromatics like phenol and aniline (table 5.13).

While trying to brominate activated aromatics like aniline or phenol with organic ammonium tribromides we observed the formation of a mixture of mono-, di- and tri- brominated products (schemes 5.10 and 5.11). However, maintaining the substrate:tribromide stoichiometry at 1:1 regioselectivity could be achieved to some extent (table-5.13). Interestingly, when TPATB was used as the brominating reagent high degree of *p*-selectivity was observed. The high regioselectivity observed in case of TPATB renders it as important brominating reagent in the organic synthesis. It may be noted, direct *p*-selectivity could not be achieved for the activated aromatics like aniline and phenol by simple brominating reagents. Traditional method involves the derivatization of such activated aromatics e.g. acetylation of aniline to the corresponding acetanilide to achieve *para* selectivity. Such derivatization is not desirable from the "green chemistry" point of view.

To expand the scope of TPATB as brominating reagent a number of reactions were conducted. The specific molar ratios of substrates, reagents, solvent used along with the reaction conditions and percentage yield of the corresponding products are given in table 5.14.

Table 5.14: Application of TPATB as a brominating reagent for the bromination of various organic substrates

Substrate	Substrate: TPATB	Reaction condition	Time	Product	% yield[a]
	1:1	RT, CH_3CN	45 min		85%
	1:1	RT, CH_3CN	40 min		87%
	1:1	RT, CH_3CN	2.5h		89%
	1:1	RT, CH_3CN, $CaCO_3$	1.5 h		70%
	1:2	RT, CH_3CN, $CaCO_3$	2 h		50%
	1:1	RT, CH_3CN, $CaCO_3$	1.5 h		28%
	1:2	RT, CH_3CN, $CaCO_3$	1.5 h		65%
	1:1	RT, CH_3CN	1.5 h		98%

	1:1	RT, CH_3CN, $CaCO_3$	1.5 h		45%
	1:1	RT, DCM	1.5 h		83%
	1:1	RT, DCM	50 min		99%
	1:1	RT, CH_3CN	2 h		43%
	1:1	RT, MeOH-DCM mixture (1:1)	3 h		44%

[a]Isolated Yield

Since all the tribromides that we have synthesized so far are similar from the structural point of view, hence there must be an electronic factor that might be responsible for the reactivity difference, as observed. To rationalize the reactivity of the different tribromides we took help of the density functional theory (DFT) method, which is elaborated in the next section.

5C. 7 Theoretical investigations

DFT has played an important role in determining structure and reactivity of chemical compounds [54-57]. The global reactivity descriptors namely, global hardness (η), global softness (S), electronegativity (χ), chemical potential (μ) and electrophilicity index (ω) introduced within the context of conceptual DFT represent properties of a molecule as a whole [58- 60]. Other type of descriptors are local reactivity descriptors such as local softness ($s(\vec{r})$), Fukui functions ($f(\boldsymbol{r})$) etc., which have attracted considerable interests to describe the relative reactivity and site

selectivity in chemical reactions [60, 61]. Fukui functions, f_k^+ and f_k^-, are evaluated to locate the electrophilic and nucleophilic sites, respectively. In most cases these are found to be successful in explaining experimentally observed trends of reactivity. However, in some systems, atom with high electrophilicity i.e. having higher value of f_k^+ may also show high nucleophilicity i.e. having higher value of f_k^-. Then their ratios 'relative electrophilicity'(f_k^+ / f_k^-), and 'relative nucleophilicity'(f_k^- / f_k^+), expresses the reactivity of atoms in molecules in a better way. We have calculated local reactivity descriptors namely, Fukui functions f_k^+ and f_k^- and their ratio, the relative nucleophilicity (f_k^- / f_k^+) of the bromine atoms of the tribromide molecules to derive their reactivity sequence [62].

The calculated global reactivity descriptors of the tribromide molecules are given in table 5.15. It is seen that the global softness value for BTEATB is maximum indicating the highest reactivity of this reagents among the tribromides. The global softness value represents how soft is a molecule towards and incoming electrophile or a nucleophile. However, the global parameters cannot provide the sites (atoms) which take part in chemical reaction. In order to determine the active sites of the complexes we calculated the Fukui functions (f^+, f^-) and relative nucleophilicity of each atom of the tribromides. The Fukui function value of 'electrophilic attack on the system' of the compounds is shown in figure 5.7. In table 5.16 we present the average Fukui function and relative nucleophilicity values of Br atoms. The relative nucleophilicity values confirm that the BTEATB is the most reactive and TPATB is the least reactive tibromide in the series.

Table 5.15: Energy values of HOMO, LUMO, HOMO-LUMO gap and global reactivity descriptors, chemical hardness and softness of tribromides

MOLECULE	E_{HOMO} au	E_{LUMO} au	$E_{HOMO-LUMO}$ au	HARDNESS au	SOFTNESS au
TBATB	-0.145	-0.049	0.096	0.048	10.422
BTEATB	-0.151	-0.071	0.080	0.040	12.493
CTMATB	-0.151	-0.055	0.096	0.048	10.432
TDTMATB	-0.139	-0.054	0.084	0.042	11.870
TPATB	-0.162	-0.067	0.095	0.048	10.516

Table 5.16: The average Fukui function and relative nucleophilicity values of Br atoms of the complexes

Molecule	f^-	f^+	$f+/f^-$
TBATB	0.39	0.33	0.86
BTEATB	0.32	0.15	0.46
CTMATB	0.35	0.33	0.95
TDTMATB	0.10	0.10	1.02
TPATB	0.32	0.03	0.10

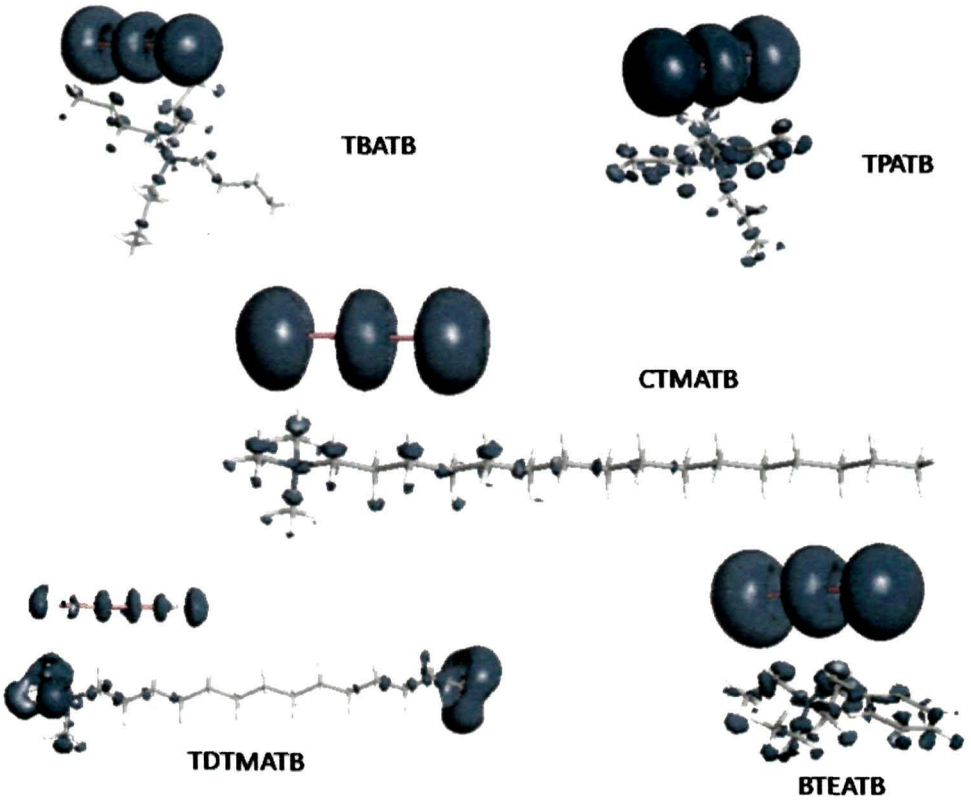


Figure 5.7: Graphical representation of the Fukui function value for 'nucleophilic attack on the system' derived from DFT/GGA/BLYP calculations

5C. 8 Conclusions

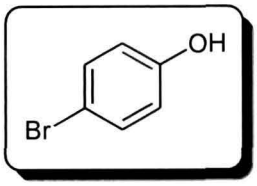
In summary, we have reported the synthesis, structure and properties of structurally diverse OATBs. Two synthetic methods for organicammonium tribromide are described in this chapter. For small scale synthesis, both the methods are effective to get organic ammonium tribromides. However first (Method-I) is preferable for large

scale synthesis of OATBs. The reactivities of TBATB, TPATB, TMATB, CTMATB and BTEATB have been compared. The experimental results are well supported by DFT calculations. BTEATB is found to be more reactive than others OATBs in the series. Both structural and the electronic parameters conforms the high reactivity of the BTEATB.

Remarkably, selective *p*-bromination of activated aromatics e.g. phenol, aniline are achieved by using TPATB as the brominating reagent. Unlike the other tribromides that we have synthesized so far TPATB shows some unusual reactivity towards the bromination of activated aromatics. The most exciting result that was observed using TPATB is the selective monobromination of imidazole. Density functional theory (DFT) implies TPATB to be the least reactive tribromide in the series. Less reactivity of TPATB might be the region behind the selectivity that we observe during bromination of organics. Most interesting aspect of our study is that the important role played by the intermolecular hydrogen bond in determining reactivity of tribromides. Stronger intermolecular hydrogen bonding interaction possible in case of BTEATB decreases electron density over the corresponding Br_3^-, makes it facile to release Br^+.

5C. 9 Physical and Spectral data

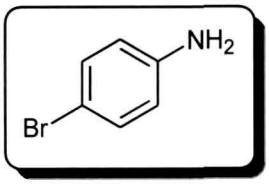
4-Bromo-phenol



Oily liquid.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 5.03 (brs, 1H), 6.70 (d, *J*=8.8 Hz, 2H),7.30 (d, *J*= 7.6 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 113, 117.4, 133.2, 154.4

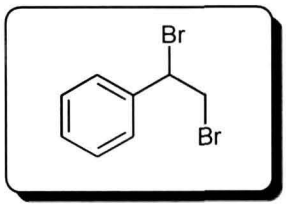
4-Bromo-aniline



Greenish solid. m.p: 58-62 °C

^{1}H NMR (400 MHz, $CDCl_3$):δ 3.65 (brs, 2H), 6.56 (d, *J*=8 Hz, 2H), 7.24 (d, *J*=6.4 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$):δ 110.3, 116.8, 132.1, 145.5.

(1,2-Dibromo-ethyl)-benzene

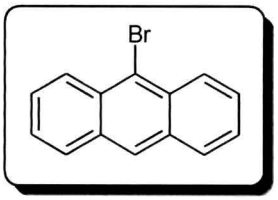


White solid. m.p. 71-73 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.02-4.07 (m, 2H), 5.12-5.15 (t, 2H), 7.36-7.40 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 35.09, 50.94, 127.7, 128.9, 129.28, 138.69

9-Bromo-anthracene

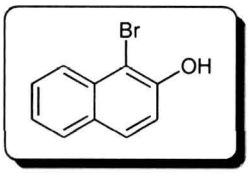


Yellow solid: m.p. 96-100 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.53 (t, 2H), 7.58-7.62 (t, 2H), 7.98-8.0 (d, *J*=8, 2H), 8.44(s, 1H), 8.507-8.509 (d,*J*=13.2, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 122, 125.72, 127.18,127.26,127.71,128.68,130, 132

1-Bromo-naphthalen-2-ol

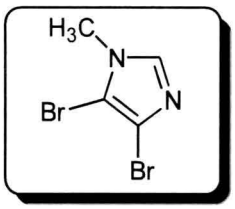


Black Solid. m.p.: 79-80 °C

^{1}H NMR (400 MHz, DMSO-d6): δ 7.23-7.25 (d, *J*=8, 1H), 7.26-7.28(t, 1H), 7.45-7.47(t, 1H),7.75-7.79 (m, 2H), 7.95-7.98 (d, *J*=12,1H), 10.49 (brs, OH)

^{13}C NMR (100 MHz, DMSO-d6):δ 104.79, 118.82, 123.96, 125.26, 128.27, 128.75, 129.17, 129.42, 152.92, 206.99

4,5-Dibromo-1-methyl-1*H*-imidazole

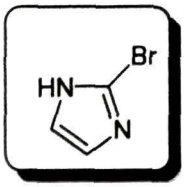


White solid. m.p: 74-78 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s. 1H), 3.65 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.85,116.36,104.75,34.18

2-Bromo-1*H*-imidazole

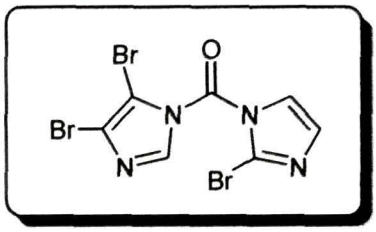


White solid. m.p: 197-202 °C

^{1}H NMR (400MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.6 (s, 1H), 12.35 (bs, 1H)

^{13}C NMR (100MHz, $CDCl_3$): δ 116.18, 114.00, 136.43

(2-Bromo-imidazol-1-yl)-(4,5-dibromo-imidazol-1-yl)-methanone



White solid. m.p: 120-124

^{1}H NMR (400 MHz, DMSO-d6): δ 8.26 (s, 1H), 7.28 (s, 2H)

^{13}C NMR (100 MHz, DMSO-d6): δ 109.21,121.16,135.33

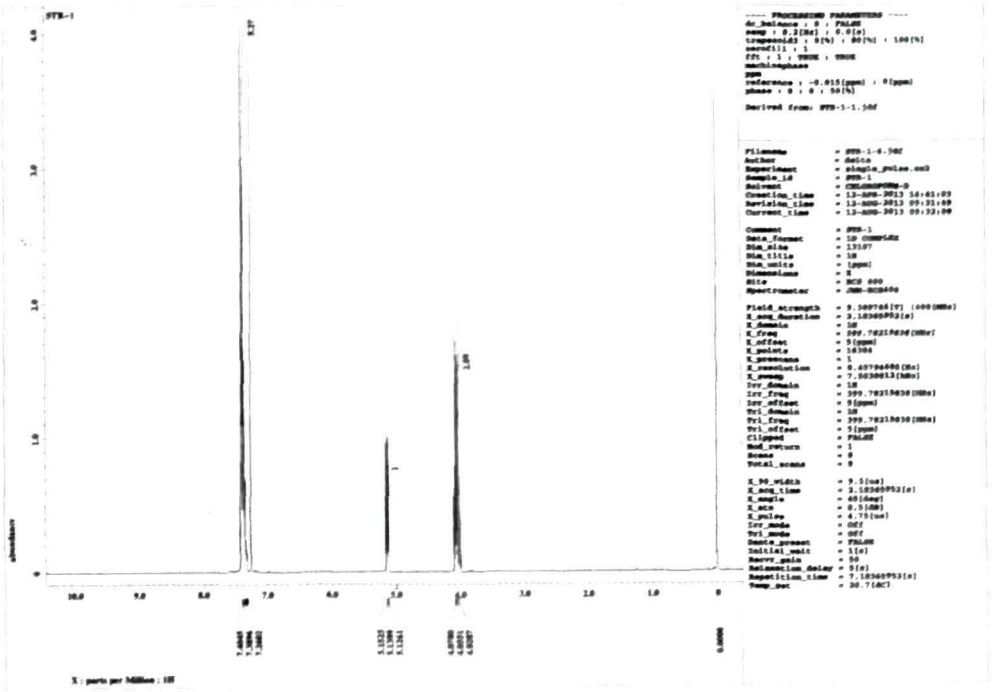


Image 32: ^{1}H NMR spectrum of (1,2-Dibromo-ethyl)-benzene

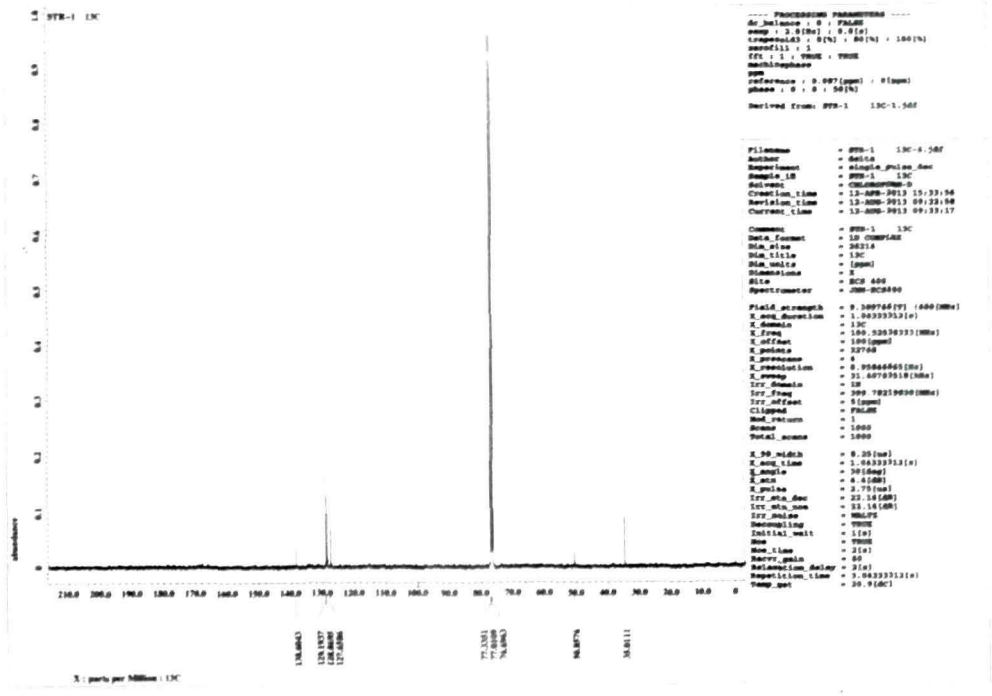


Image 33: ^{13}C NMR spectrum of (1,2-Dibromo-ethyl)-benzene

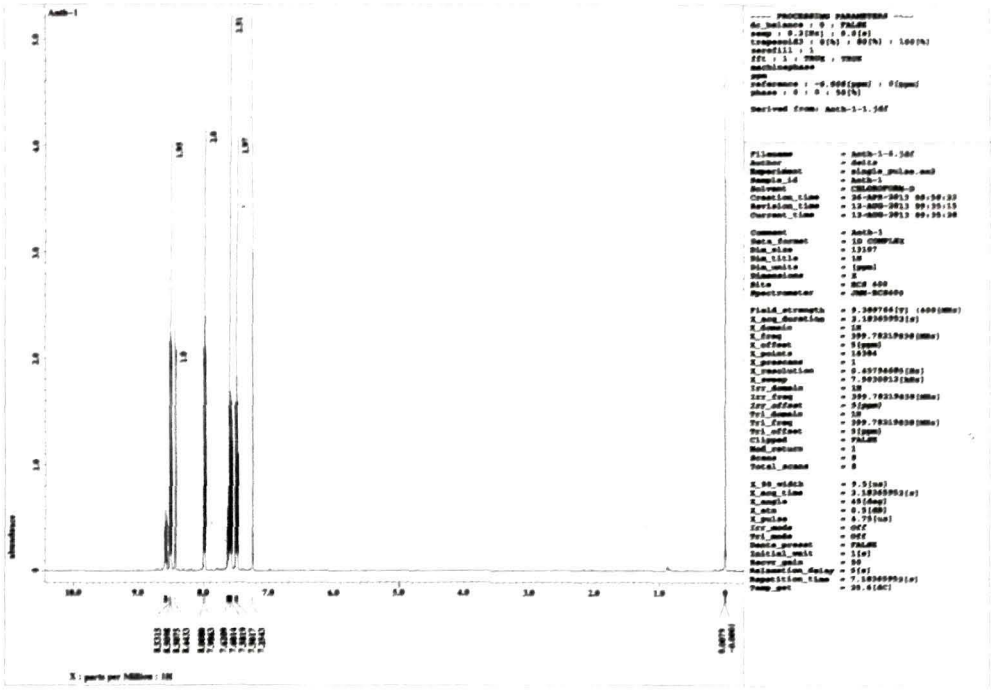


Image 34: ^{1}H NMR spectrum of 9-bromoanthracene

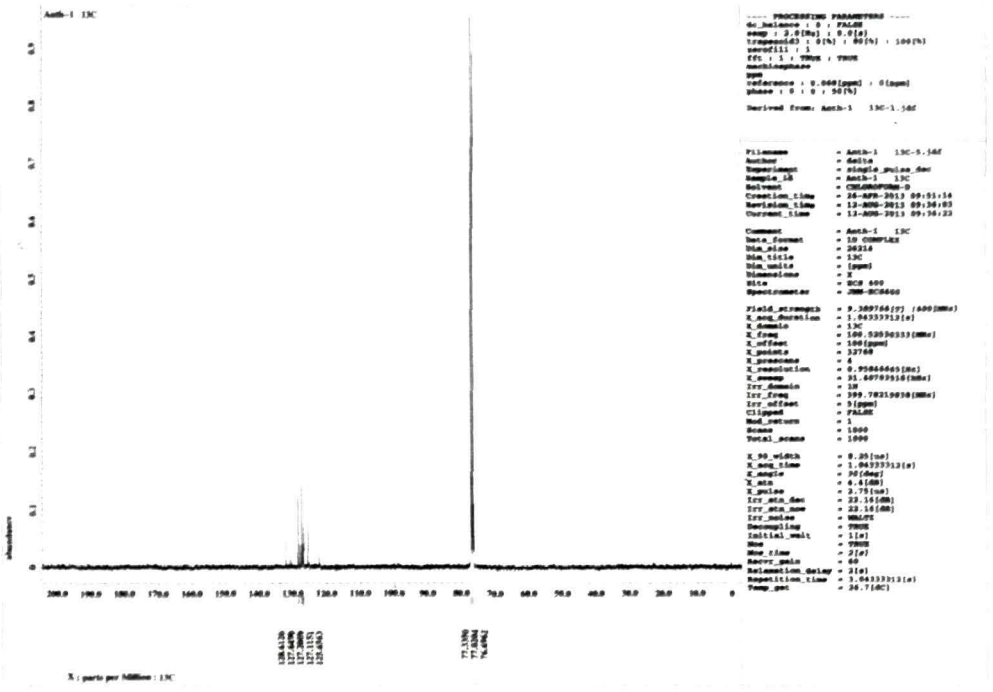


Image 35: ^{13}C NMR spectrum of 9-bromoanthracene

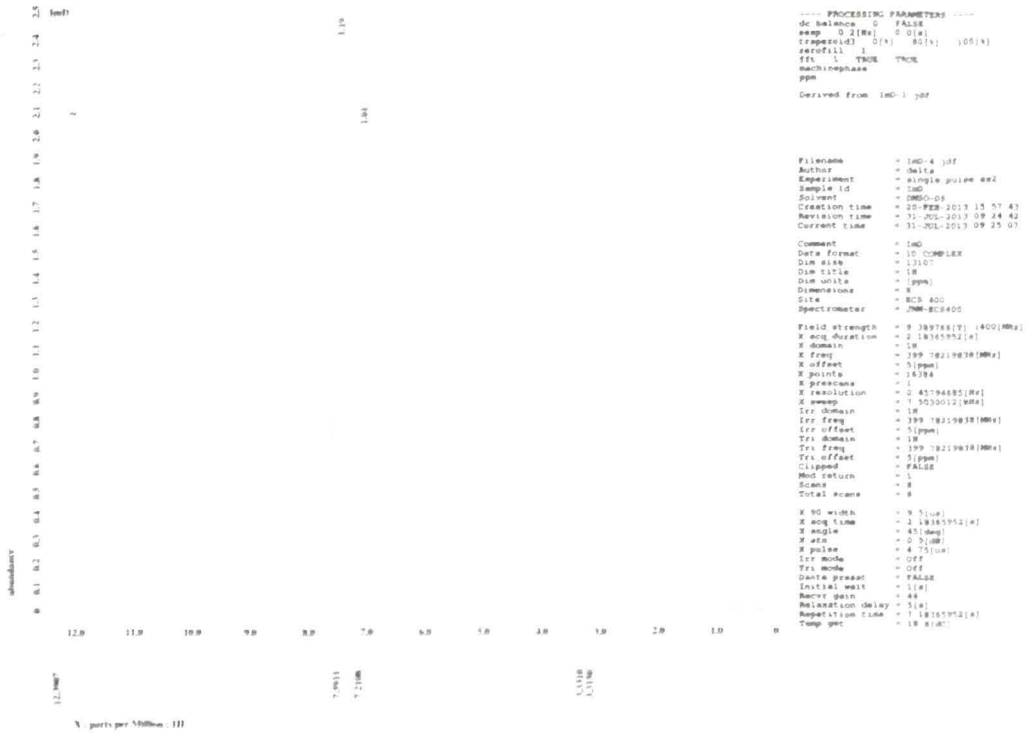


Image 36: ^{1}H NMR spectrum of 2-Bromo-1H-imidazole

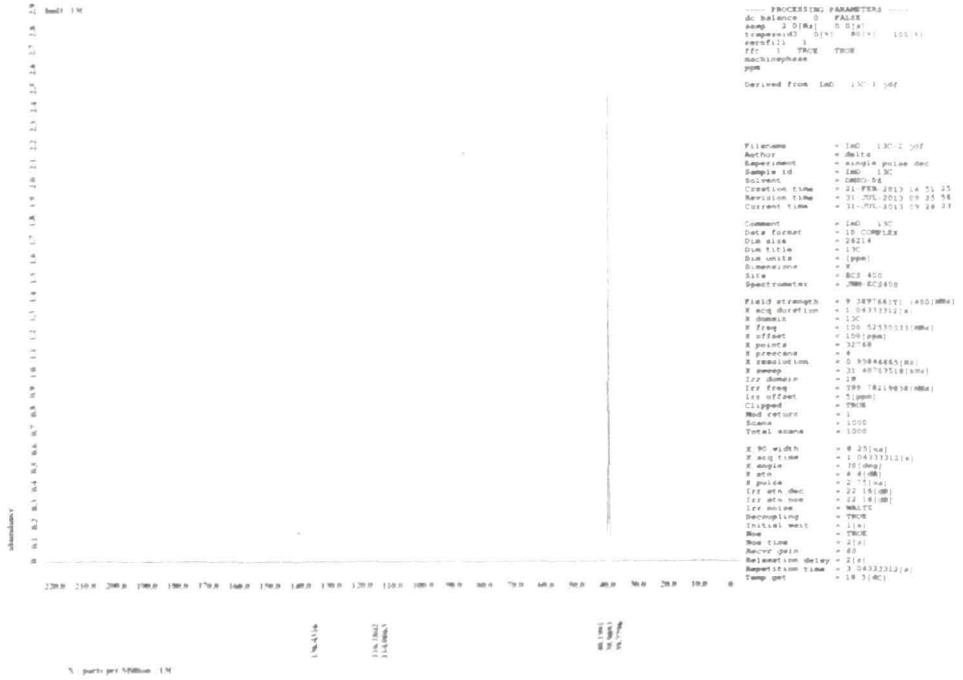


Image 37: ^{13}C NMR spectrum of 2-Bromo-1H-imidazole

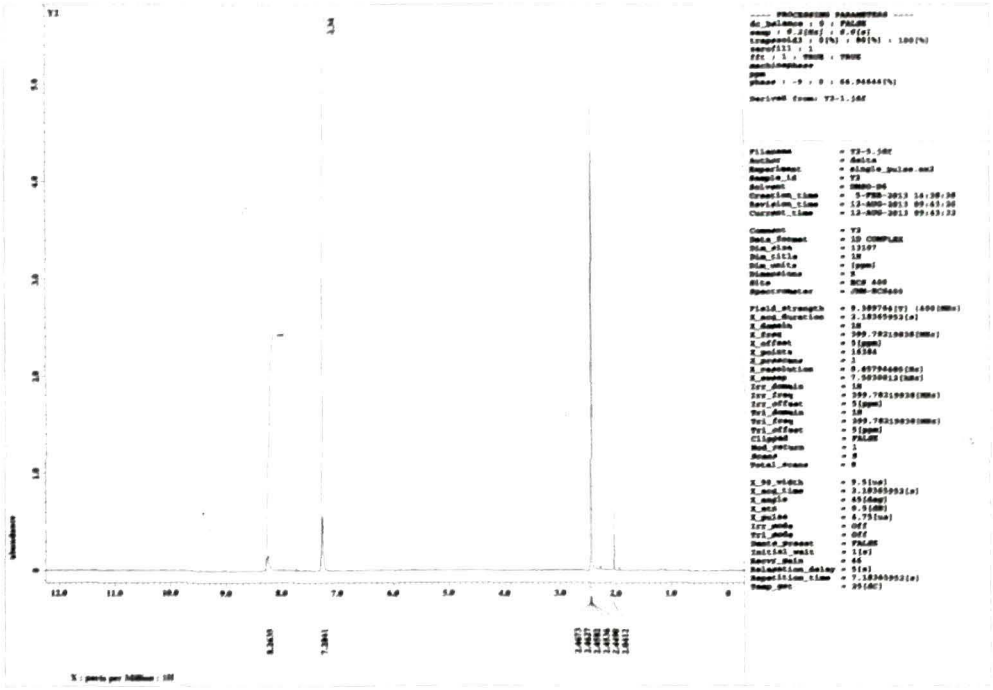


Image 38: ^{1}H NMR spectrum of (2-Bromo-imidazol-1-yl)-(4,5-dibromo-imidazol-1-yl)-methanone

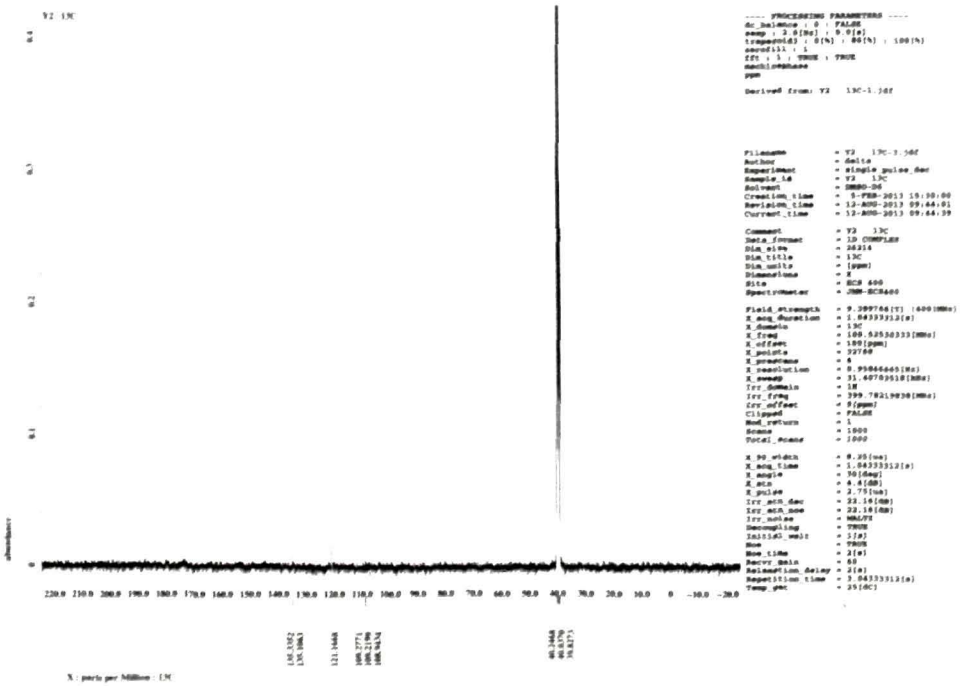


Image 39: ^{13}C NMR spectrum of (2-Bromo-imidazol-1-yl)-(4,5-dibromo-imidazol-1-yl)-methanone

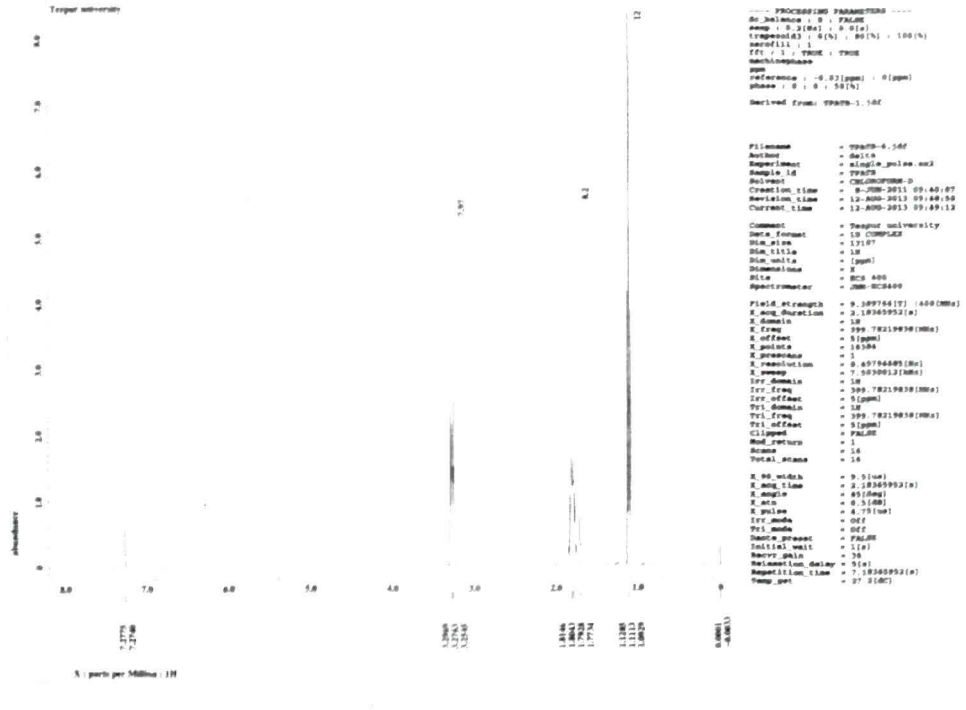


Image 40: ^{1}H NMR spectrum of TPATB

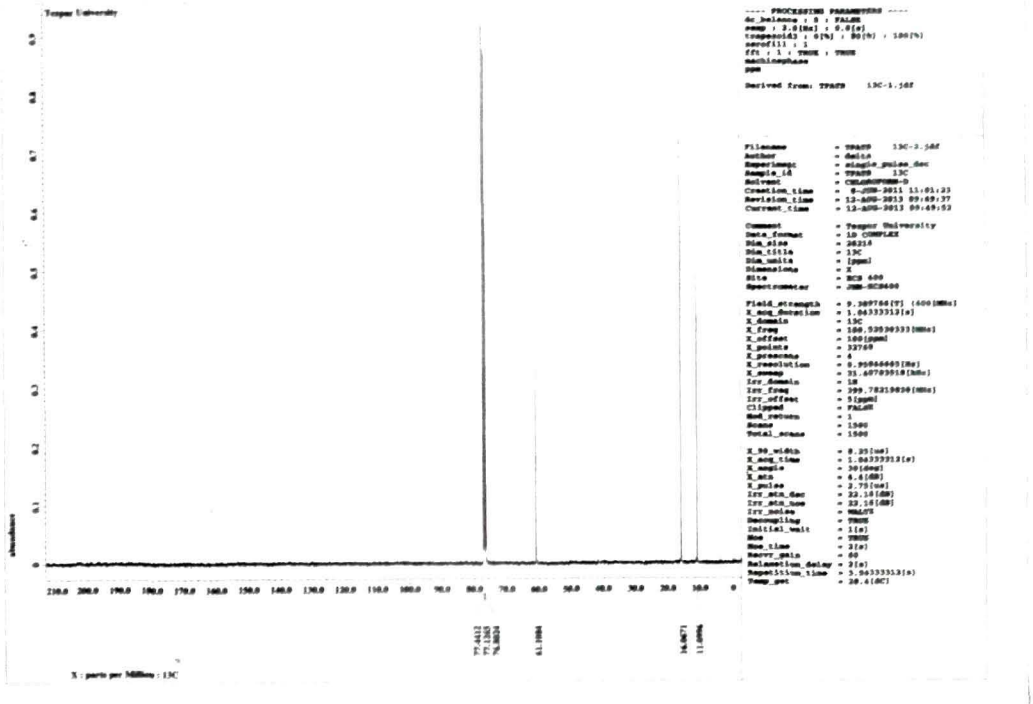


Image 41: ^{13}C NMR spectrum of TPATB

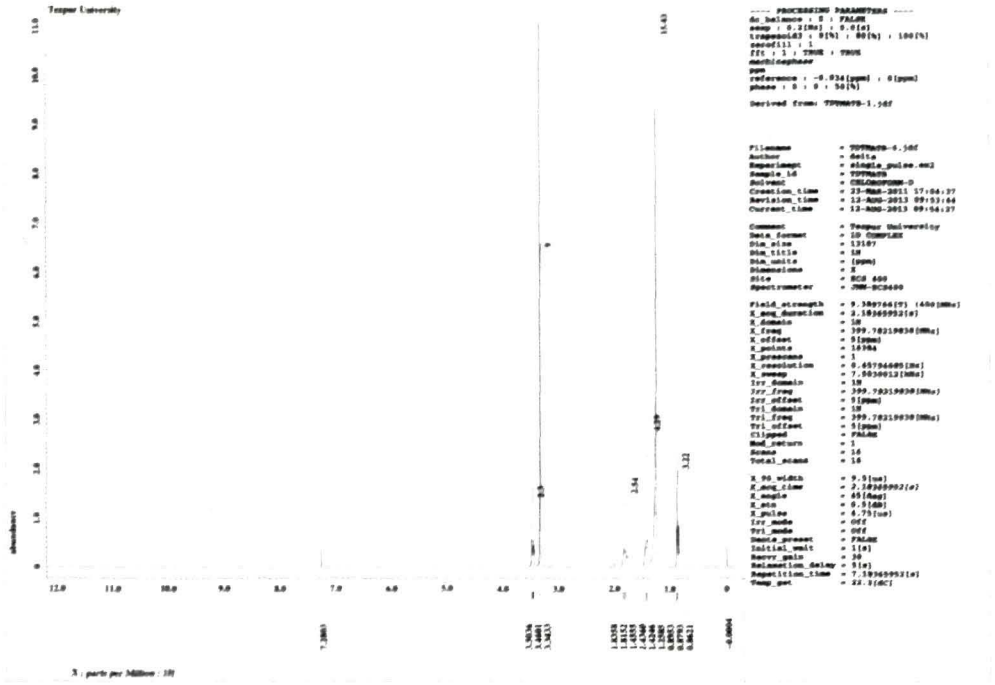


Image 42: ^{1}H NMR spectrum of TDTMATB

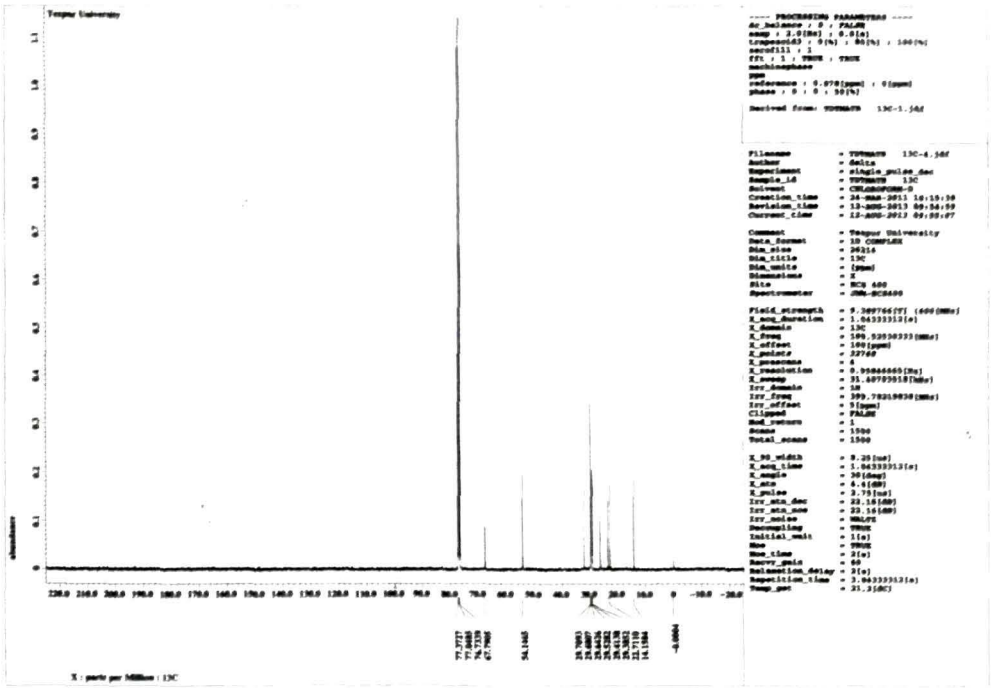


Image 43: ^{13}C NMR spectrum of TDTMATB

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Appendices

a. List of Publications:

1. **Talukdar. D.**, Saikia, L. N. & Thakur, A. J. Zirconyl Chloride: An Efficient,Water- Tolerant and Reusable Catalyst for the synthesis of *N*-methylamides, ***Synlett.*** **11**, 1597-1601, 2011
2. Saikia, L. N., **Talukdar, D.,** Deka, R. C. & Thakur, A. KI-$VO(acac)_2$-H_2O_2 AcOH, A new Iodination system for the selective iodination at C-5 position of activated pyrimidinediones, ***Journal of Heterocyclic Chemistry***, 2013 (Published online, DOI: 10.1002/jhet.1575)
3. **Talukdar, D.** & Thakur, A. A Green Synthesis of Symmetrical Bis (indole-3-yl)methanes Using phosphate impregnated titania catalyst under solvent Free grinding condition, ***Green Chemistry Letters and Reviews*** **6**(1), 55-61 , 2013
4. Hussain, S., **Talukdar, D.**, Bharadwaj, S.K. & Chaudhuri, M.K. $VO_2F(dmpz)_2$: A new catalyst for selective oxidation of organic sulfides to sulfoxides with H_2O_2, ***Tetrahedron Lett.*** **53**, 6512-6515, 2012
5. **Talukdar, D.**, Sharma, K., Bharadwaj, S.K. & Thakur, A. J. $VO(acac)_2$: An efficient catalyst for the oxidation of aldehydes to the corresponding acids in presence of aqueous H_2O_2. ***Synlett.*** **24**, 963-966, 2013
6. **Talukdar, D.,** Das, G., Thakur, S., Karak, N. & Thakur, A.J. Copper nanoparticle decorated OMMT as an efficient catalyst for the *N*-aryllation of indoles and similar heterocyces. ***Catalysis Communications*** *(Communicated)*

b. Patents

1. "Insuline mimetic active comprising oxoperoxo vanadates and a pharmaceutical composition obtained thereof"–PCT International application no. **PCT/IN2011/000386**
2. "Insuline mimetic active comprising oxoperoxo vanadates and a pharmaceutical composition obtained thereof"-Indian Patent Application no. **401/KOL/2011 dt.25.03.2011**

c. Seminar/Conference/Workshop/Symposium attended:

1. Finland-India-Sweden seminar on various aspects of 'Green Chemistry' from 19th to 22nd March 2012, Åbo Academi, Finland & Umeå University, Sweden.
2. National Conference on Chemistry, Chemical Technology and Society from 11th-12th November, 2011, Tezpur University.
3. CRSI-RSC Symposium on Chemistry, 2010, KIIT, Bhubaneswar.
4. Workshop on Intellectual Property Right Sensitization-2010, Tezpur University.
5. Frontier Lecture Series, from 20-22 November 2009, Tezpur University.
6. 14th National Workshop on Catalysis, from 21st-23rd December 2009, Tezpur University.
7. Summer School on green Chemistry, 2-22nd June 2009, Tezpur University.
8. Workshop on spectroscopic tools and their applications, 6th April 2013, Tezpur University.
9. Workshop on Integrated arsenic and iron removal from groundwater: Arsiron Nilogon, 25th June, 2011, Tezpur University.
10. Indo-Finnish Symposium on Role of catalyst on production of green fuel, 1st February, 2013, Tezpur University.