Synopsis
The thesis submitted by Mr. ANAND D. SAWANT, entitled "Synthesis and Applications of Spin-labeled Oligonucleotides and Ionic Liquids" is divided into two parts and six chapters.

PART A : Synthesis and Applications of Spin-labeled Oligonucleotides

Chapter-1: Synthesis of Oligonucleotides and Spin-labeling Technique

This Chapter deals with the basic structure of DNA, various approaches in synthesis of oligonucleotides and spin-labeling techniques. DNA was first isolated in 1869 from the nuclei of white blood cells. As this material was found in the nucleus and was acidic, it was called nucleic acid. Eventually, scientist found that nuclei of all cells contain DNA and it acts as carrier of genetic information. In 1953, James Watson and Francis Crick described the three dimensional structure of DNA - the famed Double helix, for which they were awarded 1962 Nobel price in medicine. Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids with defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence.

McConnell first introduced spin labeling in 1965 and since then it has rapidly emerged as one of the most powerful and extensively used tools for research in biophysics. Owing to the relatively low content of stable paramagnetic species in biological systems, a paramagnetic reporter group which is ESR-sensitive constitutes a physically distinct moiety from the rest of system. A paramagnetic reporter group is termed as a spin label. The technique which involves the introduction of spin labels as a paramagnetic probe into a system followed by the monitoring of the changes in its ESR spectra is called spin labeling.
Chapter-2: Synthesis of Nitroxide Spin Labels and Incorporation of Spin-label into Oligonucleotide

One potential technique for probing dynamic interactions in biomolecules is electron spin-labeling wherein a stable nitroxide is attached to a specific residue on the biopolymer under study. Site-directed spin labeling (SDSL) has become an increasingly important probe of structure and dynamics in biopolymers because of its sensitivity to motion, probe–probe interactions and local environment. The recent development of the method of site directed spin-labeling of proteins opens the potential to examine the local dynamical modes at or near each labeled residue (plus the overall motions) thereby ultimately leading to a “map” of the dynamic structure throughout the protein or other macromolecules.

This chapter deals with incorporation of a nitroxide spin label in dimeric blocks of DNA. The incorporation was further confirmed from ESR and $^{31}$P NMR analysis of the samples. The synthesis of hybrid nitroxide spin label prepared from 16-DPA following a sequence of reactions and synthesis of nitroxide spin label of Zidovudine molecule by copper catalyzed 1-3 dipolar cycloaddition reaction is also presented in this chapter.

PART B: Ionic Liquids

Chapter-3: Recent Developments of Task Specific Ionic Liquids in Organic Synthesis.

This chapter deals with the introduction to ‘Designer Solvents- Ionic Liquids’ and their applications in organic synthesis. The trend known as ‘Green Chemistry’ or ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the
use of toxic and/or hazardous substances. Recently, ionic liquids are regarded as eco-friendly alternatives to volatile organic solvents in chemical processes. The link between ionic liquids and green chemistry is clearly related to the solvent properties of ionic liquids. Their intrinsic properties such as negligible vapor pressure, non-flammable, ability to dissolve a wide range of organic, inorganic and organometallic compounds and also solubility of gases e.g. H₂, CO and O₂; make ionic liquids as an appropriate solvents for variety organic reactions. In addition, their physical and chemical properties such as hydrophobicity, hydrophilicity or solvent miscibility can be tuned by selecting the appropriate cation and anion, which render them more useful for facilitating catalyst recovery from the reaction mixture. Ionic liquids have been extensively studied in the last few years as media for organic synthesis and catalysis in particular. Due to their enormous utility in various fields of chemistry and other fields and also considering the scope of this thesis, review on some of the recently executed reactions including reactions in neutral ionic liquids, catalytic reactions by task specific ionic liquids, reactions carried out using polymer supported ionic liquids and syntheses and applications of chiral ionic liquids have been in this chapter. This review has been accepted for publication in Green Chem. Lett. and Rev. (in 2010).

Chapter 4, Section 1: A Basic Ionic Liquid [bmim]₃PO₄ Catalyzed Michael Reaction of Active methylene Compounds and Conjugated Ketones, Esters and Nitriles

Tandem reactions can link a series of reaction steps together in a single operation. Over the past decades, tandem reactions have gained a wide interest since they can offer extremely high efficiency and selectivity without relying on a series of separate operations. The conjugate addition of nucleophilic species to α-β-unsaturated systems is a fundamental concept in organic chemistry and is considered as one of the most versatile methods in organic synthesis. Among the
manifold of carbon–carbon bond forming reactions, the Michael addition, also termed 1,4-addition, is especially valuable for selectively creating a new bond at the β-position of activated olefins. The C-C bond-forming reactions, especially Michael reaction\(^8\) occupy the central position in the organic synthesis because they are the key to the construction of molecular frameworks of increasing complexity.

In this chapter, we have described synthesis of \([\text{bmim}]_3\text{PO}_4\) – an imidazolium based ionic liquid and its application to Michael addition reaction. It was observed that there was exclusive mono-Michael addition of active methylene compounds on conjugated esters, nitriles and ketones with good yields. A wide range of substrates including Ethyl Aceto Acetate (EAA), dimethyl malonate, malononitrile, cyclopentanone ethyl carboxylate as active methylene compounds (Michael adducts) and methyl acrylate, acrylonitrile, butyl acrylate, cylohexenone and chalcones as olefinic compounds (Michael acceptors) underwent reaction smoothly. \([\text{bmim}]_3\text{PO}_4\) could be reused up to five times.

**Section 2: A Basic Ionic Liquid \([\text{bmim}]_3\text{PO}_4\) as Catalyst and Reaction Media for Aza-Markovnikov Addition of N-Heterocycles on Vinyl Esters**

Heterocyclic compounds form by far the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only both biologically and industrially but to the functioning of any developed human society as well. Their applications in a wide range of areas can not be underestimated. The majority of pharmaceutical products that mimic natural products with biological activity are heterocycles. Most of the significant advances against disease have been made by designing and testing new structures, which are often heteroaromatic derivatives. Markovnikov type addition is among the most useful carbon-carbon, oxygen-carbon, or nitrogen-carbon bond forming reaction. This reaction was traditionally promoted by harsh bases, strong acids, or high
temperatures,\textsuperscript{9} which would lead to environmentally hazardous residues and unwanted byproducts.

This chapter deals with use of basic ionic liquid, [bmim]\textsubscript{3}PO\textsubscript{4} as a catalyst for the Markovnikov addition of \textit{N}-heterocycles to vinyl esters giving the corresponding \textit{N}-heterocyclic derivative.

\textbf{Chapter 5 Section 1: A Multifunctional Ionic Liquid for Pd(II) Catalyzed Heck Reaction}

C-C bond formation reactions mostly required the use prefunctionalized starting materials. The transition metal catalyzed C-C bond formations have attracted much interest in recent years.\textsuperscript{10} Among various methods of C-C bond formations, the development of catalytic systems involving the addition of aryl halides to unsaturated substrates (Heck reaction) using palladium constitutes an extremely important field of contemporary organic chemistry.

This chapter deals with synthesis of an ester functionalized, basic imidazolium based multifunctional Ionic Liquid (IL 2) viz. 3-methyl-1-(ethoxycarbonylmethyl) imidazolium hydroxide. The ionic liquid was used for palladium catalyzed Heck reaction of aryl halides and olefins. This phosphine-free Pd-IL system showed excellent activity and reusability at relatively lower reaction temperature (80°C). The \textit{in-situ} generation of palladium nano-particles was confirmed by TEM analysis. The high activity of this catalytic system at relatively lower temperatures could be based on \textit{in situ} generation of Pd nanoparticles. This catalyst system could be reused up to five times without any substantial loss of catalytic activity.
Section 2: Palladium Catalyzed Cross Coupling Reaction of Aryl Boronic Acids in [bmim]OH

The control of regioselectivity is a fundamental feature of organic synthesis, yet it is still a challenge to direct the regioisomeric outcome of many transition-metal-catalyzed processes. The formation of aryl-aryl bonds has been one of the most important methods in organic synthesis since the Ullmann reaction, a homocoupling of aryl halides with a stoichiometric amount of copper was discovered one century ago.11

This chapter involves discussion on use of basic ionic liquid [bmim]OH to bring about palladium catalyzed cross-coupling reaction of aryl boronic acids. The reaction was applied to a range of substrates giving moderate to good yields for cross-coupled products.

Section 3: Synthesis of Thiocarbonyl Functionalized Ionic Liquids for Nanoparticle Synthesis

The catalysis plays a central role in the development of environmentally safe and clean chemical processes. The search for more efficient catalytic systems that might combine the advantages of both homogeneous (catalyst modulation) and heterogeneous (catalyst recycling) catalysis is an essential requirement of modern chemistry.12 In most of the cases the concepts behind these methods involve the heterogenization of homogeneous catalysts or inversely the homogenization of heterogeneous catalysts. With the advances in nanochemistry it has been possible to prepare “soluble” analogues of heterogeneous catalysts. Transition-metal nanoparticles have attracted a great deal of attention in the last 15 years; their preparation, structure determination, and applications are topics of current interest.13,14
This chapter deals with discussion on design and synthesis of thiocarbonyl functionalized room temperature ionic liquids. As a part of study to explore the use of ionic liquids in nanoparticle synthesis we have synthesized thiocarbonyl functionalized ionic liquids. The synthesis of these ionic liquids is concise and practical due to the easy availability of the starting materials. Both hydrophilic and hydrophobic ionic liquids have been prepared.

**Chapter 6: Silica-supported Orthophosphoric Acid Catalyst for Oxathioacetalization and Tetrahydropyranylation**

In general considerations, heterogeneous catalysis is preferred in industrial processes to homogeneous catalysis as the extraction of the product and recovery of the catalyst are relatively easier. Today organic synthesis has reached a remarkable level of competence and even the most complex molecules are accessible. The prerequisites for this success are both the availability of a wide range of efficient synthetic methods and reagents. However, the complex synthetic intermediates and products contain, in general, a multiplicity of functional groups most of which must be blocked and, at an appropriate point in the synthesis, liberated. Hence the chemistry of protection and deprotection of a functional group has gained increasing importance.

This chapter deals with preparation, characterization and application of silica-supported orthophosphoric acid catalyst for chemoselective oxathioacetalization of aldehydes and tetrahydropyranylation of alcohols. The yields are good to excellent. Solvent free reaction conditions and applicability to a wide range of substrates are the other advantages of this catalyst.
Scheme 1: Incorporation of spin label in DNA backbone
Scheme 2: Synthesis of hybrid nitroxide spin label
Scheme 3: Synthesis of nitroxide spin label from zidovudine

Scheme 4: The mono-Michael addition of active methylene compounds on conjugated esters, nitriles and ketones

\[ X = \text{CN, COOMe, COOBu} \]
Scheme 5: Markovnikov addition in [bmim]$_3$PO$_4$

Scheme 6A: Synthesis of an ester appending ionic liquid

Scheme 6B: Heck reaction in an ester appending ionic liquid

Scheme 7: Pd(II) catalyzed cross-coupling reaction of aryl boronic acids in [bmim]OH
Reaction conditions: (i) Benzyl Chloride, Ethanol amine (excess), KI, DCM, reflux 6 h; (ii) NaH, THF, CS₂, CH₃I, 0 °C, to R.T., 2 h; (iii) n-BuCl, acetonitrile, 80 °C. (to get 4A) followed by KPF₆, acetone, 24 h, R. T. (to get 4B)

Scheme 8: Synthesis of thiocarbonyl functionalized ionic liquids

Scheme 9 Silica supported orthophosphoric acid for oxathioacetalization of aldehydes and tetrahydropyranylation of alcohols
References:


(5) *Benign by Design: Alternative Synthetic Design for Pollution Prevention*; Anastas, P., Farris, C., Eds.; American Chemical Society: Washington, DC, **1994**.


