CHAPTER-1

Brief introduction to the importance of developing novel and polymer supported catalysts in organic synthesis in the context of green chemistry
Chapter: 1 Introduction

Organic chemistry is a sub discipline within chemistry involving the scientific study of the structure, properties, composition, reactions, and preparation (by synthesis or by other means) of carbon-based compounds, hydrocarbons, and their derivatives. The range of application of organic compounds is enormous. They form the basis of, or are important constituents of many products (plastics, drugs, petrochemicals, food, explosives, paint, etc.) and, with very few exceptions; they form the basis of all earthly life processes. The role played by organic chemistry in the pharmaceutical industry continues to be one of the main drivers in the drug discovery process. Pharmaceutical Companies provide medicine and health care products to the customers. Without pharmaceutical companies, the death rate of human beings as well as animals would never have declined and these fields are like blessings of science to the human world. The services that these organizations providing are very helpful to the society as they ensure a happy and healthy life to the society.

In the early nineteenth century, chemists have believed that compounds obtained from living organisms were too complex to be obtained synthetically. According to the concept of vitalism, organic matter was endowed with a "vital force". The credit of destroying the theory of vital force goes to Friedrich Wohler when he synthesized the organic chemical urea (carbamide), a constituent of urine from the inorganic ammonium cyanate NH₄CNO, what is now called the Wohler synthesis.

Human society interacts with environment in two ways as a source of natural resources and as a sink for emissions and wastes. With respect to organic synthesis the most important thing to be dealt is the impact of organic synthesis to the environment. There is growing concern for potential
adverse human and ecological health effects resulting from the production, use, and disposal of chemicals that offer improvements in industry, agriculture, medical treatment, and even common household conveniences. In order to efficiently minimize the detrimental effects to the environment, improvements in chemical processes have to take place at the designing stage. Methodology development in organic synthesis exactly does the same. Tightening the environmental legislation is driving the fine and speciality chemical industries to find alternate processes. There has been significant growth in the principles of green chemistry, clean technology and in particular clean synthesis programmes thereby encouraging research into novel and environmentally benign chemical processes and products. Green chemistry does exactly this. It offers technologies that are more benign than traditional chemical systems.

**Methodology development and Green Chemistry**

Our environment, which is endowed by nature, needs to be protected from ever increasing chemical pollution. The challenge for the institutions and industries is to come forward and pursue development in the field of greener chemistry by reducing or eliminating the use and generation of hazardous substances. Designing and development of environment-friendly chemistry practices ensure that minimal waste is introduced into the environment. Due to large-scale production of pesticides, pharmaceuticals, petrochemicals, and other consumer durables, there is a great potential for green chemistry research in India to refine the existing technologies and also to find more environmentally benign alternatives. Practicing green chemistry can be achieved by many ways which include concentrating in avoiding environmentally noncompatible reagents, modification of synthetic routes to decrease the number of steps and to increase the overall yield which is characteristic of multicomponent reactions, usage of newer catalysts and simplification of classical procedures of reaction. Catalyst and reagent chemistry is
one of the most important aspects of eco-friendly chemistry. Reagent chemists work toward development of more benign and selective reagents that require ambient conditions. Keeping this in mind, the present work involves the development of economical, reusable and simple methods of synthesis of organic compounds of pharmaceutical interest.

Chapter -2 consists of a new catalytic system developed for the synthesis of 2- amino-5-nitro-4, 6-diarylcylohex-1-ene-1,3,3-tricarbonitriles using carbonate on polymer support (Amberlyst A-26 NaCO3\(^{−}\)). Cyclohexene unit is featured in many naturally occurring compounds and synthetic drugs. Oseltamivir (commercially sold as Tamiflu) is an antiviral drug which slows down the spread of influenza virus. Salinosporamide A is a potent proteasome inhibitor used as an anticancer agent. Tilidine is a synthetic opioid analgesic used for the treatment of mild and severe pain. Limonene is a colorless liquid classified as cyclic terpene is used in chemical synthesis as precursor to carvone and as renewably-based solvent in cleaning. Previously 2-amino-5-nitro-4,6-diarylcylohex-1-ene-1,3,3-tricarbonitriles were prepared using various catalysts including piperidine under microwave conditions,\(^1\) KF-Al\(_2\)O\(_3\),\(^2\) imidazole,\(^3\) and Mg/Al:HT under solvent free conditions.\(^4\) However there are no reports available in literature which employ polymer supported reagents in the synthesis of these compounds. In the context of cyclohexene unit being important chemically and biologically this work describes the development of constructing highly functionalized cyclohexenes using aldehydes, malononitrile and nitromethane using polymer bound carbonate as mild and recyclable catalyst. Short reaction time, simplicity of isolation, safe catalyst and high yields of product are the features of this method. The catalyst was easily recovered from the mixture by filtration.
Chapter -3 consists of simple, efficient method for selective oxidation of alcohols to carbonyl compounds using polymer bound bromide (Amberlyst A 26-Br₃) in DMSO. Oxidation of alcohols to carbonyl compounds is an important reaction in organic chemistry and various reagents have been developed to effect this transformation. These include (a) Chromium-based reagents, such as Collins reagent (CrO₃·Py₂), PDC or PCC.⁵ (b) Activated DMSO,⁶ resulting from reaction of DMSO with electrophiles such as oxalyl chloride (Swern oxidation), a carbodiimide (Pfitzner-Moffatt oxidation) or the complex SO₃·Py (Parikh-Doering oxidation). (c) Hypervalent iodine compounds,⁷ such as Dess-Martin periodinane or 2-Iodoxybenzoic acid (d) Catalytic TRAP in presence of excess of NMO (Ley-Oxidation) ⁸ (e) Catalytic TEMPO in presence of excess bleach (NaOCl).⁹ Several other methods employing different reagents and modifications to the above methods have been reported.¹⁰ All of these methods are having drawbacks such as highly acidic catalyst, expensive, difficult to remove catalyst, side product formation and less yield. Keeping the above drawbacks in mind an alternative method is developed for oxidation of alcohols to carbonyl compounds using polymer supported bromide in DMSO. Advantage of this method is that after the reaction is over the decolorized resin was filtered and converted into tribromide by the addition of bromine. Reuse of the same reagent using the optimized conditions gave the carbonyl compounds with the yields almost comparable. This makes the reusability of the resin thereby eliminating the drawback of the cost factor.

The yields of the reactions are also very high and are an excellent alternatives to the existing methods for the oxidation of alcohols to carbonyl compounds.

In Chapter -4, a novel method for demethylation of aryl methyl ethers is described using polymer bromide at room temperature. Phenols are important from the point of medicine, natural occurrence and industrial processing. They have unique properties compared to alcohols
and are more sensitive to other reagents. This makes synthetic organic chemists to protect them in order to get selectivity. Phenols can be protected in many ways as benzyl, methoxy methyl, allyl, ethoxy ethyl, tetrahydroxypyranyl, silyl and methyl ethers etc. When highly stable protection is required methylation is one of the best choices since it is highly stable towards most of the reagents and reaction conditions. At the same time demethylation is often tedious under conditions where milder reaction conditions have to be employed because of sensitive groups present in the molecule. There are various methods to demethylate the methyl phenyl ether. the reagents fall under strong acids, Lewis acids, strong bases, alkali metals, oxidizing agents and reducing agents. There are reagents which do the job below room temperatures like boron trihalides. A new mild condition is also developed for O-demethylation using L-Selectride. However many of these methods suffer from one or other limitations including toxicity, incompatibility with acid sensitive groups, high temperature, scale up problems, use of high boiling solvents and especially longer time is required in most of the methods. In the background of this and availability of numerous methods in the literature to efficiently methylate the phenols, developing milder and convenient methods to cleave the methyl group appears to be a welcome goal in making protection of phenols as methyl ethers a convenient strategy. In this chapter polymer supported bromide has been used for the cleavage of aryl methyl ethers. The reactions are clean and high yielding. The catalyst has been recovered at the end of the reaction and converted back to the polymer bromide and used for cleavage of aryl methyl ethers making it more ecofriendly.

In Chapter 5, highly efficient, three-component condensation of aromatic aldehyde, malononitrile and 4-hydroxycoumarin promoted by neat silica gel at room temperature is described. This method offers an excellent alternative route for the synthesis of 3, 4-
dihydropyrano[e]chromenes. 3, 4-Dihydropyrano[c]chromenes and its derivatives are very useful compounds in various fields of chemistry, biology and pharmacology. Some of these compounds exhibit spasmolytic, diuretic, anticoagulant, anti-cancer, and anti-anaphylactic activity. In addition, they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome for the treatment of schizophrenia and myoclonus. Previously synthesis of 2-amino-4-aryl-5-oxo-4H,5H-pyrano[3,2-c]chromene-3-carbonitrile from aromatic aldehyde, malononitrile and 4-hydroxycoumarin has been achieved in the presence of a variety of catalysts such as diammonium hydrogen phosphate, H₆P₂W₁₈O₆₂·18H₂O, TBABr, K₂CO₃ under microwave irradiation. Various organic bases like piperidine, pyridine in organic solvents like ethanol and pyridine, and (S)-proline are some of the other catalysts used for the synthesis of this molecule. However, many of these methods suffer from drawbacks such as harsh reaction conditions, unsatisfactory yields, prolonged reaction times, cumbersome product isolation procedures and difficulty in recovery and reusability of the catalysts. The development of new methods with an objective of improving the yields by green chemistry for the synthesis of above said molecules is a welcome goal because of possessing wide spectrum of biological activities of these molecules. So the protocol described in the present work employs silica gel as reusable catalyst for the synthesis of above said molecules. The reactions are fast and clean, and the products are obtained with good yield and purity. The reusability of the catalyst is also studied and the catalyst could be reused for minimum of four times without drastic decrease in the activity.

In Chapter - 6, an atom- efficient, environmentally benign and mild condition for the synthesis of amidoalkyl naphthols catalysed by substoichiometric amount of LiBr is described. Short
reaction time, solvent free condition, simplicity of isolation and safe catalyst are the features of
this method. 1-amidoalkyl-2-naphthols are precursors for 1, 3-amino-oxygenated functional
motifs prepared by hydrolysis of amide or carbamate (in case of 1-carbamato-alkyl-2-naphthols).
1,3-amino-oxygenated functional motifs are common in a variety of biologically important
natural products and potent drugs, including a number of nucleoside antibiotics and HIV protease
inhibitors, such as ritonavir and lopinavir.\textsuperscript{40} The hypotensive and bradycardiac effects of these
compounds are also studied.\textsuperscript{41} 1-amidoalkyl-2-naphthols are the molecular complexes generated
by chemical transformations undergone by the three components viz 2-naphthol, aldehyde and
amide Lewis acids or Bronsted acids as driving forces such as montmorillonite \textsuperscript{K10} clay,\textsuperscript{42}
Ce(SO\textsubscript{4}),\textsuperscript{43} Iodine,\textsuperscript{44} K\textsubscript{2}CoW\textsubscript{12}O\textsubscript{40}. 3H\textsubscript{2}O,\textsuperscript{45} p-TSA,\textsuperscript{46} sulfamic acid,\textsuperscript{47} cationic resins\textsuperscript{48}
and P\textsubscript{2}O\textsubscript{5}.\textsuperscript{49} Several structural modifications are also done to increase the usefulness of these compounds.
Ureas, substituted ureas and carbamates are also used instead of simple amide or acetonitrile to
get amido alkyl naphthols and carbamato alkyl naphthols.\textsuperscript{50} However many of these protocols
suffer from drawbacks such as prolonged reaction time, use of highly acidic and highly
hygroscopic reagents and chlorinated solvents. In the background of amidoalkyl naphthols being
potential biologically active compounds, development of newer methodologies using mild
catalysts and solvent free conditions is a welcome goal. In view of this the new protocol
described in this work uses substoichiometric amount of readily available LiBr to effect the
synthesis of amidoalkyl naphthols. The reactions are fast and the yields obtained are excellent.
Chapter: 1 Reference


