SYNOPSIS
SYNTHESIS AND CHARACTERISATION OF BIOLOGICALLY ACTIVE COMPOUNDS

The thesis entitled 'Synthesis and characterization of biologically active compounds' is divided into six chapters

CHAPTER – I

Introduction

There is a great demand for the design and development of simple, efficient and environmentally benign chemical processes or methodologies for widely used biologically active compounds from readily available resources. One approach to address this challenge involves the development of multi-component reactions (MCRs) in eco-friendly solvents such as polyethylene glycols (PEGs), water and PEG-water. Other approach is to develop new catalysts and their applications in organic transformations. Both approaches are important to address highly demanding issue, "Green Chemistry" in academic and industrial research.

This chapter deals with the description of a verity of reagents or solvents that have been playing important role in current synthetic trend.
Zinc Oxide Mediated Organic Reactions

Section 1: Zinc Oxide Catalyzed a Simple and Clean Synthesis of Chalcones

Chalcone is a unique template that is associated with several biological activities and useful as intermediate for the synthesis of natural products and active pharmaceutical ingredients. Because of biological importance of chalcones, although various methods are known, newer methods continue to attract attention for their experimental simplicity and effectiveness. One of the straightforward routes leading to the synthesis of chalcones is Friedel-Crafts acylation of arenes with α, β-unsaturated aryl acid halides. However, due to the limited regioselectivity, the products of this reaction are usually obtained as hard-to-separate isomeric mixture. Furthermore, the reaction conditions tend to be incompatible with certain functional groups. It requires a stoichiometric amount of aluminium chloride that brings about environmental pollution after work-up and is not applicable to the synthesis of acid-sensitive chalcones because they are easily polymerized by an acid.

The present work describes our endeavors to develop a very simple and efficient zinc oxide catalyzed regioselective synthesis of chalcones under solvent-free conditions at room temperature.

![Scheme 1](image)

Various activated as well as unactivated aromatic compounds with α,β-unsaturated aromatic acid chlorides underwent smooth Friedel-Crafts acylation furnishing excellent yields of the chalcones in a short reaction time.
Section 2: Convenient and Efficient Synthesis of Thiol Esters under Solvent-free Condition using Zinc Oxide as a Catalyst

Thiol ester is an important functional group in organic synthesis. It is used in the formation of carbon carbon bonds and other functionalities. Because of the growing importance of thiol esters, various improved methods have been developed for their direct preparation from carboxylic acids. This protocol requires essentially the activation of acid. All these reported methods have one or the other disadvantages like expensive reagents, tedious work-up procedures and sometimes isolation of intermediate is essential.

Because of importance of solid state synthetic organic chemistry, we report here a mild, general and efficient method for the synthesis of thiol esters from acid chlorides and thiols in the presence of zinc oxide under solvent-free condition.

\[
\begin{align*}
R^1\text{C}^{-}\text{Cl} & \quad + \quad R^2\text{SH} \quad \xrightarrow{\text{ZnO, r.t.}} \quad R^1\text{C}^{-}\text{SR}^2 \\
R^1 & = \text{alkyl or aryl or arylalkyl; } R^2 = \text{alkyl or aryl}
\end{align*}
\]

Scheme 2

The methodology is found to be general as both aliphatic as well as aromatic acid chlorides smoothly reacted with aliphatic and aromatic thiols resulting in the formation of the corresponding thiol esters in excellent yields in a short reaction time. The reactions are remarkably clean and no chromatographic separation is necessary to get pure products.
Organic Transformations Catalyzed by Cyanuric Chloride

Section 1: Organic Reactions in Aqueous Media: In-situ Generated HCl Catalyzed Synthesis of 14H-dibenzo [a,j]xanthenes.

Xanthenes and particularly benzoxanthenes constitute an important group of oxygen heterocycles. These compounds have attracted great interest due to their spectroscopic properties and many applications in laser technology. Benzoxanthene derivatives have shown good promise as sensitizer in photodynamic therapy (PDT), a well known method of controlling the localized tumors. Additionally, these compounds also have promising antibacterial, antiviral and anti-inflammatory activities and can be used as luminescent sensors. Various methods were known for the synthesis of xanthenes and benzoxanthenes, such as the reaction of β-naphthol with formamide, or from the reaction of 2-naphthol-1-methanol, and carbon monoxide. However, these methods suffer from one or more disadvantages such as low yields, extended reaction times, the use of toxic organic solvents and excess reagents. To overcome these limitations, the reaction has been improved by mixing β-naphthol with aldehydes in presence of catalyst, such as pTSA, sulfamic acid, I₂, LiBr, and AcOH H₂SO₄. These protocols also suffer from some disadvantages like long reaction time, the use of toxic solvents and need of special apparatus. Consequently, there is a scope for further improvement.

Herein, we would like to report an eco-friendly route for the synthesis of 14-substituted-14H-dibenzo[a,j]xanthene derivatives under aqueous media.

![Scheme 3](image)

The noteworthy features of the present protocol are use of universal green solvent, short reaction times and excellent yields of product.
Section 2: An Eco-friendly Approach to Polysubstituted Quinolines Catalyzed by 'Insitu' Generated HCl from Water and Cyanuric Chloride at Room Temperature

The substituted quinolines are found to possess a wide spectrum of biological and pharmaceutical activities such as anti-malarial, anti-inflammatory, anti-asthmatic, anti-bacterial, anti-hypertensive and tyrosine kinase inhibiting agents. In addition quinolines are valuable synthones used for the preparation of nano- and meso-structures with enhanced electronic and photonic properties. Consequently, large numbers of methods were developed for the synthesis of quinoline derivatives. The Friedländer annulation has been catalyzed by both acids and bases. Recently, Lewis acids such as CeCl₃.7H₂O, Mg(ClO₄)₂, ZnCl₂, SnCl₂, Bi(Otf)₃, Sc(Otf)₃, NaAuCl₄.H₂O and sodium fluoride have been used in presence of organic solvent for the synthesis of quinolines. However, many of these methods have suffered from harsh reaction conditions, low yields, difficulties in work-up procedure and unlimited use of organic solvents and expensive reagents.

In continuation of our work in the development of synthetic methods using cyanuric chloride, here we report the Friedländer annulation followed by cyclodehydration of ketones catalysed by insitu generated hydrochloric acid at the room temperature (Scheme 4 and 5).

\[ \text{Scheme 4} \]

\[ \text{Scheme 5} \]

Mild conditions, simple work-up procedure, pure products and excellent yields are the salient features of the present method.
CHAPTER - IV

Multi-component Reactions In Aqueous Medium

Section 1: A Simple and Convenient Procedure for the Synthesis of 4-Substituted- 1,4-dihydropyridine Derivatives under Aqueous Medium

More than a century ago the first 1,4-dihydropyridine derivatives (1,4DHPs) were obtained by Hantzsch. This reaction involves a one-pot condensation of an aldehyde with ethylacetoacetate and ammonia in acetic acid or refluxing in alcohol for a longer time. However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Eventhough a number of methods under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, longer reaction times, need of special apparatus, use of toxic catalysts and large quantities of hazardous solvents.

Recently attention has been drawn to the development of environmentally benign solvents such as ionic liquids, polyethylene glycols and water. Herein, we wish to report a simple one-pot, three-component condensation reaction of ethylacetoacetate, aldehyde and ammonium acetate under aqueous medium in absence of added catalyst for the synthesis of 1,4-dihydropyridine derivatives.

\[
\begin{align*}
\text{Scheme 6}
\end{align*}
\]

The reactions are clean with good yields and no chromatographic separation is required to get pure products.
Section 2: Uncatalyzed One-Pot Four Component Synthesis of Polyhydroquinoline Derivatives in Water

The environmental acceptability of the process is improved if the multicomponent strategy is applied. Indeed, it is well known that multicomponent reactions (MCR), consisting of two or more synthetic steps, which are carried out without isolation of any intermediate, allow to reduce time, save money, energy and raw materials. Literature survey indicated that various methods were reported for the synthesis of polyhydroquinoline derivatives because of their biological importance. These reported methods required conventional heating and refluxing approaches in the presence of catalyst and organic solvent. However, these methods have one or the other limitations such as long reaction time, harsh reaction conditions, the use of large quantity of organic solvents and unsatisfactory yields of products.

To the best our knowledge, the synthesis of polyhydroquinoline derivatives without catalyst in the aqueous medium has not been reported so far. Consequently, there is a scope for further renovation of such synthetic methods, which avoids both an organic solvent and catalyst.

We report here in this communication, uncatalyzed synthesis of polyhydroquinoline derivatives via four-component coupling reaction of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate in water.

![Scheme 7](image)

Excellent yields, simple work-up and pure products are the important features of this method.
Section 3: One-Pot Three-Component Synthesis of 4(3H)-Quinazolinone Derivatives under Aqueous Medium as well as Solvent-Free Conditions

4(3H)-quinazolinone derivatives have attracted considerable attention since they exhibit a wide range of biological properties e.g. anti-cancer, anti-inflammatory, anti-convulsant and anti-hypertensive activities. A few numbers of quinazolinone have been reported as potent chemotherapeutic agents in the treatment of tuberculosis. In view of the biological importance of quinazolinone and its derivatives, large number of methods were reported for their synthesis. Unfortunately, many of these methods suffer from one or more disadvantages like lengthy procedure for the synthesis of precursors, low yields of products, tedious isolation techniques, use of expensive, highly toxic and hazardous reagents and solvents. Furthermore, for the preparation of starting materials like 4H-3,1-benzoxazine-4-ones, benzoxazine-4-one carboxylic esters or diamide, multi-step procedure is required. Consequently, there is a need to develop synthetic method which will avoid the use of expensive reagents, organic solvents and multi-steps.

One approach to address this challenge involves the development of multi-component reaction. Herein we would like to report a simple, efficient, one-pot, three-component method for the preparation of 4(3H)-quinazolinones under aqueous medium as well as solvent-free conditions.

\[ \text{Scheme 8} \]

\[ \text{Scheme 9} \]

It is noteworthy to mention that anilines bearing electron-withdrawing and electron-donating substituents underwent smooth condensation into the corresponding 4(3H)-quinazolinone derivatives in high yields and short reaction time.

"Synthesis & Characterisation of Biologically Active Compounds" 164
CHAPTER – V

PEG Mediated Organic Transformations

Section 1: A simple, One-Pot Green Procedure for the Synthesis of 2,4,5-Triaryl Imidazoles Employing Polyethylene Glycol (PEG) as an Efficient Recyclable Medium

Compounds with imidazole ring system have many biochemical and chemical properties. Therefore, there are several methods reported in literature for the synthesis of imidazoles such as hetero-Cope rearrangement, four component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin, reaction of N-(2-oxo)-amides with ammonium trifluoroacetate, reaction of diketones, aldehyde, amine and ammonium acetate in phosphoric acid, in acetic acid, organo catalyst in acetic acid as well as H₂SO₄ and DMSO. These reported protocols for the synthesis of imidazoles have one or the other disadvantages such as harsh reaction conditions, poor yields, prolonged reaction time, use of hazardous and often expensive acid catalysts. Moreover, these methods have been carried out in polar solvents such as acetic acid, DMF and DMSO leading to complex isolation and recovery procedures.

PEG, a biologically acceptable polymer used extensively in drug delivery and in bioconjugates as tool for diagnostics, has hitherto not been widely used as a solvent medium but has been used as a support for various transformations. As a part of our ongoing programme on the development of novel methods in organic synthesis herein, we wish to report an efficient one-pot condensation of 1,2-diketone, aromatic aldehydes and ammonium acetate in PEG 600 at 80°C which afforded a diverse array of 2,4,5-triaryl imidazoles in excellent yields.

![Scheme 10.](image)

All the reactions are clean and pure products are obtained without chromatographic separations. Excellent yields, short reaction times, higher selectivity and recyclable solvent are the features of this methodology.
Section 2: One-Pot Synthesis of Octahydroquinazolinone Derivatives Using Environmentally Benign Conditions

Octahydroquinazolinones have emerged as an important class of nitrogen heterocycles that have attracted significant attention because of their potent antibacterial activity against *Staphylococcus aureus*, *Escherichia Coli*, *Pseudomonas aeruginosa* and calcium antagonist activity. Various methods have been developed for the synthesis of quinazolinone derivatives such as cyclodehydration of anthranilic acid by acetic anhydride; reaction of anthranilic acid with acid chloride in pyridine; reaction of aldehyde with SOCl₂ and pyridine and then with 2-aminobenzylamine in refluxing solvent such as benzene or xylene with azeotropic water removal and treatment of 2-ureidobenzoates with concentrated sulfuric acid. In general, the reported methods for the synthesis of octahydroquinazolinone derivatives involve hazardous and expensive reagents or solvents, longer reaction times and display moderate to low yields with low atom efficiency.

In continuation of our ongoing program on the development of novel synthetic methods under mild conditions, we now wish to report a simple and efficient, one-pot, three-component version of the Biginelli reaction for the synthesis of octahydroquinazolinones in PEG(600)-water using no catalyst.

![Scheme 11](image)

This method not only offers substantial improvements in the reaction rates but also avoids the use of corrosive Bronsted acids or heavy metal ions Lewis acid as a catalyst.
CHAPTER-VI

Biological Activity Studies

The series of synthesized compounds were subjected for evaluation of biological activities. Based on the literature survey, the antioxidant and anti-microbial activities were tested. The antioxidant potential was evaluated using 1,1-diphenyl-2-picrylhydrazine (DPPH) reduction assay and the potassium ferricynide reduction assay. The antimicrobial profile was determined using agar diffusion assay. Both antioxidant and antimicrobial activities were compared with standard reference compounds. The test samples were found to be moderate to poor antioxidant agents while the compounds were found to be effective antibacterial agents. However the samples were not effective against the Candida albicans: a pathogenic fungus predominant in HIV patients.