USE OF MODERN TECHNIQUES FOR SYNTHESIS OF SOME HETEROCYCLIC COMPOUNDS

Introduction

Current protocol to new researchers during recent years is to design and develop green procedures that are both environmentally desirable and economically acceptable. “Green Chemistry” is considered an integral part of a comprehensive program to protect human health and the environment. Most of organic solvents used in industry are toxic, costly and problematic to use caring out reactions with lesser amount or no solvent wood lead to clean, efficient and economical processes with the increasing environmental concerns and the regulatory constraints faced by the chemical and pharmaceutical industries, development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research.\(^1\) Therefore more and more chemists are devoted to the researching ‘safer synthetic routes’ which means the reagents, solvents and catalysts are environmentally friendly in the organic chemical reactions.

New strategies have recently been developed which contributes to green and safer synthesis. Some of the methods, which are used in organic synthesis, are mentioned below.
• Use of Microwaves.
• Use of Ultrasound in organic synthesis.
• Use of neat reaction conditions.
• Use of water mediated reaction conditions.

Among the non-conventional methods in organic synthesis\textsuperscript{2}, microwave irradiation takes a particular place being an emerging technique that provides an alternative to conventional heating for introducing energy into chemical reactions by using the ability of some liquids and solids to transform electromagnetic energy into heat with microwaves, the heating is created in the interior of the sample and is then radiated outward. This is contrast with conventional heating, where the heat is generated in the outer region and directed towards the center.

In electromagnetic spectrum, the microwave radiation region is located between infrared radiation and radio waves. Microwaves have wavelength 1mm-1m corresponding to frequencies between 0.3-300 GHz. Main benefits of microwave heating are\textsuperscript{3-4}

• Very fast heating.
• Absence of inertia. Only the reaction contents are heated, not the reaction vessel.
• Easy to use. Power regulator is easy with instantaneous on and off.
• Better homogeneity in temperature with quick transfer of energy in the whole mass without superficial heating.
• The selective heating of polar molecules.

In MW oven, microwaves are generated by a magnetron\textsuperscript{5}, was designed by Randall and Booth at University of Birmingham as part of the development of RADAR during the Second World War. A magnetron is thermionic diode having an anode and a directly heated cathode. As the cathode is heated, electrons are released and are attracted towards anode. The anode is made up of an even no. of small cavities, each of which acts as a tuned circuit. The anode is therefore, a series of circuits, which are tuned to oscillate at a specific frequency or its overtones. A very strong magnetic field is induced axially through the anode assembly and has the effect of bending the path of electrons as they travel from the cathode to the anode. As the deflected electrons pass through the cavity gaps, they induced a small charge cavity. Alternative cavities are linked by two small wires straps, which ensure the correct phase relationship. This process of oscillation continues until the oscillation has achieved sufficiently high amplitude. It is then taken off the anode via an antenna. The variable power available in domestic oven is
produced by switching the magnetron on and off according to duty cycle. Even in early days, it was recognized that microwaves could heat water in dramatic fashion and domestic and commercial applications for heating and cooking foodstuffs began to appear in 1950s. In 1955 Tappan introduced first kitchen microwave oven but its widespread domestic use occurred during the 1970s and 1980s. the first application of microwave energy in organic synthesis is the aqueous emulsion polymerization of butyl acrylate, acrylic acid and methacrylic acid using pulsed electromagnetic radiation\textsuperscript{6}, after that several groups, have demonstrated that chemical synthesis may be dramatically accelerated using MW irradiation. The superheating conditions caused by this kind of heating, lead directly to acceleration in the reaction times compared with conventional reflux conditions. The first application of MW in chemical synthesis was published in 1986 by Gedye\textsuperscript{7} and et. al. using domestic microwave oven. Giguere\textsuperscript{8} et. al. in 1989 appeared the first review dealing with microwave heating in organic synthesis. Since then an increasing no. of articles has been published\textsuperscript{9-33}.

Sonochemistry: chemical reaction under the influence of ultrasonic energy field is one of the promising experimental techniques recently introduced in to the tools of chemical synthesis\textsuperscript{34-37}. 
The first report about the effect of ultrasound to chemical reactions is from 1927, by Richards and Looms involving rate studies on the hydrolysis of dimethyl sulfate and the iodine “clock” reaction (the reduction of potassium iodate by sulfurous acid)\(^{38}\).

In 1938, Porter and Young reported that ultrasound increased the rate of the Curtius rearrangement\(^ {39}\). In 1950, Renaud reported an organometallic compound using ultrasound\(^ {40}\). Since 1982 when Han and Boudjouk significantly increased the yields and rates of Reformatsky reaction, \(^ {41}\) ultrasound has been investigated intensively in organic synthesis.

The driving force for ultrasound developments in organic synthesis has many advantages. The increasing requirement for environmentally clean and safer technology, that minimizes the production of waste at source\(^ {42}\). Ultrasound may offer cleaner reactions by improving product yields and selectivities, enhancing product recovery and quality through application to crystallization and product recovery and purification processes. Ultrasound enhances the ratio of reactions\(^ {43}\). Sonication allows the use of non-activated and crude reagents as well as an aqueous solvent system; therefore it is friendly and non-toxic. Ultrasound is widely use for improving the traditional reactions
that use expensive reagents, strongly acidic conditions, long reaction times, high temperatures, unsatisfactory yields and incompatibility with other functional groups.\textsuperscript{44}

During the last few years a large number of short communications have appeared on the use of this versatile technique and excellent reviews are also available\textsuperscript{45-48}. Ultrasounds are waves at frequencies above those within the hearing range of the average person, i.e., at frequencies above 16 KHz. Many sonicators are useful for the production of ultrasound. The important one is ultrasonic cleaning bath, ultrasonic probe systems, the cuphorn system, the flow cell system etc.

When ultrasonic energy at high power is applied to a liquid, a phenomenon called ‘cavitation’ occurs. Cavitation is the formation, growth and collapse of bubbles in the liquid. This results in ‘cold boiling’ of liquid. Ultrasonic vibration reduces the thickness of liquid films. Ultrasonic energy (high energy sound waves) produces an alternating adiabatic compression and rarefaction of the liquid media being irradiated. In the rarefaction part of the ultrasonic wave (when liquid is unduly stretched or “torn apart”), microbubbles form because of reduced pressure. These microbubbles contain vaporized liquid or gas that was previously dissolved in the liquid. The microbubbles can be
either stable about their average size for many cycles (stable cavitation) or transient when they grow to certain size and violently collapse or implode during the compression part of the wave (transition cavitation). The critical size depends on liquid and the frequency of the sound (Fig. 1).

**Fig. 1: Generation of an acoustic bubble**
With the increasing environmental concerns and the regulatory constraints faced by the chemical and pharmaceutical industries, development of environmentally benign organic reactions have become a crucial and demanding research area in modern chemical research\(^\text{49}\). Therefore more and more chemists are devoted to the researching “Green Synthesis,” which means the reagent, solvent and catalyst are environmentally friendly in the organic chemical reactions. Recently organic reactions in water without use of harmful organic solvents have attracted much attention, because water is a cheap, safe and environmentally benign solvent\(^\text{50-52}\)

In view of the wide range of biological activities associated with the heterocyclic compounds based on our interest in non-conventional modern methods of reaction activation, in present work, various heterocyclic system like amino coumarins, styryl chromone, quinoline acrylates, quanazolinones, benzylidine, amino quanazolinones, oxazolones, imidazolones, pyridopyrimidine carboxylates, thiopyridopyrimidine carboxylates, dibenzoxanthes have been synthesized by the use of modern techniques. We have exploited modern techniques (microwave, ultrasound, reactions under neat conditions and water mediated reactions) for achieving the improved reaction paths for the synthesis of above heterocyclic compounds.
Present Work

The present work entitled “Use of Modern Techniques For Synthesis of Some Heterocyclic Compounds” is described into four Parts.

Part I

The first part describes the general introduction and literature survey.

Part II

This part describes the different reactions under microwave and ultrasound irradiation. It is divided into three sections.

Section A

This section describes an efficient and solvent-free method for the synthesis of \((2E)-3-(4\text{-oxo}-4H\text{-chromen}-3\text{-yl})\) acrylic acid from substituted formyl chromones and malonic acid, using basic alumina as solid support under microwave and under ultrasound irradiation in pyridine.

Section B

This section describes the Knoevenagel condensation of 2-chloro-substituted-3-quinolines with ethyl cyanoacetate, under ultrasound irradiation and at room temperature stirring using 1,8-Diazabicyclo-undec-7-ene (DBU) catalyst.
Section C

This section describes an efficient, one-pot synthesis of 3-amino-6-substituted-2H-chromen-2-one, from substituted salicylaldehyde and glycine under microwave irradiation using basic alumina as a solid support and under ultrasound irradiation in piperidine as a catalyst.

Part III

This part deals with the synthesis of 2-phenyl-3H-substituted quinazolin-4(3H)-ones, 3-(substituted benzylidine amino)-2-phenyl-quinazolin-4(3H)-ones, 4-(2-hydroxybenzylidene) -2-phenyl oxazol-5(4H)-ones and 4-(2-hydroxy5-substituted, 1-substituted-phenyl-2-phenyl-1H-imidazol-5(4H)-ones under microwave and ultrasound irradiation. It is divided into four sections.

Section A

This section describes newer route for the synthesis of 2-phenyl-3H-substituted quinazolin-4(3H)-ones from 2-phenyl-4H-benzo[d][1,3]oxazin-4-one and substituted aromatic and aliphatic amine under ultrasound irradiation using anhydrous ZnCl₂ as a catalyst.
Section B

This section describes a safer route for the synthesis of 3-(substituted benzylidene amino)-2-phenyl-quinazolin-4(3H)-ones from 2-phenyl-4H-amino[d][1,3]oxain-4-ones and substituted aromatic aldehydes under irradiation at room temperature in dry ethanol and drop of acetic acid.

Section C

This section describes a newer route for the synthesis of 4-(2-hydroxybenzylidene)-2-phenyl oxazol-5(4H)-ones from substituted salicylaldehydes and hippuric acid under microwave irradiation using anhydrous K$_3$PO$_4$ catalyst.

Section D

This section describes a newer route for the synthesis of 4-(2-hydroxy 5-substituted, 1-substituted-phenyl-2-phenyl-1H-imidazol-5(4H)-ones from oxazolone and substituted aromatic amines under microwave irradiation using anhydrous ZnCl$_2$ as a catalyst in EtOH as a solvent.

Part IV

This part describes the synthesis of different heterocyclic compounds like Polyhydropyridopyrimidine, polyhydrothiopopyridopyrimidines and Dibenzoxanthenes under solvent-free conditions and in aqueous medium. It is divided into three sections.
**Section A**

This section describes an efficient and solvent-free method for the synthesis of ethyl 1,2,3,4,5, 8-hexahydro-7-methyl 2,4-diono-5-phenylpyrido[2,3d]pyrimidine-6-carboxylate, from substituted aromatic aldehydes, ethyl cyanoacetate, barbituric acid and ammonium acetate using sulphamic acid catalyst, on heating at 90°C temperature under neat condition.

**Section B**

This section describes an efficient and solvent-free method for the synthesis of ethyl 1,2,3,4,5, 8-hexahydro-7-methyl 4-oxo-5-phenyl-2-thionopyrido[2,3d]pyrimidine-6-carboxylate, from substituted aromatic aldehyde, ethyl cyanoacetate, thiobarbituric acid and ammonium acetate by using sulphamic acid catalyst, on heating at 90°C temperature under neat condition.

**Section C**

This section describes an efficient procedure for the synthesis of 14-aryl-14-\(H\)-dibenzo \([a,j]\) xanthenes by the condensation of \(\beta\)-naphthol and substituted aromatic aldehydes using phase transfer catalyst in aqueous medium.
References


