DEVELOPMENT OF NEWER METHODS FOR THE SYNTHESIS OF SOME BUILDING BLOCKS OF BIOACTIVE MOLECULES

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

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Dedicated to my Parents.....

Abstract

The motivation of this research work was to develop newer methods for the synthesis of some basic building units of heterocyclic molecules of biological significances. Development of more efficient, simple and eco-friendly methods is one of the key features of sustainable chemistry. Regarding development of methodology, we utilised the concept of microwave assisted solvent-free organic reactions for the synthesis of oxygen and nitrogen containing few building blocks such as 1,3-dioxanes, coumarins and pyrido[2,3-*d*]pyrimidine derivatives through Prins reaction, Pechmann reaction and multi-component one pot cyclocondensation reactions respectively. Thermal heating condition is employed for tetrahydropyrans and pyrimido[4,5-*d*]pyrimidines synthesis. By keeping in mind the wide advantages of solid heterogeneous catalysts, we employed polymer supported acid as reusable catalysts. Other solid supports such as silica, alumina were also used. Poly(4-vinylpyridine) supported Brønsted acid catalysts were synthesized, characterized and applied in organic reactions. Some simple and readily available reagents and catalysts were used for the synthesis of β-amino carbonyl compounds, 1,3-dioxanes and pyrimidine derivatives. Throughout our work, the greener components such as simplicity in procedure, milder reaction condition, enhancement in reaction rates, higher yields and selectivity, and reusability of catalysts were envisaged.

Chapter 1: General Introduction and Review

The molecules that have capacity to interact with living tissue or system are termed as bioactive molecules. Many heterocyclic compounds are known for their biological significances and majority of clinically employed compounds are heterocycles. Many oxygen and nitrogen containing heterocyclic units are the basic skeleton of several natural products and some of them have received considerable attention due to their wide range of biological activities.

The important name reactions like Prins, aza-Michael addition and Pechmann reactions are well known for the construction of oxygen and nitrogen containing building blocks such as 1,3-dioxanes, tetrahydropyrans, β-amino carbonyl compounds and coumarins. Pyrimidines are also another important class of nitrogen heterocycles readily obtained from multi-component condensation reactions. This chapter contains a thorough review of Prins reaction, aza-Michael reaction, Pechmann reaction and synthesis of pyrimido[4,5-*d*] and pyrido[2,3-*d*] pyrimidine derivatives via hetero Diels-Alder reactions. Reviews on polymer supported

heterogeneous catalysts, solvent-free microwave assisted reactions and multi-component reactions are also emphasized.

Transferring solution phase reactions to solid phase and development of solvent-free reactions become an intense area of research. The application of microwave energy in organic synthesis has brought renaissance because of minimum reaction time, enhanced reaction rate, higher yield and selectivity, procedural simplicity and mild condition.

Ionic liquids may provide a media for organic reactions with numbers of eco-friendly approaches viz. non volatility, recyclability, non explosive, excellent thermal stability and intrinsic physicochemical characteristics.

Use of heterogeneous catalysts, e.g. polymer supported catalysts make processes more benign and economical as they are compatible to environment, can be recovered and recycled and reduce waste and pollution.

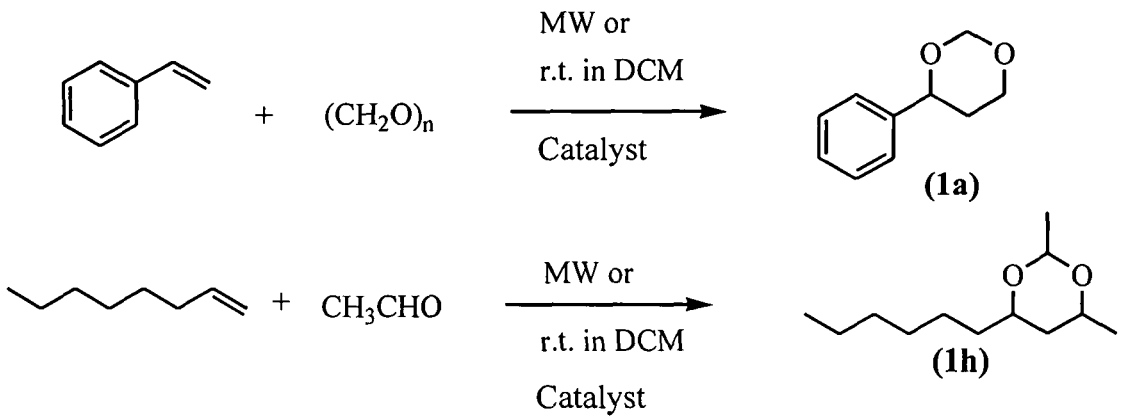
Similarly, multi-component reactions have attracted considerable attention from the point of view of combinatorial chemistry because of convergence, productivity, facile execution and high yields.

In this chapter we have also discussed the objectives of the thesis.

Chapter 2: Preparation of 1,3-Dioxanes and Tetrahydropyran Derivatives via Prins Reaction

Section A: Prins Reaction of Aliphatic Aldehydes and Alkenes for the Synthesis of 1,3-Dioxanes

Acid catalysed condensation reaction between olefin and carbonyl compound is known as Prins reaction. This reaction is one of the efficient methods for the synthesis of 1,3-dioxanes in presence of conventional Lewis or Brønsted acids in volatile organic solvents. Reports on a large number of synthetic methods involve high temperature reaction condition, prolonged reaction time, use of stoichoimetric amount of catalyst, environmental pollution from organic solvents and complicated product purification. So, new methods and environment friendly conditions for the synthesis of 1,3-dioxanes are still in demand.



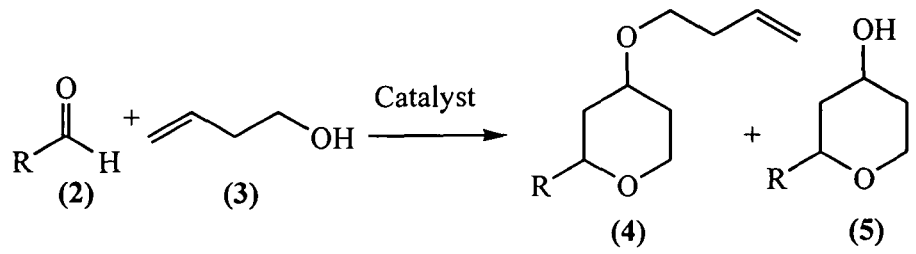
This section describes a comparative study of TsOH/TsOH-SiO_2 catalysed Prins reaction of paraformaldehyde and various alkenes in dichloromethane at room temperature and by microwave irradiation under solvent-free condition. The study revealed that microwave assisted reaction show excellent results within 2-5 min as compared to the solution phase. Formalin was also used as formaldehyde source. Other aldehydes such as acetaldehyde, pentanal and octanal also produced corresponding dioxanes in good yields.

The catalytic activity of polyaniline supported p-toluene sulfonic acid and $FeCl_3$ were also observed for the same reaction in dichloromethane. Both catalysts were found to be less effective than the above mentioned catalysts.

Section B: Synthesis of 2,4-Disubstituted Tetrahydropyran Derivatives through Prins Cyclization Reaction in Presence of Polyaniline Supported Acid Catalysts

Acid catalysed coupling of homoallylic alcohol with aldehyde forms tetrahydropyran derivative and is known as Prins cyclization. In some cases, it forms acetal depending upon the nature of aldehyde. Tetrahydropyran ring is widely distributed through nature, e.g. in carbohydrates and natural products. Under classical conditions, the Prins cyclisation requires strong acid as catalyst and high reaction temperature which often produces a mixture of products. Many polyaniline supported acids (TsOH, H_2SO_4, $FeCl_3$, $AlCl_3$ etc.) exhibit excellent catalytic activity in organic synthesis.

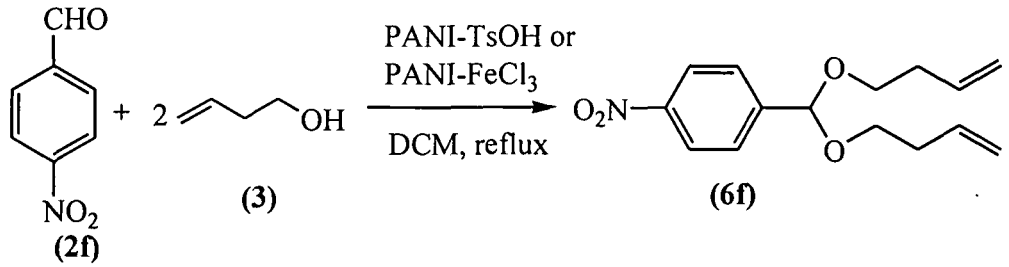
In this section, we examined the catalytic activity of TsOH and $FeCl_3$ for the Prins cyclization of 3-butene-1-ol with benzaldehyde in organic solvents as well as in ionic liquids to form 2,4-disubstituted tetrahydropyran derivatives. The results showed low yield and less selectivity of the desired product.



R=Aryl

	R
a	C_6H_5
b	4-MeC_6H_4
c	4-ClC_6H_4
d	2-ClC_6H_4
e	3-BrC_6H_4
f	4-$NO_2C_6H_4$
g	3-$NO_2C_6H_4$
h	2-$NO_2C_6H_4$

The catalytic activity and selectivity of polyaniline supported TsOH and $FeCl_3$ (PANI-TsOH, PANI-$FeCl_3$) were studied for the Prins reaction of 3-butene-1-ol with different aromatic aldehydes under reflux condition in dichloromethane. The two catalysts produced *cis*-2,4-disubstituted tetrahydropyran ether as single product. In case of electron deficient aldehydes (*o*-, *p*-, *m*-nitro-benzaldehyde) corresponding acetal were produced as single product with excellent yields.



Chapter 3: Synthesis, Characterization and Application of Poly(4-vinylpyridine) Supported Brønsted Acid as Reusable Catalyst for Acetylation and Pechmann Reaction

Section A: Synthesis, Characterization and application of Poly(4-vinylpyridine) Supported Brønsted Acid as Reusable Catalyst for Acetylation Reaction

The use of efficient, non-toxic and more selective supported solid acidic catalysts have received attention in organic synthesis because of their environmental compatibility,

reusability, high selectivity, simple operation and ease of isolation of products. Polymers are widely used as solid support as they make processes more convenient, economic and environmentally benign. Direct use of mineral acids as catalyst is not favourable because of vigorous reaction condition, toxicity, corrosive and hygroscopic nature, difficulty in separation, recovery and recycling. Poly(4-vinylpyridine) seems to be an attractive support to immobilise mineral acids because of the basic nature of pyridyl group.

This section reports the synthesis of three poly(4-vinylpyridine) supported Brønsted acid (H_2SO_4, HCl, H_3PO_4) catalysts viz. P4VP-H_2SO_4, P4VP-HCl and P4VP-H_3PO_4 in ether solution at room temperature.

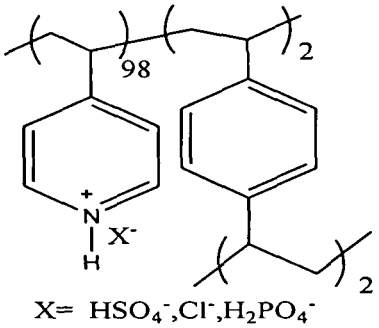
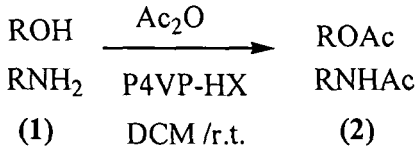


Fig. 1. Structure of poly (4-vinylpyridine) supported acid catalyst (P4VP-HX)

The catalysts were characterised by FT-IR, SEM, SEM-EDX and TGA studies. The catalytic activities of P4VP-HX were investigated for acetylation of alcohols, phenols and amines in dichloromethane at room temperature.



Out of these three catalysts, P4VP-H_2SO_4 performed well in terms of reaction time and yield. After completion of the reactions, the catalysts were recovered, reactivated and reused.

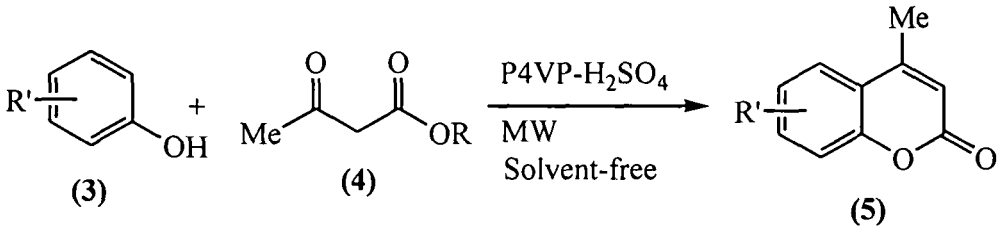
Section B: Poly(4-vinylpyridine) Supported Sulphuric Acid as Efficient Reusable Catalyst for the Pechmann Coumarin Synthesis under Solvent-free Microwave Conditions

Coumarins occupy a special role in realm of natural and synthetic organic chemistry, many of which exhibited broad spectrum of biological activity such as antitumor, anti-HIV, antioxidation, anticoagulant, anticancer, antimicrobial, hypnotic and insecticidal properties.

They are widely used as additives in food, cosmetics, perfumes, and optical brighteners and dispersed fluorescent and tunable laser dyes.

Pechmann reaction is usually employed route for coumarin synthesis, as it involves simple starting materials, that is, β-keto ester and phenol in presence of acidic condensing agent. Though several acidic catalysts have been well documented in literature for coumarin synthesis, most of the methods have their own merits and demerits. It is seen that solid supported heterogeneous catalysts, e.g. polymer supported acid catalysts are sometimes more efficient than their homogeneous counterpart with several eco-friendly approaches.

In this part we utilize poly(4-vinylpyridine) supported H_2SO_4 (P4VP-H_2SO_4) as highly efficient, simple and regenerable catalyst for the synthesis of coumarin derivatives via Pechmann condensation reaction of β-keto esters with structurally diverse phenols under microwave irradiation in solvent-free conditions. It was observed that the reactions proceed smoothly in presence of 0.2 equivalents of the catalyst within 8-15 min and afforded corresponding coumarin derivatives in excellent yields.



R= Me, Et

We also investigated the catalytic efficacy of H_2SO_4 and TFA in presence of acidic alumina as support for the same reaction under similar reaction condition. These two catalysts were also effective for both electron rich and electron poor phenols to produce coumarins in good yields within 8-20 min.

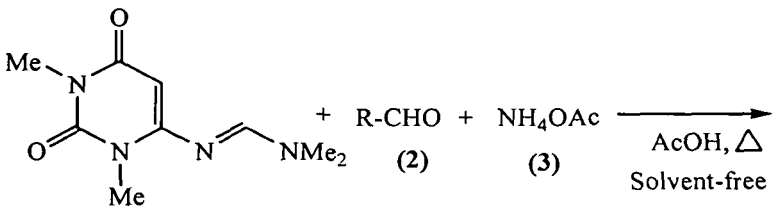
Chapter 4: One-Pot Multi-Component Synthesis of Novel Dihydropyrimido[4,5-*d*] Pyrimidine and Dihydropyrido[2,3-*d*]Pyrimidine Derivatives

Section A: An Efficient Regiospecific Synthesis of Highly Functionalised Novel Dihydropyrimido[4,5-*d*]Pyrimidine Derivatives by Three-Component Condensation under Solvent-Free Conditions

The importance of uracil and its annulated substrates is well recognised by medicinal

chemists and biologists. Pyrimido[4,5-*d*]pyrimidines are an important class of annelated uracils of biological significances. Some analogues have been found to show antitumor, anti-inflammatory, anticancer, antiviral and CNS depressant activities.

This section describes a three-component one-pot condensation of aldehydes, ammonium acetate and 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil in presence of catalytic amount of acetic acid under thermal treatment at 90 °C in solvent-free conditions that afforded novel dihydropyrimido[4,5-*d*]pyrimidine derivatives in excellent yields.



(1) **(4)**

	R
4a	4-MeC_6H_4
4b	C_6H_5
4c	4-ClC_6H_4
4d	4-$MeOC_6H_4$
4e	4-$NO_2C_6H_4$
4f	4-BrC_6H_4
4g	2-SC_4H_3
4h	n-$Me(CH_2)_3$
4i	$CH{=}CHC_6H_5$

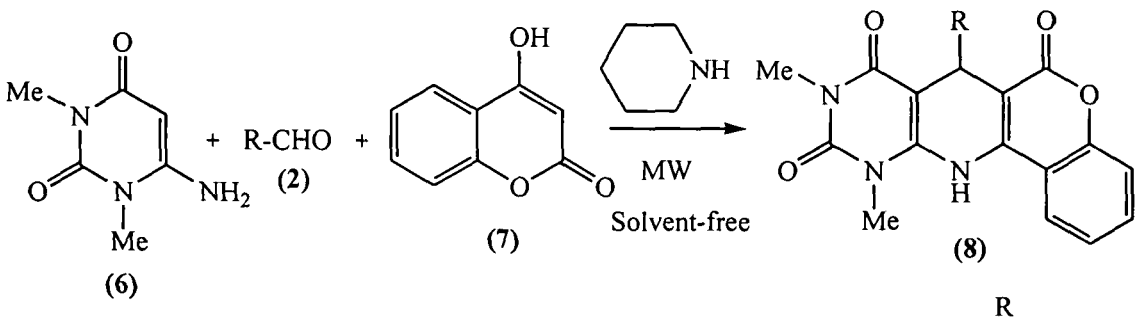
6-[(dimethylamino)methylene]amino-1,3-dimethy uracil was readily obtained by the reaction of 6-amino-1,3-dimethyl uracil with DMF-DMA under thermal condition in solid state. The same can be obtained more efficiently under microwave irradiation and takes only 3 min to complete the reaction in 90% yield.

Section B: Synthesis of Novel Tetracyclic Dihydropyrido[2,3-*d*]Pyrimidine Derivatives under Solvent-Free Conditions

Pyrido[2,3-*d*]pyrimidines represent a heterocyclic ring system of considerable interest because of several biological activities associated with this scaffold. Many compounds having this ring system are known for antitumor, antibacterial, antiallergic, antihypertensive, cardiotonic activity. Some of them exhibit antimalarial, antifungal and analgesic properties.

This section of the chapter explains the synthesis of novel tetracyclic dihydropyrido[2,3-*d*]pyrimidine derivatives utilising three component one pot condensation

of aromatic aldehydes, 4-hydroxy coumarin and 6-amino-1,3-dimethyl uracil in presence of catalytic amount of piperidine under microwave irradiation in solvent-free conditions. The reaction proceeded smoothly at 90 °C and corresponding dihydropyrido[2,3-*d*]pyrimidine derivatives were isolated in good yields.

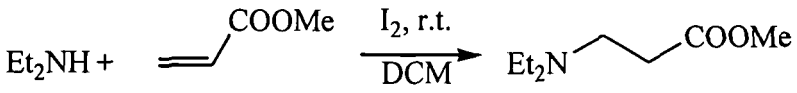


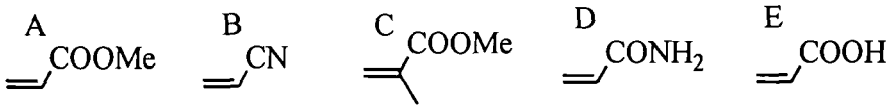
R	
4a	4-MeC_6H_4
4b	C_6H_5
4c	4-$MeOC_6H_4$
4d	4-ClC_6H_4
4e	4-BrC_6H_4
4f	SC_4H_3

Chapter 5: Aza-Michael Addition of Amines to α,β-Unsaturated Compounds using Molecular Iodine as Catalyst

The conjugate addition of nitrogen nucleophile to α,β-unsaturated carbonyl compound leading to the formation of β-amino carbonyl compound is known as aza-Michael addition reaction. β-amino carbonyl compounds are not only important building unit of natural products including β-lactam, but also versatile intermediate of β-amino alcohol, β-amino acid, β-lactam antibiotics and 1,2-diamines. Several groups have reported stoichoimetric and sub-stoichoimetric use of some Lewis acid catalysts. Here we discussed the use of iodine as mild and simple Lewis acid catalyst for the aza-Michael addition at room temperature in organic solvent and under solvent-free condition.

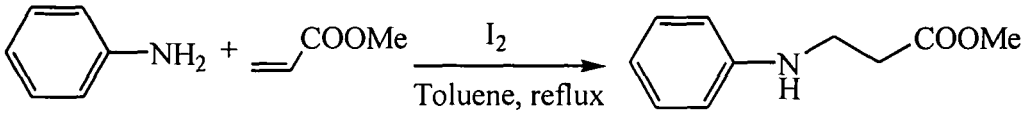
We employed iodine (I_2) as Lewis acid catalyst for conjugate addition of different aliphatic and aromatic amines to a range of α,β-unsaturated compounds (A, B, C, D, E). Initially, we studied 1,4-addition acyclic and cyclic aliphatic amines in presence of catalytic amount of iodine in dichloromethane at room temperature and observed excellent conversion to the corresponding adducts within short time.





We also observed the solvent effect of different solvents on aza-Michael reaction using molecular iodine as catalyst. Solvent-free studies for the synthesis of aza-Michael adduct were carried out.

In order to extend scope of iodine, we carried out addition of aromatic amines to α,β-unsaturated compounds under reflux condition in toluene and isolated the corresponding desired products in moderate to good yield.



Chapter 6: Summary and Future Scope of the Present Work

In this chapter we discuss the overall summary and future scopes of the work done.

Declaration

I, Mr Kalyan Jyoti Borah, hereby declare that the thesis entitled "Development of Newer Methods for the Synthesis of Some Building Blocks of Bioactive Molecules" is submitted to Tezpur University in the Department of Chemical Sciences under the School of Science and Technology in partial fulfillment of the requirements for the award of the degree of Doctor of Philosophy. The research work has been carried out under the joint guidance of Dr. Ruli Borah, Associate Professor, Department of Chemical Sciences, Tezpur University, Napaam and Dr. Dipak Prajapati, Scientist-G & Head, Medicinal Chemistry Division, NEIST (formerly RRL, Jorhat), Jorhat.

No part of this thesis has been submitted elsewhere for award of any other degree.

Kalyan Jyoti Borah

Date: 2.06.2011

Kalyan Jyoti Borah

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Department of Chemical Sciences
School of Science & Technology

Date: 2/6/2011

Certificate

This is to certify that the thesis entitled "Development of Newer Methods for the Synthesis of Some Building Blocks of Bioactive Molecules" submitted to the School of Science and Technology, Tezpur University in partial fulfillment for the award of the degree of Doctor of Philosophy in Chemical Sciences is a record of research work carried out by Mr Kalyan Jyoti Borah under my supervision and guidance.

All helps 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.

R. Borah

(Signature of Supervisor)

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Dr Dipak Prajapati
Scientist G & Head
Medicinal Chemistry Division

Dated 13th June, 2011

Certificate

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All helps 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.

(Dr Dipak Prajapati)
Signature of Co-supervisor

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Signature of:

Supervisor External Examiner

Co-supervisor

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It gives me immense pleasure to express my profound gratitude and regards to my esteemed supervisor Dr. Ruli Borah, Associate Professor, Department of Chemical Sciences, Tezpur University, for her invaluable guidance, suggestions, constant encouragement and concern throughout the period of research and preparation of this manuscript. I will remain ever grateful to her.

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Kalyan Jyoti Borah

Date: 2. 06. 2011

(Kalyan Jyoti Borah)

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Abbreviations/Symbols used:

Ac	: acetyl
Anal	: analytical
Ar	: aromatic
bmim	: butylmethylimidazolium
bs	: broad singlet
°C	: degree centigrade
^{13}C	: carbon-13
Calcd	: calculated
CHN	:carbon hydrogen nitrogen
d	: doublet
DCM	: dichloromethane
DMF-DMA	: dimethylformamide-dimethylacetal
Et	: ethyl
emim	:ethylmethylimidazolium
FT	: furrier transform
g	: gram
GC	: gas chromatography
h	: hour
^{1}H	: proton
Hz	: hertz
IL	: ionic liquid
IR	: infrared
m	: multiplet
MCR	: multi-component reaction
Me	: methyl

MHz	: mega hertz
min	: minute
mp	: melting point
MW	: microwave
MAOS	: microwave assisted organic synthesis
MPy	: methylpyridinium
PANI	: polyaniline
Ph	: phenyl
ppm	: parts per million
PTSA	: para-toluene sulfonic acid
P4VP	: poly(4-vinylpyridine)
q	: quartet
r.t.	: room temperature
s	: singlet
t	: triplet
TLC	: thin layer chromatography
ν	: neu (frequency)
δ	: chemical shift
J	: coupling constant

General Remarks:

- All the commercially available chemicals were used directly without purification unless otherwise whenever needed.
- Reaction progress was monitored by ascending TLC on glass baked plates using Silica Gel G. Visualisation of spots on TLC plates was achieved by development with iodine chamber.
- Products were purified by either preparative TLC using Silica Gel G or column chromatography using Silica Gel 60-120 mesh.
- Melting points were recorded in Buchi-540 micro melting point apparatus using open capillary tube and are uncorrected.
- Microwave reactions were conducted in Catalyst System microwave reactor and in Samsung C 103FL domestic microwave oven.
- IR spectra were recorded on a Nicolet Impact Model-410 spectrometer.
- ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in JEOL JNM ECS-400 MHz FT-NMR spectrometer and Bruker Avance DPX-400 NMR spectrometer, considering TMS as an initial standard and chemical shift values were given in δ ppm values.
- Mass spectra were recorded in a Perkin-Elmer Clarus 600 GC mass spectrometer. Few LC mass spectra were recorded in Brucker Daltonic Data Analysis 2.0 spectrometer.
- Elemental analyses were done using Perkin-Elmer series II CSNS/ O Model 2400 machine calibrated against standard acetanilide.
- SEM-EDX analyses were done in JEOL JSM-6390 LV Scanning Electron Microscope equipped with energy dispersive X-ray detector.
- Thermogravimetric analyses were done in SHIMADZU TGA-50 at a heating rate of 10 ^{o}C/min under nitrogen atmosphere.

Chapter 1

General Introduction and Review

Chapter 1

1.1 General Introduction:

1.1.1 Heterocyclic Compounds as Building Blocks of Bioactive Molecules:

Heterocyclic compounds are those where one or more atom(s) of the ring are hetero atoms such as N, O, S, P and so on. More than half of the known organic compounds are heterocyclic compounds. These are widely distributed in nature, and many of them are of fundamental importance for life processes. For example, nucleic acid bases containing purines and pyrimidines; hemoglobin and chlorophyll containing porphyrin rings; essential dietary ingredients containing vitamins B_1, B_2, B_3, B_6 and ascorbic acid; the three important amino acids namely histidine, proline and tryptophan; almost all the drugs and pharmaceuticals; and many natural products like alkaloids, carbohydrates, and plant pigments. All these compounds contain hetero ring(s) in their molecules. Although, many bioactive molecules have been isolated from plants to fight against the germs that cause diseases; but due to very low abundance in nature and complex isolation procedure, synthesis of bioactive molecules or their building blocks occupy a significant position in synthetic organic chemistry. These are the reasons why a great deal of recent research work is concerned with the method of synthesis of hetero rings and studying their properties.

There are large numbers of biologically active heterocyclic compounds, many of which are of regular clinical use. Some heterocyclic compounds are isolated from nature and a large numbers are of synthetic origin which are widely used as anticancer, antitumor, antibacterial, analgesics, hypnotics etc. Oxygen and nitrogen containing heterocycles are the basic skeleton of numerous natural products and some of them received considerable attention over the past years due to their wide range of biological activities.[1-4] Discussion of these heterocycles is more relevant as the thesis focuses on

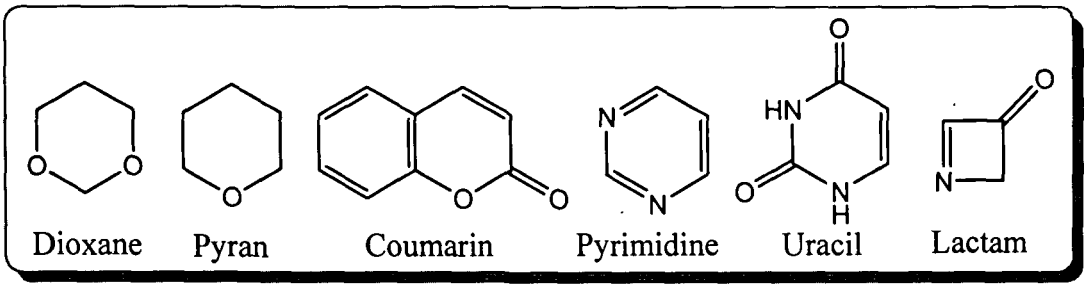


Figure 1.1 Structures of some basic heterocyclic units

development of newer methods for the synthesis of some oxygen and nitrogen containing heterocyclic units (Fig. 1.1) of bioactive molecules.

For construction of these heterocyclic rings different synthetic strategies have been reported in literature.[5] The Prins and Pechmann reactions are two well known name reactions used for the formation of 1,3-dioxane, tetrahydropyran and coumarin units, respectively. Pyrimidines are also another important class of nitrogen heterocycles readily obtained from multi-component hetero Diels-Alder reaction. Nitrogen containing four-membered unit β-lactam is the cyclization product of β-amino carbonyl compound. The conjugate addition of amino compound to α,β-unsaturated carbonyl compound leads to the formation of β-amino carbonyl compound which is called aza-Michael addition. This chapter contains a thorough review of Prins reaction, Pechmann reaction, synthesis of pyrimido[4,5-*d*] and pyrido[2,3-*d*]pyrimidine derivatives via hetero Diels-Alder reaction, and aza-Michael reaction for the synthesis of β-amino carbonyl compound.

1.1.2 General Methodologies for Synthesis of Heterocyclic Units:

1.1.2.1 Solvent-Free Organic Synthesis:

The development of environmentally benign technology and reagent is the demand of time to carry out chemical research in terms of sustainable chemistry. In last few decades, invention of some innovative techniques and novel reagents have brought revolutionary changes in organic chemistry which made organic synthesis more dynamic and effective than ever before. A new technique that is set to display significant advances in synthesis has moved to the forefront of chemical research, Microwave Assisted Solvent-Free Organic Synthesis.

From earlier times it is seen that chemistry is dominated by the study of reactions in solution. One reason for this might be Aristotle's famous philosophy "No coopora nisi Fluida", which means no reaction occurs in the absence of solvent.[6] It is very curious that almost all reactions are still carried out in solution, though there is no any special reason for the use of solvent. The major problem with organic solvents in relation to human health and the environment is their ability to volatilise and thus have a detrimental effect by exposing individuals and contaminating to air. However, as the

introduction of cleaner technologies has become a major concern throughout both industry and academia, the search for alternatives to the most damaging solvents has become a high priority.

One alternative of avoiding conventional solvents is to carry out reactions in solvent less condition.[7] The solvent-free syntheses are found to be superior over those carried out in solution[8] phase. Solvent-free reaction has many advantages such as avoid of volatile organic solvent, high yield and product selectivity, low cost, faster rate as compared to reactions in organic solvent and simple purification techniques. The word 'neat' to be a better description to explain the highly concentrated nature of the reagents which lack additional solvent in order to remove confusion in many instances.[9] In some cases, it is found that solid state organic reaction occurs more efficiently and selectively than does in solution reaction, since molecules in crystal are arranged tightly and regularly. Currently it attracts chemists, as reactions are easy to handle, comparatively cheap to operate, simple work up procedure and reduce pollution.[10] A solid state organic synthesis can be carried using the reactants alone or incorporating them in a solid support such as silica gel, alumina, clays or other matrices. Some of the solid phase reactions have been reported to be solvent-free but they clearly involve the formation of a liquid phase, e.g. Aldol condensation and oligomerisation of benzylic compounds to form cavitands, proceed via a liquid phase. Rothenberg *et al.*[11] clearly distinguished these so called solvent free reactions from solid-phase synthesis and solid-solid reactions or solid-state synthesis. Accordingly, *solid-phase synthesis* is the reaction of molecules from a fluid phase with a solid substrate, e.g. solid phase peptide synthesis. *Solvent-free synthesis* involves any system in which neat reagents react together, in the absence of a solvent and *solid-state synthesis* or solid-solid reactions, in which two macroscopic solids interact directly and form a third, solid, product without intervention of a liquid or vapour phase.

1.1.2.2 Microwave Assisted Organic Reactions:

The combination of solvent-free condition and microwave irradiation[12] leads to large reduction in reaction time, enhancement in conversions and sometimes in selectivity with several advantages of eco-friendly approach. Microwave range of electromagnetic spectrum covers the area of ultrahigh frequencies from 30 GHz to 300

MHz. The frequencies of 915, 2450, 5800 and 22125 MHz were accepted by international agreement as working frequencies for scientific and industrial microwave facilities.[13,14] 2450 MHz frequency is most oftenly used in research practise. Although this energy is not sufficient to break chemical bonds; but it facilitates chemical reactions tremendously through dielectric heating produced by interaction of microwave energy and matter (reactant and solvent molecule in case of chemical reaction).

Over past three decades, microwave chemistry has evolved as an established field of science, due to intensified research in this area. Microwave technology has been used in chemistry in late 1970s; but Giguere[15] and Gedye[16] first implemented it in organic synthesis in 1986. At present about 30,000 chemists use microwave technology to conduct chemical reactions worldwide. Many of the top pharmaceutical, agrochemical and biotechnology companies were already using Microwave Assisted Organic Synthesis (MAOS) as a forefront technology for library generation and lead optimisation as they realise the ability of this enabling technology to speed chemical reactions. Higher yield and better selectivity are consequences of selective absorption of microwave radiation by polar or polar transition state intermediates during the course of the reaction. Regardless of the exact origin of the observed rate enhancement, microwave synthesis is extremely efficient and applicable to a wide range of practical synthesis.

Almost any type of organic reactions requiring heating or thermal conditions can be performed by microwave irradiation. Microwave dielectric heating is dependent on the ability of a solvent or matrix to absorb microwave energy and to convert it into heat.[17,18] The absorption of microwave radiation occurs via two mechanisms: dipole polarisation and conduction.

When irradiated at microwave frequencies, the dipoles of the sample align in the applied electric field. As the field oscillates, the dipole attempts to realign itself with the alternating electric field. In this process heat energy is lost through molecular friction and dielectric loss. The amount of heat generated is directly related to the ability of the matrix to align itself with the frequency of the applied electric field. Microwave irradiation produces intense internal heating, resulting in even heating throughout the sample, as compared to wall heat transfer when an oil bath is applied as energy source. It is obvious that compounds with higher dielectric constants tend to absorb microwave

frequency readily, while less polar or compounds with no net dipole moment are microwave inactive.

Two different types of microwave reactors are emerging for MAOS: multimode and monomode reactors. In multimode reactor, microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. A mode stirrer ensures that the field distribution is as homogeneous as possible. The domestic microwave oven that is widely used for organic synthesis operates in multimode fashion. However in monomode reactor, only one mode is present and the microwave irradiation is focused directly through an accurately designed wave guide on to the reaction vessel mounted at a fixed distance from the radiation source.

Microwave heating has been shown to be an invaluable optimisation technique since it reduces reaction time dramatically, from days or hours to minutes or seconds[19] and affords the desired product in suitable yield and purity. Several chemical industries have reported dramatic productivity increase in switching from conventional heating to MAOS.[20-25] Although the initial investment cost is considerable, the dramatically increased efficiency of the microwave method allows a return of investment in a short time span. The success stories of MAOS have been documented in more than 2000 publications.[26] Thus; solvent-free microwave irradiation has emerged as the newest trends of green methodologies.

1.1.2.3 Ionic Liquid as Reaction Medium:

With increasing environmental concerns and the regulatory constrains faced in the industry, use of environmentally benign reaction media[27] has become a crucial and demanding area in synthetic chemistry. Ionic liquids[28] (IL) offer a new and safe approach to modern chemical processes when used as alternative to conventional volatile organic solvents.[27,29] During this decade much attention has been focused on ionic liquids and many organic reactions were performed in ILs with good performances. Ionic liquid is a salt in which ions are poorly coordinated, which allows these solvents being liquid below 100 °C and even at room temperature. Here, at least one ion has a delocalised charge and one component is organic, which prevents the formation of stable crystal lattice. Imidazolium and pyridinium salts are commonly used ionic liquids e.g. [emim]BF_4, [bmim]BF_4, [bmim]PF_6, [2-MPyH]Tfa, [2-MPyH]OTf

etc.

Ionic liquids are non volatile, recyclable, non explosive, easy to handle, have excellent thermal stability and interesting intrinsic physiochemical characteristics. They may provide a media for clean reaction with minimal waste and efficient product extraction. Their high polarity and ability to solubilise both organic and inorganic compounds can result in enhanced rates of chemical processes and they can provide higher selectivities compared to conventional solvents. Furthermore, ionic liquids with the catalyst can be easily recovered and recycled without the lost of activity for several times.[30]

1.1.2.4 Polymer Supported Acids as Heterogeneous Catalysts:

Nowadays, the use and design of environment-friendly heterogeneous catalyst[31] has played a vital role in the economic development of the chemical industry. Usually, the majority of fine, specialty and pharmaceutical chemicals manufacturing processes depend on homogeneous reagents and catalysts. Many of the processes have been developed simply to maximize product yields, neglecting the environmental aspect of waste and toxic by-products formed during the reaction. Most of the waste is generated during separation stage of the processes and release[32] large volume of hazardous waste to the environment. The waste not only causes pollution but also requires expenditure for cleaning up. The efficient use of non-toxic and more selective solid catalyst is very desirable and represents an important goal of the proposed scheme in the context of clean synthesis. Heterogeneous materials have a lot of useful properties, for examples, high versatility, easy treatment, and work-up, mild reaction conditions, high yields and selectivity and often reusable. The atom efficiency of the reaction is improved and the volume of waste is significantly reduced.

In heterogeneous catalysis, the reactants diffuse to the catalyst surface and adsorb onto it. After reaction the product desorbs from the surface and diffuses away. The total surface area of the solid catalyst has an important effect on the reaction rate as it determines the availability of catalytic sites. The most common approach to maximise surface area is the use of catalyst supports.

Heterogeneous catalysts are typically supported which means that catalyst is dispersed on a second material that enhances the effectiveness or minimises the cost.

Supports are porous material with high surface area, most commonly alumina, silica or various kinds of polymers. The study of polymer supported catalyst is motivated by the major advantages of the physical separation of the supported catalyst from the substrates and products, thereby allowing the recycling of expensive or toxic catalyst and thus releases less waste material to the environment which make organic reaction methods more convenient, economic and environmentally benign. The reactions can be performed under mild conditions and product purification is simple due to easy separation of insoluble polymer support from the reaction medium. Many reactions[33] can be carried out cleanly, rapidly and in high yields. In polymer supported catalyst, active sites of catalysts are immobilised through chemical bonds or weaker interactions such as hydrogen bonds or donor acceptor interactions. Polystyrene, poly(4-vinyl pyridine), polyaniline etc are widely used support for the preparation of solid catalysts.

Different types of Brønsted or Lewis acids are widely used as catalyst in various organic transformations. The direct[34] use of Lewis acid or mineral acid in liquid state such as H_2SO_4, HCl, H_3PO_4 etc. are not favourable because of vigorous reaction condition, corrosive nature, toxicity, and hygroscopic nature, difficulty in separation, recovery and recycling. Furthermore, homogeneous catalysts have disadvantages such as difficulty in product separation and corrosive effect of the catalyst on the reactor material. In order to overcome the drawbacks of homogeneous catalysts, immobilisation of homogeneous catalysts using a solid support is thought to be effective. The use of recyclable polymer supported acids can easily eliminate these problems associated with conventional catalysts and reduce the amount of waste material to the environment.

1.1.2.5 One-Pot Multi-Component Synthesis:

'One pot' reactions are gaining importance due to their environmental advantages and cost effectiveness in organic synthesis. The main advantages of one-pot protocol are simple operation, higher overall yields, and formation of fewer or no side products. The one-pot protocol avoids the isolation of unstable reaction intermediate, and increases the rate of reaction to form the selective product. Multi-components reactions (MCRs) constitute an especially attractive synthetic strategy for rapid and efficient library generation because the products are formed in a single step and diversity can be achieved simply by varying the reacting components.[35] This route combines three or

more reactants in one-pot to form single product that incorporates structural features of each reagent. Here, the components do not react simultaneously in one step, rather in a sequence of elementary chemical reactions. Thus, new routes utilizing a MCR protocol for the synthesis of different products can attract considerable attention in the search for rapid-entry methods to these heterocycles over conventional chemical reactions. MCRs have emerged as a highly valuable synthetic tool in the context of modern drug discovery. Design of highly efficient chemical reaction sequences that provide minimum number of synthetic steps to assemble compounds with interesting properties is a major challenge of modern drug discovery.[36] Used in conjunction with target-oriented synthesis, combinatorial chemistry approaches can be employed to introduce or broaden structural variations in a lead compound of interest. The atom economy and convergent character, the possible structural variations, the accessible complexity of the molecules, and the very large number of accessible compounds are among the described other advantages of multi-components reactions.[37] Thus they are perfectly adaptable to automation for combinatorial synthesis.[37]

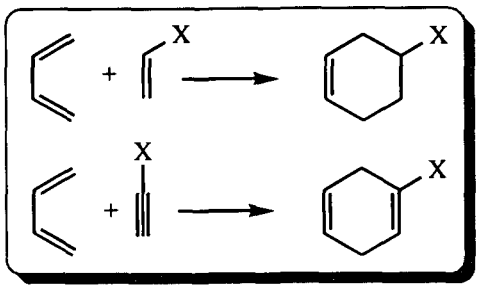
The concept of MCRs to construct complex libraries is not new in Chemistry. The Strecker synthesis of α-amino acids from α-amino cyanides was first published in 1850 and is generally considered as the first MCR.[38] Some other notable MCRs are Mannich reaction, Biginelli reaction, Hantzsch pyridine synthesis, Passerini reaction and Ugi reaction. Due to their inherited advantages over two-component reactions in several aspects, continued efforts are being made to explore new MCRs for developing popular organic reactions.

1.1.2.6 Cycloaddition Reactions in Synthesis:

Cycloaddition reaction is a ring closure reaction where number of σ-bonds increases at the expense of π-bonds without loss of any fragment and results in the formation of cyclic compound. It is highly atom economic reaction. Diels-Alder reaction laid the foundation for remarkable development of cycloaddition chemistry.

Diels-Alder reaction[39] is a thermally allowed [4π+2π] cycloaddition, where two new σ- bonds are formed at the expense of two π-bonds. The reactants are a conjugated diene and a dienophile. The diene component may be cyclic or acyclic and the dienophile may be an alkene, alkyne or heterodienophile (N=N, N=O, C=O, C=S). The

conjugated double bonds must be in *cis* form to obtain overlap of p-orbitals of diene with those of dienophile. The resulting product is an unsaturated six membered (Scheme 1.1) carbacycle or a heterocycle.



Scheme 1.1

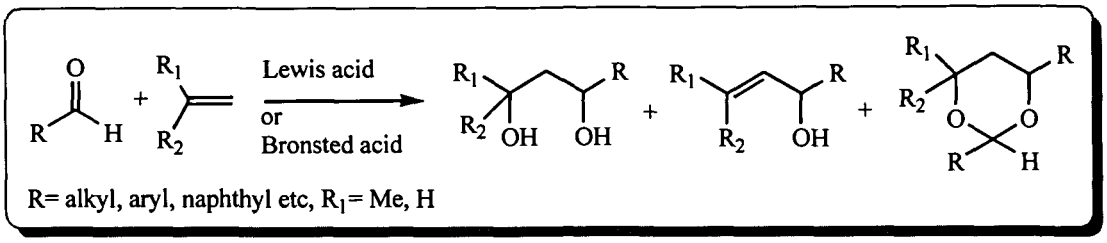
Substituents of the diene and dienophile control the outcome of the Diels-Alder reaction. They can act to enhance or inhibit reactivity and control the stereo and regioselectivity. Frontier Molecular Orbital (FMO) theory has been employed for explaining the reactivity and selectivity in cycloaddition reaction. Diels-Alder reaction has been classified into three types, viz. normal, neutral and inverse electron demand, depending on possible arrangements of HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) of the substituents. In case of normal Diels Alder reaction, electron donating substituents on diene and electron withdrawing substituents on dienophile accelerates the reaction.

The versatility of cycloaddition reaction has increased with the advent of hetero atom substituted dienes and dienophiles. Hetero Diels-Alder reactions are becoming a mainstay in natural product synthesis.

1.2 Review of Literature for the Synthesis of Building Blocks of Bioactive Molecules:

1.2.1 Prins Reaction:

The acid catalysed condensation reaction (Scheme 1.2) between olefin and carbonyl compound is known as Prins reaction. This reaction can be used to produce 1,3-dioxanes, 1,3-glycols, unsaturated alcohols, diolefins and tetrahydropyran derivatives depending on reaction condition. 1,3 dioxanes are generally used in organic synthesis as solvents and reaction intermediates.



Scheme 1.2

Dioxane rings are common structural unit of various bioactive molecules such as (+)-Dactylolide (a cytotoxic agent),[40] derivatives of 2-substituted-1,3-dioxanes (antimuscarinic agents),[41] and (+)-SCH 351448 (a novel activator of low-density lipoprotein receptor promoters).[42] 1,3-dioxane derivatives have been found to be effective modulators for multidrug resistance.[43] A variety of biologically active molecules have been identified from libraries of diverse, natural product-like 1,3-dioxanes.[44] The tetrahydropyran ring is backbone of many natural products such as carbohydrates, polyether antibiotics and marine toxins. It is a core unit of several natural products (Fig. 1.2) such as phorboxazole A, pysmberin, centrolobine, avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins and acutiphycins.[45] The basic structural motif of latrunculins[46] (sea sponge derived bioactive molecule) is a macrolide 1,3 fused to a tetrahydropyran ring.

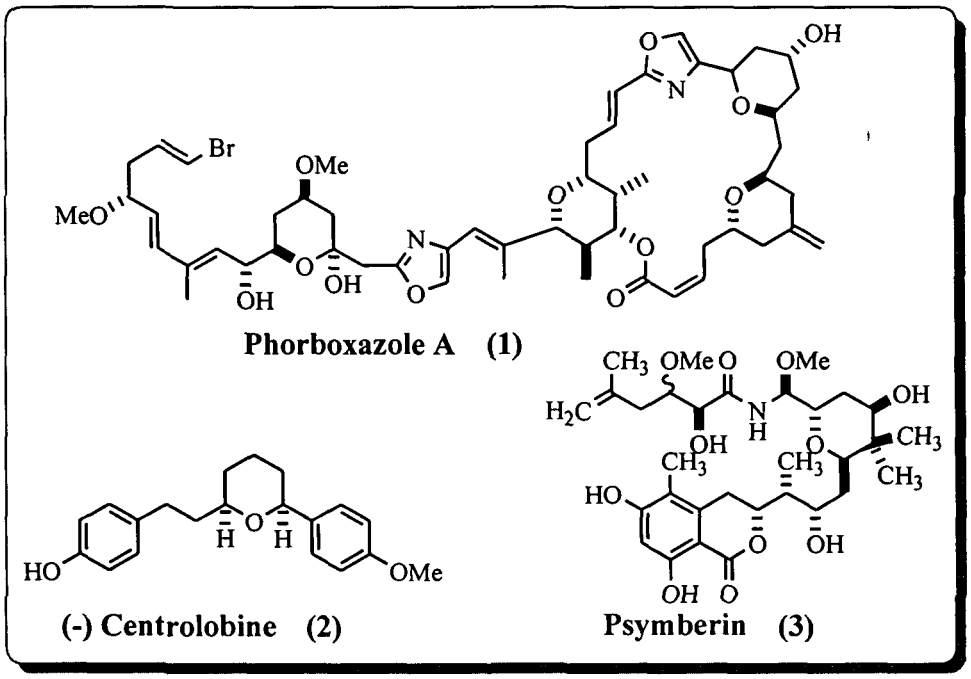
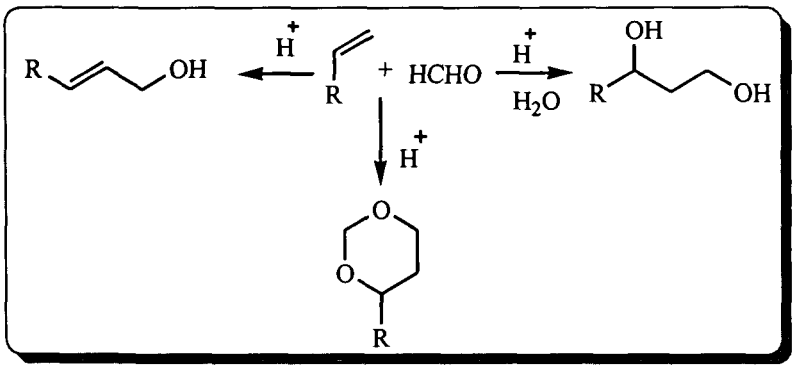


Figure 1.2: Structures of bioactive molecules containing pyran ring

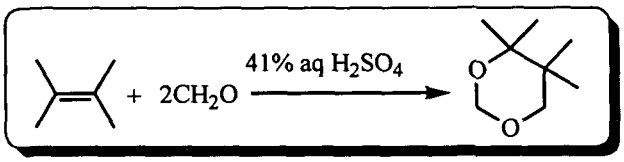
1.2.1.1 Methods for Synthesis of 1,3-Dioxanes:

The Prins reaction is an electrophilc addition of an aldehyde or ketone to an alkene or alkyne followed by capture of a nucleophile.[47] The original reaction was reported by Dutch chemist Hendrik Jacobus Prins[48] in 1919. The outcome of the reaction depends on reaction conditions[49] (Scheme 1.3). With water and protic acid as the reaction medium, it produces 1,3-diol. In absence of water, dehydration takes place to an allylic alcohol. With an excess of formaldehyde and at low reaction temperature, the reaction product is dioxane. When water is replaced by acetic acid, the corresponding esters are formed.



Scheme 1.3

As a result, the acid-catalyzed Prins reaction of simple olefins and formaldehydes lead to the formation of major amounts of 1,3-dioxanes and glycols along with various side products such as tetrahydropyranols, tetrahydrofuran derivatives and monoalcohols. A variety of acid catalysts have been employed[50] in the Prins reaction which include sulphuric, hydrochloric, acetic, hypochlorous, nitric, and phosphoric acids. Out of these acids, dilute sulphuric acid appears to be the most useful catalyst for the synthesis of 1,3-dioxanes at room temperature to higher temperature for longer reaction period. In addition, cation exchange resins, boron trifluoride, aluminium chloride, zinc chloride, and titanium(IV) chloride have also been used[51] in the synthesis of 1,3-dioxanes.The amount of major products depend on the concentration of acid catalysts and the reaction temperature. For examples, the reaction of lower molecular weight tertiary[52] alkenes like 2,3-dimethyl-2-butene and 37% aqueous formaldehyde at 32 °C in the presence of 41% aqueous sulphuric acid gave 93% 4,4,5,5-tetramethyl-1,3-dioxane (Scheme 1.4).

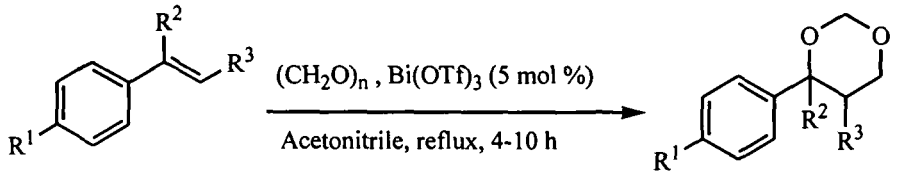


Scheme 1.4

For olefins of structure R^1-CH=CH_2, R^1-CH=CH-R^2 (R^1, R^2=alkyl or R^1=aryl) and the higher molecular weight tertiary olefins, higher temperature and/or stronger solutions of acid catalysts are required.

Along with conventional Brønsted or Lewis acid catalyzed synthesis of 1,3-dioxane derivatives several modified methods have been reported in literature in solution or solvent-free conditions.

Sreedhar *et al.* used[53] bismuth(III) triflate as efficient catalyst (Scheme 1.5) for the Prins reaction of styrenes and formaldehyde in acetonitrile under reflux for 4-10 h to form good yields of 1,3-dioxanes.

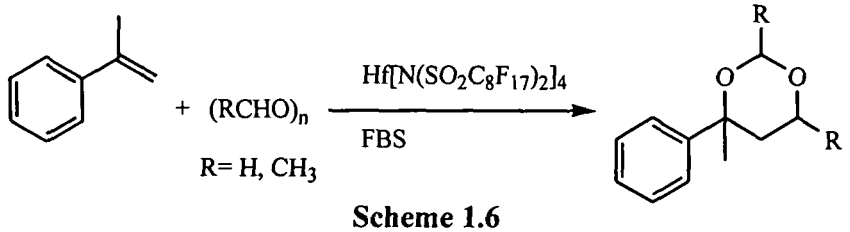


(4): R^1= H **(7)**: R^1=OMe
(5): R^1= Me **(8)**: R^1=OAc
(6): R^1=Cl

(4-8)
(77-90%)

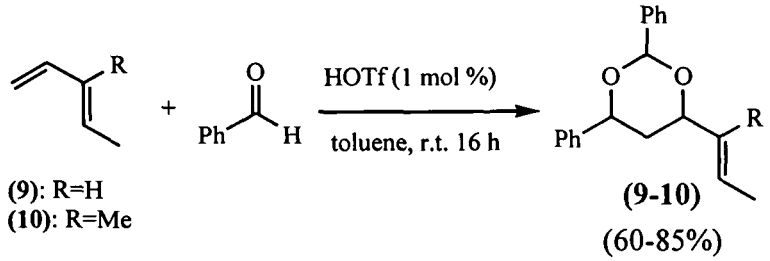
Scheme 1.5

Xiuhua[54] *et al.* described a facile and recyclable method for the Prins reaction of α-methylstyrene with Aldehydes (Scheme 1.6) using hafnium(IV) bis (perfluorooctanesulfonyl)amides in fluorous biphasic system. The reaction proceeds smoothly and affords the corresponding 1,3-dioxanes in good yields. Furthermore, the recovered fluorous phase containing catalyst can be recycled upto 17 times with yields consistently above 80%.



Scheme 1.6

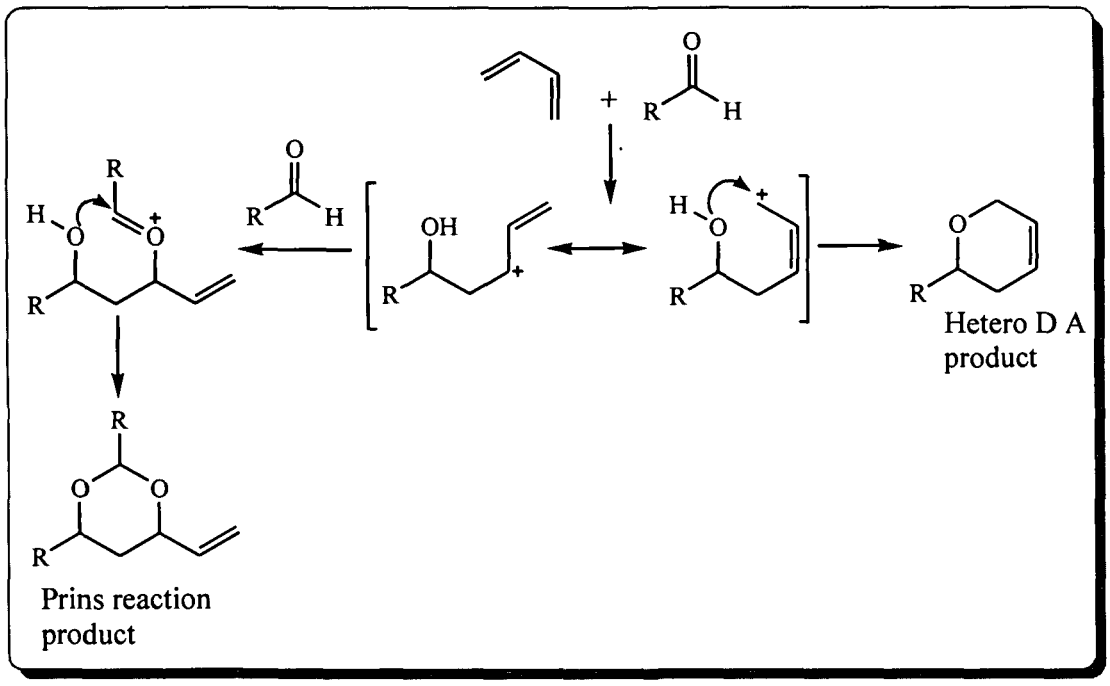
Aggarwal[55] and co-workers observed that trifluromethanesulfonic acid catalyzed the Prins reaction between aldehydes and dienes (Scheme 1.7) with a substituent in the 1-position to form the corresponding 1,3-dioxanes in moderate yield, which can be increased using an excess of the aldehyde. The reaction also formed hetero Diels-Alder product when a non-concerted mechanism is involved (Scheme 1.8).



(9): R=H
(10): R=Me

(9-10)
(60-85%)

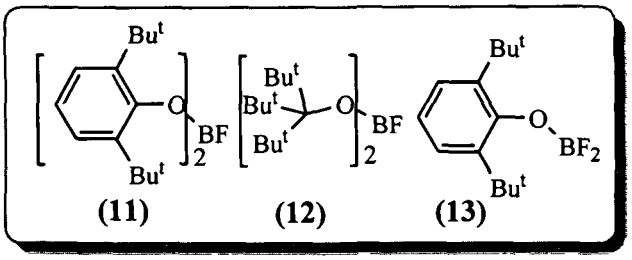
Scheme 1.7

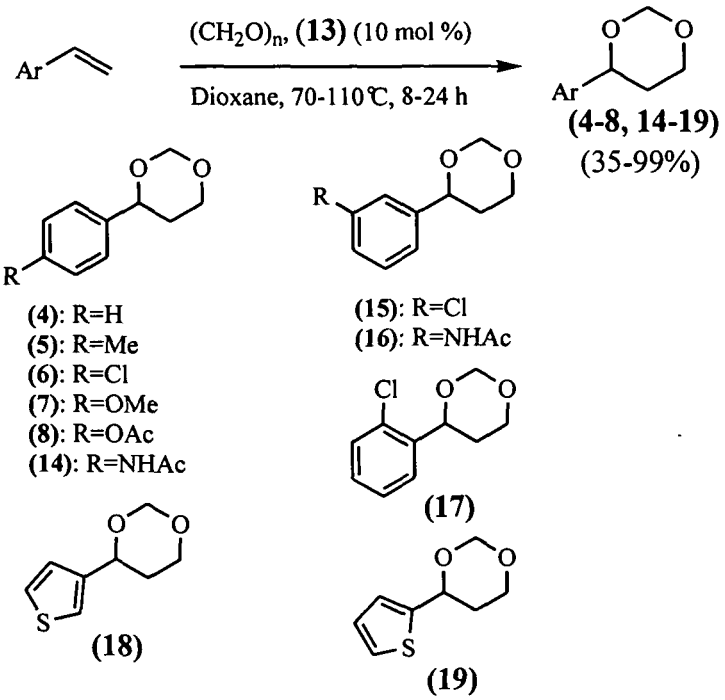


Scheme 1.8: Mechanism of the Prins reaction between aldehyde and diene

Bach and Lobel tested[56] different boron catalysts **(11-13)** in the Prins reaction of several styrenes with formaldehyde (Scheme 1.9) to form exclusively the corresponding 1,3-dioxane derivatives. While diaryloxyboron fluoride **(11)** and dialkoxyboron fluoride **(12)** turned out to be not sufficiently active, the arylloxyboron difluoride **(13)** showed to be effective as catalyst in the Prins reaction of styrenes. Performing the reaction with paraformaldehyde in 1,4-dioxane with a 10 mol % catalyst loading, the products were

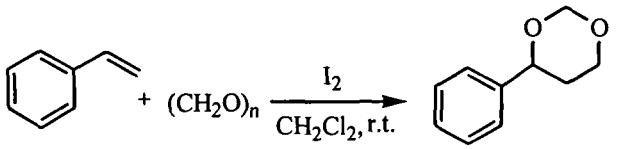
obtained with moderate to good yields (Scheme 1.9).



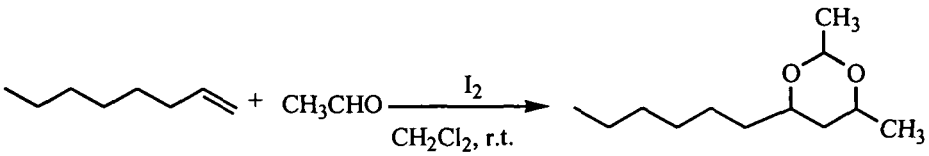


Scheme 1.9

Yadav and co-workers[57] used iodine as a mild and efficient catalyst for cross coupling of olefins and aldehydes to produce 4-substituted 1,3-dioxane derivatives via Prins reaction (Scheme 1.10) by stirring in dichloromethane at r.t. for 40-90 min.

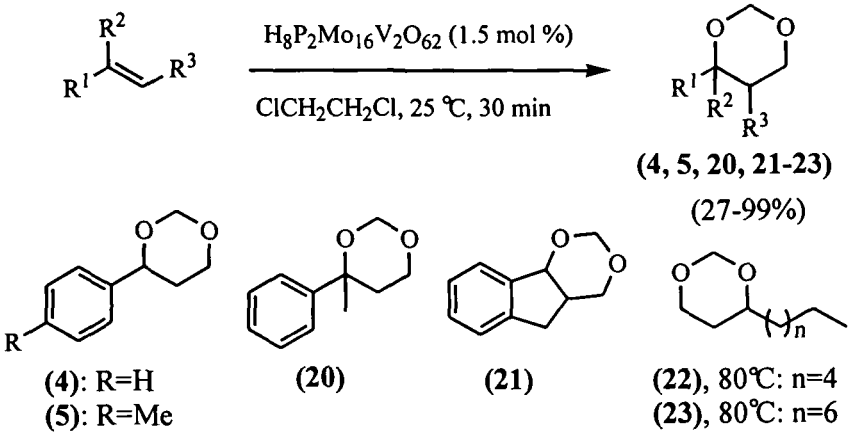


Scheme 1.10a



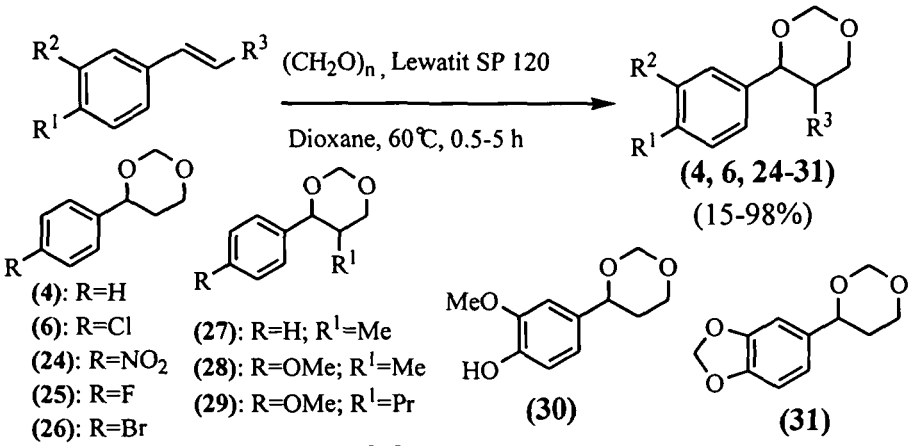
Scheme 1.10b

The use of Wells-Dawson-type molybdenovanadophosphoric heteropolyacids ($H_8P_2Mo_{16}V_2O_{62}$, $H_6P_2Mo_{18}O_{62}$,) in the Prins reaction of olefins (Scheme 1.11) with paraformaldehyde was reported by Li *et al.*[58] in 1,2 dichloromethane at room temperature using 1.5 mol% of catalysts. Various styrene and linear olefins were converted into the corresponding 1,3-dioxanes derivatives using the above reaction condition. It was observed that the Lewis acids help in the formation of monomeric formaldehyde in addition to catalyze the Prins reaction.



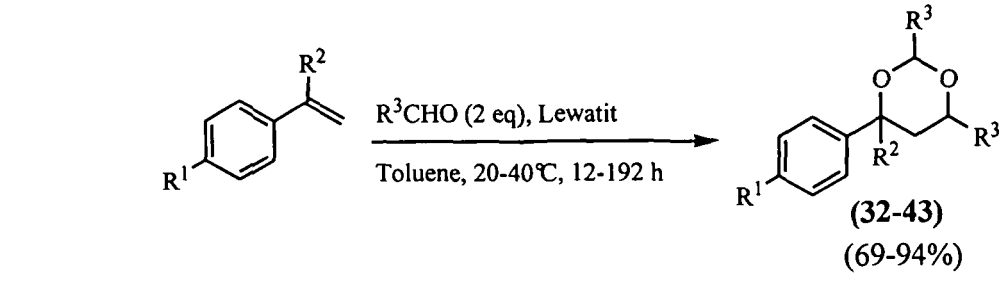
Scheme 1.11

Delmas and co-workers described[59] that cation-exchange resins in their acid forms (e.g. Amberlyst-15, C 350, Dowex MSC 1, and IR 120) catalyzed the Prins reaction of styrene with formaldehyde and yielded 92% 4-phenyl-1,3-dioxane. In another report[60] Gaset and Delmas prepared (Scheme 1.12) 1,3-dioxanes derivatives (4, 6, 24-31) without any by-product formation from styrene derivatives and formaldehyde in presence of macroporous cation exchange resin Lewatit SP 120 in dioxane at 60 °C within 0.5-5 h.



Scheme 1.12

The resin remained unchanged after the reaction and could be reused several times without regeneration. The extension of this methodology[61] allowed (Scheme 1.13) the preparation of substituted 1,3-dioxanes from other aldehydes.



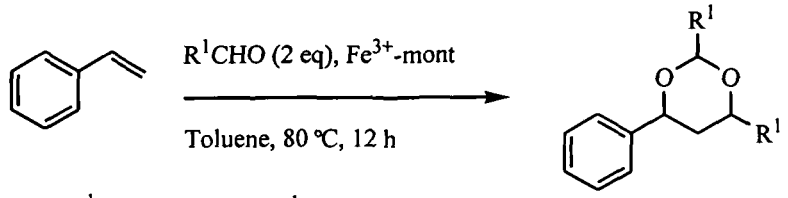
(32): R=Me
(33): R=Et
(34): R=$(CH_2)_4CH_3$
(35): R=Ph
(36): R=3-ClC_6H_4
(37): R=2-FC_6H_4

(38): R=Me
(39): R=Et
(40): R=$(CH_2)_4CH_3$
(41): R=Ph
(42): R=3-ClC_6H_4
(43): R=2-FC_6H_4

Scheme 1.13

Uemura and co-workers[62] used cation exchanged montmorillonite (M^{n+}-mont), as a Brønsted acid catalyst, for the Prins reaction of (Scheme 1.14) styrenes with paraformaldehyde or 1,3,5-trioxanes in toluene at 80 °C to produce 4-aryl-1,3-dioxane selectively up to 99% yield.

Among the 21 examined, the Ce^{3+} and Fe^{3+}-montmorillonites were found to be quite effective. Regeneration of the catalyst was confirmed with the Ce^{3+}-mont and it can be recycled at least three times. Other aldehydes also worked well under these conditions.



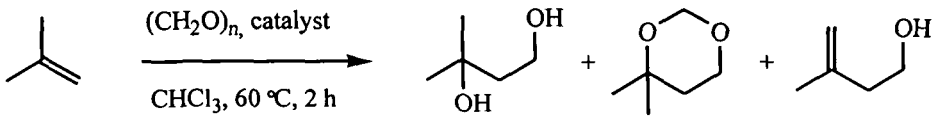
(44): R^1=Me
(45): R^1=Et
(46): R^1=Bu
(47): R^1=$(CH_2)_4CH_3$

Scheme 1.14

Aramendia *et al.*[63] studied the Prins reaction of various arylalkenes with paraformaldehyde on different zeolites as solid acid catalysts under reflux in 1,4-dioxane for 15 h to give major amount of 1,3-dioxanes. The highest conversions and selectivity were obtained with beta zeolite. Other zeolites such as USY and ZSM-5

provided much lower yields.

The catalysts tin chloride supported on quaternary ammonium chloride functionalized silica gel and MCM-41[64] was tested in the Prins condensation of isobutene with formaldehyde (Scheme 1.15). The complex immobilized on MCM-41 showed the highest yield of the unsaturated alcohol (**50**) (90%) in addition to 1,3-diol and 1,3-dioxane.



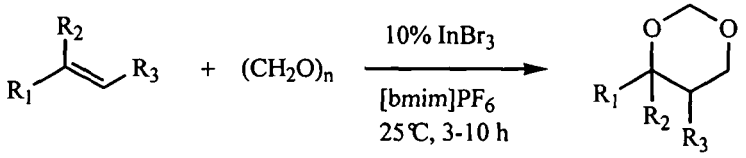
(48) (49) (50)

Scheme 1.15

Reddy and his group[65] synthesized sulfonic acid functionalized mesoporous SBA-15 as highly active and selective catalyst for the prins reaction of styrene with formaldehyde in dichloromethane under reflux for longer reaction time. The higher conversion and the selectivity to 4-phenyl-1,3-dioxane were found to be consistent in four repeated cycles.

Recyclable acidic ionic liquid catalyzed synthesis of 1,3-dioxanes was reported by Fang *et al.*[66] via Prins reaction. The products were easily separated from the catalysts by decantation.

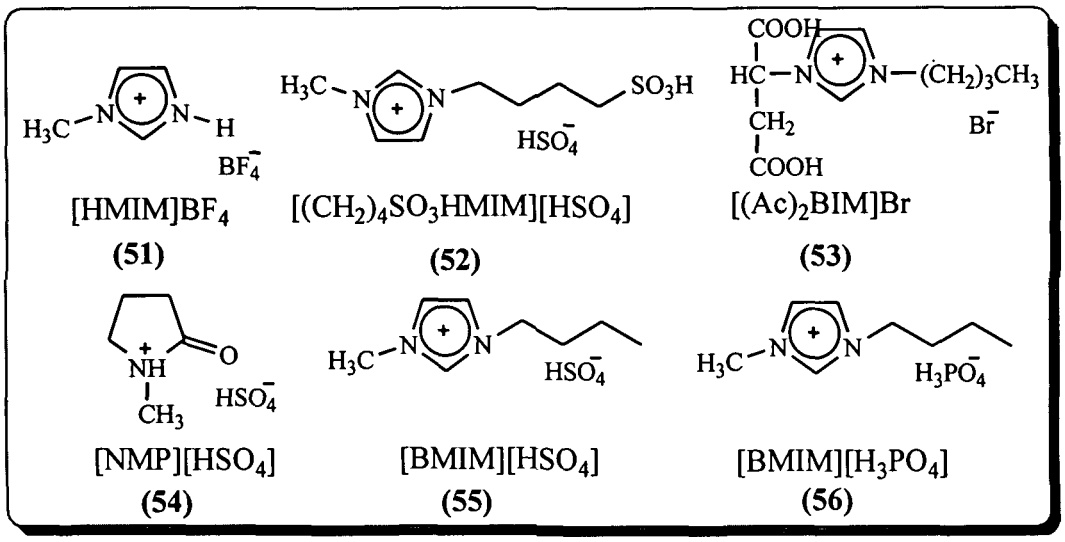
Yadav and co-workers[67] employed $InBr_3$ catalyst in [bmim]PF_6 or [bmim]BF_4 as recyclable reaction medium (Scheme 1.16) for the synthesis of 1,3-dioxane derivatives through condensation of styrene derivatives with paraformaldehyde in moderate to excellent yields under mild condition within 3-10 h reaction time. The efficiency of the reaction was strongly influenced by the nature of the ionic liquid, so other systems such as tetrabutyl ammonium chloride or 1-butyl-3-methylimidazolium chloride did not produce any turnover in the reaction.

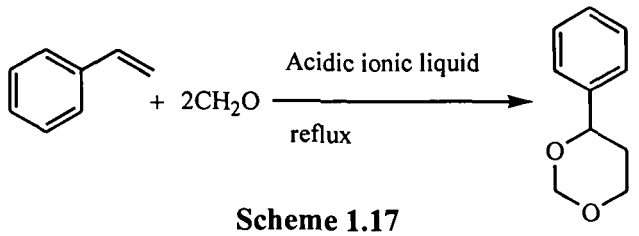


R_1= aryl, naphthyl: 85-91%, 25℃ R_2= H, Me
= hexyl, octyl: 49-55%, 90℃ R_3= H, Me, Ph

Scheme 1.16

Wang and co-workers[68] reported a method using water stable Brønsted acidic task-specific ionic liquids **(51-56)** as catalysts for the Prins reaction of styrene and formaldehyde (Scheme 1.17) under reflux for 2-10 h. The catalyst [BMIM][HSO_4] can be easily recycled to catalyze Prins reaction again with excellent yields.

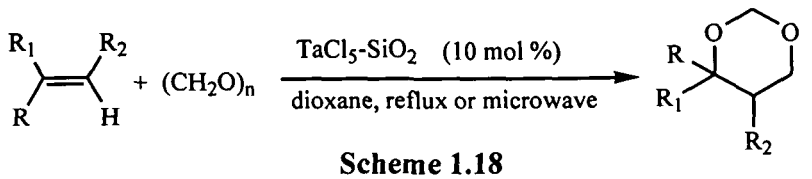




Scheme 1.17

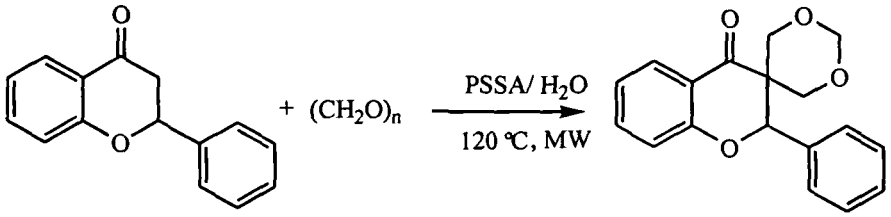
The effect of microwave irradiation on the condensation of olefins with formaldehyde was studied by Zorin and his groups.[69] The kinetics of accumulation of 4-phenyl-1,3-dioxane and 4-methyl-4-phenyl 1,3-dioxane suggest that the microwave-enhanced reactions were 2.6 times faster than those occurring with thermal heating.

Chandrasekhar *et al.*[70] reported the comparative studies of conventional heating in solution with solvent-free microwave irradiation (Scheme1.18) using $TaCl_2$-SiO_2 catalysed Prins reaction to afford 1,3-dioxanes. The results indicated that the conventional heating (reflux in dioxane) required longer reaction time than microwave irradiation. MW irradiation shifts 10-13 h to 3-5 min with similar or better yields. Different styrenes were reacted with paraformaldehyde under microwave energy to produce the corresponding 1,3-dioxane derivatives with more than 80-90% yields.



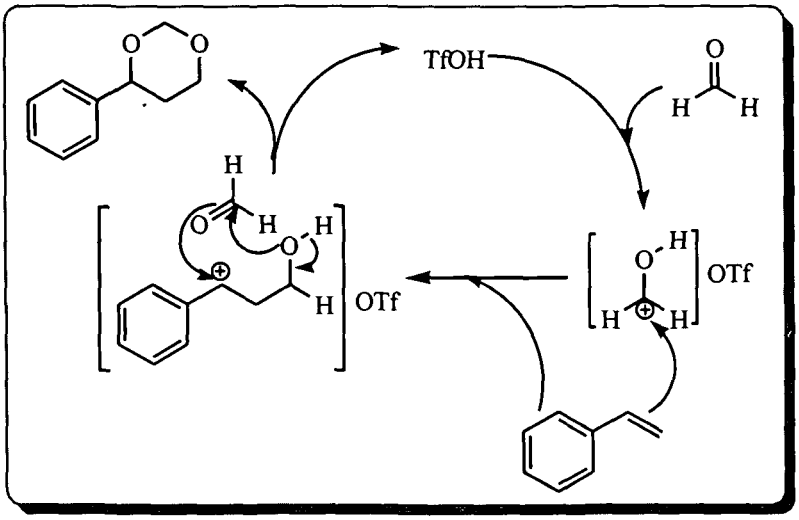
Scheme 1.18

Polshettiwar *et al.*[71] synthesised 1,3-dioxane by tandem bis-aldol reaction of ketones with paraformaldedyde employing polystyrenesulfonic acid (Scheme 1.19) in aqueous medium under microwave irradiation at 120 °C.

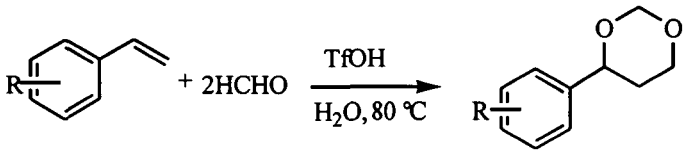


Scheme 1.19

Du *et al.*[72] reported the synthesis of 1,3-dioxane by prins reaction (Scheme 1.20 & Scheme 1.21) of styrene derivatives with formalin as formaldehyde source using trifluoromethanesulfonic acid as catalyst in water by stirring at 80 °C within 10-30 h. While excellent yield was obtained in the Prins cyclization of styrene in the presence of TfOH, low yields or no reaction were observed when other traditional mineral acid catalysts were used.



Scheme 1.20



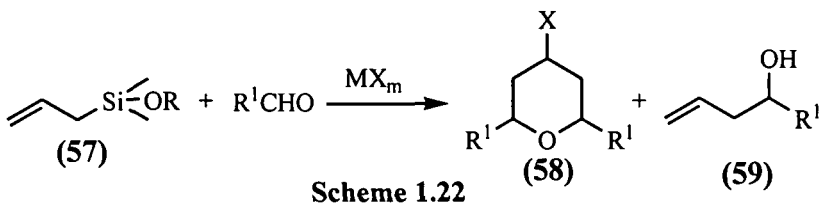
Scheme 1.21

From the literature survey, it is observed that a large number of synthetic methods involve high temperature reaction with longer reaction time, less selectivity in product formation, use of toxic organic solvents and problems in product purification. As a result, there are still demand for new methods under environmentally benign conditions in the context of solvent-less condition, higher selectivity for product formation, shorter reaction time and simplification of product isolation procedure.

1.2.1.2 Methods for Synthesis of Tetrahydropyran Derivatives:

The Prins cyclization is another attractive synthetic tool for the construction of six-membered tetrahydropyran derivatives.[73] The Prins reactions of 3-butene-1-ol with a series of aldehydes and ketones were studied by Hanschke[74] with an observation that the different products can be isolated depending on the acid catalyst used. The major products are the substituted tetrahydropyran-4-ols or dihydropyrans in the presence of sulfuric acid catalyst. The use of hydrochloric acid results in the formation of 4-chlorotetrahydropyrans. After this original report, different methods have been developed for the formation of tetrahydropyran derivatives via Prins cyclization using varieties of acid catalysts.

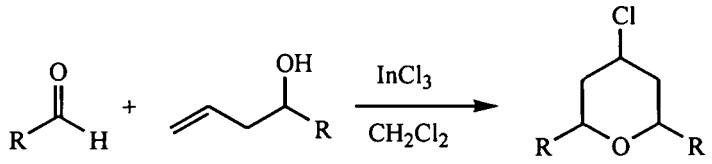
Chan and co-workers[75] developed the condensation of alkoxyallylsilanes with carbonyl compounds in dichloromethane at -78 °C under Lewis acid conditions ($AlCl_3$, $SnCl_4$, $TiCl_4$, $BF_3.OEt_2$) to give *cis*-2,4,6-trisubstituted tetrahydropyrans **(58)** or the homoallylic alcohols **(59).** It was observed that the relative distribution of the two possible products, **(58)** and **(59)** (Scheme 1.22) can be selectively controlled, depending on the nature of the alkoxy group -OR, the nature and quantity of the Lewis acid used, and the temperature of the reaction.



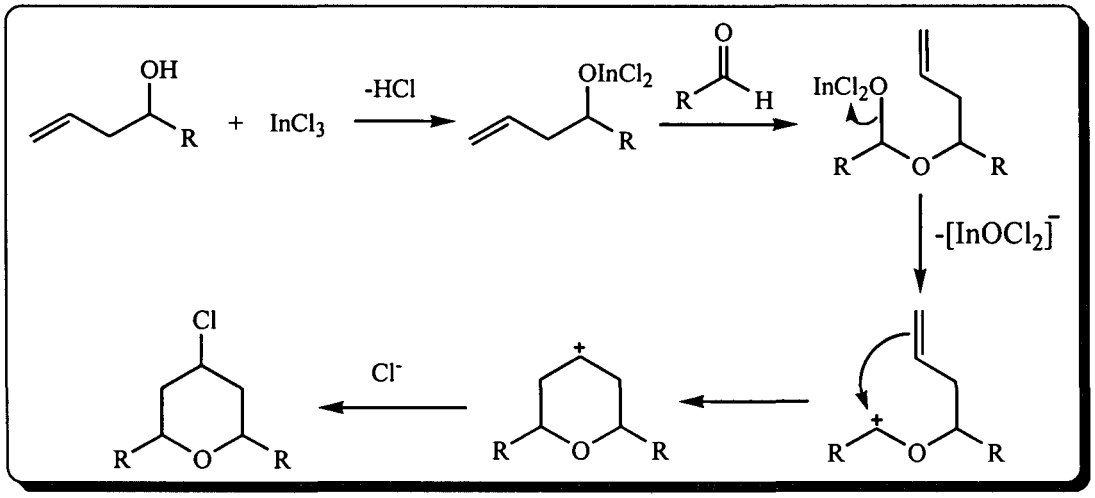
(57) (58) (59)

Scheme 1.22

Li and co-workers[76] observed the reaction of aldehyde with homoallylic alcohols mediated by indium trichloride in dichloromethane at room temperature to generate 4-chlorotetrahydropyrans (Scheme 1.23 & 1.24) in high yields and with high stereoselectivity. The same type of compounds can also be prepared through a single step, multi-component coupling between aldehydes and allyl bromide mediated by indium.

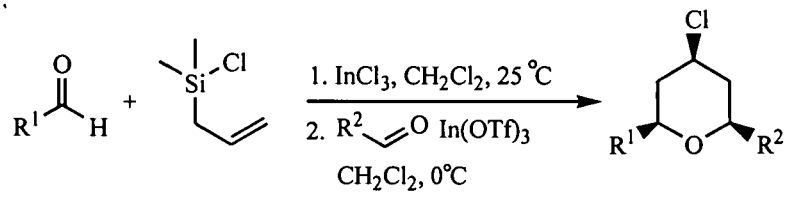


Scheme 1.23



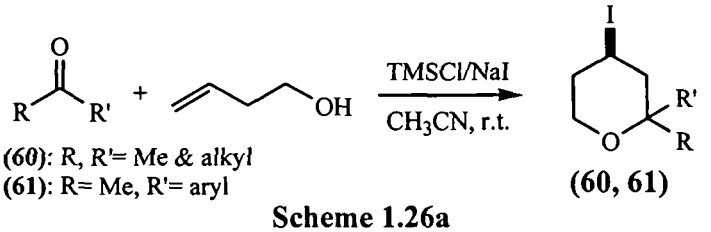
Scheme 1.24: Plausible mechanism for Indium trichloride mediated tetrahydropyran formation

A one-pot multi-component $InCl_3$ or $In(OTf)_3$ Lewis acid-catalyzed Prins cyclization was developed with high yield and selectivity (Scheme 1.25) by Chan and his co-workers.[77] The crossed 2,4,6-trisubstituted tetrahydropyran products were formed with high stereoselectivity. This catalytic method could also be used with α,β-unsaturated aldehydes affording moderate yields of products.



Scheme 1.25

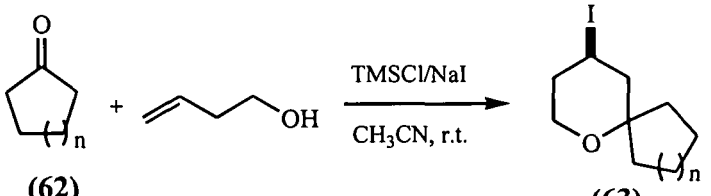
Yadav and co-workers reported[78] the synthesis of iodopyrans for the first time via Prins cyclization of ketones with homoallylic and homopropargylic alcohols in the presence of TMSI generated in situ from TMSCl and NaI (Scheme 1.26) in acetonitrile as reaction medium. This reaction produced 2,2-disubstituted- or spirocyclic-4-iodo-tetrahydropyrans and spirocyclic-4-iodo-5,6-dihydro-2*H*-pyrans in good yields.



(60): R, R'= Me & alkyl
(61): R= Me, R'= aryl

(60, 61)

Scheme 1.26a

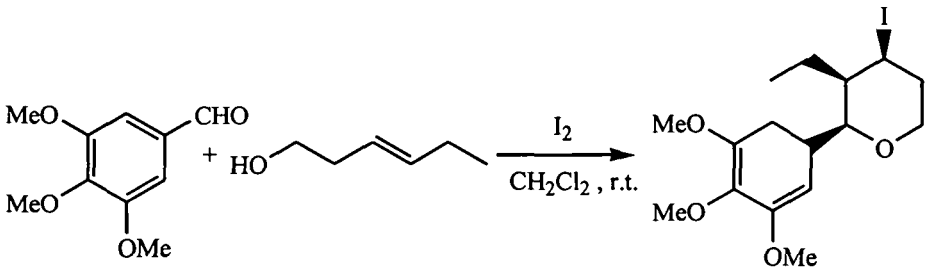


(62)

(63)

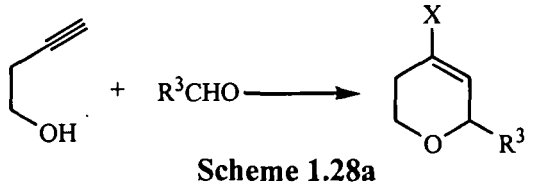
Scheme 1.26b

In another report from the same group[79] iodine was found to be an efficient reagent (Scheme 1.27) for the coupling of homoallylic alcohols with aldehydes under mild conditions to produce 4-iodotetrahydropyran derivatives in excellent yields in a short reaction time with high selectivity. The use of iodine makes this procedure simple, convenient and cost-effective.

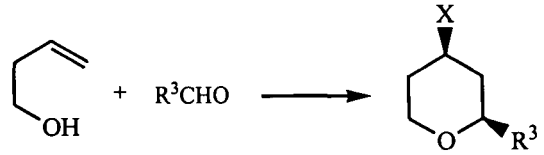


Scheme 1.27

Miranda *et al.*[80] showed the Prins-type cyclization of homopropargylic alcohols and aldehydes in dichloromethane to yield 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans in presence of iron(III) halides at room temperature (Scheme 1.28a). In addition, anhydrous ferric halides are also shown to be excellent catalysts for the standard Prins cyclization (Scheme 1.28b) with homoallylic alcohols.

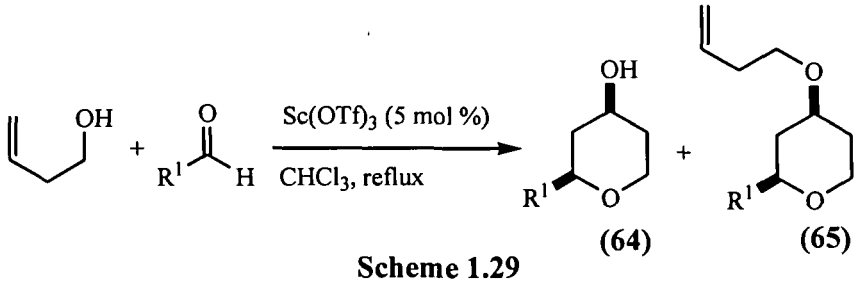


Scheme 1.28a



Scheme 1.28b

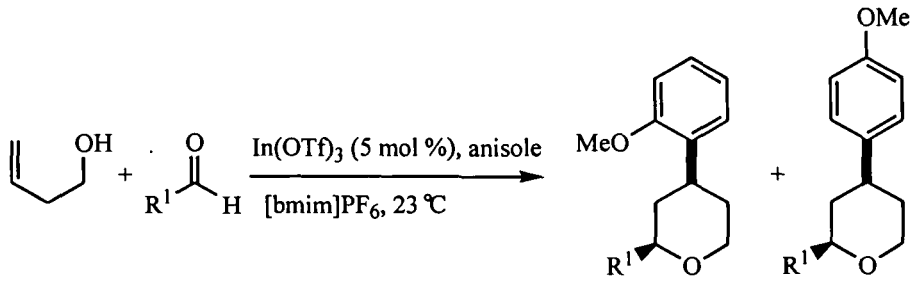
Li and co-worker developed the scandium triflate[81] (Scheme 1.29) catalyzed formation of 2-substituted-4-tetrahydropyranols **(64)** and related ethers **(65)** from 3-butene-1-ol and different aldehydes, in good overall yields with cis diastereoselectivity.



Scheme 1.29

The same observation was retained for the above reaction in case of indium triflate and ytterbium triflate catalysts.

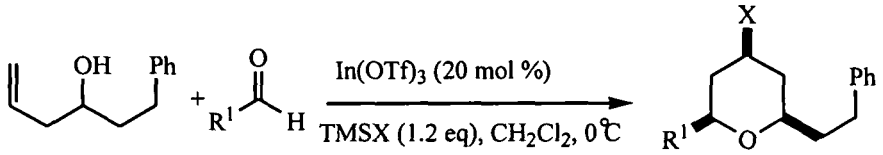
Yang *et al.*[82] observed the indium triflate catalyzed (Scheme 1.30) Prins reaction in presence of excess amount of anisole in ionic liquid which yielded another 2,4-disubstituted tetrahydropyran derivatives (Scheme 1.30) via three-component Prins-Fridel-Craft reaction.



Scheme 1.30

Similarly indium triflate in combination with trimethylsilyl halides (Scheme 1.31) catalyzed the coupling between 1-phenyl-5-hexene-3-ol and various aldehydes,

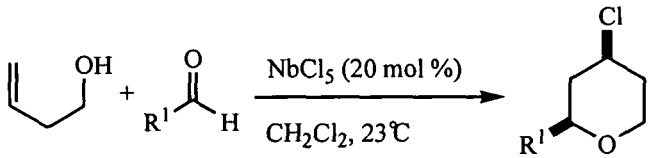
accomplishing stereoselectively the formation of all *cis*-4-halo-2,6-disubstituted THP derivatives[83] **(66)**.



(66)

Scheme 1.31

Yadav and his co-workers[84] utilized niobium chloride (Scheme 1.32) for the same coupling between aldehydes and 3-butenel-ol for the synthesis of 4-chlorotetrahydropyran derivatives **(67)** in dichloromethane at room temperature.

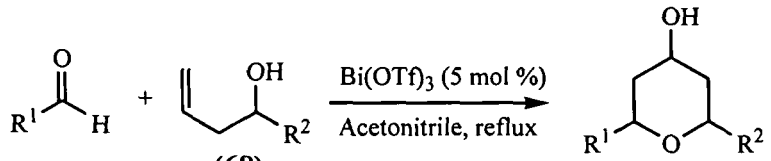


(67)

Scheme 1.32

Miranda showed that iron(III) chloride[85] as Lewis acid catalyst efficiently produced the product **(67)**.

Sreedhar *et al.*[53] condensed homoallylic alcohol with aldehydes using bismuth (III) triflate as catalyst to (Scheme 1.33) produce 2,4,6-trisubstituted tetrahydropyrans **(69)** in good yields.



(68) **(69)**

(65-82%)

(69a): R^1=cyclohexyl, R^2=Ph
(69b): R^1=cyclohexyl, R^2=4-$NO_2C_6H_4$
(69c): R^1=cyclohexyl, R^2=4-$MeOC_6H_4$
(69d): R^1=Ph, R^2=4-ClC_6H_4

Scheme 1.33

Montmorillonite KSF[86] was efficient to form the trisubstituted tetrahydropyran in organic solvent at different temperatures from the coupling of homoallylic alcohol with Aldehydes. Furthermore, the solid acids H-ZSM-5 zeolite and Amberlyst-15 ion exchange resin[87] also catalyzed the reaction in ionic liquids.

The use of chloroaluminate ionic liquids as an alternative Lewis acidic reaction medium was developed by Yadav and coworkers[88] to catalyze the same Prins cyclization reaction of homoallylic alcohol with various aldehydes.

Kumar *et al.* used soluble[89] PEG-anchored homoallylic alcohols (Fig. 1.3) with aldehydes in the presence of boron trifluoride in order to prepare mixture of 4-hydroxy and 4-fluro-2,6-disubstituted tetrahydropyrans after final cleavage from the support.

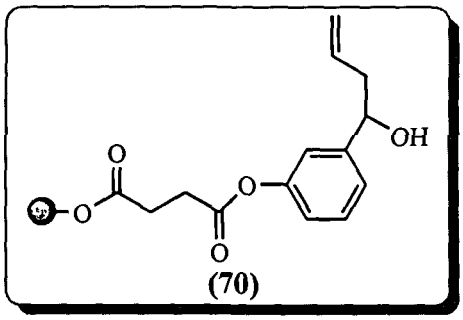
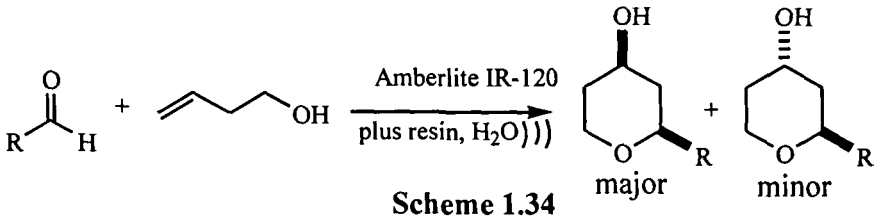


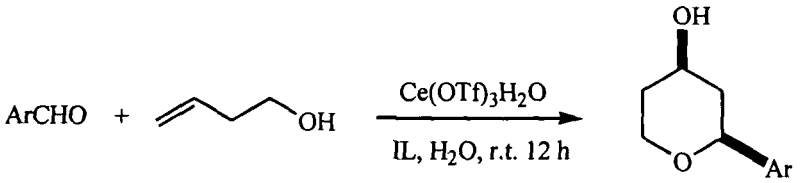
Figure 1.3: Structure of PEG-anchored homoallylic alcohol

Keh *et al.*[90] reported the direct formation of (Scheme 1.34) tetrahydropyranol derivatives in water using the Amberlite IR-120 plus resin. A mixture of an aldehyde and homoallyl alcohol in water in presence of resin under sonication at room temperature yielded the desired tetrahydropyranol derivative.



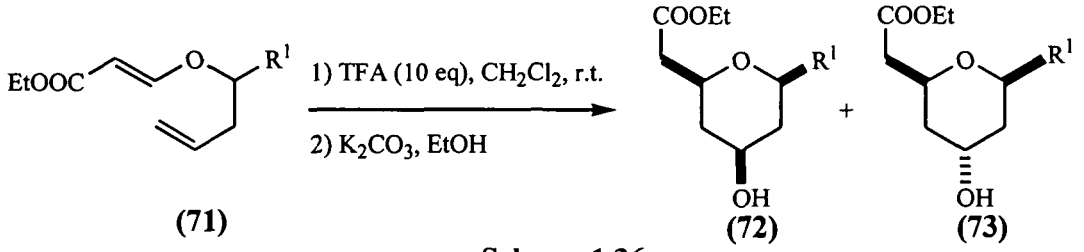
Scheme 1.34

Keh and co-workers[91] reported cerium triflate catalysed (Scheme 1.35) direct stereoselective formation of tetrahydropyranol derivative in ionic liquid utilising simple homoallyl alcohol and aldehyde.



Scheme 1.35

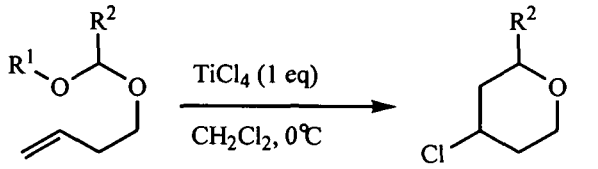
Trifluoroacetic acid efficiently catalyzed[92] the Prins cyclization of enol ethers to provide a mixture of tertrahydropyrans (Scheme 1.36) after ester ethanolysis under basic conditions. When this reaction was performed using $TiCl_4$, $SnBr_4$, $TiBr_4$ as catalysts, the corresponding 4-halotetrahydropyrans were obtained with lower yield and selectivity.



(71) (72) (73)

Scheme 1.36

The Prins cyclization of homoallylic acetals in presence of titanium chloride afforded the corresponding 4-chloro-2-substituted tetrahydropyrans (Scheme 1.37) in dichloromethane at 0 °C temperature. In that way different substituted tetrahydropyrans[93] can be prepared starting from homoallylic acetals



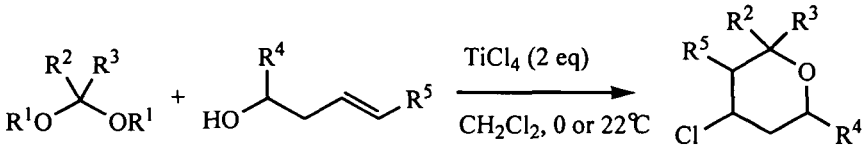
(74) (75)

(87-95%)

(75a): R^2=H
(75b): R^2=Me
(75c): R^2=$(CH_2)_3CH_2OH$

Scheme 1.37

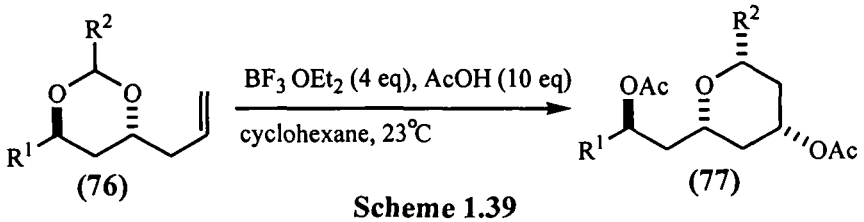
The extension of the above reaction conditions were obtained[94] by condensing symmetrical acetals (derived from formaldehyde, acetaldehyde, acetone, cyclohexanone and cyclopentanone) with homoallylic alcohols (Scheme 1.38).



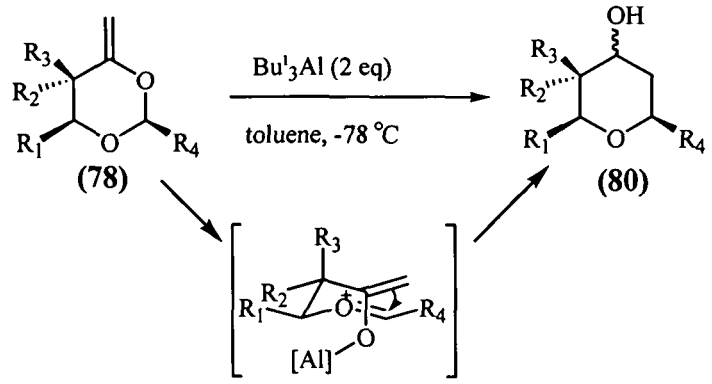
Scheme 1.38

Rychnovsky and co-workers[95] studied the Prins cyclization of 4-allyl-1,3-dioxanes with $TiCl_4$ as catalyst, which proceeded with the formation of 4-chlorotetrahydropyran. However, the use of boron trifluoride in the presence of acetic

acid produced (Scheme 1.39) the related 4-acetoxy derivatives with high *cis* selectivity between the acetoxy and R^2 substituent.



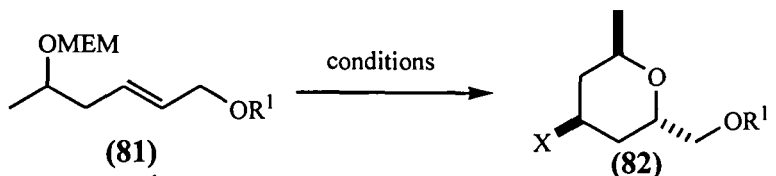
Scheme 1.39



Scheme 1.40

Other 1,3-dioxanes with a methylene substituent **(78)** (Scheme 1.40), in the presence of triisobutylaluminium[96] at -78 °C generated the oxocarbenium intermediates **(79)**, which then cyclized to the corresponding THP derivatives **(80)**.

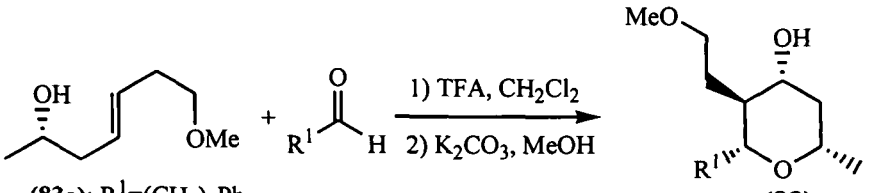
Under acidic conditions, the cyclization of homoallylic acetals **(81)** produced 2,4,5-trisubstituted tetrahydropyrans[97] **(82)**. The reaction was very selective with the formation of one isomer and different nucleophilic substituents were added in C4 by varying the reaction conditions (Scheme 1.41)



(82a): X=Cl, R^1=H, [conditions: $TiCl_4$, CH_2Cl_2]
(82b): X=Cl, R^1=TBDPS, [conditions:$TiCl_4$, CH_2Cl_2]
(82c): X=Br, R^1=TBDPS, [conditions:$TiBr_4$, CH_2Cl_2]
(82d): X=OH, R^1=H, [conditions: (1) anh TFA, CH_2Cl_2, (2) K_2CO_3]
(82e): X=OAc, R^1=H, [conditions: BF_3 OEt_2, AcOH, TMSOAc]
(82f): X=NHAc, R^1=TBDPS, [conditions: CF_3SO_3H, CH_3CN]

Scheme 1.41

Trifluoroacetic acid catalyzed reaction of homoallylic alcohols with aldehydes gave, after hydrolysis of the ester functionality, 4-hydroxy-2,3,6-trisubstituted tetrahydropyrans[98, 99] (Scheme 1.42) with the creation of three new stereocenters.

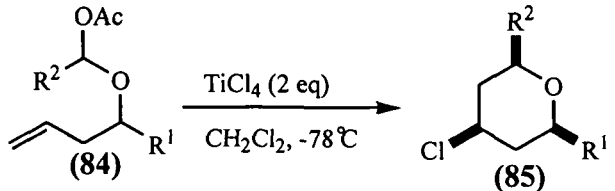


(83a): $R^1=(CH_2)_2Ph$
(83b): $R^1=4\text{-}MeOC_6H_4$

(83)
(66-81%, >99% ee)

Scheme 1.42

Rychnovsky[100] showed that α-acetoxy ethers **(84)** (Scheme 1.43), prepared easily from the related esters are appropriate starting materials to prepare THP units via the Prins route.



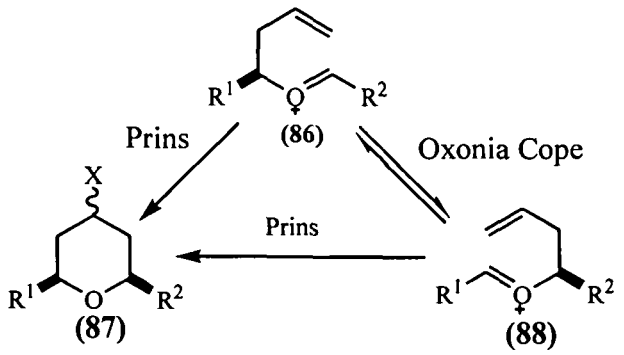
(84)

(85a): $R^1=(CH_2)_5CH_3$, $R^2=Me$
(85b): $R^1=(CH_2)_5CH_3$, $R^2=CH_2Cl$
(85c): $R^1=(CH_2)_2Ph$, $R^2=CF_3$

(85)
(65-95%)

Scheme 1.43

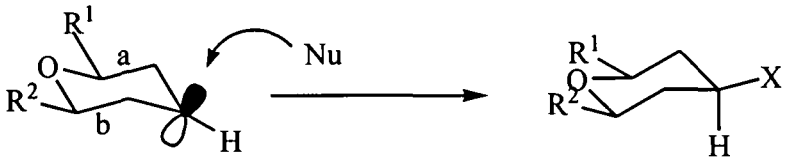
The mechanistic studies of the Prins cyclization[101-103] revealed the participation of Oxonia Cope rearrangements (Scheme 1.44). So, when the oxocarbenium ion **(86)** is formed it can undergo either a Prins cyclization followed by a nucleophilic capture of the carbocation or an oxonia-Cope rearrangement giving a new oxocarbenium **(88)** which then cyclizes to form a compound **(87)**.



(87) **(88)**

Scheme 1.44

The *cis*-stereoselectivity of tetrahydropyran derivatives was studied by the computational work of Alder and co-workers.[104] They predicted a chair-like transition state from the initial Prins cyclization (Scheme 1.45) of an oxocarbenium ion which increases the stability through delocalization by taking an optimal geometry that places the C4 hydrogen in a pseudoaxial position, thereby favouring the nucleophilic attack from an sequatorial side.



(89) all-cis-THP

Scheme 1.45

The Prins reaction is a very interesting route to form carbon-carbon bonds. Various types of catalysts have been developed in order to control the formation of different products. The Prins cyclization reaction in combination with other tandem reactions represents an attractive method for the construction of heterocyclic rings which are the building blocks of natural products.

1.2.2 Pechmann Condensation Reaction:

Pechmann condensation is a synthetic route to coumarins from a phenol and a carboxylic acid or ester containing a β-carbonyl group.[105] The condensation is performed under acidic conditions. The mechanism involves an esterification/ transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new ring. The final step is a dehydration following an aldol condensation. This reaction was discovered by German chemist Hans von Pechmann.[106]

2-Oxo-2*H*-chromenes (coumarins) and their derivatives have stimulated extensive research in biology, organic chemistry and medicine, due to their antibiotic,[107] anti-coagulant,[108] anticancer,[109] anthelmintic, anti-inflamatory, antioxidant,[110] antitumor,[111] anti-HIV,[112] hypnotic and insecticidal[113] properties. Coumarins are important group of organic compounds belonging to benzopyran family. A number of natural or synthetic derivatives of coumarin have found pharmaceutical applications.[114] Bis-hydroxy coumarins, warfarin and psoralen (Fig. 1.4) are known[115] for their anti-platlet and antitumar activities respectively. Moreover, coumarins have a broad range of

applications in the perfumes, cosmetics, food industry[116] and optical brightners and dispersed fluorescent and tunable laser dyes. Coumarins also act as intermediate for the synthesis of chromones, furocoumarins, coumarones and 2-acyl resorcinols.[117] Coumarins have been synthesized by several methods including *Von Pechmann*,[118] *Knovenagel*,[119] *Perkin*,[120] *Reformatsky*[121] and *Wittig reactions*.[122]

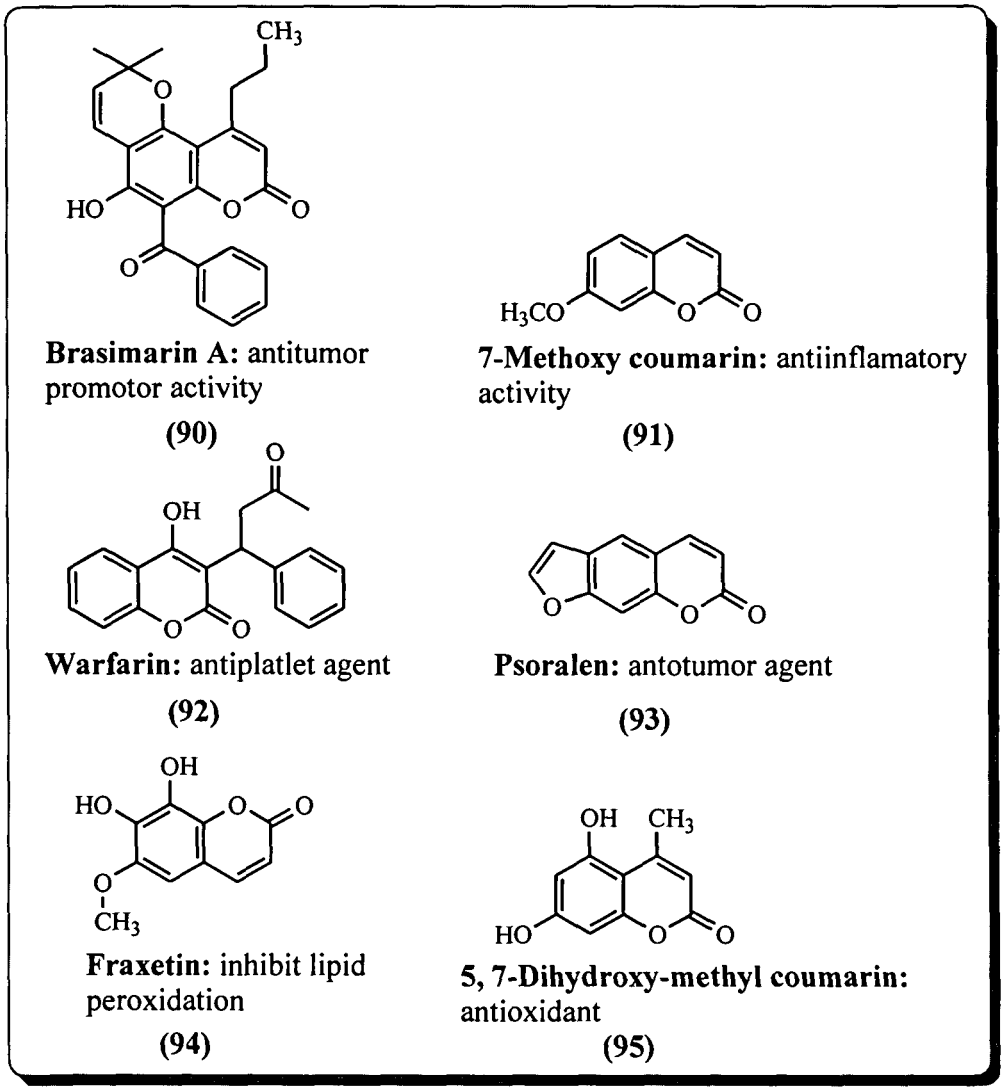


Figure 1.4: Structures of some biologically active coumarins

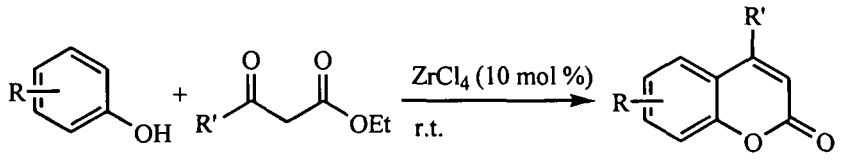
1.2.2.1. Methods for Synthesis of Coumarin Derivatives:

The von Pechmann reaction is a venerable reaction and it is one of the most simple and straightforward methods used to produce coumarins as it involves the condensation of phenols with β-ketonic esters in the presence of a variety of acidic

condensing agents and gives good yields of 4-substituted coumarins. Several acid catalysts have been used in the Pechmann reaction including sulphuric acid,[123] phosphorus pentoxide,[124] aluminium chloride,[125] trifluoroacetic acid[126] and many more.[127] However, these catalysts have to be used in excess; for example, sulphuric acid in 10-12 equiv,[128] trifluoroacetic acid in 3-4 equiv[126] and phosphorous pentoxide is required in a five-fold[124] excess. Moreover, in some cases, mixtures of substituted phenols, β-ketoesters and the acidic catalyst were allowed to stand overnight or for a number of days (depending on their reactivity) or were heated above 150 °C, and undesired side-products such as chromones, in addition to coumarins were isolated. Further, the disposal of acid waste leads to environmental pollution. For the last several years there has been an upsurge in the field of synthesis of coumarins through the catalysis of von Pechmann reaction by a variety of Lewis acids.[129-131] Several cleaner and safer methods have been developed: using microwave irradiation,[131] ionic liquids,[132] solid acids as catalysts to prompt the Pechmann condensation,[133] and the search for new readily available and green catalysts is still being actively pursued.

In this review we have presented the development of Pechmann reaction for the synthesis of coumarin derivatives using different types of acid catalysts in solvent-free condition as well as in solution phase medium.

Sharma and his group developed[134] a versatile and efficient route to 4-substituted coumarins via Pechmann reaction (Scheme 1.46) using $ZrCl_4$ as the catalyst (10 mol %) with several advantages such as mild, solvent-free conditions at ambient temperature, shorter reaction time (5-10 min) and direct isolation of the products in high yields.



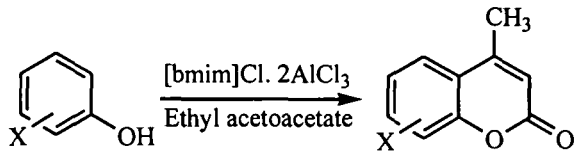
R'= CH_3, CH_2Cl, Ph, Fur

Scheme 1.46

Indium(III) chloride was used as an efficient catalyst by Bose *et al.*[135] in the von Pechmann condensation of phenols with β-ketoesters at 65 °C under reflux for one hour in nitrogen atmosphere leading to the formation of coumarin derivatives in excellent yields with good purity.

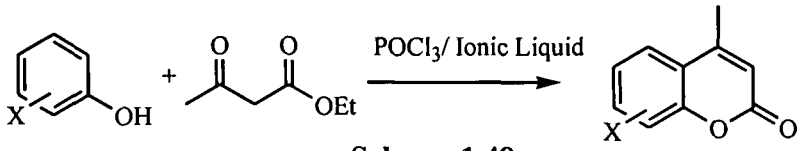
The ability of titanium(IV) chloride as a catalyst to promote the Pechmann condensation reaction with a range of phenols and β-keto esters was described by Valizadeha *et al.*[130] through stirring in absence of solvent at room temperature. The yields of coumarins obtained via this novel protocol were significantly higher than those using conventional method and the reaction duration was reduced to a few minutes or even a few seconds.

Potdar *et al.*[132] used 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·2$AlCl_3$ as Lewis acidic ionic liquid (Scheme 1.47) in the Pechmann condensation of phenols with ethyl acetoacetate leading to the formation of coumarin derivatives The reaction time was reduced drastically even at ambient conditions. The ionic liquid plays the dual role of solvent and Lewis acid catalyst providing a quick and efficient route to the syntheses of coumarins.



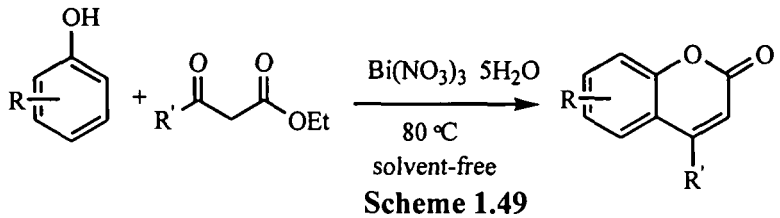
Scheme 1.47

The same group also successfully synthesised coumarin[136] employing neutral ionic liquid ([bmim]PF_6) and catalytic amount of $POCl_3$ (Scheme 1.48) within 45-60 min at ambient temperature. They also carried out the reaction in [bmim]PF_6 at 100 °C in absence of the acid catalyst.



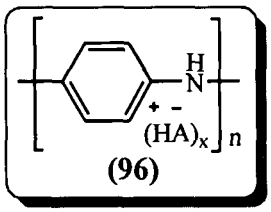
Scheme 1.48

Alexander and co-workers reported[137] bismuth(III) nitrate (Scheme 1.49) for Pechmann reaction of phenols and β-keto esters under solvent free condition at 80 °C and afforded coumarins within 15-300 min.



Scheme 1.49

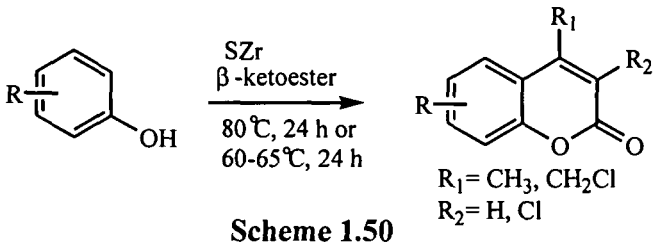
Palaniappan *et al.* performed polyaniline supported sulfuric acid[138] (Fig. 1.5) as reusable solid acid catalyst for the synthesis of 7-hydroxy-4-methyl-coumarin through condensation reaction of resorcinol with ethyl acetoacetate without using solvent at 150 °C in six h.



(96)

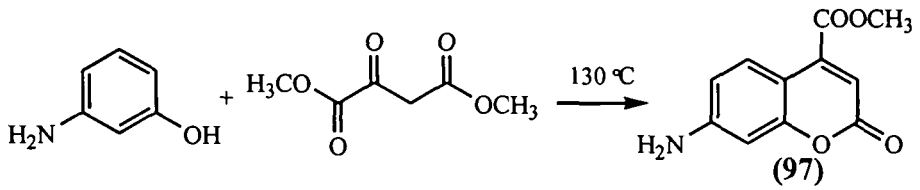
Figure 1.5: Structure of polyaniline supported acid

Kirsch *et al.* employed[139] sulfated zirconia (1%) as Pechmann's catalyst (Scheme 1.50) without solvent or in some cases using a small amount of ethanol to obtain coumarins in moderate to good yields. With this procedure, no significant acidic waste was obtained and an environment friendly alternative to obtain coumarins is provided.

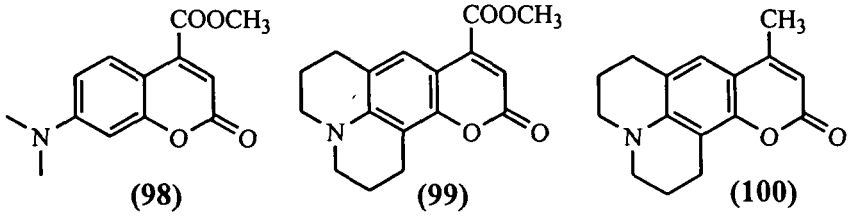


Scheme 1.50

Efficient synthesis of 7-aminocoumarins was performed by Besson *et al.*[133(b)] via the Pechmann reaction by microwave irradiation (Scheme 1.51) of the reactants on solid support (graphite: montmorillonite K-10). In this methodology, the strong thermal effect due to graphite: microwaves interaction is associated with the acidic catalyst role of the clay.



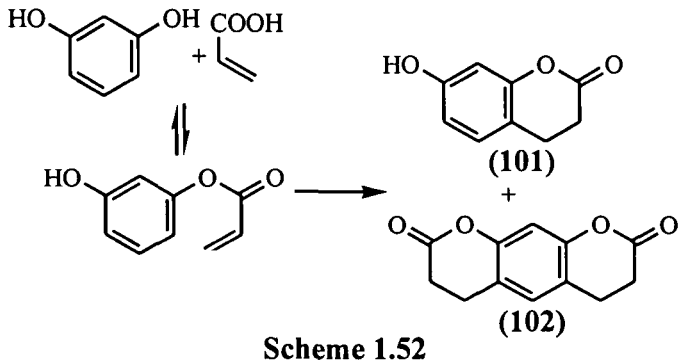
(97)



(98) (99) (100)

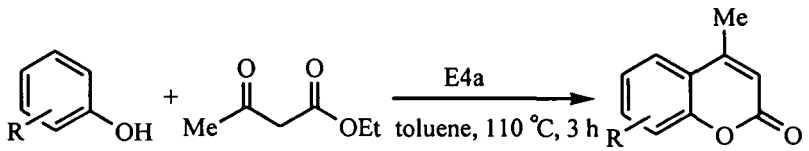
Scheme 1.51

The direct synthesis of coumarin derivatives from m-substituted phenols and α,β-unsaturated carboxylic acids catalyzed by reusable solid-acid, such as zeolite *H*-Beta or Amberlyst-15, in toluene as solvent was studied by Gunnewegh *et al.*[140] using thermal energy. The conversion involves esterification followed by alkylation (Scheme 1.52, ring closure). Ring closure of the ester is promoted both by an appropriate substituent on the aromatic ring and by Michael activation of the β-carbon of the ester. These influences were studied by variation of the reactants. 7-Hydroxy-3,4-dihydrocoumarin is formed in high yield when resorcinol and propenoic acid are used as reactants.



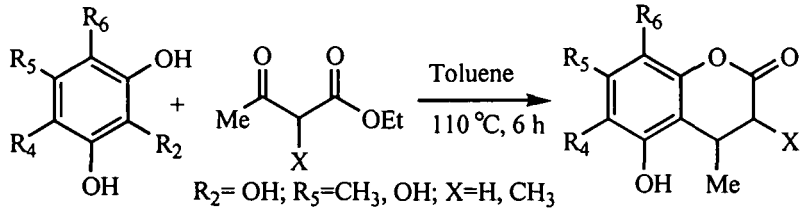
Scheme 1.52

Hegedus *et al.* also[133(a)] carried out Pechmann condensation of phenols with ethyl acetoacetate in presence of a modified small pore size zeolite E4a (Scheme 1.53) resulting in the formation of coumarin derivatives by refluxing in toluene for 3 h.



Scheme 1.53

Reddy and co-workers reported[141] an ecofriendly W/ZrO_2 solid acid catalyst for the synthesis of substituted (Scheme 1.54) coumarins from resorcinol and substituted resorcinols with ethyl acetoacetate and ethyl-α-methylacetoacetate by refluxing in toluene for 6 h.

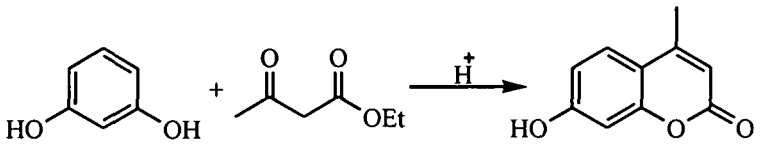


R_2= OH; R_5=CH_3, OH; X=H, CH_3

Scheme 1.54

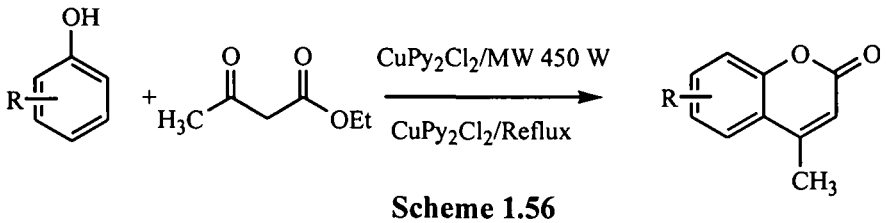
Sun *et al.* employed[142] gallium triiodide (GaI_3), generated in situ by the reaction of gallium metal and iodine for Pechmann reaction of phenols and ethyl acetoacetate, leading to the formation of coumarins in dichloromethane at room temperature within 0.7-10 h.

Microwave initiated PTSA catalyzed (Scheme 1.55) solvent-free Pechmann coumarin synthesis of phenols and β-keto esters was shown by Manhas and co-workers.[143] They obtained a variety of coumarins by this method in about 20 min.



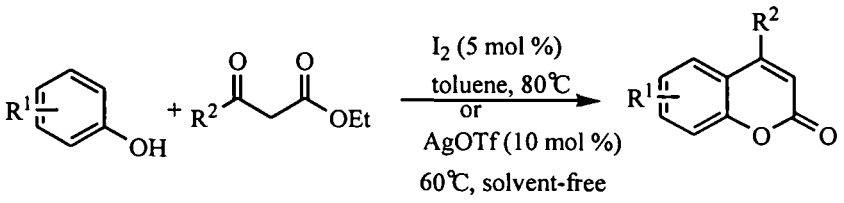
Scheme 1.55

Rajitha *et al.* used[144] dipyridine copper chloride (Scheme 1.56) as an efficient catalyst for comparative studies of Pechmann coumarin synthesis in solvent free media under conventional heating and microwave irradiation. Under microwave irradiation the reaction completed within 10-12 min whereas longer time (30-135 min) was required under conventional heating.



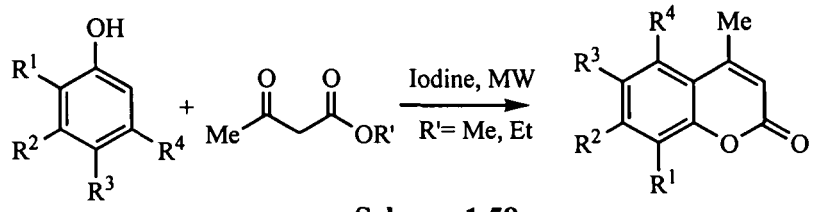
Scheme 1.56

Molecular iodine catalyzed (Scheme 1.57) coumarin synthesis was done by Wu *et al.*[145] under reflux in toluene at 80 °C. They also carried out the reaction under solvent-free condition at 60 °C in presence of AgOTf for 3-12 h.



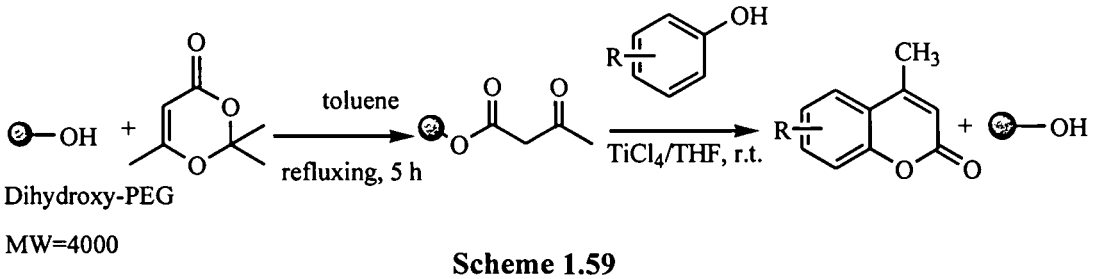
Scheme 1.57

The use of molecular iodine under microwave irradiation was studied by Prajapati *et al.*[131] for (Scheme 1.58) the synthesis of substituted coumarin via von Pechmann reaction and obtained the products within 1.5-5 min.



Scheme 1.58

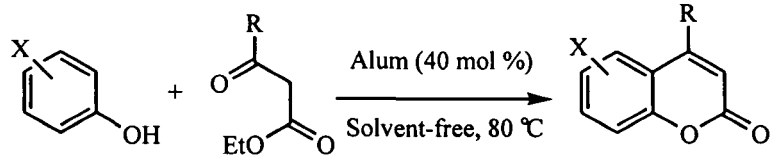
Sheng *et al.* reported[146] the synthesis of coumarin derivatives through PEG-bound acetoacetate reagent (Scheme 1.59) with phenols in presence of $TiCl_4$. They carried out the reaction in anhydrous THF under nitrogen atmosphere at room temperature and stirred for 30-50 min.



Scheme 1.59

Heravi *et al.* showed[147] a variety of heteropoly anions as catalysts for Pechmann condensation under solvent free thermal treatment. Out of them, sodium30-tungsto pentaphosphate, $[NaP_5W_{30}O_{110}]^{14-}$ (Preyssler's anion) was found to be a green and reusable catalyst for efficient and selective synthesis of coumarins within 30-300 min at 130 °C.

Dabiri and co-workers developed[148] alum $KAl(SO_4)_2 \cdot 12H_2O$ catalyzed (Scheme 1.60) one pot synthesis of coumarin under solvent-free conditions at 80 °C within 2-3 h.

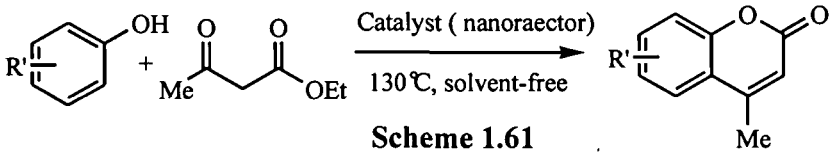


Scheme 1.60

Cerric Ammonium Nitrate (CAN) was found as efficient catalyst by Reddy *et al.*[149] for the synthesis of substituted coumarin via Pechmann reaction in solvent-free

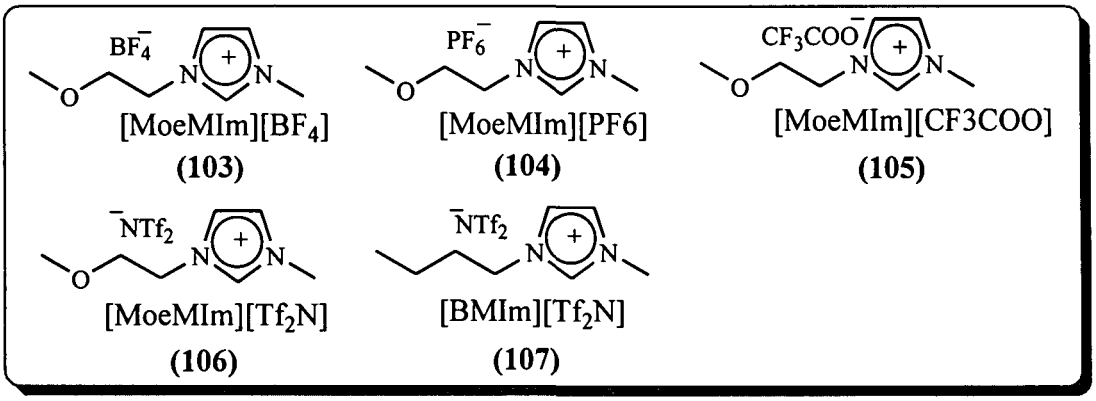
media using both conventional heating and microwave irradiation. Under microwave irradiation the reaction completed within 2-3 min and it took 10-15 min under conventional heating at 110 °C.

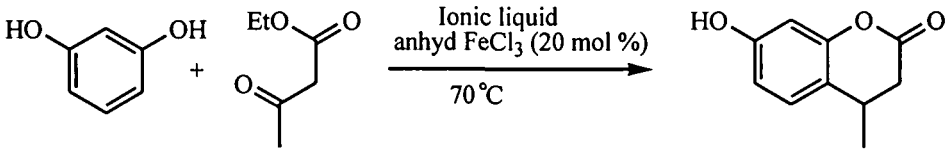
Karimi *et al.* designed[150] a highly efficient and water-tolerant sulfonic acid nanoreactor for Pechmann reaction (Scheme 1.61) of different phenols and ethyl acetoacetate. The reaction completed within 10 min-10 h at 130 °C under solvent-free conditions.



Scheme 1.61

Kumar *et al.*[129] described a method for the synthesis of coumarin derivatives via Pechmann condensation reaction using anhydrous $FeCl_3$ as Lewis acid catalyst (Scheme 1.62) in ionic liquid medium stirring at 70 °C.





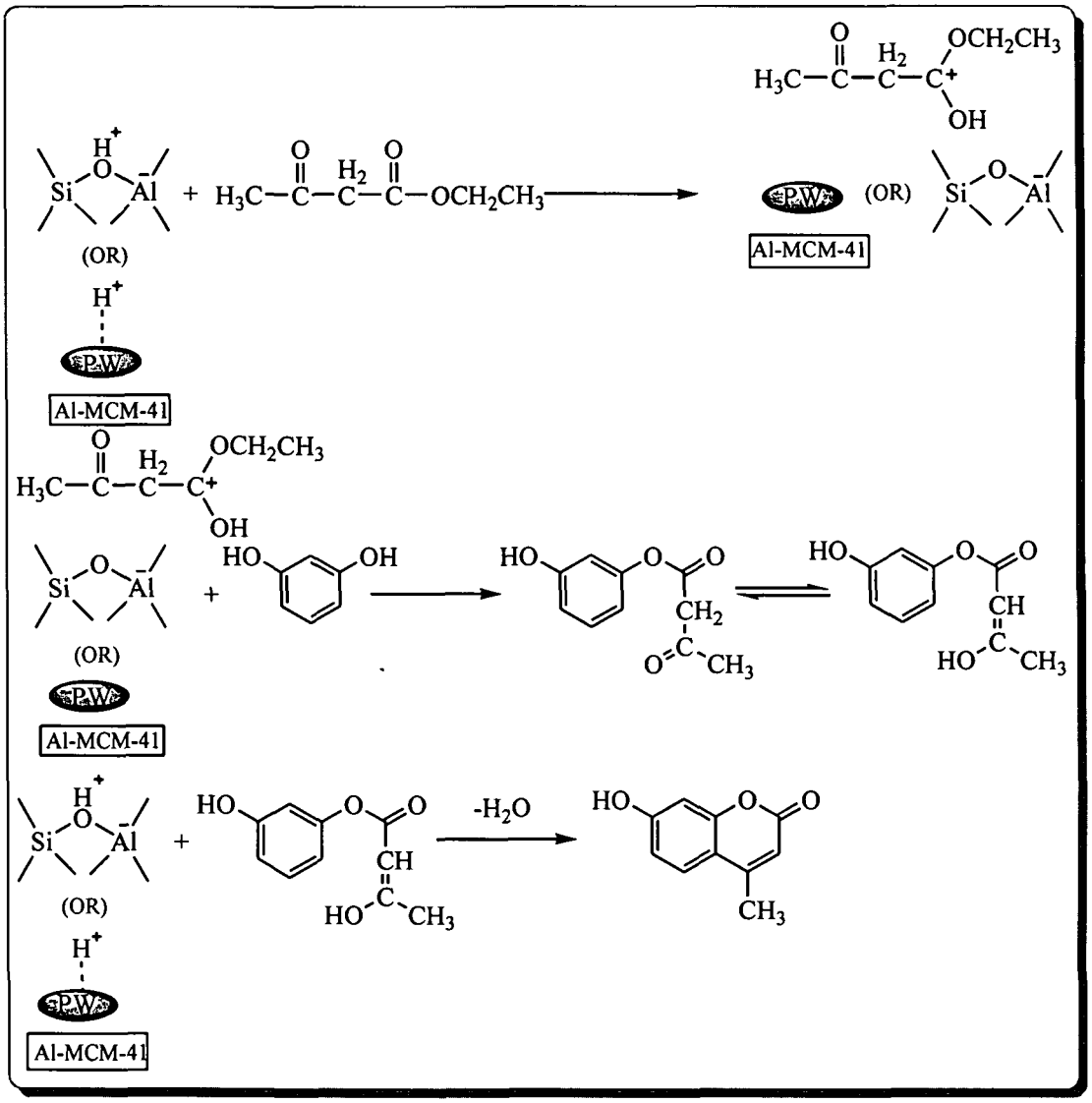
Scheme 1.62

In solvent-free condition, Singh *et al.* used[151] sulfamic acid as an efficient solid acid catalyst for synthesis of substituted coumarin from condensation of phenol with β-keto ester by stirring at 130 °C for 20-80 min. Similarly, De *et al.* employed[152] $BiCl_3$ as catalyst for Pechmann condensation of phenols with β-keto ester under solvent-free conditions at 75-125 °C temperature within 1-4 h. The same solvent-free[153] method was equally applicable with zirconyl chloride as catalyst under neat condition or in presence

of small volume of ethanol at 80 °C or 60-65 °C within 24 h.

Sandhu and his group carried out LiBr-mediated[154] Pechmann reaction at 75 °C in absence of solvent within 15-90 min reaction period.

Sudha *et al.* reported[155] that Al-MCM-41 (Mobil Composition Mater) (Si/Al = 25) molecular sieve efficiently catalyzed the liquid phase condensation of phenol and ethyl acetoacetate at 150 °C within 2-8 h to coumarin derivatives. The plausible mechanism for the formation of 7-hydroxy-4-methylcoumarin is the chemisorption of carbonyl group of ethyl acetoacetate (Scheme 1.63) on the Brønsted acid sites of the catalyst.



Scheme 1.63: Plausible mechanism for the formation of 7-hydroxy-4-methyl-coumarin over Al-MCM-41 and PW/Al-MCM-41

Sinhamahapatra and co-workers showed[156] the use of mesoporous zirconium phosphate (m-ZrP) as highly active solid acid for the condensation of phenols and ethyl acetoacetate to coumarins in both conventional heating as well as microwave assisted method. The condensation reaction was studied in detail by varying the reaction parameters like effect of solvent, molar ratio of the reactants, temperature, and catalyst loading. Among the substituted phenols, *m*-amino phenol was more reactive and 100% yield was obtained in very short time at low temperature due to the presence of ring activating amine group in meta position. Microwave assisted synthetic method was found to be advantageous over conventional heating for the synthesis of coumarins, as it provided good yield in very less time

The literature review on Pechmann reaction revealed that reported methods have their own merits and demerits. Many methods suffer from some serious problems such as longer reaction time, high temperature reaction, non-recycling of catalyst, use of excess amount of catalysts and formation of side products. It is very difficult to solve all problems with a modified catalyst. Therefore, the search for alternative systems on von Pechmann reaction is still an important area of research with more eco-friendly approach.

1.2.3 Pyrimidines and Fused Pyrimidines:

Pyrimidines are heterocyclic aromatic compounds and belong to the 1,3-diazine groups (Fig. 1.6) of heterocycles. Three nucleobases found in nucleic acids, uracil, thymine and cytosine are pyrimidine derivatives. Pyrimidines can annulate with a varity of ring systems that are available in natural sources, like nucleosides and nucleotides. At a very early date, the compounds belonging to this group were known as breakdown products of uric acid. The systematic study of this ring system started from 1885 with the work of Pinner[157], who first applied the name pyrimidine to the unsubstituted parent unit.

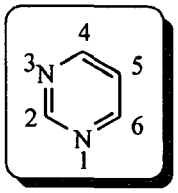


Figure 1.6: Pyrimidine ring

The reactivity of 2, 4 and 6 position of pyrimidine ring is similar; but position 5 stands somewhat different being aromatic in character. The ring may be considered as resonance hybrid of four equivalent structures (Fig. 1.7). As a result of resonance electron deficiencies are anticipated at 2, 4 and 6 positions. The position 5 will suffer a concequent smaller loss in electron density due to induction of its neighbours.

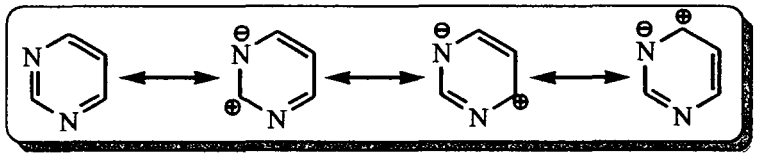


Figure 1.7: Resonance structures of pyrimidine ring

Uracil (naturally occurring pyrimidine derivative) was originally discovered in 1900 and it was isolated by hydrolysis of yeast nuclin found in bovin thymus and spleen, herring sperm, and wheat germ. The structure of uracils was established by Emil Fisher[158] in 1901; however 6-methyluracil was made as early as 1885.[159] The IUPAC name of uracils is pyrimidine-2,4(1*H*,3*H*)-dione. It undergoes amide-imidic acid tautomeric shifts (Fig. 1.8).

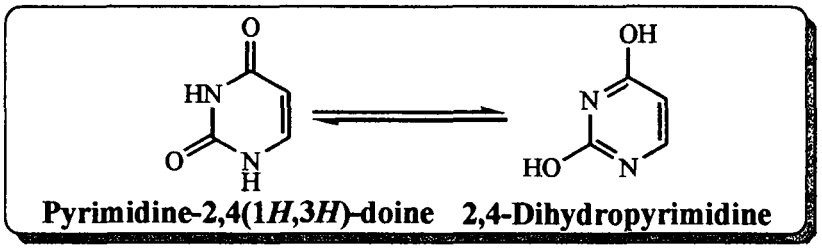


Figure 1.8: Tautomers of uracil

1.2.3.1 Pyrimidopyrimidine and Pyridopyrimidine Derivatives:

Pyrimidopyrimidine and pyridopyrimidine are heterocyclic organic compounds, consisting of a pyrimidine ring fused to a pyrimidine and pyridine ring, respectively (Fig. 1.9).

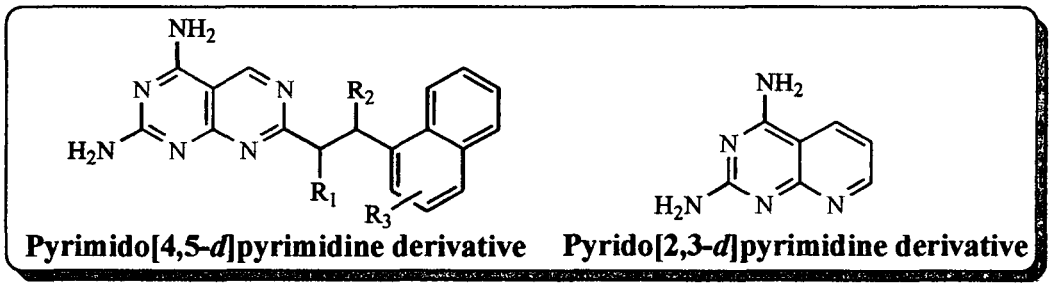


Figure 1.9: Structure of pyrimido[4,5-*d*]pyrimidine and pyrido[2,3-*d*]pyrimidine ring

These heterocycles form basic skeleton of many natural products of biological significance. Pyrimidines and fused pyrimidines are broad class of aza heterocyclic system of remarkable pharmacological potency. They show anticancer,[160] antiviral, antitumor,[161] antibacterial[162] and antiinflamatory activity. Uracil and its annulated substrates occupy a unique place in the field of medicinal chemistry as useful anticancer and antiviral drug.[163-165]

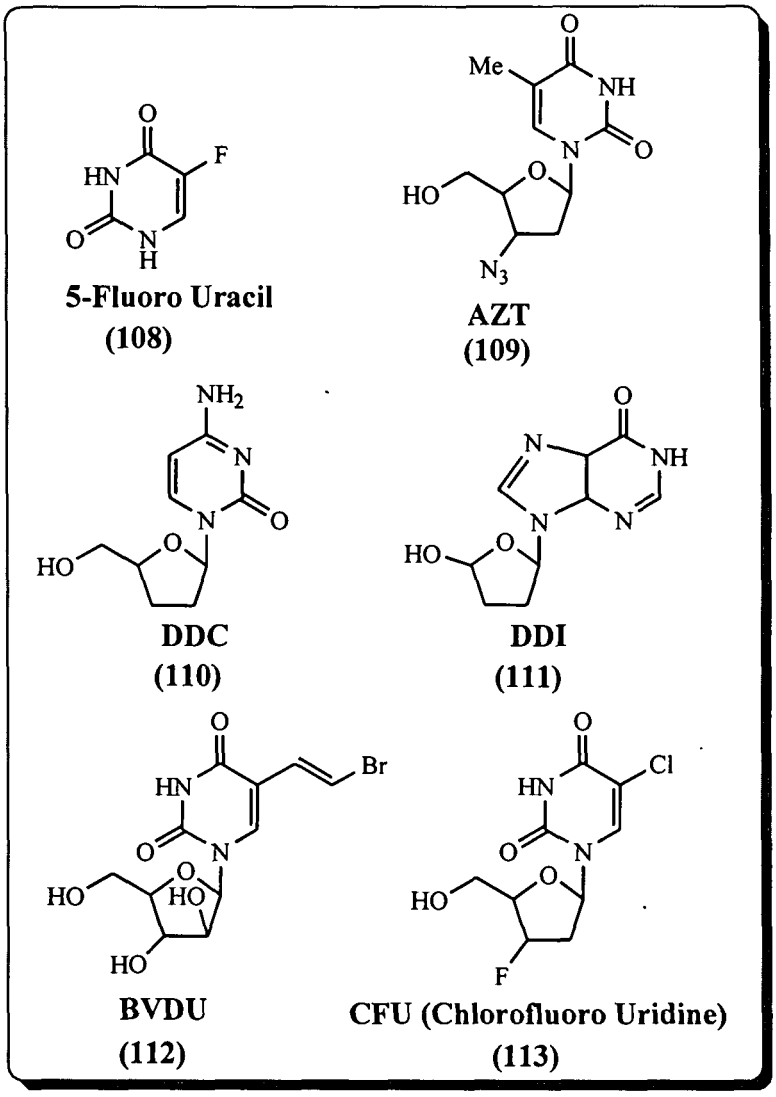


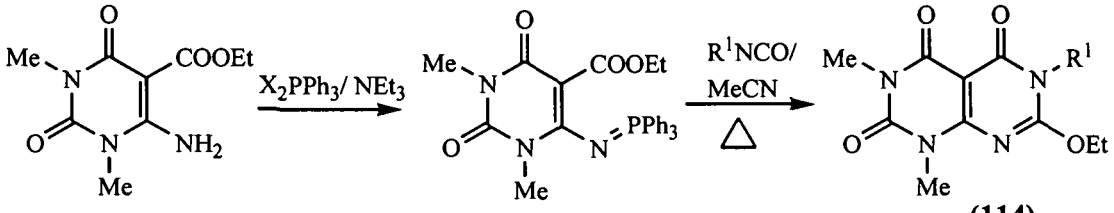
Figure 1.10: Structures of some bioactive pyrimidine derivatives

Preparation of naturally occurring complex molecules containing uracil ring pose significant synthetic challanges. The development of clinically useful anticancer (5-fluorouracil)[166] and antiviral drugs (AZT, DDC, DDI, BVDU)[167] has (Fig. 1.10) renewed interest in the synthetic manipulation of uracils. Pyrido[2,3-*d*]pyrimidines and pyrimido[4,5-*d*]pyrimidines are an important class of annulated uracils of biological

significances. A number of compounds having these systems are synthesised with diverse pharmacological activity. The discovery of many pyrimido[4,5-*d*] and pyrido[2,3-*d*]pyrimidine derivatives with potential antitumor,[168,169] antiinflamatory and CNS depressant activities[170] have stimulated considerable interest in the synthesis of these heterocycles via new and efficient routes. Therefore, preparation of these complex molecules has been remarkable interest in synthetic manipulation of uracils.

1.2.3.2 Synthesis of Pyrimido[4,5-*d*]Pyrimidine Derivatives:

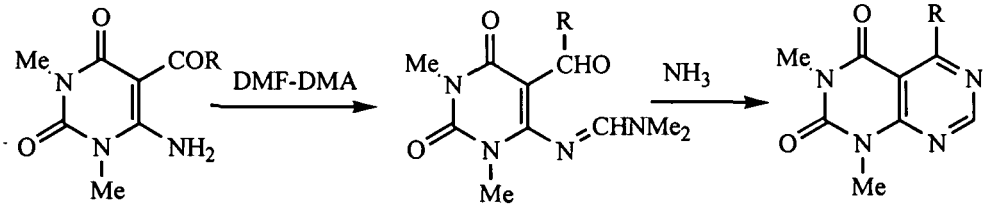
Wamhaff *et al.* reported[171] that ethyl-1,3-dimethyl-6-(triphenyl-phosphoranylideneamino)uracils-5-carboxylate reacts with isocyanates via a uracil-carbodiimide derivative (Scheme 1.64) to afford a new approach to 7-ethoxypyrimido[4,5-*d*]pyrimidines (**114**).



(114)

Scheme 1.64

Matyus *et al.* reported[172] the synthesis of 5-substituted pyrimido[4,5-*d*]pyrimidines (**115**) by reaction of 5-acyl-6-amino uracil with *N,N*-dimethylfomamide dimethyl acetal (DMF-DMA) and subsequent cyclization by ammonia (Scheme 1.65).

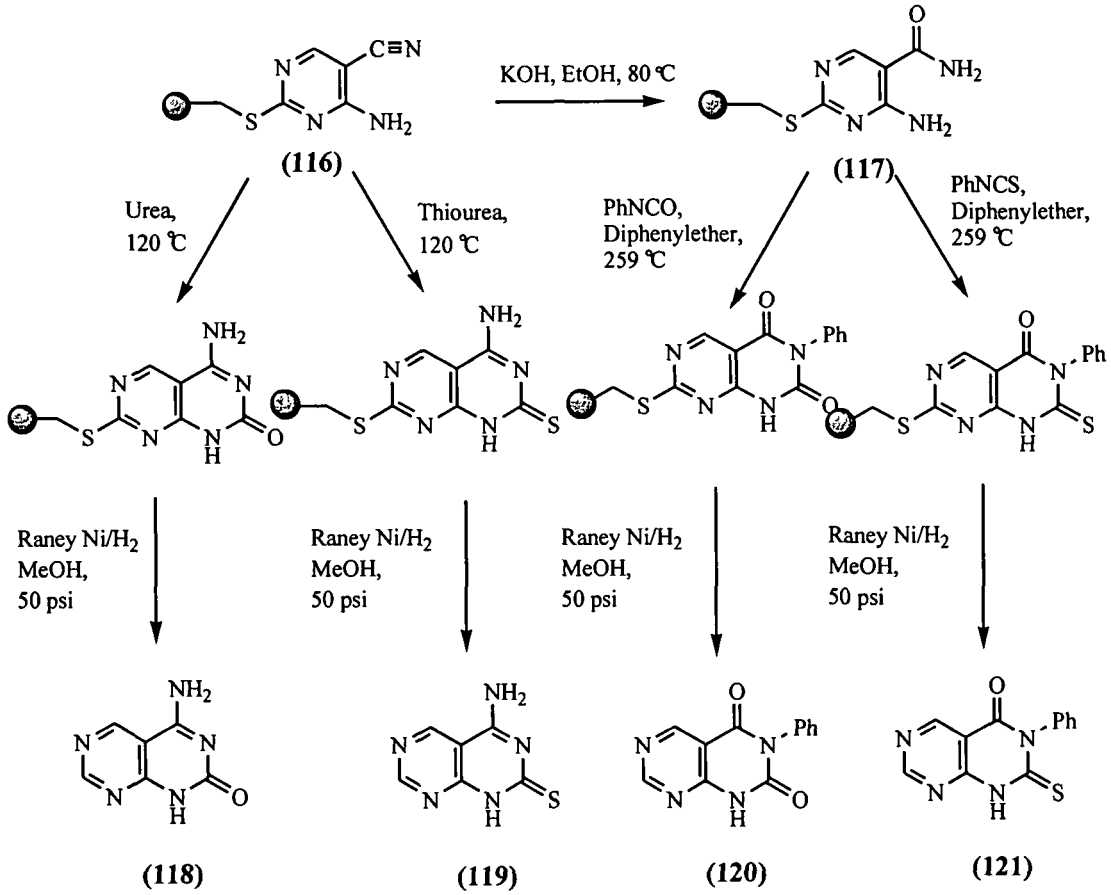


(115)

Scheme 1.65

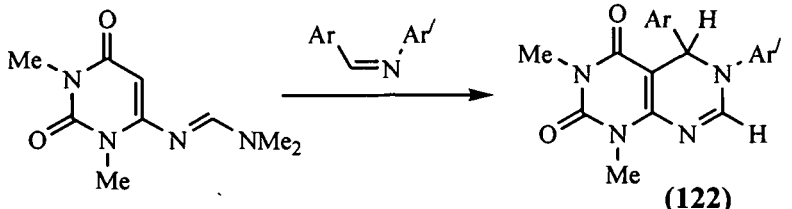
Srivastava *et al.* reported[173] that (Scheme 1.66) reaction of polymer bound pyrimidine (**116**) with urea or thiourea followed by cleavage from the support afforded 4-aminopyrimido[4,5-*d*]pyrimidines (**118, 119**); while treatment of (**117**) with phenyl

isocyanate or phenyl isothiocyanate followed by cleavage from resin afforded 3-phenylpyrimido[4,5-*d*]pyrimidines **(120, 121)**.



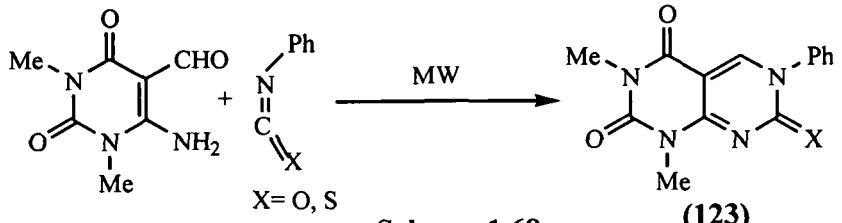
Scheme 1.66

Thakur *et al.* reported[174] a facile one pot synthesis of pyrimido[4,5-*d*]pyrimidines **(122)** from 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil with imines (Scheme 1.67).



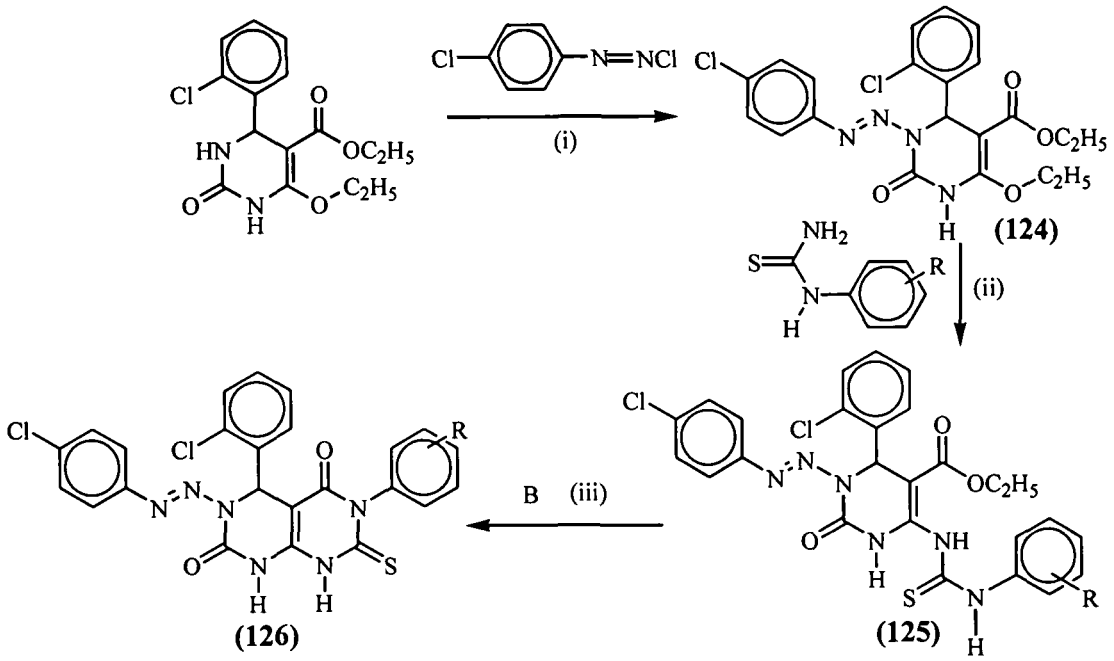
Scheme 1.67

Bhuyan and co-workers[175] synthesised (Scheme 1.68) pyrimido[4,5-*d*]pyrimidines **(123)** with high yield under microwave irradiation in solid state by the reaction of *N, N*-dimethyl-6-amino-5-formyluracide with phenyl isocyanate/phenyl isothiocyanate.



Scheme 1.68

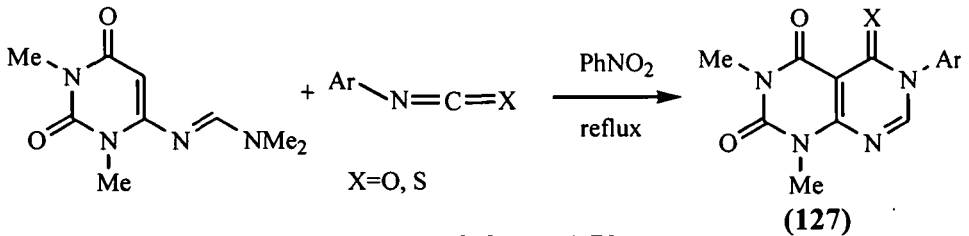
Sharma *et al.* synthesised[176] (Scheme 1.69) a number of pyrimido[4,5-*d*]pyrimidine-2,5-dione derivatives and screened their antibacterial and antifungal activities.



Reagents and conditions: (i) 0-5 °C, 3 h; (ii) EtOH, reflix, 4 h; (iii) CH_3OH/CH_3Na, r.t., 6 h

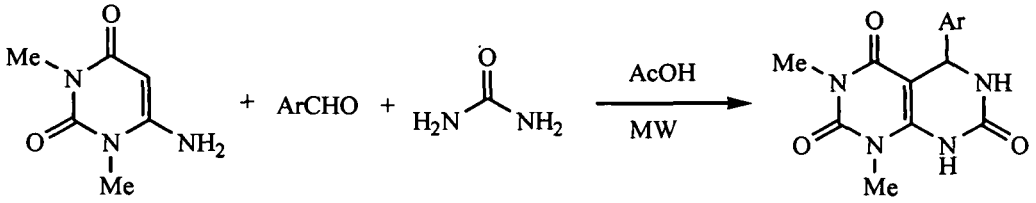
Scheme 1.69

Prajapati *et al.* reported[177] a facile one pot synthesis of novel pyrimido[4,5-*d*] pyrimidine derivatives by the reaction of 6-[(dimethyamino)methylene]aminouracil with various heterocumulenes such as aryl isocyanates and isothiocyanates under refluxing in nitrobenzene (Scheme 1.70).



Scheme 1.70

1,3-dimethyluracil, aromatic aldehyde and urea in presence of acetic acid under microwave assisted conditions.

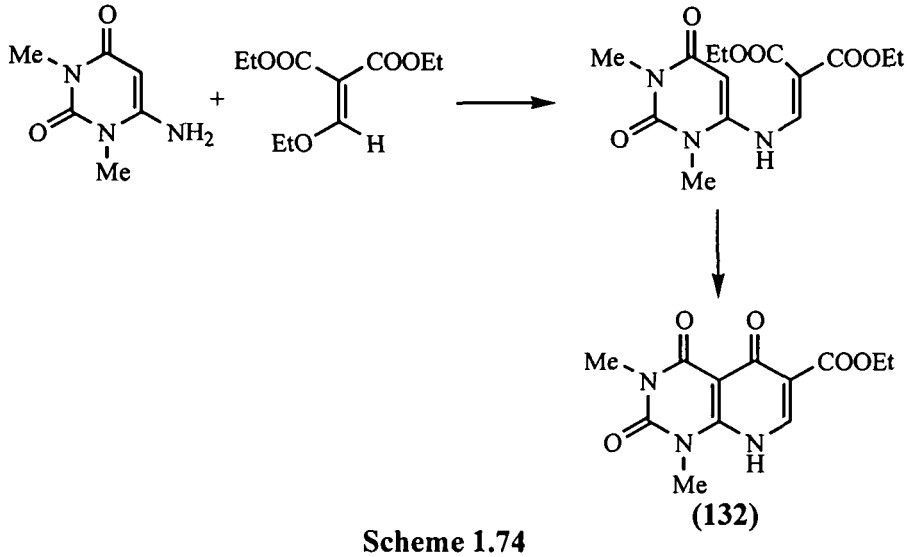


(131)

Scheme 1.73

1.2.3.3 Synthesis of Pyrido[2,3-*d*]Pyrimidine Derivatives:

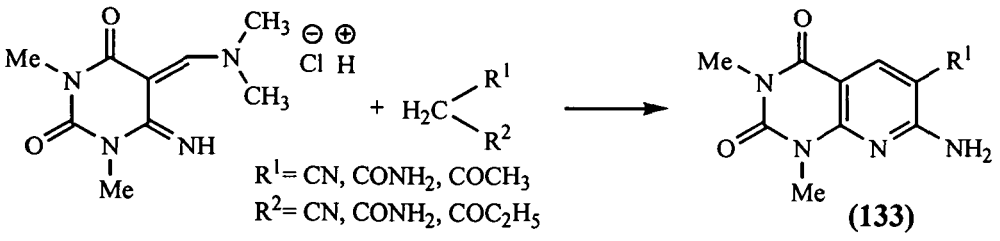
Anderson reported[181] (Scheme 1.74) the reaction of 6-amino uracils with diethyl ethoxymethylene malonate for the synthesis of 5-oxo-6-carbethoxy pyrido[2,3-*d*] pyrimidine **(132)**



(132)

Scheme 1.74

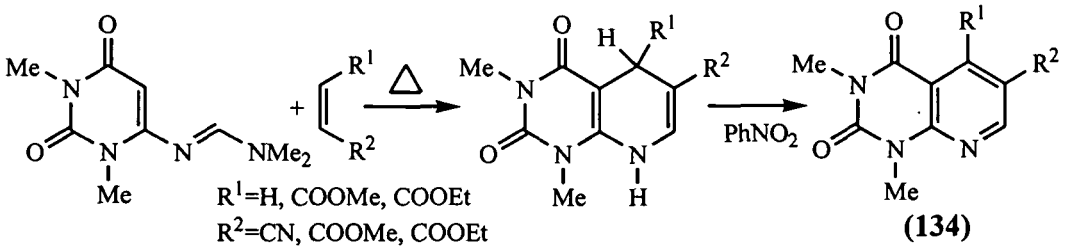
Hirota *et al.* reported[182] preparation of pyrido[2,3-*d*]pyrimidines **(133)** by the reaction of uracils derivative with active methylene compounds (Scheme 1.75).



(133)

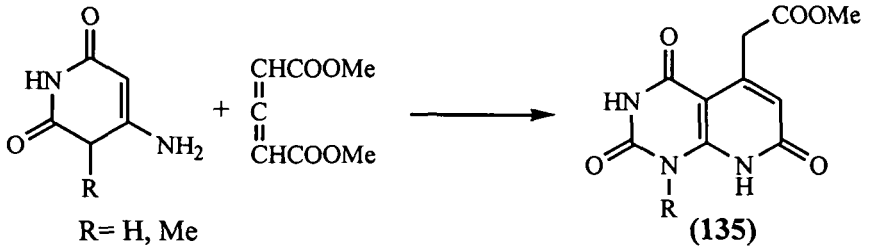
Scheme 1.75

Walsh *et al.* reported[183] that 6-[(dimethylamino)methylene]amino-1,3-dimethyl uracil undergoes formal Diels-Alder reaction (Scheme. 1.76) with electron deficient olefins to give pyrido[2,3-*d*]pyrimidines **(134)**.



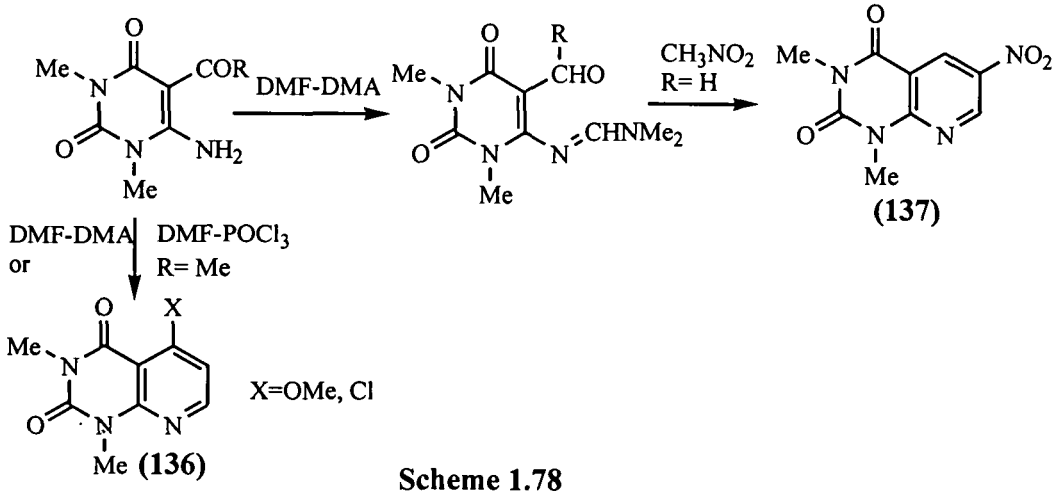
Scheme 1.76

Doad and his co-worker[184] synthesized pyrido[2,3-*d*]pyrimidines **(135)** by the reaction of 6-aminouracil with dimethyl-1,3-dicarboxylate where Michael addition occurred by attack of enamine carbon at C-5 on the central carbon atom of dimethyl alkene-1,3-dicarboxylate (Scheme 1.77).



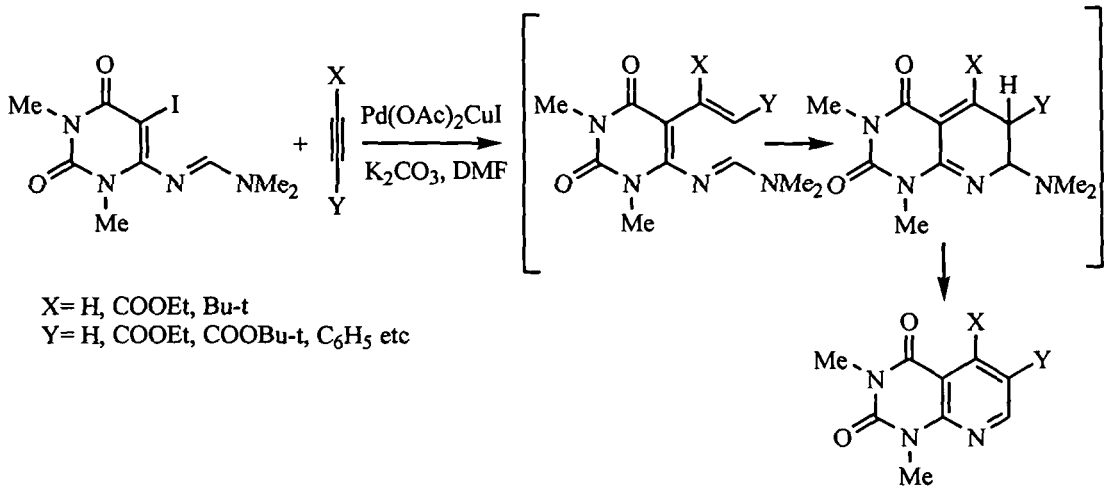
Scheme 1.77

Matyus *et al.* reported[172] (Scheme 1.78) the synthesis of 5-Substituted pyrido[2,3-*d*]pyrimidines **(136)** by the reaction of 5-acyl-6-amino uracil with *N,N*-dimethylfomamide dimethyl acetal (DMF-DMA). When nitromethane was used 6-nitropyrido[2,3-*d*]pyrimidines **(137)** formed, starting from the 5-formyluracil.



Scheme 1.78

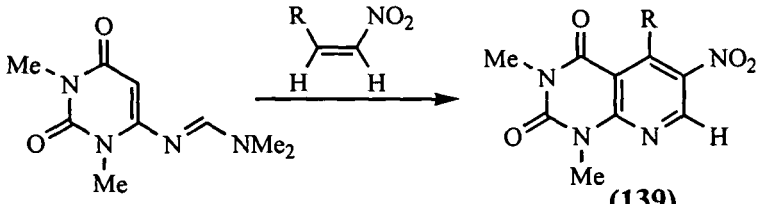
Pyrido[2,3-*d*]pyrimidines were regioselectively synthesized[185] by the reaction of 5-iodo-6-[(dimethylamino)methylene]amino-1,3-dimethyluracil, which was prepared from the reaction of 6-amino-1,3-dimethyluracil with DMF-DMA followed by iodination, with various acetylenes in the presence of catalytic amount of $Pd(OAc)_2$, CuI and K_2CO_3 in DMF at 100 °C (Scheme 1.79).



(138)

Scheme 1.79

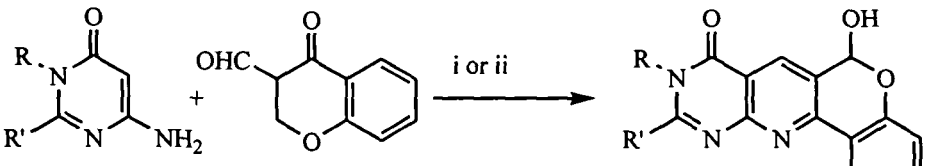
Thakur *et al.* reported[174] a facile (Scheme 1.80) one pot synthesis of pyrido[2,3-*d*]pyrimidines **(139)** from 6-[(dimethylamino) methylene]amino-1,3-dimethyluracil with α,β-unsaturated nitro compounds.



Scheme 1.80

(139)

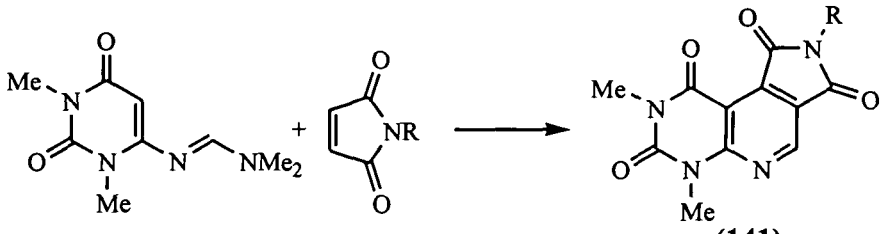
The reaction of 6-aminopyrimidines with 3-formyl-chromone (Scheme 1.81) under microwave-irradiation in dry media and classical heating in absolute ethanol afforded 6-hydroxy-6,9-dihydrobenzopyranopyrido[2,3-*d*]pyrimidin-8-ones[186]**(140)**.



(140)

Scheme 1.81

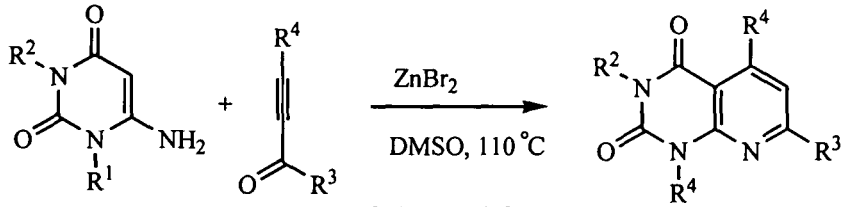
Saikia *et al.* also reported[187] (Scheme 1.82) the synthesis of fused pyrido[2,3-*d*]pyrimidines **(141)** by the reaction of 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil with various maleiimides.



(141)

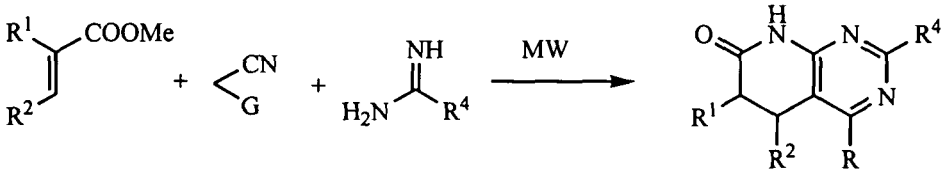
Scheme 1.82

Hughes *et al.* reported[188] that the Michael addition and cyclodehydration of 6-amino uracils and alkynone leads to give pyrido[2,3-*d*]pyrimidines with total control of regiochemistry. The cyclocondensation process was catalysed by $ZnBr_2$ or $Yb(OTf)_3$ at 110 °C (Scheme 1.83) providing the heteroannulated pyrido[2,3-*d*]pyrimidines up to 94%.



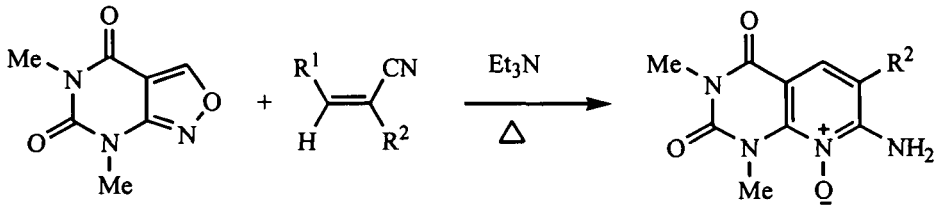
Scheme 1.83

A high yielding three-component reaction (Scheme 1.84) providing multifunctionalised pyrido[2,3-*d*]pyrimidines in a microwave-assisted one-pot cyclocondensation of α,β-unsaturated esters, amidine systems and malonitrile/ethyl cyanoacetate was described by Kappe *et al.*[189]



Scheme 1.84

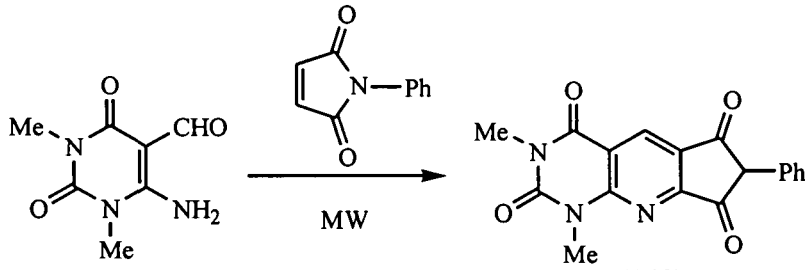
Bhuyan *et al.*[190] reported an unprecedented synthesis (Scheme 1.85) of pyrido[2,3-*d*]pyrimidine N-oxides **(142)** via the ring transformation of isoxazolo[3,4-*d*]pyrimidines by reaction with cyano-olefin in the presence of Et_3N as catalyst.



Scheme 1.85

(142)

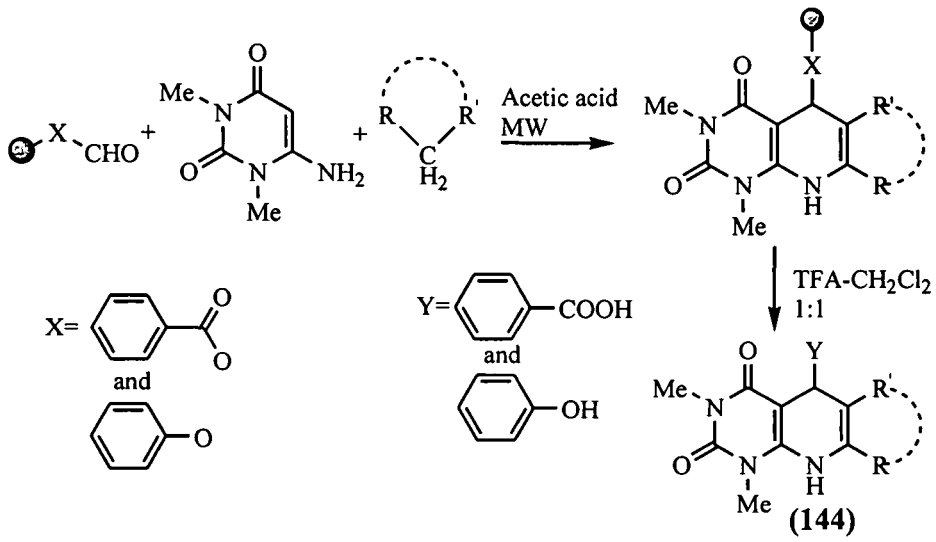
The same group[175] synthesised (Scheme 1.86) pyrido[2,3-*d*] pyrimidines **(143)** with high yield under microwave irradiation in solid state by the reaction of *N, N*-dimethyl-6-amino-5-formyluracide with maleimide.



Scheme 1.86

(143)

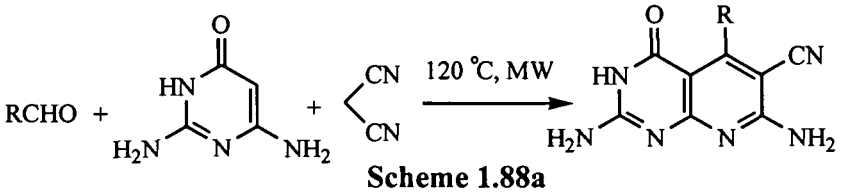
Agarwala *et al.* Synthesised[191] (Scheme 1.87) structurally diverse dihydropyrido[2,3-*d*]pyrimidines **(144)** by three-component reactions of resin bound aldehydes, 6-amino-1,3-dimethyluracils and compounds having active methylene groups using microwave irradiations.



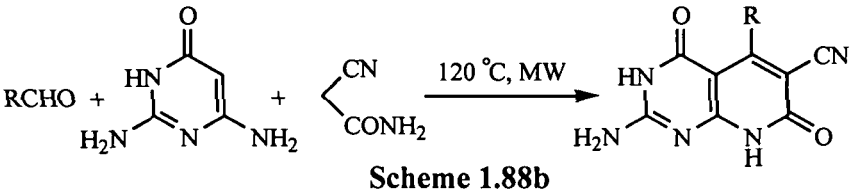
Scheme 1.87

(144)

Tu and co-workers reported[192] (Scheme 1.88) a simple and efficient synthesis of 2-amino pyrido[2,3-*d*]pyrimidine derivatives by a three-component reaction under microwave irradiation without catalyst.

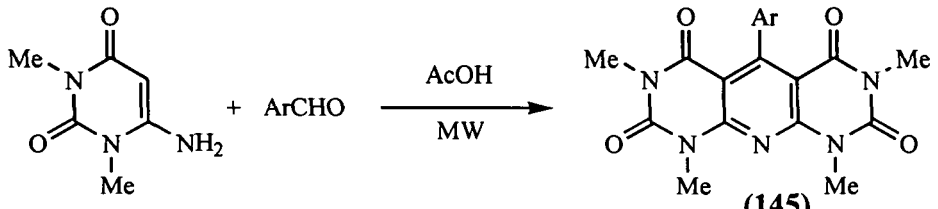


Scheme 1.88a



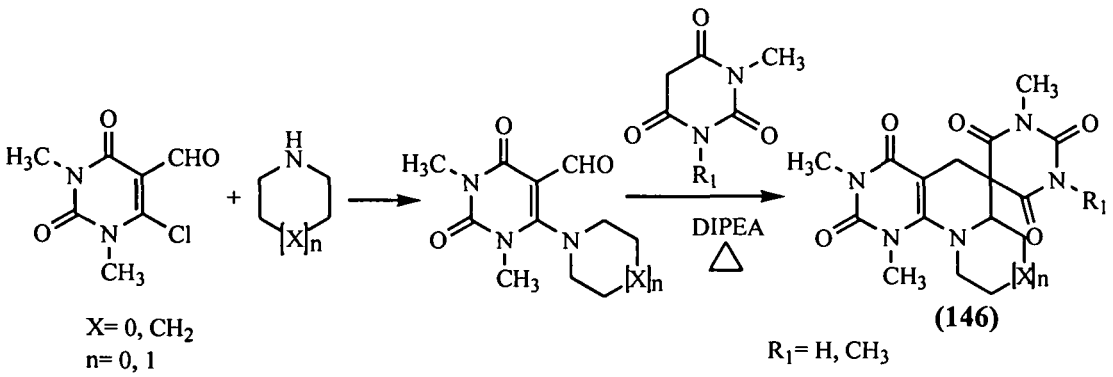
Scheme 1.88b

Dabiri *et al.* reported[180] that the reaction (Scheme 1.89) of 6-amino-1,3-dimethyl uracil with aromatic aldehyde in presence of acetic acid under microwave assisted conditions gave pyrido[2,3-*d*: 6,5-*d*]dipyrimidine-2,4,6,8-tetrone derivatives **(145)**.

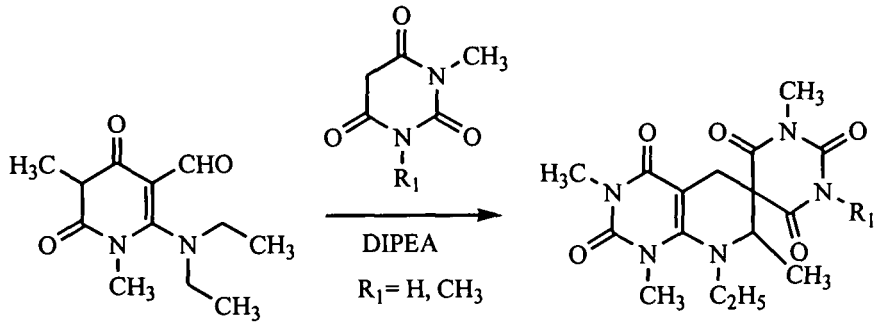


Scheme 1.89

Baruah *et al.* synthesised[193] (Scheme 1.90) spirosubstituted pyrido[2,3-*d*]pyrimidines **(146, 147)** by the reaction of 5-formyl-6-tertiaryaminouracils with barbituric acid in presence of base catalyst. 5-formyl-6-tertiaryamino uracyil can be prepared from 6-chloro-5-formyl uracils derivative.



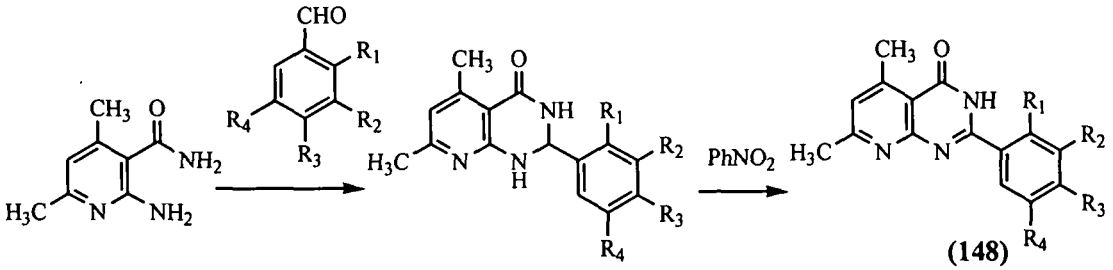
Scheme 1.90a



(147)

Scheme 1.90b

Narayana and co-workers[194] synthesised (Scheme 1.91) 2-substituted pyrido[2,3-*d*]pyrimidin-4(1*H*)-ones **(148)** by oxidation of 2-substituted-5,7-dimethyl-dihydropyrido [2,3-*d*]pyrimidin-4(1*H*)-ones which were in turn prepared from 2-amino-4,6-dimethyl-nicotinamide and substituted aryl aldehyde.



(148)

Scheme 1.91

From the literature survey it is seen that a numbers of protocols have been developed for generating libraries of new pyrimidine derivatives. From the point of view of green chemistry and wide biological applications of these heterocycles, solvent-free multi-component reaction is becoming a subject of current interest in the context of library building of molecules for the discovery of biologically active lead and also for optimisation of potent drug candidates.

1.2.4 Aza-Michael Addition Reaction:

The Michael addition is the conjugate addition of a nucleophile to α,β-unsaturated carbonyl compound. It belongs to the large class of conjugate additions. The nucleophile is termed as Michael donor and α,β-unsaturated compound as Michael acceptor. Arthur Michael defined it as addition of an enolate of a ketone or aldehyde to α,β-unsaturated carbonyl compound at the β carbon. According to the newer definition proposed by Kohler, Michael reaction is 1,4 addition of doubly stabilised carbon

nucleophile to α,β-unsaturated carbonyl compound. Nitrogen or aza nucleophile donor version of Michael reaction is often referred as aza-Michael addition. The conjugate addition of nitrogen nucleophile to α,β-unsaturated carbonyl compound leading to the formation of β-amino carbonyl compound is known as aza-Michael addition.[195] Amines are usually used as donors. Conjugated aldehydes, esters, nitriles, amides, and nitro compounds can all act as an electrophilic acceptor component.

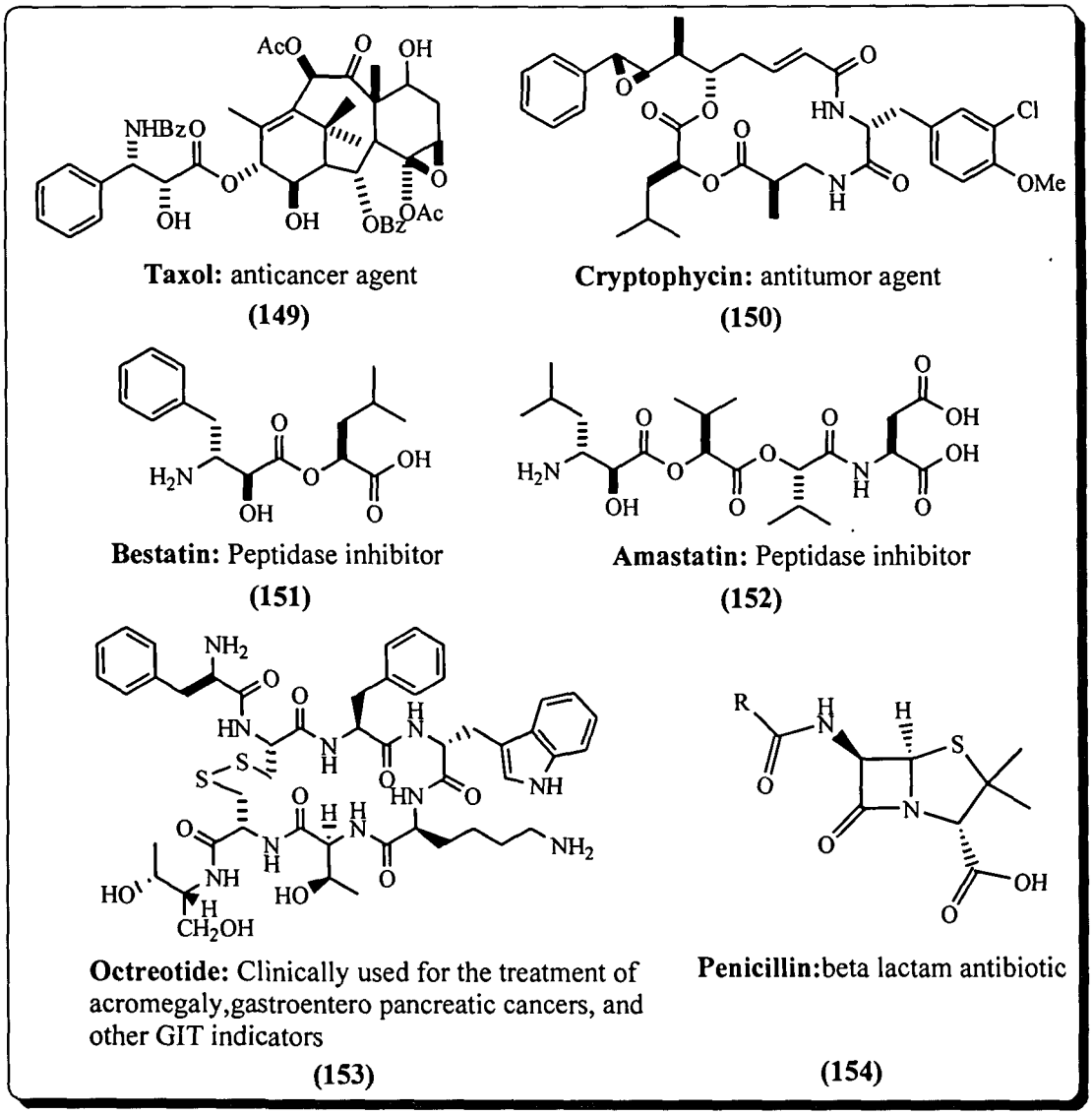


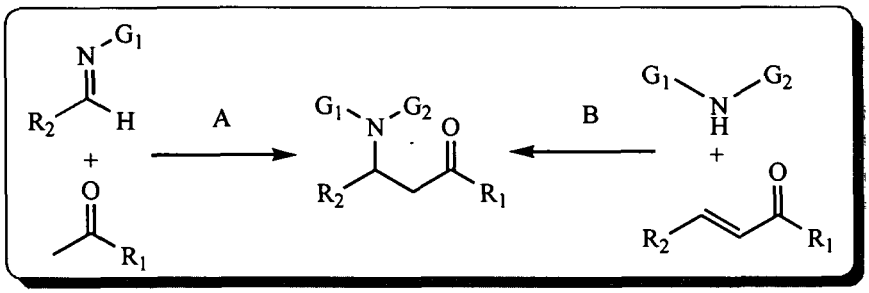
Figure 1.11: Structures of some bioactive compounds containing β-amino ketone moity

The products of aza-Michael additions, β-amino carbonyl compounds and derivatives, can be used in peptide analogues or as precursors to optically active amino acids, β-amino alcohols, 1,2-diamines, and lactams, many of which serve as powerful

antibiotics or other drugs.[196] These compounds are also widely used as building blocks for molecules with applications in pharmaceuticals[197] and fine chemicals. A large number of biologically active compounds (Fig. 1.11) contain β-amino ketone or ester moiety.

1.2.4.1 Methods for Synthesis of β-Amino Carbonyl Compounds:

The synthetic strategies for the β-amino carbonyl compounds can be categorized into two basic types as shown in scheme 1.92: (A) C-C bond formation by the Mannich-type reaction[198] and the addition of carbon nucleophile to imines and (B) C-N bond formation by the aza-Michael type reaction that is the conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds or activated olefins.



Scheme 1.92

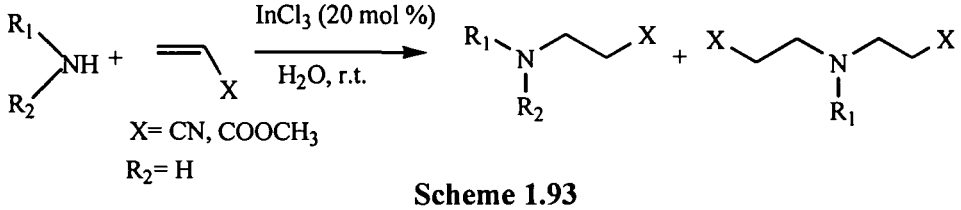
Among the various methods for generating β-amino carbonyl compounds, the conjugate addition of nitrogen nucleophiles to α,β-unsaturated compounds is one of the most simple and effective methods for preparing β-amino carbonyl compounds.[195] Although Mannich reaction[199] is another classical method for the preparation of β-amino carbonyl compounds, however, the drastic reaction condition and longer reaction time causes serious disadvantages.

Most of the aza-Michael reactions use aliphatic/aromatic amines, alkoxyamines, aldoximes, hydrazoic acid, azides ions and carbamates as nitrogen nucleophiles.[200] While sufficiently reactive nucleophiles (such as amines) can perform the aza-Michael reaction by themselves, less reactive nucleophiles generally require catalysts (Brønsted or Lewis acid catalysts) or catalytic amount of a strong base which can activate either the Michael acceptor or the nitrogen nucleophiles, respectively.

Various acid or base[201] catalyzed procedures have been reported in literature for these conjugate aza-Michael additions in organic solvent or solvent-less condition. It has also been observed that use of stoichiometric amount of several Lewis acids catalysts such as $AlCl_3$, $TiCl_4$ or $SnCl_4$ cause serious environmental problems due to strongly acidic waste streams.[202] Additionally, most Lewis acid catalysts are likely to be poisoned by alkyl and arylamine regents.[203] Due to the inertness of aromatic amines relative to aliphatic ones, most of the procedures are not successful with arylamines.

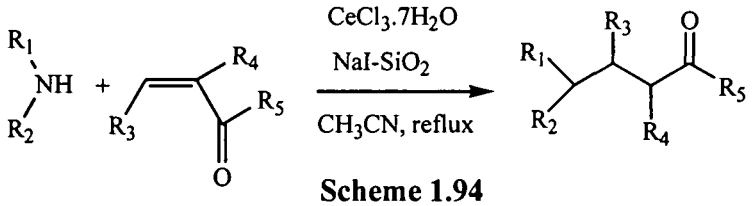
Here, we have included the recent development of aza-Michael addition using different Brønsted or Lewis acid catalysts to synthesize β-amino carbonyl compound.

Loh *et al.*[204] employed indium (III) trichloride as an efficient and reusable catalyst for conjugate addition of amines to α,β-ethylenic compounds in water under mild conditions (Scheme 1.93) within 6 h to 3 days.



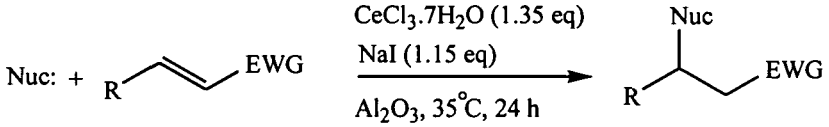
Scheme 1.93

Bartoli and co-workers[205] observed the conjugate addition of amines to α,β-unsaturated enones promoted by $CeCl_3 \cdot 7H_2O$-NaI supported on silica gel in acetonitrile (Scheme 1.94) under reflux during 4.5-6 h reaction period to form 75-91% yields of the β-amino carbonyl compounds.



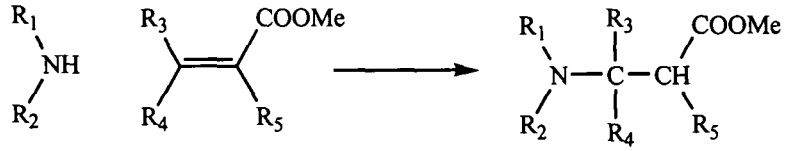
Scheme 1.94

The same group published another work[206] on aza-Michael reaction using $CeCl_3 \cdot 7H_2O$/ NaI system supported on alumina in solvent-free conditions at 35 °C within 24 h (Scheme 1.95).



Scheme 1.95

Jenner *et al.* produced[207] hindered β-aminoester in fair to good yields by the conjugate addition of amines to α,β-unsaturated ester, both substrates containing bulky groups, under high pressure in presence of catalytic amount of $Yb(OTf)_3$ (Scheme 1.96)

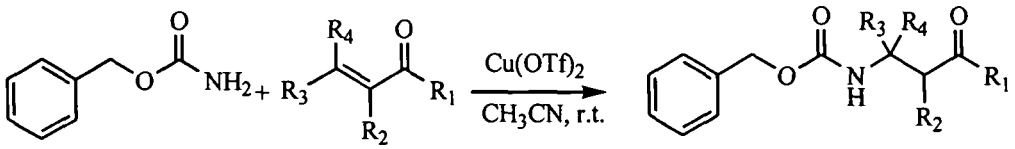


Scheme 1.96

Srivastava *et al.*[208] developed bismuth nitrate-catalyzed versatile Michael reaction for facile preparation of organic compounds of diverse structures. For example, several substituted amines, imidazoles, thio compounds, indoles, and carbamates were prepared at room temperature by following this method. In contrast to the existing methods using many acidic catalysts, this method was very general, simple, high-yielding, environment friendly, and moisture tolerant.

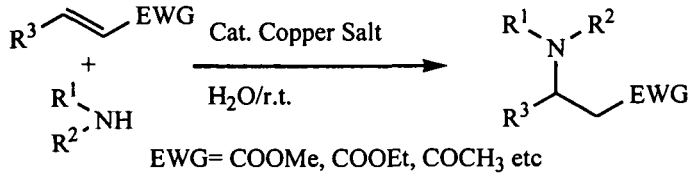
The use of bismuth triflate catalyzed aza-Michael addition was performed by Adapa and co-workers[209] for the conjugate addition of aliphatic amines to α,β-ethylenic compounds in acetonitrile under mild conditions. The reaction is chemoselective, as aromatic amines do not participate in the reaction. Further, the catalyst can be easily recovered and reused.

A convenient synthesis of Cbz-protected β-amino ketones was reported[210] by Wabnitz and co-workers. Benzyl carbamates and α,β-unsaturated ketones furnished the conjugate addition products (Scheme 1.97) in the presence of a Cu(II) catalyst under mild conditions. Other weakly basic nitrogen nucleophiles can also be used in this reaction.



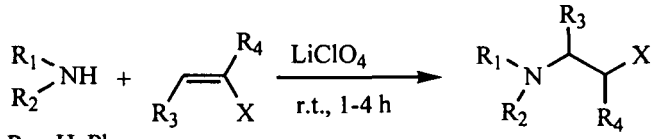
Scheme 1.97

Similarly, Xu and his group[211] performed simple copper salt catalyzed highly efficient, conjugate addition of aliphatic amines to α,β-unsaturated compounds in water (Scheme 1.98).



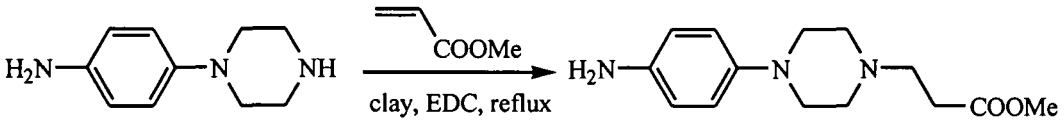
Scheme 1.98

$LiClO_4$ accelerated Michael addition (Scheme 1.99) of amines to α,β-unsaturated olefins under solvent-free condition at room temperature was introduced by Saidi *et al.*[212] using primary and secondary amines.



Scheme 1.99

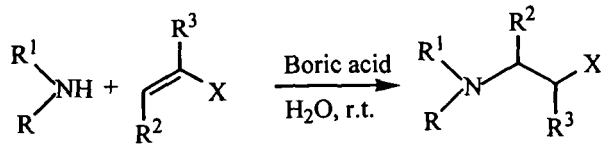
Applications of acidic clays as heterogeneous catalysts for the Michael type addition reaction of aliphatic amines to α,β-ethylenic compounds was presented by Shaikh *et al.*[213] in 1,2-dichloroethane under reflux (Scheme 1.100) and this method was not effective for aromatic amines.



Scheme 1.100

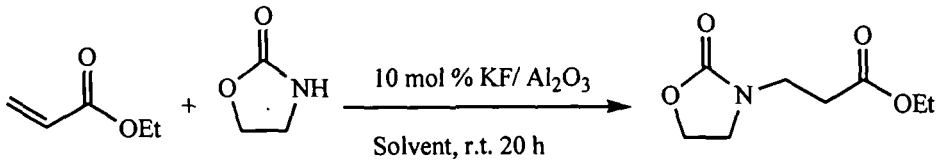
Basu *et al.*[214] utilized silica gel as recyclable surface for the synthesis of β-amino esters and amines via conjugate addition of amines to electron deficient alkenes at 120-130 °C under vacuum. Both aliphatic and aromatic primary or secondary amines worked efficiently to yield the desired adducts in good to excellent yield. Another silica gel catalyzed aza-Michael addition of amines to α,β-unsaturated amides had been developed by You *et al.*[215] in acetonitrile under reflux for 4 h.

Choudhuri and co-workers reported[216] boric acid (Scheme 1.101) as safe and efficient catalyst for aza-Michael addition of aliphatic amines to α,β-unsaturated compounds to produce β-amino compounds with excellent yields in water by stirring at room temperature within 1-6 h.



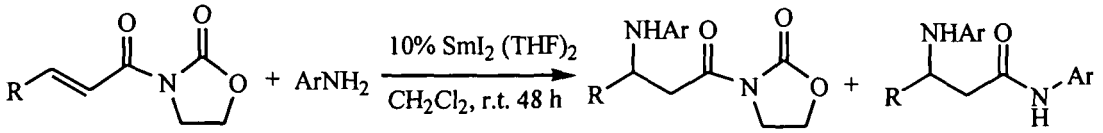
Scheme 1.101

Yang *et al.* observed[217] the first example of KF/Al_2O_3-catalyzed hetero-Michael addition reaction (Scheme 1.102) of nitrogen, oxygen, and sulfur nucleophiles for preparation of organic compounds of widely different structures in acetonitrile at room temperature within 18-24 h reaction period.



Scheme 1.102

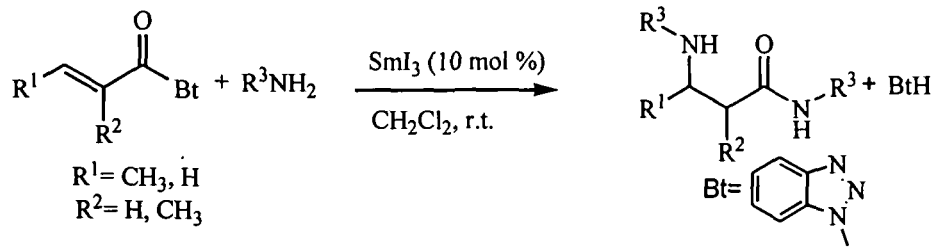
Reboule *et al.* reported[218] samarium diiodide catalyzed aza-Michael (Scheme 1.103) addition of aromatic amines onto α,β-unsaturated N-acyloxazolidinones to form β-aminoacid derivatives. Aza-Michael reactions can be followed by an amidation reaction with the aromatic amine, leading to β-aminoamides. β-Amino-N-acyloxazolidinones was selectively obtained with o-anisidine, while amidation reaction was observed with *p*-anisidine.



R= COOEt, CH_3, C_3H_7, H

Scheme 1.103

In addition, Wang *et al.*[219] reported SmI_3 catalysed (Scheme 1.104) addition of amines to α,β-unsaturated N-acylbenzotriazoles at ambient temperature within 0.5-20 h. Unsaturated aliphatic N-acylbenzotriazoles afforded bis addition products, whereas cinnamoyl benzotriazoles gave acylated products.



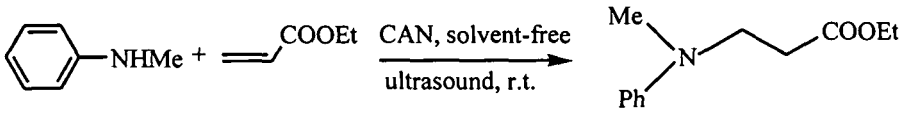
$R^1 = CH_3$, H
R^2= H, CH_3

Scheme 1.104

Kantam and co-workers[220] used Cu-Al hydrotalcite as reusable catalyst for the synthesis of β-amino carbonyl compounds through aza-Michael addition in methanol at room temperature during 3-5.5 h reaction time.

Ceric ammonium nitrate catalyzed[221] aza-Michael addition of aliphatic amines to α, β-unsaturated carbonyl compounds and nitrile in water was developed by Adapa and co-workers. The reaction is procedurally simple and displays limited chemoselectivity, as aromatic amines were found to be unreactive.

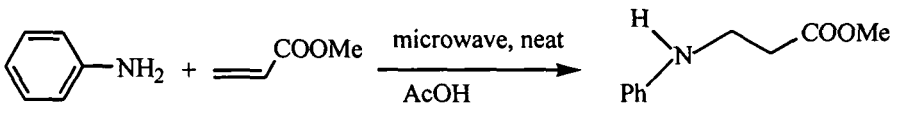
Interestingly, under ultrasound irradiation CAN efficiently catalyze[222] the aza-Micahel addition of aromatic and aliphatic ammines with α,β-unsaturated electrophiles in the absence of solvent (Scheme 1.105). The reaction took less time (20-40 min) with primary and secondary aliphatic amines. For aromatic amines, it needed 4-6 h to give good to moderate results.



Scheme 1.105

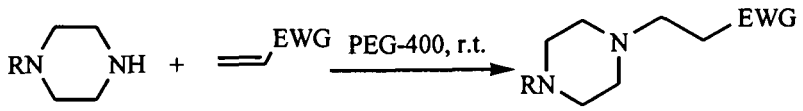
Zhang *et al.*[223] used $RuCl_3$ in poly (ethylene glycol) as highly efficient and recyclable catalyst for the conjugate addition of 1°, 2° and aromatic amines to α,β-unsaturated compounds at 50 °C for longer reaction time (3-24 h).

Microwave assisted Michael addition of aniline to α,β-unsaturated alkenes was performed by Amore and co-workers[224] in neat at (Scheme 1.106) 200 °C for 20 min using acetic acid as catalyst.



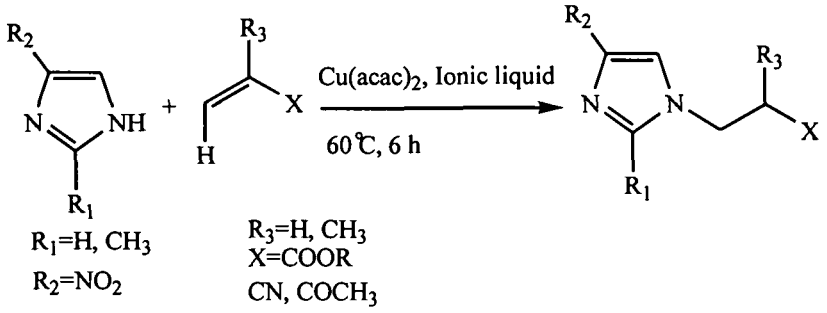
Scheme 1.106

Kumar *et al.*[225] found PEG-400 as a recyclable reaction medium for the conjugate addition of amines to conjugated alkenes (Scheme 1.107) at room temperature without any use of acid and base catalyst. The reaction did not generate any toxic waste and by products.



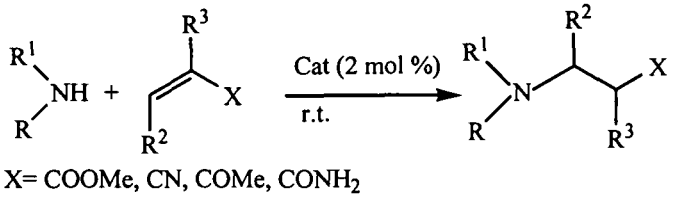
Scheme 1.107

Kantam *et al.* used[226] Copper (II) Acetylacetonate in ionic liquid (Scheme 1.108) for the synthesis of *N*-substituted imidazoles via aza-Michael addition of imidazoles to α,β-unsaturated compounds at ambient temperature within 6 h.



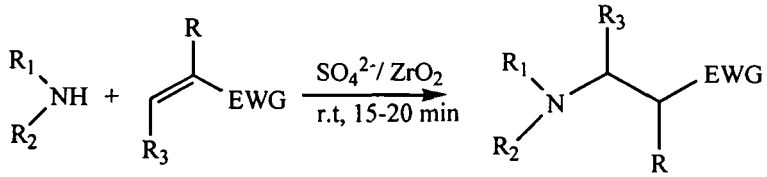
Scheme 1.108

Nath *et al.*[227] carried out (Scheme 1.109) aza-Michael addition of aliphatic and aromatic amines with α,β-unsaturated compounds using phosphate impregnated titania as a reusable heterogeneous catalyst under solvent-free condition within 15 min-24 h.



Scheme 1.109

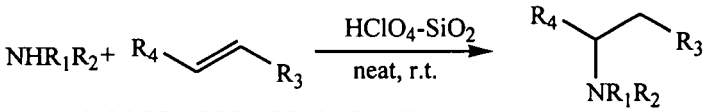
Reddy and co-workers employed[228] sulphated zirconia (Scheme 1.110) as a reusable heterogeneous catalyst for aza-Michael reaction of amines with α,β-unsaturated compounds at room temperature under solvent-free conditions within 30 min-2 h.



Scheme 1.110

Mukhaerjee *et al.* reported[229] (Scheme 1.111) aza-Michael addition of aliphatic and aromatic amines to a series of α,β-unsaturated ketones, esters, nitriles and chalcones

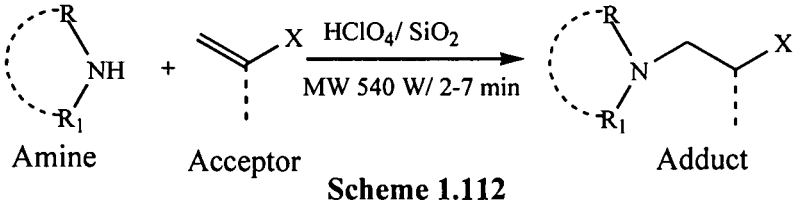
using perchloric acid supported over silica gel ($HClO_4$-SiO_2) at room temperature under solvent-free condition. The reaction completed within 0.5-7 h for different substrates.



R_3= CN, COOEt, COEt, COMe; R_4= H, Ar

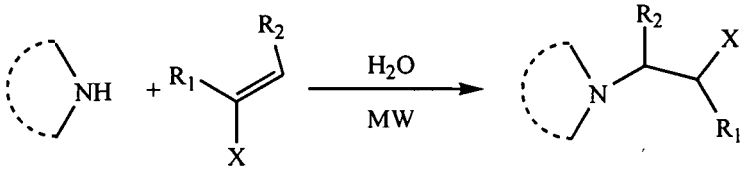
Scheme 1.111

Singh *et al.* observed[230] the effect of microwave irradiation with the above catalyst under solvent-free medium for the aza-Michael addition of primary and secondary amines with α,β-unsaturated carbonyl compounds which decreased the reaction time to 2-7 min (Scheme 1.112).



Scheme 1.112

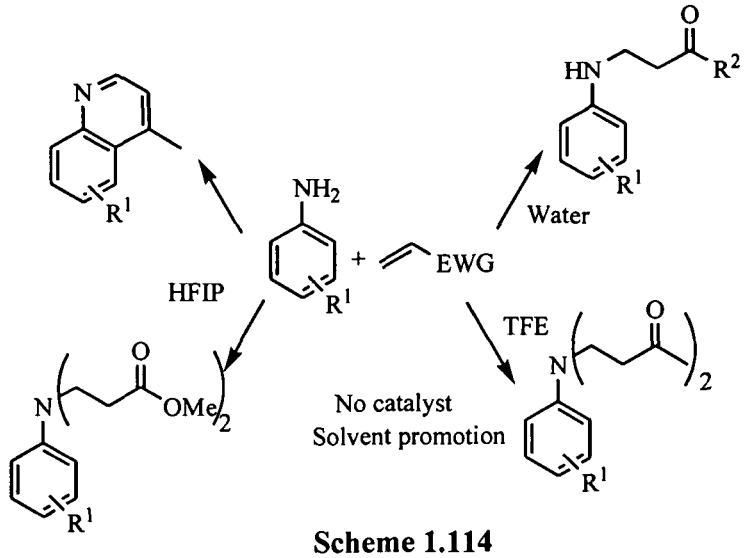
Kall *et al.*[231] reported (Scheme 1.113) a microwave induced fast addition of amines to conjugated carbonyl compounds in water without using any catalyst. Primary, secondary, benzylic and aromatic amines afforded desired β-amino carbonyl compounds in excellent yield within 1-3 min.



R_1, R_2 = H, alkyl
X= CO_2Me, COMe, CN, COOEt

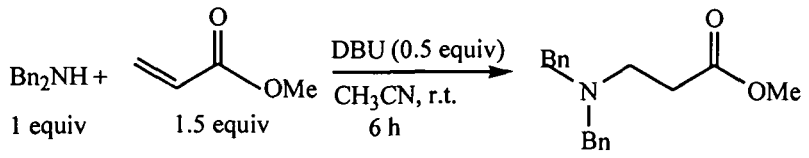
Scheme 1.113

De *et al.* carried[232] out (Scheme 1.114) solvent promoted and controlled 1,4-addition of anilines on to Michael acceptors in specific polar protic solvents. They found monoadduct in water and diadduct in hexafluoroisopropyl alcohol with methyl acrylate as elecrophile. With methylvinyl ketone they observed monoadduct in water, diadduct in trifluoroethanol and quinoline in hexafluoroisopropyl alcohol.



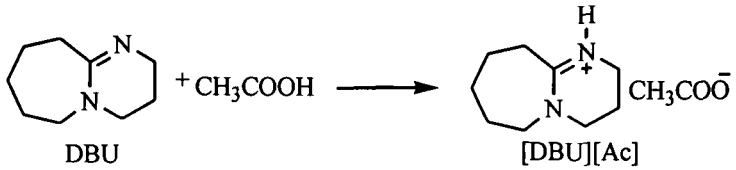
Scheme 1.114

Yeom and co-workers[233] employed 1,8-Diazabicyclo[5.4.0]undec-7ene (DBU) for aza-Michael addition of various nitrogen nucleophiles to α,β-unsaturated carbonyl compounds at room temperature and at 50 °C in acetonitrile (Scheme 1.115). The reaction time varied from 3-18 h depending on substrates.



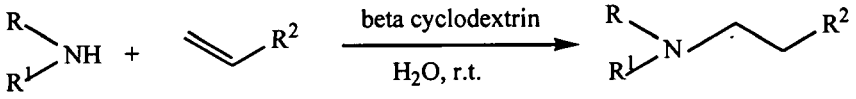
Scheme 1.115

Similarly, Ying *et al.*[234] utilized a task-specific ionic liquid, 1,8-diazabicyclo[5,4, 0]-undec-7-en-8-ium acetate (Scheme 1.116) as a catalyst for conjugate addition of aliphatic and aromatic amines to various electron deficient alkenes under solvent-free conditions at room temperature. They recycled the catalyst for six times without significant loss of activity.



Scheme 1.116

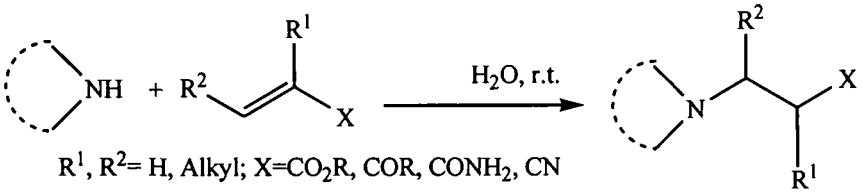
Surendra *et al.* reported[235] (Scheme 1.117) β-cyclodextrin promoted aza-Michael addition of amines to conjugated alkenes in water at r.t. Here, the reaction occurred within 6-8 h in all cases.



$R=R^1$= aryl, benzyl, alkyl
R^2= COMe, CN, CO_2Me

Scheme 1.117

Ranu *et al.*[236] carried out addition of amine to conjugated alkenes in water at room temperature by stirring for 20-50 min without any catalyst (Scheme 1.118). They reported that in contrast to aliphatic amine, aniline (aromatic amine) did not afford the adduct up to 24 h.

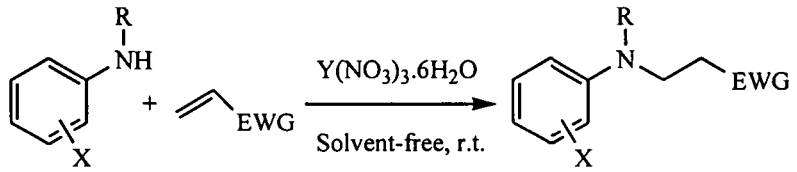


R^1, R^2= H, Alkyl; X=CO_2R, COR, $CONH_2$, CN

Scheme 1.118

Beletskaya and co-workers reported[237] poly (N-vinylimidazole) as effective and regenerable catalyst for aza-Michael addition of 1*H*-1,2,4-triazole, 3,5-dimethyl-1*H*-1,2,4-triazole, uracil, oxazolidin-2-one, methyl acrylate and succinimide to but-3-en-2-one, cyclohex-2-en-1-one, methyl acrylate and methyl vinyl sulfone by stirring in water for 2-48 h at room temperature. They reused the catalyst for five times without loss in activity.

$Y(NO_3)_3 \cdot 6H_2O$ catalyzed solvent-free aza-Michael addition of aromatic and hetero aromatic amines with α,β-unsaturated compounds like esters, nitriles and amides was performed by Bhanushali *et al.*[238] (Scheme 1.119) within 3-24 h at ambient temperature.



R=H, CH_3 EWG=COOMe, $CONH_2$, CN, COOBu
X=Me, OMe, Cl, Br, CF_3

Scheme 1.119

Trivedi *et al.* used[239] vanadyl(IV) acetate[$VO(OAc)_2$] for conjugate addition of aliphatic and aromatic amines to α,β-unsaturated carbonyl compounds in solvent free

media at room temperature to afford corresponding amino compound within 30 min-24 h.

Vijender *et al.*[240] reported aza- Michael addition of amines with electron deficient olefins using cadmium chloride as a catalyst at room temperature in dichloromethane within 2.5-4 h.

Zheng *et al.* developed[241] a novel efficient procedure for conjugate addition of amines to electron deficient alkenes using K_2CO_3 supported on different carriers. Out of different supports such as MgO, CaO, Al_2O_3, TiO_2, SnO_2, SiO_2, ZrO_2, they found K_2CO_3/ MgO as the most efficient catalyst. In presence of K_2CO_3/ MgO, the reaction went smoothly at room temperature under solvent-free conditions within 10-40 min.

The investigation of literature survey on aza-Michael revealed that although a large number of alternative procedures have been developed using various types of Lewis as well as Brønsted acid catalysts, still the development of less expensive, simpler and efficient mild Lewis acid catalysts is highly desirable for aza-Michael addition.

1.3 Objectives:

1. Investigation of organic reactions such as Prins reaction, Aza-Michael addition, Pechmann reaction etc. in organic solvent and in solvent-free condition.
2. Synthesis of important structural unit of bioactive molecules such as dioxanes, pyrans, β-amino carbonyl compounds and coumarins via the above mentioned reactions.
3. Development of improved newer methods for the synthesis of building blocks of bioactive molecules.
4. Synthesis of novel aza-heterocyclic biologically significant molecules applying green strategies via MCR.
5. Use of cost effective and green catalyst/reaction medium for the synthesis of above compounds.
6. Synthesis and application of polymer supported heterogeneous solid acid catalyst in Organic synthesis.
7. Development of milder reaction condition; i.e. use of microwave irradiation.

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Chapter 2

Preparation of 1,3-Dioxanes and Tetrahydropyran Derivatives via Prins Reaction

Chapter 2

Section A:

Prins Reaction of Aliphatic Aldehydes and Alkenes for the Synthesis of 1,3-Dioxanes

2.A.1 Introduction:

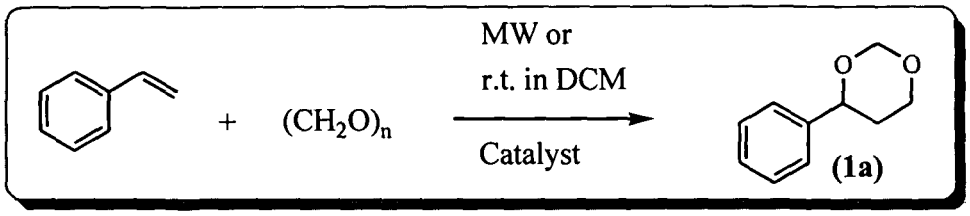
The acid-catalyzed condensation of olefins with carbonyl compounds is an important reaction for carbon-carbon bond formation,[1] which is well known as the Prins reaction (Scheme 2.A.1). This reaction is one of the efficient methods for the synthesis of 1,3-dioxanes in the presence of conventional Lewis or Brønsted acids using volatile organic solvents. Reports on a large number of synthetic methods[1-3] involve high temperature reaction conditions, prolonged reaction time (6-20 h), use of stoichiometric amount of catalyst, environmental pollution from organic solvents, and complicated product purification. In recent years, the use of solid catalysts such as resin,[4] zeolite,[5] and K-10 clay[2] have gained importance in the Prins[6] reaction because of their environmental compatibility, greater selectivity, experimental simplicity, low cost, and simple purification of the products. Chandrasekhar and Reddy[7] first reported the microwave-assisted Prins synthesis of 1,3-dioxane using $TaCl_2$-SiO_2 as catalyst under solvent-free conditions. Generally, most of the conventional methods[8] include the use of paraformaldehyde as a formaldehyde source. The direct use of formalin solution is highly desirable because it reduces the use of toxic and volatile organic solvents such as acetonitrile, toluene, and dioxane to dissolve solid paraformaldehyde. Only a few[3] reports are available in literature regarding the use of formalin as a starting compound.

Therefore, new methods and environmentally friendly conditions for the synthesis of 1,3-dioxane is still demand in terms of greater selectivity, shorter reaction time, and simple workup procedure.

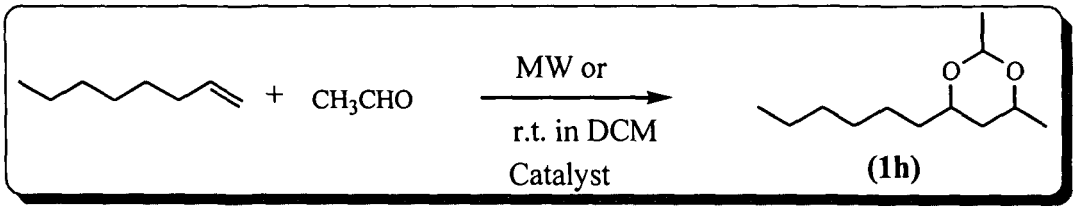
Part of this work is published in

Synth.Commun. **38**, 3082–3087 (2008)

2.A.2 Results and discussion:



Scheme 2.A.1a

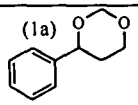
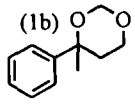
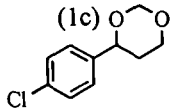
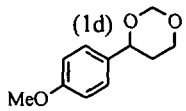
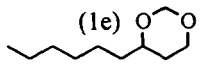


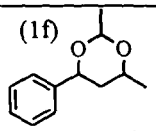
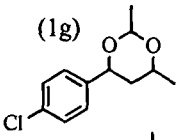
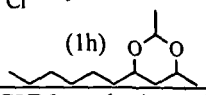
Scheme 2.A.1b

For comparative study, we investigated TsOH/TsOH-SiO_2-catalyzed Prins reaction of paraformaldehyde (Tables 2.A.1 and 2.A.2) and various alkenes under both solvent and solvent-free conditions. These studies revealed that the Prins reaction of paraformaldehyde and substituted styrene selectively produced 1,3-dioxane in the presence of TsOH-SiO_2 as catalyst within 5 min (Table 2.A.2, entries 2, 5, 8, 10) under microwave irradiation (180 W) as compared to reaction in dichloromethane (Table 2.A.1, entries 2, 6, 8, 10). In addition, p-toluene sulfonic acid catalyzed Prins reaction of formalin and styrene derivatives (Table 2.A.2, entries 6, 9, 11) showed excellent results under microwave irradiation. Interestingly, Du and Tian[3] reported that no 1,3-dioxane product was found for TsOH catalyzed Prins reaction of formalin and styrene under reflux for 20 h. Similarly, in this case also, no reaction was observed for the Prins reaction of formalin and styrene in dichloromethane after 24 h (Table 2.A.1, entries 3 and 4), at room temperature using TsOH/TsOH-SiO_2 as catalysts. The results in Table 2.A.1 indicate that in contrast to the conventional methods[2,3,9] TsOH/TsOH-SiO_2-catalyzed Prins reaction of different olefins and paraformaldehyde took less reaction time (30 min-3 h) in dichloromethane at room temperature. All other aldehydes, such as pentanal and octanal, were similarly transformed to the corresponding 1,3-dioxanes (Table 2.A.2, entries 14, 15, 16) after irradiating microwave radiation for 2-7 min. Furthermore, the TsOH-SiO_2-catalyzed Prins reaction gave higher yield of the product

(Table 2.A.1, entries 2, 6, 8, 10) as compared to TsOH-catalyzed reaction (Table 2.A.1, entries 1, 5, 7, 9) in dichloromethane within a short period. Again, microwave irradiation decreases the selectivity of TsOH-catalyzed Prins reaction for the formation of 1,3-dioxane (Table 2.A.2, entry 1) derivatives and gives by products. It was found that the alkyl-substituted olefins afforded the corresponding 1,3-dioxanes in low yields (Table 2.A.1, entries 12, 13, and Table 2.A.2, entry 12) as compared to styrene derivatives.

Table 2.A.1: Prins reaction in dichloromethane catalysed by TsOH/TsOH-SiO_2

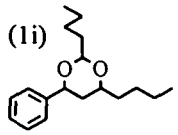
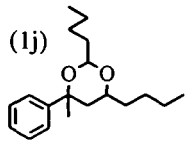
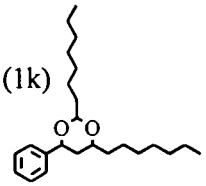
Entry	Alkene	Aldehyde	Amount of Silica gel (g)	Time [min]/h	Product	% Yield[a,b]
1	Styrene	$(CH_2O)_n$	-	1	(1a) 	75
2	Styrene	$(CH_2O)_n$	1	[30]	(1a)	82
3	Styrene	Formalin	-	24	NR	NA
4	Styrene	Formalin	1	24	NR	NA
5	α-Methyl styrene	$(CH_2O)_n$	-	[90]	(1b) 	70
6	α-Methyl styrene	$(CH_2O)_n$	1	[30]	(1b)	85
7	p-Chloro styrene	$(CH_2O)_n$	-	3	(1c) 	85
8	p-Chloro styrene	$(CH_2O)_n$	1	2	(1c)	89
9	p-Methoxy styrene	$(CH_2O)_n$	-	[90]	(1d) 	78
10	p-Methoxy styrene	$(CH_2O)_n$	1	[70]	(1d)	86
11	1-Octene	Formalin	-	20	NR	NA
12	1-Octene	$(CH_2O)_n$	-	[90]	(1e) 	67
13	1-Octene	$(CH_2O)_n$	1	2	(1e)	62

14	Styrene	CH_3CHO	1	[70]	(1f) 	80
15	p-Chloro styrene	CH_3CHO	1	[90]	(1g) 	83
16	1-Octene	CH_3CHO	1	2	(1h) 	63

[a] All products were characterized by ^1H NMR, ^{13}C NMR, MS and CHN analysis and also by their comparison with literature[2,5,8,9] data. [b] Isolated yields.

Table 2.A.2: Microwave assisted Prins reaction catalysed by TsOH/TsOH-SiO_2

Entry	**Alkene**	**Aldehyde**	**MW Power (W)**	**Amount of silica gel (g)**	**Time (min)**	**Product**	**% Yield[a,b]**
1	Styrene	$(CH_2O)_n$	180	-	5	(1a)	35[c]
2	Styrene	$(CH_2O)_n$	180	1	5	(1a)	85
3	Styrene	Formalin	180	-	2	(1a)	90
4	Styrene	Formalin	180	1	2	NR	NA
5	α-Methyl styrene	$(CH_2O)_n$	180	1	4	(1b)	90
6	α-Methyl styrene	Formalin	180	-	4	(1b)	85
7	α-Methyl styrene	Formalin	180	1	4	(NR)	NA
8	p-Chloro styrene	$(CH_2O)_n$	180	1	5	(1c)	95
9	p-Chloro styrene	Formalin	180	-	3	(1c)	96
10	p-Methoxy styrene	$(CH_2O)_n$	180	1	4	(1d)	94
11	p-Methoxy styrene	Formalin	180	-	2	(1d)	92
12	1-Octene	$(CH_2O)_n$	300	1	3	(1e)	70

13	1-Octene	Formalin	300	-	5	NR	NA
14	Styrene		180	1	1	(1i) 	76
15	α-Methyl styrene		180	1	2	(1j) 	72
16	Styrene	$CH_3(CH_2)_6CHO$	180	1	7	(1k) 	52
17	Styrene	CH_3CHO	180	1	5	(1f)	83
18	p-Chloro styrene	CH_3CHO	180	1	5	(1g)	92
19	1-Octene	CH_3CHO	180	1	4	(1h)	70

[a] All products were characterized by ^1H NMR, ^{13}C NMR, FT-IR, MS, and CHN analysis and also by their comparison with literature[2,5,8,9] data. [b] Isolated yields. [c] More number of side products formed.

Subsequently, we examined the polyaniline supported TsOH/$FeCl_3$ catalyzed Prins reactions of paraformaldehyde and various alkenes in dichloromethane at different temperatures. These results (Table 2.A.3, entries 2, 10, 13, 15) revealed that both catalysts decrease their reactivity in presence of polymer support for the synthesis of 1,3-dioxane in dichloromethane with respect to TsOH/$FeCl_3$ catalysts. The use of formalin was found to be efficient in certain cases under reflux condition within short time (Table 2.A.3, entries 5, 8, 17). Both supported catalysts showed improved results with 1-octene under reflux condition in dichloromethane (Table 2.A.3, entry 16).

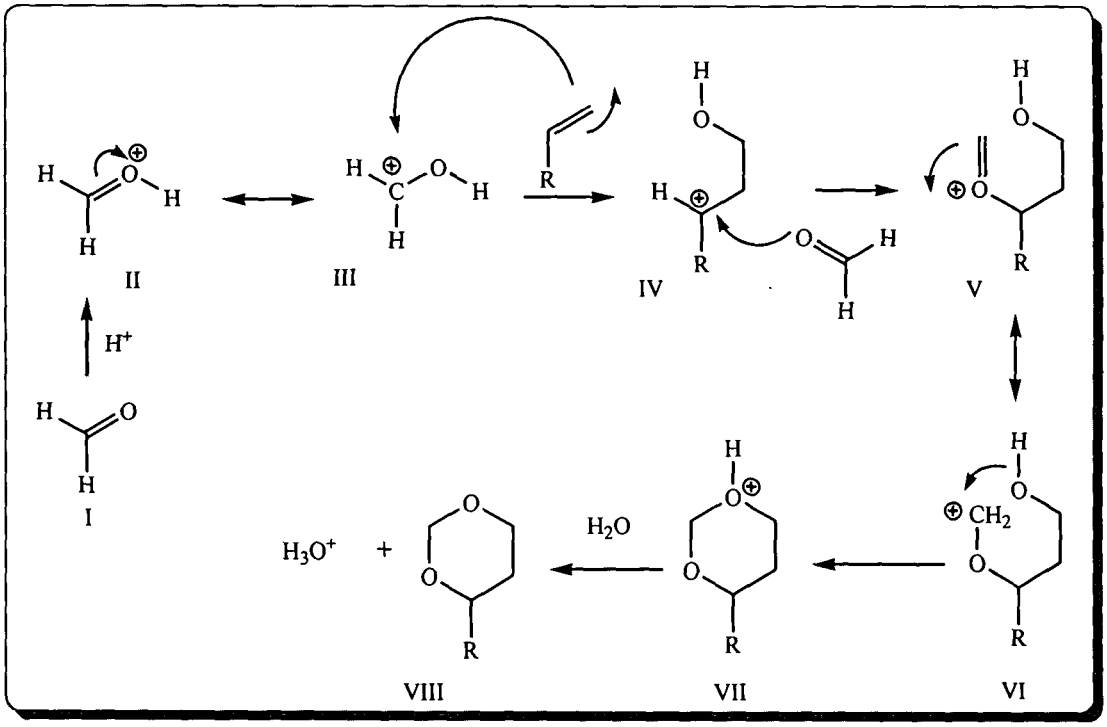
Table 2.A.3: Synthesis of 1,3-dioxane using PANI-TsOH and PANI-$FeCl_3$ in dichloromethane

Entry	Alkene	Aldehyde	Catalyst	Temp (°C)	Time [min]/h	Product	% Yield [a,b]
1	Styrene	$(CH_2O)_n$	TsOH $FeCl_3$	r.t.	1 [45]	(1a)	75 85
2	Styrene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	r.t.	20	NR	NA
3	Styrene	$(CH_2O)_n$	PANI-TsOH	40	12	NR	NA
4	Styrene	Formalin	PANI-TsOH	r.t.	16	NR	NA
5	Styrene	Formalin	PANI-TsOH PANI-$FeCl_3$	40	1 [90]	(1a)	86 80
6	α-Methyl styrene	$(CH_2O)_n$	TsOH $FeCl_3$	r.t.	[90] 1	(1b)	70 82
7	α-Methyl styrene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	40	2 4	(1b)	90 88
8	α-Methyl styrene	Formalin	PANI-TsOH PANI-$FeCl_3$	40	2 3	(1b)	70 70
9	p-Chloro styrene	$(CH_2O)_n$	TsOH $FeCl_3$	r.t.	3 2	(1c)	85 80
10	p-Chloro styrene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	r.t.	12	(1c)	85 75
11	p-Chloro styrene	Formalin	PANI-TsOH PANI-$FeCl_3$	40	12	NR	NA
12	p-Methoxy styrene	$(CH_2O)_n$	TsOH $FeCl_3$	r.t.	[90] 1	(1d)	78 77
13	p-Methoxy styrene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	r.t.	12	NR	NA
14	1-Octene	$(CH_2O)_n$	TsOH $FeCl_3$	r.t.	2 1	(1e)	62 67
15	1-Octene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	r.t.	8 10	(1e)	60 60

16	1-Octene	$(CH_2O)_n$	PANI-TsOH PANI-$FeCl_3$	40	2 [150]	(1e)	80 78
17	1-Octene	Formalin	PANI-TsOH PANI-$FeCl_3$	40	1	(1e)	80 76

[a] All products were characterized by ^1H NMR, ^{13}C NMR, FT-IR, MS, and CHN analysis and their comparision with reported data. [b] Isolated yields.

In all cases, the role of the acid catalyst appears to be (Scheme 2.A.2) the protonation of carbonyl reactant to the oxonium ion (II) which is a resonance hybrid of two structures. This electrophile again involves in an electrophilic addition with the alkene to the carbocationic intermediate (III). The oxo-carbenium intermediate (IV) generates another positive charge containing intermediate (V) where positive charge is dispersed over oxygen and carbon in the resonating structures (V) and (VI). Ring closure leads through intermediate (VII) to the dioxane (VIII).



Scheme 2.A.2

2.A.3 Conclusion:

We have developed an efficient greener method for the synthesis of 1,3-dioxanes under solvent-free microwave condition via Prins reactions using TsOH-SiO_2 as catalyst. The same reactions took more reaction time to yield the corresponding 1,3-

dioxane in dichloromethane at room temperature. In addition, it was observed that both catalysts decrease their reactivity in presence of polymer support for the synthesis of 1,3-dioxane in dichloromethane with respect to TsOH/$FeCl_3$ catalysts . The advantages of the microwave assisted protocol lies in avoidance of organic solvent, short reaction time, and selective formation of required product, high yield and also direct use of formalin as a source of formaldehyde.

2.A.4 Experimental:

General

All chemicals are commercially available and were used without purifications. The product were characterized by ^1H NMR, ^{13}C NMR, FT-IR, MS and CHN analysis and also by comparison with literature data.[2,4,8,9] We will describe the preparation method of polyaniline supported catalyst in Section B of this chapter.

2.A.4.1 General procedure for synthesis of 1,3-dioxanes catalysed by TsOH-SiO_2:

Microwave Method:

A mixture of styrene (3 mmol), paraformaldehyde (3 mmol), and p-toluene sulfonic acid (0.5 mmol) was mixed thoroughly with activated silica gel (1 g, dried overnight at 100 °C) at room temperature for 15 min. The mixture was irradiated in a microwave oven (Samsung C103FL, 180 W) for 5 min. After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction mixture was cooled to room temperature. The resulting product was directly charged onto a small silica-gel column and eluted with a mixture of ethyl acetate–n-hexane (1:9) to find pure 1,3-dioxane (85%) derivatives.

Conventional Method:

A mixture of styrene (3 mmol), paraformaldehyde (3 mmol), and p-toluene sulfonic acid (0.5 mmol) was stirred in dichloromethane (5 ml) at room temperature for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ether (2x10 ml). The combined organic layers were dried over anhydrous sodium sulphate and distilled under reduced pressure in

rotary evaporator. The crude reaction mixture was further purified by column chromatography using ethyl acetate-n-hexane (1:9) as eluent to find pure 1,3-dioxane (75%).

2.A.4.2 General procedure for synthesis of 1,3-dioxanes catalysed by PANI-TsOH/PANI-$FeCl_3$:

A mixture of styrene (3 mmol) and paraformaldehyde (3 mmol) and PANI-TsOH (0.5 mmol) or PANI-$FeCl_3$ (0.5 mmol) was stirred/refluxed in dichloromethane at the specified reaction temperature. After completion of the reaction as indicated by TLC, the catalyst was separated by filtration. Added water to the filtrate and extracted with diethylether (2×10 ml). The combined organic layers were dried over anhydrous sodium sulphate and distilled under reduced pressure in a rotary evaporator. The crude reaction mixture was further purified by column chromatography using ethyl acetate-n-hexane (1:9) as eluent to find pure 1,3-dioxane.

2.A.4.3 Spectral and elemental data:

4-Phenyl-1,3-dioxane (1a): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68-1.75 (m, 1H), 2.04-2.17 (m, 1H), 3.83-3.93 (m, 1H), 4.17-4.23 (m, 1H), 4.65 (d, J = 11.2 Hz, 1H), 4.90 (d, J = 6.4 Hz, 1H), 5.20 (d, J = 6.4 Hz, 1H), 7.23-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.9, 66.9, 78.7, 94.2, 125.7, 127.9, 128.5, 141.5; IR (KBr): ν 3429, 2923, 1600, 1493, 1451, 1375, 1260, 1172, 1089, 1026, 799, 698 cm^{-1}; MS: m/z 164 [M^+]; Anal. Calcd (%) for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73; H, 7.61.

4-Methyl-4-phenyl-1,3-dioxane (1b): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 3H), 2.04-2.11 (m, 1H), 2.12-2.23 (m, 1H), 3.58-3.65 (m, 1H), 3.84-3.88 (m, 1H), 4.65 (d, J = 6.4 Hz, 1H), 4.84 (d, J = 6.4 Hz, 1H), 7.25-7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.1, 34.9, 63.6, 75.7, 89.1, 125.7, 127.1, 128.8, 144.2; IR (KBr): ν 3430, 2958, 2924, 1599, 1494, 1445, 1378, 1261, 1077, 1028, 760, 698 cm^{-1}; MS: m/z 178 [M^+]; Anal. Calcd (%) for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.98.

4-(4-Chlorophenyl)-1,3-dioxane (1c): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.59 (m, 1H), 1.84-1.95 (m, 1H), 3.66-3.76 (m, 1H), 4.04-4.09 (m, 1H), 4.50 (dd, J = 10.4, 2.8 Hz, 1H), 4.75 (m, 1H), 5.10 (d, J = 6.4 Hz, 1H), 7.17-7.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34, 66.5, 77.8, 94.0, 127.2, 128.7, 133.3, 140.2; IR (KBr): ν 3427, 2935, 1593, 1458, 1329, 1155, 1096, 751 cm^{-1}; MS: m/z 198 [M$^+$]; Anal. Calcd (%) for $C_{10}H_{11}O_2Cl$: C, 60.45; H, 5.54. Found: C, 60.59; H, 5.66.

4-(4-Methoxyphenyl)-1,3-dioxane (1d): Colourless crystal, m.p. 70-71^{0}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62-1.72 (m, 1H), 2.05-2.18 (m, 1H), 3.78 (s, 3H), 3.81-3.89 (m, 1H), 4.14-4.22 (m, 1H), 4.60 (dd, J = 11.3, 2.5 Hz, 1H), 4.90 (d, J = 6.5 Hz, 1H), 5.20 (d, J = 6.5 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.29 (m, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.2, 55.5, 67.1, 78.4, 94.3, 114, 127.3, 133.8, 159.4; IR (KBr): ν 3438, 2936, 1599, 1457, 1326, 1157, 1078, 1029, 765 cm^{-1}; MS: m/z 194 [M$^+$]; Anal. Calcd (%) for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.85; H, 7.25.

4-Hexyl-1,3-dioxane (1e): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, J = 6.9 Hz, 3H), 1.23-1.27 (m, 8H), 1.34-1.38 (m, 2H), 1.60-1.67 (m, 2H), 3.77-3.84 (m, 1H), 3.89-4.2 (m, 2H), 4.88-4.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 23.3, 24.2, 30.4, 32.7, 35.3, 38.5, 66.4, 73.8, 96.2; IR (KBr): ν 2931, 1597, 1545, 1326, 1155, 1095, 756 cm^{-1}; MS: m/z 172 [M$^+$]; Anal. Calcd (%) for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 70.02; H, 11.74.

2, 6-Dimethyl-4-phenyl-1,3-dioxane (1f): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 5.8 Hz, 3H), 1.45 (d, J = 5.1 Hz, 3H), 1.57 (ddd, J = 13, 11.5, 10.9 Hz, 1H), 1.76 (ddd, J = 12.8, 3.0, 2.6 Hz, 1H), 3.87 (ddd, J = 11, 5.8, 2.6 Hz, 1H), 4.65 (dd, J = 11.3, 3.0 Hz, 1H), 4.90 (q, J = 5.1 Hz, 1H), 7.10-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 21.8, 40.4, 72.6, 78.3, 98.7, 125.7, 127.8, 128.6, 141.6; IR (KBr): ν 3060, 2936, 2925, 1598, 1451, 1328, 1160, 1091, 1028, 758 cm^{-1}; MS: m/z 192 [M$^+$]; Anal. Calcd (%) for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.15; H, 8.35.

4-(4-Chlorophenyl)-2,6-dimethyl-1,3-dioxane (1g): Solid, m.p: 78^{0}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (d, J = 5.8 Hz, 3H) 1.41 (d, J = 5.3 Hz, 3H), 1.44-1.49 (m, 1H), 1.70 (td, J = 2.1, 13.7 Hz, 1H), 3.85 (m, 1H), 4.60 (dd, J = 3.1, 11.2 Hz, 1H), 4.85 (q, J = 5.4 Hz, 1H), 7.20-7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21, 21.5, 40.4, 72.3, 77.6, 98.6, 127.3, 128.5, 133.4, 140.3; IR (KBr): ν 3437, 3330, 2928, 2858, 1647, 1545, 1445, 1376, 1080, 970, 699 cm^{-1}; MS: m/z 226 [M^+]; Anal. Calcd (%) for $C_{12}H_{15}O_2Cl$: C, 63.58; H, 6.62. Found: C, 63.65; H, 6.57.

2,6-Dimethyl-4-hexyl-1,3-dioxane (1h): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H), 1.22 (d, J = 5.7 Hz, 3H), 1.27-1.34(m, 8H), 1.37 (d, J = 5.5 Hz, 3H), 1.40-1.43 (m, 2H), 1.59-1.61 (m, 2H), 3.78 (m, 1H), 3.96 (m, 1H), 4.85 (q, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 21, 21.9, 23, 24.5, 30.2, 32.5, 36.1, 45.7, 65.5, 68.5, 95.4; IR (KBr): ν 2930, 1598, 1545, 1325, 1157, 1094, 755 cm^{-1}; MS: m/z 200 [M^+]; Anal. Calcd (%) for $C_{12}H_{24}O_2$: C, 72; H, 12. Found: C, 72.12; H, 12.10.

2,6-Dibutyl-4-phenyl-1,3-dioxane (1i): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.1 Hz, 6H), 1.34-1.80 (m, 14H), 3.72 (m, 1H), 4.64 (dd, J = 11.2, 2.3 Hz, 1H), 4.72 (t, J = 5.5 Hz, 1H), 7.22-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.5, 22.8, 26.6, 27.4, 35, 35.6, 39.5, 76.5, 78.2, 102.2, 125.8, 127.6, 128.6, 142.2; IR (KBr): ν 3056, 2934, 1597, 1446, 1326, 1160, 1089, 754 cm^{-1}; MS: m/z 276 [M^+]; Anal. Calcd (%) for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.28; H, 10.23.

2,6-Dibutyl-4-methyl-4-phenyl-1,3-dioxane (1j): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.2 Hz, 6H), 1.32-1.58 (m, 12H), 1.60 (s, 3H), 1.90 (m, 2H), 3.74 (m, 1H), 4.70 (m, 1H), 7.18-7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 23, 23.5, 26.8, 28.2, 36.8, 36, 51.2, 66.2, 70.1, 96.3, 125.6, 128.3, 139.5; IR (KBr): ν 3054, 2932, 1591, 1453, 1328, 1157, 1099, 755 cm^{-1}; MS: m/z 290 [M^+]; Anal. Calcd (%) for $C_{19}H_{30}O_2$: C, 78.62; H, 10.34. Found: C, 78.65; H, 10.40.

2,6-Diheptyl-4-phenyl-1,3-dioxane (1k): Colourless oil

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 6.8 Hz, 6H), 1.23-1.81 (m, 26H), 3.72 (m, 1H), 4.64 (dd, J = 11.3, 2.2 Hz, 1H), 4.72 (t, J = 5.2 Hz, 1H), 7.19-7.42 (m, 5H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 14.2 , 22.6, 24.5, 25.2, 29.3, 29.6, 29.8, 31.8, 35.0, 36, 39.5, 76.6, 78.5, 102.2, 125.8, 127.6, 128.5, 142.2; IR (KBr): ν 3435, 2935, 2924, 1598, 1446, 1324, 1158, 1077,1030, 763 cm^{-1}; MS: m/z 360 [M^+]; Anal. Calcd (%) for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 80.20; H, 11.21.

Section B:

Synthesis of 2,4-Disubstituted Tetrahydropyran Derivatives through Prins Cyclization Reaction in Presence of Polyaniline Supported Acid Catalysts

2.B.1 Introduction:

The Prins cyclization reaction has been shown to be a very useful reaction for the construction of oxygen-containing heterocyclic units that appear in many natural products.[10] This acid catalyzed[11] coupling (Scheme 2.B.1) of homoallylic alcohol with aldehyde leads to the formation of tetrahydropyran derivatives. In some cases, it forms acetal depending upon the nature of the aldehyde. The tetrahydropyran ring is widely distributed throughout nature e.g. in carbohydrates and natural products.[12] Under the classical condition, the Prins cyclization requires strong acid as catalyst (e.g. HCl, H_2SO_4 acid) and high temperature reaction condition which often produces a mixture of products. Specifically, Lewis or Brønsted acid induced polymerization of olefin can severely interfere with desired C-C bond formation. Therefore, research efforts are being directed to develop eco-friendly catalytic routes for the Prins cyclization reaction. Li and co-workers reported[13] the scandium triflate catalyzed in situ Prins cyclization reactions for the synthesis of tetrahydropyran-4-ol and ethers in chloroform.

Presently, the efficient use of non-toxic and more selective supported solid acidic[14] catalysts have received more attention in different areas of organic synthesis because of their environmental compatibility, reusability, high selectivity, simple operation, low cost and ease of isolation of the products. As a result, various solid supported catalysts[15] such as MCM-41, Amberlyst-15 ion exchange resin, zeolite etc.

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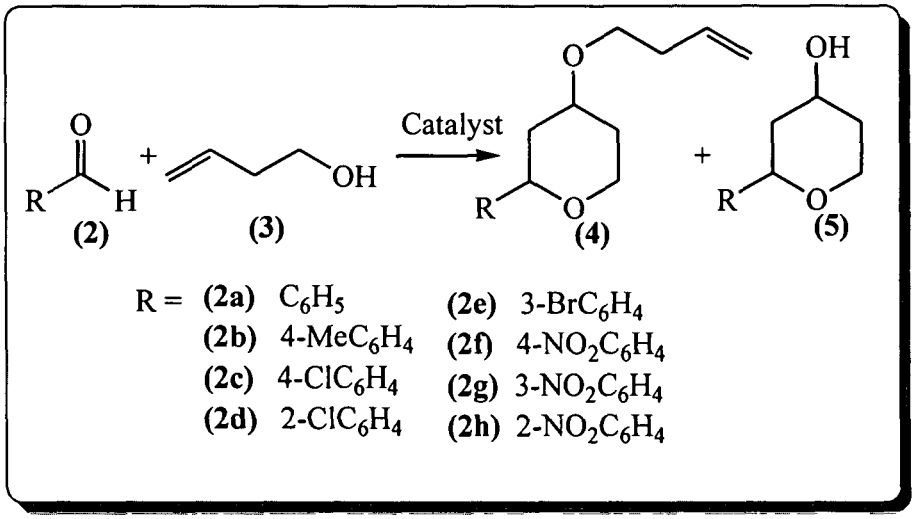
have gained importance in the Prins reactions. The potential use of polymer supported catalysts as heterogeneous and regenerable catalysts in organic transformation make reaction methods more convenient, economic and environmentally benign. Many reactions can be carried out cleanly, rapidly, and in high yields. Reaction can be performed under mild conditions, and product purification is simplified because of the use of an insoluble solid support. Polymer-supported catalysts can also be recycled after use. Generally, the polystyrene-based polymer bound Lewis acid catalysts show relatively low activity, and the activity of the catalyst decreases due to insufficient stability of the aromatic ring of the polymer and slow diffusion of substrate into the network. Moreover, the actual loading is limited by Lewis acid catalyzed cross linking of chloromethyl groups within the polystyrene based resin. The best method to increase the maximal loading of the carrier material is obtained by using low molecular weight functional polymers.[16] Polyaniline (PANI) is one of the polymers which can be used as a matrix for catalysis. It is cheap, easy to synthesize, and has light weight, excellent electrical and chemical properties, number of intrinsic redox states, stability and insolubility in a large majority of commonly used solvents, which is the main advantage of supported catalysts.[17] Many polyaniline supported salts and complexes[18] (TsOH, H_2SO_4, $FeCl_3$, $AlCl_3$ etc) are exhibiting excellent catalytic activity with less amount of catalyst in organic synthesis. Polyaniline has acid/base doping response due to presence of different intrinsic redox states. In view of this, we studied the catalytic activity and selectivity of already known polyaniline-supported TsOH and $FeCl_3$ for the Prins cyclization of homoallylic alcohol with different aldehydes to produce tetrahydropyran derivatives.

2.B.2 Results and discussion:

In the previous section of this chapter, we have reported TsOH-SiO_2 and polyaniline supported TsOH/$FeCl_3$ catalyzed Prins reaction for the synthesis of 1,3-dioxane in solvent-free medium as well as in organic solvent. Here, initially we have examined the catalytic activity of TsOH and $FeCl_3$ for the Prins cyclization of 3-butene-1-ol with p-chlorobenzaldehyde in organic solvents as well as in ionic liquids at different temperatures to form 2,4-disubstituted tetrahydropyran derivatives. The results

are shown in Table 2.B.1. But in both cases, low yield and less selectivity were observed for the formation of desired products.



Scheme 2.B.1

Table 2.B.1: TsOH and $FeCl_3$ catalyzed Prins cyclization of 3-butene-1-ol with 4-chlorobenzaldehyde in different solvents

Entry	Solvent	Catalyst	Temp (°C)	Time (h)	% Yield of (4c)	% Yield[a] (5c)
1	CH_2Cl_2	TsOH	r.t.	5	42	38
		$FeCl_3$			38	35
2	CH_2Cl_2	TsOH	40	8	45	40
		$FeCl_3$			37	34
3	$CHCl_3$	TsOH	65	7	40	42
		$FeCl_3$			39	36
4	EtOH	TsOH	70	6	15	23
		$FeCl_3$			17	25
5	[bmim]BF_4	TsOH	r.t.	20	20	18
		$FeCl_3$			15	10

6	[bmim]BF_4	TsOH	70	12	25	22
		$FeCl_3$			21	17
7	[bmim]PF_6	TsOH	r.t.	12	35	15
		$FeCl_3$			30	10

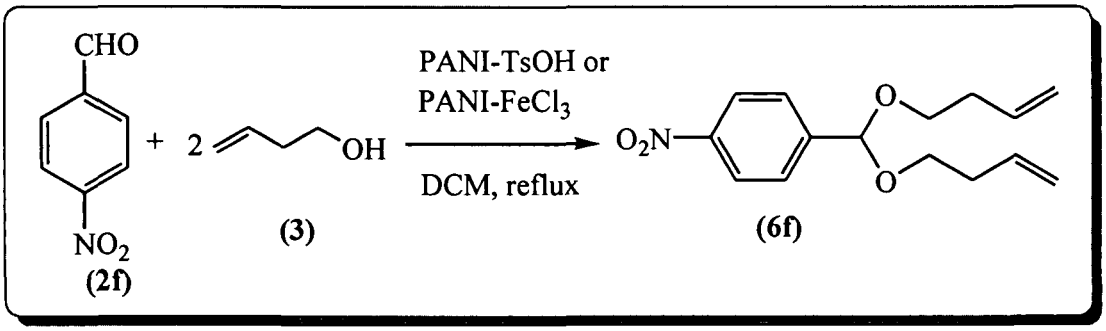
[a] Isolated yield

As such no reported work has been found regarding introduction of polyaniline-supported acid as suitable catalyst in Prins cyclization. We have improved the yield and selectivity of the Prins cyclization (Scheme 2.B.1) by refluxing aromatic aldehydes (**2**) (2 mmol) and 3-butene-1-ol (**3**) (4 mmol) in presence of catalytic amount of polyaniline-supported TsOH (0.25 mmol) or $FeCl_3$ (0.25 mmol) in dichloromethane. These two catalysts produced 2,4-disubstituted tetrahydropyran ether (**4**) as single product from various aromatic aldehydes (Table 2.B.2, entry 3-7). Treatment of equal amount of 4-chlorobenzaldehyde (1 mmol) and 3-buten-1-ol (1 mmol) also resulted incompletion of reaction with the formation of 2,4-disubstituted tetrahydropyran ether (**4**) (Table 2.B.2, entry 8) as single product. The selectivity of TsOH and $FeCl_3$ catalysts were found to be better on the surface of polymer support for the Prins cyclization as compared to non-supported catalysts (Table 2.B.1). The reusability of the two catalysts was also observed four times without loss of their catalytic activity and selectivity in case of reaction between 4-chlorobenzaldehyde and 3-butenel-ol to form the corresponding tetrahydropyran product (Table 2.B.3). A possible mechanism for this Prins cyclization is shown in Scheme 2.B.3. Interestingly the reaction of electron deficient aldehydes like *o*-, *m*- and *p*-nitrobenzaldehydes (Table 2.B.2, entries 9, 10, 11) with 3-buten-1-ol generated (Scheme 2.B.2) acetal (**6**) as single product. The presence of nitro group increases the electrophilic character of carbonyl carbon of aldehyde which shows more tendency to react with strong nucleophile like alcoholic group of 3-butene-1-ol to form (**6**) as the only product. Other aromatic aldehydes prefer to form (**4**) via Prins cyclization due to less electrophilic nature of carbonyl carbon as compared to nitrobenzaldehydes.

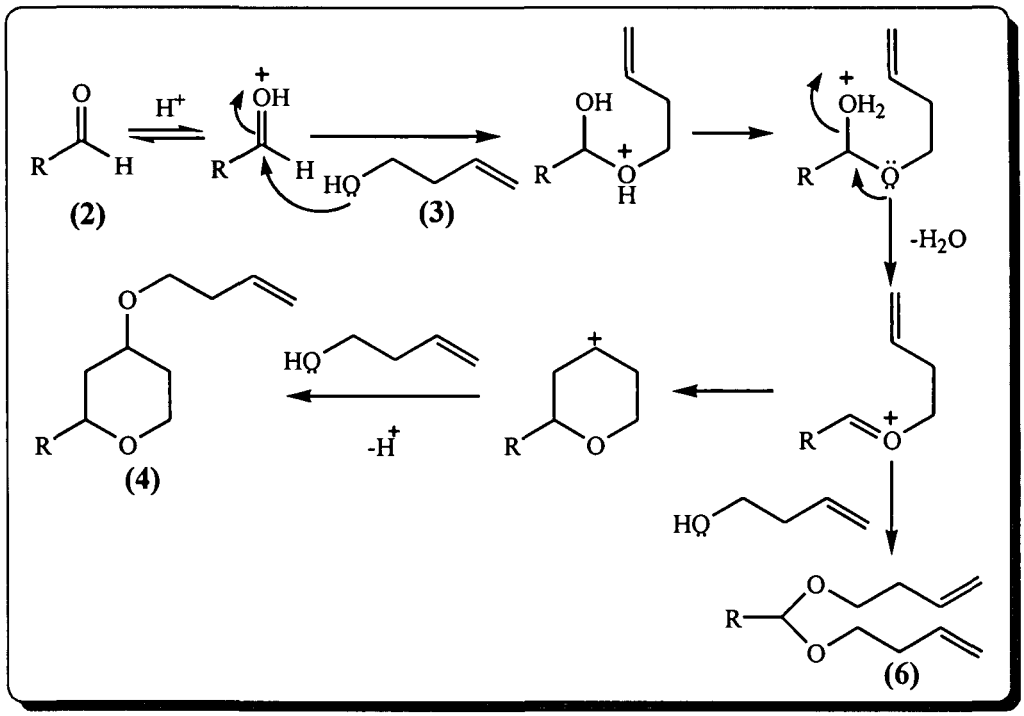
Table 2.B.2: PANI-TsOH and PANI-$FeCl_3$ catalyzed Prins cyclization of 3-butene-1-ol with various aldehydes in dichloromethane under reflux condition

Entry	Ar	Catalyst	Time (h)	Product (4)/(6)	% Yield [a] (4)/(6)	Product (5)	% Yield (5)
1	C_6H_5	TsOH	8	(4a)	45	(5a)	40
		$FeCl_3$	6		37		34
2	C_6H_5	PANI-TsOH	22	(4a)	55[b]	-	-
3	C_6H_5	PANI-TsOH	8	(4a)	55	-	-
		PANI- $FeCl_3$	9		50		
4	4-MeC_6H_4	PANI-TsOH	6	(4b)	45	-	-
		PANI- $FeCl_3$	6.5		42		
5	4-ClC_6H_4	PANI-TsOH	5	(4c)	76	-	-
		PANI- $FeCl_3$	6		72		
6	2-ClC_6H_4	PANI-TsOH	8	(4d)	63	-	-
		PANI- $FeCl_3$			57		
7	3-BrC_6H_4	PANI-TsOH	8	(4e)	60	-	-
		PANI- $FeCl_3$			55		
8	4-ClC_6H_4	PANI-TsOH	7	(4c)	40[c]	-	-
		PANI- $FeCl_3$	8		38		
9	4-	PANI-TsOH	4	(6f)	85	-	-
	$NO_2C_6H_4$	PANI- $FeCl_3$			82		
10	3-	PANI-TsOH	4.5	(6g)	84	-	-
	$NO_2C_6H_4$	PANI- $FeCl_3$			83		
11	2-	PANI-TsOH	4	(6h)	86	-	-
	$NO_2C_6H_4$	PANI- $FeCl_3$	6		80		

[a] All products were characterized by FT-IR, ^1H NMR, ^{13}C NMR, CHN analysis and also their comparison with authentic sample. [b] Room temperature reaction. [c] This reactions was carried out in 1 mmol scale with molar ratio 1:1:0.12 of aldehyde: 3-buten-1-ol: catalyst.



Scheme 2.B.2



Scheme 2.B.3: Plausible mechanism for Prins cyclization reaction

The stereochemistry of 2,4-disubstituted tetrahydropyran ether (**4**) was reported[13(b)] as *cis*- based on the coupling constants of the protons at the H-2 and H-4. The presence of an axial-axial coupling was identified from the coupling constant value of approximately 11 Hz for such protons.

A DEPT study of the three new compounds (**6f, 6g, 6h**) revealed that (Fig. 2.B.1) each DEPT-135 spectrum shows three negative signals for six -CH_2- groups and different positive signals for seven -CH- groups while no peaks for two quaternary carbons. In addition, the COSY spectrum of compound (**6f**) reveals that the signal at δ 2.28 (q, J = 6.7 Hz C-2) shows large cross peaks with the signals at δ 3.47-3.49 (C-1)

and δ 5.73-5.75 (C-3) of 3-butenoxy groups of acetal. The other two compounds (**6g, 6h**) also showed similar correlation pattern among the three nearby protons at C-1, C-2 and C-3 of 3-butenoxy group.

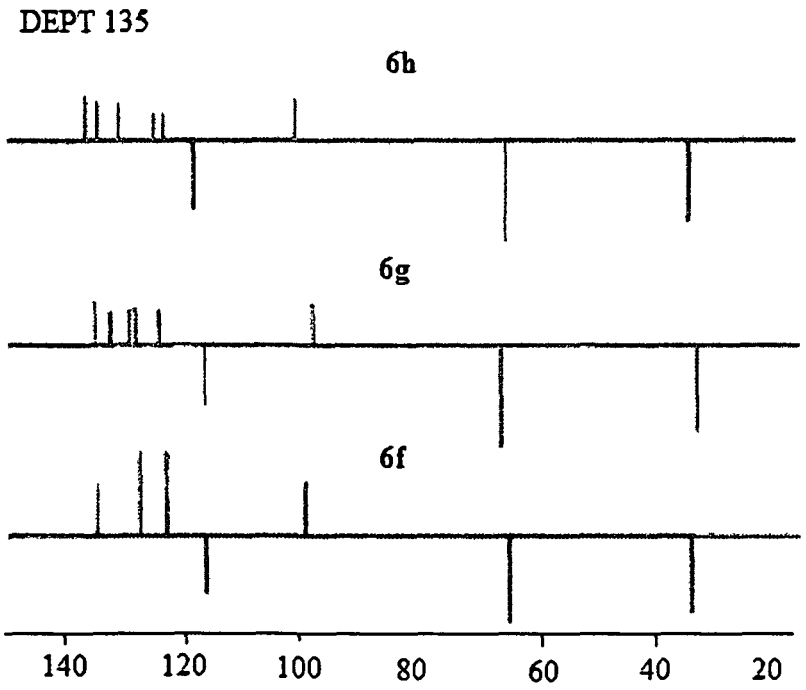


Figure 2.B.1: DEPT-135 for **(6f), (6g)** and **(6h)**

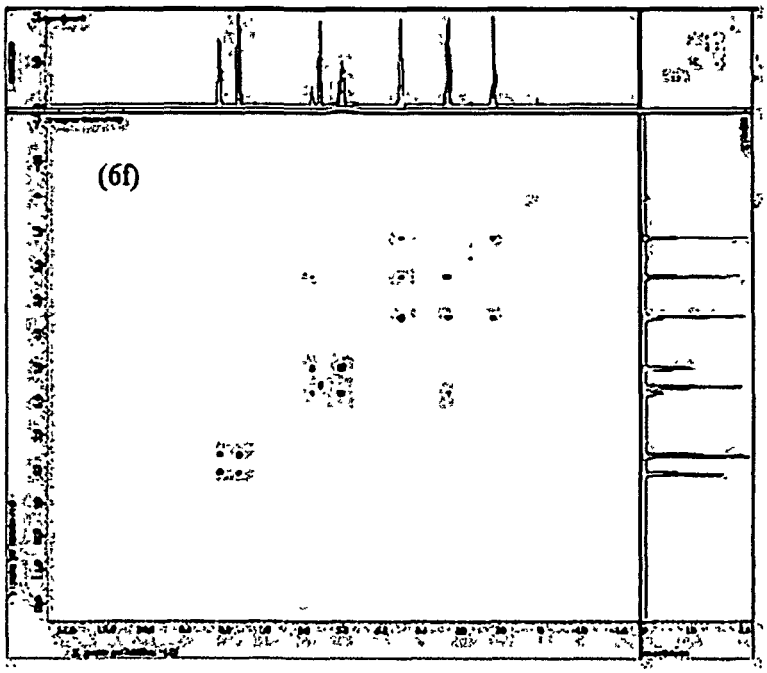


Figure 2.B.2: COSY of **(6f)**

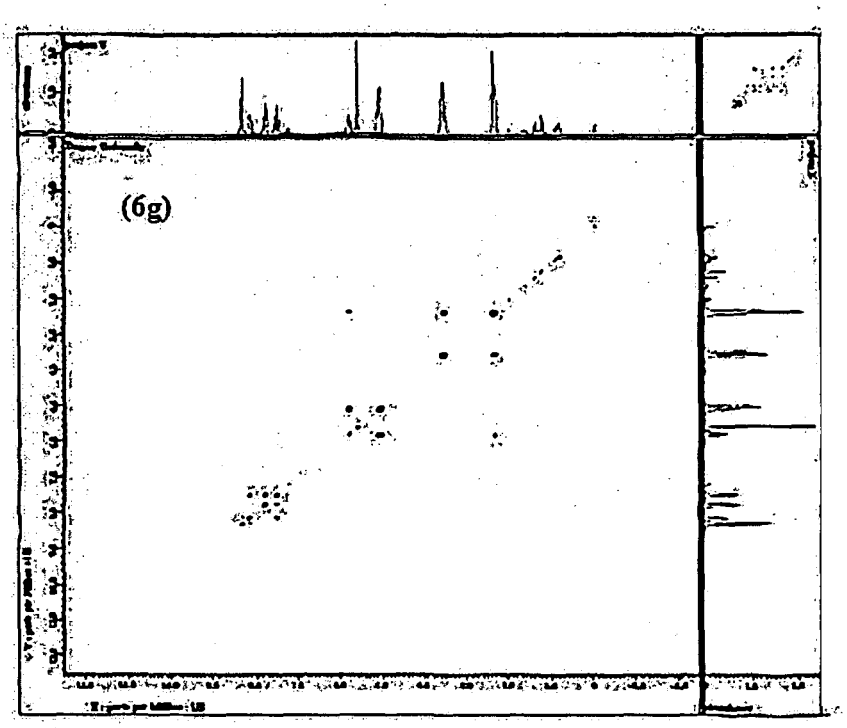


Figure 2.B.3: COSY of **(6g)**

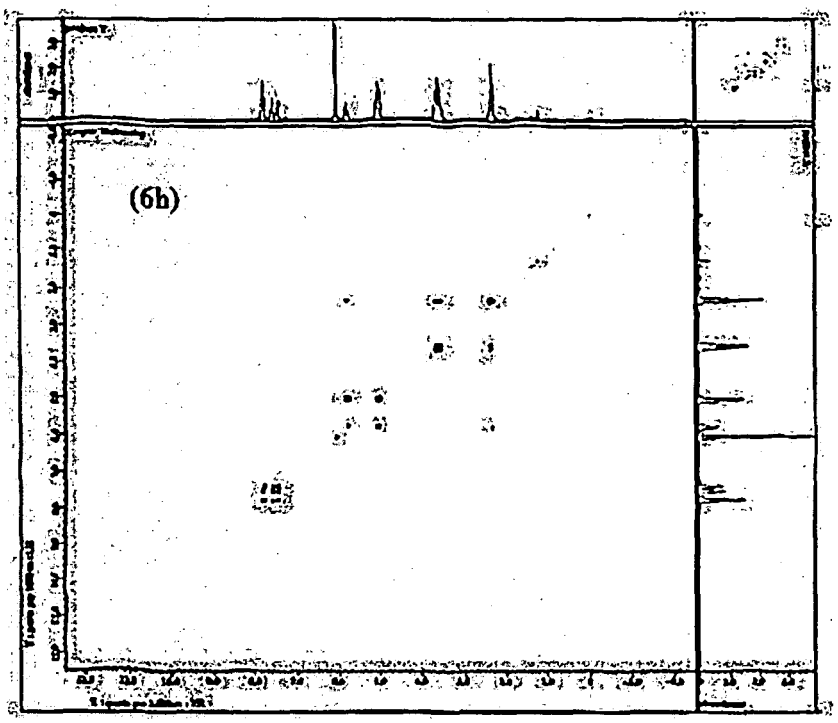


Figure 2.B.4: COSY of **(6h)**

Table 2.B.3: Recycling of PANI-TsOH and PANI-$FeCl_3$ for Prins cyclization of 3-butene-1-ol with 4-chlorobenzaldehyde in dichloromethane under reflux condition

Entry	Catalyst	Time (h)	Number of cycles	% Yield[a] (4c)
1	PANI-TsOH	5	1	76
			2	74
			3	75
			4	74
2	PANI- $FeCl_3$	6	1	72
			2	72
			3	70
			4	71

[a] This reactions was carried out in 1 mmol scale with molar ratio 1: 2 :0.12 of aldehydes/3-butene-1-ol/catalyst.

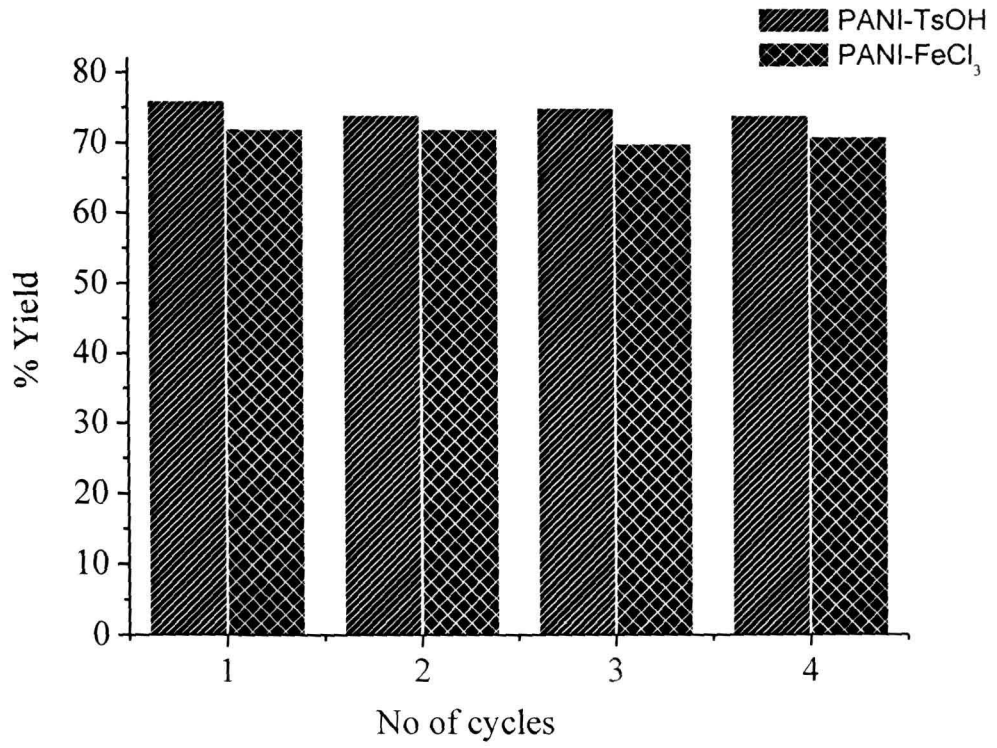


Figure 2.B.5: Histogram representing recycling of catalysts for Prins cyclization reaction of 3-butene-1-ol with 4-chlorobenzaldehyde

2.B.3 Conclusion:

This section describes the comparative studies of polyaniline supported catalysts (PANI-TsOH and (PANI-$FeCl_3$) for Prins cyclization of homoallylic alcohol with different aromatic aldehydes to afford the corresponding 2,4-disubstituted tetrahydropyran derivatives in organic solvents. In presence of polymer support the Prins cyclization of 3-butene-1-ol with aromatic aldehyde generates only 2,4-disubstituted tetrahydropyran ether **(4)** as single product under reflux condition in dichloromethane. The selectivity of TsOH/$FeCl_3$ catalyzed Prins cyclization decreases in absence of polymer support which leads to the formation of 2,4-disubstituted tetrahydropyranols **(5)** and ethers **(4)** as mixture of products at different temperature. In summary, the present procedure provides an efficient and improved modification of the Prins cyclization in terms of product selectivity and use of polymer supported reusable solid acid catalyst.

2.B.4 Experimental:

General

All chemicals are commercially available and were used without further purification. The products were identified by comparison of their FT-IR, ^1H NMR, ^{13}C NMR, GC-MS and CHN analysis data with those of authentic compounds (prepared by known method) and literature reported data.[13] The polyaniline supported catalysts were prepared by reported method.[18]

2.B.4.1: Methods for the preparation of polyaniline supported acid catalysts:

The synthesis of polyaniline supported TsOH and $FeCl_3$ catalysts involved in three steps. The polyaniline salt and base were prepared by aqueous polymerization pathways.[18]

Preparation of polyaniline salt:

In a 500 ml round bottom flask, 15 ml of sulphuric acid was slowly added to a solution of 350 ml of water with stirring. To the stirring solution, 5 ml of aniline was

added and the temperature was maintained at 5-10 °C. The above solution was allowed to continue for stirring for 4 h in presence of 130 ml aqueous solution of sodium persulphate (12 gm) at 5-10 °C. The precipitated polyaniline powder was filtered and washed with 2 L distilled water followed by 200 ml acetone. The polyaniline salt powder was dried at 100 °C till a constant weight.

Synthesis of polyaniline base:

In this step, polyaniline salt powder (3.5 gm) was taken in a 500 ml round bottom flask and stirred in 350 ml aqueous sodium hydroxide solution (1.0 M) for 8 h at ambient temperature. Polyaniline base was precipitated, washed with water and acetone. The base was dried at 100 °C till a constant weight.

Redoped polyaniline salt:

Initially, 50 ml of 1.0 M two standard solution of PTSA and $FeCl_3$ in acetone was prepared separately. Polyaniline base (0.5 gm) was added to each of the above solution and kept under constant stirring at ambient temperature for 4 h. Solid was filtered, washed with acetone and the solid was dried at 100 °C till a constant weight. Amount of acid group present in the polymeric chain was calculated based on the weight of redoped polyaniline salt obtained and the weight of poly aniline base used. Amount of dopant present in PANI-TsOH and PANI-$FeCl_3$ were found to be 42.5% and 29.5%, respectively.

2.B.4.2 Method for preparation of tetrahydropyran derivatives:

A mixture of 3-butene-1-ol (4 mmol), 4-chlorobenzaldehyde (2 mmol) and PANI-TsOH (0.25 mmol) or PANI-$FeCl_3$ (0.25 mmol) in dichloromethane (10 ml) was refluxed for the specified reaction period. On completion, as indicated by TLC, the catalyst was filtered and washed with dichloromethane (2×15 ml). The combined organic layers were washed with water, sodium bicarbonate solution, dried over anhydrous sodium sulphate and concentrated in vacuum. The resulting reaction mass was purified by column chromatography on silica gel (Merck, 60-120 mesh) using hexane and ethyl acetate as eluent to isolate the pure product.

2.B.4.3 Spectral and elemental data:

cis-2-Phenyl-4-(3-butenoxy)-tetrahydropyran (4a):

Light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.23 (m, 5H), 5.84 (m, 1H), 5.13-5.08 (m, 2H), 4.31 (dd, *J* = 11.3, 2.4 Hz, 1H), 4.22 (ddd, *J* = 11.5, 4.2, 1.3 Hz, 1H) 3.65 (m, 1H), 3.60 (t, *J* = 6.7 Hz, 2H), 3.57 (m, 1H), 2.39 (q, *J* = 6.7 Hz, 2H), 2.23 (m, 1H), 2.00 (m, 1H) 1.63 (m, 1H), 1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 135.2, 128.3, 127.7, 126.0, 116.2, 78.2, 75.3, 67.1, 66.0, 40.2, 34.8, 32.5; IR (KBr): ν 1493, 1447, 1350, 1327, 1309, 1165, 1145, 1098, 1082, 1037, 1021, 986, 954, 907 cm^{-1}; GC-MS: m/z (% base peak) 233 [$M^{+.}$ + 1], 232, 177, 161, 160, 159, 131, 117, 105, 91, 77, 71, 55(100); Anal. Calcd (%) for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.50.

cis-2-(4-Methylphenyl)-4-(3-butenoxy)-tetrahydropyran (4b):

Light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.87 (m, 1H), 5.14-5.06 (m, 2H), 4.32 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.20 (ddd, *J* = 11.6, 4.5, 1.7 Hz, 1H), 3.64 (m, 1H), 3.57 (t, *J* = 6.9 Hz, 2H), 3.56 (m, 1H), 2.38 (q, *J* = 6.9 Hz, 2H), 2.35 (s, 3H), 2.23(m, 1H), 2.03 (m, 1H), 1.64 (m, 1H), 1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 137.4, 135.3, 129.0, 126.1, 116.5, 78.2, 75.5, 67.0, 66.4, 40.2, 34.5, 32.8, 21.2; IR (KBr): ν 1638, 1540, 1436, 1363, 1309, 1245, 1164, 1144, 1108, 1082, 1022, 993, 959 cm^{-1}; GC-MS: m/z (% base peak) 247 [M^+ + 1], 246, 245, 231, 205,1 75, 174(100), 173, 159, 146, 145, 129, 121, 120, 119, 118, 105, 93, 87, 77, 71, 55; Anal. Calcd (%) for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.20; H, 9.01.

cis-2-(4-Chlorophenyl)-4-(3-butenoxy)-tetrahydropyran (4c):

Light yellow liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.84 (m, 1H), 5.13-5.04 (m, 2H), 4.31 (dd, *J* = 11.3, 2.0 Hz, 1H), 4.19 (ddd, *J* = 11.3, 4.8, 1.7 Hz, 1H), 3.61 (m,1H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.55 (m, 1H), 2.34 (q, *J* = 6.7 Hz, 2H), 2.22 (m, 1H), 2.05 (m, 1H), 1.58 (m, 1H), 1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 135.3, 133.1, 128.4, 127.0, 116.2, 77.6, 75.1, 67.0, 66.2, 40.1, 34.3, 32.6; IR (KBr): ν 1639, 1492, 1436, 1357, 1309, 1245, 1156, 1108, 1077, 1012, 993 cm^{-1}; GC-MS: m/z (% base peak) 269 [M^+ + 1], 268, 266, 232, 195,

194, 193(100), 165, 140, 139, 128, 125, 111, 103, 98, 77, 71, 56, 55, 43, 41; Anal. Calcd (%) for $C_{15}H_{19}O_2Cl$: C, 67.54; H, 7.18. Found: C, 67.45; H, 7.16.

cis-2-(2-Chlorophenyl)-4-(3-butenoxy)-tetrahydropyran (4d):

Light yellow liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, J = 7.7, 1.9 Hz, 1H), 7.32-7.15 (m, 3H), 5.85 (m, 1H), 5.13-5.04 (m, 2H), 4.68 (dd, J = 11.5 ,2.0 Hz, 1H), 4.18 (ddd, J = 11.5, 4.6, 1.4 Hz, 1H), 3.67 (m, 1H), 3.59 (m, 1H), 3.52 (t, J = 6.9 Hz, 2H), 2.37 (m, 1H), 2.31 (q, J = 6.9 Hz, 2H), 2.00 (m, 1H), 1.62 (m, 1H), 1.28 (m, 1H); IR (KBr): ν 1637, 1566, 1472, 1362, 1247, 1203, 1144, 1108, 1082, 1052, 988 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{19}O_2Cl$: C, 67.54; H, 7.18. Found: C, 67.57; H, 7.22.

cis-2-(3-Bromophenyl)-4-(3-butenoxy)-tetrahydropyran (4e):

Light yellow liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 5.84 (m, 1H), 5.10-5.04 (m, 2H), 4.28 (dd, J = 11.5, 2.0 Hz, 1H), 4.18 (ddd, J = 11.5, 4.8, 1.6 Hz, 1H), 3.58 (m, 1H), 3.53 (t, J = 6.8 Hz, 2H), 3.48 (m, 1H), 2.30 (q, J = 6.8 Hz, 2H), 2.20 (m, 1H), 2.02 (m, 1H), 1.62 (m, 1H), 1.45 (m, 1H); IR (KBr): ν 1636, 1592, 1560, 1467, 1363, 1247, 1205, 1166, 1144, 1107, 1082, 1022, 992 cm^{-1}; Anal. Calcd (%) for $C_{15}H_{19}O_2Br$: C, 57.89; H, 6.15. Found: C, 57.92; H, 6.17.

Di-(3-butenoxy)methyl-4-nitrobenzaldehyde (6f):

Colourless liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 5.75-5.73 (m, 2H), 5.52 (s, 1H), 4.97-5.04 (m, 4H), 3.47-3.49 (m, 4H), 2.28 (q, J = 6.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 146.0, 145.7, 135.0, 127.8, 123.4, 116.7, 100.0, 64.8, 34.3; IR (KBr): ν 2927, 2877, 1641, 1605, 1524, 1343, 1203, 1103, 1055, 915, 852, 717, 634, 546 cm^{-1}; GC-MS: m/z (% base peak) 277 [M^+], 222, 206, 176, 152, 136, 121, 105, 77, 76, 71, 56, 55(100); Anal. Calcd (%) for $C_{15}H_{19}NO_4$: C, 64.72; H, 6.88; N, 5.07. Found: C, 64.90; H, 6.85; N, 5.05.

Di-(3-butenoxy) methyl -3-nitrobenzaldehyde (6g):

Colourless liquid ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.53 (t, J = 7.7 Hz, 1H), 5.81-5.82 (m, 2H), 5.60 (s, 1H), 5.07-5.12 (m, 4H), 3.55-3.56 (m, 4H), 2.38 (q, J = 6.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 140.6, 134.6, 132.6, 128.9, 123.0, 121.7, 116.5, 99.6, 64.5, 34.3; IR

(KBr): ν 2921, 1704, 1642, 1530, 1473, 1436, 1350, 1206, 1111, 1051, 990, 916 cm^{-1}; GC-MS: m/z (% base peak) 277 [M^+], 222, 206, 205, 176, 153, 152, 136, 121, 105, 77, 57, 55(100); Anal. Calcd (%) for $C_{15}H_{19}NO_4$: C, 64.70; H, 6.86; N, 5.07. Found: C, 64.90; H, 6.85; N, 5.05.

Di-(3-butenoxy) methyl -2-nitrobenzaldehyde (6h):

Colourless liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.81-7.83 (m, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 6.09 (s, 1H), 5.79-5.86 (m, 2H), 5.07-5.13 (m, 4H), 3.68-3.70 (m, 2H), 3.59-3.61 (m, 2H), 2.39(q, J = 6.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 134.8, 133.1, 132.4, 129.2, 128.1, 124.1, 116.7, 98.3, 66.9, 34.0; IR(KBr): ν 2925, 1702, 1530, 1441, 1351, 1270, 1193, 1110, 1062, 917 cm^{-1}; GC-MS: m/z (% base peak) 277 [M^+], 222, 206, 205, 176, 152, 136, 121, 105, 104, 77, 56, 55(100); Anal. Calcd (%) for $C_{15}H_{19}NO_4$: C, 65.00; H, 6.89; N, 5.08. Found: C, 64.90; H, 6.85; N, 5.05.

***cis*-2-(4-Chlorophenyl)-4-hydroxy-tetrahydropyran (5c):**

Colourless liquid, ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 4.25 (dd, J = 11.2, 2.3 Hz, 1H), 4.18 (ddd , J = 12.2, 4.9, 1.7 Hz, 1H), 3.89 (tt, J = 11.3, 4.5 Hz, 1H), 3.53 (dt, J = 12.2, 2.3 Hz, 1H), 2.17 (m, 1H), 1.94 (m, 1H), 1.65 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 133.2, 128.7, 127.3, 77.5, 68.5, 66.2, 43.1, 35.2; IR (KBr): ν 3378, 2935, 2845, 1494, 1449, 1413, 1367, 1305, 1253, 1145, 1089, 1020, 990 cm^{-1}; GCMS: m/z (% base peak) 214 [M^+], 212, 211, 196, 195, 194, 179, 177, 160, 159, 140, 139 (100), 138, 127, 125, 113, 112, 111, 105, 103, 77, 75, 57, 55, 44, 43; Anal. Calcd (%) for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.12. Found: C, 62.09; H, 6.10.

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Chapter 3

Synthesis, Characterization and Application of Poly(4-vinylpyridine) Supported Brønsted Acid as Reusable Catalyst for Acetylation and Pechmann Reaction

Chapter 3

Section A:

Synthesis, Characterization and Application of Poly(4-vinylpyridine) Supported Brønsted Acid as Reusable Catalyst for Acetylation Reaction

3.A.1 Introduction:

In recent years economic and environmental concerns encourage the application of heterogeneous catalyst[1] to carry out various organic transformations. Heterogeneous catalysts are typically supported[2] which means that the catalyst is dispersed on a second material that enhances the effectiveness or minimizes their cost. Sometimes the support is merely a surface on which the catalyst is spread to increase the surface area. More often, the support and the catalyst interact, affecting the catalytic reaction. The total surface area of solid has an important effect on the reaction rate. The study of polymer supported catalyst[3] is motivated by the major advantages of the physical separation of the supported catalyst from the substrates and products, thereby allowing the recycling of expensive catalyst and thus releases less waste material to the environment. The reactions can be performed under mild conditions and product purification is simple due to easy separation of insoluble polymer support from the reaction medium. Many reactions[4] can be carried out cleanly, rapidly and in high yields. Generally, polystyrene-based solid acidic catalysts show relatively low activity and the activity of the catalyst decreases due to insufficient stability of the aromatic ring of the polymer and slow diffusion of substrate into the polymer network. Moreover, the actual loading is limited by Lewis acid catalyzed cross linking of chloromethyl groups within the polystyrene-based resin. The best effective method to increase the maximal loading of the carrier material is obtained by using low molecular weight functional monomers.[5] Poly(4-vinyl pyridine) is an interesting material because of its stable pyridine ring and ability to form charge transfer complex with acidic dopants.[6] It is widely used universal surface

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modifier for immobilization[7] of metal triflates, ruthenates, and nanoparticles. Mineral acids such as H_2SO_4, HCl, H_3PO_4 are widely used as catalyst in several organic syntheses.[8] But direct use of the mineral acid in liquid state is not favourable because of vigorous reaction condition, corrosive nature, toxicity, hygroscopic nature, difficulty in separation, recovery and recycling. Poly(4-vinylpyridine) seems to be an attractive support to immobilize mineral acids because of the basic nature of pyridyl group. Herein, we report the successful synthesis of P4VP supported Brønsted acid catalyst (P4VP-HX) in ether solution at room temperature, their characterization and applications as simple reusable solid acid catalysts in acetylation of -OH and $-NH_2$ functionality.

3.A.2. Results and discussion:

3.A.2.1 Catalyst characterization:

In order to develop greener methodologies, initially we prepared poly(4-vinyl pyridine) supported acids. For this, different Brønsted acids were loaded on the polymer, poly(4-vinylpyridine) cross linked with 2% DVB (Fig. 3.A.1) following an incipient wet impregnation technique. Amount of acid group present in the polymeric chain was calculated based on the weight of supported polymer salt obtained and the weight of poly(4-vinylpyridine) used. Amount of dopant present in poly(4-vinylpyridine) supported acids were found to be 0.652 mol %, 1.102 mol % and 0.492 mol % for P4VP-H_2SO_4, P4VP-HCl and P4VP-H_3PO_4, respectively against 500 mg of P4VP. Higher amount of dopant was obtained in the case of P4VP-HCl. Characterization of the polymer supported acid catalysts so formed were performed by FT-IR, SEM-EDX and TGA studies.

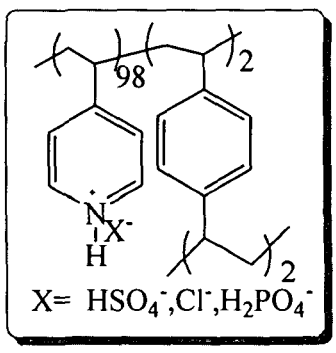


Figure 3.A.1: Structure of poly(4-vinylpyridine) supported acid catalyst (P4VP-HX)

3.A.2.1.1 FT-IR spectroscopy:

The IR spectra of the P4VP and the supported catalysts (blends) are compared in Figure 3.A.2. The pyridine rings exhibit strong C=C stretching band at 1604 cm^{-1} and C=N stretching absorption at 1414 cm^{-1}. The monomer units of P4VP corresponding to the ring deformation appear around 993-994 cm^{-1}, suffer a shift towards higher wave number, (1000-1008 cm^{-1}) when the pyridine ring is protonated with Brønsted acid. This interaction increases the stiffness of the associated ring and consequently more energy is required to deform the aromatic cycle, reflected in a higher wave number value. The P4VP (A) has no N^{+}-H stretching frequencies (Fig. 3.A.2); but polymer salts P4VP-H_2SO_4 (B) , P4VP-HCl (C) and P4VP- H_3PO_4 (D) have this stretching vibrations at 3200-3400 cm^{-1} along with O-H absorption. The polymer blend B indicates ν_{asym} S=O at 1283-1177(vs) cm^{-1} and ν_{sym} S=O 1068 cm^{-1}, respectively. The sharp band at 579 cm^{-1} is assigned to the O=S=O rocking band.[9] Similarly, the polymer blend D shows an absorption band at 1161-988 cm^{-1} for the stretching of (P-O)H.

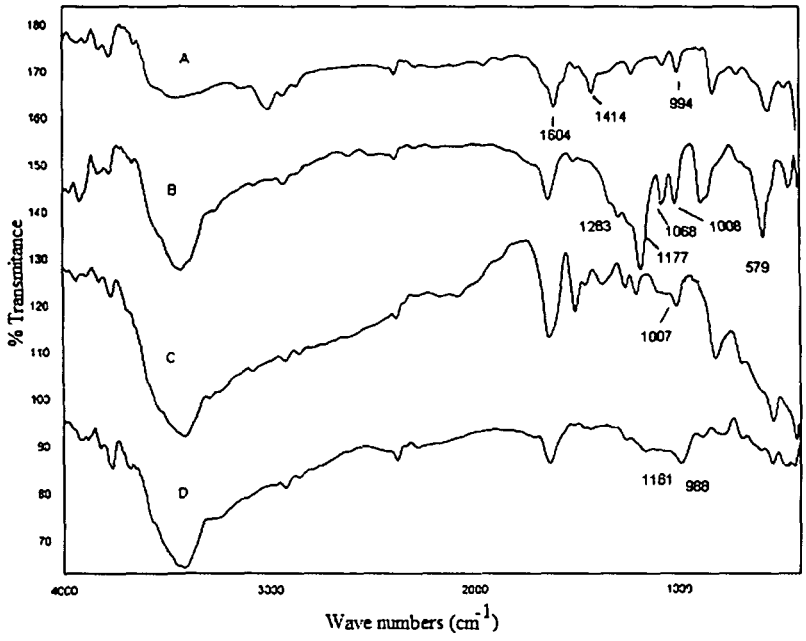
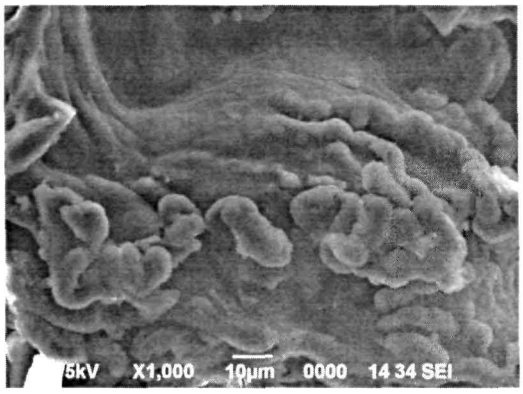


Figure 3.A.2: FT-IR spectrum of P4VP (A), P4VP-H_2SO_4 (B), P4VP-HCl (C), and P4VP-H_3PO_4 (D)

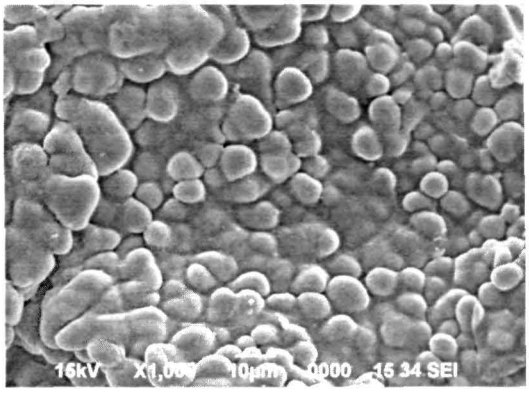
3.A.2.1.2 SEM analysis:

The SEM micrographs of P4VP and other supported acid catalysts are shown in Figure 3.A.3. It is seen from the figure that the surface of the polymer is distinctly altered in each supported catalysts. No definite size particles are observed in case of

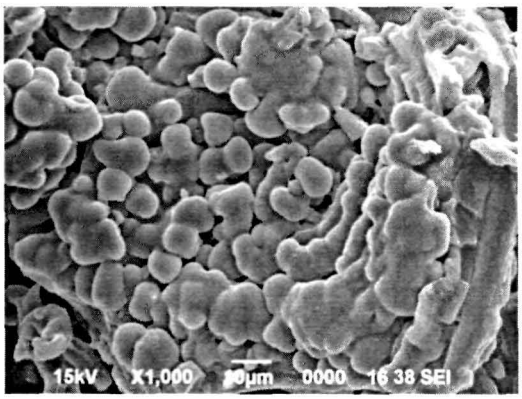
P4VP (A). In P4VP-H_2SO_4 (B) catalyst, particles are spherical with uniform morphology as compared to other two catalysts (C, D). The SEM micrograph of C and D indicates the presence of two types of particles, spherical and elliptical. Major amounts of particles are elliptical in case of D (P4VP-H_3PO_4). The surface of each particle is rough in case of B and smooth in case of C and D (Fig. 3.A.3). Micrographs of B, C and D indicate coupling between poly(4-vinyl pyridine) and acids.



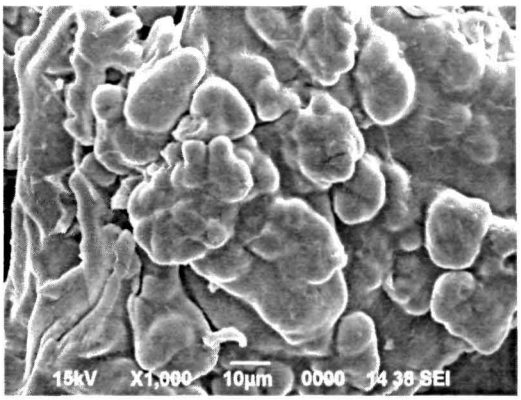
SEM micrograph of P4VP (A)



SEM micrograph of P4VP-H_2SO_4 (B)

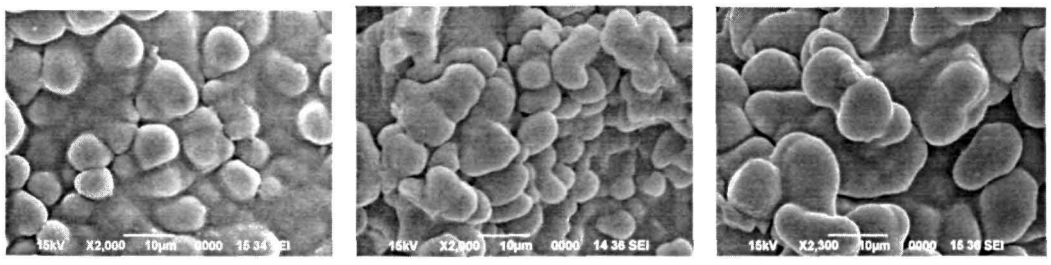


SEM micrograph of P4VP-HCl (C)



SEM micrograph of P4VP-H_3PO_4 (D)

Figure 3.A.3.1: SEM micrograph of P4VP and P4VP-HX (x1000)



B C D

Figure 3.A.3.2: SEM micrograph of P4VP-HX (x2000)

3.A.2.1.3 EDX analysis:

Energy dispersive X-ray (EDX) analyses of the catalysts were carried out for identification of Brønsted acids on the surface of poly(4-vinylpyridine) support, as shown in Figure 3.A.4 (B, C, D).

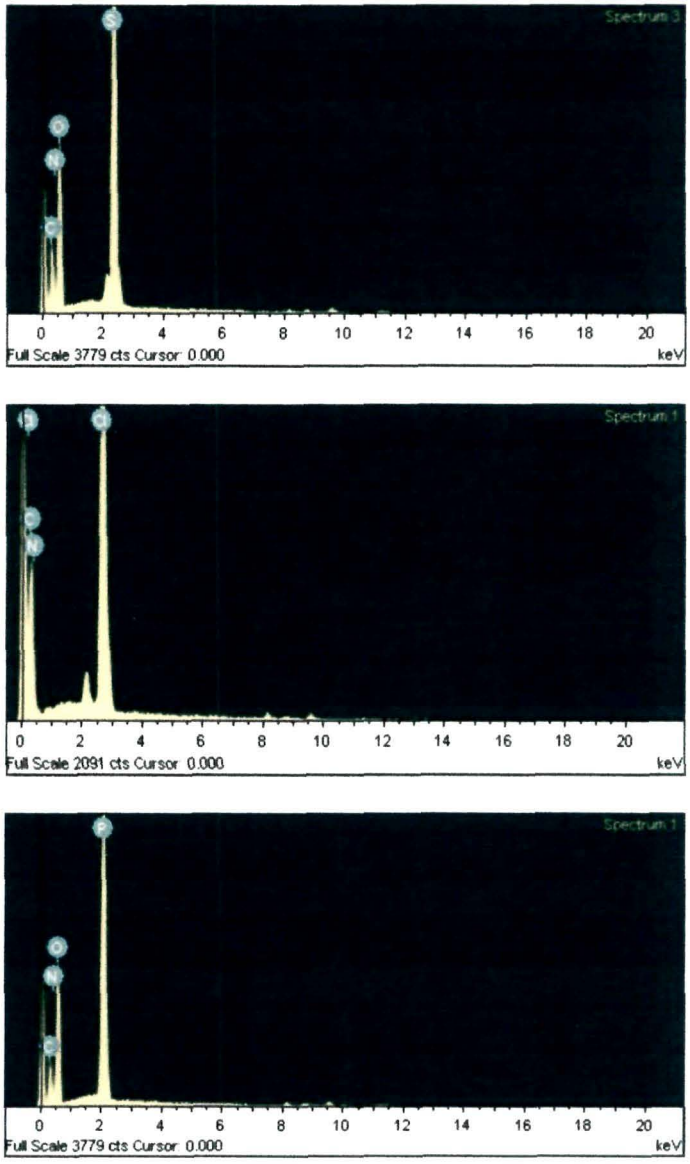


Figure 3.A.4: EDX pattern of supported acid catalysts (B, C, D)

3.A.2.1.4 Thermogravimetric analysis:

TGA curve of the pure polymer (A) shows a one-step thermal decomposition with maximum decomposition temperature at 388 °C (Fig. 3.A.5). The TGA curves of other supported polymers show two steps for P4VP-H_2SO_4 (B) and three steps

decompositions patterns for both P4VP-HCl (C) and P4VP-H_3PO_4 (D) catalysts. The stability of poly(4-vinylpyridine) decreases as shown by TGA curves (A, B & C) when it forms complex with sulphuric acid and hydrochloric acid. The blend (D) shows higher stability up to 400 °C as compared to pure polymer (A). Above 50 °C, a weight loss can be observed which can be attributed to the self condensation of phosphoric acid which ranges up to 350 °C; however the loss rate doesn't correspond to the phosphoric acid content in the blends.

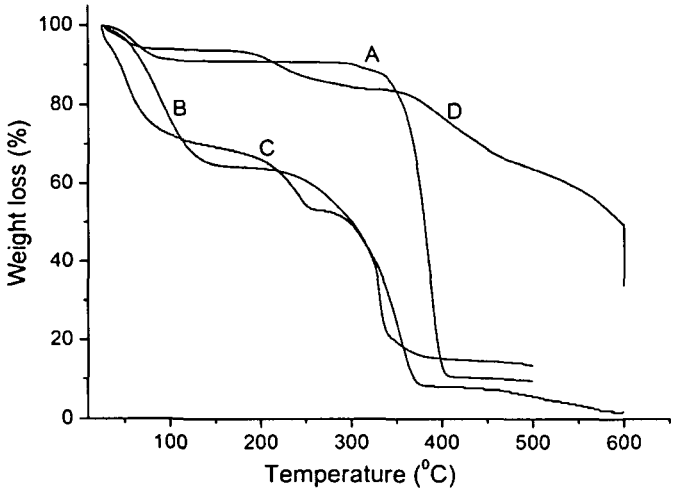
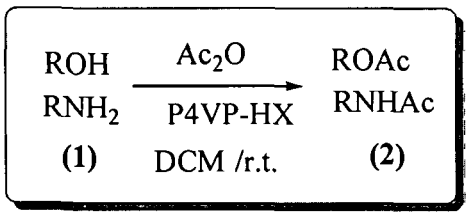


Figure 3.A.5: TGA curve of polymer (A) and supported acid catalysts (B, C, D)

3.A.2.2 Catalyst testing:

We have examined the catalytic activity of the newly developed P4VP-HX system for the acylation of alcohols, phenols and amines in dichloromethane at room temperature (Scheme 3.A.1). The reactions were monitored by thin layer chromatography and products were identified by comparing their spectroscopic data with literature data.[10]



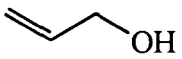
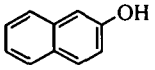
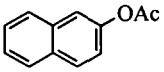
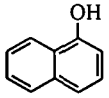
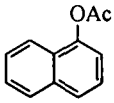
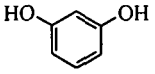
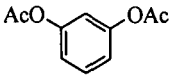
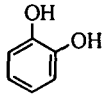
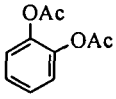
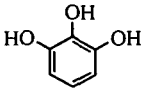
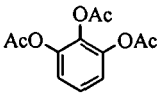
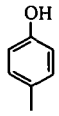
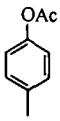
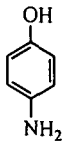
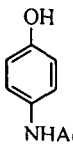
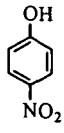
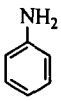
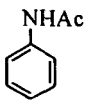
Scheme 3.A.1

Initially we used P4VP-H_2SO_4 for acetylation of different substrates having -OH and -NH_2 group. The results are summarized in Table 3.A.1. The molar quantity of

acetic anhydride is very important to the success of the acetylation reaction. With 1:1 and 1:2 ratios of cholesterol and acetic anhydride, the reactions were incomplete within 15-24 h (Table 3.A.1, entries 1, 2) reaction periods. It was found that 1:3 ratio of alcohol and acetic anhydride decreases the reaction time to half an hour for cholesterol (Table 3.A.1, entry 3). We have extended the scope of the acetylation reaction for other monohydroxy and polyhydroxy compounds and amines in the same reaction condition. For polyhydroxy phenol and alcohol compounds we found fully acetylated products (Table 3.A.1, entries 11, 16, 17, 18). Spectroscopic analysis revealed the conversion of all hydroxyl groups to acetate groups. Primary (Table 3.A.1, entries 8, 9, 10) and secondary alcohols (Table 3.A.1, entries 3-7) can be easily acetylated at room temperature in dichloromethane using P4VP-H_2SO_4 within short reaction period (8-35 min). But t-butyl alcohol failed to give corresponding acylated product (Table 3.A.1, entry 22). Amino group can be preferentially acetylated within 1 min in the presence of hydroxyl group (Table 3.A.1, entry 20) in case of 4-amino phenol. In presence of this catalyst, monohydroxy phenolic -OH reacts slowly as compared to amino group (Table 3.A.1, entries 13, 14, 23). But polyhydroxy phenolic compounds showed higher reactivity for acetylation reaction and the reaction completed within 1 min with P4VP-H_2SO_4 (Table 3.A.1, entries 16-18).

Table 3.A.1: Acetylation of alcohols, phenols and amines with acetic anhydride catalyzed by P4VP-H_2SO_4

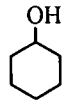
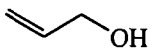
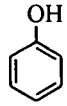
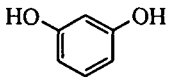
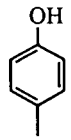
No	Substrate	Product		Ratio (Substrate & Ac_2O)	Time Min/ [h]	Yield[a] %
1	Cholesterol	Cholesteryl acetate	(2a)	1:1	[24]	50
2	Cholesterol	Cholesteryl acetate	(2a)	1:2	[15]	60
3	Cholesterol	Cholesteryl acetate	(2a)	1:3	30	98
4	$C_6H_5CH(OH)C_6H_5$	$C_6H_5CH(OAc)C_6H_5$	(2b)	1:3	30	96
5	$C_6H_5COCH(OH)C_6H_5$	$C_6H_5COCH(OAc)C_6H_5$	(2c)	1:3	10	95
6			(2d)	1:3	8	99
7	$C_6H_5CH(OH)CH_3$	$C_6H_5CH(OAc)CH_3$	(2e)	1:3	35	93

8	$CH_3(CH_2)_7OH$	$CH_3(CH_2)_7OAc$	(2f)	1:3	35	94
9	$CH_3(CH_2)_{15}OH$	$CH_3(CH_2)_{15}OAc$	(2g)	1:3	20	96
10	$C_6H_5CH_2OH$	$C_6H_5CH_2OAc$	(2h)	1:3	15	95
11	$CH_2(OH)CH_2(OH)$	$CH_2(OAc)CH_2(OAc)$	(2i)	1:6	1	99
12		NR	-	1:3	[12]	NA
13			(2j)	1:3	[1]	95
14			(2k)	1:3	90	87
15			(2l)	1:3	210	85
16			(2m)	1:6	1	97
17			(2n)	1:6	1	97
18			(2o)	1:9	1	99
19			(2p)	1:3	75	96
20			(2q)	1:3	1	98
21		NR	-	1:3	[12]	NA
22	$(CH_3)_3COH$	NR	-	1:3	[3]	NA
23			(2r)	1:3	1	95

[a]All products were characterized by ^1H NMR, FT-IR and also their TLC comparison with authentic sample prepared by reported method.

Allylic alcohol and nitro phenols are found to be inactive for the reaction (Table3.A.1, entries 12, 21).

Table 3.A.2: Acetylation reaction catalysed by P4VP-HCl and P4VP-H_3PO_4

Entry	Substrate	Ratio (Substrate & Ac_2O)	Product	P4VP-HCl		P4VP-H_3PO_4	
				Time min/[h]	% Yield[a]	Time min/[h]	% Yield[a]
1	Cholesterol	1:3	(2a)	[6]	70	[7]	68
2		1:3	(2d)	35	97	40	95
3	$CH_3(CH_2)_7OH$	1:3	(2f)	80	94	[2]	90
4	$CH_3(CH_2)_{15}OH$	1:3	(2g)	[4]	75	[4]	70
5		1:3	NA	[12]	NR	[12]	NR
6		1:3	NA	[7]	NR	[7]	NR
7		1:6	(2m)	[8]	60	[6]	55
8		1:3	NA	[8]	NR	[8]	NR

[a] All products were characterized by ^1H NMR, FT-IR and also their TLC comparison with authentic sample prepared by reported method.

We also investigated the catalytic activity of P4VP-HCl and P4VP-H_3PO_4 (Table 3.A.2) for acetylation reaction. Out of the three supported catalysts, P4VP-H_2SO_4 works better than P4VP-HCl and P4VP-H_3PO_4 in terms of reaction time and yields (Table 3.A.1, entries 3, 6, 8, 9, 13, 16, 19). The catalysts P4VP-HCl and P4VP-H_3PO_4 were found to be reactive for primary (Table 3.A.2, entries 3, 4) and secondary alcohols (Table 3.A.2, entries 1, 2) as well as for polyhydroxy compounds with (Table 3.A.2, entry 7) longer reaction time. There were no reactions observed with phenol (Table 3.A.2, entry 6). All three catalysts were reactivated after washing with dichloromethane and drying at 70 °C for 2 h. They retained their catalytic activities up to four times in case of acetylation of cholesterol (Table 3.A.3).

Table 3.A.3: Recycling of P4VP-H_2SO_4, P4VP-HCl and P4VP-H_3PO_4 for acetylation of cholesterol

Entry	Catalyst	Time min/[h]	No of cycles	% Yield of (2a)
1	P4VP-H_2SO_4	30	1	98
			2	97
			3	97
			4	96
2	P4VP-HCl	[6]	1	70
			2	68
			3	67
			4	67
3	P4VP-H_3PO_4	[7]	1	68
			2	67
			3	67
			4	66

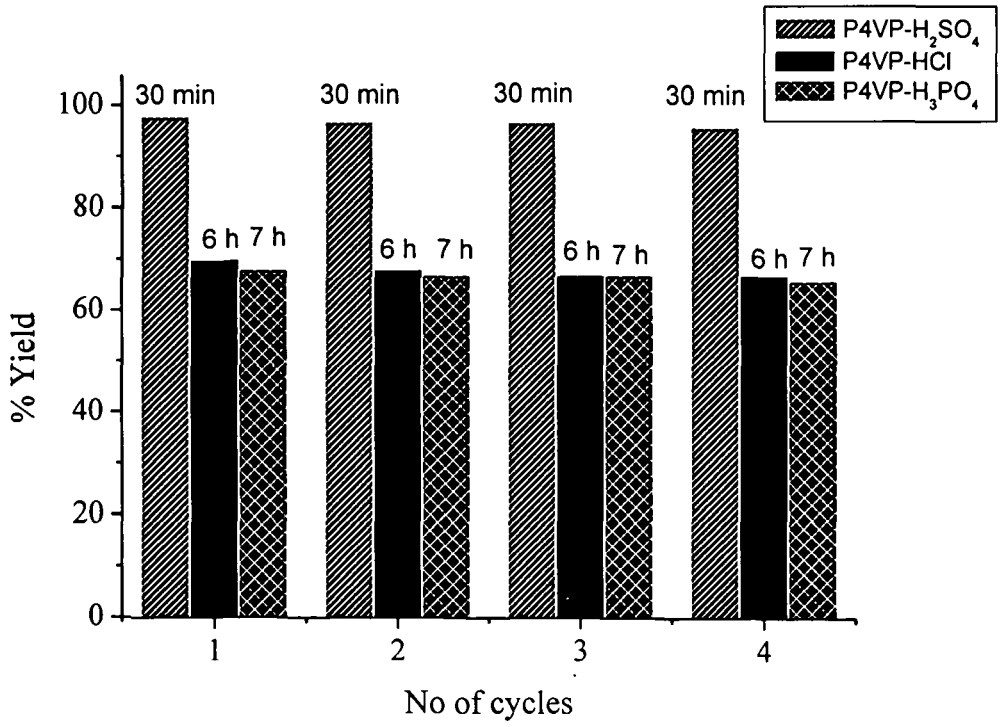


Figure 3.A.6: Histogram representing recycling of P4VP-H_2SO_4, P4VP-HCl and P4VP-H_3PO_4 for acetylation of cholesterol

3.A.3 Conclusion:

We have successfully synthesised, characterised and tested the catalytic activity of three catalysts, P4VP-H_2SO_4, P4VP-HCl and P4VP-H_3PO_4. Out of these three P4VP-H_2SO_4 is found to be very efficient for acetylation of various substrates. In conclusion, we have demonstrated the various advantages of poly(4-vinylpyridine) supported Brønsted acids; viz. simple method of preparation, good stability, easy recovery and recycling without loss of activity, safe handling, better reactivity and possibility of wide applications as solid acid catalyst in other organic reactions.

3.A.4 Experimental:

General:

All chemicals are commercially available and were used without purifications. Poly(4-vinylpyridine), cross linked with 2% DVB, was purchased from ACROS ORGANICS. Reagent grade sulphuric acid, hydrochloric acid and phosphoric acid were used without further purification. The products were characterized by ^1H NMR and IR analysis and also by comparison with literature data.[10]

3.A.4.1 Preparation of the catalyst P4VP-HX:

Poly (4-vinyl pyridine) (500 mg) and the respective acids (0.6 mL of H_2SO_4, HCl and H_3PO_4) were stirred in diethyl ether (5 ml) at room temperature for 15 minutes. Filtered and washed the solid catalyst with diethyl ether for three times. Finally, the catalysts were dried at 70 °C for 2 h and stored in vacuum decicator for use as catalyst.

3.A.4.2 Catalyst Characterization:

FT-IR spectra of various catalyst samples were recorded on a Nicolet Impact Model-410 spectrometer with 1 cm^{-1} resolution within 400-4000 cm^{-1} region using the KBr pellet technique. The SEM analyses were carried out using a JEOL JSM-6390LV Scanning Electron Microscope equipped with an Energy-Dispersive X-ray analyzer (EDX). The images were taken at an accelerator voltage of 15 kV and magnification of micrographs ranges from x1000 to x2000. Thermal stability of the supported catalysts was examined by SHIMADZU Thermo-gravimetric Analyzer-50 (TGA) in the temperature range of 20 to 600 °C.

3.A.4.3 Typical procedure for acetylation of Cholesterol:

To a mixture of cholesterol (1 mmol) and acetic anhydride (3 mmol) in dichloromethane (5 ml) P4VP-H_2SO_4 (0.12 mmol) was added and allowed to stirr at room temperature for 30 min. After completion of the reaction (monitored by TLC) the catalyst was removed by filtration and washed with dichloromethane (10 ml) for reuse. The filtrate was washed with aqueous sodium bicarbonate solution for removal of excess amount of acetic anhydride. Then the aqueous layer was extracted with dichloromethane (10 ml) to get the pure product. The solvent was evaporated under reduced pressure. The residue was pure enough for general purposes and further purification was achieved by thin layer chromatography using ethyl acetate and hexane to get analytically pure product (98 % yield).

3.A.4.4 Spectroscopic data of acetylated products:

Cholesteryl Acetate (2a):

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (d, J = 3 Hz, 1H), 4.64 (m, 1H), 2.05 (s, 3H), 1.04 (s, 3H), 0.72 (s, 3H); IR (KBr): ν 2900, 1750, 1625, 1500, 1400 cm^{-1}

Diphenyl Methanylacetate (2b):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.22 (m, 10H), 6.35 (s, 1H), 2.03 (s, 3H); IR (KBr): ν 2930, 1763, 1508, 1363 cm^{-1}

Benzoin Acetate (2c):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–8.02 (m, 10H), 5.84 (s, 1H), 2.06 (s, 3H); IR (KBr): ν 3034, 2921, 1765, 1665, 1512, 1368 cm^{-1}

Cyclohexyl Acetate (2d):

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 3.17 (m, 1H), 1.23–1.61 (m, 10H); IR (KBr): ν 2900, 2825, 1725, 1438, 1375, 1238, 1138 cm^{-1}

Methyl-Phenyl-Methanylacetate (2e):

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95-7.17 (m, 5H), 5.50 (q, J = 6 Hz, 1H), 2.02 (s, 3H), 1.85 (d, J = 6 Hz, 3H); IR (KBr): ν 1725, 1438, 1375, 1250, 1148 cm^{-1}

1-Octyl Acetate (2f):

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.05 (t, J = 6.8 Hz, 2H), 2.05 (s, 3H), 1.76 (m, 2H), 1.19-1.43 (m, 10H), 0.89 (t, J = 7.1 Hz, 3H); IR (KBr): ν 2897, 2845, 1748, 1472, 1257

cm^{-1}

1-Cetyl Acetate (2g):

^1H NMR (400 MHz, $CDCl_3$): δ 4.08 (t, J = 6.9 Hz, 2H), 2.05 (s, 3H), 1.60 (m, 2H),1.27-1.35 (m, 26H), 0.98 (t, J = 7.0 Hz, 3H); IR (KBr): ν 2900, 2850, 1750, 1475, 1375, 1262 cm^{-1}

Benzyl Acetate (2h):

^1H NMR (400 MHz, $CDCl_3$): δ 6.95-7.32 (m, 5H), 4.80 (s, 2H), 2.2 (s, 3H); IR (KBr): ν 3033, 2949, 1738, 1451, 1375, 1235, 1030 cm^{-1}

Ethane-1,2-Diyl Diacetate (2i):

^1H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H), 4.90 (s, 4H); IR (KBr): ν 2963, 1739, 1442, 1376, 1230, 1056 cm^{-1}

Phenyl Acetate (2j):

^1H NMR (400 MHz, $CDCl_3$): δ 7.0 -7.5 (m, 5H), 2.5 (s, 3H); IR (KBr): ν 1745, 1550, 1450, 1350, 1200 cm^{-1}

2-Napthyl Acetate (2k):

^1H NMR (400 MHz, $CDCl_3$): δ 7.78-7.86 (m, 3H), 7.54 (s, 1H), 7.45-7.50 (m, 2H), 7.23-7.24(m, 1H), 2.34 (s, 3H); IR (KBr): ν 3057, 2928, 1758, 1601, 1514, 1375, 1216, 1156 cm^{-1}

1-Napthyl Acetate (2l):

^1H NMR (400 MHz, $CDCl_3$): δ 7.65-7.83 (m, 3H), 7.42-7.47 (m, 2H), 7.20-7.28 (m, 2H), 2.42 (s, 3H) ; IR (KBr): ν 2929, 1755, 1603, 1495, 1367, 1219 cm^{-1}

Benzene-1, 3-Diyl Diacetate (2m):

^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.18 (m, 1H), 6.59-6.64 (m, 2H), 6.53 (s, 1H); IR (KBr): ν 2925, 2856, 2372, 1762, 1599, 1444, 1368, 1197, 1122, 1013 cm^{-1}

Benzene-1, 2-Diyl Diacetate (2n):

^1H NMR (400 MHz, $CDCl_3$): δ 6.99-7.05 (m, 4H), 2.27 (s, 6H); IR (KBr): ν 2928, 2854, 1772, 1600, 1446, 1194 cm^{-1}

Benzene-1,2,3-Triyl Triacetate (2o):

^{1}H NMR (400 MHz, $CDCl_3$):δ 7.24 (t, J = 7.6 Hz, 1H); 7.11 (d, J = 7.9 Hz, 2H), 2.28 (s, 9H); IR (KBr): ν 2932, 1766, 1610, 1444, 1192 cm^{-1}

4-Methylphenyl Acetate (2p):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 2.27 (s, 3H), 2.21 (s, 3H); IR (KBr): ν 3033, 2927, 1761, 1506, 1371, 1198, 1020 cm^{-1}

***N*-(4-Hydroxy-Phenyl)-Acetamide (2q):**

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, NH), 7.42-7.46 (m, 2H), 6.68 (m, 2H), 2.26 (s, 3H), OH not observed; IR (KBr): ν 3497, 3293, 3077, 2935, 1754, 1666, 1555, 1243 cm^{-1}

Acetanilide (2r):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (br, 1H), 6.6-6.8 (m, 5H), 2.0 (s, 3H); IR (KBr): ν 3330, 2950, 1755, 1660, 1500, 1450, 1400, 1350, 1250 cm^{-1}

Section B:

Poly(4-vinylpyridine) Supported Sulphuric Acid as Efficient Reusable Catalyst for the Pechmann Coumarin Synthesis under Solvent-free Microwave Conditions

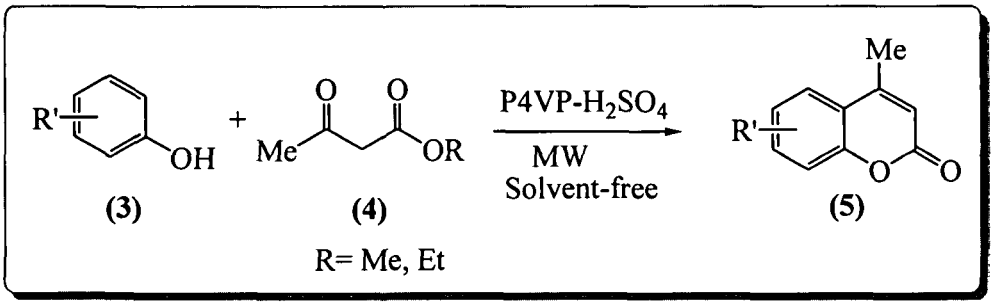
3.B.1 Introduction:

Pechmann reaction is the most widely used method for preparing coumarins (Scheme 3.B.1) since it starts from simple starting materials and offers high yield. Mineral acids like H_2SO_4, HCl and H_3PO_4, CF_3COOH, $HClO_4$ and Lewis acids such as $FeCl_3$, $AlCl_3$, $TiCl_4$, $ZnCl_2$, $SnCl_4$ and $TiCl_4$ were used as catalysts in the conventional coumarin synthesis.[11] However, most of the methods using strong acid catalysts[8a,12] involve high temperature reaction conditions, prolonged reaction times, use of excess amount of catalysts, environmental pollution from organic solvents, non-recycling of catalysts, side product formation and complicated product purification. The disposal of toxic and corrosive acidic waste leads to environmental pollution. Recently many cleaner and safer methods have been developed for Pechmann reaction using ionic liquid,[13] microwave irradiation[14] and solid acid catalysts.[15] Consequently, there is scope for development of milder reaction condition for the Pechmann reaction using eco-friendly and reusable solid acid catalysts. The potential use of polymer supported[4,16] reusable solid catalysts in organic transformation make reaction methods more convenient, safer and environmentally benign. Poly(4-vinylpyridine) seems to be an attractive support to immobilize acidic dopants[6] because of the basic nature of pyridyl group. In continuation of our previous section (Section A, Chapter 3) work on poly(4-vinylpyridine) supported acid catalysts, herein, we report the successful synthesis of coumarins via Pechmann reaction under solvent-free microwave irradiation using P4VP-H_2SO_4 acid as reusable acid catalyst.

Part of this work is under revision in

Monatsh. Chem. (2011)

3.B.2 Results and discussion:



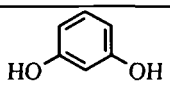
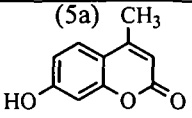
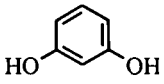
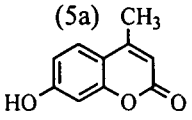
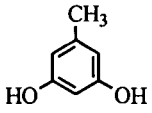
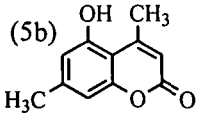
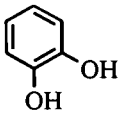
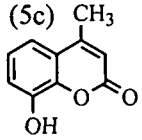
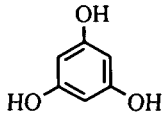
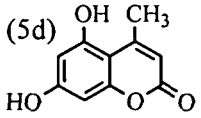
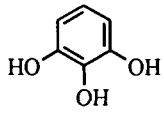
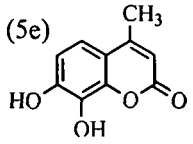
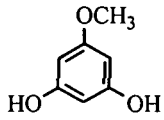
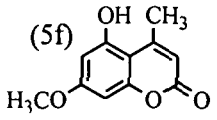
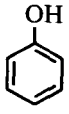
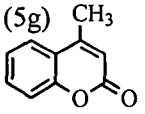
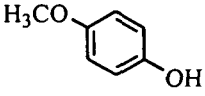
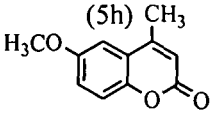
Scheme 3.B.1

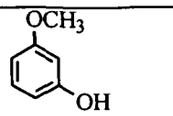
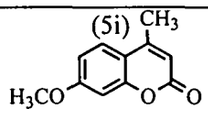
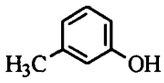
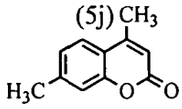
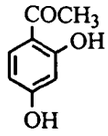
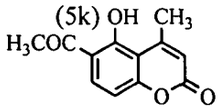
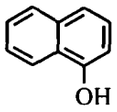
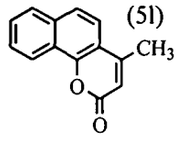
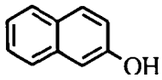
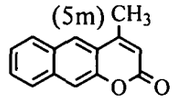
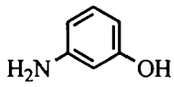
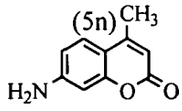
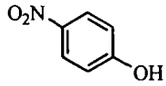
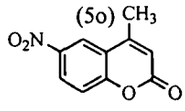
In contrast to conventional methods, here we describe the use of only 0.2 equivalent of P4VP-H_2SO_4 as acid catalyst for Pechmann reaction under solvent-free microwave condition without forming any side product. The catalyst P4VP-H_2SO_4 was prepared by simple wet impregnation technique following the procedure described in section A of this chapter. Amount of acid group present in the polymeric chain was calculated based on the weight of supported polymer salt obtained and the weight of poly(4-vinylpyridine) used. The amount of dopant present in poly(4-vinylpyridine)-sulphuric acid (P4VP-H_2SO_4) was found to be 0.652 mol % against 500 mg P4VP. The characterization of the polymer supported catalyst so formed was done by FT-IR, SEM-EDX and TGA studies. It is relatively non toxic, safer to handle and can be reused after reactivation which make the process more economical and benign.

To study the feasibility of P4VP-H_2SO_4 catalyzed Pechmann reaction, the reaction of resorcinol (1 mmol) and ethyl acetoacetate (1 mmol) was irradiated by microwave radiation in presence of P4VP-H_2SO_4 catalyst under solvent free condition. The best result was observed with 0.2 equivalent of catalyst at microwave power 560 W (Table 3.B.1, entry 1) at 65 °C (Catalyst System Microwave Reactor). An increase in the catalyst to 0.5 equivalents (Table 3.B.1, entry 2) showed no significant improvement in yield, though a slight improvement in reaction time was observed. From these observations, we selected 0.2 equivalent of acid as standard amount to generalize this protocol for different structurally diverse monohydric and polyhydric phenols to react with β-keto ester (**4**) to obtain the corresponding coumarins (Table 3.B.1). All these results showed that this method is effective for both electron rich and electron poor phenols to afford the corresponding coumarins in good to moderate yields. The reaction

of catechol with β-keto ester (**4**) yielded good conversion (Table 3.B.1, entry 4) of coumarin although most of the reported protocols[11-12] failed to produce the corresponding product.

Table 3.B.1: P4VP-H_2SO_4 catalysed Pechmann condensation reaction of phenols (**3**) with β-keto esters (**4**) under solvent-free microwave irradiation at 560 W

Entry	Phenol	Product	Time (min)	% Yield[a,b]	Mp (°C)
1		(5a) 	7	85	182-184
2		(5a) 	5	86[c]	182-184
3		(5b) 	10	86	257-258
4		(5c) 	12	77	Semi solid
5		(5d) 	9	85	284-285
6		(5e) 	10	84	241-243
7		(5f) 	12	83	117-120
8		(5g) 	15	71	82-83
9		(5h) 	10	77	164-166

10		(5i) 	12	75	160-161
11		(5j) 	12	78	130-132
12		(5k) 	15	73	163-165
13		(5l) 	15	71	152-154
14		(5m) 	15	70	182-183
15		(5n) 	14	75	222-223
16		(5o) 	20	50	151-154

[a] All products are characterised by ^{1}H NMR, ^{13}C NMR, FT-IR, and CHN analysis, [b] isolated yield, [c] reaction is carried out with 0.5 equivalent of catalyst

Heravi *et al.*[17] carried out the Pechmann reaction of catechol at 130 °C during 1.7 h reaction period using sodium-30-tungstopentaphosphate as catalyst. Interestingly, resacetophenone reacted efficiently in presence of supported sulphuric acid (Table 3.B.1, entry 12) catalyst under solvent-free condition, but in conventional method using liquid sulphuric acid[8(a),12(a)] it did not give any coumarin product. With this catalyst, the reaction of 4-nitrophenol with β-keto ester (**4**) ester yielded only 50% product (Table 3.B.1, entry 16) within 20 min reaction time. Methyl acetoacetate in place of ethyl acetoacetate gave similar results. The catalyst was separated by simple filtration, washed with organic solvent, dried and reactivated for further use and recycled (Table 3.B.2) for three times without loss of catalytic activity. The reactivation of catalyst is necessary, since the supported catalyst loses some amount of sulphuric acid above 80 °C. Depending on the polarity of substrate molecules, we observed the variation of reaction

No of cycles

Figure 3.B.1: Histogram representing recycling of P4VP-H_2SO_4 for the reaction of resorcinol and ethyl acetoacetate under solvent-free MW irradiation

We also investigated the application of sulphuric acid and trifluoroacetic acid in presence of acidic alumina as support for Pechmann coumarin synthesis of ethyl acetoacetate with various phenols under solvent-free microwave irradiation. The results are summarised in the Table 3.B.3 and Table 3.B.4. These two catalysts were also effective for both electron rich and electron poor phenols to produce coumarin. It was

temperature within the range of 65-70 °C at 560 W microwave power of Catalyst System Microwave Reactor.

Table 3.B.2: Recycling of P4VP-H_2SO_4 catalyzed Pechmann reaction of resorcinol with ethyl acetoacetate under solvent-free microwave irradiation

Entry	Time (min)	No of cycles	Product (5a) Yield %[a]
1	7	1	85
2	7	2	85
3	7	3	84

[a] This reactions was carried out in 1 mmol scale with molar ratio 1:1:0.2 of resorcinol/ethyl acetoacetate/catalyst

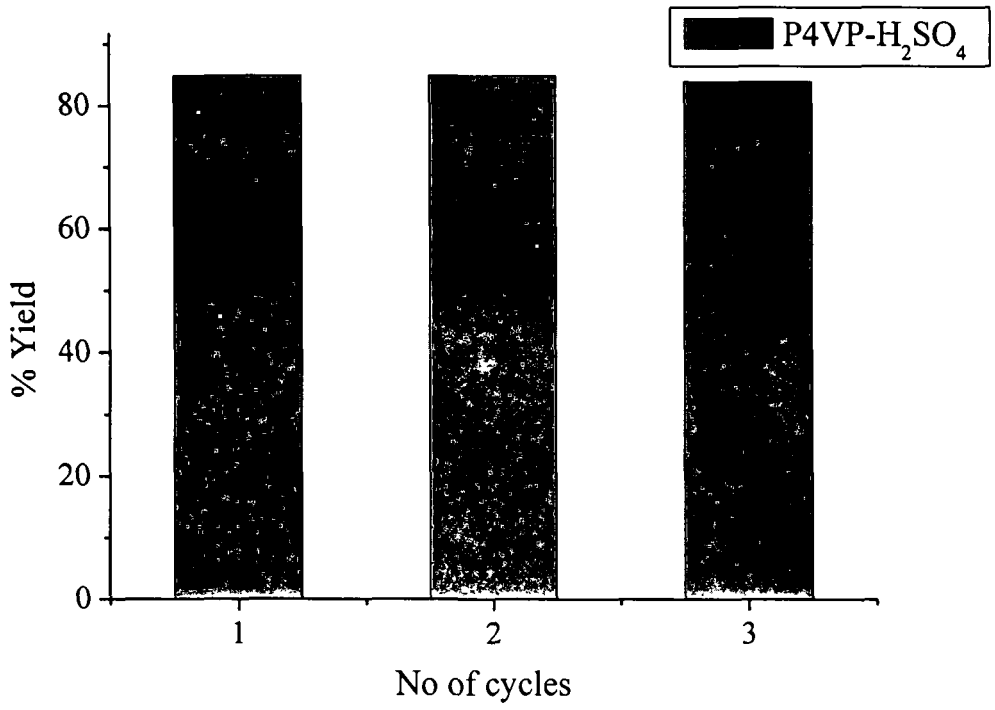


Figure 3.B.1: Histogram representing recycling of P4VP-H_2SO_4 for the reaction of resorcinol and ethyl acetoacetate under solvent-free MW irradiation

We also investigated the application of sulphuric acid and trifluoroacetic acid in presence of acidic alumina as support for Pechmann coumarin synthesis of ethyl acetoacetate with various phenols under solvent-free microwave irradiation. The results are summarised in the Table 3.B.3 and Table 3.B.4. These two catalysts were also effective for both electron rich and electron poor phenols to produce coumarin. It was

observed that in case of alumina-TFA the reactions occur comparatively at shorter time with better yield at lower microwave power than alumina-H_2SO_4. So, the former seems to be more efficient to afford coumarin. Acidic alumina alone can also act as catalyst for this reaction with 50% yield of coumarin.

Table 3.B.3: Alumina-H_2SO_4 catalysed Pechmann reaction under solvent-free MW irradiation at 700 W

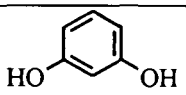
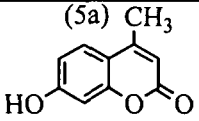
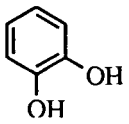
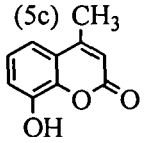
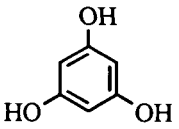
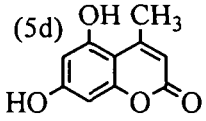
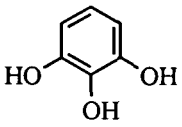
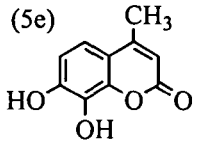
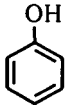
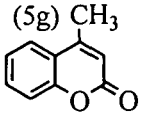
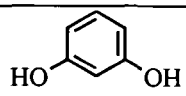
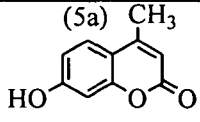
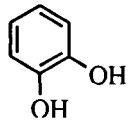
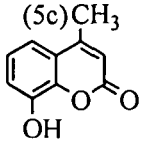
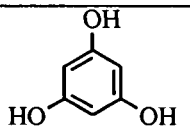
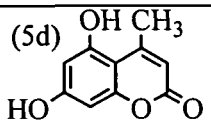
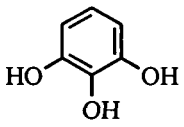
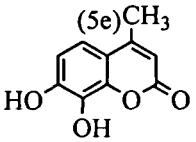
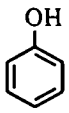
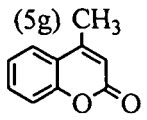
Entry	Phenol	Product	Time (min)	% Yield
1		(5a) 	12	78
2		(5c) 	20	73
3		(5d) 	12	79
4		(5e) 	20	74
5		(5g) 	20	68

Table 3.B.4: Alumina-TFA catalysed Pechmann reaction under solvent-free MW irradiation at 560 W

Entry	Phenol	Product	Time (min)	% Yield
1		(5a) 	8	87
2		(5c) 	12	78

3		(5d) 	6	85
4		(5e) 	12	82
5		(5g) 	15	72

3.B.3 Conclusion:

From this investigation, we have found an efficient microwave assisted solvent-free protocol for the synthesis of variety of coumarins in good to moderate yields using poly(4-vinylpyridine) supported H_2SO_4 acid as reusable solid acid catalyst. Furthermore, TFA and H_2SO_4 in presence of acidic alumina also worked well with this reaction.

3.B.4 Experimental:

General

All chemicals are commercially available and were used without purifications. The products were characterized by ^1H NMR, ^{13}C NMR, FT-IR and CHN analysis and also by comparison with literature data.[11,12,13,14] We have described the preparation method of polymer supported catalyst in Section A of this chapter

3.B.4.1 General procedure for P4VP-H_2SO_4 catalysed Pechmann coumarin synthesis:

β-keto ester (**4**)(1 mmol) and Phenol (**3**) (1 mmol) are mixed thoroughly and added P4VP-H_2SO_4 (0.2 mmol). The reaction mixture was irradiated by microwave irradiation at power 560 W and temperature 65-70 °C in a microwave reactor (Catalyst System) for specified period. After completion of the reaction as indicated by TLC, the reaction mixture is cooled to room temperature and added ethanol in order to recover the insoluble catalyst by filtration. The product is purified by column chromatography

using ethyl acetate and hexane in 1:5 solvent system. The recovered catalyst is dried, reactivated and reused.

3.B.4.2 General procedure for alumina-sulphuric acid/trifluoroacetic acid catalysed Pechmann coumarin synthesis:

A mixture of ethyl acetoacetate (1 mmol), phenol (1 mmol) and sulphuric acid/ TFA (0.25 mmol) was mixed thoroughly with acidic alumina (0.300 g) at room temperature for 10 min. The mixture was irradiated with microwave radiation for specified period in a microwave reactor (Catalyst System). After completion of the reaction as indicated by TLC, the reaction mixture is cooled to room temperature and added ethanol. The catalyst is separated by filtration. The product is purified by column chromatography using ethyl acetate and hexane in 1:5 ratio.

3.B.4.3 Spectral and elemental data:

7-Hydroxy-4-methylcoumarin (5a):

^{1}H NMR (400 MHz, CD_3OD): δ 7.58 (d, J = 8.7 Hz, 1H), 6.81 (m, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.08 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 18.9, 103.2, 110.9, 112.7, 113.5, 126, 153.5, 155.4, 161.6, 161.9; IR (KBr): ν 3498, 3106, 2937, 1669, 1606, 1387, 1268, 1138, 1069, 846 cm^{-1}; Anal. Calcd (%) for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 68.13; H 4.53.

5-Hydroxy-4, 7-dimethylcoumarin (5b):

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO): δ 6.62 (s, 1H), 6.59 (s, 1H), 6.04 (s, 1H), 2.55 (s, 3H), 2.27 (s, 3H), OH not observed ; IR (KBr): ν 3455, 2925, 1670, 1604, 1560, 1396, 1319, 1272, 1142, 1065, 979, 691 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.40; H, 5.22.

8-Hydroxy-4-methlycoumarin (5c):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.21 (m, 1H), 7.03 (m, 1H), 6.93 (m, 1H) , 6.16 (s, 1H,), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 100.1, 101.7, 117.7, 121, 122.1, 127.4, 161.5, 169.3, 181.3; IR (KBr): ν 3393, 3247, 2927, 1724, 1655, 1444, 1260, 1072, 757 cm^{-1}; Anal. Calcd (%) for $C_{10}H_8O_3$: C, 68.18; H, 4.55. Found: C, 68.15; H, 4.50.

5, 7-Dihydroxy-4-methylcoumarin (5d):

^{1}H NMR (400 MHz, CD_3OD): δ 6.29-6.32 (m, 2H), 5.8 (s, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 23.9, 95.1, 99.5, 102.9, 109, 155.7, 156.7, 158.8, 161.1, 161.6; IR (KBr): ν 3459, 3413, 2923, 2854, 1667, 1365, 1296, 1155, 1078, 828 cm^{-1}; Anal. Calcd (%) for $C_{10}H_8O_4$: C, 62.5; H, 4.17. Found: C, 62.46; H, 4.14.

7, 8-Dihydroxy-4-methylcoumarin (5e):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.10 (s, 1H), 2.24 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 110.6, 112.2, 113.1, 115.2, 132, 143.2, 149, 153.5, 160.9; IR (KBr): ν 3409, 3145, 2925, 1643, 1591, 1307, 1057, 770 cm^{-1}; Anal. Calcd (%) for $C_{10}H_8O_4$: C, 62.5; H, 4.17. Found: C, 62.44; H, 4.13.

5-Hydroxy-7-methoxy-4-methylcoumarin (5f):

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO): δ 6.86 (s, 1H), 6.75 (s, 1H), 6.22 (s, 1H), 3.80 (s, 3H), 2.39 (s, 3H) ; IR (KBr): ν 3458, 3020, 2932, 1685, 1615, 1561, 1373, 1261, 1154, 1065, 977, 691 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{10}O_4$: C, 64.08; H, 4.85. Found: C, 63.80; H, 4.82.

4-Methylcoumarin (5g):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15-7.60 (m, 4H), 6.42 (s, 1H), 2.60 (s, 3H); IR (KBr): ν 3021, 2933, 1665, 1607, 1510, 1452, 1400, 1371, 1268, 1143, 1061, 690 cm^{-1}; Anal. Calcd (%) for $C_{10}H_8O_2$: C, 75; H, 5. Found: C, 74.95; H, 5.12.

6-Methoxy-4-methylcoumarin (5h):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 9.1 Hz, 1H), 7.24 (s, 1H),7.16 (d, J = 9.1 Hz, 1H), 6.39 (s, 1H), 3.85 (s, 3H), 2.45 (s, 3H); IR (KBr): ν 3018, 2931, 1680, 1617, 1565, 1372, 1262, 1155, 1065, 971, 690 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.44; H, 5.31.

7-Methoxy-4-methylcoumarin (5i):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.72 Hz, 1H), 6.90 (d, J = 8.72 Hz, 1H), 6.82 (s, 1H), 6.18 (s, 1H), 3.82 (s, 3H), 2.43 (s, 3H); IR (KBr): ν 3049, 2930, 1688, 1615, 1567, 1260, 1213, 1085, 975, 691 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26. Found: C, 69.40; H, 5.34.

4,7-Dimethylcoumarin (5j):

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 6.90 (s, 1H), 6.40 (s, 1H,), 2.82 (s, 3H), 2.64 (s, 3H); IR (KBr): ν 3019, 2930, 1682, 1605, 1510, 1450, 1403, 1370, 1265, 1141, 1060, 691 cm^{-1}; Anal. Calcd (%) for $C_{11}H_{10}O_2$: C, 75.86; H, 5.75. Found: C, 75.83; H, 5.71.

6-Acetyl-5-hydroxy-4-methylcoumarin (5k):

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.24 (s, 1H), 2.58 (s, 3H), 2.23 (s, 3H), OH not observed ; IR (KBr): ν 3445, 3017, 2934, 1740, 1680, 1558, 1375, 1265, 1150, 1060, 970, 685 cm^{-1}; Anal. Calcd (%) for $C_{12}H_{10}O_4$: C, 66.06; H, 4.59. Found: C, 65.90; H, 4.62.

4-Methyl-7,8-benzocoumarin (5l):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38-8.5 (m, 1H), 7.90 -8.10 (m, 1H), 7.46-7.72 (m, 4H), 6.42 (s, 1H), 2.51 (s, 3H); IR (KBr): ν 3014, 2932, 1709, 1576, 1375, 1236, 1144, 1059 cm^{-1}; Anal. Calcd (%) for $C_{14}H_{10}O_2$: C, 80; H, 4.76. Found: C, 79.95; H, 4.82.

4-Methyl-6,7-benzocoumarin (5m):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54-8.59 (m, 1H), 7.88-8.11 (m, 1H), 7.89-7.92 (m, 4H), 6.43 (s, 1H), 2.52 (s, 3H); IR (KBr): ν 3023, 2931, 1705, 1569, 1377, 1244, 1146, 1040 cm^{-1}; Anal. Calcd (%) for $C_{14}H_{10}O_2$: C, 80; H, 4.76. Found: C, 79.91; H, 4.72.

7-Amino-4-methylcoumarin (5n):

^{1}H NMR (400 MHz, $CDCl_3$ + DMSO): δ 7.45 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.42 (s, 1H), 6.20 (s, 1H), 2.32 (s, 3H); IR (KBr): ν 3466, 3310, 2998, 1690, 1568, 1371, 1241, 1138, 1053 cm^{-1}; Anal. Calcd (%) for $C_{10}H_9NO_2$: C, 68.57; H, 5.14; N, 8. Found: C, 68.53; H, 5.22; N, 7.88.

4-methyl-6-nitro coumarin (5o):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.35 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 6.21 (s, 1H), 2.15 (s, 3H); IR (KBr): ν 3023, 2934, 1672, 1612, 1511, 1450, 1405, 1375, 1266, 1145, 1060, 692 cm^{-1}; Anal. calcd (%) for $C_{10}H_7NO_4$: C, 58.53; H, 3.41; N, 6.82. Found: C, 58.47; H, 3.38; N, 6.85.

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Chapter 4

One-Pot Multi-component Synthesis of Novel Dihydropyrimido[4,5-*d*] Pyrimidine and Dihydropyrido[2,3-*d*] Pyrimidine Derivatives

Section A:

An Efficient Regiospecific Synthesis of Highly Functionalised Novel Dihydropyrimido[4,5-*d*] pyrimidine Derivatives by Three-Component Condensation under Solvent-Free Conditions

4.A.1 Introduction:

Pyrimidopyrimidines are annulated uracils that have attracted considerable interest as useful anticancer and antiviral drugs.[1-3] General methods for their synthesis involve the annulation reactions starting from either suitably substituted 6-aminouracils[4] or 2-amino-3-cyanopyridines[5] and related substrates.[6] However, many of these methods suffer from drastic reaction conditions and complex procedures, and use of expensive or not readily available starting materials.[4,6] Previously, pyrimido[4,5-*d*]pyrimidine analogues of folic acid have been screened for antitumor activity.[7] Hence, there has been remarkable interest in the synthetic manipulations of uracils,[8] although the synthetic exploitation of the nucleophilic double bond of uracil is an undeveloped field in view of a great varity of potential products.[9] 4-Deazatoxaflavin, a member of the pyrimido[4,5-*c*]pyridazines, inhibits the growth of Pseudomonus 568 and also binds to herring sperm DNA.[10] Another approach to the synthesis of pyrimido[4,5-*d*]pyrimidines reported by Wamhoff and Muhr[11] is the aza-Wittig-type reaction of iminophosphoranes of 5-amino uracils leading to functionalised pyrimido[4,5-*d*]pyrimidines. Our synthetic strategy utilizing a three-component reaction of various carbonyl compounds and ammonium acetate with 6-[(dimethylamino)methylene]aminouracil affords regiospecific one-pot synthesis of novel pyrimido[4,5-*d*]pyrimidines in excellent yields when carried out under solvent-free conditions based on cycloaddition strategy.

In the past a cycloaddition approach has had little appeal since the dienophilic

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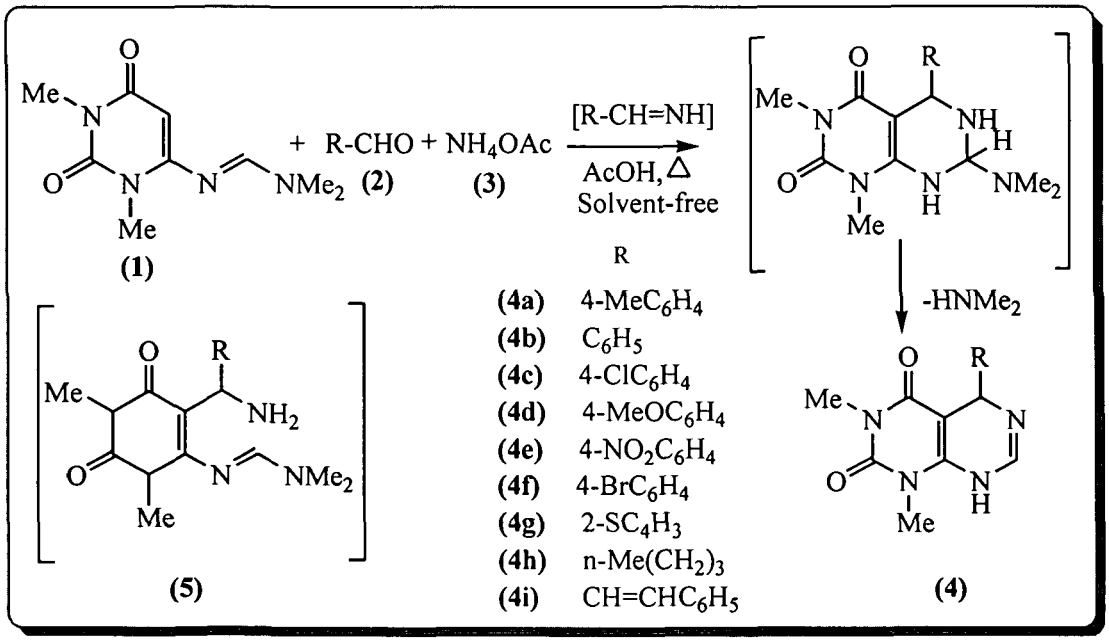
nature of the pyrimidine ring is rather limited, and the diene properties of vinylpyrimidines had not yet been established.[12] It was postulated that if a vinylpyrimidine system were appropriately substituted with strong electron-donating groups, cycloaddition might occur with electron-deficient dienophiles. In one report, the diene character of furan was enhanced by incorporation of a dimethylhydrazino group[13] and 1-(dimethylamino)-3-methyl-2-azabutadiene[14] to function as azadiene suggests that the dienic character of vinylpyrimidines would be increased by similar substituents, which is also supported by HOMO calculations.[15] Furthermore, in recent years, the multi-component one-pot condensations constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that products are formed in a single step and the diversity can be achieved simply by varying the reaction components.[16] We employed ammonium acetate as it is biodegradable and sometimes it alone or along with other species shows excellent catalytic activity in various reactions.[17] The versatility of ammonium acetate is witnessed from the fact that it is an efficient reagent in different reaction conditions as in common solvents at room temperature,[18] refluxing in high-boiling organic solvents,[19] water,[20] ionic liquids[21] and microwave-promoted reactions.[22]

4.A.2 Results and discussion:

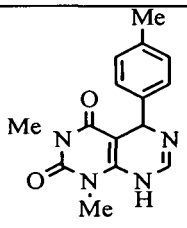
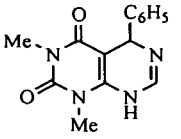


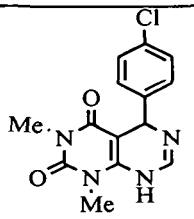
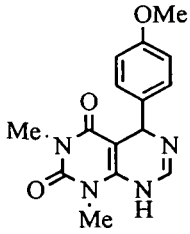
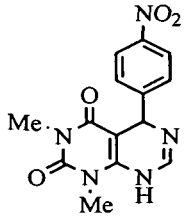
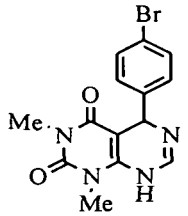
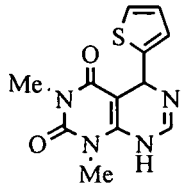
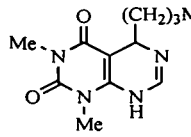
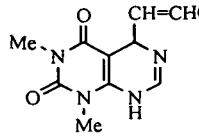
Scheme 4.A.1

Herein, we report a one pot synthesis of various novel pyrimido[4,5-*d*]pyrimidine derivatives through a three-component coupling reaction of aldehydes, ammonium acetate and 6-[(dimethylamino)methylene]aminouracil in the presence of acetic acid under thermal conditions. Here, the reaction proceeds efficiently at 90 °C in excellent yields. The 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil (1) was readily obtained by the reaction of 6-amino-1,3-dimethyluracil with DMF-DMA under thermal conditions in the solid state. The reaction proceeds more efficiently when carried under microwave irradiations and takes only 3 min to complete the reaction in 90% yield. Thus, treatment of 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil (1), with an equimolar amount of tolualdehyde **(2a)** and ammonium acetate in presence of acetic acid heated at 90 °C for 2 h gave, after elimination of dimethylamine from the 1:1 cycloadduct and oxidative aromatisation, the corresponding dihydropyrimido[4,5-*d*]pyrimidine derivative **(4a)** as the only product in 90% yield. The reaction is comparatively less effective when carried out in a Prolabo Synthawave Microwave Reactor and irradiated at 120 °C for five minutes, which gave after usual work-up the pyrimido[4,5-*d*]pyrimidine derivative **(4a)** in 75% yield only. Further increase of reaction time did not yield any fruitful results; rather decomposition of starting material occurred. The structure of product **(4a)** as a dihydropyrimido[4,5-*d*]pyrimidine derivative was assigned on the basis of its elemental and spectral analyses. The diagnostic signal for azomethine (formed in situ) proton at δ = 8.20 ppm was absent in the cycloadduct, whilst upfield shift of this proton from δ = 8.20 ppm to δ = 5.44 ppm showed that the cycloaddition had occurred at the C=N bond of the imine. Also, the ^{1}H NMR spectrum showed the absence of the H-5 proton of uracil **(1)** and the presence of two methyl groups from cycloadduct **(4a)** at δ = 3.10 (s, 3H, NCH_3) ppm and at δ = 3.48 (s, 3H, NCH_3) ppm, and other peaks at δ = 2.30 (s, 3H, CH_3), 6.62-7.28 (m, 4H, ArH and 1H, CH=N-) ppm. The mass spectrum of **(4a)** revealed a strong molecular ion peak at m/z = 285 [M^+ + 1]. To generalize this reaction, we reacted various aromatic, aliphatic and heterocyclic aldehydes with uracil amidine **(1)** and ammonium acetate and isolated the corresponding pyrimido[4,5-*d*]pyrimidines **(4b-i)** in 75-93% yields. The reaction is also effective when we employed a conjugated aldehyde like cinnamaldehyde; but 2-furfuraldehyde did not yield any fused pyrimidine derivatives, rather decomposition of starting material was observed under the reaction condition. The physical characteristics of these products are recorded in Table 4.A.1. This three-component one-pot reaction

yields only the pyrimido[4,5-*d*]pyrimidine derivatives (**4**) and we did not observe the formation of any Michael-type products (**5**). Our finding is in contrast to an earlier report[23] where Sandhu *et al.* obtained simple Michael adducts and failed to prepare fused pyrimidines from the reactions of α,β-unsaturated nitro compounds with 6-amino-, 6-hydroxyamino- and 6-hydrazino-1,3-dimethyluracils. The ^{1}H NMR spectrum of (**4a**) shows the absence of the –CH proton in the α-carbon atoms (characteristic peak for Michael adduct) and the presence of a –CH=N- proton along with aromatic protons which rules out the formation of any Michael adduct. Approximately 0.1 equivalent of acetic acid were found to be sufficient for these reactions to proceed and the use of large excess did not lead either to higher yields or faster reaction rates. The high regiospecificity observed in these reactions is inconsistent with the electron-donating effect of the dimethlyamino substituent increasing the nucleophilicity of the C-5 position. Although we could not isolate any intermediates from the reaction mixture, a reasonable mechanism for the formation of the product would involve initial electrophilic attack of the in situ generated imine at the C-5 position of the uracil amidine (**1**) to give the Michael adduct which suffers a subsequent nucleophilic attack on the imino carbon atom eliminating dimethylamine followed by oxidative aromatisation to give products (**4**).

Table 4.A.1: Physical characteristics of Dihydropyrimido[4,5-*d*]pyrimidine derivatives

Entry	R	Time (h)	Product	% Yield[a, b]	Mp (°C)
1	4-MeC$_6$H$_4$	2.0		90	207-209
2	C$_6$H$_5$	1.5		88	217-219

3	4-ClC_6H_4	2.5		93	203-205
4	4-$OMeC_6H_4$	2.0		91	187-189
5	4-$NO_2C_6H_4$	3.0		84	232-234
6	4-BrC_6H_4	3.0		80	225-227
7	2-SC_4S_3	2.0		85	263-265
8	n-$Me(CH_2)_3$	2.0		75	144-147
9	C_6H_5CH=CH-	3.0		70	133-135

[a] Isolated Yield. [b] All products are characterised by ^1H NMR, ^{13}C NMR, IR, MS and CHN analysis.

4.A.3 Conclusion:

In conclusion, our results demonstrate a new and efficient synthesis of novel complex pyrimido[4,5-*d*]pyrimidine derivatives of biological significance in excellent

yields. These results also illustrate that the title compound **(1)** is a useful substrate for the generation of an array of fused nitrogen heterocycles. The main advantages of this methodology are: operational simplicity, short reaction times, excellent yield of products and the use of relatively non toxic reagents.

4.A.4 Experimental:

4.A.4.1 General procedure for the synthesis of Dihydropyrimido [4,5-*d*]pyrimidine derivatives (4) by the reaction of uracil amidine (1) with aldehyde (2) and ammonium acetate (3):

An equimolar amount of 6-[(dimethylamino)methylene]amino-1,3-dimethyuracil (0.210 g, 1 mmol), tolualdehyde **(2a)** (0.123 g, 1 mmol), NH_4OAc (0.077 g, 1 mmol) in the presence of AcOH (0.006 g, 0.1 mmol) were mixed well and heated about 2 h at 90 °C. After completion of the reaction (monitored by TLC) the reaction vessel was allowed to cool to r.t. and added 30 mL of cold water. The crude product was extracted with EtOAc (3×30 mL) and washed with water. The combined organic phases were dried over anhydrous Na_2SO_4 and subjected to column chromatography using EtOAc-hexane (1:6) as the eluent to afford the corresponding dihydropyrimido[4,5-*d*]pyrimidine **(4a)** in 90% yield; mp 206-209 °C. The other dihydropyrimido[4,5-*d*]pyrimidine derivatives **(4b-i)** were prepared in a similar manner.

4.A.4.2. Spectroscopic and elemental data of Dihydropyrimido[4,5-*d*] pyrimidine derivatives (4a-i):

1,3-Dimethyl-5-(4-methylphenyl)-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4a):

IR (KBr): ν 3255 (NH), 1687, 1644 (C=O), 1551 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.10 (s, 3H, NCH_3), 3.48 (s, 3H, NCH_3), 2.30 (s, 3H, CH_3), 5.44 (s, 1H), 6.44 (br, 1H, NH), 6.62-7.28 (m, 4H, ArH and 1H, CH=N-); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.84 (C-2), 152.70 (C-4), 152.43 (C-8a), 150.99 (C-7), 141.35, 138.84, 129.86, 127.12, 90.53 (C-4a), 52.36 (C-5), 29.76 (C-9), 28.09 (C-10), 21.55 (C-Me); MS: m/z 285 [M^+ + 1]. Anal. Calcd (%) for $C_{15}H_{16}N_4O_2$: C, 63.38; H, 5.63; N, 19.72. Found: C, 63.47; H, 5.77; N, 19.65.

1,3-Dimethyl-5-phenyl-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4b):

IR (KBr): ν 3260 (NH), 1690, 1645 (C=O), 1570 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.24 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 5.60(s, 1H), 6.46 (br, 1H, NH), 7.05-7.61 (m, 5H, ArH and 1H, CH=N-); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8 (C-2), 151.4 (C-4), 151.1 (C-8a), 149.2, 140.5, 139.1, 128.1, 126.1, 90.1 (C-4a), 54.1(C-5), 29.1 (C-9), 27.5 (C-10); MS: m/z 271 [M^+ + 1]. Anal. Calcd (%) for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.18; N, 20.74. Found: C, 62.31; H, 5.10; N, 20.82.

1,3-Dimethyl-5-(4-chlorophenyl)-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4c):

IR (KBr): ν 3265 (NH), 1700, 1650 (C=O), 1560 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H, NCH_3), 3.62 (s, 3H, NCH_3), 5.55 (s, 1H), 6.44 (br, 1H, NH), 7.01-7.65 (m, 4H, ArH and 1H, CH=N-); MS: m/z 305 [M^+ + 1]; Anal. Calcd (%) for $C_{14}H_{13}N_4O_2Cl$: C, 55.26; H, 4.27; N, 18.42. Found: C, 55.31; H, 4.32; N, 18.33.

1,3-Dimethyl-5-(4-methoxyphenyl)-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4d):

IR (KBr): ν 3260 (NH), 1695, 1650 (C=O), 1570 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.19 (s, 3H, NCH_3), 3.51(s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 5.44 (s, 1H), 6.47 (br, 1H, NH), 6.81 (d, 2H, ArH), 7.26-7.85 (m, 2H, ArH and 1H, CH=N-); MS: m/z 301 [M^+ + 1]; Anal. Calcd (%) for $C_{15}H_{16}N_4O_3$: C, 60.00; H, 5.33; N, 18.67. Found: C, 60.12; H, 5.41; N, 18.55.

1,3-Dimethyl-5-(4-nitrophenyl)-5,8-dihydro-8H-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4e):

IR (KBr): ν 3255 (NH), 1700, 1650 (C=O), 1560 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.12(s, 3H, NCH_3), 3.44 (s, 3H, NCH_3), 5.58 (s, 1H), 6.42 (br, 1H, NH), 6.95-7.55 (m, 4H, ArH and 1H, CH=N-); MS: m/z 316 [M^+ + 1]; Anal. Calcd (%) for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.12; N, 22.22. Found: C, 53.42; H, 4.23; N, 22.08.

1,3-Dimethyl-5-(4-bromophenyl)-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4f):

IR (KBr): ν 3260 (NH), 1695, 1655 (C=O), 1560 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.18 (s, 3H, NCH_3), 3.58 (s, 3H, NCH_3), 5.61 (s, 1H), 6.45 (br, 1H, NH), 7.05-7.66 (m, 4H, ArH and 1H, CH=N-); MS: m/z 350 [M^+ + 1]; Anal. Calcd (%) for $C_{14}H_{13}N_4O_2Br$: C, 48.13; H, 3.72; N, 16.04. Found: C, 48.22; H, 3.85; N, 15.94.

1,3-Dimethyl-5-thiophen-2-yl-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4g):

IR (KBr): ν 3320 (NH), 1685, 1650 (C=O), 1560 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H, NCH_3), 3.60 (s, 3H, NCH_3), 5.45 (s, 1H), 6.35 (br, 1H, NH), 6.75 (dd, 1H), 6.95-7.15 (m, 2H), 7.65 (s, 1H, CH=N-); MS: m/z 277 [M^+ + 1]; Anal. Calcd (%) for $C_{12}H_{12}N_4O_2S$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.23; H, 4.26; N, 20.36.

1,3-Dimethyl-5-butyl-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4h):

IR (KBr): ν 3310 (NH), 1700, 1655 (C=O), 1560 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3), 1.25 (m, 6H), 3.15 (s, 3H, NCH_3), 3.45 (s, 3H, NCH_3), 5.45 (s, 1H), 6.40 (br, 1H, NH), 7.65 (s, 1H, CH=N-); MS: m/z 251 [M^+ + 1]; Anal. Calcd (%) for $C_{12}H_{18}N_4O_2$: C, 57.60; H, 7.20; N, 22.40. Found: C, 57.52; H, 7.32; N, 22.47.

1,3-Dimethyl-5-styryl-5,8-dihydro-8*H*-pyrimido[4,5-*d*]pyrimidine-2,4-dione (4i):

IR (KBr): ν 3270 (NH), 1695, 1645 (C=O), 1565 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.22 (s, 3H, NCH_3), 3.55 (s, 3H, NCH_3), 5.50 (s, 1H), 6.40 (br, 1H, NH), 6.66-7.65 (m, 7H, ArH, CH=CH and 1H, CH=N-); MS: m/z 297 [M^+ + 1]; Anal. Calcd (%) for $C_{16}H_{16}N_4O_2$: C, 64.86; H, 5.40; N, 18.92. Found: C, 64.93; H, 5.43; N, 18.83.

Chapter 4

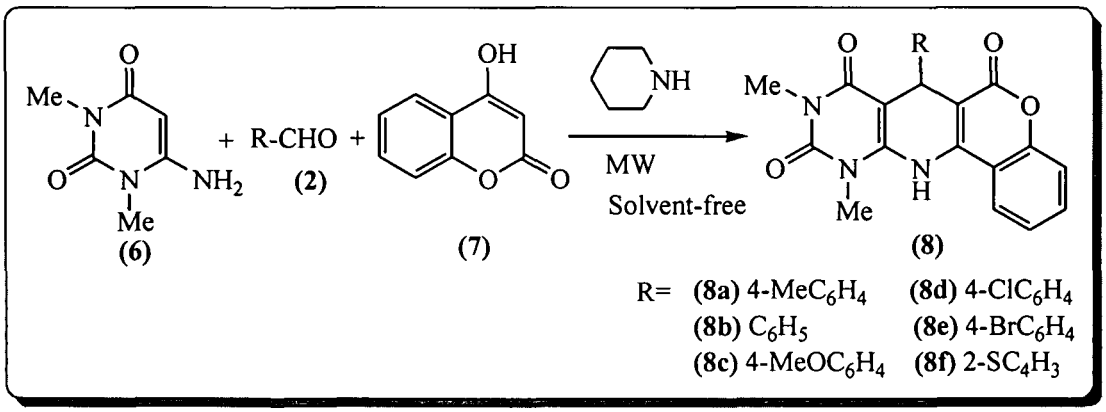
Section B:

Synthesis of Novel Tetracyclic Dihydropyrido[2,3-*d*] Pyrimidine Derivatives under Solvent-Free Conditions

4.B.1 Introduction:

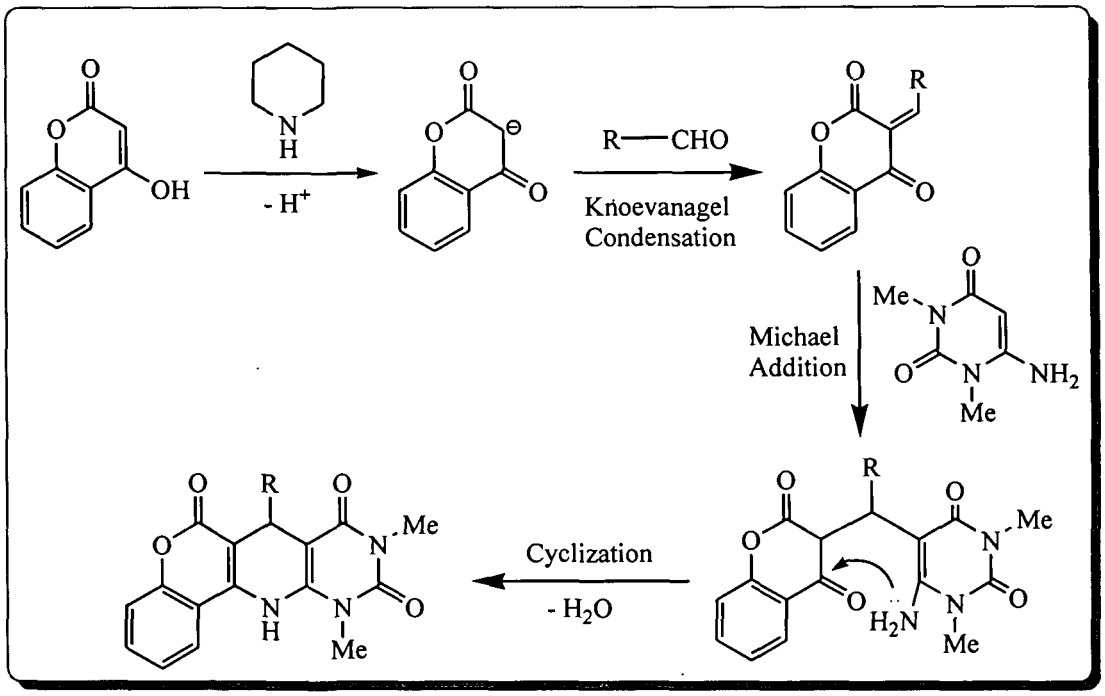
Pyrimidines and fused pyrimidines represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activities.[24-26] Among them Pyrido[2,3-*d*]pyrimidines are important class of annulated uracils showing biological significance.[27] Compounds with this ring system have antitumor,[28] anticancer,[29] bhronchiodilator,[30] vasodilator,[30] antiallergic,[31] antihypertensive,[32] cardiotonic[32] and hepatoprotective activity.[32] Some of them exhibit antifungal,[33] antimalarial[34] and analgesic[35] properties. Synthesis of this ring system is well documented;[36] but the synthetic methods usually require drastic reaction condition, long reaction time and complex synthetic pathways. Although a few new routes for the synthesis of some annulated uracils based on [4+2] cycloaddition[37] have been reported, these reactions have some limitations. In order to develop highly expedient method for the synthesis of annulated uracil libraries, we report herein a novel three-component one-pot synthesis of various tetracyclic dihydropyrido[2,3-*d*]pyrimidines under microwave irradiations in solvent-free condition.

4.B.2 Results and discussion:



Scheme 4.B.1

Treatment of 6-amino1,3-dimethyluracil (**6**) with an equimolar amount of tolualdehyde (**2a**) and 4-hydroxycoumarin (**7**) in presence of pipyridine under microwave irradiation (Catalyst Systems microwave reactor) at 90 °C for 2 min in solvent-free condition gave, after elimination of water, the corresponding dihydropyrido[2,3-*d*]pyrimidine derivative (**8a**) as the only product with 72% yield and there was no evidence for the formation of any other side products. The reaction is lesser effective under thermal condition upto 130 °C for 3 h, which gave only 30% yield of dihydropyrido[2,3-*d*]pyrimidine derivative. Further increase in temperature did not improve the yield; rather decomposition of starting material occurred.

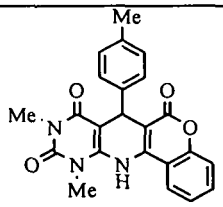
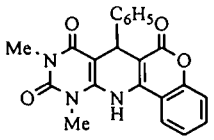
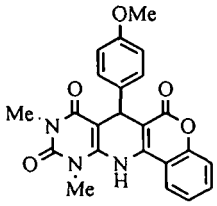
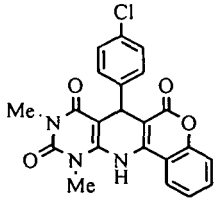
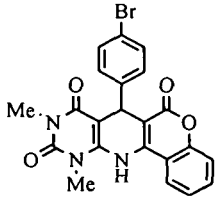
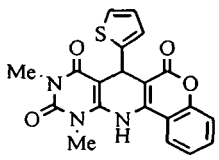


Scheme 4.B.2: Plausible mechanism of the reaction

The structure of the compound (**8a**) as a dihydropyrido[2,3-*d*]pyrimidine was confirmed on the basis of spectroscopic data and elemental analysis. Typically in ^{1}H NMR spectrum, the alkenic proton at 4.9 for H-5 of uracil was absent in the final product (**8a**). Appearance of a signal at δ 5.50 ppm (1H, sp^3-C-5) as singlet clearly showed that cycloaddition occurred at azadiene moiety. Also, ^{1}H NMR spectrum showed the appearance of other signal at 3.20 (s, 3H, NH_3), 3.52 (s, 3H, NH_3), 2.35 (s, 3H, CH_3), 6.45 (br, 1H, NH) and 6.94-7.63 (m, 8H, ArH). The mass spectrum revealed a strong molecular ion peak (m/z) at 402 [M^+ + 1]. These data were supported by IR

values at 3264 (NH), 1695, 1678, 1651 (C=O), 1150, 1065 (C-O) cm^{-1}. The reaction is generalised with various aromatic and heterocyclic aldehydes and isolated the corresponding dihydropyrido[2,3-*d*]pyrimidines in 69-75% yield. Aliphatic aldehydes did not perform well.

Table 4.B.1: Physical characteristics of Dihydropyrido[2,3-*d*]pyrimidine derivatives

Entry	Ar	Time (min)	Product	% Yield[a, b]	Mp (°C)
1	4-MeC_6H_4	2		72	142-145
2	C_6H_5	3		70	220-223
3	4-$OMeC_6H_4$	3		71	136-139
4	4-ClC_6H_4	3		73	225-228
5	4-BrC_6H_4	2		75	229-231
6	2-SC_4H_3	3		69	184-187

[a] Isolated yield. [b] All products are characterised by ^1H NMR, IR, MS and CHN analysis

4.B.3 Conclusion:

We have described a novel, efficient and one-pot synthesis of dihydropyrido[2,3-*d*]pyrimidine derivatives via a three component cyclocondensation reaction of 6-amino-1,3-dimethyluracil, aromatic aldehydes and 4-hydroxycoumarin under solvent-free microwave irradiations in almost quantitative yield. The results demonstrated that microwave assisted reaction allow easy and rapid access to novel heterocycles and reduce reaction times from hours to minutes with improved yields.

4.B.4 Experimental:

4.B.4.1 General procedure for the synthesis of Dihydropyrido[2,3-*d*] pyrimidine derivatives (8) by the reaction of 6-amino-1,3-dimethyluracil (6) with aldehyde (2) and 4-hydroxycoumarin (7):

An equimolar amount of 6-amino-1,3-dimethyluracil (1 mmol), tolualdehyde **(2a)** (1 mmol), 4-hydroxy coumarin (1 mmol) in presence of pipyridine (0.1 mmol) were mixed well and irradiated by microwave radiation about 2 min at 90 °C. After completion of the reaction (monitored by TLC) the reaction vessel was allowed to cool to r.t. and added 30 mL of cold water. The crude product was extracted with $CHCl_3$ (30×3 mL) and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4 and subjected to column chromatography using EtOAc-hexane (4:1) as the eluent to afford the corresponding dihydropyrido[2,3-*d*]pyrimidine **(8a)** in 72% yield. The other dihydropyrido[2,3-*d*]pyrimidines **(8b-f)** were prepared in a similar manner.

4.B.4.2 Spectral and elemental data of Dihydropyrido[2,3-*d*] pyrimidine derivatives (8a-f):

1,3-Dimethyl-5-(4-methylphenyl)-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*] pyrimidine-2,4-dione (8a):

IR (KBr): ν 3256 (NH), 1689, 1667, 1645 (C=O), 1142, 1059 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H, NH_3), 3.52 (s, 3H, NH_3), 2.35 (s, 3H, CH_3), 5.50 (s, 1H),

6.45 (br, 1H, NH), 6.94-7.63 (m, 8H, ArH); MS: m/z 402 [M^+ + 1]; Anal. Calcd (%) for $C_{23}H_{19}N_3O_4$: C, 68.85; H, 4.74; N, 10.48. Found: C, 68.72; H, 4.88; N, 10.41.

1,3-Dimethyl-5-phenyl-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine-2,4-dione (8b):

IR (KBr): ν 3262 (NH), 1690, 1670, 1648 (C=O), 1145, 1061 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.30 (s, 3H, NCH_3), 3.58 (s, 3H, NCH_3), 5.65 (s, 1H), 6.53(br, 1H, NH), 7.06-7.68 (m, 9H, ArH); MS: m/z 388 [M^+ + 1]; Anal. Calcd (%) for $C_{22}H_{17}N_3O_4$: C, 68.24; H, 4.39; N, 10.85. Found: C, 68.30; H, 4.42; N, 10.74.

1,3-Dimethyl-5-(4-methoxyphenyl)-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*] pyrimidine-2,4-dione (8c):

IR (KBr): ν 3264 (NH), 1695, 1678, 1651 (C=O), 1150, 1065 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.25 (s, 3H, NCH_3), 3.57 (s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 5.60 (s, 1H), 6.49 (br, 1H, NH), 6.65-7.67 (m, 8H, ArH); MS: m/z 418 [M^+ + 1]; Anal. Calcd (%) for $C_{23}H_{19}N_3O_5$: C, 66.21; H, 4.55; N, 10.07. Found: C, 66.14; H, 4.60; N, 10.02.

1,3-Dimethyl-5-(4-chlorophenyl)-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*] pyrimidine-2,4-dione (8d):

IR (KBr): ν 3267 (NH), 1699, 1682, 1655 (C=O), 1155, 1068 (C-O) cm^{-1}; ^1H NMR (400 MHz $CDCl_3$): δ 3.27 (s, 3H, NCH_3), 3.67 (s, 3H, NCH_3), 5.60 (s, 1H), 6.51 (br, 1H, NH), 7.00-7.70 (m, 8H, ArH); MS: m/z 422.5 [M^+ + 1]; Anal. Calcd (%) for $C_{22}H_{16}N_3O_4Cl$: C, 62.66; H, 3.79; N, 9.97. Found: C, 62.60; H, 3.85; N, 9.94.

1,3-Dimethyl-5-(4-bromophenyl)-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*] pyrimidine-2,4-dione (8e):

IR (KBr): ν 3264 (NH), 1697, 1680, 1652 (C=O), 1152, 1065 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.23 (s, 3H, NCH_3), 3. 62 (s, 3H, NCH_3), 5.65 (s, 1H), 6.49 (br, 1H, NH), 6.95-7.68 (m, 8H, ArH); MS: m/z 467 [M^+ + 1]; Anal. Calcd (%) for $C_{22}H_{16}N_3O_4Br$: C, 56.68; H, 3.43; N, 9.02. Found: C, 56.70; H, 3.48; N, 8.92.

1,3-Dimethyl-5-thiophen-2-yl-5,8-dihydro-coumarino[3′,4′:5,6]pyrido[2,3-*d*] pyrimidine-2,4-dione (8f):

IR (KBr): ν 3325 (NH), 1690, 1675, 1655 (C=O), 1147, 1062 (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (s, 3H, NCH_3), 3.65 (s, 3H, NCH_3), 5.50 (s, 1H), 6.40 (br, 1H,

NH) 6.72 (dd, 1H), 6.91-7.20 (m, 2H), 7.20-7.66 (m, 4H, ArH); MS: m/z 394 [M^+ + 1]; Anal. Calcd (%) for $C_{20}H_{15}N_3O_4S$: C, 61.08; H, 3.81; N, 10.69. Found: C, 61.01; H, 3.89; N, 10.62.

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Chapter 5

Aza-Michael Addition of Amines to α,β-Unsaturated Compounds using Molecular Iodine as Catalyst

Chapter 5

5.1 Introduction:

Aza-Michael addition is widely recognised as one of the most important carbon-nitrogen bond forming reactions, leading to the formation of β-amino carbonyl compound by 1,4-addition[1] (Scheme 5.1) of aza nucleophile to α,β-unsaturated carbonyl compound. β-amino carbonyl compounds have been considered not only as building unit of biologically important natural products including β-lactam, but also versatile nitrogen containing intermediate such as β-amino alcohol, β-amino acids, β-lactam antibiotics and 1,2-diamines.[2] Among the methods for generating β-amino carbonyl compounds, the Mannich reaction is a classical method for the preparation of these derivatives. The conjugate addition of nitrogen nucleophiles to an unsaturated system requires either basic or acid catalysis.[3] Lewis acid catalysts, such as $SnCl_4$, $AlCl_3$ or $TiCl_4$, etc. have been employed to effect this addition, but their use in stoichiometric amounts often poses severe environmental problem in waste streams. Several groups have reported[4] sub-stiochiometric use of some Lewis acids such as $InCl_3$, $Bi(NO_3)_2$, $Cu(OTf)_2$, $Bi(OTf)_2$, $LiClO_4$ and hydrated $CeCl_3$-NaI supported on silica gel or clay over the last few years.

Molecular iodine and compounds containing iodine are important in the field of chemistry and biology because of their application as intermediates, in protection and deprotection chemistry and are very useful in medicine. The Lewis acidity of iodine is prime in its behaviour as a catalyst.[5] Organic chemistry has witnessed many beautiful applications of molecular iodine in synthesis,[6] e.g. dehydration of secondary alcohols to alkenes,[7a] in the synthesis of alkyl benzyl ethers,[7b] in the synthesis of mixed ethers[7c] and in iodolactonisation. Molecular iodine has received considerable attention in organic chemistry because it is inexpensive and readily available, less toxic than alternatives, moisture stable, mild acid, has easy work up method and simplicity in procedure. Many reactions can be carried out under mild conditions within short reaction period and greater stereo and regioselectivities can be obtained.

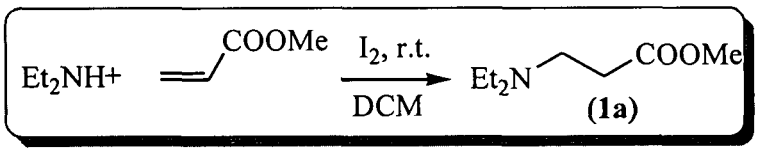
Part of this work is published in

Synth. Commun. **40**, 2830-2836 (2010)

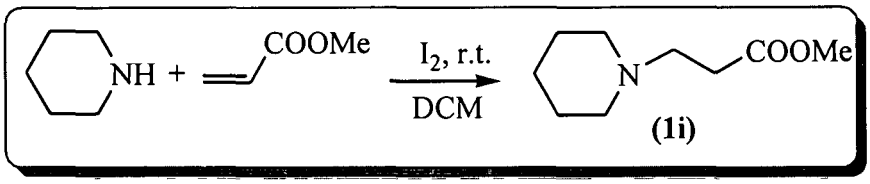
Chapter 5

In this chapter, we report the catalytic activity of iodine on the conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds in organic solvents as well as in neat condition.

5.2 Results and discussion:



Scheme 5.1a



Scheme 5.1b

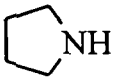
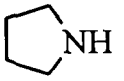
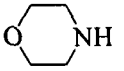
Initially, we studied the solvent effect for the conjugate addition of diethylamine to acrylonitrile as a model reaction in different solvents at room temperature using molecular iodine as catalyst. The results are summarised in Table 5.1.

Table 5.1: Effect of solvents on aza-Michael addition of diethylamine to acrylonitrile using molecular iodine as catalyst

Entry	Solvents	Time (min)	%Yield Product (1b)
1	C_2H_5OH	40	85
2	CH_3CN	60	81
3	THF	70	75
4	H_2O	120	80
5	CH_2Cl_2	15	92
5	$CHCl_3$	20	89

From the above results it is clear that, as the solvent varies from polar to non polar, the reaction takes lesser time for conversion to the product with good yield. The catalytic activity of iodine was found to be more in dichloromethane. Molecular iodine is highly soluble in non-polar organic solvents due to its lack of polarity. But it is slightly soluble in water. The studies were extended in neat condition at room temperature using molecular iodine as catalyst for addition of acyclic and cyclic aliphatic amines to α,β-unsaturated compounds. The results are summarised in Table 5.2. Under this reaction condition, addition of diethylamine to acrylonitrile gave only 65% yield at 85 min. Similarly cyclic aliphatic amines took longer time with moderate conversion.

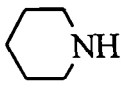
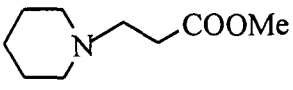
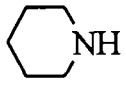
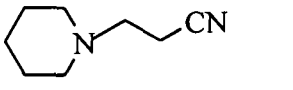
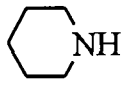
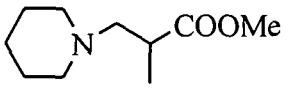
Table 5.2: Aza-Michael reaction in neat condition at room temperature stirring using molecular iodine as catalyst

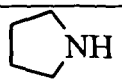
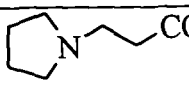
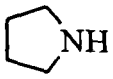
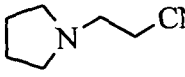
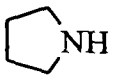
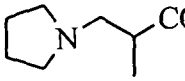
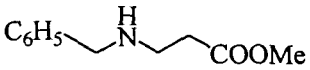
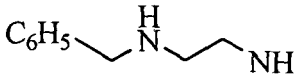
Entry	Amine	Alkene	Time (min)	Product	% Yield of Product
1	Et_2NH		85	(1b)	65
2			95	(1l)	70
3			110	(1m)	65
4			45	(1y)	75

After the above studies we carried out the addition of aliphatic amine to α,β-unsaturated system in dichloromethane at room temperature in presence of molecular iodine as catalyst. In a typical procedure, treatment of 0.1 mmol of iodine with a mixture of diethylamine (3 mmol) and methylacrylate (3.3 mmol) in dichloromethane (3 ml) at ambient temperature gave the corresponding β-aminocarbonyl compound in 93% yield within 15 min. The same reaction was done at room temperature in absence of iodine and after 5 h, 60% of β-aminocarbonyl compound was isolated. Various acyclic and cyclic aliphatic amines showed excellent 1,4-addition with a range of α,β-unsaturated compounds to gave the corresponding adducts (Table 5.3). The reaction

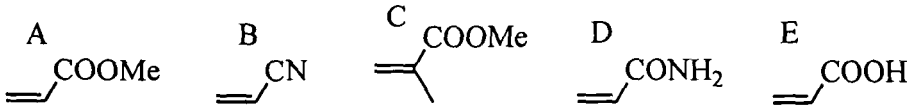
completed within 15-40 min for secondary aliphatic amine with methylacrylate, acrylonitrile and methylmerthacrylate. However, with the primary amine (Table 5.3, entries 5, 6, 17, 18), the reaction was sluggish and took more reaction time (2.5-3 hr). This protocol of aza-Michael addition was inactive for nucleophilic addition of aliphatic amine to acryl amide and acrylic acid (Table 5.3, enries 4, 10).

Table 5.3: I_2 catalyzed aza-Michael addition of aliphatic amine in dichloromethane at ambient temperature

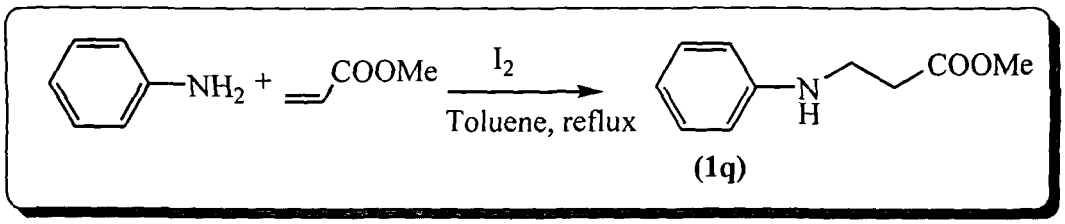
Entry	Amine	Olefin	Time min/[h]	Product		% Yield [a,b]
1	Et_2NH	A	15	Et_2N–COOMe	(1a)	93
2	Et_2NH	B	15	Et_2N–CN	(1b)	92
3	Et_2NH	C	25	Et_2N–CH(COOMe)–CH$_3$	(1c)	89
4	Et_2NH	E	[48]	NR		NA
5	n-$BuNH_2$	A	[3]	n-BuHN–COOMe	(1d)	86
6	n-$BuNH_2$	B	[3]	n-BuHN–CN	(1e)	85
7	$(iPr)_2NH$	A	40	$(iPr)_2N$–COOMe	(1f)	82
8	$(iPr)_2NH$	B	20	$(iPr)_2N$–CN	(1g)	90
9	$(iPr)_2NH$	C	30	$(iPr)_2N$–CH(COOMe)–CH$_3$	(1h)	87
10	$(iPr)_2NH$	D	[48]	NR		NA
11		A	20		(1i)	85
12		B	15		(1j)	90
13		C	30		(1k)	91

14		A	15		(1l)	89
15		B	15		(1m)	90
16		C	25		(1n)	91
17	$C_6H_5CH_2NH_2$	A	150		(1o)	75
18	$C_6H_5CH_2NH_2$	B	150		(1p)	70

[a] All the products were characterized by ^{1}H NMR, IR and MS and elemental analysis. [b] Isolated yields



In order to extend the scope of this methodology, we tested the catalytic activity of iodine for addition of aniline and methyl acrylate (Scheme 5.2). At room temperature no addition occurred, however in refluxing toluene the reaction went satisfactorily. We generalised the reaction with other aromatic amines and results are summarized in Table 5.4. The presence of nitro group decreases the nucleophilic character of aniline because of which it becomes inactive for addition reaction across the, α,β-unsaturated system (Table 5.4, entries 3, 4). With electron donating group in aniline the nucleophilic addition shows good to moderate results (Table 5.4, entries 5, 6, 7). Interestingly, aza-Michael addition of imidazole gave moderate yield under reflux (Table 5.4 entries 8, 9, 10) in toluene for longer reaction period.



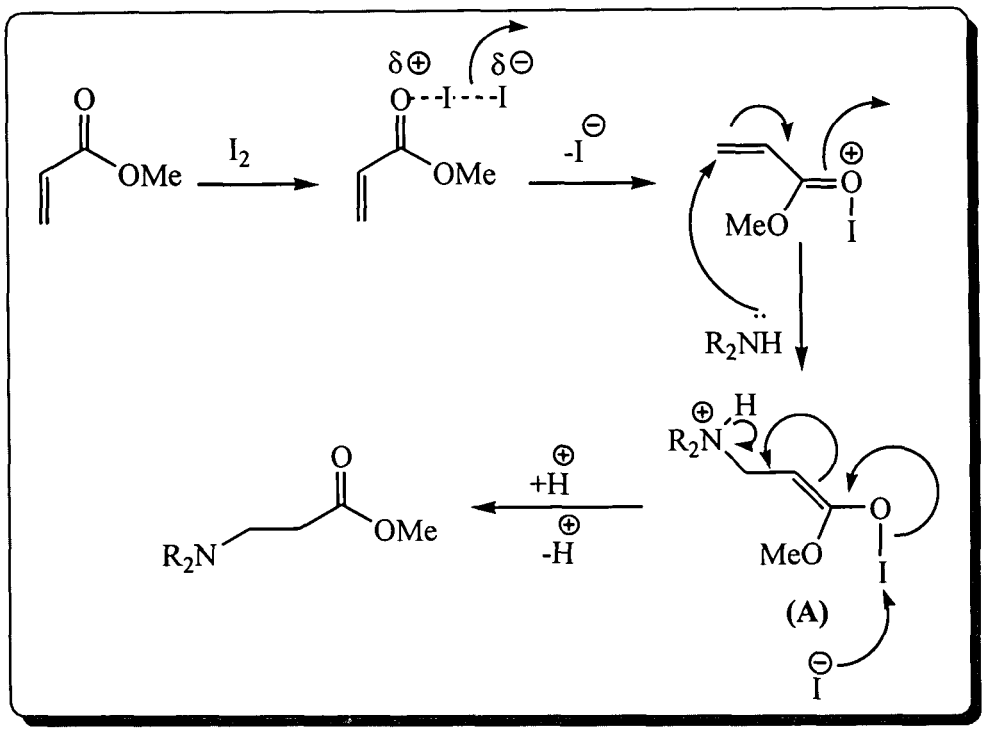
Scheme 5.2

Table 5.4: I_2 catalyzed aza-Michael addition of aromatic amine under reflux condition using toluene as solvent

Entry	Amine	Olefin	Time (h)	Product		% Yield[a,b]
1	$C_6H_5NH_2$	A	7	C_6H_5HN–COOMe	(1q)	70
2	$C_6H_5NH_2$	B	8	C_6H_5HN–CN	(1r)	65
3	O_2N–NH_2	A	20	NR		NA
4	NO_2, NH_2	A	20	NR		NA
5	MeO–NH_2	A	7	MeO–N(H)–COOMe	(1s)	85
6	MeO–NH_2	B	8	MeO–N(H)–CN	(1t)	65
7	Cl–NH_2	A	9	Cl–N(H)–COOMe	(1u)	60
8	H, N, N	A	9	N, N–COOMe	(1v)	50
9	H, N, N	B	10	N, N–CN	(1w)	48
10	H, N, N	C	12	N, N–CH(COOMe)–CH$_3$	(1x)	49

[a] All the products were characterized by ^{1}H NMR, IR and MS and elemental analysis. [b] Isolated yields

The possible mechanism (Scheme 5.3) involves with the activation of carbonyl group of α,β-unsaturated ester in presence of iodine for nucleophilic addition of amino compound to form the positive charge containing Michael adduct (A). Removal of iodine followed by protonation generates the addition product.



Scheme 5.3: Plausible mechanism of iodine catalysed aza-Michael addition

5.3 Conclusion:

In conclusion, we have developed a mild and efficient aza-Michael addition of aliphatic and aromatic amines to α,β-unsaturated compounds in organic solvent using molecular iodine as catalyst. The solvent studies revealed the use of water as reaction medium for this reaction with longer reaction time. The advantages of this method include excellent yield, simple workup procedure, product selectivity; cheaper catalyst, short reaction time for aliphatic aldehyde and most importantly moderate to good reactivity towards aromatic amine at high temperature in toluene.

5.4 Experimental:

General:

All reactions were monitored by thin-layer chromatography using silica gel. The products were characterized by FT-IR, ^{1}H NMR, mass spectra, elemental analysis and also compared with authentic samples.[4(e),8] The starting chemicals were obtained from commercial suppliers and used without further purification.

5.4.1 General procedure for the synthesis of β-amino carbonyl compound:

5.4.1.1 Iodine catalyzed aza-Michael addition of aliphatic amine in dichloromethane/neat condition:

A mixture of aliphatic amine (3 mmol), α,β-unsaturated compound (3.3 mmol) and I_2 (0.1 mmol) in 3 ml of dichloromethane (or neat condition) was stirred at ambient temperature for a definite period. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with 10 ml of distilled water and washed with an aqueous solution of sodium thiosulfate for removal of iodine. Then the mixture was extracted with dichloromethane (3×10 ml). The dichloromethane extracts were dried over anhydrous sodium sulfate and removed in rotary evaporator under reduced pressure. The crude reaction mixture was further purified by silica gel column chromatography with different ratios of n-hexane and ethyl acetate as solvent system. The product was isolated in pure form.

5.4.1.2 Iodine catalyzed aza-Michael addition of aromatic amine in toluene:

A mixture of aromatic amine (3 mmol), α,β-unsaturated compound (3.3 mmol) and I_2 (0.1 mmol) in toluene (3 ml) was refluxed at 110 °C for a definite period. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with 10 ml of distilled water and washed with an aqueous solution of sodium thiosulfate for removal of iodine. Then the mixture was extracted with ethyl acetate (3×10 ml). The ethyl acetate extracts were dried over anhydrous sodium sulfate and removed in rotary evaporator under reduced pressure. The crude reaction mixture was further purified by silica gel column chromatography with different ratio of n-hexane and ethyl acetate as solvent system. The product was isolated in pure form.

5.4.2 Spectral and elemental data:

Methyl-3-(*N*, *N*-Diethylamino)-Propionate (1a): oil

IR (KBr): ν 2970, 2813, 1740, 1630, 1564, 1439, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.65 (s, 3H), 2.77 (t, J = 7.2 Hz, 2H), 2.54 (q, J = 7.3 Hz, 4H), 2.49 (t, J = 7.2

Hz, 2H), 0.98 (t, J = 7.3 Hz, 6H); GC-MS: m/z 160, 159, 144, 130, 102, 86 (100), 72, 58, 42; Anal. Calcd (%) for $C_8H_{17}NO_2$: C, 60.38; H, 10.69; N, 8.81. Found: C, 60.45; H, 10.75; N, 8.84.

3-(*N, N*-Diethylamino)-Propionitrile (1b): oil

IR (neat): ν 2969, 2916, 2247, 1630, 1462, 1378 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.76 (t, J = 7.0 Hz, 2H), 2.40 (q, J = 7.3 Hz, 4H), 2.30 (t, J = 7.0 Hz, 2H), 0.92 (t, J = 7.3 Hz, 6H); MS (EI-70eV): m/z 127 [M^+ + 1]; Anal. Calcd (%) for $C_7H_{14}N_2$: C, 66.67; H, 11.11; N, 22.22. Found: C, 66.72; H, 11.20; N, 22.30.

Methyl-3-(*N, N*-Diethylamino)-2-Methyl-Propionate (1c): oil

IR (neat): ν 2972, 2917, 1736, 1628, 1440 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.72-2.74 (m, 1H), 2.68-2.70(m, 2H), 2.56 (q, J = 7.2 Hz, 4H), 1.22 (d, J = 6.9 Hz, 3H), 1.12 (t, J = 7.2 Hz, 6H); Anal. Calcd (%) for $C_9H_{19}NO_2$: C, 62.43; H, 10.98; N, 8.09. Found: C, 62.50; H, 11.01; N, 7.99.

Methyl-3-Butylaminopropionate (1d): oil

IR (neat): ν 3410, 2962, 2873, 1738, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.92 (t, J = 7.2 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 1.46-1.51 (m, 2H), 1.35-1.38 (m, 2H), 1.1 (t, J = 7.5 Hz, 3H); Anal. Calcd (%) for $C_8H_{17}NO_2$: C, 60.38; H, 10.69; N, 8.81. Found: C, 60.42; H, 10.74; N, 8.86.

3-Butylaminopropionitrile (1e): oil

IR (neat): ν 3440, 2960, 2916, 2253, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.92(t, J = 6.65 Hz, 2H), 2.59 (t, J = 7.15 Hz, 2H), 2.5 (t, J = 6.64 Hz, 2H), 1.43-1.47 (m, 2H), 1.33-1.37 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H); MS (EI-70eV): m/z 127 [M^+ + 1]; Anal. Calcd (%) for $C_7H_{14}N_2$: C, 66.67; H, 11.11; N, 22.22. Found: C, 66.72; H, 10.99; N, 22.25.

Methyl-3-(*N,N*-Diisopropylamino)-Propionate (1f): semi solid

IR(KBr): ν 2934, 2812, 1725, 1347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.46 (s, 3H), 2.67 (hept, J = 6.5 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.2 Hz, 2H), 0.89 (d, J = 6.5 Hz, 12H); Anal Calcd (%) for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.23; N, 7.49. Found: C, 64.28; H, 11.40; N, 7.60.

3-(*N, N*-Diisopropylamino)-Propionitrile (1g): oil

IR (neat): ν 2980, 2934, 2245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.79 (hept, J = 6.3 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 1.03 (d, J = 6.3 Hz, 12H); Anal. Calcd (%) for $C_9H_{18}N_2$: C, 70.13; H, 11.69; N, 18.18. Found: C, 69.98; H, 11.77; N, 18.23.

Methyl-3-(*N,N*-Diisopropylamino)-2-Methyl-Propionate (1h): oil

IR (neat): ν 2936, 2917, 1738, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.80 (m, 2H), 2.72-2.75 (m, 2H), 2.68-2.70 (m, 1H), 1.25 (d, J = 7.1 Hz, 3H) ,1.07(d, J = 6.2 Hz, 12H); Anal. Calcd (%) for $C_{11}H_{23}NO_2$: C, 65.67; H, 11.44; N, 6.97. Found: C, 65.69; H, 11.55; N, 7.01.

Methyl -3-Piperidinyl-Propionate (1i): oil

FTIR (neat): ν 2936, 2856, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H), 2.62 (t, J = 8.0 Hz, 2H), 2.45 (t, J = 8.0 Hz, 2H), 2.32-2.34 (m, 4H), 1.55-1.34 (m, 6H); MS (EI-70eV): m/z 172 [M^+ + 1]; Anal. Calcd (%) for $C_9H_{17}NO_2$: C, 63.16; H, 9.94; N, 8.19. Found: C, 63.19; H, 9.97; N, 8.25.

(3-Piperidinyl)-Propionitrile (1j): oil

IR (neat): ν 2934, 2857, 2806, 2244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.65-2.70 (m, 2H), 2.51(m, 2H) 2.43(m, 4H), 1.55-1.57(m, 4H), 1.44 (m, 2H); MS (EI-70eV): m/z 139 [M^+ + 1]; Anal. Calcd (%) for $C_8H_{14}N_2$: C, 69.57; H, 10.14; N, 20.29. Found: C, 69.62; H, 10.22; N, 20.34.

Methyl-(2-Methyl-3-Piperidinyl)-Propionate (1k): oil

IR (neat): ν 2934, 2855, 2995, 1744, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.64-2.68 (m, 1H), 2.56-2.60 (m, 2H), 2.32-2.38 (m, 4H), 1.53-1.56 (m, 4H), 1.37-1.42 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H); Anal. Calcd (%) for $C_{10}H_{19}NO_2$: C, 64.86; H, 10.27; N, 7.57. Found: C, 64.87; H, 10.29; N, 7.64.

Methyl -3-Pyrrolidinyl-Propionate (1l): oil

IR (neat): ν 3410, 2958, 2792, 1739, 1441, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 2.85 (t, J = 7.0 Hz, 2H), 2.58-2.62 (m, 6H), 1.18 (m, 4H); MS (EI-70eV): m/z = 158(M+1); Anal. Calcd (%) for $C_8H_{15}NO_2$: C, 61.15; H, 9.55; N, 8.92. Found: C, 61.28; H, 9.59; N, 8.95.

3-Pyrrolidinyl-Popionitrile (1m): oil

IR (KBr): ν 2961, 2800, 2248, 1739, 1630, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.79 (t, J = 7.6 Hz, 2H), 2.52 - 2.59 (m, 6H), 1.79-1.82 (m, 4H); GC-MS: m/z 124, 98, 84 (100), 56, 41, 27; Anal. Calcd (%) for $C_7H_{12}N_2$: C, 67.74; H, 9.67; N, 22.58. Found: C, 67.80; H, 9.60; N, 22.67.

Methyl (2-Methyl-3-Pyrrolidinyl)-Propionate (1n): oil

IR (neat): ν 3405, 2966, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 2.82-2.40 (m, 7H), 1.75 (m, 4H), 1.15 (d, J = 8.5 Hz, 3H); MS (EI-70eV) m/z 172 [M^+ + 1]; Anal. Calcd (%) for $C_9H_{17}NO_2$: C, 63.16; H, 9.94; N, 8.18. Found: C, 63.10; H, 9.85; N, 8.13.

Methyl-3-Benzylaminopropionate (1o): oil

IR (neat): ν 3378, 2979, 2830, 1734, 1600, 1495 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20-7.25 (m, 2H) 7.06-7.09 (m, 3H), 3.75 (s, 2H), 3.67 (s, 3H), 2.92-2.98 (t, J = 6.3 Hz, 2H), 2.56-2.63 (t, J = 6.3 Hz, 2H); Anal. Calcd (%) for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.42; H, 7.79; N, 7.20.

3-Benzylaminopropionitrile (1p): oil

IR (KBr): ν 3330, 3029, 2920, 2248, 1882, 1759, 1640, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24-7.33 (m, 5H), 3.81 (s, 2H), 2.88 (t, J = 6.3 Hz, 2H), 2.48 (t, J = 6.3 Hz, 2H) ; GC-MS: m/z 160, 134, 120, 91 (100), 83, 43, 29; Anal. Calcd (%) for $C_{10}H_{12}N_2$: C, 75; H, 7.5; N, 17.5. Found: C, 74.90; H, 7.56; N, 17.40.

Methyl-3-Phenylaminopropionate (1q): oil

IR (neat): ν 3377, 2929, 2727, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16-7.23 (m, 2H), 6.67 (m, 1H), 6.63 (d, J = 7.7 Hz, 2H), 4.00 (br, 1H), 3.68 (s, 3H), 3.47 (t, J = 6.5 Hz, 2H), 2.65 (t, J = 6.5 Hz, 2H); MS (EI-70eV): m/z 180 [M^+ + 1); Anal. Calcd (%) for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82. Found: C, 66.90; H, 7.19; N, 7.70.

3-Phenylaminopropionitrile (1r): oil

IR (neat): ν 3356, 2960, 2926, 2245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.25 (m, 2H), 6.75-6.77 (m, 1H), 6.67-6.63 (d, J = 7.6 Hz, 2H), 4.00 (br, 1H), 3.47 (t, J = 6.5 Hz, 2H), 2.61 (t, J = 6.5 Hz, 2H); MS (EI-70eV): m/z 147 [M^+ + 1]; Anal. Calcd (%) for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.90; H, 6.76; N, 19.03.

Methyl-3-(4-Methoxyphenylamino)-Proprionate (1s): oil

IR (neat): ν 3363, 2927, 2830, 1735, 1626, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78-6.80 (d, J = 7.2 Hz, 2H), 6.54-6.59 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.65 (s, 3H), 3.48 (t, J = 6.5 Hz, 2H), 2.58 (t, J = 6.5 Hz, 2H); Anal. Calcd (%) for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.18; N, 6.70. Found: C, 63.22; H, 7.22; N, 6.74.

3-(4-Methoxyphenylamino)-propionitrile (1t): oil

IR (neat): ν 3357, 2959, 2828, 2243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.45 (t, J = 6.5 Hz, 2H), 2.62 (t, J = 6.5 Hz, 2H); MS (EI-70eV): m/z 177 [M^+ + 1]; Anal. Calcd (%) for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.82; N, 14.20. Found: C, 68.03; H, 6.75; N, 14.12.

Methyl-3-(4-Chlorophenylamino)-Proprionate (1u): oil

IR (neat): ν 2928, 2833, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24-7.26 (d, J = 6.9 Hz, 2H), 6.42-6.45 (d, J = 6.9 Hz, 2H), 3.66 (s, 3H), 3.47 (t, J = 6.2 Hz, 2H), 2.52 (t, J = 6.2 Hz, 2H); Anal. Calcd (%) for $C_{10}H_{12}NO_2$: C, 56.21; H, 5.62; N, 6.56. Found: C, 55.98; H, 5.56; N, 6.47.

Methyl- 3-(Imidazol-1-yl)-Propionate (1v): oil

IR (neat): ν 1732, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.05 (s, 1H), 6.93 (s, 1H), 4.27 (t, J = 6.6 Hz, 2H), 3.70 (s, 1H), 2.78 (t, J = 6.6 Hz, 2H); MS (EI-70eV): m/z 155 [M^+ + 1]; Anal. Calcd (%) for $C_7H_{10}N_2O_2$: C, 54.55; H, 6.49; N, 18.18. Found: C, 54.46; H, 6.38; N, 18.06.

3-Imidazol-1-yl-propionitrile (1w): oil

IR (neat): ν 2251, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.05 (s, 1H), 7.02 (s, 1H), 4.22 (t, J = 6.6 Hz, 2H), 2.84 (t, J = 6.6 Hz, 2H); MS: m/z 122 [M^+ + 1]; Anal. Calcd (%) for $C_6H_7N_3$: C, 59.50; H, 5.79; N, 34.71. Found: C, 59.41; H, 5.68; N, 34.62.

Methyl-(3-Imidazol-1-yl-2-Methyl)-Propionate (1x):

IR (neat): ν 2928, 1736, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 4.13 (m, 2H), 3.72 (s, 3H), 2.94-2.96 (m, 1H), 1.26 (d, J = 7.5 Hz, 3H); Anal. Calcd (%) for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.14; N, 16.67. Found: C, 57.24; H, 7.20; N, 16.72.

3-(Morpholine-1-yl) Propionitrile (1y): oil

IR (KBr): ν 2952, 2852, 2248, 1725,1639, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.7 (t, J = 4.4 Hz, 4H), 2.66 (t, J = 6.8 Hz, 2H), 2.47-2.52 (m, 6H); Anal. Calcd (%) for $C_7H_{12}N_2O$: C, 60.0; H, 8.57; N, 20.0. Found: C, 60.30; H, 8.72; N, 20.54.

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Chapter 6

Summary and Future Scope of the Present Work

Chapter 6

6.1 Summary:

- We have synthesised some oxygen and nitrogen containing building blocks of heterocyclic molecules of biological significances.
- We have employed some newer components of synthetic methodologies such as microwave assisted reactions, solvent-free conditions, heterogeneous (solid supported) catalysts and multi-component reactions.
- 1,3-dioxanes have been synthesised efficiently in presence of TsOH-SiO_2 under solvent-free microwave irradiation.
- 2,4-disubstituted tetrahydropyran ether derivatives have been obtained as single product in presence of PANI-TsOH/PANI-$FeCl_3$ by Prins cyclization of 3-butene-1-ol with aromatic aldehydes. Corresponding acetals were formed in case of *o*, *m*, *p*-nitrobezaldehydes.
- Three polymer supported Brønsted acids, namely P4VP-H_2SO_4, P4VP-HCl, P4VP-H_3PO_4 have been successfully synthesised, characterized and tested their catalytic activity for acetylation of various substrates having -OH and, -NH_2 functionality.
- Coumarin derivatives have been synthesised via Pechmann reaction using P4VP-H_2SO_4 as a simple, efficient and reusable catalyst under solvent-free microwave irradiation.
- Novel dihydropyrimido[4,5-*d*]pyrimidine and dihydropyrido[2,3-*d*]pyrimidine derivarives have been synthesised under solvent-free conditions employing one-pot multi-component cycloaddition strategy.
- Molecular iodine has been successfully used as simple, mild and efficient Lewis acid catalyst for aza-Michael addition of different aliphatic and aromatic amines to α,β-unsaturated compounds.
- Throughout our work, the greener components such as simplicity in procedure, milder reaction condition, enhancement in reaction rates, higher yields and selectivity and reusability of catalysts were envisaged.

6.2 Future scope:

- The compounds we have synthesised, i.e. 1,3-dioxanes, 2,4-disubstituted tetrahydropyran derivatives, acetals, coumarins, β-amino carbonyl compounds can be used as building unit for the construction of heterocyclic molecules of biological significances.
- There is scope for biological testing of the novel dihydropyrimido[4,5-*d*]pyrimidine and dihydropyrido[2,3-*d*]pyrimidine derivatives. There is possibility of using these pyrimidine derivatives for construction of libraries of complex heterocyclic molecules.
- The poly(4-vinylpyridine) supported Brønsted acid catalysts, that we have synthesised can be employed for various organic transformations. There is scope for preparation of other new poly(4-vinylpyridine) supported catalysts.
- We have developed the synthetic methodologies of the aforesaid compounds to some extent within our limitations. There is still scope for improvement in terms of Green Chemistry.

Appendix I:

List of Published/Accepted/Communicated Research Papers:

1. **Borah, K. J.;** Borah, R. Poly(4-vinylpyridine) supported sulphuric acid as efficient reusable catalyst for the Pechmann coumarin synthesis under solvent-free microwave method, *Monatsh. Chem* (under revision)
2. **Borah, K. J.;** Borah, R. Investigation of Prins reaction for the synthesis of 2,4-disubstituted tetrahydropyran derivatives and 1,3-dioxanes using polyaniline supported acid as reusable catalyst, *J. Chem. Sci* (accepted for publication)
3. **Borah, K. J.;** Dutta, P.; Borah, R. Synthesis, characterization and application of poly(4-vinylpyridine) supported Brønsted acid as reusable catalyst for acetyation reaction, *Bull. Korean Chem. Soc.* **32**, 225-228 (2011)
4. Sharma, R.; **Borah, K. J.;** Dommaraju, Y.; Prajapati, D. Unexpected deviation from diene behavior of uracil amidine: towards synthesis of some pyrido[2,3-*d*]pyrimidine derivatives, *Molecular Diversity* (Published online-25 November, 2010)
5. **Borah, K. J.;** Phukan, M.; Borah, R. Aza-Michael addition of amines to α,β-unsaturated compounds using molecular iodine as catalyst, *Synth. Commun.* **40**, 2830-2836 (2010)
6. Phukan, M.; **Borah, K. J.;** Borah, R. Henry reaction in environmentally benign methods using imidazole as catalyst, *Green Chem. Lett. Rev.* **2**, 249-253 (2009)
7. **Borah, K. J.;** Phukan, M.; Borah, R. Synthesis of 1,3-dioxanes catalysed by TsOH-SiO_2 under solvent-Free conditions, *Synth. Commun.* **38**, 3082- 3087 (2008)
8. Phukan, M.; **Borah, K. J.;** Borah, R. Imidazole catalysed Henry reactions in aqueous medium, *Synth. Commun.* **38**, 3068-3073 (2008)
9. Prajapati, D.; **Borah, K. J.** The tert-amino effect in heterocyclic chemistry: Synthesis of new fused pyrazolinoquinolizine and 1,4-oxazinopyrazoline derivatives, *Beilstein Journal of Organic Chemistry* **3**, 43 (2007)
10. Prajapati, D.; **Borah, K. J.;** Gohain, M. An efficient regiospecific synthesis of highly functionalised novel dihydropyrimido[4,5-*d*]pyrimidine derivatives by a three-component one-pot condensation under solvent-free conditions, *Synlett* 0595-0598 (2007)

Appendix II:

List of Symposium/Seminar Papers:

1. 11th CRSI National Symposium in Chemistry, Feb 6-8, 2009 held at National Chemical Laboratory, Pune.

   Poster: Formation of tetrahydropyran derivatives via Prins cyclization using polyaniline supported acid as reusable catalyst. **Kalyan Jyoti Borah** and Ruli Borah.

2. 10th CRSI National Symposium in Chemistry, Feb 1-3, 2008 held at Indian Institute of Science (IISc), Bangalore.

   Poster: Investigation of Prins reaction of paraformaldehyde with substituted styrene. **Kalyan Jyoti Borah**, Mridula Phukan and Ruli Borah.

3. National Seminar on Green Chemistry and Natural Products, Nov 26-27, 2007 held at University of Delhi, Delhi-110007.

   Poster: Lewis base catalysed Henry reactions in aqueous medium. Mridula Phukan, **Kalyan Jyoti Borah** and Ruli Borah.

4. 9th CRSI National Symposium in Chemistry, Feb 1-4, 2007 held at Department of Chemistry, University of Delhi, Delhi-110007.

   Poster: Multi-component one-pot synthesis of novel tetracyclic dihydropyrido [2,3-*d*]pyrimidine derivatives. **Kalyan Jyoti Borah** and Dipak Prajapati.

5. International Symposium on Current Perspectives in Organic Chemistry, Dec 7-9, 2006 held at Indian Association for the Cultivation of Science (IACS), Kolkata.

   Poster: Regiospecific synthesis of highly functionalised novel pyrimido[4,5-*d*] pyrimidine derivatives under solvent-free conditions. **Kalyan Jyoti Borah** and Dipak Prajapati.