ABSTRACT

Heterocyclic compounds are most important class of compounds in the pharmaceutical and agrochemical industries, in which heterocycles comprising around 60% are covered as drug substances. Heterocycles play a major part in biochemical processes and are also side groups of the most typical and essential constituents of living cells. They are also used as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators etc. They also play an important role in the biosynthesis as well as in drug metabolism. Therefore, study of heterocycles is of great interest both from the theoretical as well as practical point of view. In recent years, synthesis of heterocycles has been among the most important research areas in synthetic chemistry because of their immense medicinal importance.

Nowadays green chemistry directs synthetic chemists to redesign the synthetic methodologies taking environment into concern for sustainable development of the society. Thus, designing the new reagents and catalysts which are nontoxic, preferably biodegradable, easily separable and recyclable, more active, selective, and relatively non-hazardous than the traditional ones are the central theme of green chemistry. In this regard, the thesis entitled “Studies in Chemistry of Bioactive Heterocycles” clearly emphasizes on environmentally begin approach towards the synthesis of various novel heterocyclic compounds such as benzopyranopyridine derivatives, quinolinyl alkene, β-enaminones, chalcones, imidazoles and dihydropyrimidin-2(1H)-ones. The environmentally benign approach includes the synthesis and application of different catalyst which are inexpensive and recyclable as well as less toxic. The research work described in the thesis is divided into seven chapters. The chapter wise organization of the thesis is as follows:

CHAPTER 1
General Introduction

Green chemistry is a new way for the synthesis of pharmaceutically important heterocyclic compounds, offering important environmental and economic advantages over traditional synthetic processes. ‘Sustainable Technology’ necessitates a paradigm shift from traditional concepts of process efficiency, that focuses largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding
the use of toxic and/or hazardous substances. Therefore, it is a major challenge to develop environmentally benign synthetic protocols employing less toxic reagents in order to minimize waste with biodegradable by-products and to reduce costs. Recently, the central focus area for sustainable technology is the application of catalysis, a fundamental pillar in chemical sciences as evidenced by the improvement of known industrial processes and the development of new reaction pathways. The eco-friendly and economically viable catalysts, an essential aspect of sustainability, make the organic transformations useful and are highly demanded by academic laboratories and industries. The design and application of new catalysts and catalytic systems are simultaneously achieving the dual goals of environmental protection and economic benefit. Immobilization of a catalyst on solid support simplifies reaction procedure, increases stability and recyclability of the catalyst and has proved to be an efficient approach leading towards green synthesis. Use of recoverable homogeneous catalyst also contributes to sustainability. Thus, this chapter described scope of the present work.

CHAPTER 2

A green synthetic protocol for Friedländer annulation under solvent-free conditions using chitosan as biodegradable and efficient catalyst

Benzopyranopyridine is a pharmaceutically important heterocyclic scaffold. The examples of approved therapeutic agents incorporating this molecular framework include amlexanox and pranoprofen as antiallergic and NSAID, respectively. In addition, many of these compounds possess anti-proliferative, hypotensive, antibacterial (including anti-tubercular), anti-myopic, anti-histaminic, anti-rheumatic, cancer chemopreventive, and anti-asthmatic activities. Some benzopyranopyridines have been found to inhibit mitogen-activated protein kinase-activated protein kinase 2 and attenuate the production of pro-inflammatory TNFα, and histamine-stimulated gastric acid secretion in animals. The immense biological importance enthused researchers, therefore, to synthesize and study their potential biological activities.

Recently, there has been increasing concern with regard to the maintenance of ‘greenness’ in synthetic pathways and processes. Green chemistry strongly influences chemical research, and there is an insistence on the use of ‘greener’ reaction conditions. In this regard, chitosan is an attractive candidate. Chitosan offers a unique set of environmentally benign properties such as bio-degradability to harmless products, non-toxicity, biocompatibility, recyclability, physiological inertness, stability to air and
moisture, and inexpensiveness. Due to the presence of free hydroxyl and amino groups, it is employed as catalyst for many organic transformations. In this chapter, we have discussed Friedländer condensation of 4-amino-3-formylcoumarin (1) and different active methylene compounds (2a-n) in the presence of chitosan under solvent-free conditions to give novel benzopyranopyridine derivatives (3a-n). However, reaction of 1 with 2i and 2j didn't give the expected product, instead it afforded a rearranged product 5 and 3j, respectively.

Scheme 1
CHAPTER 3

Synthesis of quinolinyl alkenes via Knoevenagel condensation involving [Et₃NH][HSO₄]: a green protocol

Quinolines and their derivatives, represent a major class of heterocycles and are widely found in natural products. The quinoline ring is endowed with various activities, such as antimicrobial, antituberculosis, antimalarial, anti-inflammatory, anticancer, antibiotic, antihypertensive, tyrosine kinase PDGF-RTK inhibiting agents, anti-HIV and anti-convulsants. Amongst the various activities of their derivatives, antimicrobial & antimalarial activity is noteworthy.

In recent years, ionic liquids have been the subject of considerable interest in the context of green synthesis because of their adjustable physical and chemical properties. They have been introduced as alternative green reaction media due to their unique chemical and physical properties such as low vapour pressure, high thermal and chemical stability, good solvating ability, ease of recyclability, and controlled miscibility. Acidic Bronsted ionic liquids (ABILs) are of special importance because they possess simultaneously the proton acidity and the characteristic properties of an ionic liquid. In this regard, triethylammonium hydrogen sulphate [Et₃NH][HSO₄] is a good candidate. This ionic liquid has been proved to be the very excellent catalyst as well as solvent for many organic transformations. In this chapter, we have described the synthesis of some novel quinolinyl alkene derivatives 10(a-j) via the Knoevenagel condensation of 2-chloro-3-formylquinoline (9a) and active methylene compounds 2(a-j) using ionic liquid [Et₃NH][HSO₄] as reaction medium as well as catalyst. Excellent yield of the products were obtained within shorter reaction time. The reaction of heteroaldehyde (9a) with dimedone (2d), 4-hydroxycoumarin (2h) and triacetic acid lactone (2j), did not give the expected Knoevenagel condensation products; instead, it afforded 10d, 10h and 10j, respectively (Scheme 2).
CHAPTER 4

Synthesis of chalcone derivatives via Claisen-Schmidt condensation using piperidine functionalized silica as an efficient and environmentally benign catalyst

Chalcones constitute an important group of natural compounds that are especially abundant in fruits (e.g. citrus, apples), vegetables (bean sprouts, potatoes, tomatoes, shallots) and various plants and spices (e.g. licorice). Some of the naturally occurring bioactive chalcones are isoliquiritigenin, Flavokawain A and Cardamonin etc. Chalcones also display a wide spectrum of biological activities including antibacterial, antifungal, antipyretic, antileishmanial, antiangiogenic, antioxidant, anti-inflammatory, anticancer, anti-hyperglycemic, nitric oxide regulation, insecticidal, phytoestrogenic activities etc. Chalcones thus, comprise a class of compounds with important therapeutic potential. They also serve as intermediates in the synthesis of various heterocycles. The most convenient method for the synthesis of chalcones is the Claisen-
Schmidt condensation of equimolar quantities of benzaldehyde and acetophenone in the presence of acids or bases.

The utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. Homogeneous catalysts can catalyze a much larger variety of reactions than traditional solid catalysts but suffer from regeneration and recycling problems. The immobilization of homogeneous catalytic entities onto solid support provides avenues to recovery and possibly recyclability of the organic active sites. Based on these facts, in this chapter, we have described the synthesis and application of piperidine bonded on solid support silica as novel heterogeneous basic catalyst. This novel catalyst was applied for the synthesis of chalcones (12a-p) via Claisen-Schmidt condensation of aldehydes (9a-e) and active methyl compounds (11a-k) under solvent-free conditions. Good yields of the product were obtained within relatively shorter time period.

![Chemical Structures](image)

**Scheme 3**

**CHAPTER 5**

Sulphuric acid modified nano fibrous silica as solid acid for environmentally benign synthesis of β-enaminones

Enaminones are potential building block to access several types of heterocyclic ring systems such as 1,4-dihydropyridines, pyrroles, oxazoles, pyridinones, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, azasteroids, (1H)-pyridin-
2-one, pyrazolo-[1,5-α]-pyrimidine and isoxazole derivatives, which are well-known as anti-inflammatory, antitumor, antibacterial, and anticonvulsant activities. Chiral ligands for diastereoselective synthesis can also be obtained from the optically active enaminones.

The development of nanoscience, has made the greening of chemistry possible. Nanosilica functionalized by incorporating organic and inorganic functional groups within their mesopores are of great interest for their use as heterogeneous catalysts. Nanocatalysis enhances sustainability through higher activity with less amount of catalysts. It also avoids drastic reaction conditions and increases energy efficiency, and higher selectivity, which reduces the by-products and allows to perform chemical reactions in a selective manner with the least possible consumption of substances. This, in turn, improves atom economy and waste prevention. Thus, in this chapter, we have discussed the synthesis of sulphuric acid functionalized high-surface area fibrous SiO₂ spheres (KCC-1-SA) as solid acid catalyst. The high surface area of KCC-1 is attributable to fibres and not to pores, which dramatically increase its accessibility of active sites. We have also described application the synthesized solid acid catalyst, KCC-1-SA for the synthesis of β-enaminones under solvent-free conditions taking into consideration green principle of chemistry.

![Scheme 4](image-url)
CHAPTER 6

Chitosan sulphuric acid: an efficient and biodegradable solid acid catalyst for the synthesis of highly substituted imidazole derivatives

The imidazole nucleus is a prolific source of pharmaceutically important molecules. They are present in compounds possessing various pharmaceutical properties such as anti-inflammatory, anti-bacterial, CSBP kinase inhibitor, glucagon receptor antagonists, p38 MAP kinase inhibitors, modulators of Pgp-mediated multidrug resistance, antitumor agents, inhibitors of mammalian 15-LOX, CB1 cannabinoid receptor antagonists, and inhibitors of B-Raf kinase. It is the core structural skeleton in many important biological molecules like biotin, histamine and histidine.

The utilization of polymer bound catalysts is now well recognized because of their ease of workup and separation of products and catalysts, from the economical point of view. One such polymer which is used as catalytic support is chitosan. Its properties such as easy availability, non-toxicity, biocompatibility, biodegradability, and insolubility in the vast majority of solvents makes it an ideal support material. The amino groups and hydroxyl groups in chitosan provide active sites for numerous attractive chemical modifications. One such modification is sulfonation which leads to the formation of chitosan-\( \text{SO}_3\text{H} \). This chapter deals with the synthesis and characterization of chitosan-\( \text{SO}_3\text{H} \) as recyclable solid acid catalyst, for the microwave assisted synthesis of a library of 2,4,5-trisubstituted as well as 1,2,4,5-tetrasubstituted imidazole derivatives.
Chapter 7

The generation of dihydropyrimidine library via Biginelli reaction using MCM-41 supported perchloric acid

Development of new and efficient catalytic protocols is essential for the sustainable development of society as it provides economical, and efficient ways to convert raw materials into valuable chemicals. In order to avoid the use of volatile organic solvents, toxic reagents, hazardous, and/or harsh reaction conditions as well as challenging and
time-consuming wasteful separations, greener and environmentally benign catalytic protocols have recently become more popular. In this regard, heterogenization of homogeneous counterpart on solid support can add greenness to the synthetic procedure by offering the possibility of simple recovery and recycling as well as easy product purification and isolation. Utilizing mesoporous silica as inorganic support has advantages due to its excellent stability, good accessibility and high surface area which will be beneficial to the enhancement of loading amount and dispersion of catalytic active. Moreover, its porosity ensures high dispersion of active sites whereas large pore size and pore volume favours an easy accessibility of the organic functions within the insoluble solid. Therefore, they are preferred as solid support for the synthesis of heterogeneous catalysts and in this context a large number of MCM-41 supported catalysts have been reported.

In Multicomponent reactions (MCRs) three or more components react to produce complicated molecules with high atom economy by incorporating all the starting materials. MCRs are economical and time effective as products are obtained in a single step in good yields under simple and mild reaction conditions. From an environmental and economic perspective, multicomponent reactions (MCRs) are valuable tools for the preparation of structurally diverse drug-like compounds. One MCR that produces an interesting class of nitrogen heterocycles is Biginelli reaction giving 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs). DHPMs have various biological activities such as antibacterial, antiviral, antitumor, anti-inflammatory, antiarrhythmic agents, calcium channel modulators, adrenergic receptor antagonists, mitotic kinesin inhibitors, and drugs such as enastron, monastrol, piperastrol etc.

In this context, this section deals with the synthesis of novel mesoporous silica supported perchloric acid which is easy preparable, recyclable and non-corrosive solid acid. Its catalytic activity were evaluated by synthesizing a library of 3,4-dihydropyrimidin-2(1H)-one/thiones derivatives (22a-o) by the reaction of substituted aldehydes (9c-e, 19a-e) with different acyclic active methylene compounds (2m, 20) and urea (21a)/ thiourea (21b) in the presence of MCM-41-HClO4 under solvent-free conditions in excellent yield (95-98%) within a short span of time (Scheme 6).
Abstract

Scheme 6

Characterization of the prepared catalytic systems:
Structures of the catalysts were confirmed through rigorous analyses of their FT-IR, $^1$H NMR, powder XRD, SEM-EDX, TEM, TG/DTA, BET and DSC techniques.

Characterization of heterocyclic compounds:
The structures of all compounds were established by their spectral (FT-IR, $^1$H NMR, $^{13}$C NMR and Mass spectrometry) and elemental analyses.

Optimization of reaction conditions:
The experimental procedures were used to evaluate the catalytic activity of catalyst under optimized reaction conditions taking into consideration various parameters such as effect of reaction temperature, solvents, catalysts, comparison with reported catalysts, effect of different catalyst loadings on support and amount of catalyst used by selecting an appropriate model reaction.
The reusability of all the catalysts was also investigated and checked by powder XRD and SEM-EDX analyses.
STUDIES IN CHEMISTRY OF BIOACTIVE HETEROCYCLES

THESES
SUBMITTED FOR THE AWARD OF THE DEGREE OF

Doctor of Philosophy
In
Chemistry

By
KULSUM

UNDER THE SUPERVISION OF
PROF. ZEBA N. SIDDIQUI

DEPARTMENT OF CHEMISTRY
ALIGARH MUSLIM UNIVERSITY
ALIGARH (INDIA)
2014
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I, Kulsum, Department of Chemistry certify that the work embodied in this Ph.D thesis is my own bonafide work carried out by me under the supervision of Prof. Zeba N. Siddiqui at Aligarh Muslim University, Aligarh. The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree.

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Department: CHEMISTRY

(Signature of the Chairman of the Department with seal)
Department of Chemistry
A.M.U., Aligarh
COURSE/ COMPREHENSIVE EXAMINATION/ PRE-SUBMISSION SEMINAR COMPLETION CERTIFICATE

This is to certify that Miss. Kulsum, Department of Chemistry has satisfactorily completed the course work/comprehensive examination and pre-submission seminar requirement which is part of her Ph.D. programme.

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ACKNOWLEDGEMENTS

"And will provide for him from where he does not expect. And whoever relies upon Allah then He is sufficient for him. Indeed, Allah will accomplish His purpose. Allah has already set for everything a [decreed] extent." 65: 3

At the very outset, I bow in reverence to the Almighty ALLAH, (swt), the Benevolent, the Sustainer and the Cherisher, Who inspires entire humanity towards knowledge, truth and eternal commendation. He bestowed upon me the strength, the zeal and zest combined with courage and patience to embark upon this work and carry it to its completion. Words are not enough for expressing my gratitude to the One, without His mercy and His choicest blessings I won’t be able to accomplish this work, I pray for His mercifulness and blessings always.

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Kulsum
“My Lord! Bestow on them Your Mercy as they did bring me up when I was small”

Al-Quran [17:24]

Dedicated to
My Loving
Parents
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PREFACE
Preface

Heterocyclic compounds are endowed with very high structural complexity and diversity and play a pivotal role in any developed society as evident from the fact that pharmaceuticals, agrochemicals, dyes and many other kinds of products are heterocyclic in nature. Consequently, designing of simple, facile, efficient and environmentally benign chemical processes or methodologies for the synthesis of heterocycles and their derivatives is one the main goal of modern organic synthesis. In this context the work embodied in this thesis entitled “Studies in Chemistry of Bioactive heterocycles” focuses on the design and development of environmentally benign and efficient protocols for the syntheses of novel, biologically important heterocyclic derivatives from readily available starting materials such as 4-Amino-3-formylcoumarin, 2-Chloro-3-formylquinoline, 5-Chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde and 3-Formylindole. To discuss systematically, the thesis is divided into seven chapters, which are as follows:

Chapter 1

One of the most attractive concepts in chemistry for sustainability is Green Chemistry, which is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products. Therefore, it is a major challenge to develop environmentally benign synthetic protocol employing less toxic reagents in order to minimize waste with biodegradable by-products and to reduce costs. Catalysis in one of the important green chemistry tools as evidenced by the improvement of known industrial process and the development of new reaction pathways. The design and application of new catalysts and catalytic systems are simultaneously achieving the dual goals of environmental protection and economic benefit Immobilization of a catalyst on solid support simplifies reaction procedure, increases stability and recyclability of the catalyst and has proved to be an efficient approach leading towards green synthesis. Use of recoverable homogeneous catalyst also contribute to sustainability. Thus, this chapter describes the scope of present work.

Chapter 2

Friedlander condensation is an acid or base catalysed condensation cyclodehydration reaction which takes place between an aromatic 2-aminoaldehyde or ketone and
reactive active methylene compounds and affords heteroannulated pyridines. The synthesis of this condensed heterocyclic system is interesting because of potential biological activities associated with its structure. This chapter focusses on the Friedländer condensation of 4-amino-3-formylcoumarin (1) and different active methylene compounds (2a-n) in the presence of chitosan under solvent-free conditions to give novel benzopyranopyridine derivatives (3a-n). This methodology has some preferred advantages as it combines two green strategy, namely use of biodegradable polymer chitosan as catalyst which breaks down to harmless products and other is solvent-free conditions.

Chapter 3

Ionic liquids have been the subject of considerable interest in the context of green synthesis because of their adjustable physical and chemical properties. They have been introduced as alternative green reaction media due to their unique chemical and physical properties such as low vapour pressure, high thermal and chemical stability, good solvating ability, ease of recyclability, and controlled miscibility. Acidic Bronsted ionic liquids (ABILs) are of special importance because they possess simultaneously the proton acidity and the characteristic properties of an ionic liquid. In this regard, [Et$_3$NH][HSO$_4$] is a good candidate. Knoevenagel condensation reaction is a facile and versatile method for the formation of carbon–carbon double bond between carbonyl compounds (aldehydes/ketones) and an active methylene compound. In this chapter, we have described the synthesis of some novel quinolinyl alkene derivatives 10(a-j) via Knoevenagel condensation of 2-Chloro-3-formylquinoline (9a) and active methylene compounds 2(a-j) using ionic liquid [Et$_3$NH][HSO$_4$] as reaction medium as well as catalyst. Excellent yield of the products were obtained within shorter reaction time.

Chapter 4

The utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. Homogeneous catalysts can catalyse a much larger variety of reactions than traditional solid catalysts but suffer from regeneration and recycling problems. The immobilization homogeneous of catalytic entities onto solid support provide avenues to recovery and possibly recyclability of the organic active site. Based on These facts, in this chapter the synthesis of piperidine bonded on solid support silica as novel heterogeneous basic catalyst has been discussed. This novel catalyst was applied for the synthesis of chalcones (12a-p) by Claisen
Schmidt condensation between aldehydes (9a-e) and active methyl compounds (11a-k) under solvent-free conditions. Good yields of the product were obtained within relatively shorter time period. The catalyst has been characterized well using various techniques such as FT-IR, solid state NMR, scanning electron microscopy, energy-dispersive X-ray, thermogravimetric, elemental, and NH₃ and CO₂ temperature-programmed desorption analyses. Surface area was also evaluated through Brunauer-Emmett-Teller analysis.

Chapter 5

Nanocatalysis enhances sustainability through higher activity with less amount of catalysts. It also avoids drastic reaction conditions and increases energy efficiency, and higher selectivity, reduces the by-products and allows to perform chemical reactions in a selective manner with the least possible consumption of substances. This, in turn, improves atom economy and waste prevention. Thus, in this chapter we have discussed the synthesis of sulphuric acid functionalized high-surface area fibrous SiO₂ spheres (KCC-1-SA) as solid acid catalyst. The high surface area of KCC-1 is attributable to fibres and not to pores, which dramatically increase its accessibility of active sites to the reactants thereby enhancing rate of reaction. We have also described application the synthesized solid acid catalyst, KCC-1-SA for the synthesis of β-enaminones (14a-p) using different amines (13a-k) and active methylene compounds (2d, 2n) under solvent free conditions.

Chapter 6

Multicomponent reactions (MCRs) have drawn special attention and have an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity. MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery. Imidazoles are a class of heterocyclic compounds that contain nitrogen and are currently under intensive focus due to their wide range of applications.

Thus, this chapter deals with the synthesis and characterization of chitosan-SO₃H as a biodegradable and recyclable solid acid catalyst, for the microwave assisted multicomponent synthesis of a library of 2,4,5-trisubstituted imidazole derivatives
(18a-f) using different aldehydes (15a-d), benzyl (16) and ammonium acetate (17). This protocol was also applied for the synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives (18g-p) employing 5-Chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (15a) and 3-Formylindole (15b), amine (13a-e, l) benzil (16) and ammonium acetate (17).

Chapter 7

Dihydropyrimidinones (DHPMs) are important class of heterocyclic compounds due to their wide range of bioactivities and their applications in the field of drug research. Many functionalized DHPMs derivatives are used as antibacterial, antiviral, antitumor, anti-inflammatory and antiarrhythmic agents. To improve the efficiency of a catalytic process, an intense research activity has recently been devoted towards the development of solid supported catalysts involving simple catalyst recovery and recycling. In this context, this chapter deals with the synthesis of novel mesoporous silica supported perchloric acid which is easy preparable, recyclable and non-corrosive solid acid. Its catalytic activity was evaluated by synthesizing a library of 3,4- dihydropyrimidin-2(1H)-one/thiones derivatives (22a-o) by the reaction of substituted aldehydes (9c-e, 19a-e) with different methylene compounds (2m, 20) and urea (20a)/ thiourea (20b) in the presence of MCM-41-HClO₄ under solvent-free conditions in excellent yield (95-98 %) within a short span of time.
### Abbreviations and Symbols

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<td>N, N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>h or hrs</td>
<td>Hours</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
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<td>I₂</td>
<td>Iodine</td>
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<tr>
<td>Me</td>
<td>Methyl</td>
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<tr>
<td>MeOH</td>
<td>Methanol</td>
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<tr>
<td>mg</td>
<td>Milligram</td>
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<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>meq.</td>
<td>miliequivalent</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic Resonance</td>
</tr>
<tr>
<td>PEG</td>
<td>Poly ethylene glycol</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-Toluenesulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>M.W.</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>))</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TPD</td>
<td>Temperature programmed desorption</td>
</tr>
</tbody>
</table>
GENERAL REMARKS

➢ Melting points were determined on a Riechert Thermover instrument and are uncorrected.

➢ The $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker DRX-300 and Bruker Avance II-400 Spectrometer using tetramethyl silane (TMS) as an internal standard, DMSO-$d_6$/CDCl$_3$ as solvent. Chemical shifts are reported in ppm downfield from TMS as internal standard and coupling constants $J$ are given in Hz.

➢ The micro-analytical data were collected on an Elementar vario EL III elemental analyser and their results were found to be in agreement with the calculated values.

➢ FT-IR spectra were obtained using a Perkin–Elmer RXI spectrometer in KBr. The spectra were recorded in the 400–4000 cm$^{-1}$ wave-number range.

➢ Mass spectra were obtained on 5Micromass Quattro II (ESI) and THERMO Finnigan LCQ Advantage max ion trap mass (ESI-MS) spectrometer.

➢ All starting materials of commercial grade were purchased from Sigma-Aldrich (Switzerland), Merck (Mumbai, India) and used without further purification.

➢ The purity of all compounds was checked by TLC on glass plates coated with silica gel (E-Merck G$_{254}$). The plates were run in chloroform-methanol (3:1) mixture as mobile phase and were visualized by iodine vapours.

➢ X-ray diffractograms (XRD) of the catalyst were recorded in the 2θ range of 10–70° (scan rate of 4° min$^{-1}$) on a Rigaku Miniflex X-ray diffractometer with Ni-filtered Cu Kα radiation at a wavelength of 1.54060Å.

➢ The SEM-EDX analyses was obtained using a JEOL JSM-6510 scanning electron microscope equipped with energy dispersive X-ray spectrometer (acc. voltage: 20 kV) at different magnification.

➢ Transmission electron microscope (TEM) was obtained using JEM-2100 F model (acc. voltage: 200 kV) with magnification up to 100000x.

➢ Thermogravimetric/differential thermal analyses (TG/DTA) were obtained with a DTG-60H, with a heating rate of 25 °C min$^{-1}$ from 100 to 1000 °C under N$_2$ atmosphere, and the differential scanning calorimetry (DSC) data was obtained with DSC-60 (Simultaneous DTA-TG Apparatus), Shimadzu (TGA) instrument with a heating rate of 20 °C min$^{-1}$ from 0 to 500 °C under N$_2$ atmosphere.
Nitrogen adsorption–desorption isotherms were obtained using a Quantachrome Autosorb 1C at 77 K.

$^{13}$C CP MAS NMR was done using a Bruker Avance 500WB with 15 kHz speed.

TPD of ammonia (TPD-NH$_3$) and carbon dioxide (TPD-CO$_2$) were carried out with a Micromeritics Instrument Corporation Chemisorb version 1.

The small angle X-ray diffraction (XRD) study of samples was carried out using X-ray diffractometer (Bruker, Advanced D8) with Cu K$_\alpha$ radiation ($\alpha = 1.5418\text{Å}$). The sample was scanned in 2θ range of 1°–10° with a scanning rate of $0.02°\text{ s}^{-1}$.

Microwave synthesis was carried out using Microwave Synthesis Reactor, monowave 300 (Anton paar).
LIST OF PUBLICATIONS

Publications from the research work presented in the thesis

Chapter-2

(I) Zeba N. Siddiqui and Kulsum Khan, Friedlander synthesis of novel benzopyranopyridines in the presence of chitosan as heterogeneous, efficient and biodegradable catalyst under solvent-free condition. *New Journal of Chemistry*, 2013, 37, 1595.

Chapter-3


Chapter-4


Chapter-5


Chapter-6

(V) Kulsum Khan and Zeba N. Siddiqui, Chitosan-SO₃H as biodegradable and efficient solid acid catalyst for the synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives. *(Communicated).*

Chapter-7

(VI) Kulsum Khan and Zeba N. Siddiqui, MCM-41 supported perchloric acid for efficient synthesis of 3,4-dihydro-pyrimidin-2-(1H)-ones via Biginelli reaction. *(Communicated).*
CHAPTER - 1

General Introduction
1.1. GENERAL INTRODUCTION
Heterocycles form the largest classical divisions of organic chemistry. They are of immense importance not only biologically and industrially but also to the functioning of any developed human society. Heterocyclic compounds constitute the largest and most varied family of organic compounds. It holds a special place among pharmaceutically significant natural products and synthetic compounds. The remarkable ability of heterocyclic nuclei to mimic natural products and to serve as reactive pharmacophores have largely contributed to their unique value as traditional key elements of numerous drugs.\(^1\) Heterocyclic subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds.\(^2\) Most of the alkaloids are nitrogenous bases, occurring in plants. Further, many antibiotics including penicillin and streptomycin also contain heterocyclic ring systems. Many pigments such as indigo, haemoglobin and anthocyanin are also heterocyclic compounds. Drugs such as sulphathiazol, pyrethrin, rotenine, cocaine, barbiturates also possess heterocyclic system\(^3\) and play an important role in biochemical processes as well as are present as the side groups of the most typical and essential constituents of living cells. Other important practical applications of heterocycles can also be cited, for instance, additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Heterocyclic chemistry is thus an inexhaustible resource of novel compounds. A huge number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most diverse physical, chemical, and biological properties.\(^4\) In fact, in the Comprehensive Medicinal Chemistry (CMC) database, more than 67% of the compounds listed contain heterocyclic rings, and nonaromatic heterocycles are twice as abundant as heteroaromatics.\(^5\) Therefore, the development of new methods and the strategic deployment of known methods for the syntheses of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry. Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Contemporary developments in discovery and process chemistry emphasize new sustainable synthetic routes, requiring rapid and environmentally acceptable alternatives to the classic methods.
One of the most attractive concepts in chemistry for sustainability is Green Chemistry, which is the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and applications of chemical products. It should be noted that the rapid development of Green Chemistry is due to the recognition that environmentally friendly products and processes will be economical on a long term. Catalysis is one of the fundamental pillars of green chemistry. The design and application of new catalysts and catalytic systems are simultaneously achieving the dual goals of environmental protection and economic benefit. It offers numerous green chemistry benefits including lower energy requirements, catalytic versus stoichiometric amounts of materials, increased selectivity, decreased use of processing and separation agents, and allows for the use of less toxic materials.

Catalysis is thus, an important field in chemistry, with some 90% of chemical processes involving catalysts in at least one of their steps. The International Union of Pure and Applied Chemistry (IUPAC) has defined a catalyst as “a substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction”. The chemical process of increasing the reaction rate is called catalysis, and the catalyst is both a reactant and a product of the reaction, i.e., the catalyst is restored after each catalytic act. Furthermore, the catalyst does not influence the thermodynamical equilibrium composition after the cessation of the reaction. Catalysts fall into two categories, homogeneous and heterogeneous, depending on their relationship to the phase of the reaction in which they are involved. A homogeneous catalyst is in the same phase as the components of the reaction that it is catalysing. A heterogeneous catalyst is in a different phase from the components of the reaction for which it is acting as catalyst. A great variety of homogeneous catalysts are known, ranging from Brønsted and Lewis acids widely used in organic synthesis, metal complexes, metal ions, organometallic complexes, organic molecules, enzymes etc. Nowadays ionic liquids are also included in homogeneous catalysts. In the case of homogeneous catalysts, every single catalytic entity can act as a single active site. This makes homogeneous catalysts intrinsically more active and selective. High selectivity of homogeneous catalyst is a means to reduce waste, to reduce the work-up equipment of a plant, and to ensure a more effective use of the feedstocks. The main disadvantage of homogeneous catalytic reaction is that the catalyst in general cannot be regenerated
or reused. But nowadays, scientists are working towards the regeneration or reusability of homogeneous catalysts. Using ionic liquids as both reaction medium as well as catalysts and use of modified soluble polymer (Polyethylene glycols) are better alternative to conventional synthesis as it can be regenerated and reused for several cycles. There are many families of solid catalysts which are heterogeneous catalysts like metals, oxides, sulphides, carbons, etc. as bulk materials or supported on a more or less catalytically active support like silica, alumina, zirconia, titania, ceria, organic polymers, carbons, etc. These materials may possess specific chemical properties, such as acid-base or redox or dehydrogenating or hydrogenating or oxidizing, and physical properties like porosity, high surface area, attrition resistance, thermal and/or electrical conductivity, etc. The largest family corresponds to oxides such as zeolites, clays, mesoporous materials, mixed oxides as catalysts or as supports. Heterogeneous catalysts have several advantages. First, the separation of catalysts from the reaction mixture can easily be performed by simple filtration or decantation. Furthermore, it can often be used under solvent-free conditions. A very important feature is that heterogeneous catalysts can easily be recovered and reused for several catalytic cycles, which make their application highly economical. However, main disadvantage of heterogeneous catalysts is that the distribution of active site is not uniform, therefore, some of the active site cannot be reached by the reactants.

Exploiting the advantages of both homogeneous and heterogeneous catalytic system, we have taken up the work to synthesize various heterocyclic compounds such as benzopyranopyridine, enamiones, quinoline derivatives, dihydropyrimidinones, chalcones and imidazole derivatives etc. from easily available starting materials such as 4-Chloro-3-formylcoumarin, 2-Chloro-3-formylquinoline, 5-Chloro-3-methyl-1-phenylpyrazol-4-carboxaldehyde, 3-Formylindole, 5-Acetyl-1,3-dimethylbarbituric acid, 5-Acetylbarbituric acid, 3-Acetyl-4-hydroxycoumrin, Dehydroacetic acid etc. Both the catalyst and novel compounds were characterized well with different techniques.
1.2. REFERENCES


   (d) Druzhinin, S. V.; Balenкова, E. S.; Nenajdenko, V. G. Tetrahedron 2007, 63, 7753.


CHAPTER 2

A Green Synthetic Protocol for Friedländer Annulation under Solvent-free Conditions using Chitosan as Biodegradable and Efficient Catalyst
2.1. INTRODUCTION
The Friedländer annulation was first reported in 1982 by Paul Friedländer and is the simplest synthetic approach for the preparation of polysubstituted pyridines and related aza-heterocycles. Friedländer condensation is considered as an atom economic reaction which proceeds through a double condensation of 2-aminoarylcarbonyl structures with other carbonyl compounds possessing enolizable hydrogens. The significance of this reaction is largely due to the broad range of functional group compatibility. Regarding 2-aminocarbonyl component (aldehyde/ketone), a wide range of functional groups are tolerated on the aromatic ring. In the Friedländer reaction, majority of 2-amino-substituted carbonyl compounds used are 2-aminobenzaldehyde, 2-aminoacetophenone, or 2-aminobenzophenone and their derivatives. Both electron-rich and electron-poor 2-aminobenzocarbonyl compounds undergo the Friedländer reaction. Some ortho-aminoheteroaldehydes such as 3-amino-2-formylimidazo[1,2-a]pyridine, 2-aminothiophencarboxaldehyde, 3-aminoacrolein (3AA), 2-amino-3-formylchromone etc. have also been employed. With respect to the enolizable ketones, a number of different types have been employed including symmetrical ketones and ketones with additional activating groups alpha to the carbonyl function etc. Substituent on ketone may be hydrogen, alkyl, aryl, nitro, acyl, carboxy, carbalkoxy, carboxamido, cyano, hydroxyl, sulfonyl and acetoxyc etc. Utilizing the potential of Friedländer reaction, we have described synthesis of bezopyranopyridines via Friedländer annulation, as benzopyranopyridine scaffold is of significant medicinal relevance. The examples of approved therapeutic agents incorporating this molecular framework include amlexanox and pranoprofen as antiallergic and NSAIID, respectively. In addition, many of these compounds also possess antiproliferative, cancer chemopreventive, antibacterial (including antitubercular), antimyopic, anti-histaminic, hypotensive, anti-inflammatory and antiasthmatic activities. Some benzopyranopyridines have been found to inhibit mitogen-activated protein kinase-activated protein kinase 2 and attenuate the production of pro-inflammatory TNFα, and histamine stimulated gastric acid secretion in animals. Friedländer annulations are generally carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base or acid or by heating a mixture of the reactants at 150-220 °C in the absence of a catalyst. In recent years,
various experimental protocols have been developed for the Friedlander annulation such as the use of microwaves,\textsuperscript{15} use of acidic and basic catalysts such as ZnCl\textsubscript{2},\textsuperscript{16} NaOEt,\textsuperscript{17} FeCl\textsubscript{3},\textsuperscript{18} SnCl\textsubscript{2},\textsuperscript{19} sulfamic acid,\textsuperscript{20} concentrated HCl,\textsuperscript{21} pyridine, piperidine,\textsuperscript{22} NaHSO\textsubscript{4}.SiO\textsubscript{2},\textsuperscript{23} HClO\textsubscript{4}.SiO\textsubscript{2},\textsuperscript{24} Amberlyst-15\textsuperscript{25} multicomponent reactions,\textsuperscript{26} ionic liquid,\textsuperscript{27} nanoparticles,\textsuperscript{28} Zn(L-proline)\textsubscript{2},\textsuperscript{29} camphorsulfonic acid,\textsuperscript{30} polyphosphoric acid,\textsuperscript{31} MCM-41 supported protic ionic liquid,\textsuperscript{32} enzyme,\textsuperscript{33} proline potassium salt,\textsuperscript{34} lanthanum chloride,\textsuperscript{35} chitosan-SO\textsubscript{3}H,\textsuperscript{36} amino-grafted MCF,\textsuperscript{37} lithium triflate,\textsuperscript{38} PEG-SO\textsubscript{3}H,\textsuperscript{39} nano TiO\textsubscript{2}\textsuperscript{40} etc. Previous investigations required prolonged reaction times, use of hazardous reagents and tedious workup procedures, complicated syntheses of catalysts etc. Taking into consideration of all these limitations there is still a chance to develop a simpler and clean method for the Friedlander synthesis. In this respect, chitosan is an attractive candidate.

2.2. REVIEW AND LITERATURE

Chitosan is N-deacetylated derivative of chitin (Fig. 1). It is obtained from chitin by treatment with alkali.\textsuperscript{41}

![Diagram of Chitin and Chitosan](image)

**Fig. 1** Chitosan as N-deacetylated chitin.

It possesses environmentally benign properties such as biodegradability to harmless products, non-toxicity, biocompatibility, recyclability,\textsuperscript{42-45} physiological inertness, inexpensiveness and stability to air and moisture. Due to its insolubility in most of the organic compounds and solvents including water, it is most suitable candidate for heterogeneous catalysis. Chitosan contains free amino groups and primary and secondary hydroxyl groups in higher concentration. Therefore, it can activate the nucleophilic as well as electrophilic components of the reagents by hydrogen bonding and lone pair of electrons. Thus, chitosan has emerged as a potential catalyst for many organic transformations.
2.2.1. Some recent examples of chitosan catalyzed organic reactions

2.2.1a. Synthesis of monoglycerides catalyzed by chitosan
Quignard et al. in 2003 showed for the first time that chitosan microspheres, obtained under supercritical CO₂ conditions, could be used as a catalyst in the esterification of fatty acid. Thus lauric acid reacted with glycidol to give monoglyceride.⁴⁶

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_{10}^-\text{C}-\text{OH} & \xrightarrow{\text{Chitosan}} \text{CH}_3(\text{CH}_2)_{10}^+\text{C}-\text{O}^-\text{C}-\text{O}^-\text{OH} \\
\text{HO}^- & \xrightarrow{\text{Toluene, 70 °C}} && \text{CHO}^-\text{C}-\text{O}^-\text{C}-\text{O}^-\text{OH}
\end{align*}
\]

2.2.1b. Chitosan as basic catalyst for Knoevenagel and aldol condensation
Chitosan hydrogel was efficiently utilized by Reddy et al. as an organocatalyst for aldol and Knoevenagel condensation reactions, providing the products in high yields with a high chemoselectivity under biphasic conditions. The catalyst was recovered by simple filtration and reused several times without significant loss of activity.⁴⁷

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{Chitosan hydrogel}} \text{H}_3\text{C}-\text{C}=\text{CH}_3 \\
\text{R} & \xrightarrow{\text{DMSO, r.t.}} \text{OH} & \xrightarrow{\text{EWG}} \text{OCOEt} \\
\text{EWG} & \xrightarrow{\text{EWG}} & \text{EWG} = \text{CN}, \text{COOEt}
\end{align*}
\]

\[R = 4-\text{NO}_2, 4-\text{Cl}, 4-\text{F}, 4-\text{Me}\]

2.2.1c. Chitosan as green catalyst for the synthesis of pyridazines
Syntheses of pyridazines and fused pyridazines via [3+3] atom combination was successfully achieved using chitosan as a green catalyst.⁴⁸
To explore the scope of this reaction, the present protocol was applied for the synthesis of various benzopyranopyridine derivatives (3a-n) from 4-amino-3-formylcoumarin (1) and active methylene compounds (2a-n) in molar ratios under solvent-free conditions at 80 °C. The obtained results are summarized in Table 2.

Table 2 Chitosan catalyzed synthesis of benzopyranopyridine compounds 3a–n

<table>
<thead>
<tr>
<th>Entry</th>
<th>Active methylene compounds</th>
<th>Product</th>
<th>Reflux (MeOH/piperidine) Time (h)</th>
<th>Yield (%)</th>
<th>Solvent-free (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2a</td>
<td>3a</td>
<td>8</td>
<td>69</td>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>2.</td>
<td>2b</td>
<td>3b</td>
<td>10</td>
<td>68</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>3.</td>
<td>2c</td>
<td>3c</td>
<td>10</td>
<td>67</td>
<td>5</td>
<td>87</td>
</tr>
<tr>
<td>4.</td>
<td>2d</td>
<td>3d</td>
<td>7</td>
<td>70</td>
<td>4</td>
<td>88</td>
</tr>
</tbody>
</table>
Friedländer condensation

5.  

\[
\begin{align*}
2e & : H_2C - \text{C} = \text{O} \\
3e & : \text{O} = \text{C} - \text{O} - \text{CH}_3 - \text{CH}_3
\end{align*}
\]

6.  

\[
\begin{align*}
2f & : \text{C} = \text{O} \\
3f & : \text{O} = \text{C} - \text{O}
\end{align*}
\]

7.  

\[
\begin{align*}
2g & : \text{S} - \text{H} - \text{C} = \text{O} \\
3g & : \text{N} - \text{H} - \text{C} = \text{O}
\end{align*}
\]

8.  

\[
\begin{align*}
2h & : \text{OH} - \text{C} = \text{O} \\
3h & : \text{O} = \text{C} - \text{O}
\end{align*}
\]

9.  

\[
\begin{align*}
2j & : \text{OH} - \text{C} = \text{O} - \text{CH}_3 \\
3j & : \text{O} = \text{C} - \text{O} - \text{CH}_3
\end{align*}
\]

10.  

\[
\begin{align*}
2k & : \text{NC} - \text{CN} \\
3k & : \text{O} = \text{C} - \text{N} - \text{NH}_2
\end{align*}
\]
All the newly synthesized compounds were recrystallized from suitable solvents and characterized by elemental analysis and spectroscopic data. The IR spectrum (Fig. 3) of compound 3d showed a strong absorption band for carbonyl groups of coumarin and dimedone moieties at 1738 and 1694 cm\(^{-1}\), respectively. Another sharply absorbed band at 1603 cm\(^{-1}\) was assigned to C=O group. The \(^1\)H NMR spectrum (Fig. 4) showed a singlet for six protons of two methyl groups at \(\delta 1.09\) whereas four protons of two CH\(_2\) groups were present as singlets at \(\delta 2.69\) and \(\delta 3.23\). The H-11 proton appeared as double doublet with \(J=1.8, 6.5\) Hz due to its spin coupling with H-9 and H-10 proton. The aromatic protons (H\(_5\), H\(_6\), and H\(_{10}\)) appeared as multiplets in the range of \(\delta 7.48-7.74\). The H-5 proton appeared as sharp and downfield singlet at \(\delta 8.77\). The \(^{13}\)C NMR spectrum (Fig. 5) showed signals at \(\delta 168.3\) and 196.2 for carbonyl groups of coumarin and dimedone moieties whereas signal for C-5 carbon appeared at \(\delta 135\). Further confirmation for the structure was provided by mass spectrum, which showed molecular ion peak at 294.1 (M\(^+\)+1) (Fig. 6).
Figure 4: ^1H NMR spectrum of compound 3d

Figure 3: FT-IR spectrum of compound 3d
Fig. 5 $^{13}$C NMR spectrum of compound 3d

Fig. 6 Mass spectrum of compound 3d
The reaction of 4-amino-3-formylcoumarin 1 with triacetic acid lactone 2j did not give the expected product 4, instead it afforded a rearranged product 3j as shown in Scheme 2. The rearranged product 3j was formed due to translactonization leading to the opening of the lactone ring in 1 by nucleophilic attack of amino group. Such type of translactonization has been reported earlier from our lab.\textsuperscript{57}

**Scheme 2** Formation of 3-acetoacetyl benzopyranopyridone, 3j.

Further evidence for the formation of the rearranged product 3j was provided by spectral data. The IR spectrum of 3j (Fig. 7) showed absorption band at 1732, 1647, 1615 cm\(^{-1}\) for coumarin, lactam, and chelated carbonyl groups, respectively. In the \(^1\)H NMR spectrum (Fig. 8) the presence of acetoacetyl group was established in the form of two singlets at \(\delta\) 2.24 and \(\delta\) 7.16 for methyl and H-2' protons, respectively. Moreover, the compound gives positive ferric chloride test suggesting that acetoacetyl chain exists in the enolic form also (3j). \(^{13}\)C NMR (Fig. 9) showed signals at \(\delta\) 196.1, 181.2, 163.5 and 159.4 for C-3', C-1', C-2, and C-5, respectively. Another carbon signal appeared at their appropriate positions and is given in experimental section. Further evidence was provided by mass spectrum, which showed molecular ion peak at 298.1 (M\(^{+}\)+1) (Fig. 10).
Fig. 7 FT-IR spectrum of compound 3j

Fig. 8 $^1$HNMR spectrum of compound 3j
Fig. 9 $^{13}$C NMR spectrum of compound 3j

Fig. 10 Mass spectrum of compound 3j
The reaction of aldehyde 1 with another active methylene compound 2i again did not give the expected product 3i (Scheme 3) and instead, afforded dimer 5 which was reported earlier.\(^{58}\)

![Scheme 3 Formation of bispyrazole, 5.](image)

The reaction of 1 with 4-hydroxycoumarin 2h, gave pentacyclic benzopyranopyridine 3h (Scheme 4). The reaction did not stop at Knoevenagel condensation product 6 stage and proceeded further for regioselective cyclodehydration involving C-4 carbonyl group via route a to give the product 3h. The formation of structure 8 was again discarded because 8 did not give ferric chloride test. The IR spectrum of compound (Fig. 11) exhibited a strong absorption band for coumarin carbonyl group at 1751 cm\(^{-1}\) and didn’t show the characteristic absorption band for chromone carbonyl group at 1640 cm\(^{-1}\) (7).\(^ {59}\)
Scheme 4 Formation of pentacyclic benzopyranopyridine 3h.

Fig. 11 FT-IR spectrum of compound 3h
A plausible mechanism for the Friedlander condensation catalyzed by chitosan is shown in Scheme 5. The Chitosan has free hydroxyl as well as amino group distributed on its surface. Due to the presence of amino group, it behaves as Lewis base which abstracts proton from active methylene compounds (2a-n) to generate carbanion I. The free hydroxyl group through hydrogen bonding facilitates the nucleophilic attack of carbanion of active methylene compounds on aldehydic group of 4-amino-3-formylcoumarin (1) to give II. Dehydration of II forms intermediate III. This is followed by subsequent cyclization and dehydration to afford the final product (3a-n). This cyclocondensation step is facilitated due to hydrogen bonds (III, IV).

Scheme 5 Plausible mechanism for the synthesis of (3a-n).
2.4.3. Comparative study of chitosan

To show the efficiency of chitosan as a heterogeneous basic catalyst for this reaction, a comparative study of chitosan with different acidic and basic catalysts was conducted (Table 3). When the model reaction was examined with heterogeneous acid catalysts (91 mg) such as sulfamic acid, HClO₄·SiO₂, NaHSO₄·SiO₂, P₂O₅·SiO₂, PTS, ZnCl₂, under solvent-free conditions at 80 °C, the reaction took longer time period, and yields were not satisfactory (Table 3, entries 2-7), whereas using basic catalysts such as piperidine, NaOMe (Table 3, entries 8, 9), the reaction again took longer time period for completion with lower yields and impure products. When chitosan was used as catalyst (Table 3, entry 10), the yield of the products increased significantly, suggesting chitosan as the catalyst of choice for Friedländer annulation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No catalyst</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Sulfamic acid</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>HClO₄·SiO₂</td>
<td>15</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>NaHSO₄·SiO₂</td>
<td>30</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>P₂O₅·SiO₂</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>PTS</td>
<td>20</td>
<td>59</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl₂</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>Piperidine</td>
<td>35</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>NaOMe</td>
<td>28</td>
<td>55 (impure)</td>
</tr>
<tr>
<td>10</td>
<td>Chitosan</td>
<td>2</td>
<td>89</td>
</tr>
</tbody>
</table>

2.4.4. Recycling study of the catalyst

The reusability of the chitosan catalyst was also tested upon the model reaction. After completion of the reaction, product was extracted with hot ethyl acetate (3x10 mL). The catalyst left after extraction was washed with methanol, dried in air and used for
the subsequent cycles. The results (Fig. 12) showed that there was no significant decrease in reaction yield up to five cycles showing that the catalyst was active up to five cycles.

![Recycling Study](image)

**Fig. 12** Reusability of the catalyst for the model reaction.

### 2.5. CONCLUSION

In this chapter, we have described a highly efficient, simple, and environmentally benign methodology for the synthesis of new benzopyranopyrano[4,3-b]pyridine derivatives. This eco-friendly protocol offers advantages such as excellent yields of products, shorter reaction time period, simple operational procedure, and reusability of the catalyst.

### 2.6. EXPERIMENTAL

4-amino-3-formylcoumarin was synthesized according to the reported procedure.⁶⁰

#### 2.6.1. General procedure for synthesis of benzopyranopyridines[4,3-b]derivatives (3a-n)

To a mixture of 4-amino-3-formylcoumarin, 1 (1 mmol), active methylene compounds, 2a-n (1 mmol), chitosan (20 mol%) was added. The reaction mixture was heated at 80 °C on a heating mantle for specified time (Table 2). After completion of the reaction (monitored by TLC) the product (3a-n) was isolated from the reaction mixture by hot ethylacetate (3×10 ml). The catalyst was removed by filtration and reused. After separation of catalyst, the solvent was evaporated from

---

26
filtrate under reduced pressure. The solid thus obtained was further purified by recrystallization using appropriate solvent. The recovered catalyst was further used for subsequent cycles.

2.7. Spectral data of the compounds

1,3-Dimethyl-2-oxo-2H-1-benzopyranof3,4:5,6|pyrido[2,3-e]pyrimidine-2,4-dione
(3a)

Nature of compound: White crystalline solid; m. p. >350 °C.

IR (KBr) cm\(^{-1}\): 1607 (C=O), 1666 (C=O), 1718 (C=O), 1746 (C=O).

\(^1^H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 3.78 (6H, s, 2xN-CH\(_3\)), 7.46-7.51 (2H, m, arom.H), 7.72-7.74 (1H, m, arom.H), 8.55-8.57 (1H, m, arom.H), 8.98 (1H, s, Ha).

\(^1^3^C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 30.51, 99.49, 105.62, 116.32, 118.34, 121.91, 125.64, 126.01, 133.17, 152.06, 156.81, 159.41, 162.66, 163.21, 163.84.

ESI-MS: \((m/z)\) 309 (M\(^+\)+1).


2-oxo-2H-1-benzopyranof3,4:5,6|pyrido[2,3-e]pyrimidine-2,4-(1H,3H)-dione (3b)

Nature of compound: White powder; m. p. >350 °C.

IR (KBr) cm\(^{-1}\): 1602 (C=O), 1697 (C=O), 1725 (C=O), 3161, 3037(NH).

\(^1^H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 7.45-7.50 (2H, m, arom. H), 7.71-7.75 (1H, m, arom. H), 8.43-8.45 (1H, m, arom.H), 8.88 (1H, s, Ha), 11.81 (1H, s, NH), 12.34 (1H, s, NH).

\(^1^3^C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 99.49, 108.9, 116.32, 118.34, 121.91, 125.64, 126.01, 138.17, 148.62, 152.01, 156.78, 159.72, 162.20, 163.19.

ESI-MS: \((m/z)\) 282 (M\(^+\)+1).

Elemental analysis for \(\text{C}_{14}\text{H}_{7}\text{N}_3\text{O}_4\): Calculated: C, 59.83, H, 2.51, N, 15.21; Found: 50.92, H, 2.48, N, 15.23.
2-Thioxo-2-oxo-2H-1-benzopyrano[3',4:5,6]pyrido[2,3-e]pyrimidine-(1H,3H)-4-one (3c)

**Nature of compound:** Light yellow solid; m. p. >350 °C.

**IR (KBr) cm⁻¹:** 1607 (C=N), 1686 (C=O), 1730 (C=O), 3165, 3055 (NH).

**¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 7.46-7.55 (2H, m, arom.H), 7.73-7.77 (1H, m, arom.H), 8.41-8.43 (1H, m, arom.H), 8.82 (1H, s, Ha), 13.60 (1H, s, NH), 12.89 (1H, s, NH).

**¹³C NMR (100 MHz, DMSO-d₆):** δ (ppm) 114.5, 116.4, 118.1, 119.4, 125.4, 126.8, 131.1, 147.0, 152.0, 154.5, 158.0, 166.2, 161.2, 177.4

**ESI-MS:** (m/z) 298 (M⁺+1).

**Elemental analysis for C₁₄H₁₀N₂O₃S:** Calculated: C 56.61, H, 2.37, N, 14.20; Found: C, 56.34, H, 2.51, N, 14.40.

2,2-dimethyl-6-oxo-6H-1-benzopyrano[3,4-b]quinolin-4-(4H)-one (3d)

**Nature of compound:** White crystalline solid; m. p. 243-248 °C

**IR (KBr) cm⁻¹:** 1603 (C=N), 1694 (C=O), 1738 (C=O).

**¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 1.09(s, 6H, 2xCH₃), 2.69(s, 2H, CH₂), 3.32(s, 2H, CH₂), 7.48-7.51(m, 2H, arom.H), 7.72-7.74(m, 1H, arom.H), 8.50-8.52(m, 1H, arom.H), 8.77(s, 1H, Ha)

**¹³C NMR (100 MHz, DMSO-d₆):** δ (ppm) 27.75, 32.51, 46.18, 50.98, 99.56, 116.37, 117.34, 118.44, 125.06, 125.14, 126.87, 133.67, 135.86, 152.99, 153.59, 160.03, 168.33, 196.26

**ESI-MS:** (m/z) 294 (M⁺+1).

**Elemental analysis for C₁₈H₁₅NO₃:** Calculated: C 73.78, H, 5.16, N, 4.80; Found: C, 73.52, H, 5.28, N, 4.73.

2,2-Dimethyl-1,3-dioxan-chromen[3,4-b]quinoline-4,6(4H,6H)-dione (3e)

**Nature of compound:** White solid m. p. >300 °C.

**IR (KBr) cm⁻¹:** 1608 (C=N), 1700 (C=O), 1751 (C=O).
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ (ppm) 1.83 (6H, s, 2xCH$_3$), 7.73-7.74 (2H, m, arom.H), 7.66-7.71 (1H, m, arom.H), 8.39-8.42 (1H, m, arom.H), 8.99 (1H, s, Ha).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 27.60, 99.59, 112.61, 117.6, 124.0, 125.1, 126.8, 129.01, 133.6, 141.4, 152.9, 155.1, 159.1, 163.01, 165.9.

ESI-MS: (m/z) 298 (M$^+$+1).

Elemental analysis for C$_{16}$H$_{11}$NO$_5$: Calculated: C 64.70, H, 3.73, N, 4.73; Found: C, 64.42, H, 3.81, N, 4.51.

2-oxo-2H-1-benzopyranof3,4-b]-5-oxo-5H-indeno[2,3-e]pyridine (3f)

Nature of compound: Orange crystal; m. p. >325 °C.

IR (KBr) cm$^{-1}$: 1610 (C=N), 1681 (C=O), 1737 (C=O).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ (ppm) 7.42-7.44(1H, m, arom.H), 7.48-7.52(1H, m, arom.H), 7.65-7.73(2H, m, arom.H), 7.79-7.84(2H, m, arom.H), 8.13-8.14(1H, m, arom.H), 8.61(1H, s, Ha), 8.73-8.76(1H, m, arom.H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 116.0, 119.6, 123.6, 123.8, 124.21, 124.24, 124.50, 125.2, 125.3, 128.1, 129.2, 132.3, 142.5, 143.4, 150.7, 155.1, 161.8, 191.6

ESI-MS: (m/z) 300 (M$^+$+1).

Elemental analysis for C$_{19}$H$_9$NO$_5$: Calculated: C 76.32, H, 3.03, N, 4.70; Found: C, 76.51, H, 3.41, N, 4.73.

2-oxo-2H-1-benzopyranof3,4:5,6]pyrido[2,3-b]benzothiazine (3g)

Nature of compound: Yellow powder; m. p. >350 °C

IR (KBr) cm$^{-1}$: 1611 (C=N), 1731 (C=O), 3297(N-H).

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ (ppm) 7.40-7.51(4H, m, arom.H), 7.74-7.78(1H, m, arom.H), 7.87-7.89 (1H, m, arom.H), 8.01-8.03(1H, m, arom.H), 8.31-8.33(1H, m, arom.H), 9.40 (1H, s, Ha), 10.89(1H, s, NH)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 92.57, 113.59, 117.60, 122.16, 122.30, 124.82, 126.58, 133.43, 151.40, 153.41, 157.50, 161.52, 164.13
ESI-MS: (m/z) 319 (M⁺ +1).

Elemental analysis for C₁₈H₁₀N₂O₂S: Calculated: C 67.98, H, 3.16, N, 8.84; Found: C, 67.92, H, 3.29, N, 8.64.

2-oxo-2H-1-benzopyran-3,4:2,3|pyrido[5,6-c]-2-oxo-2H-1-benzopyran-2-one (3h)

Nature of compound: White powder m. p. >350 °C

IR (KBr) cm⁻¹: 1603 (C=N), 1694 (C=O), 1738 (C=O).

¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 7.52-7.58(m, 4H, arom.H), 7.78-7.82(m, 2H, arom.H), 8.81-8.84(m, 2H, arom.H), 9.12 (1H, s, Ha).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 117.3, 118.3, 119.6, 122.3, 125.1, 134.2, 143.2, 153.3, 155.6, 161.2.

ESI-MS: (m/z) 316 (M⁺ +1).

Elemental analysis for C₁₉H₁₉NO₄: Calculated: C 72.44, H, 2.87, N, 4.46; Found: C, 72.86, H, 2.93, N, 4.71.

3-Acetoacetyl-2-oxo-2H-[1]benzopyran-3,4-|pyridin-2-one (3j)

Nature of compound: Light yellow solid; m. p. >300 °C.

IR (KBr) cm⁻¹: 1615 (C=O), 1647 (C=O), 1732 (C=O), 3073(N-H).

¹H NMR (400 MHz, DMSO-d₆): δ (ppm) 2.24 (3H, s, CH₃), 7.16 (1H, s, C-H), 7.43-7.45 (2H, m, arom.H), 7.70-7.74 (1H, m, arom.H), 8.65-8.67 (1H, m, arom.H), 8.78 (1H, s, Ha), 13.14 (1H, s, NH), 16.08 (1H, s, OH).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 31.51, 97.94, 105.11, 116.88, 117.93, 123.15, 124.94, 127.19, 135.91, 138.76, 146.32, 152.69, 159.43, 163.53, 181.28, 196.16.

ESI-MS: (m/z) 298 (M⁺ +1).

Elemental analysis for C₁₆H₁₁NO₅: Calculated: C 64.70, H, 3.73, N, 4.73; Found: C, 64.32, H, 3.96, N, 4.81.

2-Amino-5-oxo-5H-[1]benzopyran-4,3-b|pyridine-3-carbonitrile(3k)

Nature of compound: White crystalline solid; m. p. 288-290 °C (Lit. 288-289 °C)
IR (KBr) cm⁻¹: 16014 (C=\(\text{N}\)), 1725 (C=O), 3211(\(\text{NH}_2\)).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 7.42-7.44 (1H, m, arom.H), 7.45-7.47(1H, m, arom.H), 7.70-7.73(1H, m, arom.H), 8.32-8.33(1H, m, arom.H), 8.65 (1H, s, \(H_a\)).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 103.8, 106.5, 114.1, 123.5, 126.5, 127.8, 128.9, 130.6, 144.9, 153.6, 158.8, 162.1, 164.01,

ESI-MS: \(m/z\) 238 (\(M^+ +1\)).

Elemental analysis for \(C_{13}H_7N_3O_2\): Calculated: C 68.82, H, 2.97, N, 17.71; Found: C, 68.84, H, 2.96, N, 17.19.

\(\text{Ethyl 1,5-Dihydro-2,5-dioxo-2H-[1]benzopyranof4,3-bpyridine-3-carboxylate(3l)}\)
Nature of compound: colourless crystal; m. p. 312-315 °C (Lit. 313-315 °C)

IR (KBr) cm⁻¹: 3100(NH), 1603 (C=\(\text{N}\)), 1696(C=O), 1710 (C=O).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 1.28(3H, t, CH\(_3\)), 4.25(2H, q, OCH\(_2\)), 7.36-7.38 (1H, m, arom.H), 7.40-7.43(1H, m, arom.H), 7.65-7.67(1H, m, arom.H), 8.43-8.45(1H, m, arom.H), 8.40 (1H, s, \(H_a\)).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 10.01, 34.90, 99.81, 115.6, 117.81, 122.8, 124.6, 127.9, 138.1, 144.1, 152.8, 153.9, 158.9, 162.1, 199.98.

ESI-MS: \(m/z\) 270 (\(M^+ +1\)).

Elemental analysis for \(C_{13}H_{11}NO_4\): Calculated: C 66.91, H, 4.11, N, 5.20; Found: C, 66.89, H, 4.10s, N, 5.22.

\(\text{Ethyl 2-Methyl-5-oxo-5 H-[1]benzopyranof4,3-bpyridine-3-carboxylate(3m)}\)
Nature of compound: colourless crystal; m. p. 164-168 °C (Lit. 166-167 °C).

IR (KBr) cm⁻¹: 16042 (C=\(\text{N}\)), 1720 (C=O), 1733 (C=O).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 1.37(3H, t, CH\(_3\)), 2.99(3H, s, CH\(_3\)), 4.44(2H, q, OCH\(_2\)), 7.47-7.49 (1H, m, arom.H), 7.50-7.53(1H, m, arom.H), 7.74-7.76(1H, m, arom.H), 8.50-8.61(1H, m, arom.H), 8.78 (1H, s, \(H_a\)).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) (ppm) 22.3, 8.01, 35.10, 114.81, 123.5, 124.6, 127.9, 130.6, 138.1, 144.1, 150.8, 153.6, 158.8, 162.1, 166.61, 199.69.
**Friedländer condensation**

ESI-MS: \( m/z \) 284 (M\(^+\)+1).

Elemental analysis for C\(_{16}\)H\(_{12}\)NO\(_4\): Calculated: C 67.83, H, 4.62, N, 4.94; Found: C, 67.82, H, 4.61, N, 4.94.

3-Acetyl-2-methyl-5-oxo-5 H-1-benzopyran-4,3-b]pyridine(3n)

Nature of compound: Yellow powder; m. p. >350 °C

IR (KBr) cm\(^{-1}\): 1607 (C=N), 1690(C=O), 1746 (C=O).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 2.72(3H, s, CH\(_3\)), 2.89(3H, s, OCH\(_3\)), 7.42-7.47 (2H, m, arom.H), 7.67-7.70(1H, m, arom.H), 8.57-8.59(1H, m, arom.H), 8.88 (1H, s, Ha).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) (ppm) 25.44, 29.17, 116.84, 117.4, 121.4, 124.7, 124.9, 127.8, 133.1, 138.9, 141.2, 153.2, 153.8, 160.9, 198.2.

ESI-MS: \( m/z \) 254 (M\(^+\)+1).

Elemental analysis for C\(_{15}\)H\(_{11}\)NO\(_3\): Calculated: C 71.20, H, 4.38, N, 5.55; Found: C, 71.15, H, 4.19s, N, 5.05.
2.8. REFERENCES

1. Friedländer, P. *Ber.* 1882, 15, 2572.

CHAPTER 3

Synthesis of Quinolinyl Alkenes via Knoevenagel Condensation using $[\text{Et}_3\text{NH}][\text{HSO}_4]$: A Green Protocol
3.1. INTRODUCTION

Ionic liquids (ILs) are organic salts mainly composed of organic cations and inorganic anions. They are liquid below 100 °C and have been known for a long time, but their extensive use as reaction media for synthesis and catalysis has recently become remarkable. [EtNH$_3$][NO$_3$], which has a melting point of 12 °C, was first ionic liquid reported in 1914. The terms room temperature ionic liquid (RTIL), non-aqueous ionic liquid, molten salt, liquid organic salt and fused salt have all been used to describe these salts in the liquid phase. The first generation ionic liquids, organo-aluminates were unstable to air and water, hence have limited applications. Furthermore, these organo-aluminates were not inert towards various organic compounds. After the first report on the syntheses and applications of air stable ILs such as 1-n-butyl-3-methylimidazolium tetrafluoroborate ([bmmim][BF$_4$]) and 1-n-butyl-3-methylimidazolium hexafluorophosphate ([bmmim][PF$_6$]), the number of air and water stable ionic liquids have increased rapidly. Recently, ionic liquids are of considerable interest in the context of green synthesis because of their adjustable physical and chemical properties. They have been introduced as alternative green reaction media due to their unique chemical and physical properties such as low vapour pressure, high thermal and chemical stability, good solvating ability, ease of recyclability, and controlled miscibility. Researchers have discovered that ILs have several applications such as sensors, fuel cells, batteries, capacitors, thermal fluids, plasticizers, lubricants, extractants and solvents in synthesis and catalysis. Due to their interesting properties, they find also numerous applications at industrial scale, e.g. BASF (BASIL, aluminium plating, cellulose dissolution), Institut Francais du Petrole (Difasol), Degussa (paint additives), Linde (hydraulic ionic liquid compressor), and Pionics (batteries). They also act as solvents in enzymatic, whole-cell biocatalysis and as protein stabilisation agents. In addition, their potential use as active pharmaceutical ingredients are being explored exhibiting their potential in biochemical studies. In this regard, [Et$_3$NH][HSO$_4$] could serve the purpose as it is prepared via a simple and atom economic acid-base neutralization reaction from cheap amine and acid. In the context of organic synthesis, acidic Bronsted ion liquids (ABILs) are of special importance because they possess simultaneously the proton acidity and the characteristic properties of an ionic liquid. Particularly, acidic Bronsted or Lewis ionic liquids, offer environmental-friendly catalysts properties due to the combination of the advantages of liquid acids and solid acids, such as uniform
acid sites, stability in water and air, easy separation and reusability. In this regard, this ionic liquid has been proved to be very excellent catalyst as well as solvent for many organic transformations which are listed below.

3.2. REVIEW AND LITERATURE

3.2.1a. [Et₂NH][HSO₄] as catalyst and solvent for cinnamic acid synthesis.

Weng et al. described the hydrolyzation of 1,1,1,3-tetrachloro-3-phenylpropane to synthesize cinnamic acid in [Et₂NH][HSO₄] without any additional catalyst and solvent. This ionic liquid could be easily separated and reused without losing its activity and quality. Also, the yields obtained with this methodology were very good.³⁸

\[
\begin{align*}
\text{R} = \text{C}_6\text{H}_5, \ R', R'' = \text{H} \\
\text{Cl} & \quad \text{R'} & \quad \text{Cl} & \quad \text{R'} \\
\text{CCl}_3 & \quad \text{H}_2\text{O} & \quad \text{[Et}_2\text{NH][HSO}_4] & \quad 120 \ ^\circ\text{C}, 8 \text{h} \\
\rightarrow & \quad \text{R} & \quad \text{R'} & \quad \text{COOH} & \quad 4\text{HCl}
\end{align*}
\]

3.2.1b. [Et₂NH][HSO₄] catalyzed synthesis of Bis(indolyl)methanes.

Bis(indolyl)methanes were efficiently synthesized in the presence of [Et₂NH][HSO₄]. The yields obtained were good to excellent (83-95%). The reaction, however, was highly chemo selective and applicable only to aldehydes and not to ketones. The ionic liquid was recovered and reused with no appreciable change in activity.³⁹

\[
\begin{align*}
\text{R} = & \quad -\text{Ph}\quad, \quad -\text{Ph}-\text{NO}_2, \quad -\text{Ph}-\text{Cl}, \quad -\text{Ph}-\text{OCH}_3 \\
\text{HO} & \quad -\text{Ph}\quad, \quad -\text{Ph}
\end{align*}
\]

3.2.1c. Biginelli reaction mediated by [Et₃NH][HSO₄]

[Et₃NH][HSO₄] were efficiently utilized as solvent and catalyst for the Biginelli reaction in solvent-free conditions. This protocol was very efficient and green providing good to excellent yield of the products.⁴⁰
3.2.1d. Ionic liquid $[\text{Et}_3\text{NH}][\text{HSO}_4]$ as efficient catalyst for $\beta$- amino carbonyl pyrimidines synthesis.

Ionic liquid $[\text{Et}_3\text{NH}][\text{HSO}_4]$ was found to be an efficient catalyst for the synthesis of $\beta$-amino carbonyl pyrimidines through the Mannich condensation reaction of substituted pyrimidin-2(1H)-ones, cyclohexanone and 4-fluoro/chlorobenzaldehyde under ultrasonic irradiation at room temperature. This protocol was simple, high-yielding (83%), and environmentally benign.\(^{41}\)

\[
\text{R'} = \text{C}_6\text{H}_5, 4-\text{Cl-C}_6\text{H}_4, 4-\text{OCH}_3-\text{C}_6\text{H}_4, 4-\text{NO}_2-\text{C}_6\text{H}_4, 4-\text{CH}_3-\text{C}_6\text{H}_4, 2-\text{Cl-C}_6\text{H}_4, 2,4-\text{di-Cl-C}_6\text{H}_3, 3-\text{NO}_2-\text{C}_6\text{H}_4, 4-\text{OH-C}_6\text{H}_4, 4-\text{Br-C}_6\text{H}_4
\]

\[
\text{R}'' = \text{OEt, OMe}
\]

3.2.1e. Octahydroxanthenes synthesis by employing $[\text{Et}_3\text{NH}][\text{HSO}_4]$.

Zhou et al. reported a simple and efficient protocol for the synthesis of 1,8-dioxo-octahydroxanthenes by condensation of aromatic aldehydes with 5,5-dimethyl-1,3 cyclohexanedione under solvent-free conditions using $[\text{Et}_3\text{NH}][\text{HSO}_4]$ as catalyst. The advantages associated with this protocol were neat reaction condition, high yield (94%) of products and simple experimental and work-up procedures.\(^{42}\)

\[
\text{R}_1 = \text{H, OH, OCH}_3, \text{Cl}
\]

\[
\text{R}_2 = \text{H, Cl}
\]

\[
\text{R}_3 = \text{H, OCH}_3, \text{Cl}
\]

\[
\text{R}_4 = \text{Cl, F}
\]
3.2.1f. Cracking reaction of dialkoxypropanes in [Et₃NH][HSO₄] ionic liquid.

Ionic liquid [Et₃NH][HSO₄] had been used in cracking reaction. Thus, alkoxypropanes were obtained in excellent yield with greater selectivity. This protocol provide a good alternative way for the synthesis of alkoxypropanes at industrial scale.⁴³

3.2.1g. [Et₃NH][HSO₄] as both catalyst and reaction medium for the preparation of dialkoxypropanes.

Hui Jiang et al reported use of [Et₃NH][HSO₄] as catalyst as well as environmentally benign reaction medium for preparation of dialkoxypropanes, eliminating the need for volatile organic solvents and harmful hydrogen chloride catalysts. This methodology provided good yield of the products (98%), easy separation of the products from the catalyst/solvent, recyclable catalyst which was applicable at industrial level also.⁴⁴

3.2.1h. [Et₃NH][HSO₄] promoted Saucy-Marbet reaction.

Saucy-Marbet reaction was well promoted by [Et₃NH][HSO₄] as catalyst as well as solvent with the conversion of 88% and selectivity of 97%. It provided a good alternative way for the industrial synthesis of unsaturated ketones.⁴⁵
3.2.1i. Esterification reaction catalysed by eco-friendly ionic liquid [Et$_3$NH][HSO$_4$].

[Et$_3$NH][HSO$_4$] had also been used in esterification of carboxylic acids. Thus, acetic acid reacts with 1-octanol in the presence of [Et$_3$NH][HSO$_4$] to give corresponding esters in high yield.\(^{45}\)

\[
\text{CH}_3\text{COOH} + \text{CH}_3\text{(CH}_2\text{)}_7\text{CH}_2\text{OH} \xrightarrow{[\text{Et}_3\text{NH}[\text{HSO}_4]} \text{CH}_3\text{COO-CH}_2\text{(CH}_2\text{)}_6\text{CH}_3 + \text{H}_2\text{O}
\]

90 °C, 4h

3.2.1j. Friedländer condensation catalysed by [Et$_3$NH][HSO$_4$] under solvent-free conditions.

A rapid and efficient synthesis of a variety of substituted quinolines had been reported through the reactions of o-aminoarylketones with carbonyl compounds containing a reactive α-methylene moiety in the presence of molten [Et$_3$NH][HSO$_4$] under solvent-free conditions in high yields (94%).\(^{47}\)

3.3. PRESENT WORK

Knoevenagel reaction is a facile and versatile method for the formation of carbon-carbon bonds,\(^{49}\) with numerous applications in the synthesis of intermediates of fine chemicals,\(^{50}\) hetero-Diels–Alder reactions\(^{50}\) and in the synthesis of carbocyclic as well as hetero cyclic compounds of biological significance.\(^{51}\) The reaction has also been utilized in the preparation of coumarin derivatives,\(^{52}\) cosmetics,\(^{53}\) perfumes\(^{54}\) and pharmaceutical chemicals.\(^{55}\) A variety of ionic liquids have been employed for Knoevenagel condensation reaction such as [6-mim]PF$_6$,\(^{56}\) [bmim]Cl-xAlCl$_3$ and [bpy]Cl-xAlCl$_3$,\(^{57}\) [bmim]BF$_4$,\(^{58}\) guanidinium lactate ionic liquid,\(^{59}\) ethylammonium
Quinolinsyl alkenes.

Nitrate (EAN), ionic liquid [bmim]OH, glycine in ionic acid, HMTA–AcOH, [C4-choline][Ac], ethylenediammonium Diacetate, 2-hydroxyethylammonium formate, and 2-HEAA etc. However, these ionic liquids are not entirely satisfactory, due to drawbacks such as long reaction times, low yield of products, instability in moisture and air, expensiveness, and need of extra catalysts.

Quinolines and their derivatives, represent a major class of heterocycles and are widely found in natural products. The quinoline ring is endowed with various activities, such as antimicrobial, antituberculosis, antimalarial, anti-inflammatory, anticancer, antibiotic, antihypertensive, tyrosinase PDGF-RTK inhibiting agents, antiHIV and anti-convulsant. Amongst the various activities of their derivatives, antimicrobial & antimalarial activity is noteworthy.

In this chapter we have discussed the synthesis of quinolinsyl alkenes via Knoevenagel condensation using ionic liquid [Et3NH][HSO4] as an eco-friendly solvent and as highly efficient catalyst. Using this environmentally benign protocol, excellent yields of quinolinsyl alkenes were obtained within short time period. The ionic liquid was characterized well with 1H NMR and 13C NMR spectroscopy.

3.4 RESULTS AND DISCUSSION

3.4.1. Characterization of ionic liquid [Et3NH][HSO4]

The ionic liquid [Et3NH][HSO4] was characterized with 1H NMR and 13C NMR spectroscopy. 1H NMR spectrum of [Et3NH][HSO4] (Fig. 13) showed signal for OH proton at δ 8.60. CH2 protons were discernible as a multiplet at δ 3.18. A triplet at δ 2.7 was attributed to CH3 protons. 13C NMR spectrum (Fig. 14) showed two signals δ 45.89 and δ 8.40 for CH2 and CH3 carbons, respectively.
Fig. 13 1H NMR spectrum of [Et₃NH][HSO₄]

Fig. 14 ¹³C NMR spectrum of [Et₃NH][HSO₄]
3.4.2. Optimization of reaction conditions

3.4.2a. Effect of solvents

Our study started with the investigation of the optimum reaction conditions regarding the solvent, amount of catalyst, and temperature of the reaction. For this purpose, a model reaction was studied using 2-chloro-3-formylquinoline 9a and 1,3-dimethylbarbituric acid 2a as model substrates for the synthesis of quinolinyl alkene 10a (Scheme 6). Initially, effect of different solvents on the model reaction was studied using model substrates and 20 mol % of [Et₃NH][HSO₄] as catalyst in different solvents (Table 4) under reflux condition. In polar protic solvents like MeOH, EtOH, and (CH₃)₂CHOH (Table 4, entries 1, 2 and 3), the reaction took longer time period (6-14 h) with moderate yield of the products, whereas in water (Table 4, entry 4), the product was obtained in trace amount after 3 h. In polar aprotic solvent such as CH₃CN (Table 4, entry 5), a lower yield of the product was obtained in 7 h. Conducting the reaction in THF and C₆H₅CH₃ (Table 4, entries 6, 7), only a trace amount of the product was obtained. However, when the model reaction was carried out under a solvent-free condition (Table 4, entry 8), there was significant increase in the yield of the product in a shorter time period. Thus, it is concluded that solvent-free is the best condition for this Knoevenagel condensation.

Table 4 Optimization of reaction conditions for the synthesis of quinoline derivative catalysed by [Et₃NH][HSO₄].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Catalysts (mol%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeOH</td>
<td>reflux</td>
<td>6</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>2.</td>
<td>EtOH</td>
<td>reflux</td>
<td>7</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>3.</td>
<td>(CH₃)₂CHOH</td>
<td>reflux</td>
<td>14</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>4.</td>
<td>H₂O</td>
<td>reflux</td>
<td>3</td>
<td>20</td>
<td>Trace</td>
</tr>
<tr>
<td>5.</td>
<td>CH₃CN</td>
<td>reflux</td>
<td>7</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>6.</td>
<td>THF</td>
<td>reflux</td>
<td>9</td>
<td>20</td>
<td>Trace</td>
</tr>
</tbody>
</table>

44
7. C₆H₅CH₃ reflux 15 h 20 Trace
8. Solvent-free 80 5 min 20 99

3.4.2b. Effect of temperature

To optimize the reaction temperature, the model reaction employing model substrates and 20 mol % of ionic liquid was carried out at different temperatures (Table 5). The yield of the product increased when the reaction temperature was raised from room temperature to 80 °C. However, no increase in the yield of product was observed when the reaction temperature was further increased to 100 °C whereas a decrease in product yield was observed when reaction was conducted at 110 °C. Therefore, all further reactions were carried out at 80 °C.

Table 5 Effect of temperature on the model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>r.t.</td>
<td>1.5 h</td>
<td>42</td>
</tr>
<tr>
<td>2.</td>
<td>40</td>
<td>45 min</td>
<td>51</td>
</tr>
<tr>
<td>3.</td>
<td>60</td>
<td>20 min</td>
<td>74</td>
</tr>
<tr>
<td>4.</td>
<td>80</td>
<td>5 min</td>
<td>99</td>
</tr>
<tr>
<td>5.</td>
<td>100</td>
<td>5 min</td>
<td>99</td>
</tr>
<tr>
<td>6.</td>
<td>110</td>
<td>5 min</td>
<td>97</td>
</tr>
</tbody>
</table>

3.4.2c. Effect of catalyst concentration

Different concentration of the ionic liquid [Et₃NH][HSO₄] such as 5, 10, 15, 20, and 25 mol % were examined for model reaction at 80°C under solvent-free conditions to get the optimum yield in minimum time period (Fig. 15). It was observed that the product was obtained in 90%, 92%, 97%, 99%, and 99% yield, respectively. Thus, it is concluded that 20 mol % of [Et₃NH][HSO₄] is sufficient for the best result. Therefore,
all reactions were carried out at 80°C in the presence of 20 mol % of [Et$_3$NH][HSO$_4$] under solvent-free conditions.

Fig. 15 Effect of catalyst loading on the model reaction.

3.4.2d. Effect of different anions and cations on the catalytic activity of ionic liquid

To show the superiority of [Et$_3$NH][HSO$_4$], the model reaction was also carried out in the presence of other acidic Bronsted ionic liquids (Table 6). The catalytic activity of the ionic liquid with the [HSO$_4$]$^-$ anion (Table 6 entry 1) was higher than the other two [H$_2$PO$_4$]$^-$ and [CH$_3$COO]$^-$ (Table 6, entries 2, 3). This is primarily due to higher acidity of the former as compared to the other two. When the [Me$_3$NH][HSO$_4$] ionic liquid was used (Table 6, entry 4), the yield of the reaction decreased as compared to [Et$_3$NH][HSO$_4$].

Table 6 Comparison of the efficiency of [Et$_3$NH][HSO$_4$] for synthesis of 10a

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[Et$_3$NH][HSO$_4$]</td>
<td>5</td>
<td>99</td>
</tr>
<tr>
<td>2.</td>
<td>[Et$_3$NH][H$_2$PO$_4$]</td>
<td>9</td>
<td>97</td>
</tr>
</tbody>
</table>
3.4.2e. Comparison of catalytic activity of ionic liquid [Et$_3$NH][HSO$_4$] with other reported ionic liquids for Knoevenagel condensation

The efficiency of [Et$_3$NH][HSO$_4$] was also compared with other ionic liquids reported earlier for Knoevenagel condensation. The data summarized in Table 7 show the advantages of the present method in terms of reaction rate and yield as compared with those reported in the literature. Additionally, the present catalyst is more beneficial from the economical and accessibility point of view and is stable both in air and water.

Table 7 Comparison of ionic liquids used as catalysts for Knoevenagel condensation

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Ionic liquids</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>n-butylpyridinium nitrate</td>
<td>15 min</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>2.</td>
<td>[emim][BF$_4$]</td>
<td>12 h</td>
<td>97</td>
<td>82</td>
</tr>
<tr>
<td>3.</td>
<td>[bmim] PF$_6$</td>
<td>6 h</td>
<td>96</td>
<td>83</td>
</tr>
<tr>
<td>4.</td>
<td>EAN</td>
<td>3 h</td>
<td>94</td>
<td>60</td>
</tr>
<tr>
<td>5.</td>
<td>[DBU][Lac]</td>
<td>30 min</td>
<td>96</td>
<td>84</td>
</tr>
<tr>
<td>6.</td>
<td>[bmIm]OH</td>
<td>10 min</td>
<td>93</td>
<td>61</td>
</tr>
<tr>
<td>7.</td>
<td>[Hmim]Tfa</td>
<td>4 h</td>
<td>91</td>
<td>85</td>
</tr>
<tr>
<td>8.</td>
<td>[2-aemim][PF$_6$]</td>
<td>30 min</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>9.</td>
<td>[bnmim]Cl</td>
<td>20 min</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>10.</td>
<td>[$^{13}$Pr$_2$N(CH$_2$)$_2$(OCH$_2$CH$_2$)$_2$-]</td>
<td>20 min</td>
<td>91</td>
<td>88</td>
</tr>
</tbody>
</table>
3.4.3. Synthesis of quinoliny1 alkene derivatives

With the optimized reaction condition in hand, the scope and efficiency of this approach were explored for the synthesis of other quinoliny1 alkene derivatives, 10 (a-j), Scheme 6.

Scheme 6 Synthesis of quinoline derivatives.

It was observed that excellent yield of products were obtained within a relatively shorter time period and the obtained results are summarized in Table 8.
Table 8 [Et$_3$NH][HSO$_4$] catalysed synthesis of Quinolinyl alkene 10a-j

<table>
<thead>
<tr>
<th>Entry</th>
<th>Active methylene compound</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="2a" /></td>
<td><img src="image" alt="10a" /></td>
<td>5</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="2b" /></td>
<td><img src="image" alt="10b" /></td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="2c" /></td>
<td><img src="image" alt="10c" /></td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="2d" /></td>
<td><img src="image" alt="10d" /></td>
<td>7</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="2e" /></td>
<td><img src="image" alt="10e" /></td>
<td>6</td>
<td>90</td>
</tr>
</tbody>
</table>

Quinolinyl alkenes
The structures of the compounds isolated were characterized by elemental and spectral analyses (IR, $^1$H NMR $^{13}$C and Mass spectrometry). The infrared (IR) spectrum (Fig. 16) of 10a showed the carbonyl absorption bands of barbituric acid moiety at 1693 cm$^{-1}$. Another slightly broadened and strongly absorbed at 1655 cm$^{-1}$ was assigned to conjugated carbonyl groups. The absorption band at 1580 cm$^{-1}$ was assigned to carbon-carbon double bond of alkene. The $^1$H-NMR spectrum (Fig. 17) showed two sharp singlets at $\delta$ 9.10 and $\delta$ 8.54 and were assigned to H-4' and H-1''', respectively. Four aromatic protons of the quinoline moiety appeared as multiplet in the range of $\delta$ 7.78-7.25 ppm. Two sharp singlets integrating for three protons at $\delta$ 3.24 and $\delta$ 3.20 were due to N-CH$_3$ groups of barbituric acid moiety. The $^{13}$C NMR spectrum (Fig. 18) showed signals at $\delta$ 162.0, 161.6 and 160.7 for carbonyl groups of barbituric acid moiety whereas signal for olefinic carbons C-1''' and C-5 appeared at $\delta$ 145.5 and $\delta$ 133.3, respectively. Two CH$_3$ group of barbituric acid moiety were discernible at $\delta$ 28.6 and $\delta$ 28.1. Other carbon signals were present at their appropriate positions and are given in experimental section. Mass spectrum (Fig. 19), showed molecular ion peak at m/z 330.1 (M$^+$+1) confirming the assigned structure of compound 10a. The spectral data of other compounds followed similar pattern.
Fig. 16 FT-IR spectrum of the compound 10a

Fig. 17 $^1$H NMR spectrum of the compound 10a
Fig. 18 $^{13}$C NMR spectrum of 10a

Fig. 19 Mass spectrum of the compound 10a
It was observed that due to higher reactivity of dimedone 2d and lactones 2h, 2j the reaction did not stop at the Knoevenagel condensation stage and proceeded further for Michael addition with another molecule of 2d, 2h and 2j to the double bond of the initially formed Knoevenagel intermediates followed by cyclization to give cyclized products 10(d, h, j). The IR spectrum of 10d (Fig. 20) showed absorption band at 3289 for hydroxyl group. The sharp and strong absorption bands at 1664 cm\(^{-1}\) and 1628 cm\(^{-1}\) were due to \(\alpha, \beta\) unsaturated carbonyl groups. The \(^1\)H NMR (Fig. 21) exhibited sharp singlets at \(\delta\) 0.98 and \(\delta\) 1.08 for CH\(_3\) groups and a multiplet at \(\delta\) 2.10-2.44 for CH\(_2\) groups of dimedone moieties. Another singlet integrating for one proton at \(\delta\) 4.62 was assigned to methine protons. Aromatic protons appeared in the range of \(\delta\) 7.78-7.11. Hydroxyl proton was discernible as singlets at \(\delta\) 11.35. The \(^{13}\)C NMR spectrum (Fig. 22) showed peaks at \(\delta\) 196.3, \(\delta\) 164.1 and \(\delta\) 160.1 for C-OH, C=O, C=O of dimedone moiety. The peaks for aromatic carbons appeared in the range of \(\delta\) 114.5-131.9. Peaks at \(\delta\) 26.6 and \(\delta\) 29.1 was assigned to CH\(_3\) group and C-6 carbon, respectively. Signals for carbons bearing methyl groups of dimedone moieties were present at \(\delta\) 31.8 and \(\delta\) 30.4. The CH\(_2\) carbon signals were present at \(\delta\) 50.6 and \(\delta\) 43.2. Further confirmation of the structure was provided by mass spectrometry which showed molecular ion peak at \(m/z\) 418.2 (M\(^+\)+1) (Fig. 23).

Fig. 20 FT-IR spectrum of compound 10d
Fig. 21 $^1$H NMR spectrum of compound 10d

Fig. 22 $^{13}$C NMR spectrum of compound 10d
Fig. 23 Mass spectrum of compound 10d

A plausible mechanism for the synthesis of quinoline derivatives via Knoevenagel condensation catalyzed by [Et$_3$NH][HSO$_4$] is shown in Scheme 7. As [Et$_3$NH][HSO$_4$] is a protic ionic liquid, initially aldehyde (9a) was protonated to form intermediate II. It facilitated the nucleophilic attack of the active methylene compound (2a) for C-C bond formation. The final Knoevenagel product 10a was formed by the elimination of a water molecule from III and an ionic liquid I regenerated.
Scheme 7 Probable mechanism for the synthesis of quinoliny1 alkene (10a).

3.4.4. Recycling study of [Et$_3$NH][HSO$_4$]

The reusability of the catalyst is a significant advantage particularly for commercial applications. Thus, the recovery and reusability of [Et$_3$NH][HSO$_4$] were also investigated (Fig 24). After the completion of the reaction, cold water was added to the reaction mixture, and the product was isolated by filtration. The ionic liquid was recovered by removing the water under reduced pressure and was reused at least seven times without any appreciable decrease in yield.
Fig. 24 Reusability of the catalyst for the model reaction.

3.5. CONCLUSION

We have developed a simple, efficient, mild, and environmentally benign method for the synthesis of new quinolinyl alkenes. The green protocol offers several advantages such as excellent yield of products, shorter reaction time period, simple operational procedure and easy preparation of the catalyst and reusability of the catalyst.

3.6. EXPERIMENTAL

2-Chloro-3-formylquinoline was synthesized by using DMF/POCl₃ according to the reported method.⁹⁰

3.6.1. Preparation of [{Et₃NH}][HSO₄]

Sulfuric acid (19.6 g, 0.2 mol) 98% solution in water was dropped into triethylamine (20.2 g, 0.2 mol) while stirring at 60 °C for 1 h. After the addition, the reaction mixture was stirred for another 1 h at 70 °C. Water was removed by heating the residue at 80 °C in high vacuum until the weight of the residue remained constant.

3.6.2. General procedure for synthesis of quinolinyl alkenes (10a-j)

To a mixture of 2-chloro-3-formylquinoline (9a, 1.00 mmol) and active methylene compounds (2a-j, 1.00 mmol), 20 mol % [{Et₃NH}][HSO₄] was added, and the mixture was heated on an oil bath at 80 °C with good stirring. During the reaction process, the
mixture spontaneously solidified. After completion of the reaction (monitored by TLC), the reaction was cooled to room temperature, water was added, and the mixture was stirred for 5 min. The solid obtained was removed by filtration and recrystallized from methanol. Filtrate was dried under reduced pressure to recover ionic liquid, which was reused in subsequent cycles.

3.7. Spectral data of compounds

5(2-chloroquinolin-3-yl)methylene-1,3-dimethyl-2,4,6-pyrimidinetrione (3a)

**Nature of compound:** Yellow solid; **m. p.** 280 °C.

**IR (KBr) cm⁻¹:** 1580 (C=C), 1693 (C=O).

**¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 3.20 (3H, s, N-CH₃), 3.24 (3H, s, N-CH₃), 7.25-7.28 (2H, m, arom.H), 7.33-7.35 (1H, m, arom.H), 7.61-7.65 (1H, m, arom.H), 7.76-7.78 (1H, m, arom.H), 8.54 (1H, s, CH=C) 9.10 (1H, s, arom.H).

**¹³C NMR (100 MHz, DMSO-d₆):** δ (ppm) 28.15, 28.69, 115.35, 118.39, 119.98, 122.68, 124.55, 129.98, 133.14, 140.22, 145.47, 149.41, 151.14, 160.71, 161.06, 162.06

**ESI-MS:** (m/z) 330(M⁺+1).

**Elemental analysis for** C₁₆H₁₂ClN₃O₃: Calculated: C 58.41, H, 3.67, N, 12.82; Found: C, 58.40, H, 3.51, N, 12.79.

5-(2-chloroquinolin-3-yl)methylene-2,4,6-pyrimidinetrione (3b)

**Nature of compound:** White solid; **m. p.** >300 °C.

**IR (KBr) cm⁻¹:** 1537 (C=C), 1716 (C=O), 3443 (N-H).

**¹H NMR (400 MHz, DMSO-d₆):** δ (ppm) 7.55-7.74 (1H, m, arom.H), 7.84-7.96 (3H, m, arom.H), 8.11 (1H, s, CH=C), 8.25(1H, s, arom.H).

**¹³C NMR (100 MHz, DMSO-d₆):** δ (ppm) 115.28, 118.31, 119.63, 122.45, 124.41, 129.80, 132.91, 140.23, 145.52, 149.67, 150.93, 160.55, 161.01, 161.8.

**ESI-MS:** (m/z) 302(M⁺+1).
Quinolinyl alkenes

Elemental analysis for C_{14}H_{8}ClN_{3}O_{2}: Calculated: C 55.86, H, 2.67, N, 14.01; Found: C, 55.90, H, 2.71, N, 14.23.

5-(2-chloroquinolin-3-yl)methylene-2-mercapto-4,6-pyrimidinedione(3c)

Nature of compound: Yellow solid; m. p. >300 °C.

IR (KBr) cm\(^{-1}\): 1539 (C=C), 1706 (C=O), 3445 (N-H).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)):\(\delta\) (ppm) 7.28-7.31 (1H, m, arom.H), 7.32-7.38 (1H, m, arom.H), 7.65-7.70 (1H, m, arom.H), 7.82-7.84 (1H, m, arom.H), 8.22 (1H, s, CH=C) 9.80 (1H, s, arom.H).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)):\(\delta\) (ppm) 127.12, 127.32, 127.48, 127.73, 127.93, 128.18, 129.46, 129.92, 133.48, 140.90, 149.80, 163.27, 188.78.

ESI-MS: (m/z) 318 (M\(^+\)+1).

Elemental analysis for C_{14}H_{8}ClN_{3}O_{2}S: Calculated: C 53.04, H, 2.54, N, 13.31; Found: C, 53.09, H, 2.61, N, 13.35.

6-(1-hydroxy-5,5-dimethyl-3-oxocyclohex-1-en-2-yl)-9,9-dimethyl-7,8,9,10-tetrahydro-1H-chromeno[2,3-b]quinolin-7-one (3d)

Nature of compound: White solid; m. p. >300 °C.

IR (KBr) cm\(^{-1}\): 1628 (C=O), 1664 (C=O) 3289 (O-H).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)):\(\delta\) (ppm) 0.98 (6H, s, 2xCH\(_3\)), 1.08 (6H, s, 2xCH\(_3\)), 2.10 (2H, d, J = 16.2 Hz, CH\(_2\)), 2.24 (2H, d, J = 16.2 Hz, CH\(_2\)), 2.41 (4H, d, J = 17.5 Hz, CH\(_2\)), 4.62 (1H, s, C-H), 7.08-7.11 (1H, m, arom.H), 7.23-7.25 (1H, m, arom.H), 7.33-7.37 (1H, m, arom.H), 7.55-7.57 (1H, m, arom.H), 7.78 (1H, s, arom.H), 11.35 (1H, s, O-H).

\(^13\)C NMR (100 MHz, DMSO-\(d_6\)):\(\delta\) (ppm) 26.67, 29.18, 30.40, 31.88, 43.26, 52.61, 111.50, 114.64, 119.36, 121.35, 127.44, 129.16, 131.97, 138.31, 139.06, 160.90, 164.15, 196.32.

ESI-MS: (m/z) 418 (M\(^+\)+1).

Elemental analysis for C_{26}H_{27}NO_{4}: Calculated: C 74.80, H, 6.52, N, 3.35; Found: C, 74.82, H, 6.49, N, 3.38.
5-(2-chloroquinolin-3-yl) methylene-2,2-dimethyl-1,3-dioxo-4,6-dione(3e)

**Nature of compound:** Yellow solid; m. p. 201-215°C.

**IR (KBr) cm⁻¹:** 1546 (C=O), 1691 (C=O).

**¹H NMR (400 MHz, DMSO-δ6):** δ (ppm) 1.83 (6H, s, 2xCH₃), 7.38-7.43 (2H, m, arom.H), 7.66-7.71 (1H, m, arom.H), 7.97 (1H, s, CH=C), 8.39-8.42 (1H, m, arom.H), 8.99 (1H, s, arom.H).

**¹³C NMR (100 MHz, DMSO-δ6):** δ (ppm) 30.75, 112.99, 115.89, 116.38, 122.71, 123.54, 124.51, 131.87, 132.62, 152.00, 152.34, 159.63, 161.17, 161.97.

**ESI-MS:** (m/z) 318 (M⁺ +1).


2-(2-chloroquinolin-3-yl)methylene-1,3-indanedione(3f)

**Nature of compound:** Yellow solid; m. p. >300°C.

**IR (KBr) cm⁻¹:** 1590 (C=O), 1690 (C=O).

**¹H NMR (400 MHz, DMSO-δ6):** δ (ppm) 7.27-7.31 (1H, m, arom.H), 7.36-7.38 (1H, m, arom.H), 7.65-7.70 (1H, m, arom.H), 7.82-7.86 (1H, m, arom.H), 7.97-8.04 (3H, m, arom.H), 8.59 (1H, s, CH=C), 9.80 (1H, s, arom.H).

**¹³C NMR (100 MHz, DMSO-δ6):** δ (ppm) 120.65, 123.70, 124.77, 125.34, 125.39, 126.07, 127.39, 128.52, 135.73, 137.06, 144.53, 145.97, 153.98, 155.87, 159.35, 189.12.

**ESI-MS:** (m/z) 320 (M⁺ +1).

**Elemental analysis for C₁₉H₁₀ClNO₂:** Calculated: C, 71.53, H, 3.15, N, 4.40; Found: C, 71.49, H, 3.19, N, 4.38.

2-(chloroquinolin-3-yl)methylene-1,4-benzothiazin-3-one(3g)

**Nature of compound:** Yellow solid; m. p. >300°C.

**IR (KBr) cm⁻¹:** 1516(C=O), 1631(C=O), 3388(N-H).
**Quinolyl alkenes**

**1H NMR (400 MHz, DMSO-d$_6$):** δ (ppm) 7.06-7.10 (2H, m, arom.H), 7.25-7.28 (2H, m, arom.H), 7.50-7.52 (2H, m, arom.H), 7.63-7.67 (2H, m, arom.H), 7.79-7.82 (2H, m, arom.H), 7.96-7.98 (2H, m, arom.H), 8.03-8.08 (2H, m, arom.H), 8.60 (1H, s, CH=CH)

**13C NMR (100 MHz, DMSO-d$_6$):** δ (ppm) 115.50, 117.17, 118.13, 118.59, 122.50, 122.69, 125.55, 126.71, 127.13, 130.68, 133.39, 137.36, 141.20, 155.63, 158.95, 161.53, 164.99.

**ESI-MS:** (m/z) 339 (M$^+$+1).

**Elemental analysis for C$_{19}$H$_{11}$ClN$_2$OS:** Calculated: C 63.96, H, 3.27, N, 8.32; Found: C 63.96, H, 3.27, N, 8.32.

**6-(4-hydroxy-2-oxo-2H-chromeno-3-yl)quinolino[2,3:5,6]6H-pyran[2,3-c-1-benzopyran-7-one (3h).**

**Nature of compound:** White solid; m. p. >300°C.

**IR (KBr) cm$^{-1}$:** 1721 (C=O), 3308 (O-H).

**1H NMR (400 MHz, DMSO-d$_6$):** δ (ppm) 5.94 (1H, s, C-H), 7.43-7.52 (4H, m, arom.H), 7.57-7.60 (1H, m, arom.H), 7.62-7.73 (2H, m, arom.H), 7.73-7.82 (1H, m, arom.H), 7.82-8.02 (2H, m, arom.H), 8.09-8.25 (2H, m, arom.H), 8.64 (1H, s, arom.H), 11.41 (1H, s, O-H).

**13C NMR (100 MHz, DMSO-d$_6$):** δ (ppm) 33.23, 99.49, 102.29, 113.06, 114.81, 116.50, 118.91, 121.76, 123.12, 124.76, 128.05, 130.07, 132.94, 138.56, 140.68, 152.09, 154.64, 159.71, 160.49.

**ESI-MS:** (m/z) 484 (M$^+$+23)

**Elemental analysis for C$_{28}$H$_{15}$NO$_6$:** Calculated: C 72.95, H, 3.27, N, 3.05; Found: C, 72.96, H, 3.22, N, 3.08.

**4-(2-chloroquinol-3-yl)methylene-3-methyl-1-phenylpyrazol-5-one (3i)**

**Nature of compound:** White solid; m. p. 171-180°C.

**IR (KBr) cm$^{-1}$:** 1545 (C=C), 1692 (C=O).
\begin{align*}
\text{\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6):} & & \delta \text{ (ppm)} & 2.36 \ (3 \text{H}, \text{s}) , 7.20 - 7.23 \ (2 \text{H}, \text{m}), 7.33 - 7.36 \ (1 \text{H}, \text{m}), 7.53 - 7.57 \ (1 \text{H}, \text{m}), 7.71 - 7.78 \ (5 \text{H}, \text{m}), 8.13 \ (1 \text{H}, \text{s}, \text{CH=C}), 8.26 \ (1 \text{H}, \text{s}, \text{arom.H}). \\
\text{\textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6):} & & \delta \text{ (ppm)} & 20.21, 111.59, 114.68, 119.31, 121.21, 124.74, 126.80, 127.13, 129.17, 131.89, 138.39, 139.04, 144.51, 159.32, 160.95, 164.18. \\
\text{ESI-MS:} & & (m/z) & 348 \ (\text{M}^+ + 1). \\
\text{Elemental analysis for C}_{20}\text{H}_{14}\text{ClN}_{3}\text{O:} & & \text{Calculated:} & C, 69.22, H, 4.06, N, 12.16; \text{Found:} \ C, 69.50, H, 4.09, N, 12.20. \\
\text{6-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)quinolino-[2,3:5,6]-6H-pyran}[2,3-cf]-
8-methylpyran-7-one \ (3j). \\
\text{Nature of compound:} & & \text{Yellow solid; m. p.} & >300^\circ \text{C}. \\
\text{IR (KBr) cm}^{-1}: & & 1664 \ (\text{C=C}), 3442 \ (\text{O-H}). \\
\text{\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6):} & & \delta \text{ (ppm)} & 2.24 \ (6 \text{H}, \text{s}, 2\times \text{CH}_3), 4.62 \ (1 \text{H}, \text{s}, \text{C-H}), 6.18 \ (2 \text{H}, \text{s}, \text{C-H}), 7.16 - 7.18 \ (1 \text{H}, \text{m, arom.H}), 7.30 - 7.33 \ (1 \text{H}, \text{m, arom.H}), 7.41 - 7.43 \ (1 \text{H}, \text{m, arom.H}), 7.63 - 7.64 \ (1 \text{H}, \text{m, arom.H}), 7.91 \ (1 \text{H}, \text{s, arom.H}), 11.40 \ (1 \text{H}, \text{s, O-H}). \\
\text{\textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}_6):} & & \delta \text{ (ppm)} & 19.16, 19.30, 32.45, 99.49, 100.76, 101.06, 122.50, 124.96, 126.63, 127.12, 127.73, 128.08, 138.99, 148.05, 148.96, 159.85, 160.54, 161.43, 164.70, 166.18, 188.69, 189.09. \\
\text{ESI-MS:} & & (m/z) & 412 \ (\text{M}^+ + 23). \\
\text{Elemental analysis for C}_{22}\text{H}_{15}\text{NO}_6:} & & \text{Calculated:} & C, 67.92, H, 3.88, N, 3.61; \text{Found:} \ C, 67.91, H, 3.80, N, 3.59.
\end{align*}
3.8. REFERENCES


CHAPTER 4

Synthesis of Chalcone Derivatives via Claisen-Schmidt Condensation using Piperidine Functionalized Silica as an Efficient and Environmentally Benign Catalyst.
4.1. INTRODUCTION

The chemistry of chalcones has generated intensive scientific studies throughout the world. The name “Chalcone” was given by Kostanecki and Tambor.¹ Chalcones or 1,3-diaryl-2-propen-1-ones, belong to the flavanoid family. Chemically, chalcones consist of open-chain flavonoids in which two aromatic or heteroaromatic rings are joined by three carbons viz. α, β-unsaturated carbonyl system. They also serve as intermediates in the biosynthesis of flavonoids.² They constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (bean sprouts, potatoes, tomatoes, shallots) and various plants and spices (e.g., licorice). Some of the naturally occurring bioactive chalcones are isoliquiritigenin, Flavokawain A and Cardamonin etc. Isoliquiritigenin exhibits significant chemopreventive activities against lung, breast, prostate, and colorectal cancers.³ Flavokawain A suppresses bladder tumour growth⁴ and Cardamonin inhibits inflammation.⁵ The naturally occurring chalcones with varied biological activity are listed in Fig. 25. Chalcones also display a wide spectrum of other biological activities including antimicrobial,⁶ antipyretic,⁷ antileishmanial,⁸ antiangiogenic,⁹ antioxidant,¹⁰ anti-inflammatory,¹¹ anticancer,¹² anti-hyperglycemic,¹³ nitric oxide regulation,¹⁴ phytoestrogenic activities¹⁵ etc. Chalcones thus comprise, a class of compounds with important therapeutic potential.
Fig. 25 Chemical structures of some pharmaceutically important chalcones.

In literature, different methods are available for the preparation of chalcones. The most convenient method is Claisen-Schmidt condensation between benzaldehyde and acetophenone. Conventionally, this reaction is catalyzed by acids and bases under homogeneous conditions. The acid catalyzed Claisen-Schmidt condensation include

the use of HCl, TiCl₄, p-toluenesulfonic acid, BF₃·Et₂O, etc. In basic medium this condensation reaction is usually carried out in the presence of NaOH, KOH, etc. Main disadvantages of methodologies employing homogeneous conditions are catalyst recovery and waste-disposal problems. In this regard, heterogeneous catalyst is a better alternative for the synthesis of fine chemicals, since use of heterogeneous catalysts allow easier separation, recovery and recycling of the catalyst from the reaction mixture. In recent years, various heterogeneous catalysts have been applied to Claisen-Schmidt condensation such as alumina, magnesium oxide, natural phosphates modified with sodium nitrate or potassium fluoride, zeolites, hydrotalcites, alkaline doped carbons, potassium hydroxide impregnated on silica gel, acid montmorillonites, silica-sulphuric acid, AISBA-15-SO₃H, commercial acid clays, and metal nanoparticles etc.
4.2. REVIEW AND LITERATURE

4.2.1. Some recent examples of Claisen-Schmidt condensation under green conditions

4.2.1a. Metal-organic framework Fe(BTC) as heterogeneous catalyst in Claisen-Schmidt condensation

Dhakshinamoorthy et al. reported Metal-organic framework (MOF), Fe(BTC) (BTC=1,3,5-benzenetricarboxylic acid) catalyzed synthesis of chalcones in excellent yields. The catalyst could be recycled without any appreciable loss in catalytic efficiency in subsequent cycles.\(^{34}\)

\[
\text{CHO} \quad + \quad \text{R} = \text{CH}_3 \\
\rightleftharpoons \text{R} = \text{CH}_3 \\
\xrightarrow{[\text{Fe(BTC)}]} \quad \text{Toluene, 110 °C} \\
\]

4.2.1b. Hydroxyapatite as a reusable catalyst for chalcone synthesis.

Chalcone derivatives were efficiently prepared via Claisen–Schmidt condensation using hydroxyapatite (HAP) as heterogeneous catalyst and microwave irradiation. The catalyst was easily recovered and recycled efficiently.\(^{35}\)

\[
\text{CHO} \quad + \quad \text{CHO} \\
\xrightarrow{\text{HAP}} \quad \text{H}_2\text{O, MW} \\
\]

\[R_1 = \text{H, 4-Cl, 3-NO}_2, 4-\text{OMe, 4-OH},\]

\[R_2 = \text{H, 4-NO}_2, 4-\text{OMe}\]

\[\text{HAP} = [\text{Ca(PO}_4)_6(\text{OH})_2]\]

4.2.1c. Claisen-Schmidt condensation catalyzed by aminozeolite

Highly efficient sonochemical synthesis of chalcones via Claisen-Schmidt condensation between benzaldehyde and acetophenone catalyzed by amino grafted zeolite was reported by Romanelli et al. In this green and solvent-free protocol, chalcones were selectively produced in very high yields under ultrasonication.\(^{36}\)
Aminopropylated nano silica was employed as basic catalyst for the preparation of chalcones from substituted acetophenones and benzaldehydes under solvent-free conditions. High conversions of substrates were obtained with high loading of aminopropyl groups on silica. The catalysts were recovered and can be recycled up to two cycles without appreciable loss in catalytic activity.\textsuperscript{37}

Aranda \textit{et al.} reported an environmentally benign protocol for the synthesis of chalcones catalyzed by alkaline-doped carbons under ultrasonic activation in solvent-free conditions to yield the chalcone in excellent yield.\textsuperscript{37}
4.2.1f. Chalcone synthesis by grinding technique in the presence Barium hydroxide as catalyst

A simple, efficient and environmentally benign methodology for the synthesis of chalcones had been reported by grinding aryl aldehydes and acetophen ones with anhydrous barium hydroxide (C-200) in solvent-free conditions. This method was important from energy sustainable point of view.\(^{38}\)

\[
\begin{align*}
&\text{CHO} \\
&\begin{array}{ccc}
R_1 & R_2 & R_3 \\
\text{R} & \text{R} & \text{R}
\end{array} & + & \begin{array}{ccc}
O & \text{CH}_3 \\
R_4 & R_5 & R_6
\end{array} \\
& \text{Ba(OH)}_2 \\
& \text{Grinding, r.t.} \\
\rightarrow & \begin{array}{ccc}
R_1 & R_2 & R_3 \\
\text{R} & \text{R} & \text{R}
\end{array} & + & \begin{array}{ccc}
O & \text{R} & \text{R}
\end{array}
\end{align*}
\]

R = H, OH  \quad R_4 = H, OCH_3 \\
R_1 = H, NO_2  \quad R_5 = H \\
R_2 = H, Br, OCH_3  \quad R_6 = H, CH_3, OCH_3, NO_2, Cl \\
R_3 = H

4.2.1g. Brønsted acidic ionic liquid as dual catalyst and solvent for chalcones synthesis

\([\text{HSO}_3\text{BBIM}]\text{HSO}_4\), a brønsted acidic ionic liquids had been reported as dual catalyst and solvent for Claisen–Schmidt condensation between acetophenone and benzaldehyde. This ionic liquid showed good catalytic activity and recyclability towards the formation of chalcone.\(^{39}\)

\[
\begin{align*}
&\text{CHO} \\
&\begin{array}{ccc}
& & \\
& & \\
& & 
\end{array} & + & \begin{array}{ccc}
O & \text{CH}_3 \\
& & \\
& & 
\end{array} \\
& \text{[(HSO}_3\text{BBIM}]\text{HSO}_4 \\
& \rightarrow & \begin{array}{ccc}
O & \\
& & \\
& & 
\end{array}
\end{align*}
\]

4.2.1h. Claisen–Schmidt mediated by task specific ionic liquid

Dong \textit{et al.}, had also reported efficient synthesis of chalcones in task specific ionic liquid, \textit{viz.} N,N,N-trimethyl-N-propanesulfonic acid ammonium hydrogen sulfate [TMPSA][HSO_4]. The catalyst could be reused at least six times without appreciable decrease in yield and reaction rate.\(^{40}\)
**Claissen-Schmidt condensation**

\[
\text{CHO} + \text{R}_1 \rightarrow \text{R}_2 + [\text{TMPSA}][\text{HSO}_4] \rightarrow \text{O}
\]

\[
\text{R}_1 = \text{H}, \text{4-OCH}_3, \text{4-NO}_2
\]

\[
\text{R}_2 = \text{H}, \text{4-OCH}_3, \text{3-OCH}_3, \text{2-OCH}_3, \text{4-Cl}, \text{3-Cl}
\]

**4.2.1. Silicotungstic acid promoted synthesis of chalcones**

Another efficient and clean synthesis of chalcones had been in the presence of silicotungstic acid (STA). This method provided an ecofriendly, chemoselective, efficient and green synthesis of chalcones in excellent yields.\(^{41}\)

\[
\text{CHO} + \text{R}_1 \rightarrow \text{R}_2 \xrightarrow{\text{STA (10mol\%)} \text{ Stirring, r.t.}} \text{O}
\]

\[
\text{R}_1 = \text{H}, \text{2-OH}, \text{4-Cl}
\]

\[
\text{R}_2 = \text{H}, \text{4-Cl}, \text{2-Cl}, \text{3-NO}_2, \text{4-OCH}_3, \text{3,4-di-OCH}_3
\]

**4.2.1j. Graphene acid as a solid acid for chalone synthesis.**

Very recently graphene acid was used for the synthesis of chalcone using acetophenone and benzaldehyde as the reactant. Good yield of the products were obtained with a provision of recycling of catalyst.\(^{42}\)

\[
\text{CHO} + \text{R}_1 \rightarrow \text{R}_2 \xrightarrow{\text{Graphene acid} \ 140 \ ^\circ \text{C}} \text{O}
\]

**4.3. PRESENT WORK**

Challenges facing chemists is to develop new transformations that are not only efficient, selective, and high yielding but also environmentally benign. During the last decade, the topic of ‘green chemistry’ has received great attention. ‘Green chemistry’ aims at the total elimination (or at least the minimization) of waste, and the implementation of sustainable processes. The utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. Homogeneous catalysts can catalyze a much larger variety of reactions than traditional solid catalysts but suffer from regeneration and recycling problems. The immobilization of homogeneous catalytic entities onto solids to form heterogeneous catalysts can be accomplished with some aspects of design. The goal is to utilize the homogeneous part
as the active site and the solid to provide avenues to recovery and possibly recyclability of the organic active site. These heterogeneous catalysts can be synthesized by a number of methods such as (i) adsorption of the species on solid support; (ii) construction of the homogeneous catalyst within the confines of cavities of the support (iii) linking of the desired functionality to the support by covalent bond formation; (iv) direct synthesis into the final composite material. Among various inorganic supports, silica gel is very advantageous since it possesses high surface area, good thermal and mechanical stability, easy availability, inexpensiveness, and relatively simple covalent modification with organic or organometallic moieties.\cite{43,44}

In this chapter, synthesis of piperidine bonded silica as a novel heterogeneous basic catalyst, and its application for the synthesis of chalcones by Claisen-Schmidt condensation under solvent-free conditions has been discussed. The catalyst has been characterized well using various techniques such as FT-IR, solid state NMR, scanning electron microscopy, energy-dispersive X-ray, thermogravimetric, elemental, and NH\textsubscript{3} and CO\textsubscript{2} temperature-programmed desorption analyses. Surface area was also evaluated through Brunauer–Emmett–Teller analysis.

4.4. RESULTS AND DISCUSSION

4.4.1. Catalyst preparation and characterization

Piperidine functionalized silica was synthesized by condensing silica chloride in excess of piperidine in toluene at reflux temperature (Scheme 8).

\[
\begin{align*}
\text{Silica chloride} & \quad \text{Piperidine} \\
& \xrightarrow{\text{Toluene, Reflux}} \\
\text{Silica-piperidine}
\end{align*}
\]

Scheme 8 Synthesis of piperidine functionalised silica.

4.4.1a. FT-IR spectral analysis of the catalyst

IR spectrum of piperidine (Fig. 26 a) showed its characteristic peaks at 3300, 2900, 2800, 1468,1386, 1200-1000, 964 cm\textsuperscript{-1} etc.\cite{45} The FT-IR spectrum of the silica chloride (Fig 26 b) showed broad asymmetric Si–O–Si stretching band in the range of 1200 to 1000 cm\textsuperscript{-1} and symmetric Si–O–Si stretching near 800 cm\textsuperscript{-1}.\cite{46} A small shoulder at about 900 cm\textsuperscript{-1} was assigned to the Si–O group.\cite{46} Piperidine bonded silica as expected (Fig 26 c) showed a moderately different behaviour from that of non-functionalized silica. A weak absorption band appearing at around 1460 cm\textsuperscript{-1} was attributed to bending vibration of C-N bond whereas a strong and sharp absorption band at 1100 cm\textsuperscript{-1} was
assigned to C–N–C stretch. The absorption band for Si-N bond at about 900 cm⁻¹ merged with the absorption band for Si-O stretch. The peaks at 2927 and 2859 cm⁻¹ were due to C-H symmetric and asymmetric stretching vibrations of piperidine moiety, respectively. The absorption band at 3400 cm⁻¹ was due to the hydrogen bonded Si-OH groups and adsorbed water molecules and deformational vibrations of adsorbed water molecules caused the absorption band to appear at 1643 cm⁻¹. The IR spectrum thus, confirmed the presence of organic moieties linked covalently to the silica framework in the final hybrid materials.

![FT-IR spectra](image)

**Fig. 26** FT-IR spectra of a) Piperidine b) Silica Chloride c) Silica bonded piperidine (SiP).

4.4.1b. **Solid state cross-polarization magic angle spinning carbon-13 NMR spectrum of the catalyst**

The solid state carbon-13 CP MAS NMR spectrum of the catalyst, (SiP) (Fig. 27) showed carbon signals at δ 21.89 corresponding to (b, c) carbons and at δ 43.63 for (a) carbon. This further confirmed the presence of piperidine moieties on silica.
4.4.1c. Thermal analysis of the catalyst

Thermal stability of the catalyst was evaluated by DSC analysis (Fig 28). The endothermic transition at 70 °C represented the removal of adsorbed water molecules from the silica framework. A broad exothermic transition from 200-500 °C was due to decomposition of piperidine in SiP.
In TGA analysis (Fig. 29) of SiP, a weight loss of 4.7% could be attributed to desorption of adsorbed water or other solvent molecules. Another weight loss of 6.7% at 207 °C was due to the combustion of piperidine incorporated into silica network. The loading of piperidine on silica was calculated from TGA and was found to be 0.79 mmol/g.

![Fig. 29 TG analysis of the SiP.](image)

4.4.1d. **Powder X-ray diffraction (XRD) analysis of the catalyst**

A broad XRD Diffraction peak at around $2\theta = 22^\circ$ (Fig. 30) was assigned to silica, which is also its characteristic peak.

![Fig. 30 XRD of SiP.](image)
4.4.1e. **EDX analysis of the catalyst**

The EDX spectrum of the catalyst (Fig 31), showed peaks for N in addition to Si and O elements thus, confirming the successful incorporation of piperidine moiety onto silica.

![EDX analysis of SiP](image)

**Fig. 31. EDX analysis of SiP.**

4.4.1e. **CHN analysis of catalyst**

Further, the elemental analysis of SiP showed the carbon, hydrogen and nitrogen content to be 5.22%, 0.87% and 1.04 %, respectively. The calculated C/N ratio of silica bound piperidine was 4.28 and found C/N ratio was 5.01. Based on elemental analysis, considering N only comes from bound piperidine, loading of piperidine was calculated to be 0.74 mmol/g. This data agrees well with the loading of piperidine calculated from TGA data as 0.79 mmol/g. These facts provide enough evidence that piperidine has been incorporated in the silica framework.

4.4.1f. **Temperature programmed desorption studies of the catalyst**

The carbon dioxide desorption experiment was performed to know the basic/acidic properties of catalyst. The TPD results have been considered up to 200 °C as thermogravimetric analysis (TGA) of the sample confirmed a mass loss at higher temperatures. The data showed desorption of carbon dioxide below 200 °C (Fig. 32) confirming the presence of basic sites which are responsible for catalyzing the reaction. The catalyst also has acidic sites as confirmed by ammonia TPD (Fig. 33).
presence of acidic sites could be due to presence of surface silanol groups. In the present investigation, the basic sites are responsible for the Claisen-Schmidt condensation, as there is no product formation when the said reaction was conducted with silica as catalyst (Table 12, entry 17).

![Graph](image1)

**Fig. 32** CO$_2$-TPD pattern of piperidine functionalised Silica.

![Graph](image2)

**Fig. 33** NH$_3$-TPD pattern of piperidine functionalized silica.

4.4.1g. *Scanning electron microscopy of the catalyst*

Scanning electron microscopy studies were undertaken to observe the morphology of piperidine functionalized silica gel (Sip). The micrograph obtained by SEM showed the particles of irregular shape with diameters in the range of several hundreds of
nanometre up to a few micrometres. There was slight change in the morphology of the silica after functionalization as shown in Fig. 34.

Fig. 34. SEM i) silica ii) functionalized silica SiP.

4.4.1b. BET Surface area of the catalyst

The BET surface area of SiP was estimated from N$_2$ adsorption desorption isotherm (Fig. 35) and was found to be 382 m$^2$g$^{-1}$.

Fig. 35 N$_2$ adsorption/desorption isotherm of SiP.

4.4.1i. Hot filtration test of the catalyst

To check the heterogeneity of SiP, a hot filtration test was performed.$^{31}$ For this purpose, the reaction of 9a and 11a in the presence of SiP catalyst using methanol as a solvent were studied. The reaction was allowed to reflux for 20 min after which the catalyst was filtered without cooling the reaction mixture. The reaction was then continued at the same temperature and it was found that no further conversion occurred following this hot filtration.
4.4.2. Optimization of reaction condition

Optimum reaction conditions were explored for the synthesis of chalcones via Claisen-Schmidt condensation using 2-chloro-3-formylquinoline (9a, 1mmol) and acetyl-1,3-dimethylbarbituric acid (11a, 1mmol) as model substrates for the synthesis 12a (Scheme 9).

4.4.2a Effect of solvents

To find an appropriate reaction medium for the said reaction, model reaction was carried out using equimolar quantity of model substrates and 100 mg of SiP as catalyst in different solvents (Table 9) under reflux condition. In MeOH, EtOH and (CH₃)₂CHOH (Table 9, entries 1, 2 and 3), the reaction proceeded slowly (4-4.5 h) with moderate yield of the products whereas in water (Table 9, entry 4), the product was obtained in low yield (55% yield) after 6 h. In PEG-200 and PEG-400 (Table 9, entries 5, 6) again lower yields of the product was obtained with long reaction time whereas the reaction in glycerol and ethylene glycol (Table 9, entries 6, 7) did not complete. However, when the model reaction was carried out under solvent-free conditions there was significant increase in the yield of the product in shorter time period. Thus, it was concluded, solvent-free condition as the best condition for the synthesis of chalcones by Claisen-Schmidt condensation.

Table 9 Effect of solvents on model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeOH</td>
<td>Reflux</td>
<td>4 h</td>
<td>74</td>
</tr>
<tr>
<td>2.</td>
<td>EtOH</td>
<td>Reflux</td>
<td>3.5 h</td>
<td>76</td>
</tr>
<tr>
<td>3.</td>
<td>(CH₃)₂CHOH</td>
<td>Reflux</td>
<td>4.5 h</td>
<td>65</td>
</tr>
<tr>
<td>4.</td>
<td>H₂O</td>
<td>Reflux</td>
<td>6 h</td>
<td>55</td>
</tr>
<tr>
<td>5.</td>
<td>PEG-200</td>
<td>100</td>
<td>7 h</td>
<td>45</td>
</tr>
<tr>
<td>6.</td>
<td>PEG-400</td>
<td>100</td>
<td>8 h</td>
<td>60</td>
</tr>
<tr>
<td>7.</td>
<td>Glycerol</td>
<td>100</td>
<td>24 h</td>
<td>incomplete</td>
</tr>
<tr>
<td>8.</td>
<td>Ethylene glycol</td>
<td>100</td>
<td>24 h</td>
<td>incomplete</td>
</tr>
<tr>
<td>9.</td>
<td>Solvent-free</td>
<td>80</td>
<td>6 min</td>
<td>96</td>
</tr>
</tbody>
</table>
4.4.2b. Effect of Temperature

Next, the effect of temperature on model reaction using 100 mg of catalyst under solvent-free conditions was examined to optimize the reaction condition in terms of reaction time and yield of the product (Table 10). It was observed that the reaction did not proceed at room temperature (Table 10, entry 1). At 60 °C, (Table 10, entry 2) the reaction proceeded smoothly but the yield was low whereas maximum yield was obtained at 80 °C (Table 10, entry 3). A higher reaction temperature 100 °C and 110 °C did not make an obvious difference in the yield of product (Table 10, entries 4, 5). Therefore, 80 °C temperature was considered as optimized temperature for SiP catalyzed Claisen-Schmidt condensation.

**Table 10 Effect of temperature on model reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>r.t.</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>45</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>6</td>
<td>96</td>
</tr>
</tbody>
</table>

4.4.2c. Effect of catalyst loading

The catalyst loading was optimized by studying the template reaction with different catalyst loadings. With 100 mg of catalyst loading almost 96% yield was obtained. Lowering the catalyst amount to 20-80 mg resulted in 43-85% yield of product, whereas increasing the amount of catalyst to 120 mg had no significant effect on the yield of the product (Fig. 36).
4.4.2d. Effect of different catalyst

A comparative study was also undertaken using model substrates, 0.079 mmol of different acidic and basic catalysts under solvent free conditions at 80 °C, and the results are summarized in Table 11. Initially, the experiment was performed in the absence of any catalyst and it was observed that no reaction occurred even after 10 h (Table 11, entry 1) justifying the need of a catalyst. In the presence of NaOH and KOH, the reaction gave 55% and 50% isolated yield of product only after 1 h and 1.3 h, respectively (Table 11, entries 2, 3). The reaction was then performed in the presence of metal oxides such as CaO, MgO, and ZnO (Table 11, entries 4–6). However, these catalysts were found less effective. We then examined some heterogeneous basic catalysts such as SiO2-imine, NaHSO4-SiO2, NH4OAc-SiO2, basic Al2O3 (0.1g), aminopropyl silica for this reaction and observed that there was not much improvement in reaction in terms of yield of the product. We then tested the reaction in the presence of silica bonded amines (Table 11, entries 13-16). SiO2 (0.1g), and SiO2Cl (Table 11, entries 17-18). It was observed that both silica and silica chloride failed to catalyse the reaction. However, various silica bonded amines catalysed the reaction to a greater extent but maximum yield of the product in minimum time period was obtained when silica bonded piperidine was employed as the catalyst (Table 11, entry 12). Employing piperidine alone in various concentrations also did not work out (Table 11, entries 19-
23. Employing piperidine in combination with HCl and silica (Table 11, entries 24-25) were again not fruitful.

**Table 11** Influence of different catalyst on the model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No base</td>
<td>10 h</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>NaOH</td>
<td>12 h</td>
<td>52</td>
</tr>
<tr>
<td>3.</td>
<td>KOH</td>
<td>14 h</td>
<td>49</td>
</tr>
<tr>
<td>4.</td>
<td>CaO</td>
<td>24 h</td>
<td>65</td>
</tr>
<tr>
<td>5.</td>
<td>MgO</td>
<td>20 h</td>
<td>70</td>
</tr>
<tr>
<td>6.</td>
<td>ZnO</td>
<td>18 h</td>
<td>70</td>
</tr>
<tr>
<td>7.</td>
<td>SiO₂-Imine</td>
<td>1.5 h</td>
<td>61</td>
</tr>
<tr>
<td>8.</td>
<td>NaHSO₄-SiO₂</td>
<td>55 min</td>
<td>72</td>
</tr>
<tr>
<td>9.</td>
<td>NH₄OAc-SiO₂</td>
<td>50 min</td>
<td>70</td>
</tr>
<tr>
<td>10.</td>
<td>Basic Al₂O₃</td>
<td>10 min</td>
<td>59</td>
</tr>
<tr>
<td>11.</td>
<td>Aminopropyl silica</td>
<td>1.5 h</td>
<td>40</td>
</tr>
<tr>
<td>12.</td>
<td>SiO₂-Piperidine</td>
<td>6 min</td>
<td>96</td>
</tr>
<tr>
<td>13.</td>
<td>SiO₂-Pyrrolidine</td>
<td>10 min</td>
<td>90</td>
</tr>
<tr>
<td>14.</td>
<td>SiO₂-NEt₂</td>
<td>12 min</td>
<td>87</td>
</tr>
<tr>
<td>15.</td>
<td>SiO₂-NMe₂</td>
<td>14 min</td>
<td>82</td>
</tr>
<tr>
<td>16.</td>
<td>SiO₂-Piperazine</td>
<td>50 min</td>
<td>74</td>
</tr>
<tr>
<td>17.</td>
<td>SiO₂</td>
<td>6 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>18.</td>
<td>Silica Chloride</td>
<td>6 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>19.</td>
<td>Piperidine</td>
<td>2 h</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>(0.020 mmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Piperidine</td>
<td>45 min</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>(0.050 mmol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.4.3. Synthesis of chalcones

In the next step the scope, and efficiency of the process was explored under the optimized conditions. For this purpose, the present study was extended to various aromatic aldehydes carrying electron-withdrawing/releasing substituents, heteroaldehyde (9a-e) and acetophenones (11a-k) substituted with electron donating/electron withdrawing groups (Scheme 9).

![Scheme 9 Claisen-Schmidt condensation in the presence of SiP.](image)

All the reactions have proceeded efficiently and resulted in high to excellent yields within relatively short reaction times and the observed results are presented in Table 12. This very simple and convenient experimental procedure tolerates a variety of other
functional groups such as methoxy, nitro, hydroxyl, and halides as well under the present reaction conditions.

Table 12 Scope of SiP catalysed Claisen Schmidt condensation under solvent-free conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image" alt="Product 12a" /></td>
<td>6</td>
<td>96</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image" alt="Product 12b" /></td>
<td>10</td>
<td>94</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="Product 12c" /></td>
<td>10</td>
<td>93</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="Product 12d" /></td>
<td>7</td>
<td>95</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image" alt="Product 12e" /></td>
<td>6</td>
<td>96</td>
</tr>
</tbody>
</table>
Claisen-Schmidt condensation

6.  ![Chemical Structure 12f]

7.  ![Chemical Structure 12g]

8.  ![Chemical Structure 12h]

9.  ![Chemical Structure 12i]

10.  ![Chemical Structure 12j]

11.  ![Chemical Structure 12k]

12.  ![Chemical Structure 12l]
A plausible mechanism for the synthesis of chalcone \textbf{12a} via Claisen-Schmidt condensation in the presence of SiP is depicted in \textbf{Scheme 10}. SiP removes acidic hydrogen from \textbf{11a} and forms enolate ion \textbf{I} which attacks aldehydic carbon of \textbf{9a} to give \(\beta\)-hydroxy ketone \textbf{III}. Dehydration of \textbf{III} leads to the formation of final product \textbf{12a}.
Scheme 10 A plausible mechanism for the synthesis of chalcone (12a).

The structures of the synthesized chalcones were characterized by elemental and spectral analyses (IR, $^1$H NMR, $^{13}$C NMR and Mass spectrometry). The infrared (IR) spectrum of 12a (Fig. 37) showed the carbonyl absorption bands at 1716 and 1647 cm$^{-1}$ for barbituric acid and propenone moieties, respectively. Another sharp and strongly absorbed band at 1623 cm$^{-1}$ was assigned to carbon-carbon double. The $^1$H NMR spectrum (Fig. 38) showed trans olefinic protons $H_b$ and $H_a$ of $\alpha$, $\beta$-unsaturated carbonyl system as ortho coupled doublets at $\delta$ 8.72 with $J$ value 15.8 Hz and at $\delta$ 8.36 with $J$ value 15.8 Hz respectively. H-4 proton of quinoline appeared as singlet at $\delta$ 8.29. Four aromatic protons of the quinoline moiety appeared as multiplet in the range of $\delta$ 8.14-7.61 ppm. Six protons of N-CH$_3$ groups of barbituric acid moiety were discernible as a sharp singlet at $\delta$ 2.12. The $^{13}$C NMR spectrum (Fig. 39) showed signals at $\delta$ 194.8, 186.2 and $\delta$ 160.1 for carbonyl groups of propenone and barbituric acid moiety respectively, whereas signal for olefinic carbons C-2 and C-3 appeared at $\delta$ 150.2 and $\delta$ 141.1. Two CH$_3$ groups of barbituric acid moiety were discernible at $\delta$ 29.1 and $\delta$ 29.0. Other carbon signals were present at their appropriate positions and are given in the experimental section. Further confirmation for the structure was provided by mass
spectrometry (Fig. 40), which showed molecular ion peak at m/z 372.1 (M+1). The spectral data of other compounds followed similar pattern.

Fig. 37 IR spectrum of compound 12a

Fig. 38 $^1$HNMR spectrum of compound 12a
Fig. 39 $^{13}$C NMR spectrum of compound 12a

Fig. 40 Mass spectrum of compound 12a
4.4.4. Recycling study

For practical applications of the heterogeneous system, recovery of the catalyst is an important aspect. Thus, the reusability of the catalyst was also examined (Fig 41) using model substrates under solvent-free conditions with 100 mg of the catalyst. After the completion of the reaction, products were extracted by ethyl acetate and the recovered catalyst was washed with ethyl acetate, acetone and dried in oven at 110 °C for 2 h. The recovered catalyst was reused at least five times with a slight loss in catalytic activity. The catalyst morphology was preserved during the catalytic recycling studies as can be seen from SEM-EDX analyses and XRD (Fig. 42, 43, 44) of the catalyst after five catalytic cycles. The XRD analysis of recovered catalyst showed the same pattern but with some change in intensities, which may be due to some impurities remaining after reuse of the catalyst.

![Bar chart showing recycling study results](chart.png)

Fig. 41. Recycling study of the catalyst.
Fig. 42 SEM images of the recovered catalyst.

Fig. 43 SEM images of the recovered catalyst.

Fig. 44 XRD of recovered catalyst.
4.5. CONCLUSION

In this chapter, we have described synthesis and application of piperidine functionalized silica (SiP) for the synthesis of chalcones via Claisen-Schmidt condensation. The present protocol has advantages such as use of inexpensive and heterogeneous as catalyst under solvent-free conditions. This environmentally benign and safe protocol has a simple reaction setup, mild reaction conditions, provide high product yields in shorter reaction times. Moreover, the catalyst can be reused several times.

4.6. EXPERIMENTAL

2-Chloro-3-formylquinoline and 3-formylquinolin-2-one was synthesized by using DMF/POCl₃ according to the reported method.⁵²

4.6.1. Synthesis of catalyst

Silica chloride (SiCl) was synthesized according to the reported method.⁵³

Synthesis of silica bonded piperidine (SiP): A suspension of 3g of silica chloride in toluene (20 mL) was refluxed and stirred in an excess of piperidine (1 g) for 6 h. The modified silica was filtered, and washed with (50 mL), dichloromethane (20 mL), ether (20 mL) and air dried.

4.6.2. Synthesis of chalcones (12a-p)

Aldehyde (9a-e, 1 mmol), active methyl compounds (11a-k, 1mmol), and the catalyst (100 mg) were taken in a 25 mL beaker. This reaction mixture was stirred at 80 °C and the progress of reaction was monitored by TLC after every 30 seconds, till the completion of the reaction. After completion of the reaction, ethyl acetate was added to the reaction mixture and the catalyst filtered off. The solvent of the filtrate was evaporated and the crude product (12a-p) was purified by recrystallization from appropriate solvents. The filtered catalyst was washed with ethyl acetate (10 mL), acetone (10 mL) and activated at 100 °C for 1 h, and used for the next catalytic cycle.

4.7. Spectral data of compounds

\((2E)-3-(2\text{-chloro-3-quinolinyl})-1-(1,3\text{-dimethyl-2,4,6-pyrimidinetione-5-yl})prop-2-en-1-one\) (12a)

**Nature of compound:** Yellow solid; m.p. >300 °C.

**IR (KBr) cm⁻¹:** 1623 (C=C), 1647 (C=O), 1716 (C=O).

**¹H NMR (400 MHz, CDCl₃):** δ (ppm) 2.12 (6H, s, 2xCH₃), 7.77-7.81 (1H, m, arom.H), 7.84-7.88 (1H, m, arom.H), 7.93-7.95 (1H, m, arom.H), 8.03(1H, s, O=CH-CH=O),
8.12-8.14 (1H, m, arom.H), 8.36 (1H, d, Hα, J=15.87 Hz), 8.72 (1H, d, Hβ, J=15.84 Hz), 8.82 (1H, s, arom.H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$): δ (ppm) 29.04, 29.11, 94.49, 127.22, 12.32, 127.48, 127.73, 127.83, 128.18, 129.36, 129.61, 132.48, 141.10, 150.20, 160.17, 186.27, 194.87.

ESI-MS: (m/z) 372.1 (M$^+$+1).

Elemental analysis for C$_{15}$H$_{14}$ClN$_3$O$_4$: Calculated: C, 58.26, H, 3.80, N, 11.37; Found: C, 58.27, H, 3.82, N, 11.03.

(2E)-3-(2-chloro-3-quinolinyl)-1-(2,4,6-pyrimidinetrione-5-yl)prop-2-en-1-one (12b)

Nature of compound: Yellow solid; m.p. $>$300 °C.

IR (KBr) cm$^{-1}$: 1619 (C=C), 1646 (C=O), 1734 (C=O), 3174, 3222 (N-H).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.41-7.45 (1H, m, arom.H), 7.57-7.61 (1H, m, arom.H), 7.75-7.80 (2H, m, arom.H), 7.93 (1H, d, Hα, J=15.87 Hz), 8.32 (1H, d, Hβ, J=15.84 Hz), 8.64 (1H, s, O=C-CH=C=O), 8.89 (1H, s, arom.H) 10.40 (1H, s, N-H), 10.97 (1H, s, N-H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$): δ (ppm) 95.09, 127.12, 127.32, 127.48, 127.73, 127.93, 128.18, 129.46, 129.92, 133.48, 140.90, 149.80, 163.27, 188.78, 194.67.

ESI-MS: (m/z) 344.4 (M$^+$+1).

Elemental analysis for C$_{16}$H$_{10}$ClN$_3$O$_4$: Calculated: C, 56.02, H, 2.93, N, 12.30; Found: C, 56.12, H, 3.01, N, 12.32.

(2E)-3-(2-chloro-3-quinolinyl)-1-(2-mercapto-4,6-pyrimidinedione-5-yl)prop-2-en-1-one (12c)

Nature of compound: Yellow solid; m.p. $>$300 °C.

IR (KBr) cm$^{-1}$: 1619 (C=C), 1646 (C=O), 1734 (C=O), 3174, 3222 (N-H).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.42-7.48 (1H, m, arom.H), 7.57-7.63 (2H, m, arom.H), 7.97-8.13 (2H, m, Hα+arom.H), 8.17 (1H, s, O=C-CH=C=O), 8.22 (1H, s, arom.H), 8.79 (1H, d, Hβ, J=15.87 Hz), 12.17 (1H, s, N-H), 12.69 (1H, s, N-H).

$^{13}$C NMR (100 MHz, DMSO-d$_6$): δ (ppm) 94.64, 127.21, 127.43, 127.50, 127.60, 127.72, 128.19, 129.90, 130.16, 130.47, 142.18, 149.61, 180.11, 188.43, 196.24.

ESI-MS: (m/z) 360.2 (M$^+$+1).
Elemental analysis for C_{16}H_{16}ClN_{3}O_{5}S: Calculated: C, 53.52, H, 2.80, N, 11.75; Found: C, 53.48, H, 2.89, N, 11.80.

(2E)-3-(2-chloro-3-quinolinyl)-1-(4-hydroxy-1-benzopyran-2-one-3-yl)prop-2-en-1-one (12d)

Nature of compound: Yellow solid; m.p. >300 °C.

IR (KBr) cm⁻¹: 1611 (C=O), 1650 (C=O), 1722 (C=O), 3448 (O-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.10-7.14 (1H, m, arom.H), 7.14-7.18 (1H, m, arom.H), 7.38-7.42 (1H, m, arom.H), 7.51-7.59 (2H, m, arom.H), 7.68-7.70 (1H, m, arom.H), 8.13 (1H, d, Hᵦ, J=15.71 Hz), 8.72 (1H, d, Hₘ, J=15.69 Hz), 8.58 (1H, s, arom.H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 102.61, 115.82, 116.96, 122.63, 123.59, 124.50, 127.21, 127.36, 127.41, 127.90, 128.66, 128.76, 129.33, 129.40, 132.49, 144.60, 151.91, 152.12, 165.82, 180.35, 182.01.

ESI-MS: (m/z) 378.1 (M⁺+1).

Elemental analysis for C_{21}H_{12}ClNO₄: Calculated: C, 66.89, H, 3.43 N, 3.73; Found: C, 66.85, H, 3.40, N, 3.81.

(2E)-3-(2-chloro-3-quinolinyl)-1-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)prop-2-en-1-one (12e)

Nature of compound: Yellow solid; m.p. >300 °C.

IR (KBr) cm⁻¹: 1627 (C=O), 1655 (C=O), 1723 (C=O), 3446 (O-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.30 (3H, s, CH₃), 6.25 (1H, s, C-H), 7.63-7.67 (1H, m, arom.H), 7.80-7.84 (1H, m, arom.H), 7.92-7.94 (1H, m, arom.H), 8.12-8.14 (1H, m, arom.H), 8.18 (1H, d, Hᵦ, J=15.76 Hz), 8.32 (1H, d, Hₘ, J=15.72 Hz), 8.33 (1H, s, arom.H), 17.28 (1H, s, O-H).


ESI-MS: (m/z) 342.1 (M⁺+1).

Elemental analysis for C_{18}H_{12}ClN₃O₄: Calculated: C, 63.39, H, 3.54, N, 4.12; Found: C, 63.27, H, 3.67, N, 4.06.

(2E)-3-(2-oxo-3-quinolinyl)-1-(phenyl)prop-2-en-1-one (12f)

Nature of compound: Yellow solid; m.p. 273-276°C (lit. 273-274 °C).
Clairen-Schmidt condensation

IR (KBr) cm⁻¹: 1584 (C=C), 1672 (C=O), 3116 (N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.21-7.24 (1H, m, arom.H), 7.33-7.35 (1H, m, arom.H), 7.52-7.54 (1H, m, arom.H), 7.60-7.62 (2H, m, arom.H), 7.66-7.70 (1H, m, arom.H), 7.71-7.73 (1H, m, arom.H), 7.86 (1H, d, Hα, J=15.61 Hz), 8.02-8.04 (2H, m, arom.H), 8.36 (1H, d, H₆, J=15.60 Hz), 8.66 (1H, s, arom.H), 12.10 (1H, s, N-H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 115.7, 119.7, 122.8, 124.5, 126.4, 128.8, 129.2, 129.4, 132.3, 133.6, 138.2, 139.5, 139.6, 141.8, 161.4, 189.8.

ESI-MS: (m/z) 276.1 (M⁺+1).

Elemental analysis for C₁₈H₁₃NO₂: Calculated: C, 78.53; H, 4.76; N, 5.09; Found: C, 78.62; H, 4.55; N, 5.00.

(2E)-3-(2-oxo-3-quinolinyl)-1-(4-nitrophenyl)prop-2-en-1-one (12g)

Nature of compound: Yellow solid; m. p. 303-306°C (lit. 304-305°C). ⁵⁴

IR (KBr) cm⁻¹: 1585 (C=C), 1670 (C=O), 3119 (N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.23-7.25 (1H, m, arom.H), 7.33-7.34 (1H, m, arom.H), 7.55-7.56 (1H, m, arom.H), 7.75-7.76 (1H, m, arom.H), 7.80-7.83 (2H, m, arom.H), 7.84 (1H, d, Hα, J=15.63 Hz), 8.02-8.03 (2H, m, arom.H), 8.26 (1H, d, H₆, J=15.62 Hz), 8.64 (1H, s, arom.H), 12.10 (1H, s, N-H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 115.6, 119.7, 122.7, 125.0, 126.7, 127.3, 129.1, 130.6, 132.1, 132.3, 137.6, 139.7, 140.0, 141.7, 161.3, 189.8.

ESI-MS: (m/z) 321.0 (M⁺+1).

Elemental analysis for C₁₈H₁₂N₂O₄: Calculated: C, 67.50; H, 3.78; N, 8.75; Found: C, 67.66; H, 3.84; N, 8.68.

(2E)-3-(2-oxo-3-quinolinyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (12h)

Nature of compound: Yellow solid; m. p. 328-332°C (lit. 329-330°C). ⁵⁴

IR (KBr) cm⁻¹: 1564 (C=C), 1669 (C=O), 3143 (O-H, N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.89-6.91 (2H, m, arom.H), 7.21-7.24 (1H, m, arom.H), 7.33-7.36 (1H, m, arom.H), 7.54-7.56 (1H, m, arom.H), 7.70-7.72 (1H, m, arom.H), 7.74 (1H, d, Hα, J=15.60 Hz), 8.02-8.05 (2H, m, arom.H), 8.30 (1H, d, H₆, J=15.62 Hz), 8.59 (1H, s, arom.H), 9.94 (1H, s, O-H), 12.11 (1H, s, N-H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 115.6, 116.0, 119.6, 122.8, 124.6, 126.6, 129.1, 129.7, 131.4, 132.1, 138.2, 139.4, 141.2, 161.5, 162.7, 187.9.

ESI-MS: (m/z) 292.0 (M⁺+1).

Elemental analysis for C₁₈H₁₅NO₃: Calculated: C, 74.22; H, 4.50; N, 4.81; Found: C, 74.10; H, 4.68; N, 4.94.
(2E)-3-(2-oxo-3-quinolinyl)-1-(4-Chlorophenyl)prop-2-en-1-one (12i)

Nature of compound: Yellow solid; m. p. 276-279°C (lit. 277-278°C). ⁵⁴

IR (KBr) cm⁻¹: 1565 (C=C), 1683 (C=O), 3155 (N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.25-7.27 (1H, m, arom.H), 7.33-7.35 (1H, m, arom.H), 7.53-7.56 (1H, m, arom.H), 7.63-7.64 (2H, m, arom.H), 7.74-7.75 (1H, m, arom.H), 7.82 (1H, d, Ha, J=15.39 Hz), 8.00-8.01 (2H, m, arom.H), 8.36 (1H, d, H₈, J=15.40 Hz), 8.63 (1H, s, arom.H), 12.15 (1H, s, N-H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 115.7, 119.6, 122.7, 124.8, 126.6, 129.1, 129.4, 130.6, 132.1, 137.1, 138.4, 139.7, 140.0, 141.8, 161.3, 189.4.

ESI-MS: (m/z) 310.1 (M⁺+1).

Elemental analysis for C₁₈H₁₂ClNO₂: Calculated: C, 69.80; H, 3.90; N, 4.52; Found: C, 69.91; H, 3.83; N, 4.42.

(2E)-3-(2-oxo-3-quinolinyl)-1-(p-tolyl)prop-2-en-1-one (12j)

Nature of compound: Yellow solid; m. p. 265-267°C (lit. 266-267°C). ⁵⁴

IR (KBr) cm⁻¹: 1586 (C=C), 1664 (C=O), 3111 (N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 2.42 (3H, s, CH₃), 2.23-2.24 (1H, m, arom.H), 7.33-7.36 (1H, m, arom.H), 7.38-7.40 (2H, m, arom.H), 7.53-7.57 (1H, m, arom.H), 7.70-7.72 (1H, m, arom.H), 7.81 (1H, d, Ha, J=15.80 Hz), 8.00-8.01 (2H, m, arom.H), 8.01 (1H, m, arom.H), 8.32 (1H, d, H₈, J=15.61 Hz), 8.61 (1H, s, arom.H), 12.06 (1H, s, N-H).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 21.7, 115.8, 119.8, 122.7, 124.4, 125.6, 127.8, 129.8, 129.9, 132.2, 137.4, 139.0, 139.3, 141.6, 161.8, 188.5.

ESI-MS: (m/z) 290.3 (M⁺+1).

Elemental analysis for C₁₉H₁₃NO₂: Calculated: C, 78.87; H, 5.23; N, 4.84.; Found: C, 79.01; H, 5.12; N, 4.98.

(2E)-3-(2-oxo-3-quinolinyl)-1-(4-methoxyphenyl)prop-2-en-1-one (12k)

Nature of compound: Yellow solid; m. p. 260-261 °C (lit. 260-261°C). ⁵⁴

IR (KBr) cm⁻¹: 1593 (C=C), 1660 (C=O), 3140 (N-H).

¹H NMR (400 MHz, CDCl₃): δ (ppm) 3.80 (3H, s, OCH₃), 7.07-7.08 (2H, m, arom.H), 7.21-7.22 (1H, m, arom.H), 7.36-7.39 (1H, m, arom.H), 7.53-7.55 (1H, m, arom.H), 7.70-7.72 (1H, m, arom.H), 7.74 (1H, d, Ha, J=15.71 Hz), 8.01-8.04 (2H, m, arom.H), 8.22 (1H, d, H₈, J=15.66 Hz), 8.46 (1H, s, arom.H), 11.07 (1H, s, N-H).
Claisen-Schmidt condensation

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 56.1, 114.7, 115.6, 119.7, 122.6, 125.4, 127.0, 129.0, 131.0, 131.5, 131.8, 138.5, 139.5, 141.1, 161.4, 163.81, 188.8.

ESI-MS: ($m/z$) 306.2 (M$^+$+1).

Elemental analysis for C$_{19}$H$_{12}$NO$_3$: Calculated: C, 74.74; H, 4.95; N, 4.59; Found: C, 74.80; H, 5.00; N, 4.47.

1,3-Diphenylpropenone (12l)

Nature of compound: Yellow crystalline solid; m. p. 53-56 °C (lit. 55-56 °C).

IR (KBr) cm$^{-1}$: 1580 (C=C), 1667 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.41-7.67 (9H, m, arom.H + Ha), 7.82 (1H, d, Hb, J=15.96 Hz), 8.02-8.05 (2H, m, arom.H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 120.06, 127.01, 127.09, 128.61, 128.79, 133.66, 134.28, 144.41, 188.61.

ESI-MS: ($m/z$) 209.2 (M$^+$+1).

Elemental analysis for C$_{15}$H$_{12}$O: Calculated: C, 86.51; H, 5.81; Found: C, 86.53; H, 5.83.

(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (12m)

Nature of compound: Yellow powder; m. p. 110-115 °C (lit. 113-114 °C).

IR (KBr) cm$^{-1}$: 1585 (C=C), 1664 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.29-7.35 (2H, m, arom.H), 7.73-7.59 (6H, m, arom.H + Ha) 7.85 (1H, d, Hb, J=16.00 Hz), 8.08-8.10 (2H, m, arom.H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 121.18, 127.88, 128.04, 128.07, 128.97, 133.20, 134.00, 137.11, 138.91, 144.46, 187.00.

ESI-MS: ($m/z$) 244.2 (M$^+$+1).

Elemental analysis for C$_{15}$H$_{11}$ClO: Calculated: C, 74.23; H, 4.57; N, 4.59; Found: C, 74.26; H, 5.00.

(E)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (12n)

Nature of compound: Yellow crystalline solid; m. p. 93-96 °C (lit. 94-96 °C).

IR (KBr) cm$^{-1}$: 1585 (C=C), 1664 (C=O),

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.10-7.12 (2H, m, arom.H), 7.45-7.62 (6H, m, arom.H + Ha), 7.86 (1H, d, Hb, J=16.00 Hz), 8.03-8.04 (2H, m, arom.H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ (ppm) 21.67, 122.16, 127.98, 128.01, 128.04, 128.77, 133.00, 134.26, 137.91, 138.11, 144.39, 189.01.

ESI-MS: ($m/z$) 223.0 (M$^+$+1).
Elemental analysis for C_{16}H_{14}O: Calculated: C, 86.54; H, 6.35; Found: C, 86.55; H, 6.32.

(E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (12o)

Nature of compound: Yellow powder; m. p. 97-102 °C (lit. 98-100 °C).^{55}

IR (KBr) cm⁻¹: 1573(C=C), 1687(C=O),

¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.15-7.28(3H, m, arom.H), 7.49-7.65(5H, m, arom.H + Hα), 7.68-7.70(2H, m, arom.H), 7.85(1H, d, Hβ, J=16.32 Hz).

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 123.09, 127.80, 128.11, 128.27, 128.97, 134.60, 135.01, 137.12, 138.91, 144.46, 189.01.

ESI-MS: (m/z) 244.2 (M⁺+1).

Elemental analysis for C_{13}H_{11}ClO: Calculated: C, 74.23; H, 4.57; N, 4.59; Found: C, 74.26; H, 5.00.

(E)-3-phenyl-1-(p-tolyl)prop-2-en-1-one (12p)

Nature of compound: Yellow powder; m. p. 40-48 °C (lit. 42-47 °C).^{56}

IR (KBr) cm⁻¹: 1573(C=C), 1687(C=O),

¹H NMR (400 MHz, CDCl₃): δ (ppm) 6.99-6.81(5H, m, arom.H), 7.55-7.40(3H, m, arom.H + Hα), 7.81(1H, d, Hβ, J=16.32 Hz), 7.93-7.95(2H, m, arom.H),

¹³C NMR (100 MHz, DMSO-d₆): δ (ppm) 22.10, 120.98, 127.66, 128.15, 128.07, 128.55, 133.10, 135.21, 137.77, 138.01, 145.06, 188.21.

ESI-MS: (m/z) 223.0 (M⁺+1).

Elemental analysis for C_{16}H_{14}O: Calculated: C, 86.54; H, 6.35; Found: C, 86.55; H, 6.32.
4.8. REFERENCES


CHAPTER 5

Sulphuric Acid Modified Nano Fibrous Silica as Solid Acid Catalyst for Environmentally Benign Synthesis of β-enaminones
5.1. INTRODUCTION

The class of compounds, named β-enaminones, can be presented as a general formula shown in Fig. 45. These organic molecules possess in their structure a conjugated system composed of the motif N-C=C-C=O. β-enaminones have attracted much attention over the past decades owing to their intrinsic biological properties.\(^1\)

\[
\begin{array}{c}
\text{R}_1 \\
\text{NH} \quad 3 \\
\text{R}_2 \quad 2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{O} \quad 1 \\
\text{R}_3 \\
\end{array}
\]

Fig. 45 β-enaminones

These compounds are versatile synthetic intermediates that combine the nucleophilicity of enamines with the electrophilicity of enones. They exhibit nucleophilicity due to the presence of enamines (C-2 or N), whereas C-1 and C-3 are accountable for electrophilicity of β-enaminones. As a result, they are important class of reactive intermediates in organic synthesis. They have high impacts as synthons for synthesis of various heterocyclic and biologically active analogues\(^2\) including anticonvulsant,\(^3\) anti-inflammatory (\(p\)-arylamidoacrylic acids)\(^4\) and anti-tumour agents.\(^5\)

Enaminones are frequently used as a potential building blocks to access several types of heterocyclic ring systems such as 1,4-dihydropyridines,\(^6\) pyrroles,\(^7\) pyranones,\(^8\) 2-isoxazoles,\(^9\) pyridines,\(^10\) pyrimidines,\(^11\) tetrahydropyrimidines,\(^12\) pyrazoles,\(^13\) isoquinolines,\(^14\) dihydropyridines, triacylbenzenes and naphthofurans\(^15\) etc. They also serve as synthons for γ-aminoalcohol, β-aminoacids which are a class of very stable compounds and useful in asymmetric catalysis as a chelating agent.\(^16\) They have been also used to form volatile chelate metal complexes with PdCl\(_2\) in amine medium to form palladium β-ketoimininate.\(^17\) Realizing the wide spectrum of usage, there is a quest for the development of more simple and higher yielding processes for the synthesis of enaminones. The commonly used synthetic protocol employs the condensation of 1,3-dicarbonyl compounds with amines that proceeds via an addition-elimination pathway in which the addition of amine to the carbonyl moiety results in a tetrahedral intermediate that subsequently undergoes elimination of a water molecule.
to give the desired product. The catalysts employed for this reaction include Al₂O₃,¹⁸ SiO₂,¹⁹ montmorillonite K-10,²⁰ NaAuCl₄,²¹ Zn(ClO₄)₂·6H₂O,²² AcOH under ultrasound,²³ Zn(OAc)₂·2H₂O,²⁴ Bi(OTf)₃,²⁵ I₂,²⁶ Sc(OTf)₃,²⁷ HClO₄·SiO₂,²⁸ ionic liquid [EtNH₃]NO₃²⁹ and [Hmin]Tfa,³⁰ CeCl₃·7H₂O,³¹ ZrOCl₂·8H₂O,³² H₂SO₄·SiO₂,³³ ceric ammonium nitrate (CAN),³⁴ LiHSO₄·SiO₂,³⁵ L-proline,³⁶ and [VO(acac)]₂.³⁷ A variety of other catalysts such as B₂O₃/Al₂O₃,³⁸ SbCl₅/SiO₂,³⁹ P₂O₅/SiO₂,⁴⁰ silica chloride,⁴¹ sulfamic acid,⁴² phosphotungstic acid,⁴³ and Ag⁴⁴ or Cu nanoparticles⁴⁵ and Ga(OTf)₃⁴⁶ have also been used to promote this transformation.

5.2. REVIEW AND LITERATURE

5.2.1. Some recent examples of synthesis of β-enaminones and β-enaminoester under environmentally benign conditions

5.2.1a. Natural Phosphate as green catalyst for the synthesis of β-enaminones.

Harrad et al. reported the synthesis of β-enaminoesters by simple condensation of various primary amines with β-ketoester under solvent-free conditions using natural phosphate (NP) as highly efficient heterogeneous catalyst. Very high yields of the products were obtained at room temperature.⁴⁷

\[
\begin{align*}
\text{H₃C} & \quad \text{O} \\
\text{O} & \quad + \quad \text{R₂-NH₂} \\
\text{H₃C} & \quad \text{R₁} \\
\end{align*}
\]

\[
\begin{align*}
\text{R₁} & = \text{OMe, OEt} \\
\text{R₂} & = \text{Ph, Ph-CH₃, naphthyl, o-MePh, p-MePh, p-NO₂Ph, p-BrPh, p-ClPh, p-FPh, PhCH₂, Me, isopropyl, cyclohexyl, Me, 1-ethanol-2-yl} \\
\end{align*}
\]

5.2.1b. Environment friendly synthesis of β-enaminones using reusable Zn amino acid complex.

Synthetically versatile β-enaminones were also synthesized sonochemically under solvent-free conditions using Zn[Pro]₂ and Zn[Gly]₂ (hybrid catalyst) as heterogeneous catalyst. This green protocol provided the products with excellent yields up-to 99% with simple operational procedure.⁴⁸

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$\beta$-Enaminones

\[ \text{H}_2\text{C} \text{C} \text{O} \text{C} + \text{R}_2 \text{NH}_2 \xrightarrow{\text{Hybrid catalyst, MW}} \text{R}_2 \text{NH} \text{C} \text{O} \text{R}_1 \]

\( \text{R}_1 = \text{Me, OEt} \)

\( \text{R}_2 = \text{Ph, Bn, } p-\text{MePh, } p-\text{OMePh, butyl, cyclohexyl} \)

5.2.1c. \( \text{Fe(OTf)}_3 \) mediated heterogeneous synthesis of \( \beta \)-enaminones.

Feng et al. reported a library of \( \beta \)-enaminino ketones and esters under solvent-free conditions using highly stable and efficient \( \text{Fe(OTf)}_3 \). This protocol provided various attractive features including high yield of products, short reaction periods, lower loading of catalyst and chemo- and regio-selectivity. In addition, the catalyst was easily recovered from the reaction system and readily reused with minimal loss of activity.\(^49\)

\[ \text{H}_2\text{C} \text{C} \text{O} \text{C} + \text{R}_2 \text{NH}_2 \xrightarrow{\text{Fe(OTf)}_3, \text{Solvent-free, r.t.}} \text{R}_2 \text{NH} \text{C} \text{O} \text{R}_1 \]

\( \text{R}_1 = \text{Me, OEt} \)

\( \text{R}_2 = \text{Ph, 2-Cl-6-Me-C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{Me-C}_6\text{H}_4, 4-\text{NO}_2-\text{C}_6\text{H}_4, 4-\text{OMe-C}_6\text{H}_4, \)

\( 2-\text{Me-C}_6\text{H}_4, 3-\text{Cl-C}_6\text{H}_4, \text{CH}_3(\text{CH}_2)_3, (\text{CH}_3)_2\text{CH, C}_6\text{H}_{11}, \text{PhCH}_2, \)

\( 1\text{-naphthyl, piperidinyl, morpholinyl} \)

5.2.1d. Efficient synthesis of \( \beta \)-enaminino derivatives mediated by phosphomolybdic acid.

Phosphomolybdic acid (PMA) catalyzed synthesis of \( \beta \)-enaminino derivatives had been reported by Nagaiah et al. They concluded that 1 mol % PMA provided good to excellent yields of products at room temperature.\(^50\)

\[ \text{H}_3\text{C} \text{CH}_3 + \text{NH}_2 \xrightarrow{\text{Phosphomolybdic acid, CH}_3\text{CN, r.t.}} \text{H}_2\text{C} \text{CH}_3 \text{NH} \text{R}_1 \]

\( \text{R}_1 = \text{Ph, 3-Cl-4-Me-C}_6\text{H}_3, 2,4\text{-di-F-C}_6\text{H}_3, 4-\text{Me-C}_6\text{H}_4, 3-\text{MeO-C}_6\text{H}_4, 4-\text{CF}_3-\text{C}_6\text{H}_4, \)

\( 2-\text{NO}_2-\text{C}_6\text{H}_4, 3-\text{NO}_2-\text{C}_6\text{H}_4, \text{PhCH}_2, \text{CH}_3-\text{CH(CH}_3)_2 \)

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5.2.1e. Metal complex mediated synthesis of β-enaminones under benign conditions.

A series of gold (III) N-heterocyclic carbene complexes were reported as effective catalysts in the synthesis of β-enaminones from 1,3-dicarbonyl compounds and primary amines under ambient conditions.\(^5^1\)

\[
\begin{align*}
R_1-\text{NH}_2 & \xrightarrow{\text{Gold(III) complex, Stirring, r.t.}} \text{NH}^\text{R_1} \\
\text{R}_1 &= \text{Me, Et, } \text{n-Pr, n-Bu} \\
\text{R}_2 &= \text{Me, Ph} \\
\text{R}_3 &= \text{Me, OEt,}
\end{align*}
\]

5.2.1f. Neat synthesis of β-enaminones in the presence of NaHSO\(_4\)/SiO\(_2\).

An efficient and simplified protocol for NaHSO\(_4\)/SiO\(_2\) catalyzed solvent-free synthesis of β-enaminone derivatives under microwave irradiation was described by Shingare \textit{et al.} A series of functionalized derivatives had been synthesized in shorter reaction times with moderate to good yields. The use of milder catalyst in non-conventional method offered significant advantages over conventional methods, such as higher selectivity, simplicity, solvent-free reaction and non-environmental polluting conditions.\(^5^2\)

\[
\begin{align*}
\text{H}_3\text{C} & + \text{R} \xrightarrow{\text{NaHSO}_4/\text{SiO}_2, \text{Solvent-free, MW}} \text{H}_3\text{C} \\
\text{R} &= \text{H, 4-F, 4-OMe, 4-OEt, 4-Br, 4-Me, 2,3-di-Cl, 2-Me, 3-Me, 4-Cl}
\end{align*}
\]

5.2.1g. Synthesis of β-enaminones employing silver nanoparticle.

Nanoparticles had also been employed for the synthesis of β-enaminones and β-enamino esters. Bhatte \textit{et al.} used silver nanoparticles as a heterogeneous, recyclable
and moisture stable catalyst for the condensation of different dicarbonyl compounds and amines. The advantages offered by this protocol include high yield of products under ambient conditions with diverse substrates. The catalyst was recyclable also.\(^5^3\)

\[
\begin{align*}
R &= \text{CH}_3, \text{Ph}, \\
R_1 &= \text{CH}_3, \text{OC}_2\text{H}_5 \\
R_2 &= \text{Ph}, 4-\text{MePh}, \text{C}_4\text{H}_9, \text{morpholinyl}, \text{Bn}, \text{cyclohexanyl}
\end{align*}
\]

5.2.1h. Cu nanoparticle catalyzed condensation of β-dicarbonyl compounds and various kinds of primary aliphatic/aromatic amines.

Synthesis of β-enaminones was also reported from β-dicarbonyl compound and primary aliphatic/aromatic amines using Cu-nanoparticles as catalyst. The simple work-up, mild reaction conditions, non-toxic side products formation and high yields made it environmentally benign protocol.\(^5^4\)

\[
\begin{align*}
\text{H}_2\text{C} &\quad + \quad \text{CH}_3 \quad \text{NH}_2 \\
\text{R} &= \text{CH}_3, \text{C}_2\text{H}_5, \text{Ph}, 4-\text{OMePh}, 4-\text{NO}_2\text{Ph}, \text{C}_4\text{H}_9\text{O}, \text{isopropyl}, 4-\text{BrPh}, \text{C}_2\text{H}_2
\end{align*}
\]

5.2.1i. Supported heteropolyacid catalyzed green synthesis of β-enaminones and β-enamino esters.

An eco-friendly approach for the synthesis of β-enaminones and β-enamino esters from various substituted amines and β-diketones or β-keto esters using different supported heteropoly acids (HPAs) at room temperature had been described by Rafiee \textit{et al.} A simple procedure combined with low toxicity and reusability of the catalysts, make this method an economic and waste-free chemical process for the synthesis of β-enaminones.\(^5^5\)
$\beta$-Enaminones

\[
\begin{align*}
R_1 = & p{-}\text{ClC}_6\text{H}_4, \text{Ph}, \ n{-}\text{C}_4\text{H}_9, \ (\text{CH}_3)_2\text{CH}_2, \ p{-}\text{CH}_3\text{OC}_6\text{H}_4, \ p{-}\text{NO}_2\text{C}_6\text{H}_4, \ \text{PhCH}_2, \\
\text{PhCO}, \ NH_2\text{CH}_2\text{CH}_2, \ p{-}\text{ClC}_6\text{H}_4, \ p{-}\text{CH}_3\text{C}_6\text{H}_4, \ \text{OHCH}_2\text{CH}_2, \ o{-}\text{CH}_3\text{C}_6\text{H}_4 \\
R_2 = & \text{CH}_3 \\
R_3 = & \text{CH}_3, \ \text{OC}_2\text{H}_5
\end{align*}
\]

5.2.1j. Synthesis of $\beta$-enaminones and $\beta$-enamino esters with the help of nanoreactor

A nanoreactor (Ag/HMMS) composed of hollow magnetic mesoporous spheres (HMMS) and Ag nanoparticles was reported as an efficient catalyst for synthesis of $\beta$-enamino ketones or esters from $\beta$-dicarbonyl compound under mild reaction conditions. The catalyst was easily recovered by an external magnet from the reaction mixture and recycled five times without any significant loss in activity.\(^{56}\)

\[
\begin{align*}
\text{H}_3\text{C} & \text{O} \quad \text{R}_1 + \text{R}_2\text{-NH}_2 & \xrightarrow{\text{Ag/HMMS}} & \text{R}_2 \text{NH} \quad \text{O} \\
& \text{333 K, MeOH} & & \\
\text{R}_1 = & \text{CH}_3, \ \text{OCH}_3, \ \text{OC}_2\text{H}_5 \\
\text{R}_2 = & p{-}\text{CH}_2\text{C}_6\text{H}_4, \ \text{PhCH}_2, \ n{-}\text{C}_4\text{H}_9, \ i{-}\text{C}_4\text{H}_9, \ \text{Cyclohexyl}, \ \text{C}_6\text{H}_5,
\end{align*}
\]

5.3. PRESENT WORK

The development of nanoscience has made the greening of chemistry possible. Nanoparticles have emerged as sustainable alternatives to conventional materials as
robust, high surface area heterogeneous catalysts and catalyst supports. The nanosized particles increase the exposed surface area of the active component of the catalyst, thereby enhancing the contact between reactants and catalyst dramatically, thus mimicking the homogeneous catalysts. Moreover, their insolvency in reaction solvents render them easily separable from the reaction mixture like heterogeneous catalysts, and thus, make the product isolation stage effortless. Also, the activity and selectivity of nano-catalyst can be manipulated by tailoring chemical and physical properties like size, shape, composition and morphology. Nanocatalysis thus, adds greenness to chemical processes through higher activity with less amount of catalysts. It also avoids drastic reaction conditions and increases energy efficiency, and higher selectivity, which reduces the by-products formation and allows to perform chemical reactions in a selective manner with the least possible consumption of substances.\textsuperscript{57} This, in turn, improves atom economy and waste prevention.

Nanosilica functionalized by incorporating organic and inorganic functional groups within their mesopores are of great interest for their use as heterogeneous catalysts. Various mesoporous silica compounds such as SBA, MCM and FSM that have been functionalized by sulfonic acid groups offer simpler, less costly, more reactive and more environmentally benign alternatives than their homogeneous counterparts.\textsuperscript{58-62} Although, these differently functionalized nanosilica provide large specific surface areas,\textsuperscript{63,64} yet their surface accessibility could become an issue limiting their applications in certain cases, since any molecule involved in adsorption or reaction have to travel through a long pathway and therefore the actual surface area may not be fully utilized. To overcome this problem, we have used high-surface area fibrous SiO\textsubscript{2} spheres with much more open porosity for the synthesis of sulphuric acid functionalized nanosilica. These SiO\textsubscript{2} spheres (KCC-1) with a very large specific surface area have promising applications as catalyst supports, where diffusion is no longer a limiting step in heterogeneous catalysis. The high surface area of KCC-1 is attributable to fibres and not to pores, which dramatically increase its accessibility of active sites.\textsuperscript{65} Moreover, this material exhibits excellent physical properties, including a fibrous surface morphology, good thermal, hydrothermal and mechanical stability. Therefore, it has been used as a support for many catalysts in organic transformations.\textsuperscript{66} Thus in our investigation, we have undertaken the synthesis of sulphuric acid modified KCC-1 (KCC-1-SA). The catalyst was characterized well
using various techniques and its catalytic activity was investigated for the synthesis a library of β-enaminones.

5.4. RESULTS AND DISCUSSION

5.4.1. Characterization of the catalyst

5.4.1a. Amount of acid loading on catalyst

In order to find most efficient and recyclable nano-silica bonded sulphuric acid a series of KCC-1 bonded sulphuric acid with 4, 6, 8, 10 mmol of acid loading in 1 g of KCC-1 were prepared according to the Scheme 11. The effect of acid loading (Fig 46) on the model reaction using acetylacetone (2a) and aniline (13a) as model substrates was studied (Scheme12). It was found that catalyst with 8 mmol of acid loading performed most efficiently.

Scheme 11 Preparation of fibrous nano silica sulphuric acid (KCC-1-SA).

![Diagram of Scheme 11]

Fig. 46 Effect of acid loading on KCC-1 for catalyzing model reaction.

5.4.1b. H⁺ ion concentration of the catalyst
The amount of $H^+$ in KCC-1-SA with 8 mmol of acid loading was calculated through back titration and was found to be 9 meq/g of the support.

5.4.1c. Powder X-ray diffraction (XRD) analysis of the catalyst

A broad diffraction peaks around $2\theta = 22^\circ$ (Fig. 47) was characteristics of silica. Moreover, the XRD peaks of KCC-1-SA and recovered catalysts showed the same positions with different intensities.

![XRD graph](image)

**Fig. 47** XRD (a) KCC-1-SA (b) recovered catalyst.

5.4.1d. FT-IR spectral analysis of the catalyst

The FT-IR spectrum of the catalyst (Fig. 48) showed broad asymmetric Si–O–Si stretching from 1200 to 1000 cm$^{-1}$ and symmetric Si–O–Si stretching near 800 cm$^{-1}$ for SiO$_2$. For sulfonic acid functional group, the absorption range of the O=S=O asymmetric and symmetric stretching modes were present at 1110–1240 cm$^{-1}$, 1020–1080 cm$^{-1}$, and that of the S–O stretching mode at 600–700 cm$^{-1}$, respectively. The spectrum also exhibited overlapping of asymmetric and symmetric stretching bands of SO$_2$ with Si–O–Si stretching bands in the silica sulfuric acid catalyst. The broad OH stretching absorption was present at 3500 cm$^{-1}$.
Fig. 48. FT-IR spectra of fibrous-silica sulfuric acid (KCC-1-SA).

**5.4.1e. SEM and TEM images of the catalyst**
Scanning electron microscopy (SEM) image of KCC-1 (Fig. 49a) revealed that the material consisted of colloidal spheres. Close inspection of transmission electron microscopy (TEM) image of KCC-1 (Fig. 49b) showed that the material possessed dendrimers which were arranged in 3D to form spheres of diameter 100-500 nm.

Fig. 49 SEM and TEM images of KCC-1.
TEM images (Fig. 50) of KCC-1 after functionalization with sulphuric acid showed that dendrimeric fibres were intact and arranged in three dimensions to form spheres with diameters 150-500 nm. Thus, functionalization did not alter the basic morphology of the KCC-1.
5.4.1f. **EDX analysis of the catalyst**

The EDX spectrum of KCC-1-SA (Fig. 51), showed the peaks for S, Si and O elements confirming the formation of expected catalytic system.

![EDX spectra of Fibrous-silica sulfuric acid (KCC-1-SA).](image)

5.4.1g. **Thermal analyses of the catalyst**

The TGA curve furnished information about the thermal stability of loaded sulphuric acid on silica. TG (Fig. 52) curve showed two-stage decomposition. The weight loss of about 30% at around 76 °C could be attributed to the loss of surface physisorbed water. A further weight loss of about 28% at 225 °C was due to decomposition of the SO$_3$H group bonded to KCC-1. DTA measurement (Fig. 52) also confirmed the losses of physisorbed water and SO$_3$ group from the catalyst.
5.4.1h. BET surface area analysis of the catalyst

The surface area of KCC-1 and KCC-1-SA were obtained by Brunauer-Emmett-Teller (BET) method, which employed nitrogen adsorption at different pressures at the liquid nitrogen temperature (77 K). The surface area of KCC-1 (Fig. 53) was found to be 386.16 m$^2$/g.\textsuperscript{66} After functionalization of KCC-1 the surface area reduced to 91.21 m$^2$/g (Fig. 54). The reduction in surface area was due to encapsulation of dendrimeric fibres of silica (KCC-1) by SO$_3$H groups. The pore size distributions were also obtained from these adsorption isotherms by employing Barrett-Joyner-Halenda (BJH) method. The total pore volume was estimated from the amount of nitrogen adsorbed at the highest relative pressure. Pore volume and pore diameter were found to be 0.1155 cc/g and 25Å, respectively. Shape of N$_2$ adsorption – desorption isotherm (Fig. 53) was a typical type IV isotherm.\textsuperscript{66} Large N$_2$ uptakes and hysteresis at the relative pressure near 1.0 was due to fibrous morphology of silica nanoparticles. Due this fibrous nature of the nanosilica there was easy accessibility of surface area to the reactants hence increasing the activity of the catalyst.
5.5. Catalytic activity of the catalyst KCC-1-SA

After characterization of sulphuric acid functionalized KCC-1, experiments were performed to optimize the reaction conditions for synthesis of β-enaminones, 14(a-p) from 1,3-dicarbonyl compounds, 2n and 2d and primary amines, 13(a-k) (Scheme 12). In our preliminary experiments, we investigated the optimization of reaction conditions regarding the solvent, amount of catalyst and temperature of the reaction. For this purpose, aniline 13a and acetylacetone 2n were chosen as model substrates for the synthesis of representative compound 14k.
Scheme 12 Synthesis of β-enaminones.

5.5.1. Effect of solvents

To study the effect of different solvents on the reaction, we performed the reaction using model substrates and 5 mg of KCC-1-SA as a catalyst in different solvents (5mL) (Table 13) under reflux condition. In MeOH, EtOH and (CH₃)₂CHOH (Table 13, entries 1, 2 and 3), the reaction took longer time (1.2-2 h) with moderate yield of the products whereas in water (Table 13, entry 4), the product was obtained in low yield (25% yield) only after 2.5 h. In CH₃CN (Table 13, entry 5) lower yield of the product was obtained with long reaction time. Conducting the reaction in THF and C₆H₅CH₃ (Table 13, entries 6, 7), again in only trace amount of the product was obtained. However, when the model reaction was carried out under solvent-free conditions there was significant increase in the yield of the product in shorter time period. Thus, it is concluded that solvent-free condition is the best condition for the synthesis of enaminones.

Table 13 Effect of various solvents on the model reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeOH</td>
<td>reflux</td>
<td>1.5 h</td>
<td>68</td>
</tr>
</tbody>
</table>
2. EtOH reflux 1.2 h 71
3. (CH₃)₂CHOH reflux 2 h 57
4. H₂O reflux 2.5 h 25
5. CH₃CN reflux 3 h 41
6. THF reflux 4 h trace
7. C₆H₅CH₃ reflux 4.5 h trace
8. Solvent-free 80 2 min 98

5.5.2. Effect of temperature

To get optimum temperature, model reaction was carried out at different temperatures (Fig. 55). The yield of product increased when the reaction temperature was raised from room temperature to 80 °C. However, no increase in the yield of product was observed when the reaction temperature further was raised from 80 °C to 110 °C. Therefore, all further reactions were conducted at 80 °C.

Fig. 55 The effect of temperature on the model reaction.

5.5.3. Effect of catalyst loading

Effect of amount of catalyst on model reaction was investigated to get the optimum amount of catalyst (Fig. 56). For this purpose model reaction was carried out using 2, 5, 10, 15 and 20 mg of KCC-1-SA at 80 °C under solvent-free conditions. The product was obtained in 0, 70, 98, 98, 98 and 98% yield, respectively. Thus it is concluded that 5 mg of the catalyst is sufficient for the best result. Therefore, all reactions were carried out at 80 °C in the presence of 5 mg of KCC-1-SA under solvent-free conditions.
Fig. 56. Effect of catalyst loading on the synthesis of model reaction

5.5.4. Comparison of catalytic activity of KCC-1-SA with reported catalysts

To show the superiority of KCC-1-SA, the model reaction was also carried out in the presence of other heterogeneous catalyst including nanocatalysts. The data of comparative study is summarized in Table 14. As we can see from (Table 14, entries 1-4) that in silica based heterogeneous catalysts, excellent yield of product was obtained with relatively shorter time period but amount of catalyst required as compared to our catalyst is higher. When we carried out the reaction in L-proline (Table 14, entry 5) under solvent-free conditions good yield of product was obtained after several hours. We also carried out the model reaction using nanocatalysts such as Ag and Cu (Table 14, entries 6, 7). These catalysts also took very long time period ranging from 2.5-8 h for completion of reaction with an additional requirement of solvents. Thus it can be concluded that KCC-1-SA (Table 14, entry 8) is the best catalyst as it took only 1 min for completion of reaction with 99% yield of product. Moreover, only 5 mg of catalyst is required for this conversion. This enhanced activity was explained by the excellent accessibility of active sites due to the open and flexible fibrous structure of KCC-1 and helped substrates to easily penetrate and interact with acidic sites of the catalyst and, in turn, accelerated the overall reactions.
Table 14 Comparison of the efficiency of KCC-1-SA for synthesis of 14k

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of catalyst</th>
<th>Time</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>HClO₄-SiO₂/solvent-free</td>
<td>50 mg/mol</td>
<td>14 min</td>
<td>98</td>
<td>28</td>
</tr>
<tr>
<td>2.</td>
<td>Silica chloride/solvent-free</td>
<td>10% (w/w)</td>
<td>5 min</td>
<td>91</td>
<td>41</td>
</tr>
<tr>
<td>3.</td>
<td>Fe(HSO₄)₃-SiO₂/solvent free</td>
<td>25 mol%</td>
<td>7 min</td>
<td>89</td>
<td>68</td>
</tr>
<tr>
<td>4.</td>
<td>Silica sulfuric acid/solvent-free</td>
<td>0.4 g</td>
<td>10 min</td>
<td>89</td>
<td>69</td>
</tr>
<tr>
<td>5.</td>
<td>L-Proline/solvent-free</td>
<td>5 mol%</td>
<td>4 h</td>
<td>85</td>
<td>36</td>
</tr>
<tr>
<td>6.</td>
<td>Ag nanoparticles/MeOH</td>
<td>20 mol%</td>
<td>8 h</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>7.</td>
<td>Cu nanoparticles/MeOH</td>
<td>10 mol%</td>
<td>2.5 h</td>
<td>92</td>
<td>45</td>
</tr>
<tr>
<td>8.</td>
<td>KCC-1-SA</td>
<td>5 mg</td>
<td>1 min</td>
<td>99</td>
<td>Present work</td>
</tr>
</tbody>
</table>

Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of β-enaminones using different amines and different 1,3-dicarbonyl compounds and the obtained results are summarized in Table 15. The products obtained were confirmed by comparing its melting point with authentic samples and on the basis of spectral analyses (FT-IR, ¹H NMR, ¹³C NMR and mass spectra). The IR spectrum (Fig. 57) of the β-enaminone 14c showed a sharp and strong absorption band at 3250 cm⁻¹ for N-H group of enaminone. The strongly absorbed bands at 1597 cm⁻¹, 1565 cm⁻¹, 1513 cm⁻¹ were due to C=O, C=C and C=N groups of enaminone, respectively. The ¹H NMR spectrum (Fig. 58) exhibited a sharp singlet at δ 1.06 for 6 proton of two methyl groups of dimedone moiety. The olefinic proton was discernible as a singlet at δ 5.39. Four aromatic protons were discernible as multiplets in the range δ 7.16-7.34. The N-H proton of enaminone appeared as singlet at δ 8.77. The ¹³C NMR spectrum (Fig. 59) showed signal at δ 196.8 for carbonyl carbon whereas olefinic carbons were present at δ 162.4 and δ 99.6. Aromatic carbon signals appeared at δ 136.8, δ 129.1, δ 127.5 and δ 125.0. Other carbon signals appeared at their appropriate positions and are discussed in the experimental section. Further confirmation of the structure was provided by mass spectrum (Fig. 60) which showed molecular ion peak at m/z 250.6 (M⁺+1).
Fig. 57 FT-IR spectrum of compound 14c

Fig. 58 $^1$HNMR spectrum of compound 14c
Fig. 59 $^{13}$C NMR spectrum of compound 14c.

Fig. 60 Mass spectrum of compound 14c
A plausible mechanism for the formation of \( \beta \)-enaminone (14k) has been depicted in Scheme 8. Protonation of carbonyl carbon by acidic catalyst facilitated the nucleophilic attack of amino group on it. This step is followed by removal of water leading to the formation of intermediate III. The removal of proton from this intermediate generates the product 14k.

Scheme 13 Plausible mechanism for the formation of \( \beta \)-enaminone 14k.

Table 15 KCC-1-SA catalysed synthesis of \( \beta \)-enaminones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Active methylene compound</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>( \text{NH}_2 )</td>
<td>( \text{O} )</td>
<td>( 2d )</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td>6.</td>
</tr>
<tr>
<td>---</td>
<td>------</td>
<td>------</td>
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<td>------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>13c</td>
<td>13d</td>
<td>13e</td>
<td>13f</td>
</tr>
<tr>
<td></td>
<td>2d</td>
<td>2d</td>
<td>2d</td>
<td>2d</td>
<td>2d</td>
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<tr>
<td></td>
<td>14b</td>
<td>14e</td>
<td>14d</td>
<td>14e</td>
<td>14f</td>
</tr>
<tr>
<td></td>
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<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>92</td>
<td>97</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>
Fig. 61 The reusability of the catalyst in the synthesis β-enaminones.

5.8. CONCLUSION

In conclusion, we have developed an efficient method for the preparation β-enaminones. The reactions are carried out under thermal solvent-free conditions at ambient temperature in the presence of very quantity of the catalyst yielding corresponding products within few minutes in excellent yields. The catalyst could be successfully recovered and recyclable up to seven cycles without significant loss in activity.

5.9. EXPERIMENTAL

5.9.1. Catalyst Synthesis

Synthesis of fibrous nano silica support KCC-1 is synthesized according to the reported procedure.\(^{65}\)

Synthesis of catalyst fibrous nanosilica sulfuric acid (KCC-1-SA): KCC-1 (1.0 g) was dispersed in CH\(_2\)Cl\(_2\) (10 mL) in a flask. Chlorosulfonic acid (8 mmol) was dissolved in CH\(_2\)Cl\(_2\) (10 mL) and added to KCC-1 silica suspension through a constant-pressure dropping funnel under stirring, over a period of 30 min at room temperature. After the addition was completed, the mixture was stirred for another 30 min at room temperature. The brown solid as obtained, was collected by filtration and washed with ether (50 mL). Finally it was dried at room temperature.

5.9.2. H\(^+\) ion determination of the catalyst

H\(^+\) ion of catalyst was determined by back titration analysis of KCC-1-SA. NaOH solution (20 mL, 0.1 M) was added to the catalyst (100 mg) in an Erlenmeyer flask.
5.7. Recycling study of the catalyst

The reusability of the catalyst is an important aspect from green chemistry perspective. Thus, the recovery and reusability of the catalyst were also investigated. After completion of the reaction, products were extracted by ethyl acetate and the recovered catalyst was washed with ethyl acetate, acetone and dried in oven at 110°C for 2 h. The recovered catalyst (Fig. 61) was reused at least seven times without any appreciable decrease in the product yield.
This solution was stirred for 10 min. Excess amount of the base was neutralized by addition of HCl solution (0.1 M) to the equivalence point of titration.

5.9.3. General procedure for the synthesis of β-enaminones (14a-p)

A mixture of primary aromatic amine (13a-k, 1 mmol), 1,3-dicarbonyl compound (2d, 2n, 1 mmol), and the catalyst KCC-1-SA (5 mg) was taken in a 25 mL round bottom flask. This reaction mixture was stirred at 80 °C and the progress of reaction was monitored by TLC after every 30 seconds, till the completion of the reaction. After completion of the reaction, ethyl acetate was added to the reaction mixture and the catalyst was filtered off. The solvent of the filtrate was evaporated and the crude product was purified by recrystallization from appropriate solvents. The products obtained (14a-p) were identified by IR and comparing the melting points with authentic samples.

5.10. Spectral data of the compounds

5,5-Dimethyl-3-(phenylamino)cyclohex-2-enone (14a)

Nature of Compound: Yellow solid; m.p. 183-184 °C (lit. 184-185 °C).
IR (KBr) cm⁻¹: 3227 (NH), 1598(C=O), 1566(C=C).

¹H NMR (300 MHz, CDCl₃): δ (ppm): 1.08 (6H, s, CH₃), 2.10 (2H, s, CH₂), 2.36 (2H, s, CH₂), 5.40 (s, 1H, C-H), 7.11–7.23 (3H, m, Ar-H), 7.26–7.44 (2H, m, Ar-H), 8.67 (s, 1H, N-H).

¹³C NMR (75 MHz, CDCl₃): δ (ppm): 28.12, 32.68, 43.39, 49.96(C6), 99.64, 118.9, 128.72, 138.69, 148.61, 161.46, 196.07.

ESI-MS: (m/z) 216.4 (M⁺+1).

Elemental analysis for C₁₄H₁₇NO: Calculated: C, 78.10; H, 7.95; N, 6.50; found: C, 78.12; H, 7.93; N, 6.51.

5,5-Dimethyl-3-(4-methoxyphenylamino)cyclohex-2-enone (14b)

Nature of Compound: Yellow solid; m.p. 192-194 °C (lit. 192-194 °C).
IR (KBr) cm⁻¹: 1545(C=C), 1598(C=O), 3246 (NH).

¹H NMR (300 MHz, CDCl₃): δ (ppm): 1.13 (6H, s, CH₃), 2.10 (2H, s, CH₂), 2.37 (2H, s, CH₂), 3.22(3H, s, CH₃) 5.65 (1H, s, C-H), 7.11–7.45 (4H, m, Ar-H), 8.60 (s, 1H, N-H)

¹³C NMR (75 MHz, CDCl₃): δ (ppm): 27.22, 32.58, 43.19, 48.94, 55.51, 99.54, 123.46, 125.6, 129.72, 132.69, 136.81, 162.46, 196.07.
\(\beta\)-Enaminones

**ESI-MS:** \((m/z)\) 246.08 (M\(^+\)+1).

**Elemental analysis for C\(_{18}\)H\(_{19}\)NO:** Calculated: C, 73.44; H, 7.80; N, 5.71; found: C, 73.44; H, 7.81; N, 5.72.

5,5-Dimethyl-3-(4-Chlorophenylamino)cyclohex-2-enone (14c) \(^7^0\)

**Nature of Compound:** Yellow solid; m.p. 209-210 °C (lit. 209-210 °C).

**IR (KBr) cm\(^{-1}\):** 3250 (NH), 1597(C=O), 1565(C=C).

**\(^1\)H NMR (300 MHz, CDCl\(_3\)):** \(\delta\) (ppm): 1.06 (6H, s, CH\(_3\)), 2.10 (2H, s, CH\(_2\)), 2.37 (2H, s, CH\(_2\)),

5.39 (1H, s, C-H), 7.16 (2H, m, Ar-H), 7.32 (2H, m, Ar-H), 8.77 (s, 1H, N-H), 13.2(C NMR (75 MHz, CDCl\(_3\)): \(\delta\) (ppm): 27.23, 32.52, 46.18, 50.01, 99.68, 125.06, 127.53, 129.13, 136.86, 162.03, 196.81.

**ESI-MS:** \((m/z)\) 250.1 (M\(^+\)+1).

**Elemental analysis for C\(_{14}\)H\(_{16}\)Cl NO:** Calculated: C, 67.33; H, 6.45; N, 5.60; found: C, 67.32; H, 6.44; N, 5.63.

5,5-Dimethyl-3-(p-Tolylamino)cyclohex-2-enone (14d) \(^7^0\)

**Nature of Compound:** Yellow solid; m.p. 201-204 °C (lit. 203-204 °C).

**IR (KBr) cm\(^{-1}\):** 1574(C=C), 1601(C=O), 3246 (NH).

**\(^1\)H NMR (300 MHz, CDCl\(_3\)):** \(\delta\) (ppm): 1.11 (6H, s, CH\(_3\)), 2.11 (2H, s, CH\(_2\)), 2.26(3H, s, CH\(_3\)) 2.37 (2H, s, CH\(_2\)), 5.39 (s, 1H, C-H), 7.10–7.16 (m, 4H, Ar-H), 8.67 (s, 1H, NH)

**\(^13\)C NMR (75 MHz, CDCl\(_3\)):** \(\delta\) (ppm): 22.61, 28.12, 32.58, 46.29, 50.94, 99.64, 123.26, 125.16, 129.62, 131.69, 136.81, 162.16, 196.07.

**ESI-MS:** \((m/z)\) 230.01 (M\(^+\)+1).

**Elemental analysis for C\(_{18}\)H\(_{19}\)NO:** Calculated: C, 78.56; H, 8.35; N, 6.10; found: C, 78.58; H, 8.32; N, 6.11.

5,5-Dimethyl-3-(4-hydroxyphenylamino)cyclohex-2-enone (14e) \(^7^0\)

**Nature of Compound:** Yellow solid;

**m.p.** 236-237 °C (lit. 236-237 °C).

**IR (KBr) cm\(^{-1}\):** 1575(C=C), 1606(C=O), 3429 (NH).
\[ \beta\text{-Enaminones} \]

\[^{1}\text{H NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}) \ d 
1.10 \ (6\text{H, s, CH}_3), 
2.15 \ (2\text{H, s, CH}_2), 
2.42 
(2\text{H, s, CH}_2), 
5.60 \ (1\text{H, s, C-H}), 
7.24 \ (2\text{H, m, Ar-H}), 
7.37 \ (2\text{H, m, Ar-H}), 
8.70 \ (1\text{H, s, N-H}), 
9.11 \ (1\text{H, s, O-H}). \]

\[^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}): 
28.22, 
32.88, 
43.29, 
49.94, 
99.54, 
118.60, 
119.80, 
131.11, 
148.18, 
162.46, 
196.07. \]

ESI-MS: (m/z) 232.9 (M^+1).

Elemental analysis for C\(_{14}H_{17}NO_2\): Calculated: C, 72.70; H, 7.40; N, 6.05; found: C, 72.69; H, 7.42; N, 6.05.

\(5,5\text{-Dimethyl-3-(4-nitrophenylamino)cyclohex-2-enone (14f)}\)^70

Nature of Compound: Yellow solid; m.p. 246-247 °C (lit. 246-247 °C).

IR (KBr) cm\(^{-1}\): 1576(C=C), 1599(C=O), 3267 (NH).

\[^{1}\text{H NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}) \ d 
1.10 \ (6\text{H, s, CH}_3), 
2.13 \ (2\text{H, s, CH}_2), 
2.32 
(2\text{H, s, CH}_2), 
5.76 \ (1\text{H, s, C-H}), 
7.16-7.20 \ (2\text{H, m, Ar-H}), 
7.66-7.78 \ (2\text{H, m, Ar-H}), 
8.71 \ (1\text{H, s, NH}) \]

\[^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}): 
28.22, 
32.88, 
43.29, 
49.84, 
99.54, 
121.63, 
129.81, 
137.11, 
144.8, 
162.16, 
196.07. \]

ESI-MS: (m/z) 261.7 (M^+1).

Elemental analysis for C\(_{14}H_{16}N_2O_3\): Calculated: C, 64.60; H, 6.19; N, 10.76; found: C, 64.62; H, 6.20; N, 10.76.

\(5,5\text{-Dimethyl-3-(3-hydroxyphenylamino)cyclohex-2-enone (14g)}\)^70

Nature of Compound: Yellow solid; m.p. 236-237 °C (lit. 236-237 °C).

IR (KBr) cm\(^{-1}\): 1565(C=C), 1601(C=O), 3229 (NH).

\[^{1}\text{H NMR} \ (300 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}) \ d 
1.10 \ (6\text{H, s, CH}_3), 
2.15 \ (2\text{H, s, CH}_2), 
2.42 
(2\text{H, s, CH}_2), 
5.60 \ (s, 1\text{H, C-H}), 
7.21-7.36 \ (4\text{H, m, Ar-H}), 
8.76 \ (1\text{H, s, N-H}), 
9.12 
(1\text{H, s, O-H}). \]

\[^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta \ (\text{ppm}): 
27.92, 
32.18, 
46.29, 
50.04, 
99.54, 
99.88, 
110.60, 
119.80, 
130.11, 
140.81, 
159.31, 
162.46, 
196.07. \]

ESI-MS: (m/z) 232.9 (M^+1).
Elemental analysis for C_{14}H_{17}NO_{2}: Calculated: C, 72.70; H, 7.40; N, 6.05; found: C, 72.69; H, 7.42; N, 6.05.

5,5-Dimethyl-3-(2-hydroxyphenylamino)cyclohex-2-enone (14h) \(^{70}\)

Nature of Compound: Yellow solid; m.p. 236-237 °C (lit. 236-237 °C).

IR (KBr) cm\(^{-1}\): 1575(C=C), 1606(C=O), 3429 (NH).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) d 1.10 (6H, s, CH\(_3\)), 2.11 (2H, s, CH\(_2\)), 2.22 (2H, s, CH\(_2\)), 5.38 (1H, s, C-H), 7.20-7.34 (4H, m, Ar-H), 8.70 (1H, s, N-H), 9.11 (1H, s, O-H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) (ppm): 28.22, 32.68, 43.19, 49.84, 99.54, 115.60, 116.66, 119.80; 122.67, 134.11, 143.81, 162.46, 196.07.

ESI-MS: \((m/z)\) 232.9 (M\(^+\)+1).

Elemental analysis for C_{14}H_{17}NO_{2}: Calculated: C, 72.70; H, 7.40; N, 6.05; found: C, 72.69; H, 7.42; N, 6.05.

5,5-Dimethyl-3-(3-nitrophenylamino)cyclohex-2-enone (14i) \(^{70}\)

Nature of Compound: Yellow solid; m.p. 174-175 °C (lit. 174-175 °C).

IR (KBr) cm\(^{-1}\): 1535(C=C), 1587(C=O), 3319 (NH).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) 1.10 (6H, s, CH\(_3\)), 2.19 (2H, s, CH\(_2\)), 2.42 (2H, s, CH\(_2\)), 5.63(1H, s, C-H), 7.16 (2H, m, Ar-H), 7.34 (2H, m,Ar-H), 8.78 (1H, s, NH),

\(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) (ppm): 28.12, 32.68, 43.19, 50.14, 99.44, 117.19, 119.60, 129.80, 130.01, 136.10, 142.16, 162.46, 196.17.

ESI-MS: \((m/z)\) 261.3 (M\(^+\)+1).

Elemental analysis for C_{14}H_{16}N_{2}O_{3}: Calculated: C, 64.60; H, 6.19; N, 10.76; found: C, 64.62; H, 6.20; N, 10.76.

5,5-Dimethyl-3-(2-nitrophenylamino)cyclohex-2-enone(14j) \(^{70}\)

Nature of Compound: Yellow solid; m.p. 163-164 °C (lit. 163-164 °C).

IR (KBr) cm\(^{-1}\): 1575(C=C), 1606(C=O), 3429 (NH).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) (ppm) d 1.10 (6H, s, CH\(_3\)), 2.10 (2H, s, CH\(_2\)), 2.32 (2H, s, CH\(_2\)), 5.40 (s, 1H,C-H), 7.40 (1H, m, Ar-H), 7.66 (2H, m, Ar-H), 8.10(1H, m, Ar-H), 8.77 (1H, s, N-H)
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm): 27.12, 32.78, 46.29, 49.94, 99.54, 114.67, 119.79, 125.80, 127.81, 137.31, 139.81, 162.46, 196.07.

ESI-MS: ($m/z$) 261.7 (M$^+$+1).

**Elemental analysis for C$_{14}$H$_{16}$N$_2$O$_3$:** Calculated: C, 64.60; H, 6.19; N, 10.76; found: C, 64.62; H, 6.20; N, 10.76.

**4-(Phenylamino)pent-3-en-2-one (14k)**

**Nature of Compound:** Yellow solid; m.p. 44-48 °C (lit. 45-47 °C).$^{71}$

**IR (KBr) cm$^{-1}$:** 1580(C=C), 1638(C=O), 3414 (NH).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 1.99 (3H, s, CH$_3$), 2.09 (3H, s, CH$_3$), 5.26 (1H, s, C-H), 7.11 (3H, m, Ar-H), 7.21 (2H, m, Ar-H), 12.35 (1H, s, N-H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm) 19.61, 28.92, 98.32, 115.61, 123.73, 124.90, 129.13, 139.01, 160.01, 196.11.

ESI-MS: ($m/z$) 176.2 (M$^+$+1).

**Elemental analysis for C$_{11}$H$_{12}$N O:** Calculated: C, 75.39; H, 7.47; N, 7.99; found: C, 75.40; H, 37.48; N, 7.96.

**4-(4-methoxyphenylamino)pent-3-en-2-one (14l)**

**Nature of Compound:** Pale Yellow solid; m.p. 41-43 °C (lit. 41-43 °C).$^{72}$

**IR (KBr) cm$^{-1}$:** 3563 (NH), 1603(C=O), 1559(C=C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 1.89 (3H, s, CH$_3$), 2.12 (3H, s, CH$_3$), 3.83 (3H, s, CH$_3$), 5.14 (1H, s, C-H), 7.08 (3H, m, Ar-H), 7.33 (2H, m, Ar-H), 12.65 (1H, s, N-H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 19.43, 28.86, 55.34, 96.71, 114.01, 126.41, 131.21, 157.51, 161.22, 195.51.

ESI-MS: ($m/z$) 206.1 (M$^+$+1).

**Elemental analysis for C$_{15}$H$_{15}$NO$_2$:** Calculated: C, 70.22; H, 7.36; N, 6.82; found: C, 70.23; H, 7.39; N, 6.84.

**4-(4-Chlorophenylamino)pent-3-en-2-one (14m)**

**Nature of Compound:** Pale Yellow solid; m.p. 60-63 °C (lit. 60-62 °C).$^{71}$

**IR (KBr) cm$^{-1}$:** 1562(C=C), 1639(C=O), 3460 (NH).
\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm) 2.01 (3H, s, CH\(_3\)), 2.03 (3H, s, CH\(_3\)), 4.96 (1H, s, C-H); 7.25 (2H, m, Ar-H), 7.29 (2H, m, Ar-H), 12.33 (1H, s, N-H).

\( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm) 19.8(CH\(_3\)), 29.9(CH\(_3\)), 97.5(C3), 115.7(Ar-C), 124.7(Ar-C), 125.5(Ar-C), 129.0(Ar-C), 138.6(Ar-C), 160.4(C4), 196.1(C2).

ESI-MS: \( m/z \) 210.6 (M\(^{+}\)+1).

Elemental analysis for C\(_{11}\)H\(_{12}\)ClNO: Calculated: C, 63.01; H, 5.76; N, 6.68; found: C, 63.04; H, 5.77; N, 6.69.

4-(p-Tolylamino)pent-3-en-2-one (14n)

Nature of Compound: Pale Yellow solid; m.p. 57-61 °C (lit. 58-59 °C).

IR (KBr) cm\(^{-1}\): 1545(C=C), 1610(C=O), 3444 (NH).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm) 1.93 (3H, s, CH\(_3\)), 2.18 (3H, s, CH\(_3\)), 2.32 (3H, s, CH\(_3\)), 5.19 (1H, s, C-H), 7.01(2H, m, Ar-H), 7.19 (2H, m, Ar-H), 12.48 (1H, s, N-H).

\( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm) 19.61, 21.01, 29.11, 96.91, 124.71, 129.41, 135.62, 135.98, 160.71, 195.91.

ESI-MS: \( m/z \) 190.3 (M\(^{+}\)+1).

Elemental analysis for C\(_{12}\)H\(_{15}\)NO: Calculated: C, 76.15; H, 7.98; N, 7.40; found: C, 76.14; H, 7.96; N, 7.42.

4-(4-nitrophénylamino)pent-3-en-2-one (14o)

Nature of Compound: Yellow solid; m.p. 141-142 °C (lit. 142-143 °C).

IR (KBr) cm\(^{-1}\): 1586(C=C), 1629(C=O), 3423 (NH).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm) 2.17 (3H, s, CH\(_3\)), 2.28 (3H, s, CH\(_3\)), 5.24 (1H, s, C-H), 7.23 (2ff, m, Ar-H), 7.83 (2H, m, Ar-H), 12.58 (1H, s, N-H).

\( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm) 19.94, 29.73, 95.99, 115.99, 123.92, 126.10, 129.29, 138.21, 161.21, 196.01.

ESI-MS: \( m/z \) 221.6 (M\(^{+}\)+1).

Elemental analysis for C\(_{11}\)H\(_{12}\)N\(_2\)O\(_3\): Calculated: C, 59.99; H, 5.49; N, 12.72; found: C, 59.96; H, 5.51; N, 12.73.

4-(Naphthalen-1-ylamino)pent-3-en-2-one (14p)

Nature of Compound: Yellow solid; m.p. 61-62 °C (lit. 61-63 °C).

IR (KBr) cm\(^{-1}\): 1540(C=C), 1601(C=O), 3420 (NH).
$\beta$-Enaminones

$^1$H NMR (300 MHz, CDCl₃): $\delta$ (ppm) 1.90 (3H, s, CH₃), 2.28 (3H, s, CH₃), 5.31 (1H, s, C-H), 7.23-7.56 (4H, m, Ar-H), 7.68 (1H, m, Ar-H), 7.79-7.88 (1H, m, Ar-H), 8.12-8.25 (1H, m, Ar-H), 12.86 (s, 1H, NH).

$^{13}$C NMR (75 MHz, CDCl₃): $\delta$ (ppm): 19.70, 29.12, 97.41, 121.81, 123.30, 123.01, 125.42, 125.52, 126.82, 127.02, 128.44, 134.24, 134.83, 161.91, 196.61.

ESI-MS: ($m/z$) 226.3 (M+1).

Elemental analysis for C₁₅H₁₅NO: Calculated: C, 79.97; H, 6.71; N, 6.21; found: C, 79.93; H, 6.72; N, 6.23.
5.11. REFERENCES

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CHAPTER 6

Chitosan Sulphuric Acid: An Efficient and Biodegradable Solid Acid Catalyst for the Synthesis of Highly Substituted Imidazole Derivatives
6.1. INTRODUCTION

Imidazoles belong to a class of heterocyclic compounds that contain nitrogen. The imidazole nucleus is a prolific source of pharmaceutically important molecules. They are present in compounds possessing various pharmaceutical properties such as anti-inflammatory,\textsuperscript{1} antibacterial,\textsuperscript{2} CSBP kinase inhibitor,\textsuperscript{3} glucagon receptor antagonists,\textsuperscript{4} p38 MAP kinase inhibitors,\textsuperscript{5} modulators of Pgp-mediated multidrug resistance,\textsuperscript{6} ligands of the Src SH2 protein,\textsuperscript{7} antitumor agents,\textsuperscript{8} inhibitors of mammalian 15-LOX,\textsuperscript{9} CB1 cannabinoid receptor antagonists,\textsuperscript{10} and inhibitors of B-Raf kinase.\textsuperscript{11} It is also the core structural skeleton in many important biological molecules like biotin, histamine and histidine.\textsuperscript{12,13} Recent development of sustainability and organometallic chemistry further adds to the applications of imidazoles as ionic liquids\textsuperscript{14-16} and N-heterocyclic carbenes.\textsuperscript{17,18} Imidazole derivatives in the form of ionic liquids are useful as electrolytes and also as green solvents because of their low vapour pressure and wide chemical stability,\textsuperscript{19} whereas, imidazolyldiene based carbenes have been proved to be efficient ligands in coordination chemistry, as powerful steering/controlling elements in organometallic catalysis,\textsuperscript{20} and metal-free catalysts for organic reactions.\textsuperscript{21,22} Fluorescence and chemiluminescence properties of imidazole scaffolds have also been used for the development of fluorescence labelling agents and blue light emitting materials.\textsuperscript{23-26} There are many clinical drugs based on the imidazole structure being used in the different therapeutic areas (Fig. 62).