CHAPTER 1

Introduction and Literature Review

In this chapter, Introduction of wheat straw, silica from wheat straw and applications of silica in organic synthesis has been presented. Literature available on method of extraction of silica from agricultural waste and application of silica, in general has been presented here with special emphasis on application of nano silica in preparation of pyrano[2,3-\(c\)]pyrazole-5-carbonitrile derivatives and coumarin derivatives.

Silica extraction methods from agricultural waste have been summarized in part I of this chapter. Applications of silica have been compiled in part II. Literature review on pyrano[2,3-\(c\)]pyrazole-5-carbonitrile derivatives and coumarin derivatives has been presented in part III and IV respectively.
1.1 INTRODUCTION

Million tons of rice, wheat husk and straw are generated as by-products of rice and wheat milling process. They constitute major agricultural waste products. Generally, paddy waste are discarded or destroyed by open field burning (Fig. 1.1.1) resulting in air pollution, emission of greenhouse gases with waste of energy or for land filling or abandoned resulting in occupancy of large space (Fig 1.1.2).

Fig. 1.1.1 Local farmers disposing wheat straw through open field burning

Fig. 1.1.2 Effect of burning crop residue
Instead of discarding or burning the agricultural waste, extraction of silica and silicon has been attempted by many researchers. Rice husk (RH) / wheat straws are also considered to be a potential raw material for silicon and silica based materials. Major wheat producing countries are India, Canada, Australia, France etc. In India about 120 million tonnes of wheat straw has been produced annually (Misra et al., 2013).

![Morphology of wheat plant](image)

Fig. 1.1.3 Morphology of wheat plant

Reasons responsible for agricultural waste to be considered as good silica source and have potential for the large scale productions are low cost of the raw material; high silica content (about 25 %) in agricultural waste (B. Jenkins, 1989); comparable silica quality obtained from other sources; fine sized amorphous material. Dry stalks of wheat plant after removal of grains are known as wheat straw. Wheat straw possesses an inherent structural framework of silica nanoparticles. It also contains
carbon, oxygen, potassium, and low concentration of aluminum, magnesium, sodium phosphorous and sulphur (Patel et al., 2017).

Silica is commonly produced from quartz sand with sodium carbonate at above 1000 °C and is normally crystalline (Liu et al., 2011), relatively lower temperature below 600 °C, silica can be extracted from biomass and are amorphous in nature. (Conradt et al., 1992). Biogenic silica exhibits the high surface area, high purity and small particle size and that are necessary to achieve desired performance (Athinarayanan et al., 2014).

Silica extraction methods from bio-waste have been explored by many researchers. Main methods are thermal treatments and chemical treatments. Thermal methods have serious demerits such as long reaction time, hot spot formation, incomplete oxidation of carbon etc. In chemical methods alkaline extraction method used to produce pure and high amount of silica but it is expensive because of significant longer reaction time (24-48 hrs), and also required various steps with the use of various types of chemicals. Several reports are available on the acid leaching of the metal and oxide form wheat straw and rice husk. Use of microwave digestion technique for this could not found.

Silica is an important industrial material and has extensive applications (Shirshahi et al., 2015) (Kasaai., 2015). Now-a-days silica has been used in chemical separation, sorption, insulation, biosensors and catalysis. A number of acid catalyzed reactions are also based on silica. Silica has found promising applications also in controlled release of drug, bio-sensing, and biomedical fields (Trewyn et al, 2007).

The present work uses microwave assisted acid digestion of wheat straw. Instead of torrefaction, charring of wheat straw was carried out at much lower temperature,
without formation of smoke and air borne particulates. Acid digested product was calcined to get ash.

Silica finds many applications in industry. Not many reports are available on application of silica in organic synthesis, especially to synthesize bioactive compounds like pyranopyrazoles and coumarin. A robust catalyst with high activity giving good yield with mild process parameters could be achieved from the nano sized amorphous silica obtained from wheat straw.

Literature related to silica from agricultural waste, methods of extraction and its application are summarized in the following section.

Methods of extraction of silica from agricultural waste have been summarized in part 1.2. Applications of silica have been summarized in part 1.3. Followed by work on literature review on pyrano[2,3-c]pyrazole-5-carbonitrile derivatives and coumarin derivatives.
1.2 SILICA FROM AGRICULTURAL WASTE

Several methods have been cited for extraction of silica from agricultural waste. Methods commonly used are thermal methods (include burning) and alkaline extraction method.

The major concerns associated with the use of thermal methods are the risk of silica crystallization in the agricultural ash due to high temperature, long reaction time and low carbon conversion efficiency. Conventional furnace systems used to burn agricultural husk or straw has poor performance results in law quality ash, incomplete combustion/charring. Wheat straw is one of the more difficult fuels to burn due to its peculiar silica-wood composite morphological structure, high mineral content, large bulk volume and agglomerate easily (Kapur et al., 1985). In addition, it does not combust cleanly or easily is either self-extinguishing or smoky at low temperatures (Beagle et al, 1978).

Chemical treatment such as alkaline extraction method is capable of producing high purity silica but requires considerable time (1-2 days) and required large number of steps including requirements of various chemicals. In the alkaline extraction method of silica from rice husk content 61 wt% silica and 36 wt% carbon (Kamath and Proctor, 1998), whereby the rice husk need to be subjected first to a carbonization step to remove the organic constituents of cellulose, hemicellulose and lignin.
1.2.1 Thermal Methods

Several thermal methods are used to extract silica from agricultural waste. Three thermal methods commonly used are muffle furnace, stepped grate furnace and rotary kiln. Another method, the fluidized bed method, had been used for combustion of rice husk as early as 1980 (Peel and Santos, 1980) but not for the purpose of producing amorphous silica. Other methods include: cyclone furnace and fixed bed reactor method.

![Existing Methods for Preparation of Silica](image)

Fig. 1.2.1 Existing thermal methods for preparation of silica from agricultural waste
(a) Electric/ muffle furnace method

For extraction of silica from agricultural waste electric/ muffle furnace is used in laboratory scale. The major drawback of using this method is longer reaction time, less production rate, batch-like process and risk of explosion. Since the process is takes place in a closed system, absences of free-flowing oxygen also result in incomplete oxidation of carbon in the husk. To prevent the risk of crystallization, the furnace need to be operated at a lower temperature range (such as 400-600 °C), which in turn required a long residence time (3-6 hours) (Sugita, 1994) in order to achieve high carbon conversion efficiency. Silica in amorphous form was extracted from rice husk (RH) at various temperatures by using electric furnace at 700 °C for 6 hours (Patil et al., 2014).

Meso / Macroporous biogenic silica was obtained (3 to 1500 nm) from miscanthus, cereal remnant pellets and wheat straw by using thermo chemical treatment. Extraction of silica was carried out by treating wheat straw with sulfuric acid in a ratio of 1:10 (g/L) with constant stirring at 1000 rpm at 353 K for 24 hours. The silica ash was produced after heat treatment in muffle furnace at various temperature and time (Alyosef et al., 2015). 95.55% amorphous silica was produced from rice husk ash by using acid leaching treatment followed by thermal heating treatment at 600 °C using muffle furnace (Ghorbani et al., 2015).

In one of the methods wheat straw ash was kept in furnace for combustion at temperature 500 °C for 8 hours. After combustion residue obtained was washed with distilled water and calcined again in muffle furnace with a heating rate 10 °C/min at various temperature 400 °C, 500 °C, 600 °C and 700 °C respectively for 24 hours. Characterization of calcined residue revealed that silica was obtained (Chen et al, 2010).
Pure amorphous silica extraction has been reported by Chakraverty and co-workers by using HCl, H₂SO₄ and HNO₃ in various optimized conditions. Hydrochloric acid leaching treatment was found to be most effective in removing metal ions than other acids (Chakraverty et al, 1988). Pure amorphous silica was obtained at 500-700 °C from acid treated wheat husk ash. Amorphous silica from rice husk at 600 °C in stainless steel tubular reactor placed in electronic laboratory scale muffle furnace for 4hrs. The amorphous silica converted to crystalline silica when it was heated to 1000 °C (Yang et al., 2015). Hamad and co-workers successfully recovered silica from rice husk ash by using muffle furnace and fixed bed reactor at 500 - 1150 °C (Hamad et al., 1981).

(b) Cyclone furnace method

Cyclone furnace was successfully used by Sing co-workers (Sing et al., 1980). In this kind of furnace air keeps the agricultural waste rotating in circular motion and accelerates combustion in the chamber. The advantage of using cyclone furnace for the production of husk ash with lesser carbon content product.

Fig.1.2.2 Schematic of cyclonic furnace (Sing et al.,1980)
(c) Inclined step-grate furnace method

Fig. 1.2.3 Schematic of (a) box-type inclined grate furnace and (b) furnace with cylindrical combustion chamber (Bautista Et Al., 1996)

Inclined step-grate furnace is a common device used for ash production from agricultural husk or straw. It consists of feeding component, combustion chamber and ash precipitation chamber. Rice husk is fed at the top of the grate reactor while the air flows from the bottom (Bautista et al., 1996). The major drawback of this technique is non-uniformity in fuel-to-air ratio due to the varying load of husk into the furnace (Natarajan et al., 1998), resulting in poor yield quality and high amount of unburnt carbon.

(d) Fluidized bed reactor method

With the use of modern fluidized bed reactor process, pozzolanic rice husk ash was produced with less ash content with lesser residence time in the combustion chamber. Merits of using fluidized bed reactor are distribution of uniform temperature, rapid
reaction time, high efficiency of carbon conversion, lesser operating temperature range, high combustion intensity, high reaction rates of gas-solid mixtures and exceptional mixing characteristic etc. (Pitt, 1976; Soltani et al., 2015). Luan and co-workers obtained silica from rice husk in presence of pilot flame in a modified fluidized bed reactor (Luan et al., 1990). Results showed silica containing product with high activity. Amorphous silica from rice husk was successfully obtained by using bubbling fluidized bed pilot plant using various temperatures with various velocities (Gomes et al., 2016).

Fig. 1.2.4 Schematic diagram of the fluidized bed combustor system

(Rozainee et al., 2008)
(e) Rotary Kiln method

Rotary kiln method is a modified method of electric or muffle furnace for calcination in a continuous process. In one of the processes (Sugita. 1994) active rice husk ash was obtained. In rotary kiln rice husk is heated by electrical heater, burner or other heat sources to 300-400 °C for carbonization. Carbonized rice husk is fed in rotary kiln and burn at 600 °C. The husk ash was successfully produced through this method. The disadvantage of using this method was need to auxiliary fuel to prevent crystallization of ash, reaction time was very longer and high energy required etc.

(f) Fixed bed furnace method

Yang et al. produced burst nano sized amorphous silica by using fixed bed furnace. In this process raw and acid treated rice husk was carried out for pyrolysis at temperature 600-1200 °C in fixed bed furnace. Result showed that 1-10nm size amorphous silica was obtained. The amorphous silica converts in to crystalline at 1000°C. Hamad et al. successfully discovered silica from rice husk ash by using muffle furnace and fixed bed reactor at 500–1150 °C.
1.2.2 Chemical Methods

The chemical methods for extraction of silica from wheat straw and husk can be broadly classified into two types: alkaline and acid leaching method.

**Existing Chemical Methods for Preparation of Silica**

![Diagram of chemical methods for silica preparation](image)

Agricultural waste (Wheat straw and Rice husk) → Chemical Treatment →

- Alkaline Treatment
  - Heated at 1100 °C - 1200 °C → Crystalline Silica

- Acid leaching treatment
  - Heated at 500 °C - 900 °C → Amorphous Silica

Fig. 1.2.5 Existing chemical methods for preparation of silica from agricultural waste
(a) Alkaline treatment followed by acid neutralization treatment

In one of the process rice husk ash was mixed in 1N NaOH solution in 250 ml Erlenmeyer flask and boiled for 1hr with constant stirring. Sodium silicate solution is obtained. By treating sodium silicate solution with 1M hydrochloric acid (HCl) the pH was maintained at 7 and solution was stirred for 18hrs. Gel form was obtained after stopping the stirring (Kalapathy et al., 2000). Chandrashekhar et al., reported that among different acids studied for pretreatment of biomass, hydrochloric acid is superior.

Nano structured amorphous silica from rice husk ash was produced by alkaline extraction method using 2.0 M, 2.5 M and 3.0 M NaOH solutions. Study revealed that treatment with 2.5 M NaOH resulted 90.44% silica content in rice husk ash (Selvakumar et al., 2014). Humidity indicating silica gel from rice husk ash was obtained by based on alkaline extraction followed by acid precipitation (Nayak et al. 2009). A silicate material from rice husk ash was reported by microwave heating by using 2.0 M sodium hydroxide. Microwave power was kept at 800W for 10 minutes (Rungrodnimitchai et al., 2009). Silica nano particles were obtained from Vietnamese rice husk by using alkaline sol gel method by NaOH. Silica was precipitated by H₂SO₄ / water / butanol at pH-4. Silica nano particles with high specific surface area were obtained by using method (Le et al., 2013). Spherical nano sizes silica from rice husk was obtained by using HNO₃ (65%) and sodium hydroxide. In this treatment no calcination was required for the ash formation (Adam et al., 2011). Silica with low surface area (8.23 m²/g) microsphere can be successfully obtained from wheat husk ash with alkaline and acid precipitation process (Cui et al., 2011).
The reaction equation of RH ash mixed with NaOH solution was:

\[
\text{SiO}_2 + 2 \text{NaOH} \rightarrow \text{Na}_2\text{SiO}_3 + \text{H}_2\text{O}
\]

(White Ash) + (Sodium hydroxide) \rightarrow (Sodium silicate) + (Water)

Silica was precipitated by acid neutralization from sodium-silicate

\[
\text{Na}_2\text{SiO}_3 + \text{HCl} \rightarrow \text{SiO}_2 + \text{NaCl} + \text{H}_2\text{O}
\]

(Sodium silicate) + (Hydrochloric acid) \rightarrow (Silica) (Sodium chloride) + (Water)

(Nano silica) successfully produced by alkali extraction process and used it as a green corrosion inhibitor (Awizar et al., 2013). Alkaline extraction followed by acid neutralization method is very efficient and simple method to extract amorphous silica from agricultural waste. Silica from rice husk ash obtained with minimal mineral contaminants by using alkaline extraction followed by acid precipitation.

(b) Other chemical extraction methods of silica from agricultural waste

Many other chemical treatments to produced silica material from agriculture waste. Chen and coworkers was also used ionic liquid for silica production from agricultural waste (Chen et al. 2013). Organic acid leaching treatment has also been used for extraction of amorphous silica from bio waste (Hu et al., 2014). Amorphous silica and activated carbon has been produced by using three different processes toluene/ethanol, NaClO₂ and KOH (Hu et al. 2013). The calcination process was used to produce nano sphere amorphous silica (100-120nm).
Some of methods for extraction of silica/silicate from agricultural waste are listed in Table 1.2.1.

<table>
<thead>
<tr>
<th>Study</th>
<th>objective</th>
<th>Summary of method used</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Chen et al., 2010      | To produce nano silica from wheat straw. | - Combustion of wheat straw at 500 °C in muffle furnace for 8 hrs.  
- Acid leaching  
- heating at 400 °C, 500 °C, 600 °C and 700 °C. | porous and nano amorphous silica (40nm) was obtained. |
| Tutsek et al., 1997    | Method of producing low-carbon, white husk ash | - Incineration at 500, 600, 700, 800, 900 °C and 1000 °C for 2 h under atmospheric conditions | Amorphous silica obtained at below 700 °C.       |
| Turkay et al., 2007    | Adsorbent from rice hull ash            | - Washing of rice husk with water Chemical treatments (acid leaching, alkaline leaching)  
- Incineration at 600°C under different conditions (static oven, argon flow,  
- Synthetic magnesium silicate (MgO.nSiO_2.xH_2O) is produced by mixing solutions of sodium silicate and magnesium salts | Amorphous Silica with 77% purity.  
surface area of silica was 5.9 m^2/g. |
<p>| Mukunda et al., 2004   | To evaluate the leaching of RHA         | - Extraction of silica with NaOH 1M                                                   | The best Si:Na mass ratio was 4:1, and            |</p>
<table>
<thead>
<tr>
<th>Introduction and Literature Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>with NaOH to easily obtain highly reactive colloidal silica</td>
</tr>
<tr>
<td>Yalçın and Sevin., 2001</td>
</tr>
<tr>
<td>Riveros, 1986</td>
</tr>
</tbody>
</table>
A comparison of various methods of silica extraction of silica from agricultural waste has been summarized in Table 1.2.2.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Technology/ Methodology</th>
<th>Descriptions</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Electric/ muffle Furnace</td>
<td>Amorphous Silica with specific surface area could be produced from rice husk after thermal treatment at 700 °C for 6 hours in air in an electric/ muffle furnace.</td>
<td>Simple operation</td>
<td>Poor yield, lower efficiency</td>
<td>Della et al., 2002</td>
</tr>
<tr>
<td>2.</td>
<td>Inclined step-grate furnace</td>
<td>At the top of the grate furnace rice husk was fed while the air flowed from the bottom.</td>
<td>Simple, low cost maintenance</td>
<td>High required labor</td>
<td>Bautista et al., 1996</td>
</tr>
<tr>
<td>3.</td>
<td>Cyclone furnace</td>
<td>Amorphous silica with a 12 – 14 wt% residual carbon produced from rice husk was burnt at a temperature of less than 700 °C by using cyclone furnace.</td>
<td>Automatic and continuous operating</td>
<td>High investment cost</td>
<td>Beagle., 1974</td>
</tr>
<tr>
<td>4.</td>
<td>Rotary Kiln</td>
<td>For the silica production, rice husk was carbonized in a first rotary kiln and heated at 300 – 400 °C, after charged into</td>
<td>Semi-automatic operating</td>
<td>Not developed for the higher capacity yet</td>
<td>Pitt., 1994</td>
</tr>
<tr>
<td>No.</td>
<td>Method</td>
<td>Description</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Reference</td>
</tr>
<tr>
<td>-----</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>5.</td>
<td>Alkaline extraction</td>
<td>NaOH solution was added in rice husk ash and this mixture was refluxed in a covered Erlenmeyer flask for 1 hour with constant stirring. The solution was filtered through ashless filter paper and the residue (carbon) was removed. The filtrate formed was sodium silicate solution, which was cooled to room temperature; Silica in gel form was produced after titration with acid (HCl or H₂SO₄) with constant stirring until pH 7. The solution was aged for 18 hours at room temperature to form gel (silica).</td>
<td>Efficient and simple method, good yield</td>
<td>Expensive, longer reaction time requires various steps with the use of various types of chemicals.</td>
<td>Kalapathy et al., 2002</td>
</tr>
</tbody>
</table>
1.3. APPLICATIONS OF SILICA

Silica is a very important industrial material and has found widespread applications (Glasser, 1986; Uhrlandt, 2006). In particular, silica nanoparticles with high surface area (porous silica) are of great interest for many key chemical applications, such as insulating, sorption, sensing, separation, refining and catalysis.

Recently porous silica for biomedical applications such as controlled release and biosensing has also been explored (Trewyn et al., 2007; Slowing et al., 2007). Silica in elemental form is used as a component for building material. In vitreous (glass like) form, silica is used in glass wires and optical element production. Other applications include production of various silicate base materials like silicon carbide, soluble silicates, zeolite, silicon alloy etc.

![Applications of Nano-silica](image)

Fig. 1.3.1 Applications of Nano-silica

It is also used in ceramic, glass, rubber and refractory industries. It can be also to be found used as green corrosion inhibitor to prevent metal corrosion. Silicate pigments of multiple colors, which can be applied for ceramic materials and glaze, were reported by doping silicates from rice husk silica with different elements (Yao et al., 2016). It can be used in cosmetic products as thickening agent and absorbent. In
toothpaste amorphous silica is used as an abrasive agent. In the production of inks silica is used as matting and thickening agent. Silica is used as acid catalyst in organic reactions reaction medium which are easily separable from the products after the reaction (R.Varma., 1999; Jin et al., 2002; Jin et al., 2003; Ishida et al., 2006; Nanaga et al., 2005). Mesoporous silica nanoparticles also find application as a drug carrier (Asad Mehmood et al., 2017). ‘Mohammad Bolhassani and Mohammadreza Samani.’, 2014, reported effect of type, size, and dosage of nanosilica and microsilica on properties of cement paste and mortar. Study revealed adding nano silica particles to the portland cement paste led to an increase incompressive strength.

‘Lin et al.,2009’, studied measure of hemolysis to evaluate the toxicity of nonporous and porous silica nanoparticles with varied sizes and investigates the effects of porous structure and integrity on the nanoparticle-cell interaction. The results show that both nonporous and porous silica cause red blood cell membrane damage in a concentration and size dependent manner.

‘Wang et al., 2014’, studied effects of surface modification and size on oral drug delivery of mesoporous silica formulation. They prepared different sized mesoporous silica nanoparticles (100-500 nm) and conjugated them with polyethylenimine-coated carbondots (PCD) for effective transepithelial absorption. Results demonstrated that Silica with a diameter 250 nm had the highest transepithelial transport and oral bioavailability compared to other formulations.

1.3.1 Silica as acid catalyst

The catalytic property of silica stems from the presence of silanol groups (due to hydration) and due to its mesoporous nature. Mesoporous silica is believed to be
neutral or slightly acidic (Tetsuo et al., 2017). Silicon oxide and the silanol group provide both Lewis and Brønsted acid sites.

![Lewis acid site](image1) ![Brønsted site](image2)

Fig.1.3.2 (a) Brønsted acidity arising from inductive effect of Lewis acid center coordinated to a silica support (Wilson and Clark., 2000) (b) Surface structure of hydrated amorphous silica (Hensen et al., 2012)

Briefly, the solid acid catalysts can protonate hydrocarbon molecules to form carbocations and drive important reactions, such as cracking, hydrocracking, isomerization, alkylation and aromatization (Olah, G. A., 1973) through surface complexes or transition states (Weitkamp et al., 2007).

The catalytic activity of silica can be modified /enhanced by functionalizing it with sulfuric acid (Kurosh Rad-Moghadam et al., 2009), organic molecules/acids also by with oxides such as alumina, zirconia. (Sinhaalmahapatra et al., 2011)

Presence of silanol groups in the surface allows modification in the chemical nature of silica after synthesis by grafting different functionalities through covalent linkages. For example, silanol they can react with alkylchloro-silanes in order to obtain hydrophobic surface (Olah et al., 1995). ‘Corma et al.,1994’ synthesized MCM-41 with both tetrahedrally coordinated silicon and aluminum atoms incorporated into the framework resulted bridging Si-OH-Al hydroxyl groups from Brønsted acid sites, which was similar to amorphous alumino-silicates. MCM-41 has
been used in Liquid-phase Friedel–Crafts alkylation and acylation reactions (Armengol et al., 1995; Armengol et al., 1997; Gunnewegh et al., 1996). ‘Armengol et al., 1995’ reported the advantages of increased pore size of MCM-41 in the alkylation of 2,4-di-tert-butylphenol using cinnamyl alcohol. ‘Corma .,1995 and Busca., 2007’ reported that amorphous silica-alumina (ASA) is of considerable practical importance in industrial catalysis. It is widely used as a solid acid or serves as a carrier material for finely dispersed metal sulfides or metals in a wide range of processes. ‘Hensen et al., 2012’ reported heterogeneous nature of the surface of amorphous silica-alumina. It contains Brønsted and Lewis acid sites of varying acidity. The number of strong Brønsted acid sites of zeolitic strength was very low (<10μmol/g).

Magnesium silicate synthesized from RH silica was used to catalyze a ring-opening reaction to synthesize propranolol glycol from glycidol and 1-naphthol and achieved a conversion rate of 85% (Lu et al., 2009). Sodium silicate was also prepared from RH silica, which served as a solid catalyst for transesterification reaction of oil to biodiesel, and exhibited high performance (Mashhadi et al., 2016). A number of papers have been published in the last 20 years to using silica in organic reactions, and the number is increasing. Silica supported NaHSO₄ was used as an efficient catalyst in the Pechmann condensation of aromatic phenols using ethyl acetoacetate. It is of great significance formation of coumarin and its derivatives. In one case reaction proceeded in acetonitrile at reflux temperature giving good to excellent yields. (Chavana et al., 2008).

Silica supported Baeyer-Villiger oxidation with potassium peroxomonosulfate was reported by González-Núñez et al. Potassium peroxomonosulfate (KHSO₅)
deposited over silica and could convert ketones at room temperature to esters and lactones with good yield.

Nano-TiCl₄⋅SiO₂ is an efficient and reusable catalyst for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles using benzil, aromatic aldehyde and an amine in presence of ammonium acetate. This one-pot procedure is very simple and resulted good yields (Mirjalili et al., 2012).

Concentrated nitric acid supported on nano silica (HNO₃ - nano SiO₂) has been utilized as an effective catalytic system for the synthesis of various 2,4,5-trisubstituted imidazoles under solvent-free conditions at 100 °C in good to excellent yields (Nikoofar et al., 2017).

Safari and Co-workers reported, one-pot cyclo-condensation of benzil, aldehydes, ammonium acetate and primary amines were used to synthesize 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted-1H-imidazole derivatives under microwave irradiation with silica-supported SbCl₃ (SbCl₃/SiO₂) as a heterogeneous catalyst.

It could be concluded that silica can be used as solid acid. It surface property can be modified by functionalizing it with different groups or, molecules. The catalytic property also depends on the porosity, amorphosity and particle size.
1.4 BIOACTIVE 1,4 DIHYDROPYRANO[2,3-c] PYRAZOLE-5-CARBONITRILE DERIVATIVES

Multicomponent reactions (MCRs) have been known for over 150 years. It is a widely favored methods for synthesis of heterocyclic components in the pharmaceuticals industry (Gein et al., 2017). Moreover, MCRs offer advantages in terms of synthesis of organic compounds from simple and readily available raw materials, cost effectiveness, shorter reaction time, energy efficiency, environmental friendliness, etc. (Maleki et al., 2012) (Guo et al., 2013).

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Bio-active Dihydropyrano Derivatives</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Antibacterial</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Antibacterial</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Antibacterial and Anticancer X = O, S.NH</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Anticancer</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Anticancer</td>
</tr>
</tbody>
</table>
Compounds with dihydropyrano[2,3-c]pyrazole scaffolds are important class of heterocyclic compounds and they are predominant in nature and presenting a wide range of biological and pharmaceutical activities such as anticancer (Wang et al., 2000) (Wu et al., 2003), antimalarial (De Andrade-Neto et al., 2004), antiviral (Martínez-Grau et al., 1997), antihuman- immunodeficiency virus (HIV) (Rueping et al., 2008), antimicrobial (Morgan et al., 2002), (El-Tamany et al.,1999), antiinflammatory (Moon et al., 2007), (Zaki et al., 2006), analgesic (Kuo et al.,1984), antiproliferative (Venkatesham et al., 2012), and molluscicidal activities (Abdelrazek et al., 2007). In inclusion, the biological activities of fused azoles have led to exhaustive research on their synthesis (Shi et al., 2004).

1.4.1 Different Synthetic Study for the Synthesis of 1,4-Dihydropyrano[2,3-c]-Pyrazole-5-Carbonitriles

A number of methods for synthesis of dihydropyrano [2,3-c]pyrazole derivatives. Various methods have been reported using using different catalysts such as piperidine (Katariya et al.,2014), Ba(OH)₂ (Azzam et al., 2012), CH₃COOH (Pagore et al., 2015), meglumine (Guo et al., 2013), citric acid (Kangani et al., 2015), iodine (Parshad et al., 2014), nano-Fe₃O₄ (ElAleem et al., 2014), nano-CuI (Ziarati et al., 2013), DABCO (Keyume et al., 2014), per-6-amino-β-cyclodextrin (per-6-ABCD) (Kanagaraj Kuppusamy and Kasi Pitchumani, 2010), CsF (Bhosale et al., 2015), borax (Adibi et al., 2013), β-cyclodextrin (Tayade et al., 2015), CeCl₃ (Ablajan et al., 2014), pyrrolidine (Liju, et al., 2014), urea (Brahmachari et al., 2014), ethylenediammonium diformate (EDDF) (Thakur et al., 2013), Amberlyst A21 (Bihani et al., 2013), NaOH (Ilovaisky et al., 2014), CsF (Bhosale et al., 2014), SnO₂ quantum dots (Paul et al., 2014), cetyltrimethylammoniumchloride (CTACl)
(Wu, et al., 2013), maltose (Kangani, et al., 2015), tungstate sulfuric acid (TSA) 
(Farahi et al., 2014) saccharose (Kangani, et al., 2015), nano-ZnO (Tekale et al, 
2014), DBU (Bhavanarushi et al., 2013), Sodium Benzoate (Kiyani et al., 2013), 
cerium ammonium nitrate (CAN) (Ablajan et al., 2013) but not much work is 
available using silica.

Atar et al., have utilized silica supported tetramethylguanidine (SiO₂ TMG) as a 
recyclable catalyst for the synthesis of pyrano[2,3-c]pyrazole-5-carbonitrile 
derivatives through multicomponent reaction of ethyl acetoacetate, hydrazine 
hydrate, various aldehydes and malononitrile under solvent free conditions (Scheme 
1.4.1).

Scheme 1.4.1 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using Silica Supported 
Tetramethylguanidine (SiO₂ TMG)

Tekale and co-workers have used ZnO catalyst for the one-pot, four-component 
synthesis of ethyl acetoacetate, hydrazine hydrate, various aldehydes and 
malononitrile in aqueous media at reflux condition to afford products in excellent 
yields (Scheme 1.4.2). Various solvents such as dichloromethane, acetonitrile, 
tetrahydrofuran, ethanol and methanol were examined for this reaction. However, 
good results were obtained in water in terms of product yield and reaction time.

\[ R = \text{Aromatic/Heteroaromatic/Aliphatic} \]
Gujar et al., reported preparation of pyrano[2,3-c]pyrazole derivatives via one-pot, four-component synthesis of ethyl acetoacetate, hydrazine hydrate, various aldehydes and malononitrile catalyzed by molecular sieves (MS) with using ethanol as solvent under reflux condition (Scheme 1.4.3).

Gujar et al., reported preparation of pyrano[2,3-c]pyrazole derivatives via one-pot, four-component synthesis of ethyl acetoacetate, hydrazine hydrate, various aldehydes and malononitrile catalyzed by molecular sieves (MS) with using ethanol as solvent under reflux condition (Scheme 1.4.3).

Various inorganic catalysts such as Amberlite, acidic alumina, natural alumina, basic alumina, silica gel, MS 3A° and MS 5A° were investigated. 90% yield was obtained using catalyst MS 4A with ethanol solvent.

Various inorganic catalysts such as Amberlite, acidic alumina, natural alumina, basic alumina, silica gel, MS 3A° and MS 5A° were investigated. 90% yield was obtained using catalyst MS 4A with ethanol solvent.
Guo and co-workers, have utilized meglumine as a biodegradable and highly efficient and reusable catalyst for one-pot, four-component synthesis of ethyl acetoacetate, hydrazine hydrate, various aldehydes and malononitrile in aqueous ethanol at room temperature (Scheme 1.4.4). An efficient protocol for the synthesis of pyrano[2,3-c]pyrazole derivatives by a one-pot, four component reaction of ethyl acetoacetate, hydrazine hydrate, various aldehydes and malononitrile in the presence of a catalytic amount of DABCO under refluxing water, which was demonstrated by Waghmare and co-workers (Scheme 1.4.5).

Scheme 1.4.4 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using Meglumine

Scheme 1.4.5 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using DABCO
Azzam et al. have reported preparation of pyrano[2,3-c]pyrazole derivatives through the one-pot cyclocondensation reaction of ethyl acetoacetate, hydrazine hydrate, various aldehydes and meldrums acid utilizing Ba(OH)$_2$ (Scheme 1.4.6) as an efficient catalyst in water in refluxing conditions. The yields are high and the reactions go to completion in 1–2 h.

![Scheme 1.4.6 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using Ba(OH)$_2$](image)

Ar = 3,4,5-(MeO)$_3$H; 4-MeO; 3-MeO; 2-Cl; 2-OH; -FC$_6$; 3-NO$_2$; CH$_2$CH$_3$; CH$_2$CH$_2$CH$_3$

Scheme 1.4.7 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using Homogeneous Catalyst Saccharose

Pyrano[2,3-c]pyrazole derivatives catalyzed by saccharose via one-pot reaction of ethyl acetoacetate, hydrazine hydrate, various aldehydes and malononitrile under thermal solvent-free condition discovered by Kangani et al. (Scheme 1.4.7).
Chaudhari et al., have discovered green methodology for the preparation of pyrano[2,3-c]pyrazole derivatives via a one-pot reaction of various aldehydes ethyl acetoacetate, hydrazine hydrate, and malononitrile utilizing polystyrene supported $p$-toluenesulfonic acid as a reusable catalyst in refluxing water (Scheme 1.4.8). Solvents such as methanol, ethanol, acetone, dichloromethane, tetrahydrofuran, acetonitrile and water, were examined to promote this reaction. The good result was found in water in terms of product yield and reaction time.

![Reaction Scheme](image)

R = H, 4-Cl; 2-Cl; 3-Cl; 4-OCH$_3$; 4-Br; 2-OH; 3-OH; 4-OH; 2-NO$_2$; 3-NO$_2$; 4-NO$_2$ etc.

Scheme 1.4.8 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using PS-PTSA

Shaterian et al. have discussed an efficient and solvent-free protocol for the preparation of pyrano[2,3-c]pyrazole-5-carbonitrile derivatives via one-pot reaction various aldehydes, hydrazine hydrate, ethyl acetoacetate, and malononitrile catalyzed by titanium dioxide nano-sized particles (Scheme 1.4.9).
Scheme 1.4.9 Synthesis of Pyrano[2,3-c]pyrazole Derivatives using TiO$_2$ nano particles

R = H, 4-Cl; 2-Cl; 3-Cl; 4-OCH$_3$; 4-Br; 2-OH; 3-OH; 4-OH; 2-NO$_2$; 3-NO$_2$; 4-NO$_2$; 4F; 2,5-diOCH$_3$; 3,4-diOCH$_3$; 3,4,5-tri OCH$_3$ etc.
1.5 BIOACTIVE COMPOUND COUMARIN AND ITS DERIVATIVES

Coumarins are an important group of naturally occurring compounds widely spread in the plant kingdom. However, they have been produced synthetically for many years for commercial use. Coumarin and its derivatives have been studied for physiological activity. This interest arises from the fact that a variety of natural and synthetic compounds which contain the coumarin substructure exhibit significant biological activities such as antibacterial (Wang et al., 2002) (Fan et al., 2001 inhibitory of HIV-1 protease (Mitra et al., 1998), anticancer (Patil et al., 1993) (Weber et al., 1998), antitumor (Kuznetsova et al., 1992), antioxidative (Musgrove et al., 1986), inhibitory of steroid 5α-reductase (Yun et al., 2001), and inhibitory of platelet aggregation (Murray et al., 1982).

The coumarin derivatives find their applications also in fragrance, agrochemicals, optical brightening agent, dispersed fluorescent and anticoagulants (Gunnewegh et al 1995). Among the various coumarin derivatives, 7-hydroxy-4-methylcoumarin is the most widely used one in fine chemical industries. It is used as fluorescent brightener and as a standard for fluorometric determination of enzymatic activity. It acts as a starting material in the preparation of insecticide hymecromone. Pechmann reaction is one the most widely applied method for the preparation of substituted coumarins as it proceeds from very simple starting materials and also offers good yield.

1.5.1 Different Synthetic Routes for the Synthesis of Coumarin and Derivatives

Several heterogeneous and homogenous catalysts have been employed for coumarin synthesis including Nafion-H (Horning et al., 1955), montmorillonite clay (Chaudhari et al., 1983), TiCl₄ (Valizadeh et al., 2005), Amberlyst ion-exchange resins (Sabou et al., 2005), furic acid (Pechmann et al., 1884), ZrCl₄ (Sharma et al.,
Introduction and Literature Review

2005), phosphorus pentoxide (Robertson et al., 1931), CuFe$_2$O$_4$ nanoparticles (Seyed Meysam Baghbanian and Maryam Farhang, 2014) zeolite H-BEA (Gunnewegh et al., 1996), Nafion/silica composites (Hoelderich et al., 2003), Aluminium chloride (Sethna et al., 1938), polyaniline sulfate salt (Palaniappan et al., 2004), sulfonic acid functionalized SBA-15 silica (Karimi et al., 2008), heteropoly acids (Romanelli et al., 2004), nano-crystalline sulfated-zirconia (Tyagi et al., 2007), zeolites (Hoefnagel et al., 1995), Yb(OTf)$_3$ (Wang et al., 2003), BiCl$_3$ (Sachin et al., 2006), chloroaluminate ionic liquids (Amit et al., 2002), Sm(NO$_3$)$_3$ (Sushilkumar et al., 2004), p-TsOH (Sugino et al., 2001), Cellulose sulfuric acid (Kuarm et al., 2010), and CuPy$_2$Cl$_2$ (Rajitha et al., 2006).

Rajitha et al., have discussed an efficient and solvent-free protocol for the preparation of coumarin derivatives using both conventional heating and microwave irradiation in excellent yields with good purity. Reaction was carried out using phenols with ethyl acetoacetate and Dipyridine copper chloride is used as an efficient catalyst Scheme 1.5.1.

![Scheme 1.5.1 Synthesis of Coumarin Derivatives using Dipyridine Copper Chloride Catalyst](image)

R= H; OH; CH$_3$OH; Ph-OH etc
Rani et al., has been discovered synthesis of 7-hydroxy-4-methylcoumarin via pechman condensation using resorcinol and ethyl acetoacetate catalyzed by in the presence of sulphuric acid Scheme 1.5.2.

Scheme 1.5.2 Synthesis of Coumarin Derivatives using Concentrated Sulphuric Acid

Synthesis of 7-Alkoxy-4-trifluoromethylcoumarins via the Pechmann Condensation using Resorcinol, ethyl 4,4,4-trifluoroacetoacetate, ethyl acetate catalyzed by Iodine in presence of toluene has been disclosed by ‘Jami DeGrote’ (Scheme 1.5.3).

Scheme 1.5.3 Reaction Scheme for Pechmann Condensation Reaction of 7-Alkoxy-4-Trifluoromethylcoumarins Catalyzed by Iodine.

Jitender Kumar and co-workers has been discovered solvent free synthesis of coumarin has been developed via sold phase. Reaction was carried out using phenols were ground with ethylacetoacetate in presence of P₂O₅ at room temperature. Product coumarin in good yield was obtained in a minutes of time (Scheme 1.5.4.).
Scheme 1.5.4 Synthesis of Coumarin and Derivatives using P$_2$O$_5$ with Grinding.

Sharma et al., have discussed an efficient and solvent-free protocol for the preparation of coumarin derivatives with grinding of the different phenols and β-ketoesters in the presence of silica supported sulfuric acid at room temperature by using silica supported sulfuric acid as catalyst with good yield (Scheme 1.5.5).

Scheme 1.5.5 Synthesis of 2H-Chromen-2-ones using Silica Supported Sulphuric Acid

Gopalakrishnan and co-workers synthesized 7-hydroxy-4-methyl coumarin catalyzed by Lewis acid metal ion-exchanged ZAPO-5 molecular sieves under solvent free condition using resorcinol and ethyl acetoacetate in the liquid phase with good yield (Scheme 1.5.6).

Scheme 1.5.6 Synthesis of 7-Hydroxy-4-Methylcoumarin using ZAPO-5
1.5.2 Significance of the Present Work

From the literature review on the methods of extraction of silica it was found that no single method was complete in itself. Amorphous silica can be produced from agricultural husk or straw by various thermal treatment methods and alkaline extraction. Major concern of silica associated with the use of thermal methods is the risk of crystallization in the agricultural ash, due to high temperature, long reaction time and low carbon conversion efficiency. Alkaline extraction method was capable of producing high purity silica but involves a significant amount of time (1-2 days) and required high number of steps such as use of various chemicals, resulting in increased production cost. An alternative method for silica extraction, using microwave digestion followed by calcination was used in the present work.

Literature on application of silica as catalyst in organic synthesis, especially those for bioactive materials are scanty. Most of the catalysts used are either expensive, follow cumbersome method. Some of the existing methods destroy the catalysts in the workup procedure and they cannot be recovered or reused. These shortcomings surely demanded for a safe, ecofriendly, and efficient catalyst/method for synthesis of bioactive materials. An alternative method for synthesis of bioactive materials 6-Amino-1,4- Dihydropyran[2,3-c]-Pyrazole-5-Carbonitrile and derivatives and 7-hydroxy-4-methylcoumarin was attempted using green chemistry route.
REFERENCES


Khurana, J. M.; Chaudhary, A. (2012). Efficient and *greensynthesis* of 4H-pyrans and 4H-


Chapter 1: References


Zhao, X., Wang, M., Liu, H., Zhao, C., Ma, C. and Song, Z., (2013). Effect of temperature and additives on the yields of products and microwave pyrolysis