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REVIEW

Exploration of heterocyclic compounds from bio waste sugars: a Review

V.R.Remya[1], V.K.Abitha[2]*, Ajay Vasudeo Rane[3]

[1]Department of Chemistry, Devaswom Board Pampa College, Parumala, Pathanamthit, Mahatma Gandhi University, Kottayam, Kerala, (INDIA)

[2]Department of Polymer Science and Rubber Technology, Cochin University of Science and Technology, Kerala, (INDIA)

[3]Centre for Green Technology, Institute of Chemical Technology, Centre of Excellence and Elite Status-Government of Maharashtra, Mumbai, (INDIA)

E-mail: abithavk@gmail.com

Abstract : The quest for renewable and sustainable production of heterocyclic compounds to be used in various industries like petroleum-based liquid fuels, polymers, pharmaceuticals, etc. continues to be an area of intensive research around the globe. Because the fossil raw materials have their foreseeable limits as they are costly, depleting and are irreplaceable. Hence, considering the economic and environmental aspects along with green chemistry context, sugars from bio waste material are widely into research to be used as the renewable feedstock in the synthesis of various heterocyclic compounds. The bio waste rich in sugars obtained by hydrolysis of sugars obtained from lignocellulosic biomass can be dehydrated or made to undergo treatment to release important heterocyclic compounds like furans, pyrans and thiophenes which are O-, N- and S- containing unsaturated heterocycles respectively. This report describes the various ways in which these heterocyclic compounds are being synthesized from sugars obtained from biowaste with or without biowaste pre-treatment. Thus, this type of synthesis plays a part in applying green chemistry principle of using renewable feedstock.

Keywords : Heterocyclic; Bio waste sugars; Green Chemistry; Feed stock; Renewable

INTRODUCTION

1. Heterocyclic molecules

The Encyclopaedia Britannica, a classical reference book, describes a heterocyclic compound, also called a heterocycle, as:

"Any of a class of organic chemical compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon(C), most frequently oxygen(O), nitrogen(N), or sulphur(S)".

The heterocyclic molecules are structurally similar to cyclic organic hydrocarbons, but their properties can vary widely from those of their hydrocarbon counterparts and are largely governed by the identity, location and number of heteroatoms present in the molecule. It is this rich diversity of physical and biological properties that has led to intense study of heterocyclic compounds. The most common heterocycles are those having five- or six-membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). Figure 1.1 shows the examples of certain best known simple heterocyclic compounds.

The heterocyclic compounds are usually classified

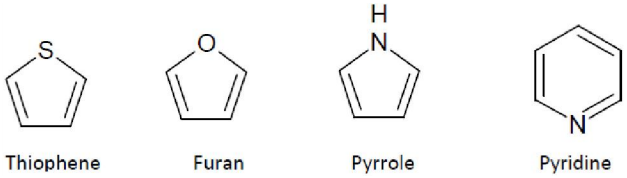

Figure 1.1 : Examples of Heterocyclic compounds

on the basis of their rings- three, four, five and six member ring structures. They can be saturated or unsaturated. The saturated heterocycles behave like the acyclic derivatives. Thus, piperidine and tetrahydrofuran are conventional amines and ethers, with modified steric profiles. Therefore, the study of heterocyclic chemistry focuses especially on unsaturated derivatives, and the preponderance of work and applications involves unstrained 5- and 6-membered rings.

Applications of heterocycles

Heterocyclic compounds include many of the biochemical material essential to life. For example, nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics (www.britannica.com). Few applications of heterocyclic compounds are listed in TABLE 1.1.

2. Feedstock for synthesis of Heterocyclic molecules

"A raw material as feedstock should be renewable rather than depleting wherever technically and economically practicable."

TABLE 1.1 : Applications of Heterocyclic compounds

Industries	Compound/Product	Application
Pharmaceutical	90% medicines-hetrocycles, e.g. Penicillin, quinoline	As antibiotics, analgesics, anti-tumor drugs
Textiles	Sulpholane	Solvent for textile finishing
Food and nutrition	Caffeine in coffee, vitamins C,B2,B6,	As flavouring agents and nutrients in food & drinks
Dyes and Paints	Pyridine dyes	For dyeing
Bio-engineering	Adenine, guanine, cytosine, thymine	As nitrogenous bases in DNA(genetic unit of life)

This quotation, being one of the 12 principles of green chemistry (Anastas, 1998), is probably one of the least realized in chemical industry, since production of organic chemicals from renewable feedstocks is, with very few exceptions, neither technically nor economically practicable at present. However, Lichtenthaler and Peters[1] reviewed that the end of cheap oil is realistically prognosticated for 2040 at the latest- and as the pressure on our environment is building up, the progressive changeover of chemical industry to renewable feedstocks emerges as an inevitable necessity. Thus, taking the prognostication for the end of cheap oil, the curve shown in Figure 1.2 for the utilization of renewable feedstocks for synthesis in chemical industry will have to rise such that it meets that of fossil raw materials somewhere around 2030–2040. Furthermore, as reviewed by Dumesic et al.[3], the combustion of fossil fuels or their derivatives for the production of heat and power is associated with a net increase in greenhouse gas levels worldwide.

A greener way of addressing this sensitive issue could be through the development of biowaste as an alternative and renewable energy resource. Biowaste is any waste material of organic origin that emanates from biological sources, hence, biodegradable in nature.

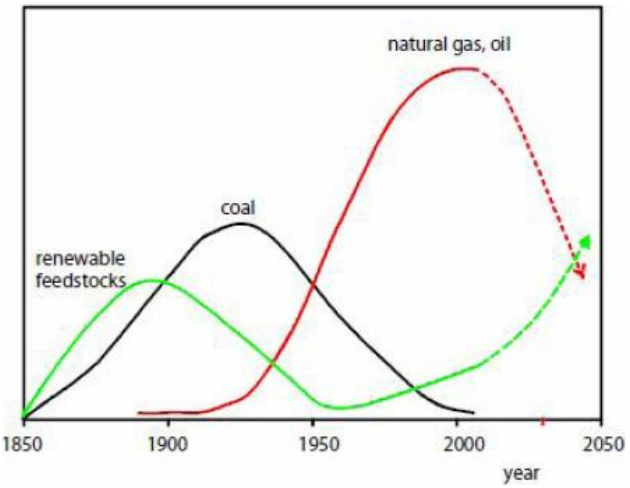

Figure 1.2 : Raw materials basis of chemical industry in historical perspective[1]

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It constitutes a multifaceted accumulation of low and high molecular weight products, exemplified by sugars, amino acids, lipids, and biopolymers such as cellulose, hemicelluloses, chitin, starch, lignin, and proteins. Of these, carbohydrates (sugars) represent roughly 75% of the annually renewable biomass of about 200 billion tons. Of these, only a minor fraction (ca. 4%) is used by man, the rest decays and recycles along natural pathways[1].

Our fossil resources are *hydrocarbons*, distinctly hydrophobic, oxygen-free, and lacking functional groups; annually renewables are *carbohydrates*, over-functionalized with hydroxyl groups and pronouncedly hydrophilic. Needless to say, the methods required for converting carbohydrates into viable industrial chemicals- reduction of oxygen content with introduction of C=C and C=O unsaturation- are diametrically opposed to those prevalent in the petrochemical industry. As higher oil prices, environmental issues, and regulations begin to adversely affect the manufacture of chemicals from fossil raw materials, it manifests the use of biowaste sugars as the bio feedstock for heterocyclic molecule synthesis[4]. Thus, the biowaste sugars in synthesis will not only work as a renewable feedstock but also address the other green aspects like reduced CO_2 emissions from fossil fuels, new energy platforms for local energy supply, etc.

OBJECTIVE AND SCOPE

The prime objective of this seminar is to discuss the different ways of synthesis of heterocyclic molecules using sugars obtained from biowaste. As biowaste is renewable and abundantly available, sugars obtained from them will serve as the promising feedstock for heterocycle synthesis as they will be environmentally benign. If the feedstock utilized in synthesis is green i.e. renewable, it would satisfy the green chemistry context hence further optimization in process conditions would make the process of synthesis move towards greener aspect.

Further, more green aspects that would be aimed at synthesis will be:

- Minimum number of steps
- Mild operating conditions
- One pot synthesis
- Increased yield
- Increased conversion
- Increased selectivity
- Less downstream processing

If few or all above aims are achieved in synthesis methods, then biowaste sugar based heterocyclics will have good scope to bring about transformations in chemical industries as the heterocycles are the platform chemicals for many other products or liquid fuels. Effective utilization of Carbohydrates (biowaste sugars) will help address the sustainability issue and commercial scale application opportunity.

Due to the plethora of potential industrial products derivable from carbohydrate feedstocks, this report mainly overviews practical procedures available to convert the sugars derived from biowaste into unsaturated *O*-, *S*- and *N*-heterocycles of established or presumed industrial relevance, with emphasis on those transformations that can be performed in either one-pot, in an environmentally benign way or minimum number of steps.

LITERATURE SURVEY

1 Biowaste sources

Life is associated with waste production and the exploitation of these materials as a renewable resource for bioproduct or any other chemical product development could be a major challenge for researchers in the respective fields. TABLE 3.1 lists the different sources of biowaste with examples which can be utilized as raw materials.

Based on their contents, we can consider three general classes of feedstocks derived from biomass that are appropriate for the production of heterocyclic molecules which in turn produce renewable fuels:

a] Starchy feedstocks (including sugars)- comprised of glucose polysaccharides joined by aglycosidic linkages, such as amylase and amylopectin, which are easily hydrolyzed into the constituent sugar monomers

b] Triglyceride feedstocks- comprised of fatty acids and glycerol derived from both plant and animal sources. Sources of triglycerides for the production of biofuel include various vegetable oils, waste oil products (*e.g.*, yellowgrease, trap grease), and algal sources

c] Lignocellulosic feedstocks- contribute structural

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TABLE 3.1 : Sources of biowaste with examples (Source: www.naturesfurnace.com)

Source of biowaste	Example
Agricultural	Corn husks, corn stalks, cereal straws, crop residues,nut hulls, seed stalk waste, bean stubble, tobacco, yard waste, weeds, tomato, and harvest wastes.
Animals and Poultry wastes	Beddings and droppings
Forest crops and wood residues	Ground, chipped or shredded tree limbs, pallets, paper, cardboard, construction waste, sawdust, and such
Municipal solid waste	Everyday items like packaging, clothing, furniture
Industrial waste	Hotel industries and food industries

integrity to plants and are thus always present. Figure 3.1 compares the chemical structure of starches and triglycerides to that of cellulose-the predominant component of lignocellulosic feedstock. Figure 3.2 shows the different fuel products obtained from these feedstocks[3].

In general, most energy crops and waste biomass considered for energy production are lignocellulosic feedstock (also called biopolymers). Literature of Dumesic at al.[3] gives the composition of three different fractions of Lignocellulose as: lignin (15-20%), hemicelluloses (25-35%), and cellulose (40-50%) and these structures are given in Figure 3.3. Structural polymers that could be used as starting materials for the synthesis are given in TABLE 3.2.

Lignocellulosic biomass

Hemicellulose and Lignin

Hemicelluloses are branched polymers of xylose, arabinose, galactose, mannose and glucose. These biopolymers bind bundles of cellulose fibrils to form microfibrils, which enhance the stability of the cell wall. They also cross-link with lignin, creating a complex web of bonds that provide structural strength. Lignin is a complex polymer of phenylpropane units, which are cross-linked to each other with a variety of different chemical bonds.

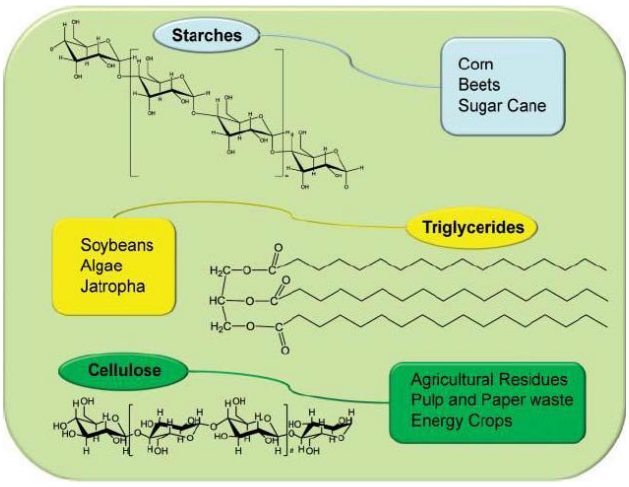

Figure 3.1 : The chemical structure of biomass[3]

Cellulose

Cellulose is a long chain of glucose molecules, linked to one another primarily by β(1→4)glycosidic bonds; the simplicity of the cellulose structure means that it can be degraded.

2 Coversion of Biowaste to sugars

While attractive as an inexpensive and abundant feedstock, lignocellulosic biomass must be broken into

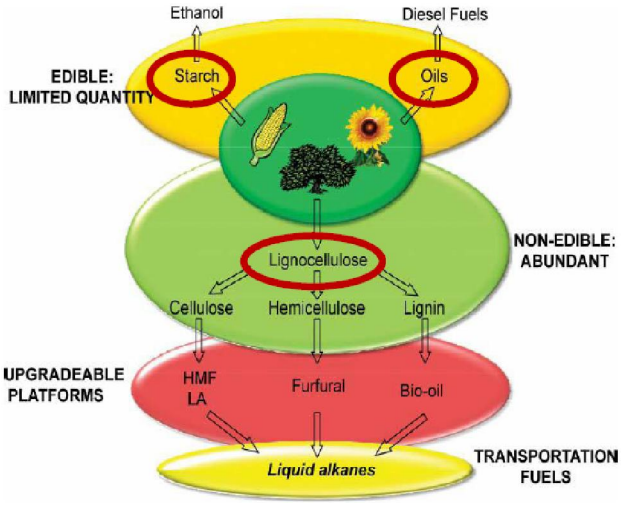

Figure 3.2 : Biomass derived feedstock and platforms for conversion[3]

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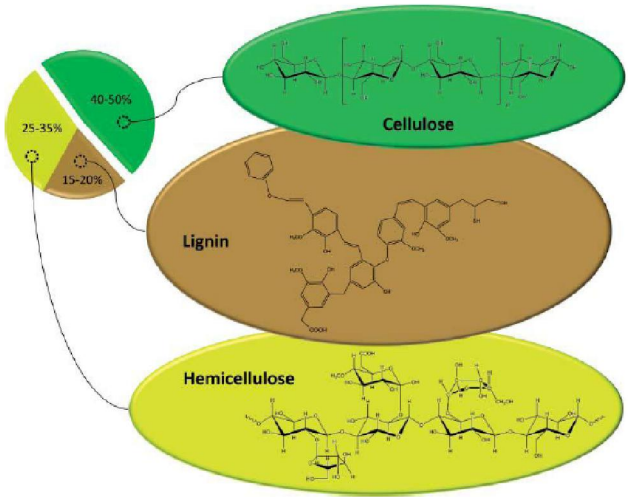

Figure 3.3 : Lignocellulose composition: cellulose, hemicellulose and lignin[3]

its constituent parts i.e. sugars to be efficiently processed as starting material for biosynthesis of many bioproducts. The isolation of biomass fractions typically proceeds through pre-treatment followed by hydrolysis. The pre-treatment stage is comprised of both physical (*e.g.*, milling, comminuting, steam) and chemical (*e.g.*, acid or base hydrolysis) methods, and is intended as a means of increasing the susceptibility of crystalline cellulose to degradation in subsequent hydrolysis steps to give sugars i.e. glucose, given in Figure 3.4. Pre-treatment achieves this objective by penetration/depolymerization of the lignin seal and extraction/preservation of the pentose (hemicellulose derived) fraction of biomass[3]

Hydrolysis of lignocellulosic biomass is most commonly either acid or enzyme catalyzed:

TABLE 3.2 : The relative content (%) of Lignocellulose in biowaste[5]

	Lignocellulosic biomass (%)		
	Cellulose	**Hemicellulose**	**Lignin**
Agricultural residues	38	32	17
Sorted municipal solid waste	45	9	10
Underutilized hardwood	50	23	22
Herbaceous energy crops	45	30	15

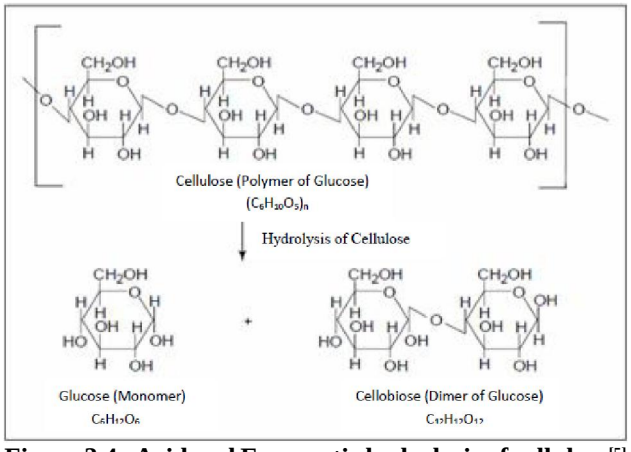

Figure 3.4 : Acid and Enzymatic hydrolysis of cellulose[5]

a) Acid catalyzed (Chemical method)

Dilute acid treatment is one of the most effective pre-treatment methods for lignocellulosic biomass. In general there are two types of weak acid hydrolysis:

1. High temperature and continuous flow process for low-solids loading (T> 160 °C).
2. Low temperature and batch process for high-solids loading (T≤160 °C).

Dilute (mostly sulphuric) acid is sprayed onto the raw material and the mixture is held at 160-220°C for short periods up to a few minutes. Hydrolysis of hemicellulose then occurs, releasing monomeric sugars and soluble oligomers from the cell wall matrix into the hydrolysate. Hemicellulose removal increases porosity and improves enzymatic digestibility, with maximum enzymatic digestibility usually coinciding with complete hemicellulose removal. As an alternative to inorganic acids, organic acids (e.g. maleic acid, fumaric acid) can be used for dilute acid pre-treatment[6].

b) Enzyme catalyzed (Biological method)

Enzymatic hydrolysis of waste cellulose can be performed using cellulase, a multi-component enzyme system produced by bacteria and fungi, which is highly specific with no by-product formation. Most common bacterial and fungal species for cellulose isolation are: *Clostridium thermocellum* and *Trichoderma viride* respectively. High glucose yields (>90% of theoretical

maximum) are achieved *via* enzymatic hydrolysis of cellulose following biomass pre-treatment as reported in the literature of Dumesic et al.[3].

3 Synthesis of Heterocycles from biowaste sugars

As saturated heterocycles behave almost similar to acyclic derivatives, synthesis study is mainly focussed on unsaturated heterocycles like furan, pyran, Thiophene and like. The following section discusses the synthesis of most important O-, N- and S- containing heterocycles.

(a) *O*-Heterocycles

Oxygen heterocycles are important classes of building blocks in organic synthesis, and several derivatives of these oxygen heterocycles have attracted much attention over the years. Furan is an oxygen-containing heterocycle employed primarily for conversion to other substances (including pyrrole). Furfural and 5-Hydroxymethylfurfural (5-HMF) are the valuable furans for which synthesis methods are discussed here.

Production of 5-hydroxymethylfurfural (HMF) and furfural from lignocellulosic biomass (Figure 3.5) was studied in ionic liquid in the presence of $CrCl_3$ under microwave irradiation (MI). Corn stalk, rice straw and pine wood treated under typical reaction conditions produced HMF and furfural in yields of 45–52% and 23–31%, respectively, within 3 min. This method should be valuable to facilitate energy-efficient and cost-effective conversion of biomass into biofuels and platform chemicals[7].

An isolated yield of products obtained after irradiation of reaction at 400 W is shown in TABLE 3.3.

Synthesis of furfural

Furfural is 5- carbon contaoining O-heterocycle. The technical process involves exposure of agricultural or forestry wastes like oat hulls and corncobs (rich in hemicelluloses) to aqueous acid and fairly high temperatures, the pentosans first being hydrolyzed to pentoses and then undergoing cyclodehydration (Lichtenthaler, 2002). Hydrolysis of hemicelluloses will give pentose sugars. Scheme 1 shows the schematic of furfural synthesis.

The patented work of Lightner[8] describes the synthesis of furfural and hydroxymethyl furfural from biomass. It involves acidic hydrolysis of biomass to give glucose and xyloses which on dehydration within hydrolysis environment give furfural and hydroxymethylfurfural. Hydrolysate containing acid and heterocyclic compounds is formed in hydrolysis vessel. Heterocylic compounds are separated from hydrolysate by separation and withdrawn hydrolysate free from heterocyclic compounds is recycled back to vessel. Also, solids, containing lignins from the agricultural biowaste are filtered from the vessel to return the filtrate back to vessel and solids are processed subsequently. Figure 3.6 shows the approach for the heterocyclic compound synthesis from biomass (modified from Patent document- Lightner[8]).

Synthesis of 5-Hydroxymethyl furfural (5-HMF)

Nowadays, the catalytic transformation of hexoses into furans is very interesting in the point of chemistry because it involves several steps as dehydration, hydrolysis, isomerization, reforming, aldol condensation, hydrogenation and oxidation, etc., which are of general interest. The furanic products involved in this strategy include 5-hydroxymethylfurfural (5-HMF), 2,5-diformylfuran (2,5-DFF), 2,5-furandicarboxylic acid (2,5-FDCA), 2,5-bis(hydroxymethyl)-furan (2,5-BHF) and 2,5-dimethylfuran (2,5-DMF) (structures are shown in Figure 3.7). These can be used as the starting materials for new products as well as for the replacement of oil-derived chemical. As a dehydration product of hexoses,

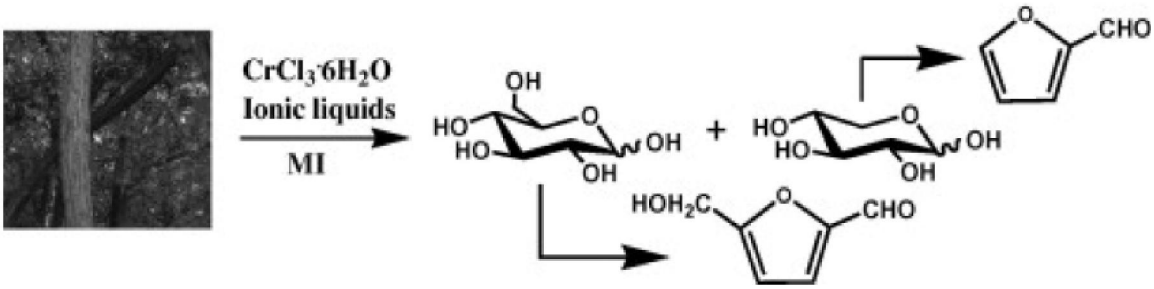

Figure 3.5 : Schematic illustration of HMF and furfural production from lignocellulosic biomass[7]

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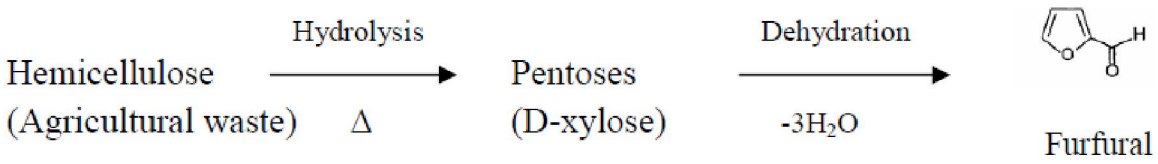
TABLE 3.3 : Yields of furan compounds obtained by microwave irradiation[a] [7]

Entry	Sample	Catalyst	Time (min)	HMF yield (%)	Furfural yield (%)
1	Cellulose	$CrCl_3 \cdot 6H_2O$	2.5	62	Nd
2	Xylan	$CrCl_3 \cdot 6H_2O$	2	Nd	63
3	Xylan	-	2	Nd	18
4	Cellulose + Xylan	$CrCl_3 \cdot 6H_2O$	2	39	55
5	Cellulose + Xylan	$CrCl_3 \cdot 6H_2O$	2.5	53	33
6	Corn stalk	$CrCl_3 \cdot 6H_2O$	3	45	23
7	Rice straw	$CrCl_3 \cdot 6H_2O$	3	47	25
8	Pine wood	$CrCl_3 \cdot 6H_2O$	3	52	31
9[b]	Pine wood	$CrCl_3 \cdot 6H_2O$	3	44	28
10[c]	Pine wood	HCl	60	2.1	4.4
11[d]	Pine wood	$CrCl_3 \cdot 6H_2O$	60	6.4	7
12[e]	Pine wood	$CrCl_3 \cdot 6H_2O$	6	35	18

Nd= not detected; [a] Unless otherwise specified, reaction conditions were: substrate (100 mg) and $CrCl_3 \cdot 6H_2O$ (10 mg, 0.0375 mmol) were added to 2.0 g of $[C_4mim]Cl$, followed by MI at 400 W for the desired time. Yields of HMF from corn stalk, rice straw and pine wood were based on a hexose content of 36.1%, 37.5% and 54%, and yields for furfural were based on a pentose content of 21.4%, 21.2% and 7.6%, respectively.; [b] $[C_4mim]Br$ was used as a reaction medium.; [c] Reaction conditions were: 20 mg of hydrochloric acid, 2.0 g of $[C_4mim]Cl$, 30 mg of H_2O, 0.1 g of pine wood, 100 °C with an oil bath.; [d] Otherwise was the same as Entry 11 except for the reaction temperature at 200 °C.



Scheme 1 : Furfural synthesis from agricultural waste

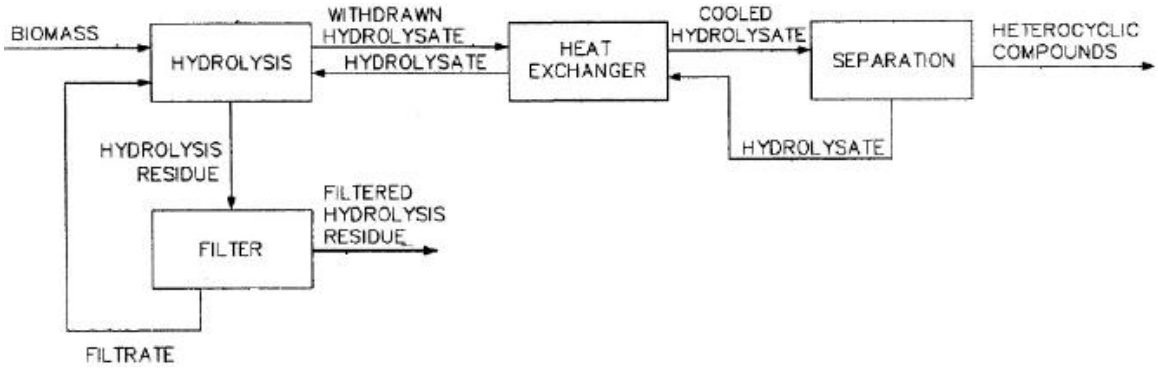


Figure 3.6 : Heterocycle synthesis from biomass (modified from Source: Lightner, 2003)

5-HMF has been considered to be an important and renewable platform chemical in the bio-based renaissance[9].

There has been ample amount of work done for synthesizing 5-HMF from carbohydrate sources with different catalysts, carbohydrates and reaction

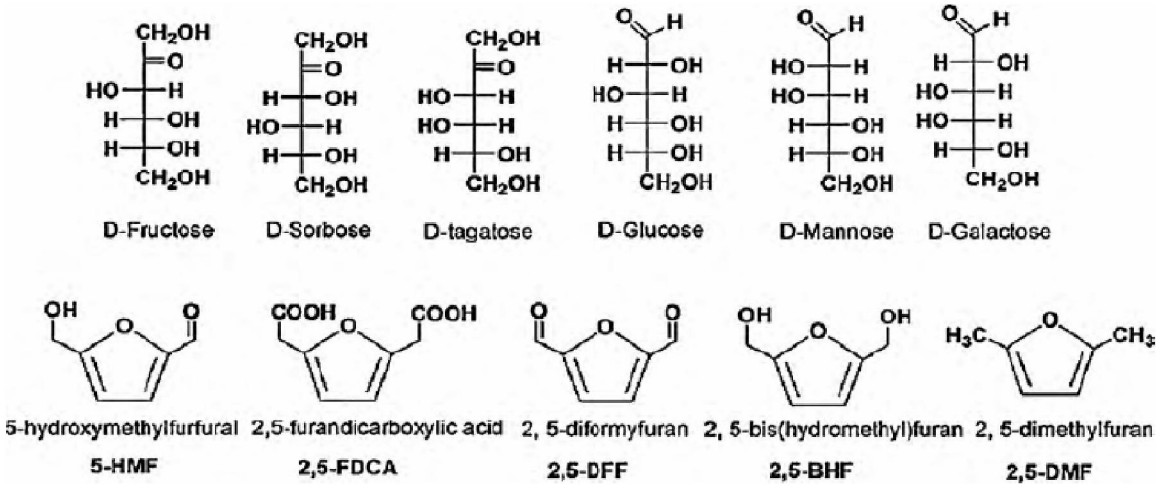


Figure 3.7 : The structures of the representative hexoses and furans[9]

conditions and these resulting into different yields of 5-HMF. Here, few of them are discussed.

5-HMF from Fructose

Bicker et al. investigated the synthesis of 5-HMF in the presence of H_2SO_4 when sub-critical or supercritical acetone–water mixture was employed as a reaction medium. It was found that the carbon atom efficiency is quite good and that no solid impurities are formed. In the supercritical acetone–water mixture, the maximum yield of 5-HMF reached 78% at 180 °C. Some significant progress for the metal-catalyzed dehydration of hexoses has been reported by Zhao et al. They have reported that metal halides in 1-ethyl-3-methylimidazolium chloride ([EMIM]+Cl-) are very efficient dehydration catalysts, among which $CrCl_2$ was uniquely effective, leading to about 70% yield of 5-HMF from d-fructose and glucose (Figure 3.8). In the dehydration of glucose, $CrCl_3$- anion plays a role in proton transfer, and promotes the isomerisation of glucose to fructose in [EMIM]+Cl- solvent.

Cao et al. has reported 5-HMF synthesis from fructose by using ammonium salts. They have reported a new approach to the conversion of fructose to HMF using relatively cheap ammonium salts and high fructose loadings. The tetraethyl ammonium chloride (TEAC)/ fructose low melting mixtures with high substrate contents have shown to efficiently catalyse the fructose dehydration solely or by using $NaHSO_4 \cdot H_2O$ as a catalyst with the ability to achieve 81.3% HMF yield with 33.3 wt% fructose concentration at 120 °C. To obtain the maximum selectivity towards HMF, optimum temperature and reaction time are essential. The results of temperature affecting HMF yield, conversion and selectivity are shown in TABLE 3.4. 79.2% HMF yield is reported with 50 wt% fructose concentration in the TEAC/fructose system using 5 mol% $NaHSO_4 \cdot H_2O$ as a co-catalyst. A semi continuous biphasic system of TEAC/fructose/$NaHSO_4 \cdot H_2O$ melt using tetrahydrofuran (THF) to recover HMF has been

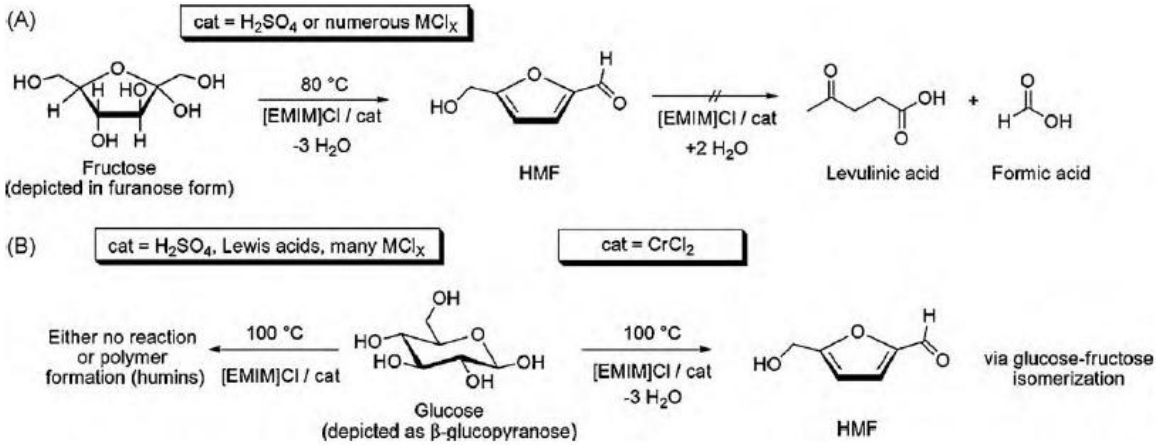


Figure 3.8 : Synthesis of HMF from D-Fructose (A) or Glucose in $[EMIM]^+Cl^-$[9]

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TABLE 3.4 : Effect of temperature on HMF yield in the fructose/TEAC system (Source: Cao et al., 2011)

Temperature (°C)	HMF yield (%)	Conversion (%)	Selectivity (%)
100	33.2	58.2	57
110	71.6	96.3	74.3
120	81.3	100	81.3
140	74.6	100	74.6

Reaction conditions: TEAC 1 g, fructose 0.5 g, 70 min reaction time

proposed and demonstrated in a laboratory scale process operating at 120 °C.

Typical experiment conditions: The biphasic reaction carried out in an autoclave vessel lined with Teflon. 1.0 g TEAC, 1.0 g fructose, 0.038 g $NaHSO_4 \cdot H_2O$ (5 mol% corresponding to 1.0 g fructose) and 10 mL THF were added into the vessel. The vessel was sealed and heated at 120 °C with magnetic stirring in an oil bath for 30 min and then cooled to room temperature to refresh the THF for the next batch. The THF layer recovered from the reactor vessel after each batch was flashed in vacuum to remove the volatile components for reuse. The residue then analysed to determine the content of HMF. Figure 3.9 gives the schematic of the semi-continuous process for conversion of fructose to HMF.

5-HMF from cellulose

Recently, Su et al. reported single step conversion of cellulose to 5-HMF wherein cellulose as feedstock is rapidly depolymerised and resulting glucose is converted to 5-HMF under mild conditions. A pair of metal chlorides ($CuCl_2$ and $CrCl_2$) dissolved in 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl) at temperatures of 80–120 °C collectively catalyze the single-step process of converting cellulose to HMF with an unrefined 96% purity among recoverable products (at 55.4 ± 4.0% HMF yield).

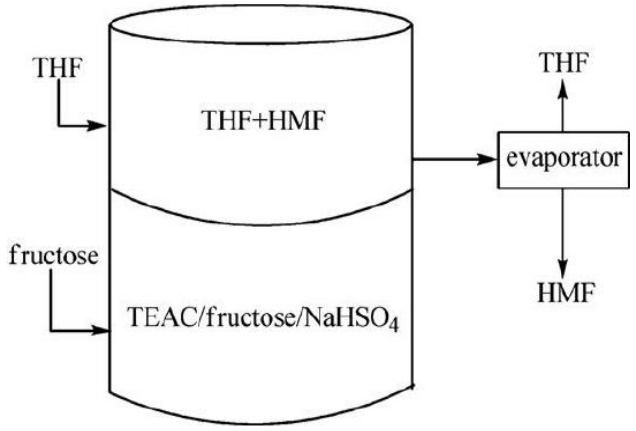

Figure 3.9 : Schematic of the semi-continuous process for conversion of fructose to HMF (Source: Cao et al., 2011)

Standard experiment conditions: 500 mg [EMIM]Cl with catalyst (i.e., $CuCl_2$, $CrCl_2$, or $CrCl_3$) corresponding to 6 mol% with respect to calculated glucose unit in the cellulose feed was loaded into vials of 15.5 mm x 50 mm. The vials were then sealed and inserted into a high-throughput batch reactor. The vials were heated to 150 °C and shaken at 600 rpm for 30 min. After the reactor was cooled to room temperature, 50 mg cellulose was added to each vial. The vials were sealed and reinserted into the high-throughput reactor. During the dissolution process, the vials were heated to 100 or 120 °C and shaken at 600 rpm for 1 h. Then the reactor was cooled to room temperature, and 50 ml H_2O was added to each vial. The vials were sealed and reinserted into the high-throughput reactor at 80, 100, or 120 °C for a time period as specified in the paper, and shaken at 600 rpm. 2.0 ml of water was consequently added to each vial after the reactor was cooled to room temperature. The vials were sealed and centrifuged at 2000 rpm for 30 min. A single liquid layer was formed and the liquid products were analyzed by HPLC. The product yields of this experiment with different reaction time and temperature are mentioned in TABLE 3.5.

The total loading of $CuCl_2/CrCl_2$ was maintained constant at 37 μmol/g [EMIM]Cl and mole fraction of $CuCl_2$, $\chi CuCl_2$= 0.17. More than 90% HMF was extracted using MIBK solvent after each run of the 8h experiment. It was stated that the most active paired metal chloride catalysts also cause product degradation even at 120 °C. A balanced metal chloride composition, such as $CuCl_2$ and $CrCl_2$ at $\chi CuCl_2$= 0.17 (n_{total} = 0.005), offers the highest HMF yield that is not appreciably degraded at the reaction temperature of 120 °C. Hence, this mechanism seems promising to remove a major barrier to the development of a sustainable HMF platform because of the ability to obtain HMF from raw cellulose.

(b) N- heterocycles

Nitrogen heterocycles are abundant in nature and

TABLE 3.5 : Product yields from cellulose with different reaction time and temperature (Source: Su et al., 2009)

Entry	1	2	3
Feed	**Cellulose**	**Cellulose**	**Cellulose**
Reaction temp. (°C)	100	120	120
Reaction time (h)	4	4	8
Product yield (%)			
Cellobiose	15	12.9	0
Glucose	23	8.5	0.96
Mannose	7.5	0	0
Sorbitol	0	0	1.27
1,6-Anhydro-β-D-Glucose	3.6	1.8	0.26
Formic acid	0	0	0
Levulinic acid	1.2	1.4	0
HMF	17	43	57.5
Total yield	67	67	60
HMF concentration in product	25	65	96

are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds. Pyridine and pyrrole are both nitrogen heterocycles—their molecules contain nitrogen atoms along with carbon atoms in the rings. The molecules of many biological materials consist in part of pyridine and pyrrole rings, and such materials yield small amounts of pyridine and pyrrole upon strong heating. In fact, both of these substances were discovered in the 1850s in an oily mixture formed by strong heating of bones. Today, pyridine and pyrrole are prepared by synthetic reactions. Their chief commercial interest lies in their conversion to other substances, chiefly dyestuffs and drugs. Pyridine is used also as a solvent, a waterproofing agent, a rubber additive, an alcohol denaturant, and a dyeing adjunct. (www.brittanica.com)

For N-heterocycles, procedures meeting preparative standards from carbohydrates are exceedingly scarce those allowing large scale adaptation being essentially non-existent. Only recently, improvement of existing procedures and development of new methodologies have led to the more ready acquisition of various *N*-heterocycles from carbohydrates: imidazoles, pyrroles, pyrazoles, pyridines, and pyrazines, which due to their sugar derivation have hydrophilic side chains[4].

Pyrroles

Pyrrole is a heterocyclic aromatic organic compound, a five-membered ring with the formula C_4H_4NH. Substituted derivatives are also called pyrroles, e.g., N-methylpyrrole, $C_4H_4NCH_3$. Porphobilinogen, a trisubstituted pyrrole shown in Figure 3.10, is the biosynthetic precursor to many natural products such as heme. Pyrroles are components of more complex macrocycles, including the porphyrins of heme, the chlorins, bacteriochlorins, chlorophyll, porphyrinogens ((http://en.wikipedia.org/wiki/Pyrrole).

Thermal decomposition of the galactose derived ammonium mucate appears to be the only generation

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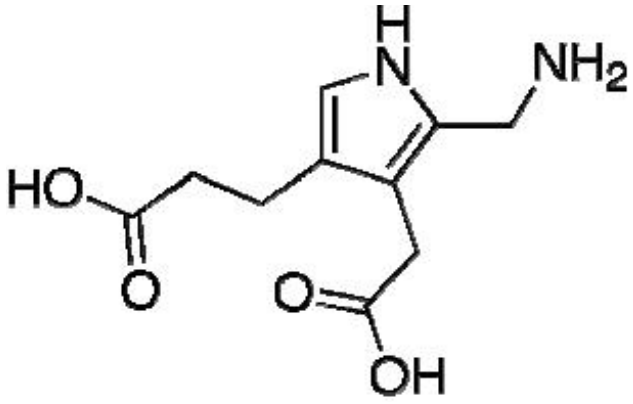
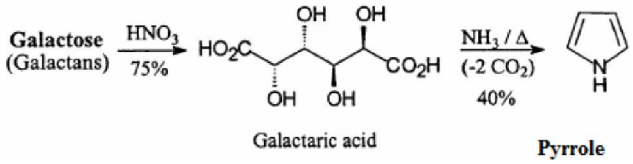


Figure 3.10 : Structure of Porphobilinogen (Source: en. wikipedia. org)



Scheme 2 : Pyrrole synthesis

of pyrrole itself from a carbohydrate source, a process not exploited industrially due to more efficient accesses from petrochemicals as mentioned in the literature of Lichtenthaler[4].

3-Pyridinols

3-Pyridinol figures as an intermediate chemical for herbicides and insecticides, as well as for cholinergic drugs of the pyridostigmine type (Figure 3.11). The conversion of pentoses into 3-pyridinol can be effected in a practical three-step sequence (Scheme 3), involving acid-induced dehydration to furfural, reductive amination to furfurylamine, and oxidation with hydrogen peroxide, the last step conceivably proceeding through the stage of a 2,5-dihydroxy-2,5-dihydrofurfurylamine, which elaborates the pyridine nucleus via dehydration to a 5-aminopentenal intermediate and cycloaldimine formation[4].

Imidazoles

Imidazoles are well known heterocyclic compounds with the formula $(CH)_2N(NH)CH$, which are common and have important feature of a variety of medicinal agents and as biological molecules. Imidazole is a 5-membered planar ring, which is soluble in water and other polar solvents.

Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid histidine, which has an imidazole side-chain. Histidine is present in many proteins and enzymes and

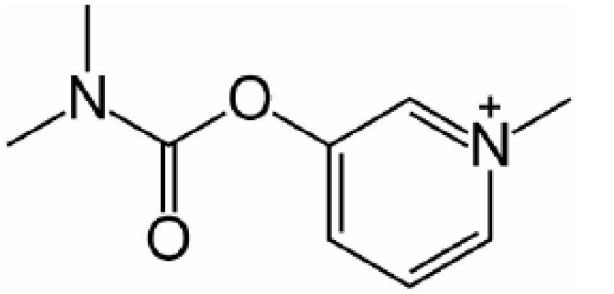
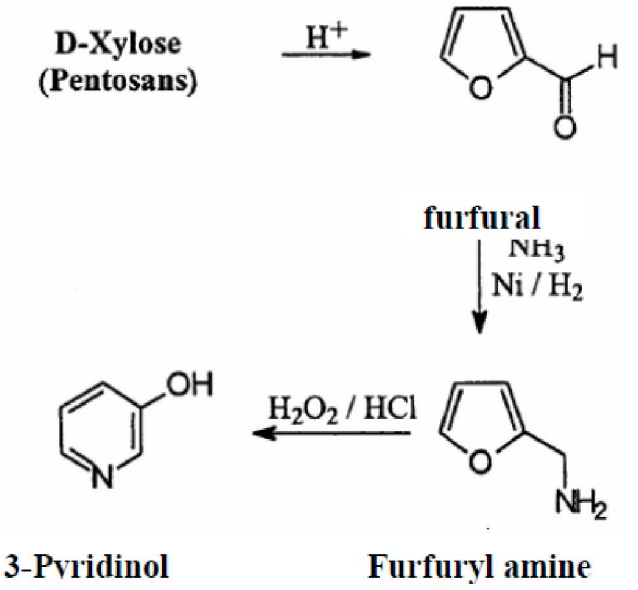


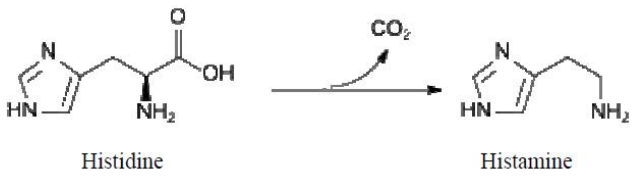
Figure 3.11 : Structure of Pyridostigmine (Source: en.wikipedia.org)



Scheme 3 : 3-Pyridinol synthesis

plays a vital part in the structure and binding functions of haemoglobin. Histidine can be decarboxylated to histamine, which is also a common biological compound. It is a component of the toxin that causes urticaria, which is another name for allergic hives. The relationship between histidine and histamine (Scheme 4) are shown below:

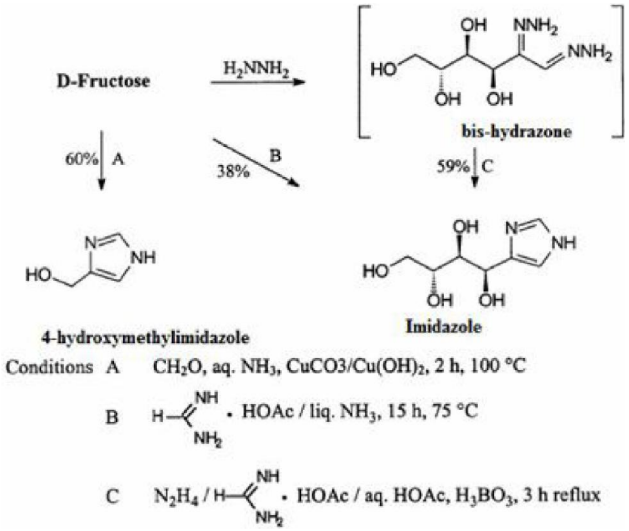
Imidazole has become an important part of many pharmaceuticals. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans that stimulate the central nervous system. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA



Scheme 4 : Relationship between Histidine to Histamine

activities. Hence, its multifaceted application signifies imidazole synthesis. (http://en.wikipedia.org/wiki/Imidazole).

Various imidazoles carrying hydrophilic substituents in the 4-position are readily accessible in one pot procedures from the standard monosaccharides. Of those, the formation of 4-hydroxymethylimidazole, as shown in Scheme 5, on Cu (II)-promoted reaction with formaldehyde and concentrated ammonia is rather unique as retro-aldolization to glyceraldehyde and dihydroxyacetone is involved. The retro-aldol fission can be partially suppressed though by heating D-fructose with formamidinium acetate in liquid ammonia in a pressure vessel, allowing the isolation of imidazole in albeit modest yield (38%). These somewhat impractical conditions can be simplified by briefly heating fructose with formamidinium acetate in the presence of boric acid and a dehydrating agent (hydrazine), the imidazole (now isolable in 59% yield) obviously being elaborated via a borate complex of the bis-hydrazone[4].



Scheme 5 : Imidazole synthesis

(c) S- heterocycles

Thiophene, a sulfur heterocycle, resembles benzene in its chemical and physical properties. It is a frequent contaminant of the benzene obtained from natural sources and was first discovered during the purification of benzene. Like the other compounds, it is used primarily for conversion to other substances (www.brittanica.com). In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. Many thiophene derivatives have been developed as

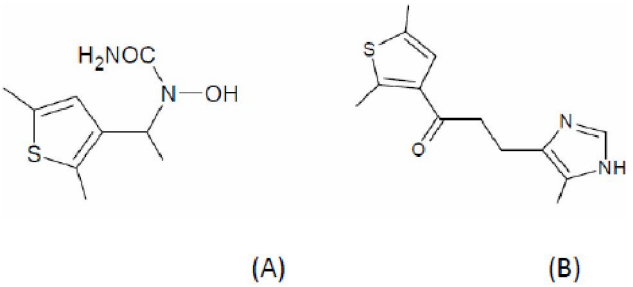
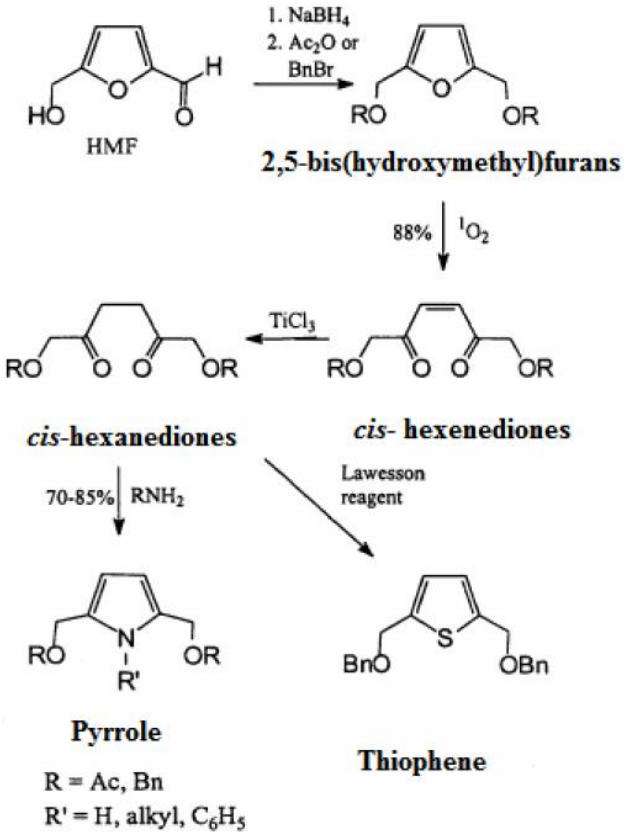


Figure 3.12 : Structures of Thiophene carrying compounds[12]

chemotherapeutic agents and are widely used. Thiophene nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities. Thiophene moiety carrying compounds (Figure 3.12) exhibit various activities like for example 1-[1- (2, 5- dimethylthiophen- 3- yl) ethyl]- 1-hydroxyurea (A) shows anti-inflammatory activity; the maleate salt of 1-(2,5-dimethylthiophen- 3- yl)- 3-(5-methyl- 1 Himidazol-4- yl) propan-1-one (B) act as serotonin antagonists and is used in the treatment of Alzheimer's disease[12].

Thiophene is synthesized generally by conversion of furans in various steps as shown in Scheme 6. Conversion of furans into S-heterocycles like Thiophene presupposes that furan opening to 1,4-dicarbonyl



Scheme 6 : Thiophene synthesis

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compounds can be effected in a preparatively satisfactory manner as exposure to thiation reagent would follow standard methodologies. Oxidants used are singlet oxygen or bromine in water-methanol or aqueous acetone for evaluating their applicability to the HMF derived, 2,5-bis(hydroxymenthyl)furans. On exposure to bromine in aqueous acetone, addition to dibromide is directly followed by hydrolysis to the respective *cis*-hexenediones. Saturation of the olefinic double bond could be affected by reduction with $TiCl_3$ providing desired hexandiones with >90% yields. Now, bis(benzyloxy)hexanedione on exposure to Lawesson's thiation reagent resulted in 74% Thiophene formation (Lichtenthaler et al., 2001).

CONCLUSION

The quest for renewable and sustainable production of alternatives to be used in chemical industry has led to research on the usage of biowaste sugars as the renewable feedstock. However, this report outlines the current practical conversions of inexpensive, bulk-scale-available sugars into unsaturated *O*- and *N*-heterocycles with versatile industrial application profiles. For effective synthesis of heterocycles, the bioconversion of cellulose into glucose or sugars needs to be optimized, a process hampered by several factors such as the heterogeneous nature of the reaction, product inhibition and the interaction of cellulose with lignin. Even for the synthesis of heterocycles from sugars, although, there are many catalysts or different reaction methods developed or found to be workable but there is need to optimize the reaction conditions to have improved yield, improved selectivity to desired compound and last but not the least, the synthesis should be environmentally benign or green in the context of green chemistry.

FUTURE CHALLENGES

Though there are different ways mentioned for heterocycle synthesis from biowaste sugars, there are many challenges involved:

- Efficient extraction of sugars that are covalently trapped inside the lignocellulosic biomass
- Development of suitable catalyst for sugar extraction as well as further conversion to heterocyclic molecule
- Increasing yield and selectivity of desired heterocyclic molecules
- Efficient separation of heterocyclic molecule from the reaction system
- Exploring methods for N and S- heterocycles from biowaste sugars
- Development of synthesis methods that are green and hence, sustainable

ABBREVIATIONS

Abbreviation	-	Full form
Compounds		
Ac	-	Aceto
Bn	-	Benzyl
BHF	-	Bis hydroxymethylfurfural
CO_2	-	Carbon dioxide
$CrCl_2$	-	Chromium chloride
$CuCl_2$	-	Copper chloride
DFF	-	Diformylfuran
DMF	-	Dimethylfuran
[EMIM]Cl	-	Ethylmethylimidazolium chloride
FDCA	-	Furandicarboxylic acid
H_2SO_4	-	Sulphuric acid
H_3BO_3	-	Boric acid
H_3PO_4	-	Phosphoric acid
HMF	-	Hydroxymethylfurfural
MIBK	-	Methyl isobutyl ketone
$NaHSO_4$	-	Sodium bisulphate
NH_3	-	Ammonia
TEAC	-	Tetraethyl ammonium chloride
THF	-	Tetrahydofuran
Symbols		
T	-	Temperature
χ	-	Mole fraction
Miscellanoeus		
HPLC	-	High performance liquid chromatography
MI	-	Microwave irradiation

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