CATALYTIC PREPARATION AND VALUE ADDITION OF RENEWABLE CHEMICAL INTERMEDIATES FROM CARBOHYDRATES

Thesis

Submitted in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

NAVYA SUBRAY BHAT

DEPARTMENT OF CHEMISTRY

NATIONAL INSTITUTE OF TECHNOLOGY KARNATAKA,

SURATHKAL, MANGALURU-575025

APRIL, 2023

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DECLARATION

By the Ph.D. Research Scholar

I hereby *declare* that the Research Thesis titled **"Catalytic Preparation and Value Addition of Renewable Chemical Intermediates from Carbohydrates,"** which is being submitted to the ***National Institute of Technology, Karnataka, Surathkal,*** in partial fulfilment of the requirements for the award of the *Degree* of ***Doctor of Philosophy*** in ***Chemistry*** is *a bonafide report of the research work carried out by me*. The materials contained in this Research Thesis have not been submitted to any University or Institution for the award of any degree.

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CERTIFICATE

This is to *certify* that the Research Thesis titled **"Catalytic Preparation and Value Addition of Renewable Chemical Intermediates from Carbohydrates,"** submitted by **NAVYA SUBRAY BHAT** (Registration Number: 187063CY004) as the record of the research work carried out by her, is *accepted* as the *Research Thesis submission* in partial fulfilment of the requirements for the award of the degree of ***Doctor of Philosophy***.

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ABSTRACT

Adopting biomass-derived fuels and chemicals could help to relieve the economic and environmental distresses triggered by the excessive use of petrofuels and petrochemicals. Moreover, the suitable integration of biomass carbon in the chemical industry would be a giant step toward their long-anticipated sustainability. Carbohydrate-derived furfural (FUR), 5-(hydroxymethyl)furfural (HMF), and levulinic acid (LA) have received significant attention over the past three decades as renewable chemical platforms for the synthesis of a variety of biofuels and chemicals of commercial significance. The elegant acid-catalyzed processes allow the selective removal of excess oxygen atoms from the parent sugar molecules in the form of water under energy-efficient conditions. The inherent instability in aqueous acid, hydrophilicity, and poor thermal stability of HMF complicates its isolation from the aqueous/polar reaction media and challenges the scalability of the process. In this regard, the hydrophobic analogs of HMF have received significant interest as the functional equivalent of HMF. 5-(Chloromethyl)furfural has also gained considerable interest as a substitute for HMF and has shown promise as the hydrophobic congener of HMF. Similarly, the esters of HMF, such as 5-(acyloxymethyl)furfural, are particularly interesting since they are halogen-free, hydrolytically stable, and hydrophobic analogs of HMF. The functionalities present in platform molecules are exploited for selective synthetic transformations, preferably under catalytic conditions, to make products of desired structural and functional characteristics. For example, the Baeyer-Villiger oxidation of furanics, especially FUR to 2-furanone, remains largely underexplored. The catalytic esterification or transesterification of biomass-derived intermediates will lead to corresponding esters with potential applications as green solvents, novel oxygenates, plasticizers, surfactants, and chemical reagents. Carbohydrate-derived renewable chemicals are of academic and commercial interest. Even incremental improvement in their yields and simplification of the processes for their production will significantly benefit this area of research.

***Keywords**: Renewable synthesis; Furfural; 5-(chloromethyl)furfural; 5-(Acyloxymethyl)furfural; 2(5H)-furanone; Alkyl esters; Isosorbide esters.*

TABLE OF CONTENTS

CHAPTER 1: GENERAL INTRODUCTION

CHAPTER 2: LITERATURE REVIEW, SCOPE, AND OBJECTIVES OF THE WORK

CHAPTER 3: HYDROCHLORIC ACID-CATALYZED COPRODUCTION OF FURFURAL AND 5-(CHLOROMETHYL)FURFURAL ASSISTED BY A PHASE TRANSFER CATALYST

CHAPTER 4: STRAIGHTFORWARD AND SCALABLE PREPARATION OF 5-(ACYLOXYMETHYL)FURFURALS DIRECTLY FROM

CARBOHYDRATES AS A VIABLE SUBSTITUTES FOR 5-(HYDROXYMETHYL)FURFURAL

CHAPTER 5: SELECTIVE OXIDATION OF BIOMASS-DERIVED FURFURAL TO 2(5H)-FURANONE USING TRIFLUOROACETIC ACID AS THE CATALYST AND HYDROGEN PEROXIDE AS A GREEN OXIDANT

CHAPTER 6: PREPARATION OF HIGH-VALUE ESTERS FROM BIOMASS-DERIVED CHEMICAL PLATFORMS VIA ESTERIFICATION AND TRANSESTERIFICATION REACTIONS

CHAPTER 7: SOLVENT-FREE SYNTHESIS OF NOVEL 3,4-DIHYDROPYRIMIDIN-2(*1H*)-ONES AND 1,4-DIHYDROPYRIDINES FROM BIORENEWABLE FURFURALS USING 1,4-DIAZABICYCLO[2.2.2]OCTANIUM DIACETATE AS THE IONIC LIQUID CATALYST

CHAPTER 8: SUMMARY AND CONCLUSIONS

LIST OF FIGURES

CHAPTER 1

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

CHAPTER 7

LIST OF SCHEMES

CHAPTER 1

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

CHAPTER 7

LIST OF TABLES

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

CHAPTER 7

ABBREVIATIONS

A15	Amberlyst 15
AcMF	5-(Acetoxymethyl)furfural
AGL	α-Angelica lactone
AL	Alkyl levulinate
AMF	5-(Acyloxymethyl)furfural
Aq.	Aqueous
BTBAC	Benzyltributylammonium chloride
BPA	Bisphenol acetone
BA	Butyric acid
BF	Butyl 2-furoate
BHMF	2,5-Bis(hydroxymethyl)furan
BL	Butyl levulinate
BS	Butyl stearate
BuMF	5-(Butyloxymethyl)furfural
CMF	5-(Chloromethyl)furfural
DABCO-Ac	1,4-Diazabicyclo[2.2. 2]octane diacetate
DALA	δ-Aminolevulinic acid
DCE	1,2-Dichloroethane
DCM	1,2-Dichloromethane
DFF	2,5-Diformylfuran
DHPM	3,4-Dihydropyrimidin-2-(*1H*)-one
DMF	2,5-Dimethylfuran
DHP	1,4-dihydropyridine
DPA	Diphenolic acid
EF	Ethyl 2-furoate
EL	Ethyl levulinate
EMF	5-(Ethoxymethyl)furfural
Endo-ISMB	Isosorbide *Endo*-monobenzoate
Endo-ISMLu	Isosorbide *Endo*-monolaurate

ES	Ethyl stearate
Exo-ISMB	Isosorbide *Exo*-monobenzoate
Exo-ISMLu	Isosorbide *Exo*-monolaurate
FAA	Free fatty acid
FAL	Furfuryl alcohol
FDCA	2,5-Furandicarboxylic acid
FDM	2,5-Furandimethanol
FFBG	Ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
FFHz	Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate
FMF	5-(Formyloxymethyl)furfural
FTIR	Fourier transform infrared
FUR	Furfural
2FA	2-Furoic acid
2FN	2(5H)-furanone
GVL	γ-Valerolactone
HDO	Hydrodeoxygenation
HL	Hexyl levulinate
HMF	5-(Hydroxymethyl)furfural
II	Isoidide
IIDB	Isoidide-2,5-dibenzoate
IIMB	Isoidide monobenzoate
IL	Ionic liquid
IM	Isomannide
IMDB	Isomannide-2,5-dibenzoate
IMMB	Isomannide monobenzoate
IS	Isosorbide
ISDA	Isosorbide-2,5-diacetate
ISDB	Isosorbide-2,5-dibenzoate
ISDP	Isosorbide-2,5-dipropionate

ISMAr	Isosorbide monoacryalate
ISDN	Isosorbide dinitrate
IPL	Isopropyl levulinate
LA	Levulinic acid
LE	Levulinate ester
LeMF	HMF-levulinate
MA	Maleic acid
MB	Methyl butyrate
MBMF	5,5'-((5-((5-Methylfuran-2-yl)methyl)furan-2-yl)methylene)bis(2methylfuran)
MeO	Methyl oleate
MeS	Methyl stearate
MF	Methyl 2-furoate
ML	Methyl levulinate
MMF	5-(Mesitylmethyl)furfural
MTHF	Methyltetrahydrofuran
MW	Microwave
2MF	2-Methylfuran
5MF	5-Methylfurfural
5MFBG	Ethyl 6-methyl-4-(5-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate
5MFHz	Diethyl 2,6-dimethyl-(5-methylfuran-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate
NMR	Nuclear magnetic resonance
OA	Oleic acid
PDO	1,5-Pentanediol
PF	Propyl 2-furoate
PiAc	Piperidinium acetate
PL	Propyl levulinate
PrMF	5-(Propionyloxymethyl)furfural
PS	Propyl stearate

PTC	Phase transfer catalyst
PX	*p*-Xylene
RT	Room temperature
SA	Succinic acid
StA	Stearic acid
TEAA	Triethylammonium acetate
THF	Tetrahydrofuran
TEAHS	Triethylammonium hydrogen sulfate
TEA	Triethylamine
TFA	Trifluoroacetic acid
TFPAA	Trifluoroperacetic acid

SYMBOLS

°C	Degree Celsius
wt.%	Weight percent
min	Minute
H	Hour
s	Second
mL	Milliliter
mmol	Millimole
sc.	Supercritical
eq.	Equivalent
mg	Milligram
L	Liter
M	Molar
Å	Angstrom
mol%	Mole percent
MHz	Megahertz
Δ	Delta
Hz	Hertz
%	Percent
ppm	Parts per million
γ	Gamma
α	Alpha
β	Beta
cm^{-1}	Reciprocal centimeters

CHAPTER 1

GENERAL INTRODUCTION

1.1 INTRODUCTION

One of the significant challenges for industrialized societies is to ensure fast economic development with minimal impact on health and the environment. With the increasing population and their aspirations for a better life, the demand for energy, fuels, and materials is reaching newer heights. Since its widespread commercialization in the early twentieth century, most bulk and fine chemicals and transportation fuels are primarily sourced from crude oil (Corma et al. 2017; Yadav et al. 2020). Decades of research in petroleum refining have built an extensive and robust infrastructure for petrofuels and petrochemicals. However, the increasing demand for crude oil has stressed the depleting reserves, created an imbalance between supply and demand, and increased market volatility. The level of CO_2 in the atmosphere has peaked from 280 parts per million (ppm) to 412 ppm in recorded history and continues rising (Figure 1.1). As a result, there are seemingly irreversible environmental problems such as global warming.

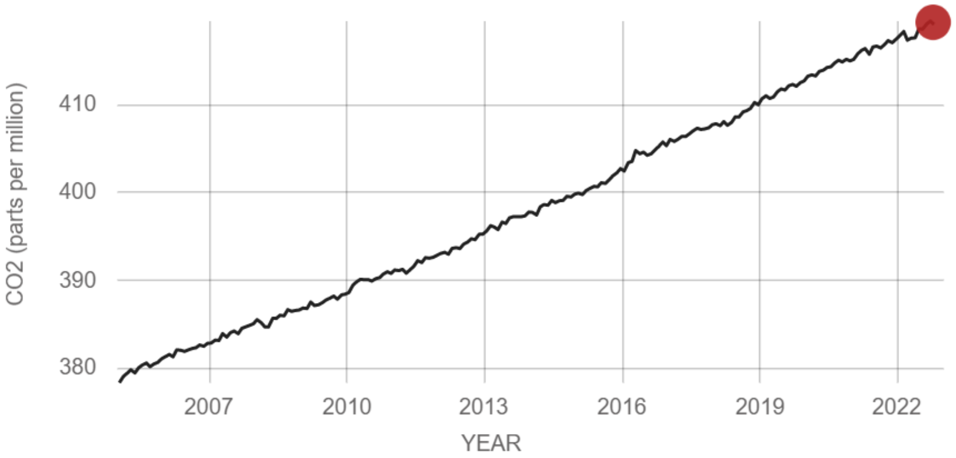
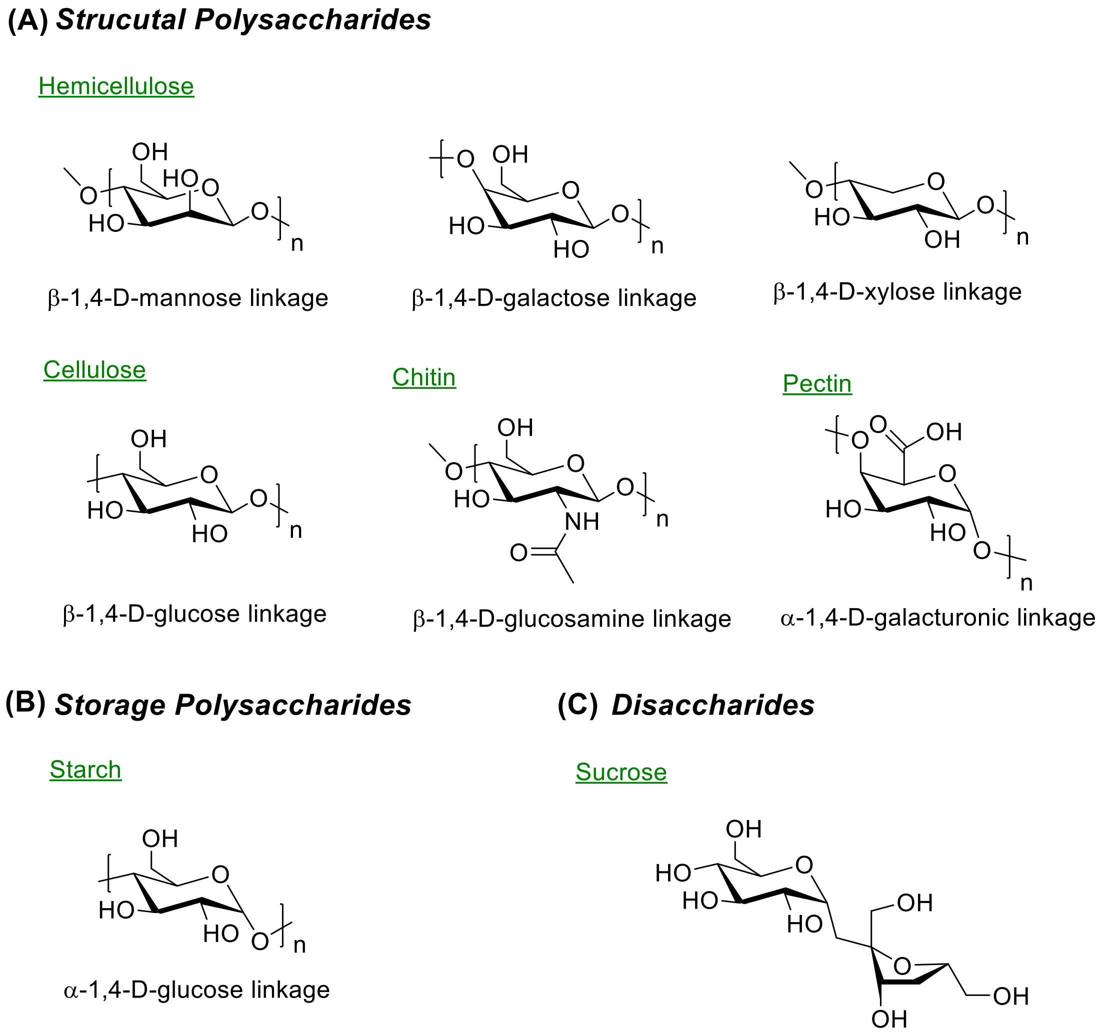


Figure 1.1 Carbon dioxide level in the atmosphere (Image credit: NASA climate change website, https://climate.nasa.gov/vital-signs/carbon-dioxide/).

Besides, the countries dependent on foreign oil import risk compromising their geopolitical, societal, and economic interests (Brundtland 1987; Yang et al. 2017). Therefore, there has been a coordinated effort by scientists and technologists to find a sustainable and greener alternative to crude oil, which has found governmental and public support. Ultra-clean technologies like solar and hydrogen fuel cells have made tremendous progress over the past decade, and electric vehicle manufacturers are emerging as the new market players (Al-Othman et al. 2022; Mohammed et al. 2022; Ramya and Senthil Kumar 2022). However, the market is not yet ready to shy away completely from petroleum-based infrastructure. Therefore, the transportation sector will continue to use carbon-based liquid fuels in the near future, and the chemical industries will also require carbon-based chemical feedstock (Balat 2011; Zhou et al. 2011). In search for a renewable and preferably carbon-neutral source, many found biomass as a commercially feasible replacement for fossilized carbon. Interestingly, biomass had a much larger share of the fuels and chemicals market before the advent of petroleum. For example, methyl- and ethyl esters of fatty acid, commonly called biodiesel, can be used as a fuel and fuel additive. Similarly, bioethanol is presently used as a fuel oxygenate and an octane booster for gasoline (Balat 2011; Röttig et al. 2010). However, biodiesel and bioethanol have limitations such as low energy density, low flame luminosity, miscibility with water, low cold flow properties, lower vapor pressure, and poor oxidative stability. Therefore, the growing demand for chemicals, fuels, and materials should be addressed by developing sustainable new technology that can be adapted to the existing infrastructure (Katakojwala and Mohan 2021; Sun et al. 2018).

The biorefinery concept, where abundant, inexpensive, and preferably waste biomass is transformed into fuels and chemicals, has revolutionized the field. In a biorefinery, advanced biofuels, biochemicals, and energy in the form of heat are produced starting from abundant non-food biomass in an integrated approach. The opportunities in a biorefinery are manifold, which include the domestic production of fuels and chemicals, the creation of new jobs, reducing the cost of imported oil, and creating a healthier environment. However, there are serious technical challenges to be solved (Maity 2015). Petroleum is primarily made of hydrocarbons (alkanes), and the composition varies slightly based on the origin. On the other hand, biomass is made of complex and highly oxygenated biopolymers (carbohydrates such as cellulose and hemicellulose) along with various extractives and ash. The composition depends on the type of biomass, season, storage conditions, and where it is grown (Bayu et al. 2019).

Biomass is an animal- or plant-based organic contemporary product derived from natural and anthropogenic processes. The definition of biomass will vary slightly depending on the origin and the usage due to its heterogeneity. So, in general, biomass is the naturally originating materials such as crops, shrubs, algae, trees, and materials composed of the organic matrix, except fossil materials and petrochemicals. Traditionally, biomass has been used as a domestic fuel for decades (Vassilev et al. 2010, 2012). Overall, considering the huge potential of biomass for fuels, chemicals, and materials synthesis with zero carbon emission, the combined effect has been made toward value addition and synthetic upgradation (Wettstein et al. 2012b).



Scheme 1.1 A structural representation of saccharides.

Biomass primarily consists of carbohydrates, which can be divided into categories based on nature and chemical content. It consists of structural polysaccharides (e.g., hemicellulose, cellulose, chitin, and pectin), storage polysaccharides (e.g., inulin and starch), and disaccharides (e.g., sucrose) (Scheme 1.1) (Alonso et al. 2010; Kobayashi and Fukuoka 2013). In particular, lignocellulose is the fibrous plant material that constitutes a large portion of the biomass.

1.2 LIGNOCELLULOSIC BIOMASS

Lignocellulosic biomass is the most abundant and inexpensive non-edible fibrous biomass with 1.1x10^{11} metric tons annual production, which is divided into 40% aquatic and 60% terrestrial biomass. The efficient utilization of lignocellulosic biomass will reduce CO_2 emissions and global warming. It mainly consists of polymeric constituents such as lignin (~15-20%), hemicellulose (~25-30%), and cellulose (~40-50%) (Zhou et al. 2011). Along with that small quantity of extractives, ash, proteins, and inorganic impurities consisting of proteins, chlorophyll, waxes, and non-combustible inorganic contents are found (Figure 1.2).

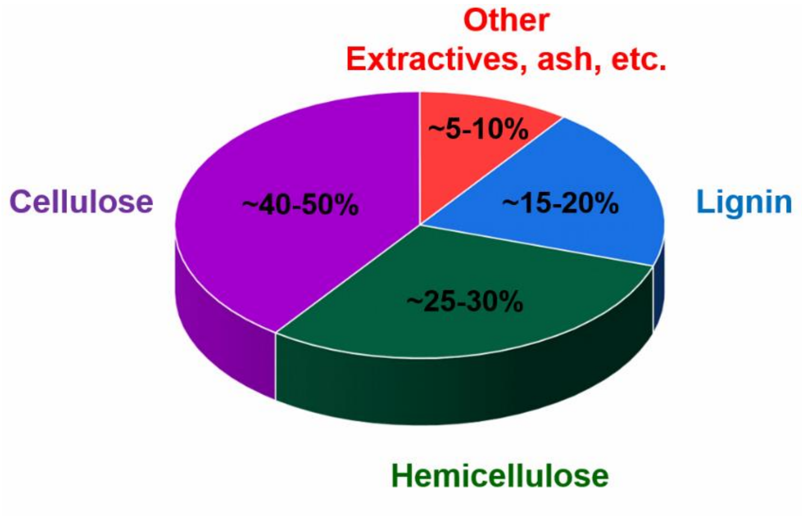


Figure 1.2 The composition of lignocellulosic biomass.

Cellulose is the largest fraction of lignocellulosic biomass (40-50%). Cellulose is a straight-chain polymer made of glucose units connected by the 1,4-β-glycosidic ether linkage. Extensive hydrogen bonding between the chains of cellulose is responsible for its chemical recalcitrance and high crystalline nature. An average of 700 billion metric tons are produced annually, but only around 0.1 billion tons are used as a substrate (Li et al. 2018; Muratore et al. 2018). Hemicellulose fraction is an amorphous polymer with hexose and pentose monomers such as D-glucose, D-mannose, D-xylose, D-galactose, and L-arabinose, with D-xylose being the most abundant (Alonso et al. 2010). Lignin is another important portion of lignocellulosic biomass composed of methoxylated phenylpropanes, such as sinapyl alcohol, coumaryl alcohol, and coniferyl alcohol. Lignin provides structural rigidity and protection to plants. The depolymerization of lignin received tremendous attention for synthesizing phenols, anisoles, aromatic acids, and esters (Kumar et al. 2021; Sudarsanam et al. 2020; Sun et al. 2018). The major technological impediment in biomass value addition is the selective conversion of complex biopolymers into small molecules with desired functionalities and properties under environmentally-benign conditions. Therefore, pretreatment of lignocellulosic biomass is routinely applied before its valorization. The separation of lignocellulosic biomass proceeds using pretreatment followed by hydrolysis, which includes physical (e.g., comminuting, milling, and steam) and chemical (e.g., hydrolysis) methods. The selective defunctionalization and refunctionalization of biomass resulted in the formation of fuels and chemicals. There are mainly three technologies for the value addition of biomass: thermochemical, biotechnological, and chemocatalytic (Briens et al. 2008; Escobar et al. 2015; Song et al. 2021).

Thermochemical value addition of biomass is fast (seconds to minutes), technologically familiar, biomass independent, and could potentially be integrated into present infrastructure. For example, lignocellulosic biomass can be converted into a hydrocarbon-rich mixture within a short time (ca. seconds to minutes) by subjecting them to high temperatures without oxygen. However, thermochemical value addition gives a complex mixture of compounds and is often unstable to be used directly in the downstream processing (Bharath et al. 2020; Jahirul et al. 2012). The biotechnological value addition processes are selective, work under ambient conditions, but are slow (ca. days). For example, the commercial production of bioethanol, lactic acid, and succinic acid using an enzyme-catalyzed process. The main obstacles are that the process is prolonged and requires days, the usage of expensive enzymes, and the requirement of genetically engineered animals (Amin 2009; Balat 2011; Sheldon 2018).

The chemocatalytic conversion of biomass is particularly interesting since they are fast, selective, biomass agnostic, and can potentially be integrated into the existing petrochemical infrastructure. The production of biodiesel by the catalytic transesterification of triglycerides in oils and fats is a classic example of a chemocatalytic value addition pathway that has been commercialized (Al-Zuhair 2007; Narasimharao et al. 2007). A major challenge in the chemocatalytic pathway is to develop a new generation of efficient, robust, selective, recyclable, and inexpensive catalysts that can deconstruct the various biopolymers selectively into simple molecules. In a biorefinery, in analogy to a petrorefinery, a handful of chemical building blocks are produced, which are then synthetically upgraded into products of commercial value (Figure 1.3).

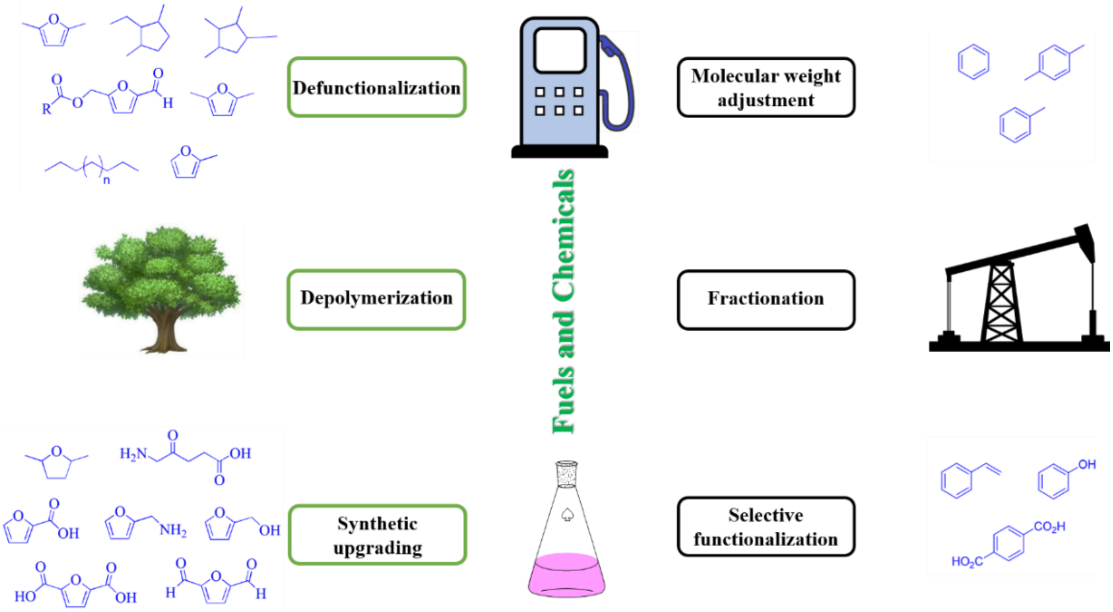
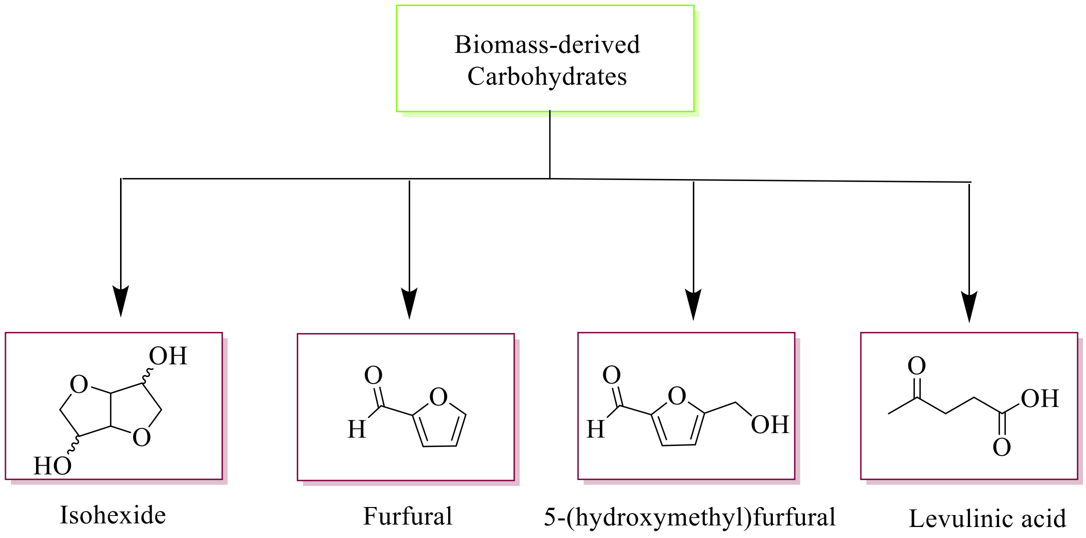


Figure 1.3 Schematic of the processes for making fuels and chemicals from petroleum and biomass (Adopted from (Dutta et al. 2022)).

Cellulose is a major component of terrestrial lignocellulosics and algal biomass. It is the single most abundant biopolymer with surplus production and a potential feedstock for chemocatalytic value addition. The acid-catalyzed depolymerization and dehydration of biomass-derived carbohydrates into furanics, levulinates, and isohexides are an elegant way of removing excessive functionalities and oxygen atoms and to from the carbohydrate moieties without carbon-carbon bond scission (Scheme 1.2) (Dutta and Bhat 2022).

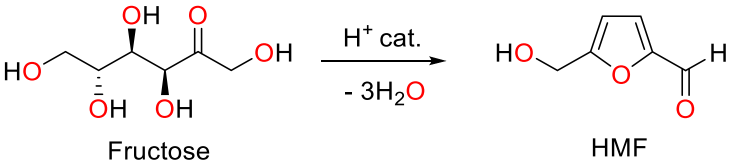


Scheme 1.2 Production of renewable chemical building blocks from biomass-derived carbohydrates.

The acid-catalyzed dehydration of glucose leads to 5-(hydroxymethyl)furfural (HMF). The sequential removal of three water molecules from glucose leads to HMF, whose oxygen content is 50% of glucose. However, HMF retains key functionalities such as hydroxymethyl, aldehyde, and the furan ring. HMF has been exploited as a renewable chemical building block for synthesizing various products with varying complexities ranging from fuel and fuel additives, solvents, monomers, plasticizers, home care products, agrochemicals, and pharmaceuticals (Shen et al. 2020; Xu et al. 2020). The ring-opening of HMF in aqueous acid leads to levulinic acid (LA) and a formic acid molecule. LA has been recognized as one of the top-ten renewable chemicals of commercial significance by the National Renewable Energy Laboratory (NREL), USA (Pileidis and Titirici 2016). The derivatives of LA are complementary to those of HMF. The derivatives of HMF where the furan ring remains intact are termed furanics, whereas the ring-opened products are called levulinates. The catalytic hydrogenation of glucose leads to sorbitol. The acid-catalyzed dehydration of sorbitol leads to isosorbide (IS) (Dutta and Bhat 2022). IS is the starting material for isosorbide dinitrate (ISDN), used to dilate the blood vessels. IS has a vast potential market as a diol-based monomer for renewable polymers and plasticizers. The dehydration of pentose sugars like xylose leads to furfural (FUR). FUR and its derivatives, such as furfuryl alcohol (FAL), 2-furoic acid (2FA), 2-methylfuran (2MF), and maleic anhydride, have established commercial applications (Li et al. 2016a). Discussions on the above chemical building blocks are as follows:

1.3 5-(HYDROXYMETHYL)FURFURAL (HMF)

HMF is a furanic compound where an aldehyde and a hydroxymethyl group are attached to the 2 and 5 positions of the furan ring. Keeping the huge commercial potential in mind, HMF is often termed the '*sleeping giant*.' HMF is routinely produced by the acid-catalyzed dehydration of sugars and polymeric carbohydrates by depolymerization, hydrolysis, and dehydration reactions (Scheme 1.3). It is formed by the subsequential removal of three water molecules and is generally isolated in excellent yields from simple sugars like fructose. Good yields of HMF from other sugars and carbohydrates have also been reported, but they typically require special reaction conditions and additives (Rosatella et al. 2011; Shen et al. 2020). Scalable and high-yielding production of HMF from untreated biomass is required for the commercial feasibility of its derivative chemistries. An acid catalyst of some sort is routinely used to produce HMF from carbohydrates. The acid catalyst examined includes various homogeneous and heterogeneous acid catalysts such as mineral acids, metal salts, solid acids, zeolites, and ion-exchange resins (Dutta et al. 2013). The use of special reaction conditions like microwave heating, supercritical or subcritical reaction media, and ionic liquid are also not uncommon. The hydrophilic character of HMF poses a major challenge in the isolation and purification of HMF from the aqueous or polar reaction mixture. Although the problem can somewhat be solved by a 'salting-out' strategy or by using an organic solvent of appropriate polarity, the process increases the production cost. In addition, HMF is relatively unstable in aqueous acid and transforms into a complex mixture of furanic resins collectively called humin.



Scheme 1.3 The acid-catalyzed dehydration of fructose to HMF.

Over the past two decades, hundreds of patents and journal publications have been devoted to the production and downstream applications of HMF as a biorenewable chemical building block. The presence of reactive functional groups in HMF makes it a branching point to synthesize commodity chemicals and materials of varying structural complexities. The synthesis of diesel-range hydrocarbons has been attempted from HMF (Cueto et al. 2017). A typical strategy involves condensing HMF with biogenic ketones such as acetone to lengthen the carbon chain in the diesel range and then deoxygenate the molecule using catalytic hydrogenation and hydrodeoxygenation (HDO). Aldol-type condensation of HMF and biogenic ketones followed by HDO gives rise to ‘drop-in’ substitutes of petroleum-derived alkanes (Chheda and Dumesic 2007). Several promising fuels oxygenates, such as 5-(ethoxymethyl)furfural (EMF) and ethyl levulinate (EL), have also been produced from HMF (Liu et al. 2013; Peixoto et al. 2021). Both products can be produced by acid-catalyzed ethanolysis of HMF. Selective hydrogenation of HMF leads to 2,5-dimethylfuran (DMF). DMF is a promising high-octane fuel with similar physicochemical properties as petrol. DMF is also a renewable chemical intermediate for producing *p*-xylene (PX), a feedstock for terephthalic acid (Dutta and Bhat 2020). The selective oxidation of HMF leads to 2,5-diformylfuran (DFF) and 2,5-furandicarboxylic acid (FDCA). Both DFF and FDCA are being used as renewable monomers for polymeric applications (Antonyraj et al. 2017; Wang et al. 2019). For example, FDCA is used to prepare poly(ethylene furoate), a renewable alternative to poly(ethylene terephthalate) (Figure 1.4).

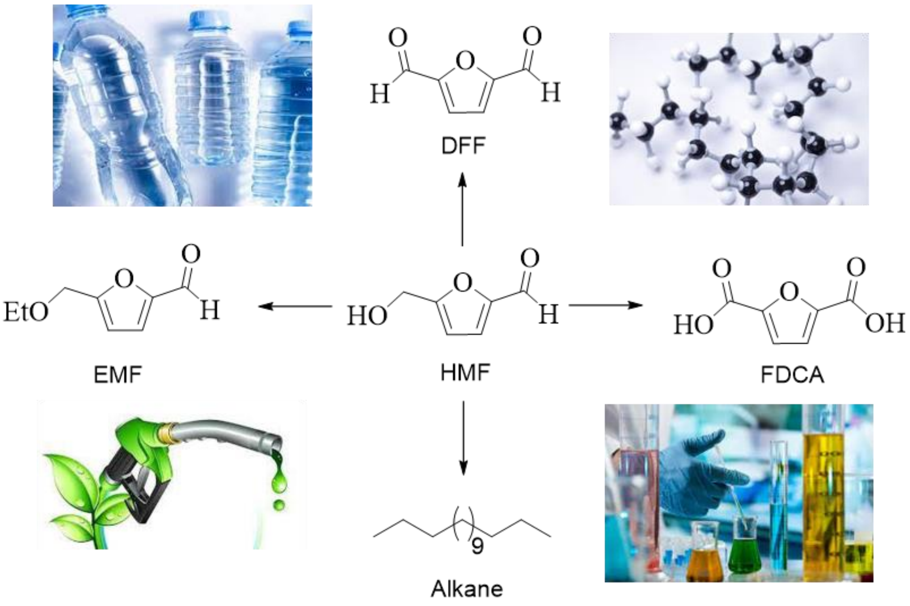
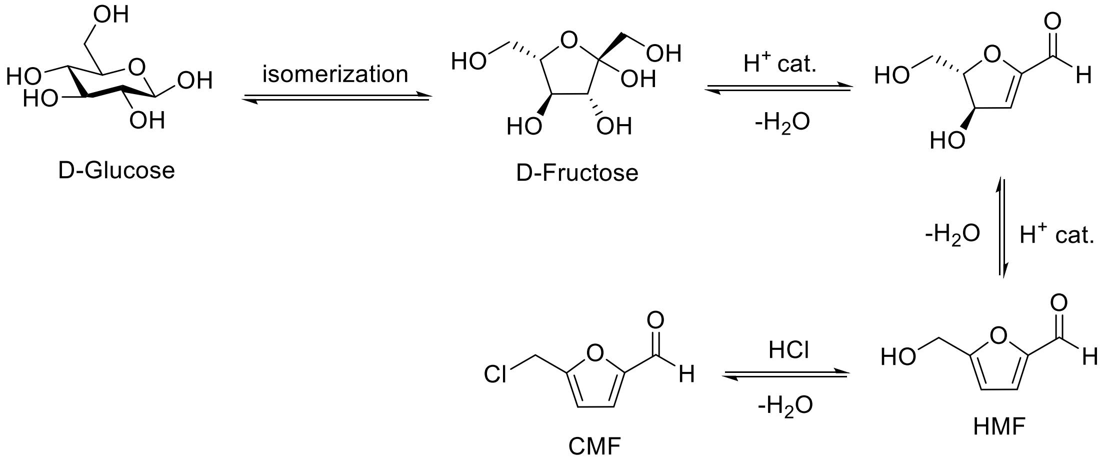


Figure 1.4 Derivatives of HMF and their application.

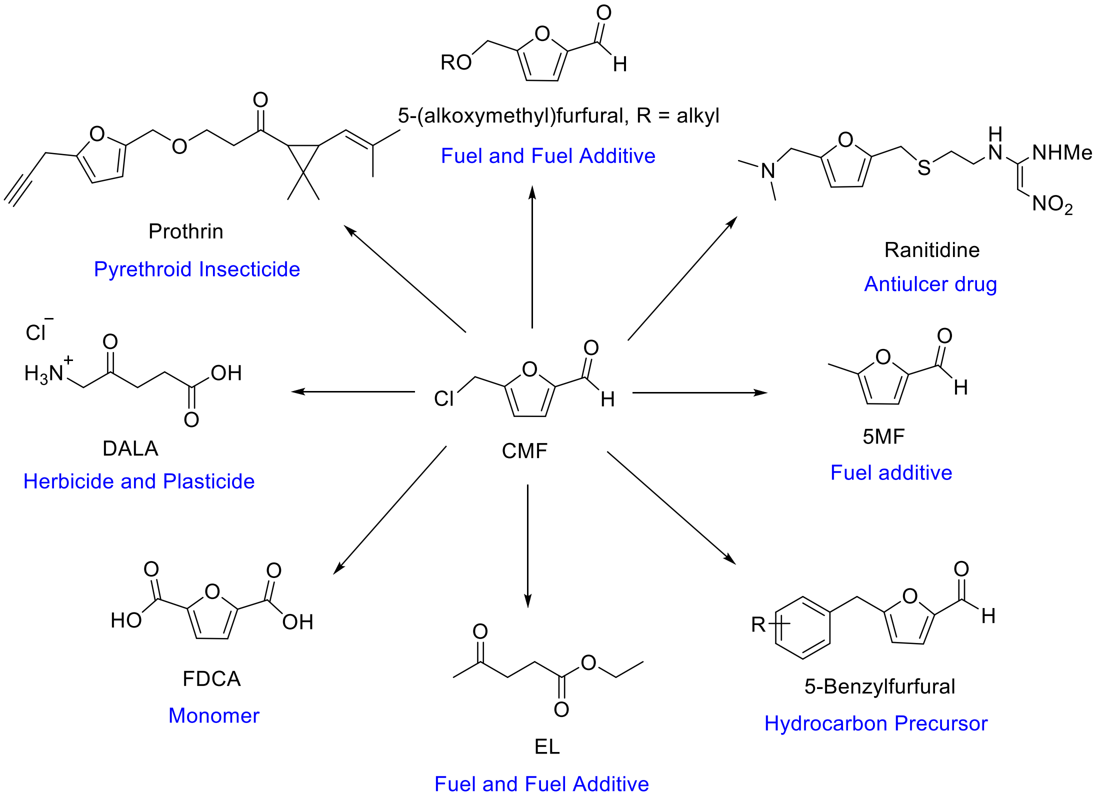
1.4 5-(CHLOROMETHYL)FURFURAL (CMF)

CMF is a hydrophobic congener of HMF where the hydroxymethyl group in HMF is converted into a chloromethyl group. CMF can be prepared by treating HMF with concentrated HCl. CMF can also be produced directly from biomass-derived carbohydrates (Scheme 1.4). The synthesis of CMF was first reported in 1901 by treating cellulose with ethereal HCl. It is hydrophobic and can conveniently separate from the aqueous reaction mixture by simple solvent-solvent extraction. An aqueous-organic biphasic reaction medium is frequently used where the CMF formed gets extracted into the organic solvent and shielded from further acid-catalyzed decomposition pathways (Mascal 2015, 2019). High isolated yields of CMF have been reported from sugars, carbohydrates, and even untreated biomass. It can potentially participate in all derivative chemistries of HMF. CMF has a superior reactivity pattern in some reactions due to the halide ion's better-leaving group ability. CMF can also be hydrolyzed in water to HMF, as well as LA.



Scheme 1.4 The mechanistic pathway of acid-catalyzed dehydration of carbohydrates to CMF.

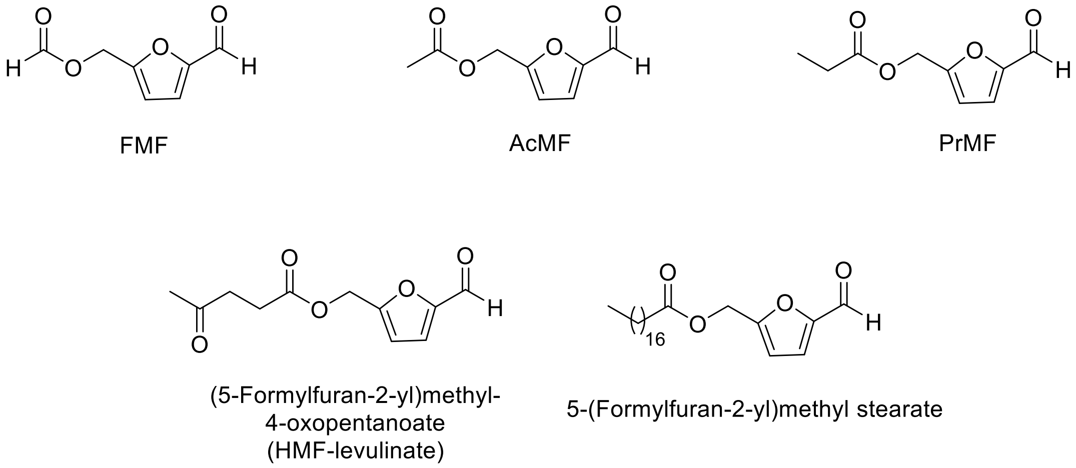
CMF has been converted into high-value derivatives due to its superior reactivity. It can be conveniently converted into HMF in boiling water, and simple substitution of chloride with alcohols gives 5-(alkoxymethyl)furfural at room temperature, a fuel oxygenates (Scheme 1.5). It can also be converted into LA and EL at elevated temperatures in water and alcoholic solution, respectively (Mascal and B. Nikitin 2010). Like HMF, the oxidation of CMF gives rise to DFF and FDCA, the renewable monomer used in the polymer industry (Dutta et al. 2015a). Friedel-Crafts alkylation followed by HDO was reported to synthesize diesel-range hydrocarbons from CMF (Shinde and Rode 2018). It can also be converted into high-value derivatives such as the anti-ulcer drug ranitidine, pyrethroids like prothrin, natural herbicides, and pesticides like δ-aminolevulinic acid (DALA). The synthesis of DALA from CMF starts from substituting the chloromethyl group with azide to give 5-(azidomethyl)furfural, followed by photocatalyzed addition of singlet oxygen to furan ring and hydrogenation using Pd/C in the presence of aq. HCl (Mascal and Dutta 2011a). Similarly, in four steps, ranitidine, an anti-ulcer agent, was prepared from CMF (Mascal and Dutta 2011b). Synthesis of 5-methylfurfural (5MF) was reported by catalytic reduction of CMF in the presence of palladium. Further, CMF has also been converted into DMF, a renewable precursor for bio-terephthalic acid (Dutta and Mascal 2014).



Scheme 1.5 Derivative chemistry of CMF.

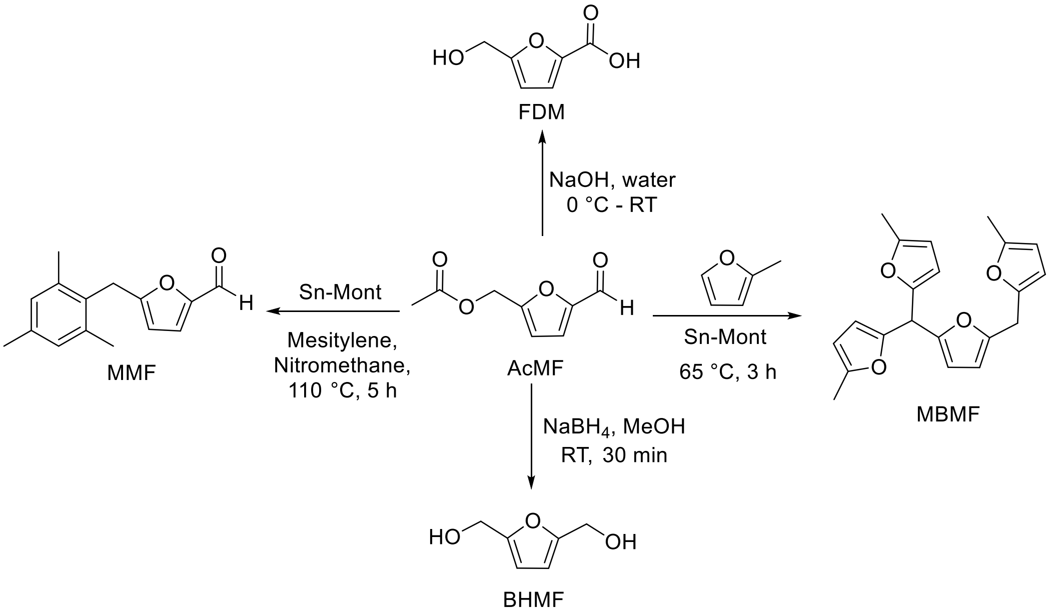
1.5 5-(ACYLOXYMETHYL)FURFURAL (AMF)

AMF are non-halogenated, hydrophobic derivatives of HMF, obtained when the hydroxyl group in HMF was converted into an ester functionality by reacting with a suitable carboxylic acid or its derivatives (Scheme 1.6) (Shinde et al. 2018). The long-chain fatty esters are naturally found in latifolinal, isolated from dried fruits and *Cordia latifolia* (Siddiqui et al. 2010). 5-(aryloxymethyl)furfural have potential application as fungicide surfactants, fuel additives, and for treating sickle cell anemia (Xu et al. 2017). AMFs can be entirely biorenewable in nature. For example, acetic acid and propionic acid can be synthesized from biomass via enzymatic pathways and were used for the synthesis of 5-(acetoxymethyl)furfural (AcMF) and 5-(Propionyloxymethyl)furfural (PrMF) (Eş et al. 2017; La China et al. 2018). Similarly, chemocatalytic deconstruction of biomass gives rise to LA, formic acid, and stearic acid (StA), which can be used for the synthesis of HMF-levulinate, 5-(formyloxymethyl)furfural (FMF), and long-chain fatty esters of HMF (Jahromi et al. 2021; Ma et al. 2021).



Scheme 1.6 Molecular structure of biomass-derived AMFs.

One-pot synthesis of AMFs, such as FMF and AcMF, directly from sugars has been reported (Dutta 2020). The major challenge of synthesizing AMFs directly from carbohydrates is low Brønsted acidity of acetic acid. Many of the acids with strong Brønsted acidity are also nucleophilic in character. The enzyme-catalyzed transesterification of HMF results in the formation of AMF. The esterification of HMF in the presence of carboxylic acid often requires special catalyst or reaction conditions due to the inherent challenges associated with using HMF (Kumar et al. 2018a). Alternatively, it can be synthesized from acid chlorides, acid halides, and anhydride from HMF. Nucleophilic substitution of the chloromethyl group in CMF with the salt of carboxylic acids can lead to AMFs (Bhat et al. 2022).

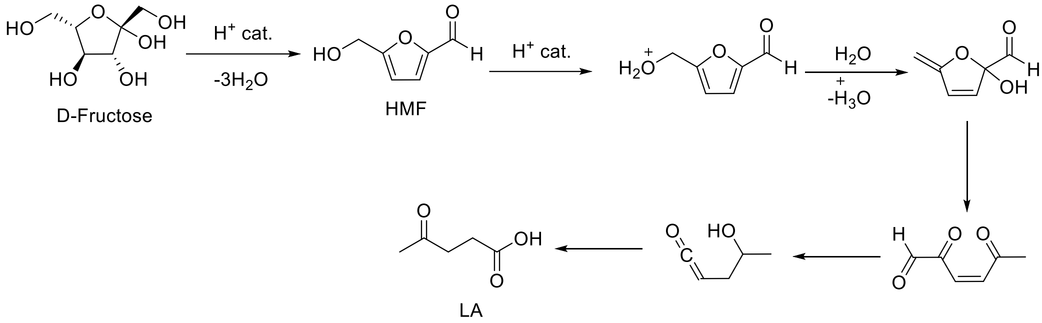


Scheme 1.7 Synthesis of value-added chemicals from AcMF.

AMFs can virtually access all the derivative chemistry of HMF. Due to the straightforward preparation and bulk availability of reagents, AcMF and FMF were studied extensively for synthesizing different classes of renewable chemicals (Scheme 1.7). For example, Friedel-Crafts reaction between AcMF and mesitylene in the presence of a Lewis acid afforded 5-(mesitylmethyl)furfural (MMF) (Shinde and Rode 2018). 2,5-Bis(hydroxymethyl)furan (BHMF) can be synthesized by reducing AcMF in a methanolic suspension of sodium borohydride at room temperature. Furthermore, the Cannizaro reaction of AcMF in a strong base like sodium hydroxide gave 2,5-furandimethanol (FDM) in an aqueous reaction medium. Acid-catalyzed condensation of AcMF with 2-methylfuran has been reported for synthesizing 5,5'-((5-((5-methylfuran-2-yl)methyl)furan-2-yl)methylene)bis(2methylfuran) (MBMF) as a diesel fuel precursor (Kumar et al. 2018a; Shinde et al. 2018).

1.6 LEVULINIC ACID (LA)

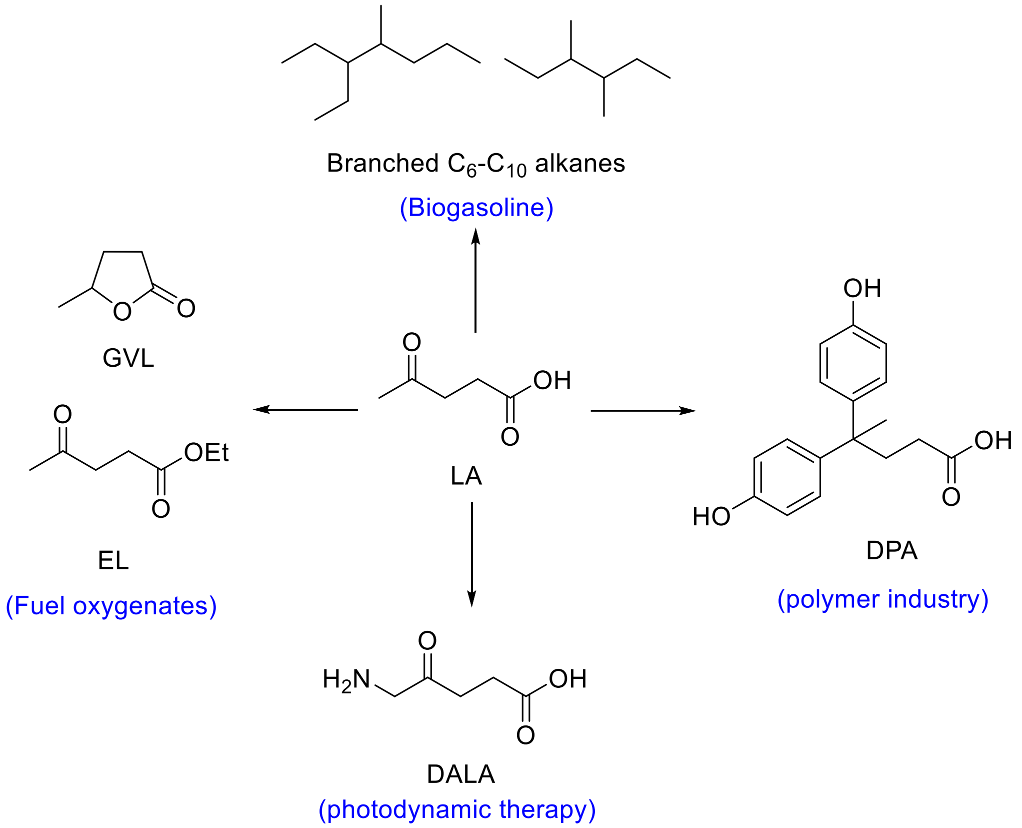
LA is a well-recognized renewable chemical building block in a carbohydrate-based biorefinery setting. LA can be sourced from both the hemicellulose and cellulose fraction of biomass. The rehydration of HMF followed by ring-opening leads to LA and a molecule of formic acid (Scheme 1.8) (Rackemann and Doherty 2011). The hydrolysis of FAL, produced by the partial reduction of FUR, also leads to LA. Von Grote and Tollens reported the first synthesis of LA in 1836 from sucrose using concentrated sulphuric acid. The *Biofine process* is a promising commercial method of preparing LA from cellulosic biomass (e.g., paper sludge). The two-stage process first hydrolyzed cellulose into HMF and hemicellulose into FUR in a plug-flow reactor operating at relatively harsher conditions (210-220 °C, 25 bar) but a short residence time (ca. 20 s) using dilute H_2SO_4 as the catalyst. The back-mix reactor in the second stage converts HMF into LA and formic acid under relatively milder conditions (190 °C, 14 bar), but longer residence time (ca 20 min) (Hayes et al. 2005). Various classes of acid catalysts, including mineral acids, zeolites, ionic liquids, acidic resins, and metal salts have been examined for producing LA from cellulose and hemicellulose fractions following a sequence of hydrolysis and dehydration steps (Pileidis and Titirici 2016).



Scheme 1.8 Synthesis of LA from fructose.

LA is a synthetically versatile compound containing two highly reactive functional groups, i.e., ketone and carboxylic acid. The derivatives of LA are somewhat complementary (straight-chain vs. furanic) to those prepared from HMF and FUR. The esters of LA with short-chain (C1-C4) monohydric alkyl alcohols, such as EL, are promising diesel additives. EL improves the cold-flow properties of biodiesel, increases lubricity of ultra-low-sulfur diesel fuel, and promotes the complete burning of diesel in the internal combustion engine (Bhat et al. 2021). Intramolecular dehydration of LA leads to angelica lactones (a mixture of the α- and β-isomers), renewable intermediates for producing petrol-range branched hydrocarbon fuels and novel monomers. Catalytic hydrogenation and lactonization of LA lead to γ-valerolactone (GVL) (Lima et al. 2018; Martin Alonso et al. 2013). GVL has huge potential markets as a renewable solvent, as feedstock for butenes, for making biorenewable polymers, and for producing other oxygenates such as 2-methyltetrahydrofuran (MTHF). GVL on ring opening, decarboxylation, and oligomerization give long-chain alkanes. DALA, a photodynamic therapy drug and a natural herbicide, can be synthesized in three steps starting from LA

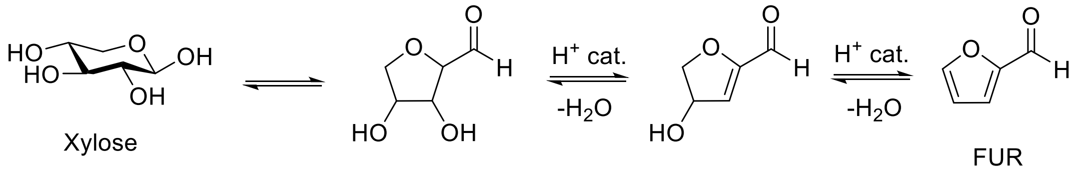
(Zhang et al. 2012). LA or its esters can be reacted with phenol in the presence of a suitable acid catalyst to make 4,4'-diphenolic acid (DPA), a renewable substitute for bisphenol acetone (BPA) in the polymer and resin industry (Scheme 1.9).



Scheme 1.9 Derivatives of LA and their applications.

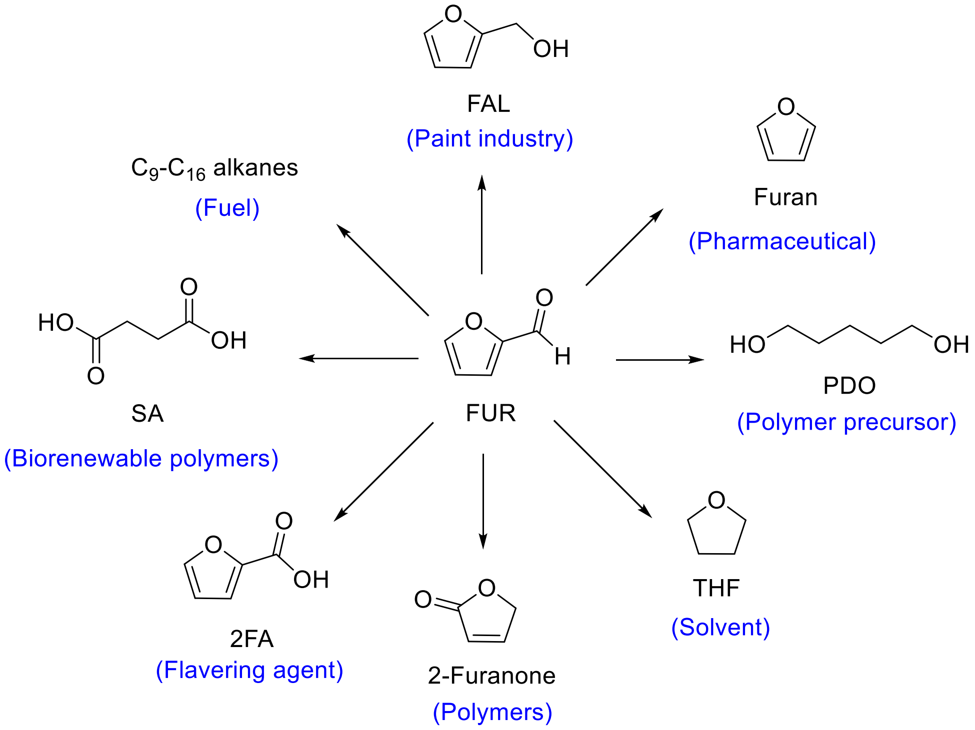
1.7 FURFURAL (FUR)

FUR can be produced from lignocellulosic materials rich in pentosan polymers (e.g., xylan) by acidic degradation. The reaction involves acid-catalyzed hydrolysis of pentosan into pentoses (e.g., xylose) and then successive dehydration to FUR (Scheme 1.10). The commercial utility of FUR was first discovered in 1921 by Quaker Oats at Cedar Rapids, Iowa using H_2SO_4 as a catalyst (Li et al. 2016a; Mariscal et al. 2016). Annual FUR production is estimated at around $2.1x10^5$ tons, and Kane mastu chemicals, China, is the major FUR producer.



Scheme 1.10 The acid-catalyzed dehydration of xylose to FUR.

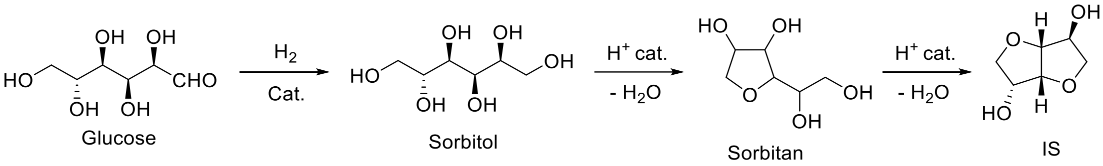
FUR is well known for its thermosetting properties, corrosive resistance, and physical strength, so it has a broad spectrum of applications in non-petroleum-derived chemicals. Catalytic hydrogenation of FUR leads to FAL being used as a chemical intermediate in the paint industry (Villaverde et al. 2013). FAL on ring-opening results in the formation of levulinate, a class of products with potential industrial applications. Selective oxidation of FUR forms 2FA, a flavoring agent and a starting material for various pharmaceuticals (Papanikolaou et al. 2021). The ring oxidation of FUR leads to 2-furanone, which gets further oxidized into maleic acid (MA) and succinic acid (SA) (Li et al. 2016b). The decarbonylation of FUR gives furan, which is a known reagent and a chemical intermediate for organic synthesis (Ishida et al. 2016). A multistep reaction of FUR via reduction, alkylation, and hydrogenation gives rise to C9 to C16 alkanes, which can be used as diesel-like fuel. The decarbonylation and ring-hydrogenation of FUR give tetrahydrofuran (THF) (Lange and Wadman 2020). FUR can also be selectively converted into 1,5-pentanediol (PDO), a precursor to polyurethanes and polyesters (Scheme 1.11) (Fu et al. 2021).



Scheme 1.11 Some commercially-relevant derivatives of FUR.

1.8 ISOHEXIDES

Glucose is an inexpensive and abundant sugar and monomeric unit of cellulose. Glucose can be transformed into D-sorbitol under catalytic hydrogenation conditions. The acid-promoted double dehydration of sorbitol forms 1,4:3,6-dianhydro-D-sorbitol, familiarly known as isosorbide (IS) (Scheme 1.12). Various homogeneous and heterogeneous acid catalysts have been examined for the dehydration reaction. With high thermal and chemical stability, IS has been identified as a diol-based renewable monomer for various high-volume polymers such as polyesters, polycarbonates, and polyurethanes. They are also used for the preparation of novel surfactants and plasticizers (Dussenne et al. 2017; Kadraoui et al. 2015; Rose and Palkovits 2012).



Scheme 1.12 Schematic of the formation of IS from glucose.

Similarly, isomannide (IM) and isoidide (II), the stereoisomers of IS, can be sourced from mannose and idose, respectively. The three isomers are collectively called isohexides (Figure 1.5). The two -OH groups in IS are in the *exo* and *endo* geometry. The spatial geometry of the hydroxyl groups modulates their reactivity, and they can be selectivity derivatized. In this regard, the *exo, exo* geometry of the two –OH groups in II makes it a better monomer for high molecular weight polymers with superior physicochemical properties than those obtained from IS. Interestingly, the inexpensive IS can be isomerized into the other two more expensive isomers under catalytic hydrogenation conditions (Gross et al. 2014; Saska et al. 2021).

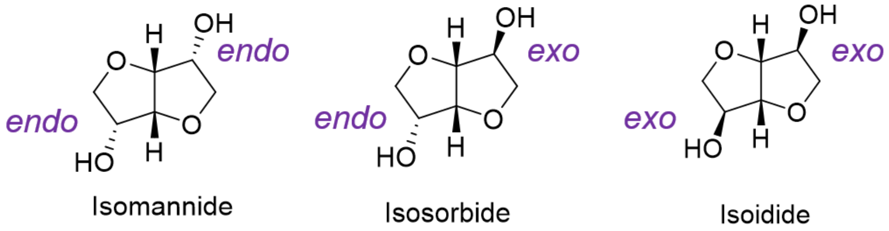
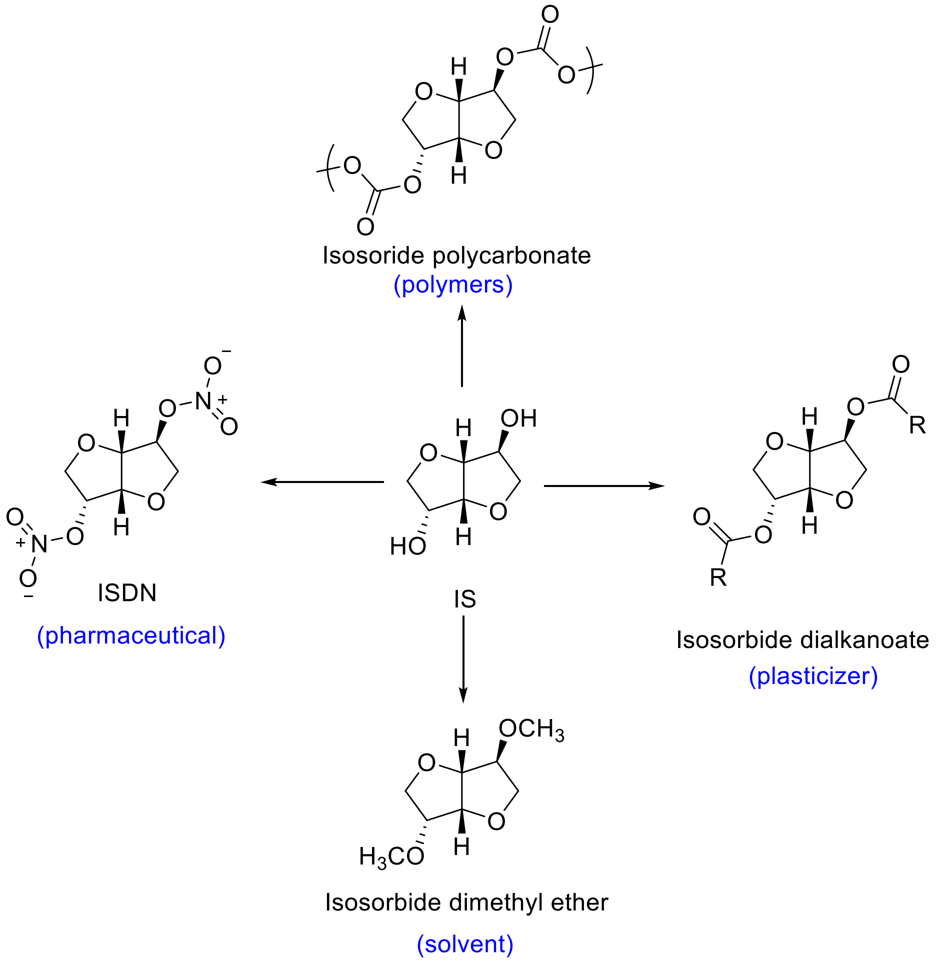


Figure 1.5 The structure of biomass-derived isohexides.

Direct preparation of IS from cellulose via a catalytic route has also been developed. Therefore, the derivative chemistry of IS is most explored among the three isohexides. A new generation of renewable polymers is being developed by several companies worldwide, such as isosorbide polycarbonate. The dimethyl ether of IS is a potential green solvent in the cosmetic industry (Wilson et al. 2018). For example, ISDN is a well-known medication for heart ailments. IS has huge potential markets as a diol-based monomer for synthesizing various high-volume polymers, including polycarbonates, polyesters, and polyurethanes. The diesters of IS have potential application as a plasticizer. ISDN is a drug to dilate blood vessels and helps prevent heart attack (Scheme 1.13). IS can also be used as a comonomer in existing polymers like polyethylene terephthalate providing superior properties. IS has been used as a renewable building block for surfactants and plasticizers with promising properties. The mono- and diesters of IS have potential applications as renewable solvents, plasticizers, and surfactants. For example, isosorbide-2,5-diacetate (ISDA) can be synthesized by acid-catalyzed esterification or by reacting with acidic anhydride or chloride, a biorenewable plasticizer (Inayat et al. 2018).



Scheme 1.13 Some derivatives of IS and their potential applications.

CHAPTER 2

LITERATURE REVIEW, SCOPE, AND OBJECTIVES OF THE WORK

2.1 LITERATURE REVIEW

There are recent high-profile reviews and research articles on the production and synthetic upgrading of biomass-derived chemical building blocks such as furfural (FUR), 5-(chloromethyl)furfural (CMF), 5-(hydroxymethyl)furfural (HMF), isosorbide (IS), 5-(acetoxymethyl)furfural (AcMF), and levulinic acid (LA). This chapter attempts to summarize the existing processes, opportunities, and challenges in this research area.

2.1.1 Literature review of the production of furanic and LA from carbohydrates by acid-catalyzed dehydration

Sustainable organic synthesis is an astonishingly growing field, which routinely involves the use of catalysts for various transformations. HMF, LA, and FUR, the dehydration products of hexose and pentose sugars like glucose, fructose, and xylose, is one of the most promising chemical platforms of renewable nature. Although the first synthesis was reported more than a century ago, it has received renewed interest during the last two decades as a biomass-derived chemical platform molecule. This section discussed a few important published review articles on the synthesis of renewable platforms and their downstream applications. Also, tabulated representative literature published since 2005 (Table 2.1).

Yan et al. published a review on the production and catalytic upgrading of LA into fuels and specialty chemicals (Yan et al. 2015). The review discussed the mechanistic pathways and current technologies available for producing LA. The production of LA was attempted using different homogeneous and heterogeneous catalysts starting from isolated carbohydrates and raw biomass. In general, homogeneous mineral acid catalysts provide better yields of LA under milder conditions when compared to heterogeneous catalysts. LA was converted into diphenolic acid (DPA), a promising alternative to bisphenol, by reacting with phenol under acid catalysis. Recent developments in the preparation of 5-aminolevulinic acid (DALA) from LA was also described. The preparation of γ-valerolactone (GVL), 2-methyltetrahydrofuran (MTHF), and levulinate esters (LEs) were discussed. The review concluded that regardless of significant breakthroughs in the preparation of LA over the past decades, the isolation of LA and recovery of the acid catalyst remain challenging. The development of robust, inexpensive, and preferably heterogeneous catalysts is warranted for the commercial production of LA.

Li et al. published a review on the recent advances in the production of FUR by heterogeneous acid-catalyzed dehydration of pentosans and converting FUR into C4 and C5 value-added chemicals (Li et al. 2016a). The C5 chemicals were synthesized without a carbon-carbon bond scission reaction, such as the synthesis of furfuryl alcohol (FAL) by the selective catalytic hydrogenation of FUR. Alternatively, the carbon-carbon bond breakage reaction during catalytic reduction or oxidation led to chemicals such as furan and maleic anhydride. In the gas-phase reaction, Cu, Ni, Pd, and Pt-based catalysts afforded >70% yield of 2-furoic acid (2FA) using O_2 as the terminal oxidant. In the liquid phase oxidation, 2FA was obtained in yields as high as 90%. Tetrahydrofurfuryl alcohol was produced by hydrogenation of FUR using Pd, Ni, and Ru-based catalysts. FUR was catalytically converted to GVL in excellent yield by using an Au-ZrO_2 catalyst combined with ZSM-5. The review highlighted the requirement of stable, selective, and inexpensive catalysts for the preparation and derivative chemistries of FUR.

Mascal published a mini-review on the production of CMF from biomass-derived carbohydrates and even untreated biomass within an aqueous-organic biphasic reaction (Mascal 2019). The review discussed the reactor design, the handling and recovery of HCl, and isolating CMF from the biphasic reaction medium. CMF can be produced in high isolated yield (70-80%) by treating various carbohydrates and even untreated cellulosic biomass within a concentrated HCl (35%)-1,2-dichloroethane (DCE) biphasic reaction medium. The batch and continuous processes for CMF production were compared and analyzed. The review explained the advantage of producing CMF over HMF owing to the hydrophobic character and better stability (e.g., thermal, storage) of the former. The review also elaborated on the derivative chemistries of CMF. CMF could be converted to both HMF and LA by aqueous hydrolysis and could potentially participate in all derivative chemistries of HMF. CMF has been selectively converted into 5-(ethoxymethyl)furfural (EMF), a promising fuel oxygenate. CMF was also converted into 2,5-dimethylfuran (DMF), a gasoline-additive and chemical feedstock for the synthesis of terephthalate polymers. CMF was also selectively oxidized into renewable monomers such as 2,5-diformylfuran (DFF) and 2,5-furandicarboxylic acid (FDCA). The synthesis of agrochemicals like DALA and furan-based pyrethroids like prothrin were synthesized from CMF. CMF was also converted into ranitidine, an anti-ulcer drug, in four efficient steps.

Shen et al. in 2020 reviewed the synthesis of FUR and HMF, two pivotal biorenewable chemical intermediates (Shen et al. 2020). The authors highlighted the challenges during the synthesis of FUR and HMF in terms of feedstock availability, solvent choice, and the use of suitable acid catalyst. Furthermore, the review focused on the synthesis of fine chemicals and green solvents from FUR and oxidation/reduction chemistries of HMF for synthesizing biorenewable monomers.

Table 2.1 Representative table of acid-catalyzed dehydration of carbohydrates into FUR, CMF, and LA

Feedstock	**Reaction Conditions**	**Yield (%)**	**Reference**
(A) Synthesis of FUR from pentose sugars			
Xylose	150 °C, 2 h, Nafion 117, DMSO	60	(Lam et al. 2011)
Xylose	140 °C, 45 min, $AlCl_3·6H_2O$, water-THF, NaCl, MW	75	(Yang et al. 2012)
Xylose	170 °C, 12 min, aq. HCl, water-DMSO/DCM (1/1 v/v)	69	Chheda 2007
Xylan	170 °C, 25 min, water-DMSO/DCM (1/1 v/v)	66	
Xylose	145 °C, 2 h, aq. HCl (0.1 M), $CrCl_3·6H_2O$ (6 mM), water/toluene (1/1 v/v)	76.4	(Choudhary et al. 2012)
Xylan	150 °C, 2 h, $SnCl_4·5H_2O$, water/MTHF (5/2 v/v)	78.1	(Wang et al. 2015)
Xylose	120 °C, 3 h, Nb_2O_5, water/toluene (2/3 v/v)	71.2	(Gupta et al. 2017)

Jute	170 °C, 3 h, BAIL, water/toluene (1/5 v/v)	82	(Matsagar et al. 2017)
Corncob	170 °C, 30 min, aq. HCl, SO_4^{2-}/SnO_2-diatomic	40.1	(Jiang et al. 2018)
Xylose	130 °C, 1 h, $SnCl_4$, EMIMBr	71.1	(Nie et al. 2019)
Xylan	190 °C, 1.5 h, GO-SO_3H, water	86	(Upare et al. 2019)
Xylose	170 °C, 3.5 h, FAS, water-toluene (1/1.5 v/v)	68	(Chatterjee et al. 2019)
(B) Synthesis of CMF from carbohydrates			
Cellulose	100 °C, 3 h (extraction after each hour), aq. HCl/DCM (1/2 v/v)	78.2	(Mascal and Nikitin 2009)
Fructose	45 °C, 20 h, aq. HCl-H_3PO_4/$CHCl_3$ (4/1/5 v/v)	47	(Gao et al. 2013)
Bagasse Pulp	45 °C, 10 h, aq. HCl/ $CHCl_3$ (1/3 v/v)	50.1	(Fusheng et al. 2015)
Bagasse	100 °C, 3 h (extraction after each hour), aq. HCl/DCE (1/2 v/v)	74.1	(Howard et al. 2016)
Glucose	79-83 °C, 30 min, aq. HCl	1.5*	(Lane et al. 2016)
Fructose	100 °C, 1.5 min, aq. HCl/DCE (1/1 v/v), continuous flow reactor	74	(Kohl et al. 2017)
Sucrose	90 °C, 3 h, BTBAC, aq. HCl/DCE (1/2 v/v)	72	(Onkarappa and Dutta 2019)
(C) Synthesis of LA from carbohydrates			
Cellulose	180 °C, 2 h, $CrCl_3$, water	67	(Peng et al. 2010)
Cellulose	155 °C, 1.5 h, aq. HCl/GVL (1/1 v/v), NaCl	72	(Wettstein et al. 2012a)
Cellulose	140 °C, 3 h, $ChH_4AlW_{12}O_{40}$, MIBK/water (10/1 v/v)	74.8	(Sun et al. 2016)

Fructose	140 °C, 30 min, A15, water	58.9	(Acharjee and Lee 2018)
Cellulose	200 °C, 3 h, aq. HCl-water/DCM (1/5 v/v)	38	(Kumar et al. 2018b)
Glucose	150 °C, 9 h, Lys-PM$_2$, water	57.9	(Qu et al. 2019)
Cellobiose	180 °C, 10 h, [HO$_3$S-(CH$_2$)$_3$-mim]Cl-FeCl$_3$, water	67.5	(Liu et al. 2019)
Cellulose	185 °C, 2 h, lignin-based catalyst, water/GVL (1/10 v/v)	35.6	(Han et al. 2019)
Glucose	120 °C, 3 h, BTBAC, aq. HCl	80	(Onkarappa et al. 2019)

Abbreviations: DMSO: Dimethyl sulfoxide; DCM: Dichloromethane; DCE: Dichloroethane; BTBAC: Benzyltributylammonium chloride; FAS: Sulphuric acid treated fly ash; GVL: γ-Valerolactone; EMIMBr: 1-Ethyl-3-methylimidazolium bromide; THF: Tetrahydrofuran; BAIL: 1-Methyl-3(3-sulfopropyl)-imidazolium hydrogen sulfate; GO: Graphene oxide; A15: Amberlyst 15; Lys-PM$_2$: Lysine functionalized phosphotungstic acid; MW: Microwave. * mmol glucose/mL.

There are thousands of research articles and reviews available on the synthesis of FUR, LA, and CMF. Over the past few years, remarkable improvements have been made in this area for the production of platform chemicals from inexpensive carbohydrates and untreated biomass. Most of the attempts in producing platform chemicals used simple monomeric carbohydrates as the feedstock and generally achieved good to excellent yields depending on the catalyst used. However, satisfactory yields often require special reaction conditions to be employed. In this regard, the synthesis and coproduction of FUR, CMF, and LA would play a pivotal role in the development of biorefinery.

2.1.2 Literature review of the synthesis of 5-(acyloxymethyl)furfurals (AMFs)

The synthesis of 5-(acyloxymethyl)furfural (AMFs) from HMF, CMF, or directly from carbohydrates with carboxylic acid under suitable catalysts is known in the literature. The major limitations associated with the production of AMFs is the low Brønsted activity of the carboxylic acid, which enables to shift the reaction kinetics toward the product. In this regard, the use of suitable catalysts will make the process kinetics fast and selective. Although several literatures are available for the synthesis of AMFs starting from purified HMF and CMF. The process required intermediate extraction and purification. However, for evident reasons, one-pot synthesis of AMFs directly from carbohydrates is more desirable. The following section provides a brief discussion about the existing process and challenges of synthesis of AMFs.

Table 2.2 Literature reports of the synthesis of AMFs from HMF, CMF, and carbohydrates

Feedstock	**Reaction Conditions**	**Product**	**Yield (%)**	**Reference**
Fructose	sc. AcOH (excess), 20 MPa, H_2SO_4	AcMF	37	(Bicker et al. 2005)
CMF	RT, overnight, K_2CO_3 (1.08 eq.), AcOH (1.08 eq.), DMF	AcMF	70	(Dai et al. 2011)
HMF	RT, 24 h, immo-CAL-B (10 mg/L), ethyl acetate (150 mM)	AcMF	90	(Krystof et al. 2013)
	40 °C, 24 h, immo-CAL-B (10 mg/L), PrOH, *tert*-butanol	PrMF	91	
CMF	RT, 10 min, TBAA (1.1 eq.), acetonitrile	AcMF	96	(Kang et al. 2015)
BM Chitin	80 °C, 168 h, formic acid (excess)	FMF	35	(Zhang and Yan 2016)
Fructose	150 °C, 2.5 h, formic acid (excess), NaBr (5 mmol)	FMF	33.2	(Jiang et al. 2016)
HMF	40 °C, LA (24.5 eq.), Novozym 435 (10 mg/L), MS (0.1 g), MTHF (1 mL)	LeMF	92*	(Qin et al. 2016)

HMF	0 °C-RT, 30 min and 15 h, acetic anhydride (2 eq.), acetonitrile (2 mL), pyridine (1 eq.)	AcMF	62	(Xu et al. 2017)
Cellulose acetate	200 °C, 2 h, H_2SO_4 (2 eq.), AcOH (excess)	AcMF	36.4	(Gavilà and Esposito 2017)
HMF	105 °C, 5 h, LA (5 eq.), [SMIM][$FeCl_4$] (0.15 g), MS (0.15 g)	LeMF	78.1	(Kumar et al. 2018a)
		PrMF	77	
Fructose	150 °C, 3 h, Sn-Mont(0.3 M) (0.2 g), AcOH (excess)	AcMF	55	(Shinde et al. 2018)
Glucose			43	
Fructose	140 °C, 2 h, formic acid (excess)	FMF	43.8	(Xiong et al. 2018)
Fructose	80 °C, 8 h, formic acid (20 mL, 85%), HBr (160 mol%), DCE	FMF	68	(Dutta 2020)
HMF	30 °C, 10 min, isopropenyl acetate (1.5 eq.), Cs_2CO_3 (70 mol%)	AcMF	98	(Rigo et al. 2021)
CMF	80 °C, 1.5 h, TEAA (1.5 eq.)	AcMF	90	(Bhat et al. 2022)

Abbreviations: DMF: Dimethylformamide; TBAA: Tetrabutylammonium acetate; DCE: Dichloroethane; RT: Room temperature; BM: Ball-milled; AcOH: Acetic acid; PrOH: Propionic acid; MTHF: Methyltetrahydrofuran; MS: Molecular sieve; LA: Levulinic acid, THF: Tetrahydrofuran; TEAA: Triethylammonium acetate; AcMF: 5-(Acetoxymethyl)furfural; FMF: 5-(Formyloxymethyl)furfural; PrMF: 5-(Propionyloxymethyl)furfural; LeMF: HMF-levulinate. * Conversion.

Recently, we reported the synthesis of AMFs starting from CMF using slightly excess triethylammonium carboxylates under solvent-free conditions (Bhat et al. 2022).

Under optimized conditions (80 °C, 1.5 h), more than 85% of AMFs are isolated under solvent-free conditions, and the reaction was scaled up to 5 g.

Rigo et al. reported the synthesis of 5-(acetoxymethyl)furfural (AcMF) starting from HMF by using base-catalyzed acetylation reaction in the presence of isopropenyl acetate (Rigo et al. 2021). They studied the catalytic activity of different acid and base catalysts like amberlyst 15 (A15), hydrotalcite, sulphuric acid, acetic acid, potassium carbonate, sodium carbonate, and cesium carbonate. Among all the catalysts, cesium carbonate gave a maximum yield of 98% at 30 °C for 2 h.

Dutta reported the direct synthesis of 5-(formyloxymethyl)furfural (FMF) from carbohydrates in the presence of an aqueous-organic biphasic system using a mixture of formic acid and a Brønsted acid catalyst (Dutta 2020). The use of HBr as a strong Brønsted acid catalyst in combination with formic acid gave the best yield of FMF starting from fructose at 80 °C for 8 h in the presence of DCE as an organic extract. The use of other feedstocks like glucose, sucrose, and starch gave 52%, 58%, and 10% of FMF, respectively. Furthermore, the derivative chemistries of FMF were tried, and synthesized value-added molecules like 5-methylfurfural (5MF), HMF, DFF, and FDCA starting from FMF.

Xiong et al. reported the synthesis of FMF from fructose using pure formic acid or by two-step method via HMF intermediate in the presence of choline chloride/fructose deep eutectic solvents system (Xiong et al. 2018). The FMF yield reached up to 63% using a two-step approach, whereas pure formic acid afforded only 43% of FMF starting from fructose.

Jiang et al. reported the one-pot synthesis of FMF from cellulose in the presence of formic acid and alkali metal chloride (Jiang et al. 2016). The use of different metal chlorides like NaCl, LiBr, and KBr gave 19.8%, 28.1%, and 30% of FMF, respectively starting from cellulose. They concluded that bromine ions would facilitate the reaction in the presence of formic acid. Under optimized conditions (150 °C, 2.5 h), the isolated yield of FMF was 33.2% and 28.1% from fructose and pulp, respectively.

In 2017, the synthesis of AcMF was attempted starting from cellulose acetate in acetic acid in the presence or absence of additional homogeneous catalysts. Scandium triflate, hydrochloric acid, hydrogen bromide, and sulphuric acid afforded 13%, 19%, 9%, and 36% of AcMF, respectively at 200 °C for 2 h. Furthermore, to evaluate the real biomass scenario, the reaction was carried out using acetylated organocat pulp and crude beech wood and isolated 47% and 37% of AcMF, respectively (Gavilà and Esposito 2017).

A series of different bifunctional ionic liquids (ILs) are synthesized, characterized, and used for the catalytic conversion of HMF to HMF-levulinate in the presence of LA. Among the synthesized catalysts, [SMIM][$FeCl_4$] gave a maximum yield of 78.1% using a 5:1 molar ratio of LA and HMF at 105 °C for 5 h in the presence of molecular sieves (4 Å). The synthesized ILs showed good catalytic activity due to the synergistic effect of Lewis and Brønsted acidic sites. Furthermore, the conversion of different biomass-derived acids to HMF-esters was reported using this protocol. The use of lactic acid, propionic acid, acetic acid, and formic acid afforded 53%, 77%, 73%, and 68% yield of the corresponding HMF-ester, respectively (Kumar et al. 2018a).

In the same year, Shinde et al. reported the synthesis of AcMF directly from biomass-derived carbohydrates using Sn-Mont catalyst. The presence of Lewis and Brønsted acidic nature of Sn-Mont catalyst facilitate the isomerization of glucose to fructose and dehydration of fructose to AcMF in the presence of acetic acid. Initially, the heterogeneous catalysts were synthesized by mixing different molar concentrations of $SnCl_4.5H_2O$ with montmorillonite. The use of synthesized catalyst afforded 43%, 53%, and 58% of AcMF starting from glucose, sucrose, and fructose, respectively in the presence of acetic acid. Furthermore, AcMF was transformed into different value-added molecules using different catalytic transformations (Shinde et al. 2018).

Kang et al. reported the conversion of CMF into AcMF by using alkylammonium acetate (Kang et al. 2015). The reactivity pattern of alkylammonium acetate was studied using different alkyl substitutions. The use of tetrabutylammonium acetate afforded 96% of AcMF from CMF in the presence of acetonitrile as a solvent at room temperature in 10 min of reaction time. The good reactivity of salts was attributed due to the ability of the alkylammonium salts to act as a phase transfer catalyst (PTC). Furthermore, the effect of solvent on the reaction was studied, and the presence of chlorinated solvents like dichloromethane (DCM) and DCE afforded 86% and 85% of AcMF, respectively. The use of heterogeneous catalysts like polymer-supported alkylammonium acetates afforded 90% of AcMF at a slightly higher temperature (50 °C) for a longer reaction time (12 h).

2.1.3 Literature review of 2-furanone from FUR

The first attempt of the synthesis of 2(5H)-furanone (2FN) from FUR was reported in 1996. Cao research group reported the H_2O_2-mediated selective oxidation of FUR under reflux conditions (Cao et al. 1996). They isolated 37% of 2FN and 18% of 3(2H)-furanone from FUR. Furthermore, Grunskaya and Poskonin attempted selective synthesis using different metal salts like sodium molybdate, niobium acetate, sodium vanadate, niobium oxide, and sodium dichromate. They isolated 22-64% of 2FN from H_2O_2 and metal salt mediated reaction (Grunskaya et al. 1998; Poskonin et al. 1999; Poskonin 2009; Badovskaya and Poskonin 2015).

Table 2.3 The synthesis of 2FN from FUR using homogeneous and heterogeneous catalysts

Substrate	Reaction Conditions	Yield (%)	Reference
FUR	(i) 60-70 °C, 2 h, DCM, Na_2SO_4, H_2O_2 (ii) Reflux, 10 h	37	(Cao et al. 1996)
FUR	60 °C, 2 h, H_2O_2, Na_2MoO_4	33	(Grunskaya et al. 1998)
FUR	60 °C, 3.5 days, water, H_2O_2, $Nb(OAc)_2{\cdot}4H_2O$	64	(Poskonin 2009)
FUR	60 °C, 3 h, DCM/water (10/1.5 v/v), Na_2SO_4, H_2O_2, formic acid (88%)	62	(Li et al. 2016b)
FUR	70 °C, 1 h, water, H_2O_2, $Mg(OH)_2$	44.8	(Xiang et al. 2016)
FUR	60 °C, 14 h, H_2O_2, 1-(butylsulfonic)-3-methylimidazolium chloride	68	(Amarasekara and Okorie 2018)

FUR	60 °C, 24 h, water, H_2O_2, acetic acid	71	(Zvarych et al. 2019)

Abbreviations: DCM: Dichloromethane.

Li et al. reported the formic acid-mediated selective oxidation of FUR to 2FN, maleic acid (MA), and succinic acid (SA) using an aqueous/organic biphasic reaction medium in the presence of H_2O_2 (Li et al. 2016b). The oxidation reaction was first attempted using bi- and monophasic systems in the presence of DCM and methanol, respectively as a solvent using different mineral acids. Under optimized reaction conditions (60 °C, 3 h), 62.3% of 2FN was obtained with 96.9% of FUR conversion.

The oxidation of FUR in H_2O_2 and $Mg(OH)_2$ system to 2FN was reported (Xiang et al. 2016). They studied the detailed catalytic pathways for the oxidation of FUR with H_2O_2 and H_2O_2-$Mg(OH)_2$ and showed that the addition of $Mg(OH)_2$ supressed the furan ring oxidation and improved the 2FN selectivity.

Amarasekara and Okorie reported 1-(alkylsulfonic)-3-methylimidazolium chloride catalyzed H_2O_2 oxidation of biomass-derived furan aldehyde (Amarasekara and Okorie 2018). They synthesized 1-(propylsulfonic)-3-methylimidazolium chloride and 1-(butylsulfonic)-3-methylimidazolium chloride acidic IL. Among two synthesized catalysts, 1-(propylsulfonic)-3-methylimidazolium chloride afforded 92% of succinic anhydride. Whereas, 1-(butylsulfonic)-3-methylimidazolium chloride afforded 68% of 2FN under optimized conditions (60 °C, 14 h) in the presence of H_2O_2. The ILs are recycled and reused for four consecutive cycles without loss of their activity.

The acetic acid promoted selective oxidation of FUR to 2FN in the presence of H_2O_2 as an oxidant was reported (Zvarych et al. 2019). The use of catalytic amount of acetic acid resulted excellent yield of 2FN (71%) at 60 °C for 24 h.

2.1.4 Literature review of esterification and transesterification of biomass-derived intermediates

Several homogeneous and heterogeneous catalysts are explored for the esterification and transesterification of biomass-derived intermediates. Generally, the reaction was carried out at elevated temperatures in the presence of alcohol/carboxylic acid using suitable catalysts for esterification reaction. Whereas, in case of transesterification, alcohol and suitable ester is used to synthesis the targeted ester.

Many researchers attempted the synthesis of esters from biomass-derived intermediates and these works have been reviewed periodically.

We recently reviewed the synthesis of alkyl levulinates (ALs) from biomass-derived carbohydrates using polyoxometalate based catalysts (Bhat et al. 2021). In this review article, we elaborated the accomplishments of polyoxometalate-catalyzed preparation of LEs to date starting from various renewable feedstock, highlighted the challenges encountered in this field, and proposed future directives.

Liu et al. elaborated the recent advances on synthesizing ALs from LA, FAL, CMF, and carbohydrates. The review focused on biomass pretreatment, nature of acid catalysts employed, and mechanistic details (Liu et al. 2020). Furthermore, this review also elaborated the wide range of potential intermediates like ethoxymethylfuran, 4,5,5-triethoxy-2-pentanone, ethyl-D-fructofuranoside, and ethyl-D-glucopyranoside.

Badgujar et al. in 2020 reviewed the catalytic synthesis of ethyl levulinate (EL) from LA and investigated the role of acid-functionalized catalyst (Badgujar et al. 2020). In that review, the authors analyzed the potential markets of EL. They also elaborated on producing ALs from chemical intermediates like LA, FAL, FUR, and also directly from carbohydrates under acid catalysis. Furthermore, they explored the impacts of catalyst, different solvent, reaction temperature, stirring speed, and substrate on AL synthesis. The mechanistic pathways for producing ALs were also detailed.

In 2018, Tiong et al. reviewed the synthesis of ALs from FAL and LA using IL-based catalysts (Tiong et al. 2018a). They elaborated the biomass pretreatment and synthesis of LA and LEs using IL as both catalyst and solvents. They represented the comparative studies of ALs synthesis using different ILs and overview of current catalytic status and challenges associated with product purification and catalyst recyclability.

Hoydonckx et al. (2014) reviewed the transesterification and esterification of renewable chemicals (Hoydonckx et al. 2004). They elaborated the homogeneous and heterogeneous catalysts used for esterification and transesterification. Also, the catalysts used for renewable feedstock like biodiesel, fatty acids and esters, sugar esters, and FAL conversion.

The following table lists the representative journal publications on catalytic esterification and transesterification of biomass-derived intermediates.

Table 2.4 The representative literature reports of the synthesis of alkyl esters of biorenewable intermediates via esterification and transesterification

Substrate	Catalyst	Reaction Conditions	Product	Yield (%)	Reference
LA	A15 (2.5 wt.%)	70 °C, 5 h, LA/ethanol (1:5)	EL	55	(Fernandes et al. 2012)
LA	Pr-SO_3H-SBA-15 (7 wt.%)	100 °C, 2 h, LA/ethanol (1:5)	EL	99.1	(Melero et al. 2013)
LA	SiO_2-ZrO_2 (5 wt.%)	70 °C, 10 h, LA/ethanol (1:10)	EL	65.6*	(Kuwahara et al. 2014)
LA	UiO-66-NH_2 (1.8 wt.%)	120 °C, 5 h, LA/butanol (1:6)	BL	99	(Cirujano et al. 2015)
LA	$SnCl_4$ (20 mol%)	110 °C, 10 min, methanol (excess), 400 W (MW)	ML	96.8	(Huang et al. 2016)
LA	Al-MCM-41 (1 wt.%)	120 °C, 8 h, LA/ethanol (1:5)	BL	90	(Najafi Chermahini and Nazeri 2017)
			IPL	89	
LA	SAFBPIL (15 wt.%)	70 °C, 9 h, LA/ethanol (1:10)	EL	99	(Khiratkar et al. 2018)
LA	$HClO_4/SiO_2$ (10 wt.%)	100 °C, 2 h, ethanol (excess)	EL	100	(Yang and Tang 2019)
FAL	$AlCl_3$ (21 mol%)	123 °C, 162 min, ethanol (excess)	EL	95.7	(Peng et al. 2015)

FAL	[MIMBS] $[AlW_{12}O_{40}]$ (5 mol%)	120 °C, 6 h, butanol (excess)	BL	94	(Hao et al. 2017)
FAL	H-ZSM-5-50 (0.2 g)	170 °C, methanol (excess), continuous flow reactor	ML	80	(Zhao et al. 2018)
FAL	Al/DFNS/Pr-SO_3H (~14 wt.%)	130 °C, 3 h, butanol (excess)	HL	93.5	(Mohammadbagheri and Najafi Chermahini 2019)
StA	A-SZr (6 wt.%)	60 °C, 7 h, SA/methanol (1:20)	MeS	88	(Saravanan et al. 2016)
OA	FCHC-SO_3H (4 wt.%)	80 °C, 3 h, OAA/methanol (1:1.5)	MeO	96.7	(Wang et al. 2018)
BA	UiO-66$(COOH)_2$ (5 wt.%)	110 °C, 24 h, BA/methanol (1:1.5)	MB	95*	(Jrad et al. 2019)
StA	ZrO_2/SiO_2 (10 wt.%)	120 °C, 3 h, ethanol (excess)	ES	76.9*	(Mahmoud et al. 2020)
2FA	ZrPEGTPA00$_{T100}$ (~166 wt.%)	140 °C, 24 h, 2FA/butanol (1:33)	BF	95*	(Escobar et al. 2015)
2FA	$K_{12.5}Na_{1.5}(NaP_5W_{30}O_{110})15H_2O$ (~42.3 wt.%)	125 °C, 10 h, 2FA/butanol (1:2)	BF	93	(Escobar et al. 2019)

IS	pTSA (1 mol%)	reflux, 24 h, acetic acid (excess)	ISDA	80	(Fraile and Saavedra 2017)
IS	A15 (5 wt.%)	111 °C, 24 h, Acetic acid (excess), toluene	ISDA	90	(Inayat et al. 2018)
IS	$ZnCl_2$ (1.23 eq.)	40 °C, overnight, IS/acrylic acid (1.5/1.0 eq.)	ISMAr	17	(Nonque et al. 2020)
IS	$Sc(OTf)_3$ (0.02 wt.%)	RT, 4 h, IS/methacrylic anhydride (1.5/1.0 eq.)	ISMAr	32	(Nonque et al. 2021)
IS	K_2CO_3 (70 mol%)	159 °C, 15 min, DMF (2 mL), Bu_4NBr (4 wt.%), IS/methyl laurate (1.0/2.0 eq.), MW (20 W)	*Exo*-ISMLu	38	(Limousin et al. 1998)
			Endo-ISMLu	25	
Cottonseed oil	1-(4-sulfonic acid)butylpyridinium hydrogen sulfate	170 °C, 6 h, oil/methanol (1/12)	Methyl ester	92	(Wu et al. 2007)

Abbreviations: SAFBPIL: Sulphonic acid-functionalized benzimidazolium poly ionic liquid; A15: Amberlyst 15; MW: Microwave; DFNS: Dendritic fibrous nanosilica; A-SZr: Aerogel sulfonated zirconia; FCHC-SO_3H: Fe_3O_4@CS-HW-CS-SO_3H (magnetic acid catalyst); DMF: Dimethylformamide; Bu_4NBr: Tetrabutylammonium bromide; StA: Stearic acid; OA: Oleic acid; BA: Butyric acid. * Conversion.

Several homogeneous and heterogeneous catalysts were reported for the synthesis of esters from biorenewable intermediates under operationally simple and elegant reaction procedure. Both commercial and synthesized catalysts have been studied and proved as a good catalyst. The esters of 2FA, LA, and IS were typically synthesized by Fischer esterification protocol by using conventional or microwave heating. Fatty acid esters were produced by the base-catalyzed transesterification of triglyceride or acid-catalyzed esterification of free fatty acids (FAAs). The main challenges associated with the synthesis of esters are scalability, process economics, and purification of intermediates.

2.1.5 Literature review of the synthesis of 3,4-Dihydropyrimidin-2-(*1H*)-ones (DHPMs) and 1,4-dihydropyridines (DHPs)

DHPMs and DHPs are well-known heterocyclic compounds that have promising biological activities. So, there are numerous research articles and reviews present in the literature, which showed the high-yielding synthesis of DHPMs and DHPs. The following section elaborated the synthesis of DHPMs and DHPs from biorenewable furfurals.

The Preyssler heteropoly acid encapsulated on silica framework was reported for the three-component Biginelli reaction starting with biorenewable furfurals. Initially, the reaction was carried out using Preyssler heteropoly acid, silica, and supported catalyst. The use of supported Preyssler under solvent-free condition afforded a maximum 82% yield of DHPM at 80 °C. They studied the effect of reaction temperature, time, molar ratio of reactant, and catalyst amount on the product yield. Finally, they extended the synthetic protocol to the synthesis of DHPMs from HMF and 5MF (Portilla-Zuñiga et al. 2018).

In 2018, Fan et al. reported the multicomponent Biginelli reaction starting HMF using Brønsted and Lewis acid catalysts. Initial studies were caried out by using acetylacetone, HMF, and urea using HCl as a catalyst in refluxing ethanol. Even though HMF converted in the presence of ethanol under reflux conditions, no Biginelli product was observed. Furthermore, when different catalysts like $ZnCl_2$, $ZnBr_2$, $Zn(ClO_4)_2 \cdot 6H_2O$, and A15 was used for the synthesis, good yield of DHPMs was isolated. The use of mild Lewis acids showed good catalytic activity at 80 °C under neat reaction conditions affording up to 93% yield of DHPM. The mass balance was the formation of small amount of Knoevenagel and Hantzsch esters (Fan et al. 2018).

Table 2.5 The literature reports of synthesis of DHPMs and DHPs from furfurals

Substrate	**Reaction Conditions**	**Product**	**Yield (%)**	**Reference**
FUR	Reflux, 6 h, A15, ion exchange resin, EAA, urea, acetonitrile	DHPM	50	(Joseph et al. 2006)
FUR	60-65 °C, 7 h, yttria-zirconia, MAA, urea, aq. CH_3CN	DHPM	86	(Ramalingam and Kumar 2009)
FUR	Reflux, 20 min, $[(CH_2)_4SO_3HMIM][HSO_4]$, 1,3-cyclohexanedione, ammonium acetate, ethanol	DHP	92	(Heravi et al. 2010)
FUR	RT, 45 min, Bi_2WO_6, EAA, ammonium acetate, water	DHP	88	(Paplal et al. 2014)
FUR	80 °C, 1.5 h, $Fe_3O_4/SiO_2–SO_3H$, EAA, urea	DHPM	90	(Martínez et al. 2014)
FUR	80 °C, 1.5 h, $Fe_3O_4/SiO_2–SO_3H$, EAA, ammonium acetate	DHP	90	(Martínez et al. 2014)
FUR	60 °C, 5 h, TBAB, EAA, ammonium acetate, water	DHP	89	(Ananda Kumar et al. 2014)
FUR	90 °C, 30 min, [Btto][*p*-TSA], EAA, urea	DHPM	79	(Zhang et al. 2015)
FUR	80 °C, 6 h, $GaCl_3$, EAA, urea	DHPM	90	(Yuan et al. 2017)
FUR	80 °C, 4 h, $H_{14}NaP_5W_{29}MoO_{110}@SiO_2$, EAA, urea	DHPM	82	(Portilla-Zuñiga et al. 2018)
HMF	80 °C, 4 h, $ZnCl_2$, acetylacetone, urea	DHPM	93	(Fan et al. 2018)

5MF	70 °C, 35 min, Fe_3O_4@SiO_2@ADMPT/$H_6P_2W_{18}O$, EAA, ammonium acetate, ethanol	DHP	85	(Ghanbari et al. 2018)
FUR	Concentrated solar radiation, chlorophyll, MAA, urea	DHPM	72	(Harsh et al. 2020)
FUR	Reflux, 1 h, FeF_3, EAA, urea, ethanol	DHPM	92	(Krishna et al. 2020)
FUR	90 °C, 2.5 h, COF-IM-SO_3H, EAA, urea	DHPM	89	(Yao et al. 2021)
FUR	80 °C, 22 min, [BCMIM][Cl], EAA, urea	DHPM	90	(Madivalappa Davanagere and Maiti 2021)

Abbreviations: EAA: Ethyl acetoacetate; MAA: Methyl acetoacetate; A15: Amberlyst 15; [Btto][*p*-TSA]: 1-Butyl-1,3-thiazolidine-2-thione paratoluenesulfate; COF-IM-SO_3H: Imidazolium and sulfonic acid functionalized covalent organic framework; [BCMIM][Cl]: 1,3-Bis(carboxymethyl)imidazolium chloride; DHPM: 3,4-Dihydropyrimidin-2-(*1H*)-ones; DHP: 1,4-Dihydropyridine; $[(CH_2)_4SO_3HMIM]$ $[HSO_4]$: 1-(4-Sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate; TEAB: Triethylammonium bromide.

Numerous literatures have been performed on the preparation of DHPMs and DHPs from aldehydes, emphasizing on design, efficiency, selectivity, and recyclability of the catalyst. The homogeneous and heterogeneous catalysts were successfully used for the aforementioned reaction. The use of strong acid catalysts worked in case for benzaldehyde derivatives, whereas, in case of FUR derivatives moderate or mild acids will work best. The synthesis requires mild reaction conditions (<120 °C, 10 min to 24 h). The reaction was attempted under conventional and microwave heating conditions under solvent-free and using different solvents like water, ethanol, methanol, and acetonitrile. The use of biorenewable furfurals for this reaction is limited in the literature. In this regard, the development of mild, selective, inexpensive, and recyclable catalysts for transformation of biorenewable furfurals to DHPMs and DHPs has immense importance.

Tamaddon and Moradi reported the controllable selectivity of Biginelli and Hantzsch reactions using nano ZnO as base catalyst (Tamaddon and Moradi 2013). Biginelli reaction occurs at lower temperature using solvent-free condition. Whereas, Hantzsch reaction occurs in the presence of water at higher temperature. They isolated more than 90% of products after the reaction.

Ming et al. reported the one-pot synthesis of Biginelli and Hantzsch reaction products using inexpensive ILs as catalysts (Li et al. 2006). They synthesized series of imidiazolium based catalysts and used for the reaction. They obtained maximum yields of 69% and 22% of DHPM and DHP from FUR, respectively.

2.2 SCOPE OF THE WORK

Although significant research has been done over the past several years for the production of furanics and levulinic acid from biomass-derived carbohydrates, there is still plenty of room for improvement in terms of catalyst and the reaction conditions used. In recent years, improved production of CMF and LA have been reported using quaternary ammonium chlorides as a surface-active agent. The strategy may be extended to the production of FUR. It has never been tried before to act as a phase transfer catalyst in coproducing FUR and CMF starting from a mixture of substrates (i.e., pentose and hexose sugars). LA can also be isolated from the reaction mixture to demonstrate the overall high yield of the process producing minimum waste, which is also crucial from the industrial perspective. Even an incremental improvement in the production of FUR, CMF, and LA could revolutionize their industrial production as biorenewable chemicals. However, the inherent hydrophilicity and poor stability (hydrolytic, storage, thermal) of HMF and CMF continue to overshadow its potential as a biorenewable chemical platform. Therefore, preparing hydrophobic, stable congeners of HMF from carbohydrates has received considerable interest. In this regard, AMFs are promising hydrophobic congeners of HMF since they use relatively innocuous biorenewable carboxylic acids as reagents and do not contain halogen atoms in their moiety. There have been intermittent efforts to prepare AMFs, such as FMF and AcMF, from sugars using various catalyst systems. The derivative chemistry of FMF and AcMF has shown promise as a viable substitute for HMF. However, inexpensive sugars like glucose and polymeric carbohydrates (e.g., starch, cellulose) gave poor yields. The two-step synthesis of various AMFs from carbohydrates using CMF as a reactive intermediate are reported in the literature. A general preparative strategy for the straightforward preparation of AMFs directly from carbohydrates is a significant research gap in the literature. In addition, it is important to explore derivative chemistries of biomass-derived platforms to understand their reactivity pattern. For example, alkyl/aryl esters of biomass-derived platform chemicals like 2FA, LA, IS, and stearic acid (StA), which has potential applications as fuel and fuel oxygenates, plasticizers, green solvent, fragrance agent, and so on. The alkyl/aryl esters can be synthesized using esterification or transesterification protocol using acid/base catalyst. The acid-catalyzed esterification of LA, 2FA, StA, and IS in the presence of alcoholic medium affords the alkyl esters. Choosing right catalyst is paramount importance for esterification of biomass-derived intermediates. In this regard, ILs have been used by many as suitable reaction media for the production as well as value addition of various biorenewable chemical building blocks. However, a major roadblock for the commercial viability of the processes is the high cost of ILs and difficulty in their recycling. In this regard, inexpensive ILs such as triethylammonium hydrogen sulfate (TEAHS) are of great interest. TEASH has already been used as a catalyst and the reaction medium for various organic transformations. However, the use of TEAHS in renewable synthesis is limited. The Brønsted acidity and hygroscopic nature of TEAHS may be exploited for the esterification and etherification reaction. For example, alkyl stearate may be prepared by reacting StA with alkyl alcohols in the TEAHS medium. The inexpensive ionic liquid TEAHS could be an appropriate reaction medium for the reaction. Alternatively, esters can also be synthesized by the transesterification protocol. The mono- and diesters of glucose-derived IS, isomannide (IM), and isoidide (II), collectively called as isohexide can be used as novel surfactants or plasticizers, which can be synthesized from base-catalyzed transesterification under solvent-free conditions. The esters are generally synthesized using a reactive intermediate like acid anhydride or acid chloride. However, the process can be made simpler and inexpensive by using inorganic base like anhydrous potassium carbonate, potassium phosphate tribasic, sodium hydroxide, and potassium *tert*-butoxide. Furthermore, the biomass-derived furfurals can be converted into novel heterocyclic compounds, and their properties may be studied. The use of biorenewable furfurals in the multi-component reaction has been leading to a series of functionalized DHPMs and DHPs with a wide range of 1,3-dicarbonyl compounds and urea building blocks, which has potential applications as anti-tumour, anti-bacterial, anti-inflammatory, and anti-viral activities.

2.3 OBJECTIVES OF THE PRESENT WORK

Based on detailed literature review, the following objectives have been deliberated in the present work.

1. The use of inexpensive ionic liquid as catalyst and reaction medium for the synthesis of renewable compounds.
2. Hydrochloric acid-catalyzed coproduction of furfural and 5-(chloromethyl)furfural from biomass-derived carbohydrates using phase transfer catalyst.
3. Straightforward and scalable preparation of 5-(acyloxymethyl)furfurals directly from carbohydrates.
4. The selective oxidation of furfural to 2(5H)-furanone using inexpensive oxidants in the presence of acid catalysts.
5. Synthesis and characterization of novel diesters of biomass-derived isohexides.
6. Synthesis and characterization of novel heterocyclic compounds from biomass-derived renewable chemicals.

Overall, the present work is to explore novel strategies to synthesize CMF, FUR, and AMFs from biomass-derived carbohydrates and using them as chemical platforms to synthesis high-value fuels and chemicals. The entire thesis comprises of eight chapters. **CHAPTER 1** provides the general introduction about biomass and its valorization techniques, followed by catalytic strategy of biomass conversion into value-added chemicals. **CHAPTER 2** briefly discusses about literature reviews and journal articles reported in the past few decades on the catalytic value addition of biomass-derived carbohydrates. The research gaps associated with the existing literature have been highlighted. Finally, the scope and objectives of the present work have been listed. **CHAPTER 3** reported the synthesis and coproduction of FUR and CMF from carbohydrates using quaternary ammonium salts as PTC in an organic-aqueous biphasic batch reaction. FUR has been produced in good isolated yields from

D-xylose within an aqueous HCl-DCE biphasic reaction mixture using benzyltributylammonium chloride (BTBAC) as a PTC. The use of BTBAC noticeably improved the yield of FUR compared to that in the control reaction. The reaction was optimized on the reaction temperature, duration, concentration of HCl, and the loading of BTBAC. FUR and CMF have also been coproduced from a mixture of pentose and hexose sugars. In addition, LA was also isolated from the reaction mixture to demonstrate the overall high yield of the process producing minimum waste, which is also crucial from the industrial perspective. **CHAPTER 4** described the straightforward preparation of AMFs directly from carbohydrates. This chapter, describes the synthesis of AMFs using a combination of carboxylic acid as the Brønsted acid (and reagent) and $ZnCl_2$ as Lewis acid catalyst directly from sugars and polymeric carbohydrates under solvent-free conditions. The use of mild Lewis acid accelerates the reaction kinetics under mild reaction conditions. Furthermore, the reaction conditions are optimized and extended for the synthesis of a series AMFs. **CHAPTER 5** reported the synthetic upgradation of FUR into 2FN using aqueous H_2O_2 as the green oxidant in the presence of trifluoroacetic acid (TFA) as acid catalysts. Initially, various acid catalysts were screened and the use of TFA worked very well under mild reaction conditions. The reaction parameters like amount of acid and H_2O_2, reaction time, and temperature were optimized to obtain maximum FUR conversion and selectivity of 2FN. **CHAPTER 6** consists of two parts; first part outlined the esterification of biomass-derived platform chemicals to corresponding esters by Fisher-esterification protocol. TEAHS has been used as an inexpensive protic liquid catalyst for the preparation of various biomass-derived renewable compounds. TEAHS efficiently catalyzed the esterification of biomass-derived chemical intermediates such as LA, 2FA, StA, and IS and conveniently separated from the reaction mixture and reused without significant loss of activity. Whereas, the second part outlined the base-catalyzed transesterification of isohexide. This work reports a high-yielding and scalable synthesis of the mono- and diesters of IS by transesterification reaction using anhydrous potassium carbonate as an efficient, inexpensive, and recyclable base catalyst. The methodology was also extended for synthesizing the mono- and diesters of the other two isohexide, i.e., IM and II. **CHAPTER 7** discussed the synthesis of DHPMs and DHPs from biorenewable furfurals using 1,4-diazabicyclo[2.2.2]octanium diacetate (DABCO-Ac) as an efficient acidic IL catalyst and reaction medium for the solvent-free synthesis. **CHAPTER 8** outline the conclusions of present work, and highlights the scope for future work.

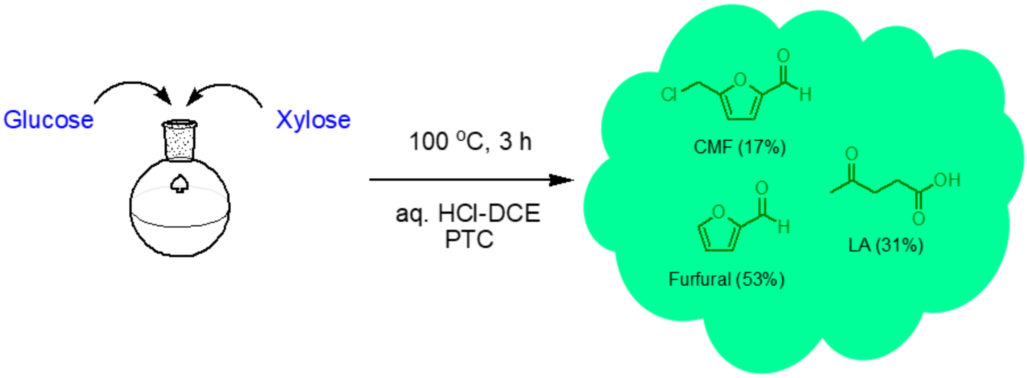
CHAPTER 3

HYDROCHLORIC ACID-CATALYZED COPRODUCTION OF FURFURAL AND 5-(CHLOROMETHYL)FURFURAL ASSISTED BY A PHASE TRANSFER CATALYST

Abstract

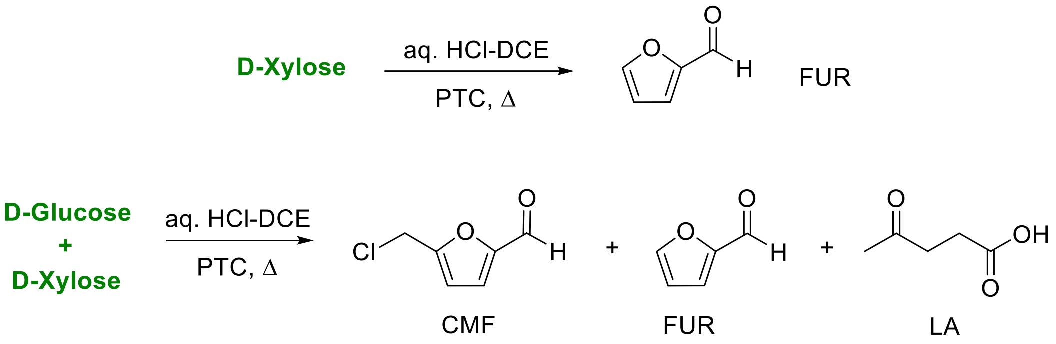
Furfural (FUR) has been produced in a 53% isolated yield from D-xylose within an aqueous HCl-1,2-dichloroethane biphasic batch reaction using benzyltributylammonium chloride (BTBAC) as a phase transfer catalyst. The use of BTBAC noticeably improved the yield of FUR compared to that in the control reaction. The reaction was optimized on the reaction temperature, duration, concentration of HCl, and the loading of BTBAC. FUR and 5-(chloromethyl)furfural (CMF) have also been coproduced from a mixture of pentose and hexose sugars. Under optimized conditions (100 °C, 3 h, 20.2% HCl, 10 wt.% BTBAC), CMF and FUR were isolated in 17% and 53% yields, respectively, from a mixture of glucose and xylose. In addition, levulinic acid was isolated from the aqueous layer in a 31% isolated yield.

Graphical Abstract



3.1 INTRODUCTION

As discussed in CHAPTER 1, the production of furfural (FUR) and 5-(hydroxymethyl)furfural (HMF) from xylose and glucose, respectively, are known for over a century, and the commercial production of FUR was realized as early as 1921. FUR and HMF retain some of the reactive functional groups of the parent sugars that can be exploited for downstream synthetic value-addition pathways (Lange et al. 2012; Shen et al. 2020). Over the past three decades, hundreds of publications and patents have been dedicated to the production and application of FUR and HMF, and several comprehensive reviews have summarized these works (Li et al. 2016b; Mariscal et al. 2016; Menegazzo et al. 2018; Rosatella et al. 2011). Although HMF is routinely obtained in high yields from simple sugars like fructose, the high-yielding production of HMF from cellulosic biomass often requires special reaction conditions. The commercial production of HMF is plagued by its hydrophilicity and inherent instability in aqueous acid. The coproduction of HMF and FUR from a mixture of pentose and hexose sugars, as well as lignocellulosic biomass, is also reported. In recent years, 5-(chloromethyl)furfural (CMF), a hydrophobic congener of HMF, has been explored as a functional substitute for HMF. CMF can be synthesized in satisfactory isolated yields from polymeric carbohydrates and even untreated cellulosic biomasses (Mascal and Nikitin 2009). CMF has been demonstrated as a renewable chemical platform for the synthesis of a diverse range of specialty chemicals. Therefore, an efficient coproduction of FUR and CMF from the mixture of glucose and xylose could work as a working model for terrestrial and algal biomasses. An aqueous-organic biphasic reaction is frequently used for the production of furanics from biomass. The idea is to sequester the furanic molecules into the organic phase as soon as they form and slow down their decomposition in aqueous acid (Gao et al. 2013; Mascal and Nikitin 2009; Wang et al. 2015). The benzyltributylammonium chloride (BTBAC) was successfully reported as a phase transfer catalyst (PTC) for various reactions (Glatzer and Doraiswamy 2000). In a recent report, CMF was prepared from various carbohydrates in concentrated (ca. 35%) HCl-1,2-dichloroethane (DCE) biphasic reaction using BTBAC as a PTC (Onkarappa and Dutta 2019). The use of BTBAC afforded higher isolated yields of CMF when compared to the control reactions. The hydrophobic environment created by the PTC shielded the reactive intermediate species during the formation of CMF, thereby increasing the selectivity and yields of the same. We envisaged that the process could also be extended for the production of other furanic molecules such as FUR. In this work, we report the production of FUR from biomass-derived pentose sugars like xylose in aq. HCl-DCE biphasic system using BTBAC as a PTC. The reaction was optimized on the reaction temperature, duration, loading of BTBAC, and concentration of HCl. The optimized reaction condition was then applied for the one-pot coproduction of FUR and CMF from a mixture of pentose and hexose sugars such as glucose and xylose (Scheme 3.1). In addition, levulinic acid (LA) was isolated from the aqueous layer. The HCl (20.2%)-DCE biphasic reaction was conducted in a glass pressure reactor in the presence of BTBAC (10 wt.% of feedstock) as an additive. The azeotropic concentration of HCl was used to allow straightforward recovery of the aqueous acid by distillation while minimizing the decomposition of BTBAC.



Scheme 3.1 Preparation of (a) FUR from xylose and (b) coproduction of CMF and FUR from a mixture of glucose and xylose in the presence of a PTC.

3.2 EXPERIMENTAL SECTION

3.2.1 Materials

Microcrystalline cellulose (99%), benzyltributylammonium chloride (98%), and starch (soluble, 99%) were purchased from Sigma. Hydrochloric acid (35%), anhydrous sodium sulfate (99%), silica gel (60-120 mesh), glucose (99%), fructose (99%), and sucrose (99%) were purchased from Loba Chemie Pvt. Ltd. D-Xylose (99%) and Inulin (99%) were purchased from TCI, Japan. 1,2-Dichloroethane (98%) was obtained from MolyChem. The glass pressure reactor with the Teflon screw-top was purchased from Sigma Aldrich. All the chemicals were used as received without further purification.

3.2.2 Experimental Procedures

3.2.2.1 Production of FUR from xylose

Xylose (1.001 g) was taken in a 100 mL round-bottomed glass pressure reactor fitted with a Teflon screw-top. To this, aq. HCl (20.2%, 20 mL), DCE (40 mL), and BTBAC (0.100 g) were added. A magnetic stirring bead was added, and the pressure reactor was sealed. The reactor was placed in a pre-heated oil bath (100 °C) the reaction mixture was magnetically stirred continuously for 3 h. After the reaction, the reactor was removed from the oil bath and cooled down to room temperature. The reactor was opened, and the reaction mixture was transferred into a separating funnel. The DCE layer was separated, and the aqueous phase was extracted with fresh DCE (2×10 mL).

The DCE layers were combined, dried over anhydrous Na_2SO_4, and passed through a plug of silica gel (60-120 mesh). Evaporation of DCE in a rotary evaporator under reduced pressure provided FUR as a light yellow oil (0.340 g, 53%). The control reactions were performed as described above, except no BTBAC was used.

3.2.2.2 Coproduction of CMF and FUR from the mixture of glucose and xylose

Xylose (0.500 g) and glucose (0.500 g) were taken in a 100 mL round-bottomed glass pressure reactor fitted with a Teflon screw-top. To this, aq. HCl (20.2%, 20 mL), DCE (40 mL), and BTBAC (0.100 g) were added. A magnetic stirring bead was added, and the pressure reactor was sealed. The reactor was placed in a pre-heated oil bath (100 °C) the reaction mixture was magnetically stirred continuously for 3 h. After the reaction, the reactor was removed from the oil bath and cooled down to room temperature. The reactor was opened, and the reaction mixture was filtered through filter paper. The filtrate was transferred into a separating funnel. The DCE layer (bottom) was separated, and the aqueous phase was extracted with fresh DCE (2×10 mL). The DCE layers were combined, dried over anhydrous Na_2SO_4, and evaporated in a rotary evaporator under reduced pressure to provide the crude mixture of CMF and FUR as a brown oil. The components were separated by column chromatography (silica gel 60-120 mesh) using a mixture of petroleum ether and ethyl acetate as eluent. Evaporation of the solvent produced FUR (0.170 g, 53%) and CMF (0.068 g, 17%) as light yellow oil. The control reactions were performed as described above, except no BTBAC was used. The ^{1}H-NMR spectrum of the mixture of CMF and FUR showed the same molar ratio of products as calculated by the integrals of the relevant peaks of each compound.

3.2.2.3 Isolation of LA

The aqueous layer was filtered through a filter paper, and the filtrate was saturated by adding solid sodium chloride. The saturated solution was cooled and extracted with ethyl acetate (6×20 mL). The ethyl acetate layers were combined, dried over anhydrous Na_2SO_4, and evaporated in a rotary evaporator under reduced pressure to yield a brown liquid. The liquid was chromatographed over silica gel (60-120 mesh) using diethyl ether as eluent. Evaporation of the solvent provided LA as a light yellow oil (0.099 g, 31%).

3.2.2.4 Quantification of Humin

The aqueous layer was passed through a filter paper, and the filter paper was washed with excess distilled water. The filter paper was dried in a hot-air oven at 60 °C till a constant weight was achieved.

3.2.2.5 Recovery of BTBAC

After isolating CMF from the silica gel column, the column was eluted with 20% methanol/dichloromethane to recover the BTBAC. A 97% recovery of BTBAC was obtained using this technique. Alternatively, the mixture of FUR, CMF, and BTBAC was triturated with boiling petroleum ether (60-80 °C). Both CMF and FUR dissolved in hot petroleum ether and decanted, whereas BTBAC is recovered as a beige solid in nearly quantitative yield.

3.3 CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

The progress of a reaction, the identification of the product(s) formed, and even the purity of the same was confirmed by using different spectroscopic techniques. The Fourier Transform Infrared (FTIR) is used to identify the functional group(s) present in organic and inorganic materials. FTIR spectra were recorded on a Bruker Alpha 400 FTIR spectrometer, which is equipped with silicon carbide as an IR source. All sample spectra were recorded using the ATR technique. The FTIR spectra were collected by performing 24 scans at a scanning rate of 4 cm^{-1}/s in the range between 500-4000 cm^{-1}. The ^{1}H-NMR spectra of the synthesized compounds were collected by dissolving the compounds in suitable deuterated solvent and then recording the data in a Bruker NanoBay® instrument operating at 300 MHz. The ^{13}C-NMR spectra (broadband decoupling) were recorded in the same instrument at a calculated frequency of 75 MHz. Some of the NMRs were collected at an NMR instrument operating at 400 MHz (^{1}H-NMR) and 100 MHz (calculated, ^{13}C-NMR).

3.3.1 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of FUR

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 9.58 (s, 1H), 7.62 (d, 1H, J = 2.7 Hz), 7.19 (t, 1H, J = 2.7 Hz), 6.53 (t, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm): 177.9, 153.0, 148.1, 121.2, 112.6; FTIR (ATR, cm^{-1}): 3133, 2924, 2852, 1669, 1567, 1018.

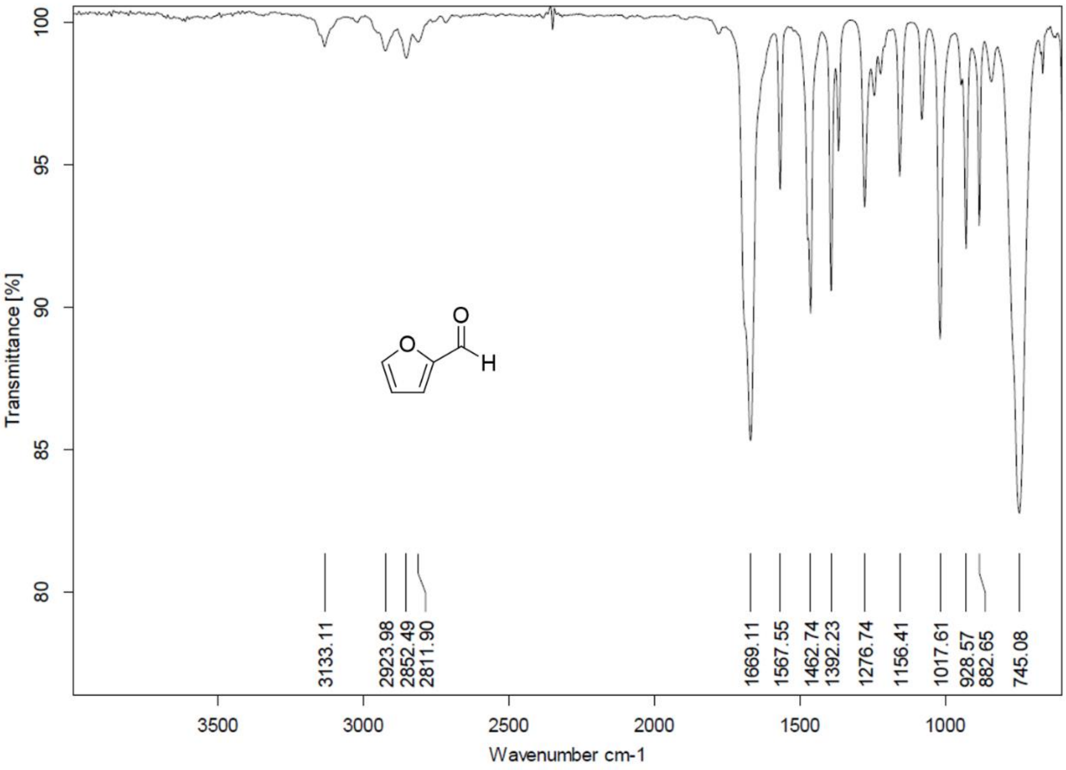


Figure 3.1 The FTIR spectrum of FUR.

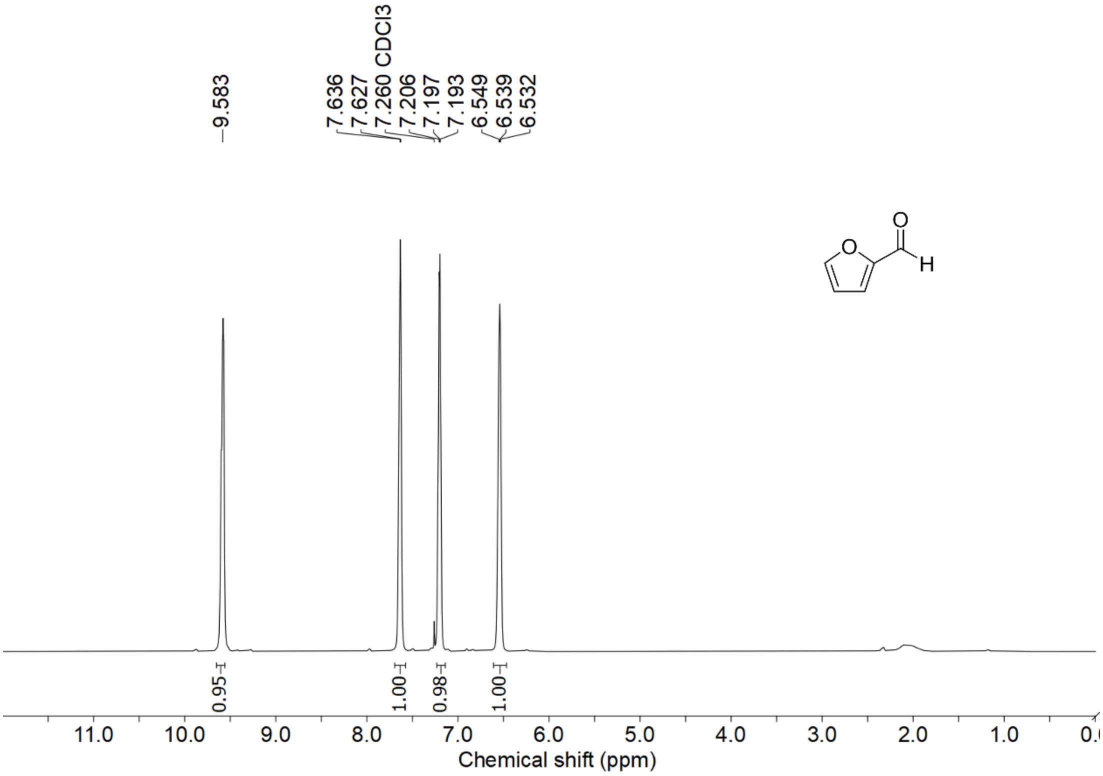


Figure 3.2 The ^{1}H-NMR spectrum of FUR.

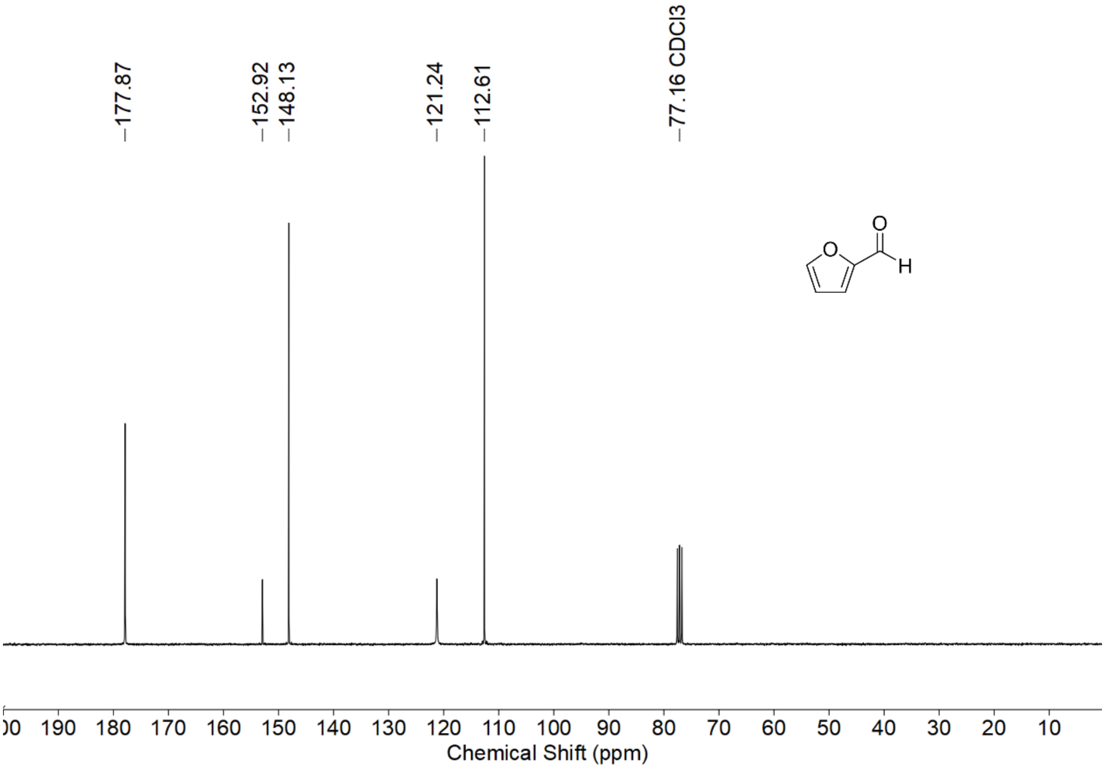


Figure 3.3 The ^{13}C-NMR spectrum of FUR.

3.3.2 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of CMF

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 9.56 (s, 1H), 7.16 (d, 1H), 6.54 (d, 1H), 4.56 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm): 177.7, 156.0, 152.7, 122.0, 112.0, 36.5; FTIR (ATR, cm^{-1}): 3124, 2834, 1674, 1518, 1021.

3.3.3 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of LA

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm): 2.75 (t, 2H, J = 6.1 Hz), 2.62 (t, 2H, J = 6.7 Hz), 2.20 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm): 206.6, 177.8, 37.7, 29.8, 27.7; FTIR (ATR, cm^{-1}): 3163, 2923, 1702, 1236, 1161.

3.3.4 The ^{1}H-NMR and ^{13}C-NMR of the coproduction of CMF and FUR from glucose and xylose

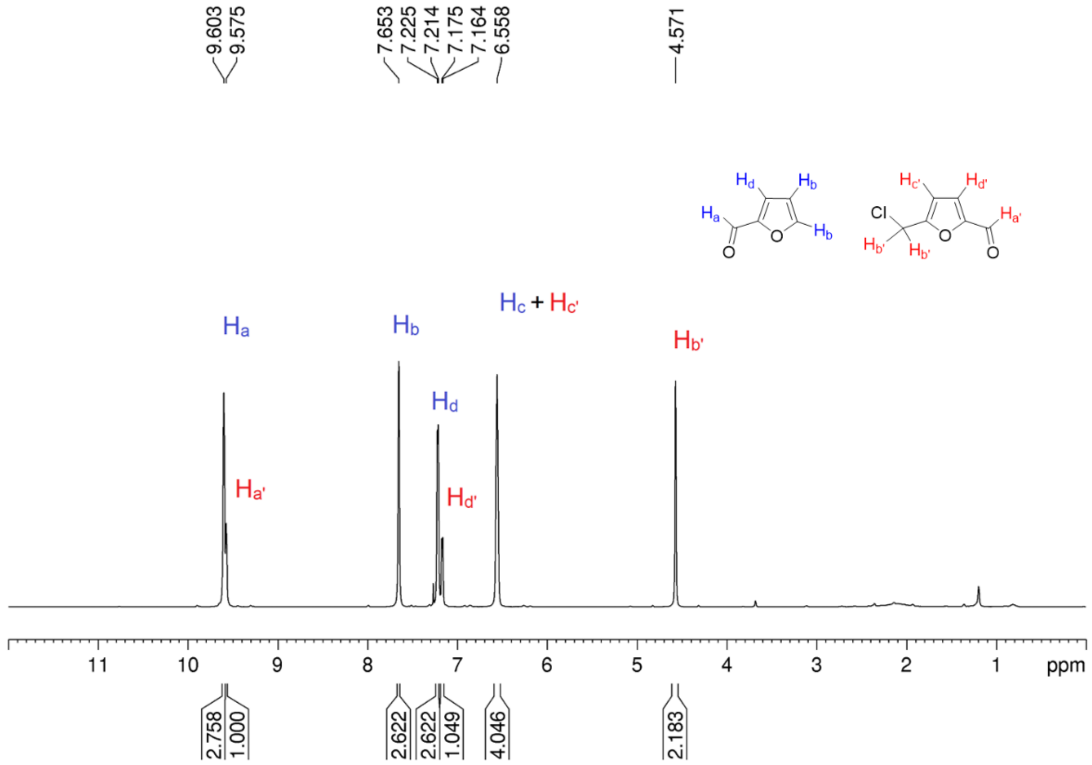


Figure 3.4 The ^{1}H-NMR spectrum of the coproduced CMF and FUR.

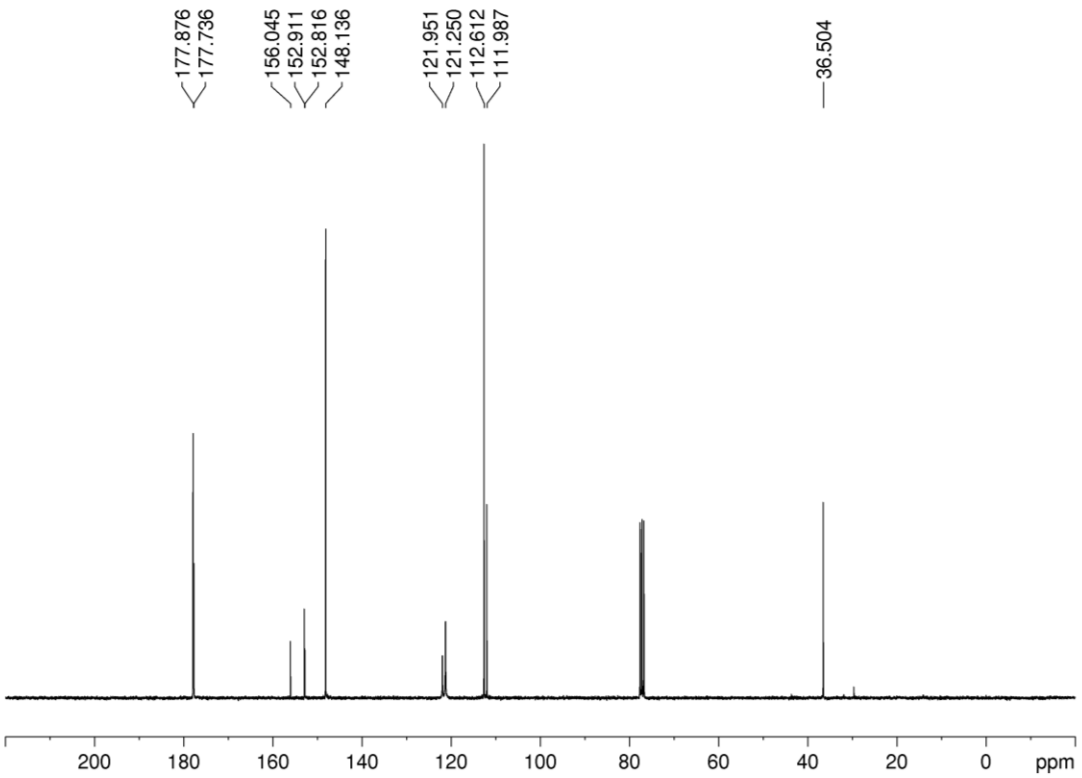


Figure 3.5 The ^{13}C-NMR spectrum of coproduced CMF and FUR.

3.4 RESULTS AND DISCUSSION

Initially, the preparation of FUR from xylose was attempted using aq. HCl (20.2%)-DCE biphasic medium. The use of azeotropic HCl helped to avoid degassing of hydrogen chloride during the reaction. The acid catalyst could be recovered conveniently via distillation without altering the concentration. DCE was chosen as the solvent due to its availability in bulk, intermediate boiling point, chemical inertness under the reaction conditions used, and recoverability by distillation. The loading of xylose was initially fixed at 5 wt.% compared to the amount of aq. HCl used. In a typical reaction, xylose was dissolved in aq. HCl (20.2%) taken in a sealed round-bottomed glass pressure reactor fitted with a Teflon screw-top and a magnetic stir bar. The solvent (i.e., DCE) and BTBAC (10 wt.% of xylose) were added before the reactor was sealed. The reactor was then placed in a preheated (100 °C) oil bath and stirred magnetically for 3 h. The reactor was then cooled down to RT, opened, and the mixture was transferred into a separatory funnel. The DCE layer was separated, dried, and distilled off under reduced pressure to isolate FUR. The control reaction was carried out under the same reaction conditions, except no BTBAC was added. The reaction with BTBAC as the PTC afforded FUR in 53% isolated yield, whereas the yield of FUR in the control reaction was only 34% (Figure 3.6). The mass balance is the soluble and insoluble humin formation, which was noticeably more in the control reaction.

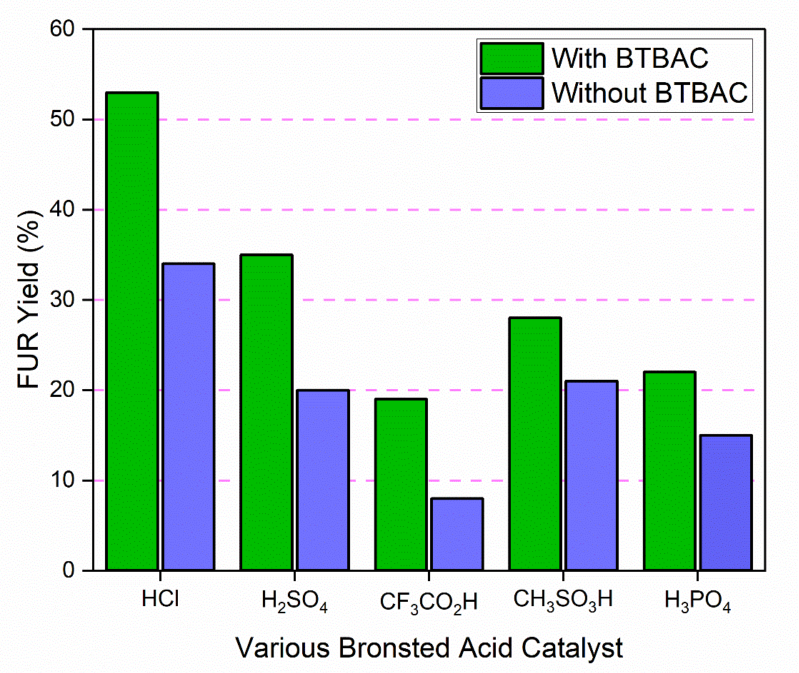


Figure 3.6 Preparation of FUR from D-xylose using various Brønsted acid catalysts. **Reaction Conditions:** Xylose (1 g), aqueous acid (20 mL, 6 M), DCE (40 mL), BTBAC (0.1 g), 3 h (in case of HCl, H_2SO_4, CH_3SO_3H), 5 h (in case of H_3PO_4), 20 h (in case of CF_3CO_2H).

Various frequently used Brønsted acid catalysts were examined for the preparation of FUR, as described in Figure 3.6. When sulfuric acid was used as the acid catalyst, FUR was isolated in 35% yield within 3 h at 100 °C, whereas the control reaction provided only 20% yield under identical conditions. Methanesulfonic acid provided a marginally lower yield, but the positive effect of BTBAC on the FUR yield was still pronounced. Weaker acids, like trifluoroacetic acid and orthophosphoric acid, provided lower yields of FUR even after significantly longer reaction times. Interestingly, the yields of FUR in the control reactions were still noticeably lower. The results may be explained by the continuous decomposition of FUR during the course of the reaction, even when the conversion of xylose remains low.

Since aq. HCl (20.2%) was found to be the most effective catalyst; the reaction was further optimized on other reaction parameters for the best selectivity and yield of FUR starting from xylose.

At first, the effect of reaction temperature was studied by keeping other reaction parameters unchanged. When the reaction was conducted at 80 °C, only a 35% yield of FUR was isolated (Figure 3.7a). Increasing the reaction temperature to 100 °C increased the yield significantly to 53%. Further increase in temperature marginally decreased the yield of FUR. The results may be explained by the incomplete conversion of xylose at lower temperatures, whereas faster decomposition at higher temperatures. When the reaction was carried out under reflux, FUR was isolated in only 23% yield after 3 h, which increased up to 29% after 6 h of reaction time. The control reaction under identical conditions (reflux, 3 h) provided a 14% yield of FUR.

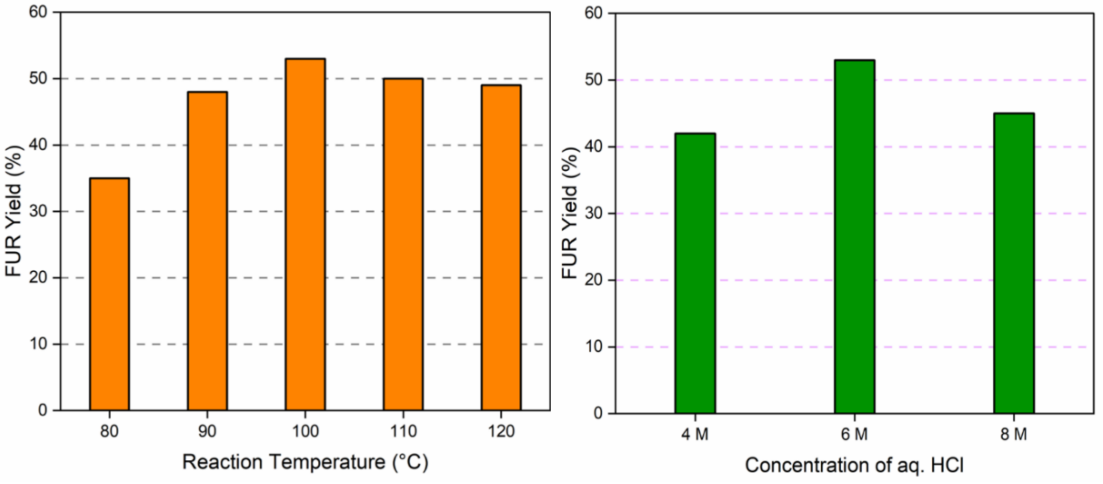


Figure 3.7 (a) The effect of reaction temperature and (**b**) the effect of aq. HCl concentration on FUR yield.

Reaction conditions: (a) Xylose (1 g), BTBAC (0.1 g), DCE (40 mL), aq. HCl (20.2%, 20 mL), 3 h, and (b) xylose (1 g), BTBAC (0.1 g), DCE (40 mL), aq. HCl (20 mL), 100 °C, 3 h.

The effect of the concentration of aq. HCl on the isolated yield of FUR was then explored. The use of 4 M HCl provided only 42% of FUR (100 °C, 3 h) (Figure 3.7b). The result may be rationalized by the incomplete conversion of xylose at lower acid concentrations. Increasing the acid concentration to 8 M also lowered the yield of FUR to 45% compared to 53% in 20.2% (6 M) HCl. The result may be explained by the instability of the BTBAC catalyst at higher concentrations of HCl.

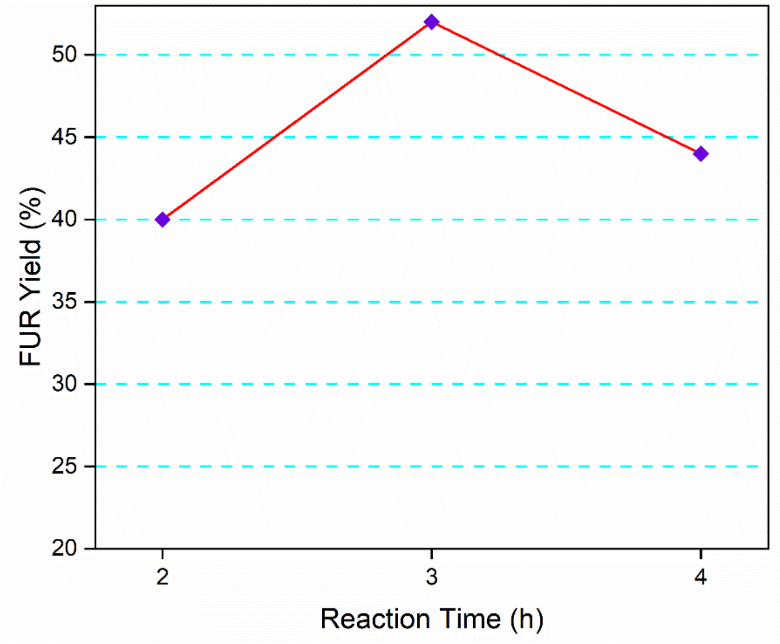


Figure 3.8 The effect of the duration of reaction on the yield of FUR.

Reaction conditions: Xylose (1 g), BTBAC (0.1 g), DCE (40 mL), aq. HCl (20.2%, 20 mL), 100 °C.

The effect of the duration of the reaction, keeping the reaction temperature fixed at 100 °C (Figure 3.8). After 2 h of reaction time, the yield of FUR was only 40% due to an incomplete reaction. However, prolonged reaction time (ca. 4 h) also lowered the yield of FUR due to more decomposition. Though the use of less BTBAC (5 wt.%) led to a lower yield of FUR (ca. 48%), higher loadings of BTBAC (10 wt.%) did not show any discernible improvement in the yield of the same. The formation of insoluble humin as a black solid was found to be only 0.036 g for 1 g of xylose under the optimized conditions.

The optimized reaction was then applied for the coproduction of CMF and FUR starting from a mixture of xylose and various hexoses. The products could be separated by column chromatography on the laboratory scale or by fractional distillation on a larger scale. The relative ratio of products was also calculated by the integration of peaks in the ^{1}H-NMR spectrum. The isolated mass of CMF and FUR conformed well to the NMR data. When a mixture of glucose and xylose was used as the feedstock, CMF and FUR were isolated in 17% and 53% yields, respectively, under the optimized conditions (Table 3.1, entry 1). Interestingly, when glucose was used alone, CMF was isolated in similar yields (ca. 18%). Therefore, the use of a physical mixture of pentose and hexose sugars did not affect the individual yields of FUR and CMF.

Table 3.1 Coproduction of FUR and CMF

S/N	Substrate	Yield (%) with BTBAC		Yield (%) without BTBAC	
		CMF	FUR	CMF	FUR
1[a]	Glucose+Xylose	17	53	12	34
2	Sucrose+Xylose	16	51	10	34
3	Fructose+Xylose	16	52	12	35
4	Inulin+Xylose	15	49	11	32
5	Starch+Xylose	16	48	11	33
6	Cellulose+Xylose	15	48	10	32

[a] LA was isolated from the aqueous layer in 31% (with BTBAC), and 15% (without BTBAC) yields, respectively. **Reaction conditions**: Aq. HCl (20.2%, 20 mL), DCE (40 mL), 100 °C, 3 h, 0.5 g of each substrate, 0.1 g BTBAC.

Due to the low concentration of chloride ions, the yields of CMF remained low for all the hexoses studied. When NaCl was used in excess, the yield of CMF improved to 29% (with BTBAC). We envisioned that instead of forming CMF, the HMF intermediate would likely transform into LA in the aqueous layer. Extraction of the aqueous acid with ethyl acetate afforded 31% of LA in the reaction using BTBAC. The yields of CMF and FUR in the control reaction were 12% and 34%, respectively. When the combination of sucrose and xylose was used (entry 2), CMF and FUR were isolated in 16% and 51% yields. The combination of fructose and xylose (entry 3) provided comparable yields. The yields of CMF were nearly the same for all the polymeric carbohydrates (entries 4-6) and higher than those in the control reactions. Interestingly, FUR was isolated in similar yields from all the mixtures of sugars examined. The insoluble humin formation is noticeably higher in the control reaction compared to reactions using BTBAC. For example, the mixture of glucose and xylose (entry 1) produced 0.025 g of insoluble humin as a black solid compared to 0.052 g of the same in the control reaction.

3.5 CONCLUSIONS

The use of BTBAC afforded significantly higher yields of FUR starting from xylose when compared to the control reaction. The insoluble humic matter formed in noticeably lower quantities in reactions using BTBAC. CMF and FUR were coproduced from a physical mixture of xylose and hexose carbohydrates. The yields of CMF and FUR were higher when using BTBAC as PTC. The azeotropic concentration of HCl allowed conducting the reaction under the refluxing condition without evaporative loss of the HCl gas. No chemical decomposition of BTBAC was observed, and it was recovered in near-quantitative yield after the reaction. BTBAC was conveniently separated from the product mixture by chromatography or trituration with petroleum ether.

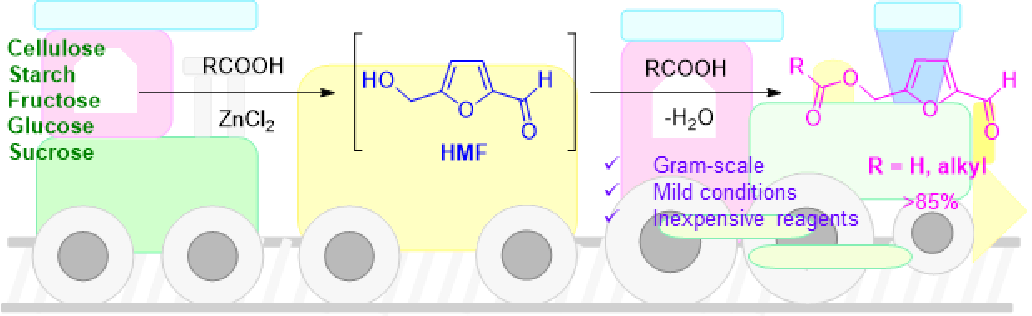
CHAPTER 4

STRAIGHTFORWARD AND SCALABLE PREPARATION OF 5-(ACYLOXYMETHYL)FURFURALS DIRECTLY FROM CARBOHYDRATES AS A VIABLE SUBSTITUTES FOR 5-(HYDROXYMETHYL)FURFURAL

Abstract

5-(Acyloxymethyl)furfurals (AMFs) have received considerable attention as hydrophobic, stable, and halogen-free congeners of 5-(hydroxymethyl)furfural (HMF) for synthesizing biofuels and biochemicals. In this work, AMFs have been prepared directly from carbohydrates in satisfactory yields using the combination of $ZnCl_2$ as the Lewis acid catalyst and carboxylic acid as the Brønsted acid catalyst. The process was initially optimized for 5-(acetoxymethyl)furfural (AcMF) and then extended to producing other AMFs. The effects of reaction temperature, duration, loading of the substrate, and dosage of $ZnCl_2$ on AcMF yield were explored. Fructose and glucose provided AcMF in 80% and 60% isolated yield under optimized parameters.

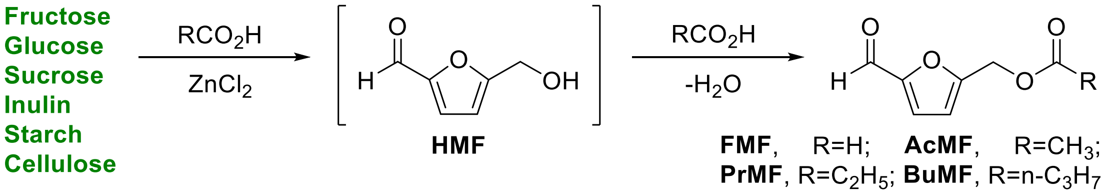
Graphical Abstract



4.1 INTRODUCTION

As discussed in CHAPTER 1, 5-(acyloxymethyl)furfural (AMF), produced by the esterification of HMF with carboxylic acids, are particularly interesting since the hydrophobic molecules contain no halogen atoms in their moiety and have better hydrolytic stability than HMF (Anchan and Dutta 2021; Chen et al. 2020). 5-(Acetoxymethyl)furfural (AcMF) has particularly received attention since AcOH is inexpensive, thermally stable, available in bulk quantities, non-toxic, and can be produced renewably from biomass. AcMF can be conveniently converted into HMF by hydrolysis/alcoholysis and can participate virtually in all derivative chemistry of the latter. Unlike HMF, AcMF can be used directly as a promising fuel blending agent. AcMF has also been used for the synthesis of molecules with promising therapeutic activities and as the sweet taste modulator in balsamic vinegar. In a two-step strategy, AcMF has been produced in good yield by the nucleophilic substitution of CMF using suitable bases (Kang et al. 2015). In a recent report, CMF was reacted with the triethylammonium salt of various alkyl and aryl carboxylic acids to synthesize various AMFs in good scalability and yield (Bhat et al. 2022). HMF can be esterified with AcOH in the presence of a suitable acid catalyst, forming AcMF. Fructose was transesterified into 1,6-diacetylfructose by vinyl acetate using the lipase catalyst, which was then dehydrated and partially deacetylated into AcMF using a cation-exchange resin (Krystof et al. 2013). In the above cases, AcMF was prepared from carbohydrates in a two-step strategy necessitating the intermediary of another furanic chemical platform. Recently, a one-pot production of AcMF from hexose sugars in the AcOH medium has been reported (Shinde et al. 2018). The reaction was performed at 150 °C in a batch-type pressure reactor using Sn^{4+}-exchanged montmorillonite clay (Sn-Mont) as the heterogeneous acid catalyst. The use of Sn-Mont was necessary as the weak AcOH alone could not catalyze the dehydration of sugars at an appreciable rate. Besides, esterification of the HMF intermediate with AcOH mandates a strong acid catalyst. Even though fructose afforded a 58% yield of AcMF, glucose afforded a much lower yield. However, unless AcMF can be produced from abundant and inexpensive feedstock, the commercial prospects of its derivatives would remain questionable. 5-(Formyloxymethyl)furfural (FMF) has also received interest as a potential alternative to HMF. Simple sugars like fructose provided good yields of FMF in the formic acid medium, but its production from glucose or cellulose in acceptable yields remained a challenge (Dutta 2020). FMF has shown promise as a renewable chemical intermediate for synthesizing several value-added products. 5-(Propionyloxymethyl)furfural (PrMF) and 5-(butyryloxymethyl)furfural (BuMF), the propionic acid and butyric acid ester of HMF, respectively, are relatively less explored. Although PrMF and BuMF have been prepared from HMF, their direct preparation from carbohydrates is practically absent in the literature. Carboxylic acids with short alkyl chain lengths (C1-C4) can be produced by the catalytic or enzymatic degradation of carbohydrates, making the corresponding HMF-esters entirely biorenewable. Interestingly, the dehydration of sugars into HMF using organic acid catalysts has been reported. However, the isolation of AMFs starting from HMF often requires a strong acid catalyst, special reaction media, and dehydrating agents. Therefore, a one-pot, scalable, high-yielding procedure for preparing AMFs from inexpensive sugars and carbohydrates under relatively mild reaction conditions is desired to improve the commercial prospects of these biorenewable chemicals.

In this regard, the wealth of literature available on HMF preparation can be churned to obtain valuable information in producing AMFs. Lewis acidic metal salts have shown promising catalytic activity for dehydrating sugars into HMF (Deng et al. 2012). The synergy between Lewis and Brønsted acid catalyst during HMF synthesis has been established. It can be envisioned that adding a Lewis acidic metal salt would assist in the AcOH-catalyzed dehydration of sugars to HMF and promote its esterification to AcMF in situ. Therefore, AcOH would assume the role of catalyst, reagent, and solvent during the transformation. This work reports a one-pot, scalable, and high-yielding preparation of AcMF in the AcOH medium using $ZnCl_2$ as an inexpensive and non-toxic Lewis acid catalyst. The process was optimized on various reaction parameters for the best selectivity and yield of AcMF and scaled up to 10 g of fructose. The process was then extended to the one-pot preparation of other AMFs using biorenewable carboxylic acids, such as formic acid, propionic acid, and butyric acid (Scheme 4.1).



Scheme 4.1 One-pot preparation of AMFs starting from biomass-derived sugars and polymeric carbohydrates.

4.2 EXPERIMENTAL SECTION

4.2.1 Materials

D-Fructose (98%), zinc chloride anhydrous (95%), mesitylene (>99%), aluminum chloride anhydrous (>99%), formic acid (98%), propionic acid (99%), levulinic aid (99%), and silica gel (60-120 mesh) were purchased from Spectrochem. Microcrystalline cellulose (99%), D-glucose (>99.5%), sucrose (99%), and soluble starch (98%) were purchased from Sigma Aldrich. Sodium sulfate anhydrous (99%), chloroform (99%), glacial acetic acid (99.5%), and ethyl acetate (99%) were purchased from Finar. Lithium chloride (99%) and magnesium chloride (97%) were purchased from Spectrum. Inulin, butyric acid (99%), calcium chloride (98%), and zinc acetate (99%) were purchased from Molychem. All the reagents and solvents were used as received without additional purification.

4.2.2 Synthetic procedures

D-Fructose (1.002 g, 5.57 mmol) and $ZnCl_2$ (3 g, 22.01 mmol, anhydrous) were added sequentially into glacial AcOH (20 mL) taken in a round-bottomed flask (100 mL) fitted with a reflux condenser and a magnetic stir bar. The flask was placed in the pre-heated oil bath (100 °C) cum magnetic stirrer and heated for 6 h. After completing the reaction, the mixture was cooled down to room temperature and diluted with water. The crude reaction mixture is extracted with chloroform and evaporated under reduced pressure. The crude product is passed through a plug of silica gel (60-120 mesh), and its evaporation in a rotary evaporator under reduced pressure formed AcMF (0.698 g, 75%) as a yellow oil.

Alternatively, excess acetic acid was distilled off (40-50 °C) under reduced pressure. The crude reaction mixture was diluted in water (20 mL) and then extracted with chloroform (3x10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered through a plug of silica gel (60-120 mesh) to remove colored impurities. Evaporation of the solvent under reduced pressure afforded spectroscopically pure AcMF as a pale-yellow oil.

4.2.3 Isolation of levulinic acid (LA)

After extracting AcMF, the aqueous layer was cooled down in an ice-water bath and extracted with ethyl acetate (4x10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated in a rotary evaporator under reduced pressure to get crude LA. The crude LA was purified by passing through a small plug of silica gel (60-120 mesh) using ethyl acetate as the eluent. Evaporation of ethyl acetate afforded pure LA as a light yellow oil (0.058 g, 9%).

4.3 CHARACTERIZATION OF SYNTHESIZED AMFs

4.3.1 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of AcMF

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.58 (s, 1H), 7.17 (d, 1H), 6.55 (d, 1H), 5.07 (s, 2H), 2.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 177.8, 170.3, 155.4, 152.8, 121.8, 112.6, 57.8, 20.6; FTIR (ATR, cm^{-1}): 3124, 2923, 2847, 1744, 1679, 1025.

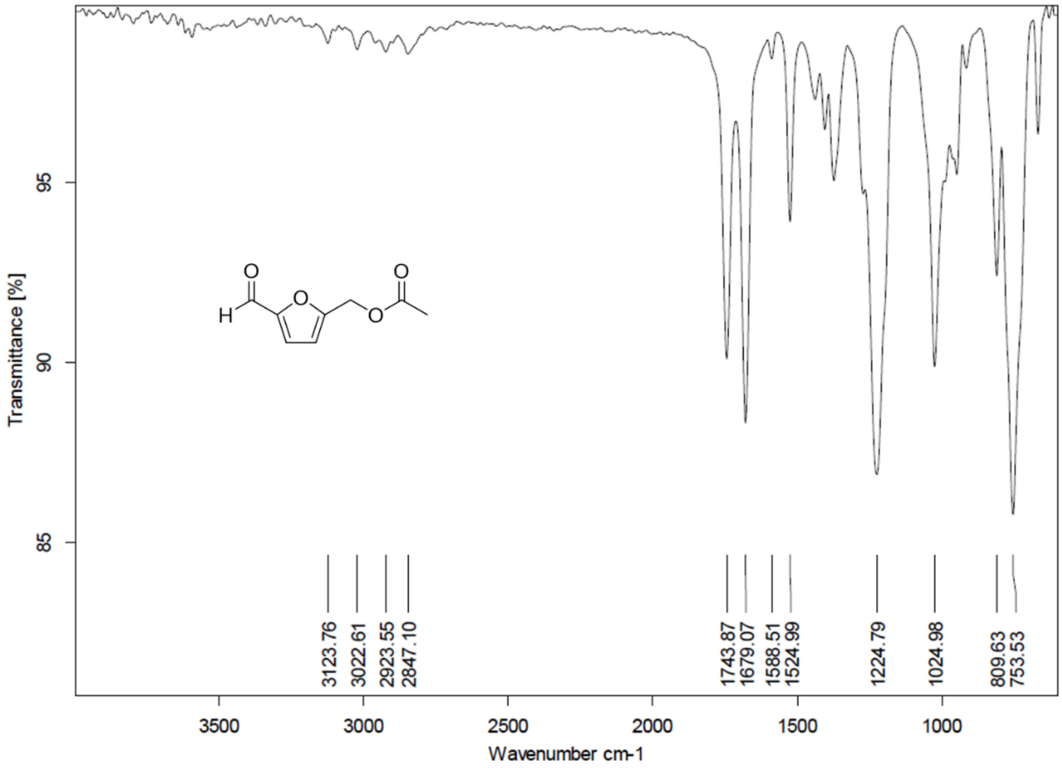


Figure 4.1 The FTIR spectrum of AcMF.

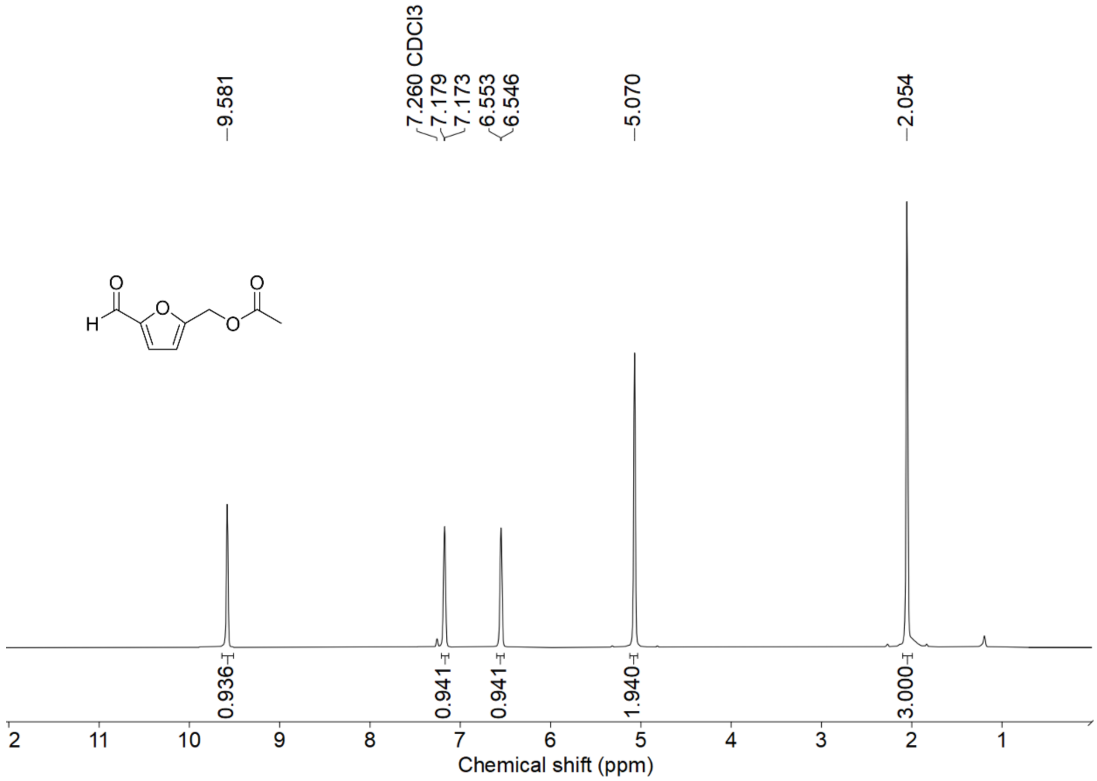


Figure 4.2 The ^{1}H-NMR spectrum of AcMF.

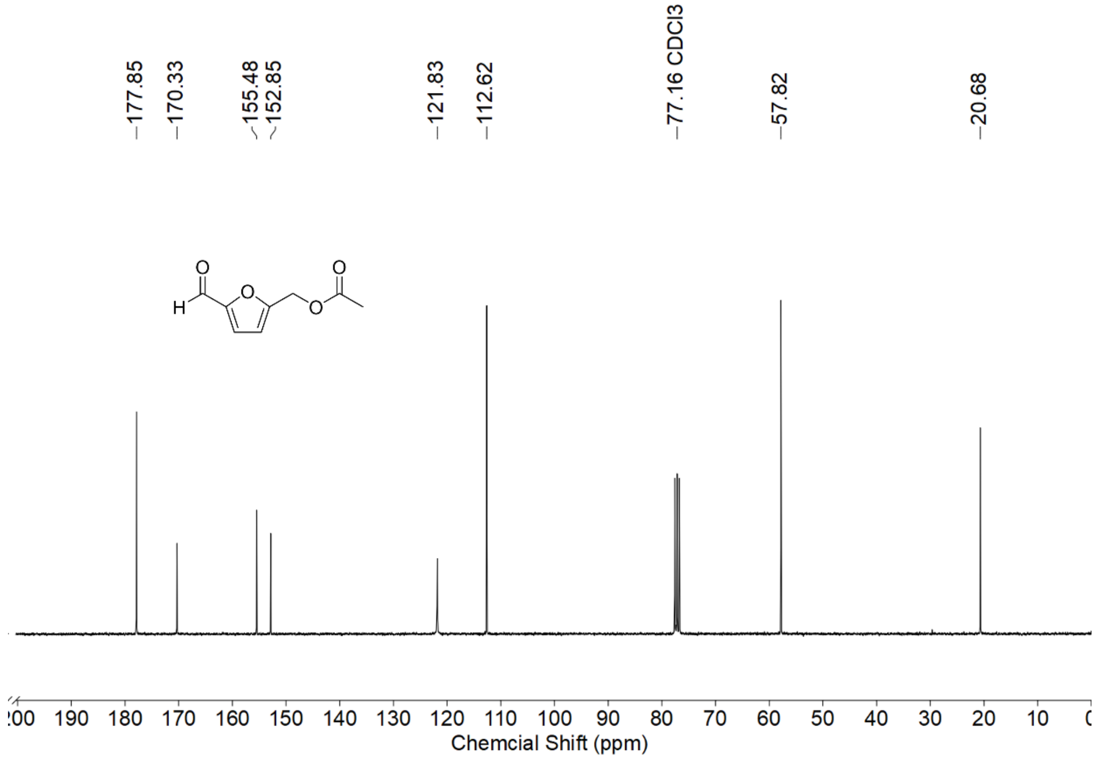


Figure 4.3 The ^{13}C-NMR spectrum of AcMF.

4.3.2 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of FMF

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.47 (s, 1H), 7.98 (s, 1H), 7.12 (d, 1H, J = 3.6 Hz), 6.51 (d, 1H, J = 3.6 Hz), 5.08 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 177.7, 160.0, 154.4, 152.6, 121.8, 112.7, 56.8; FTIR (cm^{-1}): 3022, 2924, 2853, 1728, 1680, 1021.

4.3.3 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of PrMF

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.46 (s, 1H), 7.10 (d, 1H), 6.45 (d, 1H), 4.97 (s, 2H), 2.20 (q, 2H), 0.96 (t, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 177.5, 173.4, 155.4, 152.5, 121.8, 112.2, 57.4, 26.9, 8.6; FTIR (cm^{-1}): 3124, 2984, 2850, 1741, 1680, 1020.

4.3.4 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of BuMF

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.52 (s, 1H), 7.14 (d, 1H), 6.50 (d, 1H), 5.03 (s, 2H), 2.23 (t, 2H), 1.54 (m, 2H), 0.83 (t, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 177.6, 172.7, 155.6, 152.7, 121.8, 112.3, 57.5, 35.6, 18.1, 13.4; FTIR (cm^{-1}): 2965, 2877, 1737, 1682, 1085.

4.3.5 The FTIR, ^{1}H-NMR, and ^{13}C-NMR of HMF-levulinate

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 9.47 (s, 1H), 7.12 (d, 1H), 6.48 (d, 1H), 5.01 (s, 2H), 2.65 (t, 2H), 2.48 (t, 2H), 2.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 206.5, 177.8, 172.0, 155.4, 152.6, 122.1, 112.4, 57.9, 37.6, 29.6, 27.6; FTIR (cm^{-1}): 3125, 2960, 2854, 1740, 1716, 1679, 1023.

4.4 RESULTS AND DISCUSSION

The dehydration reaction of fructose (5 wt% of AcOH) was attempted in refluxing glacial AcOH alone, resulting in a 24% yield of AcMF after 3 h of refluxing, which increased further to 37% after 6 h. In comparison, performing the reaction in the presence of $ZnCl_2$ yielded 40% AcMF after only 3 h of refluxing. Fructose and $ZnCl_2$ dissolved in glacial AcOH within a few minutes of heating, making a clear homogeneous solution that turned yellow to brown over time. The decrease in the reaction temperature to 100 °C significantly improved the yield to 75% in 6 h, whereas the control reaction (without $ZnCl_2$) under analogous conditions afforded only a 15% yield of AcMF. Compositional analysis of the reaction mixture by thin-layer chromatography showed the formation of AcMF along with CMF and HMF in trace amounts. Higher doses of $ZnCl_2$ (5 g) led to humin formation in large quantities, and the yield of AcMF decreased drastically (ca. 31%). After establishing the conducive roles of $ZnCl_2$ as a Lewis acid catalyst in the transformation, its efficiency was compared with other metal chloride salts (Table 4.1). The non-Lewis acid additive like NaCl showed no impact on the yield of AcMF. Using metal salts like LiCl, $AlCl_3$, $MgCl_2$, and $CaCl_2$ as additives afforded 59, 28, 48, and 52% yield of AcMF under the same molar loading. The noticeably lower yield of AcMF with $AlCl_3$ additive is possibly due to its insolubility in the reaction mixture leading to mass transfer limitations. When $Zn(OAc)_2$ was employed instead of $ZnCl_2$, the salt remained largely insoluble in the reaction mixture, and AcMF was isolated in only 10% yield after 6 h at 100 °C.

Table 4.1 Effect of various Lewis acid additives on AcMF production starting from fructose.

Entry	**Lewis acid additive**	**Yield of AcMF (%)[a]**
1	LiCl	59
2	$AlCl_3$	28
3	$ZnCl_2$	75
4	$MgCl_2$	48
5	$CaCl_2$	52
5	$Zn(OAc)_2$	10
7[b]	NaCl	14
8[b]	No Additive	15

[a] Isolated yield. [b] Around 7-9% HMF was coproduced. **Reaction Conditions**: Fructose (1.002 g), AcOH (20 mL), Lewis acid catalyst (4 eq. of fructose), 100 °C, 6 h.

The fructose to AcMF transformation was then optimized on various reaction parameters to ensure the optimal isolated yield. The reaction temperature influences the reaction kinetics and product distribution and determines the process's energy input and reactor design. Therefore, the reaction temperature was optimized first. When the reaction temperature was decreased to 100 °C, the isolated yield of AcMF significantly increased to 75% after 6 h reaction (Figure 4.4). The accelerated decomposition of

AcMF at higher reaction temperatures may explain the observation. However, only 52% of AcMF was isolated at 80 °C after 6 h due to incomplete conversion of fructose.

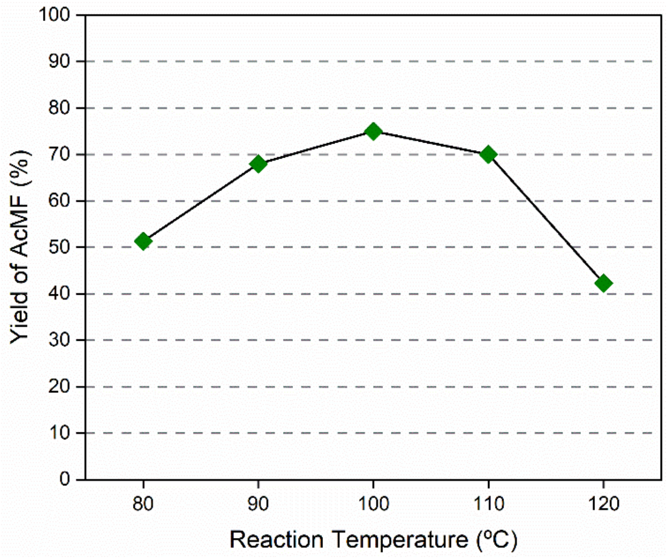


Figure 4.4 The effect of reaction temperature on AcMF yield.

Reaction Conditions: Fructose (1.002 g), AcOH (20 mL), $ZnCl_2$ (3 g), 6 h.

Lowering the reaction duration to 4 h at 100 °C afforded only a 54% yield of AcMF due to incomplete conversion. On the other hand, extending the reaction time to 8 h also lowered the yield of AcMF to 50% due to partial decomposition at elevated temperatures. When fructose loading was doubled (i.e., 2 g of fructose in 20 mL AcOH), the yield of AcMF decreased marginally to 69%. The optimized process was successfully scaled up to 10 g of fructose, affording an 80% isolated yield of AcMF. The optimized procedure was also extended to dehydrating other carbohydrates like glucose, sucrose, inulin, starch, and microcrystalline cellulose. Under optimized conditions (100 °C, 6 h), sucrose and inulin gave 51% and 47% AcMF, respectively (Figure 4.5). The use of glucose as a substrate afforded 48% of AcMF after 12 h, which reached 60% after 24 h. However, the yield did not improve by extending the duration beyond 24 h. The result is relatable to literature reports, where glucose typically affords lower yields of HMF than fructose. Starch and microcrystalline cellulose afforded 36% and 8% of AcMF, respectively, after 24 h reaction at 100 °C. The lower yields of AcMF can be explained by the additional requirement of hydrolysis of the polymeric carbohydrates into glucose before the latter dehydrates into AcMF. Microcrystalline cellulose and starch afforded 21% and 46.1% of AcMF, respectively, when the reaction was performed for 12 h under reflux.

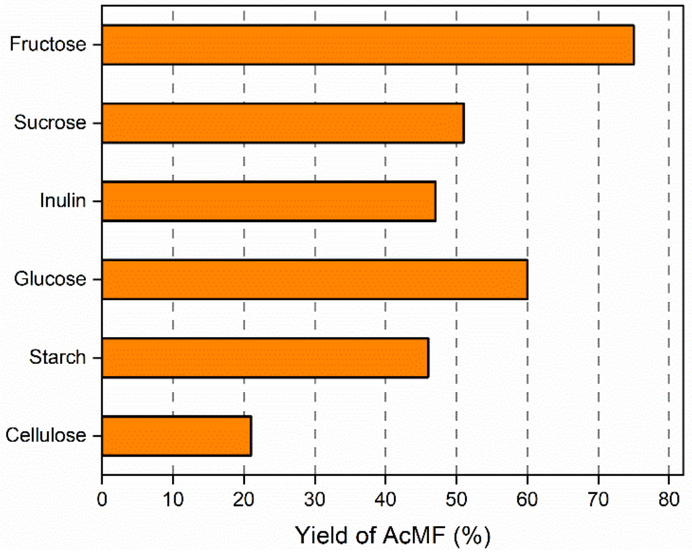


Figure 4.5 Production of AcMF from sugars and carbohydrates.

Reaction conditions: Substrate (1 g), $ZnCl_2$ (3 g), AcOH (20 mL), 100 °C, 6 h (for fructose, sucrose, and inulin); 100 °C, 24 h (for glucose); Reflux, 12 h (for starch and cellulose).

The process was then extended for producing other HMF-esters, such as FMF, PrMF, and BuMF (Table 4.2). All the products were obtained in satisfactory yields (≥60%), starting from fructose under the conditions optimized for AcMF, which may be improved substantially by tweaking the reaction parameters for the individual molecules. In this regard, HMF-levulinate, prepared by esterifying HMF with LA, is a potential fuel oxygenate. The synthesis of HMF-levulinate requires purified HMF, but the present protocol afforded a 30% isolated yield (100 °C, 6 h) of HMF-levulinate directly from fructose.

Table 4.2 One-pot preparation of AMFs from fructose.

Entry	**Name of AMF**	**Yield (%)**
1[a]	FMF	60
2	AcMF	75
3	PrMF	70
4	BuMF	60

Reaction Conditions: Fructose (1.002 g), carboxylic acid (20 mL), $ZnCl_2$ (3 g), 100 °C, 6 h; [a] 80 °C, 6 h.

4.5 CONCLUSION

In conclusion, AMFs were prepared directly from carbohydrates using carboxylic acid as the Brønsted acid catalyst (and reagent) in the presence of $ZnCl_2$ as a Lewis acid catalyst. Other metal chloride salts and other salts of zinc showed much lower catalytic activity. The sugars gave noticeably higher yields of AcMF compared to polymeric carbohydrates. The direct synthesis of 5-(propionyloxymethyl)furfural, 5-(butyloxymethyl)furfural, and HMF-levulinate from fructose first time attempted in the present work. Future research will focus on improving the yield of AcMF from polymeric carbohydrates (e.g., cellulose) and expanding its derivative chemistry following catalytic routes.

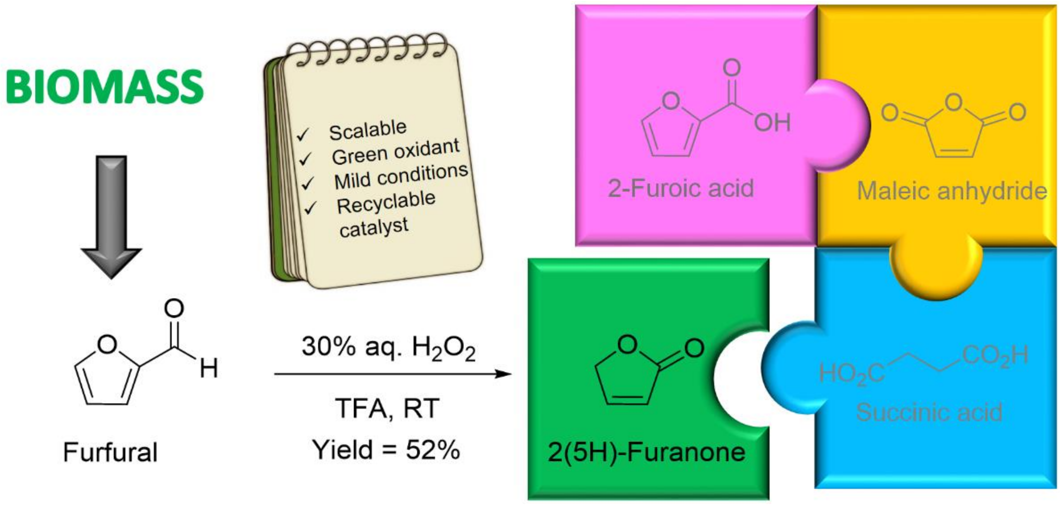
CHAPTER 5

SELECTIVE OXIDATION OF BIOMASS-DERIVED FURFURAL TO 2(5H)-FURANONE USING TRIFLUOROACETIC ACID AS THE CATALYST AND HYDROGEN PEROXIDE AS A GREEN OXIDANT

Abstract

In this work, biomass-derived furfural (FUR) has been selectively oxidized to 2(5H)-furanone (2FN) using aqueous hydrogen peroxide as the green oxidant. Among various homogeneous acid catalysts screened for the transformation, trifluoroacetic acid (TFA) was found to be the most suitable candidate the afforded up to 52% isolated yield of 2FN under mild conditions (RT, 1 h). In addition, succinic acid was recovered in nearly 20% yield from the aqueous layer. The organic solvent-free, gram-scale preparation was optimized on temperature, the molar ratio of H_2O_2 *and FUR, and the amount of TFA used.*

Graphical Abstract



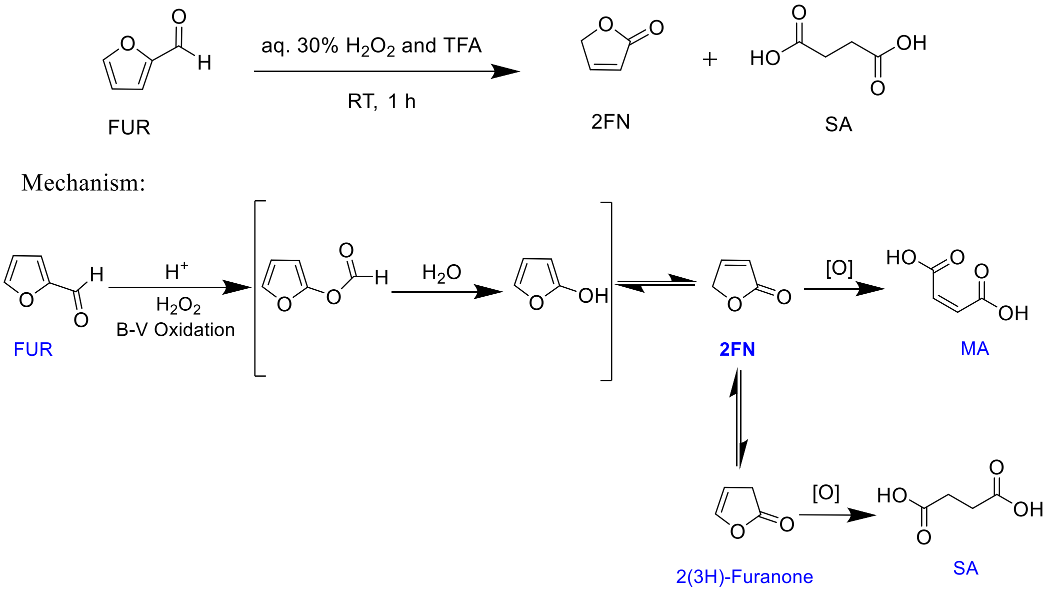
5.1 INTRODUCTION

As discussed in CHAPTER 1, chemocatalytic oxidation of furfural (FUR) leads to important renewable compounds such as 2-furoic acid (2FA), maleic acid (MA), and succinic acid (SA) (Li et al. 2016b; Mariscal et al. 2016). Both MA and SA can also be sourced from other biomass-derived chemicals and have huge commercial potential as a renewable monomer for polymeric applications. However, the selective oxidation of FUR to 2-furanone, a mixture of two isomers 2(5H)-furanone (2FN) and 2(3H)-furanone is relatively less explored possibly because they are highly reactive and behave as transient intermediates for thermodynamically stable products. As a renewable chemical intermediate, 2FN can be used to synthesize a wide variety of products of commercial significance, including butyrolactone and tetrahydrofuran (Li et al. 2016b; Xiang et al. 2016). Various derivatives of 2FN have found applications as fuels and fuel additives, solvents, aroma chemicals, antifouling agents, and biologically-important compounds. Recently, 2FN has been employed as feedstock for the synthesis of novel, biorenewable surfactants (Gassama et al. 2010).

The preparation of 2FN has been attempted by the lactonization of 3-alkenoic acid, aerobic oxidation followed by lactonization of 2-butene-1,4-diol, and photooxidation of 2,3-dihydrofuran (Chen et al. 2006; Xie and Stahl 2015; Yan et al. 2009). However, the processes suffer from one or more issues, such as the use of expensive reagents, intricate setup, demanding reaction conditions, and poor yields. Given the bulk availability, inexpensiveness, and of renewable origin, FUR could prove to be the most suitable feedstock for the production of 2-furanone. In compliance with the principle of green chemistry, aqueous hydrogen peroxide or molecular oxygen are frequently employed as inexpensive and eco-friendly oxidants for the oxidation of biomass-derived renewable chemicals, including FUR (Ping Teong et al. 2019). Aqueous hydrogen peroxide is particularly interesting in this regard since it is commercially available in various concentrations, does not require overpressure of oxygen gas, works under milder reaction conditions, and affords higher selectivity towards specific products. Xiang et al. reported 44.8% yield (70 °C, 1 h) of 2FN using 30% H_2O_2 and magnesium hydroxide (Xiang et al. 2016). The highest-yielding synthesis of 2FN from FUR involves the use of performic acid as an oxidant that formed in situ by reacting 30% H_2O_2 solution with formic acid. The reaction was conducted at 60 °C in an aqueous-organic biphasic reaction, and 2FN was isolated in 62% yield along with around 20% combined yield of SA and MA (Li et al. 2016c). Among the various organic solvent studied, 1,2-dichloroethane (DCE) performed best. Apart from the use of chlorinated solvent, the process also mandated the use of an excess of Na_2SO_4 (anhydrous) to remove water. In other reports, the use of the combination of formic acid and H_2O_2 led to lower (ca. 42-48%) yields. In some cases, the stoichiometric amount of an inorganic base or excess of a drying agent were used that led to the generation of wastes. Besides, the recovery of formic acid is rather challenging due to its thermal instability. The use of heterogeneous acid catalysts have also been examined; however, the selectivity of 2FN remained poor (Xiang et al. 2016). In 2019, Zvarych et al.

reported the targeted synthesis of 2FN from FUR using H_2O_2 as the oxidant and acetic acid as the catalyst. The reaction required 24 h to complete around 60 °C and 2FN was obtained in 71% yield (Zvarych et al. 2019).

We anticipated that trifluoroacetic acid (TFA) could be a superior alternative to formic acid for the selective oxidation of FUR due to its strong Brønsted acidity (pKa = 0.23), thermal and chemical stability, availability in the anhydrous form, and recyclability by distillation (López and Salazar 2013). TFA is known to react with aqueous H_2O_2 forming trifluoroperacetic acid (TFPAA), a more powerful oxidant than H_2O_2 itself (Venier et al. 1982). The synthesis of phenol derivatives from benzaldehydes containing electron-donating substituents has been reported using a combination of TFA and aqueous H_2O_2 (Natu et al. 2014). Interestingly, metal-free oxidation of biomass-derived levulinic acid into succinic acid has also been reported using TFA as an acid catalyst and H_2O_2 as a clean oxidant (Dutta et al. 2015b).



Scheme 5.1 Selective oxidation of FUR to 2-furanone and SA by 30% H_2O_2 in TFA.

The Baeyer-Villiger oxidation of FUR by H_2O_2 produces 2-hydroxyfuran as an intermediate that quickly equilibrates 2FN and 2(3H)-furanone. Further oxidation of 2FN forms MA, whereas the oxidation of 2(3H)-furanone leads to SA. The acid-promoted degradation of FUR into intractable products is also routinely encountered.

5.2 EXPERIMENTAL SECTION

5.2.1 Materials

Furfural (99%), triethylamine anhydrous (99%), formic acid (>98%), and 5%Pd/C were purchased from Spectrochem. Aqueous hydrogen peroxide (30%) was purchased from Alfa Aesar. Trifluoroacetic acid (99.5%), acetic acid glacial (99%), sulphuric acid (98%), 1,2-dichloroethane (>98%), diethyl ether (>99%), methanesulphonic acid (98%), sodium sulphate anhydrous (>99%), and chloroform (99%) were purchased from Loba Chemie Pvt. Ltd. Silica gel (60-120 mesh) was purchased from SRL. All the chemicals were used as received and without further purification.

5.2.2 Preparation of 2FN

TFA (5 mL, 6.26 eq.) was taken in a 50 mL round-bottomed flask fitted with a magnetic stir rod and placed in a water bath. Aqueous H_2O_2 (30%, 4 mL) was added slowly over 15 min while stirring in a water bath at RT. Then, FUR (1.00 g, 10.42 mmol) was added dropwise, and the solution was stirred continuously for 1 h. The reaction's progress was monitored by thin-layer chromatography (TLC) (silica gel, chloroform) and stopped as soon as the FUR spot disappeared (visualized by the $KMnO_4$ stain). After the reaction, the colorless solution was transferred into a separatory funnel and extracted with diethyl ether (3×10 mL). The diethyl ether layers were combined and washed with saturated NaCl solution. The diethyl ether extract was dried over anhydrous Na_2SO_4 and evaporated in a rotary evaporator under reduced pressure to get 2FN as a light-yellow liquid. The liquid was passed through a plug of silica gel (60-120 mesh) using diethyl ether as the eluent. Evaporation of diethyl ether under reduced pressure produced 2FN as a colorless oil (0.455 g, 52%).

5.2.3 Isolation of SA

After extracting 2FN, the aqueous TFA layer a was placed in a pre-heated (50 °C) oil-bath, and a pinch of 10%Pd/C was added to decompose the unreacted H_2O_2. After the decomposing of H_2O_2 was complete, the solution was filtered and carefully evaporated in a rotary evaporator under reduced pressure. The sticky white solid was dissolved in diethyl ether, dried over anhydrous Na_2SO_4, and evaporated to give SA

(0.242 g, 20%) as a white crystalline solid. Melting point and NMR spectra of the solid matched with the literature data.

5.3 CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

5.3.1 FTIR, ^{1}H-NMR, ^{13}C-NMR spectra of 2FN

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.58 (1H, d), 6.07 (1H, q), 4.85 (2H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.1, 153.5, 121.1, 72.3; FTIR (ATR, cm^{-1}): 3020, 2923, 2853, 1773, 1740, 1093.

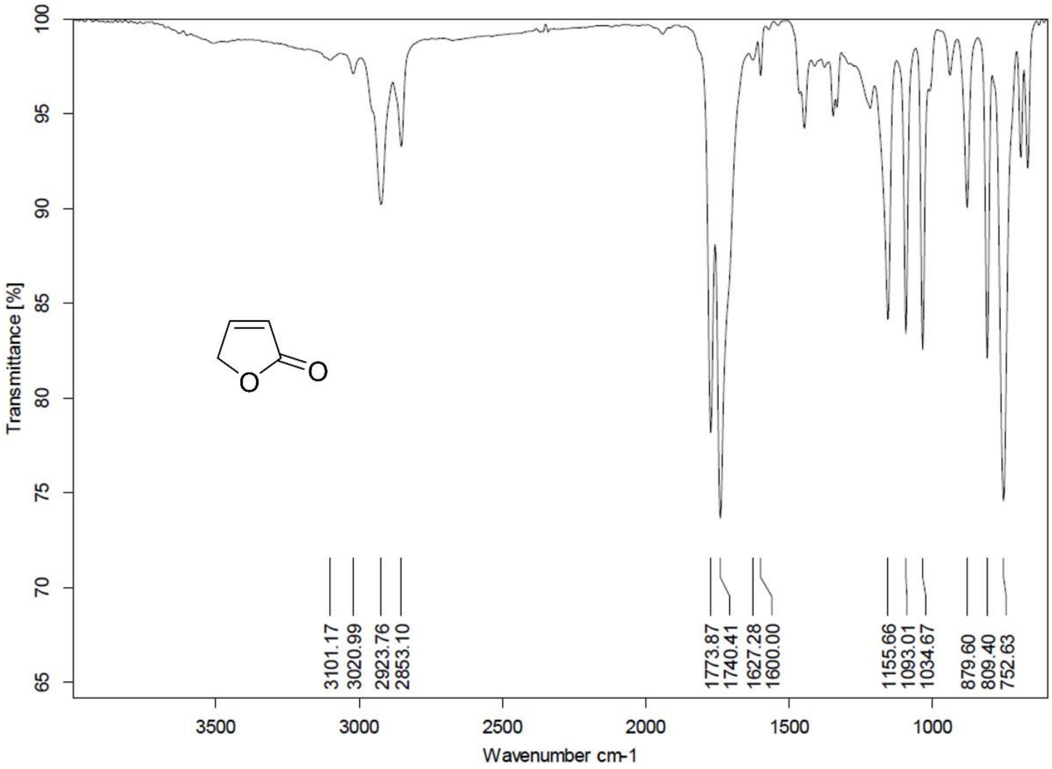


Figure 5.1 The FTIR spectrum of 2FN.

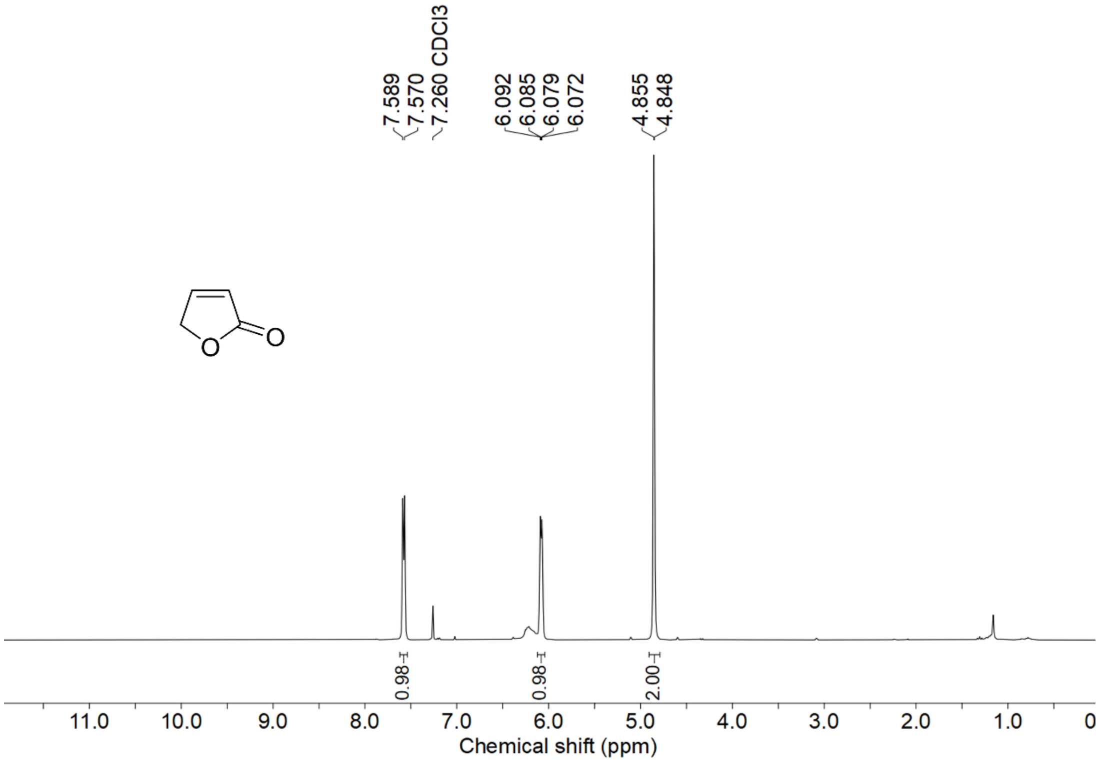


Figure 5.2 The ^{1}H-NMR spectrum of 2FN.

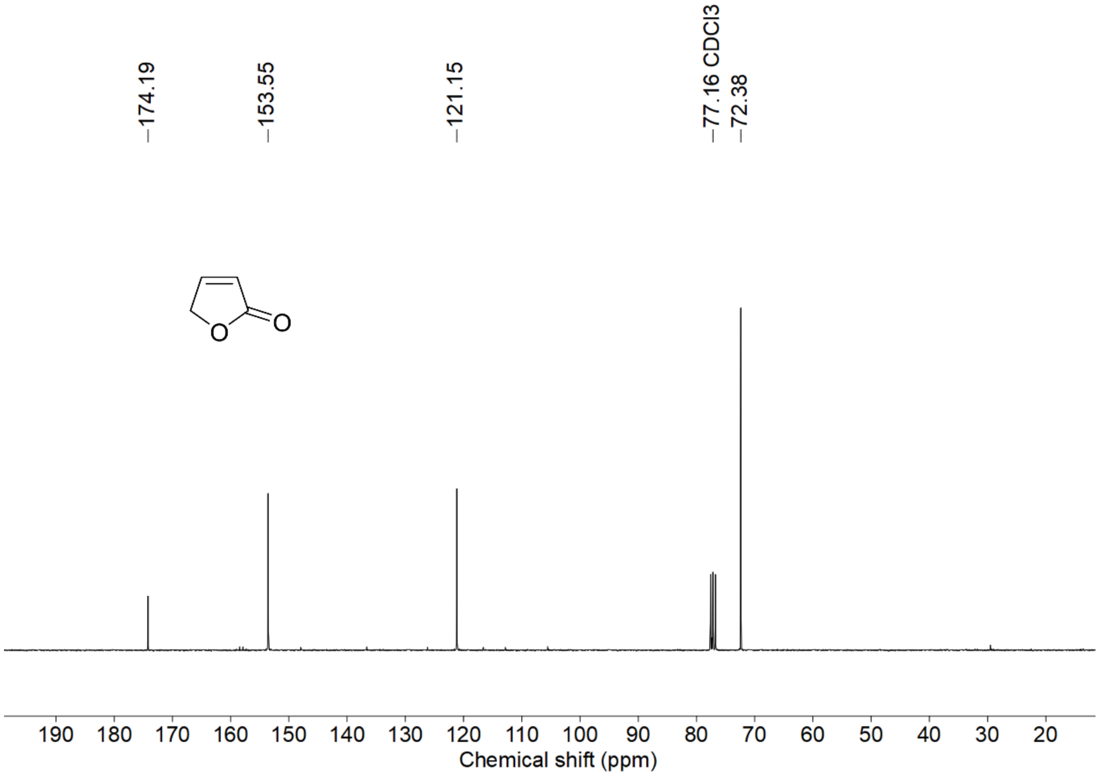


Figure 5.3 The ^{13}C-NMR spectrum of 2FN.

5.3.2 FTIR, ^{1}H-NMR, ^{13}C-NMR spectra of SA

^{1}H-NMR (D_2O, 400 MHz) δ (ppm): 2.59 (4H, s); ^{13}C-NMR (D_2O, 100 MHz) δ (ppm): 176.9, 28.7; FTIR (ATR, cm^{-1}): 3032, 2929, 1719, 1689, 1178.

5.4 RESULTS AND DISCUSSION

Initially, the oxidation of FUR was attempted using 30% H_2O_2 alone without employing any acid catalyst. The progress of the reaction was monitored by TLC (silica gel, chloroform) and allowed to run till quantitative conversion of FUR was achieved. When the reaction was carried out in excess of 30% H_2O_2 (6 eq.), the conversion of FUR was low (<10%) even after 24 h at RT. When the reaction temperature was increased to 60 °C, the FUR conversion was complete within 12 h. However, the lactone 2FN was isolated by extracting the aqueous reaction mixture using diethyl ether in only a 19% yield. The ^{1}H-NMR spectral analysis of the product showed that the 2FN formed almost exclusively. A mixture of over-oxidized solid products, including SA, MA, and their corresponding anhydrides, was recovered from the aqueous layer after distilling out the volatiles under reduced pressure. An acid catalyst of some sort is customarily used in combination with H_2O_2 for the Baeyer-Villiger type oxidation of aromatic aldehydes. Therefore, various homogeneous acid catalysts were screened to explore their effectiveness in catalyzing the oxidation of FUR. The reaction conditions and yield of 2FN for the acid catalysts examined are tabulated in Table 5.1. All the reactions were performed in triplicate, and the average yield is reported. In addition, the experiments ensured complete conversion of FUR to avoid complications in the purification of products and to obtain the highest yield of products.

Table 5.1 Effect of various homogeneous acid catalysts for the preparation of 2FN.

Entry	Catalyst	Reaction conditions[a]	Yield of 2FN (%)[b]
1	CH_3SO_3H	0.2 g MSA, 60 °C, 4 h	30
2	$H_3PW_{12}O_{40}$	0.2 g PTA, 60 °C, 4 h	25
3	HCO_2H	5 mL formic acid, 60 °C, 3 h	40
4	CF_3CO_2H	5 mL TFA, RT, 1 h	52
5	$[Et_3NH][HSO_4]$	1 g ionic liquid, 60 °C, 4 h	38

6	CH_3COOH	2.7 mL acetic acid, 60 °C, 6 h	42
7	No Catalyst	60 °C, 12 h	19
8	CF_3CO_2H	0.5 mL TFA, 60 °C, 3 h	44

[a] The reactions were conducted using FUR (1.00 g, 10.42 mmol) and 4 mL of 30% H_2O_2. [b] Isolated yield after chromatographic purification.

The use of mineral acid catalysts such as methanesulfonic acid (MSA, Table 5.1, entry 1) provided a better yield of 2FN compared to the control reaction. The improvement in yield may be explained by the milder reaction conditions used for the catalytic reaction that led to lesser decomposition of 2FN. When phosphotungstic acid ($H_3PW_{12}O_{40}$), a Keggin heteropoly acid, was used as a solid acid catalyst, 2FN was obtained in a 25% isolated yield when the reaction was conducted at 60 °C for 4 h. Higher loadings of the catalyst allowed the reaction to complete at lower temperatures; however, no significant improvement in the yield of 2FN was observed. The reaction was also carried out using triethylammonium hydrogen sulfate (TEAHS) as an inexpensive, Brønsted acidic ionic liquid catalyst. The lactone 2FN was isolated in a 38% yield under similar reaction conditions. In our case, the use of formic acid (85%) provided 40% yield of 2FN after 4 h at 60 °C and acetic acid provided 42% of 2FN after 6 h at 60 °C. When TFA was used as the solvent (entry 4), the conversion of FUR was complete within 1 h at room temperature, and the yield of 2FN was found to be around 52%. The use of an organic solvent such as DCE gave 54% of 2FN, an only marginal improvement over the organic solvent-free reaction.

Since TFA provided the best selectivity and yield of 2FN, the reaction was further optimized on temperature, the molar ratio of H_2O_2 and FUR and the amount of TFA used. In a typical procedure, the reaction was conducted by dissolving 1 g of FUR in a mixture of 5 mL of TFA and 4 mL of 30% H_2O_2 and stirring the homogeneous reaction mixture in a water bath at room temperature. The reaction was studied by TLC, and FTIR and complete conversion of FUR was observed after 1 h. The reaction mixture was extracted with diethyl ether. The diethyl ether layer was dried and evaporated under reduced pressure to yield the crude product, which was purified by column chromatography. The reaction afforded 2FN in 52% isolated yield. The unreacted H_2O_2 was first decomposed with a catalytic amount of 10% Pd/C, and the aqueous TFA was then distilled to get 20% SA as a white crystalline solid. The aqueous reaction mixture (after extracting 2-furanone), was distilled at atmospheric pressure and resubmitted for the next cycle without attempt to separate water from TFA. The reaction completed in 24 h at RT and 2FN was obtained in a 33% yield. The result can be explained by the dilution of TFA with water. There are novel ways being developed to recover TFA in sufficient purity from the industrial effluents. Quantitative conversion of FUR was achieved within 3 h at 90 °C; however, 2FN was isolated in 22% yield. The isolated yield of SA from the aqueous layer increased to 35%. The result can be explained by over-oxidation of 2FN into SA at elevated temperatures.

When the reaction was conducted at lower temperatures (ca. 0 °C), the reaction kinetics slowed down and took >4 h to complete; however, no significant improvement in the yield of 2FN was observed. Yet, noticeably more (ca. 30%) SA was isolated from the aqueous layer. The results may be explained by further oxidation of 2FN during the extended course of the reaction. The higher combined yield of 2FN and SA may be due to the less acid-promoted decomposition of FUR into intractable products. The presence of less TFA leads to a lower concentration of TFPAA in the reaction mixture, which is considered as the active oxidizing agent. Therefore, the kinetics of the reaction got slowed down with lower selectivity of 2FN. The yield of SA remained nearly unaltered.

The amount of TFA plays a pivotal role in the selectivity of 2FN. The reaction was slow at room temperature when the catalytic amount of TFA (0.5 mL/1 g FUR) was used (Table 5.1, entry 8). Therefore, the reaction had to be conducted at elevated temperatures to achieve a quantitative conversion of FUR. The reaction completed within 3 h at 60 °C, affording a 44% yield of 2FN. In excess TFA (5 mL of TFA for 1 g of FUR), the reaction completed within one hour at RT and provided a maximum 52% isolated yield of 2FN. At higher amounts of TFA (>5 mL), no noticeable improvement in the yield of 2FN was observed. The results may be explained by the fact that higher amounts of TFA lead to the higher equilibrium concentration of TFPAA, the active oxidizing species in this reaction, allowing the reaction to complete faster under the mild condition with improved selectivity towards 2FN.

The effect of the amount of H_2O_2 on the selectivity and yield of 2FN was then examined (Figure 5.4). While 30% H_2O_2 worked best for the reaction, lower concentrations of H_2O_2 slowed down the reaction and did not complete even after several hours of reaction at room temperature.

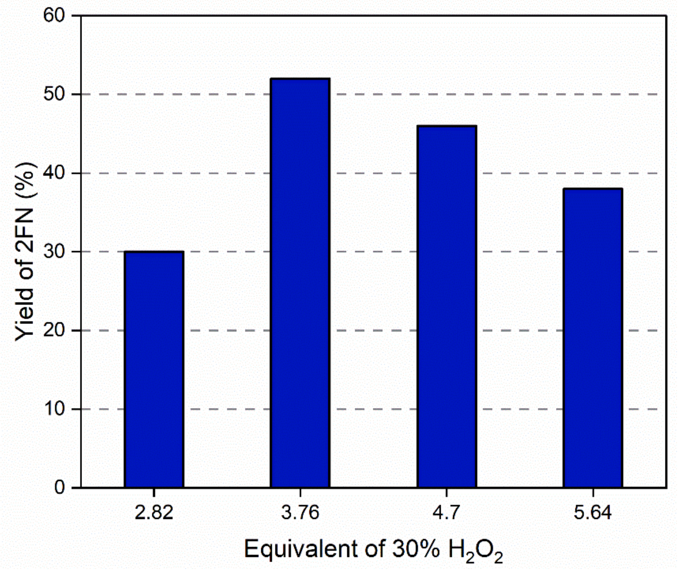


Figure 5.4 The effect of H_2O_2 equivalence on the yield of 2FN.

Reaction conditions: FUR (1.00 g, 10.42 mmol), TFA (5 mL, 6.26 eq.), RT.

The reactions using lower amounts of H_2O_2 provided a noticeable lower yield of 2FN. For 1 g of FUR, 4 mL of 30% H_2O_2 (3.76 eq.) was found to be the optimal amount that allowed the reaction to complete within 1 h at room temperature, providing up to 52% yield of 2FN. Any higher quantities of H_2O_2 allowed the reaction to complete faster but lowered the yield of 2FN due to overoxidation (Figure 5.4). Lower quantities of H_2O_2 did not allow complete conversion of FUR. This can be due to the auto decomposition of H_2O_2 during reaction leaving lesser than the required amount of H_2O_2 available for the oxidation reaction.

The mixture of FUR, TFA, and aq. 30% H_2O_2 formed a homogeneous and monophasic reaction medium. The oxidation reaction was also attempted in an aqueous-organic biphasic reaction medium using a suitable organic solvent. Chlorinated solvents like chloroform and DCE were chosen for their insolubility in water, chemical inertness, and convenient recovery by distillation. The idea was to extract 2FN into the organic layer as soon as it forms in the aqueous layer and shield it from further oxidation or decomposition. However, the use of the solvent did not provide any significant advantage on the selectivity or yield of 2FN. Since the reaction kinetics slowed down, the reaction had to be conducted at elevated temperatures (ca. 50 °C). The result may be justified by the fact that TFPAA has appreciable solubility in chlorinated solvents, and therefore the shielding of 2FN from further oxidation was not very effective. Besides, the requirement of the higher reaction temperature in a biphasic reaction media accelerated the decomposition of 2FN.

It was found that the reaction temperature plays a crucial role on the selectivity and yield of 2FN (Figure 5.5). Under optimized quantities of TFA and 30% H_2O_2 (i.e., 5 mL TFA and 4 mL 30% H_2O_2 per gram of FUR), the reaction completed within 1 h at room temperature. Elevated temperatures made the reaction faster but lowered the selectivity of 2FN, leading to enhanced formation of SA. The result may be explained by the faster overoxidation of 2FN at elevated temperatures. Interestingly, when the reaction was conducted at lower temperatures (ca. 10 °C), the reaction took >4 h to complete, but the selectivity of 2FN did not improve significantly. The result may be explained by the fact that the over-oxidation of 2FN happens even at lower temperatures, and longer reaction time leads to the accumulation of SA over time.

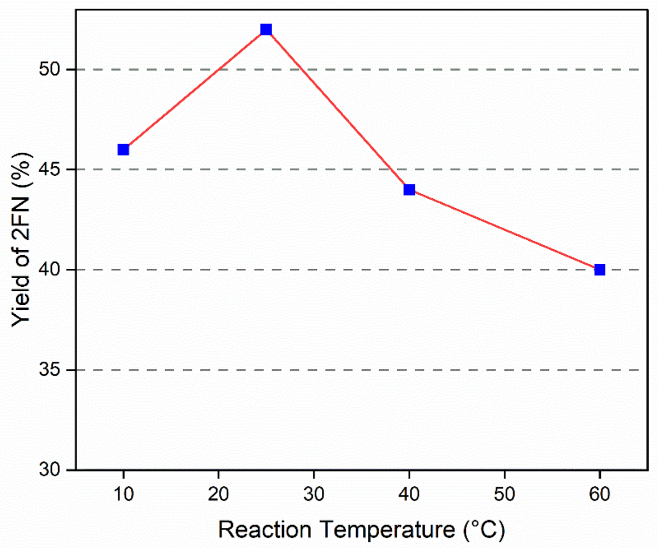


Figure 5.5 The effect of reaction temperature on the yield of 2FN.

Reaction conditions: FUR (1.00 g, 10.42 mmol), TFA (5 mL, 6.26 eq.), H_2O_2 (4 mL, 3.76 eq.).

The oxidation reaction was also attempted in the presence of a drying agent like anhydrous Na_2SO_4. However, no noticeable improvement in the yield of 2FN was observed. Besides, the use of drying agents makes the isolation of SA challenging.

5.5 CONCLUSION

In summary, biomass-derived FUR has been selectively oxidized into 2FN providing up to 52% isolated yield by 30% H_2O_2 as the oxidant in the TFA medium under mild conditions. The gram-scale reaction worked without organic solvent or additives. SA was isolated from the aqueous layer in around 20% yield after the volatiles were distilled out. The use of a catalytic amount of TFA provided a 44% isolated yield of 2FN.

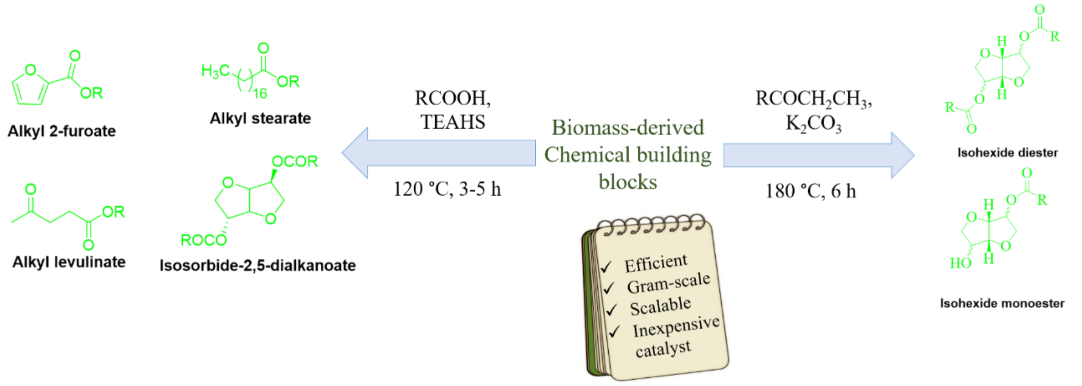
CHAPTER 6

PREPARATION OF HIGH-VALUE ESTERS FROM BIOMASS-DERIVED CHEMICAL PLATFORMS VIA ESTERIFICATION AND TRANSESTERIFICATION REACTIONS

Abstract

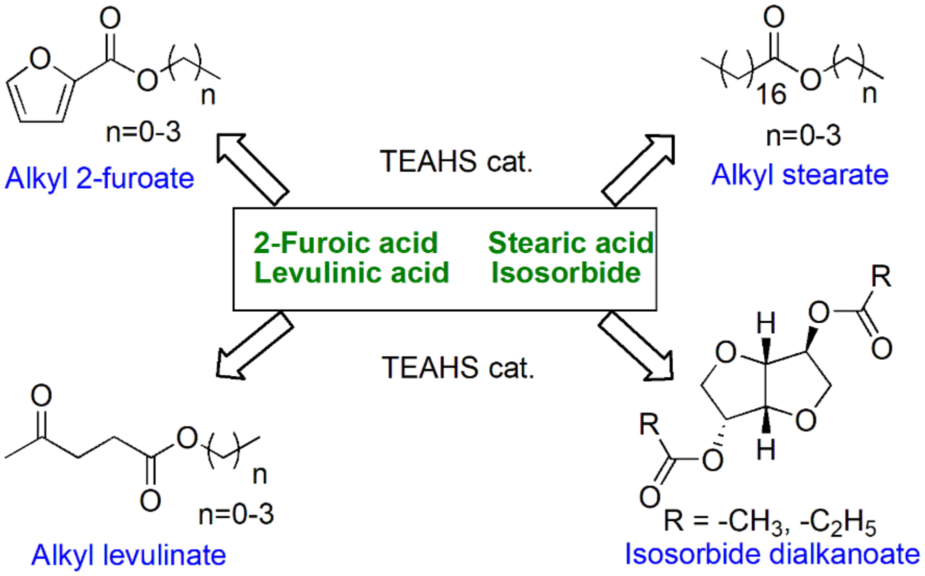
The esters of biomass-derived platforms have numerous potential applications, including fuel and fuel additives, solvents, dispersants for pigments, surfactants for detergents, emulsifiers for cosmetics, and plasticizers for vinyl polymers. The acid-catalyzed esterification and base-catalyzed transesterification are routinely used strategies for synthesizing esters. Triethylammonium hydrogen sulfate (TEAHS) has been employed as an efficient and inexpensive protic ionic liquid catalyst for the preparation of various biomass-derived renewable compounds such as levulinic acid, 2-furoic acid, stearic acid, and isosorbide. The scalable, organic solvent-free preparations were conducted in a batch-type glass pressure reactor, which provided excellent yields (>80%) of the esters under moderate conditions. Similarly, anhydrous potassium carbonate has been used as an efficient, inexpensive, and recyclable base catalyst for the transesterification of isohexides for the synthesis of mono- and diesters. Excellent isolated yields (>90%) of the isosorbide benzoates were obtained, and the methodology was successfully extended to synthesize the mono- and diesters of the other two isohexides, i.e., isomannide and isoidide.

Graphical Abstract



6.1 INTRODUCTION

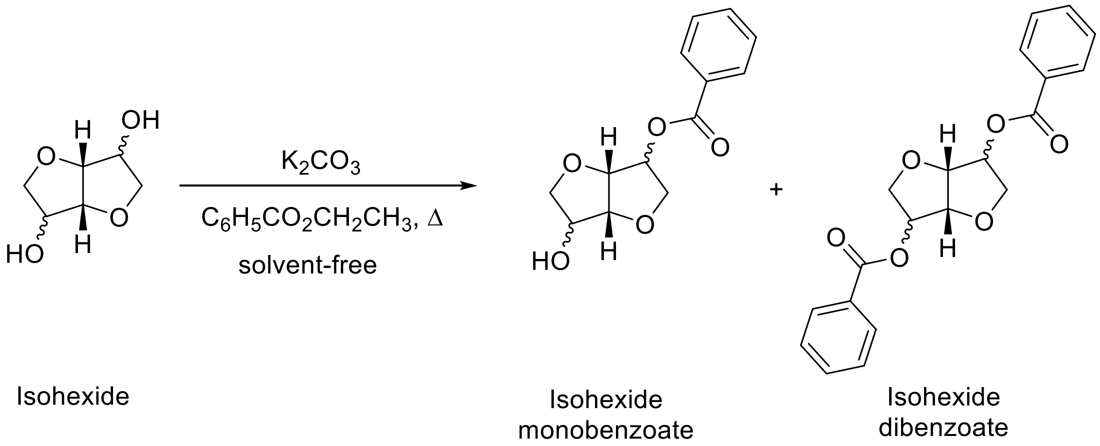
The development of efficient, robust, inexpensive, and eco-friendly catalysts is paramount for the chemical-catalytic biomass value addition pathways. In this regard, using ionic liquids (ILs) as a catalyst and alternative reaction media has become mainstream in synthetic organic chemistry. ILs have been utilized as selective and environment-friendly catalysts as well as a greener reaction media in sustainable synthesis, production of biofuels, and renewable chemicals (Fang et al. 2006; Pârvulescu and Hardacre 2007). For example, protic ILs have been used as acid catalysts for the hydrolysis and dehydration of biomass-derived carbohydrates into renewable chemical platforms such as 5-(hydroxymethyl)furfural (HMF), levulinic acid (LA), and furfural (FUR). ILs have also been employed in the downstream synthetic upgrading of the aforementioned biorenewable chemical intermediates (Troter et al. 2016; Wang et al. 2014). However, one of the major obstacles associated with the scalability of the processes using ILs is their limited availability and high cost. Triethylammonium hydrogen sulfate (TEAHS), prepared by reacting triethylamine with sulfuric acid in equimolar quantities, has received considerable attention over the past decade as an inexpensive Brønsted IL catalyst (Chen et al. 2014). TEAHS has been shown to catalyze the esterification reaction between alkyl carboxylic acid and alkyl alcohols of different chain lengths (Ganeshpure et al. 2007). TEAHS has also been applied as a catalyst for the preparation of coumarins and various biologically important heterocycles (Karimi-Jaberi et al. 2020). TEAHS has served as an IL medium for the pretreatment of lignocellulosic biomass, and for producing biodiesel from palm oil (Liu et al. 2012). However, the application of TEAHS for the synthetic upgrading of biomass-derived chemical building blocks is virtually absent in the literature. In this work, we report TEAHS as an inexpensive, efficient, and recyclable catalyst for the esterification of various biomass-derived chemical intermediates into products of commercial significance. The alkyl esters of LA are of immense interest as renewable fuel oxygenate, green solvent, and chemical intermediate for further value-addition (Démolis et al. 2014; Tiong et al. 2018a). Hereby, we show TEAHS as an inexpensive but efficient catalyst for the preparation of methyl- to butyl levulinate starting from biomass-derived LA (Scheme 6.1). The alkyl esters of fatty acids have commercial applications as biodiesel and surface-active agents, among others. The acid-catalyzed esterification of free fatty acid (FAA) is of significant interest lately for the production of biodiesel from FAA-rich inexpensive feedstock (Mehta et al. 2014; Usha and Maitra 2016). We report the preparation of alkyl stearates by the esterification of stearic acid (StA) with monohydric alkyl alcohols using TEAHS as the catalyst as well as the reaction medium. Alkyl 2-furoates are also important compounds with potential applications as novel oxygenate, green solvent, and a constituent in various personal care products (Manzoli et al. 2016). Alkyl 2-furoates have been produced in decent yields from biomass-derived 2-furoic acid (2FA) and alkyl alcohol using TEAHS as the catalyst. The diesters of isosorbide (IS), a glucose-derived diol, have potential applications as renewable plasticizers, surfactants, and monomers for polymeric applications (Dussenne et al. 2017). The diacetates and dipropionates of IS have been produced in satisfactory yields using TEAHS as the catalyst. Since the small-chain (C1-C4) monohydric alkyl alcohols and carboxylic acids (C2-C3) are also sourced from biomass, the esters discussed here are biorenewable to their entirety.



Scheme 6.1 TEAHS catalyzed esterification of various biomass-derived renewable chemicals.

The monoesters and diesters of isohexides (IS, isomannide (IM), and isoidide (II)) have potential applications as monomers for renewable polymers, chemical intermediates, green solvents, surfactants, and plasticizers (Dussenne et al. 2017; Rose and Palkovits 2012). The monoesters and diesters of isohexides are routinely prepared by acid-catalyzed esterification following the Fischer esterification protocol. For example, a gram-scale preparation of isosorbide-2,5-diacetate (ISDA) has been reported using glacial acetic acid as the reagent and amberlyst 15 (A15) as a heterogeneous acid catalyst (Fraile and Saavedra 2017). In an alternative strategy, the isohexides are reacted with reactive carbonyl compounds, such as carbonyl chloride and acid anhydride. In recent work, the esters of IS have been synthesized by oxidative esterification using aldehydes in the presence of an N-heterocyclic carbene catalyst (Ragno et al. 2021). The benzyl ether of IS has been converted into isosorbide-2,5-dibenzoate (ISDB) by aerobic oxidation using dye-sensitized semiconductor under visible light photocatalysis (Ren et al. 2017).

In this regard, base-catalyzed transesterification is a convenient and scalable strategy for synthesizing esters. The synthesis of various biorenewable fuels and chemicals has already been reported following the transesterification strategy. The base-catalyzed transesterification of isohexides has never been studied systematically, and only some isolated literature in the form of patents are available. One of the primary challenges in base-catalyzed transesterification is identifying an efficient, inexpensive, and recyclable base catalyst for the transformation. This work reports potassium carbonate anhydrous (K_2CO_3) as an inexpensive but efficient base catalyst for the selective synthesis of various monoesters and diesters of isohexides. The gram-scale synthesis afforded excellent isolated yields of the esters.



Scheme 6.2 Base-catalyzed transesterification of isohexides under solvent-free conditions.

6.2 EXPERIMENTAL SECTION

6.2.1 Materials

Levulinic acid (99%) and stearic acid (99%) were bought from Loba Chemie Pvt. Ltd. Isosorbide (99%) was purchased from Merck. Potassium triphosphate was purchased from Sigma Aldrich. Isosorbide, isomannide, and ethyl furoate were purchased from TCI. Potassium carbonate anhydrous (99%) was purchased from Spectrum. Methanol (99.5%) was purchased from Fischer Scientific. Ethanol (200 proof), 1-propanol (99.5%), 1-butanol (99%), chloroform (98%), sulfuric acid (98%), silica gel (60-120 mesh), glacial acetic acid, sodium sulfate (99%, anhydrous), Ethyl oleate (99%) and ethyl benzoate (99%) were purchased from Loba Chemie Pvt. Ltd. Ethyl acrylate (99%), sodium hydroxide (97%), potassium *tert*-butoxide (98%), silica gel (60-120 mesh), Molecular sieves (4 Å), triethylamine (99%), and furfural (99%) were purchased from Spectrochem. Ethyl acetate (99%), and petroleum ether (60-80, 95%) were purchased from Finar. The round-bottomed glass pressure reactor (75 mL) with Teflon screw-top was purchased from Sigma. The alcohols were used after overnight drying over pre-activated molecular sieves (4 Å). 2FA was synthesized from FUR by a slight modification of a literature procedure (Wilson 1926). TEAHS was prepared by reacting equimolar quantities of triethylamine and sulfuric acid (98%) following a literature procedure (Ganeshpure et al. 2007). All other chemicals were used as received without further purification.

6.2.2 Method A: Esterification of biomass-derived intermediates using an efficient and inexpensive ionic liquid catalyst

6.2.2.1 Synthesis of ethyl stearate (ES)

StA (1.002 g, 3.51 mmol), ethanol (5 mL), and TEAHS (0.2 g, 1.004 mmol, 28.60 mol%) were charged in a 75 mL high-pressure glass reactor fitted with a Teflon screw-top and magnetically stirred for 4 h in a pre-heated oil bath at 120 °C. After the reaction, the reactor was cooled down to room temperature. Excess ethanol was evaporated under reduced pressure in a rotary evaporator. The reaction mixture was then diluted with petroleum ether (20 mL), and IL catalyst was separated by phase separation. The petroleum ether layer was then dried by anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed (silica gel, petroleum ether) to get ES (1.05 g, 96%) as a colorless oil. The same synthetic procedure was applied for the synthesis other three stearates.

6.2.2.2 Synthesis of ethyl levulinate (EL)

LA (1.002 g, 8.62 mmol), ethanol (5 mL), and TEAHS (0.5 g, 2.510 mmol, 29.11 mol%) were charged in a 75 mL high-pressure glass reactor fitted with a Teflon screw top. The reactor was sealed and placed in a pre-heated oil bath (120 °C) for 3 h under continuous magnetic stirring. The reactor was cooled down to room temperature, and excess ethanol was evaporated in a rotary evaporator under reduced pressure. Chloroform (10 mL) was added to the mixture, and the IL catalyst was phase separated. The chloroform layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed (silica gel, chloroform) to get EL (0.999 g, 80%) as light-yellow oil. The same synthetic procedure was applied for the synthesis other three levulinates.

6.2.2.3 Synthesis of ethyl 2-furoate (EF)

2FA (0.502 g, 4.47 mmol), ethanol (5 mL), TEAHS (0.5 g, 2.510 mmol, 56.15 mol%), and A15 (0.1 g) were charged into a 75 mL round-bottomed flask fitted with a Teflon screw-top. The reaction mixture was placed in a pre-heated (120 °C) oil bath and magnetically stirred continuously for 5 h. After completion of the reaction, the reactor was cooled down to room temperature, and excess ethanol was evaporated. Chloroform (10 mL) was added to the reaction mixture, and TEAHS was phase separated. The chloroform layer was dried over anhydrous Na_2SO_4 and evaporated in a rotary evaporator under reduced pressure, and the crude product was chromatographed (silica gel, chloroform) to get EF (0.440 g, 70%) as a clear liquid. The same synthetic procedure was applied for the synthesis other three furoates.

6.2.2.4 Synthesis of isosorbide-2,5-diacetate (ISDA)

IS (1.002 g, 6.85 mmol), glacial acetic acid (5 mL), and TEAHS (1.0 g, 5.020 mmol, 73.28 mol%) were charged into a 75 mL ACE glass pressure reactor fitted with a Teflon screw top with a magnetic stirrer bar. The reactor is placed in the pre-heated oil bath at 120 °C for 4 h with continuous stirring. After the reaction, the reactor was cooled down to room temperature and opened. Excess acetic acid was evaporated in a rotary evaporator under reduced pressure. The reaction mixture was extracted with chloroform (10 mL), and TEAHS was phase separated. The chloroform layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed (Silica gel, chloroform) to get ISDA (0.790 g, 50%) as a clear oil. The same synthetic procedure was followed for the synthesis of isosorbide-2,5-dipropionate (ISDP).

6.2.3 Method B: Transesterification of isohexide under solvent-free conditions

6.2.3.1 Synthesis of ISDB from IS

IS (0.502 g, 3.42 mmol), ethyl benzoate (2.57 g, 17.11 mmol), and anhydrous potassium carbonate (0.237 g, 50 mol%) were taken in a 50 mL round-bottomed flask. The mixture was placed in a pre-heated (180 °C) oil bath (open reactor) and stirred magnetically for 6 h. After the reaction, the reaction mixture was cooled to room temperature. The reaction mixture is diluted with ethyl acetate (20 mL) and filtered using Whatmann filter paper. The ethyl acetate layer was dried over anhydrous Na_2SO_4 and evaporated in a rotary evaporator under reduced pressure. After evaporation, crude product along with excess ethyl benzoate was subjected to column chromatography to obtain pure mono- and diesters. The pure white solid of ISDB (1.120 g, 94%) was obtained.

6.3 CHARACTERIZATION OF SYNTHESIZED COMPOUNDS

6.3.1 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Methyl 2-furoate (MF)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.57 (1H, s), 7.18 (1H, d, J = 3.6 Hz), 6.50 (1H, t, J = 3.6 Hz), 3.89 (3H, s); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 159.2, 146.4, 144.7, 118.0, 111.9, 52.0; FTIR (ATR, cm^{-1}): 3143, 3024, 2954, 1722, 1299, 1116.

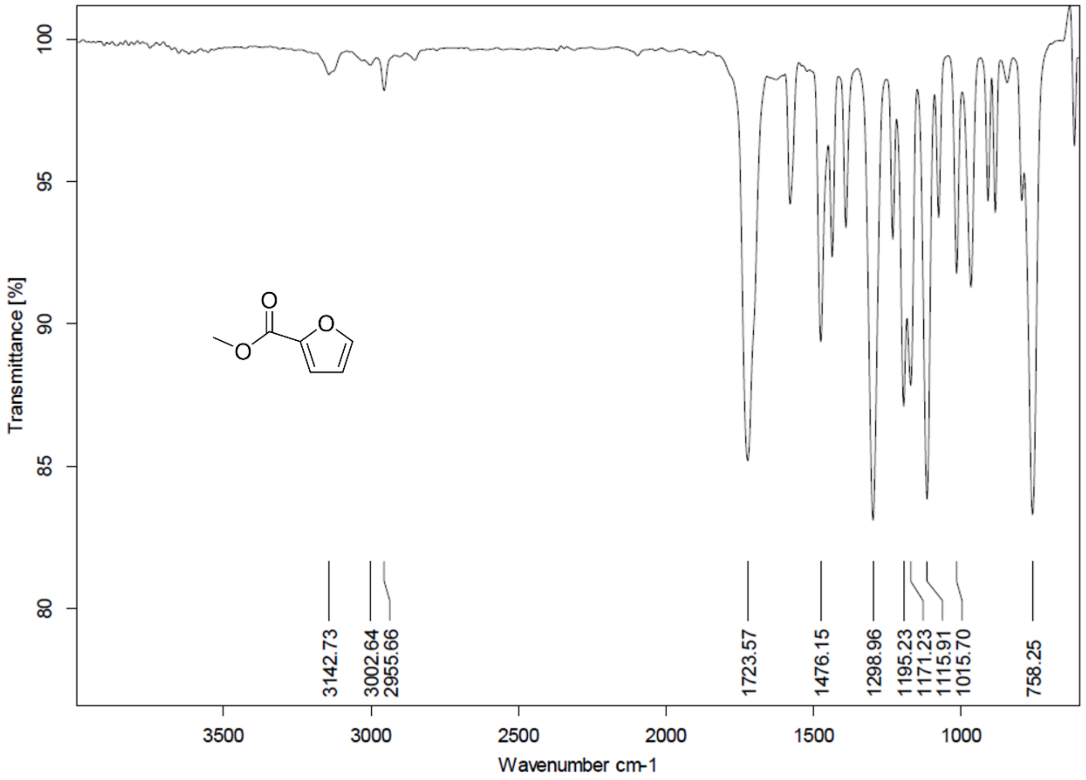


Figure 6.1 The FTIR spectrum of MF.

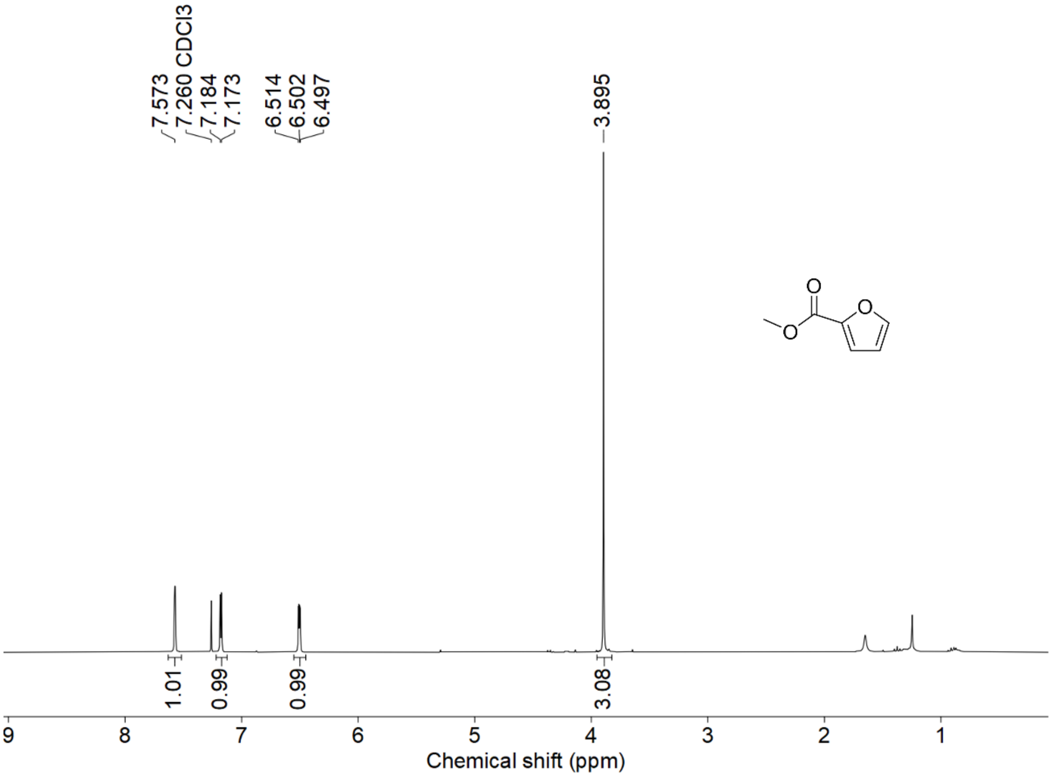


Figure 6.2 The ^{1}H-NMR spectrum of MF.

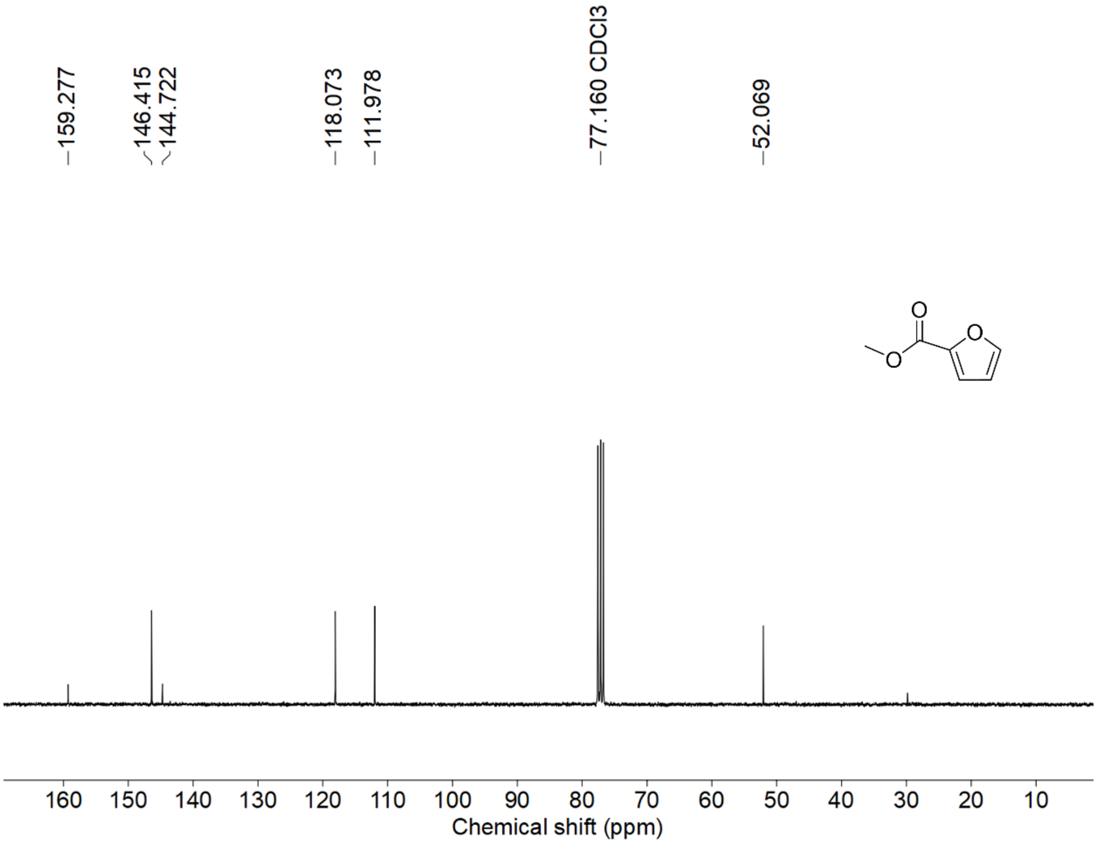


Figure 6.3 The ^{13}C-NMR spectrum of MF.

6.3.2 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of EF

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.48 (1H, q, J = 0.9 Hz), 7.09 (1H, q, J = 0.9 Hz and 2.7 Hz), 6.41 (1H, q, J = 2.7 Hz), 4.27 (2H, q, J = 7.2 Hz), 1.28 (3H, t, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.6, 146.1, 144.8, 117.6, 111.7, 60.8, 14.2; FTIR (ATR, cm^{-1}): 3142, 3126, 2983, 2874, 1714, 1292, 1008.

6.3.3 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Propyl 2-furoate (PF)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.49 (1H, s), 7.08 (1H, s), 6.40 (1H, s), 4.17 (2H, t, J = 6.6 Hz), 1.67 (2H, m, J = 6.6 Hz and 7.2 Hz), 0.91 (3H, t, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 158.7, 146.1, 144.8, 117.6, 111.7, 66.3, 22.0, 10.2; FTIR (ATR, cm^{-1}): 3142, 3126, 2968, 2856, 1715, 1291, 1114.

6.3.4 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Butyl 2-furoate (BF)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.48 (1H, s), 7.07 (1H, s), 6.40 (1H, s), 4.20 (2H, t, J = 6.6 Hz), 1.62 (2H, m, J = 6.6 Hz and 7.5 Hz), 1.34 (2H, m, J = 7.5 Hz), 0.86 (3H, t, J = 7.5 Hz); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm):158.7, 146.0, 144.8, 117.5, 111.6, 64.6, 30.6, 19.0, 13.5; FTIR (ATR, cm^{-1}): 3142, 3125, 2960, 2873, 1715, 1292, 1011.

6.3.5 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Methyl levulinate (ML)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.60 (s, 3H), 2.69 (t, 2H, *J* = 6.4 Hz), 2.50 (d, 2H, *J* = 6.4 Hz), 2.12 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.7, 173.2, 51.8, 37.9, 29.8, 27.7; FTIR (ATR, cm^{-1}): 2955, 1712, 1360, 1157.

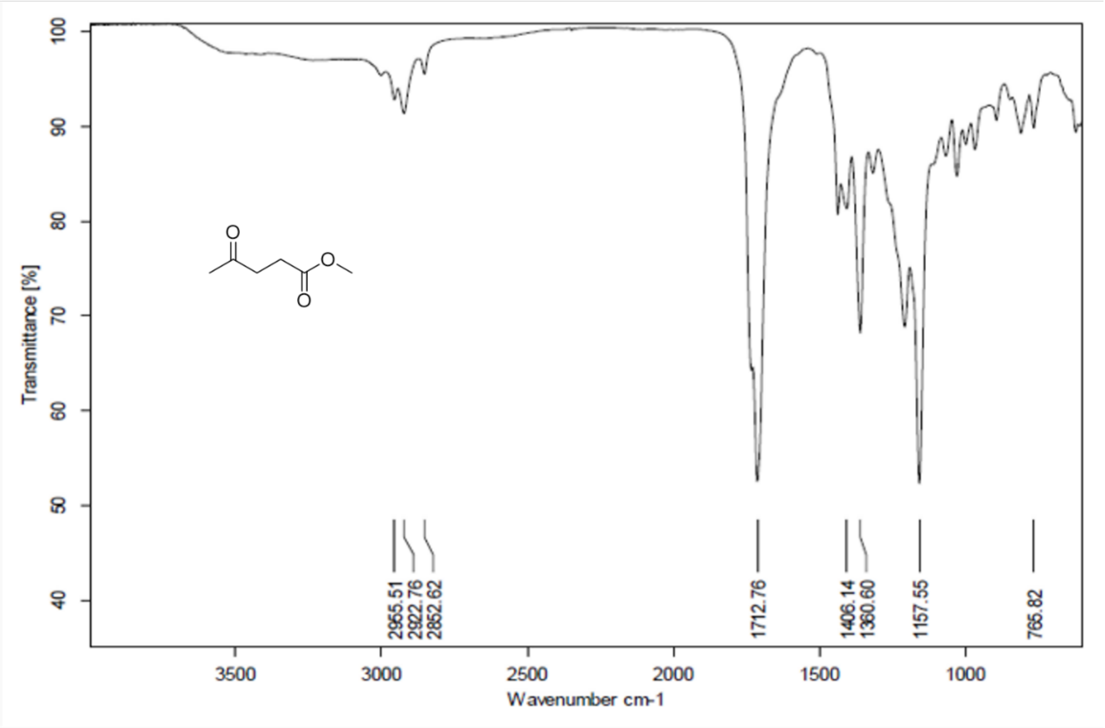


Figure 6.4 The FTIR spectrum of ML.

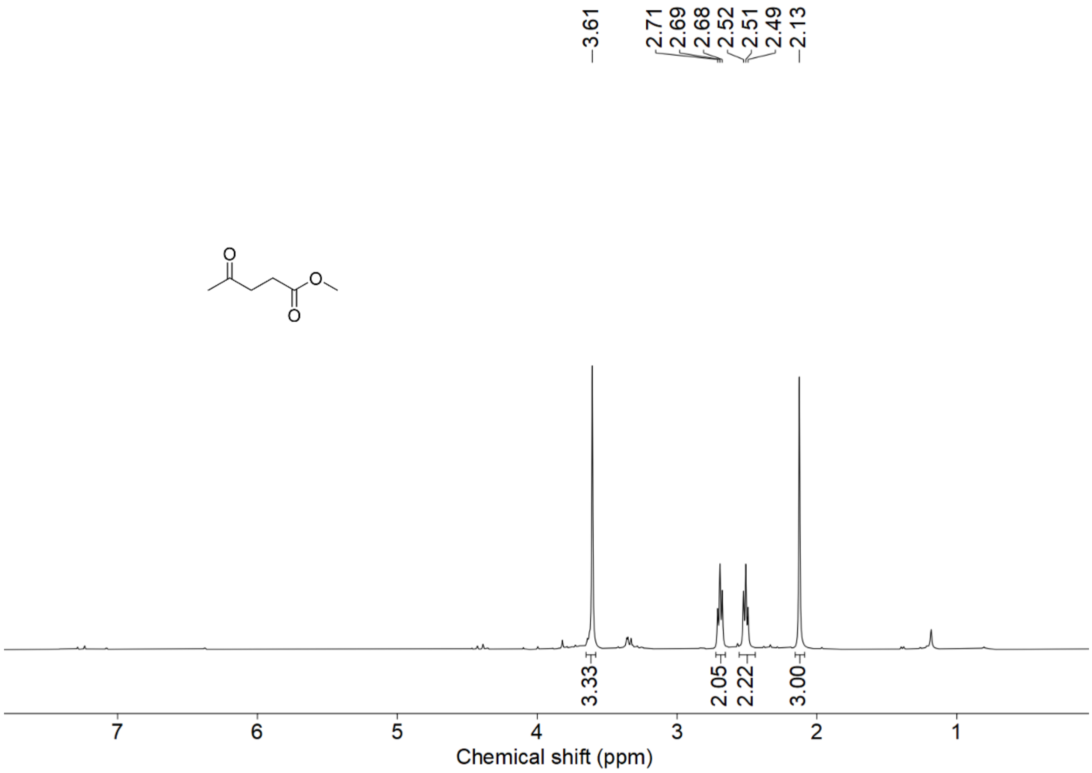


Figure 6.5 The ^{1}H-NMR spectrum of ML.

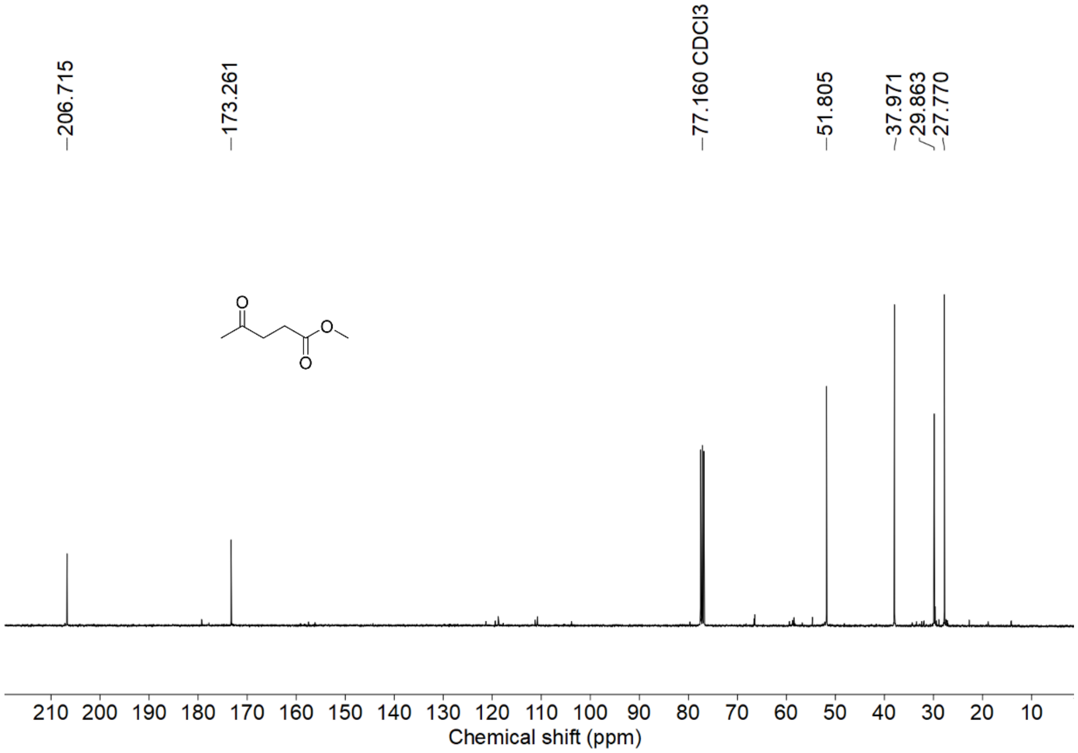


Figure 6.6 The ^{13}C-NMR spectrum of ML.

6.3.6 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of EL

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.09 (q, 2H, *J* = 7.2 Hz), 2.71 (t, 2H, *J* = 6.4 Hz), 2.52 (t, 2H, *J* = 6.4 Hz), 2.15 (s, 3H), 1.21 (t, 3H, *J* = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 202.4, 172.0, 59.6, 36.9, 28.8, 27.0, 13.1; FTIR (ATR, cm^{-1}): 2982, 2931, 1716, 1155.

6.3.7 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Propyl levulinate (PL)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.95 (t, 2H, *J* = 6.7 Hz), 2.68 (t, 2H, *J* = 6.5 Hz), 2.49 (t, 2H, *J* = 6.5 Hz), 2.12 (s, 3H), 1.56 (m, 2H, J = 6.7 Hz and 7.4 Hz), 0.86 (t, 3H, *J* = 7.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.6, 172.7, 66.1, 37.8, 29.7, 27.9, 21.8, 10.2; FTIR (ATR, cm^{-1}): 2969, 2940, 1715, 1358, 1155.

6.3.8 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Butyl levulinate (BL)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.04 (t, 2H, *J* = 6.8 Hz), 2.72 (t, 2H, *J* = 6.4 Hz), 2.54 (t, 2H, *J* = 6.4 Hz), 2.16 (s, 3H), 1.56 (m, 2H), 1.34 (m, 2H), 0.90 (t, 3H, *J* = 8.0 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 206.6, 172.7, 64.5, 37.9, 30.5, 29.8, 27.9, 19.0, 13.6; FTIR (ATR, cm^{-1}): 2960, 2935, 1716, 1357, 1156.

6.3.9 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Methyl stearate (MeS)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.68 (s, 3H), 2.31 (t, 2H, J = 7.5 Hz), 1.63 (t, 2H, J = 7.5 Hz), 1.33 (m, 28H, J = 6.3 Hz), 0.89 (t, 3H, J = 6.3 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm):174.3, 51.4, 34.1, 31.9, 29.7, 29.66, 29.6, 29.4, 29.3, 29.2, 29.1, 24.9, 22.6, 14.1; FTIR (ATR, cm^{-1}): 2921, 2852, 1742, 1169.

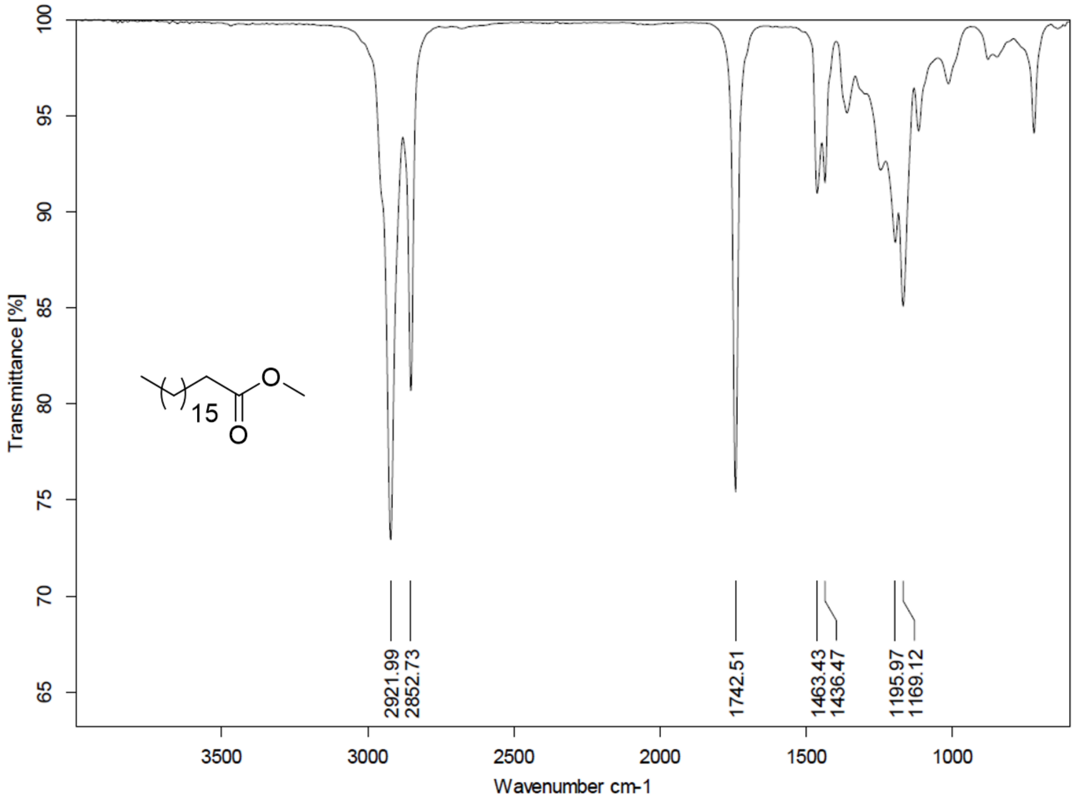


Figure 6.7 The FTIR spectrum of MeS.

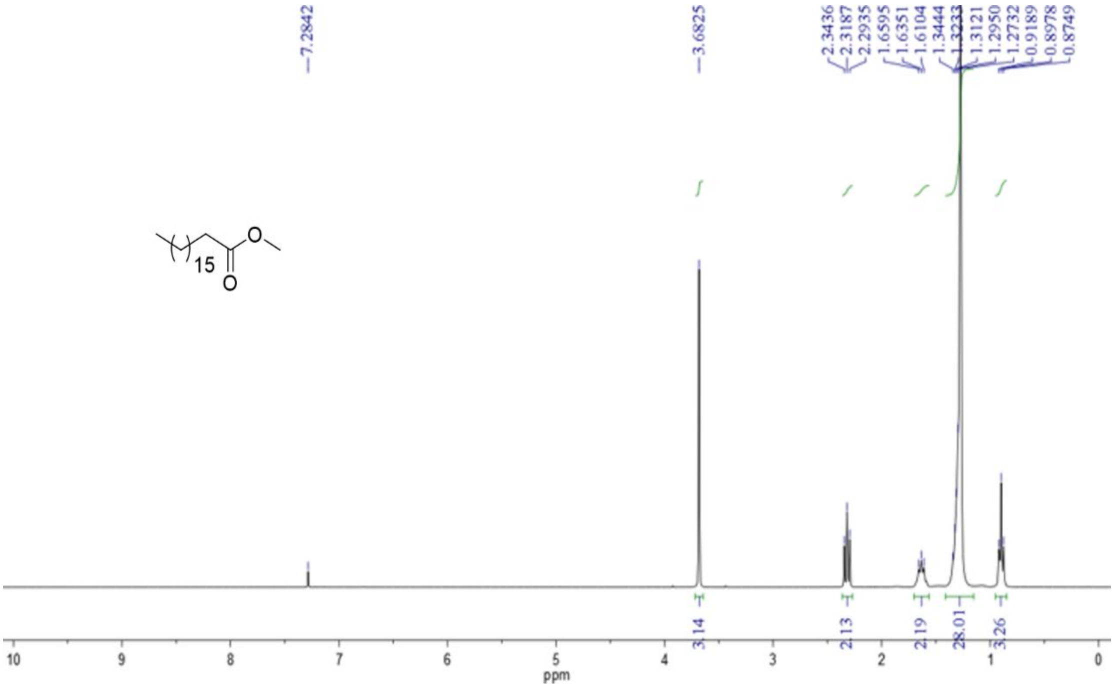


Figure 6.8 The ^{1}H-NMR spectrum of MeS.

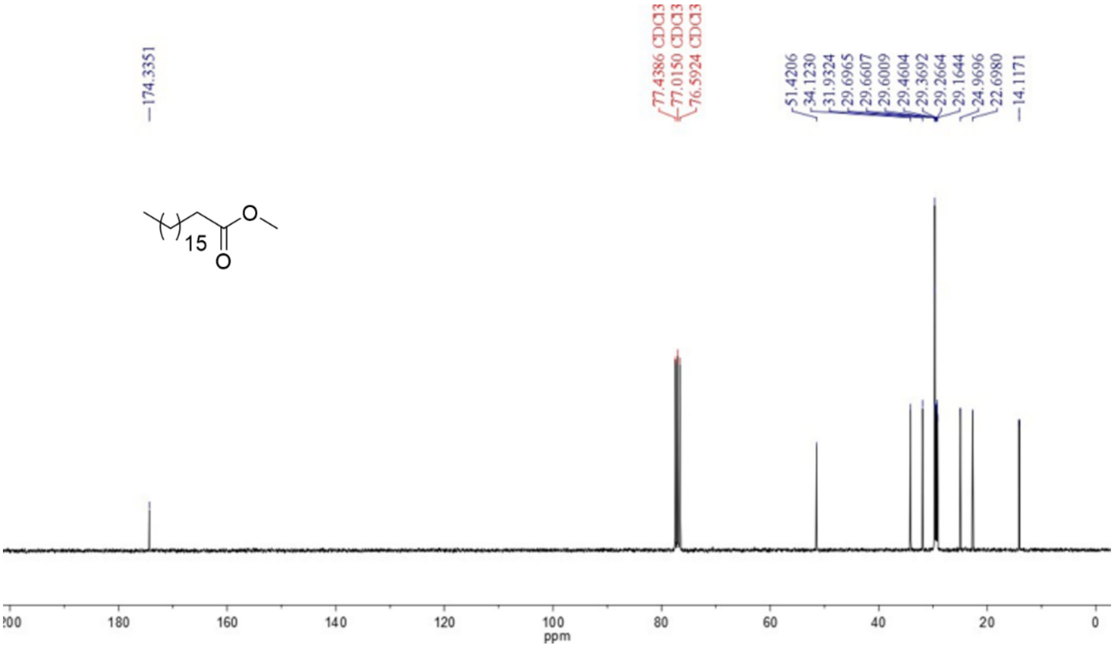


Figure 6.9 The ^{13}C-NMR spectrum of MeS.

6.3.10 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ES

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm):4.15 (q, 2H, J = 7.1 Hz), 2.30 (t, 2H, 7.6 Hz), 1.63 (m, 2H, J = 7.6 Hz), 1.27 (m, 31H), 0.90 (t, 3H, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 173.9, 60.1, 34.4, 31.9, 29.69, 29.65, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, 22.6, 14.2, 14.1; FTIR (ATR, cm^{-1}): 2922, 2853, 1738, 1176.

6.3.11 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of Propyl stearate (PS)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.04 (t, 2H), 2.31 (t, 2H, J = 7.5 Hz), 1.64 (t, 4H, J = 7.5 Hz), 1.27 (m, 28H), 0.96 (t, 3H), 0.90 (t, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.0, 65.8, 34.4, 31.9, 29.7, 29.65, 29.59, 29.4, 29.3, 29.2, 29.1, 25.0, 22.6, 22.0, 14.1, 10.3; FTIR (ATR, cm^{-1}): 2922, 2853, 1738, 1173.

6.3.12 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of butyl stearate (BS)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.08 (t, 2H, J = 6.7 Hz), 2.30 (t, 2H, J = 7.5 Hz), 1.63 (t, 4H, J = 6.7 Hz and 7.5 Hz), 1.27 (m, 30H), 0.95 (m, 3H), 0.90 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 174.0, 64.0, 34.4, 31.9, 30.7, 29.7, 29.6, 29.5, 29.47, 29.45, 29.36, 29.26, 29.16, 25.0, 22.6, 19.1, 14.1, 13.7; FTIR (ATR, cm^{-1}): 2922, 2853, 1737, 1171.

6.3.13 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ISDA

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 5.14 (m, 2H), 4.80 (t, 1H), 4.46 (d, 1H), 3.95 (m, 3H), 3.76 (m, 1H), 2.10 (s, 3H), 2.05 (s, 3H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 170.4, 170.1, 85.8, 80.6, 78.0, 73.9, 73.3, 70, 20.8, 20.5; FTIR (ATR, cm^{-1}): 2980, 2875, 1742, 1718, 1089.

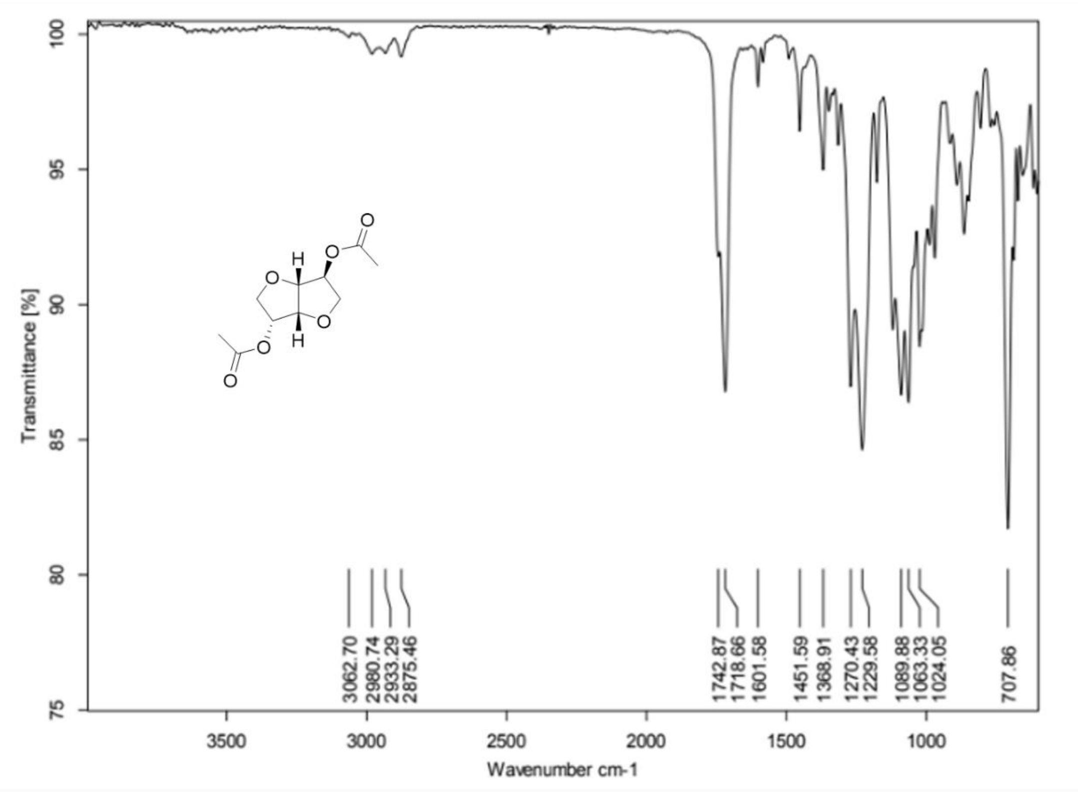


Figure 6.10 The FTIR spectrum of ISDA.

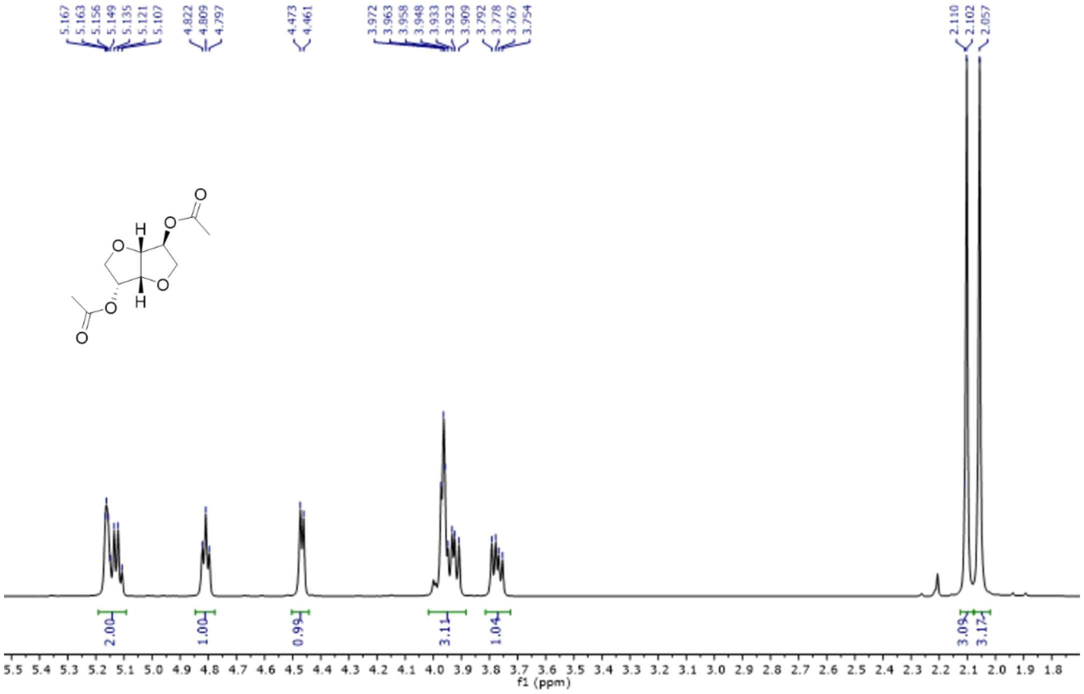


Figure 6.11 The ^{1}H-NMR spectrum of ISDA.

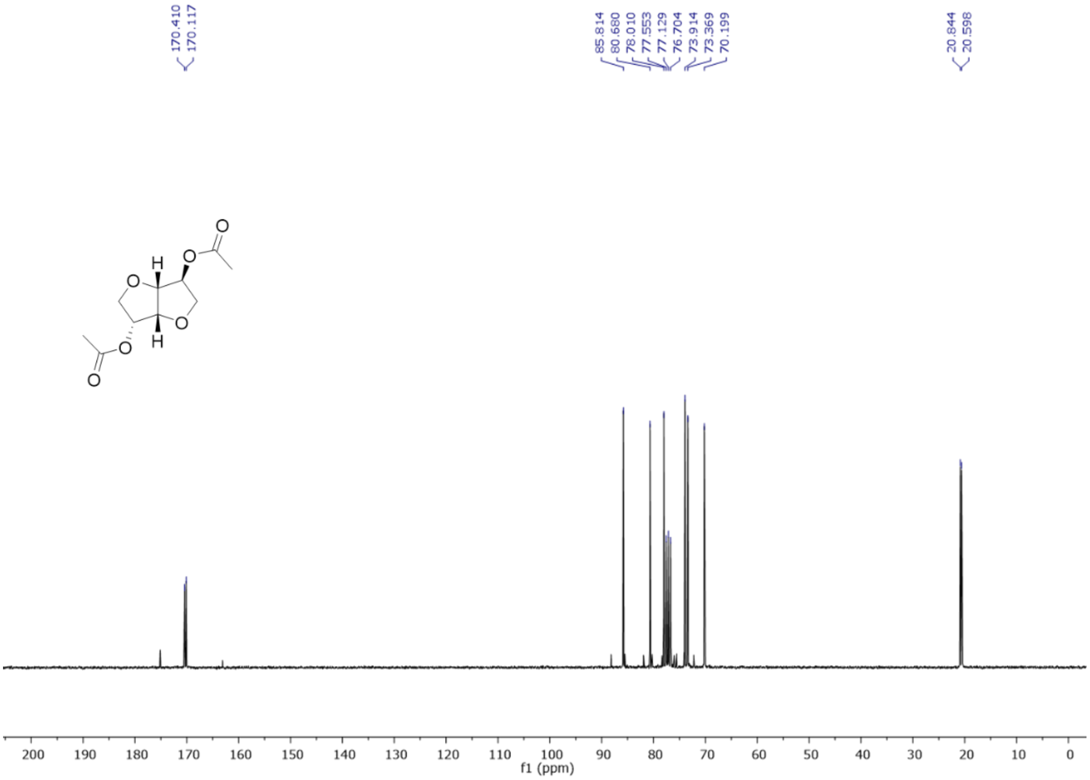


Figure 6.12 The ^{13}C-NMR spectrum of ISDA.

6.3.14 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ISDP

^{1}H-NMR (CDCl$_3$, 300 MHz) δ (ppm): 5.18 (t, 2H), 4.84 (s, 1H), 4.49 (s, 1H), 3.93 (m, 3H), 3.81 (m, 1H), 2.37 (m, 4H), 1.05 (q, 6H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ (ppm): 173.6, 173.3, 85.8, 80.6, 77.3, 73.7, 73.2, 70.2, 27.3, 27.1, 8.9, 8.8; FTIR (ATR, cm^{-1}): 2982, 2880, 1735, 1015.

6.3.15 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ISDB

^{1}H-NMR (CDCl$_3$, 300 MHz) δ (ppm): 8.10-8.08 (m, 4H), 7.58-7.54 (m, 2H), 7.48-7.41 (m, 4H), 5.49-5.40 (m, 2H), 5.07 (t, 1H), 4.69 (d, 1H), 4.13-4.05 (m, 4H); ^{13}C-NMR (CDCl$_3$, 75 MHz) δ (ppm): 166.0, 165.7, 133.5, 129.9, 129.8, 128.6, 86.3, 81.2, 78.6, 74.6, 73.6, 70.8; FTIR (ATR, cm^{-1}): 3064, 2991, 1719, 1069.

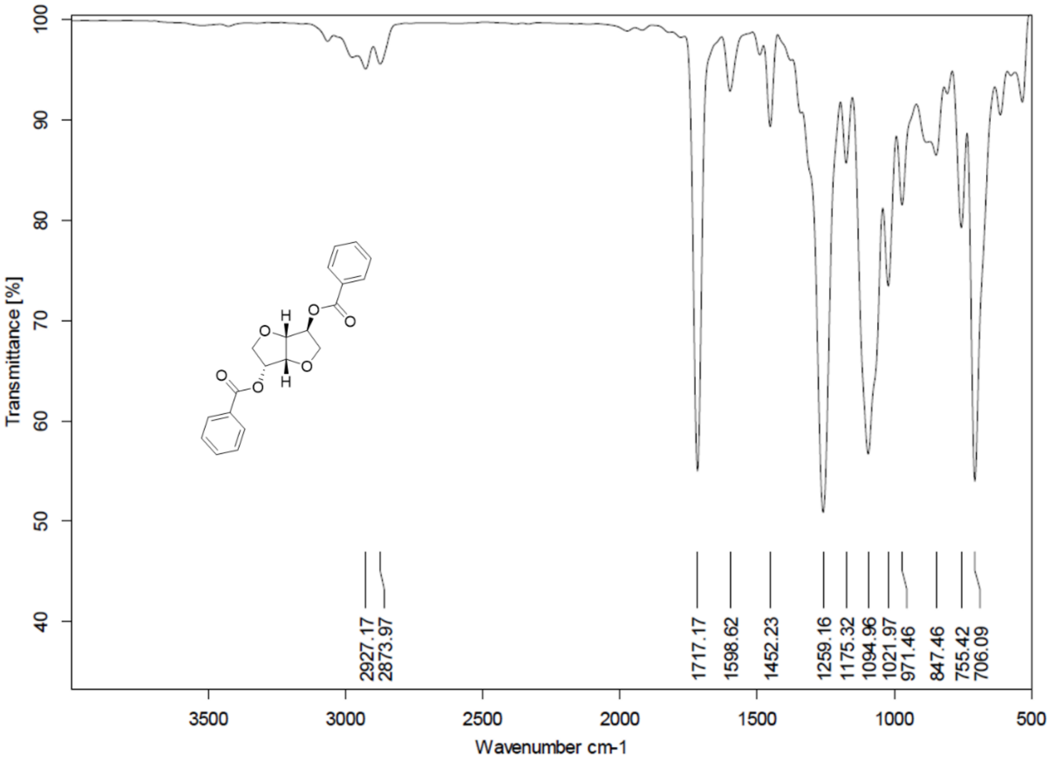


Figure 6.13 The FTIR spectrum of ISDB.

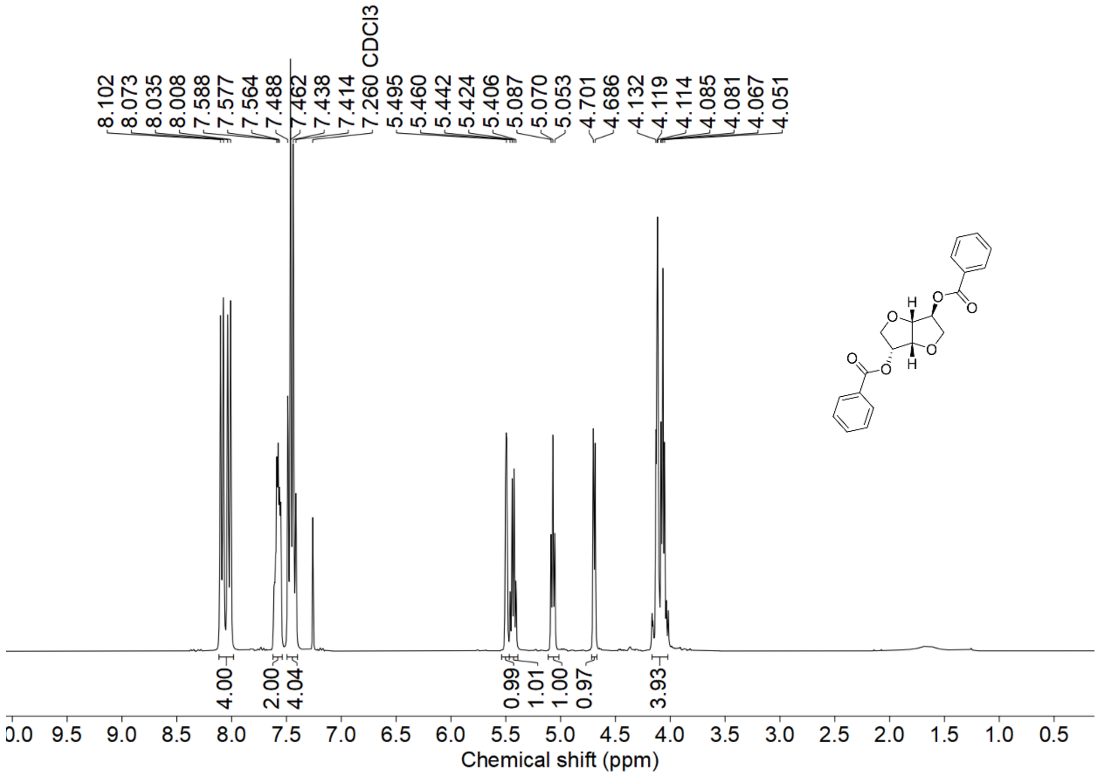


Figure 6.14 The ^{1}H-NMR spectrum of ISDB.

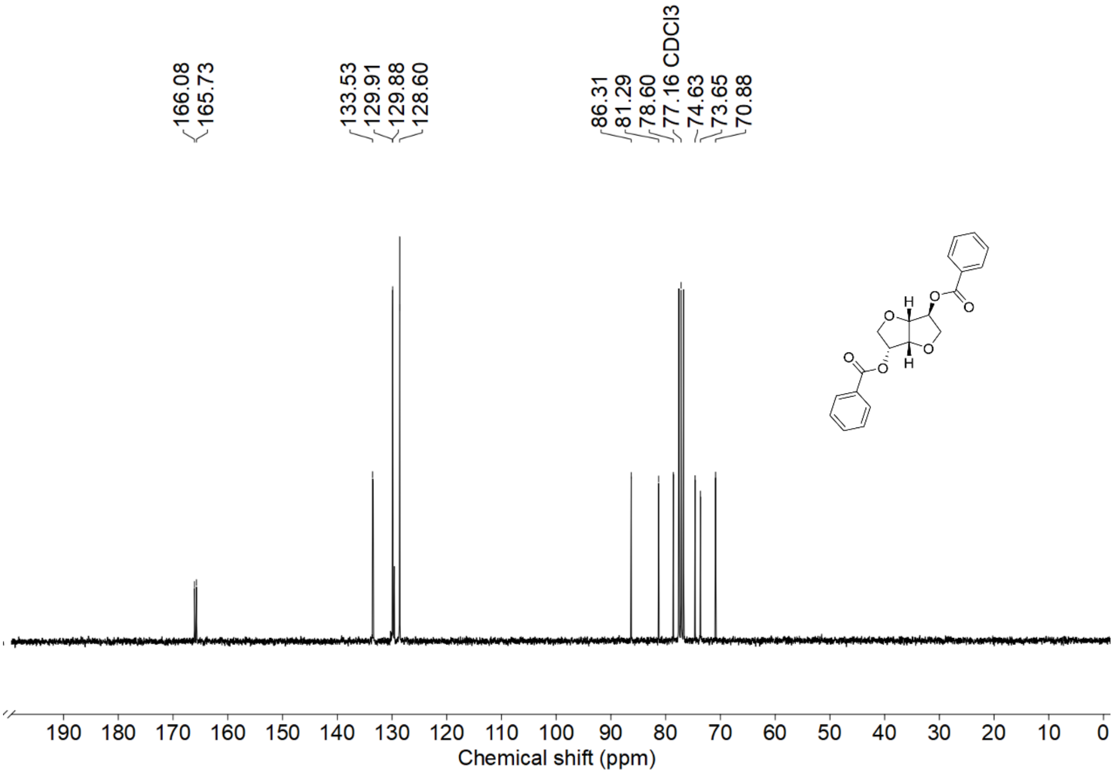


Figure 6.15 The ^{13}C-NMR spectrum of ISDB.

6.3.16 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isosorbide *exo*-monobenzoate (*Exo*-ISMB)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.02 (m, 2H), 7.58 (t, 1H), 7.44 (m, 2H), 5.46 (d, 1H), 4.71 (t, 1H), 4.62 (d, 1H), 4.35 (t, 1H), 4.13 (m, 2H), 3.92 (m, 1H), 3.60 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.5, 133.4, 129.7, 129.4, 128.5, 85.7, 82.1, 78.8, 73.6, 73.5, 72.4; FTIR (ATR, cm^{-1}): 3462, 3066, 2955, 2875, 1716, 1451, 1071.

6.3.17 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isosorbide *endo*-monobenzoate (*Endo*-ISMB)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.05 (t, 2H), 7.58 (t, 1H), 7.45 (t, 2H), 5.39 (q, 1H), 4.98 (t, 1H), 4.45 (d, 1H), 4.02 (t, 1H), 3.94 (m, 4H), 1.93 (br, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 166.0, 133.2, 129.7, 129.5, 128.4, 88.4, 80.6, 76.2, 75.4, 74.5, 70.7. FTIR (ATR, cm^{-1}): 3489, 1703, 1450, 1085.

6.3.18 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isomannide-2,5-dibenzoate (IMDB)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.18 (d, 4H), 7.61 (t, 2H), 7.48 (t, 4H), 5.37 (q, 4H), 4.92 (d, 2H), 4.17 (m, 2H), 4.04 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.9, 133.3, 129.8, 129.4, 128.4, 80.7, 74.1, 70.7; FTIR (ATR, cm^{-1}): 3062, 2982, 2875, 1715, 1092.

6.3.19 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isomannide monobenzoate (IMMB)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.09 (d, 2H), 7.60 (t, 1H), 7.47 (t, 2H), 5.42 (q, 1H), 4.86 (t, 1H), 4.56 (t, 1H), 4.35 (q, 1H), 4.24 (q, 1H), 4.07 (m, 2H), 3.63 (t, 1H), 2.49 (br, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.9, 133.3, 129.8, 129.3, 128.4, 81.6, 80.7, 74.5, 73.8, 72.2, 71.1; FTIR (ATR, cm^{-1}): 3468, 3078, 2944, 1716, 1584, 1086.

6.3.20 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isoidide-2,5-dibenzoate (IIDB)

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.06 (d, 4H), 7.60 (t, 2H), 7.47 (t, 4H), 5.53 (s, 2H), 4.90 (s, 2H), 4.14 (s, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 165.4, 133.4, 129.7, 129.4, 128.4, 85.5, 78.0, 72.7; FTIR (ATR, cm^{-1}): 3064, 2965, 2879, 1718, 1585, 1095.

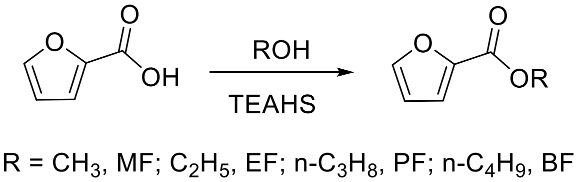
6.3.21 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of isoidide monobenzoate (IIMB)

^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.08 (d, 2H), 7.57 (t, 1H), 7.45 (t, 2H), 5.41 (s, 1H), 4.82 (d, 1H), 4.66 (s, 1H), 4.39 (s, 1H), 4.03-3.90 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 165.6, 133.4, 129.7, 129.4, 128.4, 87.8, 85.1, 78.1, 76.7, 74.6, 70.7; FTIR (ATR, cm^{-1}): 3362, 3064, 2879, 1715, 1060.

6.4 RESULTS AND DISCUSSION

6.4.1 Esterification of biomass-derived intermediates

Initially, the preparation of alkyl 2-furoates was undertaken by the esterification of 2FA with C1-C4 alkyl alcohols using TEAHS as the acid catalyst (Scheme 6.3).



Scheme 6.3 Preparation of alkyl 2-furoates from 2FA.

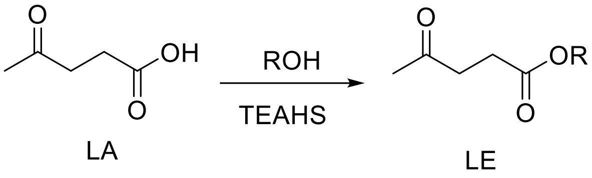
An attempt to esterify 2FA with excess ethanol in the absence of an acid catalyst did not afford alkyl 2-furoates in perceptible yields even after heating the reaction mixture at 120 °C for an extended time. However, when TEAHS (20 wt.% of 2FA) was used as the catalyst, EF was isolated in a 58% isolated yield within 5 h at 120 °C (Table 6.1, entry 2). The mass balance was essentially the unreacted 2FA. Extended reaction time or increased reaction temperature did not improve the yield of EF appreciably. In all cases, attempts were made to attain equilibrium and maximize the conversion of the starting carboxylic acid. Lower temperatures require a long duration for the reaction to establish equilibrium and make the process economically less attractive. The use of lesser amounts of TEAHS significantly lowered the yield of EF. We reasoned that the concomitant use of a sulfonic acid-based co-catalyst could help to establish the equilibrium faster due to the availability of superior Brønsted acidic sites and potentially afford better yields of the ester products. Amberlyst 15 (A15) was selected as a co-catalyst since it is robust, heterogeneous, and available in bulk. As expected, the use of A15 as a co-catalyst noticeably improved the isolated yield of EF (Table 6.1, entry 3). The texture and heterogeneity of the A15 catalyst were visibly unchanged after the reaction. The reaction was then extended to the preparation of other alkyl 2-furoates. MF was obtained in 64% isolated yield when 2FA was reacted with excess anhydrous methanol in the presence of the combination of TEAHS and A15. PF and BF were produced in 72% and 74% isolated yields, respectively. The slightly better yields of the esters with higher alcohol may be explained by their capability of forming a low-boiling azeotrope with the water byproduct.

Table 6.1 The preparation of alkyl 2-furoates from 2FA

Entry	**Reaction conditions**[a]	**Product**	**Yield (%)**[b]
1	Ethanol (0.5 mL), TEAHS (0.1 g, 11.22 mol%), 120 °C, 5 h	EF	35
2	Ethanol (5 mL), TEAHS (0.5 g, 56.15 mol%), 120 °C, 5 h	EF	58
3	Ethanol (5 mL), TEAHS (0.5 g, 56.15 mol%), A15 (0.1 g), 120 °C, 5 h	EF	70
4	Methanol (5 mL), TEAHS (0.5 g, 56.15 mol%), A15 (0.1 g), 120 °C, 5 h	MF	64
5	1-Propanol (5 mL), TEAHS (0.5 g, 56.15 mol%), A15 (0.1 g), 120 °C, 5 h	PF	72
6	1-Butanol (5 mL), TEAHS (0.5 g, 56.15 mol%), A15 (0.1 g), 120 °C, 5 h	BF	74

[a] The reactions used 0.5 g of 2FA. [b] Isolated yields.

Thereafter, the esterification of biomass-derived LA was attempted using TEAHS as the catalyst as well as reaction medium (Scheme 6.4).



R = CH_3, ML; C_2H_5, EL; n-C_3H_8, PL; n-C_4H_9, BL

Scheme 6.4 Esterification of LA using TEAHS as an acid catalyst.

Although levulinate esters (LEs) formed even under the reflux condition, superior yields of the same were achieved when the reactions were conducted in a sealed glass vessel. The result may be explained by the higher reaction temperature achievable in the closed system and no evaporative loss of the alcohol reagent. Initially, the reaction was carried out by using only triethylamine and H_2SO_4 as a catalyst. The use of triethylamine alone formed the salt of LA and did not form any ester. However, when conc. H_2SO_4 was used as a catalyst, EL was isolated in 75% yield under the same reaction conditions employed for TEAHS (1 g LA, 5 mL ethanol, 120 °C, 3 h, H_2SO_4 (0.245 g, 29 mol%). ML was obtained in an 82% yield using excess anhydrous methanol and 50 wt.% of TEAHS as catalyst and reaction medium (Table 6.2, entry 1). EL was obtained in an 80% yield within 3 h at 120 °C using excess absolute ethanol. PL and BL were isolated in 83% and 84% yields, respectively, under identical conditions (Table 6.2, entries 3&4).

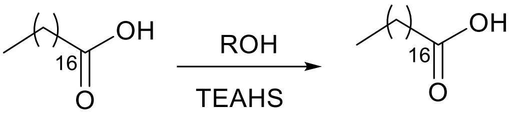
Table 6.2 The preparation of alkyl levulinates from LA

Entry	**Reaction conditions**[a]	**Product**	**Yield (%)**[b]
1	Methanol (5 mL), TEAHS (0.5 g, 29.11 mol%), 120 °C, 3 h	ML	82
2	Ethanol (5 mL), TEAHS (0.5 g, 29.11 mol%), 120 °C, 3 h	EL	80
3	Propanol (5 mL), TEAHS (0.5 g, 29.11 mol%), 120 °C, 3 h	PL	83
4	Butanol (5 mL), TEAHS (0.5 g, 29.11 mol%), 120 °C, 3 h	BL	84

5	Ethanol (5 mL), H_2SO_4 (0.245 g, 29 mol%), 120 °C, 3 h	EL	75

[a] The reactions used 1.0 g of LA. [b] isolated yield.

The gram-scale preparation of alkyl stearates was attempted from StA using excess alcohol reagent and 20 wt.% of TEAHS as catalyst (Scheme 6.5).



R = CH_3, MeS; C_2H_5, ES; n-C_3H_8, PS; n-C_4H_9, BS

Scheme 6.5 Esterification of StA using the TEAHS catalyst.

The reactions were performed in a 75 mL glass pressure reactor fitted with a Teflon screw-top. ES was obtained in 96% isolated yield within 3 h at 120 °C. After the reaction, the excess alcohol was distilled under reduced pressure. Alkyl stearate was conveniently separated from the TEAHS catalyst by extracting with petroleum ether. The catalyst was then dried under vacuum at elevated temperature (ca. 110 °C) for 12 h before resubmitting for the next reaction. Longer duration or higher reaction temperature had a negligible effect on the isolated yield of ES (Table 6.3, entry 3). The use of more TEAHS lowered the reaction time but did not improve the yield appreciably. However, a lower quantity of TEAHS decreased the yield of ES due to the low conversion of StA (Table 6.3, entry 2). The use of only slight excess of the alcohol reagents afforded lesser yields of alkyl stearates. Methanol, propanol, and butanol provided similar yields of their corresponding stearates (MeS, PS, & BS) under identical reaction conditions. The use of recycled (and dried) TEAHS provided only a slightly diminished yield of ES (Table 6.3, entry 7).

Table 6.3 Esterification of StA with monohydric alkyl (C1-C4) alcohols

Entry	**Reaction conditions[a]**	**Product**	**Yield (%)[c]**
1	Ethanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h	ES	96
2	Ethanol (5 mL), TEAHS (0.08 g, 11.43 mol%), 120 °C, 3 h	ES	30

3	Ethanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 130 °C, 4 h	ES	97
4	Methanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h	MeS	92
5	1-Propanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h	PS	95
6	1-Butanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h	BS	97
7[b]	Ethanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h	ES	88

[a] The reactions used 1.00 g of StA. [b] Recycled TEAHS. [c] isolated yield.

The recyclability and stability studies of TEAHS were then undertaken for the synthesis of ES. After each reaction, the excess ethanol was evaporated in a rotary evaporator under reduced pressure and ES was extracted using light petroleum ether. The ionic liquid was then dried at 110 °C under vacuum for 4 h before subjecting it to the consecutive reaction. Figure 1 shows the results of the recyclability studies of TEAHS. The ionic liquid catalyst was recycled for four cycles, and only a marginal decrease in the yield of ES was observed. The chemical identity and stability of the recycled TEAHS were confirmed by ^{1}H-NMR and TGA. The data showed that no chemical decomposition occurred to TEAHS during the reaction. Interestingly, when the recycled TEAHS was subjected to the next catalytic cycles without undergoing the drying process, the yield of ES was significantly lowered. This result can be justified by the fact that TEAHS not only acts as a Brønsted acid catalyst for the esterification reaction but also helps to absorb the water byproduct formed during the esterification reaction, thereby favoring the reaction equilibrium to the product side.

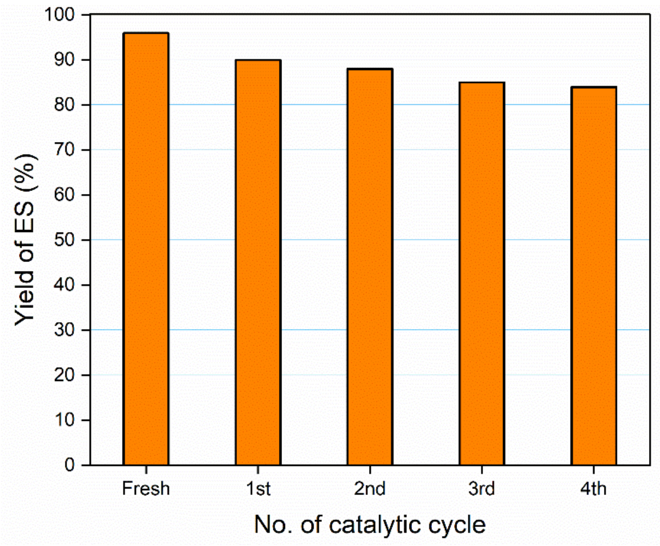
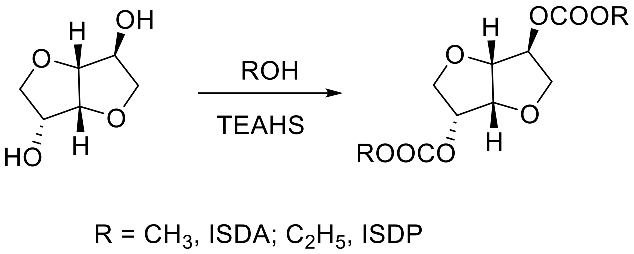


Figure 6.16 Recyclability study of TEAHS during the preparation of ES.

Reaction Conditions: StA (1.002 g, 3.52 mmol), ethanol (5 mL), TEAHS (0.2 g, 28.60 mol%), 120 °C, 3 h.

Finally, the preparation of isosorbide-2,5-dialkanoates was attempted by the TEAHS catalyzed esterification of glucose-derived IS using excess carboxylic acids (Scheme 6.6).



Scheme 6.6 TEAHS catalyzed preparation of isosorbide-2,5-dialkanoates from IS.

ISDA was prepared in 50% isolated yields by reacting isosorbide with excess glacial acetic acid in the presence of the TEAHS catalyst. The mass balance was unreacted IS and monoacetates of isosorbide. ISDP was isolated in 56% yield under identical conditions (Table 6.4, entry 2).

Table 6.4 Preparation of isosorbide-2,5-dialkanoates from IS

Entry	**Reaction conditions**[a]	**Product**	**Yield (%)**[b]
1	Acetic acid (5 mL), TEAHS (1 g, 73.28 mol%), 120 °C, 4 h	ISDA	50

2	Propanoic acid (5 mL), TEAHS (1 g, 73.28 mol%), 120 °C, 4 h	ISDP	56

[a] The reactions used 1.0 g of isosorbide. [b] Isolated yield.

The TEAHS catalyst was recovered and characterized by ^{1}H-NMR and TGA to confirm its chemical integrity. No organic contaminants were found (studied by ^{1}H & ^{13}C-NMR spectroscopy) in the recycled TEAHS.

6.4.2 Transesterification of isohexide under-solvent free conditions

Initially, the transesterification of IS was attempted using ethyl benzoate as the reagent in an open reactor under thermal, uncatalyzed conditions. The progress of the reaction was monitored by TLC (silica gel, chloroform). Even when the reaction was performed in excess ethyl benzoate (5 eq.), IS remained virtually unreacted even after extended durations at high temperatures (ca. 160 °C). When inorganic bases were used as catalysts, the reaction progressed at elevated temperatures. The reaction was carried out using different catalysts like sodium hydroxide (NaOH), potassium phosphate tribasic (K_3PO_4), potassium carbonate (K_2CO_3), and potassium tert-butoxide (K^{t}OBu). The reaction was conducted in an open reactor.

Table 6.5 Effect of various inorganic base catalysts for transesterification of isosorbide with ethyl benzoate.

Sl. No.	Base Catalyst	Yield of ISDB (%)	Yield of ISMBs (%)
1	K_2CO_3	78	18
2	K_3PO_4	48	12
3	NaOH	18	50
4	K^{t}OBu	70	24
5	Without catalyst	No reaction	

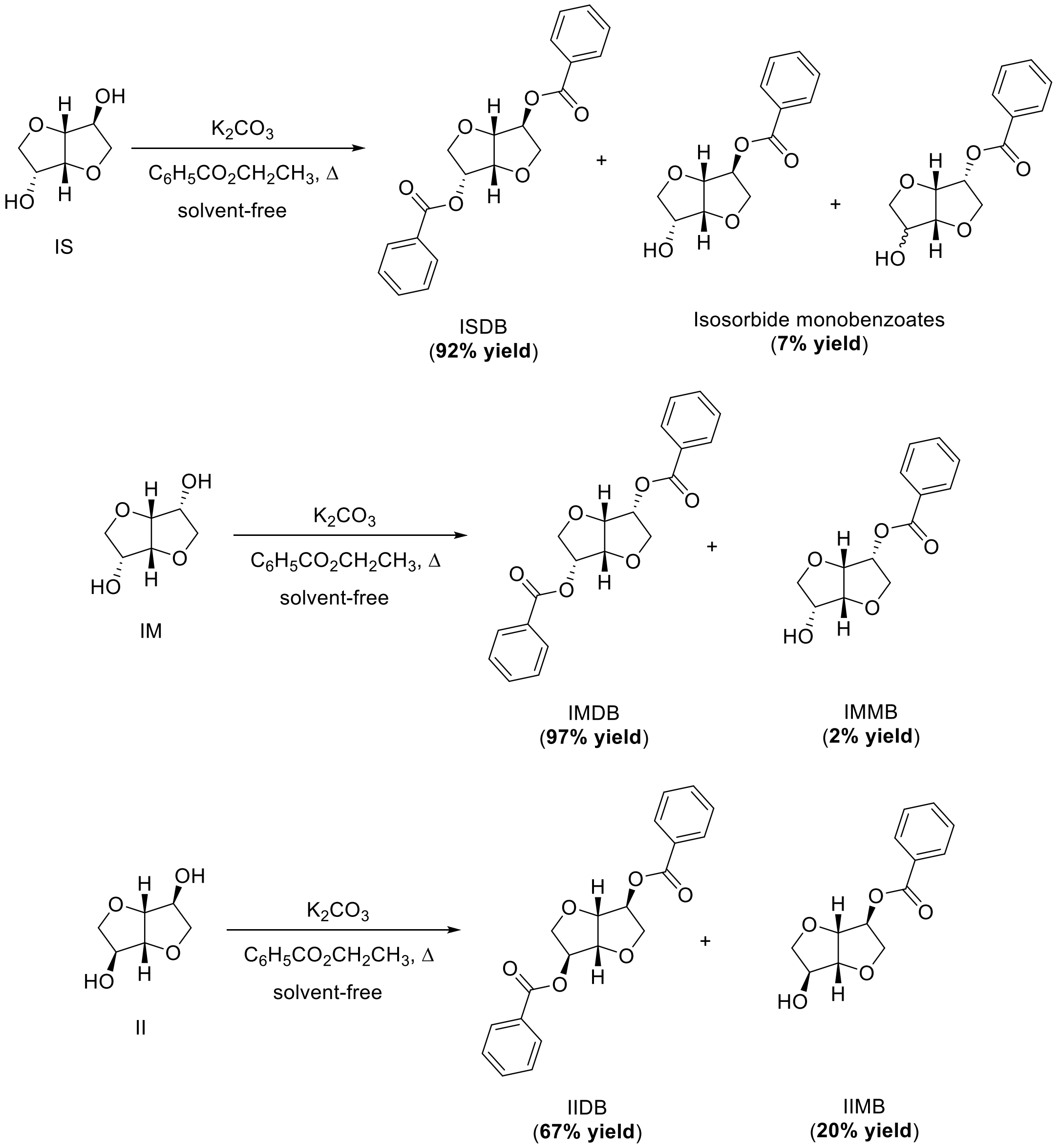
Reaction Conditions: IS (0.5 g, 3.42 mmol), ethyl benzoate (2.57 g, 17.11 mmol), catalyst (50 mol%), 160 °C, 12 h.

The reaction of IS with ethyl benzoate was carried out at 160 °C for 12 h using 50 mol% of the base catalyst. Among the catalysts examined, anhydrous K_2CO_3 was found to be the best candidate for transesterifying IS (Table 6.5). The use of K_2CO_3

provided 78% of ISDB, whereas using a stronger base like K^tOBu gave a slightly lower yield (ca. 70%) of ISDB. This result may be explained by the observation that a fraction of IS formed the potassium salt, precipitated from the reaction medium, and remained unreacted. The use of other inorganic bases, such as NaOH and K_3PO_4, afforded 18% and 48% of ISDB, respectively.

Initially, the reaction temperature was optimized by keeping other reaction parameters unaltered. At a reaction temperature of 180 °C, the yield of ISDB reached 92% in 6 h. Decreasing the reaction time to 140 °C significantly lowered the ISDB yield to 54%. The amount of catalyst was varied between 25, 50, and 75 mol% for the synthesis of ISDB. The use of 25 mol% of K_2CO_3 gave an 83% yield of ISDB, and 75 mol% of K_2CO_3 gave a 93% yield of ISDB within 6 h of reaction time at 180 °C.

The optimized reaction protocol was extended for synthesizing the esters (mono- and di-) of isomannide and isoidide (Scheme 6.7).



Scheme 6.7 The synthesis of isohexide mono- and dibenzoate from isohexide.

Reaction Conditions: IS (0.5 g, 3.42 mmol), ethyl benzoate (2.57 g, 17.11 mmol), K_2CO_3 (50 mol%, 0.237 g), 180 °C, 6 h.

6.5 CONCLUSIONS

High-yielding, gram-scale preparation of the esters of various biomass-derived chemical platforms has been attempted. TEAHS was employed as an inexpensive but efficient IL-based acid catalyst and reaction medium for synthesizing esters from carboxylic acids and alcohols following the Fischer esterification protocol. Anhydrous potassium carbonate has been used as a base catalyst for synthesizing the mono- and diesters of isohexides by transesterification. The catalysts were successfully recovered and reused for multiple catalytic cycles. The same strategy can be extended for the synthesis of various aromatic and aliphatic mono- and diesters of commercial interest.

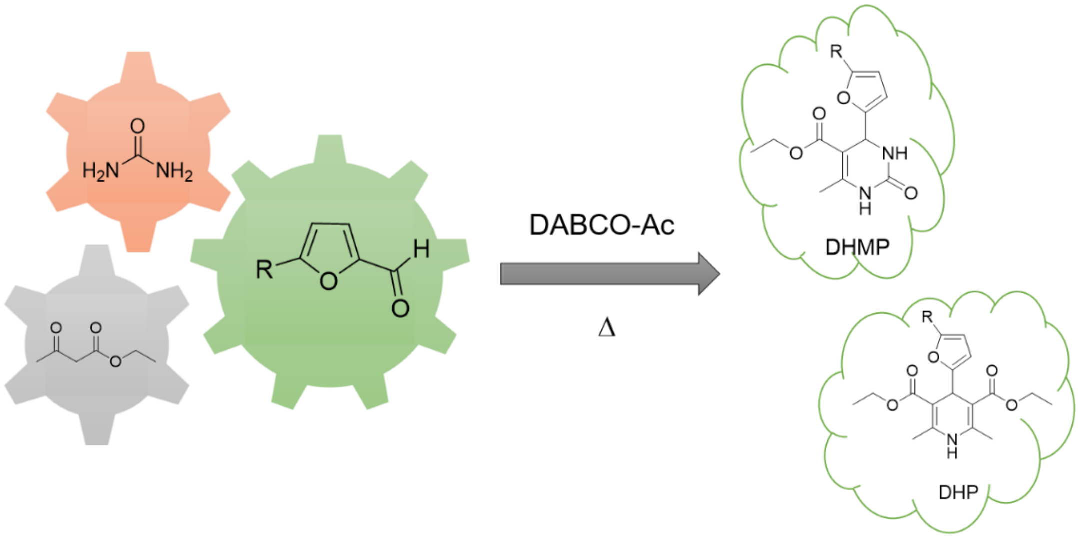
CHAPTER 7

SOLVENT-FREE SYNTHESIS OF NOVEL 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES AND 1,4-DIHYDROPYRIDINES FROM BIORENEWABLE FURFURALS USING 1,4-DIAZABICYCLO[2.2.2]OCTANIUM DIACETATE AS THE IONIC LIQUID CATALYST

Abstract

3,4-Dihydropyrimidin-2-(1H)-ones (DHPMs) and 1,4-dihydropyridines (DHPs) are well-known heterocyclic compounds that have prominent biological activities and are important pharmacophores for drug discovery research. In this work, 1,4-diazabicyclo[2.2.2]octanium diacetate (DABCO-Ac) has been used as an efficient acidic ionic liquid catalyst and reaction medium for the solvent-free synthesis of novel DHPMs and DHPs starting from biomass-derived furfurals.

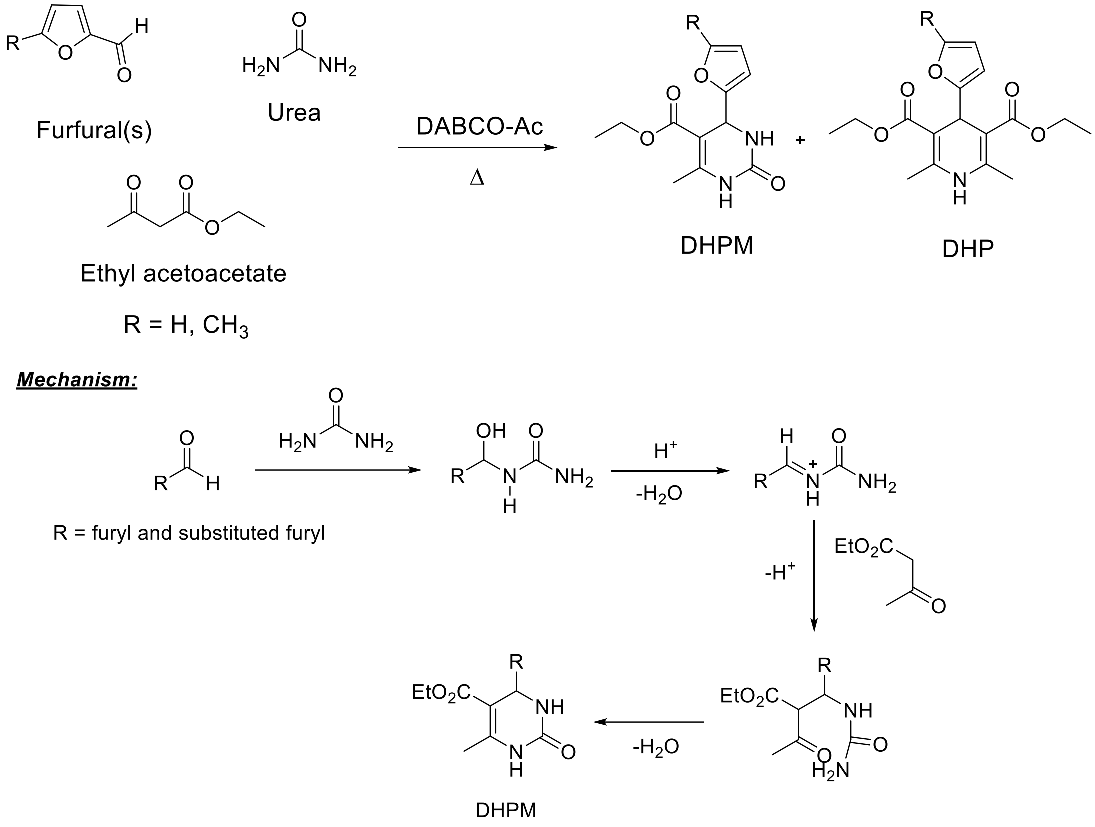
Graphical Abstract



7.1 INTRODUCTION

The study of heterocyclic compounds is indispensable in the realm of synthetic organic chemistry. 3,4-Dihydropyrimidin-2-(*1H*)-ones (DHPMs) and 1,4-dihydropyridines (DHPs) are well-documented classes of heterocyclic compounds known for their wide spectrum of biological and therapeutic activities. They have been used as the molecular scaffold for the target-oriented synthesis of pharmaceuticals with anti-tumor, anti-bacterial, anti-viral, and anti-inflammatory activities (Kaur et al. 2017; Singhal et al. 2010; Yang et al. 2013). The DHPMs are routinely synthesized by following the Biginelli reaction protocol, where a one-pot condensation between an aromatic aldehyde, a β-keto ester, and urea is carried out in the presence of a suitable acid catalyst. On the other hand, DHPs are synthesized using Hantzsch pyridine synthesis (Borah et al. 2022; Sánchez-Sancho et al. 2022). Hundreds of DHPMs and DHPs are reported in the literature, where structural features have been introduced in one or more of the three chemical building blocks. Various acid catalysts have been explored over the years to improve the selectivity and yield of DHPMs under environmentally acceptable reaction conditions and safer synthetic auxiliaries. The synthesis of DHPMs and DHPs has been attempted using mineral acids, metal salts, inorganic oxides, acidic resins, and various other solid-supported Brønsted and Lewis acids. In this regard, ionic liquids (ILs) with Brønsted acidity have received significant interest as the catalyst and reaction media for various organic transformations in academic and industrial settings (Kusumawati and Shirai 2022).

Recently, chemicals derived from biogenic carbon have received significant attention since they are renewable and have low carbon footprints. Inexpensive and abundant biomass such as lignocellulosic and algal biomass could substitute petroleum, at least partially, by providing a sustainable route to many bulk and fine chemicals. Furanic compounds, such as furfural (FUR) and 5-(hydroxymethyl)furfural (HMF), are well-established biomass-derived renewable chemical intermediates that can be synthetically upgraded into various classes of products of commercial significance (Mariscal et al. 2016; Shen et al. 2020). The products targeted from furanic compounds include fuels and fuel additives, solvents, polymers and plasticizers, dyes, agrochemicals, and pharmaceuticals. This work uses biomass-derived renewable furanics as the aldehyde moiety for synthesizing novel DHPMs and DHPs using DABCO diacetate (DABCO-Ac) as an acid catalyst has been reported. The reaction was optimized on the type and loadings of acid catalyst used, the molar ratio of the reagents, and the reaction temperature.



Scheme 7.1 One-pot, multicomponent synthesis of novel DHPMs and DHPs from biorenewable furfurals.

7.2 EXPERIMENTAL SECTION

7.2.1 Materials

Piperidine (>99%), DABCO (99%), chloroform (99%), ethyl acetate (99%), petroleum ether (60-80 °C, 99%), hydrochloric acid (35%), sodium chloride (99%), sodium sulfate (99%), and triethyl amine (anhydrous, 99.9%) were purchased from Loba Chemie Pvt. Ltd. Furfural (99%), 5-methylfurfural (>99%), glacial acetic acid (99.9%), Silica gel (60-120 mesh), and urea were purchased from Spectrochem. All the chemicals were used without further purification.

7.2.2 Synthesis of DABCO-Ac catalyst

DABCO (1.002 g, 8.93 mmol) was taken in a round-bottomed flask and placed in an ice bath. Glacial acetic acid (1.07 g, 17.83 mmol) was added dropwise under constant magnetic stirring. After the addition was complete, stirring was continued at 60 °C for 3 h to get DABCO-Ac as a viscous semisolid.

7.2.3 Synthesis of 3,4-Dihydropyrimidin-2-(*1H*)-ones (DHPMs) and 1,4-dihydropyridines (DHPs)

FUR (0.502 g, 5.22 mmol), ethyl acetoacetate (0.679 g, 1.0 eq.), urea (0.493 g, 1.5 eq.), DABCO-Ac (0.302 g, 25 mol%) were charged in a round-bottomed flask fitted with a reflux condenser and magnetically stirred for 12 h in a pre-heated oil bath at 80 °C. After the reaction, the mixture was cooled to room temperature and diluted in ethyl acetate (20 mL). The reaction mixture was then washed with water. The crude reaction mixture was evaporated under reduced pressure and column chromatographed (silica gel, pet ether/ethyl acetate) to get ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (FFBG, 0.980 g, 75%) and diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (FFHz, 0.365 g, 24%). The same synthetic strategy was extended for the synthesis of ethyl 6-methyl-4-(5-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5MFBG), diethyl 2,6-dimethyl-(5-methylfuran-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (5MFHz) from 5-methylfurfural (5MF).

7.3 STRUCTURAL CHARACTERIZATION OF SYNTHESIZED DHPMs, DHPs, AND DABCO-Ac

7.3.1 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (FFBG)

^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.26 (s, 1H), 7.77 (s, 1H), 7.55 (d, 1H), 6.35 (t, 1H), 6.10 (d, 1H), 5.21 (s, 1H), 4.02 (q, 2H), 2.23 (s, 3H), 1.14 (s, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 165.2, 156.1, 152.6, 149.6, 142.3, 110.5, 105.5, 96.8, 59.4, 47.9, 17.9, 14.3; FTIR (cm^{-1}): 3242, 3115, 2983, 1729, 1704, 1091.

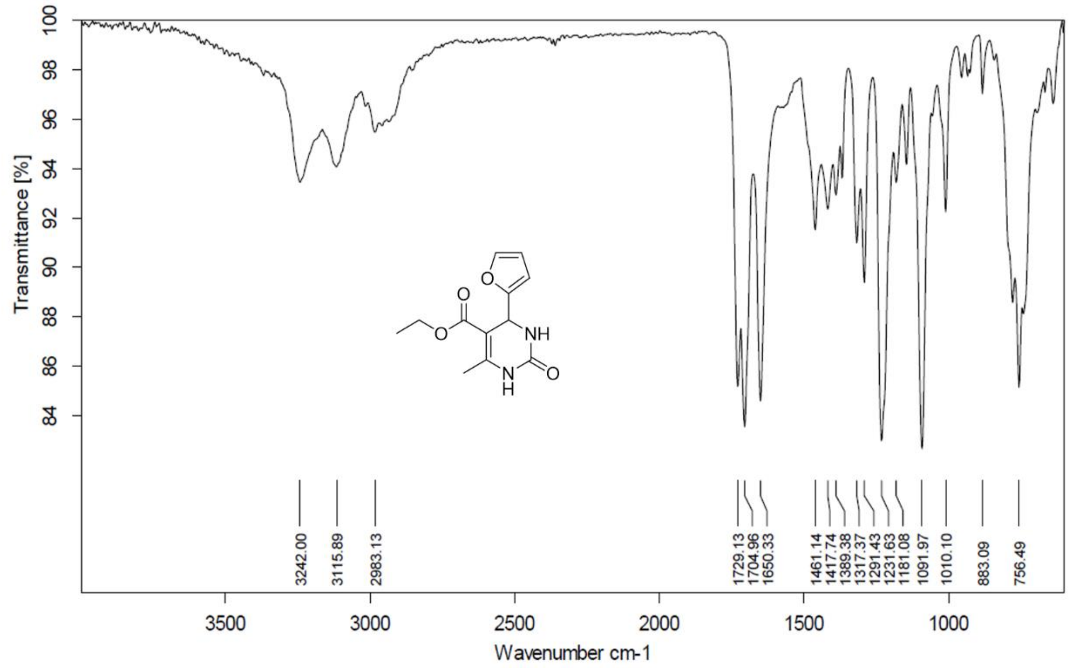


Figure 7.1 The FTIR spectrum of FFBG.

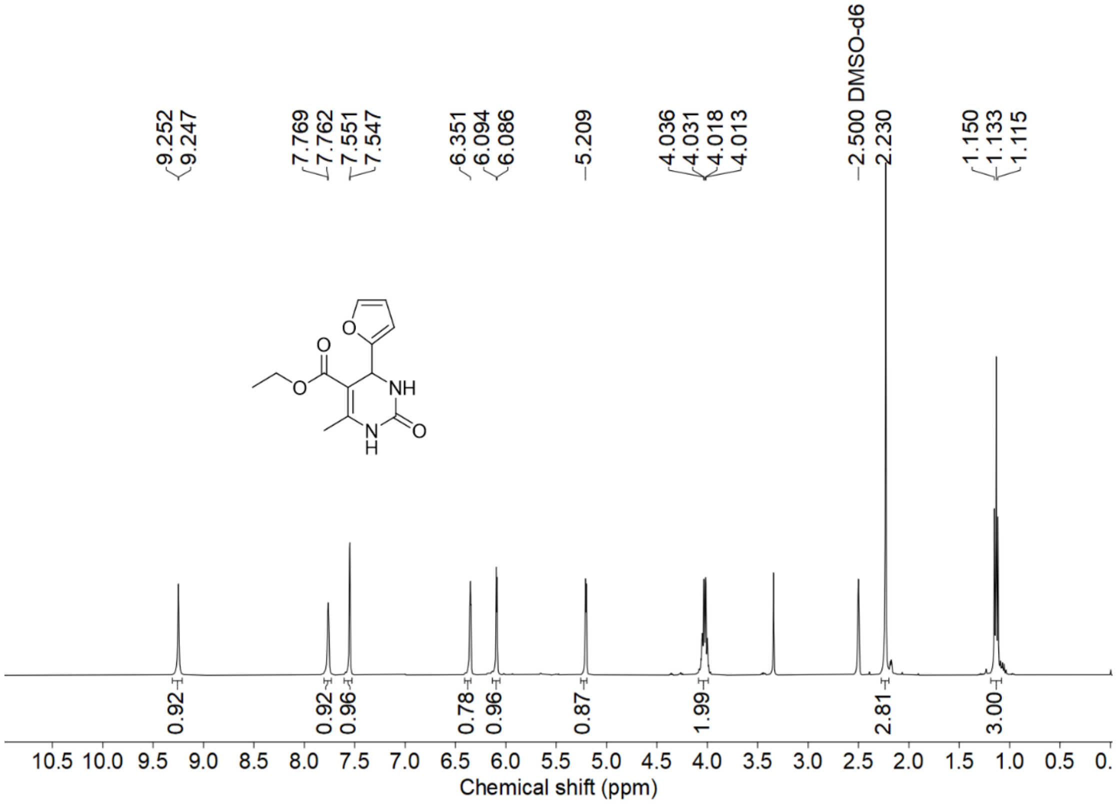


Figure 7.2 The ^{1}H-NMR spectrum of FFBG.

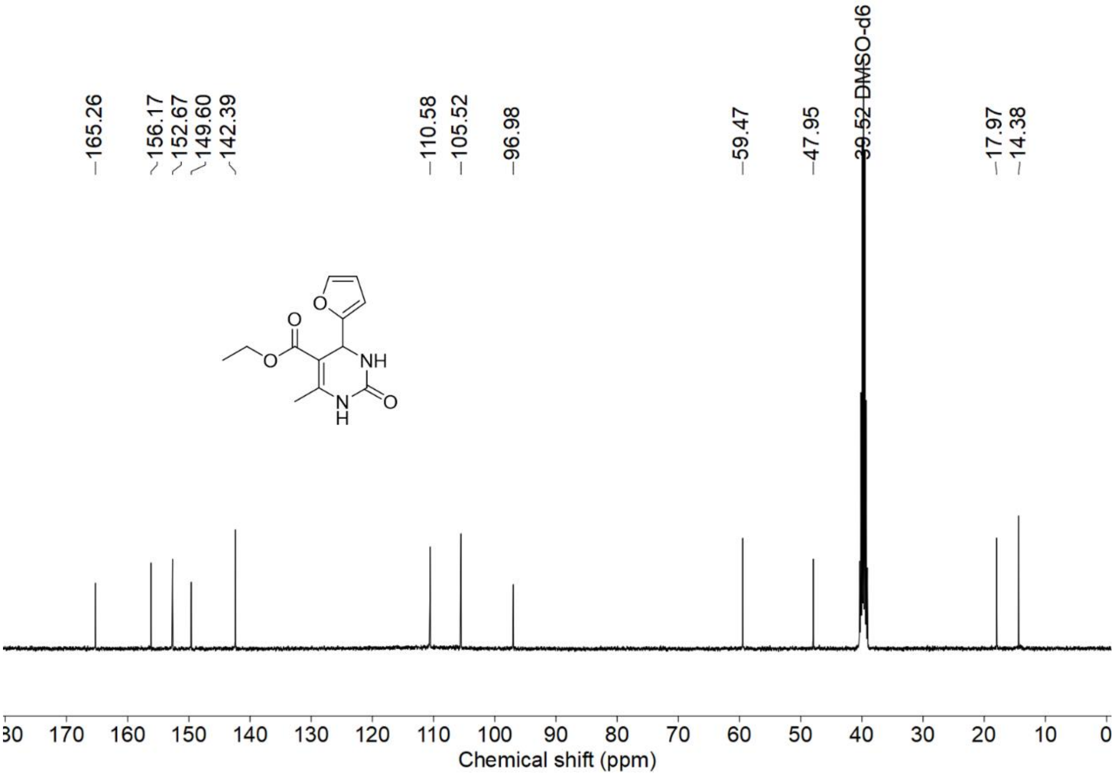


Figure 7.3 The ^{13}C-NMR spectrum of FFBG.

7.3.2 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (FFHz)

^{1}H-NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.91 (s, 1H), 7.38 (s, 1H), 6.23 (t, 1H), 5.82 (d, 1H), 5.04 (s, 1H), 4.06 (q, 4H), 2.24 (s, 6H), 1.16 (t, 6H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ (ppm): 166.9, 159.0, 146.6, 141.2, 110.3, 104.1, 98.7, 59.2, 33.0, 18.4, 14.4; FTIR (cm^{-1}): 3241, 3118, 2984, 2850, 1732, 1010.

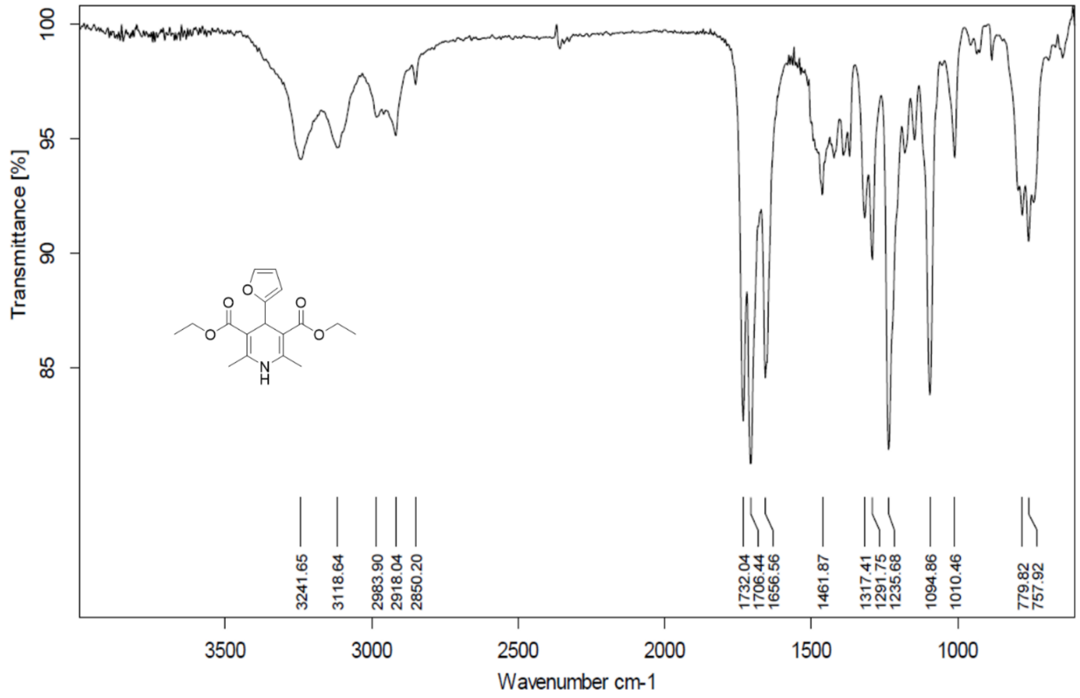


Figure 7.4 The FTIR spectrum of FFHz.

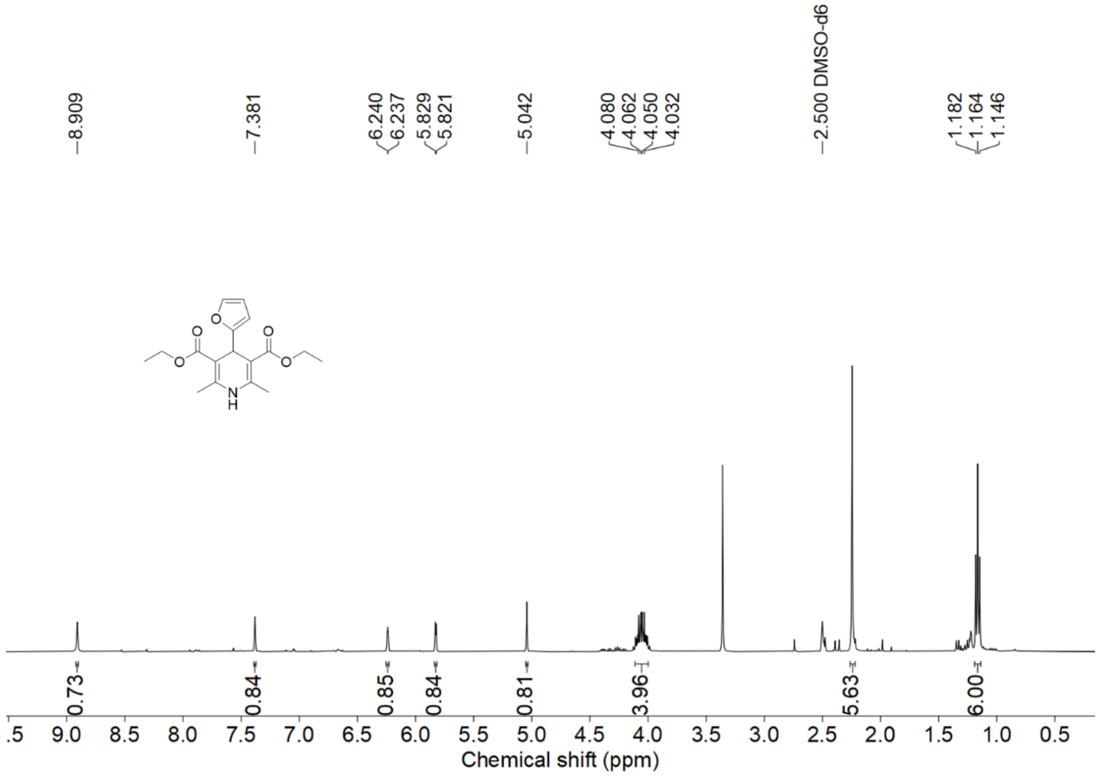


Figure 7.5 The ^{1}H-NMR spectrum of FFHz.

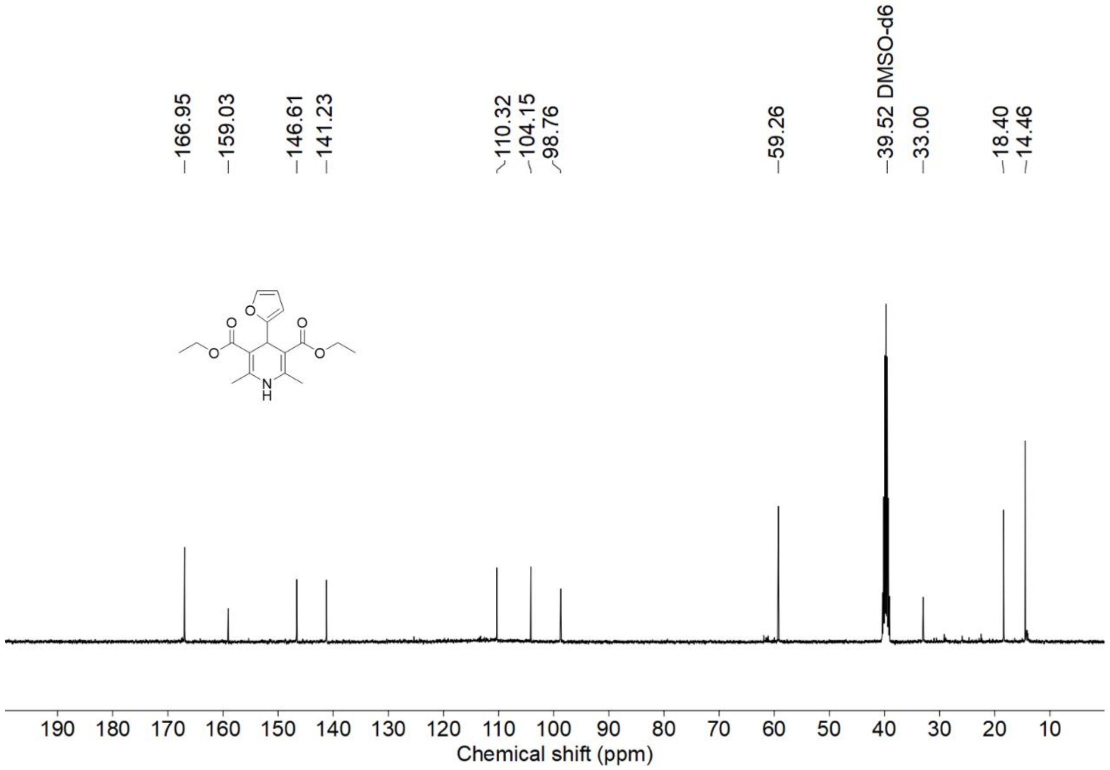


Figure 7.6 The ^{13}C-NMR spectrum of FFHz.

7.3.3 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of ethyl 6-methyl-4-(5-methylfuran-2-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5MFBG)

^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 9.81 (s, 1H), 7.70 (s, 1H), 5.94 (d, 2H), 5.13 (s, 1H), 4.02 (q, 2H), 2.21 (s, 6H), 1.13 (t, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm): 167.1, 154.2, 152,4, 150.7, 149.2, 106.3, 106.0, 96.8, 59.2, 47.7, 17.7, 14.2, 13,4; FTIR (cm^{-1}): 3232, 3106, 2918, 1706, 1653, 1089.

7.3.4 The FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra of diethyl 2,6-dimethyl-(5-methylfuran-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (5MFHz)

^{1}H-NMR (DMSO-d_6, 300 MHz) δ (ppm): 8.85 (s, 1H), 5.82 (s, 1H), 5.64 (d, 1H), 4.96 (s, 1H), 4.06 (q, 4H), 2.23 (s, 6H), 2.12 (s, 3H), 1.16 (t, 3H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ (ppm): 166.8, 157.2, 149.4, 146.2, 106.1, 104.7, 98.7, 59.0, 32.7, 18.2, 14.3, 13.5; FTIR (cm^{-1}): 3204, 3108, 2923, 2834, 1724, 1010.

7.3.5 The ^{1}H-NMR and ^{13}C-NMR spectra of DABCO-Ac

^{1}H-NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.92 (bs, 2H), 2.51 (s, 12H), 1.41 (s, 6H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ (ppm): 175.1, 44.6, 22.5.

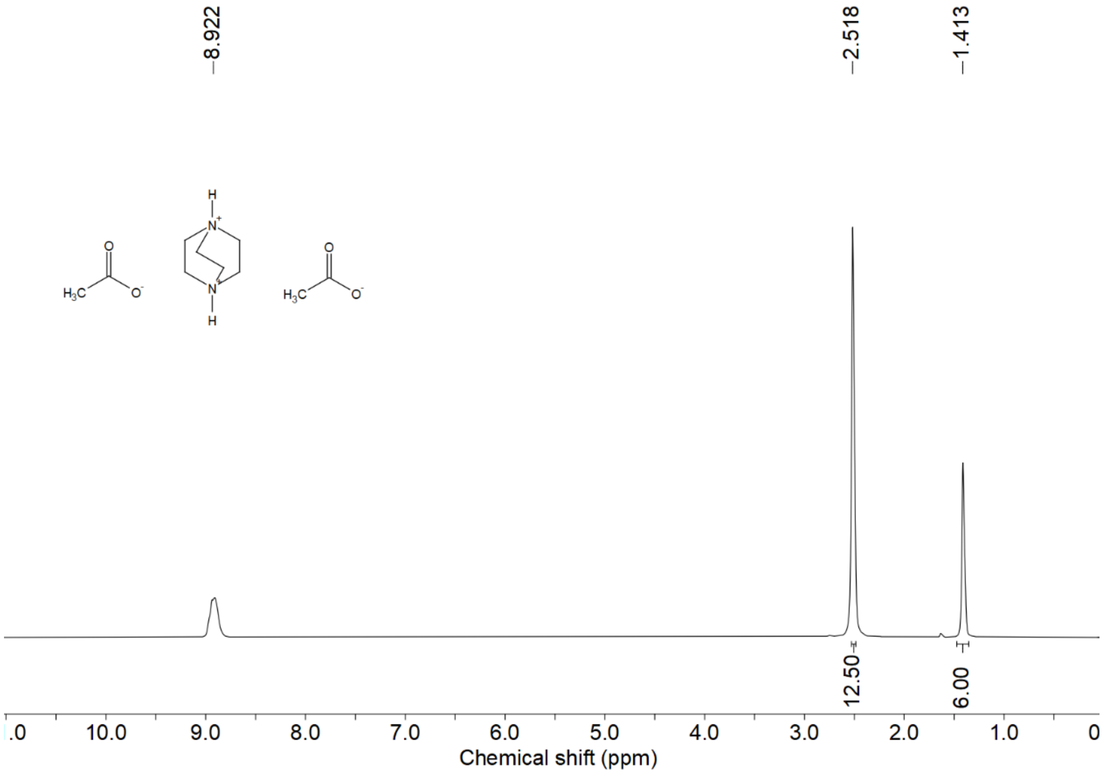


Figure 7.7 The ^{1}H-NMR spectrum of DABCO-Ac.

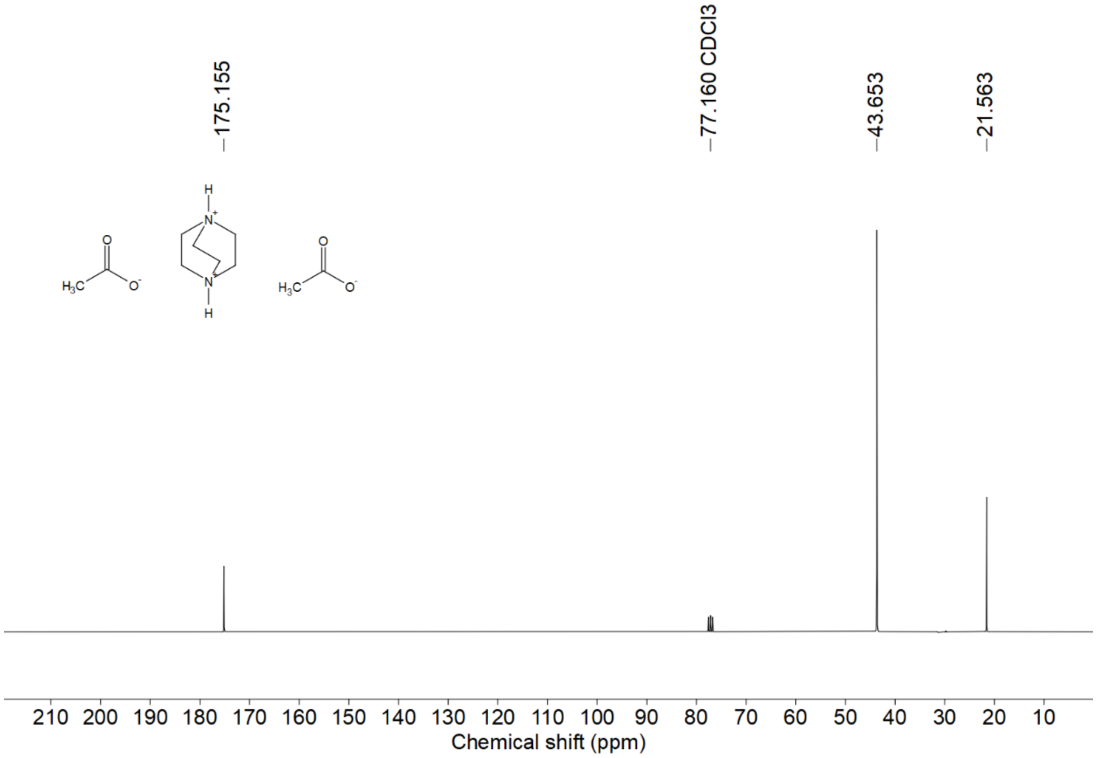


Figure 7.8 The ^{13}C-NMR spectrum of DABCO-Ac.

7.4 RESULTS AND DISCUSSION

The one-pot reaction between FUR, ethyl acetoacetate, and urea led to forming DHPM and DHP. The compounds FFBG and FFHz, synthesized from FUR, were chosen as the model substrates. The reaction was carried out using conventional heating under solvent-free conditions. The aldehyde was used as a limiting reagent, and the progress of the reaction was monitored by thin-layer chromatography. After the reaction, the product was extracted with ethyl acetate. The product was purified by column chromatography from a mixture of pet ether and ethyl acetate.

Initially, the efficiency of the DABCO-Ac catalyst was compared against other catalysts. When acetic acid was used as a catalyst and reaction medium, the reaction did not complete at room temperature, and only 46% yield of FFBG was isolated. The catalytic amount of acetic acid (25 mol%) gave 32% of FFBG at room temperature for 12 h. Further increase in temperature to 80 °C gave 72% and 6% of FFBG and FFHz, respectively. On the contrary, using DABCO-Ac gave 97% (overall yield) at 80 °C in 12 h. The reaction was found to be slow at RT, and the conversion of FUR was <50% even after 24 h. However, higher reaction temperatures (>100 °C) diminished the yield due to the decomposition of FUR. The efficiency of various catalysts used in the transformation is listed in Table 7.1.

Table 7.1 Screening of catalysts for DHPM and DHP synthesis from biomass-derived FUR

Entry	**Catalyst**	**Reaction Temperature**	**Observation/ Yield***
1	Acetic acid (excess)	RT	46%
2	Acetic acid (25 mol%)	RT	32%
3	DABCO (1 eq.)	RT	Complex mixture
4	[H-DABCO][HSO_4]	RT	Decomposition
5	[H_2-DABCO][HSO_4]$_2$	RT	Decomposition
6	DABCO-Ac (25 mol%)	RT	40%
7	DABCO-Ac (25 mol%)	80 °C	97% (overall)
8	TEAA (25 mol%)	80 °C	55% (overall)

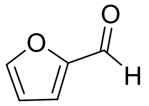
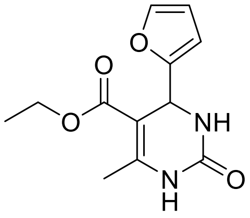
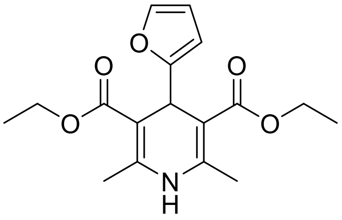
9	PiAc (25 mol%)	80 °C	40% (overall)

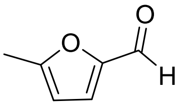
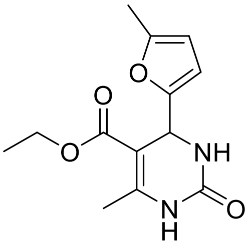
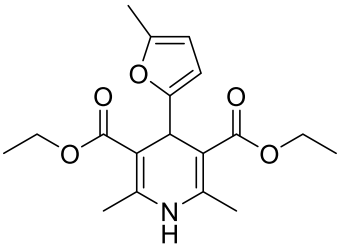
Reaction Conditions: FUR (0.502 g, 5.22 mmol), ethyl acetoacetate (0.679 g, 5.22 mmol, urea (0.470 g, 7.83 mmol), 12 h.

[H-DABCO][HSO_4] and [H_2-DABCO][HSO_4]$_2$ as a catalyst resulted in the formation of black char. Other IL catalysts, such as triethylammonium acetate (TEAA) and piperidinium acetate (PiPA), gave 55% and 40% combined yield of DHPM and DHP.

When the reaction was carried out using higher catalyst loading (50 mol%), isolated yield of DHPM and DHP remained almost same. Further, a decrease in the catalyst loading to 10 mol% and 20 mol% gave less yield. Furthermore, the optimized reaction condition (80 °C and 12 h) was applied for the synthesis of 5MFBG and 5MFHz from 5MF under solvent-free conditions (Table 7.2, entry 2).

Table 7.2 Synthesis of DHPMs and DHPs from biorenewable furfurals

Entry	**Starting Material**	**Product**	**Yield (%)**
1	 FUR	 FFBG	74
		 FFHz	23

2	 5MF	 5MFBG	45
		 5MFHz	40

Reaction Conditions: FUR/5MF (0.502 g), ethyl acetoacetate (1.00 eq), urea (1.5 eq.), 80 °C, 12 h.

7.5 CONCLUSION

In summary, novel DHPMs and DHPs have been synthesized, starting from biorenewable FUR and 5MF, using DABCO-Ac as a robust, efficient, and inexpensive acid catalyst. The solvent-free, gram-scale reactions worked under mild conditions, and the products were obtained in excellent isolated yields. Under optimized reaction conditions, FUR gave 74% FFBG and 23% FFHz. Future research will focus on the selective synthesis of DHPMs and DHPs from other 5-substituted furfurals derived from carbohydrates.

CHAPTER 8

SUMMARY AND CONCLUSIONS

This chapter includes the summary and important conclusions of the present research work. It also consists of a brief account of the scope for future work.

8.1 SUMMARY

- Over the past several years, significant research has been done for producing furanic compounds and levulinic acid from biomass-derived carbohydrates for their downstream synthetic transformation into specialty chemicals.
- The present work attempted to produce furfural (FUR), 5-(chloromethyl)furfural (CMF), and levulinic acid (LA) from pentose and hexose sugars. Catalytic synthesis of specialty chemicals, such as 2(5H)-furanone (2FN), alkyl levulinates (ALs), alkyl furoates, alkyl stearates, and the esters of isohexides, have also been explored. Further, it focused on using mild acid catalysts to synthesize 5-(acyloxymethyl)furfural (AMF) directly from carbohydrates. It also reported the renewable synthesis of 3,4-dihydropyrimidinones (DHPMs) and 1,4-dihydropyridines (DHPs) from biomass-derived furfurals.
- Over the past decade, CMF has received renewed interest as a stable, hydrophobic analog of HMF for synthesizing a diverse range of specialty chemicals. The present research reported FUR production from biomass-derived pentose sugars like xylose in an aqueous HCl-1,2-dichloroethane (DCE) biphasic system using benzyltributylammonium chloride (BTBAC) as a phase transfer catalyst (PTC). The reaction was optimized on the reaction temperature, duration, loading of BTBAC, and concentration of HCl. The optimized reaction condition was then applied for the one-pot coproduction of FUR and CMF from a mixture of pentose and hexose sugars. In this regard, an efficient coproduction of FUR and CMF from the mixture of glucose and xylose could work as a working model for terrestrial and algal biomasses.
- A one-pot, scalable, high-yielding procedure for synthesizing AMFs, as a hydrophobic and halogen-free congener of HMF and CMF, from inexpensive sugars and carbohydrates under relatively mild reaction conditions is desired to improve the commercial prospects of biorenewable chemicals. The present work reported the AcOH-catalyzed dehydration of sugars to HMF and promoted

its esterification into AcMF, adding a Lewis acidic metal salt. The process reported the general preparative strategy of AMFs using $ZnCl_2$ as an inexpensive and non-toxic Lewis acid catalyst in the presence of C1-C4 carboxylic acid.

- The selective oxidation of FUR to 2FN is relatively less explored in the literature. The preparation of 2FN was attempted using aqueous hydrogen peroxide as a green and cheap oxidant in the presence of trifluoroacetic acid as an acid catalyst and reaction medium. Interestingly, the reaction worked under relatively mild conditions and obtained an excellent isolated yield of 2FN.
- Furthermore, triethylammonium hydrogen sulfate (TEAHS) has been employed as an efficient and inexpensive protic ionic liquid (IL) catalyst for esterifying various biomass-derived renewable compounds, such as levulinic acid, 2-furoic acid, stearic acid, and isosorbide (IS). Anhydrous potassium carbonate has been used as an efficient, inexpensive, and recyclable inorganic base catalyst for solvent-free transesterification of isohexides (IS, isomannide, and isoidide) for synthesizing mono- and diesters.
- Recently, the heterocyclic chemistry of furanics gained significant attention for synthesizing pharmaceutically important compounds. This work uses biomass-derived renewable furanics as the aldehyde moiety for synthesizing novel DHPMs and DHPs using DABCO diacetate (DABCO-Ac) as an acid catalyst. The reaction was optimized on the type and loadings of acid catalyst used and the reaction temperature.

8.2 CONCLUSIONS

The main objectives of the thesis were the preparation and value addition of renewable chemical intermediates from carbohydrates. Based on experimental results, the following conclusions were drawn.

- FUR has been produced in a 53% isolated yield from xylose within an aq. HCl-DCE biphasic batch reaction using BTBAC as a PTC. BTBAC afforded significantly higher yields of FUR starting from xylose compared to the control reaction. The insoluble humin formed in noticeably lower quantities in reactions using BTBAC. CMF and FUR were coproduced from a physical mixture of xylose and hexose carbohydrates. The yields of CMF and FUR were higher when using BTBAC as PTC. Under optimized conditions (100 °C, 3 h, 20.2% HCl, 10 wt.% BTBAC), CMF and FUR were isolated in 17% and 53% yields, respectively, from a mixture of glucose and xylose. In addition, LA was isolated from the aqueous layer in a 31% isolated yield. No chemical decomposition of BTBAC was observed after the reaction and recovered in near-quantitative yield.

- AMFs were prepared directly from carbohydrates using carboxylic acid as the Brønsted acid catalyst (and reagent) in the presence of $ZnCl_2$ as a Lewis acid catalyst. The process was initially optimized for 5-(acetoxymethyl)furfural (AcMF) and then extended to producing other AMFs. Fructose and glucose provided AcMF in 80% and 60% isolated yield under optimized parameters. Other metal chloride salts and other salts of zinc showed much lower catalytic activity. The sugars gave noticeably higher yields of AcMF compared to polymeric carbohydrates. The direct synthesis of 5-(propyloxymethyl)furfural, 5-(butyloxymethyl)furfural, and HMF-levulinate from fructose was attempted for the first time in the present work.
- Biomass-derived FUR has been selectively oxidized into 2FN, providing up to 52% isolated yield by 30% H_2O_2 as the oxidant in the TFA medium under mild conditions. The gram-scale reaction worked without organic solvents or additives. SA was isolated from the aqueous layer in around 20% yield after distilling the volatiles. Using a catalytic amount of TFA provided a 44% isolated yield of 2FN.
- High-yielding, gram-scale preparation of the esters of various biomass-derived chemical platforms has been attempted. TEAHS was employed as an inexpensive but efficient IL-based acid catalyst and reaction medium for synthesizing esters from carboxylic acids and alcohols following the Fischer esterification protocol. The scalable, organic solvent-free preparations were conducted in a batch-type glass pressure reactor, which provided excellent yields (> 80%) of the esters under moderate conditions.

- Anhydrous potassium carbonate has been used as a base catalyst for synthesizing the mono- and diesters of isohexides by transesterification. The catalysts were successfully recovered and reused for multiple catalytic cycles. Excellent isolated yields (>90%) of the isosorbide benzoate were obtained, and the methodology was successfully extended to synthesizing the mono- and diesters of the other two isohexides, i.e., isomannide and isoidide.
- Novel DHPMs and DHPs have been synthesized, starting from biorenewable FUR and 5-methyl furfural, using DABCO-Ac as a robust, efficient, and inexpensive acid catalyst. The solvent-free, gram-scale reactions worked under mild conditions affording products in excellent isolated yields. Under optimized reaction conditions, FUR gave 74% DHPM and 23% DHP.

8.3 FUTURE WORK

This work has described the chemocatalytic preparation and value-addition of renewable chemical intermediates from carbohydrates. The present work demonstrates the coproduction of FUR, CMF, and LA using BTBAC as a PTC. PTC provides a noticeably high yield and considerably reduces the side product formation. A similar strategy can be extended for the coproduction of other biorenewable compounds from various biomass feedstocks. The effect of PTC on the derivative chemistry of CMF and HMF may also be explored. The esters of HMF, such as AMFs, are particularly interesting since they are halogen-free, hydrolytically stable, and hydrophobic analogs of HMF. However, the present work first attempted to synthesize different AMFs directly from carbohydrates. But using polymeric carbohydrates (e.g., starch, cellulose) gave relatively lower yields of AMFs than sugars. In this regard, new catalytic systems to synthesize AMFs in satisfactory yields directly from polymeric carbohydrates should be investigated. Heterogeneous catalysts are preferred over their homogeneous counterparts for the derivative chemistry of biomass-derived intermediates. In this regard, the design and synthesis of novel, robust, inexpensive, selective, and environment-friendly heterogeneous catalysts for biomass value addition must be undertaken.

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LIST OF PUBLICATIONS

Journal publications published/communicated from this thesis work

1. **Bhat, N. S.**, Vinod, N., Onkarappa, S. B., and Dutta, S. (2020). "Hydrochloric acid-catalyzed coproduction of furfural and 5-(chloromethyl)furfural assisted by a phase transfer catalyst." *Carbohydr. Res.*, 496, 108105.
2. **Bhat, N. S.**, Mal, S. S., and Dutta, S. (2020). "[Et_3NH][HSO_4] as an efficient and inexpensive ionic liquid catalyst for the scalable preparation of biorenewable chemicals." *Biomass Conver. Biorefin.*, 12, 5619–5625.
3. **Bhat, N. S.**, Kumar, R., Jana, A., Mal, S. S., and Dutta, S. (2021). "Selective oxidation of biomass-derived furfural to 2(5H)-furanone using trifluoroacetic acid as the catalyst and hydrogen peroxide as a green oxidant." *Biomass Conver. Biorefin.*, 13, 1029–1034.
4. **Bhat, N. S.**, Mal, S. S., and Dutta, S. (2021). "Recent advances in the preparation of levulinic esters from biomass-derived furanic and levulinic chemical platforms using heteropoly acid (HPA) catalysts." *Mol. Catal.*, 505, 111484.
5. **Bhat, N. S.**, Yadav, A. K., Karmakar, M., Thakur, A., Mal, S. S., Dutta, S. (2022) "Preparation of 5-(acyloxymethyl)furfurals from carbohydrates using zinc chloride/acetic acid catalyst system and their synthetic value addition." *ACS Omega*, 8, 8119–8124.
6. **Bhat, N. S.**, Vinod, N., Nayak, M. K., Jana, A., Tarafder, K., Mal, S. S., Dutta, S. (2023) "Efficient preparation of the esters of biomass-derived isohexides by base-catalyzed transesterification under solvent-free conditions." (communicated).
7. **Bhat, N. S**., Kumari, M., Naik, P. C., Mal, S. S., Dutta, S. (2023) "Synthesis of novel Biginelli and Hantzsch products from biorenewable furfurals using 1,4-diazabicyclo[2.2.2]octanium diacetate as an efficient and recyclable catalyst." (communicated).

Journal publications from other projects

1. **Bhat, N. S.**, Hegde, S. L., Dutta, S., Sudarsanam, P. (2022). "Efficient synthesis of 5-(hydroxymethyl)furfural esters from polymeric carbohydrates using 5-

(chloromethyl)furfural as a reactive intermediate." *ACS Sustainable Chem. Eng.*, 10, 5803-5809.

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3. Dutta, S., **Bhat, N. S.** (2022). "Chemocatalytic value addition of glucose without carbon-carbon bond cleavage/formation reactions: Overview." *RSC Adv.*, 12, 4891-4912.
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2. **Bhat, N. S.**, Dutta, S., Tarafder, K., Vinod, N., (2023). "Transesterification of isohexides under solvent free conditions." Application number 202241069622 (Published).

BOOK CHAPTERS

1. Dutta, S., **Bhat, N. S.**, Vinod, N., (2020). "Oxidation and reduction of biomass-derived 5-(hydroxymethyl)furfural and levulinic acid by nanocatalysis." In *Advanced Heterogeneous Catalysts Volume 1: Applications at the Nano-Scale*, American Chemical Society, pp. 239-259.
2. Dutta, S., **Bhat, N. S.**, Anchan, H. N., (2022). "Nanocatalysis for renewable aromatics." In *Heterogeneous Nanocatalysis for Energy and Environmental Sustainability Volume 1*, Wiley-VCH, pp. 61-99.

CONFERENCES AND WORKSHOPS ATTENDED

1. Presented oral presentation on AICTE-sponsored "**National Conference on Energy and Chemicals from biomass (NCECB-2019)"** organized by Pondicherry Engineering College, Pondicherry, India, during 10-11 October 2019.

2. Presented poster presentation on "**International Conference on Advances in Chemical and Materials Science (ICCM-2019)"** organized by the Department of Chemistry, Mangalore University, Mangalagangotri, Karnataka, India, during 17-19 October 2019.
3. Presented oral presentation on RSC-sponsored **International Conference on Advances in Material Science and Chemistry (ICAMSC-2020)** conducted by the Department of Chemistry, Amrita Vishwa Vidyapeetham, Amritapuri campus, Kerala, India, during 10-12 August 2020 (virtual conference).

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