# BIOSOURCE 5-HYDROXYMETHYLFURFURAL DERIVED DERIVATIVES IN INTRAMOLECULAR DIELS- ALDER REACTION

## DISSERTATION

Submitted in partial fulfilment of

The Degree of M.Sc. in Organic Chemistry

By

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To

School of Chemical Sciences

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Taleigao, Goa-403401

August 2020

# STATEMENT

I hereby declare that the matter presented in this dissertation entitled, '**BioSource 5-Hydroxymethylfurfural Derived Derivatives in Intramolecular Diels-Alder reaction'** is based on the result carried out by me in the School of Chemical Sciences, Goa University under the supervision of **Prof. Santosh G. Tilve** and same has not been submitted elsewhere for the award of degree or diploma.

**Anagha Devidas Marathe**

**CH-18-044**

# CERTIFICATE

This is to certify that the dissertation entitled, **'Bio Source 5-Hydroxymethylfurfural Derived Derivatives in Intramolecular Diels- Alder reaction'** is a bonafide work carried out by **Miss Anagha Devidas Marathe** under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

**Prof. Santosh G. Tilve**

**Guiding Teacher, School of Chemical Sciences**

**Goa University**

# CERTIFICATE

This is to certify that the dissertation entitled, **'Bio Source 5-Hydroxymethylfurfural Derived Derivatives in Intramolecular Diels- Alder reaction'** is a bonafide work carried out by **Miss Anagha Devidas Marathe** under the supervision of **Prof. Santosh G. Tilve** for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

**Dean, School of Chemical Sciences**

**Goa University**

# ACKNOWLEDGEMENT

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I would also like to thank Prof. V.S. Nadkarni, Dean of School of Chemical Sciences, Goa university, for permitting the use of all facilities and timely suggestions.

I also express my gratitude to the research scholars namely Mr Shashank, Mr Ketan Mandrekar for their help in spectral analysis and other difficulties. I would also like to thank Mr Mehul Shirodkar for his help when required.

Last but not the least I would like to express my gratitude and love to my parents and friends for their support and motivation, and above all almighty for providing strength and blessings.

# INDEX

# INTRODUCTION

The contribution to rapid development of economy and progress of society is because of petroleum, fossils and other non-renewable energy sources. However, the over diminishing non-renewable resources, the increasing demands for fuels, as well as the environmental pollution caused by overuse and exploitation of fossil resources, has become a huge challenge for mankind. Faced with this dilemma, people have put forward strategies to search for renewable alternative resources. Biomass is the only renewable organic carbon source in nature. Amongst various valuable compounds derived from biomass, HMF is identified to be a top building block chemical.

HMF is synthesised by dehydration of monosaccharides, Disaccharides, polysaccharides as well as raw biomass such as wheat straw. The production of HMF from biomass generally include acid catalysed hydrolysis of biomass to produce hexose in first step. The second dehydration step starts from ketohexose e.g. Fructose. Generally, ketohexose is more efficient and selective than aldohexose e.g. glucose. This is because structure of aldohexose is more stable and it enolyses slowly. As enolization is rate determining step for HMF synthesis its formation from fructose is preferred over glucose. Over past years many synthetic methodologies for synthesis of HMF have been developed taking into account the reaction conditions such as solvent, substrate and their concentration, as well as catalyst and their reuse[1].

The structural motifs present in 5-Hydroxymethylfurfural namely furan, primary hydroxy group and formyl functionalities makes it as an appealing starting material to undergo further reactions like selective oxidation and reduction of formyl group etc. These reactions proceed through homogeneous, heterogeneous, bio, and electrochemical catalysis technique. Some of the derivatives synthesised from HMF are as follows [2].

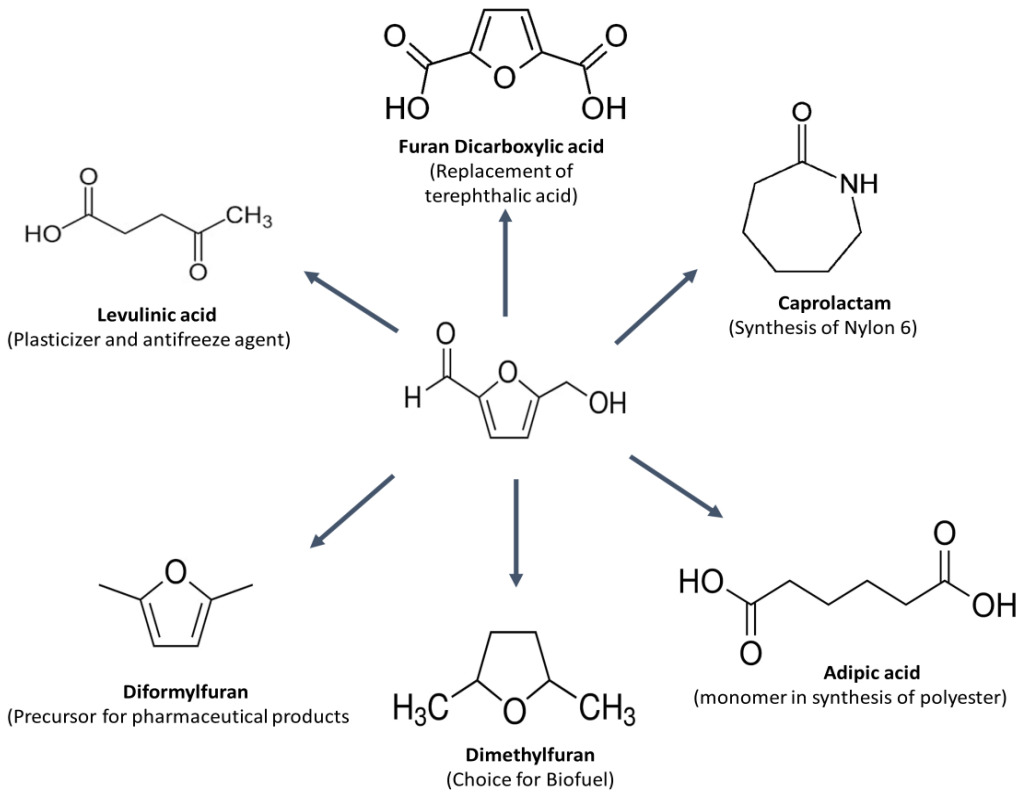
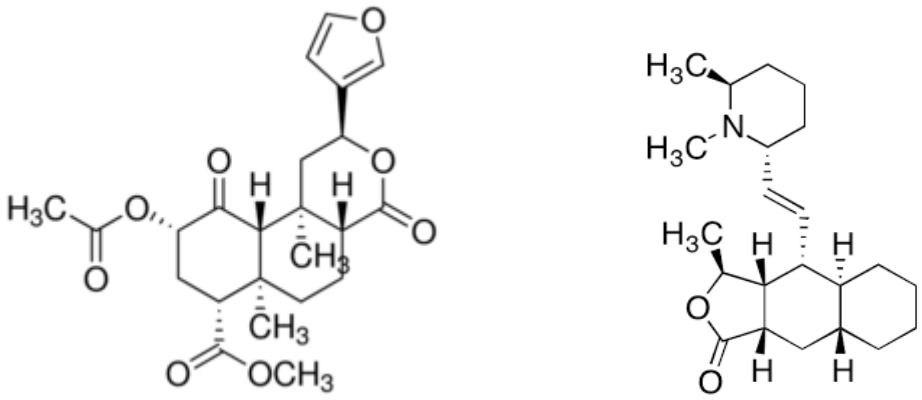



**FIG 1** -Transformation of HMF into value added chemicals

However, amongst the above-mentioned reactions, Diels -Alder reaction proves to be an efficient route for construction of six membered rings with high degree of structural complexity in a single synthetic step. Diels Alder reaction is a (4+2) cycloaddition reaction between 1,3-diene and dienophile. Within this class, Intramolecular Diels- Alder reactions (IMDA) are important and are established as versatile and useful reactions in synthetic organic chemistry. The first example of an IMDA was an unpublished result mentioned by Alder, which converted 1,4-pentadiene and dimethyl acetylenedicarboxylate via an unisolated ene adduct, to a bicyclo [4.1.0] heptane derivative[3]. Subsequently there are couple of more isolated reports until 1963, one involving an attempted synthesis of Longifolene[4] and the other included a simple synthesis of dehydration product of podophyllotoxin[5]. The high degree of regioselectivity, stereoselectivity and diastereoselectivity attained by these reactions have attracted the attention of organic chemist. Thus, many reactions of IMDA have been documented over mounting citations of associated articles in chemical literature.

The IMDA reaction is quite general with respect to the diene component, the dienophile component, and the connecting tether between the two. IMDA reaction occur in presence of both electron-donating and electron-withdrawing substituents on diene (furan) component while a variety of activated (electron deficient) and inactivated dienophile participate in the cycloaddition reactions, including alkenes, alkynes, allene, and benzynes. However, IMDA reactions are well accelerated by presence of electron withdrawing group on dienophile. In addition, a range of conditions have been developed to facilitate the IMDA reactions, including use of Lewis acid, microwave irradiation, high pressure and photochemical excitation. They proceed more easily than Intermolecular Diels -Alder reaction owing to favourable entropy factor.

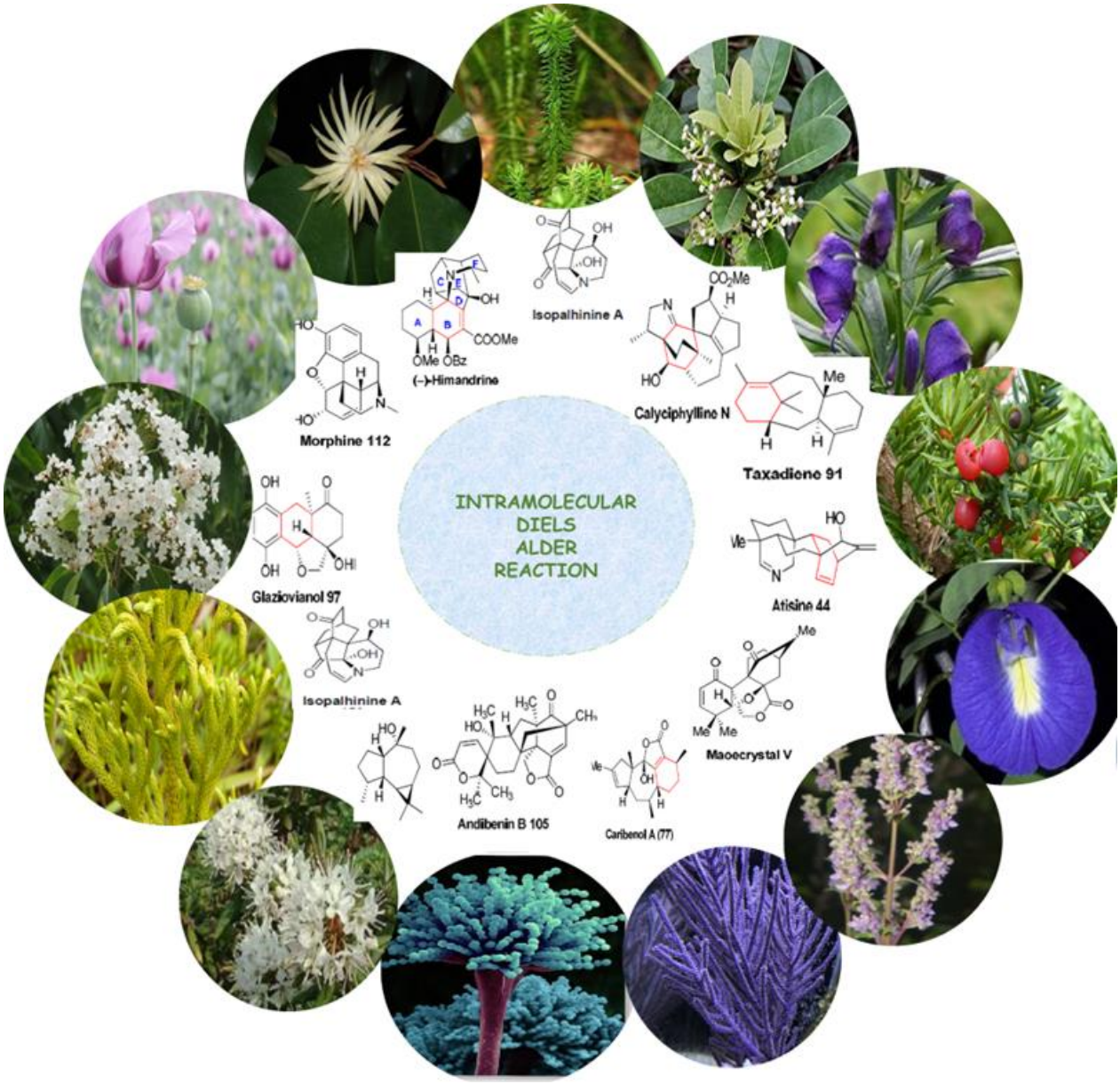
IMDA is also a powerful tool for synthesising drugs. Some useful drugs synthesised using the Intramolecular Diels- Alder reaction are Salvinorin A [6] and Himbacine [7].



Salvinorin A Himbacine

**FIG 2** Salvinorin A is used in psychotherapeutic treatment and Alzheimer's treatment and Himbacine is promising lead in Alzheimer's disease research.

The most important application of IMDA include synthesis of biologically active natural products mainly terpene and alkaloids[8]. Some of the biologically active natural products whose complete synthesis is accompanied using Intramolecular Diels -Alder reaction is shown in **FIG 3**.




Recently, Diels -Alder reaction on 5-hydroxymethylfurfural are also reported . The main advantage of using Diels- Alder reaction on HMF include synthesis of tricyclic compounds which possess biologically activity . This reaction has also lead to the replacement of petroleum derived plastics into alternative bio-based polymers .

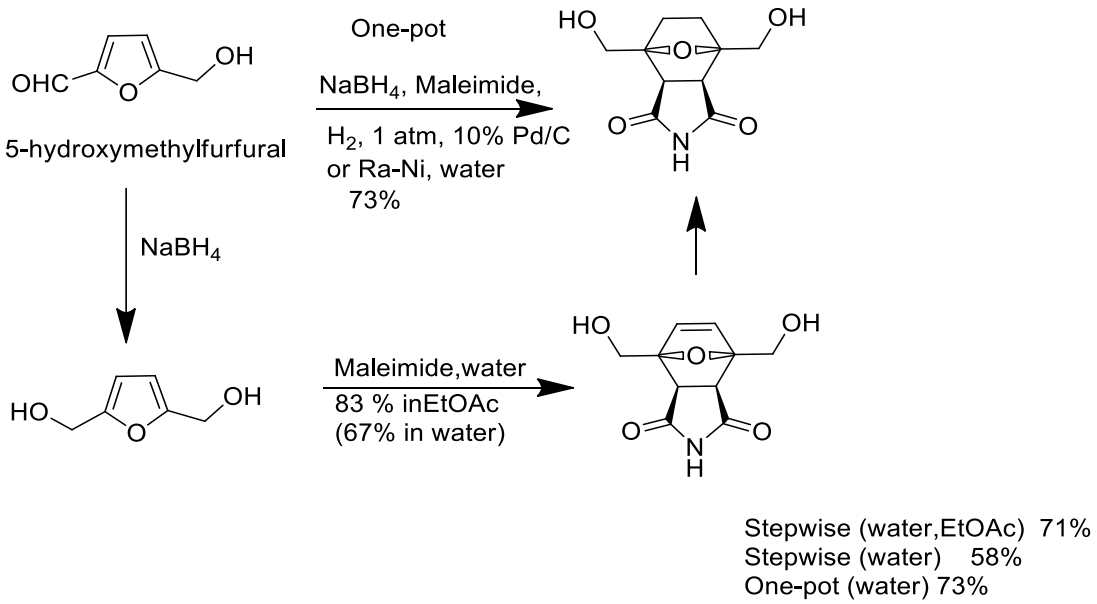
Since there have been very few Intramolecular Diels -Alder reactions on HMF reported in literature,we rather decided to carry IMDA on HMF.

# LITERATURE REVIEW

- **EFFICIENT ROUTE FOR CONSTRUCTION OF POLYCYLIC SYSTEM FROM BIODERIVED HMF**

Since the tricyclic compound synthesised from bioderived HMF contain structural cores of naturally occuring biologically active compound F.A Kucherov,K.I.Galkin,E.G Gordeev and V.P. Ananikov[9] carried out Diels- Alder reaction on functionalised amines, ethers, esters and hydroxyl derivatives of HMF.

## SCHEME-1



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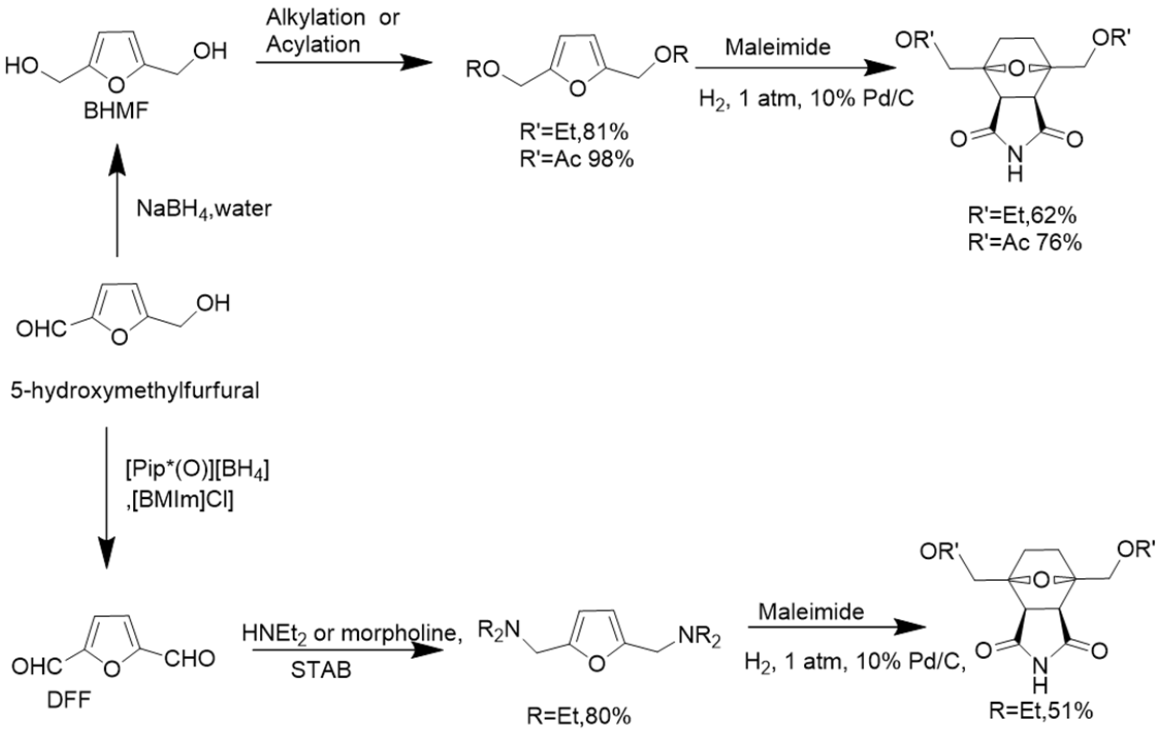


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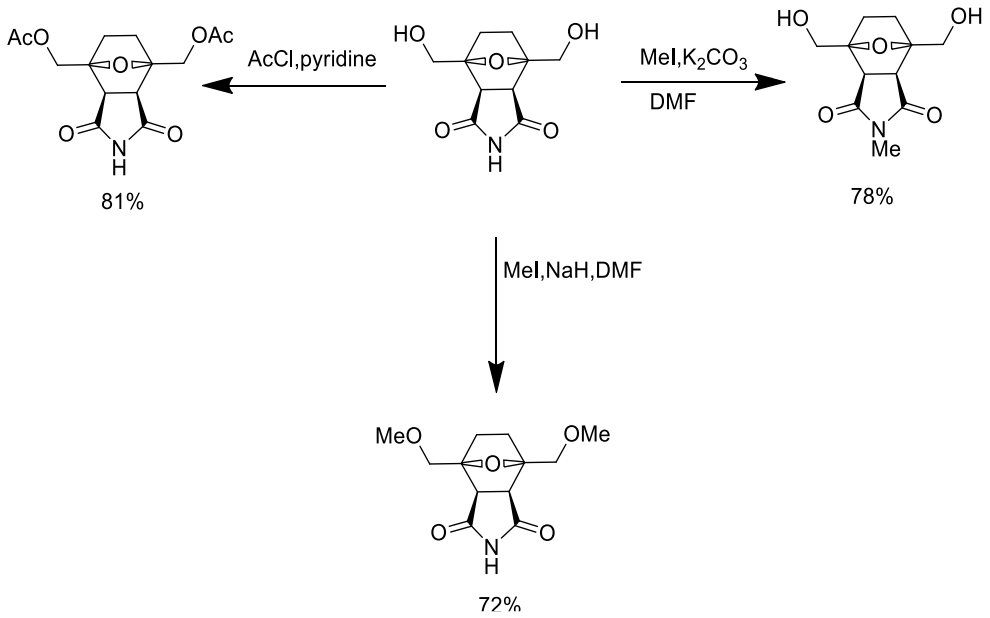
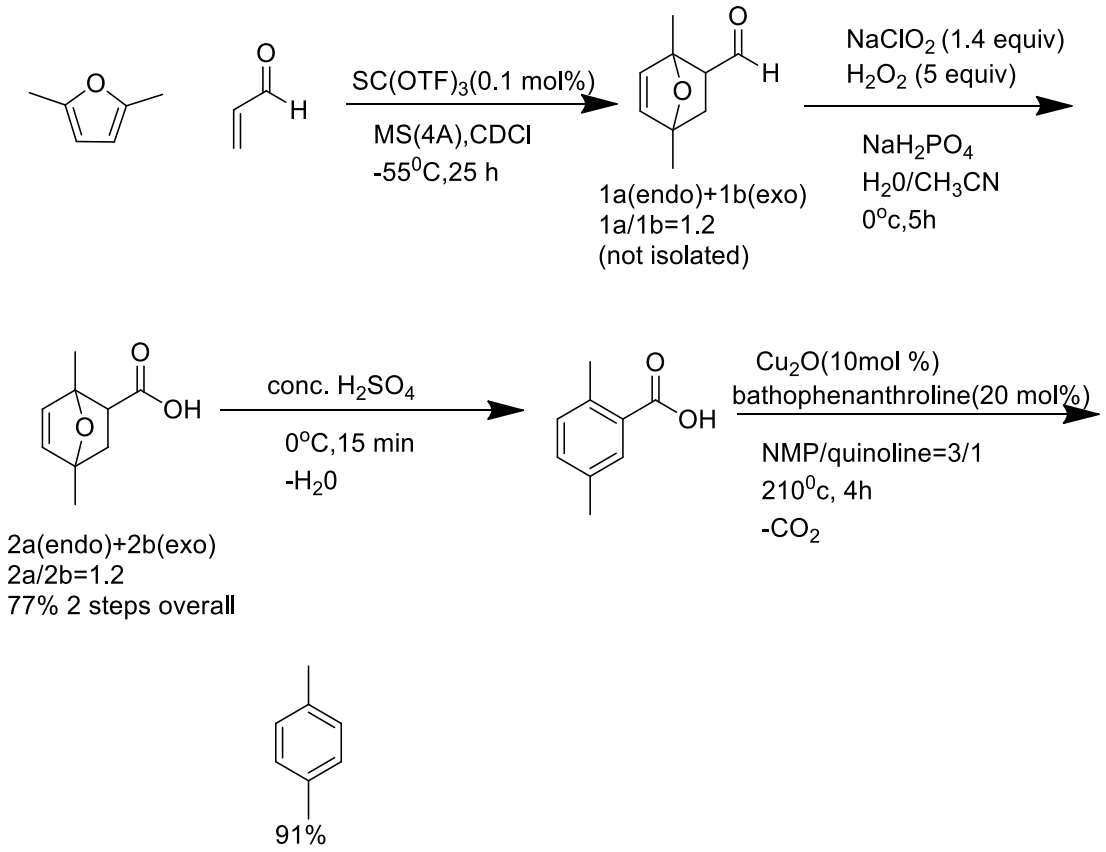


❖ **ON THE DIELS- ALDER APPROACH SOLELY BIOMASS DERIVED POLYETHYLENE TEREPHTHALATE (PET): CONVERSION OF 2,5 DIMETHYL FURAN AND ACROLEIN INTO P-XYLENE**

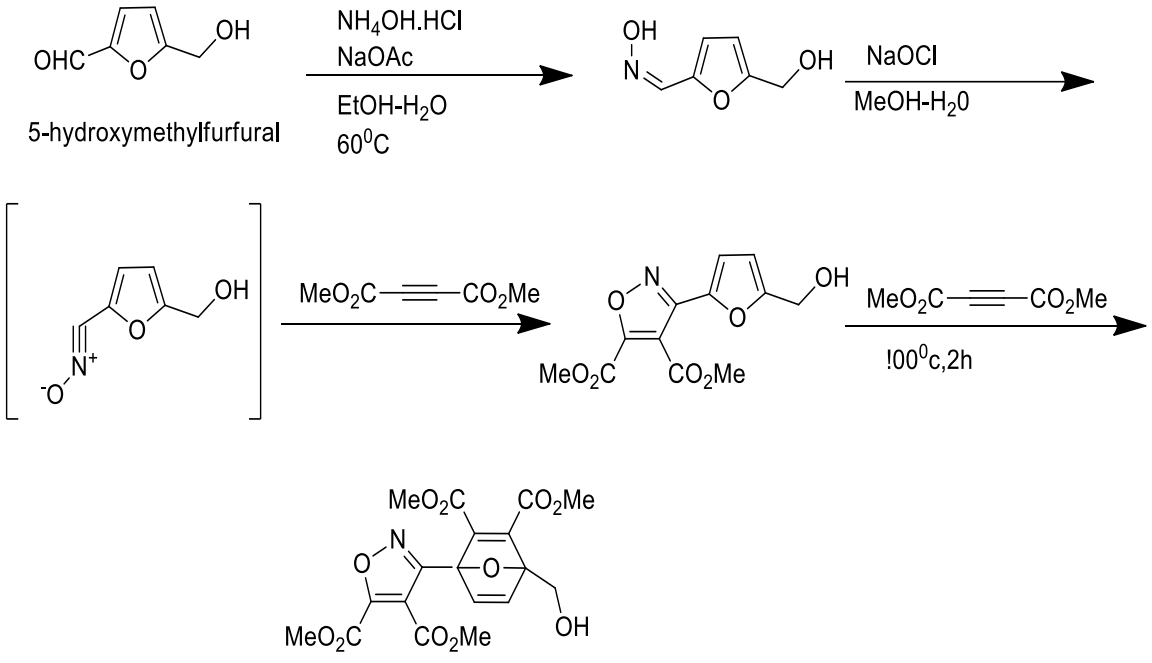
Mika Shiramiza and F. Dcan Toste[10] Carried out route to convert DMF and Acrolein into p-xylene for bio renewable PET production. This scheme involved Diels -Alder reaction, oxidation, dehydration, Aromatisation and decarboxylation to obtain high yield and prevent formation of side product.



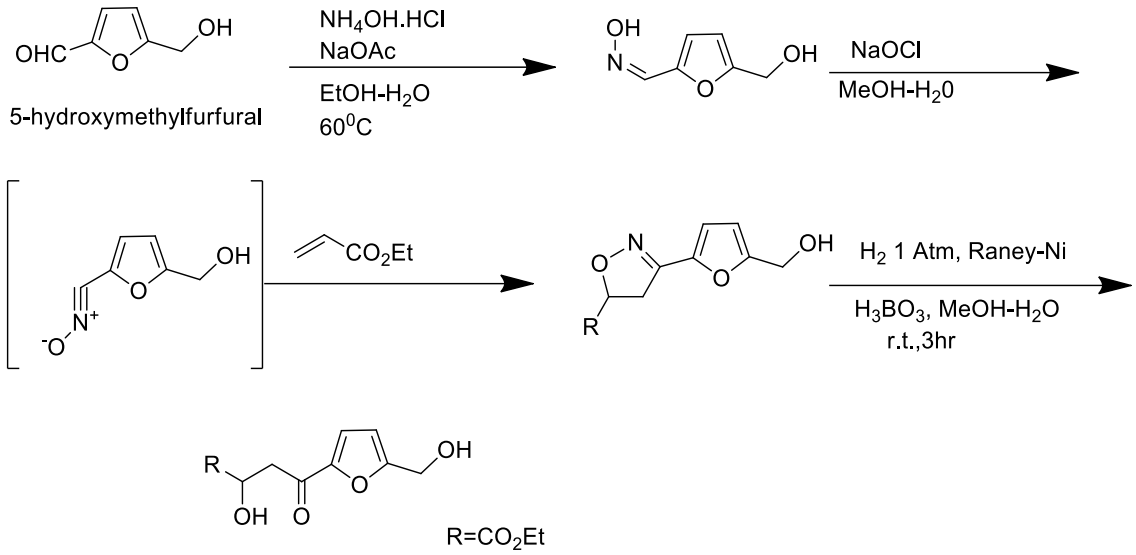
## ❖ CYCLOADDITION REACTION OF 5-HYDROXYMETHYL-FURAN –NITRILE OXIDE

Ananda S. Amarasekara, Osayamen Edigin and Wendy Hernandez[11] carried out following reaction in which 5-Hydroxymethyl-furan-2-nitrileoxide undergoes [3+2] cycloadditions with alkenes to give 3-(2-furanyl)-4,5dihydo-isoxazole ring system in 71-84% yield. Cycloaddition with one equivalent of dimethyl acetylene dicarboxylate gave a 1:1 adduct with 3-(2-furanyl)-isoxazole ring system and further reaction with a second equivalent in a [4+2] Diels Alder reaction yielded a 3-(7-oxa-bicyclo [2.2.1] hepta-2,5-dien-1-yl)-isoxazole. Hydrogenolysis of 3-(2-furanyl)-4,5dihydo-isoxazole adducts with Raney-Ni catalyst resulted the ring opening of the 4,5-dihydro-isoxazole ring.

**SCHEME 1**

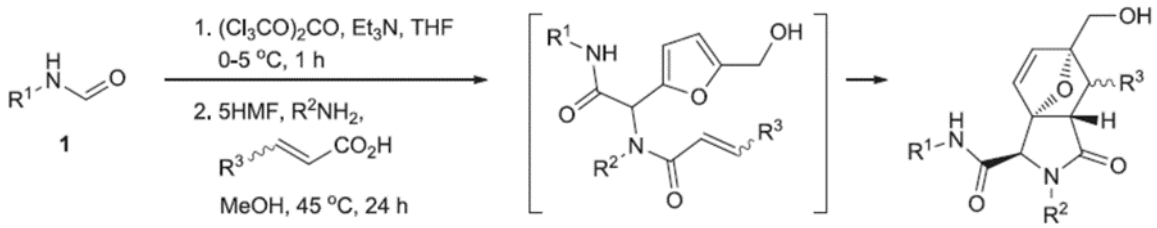


**SCHEME 2**



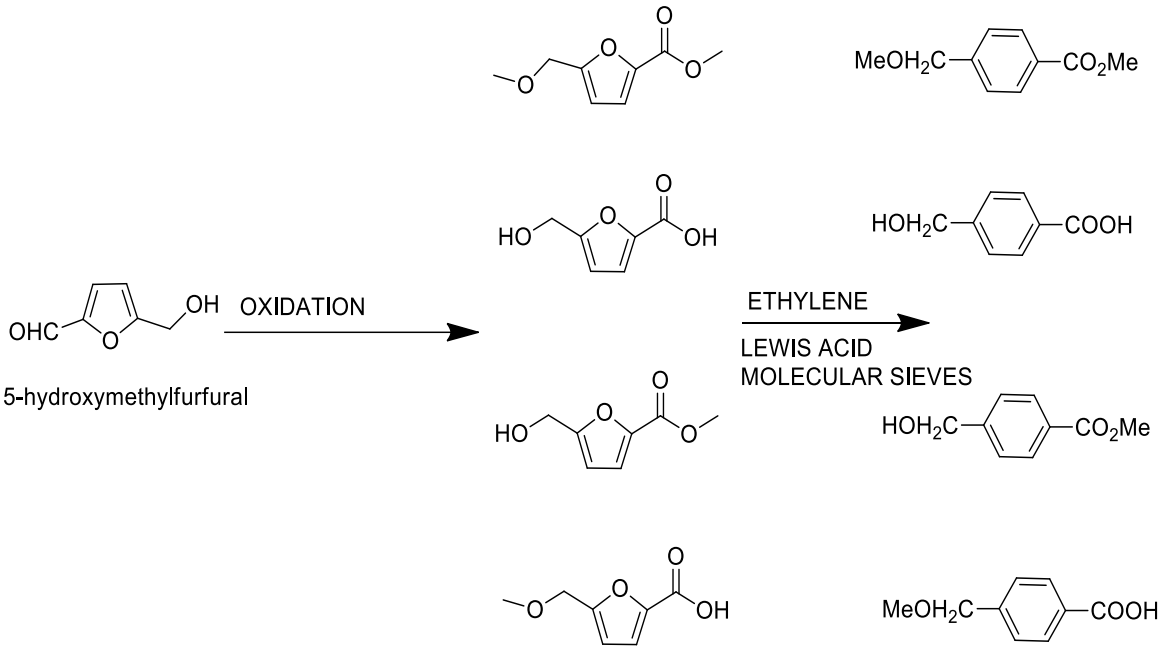

## ❖ ISOCYANIDE-LESS" UGI/INTRAMOLECULAR DIELS-ALDER REACTION OF 5-HYDROXYMETHYLFURFURAL

Golubev⇑, Alena Pankova, Mikhail Krasavin[12] carried out the following one-pot, three-step, four-component Ugi-IMDAF reaction with 5-hydroxymethylfurfural which provides simple access to hydroxymethyl-substituted epoxyisoindolones in a diastereoselective and stereospecific manner.



## ❖ SYNTHESIS OF TEREPHTHALIC ACID VIA DIELS-ALDER REACTION WITH ETHYLENE AND OXIDISE VARIANTS OF 5-HYDROXYMETHYLFURFURAL

Davis et al[13]. have developed new alternative pathway to synthesis terephthalic acid (PTA) by reaction of oxidised product of HMF and ethylene over solid Lewis acid catalyst like Sn-Beta and Zr-Beta

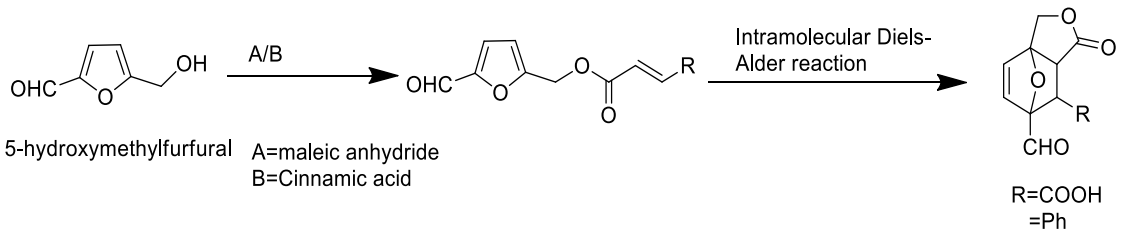



These products were oxidised to produce DMT or PTA. It was also observed that 2,5-furandicarboxylic acid fails to undergo Diels -Alder reaction with ethylene.

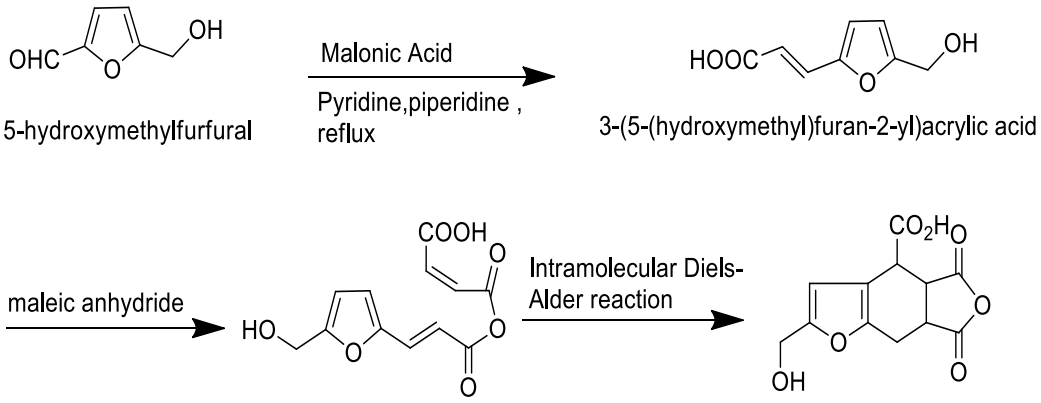
# PRESENT WORK

After studying literature, we decided to carry following schemes.

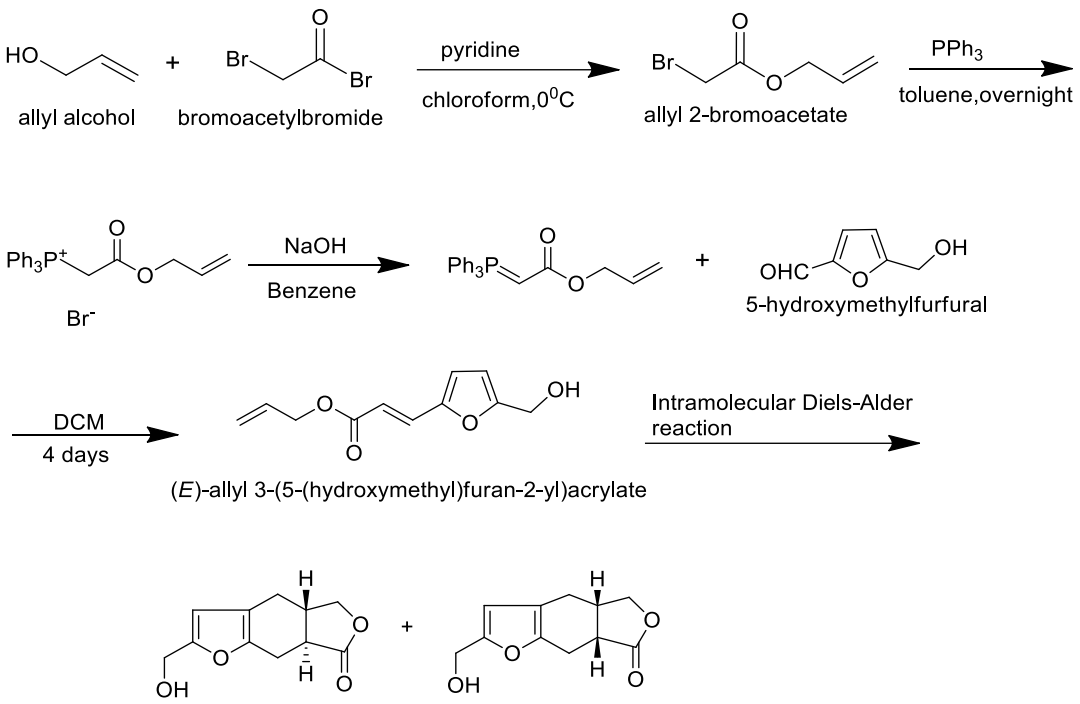
**SCHEME 1**




**SCHEME 2**



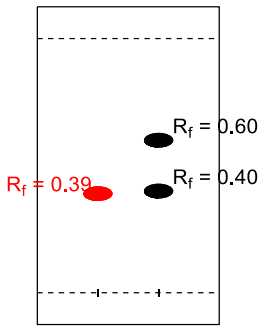
**SCHEME 3**


HO
allyl alcohol
Br
Br
bromoacetylbromide
pyridine
chloroform,0$^0$C
Br
O
allyl 2-bromoacetate
$PPh_3$
toluene,overnight
$Ph_3P^+$
$Br^-$
NaOH
Benzene
$Ph_3P$
OHC
OH
5-hydroxymethylfurfural
DCM
4 days
(E)-allyl 3-(5-(hydroxymethyl)furan-2-yl)acrylate
Intramolecular Diels-Alder reaction
OH
OH

# RESULT AND DISCUSSION

- **HMF synthesis**

We attempted to synthesis HMF from Fructose using homogenous catalyst under refluxing condition. The reaction showed a colour change from yellow to orange red to brown. The formation of the product was confirmed with TLC using an authentic sample.




The reaction was carried out in presence of homogenous catalyst like HCl and $H_2SO_4$. In both cases the yield obtained was 49%.

The crude HMF was distilled under vacuum. However, the TLC (60% ethyl acetate and pet ether) showed multiple spots indicating that the reactivity of HMF increases at higher temperature.

The purification of crude HMF was also done via

Column chromatography. However, the method was tedious and also

Synthesised HMF

Authentic HMF

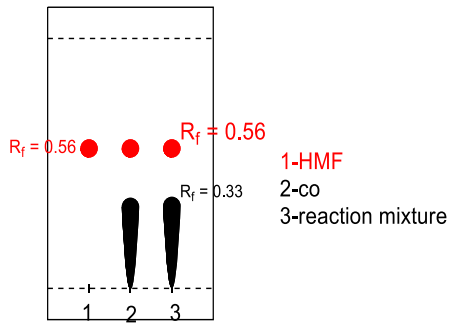
resulted in formation of additional compounds indicating that HMF is unstable under acidic condition. Hence Purification techniques like Flash Chromatography, HPLC, HPGC must be used.

- **Intramolecular Diels -Alder reaction on HMF**

From literature it was clear that no Diels- Alder reaction was reported on HMF. Hence, we thought of studying Intramolecular Diels- Alder reaction on HMF.

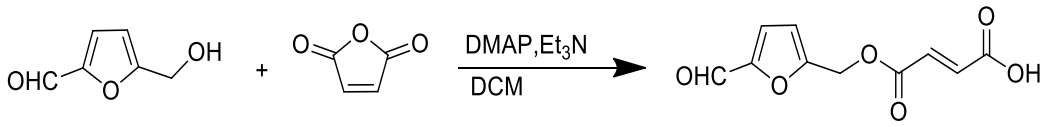
1. Synthesis of 4-((5-formylfuran-2-yl) methoxy)-4-oxobut-2-enoic acid.

   To synthesise mono Ester of HMF, 1 equivalent of HMF and 1 equivalent of maleic anhydride were stirred for 3 hrs at room temperature. However, the expected product was not obtained as concluded from TLC.

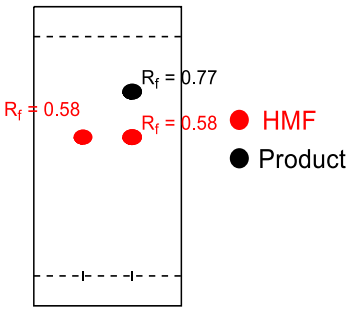



In order to obtain the desired product, the reaction the was now stirred overnight at $0^0$C by using 2 equivalent of maleic anhydride and 1 equivalent of HMF. However, again the expected product was not obtained as concluded from TLC.

60%ethylacetate pet ether



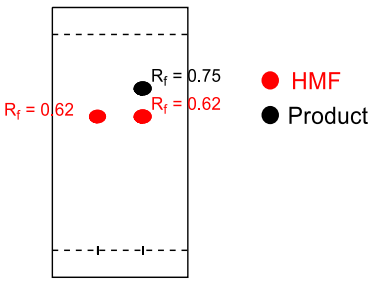

5-hydroxymethylfurfural Maleic anhydride 4-((5-formylfuran-2-yl) methoxy)-4-oxobut-2-enoic acid




60% ethylacetate pet ether

Microwave acceleration is particularly useful for facilitating IMDA reactions of sluggish substrates. Hence, Microwave assisted reaction was carried out using 1 equivalent of HMF and 1.2 equivalent of maleic anhydride at $150^0$C for 30 min. However, the expected product was not formed, instead TLC showed two spots at Rf=0.2 and Rf=0.4, where Rf=0.2 corresponds to the formation of an acid and Rf =0.4 indicates that HMF has not reacted. Hence 0.3 ml of N, N- diisopropylethylamine was added as base and the reaction mixture was irradiated for 30 mins (2 times) at $140^0$C.

The TLC showed spot at Rf= 0.77 which may be indicating formation of product but the reaction was however incomplete.

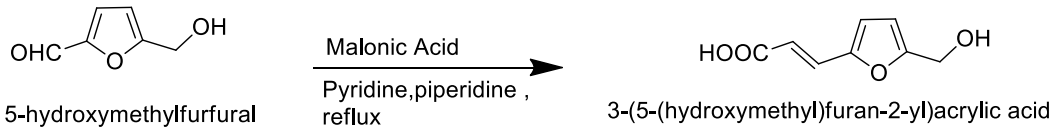


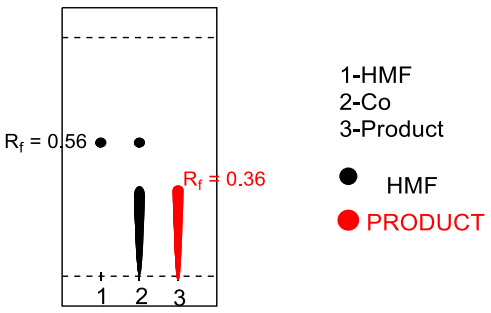

60% ethylacetate pet ether

Finally, we carried out reaction between 1 equivalent of HMF and 1 equivalent of maleic anhydride under inert condition. The TLC of the reaction mixture showed the formation of product but the reaction was incomplete.

Due to time constraint further modification of this reaction and separation of the desired product from HMF was limited.

2. synthesis of 3-(5-(hydroxymethyl) furan-2-yl) acrylic acid



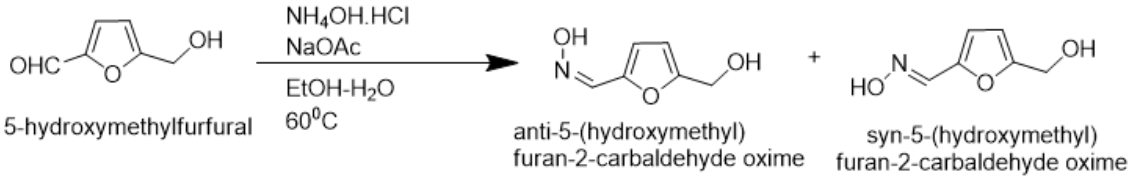

1-HMF
2-Co
3-Product

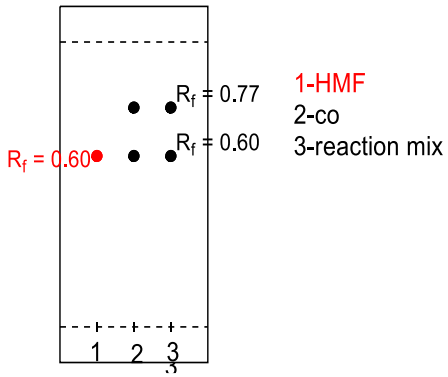
HMF
PRODUCT

60% ethylacetate pet ether

3-(5-(hydroxymethyl) furan-2-yl) acrylic acid was synthesised using 1 equivalent of HMF and 1 equivalent of malonic acid. The reaction was refluxed for 7 hr and the TLC showed the presence of HMF and a product. The reaction was however, stopped after knowing that there is presence of moisture in pyridine and piperidine. 23% of product was obtained and 40 % of HMF was recovered via solvent extraction.

3. Synthesis of oxime




60%ethylacetate pet ether

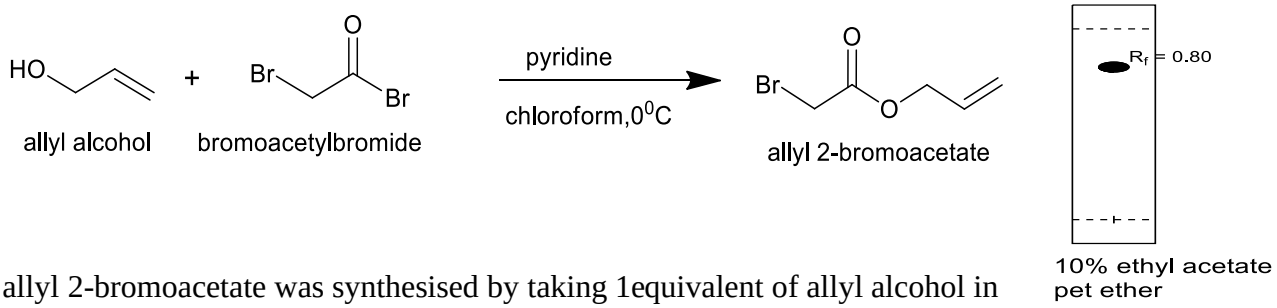
In this synthesis, TLC showed two spots indicating that there may be formation of syn and anti-oxime.

IR spectra showed the absence of HMF. But the formation of oxime could not be confirmed.

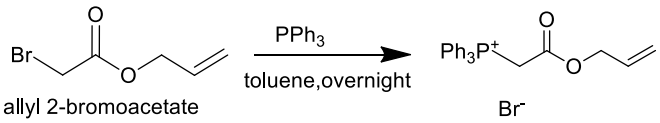
4. Synthesis of (E)-allyl 3-(5-(hydroxymethyl) furan-2-yl) acrylate.

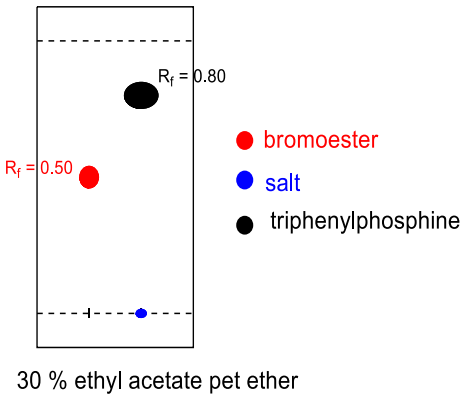
(E)-allyl 3-(5-(hydroxymethyl) furan-2-yl) acrylate was obtained using Wittig reaction.

Stabilised ylide was synthesised from bromo ester.

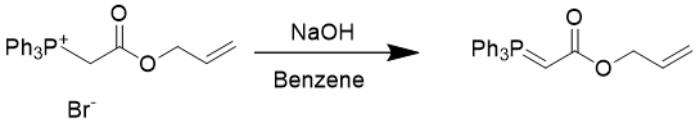


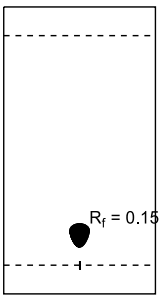

allyl 2-bromoacetate was synthesised by taking 1equivalent of allyl alcohol in chloroform and cooling the reaction mixture in ice for 15 mins. Then bromoacetylbromide was added dropwise. This resulted in evolution of fumes of pyridine hydrobromide. The reaction mixture was then stirred for 2 hrs. and after confirming the formation of desired product which was observed on TLC, the product was extracted via solvent extraction. Brown liquid of allyl 2-bromoacetate was obtained in 54.2 % yield.



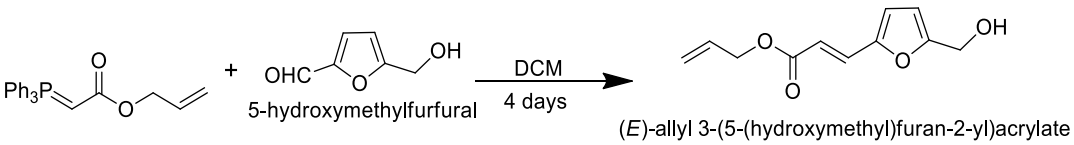

To the above bromo ester triphenyl phosphine was added. The formation of the product took place immediately and the complete consumption of bromo ester was confirmed by taking TLC. Salt was obtained in 84.3% yield.



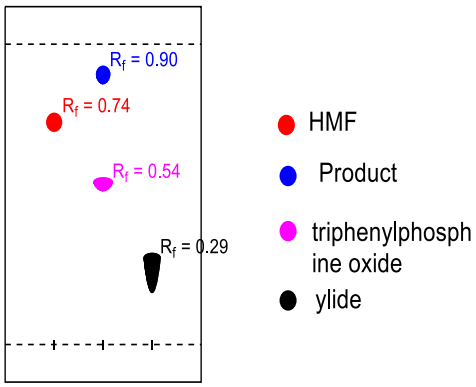




30 % ethylacetate
pet ether

In order to obtain the stabilised ylide, salt was dissolved in water and benzene was added as an extracting solvent along with a drop of phenolphthalein. Required amount of NaOH was added and the ylide was extracted in benzene. The TLC showed characteristic spot which is similar to that observed for any ylide. The ylide was obtained in 59%yield.



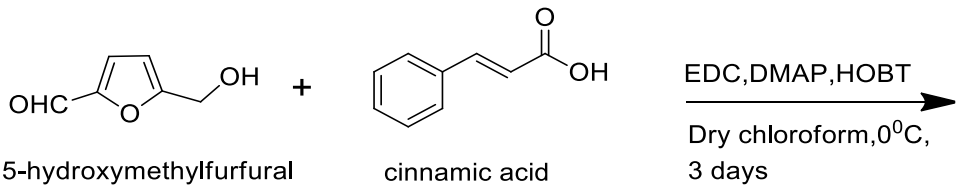

(*E*)-allyl 3-(5-(hydroxymethyl)furan-2-yl)acrylate



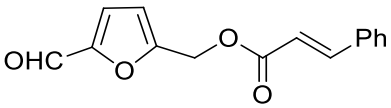

60% ethyl acetate and pet ether

The ylide was refluxed with HMF for 4 days at room temperature. The TLC showed the formation of product at Rf=0.9. The product was separated from triphenyl phosphine oxide via Column chromatography with 10% ethyl acetate and pet ether as mobile phase. The yellow solid was obtained in 94.8% yield.

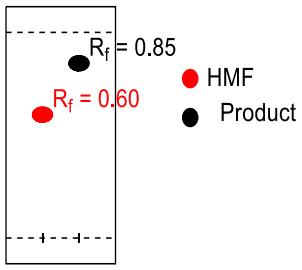
5. Synthesis of (5-formylfuran-2-yl) methyl cinnamate




5-hydroxymethylfurfural cinnamic acid




(5-formylfuran-2-yl)methyl cinnamate




60 % ethyl acetate and pet ether

The desired product was obtained by taking 1 equivalent of HMF and 1.2 equivalent of cinnamic acid in presence of EDC as a coupling agent. The reaction continued for 2 days. However, the reaction was incomplete as observed on TLC. Hence 0.5 equivalent of EDC was added and reaction was completed in 4hrs. The product was obtained via solvent extraction. Confirmation of the product was incomplete due to time constraint.

However, the Intramolecular Diels- Alder reaction on above derivatives of HMF could not be achieved due to time constraint.

# EXPERIMENTAL PROCEDURE

**Procedure for synthesis of HMF from Fructose**

A mixture fructose (5g),10% NaCl solution (15ml), DMSO(5ml), MIBK (80ml) and conc. $H_2SO_4$ (1ml) were refluxed at $170^0$C for 3 h. The reaction mixture was then filtered and the filtrate was neutralised and then aqueous layer was extracted with ethyl acetate. Subsequently, combined organic phase (including MIBK and ethyl acetate) was dried over anhydrous $Na_2SO_4$ and evaporated to obtain brown oil of crude HMF. % yield=49.

**General procedure for synthesis of 4-((5-formylfuran-2-yl) methoxy)-4-oxobut-2-enoic acid**

1)In a 50ml Rb, (1mmol) HMF and maleic anhydride (1mmol) were dissolved in DCM. To this mixture (1.2mmol) triethylamine and (0.01mmol) of DMAP was added. The reaction was stirred for 3 hr. To this reaction mixture, 20ml of ethyl acetate and 8ml of 2N HCl was added and the product was extracted in ethyl acetate layer. Further the solvent was evaporated and the brown solid was obtained. But the expected product was not formed as indicated on TLC.

2)In a 50 ml Rb, (1mmol) HMF was taken. To this 10ml of DCM was added followed by (1.2mmol) of triethylamine and (0.01mmol) of DMAP. The reaction mixture was cooled to $0^0$C and then (1mmol) of maleic anhydride was added slowly. The reaction was refluxed for 3 hr. After 3 hr, TLC was taken and it showed the presence of reactant and hence one more equivalent of maleic anhydride was added and reaction was kept overnight. TLC again showed incomplete reaction. Further to this reaction mixture ethyl acetate(20ml) and 2N HCl (8ml) was added and the product was extracted in ethyl acetate layer, then the solvent was evaporated and the brown solid was obtained. But the expected product was not formed as indicated on TLC.

3)In a 10 ml Rb, HMF (1mmol) and Maleic anhydride (1mmol) was subjected to Argon gas. This reaction mixture was then heated to $60^0$C with stirring in presence of argon gas. While heating, an exotherm was observed where the reaction mixture temperature rose to $76^0$C. The reaction mixture was then allowed to cool to $60^0$C.The reaction continued for 3.6 hrs. However, the TLC showed the presence of both product and reactant. Further separation of product could not be achieved due to time constraint.

**General procedure for synthesis of 3-(5-(hydroxymethyl) furan-2-yl) acrylic acid.**

In a 100ml Rb, (1 mmol) of HMF and (1mmol) of malonic acid was taken. To this mixture, 0.5 ml of pyridine and 3 drops of piperidine were added. The reaction was refluxed for 7 hrs. TLC indicated the presence of product as well as reactant. The reaction was stopped after 7 hrs of reflux due to the presence of moisture in solvents. To the reaction mixture cold water was added and conc. HCl was then added dropwise till the reaction mixture turned acidic. The reactant and product were extracted in ethyl acetate. The organic layer was washed with sat. sodium bicarbonate and the obtained aqueous layer was acidified. Further the product was extracted in diethyl ether. Solvent was evaporated and the brown colour solid was obtained in 23 % yield. 40% yield of HMF was recovered.

**General procedure for synthesis of oxime.**

In a 50 ml Rb, 100mg of HMF and 100mg of hydroxyl ammine hydrochloride were dissolved in Ethanol (1ml). 1ml of sodium acetate was added and mixture was heated for 50 min in boiling water bath. TLC showed presence of two spots (may be syn and anti-oxime). water was then added to the mixture and products were extracted in ethyl acetate.

**General procedure for preparation of allyl 2-bromoacetate**

A solution of allyl alcohol (1 mmol) and pyridine (1mmol) in chloroform (10ml) was cooled at $0^0$C. Bromo acetyl bromide was added dropwise with stirring over period of 15 min. The

mixture was stirred for 1 h at $0^0$ C and further at room temperature for 1 hr. To the reaction mixture 2N HCl(3×15ml) was added and extracted in chloroform (20ml). The organic layer was washed with sat sodium bicarbonate (3×15ml) and finally with water (3×15ml). The chloroform layer was dried over anhydrous sodium sulphate and evaporated under vaccum to give yellow liquid. % yield=54.2

**General procedure for preparation of phosphonium salt**

The solution of substituted allyl bromoacetate (1mmol) and triphenyl phosphine (1mmol) in dry toluene (10ml) was stirred overnight at room temperature. The resultant phosphonium salt was obtained in 84.3 % yield.

**General procedure for preparation of allyl(triphenylphosphoranylidine)acetate**

The salt formed was dissolved in 50ml of water. To this mixture 20 ml of benzene and a drop of phenolphthalein was added. Then NaOH was added till the aqueous layer turned pink. The phosphorane was extracted in benzene and then the organic layer was washed with water. The organic layer was then dried over anhydrous sodium sulphate and solvent was evaporated to give substituted allyl(triphenylphosphoranylidine) acetate. % yield=59

**General procedure for Wittig reaction**

A solution of HMF(1mmol) and allyl(triphenylphosphoranylidine) (1.5 mmol) acetate was stirred in chloroform for 4 days. The solvent was evaporated under reduced pressure and crude product was purified by Column chromatography (SiO2, AcOEt/hexane/1/10) to remove triphenyl phosphine oxide. % yield=94.8

**General procedure for preparation of (5-formylfuran-2-yl) methyl cinnamate**

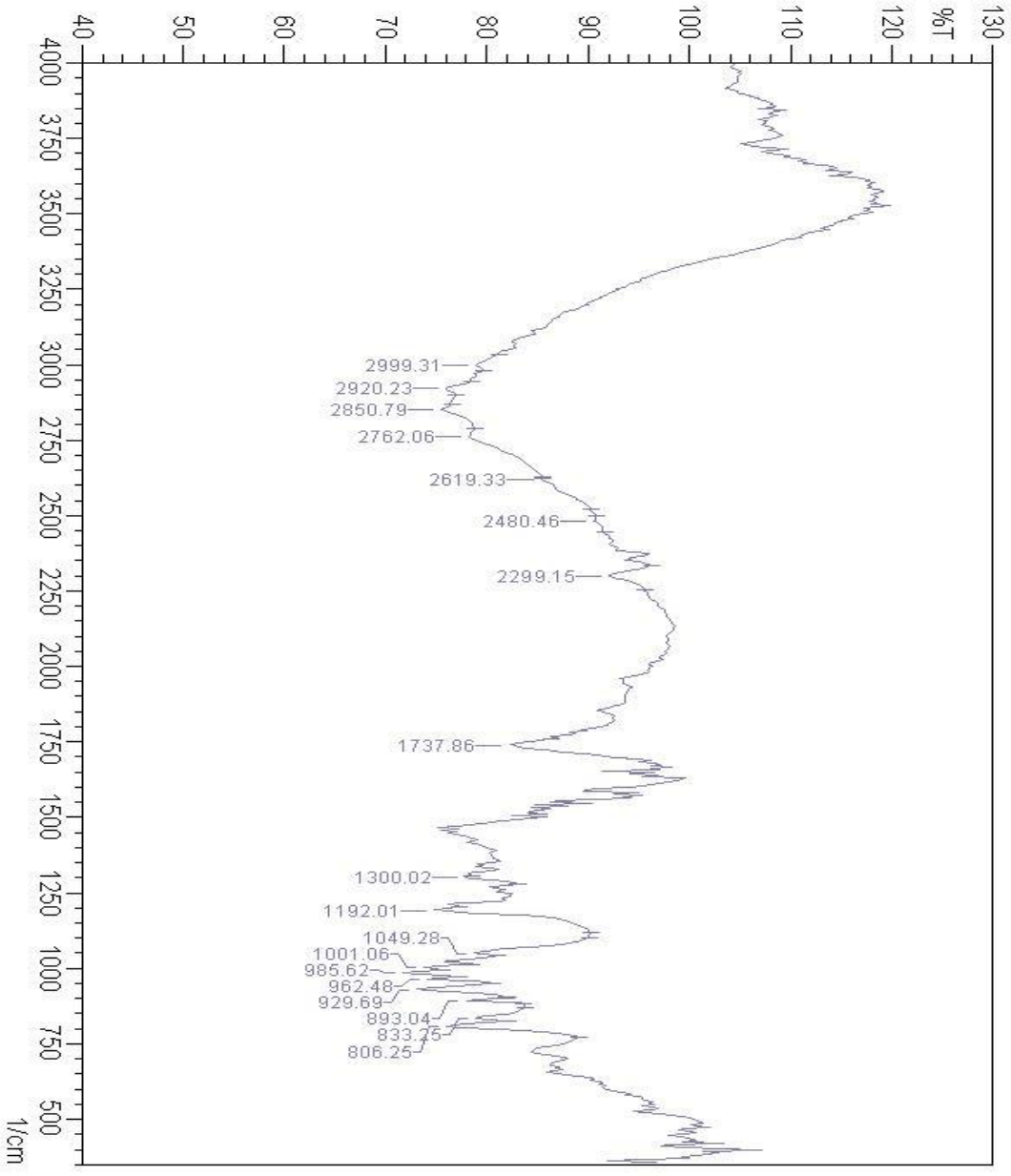
HMF (1 mmol), Cinnamic acid (1.2 mmol) and HOBT (1.3 mmol) was dissolved in dry chloroform and the solution was cooled to $0^0$C. To this solution EDC (2 mmol) was added slowly. The reaction was stirred for 3 days. To the reaction mixture, water (2 ×20ml) was added and the product was extracted in chloroform. The organic layer was washed with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and solvent was evaporated to yield crude product.

**Microwave assisted Intramolecular Diels Alder reaction**

To the quartz vessel, (1mmol) of HMF, dry toluene(5ml), (1.2 mmol) of maleic anhydride and 0.3 ml of N, N -Diisopropylethylamine was added. The resulting mixture was heated at $140^0$C in microwave for 30 mins. One more run was conducted. TLC of the reaction showed there may be formation of product but the reaction was incomplete. Further isolation of product could not be achieved due to time constraint.

# IR SPECTRA

IR spectra of oxime



# CONCLUSION

In this project, considerable efforts were made in synthesising HMF from fructose using homogenous catalyst. Isolation of HMF could not be achieved via distillation technique, indicating that reactivity of HMF increases with increase in temperature. However, isolation via column chromatography was tedious and hence isolation methods like flash chromatography, HPLC and HPGC may be considered effective.

In an attempt to synthesis the derivatives of HMF, we may have been successful in synthesising two, namely allyl-3-(5-hydroxy methyl) furan -2-yl) acrylate and (5-formyl furan-2-yl) methyl cinnamate. Further it was planned to carry out Intramolecular Diels- Alder reaction on the above derivatives. However, due to time constraint it could not be achieved. But as known from the literature, when Intramolecular Diels-Alder reaction is performed on the above derivatives, the products are expected to have benzofuran and bridged polycyclic framework which represents the synthetic block in variety of biological natural products. Hence it would be worthwhile to carry out this idea as future scope.

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