

Preparation of 5-(Acyloxymethyl)furfurals from Carbohydrates Using Zinc Chloride/Acetic Acid Catalyst System and Their Synthetic Value Addition

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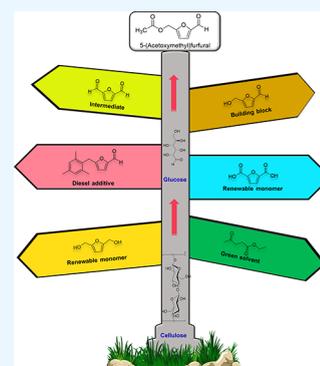
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ABSTRACT: 5-(Acyloxymethyl)furfurals (AMFs) have received considerable attention as hydrophobic, stable, and halogen-free congeners of 5-(hydroxymethyl)furfural (HMF) for synthesizing biofuels and biochemicals. In this work, AMFs have been prepared directly from carbohydrates in satisfactory yields using the combination of ZnCl_2 as the Lewis acid catalyst and carboxylic acid as the Bronsted 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, respectively, under optimized parameters (5 wt % substrate, AcOH, 4 equiv ZnCl_2 , 100 °C, 6 h). Finally, AcMF was converted into high-value chemicals, such as 5-(hydroxymethyl)furfural, 2,5-bis(hydroxymethyl)furfural, 2,5-diformylfuran, levulinic acid, and 2,5-furandicarboxylic acid in satisfactory yields to demonstrate the synthetic versatility of AMFs as carbohydrate-derived renewable chemical platforms.



1. INTRODUCTION

5-(Hydroxymethyl)furfural (HMF) spearheads the biorefinery research as a carbohydrate-derived chemical building block for the renewable synthesis of liquid fuels, chemicals, and polymers.^{1,2} The dehydration of hexose sugars (e.g., glucose) into HMF is an elegant process where an acid catalyst reduces the oxygen content of the parent sugar by 50% without undergoing C–C bond scission reactions, forming an innocuous byproduct, i.e., water. HMF retains some of the key functionalities of the parent sugar molecule, which can be exploited for its downstream synthetic upgrading.³ Although HMF can be produced in satisfactory yields from various carbohydrates under acceptable reaction conditions, its inherent hydrophilicity and poor stability (e.g., hydrolytic, thermal) complicate isolation and purification from aqueous or polar reaction media.⁴ One way to circumvent this problem is to isolate HMF in the form of a hydrophobic, stabler congener.⁵ 5-(Chloromethyl)furfural (CMF) and 5-(bromomethyl)furfural (BMF) have shown promise as the hydrophobic congeners of HMF.^{6,7} However, CMF and BMF contain halogen atoms in their moiety and require concentrated mineral acids for their production. In this regard, 5-(acyloxymethyl)furfural (AMF), produced by the esterification of HMF with carboxylic acids, is particularly interesting since the hydrophobic molecules contain no halogen atoms in their moiety and have better hydrolytic stability than HMF.⁸ 5-(Acetoxymethyl)furfural (AcMF) has particularly received attention since AcOH required for its preparation is

inexpensive, thermally stable, available in bulk quantities, nontoxic, and can be produced renewably from biomass.⁹ AcMF can be conveniently converted into HMF by hydrolysis and can participate virtually in all derivative chemistry of the latter.¹⁰ AcMF has recently been oxidized into 2,5-furandicarboxylic acid (FDCA), a promising monomer for biorenewable polyesters, over Co/Mn/Br homogeneous catalysts using air as oxidant.¹¹ Unlike HMF, AcMF can be used directly as a promising fuel blending agent.¹² AcMF has also been used for the synthesis of molecules with promising therapeutic activities and as the sweet taste modulator in balsamic vinegar.^{13,14}

In a two-step strategy, AcMF has been produced in good yield by the nucleophilic substitution of CMF using suitable bases.¹⁵ 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.¹⁶ HMF can be esterified with AcOH in the presence of a suitable acid catalyst, forming AcMF.¹⁷ Fructose was transesterified into 1,6-diacetylfructose by vinyl acetate using lipase catalyst,

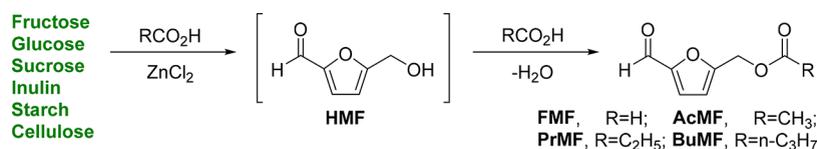
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Scheme 1. One-Pot Preparation of 5-(Aclyoxymethyl)furfurals Starting from Biomass-Derived Sugars and Polymeric Carbohydrates



which was then dehydrated and partially deacetylated into AcMF using a cation-exchange resin.¹⁸ 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. The reaction was performed at 150 °C in a batch-type pressure reactor using Sn⁴⁺-exchanged montmorillonite clay (Sn-Mont) as a 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. Even though fructose afforded a 58% yield of AcMF, glucose afforded a much lower yield.¹⁹ 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.²⁰ 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.²¹ FMF has shown promise as a renewable chemical intermediate for synthesizing several value-added products.^{22,23} 5-(Propionyloxymethyl)furfural (PrMF) and 5-(butyryloxymethyl)furfural (BuMF), the propionic acid and butyric acid ester of HMF, respectively, are relatively less explored.²⁴ 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.^{25,26} Interestingly, the dehydration of sugars into HMF using organic acid catalysts has been reported.²⁷ However, the isolation of AMFs starting from HMF often requires a strong acid catalyst, special reaction media, and dehydrating agents.²⁸ Therefore, a one-pot, scalable, high-yielding, and general procedure for preparing AMFs from inexpensive sugars and carbohydrates under relatively mild reaction conditions are 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.^{29–31} The synergy between Lewis and Brønsted acid catalyst during HMF synthesis have been established.³² The authors envisioned that adding a Lewis acidic metal salt would assist in the AcOH-catalyzed dehydration of sugars to HMF and promote its esterification into AcMF. 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 ZnCl₂ as an inexpensive and nontoxic 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 1). Finally, AcMF was converted into high-value derivatives, such as HMF, 2,5-bis(hydroxymethyl)furan (BHMF), 2,5-diformylfuran (DFF), and FDCA, to showcase its versatility as a chemical platform.

2. EXPERIMENTAL SECTION

2.1. Materials and Instruments.

D-Fructose (98%), zinc chloride (anhydrous, 95%), mesitylene (>99%), aluminum chloride (anhydrous, >99%), formic acid (98%), propionic acid (99%), nitromethane (99%), levulinic acid (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%), methanol (99.5%), ethyl acetate (99%), and petroleum ether (60–80, 95%) were purchased from Finar. Raney nickel (slurry in water) was purchased from TCI. Lithium chloride (99%) and magnesium chloride (97%) were purchased from Spectrum. Inulin, butyric acid (99%), calcium chloride (98%), 1,2-dichloroethane (DCE, 99%), and zinc acetate (99%) were purchased from Molychem. Nitric acid (69–72%) and ethanol (99.9%) were purchased from Loba Chemie Pvt. Ltd. All the reagents and solvents were used as received without additional purification. The Fourier transform infrared (FTIR) spectra of the synthesized compounds were recorded on a Bruker FTIR 4000 instrument equipped with a zinc selenide (ZnSe) ATR. The FTIR spectra were collected by performing 24 scans at a scanning rate of 4 scans/s in the range between 500 and 4000 cm⁻¹. Nuclear magnetic resonance (NMR) spectra of the synthesized compounds were collected in a Bruker NanoBay NMR instrument. The ¹H NMR spectra were collected at the operating frequency of 300 and 400 MHz, whereas the ¹³C NMR spectra were collected in the same instrument at a calculated frequency of 75 and 100 MHz, respectively.

2.2. Synthetic Procedures.

D-Fructose (1.002 g, 5.57 mmol) and ZnCl₂ (3 g, 22.01 mmol, anhydrous) were added sequentially into glacial acetic acid (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 preheated oil bath (100 °C) cum magnetic stirrer and heated for 6 h under constant stirring (400 rpm). After completing the reaction, the mixture was cooled down to room temperature and diluted with water. The crude reaction mixture was extracted with chloroform and evaporated under reduced pressure. The crude product was passed through a plug of silica gel (60–120 mesh), and solvent evaporation in a rotary evaporator under reduced pressure gave AcMF (0.698 g, 4.155 mmol, 75%) as a yellow oil. The AcMF isolated by following this protocol was pure by NMR. ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 9.46 (s, 1H), 7.10 (d, 1H), 6.46 (d, 1H), 4.96 (s, 2H), 1.94 (s, 3H);

^{13}C NMR (CDCl_3 , 75 MHz) δ (ppm) 177.7, 170.5, 155.4, 152.6, 122.5, 112.5, 57.6, 20.4; FTIR (ATR, cm^{-1}): 3124, 2923, 2847, 1744, 1679, 1025.

Alternatively, excess AcOH was distilled off (40–50 °C) under reduced pressure. The crude reaction mixture was diluted with water (20 mL) and then extracted with chloroform (3×10 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 the trace colored impurity. Evaporation of the solvent under reduced pressure afforded AcMF that was found pure by NMR. The purity of isolated AcMF was found to be around 96% as confirmed by quantitative ^1H NMR spectroscopy using mesitylene as the internal standard (Figure S35, SI). In all cases, the reported isolated yields of AMFs and their derivatives are an average of experiments performed in triplicate with a 2–3% deviation in the values.

3. 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 (Figures S1 and S2, SI). 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 similar 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%). When fructose loading was increased (10 wt % of AcOH), the yield of AcMF diminished under similar reaction conditions. 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 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, respectively, 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. No discernible change in

Table 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	$\text{Zn}(\text{OAc})_2$	10
7 ^b	NaCl	14
8 ^b	No Additive	15

^aIsolated yield. ^bAround 7–9% HMF was coproduced. Reaction Conditions: fructose (1.002 g), AcOH (20 mL), Lewis acid catalyst (4 equiv of fructose), 100 °C, 6 h.

the yield of AcMF was observed at higher stirring speed to minimize the mass transfer limitations. When $\text{Zn}(\text{OAc})_2$ was employed instead of ZnCl_2 , the salt remained largely insoluble in the reaction mixture and AcMF was isolated in a meagre 10% yield after 6 h at 100 °C.

The fructose to AcMF transformation was then optimized on various reaction parameters to ensure the optimal isolated yield. The reaction temperature not only influences the reaction kinetics and product distribution but also 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 1). The accelerated decomposition of AcMF at higher reaction

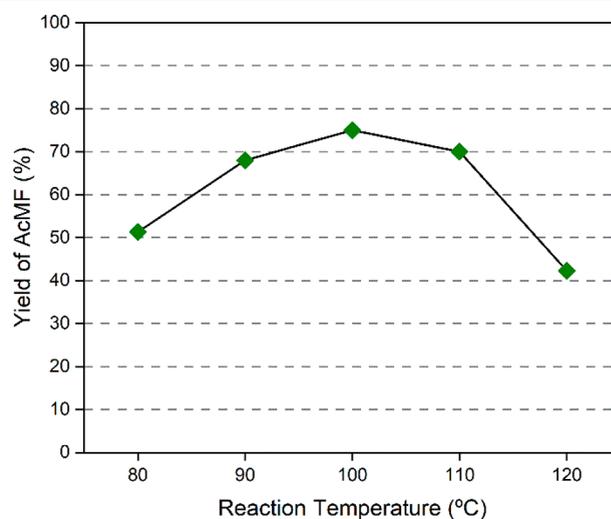


Figure 1. Effect of reaction temperature on AcMF yield. Reaction Conditions: fructose (1.002 g), AcOH (20 mL), ZnCl_2 (3 g), 6 h.

temperatures may explain the observation. In fact, when isolated AcMF was heated at 100 °C in a mixture of ZnCl_2 and glacial acetic acid, it slowly recomposed into LA and humin. However, only 52% of AcMF was isolated at 80 °C after 6 h due to incomplete conversion of fructose. In general, the process optimization for producing HMF or its congeners (e.g., AcMF) attempts to find a point where the concentration of the product is maximum in the reaction medium.

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 the loading of fructose 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 2). The use of glucose as a substrate afforded 48% of AcMF after 12 h, which improved to 60% after 24 h. However, the yield did not increase by extending the duration further. 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

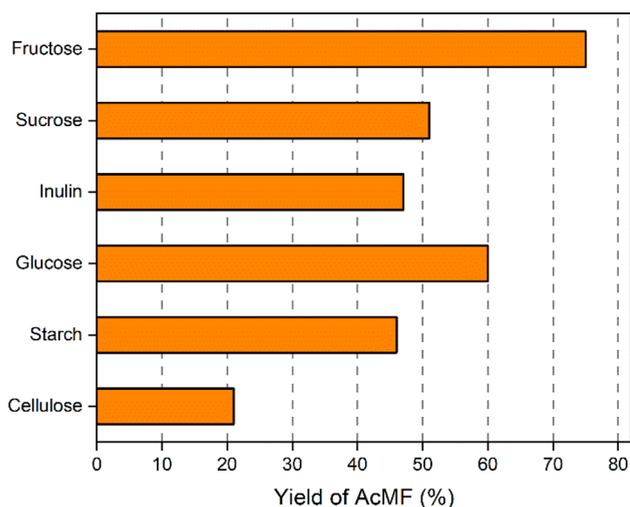


Figure 2. Production of AcMF from sugars and carbohydrates. Reaction conditions: substrate (1.002 g), ZnCl_2 (3 g), AcOH (20 mL), 100 °C, 6 h (for fructose, sucrose, and inulin); 100 °C, 24 h (for glucose); reflux, 12 h (for starch and cellulose).

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.

As discussed in the synthetic procedure, a significant roadblock for scaling up the production of AcMF (AMFs, in general) is the issue of a relatively large concentration of ZnCl_2 . However, the abundant, inexpensive, and nontoxic metal salt can be used in a loop for multiple cycles (after distilling off AcOH and extracting/distilling AcMF) until it is heavily contaminated with organic impurities (e.g., humin). The salt can be dissolved in water and separated from impurities by recrystallization. The optimized process of producing AcMF was then extended to the production of other HMF-esters, such as 5-(formyloxymethyl)furfural (FMF), PrMF, and BuMF (Table 2). All the products were

Table 2. One-Pot Preparation of AMFs from Fructose^a

Entry	Name of AMF	Yield (%)
1 ^b	FMF	60
2	AcMF	75
3	PrMF	70
4	BuMF	60

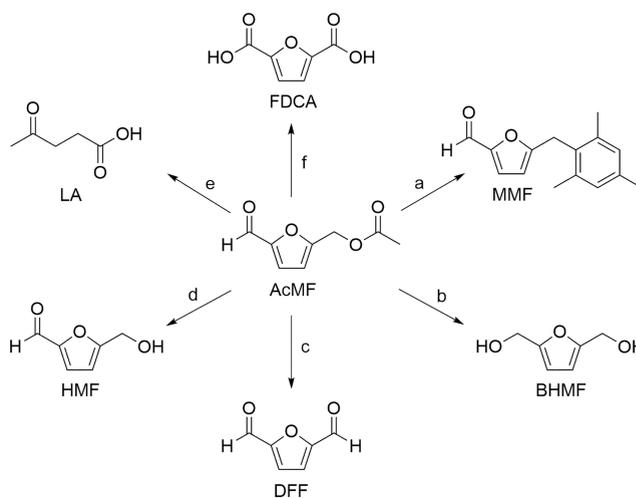
^aReaction conditions: fructose (1.002 g), carboxylic acid (20 mL), ZnCl_2 (3 g), 100 °C, 6 h. ^b80 °C, 6 h.

obtained in satisfactory yields ($\geq 60\%$), starting from fructose under the conditions optimized for AcMF, which may be improved substantially by tweaking the reaction parameters for the individual molecules. HMF-levulinate, prepared by esterifying HMF with levulinic acid (LA), is a potential fuel oxygenate.³³ 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.

After establishing a straightforward, scalable, and general procedure for producing AMFs from carbohydrates, the potential of AMFs as renewable chemical platforms was

demonstrated. The reactivity patterns of AcMF were explored, and some high-value derivatives were synthesized in satisfactory yields under moderate conditions. Initially, attempts were taken to hydrolyze AcMF into HMF selectively. Interestingly, the hydrolysis of AcMF did not proceed appreciably even after treating AcMF in boiling water for 2 h. In this respect, CMF hydrolyzes to HMF quantitatively in less than a minute under such conditions.³⁴ The storage stability of AcMF was noticeably better than HMF and other commonly used congeners like CMF and BMF (Figure S36, SI). AcMF was then attempted to react with ethanol to form HMF and ethyl acetate as the byproduct. However, the conversion was low (<10%) even under reflux, reaffirming at the high stability of AcMF. The reaction completed within 2 h in refluxing ethanol when K_2CO_3 (10 wt %) was used as a base catalyst, affording pure HMF in an 89% isolated yield. The synthesis of 5-(mesitylmethyl)furfural (MMF) from AcMF was attempted next. MMF is a hybrid diesel fuel where the reactants are sourced from both biomass and petroleum.³⁵ The Friedel–Crafts reaction between AcMF and mesitylene was performed in nitromethane solvent using ZnCl_2 as the catalyst. Under optimized parameters (reflux, 3 h), MMF was obtained in a 74% isolated yield. The redox chemistry of AcMF was explored next. Stirring AcMF in 69% HNO_3 at 50 °C oxidized it smoothly into DFF in a 50% yield. DFF is a reactive chemical intermediate for further value addition pathways and a potential monomer for various biopolymers.³⁶ DFF yield improved to 64% using a biphasic reaction mixture comprising DCE and aq. HNO_3 . The DCE layer protected DFF from undergoing further oxidation or other decomposition reactions. When AcMF was refluxed in 69% HNO_3 for an extended period (12 h), AcMF was oxidized to FDCA in a 60% isolated yield (Scheme 2). FDCA is one of the most commercially attractive sugar-derived monomers for synthesizing biorenewable polyesters.³⁷ LA is a carbohydrate-derived chemical platform in its own merit and has an extensive derivative chemistry.³⁸ The hydrolysis of AcMF in aqueous HCl (6 N) afforded an 85% isolated yield of LA.

Scheme 2. Synthesis of Some Furanic Compounds Using AcMF as a Chemical Platform



Reaction Conditions: (a) mesitylene, ZnCl_2 , CH_3NO_2 , reflux, 3 h, 74%; (b) (i) Raney Ni, H_2 , MeOH, RT, 3 h (ii) K_2CO_3 , MeOH, 50 °C, 1.5 h, 82%; (c) 69% HNO_3 , 50 °C, 3 h, 50%; (d) EtOH, K_2CO_3 , 89%; (e) HCl (aq., 6 N), 120 °C, 4 h, 85%; (f) 69% HNO_3 , reflux, 12 h, 60%.

Selective hydrogenation of the aldehyde group in AcMF using Raney Ni catalyst followed by methanolysis of the acetoxy group led to 2,5-bis(hydroxymethyl)furan (BHMF), a promising diol-based monomer, in a 82% isolated yield.³⁹ Interestingly, an attempt for the catalytic hydrogenation and methanolysis of AcMF in a single pot did not form BHMF. The reaction stopped at the HMF intermediate, which may be justified by the activation of the aldehyde group toward hydrogenation in the presence of trace acid. Other AMFs also showed similar reactivity patterns, which undoubtedly improves the substrate scope of this chemistry.

4. CONCLUSION

In summary, AMFs were prepared directly from carbohydrates using carboxylic acid as the Brønsted acid catalyst (and reagent) in the presence of ZnCl₂ 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. Acetic acid was recovered by distillation, and AcMF was purified. AcMF showed significantly better hydrolytic and thermal stability than HMF and even CMF. AcMF was selectively converted into MMF, BHMF, DFF, HMF, LA, and FDCA to demonstrate its synthetic versatility as a renewable chemical platform. Future research will focus on improving the yield of AcMF from polymeric carbohydrates (e.g., cellulose) and expanding its derivative chemistry following catalytic routes.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c00143>.

Spectral characterization (FTIR, ¹H NMR, ¹³C NMR) of all the synthesized compounds. Some photographic images of the reaction mixtures highlighting important observations are also included (PDF)

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Notes

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■ ABBREVIATIONS

AMF, 5-(acyloxymethyl)furfural; AcMF, 5-(acetoxyethyl)furfural; BuMF, 5-(butyryloxymethyl)furfural; BHMF, 2,5-bis(hydroxymethyl)furan; BMF, 5-(bromomethyl)furfural; CMF, 5-(chloromethyl)furfural; DCE, 1,2-dichloroethane; DFF, 2,5-diformylfuran; FDCA, 2,5-furandicarboxylic acid; FMF, 5-(formyloxymethyl)furfural; HMF, 5-(hydroxymethyl)furfural; LA, levulinic acid; MMF, 5-(mesitylmethyl)furfural; PrMF, 5-(propionyloxymethyl)furfural

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