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Step-by-Step Hybrid Conversion of Glucose to 5-acetoxymethyl-2-furfural Using Immobilized Enzymes and Cation Exchange Resin

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Abstract: An alternative to 5-hydroxymethyl-2-furfural (HMF), which is a promising furan derivative that can be used as a starting material for the preparation of non-petroleum-derived polymeric materials from sugars, is 5-acetoxymethyl-2-furfural (AMF). The less-hydrophilic acetyl group of AMF has advantages over the hydroxy group of HMF in terms of thermal stability and isolation. In previous studies, fructose has been used as a starting material along with lipases for the enzymatic synthesis of AMF. In this study, we designed a hybrid synthesis system that includes the isomerization and esterification of glucose into AMF. For the step-by-step conversion of glucose to 1,6-diacetylfructose (DAF), glucose-isomerase and immobilized lipase (Novozym 435) were used as enzymes. Furthermore, for the synthesis of AMF, the direct dehydration of DAF was performed using a cation exchange resin (Amberlyst 15), combined with several industrial solvents, such as dimethylsulfoxide (DMSO), acetonitrile (AN) and dimethylformamide (DMF) for the synthesis of AMF. In order to improve the final yield of AMF, we determined the best solvent conditions. While the AMF yield after the direct dehydration of DAF in a single solvent was maximum 24%, an AMF and HMF yield in the mixed solvent such as dioxane and DMS (9:1) was achieved each 65% and 15%. According to these results, we found that the addition of dioxane in aprotic polar solvents could affect the dehydration reaction and dramatically improve the formation of AMF and HMF.

Keywords: glucose; 5-acetoxymethyl-2-furfural (AMF); isomerization; trans-esterification; dehydration

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1. Introduction

Recently, significant efforts have been dedicated to overcoming the depletion of the earth's natural resources. Petroleum-derived products, in particular, have a limited supply. The earth's finite supply of petroleum cannot keep up with the demand for petroleum products. Bio-based chemicals are regarded as a renewable and sustainable alternative to limited resources. Furan derivatives made from sugars are a promising source of energy and chemicals in green chemistry [1,2]. Among them, 2,5-dimethylfuran and 5-ethoxymethylfurfural (EMF) can be used as biofuels. Furthermore, 2,5-dimethylfuran, in particular, has a high energy density that is similar to gasoline [3,4]. One compound, 2,5-furan-dicarboxylic acid (FDCA), has a wide range of applications. FDCA can be used as a monomer in polymeric materials, such as terephthalic acid (TPA), which is a well-known precursor of the polyethylene terephthalate (PET) polyester used in clothing [5–7]. Additionally, 5-hydroxymethyl-2-furfural (HMF) has the potential to form a network of numerous furan derivatives. Furan compounds, such as FDCA and 2,5-dimethylfuran, which are considered

promising starting materials for bioplastics and biofuels, can be produced from HMF via hydrogenation and dehydration [8–10]. Despite HMF's potential, its hydrophilic molecule makes the liquid–liquid extraction of the final product from the solvent difficult. Aprotic polar solvents, such as dimethylsulfoxide (DMSO), are necessary for the dehydration of sugars, even though they have limitations in terms of cost, toxicity, and stability. The acetoxy group of 5-acetoxymethyl-2-furfural (AMF) is less hydrophilic than the hydroxy group of HMF. This difference between HMF and AMF makes isolation and purification easy. Easier isolation and purification have significant advantages on an industrial scale because the cost of a complex process is directly related to its complexity [11].

In previous studies, we used enzymes and a cation exchange resin (Amberlyst 15), together with common industrial solvents, to synthesize AMF from D-fructose via 1,6-diacetylfructose (DAF) [12]. Although glucose is a more cost-effective source of hexoses than fructose and is easier to obtain in nature, more than 99% of glucose exists as pyranose in an aqueous solution, while fructose forms the majority of furanose. To improve the DAF yield, we propose the step-by-step hybrid conversion of derivatives from glucose. As shown in Figure 1, the system includes isomerization with isomerase [13], transesterification with an acetyl donor and lipase [14,15], and dehydration with Amberlyst 15 for AMF synthesis. To improve the conversion of 6-monoacetyl-glucopyranose (MAG) to DAF, an iterative process of isomerization and esterification was performed five times after the first isomerization and esterification. The MAG generated from the transesterification of glucose can be isomerized to 6-monoacetyl-fructofuranose (MAF), which is an intermediate for DAF, via re-isomerization after the first transesterification. MAG gradually decreased and DAF gradually increased during the iterative isomerization and esterification process. The DAF and MAG ratios in the final product were 86% and 15%, respectively, after five isomerization and esterification cycles, compared to a 70% DAF ratio after the first cycle.

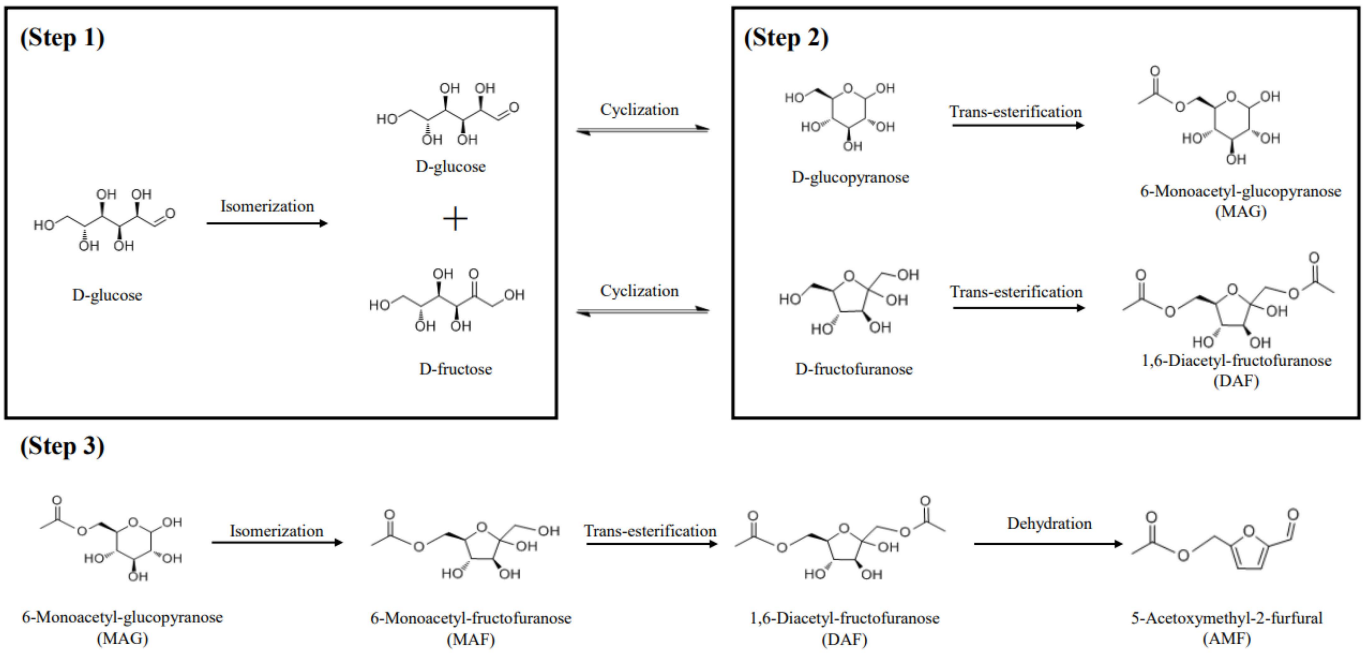

Figure 1. The synthesis route of 1,6-diacetylfructose (DAF). (**Step 1**) Isomerization of glucose to fructose. (**Step 2**) Hybrid esterification of the fructose and glucose mixture. (**Step 3**) Re-isomerization of 6-Monoacetyl-glucopyranose (MAG) and re-esterification of 6-Monoacetyl-fructofuranose (MAF).

2. Materials and Methods

2.1. Materials

Acetone (95.5%), acetonitrile (anhydrous, 99.8%), D-glucose and D-fructose (99%), ethanol (anhydrous, 99.5%), ethyl acetate (anhydrous, 99.8%), ethyl ether (anhydrous,

99.0%), vinyl acetate (99%), glucose isomerase (350 U/g), tetrahydrofuran (THF, anhydrous, 99.9%), N,N-dimethylformamide (anhydrous, 99.8%), dimethyl sulfoxide (anhydrous, 99.9%), 1,4-dioxane (anhydrous, 99.8%), Amberlyst 15 (hydrogen form), and an immobilized lipase, such as Lipozyme (immobilized from Mucormiehei, 30 U/g), were purchased from Sigma-Aldrich. Lipozyme TL IM, Lipozyme RM IM, and Novozym 435 were purchased from Novozymes (Copenhagen, Denmark). An HPLC system (Agilent, 1200 series) with a diode array detector (DAD) at 254 nm and a refractive index detector (RID) was used to determine the DAF and AMF yields. Sugars, such as fructose and glucose, were detected using the RID, while furan compounds could only be detected using the DAD at 254 nm. In this study, the Bio-rad Aminex HPX-87H and HPX-87P columns [16] were used to clearly separate the peaks between the sugars and ring compounds, such as DAF and MAG. To calculate the product yields, the results from the DAD and RID should be compared. DAF and AMF were also verified using gas chromatography and mass spectrometry (GC–MS; Shimadzu Gc-2010 plus) with a QP2010 Ultra mass spectrometer detector.

2.2. Isomerization of Glucose

The reaction pathway from glucose to fructose is shown in Figure 1 (Step 1). The fructose in step 1 was changed to AMF through the DAF intermediate, as shown in step 2, and the unreacted glucose was converted to MAG through esterification. Isomerization was carried out in a 500 mL round-bottomed (RB) flask with magnetic stirring. Here, 1.0 g of glucose isomerase was added to a 1.0 g glucose solution in a 100 mL mixture of 10% H_2O and THF. The reaction was performed at 60 °C and 300 rpm for 15 h [17,18]. After the reaction, the glucose isomerase was separated using filter paper. The filtrate was evaporated using a rotary evaporator at 40 °C with a pressure pump to remove the solvents. However, H_2O remained in the solvent mixture after evaporation because it has a higher boiling point than the organic solvents. Since H_2O prevents transesterification, it must be removed after isomerization. Freeze-drying is the perfect procedure for selectively removing H_2O while maintaining thermal stability in this reaction. H_2O can be evaporated from the product mixture by freeze-drying at −60 °C and 5 mbar for 24 h. The crude product was obtained in a dried white solid form rather than a syrup form. During the reaction, we could not observe other by-products from the isomerization of glucose. We also propose that the isomerization of glucose with glucose isomerase (GI) occurs via the Lobry–de Bruyn–van Ekenstein transformation, shown in Figure 2 [19,20].

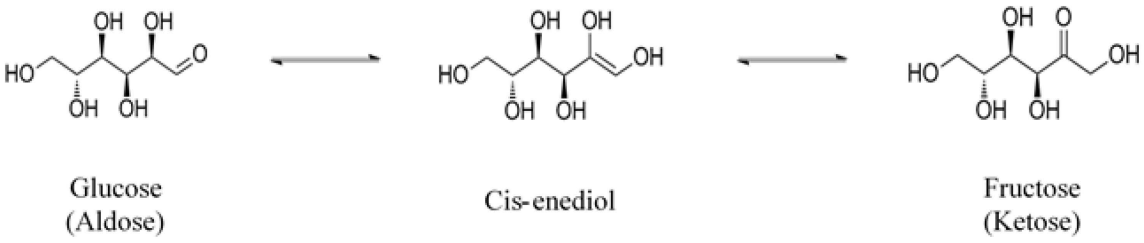

Figure 2. Proposed mechanism of isomerization of glucose into fructose with glucose isomerase (GI) via the Lobry–de Bruyn–van Ekenstein transformation.

2.3. Transesterification of the Glucose and Fructose Mixture

After isomerization, the transesterification of glucose and fructose was performed simultaneously, as shown in Figure 1 (Step 2). An RB flask was filled with 1.0 g of lipase, 100 mL of the solvent, and 1.54 mL of vinyl acetate (3 equiv.) as an acyl donor. The reaction was performed at 60 °C and 300 rpm for 4 h [21,22]. After esterification, the lipase and solvent were removed using filter paper and an evaporator. The formation of MAG and DAF from the transesterification of glucose and fructose was demonstrated using a thin-layer chromatography (TLC) test with an eluent system using a chloroform, acetic acid, and water mixture (3:3.5:0.5) [23] and high-performance liquid chromatography

(HPLC) analysis. The results of both analyses indicate the formation of MAG (R_f = 0.36 and R_t = 9.42 min) and DAF (R_f = 0.59 and R_t = 10.08 min) from the transesterification of glucose and fructose. After an appropriate reaction time, most of the reactants (glucose and fructose) were converted to products during the reaction. When glucose forms a pyranose ring by esterification, not only the primary alcohol of C6-carbon but also another secondary alcohol group could be substituted with an acetyl group from an acyl donor [24]. In that scenario, two kinds of glucopyranose are synthesized; one is 6-monoacethyl-glucopyranose, which can be turned into DAF by the isomerization and esterification cycle, and the other is diacethyl-glucopyranose (DAG, R_f = 0.54), which is not reactive during isomerization and dehydration. The DAG remained during every cycle and in dehydration as a side-product, with a yield of 10%. When MAG, DAG, and DAF coexist in products, it is difficult to separate them using column chromatography because of their similar physical properties.

2.4. Dehydration of DAF

DAF, obtained from the isomerization and trans-esterification cycles, was used as the starting material for this reaction. For the dehydration of DAF, Amberlyst 15, which is a type of cation exchange resin (CER), was chosen as an acidic catalyst. The reaction was performed at 120 °C and 500 rpm with a magnetic stirring for 24 h. In order to determine the best conditions for the dehydration process, polar aprotic solvents, such as dimethyl-sulfoxide (DMSO) and dimethylformamide (DMF), were used. For the optimization of dehydration, we also used mixed solvents by adding polar aprotic solvents, such as DMSO, DMF, and acetonitrile in dioxane, in order to observe the reactivity. In the single-solvent system, the reaction was carried out for 6 h. However, when the mixed solvents with DMSO and DMF were used, the reaction was delayed for 24 h. Therefore, every reaction should be monitored in the mixed-solvent system.

3. Results and Discussion

The fructose yield from the isomerization of glucose was limited in the solvent system, and it remains a challenge in the green chemical industry and food industry. DAF, the main starting material for AMF synthesis, can be made directly from fructose via transesterification, while pyranose is made, in the majority, from glucose. Even on industrial scales, the high cost of fructose, compared to the low cost of glucose, is an obstacle. For these reasons, the synthesis process from glucose to furanose compounds must be optimized for maximum efficiency.

3.1. Influence of Solvents on Isomerization and Esterification

As shown in Table 1, well-known organic solvents were used for the isomerization of glucose. After isomerization, a small amount of fructose was found in most of the organic solvents. Only the ether and acetate solvents did not completely produce fructose. However, in the case of water and a water-containing solvent, the maximum fructose yield was 67%. These results show that the presence of water can dramatically affect enzymatic isomerization [25]. Additionally, the fructose yield was higher when using 5% and 10% of water in THF as the solvent than when using only water as the solvent. The alternation of the reaction media by replacing water with phosphate buffer (pH = 7) was also researched to investigate the significance of pH. However, it was found that the fructose yield in the phosphate buffer solution was 29% lower than the yield in pure water.

Table 1. Enzymatic isomerization in several solvents.

Entry	Solvent	Fructose Yield (%)
1	Acetone	3
2	1,4-Dioxane	3
3	Ethanol	4
4	Ethyl acetate	0
5	Ethyl ether	0
6	THF	5
7	Vinyl acetate	0
8	H_2O	50
9	Buffer pH7 solution	29
10	1% H_2O in THF	5
11	5% H_2O in THF	64
12	10% H_2O in THF	67
13	15% H_2O in THF	38
14	20% H_2O in THF	20

Reaction conditions: glucose 50 mg, glucose isomerase 50 mg, solvent 5 mL, 60 °C 15 h, 500 rpm.

We examined different types of lipases to find the most suitable lipase for transesterification. The esterification was conducted with five types of lipases [26], while the reaction was performed using 50 mg of fructose, 50 mg of lipases, and 0.077 mL of vinyl acetate in 5 mL of the solvent at 60 °C for 4 h. Figure 3 depicts the results.

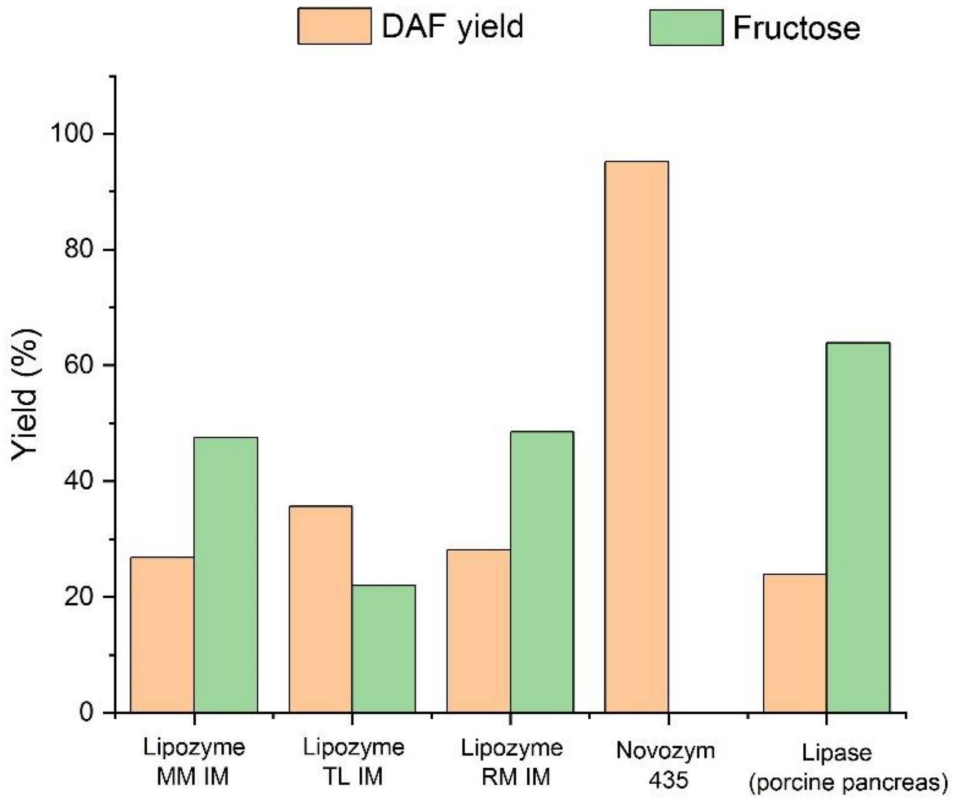

Figure 3. Esterification of fructose with different lipases for DAF synthesis.

Novozym 435 stood out for its surprising selectivity in DAF synthesis, while other lipases not only formed DAF but also formed side products, causing a great deal of unreacted fructose to remain. As we expected, Novozym 435 was the most suitable lipase for esterification. Novozym 435 is a promising lipase and biocatalyst for such applications as esterification, glycerolysis, and hydrolysis in biochemistry [27]. Novozym 435 also shows stability at high temperatures and tolerance for organic solvents [28]. To optimize transesterification, we monitored the reaction for 6 h in different solvent conditions, the results of which are presented in Table 2. Every hour, a sample was taken to calculate the yield. Most of the organic solvents produced a respectable DAF yield with Novozym 435. Dioxane, THF, ethyl acetate, and vinyl acetate, in particular, achieved more than 90% AMF yield. Although the DAF yield was high in dioxane, THF, and ethyl acetate, the amount of DAF decreased after 5 h of reaction time. Even though the fructose conversion was 100%, the amount of by-product and fructose increased for up to 5 h. In the case of water and ethanol, DAF formation was inhibited. THF was chosen as the ideal solvent in our transesterification reaction for 4 h, based on these results.

Table 2. Enzymatic transesterification of fructose with various solvents and reaction times.

Entry	Solvent	DAF Yield (%)				
		1 h	2 h	3 h	4 h	5 h
1	Acetone	45	46	44	47	48
2	1,4-Dioxane	90	87	94	89	88
3	Ethanol	0	0	0	0	0
4	Ethyl acetate	96	93	93	87	89
5	Ethyl ether	32	44	46	48	54
6	H_2O	0	0	0	0	0
7	THF	89	93	96	95	80
8	Vinyl acetate	68	84	85	90	92

Reaction conditions: fructose 50 mg, lipase (Novozym 435) 50 mg, vinyl acetate 0.077 mL (3 eq.), solvent 5 mL, 60 °C, 500 rpm.

3.2. Cycle of Isomerization and Trans-Esterification

After the first isomerization and esterification process, the MAG and DAF ratios were 30% and 70%, respectively. There was still much of the MAG remaining, which was another obstacle to the final AMF yield production. Thus, isomerization and esterification were performed iteratively as a strategy for increasing the yield. MAF can be generated from MAG via the second isomerization and under the same conditions as the first. The amount of MAG in the DAF mixture progressively reduced, as shown in Figure 1 (step 3). Additionally, the second esterification process was conducted in the same manner as the first. MAF could be converted to DAF via the second transesterification process since it is directly isomerized from MAG and offers a primary alcohol. The second set of processes was performed under the same conditions as the first set of processes. An iterative process could increase and decrease the DAF and MAG yields, respectively. We repeated the isomerization and esterification reactions five times, replacing the solvents and enzymes with new ones after each reaction. As expected, the DAF yield in the final product was 86%. Figure 4 depicts the changes in the yield. Since there was not much difference in the conversion of MAG to DAF between the fourth and fifth cycles, we stopped the isomerization and esterification cycle at the fifth cycle.

3.3. Dehydration of Mixture of DAF and MAG

Dehydration from sugar to furanic compounds was conducted with a chromium-based catalyst [29,30]. However, considering the environmental problems caused by chromium-based catalysts, other catalysts should be studied for the dehydration of sugars. As an alternative to catalyst-based heavy metals or noble metals, which showed high efficiency in the dehydration of furanic compounds, Amberlyst 15 was chosen in this study. Amberlyst

15 was used as a catalyst for the synthesis of HMF from fructose, with remarkable conversion, yield, and reusability rates [31–34]. We also optimized the dehydration conditions for AMF synthesis using several polar organic solvents that can be used at high reaction temperatures, such as DMF [12,35], DMSO [12,36], acetonitrile, and dioxane, which is widely used for hexose dehydration [37–40]. For the screening test, dehydration was performed using 50 mg of DAF, 5 mL of solvent, and 50 mg of Amberylst 15 at 120 °C for 6 h, and the results are shown in Figure 5.

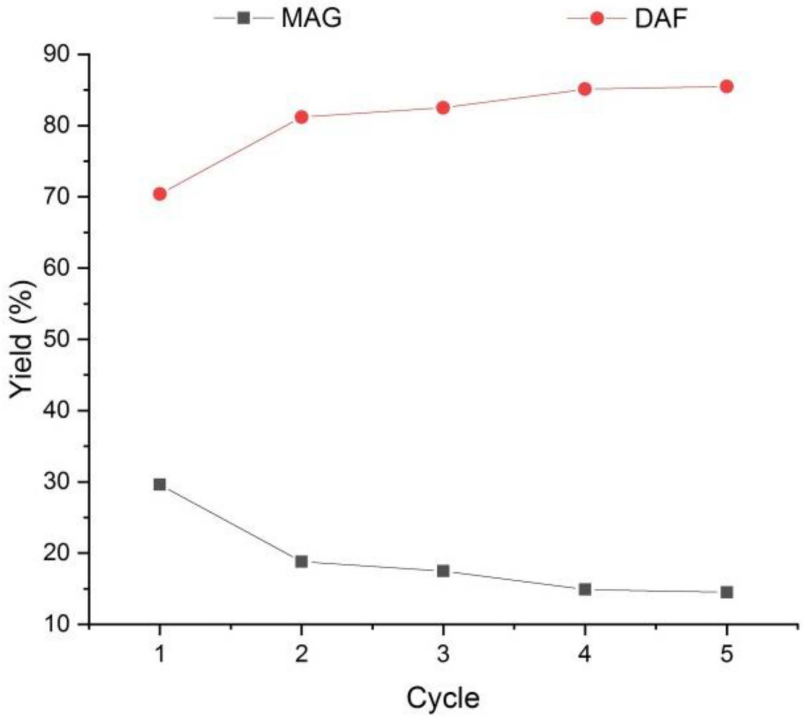

Figure 4. Conversion of MAG to DAF through iterative isomerization and esterification.

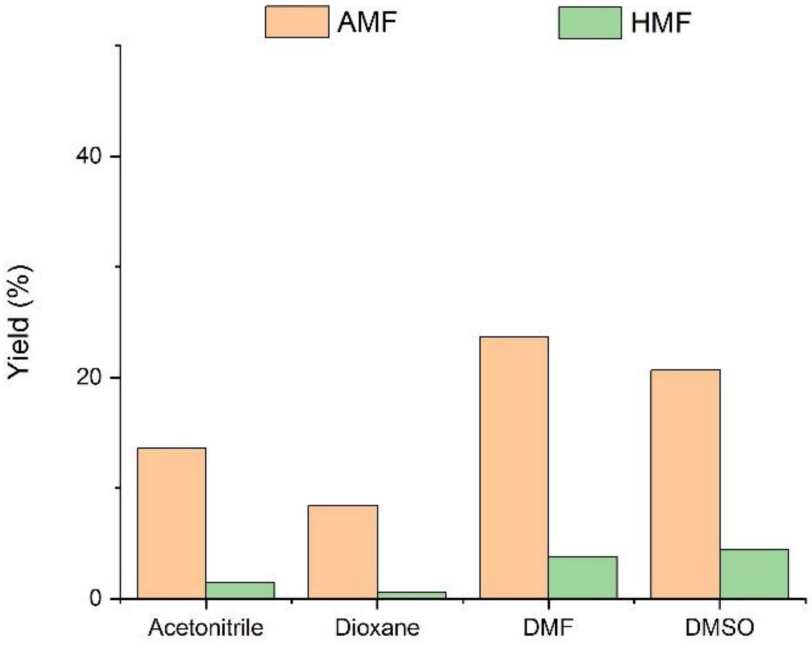

Figure 5. The yield of AMF and HMF after the dehydration of DAF in a single-solvent system.

Most of the solvents in the single-solvent system had a low AMF yield of 8–24%. Based on these results, we discovered that the single-solvent system was not suitable for DAF dehydration. Acetonitrile (81.6 °C) and dioxane (101.3 °C) had lower boiling points than the reaction temperature (120 °C), compared to DMF (153.0 °C) and DMSO (189.0 °C). To make the reaction conditions stable and observe the results, DMF and DMSO, which have high boiling points and exhibit a better yield for AMF synthesis, were added to acetonitrile and dioxane [41,42]. The reaction was performed in a mixed-solvent system for 16 h using the same amount of DAF and Amberlyst 15. During this reaction, we extended the reaction time to 16 h because the addition of DMF and DMSO delayed the reaction. Figure 6 depicts the results.

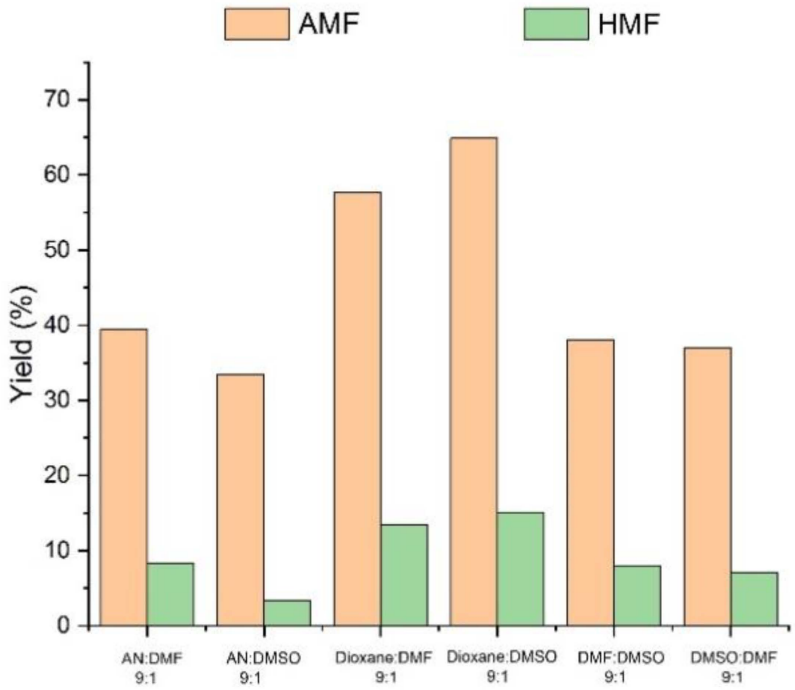

Figure 6. The yield of AMF and HMF after the dehydration of DAF in a dual-solvent system.

There was a noticeable change in AMF yield in the mixture of dioxane with DMF or DMSO. We expected that the polar aprotic solvents (i.e., acetonitrile, DMF, and DMSO), which are widely used to synthesize HMF from fructose, would be suitable for DAF dehydration. Thus, we focused on the use of DMSO and DMF. However, the mixture of dioxane with DMF or DMSO produced higher AMF yields (58% and 65%, respectively) than the other polar aprotic solvent mixtures. The AMF and HMF yields were the lowest (8% and 1%, respectively) in single dioxane. We were able to obtain maximum AMF and HMF yields of 65% and 15%, respectively, in the mixed-solvent system, particularly in the DMSO/dioxane (9:1) mixture. We discovered that the interaction between dioxane and the aprotic polar solvent could affect the reaction, resulting in a more than 50% increase in AMF yield. However, the solvent mixture of acetonitrile with DMF and DMSO has an unsuitable boiling point of 120 °C. Even when the DMF and DMSO concentrations in dioxane or acetonitrile were higher than 10%, there was no remarkable difference in AMF yield. The addition of DMF and DMSO could not only help with reaction thermal stability (owing to dioxane having a lower boiling point than the reaction temperature) but it could also affect the formation of AMF and HMF. From these results, a mixed-solvent system that includes a solvent with a lower dielectric constant could accelerate the overall reaction [43]. Furthermore, DMSO and DMF could inhibit the side reaction in dioxane, which mainly formed side-products from DAF. The side-product yield was somewhat higher in the DMF/dioxane mixture than in the DMSO/dioxane mixture. However, MAG

and DAF were inseparable on the HPLC and TLC plates and in the column chromatography. Therefore, we propose dehydrating a MAG and DAF mixture simultaneously to easily separate AMF and residues from the products.

In our previous study, we discovered that MAG did not form other furan compounds, such as HMF, after dehydration with aprotic polar solvents and Amberlyst 15. Therefore, dehydration of the MAG and DAF mixture (15% and 86%, respectively) was performed under the same reaction conditions, the results of which are shown in Figure 7. After 24 h, the final AMF and HMF yields were about 56% and 6%, respectively, in the DMF/dioxane (1:9) mixture, and 53% and 7%, respectively, in the DMSO/dioxane (1:9) mixture. In the case of the 16-hour reaction, dehydration was not completed because of the addition of DMSO. The DMF/dioxane mixture exhibited a higher yield and reaction rate than the DMSO/dioxane mixture.

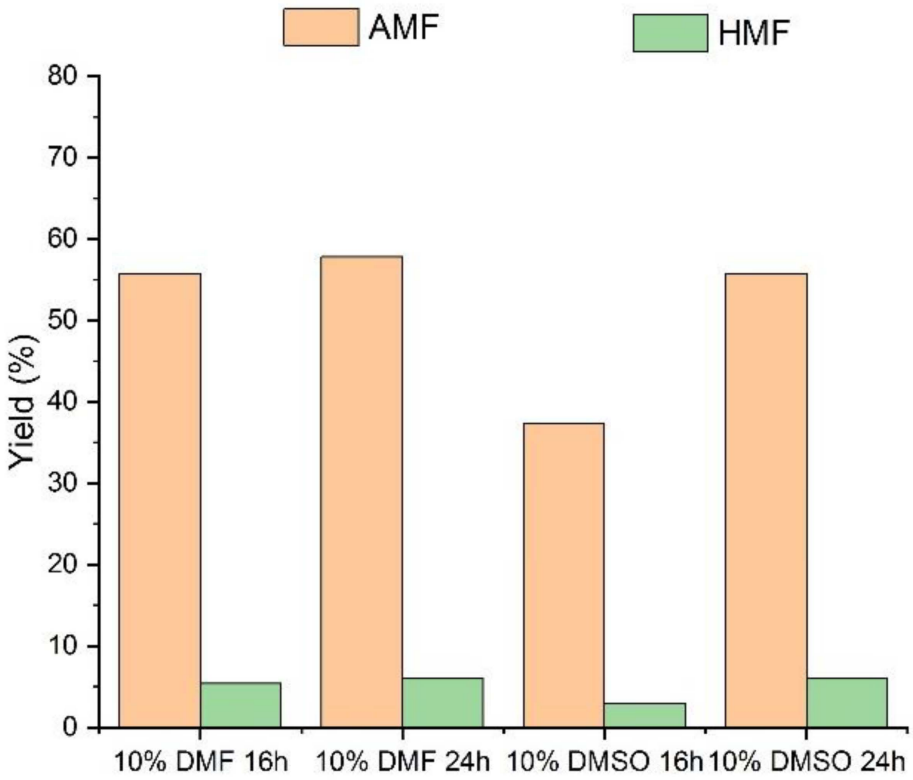

Figure 7. The yield of AMF and HMF after dehydration of the MAG and DAF mixture in a dual-solvent system.

4. Conclusions

We propose an enzymatic step-by-step synthesis process that consists of iterative isomerization and esterification, using glucose as a starting material for AMF synthesis and improving the efficiency of DAF formation. While most of the organic solvents showed a poor fructose yield from glucose isomerization, a fructose yield of 67% was achieved under the solvent conditions of a H_2O and tetrahydrofuran mixture. For the formation of DAF from fructose, Novozym 435 was selected as the best enzyme for transesterification, with a DAF yield of more than 96%. After the first hybrid conversion of the glucose and fructose mixture, the ratio of MAG and DAF in the products was 30% and 70%, respectively. In order to improve the DAF yield, we repeated the isomerization and transesterification for each cycle. After five iterative cycles, the final yield of DAF was achieved at 86%. For the dehydration of DAF to AMF with a cation exchange resin (Amberlyst 15), we identified the best solvent conditions and achieved an AMF yield of 56%. However, the low yield of AMF from DAF and the amount of MAG left over after dehydration both remain a challenge.

Considering the potential of AMF in green chemistry and for more eco-friendly products, AMF should be investigated extensively. Therefore, we must begin concerted research efforts to find the best conditions, solvent, catalyst, or enzyme. Enzymes, in particular, are suitable materials for green chemistry and eco-friendly systems.

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Data Availability Statement: The data is contained within the article.

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Conflicts of Interest: The authors declare no conflict of interest.

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