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Short Note

(*E*)-1-(5-(Hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one

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Abstract: This study presents a novel approach in the realm of catalytic organic synthesis by integrating biomass catalytic conversion with organic synthesis techniques. Utilizing *N*-acetylglucosamine as the primary feedstock, the first phase of the research involves its catalytic transformation into 5-hydroxymethylfurfural (HMF). The subsequent phase employs a condensation reaction between HMF and 3,3-Dimethyl-2-butanone to synthesize a new compound, (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one. This two-step process not only demonstrates the feasibility of converting biomass into valuable chemical precursors but also exemplifies the synthesis of novel compounds through green chemistry principles. The successful execution of this methodology offers fresh insights and opens new avenues for advancements in catalytic organic synthesis, emphasizing sustainability and efficiency.

Keywords: N-acetylglucosamine; 5-hydroxymethylfurfural; chalcone; catalysis; organic synthesis

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1. Introduction

Biomass is progressively recognized as a sustainable alternative to fossil fuels due to its renewable nature [1]. Currently, a diverse range of small-molecule platform compounds, especially those featuring furan rings like furfural, furfuryl alcohol, and furan carboxylic acids, have been efficiently catalyzed from biomass [2]. Furan derivatives, representing the simplest class of oxygen-containing five-membered heterocyclic compounds with a diene ether structure, are categorized as 6π-electron systems [3]. These compounds exhibit considerable chemical reactivity. Notably, 5-hydroxymethylfurfural (HMF) stands out as an exceptionally valuable platform compound [4]. Its significance lies not only in its role as a precursor for fuels, pharmaceuticals, and various other applications but also in the substantial biological activity of its derivatives [5], highlighting its versatility and potential in sustainable chemistry and green technology.

Chalcones are organic molecules with an open aromatic ring structure, serving as precursors to flavonoid compounds [6]. Characterized by two aromatic rings linked by a three-carbon chain bearing an α, β-unsaturated ketone group (-CO-CH=CH-), these compounds have garnered significant attention in the fields of medicinal chemistry and biopharmaceutical research due to their wide range of biological activities, including antimicrobial, anti-inflammatory, antitumor, antioxidant, and antiviral effects [7]. As a bio-based platform compound, HMF, with its furan ring and active functional groups, serves as an ideal precursor for the synthesis of chalcone derivatives [8]. Via a condensation reaction, while preserving the α, β-unsaturated ketone structure, the specific aromatic ring structure of chalcone was substituted with a furan ring structure [9]. This modification not

only retains the biological activities of chalcones but also exhibits functions distinct from traditional chalcones due to its unique structural features.

In recent years, the fusion of organic synthesis with innovative catalytic reactions has emerged as a significant area of interest [10]. This is particularly true for the synergistic process of biomass catalytic conversion coupled with the synthesis of high-value small molecules, marking a crucial step towards sustainable development and green chemistry by diminishing dependency on fossil fuels [11]. Based on the foregoing, this study aims to use *N*-acetylglucosamine as a starting material. In the first step, formic acid serves as the catalyst for the catalytic conversion of *N*-acetylglucosamine to HMF in a methyl isobutyl ketone (MIBK)/H_2O solvent system. In the second step, it reacts with 3,3-Dimethyl-2-butanone to synthesize the target product (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one (Figure 1). This process effectively transforms biomass of lesser value into chemicals of significant worth, offering fresh insights into innovative catalytic techniques for organic synthesis.

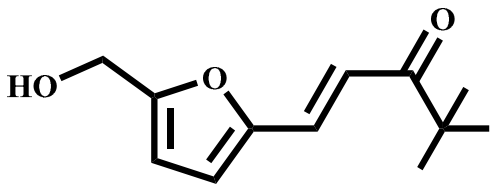
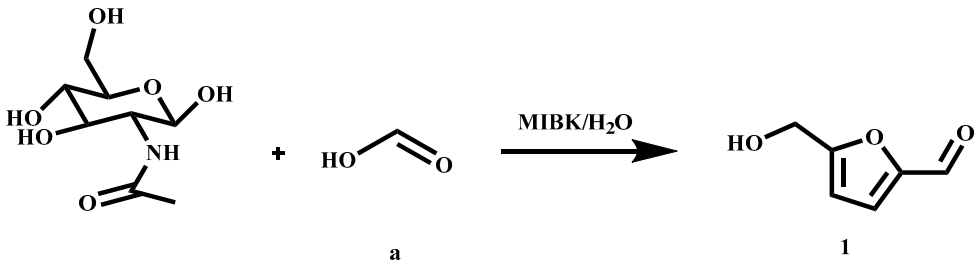


Figure 1. Structure of (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one.

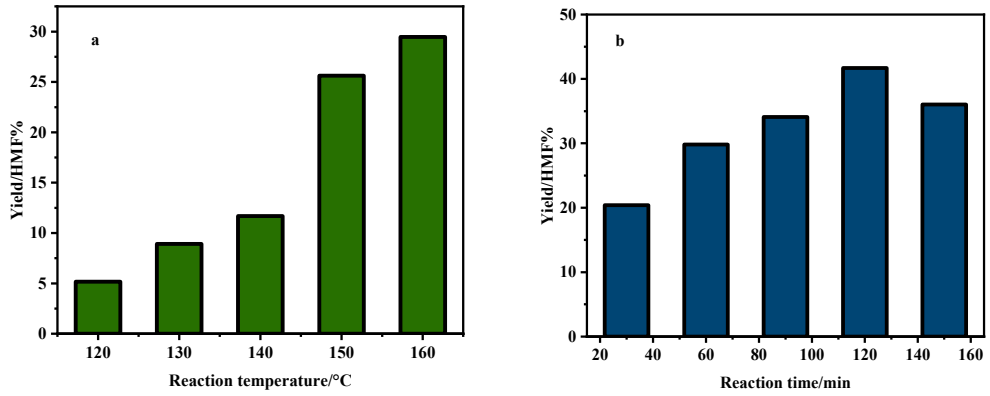
2. Results and Discussion

Chemistry

To synthesize the target compound (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one, our first step involved catalytically converting N-acetylglucosamine to HMF, choosing formic acid as the catalyst in an MIBK/H_2O solvent system through a hydrothermal reaction to prepare HMF (Scheme 1). N-acetylglucosamine, catalyzed by formic acid, undergoes protonation of its hydroxyl groups, increasing the positive charge density on the carbonyl carbon, making it more susceptible to nucleophilic attack [12]. The protonated hydroxyl group reacts with an adjacent water molecule through a dehydration reaction to form an enol intermediate [13]. This is followed by an intramolecular rearrangement where a hydrogen atom from a carbon atom is transferred to an oxygen atom, creating a more stable carbonyl structure [14]. Further dehydration and carbonylation reactions lead to the formation of HMF. Formic acid, as an organic acid, provides ample acidic conditions for the catalysis and dehydration steps of *N*-acetylglucosamine due to its strong acidity and relatively low corrosiveness [15,16]. Using MIBK/H_2O as the solvent facilitates the continuous extraction of HMF into the organic phase during its formation, further reducing by-product formation and enhancing the yield of HMF. Experiments were carried out to optimize the reaction conditions and investigate the effect of different reaction temperatures and times on the HMF yield (Figure 2). The results indicated that increasing the temperature could improve the yield of HMF to some extent. Under this system, the optimal reaction conditions were found to be 160 °C for 120 min, with an HMF yield reaching 41.7%; these were then used as the conditions for subsequent research. HMF was isolated and purified by column chromatography and used as a precursor for the next step in the synthesis of chalcone compounds.



Scheme 1. Synthesis of 5-hydroxymethylfurfural by catalytic conversion of *N*-acetylglucosamine. (a) Formic acid.



(**a**) (**b**)

Figure 2. (**a**) Effect of different reaction temperatures on HMF yield. (**b**) Effect of different reaction times on HMF yield.

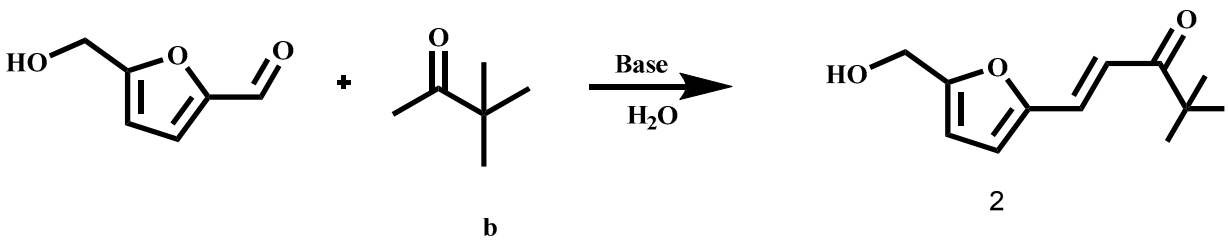
The reaction between 5-hydroxymethylfurfural (HMF) and 3,3-Dimethyl-2-butanone results in the formation of (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one, through a Knoevenagel condensation reaction, achieving a post-purification yield of 50.78% using straightforward column chromatography. In this reaction, HMF acts as an electrophilic agent, while 3,3-Dimethyl-2-butanone, containing an active hydrogen, functions as a nucleophilic agent. The active hydrogen on the carbon of 3,3-Dimethyl-2-butanone is deprotonated under alkaline conditions to form a carbanion, marking the beginning of electron rearrangement. This carbanion then attacks the carbonyl carbon of HMF, causing the π electrons on the carbonyl carbon to shift towards the oxygen atom, creating an enolate anion intermediate. This step is crucial for electron rearrangement, triggering the formation of a new C-C bond. The resulting intermediate undergoes one or multiple proton transfers, eventually leading to an α, β-unsaturated carbonyl compound through a dehydration reaction [17]. This reaction spontaneously occurs in a water–methanol mixed solvent medium, where water likely aids in deprotonation, and methanol helps stabilize the intermediates and the final product. The newly formed hydroxyl group may undergo a nucleophilic exchange reaction with a methanol molecule, leading to esterification and the release of a water molecule. The final product is thus formed through the protonation of intermediates followed by a dehydration reaction, illustrating a coherent pathway from reactants to product, emphasizing the role of the solvent in promoting deprotonation, intermediate stabilization, and facilitating critical steps such as nucleophilic exchange and esterification. The structural integrity of the target compound was validated through ^{1}H and ^{13}C NMR spectroscopy (Figures S2 and S3), ensuring precise and accurate portrayal of the synthetic pathway and molecular architecture. Based on the analysis of the $^{\wedge 1}$H NMR spectrum, the doublet signals at δ 7.37 (d, J = 15.3 Hz, 1H) and δ 6.98 (d, J = 15.3 Hz, 1H) are likely attributed to the hydrogen atoms of the olefinic part, and the J value indicates that these two hydrogen atoms are geometrically in a trans configuration, conforming to the (*E*)-configuration. This is consistent with the hydrogen atoms on either side of the double bond

splitting into a double peak. The signals at δ 6.57 (d, J = 3.3 Hz, 1H) and δ 6.37 (d, J = 3.3 Hz, 1H) likely originate from the hydrogen atoms on the furan ring, with the J value suggesting they are coupled through two chemical bonds, indicating these are adjacent hydrogen atoms on the furan ring. The singlet signal at δ 4.65 (s, 2H) represents two hydrogen atoms in the same chemical environment, likely being the two hydrogen atoms on the hydroxymethyl group (-CH_2OH), and the signal at δ 1.20 (s, 9H) represents nine hydrogen atoms in the same chemical environment, indicating these are the hydrogen atoms of three methyl groups (-CH_3). According to the analysis of the ^{13}C NMR spectrum, δ 204.42 indicates the presence of a carbonyl group (C=O), δ 156.26, 151.53 likely belong to the carbon atoms on the furan ring affected by an oxygen atom. The values δ 129.08, 118.35, 116.56, 110.47 could belong to the carbon atoms of the olefinic part and other carbon atoms on the furan ring, where some carbon atoms show higher chemical shift values due to interaction with the double bond or oxygen atom. The value δ 57.60 likely corresponds to the carbon atom on the hydroxymethyl group (-CH_2OH). The values δ 43.17, 26.31 likely belong to saturated carbon atoms, including the carbon atoms of methyl groups (-CH_3) and those near the furan ring or olefinic part. Through the analysis of its NMR spectra, we have determined the basic structure of (E)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one.

Sodium hydroxide (NaOH), serving as a potent base, plays a crucial role in providing the necessary alkaline conditions for the reaction. Under these conditions, active methylene compounds undergo deprotonation to form methylene anions, which increases their nucleophilicity and facilitates subsequent attacks on the carbonyl carbon atoms. The use of a water–methanol mixture is strategically chosen to optimize the solvent properties, balancing both polarity and non-polarity to enhance the solubility of the reactants. This balance is essential for maintaining a homogeneous reaction mixture and for accelerating the reaction kinetics. Specifically, water as a polar solvent efficiently dissolves NaOH and ensures the required hydration environment, whereas methanol enhances the solubility of organic components, notably the active methylene compounds.

3. Materials and Methods

Chemicals. In this research, we accomplished the synthesis of (E)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one (Scheme 2). All solvents and raw materials were sourced commercially and employed as delineated in our experimental procedure. Formic acid was obtained from Sinopharm Group, whereas 3,3-Dimethyl-2-butanone and methyl tert-butyl ketone were procured from Aladdin Reagent Group. The specific steps of the catalytic process are as follows: a mass of 250 mg of N-acetylglucosamine was added to a 35 mL pressure-resistant bottle, followed by the addition of formic acid (2 mL), methyl isobutyl ketone (MIBK) (8 mL), and H_2O (2 mL) as solvents. The mixture was then subjected to a reaction at 160 °C for 120 min. Upon completion of the reaction, the mixture was processed to extract the reaction solution, and the organic phase was isolated via column chromatography using ethyl acetate/petroleum ether as the eluent, yielding the purified catalytic product, HMF.



Scheme 2. Synthesis of (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one. (b) 3,3-Dimethyl-2-butanone.

In the synthesis phase, 0.02 mol of the purified HMF was combined with an equivalent amount of 3,3-Dimethyl-2-butanone in a reaction medium comprising 40% NaOH in a

water–methanol mixture. This mixture was stirred at 30 °C for 3 h and its progress was monitored through thin-layer chromatography (TLC). Following the reaction, methanol was removed via rotary evaporation. Ethyl acetate was then introduced to the residual reaction mix, followed by triple water washes, and subsequently, compound **2** was isolated through column chromatography, resulting in 0.025 mol of a yellow oily substance. This meticulous approach ensures precise adherence to protocol, ensuring the accurate and efficient synthesis of the target compound.

(*E*)-1-(5-(hydroxymethyl)furan-2-yl)-4,4-dimethylpent-1-en-3-one. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.37 (d, J = 15.3 Hz, 1H), 6.98 (d, J = 15.3 Hz, 1H), 6.57 (d, J = 3.3 Hz, 1H), 6.37 (d, J = 3.3 Hz, 1H), 4.65 (s, 2H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, Chloroform-d) δ 204.42(s), 156.26(s), 151.53(s), 129.08(s), 118.35(s), 116.56(s), 110.47(s), 57.60(s), 43.17(s), 26.31(s). Anal. Calcd. for $C_{12}H_{16}O_3$(208.11): C, 69.21; H, 7.74. Found C, 68.37; H, 7.45.

Instrumental Analysis. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent DD2 500 spectrometer (Brand, Agilent, United States). HMQC NMR spectra were recorded on an AVANCE NEO 600 (Bruker, Billerica, MA, USA). HPLC was detected on an LC-2030C 3D PLUS (Shimadzu, Japan).

4. Conclusions

In summary, we have integrated biomass catalytic conversion with organic synthesis, using N-acetylglucosamine as the starting material. N-acetylglucosamine was catalytically converted to HMF, which was then combined with 3,3-Dimethyl-2-butanone through a Knoevenagel condensation reaction, resulting in the synthesis of a novel chalcone compound, (E)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one.

Supplementary Materials: Figure S1: HPLC profiles of 5-hydroxymethylfurfural; Figure S2: (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one nuclear magnetic hydrogen spectrum; Figure S3: (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one nuclear magnetic carbon spectrum; Figure S4: (*E*)-1-(5-(hydroxymethyl) furan-2-yl)-4,4-dimethylpent-1-en-3-one Nuclear magnetic HMQC spectrum.

Author Contributions: Data curation, formal analysis, methodology, validation, writing—original draft, Z.W.; methodology, L.Z.; project administration, resources, P.H.; conceptualization, writing—review and editing, Y.Q. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The spectroscopic data presented in this study are available as Supplementary Materials.

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

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