

Efficient Synthesis of Novel Biginelli and Hantzsch Products Sourced from Biorenewable Furfurals Using Gluconic Acid Aqueous Solution as the Green Organocatalyst

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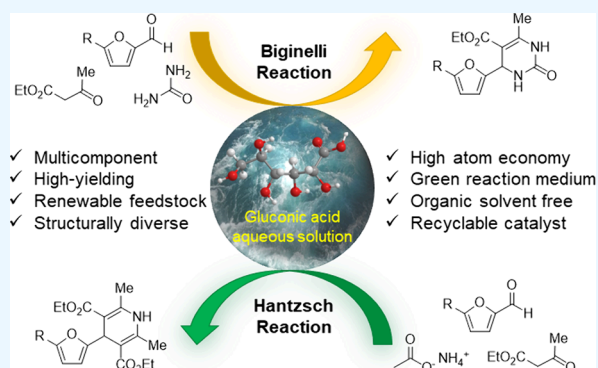
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ABSTRACT: The Biginelli reaction provides 3,4-dihydropyrimidin-2(1H)-ones (DHPMs), whereas the Hantzsch reaction leads to 1,4-dihydropyridines (DHPs) by the one-pot, multicomponent, and operationally simple transformations starting from readily available starting materials. DHPMs and DHPs are well-established heterocyclic moieties in the synthetic organic chemistry literature and have pronounced pharmacological activities. This work reports the synthesis of novel DHPMs and DHPs from carbohydrate-derived 5-substituted-2-furaldehydes by employing gluconic acid aqueous solution (GAAS) as an efficient, inexpensive, and eco-friendly catalyst. The use of urea (or thiourea) as the reagent led to DHPMs, whereas ammonium acetate produced DHPs, selectively, keeping the other two starting materials (i.e., furfurals and ethyl acetoacetate) and the reaction parameters unaltered. Using the general synthetic protocol under optimized reaction conditions (60 °C, 3–6 h, 25 mol % GAAS cat.), all the DHPM and DHP derivatives were obtained in good to excellent isolated yields.



■ SEC1INTRODUCTION

Carbohydrates have received significant attention over the past three decades as a commercially viable source of biogenic carbon for sustainably synthesizing value-added organic chemicals that are otherwise sourced from exhaustible feedstock like petroleum.¹ The catalytic value addition of carbohydrates has received particular interest since the processes are fast, selective, scalable, eco-friendly, and can be integrated seamlessly into the petrorefinery infrastructure.² For chemical products that do not necessitate preserving the native structure of sugars, a two-step synthetic strategy is adopted. Carbohydrates are initially converted to a handful of functionalized small molecules that act as chemical building units. In the second step, the reactive intermediates are synthetically transformed into products of desired structural features.^{2,3} In this regard, the acid-catalyzed dehydration of pentoses (e.g., xylose) leads to furfural (FF, **1a**), whereas the dehydration of hexoses (e.g., glucose) forms 5-(hydroxymethyl)furfural (HMF, **1e**).^{4,5} The processes typically use an acid catalyst of some sort and produce water as an innocuous byproduct. The production and derivative chemistry of FF and HMF have been explored scrupulously over the past decades.^{6,7} In this regard, the synthesis and study of heterocycles is one of the cornerstones of synthetic organic chemistry primarily due to the remarkable properties and fascinating pharmacological activities of the heterocyclic

molecules.^{8–10} Significant importance has been given to designing green synthetic protocols for various heterocyclic moieties.^{11–13} FF and HMF are often used as representative furanic molecules to demonstrate the diverse substrate scope of various synthetic methodologies, such as the synthesis of heterocycles.¹⁴ However, the systematic study of carbohydrate-derived 5-substituted-2-furaldehydes as substrates for synthesizing various classes of heterocyclic molecules is underexplored.¹⁵ Such systematic studies will assist in unraveling the much-desired reactivity patterns of these biorenewable molecules and expanding the horizon of their derivative chemistry. Moreover, the study will pave the way for synthesizing hitherto unknown products to explore their properties and potential applications. Some of the commonly encountered biorenewable 5-substituted-2-furaldehydes apart from HMF, **1e** include 5-methylfurfural (MF, **1b**), 5-(acetoxymethyl)furfural (AcMF, **1c**), and 5-(ethoxymethyl)furfural (EMF, **1d**) (Scheme 1). MF is a potential biofuel and a renewable chemical intermediate that can be produced by

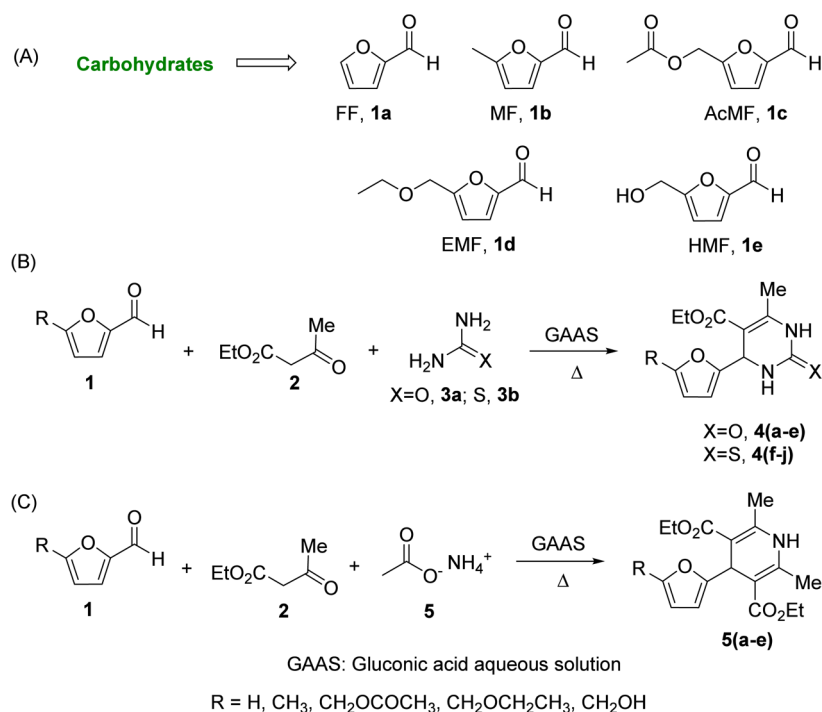
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Scheme 1. (A) Structures of Various 5-Substituted-2-furaldehydes Obtained from Carbohydrate, (B) Synthesis of the Novel 3,4-Dihydropyrimidin-2(1*H*)-ones, and (C) Synthesis of 1,4-Dihydropyridines from Biorenewable Furfurals



reducing HMF or directly from carbohydrates.¹⁶ EMF is a potential fuel oxygenate obtained by acid-catalyzed ethanolysis of sugars and polymeric carbohydrates.¹⁷ AcMF has recently received significant attention as a hydrophobic congener of HMF with several markets.¹⁸ These five compounds (i.e., **1a–1e**) have been used as representative examples of biorenewable furaldehydes for developing a general synthetic protocol of the Biginelli and Hantzsch reactions.

In this regard, 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) and 1,4-dihydropyridines (DHPs) are well-established classes of heterocyclic compounds with pronounced therapeutic properties.^{19,20} DHPMs are produced by the Biginelli reaction protocol involving a multicomponent reaction (MCR) between an aromatic aldehyde, esters of acetoacetic acid, and urea (or thiourea).²¹ The acid-catalyzed process typically affords products in excellent isolated yield, possesses excellent atom economy, and forms water as the only byproduct. Similarly, DHPs are produced by the Hantzsch reaction between an aromatic aldehyde, esters of acetoacetic acid, and an ammonium salt.²² MCRs are where more than two reactants with complementary reactive functionalities combine sequentially and produce the product in high selectivity and excellent atom economy.²³ MCRs allow the introduction of significant structural complexity in the product molecule starting from inexpensive and readily available starting materials in a one-pot reaction, predominantly following catalytic steps, decreasing the number of synthetic steps, and minimizing waste formation.^{24,25} Therefore, MCRs are an important part of sustainability in synthetic organic chemistry, and there have been continuing attempts to identify such transformations and use them coherently to design molecules of desired structural features and properties.²⁶ Biginelli and Hantzsch transformations are well-documented MCRs, and their products have remarkable pharmacological properties. Even though FF **1a** is typically used as one of the substrates for

these transformations to demonstrate the substrate scope of the catalyst systems, systematic study involving the biorenewable 5-substituted-2-furaldehydes is virtually unexplored in the literature.

Numerous homogeneous and heterogeneous acid catalysts have been screened for Biginelli and Hantzsch transformations.^{27,28} Metal-free organocatalysts have shown promising activities for these transformations.^{29,30} A SciFinder search on the Biginelli product of MF **1b** as a model 5-substituted-2-furaldehyde revealed that heterogeneous catalysts, such as sulfated zirconia, Zn²⁺-modified MCM-41, silica-supported sulfonic acid, preyssler heteropolyacids, and titanium silicate had been used that afforded acceptable yields of **4b** under moderate reaction conditions.^{31–35} However, there is still an active search for an efficient, inexpensive, and eco-friendly catalyst that allows the reactions to happen under mild conditions and affords products with desired selectivity and yield.³⁶ Gluconic acid aqueous solution (GAAS) has received much interest as an acid-based organocatalyst and a green reaction medium for various organic transformations.^{37,38} Gluconic acid has roughly 10 times stronger Brønsted acidity ($pK_a = 3.86$) than acetic acid ($pK_a = 4.76$) and is nontoxic, nonvolatile, noncorrosive, and biodegradable. GAAS can be conveniently produced from glucose via catalytic or enzymatic oxidation in water.^{39,40}

This work reports the organic solvent-free synthesis of novel DHPMs and DHPs starting from carbohydrate-derived 5-substituted-2-furaldehydes using GAAS as an efficient but inexpensive catalyst. When the combination of a suitable 5-substituted-2-furaldehyde, urea (or thiourea), and ethyl acetoacetate was heated using GAAS as the catalyst, the resulting Biginelli transformation formed DHPMs. When urea (or thiourea) was replaced with an ammonium salt (e.g., ammonium acetate), the Hantzsch reaction formed DHPs. The substitution pattern at the 5-position of carbohydrate-derived

2-furaldehydes has noticeably different reactivity. Therefore, a general synthetic protocol for synthesizing a specific class of product from these biorenewable chemicals is challenging but rewarding. In this study, a general synthetic protocol for DHPMs and DHPs has been developed that works on all of the 5-substituted-2-furaldehydes and produces the desired products selectively by reagent control.

SEC2RESULTS AND DISCUSSION

Initially, the catalytic efficiency of some commonly encountered water-soluble biogenic carboxylic acids was explored toward the Biginelli reaction of FF (**1a**) with ethyl acetoacetate (**2**) and urea (**3a**) forming DHPM **4a**. Table 1 shows the

Table 1. Synthesis of DHPM (4a**) from FF (**1a**) Using an Aqueous Solution of Biogenic Carboxylic Acids as an Efficient and Innocuous Catalyst**

entry	catalyst	yield of 4a (%) ^a
1	formic acid	74
2	acetic acid	65
3	lactic acid	82
4	GAAS	88
5 ^b	oxalic acid	46 (51)
6	succinic acid	58

^aReaction conditions: FF **1a** (0.502 g, 5.225 mmol), ethyl acetoacetate (0.680 g, 5.225 mmol), urea (0.470 g, 7.837 mmol), catalyst (50% aq., 25 mol %), 60 °C, 6 h. ^bYield in parentheses used oxalic acid amount assuming it as a monobasic acid.

results obtained by performing the Biginelli reaction of **1a** with **2** and **3a** in the presence of various aqueous carboxylic acids as innocuous catalysts under organic solvent-free conditions.

When a 25 mol % loading of an aqueous solution (50%) of formic acid ($pK_a = 3.75$) was employed as the catalyst, the reaction completed within 6 h at 60 °C and DHPM **4a** was obtained in a 74% isolated yield (entry 1, Table 1). The reaction progress was monitored by thin-layer chromatography (TLC) for the disappearance of **1a** or until the reaction mixture stopped evolving any further. The reaction mixture was quenched in ice-cold water to precipitate **4a**. The reported yields of **4a** were obtained after purifying the crude product via column chromatography. When acetic acid (50%, aq) was used as the catalyst, a 65% yield of **4a** was observed (entry 2, Table 1). The low yield can be attributed to the lower acidity of acetic acid ($pK_a = 4.76$). Lactic acid and GAAS afforded excellent isolated yields of **4a** (>80%) under the reaction conditions employed (entries 3 and 4, Table 1). Interestingly, oxalic acid and succinic acid provided only moderate yields of **4a** (entries 5 and 6, Table 1). The result was attributed to the partial decomposition of **1a** during the reaction. Evidently, GAAS showed the highest efficiency in terms of selectivity for synthesizing **4a** under the reaction conditions explored. Therefore, the process optimization of the Biginelli reaction using GAAS as a catalyst was studied next using **1a**, **2**, and **3a** as model substrates/reagents. The mixture was heated in an oil bath and magnetically stirred during the reaction. When the reaction was carried out without adding any catalyst, the product was not formed, even at elevated temperatures. Initially, the reaction was carried out using excess GAAS starting from a 1:1:1.5 molar ratio of **1a**, **2**, and **3a** at room temperature (Figure 1). Even after a prolonged reaction time of 24 h, the reaction did not complete, and only a 65% isolated

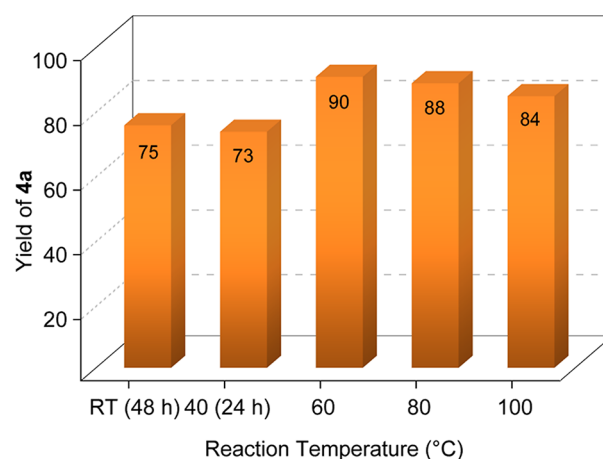


Figure 1. Effect of the reaction temperature on yield **4a**. Reaction conditions: FF **1a** (0.502 g, 5.225 mmol), ethyl acetoacetate (0.680 g, 5.225 mmol), urea (0.470 g, 7.837 mmol), and GAAS (0.50 g, 25 mol %).

yield of **4a** was obtained. When a catalytic amount of GAAS (25 mol % of **1a**) was employed and the reaction was allowed to run for 48 h, the yield of **4a** reached 75%. When the reaction temperature was increased slightly to 40 °C, the isolated yield of **4a** reached 73% within 24 h. The mass balance of the reaction was the unreacted starting materials. When the reaction temperature was elevated to 60 °C, the reaction was completed in 6 h, affording a 90% isolated yield of **4a**. Further increase of the reaction temperature to 80–100 °C for faster kinetics and shorter duration marginally lowered the yield of **4a**, possibly due to diminished selectivity.

The effect of reaction duration was studied by varying reaction time from 4 to 8 h (Figure 2). When the reaction was

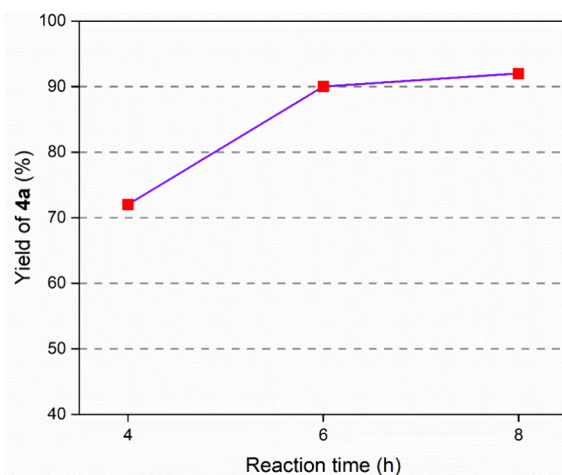


Figure 2. Effect of reaction time on the yield of **4a**. Reaction conditions: FF **1a** (0.502 g, 5.225 mmol), ethyl acetoacetate (0.680 g, 5.225 mmol), urea (0.470 g, 7.837 mmol), GAAS (0.50 g, 25 mol %), 60 °C.

carried out for 4 h, the isolated yield of **4a** was only 72% at 60 °C using 25 mol % of GAAS as a catalyst. In comparison, the reaction conducted for 6 h gave 90% **4a** under similar reaction conditions. Increasing the reaction duration to 8 h gave only a marginal increase in the amount of **4a** (ca. 92%). Therefore, a reaction temperature of 60 °C and a duration of 6 h were taken as optimized parameters for synthesizing **4a** from biomass-

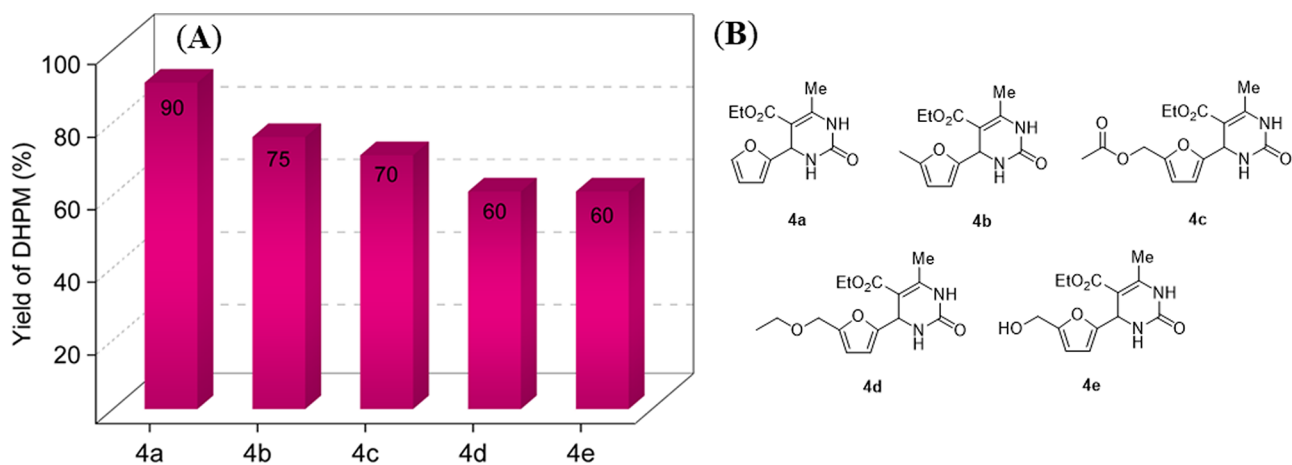


Figure 3. Isolated yields (A) and chemical structures (B) of 3,4-dihydropyrimidin-2(1H)-ones from biorenewable furfurals. Reaction conditions: substituted furfuraldehyde (0.502 g), ethyl acetoacetate (1 equiv), urea (1.5 equiv), GAAS (25 mol %), 60 °C, 6 h.

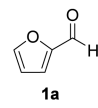
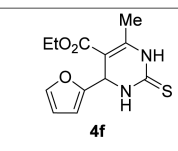
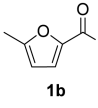
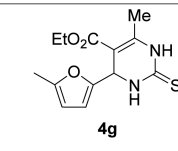
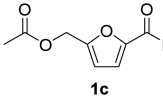
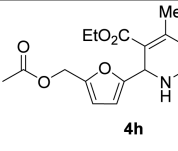
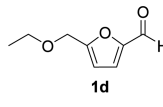
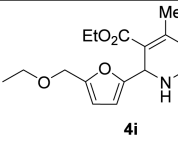
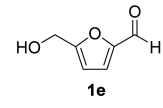
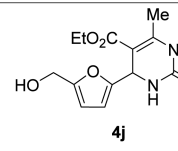
derived **1a** using GAAS (25 mol %) as the catalyst. The reaction was successfully scaled up to 10 g of **1a** (Figure S46, Supporting Information).

The amount of GAAS catalyst was varied between 10 and 30 mol % to check the catalytic activity during the formation of **4a**. When only a 10 mol % loading of the GAAS catalyst was employed, **4a** was obtained in a 72% isolated yield (60 °C, 6 h), and the mass balance was predominantly the unreacted starting materials. Increasing the loading of GAAS to 30 mol % did not show any observable change in the yield of **4a**. Therefore, a 25 mol % loading of GAAS was considered optimum for the reaction. The molar ratio of the starting materials was studied next to improve the process economy and minimize waste formation. It was found that urea needed to be used more than the equivalent amount due to its instability during the reaction, especially at elevated temperatures. A 1:1:1.5 molar ratio between **1a**, **2**, and **3a** was found to be most suitable for the Biginelli reaction affording a satisfactory yield of **4a**.

After optimization of the reaction conditions, the synthetic protocol was applied for the synthesis of novel DHPMs from representative 5-substituted-2-furaldehydes, such as MF (**1b**), AcMF (**1c**), EMF (**1d**), and HMF (**1e**). Interestingly, the reaction kinetics was slower for 5-substituted-2-furaldehydes than **1a**. Under the optimized conditions (60 °C, 6 h), **1b**, **1c**, **1d**, and **1e** gave 75, 70, 60, and 60% of their corresponding DHPM, respectively (Figure 3). This observation is in line with previously published literature reporting noticeably differing reactivities of various 5-substituted-2-furaldehydes.⁴¹

The synthesis of 3,4-dihydropyrimidin-2(1H)-thiones from 5-substituted-2-furaldehydes was attempted next by replacing urea with thiourea (Table 2). However, only a 30% yield of **4f** was obtained under the previously optimized molar ratio or reagents due to the faster decomposition of thiourea under the reaction conditions. Excess thiourea (4 equiv) had to be used to compensate for the decomposition of thiourea during the reaction, but less yield of **4f** was observed (~30%) under identical conditions (60 °C, 6 h, 25 mol % GAAS) due to slower kinetics. The use of a 1:1:4 molar ratio between furfural(s), ethyl acetoacetate **2**, and thiourea **3b** gave 85, 70, 67, 64, and 60% yields of **4f**, **4g**, **4h**, **4i**, and **4j** from **1a**, **1b**, **1c**, **1d**, and **1e**, respectively, by performing the reaction for 12 h at 80 °C using 50 mol % GAAS as the catalyst.

Table 2. Synthesis of 3,4-Dihydropyrimidin-2(1H)-thiones from Biorenewable Furfurals^a

Entry	Starting material	Product structure and code	Yield (%)
1			85
2			70
3			67
4			64
5			60

^aReaction conditions: substituted furfuraldehyde (0.502 g), ethyl acetoacetate (1 equiv), thiourea (4 equiv), GAAS (50 mol %), 80 °C, 12 h.

A similar catalyst system was used for synthesizing 1,4-dihydropyridines using the Hantzsch condensation protocol (Figure 4). When a 1:2:1.5 molar ratio of **1a**, ethyl acetoacetate **2**, and ammonium acetate **5** was used, the reaction was completed within 3 h at 60 °C and 97% of **5a** was isolated. Using similar reaction conditions, 85, 90, 89, and 84% of **5b**, **5c**, **5d**, and **5e** were isolated from **1b**, **1c**, **1d**, and **1e**, respectively.

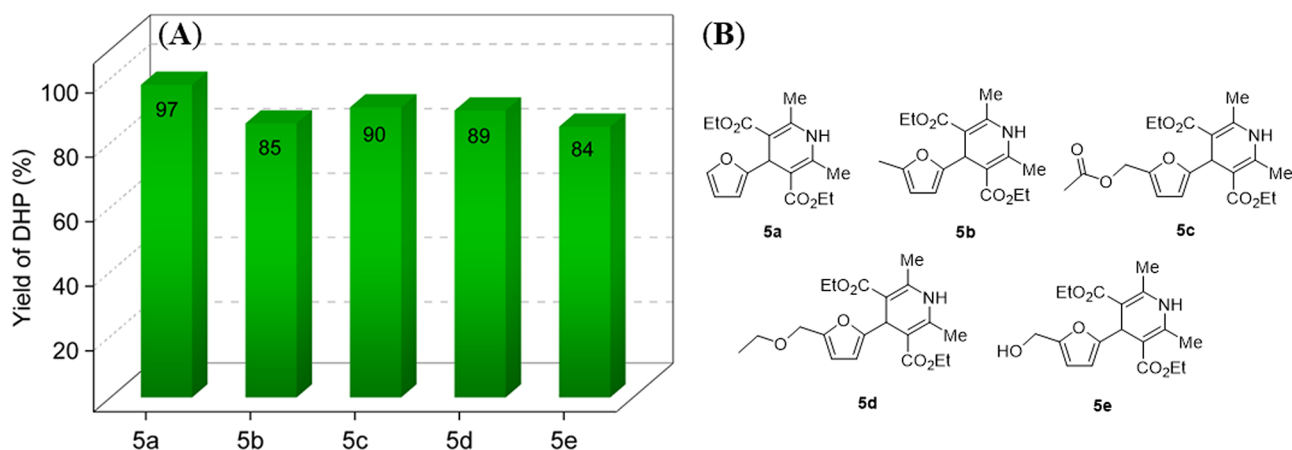


Figure 4. Isolated yields (A) and chemical structures (B) of 1,4-dihydropyrimidines from biorenewable furfurals. Reaction conditions: substituted furfuraldehyde (0.502 g), ethyl acetoacetate (2 equiv), ammonium acetate (1.5 equiv), GAAS (25 mol %), 60 °C, 3 h.

We envisaged that using the ammonium salt of gluconic acid would improve the atom economy of the process. When using ammonium acetate as the reagent, the incorporation of ammonia in the Hantzsch product leaves an acetic acid impurity in GAAS, whereas the use of aqueous ammonia keeps gluconic acid unadulterated. However, when ammonium gluconate was used as the reagent to prepare **5a**, the reaction did not proceed appreciably even after 6 h at 60 °C. However, performing the reaction at 90 °C for 12 h afforded a 70% yield of **5a**. The observation may be justified by the high stability of ammonium gluconate. Finally, the recyclability of the GAAS catalyst for the synthesis of the Biginelli product **4a** was also studied using optimized reaction conditions. The reaction was performed with a 1:1:1.5 molar ratio of **1a**, **2**, and **3a**. After the reaction, the reaction mixture was quenched in ice water, and precipitated **4a** was recovered by vacuum filtration. The minor organic-soluble impurities in the aqueous layer were removed by extracting with chloroform. The water layer was then evaporated to dryness under a controlled vacuum to get gluconic acid as a white solid. The concentration was finally adjusted to 50% by adding the required amount of deionized water and used for the next catalytic cycle. The isolated yield of **4a** with the fresh GAAS catalyst was 88%. The yield of **4a** dropped to 77% after the first cycle, which may be responsible for organic contamination during the recovery. Interestingly, the yield of **4a** remained 72–74% until the fourth recycle.

CONCLUSIONS

In summary, novel 3,4-dihydropyrimidin-2(1H)-ones, 3,4-dihydropyrimidin-2(1H)-thiones, and 1,4-dihydropyrimidines have been synthesized from carbohydrate-derived 5-substituted-2-furaldehydes in good to excellent isolated yields following the Biginelli and Hantzsch reaction protocols, respectively. The gluconic acid aqueous solution proved to be an excellent catalyst and reaction medium that is renewable, nontoxic, inexpensive, and recyclable. The reactions were completed within 6 h at 60 °C using equivalent or only slight excess of the reagents. The optimized conditions were then applied on 10 g of furfural to demonstrate the scalability of the general synthetic protocol developed for both Biginelli and Hantzsch products. The gluconic acid aqueous solution catalyst was also successfully recycled and showed only a marginal dip in activity.

EXPERIMENTAL SECTION

Materials. Furfural (99%), ethyl acetoacetate (99%), urea (99.5%), formic acid (98%), and thiourea (98%) were purchased from Spectrochem. 5-Methylfurfural (99%) was purchased from Sigma-Aldrich. DI water, oxalic acid dihydrate (99%), succinic acid (99%), glacial acetic acid (99%), pet ether (60–80 °C), and ethyl acetate (99.5%) were purchased from Loba Chemie Pvt. Ltd. The gluconic acid aqueous solution (GAAS, 50%) and lactic acid (85%, aq) were purchased from TCI chemicals. Ethanol (99.9%) was purchased from CSS China. 5-(Acetoxymethyl)furfural (AcMF), 5-(hydroxymethyl)furfural (HMF), 5-(chloromethyl)furfural (CMF), and 5-(ethoxymethyl)furfural (EMF) were synthesized and purified using the literature process.^{18,42–44}

Synthetic Procedures. Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) from Furfurals. A mixture of furfural (**1a**, 0.502 g, 5.225 mmol), ethyl acetoacetate (0.680 g, 5.225 mmol), urea (0.470 g, 7.837 mmol), and GAAS (0.50 g, 25 mol %) was stirred at 60 °C. The progress of the reaction was monitored by using thin-layer chromatography (TLC). After the completion of the reaction (6 h), the reaction mixture was cooled to room temperature and poured into crushed ice. The solid was filtered using vacuum filtration, dried in a hot-air oven (60 °C, 12 h), and recrystallized using absolute ethanol to get pure **4a** (1.180 g, 90%).

A similar synthetic strategy was applied for synthesizing **4a–4e**. The synthesized compounds were confirmed by FTIR, NMR, and elemental analysis. The melting point of new compounds is reported.

Synthesis of 3,4-Dihydropyrimidin-2(1H)-thiones Using Biginelli Condensation. Furfural **1a** (0.502 g, 5.225 mmol), ethyl acetoacetate (0.680 g, 5.225 mmol), thiourea (1.590 g, 20.899 mmol), GAAS (1.10 g, 50 mol %) were charged in a round-bottomed flask fitted with a reflux condenser and magnetically stirred in a preheated oil bath at 80 °C for 12 h. After the reaction, the mixture was cooled to room temperature and poured into crushed ice. The solid product is filtered under vacuum, dried in a hot-air oven (60 °C, 12 h), and recrystallized using absolute ethanol to get pure **4f** (1.179 g, 85%).

A similar synthetic strategy was applied for the synthesis of **4g–4j**. The synthesized compounds were confirmed by FTIR, NMR, and elemental analysis. The melting point of all synthesized compounds is also reported.

Synthesis of 1,4-Dihydropyridines (DHPs) Using Hantzsch Condensation. Furfural **1a** (0.502 g, 5.225 mmol), ethyl acetoacetate (1.359 g, 10.449 mmol), ammonium acetate (0.604 g, 7.837 mmol), and GAAS (0.50 g, 25 mol %) were charged in a round-bottomed flask fitted with a reflux condenser and magnetically stirred in a preheated (60 °C) oil bath for 3 h. After the reaction, the mixture was cooled to room temperature and poured into crushed ice. The solid product is filtered under vacuum, dried, and recrystallized using ethanol to get pure **5a** (1.618 g, 97%).

A similar synthetic strategy was applied for the synthesis of **5b–5e**. The synthesized compounds were confirmed by FTIR, NMR, and elemental analysis. The melting points of new compounds is reported.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c05106>.

(Schemes S1 and S2) Proposed mechanism of Biginelli and Hantzsch reaction catalyzed by GAAS; (Figures S1–S45) spectral characterization data of synthesized DHPMs and DHPs; and (Figure S46) photographs of synthesized DHPM **4a** and DHP **5a** by scaling up the reaction with 10 g of furfural **1a** (PDF)

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Author Contributions

H.N.A. and C.P.N. performed the experiments and analyzed data. N.S.B. assisted in data analysis and wrote the original draft. M.K. assisted in the experiments. S.D. was responsible for the conceptualization, supervision, and data curation.

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Notes

The authors declare no competing financial interest.

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