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Facile Preparation of 3-Acetamido-5-acetylfuran from *N*-Acetyl-D-glucosamine Using Commercially Available Aluminum Salts

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Abstract: 3-Acetamido-5-acetylfuran (3A5AF) is a promising intermediate obtained from chitin for the production of N-containing value-added chemicals. However, the synthetic method is complicated so far, which has limited further investigation using 3A5AF. Herein, we provide a facile method for synthesizing 3A5AF from *N*-acetyl-D-glucosamine (NAG), including a simple isolation procedure. A 30% yield of 3A5AF is given by performing the dehydration of NAG in *N,N*-dimethylformamide (DMF) solvent in the presence of $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ at a temperature as low as 120 °C by conventional heating for 30 min. This method adapts a wide range of temperature and concentration of substrate, thus easily allowing scale up of the reaction. The produced 3A5AF is isolated with 98% purity by a simple column chromatography. We also identified a highly functionalized N-containing lactone as a by-product under this reaction condition.

Thermo-catalytic biomass transformation is a mean to respond to the chemical industry need of shifting away from fossil fuel dependency. Marine biomass waste such as crustacean shell is the second largest biomass material after lignocellulose, representing a realistic opportunity for chemical valorization.¹ Its main constituent is chitin, a linear polymer constituted of an amino sugar, *N*-acetyl-D-glucosamine (NAG), and it can be depolymerized into its constitutive unit in a very similar fashion to cellulose.^{2,3} NAG is a rather peculiar molecule, as it possesses a naturally fixed nitrogen atom, therefore, represents an immense opportunity for the chemical industry. At present, nitrogen-containing platform molecules, vital for pharmaceuticals, solvents and polymers, rely on the energy intensive and fossil fuel-dependent ammonia synthesis process. For these reasons, transformation of NAG into N-containing molecules is very desirable and many works have already shown the possible transformation routes that may be carried out. Examples of successful valorization of chitin and NAG are given by the production of N-containing molecules such as acetylglycine,⁴ 2-acetamido-2-deoxysorbitol⁵ and 2-acetamido-2-deoxyisorbide.⁶ Another attractive molecule derived from NAG is 3-acetamido-5-acetylfuran (3A5AF),^{7,8} which can be obtained in an apparently similar fashion to 5-hydroxymethylfurfural (HMF) production from glucose (Scheme 1).

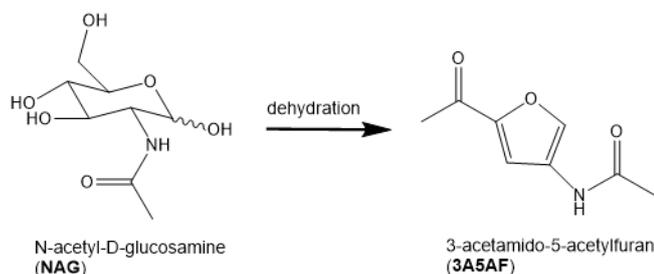
3A5AF has the potential to become an important building block for N-containing aromatic chemicals and examples of its utilization are present in literatures.⁹⁻¹³ This compound was first obtained as a by-product in a low yield in the pyrolysis of chitin.¹⁴⁻

¹⁶ Recently, liquid-phase reactions to synthesize 3A5AF from

NAG have been proposed. However, the production of 3A5AF has been proven to be a challenging reaction, and often non-conventional methods or harsh conditions are employed. Drover *et al.* reported a 3A5AF yield of 60% when NAG was converted in ionic liquid and in the presence of boric acid $[\text{B}(\text{OH})_3]$ at 180 °C.⁷ Omari *et al.* used microwave irradiation to convert NAG into 3A5AF with 58% yield in the presence of $\text{B}(\text{OH})_3$ and NaCl at 220 °C.¹⁷ A similar system using $\text{B}(\text{OH})_3$ and NaCl was applied to directly convert chitin into 3A5AF with 7% yield at 180 °C.¹⁸ Finally, 53% yield of 3A5AF was obtained by employing glycine chloride and additives at 200 °C.¹⁹ In all these systems several common features can be observed, which are high temperatures above 180 °C, nitrogen-containing aprotic solvents and the presence of chloride anions. At present, the lack of an easy and handy procedure that do not require unconventional methods or equipment including ionic liquids or microwave irradiation is hindering the synthesis of 3A5AF even at laboratory scale. Therefore, an easy method that can be followed by everyone is essential for the expansion and development of the research on this field.

Here, we report a new and facile method for making 3A5AF using $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ catalyst and *N,N*-dimethylformamide (DMF) solvent under a conventional heating. Our work also provides an isolation method of 3A5AF from the reaction mixture.

This work was started by testing the existing best system, $\text{B}(\text{OH})_3$ and NaCl in *N,N*-dimethylacetamide (DMA) solvent, under milder conditions and conventional heating (oil bath) to benchmark the operability window of this system with traditional reaction methods. It is known that the presence of both $\text{B}(\text{OH})_3$ and NaCl is essential (Figure S1). At a high temperature (160 °C), only a modest amount of 3A5AF was formed (Figure 1, top). Surprisingly, when the temperature was lowered to 140 °C, negligible production of 3A5AF was observed, despite almost complete NAG conversion. NaCl is poorly soluble in DMA, and therefore we speculate that even modest drop of temperature can dramatically decrease the concentration of chloride anions in solution, heavily affecting the performance. These results clearly show that new reaction systems need to be considered for obtaining 3A5AF under milder conditions with conventional easy handling.



Scheme 1. Synthesis of 3A5AF from NAG dehydration.

To develop a facile synthetic method of 3A5AF, we found that a commercial and inexpensive Lewis acid catalyst, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ works for this reaction (Figure S2). The reaction at 160 °C lead the yield of 3A5AF to be almost doubled (18% yield) compared to the previous $\text{B}(\text{OH})_3\text{-NaCl}$ system (Figure 1, bottom). A more remarkable finding is that this catalyst does not need additional chloride salts such as NaCl, making this new system completely homogeneous. When the reaction temperature was lowered this system retained the performance in a temperature down to 100 °C.

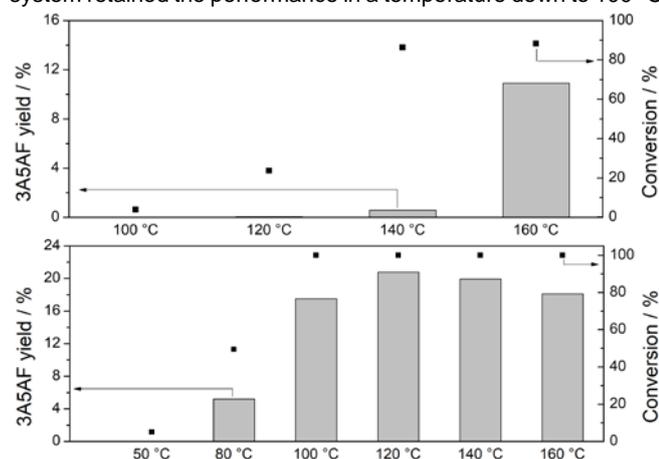
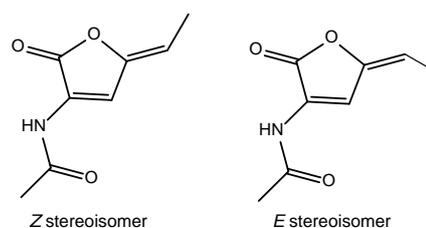


Figure 1. NAG dehydration to 3A5AF with (top) $\text{B}(\text{OH})_3\text{-NaCl}$ and (bottom) $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$. Reaction conditions: 5 mL of 5 wt. % of NAG in DMA, 1 h, $\text{B}(\text{OH})_3$ 1 eq. and NaCl 2 eq. for (top), $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 1 eq. for (bottom).

Before to investigate different reaction conditions we identified reaction by-products. Being chitin conversion a relatively unexplored area, many other interesting N-containing molecules may be produced and yet not identified. Identification of new N-containing products is very important to set the fundamentals for a future and more focused investigation. Previous studies have shown the formation of HMF in the 3A5AF synthesis, where elimination of the acetamido group occurs. Analysis of our HPLC chromatogram represented the second largest peak among by-products next to HMF. Preliminary analysis on this product clearly showed the presence of acetamido group, attracting our interest for a deeper characterization. Upon isolation by column chromatography a more accurate analysis with several NMR techniques and GC-MS was carried out (see Figures S7-S15 for full characterization), we found the structure of this product very likely resembling β -angelica lactone, but containing acetamido and ethylidene groups, named 3-acetamido-5-ethylidene furanone (AEF) (Scheme 2). The ^1H NMR analysis has suggested that our AEF is a mixture of E and Z isomers at a ratio of 1:7 for the ethylidene group. A very recent work carried out by Banwell *et al.* identified these two compounds amongst other new N-containing products obtained from chitin pyrolysis.¹⁶ The Z isomer is thermodynamically favorable perhaps due to less steric

repulsion, which is supported by Møller-Plesset perturbation theory (MP2)²⁰ and CBS-QB3^{21,22} calculations (Table S1). We noticed that this molecule possesses an intense and sweet fragrance resembling the scent of some dairy products, such as milk and yogurt. The yield of AEF was 1.5 to 4.7% in the reaction with AlCl_3 catalyst while 7% in the presence of $\text{Al}(\text{OTf})_3$ catalyst without any system optimization (Figure S3). If AEF synthesis will be targeted in future, this might represent a good starting point with still high scope of improvement.

3-acetamido-5-ethylidene furanone (AEF)



Scheme 2. Proposed structures of 3-acetamido-5-ethylidene furanone (AEF) isomers obtained as by-products of NAG conversion.

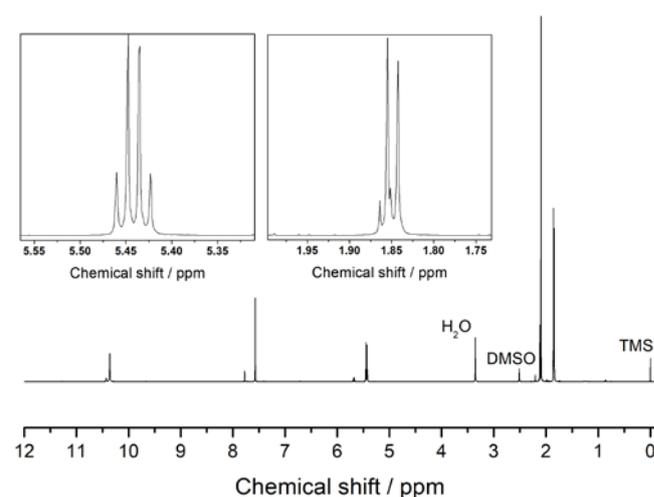


Figure 2. ^1H NMR spectra of AEF in DMSO-d_6 .

Given the encouraging results obtained in the synthesis of 3A5AF, more reaction parameters have been investigated. First, the choice of solvent is a decisive factor for the biomass conversion reactions. It has been already seen that for the production of 3A5AF the solvent array is quite limited only to N-containing aprotic solvents, while other solvents such as water and dimethyl sulfoxide mainly lead to chromogen I and III^{23,24} and to HMF.²⁵ Therefore, we tested DMF and *N*-methyl pyrrolidone (NMP) at different temperatures (Figure 3). NMP showed poorer performance and a more limited operational window, with 3A5AF yield decreasing above 140 °C. In contrast, DMF showed remarkable performance, leading to the highest yield of 3A5AF for this system (29%) at a temperature as low as 120 °C. Besides the good yield of 3A5AF, the possibility of working in a wide range of temperatures make this system very versatile and a very good candidate for performing practical one-pot reaction.

To demonstrate the usability of this reaction we performed a larger scale synthesis of 3A5AF with the following parameters: 5 wt. % NAG DMF solution 100 mL, 120 °C, Al to NAG molar ratio 1:1, reaction time 30 min. As a result, we obtained the same yield of 3A5AF (29%) as that in the 5 mL-scale reaction described above. The product was then isolated by a silica gel column

chromatography, giving 0.70 g (18 % isolated yield) of 3A5AF with purity above 98 wt. % (Figure S4). Our method is practical for the synthesis of 3A5AF at least in laboratory scale. The detailed procedure is reported in the SI.

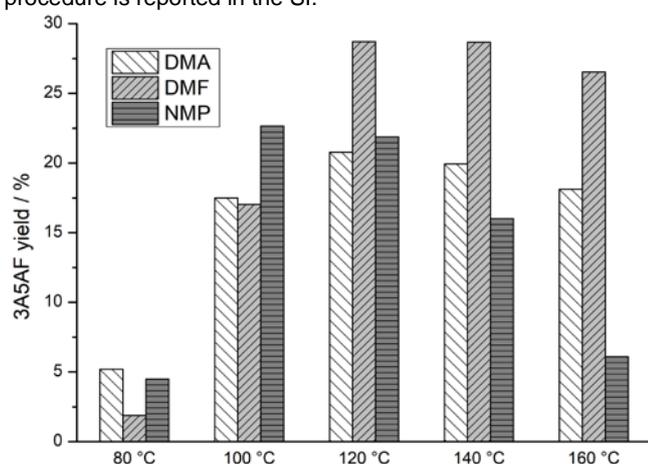


Figure 3. Temperature and solvent effect on 3A5AF formation. Reaction conditions: 5 mL of 5 wt. % of NAG, 1 h, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 1 eq.

Successively, we explored the influence of Al to NAG ratio and resulted that the formation of 3A5AF is not very sensitive to the ratio in the range of 0.5:1 to 2:1 (Figure S5). The ratio of 1:1 is found to be the optimal choice for this system.

Interesting findings were observed when the effect of NAG concentration was investigated. Substrate concentration is a very important factor in sugar chemistry; intermolecular interactions drastically decrease selectivity for desired products with increasing substrate concentration due to humin formation. Thus, specially designed systems are often required to gain the selectivity.²⁶ Our study, however, showed that the decrease in yield of 3A5AF was modest by increasing the NAG concentration from 1 to 15 wt.% (Figure 4). The maximum yield of 3A5AF (30%) was obtained at 2.5 wt. % concentration of NAG, but the yield was still 20% even at 10 wt. % NAG. Interestingly, as to the two by-products, AEF and HMF followed an opposing trend each other; AEF was more favored at higher NAG concentration, whereas HMF decreased. Formation of AEF may be enhanced by intermolecular interactions of substrate and intermediates. HMF has a reactive aldehyde group, and therefore undergoes intermolecular side-reactions, disfavoring high concentration.²⁶

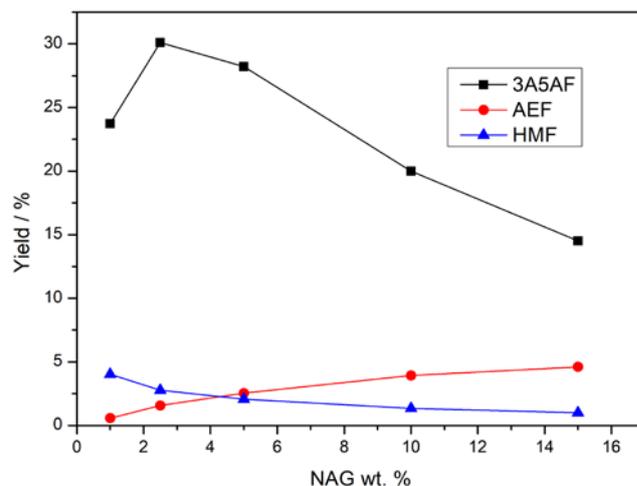


Figure 4. Yield of different NAG dehydration products as function of initial NAG concentration. Reaction conditions: 5 mL of NAG in DMF solution, 120 °C, 30 min, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 1 eq.

To have a better understanding of the kinetic, we studied time course of the NAG dehydration reaction by selecting three different concentration, specifically 2.5, 5 and 10 wt.% (Figure 5). Conversion of NAG is nearly completed after 30 min for all the cases, showing conversion value above 88%. We can clearly see that, for 2.5 and 5 wt. %, the yield of 3A5AF reaches the maximum at 30 min after increasing in a sigmoidal curve, and barely changes during the course of two hours, indicating good thermal stability. Instead, when a higher concentration of NAG is employed, 3A5AF is slowly produced, and continuously increased for all the duration of the experiment. The slower formation of 3A5AF might be due to higher concentration of water produced during the reaction, as this is a dehydration reaction. Water was found to be detrimental for the $\text{B}(\text{OH})_3\text{-NaCl}$ system.¹⁷ During early-stage parameters screening, we observed that addition of water (20 vol. %) drastically decreased the production of 3A5AF in our $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ system (Figure S6).

In summary, our new method of synthesizing 3A5AF (30% yield) can be performed completely using commercial reagents and standard laboratory equipment at the lowest temperature reported so far. Easy recovery of 3A5AF in high purity with simple column chromatography has also been demonstrated. Hence, our reaction would be successfully reproduced in any laboratory in order to obtain 3A5AF in good amount and with high purity so that making 3A5AF more easily accessible and expanding the investigation in this area. Additionally, a new interesting N-containing lactone, recently identify as a by-product of chitin pyrolysis, has been observed during liquid-phase catalysis under our reaction conditions and detailed characterizations have been provided.

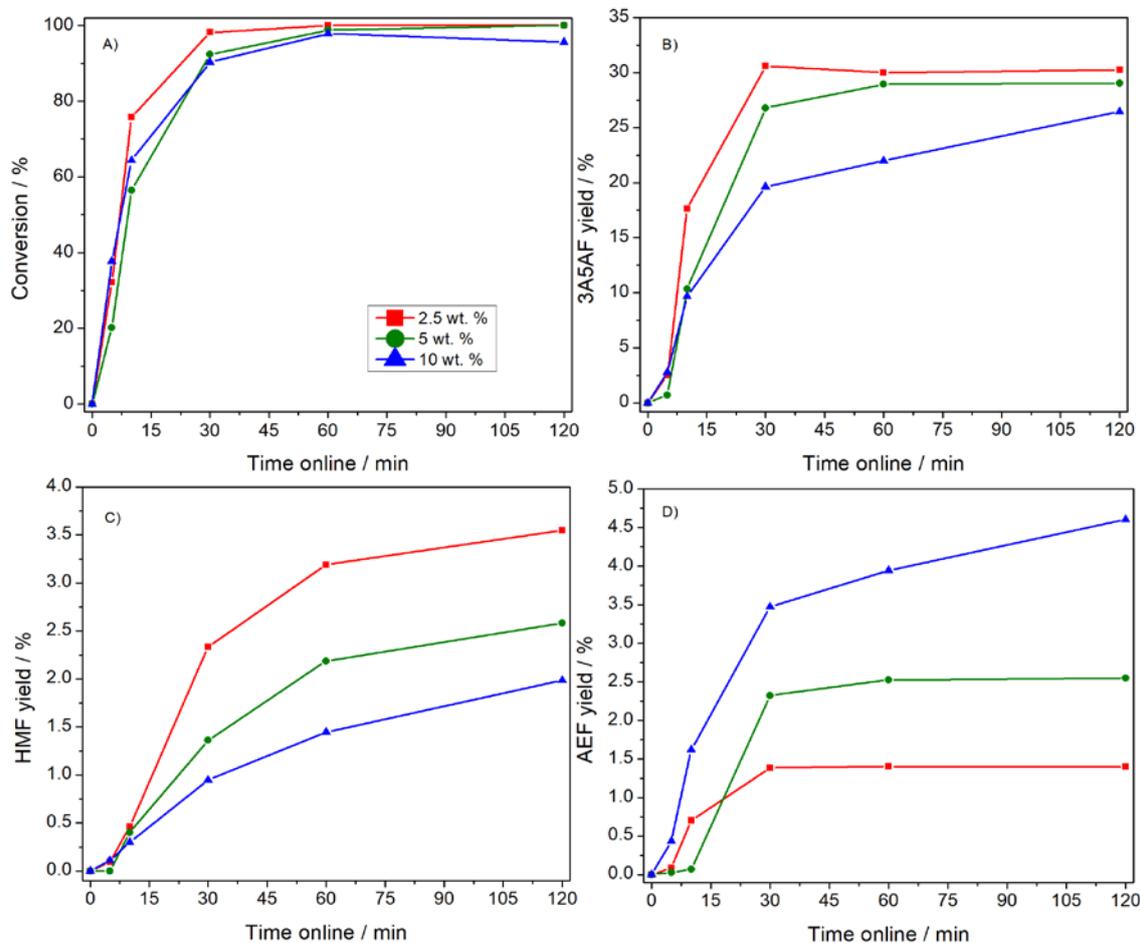


Figure 5. Time online plots of (A) NAG Conversion, (B) 3A5AF, (C) HMF and (D) AEF yields are plotted when different initial NAG concentrations are employed. Reaction conditions: 5mL NAG solution in DMF, 120 °C, $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ 1 eq.

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Keywords: biomass valorization • homogeneous catalysis • *N*-acetylglucosamine dehydration • aluminum catalysis • 3-acetamido-5-acetylfuran

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Entry for the Table of Contents



N-acetyl-D-glucosamine (NAG) dehydration was performed by using a cheap and commercial aluminum chloride salt. Reaction parameters screening, including solvents, temperature and catalysts, allowed us to maximize 3-acetamido-5-acetylfuran (3A5AF) yield at mild and easily reproducible conditions. Time course of the reaction showed that by-products formation and their distribution varied as function of initial NAG concentration. Finally, a highly functionalized new N-containing molecule was discovered and characterized.