1-1-2019

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Recent Advances in the Application of Carbohydrates as Renewable Feedstocks for the Synthesis of Nitrogen-Containing Compounds

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Keywords: carbohydrates, green materials, levulinic acid, furan, renewable feedstocks, biomaterials.

Abstract: Carbohydrates, in the form of chitin, chitosan and cellulose, are one of the most available, renewable, and sustainable chemical feedstocks. Their conversion to biofuels, fine chemicals, and industrially-relevant monomers is becoming increasingly viable and promising as innovation decreases the price of this technology, and climate change and the price of fossil fuels increases the social and economic costs of using traditional feedstocks. In recent years, carbohydrates have been increasingly used as sources for nitrogen-containing fine chemicals. This chapter, with 86 references, provides a brief overview of the conversion of carbohydrate biomass to the standard hydrocarbon and oxygen-containing derivatives, and then provides a survey of recent progress in converting the biopolymers, and the derived mono and di-saccharides, into nitrogen-containing molecules with a special focus on N-heterocycle synthesis for medicinal applications.

Keywords: Chitin, biomass, heterocycles, sustainable chemistry, cellulose, chitosan

Contents

Abbreviations

3A5AF	3-acetamido-5-acetylfuran
AgOTf	Silver Triflate
$Cu(OTf)_2$	Copper triflate
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFA	di-D-fructose dianhydrides
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dtbpy	4,4’-di tert butyl-2,2’-bipyridine
EG	Ethylene glycol
Fruf	Fructofuranosyl
Gal	Galactose
GC-MS	Gas chromatography–mass spectrometry
GPC	Gel permeation chromatography
GlcNAc	*N*-acetyl-2-deoxy-2-amino-D-glucose

1	Glcp	Glucopyranosyl
2	α-Gls	α-glucosidase
3	Gly	Glycerine
4	5-HMF	5-(hydroxymethyl)furfural
5	LA	Levulinic acid
6	LC-MS	Liquid Chromatography-Mass Spectrometry
7	2-MP	2-methyl pyrazine
8	Ms	Mesyl
9	MsCl	Mesyl Chloride
10	NAG	*N*-acetyl-2-deoxy-2-amino-D-glucose
11	NMP	N-methyl-2-pyrrolidone
12	PFH's	Pyrimidine Fused Heterocycles
13	PHPFH	Polyhydroxylated pyrimidine-fused heterocycles
14	PTSA	p-toluenesulfonic acid
15	Pyr	Pyridine
16	RT	Room temperature
17	THF	Tetrahydrofuran

1	TMSOTf	Trimethylsilyl Trifluoromethanesulfonate
2	Tf_2O	Trifluoromethanesulfonic Anhydride
3	USD	United States Dollar

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1. Introduction:

As the concurrence of concerns regarding climate change, and the inevitable knowledge that over the coming decades the price of oil will increase as a combination of scarcity and decreased reliance on it as an energy source will drive up the costs of fine chemicals, there is a growing interest in accessing complex materials, feedstocks and polymers from renewable resources.[1-4] One of the most promising potential sources are the polysaccharides, cellulose, chitosan and chitin. These form the predominant bulk mass of the material obtained from agricultural and fisheries waste products, and would make excellent sources of complex oxygenated materials for the future of the chemical and polymer industries,[5-7] and even as catalysts.[8] Research and manufacturing in this field has been ongoing for many years,[9] and there are many excellent recent reviews of the subject.[10-16] The primary intermediates generated from these waste polysaccharides are levulinic acid (LA) and 5-Hydroxymethylfurfural (HMF**, Figure 1**) derived from heating lignocellulose (a complex mixture of cellulose and lignins obtained from the waste biomass of crops and trees) in acid.[17] Sequential dehydrations lead to the formation of the thermodynamically preferred HMF, that can then be further oxidized and degraded to a combination of formic acid and LA.

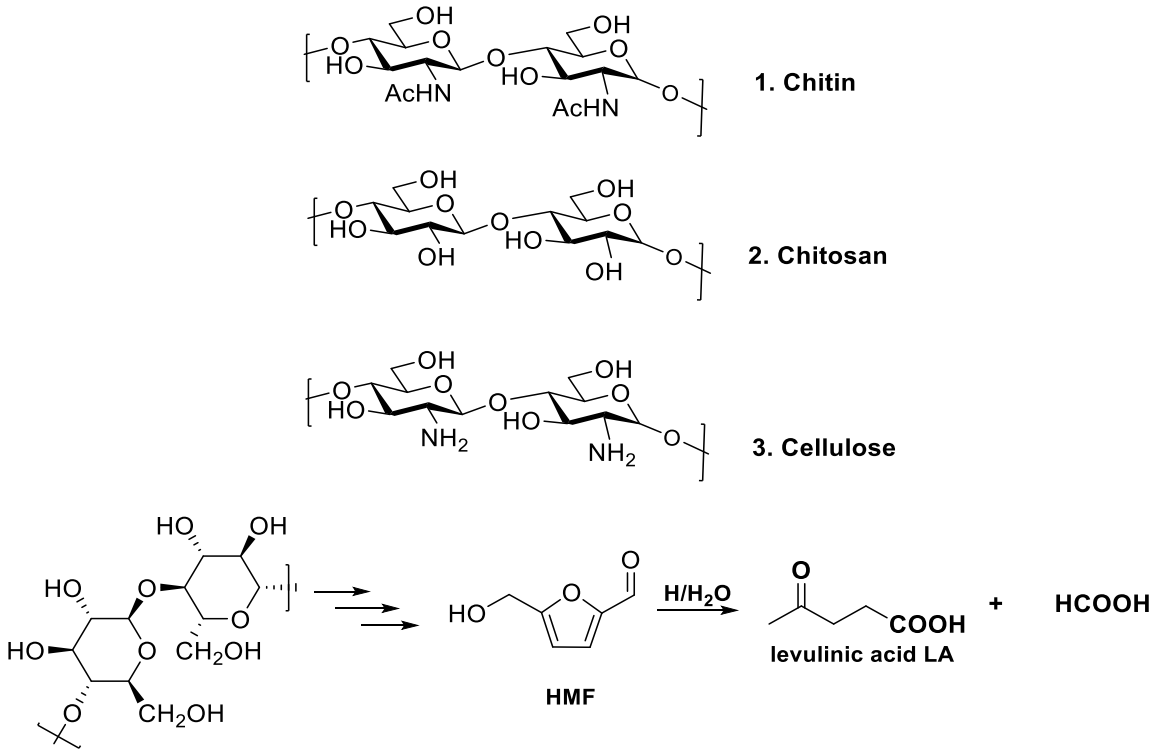


Figure 1. Structures of the three predominant sources of carbohydrate biomass: chitin, chitosan, and cellulose, and the primary degradation products obtained from these polysaccharides HMF and LA.

This current chapter seeks to describe recent advances in this field, with a particular focus on nitrogenous compounds derived from carbohydrates. It is divided into several sections: this introduction; a very brief overview of the chemistry of carbohydrate conversion to LA and HMF; a discussion of some recent work derivatizing HMF into complex natural-products; a discussion around the elaboration of HMF with nitrogen-containing functionalities; a review of the synthesis of nitrogen-containing heterocycles with HMF functionalities; and a review of the preparation of nitrogen containing heterocycles from HMF.

2. Levulinic Acid and Derivatives

Levulinic acid is the end-product of the acidic digestion of the carbohydrate feedstocks. It has been extensively examined as a potential starting material for the preparation of biofuels, and other materials.[18] This has been an extensively reviewed class of transformations, and there are numerable excellent studies investigating particular aspects or products that can be accessed from this important material including β-acetylacrylic acid, succinic and acrylic acid, acetic acid,[19,20] and γ-valerolactone[21] (**Figure 2**).

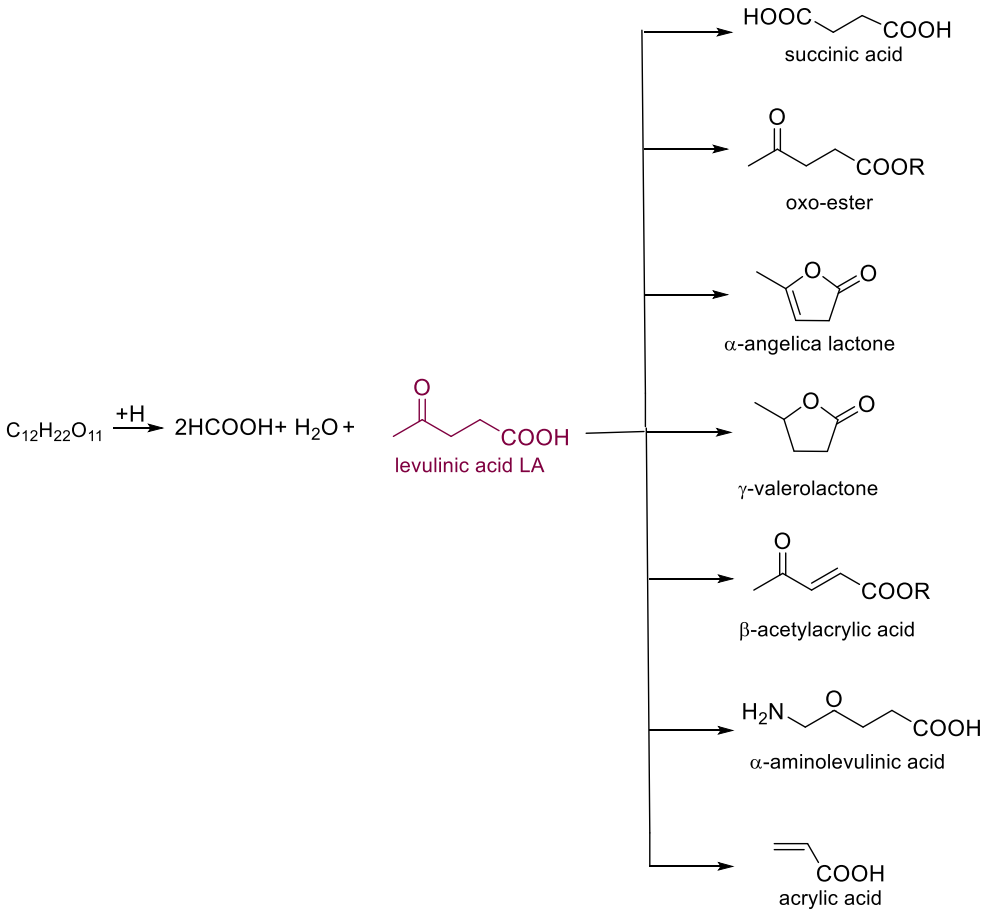


Figure 2. Possible Products Derived from Levulinic Acid

A recent advance in the field was provided by Mika and Dibó, who demonstrated that polysaccharides, both cellulose and chitin, could be readily converted to levulinic acid under microwave irradiation, accelerating the transformation.[22] Estimates indicate that innovation could drive the production costs as low as 0.08-0.20 USD per kg of LA.[23] The flexibility and ease of synthesis of this material shows great promise, especially as it can access the incredibly important acrylic acid monomer.[24] There is also significant discussion about using LA and other cellulosic derivatives as a route into biofuels.[25] However, the deoxygenation and defunctionalisation of levulinic acid is not economically ideal due to the loss of the complex oxygenated functionalities. Additionally, it is not currently a particularly energy efficient process, although this could evolve over coming decades as oil prices increase and biomass conversion improves.[26,27] Thus, the potential for levulinic acid to provide access to other heteroatom-containing systems[28] such as maleic anhydride through oxidation using vanadium-based catalysts,[29] and the nitrogenous systems described below, might prove a more fruitful use for this material, especially as bio-oil becomes increasingly viable.[30]

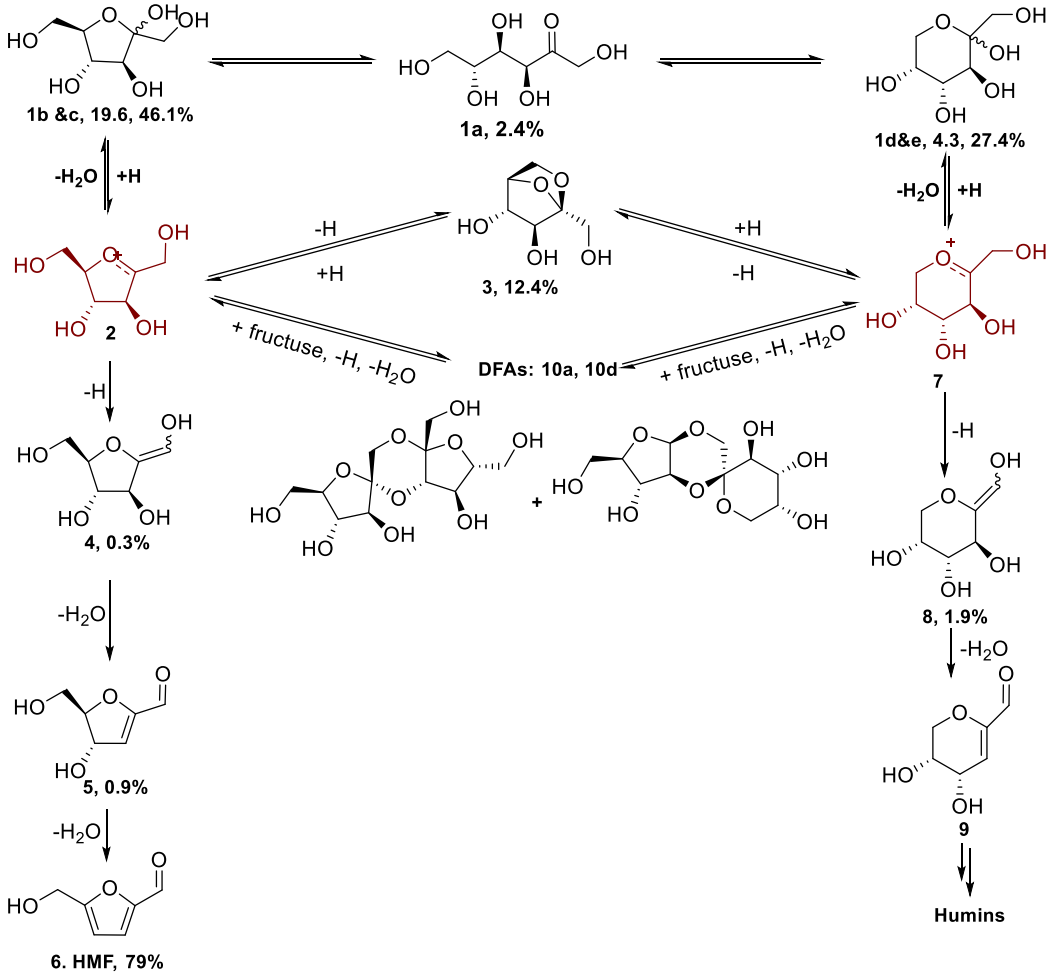
3. Complex derivatives from HMF

3.1 HMF Overview

5-(Hydroxymethyl)furfural (5-HMF, **6**) is commonly synthesized from chitosan *via* its monomer GlcNAc, prepared from hydrolyzing chitosan with strong acid, often nitric acid with DMSO as solvent. There have also been other reports using different organic acids in the presence of DMSO for the synthesis of 5-HMF. Significant effort has been dedicated to identifying more efficient routes to HMF, especially through the dehydration of carbohydrates;[31-34] however most suffer from low yields. The major complication is the complex thermodynamics of this system which leads to the generation of a variety of by-products, including the humins,[35] as well as a

mixture of various oligomers and polymers that can foul the reaction vessel making the transformation complicated to perform on an industrial scale. A better understanding of the pathways and energetics involved could provide important information about the preferred biofeedstocks or the nature of any required pre-treatment. Horvath and co-workers have extensively investigated these issues, especially through careful characterization of the by-products.[36] Much of this science revolves around the formation of fructose, a necessary intermediate in most of the conventional approaches to convert glucose to HMF, involving **1b** and **1c**.[37,38]

3.2 Mechanism of Formation of HMF

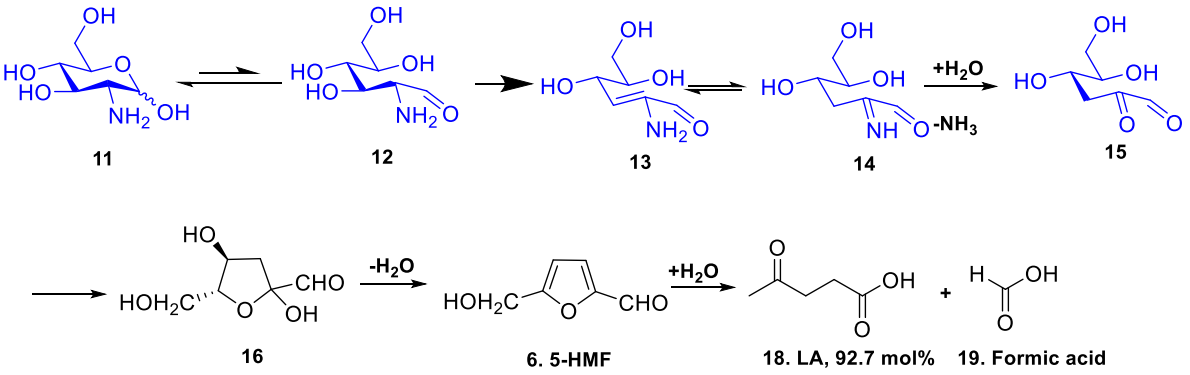


Scheme 1. Formation of HMF and By-products Acid Catalyzed Dehydration Processes.

The acid-catalyzed elimination of water from the furanose form of fructose, providing fructosyl oxocarbenium ion **2**, is the preferred thermodynamic pathway, **Scheme 1**. This oxocarbenium is highly sensitive to anhydro-sugar formation, and the C-6 hydroxyl group can attack intramolecularly, to provide bicyclic **3**. The same oxocarbenium is also highly susceptible to dimerization to form di-D-fructose dianhydrides (DFA) which are reversibly generated. Both pathways can isomerize the furan ring to the pyran. Productively, oxocarbenium **2** can be resolved through α-deprotonation to generate enol ether **4**. Under acidic conditions, this rapidly equilibrates to the enal **5**, which rapidly dehydrates to generate the aromatic HMF *via* dehydration. In the pyran series, oxocarbenium **7** can follow similar chemistry through **8** to **9**. With an inability to collapse to a low energy aromatic structure, this material generally decomposes to the highly-branched polymeric humin polymers. Curiously the balance of these intermediates fluctuates significantly as the reaction proceeds: in early stages, and in concentrated reaction mixtures, the oxocarbeniums appear to be sequestered as complex **3**, and over time this is consumed through its downhill transformation to HMF or humins. However, as the concentration of water increases, the material primarily returns to resting as either furanosyl sugar **1b** or **1c**, and the solution concentration of both **3** and **4** drops. They determined that the rate-limiting step of this entire mechanism if the tautomerization of oxocarbenium **2** to **3**. Consequently, adjusting the concentration of the reaction mixture has little impact on the yield or reaction rate as has been noted experimentally. There appears to be a theoretical maximum to the yields when using protic solvents.

3.3 Alternative Routes to HMF

Alternatively, gentler conditions can be used: Kerton reported the generation of levulinic acid (4-oxopentanoic acid, LA) and 5-hydroxymethylfurfural (5-HMF) *via* Lewis acid catalyzed hydrolysis of Chitosan under microwave conditions with $SnCl_4 \cdot 5H_2O$.[39] This approach provided higher yields than traditional protic acid chemistry, providing 23.9 wt% LA and 10.0 wt% HMF when run under concentrated or dilute conditions respectively. The proposed mechanism (**Scheme 2**) involves the chelation of the Lewis acid to the C2-amine, which in turn weakens the glycosidic bond. This makes the system more sensitive to hydroxide attack at the anomeric position, hydrolysing the polymer. Elimination of the C3-hydroxyl generates the enal (**13**) which can tautomerize to the imine (**14**) and hydrolyze to the 1,2-dicarbonyl species, **15**. Kinetic cyclization to **16**, followed by double elimination generates the 5-HMF (**6**).



Scheme 2. Synthesis of levulinic acid through formation of 5-HMF from glucosamine **11**.

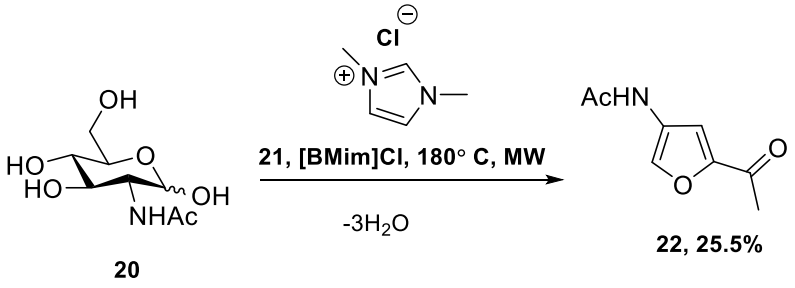
Other catalytic processes are also showing significant progress, as are engineering controls. Chemoenzymatic approaches that combine primary processing in a bioreactor with HMF-formation in traditional chemistry processes also show promise.[40] Consequently, it seems likely

that alternatives to the protic acid process will become highly viable industrial processes allowing for the generation of large amounts of HMF for further derivatization. HMF can readily used for derivatization to levulinic acid (**18**), and can also act as a source for other simple structures through simple treatment: for example, 5-(chloromethyl) furfural can be prepared from HMF in the presence of HCl.[41] However, most efforts have focused on hydrocarbons or carbon-oxygen species. The core furan ring, however, provides significant opportunities for elaboration with nitrogen to access biomedically-relevant materials, and this progress is the focus of the remainder of this review.

4. Amine-substituted derivatives of HMF

4.1 Ionic Liquids as Mild Reagents

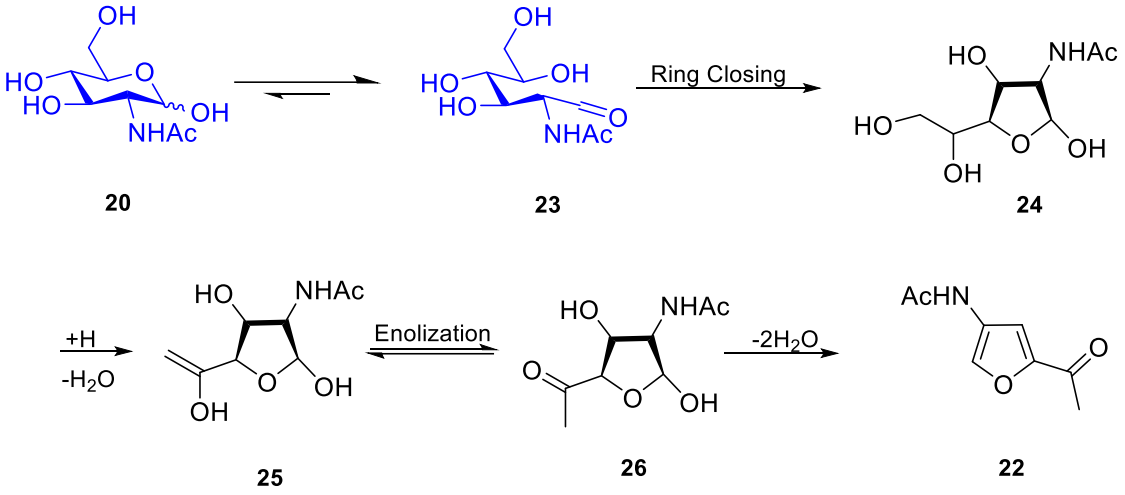
The furan core provides a useful pharmaceutical pharmacophore,[42,43] and the presence of the C-2 amine on chitosan and chitin allows for ready access of 3-amino substituted furans if it can be retained during the hydrolysis. One way to do this is to use more gentle conditions. Ionic liquids are non-flammable, non-volatile, re-usable materials.[44] They're generally considered as "green solvents" due to their easy recyclability, and have seen increasing use in carbohydrate chemistry as their polarity provides an attractive alternative to the often incompatible water.[45,46] Previously, research on the generation of "renewable" amines have been done through the use of ammonia as the nitrogen source.[47] The work presented by Kerton[48] was the first reported using NAG as a source of nitrogen in the nitrogen-containing furan derivatives. They reported the direct conversion of NAG (**20**) to 3-acetamido-5-acetylfuran **22** (3A5AF) in a reasonable yield of 25.5% (**Scheme 3**) *via* an ionic liquid-solution phase approach. 3-acetamido-5-acetylfuran has been previously identified as part of the complex mixture obtained from the thermal degradation of NAG, but only in a 2% yield.[49,50]



Scheme 3. Direct conversion of NAG to 3-acetamido-5-acetylfuran.

In their initial attempt, NAG and ionic liquids were mixed and heated under microwave conditions with quantitative reaction monitoring using calibrated LC-MS analysis. The dehydration was followed at 120 ˚C in six different ionic liquids including 1-ethyl-3-methylimidazolium bromide ([EMim]Br) and acetate ([EMim]OAc); 1-butyl-3-methylimidazolium chloride ([BMim]Cl), bromide ([BMim]Br), and acetate ([BMim]OAc); and 1,2-dimethyl-3-butylimidazolium chloride [BMMim]Cl (**21**). The reactions were investigated with various hydrocarbon and anionic additives. The results indicated that the best conditions of those screened treated NAG in [BMim]Cl at 120 ˚C for 3 minutes in the microwave to provide a 14.1% yield of 3A5AF; however, when the temperature was increased to 180˚ C, the product was obtained in a 25.5% yield. With preferred temperature and ionic liquid identified, the nature of the additives was investigated. The addition of a small amount of water, often critical for biomass transformations, showed only a minimal change in the observed yield (28.7 %). During the reactions, a minor impurity had been detected and identified as 1-methylimidazole, which could be isolated in the organic phase following work-up. This material was proposed to result from the partial thermal decomposition of the ionic liquids. Addition of 1-methylimidazole to the reaction however reduced efficiency significantly, and only a 2.9 % yield of 3A5AF could be isolated. The

study concluded that using more inert reaction conditions would improve the yield as they suspected that the presence of the ionic liquids catalyzes the decomposition of the final products.



Scheme 4. The proposed mechanism of formation of 3A5AF (**22**).

The proposed mechanism justifies the difference between this and the other approaches described above. Under aqueous acid and the high temperatures employed, the NHAc group is hydrolyzed and the resulting amine undergoes the elimination sequence described above in Scheme 1. Under dryer conditions, this sequence is unlikely. Hydrogen-bonding between the imidazolium ring and the carbohydrate favours the open chain form **23** to a much greater extent than in water **(Scheme 4)**. The ionic liquid disturbs the usual equilibria of the hexoses, and a significant amount of the furanose form **24** can be generated. Elimination of the C-6 hydroxyl provides enol **25**, and this readily tautomerizes to the ketone form **26**. Two eliminations, favourable in the low-water environment (presumably first of the C-3 hydroxyl to set up the enone, and rapidly thereafter of the anomeric hydroxyl group to generate the aromatic furan) provide the N-acetylated product **22**. Although NAG is the monomeric unit of chitin, breaking the polymer down into the parent monosaccharide is challenging and the same conditions are not necessarily amenable to a

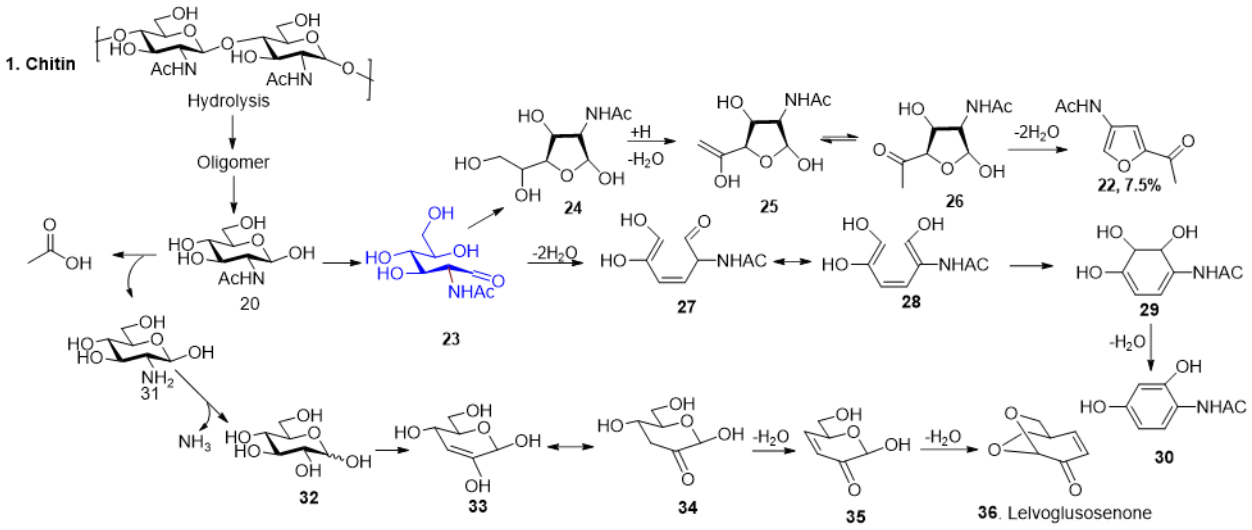
direct conversion of the bio-feedstock chitin to a furan derivative. Building upon this success Kerton and Yan, in 2014, reported the first direct efficient conversion of chitin into this same N-containing furan derivative (3A5AF).[51]

4.2 High Boiling Point Solvents for Thermal Conversion of Chitin to N-Acetyl Furans

Heterocyclic compounds such as pyrroles, pyrazines, furans, and pyridines have been obtained by the pyrolysis or radiolysis of chitin, and chitosan to generate volatile aromatics, but these approaches are extremely energy inefficient, very low yielding, provided a complex mixture of products. Additionally, many of the materials lost their nitrogen-content during the transformation.[52,53] The added challenges in working with chitin itself instead of the monomer to produce 3A5AF (**22**) include controlling the degradation of the chitin, avoiding denitration that can readily occur in aqueous acid, and physically breaking up the polymer aggregates that make chitin such a highly insoluble material to work with. Thermal decomposition in the presence of ionic liquids had clearly proven practicable for the conversion of the monomer, and consequently high boiling point solvents were investigated including ethylene glycol (EG) and glycerol (Gly), which are well suited to disturb the inter- and intra-chain hydrogen bonding network present in the biopolymer. These solvents were coupled with the usual polar aprotic solvents to remove the water formed during the conversion process, as water clearly could lead to denitration. However, no product was observed under any of the examined reaction conditions at 215° C in the presence of lithium chloride as a Lewis acid. Other additives, such as HCl or boric acid did result in the formation of low yields of 3A5AF, but the presence of protic solvents, either EG or Gly completely suppressed product formation. NMP proved to be the best solvent, and 215 °C provided higher yields than either lower or higher temperatures. Alternative additives were screened, including heteropolyacids, metal chlorides, various bases, and organic and inorganic acids. Most bases, the

heteropolyacids, and the organic acids completely inhibited product formation, while metal chlorides afforded the N-acetylated furan in a low yield. Boric acid proved to be the most effective additive for the reaction, providing 3A5AF in a very modest yield of 3.6%. The challenge with the system is the incompatible requirements of the various steps (Scheme 4). Chitin hydrolysis requires water and the ability to solubilize the chitin chains, breaking up the aggregates formed by the very strong hydrogen bonds; while NAG conversion requires mildly Lewis Acidic conditions, and the absence of water to drive the reaction forward and avoid the elimination or hydrolysis of the NAG group. The best results were obtained by using either $CrCl_3$, LiCl, NaCl or $CaCl_2$ in combination with boronic acid; and further improvement was attained using dry HCl. Adding water was also examined: it would certainly accelerate the hydrolysis of chitin; however, it would reduce the rate of dehydration and decrease the solubility of chitin in the solvent. Water showed only an adverse effect on the yield through reducing the conversion of starting material: clearly the solubility of the chitin plays a leading role in determining the pattern of this reactivity. GC-MS analysis was used throughout to identify the by-products formed in this complex mixture including 4-(acetylamino)-1,3-benzenediol (**30**), levoglucosenone (**36**), and acetic acid. The research team also identified nitrogen in the inevitable black solid, a chitin-derived analogue of the humins. A mechanistic pathway is proposed to explain these outcomes and to demonstrate the complexity of the competing reactions. Arising from this analysis, and disregarding the complex possibilities involving polymeric chitin, or higher order oligomers, three main sequences define the fate of the NAG under these conditions (**Scheme 5**). The first pathway involves the route described above: a formation of the furanose, followed by enolization, and aromatization to provide the desired product. In the second pathway, a proposed diene is generated through the double dehydration of NAG; keto–enol tautomerism provides the hexatriene that would undergo a rapid electrolytic

rearrangement, which followed by dehydration, would generate the amide-substituted resorcinol. In the final pathway, acetic acid is first produced by hydrolysis of the amide; a sequence of eliminations and tautomerizations leads to **36**.



Scheme 5. Proposed mechanistic pathways leading to the synthesis of levoglucosenone, 3A5AF, and 4-(acetylamino)1,3-benzenediol.

5. Nitrogenous heterocycles from sugars

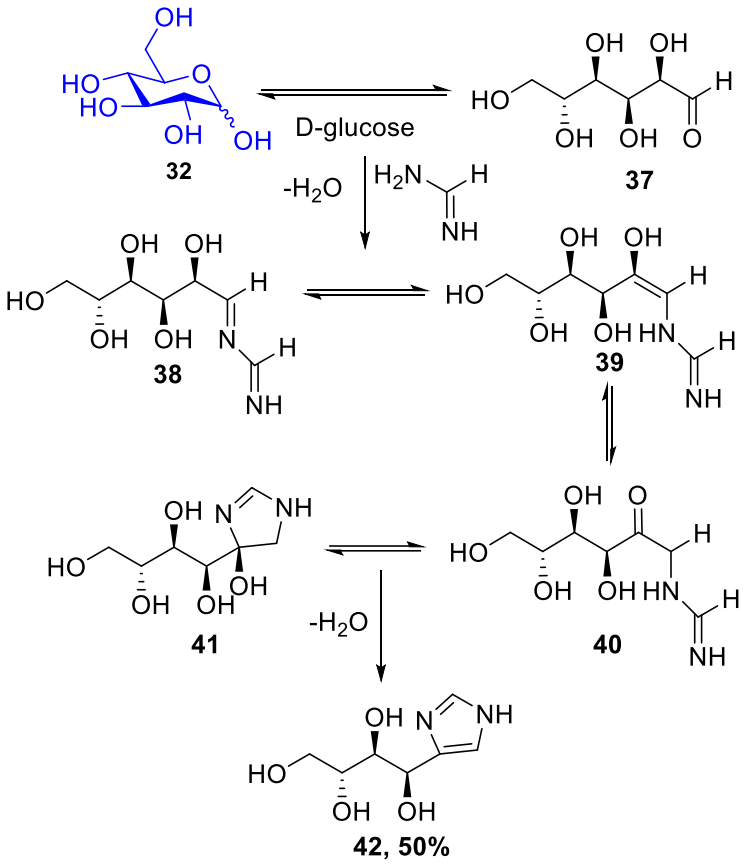
5.1 Elaboration of a nitrogen heterocycle

5.1.1 Synthesis of Imidazoles

Although these routes retain the nitrogen of the chitin, more interesting products can arise through interrupting the degrading carbohydrates with a trapping moiety to generate pharmaceutically relevant materials. The synthesis of glycoconjugates with medicinal activity is a very broad subject but using carbohydrates as a source of polyhydroxylated chiral side chains rather than as carbohydrates *per se* is a promising avenue to access new chemical space.

This can allow for the *in situ* generation of highly complex decorated heterocycles, including many involving nitrogen. Some of the earliest of this work was done by Streith, attempting to provide a rapid, protecting-group-free access of glycosylated bioactive imidazole derivatives.[54] In a recent iteration of this approach,[55] Brust and co-workers reported a procedure to obtain disubstituted imidazoles with elaborate poly-hydroxylated side-chains derived from mono- and disaccharides using a high pressure *de novo* heterocycle synthesis employing D-fructose or D-glucose, ammonium carbonate and formamidine acetate, or higher order derivatives, as the source of the imidazole nitrogens.

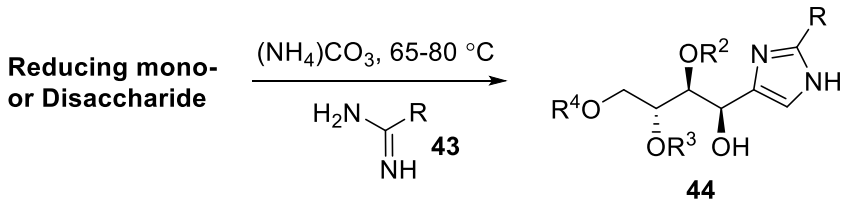
Several different amidines were used as the nitrogen source to generate a small library of 2-substituted imidazole derivatives using ammonium carbonate as acid. The very mild reaction conditions enable this methodology to be readily adapted using different mono- or di-saccharides (and presumably higher order systems as well) to obtain a variety of different products. The combination of formamidine acetate, ammonium carbonate, and carbohydrates (5:1.6:1) forms a low viscosity melt above 60 °C allowing for easy agitation. Presumably the ammonium carbonate decomposes *in situ* to generate ammonia, water, and carbon dioxide, providing a very convenient high concentration ammonia solution. Mechanistically, the carbonyl moiety of the carbohydrate condenses with the amidines (derived from the aminolysis of imido esters or their salts by ammonia, **(Scheme 6**), and undergoes an Amadori rearrangement,[56] to provide ketone **40**, which condenses with the remaining primary amine to provide the imidazole after aromatization in 50% yield.



Scheme 6. Proposed mechanism of imidazole (**42**).

In this same report, the team investigated large scale synthesis of hydrophilic tetrahydroxybutyl imidazoles with different glycosidic linkages from available disaccharides: melibiose, leucrose, maltose, cellobiose, lactose, lactulose, and isomaltulose, most of the readily available disaccharides **Scheme 6**. Maltose, cellobiose, lactose, isomaltulose and lactulose are bulk-scale, readily available, and sustainably isolated.[9] They generated the 2-substituted imidazoles in a one pot procedure, using ethylacetimidate, formamidine acetate, and benzylamidine hydrochloride to

introduce a 2-phenyl or 2-methyl moiety into the imidazole. They used the reducing-end ketose, isomaltulose (α-D-Glcp-(1→6)-D-Fruf), as their test case to investigate its applicability to the reaction, and the stability of the glycosidic linkage towards their reaction conditions. The results indicated successful conversion of starting materials to the products, but the amidines are not highly tolerant of substitution, and the yield decreased for both the methyl, and especially the phenyl substituted products. This was attributed to the higher degree of hydrolytic instability of the substituted amidines under the ammonium carbonate melt conditions, and was consistent with the observation that reactions with benzylamidine produced a significant amount of benzoic acid amide as an isolatable side-product. The highest yields were obtained with isomaltulose (49%) with the other disaccharides showing lower conversions (25-40%); this is consistent with the observation that the ketose fructose provided a higher conversion to product (50%) than the aldose glucose (47%). This does not appear to be a theoretically-limited yield reaction, as the moderate yields are justified through the loss of this highly polar material on the silica chromatography columns or the generation of polymeric Maillard by-products **Table 1**.



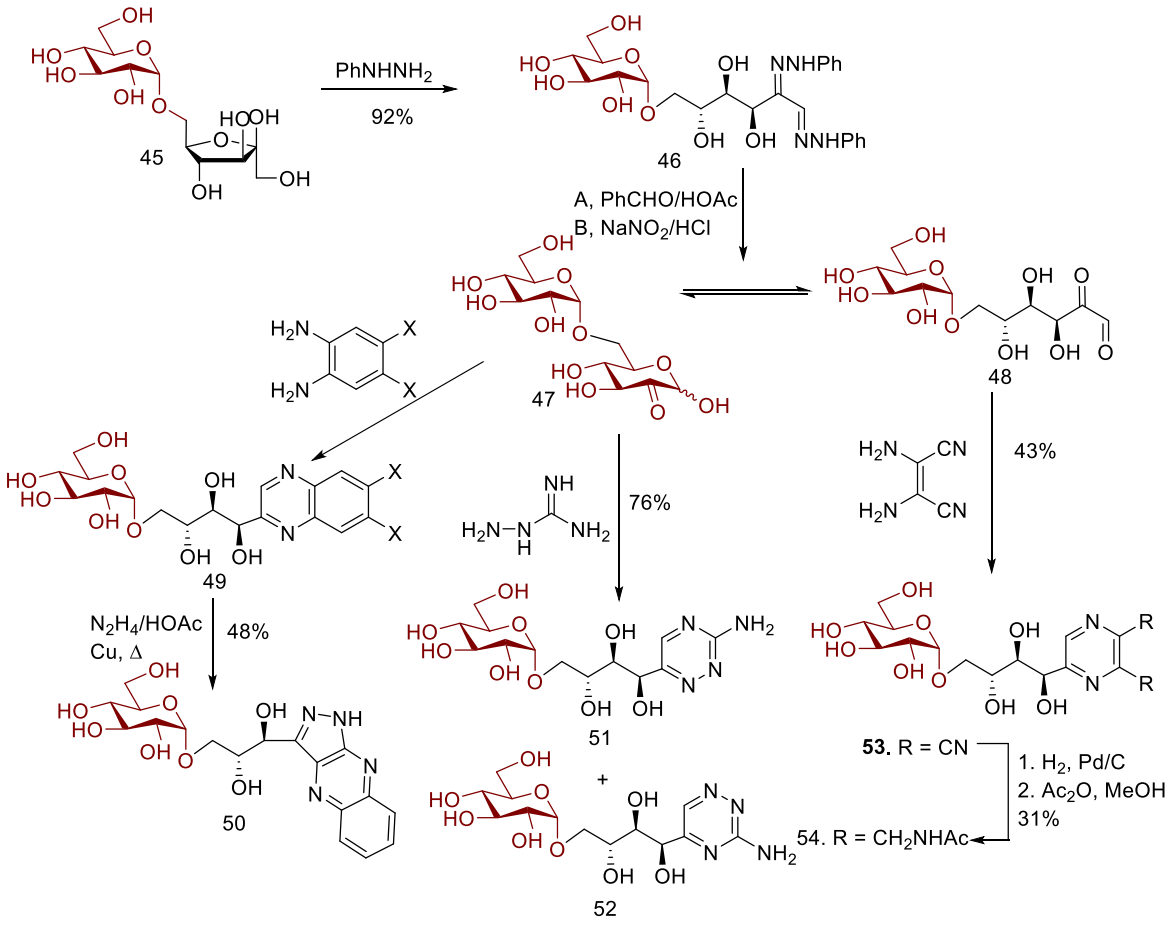
Scheme 6. Condensation of Carbohydrates with Amidines in an Ammonium Carbonate Melt.

Table 1. Conversion of sugars into imidazoles using different amidine sources as shown in Scheme 6.

Sugar	R	R4	R3	R2	Yield %
Fructose	H[a]	H	H	H	50
Glucose	H	H	H	H	47
Isomaltose	H	α-D-Glc	H	H	49
Isomaltose	Me[b]	α-D-Glc	H	H	30
Isomaltose	Ph[c]	α-D-Glc	H	H	5
Melibiose	H	α-D-Glc	H	H	38
Melibiose	Me	α-D-Glc	H	H	27
Leucrose	H	H	α-D-Glc	H	38
Leucrose	Me	H	α-D-Glc	H	26
Maltose	H	H	H	α-D-Glc	28
Cellobiose	H	H	H	β-D-Glc	25
Lactose	H	H	H	β-D-Gal	40
Amidines applied in this research: a) Formamidine acetate. b) Ethylacetimidate. c) Benzamidine					

5.1.2 Synthesis of Quinoxolines, Triazines, and Related Heterocycles

In a follow-up report, the research team used 2-aminoanilines in combination with hydrazines to trap the same Amadori rearrangement products into polycyclic heterocycles: the pyrazoloquinoxalines, quinoxalines, and 1,2,4-triazines.[57] Again, the yields are better for the ketoses than the aldoses, and the products are obtained in useful yields (**Scheme 7**).

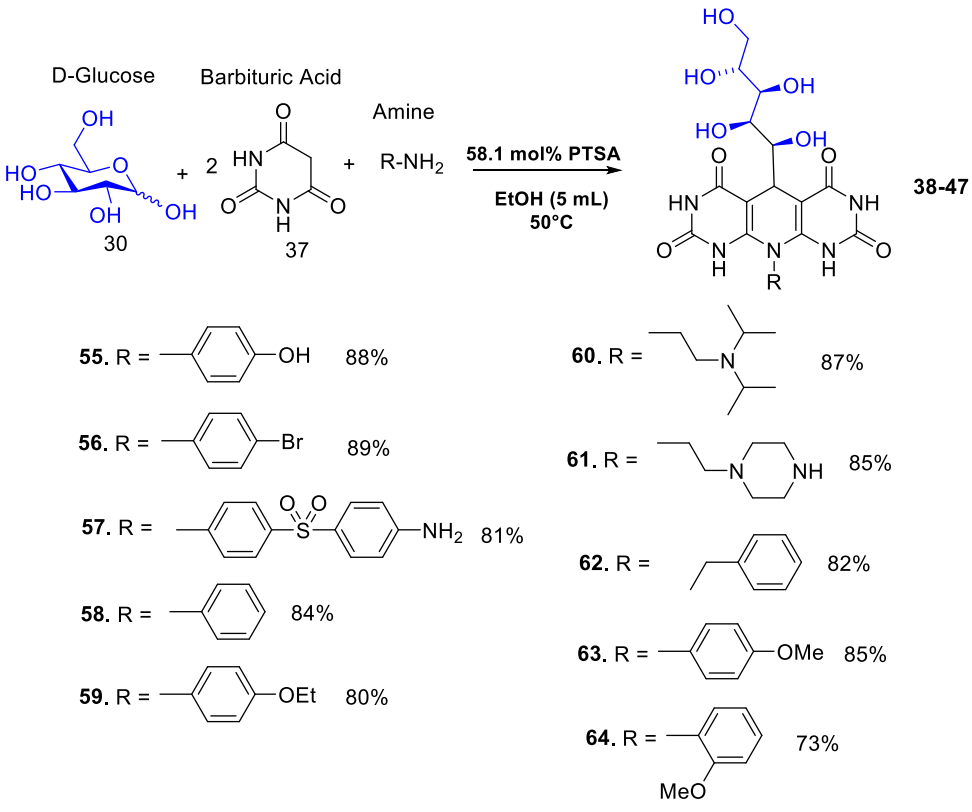


Scheme 7. Synthesis of Polycyclic Heterocycles, Pyrazoloquinoxalines, quinoxalines, and 1,2,4-Triazines.

5.1.3 Synthesis of Pyrimidine-fused Heterocycles

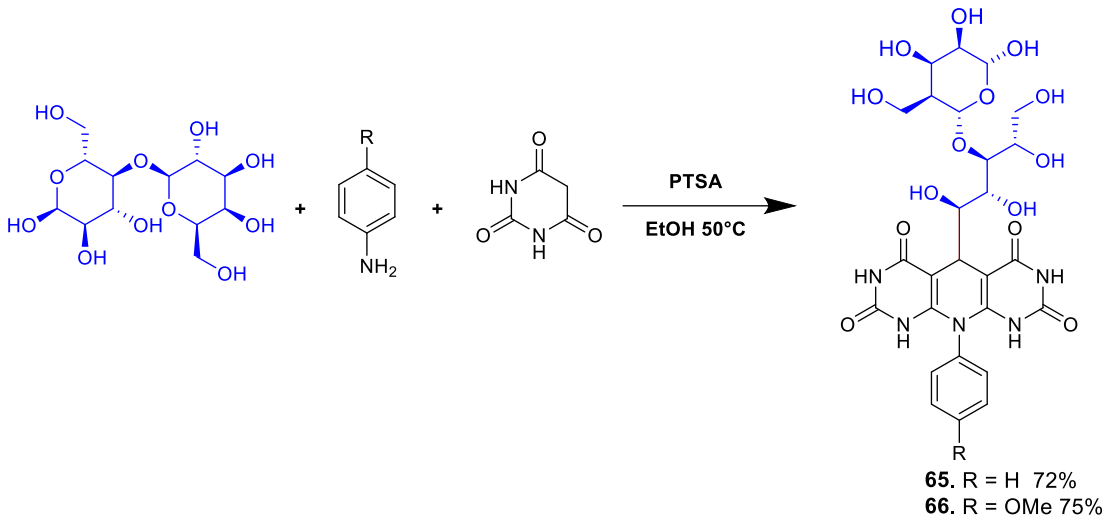
Pyrimidine-fused heterocyclic (PFH) compounds have attracted much attention due to their various biological activities[58,59] such as antioxidant effects, tyrosine kinase inhibitory activity,[60,61] antimicrobial,[62] anticancer,[63,64] antiviral activity,[65] and anti-inflammatory properties.[66] Building on this chemistry, Yousefi and Khalafi-Nezhad reported the first synthesis of PFH derivatives, riboflavin analogues, that act as inhibitors of α-Glucosidase (α-Gls).[67] They synthesized a series of polyhydroxylated pyrimidine-fused heterocycles (PHPFH) incorporating either aliphatic- or aromatic N-substituted systems, and then they investigated their glycosidase inhibitory activities

(Scheme 8). This enzyme plays a significant role is the progression of type II diabetes. (+)-D-glucose and primary amines or anilines were treated with barbituric acid and catalytic *p*-toluenesulfonic acid in ethanol to obtain complex tricyclic products in good yield (**Scheme 8**). Compounds **55-57, 60**, **61** were then screened against both yeast and mouse α-Gls enzymes to determine their inhibitory activity. The aromatic-substituted systems showed stronger inhibitory activity than their aliphatic counterparts with the best performing 4-(4-aminophenylsulfonyl) phenyl **(57)** demonstrating low micromolar non-competitive inhibition with the yeast enzyme, and competitive inhibition against the mouse enzyme, and this difference in activity was ascribed to different binding modes with the two different enzymes.



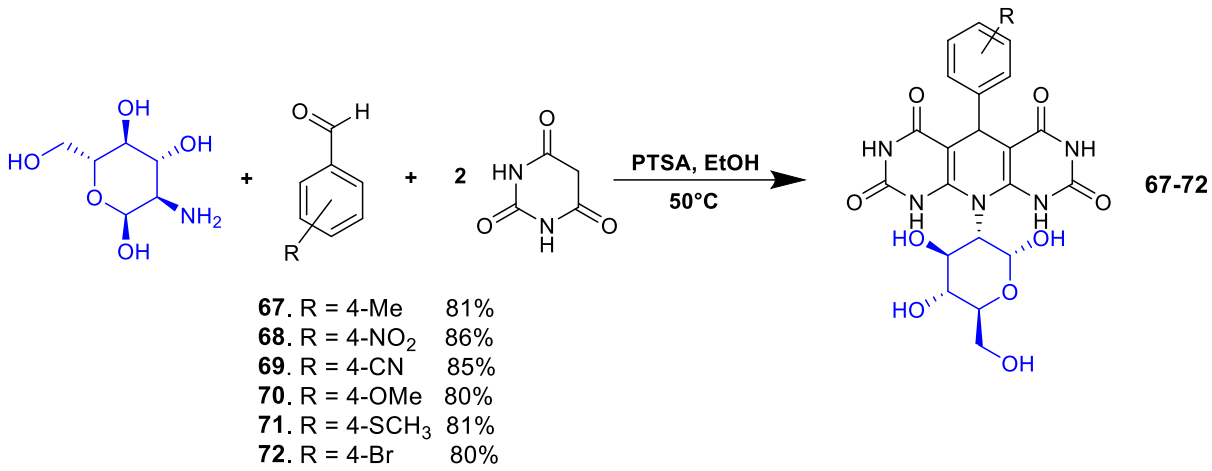
Scheme 8. Yousefi and Khalafi-Nezhad's Synthesis of Poly-Hydroxy Functionalized Pyrimidine-Fused Heterocycles (PHPFHs) using the reaction of D-(+)-Glucose, Barbituric Acid and Amines.

They then extended this research into additional sugars with additional anilines.[68] Electron-rich anilines (**55,58,59, 63, 64**) proved to provide better yields of the required tricyclic system, (>73% for the three component reaction). Glycosidic bonds are stable to the reaction conditions, allowing for functionalization with di-, oligo-, and poly-saccharides (**Scheme 9**).



Scheme 9. Coupling of Aniline with Lactose (Disaccharide).

The reactivity could be inverted by using benzaldehyde derivatives and 2-deoxy-2-amino sugars like glucosamine. Unlike the aniline case above, the nature of the substituent on the benzaldehyde had little effect on the yield of the reaction (**67-72**). This allows for the easy introduction of complex functionality (**Scheme 10**). Again, these types of molecules might show promise as vitamin B_2 analogues and competitive inhibitors or chemical biology probes.



Scheme 10. Expanded Scope of Amino Sugars Coupling to Functionalized Benzaldehydes.

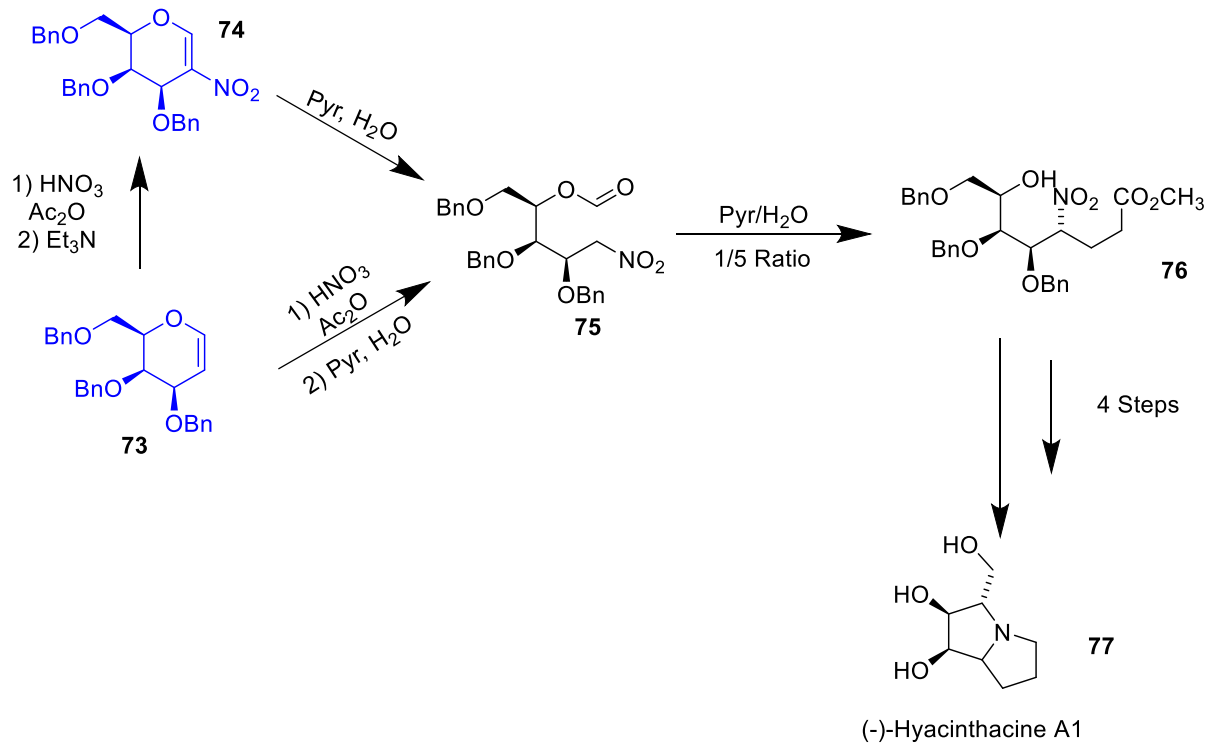
5.2 Formation of N-heterocycles from carbohydrates

5.2.1 Synthesis of Pyrrolizidines

The above examples used either the aldehydes, dicarbonyls, or amine functionalities on carbohydrates to form new heterocycles. However, the carbohydrate chain itself was not integrated into the heterocycle. Alternatively, the alkyl chain of the carbohydrate can provide direct access to highly functionalized nitrogen-containing heterocycles. These can be difficult targets to access in other ways: carbohydrates can provide an excellent route to these compounds, especially as the monosaccharides can be readily obtained from biomass waste.[69] The following examples demonstrate how simple carbohydrates can be converted into valuable nitrogen-containing heterocycles for both pharmaceutical and bulk chemical applications.[70]

Pyrrolizidine based heterocycles are found naturally in many plants, and are generally very toxic, acting as defense mechanisms against herbivore consumption.[71] Xin-Shan Ye recently reported a simple synthesis of these bicyclic scaffolds from nitroglycals (**74**), which are readily accessible from the parent glycal,[72] and are useful reagents to access bicyclic and C-glycoside derivatives through Henry, Michael and various cycloaddition reactions. In the current report, the

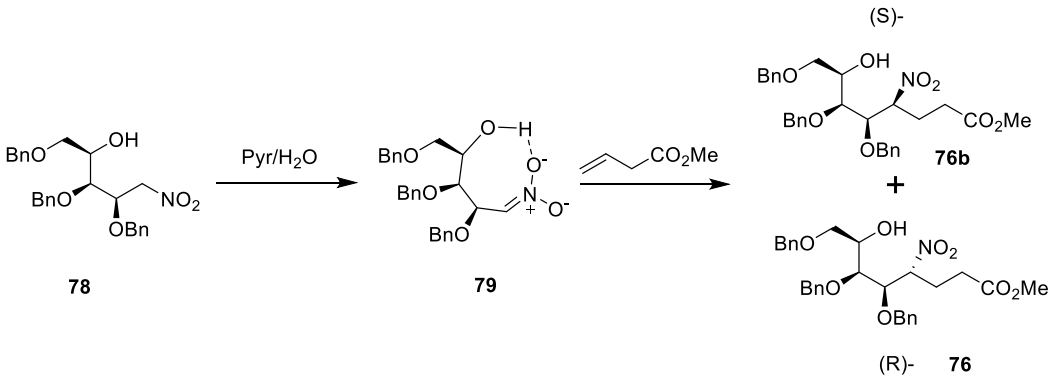
glycal is cleaved in the presence of water to generate a formate (**75**) intermediate that readily hydrolyzes to lose the C1-carbon (**75**) (**Scheme 11**). This is a promising route to access the analogues of the natural product (−)-Hyacinthacine (**77**).[73]



Scheme 11. Generalized Synthetic Pathway of (-)-Hyacinthacine A1.

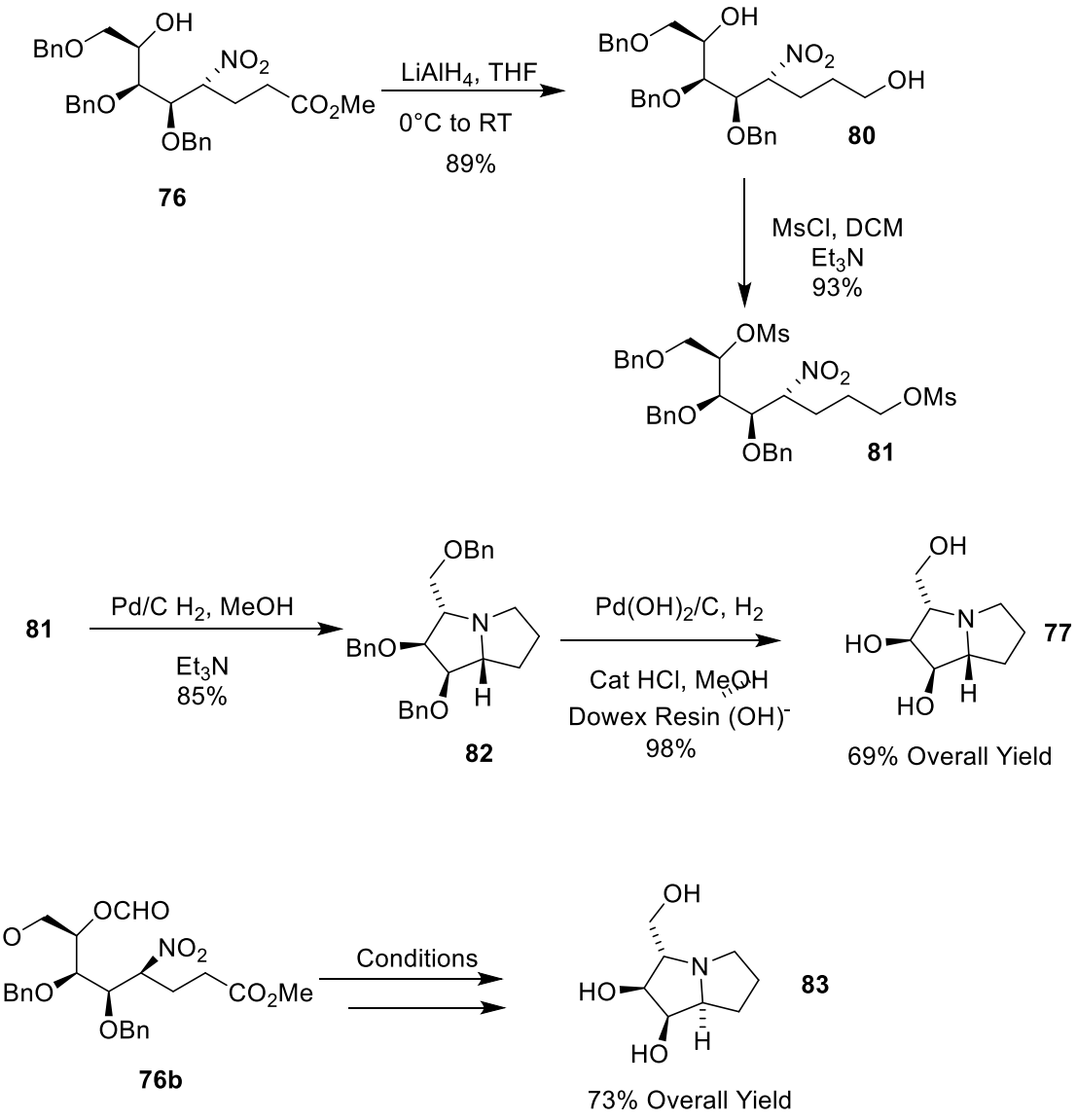
The complicating step is the hydrolysis, and the choice of carbohydrate protecting group can have a significant influence on reaction success. Both a 1-pot (treatment of the glycal with nitric acid) and 2-pot (treatment of the isolated nitroglycal) provided the product, although the isolated yields were moderately higher for the two-pot process (90 – 99%). In some cases this was not a significant improvement over the more convenient one-pot system (50-80%), especially for benzylated systems. Pyridine proved to be a privileged base, substitution with inorganic (KO^tBu, NaOH, K_2CO_3) or tertiary amines (Et_3N) resulted in little to no conversion. The various nitro-polyols were treated with methyl acrylate and pyridine to install the final three carbons required

for the pyrrolizidine skeleton through a Michael reaction. Mechanistic studies justified the high observed diastereoselectivity of the Michael by invoking an eight-membered hydrogen-bond-organized intermediate (**79**). The induced conformation effectively shields the *Si*-face of the carbon-nitrogen double bond, force *Re*-attack **(Scheme 12**).



Scheme 12. Transition State of Michael Addition.

The synthesis is completed through a selective reduction of the ester in the presence of the nitro group using $LiAlH_4$ (**80**). Mesylation of the alcohol (**81**), followed by two sequential catalytic hydrogenations allows for the intramolecular cyclization to take place spontaneously (**82**) (after nitro reduction), and perdebenzylation (**77**) to occur (**Scheme 13**).

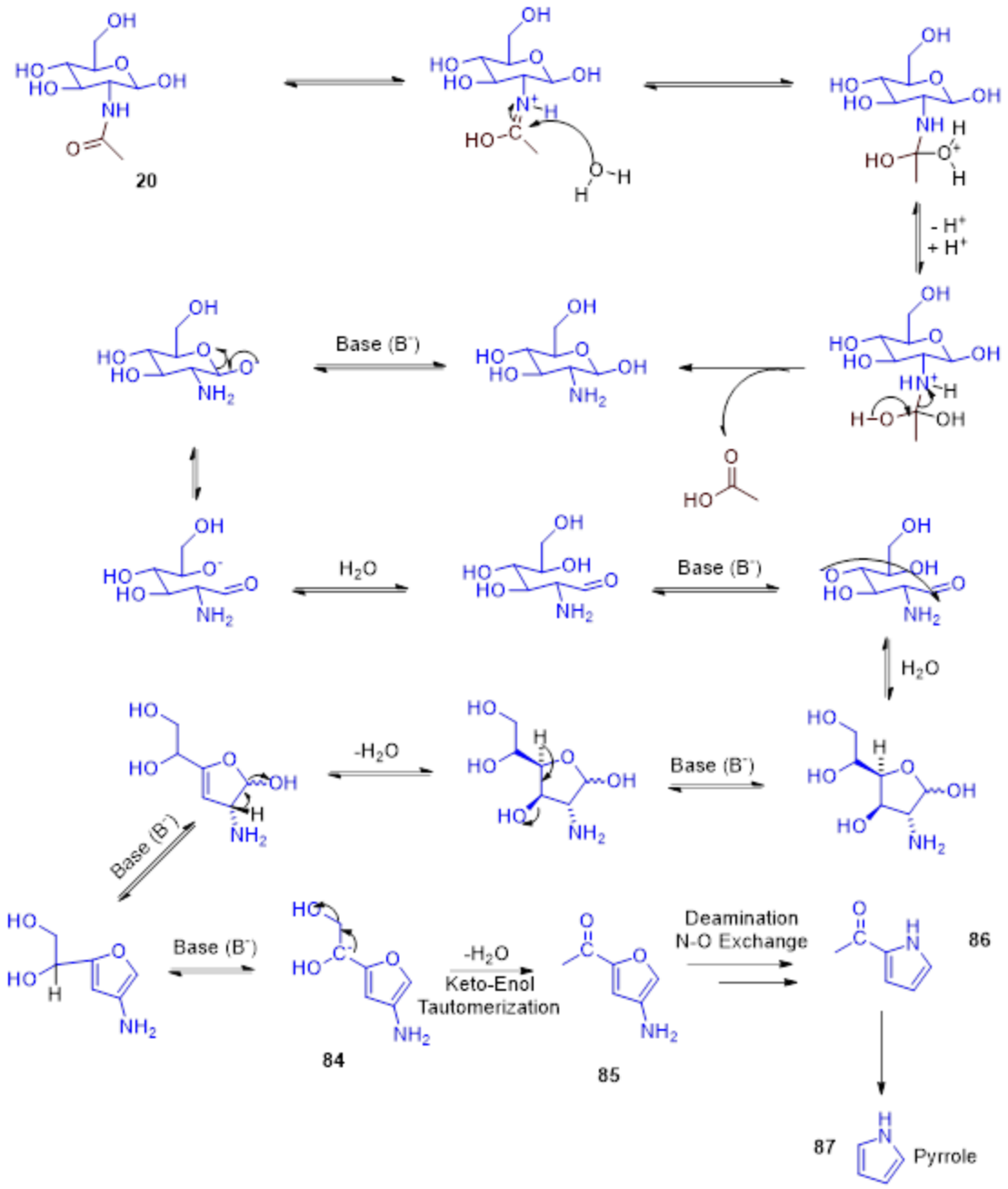


Scheme 13. Synthesis of epi-(-)-Hyacinthacine and (-)-Hyacinthacine A1.

5.2.2 Synthesis of Pyrroles

In the previous example, the chirality of the carbohydrate is conserved to provide information in the product. But the highly hydroxylated systems also allow for the formation of aromatic pyrroles in a mechanism related to the formation of HMF, obtained from the hydrolytic pyrolysis of polysaccharides in water.[19] Through a nitrogen exchange reaction, furans can be

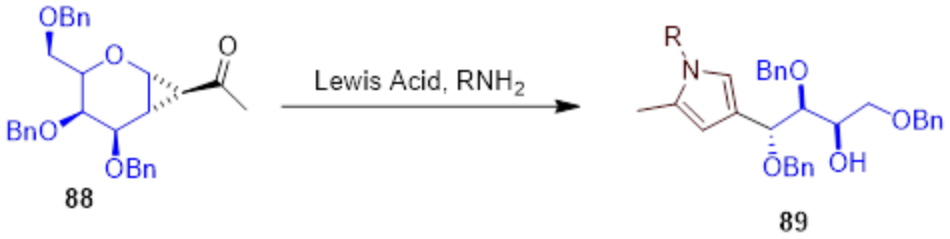
converted to pyrrole in the presence of ammonia. Shown below is a generalized mechanism illustrating how pyrrole is synthesized in **Scheme 14**.



Scheme 14. General Mechanism for Pyrrole Formation.

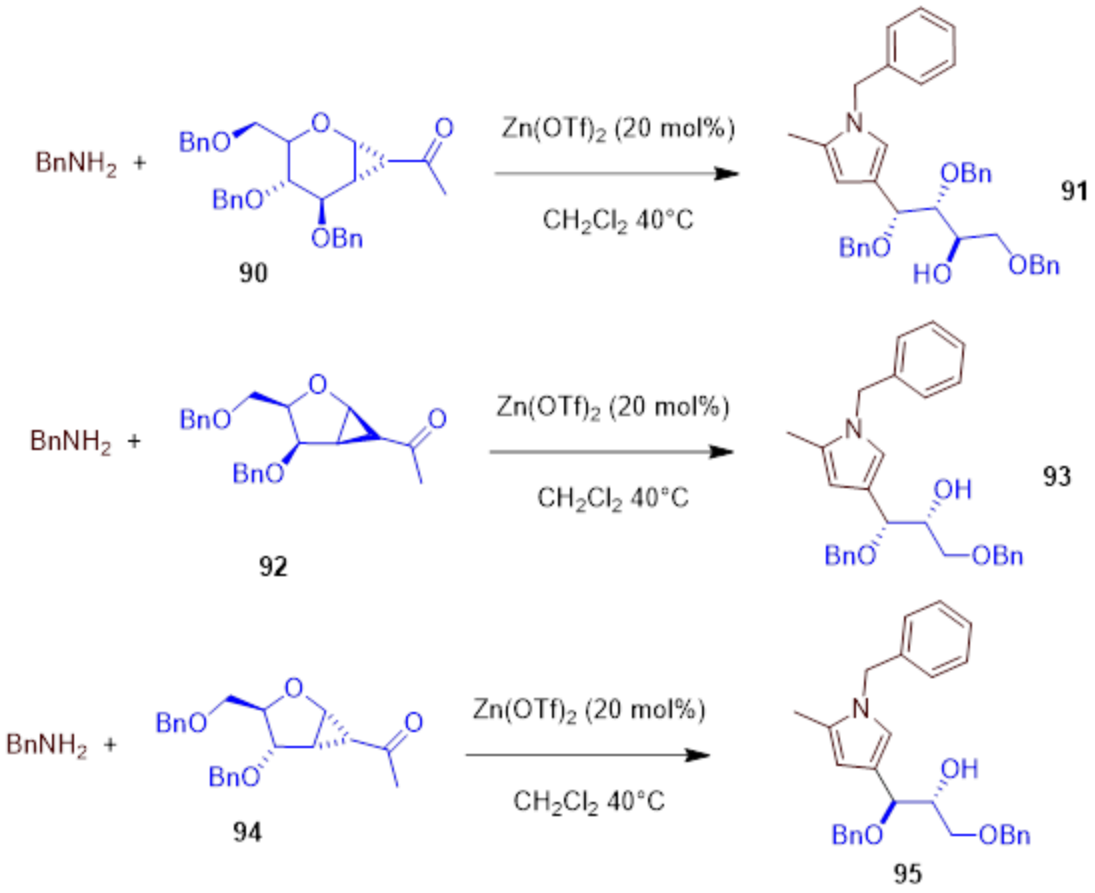
The polysaccharide (chitin) readily undergoes hydrolysis to yield the monomer **20**, which is then hydrolyzed to release acetic acid as shown above to generate the 2-aminofurnaose which dehydrates to the furan. The authors propose that the furan then dehydrates derivative which rapidly undergoes dehydration (**84**), deamination and N-O exchange to yield the acetyl pyrrole (**86**).[19] This acetyl pyrrole is a useful building block in its own right, but it can decompose to the pyrrole (**87**). GC analysis of the reaction mixture indicated that there were other nitrogen compounds present including pyrazine, pyridine, and amide derivatives. Overall this process to yield acetic acid and pyrrole will not be a viable industrial process until the extraction of chitin from crustacean shells can be done more efficiently, and the route does not provide substituted pyrroles, which are of far greater interest for the fine chemical industry.

A recent report from Huawu Shao does make substituted pyrroles from a carbohydrate derivative, however it uses a far more advanced intermediate: 1,2 cycloproponated sugars (still readily available from glycals).[74] Donor-Acceptor cyclopropanes are extremely useful synthons, and are reactive with a wide variety of nucleophiles and electrophiles. In the presence of Lewis acids they can be readily converted to a number of valuable heterocyclic scaffolds.[75] Specifically, Charette reported in 2005 that donor-acceptor cyclopropanes undergo reaction with amines to yield 4-pyrrole derivatives.[76] This carbohydrate variant involves a $Zn(OTf)_2$-mediated rearrangement of 1,2-cycloproponated sugars to afford 3-polyhydroxylalkyl-substituted pyrroles (other metals were far less efficient).[77] The general reaction scheme outlining the Lewis acid mediated synthesis of polyhydroxyalkyl pyrroles is shown below in **Scheme 15**.



Scheme 15. Lewis Acid Mediated Donor Acceptor Cyclopropanated Sugars

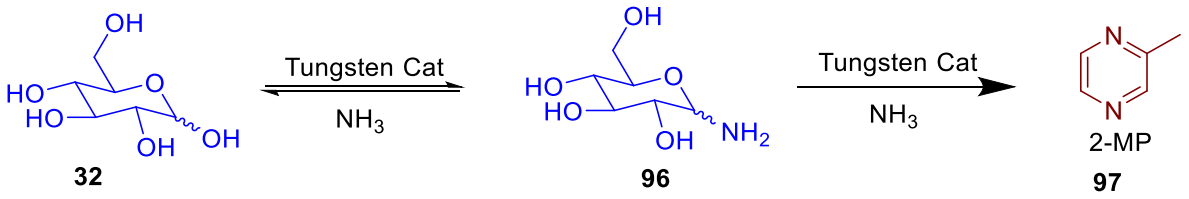
With respect to the amine, the reaction appears tolerant of standard unhindered aliphatics (i.e., octyl, hexyl, butyl, allyl, propargyl,77-84% yield), although a t-butyl group provides no conversion most likely due to high steric hinderance. Electron rich anilines work well, and ester, ether, and amide functionalities on the amines are also tolerated. Electron poor anilines do not fare so well, limiting access to this important class of pyrrole derivatives. In terms of the carbohydrate, the reaction works well with all examined cyclopropanated furanose and pyranose sugars (**Scheme 16**). Additional synthetic complexity can be introduced by inverting the liberated C-5 hydroxyl group to access epimeric hydroxylated chains. These units could provide useful building blocks for drug-like molecules.



Scheme 16. Lewis Acid Mediated Donor Acceptor Cyclopropanated Sugars.

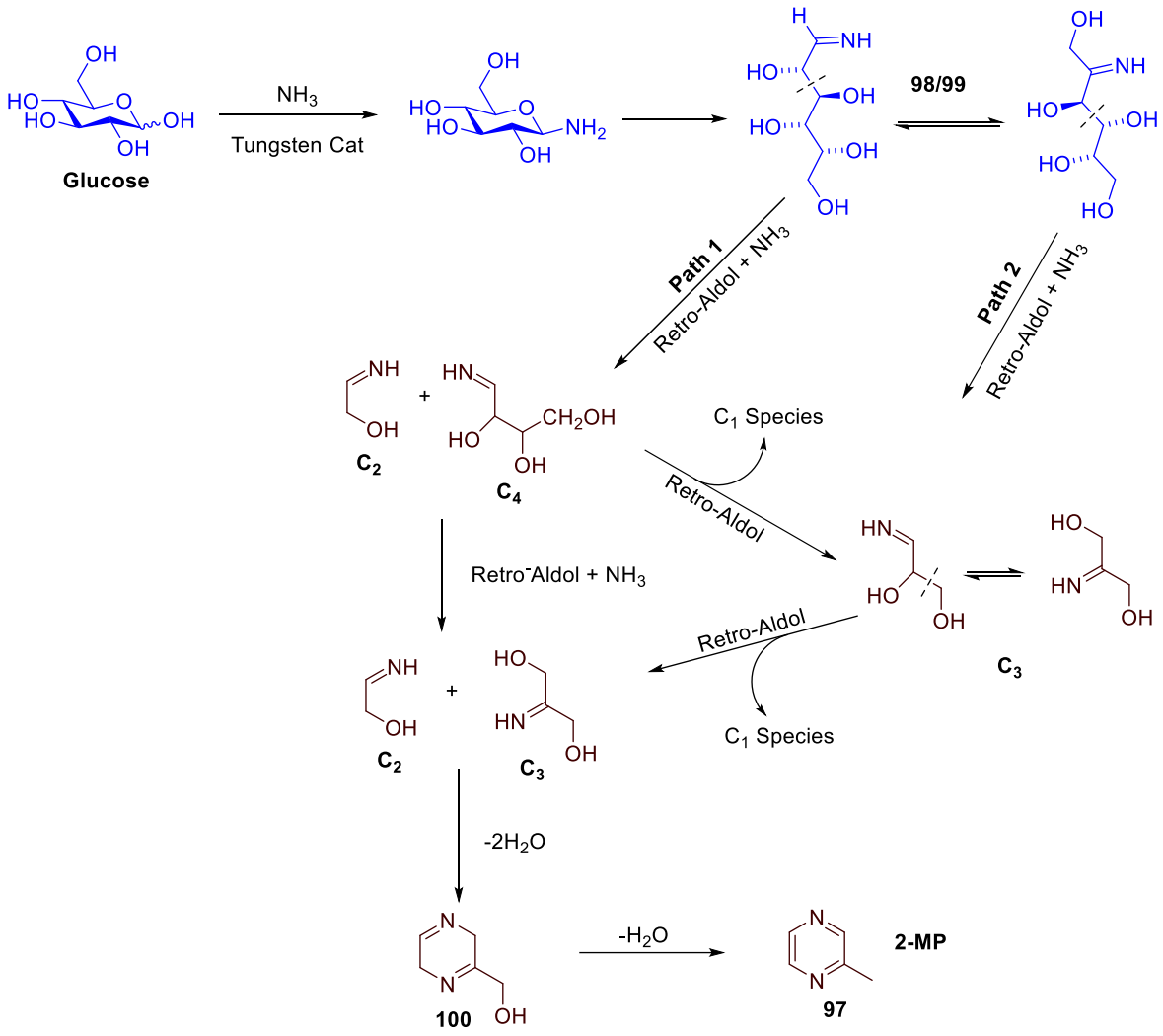
5.2.3 Synthesis of Pyrazines

Pyrazines are another very useful bulk material, with the scaffold being used extensively in both flavouring agents and pharmaceuticals,[78-80] and are produced during the cooking of carbohydrate-containing food from Maillard reactions.[81] Consequently, they should be accessible from carbohydrate-containing biomass. Yan an co-workers recently reported the use of tungsten-based catalysts to prepare 2-methyl pyrazine (**97**) from glucose (**32**), cleverly applying the chemistry developed by Tao Zhang to convert cellulose biomass to ethylene glycol (**Scheme 17**).[82]



Scheme 17. Generalized Tungsten Mediation of Aminosugars.

The initial studies used glucose, ammonia, and tungsten-based catalysts (the best results were obtained using phosphotungstic acid, although most tungsten (VI) species performed well). The yields were temperature dependent with the best results obtained at 220 ºC in the presence of 25 mass% ammonia and 150% w/w catalyst loading. The yield is also dependent on the stereochemistry of the sugar. Glucose, and its C-6 deoxy sugar, xylose, provided the best yields at 25 and 23% respectively, while glucosamine and fructose generated 2MP in approximately 20% yield. Excellent mechanistic studies demonstrate that the aldehyde is essential for conversion, sorbitol was unreactive, and 5-HMF also gave no conversion, suggesting that it is not an intermediate in the series. Consequently, they propose an oxidative cleavage reaction which requires the C2 and C3 fragments shown in **Scheme 18**.

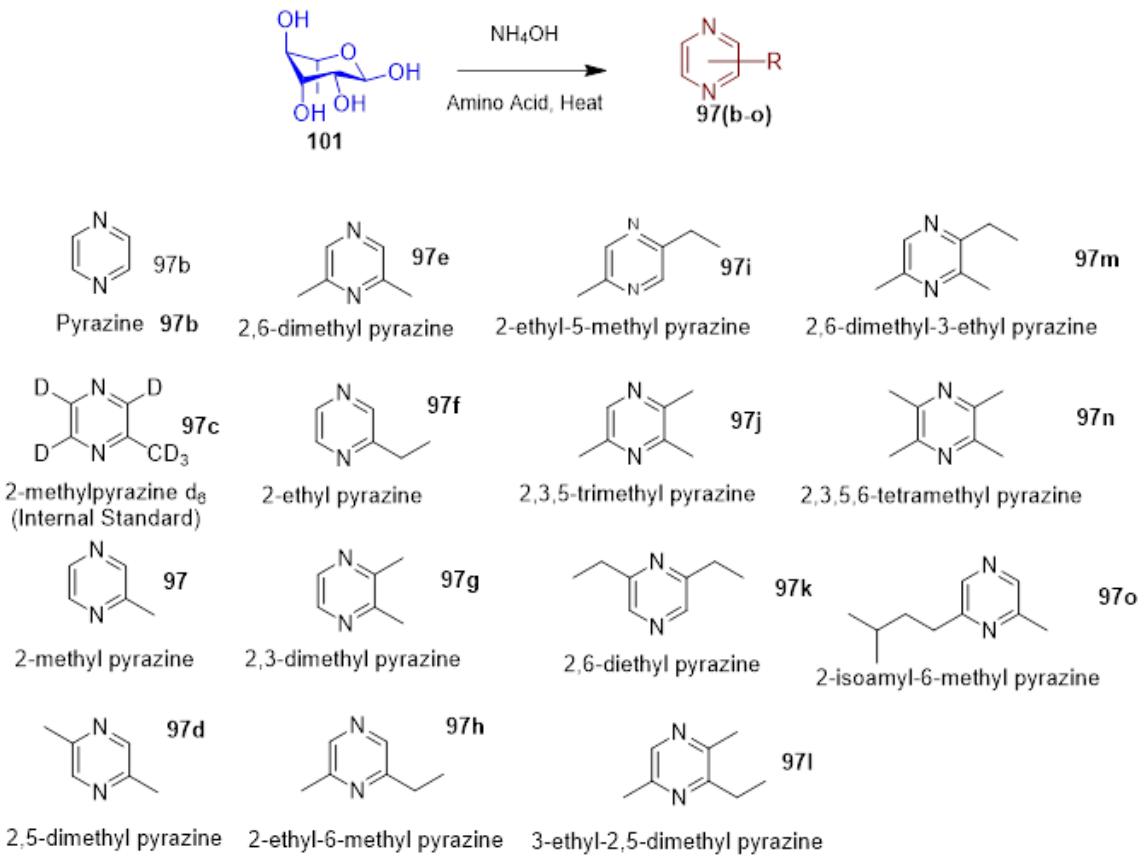


Scheme 18. Proposed Mechanism of 2-Methylpyrazine Using Tungsten Catalysts.

The proposed mechanism shows the conversion of glucose to the corresponding amino sugar which ring opens to form the isomeric imines **98** and **99** that interconvert under the reaction conditions. Based on DFT Calculations, if the reaction progressed through path 1, the homolytic bond cleavage favors breaking the C-C bond between C-2 and C-3 through a retro-aldol mechanism to produce intermediates C2 and C4. Further retro-aldol reactions can either yield a C1 fragment and a C3 fragment which is in equilibrium with the fructose form or a C2 and a C3 fragment. If path 2 was followed that would mean fructose-based imine would be the reactive

intermediate. Compound **99** was not detected even fructose was used as the starting material in place of glucose. This indicates that the retro-aldol of Path 2 is fast so no accumulation of the fructose intermediate **99** occurs. Both pathways are accessible to glucose, and both lead to similar intermediated eventually becoming degenerated through the formation of **100**. When both C2 and C3 fragments have been formed, the final condensation reaction occurs followed by dehydration to give 2-methylpyrazine (2-MP).

Alternatively, Taylor and co-workers have very recently described the direct conversion of sugars into pyrazines using ammonium hydroxide, heat and L-leucine.[83] The reaction works well with a variety of carbohydrates: glucose, fructose or a combination of the two (typical of fruit extracts, or corn syrup, glucose-fructose) but only a few derivatives were synthesized. Rhamnose provided much lower chemical yields, but also provided a wider variety of pyrazine derivatives were detected including an interesting branched example: 2-isoamyl-6-methylpyrazine. The varying pyrazines were identified from the mixture using GC/MS (**Scheme 19**).



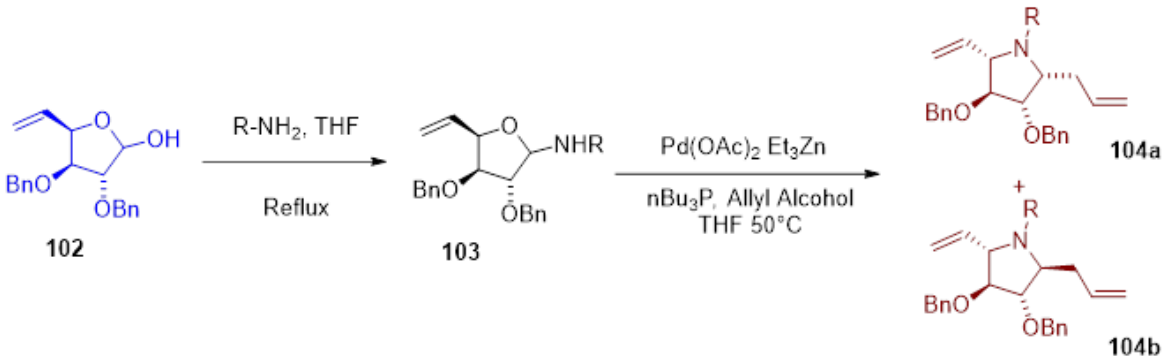
Scheme 19. Derivatives of Pyrazine Recovered By GC/MS.

This ratio of products is highly influenced by varying temperature, concentration of rhamnose, concentration of ammonium hydroxide and the concentration of the amino acid. Similar results were obtained regardless of the amino acid: L-threonine, L-valine and L-leucine were all screened, and all generated a mixture of pyrazines. The differences were comparably minor: L-valine gave the highest amount of total pyrazine mass, whereas L-leucine provided better selectivity with comparable recovery of pyrazine mass (primarily 2-methyl pyrazine and the 2,6-dimethyl derivative). Threonine provided the poorest mass recovery, although the reaction was cleaner: only 8 pyrazines were formed, compared to 11 with leucine and valine. Temperature and reaction time have the biggest influence on the reaction. At 90°C for 1 hour, the conversion was very poor and many of the pyrazines were not formed. Increasing the temperature to 110°C for the

same 1-hour incubation yielded all 13 pyrazines, but again in low yield. However, heating to 110°C over 2 hours provided 4.5 times the amount of total pyrazine content. The yields are still very low as a percent of the biomass, but this is plenty of material if flavouring agents are what is required. As the conditions of the reaction can be tightly controlled, this could provide access to flavour compounds and flavour mixtures relatively effectively and could be important for the flavouring industry going forward.

5.2.4 Synthesis of Tetrahydropyrrole

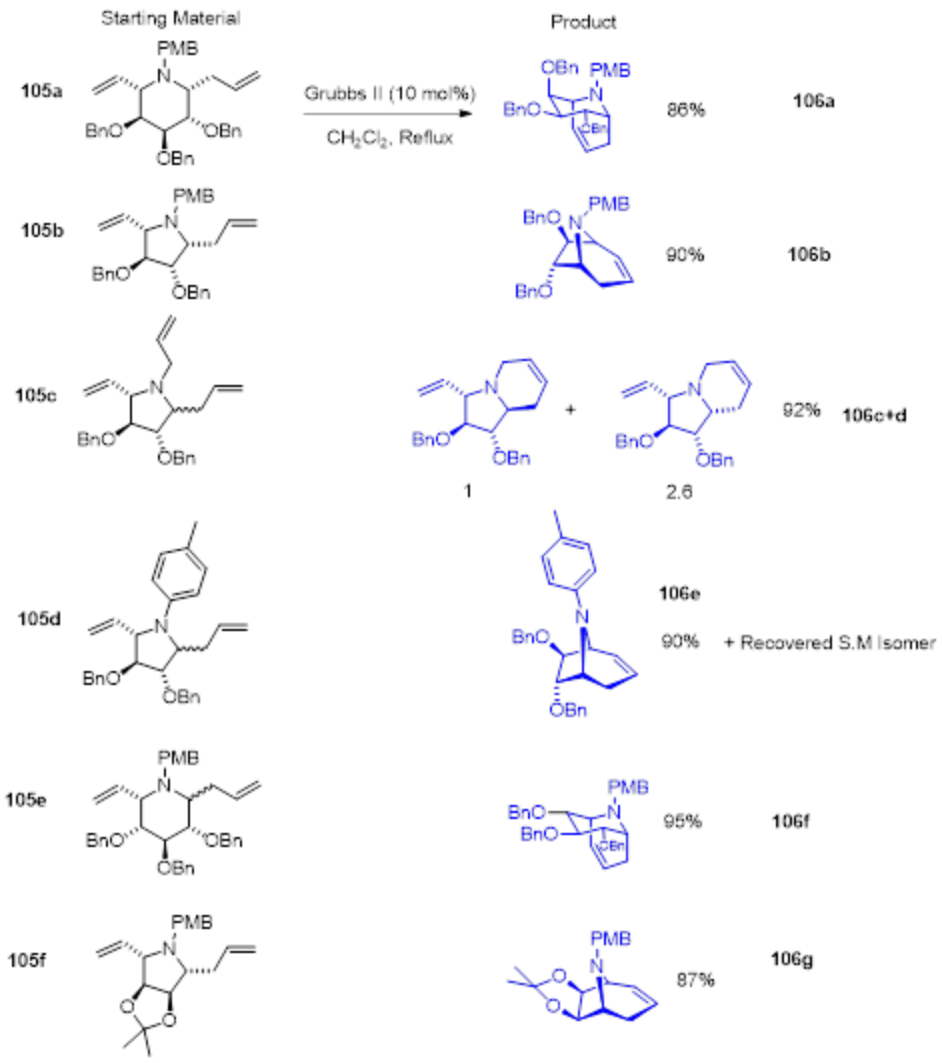
Iminosugars form an important class of competitive inhibitors of glycosidase and glycosyltransferases, the mis-regulation of which is important in many diseases.[84] Consequently, they form the basis of a number of current pharmaceuticals including Glycet, Zavesca and celgosivir.[84] However, the syntheses have often been challenging and somewhat lengthy.[85] Venkateswara Rao and coworkers recently reported on the conversion of vinyl pyranosylamine and furanosylamines to 2,6- and 2,5-disubstituted pyrrolidine and piperidine iminosugars in a one-pot procedure (**Scheme 20**).[86]



Scheme 20. General allylation of iminosugars**.**

These iminosugars were then elaborated for the synthesis of polyhydroxylated piperazines, pyrrolidines and indolizidine compounds. The initial reactions used a protected free-reducing end

sugar and a primary amine to generate the hemiaminal. Treatment using a palladium catalyst forces the rearrangement to the iminosugar in the presence of an allyl alcohol. In terms of aliphatic amines, only allyl amine (55% yield) provided moderate conversion with both hindered (cyclohexylamine) and unhindered (n-hexylamine) alkylamines providing only low conversion. Benzyl amine and electron-rich anilines were far more effective (60-72% yield). The reaction was far more tolerant in terms of the protecting group strategy and identity of the carbohydrate, and examples are provided below (**Scheme 21**). These systems are perfectly positioned for ring closing metathesis to generate complex polycyclic systems. These pyrrolidines, piperazines and indolizidines are highly promising scaffolds for the development of carbohydrate-based glycosidase inhibitors.



Scheme 21. Yields of Ring Closing Metathesis of N-Containing Heterocycles.

6. Conclusion

There has been significant focus over the years on converting carbohydrate biomass to HMF, LA, and their derivatives including hydrocarbons for bio-derived fuels and building blocks for polymers. However, in very recent years, there has been excellent progress on derivatizing

these same readily available building blocks into the complex heterocycles that form the basis of so many of the pharmaceutically active materials. The examples shown here are just the initial forays into this field of generating valuable fine chemicals from sustainable sources, and we can expect this field of research to continue to expand in the coming years and decades as the social, environmental, and economic cost differential between fossil fuels and biomass conversion continues to shift.

7. Acknowledgements

The authors would like to thank the University of Windsor for supporting the writing of this Chapter through Start-Up Funds to JFT. BSO would like to thank his supervisor, Prof. J. Green, for his support during the writing process.

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