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Cycloamination strategies for renewable N-heterocycles

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Biomass resources have infinite possibilities for introducing nitrogen, sulfur, or phosphorus heteroatoms into their structures by virtue of controllable carbon–heteroatom bond formation. In this review, cycloamination approaches for thermal (catalyst-free) and catalytic transformation of biomass feedstocks into N-heterocyclic molecules including mechanistic pathways are analyzed. Bottom-up (small molecule substrates) and top-down (large molecule substrates) are considered. Sustainable routes for synthesis of five-membered (pyrroles, pyrrolidones, pyrazoles, imidazoles), six-membered (pyridines, pyrazines), fused (indoles, benzimidazoles), and other relevant azaheterocycles are critically assessed. Production of biomass-derived six-, seven-, and eight-membered as well as fused N-heterocyclic compounds with present approaches have relatively low selectivities. Attention to methods for forming analogous sulfur or phosphorus heteroatom compounds from biomass resources using either bottom-up or top-down strategies appear to have been greatly overlooked. Synthetic auxiliaries (heating modes, nitrogen sources) that enhance reaction efficiency and tunability of N-heterocyclic ring size/type are considered and plausible reaction mechanisms for pivotal pathways are developed.

1. Introduction

Renewable biomass is a future replacement for fossil resources being used to produce energy and chemicals.[1–6] Due to the presence of abundant oxygen species, biomass derivatives have been considered as consummate intermediates or platform molecules for the synthesis of oxygen-containing chemicals such as esters, acids, aldehydes, ketones, phenolics, and alcohols,[7–12] that contain unsaturated hydrocarbon moieties (*e.g.*, alkenyl, alkynyl, aryl groups),[13–18] as shown in Fig. 1. The specific functional groups of biomass-derived compounds provide infinite possibilities in the introduction of heteroatoms (*e.g.*, N, S, P) and even construction of heterocycles by virtue of controllable carbon–heteroatom bond formation,[19–22] which are not readily available from conventional fossil resources. Over the past several decades, there has been increasing interest in development of sustainable processes with simple and green approaches to accessing value-added heteroatom-containing chemicals.[23–26]

Nitrogenous compounds hold a privileged position in the preparation of drugs, agrochemicals, polymers, and other functional materials.[27,28] In particular, nitrogen species are presented in more than 80% of the top 200 pharmaceuticals,[29,30] and two thirds of these N-containing medicines contain N-heterocyclic skeletons.[31] Given the above considerations, urgent attention is needed to develop green and efficient approaches to task-specific azaheterocycles from renewable biomass feedstocks *via* sustainable chemistry. The employed nitrogen sources can be derived from ammonia, amines/amides pre-prepared by C–N coupling reactions (*e.g.*, reductive amination, aminolysis, and amidation),[32–36] or natural *N*-reservoirs (*e.g.*, chitin, proteins) for producing amines and derivatives (*e.g.*, glucosamine, *N*-acetyl-D-glucosamine, amino acids).[37–41] Beginning from the accessible bio-based functional molecules, N-heterocycles can be constructed by C–N and/or C–C bond formation typically *via* three dominant synthetic routes including intramolecular cyclization, cycloaddition (*e.g.*, aza-Diels–Alder), and multicomponent condensation reactions (Fig. 2).[42,43] Relevant reaction processes and pathways in the presence or absence of designed catalysts have been investigated under optimized thermal conditions,[42,43] for which these cycloamination strategies are attractive for the sustainable synthesis of bio-based N-heterocycles, with much development needed to further expand substrate scope and generality.

Previously published review articles have focused on design of functional catalytic materials and conversion means for

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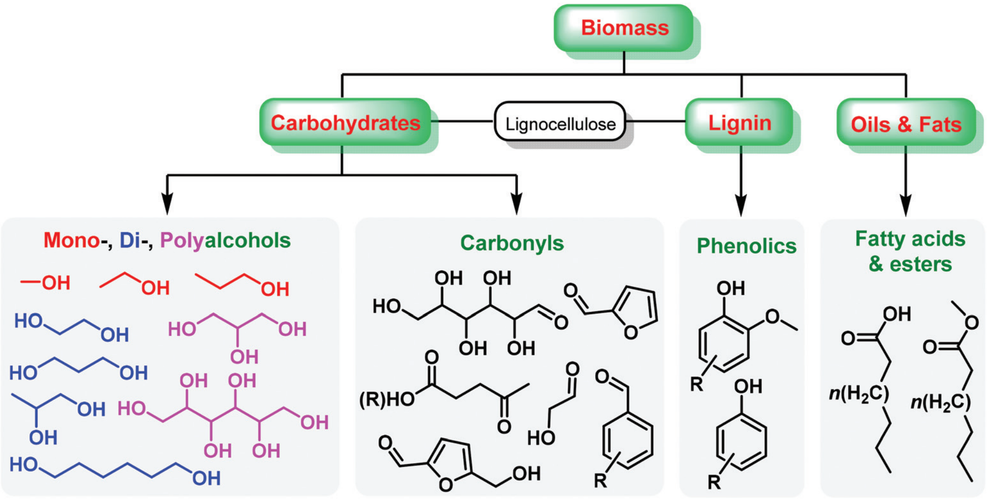

Fig. 1 General pathways for upgrading biomass to oxygen-containing chemicals.

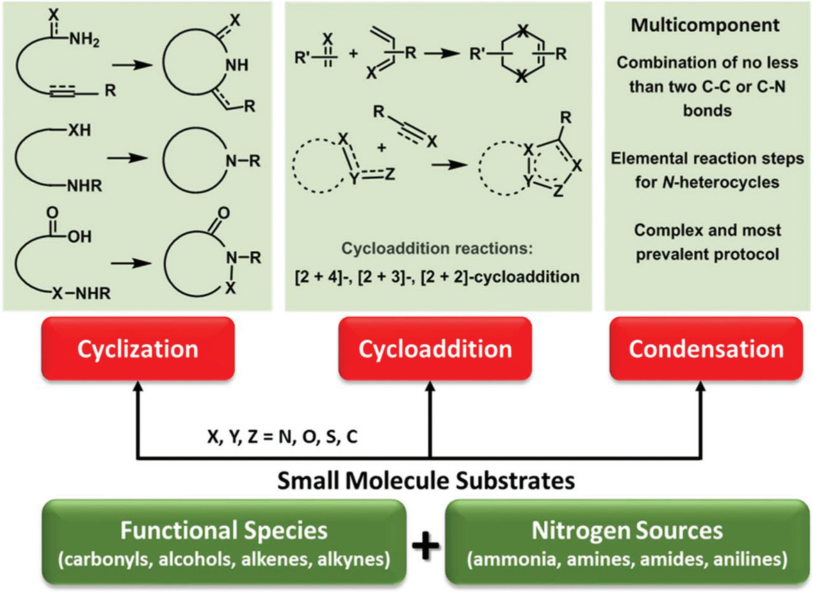

Fig. 2 Bottom-up strategy to N-heterocycles *via* small molecule substrates.

efficient production of specific/desired platform molecules and biofuels from lignocellulosic biomass.[44–55] However, increasing attention is on the synthesis of heteroatom-containing chemicals *via* green and sustainable routes, with emphasis on the exploitation of approaches to acyclic amines and correlative N-containing commodities or fine chemicals.[56–58] In view of the much higher versatility of azaheterocycles, this review aims to critically assess the cycloamination strategies developed for the preparation of five-membered (section 2), six-membered (section 3), fused (section 4), and other (section 5) biomass-derived N-heterocyclic products. Auxiliaries such as heating modes and solvent or substrate types optimized to overcome reaction barriers are discussed, with reaction mechanisms and pathways being outlined for representative processes and systems.

2. Five-membered N-heterocycles

2.1. Pyrroles

Pyrrole-containing N-heterocycles are important structural motifs and are widely applied in pharmaceuticals, pesticides, catalysts, functional materials, and supramolecular chemistry.[59–61] The Hantzsch, Knorr, Paal–Knorr, Van Leusen, Barton–Zard, and Piloty–Robinson reactions are typical approaches toward the synthesis of pyrroles.[62–68] In view of the

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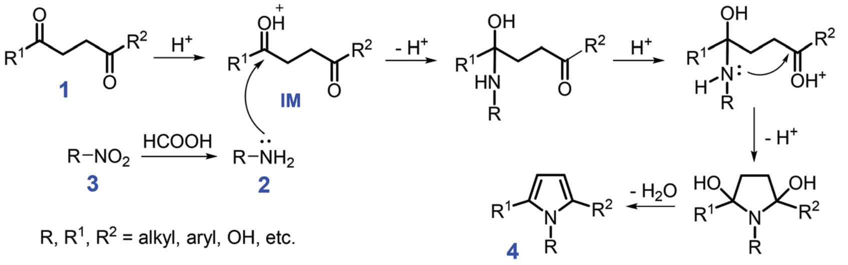
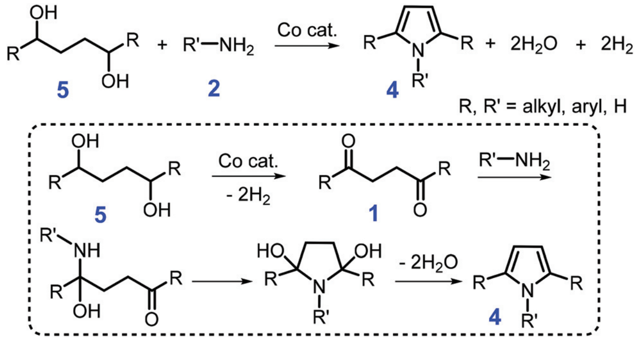


Scheme 1 Synthesis of *N*-substituted pyrroles **4** from 1,4-dicarbonyls **1** with amines **2** or nitro compounds **3**. Adapted with permission from ref. 81 and 82, Copyright © 2017 Royal Society of Chemistry; Copyright © 2010, American Chemical Society.

versatility of substituted pyrroles, many renewed synthetic methods have been developed to construct these types of unique N-heterocycles, such as metal-catalyzed cyclization, cycloaddition, rearrangement, aza-Wittig, multicomponent/oxidative coupling, hydroamination/cyclization, and isocyanide-based reactions.[69–79] Instead of fossil-based resources, synthesis of pyrroles by full or partial use of renewable resources *via* newly-developed reaction routes is a highly desirable goal in sustainable chemistry. However, in these methods, leaching of metal species may cause serious environmental issues that should be taken into consideration for metal-mediated catalytic systems, especially with respect to the catalyst stability and reusability.

Beginning from 1,4-dicarbonyl compounds **1**, especially since 2,5-hexadione is derivable from hexose sugars,[80] *N*-substituted pyrroles **4** can be synthesized by Paal–Knorr condensation with primary amines **2** over acid catalysts or with nitro compounds **3** over metal catalysts (Scheme 1). The combination of a heterogeneous cobalt–nitrogen catalyst (Co–N_x/C-800-AT) with formic acid serving as both hydrogen donor and an acid catalyst is efficient for one-pot synthesis of 2,5-dimethyl-1-phenylpyrrole (95.2% yield, 110 °C, 12 h) from nitrobenzene and 2,5-hexadione in ethanol.[81] Nitrobenzene is subjected to transfer hydrogenation with formic acid over the Co–N_x/C-800-AT catalyst, affording aniline (Scheme 1). The carboxide species of 2,5-hexadione is protonated by formic acid to yield the intermediate (**IM**), which is then attacked by aniline, followed by cascade cyclization and dehydration to afford the product.[81] The reaction system is applicable to heterocyclization of substituted nitrobenzenes with 2,5-hexadione to produce corresponding *N*-substituted pyrroles with yields of up to 100%. Notably, the developed cobalt–nitrogen catalyst is tolerable to the acidic liquid H-donor (HCOOH), which may be ascribed to the highly dispersed metal particles that are coordinated and stabilized by nitrogen species of the solid carbonaceous supports. This unique heterogeneous feature of the non-noble metal catalyst is able to not only remarkably reduce the loss of metal species in the reaction processes and the overall production cost, but also provides an example of using sustainable HCOOH instead of flammable hydrogen gas as H-donor.



Scheme 2 Catalytic coupling of primary or secondary diols **5** with primary amines **2**. Adapted with permission from ref. 86 and 87, Copyright © 2016 Wiley-VCH; Copyright © 2019, American Chemical Society.

Lignocellulosic biomass-derived alcohols are another green feedstock for synthesis of pyrroles, although complex byproducts (*e.g.*, cyclic imides, pyrrolidines, and lactones) were often frequently obtained by coupling of carbonyl intermediates **1** *in situ* formed from catalytic dehydrogenation of alcohols.[82–85] With hydrogen and water as co-products, catalytic acceptorless dehydrogenative coupling of 1,4-butanediol or 1,4-substituted 1,4-butanediols **5** and amines **2** over base-metal complexes (*e.g.*, cobalt or manganese pincer complex) generate **1** or 1,2,5-substituted pyrroles **4**, respectively, at 150 °C for 24 h with 90% yield (Scheme 2).[86,87] In the catalytic process, an aldehyde or ketone intermediate **1** is initially formed by dehydrogenation of alcohol to liberate H_2, followed by coupling with the primary amine **2** to produce the *N*-substituted pyrrole **4** and water *via* Paal–Knorr condensation (Scheme 2).[86,87] A synergic effect between the metal and ligand species is observed in the dehydrogenative coupling reaction, which mainly contributes to the enhanced selectivity towards the product pyrrole.[87] Although these homogeneous catalytic systems exhibit pronounced performance in the Paal–Knorr condensation reaction, difficulty in the catalyst recovery will lead to additional cost and negative impact on the environment.

Unsaturated diols, such as butene-1,4-diol or butyne-1,4-diol, can be used to construct substituted pyrroles by reaction with primary amines (Scheme 3) over precious metals (*e.g.*, Ru, Pd) in the presence of phosphine ligands, although they afford relatively low selectivities.[88,89] The application of earth-abun-

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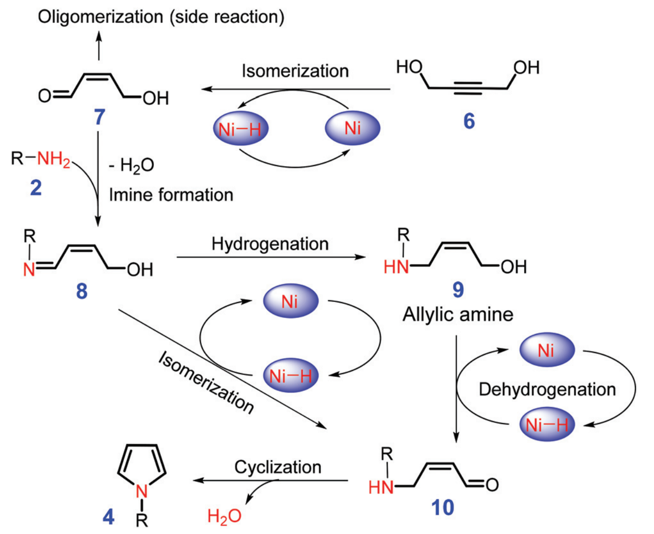
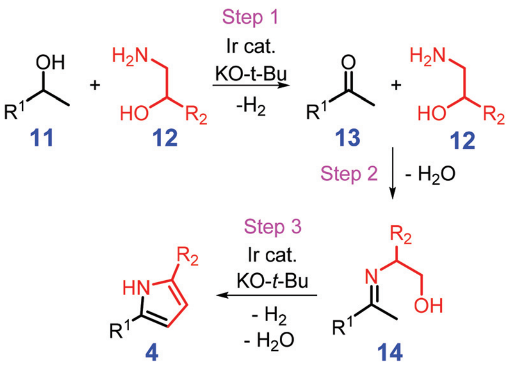


Scheme 3 Intermolecular cyclization of butene-1,4-diol or butyne-1,4-diol **6** with primary amines **2** to pyrroles **4** catalyzed by base metal (*e.g.*, Ni). Adapted with permission from ref. 92 and 93, Copyright © 2017, American Chemical Society; Copyright © 2016 Wiley-VCH.



Scheme 4 Catalytic synthesis of pyrroles from secondary alcohols and amino alcohols *via* cascade dehydrogenation (step 1), imine formation (step 2), intramolecular C–C coupling and isomerization (step 3). Adapted with permission from ref. 96, Copyright © 2013, Springer Nature.

dant base metals (*e.g.*, Ni, Co, Fe, and Mn) to catalysis with specific nitrogen ligands is able to overcome the long-standing problem of high catalyst cost and low productivity.[90,91] It is postulated by the authors that the nonprecious metal (*e.g.*, Fe and Ni) catalyze dehydrogenation or isomerization of *cis*-butene-1,4-diol or butyne-1,4-diol (**6**) to afford **7** that is then condensed with primary amine **2**, leading to the formation of allylic amine **9** *via* hydrogenation of imine **8**.[92,93] In a one-pot operation, subsequent dehydrogenation of **9** gives intermediate **10**, which is further subjected to cascade intermolecular cyclization and dehydration to construct *N*-substituted pyrroles **4** (Scheme 3). In parallel, *N*-substituted pyrroles may also be generated by sequential metal-catalyzed isomerization and intermolecular cyclization of the imine **8** *via* intermediate **10**.[92,93] Due to the presence of C═C or C≡C bond in the diols, the reaction system is tolerant of free halides and alcohols, leading to pyrrole yields of up to 90%.[90,91]

Metal-catalyzed hydrogen autotransfer or the borrowing of hydrogen is capable of converting alcohols to carboxides together with the liberation of H_2, followed by condensation to give imine species that could be further reduced to amines by the *in situ* formed hydrogen (Scheme 3).[94,95] Michlik and Kempe reported on the synthesis of 2,5-disubstituted pyrroles **4** from sustainable secondary alcohols **11** and amino alcohols **12** initiated by alcohol dehydrogenation in the presence of sodium *tert*-butoxide (NaO-*t*-Bu) and an organoiridium catalyst *via* sequential formation of C–N and C–C bonds (Scheme 4).[96] This synthetic protocol was implemented under relatively mild reaction conditions (90 °C, 24 h) with ketone **13** and imine **14** as key intermediates, and could tolerate a wide range of functional groups like olefins, Cl, Br, NH_2, OH, and organometallic moieties with moderate to high yields of pyrroles (42–97%).[96] Other types of N/P-ligands stabilized Ir and Ru complexes are demonstrated to be efficient for the synthesis of pyrrole derivatives,[97–101] although it would be desirable to develop catalysts based on earth-abundant base metals in view of recycle and reuse requirements. Kallmeier *et al.* reported that pyrrole could be synthesized in isolated yields of up to 93% over Mn PN5P-pincer catalysts, whereas no significant activity was observed for related Fe and Co complexes.[102] The Mn-mediated reaction smoothly progressed at moderate reaction temperatures (78 °C) with 2-methyltetrahydrofuran as solvent, which is a lower temperature than that used for Ir- and Ru-catalyzed processes (≥90 °C),[96–102] and is an inspiring example of nonprecious metal-based catalysis for replacing noble metal complexes in the synthesis of heterocycles. The release of H_2 from the used reagent alcohols over the metal catalysts can eliminate the use of flammable and high-pressure hydrogen gas, while the development of active heterogeneous counterparts will be helpful for practical applications.

Another method to synthesize pyrroles (Scheme 5) is *via* catalytic amination of bio-derived furanic compounds **15** with primary amines **2** in the presence of an acid catalyst (*e.g.*, Al_2O_3 and TiO_2) that affords pyrrole derivatives at 20–60% yields at high-temperature (250 °C to 400 °C).[103,104] Under relatively mild reaction conditions (150 °C, 5 bar N_2, 0.7 h), Tao *et al.* demonstrated that a solid acid H-form zeolite H-Y(2.6) gave *N*-(*m*-tolyl)-2,5-dimethylpyrrole **4a** in nearly quantitative yields (99%) from the condensation of 2,5-dimethylfuran **15a** and *m*-methylaniline **2a.**[105] Besides the porous structure, moderate Lewis/Brønsted acid strength of H-Y(2.6) as determined by NH_3-TPD and pyridine-adsorbed FT-IR, contribute to the optimized pyrrole yield. In contrast, H-MOR(12.5) and H-ZSM-5(18) with strong acidity significantly inhibit the desired condensation reaction (9–34% yields), possibly due to deactivation of the active sites by a strong binding interaction with N-containing intermediates.[105] Rather than from the direct reaction between aniline and 2,5-dimethylfuran, 2,5-hexanedione **16** was identified to be the key intermediate that reacts with different anilines *via* Paal–Knorr reaction to afford pyrrole derivatives. With water as the only co-product, this

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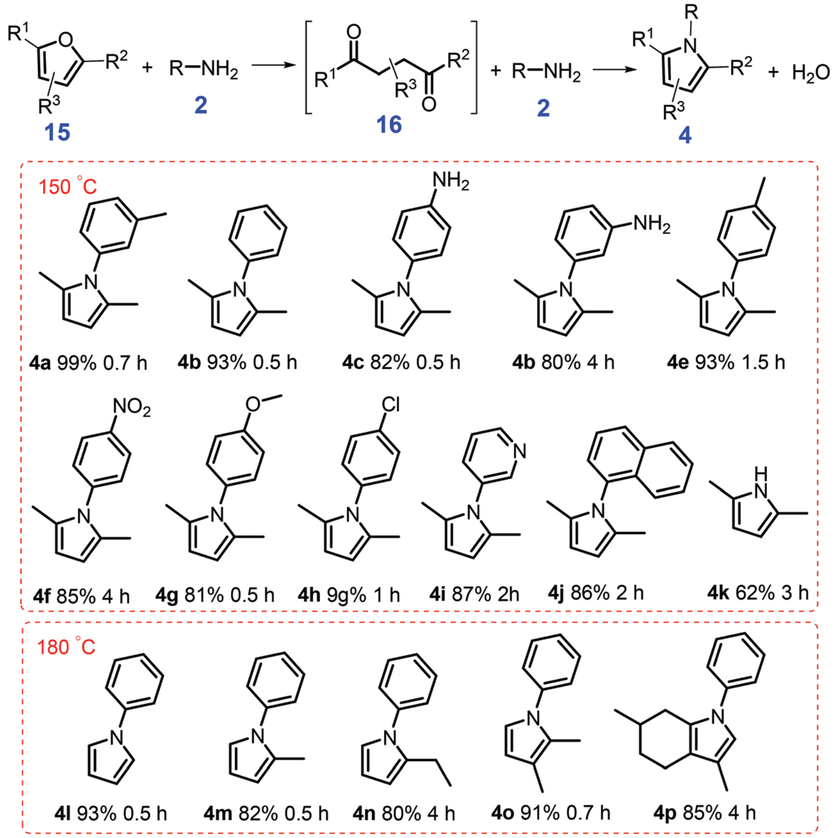
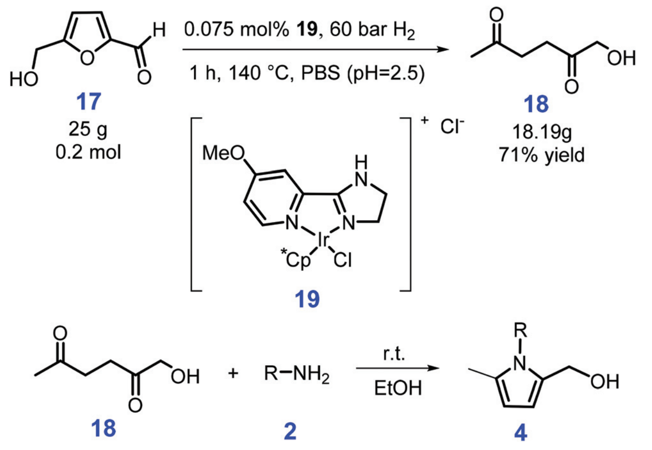


Scheme 5 Catalytic condensation of furans **15** with anilines **2** to give pyrroles **4**. Reaction conditions: 1 mmol furan, 1 mmol aniline, 2 mL toluene, 150 mg of H-Y(2.6), p_{N_2} = 5 bar. Adapted with permission from ref. 105, Copyright © 2017, American Chemical Society.

atom-economic H-Y(2.6)-catalytic system (Scheme 5) shows good generality for synthesis of polysubstituted pyrroles **4** (62–93% yields) from anilines **2** and bio-derived furans **15** (*e.g.*, 2,5-dimethylfuran, 2-methylfuran, and furan) at 150 °C or 180 °C for 0.5 h to 6 h.[105] Unlike conventional Paal–Knorr reactions that typically use 1,4-diketones as substrates, this catalytic approach based on biofurans and commercial zeolites is a promising method to construct pyrrole-based scaffolds.

Starting from biomass-derived 5-hydroxymethyl-furfural (HMF, **17**), *N*-substituted 2-hydroxymethyl-5-methylpyrroles **4** (74–99% yields) can be synthesized using ethanol as solvent at room temperature after reaction for 10 min to 48 h *via* a two-step catalyst-free process, involving the hydrogenation of HMF (**17**) to 1-hydroxyhexane-2,5-dione (HHD, **18**) over Ir-complex **19**, followed by Paal–Knorr reaction with amines and anilines (**2**) bearing both electron-withdrawing and electron-donating groups (Scheme 6).[106] The presence of hydroxyl functionality has the possibility for further modification to afford bioactive compounds and to introduce desired ligating groups, with no detailed purification steps being required to obtain the desired products, except for simple evaporation of the solvent (ethanol) and vacuum drying.



Scheme 6 Synthesis of *N*-substituted 2-hydroxymethyl-5-methylpyrroles from 5-hydroxymethyl-furfural (HMF) *via* 1-hydroxyhexane-2,5-dione (HHD). Adapted with permission from ref. 106, Copyright © 2018, Wiley-VCH.

Conventionally, reaction of hexose sugars (*e.g.*, glucose and fructose) directly with amines **2** are able to proceed either Amadori rearrangement of glycosylamine **20** or Maillard reaction, affording the equilibrium mixture of furanose **21a**, pyranose **21b**, and the open chain isomer **21c** in solution[107] or a complex mixture of poorly characterized molecules at 200 °C or higher,[108] respectively (Scheme 7). In the presence of an organic acid (oxalic acid), Adhikary *et al.* found that glucose

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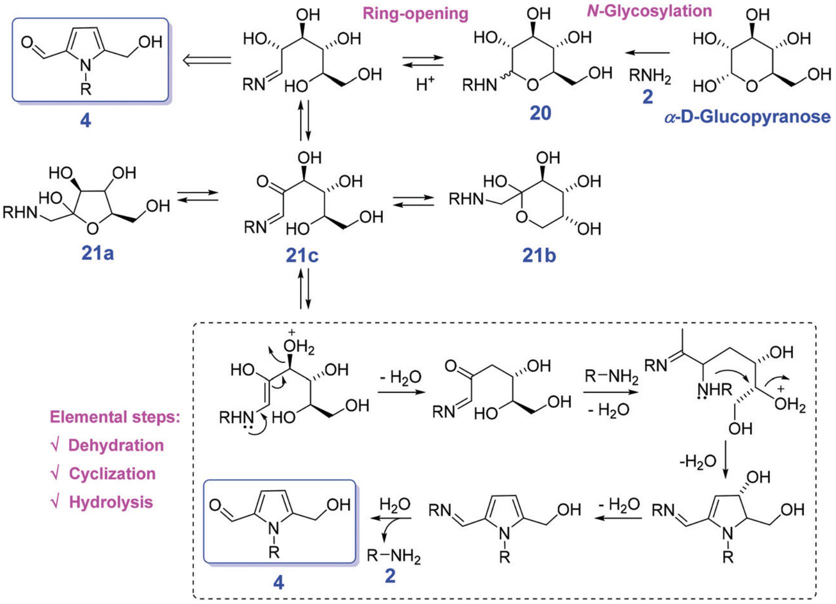
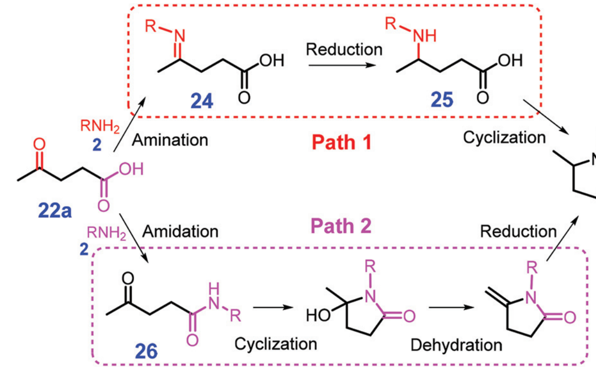


Scheme 7 Direct conversion of hexose sugars by reacting with amines **2** to *N*-substituted 5-(hydroxymethyl)pyrrole-2-carbaldehydes **4**. Adapted with permission from ref. 109, Copyright © 2015, American Chemical Society.

directly reacting with *N*-benzylamine gives 1-benzyl-5-(hydroxymethyl)pyrrole-2-carbaldehyde with a maximum yield of 40% in DMSO at 90 °C for 0.5 h.[109] In contrast, acetic acid (pK_a 4.7), trifluoroacetic acid (pK_a 0.23), and sulfuric acid (pK_a −3.0) afford the pyrrole in yields of 8%, 28%, and 16%, respectively. The optimal acidity of oxalic acid (pK_a 12.5) most likely contributed to its superior reactivity in the cascade process involving nonaqueous Maillard reaction, ring-opening, dehydration, cyclization, and hydrolysis to produce the pyrrole **4** and regenerate the amine **2** (Scheme 7).[109] The hydroxyl configuration of sugars does not remarkably affect the reaction efficiency, and corresponding *N*-substituted 5-(hydroxymethyl) pyrrole-2-carbaldehydes in comparable yields (21–53%) is obtained from galactose, mannose, ribose, or xylose by reacting with primary amines. Due to the existence of active species (–OH, –CHO), the pyrrole-2-carbaldehyde skeleton shows great potential for production of pyrrole alkaloid natural products (Scheme 7). The use of more easily available bio-based feedstocks can remarkably reduce production cost, and improve development of correlated reaction routes with recoverable and lost-cost catalysts in the presence of low-pressure liquid H-donor sources (*e.g.*, HCOOH, alcohols) and is thus highly desirable for the synthesis of pyrroles.



Scheme 8 Catalytic reductive amination of levulinic acid (LA, **22a**) with primary amines **2** to pyrrolidones *via* amination–reduction–cyclization (path 1) or amidation–cyclization–dehydration–reduction (path 2). Adapted with permission from ref. 112 and 113, Copyright © 2017 & 2018, Royal Society of Chemistry.

2.2. Pyrrolidones

Pyrrolidones are important core scaffolds widely applied in pharmaceutical products, printing inks and fiber dyes, which are also directly employed as surfactants and solvents.[110,111] In the presence of homogeneous or heterogeneous metal catalysts, pyrrolidones **23** could be produced from biomass-derived levulinic acid (LA, **22a**) or keto acids (**22**) through either reductive amination or amidation processes with H_2, formic acid or hydrosilane as hydrogen source (Scheme 8).[112,113] In most cases, imines **24** are reported to be first formed from amination of LA (**22a**) with primary amines **2**, followed by hydrogenation to give γ-amino-pentanoic acid **25** that is finally subjected to intramolecular amidation to yield pyrrolidones **23** (path 1, Scheme 8).

Molecular hydrogen gas is frequently used as H-donor in schemes for cascade reductive amination and amidation of LA (**22a**) or its ester to synthesize pyrrolidones. Among the developed catalytic systems, noble metal catalysts (*e.g.*, Pt/P-TiO_2, Pt-MoO_x/TiO_2, Pt/TiO_{2D}, Ru/TiO_2, Ir/SiO_2-SO_3H, and iridium complexes) are highly efficient for the cascade reaction process (up to 99% yield of pyrrolidones) under mild conditions (room temperature to 120 °C, $P(H_2) \lesssim 1$ MPa).[114–120] Apart from LA (**22a**) and primary amines, carbohydrates (*e.g.*, glucose) and

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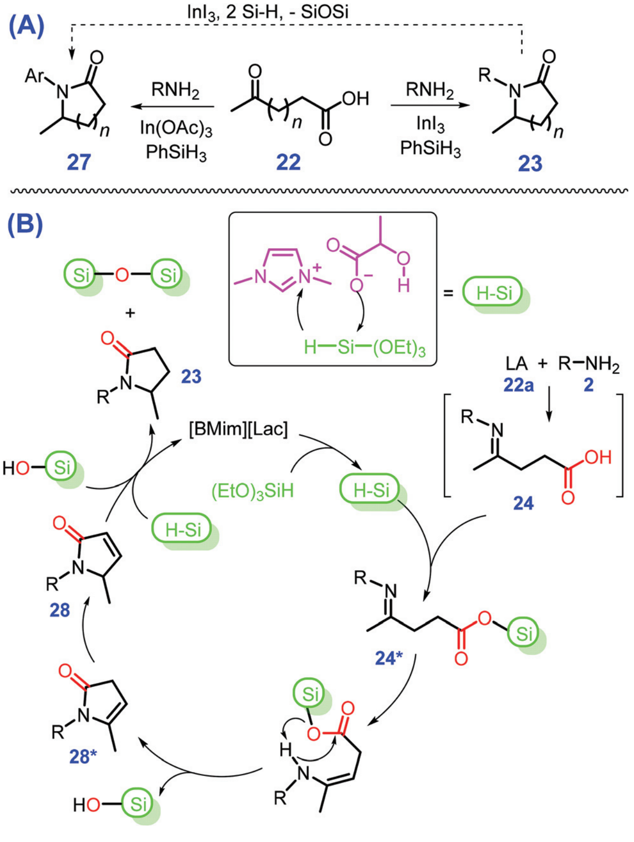
nitro compounds can be employed as the precursor of LA (**22a**) and nitrogen sources for producing pyrrolidones *via* additional acid-catalyzed hydrolysis and *in situ* hydrogenation steps, respectively.[121,122] The replacement of precious elements in Scheme 8 with abundant and low-cost metals is highly desirable, for which several well-designed base metal catalysts, such as Cu_{15}/Al_2O_3 doped with Pr ($Cu_{15}Pr_3/Al_2O_3$),[123] carbon-supported FeNi nanoparticles,[124] and carbon nanotubes supported porous-carbon-coated Ni (CNF_x@Ni@CNTs)[125] have been explored for synthesis of *N*-substituted pyrrolidones (up to 99% yield) from LA (**22a**) and amines although they require relatively harsh reaction conditions (130 °C to 175 °C, 1 to 5 MPa H_2). Well dispersed metal particles (*e.g.*, Cu and Ni) on porous solid supports (*e.g.*, γ-Al_2O_3, carbon nanotubes) and the use of continuous fixed-bed reactors enhance catalytic performance of prepared non-noble metals.[123–125] Solid supports not only increase metal stability and improve reusability, but also provide acid sites with appropriate acid strength and density that enhances substrate adsorption onto active sites of the catalyst that facilitates tandem condensation and hydrogenation processes.

In comparison with non-noble metals (*e.g.*, Ni), precious metals (*e.g.*, Pt) typically show stronger chemisorption of the imine generated from LA (**22a**) and an amine (*e.g.*, benzyl amine) *via* condensation, but they have lower affinity for H_2.[126,127] With respect to non-noble metal catalysts, weak chemisorption towards the intermediate leads to difficulty in activation of the imine, while strong H_2 adsorption results in excessive blocking of the metal surface. These two factors might eventually result in the non-noble metal catalyst to have relatively low hydrogenation activity based on the Sabatier principle.[128] In good agreement with the above statement, Gao *et al.* elaborated an unconventional pathway for the reductive amination of LA (**22a**) over a base metal catalyst, in which Ni/C first promotes the formation of amides **26** followed by undergoing cascade cyclization, dehydration, and reduction to yield the target product pyrrolidone **23** (path 2, Scheme 8),[125] in accordance with the Sabatier principle.

Instead of using flammable H_2 gas, air-stable and safe hydrosilane (*e.g.*, $PhSiH_3$ and $(EtO)_3SiH$) can be used as a mild reductant for reductive cycloamination of LA (**22a**) with primary amines to produce pyrrolidones **23** in moderate to good yields (up to 99%) over $B(C_6F_5)_3$,[129] Fe-complex,[130] or transition metal salts such as $In(OAc)_3$ and $AlCl_3{\cdot}6H_2O$[131,132] at 30 to 120 °C for 1 to 24 h, as in Scheme 9. Particularly, by changing the transition metal salt from $In(OAc)_3$ or $AlCl_3{\cdot}6H_2O$ to either InI_3 or $RuCl_3{\cdot}3H_2O$ that bear stronger Lewis acidity, affords pyrrolidines **27** in good yields (55–93%) under similar reaction conditions to those used in the synthesis of pyrrolidones **23**.[131,132] Namely, the removal of oxygen from the lactam (pyrrolidone, **23**) with hydrosilane ($PhSiH_3$) to give the cyclic amine (pyrrolidine, **27**) and corresponding siloxane needs to be activated by a Lewis acidic metal salt that is stronger than $In(OAc)_3$ or $AlCl_3{\cdot}6H_2O$. In other words, the selectivity toward pyrrolidones can be controlled by design of the catalyst with appropriate Lewis acidity or basicity. Similar to metal salts, a pharmaceutically acceptable and nontoxic ionic liquid 1-butyl-3-methylimidazolium lactate ([BMIm][Lac]), in combination with $(EtO)_3SiH$, is efficient for production of pyrrolidones **23** (36–96% yields) at 80 °C within 1 h to 3 h.[133] Serving as a multifunctional catalyst, [BMIm][Lac] with both acidic (–OH) and basic (–COO$^-$) sites concurrently promotes activation of hydrosilane and cycloamination of LA (**22a**) or keto acids (**22**) successively to **24** and **28**, to finally afford pyrrolidones **23** (Scheme 9B). However, the use of hydrosilanes as H-donor may co-produce waste due to the formation of silicon resins, and the spent homogeneous catalysts suffer from issues regarding reusability and potential environmental contamination. Exploration of benign and eco-friendly alternatives for both aspects is thus highly desirable for sustainable synthesis of pyrrolidones and other relevant azaheterocycles.



Scheme 9 Schematic illustration for (A) reductive cycloamination of LA (**22a**) or keto acids (**22**) to pyrrolidones/lactams **23** or pyrrolidines/cyclic amines **27** (30 °C to 120 °C for 1 h to 24 h) and (B) detailed reaction mechanism. Adapted with permission from ref. 131–133, Copyright © 2016, Wiley-VCH; Copyright © 2017, Royal Society of Chemistry; Copyright © 2017, American Chemical Society.

Formic acid (HCOOH) was a co-product of LA (**22a**) in the synthesis of LA from biomass sugars, and its use as a hydrogen source minimizes the generation of chemical waste in biorefineries.[134,135] Metal catalysts such as Au/ZrO_2-VS, Ir-complex, Ru-complex, $Ru_3(CO)_{12}$, and $Fe_3(CO)_{12}$ allow selective decomposition of HCOOH to CO_2 and H_2, while they were normally unable to tolerate CO that forms in the dehydration of

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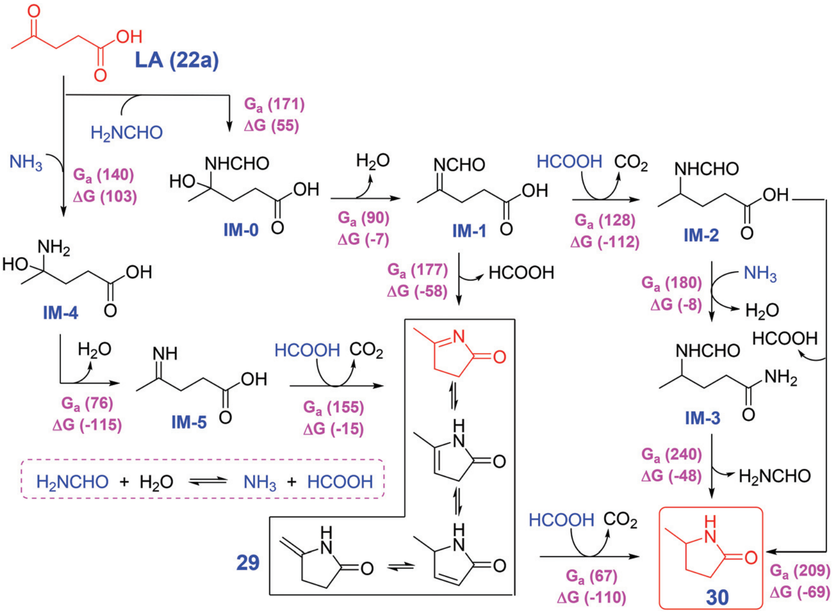
HCOOH.[136–140] In the reductive cycloamination of LA (**22a**), either straightforward hydrogenation with H_2 generated *in situ* from HCOOH or *via* transfer hydrogenation process occurs as the rate-determining step in the synthesis of pyrrolidones.[136–140] Instead of using high-pressure hydrogen or acidic HCOOH and basic ammonia or amines for the reductive amination reaction, ammonium formate ($HCOONH_4$) is a convenient nitrogen and hydrogen source. Amarasekara and Lawrence found that RANEY® Ni efficiently catalyzes cycloamination of LA (**22a**) with $HCOONH_4$ in water, affording 94% yield of 5-methyl-2-pyrrolidone (MPD) at 180 °C for 3 h,[141] and their protocol has authentic safety advantages over the conventional methods using high-pressure H_2–NH_3 gas mixture. Sun *et al.* showed that NHC (N-heterocyclic carbene)-based Ru(II)-coordination polymer is active for the synthesis of MPD (up to 99% yield) from LA (**22a**) and $HCOONH_4$ at 80 °C for 12 h, with TON value of 6.7×10^4 being reported,[142] with both catalysts being recyclable without apparent activity loss, and being applicable to producing *N*-substituted 5-methyl-2-pyrrolidones from amines and LA (**22a**).[141,142]

Under non-catalytic conditions, Wei *et al.* reported that LA (**22a**) reacts with benzylamine to give 1-benzyl-5-methylpyrrolidin-2-one (BMP) to afford a moderate yield of 72% using DMSO as solvent at 100 °C for 4 h.[143] Upon addition of equivalent triethylamine relative to LA (**22a**), BMP yield increases to 89% under otherwise identical conditions. Thus, an appropriate balance of system acidity and basic additive (*e.g.*, triethylamine) is used to obtain favorable reaction progress, and the catalyst-free system is suitable for reductive amination of LA (**22a**) with electron-deficient and -rich amines to afford a variety of *N*-substituted 5-methyl-2-pyrrolidones (up to 93% yield).[143] The use of a continuous-flow microreactor heated at 140 °C remarkably accelerated the reaction rate, and comparable yields of pyrrolidones could be achieved with a residence time of 10 min.[144] To further improve the greenness of the reaction, Ledoux *et al.* shows that the thermal treatment of LA (**22a**), HCOOH and amine mixtures allow access to a series of 5-methylpyrrolidone derivatives with >80% yields in most cases.[145] Due to the absence of catalysts, solvents or additives, this sustainable and efficient reaction system has an exceptionally low *E*-factor of 0.2 and has good potential for application on the industrial scale.

Li *et al.* developed a generic strategy that does not require catalyst or external hydrogen by involving *in situ* controlled-release of HCOOH from *N*-formyl species (*e.g.*, $HCONH_2$) with H_2O for the cycloamination of LA (**22a**) and other keto-acids (**22**), that provides access to 5-methylpyrrolidones and relevant *N*-(un)substituted lactams,[146] that is elucidated by a combination of model experiments and density functional theory calculations. An unconventional pathway *via* cyclic imines (5-methyl-3,4-dihydro-2-pyrrolone (**29**) and its tautomeric structures) as key intermediates is elucidated by density functional theory (DFT) calculations show yields of 5-methyl-2-pyrrolidone (**30**) from LA (**22a**) and $HCONH_2$, which is different from the conventional approaches encompassing cascade reductive amination and cyclization (Scheme 10).[146] The simple and eco-friendly protocol of Li *et al.*[146] may open an avenue for direct synthesis of *N*-(un)substituted pyrrolidones/lactams by cyclic diamination of keto acids without external hydrogen gas. Besides the above-discussed reductive amination of LA (**22a**) and N-containing compounds, a number of other renewed synthetic routes such as ketoamides proceeding *via* cascade cycli-



Scheme 10 Reaction pathways for cycloamination of LA (**22a**) and H_2NCHO in water with computed free energies and enthalpies in parentheses (kJ mol^{-1}). IM: intermediate; MDPY: 5-methyl-3,4-dihydro-2-pyrrolone; MPD: 5-methyl-2-pyrrolidone. Adapted with permission from ref. 146, Copyright © 2019, Wiley-VCH.

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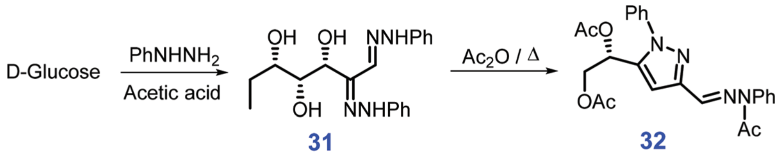
zation and ionic hydrogenation mediated by $Al(OTf)_3$ and Et_3SiH,[147] reductive transformation of itaconic acid and NH_3 over Ru/C and H_2,[148] reductive *N*-alkylation and decarboxylation of glutamic acid catalyzed by Pd/Al_2O_3 with and H_2,[149] and Zr-catalyzed *N*-acylation of lactams[150] have been explored for efficient construction of pyrrolidone-type motifs. The catalyst-free reaction system seems more sustainable and economic for producing pyrrolidones, while its reaction rate is much lower than metal- or acid-catalyzed processes. In this regard, the design of appropriate continuous flow reactors may facilitate the rapid thermal conversion routes to the synthesis of pyrrolidones.

2.3. Pyrazoles

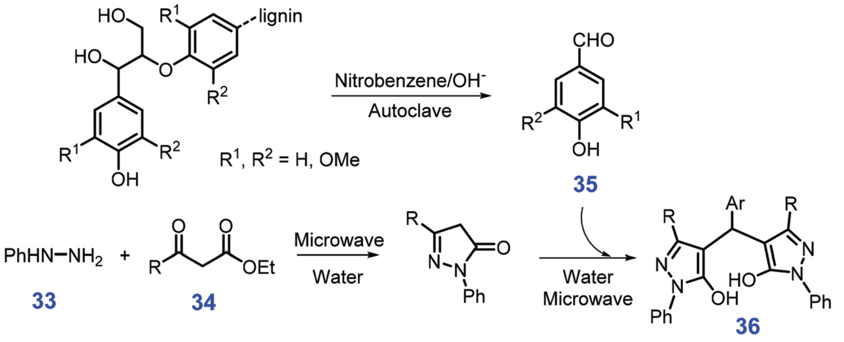
Pyrazoles are a class of structural motifs prevalent in biologically active agents and medicines, notably, Lexiscan, Xalkori, Celebrex, and Viagra,[151] and these motifs are also present in dyes and they are utilized as ligands for metal catalysts.[152,153] The synthesis of pyrazole derivative **32** from acetic anhydride reacting with glucose phenylosazone **31** which is readily derivable from glucose and phenylhydrazine in the presence of acetic acid was first reported by El Khadem *et al.* (Scheme 11).[154–156] Under microwave irradiation, cyclic addition of glucose phenylosazone goes to completion in 5 min, affording the pyrazole derivative **32** in good yields (86%).[157] The microwave-assisted reaction system[154–156] is applicable to synthesis of pyrazoles (up to 96% yield) from respective osazones derived from galactose, arabinose, and xylose, and although comparable yields of pyrazoles are obtained using conventional heating modes, more than 1 h is required.[158,159]

As shown in Scheme 12, starting from phenylhydrazine **33**, β-ketoesters **34**, and aromatic aldehydes **35** (*e.g.*, vanillin and syringaldehyde) pre-prepared from lignin by thermal treatment with 2 mol L^{-1} NaOH and nitrobenzene (170 °C, autogenous pressure 1 MPa, 2 h) in a stainless steel autoclave, a diversity of 4,4′-arylmehtylenebis(1*H*-pyrazole-5-ol)s **36** with 79–88% yields are obtained in water under microwave irradiation (300 W, 100 °C, 10 min).[160] In comparison with standard drug (Trolox), all the prepared bispyrazoles exhibit good radical scavenging activities of 2,2′-azino-bis(3-ethylenzothiazoline-sulphonic acid) diammonium salt ($ABST^{+}$) and *N*,*N*-diphenyl-*N*′-picrylhydrazyl (DPPH). Given that the environmentally benign synthetic procedures developed by Yang *et al.*,[160] these bispyrazoles derivatives have promising potential in the therapy of free radical-related diseases (*e.g.*, tumors).

Other bio-based molecules (*e.g.*, 1,3-dicarbonyl compounds, vinylogous formamides, and 1,3-diols) besides sugars or lignin derivatives can be used to produce pyrazoles.[161,162] The 1,3-dicarbonyls are commonly employed as feedstocks to construct pyrazoles by condensation with a aryl or alkyl hydrazine, while their low stability restricts their applicability for obtaining substituted pyrazoles.[163,164] On the other hand, 1,3-diacetals or vinylogous formamides **37** by reaction with hydrazines **38** allow access to substituted pyrazole motifs **39** (path A, Scheme 13), while multistep synthesis procedures were prerequisite due to the existence of sensitive functional groups.[165] Much attention has been paid to the development of more efficient routes for substituted pyrazoles. For instance, Schmitt *et al.* reported that 1,3-diols **40** used instead of the typical masked dialdehydes enable the production of pyrazoles *via* hydrogen transfer process promoted by a Ru-complex,



Scheme 11 Representative synthetic routes to pyrazole derivative **32** from glucose and phenylhydrazine *via* glucose phenylosazone **31**. Adapted with permission from ref. 157, Copyright © 2007, Taylor & Francis.



Scheme 12 Synthetic routes to 4,4′-arylmehtylenebis(1*H*-pyrazole-5-ol)s **36** from phenylhydrazine **33**, β-ketoesters **34**, and lignin-derived aromatic aldehydes **35**. Adapted with permission from ref. 160, Copyright © 2012, Wiley-VCH.

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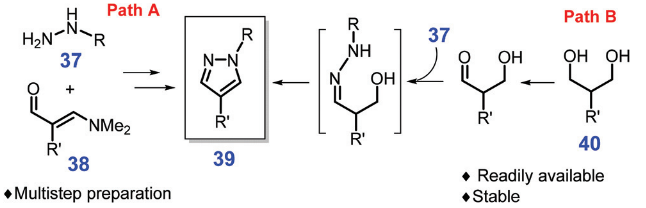


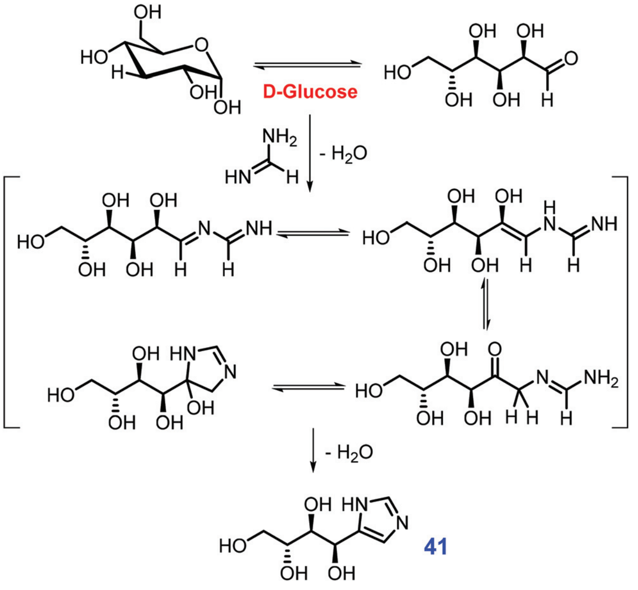
Scheme 13 Synthetic routes to pyrazoles from masked dialdehydes **38** or diols **40**. Adapted with permission from ref. 166, Copyright © 2015, American Chemical Society.

$RuH_2(PPh_3)_3CO$/xantphos (path B, Scheme 13).[166] The scope of both the diol and hydrazine components can be extended with good compatibility, and satisfactory pyrazole yields (84%) from scaled-up isopropyl diol (1 g, 8.5 mmol) and phenylhydrazine (8.5 mmol) in toluene at 110 °C after 24 h,[166] however, unreliable regioselectivity of the obtained 3-alkyl pyrazoles needs to be resolved in follow-up studies. Also, the initial acquisition of starting materials from biomass generally involves complex processes, which would be another primary task needing to take into consideration.

2.4. Imidazoles

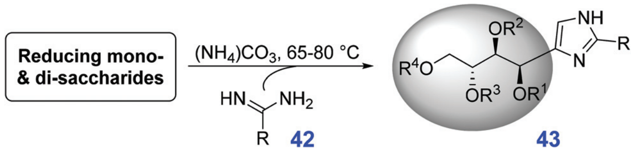
Like other five-membered N-heterocycles, substituted imidazoles occur in natural products bearing broad-spectrum biological activities, and are target-oriented in the preparation of functional molecules such as ionic liquids or N-heterocyclic carbenes (NHCs).[167–169] Industrially, simple imidazoles are synthesized from the condensation of 1,2-dicarbonyls with ammonia and aldehydes *via* the Radziszewski reaction.[170] In the presence of basic catalysts (*e.g.*, $CuCO_3/Cu(OH)_2$), 4-hydroxymethyl imidazole is obtained by thermal treatment of formaldehyde and concentrated ammonia with fructose or glucose that underwent retro-aldol fission to *in situ* release of dihydroxyacetone and glyceraldehyde.[171] If hexose sugar (*e.g.*, fructose) is heated in a pressure vessel with formamidinium acetate and liquid ammonia, the retro-aldol fission is remarkably inhibited and instead affords 4-tetrahydroxy-butyl imidazole **41** as the dominant product (Scheme 14).[172]

In a one-pot process, a variety of mono- and disaccharides react with amidines **42** in molten ammonium carbonate to give tetrahydroxybutyl substituted imidazoles **43** with varying glycosylation patterns, depending on the type of saccharide substrates (Table 1).[173] After purification by silica gel chromatography (eluent, 3 : 1 (v/v) ethanol : ammonia), moderate isolated yields (25–50%) of the imidazole products **43** are obtained from sugars like fructose, glucose, isomaltulose, melibiose, leucrose, maltose, cellobiose, and lactose (Table 1) after heating at 65 °C to 80 °C until reaction completion as monitored by thin-layer chromatography.[173] The reaction system uses a benign solvent (molten ammonium carbonate), it does not require protection groups in its chemistry, and is thus sustainable and has great potential to replace methods based on petroleum resources.



Scheme 14 Synthetic routes to 4-tetrahydroxy-butyl imidazole **41** from glucose and formamidine. Adapted with permission from ref. 172, Copyright © 2016, Thieme Chemistry.

Table 1 Thermal synthesis of tetrahydroxybutyl substituted imidazoles **43** with varying glycosylation sphere from one-pot condensation of different sugars with amidines **42** in molten ammonium carbonate. Reproduced with permission from ref. 173, Copyright © 2013, Royal Society of Chemistry



Substrate	R	Product	R^4	R^3	R^2	R^1	Yield (%)
Fructose	H[a]	2	H	H	H	H	50
Glucose	H	2	H	H	H	H	47
Isomaltulose	H	3	α-D-Glc	H	H	H	49
Isomaltulose	Me[b]	4	α-D-Glc	H	H	H	30
Isomaltulose	Ph[c]	5	α-D-Glc	H	H	H	5
Melibiose	H	6	α-D-Glc	H	H	H	38
Melibiose	Me	7	α-D-Glc	H	H	H	27
Leucrose	H	8	H	α-D-Glc	H	H	38
Leucrose	Me	9	H	α-D-Glc	H	H	26
Maltose	H	10	H	H	α-D-Glc	H	28
Cellobiose	H	11	H	H	β-D-Glc	H	25
Lactose	H	12	H	H	β-D-Glc	H	40

[a] Formamidine acetate. [b] Ethylacetimidate. [c] Benzamidine hydrochloride.

Several other synthetic approaches were also developed to produce substituted imidazoles from sugars (Scheme 15).[174–176] For example, arabinose-derived aldehyde **44** undergoes condensation with glyoxals **45** in methanol/NH_3 mixtures to yield linear imidazole sugars that can be further converted to the imidazole **46** after the removal of the trityl group with HCl in dioxane (Scheme 15A).[174] The reaction of *O*-acetylated gluco-

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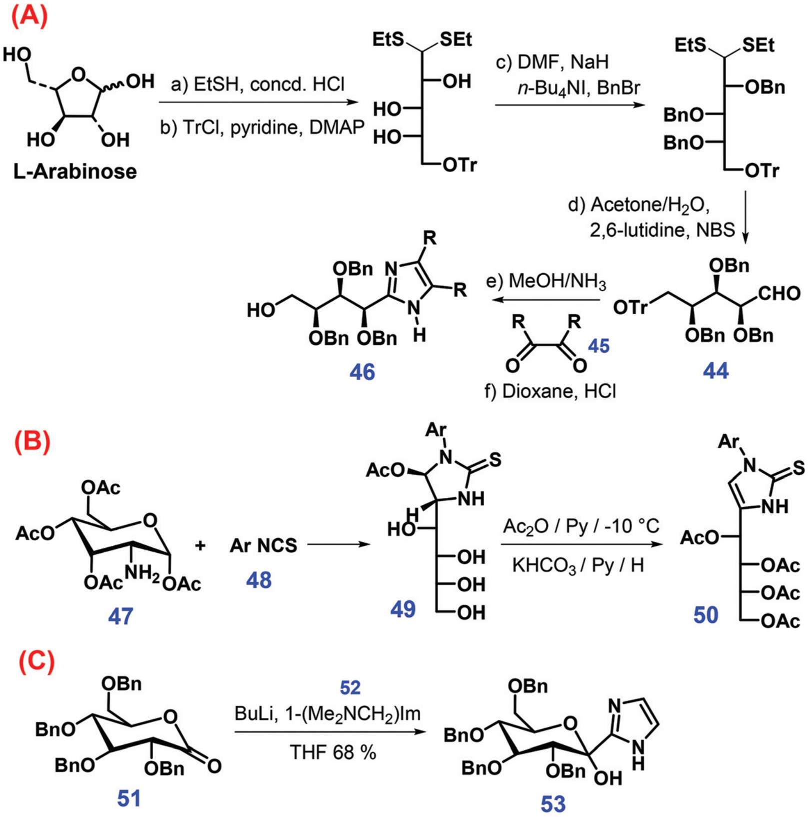
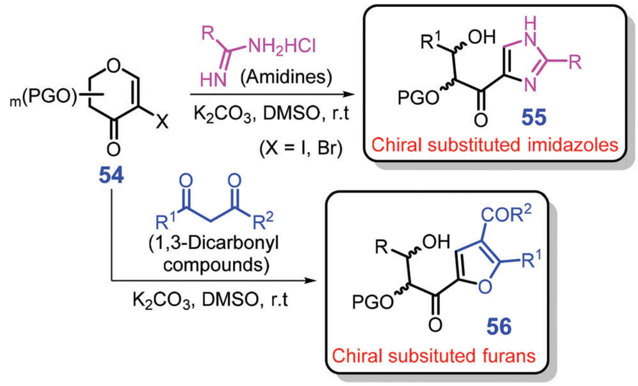


Scheme 15 Synthetic routes to imidazole derivatives from sugars: (A) L-arabinose, (B) *O*-acetylated glucoseamine **47**, and (C) 2,3,4,6-*O*-benzyl-glucono-1,4-lactone **51**. Adapted with permission from ref. 174–176, Copyright © 1995 & 2006, Wiley-VCH; Copyright © 2015, Elsevier.

seamine **47** with *o*,*o*′-disubstituted arylisothiocyanates **48** gives **49**, which when followed by treatment with acetic anhydride in pyridine and subsequent elimination of acetic acid affords the imidazoline thion **50** (Scheme 15B).[175] In another manner, direct introduction of imidazole ring is achieved through adding 2-lithio1-[(dimethylamino)methyl]-1*H*-imidazole **52** to 2,3,4,6-*O*-benzyl-glucono-1,4-lactone **51**, yielding sugar-derived imidazole **53** (Scheme 15C).[176]

The 2-haloenones **54** derivable from sugars were deemed as crucial intermediates for construction of heterocycles.[177,178] In the absence of any ligand or metal catalyst at ambient temperature, Mal and Das showed that a diversity of chiral hydroxy imidazoles **55** and furans **56** were able to be synthesized from 2-haloenones **54** with amidines or 1,3-dicarbonyl compounds, respectively, over K_2CO_3 in DMSO at room temperature (Scheme 16) through sequential Michael addition, cyclization, and sugar-ring opening reactions.[179] Notably, the benign reaction system is tolerant to the substrates with variable substituents, affording chiral substituted imidazoles **55** with moderate to good yields (43–88%) and excellent regioselectivity (single in most cases) at room temperature within 45–120 min. It is worth mentioning that the yields of imidazoles obtained from sugars are relatively low (typically <50%), possibly due to the complicated reaction processes, which has to be improved by developing more efficient catalyst systems.



Scheme 16 Synthetic routes to either chiral hydroxy imidazoles **55** or furans **56** from 2-haloenones **54**. Adapted with permission from ref. 179, Copyright © 2016, American Chemical Society.

2.5. Other five-membered N-heterocycles

Furfural, as one of five-membered oxygen-containing heterocycles, could be readily produced from xylose.[180] Through condensation of cysteine **57** with 2-cyanofuran **58** that is pre-synthesized from furfural, aqueous ammonia and iodine over basic K_2CO_3 in a mixture of methanol/water at 60 °C, 4-carboxy-2-furylthiazoline **59** could be obtained, followed by alkylation with MeI over K_2CO_3 in *N*,*N*-dimethylformamide

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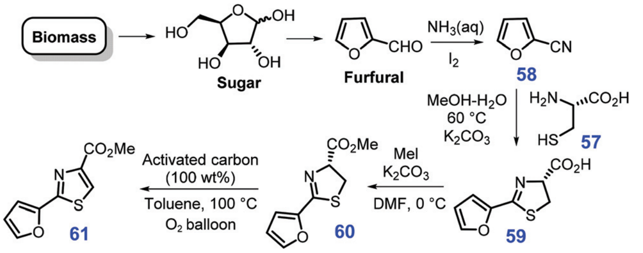
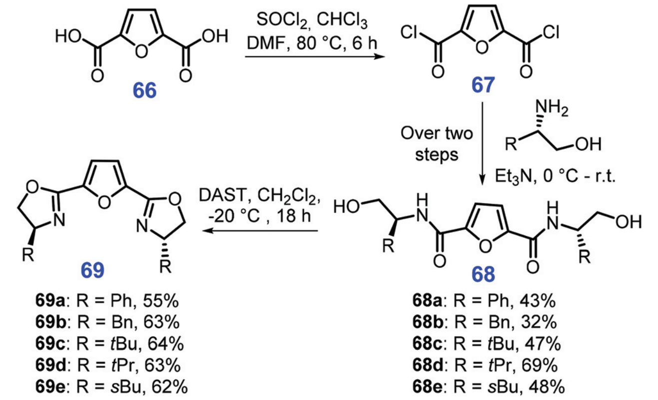


Scheme 17 Synthetic routes to 2-furylthiazole **61** from bio-based furfural.

(DMF) to produce furylthiazoline **60** in a three-step overall yield of 63% (Scheme 17).[181] Finally, 2-furylthiazole **61** (97% yield) is formed by activated carbon-promoted the thermal aromatization of the thiazoline ring of **60** in an oxygen atmosphere (1 bar, O_2 balloon) at 100 °C in toluene.

Similar to the construction of the furan-thiazole conjugated scaffold, furyloxazole **63** can be obtained (52% yield) *via* a one-pot cascade dehydrative condensation and oxidation of bio-based furfural and serine methyl ester **62** (Scheme 18).[182] At room temperature, the condensation of furfural with serine methyl ester **62** mediated by K_2CO_3 and $MgSO_4$ in *N*,*N*-dimethylacetamide (DMA) affords oxazolidine **64** in ring-chain tautomers (**64a** and **64b**), followed by oxidation over $BrCCl_3$/DBU (1,8-diazabicyclo(5.4.0)undec-7-ene) to give 2,5-dihydrooxazole **65**. The resulting intermediate is then subjected to isomerization and a second oxidation, ultimately yielding the furyloxazole **63**.[182]

The readily available feedstock 2,5-furandicarboxylic acid (FDCA, **66**) can be derived from cellulosic biomass-derived HMF (**17**) *via* oxidation.[183] Selvakumar *et al.* demonstrated that FDCA (**66**) can be used for producing chiral bisoxazolines **69** (Scheme 19).[184] Initially, FDCA (**66**) is transformed into its acyl chloride **67**, followed by condensation with chiral substituted amino alcohols to yield relevant amides **68** (32–69% yields), which are eventually cyclized to generate the bisoxazolines **69**. Furthermore, other five-membered N-heterocycles such as 1,2,3- and 1,2,4-triazoles, oxadiazoles, thiadiazoles, and tetrazoles can be synthesized from sugars in modest yields.[185] However, most reaction systems involved lack stereo- or enantioselectivity, and need to be updated to use green synthetic methods (*e.g.*, photo- and electroinduction) as such pathways are highly desirable for concise synthesis of these N-heterocycles.[186–188]

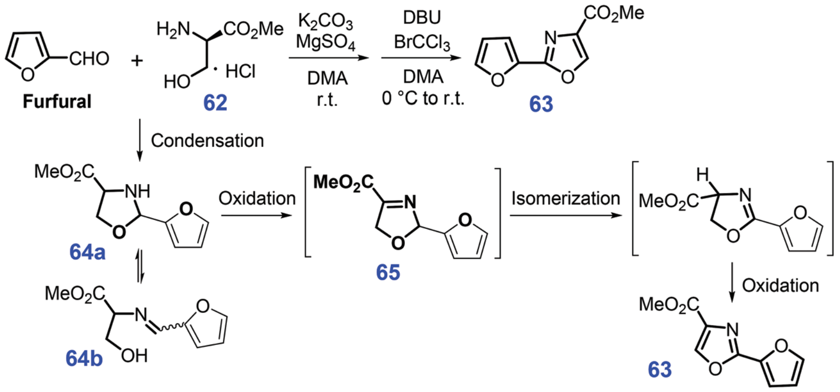


Scheme 19 Synthetic routes to chiral bisoxazolines **69** from 2,5-furandicarboxylic acid (FDCA, **66**).

3. Six-membered N-heterocycles

3.1. Pyridines

Pyridines, which have high biological activity, are prevalent in many agrochemicals and pharaceuticals,[189,190] as well as directly employed as catalysts and solvents in chemical syntheses.[191,192] Industrially, pyridines (pyridine and picolines) are mainly produced by Chichibabin condensation of aldehydes (*e.g.*, formaldehyde and acetaldehyde) with ammonia in fixed-bed reactors.[193–196] A more effective method for producing pyridines than Chichibabin to react **70** with NH_3 to afford pyridine **71** in high yields (*ca.* 70%) with up to *ca.* 60% 3-picoline **72** yield upon addition of propanal or acetaldehyde.[197] Typically, several elemental steps including C–N



Scheme 18 Synthetic routes to furyloxazole **63** from serine methyl ester **62** and furfural. Adapted with permission from ref. 182, Copyright © 2010, American Chemical Society.

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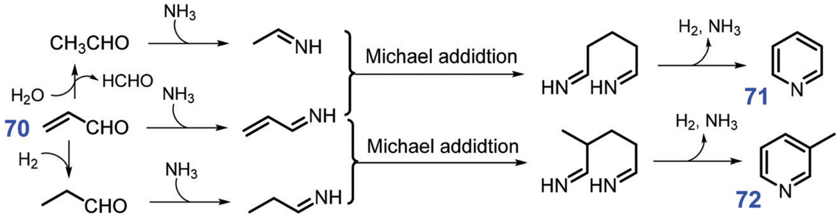
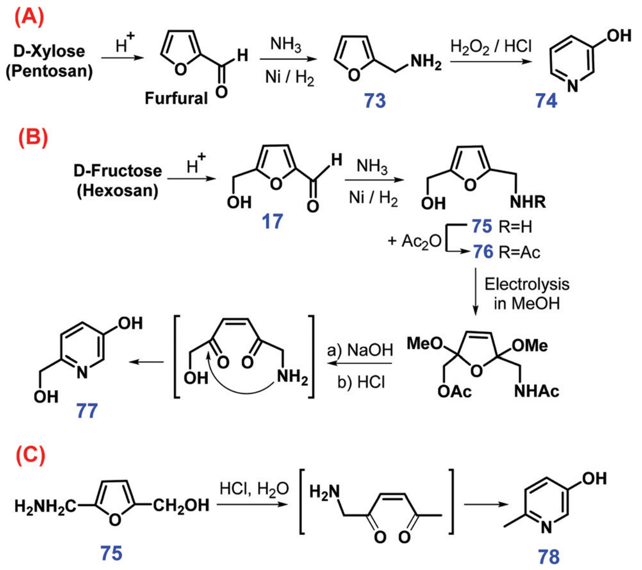


Scheme 20 Synthetic routes to pyridines (**71** and **72**) from acrolein **70** and NH_3. Adapted with permission from ref. 198 and 199, Copyright © 2019, Springer Nature; Copyright © 2011, Wiley-VCH.

condensation, Michael addition, hydrogenation, and dehydrogenation involve in the synthesis of pyridine and 3-picoline from acrolein (Scheme 20), whereas acetaldehyde formed *in situ* from acrolein *via* water-promoted retro-aldol reaction is important in the formation of pyridine while acrolein hydrogenation to propionaldehyde is necessary for 3-picoline.[198,199] Considering that acrolein is a key intermediate in the synthesis of pyridines, glycerol as the co-product of biodiesel industry and waste polylactic acid are also explored as starting material for the synthesis of pyridines despite of relatively low yields.[200–204] Zeolite-based catalysts (*e.g.*, HZSM-5) have unique features such as shape selectivity, high surface area, and good thermal stability, and they are highly active for the production of pyridines by promoting C–N condensation and Michael addition.[205–207] In most cases, the pore size and acidity of ZSM-5 have to be regulated by treatment with alkali or acids or introduction of metal oxide into their structure, so as to increase picoline yield with increased basicity or acidity in the modified catalysts.

Via a three-step sequential reaction process, 3-pyridinol **74** can be synthesized from xylose or even pentosan involving acid-catalyzed hydrolysis/dehydration to furfural, reductive amination to furfurylamine **73**, and succedent 30% H_2O_2-mediated oxidation in 3 mol L^{-1} HCl (Scheme 21A).[208] In contrast, more laborious procedures are required for the upgrading fructose (or hexosan) to 6-hydroxymethyl-3-pyridinol **77** (Scheme 21B), where N- and O-blocking (**75** → **76**) of HMF **17** are prerequisite prior to proceeding with electrocatalytic oxidation in methanol, thus leading to tandem deacetylation, acetal-hydrolysis, and cyclization to form the pyridine framework (85% yield of **77**).[208] In related ways, 2-(hydroxymethyl)-5-(aminomethyl)-furan **75** can be converted to 6-methyl-3-pyridinol **78** with a high yield of 88% *via* cascade hydrolysis and cyclization catalyzed by HCl under reflux (Scheme 21C).[209]



Scheme 21 Synthetic routes to pyridinols (**74**, **77** & **78**) from furfuryl amines: (A) **73**, (B) **75** & **76**, and (C) **75** derived from pentose and hexose sugars. Adapted with permission from ref. 208, Copyright © 1998, Elsevier.

3.2. Pyrazines

Pyrazines have two nitrogen atoms in a 6-memebered aromatic ring and exhibit good antitumor, antibacterial, and antibiotic activities, which are extensively applied in commercial medicines and in the polymer industry.[210–213] Three major routes commonly employed for the synthesis of pyrazines **81** are (a) intermolecular dehydrogenative coupling of ethylenediamine **79** with 1,2-propanediol **80** or dehydrogenative self-coupling of 2-amino alcohols **12** (Scheme 22A),[214,215] (b) intramolecular cyclization–dehydrogenation of hydroxyl diamines such as hydroxypropyl ethylenediamine **82** (Scheme 22B),[216] and (c) Maillard condensation of sugars with amino acids.[217] However, these developed approaches suffer from environmental issues due to the use of toxic organic ligands and low selectivity toward pyrazines that can be accompanied with unwanted side reactions.

Starting from glyceraldehyde **83** or 1,3-dihydroxyacetone **84** which can be derived from biomass, Song *et al.* found that 2-hydroxymethyl-5-methylpyrazine **87** is obtained in good yields (*ca.* 72%) by reacting **87** in the presence of diammonium phosphate at 90 °C for 1 h in basic mixture solvent of water and dioxane (pH = 8.0–9.1).[218] The 2-imino-1,3-propanediol **85** was identified to be a key reaction intermediate, which might be formed by ketimine condensation of 1,3-dihydroxyacetone **84** with NH_3 generated *in situ* from diammonium phosphate, followed by cyclization to **86** and final dehydration to yield the pyrazine product **87** (Scheme 23).[218] Among these three elemental steps, the rate-determining step is the cyclization reaction, which is possibly ascribed to the lack of active catalytic sites.

In the presence of a tungsten-based catalyst (ammonium metatungstate), Chen *et al.* reported that glucose in 25% aqueous ammonia is transformed directly into 2-methyl pyra-

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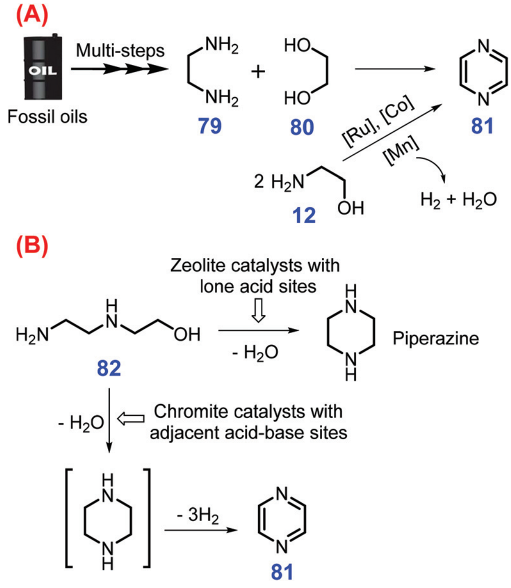
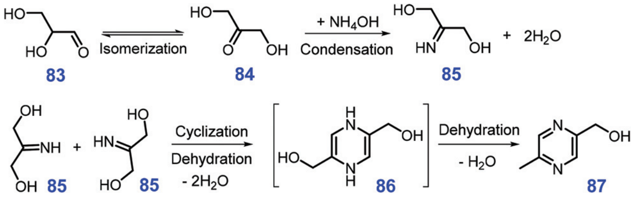


Scheme 22 Synthetic routes to pyrazines **81** *via* (A) inter- and intramolecular dehydrogenative self-coupling of amino alcohols and (B) intramolecular cyclization dehydrogenation of hydroxyl diamines. Adapted with permission from ref. 214, Copyright © 2003, Elsevier.



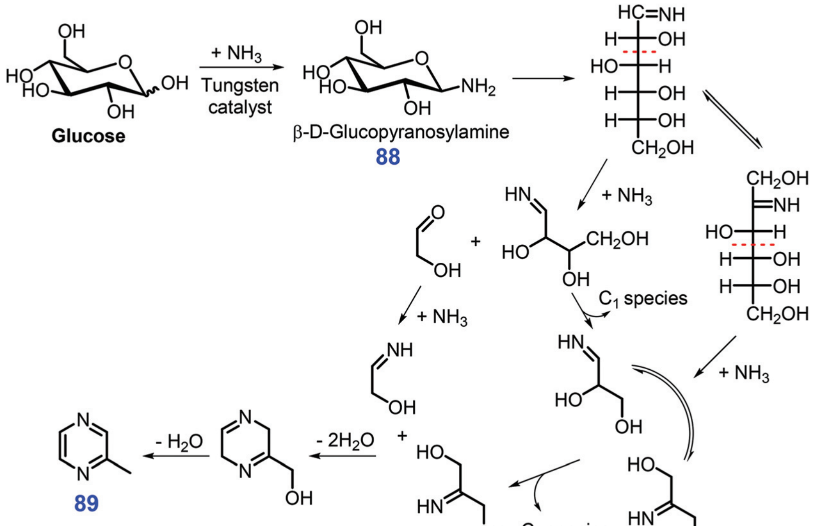
Scheme 23 Plausible pathways for synthesis of 2-hydroxymethyl-5-methylpyrazine **87** from diammonium phosphate and 1,3-dihydroxyacetone **84** at hydrothermal conditions. Adapted with permission from ref. 218, Copyright © 2017, Royal Society of Chemistry.

zine **89** in moderate yields (*ca.* 25.6%) within 15 min at 180 °C *via* tandem fragmentation and cyclization in a single pot (Scheme 24).[219] Prior to fragmentation, β-D-glucopyranosylamine **88** formed from condensation of glucose and NH_3 was identified as one of the important intermediates. The reaction system was remarkably facilitated by tungsten clusters (*e.g.*, $[HW_2O_7]^-$ and $[W_4O_{13}]^{2-}$), with 7.2–23.3% yields of 2-methyl pyrazine **89** being achieved from monosaccharides (*e.g.*, fructose, xylose, chitin monomer, glucosamine) and several disaccharides (*e.g.*, maltose and cellulose) under otherwise identical reaction conditions.[219] From the viewpoint of sustainability, it would highly desirable to further develop more robust and active catalysts for using tandem fragmentation and cyclization methodologies.

3.3. Other six-membered N-heterocycles

Apart from pyridines and pyrazines, other six-membered N-heterocycles such as pyridazines, pyrimidines, and triazines can be synthesized from bio-based feedstocks in spite of being reported for only a few works. For instance, 2,5-bis(alkoxymethyl)furan **90** undergoes oxidative ring-opening by meta-chloroperbenzoic acid (MCPBA) to give the hexene dione **91**, followed by action with hydrazine to furnish the pyridazine **92** (Scheme 25).[185,220] For producing enantiomerically pure pyridazines, β-keto ester functionalization of epoxy pyranosides is an effective way.[221] Other relevant N-heterocyclic synthons can be constructed *via* these synthetic strategies.

Under basic conditions (MeONa in methanol), nucleophilic attack of the amidinium reagent (*i.e.*, acetamidinium, benzamidinium and guanidinium salts) takes place at the C1 position of 2-formyl-galactal **93**, followed by cyclization to give the substituted 5-(1,2,4-tri-*O*-benzyl-D-lyxo-1,2,3,4-tetrahydroxybutyl)pyrimidines **94** (Scheme 26A).[222] Likewise, substituted triazines **97** can be prepared at 37 °C by condensation of ami-



Scheme 24 Possible pathways for the synthesis of 2-methyl pyrazine **89** from glucose and NH_3 over ammonium metatungstate. Adapted with permission from ref. 219, Copyright © 2017, American Chemical Society.

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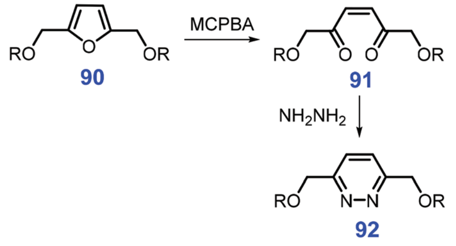
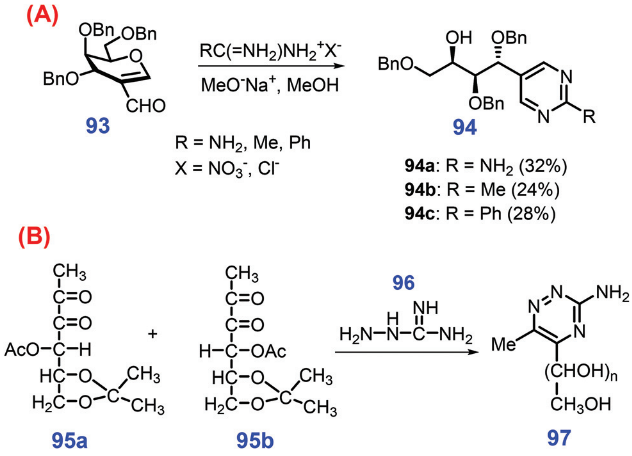


Scheme 25 Synthetic routes to pyridazine **92** from 2,5-bis(alkoxymethyl)furan **90**.



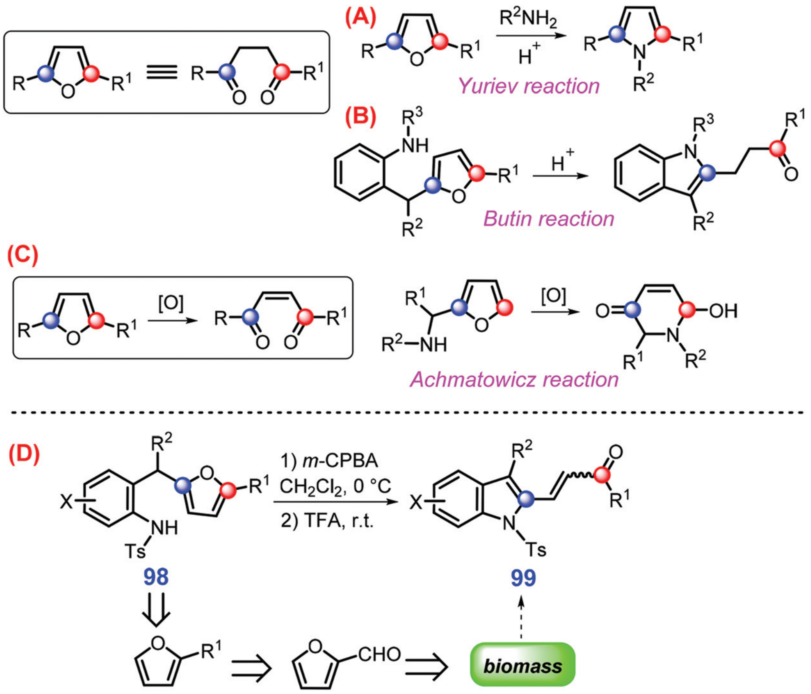
Scheme 26 Synthesis of (A) pyrimidines **94** from **93**, and (B) triazines **97** from dicarbonyl derivatives **95**. Adapted with permission from ref. 222 and 223, Copyright © 1995 & 2002, Taylor & Francis.

noguanidine **96** with two 3-deoxy-1,2-dicarbonyl derivatives **95**, including 4-*O*-acetyl-1-deoxy-5,6-*O*-isopropylidene-2,3-D-*threo*-hexodiulose **95a**, and 4-*O*-acetyl-1-deoxy-5,6-*O*-isopropylidene-2,3-D-*erythro*-hexodiul **95b** (Scheme 26B).[223] In contrast to their significance, development of more pragmatic strategies for the sustainable production of six-membered N-heterocycles from biomass resources is urgently required.

4. Fused N-heterocycles

4.1. Indoles

As one of the most important classes of azaheterocycles, indoles are used in agricultural chemicals (*e.g.*, pesticide), pharmaceuticals, dyes, and other related chemicals.[224–227] Indoles can be extracted directly from fungal biomass,[228] even though a large number of conventional methods such as Fischer, Fukuyama, Gassman, and Leimgruber–Batcho reactions have been explored for their synthesis.[229,230] With respect to upgrading "furan platform", various N-heterocycles (*e.g.*, pyrroles and indoles) can be synthesized *via* respective processes like Yuriev, Butin, and Achmatowicz reactions (Scheme 27A–C).[231] Specifically, biomass-derived 2-(2-aminobenzyl)furans **98** undergoes oxidative rearrangement successively with *m*-chloroperbenzoic acid (*m*-CPBA) at 0 °C and then application of trifluoroacetic acid (TFA) at room temperature gives 2-(2-acylvinyl)indoles **99** (up to >90% yield) in exclusive *E*- or *Z*-isomers, closely dependent on the presence or absence of electron-donating alkoxy substituents in the phenyl ring, respectively (Scheme 27D).[231]



Scheme 27 Representative pathways for upgrading furans to azaheterocycles *via* (A) Yuriev reaction, (B) Butin reaction, (C) Achmatowicz reaction, and (D) oxidative rearrangement. Adapted with permission from ref. 231, Copyright © 2016, American Chemical Society.

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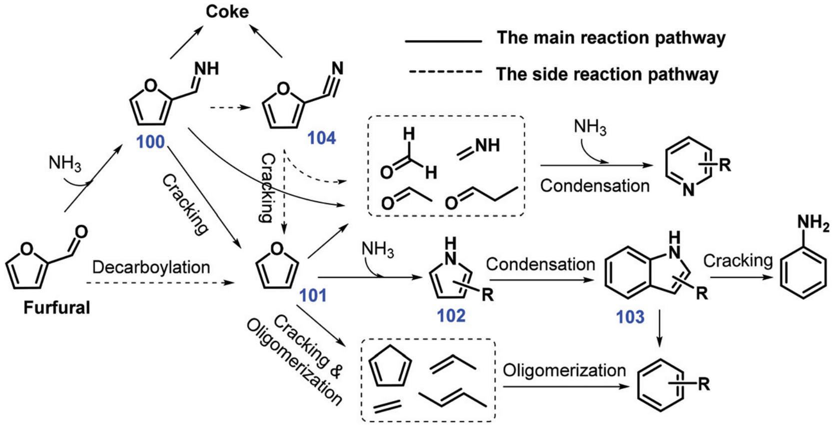
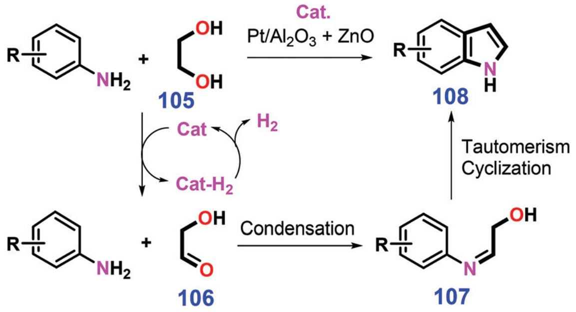


Scheme 28 Possible pathways toward indoles **103** directly from furfural over HZSM-15. Adapted with permission from ref. 232, Copyright © 2015, Elsevier.

Zeolite HZSM-5 (Si/Al = 25) was illustrated to efficiently catalyze direct gas-phase conversion of furfural *via* cascade thermal conversion and ammonization with NH_3 to give indoles (yield 20.79%) at 650 °C with a weight hourly space velocity (WHSV) of 1.0 h^{-1} and NH_3/furfural molar ratio of 2. It was proposed that the reaction between furfural and ammonia gives furfuryl imine **100**, followed by cracking reaction to furan **101** which is considered as the key intermediate leading to pyrrole **102** and ultimately to indoles **103**, with pyridines, aniline, and benzenes being concurrently generated as byproducts (Scheme 28).[232] At moderately high temperatures (500 °C), moderate yields of indoles **103** (*ca.* 32%) are obtained from furan **101** under otherwise identical reaction conditions,[233] indicating that the elemental step involving decarbonylation of furfural to furan **101** is crucial to the overall reaction. It is interesting that NH_3 diluted by N_2 is able to inhibit the formation of coke derived from 2-furonitrile **104**, thus significantly increasing the yield of indoles **103** (33%) through enhancement of the HZSM-5 stability.[234]

Bio-based diols and anilines are applicable to the production of indoles under thermal conditions (*e.g.*, 350 °C) or with metal catalysts at relatively low temperatures (*e.g.*, 175 °C).[235,236] The combined use of Pt/Al_2O_3 and ZnO catalyzes the dehydrogenation of ethylene glycol **105** to glycolaldehyde **106**, followed by condensation with anilines to the imines **107** that undergo tautomerism and acylation/elimination reaction to afford relevant pyrrole-ring unsubstituted indoles **108** (Scheme 29).[236] In view of H_2 and H_2O being the sole co-products, this type of atom-efficient reaction systems, in combination with stable and lost-cost catalysts, represents an efficient and promising synthetic approach toward indoles.



Scheme 29 Synthetic routes to indoles from anilines and ethylene glycol **105** involving acceptorless dehydrogenative condensation. Adapted with permission from ref. 236, Copyright © 2018, American Chemical Society.

4.2. Benzimidazoles

Benzimidazoles exhibit broad-spectrum bioactivities such as antifungal, antiulcer, antihelmintic, anticancer, and antiviral (*e.g.*, HIV and herpes) activities, and they are used in a number of industrial chemicals such as UVB filters, thermostable membranes (fuel cells), optical brighteners (coatings), and pigments that include the benzimidazole motif.[237–239] Classical approaches to synthesis of benzimidazoles **111** are the strong acid-catalyzed coupling of 1,2-diaminobenzene **109** with carboxylic acids, anhydride, or acyl chloride **110** (Scheme 30A).[240] As another approach, the use of aldehydes as substrates with hydrogen peroxide catalyzed by iodine or ultrasmall ZnO nanoparticles leads to enhanced benzimidazole yields (up to >90%) under benign reaction conditions (room temperature to 40 °C).[241,242] Sulfonated graphitic carbon nitride is able to efficiently catalyze direct conversion of xylose in the presence of 1,2-phenylenediamine in water to benzimidazole derivatives with good yields (*ca.* 84%) at 100 °C for 30 min, where xylose dehydration to furfural followed by cycloamination with 1,2-phenylenediamine occurs consecutively.[243] Similarly, primary alcohols, which are readily available by either fermentation or chemocatalytic valorization of lignocellulose,[244–246] are promising starting materials for *in situ* classical or photochemical oxidation or dehydrogenation to liberate more reactive aldehydes for producing benzimidazoles.

Among the developed strategies for condensation of diamines **109** with alcohols **112** to construct azaheterocycles like benzimidazoles **111**, acceptorless dehydrogenative coupling (ADC) has emerged as an attractive protocol with only mole-

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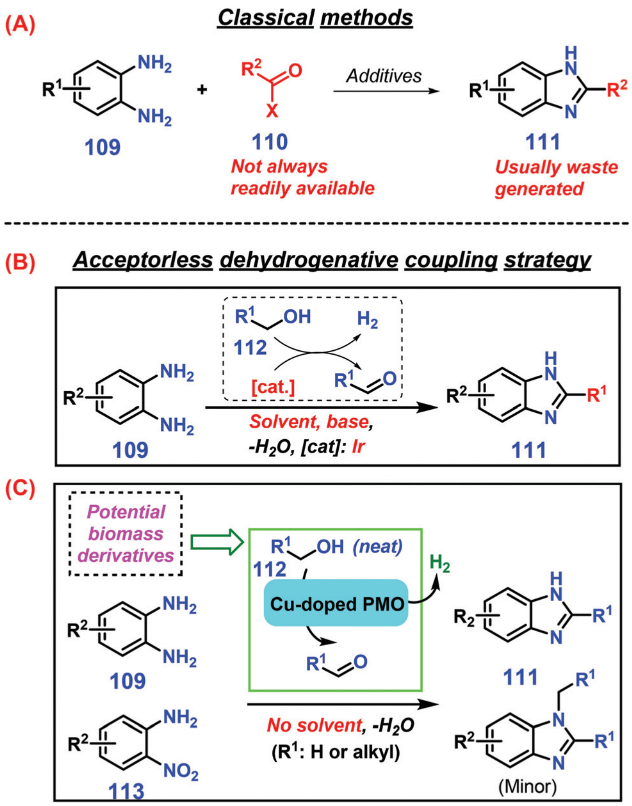


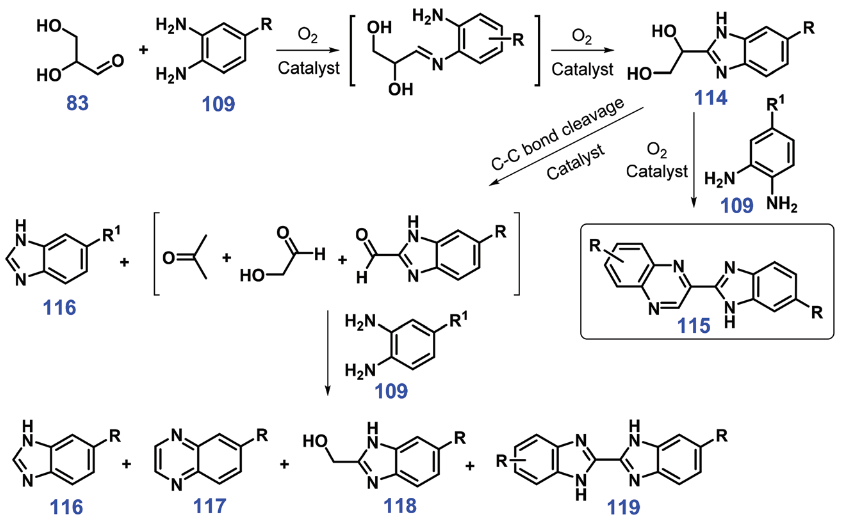
Scheme 30 Representative synthetic routes to benzimidazoles **111** *via* (A) classical methods or (B) acceptorless dehydrogenative coupling strategies with solvent or (C) acceptorless dehydrogenative coupling strategies without solvent. Adapted with permission from ref. 247, Copyright © 2013, American Association for the Advancement of Science.

cular H_2 and innocuous H_2O formed as the co-products (Scheme 30B & C).[247,248] However, the requirement of a homogeneous noble-metal-based complex with the co-addition of a strong base are prerequisite to ensure smooth reaction progress.[249,250] To make the ADC chemistry sustainable, several earth-abundant metal catalysts such as copper-doped porous metal oxides, cobalt–pincer complexes, and magnetic nanofibers confined in carbon nanotubes have been explored, and are capable of promoting efficient production of 2-substituted benzimidazoles **111** (up to 99% yield) from dehydrogenative coupling of primary alcohols **112** and aromatic diamines **109** under base-free conditions.[251–253] Sun *et al.* disclosed that readily available 2-nitroanilines **113** can be used as nitrogen sources despite the requirement of an additional hydrogenation step prior to cyclization, such that comparable yields of benzimidazoles **111** are obtained by reaction with primary alcohols **112** at 250 °C for 3 h to 5 h reaction time.[251]

Besides monohydric alcohols, polyhydric alcohols have the possibility to form azaheterocycle frameworks together with the benzimidazole ring. Climent *et al.* showed that glyceraldehyde **83** (or glycerol) undergoes oxidation–cyclization twice with *o*-phenylenediamine derivatives **109** to give various substituted benzimidazoylquinoxalines **115** (24–80% yields) catalyzed by ceria supported gold nanoparticles (Au/CeO_2) using air as the oxidant at 140 °C for 24 h (Scheme 31).[254] In the reaction pathway, glyceraldehyde **83** (possibly *in situ* generated from glycerol by oxidation) first proceeds coupling and cyclization with *o*-phenylenediamine derivatives **109** to produce the intermediate benzimidazol **114**, followed by cascade oxidation–cyclization with another *o*-phenylenediamine **109** to afford the substituted benzimidazoylquinoxalines **115**. The electron-donating substituents in the phenyl ring favor the competitive oxidative cleavage of the diol **114**, and lead to a decrease in the product selectivity by formation of other azaheterocycles **116–119** (Scheme 31).[254]

4.3. Other fused N-heterocycles

Quinolines can be synthesized by conventional Knorr, Skraup, and Camps chemistry, although the protocols typically involve



Scheme 31 Possible pathways for the formation of benzimidazoylquinoxalines **115** and byproducts **116–119**. Adapted with permission from ref. 254, Copyright © 2013, Wiley-VCH.

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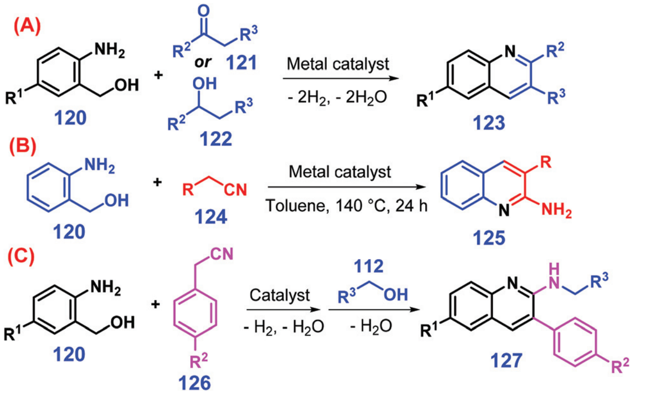
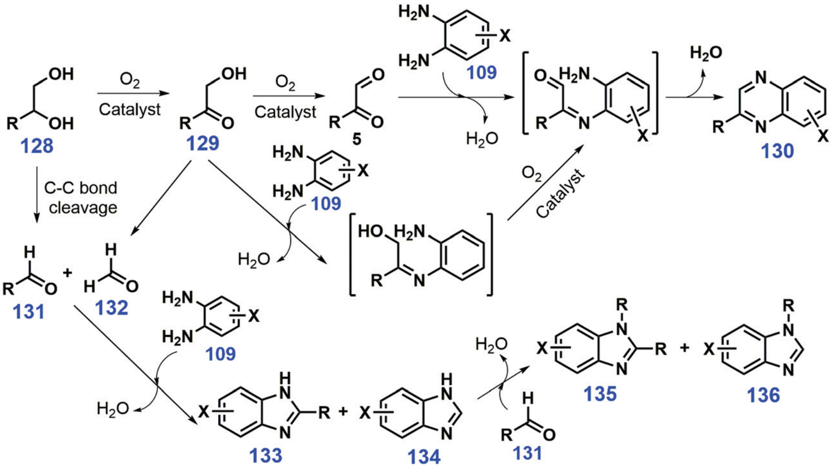


Scheme 32 Synthetic routes to quinolines from amino alcohol **120** reacting with (A) ketone **121** or secondary alcohol **122**, (B) nitrile **124**, or (C) nitrile **124** and alcohol **112**. Adapted with permission from ref. 258, 259 and 270, Copyright © 2018 & 2019, Wiley-VCH; Copyright © 2007, Elsevier.

multiple steps.[255–257] Friedländer reaction is one of the most convenient and versatile ways to access quinolines, but the major drawback is that the 2-aminobenzaldehyde feedstock is too reactive to avoid self-condensation.[258] Instead, 2-aminobenzyl alcohols **120** are stable, and readily undergo oxidative cyclization with either ketones **121** or secondary alcohols **122** catalyzed by transition metals (*e.g.*, Au, Pd, Ir, Rh, Ru) along with stoichiometric amount of bases to give quinolines **123** with improved performance (Scheme 32A).[259–263] Development of low-cost non-noble metal (*e.g.*, Fe, Mn, Co, Cu) catalytic systems under basic additive-free conditions that promote hydrogen borrowing processes are needed for production of quinolines.[264–269] Interestingly, when alcohols **122** are replaced with nitriles **124** for the annulation of 2-aminobenzyl alcohols **120**, 2-amino-quinoline derivatives **125** (*ca.* 95% yields) are obtained at 140 °C for 24 h (Scheme 32B).[258] Furthermore, the post-addition of primary alcohol **112** into the reaction mixture of amino alcohol **120** and nitrile **126** in a single pot furnishes 2-alkylaminoquinolines **127** by *in situ* *N*-alkylation (Scheme 32C).[270]

Synthesis of quinoxalines was traditionally performed by double-coupling of 1,2-carbonyls with 1,2-phenylenediamines, while the employed 1,2-carbonyls were highly reactive and cause undesired self-condensation.[271,272] Several other synthetic approaches such as oxidative coupling of α-hydroxycarbonyls and 1,2-diamines,[273,274] 1,4-addition of diazenylbutenes with 1,2-diamines,[275] oxidation trapping of epoxides and ene-1,2-diamines,[276] and cyclization–oxidation of phenacyl bromides and 1,2-phenylenediamines[277] can provide substituted quinoxalines, but with moderate or low yields in most cases. Using biomass-derived glycols or vicinal diols **128** with 1,2-phenylenediamine derivatives **109** as starting materials, Climent *et al.* reported that quinoxalines **130** (35–91% yields) are efficiently synthesized in a one-pot two-step oxidative coupling reaction process over ceria supported gold nanoparticles (Au/CeO_2) at 140 °C after 24 h in the absence of any homogeneous base with air as oxidant (Scheme 33).[278] Notably, the oxidative cleavage of the substrate diol **128** or the hydroxycarbonyl intermediate **129** inevitably took place to form aldehydes **131** and **132**, which further undergo condensation with the phenylenediamine **109** affording the benzimidazole derivatives **133**, **134**, **135**, and **136**. Similarly, starting from 1,2-dinitrobenzene and 1,2-propanediol, yields of up to 83% of 2-methylquinoxaline are realized, where the nitro-to-amino reduction is performed at 80 °C under 1 MPa H_2, followed by oxidative coupling at 140 °C for 30 h in the presence of atmospheric air.[278] The quinoxaline skeleton can also be established by tandem cyclization/hydrosilylation of 1,2-phenylenediamines and keto esters,[279] and coupling of 2-(1*H*-pyrrol-1-yl)anilines with DMSO.[280] Both of these latter methods provide sustainable approaches to quinoxalines since they use bio-based feedstocks although the protocols could be improved by possibly using earth-abundant metal catalysts or safe or renewable solvents.



Scheme 33 Reaction pathways for the formation of quinoxalines **130** and byproducts **133–136** from vicinal diols **128** and 1,2-phenylenediamines **109**. Adapted with permission from ref. 278, Copyright © 2012, Elsevier.

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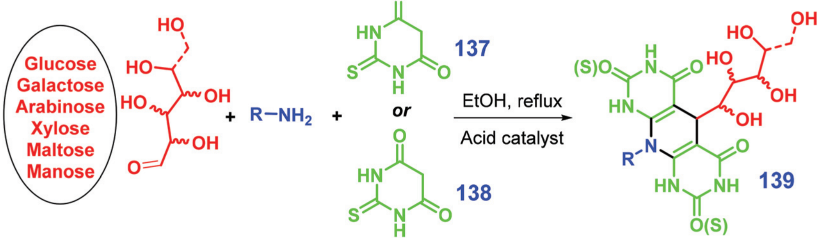
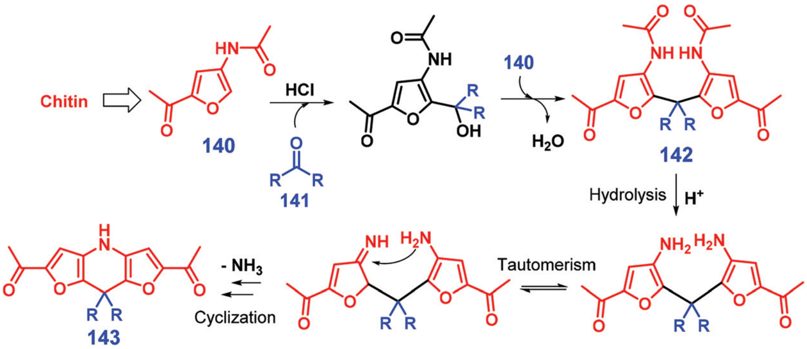


Scheme 34 Synthesis of pyrimidine-fused heterocycles **139** *via* multicomponent condensation of sugar, amine, and barbituric acid **137** or thio-barbituric acid **138**. Adapted with permission from ref. 281, Copyright © 2018, Springer Nature.

As illustrated in Scheme 34, carbohydrate substrates (*e.g.*, glucose, galactose, arabinose, xylose, maltose, mannose, lactose) combined with an amine (*e.g.*, anilines, glucosamine) and barbituric acid **137** or thio-barbituric acid **138** as reagents can be used to form pyrimidine-fused heterocycles **139** (with up to >90% yield) *via* a one-pot multicomponent condensation reaction in the presence of an acid catalyst (*e.g.*, *para*-toluenesulfonic acid, nanocrystalline cellulose sulfuric acid) under mild conditions (*e.g.*, 50 °C).[281–283] The active aldehyde group of the sugar takes part in the condensation reaction, which gives the resulting pyrimidine-fused heterocycles hydrophilicity and potentially good bioactivity.[281–283] All together with glucosamine, aldehyde, and barbituric acid, addition of malononitrile is able to allow a four-component condensation reaction, giving polyhydroxy-substituted pyrido[2,3-*d*]pyrimidines in good yields (89–94%) catalyzed by *para*-toluenesulfonic acid in ethanol heated at 50 °C.[284]

Multicomponent condensation reactions can be used for the synthesis of pyridine-fused heterocycles. For example, Shpuntov *et al.* showed that a three-component Mannich-type reaction of 2-alkylfuran, methyl 2-formylbenzoate, and carbamate in the presence of iodine at 0 °C for 2 h affords *N*-Boc-1-[2-(carbomethoxy)aryl]furfurylamines in moderate yields (51–89%), and further application of a two-step reaction process of oxidative furan-ring cleavage and *N*-Boc deprotection catalyzed by *meta*-chloroperoxybenzoic acid and HCl, respectively, gives 6*H*-isochromeno-[4,3-*b*]pyridin-6-ones in moderate yields (61–68%).[285] The coupling of chitin-derived 3-acetamido-5-acetylfuran **140** with ketones **141** catalyzed by HCl provides dihydrodifuropyridines (up to 64% yield) after reaction at 70 °C for 16 h (Scheme 35).[286] The ketone **141** initially reacts with **140** to form difurylmethane **142**, followed by sequential acid-mediated acetamide hydrolysis, tautomerism, and intramolecular cyclisation, eventually giving dihydrodifuropyridine **143** after removal of ammonia (Scheme 35), as proposed by those authors.[286]

Considering that aryl aldehydes are available from both lignin and carbohydrate components, efforts have been made to prepare dihydropyrano[2,3-*c*]pyrazoles from biomass-derived aldehydes *via* multicomponent condensation reactions. For example, Yang *et al.* reported a one-pot, two-step catalyst-free protocol for synthesis of 2*H*,4*H*- and 1*H*,4*H*-dihydro-pyrano[2,3-*c*]pyrazoles from lignin-derived aromatic aldehydes **35** (Scheme 36A).[287] In the first stage, microwave-assisted condensation of hydrazines **37** and β-ketoesters **144** in water at 80 °C in 2 min affords intermediates (pyrazolones, **145**). To the resulting mixture, malononitrile **146** and aromatic aldehydes **35** promptly added and heated under the identical irradiation conditions for another 3 min gives dihydropyrano[2,3-*c*]pyrazoles **147** (48–95% yields) by direct precipitation from the reaction mixture after cooling to room temperature.[287] In the replacement of β-ketoesters with acetylene ester, Ambethkar *et al.* illustrated that dihydropyrano[2,3-*c*]pyrazoles (65–93% yields) are directly synthesized through four-component condensation of diethylacetylene dicarboxylate, hydrazine hydrate, aryl aldehydes, and malononitrile in the presence of L-proline



Scheme 35 Reaction pathways for the synthesis of pyridine-fused heterocycles **143** from chitin-derived 3-acetamido-5-acetylfuran **140** and aliphatic ketones **141**. Adapted with permission from ref. 286, Copyright © 2018, Springer Nature.

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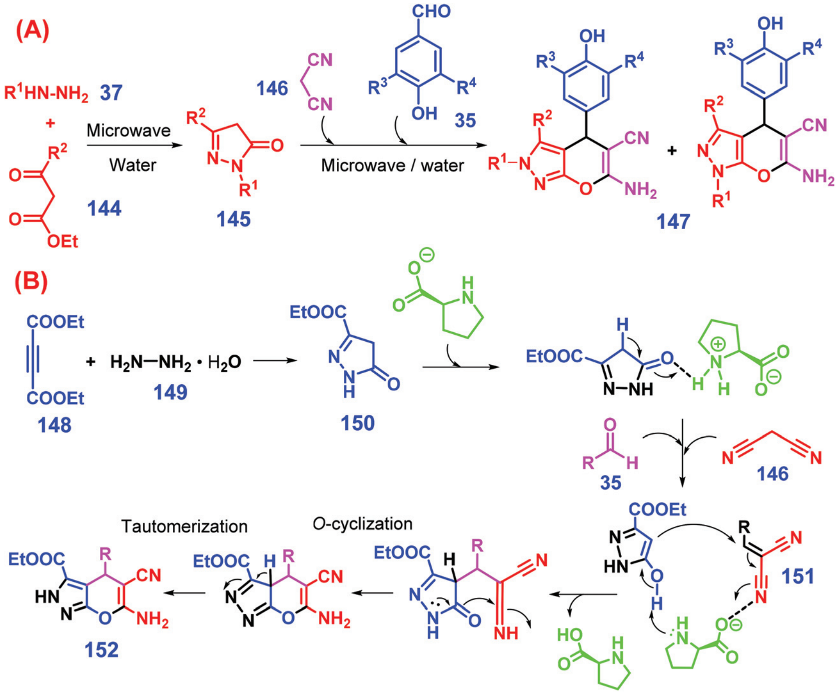

Scheme 36 Synthesis of dihydropyrano[2,3-*c*]pyrazoles **152** from biomass-derived aldehydes **35** *via* a (A) two- or (B) one-step approach. Adapted with permission from ref. 287 and 288, Copyright © 2014 & 2015, Elsevier.

under solvent-free and mechano (grinding) conditions.[288] In the single pot one-step reaction process (Scheme 36B), diethylacetylene dicarboxylate **148** is initially condensed with hydrazine hydrate **149** to give intermediate **150**, followed by Michael addition to intermediate **151** that is *in situ* formed from Knoevenagel condensation between aryl aldehyde **131** and malononitrile **146**, while the dihydropyrano[2,3-*c*]pyrazole product **152** is afforded after undergoing subsequent intramolecular cyclization and tautomerization.[288] On the whole, this synthetic protocol seems to be facile, efficient, and eco-friendly for producing dihydropyrano[2,3-*c*]pyrazole derivatives.

Besides the above-mentioned synthetic methods employed for synthesis of fused azaheterocycles, several other strategies have been developed with the aim of constructing more specific N-heterocyclic skeletons amendable to biomass feedstocks. For instance, a furan ring opening-pyrrole ring closure strategy has been adopted for the synthesis of pyrrole-fused heterocycles such as pyrrolo[1,2-*a*][1,4]diazepines and 1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-3-ones.[289,290] In view of the feasibility of furan-ring opening, biofuranics and their derivatives (*e.g.*, levulinic acid) are extensively used for the construction of complex azaheterocycles like indolo[3,2-*c*]quinolines and bicyclic heterocycles.[291,292] Direct transformation of biomass sugars to azaheterocycles has been investigated with profound results,[293,294] while most studies of upgrading lignin are more focused on its model molecules such as 2-phenoxy acetophenone and aromatic aldehydes *via* modified approaches based on conventional reactions.[295,296]

5. Other N-heterocycles

5.1. CO_2 participating N-heterocycles

Carbon dioxide is a promising C_1 source for organic synthesis with unique characteristics like abundance, low toxicity, and sustainability, while it is thermodynamically stable and kinetically inert.[297,298] Three major CO_2-incorporated cyclization strategies have been developed to construct azaheterocycles (Scheme 37): (1) carboxylative cyclization *via* cascade nucleophilic attack on CO_2 and intramolecular cyclization, (2) carbonylative cyclization *via* twice nucleophilic attack on CO_2, and (3) reductive cyclization *via* nucleophilic attack on reduced CO_2 and subsequent cyclization.[299] To a certain degree, the type of obtained N-heterocyclic compounds is highly dependent on the employed N-containing nucleophiles. For example, oxazolidinones can be synthesized by nucleophilic attack of CO_2 with aziridines or propargylic amines *via* carboxylative cyclization in the presence of a metal or base catalyst.[300–302] Similarly, benzoxazinones are formed by base-catalyzed three-component coupling of imines, benzyne, and CO_2.[303] In another case, the carbonylation using CO_2 takes place without any reductant *via* two possible pathways: (a) successive nucleophilic attack of CO_2 with the nitrogen-containing compound bearing two nucleophilic sites, and (b) initial cyclization to form an unstable cyclic intermediate followed by immediate rearrangement to a stable counterpart.[299] For example, base-catalyzed double coupling (*i.e.*, carbonylative cyclization) of 2-aminobenzonitriles with CO_2 gives quinazoline-2,4(1*H*,3*H*)-diones.[304] In the carbonylation process, either

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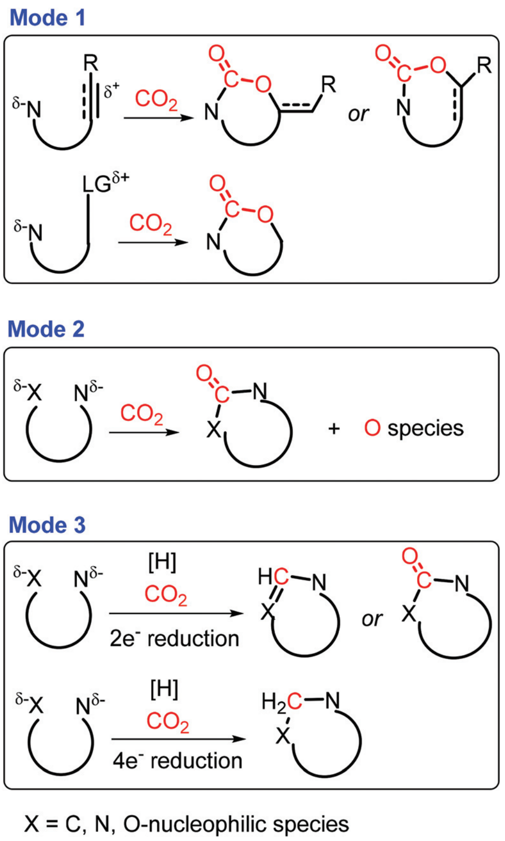

Scheme 37 CO_2-incorporated annulation triggered by C, N, or O nucleophiles. Adapted with permission from ref. 299, Copyright © 2019, American Chemical Society.

cyclization or nucleophilic attack was proposed to be initialized, which needs to be elaborated in-depth with *in situ* characterization techniques.

In the presence of a hydrogen source (*e.g.*, H_2, boranes, and silanes), CO_2 can be subjected to *in situ* reduction followed by cyclization with N-containing nucleophiles to afford a wide range of azaheterocycles.[299] The 2-electron reduction is able to promote the hydrogenation of CO_2 to formates, followed by condensation with substrates containing two nucleophilic sites to furnish quinazolinones, benzimidazoles, formamidines and their derivatives.[305–307] On the other hand, CO_2 may also serve as the methylene species *via* 4-electron reduction, giving saturated N-heterocycles after successive nucleophilic attacks.[299] Although studies on CO_2 reduction have been investigated extensively, controllable CO_2 hydrogenation combined with successive cyclization still remains a challenge.

5.2. N-heterocycles with controllable ring size/type

As discussed above, five-membered, six-membered, and fused N-heterocycles can be selectively obtained from bio-based feedstocks with specific functional groups and carbon-chain length using developed strategies. Attention is being placed on developing integrated synthetic approaches to control the ring size of N-heterocycles (Fig. 3). Using imine esters **153** as three-atom units (Fig. 3), (a) five-membered heterocyclic compounds (*e.g.*, pyrrolidines) can be acquired by [3 + 2]-cycloaddition with two-atom dipolarophiles (*e.g.*, electron-deficient alkenes);[308] (b) fused and bridged six-membered piperidines can be acquired *via* [6 + 3]-cycloaddition reactions of 6-π dipolarophiles (*e.g.*, fulvenes, 2-acyl cycloheptatrienes, tropone) with azomethine,[309–311] while six-membered heterocyclic frameworks can be acquired by cross 1,3-dipolar [3 + 3]-cycloaddition of azomethine with pyrazolidinium ylides;[312] and (c) seven-membered heterocyclic azepines can be acquired from methyl coumalate *via* tandem [4 + 3]-cycloaddition/decarboxylation/isomerization.[308] By changing the chain length of the employed substrates, other five, six, seven, and eight membered N-heterocycles are obtained using appropriate catalysts or catalytic systems.[313–315]

Cycloamination strategies are commonly used for the construction of azaheterocycles that can be well controlled by adjusting the type of nitrogen source. Starting from 1,4-dicarbonyl compounds **1** that are readily available from oxidative opening of the furan ring, pyrroles **154**, pyridazines **155**, and diazepines **156** can be selectively obtained by diamination with NH_3, N_2H_4, and *o*-phenylenediamine, respectively (Scheme 38).[316] In a similar way, reduced sugars proceeding *via* 1,2-dicarbonyl intermediates by reaction with different nitrogen sources furnish the quinoxaline, 1,2,4-triazine, pyrazine and pyrazolo[3,4-*b*]quinoxaline skeletons.[317] In these strategies, protection group chemistry is not needed for the *in situ* multi-step transformations. With respect to the synthesis of azaheterocycles *via* multicomponent reactions, selection of subcomponents allows control of the product distributions. For instance, coupling cyclization of amino alcohols and alcohols with desired functionalities with suitable spatial distances is able to selectively afford pyrrole, pyridine, quinoline, pyrazine, carbazole, or acridine derivatives.[318–322]

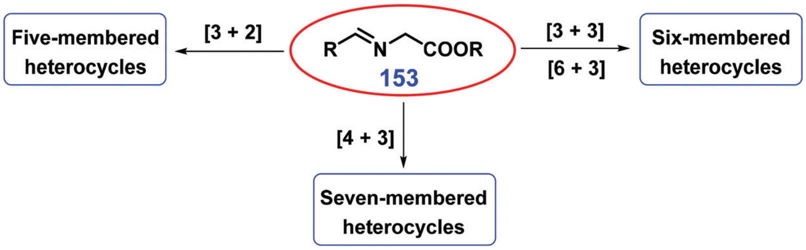

Fig. 3 Schematic illustration for the synthesis of N-heterocycles with controllable ring size from imine esters **153**.

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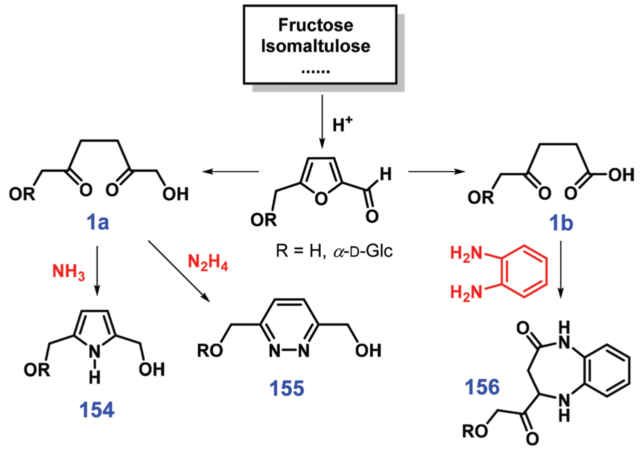

Scheme 38 Reaction routes to pyrroles **154**, pyridazines **155** and diazepines **156** from sugars by adjusting the type of nitrogen source. Adapted with permission from ref. 316, Copyright © 2001, Royal Society of Chemistry.

Chiral N-heterocyclic compounds have a privileged role in pharmaceuticals.[323] A specific chiral source of asymmetric induction (*i.e.*, chiral catalyst) is typically required for the enantioselective synthesis of N-heterocycles,[324,325] through which stereoselective upgrading of thermodynamically stable CO_2 to optically pure azaheterocycles can be realized.[326] Biomass derivatives (*e.g.*, carbohydrates, amino acid, and levoglucosenone) are inherently in enantiopure form, thus they have high feasibility for use in simple production of N-heterocycles with appropriate configuration. For example, in the absence of any chiral catalyst, cellulose-derived (−)-levoglucosenone can undergo well-controlled reactions like 1,3-dipolar cycloaddition, aza-Michael addition or isomerization, being enantioselectively converted into polysubstituted pyrrolidines or 1,2,3-triazoles.[327–329] A versatile protocol *via* multicomponent Ugi-type reactions of unprotected saccharides and L- or D-configured amino acids is accessible to 1,2-*syn* or *anti* configured products, respectively.[330] In this regard, the exploitation of synthetic protocols to biomass-derived chiral molecules, especially those with potent bioactivities, is promising with respect to green manufacturing processes.

5.3. Direct thermal amination and hydrothermal approaches

The majority of studies focus on the transformation of small platform molecules (*e.g.*, carbonyl compounds, furans, unsaturated/polybasic carboxylic acids) or simple biomass derivatives (*e.g.*, sugars, lignin model molecules like aromatic aldehydes/alcohols) into azaheterocycles.[331–335] However, direct valorization of raw biomass materials to N-heterocycles and relevant value-added chemicals could bring many opportunities to practical production (Fig. 4).

Pyrolysis or hydrothermal liquefaction of lignocellulosic biomass with NH_3 has been developed for the production of nitrogenous heterocyclic compounds, while obtained products are mixtures of pyrrole, pyridine, indole and other nitrogen-containing compounds with relatively low overall yields (<30%).[336–343]

Direct thermal conversion of nitrogenous biopolymers (*e.g.*, chitin and proteins) can be implemented by sub- and super-critical water treatment, where the overall hydrolysis process including surface hydrolysis and destruction of hydrogen and glycosidic bond is controlled by solvent conditions.[344] Mechanochemical treatment (*e.g.*, ball mill) of chitin enhances its solubility in supercritical water (400 °C) allowing rapid (1 min) transformation, while raw chitin with high crystallinity shows poor dissolution in high-temperature water (HTW).[345] After pretreatment, chitin could be transformed into *N*-acetyl-

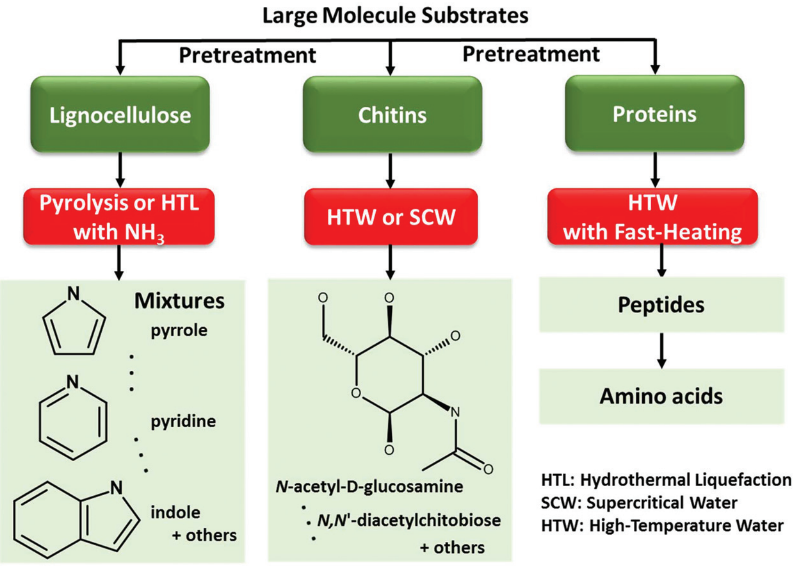

Fig. 4 Top-down strategy to N-heterocycles *via* large molecule substrates.

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D-glucosamine (the monomer) and/or *N*,*N*′-diacetylchitobiose (the dimer) with yields of no more than 8%.[346,347] At relatively high temperatures of (200 to 260) °C, treatment of proteins with HTW and fast heating rates (135 to 180) $K\ s^{-1}$ inhibits initial protein aggregation that occurs during the reaction process at slow heating rates (*ca.* 0.25 $K\ s^{-1}$), affording high-molecular-weight peptides (1500 to 8300) Da as dominant products with the transformation advantageously occurring as random-scission.[348]

On the other hand, with hydrothermal liquefaction (HTL) at temperatures between 250 °C and 350 °C, several heterocycles could originate from the components of proteins, such as piperidines and quinolines from lysine in bio-oils, while pyrazines form from the mixture of disaccharides and lysine.[349] Besides organic matter derived from HTL with liquid-N accounting for the majority of nitrogenous products,[350–353] the HTL conditions can affect the concentrations of metals (*e.g.*, Fe, Na, Mg, Ca) and inorganic species (*e.g.*, P) in algal biocrude.[354] It is worth noting that N-containing heterocycles partition undesirably into bio-crude oils after hydrothermal treatment.[355,356] leading to a future challenge for the reaction system or product separation.

The use of catalysts (*e.g.*, HZSM-5) in the reaction system remarkably increases the selectivity toward the N-containing compounds composed of up to 79% pyrroles, 63% pyridines, and 57% indoles, respectively.[357] By selecting crude shrimp shells as the starting feedstock, pyrrole is detected as the dominant nitrogen-containing product after hydrothermal treatment with NH_3 in the presence of NaOH,[358] while the co-production of N-heterocyclic bio-char and other aromatic amines are unavoidable in most cases.[359] Appropriate design of reaction processes and functional catalysts opens avenues to other elegant N-containing chemicals like β-lactam, nitrile, and isoxazole.[360–362] Last, but not least, adopting new strategies for C–N bond formation are required for sustainable and efficient valorization of raw biomass materials.

6. Conclusions and outlook

An overview of amination strategies is given for synthesis of N-heterocycles from biomass feedstocks. The C–N bond formation is typically established by reductive amination, multi-component coupling reactions, or acceptorless dehydrogenative coupling reactions, which will furnish the N-containing cyclic skeletons by double C–N bonding processes or C–N coupling combined with other elemental C–C bond formation reactions like condensation. Much attention is on the construction of five-membered N-heterocycles such as pyrroles, pyrrolidones, pyrazoles, imidazoles, thiazoles, oxazoles, triazoles, and tetrazoles from either bio-based platform molecules or directly from raw biomass materials. However, studies on the production of biomass-derived six-, seven-, and eight-membered as well as fused N-heterocyclic compounds are still in their infancy, with target products being obtained with relatively low selectivities. More effort should be devoted to the design of reaction systems specifically, by matching synthesis routes. Several points may be made for access to azaheterocycles:

(1) Organic synthesis and synthetic methodologies may provide efficient references for rationally devising effective and renewed reaction routes toward specific N-heterocycles with satisfactory stereo- or enantioselectivity, while the reaction processes can be further simplified by following the principles of green engineering and green chemistry. In contrast, studies on sustainable production of other heteroatom (S, P)-containing compounds are relatively scarce, indicating the necessity to explore synthetic approaches in the construction of S–C or P–C bonds.

(2) The presence of a suitable catalyst with designated chiral induction center can remarkably lower reaction barriers with enhanced overall rate and optical purity. Basic nitrogen sources or used together with acidic substrates can themselves act as catalyst, and most of biomass derivatives naturally bearing absolute/spatial configurations have the greatest potential to furnish the desired N-containing enantiomers without any catalyst.

(3) Hydrothermal treatment of raw biomass materials with ammonia has been demonstrated to be capable of giving N-containing compounds but with low selectivity, let alone the desired relevant azaheterocycles. In this regard, biomass pretreatment with sustainable solvents and/or ecofriendly catalysts can be a promising auxiliary to enhance reaction efficiency with respect to both selectivity and yield of azaheterocycles.

(4) Definite reaction mechanisms have been explicitly illustrated for some of the above-mentioned reactions, while a majority of reaction schemes have been revealed without neither elucidation of the reaction pathway nor the catalyst structure–activity relationship. There is no doubt that the disclosure of detailed reaction routes using modern characterization techniques will be helpful for both catalyst preparation and design of reaction processes for producing N-heterocycles.

(5) Raw biomass materials are solid-state and are not soluble in thermal reaction processes, which often results in the formation of plentiful solid biochars rather than the desired N-heterocyclic compounds. In this respect, the design of compatible reactors is needed to facilitate production in overall cycloamination processes.

In conclusion, cycloamination coupled with C–C bond formation processes is efficient for the synthesis of N-heterocycles especially five-membered azaheterocycles from biomass feedstocks. Many endeavors have been made with great achievements being made that improve the chemical avenues to bio-based N-heterocycles. Studies on the diversity of the obtained N-containing compounds need to be further strengthened. Development of efficient and renewed synthesis approaches to task-specific N-heterocyclic compounds with emphasis on sustainable chemistry will be required for comprehensive biomass valorization.

Conflicts of interest

The authors declare no conflicts of interest.

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