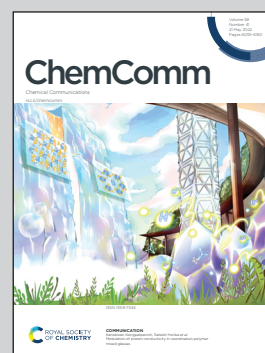


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Direct nitrogen interception from chitin/chitosan for imidazo[1,5-*a*]pyridines

A catalyst-free one-pot methodology enables direct nitrogen delivery from chitosan/chitin for value-added imidazo[1,5-*a*]pyridines. This strategy is featured by directly synthesizing important saturated 1-alkylimidazo[1,5-*a*]pyridines, deuterated imidazo[1,5-*a*]pyridines and tridentate ligands.

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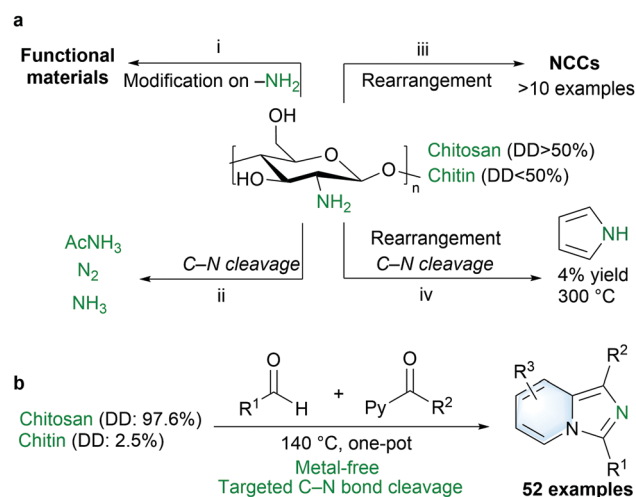
 Kui Zeng,^a Ruhuai Mei,^a Xizhou Cecily Zhang,^b Loren B. Andreas^b and Kai Zhang^{id}*^a

A catalyst-free one-pot methodology that enables direct nitrogen interception of chitosan/chitin for imidazo[1,5-a]pyridines was developed. This strategy features direct synthesis of important deuterated imidazo[1,5-a]pyridines and tridentate ligands. In particular, a broad group of previously inaccessible products including saturated 1-alkylimidazo[1,5-a]pyridines are unprecedentedly synthesized by this protocol.

Chitin and chitosan are abundant native linear polymers composed of randomly distributed units, namely, *N*-acetyl-*D*-glucosamine (GlcNAc) and *D*-glucosamine (GlcN) linked by β -1,4-linkages.¹ The quantities of GlcNAc units are generally more than 50% in chitin, while chitosan contains less than 50% GlcNAc and has thus a degree of deacetylation (DD) of more than 50%.^{2–4} Human processing of sustainable chitin-containing raw materials represents only a very minor fraction of all the chitin produced annually in nature,^{5–10} while the major fraction remains intact.¹¹ On the other hand, low molecular weight nitrogen-containing chemicals (NCCs) play a pivotal role in modern life, from pharmaceutical, agriculture and food fields to material fields.^{12–16} The nitrogen source of prevailing industrial processes for NCCs is mainly from NH₃, NO₃[−] and NO₂[−] *etc.*, which are obtained from N₂ fixation.^{17–25} The quantities of nitrogen element fixed annually in chitin *via* the biochemical process are much more than the N₂ fixed in the Haber–Bosch process.²⁶ Therefore, the transformation of renewable chitin containing fixed nitrogen into value-added NCCs has drawn much attention.¹⁴

Four types of strategies are currently known for the activation of amines in chitin/chitosan (Scheme 1a). The first strategy (i) is referred to as the direct modification of amines on the

chitosan/chitin backbone without the cleavage of C–N bonds.⁵ The second strategy (ii) involves the cleavage of C–N bonds *via* strong oxidants or acidic conditions with the simultaneous release of N₂, acetamide and ammonium salts.^{27–29} Recently, the third strategy (iii) has emerged in biorefineries by converting chitin/chitosan into a preliminary C6 backbone *via* a depolymerization and by further conversion of the C6 backbone into diversified products.^{14,26,30} Although various protocols have been established through enzymatic, catalytic and/or hydrothermal treatments, only more than 10 NCC examples (including sugar derivatives, amino alcohols and furanic amides) have been obtained with complicated conditions and a low efficiency. The fourth strategy (iv) involves the cleavage of C–N bonds of chitin for the assembly of pyrrole with a low yield



- First time accessible to saturated 1-alkylimidazo[1,5-a]pyridines
- First time targeted C–N bond cleavage for NCCs
- 52 examples (including deuterated products)

Scheme 1 (a) General strategies for the activation of amines in chitin/chitosan. (b) This work: direct incorporation of nitrogen from chitosan/chitin for imidazo[1,5-a]pyridines.

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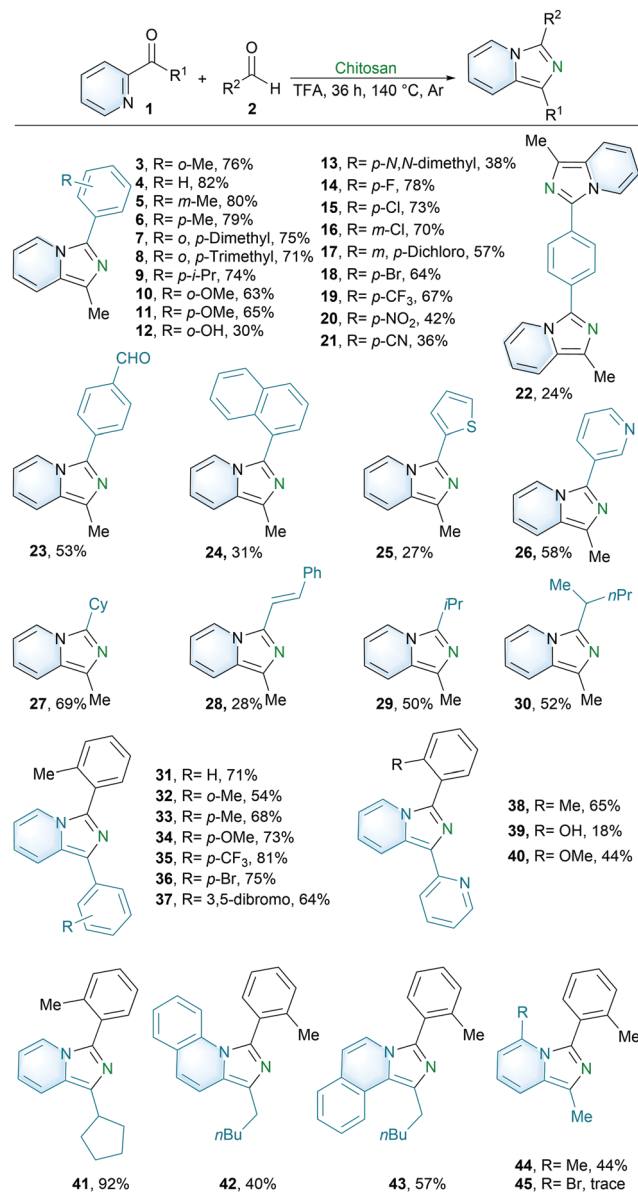


of 4%, which was realized in alkali aqueous solution at 300 °C in 2016.³¹ In particular, it should be stressed that the synthesis of N-heterocycles from chitin/chitosan biomass is challenging and introducing an unsustainable nitrogen source such as NH₃ is the main pathway for the construction of N-heterocycles from biomass.^{32–34} The C–N bond of chitin/chitosan that offers a potential reactive site for various versatile chemical diversifications generally remains intact. Therefore, a one-pot protocol enabling the targeted efficient incorporation of nitrogen from chitin/chitosan into diverse valuable NCCs like N-heterocycles is highly attractive, which will advance the existing methodologies while expanding the library of NCCs derived from renewable sources.

Herein, we developed an efficient catalyst-free one-pot protocol for the direct integration of nitrogen from the renewable feedstock chitosan/chitin that yields various valuable imidazo[1,5-*a*]pyridines (52 examples with yields up to 92%) under mild conditions (Scheme 1b), which provides ready access to 1-alkylimidazo[1,5-*a*]pyridines and 1-arylimidazo[1,5-*a*]pyridines.

We initiated our studies by using 2-acetylpyridine (**1a**) and 2-methylbenzaldehyde (**2a**) as substrates to evaluate the envisioned nitrogen interception from chitosan for desired imidazo[1,5-*a*]pyridine **3** employing metal-free conditions. At the outset, product **3** was detected by ¹H NMR analysis under conditions with a solvent mixture of AcOH/H₂O (0.9/0.1 mL) (Table S1, entries 1 and 2, †). After that, several silver salt additives were investigated. Interestingly, the yield of **3** was increased obviously from 3% to 13% when silver trifluoroacetate (AgTFA) was exploited, while silver acetate (AgOAc) was not beneficial for the efficacy (Table S1, entries 3 and 4, †). These results indicated that the anion [−]OCOCF₃ in AgTFA might facilitate the transformation. Therefore, a solvent mixture of CF₃COOH/H₂O (0.9/0.1 mL) was employed as a substitute of the previous solvent AcOH/H₂O (0.9/0.1 mL). To our delight, the yield was improved to 29% when CF₃COOH/H₂O was used as reaction media (Table S1, entry 5, †). Then, a higher yield (61%) was achieved with CF₃COOH (1.0 mL) as the solvent (Table S1, entry 6, †). Besides, diverse reaction temperatures, ranging from 90 °C to 140 °C, were examined (Table S1, entries 7 and 8, †). Thus, the optimal temperature was determined to be 140 °C and a 78% yield was obtained. Moreover, the reaction was conducted at 12 h, 24 h and 36 h with a yield of 31%, 59% and 78%, respectively. The lower equivalent of chitosan leads to inferior yield. Combining all factors regarding the equivalent of chitosan, reaction temperature and time, the optimal reaction conditions were identified as shown in entry 8: 140 °C for 36 h (Table S1, †).

With the optimized reaction conditions in hand, we next explored the versatility of metal-free nitrogen interception from chitosan with various aldehydes for NCCs (Scheme 2). A series of aromatic aldehydes, including those bearing electron-donating or electron-withdrawing groups at different positions (*ortho*, *meta* or *para*) were subjected to the optimized conditions. As a result, these aldehydes could be efficiently transformed into the corresponding products **3–23**. Aldehydes



Scheme 2 Scope of aldehydes and pyridine ketones for the synthesis of imidazo[1,5-*a*]pyridines. ^aProducts **3–30**: 2-acetylpyridine (0.1 mmol), aldehydes (2.0 equiv.), chitosan (3.0 equiv.), CF₃COOH (0.1 M), 140 °C, under Ar, 36 h. ^bProducts **31–41**: pyridine ketones (0.1 mmol), aldehydes (4.0 equiv.), chitosan (2.5 equiv.), CF₃COOH (0.14 M), 140 °C, under Ar, 36 h. ^cProduct **13** and **22**: 2-acetylpyridine (0.1 mmol), aldehyde (2.0 equiv.), chitosan (3.0 equiv.), CF₃COOH (0.14 M), 140 °C, under Ar, 4 days. Yields are those of the isolated products.

with electron-donating groups, such as methyl, isopropyl and methoxy groups (**3–11**), are well compatible with the transformations, while lower yields were obtained for substrates with a hydroxyl group and dimethylamino group (**12** and **13**). The reason could be that the dimethylamino and hydroxyl groups with high nucleophilicity are much more sensitive to carbonyl groups. Surprisingly, a larger scale (**1a**, 0.5 mmol) with a lower load of chitosan (2.0 equiv.) in a smaller volume of TFA (0.5 M) was also well compatible for the desired product **4** (Fig. S4, †). In addition, electron-withdrawing substituents, including

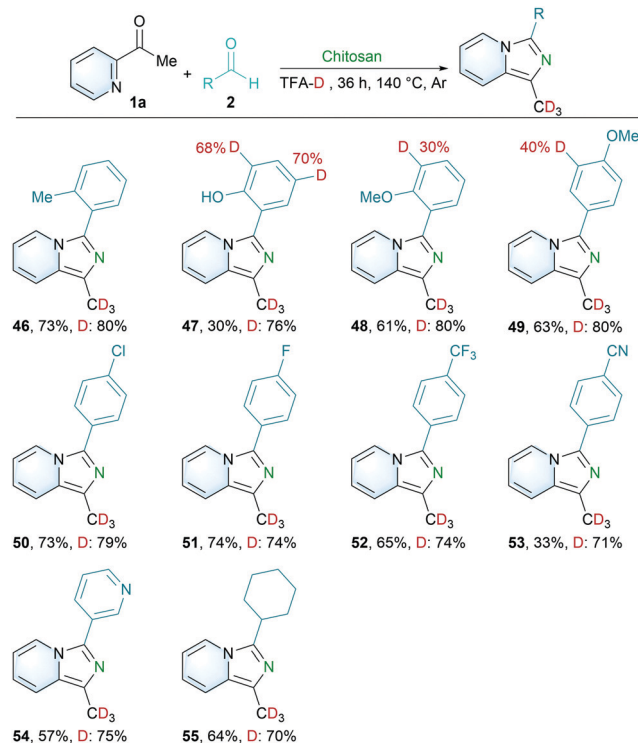


halogen and trifluoromethyl groups, were well accommodated (14–19). Moderate yields were achieved for aldehydes with nitro and nitrile groups (20 and 21). It is noteworthy that the challenging *para*-dialdehyde also delivered the corresponding products with diverse conditions (22 and 23). With the controllable reaction conditions, products 22 and 23 can be obtained separately, but it is not excluded that there is a tiny amount of 23 in 22, and a small amount of 22 in 23 (the amount can be ignored). Furthermore, 1-naphthaldehyde (24), thiophene-2-carbaldehyde (25) and nicotinaldehyde (26) were also amenable in our protocol. In addition to aromatic aldehydes, those aliphatic aldehydes (27–30) were well compatible with the protocol.

We further investigated the viable scope of differently substituted pyridine ketone 1 as the general coupling partners for this transformation (Scheme 2). The phenyl(pyridin-2-yl)methanones were well compatible with the protocol (31). Pyridine ketones with electron-donating groups (32–34) or electron-withdrawing groups (35–37) displayed good reactivity and delivered the corresponding products efficiently. These results indicated that the current protocol was not sensitive to the electronic or stereoscopic properties of pyridine ketones. N-Heterocyclic compounds play an important role in the materials and organic synthesis fields, especially as ligands in chemical transformations. Thus, the utilization of a sustainable protocol for the assembling of N-heterocyclic tridentate ligands is highly desirable. Herein, these di/tri-dentate ligands, 1-(pyridin-2-yl)-3-(*o*-tolyl)imidazo[1,5-*a*]pyridine (38), 2-(1-(pyridin-2-yl)imidazo[1,5-*a*]pyridin-3-yl)phenol (39) and 3-(2-methoxyphenyl)-1-(pyridin-2-yl)imidazo[1,5-*a*]pyridine (40), were accessed concisely through the interception of nitrogen from chitosan, which further demonstrates the practical synthetic use of our method. Moreover, cyclopentyl(pyridin-2-yl)methanone (41) and 2-quinoline/isoquinoline ketone compounds (42, 43) were also transformed efficiently. Three pyridine ketones with substituents in the pyridine ring were investigated in our protocol. As a result, a methyl group in the sixth position of pyridine was also well compatible for the desired product (44), while an electron-withdrawing group at the same position failed to deliver the corresponding product (45).

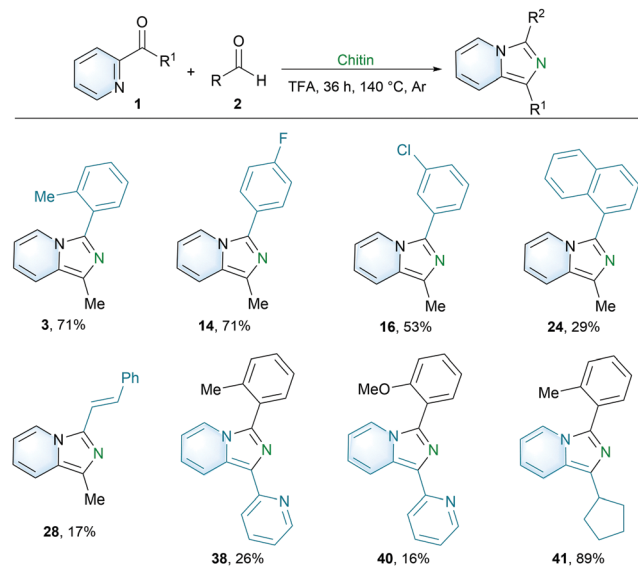
Isotope labeling showed important applications in drug absorption, distribution, metabolism and excretion.^{35–37} Inspired by the H–D exchange between α -C–H of the pyridine ketone and CF_3COOD solvent, a variety of $\text{C}(\text{sp}^3)\text{--H}$ deuterated imidazo[1,5-*a*]pyridines derivatives were synthesized in a one-pot procedure (Scheme 3). Those aromatic aldehydes, pyridine aldehyde and cyclic aliphatic aldehyde were synthesized with deuterated incorporation of products (46–55). In addition, it is worth noting that the proton of the aromatic aldehyde with a hydroxy group and methoxy group could also be deuterated under this condition (47–49).

Furthermore, sustainable biomass chitin was proven to be a viable nitrogen source as well in this transformation, which could further bypass the deacylation process from chitin to chitosan and make the reaction more useful (Scheme 4). As a result, a group of imidazo[1,5-*a*]pyridines was obtained under



Scheme 3 One-pot synthesis of deuterated $\text{C}(\text{sp}^3)\text{--H}$ bonds of imidazo[1,5-*a*]pyridines. ²-acetylpyridine, aldehydes and chitosan in CF_3COOD were stirred at 140 °C under an Ar atmosphere for 36 h. Yields are those of the isolated products. D incorporation was tested by ¹H-NMR analysis.

the standard conditions, including 3 (71%), 14 (71%), 16 (53%), 24 (29%), 28 (17%), 38 (26%), 40 (16%) and 41 (89%). However, using chitosan as a nitrogen source in Fig. S2–S5 (†), these



Scheme 4 Direct utilization of chitin for the synthesis of imidazo[1,5-*a*]pyridines. ²Pyridine ketones, aldehydes and chitin in CF_3COOH were stirred at 140 °C under an Ar atmosphere for 36 h. Yields are those of the isolated products.



products can be obtained with higher yields, including **3** (76%), **14** (78%), **16** (70%), **24** (31%), **28** (28%), **38** (65%), **40** (44%) and **41** (92%). Although it is more convenient to utilize chitin rather than chitosan, chitosan shows better reaction efficiency to deliver NCCs with higher yields.

Moreover, 11% of ammonium was trapped *via* $^1\text{H-NMR}$ analysis, which could provide support for the major release of nitrogen after condensation into an intermediate, such as imidazo[1,5-*a*]pyridine-2,4-dium or imidazo[1,5-*a*]pyridin-4-ium (Fig. S2, †). Besides, an imidazo[1,5-*a*]pyridin-4-ium 3' was confirmed by ESI-HRMS analysis (calc. for $\text{C}_{15}\text{H}_{15}\text{N}_2^+$ [M]: 223.1230, found: 223.1232) (Fig. S3, †), which reveals a pathway for imidazo[1,5-*a*]pyridine **3** *via* deprotonation of 3'. Based on the control experiment (Fig. S2 and S3, †), a plausible reaction pathway was proposed. First, deacetylation takes place which enables the transformation of chitin to chitosan.³⁸ Then, an imine intermediate is generated *via* the dehydration between an aldehyde substrate and an amine group of chitosan. The imine intermediate attacks a pyridine ketone substrate to form an iminium intermediate. Next, an imidazo[1,5-*a*]pyridine-2,4-dium intermediate forms *via* the intramolecular nucleophilic addition between pyridine and iminium in the backbone of the iminium intermediate.³⁹ With the help of TFA, the imidazo[1,5-*a*]pyridine-2,4-dium transforms into an imidazo[1,5-*a*]pyridin-4-ium (Fig. S3, †) *via* plausible pathways of dehydration and C–N bond cleavage. Finally, an imidazo[1,5-*a*]pyridine was generated *via* the deprotonation of the imidazo[1,5-*a*]pyridin-4-ium.

In summary, we have developed a new strategy for the rapid assembly of NCCs with ample scope through the direct use of native nitrogen sources from biomass. This strategy is achieved through a one-pot conversion approach of chitin/chitosan by cleaving the C–N bonds and simultaneously integrating the nitrogen in the synthesis of a broad range of imidazo[1,5-*a*]pyridines (52 examples) that show diverse potential applications. A broad group of previously inaccessible products including saturated 1-alkylimidazo[1,5-*a*]pyridines is unprecedentedly synthesized by this protocol. The amine groups of the chitin/chitosan backbone are intercepted *via* aldehyde and pyridine ketone assisted with CF_3COOH under metal-free conditions. We believe that this approach will initiate research endeavors for the targeted efficient incorporation of nitrogen from biomass for high-value NCCs.

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Conflicts of interest

The authors declare no competing financial interest.

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