Communication

Acceptorless Dehydrogenative Coupling using Ammonia: Direct Synthesis of N-Heteroaromatics from Diols Catalyzed by Ruthenium

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Acceptorless Dehydrogenative Coupling Using Ammonia: Direct Synthesis of N-Heteroaromatics from Diols Catalyzed by Ruthenium

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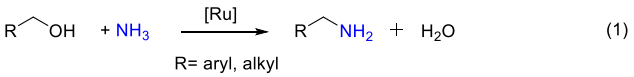
Supporting Information Placeholder

ABSTRACT: The synthesis of N-heteroaromatic compounds via an acceptorless dehydrogenative coupling process involving direct use of ammonia as the nitrogen source was explored. We report the synthesis of pyrazine derivatives from 1,2-diols, and the synthesis of N-substituted pyrroles by a multicomponent dehydrogenative coupling of 1,4-diols and primary alcohols with ammonia. The acridine-based Ru-pincer complex **1** is an effective catalyst for these transformations, in which the acridine backbone is converted to an anionic dearomatized PNP-pincer ligand framework.

Ammonia is the simplest, useful molecule employed as a nitrogen source in synthesis, with generally high atom economy.[1] It is used for the synthesis of a wide range of commercially useful products, including amines, amides, ureas, carbamates, isocyanates, amino acids, N-heteroaromatic and heterocyclic compounds.[2] Of particular interest and in the context of sustainable chemistry, environmentally benign routes to the catalytic synthesis of amines from readily available alcohols using ammonia and generating no hazardous waste is of much current attraction. In 2008, we reported the direct homogenous catalytic selective amination of primary alcohols to primary amines using ammonia, catalyzed by an acridine-based Ru pincer complex (eq. 1).[3] In 2014, Hofmann et al reported a similar acridine-based pincer ruthenium complex as an effective catalyst for the amination of primary alcohols using ammonia and also proposed a probable mechanism based on experimental and DFT studies.[4] Other research groups also explored the amination of alcohols using ammonia.[5] Multi alkylation of ammonia to form secondary or tertiary amines was developed using iridium catalysts[6]. Our group also developed the Ru(BpyPNN) pincer catalyst for the synthesis of secondary amines from the primary alcohols and ammonia.[7]

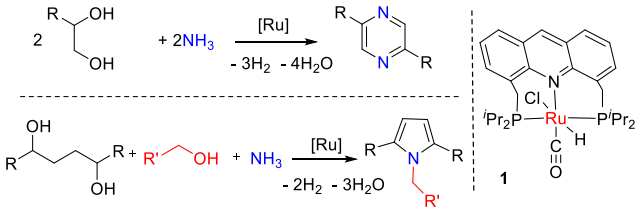


(1)

Diverse bioactive natural products and pharmaceutically important, aromatic N-heterocyclic molecules are classically synthesized by the coupling of ammonia with various carbonyl derivatives.[8] Although extensively used, most of these protocols suffer from various shortcomings, such as availability of starting materials, multi-step synthetic operations, and copious waste generation. Thus, alternative strategies involving sustainable, one-step, atom-economical methodologies for the preparation of valuable N-heteroaromatic molecules are needed. In this regard, our group has demonstrated several environmentally benign reactions involving dehydrogenative coupling of alcohols and amines, with H_2 and water as the sole byproducts, catalyzed by ruthenium pincer complexes based on pyridine and acridine backbones.[9] Notable progress has been made in recent years in the sustainable synthesis of N-heteroaromatic compounds using alcohols and amines based on acceptorless dehydrogenative coupling pathways.[10]

The direct use of ammonia in acceptorless dehydrogenative coupling reactions for the synthesis of N-heteroaromatic compounds is challenging. Noteworthy, the "glucose-ammonia model" was established for the synthesis of various pyrazine derivatives from biomass by using ammonia in presence of a metal salt under *aerobic* conditions.[11] Acceptorless dehydrogenative coupling reactions are often driven by the efficient removal of the generated H_2 in an open system, which poses an obvious problem when ammonia gas is used under pressure in a closed system.

Scheme 1. Synthesis of pyrazines and pyrroles from alcohols and ammonia catalyzed by a ruthenium complex

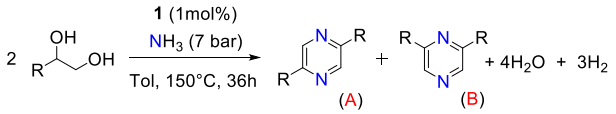


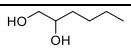
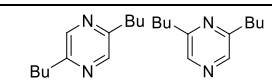
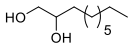
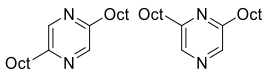
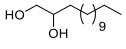
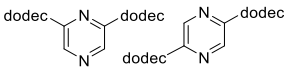
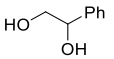
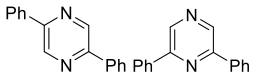
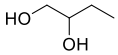
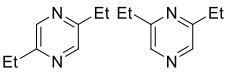
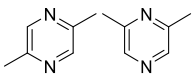
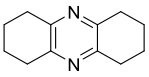
Herein, we present such reactions, including (a) formation of pyrazine derivatives from 1,2-diols and ammonia (b) 3-component synthesis of N-substituted pyrroles by the dehydrogenative coupling of 1,4-diols with primary alcohols and ammonia (Scheme 1). In both reactions, gaseous ammonia is the source of nitrogen, and the catalyst is an acridine-based ruthenium pincer complex, with no additives such as base or oxidant being required.

The optimized reaction conditions developed by our group for the amination of alcohols with ammonia[3] were explored for pyrazine formation using 1,2-diols and catalyst **1**. Heating a toluene solution of 1,2-hexanediol (1 mmol) at 150°C (bath temperature) with complex **1** (1 mol%) in a Fischer-Porter tube under 7 bar of ammonia for 36h resulted in quantitative consumption of the diol, forming a mixture of 2,6- and 2,5- dibutylpyrazine (65:35 ratio, respectively), as shown by GC-MS and NMR spectroscopy (Table 1, entry 1). Since pyrazine derivatives are of importance as potential bioactive molecules in drug research[12] several vicinal diols were screened. Employing longer linear alcohols, such as 1,2-decanediol and 1,2-tetradecanediol, resulted in quantitative conversion to form a 1:1 mixture of both isomers (Table 1, entries 2, 3). The reaction with 1-phenyl-1,2-ethanediol afforded quantitative yields of the corresponding diphenylpyrazine derivatives with 68:32 ratio (Table 1, entry 4). Treatment of 1,2-butanediol afforded 72% of the diethylpyrazine derivatives, whereas 1,2-propanediol afforded 42% of the desired product, along with some unidentified side products in both cases (Table 1, entries 5, 6). Under the same conditions, ethylene glycol did not form any pyrazine although piperazine

and its derivatives were detected as minor products along with some unidentified polymeric products. 1,2-disubstituted-1,2-diols are readily synthesized by direct hydrogenolysis of lignocellulose biomass, although these sterically hindered diols are challenging substrates for dehydrogenation. Employing such substrates, 2,3-butanediol afforded 85% of the tetramethylpyrazine as the major product, whereas reaction of 1,2-cyclohexanediol resulted in formation of octahydrophenazine in 95% yield with a minute amount hydrogenated products (entry 7, 8). Formation of octahydrophenazine as a minor product along with mixture of amines in the amination of 1,2-cyclohexanediol was reported.[5g]

Table 1. Pyrazine formation by 1,2-diol and ammonia[a]



Entry	Substrate	Products	Yield[b] [A/B]
1			99 [65/35]
2			99 [50/50]
3			99 [58/42]
4			99 [68/32]
5			72[c]
6			42[c]
7			85[c] (15)[d]
8			95 (5)[d]

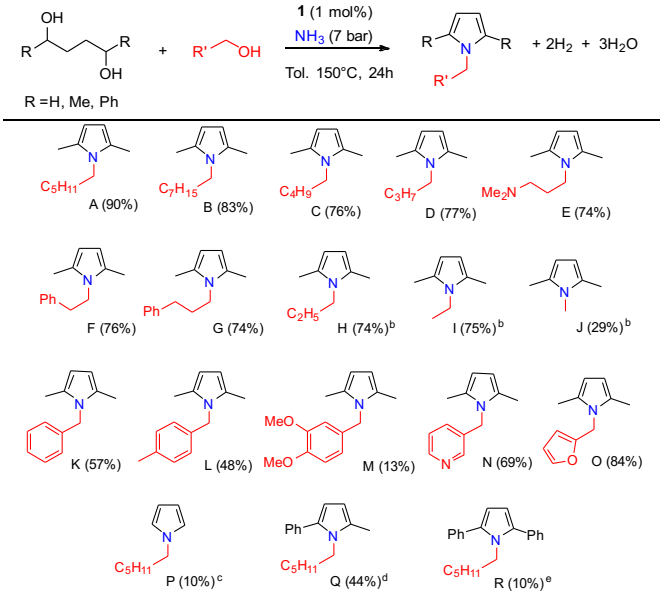
[a]Reaction conditions: Catalyst **1** (0.01 mmol), 1,2-diol (1 mmol), ammonia (7 bar), 150°C (bath temp.), 36h, toluene (2ml), [b]Isolatd yield. [c]GC-MS yield with mesitylene as internal standard. [d]hydrogenated product

Next, we examined the reaction of 1,4-butanediol derivatives with ammonia, aiming at formation of pyrroles. While reaction of 1,4-butanediol produced pyrrolidine quantitatively, employing 2,5-hexanediol resulted in 85% yield of 2,5-dimethyl-1-pyrroline and 15% yield of the 2,5-dimethylpyrrole under ammonia pressure using **1** (1 mol%) under the optimized conditions (see SI, Figure S1 for details). Interestingly, when a primary alcohol was added to 2,5-hexanediol, a multicomponent dehydrogenative coupling reaction took place, yielding N-substituted pyrroles. Classical methods for N-substituted pyrrole synthesis involve the Paal–Knorr reactions.[13] Also, the dehydrogenative coupling of 2-amino alcohol derivatives with secondary alcohols to afford pyrrole derivatives was reported by Kempe[10a] and by our group.[10g] Recently the dehydrogenative coupling of 1,4-butanediol derivatives with primary amines was reported.[10h,i] To the best of our knowledge, synthesis of N-substituted pyrroles by dehydrogenative coupling of 1,4-butanediol derivatives with primary alcohols and *ammonia* was never reported. However, we are aware of dehydrogenative coupling of ketones and primary alcohols to form N-nonsubstituted pyrrole derivatives using ammonia.[10b,c]

The optimal reaction conditions were achieved by treatment of 2,5-hexanediol (1 mmol) and 1-hexanol (2 mmol) using 1mol% of **1** under 7 bar of ammonia at 150°C for 24h in 0.5 ml toluene, affording 90% of 1-hexyl-2,5-dimethylpyrrole as the dehydrogenative coupling product (Table 2, entry A; see the reaction optimization Table S2 in SI). Encouraged by the efficient catalytic 3-component dehydrogenative coupling of alcohols with ammonia to form pyrroles, various primary alcohols were screened. Under the optimized reaction conditions 1-octanol, 1-pentanol and 1-butanol yielded 83%, 76%, and 77% of the corresponding N-substituted pyrroles, respectively (Table 2, entries B-D). (N,N-dimethyl)amino-1-propanol afforded 74% of the corresponding 1,2,5-substituted pyrrole derivative as the major product (Table 2, entry E), and 2-phenyl-1-ethanol and 3-phenyl-1-propanol afforded 76% and 74% of the desired product, respectively (Table 2, entries F, G). In case of low boiling primary alcohols, such as 1-propanol, ethanol and methanol, 4 equivalents of the alcohol with respect to 2,5-hexanediol were used (See Table 2 footnotes for conditions) and afforded good to moderate yields of the corresponding 1,2,5-substituted pyrroles (Table 2, entries H-J). Replacement of linear primary alcohols by benzyl alcohols resulted in lower reactivity under the same conditions and afforded moderate yield of the 1,2,5-substituted pyrroles. Reactions of benzyl alcohol and 4-methyl benzyl alcohol afforded 57% and 48% yields, respectively, of the corresponding pyrrole derivatives, whereas the bulkier 3,4-dimethoxybenzyl alcohol afforded only 13% of the product (Table 2, entries K-M). Under the same reaction conditions, heteroatom substituted primary alcohols also showed good yields. Nicotinyl alcohol and furfuryl alcohol afforded 69% and 84% yields, respectively, of the corresponding 2,5-dimethyl-N-substituted pyrrole as the major product (Table 2, entries N and O). The alcohols were fully consumed, and in addition to the N-substituted 2,5-dimethylpyrrole product, the side products 2,5-dimethylpyrrole and 2,5-dimethyl-1-pyrroline, the corresponding primary amine, and a minute amount of secondary amine of the primary alcohol were also observed in each case (see SI, Table S3).

Unlike the other mentioned diols, treatment of 1,4-butanediol with two equivalents of 1-hexanol and ammonia formed N-hexylpyrrolidine as the coupling product (40%) along with N-hexylpyrrole (10%) and pyrrolidine (Table 2, entry P). Under the optimized conditions, in presence of ammonia, reaction of 1-hexanol with 1-phenyl-1,4-pentanediol afforded 44% of 1-hexyl-2-phenyl-5-methyl pyrrole, whereas 1,4-diphenyl-1,4-butanediol afforded only 10% yield of the 1-hexyl-2,5-diphenyl pyrrole with N-non-substituted pyrrole and pyrroline as the major side products (Table 2, entries Q, R, also see details in SI, Figure S2). This is likely a result of the internal amine attack being preferred in the case of the more sterically hindered carbonyl moiety as compared with the external attack, giving a higher yield of the non-substituted pyrrole (See mechanism part).

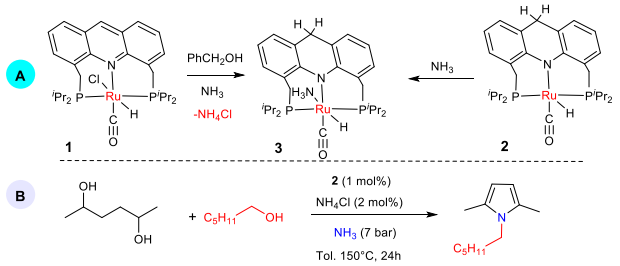
Table 2. N-substituted pyrrole formation by dehydrogenative coupling of alcohols and ammonia[a]



[a]Reaction conditions: Catalyst **1** (0.01 mmol), 2,5-hexanediol (1 mmol), primary alcohol (2 mmol), ammonia (7 bar) 150°C, 24h, toluene (0.5 ml), NMR yield with mesitylene as internal standard. [b]primary alcohol (4 mmol). [c]1,4-butanediol (1 mmol). [d]1-phenyl-1,4-pentanediol (1 mmol). [e]1,4-diphenyl-1,4-butanediol (1 mmol).

The mechanism of the direct amination of alcohols by ammonia to form primary amines (see SI) was well documented by us[3,14] and independently by Hofmann et al,[4] supported by DFT and experimental evidence. It was experimentally observed that complex **1** in the presence of alcohol and ammonia was converted to the ammonia-coordinated complex **3**, containing a dearomatized acridine backbone ligand (see SI). Complex **3** was instantly formed by treatment of complex **2**[14] with ammonia (Scheme 2A, for details see SI). Complex **2** was equally active in the alcohol amination reaction. Thus, under the optimized conditions, full conversion of benzyl alcohol yielding 90% of benzylamine and 10% of N-benzylidenebenzylamine took place. However, treatment of 2,5-hexanediol and 1-hexanol with complex **2** under the optimized condition afforded only 50% of 1-hexyl-2,5-dimethylpyrrole whereas enhancement of the yield (68%) was observed by addition of NH_4Cl (2 mol%) (Scheme 2B), which indicates that the eliminated catalytic HCl as NH_4Cl during the alcohol amination using complex **1** (Scheme 2A) promotes the subsequent reactions leading to pyrazines and pyrroles.

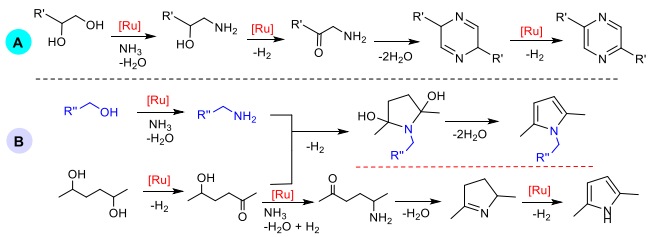
Scheme 2. Synthesis of complex **3** and a catalytic experiment with catalyst **2**



In the proposed mechanism for pyrazine formation from vicinal diols and ammonia catalyzed by **1**, the primary alcohol group of the vicinal diol undergoes amination to from a β-amino secondary alcohol intermediate. Dehydrogenation of the secondary alcohol group then takes place, followed by self-coupling to produce 2,5-dihydropyrazine by elimination of two molecules of water, followed by aromatization by further dehydrogenation to form the final pyrazine (Scheme 3A).

The pyrrole formation reaction involves dehydrogenative coupling of 2,5-hexanediol and the primary alcohol in the presence of ammonia and catalyst **1** with H_2 and water as the sole byproducts (Scheme 3B). Analysis of the gas phase by gas chromatography indicated the formation of H_2 (See Figure S24). Dehydrogenation and amination of the primary alcohol prevails over that of the secondary alcohol, affording the corresponding primary amine. Dehydrogenation of the secondary alcohol group generates a keto intermediate. Two competitive reactions can take place at this stage. The initially formed primary amine can attack the keto intermediate, eliminating two molecules of water to directly form the 1,2,5-substituted pyrrole as the target product. The second possibility is the direct ammonia attack on the keto group, followed by hydrogenation to afford an amine, which attacks the internal keto group and forms the cyclic 2,5-dimethyl-1-pyrroline, eliminating water; further dehydrogenation gives the N-H pyrrole as a side product. Increasing the ratio of primary alcohol to the 1,4-diol derivative increases the concentration of the primary amine and favors its attack to form the desired 1,2,5-substituted pyrrole (see reaction optimization, Table S2)

Scheme 3. Proposed mechanism



To understand the dehydrogenative coupling steps, treatment of equivalents of 2,5-hexanediol and 1-hexylamine with complex **2** in toluene under reflux afforded N-hexyl-2,5-dimethylpyrrole as the major product (90%). Under the same conditions, reaction of an equivalent of 2,5-dimethylpyrrole and 1-hexanol afforded hexyl hexanoate as the major product and unreacted 2,5-dimethylpyrrole, indicating that it is not an intermediate in formation of the N-substituted pyrrole. Thus, the latter is formed by attack of the primary amine on the formed carbonyl moiety of the diol followed by water elimination.

In conclusion, two significant reactions based on dehydrogenative coupling of ammonia and alcohols were developed. Dehydrogenative coupling of 1,2-diols and ammonia to form pyrazine derivatives, and the 3-component dehydrogenative coupling of 2,5-hexanediol and primary alcohol to form N-substituted pyrroles, both reactions catalyzed by the acridine-based Ru-pincer complex **1**. In both cases, ammonia was used as the nitrogen source. The acridine-based PNP-pincer ligand plays a vital role in these transformations, generating the anionic dearomatized PNP-pincer ligand framework. We believe that these discoveries provide a new approach towards heteroaromatic synthesis via acceptorless dehydrogenative coupling by direct use of ammonia.

ASSOCIATED CONTENT

The experimental procedure, GC-MS, NMR spectra of products are provided in supporting information. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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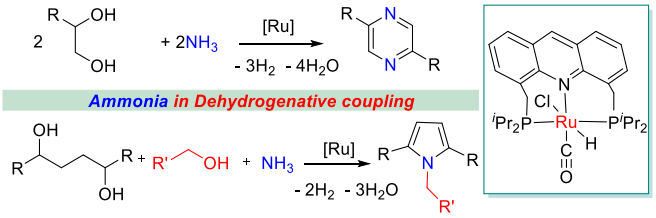
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+ 2NH3
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- 3H2 - 4H2O
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Ammonia in Dehydrogenative coupling
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- 2H2 - 3H2O
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