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Oxidant-Free Conversion of Cyclic Amines to Lactams and H_2 Using Water As the Oxygen Atom Source

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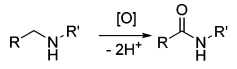
Supporting Information

ABSTRACT: Direct conversion of cyclic amines to lactams utilizing water as the only reagent is catalyzed by pincer complex **2**. In contrast to previously known methods of amine-to-amide conversion, this reaction occurs in the absence of oxidants and is accompanied by liberation of H_2, with water serving as a source of oxygen atom. Formation of a cyclic hemiaminal intermediate plays a key role in enabling such reactivity. This represents an unprecedented, conceptually new type of amide formation reaction directly from amines and water under oxidant-free conditions.

The synthesis of amides and lactams is one of the most important transformations in organic synthesis, as they are widely used as precursors for synthesis of polymers, biologically active compounds, and pharmaceuticals. Common methods for the preparation of amides include coupling of amines with carboxylic acid derivatives, nitrile hydrolysis, rearrangement of ketoximes,[1] or catalytic dehydrogenative coupling of amines with alcohols.[2,3] The direct conversion of amines to amides via oxygenation of an α-methylene group remains relatively rare. Such oxygenation reactions typically require the use of a stoichiometric oxidant such as iodosobenzene,[4] *t*BuOOH,[5] $RuO_2/NaIO_4$,[6] O_2,[7] or other oxidants[8] (eq 1).



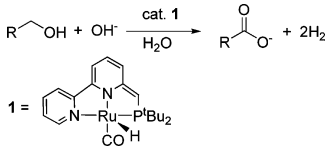
(1)

[O] = PhIO, tBuOOH, $RuO_2/NaIO_4$, O_2, etc.

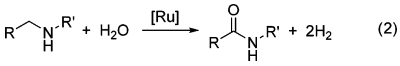
Our group has recently developed the direct dehydrogenation of alcohols in water to selectively produce carboxylic acid salts in the presence of a stoichiometric amount of base, catalyzed by a bipyridyl-based pincer Ru complex **1** (Scheme 1).[9] In this reaction, water serves as the oxygen atom source, while the reaction is accompanied by liberation of H_2.[9,10]

In effect, water can be viewed as an oxidant in this system with this very unusual role for H_2O enabled by the production of H_2.[9]

Scheme 1. Conversion of Alcohols to Carboxylate Salts Using a Stoichiometric Base and 1 as a Catalyst



This has raised the intriguing possibility of developing a reaction of amines with water to form amides, with concurrent liberation of hydrogen gas (eq 2). Developing a dehydrogenative amine-to-

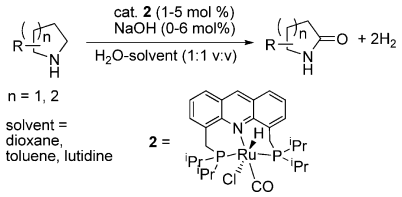


(2)

amide conversion can ultimately provide a more atom-economical method for amide synthesis that does not require the use of a stochiometric oxidant, with water serving as a source of oxygen in the amide group.

Reported herein is the dehydrogenation of cyclic amines in water to produce γ- and δ-lactams catalyzed by an acridine-based Ru pincer complex (AcrPNP)RuH(CO)Cl (**2**)[11−13] in the presence of a *catalytic* amount of a base (Scheme 2). This

Scheme 2. Lactam Formation from Cyclic Amines Catalyzed by 2



transformation is accompanied by liberation of H_2, while water serves as a source of the oxygen atom in the amide group. Since complex **2** also catalyzes the amination of 1,4-butanediol with NH_3 to pyrrolidine, this also opens up the possibility for the direct synthesis of lactams from diols and NH_3.

We have reported that complex **2** catalyzes the deamination of aliphatic amines by water to produce alcohols and NH_3 in a water−dioxane mixture at 100−135 °C (eq 3).[14] This transformation was proposed to occur via a reversible dehydrogenation/hydrogenation sequence ("borrowing hydrogen")[15] and likely involves the formation of a hemiaminal as a key intermediate (Scheme 3).[14] The major side reaction was the formation of carboxylate salts by further alcohol dehydrogenation, which could be suppressed under a H_2 atmosphere.[14]

$$RNH_2 + H_2O \xrightarrow{[Ru]} ROH + NH_3 \qquad (3)$$

The loss of NH_3 from a hemiaminal intermediate was the predominant reaction for aliphatic amines in water under these

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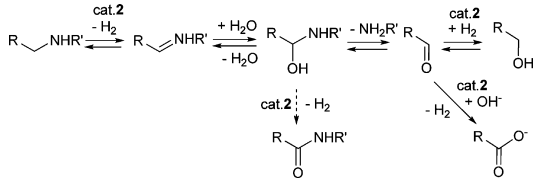
Scheme 3. Proposed Mechanisms for Deamination



conditions. However, if the deamination pathway could be prevented, further dehydrogenation of the hemiaminal intermediate could potentially lead to amides (Scheme 3).

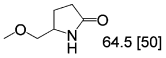
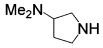
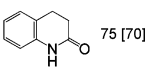
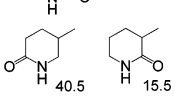
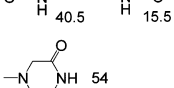
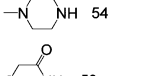
Accordingly, when *n*-butylamine was heated in a water−dioxane mixture under 5 atm of NH_3 in the presence of **2** for 65 h at 150 °C, the formation of *n*-butanamide and *N*-butyl butanamide was detected; however, the combined yields of amides did not exceed 5%, while the formation of 1-butanol (8%) and butyrate ammonium salt (7%) was also observed under these conditions. Therefore, the entropically driven loss of NH_3 could not be completely prevented even under NH_3 pressure for primary aliphatic amines.

We then employed cyclic amines which could entropically stabilize cyclic hemiaminal intermediates against deamination. Heating a pyrrolidine solution in a degassed water−dioxane mixture (1:1 v/v) under N_2 in a closed system at 150 °C in the presence of 1 mol % **2** produced 2-pyrrolidone in 24% yield (Table 1, entry 1) after 48 h, also generating H_2 gas that was detected by TCD-GC. A control experiment showed no conversion in the absence of **2** under the same conditions upon prolonged heating of pyrrolidine in water/dioxane at 150 °C.

Notably, the analogous reaction of pyrrolidine in the presence of complex **1** (1 mol %) which was previously used for alcohol-to-carboxylate conversion (Scheme 1)[9,16] produced <1% of lactam after heating at 150 °C for 48 h in the absence or in the presence of a *catalytic* amount of NaOH (1.5 mol %) and pyrrolidine remained mostly unreacted.[17] The unselective formation of 2-pyrrolidone in 19% yield was observed only in the presence of a *stoichiometric* amount of NaOH.

We have shown earlier that the more selective alcohol dehydrogenation to esters could be achieved when acridine-based pincer complex **2** was employed in combination with a catalytic amount of NaOH, while, in the absence of a base, formation of a mixture of esters and acetals was observed.[13] When the pyrrolidine solution was heated in water/dioxane in the presence of 1 mol % of **2** in combination with 1.5 mol % of NaOH, formation of pyrrolidone in 59% yield was observed (Table 1, entry 2). The beneficial effect of the base could be due to stabilization of a hemiaminal intermediate against the elimination of amine or the formation of a Ru(0) catalyst via deprotonation of **2**.[13] Hydrogen gas formation was detected by GC analysis of the gas phase above the reaction mixture, and the average yield of H_2 is 79 ± 4% based on pyrrolidine conversion determined by volumetric measurements. Further increasing the amount of a base to 6 mol % did not improve the lactam yield and led to slightly lower selectivity (entry 3). The yield and selectivity could further be increased in the presence of higher catalyst loadings (5 mol % **2** and 5 mol % NaOH) to give 2-pyrrolidone in 83% yield with ∼90% selectivity (entry 4). The yields of the reaction were unaffected in the presence of a drop of mercury metal, a common test that checks for the formation of catalytic metal particles under these conditions. Lactam formation was also observed in a biphasic toluene−water or in pyridine−water

Table 1. Cyclic Amine-to-Lactam Conversion Catalyzed by 2[a]

Entry	Substrate	t, h	Conv. %[a]	Product, % yield [isolated yield][a]
1[a,b]		48	59	 24
2[a,c]		48	78.5	 59 [37]
3[a,d]		48	88	 59
4[e]		48	91	 83
5[f]		48	88	 73
6[a,c]		48	62	 43.5 [22.5]
7[e]		72	95	 56
8[a,c]		48	70	 64.5 [50]
9[e]		48	96	 85
10[a,c]		48	>99	 79 Me$_2$NH 65
11[a,c]		48	98	 [69]
12[e]		89	85	 71
13[e]		89	99	 75 [70]
14[e]		84	65	 40.5 15.5
15[e]		87	61	 54
16[e]		87	59	 59

[a]Substrate (1 mmol), **2** (0.01 mmol, 1 mol %), water (1.5 mL), and dioxane (1.5 mL) were heated in a 50 mL thick wall pressure tube at 150 °C (silicon oil bath temperature), if not indicated otherwise. % NMR yields and conversions and isolated yields (in square brackets) are reported as averages of two runs. [b]No base added. [c]NaOH 1.5 mol %. [d]NaOH 6.0 mol %. [e]Cat. [**2**] 5 mol % and NaOH 5 mol %, dioxane/water 2:1 v/v. [f]Cat. [**2**] 1 mol % and NaOH 1.5 mol %, lutidine/water 1:1 v/v.

solutions, albeit with lower yields and selectivities.[17] The reaction in lutidine−water (1:1 v/v) solution using 1 mol % of **2** and 1.5 mol % of NaOH affords 2-pyrrolidone in 73% yield with 83% selectivity (entry 5).

The major side products formed during the reaction with pyrrolidine were identified as 4-(1-pyrrolidinyl)butanoic acid (**S1**) and a trace amount of succinic acid (**S2**). In particular, **S1** formed in 9−10% and 4−5% yield after heating for 48 h at 150 °C in the presence of 1 mol % **2** (entry 2, Table 1) and 5 mol % **2** (entry 4), respectively, while succinic acid was present only in trace amounts (<3% in entry 2).[18] Since 2 equiv of pyrrolidine are consumed during the formation of 1 equiv of 4-(1-pyrrolidinyl)butanoic acid, this may account for the mass balance of pyrrolidine conversion.[19] The possible mechanisms for the formation of **S1** an **S2** are discussed in the Supporting

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Information (SI) in more detail (Scheme S1) and likely involve 4-aminobutyric acid as an intermediate formed either via a base-catalyzed 2-pyrrolidone hydrolysis or via further oxidation of 4-amino-1-butanal **II** (n = 1, Scheme 4) resulting from the ring opening of **I** (n = 1, Scheme 4).[9,14,17]

Scheme 4. Proposed Pathway of Lactam Formation Catalyzed by 2

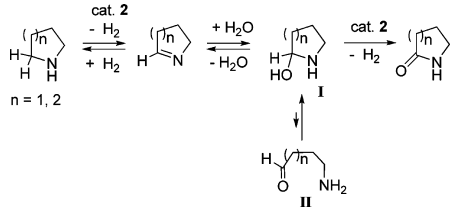
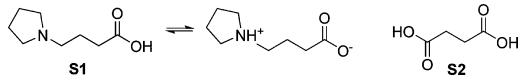


Chart 1. Byproducts of the Reactions with Pyrrolidine in Water–Dioxane Catalyzed by 2/NaOH



The substituted pyrrolidines 2-methylpyrrolidine and 2-methoxymethylpyrrolidine react in a similar way and afford the corresponding lactams in 43.5% and 64.5% yields respectively, using 1 mol % of catalyst **2** (Table 1, entries 6 and 8). The lactam product of the reaction with 2-methoxymethylpyrrolidine could be obtained in up to 85% yield when 5 mol % of **2** was used (entry 9), while the reaction with 2-methylpyrrolidine was less selective at higher catalyst loadings (entry 7).[20] The products were isolated and characterized by NMR, IR, and HR-MS. By contrast, 3-dimethylaminopyrrolidine undergoes deamination to generate Me_2NH and pyrrole under these conditions (entry 10).[21] Indoline undergoes dehydrogenation to form indole in 69% yield (entry 11), while no amide product was detected by GC-MS and NMR.

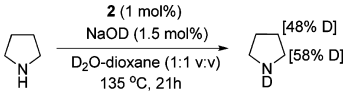
The six-membered cyclic secondary amines (entries 12–16) reacted in a similar way to produce the corresponding lactams in 54–75% yield using 5 mol % of **2** and NaOH. During dehydrogenation of 1,2,3,4-tetrahydroquinoline, no quinoline was detected among the reaction products. The major byproduct in the reaction with piperidine is most likely a 5-(1-piperidinyl)-pentanoic acid (**S3**) that was formed in 10–15% yields and was characterized by ESI-MS and NMR.[17] The yields of the lactams are generally lower for six-membered cyclic amines compared to five-membered substrates likey due to the lower stability of the hemiaminal intermediate or steric factors.

Based on previous mechanistic studies,[3,11–13] the following pathway is proposed for the lactam formation from cyclic amines (Scheme 4). In the proposed mechanism complex **2** catalyzes the initial dehydrogenation of the cyclic amine to form a cyclic imine intermediate, which undergoes a nucleophilic attack by water to afford a hemiaminal intermediate **I**, and then further dehydrogenation of the latter species catalyzed by complex **2** yields the corresponding lactam (Scheme 4).

To confirm that the O-atom in the amide group originates from water, the reaction with pyrrolidine was performed in a dioxane–$H_2{}^{18}O$ (≥98 atom % ^{18}O) mixture. Heating pyrrolidine in dioxane–$H_2{}^{18}O$ in the presence of **2** (1 mol %) and NaOH (1 mol %) at 150 °C for 72 h gave 2-pyrrolidone that was shown by HR-MS to be ≥98% ^{18}O-labeled.

The initial dehydrogenation step to produce imine (Scheme 4) is reversible as evident from an H/D exchange experiment. Thus, heating pyrrolidine in the presence of **2** (1 mol %) and NaOH (1.5 mol %) in a D_2O–dioxane mixture at 135 °C leads to 58% and 48% deuterium incorporation in α- and β-CH_2 groups, respectively (Scheme 5). Notably, the formation of 2-

Scheme 5. Deuterium Incorporation in Pyrrolidine CH_2 Groups in the Presence D_2O Catalyzed by 2



pyrrolidone under these conditions, at 135 °C, is only minimal (<5%), suggesting that the initial dehydrogenation step occurs before the rate-limiting step of the reaction and requires a lower temperature than the lactam formation. A control experiment in the absence of **2** and in the presence of 1.5 mol % NaOH shows only 3% deuterium incorporation in the α- and β-CH_2 groups of pyrrolidine under analogous conditions. The incorporation of deuterium in the β-position might be due to increased acidity of the β-CH_2 groups in the imine;[16] however, an alternative mechanism involving formation of 2-pyrroline cannot be completely excluded.[22]

As a factor that helps drive the reaction forward, we found that the formation of 2-pyrrolidone is *irreversible* under the reaction conditions. The attempted hydrogenation of 2-pyrrolidone in the presence of **2** (1 mol %) and NaOH (1.5 mol %) in water–dioxane (1:1 v/v) under 10 atm of H_2 does not yield pyrrolidine after heating at 150 °C for 60 h, and the starting material remains mainly unreacted.

Overall, the formation of amides via dehydrogenation of cyclic amines in water suggests that the stability of the hemiaminal intermediate plays an important role in determining the reactivity of amines with water catalyzed by **2**. Although deamination of primary aliphatic amines catalyzed by **2** was also proposed to occur via hemiaminal intermediates, the entropically driven loss of NH_3 leads to the predominant formation of alcohols and carboxylates. Similarly, heating an acyclic secondary amine, di-*n*-hexylamine, in water–dioxane at 150 °C for 48 h in the presence of **2**/NaOH leads to the formation of 1-hexanol (~20%) and hexanoate salt (~9%) resulting from secondary amine splitting[9,14,23] while no amides were present among the products in detectable amounts. At the same time, entropic stabilization of a cyclic hemiaminal intermediate **I** (Scheme 4) toward the loss of an amine group likely enables its further dehydrogenation leading to the lactam formation.

Combined with the ability of complex **2** to catalyze the amination of alcohols with ammonia,[12] the reactivity observed herein opens up the possibility of one-step formation of lactams directly from diols and NH_3 in water. Accordingly, we found that a one-step reaction of 1,4-butanediol under 6 atm of NH_3 in the presence of 5 mol % of **2** and 5 mol % of NaOH in water–dioxane generates a mixture of pyrrolidine (58%) and pyrrolidone (31%) after heating at 150 °C for 72 h.[17,24] The reaction was more selective at a lower concentration of NH_3: when an aqueous ammonia solution (24–27 w/w%) was used, 2-pyrrolidone and pyrrolidine were obtained in 49% and 23% yields, respectively (Scheme 6).[17]

The formation of pyrrolidine in Scheme 6 likely occurs via initial amination of 1,4-butanediol to give 4-amino-1-butanol

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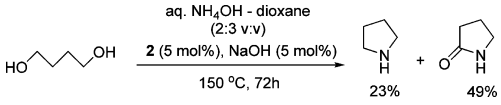
Scheme 6. Synthesis of Pyrrolidine and 2-Pyrrolidone by Amination of 1,4-Butanediol with NH_3 in Water−Dioxane



followed by the cyclization of the latter,[12,14,25] while the formation of 2-pyrrolidone may occur via two possible pathways: (i) a dehydrogenative reaction of pyrrolidine with water (Scheme 2) or (ii) dehydrogenative intramolecular amide formation directly from 4-amino-1-butanol.[3] While both pathways could be involved in the observed lactam formation via the same intermediate **I** (n = 1, Scheme 4), our experiments suggest that direct reaction of pyrrolidine with water (path i) likely contributes to the overall yield of lactam under these conditions (see SI for more detail).

In summary, we reported for the first time the formation of lactams via dehydrogenation of cyclic amines in water with H_2 liberation. The reaction is homogeneously catalyzed by complex **2** in the presence of a *catalytic* base, with water serving as a source of the oxygen atom of the formed amide. Although the currently obtained yields are in part modest, such reactivity is unique and it represents a fundamentally new type of amide formation reaction directly from amines and water under oxidant-free conditions. The lactam formation likely occurs via a cyclic hemiaminal intermediate which is entropically stabilized against the loss of amine, thus enabling its further dehydrogenation to an amide. Overall, combined with the ability of **2** to catalyze the amination of primary alcohols with NH_3, this opens up new possibilities for novel atom-economical approaches to the synthesis of lactams that avoid the use of stoichiometric oxidants.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details of catalytic reactions and characterization data. 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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(17) See SI for more detail.

(18) The lack of catalytic activity of **1** could be due to the catalyst deactivation by carboxylic acids **S1** and **S2** in the absence of a large amount of strong base.

(19) For example, the sum of pyrrolidine, pyrrolidone, and **S1** accounts for 98−100% of the mass balance in entries 2 and 4. However, a greater fraction (up to 20%) of unidentified insoluble products was observed in the presence of excess of NaOH (entry 3) where the yield of **S1** was 4−5%.

(20) The major product of reaction with 2-methylpyrrolidine is most likely 4-(2-methylpyrrolidin-1-yl)pentanoic acid, which was detected by ESI-MS in the reaction mixtures (m/z 186.1, M^*H^+).

(21) This reaction might involve tertiary amine splitting similar to that in ref 23, resulting in the formation of Me_2NH and pyrrolidin-3-one or 3-hydroxypyrrolidine. Dehydration of the latter would produce pyrroline, which could undergo dehydrogenation to the aromatic pyrrole system. However, other mechanisms cannot be excluded.

(22) *N*-Methylpyrrolidine undergoes unselective reaction to produce *N*-methyl-2-pyrrolidone in 22% yield at 69% conversion after heating for 48 h at 160 °C in the presence of 1 mol % of **2** and 1.5 mol % of NaOH, which could also indicate an alternative pathway involving enamine or iminium intermediates (see: Sundararaju, B.; Achard, M.; Sharma, G. V.; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340. Leete, E. *Planta Med.* **1990**, *56*, 339). However, the reaction with *N*-methylpiperazine (entry 15) generates secondary amide exclusively, suggesting that the imine formation (Scheme 4) is likely a predominant path towards lactams.

(23) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *Chem.—Eur. J.* **2011**, *17*, 4705.

(24) The reaction of 1,5-pentanediol in dioxane/water under 6 atm of NH_3 affords a mixture of piperidine (63%) and 2-piperidone (30%).

(25) (a) Yamaguchi, R.; Kawagoe, S.; Asai, C.; Fujita, K.-i. *Org. Lett.* **2007**, *10*, 181. (b) Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (c) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766.