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Iodine-Catalyzed Oxidative Rearrangement of Amines to α-Amino Acetals and α-Amino Aldehydes

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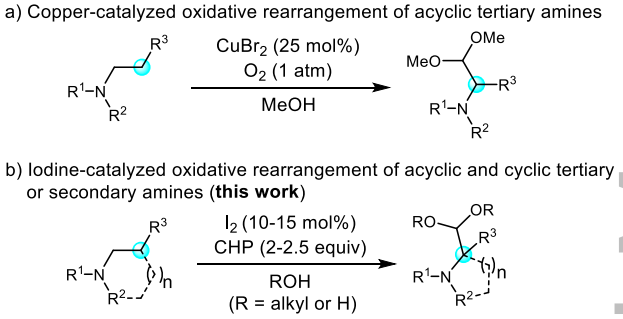
Abstract: A protocol for iodine-catalyzed oxidative rearrangement of tertiary and secondary amines has been developed. This metal-free protocol provides an atom-economical, efficient access to synthetically useful α-amino acid derivatives from readily available acyclic and cyclic tertiary or secondary amines.

Keywords: Iodine-catalysis; Oxidative rearrangement; Amine; α-Amino acid derivatives; Enamine intermediate

α-Amino acids and their derivatives are essential building blocks for the preparation of pharmaceuticals, natural products, catalysts and functional materials.[1] Therefore, the development of methods for the preparation of these compounds is of considerable interest.[2] Among the currently available methods is the catalytic oxidative rearrangement of tertiary amines, which provides a novel, atom-economical route to α-amino acid derivatives. In pioneering work, Loh and a co-worker[3] reported Cu-catalyzed oxidative rearrangement of acyclic tertiary amines to afford α-amino acetals (Scheme 1a).

We speculated that molecular iodine might be a useful catalyst for such rearrangements. Iodine is minimally toxic, environmentally benign, inexpensive, and easy to handle, and recent progress in iodine-catalyzed oxidative reactions has been impressive.[4] In particular, iodine has been shown to catalyze the oxidation of amines to α-amino radicals or iminium ions, which can undergo further conversions,[5] such as α-functionalization of the amine moiety.[6] However, to the best of our knowledge, iodine-catalyzed oxidative rearrangement of amines has not yet been explored. As a part of our long-term interest in developing novel oxidative functionalization reactions of amines,[7] we herein report the first iodine-catalyzed oxidative rearrangement of acyclic and cyclic tertiary or secondary amines to afford α-amino acetals and α-amino aldehydes under mild reaction conditions (Scheme 1b).



Scheme 1. Catalytic oxidative rearrangement of tertiary or secondary amines to α-amino acid derivatives.

We began by investigating the reaction of N,N-diethylaniline (**1a**) with *tert*-butyl hydroperoxide in 3:4 (v/v) EtOH/MeCN. In the presence of 15 mol% iodine, the reaction produced N-(2,2-diethoxyethyl)-N-ethylaniline (**2a**) in 11% yield (Table 1, entry 1). Screening of various oxidants (entries 2–5) revealed that cumyl hydroperoxide (CHP) was the best, giving **2a** in 29% yield. Addition of 4Å molecular sieves increased the yield of **2a** to 39% (entry 6). When the reaction temperature was increased from 80 to 100 °C, the yield was further increased to 54% (entry 7). Increasing the amount of CHP slightly improved the yield (entries 8 and 9).[8] Other iodine sources (NaI, TBAI, and NIS) were also examined but were found to give lower yields, even when the amount of catalyst was increased to 20 mol% (entries 10–12). Ethanol was found to be the choice of the alcohol component in the mixed solvent, giving the highest yield of the oxidative rearrangement product (for details, see Table S1 in Supporting Information). Control experiments

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indicated that both iodine catalyst and CHP oxidant are necessary for the reaction (entry 13 and 14).

Table 1. Optimization of the Reaction Conditions[a]

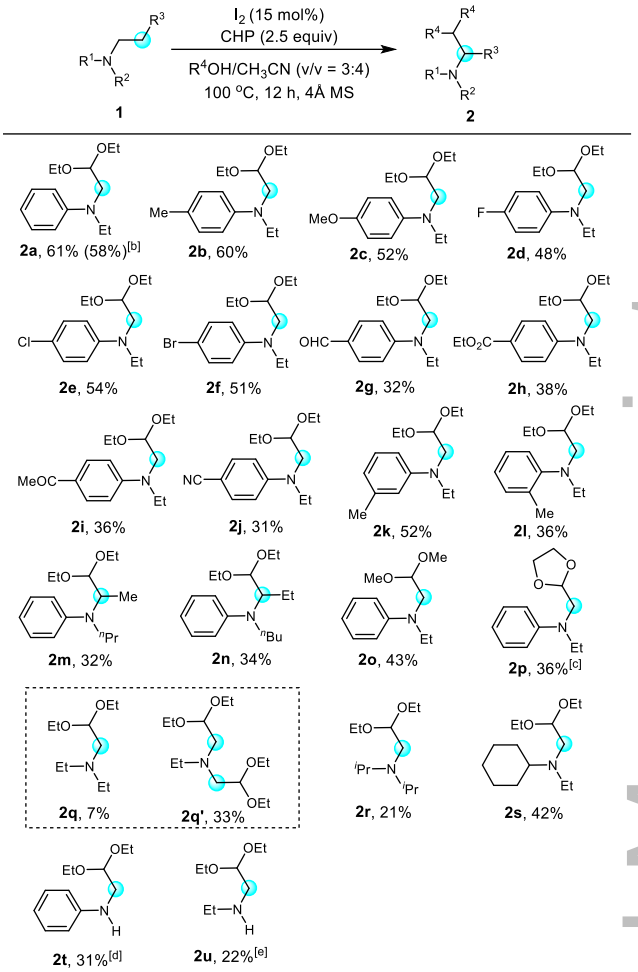
entry	catalyst (mol %)	oxidant (equiv)	T (°C)	yield of **2a** (%)[b]
1	I_2 (15)	TBHP (2.0)	80	11
2	I_2 (15)	AcOO^{t}Bu (2.0)	80	trace
3	I_2 (15)	TBP (2.0)	80	n.d.[c]
4	I_2 (15)	BPO (2.0)	80	trace
5	I_2 (15)	CHP (2.0)	80	29
6[d]	I_2 (15)	CHP (2.0)	80	39
7[d]	I_2 (15)	CHP (2.0)	100	54
8[d]	I_2 (15)	CHP (2.5)	100	63 (61)
9[d]	I_2 (15)	CHP (3.0)	100	57
10[d]	NaI (20)	CHP (2.5)	100	42
11[d]	TBAI (20)	CHP (2.5)	100	33
12[d]	NIS (20)	CHP (2.5)	100	36
13[d]	--	CHP (2.5)	100	n.d.[c]
14[d]	I_2 (15)	--	100	trace

[a]Reaction conditions: **1a** (0.5 mmol), I_2 (0.075 mmol, 15 mol%), oxidant, EtOH (3.0 mL) and CH_3CN (4.0 mL) at 80 °C or 100 °C in a sealed tube for 12 h; TBHP = *tert*-butyl hydroperoxide; TBP = di-*tert*-butyl peroxide; BPO = benzoyl peroxide; CHP = cumyl hydroperoxide; TBAI = tetrabutylammonium iodide; NIS = N-iodosuccinimide. [b]Determined by ^{1}H NMR using an internal standard. Number in parentheses is the isolated yield. [c]n.d. = not detected. [d]4Å molecular sieves (500 mg) as additive.

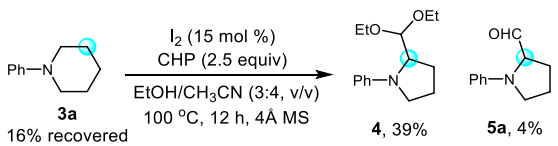
With the optimized conditions in hand, we examined the substrate scope of the reaction (Table 2). We were delighted to find that a variety of N,N-diethyl anilines bearing para functional groups such as ether, halide, aldehyde, ester, ketone, and nitrile afforded moderate yields of the corresponding products (**2a–j**). In general, substrates with an electron-donating group or a halogen atom gave higher yields than those with a strongly electron-withdrawing group (compare **2a–f** with **2g–j**). The yield was markedly affected by steric hindrance. For instance, a low yield was obtained when the substrate had an ortho methyl group (**2l**). In addition to N,N-diethyl anilines, substrates with a longer alkyl chain could also undergo the oxidative rearrangement reaction, although the yields were slightly lower (**2m** and **2n**). Moreover, other alcohols, such as methanol and ethylene glycol, can also be used in the reaction, but affording the corresponding α-amino acetals in lower yields (**2o** and **2p** vs **2a**). The reaction could be easily carried out on a gram scale, which demonstrates its practicality (Table 2, note b).

For the trialkylamines, the oxidative rearrangement reaction also take place, however, the over-oxidized product, diacetal was produced. For example, the reaction of Et_3N gave the over-oxidized product **2q'** as a major product (33% yield). When more sterically hindered trialkylamines, N,N-diisopropylethylamine and N,N-diethylcyclohexylamine were used, the over-oxidized product was suppressed, and the reac-tion proceeded selectively at the ethyl group (**2r** and **2s**). It was worth noting that the secondary amines can also be used in the reaction, providing the corresponding amino acetals (**2t** and **2u**).[9]

Table 2. Oxidative rearrangement of acyclic amines[a]



[a]Reaction conditions: **1** (0.5 mmol), I_2 (0.075 mmol), CHP (1.25 mmol), R_3OH (3.0 mL), CH_3CN (4.0 mL), 4Å MS (500 mg) at 100 °C for 12 h, unless otherwise noted. Isolated yield was given. [b]**1a** (7.0 mmol, 1.05 g). [c]2.0 mL $HO(CH_2)_2OH$ was used. [d]**2a** can be isolated in 21% yield. [e]**2q'** can be isolated in 5% yield.



Scheme 2. Oxidative rearrangement of cyclic amines in ethanol.

Having explored the iodine-catalyzed oxidative rearrangement of acyclic amines, we turned to cyclic amines. When the reaction of phenylpiperidine (**3a**) was carried out under aforementioned conditions, the cyclic oxidative rearrangement product **4** was isolated in 39%. However, the cyclic amino aldehyde **5a** was always formed as by-product in the reaction (Scheme 2). We wonder if we can switch the major product to

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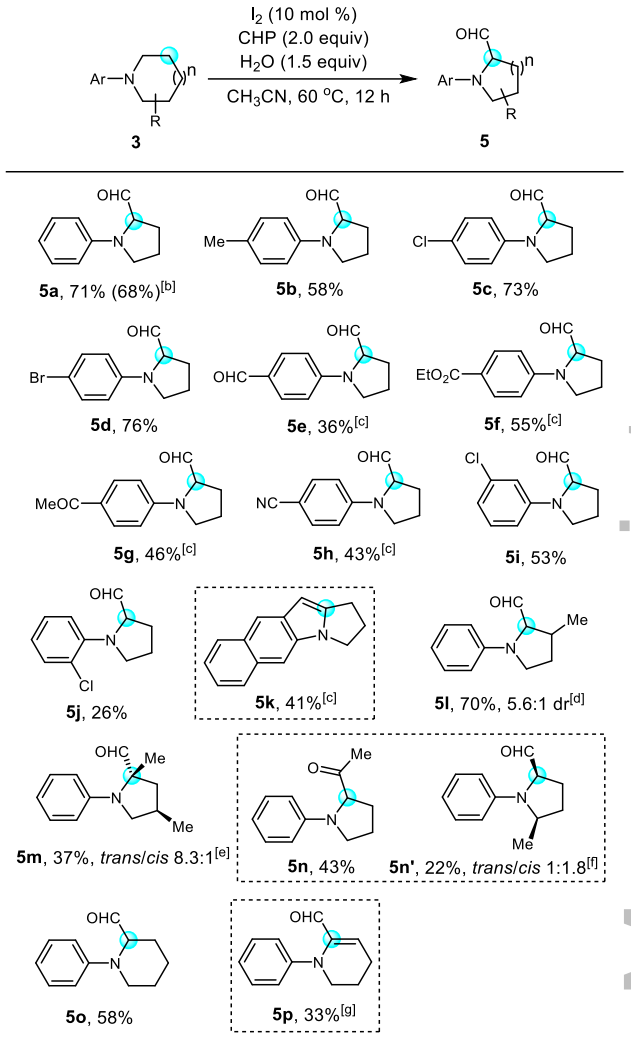
the cyclic amino aldehyde **5a** just by replacing the alcohol with water in the reaction.

After considerable effort, we were delighted to find that the replacement of the alcohol with a small amount of water as a nucleophile enabled the oxidative rearrangement of cyclic amines to be performed under milder conditions and to afford cyclic amino aldehyde as product (60 °C; for details, see Table S2 in Supporting Information).[10] For example, in the presence of 10 mol% I_2, 2 equiv of CHP, and 1.5 equiv of H_2O, 1-phenylpiperidine (**3a**) was transformed to the corresponding oxidative rearrangement product, 1-phenylpyrrolidine-2-carbaldehyde in 71% yield (Table 3, **5a**). Encouraged by this result, we explored the substrate scope of the reaction of cyclic amines. We found that 1-arylpiperidines containing various para substituents on the benzene ring smoothly underwent the oxidative rearrangement reaction, providing cyclic amino aldehydes in moderate to good yields (**5b–h**). Substrates with an electron-donating substituent or a halogen atom gave higher yields than those with an electron-withdrawing group (compare **5b–d** with **5e–h**). However, the oxidative rearrangement of a 2-chlorophenyl substrate gave only a 26% yield of the desired product (**5j**), which we attributed mainly to steric effects. We were surprised to find that the reaction of 1-(naphthalen-2-yl)piperidine at 80 °C gave 2,3-dihydro-1H-benzo[*f*]pyrrolo[1,2-*a*]indole (**5k**) as the sole product in 41% yield;[11] this product may have been produced via intramolecular condensation of the corresponding cyclic amino aldehyde.[12] Substrates with methyl groups at various positions on the piperidine ring were also examined. For example, 4-methyl-1-phenyl-piperidine could be converted to corresponding rearrangement product **5l** in 70% yield as a mixture of diastereomers (5.6:1 dr). 3,5-Dimethyl-1-phenylpiperidine (*cis*/*trans* = 6.7:1) also underwent the rearrangement reaction to afford **5m**, which has a quaternary carbon center, in moderate yield and with acceptable diastereose-lectivity. The reaction of 2-methyl-1-phenylpiperidine gave **5n** and **5n'** in 43% and 22% yields, respectively. The reaction of 1-phenylazepane was also investigated, and rearrangement product **5o** was obtained in 58% yield. Interestingly, when the catalyst and oxidant were changed to NaI and AcOO^{t}Bu, respectively, dehydrogenation product **5p** was obtained in 33% yield. We speculated that compound **5p** was formed by the oxidative dehydrogenation of **5o** under the reaction conditions. Piperidine and N-alkylpiperidine were also studied, however no rearrangement products were detected (data not shown).

To gain insight into the reaction mechanism, we conducted several control experiments (Scheme 3). The enamine **6** was prepared and reacted under the standard conditions, and the oxidative rearrangement product **7** was obtained in 21% yield (eq 1). This indicated that an enamine might be the intermediate of the reaction. When CD_3OD was used, the deuterated product ***d*-2o** with 0.41 D at the methylene group was obtained in 34% yield (eq 2). This H/D exchange result

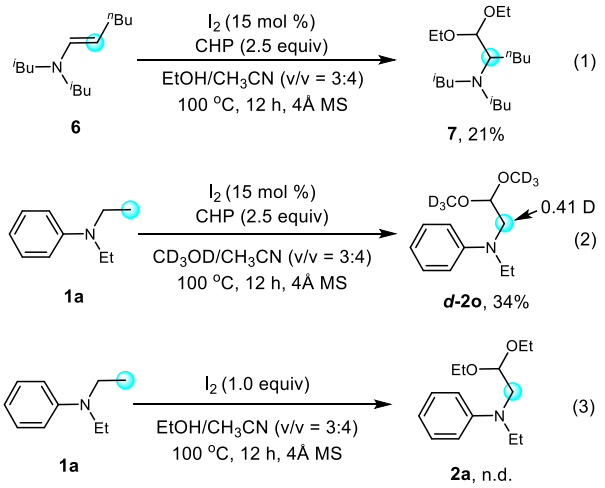
Table 3. Oxidative rearrangement of cyclic amines[a]



[a]Reaction conditions: **3** (0.5 mmol), I_2 (0.05 mmol), CHP (1.0 mmol), H_2O (14 μL, 1.5 equiv), CH_3CN (2.0 mL) at 60 °C for 12 h, unless otherwise noted. Isolated yield was given. [b]**3a** (6.5 mmol, 1.05 g). [c]At 80 °C. [d]Because the two stereoisomers cannot be separated, the rela-tive stereochemistry of the isomers were not determined. [e]Assigned by NOESY. [f]Assigned by ^{13}C HSQC and NOESY. [g]**3p** (0.5 mmol), NaI (0.1 mmol), AcOO^{t}Bu (2.0 mmol), H_2O (14 μL, 1.5 equiv), CH_3CN (2.0 mL) at 85 °C for 12 h.

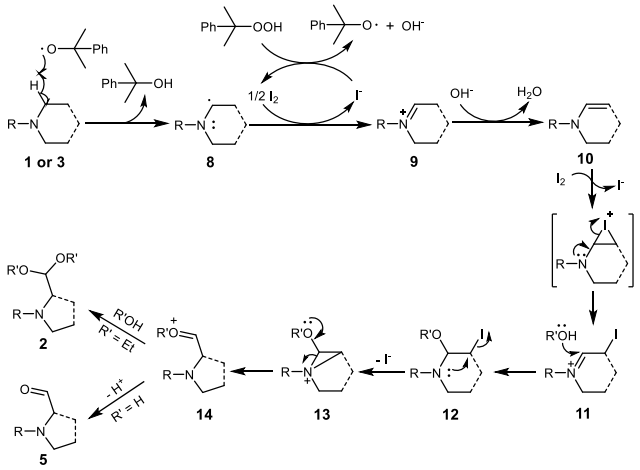
was similar to that reported by Loh and Tian[3a] and can also be explained by an enamine intermediate. When a stoichiometric amount of iodine was used in the absence of CHP, the rearrangement reaction did not occur (eq 3). However, when the enamine **6** reacted with one equivalent of iodine in the absence of CHP, the oxidative rearrangement product **7** can be obtained in 35%.[13] These results suggest that: 1) iodine itself can't oxidize amines to form enamine intermediates;[15] 2) iodine promotes the rearrangement of the enamine to product. Addition of a radical inhibitor such as 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) markedly suppressed the rearrangement reactions of both acyclic amine **1a** and cyclic amine **3a** (for details,

see Supporting Information), which suggests that the reactions probably proceeded via a radical process.



Scheme 3. Study of the reaction mechanism.

On the basis of our experimental results and previous reports,[3,5,16] we propose the mechanism depicted in Scheme 4. Initially, the hydrogen atom at the α-carbon of substrate **1** or **3** is abstracted by 2-phenylisopropoxy radical to form α-amino radical **8**. Then, a single-electron oxidation of radical **8** by iodine provides iminium ion **9** and iodide anion. The reaction of iodide anion and CHP affords 2-phenylisopropoxy radical and regenerates iodine. Deprotonation of **9** produces enamine **10**, which reacts with iodine to form iminium ion **11**. Nucleophilic attack of an alcohol or H_2O on **11**, followed by an intramolecular cyclization, yields aziridinium ion **13**. Finally, opening of the three-membered ring of **13**, followed by nucleophilic attack by the alcohol (for **2**) or deprotonation (for **5**), generates the rearranged acetal or aldehyde.[17]



Scheme 4. Proposed mechanism.

In conclusion, we have developed a protocol for iodine-catalyzed oxidative rearrangement of acyclic and cyclic amines to afford α-amino acetals and α-amino aldehydes in one step. This metal-free catalytic procedure is environmentally benign, operationally simple, and scalable and tolerates a variety of functional groups. Further studies on the reaction mechanism and the use of this rearrangement to other transformations are underway in our laboratory.

Experimental Section

Typical Procedure for Oxidative Rearrangement Reactions of Acyclic Amines: I_2 (19.0 mg, 0.075 mmol, 15 mol%) and 4Å MS (500 mg) were introduced into an oven-dried 35 mL sealed tube under argon atmosphere. CH_3CN (4 mL), EtOH (3 mL), $PhNEt_2$ (**1a**) (74.6 mg, 0.5 mmol) and CHP (238 mg, 1.25 mmol) were successively added via syringes at room temperature, and the reaction mixture was stirred at 100 °C for 12 h. After completion of the reaction, the mixture was filtere through kieselguhr and washed with CH_2Cl_2. The combined organic phase was concentrated under reduced pressure and purified by column chromatography on silica gel (PE/EA = 40:1 to 30:1) to give **2a** as yellow oil.

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[8] For details about optimization of reaction conditions such as solvents, additives and temperatures, see Supporting Information, Table S1.

[9] **2u** can also be produced efficiently via deprotection of the PMP group of **2c**. For details, see Supporting Information.

[10] Water (14 μL or 1.5 mL) is not suitable for acyclic amine **1a**, which gives only trace amount of rearranged aldehyde product (most of the start material was recovered and the by-product is PhNHEt).

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[13] For details, see Supporting Information 6.5.

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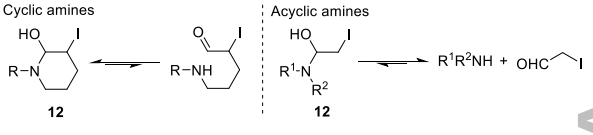
[17] With H_2O as a nucleophile, a competing decomposition of intermediate **12** involving a C-N bond cleavage is possible. For cyclic amines, the intermediate **12** can be regenerated easily from the de-composed byprodut. However, for acyclic amines, the decomposition of the intermediate **12** became the major side reaction. This can partially interpret why we used alcohol for acyclic amines and H_2O for cyclic amines.



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COMMUNICATION

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