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Synthesis of α-Formylated *N*-Heterocycles and Their 1,1-Diacetates from Inactivated Cyclic Amines Involving an Oxidative Ring Contraction

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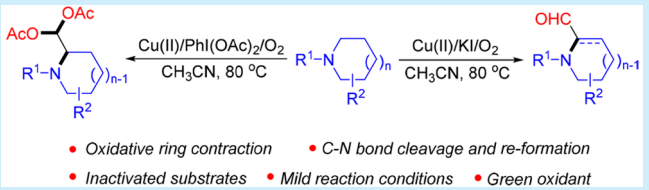
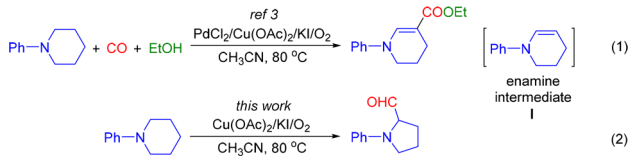
Supporting Information

ABSTRACT: A novel synthesis of pyrrolidine-2-carbaldehydes or tetrahydropyridine-2-carbaldehydes from the cascade reactions of *N*-arylpiperidines or *N*-arylazepanes is presented. Mechanistically, the formation of the title compounds involves an unprecedented oxidative ring contraction of inactivated cyclic amines via $Cu(OAc)_2/KI/O_2$-promoted oxidative cleavage and reformation of the C−N bond. Interestingly, when $PhI(OAc)_2$ was used in place of KI, 1,1-diacetates of the corresponding aldehydes were directly obtained with good efficiency. To the best of our knowledge, this is the first example of regioselective C(sp^3)−H bond functionalization and C(sp^3)−N bond activation of saturated cyclic amines using copper salt and oxygen.



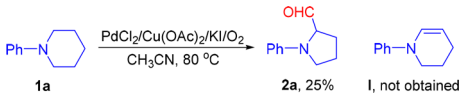
In recent years, C(sp^3)−H bond activation has attracted much attention owing to its elimination of substrate(s) preactivation and minimization of byproduct(s) production. In particular, the C(sp^3)−H bond functionalization of inactivated cyclic amines turns out to be a highly promising strategy for the synthesis of heterocyclic derivatives bearing diverse functional groups.[1,2] In this regard, we have recently disclosed a new synthesis of tetrahydropyridine-3-carboxylate via oxidative dehydrogenation of *N*-substituted piperidine followed by an alkoxy carbonylation of the in situ formed cyclic enamine intermediate with CO and alcohol under the promotion of a combination of $PdCl_2/Cu(OAc)_2/KI/O_2$ (Scheme 1, (1)).[3] In continuation of our interest in this aspect, we have serendipitously found a novel synthesis of α-formylated pyrrolidine through $Cu(OAc)_2/KI/O_2$-promoted oxidative ring contraction of *N*-substituted piperidine (Scheme 1, (2)). Herein we report our detailed study.

Scheme 1. Transformations of Inactivated Cyclic Amines via C(sp^3)−H Bond Functionalization



The initial attempt of our study was to obtain the proposed enamine intermediate as shown in Scheme 1.[3] For this purpose, 1-phenylpiperidine (**1a**) was treated with $PdCl_2$, $Cu(OAc)_2$, and KI under O_2 in CH_3CN at 80 °C. To our surprise, the expected 1-phenyl-1,2,3,4-tetrahydropyridine (**I**) was not isolated from the resulting mixture. Instead, 1-phenylpyrrolidine-2-carbaldehyde (**2a**) was obtained in 25% yield (Scheme 2; Table 1, entry 1).

Scheme 2. Unexpected Formation of 2a from 1a



Notwithstanding the proposed enamine (**I**) was not obtained, it occurred to us that the unexpected formation of **2a** was much more interesting because (1) while α-formyl pyrrole derivatives are well-known for their unique functional property and rich reactivity,[4,5] efficient and sustainable methods for their preparation are currently still highly limited[6−9] and (2) the formation of **2a** from **1a** indicated that a mechanistically interesting and synthetically promising ring contraction of **1a** through an oxidative C−N bond cleavage and reformation had taken place. Notably, while transition-metal-catalyzed cleavage of the C−N single bond in inactivated amines has evolved as a mild and convenient nitrogen and carbon source for organic synthesis,[10,11] oxidative ring contraction of inactivated saturated cyclic amines to afford α-formylated *N*-heterocycles has not been reported previously.

Aiming to develop this promising transformation into an efficient and reliable synthetic approach to hydrogenated α-formylpyrrole derivatives, various parameters were screened. First, to verify the role played by $PdCl_2$ and $Cu(OAc)_2$ in the formation of **2a**, the reaction was carried out in the presence of

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Table 1. Optimization Studies[a]

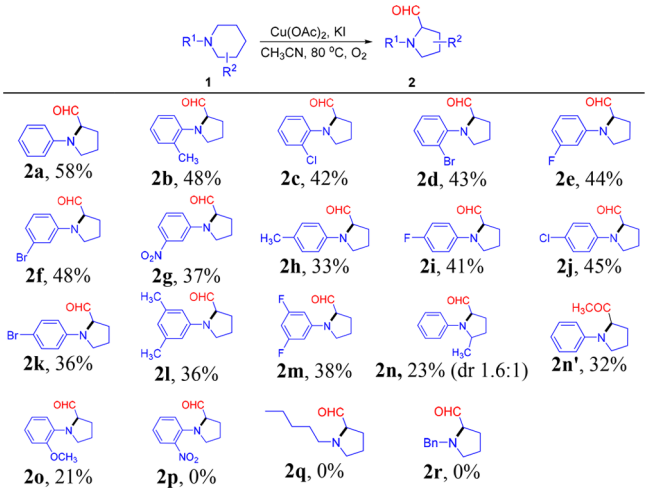
entry	oxidant (equiv)	additive	solvent	yield[b] (%)
1[c]	$Cu(OAc)_2$ (0.2)/O_2	KI	CH_3CN	25
2	$Cu(OAc)_2$ (0.2)/O_2	KI	CH_3CN	28
3	$PdCl_2$ (0.1)/O_2	KI	CH_3CN	trace
4	O_2	KI	CH_3CN	
5	$Cu(OAc)_2$ (0.5)/O_2	KI	CH_3CN	36
6	$Cu(OAc)_2$ (1)/O_2	KI	CH_3CN	58
7	$Cu(OAc)_2$ (2)/O_2	KI	CH_3CN	59
8	$Cu(OAc)_2$ (1)/O_2	I_2	CH_3CN	56
9	$Cu(OAc)_2$ (1)/O_2		CH_3CN	trace
10	$Cu(OAc)_2$ (1)/N_2	KI	CH_3CN	15
11	CuO (1)/O_2	KI	CH_3CN	
12	$CuCl_2$ (1)/O_2	KI	CH_3CN	trace
13	$CuBr_2$ (1)/O_2	KI	CH_3CN	trace
14	$Cu(OAc)_2$ (1)/O_2	KI	DCE	17
15	$Cu(OAc)_2$ (1)/O_2	KI	dioxane	23
16	$Cu(OAc)_2$ (1)/O_2	KI	DMF	trace
17	$Cu(OAc)_2$ (1)/O_2	KI	DMSO	27
18	$Cu(OAc)_2{\cdot}H_2O$ (1)/O_2	KI	CH_3CN	51

[a]Reaction conditions: **1a** (0.5 mmol), additive (0.5 mmol), solvent (5 mL), 80 °C, O_2 (1 atm, balloon), 12 h. [b]Isolated yield. [c]$PdCl_2$ (0.05 mmol).

$Cu(OAc)_2$ but in the absence of $PdCl_2$. Under these circumstances, the yield of **2a** increased from 25% to 28% compared with that using a combination of $PdCl_2$ and $Cu(OAc)_2$ (Table 1, entry 2 vs 1). When the reaction was carried out in the presence of $PdCl_2$ but in the absence of $Cu(OAc)_2$, **2a** was formed only in a trace amount (entry 3). In the absence of $PdCl_2$ and $Cu(OAc)_2$, the formation of **2a** was not observed (entry 4). These results indicate that using $Cu(OAc)_2$ alone is more beneficial than using a combination of $PdCl_2$ with $Cu(OAc)_2$ or using $PdCl_2$ alone in promoting this reaction. Further screening found that increasing the amount of $Cu(OAc)_2$ from 0.2 equiv to 0.5, 1, or 2 equiv improved the yield of **3a** significantly (entries 5−7). With 1 equiv of $Cu(OAc)_2$, KI was replaced by I_2 as the additive, but no better result was obtained (entry 8). Without an additive, however, **2a** was formed only in a trace amount (entry 9). When the reaction was carried out under nitrogen atmosphere, the yield of **2a** was low (entry 10), indicating that the presence of O_2 is essential for the efficient formation of **2a**. Following studies on the effect of different copper salts showed that CuO, $CuCl_2$, and $CuBr_2$ were less effective than $Cu(OAc)_2$ in promoting this reaction (entries 11−13 vs 6). DCE, 1,4-dioxane, DMF, and DMSO were found to be less favorable than CH_3CN as the solvent (entries 14−17 vs 6). When $Cu(OAc)_2$ was replaced by $Cu(OAc)_2{\cdot}H_2O$, **2a** was obtained in a slightly lower yield (entry 18).

With the optimized reaction conditions in hand, a range of *N*-substituted piperidines (**1**) were tried as substrates, and the results are included in Scheme 3. First, 1-phenylpiperidines with different substituents attached on the phenyl ring reacted smoothly to afford **2a−m** in moderate yields. Various functional groups, from methyl to fluoro, chloro, bromo, or nitro, were well tolerated. In another respect, this reaction was also amenable to substrate bearing a methyl group on the *ortho*-position of the piperidine ring, namely 2-methyl-1-phenylpiperidine, and afforded the corresponding products **2n** and **2n′**. It was also observed that 1-(2-methoxyphenyl)piperidine afforded **2o** in a

Scheme 3. Substrate Scope for the Synthesis of 2[a,b]

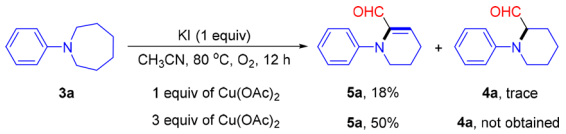


[a]Reaction conditions: **1** (0.5 mmol), $Cu(OAc)_2$ (0.5 mmol), KI (0.5 mmol), CH_3CN (5 mL), 80 °C, O_2 (1 atm, balloon), 12 h. [b]Isolated yield.

low yield of 21%. However, 1-(2-nitrophenyl)-, 1-pentyl-, or 1-benzylpiperidine remained almost intact under the conditions, and the desired products (**2p**, **2q**, and **2r**) were not obtained.[2d]

Having established a novel synthesis of pyrrolidine-2-carbaldehydes (**2**) from the reaction of *N*-arylpiperidines (**1**), we were interested in extending the substrate scope from piperidine (**1**) to azepane (**3**), from which piperidine-2-carbaldehydes were expected to be formed. To date, *α*-formylated pyridines and their hydrogenated derivatives have been widely used in the synthesis of metal complexes with relevance in medicinal and coordination chemistry. Moreover, they are also versatile intermediates in the synthesis of imidazo[1,5-*a*]pyridines, tetrahedral metal organic cages, and indolizines, etc.[12] Notwithstanding their importance, efficient preparations of piperidine-2-carbaldehydes have only been sporadically reported.[13] To develop a novel and facile synthetic protocol to hydrogenated *α*-formylpyridines, 1-phenylazepane (**3a**) was subjected to the optimized reaction conditions for the formation of **2a** (Table 1, entry 6). Surprisingly, the desired 1-phenylpiperidine-2-carbaldehyde (**4a**) was obtained only in a trace amount. Meanwhile, 1-phenyl-1,4,5,6-tetrahydropyridine-2-carbaldehyde (**5a**) was isolated in 18% yield (Scheme 4). Based

Scheme 4. Formation of 5a under Different Conditions



on this observation, we treated **3a** with reduced amounts of $Cu(OAc)_2$ or at lower reaction temperature with the aim of improving the selectivity for the formation of **4a**. However, under these conditions, the transformation of **3a** was very sluggish, and neither **4a** nor **5a** could be obtained in an efficient manner. Next, we moved our focus from **4a** to **5a** and continued our study in searching for suitable conditions for the efficient formation of **5a**. After some investigation, we were pleased to find that the yield of **5a** could be improved to 50% by treating **3a** with 3 equiv of

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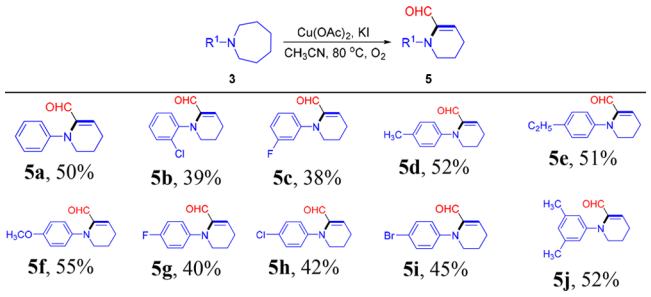
$Cu(OAc)_2$ and 1 equiv of KI under O_2 in CH_3CN at 80 °C for 12 h (Scheme 4).

Next, a range of 1-arylazepanes (**3**) were subjected to the optimized reaction conditions to explore the scope of this novel transformation. It turned out that **3** with various functional groups attached on the 1-aryl unit gave the corresponding α-formyl tetrahydropyridines (**5a–j**, Scheme 5) in moderate yields. Different substituents on the aryl group such as halides, methyl, ethyl, and methoxy were tolerated under the reaction conditions.

Scheme 5. Substrate Scope for the Synthesis of 5[a,b]



[a]Reaction conditions: **3** (0.5 mmol), $Cu(OAc)_2$ (1.5 mmol), KI (0.5 mmol), CH_3CN (5 mL), 80 °C, O_2 (1 atm), 12 h. [b]Isolated yield.

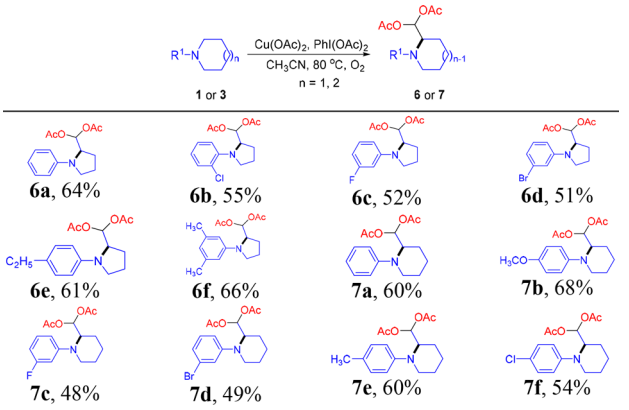
During our study on optimizing the reaction conditions for the formation of **2a** from **1a**, we observed that when $PhI(OAc)_2$[14,15] was used in place of KI as an additive, the reaction did not afford **2a**. Instead, (1-phenylpyrrolidin-2-yl)methylene diacetate (**6a**) was obtained in a yield of 64% (Scheme 6). This finding is highly

Scheme 6. Unexpected Formation of 6a

attractive as the protection of aldehydes is a frequently used strategy in organic synthesis to prevent undesired side reactions, and among various versions of aldehyde protection, 1,1-diacetates (acylals) have the advantage of being stable under a range of conditions. Moreover, 1,1-diacetates could be used as precursors in the synthesis of various functional molecules.[16] Therefore, the direct formation of **6a** from **1a** is of potential applicability in accomplishing related synthetic missions. Thus, the substrate scope of the 1,1-diacetate formation was studied. It turned out that in addition to **1a**, other 1-arylpiperidines with different substituents on the 1-aryl unit were also suitable for this reaction to give **6b–f** in moderate yields (Scheme 7). Interestingly, when **3a** was subjected to similar conditions, it gave (1-phenylpiperidin-2-yl)methylene diacetate (**7a**), the 1,1-diacetate of **4a** rather than that of **5a**. Several other *N*-substituted azepanes gave the corresponding products **7b–f** in moderate yields (Scheme 7), thus resulting in a direct and convenient approach to related aldehyde equivalents from simple starting materials.

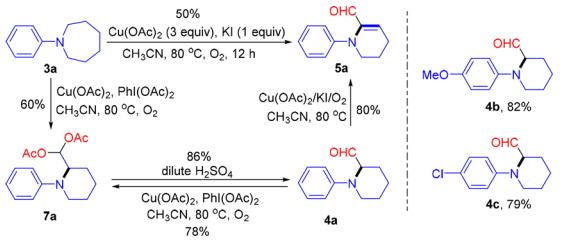
As mentioned above, aldehyde **4a** could not be obtained effectively from the reaction of **3a** as it mainly afforded **5a** under the promotion of $Cu(OAc)_2/KI/O_2$ (Scheme 4). To solve this problem, **7a** was treated with dilute sulfuric acid obtaining **4a** in 86% yield (Scheme 8). Moreover, **4b** and **4c** could also be obtained under similar conditions. In addition, when **4a** was treated with $Cu(OAc)_2/KI/O_2$ or $Cu(OAc)_2/PhI(OAc)_2/O_2$, it

Scheme 7. Substrate Scope for the Synthesis of 6 and 7[a,b]



[a]Conditions: **1** or **3** (0.5 mmol), $Cu(OAc)_2$ (0.5 mmol), $PhI(OAc)_2$ (0.5 mmol), CH_3CN (5 mL), 80 °C, O_2 (1 atm), 12 h. [b]Isolated yield.

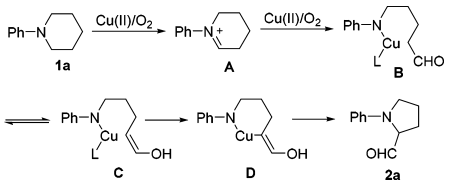
Scheme 8. Miscellaneous Transformations



gave **5a** or **7a** in yield of 80% and 78%, respectively, indicating that **4a** might be a key intermediate in the formation of **5a** and **7a** from **3a** (Scheme 8).

On the basis of the above observations and previous reports,[10,11] a plausible pathway accounting for the formation of **2a** is proposed in Scheme 9. Initially, dehydrogenation of **1a**

Scheme 9. Proposed Pathway for the Formation of 2a



under the promotion of $Cu(II)/O_2$ forms iminium ion **A**. Under the reaction conditions, **A** is further oxidized to give complex **B** with the cleavage of the C–N bond and the formation of the formyl unit. Intermediate **B** is then tautomerized into an enol intermediate **C**. Complexation of Cu(II) with the enol unit in **C** affords intermediate **D**. Finally, reductive elimination occurs in **D** to give **2a** through the C–N bond reformation. Notably, in this cascade process, copper salt should have played a dual rule as both the co-oxidant and the coupling catalyst.

Finally, it is worth noting that when 1-phenylpyrrolidine (**8**) was subjected to the optimized conditions, the formation of 1-phenylazetidine-2-carbaldehyde (**9**) was not observed. Instead, the formation of several pyrrole derivatives (including **10**, **11**, and **12**) was observed based on GC–MS and/or NMR analysis (Scheme 10).

In summary, we have developed a novel synthesis of α-formylated *N*-heterocycles and their 1,1-diacetates through the cascade reactions of inactivated cyclic amines featuring an

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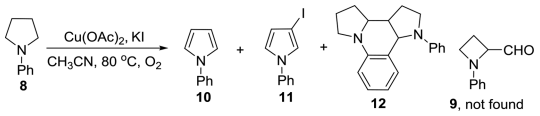
Scheme 10. Transformation of 1-Phenylpyrrolidine (8)



oxidative ring contraction. Compared with previous reports, this new protocol has advantages such as easily obtainable substrates, good functional group tolerance, mild reaction conditions, step-efficiency, and high atom-economy. Studies on the detailed mechanism are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b04029.

Experimental procedure, characterization data, and NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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