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C(sp^3)-H Dehydrogenation and C(sp^2)-H Alkoxy Carbonylation of Inactivated Cyclic Amines towards Functionalized *N*-Heterocycles

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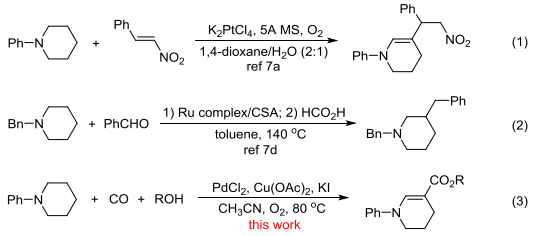
A novel and efficient synthesis of tetrahydropyridine (THP)-, dihydropyrrole (DHP)-, or tetrahydroazepine (THA)-3-carboxylates via cascade reactions of inactivated cyclic amines with CO and alcohols is presented. To our knowledge, this should be the first example in which functionalized *N*-heterocycles were prepared directly from Pd-catalyzed C(sp^3)-H dehydrogenation and C(sp^2)-H carbonylation of saturated cyclic amines. Moreover, the DHP-3-carboxylates thus obtained could readily undergo an oxidative aromatization to give pyrrole-3-carboxylates by using O_2 as a green oxidant. Notable features of the methods developed herein include simple substrates, high efficiency and excellent atom-economy, mild reaction conditions, and broad substrate scope.

Tetrahydropyridine (THP) and its derivatives are highly valuable in synthetic and medicinal chemistry since they are the essential structural motifs of numerous natural products, therapeutic agents and functional materials.[1-2] Among them, THP-3-carboxylates are well known for their diverse biological activities such as anti-bacterial, antitubercular, M_5 muscarinic receptor antagonizing, and α-glucosidase inhibiting.[3-4] Due to their importance, several elegant methods for the preparation of THP-3-carboxylates have been developed, which include the reaction of *N*-benzyl γ-chloropropyl amines with conjugated alkynoates,[4a] phosphine-promoted [3+3] annulation of aziridines with allenoates,[4b] four-component reaction of primary amines with β-dicarbonyl compounds, α,β-unsaturated aldehydes and alcohols,[4c-4d] etc.[4e-4h] While these literature methods are generally reliable, regio-selective, efficient and atom-economy synthesis of THP-3-carboxylates from simple substrates under mild conditions still remains as a challenging topic in the synthetic chemistry arena.

In recent years, transition metal-catalyzed inert C–H bond functionalization has emerged as an attractive strategy in organic synthesis as it avoids multi-step pre-activation of starting materials and minimizes production of by-products.[5] Following this trend, direct C(sp^3)–H bond functionalization of saturated cyclic amines provides a promising approach toward various heterocycles. For instance, Liang's study found that platinum could promote the dehydrogenation of piperidine to give an enamine intermediate,[6] which then reacted with nitroolefins to afford functionalized THPs (Scheme 1, 1).[7a] Kanai found that similar transformation could be realized under the promotion of Fe(III)/butyl peroxide (TBP).[7b] In addition, Bruneau reported a Ru-catalyzed cascade N- and C(3)-dialkylation of cyclic amines with alcohols involving a hydrogen autotransfer process.[7c] Following this study, the same group also developed a selective C(3)-alkylation of saturated cyclic amines *by* using aldehyde as the alkylation reagent (Scheme 1, 2).[7d] Inspired by these elegant pioneering studies,[7] we have devised and established an unprecedented synthesis of THP-3-carboxylates through a C(sp^3)-H dehydrogenation of piperidine followed by a C(sp^2)-H alkoxy carbonylation[8] of the in situ formed cyclic enamine intermediate (Scheme 1, 3). Herein, we wish to report our detailed results in this regard.



Scheme 1. Different synthetic approaches toward THP derivatives

Our study was initiated by treating 1-benzylpiperidine (**1a**) with CO (1 atm) and ethanol (**2a**) in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ in CH_3CN at 80 °C under air for 12 h, from which ethyl 1-benzyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**3a**) was obtained in 48% yield (Table 1, entry 1). Next, different Pd catalysts were tried, and $PdCl_2$ was found to be more effective than $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, and $Pd(OAc)_2$ (entries 1-4). In the absence of Pd catalyst, the formation of **3a** was not observed (entry 5). Following studies on the effect of different oxidants such as $CuCl_2$, $CuBr_2$, CuO, and O_2 showed that they were much less effective than $Cu(OAc)_2$ (entries

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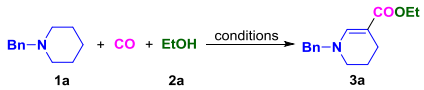
Table 1. Optimization studies on the formation of **3a**[a]



Entry	Catalyst	Oxidant (equiv)	Additive	Solvent	T (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$ (1)	-	CH_3CN	80	48
2	$PdCl_2$	$Cu(OAc)_2$ (1)	-	CH_3CN	80	55
3	$PdCl_2(PPh_3)_2$	$Cu(OAc)_2$ (1)	-	CH_3CN	80	trace
4	$Pd_2(dba)_3$	$Cu(OAc)_2$ (1)	-	CH_3CN	80	35
5	-	$Cu(OAc)_2$ (1)	-	CH_3CN	80	-
6	$PdCl_2$	$CuCl_2$ (1)	-	CH_3CN	80	trace
7	$PdCl_2$	$CuBr_2$ (1)	-	CH_3CN	80	trace
8	$PdCl_2$	CuO (1)	-	CH_3CN	80	trace
9	$PdCl_2$	O_2	-	CH_3CN	80	trace
10	$PdCl_2$	$Cu(OAc)_2$ (1)	KI	CH_3CN	80	76
11	$PdCl_2$	$Cu(OAc)_2$ (1)	KBr	CH_3CN	80	62
12	$PdCl_2$	$Cu(OAc)_2$ (1)	KCl	CH_3CN	80	53
13	$PdCl_2$	$Cu(OAc)_2$ (1)	I_2	CH_3CN	80	70
14	**$PdCl_2$**	**$Cu(OAc)_2$(0.2)/O_2**	**KI**	**CH_3CN**	**80**	**75**
15	$PdCl_2$	$Cu(OAc)_2$ (0.2)/O_2	KI	toluene	80	40
16	$PdCl_2$	$Cu(OAc)_2$ (0.2)/O_2	KI	DCE	80	58
17	$PdCl_2$	$Cu(OAc)_2$ (0.2)/O_2	KI	dioxane	80	65
18	$PdCl_2$	$Cu(OAc)_2$ (0.2)/O_2	KI	CH_3CN	60	62
19	$PdCl_2$	$Cu(OAc)_2$ (0.2)/O_2	KI	CH_3CN	100	70

[a] Reaction conditions: **1a** (0.3 mmol), CO (balloon), **2a** (3 mmol), catalyst (0.03 mmol), additive (0.3 mmol), solvent (3 mL), air, 12 h. [b] Isolated yield.

Table 2. Substrate scope for the synthesis of **3**[a,b]

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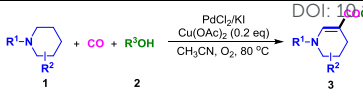
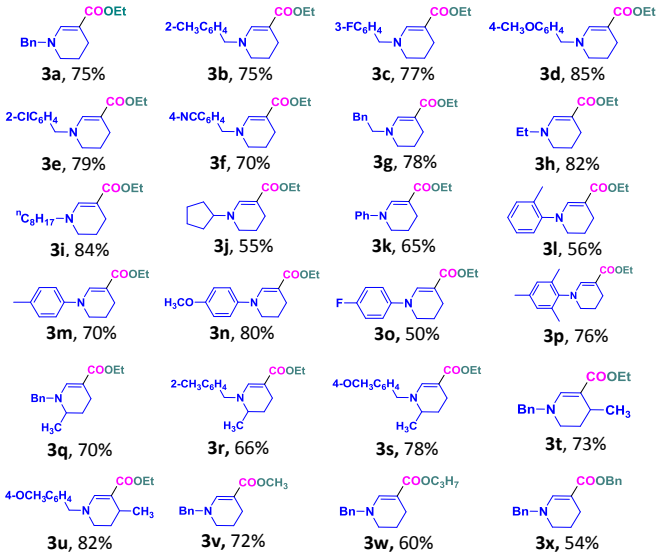




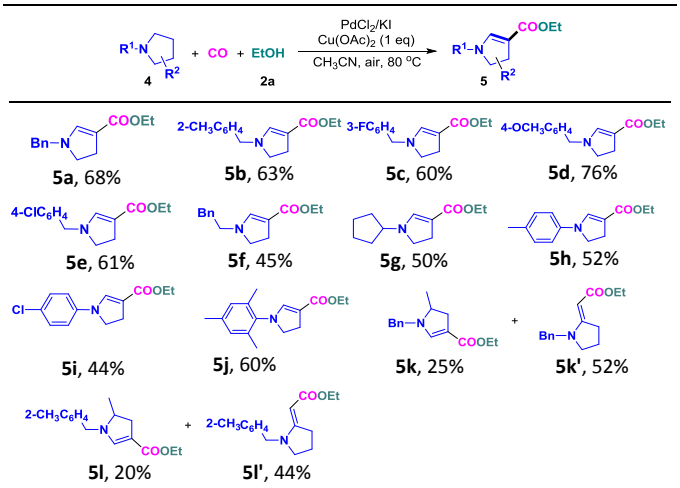
[a] Reaction conditions: **1** (0.5 mmol), CO/O_2 (5:1, balloon), **2** (5 mmol), $PdCl_2$ (0.05 mmol), $Cu(OAc)_2$ (0.1 mmol), KI (0.5 mmol), CH_3CN (5 mL), 80 °C, O_2 (1 atm), 12 h. [b] Isolated yield.

6-9 *vs* 2). Gratifyingly, the yield of **3a** improved to 76% by using KI as an additive (entry 10).[9] Next, we were delighted to find that a combination of 0.2 equiv of $Cu(OAc)_2$ with O_2 (1 atm) as the oxidant afforded **3a** in a yield of 75% (entry 14). Next, various solvents including toluene, DCE, and 1,4-dioxane were tried, and they were found less favorable than CH_3CN (entries 15-17 *vs* 14). Finally, temperatures lower or higher than 80 °C resulted in decreased efficiency (entries 18-19).

With the optimized reaction conditions in hands (Table 1, entry 14), a range of piperidines (**1**) were tried to probe the generality of this synthetic method. First, 1-benzylpiperidines with different substituents attached on the phenyl ring of the benzyl unit underwent this cascade reaction smoothly to afford **3a**-**3f** in good yields (Table 2). Various functional groups, from the electron-donating methoxy to the electron-withdrawing fluoro, chloro or cyano were well tolerated. Second, **1** with 2-phenylethyl, ethyl, octyl, or cyclopentyl unit also took part in this reaction smoothly affording **3g**-**3j** in moderate to good yields. Moreover, a range of 1-aryl substituted piperidines worked well to give **3k-3p** in 50-80% yields. The electronic nature of the 1-aryl unit affected the yield of **3** in that substrates with electron-donating groups on the aryl ring were more favourable than those with an electron-withdrawing group (**3n**, **3p** *vs* **3o**). In addition to the good tolerance of different N-substituents, this reaction was also amenable to substrates bearing a methyl group on the *o*- or *p*-position of the piperidine ring, and afforded **3q**-**3u** in 66-82% yields. Interestingly, the functionalization of *o*-methylpiperidines took place regioselectively on the less steric hindered side (**3q**-**3s**), and the formation of other regioisomers was not observed.[7e] Finally, a number of alcohols (**2**) were tested, and they gave **3v**-**3x** in moderate yields.

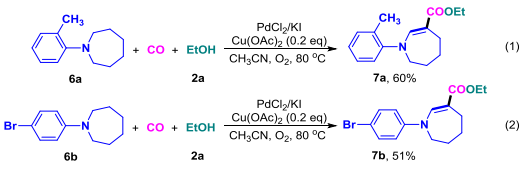
After establishing a new synthesis of THP-3-carboxylates from the reaction of piperidines, we were then curious about whether this new protocol could be extended from piperidines to pyrrolidines. If successful, it would provide a novel synthetic approach toward functionalized dihydropyrroles (DHPs), which are frequently found in natural products and pharmaceutical-related compounds.[10-11] While a number of elegant methods for the synthesis of DHPs have been established,[12,13] the synthesis of DHP-3-carboxylates directly from pyrrolidine has not been realized before. Thus, we continued our study by treating 1-benzylpyrrolidine (**4a**) with CO and **2a** under the optimized reaction conditions for the preparation of **3a** (Table 1, entry 14), and the desired ethyl 1-benzyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate (**5a**) was obtained in 38% yield. Meanwhile, 1-benzyl pyrrole was obtained along with **5a** in a yield of 42%. This result indicated that in addition to taking part into the desired alkoxy carbonylation, the in situ formed DHP intermediate also underwent an oxidative aromatization to give the pyrrole product under the reaction conditions. To suppress the formation of 1-benzylpyrrole, different reaction conditions were then screened. After some trials and errors, we found that the yield of **5a** could be improved to 68% by increasing the amount of $Cu(OAc)_2$ from 0.2 to 1 equiv and using air instead of O_2 as the co-oxidant. Next, a series of pyrrolidines (**4**) were tried to study the substrate generality, and all of them took part in this reaction to afford the corresponding DHP-3-carboxylates (**5**) in moderate to good yields (Table 3). Notably, the N-substituent in **4** could be either an alkyl or aryl unit bearing different functional groups. When it was extended to 1-benzyl-2-methylpyrrolidine (**4k**), DHP-3-carboxylate **5k** was obtained along with ethyl (*E*)-2-(1-benzylpyrrolidin-2-ylidene)acetate (**5k'**), an exo-cyclic enamino ester,[14] in 25% and 52% yield, respectively. When 2-methyl-1-(2-methylbenzyl)pyrrolidine (**4l**) was used, **5l** and **5l'** were obtained in yields of 20% and 44%, respectively.

Table 3. Substrate scope for the synthesis of **5**[a,b]



[a] Reaction conditions: **4** (0.5 mmol), CO (balloon), **2a** (5 mmol), $PdCl_2$ (0.05 mmol), $Cu(OAc)_2$ (0.5 mmol), KI (0.5 mmol), CH_3CN (5 mL), 80 °C, air, 12 h. [b] Isolated yield.

Moreover, the established protocol for the dehydrogenation and carbonylation of saturated cyclic amines could also be extended to azepanes (**6**). Thus, 1-(*o*-tolyl)azepane (**6a**) was treated with CO and **2a** under the optimized conditions for the synthesis of **3a** (Table 1, entry 14), and the desired THA-3-carboxylate **7a** was obtained in 60% yield (Scheme 2, 1). Similarly, **7b** was successfully synthesized in 51% yield from 1-(4-bromophenyl)azepane (**6b**) (Scheme 2, 2).

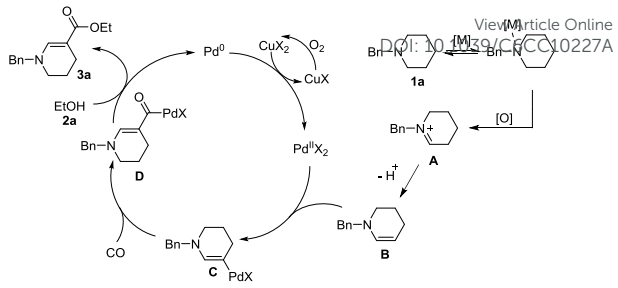


Scheme 2. Synthesis of **7a** and **7b**

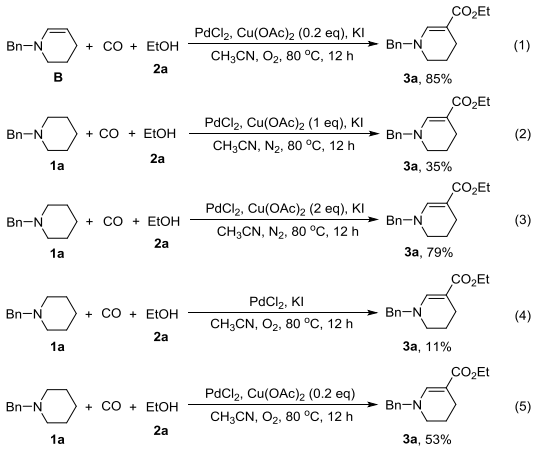
Based on the above results and previous reports[7,8], a pathway to account for the formation of **3a** is proposed in Scheme 3. Initially, **1a** is dehydrogenated under the promotion of Pd/Cu to give an iminium intermediate **A**. Subsequent β-hydrogen elimination occurs with **A** to produce an enamine intermediate **B**. Next, palladation of **B** affords intermediate **C**, which then undergoes an alkoxy carbonylation with CO and **2a** to produce **3a** and generate the Pd^0 species. The Pd^{II} species could be regenerated by Cu^{II} in the presence of O_2.

As the proposed enamine intermediate **B** could not be isolated from the reaction of **1a** with CO and **2a**, it was prepared from 1-benzylpiperidin-2-one based on a literature procedure (see SI). Then, it was subjected to the standard reaction conditions. From this reaction, **3a** was obtained in a yield of 85% (Scheme 4, 1).

In other two control experiments, the reaction of **1a** with CO and **2a** was carried out in the presence of 1 or 2 equiv of $Cu(OAc)_2$ under N_2, and **3a** was obtained in yields of 35% and 79%, respectively (Scheme 4, 2 and 3). These results together with those included in Table 1 indicate that the efficient formation of **3a** needs at least 2 equiv of $Cu(OAc)_2$ in the absence of O_2 or air as the co-oxidant. To

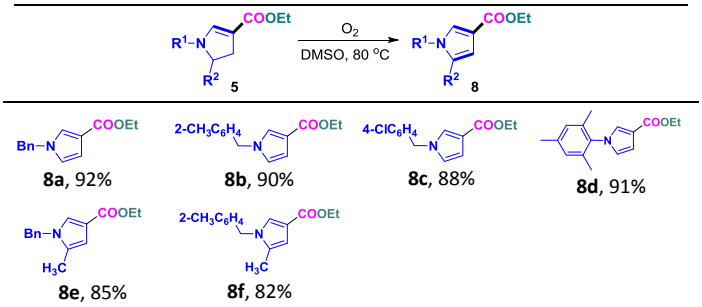


Scheme 3. Plausible pathway leading to the formation of **3a**



Scheme 4. Control Experiments

Table 4. Substrate scope for the synthesis of **8**[a,b]



[a] Reaction conditions: **5** (0.2 mmol), under O_2 (ballon), DMSO (2 mL), 80 °C, 12 h, sealed tube. [b] Isolated yield.

further verify the effect of $Cu(OAc)_2$ and KI, more control experiments were carried out. First, the reaction of **1a** with **2a** and CO was carried out under standard reaction conditions but in the absence of $Cu(OAc)_2$. Under this circumstance, the yield of **3a** decreased to 11% (Scheme 4, 4). This result told that $Cu(OAc)_2$ is indispensible as an catalyst for the efficient formation of **3a** when oxygen is used as the oxidant. Second, the reaction of **1a** with **2a** and CO was run in the absence of KI (Scheme 4, 5), and the yield of **3a** decreased to 53%, indicating that the presence of KI is beneficial to the formation of **3a**. Based on a literature report, KI might be able to improve the activity of the catalyst.[9]

Finally, to showcase the synthetic value of the DHP-3-carboxylates (**5**) obtained above and develop an alternative approach toward the synthetically and pharmaceutically significant pyrrole-3-carboxylates,[15-17] several DHP-3-carboxylates (**5**) were treated with

O_2 in DMSO. From these reactions, a series of pyrrole-3-carboxylates **8a-8f** were obtained in high efficiency (Table 4).

In summary, we have developed a novel and efficient synthesis of THP-, DHP- or THA-3-carboxylates *via* the one-pot cascade reactions of piperidines, pyrrolidines or azepanes with CO and alcohols. Mechanistically, the formation of the target products involves firstly a dehydrogenation of saturated cyclic amines followed by an alkoxy carbonylation of the *in situ* formed cyclic enamine intermediates. In addition, the DHP-3-carboxylates thus obtained could readily undergo an oxidative aromatization to give the corresponding pyrrole-3-carboxylates by using O_2 as a green oxidant. Compared with literature methods, the synthetic protocols developed herein have advantages such as readily available starting materials, practical reaction conditions, and multiple bond formation to give advanced structures in one pot with high atom-economy.

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