

# Communication

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# Construction of Tetracyclic 3-Spirooxindole through Cross Dehydrogenation of Pyridinium: Applications in Facile Synthesis of (±)-Corynoxine and (±)-Corynoxine B

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Supporting Information Placeholder

**ABSTRACT:** A facile and straightforward method was developed to construct the fused tetracyclic 3-spirooxindole skeleton, which exists widely in natural products. The formation of the tetracyclic 3-spirooxindole structure was achieved through a transition-metal-free intramolecular cross dehydrogenative coupling of pyridinium, which were formed *in situ* by the condensation of 3-(2-bromoethyl)indolin-2-one derivatives with 3-substituted pyridines. As examples of the application of this new methodology, two potentially medicinal natural products, ( $\pm$ )-corynoxine and ( $\pm$ )-corynoxine B, were efficiently synthesized in 5 scalable steps.

The tetracyclic 3-spirooxindole system is a recurring structural motif in a number of natural products, such as corynoxine,<sup>[1]</sup> corynoxine B,<sup>[1]</sup> voachalotine oxindole,<sup>[2]</sup> rhynchophylline,<sup>[1b, 3]</sup> strychnophylline,<sup>[4]</sup> strychnofoline,<sup>[4a]</sup> and formosanine<sup>[5]</sup> (Figure 1). Most of these spirooxindole alkaloids were isolated from the *Apocynaceae* and *Rubiacae* species, which play important roles in traditional Chinese medicine. Among these natural products, corynoxine and corynoxine B exhibit prominent potency in preventing or treating Parkinson's disease. The accumulation of  $\alpha$ -synuclein ( $\alpha$ -syn) in the brain is a pathogenic feature and also a causative factor in Parkinson's disease.<sup>[6]</sup> Corynoxine and corynoxine B promote the clearance of  $\alpha$ -syn, which is the major component of Lewy bodies in Parkinson's disease patients.<sup>[6-7]</sup> Strychnofoline, isolated from the leaves of *Strychnos usambarensis*,<sup>[4a]</sup> displays highly antimitotic activity in cultures of mouse melanoma and Ehrlich tumor cells.<sup>[4b]</sup>

The appealing architecture and significant biological activities of tetracyclic 3-spirooxindole alkaloids have received considerable attention from the community of synthetic organic chemists. However, limited methods have been developed to assemble the tetracyclic 3-spirooxindole moiety of these alkaloids. Biosynthetically, the tetracyclic 3-spirooxindole moiety is postulated to be formed by an oxidative rearrangement of the tetrahydro- $\beta$ -carbolines ajmalicine and its derivatives (Scheme 1).<sup>[8]</sup> The oxidative rearrangement sequences of tetrahydro- $\beta$ carboline were also employed for the synthesis of the corynanthe alkaloid dihydrocorynantheol by Martin et al.<sup>[9]</sup>. The intramolecular Mannich reaction is the most widely adopted

method for the total synthesis of tetracyclic 3-spirooxindole alkaloids, including the first total synthesis of rhynchophylline,<sup>[10]</sup> the enantioselective organocatalyzed synthesis of secoyohimbanes,<sup>[11]</sup> the diastereoselective intramolecular iminium ion spirocyclization/lactamization cascade sequence of 2halotryptamine,<sup>[12]</sup> and the unified approach to corvnoxine. corynoxine B, corynoxeine, and rhynchophylline.<sup>[13]</sup> Carreira et al. have completed a collective total synthesis of 3-spirooxindole alkaloids using a MgI2-mediated ring-expansion reaction of spiro[cyclopropane-1,3'-oxindole] with a cyclic disubstituted aldimine, in addition, a Mannich-like reaction has also been utilized.<sup>[12b, 14]</sup> Others methods for the construction of the tetracyclic 3-spirooxindole ring system have been reported, including Amat's protocol for the dissymmetric condensation of prochiral aldehyde-diesters <sup>[15]</sup> and Grieco's aza Diels-Alder reaction.<sup>[16]</sup> However, these strategies resulted in tri- or tetracyclic 3-spirooxindole intermediates that required multistep conversions to form the final natural tetracyclic 3-spirooxindole alkaloids skeleton. Therefore, a more efficient and straightforward method is still required in the development of a synthetic methodology for tetracyclic 3-spirooxindole alkaloids.



Figure 1. Naturally occurring tetracyclic 3-spirooxindole alkaloids.

Direct C-H bond transformation is an efficient method and enables wide applications in organic synthesis. Transition-metalcatalyzed coupling reactions have made significant progress since 1960s, although along with some drawbacks (such as expensive transition metals and ligands,



Scheme 1. Approaches to tetracyclic 3-spirooxindole synthesis.

sensitive to oxygen and moisture, and unpredictable additives and cocatalysts). Thus, the development of transition-metal-free coupling reactions to realize C-H functionalization is appealing, and is considered as a significant step towards advanced greener synthetic protocols in organic synthesis.<sup>[17]</sup> Due to the importance of pyridine motifs in biologically active compounds, pharmaceuticals, and functional materials, direct crossdehydrogenative alkylations of pyridines have received great attentions from chemistry community. Besides the well developed transition-metal-catalyzed pyridyl C-H bond functionalization, [18] the transition-metal-free direct alkylation of pyridines has also been acheived, albeit with limited reports.<sup>[19]</sup> Herein, we report a novel, scalable approach to the construction of the 3spirooxindole ring system through a transition-metal-free intramolecular cross dehydrogenation of pyridinium. The efficiency of this direct alkylation of pyridines made the concise total synthesis of  $(\pm)$ -corynoxine and  $(\pm)$ -corynoxine B.



Scheme 2. Preparation of the pyridinium salts.

The pyridinium salt 2a was obtained by the treatment of 3-(2-bromoethyl)indolin-2-one 1 with pyridine (Scheme 2). Subsequently, the transition-metal-free cross dehydrogenative coupling was performed under various condition under aerobic atmosphere. However, no product was detected while screening numerous solvents (THF, MeCN, DCM, MeOH and DMF) or varying the base (TEA, DIPEA, Na<sub>2</sub>CO<sub>3</sub>, DBU, and NaH). We postulated that it was due to the low reactivity of the unsubstituted pyridinium salt. To enhance the reactivity of pyridinium, an electron-withdrawing group at the 3-position of the pyridine ring is necessary.<sup>[20]</sup> Methyl nicotinate was used to condense with 3-(2-bromoethyl)indolin-2-one 1 to give the corresponding pyridinium salt 2b. As expected, the coupling reaction proceeded smoothly and the dehydrogenative coupling product 3 was obtained in the presence of TEA in 34% yield (Table 1, entry 1). A dramatical improvement was acheived when the base was switched from TEA to Na<sub>2</sub>CO<sub>3</sub> (0.5 equiv.) and gave the coupling product 3 in 85% yield (Table 1, entry 2). The ideal reaction temperature was 50 °C. We found that the reaction proceeded slowly at room temperature. When the reaction temperature was raised to 70 °C, a large amount of the byproduct spiro[cyclopropan-3,3'-oxindole] was formed. The amounts of Na<sub>2</sub>CO<sub>3</sub> were also examined. Although 0.1 equivalent of Na<sub>2</sub>CO<sub>3</sub>

could effeciently catalyzed the coupling reaction, the reaction proceeded slower and a competitive oxidation of the C3 of oxindole occured.

Table 1. Optimization of synthesis of tetracyclic 3-spirooxindole.

Source Co2Me Conditions Co2 (balloon)					
	<sup>1</sup> 2b	H 3			
Entry	Solvent	Base	Yield (%) <sup>[a]</sup>		
1	MeCN	TEA	34		
2	MeCN	Na <sub>2</sub> CO <sub>3</sub>	85		
3	MeCN	$K_2CO_3$	76		
4	MeCN	NaHCO <sub>3</sub>	70		
5	MeCN	NaH <sub>2</sub> PO <sub>4</sub>	68		
6	Toluene	Na <sub>2</sub> CO <sub>3</sub>	NR		
7	THF	Na <sub>2</sub> CO <sub>3</sub>	NR		
8	DCM	Na <sub>2</sub> CO <sub>3</sub>	trace		
9	DCE	Na <sub>2</sub> CO <sub>3</sub>	NR		
10	Acetone	Na <sub>2</sub> CO <sub>3</sub>	trace		
11	CHCl <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	60		
12	МеОН	Na <sub>2</sub> CO <sub>3</sub>	74		
13	DMF	Na <sub>2</sub> CO <sub>3</sub>	69		
14	DMSO	Na <sub>2</sub> CO <sub>3</sub>	67		

<sup>a</sup>Isolated yields by silica gel column.

A series of bases were subjected to the reaction, the results of which suggested that  $Na_2CO_3$  was the most efficient base to promote the reaction (Table 1, entries 1 - 5). Different solvents were also screened under the reaction conditions. Most of the polar solvents (MeOH, DMF, and DMSO, Table 1, entries 10 - 12) were superior to the non-polar solvents (toluene, THF, DCM, and DCE, Table 1, entries 6 - 9). These results could be ascribed to the excellent solubilities of both of the starting material **2b** and product **3** in the polar solvents.

Moreover, different oxidants were also chosen to test their efficiency. Although CAN, TBP, and TBHP (Table 2, entries 2, 6, 7) also promoted the cross dehydrogenative coupling reaction, the efficiency of these oxidants was lower in both yield and reaction time. However, none of the coupling product was detected when DDQ or  $Na_2S_2O_8$  was used as the oxidant, while less than 5% yield for  $K_2S_2O_8$ . Because molecular oxygen was the most effective and greenest oxidant for the cross dehydrogenative reaction, it was used in the subsequent coupling.

Table 2. Cross dehydrogenative coupling with different oxidants.



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5	$K_2S_2O_8$	< 5
6	TBP	46
7	TBHP	58
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<sup>a</sup>Isolated yields by silica gel column.

Using these optimized conditions, different substrates were used to test the scope of this methodology (Table 3). The pyridinium with a ketone on the C3 position also gave high yields in the coupling reaction (compounds 5, 7, 9, and 12). When the N1 of the oxindole was substituted with a methyl, allyl, or benzyl group, the cross dehydrogenative coupling reaction proceeded more efficiently with somewhat higher product yields. It was observed that when the N1 position was substituted with an acetyl group, the corresponding pyridinium 2 could not be prepared and only afforded the spiro[cyclopropan-3,3'-oxindole] byproduct. We reasoned that the acetyl group at N1 activated the C3 position, which was easily deprotonated and subsequently underwent an intramolecular  $SN_2$  reaction to form the 3-cyclopropane byproduct.

Table 3. Synthesis of tetracyclic 3-spirooxindole pyridinium salts.



To highlight the utility of the direct cross dehydrogenative coupling, two natural products,  $(\pm)$ -corynoxine and  $(\pm)$ corynoxine B, were facilely synthesized from the coupling product 5. Gram-scale coupling product 5 was treated with NaBH<sub>4</sub> in a mixture of dioxane and water (20:1) (Scheme 3). Both the pyridinium and the ketone were reduced to afford the alcohol 13. The configuration of the D ring was confirmed by 2D NMR of the ketone compound 14, which was afforded by oxidation of the alcohol 13 with DMP. Although no selectivity was observed at the newly formed hydroxyl group, it did not affect the efficiency of the total synthesis because both of the isomers afforded the same final product. The alcohol 13 was then subjected to Johnson-Claisen rearrangement<sup>[21]</sup> by heating in trimethyl orthoacetate with a catalytic amount of propanoic acid to provide the ester 15. Treatment of the ester 15 with LDA, followed by the addition of excess methyl formate, resulted in the desired enol ester intermediate in 36% yield (82% brsm.).<sup>[10, 22]</sup> The crude enol ester intermediate was then directly methylated with trimethylsilyl diazomethane to afford 16 in 62% yield.<sup>[10, 23]</sup> Finally, the catalytic hydrogenation of 16 by PtO<sub>2</sub> under a hydrogen atmosphere gave the target compound, (±)-corynoxine, in an excellent yield of 86%.<sup>[21a, 24]</sup>

Dissolution of  $(\pm)$ -corynoxine in 2,2,2-trifluoroenthanol led to formation of the epimeric  $(\pm)$ -corynoxine B (Scheme 3). We monitored this transformation in situ by TLC, which revealed an equilibrium was established between  $(\pm)$ -corynoxine and  $(\pm)$ corynoxine B within 6 h in favor of  $(\pm)$ -corynoxine B. Chromatographic separation of the mixture afforded a 90% yield of  $(\pm)$ -corynoxine B along with recovered  $(\pm)$ -corynoxine (31%). We obtained clear evidence for this equilibrium ratio when  $(\pm)$ corynoxine B was subject to identical conditions and the same ratio was reached between  $(\pm)$ -corynoxine and  $(\pm)$ -corynoxine B within 6 h. The spectroscopic data of the synthetic  $(\pm)$ -corynoxine and  $(\pm)$ -corynoxine B were in agreement with the values published for the natural products.



Scheme 3. Total synthesis of ( $\pm$ )-corynoxine and ( $\pm$ )-corynoxine B. a) NaBH<sub>4</sub>, dioxane/water, 78%; b) trimethyl orthoacetate, propanoic acid, dioxane, sealed, 120 °C, 68%; c) LDA, HCO<sub>2</sub>Me, THF, -78 °C to 0 °C; d) TMSCH<sub>2</sub>N<sub>2</sub>, Et<sub>2</sub>O/MeOH (1:1), 82% brsm; e) PtO<sub>2</sub>, H<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 86%; f) 2,2,2-trifluoroethanol, RT, 90% brsm.

In summary, we have described a cross dehydrogenative coupling reaction which provides direct access to tetracyclic 3-spirooxindole system that found in many natural products with intriguing biological activities. This novel method will be applicable to the synthesis of a number of bioactive tetracyclic 3-spirooxindole contained alkaloids. Efficiently total synthesis of  $(\pm)$ corynoxine and  $(\pm)$ corynoxine B have been achieved within 5 steps.

#### ASSOCIATED CONTENT

#### Supporting Information

Experimental procedures and compound characterization. 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 interests.

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