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Exploration of a KI-catalyzed oxidation system for direct construction of bispyrrolidino[2,3-*b*]indolines and the total synthesis of (+)-WIN 64821†

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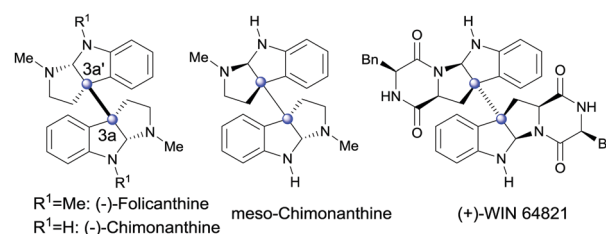
A facile and environmentally benign KI(cat.)/NaBO₃·4H₂O oxidation system has been developed for the tandem oxidative aminocyclization/coupling of tryptamines, affording a series of 3*a*,3*a*'-bispyrrolidino-[2,3-*b*]indolines with high efficiency (up to 94% yield). This reaction features an electrophilic "I⁺" mechanism, which is importantly quite different from and milder than the typical radical-involving process, and can be readily amplified for the total synthesis of (+)-WIN 64821.

Oxidation is one of the most important transformations for organisms to produce functional molecules. *In vivo*, the oxidation of tryptophan or tryptamine can result in a big family of structurally complex and biologically important 3*a*,3*a*'-bispyrrolidino-[2,3-*b*]indoline alkaloids (Fig. 1), which show antifungal, antiviral and cytostatic activities.¹ Despite its significance for biological and medicinal chemistry, realizing this biotransformation by means of organic chemistry, especially with a catalytic amount of assistant oxidation reagent, is still rare and synthetically challenging.² To date, several groups have devoted much pioneering effort to this aspect.^{3,4} However, most of the current solutions require either equivalent amounts of transition metals or excess of strong acid or base. Furthermore, these methodologies generally give insufficient yields. Therefore, the development of a catalytic and transition-metal-free oxidative system for the efficient synthesis of 3*a*,3*a*'-bispyrrolidino[2,3-*b*]indolines under mild condition is in demand.

During the past fifteen years, the iodide-catalyzed oxidative reaction has received widespread attention because of its versatile reactivity and environmentally benign property.^{5,6} In general, however, these systems are mostly limited to the application of

synthesis of relatively simple organic compounds, and only a few can give access to sterically complex frameworks, such as those with the vicinal all-carbon quaternary centers.⁷ As indicated in Scheme 1, the oxidation systems mediated by a catalytic amount of iodide have not been expanded to effect the tandem coupling/cyclizations of tryptamine or tryptophan to construct the more complex 3*a*,3*a*'-bispyrrolidino[2,3-*b*]indoline **6**, **8** and **11** with vicinal all-carbon quaternary centers. Instead, they are only applicable to mediate the simple cyclization to produce the monomer products **1–4** (Scheme 1(a)).⁸ Due to our continuing interest in the synthesis of 3*a*,3*a*'-bispyrrolidino[2,3-*b*]indoline alkaloids,⁹ we thus try to develop an alternative effective iodide-catalyzed oxidative system, which we expect will enable the coupling/cyclizations as shown in Scheme 1(b). Herein, we describe our research results.

To achieve the hypothesis above, our initial optimization started toward the oxidation of tryptamine **5a** with screening the oxidants and solvents using KI as a catalyst (Table 1). Fortunately, after testing H₂O₂ in several solvents, only TFE (trifluoroethanol) could generate the desired dimeric products (**6a** and **6a'**) with a moderate 44% yield (entry 5), while the other solvents gave inferior results (entries 1–4). Subsequently, both organic (entries 6 and 7) and inorganic oxidants were screened (entries 8 and 9), among which, NaBO₃·4H₂O gave the best yield (64%, entry 9). In addition, other conditions which involved varying the iodide catalysts, additives, concentrations and component equivalents were widely investigated,¹⁰ with the conditions in entry 10 giving the best result (68% yield).

Fig. 1 Representative bispyrrolidino[2,3-*b*]indoline alkaloids.

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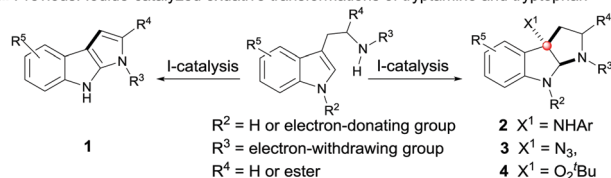
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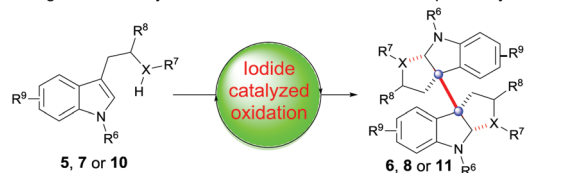
† Electronic supplementary information (ESI) available. CCDC 1940250. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc08646c

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a. Previous: Iodide-catalyzed oxidative transformations of tryptamine and tryptophan



b. Our design: Iodide-catalyzed construction of vicinal all-carbon quaternary architecture



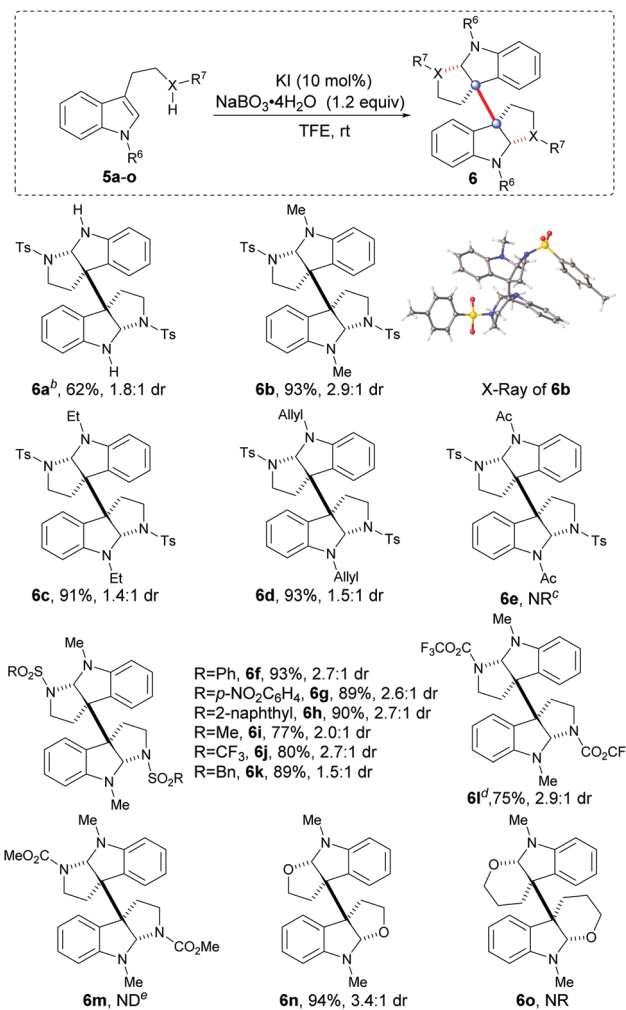
Scheme 1 (a) Previous I-catalyzed oxidation of tryptamine or tryptophan; (b) our design.

Table 1 Optimization of the conditions for the iodide-catalyzed oxidative dimerization of tryptamine^a

Entry	Solvent	Oxidant	Time	Yield ^b (%)
1	CH ₃ CN	H ₂ O ₂ ^c	24 h	NR ^d
2	Toluene	H ₂ O ₂	24 h	NR
3	THF	H ₂ O ₂	24 h	NR
4	CH ₂ Cl ₂	H ₂ O ₂	24 h	NR
5	TFE	H ₂ O ₂	4 h	44
6	TFE	^t BuO ₂ H ^e	10 h	53
7	TFE	<i>m</i> -CPBA	10 min	ND ^f
8	TFE	O ₂ ^g	24 h	NR
9	TFE	NaBO ₃ ·4H ₂ O	1.5 h	64
10 ^h	TFE	NaBO ₃ ·4H ₂ O	2 h	68

^a Unless otherwise noted, reactions were carried out with **5a** (0.2 mmol), KI (20 mol%) and oxidant (2.0 equiv.) in 2 mL solvent. The dr was 1.8:1 determined by ¹H NMR. ^b Determined by ¹H NMR. ^c 50 wt% in water. ^d No reaction was observed. ^e 5.5 M in decane. ^f Not detected. ^g 1 atm. ^h Reaction was carried out with **5a** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE.

With the optimal catalytic oxidative system in hand, we then expanded the tryptamine substrate scope by varying the substituents R⁶ and X-R⁷ (Table 2, **5a–m**). Initially, when X-R⁷ was selected as *N*-tosyl, varying the substituents R⁶ (**5b–d**) with the EDGs (electron-donating groups, e.g., methyl, ethyl and allyl) generally led to excellent reaction results (**6b–d**, 91–93% yields, 1.4:1 to 2.9:1 dr), while the EWG (electron-withdrawing group, e.g., Ac) substituted substrate (**5e**) remained inactive to give product **6e**. Subsequently, when the optimal methyl was selected as R⁶ (as indicated in **6f–l**), varying substitution of R⁷ (X = N) with the strong EWG sulfonyl (**5f–k**) and trifluoroacetyl (**5l**) could drive the reactions with satisfactory results (**6f–l**, 75–93% yields, 1.5:1 to 2.9:1 dr). Exceptionally, when a carbamate was introduced to tryptamine (**5m**, X-R⁷ = *N*-CO₂Me), the reaction could not give the desired product **6m**, but gave a complex mixture

Table 2 Investigation of R⁶ and X-R⁷ of tryptamines for oxidative dimerization^a

^a Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ¹H NMR. ^b Reacted for 2 h. ^c No reaction was observed after 24 h. ^d Reacted for 3 h. ^e Not detected.

accompanied by a partial starting material. It was also important that when tryptophol **5n** and 3-indolepropanol **5o** were separately subjected to the catalytic oxidative systems, interestingly, the former could react efficiently to give the tetrahydrofuran **6n** with an excellent yield of 94%, while the latter gave a mixture without hexahydropyran **6o** detected.

Next, a wide range of tryptamines with different substituents on the benzene rings were tested. As shown in Table 3, both EWG and EDG substituents at C₇, C₆ and C₅ of the benzene rings were effective for the expected oxidative dimerization reactions and generally gave satisfactory results (**8a–i**, 68–94% yield, 1.5:1 to 3.9:1 dr). The differences of these examples in the reaction time revealed that the EDG substituents were more favorable for reaction rates than the EWGs (**8f**, **8i** vs. **8a**, **8c**, **8j**, and **8k**). Notably, the C₄-F and C₄-Cl substituted tryptamines **7j** and **7k** could give **8j** and **8k** with excellent diastereoselectivities (11.7:1 and >20:1 dr)

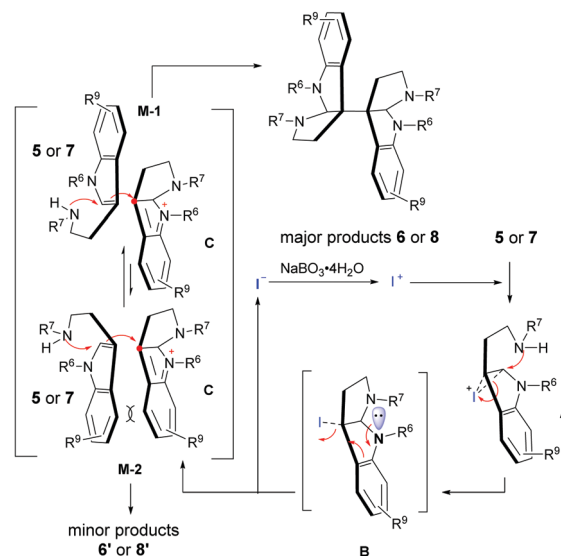
Table 3 Investigation of benzene ring substituted tryptamines for oxidative dimerization^a

8a , 68%, 2.1:1 dr, 3 h	8b , 94%, 3.2:1 dr, 1 h	8c , 83%, 2.8:1 dr, 2.5 h
8d , 70%, 2.8:1 dr, 1.5 h	8e , 90%, 3.9:1 dr, 1.5 h	8f , 79%, 2.8:1 dr, 1 h
8g , 79%, 2.9:1, 2 h	8h , 93%, 1.5:1 dr, 1 h	8i , 73%, 2.3:1 dr, 1 h
8j , 72%, 11.7:1 dr, 3 h	8k , 46%, >20:1 dr, 2 h	

^a Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and NaBO₃·4H₂O (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ¹H NMR.

and acceptable yields (72% and 46%), probably due to the steric interaction between F or Cl and C_{3a} or C_{3a'}.

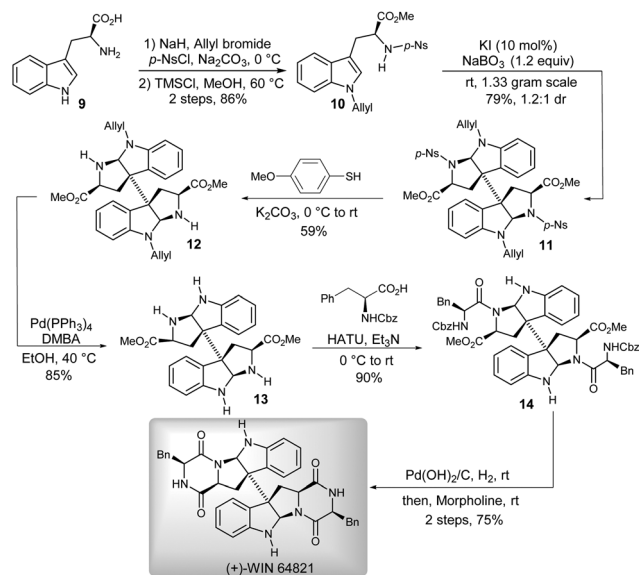
In order to elucidate the mechanism of this catalytic oxidative coupling/cyclization reaction, we also conducted some additional control experiments (Scheme S1, ESI[†]).¹⁰ According to the experimental results, addition of the radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidinoxy) or DMPO (5,5-dimethyl-1-pyrroline *N*-oxide) was found to have little influence on the reaction, while use of the electrophilic iodide reagent NIS (*N*-iodosuccinimide) could efficiently promote the desired reaction with similar results (77% yield, 2.8:1 dr) compared to the standard reaction (Table 2, **6b**). Therefore, an electrophilic "I⁺" mechanism (Scheme 2) rather than the classical radical process was proposed.^{6f} As shown in Scheme 2, the reaction would begin with the oxidation of "I[−]"; thereafter, the resulting electrophilic "I⁺" species could readily interact with the nucleophilic tryptamine (**5** or **7**) to form a cyclic iodonium

**Scheme 2** The plausible mechanism.

ion intermediate **A**.^{3g,8b,11} Subsequently, the active intermediate **A** underwent an intramolecular cyclization to generate the 3-iodohexahydropyrroloindole compound **B**, which was then transferred to indolium **C** and released iodide for further catalytic cycles. Finally, the indolium **C** could couple with another tryptamine (**5** or **7**) through an electrophilic addition/cyclization process *via* either favorable model **M-1** or a sterically hindered model **M-2** to give the major product **6** or **8** and the minor one **6'** or **8'**, respectively. It is worth noting that this stereo-control model was also consistent with the diastereoselectivities obtained from our reactions.¹⁰

To verify the utility of this methodology, the pharmacologically promising agent (+)-WIN 64821 was chosen as a synthetic target (Scheme 3).¹² The efficient construction of the 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline motif was the key to approach a concise total synthesis of (+)-WIN 64821. That could be conveniently realized by using our newly developed catalytic oxidative methodology. Initially, we synthesized the precursor **10** for the key reaction from commercially available (*L*)-tryptophan **9**. Then, compound **10** was successfully applied, at the gram-scale, to the KI-catalyzed oxidative coupling/cyclization reaction to give the 3*a*,3*a'*-bispyrrolidino[2,3-*b*]indoline **11** with satisfactory results (79% yield, 1.2:1 dr). Subsequent deprotections of *p*-nitrobenzene sulfonyl and allyl of **11** successively afforded the dimeric diamine **13**, which could be easily condensed with *N*-Cbz-*L*-phenylalanine over three steps^{4d,13} to finally give (+)-WIN 64821.

In conclusion, we have successfully established an iodide-catalyzed oxidative coupling/cyclization approach for the dimerization of tryptamine, tryptophol and tryptophan analogues. This protocol features a plausible catalytic cycle comprising iodide and hypoiodite catalyst states, the use of inexpensive and readily available as well as an environmentally benign system (KI and NaBO₃·4H₂O) and mild reaction conditions. Particularly, it provides a practical solution for the construction of synthetically challenging vicinal all-carbon quaternary motifs. Although it gives moderate diastereoselectivities in some cases, we have optimized it up to



Scheme 3 Asymmetric total synthesis of (+)-WIN 64821.

>20:1 dr by adjusting the substituent at C₄ of the substrate. Furthermore, the synthetic utility of this methodology has been verified by the asymmetric total synthesis of bioactive natural product (+)-WIN 64821.

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Conflicts of interest

There are no conflicts to declare.

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