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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.)/$NaBO_3{\cdot}4H_2O$ 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 acivities.[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 H_2O_2 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, $NaBO_3{\cdot}4H_2O$ 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).

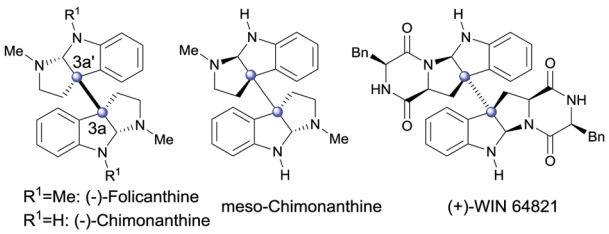

Fig. 1 Representative bispyrrolidino[2,3-*b*]indoline alkaloids.

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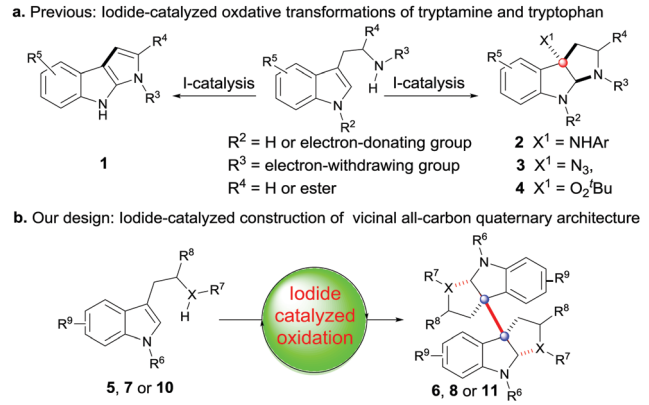
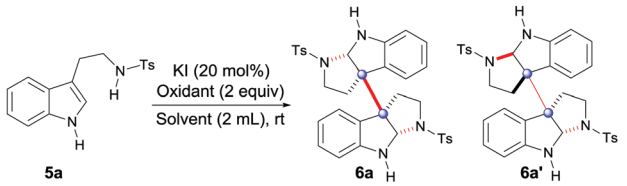


Scheme 1 (a) Previous I-catalyzed oxidation of tryptamine or tryptophan; (b) our design.

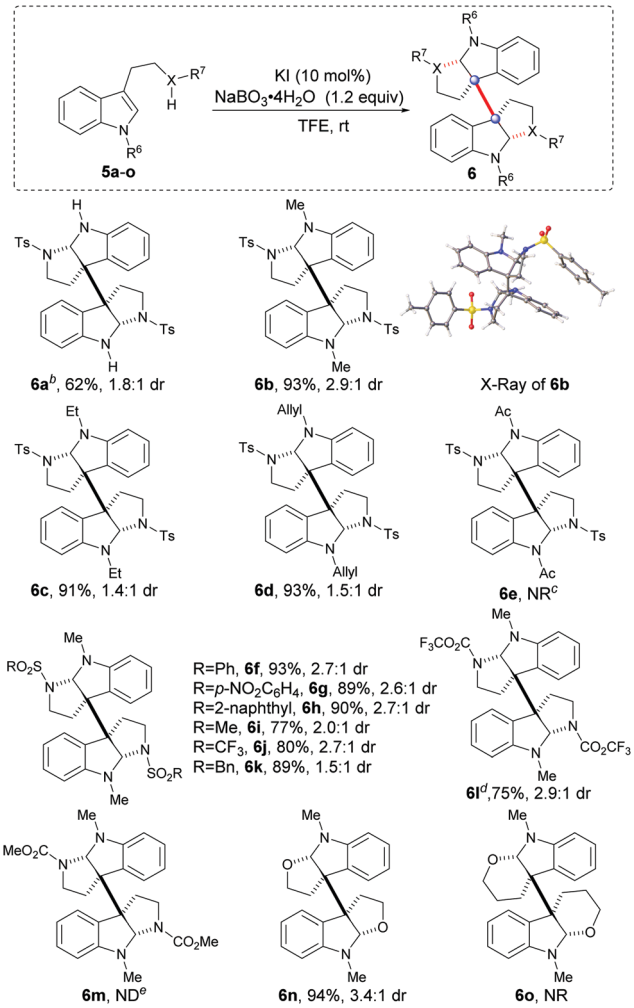
Table 1 Optimization of the conditions for the iodide-catalyzed oxidative dimerization of tryptamine[a]



Entry	Solvent	Oxidant	Time	Yield[b] (%)
1	CH_3CN	H_2O_2[c]	24 h	NR[d]
2	Toluene	H_2O_2	24 h	NR
3	THF	H_2O_2	24 h	NR
4	CH_2Cl_2	H_2O_2	24 h	NR
5	TFE	H_2O_2	4 h	44
6	TFE	$^tBuO_2H$[e]	10 h	53
7	TFE	*m*-CPBA	10 min	ND[f]
8	TFE	O_2[g]	24 h	NR
9	TFE	$NaBO_3{\cdot}4H_2O$	1.5 h	64
10[h]	TFE	$NaBO_3{\cdot}4H_2O$	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 ^{1}H NMR. [b] Determined by ^{1}H 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 $NaBO_3{\cdot}4H_2O$ (1.2 equiv.) in 2 mL TFE.

Table 2 Investigation of R^6 and X–R^7 of tryptamines for oxidative dimerization[a]

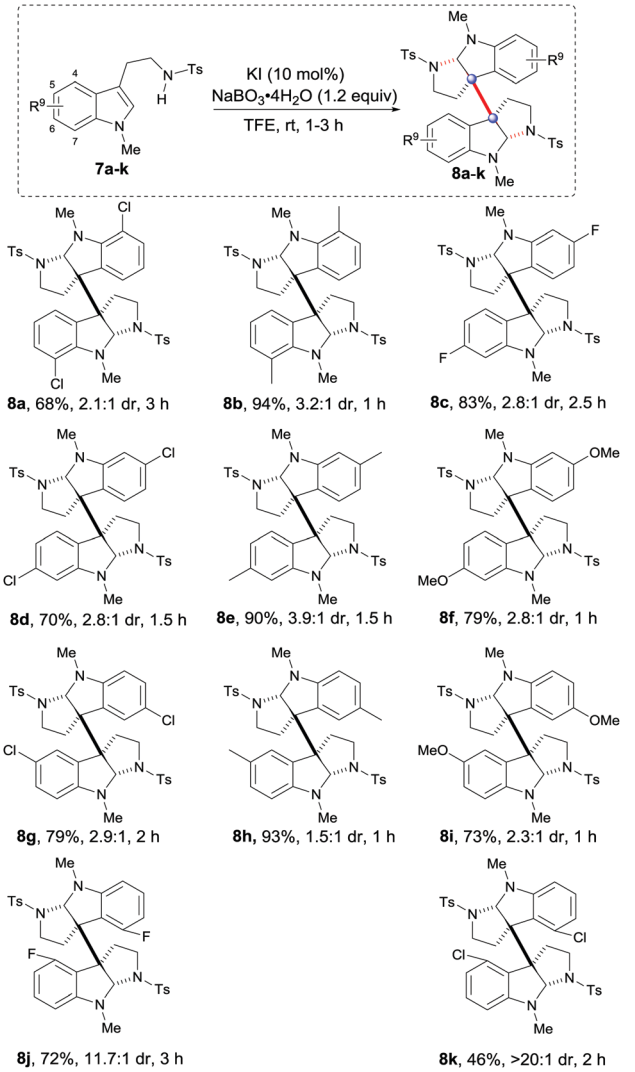


[a] Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and $NaBO_3{\cdot}4H_2O$ (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ^{1}H NMR. [b] Reacted for 2 h. [c] No reaction was observed after 24 h. [d] Reacted for 3 h. [e] Not detected.

With the optimal catalytic oxidative system in hand, we then expanded the tryptamine substrate scope by varying the substituents R^6 and X–R^7 (Table 2, **5a–m**). Initially, when X–R^7 was selected as *N*-tosyl, varying the substituents R^6 (**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 R^6 (as indicated in **6f–l**), varying substitution of R^7 (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–R^7 = *N*-CO_2Me), the reaction could not give the desired product **6m**, but gave a complex mixture 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 C_7, C_6 and C_5 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 C_4–F and C_4–Cl substituted tryptamines **7j** and **7k** could give **8j** and **8k** with excellent diastereoselectivities (11.7 : 1 and > 20 : 1 dr)

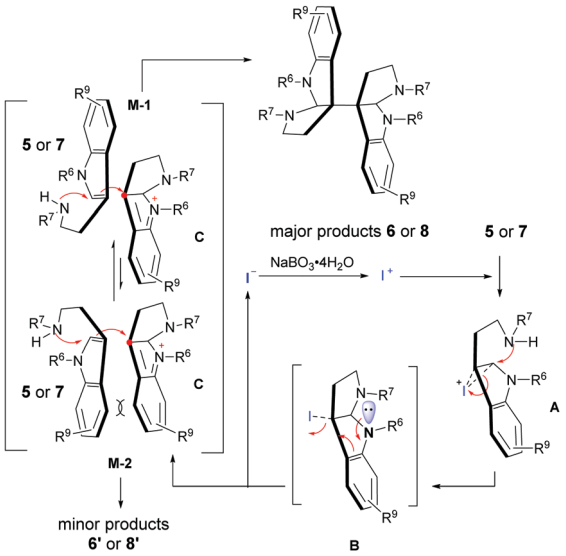
Table 3 Investigation of benzene ring substituted tryptamines for oxidative dimerization[a]



[a] Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and $NaBO_3{\cdot}4H_2O$ (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-tetramethylpiperidinooxy) 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.[6i] 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

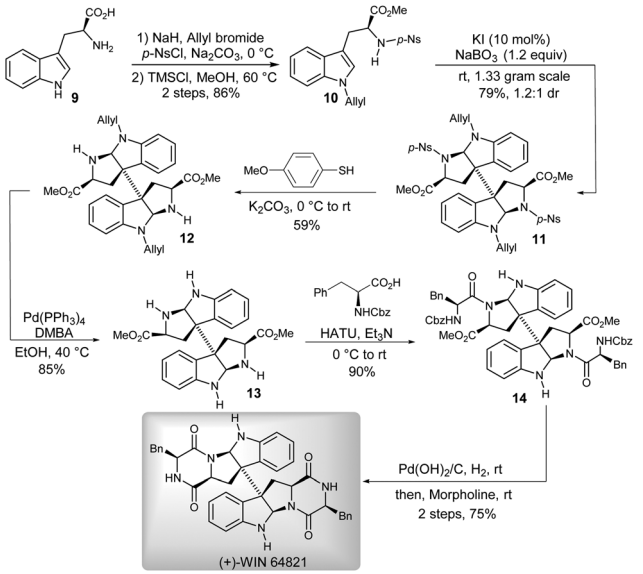


Scheme 2 The plausible mechanism.

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 $NaBO_3{\cdot}4H_2O$) 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 C_4 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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