ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2020, **56**, 121

Received 6th November 2019,
Accepted 25th November 2019

DOI: 10.1039/c9cc08646c

rsc.li/chemcomm

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).

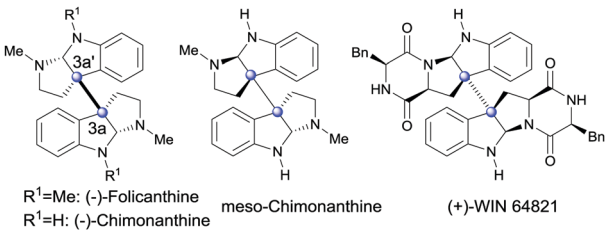

Fig. 1 Representative bispyrrolidino[2,3-*b*]indoline alkaloids.

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† 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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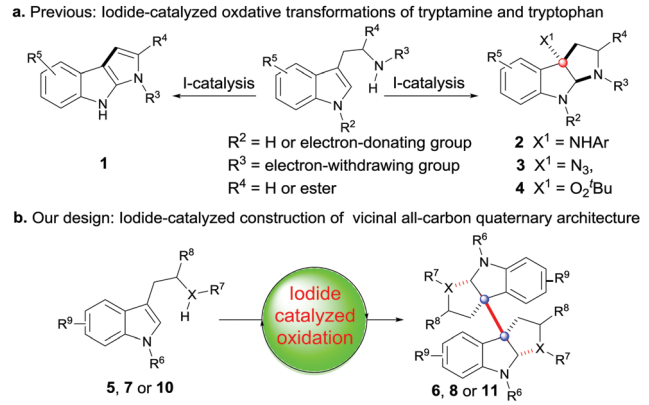
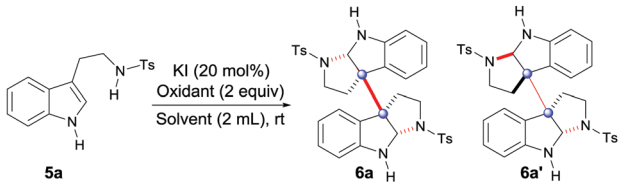


Scheme 1 (a) Previous I-catalyzed oxidation of tryptamine or tryptophan; (b) our design.

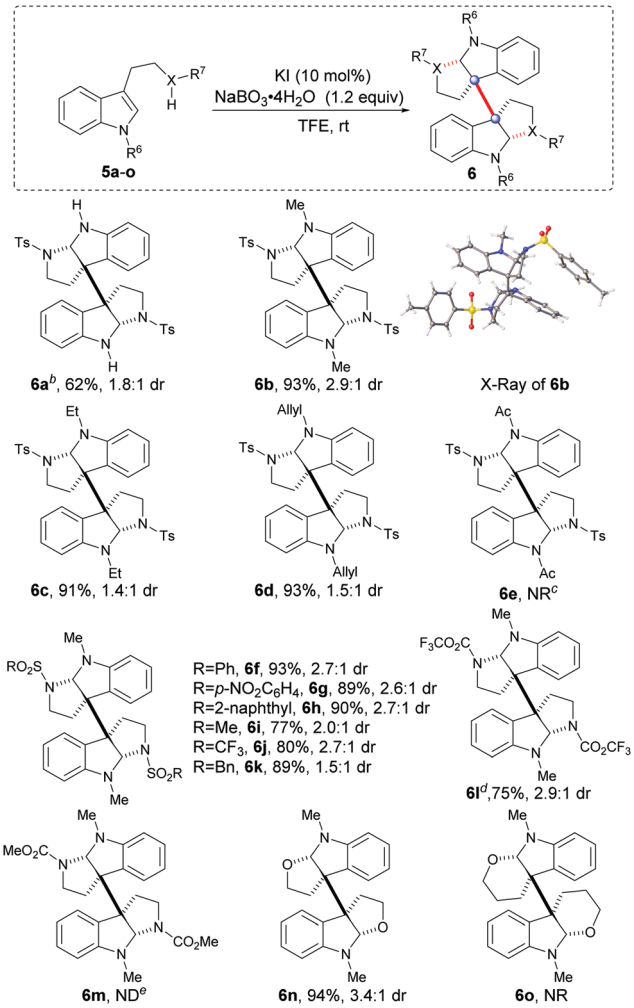
Table 1 Optimization of the conditions for the iodide-catalyzed oxidative dimerization of tryptamine[a]



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]

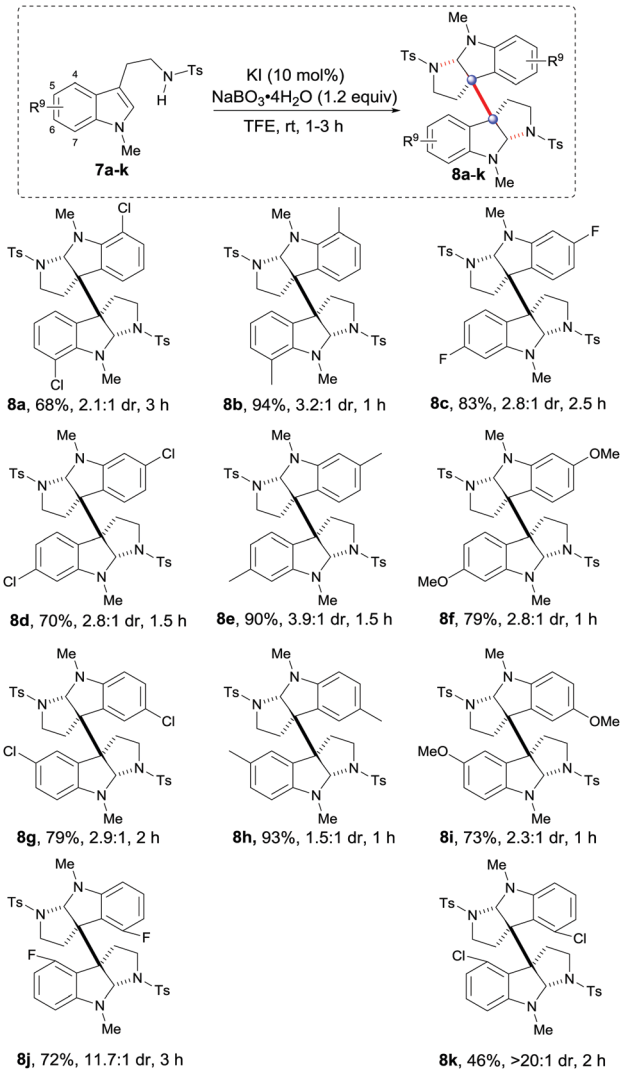


[a] Unless otherwise noted, all reactions were carried out with **5** (0.2 mmol), KI (10 mol%) and $NaBO_3{\cdot}4H_2O$ (1.2 equiv.) in 2 mL TFE and reacted for 1 h. Isolated yields and dr were determined by ^{1}H NMR. [b] Reacted for 2 h. [c] No reaction was observed after 24 h. [d] Reacted for 3 h. [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)

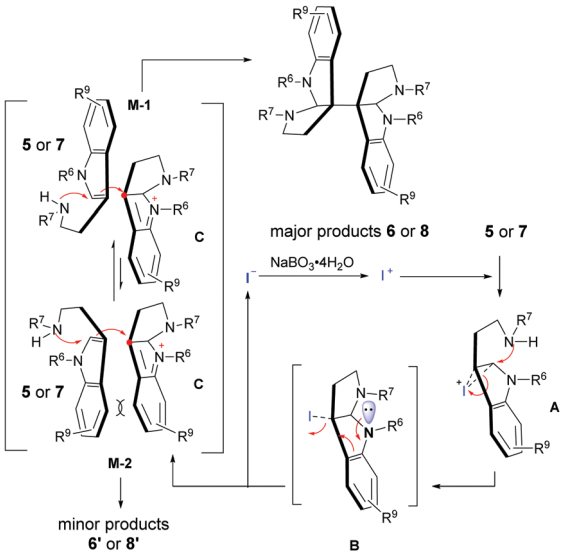
Table 3 Investigation of benzene ring substituted tryptamines for oxidative dimerization[a]



[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

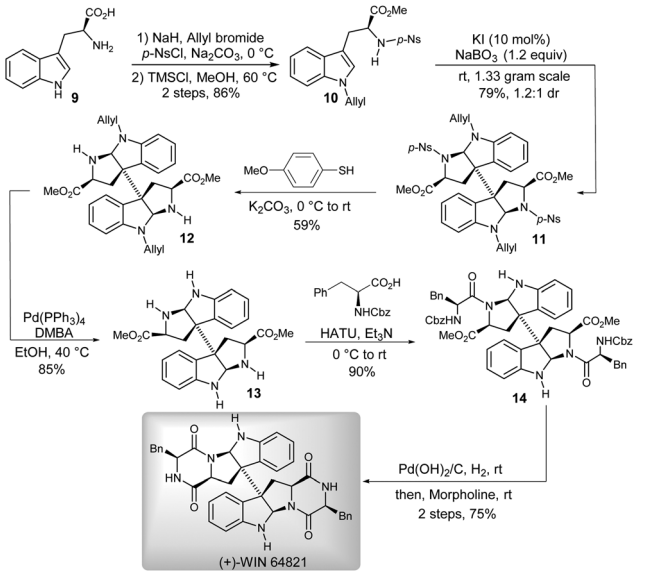


Scheme 2 The plausible mechanism.

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.

We thank the NSFC (No. 21502080, 21772071, 21871117, 21772076, 21971095), STCSM (19JC1430100) and the "111" Program of MOE for their financial support. We also thank Prof. Wei Yu (Lanzhou University) for his kind mechanism discussion.

Conflicts of interest

There are no conflicts to declare.

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