# Iodine-Mediated Intramolecular Dehydrogenative Coupling: Synthesis of N-Alkylindolo[3,2-c]- and -[2,3-c]quinoline Iodides

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S *Supporting Information*

ABSTRACT: An I_2/TBHP-mediated intramolecular dehydrogenative coupling reaction is developed for the synthesis of a library of medicinally important 5,11-dialkylindolo[3,2-c]quinoline salts and 5,7-dimethylindolo[2,3-c]quinoline salts. The annulation reaction is followed by aromatization to yield tetracycles in good yield. This protocol is also demonstrated for the synthesis of the naturally occurring isocryptolepine in salt form.

I_2 (1.1 equiv), TBHP (2 equiv)

CHCl$_3$, rt
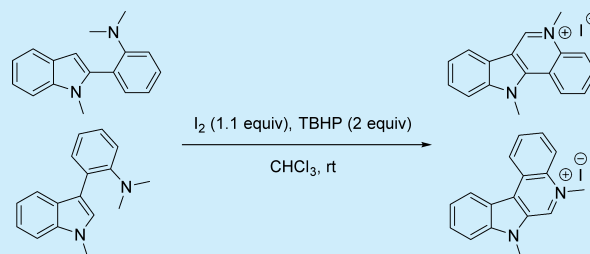
The cross-dehydrogenative coupling (CDC) reaction has gained tremendous importance in organic synthesis as it allows creation of a new C–C bond without any substrate prefunctionalization.[1] Pioneering studies in the oxidative C–H functionalization of amines have been performed by the Murahashi[2] and Li[3] groups. The oxidative reaction of the sp^3 carbon adjacent to the nitrogen atom involving C–C bond formation has been recently extensively studied by employing different metal catalysts, organocatalysts, photocatalysts, etc., with a range of nucleophiles to make diverse organic molecules.[4]

Nitrogen-containing heterocycles are found in abundance in nature.[5] The use of the CDC reaction for the synthesis of tetracycles leading to the synthesis of naturally occurring compounds or their scaffolds is a challenging task and is less explored.[6] The importance of a isocryptolepine framework in medicinal chemistry has encouraged synthetic organic chemists to devise efficient synthetic methods for their construction.[7] In continuation of our interest in iodine chemistry[8] and indoloquinoline alkaloids,[9] herein we report I_2/TBHP-mediated[10] intramolecular dehydrogenative coupling (IMDC) to give N-alkylindolo[3,2-c]- and -[2,3-c]quinoline iodides under mild reaction conditions.

One of the strategies to find new lead compounds is the isolation of active components from plant extracts used in traditional medicine. The roots of the plant *Cryptolpis sangunoleta*[11] used in traditional medicine in West and Central Africa have yielded several isomeric indoloquinoline alkaloids with antimalarial properties.[12] Isocryptolepine **1** and its synthetic compound isocryptolepine hydroiodide **2** show promising DNA binding activity accounting for anticancer and cytotoxic properties. Neoisocryptolepine salt **3** and 5,11-dimethylindolo-[3,2-c]quinoline salt **4** are synthetically derived alkaloids with the latter showing excellent antiplasmodial activity in the nanomolar range on L6 cells[13] (Figure 1). This activity prompted us to devise a new synthetic protocol to make a library of such compounds for biological evaluation.
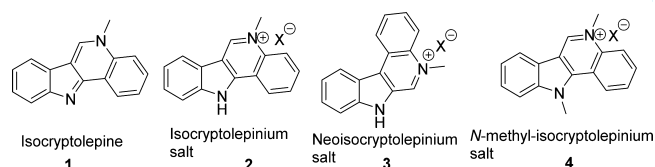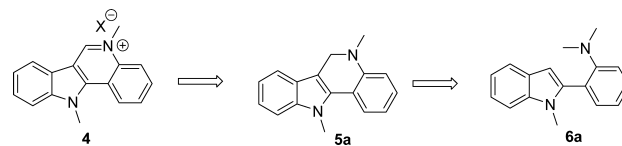

Figure 1. Isocyptolepine and its isomeric salts.

Our retrosynthetic plan for the synthesis of 5,11-dialkylindolo-[3,2-c]quinolines **4** employing an IMDC reaction is depicted in Scheme 1. It was envisaged that the key intermediate N,N-
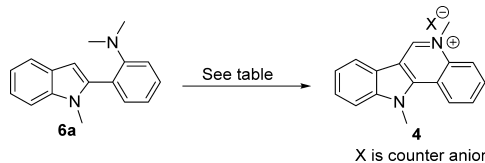
Scheme 1. Retrosynthetic Analysis

dimethyl-2-(1-methyl-1H-indol-2-yl)aniline **6a** via IMDC would yield tetracycle **5a**, which could be oxidized to **4** or in situ may be directly obtained from **6a**. Metal-catalyzed reactions suffer from toxicity of catalyst, high cost of catalyst, ligand, and metal waste as byproduct; sometimes these reactions are associated with high temperature. Iodine-mediated reactions overcome some of the drawbacks of metal-catalyzed reactions as they are inexpensive, nontoxic, and environmentally benign.[8d] Hence, we chose iodine for this coupling reaction.

Thus, the required starting **6a** was prepared by Stille coupling (SI). Once compound **6a** was in hand, the first experiment was attempted with substrate (0.1 mmol) and iodine (0.1 mmol) in excess TBHP in decane at room temperature (Table 1). Pleasingly, it gave the aromatized product **4a** directly as

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Table 1. Optimization Studies for Synthesis of N-Methylisocryptolepinium Salt[a]

| entry	halide source (equiv)	oxidant	solvent	temp (°C), time (h)	yield[f] (%)
1[b]	I$_2$	TBHP		rt, 14	24
2	I$_2$	TBHP	EtOH	60, 10	46
3	I$_2$	TBHP	EtOAc	60, 10	62
4	I$_2$	TBHP	CH$_3$CN	60, 10	67
5	I$_2$	TBHP	acetone	60, 10	62
6	I$_2$	TBHP	CH$_2$Cl$_2$	rt, 14	67
7	I$_2$	TBHP	CHCl$_3$	rt, 14	70
8	I$_2$	TBHP	toluene	60, 10	48
9	KI	TBHP	CHCl$_3$	rt, 3	nd[c]
10	NaI	TBHP	CHCl$_3$	rt, 14	nd[c]
11	KI	TBHP	CHCl$_3$, Pivalic acid	rt, 3	nd[c]
12	NIS	TBHP	CHCl$_3$	rt, 14	36
13	TBAI	TBHP	CHCl$_3$		
14	I$_2$	H$_2$O$_2$ (30%) (aq)	CH$_3$CN	60, 10	40
15	I$_2$	TBHP (aq)	CH$_3$CN	60, 10	45
16	I$_2$	O$_2$	CHCl$_3$	80, 16	nr[d]
17	−	TBHP	CHCl$_3$	60, 10	nr[d]
18	I$_2$	air	CHCl$_3$	80, 16	nr[d]
19	I$_2$(0.5)	TBHP	CHCl$_3$	rt, 14	16
20	I$_2$(1.1)	TBHP	CHCl$_3$	rt, 14	74
21	I$_2$(1.2)	TBHP	CHCl$_3$	rt, 14	73
22	I$_2$(1.5)	TBHP	CHCl$_3$	rt, 14	72
23	I$_2$(2)	TBHP	CHCl$_3$	rt, 14	74
24[e]	CuBr	TBHP		rt, 1	nd[c]
25[e]	RuCl$_3$	TBHP		rt, 1	nd[c]

[a]Reaction conditions: substrate (0.1 mmol), solvent (1 mL), oxidant (0.2 mmol), and halide source (0.1 mmol), TBHP (5.5 M in decane) is used unless noted. [b]Oxidant is used as solvent. [c]Not determined. [d]No reaction. [e]0.1 equiv of halide source. [f]Isolated yield.

envisaged in 24% yield after 14 h (entry 1). The product was precipitated out by adding 20% ethyl acetate−petroleum ether followed by filtration.

Encouraged by this result, we screened different solvents such as ethanol, ethyl acetate, acetonitrile, and acetone with 1 equiv of iodine and 2 equiv of TBHP in decane (entry 2−8). However, even after 24 h the reactions failed to reach completion at room temperature. These reactions were then conducted at 60 °C for 12 h for complete conversion with good isolated yields. Toluene gave a low yield of product. Chlorinated solvents such as DCM and chloroform showed complete conversion in 14 h at room temperature with 67 and 70% yields. We then examined the other halide sources such as KI, NaI, TBAI, and NIS (entry 9−13). Reaction with KI was found to be exothermic and resulted in a complex mixture of products. Similarly, this was observed with NaI; the only difference was that the reaction was not exothermic. Considering that the complex mixture of products could be due to overoxidation of the indole ring, we added pivalic acid[14] in the reaction medium but the same trend continued. When N-iodosuccinamide was used it gave 36% of desired product. Changing the oxidant to H$_2$O$_2$ and aq TBHP gave

relatively lower yields (entries 14 and 15). The absence of an oxidizing agent or the halogen source failed to show any change in starting material. Similarly, when the oxidizing agent was replaced with oxygen atmosphere no reaction took place. Iodine concentration was optimized, and 1.1 equiv was found to give the best results (entries 19−23). Metal-mediated reaction resulted in a complex mixture of products (entries 24 and 25).

Having established the optimum conditions (I$_2$ (1.1 equiv), TBHP (2.0 equiv), CHCl$_3$, rt; entry 20) for this transformation, we then examined the scope of the reaction with different substituents on the indole ring such as methoxy and methyl at the 5 position of indole (Scheme 2). Both substrates gave good yield,

Scheme 2. Scope of IMDC for N-Methylisocryptolepinium Iodide Derivative[a,b]
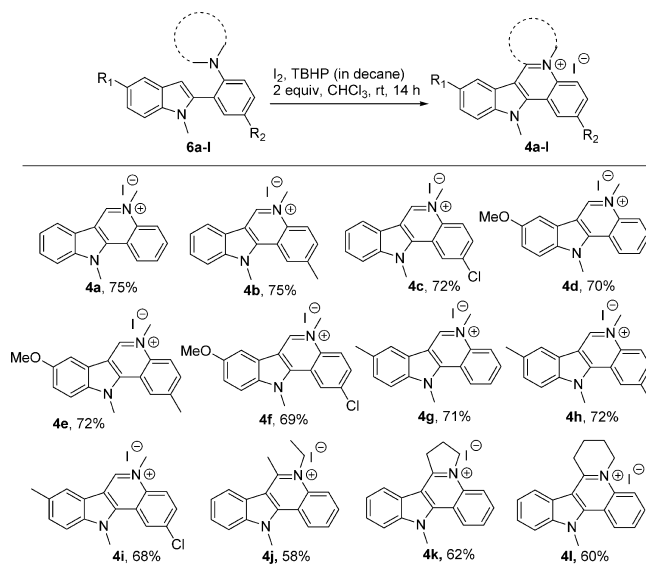
[a]Reaction conditions: substrate (0.1 mmol), chloroform (1 mL), TBHP−decane (0.2 mmol), and iodine (0.11 mmol) at rt for 14 h. [b]Isolated yield.

indicating a negligible effect of electron-donating groups like methoxy and methyl at the 5 position of indole. Similarly presence of a substituent at the *para* position of the aniline ring did not have any pronounced effect on the yield of the products. When the N,N-dimethyl group was replaced with N,N-diethyl, pyrrolidine, or piperidine it gave 4j and pentacyclic hetrocycles 4k and 4l, respectively. If the nucleophilicity of the indole ring was reduced by placing an electron-withdrawing group such as carbethoxy on the nitrogen, no reaction was observed in 24 h and a complex mixture was obtained at higher temperature.

To evaluate the protocol for the synthesis of the naturally occurring isocryptolepine 1, a free NH group on indole nucleus was required. The required substrate 8 was prepared from 7 and subjected to the same reaction conditions (Scheme 3).

Scheme 3. Synthesis of Naturally Occurring Isocryptolepine as Its Salt
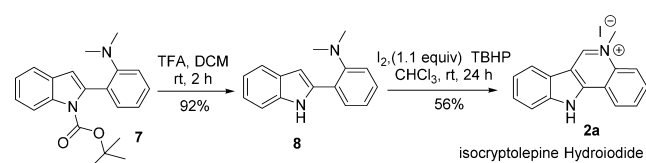
Isocryptolepinium hydroiodide **2a** was obtained in 56% yield. This salt **2a** has been reported to give isocryptolepine **1** on basification with NH_4OH.[7g] Interestingly, during this reaction the free NH group of indole did not interfere.

The scope of IMDC was further extended for the synthesis of isomeric indolo[2,3-*c*]quinoline salts (Scheme 4). Thus, **9a−c** under standard conditions provided *N*-methylneoisocryptolepinium iodide salts **10a−c** in moderate yields.
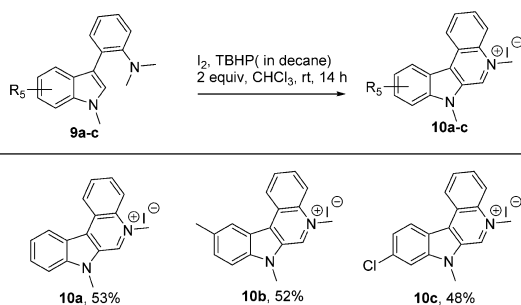
Scheme 4. Scope of IMDC for *N*-Methylisoneocryptolepinium Iodide Derivative[a,b]

[a]Reaction conditions: substrate (0.1 mmol), chloroform (1 mL), TBHP−decane (0.2 mmol), and iodine (0.11 mmol) at rt for 14 h. [b]Isolated yield.

The usefulness of the salt prepared was also tested for preparing some addition products. Thus, the salt **4a** was treated with a nucleophile such as sodium borohydride or methyl magnesium bromide to obtain the corresponding addition adducts in good overall yield (Scheme 5).

Scheme 5. Nucleophilic Addition Adducts of 4a
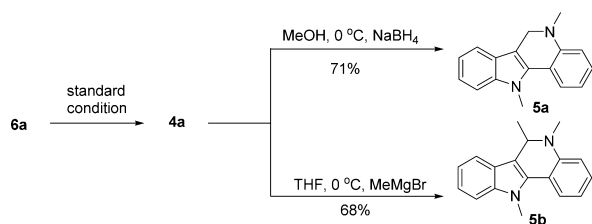
To elucidate the mechanism, when the reaction was carried out on **6a** in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), a known radical inhibitor, **4a**, was obtained in 73% yield. When TBHP was replaced with TEMPO, **4a** was obtained in 56% yield (Scheme 6). In both cases, no tempo-bound adduct **11** was observed, indicating that the reaction may

Scheme 6. Control Experiments
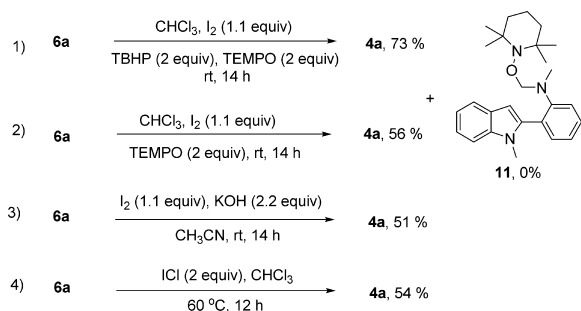
not be following a radical pathway. Compound **6a** on treatment with iodine and KOH gave **4a** in 51% yield, and treatment with 2 equiv of iodine monochloride gave **4a** in 54% yield. This suggests that the reaction may be following a (hypo)iodite-mediated pathway.[15]

A plausible mechanistic pathway for the transformation is depicted in Scheme 7 for the formation of product. Iodine must

Scheme 7. Plausible Mechanistic Pathway
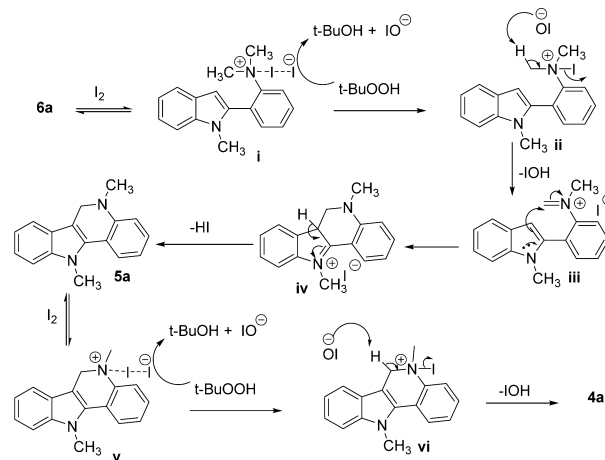
be coordinating with **6a** through the tertiary amine moiety, which is then oxidized with TBHP to give *tert*-butyl alcohol and IO^-. The hypoiodite anion then abstracts the proton from intermediate **ii** to give iminium species **iii**, which then undergoes intramolecular nucleophilic attack to give **iv**, which loses the molecule of HI to give **5a**. Further oxidation of **5a** via similar a hypoiodite intermediate provided **4a**.

In conclusion, we have developed a mild and an efficient metal-free approach for the activation of an sp[3] carbon adjacent to nitrogen with IMDC followed by aromatization to obtain hydroiodide salts of indolo[3,2-*c*]quinolines and indolo[2,3-*c*]quinolines. A hypoiodite-mediated mechanism is proposed on the basis of control experiments. The utility of the protocol was also demonstrated for the synthesis of naturally occurring indoloquinoline alkaloid isocryptolepine as its hydroiodide. Thus, we are able to show the potential of the IMDC reaction for the synthesis of complex scaffolds.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03392.

Experimental procedures, characterization data of new compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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