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COMMUNICATION

AcOH-mediated dichloroimination of indoles using chloramine-B: A facile access to 2,3-functionalized indolines

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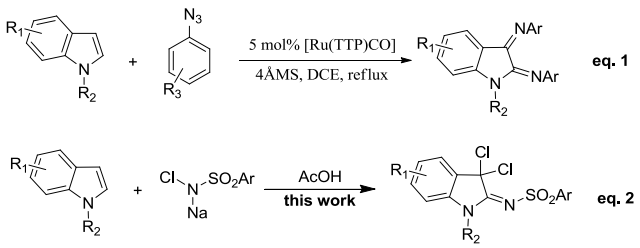
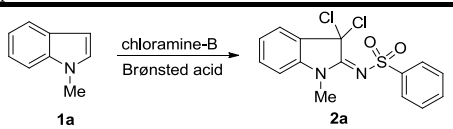
A new and mild method for the efficient synthesis of 3,3-dichloro-2-sulfonyliminoindolines *via* AcOH-mediated dichloroimination of indoles using chloramine-B is presented. Application of this method to the efficient construction of pyrrolidinoindoles and N-C3 linked pyrrolidinoindolines is demonstrated.

The indole moiety is present in numerous natural products possessing interesting biological activities[1] and represents a privileged element for synthetic pharmaceuticals.[2] Direct indole functionization has received considerable attention from organic and medicinal chemists due to its own practicality and atom-economy, and is an efficient approach toward the synthesis of indole derivatives.[3] While considerable efforts have been made for the direct C-C bond formation of indoles,[4] there are only limited reports for the direct C-N bond derivatization,[5] especially for the direct C-2 amination of indoles. Recently, Li and co-workers developed a copper-catalyzed regioselective amidation of 1-methylindoles with acetanilide derivatives.[6] Subsequently, Several methods for the direct C-N bond formation of indoles at C2 position have been documented,[7] i.e., palladium/copper-catalyzed regioselective amination of indoles with chlorosulfonamides,[7a] I_2-mediated regioselective C-2 amination of indoles with morpholine,[7b] *N*-tosylbenzenamines,[7c] azoles,[7d] or anilines.[7e] However, all these methods only afforded aminated indole derivatives. No approach toward the direct imination of indoles has been documented. Recently, Che and co-workers realized this transformation *via* a ruthenium porphyrin catalyzed diimination of indoles with aryl azides as the nitrene source (Scheme 1, eqn 1).[8] As an alternative, metal-free methods become very important from economical and environmental point of view. However, the development of a facile and metal-free method for this transformation remains a synthetic challenge. Herein, we would like to describe a novel AcOH-mediated dichloroimination of indoles using chloramine-B under mild conditions (Scheme 1, eqn 2). This protocol provides a facile access to various 3,3-dichloro-2-sulfonyliminoindolines which could be further converted to isatin analogs and 2-amino-substituted indoles. Furthermore, it also provides an efficient way for the construction of pyrrolidinoindoles and N-C3 linked pyrrolidinoindolines.



Scheme 1. Intermolecular C-H imination of indoles

Table 1. Optimization of the reaction conditions[a]



Entry	Chloramine-B (equiv.)	Brønsted acid	Solvent	Yield (%)[b]
1	2.0	-	MeCN	n.r.
2	2.0	1 N HCl in ether	MeCN	trace
3	2.0	CF_3CO_2H	MeCN	9
4	2.0	PTSA	MeCN	17
5	2.0	AcOH	MeCN	44
6	**3.0**	**AcOH**	**MeCN**	**92**
7	3.0	AcOH	MeOH	trace
8	3.0	AcOH	1,4-dioxane	59

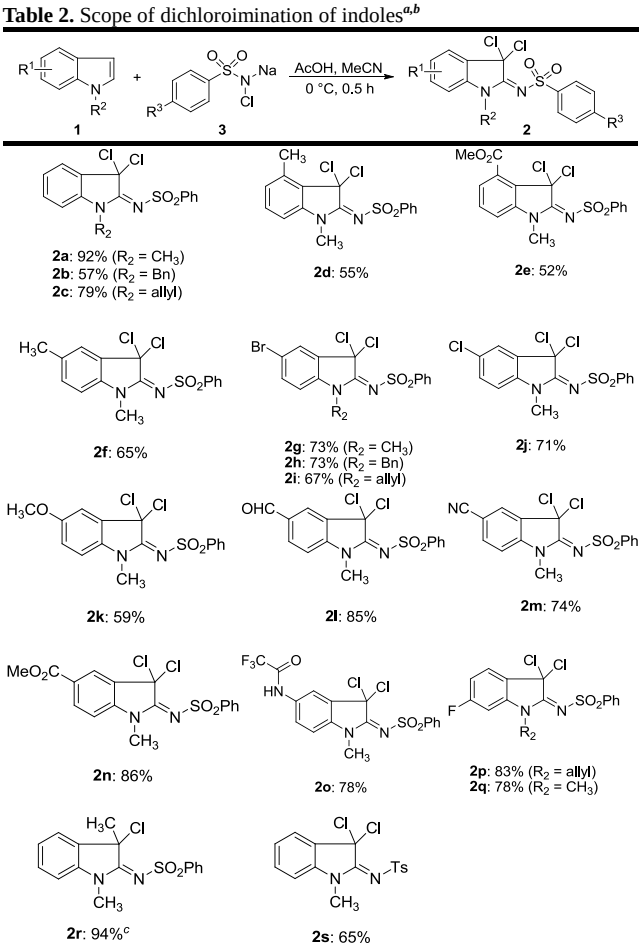
[a] Reaction conditions: **1a** (1.0 mmol), chloramine-B and indicated Brønsted acid (5.0 equiv.) were stirred in the indicated solvent (10.0 mL) at 0 °C for 0.5 h. [b] Isolated yield.

Our studies were commenced with 1-methylindole **1a** and chloramine-B as the model substrates. The reaction parameters, including Brønsted acid, solvent and equivalent of chloramine-B were investigated. The results are shown in Table 1. In an initial attempt, the reaction of indole **1a** (1.0 mmol) with chlormaine-B (2.0 mmol) was performed in acetonitrile at 0 °C without any additive, no reaction took place (Table 1, entry 1). Since the cleavage of N-Cl bond may be facilitated under acidic conditions, several acids including HCl/diethyl ether, trifluoroacetic acid, *p*-toluenesulfonic acid (PTSA) and acetic acid were investigated. The reaction proceeded smoothly in the presence of acetic acid, and the desired compound **2a**, confirmed by ^{1}H NMR, ^{13}C NMR and HRMS was obtained as a major product in 44% yield (Table 1, entry 5). Other acids led to poor yields of **2a** (Table 1, entries 2-4). To our delight, when the ratio of indole **1a** to chloramine-B

was changed from 1:2 to 1:3, the yield was increased to 92% (Table 1, entry 6). Shifting the solvent system to other solvents, no improvements were observed under the same conditions (Table 1, entries 7 and 8). Thus, the optimized reaction conditions include the use of 5.0 equiv. of acetic acid and 3.0 equiv. of chloramine-B as an amine and chlorine source in acetonitrile at 0 °C.

With the optimized conditions in hand, we began to investigate the generality of this established transformation (Table 2). A wide range of indoles reacted with chloramine-B or chloramine-T smoothly to afford the desired products in moderate to excellent yields. The protecting groups for *N*-protection, including methyl, benzyl and allyl (Table 2, **2a-2c**, **2g-2i**, **2p** and **2q**) were well toleranted. Indoles bearing electron-withdrawing substituents at C5 or C6 position were also suitable substrates, affording the desired products in good yields (Table 2, **2g-2j**, **2l-2n, 2p** and **2q**). The structure of **2i** was further confirmed by single-crystal X-ray analysis[9] (Figure 1). In contrast, introduction of electron-donating substituents such as methyl and methoxy at C5 position of the indole decreased the yields of the corresponding products (Table 2, **2f** and **2k**). Substrates bearing substituents at C4 position only afforded moderate yields (Table 2, **2d** and **2e**). It was noteworthy that 1,3-dimethylindole **1r** gave the highest yield. These results implied that the electronic effect or position of substituents had a great influence on the yields of the corresponding products. In addition, chloramine-T as the amine and chlorine source was also investigated to give moderate result (Table 2, **2s**).

Table 2. Scope of dichloroimination of indoles[a,b]



[a] Standard conditions: **1** (1.0 mmol), **3** (3.0 mmol) and AcOH (5.0 mmol) in acetonitrile (10.0 mL) were stirred for 0.5 h at 0 °C. [b] Isolated yield. [c] 1, 3-dimethyl-1*H*-indole as a substrate.

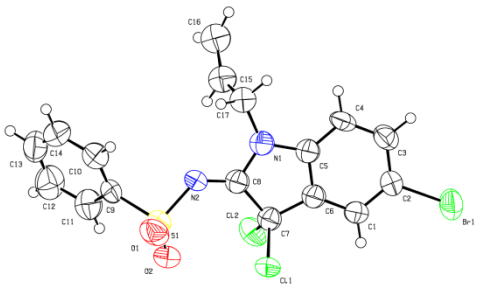
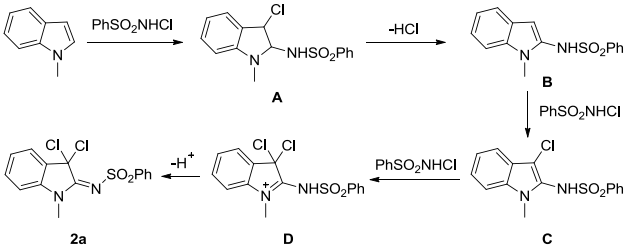


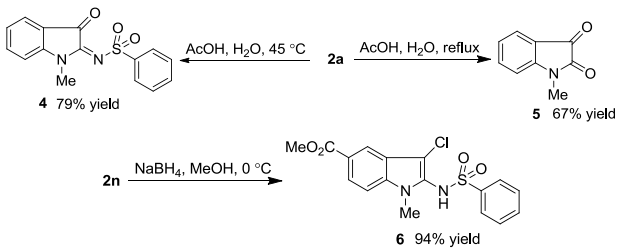
Fig 1. X-ray crystal structure of compound **2i**.

A possible mechanism for the reaction was illustrated in Scheme 2.[7c,7h] The reaction of *N*-substituted indole with *N*-chlorobenzenesulfonamide, generated *in situ* from chloramine-B and AcOH led to the formation of **A**. A subsequent elimination of HCl molecule gave **B**. The next step involved a chlorination of **B** to give **C**. Further transformation of **C** *via* a dearomatization led to the formation of cation **D**, followed by removal of a proton to provide the final product **2a**.



Scheme 2. Proposed mechanism

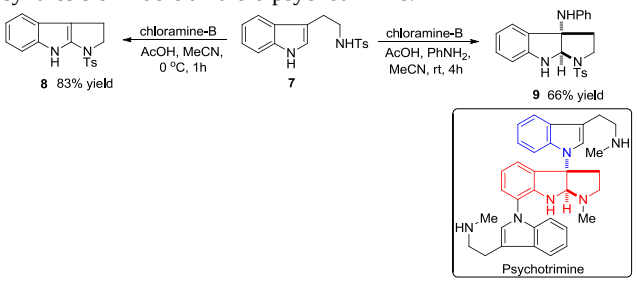
With these encouraging results in hand, we set to examine the synthetic applications of these 2,3-functionalized indolines. 3,3-Dichloro-2-sulfonyliminoindolines **2a** and **2n** were chosen as substrates for further transformations (Scheme 3). In the presence of acetic acid, **2a** was converted to the isatin analog **4** or **5** in good yields under different reaction conditions. As a class of important molecules, isatin and its derivatives exhibit rich biological activities.[10-12] In addition, isatins are often used as versatile building blocks in organic synthesis and medicinal chemistry.[13] Meanwhile, treating **2n** with $NaBH_4$ in methanol at 0 °C resulted in the formation of an interesting functionalized indole **6** in 94% yield. [7a]



Scheme 3. Synthesis of isatin analogs **4**, **5** and 2-aminoindole **6**.

To expand applicable scope of this strategy, an intramolecular amination using tryptamine **7** as a substrate was investigated (Scheme 4). To our delight, upon treating tryptamine **7** with 3.0 equiv. of chloramine-B and 5.0 equiv. of AcOH in acetonitrile at

0 °C, a desired cyclized product **8**[14] was obtained in 83% yield. Encouraged by this result, we decided to utilize this protocol to construct the N-C3 linked pyrrolidinoindoline ring system, which exists in many natural products.[15] When tryptamine **7** and excess aniline were subjected to the above reaction conditions, the desired product **9** was obtained in 66% yield, which implied that this protocol might provide a convenient way for the total synthesis of indole alkaloid psychotrimine.



Scheme 4. Intramolecular amination of tryptamine.

In summary, we have developed a AcOH-mediated dichloroimination of indoles using chloramine-B, which allows the synthesis of a series of 3,3-dichloro-2-sulfonyliminoindolines. This reaction features mild conditions, short reaction time, and high functional group tolerance. Further transformation of the indolines to isatin derivatives or 2-aminoindoles has been realized through an acid hydrolysis or a $NaBH_4$ reduction. Furthermore, application of this reaction to the synthesis of N-C3 linked pyrrolidinoindolines and pyrrolidinoindoles may provide a facile way for the total synthesis of indole alkaloid psychotrimine.

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