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Base-promoted, CBr_4-mediated tandem bromination/intramolecular Friedel–Crafts alkylation of *N*-aryl enamines: a facile access to 1*H*- and 3*H*-indoles†

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Described here is a general and highly efficient method for the synthesis of 1*H*- and 3*H*-indoles. In the presence of CBr_4 and a suitable base, the cyclization of *N*-aryl enamines proceeds with high efficiency. Unlike previous intramolecular cross dehydrogenative coupling (CDC) of the same substrates, this process does not require the use of either a transition metal or a stoichiometric amount of oxidant. This method also features operational simplicity, easy scalability and good substrate tolerability. Control experiments indicate the reactions may proceed in a tandem sequence of bromination and intramolecular Friedel–Crafts alkylation in a simple one-pot procedure.

Introduction

The importance of 1*H*- and 3*H*-indoles emerges from their extensive distribution in bioactive natural products and drug molecules.[1] For this reason, it will be never out of fashion for synthetic chemists to develop efficient and sustainable approaches to these privileged scaffolds. Since the pioneering Fischer indole synthesis, discovered more than one hundred years ago,[2] numerous synthetic strategies and methodologies have been demonstrated by using well-designed starting materials.[3] Among them, intramolecular cross dehydrogenative coupling (CDC) of *N*-aryl enamines represents one of the most straightforward and atom-efficient approaches (Scheme 1a).[4] In 2008, Glorius *et al.* firstly reported a palladium(II)-catalyzed oxidative cyclization of *N*-aryl enamines to afford the corresponding 1*H*-indoles, wherein a stoichiometric amount of $Cu(OAc)_2$ was used as the oxidant.[5] Subsequently, other metals such as copper(I)[6a] and iron(III)[6b] have proven to be efficient for this transformation as well. Recently, many efforts have been devoted to the visible light-induced C–H bond activation. In 2014, Rueping *et al.* developed a catalytic system combining a palladium catalyst and a photosensitizer, which enabled the synthesis of 1*H*-indoles in the presence of visible light, thus obviating the use of excessive oxidants and metal salts.[7] Following this work, Wu *et al.* established a visible light-induced, base- and oxidant-free strategy to synthesize 1*H*-indoles from *N*-aryl enamines by using catalytic amounts of an iridium(III) photosensitizer and cobaloxime catalysis.[8] Very recently, an electrochemical synthesis of 1*H*-indoles from the same substrates in an undivided cell was reported by Lei *et al.*[9a] The use of KI as a redox mediator was crucial for the 1*H*-indole formation and its efficiency. Some other oxidants such as hypervalent iodine reagents (PIFA, PIDA),[10] *tert*-butyl hydroperoxide (TBHP),[11a] *N*-bromosuccinimide (NBS)[11b] and $Cu(OAc)_2$[11c] can also enable such transformation. Exciting as these achievements are, the requirements of either expensive transition metals and/or stoichiometric oxidants or special experimental apparatus hampered their application in large scale preparation of related 1*H*-indole derivatives. Surprisingly, extending these methods to the preparation of 3*H*-indole skeleton using α-substituted *N*-aryl enamines is limited.[11a,12] This scarcity is partly due to the increased difficulty in tautomerization of α-substituted *N*-aryl enamines to the corresponding *N*-aryl imines, which are considered to be the key intermediates for the CDC reaction of *N*-aryl enamines. Therefore, there is an urgent need for a general, efficient and sustainable approach that could be applied to the synthesis of 1*H*- and 3*H*-indole derivatives from readily accessible precursors under simple reaction conditions.

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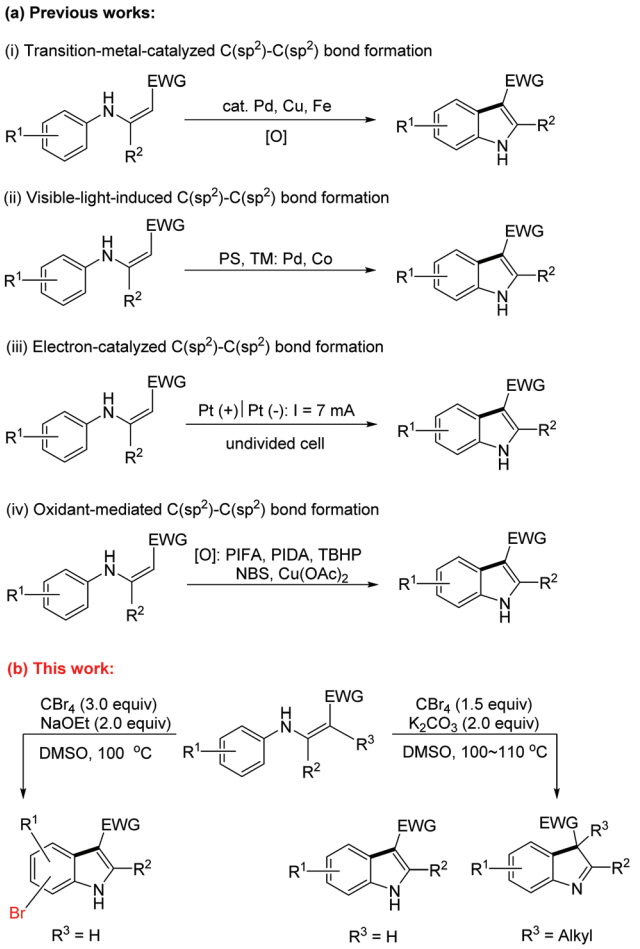
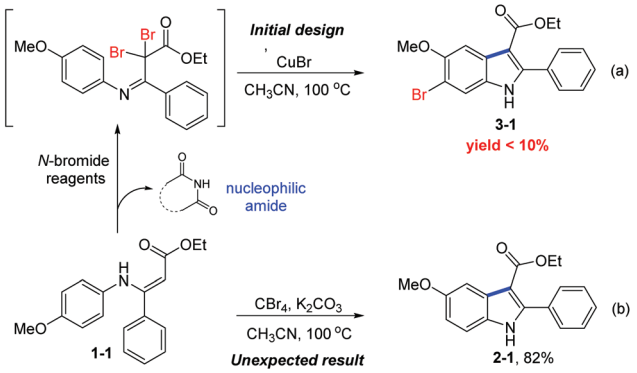


Scheme 1 Previous works and present work.

Herein, we report a base-promoted, CBr_4-mediated tandem bromination/intramolecular Friedel–Crafts alkylation of *N*-aryl enamines (Scheme 1b). This transition metal- and oxidant-free approach provides an operationally simple, expeditious and sustainable access to 1*H*- and 3*H*-indoles. More interestingly, with subtle variation of the base, we have observed the generation of brominated 1*H*-indoles.

Recently, we used α,α-dibromo β-iminoesters to develop a method toward brominated 1*H*-indoles using CuBr as a promoter.[13] At the outset of the investigation, we considered the possibility of the streamlined synthesis of these indoles from *N*-aryl enamies *via* dibromoimines intermediates. Whether the streamlined synthesis is successful or not will depend upon the compatibility of each step (bromination/cyclization). Meanwhile, in view of the carrier of Br^+ source always being a good nucleophile, we also anticipated a challenge to find a suitable brominating reagent. We started our research with *N*-pmp β-enamino ester **1-1** as model substrate. Initial evaluation of various *N*-bromide reagents (*e.g.*, NBS, DBDMH and TBCA) resulted in complex reaction mixtures, affording low yield of **3-1** (Scheme 2a). Presumably, the culprit was the side-product amide, which either conducted the nucleophilic



Scheme 2 Initial design and unexpected result.

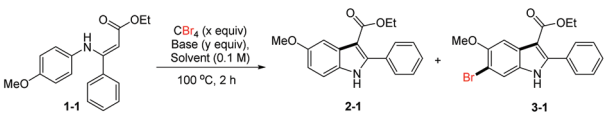
attack to the newly formed C–Br bond or the bonding with CuBr.

After considerable efforts, we identified carbon tetrabromide (CBr_4) as brominating reagent of choice in our subsequent study as its waste bromoform is non-nucleophilic. To our surprise, when the reaction was carried out in the absence of CuBr, the product **2-1** was formed in excellent yield and high selectivity, revealing a previously unknown and remarkably simple transition metal- and oxidant-free procedure for the cyclization of *N*-aryl enamines (Scheme 2b).

Results and discussion

Optimization of the reaction parameters for the synthesis of **2-1** is summarized in Table 1. Other inorganic bases (Cs_2CO_3,

Table 1 Optimization of the reaction parameters[a]



Entry	CBr_4 (equiv.)	Base (equiv.)	Solvent	Yield[b] (%) 2-1	3-1
1	2.5	K_2CO_3 (2)	CH_3CN	82	0
2	2.5	Cs_2CO_3 (2)	CH_3CN	76	0
3	2.5	K_3PO_4 (2)	CH_3CN	80	0
4	2.5	NaOH (2)	CH_3CN	57	10
5	2.5	KOH (2)	CH_3CN	25	30
6	2.5	KO^{t}Bu (2)	CH_3CN	20	28
7	2.5	NaOEt (2)	CH_3CN	40	32
8	2.5	Et_3N (2)	CH_3CN	0	0
9	2.5	pyridine (2)	CH_3CN	0	0
10	2.5	K_2CO_3 (2)	DMF	80	0
11	2.5	K_2CO_3 (2)	DMSO	85	0
12	2.5	NaOEt (2)	DMSO	17	56
13	1.5	K_2CO_3 (2)	DMSO	85	0
14	1.5	K_2CO_3 (1)	DMSO	64	0
15	3.0	NaOEt (2)	DMSO	0	66

[a] Reaction conditions: run on a 0.5 mmol scale for 2 h in a 15 mL sealed tube. [b] Yield of isolated products.

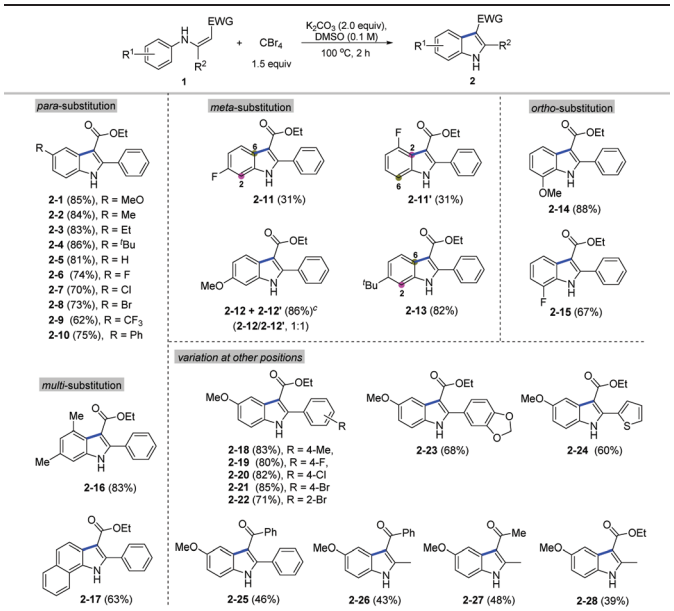
K_3PO_4) were found to be less effective (entries 2 and 3). The use of strong inorganic bases (NaOH, KOH, KO^{t}Bu, NaOEt) yielded mixtures of **2-1** and **3-1** (entries 4–7). The use of neutral organic base (Et_3N, pyridine) resulted in essentially no reaction (entries 8 and 9). Gratifyingly, when using more polar solvent DMSO instead of CH_3CN, both the yields of **2-1** and **3-1** were improved respectively (entries 11 and 12). Decreasing the amount of CBr_4 to 1.5 equiv. did not affect the reaction efficiency (entry 13). However, decreasing the amount of base led to lower yield of **2-1** (entry 14), and α-bromo *N*-pmp β-enamino ester was isolated as major side product, which may be the key intermediate for the formation of **2-1**. When 3.0 equiv. of CBr_4 was used in combination of 2.0 equiv. of NaOEt, the formation of **2-1** was totally suppressed and **3-1** was obtained exclusively (entry 15), but contaminated by small amounts of unidentified side products.

With the optimized reaction conditions in hand, we firstly examined the scope of different *N*-aryl enamines for the synthesis of 1*H*-indoles **2** (Table 2). Generally, the electronics and positions of the substituents on the *N*-aryl ring were well-tolerated in this reaction (**2-1** to **2-10**); although slightly higher yields could be obtained with electron-donating substituents. While *meta*-substituted *N*-aryl ring could use 2- and 6-positions as the nucleophilic site for the cyclization leading to regioisomeric mixtures of 4- and 6-substituted indoles (**2-11**/**2-11′**, **2-12**/**2-12′**), we wondered how the steric hindrance at *meta*-position of the *N*-aryl ring affect the reaction. Thus, *N*-aryl group bearing a *t*-Butyl group at *meta*-position (**1-13**) was prepared and subjected to the standard conditions. The cyclization of **1-13** gave exclusive reaction at 6-position (**2-13**), implying that the steric effect may result in this regioselectivity. Multi-substituted *N*-aryl groups were also facile substrates (**1-16**, **1-17**) and provided corresponding 1*H*-indoles (**2-16**, **2-17**) in moderate yields. Substituents at all positions of the aryl ring (R^2 = Ar) could be similarly tolerated (**1-18** to **1-23**). Electro-rich heterocycle (R^2 = thiophene) was also competent in this transformation (**2-24**). Replacement of (hetero)aryl groups with alkyl group (R^2 = Me) dramatically decreased the reaction efficiency (**2-26** to **2-28**). The use of ketone in place of carboxylic ester also led to decreased reaction efficiency (**2-25** to **2-27**), as decomposition of the starting materials were observed.

Compared with the synthesis of 1*H*-indole **2**, the formation of brominated 1*H*-indole **3** was dominated by the electronics and positions of substituents on the *N*-aryl ring. As shown in Table 3, electron-donating substituents (MeO, Me, EtO and BnO) on the *para*-position of *N*-aryl ring favored formation of the C6-Br indoles (**3-1**, **3-2**, **3-29** and **3-30**). No brominated indoles were detected either in the absence of electron-donating substituents or with the substituets on the *ortho*- or *meta*-positions of the *N*-aryl ring. Substrates bearing disubstituents on the *N*-aryl ring were also investigated. As expected, all the tested substrates proceeded smoothly under the optimized conditions (**3-16**, **3-31** and **3-32**). Surprisingly, the reaction of **1-17**, which bears a π-conjugating moiety on the *N*-ary ring, successfully engaged in this transformation, albeit delivering **3-17** in relatively lower yield. NMR spectrums of **3-16** and **3-31** are in consistent with previously reported work. The bromine positions in **3-17** and **3-32** were determined by ^{1}H–^{1}H NOESY experiments. The structure of **3-32** was further confirmed by X-ray crystallographic analysis.[14]

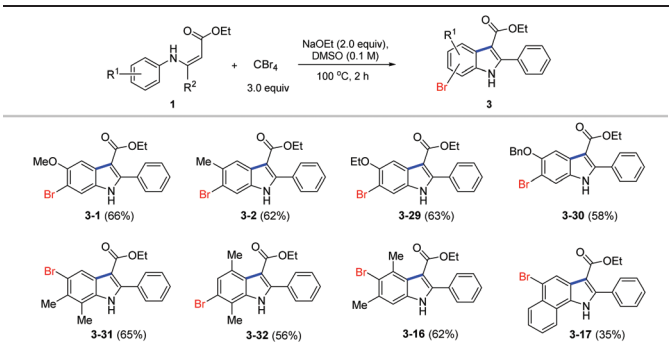
We then tried to expand the established reaction conditions for the synthesis of 1*H*-indoles **2** to 3*H*-indoles **5** shown in Table 4. In general, all the tested substrates were well tolerated in this transformation though higher reaction temperature was required. Substituents (R^1) at the *para*-position of *N*-ary ring had minimal influence on the reaction efficiency (**5-1** to **5-5**). Both electron rich and electron deficient aryl groups (R^2) worked effectively (**5-6** to **5-10**). Moreover, bulkier groups (R^3 = Et, Bn) also proceeded smoothly to give decent results, only they required a longer reaction time for completion (**5-11** and **5-12**).

Table 2 Scope of 1*H*-indole synthesis[a,b]



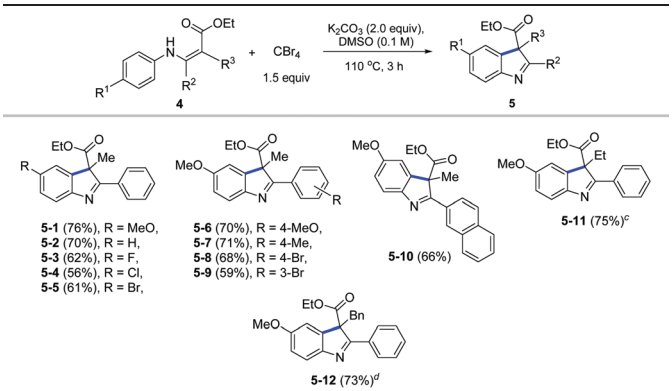
[a] Reaction conditions: run on a 0.5 mmol scale for 2 h in a 15 mL sealed tube. [b] Isolated yields. [c] Two inseparable isomers.

Table 3 Scope of brominated 1*H*-indole synthesis[a,b]



[a] Reaction conditions: run on a 0.5 mmol scale for 2 h in a 15 mL sealed tube. [b] Isolated yields.

Table 4 Scope of 3*H*-indole synthesis[a,b]

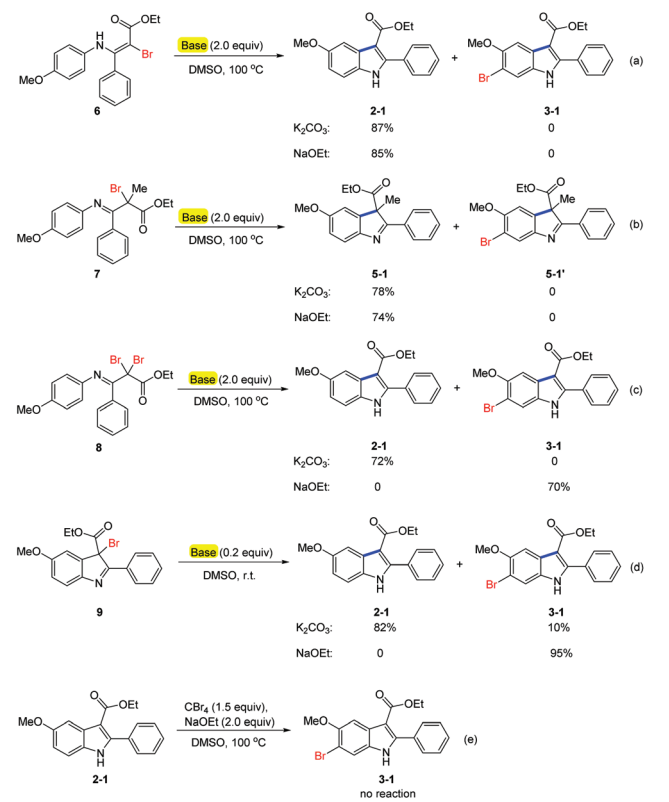


[a] Reaction conditions: run on a 0.5 mmol scale for 3 h in a 15 mL sealed tube. [b] Isolated yields. [c] 5 h. [d] 6 h.

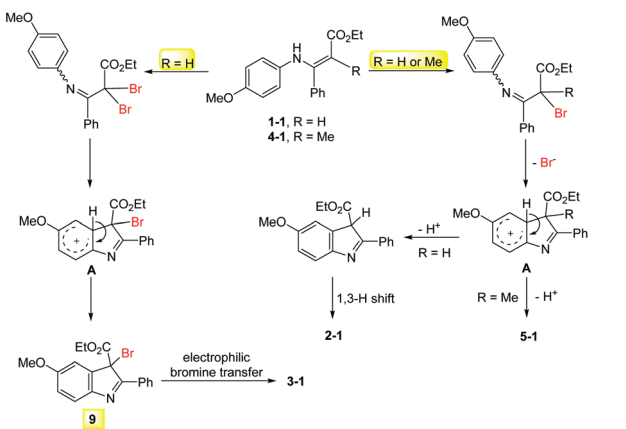
To define the possible intermediates and pathway, several control experiments were performed as shown in Scheme 3. First, compounds **6** and **7** were used as starting materials in the presence of bases (K_2CO_3, NaOEt), and the desired products **2-1** and **5-1** were obtained in comparable yields, respectively (Scheme 3a and b). No brominated indoles **3-1** and **5-1′** were observed, which indicates that the brominated indole formation does not involve the α-bromo *N*-aryl enamino/imino ester intermediates. Second, the cyclization of compound **8** in the presence of NaOEt proceeded smoothly to afford **3-1** exclusively, which was not observed at all with K_2CO_3 as base (Scheme 3c). These results indicate that the generation of α,α-dibromo β-iminoester intermediates and the choice of base are crucial to brominated indole formation and its efficiency. Third, compound **9** was prepared according to the reported methods,[15] but it was not stable at ambient temperature as evidenced by the fact that the NMR sample was partly converted to **2-1** and **3-1** after some time. The transformation from compound **9** to **3-1** occurred immediately on treatment with a catalytic amount of NaOEt at room temperature (Scheme 3d). Given the above results (Scheme 3c and d), NaOEt may accomplish both of the following two missions in the process: (i) it may facilitate the generation of α,α-dibromo β-iminoesters, which are the precusors for 3-bromo-3*H* indoles; (ii) it may promote the bromine atom translocation probably involving the generation of electrophilic Br^+ species in the form of BrOEt. Finally, **3-1** was not detected when **2-1** was subjected to the standard conditions, which ruled out the possibility that **3-1** was formed *via* late-stage bromination with CBr_4 (Scheme 3e).

On the basis of above results and previous related works,[16] a plausible mechanism for the reactions was proposed as shown in Scheme 4. The reaction begins with the formation of α(,α)-(di)bromo β-imono ester from the reaction of **1-1** (**4-1**) with CBr_4 in the presence of a suitable base. The subsequent nucleophilic attack by *N*-aryl ring onto C–Br bond *via* Friedel–Crafts alkylation presumably yields intermediate **A**, which is deprotonated with the aid of base to afford **2-1** (**5-1**). For the synthesis of **3-1**, the formed 3-bromo-3*H* indole intermediate **9** is not stable so as to deliver **3-1** *via* intramolecular electrophilic bromine transformation.

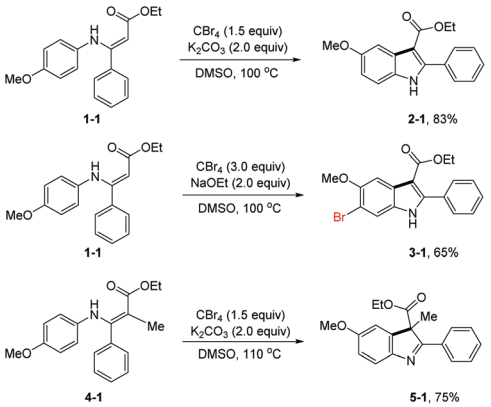
To establish the utility of the present methods, we performed 10 mmol scale reactions of **1-1** and **4-1** using standard conditions as shown in Scheme 5. The reactions proceeded nicely, and we obtained the corresponding products in comparable yields.



Scheme 3 Control experiments.



Scheme 4 Plausible mechanism.



Scheme 5 Scale-up experiments.

Conclusions

In summary, we have developed a general method for the synthesis of 1*H*-indoles and 3*H*-indoles, two important families of nitrogen-containing heterocycles whose efficient synthesis are still in high demand. Unlike the previous examples of intramolecular cross dehydrogenative coupling of *N*-aryl enamines, this process does not require the use of a transition metal or a stoichiometric amount of oxidant, making it a envirionment-friendly complement to the existing strategies for the synthesis of indole derivatives. Moreover, the synthesis of brominated indoles under subtly adjusted reaction conditions is more straightforward than that in our previous work.

Experimental section

General experimental procedures

Synthesis of 1*H*-indoles 2. To a 15 mL sealed tube was added **1** (0.50 mmol), CBr_4 (0.75 mmol), K_2CO_3 (1.00 mmol) and dry DMSO (5 mL). The resulting mixture was heated at 100 °C for the indicated time until the complete consumption of starting material as monitored by TLC or GC-MS analysis. After cooling, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with EA. The organic phase was then washed successively with water (3 × 25 mL) and brine (3 × 25 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the obtained residue was purified by silica gel column chromatography (EA/hexane) to afford desired product **2**.

Synthesis of brominated 1*H*-indoles 3. To a 15 mL sealed tube was added **1** (0.50 mmol), CBr_4 (1.50 mmol) and dry DMSO (5 mL). The mixture was stirred at room temperature and then EtONa (1.00 mmol) was added. The resulting mixture was heated at 100 °C for the indicated time until the complete consumption of starting material as monitored by TLC or GC-MS analysis. After cooling, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with EA. The organic phase was then washed successively with water (3 × 25 mL) and brine (3 × 25 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the obtained residue was purified by silica gel column chromatography (EA/hexane) to afford desired product **3**.

Synthesis of 3*H*-indoles 5. To a 15 mL sealed tube was added **4** (0.50 mmol), CBr_4 (0.75 mmol), K_2CO_3 (1.00 mmol) and dry DMSO (5 mL). The resulting mixture was heated at 110 °C for the indicated time until the complete consumption of starting material as monitored by TLC or GC-MS analysis. After cooling, the reaction mixture was filtered through a pad of Celite and the filter cake was washed with EA. The organic phase was then washed successively with water (3 × 25 mL) and brine (3 × 25 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the obtained residue was purified by silica gel column chromatography (EA/hexane) to afford desired product **5**.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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