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ARTICLE

Synthesis of *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles by cascade annulation of 2-alkynyl-*N*,*N*-dialkylanilines

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An efficient and metal-free approach to *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles from 2-alkynyl-*N*,*N*-dialkylanilines has been developed. In the presence of iodine and *tert*-butylhydroperoxide (TBHP), a variety of 2-alkynyl-*N*,*N*-dialkylanilines underwent a cascade radical annulation to yield 3-arylsulfonylindoles. In contrast, 3-arylsulfanylindoles were conveniently prepared by iodine mediated electrophilic annulation reactions. The present protocol uses the economical and environmentally friendly I_2–TBHP or I_2 system, and the potentially bioactive *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles with various functional groups were successfully synthesized in moderate to good yields.

Introduction

The indole scaffold is omnipresent in wide range of naturally derived molecules as well as biologically active compounds.[1] Among the numerous indole derivatives, those bearing sulfonyl and sulfanyl moieties at the *C*2-, *C*3- and *N*-positions exist in many pharmacologically important agents (Fig. 1). Indolyl aryl sulfones were found to exhibit interesting biological activities and therapeutic values. For example, 1-aminoalkyl-3-arylsulfonyl-1*H*-indoles **I** are human 5-HT_6 receptor ligands.[2] L-737,126 (**II**) is a selective non-nucleoside reverse transcriptase inhibitor.[3] 4-Dialkylaminoethyl-3-(phenylsulfonyl)-1*H*-indoles **III** serve as dual acting norepinephrine reuptake inhibitors (NRIs) and 5-HT_{2A} receptor antagonists.[4] *N*-Sulfonyl-*C*2-sulfonylindole derivatives **IV** are cannabinoid CB_2 receptor ligands.[5] The 3-sulfanylindoles also attracted considerable attention due to their potential uses in several disease areas. For instance, MK-886 (**V**)[6] exhibits inhibitory activity against 5-lipoxygenase as well as anti-cancer activity in human colorectal cancer and 3-(arylsulfanyl)indole **VI**[7] is capable of inhibiting tubulin polymerization and human breast cancer growth.

Due to the special pharmacological properties, there has been growing interest in developing a general and efficient route to access indole-based sulfones and sulfides. In particular, 3-arylsulfanylindoles and 3-arylsulfonylindoles can be prepared by two strategies including direct *C*3 functionalization of the indole core structures, and cascade annulation of the acyclic precursors toward construction of the indole motifs. Several sulfenylating agents such as disulfides,[8] thiols,[9] sulfinic acids,[10] sulfinate salts,[11] sulfonyl chlorides,[12] sulfenyl chlorides,[13] *N*-thioimides,[14] quinone mono-*O*,*S*-acetals,[15] arylsulfonyl cyanides,[16] sulfonyl hydrazides,[17] sulfoxides,[18] thiosulfonium salts,[19] and arylboronic acids/element sulfur[20] have been reported to effect the *C*3 sulfenylation. Similarly, methods for direct *C*3 sulfonylation of the preexisting indole ring were also reported albeit with less number of approaches.[21] Undoubtedly, 3-sulfonylindoles can also be prepared by oxidation of the corresponding 3-sulfanylindoles. Noteworthy, 2-alkynylanilines and derivatives are well-known synthetically versatile substrates employed for the preparation of substituted indoles.[22] Several research groups reported synthetic approaches to 3-arylsulfanylindoles employing 2-alkynylaniline derivatives as the substrates to react with sulfenyl chlorides, disulfides, and thiols.[23] Although a few methods were available for the preparation of 3-arylsulfonylindoles by annulation of appropriate acyclic substrates, none of these methods dealt with sulfonylating reagents.[24] Most recently, Han and coworkers disclosed an elegant synthesis of 3-sulfonylindoles from 2-alkynylazide employing sulfinic acids as the sulfonylating reagents.[25]

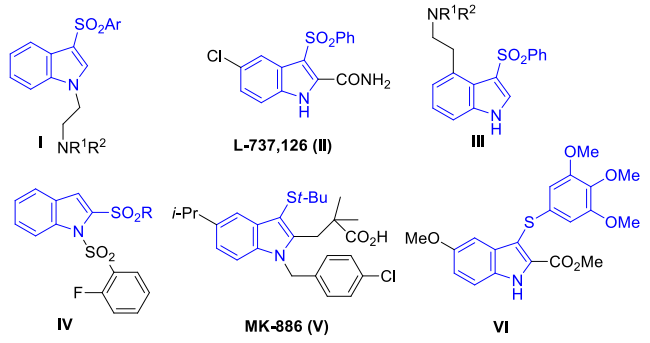

Fig. 1 Examples of biologically active sulfonyl- and sulfanylindole derivatives.

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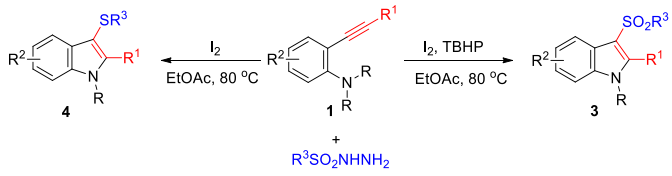
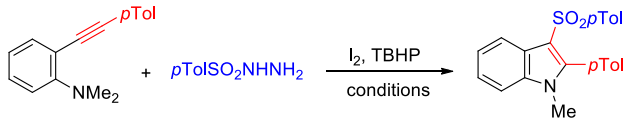
During the past few years, sulfonyl hydrazides, economical and shelf-stable reagents, received considerable attention in organic synthesis. Depending on the reaction conditions, they can serve as sulfonylating,[26] sulfenylating,[27] and arylating reagents.[28] With our continuing interest in the synthesis of organosulfur compounds via sulfonylation and sulfenylation of olefins,[29] unsaturated carboxylic acids,[30] and heterocyclic scaffolds,[31] we reported herein the synthesis of *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles using 2-alkynyl-*N*,*N*-dialkylanilines **1** and sulfonyl hydrazides **2** as the sulfur source (Scheme 1). The present work is metal-free, generates eco-friendly by-products, presents a simple experimental procedure and short reaction time, and can accommodate wide range of substrate scopes to access both 3-sulfonylindoles and 3-sulfanylindoles by tuning the combinations of molecular iodine and *tert*-butylhydroperoxide (TBHP).



Scheme 1 Synthesis of *N*-alkyl-3-sulfonylindoles **3** and *N*-alkyl-3-sulfanylindoles **4** from 2-alkynyl-*N*,*N*-dialkylanilines **1** and sulfonyl hydrazides **2**

Table 1. Synthesis of 3-sulfonylindoles **3**: Screening for optimal reaction conditions[a]



1a **2a** **3aa**

entry	**2a** (equiv)	I_2 (equiv)	aq TBHP (equiv)	solvent	time (h)	yield[b] (%)
1	2	1.5	3	EtOAc	4	14
2	2	1.5	5	EtOAc	4	15
3	3	1.5	5	EtOAc	4	47
4	3	1.5	5	EtOAc	24	46
5	3	1.5	5	EtOAc	2	48
6	3	1.5	5	DCE	2	35
7	3	1.5	5	MeOH	2	52
8	3	1.5	5	EtOH	2	51
9	3	1.5	5	MeCN	2	44
10	3	1.5	5	THF	2	41
11	3	1.5	5	1,4-dioxane	2	28
12	3	1.5	5	toluene	2	36
13	5	1.5	6	EtOAc	2	85
14	**5**	**1.2**	**6**	**EtOAc**	**2**	**87**

[a]Reaction conditions: **1a** (0.25 mmol) in solvent (2 mL) at 80 °C, open air. [b]Isolated yields after column chromatography (SiO_2).

Results and discussion

The study was first examined using *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline (**1a**) and *p*-toluenesulfonyl hydrazide (**2a**) as benchmarking substrates to screen for the optimal reaction conditions (Table 1). In the beginning, when **1a** (0.25 mmol) and **2a** (2 equiv.) were treated with molecular iodine (I_2, 1.5 equiv.) and TBHP (70% in water, 3 equiv.) and the reaction mixture was stirred in ethyl acetate (EtOAc, 2 mL, 0.125 M) at 80 °C for 4 h, the reaction readily took place and provided the corresponding 3-sulfonylindole **3aa** in 14% yield (Table 1, entry 1). Attempt to increase the amount of TBHP employed (from 3 equiv. to 5 equiv.) did not give satisfactory results (Table 1, entry 2). An increase in the quantity of **2a** (from 2 equiv. to 3 equiv.) gave **3aa** in moderate yield (47% yield; Table 1, entry 3). No appreciable results were obtained when the reaction time was extended (from 4 h to 24 h) (Table 1, entry 4). The reaction time can be shortened (from 4 h to 2 h) without lowering the product yield (Table 1, entry 5). Various solvents, including dichloroethane (DCE), methanol (MeOH), ethanol (EtOH), acetonitrile (MeCN), tetrahydrofuran (THF), 1,4-dioxane and toluene, were next screened (Table 1, entries 6–12). Among those, EtOAc was chosen as the solvent of choice to further study other reaction parameters due to the ease of handling and the reaction in general was much cleaner. Gratifyingly, with the increase of the stoichiometric amount of **2a** (from 3 equiv. to 5 equiv.) and TBHP (from 5 equiv. to 6 equiv.), the yield of **3aa** was significantly increased to 85% yield (Table 1, entry 13). Although the requirement of excess amount of TBHP cannot be explained, similar need was reported in the literature.[32] The amount of I_2 employed can be lower (from 1.5 equiv. to 1.2 equiv.) providing **3aa** in comparable yield (87% yield) (Table 1, entry 14). The effects of oxidants, including 5.5 M TBHP in decane, di-*tert*-butyl peroxide (DTBP), 30% aqueous hydrogen peroxide, and benzoyl peroxide, were also examined, but the results obtained were less satisfactory.

With the optimized reaction conditions (Table 1, entry 14), the substrate scope and limitation of the reaction were evaluated. First, we sought to examine the scope of the reaction of *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline (**1a**) with various types of sulfonyl hydrazides under the established reaction conditions and the results are summarized in Scheme 2. Although benzenesulfonyl hydrazide delivered the product **3ab** in lower efficiency (53% yield), arenesulfonyl hydrazides bearing electronically different substituents on the phenyl ring (*p*-Cl, *p*-Br, *p*-NO_2, *m*-F) gave the corresponding 3-sulfonylindoles **3ac–af** in good to excellent yields (74–97% yields). 2,4-Dimethylbenzenesulfonyl hydrazide (**2g**) reacted with **1a** to yield **3ag** in low yield (11% yield), while **1a** was completely consumed, implying that the present reaction was significantly influenced by steric effect. Finally, methanesulfonyl hydrazide failed to provide the desired 3-sulfonylindole product.

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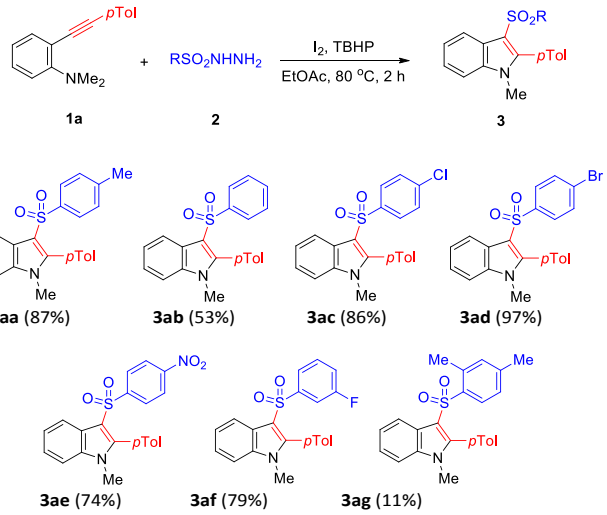
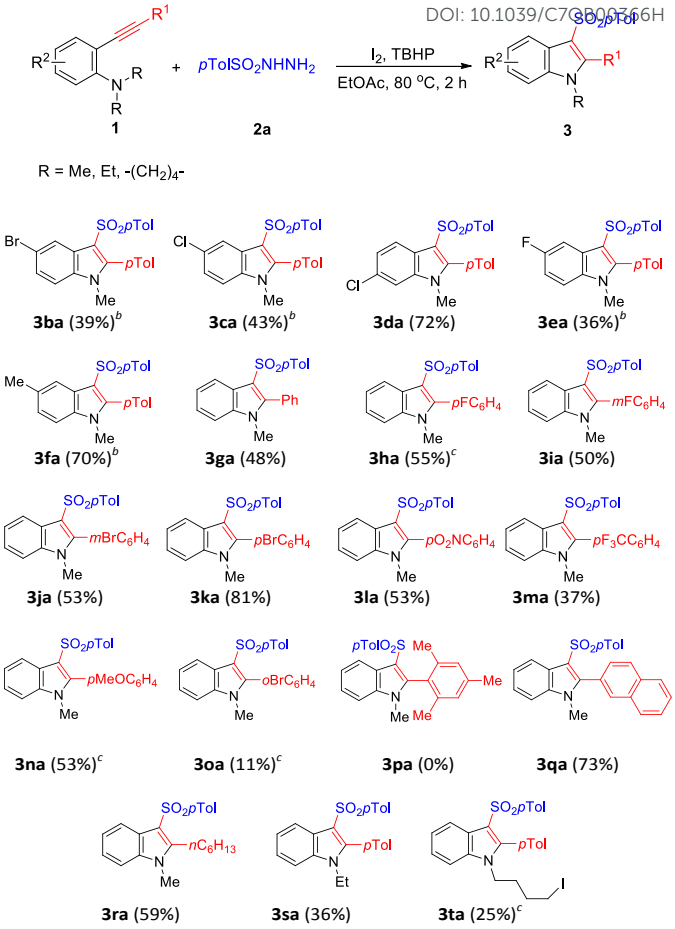


[a]Conditions: **1a** (0.25 mmol), **2** (5 equiv.), I_2 (1.2 equiv.), 70% TBHP in H_2O (6 equiv.) in EtOAc (2 mL) at 80 °C, open air, 2 h. In parentheses: isolated yields after chromatographic purification (SiO_2, column chromatography).

Scheme 2 Synthesis of 3-sulfonylindoles **3**: Scope of sulfonyl hydrazides **2**[a]

Next, the reactions between *p*-toluenesulfonyl hydrazide (**2a**) and various types of 2-alkynylanilines **1** were evaluated and the results are summarized in Scheme 3. First, various substituents (R^2) on the phenyl ring of 2-alkynylanilines were evaluated. The reaction proceeded smoothly to provide the corresponding 3-sulfonylindoles **3ba–fa** in moderate to good yields (36–72% yields). 2-Alkynylanilines **1** bearing a series of electronically different groups (*p*-F, *m*-F, *m*-Br, *p*-Br, *p*-NO_2, *p*-CF_3, *p*-OMe) on the phenyl ring of the arylethynyl moiety were well tolerated and yielded the corresponding 3-sulfonylindoles **3ga–na** in variable yields (37–81% yields). The influence of the steric effect was also emphasized and was found to disfavor the reactions. Thus, **3oa** was obtained in low yield (11% yield) and **3pa** was not observed. Other arylalkynyl group such as 2-naphthylethynyl also delivered the corresponding product **3qa** in good yield (73% yield). Gratifyingly, aliphatic alkynyl **1r** (R^1 = *n*-hexyl) readily reacted with **2a** to yielded **3ra** in 59% yield. In addition, *N*,*N*-diethyl-2-(*p*-tolylethynyl)aniline **1s** containing diethyl groups on the aniline nitrogen was also employed in this study. As expected, *N*-ethyl-3-sulfonylindole **3sa** was produced despite in low yield (36% yield). Finally, when 1-(2-(*p*-tolylethynyl)phenyl)pyrrolidine **1t** was used as a starting compound, **3ta** was isolated in 25% yield. This observation highlighted the involvement of iodide ion (I^-) in the mechanistic pathway leading to the obtained 2-sulfonylindoles **3**.



[a]Conditions: **1** (0.25 mmol), **2a** (5 equiv.), I_2 (1.2 equiv.), 70% TBHP in H_2O (6 equiv.) in EtOAc (2 mL) at 80 °C, open air, 2 h. [b]Reactions were carried out for 4 h. [c]Reactions were carried out for 6 h. In parentheses: isolated yields after chromatographic purification (SiO_2, column chromatography).

Scheme 3 Synthesis of 3-sulfonylindoles **3**: Scope of 2-alkynylanilines **1**[a]

Notably, sulfonyl hydrazides were extensively used as sulfenylating reagents as having been reported by several research groups.[27] However, to the best of our knowledge, the formation of 3-sulfanylindoles from the reaction of 2-alkynylanilines **1** and sulfonyl hydrazides **2** has not been explored so far. Therefore, the synthetic utility of the current protocol was further extended to the synthesis of *N*-alkyl-3-sulfanylindoles from 2-alkynyl-*N*,*N*-dialkylanilines. To our delight, when **1a** (0.25 mmol) was treated with **2a** (3 equiv.) in the presence of molecular iodine (I_2, 1.1 equiv.), without the addition of TBHP in EtOAc at 80 °C for 2 h, the expected 3-sulfanylindole **4aa** was isolated in 94% yield (Scheme 4). Our initial result has proved that the present protocol was a facile and convenient route to access 3-sulfanylindoles **4**.

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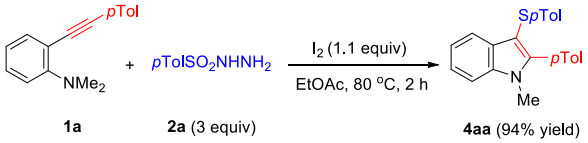
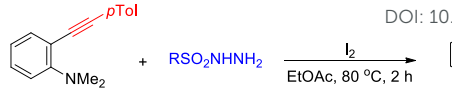


1a **2a** (3 equiv) **4aa** (94% yield)

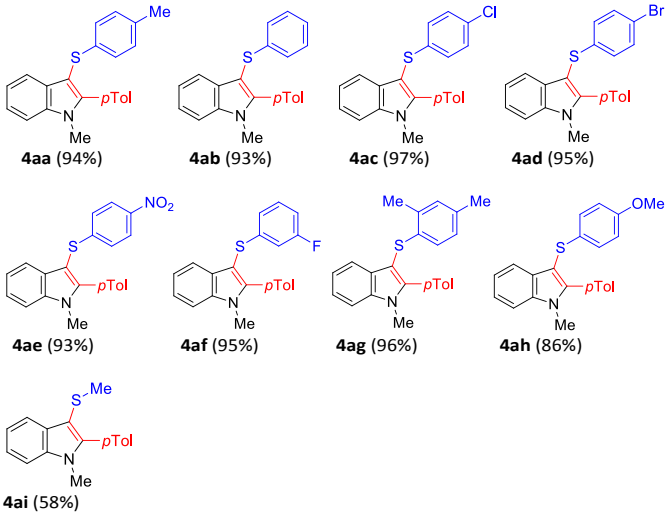
Scheme 4 Synthesis of 3-sulfanylindoles **4**

Having the optimized reaction conditions in hand (Scheme 4), we next demonstrated the generality of the present protocol by exploring the scope of sulfonyl hydrazides **2** and 2-alkynylanilines **1** as shown in Schemes 5 and 6, respectively. The results suggested that the reaction can accommodate a variety of 2-alkynylanilines **1** and sulfonyl hydrazides **2** under the optimal reaction conditions. Initially, a collection of sulfonyl hydrazides **2** were explored (Scheme 5). Arenesulfonyl hydrazides **2** bearing electronically different substituents on the phenyl ring smoothly reacted with *N*,*N*-dimethyl-2-(*p*-tolylethynyl)aniline (**1a**), producing the corresponding 3-sulfanylindoles **4aa–ah** in excellent yields (83–97% yields). Pleasingly, methanesulfonyl hydrazide also reacted readily to yield **4ai** in moderate yield (58% yield).

Subsequently, the reactions between a variety of 2-alkynylanilines **1** and *p*-toluenesulfonyl hydrazide (**2a**) were explored under the standard reaction conditions (Scheme 4) and the results are summarized in Scheme 6. To our delight, a range of substituents (R^2) on the phenyl ring of 2-alkynylanilines, including Br, Cl, F, Me, tolerated well and delivered the corresponding products **4ba–fa** in excellent yields (90–98% yields). Similarly, 2-alkynylanilines **1** bearing various electronically different groups on the phenyl ring of the arylethynyl moiety, including *p*-F, *m*-F, *m*-Br, *p*-Br, *p*-NO_2, *p*-CF_3, *p*-OMe, also underwent the reaction smoothly to yield the corresponding products in decent yields (>90% yields). Notably, the substituents on the phenyl ring of the arylethynyl moiety exhibited a significant electronic effect. Moderate yield (43% yield) of **4la** was observed when *N*,*N*-dimethyl-2-((4-nitrophenyl)ethynyl)aniline (**1l**) was employed as a starting compound. In contrast to the respective sulfonylation previously discussed in this work (Scheme 3), it turned out that the sulfenylation is not particularly sensitive to steric effect. The reactions of 2-((2-bromophenyl)ethynyl)-*N*,*N*-dimethylaniline (**1o**), 2-(mesitylethynyl)-*N*,*N*-dimethylaniline (**1p**) and 2-((2,3-dimethoxyphenyl)ethynyl)-*N*,*N*-dimethylaniline (**1u**) produced the corresponding 3-sulfanylindoles **4oa**, **4pa**, and **4ua** in high yields. These observations suggested that the present method tolerated well towards the electronically and sterically demanding substitution patterns on the phenyl rings of the aniline and arylethynyl moieties. Again, *N*,*N*-dimethyl-2-(naphthalen-2-ylethynyl)aniline (**1q**) and *N*,*N*-dimethyl-2-(oct-1-yn-1-yl)aniline (**1r**) also accommodated well under the reaction conditions, leading to the respective products **4qa** and **4ra** in 92% and 46% yields, respectively. The substituents on the aniline nitrogen were also varied; *N*,*N*-diethyl-2-(*p*-tolylethynyl)aniline **1s** gave **4sa** in 96% yield. Finally, **4ta** was obtained in 70% yield when 1-(2-(*p*-tolylethynyl)phenyl)pyrrolidine **1t** was used as a starting compound, implying the role of iodide ion (I^-) in the mechanistic pathway.



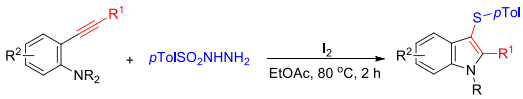
1a **2** **4**



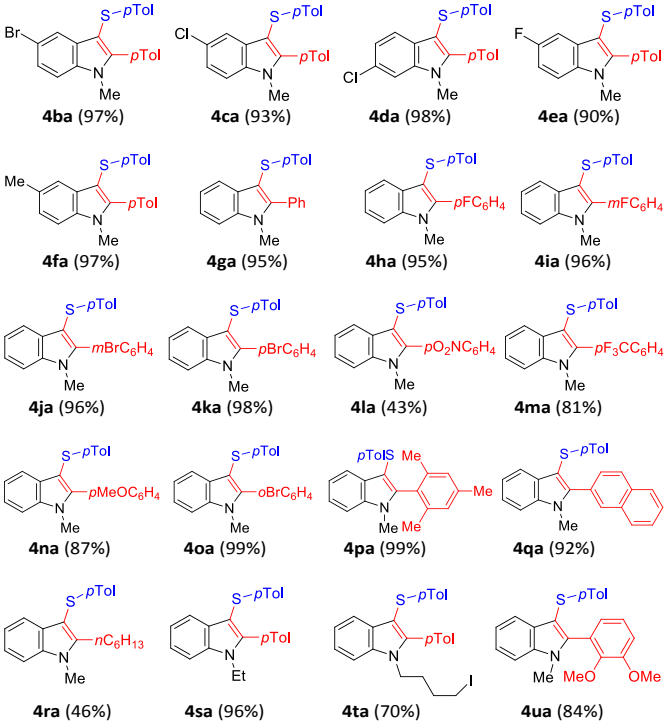
4aa (94%) **4ab** (93%) **4ac** (97%) **4ad** (95%)
4ae (93%) **4af** (95%) **4ag** (96%) **4ah** (86%)
4ai (58%)

[a]Conditions: **1a** (0.25 mmol), **2** (3 equiv.), I_2 (1.1 equiv.) in EtOAc (2 mL) at 80 °C, open air, 2 h. In parentheses: isolated yields after chromatographic purification (SiO_2, column chromatography).

Scheme 5 Synthesis of 3-sulfanylindoles **4**: Scope of sulfonyl hydrazides **2**[a]



1 **2a** **4**

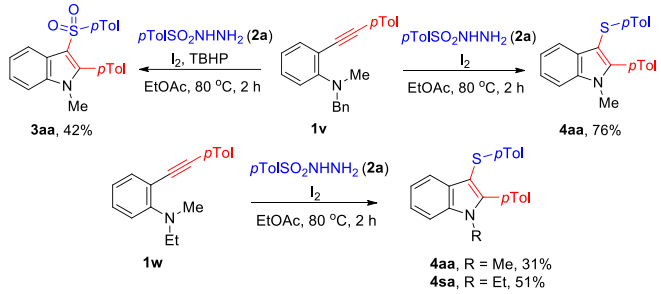


4ba (97%) **4ca** (93%) **4da** (98%) **4ea** (90%)
4fa (97%) **4ga** (95%) **4ha** (95%) **4ia** (96%)
4ja (96%) **4ka** (98%) **4la** (43%) **4ma** (81%)
4na (87%) **4oa** (99%) **4pa** (99%) **4qa** (92%)
4ra (46%) **4sa** (96%) **4ta** (70%) **4ua** (84%)

[a]Conditions: **1** (0.25 mmol), **2a** (3 equiv), I_2 (1.1 equiv) in EtOAc (2 mL) at 80 °C, open air, 2 h. In parentheses: isolated yields after chromatographic purification (SiO_2, column chromatography).

Scheme 6 Synthesis of 3-sulfanylindoles **4**: Scope of 2-alkynylanilines **1**[a]

Finally, substrates **1** bearing different alkyl groups at the nitrogen atom were also investigated (Scheme 7). *N*-Benzyl-*N*-methyl-2-(*p*-tolylethynyl)aniline (**1v**) was employed to synthesize 3-sulfonylindoles and 3-sulfanylindoles under the standard reaction conditions. To our delight, the dealkylation step took place chemoselectively at the benzyl group to yield **3aa** and **4aa** in 42% and 76% yields, respectively. Unfortunately, an inseparable mixture of products **4aa** and **4sa** was obtained when *N*-ethyl-*N*-methyl-2-(*p*-tolylethynyl)aniline (**1w**) was used as a starting material. ^{1}H-NMR integration revealed that **4aa** (R = Me) and **4sa** (R = Et) were obtained in 31% and 51% yields, respectively. This observation suggested that dealkylation preferably took place at the less steric site.



Scheme 7 Effect of the alkyl groups on dealkylation Step

To verify the reaction mechanisms, several control experiments were conducted (Scheme 8). First, to understand the role of molecular iodine, the reaction was carried out in the absence of I_2. Neither 3-sulfonylindole **3aa** nor 3-sulfanylindole **4aa** was obtained when molecular iodine (I_2) was excluded from the reaction [Scheme 8 (a)]. This outcome emphasized the important role of molecular iodine. Next, to validate that the sulfonylation reaction undergoes through the radical cascade process, the radical trapping experiments were also conducted by employing TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl) and BHT (2,6-di-tert-butyl-4-methylphenol) as radical scavengers. The reactions of **1a** and **2a** with I_2, TBHP in EtOAc at 80 °C for 2 h were suppressed when TEMPO or BHT was added in the reaction [Scheme 8 (b)]. The observed results implied that the sulfonylation process is likely to involve a radical pathway. Noteworthy, sulfonyl hydrazides have been widely used as sulfonyl radical precursors mediated by molecular iodine and TBHP.[26c,h,n] Additionally, the reactions of **1a** with freshly prepared *p*-toluenesulfonyl iodide under the standard reaction conditions (Table 1, entry 14 and Scheme 4) were examined [Scheme 8 (c)]. No desired product **3aa** or **4aa** was produced, attesting that sulfonyl iodide is unlikely an intermediate in the present reactions.

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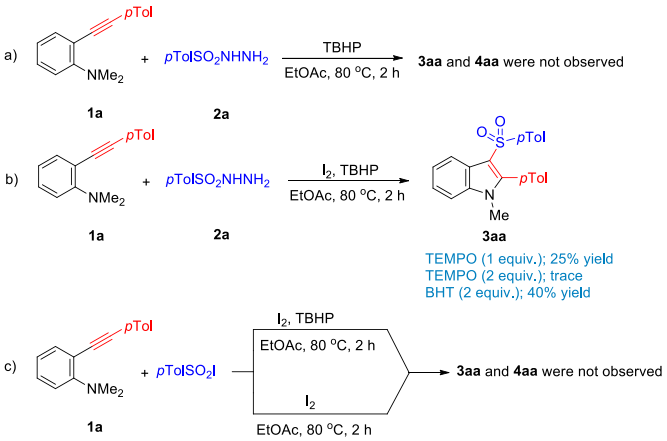
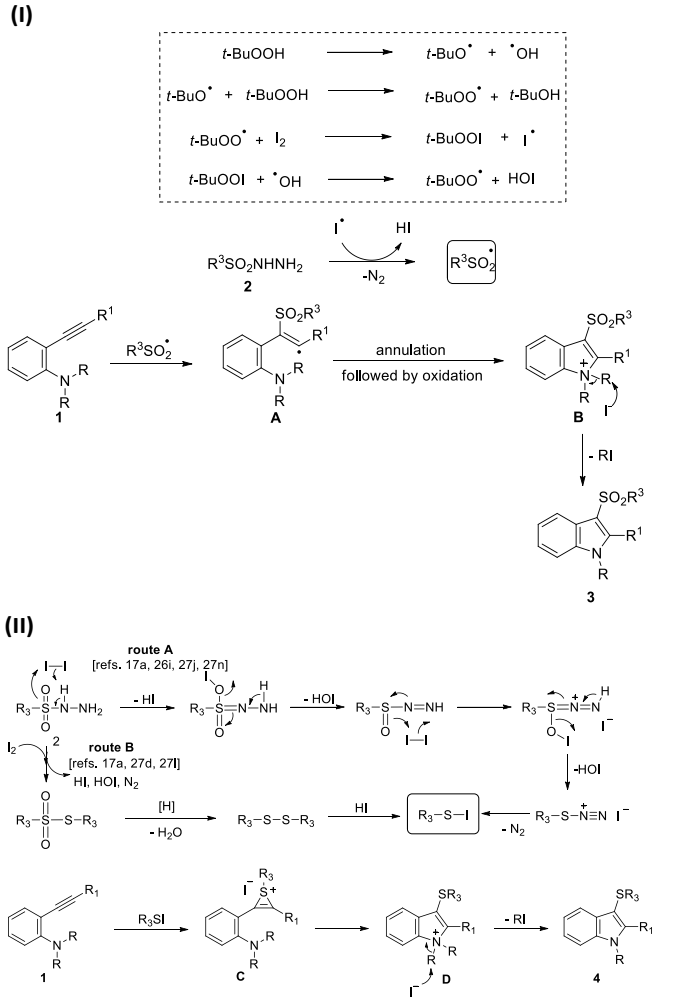


Scheme 8 Control experiments

On the basis of the above-mentioned control experiments and the reported literature,[17,23,26-27] we propose plausible reaction mechanisms as shown in Scheme 9. For the formation of *N*-alkyl-3-sulfonylindoles, a mechanism that involved a sulfonyl radical was proposed [Scheme 9 (I)]. It is well known that TBHP is thermally unstable and decomposes to the *tert*-butoxyl and *tert*-butylperoxy radicals. The reaction of these two radicals with iodine and sulfonyl hydrazide **2** produces sulfonyl radical *in situ* through the elimination of nitrogen gas. Next, the resulting sulfonyl radical then regioselectively adds to the alkynyl moiety of 2-alkynyl-*N*,*N*-dialkylaniline **1** to produce vinyl radical intermediate **A**. Subsequent cascade annulation followed by oxidation gives indolium intermediate **B** which upon dealkylation with the aid of iodide ion nucleophile to finally produce the 3-sulfonylindole product **3**.

The sulfenylation reaction begins with the reaction of sulfonyl hydrazide **2** with iodine to yield sulfenyl iodide (R^3SI), possibly through two pathways (route A[17a,26i,27j,27n] and route B[17a,27d,27l]) [Scheme 9 (II)]. Electrophilic addition of which to the alkynyl moiety of 2-alkynyl-*N*,*N*-dialkylaniline **1** gives thiirenium ion intermediate **C**.[23] Subsequent nucleophilic attack by the nitrogen nucleophile of the aniline moiety leading to indolium intermediate **D**, followed by removal of the alkyl group by iodide ion to furnish the indole ring construction.



Scheme 9 Proposed mechanism for formation of *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles

Conclusions

In conclusion, we presented metal-free and convenient iodine-promoted cascade cyclization reactions for the synthesis of the *N*-alkyl-3-sulfonylindoles and *N*-alkyl-3-sulfanylindoles from the reaction of 2-alkynyl-*N*,*N*-dialkylaniline derivatives with sulfonyl hydrazides. The reaction involves tandem C–S and C–N bonds formation followed by dealkylation. Given that various structurally different substrates can be employed for this cascade cyclization reaction, the present protocol provided a general approach to 3-sulfonylindole and 3-sulfanylindole frameworks of significance in synthetic and medicinal chemistry. Further exploration for the novel cascade sulfonylation cyclization is ongoing in our laboratory.

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