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Selective sulfonylation and diazotization of indoles†

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A metal-free synthesis of bifunctionalized indole derivatives was developed through a novel TBHP/TBAI-mediated oxidative coupling of C2,C3-unsubstituted indoles with arylsulfonyl hydrazide. Under the same conditions C3-methyl substituted indoles underwent a diazotization process, affording 2-sulfonyldiazenyl-1*H*-indoles. The former reaction simultaneously established C–S and C–N bonds through selective sulfonylation and diazotization of the indole framework, enabling a mild and practical access to polyfunctionalized indoles with good to excellent yields.

The indole skeleton is widespread in a myriad of natural products,[1] and has been considered as a "privileged structure" in a large family of medicinally relevant compounds due to its special chemical and biological properties.[2] Of particular interest, synthetic 3-arylsulfonyl-1*H*-indoles have served as valid HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)[3] (Fig. 1, type I) and 5-HT6 receptor ligands (Fig. 1, type II) useful in the treatment of CNS disorders (schizophrenia, depression, and Alzheimer's disease).[4] In view of their biological significance, many efforts have been devoted to efficient synthetic approaches toward 3-arylsulfonyl-1*H*-indole derivatives. A survey of the literature shows that three general strategies have been developed, including the direct C3-arylsulfonylation of indoles,[5] indole annulation of suitable acyclic precursors,[6] and the oxidation of the corresponding sulfide with diverse oxidants such as *m*-CPBA,[7] oxone,[8] and $KMnO_4/MnO_2$.[9] However, the majority of these methods involve either multistep sequences,[6c,g,7b] metal catalysts,[5a–e,6a–f] drastic conditions,[5d,6a–c] lengthy reaction times[6c,d] or laborious workup.[6a–c,7–9] Therefore, the development of a versatile, efficient and selective access to 3-arylsulfonyl-1*H*-indoles from simple and readily available starting materials is highly valuable.

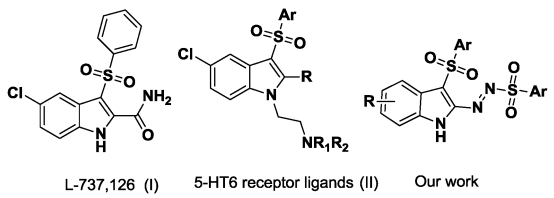
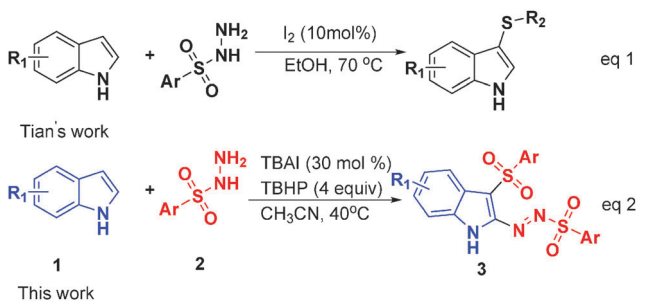


Fig. 1 Biologically active sulfonylated indoles.

Recently, Tian and co-workers have reported an iodine-catalyzed reaction between indoles and sulfonyl hydrazides affording structurally diverse indole thioethers though sulfenylation (Scheme 1, eqn (1)).[10] Enlightened by this interesting reaction and our recent findings on oxidative coupling reactions,[11,12] we assumed that the reaction of indoles with sulfonyl hydrazides would proceed in another direction to form 3-arylsulfonyl-1*H*-indole derivatives using tetrabutylammonium iodide (TBAI) and *tert*-butyl hydroperoxide (TBHP),[13] based on the fact that TBAI/TBHP-mediated sulfonylation *via* sulfonyl radicals generated *in situ* from sulfonyl hydrazides is well established.[14] Unexpectedly, in this reaction sulfonyl hydrazides play a dual role as both a sulfonyl precursor and a sulfonyl azo source, allowing regioselective formation of a series of novel 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indoles in one step without isolating or purifying any



Scheme 1 Coupling reaction of indoles with sulfonyl hydrazides.

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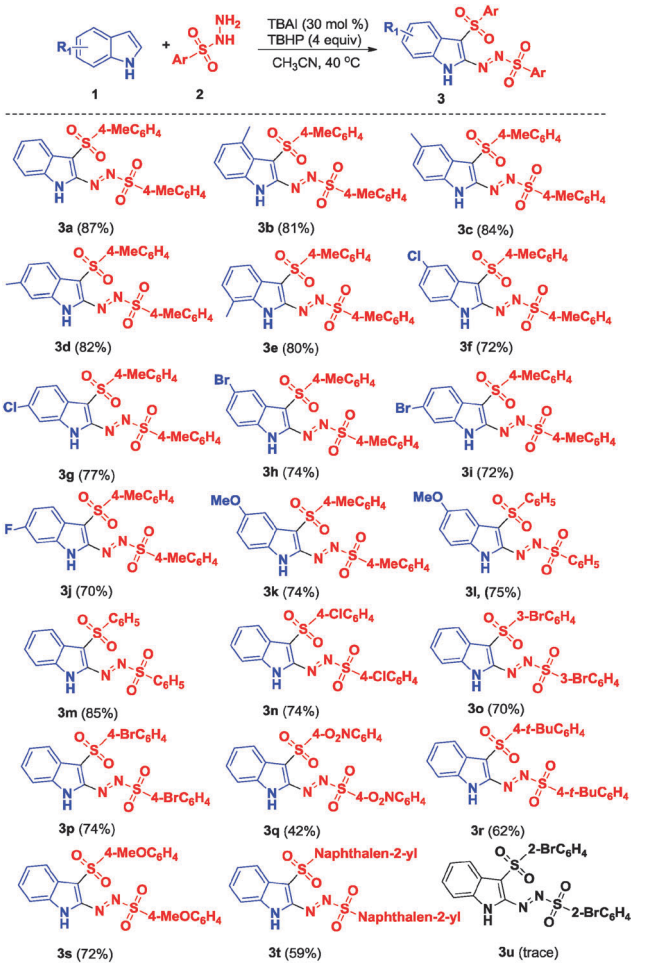
intermediates (Scheme 1, eqn (2)). Herein, we report this interesting and challenging discovery.

We started our investigation with the optimization of the oxidative coupling reaction using indole (**1a**) with *p*-toluenesulfonyl hydrazide (**2a**) in 1/2.2 mol ratio as model substrates. The above model reaction was conducted to investigate the impact of various reaction conditions on the reaction outcome, including solvents, temperatures, catalysts and oxidants. The results are listed in Table S1, ESI.† Initially, the reaction of **1a** with **2a** was performed in CH_3CN at room temperature utilizing TBHP (70% in water) as the oxidant and 30 mol% of TBAI as the catalyst. An unexpected product, **3a**, was obtained in 81% yield (Table S1, entry 1, see ESI).† Next, different solvents, such as DMSO, EtOH, MeOH, 1,2-dichloroethane (DCE) and toluene, were examined under identical conditions (Table S1, entries 2–6, ESI†). It was found that the reaction did not proceed at all and the starting materials remained completely unconsumed in DMSO (Table S1, entry 2, ESI†). Attempts to employ other solvents including EtOH, MeOH, DCE, and toluene were less effective (Table S1, entries 3–6, ESI†). An increase in reaction temperature to 40 °C delivered a higher yield of **3a** (Table S1, entry 7, ESI†); however, a higher reaction temperature (60 °C) decreased the chemical yield (Table S1, entry 8, ESI†). The effect of different amounts of TBAI was then evaluated. With substrates **1a** and **2a**, the reaction gave a lower yield of **3a** in the presence of 10 mol% of TBAI (Table S1, entry 7, ESI†). Using 50 mol% of TBAI did not improve the yield of **3a** (Table S1, entry 10, ESI†). After this, we tuned other reaction parameters such as the catalyst and the oxidant. Replacing TBAI with iodine resulted in a slightly lower yield of **3a** whereas Cu-catalysts did not promote the reaction process. Without TBAI, no product **3a** was observed. Finally, various oxidants were screened, such as benzoyl peroxide (BPO), *tert*-butyl peroxybenzoate (TBPB), H_2O_2, di-*tert*-butyl peroxide (DTBP) and *m*-chloroperoxybenzoic acid (*m*-CPBA). The use of H_2O_2 resulted in an 80% yield. Other oxidants gave unsatisfactory results (42–67% yield).

Once the feasibility of the proposed pathway had been validated, we subsequently examined its scope by using various readily available indoles and arylsulfonyl hydrazides through selective C3-sulfonylation and C2-diazotization of the indole ring. As shown in Scheme 2, substituents on different positions of the indole ring did not hamper the reaction process. A broad spectrum of substituted indoles containing both electron-donating and electron-withdrawing groups were successfully transformed into the corresponding 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indoles **3a–k** in good to excellent yields. Notably, halogen-containing indoles could be employed and were tolerated well under the optimal reaction conditions, furnishing the desired products in excellent yields, which offers possibilities for further functionalizations by modern coupling methods. After the successful utilization of different substituted indoles, we next extended our study to a variety of arylsulfonyl hydrazides with different functional groups such as chloro, bromo, *tert*-butyl and methoxy on the phenyl ring. Arylsulfonyl hydrazides bearing electron-donating, electron-neutral and electron-withdrawing groups showed high reactivity and gave high yields (Scheme 2). As per our expectation, the extended 2-naphthylsulfonyl hydrazide was also shown to be

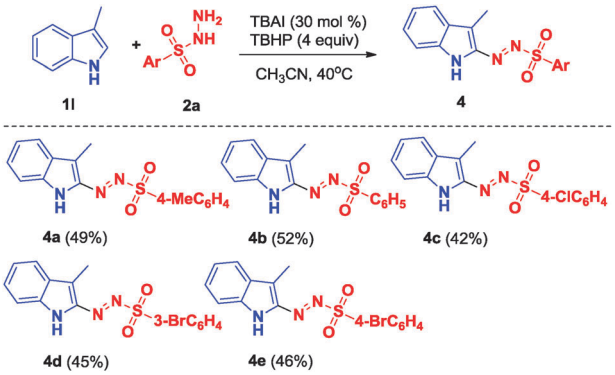


Scheme 2 Substrate scope for synthesis of **3**.

an effective substrate, resulting in a good yield of the product. However, when the more strongly electron-withdrawing nitro group was installed, the reaction became slightly sluggish and provided **3q** in 42% yield. Unfortunately, *ortho*-substituted arylsulfonylhydrazides such as 2-bromobenzenesulfonohydrazide did not work in the reaction. In general, these domino coupling reactions provide new examples for synthesizing richly decorated indoles, which are widespread structural cores in a large number of bioactive compounds.

After successfully synthesizing 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indoles **3**, we attempted to further evaluate the reaction scope using 3-methyl-1*H*-indole (**1l**) as an indole component under the same conditions (Scheme 3). The reaction proceeded smoothly, affording 2-sulfonyldiazenyl-1*H*-indoles in moderate yields. The sulfonylated products were not generated in these reactions, which suggested that the sulfonylation reaction did not take place as the C3 position of the indole ring was occupied by a methyl group. A set of arylsulfonyl hydrazides with diverse substituents, such as methyl, chloro and bromo groups, were well tolerated in this oxidative reaction.

After the formation of polyfunctionalized indoles **3** and **4**, we made efforts to explore the potential applications of **3**. The reaction between 3-tosyl-2-(tosyldiazenyl)-1*H*-indole (**3a**) and diethyl acetylenedicarboxylate was carried out in the presence

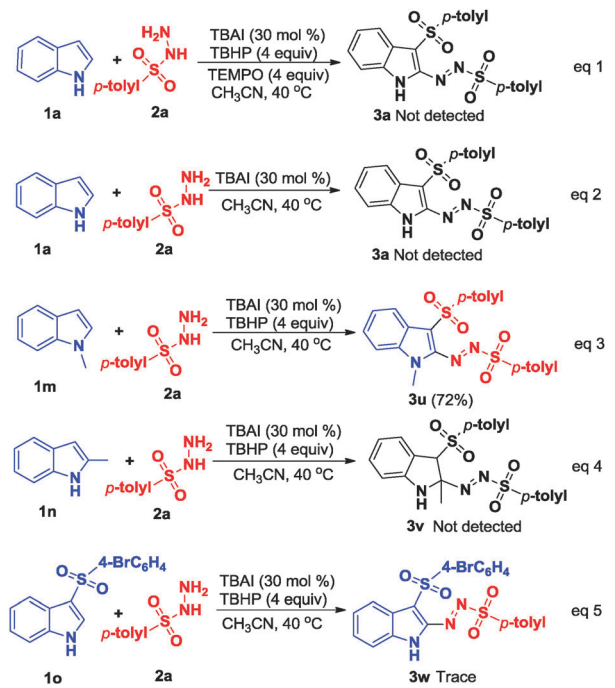


Scheme 3 Substrate scope for synthesis of **4**.

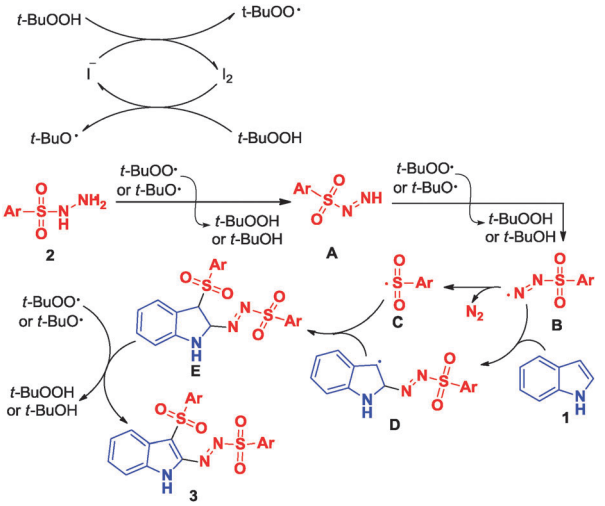
of Et_3N in EtOH at room temperature, affording tricyclic imidazo-[1,2-*a*]indole-2,3-dicarboxylate **5** in 47% yield (Scheme S4, see ESI†). The 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indole **3a** was converted into 4-methyl-*N*′-(3-tosyl-1*H*-indol-2-yl)benzenesulfonohydrazide **6** in 93% yield by hydrogenation using active zinc powder and ammonium (Scheme S4, see ESI†).[16]

Although functionalized indoles **3** and **4** were fully characterized by NMR spectroscopy and HRMS, their structures were determined by X-ray diffraction of compounds **3a** and **4b** (see ESI†).

To explore the reaction mechanism for this transformation, some control experiments were conducted (Scheme 4). When the reaction mixture of **1a** with 2.2 equivalents of **2a** and TBHP (4.0 equiv.) was treated using the radical scavenger TEMPO (4 equiv.), the reaction did not give the product **3a**, indicating the possibility of a radical mechanism (eqn (1)). To provide further support for the radical pathway, the reaction was carried



Scheme 4 Control experiments.



Scheme 5 Proposed mechanism for formation of products **3**.

out without the use of aq. TBHP. The desired product **3a** was not observed (eqn (2)). This suggested that TBAI is insufficient to form the radical and the radical initiator TBHP plays a pivotal role in this transformation. To further confirm the effect of *N*-substituents of indole on the reaction process, 1-methylindole was subjected to the reaction with **2a**, transforming readily into the corresponding functional indole **3u** (eqn (3)), which indicated that both free and *N*-substituted indoles were suitable for this protocol. However, 2-methylindole did not undergo this reaction (eqn (4)). Finally, to further probe the sulfonylation sequence, the reaction of 3-((4-bromophenyl)sulfonyl)-1*H*-indole[15] and **2a** generated a trace amount of 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indoles **3w** (eqn (5)). We therefore reasoned that the diazotization occurred prior to the sulfonylation step.

On the basis of literature reports and taking our experimental outcomes into consideration, a tentative mechanism for the formation of products **3** is outlined in Scheme 5. Initially, *tert*-butoxyl and *tert*-butylperoxy radicals are generated from the decomposition of TBHP in an I^- catalytic system.[17] Then, sequential H-abstraction of sulfonylhydrazides by the resultant radicals yields arylsulfonyldiazene radicals **B**, followed by reaction with indoles to afford indole radicals **D**.[18] The intermediates **D** are trapped by sulfonyl radical **C** generated *in situ* from **B** under the oxidative conditions with the release of molecular nitrogen,[19] producing substituted indolines **E**. The final 3-sulfonyl-2-sulfonyldiazenyl-1*H*-indoles are obtained through H-abstraction by *tert*-butoxyl radical or *tert*-butylperoxy radical.

In conclusion, we have developed a facile, selective sulfonylation and diazotization of C2,C3-unsubstituted indoles, providing a straightforward and metal-free protocol for the unprecedented synthesis of bifunctionalized indole derivatives through TBAI/TBHP-mediated oxidative reactions. Moreover, under the same conditions 3-methylindole underwent a diazotization process, affording 2-sulfonyldiazenyl-1*H*-indoles. This convergent and versatile approach presents broad substrate scope, reliable scalability and excellent functionality tolerance, allowing the rapid construction of highly functionalized indoles with the use

of readily available starting materials. Further efforts focusing on uncovering the mechanism of these transformations and evaluating the biological activity of the products are in progress.

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