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Synthesis of arylsulfonyl-substituted indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives *via* a TBAI-catalyzed radical cascade cyclization

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ABSTRACT

We have developed a metal-free radical cascade reaction of *N*-substituted 2-aryl indoles with readily available sulfonyl hydrazides for the rapid construction of arylsulfonyl-substituted indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives. With the TBAI–TBHP catalytic system, a broad series of structurally diverse indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives were obtained in moderate to excellent yields. The reaction features mild reaction conditions, operationally easiness, scaled-up feasibility, and high functional-group-tolerance.

Nitrogen-containing heterocycles, particularly fused-indole derivatives, are prevalent in numerous biologically significant natural products and pharmaceuticals [1-3]. As an important species of fused-indole derivatives, indolo[2,1-*a*]isoquinolines with a fused tetracyclic core structure have drawn considerable attention due to their wide existence in bioactive compounds (Fig. 1) [4-12]. For example, the indolo[2,1-*a*]isoquinoline derivatives **C-E** can act as an inhibitor of tubulin polymerization and estrogen receptor [7-11] and a melatonin antagonist [12], respectively. As a consequence, considerable efforts have been devoted to the construction of this type of polycyclic skeleton [13-21]. As for the assembly of indolo[2,1-*a*]isoquinolin-6(5*H*)-ones, several elegant works have been reported in the past few years [22-33]. For instance, in 2015, Nevado and coworkers developed a one-pot synthesis of CF_3-, SCF_3-, $Ph_2(O)P$-, N_3-containing indolo[2,1-*a*]isoquinolin-6(5*H*)-ones *via* a radical tandem reaction [25]. Subsequently, various functionalized indolo[2,1-*a*]isoquinolin-6(5*H*)-ones were successfully obtained with Fe(II)/(III) [26,27], Pd(II) [28,29], or Mn(III) [30,31] as a catalyst, or Ir(III) [32] as a photocatalyst. Despite all these achievements, the vast majority of the reported reactions are mediated by metal catalysts [24], which might limit their further synthetic applications. Therefore, development of a metal-free approach for the preparation of indolo[2,1-*a*]isoquinolin-6(5*H*)-ones remains highly desirable.

Synthesis of sulfone-containing compounds is a hot topic in the fields of pharmaceutical chemistry and agrochemistry because of their unique anti-HIV, anticancer, and antibacterial bioactivities [33-36]. In addition, sulfones can serve as versatile building blocks in organic synthesis [37-41]. Over the past few decades, sulfonyl hydrazides have been widely utilized to install sulfonyl functional group into organic molecules [42-52]. Most importantly, they behave as a sulfonyl radical precursor to furnish sulfonyl-substituted heterocycles *via* sulfonyl radical-initiated addition/cyclization cascade reactions [53-62]. And a series of sulfonyl-substituted compounds, including oxindoles [53-56], isoquinoline-1,3(2*H*,4*H*)-diones [57,58], 3,4-dihydroquinolin-2(1*H*)-ones [59], disubstituted oxazoles [60], thioflavones [56,61] and quinoline-2,4(1*H*,3*H*)-diones [56,62] were successively synthesized from sulfonyl hydrazides involving a sulfonyl radical intermediate. As part of our continuing interest in pursuing new methodology for heterocycle compound synthesis [63-69], herein, we re-

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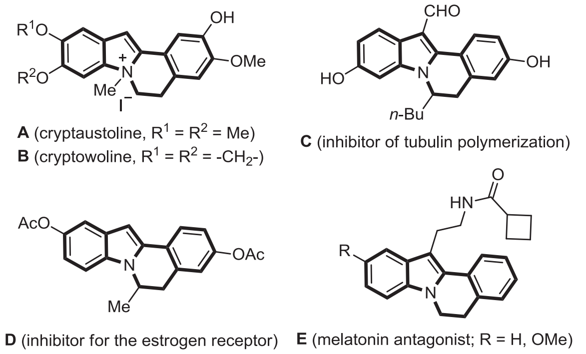
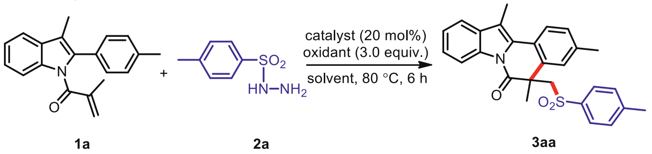


Fig. 1. Selected examples of indolo[2,1-*a*]isoquinolines.

Table 1
Screening of reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	TBAI	TBHP	CH_3CN	40
2	TBAI	TBHP	Acetone	26
3	TBAI	TBHP	Toluene	7
4	TBAI	TBHP	DMF	14
5	TBAI	TBHP	DMAc	19
6	TBAI	TBHP	1,4-Dioxane	16
7	TBAI	TBHP	THF	25
8	TBAI	TBHP	EtOH	61
9	TBAI	TBHP	MeOH	96
10	TBAI	TBHP	^{i}PrOH	41
11	KI	TBHP	MeOH	81
12	NaI	TBHP	MeOH	76
13	NH_4I	TBHP	MeOH	86
14	I_2	TBHP	MeOH	83
15	TBAI	BPO	MeOH	60
16	TBAI	TBPB	MeOH	69
17	TBAI	DTBP	MeOH	trace
18	TBAI	*tert*–butyl peroxyacetate	MeOH	55
19	TBAI	CHP	MeOH	81
20[c]	TBAI	TBHP	MeOH	66
21	/	TBHP	MeOH	trace
22	TBAI	/	MeOH	ND

ND = not detectable.

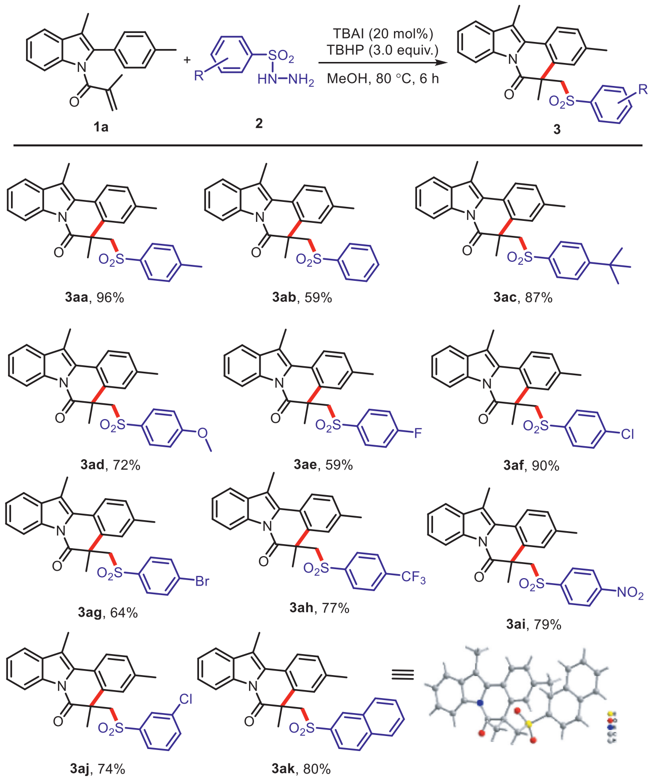
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), catalyst (20 mol%), oxidant (3.0 equiv.), solvent (1.5 mL), air, 80 °C, 6 h.

[b] NMR yield.

[c] TBHP (in decane).

port further application of readily accessible sulfonyl hydrazides to generating indolo[2,1-*a*]isoquinolin-6(5*H*)-ones with *N*-substituted 2-aryl indoles as starting materials under metal-free conditions, in which a sulfonyl group was introduced simultaneously. To the best of our knowledge, synthesis of arylsulfonyl-substituted indolo[2,1-*a*]isoquinolin-6(5*H*)-ones using sulfonyl hydrazides as free-radical precursors has never been reported.

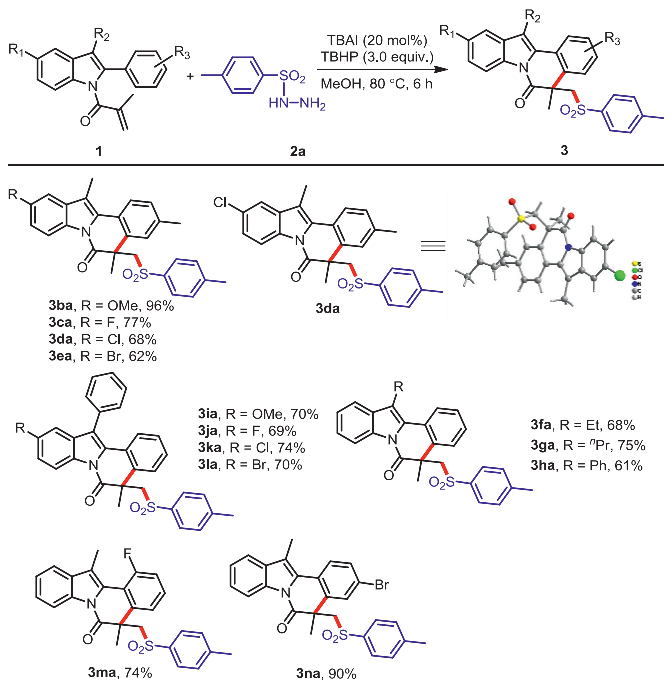
Our study commenced with the reaction between 2-methyl-1-(3-methyl-2-(*p*-tolyl)-1*H*-indol-1-yl)prop–2-en-1-one (**1a**) and tosylhydrazide (**2a**), using TBAI (20 mol%) as the catalyst and TBHP (70% solution in water, 3.0 equiv.) as the oxidant in CH_3CN under air at 80 °C for 6 h (Table 1, entry 1). Gratifyingly, the expected product, indolo[2,1-*a*]isoquinolin-6(5*H*)-one **3aa**, was obtained in 40% yield. Encouraged by the preliminary results, we next investigated other solvents such as acetone, toluene, DMF, DMAc, 1,4-dioxane, THF, EtOH, MeOH and ^{i}PrOH, revealing that MeOH was the best choice and afforded sulfone **3aa** in a yield of 96% (entries 2–10). Subsequently, several other iodine sources commonly used in radical-triggered reactions were evaluated, all of which showed slightly decreased catalytic activities compared with TBAI (entries 11–14). Therefore, TBAI was chosen for further investigations. Upon testing a series of other oxidants like benzoyl peroxide (BPO), *tert*–butyl peroxybenzoate (TBPB), di–*tert*-butylperoxide (DTBP), *tert*–butyl peroxyacetate, and cumyl hydroperoxide (CHP), TBHP was identified as the optimal one (entries 15–19). When TBHP (in decane) was used instead of TBHP (70% solution in water), the yield of **3aa** declined to 66% (entry 20). Ultimately, the control experiments showed that both TBAI and TBHP were essential for this radical cascade reaction (entries 21 and 22).



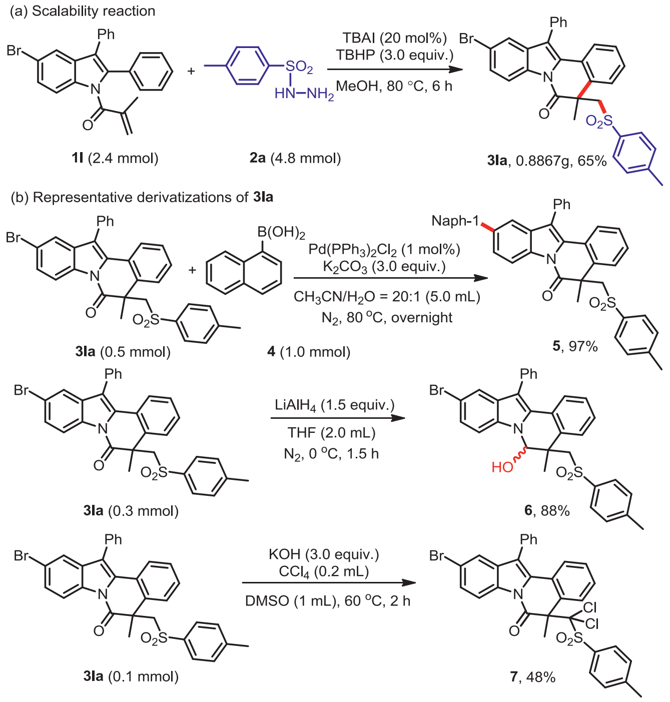
Scheme 1. Scope of the arylsulfonyl hydrazides. Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv.), TBAI (20 mol%), TBHP (3 equiv.), MeOH (3 mL), air, 80 °C, 6 h. Isolated yields.

With the optimized conditions established above (Table 1, entry 9), we explored the scope of arylsulfonyl hydrazides of this raection with *N*-methacryloyl-2-arylindole **1a** (Scheme 1). Satisfyingly, a series of sulfonyl hydrazides bearing an electron-neutral group (*e.g.*, H), an electron-donating group (*e.g.*, Me, ^{t}Bu, OMe), or an electron-withdrawing group (*e.g.*, F, Cl, Br, CF_3) at the *para* position of the aromatic ring were well tolerated, giving the desired products **3aa-3ah** in 59%–96% yields. Substrate carrying a strong electron-withdrawing group NO_2 on the benzene ring also proceeded smoothly, providing the product **3ai** in a comparable yield. Additionally, *meta*-Cl substituted substrate was compatible with this reaction and the yield of the corresponding product **3aj** was 74%. Notably, the 2-naphthalenyl (2-Np) counterpart was proven suitable for this transformation, affording indolo[2,1-*a*]isoquinolin-6(5*H*)-one **3ak** in 80% yield, whose structure was unambiguously confirmed by X-ray diffractional analysis (CCDC: 2059158).

Next, the scope of *N*-substituted 2-aryl indoles was examined for the reaction (Scheme 2). Substrates with a methoxyl, fluoro, chloro, or bromo group locating in the indole ring reacted smoothly with tosylhydrazide **2a**, delivering the desired indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives **3ba-3ea** in moder-



Scheme 2. Scope of the *N*-substituted 2-aryl indoles. Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv.), TBAI (20 mol%), TBHP (3.0 equiv.), MeOH (3.0 mL), air, 80 °C, 6 h. Isolated yields.



Scheme 3. Scalability experiment and representative derivatizations of **3la**.

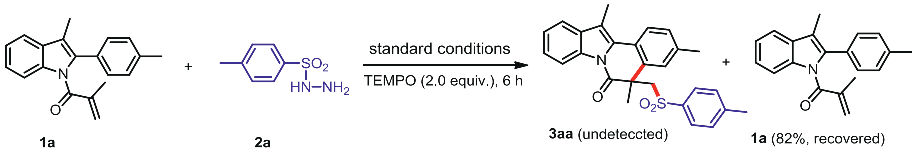
ate to excellent yields (62%–96%). And we confirmed the structure of **3da** by X-ray crystallography (CCDC: 2059157). When 2-aryl indoles containing an ethyl, *n*-propyl, or phenyl group at the C3 position of the indole ring were employed, the corresponding products **3fa-3ha** could be isolated in 61%–75% yields. As expected, 2-(4-methylphenyl)-3-phenyl-1*H*-indole derivatives bearing various functional groups (OMe, F, Cl and Br) in the C3-phenyl were also suitable to the reaction conditions, which could successfully be converted into sulfonated indolo[2,1-*a*]isoquinolin-6(5*H*)-ones **3ia-3la** in reasonable yields. Finally, other types of substrates, such as 1-(2-(2-fluorophenyl)-3-methyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1m**) and 1-(2-(4-bromophenyl)-3-methyl-1*H*-indol-1-yl)-2-methylprop-2-en-1-one (**1n**) also underwent the reaction to provide the target products **3ma** and **3na** in 74% and 90% yields, respectively.

To demonstrate the synthetic utility of this strategy, a scalability experiment was carried out under the standard conditions, in which a comparable yield (65%) of **3la** was observed (Scheme 3a). Furthermore, three notable transformations of **3la** were conducted (Scheme 3b). Specifically, Suzuki coupling of bromide **3la** with 1-naphthylboronic acid **4** afforded the desired product **5** in an excellent yield. In addition, when treated with 1.5 equiv. of $LiAlH_4$ in low temperature, **3la** could be easily reduced to aminal **6** in a good yield of 88%. Moreover, the synthetic utility of the sulfonated indolo[2,1-*a*]isoquinolin-6(5*H*)-one was exemplified by halogenation of **3la** with CCl_4 in the presense 3 equiv. of KOH to produce **7** in a moderate yield.

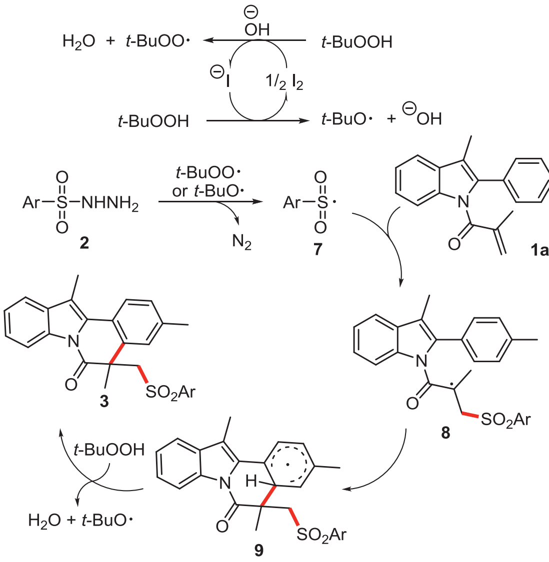
To confirm that the reaction was associated with a radical process, the radical quenching experiment was conducted as shown in Scheme 4. When the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) was added in the reaction system under the standard conditions, the cascade reaction was absolutely inhibited and the substrate **1a** was recovered in 82% yield, attesting that a radical process is really involved.

Based on the control experiments and the previous reports [53,57], a plausible mechanism for the present radical cascade reaction is proposed in Scheme 5. The reaction is likely to begin with the generation of radicals *t*-BuO$^•$ and *t*-BuOO$^•$ from TBHP through the transformation between I^- and I_2. Then, sulfonyl hydrazide **2** reacts with the resulting radicals (*t*-BuO$^•$ and/or *t*-BuOO$^•$) to produce the sulfonyl radical **7** by releasing N_2. Following that, addition of sulfonyl radical **7** to the C=C bond of **1a** leads to the formation of carbon radical intermediate **8**, which subsequently undergoes an intramolecular radical cyclization to afford intermediate **9**. Finally, hydrogen abstraction of intermediate **9** occurs in the presence of TBHP, giving sulfonated indolo[2,1-*a*]isoquinolin-6(5*H*)-one **3**.

In summary, we have developed an efficient TBAI/TBHP-mediated radical cascade reaction that provides a direct access to a broad range of sulfonated indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives from sulfonyl hydrazides with yields up to 96%. The reaction involves a sulfonyl radical intermediate generated by utilizing TBAI as the catalyst and TBHP as the oxidant. This novel protocol is characterized by metal-free conditions, easily accessible sulfonyl sources, simple operation, and broad functional group tolerance. The sulfonated indolo[2,1-*a*]isoquinolin-6(5*H*)-one derivatives



Scheme 4. Control experiment.



Scheme 5. Proposed mechanism.

should have potential applications in organic and medicinal chemistry.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in the manuscript entitled.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.06.081.

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