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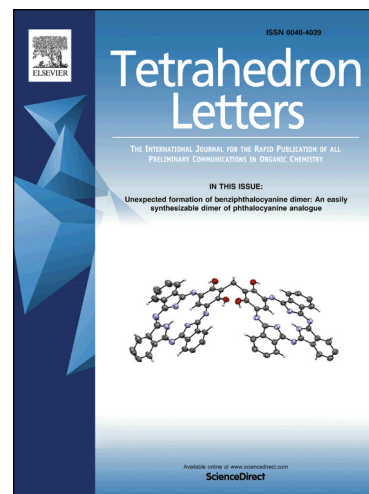
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TBAI-Mediated Regioselective Sulfenylation of Indoles with Sulfonyl Chlorides in One pot

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ABSTRACT

A versatile method for the synthesis of 3-sulfonylated indoles via TBAI promoted sulfenylation of indoles with sulfonyl chlorides in one pot has been presented. This system features highly regioselective, metal-free, easy operation, and shows a broad functional group tolerance leading to excellent yields. And this reaction could be easily conducted in 10 mmol scale with high effectivity. A plausible mechanism is proposed.

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Keywords:

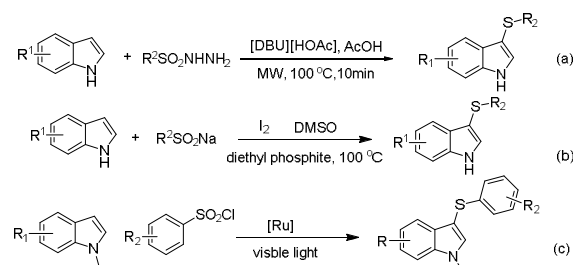
TBAI
Indoles
Sulfonyl chlorides
3-sulfonylated indoles

Introduction

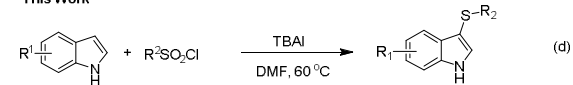
Substituted indoles are widespread in numerous natural products and are significant in medicinal chemistry.¹ Thiolated indole moieties represent a class of very important organosulfur heterocyclic compounds as they present in many important pharmacy and biology molecules.^{1a,1b,1c,1e,2,3} Therefore, considerable attention has been paid to developing strategies for the synthesis and chemical modification of indole-based heterocycles.⁴ In particular, 3-thiolated indoles have a broad range of bioactivities, and some serve as potent agents in the treatment of cancer and allergies.⁵ Many strategies have been developed for preparing the 3-arythiolation of indoles. At the start, low valent RSSR⁶ and RSH⁷ were used as the sulfur resources to react with indoles to prepare 3-thiolated indoles, however, there are some drawbacks such as using noble metal Pd as the catalyst and the substrate scope of RSH is limited. Subsequently, high valent RSO₂X (X= NHHN₂, ONa, Cl) were chosen to synthesize 3-thiolated indoles. For example, Barman's group developed a method to synthesize 3-sulfonylindoles promoted *via* a DBU-based ionic liquid from sulfonyl hydrazides and indoles under MW irradiation (Scheme 1a).⁸ Recent studies have shown that microwave could have some damage to human health,⁹ and not conducive to large-scale production. Subsequently, Deng's group described an iodine-catalyzed sulfenylation of free indoles with sodium sulfonates, the

reaction selectively afforded 3-arythioindoles in good to high yields under metal-free conditions, and sodium sulfonates are stable and easy to handle (Scheme 1b).¹⁰ Zheng's group developed a visible light-induced 3-sulfonylation of N-methylindoles with arylsulfonyl chlorides under mild condition (Scheme 1c),¹¹ which is mainly suitable for N-methylindoles, and the Ru complex is relatively expensive. Therefore, finding new methods to synthesize thioindoles is important and meaningful.

Previous Works



This Work




Scheme 1 Synthesis of 3-sulfonylindoles

Herein, we develop a new method for the synthesis of 3-thioindoles *via* TBAI promoted sulfonylation of indoles with sulfonyl chlorides in one pot, which features highly regioselective, metal-free, easy operation, mild conditions, and good functional group tolerance and could be easily conducted in 10 mmol scale with high effectivity (Scheme 1d). More importantly, sulfonyl chloride raw materials are cheap and easily available, and compared with the previous works, we can get an excellent yield (99%).

Results and discussion

Initially, we began our investigation with indole (**1a**) and p-toluenesulfonyl chloride (**2a**) as the model reaction (Table 1). The desired product 3-(p-tolylthio)-1H-indole (**3a**) was obtained in 42% yield under the conditions of (n-Bu)₄NI (1 equiv) and DMF (1 mL) in a sealed tube at 20 °C for 18 h (entry 1). Subsequently, a variety of temperatures were examined, and the results were shown in the table below. Based on the experiment above, we increased the temperature to 40 °C, the yield uprose to 59% (entry 2). Then, we increased the temperature from 40 °C to 60 °C, the yield was improved to 71% (entry 3). We continued elevating the temperature, the yield has not changed much (entry 4). So we indicated that the best choice of the reaction temperature was at 60 °C. Then, different amounts of (n-Bu)₄NI were examined, the results exposed that the optimal dosage of (n-Bu)₄NI was three equivalent (entries 5-7), and the yield could be increased to 99%. Meanwhile, we attempted to use other reagents, including NH₄I, KI, I₂, NIS, they gave products in unsatisfactory yields (entries 8-11). Then, different solvents were applied in the reaction, including CH₃CN, THF, Acetone, EtOAc, DMSO, DCE, and the

Table 1. Optimization of the Reaction Conditions^a



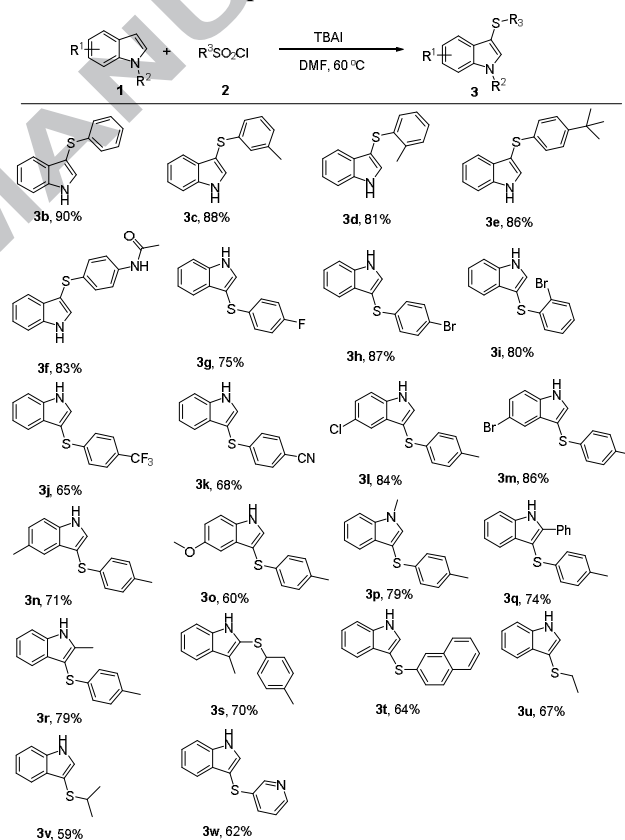
Entry	Reductant (equiv)	Solvent	Temp (°C)	Yield (%) ^b
1	(n-Bu) ₄ NI(1)	DMF	20	42
2	(n-Bu) ₄ NI(1)	DMF	40	59
3	(n-Bu) ₄ NI(1)	DMF	60	71
4	(n-Bu) ₄ NI(1)	DMF	80	70
5	(n-Bu) ₄ NI(0)	DMF	60	0
6	(n-Bu) ₄ NI(2)	DMF	60	80
7	(n-Bu) ₄ NI(3)	DMF	60	99
8	NH ₄ I(3)	DMF	60	88
9	KI(3)	DMF	60	56
10	I ₂ (3)	DMF	60	None
11	NIS(3)	DMF	60	None
12	(n-Bu) ₄ NI(3)	CH ₃ CN	60	69
13	(n-Bu) ₄ NI(3)	THF	60	60
14	(n-Bu) ₄ NI(3)	Acetone	60	74
15	(n-Bu) ₄ NI(3)	EtOAc	60	66
16	(n-Bu) ₄ NI(3)	DMSO	60	Trace
17	(n-Bu) ₄ NI(3)	DCE	60	10
18 ^c	(n-Bu) ₄ NI(3)	DMF	60	98
19 ^d	(n-Bu) ₄ NI(3)	DMF	60	98

^a Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), reductant (0.75 mmol), solvent (1 mL) in a sealed tube at 60 °C for 18 h. ^b Isolated yields based on **1a**. ^c Under N₂ atmosphere. ^d Under O₂ atmosphere.

experimental results indicated that DMF was the best choice (entries 12-17). In the end, we made a nitrogen protection experiment, the result exhibited that nitrogen had almost no effect on the reaction (entry 18). Similarly, oxygen also had no effect on the reaction (entry 19). Thus, the best conditions for this process comprised ratio (1a:2a=1:2) under air atmosphere in DMF (1ml) at 60 °C for 18h.

With the optimal conditions in hand, the different substrates indoles (**1**) and sulfonyl chloride compounds (**2**) were investigated (Table 2). We experimented all the reactions under standard conditions. First, we investigated aromatic sulfonyl chloride with different substituents, including -CH₃, -^tBu, -NHAc, -F, -Br, -CF₃ and -CN groups. The reaction tolerated both electron-donating and electron-withdrawing groups (**3a-3k**). Different positions on the phenyl ring have various effects on the yield of corresponding product. In general, the reaction activity of electron-donating groups is superior to electron-withdrawing groups, and the reaction activity of substituents at different positions is also different. The rank from strong to weak is para, meta, ortho. We can draw a parallel between **3a**, **3c**, **3d**; **3h-3i**, it may be caused by steric hindrance.

Table 2. Substrate Scope^{a, b}

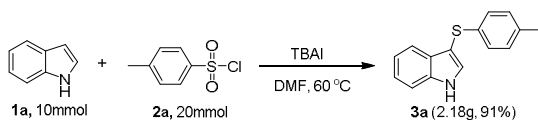


^a Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), TBAI (0.75 mmol), and DMF (1 mL) in sealed tube at 60 °C for 18 h. ^b Isolated yields.

To further explore the generality of this catalytic reaction, a wide range of indoles were then investigated (**3l-3s**). For example, indoles with electron-withdrawing substituents at the 5 position can be transformed smoothly into the desired products (**3l-3m**) in moderate to good yields under the optimal conditions. Unfortunately, when 5-nitroindole was conducted, we have not acquired what to be wanted. It may be caused by the powerful electronic effect of nitro group. Then, we used electron-donating

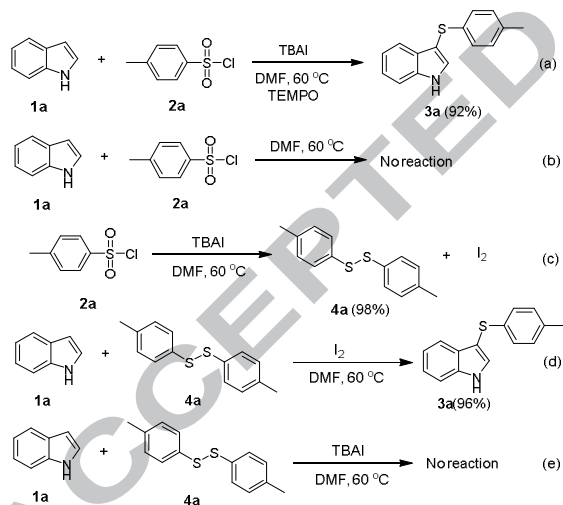
indole to conduct the experiments, the desirable product **3n** and **3o** were obtained. To be continued, we used *N*-methyl indole as the reaction substrate, and the product **3p** was obtained in 79% yield. It was noteworthy that indoles with substituents (Ph or Me) at the 2-position gave the desired products **3q** (74%) and **3r** (79%) smoothly, furthermore, we used 3-methyl indole as the reactant, we acquired the 2-thiolated indole (**3s**) with a good yield (70%).

We also explored the various sulfonyl chloride for the reaction, when naphthalenesulfonyl chloride was used for the reaction under standard condition, the product **3t** was attained in 64% yield. Then, we utilized ethanesulfonyl chloride and propanesulfonyl chloride to involve the reaction respectively, the products **3u** and **3v** were obtained in 67%, 59% yield individually. The yield of **3v** was lower than **3u**, it could engendered by steric effects. And then, we used pyridine-3-sulfonyl chloride to conduct the experiment, it also can obtain the desirable product **3w** with decent yield (62%). It can certify the reaction has a good substrate suitability.



Scheme 2 Large-scale synthesis of **3a**

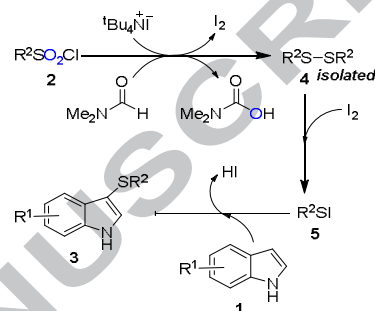
To demonstrate the reaction efficiency of this TBAI promoted thiolation reaction system, we tried to synthesis **3a** (Scheme 2) in large scale. The reaction of indole (**1a**, 10 mmol) and the *p*-Toluenesulfonyl chloride (**2a**, 20 mmol) gave the desired product **3a** in 91% yield under the optimal conditions. The method could be used to prepare precursors of some important bioactive molecules.



Scheme 3 Control experiments

During above reactions, we observed that the color of mixtures changed from light yellow to purple-black. So we speculated that the reaction involves the formation of iodine. Control experiments were carried out in order to elucidate the reaction mechanism (Scheme 3). When the radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2equiv) was employed under the optimal conditions, we could also get **3a** in 92% yield (Scheme 3a), which implies that the reaction was not a radical process. Then, in the absence of tetrabutylammonium iodide, we did not get the desired product **3a** (Scheme 3b). This

control experiment indicates that TBAI plays a crucial role in this reaction. Furthermore, in the absence of indole, the product 4-Methylphenyl disulfide (**4a**) was obtained in 96% yield under the optimized reaction conditions, meanwhile, iodide ion was oxidized into iodine (scheme 3c). **4a** was detached and structure confirmation by Nuclear magnetic resonance. So we can concluded that the disulfide compound was the reaction intermediate undoubtedly. In the presence of 1.5 equivalents iodine, indole (**1a**) smoothly reacted with 4-Methylphenyl disulfide (**4a**) to give the corresponding 3-(*p*-Tolylthio)-1H-indole (**3a**) in 98% yield (scheme 3d). next, we exchanged iodine for tetrabutylammonium iodide to participate the reaction, we did not obtain the product **3a** (scheme 3e).



Scheme 4 Possible mechanism.

On the basis of the above experimental results, a possible reaction mechanism was proposed in Scheme 4. Initially, disulfide compound **4** is generated from sulfonyl chloride **2** in the presence of reducing reagent TBAI and weak reducibility solvent DMF.¹² Then, disulfide compound **4** reacts with the preceding ferrous iodine to give the R^2SI **5**.¹³ Owing to the electronegativity of iodine is superior to sulphur, so we think the iodine indicates negative charge, the sulphur displays positive charge. In this hypothesis, the sulfonyl iodine is nucleophilic attacked by indole to generate the thioether (**3**), and the regenerate iodide reacts with sulfonyl chloride (**2**) to obtain disulfide compounds (**4**) once again. Thus repeatedly to promoted the reaction continually.

Conclusion

In conclusion, we have demonstrated an easy and efficient TBAI-promoted C(3)-H sulfenylation of free (N-H) indoles in one pot. In the presence of TBAI, the reactions performed well under mild conditions without reject of air and moisture, and generated highly regioselective indole thioethers in excellent yields. Additionally, a broad range of indoles and sulfonyl chlorides were tolerated in this method, and the method can be performed on a large scale without any problem. More significantly, compared with the traditional method of using disulfide as raw material, sulfonyl chloride raw materials are cheap and easily available. Further reaction mechanism and synthetic application studies are currently underway in our labs.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version

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Highlights:

Sulfonyl chloride was used as a sulphur source for the synthesis of 3-sulfonylated indole

Tetrabutylammonium iodide was found an effective reductant

This system features highly regioselective and shows a broad functional group tolerance leading to excellent yields

Large-scale reaction and the sequential reaction were demonstrated to show the practicality of the reaction.

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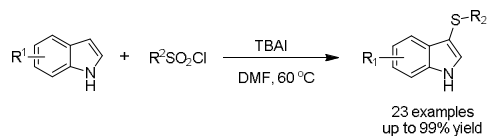
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