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ARTICLE TYPE

Catalyst-free thiolation of indoles with sulfonyl hydrazides for the synthesis of 3-sulfenylindoles in water

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A catalyst-free thiolation of indoles with sulfonyl hydrazides was efficiently developed in water under mild conditions without any ligand or additive. The reaction provided a variety of 3-sulfenylindoles with good to excellent yields and the by-products were only nitrogen and water.

Indroduction

The formation of C-S bonds represents a key step in the chemical synthesis because of their prevalence in many biologically active compounds and organic materials.[1] In the past decade, for constructing C-S bonds, the metal-catalyzed direct C-H activation, in which involved the use of the complexes and salts of palladium,[2] copper,[3] rhodium,[4] ruthenium,[5] and iron,[6] has become one of the traditional dominant methods (Figure 1a). However, with the desire of chemists to minimize synthetic steps and the amount of toxic waste in the construction of C-S bond, and, moreover, to find milder and more selective transformations, the concepts of green chemistry[7] have witnessed explosive developments in the past few years due to their advantages. As a consequence of the often green chemical character, usually these green and sustainable procedures involved various heterocatalysis,[8] metal-free catalysis[9] or catalyst-free synthesis.[10]

3-sulfenylindoles as one of the most common motifs based on the formation of C-S bonds, represent pharmaceutically and biologically important structures with their broad spectrum of biological and pharmaceutical activities, including anti-HIV activity, inhibitory activity against tubulin polymerization, anti-cancer activity, anti-obesity activity and so on.[11] With continued interest in the concepts of green chemistry, much effort has been devoted to the development of simple and general synthetic methods to access this structural moiety. Also, some significant improvements have been made in recent years. Of the many methods developed, the employment of iodine,[12] base, or nanoparticles for the tansformations to circumvent the need of the aforementioned transition-metal complexes and salts has remained one of the most widely adopted approaches (Figure 1b). For instance, in 2013, Tian et al. developed an iodine-catalyzed regioselective sulfenylation of indoles with sulfonyl hydrazides (Figure 1c).[13] Subsequently, base-promoted sulfenylation reactions to synthesize 3-sulfenylated indoles have been recently developed by Zhang[14] and Wen,[15] in which few examples of indoles were described with disulfides and thiols as the thiol source respectively.

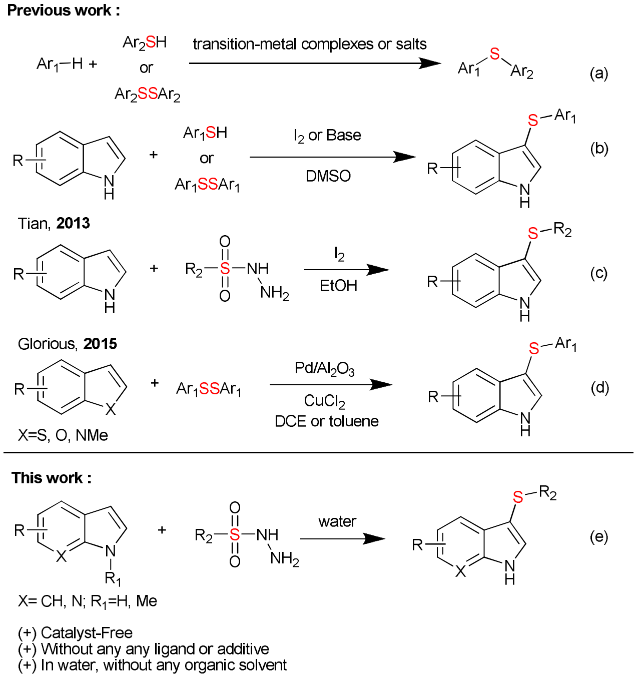

Figure 1. a) The metal-catalyzed direct C-H activation to contrast C-S bonds; b) iodine-catalyzed or base-promoted 3-sulfenylation of indoles; c) iodine-catalyzed sulfenylation of indoles with sulfonyl hydrazides; d) heterogeneously catalyzed direct C-H thiolation of heteroarenes; e) catalyst-free thiolation of indoles in water.

And very recently, a general methodology for the direct thiolation of electron-rich heteroarenes was developed by Glorius and co-workers, in which Pd/Al_2O_3, a recoverable and commercially available heterogeneous catalyst, and $CuCl_2$ were employed (Figure 1d).[16] However, the catalyst, additive and toxic organic solvent were employed in these reactions, which leaded to the concerns on the environmental amity. Particularly, for the request of environmental benignity and economical cost, the new methodology under catalyst-free conditions in water still remains an ongoing challenge for organic chemists.[17]

As a continuation of our interest in in-water and on-water

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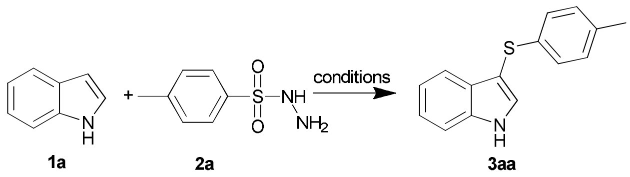
green chemical methodologies in organic synthesis,[10a,18] and, moreover, in view of the importance of 3-sulfenylindoles and related scaffolds, we report herein on a simple water promoted thiolation of indoles with sulfonyl hydrazides (Figure 1e). In combination with recent reports on the direct C-H thiolation to construct 3-sulfenylindoles, this methodology can be carried out in water without any catalyst, ligand or additive, affording a much more environmentally benign and economical way.

Results and discussion

At the outset of this investigation, indoles (**1a**) and 4-methylbenzenesulfonhydrazide (**2a**) were used as the substrates, while Pd/DNA was dispersed in water[18] as a catalyst to optimize the reaction conditions. The reaction afforded the 3-sulfenylated product **3aa** in only 25% yield, with a recovery of the starting materials (Table 1, entry 1). Similarly, Au/DNA catalyst gave a poor result with a yield of 23%. In order to increase the temperature, the template of the nano-catalyst was changed into titanium dioxide and carbon respectively, affording the corresponding product with 67% and 68% yield respectively (Table 1, entry 3 and 4). As different nano-metals has little effect on the yields (Table 1, entries 1-4), we then carried out the reaction in the absence of catalyst. Surprisingly the reaction could give the product **3aa** with a yield of 68% in net water (Table 1, entry 5).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	T (°C)	Yield(%)[b]
1	Pd/DNA	H_2O	80	25
2	Au/DNA	H_2O	80	23
3	Pd/C	H_2O	120	67
4	Au/TiO_2	H_2O	120	68
5	-	H_2O	120	68
6	-	H_2O	140	87
7	-	H_2O	160	85
8	-	EtOH	140	32
9	-	DMSO	140	Trace
10	-	DMF	140	Trace
11	-	toluene	140	18
12	-	CH_3CN	140	11
13	-	DCE	140	Trace
14	-	THF	140	25
15	-	1,4-dioxane	140	21
16	-	H_2O	140	62[c]

[a] Reaction conditions: **1a** (0. 1 mmol), **2a** (0.25 mmol), catalyst (2 mol %), solvent (1 mL), under N_2, 24 h. [b] Isolated yields based on **1a**, [c] under air.

Screening of the temperature indicated 140 °C to be optimal. Rising the temperature had no effect on the yield while lowering the reaction temperature decreased the yields largely (Table 1, entries 5-7). When the water was replaced with organic solvents, the yeilds of the products decreased a lot, affording few or trace amount of the desired products (Table 1, entries 8-15). This implied that the water promoted this thiolation. When the reaction was subjected to air atmosphere instead of nitrogen, a relatively lower yield was obtained (Table 1, entry 16). After screening, **1a** with **2a** in the presence of nitrogen at 140 °C using water as the solvent was optimized as the optimal reaction conditions.

With the optimal conditions in hand, the scope of this transformation was subsequently investigated. The examples of the reactions between indoles and sulfonyl hydrazides were presented in Scheme 1. The optimized reaction conditions were found to be applicable to a series of substituted aryl sulfonyl hydrazides (**2a-s**) and indoles (**1a-l**), affording the corresponding products with moderate to excellent yields in most cases. The effect of substituents on the aryl ring of the sulfonylhydrazides was examined. It was found that a variety of aryl sulfonylhydrazides could be converted to the desired products (**3aa**–**3am**) in good to excellent yields regardless of electron-donating groups (R = Me, Pr, ^{t}Bu, OMe, OCF_3) or electron-withdrawing groups (R = F, Cl, Br, CN, CF_3, NO_2) on the phenyl ring. In general, the substrates with electron-donating groups on the phenyl ring gave slightly higher yields (**3aa**–**3af**) than that of electron-withdrawing groups (**3ag**–**3am**). Nevertheless, the steric hindrance had great influence on the reaction. For instance, *ortho*-nitro benzene-sulfonylhydrazides afforded a trace amount of the desired product **3an**. Disubstituted benzenesulfonylhydrazides can also be employed as the reaction substrates, furnishing the thiolation product **3ao** and **3ap** with good yields. It is notable that different positions of the substituents on the naphthalene significantly affected the reaction activity. For instance, **3aq** was obtained with a yield of in 99% while **3ar** was generated with a yield of 67% . When the aryl ring of the sulfonylhydrazide was replaced by the thiophene ring, the correponding thiolation product was hardly obtained.

Next, the scope of the indoles was examined. As shown in Scheme 3, the indoles with various functional groups can be transformed into the desired products (**3bb-3lb**) smoothly. Either the electronic effect or the steric effect had little influence on the reaction except for the strong electron-withdrawing nitro-group (**3ib**) and big block ester group (**3kb**). For example, different substituents on 1-, 2-, 4-, 5-, and 6-positon of the indole ring could give the desired product with good yields (**3bb-3gb**) in spite of the substitution at different position. As for the substrate **1i**, bearing nitro group on the indole ring, the thiolation was sluggish to afford the thiolation product **3ib** with a low yield of 35%. Pleasingly, a N-heteroaryl-bearing indole could be performed well in the reaction, giving the corresponding product with a yield of 65% (Scheme 1, **3kb**). Encouraged by this green synthesis, simple manipulation and a broad scope of the reaction substrates of this developed methodology, we then proceeded to conduct scale-up experiments to examine the synthetic utility.

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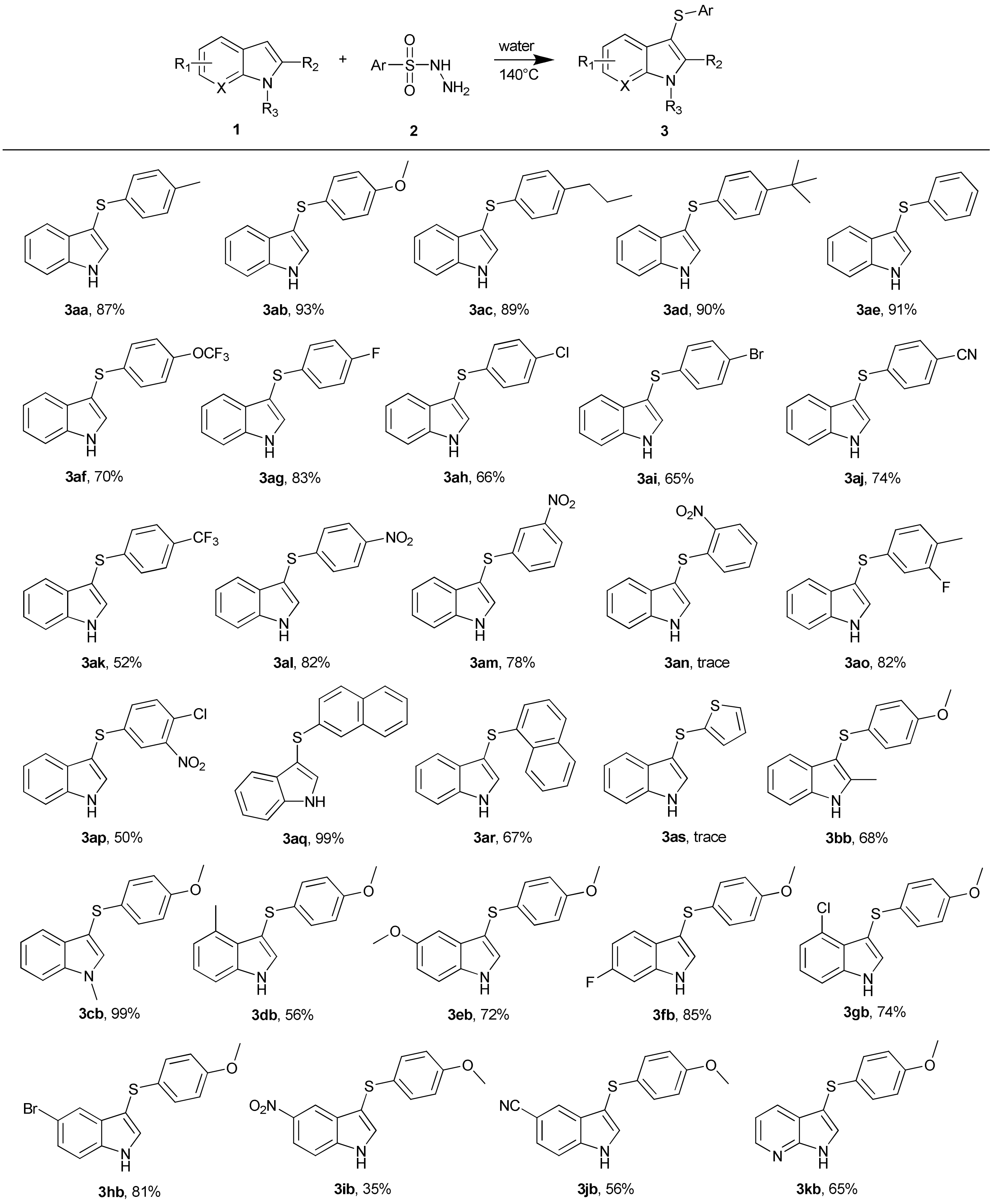

Scheme 1. Catalyst-free thiolation of indoles with sulfonyl hydrazides. General reaction conditions: indoles (0.1 mmol) and sulfonyl hydrazides (0.25 mmol) in 1 mL of H_2O, 140 °C, under N_2, 24 h. All yields refer to isolated products based on indoles.

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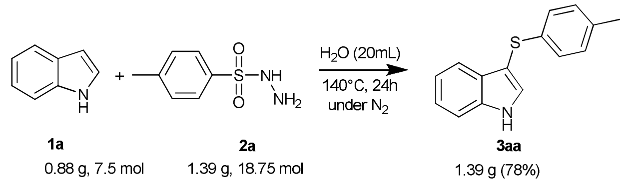
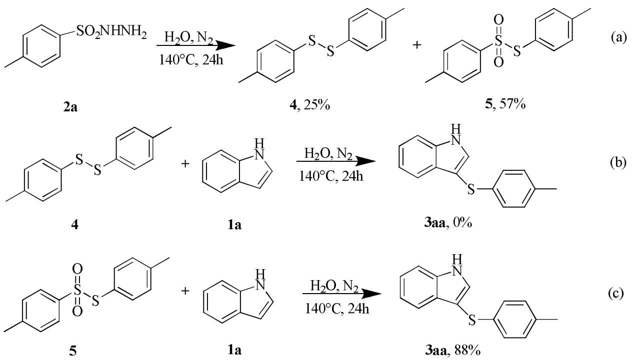


Scheme 2. The scale-up reaction: **1a** (7.5 mmol) and **2a** (18.75 mmol) in 20 mL of H_2O, 140 °C, under N_2, 24 h. Product **3aa** was isolated in 78% yeild.

When 7.5 mmol of indole **1a** was reacted with 18.75 mol of 4-methylphenyl-sulfonhydrazide **2a**, the corresponding product **3aa** can be obtained with a satisfactory yield of 78%, demonstrating a great potential in parmaceutical synthesis (Scheme 2). The method could be used to prepare precursors of some important bioactive molecules.

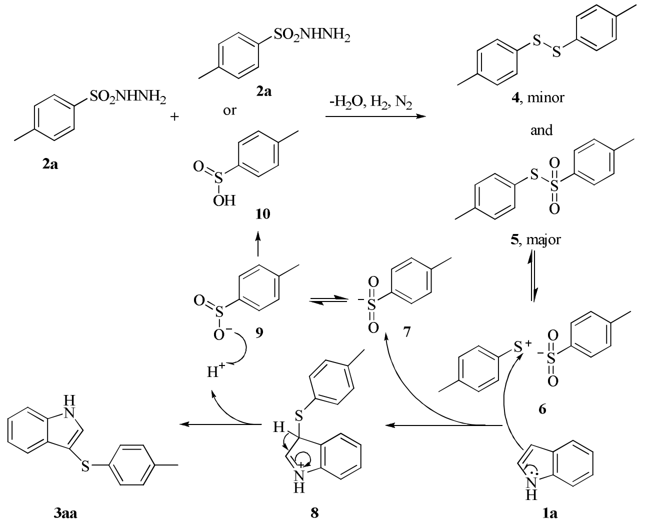
Studies on the reaction mechanism

To get an insight into the mechanism of the thiolation process, several controlled experiments were conducted. First, the beheviour of the sulfonyl hydrazides under the standard conditions was conducted. When the 4-methylbenzene sulfonhydrazide (**2a**) alone was employed, the reaction afforded **1,2-**dip-tolyldisulfane (**4**) in 25% yield and 4-methylbenzene-sulfonothioic acid S-(4-methylphenyl) ester (**5**) in 57% yield (Scheme 3b). Subsequently, using **4** as the reagent under the standard conditions had no reaction while employing **5** could afford **3aa** in 88% yield (Scheme 3b and 3c), suggesting that 4-methylbenzene-sulfonothioic acid S-(4-methylphenyl) ester (**5**) might be an intermediate in this reaction. It is noteworthy that the reaction mixture was weak acidic at the end of the reaction, which indicate that a small amount of acid is produced.



Scheme 3. Mechanistic investigations of the thiolation process.

On the basis of the aforementioned investigations and previous reports,[3,13,19] a possible reaction pathway was proposed and depicted in scheme 4. Initially, sulfonylhydrazides transform into minor product **4** and major intermediate **5** which can dissociate into **6** in the presence of water. Subsequently, the Friedel-Crafts process happens between **6** and indoles, affording intermediate **7** and **8**. The intermediate **7** resonates with sulfur-centered anion **9**, which can form sulfinic acids **10** in the presence of water. At the same time, the intermediate **8** quickly tansforms into product **3aa** with the release of hydrogen ion.



Scheme 4. The proposed mechanism for the reaction.

Conclusions

A water-promoted thiolation of indoles with sulfonyl hydrazides was developed, affording 3-sulfenylindoles with good to excellent yields. This thiolation can be carried out under environmentally benign conditions without any catalyst, additive, ligand or organic solvent. Also, the by-products were nitrogen and water, no any pollution on the environment. Besides, the reaction has a broad scope of the reaction substrates, a variety of functional groups can tolerate the reaction conditions well. Ongoing research including further mechanistic details, expanding the substrate scope and applications in organic synthesis are currently underway.

Experimental

A mixture of arylsulfonyl hydrazides (0.25 mmol) and indoles (0.1 mmol) in water (1 mL) was put into a schlenk at 140 °C under magnetic stirring for 24 h under nitrogen. After the reaction was finished, the mixture was extracted with EtOAc (3 × 5 mL) and then the combined organic extracts were washed with brine (15 mL), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 6:1) to give compound **3**.

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Notes and references

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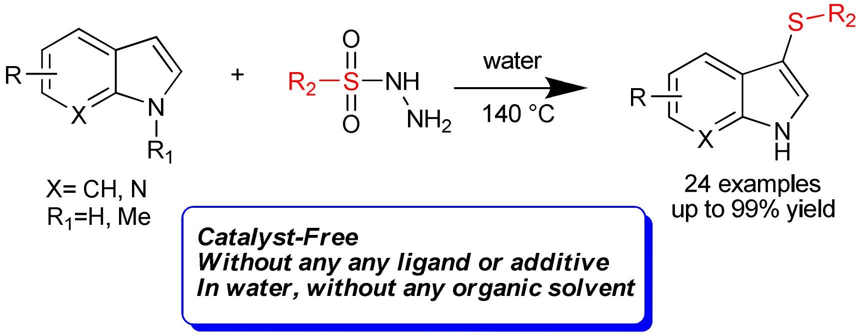

Catalyst-Free
Without any any ligand or additive
In water, without any organic solvent

A water promoted thiolation of indoles with sulfonyl hydrazides developed under mild conditions in water