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Catalyst-free sulfenylation of indoles with sulfinic esters in ethanol

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A novel catalyst-free method for synthesis of structurally diverse indole thioethers in moderate to excellent yields has been developed. In this reaction, sulfinic esters serve as new sulfur electrophiles.

Introduction

The selective formation of carbon-sulfur bonds has emerged as a significant field of research in organic chemistry because of their prevalence in the pharmaceutical industry and material science.[1] In recent years, much attention has been paid to the synthesis of organosulfur compounds.[2] Among them, efficient methods for indole thioethers formation from chemical feedstocks are highly sought after, because some of them can serve as potent agents to treat HIV,[3] cancer,[4] heart disease,[5] and allergies.[6] Due to the electron-rich nature of indole rings, many methods have recently been developed via the direct sulfenylation of indoles with sulfenylating agents, such as sulfenyl halides,[7] *N*-thioimides,[8] sulfoniumsalts,[9] thiols,[10] disulfides,[11] quinone mono-O,S-acetals,[12] arylsulfonyl chlorides,[13] sodium sulfinates,[14] sulfinic acids,[15] sulfonyl hydrazides,[16] and *N*-hydroxy sulfonamides.[17] Nevertheless, these reactions have some well-known disadvantages: (a) some of the sulfenylating agents are unstable to air and moisture, are difficult to be prepared, or possess unpleasant smelling; (b) many of these reactions involve the use of metal catalysts. It is of great importance to develop efficient processes that do not require a metal catalyst in consideration of the low threshold residual tolerance of metals for pharmaceuticals; (c) some of these reactions require excess additives, high temperature, or yield byproducts unfriendly to the environment. To address such issues, it is highly desirable to develop new sulfenylating agents and simple reaction conditions for the sulfenylation of indoles.

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In the course of exploring new methods to synthesize organic sulfides, we found sulfonyl hydrazides could serve as sulfur electrophiles through the cleavage of sulfur-oxygen bonds and sulfur-nitrogen bond,[16e] and this protocol requires iodine as catalyst. Inspired by this work, along with our interest in developing new sulfenylating agents, we envisioned that sulfinic esters which are readily accessible and free of unpleasant odor might serve as potential sulfenylating agents through the cleavage of sulfur-oxygen bonds to react with indoles to give indole thioethers under catalyst-free conditions.

Results and discussion

The model reaction of indole (**1a**) with sulfinic ester (**2a**) was performed in MeOH at 80℃ (Table 1, entry 1). To our delight, when the reaction was carried out in the absence of catalyst, the desired sulfenylation reaction can take place and give indole thioether (**3a**) in 51% yield. Encouraged by this result, a number of common solvents were examined, and a best yield was achieved when using EtOH as solvent (Table 1, entries 2-12). Further examination showed that temperature has a greater impact on the reaction (Table 1, entries 13-14). Lower yields were obtained when the reaction was run at 70℃, while increasing the reaction temperature to 90℃ afforded a better yield. For comparison, the reaction was performed under nitrogen and oxygen (Table 1, entries 15-16), unfortunately, both of them gave **3a** in a slightly lower yield. Finally, screening the ratio of starting materials showed a high yield was obtained when the ratio of **1a**, **2a** was adjusted to 1.8:1. Thus, the optimal reaction conditions were 1.8 equiv of **1a**, 1.0 equiv of **2a** in EtOH at 90℃.

The development of such a simple route for the formation of indole thioethers was highly appealing, we first investigated the substrate scope of indoles (Table 2). Under the optimized reaction conditions, a series of indoles smoothly underwent sulfenylation with sulfinic esters **2a** to give the corresponding indole thioethers in good yields. It was found that either electron-donating groups Me, Bn, Ph, and OMe (**3b-3i**) or electron-withdrawing groups F, Cl, and Br (**3m-3p**) on the N-1, C-2, C-4, C-5, C-6 or C-7 positions of the indole rings could give the corresponding 3-arylthioindoles in better

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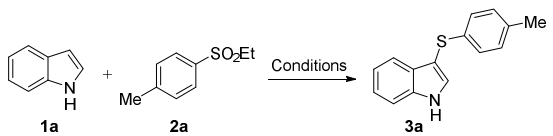
yields. Lower yields were obtained when strong electron withdrawing groups, such as carboethoxy group, nitro group, and nitrile group were present at the C-6, C-5 positions of the indole rings (**3j-3l**). To our delight, when the C-3 position was occupied by methyl group, the sulfenylation reaction took place at the C-2

Table 1. Optimization of Reaction Conditions **3a**[a]



1a 2a 3a

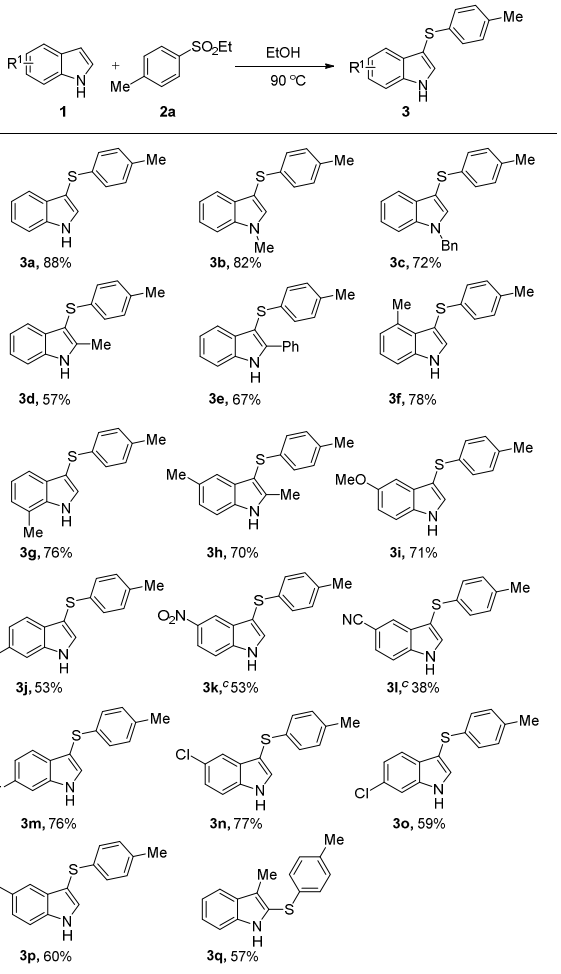
Entry	Solvent	T (°C)	1a/2a	Time (*h*)	Yield (%)[b]
1	MeOH	80	1.5/1	12	51
2	EtOH	80	1.5/1	12	73
3	DMF	80	1.5/1	12	34
4	DMSO	80	1.5/1	12	Trace
5	MeCN	80	1.5/1	12	62
6	$MeNO_2$	80	1.5/1	12	67
7	Dioxane	80	1.5/1	12	64
8	EtOAc	80	1.5/1	12	63
9	CH_2Cl_2	80	1.5/1	12	59
10	$CHCl_3$	80	1.5/1	12	50
11	DCE	80	1.5/1	12	57
12	Toluene	80	1.5/1	12	59
13	EtOH	70	1.5/1	24	52
14	EtOH	90	1.5/1	12	81
15[c]	EtOH	90	1.5/1	12	59
16[d]	EtOH	90	1.5/1	12	62
17	EtOH	90	1.8/1	12	88
18	EtOH	90	1.2/1	12	52
19	EtOH	90	1/1.5	12	Trace

[a]Reaction conditions: **1a** (0.36mmol), **2a** (0.2 mmol), in solvent (0.50 mL), at 90 °C (oil bath), For 12 h. [b]Isolated yield. [c]The reaction was performed under nitrogen. [d]The reaction was performed under oxygen.

position of the indole ring (**3q**). However, when *N*-protected indoles (Boc, Bz) were used as substrates, indole thioether **3a** instead of the desired products was obtained in 66% and 42% yields, respectively, suggesting that sulfinic ester might decompose to give sulfinic acid upon heating. In addition, a gram-scale synthesis of indole thioether **3a** was successfully performed under the standard reaction conditions (1.14 g, 79% yield).

Subsequently, the scope of sulfinic esters was tested (Table 3). The sulfenylation reaction of indole with various sulfinic esters give indole thioethers (**4a**-4**m**) in moderate to good yields. Various electron-donating substituents such as *t*-Bu and OMe (**4b**-**4c**) and electron-withdrawing substituents such as F, Cl, Br, I, and CF_3 (**4d**-**4h**) were well tolerated in this reaction. It should be noted that steric effect had little influence on the reaction, more bulky substrates such as 2,4,6-trimethylbenylsulfinic ester, 1-naphthylsulfinic ester,

Table 2. Scope of Indoles **1**[a,b,c]



[a]Reaction conditions: **1** (0.36mmol), **2a** (0.2 mmol), ethanol (0.50 mL), at 90 °C (oil bath), For 12 h. [b]Isolated yield. [c]At 120 °C.

and 2-naphthylsulfinic ester all efficiently reacted with **1a** and gave the product in good yields (**4i**-**4k**). To our delight, 2-thiophenylsulfinic ester could also afford corresponding product in moderate yield (**4l**). In addition, cyclopropanylsulfinic ester also could couple with indole to give the desired product in 54% yield

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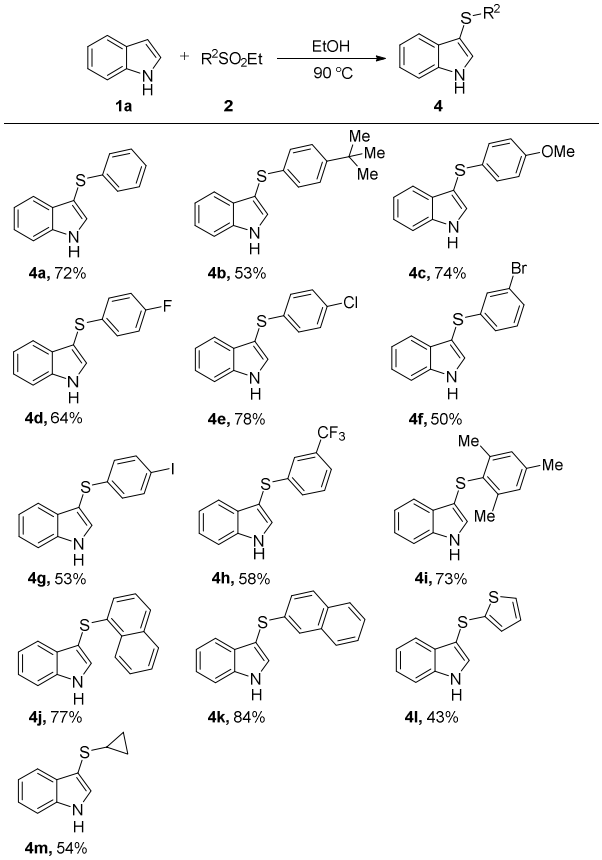
(**4m**), which indicating that the reaction might not involve sulfide radicals.[18]

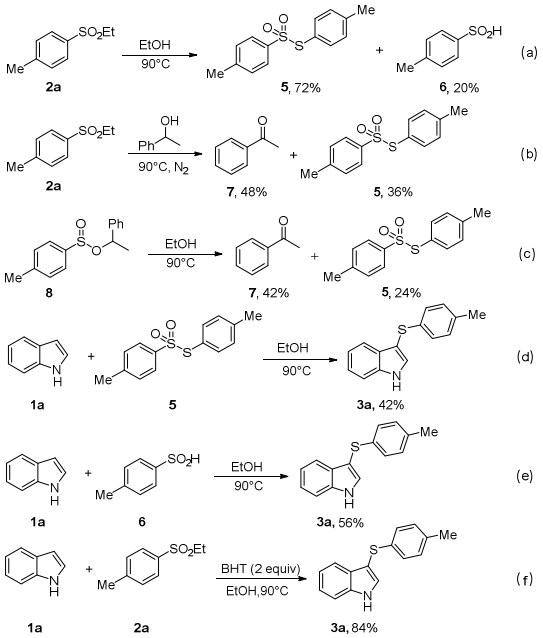
To get an insight into the mechanism of the sulfenylation process, several control experiments were performed (Scheme 1). Under the optimized reaction conditions, sulfinic ester (**2a**) decomposed to give sulfonothioate (**5**) and sulfinic acid (**6**) in 72% and 20% yields (Scheme 1a), respectively, while no disulfide was detected. The decomposition of sulfinic ester (**2a**) and sulfinic ester (**8**) both gave acetophenone as oxidation product, which substantially demonstrates that sulfinic ester is reduced by ethanol to serve as sulfur electrophile. (Scheme 1b, 1c) Replacing sulfinic ester with sulfonothioate gave the desired product (**3a**) in 42% yield, which suggests that sulfonothioate might be a major intermediate in this reaction. Indole (**1a**) could react with sulfinic acid **6** to give final product in 56% yield. Addition of free radical inhibitor 2,6-di-*tert*-butyl-*p*-cresol (BHT) to the reaction mixture of indole and sulfinic ester had no effect on the reaction efficiency, indicating that the process might not involve radical intermediates.

Table 3. Scope of Sulfinic Esters **2**[a,b]

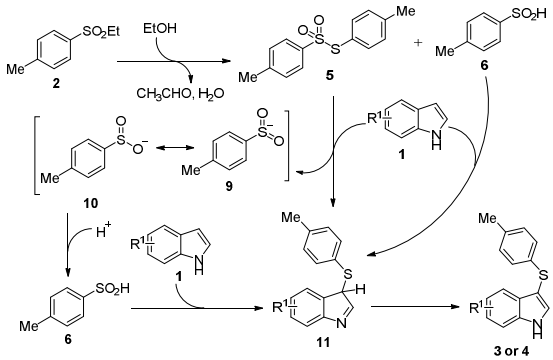


[a]Reaction conditions: **1a** (0.36mmol), **2** (0.2 mmol), ethanol (0.50 mL), at 90 °C (oil bath), For 12 h. [b]Isolated yield.

According to the above experimental results and previous relevant studies,[16a] we propose the major reaction pathway depicted in Scheme 2 for catalyst-free sulfenylation of indoles with sulfinic esters. Initially, sulfinic esters **2** is reduced by ethanol to give sulfonothioate **5** and sulfinic acid **6**,[16a, 16e] both of which undergo a electrophilic reaction with indole **1** to give intermediate **9** and intermediate **11**. And then anion **10**, resonance of intermediate **9** can react with hydrogen ions to form sulfinic acid **6**, which also can react with indole **1** to afford intermediate **11**. The intermediate **11** finally transforms into the desired product **3** or **4**.



Scheme 1. Control Experiments



Scheme 2. Proposed Reaction Pathways

Conclusions

In summary, we have developed a simple and efficient sulfenylation reaction of indoles with sulfinic esters. Under catalyst-free conditions, a range of aryl-, heteroaryl-, and alkylsulfinic esters smoothly reacted with indoles to give structurally diverse thioethers in moderate to good yields. This reaction is carried out under environmentally benign without any catalyst, additive, and ligand.

Conflicts of interest

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There are no conflicts to declare.

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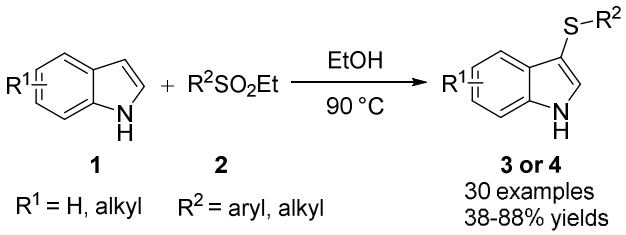

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