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Synthesis of Asymmetrical Thioethers with Sulfinamides as the Sulfenylation Agent under Metal-free Conditions

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Abstract: Using sulfinamides as a new reagent for preparation of asymmetrical thioethers has been developed under metal-free conditions. The reactions proceeded smoothly without the use of stinky thiophenol, highly toxic sulfonyl chloride or oxidant. Such a simple, efficient transformation provides an attractive approach to various diaryl sulfides in good to excellent yields.

Keywords: Sulfinamides; Sulfenylation agent; Metal-free; Asymmetrical thioethers

Introduction

Asymmetrical thioethers, widely used in medicine, bioactive substances[1-3] (e.g. Potential anti-inflammatory compounds[1], LFA-1 antagonists[2] and DHFR inhibitors[3], **Figure 1**) and functional materials[4] (e.g. BTNT and BTBT, **Figure 1**) are an important class of active compounds [5-12].

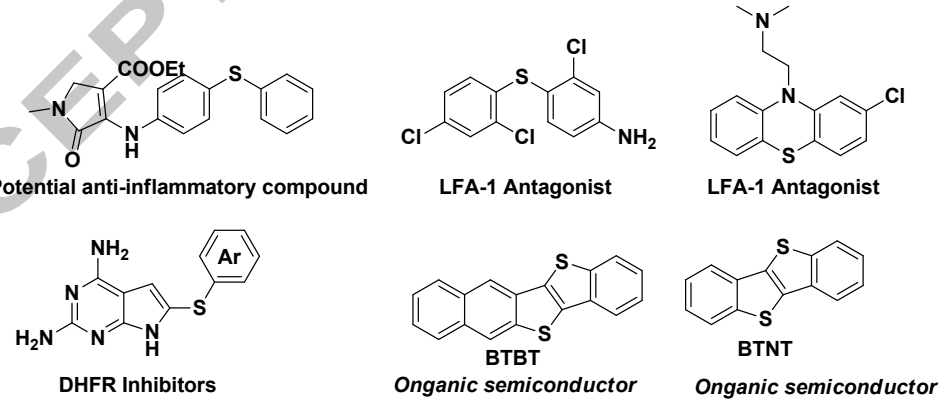
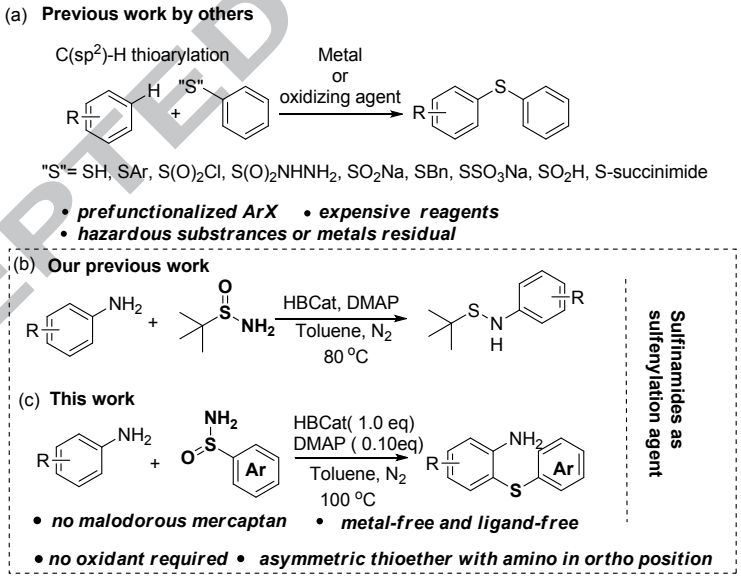


Figure 1 Applications of asymmetrical thioethers

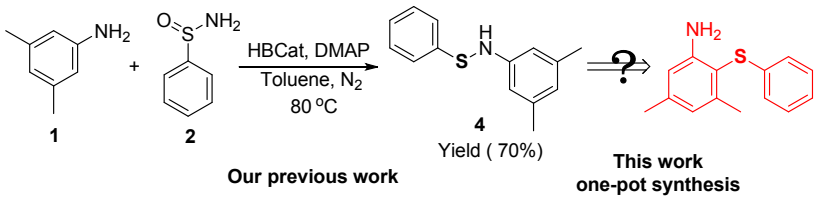
Therefore, many researchers have been focusing on developing a novel, practical, and highly efficient methods for the construction of asymmetrical thioethers. These methods can be categorized according to the sulfur source. One is the transition-metal catalyzed cross couplings of disulfides (RSSR) or thiols (RSH) with aryl halides, pseudo halides or arylboronic acids, where

transition-metal catalysts mainly focus on palladium[13-21], copper[22-26], zinc[27], iron [28-30], nickel[31-36], cobalt[37], and rhodium[38-40]. However, most of these methods have disadvantages like harsh reaction conditions, metal toxicity and high costs, which make it difficult to ensure that these methods could be applied on a large scale. Another method typically relies on the coupling of sulfenyl chlorides with organo zinc[41] or Grignard reagents[42,43]. However, new sulfenylation agents such as sulfonyl hydrazide[44-49], sulfonyl chloride[50,51], sulfinic acid[52,53] or others[54-60] have also appeared. Although these new sulfurizing agents replaced the malodorous mercaptans, they still require transition metals and prefunctionalized arenes (e.g., aryl halides) or oxidants, (e.g. (a), **Scheme 1**). Sulfinamide, an easily prepared and stable compound, has been found to have many important functions such as key compounds in the preparation of amines, efficient catalysts. What's more, sulfinamide was used as a radical donor recently[61]. Previously, we have develop an interesting method for synthesis of sulfenamide with sulfinamide as sulfurizing agent[62] (e.g. (b), **Scheme 1**). Here, we developed another example for synthesis of asymmetrical thioethers with arylsulfinamide as sulfurizing reagent (e.g. (c), **Scheme 1**).



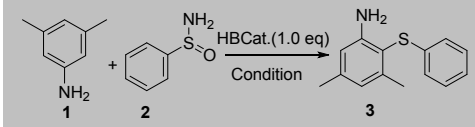
Scheme 1 Examples of sulfenylation agents

As we know, the aromatic sulfenamides (Ar-S-NHAr) could transform to the corresponding asymmetrical thioether via rearrangement according to Davis's work[63,64]. Therefore, we speculated that aromatic sulfenamide obtained with our previous method, could react continuously to afford the corresponding asymmetrical thioethers via rearrangement[65,66], (**Scheme 2**).



Scheme 2. Probability of synthesis asymmetrical thioether with in situ formed sulfenamide

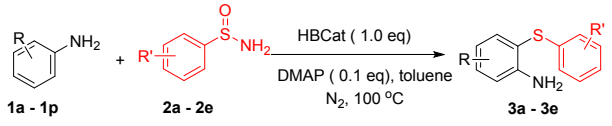
Table 1. Optimization of reaction condition for thioether[a]

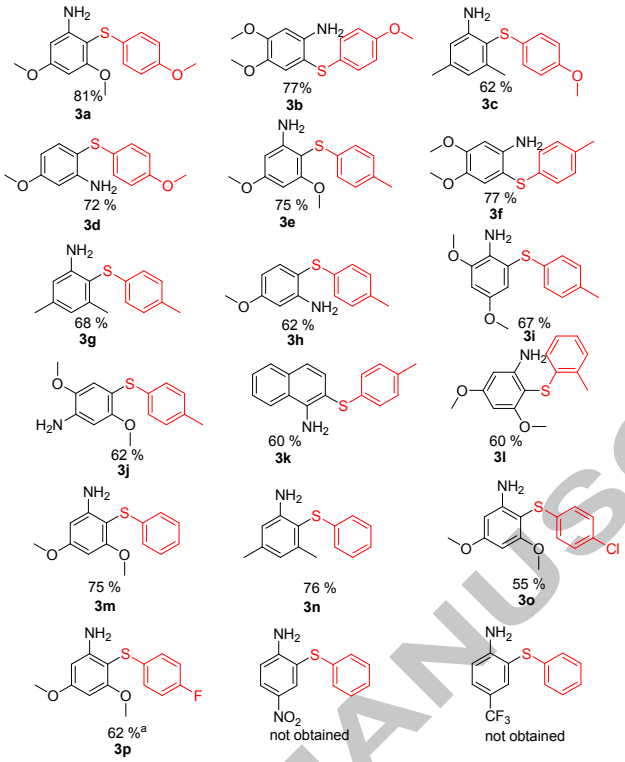


Entry	Solv.	Temp.(℃)	Additive	Yield [b] (%)
1	toluene	90	DMAP	62
2	benezene	90	DMAP	45
3	1,4-dioxane	90	DMAP	30
4	DMSO	90	DMAP	< 5
5	chlorobenzene	90	DMAP	54
6	toluene	90	TEA	47
7	toluene	90	DBU	29
8	toluene	90	DABCO	25
9	toluene	90	K_2CO_3	22
10	toluene	100	DMAP	76
11	toluene	110	DMAP	68
12	toluene	120	DMAP	70

[a]Condition:HBCat (0.25 mmol), **1** (0.25 mmol), **2** (0.3 mmol), additive (10 mol%), solvent in 0.125 M concentration for 16 h; [b] the reaction yield was calculated based on purification with fast silicon column.

Initially, the reaction was investigated with benzenesulfinamide, HBCat and aromatic amine at higher temperature. As expected, we found the target product with moderate yield, (**Table 1**, entry 1). Then the reaction solvent as well as the reaction temperature were screened, which revealed that the reaction yield could be decreased when replacing toluene with other solvents, (entries 2–5). To our delight, slightly increasing of yield was observed when the reaction temperature was raised to 100 ℃ (entry 10). However, higher temperatures didn't improve reaction yields continuously (entries 10–12). The best additive for this reaction was DMAP (entries 6–10) which consistent with the method for synthesis of sulfenamide[62]. Therefore the optimal reaction condition was considered as: DMAP as additive at 100 °C in toluene.



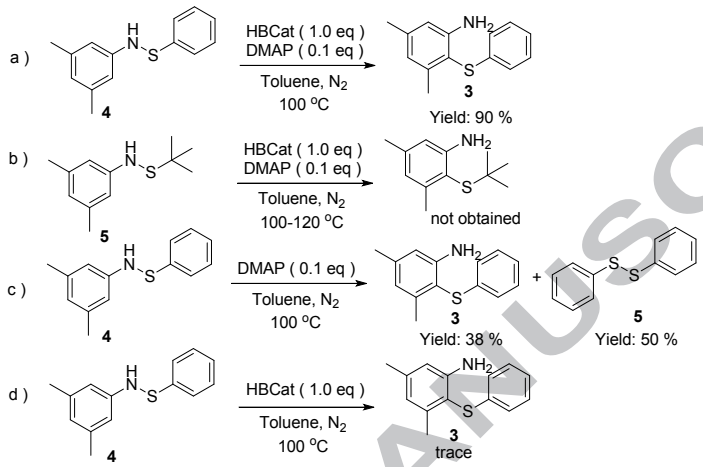


Scheme 3. Investigation of the scope of the aniline and sulfinamides [a] reaction at120 ℃

With the optimal reaction condition, we explored the substrates scope based on the different arylamines and sulfinamides with different substituents on the benzene ring. The experimental results showed that the stronger the electron donating effect of the substituent that aniline contained, the higher the yield of the target product obtained (**3a** vs **3c**, **3e** vs **3g**, **3m** vs **3n**). Especially, rearrangement to afford the para-substituted amine thioether was found when 2,5-dimethoxy-aniline was investigated (**3j**). However, When 4-nitroaniline and 4-(trifluoromethyl)aniline was investigated, there were no target product obtained. The results demonstrated that the electronic effect of substituents on the aromatic ring of aniline has a critical effects. The electron-donating substituent on the aniline was beneficial to the reaction. We also tried several heterocyclic amines like 2-aminopyridine and 2-thienylamine but did not get the product.

Sulfinamides with different substituents on the aromatic ring have also been investigated. From the results of the experiment, we found either the electron-withdrawing group or the electron-donating group could obtain target products with moderate yield. When 4-methylbenzenesulfinamide and 2-methyl-benzenesulfinamide were investigated, the

corresponding diary thioether **3e** was obtained with higher yield compared with **3l**, which was ascribed to the steric hindrance effect, (**3e** vs **3l**). Unlike other sulfinamides, 4-fluorobenzenesulfinamide requires a higher reaction temperature (120℃) to obtain the target product due to the electro withdrawing property of the fluorine substituent, (**3p**).

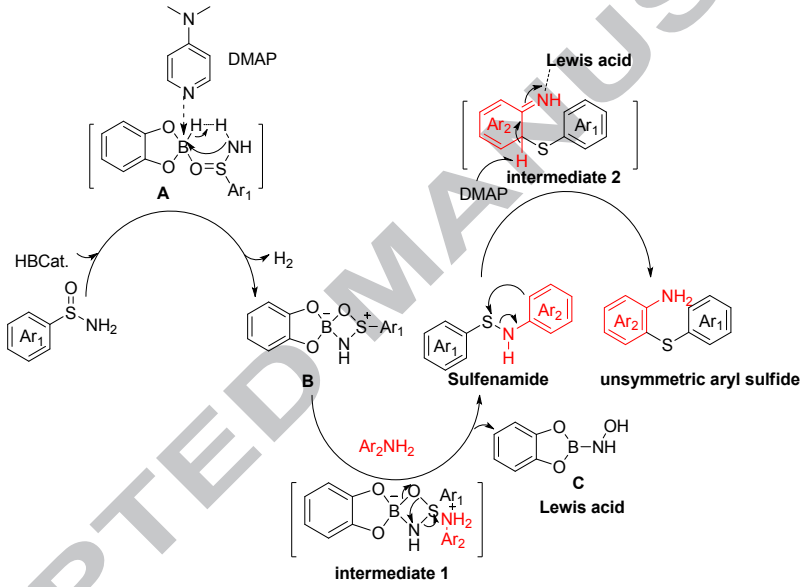


Scheme 4 Investigation of the reaction mechanism

In order to explore the mechanism of the reaction, corresponding sulfenamide **4** was prepared with previous method[62]. As we imagine, the corresponding rearrangement occurred to produce the diary thioether **3** under the reaction conditions. (**Scheme 4,** eq. a). However, when alkyl substituted sulfenamide **5** was investigated, there was no rearrangement product found although raising the temperature from 100 ℃ to 130 ℃ (**Scheme 4,** eq. b). These results are consistent with David's work[63,64]. What's more, both DMAP and HBCat played an important role in this reaction. The optimal reaction condition without adding HBCat, the target product **3** was obtained in 38% yield with 50 % 1,2-diphenyldisulfane **5** as byproduct (**Scheme 4,** eq. c). Meanwhile, there was trace **3** obtained when HBCat was added without DMAP (**Scheme 4,** eq. d). The results demonstrated that the aromatic sulfenamides were the significant intermediate formed in the reaction process. Moreover, DMAP and HBCat were indispensable for the rearrangement process.

Based on the above experiments, we proposed the possible reaction mechanism (**Scheme 5)**. Firstly, compound **B** was formed through the following procedure: coordination of sulfenamide with catechol borane promoting by DMAP[67] and release of hydrogen gas, which is the same as reported by Du[68]. Then the aromatic amine reacts with compound **B** to form intermediate **1**, which

is consistent with what we have reported previously[62]. After that, the intermediate **1** was decomposed into the sulfenamide and organic boron compound **C**, which can be regarded as a Lewis acid for the following rearrangement process. Then intermediate **2** was formed at the higher temperature, which was transformed to the final product by the cooperate catalytic effect of DMAP and organic boron compound **C**. DMAP removes hydrogen from intermediate **2** and compound **C** acts as a Lewis acid to activate the imine, which together promotes this rearrangement. The existence of C after the finish of the reaction was proved with ^{11}B NMR experiment (see supplementary information).



Scheme 5. Possible mechanism of the reaction

Conclusion

In summary, we have developed an efficient method for preparation of asymmetrical thioethers with odorless sulfinamides as sulfenylation agent. This method was efficient for transforming kinds of benzenesulfinamide to asymmetrical thioethers. Especially, the method was easy to control and avoided the use of metals. What's more, no external oxidants were needed in the process.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedure and spectroscopic data) associated with this article can be found, in the online version.

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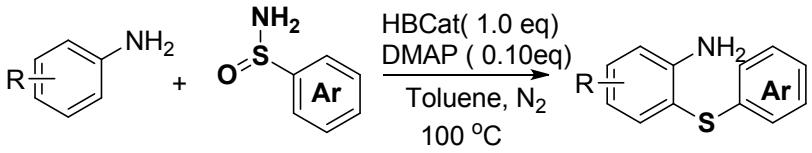
Easy to control

New sulfenylation agent without odor

No oxidant required

Sulfinamides as sulfenylation agent



- ***no malodorous mercaptan***
- ***metal-free and ligand-free***
- ***no oxidant required***
- ***asymmetric thioether with amino in ortho position***