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Using Sulfinamides as High Oxidation State Sulfur Reagent for Preparation of Sulfenamides

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Abstract: Traditional preparation of sulfenamides require the use of low oxidation state of sulfur reagent such as RSCl, $(RS)_2$ or RSH, which are toxic, odorous and difficult to deal with due to the harsh reaction conditions. Here high oxidation state of sulfur reagent—aliphatic sulfinamide, were used for preparation of sulfenamide in one step efficiently. Different aromatic amines with all sorts of functional groups, especially amino groups and hydroxyl groups, were transformed to the corresponding sulfenamides in moderate yields, which was difficult to obtain with previous methods.

Keywords: Sulfenamides; Sulfinamides; Catecholborane; *Tert*-butylsulfinamide

Introduction

Sulfenamides, with a sulfur–nitrogen bond, has garnered great attention in the chemical community over the years due to their unique bond properties and widespread applications. For example, such compounds were found to be superior to elemental sulfur as cross-linking agents in the vulcanization of natural and synthetic rubber.[1] Meanwhile, sulfenamides were efficiently applied in agriculture as fungicides, pesticides, plant growth regulators, Figure 1. In addition, sulfenamides have displayed many interesting biological activities such as inhibitors of platelet lipoxygenase, antiasthmatic agent, and antitumor activities, Figure 1.[1a] For synthetic chemists, sulfenamides are useful reagent in organic synthesis. For instance: oxidation of alcohol as a catalyst in the presence of N-chlorosuccinimide,[2] introduction of sulfur for functionalization of alkenes,[3] introduction of sulfur for asymmetric functionalization of active methenyl groups,[4] served as an useful nitrogen protecting method, especially in the peptide synthesis.[5]

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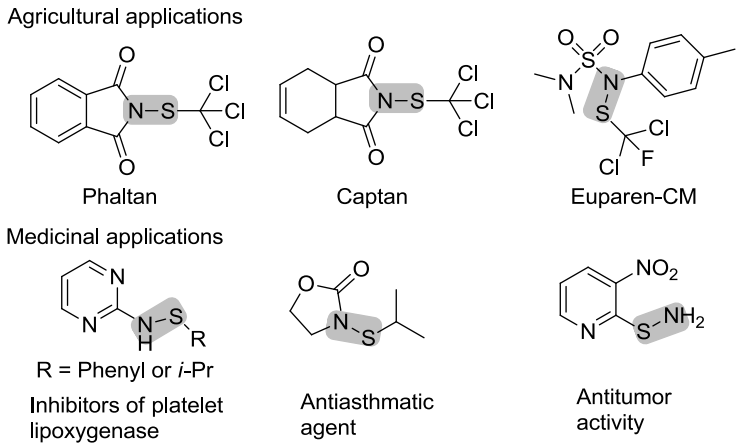
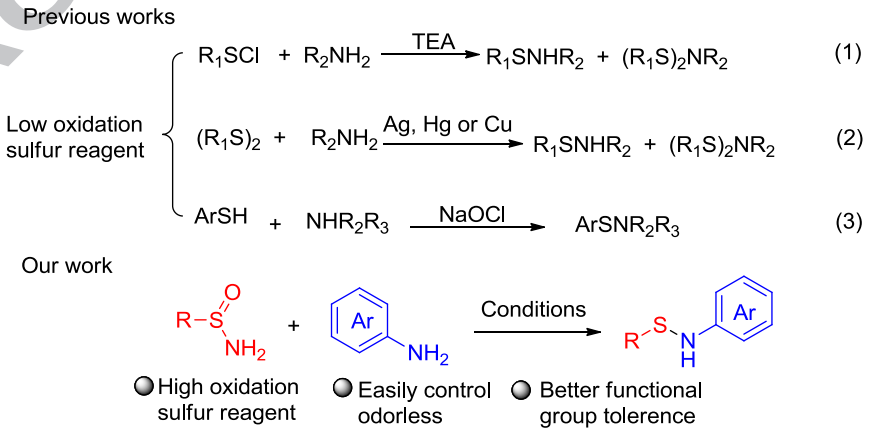


Figure 1 Biological applications of sulfenamides in agriculture and medicines

Because of their industrial applications, their utility as synthetic reagents, and their interesting biological activities, synthetic routes to sulfenamides have been developed over years.[6] These methods can be categorized according to the oxidation state of sulfur in sulfur-containing reagent, scheme (scheme 1): 1) use of sulfur reagents RSCl (eq.1);[7] 2) use of disulfides RSSR in which the oxidation state of sulfur is lower by one unit (eq. 2);[8] 3) use of thiols RSH in which the oxidation state of sulfur is lower by two units. However, using of RSCl as sulfur reagents was restricted to its thermal and moisture sensitivity.[9] Meanwhile, using of disulfides RSSR as sulfur reagent was subjected to the slightly lower yield due to the production of byproducts $(R_1S)_2NR_2$. In addition, the direct cross dehydration with RSH and amines or imines, were limited to aromatic thiols.[10] Generally, the above methods were suffered from the toxic sulfur reagent, the side products as well as the ungenerous substrates. Therefore, using of odorless high oxidation sulfur reagent as substrate for preparation of sulfenamides was significant.



Scheme 1 Background researches of sulfenamides preparation

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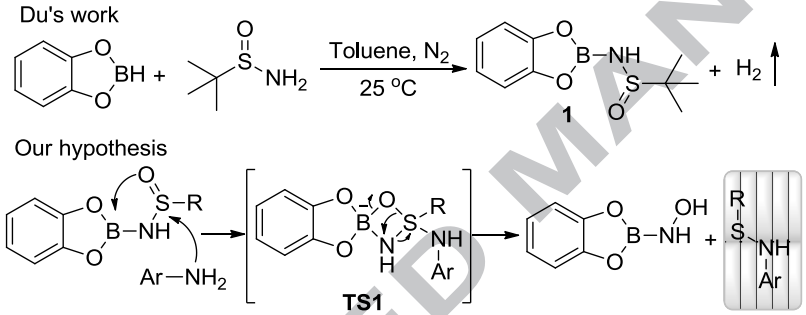
Du and co-worker's recent research indicated that catecholborane (HBCat) could react with *tert*-butylsulfinamide to afford compound **1** via coordination of oxygen and boron, Scheme 2.[11] We hypothesized that suitable nucleophiles could react with compound **1** due to the possibility of intensified electrophilic property of sulfur through intramolecular coordination between the Lewis basic oxygen and the Lewis acid boron. Meanwhile, we speculated that amine could be used as proper nucleophiles to react with compound **1** and afford corresponding sulfenamides via transition state **TS1** according to Zeng's work.[12] Herein we developed an interesting method for preparation of sulfenamides with aliphatic sulfinamides. To the best of our knowledge, reduction of sulfinamides to sulfenamides were rarely seen despite the oxidation of sulfenamindes to sulfinamides were easy.[13]



Scheme 2. Hypothesis of this work

Initially, the reaction was investigated with *tert*-butylsulfenamide, HBCat and aromatic amine at 70 ℃. As expected, we found the target product with low 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 slightly increased with toluene as solvent at 80 ℃, (Table 1, entries 2-7). However the reaction yield was generally low (<30%). To our delight, we found TEA could catalyze the reaction with higher yield (Entry 8). Therefore different catalysts including organic base and inorganic base were screened. The results revealed that DMAP was the optimal catalysts with 74% yield, (Entries 8-13). Further optimizing reaction temperature with DMAP as catalyst revealed that 80 ℃ was still optimal, (Table 1, entries 14-15). Therefore the optimal reaction condition was considered as: DMAP as catalyst at 80 ℃ in toluene for 24 h under nitrogen.

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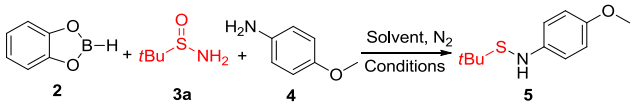
Table 1. Reaction condition screening[a]



entry	solvent	cat.	temp. (℃)	yield[b] (%)
1	toluene	-	70	24
2	benzene	-	70	20
3	1,2-DCE	-	70	12
4	THF	-	70	5
5	toluene	-	60	5%
6	toluene	-	80	29%
7	toluene	-	90	27%
8	toluene	TEA	80	51%
9	toluene	DIPEA	80	47%
10	toluene	DBU	80	30%
11	toluene	DABCO	80	30%
12	toluene	DMAP	80	74%
13	toluene	K_2CO_3	80	25%
14	toluene	DMAP	75	67%
15	toluene	DMAP	90	72%

[a] Condition: **2** (0.25 mmol), **3a** (0.25 mmol), **4** (0.3 mmol), catalyst (10 mol%), solvent in 0.125 M concentration for 16 h; [b] the reaction yield was calculated based on purification with fast silicon column.

With the optimal reaction condition, we explored the substrates scope, (Scheme 3). Firstly, aromatic amines with alkoxy groups were investigated, which revealed that corresponding sulfenamides (**5b-5f**) could be obtained with moderate to excellent yield (60-85%). Then sulfenamides with methyl groups (**5h-5i**), halogen groups (**5j-5k**) or trifluoromethyl (**5l**) were obtained under the optimal reaction condition in moderate yield (60-79%). Based on the above results, we could conclude that the method was general for aromatic amines with electron withdrawing groups or electron donating groups.

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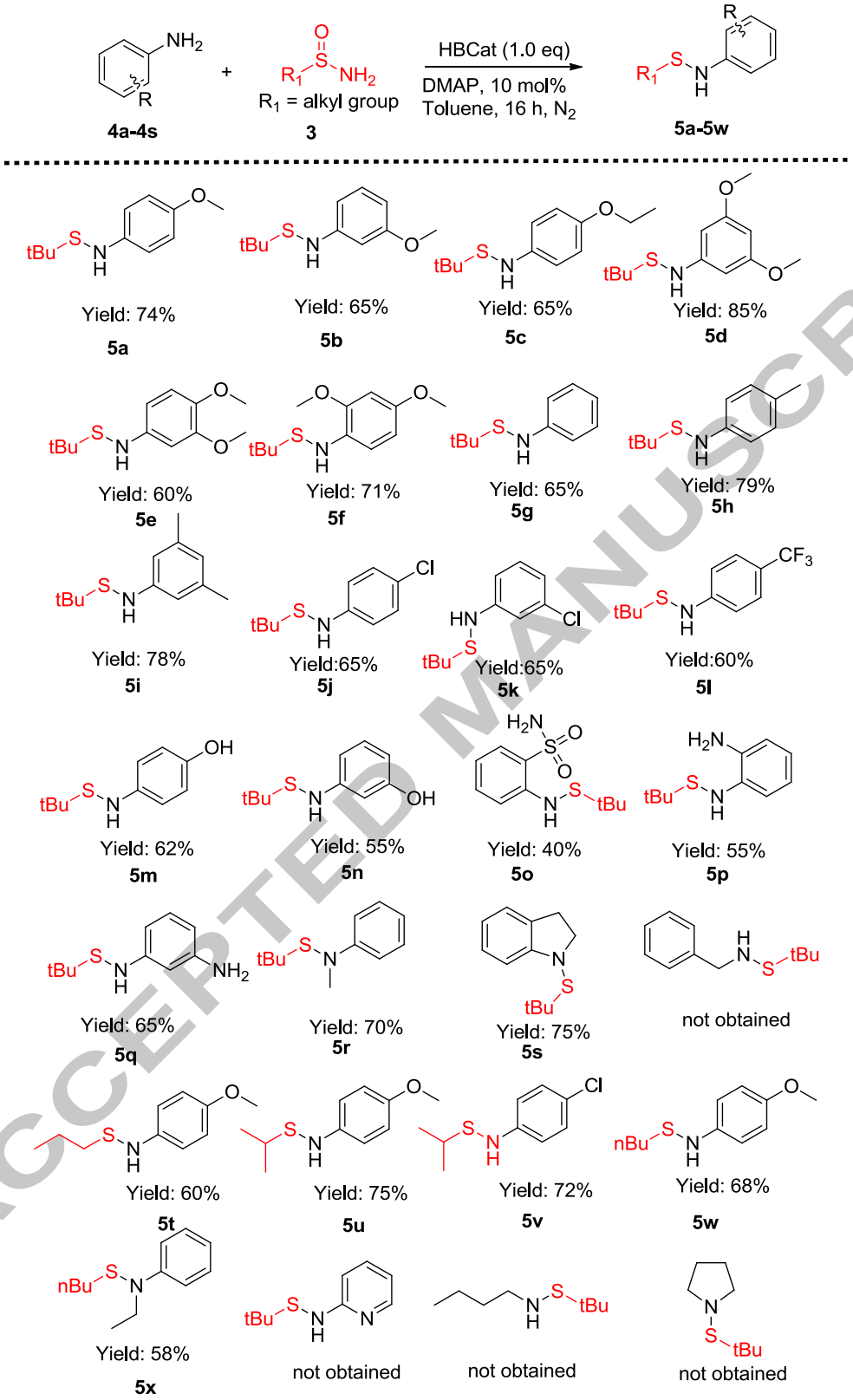

Scheme 3. Investigation of the scope of the aromatic amines

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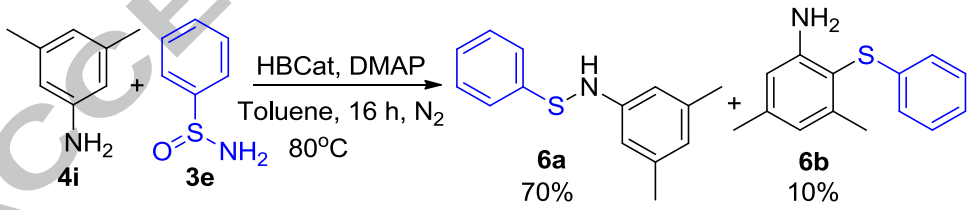
Then we turned to investigate aromatic amines with active hydroxyl group, amino groups or sulfonamide, the results revealed that these aromatic amines could be transformed to the related sulfenamides (**5m-5q**) with moderate yields (40-65%). To the best of our knowledge, these substrates were inefficient with previous methods. Meanwhile, we found that sulfenamide **5q** was selectively obtained with benzene-1,3-diamine as substrate. Moreover, secondary aromatic amines were also investigated and the corresponding sulfenamides (**5r-5s**) were obtained with moderate yield (70-75%). Benzylamine, *butan*-1-amine and pyrrolidine were investigated, which revealed that the corresponding sulfenamides could not be obtained, (Scheme 3). We speculated that aliphatic amine might coordinate with boron and retard the nucleophilic reaction. Finally, Heterocyclic amines such as pyridin-2-amine was investigated which demonstrated that heterocyclic amines didn't work in this reaction (Scheme 3).

On the other hand, other alkyl (branched or unbranched) sulfinamides were explored under the optimized reaction condition, the corresponding sulfenamides (**5t-5w**) were obtained with moderate yields (60-75%). Moreover, aromatic sulfinamide **3e** was investigated under the optimal reaction conditions, Scheme 3. Interestingly, the corresponding sulfenamide **6a** was obtained in 70% yield. Meanwhile, we found the production of unsymmetrical diaryl sufide **6b** in 10% yield. We speculated that diaryl sufide **6b** might be formed via the rearrangement of sulfenamide **6a** under high reaction temperature according to the literature.[14]



Scheme 3 investigation of aromatic sulfinamide as substrate

To verify the proposed reasonable mechanism, the reaction mixture was analyzed with HRMS and the existence of the reaction byproduct was proved by finding the related oxidation products.[15](Figure 2).

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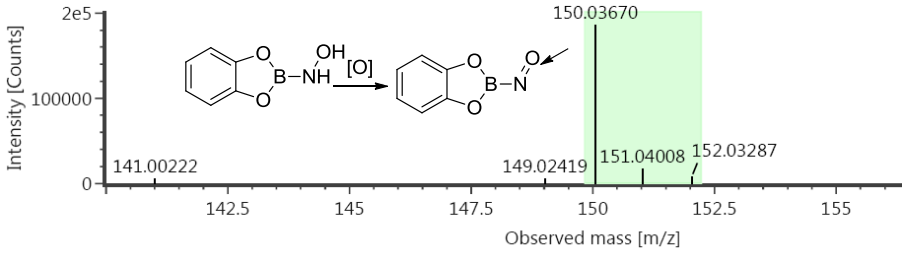

Figure 2. Detection of the by-product of the reaction

Conclusion

In summary, we have developed an efficient method for preparation of sulfenamides with high oxidation state odorless sulfinamides as sulfur reagent. This method was efficient for transforming all sorts of aromatic amines to corresponding sulfenamides. Especially, the method was efficient for aromatic amines with active hydroxyl, amino or sulfonamido groups, which were incapable with previous methods. Moreover, aliphatic and aromatic sulfinamides could be used as substrate for preparation of the corresponding sulfenamides. The reaction mechanisms and the application of this method for preparation and screening of biologically active compound are underway in our lab.

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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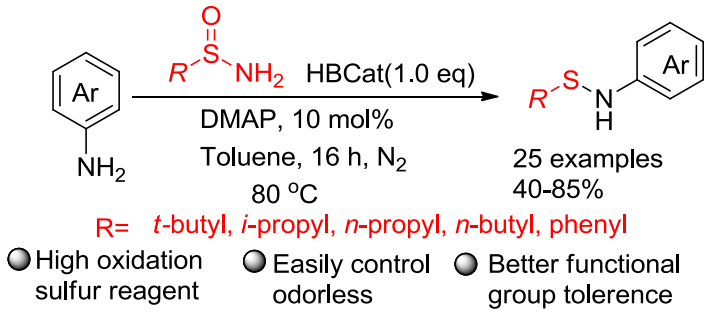
Graphical abstract



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Highlights

Better functional group tolerance;
Odorless aliphatic sulfenamide were used as sulfur reagent;
Easy to perform in one step;

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