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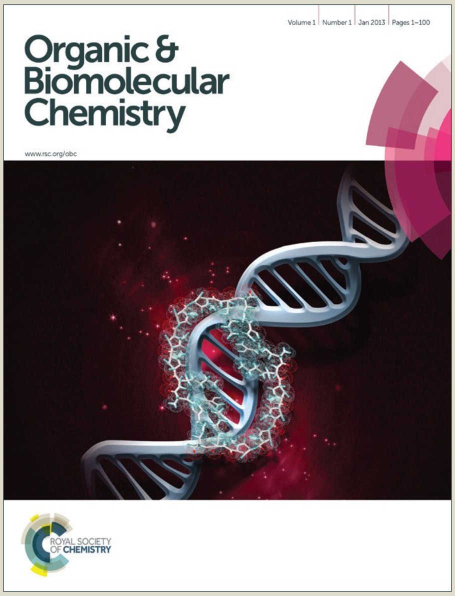

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Generation of Thioethers via Direct C-H Functionalization with Sodium Benzenesulfinate as Sulfur Source

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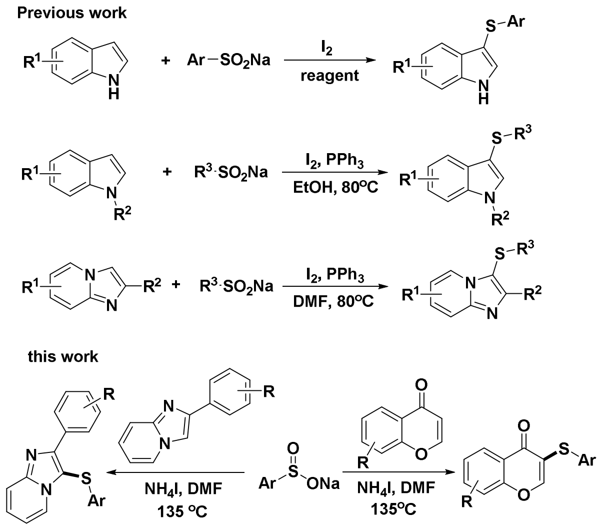
A novel ammonium iodide-induced sulfenylation method of flavones, indole and arylimidazo[1,2-a]pyridines using stable and odorless sodium benzenesulfinates as sulfur sources was developed, generating regioselective derivatives in good yields. The method enriched current thioether-producing methods and provided a good example of using ammonium iodide as a reaction inducer instead of iodine to make thioethers under environmentally friendly and odorless condition.

Sulfenylation is an important transformation to generate thioether molecules in organic chemistry.[1] Compounds containing thioether moiety widely exist in nature and some drug molecules,[2] therefore, any new method to generate these molecules via direct C-H functionalization is strongly desired. Until now, several methods of generating thioether molecules have been developed. One typically traditional method to make thioether is to react alkyl halide with a metal thiolate.[3] Later, transition metal-catalyzed reactions between halides and different sulfur agents became common methods to generate thioether molecules.[4]

Recently, thioether compounds were effectively produced via transition metal-catalyzed C(sp^2)-H functionalization.[5] Not only this kind of method does not need any prefunctionalized reactants, but also increases the selection scope for starting materials.

Very recently, several metal-free thioether-generating methods were also reported (Scheme 1).[6] Among them, the method using stable and odorless sodium benzenesulfinate as a sulfur source was also reported. In Scheme 1, three previous representative reactions to make thioethers were demonstrated.[7] It was found that iodine was commonly used as reaction inducers in these three reactions and PPh_3 was used as a reducing agent in two reactions. All reactions used stable and odorless sodium benzenesulfinate as a sulfur source. Despite these impressive achievements, the development of new methods to generate thioethers is still highly desired.



Scheme 1. Generation of thioethers via using sodium benzenesulfinate as a sulfur source.

In this paper, a new and regioselective thioether-generating method with odorless sodium benzenesulfinates as sulfur source and ammonium iodide as an inducer was reported, generating thioethers in good yields under environmentally friendly condition. To the best of our knowledgement, this kind of report has not been reported before.

Flavone, indole and arylimidazo[1,2-a]pyridine are important class of natural products with a varieties of biological activities, many medicinal chemists have put their efforts on generating their derivatives in order to explore biological activities,[8] especially new derivatives which were not studied before. In this paper, our goal is to make these valuable derivatives. Here, flavone **1a** were selected and used as one of representative molecules. Different reaction inducers, temperatures and solvents were screened in order to find a suitable reaction condition.

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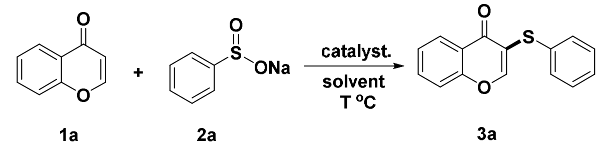
Table 1. Optimization of the reaction conditions[a]



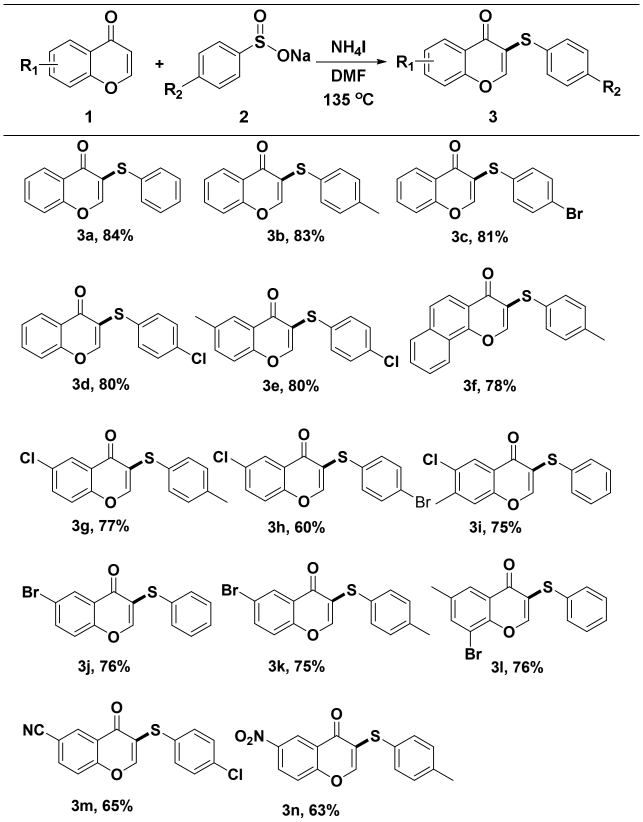
Entry	Inducer (equiv.)	Oxidant	Temp. (°C)	Solvent	Yield [b] (%)
1	KI	TBHP	80	DMF	0
2	I_2	THBP	80	DMF	10
3	TBAI	TBHP	80	DMF	trace
4	NH_4I	TBHP	80	DMF	12
5	NH_4I	TBHP	135	DMF	78
6	NH_4I	--	135	DMF	84
7	NH_4I[c]	--	135	DMF	20
8	NH_4I	--	135	CH_3CN	70
9	NH_4I	--	135	Dioxane	35
10	NH_4I	--	135	Toluene	5
11	NH_4I	--	135	DCE	8
12	NH_4I	--	135	EtOH	25

[a] *Reaction conditions*: flavone (0.5 mmol, 1.0 equiv), sodium benzenesulfinates (2.0 equiv.), KI and I_2 (1.0 equiv.), NH_4I (4.0 equiv.), aqueous TBHP (70 wt % in water, 2.0 equiv.), solvent (0.5 mL). [b] Isolated yields are based on flavone, the reaction was run for 20 hours. [c] NH_4I (1.0 equiv.).

First, KI was used as an inducer with oxidant TBHP for the above reaction, the reactions didn't give the expected product **3a** at 80 °C (entry 1). Using I_2 as an inducer with TBHP generated only 10% yield of product **3a** (entry 2). When TBAI was used as an inducer, the reaction only produced a trace amount of **3a** (entry 3). Using the combination of NH_4I/THBP in DMF gave a 12% yield of **3a** (entry 4). When temperature was raised to 135 °C, the combination of NH_4I/TBHP in DMF gave a 78% yield (entry 5). Surprisingly, using NH_4I only in DMF without TBHP afforded a good yield of 84% (entry 6). Decreasing the amount of NH_4I to one equivalent led to a low yield of product **3a** (entry 7). When CH_3CN was used as solvent instead of DMF, the yield was raised to 70% (entry 8). When dioxane was used as a solvent, the reaction gave 35 % yield (entry 9). Using toluene or DCE as solvents gave **3a** in a yield of 5% or 8%, respectively (entries 10, 11). When EtOH was used as a solvent, only a 25% yield of **3a** (entry 12) was produced. After screening, the suitable reaction conditions selected for the couplings of ethers with coumarins are: NH_4I, (4.0 equiv), temperature: 135 °C, flavone (0.5mmol, 1.0 equiv.), DMF is used as a solvent (0.5 mL).

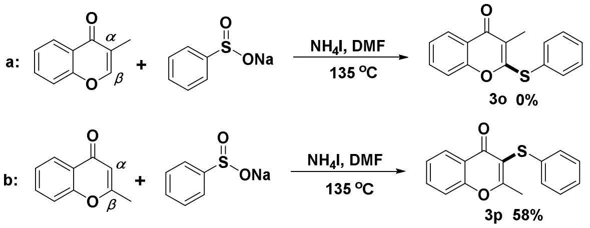
After the optimal reaction condition was obtained, different flavones were reacted with sodium sulfinates. Nine flavones with different electron-deficient or electron-donating functions and five sodium sulfinates were employed as reaction partners. All reactions proceeded well and gave good yields of regioselective flavone thioethers **3a-3n**. By comparing the reaction yields, it was found that electron-rich flavone reactions gave a little higher yields than electron-deficient flavone ones (Table 2). Based on ^1H and ^{13}C-NMR and HRMS spectra of all products, it was found that all -SAr functions were added to the α-position of flavone ketone functions, only trace amount of β-position products were observed.

Table 2. Regioselective sulfenylation of flavones via using sodium benzenesulfinate as a sulfur source[a]



[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv), sodium sulfinates (2.0 equiv.), NH_4I (4.0 equiv), DMF (0.5 mL). [b] Isolated yields are based on reactant **1a**, all reactions were run for 20 hours at 135 °C.

To explore how the substituents on α and β-position of flavones influence the regioselective sulfenylation, two methyl-substituted flavones with methyl function on α and β-position were produced and employed for the reactions in Scheme 2. When the α-positioned reaction site was blocked by methyl, no expected product **3o** was isolated, verifying that the regioselectivity of this sulfenylation was very good, and the reaction only happened on the α-position. When the methyl group is on the β-position of flavone, a decreased yield of thioether **3p** was observed, possibly due to the steric effects from neighbouring methyl function.



Scheme 2. Control reactions.

To further test if our reaction condition is also suitable for the sulfenylation of other molecules reported in Scheme 1, indole and

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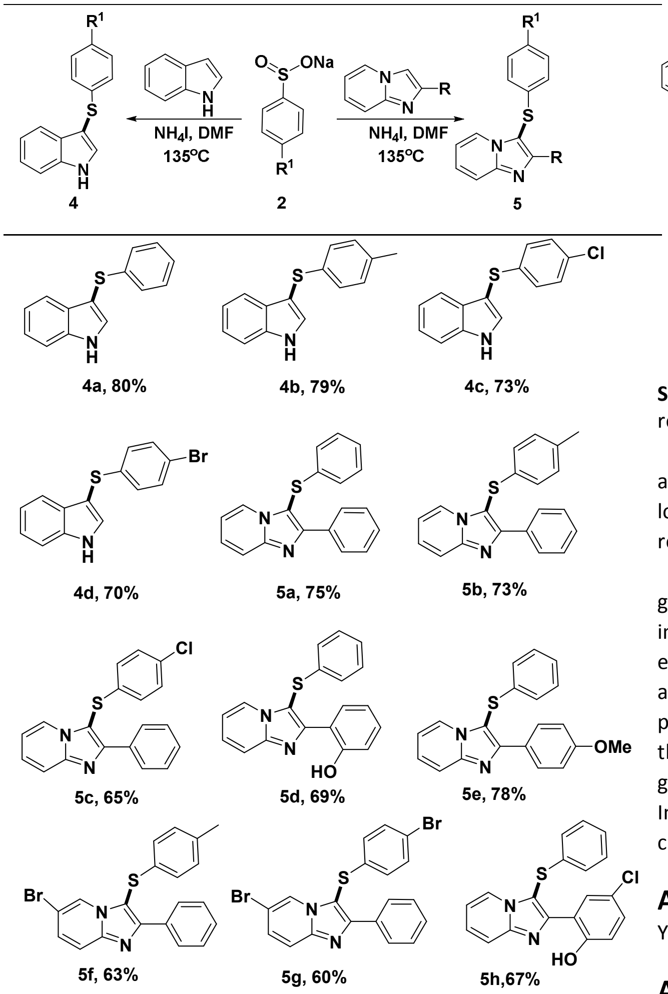
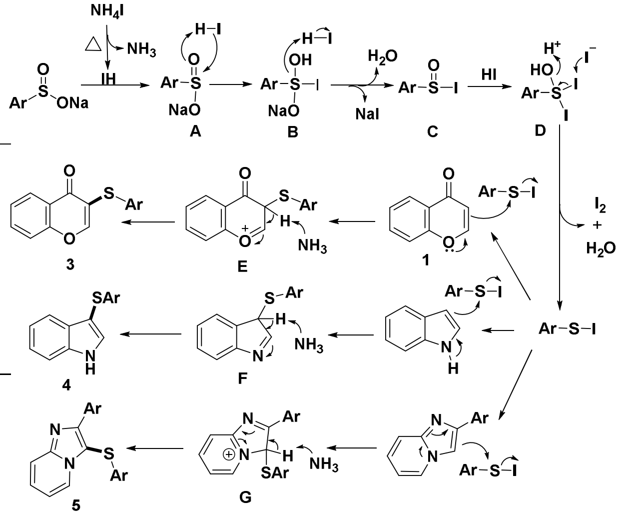
imidazo[1,2-a]pyridine were prepared and reacted with sodium sulfinate under the same reaction condition. It was found that both reactions proceeded well, the results were demonstrated in Table 3. The result showed that indole reacted well with different sodium sulfinates, giving good and regioselective indole thioethers **4a-d**, while the reactions of imidazo[1,2-a]pyridines with sodium sulfinates also generated good and regioselective ArS-substituted arylimidazo[1,2-a] pyridine derivatives **5a-h** in good yields. These results proved that our thioether-generating method has a wide application scope.

Table 3. Regioselective sulfenylation of indole and arylimidazo-[1,2-a]pyridines via using sodium benzenesulfinate as a sulfur source [a]



[a] Reaction conditions: indole or arylimidazo[1,2-a]pyridines (0.5 mmol, 1.0 equiv), sodium sulfinates (2.0 equiv.), NH_4I (4.0 equiv), DMF (0.5 mL). [b] Isolated yields are based on reactant indole or arylimidazo[1,2-a]pyridines, all reactions were run for 20 hours at 135 °C

Based on the previous literature reports[9] and the results obtained in this work, a plausible reaction mechanism was proposed below (Scheme 3). Heat split NH4I into HI and NH_3, then HI started to reduce sodium benzenesulfinate, after intermediate **A**, **B**, **C**, **D** and the loss of H_2O, NaI and I_2 molecules, electrophilic ArS-I was generated, then it continued to react with flavone, indole and arylimidazo[1,2-a]pyridine to give intermediate E, F and G, then the loss of proton from intermediate **E**, **F** and **G** to NH_3 molecule regioselectively afforded final products **3**, **4** and **5**.



Scheme 3. Proposed mechanisms for the thioether-generating reactions.

In summary, a novel ammonium iodide-induced thioether-generating method was reported. By using this method, flavones, indole and arylimidazo[1,2-a]pyridine thioether derivatives were easily made via using stable and odorless sodium benzenesulfinates as sulfur source, generating highly regioselective ArS-substituted products in good yields. The method has enriched current thioether-producing methods, providing an alternative method to generate thioethers instead of iodine-induced method. Investigation on the biological activities of these products is currently underway.

Author Contributions

Y.D. and W.W. contributed equally.

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