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Generation of ArS-substituted Flavone Derivatives Using Aryl Thiols as Sulfenylating Agents

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Wannian Zhao,[a] Ping Xie,[b] Zhaogang Bian,[a] Aihua Zhou,[a*] Haibo Ge,[c*] Ben Niu,[a] and Yingcai Ding[a]

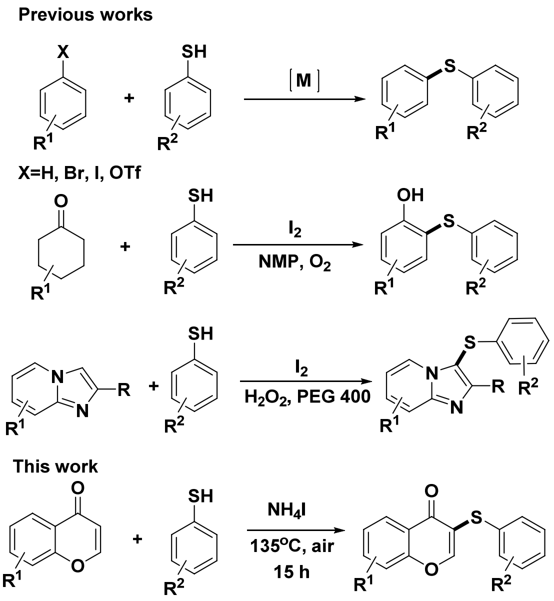
The regioselective and metal-free sulfenylation of flavones was achieved under aerobic conditions with ammonium iodide salt as an inducer instead of traditional iodine/oxidant combinations. This method enables the generation of various ArS-substituted flavone derivatives in good to excellent yields under environmentally friendly conditions, which significantly enriches current flavone chemistry.

The construction of C-S bond is a very important transformation in organic synthesis,[1] because C-S bond is widely present in natural products and drug molecules.[2] Therefore, many researchers have devoted their efforts on developing highly efficient, regioselective, and environmentally friendly C-S bond formation methods.[3] Traditionally, C(sp^3)-S bond can be constructed easily by the condensation of an alkyl halide with a metal thiolate.[4] Recently, transition metal catalyzed C(sp^2)-S bond formation were successfully developed via cross couplings between aryl halides and various sulfenylating reagents such as thiols (Scheme 1),[5] sulfonyl chlorides,[6] disulfides,[7] sodium sulfinates,[8] and sulfonyl hydrazides.[9] However, these processes require the use of prefunctionalized halides and expensive catalysts.[10]

Recently, transition metal-catalyzed C-S bond formation via direct C-H bond functionalization has risen as an efficient alternative method, which allows direct conversion of C-H into C-S bonds. Although this method is highly efficient and atom-economic, these reactions still suffer from the high loading of transition metal catalysts, additives and harsh reaction conditions sometimes.[11]

Very recently, metal-free iodine-induced sulfenylation method to construct C(sp^2)-S bond was successfully developed (Scheme 1).[12] This method doesn't need the use of any toxic and transitional metal catalysts, and proceeded well under environmentally friendly reaction conditions, generating thioesters in good yields. Despite this significant progress, the development of a new metal-fr sulfenylation method is still highly desirable.

Herein, we developed a new and regioselective sulfenylation method in which a clean and colorless ammonium iodide salt was used as an reaction inducer instead of direct usage of purple iodine. In this study, air was used as the oxidant instead of pure oxygen and some oxidants (Scheme 1)[12]; and cheap aryl thiols were used as sulfenylating agents. To the best of our knowledge, there are no such reports to date. In this paper, this ammonium iodide-induced sulfenylation method was directly applied to electron-rich flavones to generate flavone derivatives which may be potentially valuable in drug discovery.



Scheme 1 Previously reported sulfenylation methods with arylthiols as sulfenylating agents.

To find the suitable reaction conditions for the ammonium iodide-induced sulfenylation between flavones and aryl thiols, flavone **1a** and thiol **2a** were used as the representative reactants. Different catalysts/inducers, oxidants, and solvents were screened

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[a] Pharmacy School, Jiangsu University, Xuefu Road 301, Zhenjiang, Jiangsu 212013, People's Republic of China, Email: ahz@ujs.edn.cn.

[b] Scientific Information Research Institute, Jiangsu University (Library), Xuefu Road 301, Zhenjiang, Jiangsu 212013, People's Republic of China.

[c] Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, Indianapolis IN 46202 (USA), Email: geh@iupui.edu

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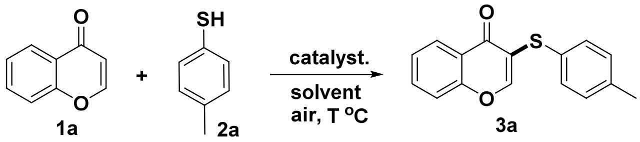
under different reaction temperature (Table 1). First, $CuCl_2$ and $FeCl_3$ were used as catalysts, and TBHP (*tert*-butyl hydroperoxide, 70 wt % in water) was employed as an oxidant. Both reactions gave a less than 5% yield or trace amount of expected product **3a** (entries 1 and 2) at 80 °C in CH_3CN. Using CuI as a catalyst with TBHP also provided a less than 5% yield of **3a** (entry 3) in CH_3CN. The combination of KI and TBHP only produced a 20% yield of **3a** (entry 4). When I_2 was employed with TBHP in CH_3CN, 45% of **3a** was observed (entry 5). The TBAI/TBHP combination in CH_3CN didn't afford **3a** at all (entry 6), while the combination of NH_4I/TBHP in CH_3CN afforded a 53% yield of **3a** (entry 7). The combination of I_2/TBHP or I_2/DTBP afforded **3a** in 70% and 65% yields, respectively (entries 8 and 9). When the reaction temperature was raised to 135 °C, the combination of NH_4I/TBHP in CH_3CN gave a 78% yield (entry 10). By converting NH_4I into I_2, the reaction afforded 75% yield of **3a** (entry 11). Using DMF instead of CH_3CN afforded 83% yield of **3a** (entry 12). Surprisingly, when NH_4I was used without TBHP, the reaction also gave an 86% yield of **3a** (entry 13). Decreasing the amount of NH_4I from 2.0 to 1.2 equivalents led to 64% yield (entry 14). Using CH_3CN or THF as a solvent generated 55% yield or trace amount of product (entries 15 and 16). When toluene was used as a solvent, 73% yield of **3a** (entry 17) was obtained. No presence of NH_4I in DMF didn't produce any product (entry 18). Using H_2O_2 instead of TBHP as an oxidant in the presence of NH_4I afforded **3a** in a 65% yield (entry 19). While the combination of I_2/H_2O_2 gave a 70% yield of **3a** (entry 20). After the above screening, the suitable conditions selected for the coupling of flavone and aryl thiol are: flavone (1.0 equiv.), thiols (1.2 equiv.), NH_4I (2.0 equiv.), DMF is used as a solvent and temperature: 135°C.

After suitable reaction conditions have been obtained, different aryl thiols were reacted with different flavones which were synthesized based on existing literature[13]. From Table 2, it can be found that all flavones with electron-donating functions gave better yields, while flavones with electron-deficient functions gave a little bit lower yields. Based on ^1H and ^{13}C-NMR spectra of all products, it was found that -SAr was regioselectively added to the *α*-position of

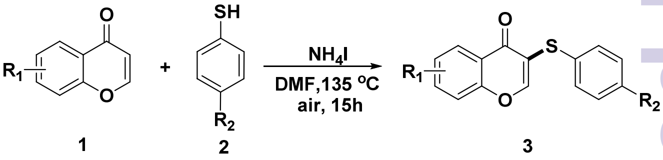
Table 1 Screening of reaction conditions[a]

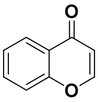
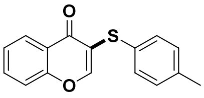
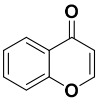
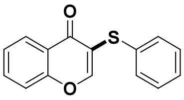
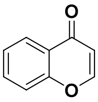
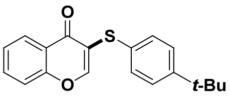
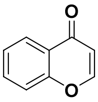
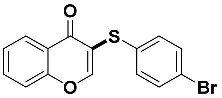
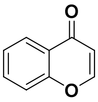
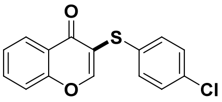
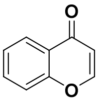
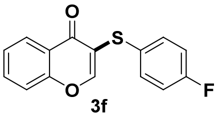
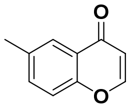
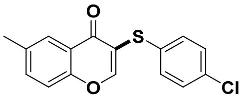
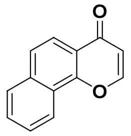
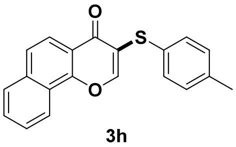


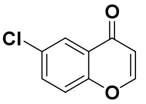
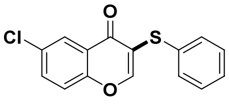
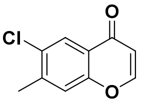
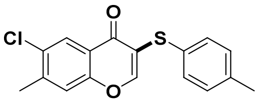
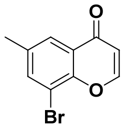
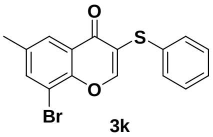
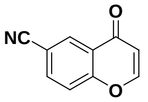
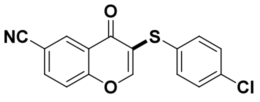
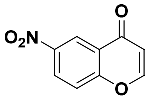
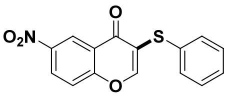
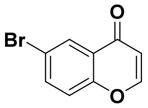
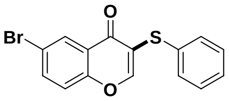
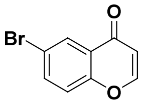
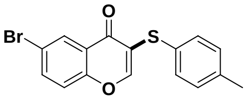
Entry	Catalyst /Inducer	Reagent	Temp. (°C)	Solvent	Yield[b] (%)
1	$CuCl_2$	TBHP	80	CH_3CN	5
2	$FeCl_3$	TBHP	80	CH_3CN	trace
3	CuI	TBHP	80	CH_3CN	<5
4	KI	TBHP	80	CH_3CN	20
5	I_2	TBHP	80	CH_3CN	45
6	TBAI	TBHP	80	CH_3CN	0
7	NH_4I	TBHP	80	CH_3CN	53
8	I_2	DCP	80	CH_3CN	70
9	I_2	DTBP	80	CH_3CN	65
10	NH_4I	TBHP	135	CH_3CN	78
11	I_2	TBHP	135	CH_3CN	75
12	NH_4I	TBHP	135	DMF	83
13	NH_4I	--	135	DMF	86
14	NH_4I[c]	--	135	DMF	64
15	NH_4I	--	135	CH_3CN	55
16	NH_4I	--	135	THF	trace
17	NH_4I	--	135	Toluene	73
18	--	--	135	DMF	0
19	NH_4I	H_2O_2	135	DMF	65
20	I_2	H_2O_2	135	DMF	70

[a] Reaction conditions: flavone (1 equiv.), aryl thiol (1.2 equiv.), NH_4I (2.0 equiv.), aqueous TBHP (70 wt % in water, 2.0 equiv.), metal catalyst (10 mol%), DMF (0.5 mL). [b] Isolated yields are based on reactant **1a**, the reaction was run for 15 hours with air. [c] NH_4I (1.2 equiv.)

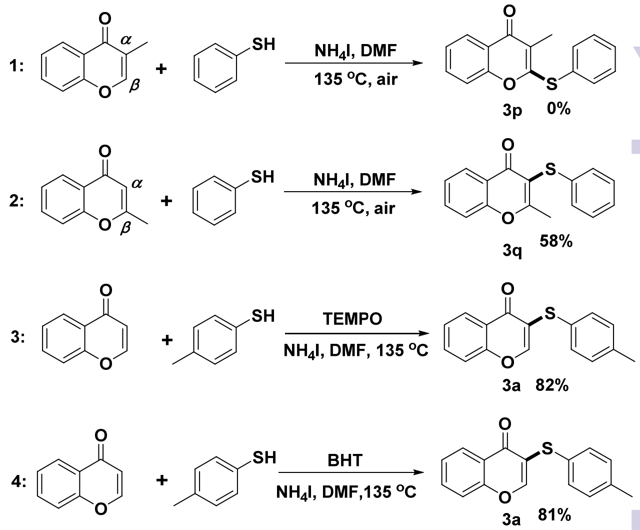
Table 2 Ammonium iodide-mediated sulfenylation reactions using thiols as sulfenylating agents[a]



Entry	Reactant **1**	Product **3**	Yield[b] (%)
1		 3a	85
2		 3b	86
3		 3c	80
4		 3d	82
5		 3e	84
6		 3f	81
7		 3g	83
8		 3h	81

9		 3i	85
10		 3j	83
11		 3k	82
12		 3l	79
13		 3m	77
14		 3n	84
15		 3o	82

[a] Reaction conditions: flavone (1.0 equiv.), aryl thiol (1.2 equiv.), NH_4I (2.0 equiv.). [b] Isolated yields are based on reactant **1a**, the reaction was run for 15 hours.

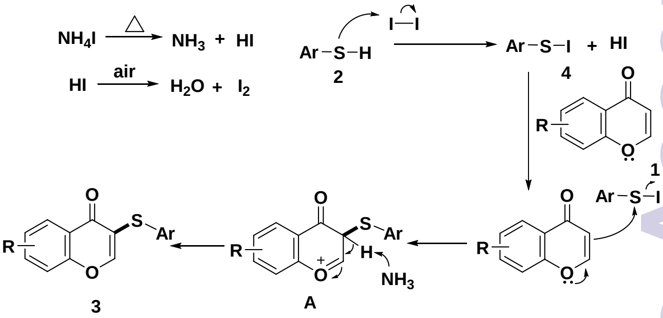


Scheme 2 Control reactions and radical trapping experiments.

the ketone function of flavones, and no β-substituted products were isolated.

To further explore how the substituents on α and β-position of flavones influence the regioselective sulfenylation, two methyl-substituted flavones were synthesized with methyl function on α and β-position of the flavone (see Scheme 2, entries 1 and 2). When the α-position reaction site was blocked, no any expected product was isolated, indicating that the regioselectivity of this sulfenylation is very good, and the reaction only happened on the α-position of flavone. When the methyl group on the β-position of flavone, a decreased sulfenylation yield was observed, possibly due to the steric effects caused by neighbouring methyl function.

To determine if a radical process is involved in this sulfenylation protocol, TEMPO (2,2,6,6-tetramethypiperidine) and BHT (butylated hydroxytoluene) were used as radical scavengers in the reaction of producing **3a**. In the presence of TEMPO or BHT, **3a** was still produced in good yields (Scheme 2). This fact indicated that radical intermediate is not involved in the sulfenylation process. Based on the above results and existing literature,[12a,14] a plausible nucleophilic substitution reaction mechanism is proposed below. At 135 °C, NH_4I was split into NH_3 and HI, and the resulting HI was further oxidized by air to generate iodine. Thiophenol was then reacted with iodine to form electrophilic species ArS-I, which reacted further with electron-rich flavone **1** to give reaction intermediate A. After the loss of a proton from intermediate A, final product **3** was obtained.



Scheme 3 Proposed reaction mechanism

Conclusion

In summary, an efficient and regioselective ammonium iodide-induced sulfenylation of flavones is herein reported with different thiophenols as sulfenylating agents, generating various ArS-substituted flavone derivatives in good to excellent yields under metal-free conditions. This method has improved the current reported protocol represented by using iodine as a catalyst. This method enriches current flavone chemistry, making it a highly valuable and practical approach in pharmaceutical industry. Investigation on biological activities of flavone derivatives is currently underway. The method is also quite suitable for compound library production.

Acknowledgment

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Notes and references

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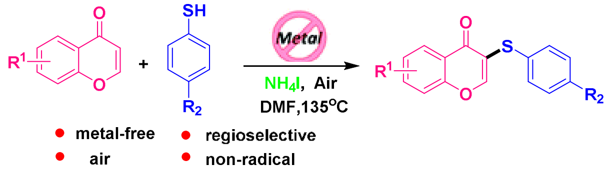
Graphic abstract:



The regioselective and metal-free sulfenylation of flavones was achieved under aerobic conditions with ammonium iodide as an inducer