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Regioselective C–S Bond Formation between Flavones and Arylsulfonyl Chlorides through the Use of Ammonium Iodide

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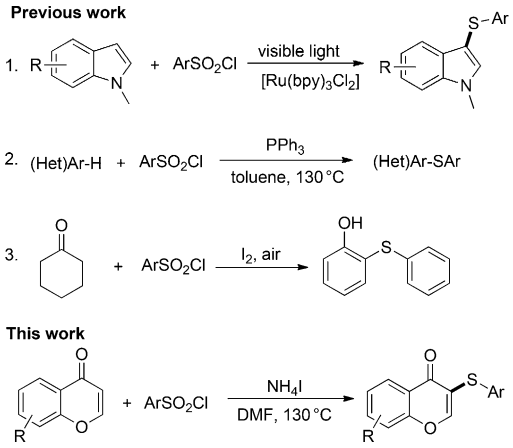
A novel and regioselective ammonium iodide mediated C–S bond formation protocol involving flavones and sulfonyl chlorides to generate different ArS-substituted flavone derivatives in high yields was developed. Different from existing metal-free C–S bond formation protocols with the use of PPh_3 or I_2 as the catalyst, this method provides an alternative way of constructing C–S bonds through the use of NH_4I as a catalyst, which makes it highly valuable for the efficient synthesis of thioether compounds.

Thioethers exist widely in natural products,[1] and many drugs also possess the thioether structure;[2] therefore, the development of efficient methods to construct C–S bonds is highly desirable.

Traditionally, the construction of a C(sp^3)–S bond is achieved by reacting an alkyl halide with a metal thiolate.[3] Later, transition-metal-catalyzed couplings between aryl halides (or aryl boronic acids, etc.) and various sulfenylating sources such as thiols,[4] sulfonyl chlorides,[5] disulfides,[6] sodium sulfinates,[7] and sulfonyl hydrazides[8] to generate C(sp^2)–S bond were developed, and various transition metals such as ruthenium, palladium, copper, nickel, cobalt, and iron salts have been used as efficient catalysts to generate thioethers.[9]

Recently, the transition-metal-catalyzed formation of C–S bonds through C–H bond functionalization was proposed as an alternative method to convert C–H bonds directly into C–S bonds,[10] but these reactions still suffer from high loadings of toxic transition-metal catalysts and some additives.

Very recently, metal-free C–S bond-formation methods have been successfully developed;[11] among these methods, the use of arylsulfonyl chlorides as sulfenylating agents was also achieved (Scheme 1). Zheng and co-workers reported the visible-light-induced sulfenylation of *N*-methylindoles with arylsulfonyl chlorides,[5a] You and co-workers demonstrated C–S bond formation by directly using arylsulfonyl chlorides as a sulfur source in the presence of triphenylphosphine,[12a] and Deng et al. reported iodine-promoted 2-arylsulfanylphenol formation by using cyclohexanones as the phenol source.[12b] All three reported reactions generate C–S bonds by using arylsulfonyl chlorides as sulfenylating agents. In this paper, we report a new method to construct C–S bond by using NH_4I as a catalyst to generate thioether flavone derivatives regioselectively in good to excellent yields without using any oxidants. To the best of our knowledge, there are no reports on such a - reaction.



Scheme 1. Sulfenylation methods with the use of arylsulfonyl chlorides as the sulfur source.

To find suitable reaction conditions for this sulfenylation reaction between flavones and arylsulfonyl chlorides, flavone **1a** and sulfonyl chloride **2a** were used as the representative reactants (Table 1), and different catalysts, oxidants, temperature, and solvents were screened. First, CuI and $FeCl_3$ were used as catalysts and *tert*-butyl hydroperoxide (TBHP, 70 wt% in water) was employed as the oxidant in CH_3CN; both reactions did not give expected product **3a** (Table 1, entries 1 and 2) at 90 °C in CH_3CN. The use of tetrabutylammonium iodide (TBAI) as a catalyst with TBHP provided less than 5% yield of **3a** (Table 1, entry 3) in CH_3CN. Upon using NaI or KI with TBHP, a trace amount of **3a** was produced (Table 1, entries 4 and 5). The I_2/TBHP combination in CH_3CN afforded **3a** in 60% yield (Table 1, entry 6), whereas the combination of NH_4I/TBHP in CH_3CN afforded **3a** in 65% yield (Table 1, entry 7). The combination of NH_4I/TBHP in DMF at 90 °C afforded **3a** in 70% yield (Table 1, entry 8). Upon increasing the temperature to 130 °C, **3a** was obtained in 79% yield (Table 1, entry 9). Surprisingly, the use of NH_4I without TBHP in DMF also afforded **3a** in 81% yield (Table 1, entry 10). If NH_4I was employed as the catalyst in benzene or toluene, **3a** was isolated in only 25 or 30% yield (Table 1, entries 11 and 12). Using THF or dioxane as the solvent generated **3a** in 48 or 30% yield, respectively (Table 1, entries 13 and 14). Decreasing the number of equivalents of NH_4I

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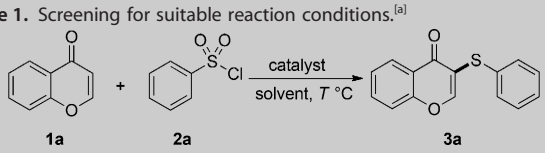
Table 1. Screening for suitable reaction conditions.[a]

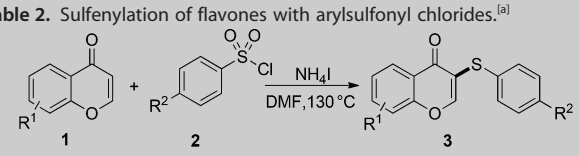


1a 2a 3a

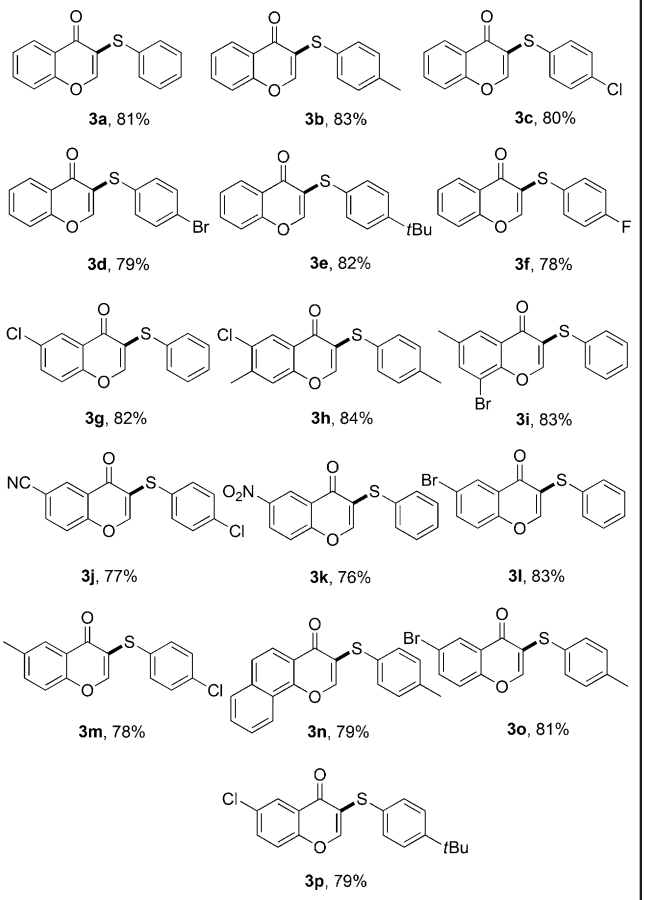
Entry	Catalyst	Oxidant	Solvent	T [°C]	Yield[b] [%]
1	CuI	TBHP	CH_3CN	90	0
2	$FeCl_3$	TBHP	CH_3CN	90	0
3	TBAI	TBHP	CH_3CN	90	5
4	NaI	TBHP	CH_3CN	90	trace
5	KI	TBHP	CH_3CN	90	trace
6	I_2	TBHP	CH_3CN	90	60
7	NH_4I	TBHP	CH_3CN	90	65
8	NH_4I	TBHP	DMF	90	70
9	NH_4I	TBHP	DMF	130	79
10	NH_4I	–	DMF	130	81
11	NH_4I	–	benzene	130	25
12	NH_4I	–	toluene	130	30
13	NH_4I	–	THF	130	48
14	NH_4I	–	dioxane	130	30
15	NH_4I[c]	–	DMF	130	62
16	–	–	DMF	130	0

[a] Reaction conditions: Flavone (0.1 mmol, 1.0 equiv.), sulfonyl chloride (1.5 equiv.), KI/I_2 (1.0 equiv.), NH_4I (4.0 equiv.), solvent (0.5 mL), metal catalyst (20 mol%). All reactions were run for 20 h. [b] Yield of isolated product based on reactant **1a**. [c] NH_4I (1.0 equiv.).

Table 2. Sulfenylation of flavones with arylsulfonyl chlorides.[a]



1 2 3

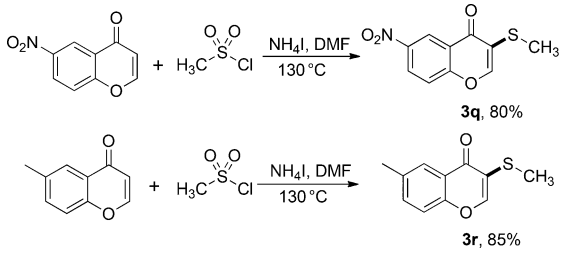


[a] Reaction conditions: Flavone (1.0 equiv.), sulfonyl chloride (1.5 equiv.), NH_4I (4.0 equiv.), solvent (0.5 mL). All reactions were run for 20 h. [b] Yields of isolated products **3a**–**p** were based on the reactant flavones.

from four to one led to the isolation of **3a** in 62% yield (Table 1, entry 15). The reaction did not produce the expected product (Table 1, entry 16) in the absence of NH_4I. After the above screening, the suitable conditions selected for the coupling of flavone and arylsulfonyl chloride included flavone (1.0 equiv.), arylsulfonyl chloride (1.5 equiv.), and NH_4I (4.0 equiv.) in DMF as the solvent at 130 °C.

After suitable reaction conditions were determined, different electron-withdrawing and electron-donating flavones were synthesized on the basis of existing literature,[13] and they were then treated with various arylsulfonyl chlorides; all sulfenylation reactions proceeded well and afforded good yields of ArS-substituted flavone derivatives **3a**–**p** (Table 2) with high regioselectivities. On the basis of the chemical shifts displayed in the ^{1}H NMR and ^{13}C NMR spectra of each ArS-substituted flavone derivative, all substrates were bonded to the more electron-rich α positions of the flavone ketone functions.

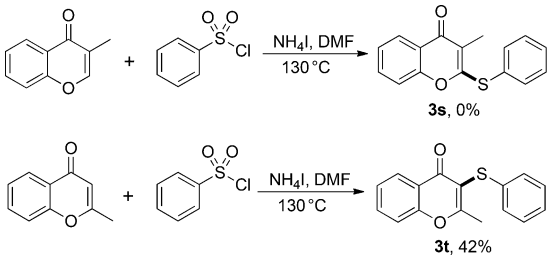
To expand the sulfenylation reaction scope, an alkylsulfonyl chloride was also tried, and methanesulfonyl chloride was used as a representative to react with electron-deficient nitro-substituted flavone and electron-rich methyl-substituted flavone; both reactions gave good yields of expected products **3q** and **3r** (Scheme 2).



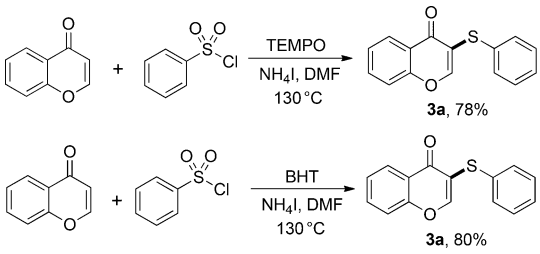
Scheme 2. Sulfenylation reactions of flavones with methanesulfonyl chloride.

To provide further insight into the regioselectivity of this sulfenylation reaction, α-methyl-substituted and β-methyl-substituted flavones were synthesized and treated with benzenesulfonyl chloride (Scheme 3). If the preferred reaction site (α position) was blocked by a methyl group, no desired product was isolated. If the β position of the flavone was bonded to a $-CH_3$ group, the sulfenylation reaction still proceeded, but because of steric factors, the isolated yield was not high (42%). This result indicates that the regioselectivity of this sulfenylation reaction is very good.

To further explore the reaction mechanism, 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and butylated hydroxytoluene (BHT) were used as radical scavengers in subsequent reactions (Scheme 4). In the presence of TEMPO or BHT, the reaction pro-



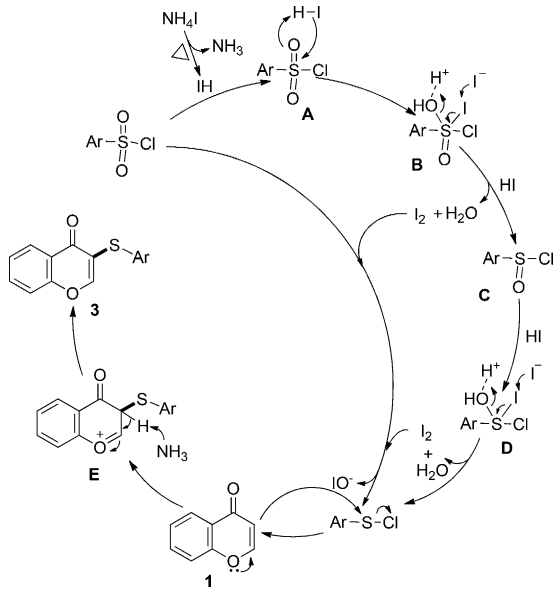
Scheme 3. Control reactions.



Scheme 4. Radical trapping experiments.

ceeded well and afforded **3a** in good yield, which indicates that radical intermediates are not involved in either of these couplings.

On the basis of these results, a plausible mechanism is proposed (Scheme 5). Heat splits NH_4I into HI and NH_3, and then HI reduces the sulfonyl chloride; after intermediates **B**, **C**, and **D** and the loss of two H_2O molecules, the electrophilic ArS–Cl species is produced, which then continues to react with flavone **1** to give intermediate **E**. The loss of a proton from **E** to NH_3 generates final product **3**. The resultant iodine reacts with the arylsulfonyl chloride to generate ArS–Cl and to release the IO^- ion.[12b]



Scheme 5. Proposed reaction mechanism.

In summary, we developed a novel and regioselective ammonium iodide mediated C–S bond-formation protocol involving flavones and arylsulfonyl chlorides to generate different ArS-substituted flavone derivatives in high yields. This method can also be extended to alkylsulfonyl chlorides. This protocol enriches current metal-free C–S bond formation chemistry by using sulfonyl chlorides as the sulfenylating agents, which makes it a good choice for the efficient synthesis of thioether compounds. This method is also suitable for the production of a library of compounds as a result of its high regioselectivity and efficiency.

Experimental Section

General procedure

Flavone **1a** (0.5 mmol, 1.0 equiv.) was added to a dried sealed tube containing DMF (0.5 mL), and this was followed by the addition of NH_4I (4.0 equiv.) and the sulfonyl chloride (1.5 equiv.). The mixture was stirred at 130 °C. After 20 h, the mixture was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried with anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (silica gel, petroleum ether/EtOAc = 15:1) to give desired product **3a** (81%) as a colorless oil. The same procedure was used to prepare compounds **3b–t**.

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Keywords: C–S bond formation · flavones · fused-ring systems · sulfenylation · sulfur

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