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Ammonium Iodide Induced Nonradical Regioselective Sulfenylation of Flavones via a C−H Functionalization Process

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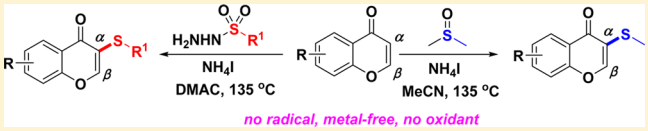
Supporting Information

ABSTRACT: A novel and highly regioselective ammonium iodide-induced nonradical sulfenylation method for the construction of a C−S bond was developed via C−H functionalization. With DMSO or $R^1SO_2NHNH_2$ as a sulfenylating agent, MeS- and R^1S-substituted flavone derivatives were obtained in good yields. This method enriches current C−S bond formation chemistry, making it a highly valuable and practical method in pharmaceutical industry.



INTRODUCTION

Organic molecules containing a C−S bond widely exist in nature, possessing a variety of valuable biological activities.[1] Therefore, considerable efforts have been devoted to the development of efficient synthetic methods to construct a C−S bond between biologically relevant molecules and sulfenylating sources.[2]

Traditionally, a C−S bond is achieved by the condensation of an alkyl halide with a metal thiolate.[3] Later, transition-metal-catalyzed couplings between vinyl/aryl halides and sulfenylating sources such as thiols, sulfonyl chlorides, and disulfides have been developed.[4] One shortcoming of these methods is that prefunctionalized reactants are needed for these reactions.

Recently, direct formation of a C−S bond via C−H bond functionalization has emerged as an efficient method which enables superior step and atom-economic transformations (see DMSO example in Scheme 1).[5] Although no prefunctionalized reactants are needed, these reactions often suffer from the high loading of transition metal catalysts, additives, and harsh reaction conditions sometimes.

Very recently, metal-free sulfenylation processes via direct functionalization of unreactive C−H bonds were also developed;[6] DMSO, $R^1SO_2NHNH_2$, R^1SO_2Na, and R^1SO_2H were often used as sulfenylating agents in these processes (Scheme 1).[7,8] Compared with smelly and unstable thiols, these sulfenylating agents are stable, odorless, and readily available.

In this paper, we reported a novel and regioselective sulfenylation method via direct C−H functionalization, in which ammonium iodide (NH_4I) was employed as a catalyst instead of previously reported iodine (I_2) (Scheme 1). Both DMSO and alkyl/arylsulfonyl hydrazines were used as sulfenylating agents. Although TBAI(Bu_4NI)/TBHP(*t*-BuOOH)-mediated sulfonylation methods have been reported to construct the ($C-SO_2R$) bond recently,[9] sulfonylation is different from sulfenylation (C−S bond construction) in which no oxygen atoms are connected with the sulfur atom. More importantly, no oxidants were needed in our sulfenylation approach.

Flavone is a well-known natural product class in drug discovery with carbonyl-conjugated olefin function in its structure; its electron-rich ring enables it to undergo direct C−H bond functionalization with electrophiles (DMSO or $R^1SO_2NHNH_2$) to form MeS- and R^1S-substituted flavone derivatives. To the best of our knowledgement, there are no reports until now.

RESULTS AND DISCUSSION

Based on previous reports of C−S bond construction,[10] we first investigated suitable reaction conditions for the couplings of flavone with DMSO. Flavone **1a** and DMSO were used as the representative reactants, and different catalysts and solvents were screened for the reaction (Table 1).

First, CuI, $CuBr_2$, or $FeCl_3$ was used as a catalyst for the coupling, and none of these reactions gave the expected product **2a** (entries 1−3) at 95 °C. Using NaI or TBAI as a catalyst did not generate product **2a** (entries 4 and 5) either. When I_2 was selected as a catalyst, the reaction product **2a** was obtained in 10% yield (entry 6). When NH_4I (1.0 equiv) was employed with water as a solvent, a trace amount of **2a** was produced (entry 7). Increasing NH_4I (4.0 equiv) to 4 equiv gave **2a** in less than 5% yield (entry 8). Elevating the reaction temperature to 135 °C in the presence of iodine led to a 79% yield of expected product **2a** (entry 9). Using NH_4I as a catalyst

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Scheme 1. Representative Sulfenylation Methods

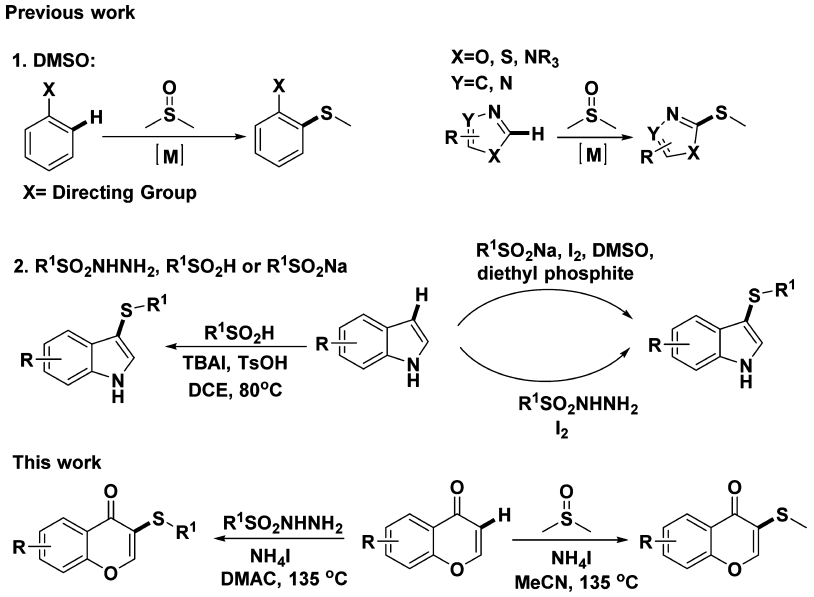
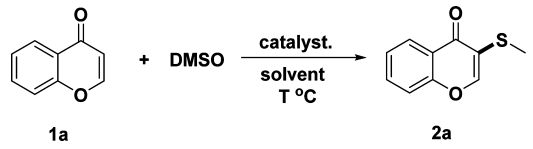


Table 1. Screening Reactions for the Sulfenylation[a]



1a 2a

entry	catalyst	solvent	temp (°C)	yield (%)
1	CuI	–	95	0
2	$CuBr_2$	–	95	0
3	$FeCl_3$	–	95	0
4	NaI	–	95	0
5	TBAI	–	95	0
6	I_2	–	95	10
7	NH_4I[b]	H_2O	95	trace
8	NH_4I	H_2O	95	<5
9	I_2	MeCN	135	79
10	NH_4I	–	135	25
11	NH_4I	H_2O	135	65
12	NH_4Cl	H_2O	135	0
13	NH_4I	DCE	135	65
14	NH_4I	MeCN	135	81
15	NH_4I	EtOAc	135	trace
16	NH_4I	THF	135	50
17	NH_4I	toluene	135	65

[a]Reaction conditions: flavone **1a** (0.5 mmol, 1.0 equiv), DMSO (0.3 mL), NaI/TBAI/I_2 (20 mol %), NH_4I/NH_4Cl (4.0 equiv), metal catalyst (20 mol %), solvent (0.5 mL); yield is based on reactant **1a**. All reactions were run for 24 h. [b]NH_4I (1.0 equiv).

only afforded a 25% yield of product **2a** (entry 10). When water was used as a solvent, a 65% yield of **2a** was obtained (entry 11). When NH_4Cl was used instead of NH_4I as a catalyst at 135 °C, no expected product **2a** was isolated (entry 12). When DCE was used as the solvent, the reaction gave a 65% yield of **2a** (entry 13). Using CH_3CN as the solvent gave **2a** in an 81% yield (entry 14). Interestingly, changing DCE to EtOAc did not generate **2a** (entry 15), but with THF or toluene as a solvent, a moderate yield of product **2a** (entries 16 and 17) was produced. After the screening, the suitable sulfenylation reaction conditions selected for the couplings of flavone with DMSO are NH_4I (4.0 equiv), DMSO (0.3 mL), and flavone (0.5 mmol, 1.0 equiv), with CH_3CN as the solvent at 135 °C.

After suitable reaction conditions were obtained, different flavones were reacted with DMSO. Eleven different flavones with electron-deficient and -donating substituents were synthesized based on existing methods[11] and used as the coupling reactant partners. From the Table 2, it can be found that all flavones with electron-donating functions (H, CH_3, −OH) gave good yields of desired products, while flavones with electron-deficient functions (−CN, $-NO_2$) gave moderate yields of desired products. All reactions selectively occurred on the α-positions of the ketone function of flavones, while only a trace amount of β-position products were isolated.

To further study the application scope of this ammonium iodide induced sulfenylation method, instead of using DMSO, another important sulfenylating agent $R^1SO_2NHNH_2$ was also employed under the same reaction conditions. It was found that **4a** was obtained in a 48% yield (entry 1, Table 3). To further explore this reaction, the molar amount of NH_4I was decreased from 4 to 1 equiv, the reaction only afforded a 5% isolated yield of the desired product (entry 2). Using THF or toluene as a solvent also gave low yields of **4a** respectively (entries 3 and 4). When DCE was selected as a solvent, a trace amount of **4a** was produced (entry 5). But using DMF as a solvent afforded a 78% yield of expected product **4a** (entry 6). When DMAC (dimethylacetamide) was used as a solvent, an 83% yield was obtained (entry 7). After the screening, the suitable sulfenylation conditions include flavone (0.5 mmol, 1.0 equiv), a temperature of 135 °C, $R^1SO_2NHNH_2$ (1.2 equiv), NH_4I (4.0 equiv), and DMAC (0.5 mL) which is used as a solvent.

After the optimal reaction conditions were obtained, different flavones were reacted with arylsulfonyl hydrazines. It was found that the majority of reactions proceeded well, and all C−H bonds on α-positions of flavones were regioselectively functionalized and replaced by ArS− functions to give products **4a**−**m** in good yields. As shown in the Table 4, different flavones and arylsulfonyl hydrazines were used for these regioselective sulfenylation reactions of flavones. Flavones

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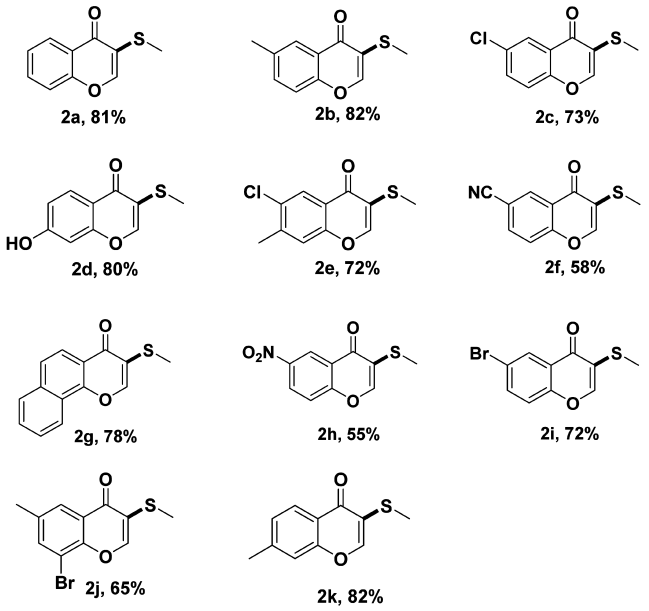
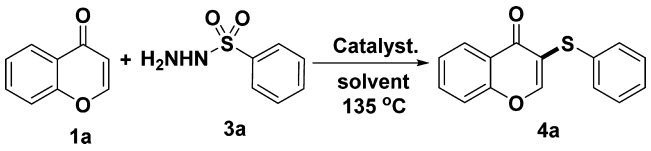
Table 2. Regioselective Sulfenylation of Flavones with DMSO[a]



[a]Reaction conditions: flavone (1.0 equiv), DMSO (0.3 mL), NH_4I (4.0 equiv), CH_3CN (0.5 mL); isolated yield is based on reactant **1**. All reactions were run for 24 h at 135 °C.

Table 3. Screening Reactions for the Sulfenylation via Using Benzenesulfonyl Hydrazine[a]



entry	catalyst	solvent	yield (%)
1	NH_4I	MeCN	48
2	NH_4I[b]	MeCN	5
3	NH_4I	THF	30
4	NH_4I	toluene	25
5	NH_4I	DCE	trace
6	NH_4I	DMF	78
7	NH_4I	DMAC	83

[a]Reaction conditions: flavone (0.1 mmol, 1.0 equiv), benzenesulfonyl hydrazine **3a** (1.2 equiv), NH_4I, (4.0 equiv), solvent (0.5 mL); all reactions were run for 24 h. [b]NH_4I (1.0 equiv).

with electron-withdrawing functions (such as −CN, $-NO_2$) gave relatively lower yields compared with other flavones.

To explore if alkylsulfonyl hydrazine is also suitable for this sulfenylation method, herein, aliphatic methylsulfonyl hydrazine ($CH_3SO_2NHNH_2$) was selected as a sulfenylating agent and two flavones were used as representative reactants, under the same reaction conditions; both reactions afforded good yields of expected products **4n**−**o** (Scheme 2).

To determine if a common sulfenylating agent, aromatic thiol, is also suitable for this sulfenylation method, instead of using alkyl/aryl sulfonyl hydrazines, *p*-toluenethiol was tested for this sulfenylation reaction. It was found that the reaction also proceeded well under the same conditions, generating a good yield of **4b**. To further extend the application scope of this method, three different electron-rich compounds were selected as reaction partners for this sulfenylation reaction instead of using flavones (Scheme 3); these selected reactants were indole **7**, 2-phenylimidazo[1,2-*a*]pyridine **9**, and benzofurazan **11** which all included electron-rich double bonds in their structures. After the reactions with *p*-toluenesulfonyl hydrazine under the same conditions, respectively, two reactions gave good yields of regioselctive sulfenylated products **8** and **10**. The reaction of benzofurazan **11** with *p*-toluenesulfonyl hydrazine did not generate sulfenylated product **12**, so further exploration was still needed, but this fact would not devalue the promising application of this ammonium iodide induced sulfenylation reaction.

Despite ^1H and ^{13}C NMR spectra have obviously confirmed the structures of products **2a**−**k** and **4a**−**m**, a chemical method to prove the chemical structure was still carried out (Scheme 4). Herein, MeS-substituted flavone **2a** was selected as a representative product. It was easily oxidized by H_2O_2 (30 wt % in water) to give sulfoxide-substituted flavone **13**, while the oxidation by excess *m*-CPBA generated methylsulfonyl-substituted flavone **14**. The same result was also achieved when flavone derivative **4a** was used as a reactant.

To further study how the substituents on the α- and β-position of flavones influenced the regioselectivity of this sulfenylation reaction, two methyl-substituted flavones with methyl functions on the α- and β-position were synthesized. When the reaction sites on the α-positions were blocked by the methyl function (Scheme 5, entries 1 and 3), both reactions did not give CH_3S- or PhS-substituted products **2l**/**4p** on β-positions, indicating that these sulfenylation reactions only regioselectively happened on α-position reaction sites. When the methyl function was on the β-position of flavone, the sulfenylation with DMSO as a sulfenylating agent proceeded well and gave a good yield of **2m**, while a decreased yield was observed when benzenesulfonyl hydrazide was used as a sulfenylating agent, possibly due to the steric effects caused by the neighboring methyl function.

The reaction mechanisms were also explored. To determine if radical intermediates are involved in both sulfenylations, TEMPO (2,2,6,6-tetramethylpiperidinooxy) and BHT (butylated hydroxytoluene) were used as radical scavengers in these reactions (Scheme 6). In the presence of TEMPO and BHT, both expected products **2a** and **4b** were still produced in good yields, indicating that radical intermediates were not involved in both sulfenylation reactions. Based on the above observations and some previous reports,[12] it is believed that nucleophilic substitution reactions might occur via the following processes (Scheme 7).

For the DMSO case, at 135 °C, NH_4I was split into HI and NH_3, and the resultant HI reduced DMSO to give electrophilic intermediate B, which easily reacted with nucleophilic flavone to generate intermediate C. Intermediate C underwent subsequent attacks from I^- and NH_3 to give final product **2**. For the sulfonyl hydrazine case, the $-SO_2NHNH_2$ function was first reduced by HI, followed by the loss of H_2O to generate intermediate G, which again underwent HI reductive dehydration to give the thiodiazonium **15**. As a good electrophile, it regioselectively reacted with flavone **1** on the α position to afford R^1S-substituted flavone derivative **4** finally.

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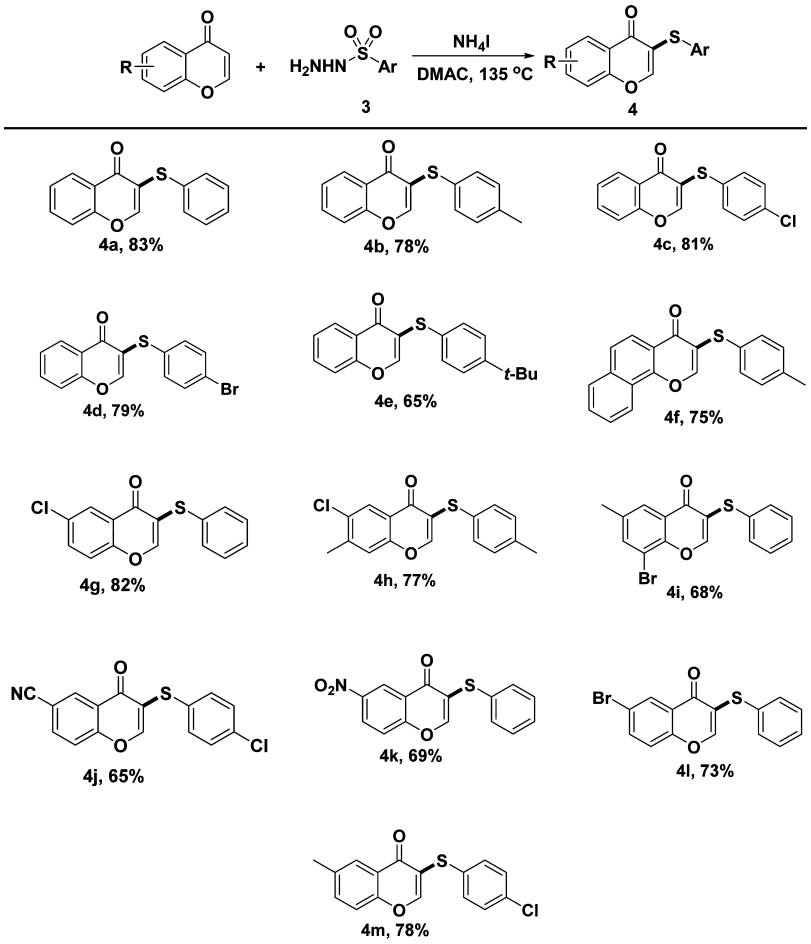
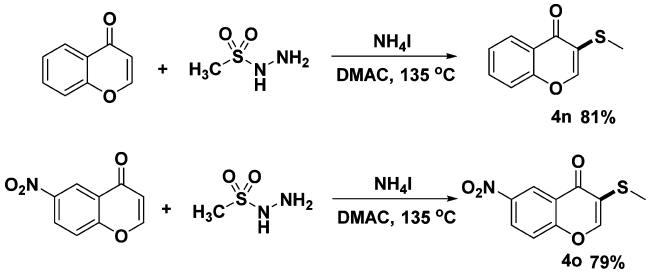
Table 4. Regioselective Sulfenylation Reactions of Flavones with Arylsulfonyl Hydrazines[a]



[a]Reaction conditions: flavone (0.5 mmol, 1.0 equiv), arylsulfonyl hydrazine (1.2 equiv), NH_4I (4.0 equiv), DMAC (0.5 mL); all reactions were run for 24 h at 135 °C.

Scheme 2. Regioselective Sulfenylation of Flavones with Methylsulfonyl Hydrazine



Alternatively, thiodiazonium **15** could be converted into R^1SI by the loss of N_2; the reaction of R^1SI with flavone also generated flavone derivative **4**.

CONCLUSIONS

In summary, a novel and efficient ammonium iodide induced sulfenylation method to construct C−S bond via regioselective C−H functionalization was developed, in which DMSO and alkyl/arylsulfonyl hydrazines were used as sulfenylating agents, generating MeS- and ArS-substituted flavone derivatives in good yields. Besides, this sulfenylation method also works well when aryl thiol was used as a sulfenylating agent and electron-rich heterocycles can also be sulfenylated by this method. The method greatly enriches current C−S bond formation chemistry, making it a highly valuable and practical method in the pharmaceutical industry despite the fact that a high temperature and an excess of ammonium iodide were used. Investigation on the biological activities of flavone derivatives is currently underway. The method is also quite suitable for compound library production.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were carried out in sealed pressure tubes; stirring was achieved with an oven-dried magnetic stirring bar. Solvents were purified by standard methods unless otherwise noted. Commercially available reagents were used throughout without further purification other than those detailed below. Flash column chromatography was performed on silica gel (200−300 mesh). All reactions were monitored by TLC analysis. ^1H and ^{13}C NMR spectra were recorded on a spectrometer operating at 400 and 100 MHz, respectively. HRMS spectrometry (LC-HRMS) data were recorded on a spectrometer operating on ESI-TOF (MeOH as a solvent). Flavones derivatives were synthesized according to existing literature.

General Procedure for the Syntheses of Compounds 2a−m. Flavone **1a** (0.5 mmol, 1.0 equiv) was added to a dried sealed tube with MeCN (0.5 mL), followed by the addition of NH_4I (4.0 equiv). Then DMSO (0.3 mL) was added to the sealed tube. The mixture was stirred at 135 °C. After 24 h, the reaction was cooled down to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was

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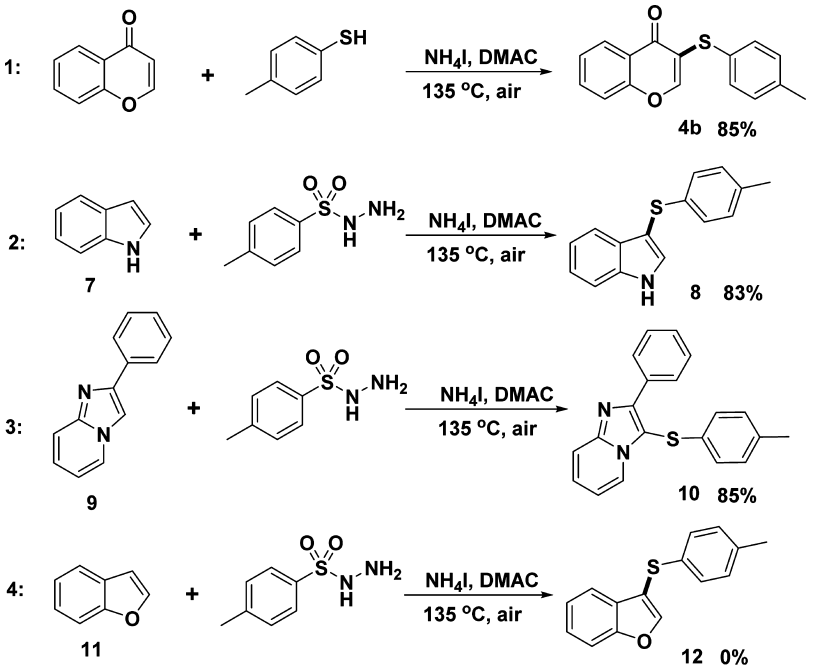
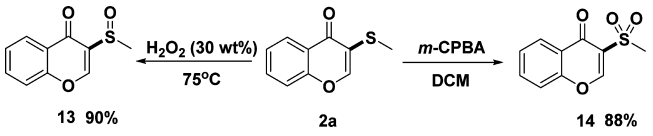
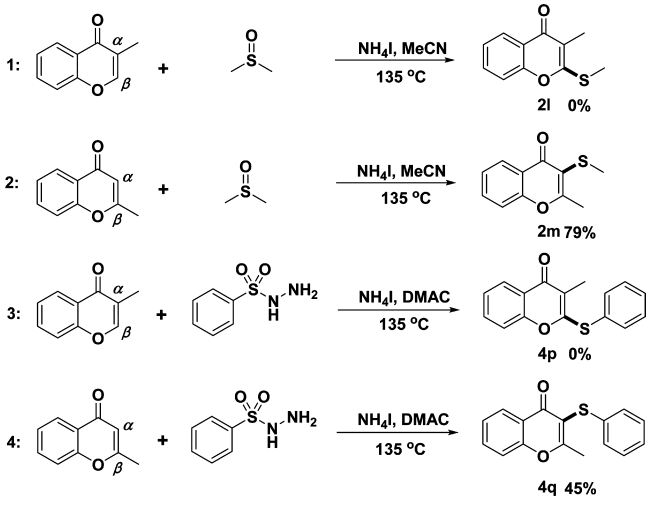
Scheme 3. Extension of This Regioselective Sulfenylation Reactions



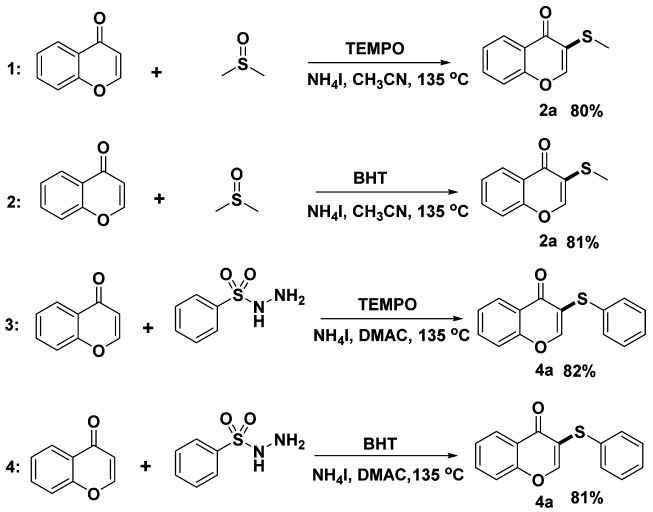
Scheme 4. Oxidation of Flavone 2a with H_2O_2 and *m*-CPBA



Scheme 5. Control Reactions



Scheme 6. Radical Trapping Experiments



purified by flash chromatography (Petroleum ether/EtOAc = 15:1) on silica gel to give the desired product **2a** as a colorless oil in an 81% yield. The same procedure was applied to the production of other compounds **2b**−**m**.

General Procedure for the Synthesis of Compounds 4a−q, 8, 10. Flavone **1a** (0.5 mmol, 1.0 equiv) was added to a dried sealed tube with DMAC (0.5 mL), followed by the addition of NH_4I (4.0 equiv) and benzenesulfonyl hydrazide (0.6 mmol, 1.2 equiv). The mixture was stirred at 135 °C (monitored by TLC). After 24 h, the reaction was cooled down to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (Petroleum ether/EtOAc = 15:1) on silica gel to give the desired product **4a** in a 83% yield as a colorless oil. The same procedure was applied for to produce other compounds **4b**−**q**, **8**, **10**.

*3-(Methylthio)-4H-chromen-4-one (**2a**).* Following the general procedure, isolated yield (77.8 mg, 81%) as a colorless oil; **FTIR**: 3072, 2922, 1628, 1466, 1357, 1084, 792 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.24 (dd, J = 8.0, 1.6 Hz, 1H), 8.05 (s, 1H), 7.69−7.65 (m, 1H), 7.45−7.40 (m, 1H), 2.40 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.6, 156.3, 153.9, 133.8, 126.1, 125.5, 123.1, 121.9, 118.1, 16.3; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_2S^+$ 215.0137 $(M + Na)^+$, found 215.0132.

*6-Methyl-3-(methylthio)-4H-chromen-4-one (**2b**).* Following the general procedure, isolated yield (84.5 mg, 82%) as a colorless oil; **FTIR**: 3064, 2920, 1639, 1486, 1149, 1082, 872 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.48 (dd, J = 8.8, 2.0 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.7, 154.6, 154.0, 135.5, 135.1, 125.3, 122.8, 121.5, 117.8, 21.0, 16.4; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M + Na)^+$, found 229.0292.

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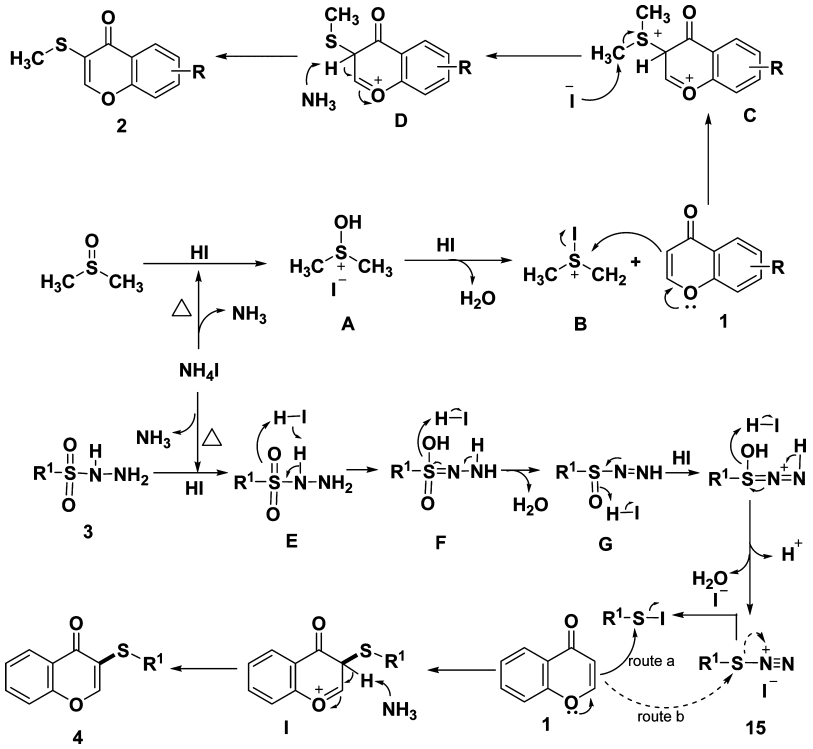
Scheme 7. Proposed Sulfenylation Mechanisms



*6-Chloro-3-(methylthio)-4H-chromen-4-one (**2c**).* Following the general procedure, isolated yield (82.5 mg, 73%) as a colorless oil; **FTIR**: 3083, 2917, 1629, 1467, 1122, 1086, 818, 651 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.21 (d, J = 2.4 Hz, 1H), 8.04 (s, 1H), 7.63 (dd, J = 8.8, 2.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.5, 154.6, 153.7, 134.0, 131.4, 125.4, 124.0, 122.2, 119.9, 16.1; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_7ClNaO_2S^+$ 248.9747 $(M + Na)^+$, found 248.9739.

*7-Hydroxy-3-(methylthio)-4H-chromen-4-one (**2d**).* Following the general procedure, isolated yield (83.2 mg, 80%) as a colorless oil; **FTIR**: 3117, 2924, 1607, 1571, 1242, 1087, 901, 851 cm^{-1}; **^{1}H NMR** (MeOD, 400 MHz): δ 8.17(s, 1H), 8.01 (d, J = 8.8 Hz, 1H), 6.94 (dd, J = 8.8, 2.0 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 2.37 (s, 3H); **^{13}C NMR** (MeOD, 100 MHz): δ 175.6, 163.4, 158.5, 153.9, 126.8, 121.4, 115.4, 115.3, 101.9, 14.6; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_3S^+$ 231.0086 $(M + H)^+$, found 231.0082.

*6-Chloro-7-methyl-3-(methylthio)-4H-chromen-4-one (**2e**).* Following the general procedure, isolated yield (86.4 mg, 72%) as a colorless oil; **FTIR**: 2923, 1633, 1365, 1128, 1090, 911, 874, 644 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17 (s, 1H), 7.99 (s, 1H), 7.33 (s, 1H), 2.49 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.5, 154.5, 153.6, 143.2, 132.1, 125.6, 122.1, 121.9, 119.9, 20.8, 16.2; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_9ClNaO_2S^+$ 262.9904 $(M + Na)^+$, found 262.9898.

*3-(Methylthio)-4-oxo-4H-chromene-6-carbonitrile (**2f**).* Following the general procedure, isolated yield (62.9 mg, 58%) as a colorless oil; **FTIR**: 3104, 2917, 1685, 1366, 1128, 1090, 912, 644 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.60 (d, J = 2.0 Hz, 1H), 8.04 (s, 1H), 7.92 (dd, J = 8.8, 2.0 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.8, 157.9, 153.0, 136.0, 131.9, 123.8, 123.3, 119.9, 117.4, 15.8; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_7NNaO_2S^+$ 240.0090 $(M + Na)^+$, found 240.0089.

*3-(Methylthio)-4H-benzo[h]chromen-4-one (**2g**).* Following the general procedure, isolated yield (94.4 mg, 78%) as a colorless oil; **FTIR**: 3067, 2922, 1624, 1392, 1211, 1110, 892, 766 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.48 (dd, J = 8.0, 0.8 Hz, 1H), 8.18 (m, 2H), 7.94 (t, J = 8.8 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.75−7.67 (m, 2H), 2.48 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.4, 153.8, 152.1, 135.8, 129.5, 128.1, 127.3, 125.6, 123.9, 123.8, 122.2, 120.9, 119.2, 15.9; **HRMS** (ESI-TOF) m/z calculated for $C_{14}H_{10}NaO_2S^+$ 265.0294 $(M + Na)^+$, found 265.0289.

*3-(Methylthio)-6-nitro-4H-chromen-4-one (**2h**).* Following the general procedure, isolated yield (65.3 mg, 55%) as a colorless oil; **FTIR**: 3093, 2920, 1642, 1513, 1342, 1094, 1057, 887, 651 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.13 (d, J = 2.8 Hz, 1H), 8.52 (dd, J = 9.2, 2.8 Hz, 1H), 8.04 (s, 1H), 7.64 (d, J = 9.2 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.2, 159.0, 152.8, 144.9, 128.1, 123.8, 123.0, 122.9, 120.0, 15.7; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NO_4S^+$ 238.0169 $(M + H)^+$, found 238.0171.

*6-Bromo-3-(methylthio)-4H-chromen-4-one (**2i**).* Following the general procedure, isolated yield (98.9 mg, 72%) as a colorless oil; **FTIR**: 2917, 1628, 1464, 1121, 1084, 917, 818 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 2.4 Hz, 1H), 8.05 (s, 1H), 7.76 (dd, J = 8.8, 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 2.42 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.4, 155.0, 153.7, 136.8, 128.7, 124.4, 122.3, 120.1, 118.8, 16.2; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_7BrNaO_2S^+$ 292.9242 $(M + Na)^+$, found 292.9245.

*8-Bromo-6-methyl-3-(methylthio)-4H-chromen-4-one (**2j**).* Following the general procedure, isolated yield (92.7 mg, 65%) as a colorless oil; **FTIR**: 3080, 2919, 1645, 1610, 1465, 1327, 1089, 957, 827 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.98 (dd, J = 1.6, 0.8 Hz, 1H), 7.74 (d, J = 1.6 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.1, 153.2, 151.1, 138.3, 136.5, 125.0, 123.8, 122.3, 111.1, 20.8, 16.0; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_9BrNaO_2S^+$ 306.9399 $(M + Na)^+$, found 306.9395.

*7-Methyl-3-(methylthio)-4H-chromen-4-one (**2k**).* Following the general procedure, isolated yield (84.6 mg, 82%) as a colorless oil; **FTIR**: 3072, 2914, 1622, 1427, 1085, 899, 772, 575 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 8.4 Hz, 1H), 8.00 (s, 1H), 7.22 (t, J = 6.8 Hz, 2H), 2.48 (s, 3H), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.5, 156.4, 153.7, 145.2, 127.0, 125.8, 121.6, 120.9, 117.8, 21.8, 16.3; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M + Na)^+$, found 229.0292.

*2-Methyl-3-(methylthio)-4H-chromen-4-one (**2m**).* Following the general procedure, isolated yield (81.5 mg, 79%) as a colorless oil; **FTIR**: 2924, 1645, 1614, 1558, 1466, 1423, 1349, 1121, 760 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.21 (dd, J = 8.0, 1.6 Hz, 1H), 7.67−7.63

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J. Org. Chem. 2015, 80, 9167−9175

(m, 1H), 7.42−7.37 (m, 2H), 2.72 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.6, 168.7, 155.5, 133.5, 126.2, 125.2, 122.7, 117.7, 117.6, 20.5, 17.1; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M + Na)^+$, found 229.0289.

*3-(Phenylthio)-4H-chromen-4-one (**4a**).* Following the general procedure, isolated yield (105.5 mg, 83%) as a colorless oil; **FTIR**: 3058, 2925, 1653, 1612, 1464, 1309, 1113, 760 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.27 (dd, J = 8.0, 1.6 Hz, 1H), 8.18 (s, 1H), 7.74−7.70 (m, 1H), 7.51−7.40 (m, 4H), 7.33−7.22 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.1, 157.4, 156.4, 134.0, 129.9, 129.2, 127.1, 126.5, 125.8, 123.7, 120.0, 118.2; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{11}O_2S^+$ 255.0474 $(M + H)^+$, found 255.0476.

*3-(p-Tolylthio)-4H-chromen-4-one (**4b**).* Following the general procedure, isolated yield (99.36 mg, 78%) as a colorless oil; **FTIR**: 3075, 2923, 1647, 1464, 1114, 892, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.25 (dd, J = 8.0, 1.6 Hz, 1H), 8.06 (s, 1H), 7.72−7.67 (m, 1H), 7.49−7.42 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.1, 156.3, 156.2, 137.6, 133.9, 131.0, 130.1, 129.8, 126.4, 125.4, 123.6, 121.1, 118.1, 21.1; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{12}NaO_2S^+$ 291.0450 $(M + Na)^+$, found 291.0447.

*3-((4-Chlorophenyl)thio)-4H-chromen-4-one (**4c**).* Following the general procedure, isolated yield (116.9 mg, 81%) as a colorless oil; **FTIR**: 3051, 1648, 1478, 1465, 1313, 1091, 827, 758 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.25 (t, J = 3.2 Hz, 2H), 7.75−7.71 (m, 1H), 7.52−7.45 (m, 2H), 7.35−7.25 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.0, 157.9, 156.4, 134.2, 133.1, 132.8, 130.9, 129.3, 126.5, 125.9, 123.7, 119.2, 118.2; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M + Na)^+$, found 310.9894.

*3-((4-Bromophenyl)thio)-4H-chromen-4-one (**4d**).* Following the general procedure, isolated yield (131.6 mg, 79%) as a colorless oil; **FTIR**: 3061, 2925, 1641, 1463, 1086, 901, 798 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 8.25 (d, J = 1.4 Hz, 1H),7.76−7.71 (m, 1H), 7.52−7.45 (m, 2H), 7.41 (dd, J = 6.8, 2.0 Hz, 2H), 7.26 (dd, J = 8.8, 6.8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.9, 158.1, 156.4, 134.2, 133.6, 132.2, 131.0, 126.5, 126.0, 123.7, 121.0, 119.0, 118.2; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9BrNaO_2S^+$ 354.9399 $(M + Na)^+$, found 354.9394.

*3-((4-(tert-Butyl)phenyl)thio)-4H-chromen-4-one (**4e**).* Following the general procedure, isolated yield (100.9 mg, 65%) as a colorless oil; **FTIR**: 3070, 2963, 1649, 1611, 1560, 1462, 1115, 846, 764 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.27 (dd, J = 8.0, 1.2 Hz, 1H), 8.09 (s, 1H), 7.73−7.68 (s, 1H), 7.49−7.43 (m, 2H), 7.40−7.33 (m, 4H), 1.30 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.2, 156.6, 156.3, 150.7, 133.9, 130.5, 130.0, 126.7, 126.4, 126.3, 125.7, 123.6, 118.1, 34.6, 31.2; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{18}NaO_2S^+$ 333.0920 $(M + Na)^+$, found 333.0917.

*3-(p-Tolylthio)-4H-benzo[h]chromen-4-one (**4f**).* Following the general procedure, isolated yield (119.4 mg, 75%) as a colorless oil; **FTIR**: 3057, 2920, 2361, 1650, 1633, 1384, 1113, 886, 765 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.40 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 8.08 (s, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.77−7.64 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.8, 154.3, 153.7, 138.0, 135.8, 131.7, 130.2, 129.5, 129.1, 128.1, 127.3, 125.7, 123.8, 123.4, 122.2, 121.0, 119.6, 21.2; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{14}NaO_2S^+$ 341.0607 $(M + Na)^+$, found 341.0603.

*6-Chloro-3-(phenylthio)-4H-chromen-4-one (**4g**).* Following the general procedure, isolated yield (118.4 mg, 82%) as a colorless oil; **FTIR**: 3068, 2925, 2360, 1653, 1466, 1303, 1122, 918, 821, 755 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 2.8 Hz, 1H), 8.12 (s, 1H), 7.65 (dd, J = 9.2, 2.8 Hz, 1H), 7.47−7.40 (m, 3H), 7.34−7.25 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.0, 157.0, 154.7, 134.2, 133.4, 131.7, 130.3, 129.3, 127.5, 125.7, 124.5, 120.5, 120.0; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M + Na)^+$, found 310.9914.

*6-Chloro-7-methyl-3-(p-tolylthio)-4H-chromen-4-one (**4h**).* Following the general procedure, isolated yield (121.9 mg, 77%) as a colorless oil; **FTIR**: 3060, 2924, 1651, 1412, 1097, 899, 786 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.19 (s, 1H), 7.98 (s, 1H), 7.35 (d, J = 8.0 Hz, 3H), 7.13 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.33 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.0, 155.9, 154.6, 143.3, 137.8, 132.3, 131.2, 130.1, 129.5, 122.5, 121.2, 119.9, 21.1, 20.9; **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{13}ClNaO_2S^+$ 339.0217 $(M + Na)^+$, found 339.0213.

*8-Bromo-6-methyl-3-(phenylthio)-4H-chromen-4-one (**4i**).* Following the general procedure, isolated yield (118.1 mg, 68%) as a colorless oil; **FTIR:** 3054, 2925, 2360, 1660, 1463, 1299, 1090, 785, 691 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H), 7.98 (d, J = 1.2 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 3.6, 1.6 Hz, 2H), 7.34−7.24 (m, 3H), 2.45 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.5, 156.4, 151.2, 138.5, 136.8, 133.2, 130.5, 129.3, 127.5, 125.3, 124.3, 120.8, 111.2, 20.8; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}BrNaO_2S^+$ 368.9555 $(M + Na)^+$, found 368. 9553.

*3-((4-Chlorophenyl)thio)-4-oxo-4H-chromene-6-carbonitrile (**4j**).* Following the general procedure, isolated yield (101.6 mg, 65%) as a colorless oil; **FTIR**: 3054, 2924, 2361, 1654, 1475, 1313, 815, 670 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.58 (d, J = 2.0 Hz, 1H), 8.16 (s, 1H), 7.94 (dd, J = 8.8, 2.0 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.2, 158.0, 156.7, 136.3, 134.1, 132.2, 132.1, 131.1, 129.6, 123.9, 121.7, 120.0, 117.2, 110.2; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_8ClNNaO_2S^+$ 335.9856 $(M + Na)^+$, found 335.9853.

*6-Nitro-3-(phenylthio)-4H-chromen-4-one (**4k**).* Following the general procedure, isolated yield (103.3 mg, 69%) as a colorless oil; **FTIR**: 3061, 2342, 1655, 1524, 1346, 1105, 835, 738 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.12 (d, J = 2.8 Hz, 1H), 8.52 (dd, J = 9.2, 2.8 Hz,1H), 8.04 (s, 1H), 7.60 (d, J = 9.2 Hz, 1H),7.48 (dd, J = 8.0, 1.6 Hz, 2H), 7.38−7.32 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.6, 159.0, 155.7, 145.0, 132.1, 131.4, 129.5, 128.2, 128.1, 123.4, 123.2, 122.7, 120.0; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9NNaO_4S^+$ 322.0144 $(M + Na)^+$, found 322.0143.

*6-Bromo-3-(phenylthio)-4H-chromen-4-one (**4l**).* Following the general procedure, isolated yield (121.6 mg, 73%) as a colorless oil; **FTIR**: 3058, 2923, 1652, 1548, 1462, 1121, 908, 818, 735 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 2.4 Hz, 1H), 8.12 (s, 1H), 7.78 (q, J = 2.4, 1H), 7.43−7.38 (m, 3H),7.34−7.24 (m, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 173.8, 157.0, 155.1, 137.0, 133.4, 130.3, 129.3, 129.0, 127.5, 124.8, 120.6, 120.2, 119.2; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9BrNaO_2S^+$ 354.9399 $(M + Na)^+$, found 354.9394.

*3-((4-Chlorophenyl)thio)-6-methyl-4H-chromen-4-one (**4m**).* Following the general procedure, isolated yield (118.1 mg, 78%) as a colorless oil; **FTIR**: 3053, 2922, 1639, 1478, 1311, 1091, 812, 789 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.24 (s, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.33−7.22 (m, 4H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.1, 158.1, 154.7, 136.1, 135.4, 133.1, 132.9, 130.7, 129.2, 125.7, 123.4, 118.8, 118.0, 21.0; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M + Na)^+$, found 325.0049.

*3-(Methylthio)-4H-chromen-4-one (**4n**).* Following the general procedure, isolated yield (77.9 mg, 81%) as a colorless oil; **FTIR**: 3072, 2922, 1628, 1466, 1357, 1084, 792 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.17 (dd, J = 8.4, 1.6 Hz, 1H), 7.99 (s, 1H), 7.64−7.60 (m, 1H), 7.40−7.34 (m, 1H), 2.35 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.6, 156.3, 153.9, 133.8, 126.1, 125.5, 123.1, 121.9, 118.1, 16.3; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_2S^+$ 215.0137 $(M + Na)^+$, found 215.0137.

*3-(Methylthio)-6-nitro-4H-chromen-4-one (**4o**).* Following the general procedure, isolated yield (93.7 mg, 79%) as a colorless oil; **FTIR**: 3093, 2920, 1642, 1513, 1342, 1094, 1057, 887, 651 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 9.10 (d, J = 2.8 Hz, 1H), 8.51 (dd, J = 9.2, 2.8 Hz, 1H), 8.03 (s, 1H), 7.64 (d, J = 9.2 Hz, 1H), 2.43 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 174.2, 159.0, 152.8, 144.9, 128.1, 123.8, 123.0, 122.9, 120.0, 15.7; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NO_4S^+$ 238.0169 $(M + H)^+$, found 238.0171.

*2-Methyl-3-(phenylthio)-4H-chromen-4-one (**4q**).* Following the general procedure, isolated yield (60.4 mg, 45%) as a colorless oil; **FTIR**: 3050, 2924, 1647, 1465, 1120, 982, 764, 691 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.23 (dd, J = 7.6, 1.2 Hz, 1H), 7.71−7.67 (m, 1H), 7.47−7.40 (m, 2H), 7.28−7.25 (m, 4H), 7.24−7.12 (m, 1H),

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J. Org. Chem. 2015, 80, 9167−9175

2.74 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 175.3, 171.5, 155.6, 135.7, 133.8, 129.3, 129.0, 127.5, 126.6, 126.0, 125.5, 122.9, 117.7, 115.3, 20.8; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{12}NaO_2S^+$ 291.0450 $(M + Na)^+$, found 291.0451.

*3-(p-Tolylthio)-1H-indole (**8**).*[12b] Following the general procedure, isolated yield (99.2 mg, 83%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.23 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.45−7.43 (m, 2H), 7.38−7.34 (m, 1H), 7.29−7.25 (m, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 2.35 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 136.5, 135.6, 134.9, 130.7, 129.7, 129.2, 126.4, 123.1, 120.9, 119.7, 111.8, 103.2, 21.0.

*2-Phenyl-3-(p-tolylthio)imidazo[1,2-a]pyridine (**10**).*[13a] Following the general procedure, isolated yield (134.3 mg, 85%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.29−8.26 (m, 3H), 7.74 (d, J = 9.2 Hz, 1H), 7.48−7.45 (m, 2H), 7.39 (t, J = 7.2 Hz, 4H), 7.31−7.27 (m, 1H), 7.02 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 6.82 (t, J = 6.8 Hz, 1H), 2.26 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 151.2, 147.0, 136.0, 133.5, 131.5, 130.2, 128.6, 128.5, 128.4, 126.6, 125.8, 124.5, 117.6, 113.0, 106.9, 20.9.

*3-(Methylsulfinyl)-4H-chromen-4-one (**13**).*[13b] Following the general procedure, isolated yield (93.6 mg, 90%) as a colorless oil; **FTIR**: 3070, 2921, 1642, 1611, 1072, 827 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.31 (s, 1H), 8.23 (dd, J = 9.6, 1.6 Hz, 1H), 7.82−7.78 (m, 1H),7.60 (d, J = 8.0 Hz, 1H), 7.55−7.51(m, 1H), 3.02 (s, 3H); **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_3S^+$ 231.0086 $(M + Na)^+$, found 231.0083.

*3-(Methylsulfonyl)-4H-chromen-4-one (**14**).* Following the general procedure, isolated yield (98.6 mg, 88%) as a colorless oil; **FTIR**: 3082 2965, 1678, 1527, 1285, 889, 782 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.75 (s, 1H), 8.30 (dd, J = 8.0, 1.2 Hz, 1H), 7.84−7.80 (m, 1H), 7.61−7.54 (m, 1H), 3.37 (s, 3H); **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_4S^+$ 247.0036 $(M + Na)^+$, found 247.0031.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01602.

Spectral characterization for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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