JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01320 • Publication Date (Web): 29 Aug 2017

Making Flavone Thioethers Using Halides and Powdered Sulfur or $Na_2S_2O_3$

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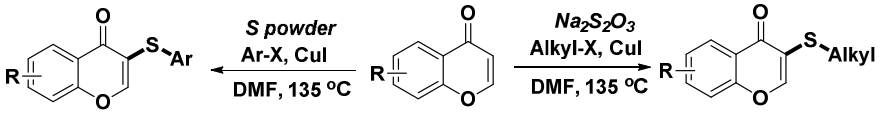


Abstract: The method for constructing C-S bonds is very important in organic synthesis. Here a new sulfenylation method to generate flavone thioether derivatives was developed by employing aromatic or alkyl halides, S powder and $Na_2S_2O_3$ as reactants. Good yields of regioselective C_{alkyl}-S and C_{aryl}-S-substituted flavones were generated under relatively environmentally friendly and simple conditions. This method might be potentially applicable to large scale production, and it enriches current sulfenylation methods.

Flavones are popular natural products in drug discovery[1] and their derivatives possess many important biological activities. Some bioactive flavone derivatives are listed in figure 1.[2] Flavone derivatives have been used as marketed drugs for a long time, so their derivatives for new drug discovery are attractive to many medicinal chemists.[3] Different valuable flavone derivatives have been synthesized and reported including flavone thioethers in scheme 1.[4] To make flavone thioethers, the construction of C-S bonds directly from inactive C-H bonds of flavone skeletons is still a challenge to many medicinal chemists.[5] Until now, they have devoted their efforts to developing highly efficient C-S bond construction (sulfenylation) methods via C-H bond functionalization,[6] because sulfenylation is highly efficient and environmentally friendly.

Recently, our group also reported several ammonium iodide-induced sulfenylation methods to make flavone derivatives by coupling flavones with different sulfenylating reagents such as thiols, sulfonyl chlorides, disulfides, sodium sulfinates, and sulfonyl hydrazides under similar reaction conditions shown in scheme 1.[7] However, these methods still have a common shortcoming with which we are not satisfied, they still require the use of prefunctionalized sulfur agents which are expensive or not easy to make. These methods are not economical for large scale production. To overcome this shortcoming, we have

developed a new and practical method to make both C_{alkyl}-S and C_{aryl}-S-substituted flavone derivatives out of odorless S powder or inorganic $Na_2S_2O_3$ along with easily available alkyl and aryl halides via direct C-H functionalization. This method is far more

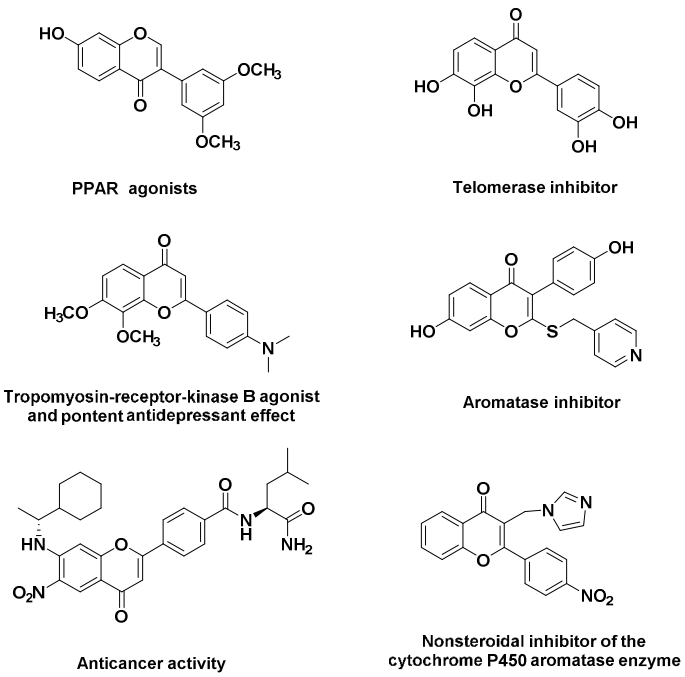
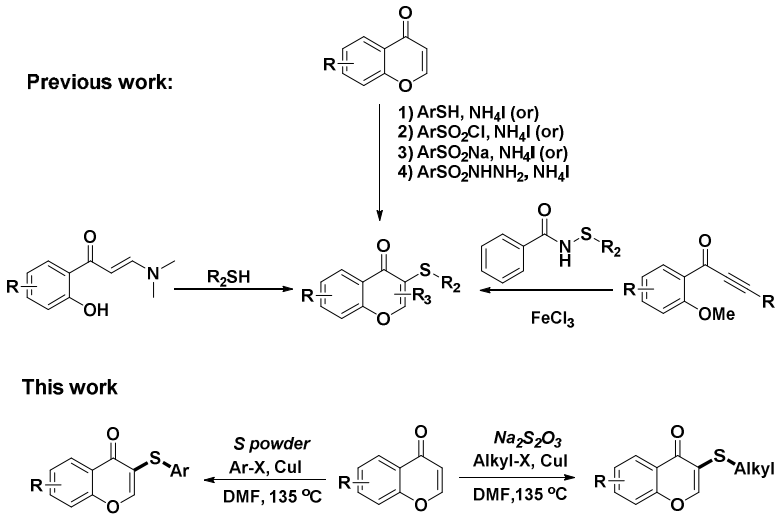


Figure 1. Biologically active flavone derivatives

practical and convienent than our previously reported methods, and it has the potential possibility for use in large scale production. All reactions proceeded as expected under relatively simple and environmentally friendly condtions, affording regioselective C_{alkyl}-S and C_{aryl}-S-substituted flavone derivatives in good yields.

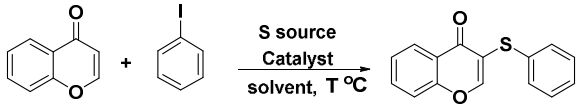
Scheme 1. Previously reported sulfenylation methods of flavones versus this new method



To find an optimal reaction condition for this C-S construction reaction, flavone **1a** was used as a representative reactant; S powder was used as a sulfur agent, and iodobenzene was selected as a representative halide. To catalyze the reaction, different

copper, iron, cobalt and nickel catalysts were screened. Different solvents, temperatures, S sources and reaction time were also tried. The results are presented in Table 1.

Table 1. Screening for suitable reaction conditions[a]



1a 2a 3a

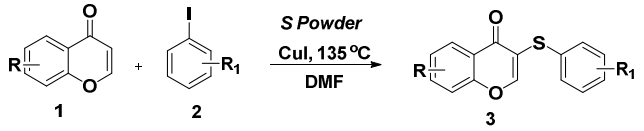
Entry	Cat.	Temp (°C)	S source	Solvent	Yield (%)[b]
1	CuI	95	S	DMF	10
2	CuI	115	S	DMF	45
3	CuI	135	S	DMF	90
4	$Cu(OAc)_2 \cdot H_2O$	135	S	DMF	63
5	$Cu(NO_3)_2$	135	S	DMF	50
6	Cu	135	S	DMF	45
7	$CuBr_2$	135	S	DMF	43
8	CuCl	135	S	DMF	85
9	CuCN	135	S	DMF	55
10	$FeCl_2 \cdot 4H_2O$	135	S	DMF	31
11	$Fe(NO_3) \cdot 9H_2O$	135	S	DMF	65
12	$CoCl_2 \cdot 6H_2O$	135	S	DMF	23
13	$NiCl_2$	135	S	DMF	0
14	CuI	135	S	DCE	14
15	CuI	135	S	Dioxane	0
16	CuI	135	S	Toluene	0
17	CuI	135	S	EtOAc	5
18	CuI	135	S	CH_3CN	15
19	CuI	135	S	DMSO	6
20	CuI	135	S	THF	63
21	CuI	135	$Na_2S \cdot 9H_2O$	DMF	0
22	CuI	135	Thiourea	DMF	52
23	CuI	135	NH_4SCN	DMF	5
24[c]	CuI	135	S	DMF	52
25[d]	CuI	135	S	DMF	76

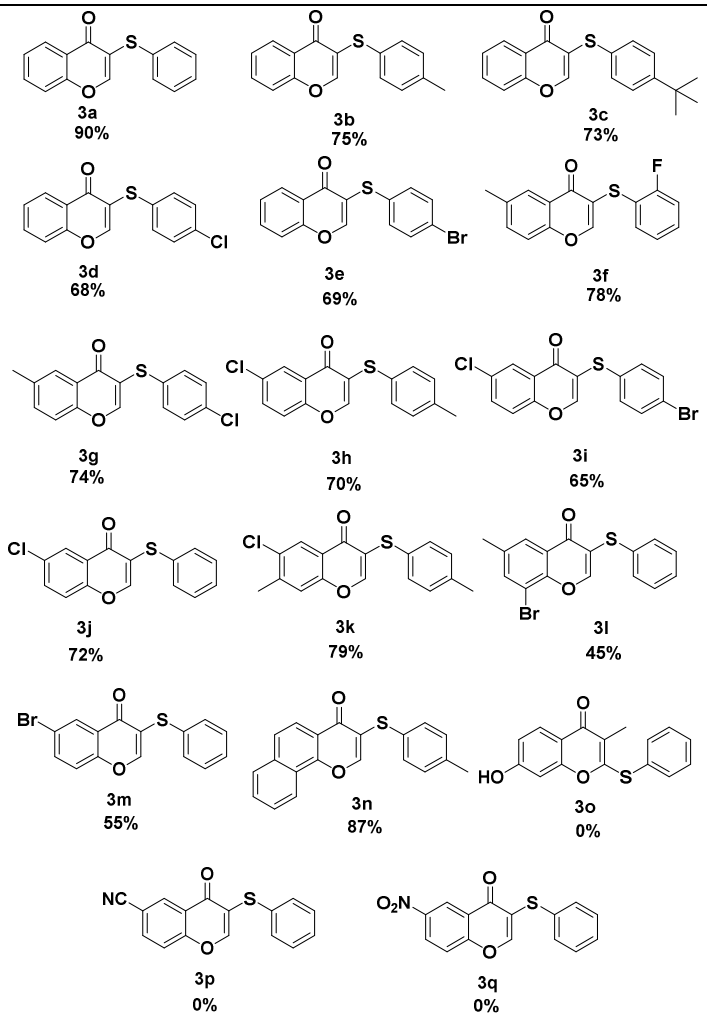
[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv.), iodobenzene (4.0 equiv.), S (4.0 equiv.), CuI (0.4 equiv.), DMF (0.5 mL), reaction time 24h. [b] Isolated yield of product **3a** was based on the reactant flavone **1a**. [c] Reaction time: 12h. [d] Reaction time:18h.

When CuI was used in DMF at 95 °C, it was found that the reaction gave a 10% yield of product **2a** (Table 1, entry 1). As the reaction temperature was raised to 115 °C, the product was isolated in a 45% yield (entry 2). When the temperature was increased further to 135 °C, the reaction proceeded well and afforded a 90% yield of PhS-substituted flavone derivative (entry 3). Therefore, the reaction temperature was set up at 135 °C after entry 3. The use of $Cu(OAc)_2 \cdot H_2O$ as a catalyst in DMF afforded a 63% yield (entry 4). When $Cu(NO_3)_2$ was used as a catalyst in DMF at 135 °C, a 50% yield of product **2a** was generated (entry 5). Using copper only as the catalyst gave product **2a** in a 45% yield (entry 6). When $CuBr_2$ was used as a catalyst, a 43% yield of the expected product **2a** was isolated (entry 7). Using CuCl or CuCN as catalysts gave a good yield of 85% and a moderate yield of 55%, respectively (entries 8 and 9). The iron catalysts $FeCl_2 \cdot 4H_2O$ and $Fe(NO_3) \cdot 9H_2O$ gave 31% and 65% yields, respectively (entries 10 and 11). When $CoCl_2 \cdot 6H_2O$ and $NiCl_2$ were employed as catalysts, the reaction afforded a 23% yield and no product,

respectively (entries 12 and 13). Changing solvent from DMF to DCE dropped the yield to 14% (entry 14). Using dioxane and toluene didn't produce any of **2a** (entries 15 and 16). Several solvents such as EtOAc, CH_3CN, DMSO and THF were also screened, but the yields were lower compared with using DMF (entries 17-20). A couple of other easily available sulfur sources were also screened, including $Na_2S \cdot 9H_2O$, thiourea and NH_4SCN. It was found that using $Na_2S \cdot 9H_2O$ gave no expected product (entry 21). When thiourea was used as a S source, the reaction afforded a moderate yield of 52% (entry 22). Using NH_4SCN only generated a 5% yield of **3a** (entry 23). Decreasing the reaction time to 12 h and 18 h decrease in the yield from 90 to 52% and

Table 2. Sulfenylation of flavones with different iodobenzene analogs [a,b]



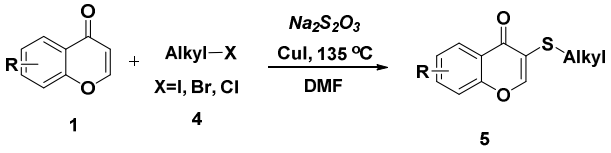


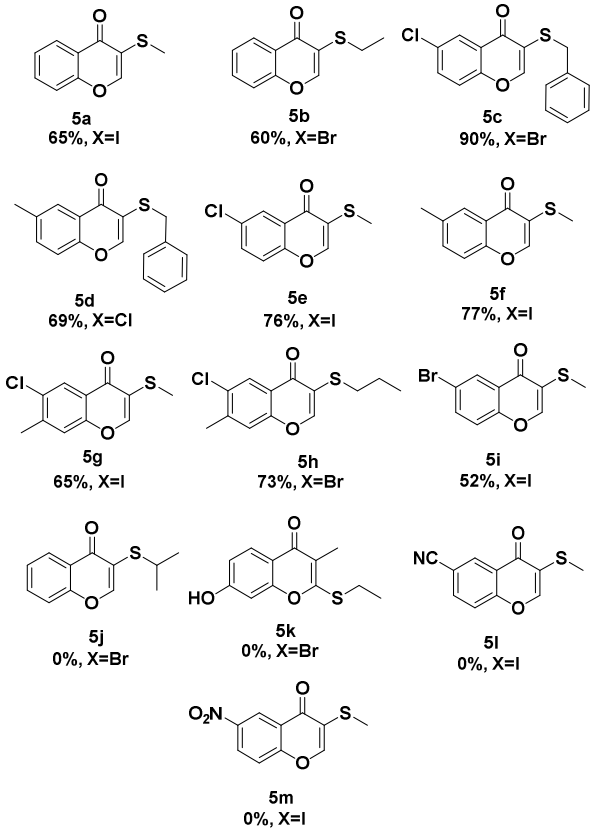
[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv.), iodobenzene (4.0 equiv.), S (4.0 equiv.), CuI (0.4 equiv.), DMF (0.5 mL). [b] Isolated yields are based on reactant **1a**, all reactions were run for 24 h at 135 °C

72%, respectively, (entries 24 and 25). From these screening reactions, the optimal reaction conditions for the sulfenylation of flavone using S and iodobenzene as reactants are: flavone (1.0 equiv.), S (4.0 equiv.), iodobenzene (4.0 equiv.) and CuI (0.4 equiv.). DMF is a suitable solvent at 135 ^{o}C for 24 h.

Flavone sulfenylation was then explored under the optimal reaction conditions. In table 2, several flavone analogs with different functional groups were synthesized and several aromatic iodobenzene homologues with electron-donating and electron-withdrawing substituents were used for exploring the sulfenylation reaction scope. Most reactions proceeded well, giving regioselective C_{aryl}-S substituted flavone derivatives via C-H functionalization. Even *ortho*-fluorobenzene iodide gave a good yield of **3f**. It was also found that strong electron-withdrawing functional groups (-NO_2 and -CN) on flavone benzene rings had a big impact on the yields, and none of the expected products **3p** and **3q** were obtained. All NMR spectra indicated that thioether

Table 3. Sulfenylation of flavones with alkyl halides [a,b]



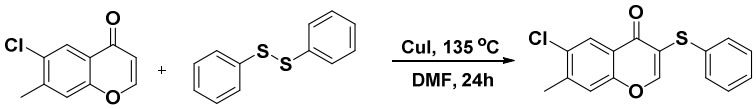


[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv), alkyl halide (4.0 equiv.), $Na_2S_2O_3$ (2.0 equiv.), CuI (0.4 equiv.), DMF (0.5 mL). [b] Isolated yields are based on reactant **1a**, all reactions were run for 24 h at 135 ^{o}C.

substituents were added to the *α*-position of flavone ketone functions. This regioselectivity was also proved by a designed chemical method. When the α-position of flavone ketone function was intentionally blocked by a methyl function (**3o**), no reaction occured. This chemical verification further proved that the reaction only occured at the α-position of flavone ketone function.

To further extend this sulfenylation scope to alkyl halides, several alkyl halides were also reacted under the same conditions in table 3. The reaction didn't proceed well when S powder was used as sulphur source. By changing from S powder to the cheap and inorganic sulphur agent $Na_2S_2O_3$, the reaction also proceeded quite well, giving good yields of expected C_{alkyl}-S-substituted products. Here, several halides including CH_3-I, CH_3CH_2-Br, $CH_3CH_2BrCH_3$, $CH_3CH_2CH_2$-Br, Bn-Cl and Bn-Br were used as representative alkyl halides. All these primary alkyl halides (I, Br and Cl halides) were feasible for the reaction under the same catalyst and solvent conditions. However, when the secondary halide, 2-bromopropane was employed, this reaction didn't generate the expected product **5j.** An elimination of 2-bromopropane to give propene may have occurred during the reaction. When a flavone with the *α*-position of the ketone function blocked by methyl group was reacted with CH_3CH_2-Br, no product was isolated. Thus, the reaction happened regioselectively only at the *α*-position. We have used two strong electron-withdrawing flavones analogs (-CN, $-NO_2$) as starting materials for the reaction. Neither of these reactions proceeded.

Scheme 2. Control experiment

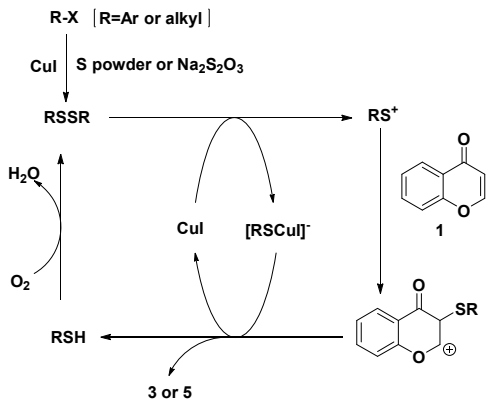


3r: 83%

To explore the reaction mechanism, a control reaction of diphenyl disulfide with flavone was also conducted under the standard conditions (Scheme 2). When flavone was reacted with diphenyl disulfide, the PhS-substitued product **3r** was afforded in an 83% yield. This result indicated that disulfides could be a possible intermediate species involved in the reaction.

Based on both literatures[8] and the above experimental results, a plausible mechanism was proposed in scheme 3. The reaction between sulphur agents (S powder or $Na_2S_2O_3$) and alkyl and aromatic halides could have generated disulfides catalyzed by CuI in DMF. The resulting disulfide intermediate reacted with CuI to give $[RSCuI]^-$ and the RS^+ cation. Then RS^+ continued to react with the flavone to generate the *α*-substitued flavone thioether derivatives. The oxidation of RSH by air regenrates disulfides which recycle in the process.

Scheme 3. Proposed reaction mechanism



CONCLUSIONS

In summary, a new method using cheap inorganic S powder or $Na_2S_2O_3$ as sulfur agents, iodobenzenes/alkyl halides and flavones as starting materials to make C_{alkyl}/C_{aryl}-S-substituted flavone derivatives was developed. All reactions were carried out under relatively practical and simple conditions, generating regioselective products in good yields. Compared with previously available methods, this method is unique and more useful because it is practical and has the potential to be used on an industrial scale. Also, this method is environmentally friendly, quite attractive and enriches current sulfenylation methods.

EXPERIMENTAL SECTION

General: All reactions were carried out in sealed tubes; stirring was achieved with an oven-dried magnetic stirring bar. Solvents were purified by standard methods unless otherwise noted. Commercially available reagents were purchased from Aladdin Company in China and 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. Deuterated solvents were purchased from Cambridge Isotope laboratories. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively. HRMS spectrometry (LC-HRMS) was recorded on a LXQ Spectrometer (Thermo Scientific) operating on ESI-TOF (MeOH as a solvent).

General procedure for the synthesis of compounds 3a-n. Flavone **1a** (0.5 mmol, 1.0 equiv.), sulfur (4.0 equiv.) and iodobenzene (4.0 equiv.) were added to a dried flask with DMF (0.5 mL), followed by the addition of CuI (0.4 equiv.). The mixture was stirred at 135 ^oC. After 24 h, the reaction was cooled 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 = 60:1) on silica gel to give the desired product **3a** as a colorless oil in a 90% yield. The same procedure was applied to the production of other compounds **3b-n**.

The procedure for the synthesis of compound 3r. Flavone (0.5 mmol, 1.0 equiv.) and disulfide (2.0 equiv.) were added to a dried flask with DMF (0.5 mL), followed by the addition of CuI (0.4 equiv.). The mixture was stirred at 135 ^oC. After 24 h, the reaction was cooled 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 = 65:1) on silica gel to give the desired product **3r** as a colorless oil in a 83% yield.

General procedure for the synthesis of compounds 5a-i. Flavone **1a** (0.5 mmol, 1.0 equiv.), $Na_2S_2O_3$ (2.0 equiv.) and halide (4.0 equiv.) were added to a dried flask with DMF (0.5 mL), followed by the addition of CuI (0.4 equiv.). The mixture was stirred at 135 ^oC. 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 =80:1) on silica gel to give the desired product **5a** as a colorless oil in a 65% yield. The same procedure was applied to the production of other compounds **5b-i**.

3-(Phenylthio)-4H-chromen-4-one (3a)

Following the general procedure, isolated yield (114.3 mg, 90%) as a colorless oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.18 (s, 1H), 7.72 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.45 – 7.40 (m, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.21 (m, 1H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.1, 157.4, 156.4, 134.0 (2 C), 129.9, 129.2, 127.1, 126.5, 125.8, 123.7, 120.0, 118.2. **FTIR**: 3057, 2925, 1652, 1612, 1464, 1301, 1113, 760 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_{10}NaO_2S^+$ 277.0294 $(M+Na)^+$, found 277.0293.

3-(p-Tolylthio)-4H-chromen-4-one (3b).

Following the general procedure, isolated yield (100.5 mg, 75%) as a colorless oil; **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 8.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.07 (s, 1H), 7.70 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.41 – 7.34 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.33 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.1, 156.3 (2 C), 137.6, 133.9, 131.0, 130.1, 129.8, 126.4, 125.6, 123.6, 121.1, 118.1, 21.1. **FTIR**: 3075, 2921, 2359, 1647, 1463, 1115, 758 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{12}NaO_2S^+$ 291.0450 $(M+Na)^+$, found 291.0453.

3-((4-(Tert-butyl)phenyl)thio)-4H-chromen-4-one (3c).

Following the general procedure, isolated yield (113.1mg, 73%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.09 (s, 1H), 7.71 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.41 – 7.32 (m, 4H), 1.30 (s, 9H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.2, 156.6, 156.3, 150.7, 133.9, 130.5, 130.0, 126.4 (2 C), 125.6, 123.6, 120.8, 118.2, 34.6, 31.2. **FTIR**: 3070, 2963, 1648, 1611, 1560, 1462, 1113, 846, 765 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{19}H_{18}NaO_2S^+$ 333.0920 $(M+Na)^+$, found 333.0921.

3-((4-Chlorophenyl)thio)-4H-chromen-4-one (3d).

Following the general procedure, isolated yield (97.9 mg, 68%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.31 – 8.21 (m, 2H), 7.73 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.39 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 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 . **FTIR**: 3050, 1648,

1478, 1465, 1313, 1090, 827, 758 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M+Na)^+$, found 310.9903.

3-((4-Bromophenyl)thio)-4H-chromen-4-one (3e).

Following the general procedure, isolated yield (114.5 mg, 60%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.26 (d, *J* = 7.0 Hz, 2H), 7.74 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 7.26 (d, *J* = 8.6 Hz, 2H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.9, 158.0, 156.4, 134.2, 133.6, 132.2, 131.0, 126.5, 125.9, 123.7, 121.0, 119.0, 118.2. **FTIR**: 3061, 2925, 1641, 1462, 1086, 902, 798 cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{15}H_9BrNaO_2S^+$ 354.9399 $(M+Na)^+$, found 354.9396.

3-((2-Fluorophenyl)thio)-6-methyl-4H-chromen-4-one (3f).

Following the general procedure, isolated yield (111.5 mg, 78%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 8.04 – 7.97 (m, 1H), 7.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.22 (tdd, *J* = 7.0, 6.0, 1.7 Hz, 1H), 7.10 – 7.00 (m, 2H), 2.44 (s, 3H). **^{13}C-NMR** ($CDCl_3$,100 MHz): 175.1, 161.1 (d, J_{C-F} = 245 Hz), 157.7, 154.6, 135.9, 135.3, 132.5, 129.2 (d, J_{C-F} = 8 Hz), 125.6, 124.6 (d, J_{C-F} = 4 Hz), 123.3, 121.1 (d, J_{C-F} = 17 Hz), 117.9, 117.8, 115.9 (d, J_{C-F} = 22 Hz), 21.0. **FTIR**: 3054, 2921, 1644, 1474, 1210, 1114, 812, 743; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}FNaO_2S^+$ 309.0356. $(M+Na)^+$, found 309.0355.

3-((4-Chlorophenyl)thio)-6-methyl-4H-chromen-4-one (3g).

Following the general procedure, isolated yield (111.7 mg, 74%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 8.03 (dd, *J* = 2.2, 1.1 Hz, 1H), 7.53 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 2H), 2.47 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.1, 158.0, 154.7, 136.1, 135.4, 133.1, 132.9, 130.7, 129.2, 125.7, 123.4, 118.8, 118.0, 21.0. **FTIR**: 3053, 2922, 1638, 1478, 1311, 1091, 812, 788 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M+Na)^+$, found 325.0066.

6-Chloro-3-(p-tolylthio)-4H-chromen-4-one (3h).

Following the general procedure, isolated yield (105.7 mg, 70%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 2.6 Hz, 1H), 8.00 (s, 1H), 7.63 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 2.34 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.0, 155.8, 154.6, 138.0, 134.1, 131.5, 131.4, 130.2, 129.2, 125.7, 124.3, 121.7, 119.9, 21.1. **FTIR**: 3065, 2923, 1657, 1468, 1305, 1112, 817, 736 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M+Na)^+$, found 325.0058.

3-((4-Bromophenyl)thio)-6-chloro-4H-chromen-4-one (3i).

Following the general procedure, isolated yield (117.3 mg, 65%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.29 – 8.15 (m, 2H), 7.67 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.28 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 100

MHz): 173.8, 157.7, 154.7, 134.4, 133.0, 132.3, 131.9, 131.4, 125.8, 124.6, 121.4, 120.0, 119.6. **FTIR**: 3055, 2923, 1653, 1468, 1301, 907, 765 cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{15}H_8BrClNaO_2S^+$ 388.9009 $(M+Na)^+$, found 388.9001

6-Chloro-3-(phenylthio)-4H-chromen-4-one (3j).

Following the general procedure, isolated yield (103.6 mg, 72%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.22 (d, *J* = 2.6 Hz, 1H), 8.12 (s, 1H), 7.65 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.34 – 7.24 (m, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.0, 157.0, 154.7, 134.2, 133.4, 131.7, 130.3, 129.3, 127.4, 125.7, 124.5, 120.5, 120.0. **FTIR**: 3068, 2925, 2360, 1652, 1466, 1303, 1122, 918, 821, 755 cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M+Na)^+$, found 310.9902.

6-Chloro-7-methyl-3-(p-tolylthio)-4H-chromen-4-one (3k).

Following the general procedure, isolated yield (124.8 mg, 79%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.98 (s, 1H), 7.36 (d, *J* = 8.3 Hz, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 2.53 – 2.48 (m, 3H), 2.33 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.0, 155.9, 154.6, 143.3, 137.8, 132.3, 131.2, 130.1, 129.5, 125.9, 122.5, 121.3, 119.9, 21.1, 20.9. **FTIR:** 3060, 2925, 1651, 1413, 1097, 899, 786 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{13}ClNaO_2S^+$ 339.0217 $(M+Na)^+$, found 339.0215.

8-Bromo-6-methyl-3-(phenylthio)-4H-chromen-4-one (3l).

Following the general procedure, isolated yield (77.8 mg, 45%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.98 (dd, *J* = 2.1, 1.0 Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.35 – 7.23 (m, 3H), 2.45 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.5, 156.3, 151.2, 138. 5, 136.8, 133.2, 130.5, 129.3, 127.5, 125.3, 124.3, 120.8, 111.2, 20.8. **FTIR:** 3054, 2925, 2360, 1660, 1462, 1299, 1090, 785, 690 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}BrNaO_2S^+$ 368.9555 $(M+Na)^+$, found 368. 9552.

6-Bromo-3-(phenylthio)-4H-chromen-4-one (3m).

Following the general procedure, isolated yield (91.3 mg, 55%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 2.5 Hz, 1H), 8.12 (s, 1H), 7.78 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.47 – 7.36 (m, 3H), 7.36 – 7.23 (m, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 173.8, 156.9, 155.1, 137.0, 133.4, 130.3, 129.3, 129.0, 127.5, 124.8, 120.7, 120.1, 119.2. **FTIR**: 3058, 2923, 1651, 1548, 1462, 1120, 908, 817, 735 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{15}H_9BrNaO_2S^+$ 354.9399 $(M+Na)^+$, found 354.9398.

3-(p-Tolylthio)-4H-benzo[h]chromen-4-one (3n).

Following the general procedure, isolated yield (138.3 mg, 87%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.40 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.08 (s, 1H), 7.92 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.78 – 7.63 (m, 3H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 2.35 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 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, 123.5, 122.2, 121.0, 119.6, 21.2. **FTIR**: 3056, 2920, 2362, 1650, 1633, 1384, 1113, 886, 765 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{20}H_{14}NaO_2S^+$ 341.0607 $(M+Na)^+$, found 341.0602

6-Chloro-7-methyl-3-(phenylthio)-4H-chromen-4-one (3r)

Following the general procedure, isolated yield (125.3 mg, 83%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 8.10 (s, 1H), 7.44 – 7.38 (m, 2H), 7.37 (d, *J* = 0.9 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 2.51 (d, *J* = 0.8 Hz, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz,) δ 173.9, 157.0, 154.6, 143.4, 133.7, 132.4, 130.0, 129.2, 127.3, 126.0, 122.6, 120.1, 119.9, 20.9. **FTIR**: 3066, 2922, 1655, 1432, 1108, 918, 795 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M+Na)^+$, found 325.0061.

3-(Methylthio)-4H-chromen-4-one (5a)

Following the general procedure, isolated yield (62.4 mg, 65%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.24 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.05 (s, 1H), 7.67 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.49 – 7.37 (m, 2H), 2.40 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.6, 156.3, 153.9, 133.8, 126.1, 125. 5, 123.1, 121.9, 118.1, 16.3. **FTIR**: 3072, 2923, 1628, 1466, 1357, 1084, 792 cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_8NaO_2S^+$ 215.0137 $(M+Na)^+$, found215.0136.

3-(Ethylthio)-4H-chromen-4-one (5b).

Following the general procedure, isolated yield (61.8 mg, 60%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.26 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.17 (s, 1H), 7.69 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.51 – 7.40 (m, 2H), 2.89 (q, *J* = 7.4 Hz, 2H), 1.26 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.9, 156.3, 156.3, 133.8, 126.2, 125.6, 123.5, 119.3, 118.1, 26.8, 14.56. **FTIR**: 2925, 2857, 1636, 1459, 1344, 1076, 887, 754cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M+Na)^+$, found 229.0295.

3-(Benzylthio)-6-chloro-4H-chromen-4-one (5c).

Following the general procedure, isolated yield (135 mg, 90%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-d) δ 8.24 (d, *J* = 2.6 Hz, 1H), 7.82 (s, 1H), 7.62 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 7.29 – 7.17 (m, 5H), 4.07 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.8, 157.2, 154.6, 137.5, 134.1, 131.6, 129.0, 128.5, 127.2, 125.6, 124.3, 119.9, 118.6, 37.0. **FTIR**: 3029, 2923, 2359, 1626, 1466, 1020, 819, 692cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M+Na)^+$, found 325.0062.

3-(Benzylthio)-6-methyl-4H-chromen-4-one (5d).

Following the general procedure, isolated yield (97.3 mg, 69%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.08 (dd, *J* = 2.1, 1.1 Hz, 1H), 7.81 (s, 1H), 7.49 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.28 – 7.18 (m, 5H), 4.07 (s, 2H), 2.49 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 176.0, 157.3, 154.6, 137.8, 135.7, 135.1, 129.0, 128.4, 127.1, 125.5, 123.2, 117.9 (2 C), 37.1, 22.0. **FTIR**: 3475, 3415, 2918, 2359, 1620, 1482, 697cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{17}H_{14}NaO_2S^+$ 305.0607 $(M+Na)^+$, found 305.0612.

6-Chloro-3-(methylthio)-4H-chromen-4-one (5e).

Following the general procedure, isolated yield (85.8 mg, 76%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 2.6 Hz, 1H), 8.04 (s, 1H), 7.63 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.43 (d, *J* = 8.9 Hz, 1H), 2.41 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz):

174.5, 154.6, 153.7, 134.0, 131.4, 125.4, 124.0, 122.2, 119.9, 16.1. **FTIR**: 3083, 2915, 1629, 1467, 1123, 1086, 818, 651cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{10}H_7ClNaO_2S^+$ 248.9747 $(M+Na)^+$, found 248.9744.

6-Methyl-3-(methylthio)-4H-chromen-4-one (5f).

Following the general procedure, isolated yield (79.3 mg, 77%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 8.03 – 8.01 (m, 1H), 7.52 – 7.45 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 175.7, 154.6, 154.0, 135.5, 135.1, 125.3, 122.8, 121.5, 117.8, 21.0, 16.4. **FTIR**: 3065, 2920, 1639, 1486, 1149, 1082, 873cm^{-1}; **HRMS** (ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M+Na)^+$, found 229.0294.

6-Chloro-7-methyl-3-(methylthio)-4H-chromen-4-one (5g)

Following the general procedure, isolated yield (78mg, 65%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 8.00 (s, 1H), 7.33 (d, *J* = 0.9 Hz, 1H), 2.49 (d, *J* = 0.9 Hz, 3H), 2.40 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.4, 154.5, 153.6, 143.2, 132.1, 125.6, 122.1, 121.9, 119.9, 20.8, 16.2. **FTIR**: 2923, 1633, 1365, 1128, 1091, 911, 645 cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{11}H_9ClNaO_2S^+$ 262.9904 $(M+Na)^+$, found 262.9901.

6-Chloro-7-methyl-3-(propylthio)-4H-chromen-4-one (5h).

Following the general procedure, isolated yield (97.8 mg, 73%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 8.11 (s, 1H), 7.34 (d, *J* = 1.0 Hz, 1H), 2.86 – 2.79 (m, 2H), 2.50 (d, *J* = 0.9 Hz, 3H), 1.60 (h, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.8, 155.8, 154.6, 143.1, 132.2, 125.8, 122.5, 119.9, 119.7, 34.7, 22.6, 20.8, 13.2. **FTIR**: 3075, 2955, 1631, 1124,1087, 859,646cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{13}H_{13}ClNaO_2S^+$ 291.0217 $(M+Na)^+$, found 291.0217

6-Bromo-3-(methylthio)-4H-chromen-4-one (5i)

Following the general procedure, isolated yield (70.2 mg, 52%) as a colorless oil; **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 8.38 (d, *J* = 2.5 Hz, 1H), 8.05 (s, 1H), 7.77 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 2.42 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 174.3, 155.0, 153.7, 136.8, 128.7, 124.3, 122.3, 120.1, 118.8, 16.2. **FTIR**: 2917, 1628, 1122, 1084, 917, 818 cm^{-1}; **HRMS (**ESI-TOF) m/z calculated for $C_{10}H_7BrNaO_2S^+$ 292.9242 $(M+Na)^+$, found 292.9241

ASSOCIATED CONTENT

Supporting Information Available

Spectral characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This investigation was generously supported by the funding (1281290006) provided by Jiangsu University.

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