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Ammonium Iodide-Mediated Regioselective Chalcogenation of Chromones with Diaryl Disulfides and Diselenides

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Ammonium iodide-mediated regioselective chalcogenation of chromones with diaryl disulfides and diselenides

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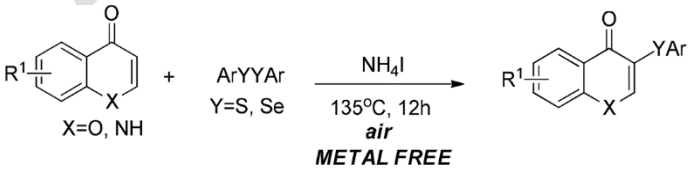
ABSTRACT

A metal-free method for the synthesis of 3-chalcogenyl-chromones/quinolones from chromones/quinolones and diorganyl dichalcogenides using ammonium iodide under air was developed. This approach allowed the preparation of a wide range of 3-selenyl- and 3-sulfenyl-chromones/quinolones in good to excellent yields.

GRAPHICAL ABSTRACT



KEYWORDS: 3-selenyl-chromones, 3-sulfenyl-chromones, chalcogenation, c-s/se bond, quinolone

Introduction

Recently, there has been an increasing interest for efficient methods to construction of the C–S and C-Se bonds owing to their important roles as structural motifs in a wide range of biologically and pharmaceutically active compounds (**Figure 1**).[1] In addition, organochalcogenides (S, Se) play an important role in material sciences,[2] and also have fundamental applications in organic synthesis and catalysis.[3] As a consequence, significant efforts have been devoted to the synthesis of new sulfur/selenium-containing substances through selective C-S/Se bond formation in the last few decades.[4]

Among the wide range of strategies employed, metal-catalyzed C-H bond activation has proven to be one of the most powerful approaches for the synthesis of organochalcogen compounds. Palladium and nickel are often used as the choice of metal catalysts.[5] Recently, Zeni and co-workers reported a copper oxide nanoparticle-catalyzed synthesis of 2-(organochalcogen)thiazoles via direct C-H bond activation in thiazoles, avoiding using noble metal catalyst (Scheme 1a).[6] With the development of green chemistry and the enhancement of people's awareness of environmental protection, many researchers have paid much attention to screening various non-metal reagents for the synthesis of organochalcogen compounds. For instance, Braga realized an easy access to 3-chacogenyl-indoles from indoles and diorganyl

dichalcogenides using DMSO/I_2 under metal-free condition in good to excellent yields (Scheme 1b).[7] Very recently, Braga and co-workers developed an efficient and regioselective iodide-induced chalcogenation of imidazo[1,2-a]pyridines with diorganoyl dichalcogenides in the absence of a metal catalyst (Scheme 1c).[8] From the examples above, we found that the diorganoyl dichalcogenides were proved to be promising chalcogenation reagents with the substrate compatibility and stability. Thus, more transformations related to diorganoyl dichalcogenides as chalcogenation reagents are still needed to be explored.

Chromones represent one of the most prevalent structural heterocycles in natural products, plant physiology and pharmaceuticals. Their low toxicity and extensive biological and pharmaceutical activities, including antitumor,[9] antibacterial,[10] and antioxidant,[11] have led them to the development of a variety of general approaches for synthesizing their large number of derivatives or analogs. To synthesize these valuable derivatives, we herein report an ammonium iodide-mediated chalcogenation of chromones/quinolones with diaryl disulfides and diselenides for the synthesis of ArS/ArSe-substituted chromones/quinolones derivatives (Scheme 1d). This approach uses air as the oxidant instead of pure oxygen or other oxidants, without a metal catalyst.

Results and Discussion

Chromone derivatives and diaryl disulfides are commercially available while diaryl diselenides could be readily prepared in gram-scale according to the known procedures.[12] Our

effort was initially focused on the direct sulfenylation of chromone **1a** with diphenyl disulfide **2a** as a model reaction. The results are summarized in **Table 1**. First, TBHP and $K_2S_2O_8$ were employed as the oxidant, and CuI was used as catalyst at 100°C in DMF; Both reactions did not give the desired product **3a** (entries 1-2). Using DMSO as a oxidant with CuI gave 30% yield of **3a** (entry 3). When I_2 was selected as a catalyst with DMSO, a slightly decreased yield was obtained (entry 4). By conducting the catalyst with KI, only a trace amount of the product was observed (entry 5). The combination of NH_4I and DMSO in DMF at 100°C resulted in **3a** at a 46% isolated yield (entry 6). Upon raising the temperature to 135°C, **3a** was obtained in 61% yield (entry 7). To our excitement, it was found that using NH_4I with air in DMF was greatly beneficial for the improvement of yield (entry 8). With an attempt to improve the efficiency of the reaction, further efforts related to the influence of solvents were examined. With dioxane and toluene as solvent, **3a** was isolated in 33% and 51% yields, respectively (entries 9-10). DMAc was the most suitable solvent and gave the best result in 88% yield (entry 11). In relation to the sources of iodine in the reaction system, a negative effect was observed when KI, I_2 and TBAI were used instead of NH_4I and this resulted in 35%, 48% and 17% yields of the product **3a**, respectively (entries 12-14). Metal catalyst, such as $FeCl_3$, CuBr were proved to be less effective (entries 15-16). In addition, obviously decreased yields were obtained while further attempt to adjusting the reaction concentration and temperature (entries 17-19). Further modifications, such as catalyst loading, reaction time, and decreasing the amount of diphenyl disulfide did not

provide improvement of the yield of **3a**. Therefore, we decided to use conditions in entry 11 as the standard reaction conditions.

After successfully identifying the optimal reaction conditions for the synthesis of 3-sulfanyl-chromone, we turned our attention to the substrate scope and generality. A wide range of chromones were first evaluated in the reaction with diphenyl disulfide (**2a**). Chromones with electron-donating and weak electron-withdrawing substituents (such as Me, MeO, F, Cl, and Br) at the 6-position or 7-position of the ring gave the desired products (**3a**–**f**) in good to excellent yields. It is worth noting that Me and Cl-disubstituted chromones also exhibited good reactivity and provided the expected product in 78% yield (**3 g**). To expand the scope of this method, various diaryl disulfides were evaluated in reaction with chromones. The reaction efficiency was not significantly affected by the electronic variation of substrates. The sulfenylation reactions of chromone **1a** with the electron-donating groups, such as methyl and methoxy groups at *para*- and *meta*- positions in diphenyl disulfide proceeded smoothly affording the corresponding products **3h** , **3j**-**3k** in 91%, 71%, 84% yields, respectively. Similar yields were observed with electron-withdrawing groups, such as halogenated diaryl disulfides (**3l**, **3n**). The efficiency of the sulfenylation was slightly affected by steric hindrance. For instance, *ortho*-chloro-diphenyl disulfide as sulfenylation reagent gave an obviously decreased yield (**33 mm**). It was gratifying to find that polycyclic, and heterocyclic disulfides could also be applied, furnishing the desired products **3o** and **3p** in 80% and 51% yields (**Table 2**).

After exploring the versatility and diversity of the present ammonium iodide-mediated coupling reactions of chromones with diaryl disulfides, its application toward the synthesis of diverse selenylchromones was explored. We were pleased to observe that selenenylation of chromone derivatives went smoothly, affording the corresponding 3-selenyl-chromones in 45%–73% yields. Notably, diaryl diselenides and chromones with electron-rich (Me, OCH_3) and electron-poor (Cl, Br, F) groups on the phenyl ring were tolerated under these coupling conditions. Furthermore, the presence of the strong electron-withdrawing group, such as 6-nitro chromone, generated the product **5 h** in 45% yield. Moveover, expanding the scope from the diaryl diselenide to polycyclic diselenide was also possible, leading to the formation of **5o** in 57% yield (**Table 3**).

To further examine whether our reaction conditions are also suitable for the chalcogenation of other compounds, the reactions of quinolone with diphenyl disulfide and diselenide were carried out under the same reaction conditions. Quinolone represents a significant class of organic molecules with core entities in many commercially available drugs, including Ofloxacin, Perfloxacin, Enoxacin, Ciprofloxacin, etc. Luckily, the chalcogenation reactions worked well, giving the desired products **7a**, **7b** in 68% and 53% yields, respectively. These results have displayed a wide application scope of our method (Scheme 2).

To investigate the reaction mechanism, some control experiments were conducted. 86% and 85% yields of **3a** were obtained in the presence of the radical inhibitor (TEMPO, 2.0 equiv.)

or radical scavenger (BHT, 2.0 equiv.). These results could indicate that radical intermediates are not involved in these couplings (Scheme 3). On the basis of these data and previous studies,[13] a possible reaction mechanism for the current ammonium iodide-mediated regioselective chalcogenation of chromones was proposed as shown in Scheme 4. First, NH_4I was split into NH_3 and HI at 135°C, and then HI was further oxidized to iodine with air. Then coordination of the chalcogenation reagents with iodine gives electrophilic species ArY–I, which further reacted with chromone to form reaction intermediate **II**. Finally, deprotonation of **II** to give the corresponding products.

Conclusion

In summary, we have developed a novel and regioselective ammonium iodide-mediated C-S/C-Se bond-formation protocol involving chromones/quinolones with diaryl disulfides and diselenides with air as oxidant. This strategy provides a convenient and efficient route for the preparation of diverse 3-sulfenyl- and 3-selenyl-chromone/quinolone derivatives. Many functional groups tolerated well under the standard conditions, delivering good to excellent yields of chromone/quinolone derivatives. Further library construction and biological activity evaluation of the derivatives are ongoing in our laboratory.

Experimental

General

Reactions were monitored by thin layer chromatography (TLC), on glass plates coated with silica gel with fluorescent indicator (Huanghai, HSGF254). Flash chromatography was performed on silica gel (Huanghai, 300–400) using PE-EtOAc as eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (500, 400 MHz) with chemical shift values in ppm relative to TMS (δH 0.00 and δC 0.0) or residual chloroform (δH 7.28 and δC 77.1) as standard. Mass spectra were recorded on Thermo-Q Exactive Plus instrument or HP-5989A instrument.

General procedure

0.5 mL DMAC was added into the flask charged with 0.25 mmol of flavones, 0.25 mmol of diaryl dichalcogenides, NH_4I (1 mmol). The mixture was stirred at 135°C for 12 hours, then cooled down to room temperature, diluted with 20 mL ethyl acetate and washed with 10 mL H_2O. The aqueous layer was extracted twice with ethyl acetate (5 mL) and the combined organic phase was dried over Na_2SO_4. After evaporation of the solvents the residue was purified by flash column chromatography (silica gel, PE/EtOAc = 5:1) to afford the desired products **3**.

Complete experimental details are available online in the Supplemental Material.

Acknowledgments

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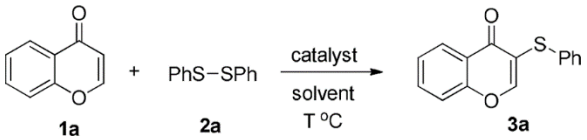
Table 1. Screening and optimization of the reaction conditions

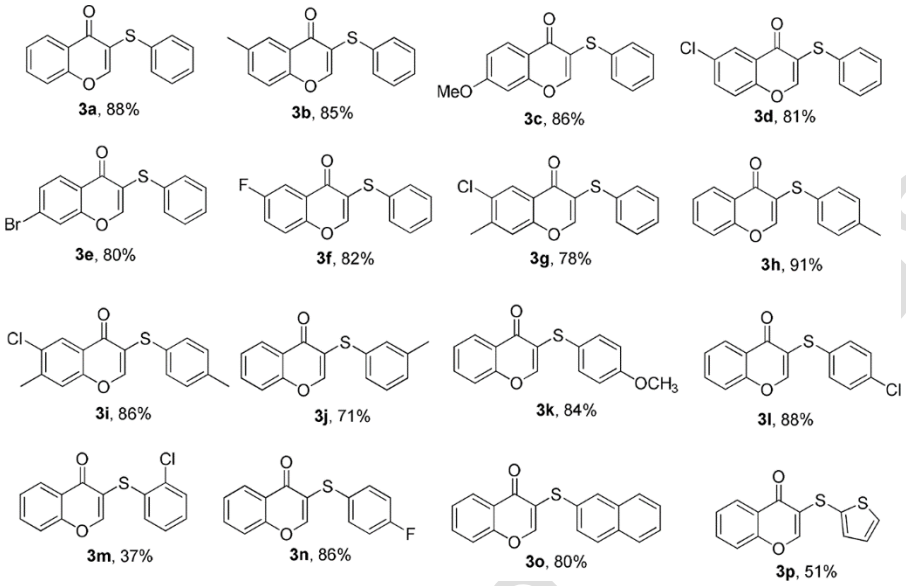


Entry[a]	Catalyst	Oxidant	Solvent	Temp. (°C)	Yield[b] [%]
1	CuI	TBHP	DMF	100	NR
2	CuI	$K_2S_2O_8$	DMF	100	NR
3	CuI	DMSO	DMF	100	30
4	I_2	DMSO	DMF	100	28
5	KI	DMSO	DMF	100	trace
6	NH_4I	DMSO	DMF	100	46
7	NH_4I	DMSO	DMF	135	61
8	NH_4I	air	DMF	135	78
9	NH_4I	air	dioxane	135	33
10	NH_4I	air	toluene	135	51
11	NH_4I	air	DMAc	135	88
12	KI	air	DMAc	135	35
13[c]	I_2	air	DMAc	135	82
14	TBAI	air	DMAc	135	17
15	$FeCl_3$	air	DMAc	135	NR
16	CuBr	air	DMAc	135	NR
17[d]	NH_4I	air	DMAc	135	62
18[e]	NH_4I	air	DMAc	135	73

19	NH_4I	air	DMAc	110	58
20[f]	NH_4I	air	DMAc	135	66

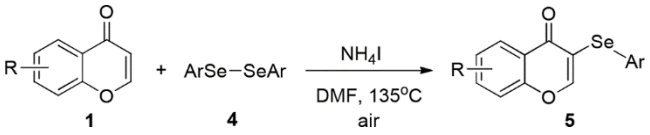
[a]Reaction conditions: chromone **1a** (0.25 mmol), diphenyl disulfide **2a** (1.0 equiv.), KI and I_2 (1.0 equiv.), NH_4I (4.0 equiv.), metal catalyst (0.2 equiv.), Oxidant (3.0 equiv.), solvent (0.5mL), 12h . [b] Isolated yields. [c] I_2 (2.0 equiv.). [d] DMAc (0.25mL). [e] DMAc (1mL). [f] NH_4I (2.0 equiv.).

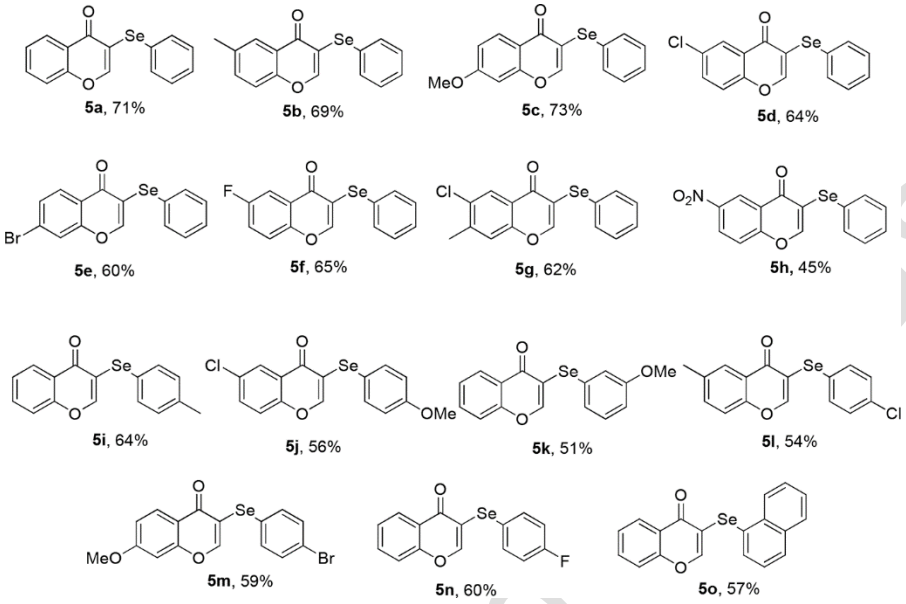
Table 2. Synthesis of 3-sulfanyl-chromones [ab]



[a] Reaction conditions: chromone **1** (0.25 mmol), diphenyl disulfide **2** (1.0 equiv.), NH_4I (4.0 equiv.), DMAc (0.5mL), 12h under air. [b] Isolated yields.

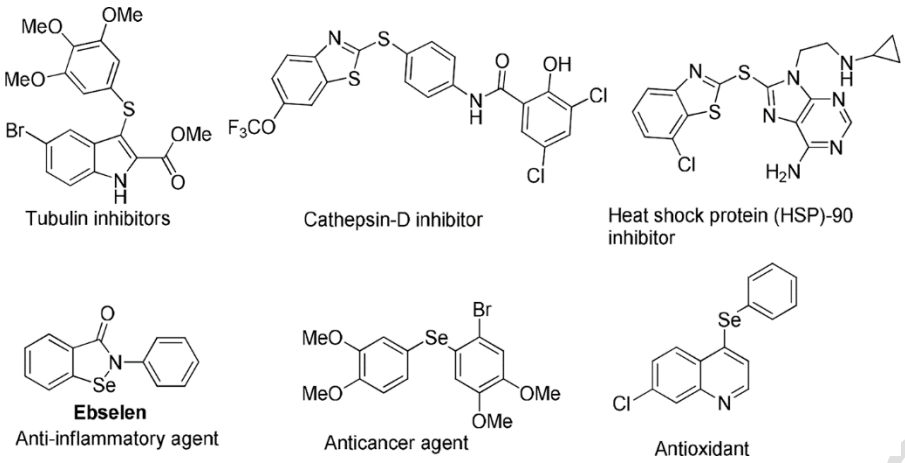
Table 3. Synthesis of 3-selenyl-chromones[ab]



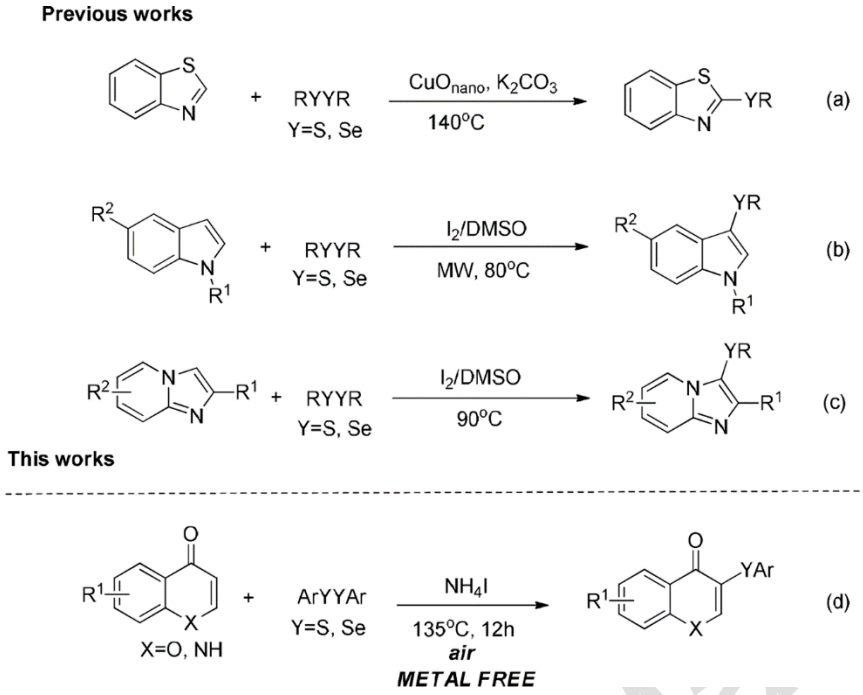


[a] Reaction conditions: chromone **1** (0.25 mmol), diaryl diselenide **4** (1.0 equiv.), NH_4I (5.0 equiv.), DMF (0.5mL), 12h under air. [b] Isolated yields.

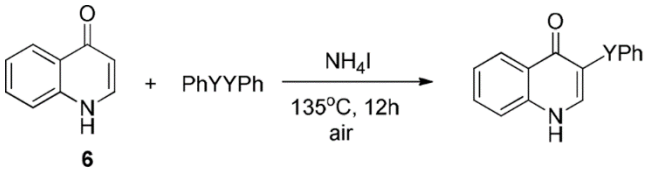
Figure 1. biologically active organochalcogen compounds.



Scheme 1. chalcogenation methods with the use of diorganoyl dichalcogenides.

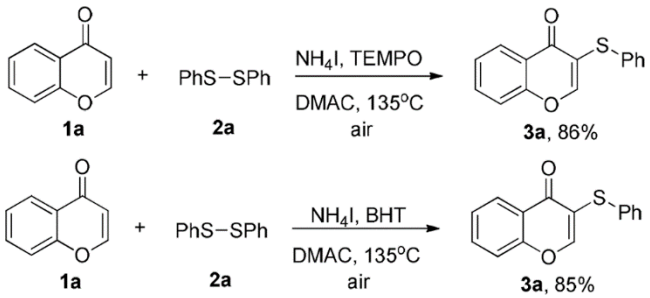


Scheme 2. Synthesis of 3-sulfenyl- and 3-selenyl-quinolones.



7a Y=S 68% yield
7b Y=Se 53% yield

Scheme 3. Control experiments.



Scheme 4. Proposed mechanism for the formation of **3** or **5**.