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Copper-Catalyzed One-Pot Synthesis of 2-Arylthiochromenones: An in Situ Recycle of Waste Byproduct as Useful Reagent

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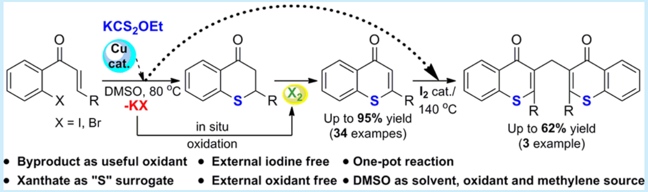
Supporting Information

ABSTRACT: Copper-catalyzed one-pot synthesis of various 2-arylthiochromenones is developed using xanthate as an odorless sulfur source from easily acquirable 2′-halochalcones. This methodology demonstrates that the cross-coupled product thiochromanone synthesized from 2′-halochalcones (upstream reaction) is oxidized to thiochromenone (downstream reaction) in the same pot using waste byproduct (KI) of the first step as powerful oxidant molecular iodine (I_2). This one-pot synthesis has been further extended for the synthesis of 3,3′-methylenebisthioflavone using dimethyl sulfoxide (DMSO) as solvent and methylene source.



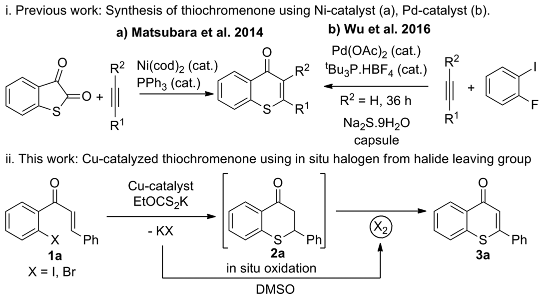
A methodology that prevents or minimizes waste production is highly important and considered to be sustainable in synthetic chemistry.[1] Based on this concept, various synthetic strategies involving catalytic and atom efficiency processes, replacement of toxic organic solvents by green media, and a one-pot tandem reactions have been achieved.[2] Among these, one-pot reaction has many advantages such as reducing the amount of chemical waste, solvent, time, cost, and manual operations, which are directly connected with intermediate isolation. Such one-pot reaction is relatively arduous to develop compared to "stop-and-go" traditional methods; because the number of reaction sequences increase, one must take into account the possibility of the following reaction in the presence of already accumulated byproducts and side-products.[3] The main criterion of an effective one-pot reaction is engaging the already produced waste in the upstream step as catalyst/cocatalyst or as a useful reagent for the downstream step in one-pot manner.[4]

Halides are the most common byproducts in transition metal-catalyzed cross coupling reactions, and it can be oxidized into halogen or hypervalent halogen in situ. These molecular halogens such as iodine and bromine are good oxidizing agents. In fact the cross coupled product can be further oxidized into another product in the same pot by activating a halide leaving group in situ into halogens after the cross coupling reactions. This method can open a prominent root for the synthesis of various molecules in one pot. Though metal-catalyzed coupling and cross coupling reactions are well-known with halocompounds,[5] converting this halide anion leaving group as an in situ generated useful molecular halogen is not known.

The thio congener of flavones called thioflavones (2-phenyl-4*H*-thiochromen-4-ones) is present as a core moiety in various natural products and biological and pharmacological activities.[6] In addition, thioflavone and its oxidized sulfone derivative are evolved as photolabile protecting groups for different kinds of functional groups.[7]

Traditional synthetic methods of thioflavone include cyclization of sulfur incorporated starting materials[8] and 2′-halochalcones or ynones with external metal sulfides as sulfur source.[9] To date, the synthetic method of thioflavones using metal catalyst are limited due to metal catalyst poisoning of sulfur; for example, Ni-catalyzed cycloaddition of thioisatin/thiophthalic anhydrides with alkynes (Scheme 1, ia),[10] and Pd-catalyzed carbonylative three/four component reaction with sodium sulfide (Scheme 1, ib).[11] However, shortcomings of these methods are competitive cyclization, narrow substrate scope, unpleasant sulfur odor, inseparable side product, poor regioselectivity, multistep synthesis, costly metal, CO source, and long reaction time.

Scheme 1. Description of Thiochromenone Synthesis



Based on the synthetic reports of thiochromone and part of our research interest in one-pot synthesis of Cu-catalyzed C−S bond formation using xanthate sulfur,[12] we hypothesized that

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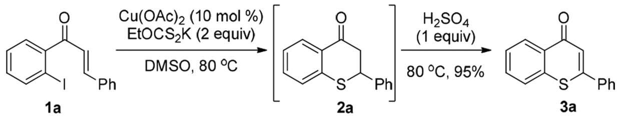
Cu-catalyzed cross-coupled product thiochromanone (**2a**) from 2′-halochalcone can be oxidized into thiochromone (**3a**) in the same pot using in situ halogen, which is generated from potassium halide byproduct (Scheme 1, ii).

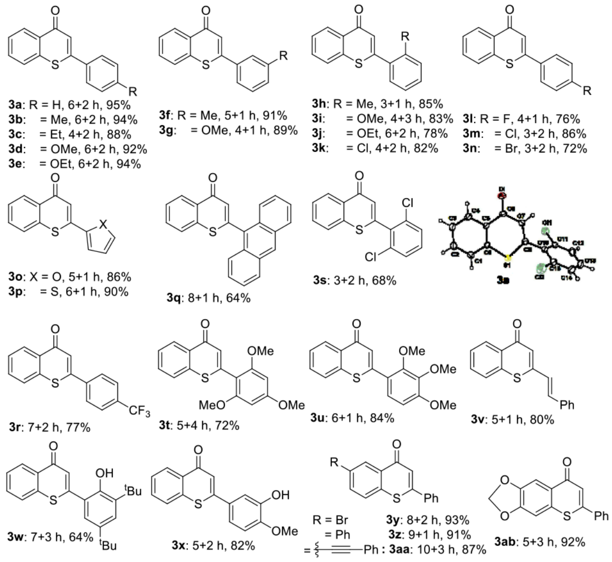
This one-pot synthesis of thiochromenone (**3a**) contains two steps. The first step is Cu-catalyzed synthesis of stable and isolable thiochromanone (**2a**) from 2′-iodochalcone and xanthate (Scheme 2).[12c] The second step is the sequential oxidation of intermediate **2a** to **3a**, which is mainly focused in this report by using the in situ generated I_2 from waste byproduct KI of the first reaction. To achieve our hypothesis, the first reaction was allowed for prolonged time assuming that the iodide leaving group from 2′-iodochalcone (**1a**) with adventitious water in the reaction can be oxidized to active iodine by DMSO. However, the desired product did not form even after 24 h. Then, the temperature of reaction mixture was increased to 100 °C. To our delight, thiochromenone (**3a**) was isolated in 48% yield after 24 h. After careful analysis of initial results, we have thoroughly optimized the reaction conditions by screening various acids, acid equivalents, reaction temperature, and reaction time to increase the efficiency of the reaction. Usage of 10 mol % $Cu(OAc)_2$ and 2 equiv of xanthate in DMSO at 80 °C for 6 h, followed by addition of H_2SO_4 (1 equiv) at 80 °C turned out to be the best reaction condition and yielded the product **3a** in 95% isolated yield (Scheme 2).[17]

Scheme 2. Optimized Reaction Condition



Having optimized reaction conditions in hand, we examined the efficacy of the newly developed one-pot synthesis of 2-arylthiochromones exposing various substituted 2′-iodochalcones (Scheme 3). 2′-Iodochalcones derived from an electron donating group substituted benzaldehyde in the *para*, *meta*, and *ortho* positions were effective to give the corresponding products **3b**–**k** in 78–94% yield. 2′-Iodochalcone containing halo group such as fluoro, chloro, and bromo groups were well tolerated and rendered the products **3l**, **3m**, and **3n** in good to excellent yields. The heteroaryl group also exhibited good reactivity, leading to the desired product **3o** in 86% and **3p** in 90% yields, respectively. Anthracenylchalcone **1q** was also a suitable substrate and gave the corresponding thioflavone **3q** in 64% yield. Importantly, the electron withdrawing group substituted substrate was compatible under the optimized condition, and **3r** was isolated in 77% yield.

Scheme 3. Generality of the One-Pot Synthesis with Various 2′-Iodochalcones[a]

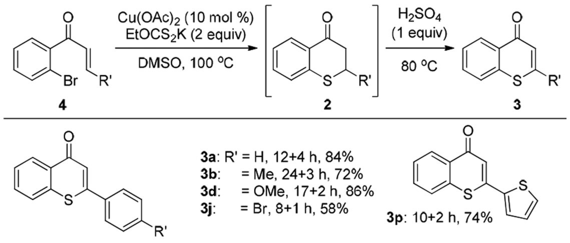


[a]Reaction conditions: **1** (0.5 mmol), xanthate (2 equiv), $Cu(OAc)_2$ (10 mol %), DMSO (2 mL) at 80 °C, then H_2SO_4 (1 equiv).

Interestingly, sterically hindered substrates were found to be appropriate for this one-pot reaction and enabled the thioflavones **3s**–**u** in 68–84% yields. The structure of **3s** was further confirmed by single-crystal X-ray analysis.[13] Moreover, the effort to extend the substrate scope toward unsaturated aldehyde derived iodochalcone such as **1v** was successful, and it gave **3v** in 80% yield. It is noteworthy to mention that the unprotected hydroxyl group containing substrates were viable and provided **3w**–**x** in good yields. The optimized reaction conditions were investigated for different 2′-iodoacetophenone derived chalcones. The chalcone bearing substituents such as bromo, phenyl, and acetylene groups underwent the reaction smoothly, resulting in the desired products **3y**, **3z**, and **3aa** in 93%, 91%, and 87% yields, respectively. Dioxo-substituted substrate **1ab** underwent the one-pot condition and provided the product **3ab** in 92% yield.

The newly developed one-pot synthesis of thiochromones was investigated using less reactive 2′-bromochalcones, and the results are shown in Scheme 4. When 2′-bromochalcone **4a** was examined under the optimized condition, delightfully, product **3a** was isolated in 84% yield. Consequently, the other substituted bromochalcones were also successfully subjected, and the thioflavones **3b**, **3d**, **3j**, and **3p** were obtained in 58–86% yields.

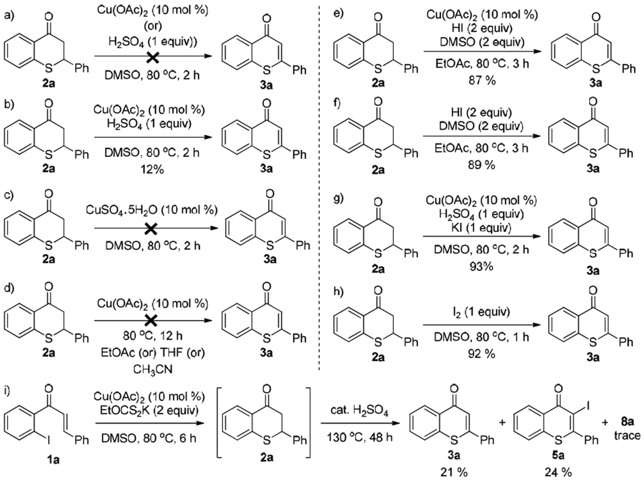
Scheme 4. Generality of the One-Pot Synthesis with Less Reactive 2′-Bromochalcone[a]



[a]Reaction conditions: **4** (0.5 mmol), xanthate (2 equiv), $Cu(OAc)_2$ (10 mol %) at 100 °C, then H_2SO_4 (1 equiv) at 80 °C.

To get an insight into the mechanism, several controlled reactions were carried out to elucidate whether the thiochromanone is actually oxidized by in situ generated halogen or not (Scheme 5). Treatment of **2a** with 10 mol % of $Cu(OAc)_2$ or H_2SO_4 (1 equiv) independently did not give the desired product **3a** (Scheme 5a). However, 12% of **3a** was isolated when the reaction of **2a** was carried out using $Cu(OAc)_2$ and H_2SO_4 (Scheme 5b). It could be explained by the Lewis acid character of $Cu(OAc)_2$ to form metal enolate complex[14] along with the known oxidation property of H_2SO_4. A control reaction revealed that $CuSO_4$ cannot be the hidden

Scheme 5. Mechanistic Experiments for the Formation of 3



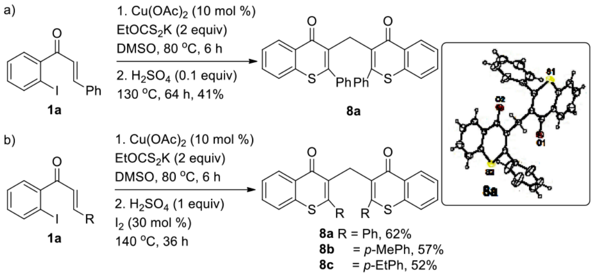
catalyst, which can possibly form from Cu(OAc)$_2$ with H_2SO_4 in the reaction medium (Scheme 5c).

Then, we surmised that the addition of HI and DMSO as external reagents, which makes iodine in situ in the reaction, can provide the product **3a** from **2a** in an appropriate nonoxidizable solvent. To confirm this hypothesis, EtOAc, THF, and CH_3CN were chosen as solvent, and the reactions were conducted using **2a** with 10 mol % of Cu(OAc)$_2$. As expected, there was no product formation even after 12 h (Scheme 5d). When the same reaction was carried out using 2 equiv of each HI (55−58%) and DMSO in EtOAc solvent, the desired product **3a** was isolated in 87% yield within 3 h (Scheme 5e). It is noteworthy that DMSO is playing a dual role as oxidant and solvent in this reaction. To clarify the role of Cu(OAc)$_2$ in the second sequential reaction, the reaction was conducted without Cu(OAc)$_2$, which provided the almost same yield of **3a** (Scheme 5, f vs e). This result suggests that the Cu(OAc)$_2$ does not play a pivotal role during the formation of oxidized product **3a** from **2a**.

The next experiment was carried out replacing HI by KI with 1 equiv of H_2SO_4 in DMSO solvent, and it furnished 93% of **3a**, which supports our hypothesis (Scheme 5g). Then, the addition of 1 equiv of I_2 with the reaction mixture containing **2a** in DMSO gave 92% of **3a**, which clearly shows that I_2 plays a crucial role in oxidation of **3a** from **2a** (Scheme 5h). During the course of reaction, we did not detect 3-iodo-2-phenylthiochroman-4-one **7** (Scheme 8), which might be due to the facile elimination of HI from **7** and the formation of stable enone conjugate compound **3a**. Since we attempted the reaction with stoichiometric H_2SO_4, it is assumed that the intermediate **7** can be possibly isolated with catalytic quantity of H_2SO_4. When the reaction was carried out with 10 mol % of H_2SO_4 at 130 °C, 21% of **3a** along with 24% of iodo product **5a** was isolated after 48 h (Scheme 5i).[15] This result indicates that compound **7** should be the intermediate for products **3a** and **5a**.[17]

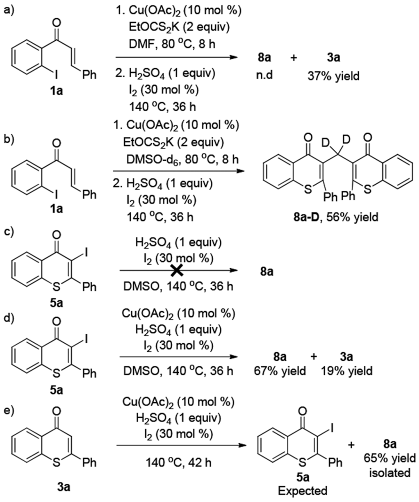
When the high temperature reaction (Scheme 5i) was allowed for longer time (64 h), a new product 3,3′-methylenebisthiochromenenone **8a** was isolated in 41% yield after the slow disappearance of **3a** and **5a** and confirmed by single crystal XRD (Scheme 6a).[13] Surprisingly, after the addition of 30 mol % of I_2 with 1 equiv of H_2SO_4, the yield of **8a** increased to 62% in a shorter reaction time of 36 h at 140 °C (Scheme 6b). Subsequently, the other substituted chalcones were treated and the corresponding products **8b** and **8c** were produced in good yields.

Scheme 6. Synthesis of 3,3′-Methylenebisthioflavone



To gain more insight into the mechanism for the formation of **8**, we performed several controlled experiments as shown in Scheme 7. To prove that the DMSO is the source of the methylene group, the reactions were carried out using DMF and DMSO-d_6 as solvent, independently. The product **8a** was not detected in DMF solvent (Scheme 7a). However, in case of DMSO-d_6 as solvent, deuterated product **8a-D** was isolated in 56% yield (Scheme 7b). The reaction did not yield **8a** when **5a** was used as reactant with 30 mol % of iodine and 1 equiv of H_2SO_4 in DMSO (Scheme 7c). However, when the same reaction was carried out using 10 mol % of Cu(OAc)$_2$, it yielded 67% of **8a** along with 19% of **3a** (Scheme 7d). These results clearly indicate the necessity of copper catalyst for the formation of **8a** via intermediate **5a**.[17] Then, a control experiment was performed to clarify the product formation of **5a** from **3a** using iodine as catalyst (Scheme 7e). However, we were able to isolate 65% of product **8a**, which clearly suggested that the product **5a** can be formed from **3a**, but in the presence of Cu-catalyst, **5a** can be easily converted to the product **8a**.[19]

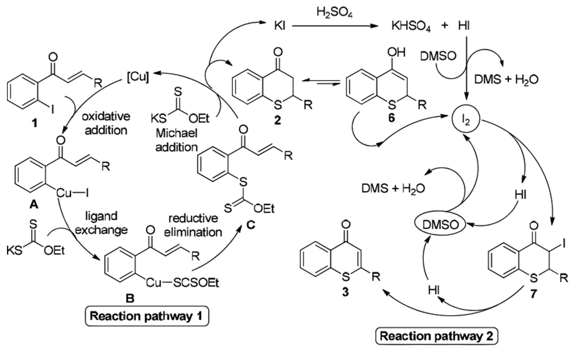
Scheme 7. Mechanistic Experiments for the Formation of 8



Also, this mild and easy handling method is scalable and applicable for the synthesis of 3′,4′-dimethoxythiochromenenone in one step, which exhibits inducing endothelium-dependent vasorelaxation property.[16] As an application and utility of this method, thiochromenone **3a** was converted into 2-phenyl-4*H*-thiochromene and 2-phenyl-4*H*-thiochromen-4-one 1,1-dioxide.[17]

On the basis of the above experiments and the previous literature reports,[12,18] a plausible reaction mechanism for this one-pot synthesis is illustrated in Scheme 8. Reaction pathway 1 is initiated by 2′-iodochalcone **1** with xanthate in the presence of copper acetate, and it expels the desired product thiochromanone **2** along with Cu-catalyst and potassium iodide (KI) as byproduct.[12c] Then, the byproduct KI is converted to HI on reacting with H_2SO_4, and further, the HI is oxidized to I_2 in situ in DMSO solvent.

Scheme 8. Plausible Mechanism for Thiochromenone 3



The reaction pathway 2 is initiated by in situ generated I_2 with enol tautomer **6** of thiochromanone **2** to yield 3-iodothioflavanone intermediate **7** (Scheme 8). The intermediate **7** produces desired product **3** by eliminating HI. The elimination product HI is further oxidized to iodine by DMSO, which is already presented in the reaction medium as solvent. Also, the plausible mechanistic pathway for the formation of **8a** from **3a** through **5a** is described.[17] However, further mechanistic study and applications of this one-pot reaction are currently underway in our laboratory.

In summary, we have disclosed an efficient Cu-catalyzed one-pot strategy for the synthesis of 2-arylthiochromenones from easily accessible 2′-halochalcones using xanthate as sulfur surrogate through 2-arylthiochromanones. To the best of our knowledge, this is the first example that takes advantage of oxidation of cross-coupled product 2-arylthiochromanone to 2-arylthiochromenone in the same pot using in situ generated halogen I_2, which is generated from byproduct KI of upstream cross-coupling reaction. In this reaction, the DMSO solvent oxidizes the byproduct KI into I_2, which avoids the use of any external oxidant. Importantly, the use of byproduct as useful reagent improves the atom-economy and obviated external iodine. Further, the one-pot methodology is extended for the synthesis of 3,3′-methylenebisthiochromenone using dimethyl sulfoxide as methylene source and Cu catalyst, which is expelled from upstream reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03508.

Details of the synthetic experimental procedure, and ^{1}HNMR and ^{13}CNMR spectra and characterization data of all the compounds (PDF)

Accession Codes

CCDC 1842182−1842183 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(13) CCDC no. 1842182 (**3s**) with 30% probability ellipsoids; CCDC no. 1842183 (**8a**) with 30% probability ellipsoids.

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(19) Since we have the authentic sample of **5a**, this authentic sample is matched with the reaction mixture and the presence of **5a** identified by TLC.

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