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Copper-Catalyzed Domino Synthesis of 2-Arylthiochromanones through Concomitant C−S Bond Formations Using Xanthate as Sulfur Source

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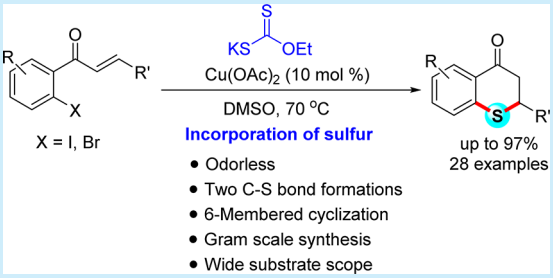
Supporting Information

ABSTRACT: An efficient domino process for the synthesis of thioflavanones has been described using a copper catalyst without addition of any external ligand. A variety of thioflavanones have been synthesized from easily accessible 2′-iodochalcones or 2′-bromochalcones in excellent yield through in situ incorporation of sulfur using xanthate as an odorless sulfur source. This domino process proceeds through Cu-catalyzed $C_{(aryl)}$−S bond formation by the coupling reaction of xanthate with 2′-halochalcones followed by C−S bond cleavage of thioester then S−C bond formation by intramolecular Michael addition.

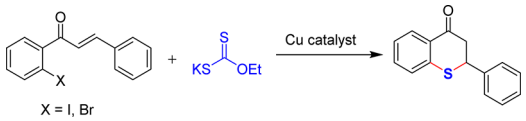


Sulfur-containing compounds are extensively found in many pharmaceutical and bioactive natural products.[1] Specifically, thioflavanones (2-phenylthiochroman-4-ones) and their analogues display a variety of biological activities such as antifungal, antibacterial, antioxidant, and inhibitory activity of nitric oxide production.[2] Furthermore, thioflavanones have been shown to induce apoptosis in human breast cancer cell lines, thereby serving as potent molecules for cancer treatment.[3] Generally, synthesis of thioflavanone requires sulfur-incorporated starting materials. For example, the Michael addition of thiophenol with ethyl cinnamates followed by Friedel−Crafts acylation,[4] reduction of thioflavones to thioflavanones,[5] cyclization of 2′-mercaptochalcone,[6] and domino reaction of 2′-iodothiophenol, allene, and carbon monoxide using Pd catalyst[7] have been reported. Recently, synthesis of 2-arylthiochroman-4-ones using sodium hydrosulfide solution was reported.[8] However, these methods are associated with several limitations such as a very unpleasant smell of the thiol precursor, air-sensitive starting material, costly metal catalyst, low yield, product mixtures, and a required multistep synthesis. Therefore, the synthesis of thioflavanones via an efficient catalytic method which can overcome all these difficulties is highly desirable.

The carbon−sulfur bond constitutes a great proportion of bond-forming reactions in organic synthesis. Thus, attention has been drawn toward the investigation of catalytic methods for the construction of a C−S bond.[9] Transition-metal catalysts have emerged as an efficient tool for $C_{(aryl)}$−S bond formation.[10] However, transition-metal-catalyzed domino reactions which involve in situ incorporation of sulfur through concomitant formation of two or more C−S bonds for the construction of sulfur-containing cyclic architecture are less explored.[11] The strong coordination and adsorption ability of sulfur compounds to transition metals concern the deactivation of catalyst,[10a] which in turn limits development in this field. Hence, the accomplishment of a new catalytic method which can overcome these complications is still a primary topic of interest.

As part of our ongoing research toward Cu-catalyzed in situ generation of thiol using xanthate as a thiol surrogate, we have reported one-pot synthesis of arylthioethers, benzothiazoles, and benzothiophenes.[12] Herein, we report Cu-catalyzed domino synthesis of 2-arylthiochroman-4-ones from 2′-halochalcones using odorless potassium ethyl xanthogenate as sulfur source (Scheme 1).

Scheme 1. Domino Synthesis of 2-Arylthiochroman-4-ones via Cu-Catalyzed Concomitant Formation of Two C−S Bonds



Initially, the reaction was performed with 2′-iodochalcone **1a** and potassium ethyl xanthogenate (3 equiv) in the presence of 10 mol % of $Cu(OAc)_2$ and 10 mol % of 1,1′-binaphthyl-2,2′-diamine [(±)-BINAM] in *N*,*N*-dimethylformamide at 80 °C. To our delight, the domino reaction yielded 78% of 2-phenylthiochroman-4-one **2a** through concomitant formation of two C−S bonds (Table 1, entry 1). To understand the role of ligand, the reaction was conducted without ligand. Interestingly, the reaction yielded 86% of product (entry 2), and this result clearly shows that ligand is not necessary for this reaction. The reaction was studied with copper salts and solvents in the absence of ligand to improve the efficiency of the reaction. Although the reaction yielded the product with all copper salts, copper acetate

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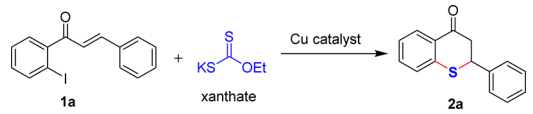
Table 1. Optimization of Reaction Conditions[a]



entry	Cu salt	xanthate (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Cu(OAc)_2$	3	DMF	80	5	78[c]
2	$Cu(OAc)_2$	3	DMF	80	2	86
3	$CuCl_2$	3	DMF	80	7	79
4	$CuBr_2$	3	DMF	80	2	75
5	CuBr	3	DMF	80	6	83
6	CuCl	3	DMF	80	5	77
7	$Cu(OAc)_2$	3	DMSO	80	2	96
8	$Cu(OAc)_2$	3	DMSO	70	3	95
9	$Cu(OAc)_2$	3	DMSO	60	12	81
10	$Cu(OAc)_2$	3	DMSO	50	18	74
11	$Cu(OAc)_2$	1	DMSO	70	48	63
12	$Cu(OAc)_2$	1.5	DMSO	70	15	76
13	**$Cu(OAc)_2$**	**2**	**DMSO**	**70**	**6**	**97**
14	$Cu(OAc)_2$	2	DMSO	70	13	81[d]
15		2	DMSO	70	24	00

[a]Standard reaction conditions: **1a** (0.5 mmol), xanthate, and Cu catalyst (10 mol %) in solvent (2 mL). [b]Isolated yield. [c]10 mol % of (±)-BINAM was used as ligand. [d]5 mol % of $Cu(OAc)_2$ was used.

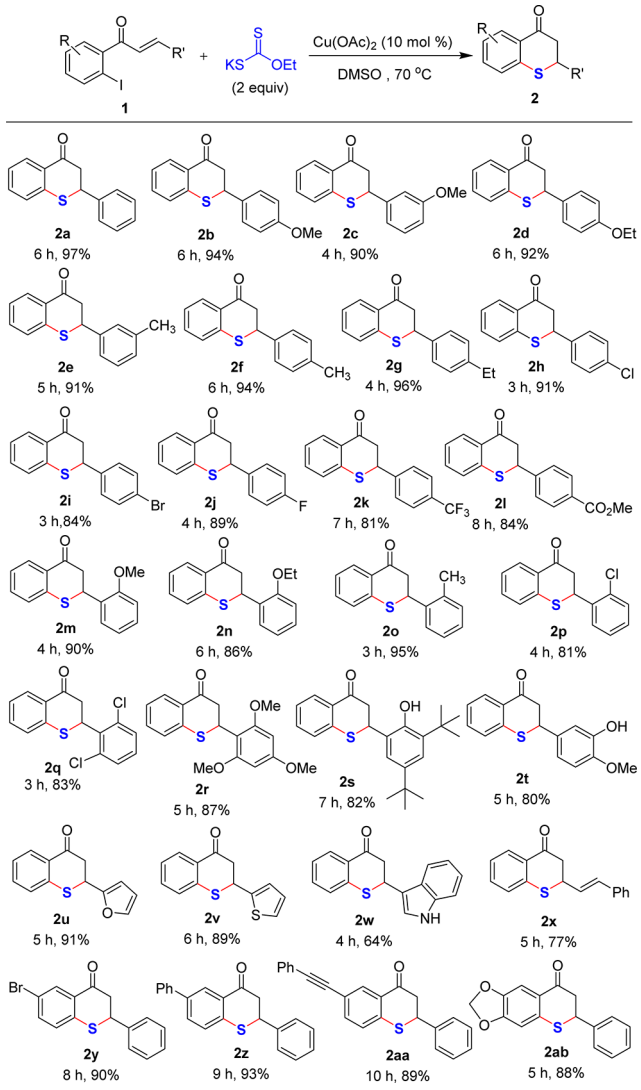
remained to be the best choice as it provided the highest yield in a short reaction time (entries 3−6 vs 2). In the study of solvent, when the reaction was performed in dimethyl sulfoxide, a drastic increase in yield of the product **2a** (96%) was observed (entry 7). In temperature study, when the reaction temperature was reduced to 70 °C, the reactivity and yield were not altered much (entry 8). However, further decrease in the temperature affected the reactivity and yield (entries 9 and 10).

Next, various equivalents of xanthate were studied. The reaction with 1 equiv of xanthate did not progress to full completion, and the product was isolated in 63% yield (entry 11). The reaction with 1.5 equiv of xanthate required longer reaction time and provided 76% yield for the product (entry 12). However, reaction with 2 equiv of xanthate gave 97% yield in 6 h (entry 13). Moreover, the reactivity and yield of the product was dropped when 5 mol % of $Cu(OAc)_2$ was used (entry 14). Very importantly, there was no product formation without $Cu(OAc)_2$ catalyst (entry 15). From the optimization studies, it was found that the reaction proceeded smoothly with 2 equiv of xanthate and 10 mol % of $Cu(OAc)_2$ in DMSO at 70 °C.

To explore the efficiency of the domino reaction, various 2′-iodochalcones were exposed to the optimized reaction conditions for the synthesis of 2-arylthiochromanones (Scheme 2). The domino reaction of 2′-iodochalcones with electron-donating substituents progressed effortlessly and gave the corresponding products **2a−g** in excellent yield. The 2′-iodochalcones with chloro, bromo, and fluoro substituents, which can be useful in further derivatization, were found to be suitable for this domino reaction (**2h−j**). The electron-withdrawing group substituted 2′-iodochalcones were well tolerated, and corresponding products **2k** and **2l** were isolated in good yield.

It is noteworthy to mention that reactivity and yield are not affected by the steric effect of substituents. For example, the domino reaction of *ortho*-substituted 2′-iodochalcones took place readily and provided the thioflavanones **2m−r** in admirable

Scheme 2. Domino Synthesis of 2-Arylthiochroman-4-ones[a]



[a]Reaction conditions: 1 (0.5 mmol), xanthate (1 mmol) and $Cu(OAc)_2$ (10 mol %) in DMSO (2 mL) at 70 °C.

yield. Interestingly, substrates containing unprotected hydroxyl groups were well tolerated and gave the products **2s** and **2t** in good yield. Besides aryl groups, substrates with heteroaryl groups were also found to be appropriate for this domino reaction, and the corresponding products **2u−w** were obtained in notable yield. When 2′-iodochalcone, which was prepared from 2′-iodoacetophenone and cinnamaldehyde, was subjected to optimized reactions conditions, **2x** was isolated in 77% yield. Next, optimized reaction conditions were applied to 2′-iodochalcones having substituents at the iodo-attached aryl ring. The substituents such as bromo, phenyl, and acetylene were applicable for the domino reaction and produced the corresponding thioflavanones **2y**, **2z**, and **2aa** in excellent yield. Above all, dioxo-substituted 2′-iodochalcone was a reasonable substrate and gave the corresponding thioflavanones **2ab** in 88% yield. The structure of **2h** was unambiguously confirmed by single-crystal XRD analysis (Figure 1).

An attempt was then made to achieve the domino synthesis of thioflavanones from less reactive 2′-bromochalcones **3**. When the optimized reaction conditions were applied to 2′-bromochalcone **3a**, the product formation was not observed.

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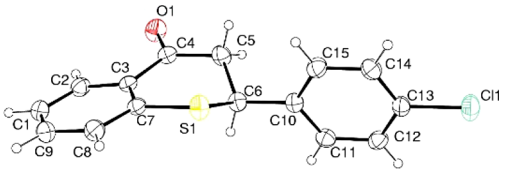
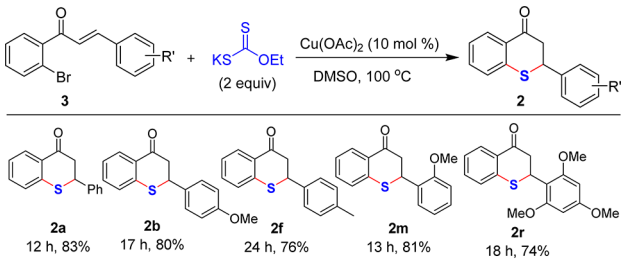


Figure 1. Single-crystal X-ray structure of compound **2h** (CCDC no. 1426817). Ellipsoids represent 30% probability level.

However, when the reaction temperature was increased to 100 °C, completion of the reaction was observed in 12 h and product **2a** was isolated in 83% yield (Scheme 3). Other substituted 2′-

Scheme 3. Domino Synthesis of 2-Arylthiochroman-4-ones from Less Reactive 2′-Bromochalcones[a]

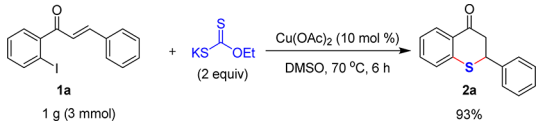


[a]Reaction conditions: **3** (0.5 mmol), xanthate (1 mmol), and $Cu(OAc)_2$ (10 mol %) in DMSO (2 mL) at 100 °C.

bromochalcones were also found to be suitable substrates for this domino reaction and provided the thioflavanones **2a**, **2b**, **2f**, **2m**, and **2r** in admirable yield.

To evaluate the efficacy of this domino reaction in gram scale, the reaction was investigated with 1 g of 2′-iodochalcone. Interestingly, the thioflavanone **2a** was isolated in excellent yield (93%) in 6 h without compromising the optimized reaction conditions (Scheme 4).

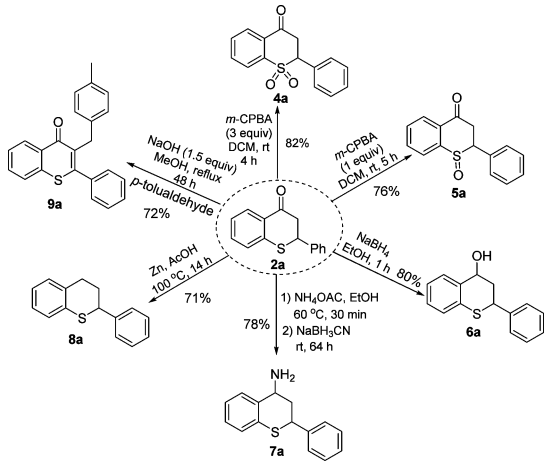
Scheme 4. Gram-Scale Synthesis



Thioflavanones can be easily functionalized to a variety of important chemical entities (Scheme 5). For example, sulfur was oxidized to sulfone (**4a**) with excess *m*-chloroperbenzoic acid (*m*-CPBA) and sulfoxide (**5a**) as a 1:1 mixture of diastereomers with controlled oxidation. The keto group of thioflavanone was reduced to alcohol (**6a**) as single diastereomer by simple reduction with sodium borohydride. Reductive amination of thioflavanones gave amine (**7a**) as 1:1 mixture of diastereomers. The thioflavanone was completely reduced to 2-phenylthiochroman (**8a**). The active methylene group was reacted with aldehyde to give substituted thiochromenone (**9a**).

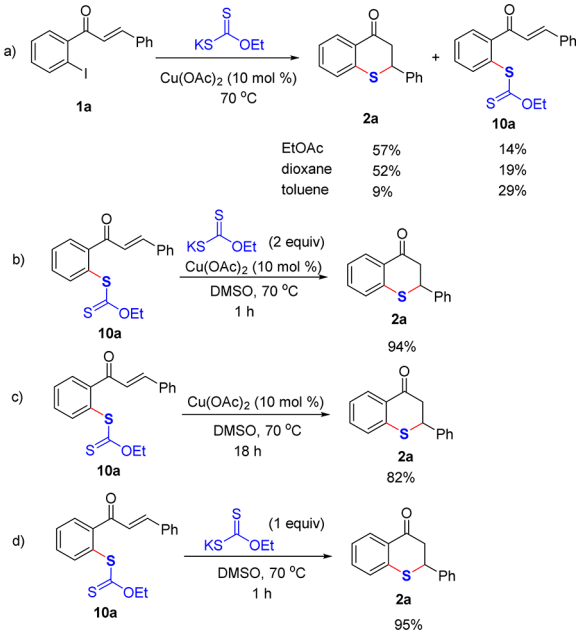
To understand the mechanism of newly developed domino reaction, an investigation was led to observe any possible intermediates. As the reaction is expected to proceed either through coupling followed by Michael addition or Michael addition followed by coupling, reactions were conducted to trap the appropriate intermediate.

Scheme 5. Functionalization of Thioflavanones



Initially, the domino reaction was quenched with hydrochloric acid, but thiol was not observed. Since thiol can move to a Michael or coupling reaction immediately, it could be very difficult to detect. Then, it was speculated that the reactivity can be controlled if the reaction is conducted in moderate or less polar solvent as the reaction is very facile in DMSO solvent. Interestingly, compound **10a** was isolated in 14% yield when the reaction was conducted in ethyl acetate (Scheme 6a). Similarly,

Scheme 6. Controlled Reactions



compound **10a** was observed with other less polar solvents such as 1,4-dioxane and toluene. These results confirm that the reaction proceeds through formation of compound **10a**. When compound **10a** was exposed to optimized reaction conditions, 94% of **2a** was isolated in 1 h (Scheme 6b). The reaction without xanthate took 18 h to give **2a** in 82% yield (Scheme 6c), whereas the reaction with only 1 equiv of xanthate was completed in 1 h (Scheme 6d). These reactions clearly show that both copper acetate and xanthate can promote the Michael addition independently. However, xanthate is more facile toward Michael addition than copper acetate (Scheme 6c vs Scheme 6d).

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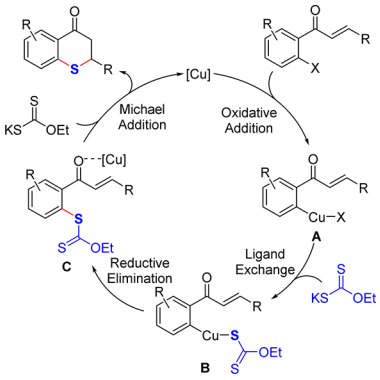
Furthermore, it was noticed that addition of water (10 equiv) with DMSO increased the reactivity, and the reaction had gone to completion in 5 h, whereas the reaction with dry DMSO under N_2 atmosphere decreased the reactivity and the reaction took 13 h for completion. These reactions are evidence for involvement of residual water in DMSO or adventitious water in the reaction medium.

From the above observations, a possible mechanism was proposed as shown in Scheme 7. Oxidative addition of 2′-

Scheme 7. Proposed Mechanism



iodochalcone with copper acetate may give intermediate **A**, which in the presence of potassium ethyl xanthate leads to intermediate **B**. The reductive elimination of intermediate **B** provides intermediate **C**, which was isolated in less polar solvent. Then, intermediate **C** undergoes Michael addition with the help of copper acetate and potassium ethyl xanthate to give the product. However, a detailed mechanistic study and application of this newly developed methodology and its asymmetric version are in progress.

In conclusion, we have developed an efficient domino process for the synthesis of thioflavanones from 2′-iodochalcone using copper catalyst without addition of any external ligand and xanthate as the sulfur precursor. The domino reaction proceeds through in situ incorporation of sulfur by concomitant formation of two carbon−sulfur bonds to provide thioflavanones in excellent yield. Thioflavanones were also synthesized from 2′-bromochalcones and derivatized to other important organic molecules. This method can be a general approach for the synthesis of thioflavanones as the reaction requires easily accessible starting materials, avoids the unpleasant smell of thiol precursor, uses inexpensive copper catalyst, and provides excellent yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02977.

Detailed experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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