



Transition metal-free tunable synthesis of 3-(trifluoromethylthio) and 3-trifluoromethylsulfinyl chromones *via* domino C–H functionalization and chromone annulation of enamines

Tao Zhou^a, Jing Zhou^{a,b}, Yunyun Liu^a, Jie-Ping Wan^{a,*}, Fen-Er Chen^{a,b,*}

^a College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, China

^b Engineering Center of Catalysis and Synthesis for Chiral Molecules, Fudan University, Shanghai 200433, China

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ABSTRACT

The new reactions between *o*-hydroxyphenyl enamines and Langlois reagent (CF₃SO₂Na) for the tunable synthesis of 3-(trifluoromethylthio) chromones and 3-trifluoromethylsulfinyl chromones are reported herein. Both type of reactions proceed under transition metal-free conditions. In addition, the conditions for the synthesis of 3-trifluoromethylsulfinyl chromones have also been found to be applicable for the synthesis of 3-alkyl/arylsulfinyl chromones.

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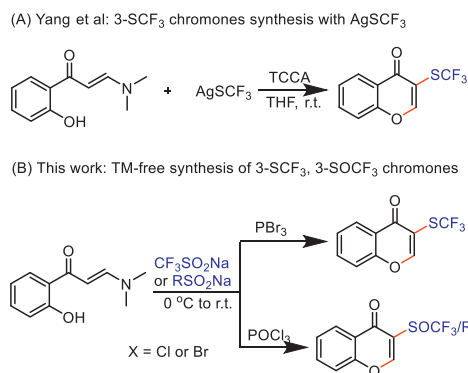
As attractive targets in organic synthesis, the chromones keep receiving extensive attention in synthetic method development [1–3]. In order to enhance the structural diversity of compounds featuring a chromone core, a plethora of synthetic protocols consisting of chromone ring construction and different other cascade chemical transformations have been established over the recent decade [4–11]. The notable advances in chromone synthesis, as expected, also have promoted the discovery of chromones possessing fantastic functions, including but not limited in biologically relevant lead compounds [12–14] and organic materials *etc.* [14–17]. Among the currently available protocols, the domino reactions consisting of a featured chromone annulation of *o*-hydroxyaryl enamines and other different C–H functionalization transformation have been identified as the most prevalently investigated and employed tactic [18]. Especially over the last decade, the *o*-hydroxyphenyl enamine-based chromone synthesis has received booming advances in terms of both reaction pathways and product diversity. By means of proper catalytic conditions, this typical chromone annulation takes place together with the formation of various other new chemical bonds in form of domino reactions, leading to the synthesis of chromones with C3-substituents such

as alkyl and functionalized alkyl [19–26], perfluoroalkyl [27–29], aryl [30–31], alkenyl [32], alkynyl [33], chalcogen atoms [34–39], nitrogen [40–41] and various other carbon- and heteroatom-based functional structures [42–45].

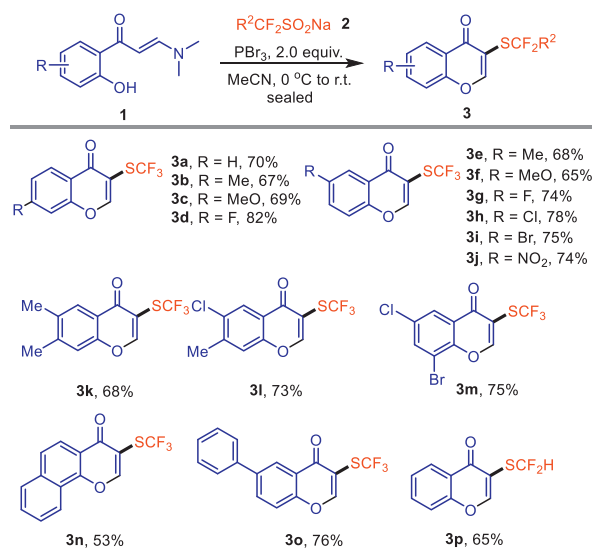
On the other hand, due to the significant role of trifluoromethylthio group in determining the functionality of organic molecules [46–49], the synthesis of trifluoromethylthiolated molecules has won highly extensive attention [50–53]. Unsurprisingly, the synthesis of trifluoromethylthiolated chromones has gained high interest of chemists. In 2014, Yang and Xiang [54] reported the synthesis of 3-trifluoromethylthiolated (3-CF₃S) chromones by employing AgSCF₃ as the source of SCF₃ group (Scheme 1A). To date, no other catalytic method enabling the synthesis of 3-(trifluoromethylthio) chromones with *o*-hydroxyphenyl enamines is available. Accordingly, developing new methods, especially the ones without relying on expensive transition metal-catalyst or reagent for the synthesis of such chromone derivatives is currently of high demand [55–64]. Herein, upon our sustaining efforts in developing enamine-based synthesis [65–71], we report the first method on the *o*-hydroxyphenyl enamine-based synthesis of 3-(trifluoromethylthio) chromones by employing CF₃SO₂Na as a cheap CF₃S source. Besides, we also have realized the chemo-selective synthesis of 3-trifluoromethylsulfinyl chromones with identical substrates by simply modifying reaction conditions. Moreover, the 3-sulfinyl chromones which are not

* Corresponding authors.

E-mail addresses: wanjieping@jxnu.edu.cn (J.-P. Wan), rfchen@fudan.edu.cn (F.-E. Chen).



Scheme 1. Known method for the synthesis of 3-(trifluoromethylthio) chromones with AgSCF₃ and this work.

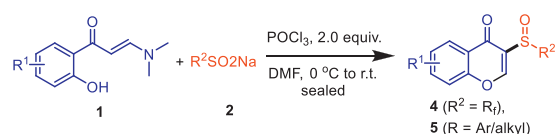


Scheme 2. Scope on the synthesis of 3-(trifluoromethylthio) chromones.

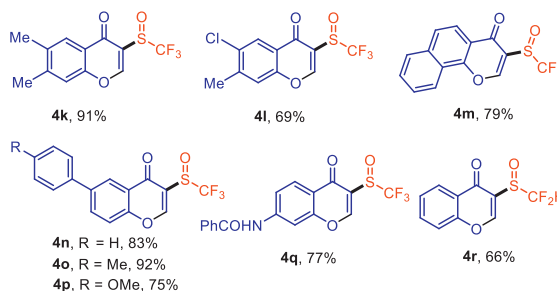
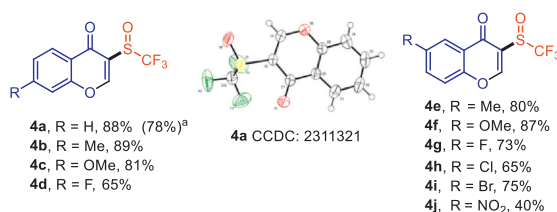
accessible by any previous synthetic efforts, have been easily furnished by our method with simple sodium sulfinates as the reaction partners (Scheme 1B).

Originally, the *o*-hydroxyphenyl enaminone **1a** and CF₃SO₂Na (**2a**) were selected as starting materials for the potential synthesis of 3-(trifluoromethylthio) chromone **3a**. By screening different reagents, the PBr₃ was found to be an applicable reagent for the synthesis of the target product **3a** by acting as both coupling and reducing agent. To explore the proper conditions enabling the efficient synthesis of **3a**, the reaction parameters, including the loading of **2a** and PBr₃, the reaction medium, concentration, as well as the reaction temperature were optimized, respectively (Tables S1–S3 in Support information). The results indicated that the optimal result of 70% **3a** was afforded by running the reaction in DMF at 0°C to room temperature. The GC–MS analysis on the reaction residue from the optimal entry indicated no presence of CF₃SO- or CF₃SO₂-substituted chromone, documenting the fine stability of the **3a** against aerobic oxidation.

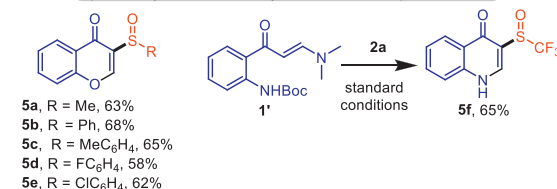
By employing the optimized conditions, the scope on the synthesis of CF₃S-functionalized chromones **3** was then investigated with various enaminones **1** as starting materials to react with **2**. As outlined in Scheme 2, the synthesis of such functionalized chromones exhibited general tolerance to the functional group in the aryl ring of **1**. The products **3a–3o** were obtained with generally good to excellent yields. While electron withdrawing group (EWG) substituted substrates gave halo-atom or nitrophenyl-based



Scope on the synthesis of 3-perfluoroalkylsulfinyl chromones



Expanded synthesis of 3-sulfinyl chromones and quinoline-4-one

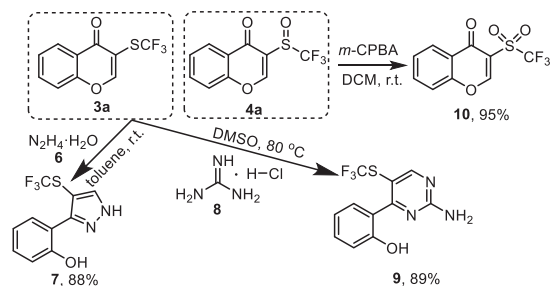


Scheme 3. Scope on the synthesis of 3-perfluoroalkylsulfinyl chromones and 3-sulfinyl chromones. ^a Yield from 1 mmol-scale reaction.

products **3d**, **3g–3j** and **3n** with 74%–82% yield, the equivalent electron donating group (EDG), such as alkyl or alkoxy functionalized products were given with slightly lower yield (**3b–3c** and **3e–3f**, Scheme 2). Additionally, fused biaryl (**3n**, Scheme 2) and linear biaryl (**3o**, Scheme 2) derived products were also afforded with practical results. When HCF₂SO₂Na was used as the reaction partner, the HCF₂S-functionalized product **3p** was acquired with 65% yield. Further efforts by employing *N*-Boc-*o*-aminophenyl enaminone for the synthesis of corresponding CF₃S-functionalized quinoline-4-one was not succeeded under current conditions.

Subsequently, considering the variable chemical valence of sulfur atom, we assumed that it would be applicable to switch the chemo-selectivity of the reaction by providing trifluoromethylsulfinyl (SOCF₃) chromones with identical substrates. To avoid the over reduction to the sulfur center, simple POCl₃ was selected as the coupling reagent. Delightfully, we successfully realized the selective synthesis of 3-trifluoromethylsulfinyl chromone **4a** via the reaction of **1a** and **2**. Analogously, the conditions for this transformation were optimized by comparing the effect of different parameters, by which the satisfactory result was acquired by running the reaction in DMF in the presence of 2.0 equiv. POCl₃ by stirring at 0°C to room temperature (see Support information for details on condition optimization). On the basis of optimization, the scope for the selective 3-trifluoromethylsulfinyl chromones synthesis was also studied. The results provided by the experiments inarguably verified the high applicability of this method in the synthesis of such unprecedented 3-substituted chromones (Scheme 3).

As shown by the results, the synthesis of 3-trifluoromethylsulfinyl chromones **4a–4q** were provided with



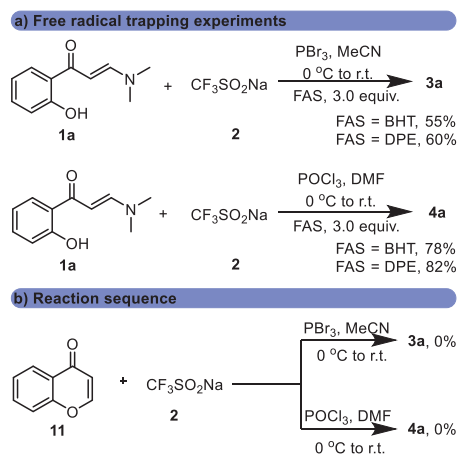
Scheme 4. Transformation of the synthesized products 3 and 4.

good to excellent yields, and the single crystal analysis on **4a** (CCDC: 2311321) confirmed the product structure. Specifically, the enaminones bearing no substitution or with EDG in the phenyl ring reacted with **2** to give the products with excellent yield (**4a-4c**, **4e-4f** and **4k**, Scheme 3). Equivalent reactions with enaminones containing EWG in the phenyl, on the contrary, provided product with lower yield (**4d**, **4g** and **4h-4j**, Scheme 3). Moreover, products with disubstituted phenyl (**4l**, Scheme 3), fused aryl (**4m**, Scheme 3) and biaryl (**4n-4o**, Scheme 3) were also synthesized with satisfactory results. The method, notably, was also proven to be applicable for the synthesis of difluoromethylsulfinyl chromone with fine efficiency (**4r**, Scheme 3). More interestingly, the method was successfully expanded to the synthesis of aryl/alkyl-based 3-sulfinyl chromones **5**. While such sulfur group-functionalized chromones had not been previously synthesized, the present method displayed attractive synthetic application by donating products **5a-5e** with generally good yield (Scheme 3). Moreover, the CF₃SO-functionalized quinoline-4-one **5f** could be efficiently synthesized by using *N*-Boc-*o*-aminophenyl enaminone **1'** as substrate, demonstrating the highly general tolerance of this method in the synthesis of novel sulfur groups functionalized chromones in the C3 site. Notably, GC-MS analysis on the reactions both for the synthesis of both **3a** and **4a** showed no formation of 3-trifluoromethyl chromone [27].

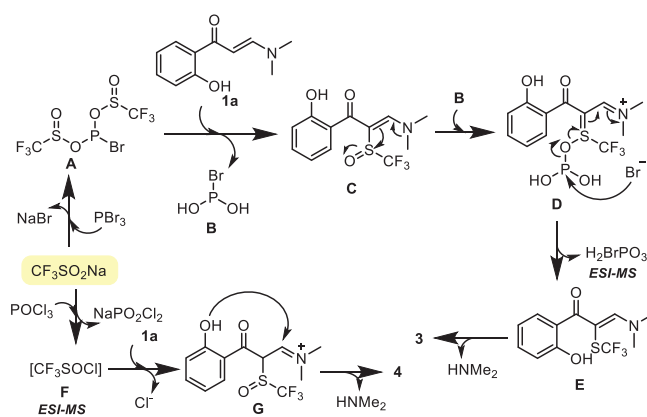
Following the examination on the switchable synthesis of both products **3** and **4**, the synthetic application of these compounds was also primarily investigated (Scheme 4). First, employing the hydrazine hydrate **6** or guanidine hydrochloride salt **8** as reaction partner of compound **3a** enabled the efficient synthesis of CF₃S-functionalized pyrazole **7** and pyrimidine **9** by simple heating, respectively. On the other hand, subjecting compound **4a** to *m*-CPBA allowed the formation of trifluoromethylsulfonyl chromone **10** with near quantitative yield. However, employing *m*-CPBA with enaminone **1a** and CF₃SO₂Na in DMF in one-step operation did not provide compound **10**.

To probe the reaction mechanism, some control experiments were executed. First, for both the synthesis of CF₃S- and CF₃SO-substituted chromones, the parallel entries in the presence of free radical scavenger (FRS) were performed. The results showed that FRS such as BHT or DPE did not inhibit the formation of product **3a** or **4a** (Scheme 5a). Successively, the reaction sequence was probed by employing chromone **11** as substrate to react with **2**, but neither **3a** nor **4a** was formed under corresponding conditions (Scheme 5b), suggesting that the chromone annulation took place after the C-H functionalization.

Based on these results and known examples involving phosphanes as deoxygenating reagents [72,73], the mechanisms for the reactions providing different chromone products are proposed (Scheme 6). For the reactions mediated by PBr₃, the CF₃SO₂Na first couples PBr₃ to generate species **A**. The nucleophilic substitution of the enaminone's α -carbon to the S-site in **A** gives sulfinylated enaminone **C** and releases compound **B**. Further, the nucleophilic



Scheme 5. Control experiments.



Scheme 6. The proposed reaction mechanisms.

substitution of the O-site in **C** to the P-Br bond in **B** affords intermediate **D** with the assistance of the electron donating effect from the amino group. Subsequently, the P to O electron pair transfer in **D** takes place to enable the break of the S-O bond to provide the trifluoromethylthiolated enaminone **E**. After that, the classical chromone annulation in the *o*-hydroxyphenyl enaminone yields the CF₃S-functionalized chromones **3** by eliminating HNMMe₂. On the other hand, for the POCl₃ mediated formation of sulfinyl chromones, the incorporation of POCl₃ and CF₃SO₂Na happens initially to give sulfinyl chloride **F**. This species couples enaminone **1** in the α -site to generate sulfinylated iminium **G** by acting as an electrophile. The nucleophilic annulation and a subsequent amine elimination would then provide 3-trifluoromethylsulfinyl chromones **4**. The sulfinyl chromones **5** are formed following similar mechanism.

In conclusion, by means of the featured C-H functionalization and chromone annulation cascade on *o*-hydroxyaryl enaminones, we have attained the first transition metal-free synthesis of 3-(trifluoromethylthio) chromones. The main tactic is the successful application of trivalent phosphine PBr₃ as reductive coupling reagent. More interestingly, the chemo-selectivity could be switched for the synthesis of 3-trifluoromethylsulfinyl chromones by using pentavalent POCl₃ as coupling reagent. Besides the synthesis of 3-trifluoromethylsulfinyl chromones, the synthesis of 3-aryl/alkylsulfinyl chromones with corresponding aryl/alkyl sulfinate as reaction partners has also been achieved. These results significantly expanded the application scope of enaminones in the synthesis of chromone derivatives. The transition metal-free

conditions as well as the sulfur-group diversity in the C3-site of the chromone products consists of the major advantages of the work.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2024.109683.

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