OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Synthesis of 3-HCF$_2$S-Chromones through Tandem Oxa-Michael Addition and Oxidative Difluoromethylthiolation

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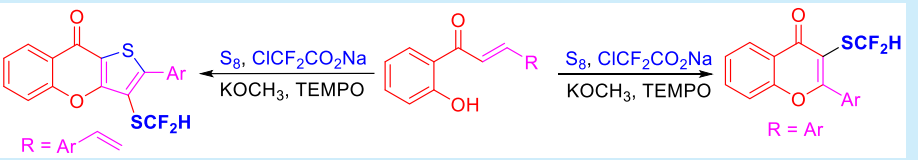
Supporting Information

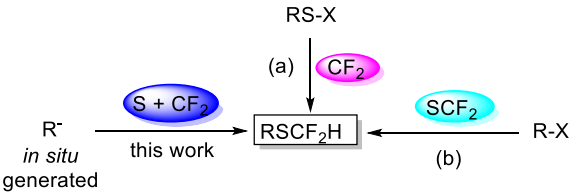


ABSTRACT: A simple protocol for the synthesis of difluoromethylthiolated chromen-4-ones using elemental sulfur and $ClCF_2CO_2Na$ as the difluoromethylthiolating agent is described. Three-component reactions of 2′-hydroxychalcones, $ClCF_2CO_2Na$, and sulfur under basic conditions using TEMPO as the oxidant afforded HCF_2S-containing 4*H*-chromen-4-one and 9*H*-thieno[3,2-*b*]chromen-9-one derivatives in good yield. The protocol is practical and efficient, and the starting materials are cheap and readily available.

Chromones occur naturally in many plants,[1] and the chroman-4-one scaffold is a privileged structure in drug discovery and development.[2] Chromone derivatives exhibit a wide range of pharmacological activities such as anti-inflammatory,[3] anticancer,[4] anti-HIV,[5] antifungal,[6] and antibacterial.[7] A number of versatile methodologies have been reported for the synthesis of chromone derivatives. Traditionally, 4*H*-chromen-4-ones can be constructed through Claisen condensation,[8] Baker−Venkataraman rearrangement,[9] and the Kostanecki−Robinson reaction.[10] Although palladium- and iridium-catalyzed tandem Sonogashira reaction and carbonylation[11] and other annulation reactions of alkynes[12] were reported in recent years, the oxa-Michael-oxidative annulation of 2′-chalcone derivatives still represents the best synthetic approach due to its mild conditions and cheap and readily available starting materials. The related progress in the preparation of chromones has recently been summarized.[2a,13]

In recent years, the incorporation of a HCF_2S− moiety into a biologically active compounds has attracted much attention because of its significance in the modification of physical and biological properties.[14] Basically, the synthesis of difluoromethyl thioethers can be accomplished through S-difluoromethylation of sulfur-containing compounds with a nucleophilic, electrophilic, or a radical CF_2 reagent (Scheme 1a). Various fluoro-containing compounds have been employed as the difluoromethylating reagents, including $ClCF_2SO_2Ph$, $BrCF_2PO(OEt)_2$, $ClCF_2CO_2Na$, $PhSO(NTs)CF_2H$, $Ph_3P^+CF_2CO_2^-$, $TMSCF_2H$, and so on.[15] Alternatively, difluoromethylthiolated compounds were obtained via C-difluoromethylthiolation with a SCF_2H reagent such as nucleophilic Ag(SIPr)(SCF_2H), electrophilic $PhSO_2SCF_2H$, *N*-difluoromethylthiophthalimide, hypervalent difluoroethanesulfonyl iodonium, HCF_2SO_2Na, HCF_2SO_2Cl, and so on.

Scheme 1. Synthetic Routes of HCF_2S-Containing Compounds[a]



[a](a) X = H, SR, CN, Cl, SO_2Ph; (b) X = halogen, OTf, $N_2^+BF_4$, $B(OH)_2$.

(Scheme 1b).[16] The introduction of a HCF_2S group to chromones would diversify their structures and bioactivities and thus is of interest for the discovery of novel chromone-based drugs and agrochemicals. Despite these approaches to HCF_2S-containing compounds,[15,16] the direct use of commodity chemicals to introduce a HCF_2S group is a goal that remains to be accomplished. We wished to develop an in-situ-generated difluoromethylthiolating reagent using cheap and commercially available materials. We herein demonstrate the rapid and selective formation of a wide range of difluoromethylthiolated chromones through the tandem oxa-Michael addition and oxidative difluoromethylthiolation of 2′-hydroxychalcones using elemental sulfur and $ClCF_2CO_2Na$ as the difluoromethylthiolating agent. A variety of HCF_2S-containing chromones were obtained in good yield.

Oxidative cyclization of 2-hydroxychalcone to flavone derivatives have been well studied using various oxidants.[17] Reaction conditions were surveyed using **1a** as the test

Received: September 25, 2019

DOI: 10.1021/acs.orglett.9b03396
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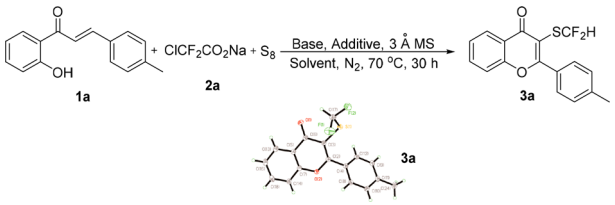
substrate. The three-component reaction of **1a**, sodium 2-chloro-2,2-difluoroacetate, and sulfur was initially performed in DMF in the presence of ^{t}BuONa, and **3a** was afforded in 28% yield (Table 1, entry 1). The structure of **3a** was undoubtedly determined by X-ray diffraction analysis.

Table 1. Optimization of Reaction Conditions



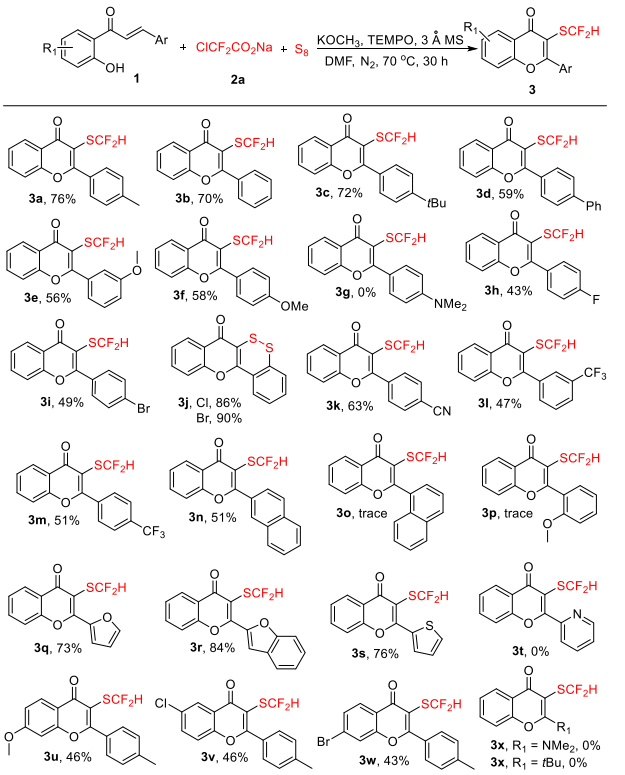
entry	base	oxidant	solvent	yield (%)
1	^{t}BuONa		DMF	28
2	^{t}BuOK		DMF	22
3	Cs_2CO_3		DMF	20
4	$KOCH_3$		DMF	34
5	DBU		DMF	20
6	Et_3N		DMF	
7	pyridine		DMF	<10
8	$KOCH_3$	$FeCl_3$	DMF	trace
9	$KOCH_3$	$NaIO_4$	DMF	<5
10	$KOCH_3$	$K_2S_2O_8$	DMF	13
11	$KOCH_3$	MnO_2	DMF	18
12	$KOCH_3$	$PhI(OAc)_2$	DMF	13
13	$KOCH_3$	1,4-BQ	DMF	54
14	$KOCH_3$	1,4-BQ	HMPA	
15	$KOCH_3$	1,4-BQ	NMP	36
16	$KOCH_3$	1,4-BQ	DMA	32
17	$KOCH_3$	DDQ	DMF	
18	$KOCH_3$	naphthalene-1,4-dione	DMF	<10
19	$KOCH_3$	phenanthrene-9,10-dione	DMF	trace
20	$KOCH_3$	pyridine-*N*-oxide	DMF	20
21	$KOCH_3$	TEMPO	DMF	76
22	$KOCH_3$	BPO	DMF	
23	$KOCH_3$	DTBP	DMF	60

[a]Reaction conditions: chalcone **1a** (0.2 mmol), $ClCF_2CO_2Na$ **2a** (0.6 mmol), S_8 (1.2 mmol), base (0.6 mmol) oxidant (0.4 mmol), 3 Å molecular sieve (100 mg), and solvent (1.5 mL) at 70 °C under N_2 for 30 h. Isolated yield. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy; BPO = benzoic peroxyanhydride; DDQ = 2,3-dicyano-5,6-dichlorobenzoquinone; DTBP = 2-(*tert*-butylperoxy)-2-methylpropane.

We envisioned that the tandem cyclization/difluoromethylthiolation reaction is initiated by oxa-Michael addition, and thus bases would be crucial. We thus examined the effect of various inorganic and organic bases, and the results showed that the yield of **3a** was not improved by a variation of the bases (Table 1, entries 1−7). The formation of 4*H*-chromen-4-one would involve oxidative dehydrogenation; therefore, additional oxidants would promote the reaction. Inorganic oxidants such as $FeCl_3$, $NaIO_4$, $K_2S_2O_8$, $PhI(OAc)_2$, and MnO_2 are not effective (Table 1, entries 8−12). Compound **3a** was isolated in 54% yield when the reaction was performed in DMF using benzoquinone as the oxidant (entry 13). Other quinones were less efficient (Table 1, entries 17−19). Finally, we found that TEMPO is a more promising oxidant; with it, **3a** was obtained in 76% yield (entry 21).

After optimization of the conditions, the substrate scope of the present protocol was explored (Scheme 2). The cyclization

Scheme 2. Scope of 2′-Hydroxychalcone[a]



[a]Reaction conditions: chalcone **1** (0.20 mmol), $ClCF_2CO_2Na$ **2a** (0.60 mmol), S_8 (1.20 mmol), $KOCH_3$ (0.60 mmol), 3 Å molecular sieve (100 mg), and TEMPO (0.40 mmol) in DMF (1.5 mL) at 70 °C under N_2 for 30 h.

and difluoromethylthiolation of the substrates bearing electron-donating substituents such as alkyl, phenyl, and alkoxy groups occurred under the mild conditions, furnishing **3a−f** in good yield (56−76%). Unexpectedly, 2′-hydroxy-4-dimethylaminochalcone did not provide the corresponding product **3g**. In this case, an unidentified mixture was yielded, which was probably ascribed to the oxidation of electron-rich aniline. Halo-containing 2′-hydroxychalcones are also applicable, and **3h** and **3i** were produced in moderate yield. However, both reactions of 2-chloro/bromo-2′-hydroxychalcone gave unexpected disulfide **3j** in excellent yield. We speculate that **3j** was formed via sequential oxa-Michael addition, thiolation, intramolecular nucleophilic substitution, and oxidative dehydrogenation. Electron-deficient chalcone bearing a cyano and CF_3 group also afforded the desired **3k−m** in comparable yield. 2′-Hydroxychalcone bearing a naphthalene-2-yl group was successfully transformed to **3n**. Unfortunately, the reactions of 2′-hydroxy-2-methoxychalcone and naphthalene-1-yl derivative failed to yield the desired products due to steric hindrance. Cyclization and difluoromethylthiolation of 2′-hydroxychalcone analogues containing a furyl or thiophenyl group proceeded smoothly, furnishing flavones **3q−s** in 73−84% yield. Unexpectedly, the pyridine derivative was totally unreactive. Finally, 2′-hydroxychalcones containing methoxy, chloro, and bromo groups at the 3′- and 4′-positions also gave the desired flavones **3u−w** in moderate yield. However, the protocol is not suitable for the synthesis of 2-*tert*-

DOI: 10.1021/acs.orglett.9b03396
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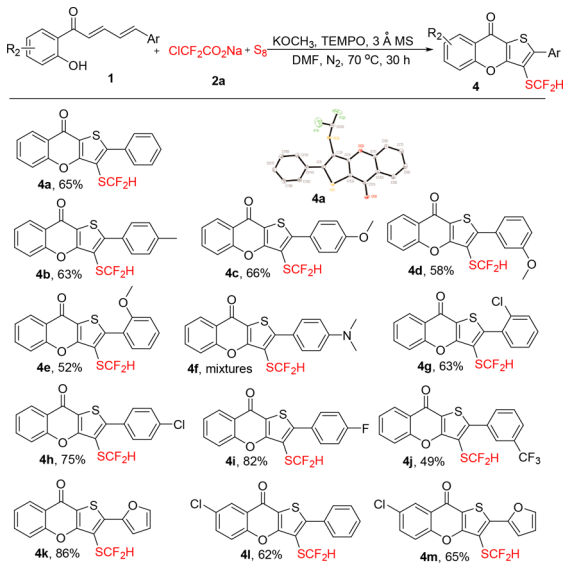
butylchromones and 2-dimethylaminochromone. To illustrate the practicality, a reaction of **1a** on a 1.2 mmol scale was performed. The expected product **3a** was isolated in 66% yield.

We next examined the reactivity of penta-2,4-dien-1-one derivatives with $ClCF_2CO_2Na$ and sulfur under the optimized conditions, and the results are summarized in Scheme 3. When

Scheme 3. Scope of 2′-Hydroxychalcone[a]



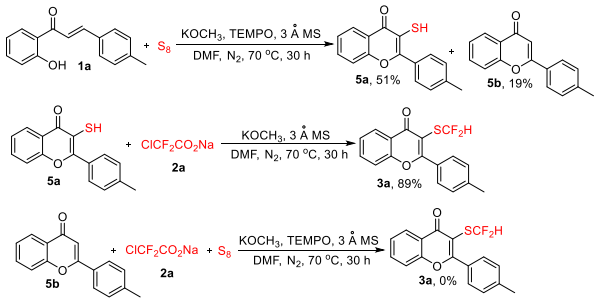
[a]Reaction conditions: chalcone **1** (0.20 mmol), $ClCF_2CO_2Na$ **2a** (0.60 mmol), S_8 (1.20 mmol), $KOCH_3$ (0.60 mmol), 3 Å molecular sieve (100 mg), and TEMPO (0.40 mmol) in DMF (1.5 mL) at 70 °C under N_2 for 30 h.

1-(2-hydroxyphenyl)-5-phenylpenta-2,4-dien-1-one was treated with $ClCF_2CO_2Na$ and sulfur in the presence of MeOK, tandem double cyclization and difluoromethylthiolation reaction occurred, and the fused compound 3-((difluoromethyl)thio)-2-phenyl-9*H*-thieno[3,2-*b*]chromen-9-one **4a** was isolated as a brown solid in 65% yield. The structure of **4a** was confirmed by X-ray diffraction analysis (Scheme 3). The substituted penta-2,4-dien-1-ones having an electron-donating group were well tolerated and gave **4b**–**e** in good yield. Again, the reaction of the dimethylamino-containing substrate resulted in a complicated mixture. The strong electron-donating group of 2′-hydroxychalcone probably reduced the tendency for nucleophilic addition. In addition, the electron-rich 2′-hydroxychalcone is more easily oxidized (cf. **3g** and **4f**) and thus inhibits oxa-Michael addition. Moreover, reactions of halo-containing substrates proceeded well, affording **4g**–**i** in 63–82% yield. These halo-containing chromone-fused thiophene compounds offer more opportunities for further functionalization through cross-coupling reactions with nucleophilic reagents. The electron-deficient penta-2,4-dien-1-one containing a CF_3 was also well compatible to deliver **4j** in 49% yield. 2′-Hydroxychalcones containing a chloro group at the 4′-position gave the desired flavones **4k**–**m** in moderate yield.

The cyclization and difluoromethylthiolation of the dienone derivatives to chromone-fused thiophene compounds is remarkable, which involves the selective formation of four C–S bonds and one C–O bond in one pot.

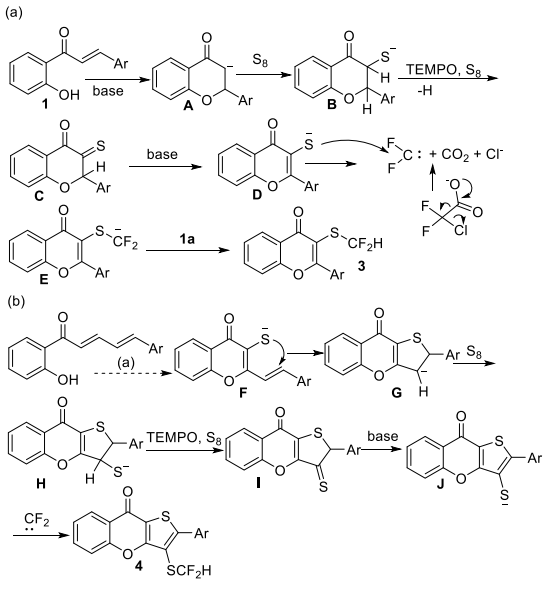
To gain some mechanistic insights into the present protocol, a few control experiments were performed (Scheme 4). It has

Scheme 4. Control Experiments



been known that the thermal decomposition of $ClCF_2CO_2Na$ would generate F_2C: species.[15c,e,18] Without $ClCF_2CO_2Na$, the reaction of **1a** with sulfur resulted in 3-mercapto-2-(*p*-tolyl)-4*H*-chromen-4-one **5a** and 2-(*p*-tolyl)-4*H*-chromen-4-one **5b** in 51 and 19% yield, respectively. The reaction of **5a** and $ClCF_2CO_2Na$ in DMF in the presence of $KOCH_3$ afforded **3a** in 89% yield. In contrast, the reaction of **5b**, S_8, and $ClCF_2CO_2Na$ under the same conditions did not afford **3a**, and **5b** was not consumed. On the basis of the above observations, a possible mechanism is proposed. The oxa-Michael addition of **1** gave carbanion **A**, which readily reacts with sulfur to form 4-oxochromane-3-thiolate **B**. The subsequent oxidation of **B** and the abstraction of a proton afforded 3-thioxochroman-4-one **C**. Both TEMPO and S_8 might serve as the oxidants. The enolization of **C** in the presence of a base afforded intermediate **D**. The nucleophilic addition of **D** toward a F_2C: molecule would finally form **3** after protonation (Scheme 5a). Similarly, **F** would be formed

Scheme 5. Plausible Mechanisms for (a) 3 and (b) 4



via cyclization in the presence of a base. Further intramolecular nucleophilic addition would generate intermediate **G**. The reaction with sulfur and the subsequent oxidation gave thioketone **I**. In the presence of the base, the reaction of **J** with in-situ-generated F_2C: would finally yield **4** (Scheme 5b).

In summary, the combination of elemental sulfur and $ClCF_2CO_2Na$ has been utilized for the first time as a difluoromethylthiolating agent. The three-component reaction of 2′-hydroxychalcones, sulfur, and $ClCF_2CO_2Na$ under basic

DOI: 10.1021/acs.orglett.9b03396
Org. Lett. XXXX, XXX, XXX–XXX

conditions using TEMPO as the oxidant selectively afforded HCF_2S-containing 4*H*-chromen-4-ones and thiophene-fused chromones in good yield. The protocol provides a novel practical approach to introduce HCF_2S functionality to organic compounds using cheap and commercially available reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03396.

Experimental details and spectral characterization (PDF)

Accession Codes

CCDC 1955549−1955550 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.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation (NSF) of China (21572203 and 21472140) and the NSF of Zhejiang Province (LZ16B020001) for financial support.

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DOI: 10.1021/acs.orglett.9b03396
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