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BF_3·OEt_2-$AgSCF_3$ Mediated Trifluoromethylthiolation/Cascade Cyclization of Propynols: Synthesis of 4-((Trifluoromethyl)thio)-2*H*-chromene and 4-((Trifluoromethyl)thio)-1,2-dihydroquinoline Derivatives

Yi-Feng Qiu,[†,∥] Xian-Rong Song,[‡,∥] Ming Li,[†] Xin-Yu Zhu,[†] An-Qi Wang,[†] Fang Yang,[§] Ya-Ping Han,[†] Heng-Rui Zhang,[†] Dong-Po Jin,[†] Ying-Xiu Li,[†] and Yong-Min Liang*[,†]

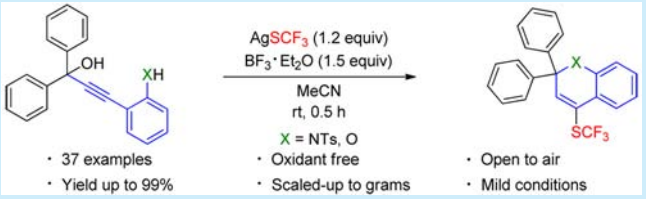
[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, People's Republic of China

[‡]Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science Technology Normal University, Nanchang, People's Republic of China

[§]College of Science, Northwest A&F University, 3 Taicheng Road, Yangling, People's Republic of China

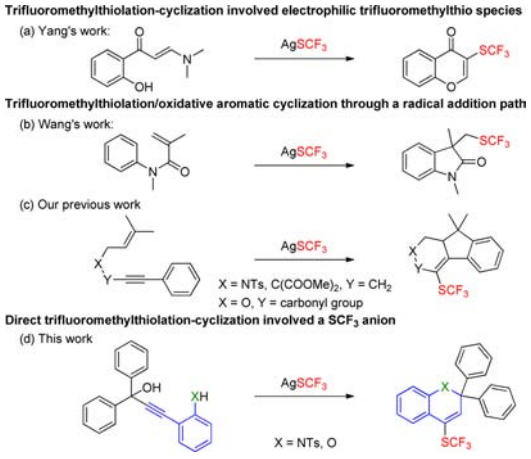
Supporting Information

ABSTRACT: A BF_3·OEt_2–$AgSCF_3$ mediated direct trifluoromethylthiolation/cascade cyclization of propynols involving the SCF_3 anion nucleophilic pathway is developed. This protocol also provides an opportunity to construct valuable trifluoromethylthio-substituted 2*H*-chromene and 1,2-dihydroquinoline systems with high efficiency under mild conditions. Additionally, the developed BF_3·OEt_2–$AgSCF_3$ reaction system could be scaled up to gram quantities in a satisfactory yield without inert gas protection.



The introduction of a fluorine-containing group to an organic molecule would usually lead to an obvious significant improvement to the parent molecule in physical, chemical, and physiological properties.[1] Specifically, the trifluoromethylthio group (SCF_3) has attracted much attention in organofluorine chemistry for its high lipophilicity, electronegativity, and metabolic stability, which leads to a great promotion of membrane permeability and absorption rate in bioavailability.[2] The traditional synthetic methods of trifluoromethylthiolation have shown inadequate capacity in accommodating the demands of modern synthetic chemistry applications.[3] Therefore, stimulated by advancing aspiration and continuous interest in new routes to introduce the trifluoromethylthio group,[4] adequate advancements have been achieved in the development of various new direct trifluoromethylthiolation reagents.[5] Very recently, a series of electrophilic trifluoromethylthiolation reagents (SCF_3^+)[6] are developed for an efficient trifluoromethylthiolation–cyclization reaction.[7] In a subsequent evolution, $AgSCF_3$, an easily-prepared and nucleophilic reagent,[8] has occurred as a powerful tool in a trifluoromethylthiolation–cyclization reaction under an oxidative system.[9] Last year, Yang et al. reported a facile approach to trifluoromethylthio-substituted 4-chromones involving electrophilic trifluoromethylthio species (Scheme 1a).[9b] Meanwhile, Wang et al. demonstrated the first Ag-mediated aryltrifluoromethylthiolation cyclization of activated alkenes to produce trifluoromethylthio-substituted oxindoles in a radical addition pathway (Scheme 1b).[9d] Soon afterward, a $AgSCF_3$-mediated trifluoromethylthiolation/radical cascade cyclization of 1,6-enynes for the synthesis of a trifluoromethylthio-substituted polycyclic fluorene system was presented by our group (Scheme 1c).[9g] Subsequently, the complicated operations, strong oxidative system, and extra additives force reconsideration for further industrial applications. Still, the exploration of trifluoromethylthiolation–cyclization by directly using the anion of $AgSCF_3$ itself is fueled by the strong and increasing aspiration.

Scheme 1. $AgSCF_3$ Participating in Cyclization Reaction



2*H*-Chromene, as a vitally important flavonoid skeletal structure, is found in a wide variety of natural products and

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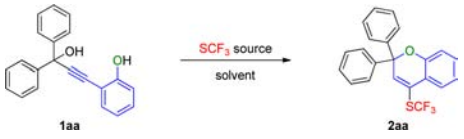
pharmaceutically active molecules.[10] Such compounds have been identified as numerous physiological or pharmacological activities and valuable intermediates in synthetic and material science.[11] With multistep reactions combined into one synthetic operation, cascade cyclization proved to be a powerful strategy for the synthesis of cyclic compounds.[12] By taking into consideration our current interest in introducing fluorine-containing groups,[9g,13] as well as the continued anticipation of new approaches to skeletons of natural products,[14] we designed a Lewis acid mediated trifluoromethylthiolation−cyclization of propynols with $AgSCF_3$. This paper reported the direct trifluoromethylthiolation−cyclization reaction proceeds along an anion pathway, with a 2*H*-chromene or 1,2-dihydroquinoline system constructed in a single step simultaneously.

Our initial attempt began by employing compound **1aa** (0.2 mmol) as the model substrate with $AgSCF_3$ (1.5 equiv) and $BF_3{\cdot}OEt_2$ (1.5 equiv) in MeCN at 80 °C under an air atmosphere. To our delight, our expected product **2aa** was isolated in 81% yield after 0.5 h (Table 1, entry 1). A subsequent brief survey on a series

Table 1. Optimization of the Reaction Conditions[a]



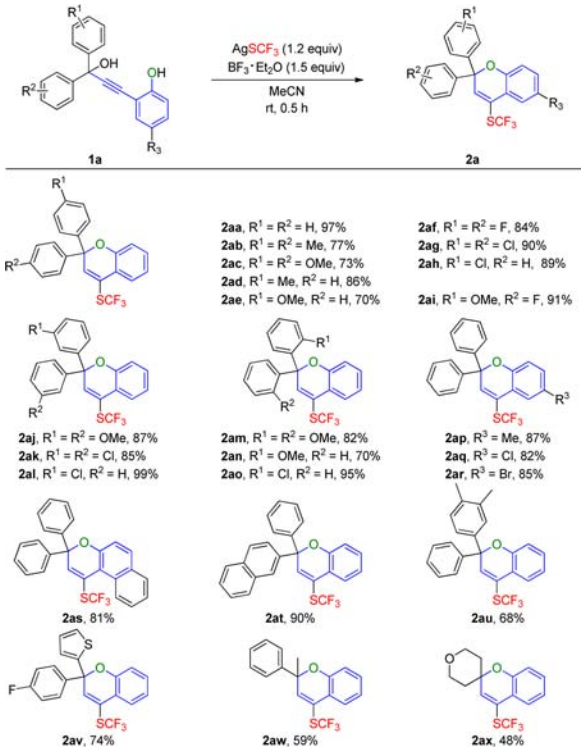
entry	acid (equiv)	solvent	SCF_3 source (equiv)	yield (%)[b]
1	$BF_3{\cdot}OEt_2$ (1.5)	MeCN	$AgSCF_3$ (1.5)	81
2	TFA (1.5)	MeCN	$AgSCF_3$ (1.5)	39
3	$FeCl_3$ (1.5)	MeCN	$AgSCF_3$ (1.5)	46
4	*p*-TsOH (1.5)	MeCN	$AgSCF_3$ (1.5)	67
5	$BF_3{\cdot}OEt_2$ (1.5)	DCE	$AgSCF_3$ (1.5)	trace
6	$BF_3{\cdot}OEt_2$ (1.5)	THF	$AgSCF_3$ (1.5)	57[c]
7	$BF_3{\cdot}OEt_2$ (1.5)	toluene	$AgSCF_3$ (1.5)	23
8	$BF_3{\cdot}OEt_2$ (1.5)	DMF	$AgSCF_3$ (1.5)	0[d]
9		MeCN	$AgSCF_3$ (1.5)	0
10	$BF_3{\cdot}OEt_2$ (1.5)	MeCN	Me_4NSCF_3 (1.5)	trace[e]
11	$BF_3{\cdot}OEt_2$ (1.5)	MeCN	$CuSCF_3$ (1.5)	<20
12	$BF_3{\cdot}OEt_2$ (1.5)	MeCN	$AgSCF_3$ (1.2)	94
13[f]	**$BF_3{\cdot}OEt_2$ (1.5)**	**MeCN**	**$AgSCF_3$ (1.2)**	**97**
14[f]	$BF_3{\cdot}OEt_2$ (1.2)	MeCN	$AgSCF_3$ (1.2)	82

[a]Unless otherwise noted, all reactions were performed with **1aa** (0.2 mmol), SCF_3 source (1.5 equiv), and acid (1.5 equiv) in solvent (2 mL) at 80 °C under an air atmosphere for 0.5 h. [b]Yields are given for isolated products. [c]A large amount of impurities was identified in ^1H NMR. [d]No reaction occurred. [e]The substrate was decomposed in this reaction. [f]This reaction was performed at rt.

of acid promoters showed that $BF_3{\cdot}OEt_2$ still performed most efficiently (entries 2−4). And no better results were obtained after further study on the effect of solvents (entries 5−8). An additional control experiment indicated that an acid promoter was necessary (entry 9). Other nucleophilic SCF_3 reagents proved ineffective for this transformation (entries 10−11). Ultimately, the subsequent investigation of the reaction temperature and reagent loadings (entries 12−14) settled the optimal conditions for the formation of **2aa** (entry 13).

A series of substituted tertiary alkynol substrates were prepared to investigate the scope of this trifluoromethylthiolation−cyclization reaction. The corresponding trifluoromethylthio-substituted 2*H*-chromenes (**2aa**−**2ax**) were obtained in moderate to excellent yields under the optimal reaction conditions (Scheme 2). The structures of **2aa**, **2am**, and **2at** were confirmed

Scheme 2. Synthesis of Products 2a from Propynols 1a[a]



[a]Unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), $AgSCF_3$ (1.2 equiv), and $BF_3{\cdot}OEt_2$ (1.5 equiv) in MeCN (2 mL) at rt under an air atmosphere for 0.5 h. Yields are given for isolated products.

by X-ray crystal structure analysis (see the Supporting Information (SI)). Both electron-rich (**1ab**−**1ae**) and -deficient (**1af**−**ah**) groups on the *para*-position of R^1 and/or R^2 could be tolerated. And the electronic effect of substituent groups exerted a clear influence on this transformation: in general, substrates with electron-deficient moieties gave excellent yields up to 90%, whereas slightly lower yields were obtained with electron-rich ones (**2ab**−**2ae** versus **2ad**−**2ah**). It was noteworthy that substrates with both strong electron-rich and -withdrawing substituent groups (**1ai**) worked smoothly and gave a surprisingly high yield of 91%. Analogous to the situation of the *para*-substituent groups, substrates containing *meta*- (**1aj**−**1al**) and *ortho*- (**1am**−**1ao**) substituent groups also showed good compatibility with similar rules. Substrates with diverse substituents (Me, Cl, and Br) as the R^3 group could also be converted into the corresponding products in very good yields (**2ap**−**2ar**). In addition, these halogenated products may provide other potential applications for further transformations through orthogonal cross-couplings. Notably, this transformation proceeded smoothly for the substrates with a multiple-ring group (naphthyl group, **1as** and **1at**), or a heterocyclic group (2-thienyl, **1av**). The final concern was that substrates containing alkyl groups (**1aw** and **1ax**) showed good compatibility in this reaction system. Gratifyingly, our expected spiral product (**2ax**) was also isolated in a satisfactory yield.

Encouraged by the above-mentioned results, the reactions of secondary propynols were further explored under the optimal conditions. As described in Scheme 3, a number of single phenyl substituted 4-((trifluoromethyl)thio)-2*H*-chromenes (**2ba**−**2bh**) were obtained in moderate to good yields. We considered

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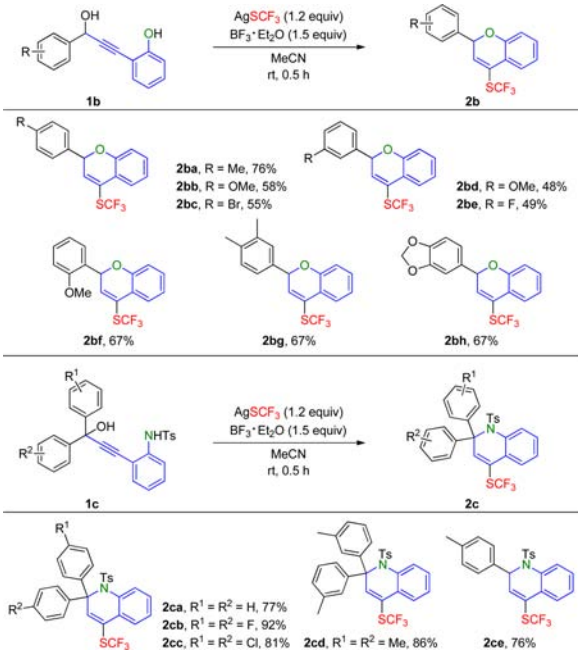
Scheme 3. Synthesis of Products 2b (2c) from Propynols 1b (1c)[a]



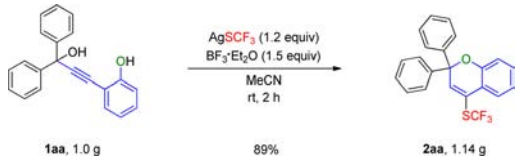
[a]Unless otherwise noted, all reactions were performed with **1b** or **1c** (0.2 mmol), $AgSCF_3$ (1.2 equiv), and $BF_3{\cdot}OEt_2$ (1.5 equiv) in MeCN (2 mL) at rt under an air atmosphere for 0.5 h. Yields are given for isolated products.

that these transformations might proceed through intermediate **C** with insufficient stability compared to tertiary propynols. Generally, the reactions showed steric and electronic effects similar to those of tertiary propynol substrates. Several propynols with a protected amine structural subunit (**1ca**−**1ce**) were studied subsequently under the optimal conditions (Scheme 3). Satisfactorily, our expected trifluoromethylthio-substituted 1,2-dihydroquinoline derivatives (**2ca**−**2ce**) were isolated in good to excellent yields. 1,2-Dihydroquinolines have been confirmed to be greatly valuable intermediates for the synthesis of pharmacologically relevant therapeutic agents and biologically active natural products. The structure of **2cb** was confirmed by X-ray crystal structure analysis (see the SI).

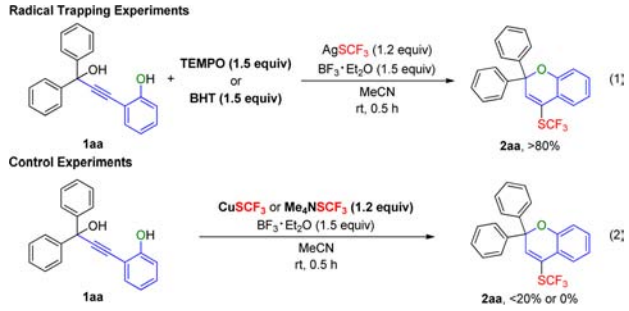
A noteworthy advantage of our developed reaction system was that this transformation could be scaled up to gram quantities; an 89% yield of product **2aa** was isolated on the gram scale under the optimal conditions, which might provide a potential application for this method in synthetic industry (Scheme 4).

To explore and verify the transformation process for this reaction, some necessary inhibition experiments were performed (Scheme 5). When 1.5 equiv of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) were added into the reactions, the transformations were found to be almost unaffected. This observation indicated the reaction may

Scheme 4. Scale-up Experiment



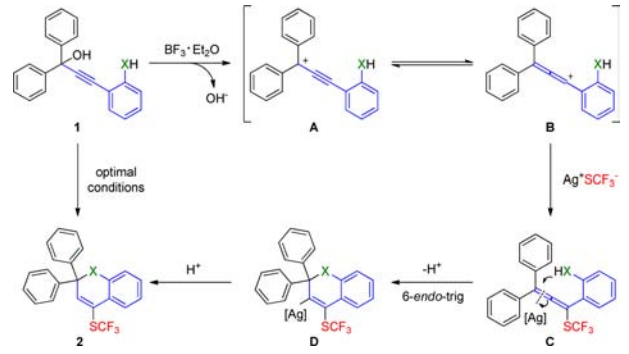
Scheme 5. Verification Experiments for the Mechanism



not proceed via a radical pathway. And the replacement of a SCF_3 source ($CuSCF_3$ and Me_4NSCF_3) led to a yield reduction, which indicated that Ag may act as a copromoter in the cyclization process (intermediate **C** to product **2**).

A plausible mechanism that is consistent with the experimental results mentioned above and the precedent literature[14] is proposed in Scheme 6. In fact, the propargyl hydroxy group of

Scheme 6. Proposed Reaction Mechanism



substrate **1** is initially activated by $BF_3{\cdot}OEt_2$ and generates propargylic cation **A**, which would undergo a subsequent tautomerism to generate the allenic cation **B**.[14c,d] The intermolecular attack of the SCF_3 anion onto **B** affords intermediate **C**, which could be activated by Ag(I) species or a proton to give intermediate **D**.[14c] Ultimately, the desired product **2** is obtained through a subsequent intramolecular endo attack of the phenolic hydroxy group followed by protonation.

In summary, we have disclosed a trifluoromethylthiolation/cascade cyclization of propynols in a $BF_3{\cdot}OEt_2$−$AgSCF_3$ system to synthesize various trifluoromethylthio-substituted 2*H*-chromene and 1,2-dihydroquinoline derivatives. This reaction occurred smoothly with a C−SCF_3 bond and C−O/N bond constructed concurrently under mild conditions in good to excellent yields (up to 99%). This transformation process proves to involve the SCF_3 anion, which avoids the addition of an oxidant and can be easily operated under an air atmosphere. In addition, the synthetic utility of our developed reaction system has been demonstrated by the applicability to a wide range of propynol substrates and a large reaction scale for potential applications in further industrial production.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00065.

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Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for **2aa** (CIF)
X-ray data for **2am** (CIF)
X-ray data for **2at** (CIF)
X-ray data for **2cb** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: liangym@lzu.edu.cn.

Author Contributions

‖Y.-F.Q. and X.-R.S. contributed equally.

Notes

The authors declare no competing financial interest.

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