Radical-mediated vicinal addition of alkoxyalkylsulfonyl/fluorosulfonyl and trifluoromethyl groups to aryl alkyl alkynes†

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The addition of sulfonyl radicals to alkenes and alkynes is a valuable method for constructing useful highly functionalized sulfonyl compounds. The underexplored alkoxy- and fluorosulfonyl radicals are easily accessed by CF₃ radical addition to readily available allylsulfonic acid derivatives and then β-fragmentation. These substituted sulfonyl radicals add to aryl alkyl alkynes to give vinyl radicals that are trapped by trifluoromethyl transfer to provide tetra-substituted alkenes bearing the privileged alkoxy- or fluorosulfonyl group on one carbon and a trifluoromethyl group on the other. This process exhibits broad functional group compatibility and allows for the late-stage functionalization of drug molecules, demonstrating its potential in drug discovery and chemical biology.

Introduction

Sulfonic acid derivatives are valuable pharmaceutical compounds, biochemical probes, novel materials, and synthetic intermediates (Scheme 1a). Moreover, sulfur(vi)-fluoride exchange (SuFEx) has recently gained intense interest as one of the most powerful reactions in click chemistry. This stems from the incredible stability and unique reactivity of the fluorosulfonyl (SO₂F) motif and provides an additional need for the development of efficient fluorosulfonylation methods. Sulfonyl esters and sulfonyl fluorides are usually obtained from the corresponding sulfonyl chlorides. However, these sulfonyl chloride precursors are generally prepared under harsh conditions with highly corrosive reagents or by the oxidative chlorination of organosulfur compounds. Consequently, these methods are not compatible with sensitive functional groups and often suffer from tedious purification procedures or limited sources of the organosulfur starting materials. Recent methods for introduction of a sulfonate moiety focus on arylsulfonates, while the diversity-oriented synthesis of alkenylsulfonate esters by Wittig reactions is limited by the strongly basic conditions employed. Alkenylsulfonyl fluorides are of special interest due to the electrophilic character of both the sulfur center and the β-carbon, representing a unique warhead for covalent binders. To access alkenylsulfonyl fluorides, the groups of Sharpless, Arvidsson, Qin, Yu, Huestis, Willis, and others reported transition-metal catalyzed cross-coupling reactions with ethenesulfonyl fluoride (ESF), 1-bromothenesulfonyl fluoride (BESF), or 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO)/N-fluorobenzenesulfonylimide (NFSI). These reactions work well, but don’t provide access to tetra-substituted alkenyl sulfonate fluorides that should also be valuable for SuFEx click chemistry.

Recently, sulfonyl radical-mediated processes have been developed that provide direct methods to construct valuable carbon–SO₂ bonds. In this context, alkoxyalkyl sulfonyl radicals (ROSO₂) were found to add to alkynes in hot benzene. Later, other groups reported the cyclization of alkoxyalkyl radicals tethered to alkynes and alkenes. Unfortunately, these methods either suffer from narrow substrate scope or restriction to intramolecular processes, limiting their applicability in the context of late-stage functionalization of complex molecules. The use of the fluorosulfonyl radical (FSO₂) in organic synthesis has rarely been reported, presumably due to its instability and limited synthetic access. In 2021, the Liao group disclosed a radical fluorosulfonylation of alkynes using sulfuryl chlorofluoride (FSO₂Cl) as the fluorosulfonyl radical source. Thus, the discovery of new SO₂-containing reagents and the development of efficient synthetic methods to access alkoxy- or fluorosulfonyl compounds are of great significance. Alkylsulfonyl compounds have been recognized as facile and practical precursors for generating such radical species through an addition-fragmentation process (Scheme 1b). However, only aryl, alkyl, and amide groups have been used as
substituents on the allylsulfonyl reagents. The generation of alkoxy- or fluorosulfonyl radicals by this process has not been reported. This prompted us to explore the use of alkyl allylsulfonates and allylsulfonyl fluorides to form useful carbon–SO$_2$ bonds by radical processes.

Trifluoromethyl compounds have been prepared by direct trifluoromethylation with the CF$_3$ radical. Thus, a few groups have independently reported the addition of the CF$_3$ radical to alkenes or alkynes followed by trapping to form sulfonic acid derivatives (Scheme 1c).

In our continuing efforts to discover new trifluoromethylation methods, we envisioned that the addition of an alkoxysulfonyl or fluorosulfonyl radical to an alkyne or alkene followed by trapping with a trifluoromethyl moiety would provide an alternative route to vicinal alkoxy- or fluorosulfonyl trifluoromethylation (Scheme 1d). This would give 3 and 5 with the opposite regiochemistry to the reactions shown in Scheme 1c, opening up access to new scaffolds for drug discovery and chemical biology. To realize this conception, we sought to use readily-prepared allylsulfonyl reagents as the sulfonyl radical sources, in combination with commercially-available bpyCu(CF$_3$)$_3$.

Results and discussion

Reaction condition optimization

The optimized reaction conditions are outlined in Table 1 (see ESI for details). Treatment of alkyne 1a with methyl allylsulfonate 2a (3 equiv.), bpyCu(CF$_3$)$_3$ (1.2 equiv.), and (NH$_4$)$_2$S$_2$O$_8$ (3 equiv.) under blue LED irradiation ($\lambda_{\text{max}}$ = 460 nm) affords 77% (19F NMR yield) of the desired CF$_3$-containing alkenylsulfonate 3a (Table 1, entry 1). The yield is lower with sodium or potassium persulfate, and only 4% of 3a is obtained in the absence of (NH$_4$)$_2$S$_2$O$_8$ (Table 1, entries 2–4). The yield is slightly lower in the absence of water (Table 1, entry 5). The reaction does not proceed in the dark and the yield is 13% lower under irradiation with 365 nm light (Table 1, entries 6 and 7). Under most conditions, an approximately 10 : 1 mixture of 3a and the isomer Z-3a is obtained (see ESI for details). The methyl protons of 3a absorb at $\delta$ 2.44 in the $^1$H NMR spectra, whereas those of the minor isomer Z-3a absorb at $\delta$ 2.01 due to shielding.

![Scheme 1](image)

Alkenyl SO$_3$R- or SO$_2$F-containing drug molecules and sulfonyl radical-involved reactions.

![Table 1](image)

| Entry | Reaction conditions | Yield of 3a/Z-3a$^a$ |
|-------|---------------------|----------------------|
| 1     | Standard conditions | 77% (73%)/6%         |
| 2     | Na$_2$S$_2$O$_5$ instead of (NH$_4$)$_2$S$_2$O$_8$ | 52%/5% |
| 3     | K$_2$S$_2$O$_5$ instead of (NH$_4$)$_2$S$_2$O$_8$ | 46%/4% |
| 4     | Without (NH$_4$)$_2$S$_2$O$_8$ | 4%/0% |
| 5     | Without H$_2$O | 64%/8% |
| 6     | 365 nm instead of blue LEDs | 64%/5% |
| 7     | Performed in dark | 0%/0% |
| 8     | 2 equiv. of 2a used instead | 66%/7% |

$^a$ Reaction conditions: 1a (0.2 mmol), 2a (0.6 mmol), bpyCu(CF$_3$)$_3$ (0.24 mmol), (NH$_4$)$_2$S$_2$O$_8$ (0.6 mmol) under blue LED irradiation for 4 h at room temperature. $^b$ Yields were determined by $^{19}$F NMR spectroscopy with trifluoromethoxybenzene as an internal standard. $^c$ Isolated yield.
by the aryl group. The selectivity likely arises from the greater steric bulk of the methoxysulfonyl moiety as compared to the methyl group. To our delight, bistrifluoromethylated product **bis-3a** was produced in no more than 15% $^{19}$F NMR yield under the standard conditions. This allowed a good isolated yield (73%) of desired product **3a**, whose structure was unambiguously determined by single-crystal X-ray diffraction.

The use of only 2 equiv. of **2a** leads to a decreased yield (66%) of **3a** and the formation of more **bis-3a** (26%) as expected (Table 1, entry 8).

**Substrate scope**

With the optimized protocol in hand, we explored the generality of this transformation on a range of alkynes with several alkyl allylsulfonates (Scheme 2). Various functional groups, such as halides, ethers, aldehydes, esters, amides, sulfonamides, nitriles, and hydroxyl groups are well tolerated, giving products **3a**–**3aq** in moderate to good yields. **Meta**-substitution on the aryl ring has little effect on the reaction efficiency (**3w**–**3y**). With **ortho**-substitution on the aryl ring, the yield of **3z** is higher than that of **3aa**, presumably because a hydroxy group is smaller than a methoxy group. As exemplified by **3v**, aryl alkyl alkynes are much more reactive than bisalkyl alkynes. We have established that a variety of heteroarenes, such as pyrazole, (benzo)thiophenes, and furans, are suitable substrates for this transformation as shown in **3ac**–**3ag**. The stereochemistry of the major products was assigned by analogy to that of **3a** and by the chemical shift of the methyl group at δ 2.51–2.41.

This reaction is compatible with primary, secondary, and tertiary alkyl groups and trimethylsilyl group as the $R^2$ substituent on the alkyne (**3ah**–**3am**). Intriguingly, the configuration in products shifts from anti- to syn-addition with the increased bulkiness of the $R^2$ group. For instance, a nearly 1:1 $E/Z$ mixture is obtained for **3ak** with an isopropyl group, while exclusively syn-addition occurs to give **3al** with a tert-buty1 group and **3am** with a TMS substituent. The structures of **3al** and **3am** were determined by single-crystal X-ray analysis (see ESI† for details). These results indicate that the methoxysulfonyl group is larger than a methyl group, smaller than a tert-buty1 or TMS group, and about the same size as an isopropyl group. Other alkyl allylsulfonates smoothly undergo this transformation to afford **3an**–**3aq** in good yields.

Considering the high value of SO$_2$F-containing compounds in SuFEx click chemistry, we next examined the reaction of

![Scheme 2](image)

**Scheme 2** Substrate scope for alkoxysulfonyltrifluoromethylation of alkynes. Unless otherwise noted, all the reactions were run on a 0.2 mmol scale under standard conditions. $^a$ 1.5 equiv. of bpyCu(CF$_3$)$_3$ was used for 8 h.
alkynes 1 with allylsulfonyl fluoride 4 (Scheme 3). To our delight, a variety of alkynes undergo this transformation smoothly to afford the desired products 5a–5o using 365 nm irradiation. In contrast to the reaction with methyl allylsulfonate 2 to give 3, which worked slightly better with blue LED than 365 nm irradiation, the yields of 5 are 10–20% lower with blue LED irradiation. The optimal wavelength appears to be a balance between its efficiency in generating trifluoromethyl radicals and photo-induced side reactions. A variety of electron-donating or electron-withdrawing aryl substituents and heteroarenes (5h, 5l, and 5m) are compatible with these reaction conditions. Anti-addition occurs predominately for alkynes with primary alkyl R1 substituents (5a–5n), and syn-addition to give 5o occurs exclusively with the bulky tert-buty1 group. The structure of 5o was established by single-crystal X-ray analysis (see ESI† for details). In comparison to the alkoxysulfonyl trifluoromethylation discussed above, slightly increased amounts of undesired Z-isomers and bistri fluoromethylated products were detected. This might arise from the subtle differences in size, stability, and reactivity between fluorosulfonyl and alkoxysulfonyl radicals.12a,16b,c

Synthetic application

To demonstrate the potential of this transformation, we applied this methodology to the late-stage functionalization of both drug-derived alkynes and allylsulfonates. As shown in Scheme 4, alkynes derived from estrone (3ar and 5p), ezetimibe (3as), 4-methylumbelliflone (3at and 5q), and fenofibrate (3au and 5r) react smoothly to afford the expected products in moderate to good yields. In addition, the etofylline-derived allylsulfonate (3av) undergo alkoxysulfonyl trifluoromethylation as well.

To further demonstrate the synthetic utility of the products, sulfonate ester 3a was efficiently converted to sulfonamide 6 in 68% yield (Scheme 5). Nucleophile substitution on sulfonyl fluoride 5f was achieved by reaction with imidazole to afford sulfonamide 7 in 48% yield, with TMSN3 to afford sulfonyl azide 8 in 71% yield, and with phenol to afford sulfonate ester 9 in 83% yield. This suggests that this method is applicable to construct molecular complexity and diversity, which is beneficial for drug discovery and chemical biology.

Computational studies

We then performed DFT calculations to provide insights on the reaction mechanism and selectivity of this process (Fig. 1, see ESI† for details). On the basis of Cook’s work22c,23 and our TEMPO-trapping studies (see ESI† for details), the alkyne 1b, methyl allylsulfonate 2a, and the initial products upon light irradiation, the CF3 radical and bpyCu(CF3)OSO3H, were chosen as the starting point. The energy of TS1, the transition state for the addition of the CF3 radical to methyl allylsulfonate 2a to give INT1, was calculated to be 9.2 kcal mol−1. This is 0.8 kcal mol−1 lower than the energy of TSA, the transition state for the

Scheme 3 Substrate scope for fluorosulfonyltrifluoromethylation of alkynes. Unless otherwise noted, all the reactions were run on a 0.2 mmol scale under standard conditions. 4.0 equiv. of 4 was used for 8 h.

Scheme 4 Late-stage functionalization of complex drug molecules.

Scheme 5 Derivatization on alkenyl sulfonate esters or alkenyl sulfonyl fluorides.
addition of the CF₃ radical to the alkyne to give INTA. The newly-formed intermediates INT1 and INTA are more stable than the corresponding transition states TS1 and TSA by >30 kcal mol⁻¹, rendering the radical addition processes irreversible. The steps from INT1 to final product 3 proceed readily because the activation barriers in the subsequent transition states are all less than 13 kcal mol⁻¹. The calculated energy for TS1 that is 0.8 kcal mol⁻¹ lower than that of TSA is consistent with the observed preferential formation of methoxysulfonyltrifluoromethylation to form 3/Z-3 rather than bistrifluoromethylation to form bis-3. Moreover, the transition state TS₄E leading to the formation of anti-addition product 3 is 1.7 kcal mol⁻¹ more stable than transition state TS₄Z leading to syn-addition product Z-3, in good agreement with the approximately 10 : 1 ratio of E- and Z-isomers observed.

Conclusion
In conclusion, a method for alkoxy- and fluorosulfonyltrifluoromethylation of alkynes has been developed. This process uses readily-prepared alkyl allylsulfonates or allylsulfonyl fluoride as sulfonyl radical donors and good selectivity is achieved. Numerous functional groups and heteroarenes are tolerated, allowing access to a broad range of tetra-substituted alklenes that are valuable for drug discovery, chemical biology and other fields. In addition, this methodology further expands the application of allylsulfonyl reagents in radical coupling reactions.

Data availability
The datasets (experimental procedures, characterization, copies of NMR spectra for all new compounds, mechanistic studies, and computational studies) supporting this article have been uploaded as part of the ESI.† Crystallographic data for 3a, 3al, 3am, and 5o has been deposited at the CCDC under 2083910-2083913 and can be obtained from https://www.ccdc.cam.ac.uk/structures.

Author contributions
X. D., W. J., D. H., and X. W. planned, conducted, and analysed the experiments. L. X. conducted the computational studies. Prof. X. W. conceived this concept, directed the project, and prepared this manuscript. All authors contributed to discussions and commented on the manuscript.

Conflicts of interest
There are no conflicts to declare.

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