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Bifluoride Ion Mediated SuFEx Trifluoromethylation of Sulfonyl Fluorides and Iminosulfur Oxydifluorides

Christopher J. Smedley,[a] Qinheng Zheng,[b] Bing Gao,[b] Suhua Li,[c] Andrew Molino,[a] Hendrika M. Duivenvoorden,[a] Belinda S. Parker,[a] David J. D. Wilson,[a] K. Barry Sharpless[b] and John E. Moses*[a]

Abstract: SuFEx is a new generation click chemistry transformation that exploits the unique properties of S-F bonds and their ability to undergo near-perfect reactions with nucleophiles. We report here the first SuFEx based protocol for the efficient synthesis of pharmaceutically important triflones and bis(trifluoromethyl)sulfur oxyimines from sulfonyl fluorides and iminosulfur oxydifluorides, respectively. The new protocol involves rapid S-F exchange with trifluoromethyltrimethylsilane ($TMSCF_3$) upon activation by potassium bifluoride in anhydrous DMSO. The reaction tolerates a wide selection of substrates and proceeds under mild conditions without need for chromatographic purification. A tentative mechanism is proposed involving nucleophilic displacement of S-F by the trifluoromethyl anion through a five-coordinate intermediate. The utility of late-stage SuFEx trifluoromethylation is demonstrated through the synthesis and selective anticancer properties of the bis(trifluoromethyl)sulfur oxyimine (**3i**).

Click chemistry is a synthesis ideology designed to support the need for reliable reactions to create functional molecules.[1] Since first described in 2001, and with the subsequent development of CuAAC in 2002, it has had a profound impact on modern science with wide application in fields as diverse as materials science, chemical biology and drug discovery, to name a few.[2]

The recent development of Sulfur-Fluoride Exchange (SuFEx) in 2014, represents a new generation of near-perfect metal-free click chemistry transformations.[3] SuFEx exploits the unique balance between stability and reactivity of high oxidation state sulfur-fluoride functionalities (e.g. sulfonyl fluorides), which unlike their S-Cl counterparts are resilient to reductive collapse, leaving a clear pathway for S-F exchange. Key to SuFEx reactivity is the special ability of fluoride ion to transit from a strong covalent bond to a leaving group—assisted by interactions with "H^+" or "R_3Si^+" in close under strict kinetic and spatial constraints catalyzed by suitable nitrogen Lewis bases (e.g. Et_3N, DBU)[3,4] and is also thought to involve bifluoride counterion species.[5]

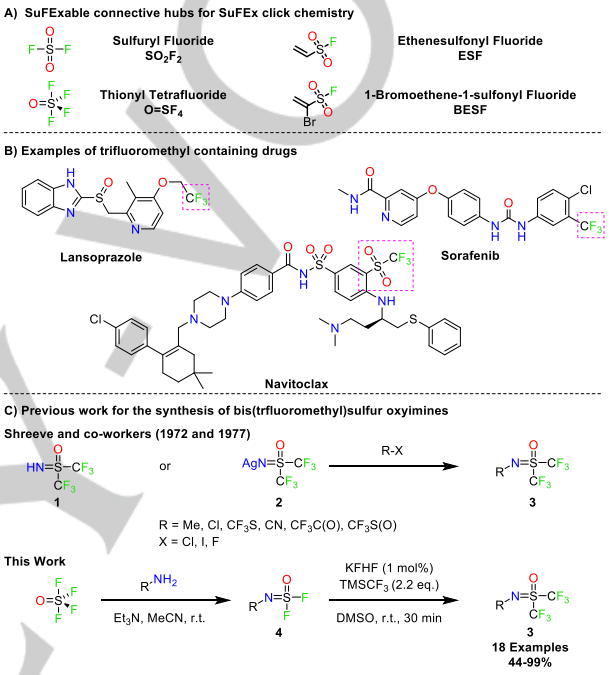

Figure 1. A) Connective SuFEx hubs; B) Drugs containing the trifluoromethyl functionality; C) SuFEx trifluoromethylation overview.

Under these conditions, the S-F exchange with nucleophiles such as aryl silyl ethers and amines reliably give stable S-O and S-N bonds, respectively, rendering SuFEx ideal for a wealth of applications.[6]

The availability of SuFExable hubs for creating new linkages is key to driving the click chemistry agenda. These include the connective gases sulfuryl fluoride (SO_2F_2)[3] and thionyl tetrafluoride ($O=SF_4$),[7] that allow modules to be united through a single sulfur hub by nucleophilic exchange and the sulfonyl fluoride based connectors ethenesulfonyl fluoride (ESF)[3,8] and 1-bromoethene-1-sulfonyl fluoride (BESF),[9] which offer additional connective pathways through 1,4-addition and cycloaddition chemistry (Figure 1A).

Expanding the repertoire of available SuFEx transformations, we report herein the development of a straightforward and efficient SuFEx trifluoromethylation protocol for the incorporation of the $-CF_3$ group into biologically relevant molecules. The method exploits the stability and tolerance of SuFExable sulfonyl fluorides and iminosulfur oxydifluorides enabling late-stage S-F exchange. Using a combination of trifluoromethyltrimethylsilane (Ruppert's reagent, $TMSCF_3$) and bifluoride, the new SuFEx protocol delivers pharmaceutically

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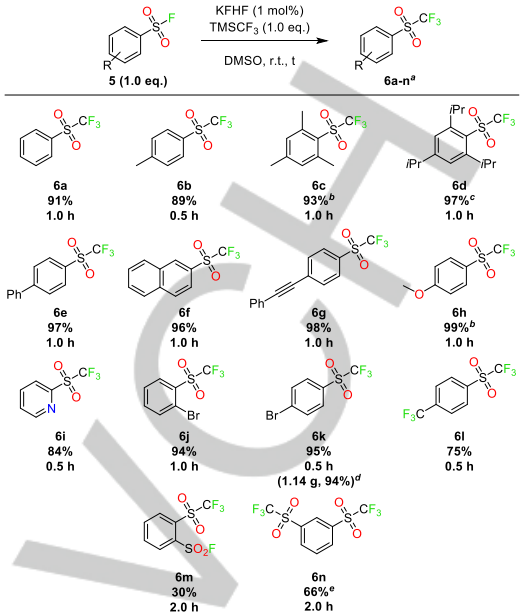
relevant triflones and bis(trifluoromethyl)sulfur oxyimines in excellent yields and rarely requires chromatographic purification.

This is significant because fluorine is an important hydrogen bioisostere—the selective incorporation of fluorine rich functionalities into therapeutic or diagnostic small molecules can impart many desirable pharmacokinetic and physicochemical properties, e.g. metabolic stability, increased lipophilicity, enhanced binding interaction and efficacy.[10,11] Several major pharmaceutical drugs contain -CF_3 groups (e.g. the proton-pump inhibitor lansoprazole; and the anti-cancer drug sorafenib (Figure 1B)), and there is increasing demand for novel trifluoromethylation protocols, including through direct nucleophilic or electrophilic addition, radical and organometallic methodologies.[10]

The development of a SuFEx trifluoromethylation protocol through the S-F to S-CF_3 exchange is highly desirable for a number of reasons: 1) sulfur bound-CF_3 has significant potential in drug development, exemplified by the triflone containing navitoclax—an experimental anti-cancer drug (Figure 1B);[12] 2) compared to the more common S-Cl functionality, S-F bonds are stable and would allow later-stage functionalization in synthetic schemes;[13] and 3) it would enable exploration of new and unprecedented sulfur bound-CF_3 functionalities like bis(trifluoromethyl)sulfur oxyimines—a novel class of fluorine-rich substrate that have scarcely been reported (Figure 1C).

We first explored the SuFEx conversion of sulfonyl fluorides with $TMSCF_3$ to give the corresponding triflones. This transformation, and related,[14] have been reported with moderate success using $TMSCF_3$ and TBAF, although due to the inevitable presence of water in the reagent mixture, the nature of the fluoride is uncertain because TBAF samples are almost always hydrated. This results in the formation of bifluoride (HF_2^-), hydroxide (OH^-) as well as fluoride ions; hence an excess of $TMSCF_3$ is often required to compensate for reagent decomposition.[15] We anticipated that anhydrous conditions with a clean source of bifluoride ion would benefit the SuFEx the trifluoromethylation process. A reaction screen was performed with 4-toluenesulfonyl fluoride and potassium bifluoride (KFHF) as a SuFEx catalyst (SI, T1). A low loading (1 mol%) of KFHF was found to be satisfactory when used in combination with 1 equiv of $TMSCF_3$ in anhydrous DMSO.[16] The optimized reaction conditions were compatible with a wide range of substrates (Scheme 1, **6a**-**6n**),[17] giving excellent yields with sterically hindered (**6c** and **6d**) and electron-rich substrates (**6h**). Despite several attempts, mono-trifluormethylation of benzene-1,2-disulfonyl difluoride (**5m**) gave the product **6m** in only 30% yield, along with unreacted starting material,[18a] whereas double trifluoromethylation of **5n** gave the corresponding 1,3-bis((trifluoromethyl)sulfonyl)benzene **6n** in 66% yield.[18b] The protocol is also amenable to gram scale synthesis (e.g. **6k**) without compromising the yield.

The SuFEx trifluoromethylation protocol with iminosulfur oxydifluorides to access the scarcely known bis(trifluoromethyl)sulfur oxyimines **3** was next explored.[7] We find only 9 examples of related bis(trifluoromethyl)sulfur oxyimine (**3**) compounds reported in the literature;[19] each synthesized primarily by the alkylation of bis(trifluoromethyl)sulfur oxyimine ($(CF_3)_2S(O)=NH$ (**1**), or the silver salt $(CF_3)_2S(O)=NAg$ (**2**) (Figure 1C).[19a] A selection of iminosulfur oxydifluorides (**4a-r**) were prepared from the reaction of $O=SF_4$ gas with the corresponding



Scheme 1. Synthesis of triflones; [a] Isolated yields, reactions performed on 1.3 mmol of the sulfonyl fluoride; [b] 5 mol% KFHF used; [c] 20 mol% KFHF and 1.2 eq. $TMSCF_3$ used; [d] Reaction performed on 3.5 mmol of the sulfonyl fluoride, 1.0 h reaction time; [e] 40 mol% KFHF and 2.9 eq. $TMSCF_3$.

primary amines under SuFEx conditions.[7] Using a modified protocol with a slight excess of $TMSCF_3$ (2.2 equiv), full consumption of the iminosulfur oxydifluoride starting materials was observed (determined by ^{19}F NMR), giving the target bis(trifluoromethyl)sulfur oxyimine products **3a-r** in mostly excellent yields (Scheme 2). The protocol is compatible with a wide array of iminosulfur oxydifluorides, including aromatic (**3a-j**) and benzyl (**3k-l**) substrates, while in the case of 4-ethynylbenzeneiminosulfur oxydifluoride, trimethylsilylation of the terminal alkyne also occurred to give the bis-trifluoromethylated product **3c**. Diminished yields were observed with substrates comprising electrophilic groups (e.g. Starting materials containing an electrophilic ketones **3g** and **3r**) due to competing addition reactions (See SI). However, simple functional group protection circumvents this issue, with the corresponding ketal trifluoromethylation product (**3h**) isolated in excellent yield. Aliphatic substrates (**3m-r**) were also compatible, including compounds with a high density of heteroatoms (**3o-q**).[20]

Until very recently the mechanism of anion-initiated trifluoromethylation remained unclear, with previous mechanistic proposals suggesting the involvement of both siliconate and carbanion pathways.[21]

A comprehensive mechanistic study by Lloyd-Jones and co-workers on the trifluoromethylation of ketones and aldehydes with $TMSCF_3$ has resolved the siliconate-carbanion dichotomy.[22] A combination of stopped-flow NMR/IR studies and DFT calculations were employed to discern that the direct transfer of CF_3 from siliconate species to carbonyl electrophiles is kinetically prohibited due to the very high barrier of inversion for the $^-CF_3$ anion, which subsequently necessitates involvement of the "free" $^-CF_3$ anion rather than a siliconate-CF_3 species. The calculations

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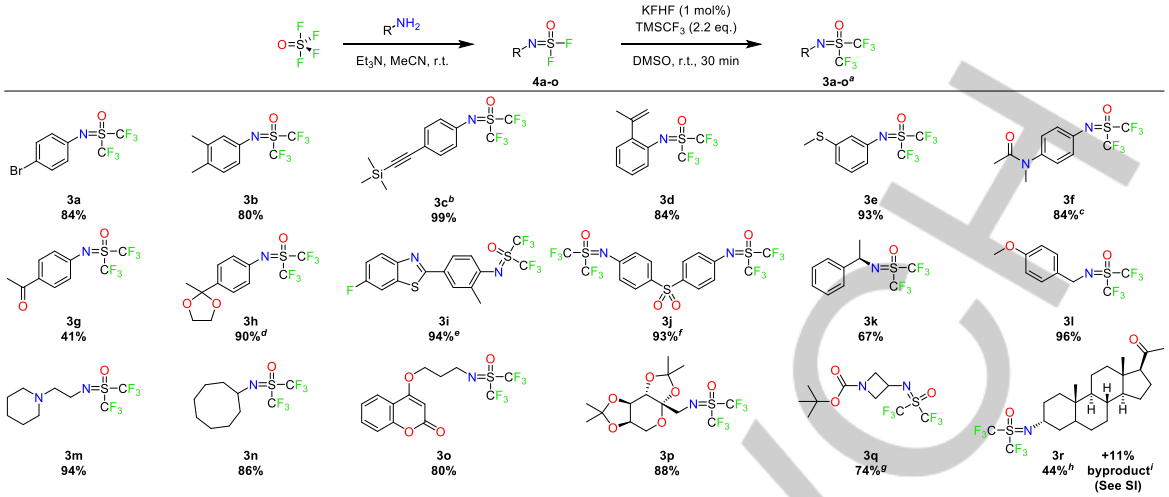
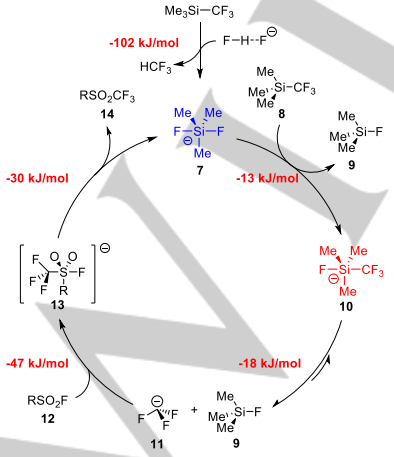


Scheme 2. Synthesis of bis(trifluoromethyl)sulfur oxyimines; [a] Isolated yields from the conversion of iminosulfur oxydifluorides **4** to the bis(trifluoromethyl)sulfur oxyimine products **3**, reactions performed on 0.25 mmol of the iminosulfur oxydifluoride; [b] Terminal alkyne of iminosulfur oxydifluoride used; [c] Total of 21 mol% KFHF and 4.4 eq. $TMSCF_3$ used, 1.5 h; [d] 10 mol% KFHF used; [e] Total of 11% KFHF used, 2 h; [f] 4.4 eq. $TMSCF_3$ used; [g] Total of 21 mol% KFHF and 4.4 eq. $TMSCF_3$ used, 3.0 h; [h] Total of 21 mol% KFHF and 6.6 eq. $TMSCF_3$, 5.0 h; [i] 11% of by product observed (See SI).

also indicate that reactions with ketones and aldehydes proceed *via* a lower-barrier process involving attack of the electrophile by a "free" $^-CF_3$ anion arising from rapid and reversible CF_3 dissociation from the siliconate.[22]

To date, the pathways empowering SuFEx catalysis remain a matter of conjecture, although interactions with "H^+" or "R_3Si^+"in the SuFEx transition state have been suggested.[3] Here we tentatively propose a bifluoride initiated pathway (Scheme 3) on the basis of theoretical calculations. Initial formation of a siliconate complex (**7**) occurs through the reaction of bifluoride and $TMSCF_3$ to release fluoroform (ΔG = -102 kJ/mol). The siliconate complex reacts with a second $TMSCF_3$ molecule to form the readily reported siliconate species (**10**) and TMSF (**9**) with ΔG of -12 kJ/mol. Reversible dissociation of CF_3 from the siliconate (**10**) gives the necessary "free" $^-CF_3$ anion (**11**) and TMSF (**9**), followed by nucleophilic attack of **11** at the activated electrophilic sulfur center to yield a five-coordinate sulfur intermediate (**13**) with ΔG of -47 kJ/mol. Dissociation of the fluoride reforms the siliconate complex (**7**), releasing the triflone product (**14**) and regenerating the proposed catalytically active species, difluorotrimethylsilicate with ΔG of -30 kJ/mol.



Scheme 3. Proposed mechanism for the bifluoride catalyzed transformation of sulfonyl fluorides to triflones with calculated free energies (ΔG).

To demonstrate the utility of SuFEx trifluoromethylation to a functional, biologically relevant compound, and to probe the biocompatibility of the underexplored bis(trifluoromethyl)sulfur oxyimine functional group, the benzothiazole derived bis(trifluoromethyl)sulfur oxyimine **3i** was synthesized from the corresponding iminosulfur oxydifluoride **4i** (Scheme 2). Benzothiazole compounds have been shown to possess significant anti-cancer activity, operating *via* a complex mechanism that culminates in the formation of reactive nitrenium species, which themselves form DNA adducts ultimately leading to cell death.[23] The *in vitro* bioactivity of **3i** was examined against MCF7 breast cancer and MCF10A mammary epithelial cells revealing a significant degree of selectivity towards the cancerous cells with an IC_{50} of 0.60 μM against MCF7 (Figure 2A). In contrast, at the concentration range utilized, only 57% cell death was observed for MCF10A and therefore the IC_{50} would exceed 50 μM when higher concentrations are administered (Figure 2A). Fluorescence imaging clearly shows uptake of compound **3i** in both MCF7 and MCF10A cells (Figure 2B). The inclusion of the -CF_3 group through the bis(trifluoromethyl)sulfur oxyimine may also offer significant potential in cases where the modification of lipophilic properties (CLogP) is required, for example the CLogP of **3i** is 4.97, which is a dramatic increase compared to the parent aniline and **4i** with CLogP values of 3.76 and 3.27 respectively.[24] Collectively, for the first time, these results demonstrate the potential of bis(trifluoromethyl)sulfur oxyimines in a biological setting, which may offer significant benefits in future drug discovery and optimization studies where biocompatible fluorine rich functionalities are desirable.

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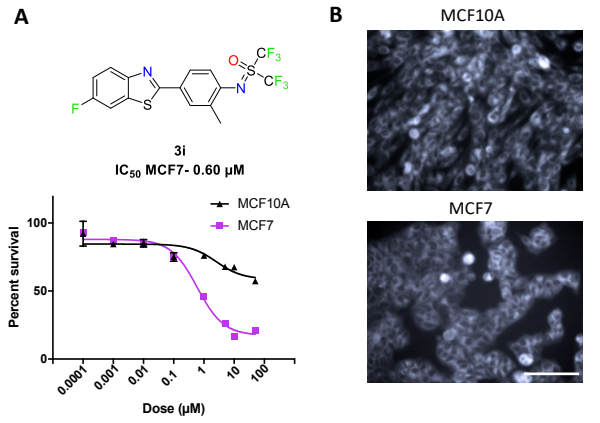

Figure 2. A) MCF7 breast cancer cells and MCF10A breast cells were treated for 72 h with **3i**. Cell viability was assessed by an MTT assay; B) **3i** was dosed to breast normal (MCF10A) or cancer (MCF7) cells following 24 h of growth. Fifty minutes after compound addition fluorescent images were acquired. Scale bar represents 100 µm.

In conclusion, we have developed an efficient and robust bifluoride ion catalyzed SuFEx click chemistry protocol for the synthesis of triflones, and previously underrepresented bis(trifluoromethyl)sulfur oxyimines. The reactions are fast, high yielding and proceed with low sub-stoichiometric quantities of bifluoride catalyst KFHF. We propose a tentative mechanism involving bifluoride activation of $TMSCF_3$ to produce the necessary "free" $^-CF_3$ anion, yielding a five-coordinate sulfur intermediate that weakens the S-F bond allowing dissociation of fluoride to reform the siliconate intermediate (**7**). With increasing interest into methods for installing trifluoromethyl functionality into drugs and drug candidates, we believe that the new SuFEx protocol will find wide application in drug discovery, as exemplified through the synthesis of the bis(trifluoromethyl)sulfur oxyimine **3i**—a benzothiazole derived compound with selective cytotoxicity activity against MCF7 breast cancer cells.

Acknowledgements

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Keywords: SuFEx • click chemistry • trifluoromethylation • bis(trifluoromethyl)sulfur oxyimine • bifluoride mediated

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[15] a) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *57*, 757-786; b) Moderately improved yields have been achieved by Yagupolski and co-workers (see reference 11a) using catalytic quantities of anhydrous TASF (10 mol%) and 2 equivalents of $TMSCF_3$, although with only a very small substrate scope.

[16] a) When reagent grade DMSO was used no conversion to the desired product was observed (SI, T1); b) We observed that anhydrous polar aprotic solvents were critical for the reaction (presumably due in-part to the improved solubility of the catalyst), with DMSO identified as the solvent of choice to ensure full conversion to the target products in under 30 min (SI, T1); c) The reaction with potassium fluoride in DMSO was unsuccessful.

[17] The optimal conditions for the procedure were found to be: 1 eq. sulfonyl fluoride, 1 eq. $TMSCF_3$, 1 mol% KFHF in anhydrous DMSO for 30 min;

[18] a) The formation of the bis-trifluoromethylated analogue of **6m** was not observed. Addition of excess $TMSCF_3$ led to a complex and unidentified mixture; b) The product **6n** was found to be relatively unstable and slowly decomposed.

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[24] CLogP values were calculated using ChemDraw Professional 17.0, **2018** PerkinElmer Informatics, Inc.

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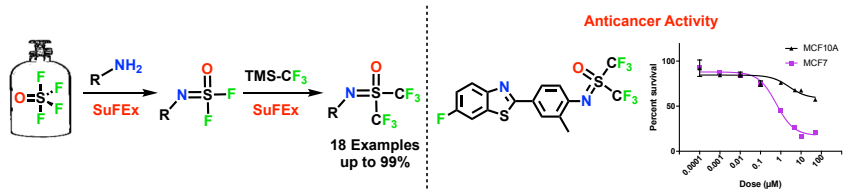

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An expedient SuFEx trifluoromethylation of sulfonyl fluorides and iminosulfur oxyfluorides is described. The efficient S-F exchange with Ruppert's reagent ($TMSCF_3$) is initiated by sub-stoichiometric quantities of bifluoride ion $[FHF]^-$ in anhydrous DMSO. DFT studies provide insight into a tentatively proposed catalytic cycle involving a five-coordinate sulfur intermediate and siliconate species. The selective anti-cancer properties of previously inaccessible bis(trifluoromethyl)sulfur oxyimines was also demonstrated.