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1-Bromoethene-1-sulfonyl fluoride (BESF) is another good connective hub for SuFEx click chemistry†

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We demonstrate 1,2-dibromoethane-1-sulfonyl fluoride (DESF) as a bench-stable and readily accessible precursor to the robust SuFEx connector, 1-bromoethene-1-sulfonyl fluoride (BESF). The *in situ* generation of BESF from DESF opens up several new reaction profiles, including application in the syntheses of unprecedented 3-substituted isoxazole-5-sulfonyl fluorides, 1-substituted-1*H*-1,2,3-triazole-4-sulfonyl fluorides, 2-amino-1-bromoethane-1-sulfonyl fluorides and 4-bromo-β-sultams in good to excellent yields. These new modules comprise a pendant sulfonyl fluoride handle, which further undergoes facile and selective SuFEx reactions with a selection of aryl silyl ethers to generate stable and useful sulfonate connections.

Sulfur–Fluoride Exchange (SuFEx) is a new generation click reaction, and a powerful technology for creating molecular connections with absolute reliability under metal free conditions.[1] SuFEx builds upon the fundamental principles of click chemistry,[2] by engaging near perfect reactivity to create stable covalent linkages between discrete modular units. SuFEx exploits the 'alien-like' nature of S–F bonds (*e.g.* sulfonyl fluorides, fluorosulfates *etc.*), which are characterised by both their remarkable kinetic stability and their robust reactivity under special activating conditions.[1] The incredible efficiency and reliability of SuFEx has already been realised in several applications, including in synthetic chemistry,[1,3] chemical biology,[4] polymers[5] and post-polymerisation modification.[6]

SuFEx brings a new dimension to the click chemistry toolbox by allowing the creation of connections through discrete hubs. These so-called 'SuFEx-able plugins', which to-date include the connective gases sulfuryl fluoride (SO_2F_2)[1] and thionyl tetrafluoride ($O{=}SF_4$),[7] along with the carbon-based linker, ethenesulfonyl fluoride (**ESF**),[1,8] serve as junctions for creating fluorosulfate, iminosulfur oxydifluoride and alkyl sulfonyl fluoride molecular connections, respectively. The resulting S–F functionality is primed for undergoing SuFEx chemistry, and creating new linkages that more often than not, arise through S–F exchange with aryl silyl ethers and/or with amine nucleophiles to give the corresponding S–O and S–N bonds, respectively.[9]

In addition to S–F exchange, **ESF** can form additional connections through carbon-based linkages—reacting with amines, alcohols and carbon nucleophiles by conjugate addition,[1] and also through cycloaddition pathways as a diene and/or dipolarophile.[8,10]

In an effort to expand the range of available SuFEx hubs that enable the formation of new and SuFEx-able functional cores, we identified 1-bromoethane-1-sulfonyl fluoride (**BESF**) as an attractive prospect.[11] In principle, **BESF** offers the same reaction pathways as **ESF**, but with the additional benefit of an embedded functional bromo-group, which creates further opportunities for reactivity. With this in mind, we envisaged a 1,3-dipolar cycloaddition/dehydrobromination sequence would lead directly to pharmaceutically relevant sulfonyl fluoride functionalised 5-membered aromatic heterocycles, including isoxazoles and triazoles.[11] In this regard, the **BESF** would formally serve as a surrogate for the as yet unreported acetylenesulfonyl fluoride **ASF** in 1,3-dipolar cycloaddition chemistry (Fig. 1).

Herein we report the development and application of 1-bromoethane-1-sulfonyl fluoride (**BESF**) as a new connector for SuFEx click chemistry. Conveniently generated *in situ* by dehydrobromination of the bench-stable 1,2-dibromoethane-1-sulfonyl fluoride (**DESF**), the versatility of this new SuFEx hub is showcased through the syntheses of 5-sulfonyl fluoride isoxazoles, 4-sulfonyl fluoride triazoles, amine nucleophile 1,4-addition products and 4-bromo-β-sultam products with excellent efficiency. On a selection of these examples, we further demonstrate their function as SuFEx linkers through reactions with a range of aryl silyl ethers.

DESF was prepared in an excellent yield of 87% directly from **ESF**, following a modified version of Vessiere's protocol.[12]

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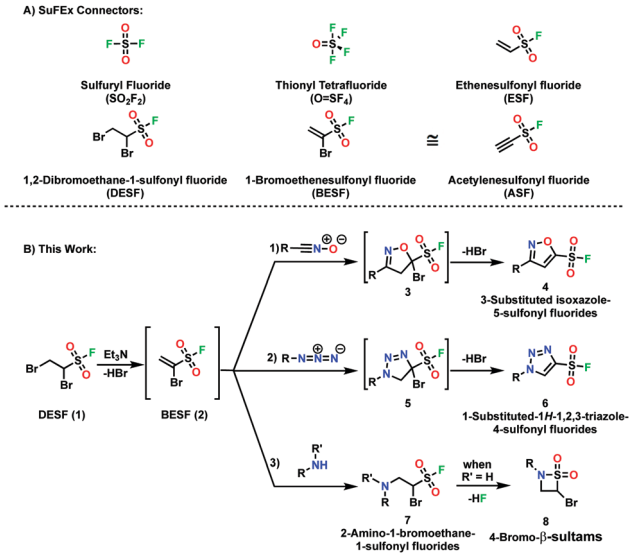


Fig. 1 (A) SuFEx connectors; (B) the *in situ* of SuFEx connector **BESF**.

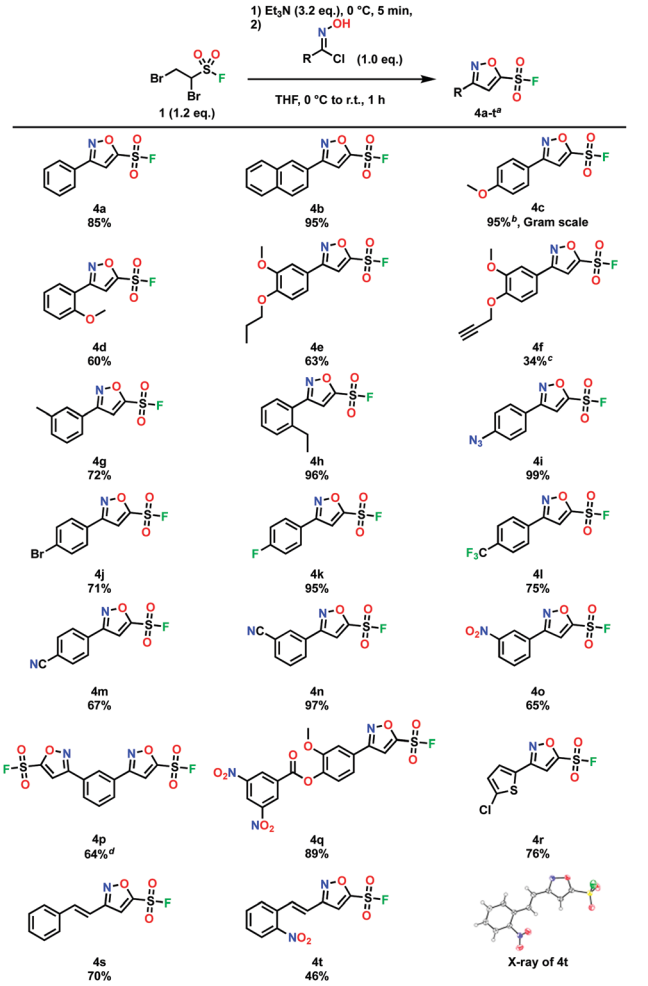
While **BESF** may itself be prepared and isolated, we found the material to be unstable under ambient conditions.[13]

We have previously reported the successful development of 1,3-dipolar cycloaddition chemistry using reactive intermediates that are generated and consumed *in situ*, and elected to investigate this strategy with **BESF**.[14] In principle, a controlled dehydrobromination of **DESF** would generate the corresponding **BESF**, which upon cycloaddition with a given 1,3-dipole (*e.g.* nitrile oxide or azide), would be thermodynamically driven to undergo a second dehydrobromination to give the corresponding 5-membered aromatic heterocycle (Fig. 1B).

This approach proved successful—a model study using **DESF** and the nitrile oxide precursor (R = 4-methoxybenzene) in the presence of triethylamine, realised the 3-substituted isoxazole-5-sulfonyl fluoride **4c**. In this particular instance, both the **BESF** dipolarophile and the reactive nitrile oxide 1,3-dipole were prepared *in situ*.[15] Optimisation of the reaction conditions revealed the following protocol (Table S1, ESI†): [3.2 equivalents of triethylamine, 1.2 equivalents of **DESF** stirring for 5 min at 0 °C in THF, followed by the addition of 1.0 equivalent of *N*-hydroxyimidoyl chloride (nitrile oxide precursor), stirring at 0 °C to room temperature for 1 h], which resulted in the regioselective syntheses of twenty 3-substituted isoxazole-5-sulfonyl fluorides in good to excellent yields (Scheme 1).

The reaction performed well with a number of aryl substituted *N*-hydroxyimidoyl chlorides (**4a–q**) to give the electron-neutral (**4a**, **4b** and **4i**), electron-rich (**4c–h**) and electron deficient (**4j–q**) analogues, and could equally be applied to an *N*-hydroxyimidoyl chloride bearing an alkyne (**4f**). Access to di-substituted products such as **4p** was possible with this method—so too was the use of non-phenyl derived *N*-hydroxyimidoyl chlorides, allowing the syntheses of a thiophene derivative (**4r**) and two styryl based analogues in good yields (**4s** and **4t**).

The regiochemistry of the cycloaddition products was determined by extensive NMR analyses and was corroborated by single crystal X-ray crystallography (**4t**, Scheme 1). Molecular modelling



Scheme 1 Synthesis of 5-sulfonyl fluoride substituted isoxazoles. [a] Isolated yields, reactions performed on a 1.00 mmol scale of *N*-hydroxyimidoyl chloride; [b] reaction performed on a 5.38 mmol scale of *N*-hydroxyimidoyl chloride; [c] reaction performed on a 0.30 mmol scale of *N*-hydroxyimidoyl chloride; [d] 2.4 eq. **DESF** and 6.4 eq. of Et_3N added.

performed at the MP2/def2-TZVPP//M06-2X/def2-TZVP[16] level of theory was used to help rationalise the regiochemical outcome of the transformation (Fig. 2). The modelling reveals the initial step to form **BESF** from **DESF** is endergonic by 38.2 kJ mol^{-1}, whereas a second dehydrobromination to give the **ASF** is significantly unfavoured at 129.9 kJ mol^{-1}. Both the 3,5- and 3,4-substituted isoxazole products are favourable by 132.8 and 136.2 kJ mol^{-1}, respectively. While the thermodynamic product is calculated to arise from a 3,4-substituted intermediate, the reaction kinetics were found to be product determining with the transition state (**TS1**) for cycloaddition found to be significantly higher by 43.7 kJ mol^{-1} for the 3,4-isoxazole. The significant difference in barrier height is consistent with the experimental observation and exclusive formation of the 3,5-isoxazole product.

The difference in reactivity can be rationalised by steric effects, with **TS1** for the 3,4-isoxazole product producing a steric clash between the $-SO_2F$ and –Ph groups, which is absent for 3,5-isoxazole. The subsequent aromatising dehydrobromination step, for both regioisomeric intermediates (**12** and **13**)

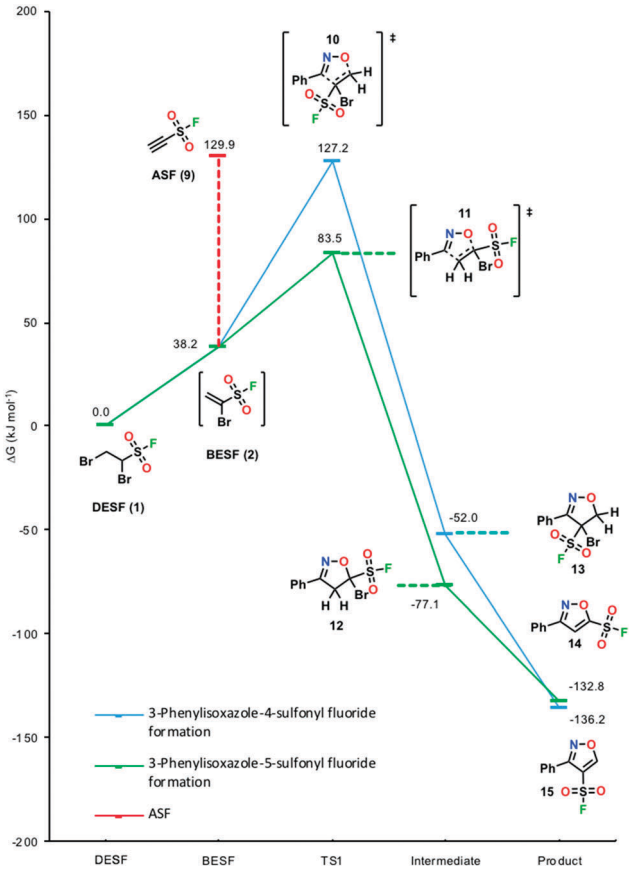
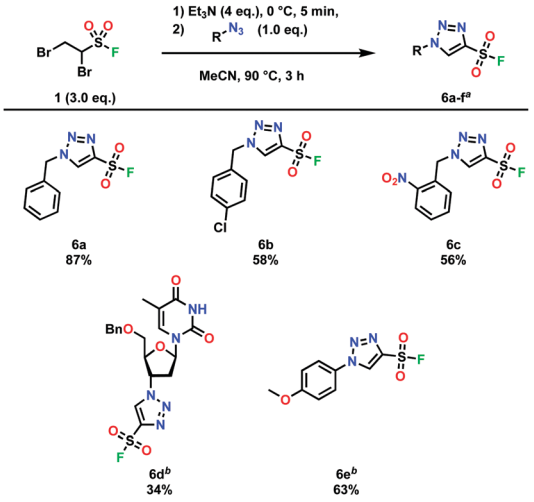


Fig. 2 Calculated free energy profile (ΔG, kJ mol^{-1}) of 3,5- and 3,4-isoxazole formation reactions at the MP2/def2-TZVPP(SMD,THF)//M06-2X/def2-TZVP level of theory.

was predicted to be a strong driving force for the formation of the isoxazole core. Mulliken charges provide further support for the 1,2-cycloaddition preference; the terminal carbon in **BESF** has a more negative charge (-0.23 *e*) and therefore favours attack from the oxygen anion (-0.40 *e*) in the nitrile oxide to the sulfonyl fluoride-bonded carbon rather than the terminal carbon.

To explore the scope of reactivity of **BESF** further, we next investigated the *in situ* 1,3-dipolar cycloaddition reaction of **BESF** with a selection of organic azides. Using slightly modified reaction conditions [4 equivalents of triethylamine, 3 equivalents of **DESF** and 1 equivalent of azide at 90 °C in MeCN for 3 h], a selection of 1-substituted-1*H*-1,2,3-triazole-4-sulfonyl fluorides were obtained (**6a–e**) in excellent yields (Scheme 2). This is important since until now, the synthesis of 1,2,3-triazoles bearing sulfonyl fluorides, which have significant potential in click chemistry applications, remained unprecedented.

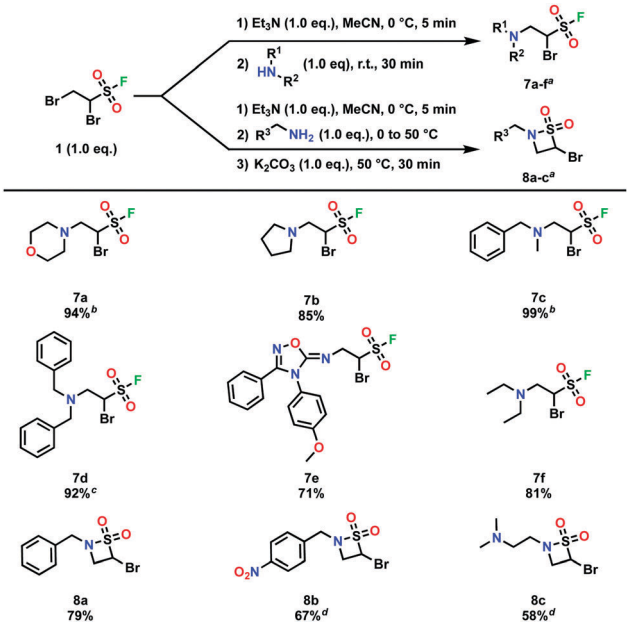
The 1,4-regioselectivity of the 1,3-dipolar cycloaddition of **BESF** with azides can be explained using a similar rationale proposed for the analogous reaction with nitrile oxides (Fig. S1, ESI†). Molecular modelling studies reveal that the corresponding energy of the transition state for **BESF**-azide cycloaddition is significantly higher than that of the analogous isoxazole, which is reflected experimentally in the higher reaction temperature required (Fig. S3, ESI†).[17]



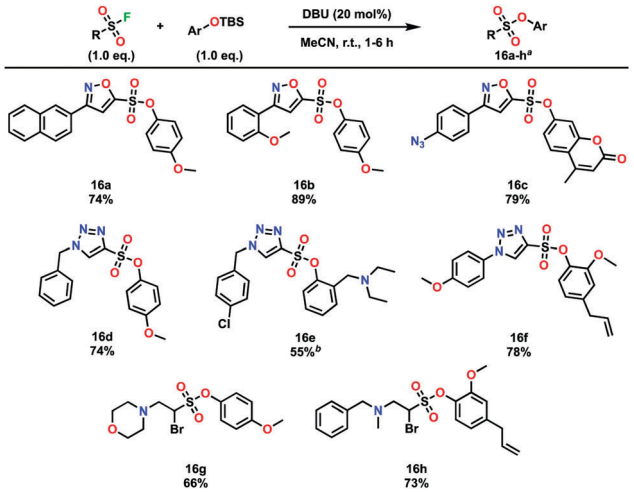
Scheme 2 Synthesis of 4-sulfonyl fluoride substituted triazoles. [a] Isolated yields, reactions performed on a 0.25 mmol scale of azide; Heated at 90 °C for 6 h.

We next explored the reactivity of the *in situ* generated **BESF** connector as a 1,4-Michael acceptor. Beginning with secondary amines, the 1,4-amino adducts (**7a–f**) were obtained in excellent yields (Scheme 3). When primary amines were employed, the corresponding 4-bromo-β-sultams were isolated—heating the reaction to 50 °C followed by the addition of potassium carbonate (1 equivalent) 30 minutes after the amine addition, led to the full conversion to the 4-bromo-β-sultams **8a–c**.

With several new sulfonyl fluoride functionalities in-hand, obtained through both cycloaddition and 1,4-addition pathways



Scheme 3 1,4-Michael addition products of secondary amines into **BESF** and 4-bromo-β-sultam synthesis with primary amines. [a] Isolated yields, reactions performed on a 0.10 mmol scale; [b] reactions performed on a 1.00 mmol scale; [c] heated to 50 °C; [d] HCl salt of amine used, 2.0 eq. of Et_3N added.



Scheme 4 SuFEx reactions with isoxazole, triazole and 1,4-addition products. [a] Isolated yields, reactions performed on a 0.10 mmol scale of sulfonyl fluoride derivative; [b] extra 20 mol% DBU added after 3 h.

from **BESF**, we elected to test the SuFEx-ability of these novel modules. Thus, SuFEx reactions with selected aryl silyl ethers were performed with chosen **BESF** derived sulfonyl fluorides to give the corresponding sulfonate products **16a–h** in excellent yields, thereby demonstrating their effectives as SuFEx-able connective hubs (Scheme 4).

In summary, we have found applications of 1,2-dibromoethane-1-sulfonyl fluoride (**DESF**), as a new and bench stable reagent. Treatment of **DESF** with triethylamine results in the *in situ* generation of the SuFEx linker 1-bromoethene-1-sulfonyl fluoride (**BESF**), which serves as a reactive dipolarophile and Michael acceptor for making covalent connections. The conditions used to generate **BESF** also allow concomitant formation of reactive nitrile oxide 1,3-dipoles from the corresponding *N*-hydroxyimidoyl chlorides, which undergo regiospecific 1,3-dipolar cycloaddition with **BESF** to form the corresponding 3-substituted isoxazole-5-sulfonyl fluorides. We also demonstrate that the reactive **BESF** undergoes regioselective 1,3-dipolar cycloaddition reactions with a number of organic azides to give the corresponding 1-substituted-1*H*-1,2,3-triazole-4-sulfonyl fluoride products, which until now were unprecedented and also reacts with secondary amines to give the 1,4-addition products, and with primary amines to give 4-bromo-β-sultams.

On these products, we have validated the capability of these SuFEx-able sulfonyl fluoride handles to react with aryl silyl ethers to give new sulfonate linkages. Finally, we have provided a rationale to explain the regiochemistry of the 1,3-dipolar cycloaddition reactions, which is supported by high level molecular modelling studies.

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Conflicts of interest

There are no conflicts to declare.

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