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Letter

A Simple Protocol for the Stereoselective Construction of Enaminyl Sulfonyl Fluorides

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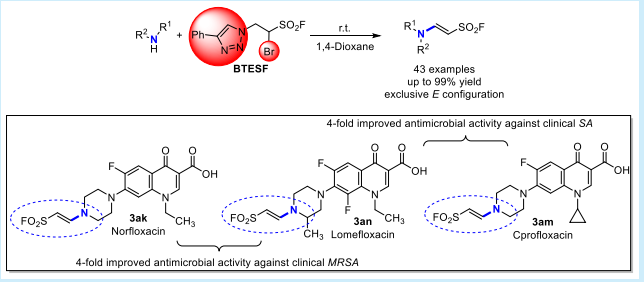
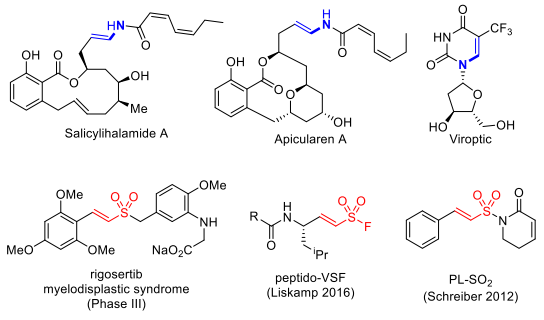
ABSTRACT: A clickable connective hub 1-bromo-2-triazol-ethane-1-sulfonyl fluoride BTESF (**1**) was developed and successfully applied for the fluorosulfonylvinylation of a host of primary and secondary cyclic or acyclic amines including amino acids and pharmaceuticals. Further antimicrobial experiments revealed that vinyl sulfonyl fluoride functionalized norfloxacin (**3ak**), ciprofloxacin (**3am**), and lomefloxacin (**3an**) exhibited 4-fold improved antimicrobial activity against Gram-positive bacteria compared to their parent drugs.



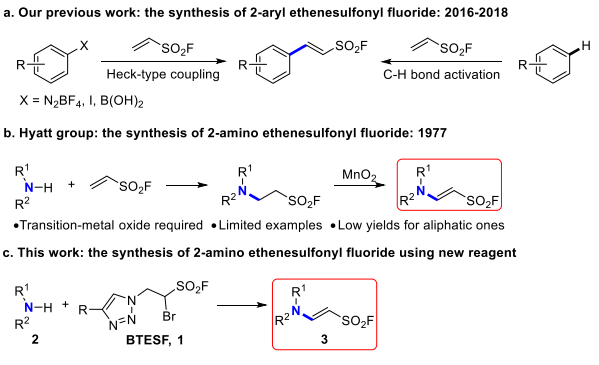
Carbon−nitrogen bonds are ubiquitous in biological systems, natural products, and materials.[1] Among all types of C−N-containing molecules, enamines have been particularly recognized as important moieties in natural products and pharmaceuticals[2,3] (Scheme 1) and as valuable synthetic intermediates for chemical transformations.[4] One of the most atom-economic strategies for the construction of enamines is hydroamination of alkynes.[5] However, the further development of these direct amination reactions has been severely hampered due to the control of reaction selectivity.[5b] In view of the high value and wide application of enamines, the development of efficient methods for the construction of enamines is of great importance and highly desirable.

Scheme 1. Representative Compounds Containing Enamine, Vinyl Sulfone, or Sulfonyl Fluoride Motifs



On the other hand, with the prevalence of sulfur fluoride exchange (SuFEx) click chemistry,[6] ethenesulfonyl fluoride (ESF)[7] and its derivatives[8] have attracted wide attention due to their versatile application in medicinal chemistry,[9] polymer syntheses,[10] and organic chemistry.[8] As a family of ESF derivatives, 2-arylethenesulfonyl fluorides bear two important electrophilic handles and covalent pharmacophores (vinyl sulfone and sulfonyl fluoride group), which were successfully applied as novel scaffolds in the discovery of covalent inhibitors and fluorogenic probes (Scheme 1). Currently, the straightforward strategies to access aryl ethenesulfonyl fluorides are achieved through Pd-catalyzed Heck-type coupling reactions[8,10c,11] and C−H bond activation oriented fluorosulfonylvinylation (Scheme 2, a).[12] 2-Aminoethenesulfonyl fluorides (*N*-ESF), another category of ESF derivatives, exhibiting somewhat structural similarity with 2-arylethenesulfonyl fluorides, bearing both a sulfonyl fluoride group and a enamine functionality, bode extremely well for their future

Scheme 2. Synthesis of Ethenesulfonyl Fluoride Derivatives



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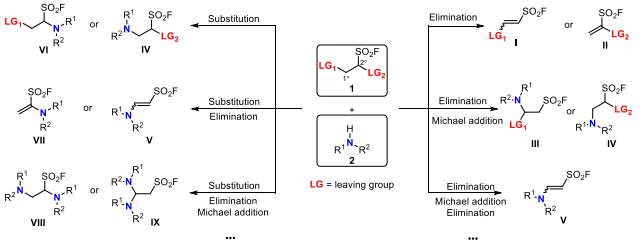
application in the discovery of targeted covalent drugs and the development of SuFEx chemistry. However, the convenient synthesis of *N*-ESF has rarely been accomplished. A cursory index of the literature indicated that only one report[13] involving the synthesis of *N*-ESF through a manganese dioxide oxidation of the Michael addition product of ESF with amines (Scheme 2, b). However, the reported conditions provided limited examples and give 2-aliphatic amino ethenesulfonyl fluoride in a low yield (33%) with the promotion of a transition-metal oxide, which largely restrained the further application of *N*-ESF.

Learning from the previous design of SuFEx reagents[14] and the difficult dehydrobromination of the Michael addition products of 1-Br-ESF with amines,[14a] we considered that synthesizing a new sulfonyl fluoride reagent bearing a C−C single bond and two leaving groups to react with nitrogen nucleophiles by substitution or elimination process will act as an effective method for achieving *N*-ESF products (Scheme 2, c).[15]

However, due to the properties of amine as both a nucleophile and a base, as well as the different reactivity of the two leaving groups, the sequence of substitution and elimination reaction on the new reagent and the preference for substitution on the primary carbon or secondary carbon were difficult to determine, which could result in the formation of a series of unexpected byproducts **I**−**IX** (Scheme 3). In theory,

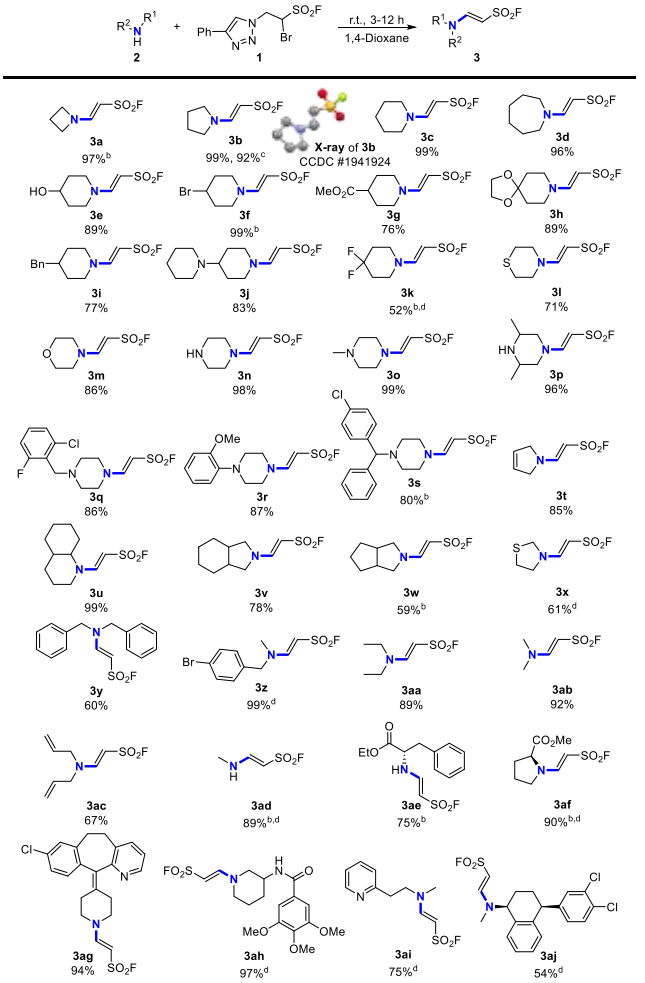
Scheme 3. Reactivity of the New SuFEx Reagent



triazole and bromide both can act as leaving groups,[16] and the triazole group was less reactive than bromide when it was connected with saturated carbon.[17] Therefore, we anticipated that with the promotion of base (amines) intermediate **I** could be generated initially followed by sequential Michael addition and elimination to provide the desired *N*-ESF.

After screening a variety of reaction conditions (for more details, see the SI), we found the best conditions for construction of *N*-ESF, and the functional group compatibility was subsequently investigated with a section of amines **2** (Scheme 4). Cyclic amines **2a**−**2d** were well transformed into their corresponding *N*-ESF **3a**−**3d** with high efficiency. Hydroxy **2e**, bromide **2f**, ester **2g**, benzyl **2i**, or piperidine **2j** groups on the *para* position of piperidine were all tolerated in this process. Acetal-protected piperidine **2h** was also transformed into fluorosulfonylvinylated product **3h** with 89% yield. Strong electron-withdrawing groups on the ring **2k** generated corresponding product **3k** in relatively lower yield, which could be attributed to the reduced nucleophilicity of amine. Thiomorpholine **2l** and morpholine **2m** with an extra heteroatom on the piperidine ring were also compatible, furnishing the corresponding products **3l** and **3m** in 71% and 86% yields, respectively. It was worth noting that only one of the amino groups on piperazines **2n** and **2p** was fluorosulfonylvinylated, leaving the other amino group for

Scheme 4. Substrates Scope of *N*-ESF[a−d]



[a]Reaction conditions: **1** (0.5 mmol, 167 mg), **2** (2.0 equiv, 1.0 mmol), 1, 4-dioxane (5 mL), rt, 3−12 h. [b]Corresponding **2**·HCl or **2**·HBr was used, Et_3N (1 mmol, 101 mg). [c]5.0 mmol scale. [d]More Et_3N (1 mmol, 101 mg) was added.

further diversification. Alkyl- or aryl-protected piperazines **2o**, **2q**, and **2r** reacted smoothly with **1** to afford the corresponding products **3o**, **3q**, and **3r** in satisfactory yields. The analogue of chlorcyclizine **2s** was also shown to have good compatibility. Bicycle substrates **2u**−**2w** generated their desired products **3u**−**3w** in good to excellent yields. Benzyl- and alkyl-substituted amines **2y**−**2ac** were smoothly converted to the target *N*-ESF products in moderate to good yields. Remarkably, primary amine substrate **2ad** was also compatible under these conditions, providing vinylated **3ad** in 89% yield. Considering that amino acids are one of the most important moieties in the life sciences and pharmaceutical industries, the generality of the newly developed protocol was also evaluated in the derivatization of amino acids. Ethyl L-phenylalaninate **2ae** and methyl L-prolinate **2af** yielded their corresponding *N*-ESF **3ae** and **3af** in 75% and 90% yields, respectively. Meaningfully, this protocol was also successfully applied to late-stage functionalization of drugs **2ag**−**2aj**. The derivatives of desloratadine **3ag**, troxipide **3ah**, betahistine **3ai**, and sertraline **3aj** were smoothly achieved in good yields (54−97%). Notably, anilines, sulfonamides, and amides were not compatible under these conditions for generating their

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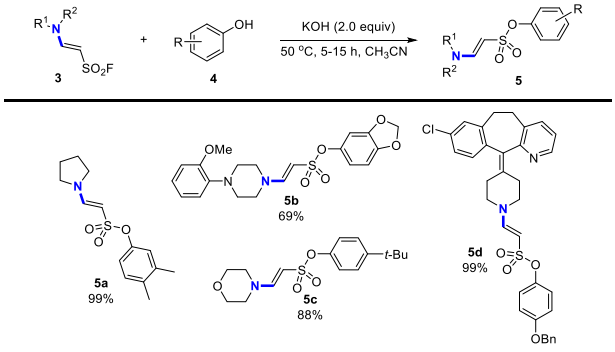
corresponding *N*-ESF products, which could be attributed to the low nucleophilicity of their nitrogen atoms.

Next, post modifications of *N*-ESF were conducted as shown in Scheme 5. α,β-Unsaturated compounds and sulfonyl

Scheme 5. SuFEx Reactions of *N*-ESF with Phenols[a]

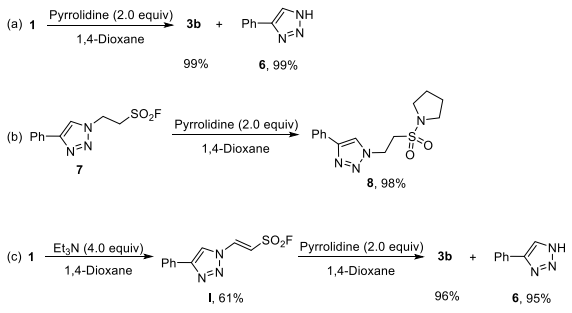


[a]Reaction conditions: **3** (0.5 mmol), **4** (2.0 equiv, 1.0 mmol), KOH (2.0 equiv, 1 mmol), CH_3CN (5 mL), 50 °C under oil bath, 5−15 h.

fluorides are two classes of well-known warheads for targeted covalent inhibitors, which could bind to amino acid residues of proteins undergoing a bond-forming event via Michael addition or SuFEx reaction.[18] Theoretically, *N*-ESF along with previously reported 2-arylethenesulfonyl fluorides could react with oxygen- and nitrogen-containing nucleophiles effectively.[8,12b,c] Interestingly, the newly generated *N*-ESF were found to be much less reactive as electrophiles compared with their vinyl sulfonyl fluoride counterparts.[13] The SuFEx reactions of *N*-ESF with phenols occurred under the promotion of strong base at elevated temperature, while the SuFEx reactions with amines were not achieved. After screening a series of bases and temperatures, we found a suitable condition for converting *N*-ESF to their corresponding sulfonates **5a**−**5d** in good to excellent yields with the assistance of 2 equiv of KOH at 50 °C.

As illustrated in Scheme 6, in order to gain more insight into the mechanism of the formation of *N*-ESF, some control

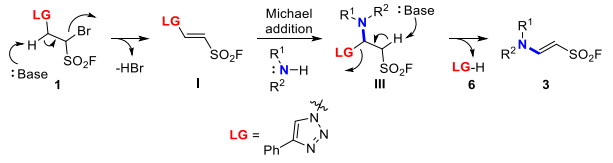
Scheme 6. Control Experiments



experiments were carried out accordingly. Quantitative yields of **3b** and 4-phenyl-1*H*-1,2,3-triazole **6** were generated under the standard reaction conditions (Scheme 6, a). When a similar starting material **7** without the substitution of bromine atom was used (Scheme 6, b), only the SuFEx reaction occurred with 98% yield of sulfamide **8** generated, which revealed that the triazole group[16] was not reactive enough as a leaving group when it was connected directly with a saturated carbon.[17] Interestingly, when pure (*E*)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethene-1-sulfonyl fluoride **I** (for more details, see the SI) was used, the corresponding **3b** and triazole **6** were obtained in 96% and 95% yields, respectively (Scheme 6, c), which indicated vinyl triazole **I** was a key intermediate during the formation of *N*-ESF.

On the basis of the results of mechanism-investigated experiments, a plausible mechanism of the fluorosulfonylvinylation of amines was proposed in Scheme 7. Initially, after β-

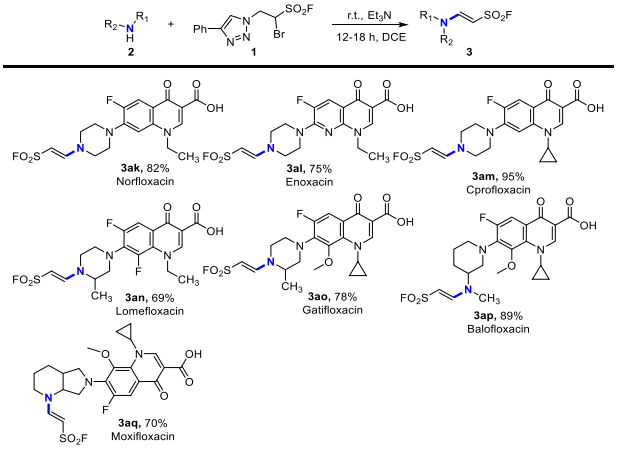
Scheme 7. Plausible Mechanism for the Generation of *N*-ESF



elimination with the promotion of base, BTESF **1** was converted into (*E*)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethene-1-sulfonyl fluoride **I** which could be stabilized by the triazole group.[19] Then, Michael addition of amine followed by the elimination of triazole **6** provided the final thermodynamically more stable *E*-configuration of vinyl product **3**.

SuFEx click chemistry is a newly developed tool for drug discovery.[9] With this amine fluorosulfonylvinylation procedure in hand, a panel of known antibacterial drugs were converted to their fluorosulfonylvinylated products, and their potential activity in antibacterial fields was further explored. Fluoroquinolones are a large and powerful group of synthetic antimicrobial compounds whose main action is the inhibition of bacterial DNA-gyrase within the bacterial cells. These compounds have been widely used to treat various diseases due to their high activity against Gram-negative and Gram-positive bacteria.[20] In Scheme 8, seven fluoroquinolone drugs were

Scheme 8. Modification of Quinolones[a]



[a]Reaction conditions: **1** (1.2 equiv, 0.6 mmol, 200.4 mg), **2** (0.5 mmol), Et_3N (0.5 mmol, 50.5 mg), DCE (5 mL), rt, 12−18 h.

successfully fluorosulfonylvinylated in the presence of 1.2 equiv of BTESF **1** and 1.0 equiv of triethylamine, and most of the substrates were transformed to their desired products **3** in moderate to good yields.

As shown in Table 1, the fluorosulfonylvinylation did not alter the antimicrobial spectrum of quinolones. Seven fluoroquinolone drugs and their vinyl sulfonyl fluoride derived

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Table 1. MIC (μM) of Quinolones against Bacteria and Fungi[a,b]

	Gram-positive		Gram-negative		fungus
	SA	MRSA	EC	PA	CA
norfloxacin	3.12	3.12	0.78	3.12	>200
3ak	1.56	0.78	0.39	6.25	>200
enoxacin	3.12	3.12	1.56	6.25	>200
3al	3.12	6.25	3.12	50.00	>200
ciprofloxacin	1.56	0.78	0.19	0.78	>200
3am	0.39	0.39	0.19	6.25	>200
lomefloxacin	3.12	3.12	0.39	6.25	>200
3an	0.78	0.78	0.78	50.00	>200
gatifloxacin	0.39	0.39	0.09	3.12	>200
3ao	0.19	0.19	0.19	12.50	>200
balofloxacin	0.39	0.39	0.19	25.00	>200
3ap	0.39	0.39	3.12	100.00	>200
moxifloxacin	0.39	0.19	0.09	6.25	>200
3aq	0.19	0.19	0.78	50.00	>200

[a]MICs representing mean values of at least three replicates. [b]SA: *Staphylococcus aureus*, MRSA: methicillin resistant *Staphylococcus aureus*, PA: *Pseudomonas aeruginosa*, EC: *Escherichia coli*, CA: *Candida albicans*.

compounds **3ak**−**3aq** showed a moderate to strong level of antibacterial activity against Gram-positive and Gram-negative bacteria but no activity against fungi (MIC values >200 μM). Among them, compounds **3ak** and **3am**−**3ao** exhibited improved antimicrobial potential against Gram-positive bacteria. In particular, compounds **3ak** and **3an** showed obviously enhanced antimicrobial activity than norfloxacin and lomefloxacin against clinical methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC = 0.78 μM). The activity of **3am** (MIC = 0.39 μM) and **3an** (MIC = 0.78 μM) against *S. aureus* (SA) also exhibited 4-fold improvement compared with ciprofloxacin and lomefloxacin. Quinolone resistance, especially the second-generation quinolones, has multiple mechanisms and significant clinical impact.[21] The vinyl sulfonyl fluoride functionalized norfloxacin, ciprofloxacin, and lomefloxacin could improve their anti-Gram-positive bacteria activity, which may be a novel approach to result in effective antibacterial therapies to sustainably combat antibacterial resistance.

In conclusion, we have developed a new SuFEx reagent 1-bromo-2-triazolethane-1-sulfonyl fluoride **1** and demonstrated its practical application in construction of novel enaminyl sulfonyl fluorides through simple reactions with amines. The general method for effective installation of vinyl sulfonyl fluoride onto amines was successfully utilized for late-stage functionalization of drugs. Antimicrobial experiments of seven vinyl sulfonyl fluoride functionalized fluoroquinolone drugs indicated that their antibacterial activities against MRSA and SA were equal or enhanced compared with their parent drugs. Notably, the vinyl sulfonyl fluoride functionalized norfloxacin **3ak**, ciprofloxacin **3am**, and lomefloxacin **3an** exhibited 4-fold improved antimicrobial activity against Gram-positive bacteria. Further explorations of this method for synthesizing *N*-ESF compound libraries for medicinal application are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01360.

General methods, synthetic procedures, and characterization (PDF)

Accession Codes

CCDC 1941924 contains 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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[§]J.L. and W.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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