HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2023 January 27.

Published in final edited form as:

Angew Chem Int Ed Engl. 2021 September 20; 60(39): 21195–21199. doi:10.1002/anie.202105583.

Fluorosulfuryl Isocyanate Enabled SuFEx Ligation of Alcohols and Amines

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Abstract

Fluorosulfuryl isocyanate (FSI, FSO_2NCO) is established as a reliable bis-electrophilic linker for stepwise attachment of an alcohol bearing module to an amine bearing module and thence a new module RO-C(=O)-NH-SO_2-NR'R" is created. FSI's isocyanate motif fuses directly and quickly with alcohols and phenols, affording fluorosulfuryl carbamates in nearly quantitative yield. A new reagent and process to deliver the FSI-derived fluorosulfuryl carbamate fragment to amines are also developed. The resulting S^{VI}-F motifs from step-1 are remarkably stable, given the great

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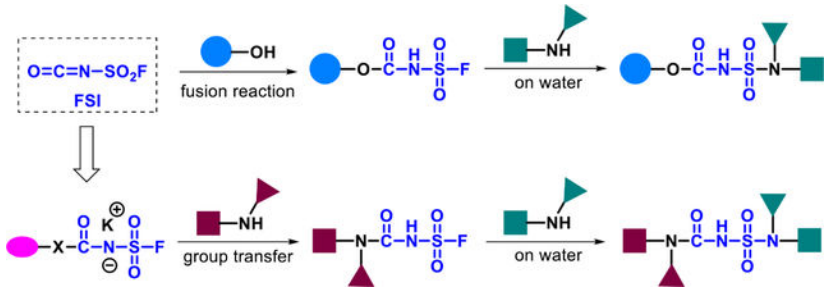
Conflict of interest
The authors declare the following competing financial interest(s): Shanghai Institute of Organic Chemistry, CAS, has filed a patent application on fluorosulfosuccinic hydroxylimide salt and its applications.

structural complexities in diverse products. In the step-2 reaction with amines, the best yield of the S-N linked products arise with water alone. This “on water” interfacial reactivity phenomenon is crucial, revealing the latent reactivity of S^{VI}-F probe for potential covalent capture of proteins in vivo which is important in today’s drug discovery. The scope of the SuFEx chemistry is largely expanded thereby and the facile entry to these phosphate-like connections should prove useful to click chemistry across diverse fields.

Graphical Abstract



SuFEx Ligation on Water: Fluorosulfuryl isocyanate (FSI, FSO_2-NCO) is established as a reliable bis-electrophilic linker for stepwise attachment of alcohol and amine bearing modules. In step-1, FSI’s isocyanate fuses directly and quickly with alcohols and phenols, and aliphatic amines are attached through the sulfuryl carbamate transfer strategy, both with remarkable selectivity. In step-2, best yields of S-N linked products arise with a unique on water process. The scope of SuFEx ligation is greatly expanded in directions which would be especially interesting for drug discovery and chemical biology.

Keywords

Click Chemistry; SuFEx reaction; Fluorosulfuryl Isocyanate; on water; Carbamate; Urea

Generating substances through modular synthesis accelerates the screening and discovery of functions. Over the last two decades, the central theme of click chemistry was to explore good reactions that meet the stringent requirements of modular synthesis, such as simple operation, inoffensive product, high selectivity and efficiency.[1] These reactions have found wide applications in materials science,[2] chemical biology,[3] medicinal chemistry, *etc*.[4] The sulfur(VI) fluoride exchange (SuFEx) click reaction was recently introduced,[5] and quickly its robust utility has been demonstrated.[6] In a typical SuFEx protocol, substrates are modified by a small linker, such as CH_2=$CHSO_2F$,[7] SO_2F_2,[5] SOF_4.[8] The resulting S^{VI}-F handles enable a second and even a third ligation through defluorination substitution with another nucleophiles.[5] The success of SuFEx ligations has exquisite requirement for the reaction environment due to the unique reactivity of S^{VI}-F handles. It has been demonstrated in chemical biology events where SuFEx handles serve as “warheads” for covalent capture of proteins.[6c,6d]

To expand the SuFEx platform, we are looking for new linker capable of diverse connections. The fluorosulfuryl isocyanate (FSI) draws our attention because of its versatile

chemistry empowered by the "O=C=N" cumulene motif.[9–12] The reaction between isocyanate and nucleophiles R-XH (X = O or NR') is zero waste-emission. Meanwhile, a "-SO_2F" group is delivered to the targeted substrates that allows for further connection. Modules including alcohols (not well suited to previous SuFEx ligations, Figure 1), phenols, and amines are abundant with great structural diversity. The sulfuryl carbamate and urea adducts are also potential phosphate mimics because they are chemically and physically (*pKa* value) alike, and these features are essential for fundamental functions in life systems (Figure 1).[13]

First reported in 1950s, FSI is derived from chlorosulfuryl isocyanate (CSI) through halogen exchange reaction.[14] Subtle reactivity difference between these two molecules could be found in Graf's early remarks, quote, "It (FSI) can in principle be used in the same way as CSI, but generally reacts a little more slowly. The *N*-sulfonyl fluorides obtained in the reaction with FSI are generally much more stable to hydrolysis and to heat than the *N*-sulfonyl chlorides."[15,16] Indeed, this feature is what SuFEx chemistry appreciates as has been discussed in our 2014 manuscript.[5] Herein, we revisited the reactivity of FSI, aiming to develop a modular SuFEx ligation process.

We prepared FSI on half kilogram scale by refluxing CSI with excess sodium fluoride in neat (b.p. 62–65 °C, Supporting information S4).[17] It is moisture sensitive but thermally stable up to 300 °C.[18] Alkyl and phenyl isocyanates could react with alcohols to afford carbamates with the aid of tertiary amines as base and catalyst.[9b,19] But FSI is more reactive because of the strong electron-withdrawing sulfonyl fluoride group, thus direct reaction with alcohols gave nearly quantitative yields within minutes in cold acetonitrile.[14] The selectivity of FSI for aliphatic alcohol groups (1°, 2°, and even 3°, Table 1) over other functional groups we found to be extraordinary. With substrates bearing a tertiary amine, inner salts precipitated instantly upon the addition of FSI, due to the low *pKa* of the resulting carbamates.[14b] Using this precipitation process, we were able to get a group of bioactive compounds modified and purified simply through filtration (**2–13** – **2–16**).

Phenols were reported to react with CSI, giving RO-SO_2-NCO as the major product through cleaving the S^{VI}-Cl bond at elevated temperature.[15] But only RO-$CONHSO_2F$ carbamate was obtained under identical reaction conditions with FSI, a clear evidence for the special stability of the S^{VI}-F bond. Selective modification of alcohol over phenol gave adduct **2–17** with one equivalent of FSI. On the other hand, the difunctionalized product **2–18** could be obtained when two equivalents of FSI were employed. Full conversion of bioactive diols and triols to the fluorosulfuryl carbamates were also realized with excess amounts of FSI (**2–21** – **2–26**).

The direct reaction between anilines and FSI worked well and afforded fluorosulfuryl ureas in good to excellent yields (Supporting information S28).[20] But primary and secondary aliphatic amines generally gave mixtures. On the other hand, some tertiary amines afforded zwitterions with isocyanates. These zwitterions were reported as key intermediates in the isocyanate dimerization or polymerization,[17,19] and they were also able to transfer the carbamate fragment to another nucleophiles under certain circumstances.[21] Rolf *etc.* prepared a few zwitterions from FSI, but did not investigate their synthetic utility.[22] We

envisioned these salts might be useful to modify primary and secondary aliphatic amines by taking advantage of the carbamate group transfer event.

A series of addition adducts from FSI and ligands were prepared accordingly (Table 2). Although many decomposed at their melting points, most salts were bench-stable for months. We then evaluated their carbamate transfer ability with primary and secondary amines. The potassium salt **4–2** proved to be the most promising candidate. With slight excess amounts of **4–2** in acetonitrile, various amines were converted to ureas in good to excellent yields (Table 3). The ligation was highly selective for amines over other functional groups, such as carboxylic acid, alcohol, phenol, indole, alkene, and alkyne. The drugs Linagliptin (**6–8**) and Alogliptin (**6–9**) were readily modified in this manner.

Both sulfuryl carbamate and urea (-$CONHSO_2X$, X = F, Cl) undergo deprotonation in the presence of base due to the low *pKa* of the N-H bond. The chlorosulfuryl motif would then eliminate chloride to afford an azasulfene (-$N{=}SO_2$) that is highly reactive and liable to hydrolysis. Therefore, anhydrous reaction conditions are usually used for its step-2 ligation with nucleophiles.[23–25] In contrast, the fluorosulfuryl motif would remain relatively stable. No ligation was observed even when it was treated with ArOTBS and DBU in dry acetonitrile.[5]

After extensive screening of the reaction conditions, we found substitution of the S^{VI}-F with amines could be achieved on water (Table 4).[26,27] The functional group compatibility was excellent on both sides of the substrates, such as the carboxylic acid (**9–1**), heterocycles (**9–2**), alcohols (**9–2**, **9–6**), olefins (**9–4**, **9–5**), and the cyano groups (**9–10**). Aniline (**9–6**) and hydrazine derivatives (**9–9**) also afforded the desired ligation with high efficiency. This would be highly valuable for drug conjugation.[28] Meanwhile, fluorosulfuryl carbamates and ureas share similar features with phosphate which are important for fundamental functions in life systems.[13] They were both acidic with *pKa* values around 2.0,[14b] relatively stable but remained active for further ligation with water as supporting medium. In this context, it is intriguing to further explore the fluorosulfuryl carbamates and ureas as phosphate mimics and covalent probes in drug discovery and chemical biology.[29]

To summarize, fluorosulfuryl isocyanate (FSI) is shown to be an outstanding SuFEx linker in stepwise unions of alcohol and amine modules, which are among the most available functional groups. This binary connection sequence exhibits near perfect efficiency complementation to the sulfamide and related libraries made [6c–6f,8] In any case, FSI seems to have been left aside because CSI is so useful already. But the chlorosulfuryl carbamoyl adducts are far less stable than their FSI counterparts. The step-2 defluorinative amminolysis reaction runs on pure water. Implications of these results are listed but not limited to: rapid access to direct-to-screen sulfamide-like chemical libraries, drug conjugation, chemical probes for covalent capture of proteins, and phosphate mimics. All together, we believe the FSI-derived SuFEx ligation would be of general interest in diverse fields.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The work conducted at Scripps Research Institute by K.B.S. and B.G. was supported by the National Institutes of Health R01GM117145. J.J.D. thank the Shanghai Science and Technology Committee(18JC1415500, 18401933502), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20020300), the Key Research Program of Frontier Sciences (CAS, Grant No. QYZDB-SSWSLH-028) for financial support.

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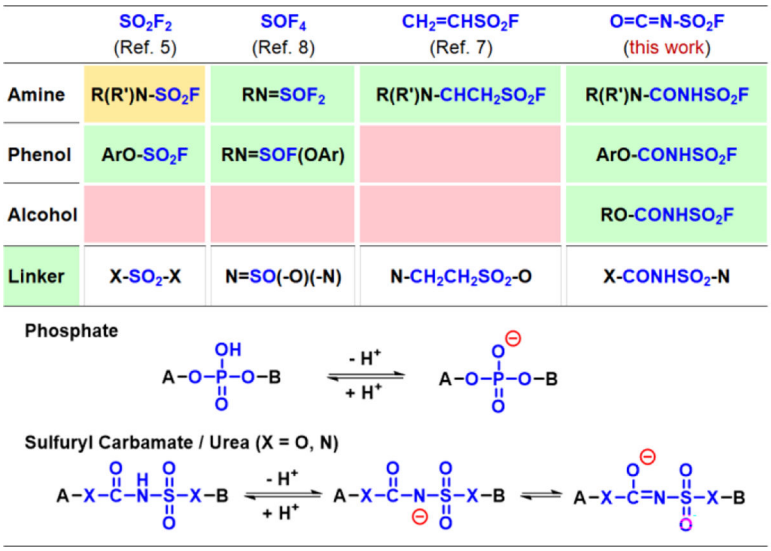


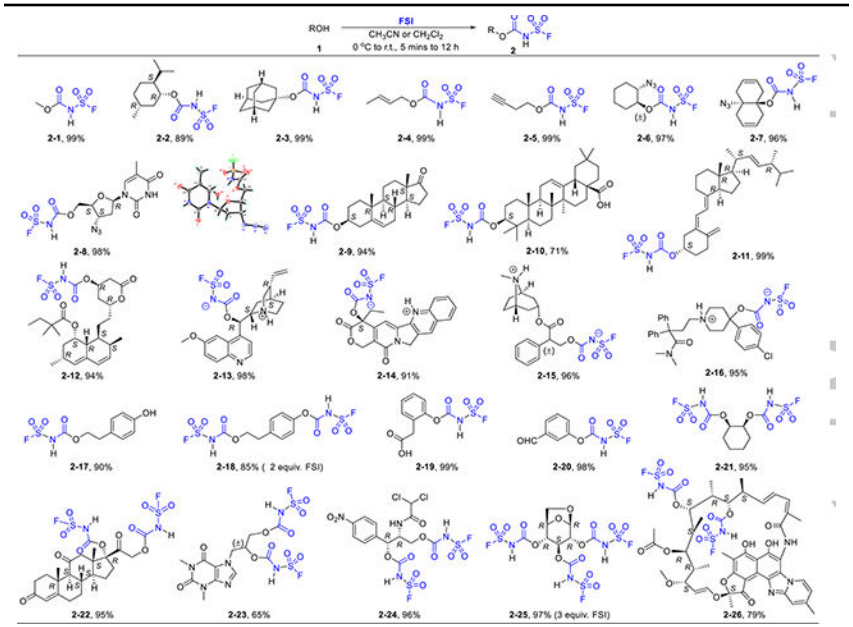
Figure 1.

Summary of SuFEx linkers, scopes and their properties (colors of each column reflect the ligation efficiency. Red represents inferior reactivity, green represents excellent, and yellow represents limited substrate scope).

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2023 January 27.

Table 1

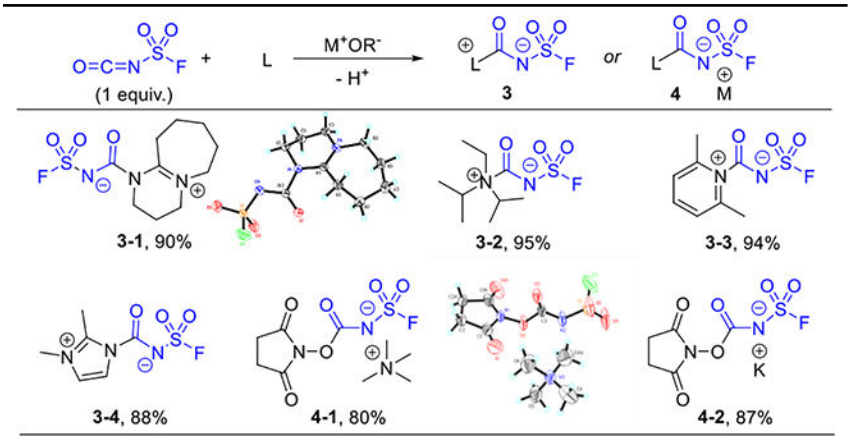
Step-1 direct ligation of alcohols and phenols with FSI.



[a]Reaction conditions: ROH (1.0 equiv), FSI (1.0 equiv, and 2.0 equiv FSI for diols), CH_3CN (or CH_2Cl_2), 0 °C to r.t., 5 mins to 12 h.

Table 2

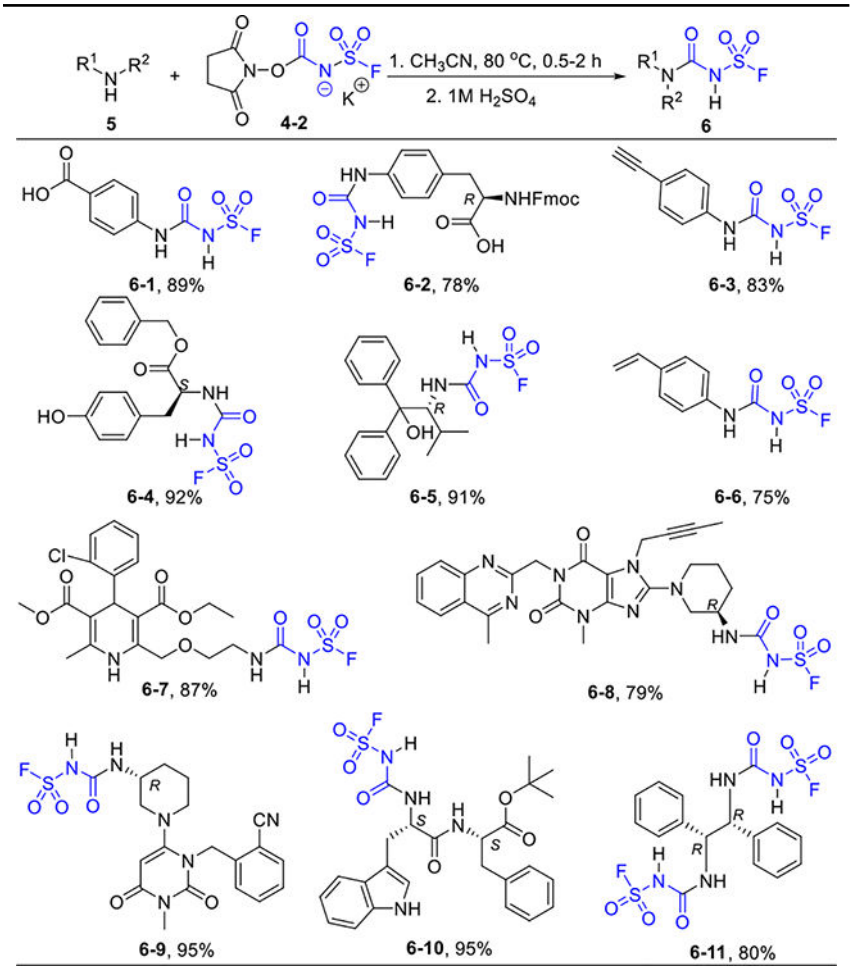
Salts formed between FSI and ligands (L).[a]



[a]**FSI** (2–5 mmol), L (1 equiv.), 1 mol/L in CH_2Cl_2 or toluene, 0 °C to r.t., 2 h.

Table 3

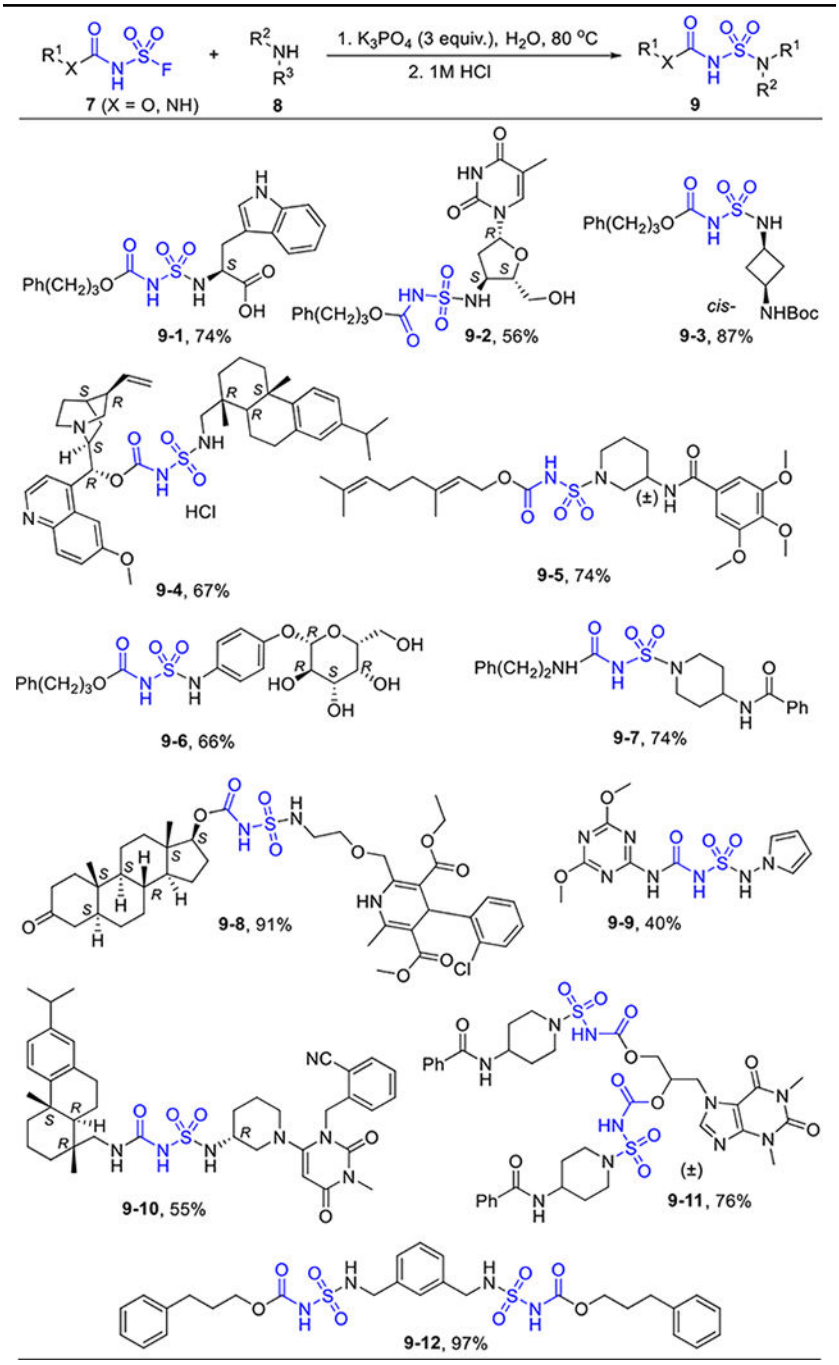
Step-1 amine modification by salt 4-2.[a]



[a] **5** (0.5–1.0 mmol), **4-2** (1.2 equiv), 0.2 mol/L in CH_3CN, 80 °C, 0.5–2 h.

Table 4

Step-2 SuFEx ligation with amines on water.[a]



[a] **7** (0.25–0.5 mmol), **8** (1.5 equiv), K_3PO_4 (3.0 equiv), H_2O (0.25 mol/L), 80 °C, 2–16 h.