Poster

Ex situ Generation of Thiazyl Trifluoride (NSF_3) as a Gaseous SuFEx Hub

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Sulfur(VI)-fluoride exchange, so-called SuFEx, is an all-encompassing term for substitution events that replace fluoride at an electrophilic sulfur(VI), allowing rapid and flexible assembly of linkages around a S^{VI} core.

In the late 1990s, many key articles on activity-based protein profiling (ABPP) were published, highlighting its ability to detect active enzymes in complex proteomes like cell lysates or whole cells.[1,2] As ABPP technologies became more widespread, there's a growing need for a diverse library of activity-based probes (ABPs) with varying reactivity and specificity. The S-F containing modulators are the new generation of warheads, like Sulfonyl fluorides, Aryl fluorosulfates, and Sulfuramidimidoyl fluorides, offering the advantage of enabling covalent modification of protein pockets without targeting cysteines. SuFEx chemistry, which involves these compounds, is noteworthy for its proximity-driven reactivity, meaning SuFEx reagents will not react with targets unless the fluoride groups are activated through proper solvation.

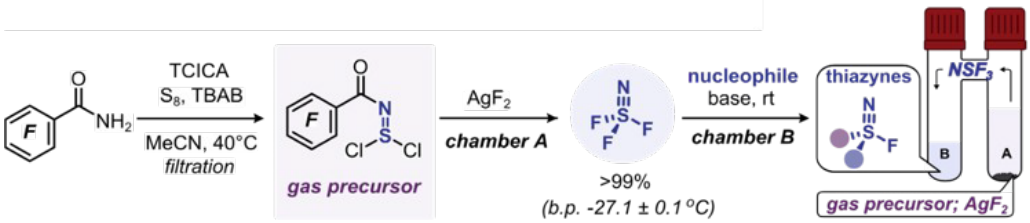

Fig. 1 The ex situ Generation of Thiazyl Trifluoride (NSF_3) as Gaseous SuFEx Hub

To date, more and more nucleophiles and applications have been discovered that can be used in SuFEx chemistry, but the thiazyl unit has not been investigated and could equally serve as a highly versatile new SuFEx hub. With room for three single-bonded substituents, it has potential to be an excellent parent compound to mono- and multi-substituted thiazynes. We have developed a two-chamber procedure for the efficient and safe ex situ processing of thiazyl trifluoride gas (NSF_3) as a new type of SuFEx hub (Fig. 1).[3] Gaseous NSF_3 evolved in a nearly quantitative fashion from commercial reagents at ambient conditions. A variety of mono- and di- substituted derivatives were built selectively. Phenolic and amine substituents were introduced to obtain several unsymmetrically disubstituted thiazynes. To confirm the structures and determine the geometrical details of the S≡N moiety, three thiazynes were characterized via X-ray diffraction (Fig. 2). We expect that the ex situ gas production approach will expand the usage of NSF_3 in lab-scale synthesis, especially in producing mono-substituted thiazynes that can then be explored as SuFEx electrophiles in various transformations.

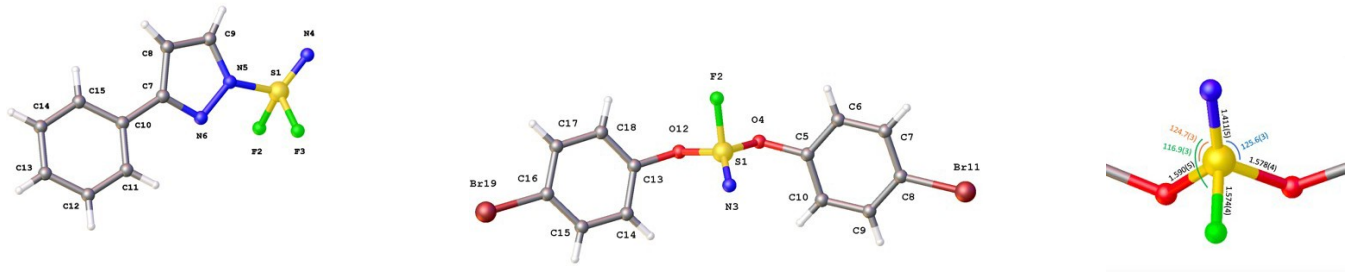

Fig. 2 Crystal structures of mono- and di-substituted thiazynes with geometrical details of the NSO_2F fragment

[1] Y. Liu, M. P. Patricelli. & B. F. Cravatt, (1999). *Proc. Natl. Acad. Sci. U. S. A.,* **96**, 14694-14699.
[2] D. Greenbaum, K. F. Medzihradszky, A. Burlingame, M. Bogyo, (2000). *Chem. Biol.,* **7**, 569-581.
[3] B. Li, K. Su, L. Van Meervelt, S. H. L. Verhelst, E. Ismalaj, W. M. De Borggraeve and J. Demaerel, (2023). *Angew. Chem. Int. Ed.*, **62** (29), e202305093.