Deoxyfluorination Reagents from 1999-Present

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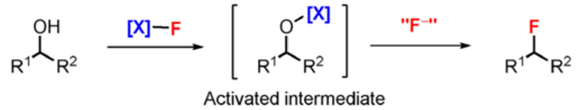
Abstract

One way to accomplish late-stage fluorination of bioactive molecules is via deoxyfluorination. Several reagents have been created with the purpose of achieving deoxyfluorination of a wider variety of substrates than available and to improve upon the various faults of their predecessors. This poster aims to explore the chronological development of some deoxyfluorination reagents from 1999 to the present including their advantages and disadvantages, mechanistic insights, scope, and practical applications.

Introduction

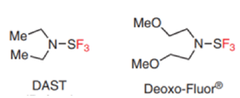
Incorporating fluorine into molecules is advantageous due to fluorine's ability to modulate a molecules chemical and physical properties including the acidity, lipophilicity, metabolic stability, and blood-brain barrier penetration of bioactive molecules. One way to accomplish late-stage fluorination of molecules is via deoxyfluorination.[1] In this method, a leaving group is attached to an oxygen to activate it followed by nucleophilic attack by fluoride in an Sn2 fashion, producing a C-F bond in the place of the C-O bond. A number of reagents have been created to achieve deoxyfluorination of a wider variety of substrates and to improve upon the various faults of their predecessors. This poster aims to explore the chronological development of a few deoxyfluorination reagents from 1999 to the present including their advantages and disadvantages, mechanistic insights, scope, and practical applications.

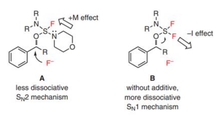


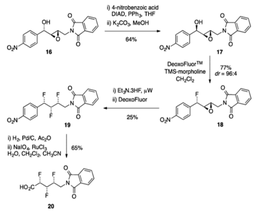
Discussion

DeoxoFluor

DeoxoFluor was developed in 1999 as a thermally stable alternative to DAST via coordination of the methoxy side chains to the sulfur. It does, however, require the use of a TMS amine to suppress Sn1 side reactions. The scope includes benzyl and secondary alcohols and possesses special applications in the production of polyfluorinated molecules.



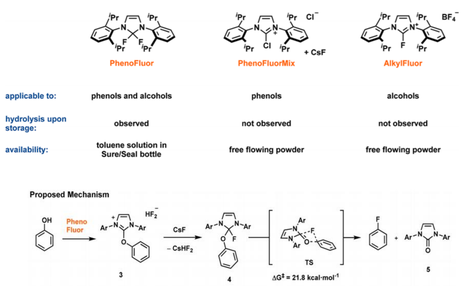




Discussion

The PhenoFluor Reagents

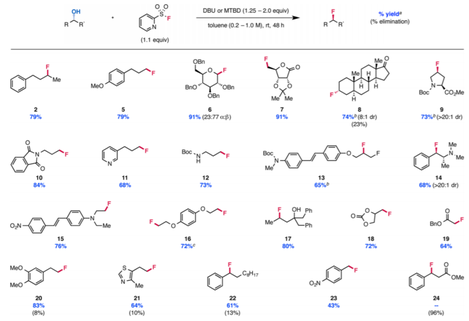
Invented in 2013, these reagents are functionally group tolerant, have no side reactions, and are stable upon heating. PhenoFluorMix overcomes the challenges that PhenoFluor faces including hydrolysis, inconvenient storage (in N_2) and lack of availability but doesn't stereospecifically fluorinate alcohols, which AlkylFluor overcomes.

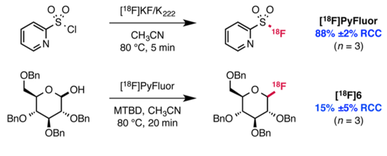


Interestingly, PhenoFluor mediated deoxyfluorination proceeds via a concerted nucleophilic aromatic substitution pathway in which nucleophile attack and leaving group loss happen concurrently. This results in a limited build up of charge on the aromatic core in the transition state and a single lower activation barrier accessible to electron-rich phenol substrates.[2]

PyFluor

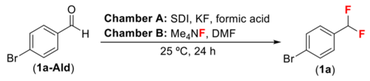
PyFluor was designed in 2015 as a stable, cheap, safe, and highly selective reagent. PyFluor does require the use of strong exogenous bases which create elimination side products and requires long reaction times(48 hours). PyFluor allowed for the first incorporation of radioactive fluorine via deoxyfluorination, the products of which are useful in PET imaging.[3]

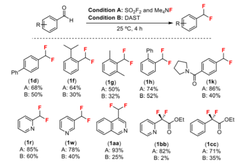




SO_2F_2 and Me_4NF

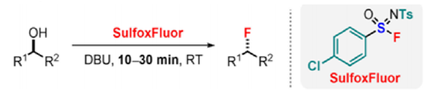
Introduced in 2017, these reagents function by reacting phenol derivatives (ArOHs) with SO_2F_2 to form aryl fluorosulfonate(ArOFs) which are then reacted with Me_4NF to form the desired aryl fluoride product. As SO_2F_2 is a toxic gas, a 2-chamber system for the ex situ production of SO_2F_2 was developed. The scope of the reaction includes a wide variety of benzaldehydes including ortho substituted arenes, aryl and heteroaryl aldehydes, pyridine, quinoline, α-ketoesters, and isoquinoline carboxaldehydes.[4]

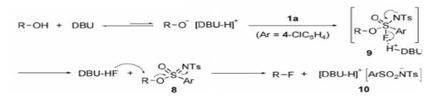


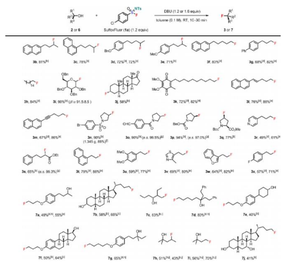


SulfoxFluor

Created in 2019, SulfoxFluor is a suflonimidoyl fluoride type reagent, the nitrogen and sulfur of which give it increased modulation potential and it possesses a wide scope. SulfoxFluor is highly selective against elimination due to the high electrophilicity of sulfonimidate ester intermediates which accelerate the nucleophilic attack.[1]







Conclusions

The development of new deoxyfluorination reagents has continued to allow for access to a wider variety of substrates in safer and unique ways, broadening their applications in drug development.

References

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Acknowledgments

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