Electrophilic Fluorination

Abstract

This review article discusses the progress made in the synthetic methods for various electrophilic fluorination and trifluoromethylation reagents. Common electrophilic fluorination reagents include N-Fluorobenzenesulfonimide (NFSI) and Selectfluor. Common electrophilic trifluoromethylation reagents include Togni's reagent and Umemoto's reagent.

Introduction

Introducing fluorine atoms and CF_3 groups to organic compounds and ligands can be useful for applications in medicinal chemistry and agrochemicals. Incorporating fluorine atoms into organic molecules can alter their properties such as affecting their metabolic stability, cellular permeability, lipophilicity, and water solubility[1]. For instance, organofluorine compounds are useful since they have high stability and solubility properties for pharmaceutical applications. Similarly, incorporating CF_3 into molecules also endow unique properties on them such as high lipophilicity and stability[2]. Thus, adding fluorine atoms and CF_3 groups to common drug moiety's is an important synthetic endeavor. Of the various methods for fluorination and trifluoromethylation (nucleophilic, radical, electrophilic), electrophilic has been the least explored but strides have been made in recent years. For example, the synthetic methods for various electrophilic fluorination and trifluoromethylation reagents have been improved and the scope of substrates has also been widely expanded in recent years.

Results

Electrophilic Fluorination

One common electrophilic fluorinating reagent in use in recent years is N-Fluorobenzenesulfonimide (NFSI) (Fig. 1). Although it is a mild fluorinating reagent, it has a large substrate scope and has been used for the fluorination of a variety of organic and organometallic compounds.

Using NFSI a 2012 paper by Lim et al. reported the synthesis of 3,3-difluoro-2-oxindoles directly from indoles via electrophilic fluorination[3]. Under the optimized conditions, various N-substituted indoles and N-benzylindoles were explored. In general, benzyl group protecting groups had moderate to high yields regardless of the substitutions on the ring. N-aryl indoles underwent the fluorination reaction slowly but gave moderate yield. However, free indoles or indoles containing electron-withdrawing N-protecting groups only gave trace amounts of the difluorinated products.

Many of the N-benzylindoles gave moderate to high yields of the corresponding difluorinated products. The reaction tolerated a variety of functional groups including bromide, nitro, ketone, nitrile, etc. However, substrates with electron-withdrawing substituents required higher temperatures to be difluorinated. Substrates with electron-donating groups had moderate yields. The one functional group that was not tolerated was the hydroxyl group.

Another common electrophilic fluorination reagent is Selectfluor (Fig. 1). For instance, in 2017, Kim et. al reported the synthesis of (−)-6′-β-Fluoro-aristeromycin via a stereoselective electrophilic fluorination reaction using Selecfluor[4]. This compound is a substituted analogue of (−)-Aristeromycin, which has been shown to be a potent inhibitor of S-adenosylhomocysteine (AdoHcy) hydrolase as well as having antiviral properties against many RNA and DNA viruses. The analogue (±)-6′-β-fluoro-aristeromycin has also demonstrated inhibitory activity against AdoHcy hydrolase. However, synthesis of the optically pure (−)-6′-β-fluoro-aristeromycin is desired since only the D-isomer has biological activity.

Electrophilic Trifluoromethylation

In recent years a popular electrophilic trifluoromethylation reagent has emerged called Togni's reagent which is a class of compounds that are hypervalent iodine reagents (Fig. 2).

In 2008 Stanek, Koller, and Togni reported the electrophilic trifluoromethylation of phenols which in notable since phenol derivatives are highly valuable in pharmaceutical synthesis[5]. Various other substituted phenols were explored. The experiments with the model substrate showed that the oxidized products were only accessible when both the ortho and para products were occupied. Otherwise, trifluoromethylation occurred at the ortho or para positions on the ring. They also found that bistrifluoromethylation was possible with substrates such as 4-tert-butyl phenol and 5-indanol. Lastly, 2,4,6- trimethylphenol was reacted with Togni's reagent which gave a product for which trifluoromethylation occurred at the benzylic position. However, this same reaction was not observed with electron-poor substrates like 4-nitrotoluene.

Another common trifluoromethylating reagent is Umemoto's reagent (Fig. 3) which is often used in place of Togni's reagents. For instance, Deng et al. reported the enantioselective Cu-catalyzed trifluoromethylation of β-Ketoesters using commercially available reagents, specifically Umemoto's reagent and Togni's reagent[6].

Under the optimized conditions, using Umemoto's reagent the scope of the substrate was expanded to various five- or six-membered rings. Notably, the five-membered rings had better yield when reacted with Togni's reagent. In general, indanone-derived tert-butyl β-ketoesters had high yields and enantioselectivity regardless of the position of the substituents. In addition, high enantioselectivity and yield was obtained with substrates containing electron-withdrawing or donating groups on the aromatic ring. Various other substituents were explored and had moderate to high yields.

For six-membered ring substrates, enantioselectivity and yield were enhanced with Umemoto's reagent. Tetralone-derived tert-butyl and cyclohexenone-derived tert-butyl β-ketoesters had high yields and enantioselectivity. However, acyclic ketoesters were unreactive under these reaction conditions. Lastly, with the trifluoromethylated products obtained, they were able to be further transformed to α-CF3 β-hydroxyesters by reacting them with Grignard reagent. These products were obtained with high yield and high diastereoselectivity.

Results

Figures

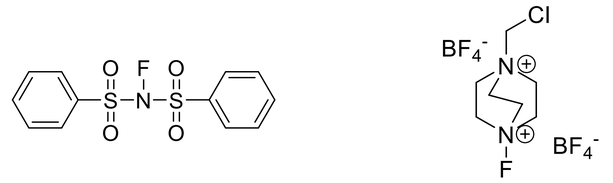

Fig. 1 Two common electrophilic fluorination reagents: N-fluorobenzenesulfonamide (NFSI) (left) and Selectfluor (right).

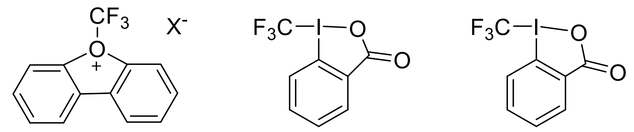

Fig. 2. Common trifluoromethylation reagents (Togni's reagents).

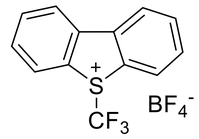

Fig. 3. Common trifluoromethylation reagent (Umemoto's reagent).

Conclusions

In recent years large developments have been made in improving the synthesis and efficacy of electrophilic fluorination and trifluoromethylation reagents as well as a large expansion in the application of these reagents. Common electrophilic fluorination reagents were used to fluorinate a variety of substrates including imidazole derivatives, indoles, alkenes, and even organometallic complexes. For electrophilic trifluoromethylation common reagents were used for the trifluoromethylation of substrates including arenes, heteroarenes, benzyl bromides, phenols, and quinones.

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