Simple Synthesis of Fluoroorganic Compounds

Mieczysław Mąkosza*

Institute of Organic Chemistry, Polish Academy of Sciences, Europe

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*Corresponding author: Mieczysław Mąkosza, Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa, Poland, Europe, Email: info@icho.edu.pl

Mini Review

Introduction of fluorine into organic molecules changes their physical, chemical and biological properties, often in desired way, hence most of the new pharmaceuticals contain fluorine [1]. It is therefore evident that methods of synthesis of fluoroorganic compounds are of continuous great interest. There are two major approaches to this goal: introduction of fluorine atom via replacement of hydrogen or other substituent’s in a molecule and introduction of fluorocontaining substituents.

Fluorine can be introduced into organic molecules via nucleophilic, electrophilic and radical mechanisms. Particularly important and simple is nucleophilic replacement of halogens or sulfonates by fluorine anions readily available in form of KF. The most convenient and efficient methodology for nucleophilic substitution with inorganic and organic anions is phase-transfer catalysis, PTC. The key feature of this methodology is continuous introduction of the reacting anions into organic solvents in form of lipophilic ion-pairs with lipophilic cations of the catalyst, most often tetra alkyl ammonium cations [2,3]. Unfortunately use of this efficient methodology for the reactions of fluorine anions encounters difficulties, because they are of low lipophilicity. Moreover fluoride anions are highly basic, hence nucleophilic substitution is often accompanied by base induced β-elimination E2 that dominates in the case of secondary halides or sulfonates. These difficulties are solved by use of triphenyl tin fluoride or chloride) reacts with solid powdered KF and tetra alkyl ammonium halide (Q X) in acetonitrile to form soluble lipophilic ion-pairs of hipervalenttriphenylin difluoride anion with tetraalkylammonium, Q’cation. In this form this hipervalent anion reacts with alkylhalides or sulfonates to form alkyl fluorides, triphenyl tin fluoride and Q’X. This catalytic cycle proceeds many times, so less than 5% molar of the both catalysts are sufficient for full conversion of alkyl halides or sulfonates into fluorides. Since the substitution proceeds with fluorides that are form of hypervalent tin anions, they do not behave as basic agent and undesired β-elimination does not proceed [4].

Of particular importance is introduction of fluorinated or perfluorinated substituent into carbo- and heterocyclic aromatic rings [5]. Most of such reported processes are catalyzed by transition metals hence are of limited use for synthesis of pharmaceuticals.

For many years we have developed efficient procedures for introduction of functionalized substituent’s into electron-deficient arenes and heteroarenes via nucleophilic substitution of hydrogen – oxidative nucleophilic substitution ONSH and vicarious nucleophilic substitution VNS [6]. Application of these reactions for perfluorocarbanions, e.g. for CF3–, generated from the Ruppert reagent, CF3SiMe3 was limited due to low nucleophilic of this anion. Nevertheless in the reaction with highly active nitroarenes e.g. m-cyan nitrobenzene or m-dinitrobenzene ONSH with CF3–carbanions proceed, Scheme 2 [7].

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Much more efficient and valuable are reactions of perfluorocarbanions with highly active azinium salts. Thus
N-benzyl and particularly N-p-methoxybenzylpyridinium, quinolinium, isoquinolinium etc. salts when treated with the Ruppert reagents in the presence of F\(^{-}\) anions add CF\(_3\) carbanions to form stable dihydroazines. Further oxidation with cerium ammonium nitrate, CAN, results in rearomatization and removal of the benzyl substituent’s to give trifluoromethyloxazines, Scheme 3 [8].

Perfluoroalkyl carbanions can be generated via addition of F\(^{-}\) anions to perfluoroalkenes. For instance exposition of readily available perfluoropropene to anhydrous KF in methylene dichloride results in reversible addition of F\(^{-}\) anions, thus some amount of potassium perfluoro-isopropyl carbanion is generated in the solution. The anions add to N-benzyl azinium salts to form stable perfluoro-iso-propyl dihydroazines. Due to large size of this carbanion the addition proceeds at positions 2-(ortho) and 4- (para) of the salts. Oxidation of these dihydroazines results in rearomatization and removal of the N-benzyl substituent’s, Scheme 4 [9].

Particularly valuable are syntheses of esters, amides and other derivatives of 2-azino-perfluoropropionic acids via 1,3-dipolar cycloaddition of azine-N-oxides to perfluoroalkenes. For instance exposure of readily available perfluoroalkenes to anhydrous KF in methylene dichloride results in reversible addition of F\(^{-}\) anions, thus some amount of potassium perfluoro-isopropyl carbanion is generated in the solution. The anions add to N-benzyl azinium salts to form stable perfluoro-iso-propyl dihydroazines. Due to large size of this carbanion the addition proceeds at positions 2-(ortho) and 4- (para) of the salts. Oxidation of these dihydroazines results in rearomatization and removal of the N-benzyl substituent’s, Scheme 4 [9].

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Azine N-oxides are analogues of aliphatic nitrones, thus nitrones can also enter 1,3-dipolar cycloaddition to perfluoroalkenes to form oxazolidines. These oxazolidines are sufficiently stable to be isolated. Upon hydrogenation N–O bond is broken to form fluorides of fluorinated β-amino acids. These fluorides cyclized in situ giving β-lactams. When the hydrogenation is carried out in acid medium, in alcohols, esters of fluorinated β-amino acids are produced Scheme 6, [11].

α-Fluoro-α-aryl acetic acid esters are interesting and versatile starting materials for further synthesis. Usually they are prepared in a complicated way [12,13]. Much simpler synthesis of this kind of compounds is vicarious nucleophilic substitution of hydrogen in nitroarenes and nitroheteroarenes with carbanions of alkyl chlorofluoroacetates generated by simple deprotonation of the commercial product, Scheme 7 [14]. In the paper are presented simple processes for synthesis of a wide variety of fluoroorganic compounds. It should be stressed that the presented reactions proceed without transition metal catalysts, thus the products can be directly used for synthesis of pharmaceuticals, without meticulous purification.

**Reference**