A Single Step Polyfluoroarylation of Amides

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Abstract: Per- and polyfluoroarenes are important synthetic chemistry targets because they are active components in many pharmaceuticals, agrichemicals, and industrial manufacturing products. Many of the current methods of synthesizing these fluoroarenes involves selectively adding fluorines one at a time. These procedures are rudimentary and often demand long and harsh reaction conditions and often result in poor yields. Novel substrates can be reached, however, through selective hydrodefluorination or functionalization, i.e. fluorine sculpting. This research compliments recently developed chemistry which synthesizes starting material fluoroarenes in two steps by shortening the synthesis by 50%. This chemistry utilizes nucleophilic aromatic substitution to synthesize per- and poly-fluoroaryl amides in a single step under mild reaction conditions which can then be utilized for fluorine sculpting.

Keywords: Polyfluoroarylation, Amides, SNAR, organofluorines, Fluorine

Introduction

Organofluorines, compounds with one or more carbon-fluorine (C–F) bonds, are important synthetic chemistry targets, because they are active components in many pharmaceuticals, agrichemicals, and industrial manufacturing products (Weaver and Senaweera 2014). The high electronegativity of the fluorine element allows it to form strong bonds with carbon, which contributes to the diverse uses of organofluorines in various fields (O'Hagan 2008). At least 20% of pharmaceuticals on the market contain fluorine. These drugs fill a variety of roles, acting as anti-inflammatories, antacids, antidepressants, cholesterol regulators, and antibiotics. (O'Hagan 2010). Their uses make them both economically and socially impactful, and therefore, it is important to understand how to best utilize them.

Chemists have not fully explored the functionalization and activation of these compounds, largely because currently synthetic chemists' ability to synthesize organofluorines is rudimentary (Day and Weaver 2017). Most of the current synthesis methods involve multiple steps, often require harsh or expensive reaction conditions that result in moderate or poor percent yields (Day and Weaver 2017), and make regioselectivity – the ability to place molecules in a desired location- (which is crucial to the function) difficult (Khaled et. al 2017). The shortcomings of current methods make organofluorines expensive to develop in terms of both time and costs, and consequently, investigations of the fluorinated chemical space of biologically active compounds is incomplete, meaning that the drugs that are emerging at the end of the drug development campaign are incomplete. In fact, it is possible that the optimal drugs have yet to be synthesized (Weaver personal communication, October 2018). Finding new straightforward ways to synthesize existing and new organofluorines in a more efficient manner with a higher percent yield is important in realizing the full potential of the functions of organofluorines (Day and Weaver 2017).

A new approach by Dr. Weaver at Oklahoma State University, is to start with a fully fluorinated compound and strategically replace the un-needed fluorines with intended functional groups to form the desired molecule, a technique coined as molecular sculpting (Figure 1). However, the current state of the

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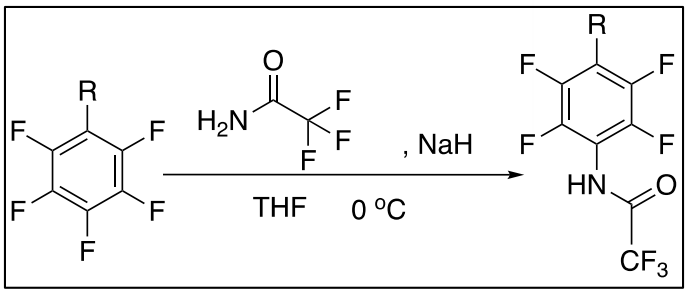

Figure 1: An example of the reactants, products, and conditions of this work.

art synthesis for the starting materials, polyfluoarene amides, used in this process is two steps from commercially available perfluoroarene. Another drawback to the synthesis is the required use of perchloric acid (Khaled et. al 2017), which is highly corrosive and difficult to work with, as it can lead to explosive salts. This research aims to shorten the process to one step, a 50% decrease, and take place under milder and more functional group tolerant conditions.

The literature has established that nucleophilic aromatic substitution (S_NAr) - an addition-elimination reaction that consists of adding a nucleophilic attack onto an electron poor aromatic ring, temporarily dearomatizing the system. The aromaticity is regained when a leaving group is displaced from the same carbon, completing the reaction (Goldstein et. al 2017). The reaction often takes place under mild conditions and produces good to excellent yields (Rodriquez *et al.* 2006). Furthermore, organic chemists have used a S_NAr reaction for the C–F functionalization by nitroalkanes, by applying it to the synthesis of perfluorinated nitroalkanes, resulting in a greater than 99% yield (Day and Weaver 2017). This research shows nucleophilic aromatic substitution is a usable method to achieve the development of synthetic methods for the formation of organofluorines with extremely high percent yields through efficient and cost-effective methods.

The purpose is to develop optimal reaction conditions for the single-step addition of an amide functional group to a polyfluroarene through a S_NAr reaction in order to more fully explore and develop synthetic methods for organofluorines. The basic plan of synthesis is to add a strong base such as sodium hydride (NaH) to an amide, such as trifluoroacetamide (CF_3CONH_2), dissolved in a solvent, such as tetrahydrofuran (THF), to deprotonate (remove a proton from) the amide, so that the amide will bond to the electron deficient aromatic benzene ring of the organofluorine starting material, such as pentafluorobenzonitrile (C_7F_5N), and replace a fluorine to form the intended product.

Methods

The optimization process calls for the continuous variation of reaction parameters, but a basic procedure similar to the methods used in Jon Day and Jimmie Weaver's work with functionalizing nitroalkane group organofluorines (2017) is as follows. First, we measure the needed mass of the base and transfer it to a flame-dried two-necked round bottom flask with a magnetic stir bar. Then, we measure out the needed mass of the amide, and dissolve it in the solvent, obtained using a syringe. Next, we use the syringe to add the amide/solvent solution to the round bottom-flask. Then we allow the mixture to stir on a magnetic stir plate for 20 minutes to provide sufficient time for the base to deprotonate the amide and the mixture to cool to the desired temperature using an ice bath or liquid nitrogen. Then we perform the addition of the polyfluorinated starting material drop-wise, and we allow the reaction to take place while continuously stirring on the stir plate. After the desired amount of time, we remove an aliquot (about 0.1 ml) from the sample and quench it with 0.1M hydrochloric acid (HCl) before preparing a sample for nuclear magnetic resonance spectroscopy (NMR).

Each time a reaction is run we change one independent variable. These variables include the identity of reagents, equivalence, temperature, reaction time, procedure, and exposure to atmosphere. After each reaction we run various tests to evaluate the contents of the completed reaction mixture. Based on

Table 1: Table example of the contents, equivalence, millimoles, and amounts of the reagents in a 50 mg scale reaction.

Name	Molecular Weight (g/mol)	Equivalence	Millimoles	Amount	Density
Pentafluorobenzonitrile	193.08	1	.259	33 µl	1.5
NaH	24	2.15	.557	22 mg	-
Trifluoroacetamide	54.1	2.1	.544	61.5 mg	-
THF	-	-	-	2.6 ml	-

the results of those tests, we alter one of the independent variables to attempt to increase the yield of the intended product, by remedying the limiting factor of the percent yield. We continued this process, meaning we ran many reactions on a small 50 mg scale (table 1) until the procedure was effective, and then we repeat that procedure on a larger scale to test the efficiency of the reaction conditions for industrial purposes.

Table 2: This table shows optimization data of the investigated reaction conditions.

Substrate	Temp °C	Eq. of Base	Eq. of F3 Acetamide	% Conversion
Pentafluoronictrobenzoate	0	2.15	2.1	100
Pentafluorobenzonitrile	-20	2.15	2.1	66
Pentafluorobenzonitrile	-10	2.15	2.1	73
Pentafluorobenzonitrile	-5	2.15	2.1	92
Pentafluorobenzonitrile	0	2.15	2.1	98
3,4,5-Trifluoronitrobenzine	25	2.15	2.1	89
3,4,5-Trifluoronitrobenzine	0	2.15	2.1	33
Pentafluoromethylbenzoate	25	2.15	2.1	48
Pentafluoromethylbenzoate	-10	2.15	2.1	65

Progress to Date

Four different polyfluoroarene substrates have been investigated (Table 2). By running the reaction at 0 ^{0}C, using 1 equivalence of the polyfluoroarene, 2.15 equivalence of the base, 2.1 equivalence of trifluoroacetamide, and THF as a solvent, moderate to good conversion has been achieved for almost every substrate. In pentafluorobenzonitrile, of the 98% of starting material converted, 91% was the intended product. 52% isolation of the product has been achieved without the use of column chromatography (Figure 3). Column chromatography, is a highly useful tool for rapid isolation of material. However, because it does not scale well and we want to be able to produce these starting materials on scale, we have given attention to trying to avoid the use of column chromatography as a means of obtaining isolated material.

Discussion:

This project is still ongoing; however, efficient reaction conditions for the single step addition of an amide to a polyfluoroarene have been developed. These mild reactions conditions promote almost 100% conversion and high yields in the reaction mixture of the intended polyfluoroarene amide products. The

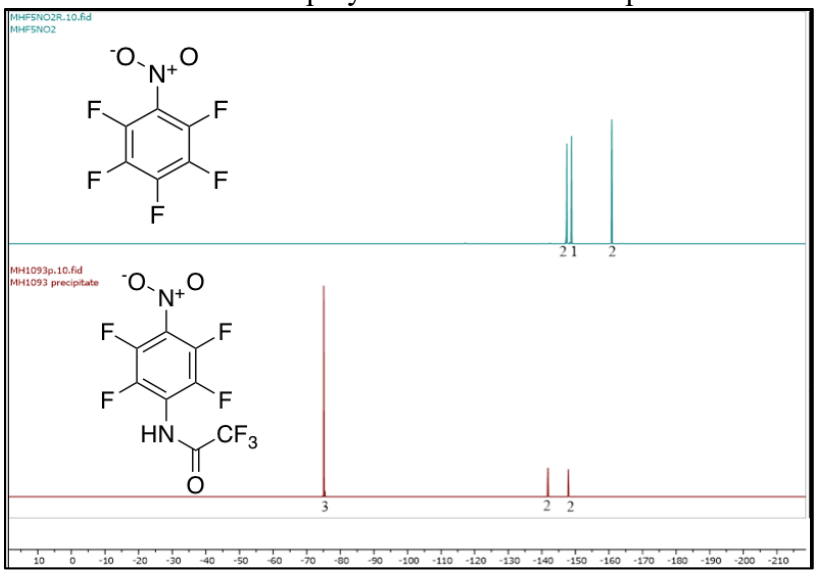

Figure 2: This Fluorine NMR spectra shows starting material fluorines (blue) vs. Isolated product fluorines (red).

mechanism of the reaction begins with the base, NaH, deprotonating the amide. Then the negatively charged amide acts as the nucleophile and undergoes para-substitution with respect to the R group. Para-substitution is preferred over ortho- or meta-substitution because the fluorine at the para position is partially positive, as the R group is electron withdrawing. This leaves the para fluorine slightly electron deficient and allows the nucleophilic aromatic substitution to take place. Two equivalence of the acetamide is necessary, because single equivalence results in double addition of the polyfluoroarene to the amide, forming the unwanted dimer product (Figure 3). The pentafluorobenzonitrile product has been isolated with a 52% yield without the use of a column, which is a moderate yield from the 91% yield in the reaction mixture that could be improved.

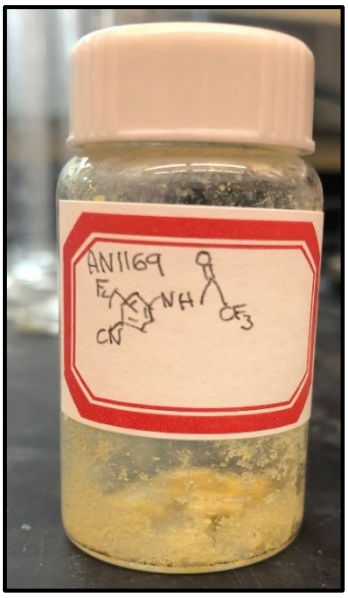

Figure 3: Image of the isolated crystallized pentafluorobenzonitrile product. (photographer: Noel)

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