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Haleigh Machost April 5, 2019

C-H Insertion of Trifluoroacetate as a Model for Trifluoromethanesulfonate. A Precursor for ^{18}F Labeling of Biomolecules

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Abstract

C-H Insertion of Trifluoroacetate as a Model for Trifluoromethanesulfonate. A Precursor for ^{18}F Labeling of Biomolecules

By Haleigh Machost

As more compounds are developed to address medical issues, methods of tracking their movement through the body are needed in order to further understand how they function within biological systems. One of the ways of tracking medicinally relevant compounds as they move through the body is positron emission tomography (PET). As certain isotopes undergo radioactive decay, they release a positron which can be detected using PET. Thus, by tracking positron emission of molecules labeled with radioactive elements through PET, the location of medical compounds in the body can be determined. ^{18}F is a radioactive isotope which undergoes β^+ decay to produce a positron in addition to ^{18}O and a neutrino, meaning it has great potential for radioactive labeling in PET. In an effort to capitalize on the mapping potential of compounds tagged with ^{18}F, this project investigated possible ways of synthesizing molecular precursors to ^{18}F insertion. Primarily, new methods of directly replacing a C-H bond with a trifluoroacetate substituent group were attempted. In theory, the trifluoroacetate group would serve as a model for the introduction of trifluoromethanesulfonate, a much stronger leaving group known to be replaceable by F^-. Unlike trifluoromethanesulfonate, trifluoroacetate is capable of surviving purification by silica, enabling easier purification and characterization. As such, the success of exploratory methods of the direct replacement of a C-H bond by a C-trifluoroacetate bond is easier to determine. Once a system capable C-H functionalization to form a trifluoroacetate is developed, similar conditions will be attempted in order to introduce trifluoromethanesulfonate, a known precursor for the insertion of ^{18}F for PET.

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Table of Contents

Table of Figures

1. *Introduction*

As medical advances continue to be made, more and more medicinally relevant compounds are developed. There is an inherent need to understand how these compounds function in and interact with the body. Once a medicine's molecular functions are known, modifications can be made to its structure to increase its medical effectiveness or to develop new medications. One frequently used method of identifying how molecules move through the body is positron emission tomography (PET). PET is a type of medical scan in which molecules containing specific isotopes undergo radioactive decay inside the body after being injected or ingested.[1] Specifically, the medicinally relevant molecules must be tagged with an isotope which releases a positron as part of its decay; these include ^{11}C, ^{13}N, ^{15}O, and ^{18}F.

$$^{18}_{9}F \rightarrow {}^{18}_{8}O + positron + neutrino \quad (1)$$

Equation 1 is an example of radioactive decay producing a positron, specifically ^{18}F undergoing β^+ decay. The positrons are emitted and they travel through the body before being detected by a specialized camera.[2] The overall process involved in PET is shown in Figure 1.

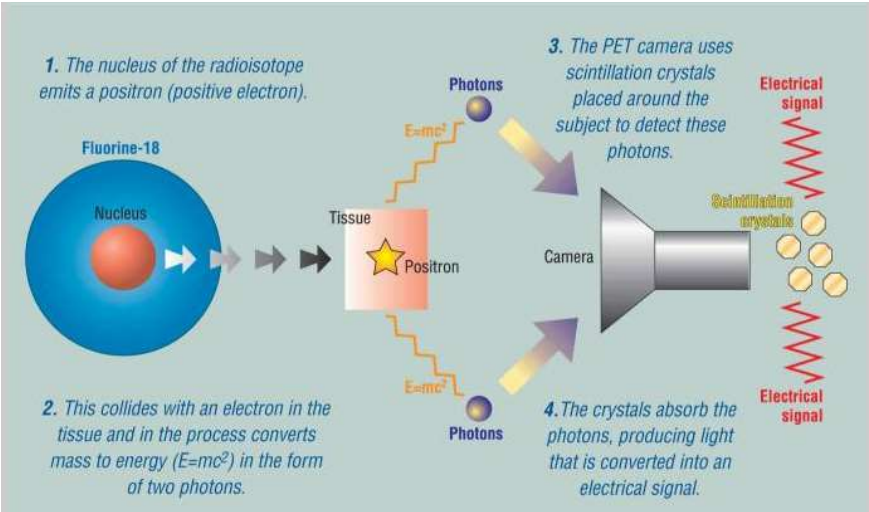


Figure 1: Diagram of PET scanning[1]

Tagged molecules contain an atom that will undergo radioactive decay to produce the desired positron. The path of these tagged molecules through the body can be determined through taking multiple scans across time. Tracking the molecules as they move through an organism gives researches evidence for which organs or systems the compound interacts with. In Figure 2, radioactively tagged molecules have accumulated near tumors.

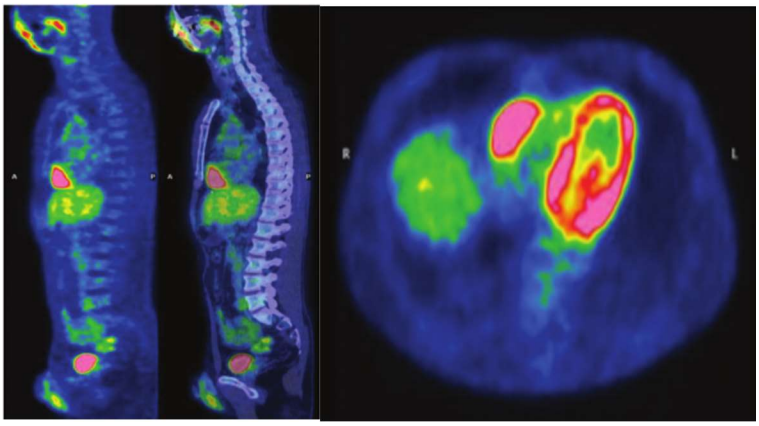


Figure 2: Examples of PET scans of a cancer patient[3]

The focus of this project is the formation of molecular precursors for radioactive tagging of medicinal compounds. Specifically, the direct C-H functionalization of alkane chains is investigated. The chemical properties of molecules investigated using PET must be as similar as possible in the tagged and un-tagged forms. This is to ensure that the data collected can be extrapolated from the radioactive molecule to the known medicinal compound. One method of maintaining the chemical behavior is to place the tag away from known or potential active sites on the molecule. Active sites are typically functional groups that interact with biological systems. This includes carboxyl, amino, and amido groups. These groups add sites of basicity or acidity that influence physical and biological properties. Furthermore, none of the functional

groups that are generally biologically active should be introduced by the tagging process. While functional groups already present in the known, medicinal compound can be substituted by their radioactive counterpart, new additions of such functional groups should not be performed.

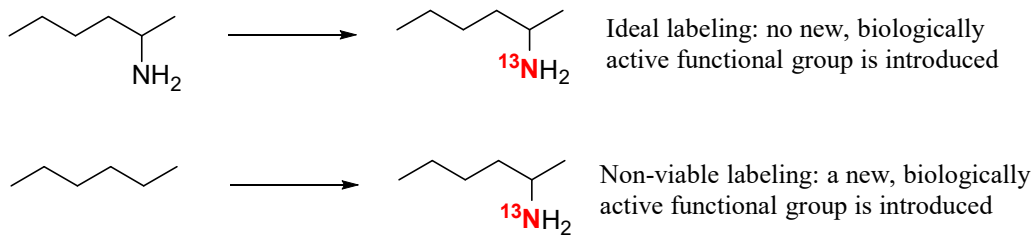


Figure 3: Ideal versus non-viable ^{13}N radioactive labeling

Figure 3 displays the difference between an ideal labeling and an undesirable labeling with a radioactive isotope that is generally biologically active.

As this project focuses on functionalizing simple alkyl chains, ^{13}N was not seen as a potential tag as a new amino group would be produced upon its introduction. Another non-viable isotope is ^{15}O. As with any radioactive decay, 50% of the labeled isotope is lost in the first half life and a further 25% of the starting amount has decayed by the end of the second half life. As such, the quicker the process of producing the radioactively tagged molecule is, including synthesis and purification, the better the molecule can serve as a reliable tracer in PET. Because the time spent in synthesis and purification relative to a short half-life is a logistical issue, ^{15}O was not seen as a feasible isotope due to its half-life of 2.037 minutes.[4] Even though the vast majority of medicines contain carbon, and therefore replacing a ^{12}C with ^{11}C would not chemically alter the compound, ^{11}C was not used as a potential tag in this project for the same reason as ^{15}O. While ^{11}C has a longer half-life than either ^{15}O or ^{13}N, which has a half-life of 9.965 minutes, ^{11}C only has a half-life of 20.38 minutes which was still not long enough for this

project.[4,5] Therefore, ^{18}F, which has a half-life of 109.8 minutes was chosen as the potential tag for PET.[4]

Isotope	^{13}N	^{15}O	^{11}C	^{18}F
Half-life (min)	9.965	2.037	20.38	109.8

Table 1: Half-life of potential isotopes for PET

The ^{18}F isotope is made inside of a cyclotron, a particle accelerator. Specifically, water which is composed of ^{18}O collides with a proton in order to produce radioactive hydrofluoric acid: $H^{18}F$. The $H^{18}F$ is then treated with K_2CO_3, producing $K^{18}F$, which is the source of $^{18}F^-$ for the formation of a radioactively tagged molecule.[6] As such, it is necessary to develop molecular precursors for ^{18}F insertion, which upon directly reacting with $K^{18}F$**,** will produce the desired product. One group known to be readily replaced by F^- is the trifluoromethanesulfonate functional group, also known as a triflate group seen in Figure 4.[7]

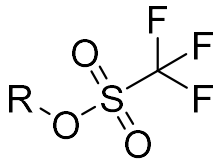


Figure 4: Trifluoromethanesulfonate functional group

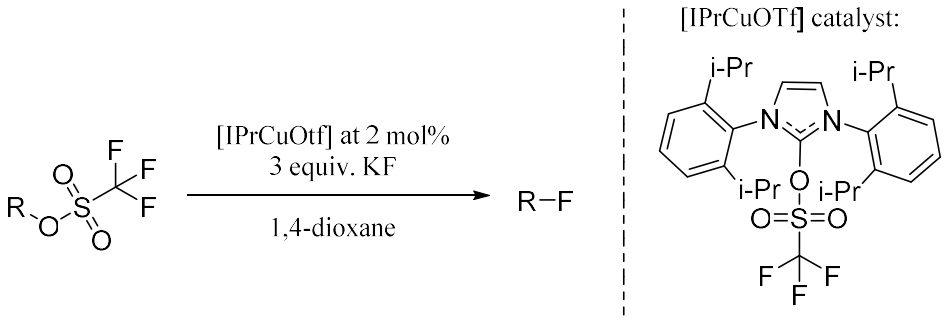


Figure 5: KF reaction with triflate[7]

The trifluoromethanesulfonate group is a highly efficient leaving group, and the reaction displayed in Figure 5 takes less than an hour to reach completion. Triflates are also acid labile, meaning that there is a high probability that molecules containing the functional group would not survive purification by silica gel chromatography, which is weakly acidic. This posed an issue for this project whose goal is the direct replacement of a C-H bond by a carbon-triflate bond, as there is not a simple way of isolating the desired product for characterization. The inability to purify by silica therefore complicates the process of ascertaining whether or not an exploratory reaction is successful. To circumvent this, the direct insertion of the trifluoroacetate group (Figure 6) to replace a C-H bond was investigated as a model for the direct insertion of trifluoromethanesulfonate.

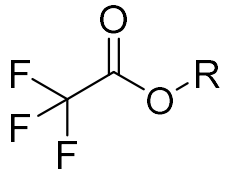


Figure 6: Trifluoroacetate functional group

If the system used for the replacement of a C-H bond by a carbon-trifluoroacetate bond proves successful, then similar conditions can be attempted for the direct introduction of the trifluoromethanesulfonate group. In summary, the goal of this project is to discover a new method of directly inserting a trifluoromethanesulfonate group into a C-H bond. In order to perform the exploratory synthesis, a model system of trifluoroacetate is used. Once a successful method of trifluoroacetate insertion is developed, the same reaction conditions will be attempted with trifluoromethanesulfonate.

In the synthesis of radioactively tagged molecules, remote functionalization was desired in order to spatially distance the radioactive isotope from potential active sites. By introducing the ^{18}F into the β position relative to potential active sites, the fluorine atom is removed from the location of biological active site by one carbon atom, minimizing the influence of the electronegative fluorine on the chemical properties of tested medicinal compounds. One example of the need for this positioning is in lipoic acid. Lipoic acid is known to reduce neuropathic pain for those with diabetes; however, the biological mechanism by which this is accomplished is not yet known.[8] On lipoic acid, there are two groups likely to be active in the interaction with the nervous system: the carboxylic acid and the di-sulfide bridged cyclopentane. By inserting a radioactive tag β to the carboxylic acid, there is minimal alteration of the chemical properties of either group. The desired separation between ^{18}F and either potentially bioactive site is demonstrated in Figure 7.

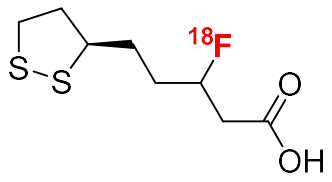


Figure 7: α -Lipoic acid with ^{18}F inserted in the β position

To assist in targeting the β position, directing groups were utilized throughout this project. Directing groups are widely used when implementing transition metal reagents for C-H functionalization. They function by coordinating to the metal through donation of electron density into the metal's empty orbitals. Once the metal is coordinated to the directing group, it is brought into close proximity to the desired carbon, allowing for selective reactivity on a specific C-H bond. This project investigated directing groups that were theorized to facilitate β C-H functionalization.

2. Results and Discussion

2.1. Carboxyl Directing Group

Because of the negative charge centered on the two oxygen atoms, the carboxyl functional group was hypothesized to be an adequate directing group for a metallic reagent as there is significant electron density available for donation to the metal. The carboxyl group, once coordinated to the metal, has the potential to bring the metal into the required position to facilitate β C-H functionalization. Furthermore, many medicinally relevant compounds, such as lipoic acid, contain carboxylic acids. With the directing group already being present on the medicinal compound, the time of the complete synthesis would be decreased as no modifications are needed after the purification performed post ^{18}F insertion. This would be ideal because fewer half-lives would pass in the time taken for the total synthesis.

2.1.1. Remote Hydroxylation via Pt(II)/Pt(IV)

Hydroxyl groups are known precursors for the formation of trifluoromethanesulfonate groups and trifluoroacetate groups, as shown in Figures 8-9.[7, 9]

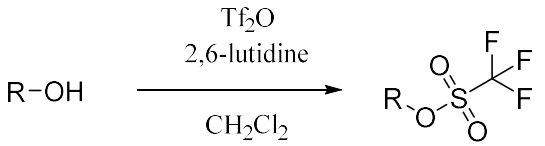


Figure 8: Alcohol reacting to form trifluoromethanesulfonate [7]

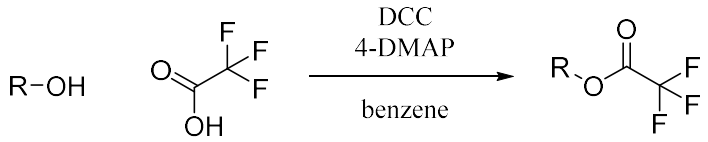


Figure 9: Alcohol reacting to form trifluoroacetate[9]

In order to achieve the aim of not affecting the medicinal properties of the compounds, remote hydroxylation was a desirable result. One literature source was found which claimed the direct, remote hydroxylation of aliphatic carboxylic acids; an example of the published reactions is reported in Figure 10.[10]

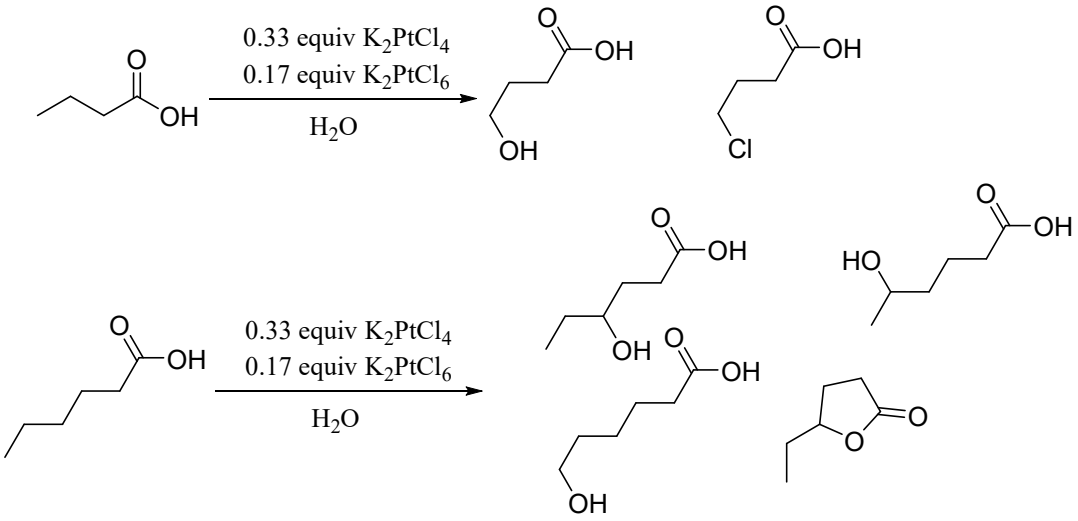


Figure 10: Previous remote hydroxylation of aliphatic compounds[10]

The published method, which includes the formation of a lactone in the mechanism, would be viable for the eventual insertion of a radioactive tag on an alkane chain attached to a carboxylic acid. In the published system, Pt(II) acts as the oxidizing agent, producing Pt(0). Kao and Sen introduced Pt(IV) to re-oxidize Pt(0) to Pt(II) in order to increase the turnover of the platinum species and to delay the precipitation of Pt(0).[10] The mechanism theorized by Kao and Sen of the carboxyl group interacting with platinum is shown in Figure 11.

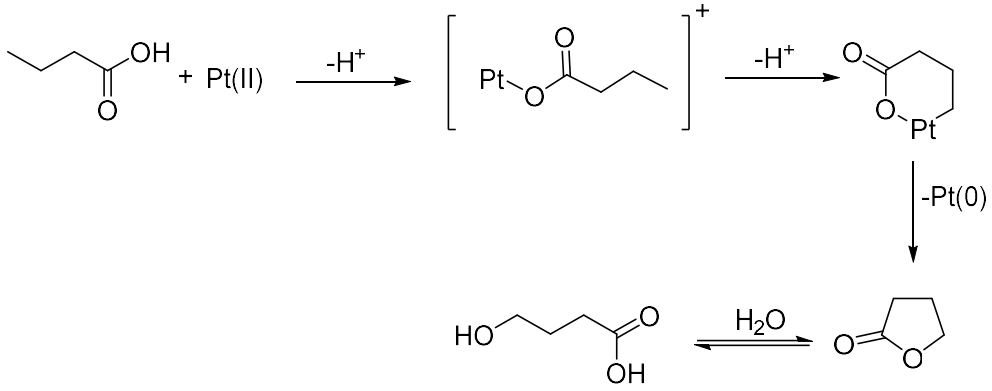


Figure 11: Literature proposed mechanism for remote hydroxylation[10]

The published method was performed with two stearic acid and lipoic acid whose structures are shown in Figure 12.

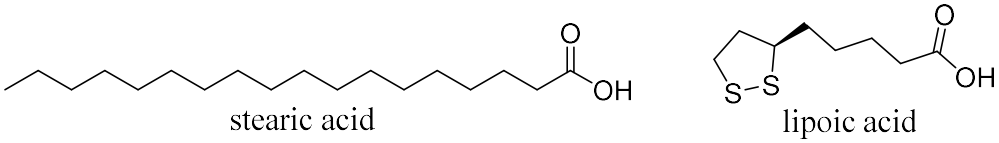


Figure 12: Structure of acids used in published system and conditions

The two reactions were run simultaneously. An attempted hydroxylation of lipoic acid and an attempted hydroxylation of stearic acid both were conducted at 80 °C for 6 days**.**

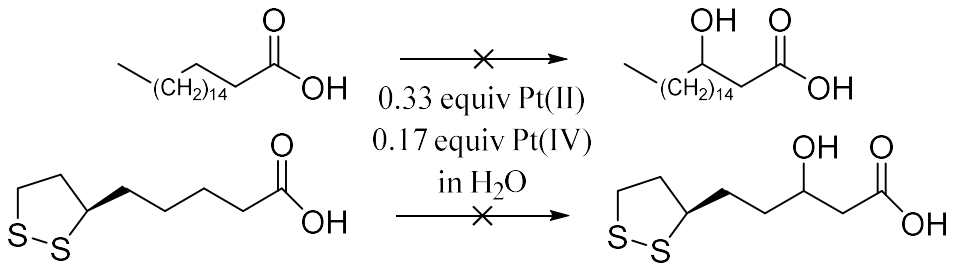


Figure 13: Attempted remote hydroxylations using Pt(II)/Pt(IV)

Following the published procedure, the stearic acid and lipoic acid were each combined with Pt(II) and Pt(IV). The desired products, which involve a hydroxyl functional group, are shown in Figure 13. The crude ^{1}H NMR (Figure 14) of neither reaction showed new peaks between 3 and 4 ppm, as would be expected by a hydrogen bonded to a carbon atom that is directly attached to the oxygen of a hydroxyl group. In fact, there was no change from the ^{1}H NMR of lipoic acid to even indicate the formation of a lactone, which would be expected as a new peak between 2 to 3 ppm (-C**H**$_2$COO-) and near 4 ppm (-C**H**$_2$O-).

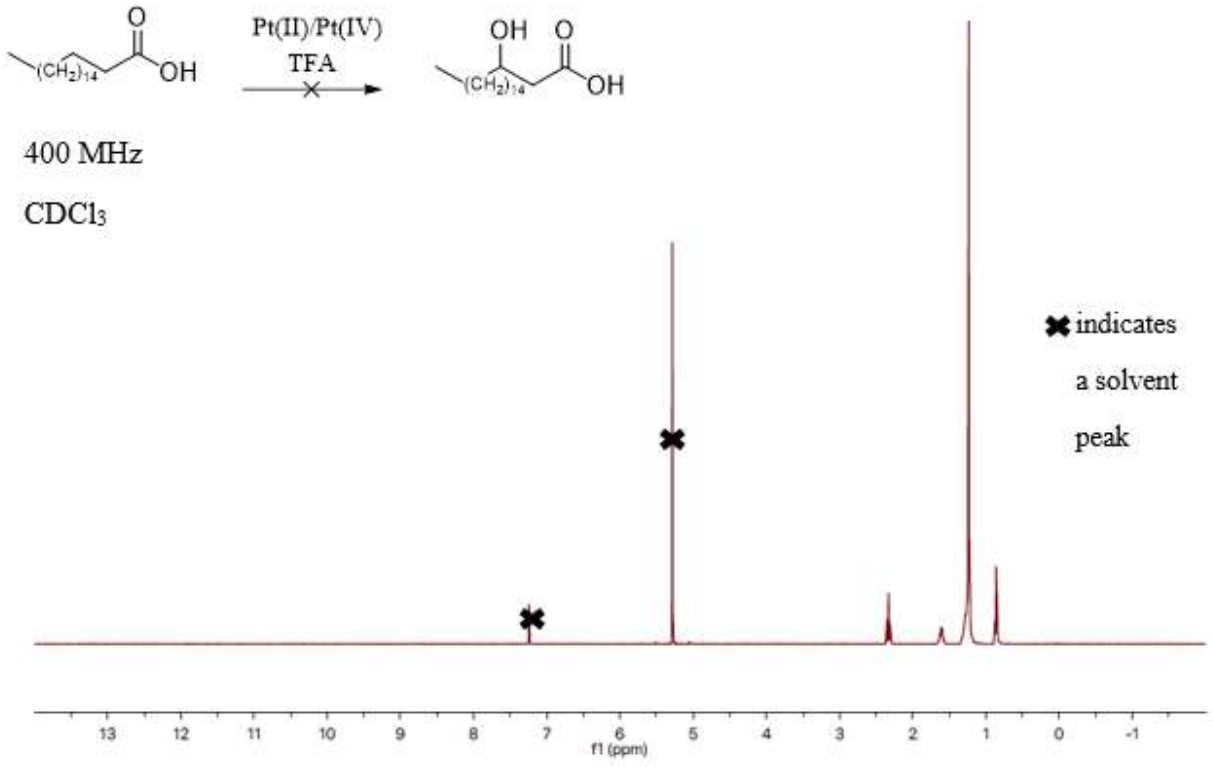


Figure 14: Crude ^{1}H NMR of failed remote hydroxylation of stearic acid

This was a surprising result given the extremely long reaction time and the previously published literature. However, as neither reaction showed signs hydroxylation or the formation of a lactone, any further attempts at using this system were abandoned. In a search of the literature, all other direct hydroxylations resulting from C-H functionalization occurred on activated carbons which places the functional group near potentially bioactive sites. The focus of this project was then shifted to the direct insertion of the trifluoroacetate directing group as a model for the potential direct insertion of trifluoromethanesulfonate.

2.2. Attempted Direct Addition of Trifluoroacetate

The trifluoroacetate group is a weak nucleophile due to its stability as a free ion resulting both from the resonance structures and the electron withdrawing effect of the three fluorine atoms. In C-H activation, a metal center inserts itself into the C-H bond, forming an M-C bond. The desired nucleophile then also coordinates to the metal. Through reductive elimination, the bonds between the metal and carbon and the metal and nucleophile break, and a new bond between the carbon and the nucleophile is formed, a process shown in Figure 15.

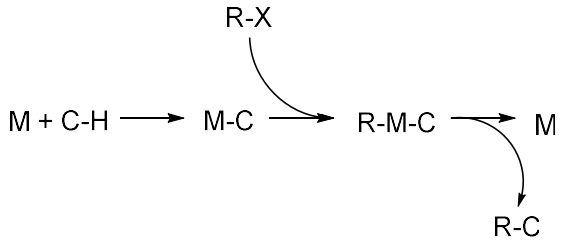


Figure 15: A mechanism of direct C-H functionalization

The more nucleophilic the desired functional group is, the more likely the system is to succeed at direct C-H functionalization. To help facilitate the addition of trifluoroacetate, widely utilized and therefore successful systems were investigated, and the reactions were run in trifluoroacetic acid (TFA) to continuously supply trifluoroacetate anions and strongly acidic reaction conditions.

2.2.1. Palladium(II) Acetate

$Pd(OAc)_2$ is a standard reagent for C-H activation, and has been shown to be successful at β C-H functionalization, including C-H arylation reactions.[11,12] Because of its proficiency in β

C-H activation, $Pd(OAc)_2$ was chosen for this project. Stearic acid was combined with $Pd(OAc)_2$ with TFA as the solvent, and the reaction was heated to 50 °C.

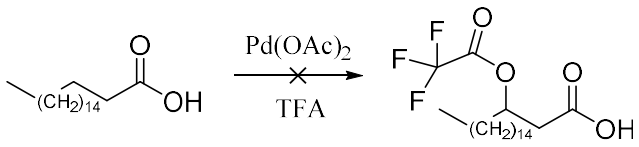


Figure 16: Stearic acid reacting with $Pd(OAc)_2$ towards attempted trifluoroacetoxylation

After running overnight, no precipitate of Pd(0) was observed. As Pd(0) is an anticipated byproduct of this reaction, the lack of its presence indicated that the reaction had not reached, nor nearly reached, completion. Subsequently, the reaction was allowed to run for four days at which point a small amount of Pd(0) was observed. Both a ^{1}H NMR (Figure 17) and an ^{19}F NMR were performed on fractions collected after a silica column. The ^{19}F NMR showed no peaks, indicating that the trifluoroacetate group was not present in the product, and that the reaction was not successful.

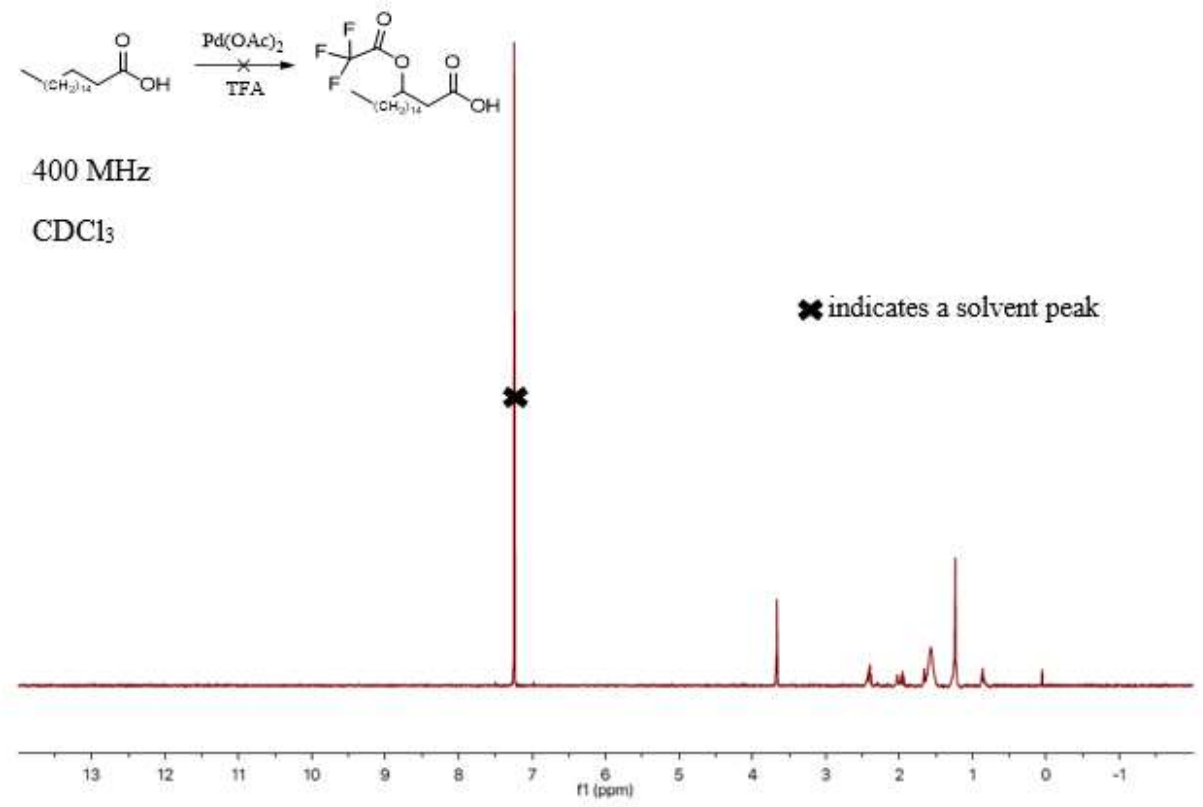


Figure 17: ^{1}H NMR of attempted trifluoroacetoxylation of stearic acid via $Pd(OAc)_2$

The ^{1}H NMR showed a new peak near 3.6 ppm. Three possible side reactions were theorized; however, none were consistent with the NMR. With the components of the reaction mixture, it was possible that an acetate was added along the alkyl chain as $Pd(OAc)_2$ is a potential source of acetate. Additionally, it is possible for stearic acid to form a lactone or for a dimer of stearic acid to be formed. These three reactions would result in functionalization of the alkyl chain and also explain the lack of any fluorine peaks in the ^{19}F NMR. However, all three would result in expected ^{1}H NMR values at or past 4 ppm.

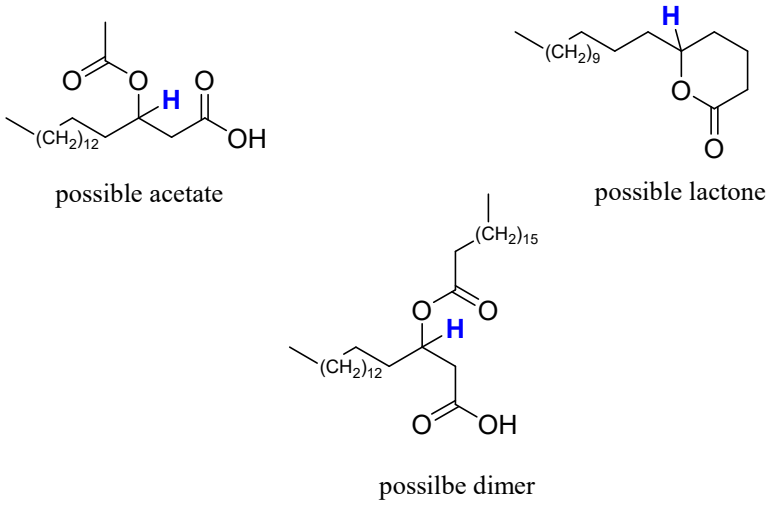


Figure 18: Possible side reactions

In Figure 18, the hydrogens that would be expected to correspond to a ^{1}H NMR peak past 4 ppm are shown in blue. Because the theorized side reactions are inconsistent with the ^{1}H NMR, none of them are believed to have occurred. This leaves the peak near 3.6 ppm unaccounted for. While what actually occurred in the reaction mixture was not deciphered, the possibility of side reactions lead to choosing a reagent which would not introduce any competing nucleophiles.

2.2.2. Thallium(III) Trifluoroacetate

After the palladium acetate was unsuccessful, thallium(III) trifluoroacetate was investigated. Thallium(III) trifluoroacetate is another reagent that is successful at C-H functionalization, including the formation or aryl halides.[13] While thallium(III) trifluoroacetate is toxic, it was chosen as the ligands already on the thallium would produce the desired functional group upon dissociation from the metal. This eliminated the possibility of one side reaction that is possible with $Pd(OAc)_2$. Thus, stearic acid was combined with thallium(III) trifluoroacetate with TFA as the solvent and held at 50 °C overnight.

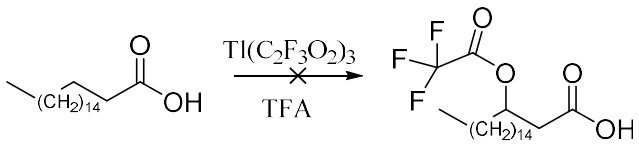


Figure 19: Stearic acid reacting with $Tl(C_2F_3O_2)_3$ towards attempted trifluoroacetoxylation

The analysis of the isolated products from this reaction showed no new peaks on the ^1H NMR (Figure 20) to indicate functionalization of the alkyl chain.

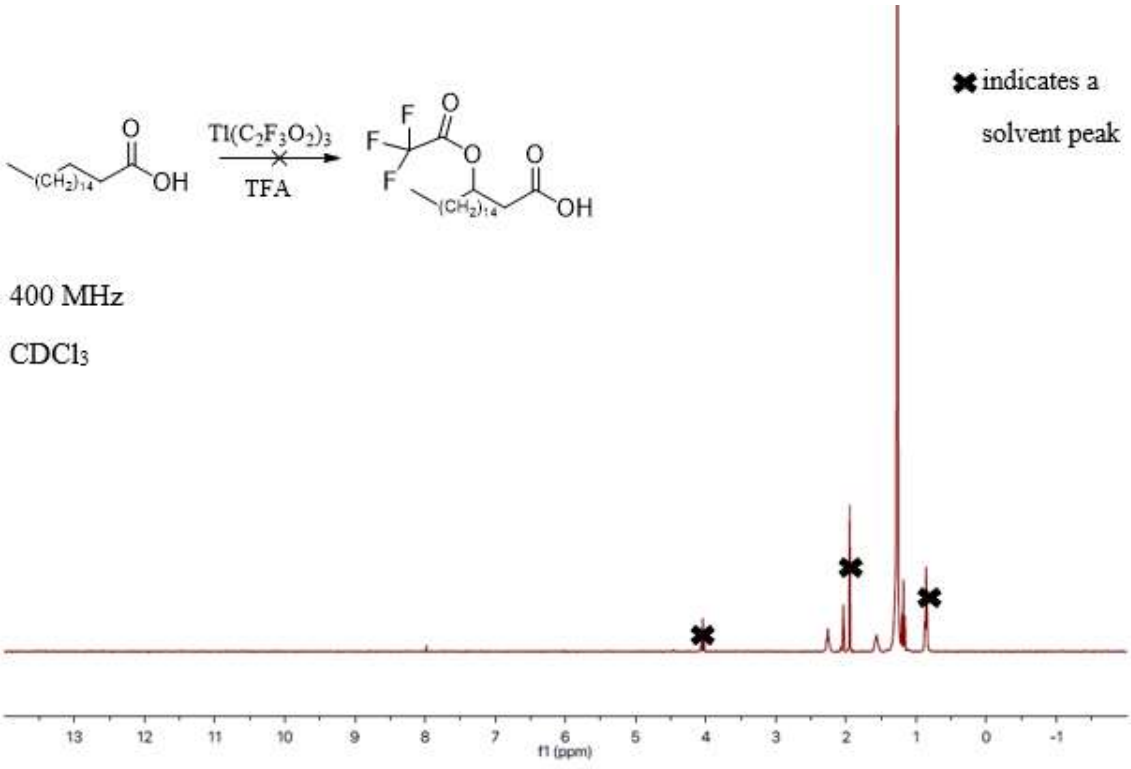
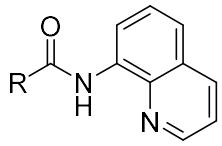


Figure 20: ^1H NMR of attempted trifluoroacetoxylation of stearic acid via $Tl(C_2F_3O_2)_3$

Additionally, a ^{19}F NMR showed no peaks, indicating that the reaction was not successful. As none of the attempted carboxyl-directed C-H functionalizations was successful, it is possible that the carboxyl directing group is not a strong enough electron donor to function with the chosen systems.

2.3. (Quinoline-8-yl)amide Directing Group

After both the palladium(II) and the thallium(III) systems failed, a stronger directing group than carboxylic acid was investigated. (Quinoline-8-yl)amides (QA), whose structure is shown in Figure 21, were chosen. QA has previously proven successful in C-H activation. [13]



(quinoline-8-yl)amide

Figure 21: QA directing group

Additionally, as shown in Figure 22, the QA directing group has been shown to facilitate C-H activation-insertion of an alkyl group when combined with $Pd(OAc)_2$.[14]

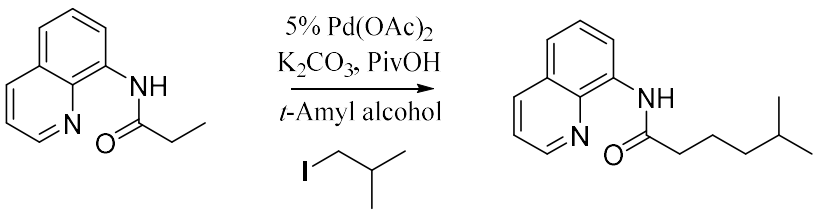


Figure 22: QA directed C-H alkylation[14]

The lone pair on the nitrogen of the quinoline is able to be donated to the metal, bringing the metal complex into the desired position to react with a C-H bond on the β carbon. The coordination between the nitrogen and a metal center is shown in Figure 23.

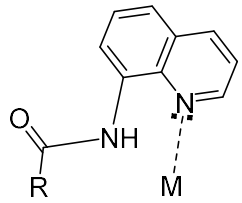


Figure 23: QA directing group coordinating to a metal center

The addition of a directing group that is not present on the biologically active molecule increases the time required for the total synthesis due to the necessary removal of the directing group. However, testing these systems with stronger directing groups will indicate whether they are potential reagents for the desired functionalization with trifluoromethanesulfonate. As trifluoromethanesulfonate is efficiently replaced by F^-, the use of the QA directing group could still produce a viable synthetic pathway despite the added time for the removal of the directing group.

2.3.1. Palladium(II) Acetate

$Pd(OAc)_2$ was reintroduced because the toxicity of thallium(III) makes it a relatively undesirable reagent even if it provides the desired transformation. As such, $Pd(OAc)_2$ was tested with the QA directing group.

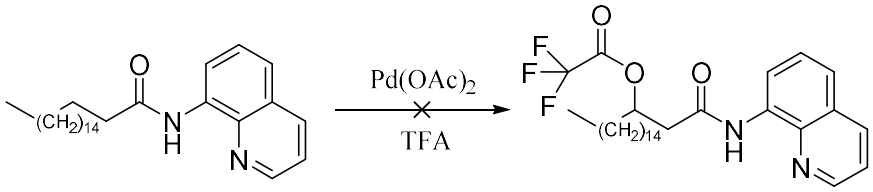


Figure 24: QA functionalized stearic acid reacting with $Pd(OAc)_2$ towards attempted trifluoroacetoxylation

The ^1H NMR (Figure 25) of this reaction was fairly complex.

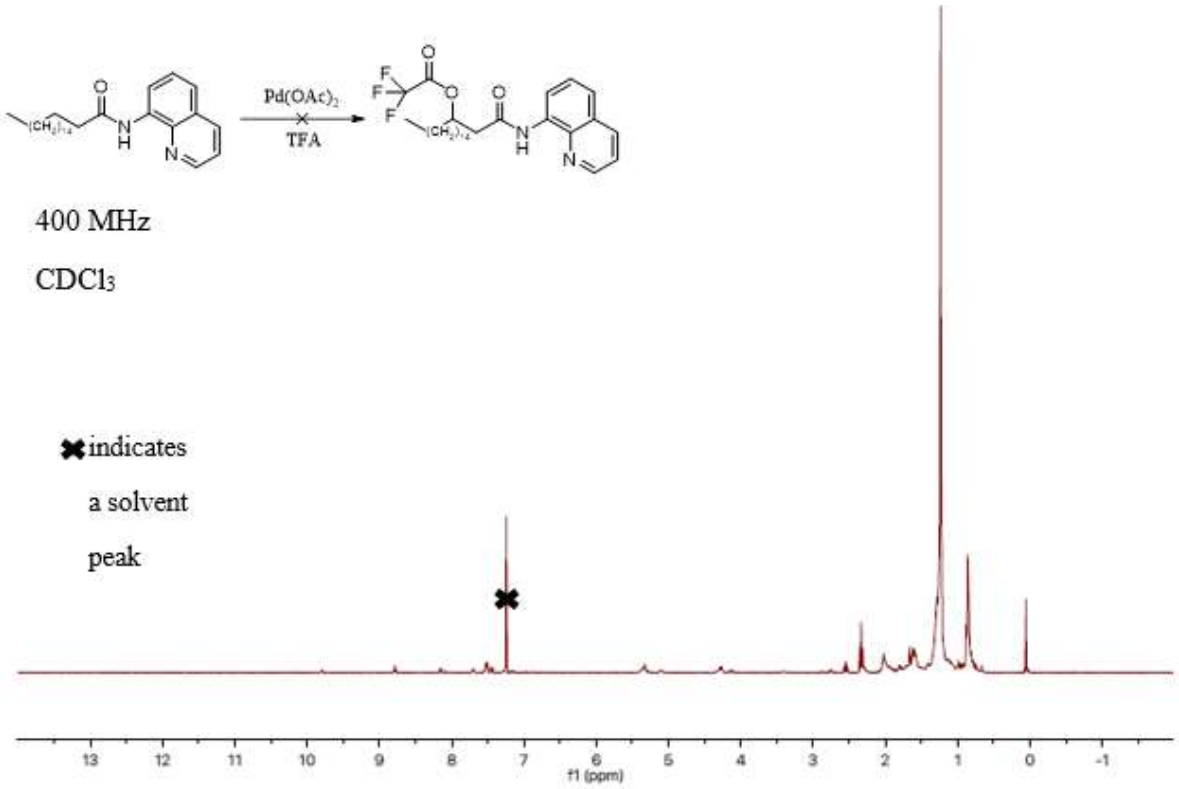


Figure 25: ^1H NMR of QA functionalized stearic acid reacting with $Pd(OAc)_2$

New peaks appeared between 4 and 5.5 ppm, indicating that the alkyl chain was functionalized. However, the integration value between 2.5 ppm and 0.5 ppm is over 70 times greater than the integration of the amido hydrogen. It is possible that the large integration is due to hexane

residues and that the small peaks shown in Figure 25 are indicative of a desired product. The new resonances could be caused by the desired transformation, trifluoroacetoxylation, in addition to a partial hydrolysis of the added trifluoroacetate group to make an alcohol. However, the small integration values indicate that if the desired product was formed, it did so in low yield, making critical analysis of the ^{1}H NMR difficult. Additionally, a ^{19}F NMR did not show any peaks; however, if the yield was small enough, the peaks from the triflurorоacetate group could have blended into the noise.

2.3.2. Thallium(III) Trifluoroacetate

After the success of the trifluoroacetoxylation reaction with palladium(II) acetate was ambiguous, the previously used thallium(III) trifluoroacetate was also tested with the QA directing group

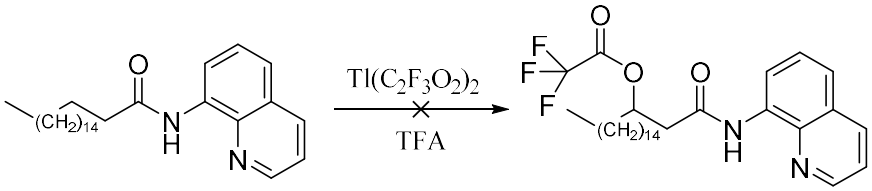


Figure 26: QA functionalized stearic acid reacting with $Tl(C_2F_3O_2)_2$ towards attempted trifluoroacetoxylation

As with the carboxyl directing group, the thallium(III) reaction performed with the QA directing group gave a ^{19}F NMR with no new signals. The ^{1}H NMR (Figure 27) also showed no evidence of functionalization.

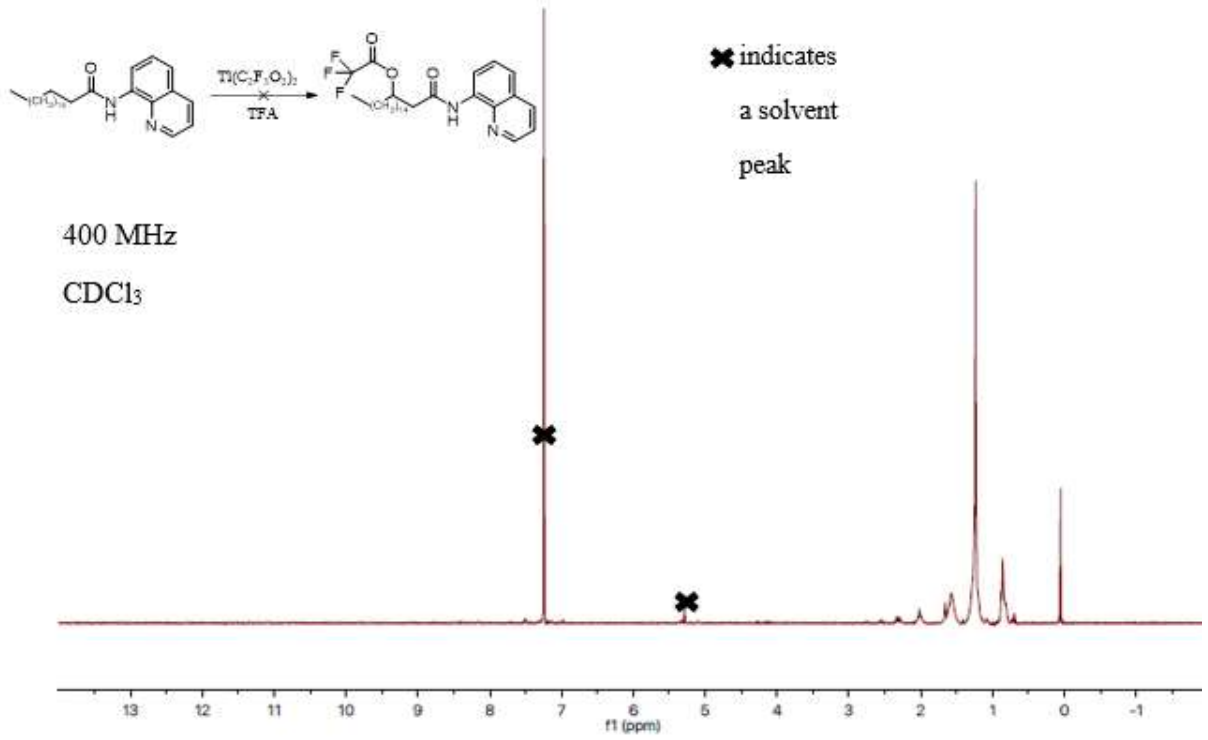


Figure 27: ^{1}H NMR of QA functionalized stearic acid reacting with $Tl(C_2F_3O_2)_3$

2.4. Hexanoic Acid Trial

Because all of the previous attempts were unsuccessful, a simpler acid was chosen to investigate the new peaks which appeared in the ^{1}H NMR when using $Pd(OAc)_2$. By using hexanoic acid instead of stearic acid, the number of carbons was lowered from 18 to 6. While a different result was not expected by simply lowering the number of carbon and hydrogen atoms present in the molecule, a more easily deciphered byproduct was thought to be possible. In a repeat of the first palladium(II) acetate experiment, a carboxyl directing group was used in conjunction with palladium acetate. Hexanoic acid was combined with $Pd(OAc)_2$ using TFA as the solvent.

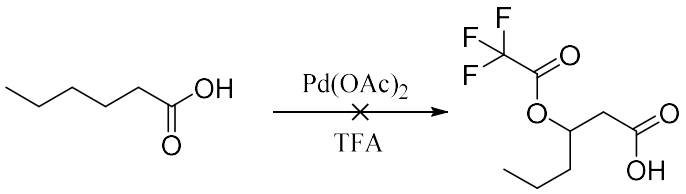


Figure 28: Attempt at $Pd(OAc)_2$ mediated trifluoroacetoxylation of hexanoic acid

As expected from previous experimentation, the reaction did not proceed with the desired direct C-H functionalization to form a trifluoroacetate group. Unfortunately, while the ^1H NMR spectrum (Figure 29) had a new signal past 4 ppm which could indicate one of the theorized side reactions, an additional peak was seen past 7.3 ppm which discounted the formed product being an acetate, lactone, or dimer.

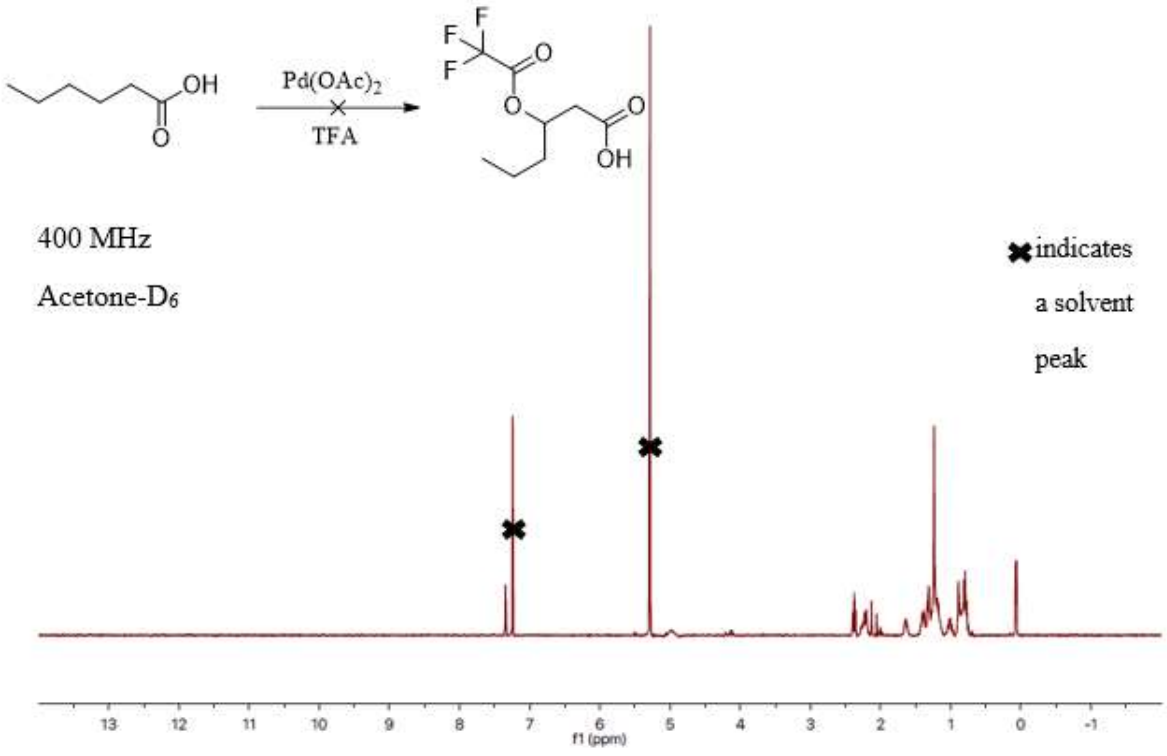


Figure 29: ^1H NMR of attempted trifluoroacetoxylation of hexanoic acid via $Pd(OAc)_2$

As the hexanoic acid trial was unsuccessful in producing an easily deciphered byproduct, no further efforts were made towards understanding the unwanted reactions. The goal of the experiments, the direct C-H functionalization to form a C-trifluoroacetate bond, had already been conclusively disproven in the chosen systems. Therefore, any further efforts would be towards accomplishing direct insertion of trifluoroacetate.

3. Conclusion and Future Directions

None of the attempted methods of synthesizing a precursor to ^{18}F insertion were apparently successful. Due to the complicated nature of the ^{1}H NMR spectra produced, it is difficult to ascertain what reactions are occurring in the utilized systems. A future direction of this project begins with the assumption that the QA directing group is non-functional in the chosen conditions because of the amount of time the nitrogen atoms spend protonated. The protonation would inhibit how the nitrogen atoms of the quinoline coordinate to the metal. A new directing group which will function while dissolved in TFA, and therefore be largely protonated at any possible site, could be developed in order to attempt the desired, direct conversion of a C-H to a C-trifluoroacetate using TFA as the solvent. Once a system which is capable of direct insertion of trifluoroacetate is developed, the direct insertion of trifluoromethanesulfonate will be attempted to form a precursor for ^{18}F labeling. Once direct C-H functionalization to form trifluoromethanesulfonate is developed, it will be a significant synthetic step for the investigation of medicinally relevant molecules through using PET.

4. Experimental

Hydrogen hexachloroplatinate(IV) hydrate and stearic acid were purchased from the Aldrich Chemical Company. Palladium(II) acetate and platinum(II) chloride were acquired from Strem Chemicals. Both hexanoic acid and thallium(III) trifluoroacetate were purchased from Oakwood chemical. α-Lipoic acid was purchased from Sigma-Aldrich, and trifluoroacetic acid was acquired from Alfa Aesar.

4.1. Setup Towards Remote Hydroxylation

Lipoic acid and stearic acid were used as reactants in the following procedure. The starting acid (0.145 mmol) was combined with Pt(II) chloride (0.048 mmol). Platinum hexachloroplatinate(IV) hydrate was the source of Pt(IV). As the hexachloroplatinate(IV) hydrate had absorbed water from the air in previous storage, an unknown amount of the compound itself was added. However, as only 0.024 mmol were needed, a sufficient amount was added to complete the system. The three reagents were combined in 3 mL of water and heated at 80 °C for 6 days. An extraction was performed with 3x2 mL of CH_2Cl_2 which was then dried with $MgSO_4$ before being filtered and concentrated in *vacuo*. A ^1H NMR analysis of the crude product was performed.

4.2. General Procedure for Palladium(II) Acetate Reactions

Either the carboxylic acid or the QA functionalized compound (0.0176 mmol) was combined with $Pd(OAc)_2$ (0.0176 mmol) in 0.2 mL of TFA and heated to 50 **°C**. The system was stirred for four days. The crude mixture was transferred to a flask using CH_2Cl_2. Both the TFA and CH_2Cl_2 were removed in *vacuo*. The crude product was run through a silica column with a mobile phase of 15% ethyl acetate, 85% hexanes. The fractions collected appeared pure on a silica gel TLC of the same mobile phase.

4.3. General Procedure for Thallium(III) Trifluoroacetate Reactions

Thallium(III) trifluoroacetate (0.0176 mmol) was combined with either the carboxylic acid or the QA functionalized compound (0.0176 mmol) in 0.2 mL of TFA . The mixture was then heated to 50 **°C** and allowed to run overnight. The crude mixture was transferred to a flask using CH_2Cl_2. Both the TFA and CH_2Cl_2 were removed in *vacuo*. The crude product was run through a silica column with a mobile phase of 15% ethyl acetate, 85% hexanes. The fractions collected appeared pure on a silica gel TLC using the same mobile phase of 15% ethyl acetate, 85% hexanes.

4.4. Synthesis of QA Functionalized Compound

Stearic acid (284.7 mg, 1.0 mmol) was dissolved in 20 mL of toluene combined with 2 drops of dimethylformamide. $SOCl_2$ (0.37 mL, 5.0 mmol) was added. The reaction was heated at 80 **°C** for five hours, after which the toluene and $SOCl_2$ were removed in *vacuo*. The remaining oil was then dissolved in CH_2Cl_2. 8-Aminoquinoline (130.1 mg, 0.9 mmol) and trimethylamine (0.14 mL, 1.0 mmol) were added to the mixture. The reaction was stirred for 2 hours at 0 **°C**. The reaction was then quenched with water and extracted with 3x10mL CH_2Cl_2 before being dried with Na_2SO_4. The mixture was then filtered and concentrated in *vacuo*. Purification was performed using a silica column with a mobile phase of 15% ethyl acetate, 85% hexanes. The pure compound was characterized by ^{1}H NMR. ^{1}H NMR (399 MHz, Chloroform-*d*) δ 8.87 – 8.73 (m, 2H), 8.17 (d, J = 8.3 Hz, 1H), 7.60 – 7.42 (m, 3H), 2.56 (t, J = 7.9, 7.3 Hz, 2H), 1.82 (p, J = 7.6 Hz, 2H), 1.24-1.46 (m, 24H), 0.88 (t, J = 7.2, 6.7 Hz, 3H).

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