Chemistry Honors Final Report

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Synthesis and Reactivity of Vinyl Iodonium Salts

Background

In Dr. Zhdankin's research lab, one of our main focuses is on the chemistry of iodine. Iodine is the largest nonradioactive nonmetal on the planet and it is environmentally friendly, commercially available and safe to work with. It is also has a special ability to exceed its octet of electrons and become hypervalent due to its large size. This ability to become hypervalent is typically only exhibited by transition metals which are commonly used in many different chemical reactions to make pharmaceuticals, agriculture chemicals, and many other useful products. Transition metals, however, tend to be expensive, environmentally toxic and can be unsafe to work with in a lab setting due to their toxic properties. Therefore, it would be useful to find an alternative to transition metals to synthesize these useful products; this is where iodine comes in. Since it is able to exhibit the same hypervalent property as transition metals, it offers an advantage since it is nontoxic and cheap. It is for this reason that research on hypervalent iodine compounds is so important for medicine, agriculture, and our overall understanding of chemistry.

Hypervalent iodine compounds can take many forms, as iodine is able to transition from its typical I (I) state (meaning it only makes a bond with one other chemical) to a I (III), I (V) or I (VII) state (bonding with 3, 5 or 7 other atoms). Typically I (III) compounds are the most studied, as the I (VII) and I (V) compounds are generally more unstable and difficult to work with. The type of iodine compound that I work with is in the I (III) state and is called an "iodonium salt." More specifically, I work with vinyl iodonium salts, and images of the general salt and the vinyl salt are shown below in figures 1 and 2.

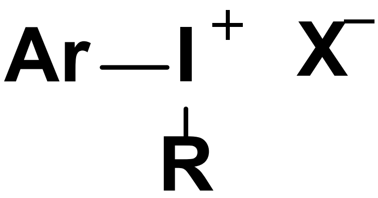


Figure 1: General iodonium salt where Ar represents an aromatic group, R represents an aliphatic group and X represents an anion

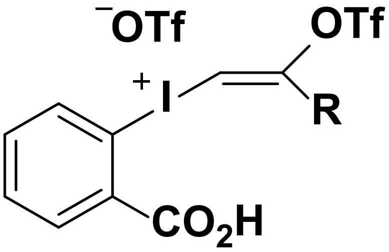


Figure 2: Vinyl iodonium salt, where the vinyl group is the section on the right containing the OTf (triflate) and R (carbon chain) groups.

When analyzing the figures, it may seem that iodine would be in an I (II) state instead of an I (III) state since it is only bonded to two atoms, but the third "atom" is the positive charge on the iodine, which can weakly interact with the negatively charged X anion.

This vinyl iodonium salt was the focus of my project, and our lab's interest in this compound arose from previous work by Kitamura *et al* in 1995[1] which described the preparation of an alkynyliodonium salt from 2-iodosylbenzoic acid, or IBA, which is described in figure 3. When we repeated this procedure in 2015 using the same reaction conditions, we were unable to synthesize the alkynyliodonium salt, but rather synthesized a vinyl iodonium salt. This reaction we performed is described in figure 4.

Previous Result: Kitamura 1995

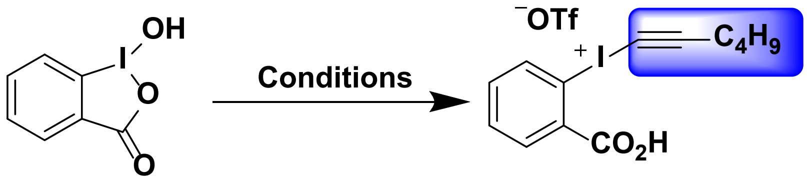


Figure 3, preparation of alkynyl (triple bond) iodonium salt from IBA

Our Result

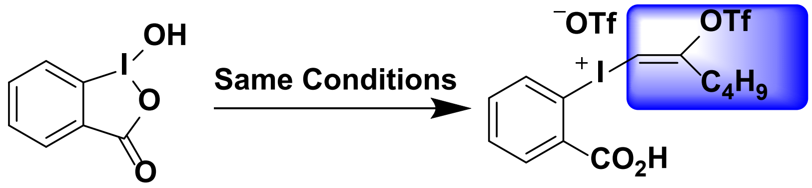


Figure 4, preparation of vinyl (double bond) iodonium salt from IBA

Conformation of our structure was given by several types of nuclear magnetic spectroscopy study (NMR, which studies the distances between atoms in a magnetic field) as well as X-ray crystallography (measures light scattering and gives a ball-and-stick image of the compound) which is considered to be the gold standard for confirming organic structures.

This difference in structure lead us to further investigate why we were getting a different compound and it also served as a jump start to look into what kind of reactions can be accomplished with this novel vinyl iodonium salt.

Project Methodology

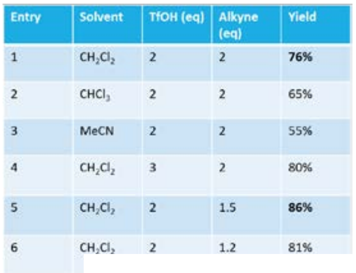
When I became a member of Dr. Zhdankin's lab in the spring of 2015, his post-doc Akira Yoshimura had just made this discovery of this vinyl iodonium salt. When I had become better acquainted with the lab and learned some organic chemistry techniques, Dr. Yoshimura gave me this project to work on.

The first step was to *optimize* the reaction. Optimization of a reaction involves finding the conditions that produce the highest yield of product from the starting material. This involves adjusting the ratios, or equivalents, of reagents that are used with respect to the starting material, as well as changing the solvent, time and temperature of the reaction. This process is outlined visually in figure 5.

Figure 5 lays out what is focused on in an optimization project, where the focus is highlighted by the dashed purple outline

The actual reaction that was optimized is shown in figure 6, with an optimization table alongside in table 7 to give an example of some of the results that were obtained.

Figure 6 shows the reaction that was optimized.



Entry	Solvent	TfOH (eq)	Alkyne (eq)	Yield
1	CH_2Cl_2	2	2	**76%**
2	$CHCl_3$	2	2	65%
3	MeCN	2	2	55%
4	CH_2Cl_2	3	2	80%
5	CH_2Cl_2	2	1.5	**86%**
6	CH_2Cl_2	2	1.2	81%

Figure 7 shows an optimization table, which shows the optimal conditions, which have their yield in bold

Through the optimization studies we determined that using two equivalents of triflic acid (TfOH) and 1.5 equivalents of the R-alkyne reagent gave the best yields. The studies also showed us that the best solvent to use was methylene chloride (CH_2Cl_2) for the reaction. The optimal temperature was 0°C for the first two hours, then room temperature for the next 24 hours. Triflic acid was added to the starting material first and allowed to react for two hours before the R-alkyne was added, then this reaction was allowed to proceed for the next 24 hours. Additionally we determined it was best to perform the reactions with a tinfoil cover over the flask since oftentimes hypervalent iodine compounds can be light-sensitive.

Once the reaction was optimized, the next step was to generate a variety of different compounds. Up until this point, the only form of the vinyl iodonium salt that had been synthesized had a -C_4H_9 as the R-group. In order to increase the scope of the project, having a variety of different compounds to work with is important. Having this variety also portrays how stable the desired product is; if a compound can support several different structures it is said to be more robust, which is a very desirable quality to have in a novel compound. To produce this variety, the only component of the reaction that had to be changed was the R-alkyne reagent; this is the significance of denoting this reagent as “R”-alkyne. “R” is commonly used organic chemistry nomenclature to describe a carbon chain, so this R-alkyne reagent describes a carbon chain attached to a triple bond (the alkyne component). For the optimization, the only version of the R-alkyne reagent was 1-hexyne, which has a structure depicted in figure 8. There are a variety of different types of these alkyne reagents that are commercially available from chemical supply websites and these reagents were used in the project to make a variety of iodonium salts. Some of the various compounds that were synthesized are shown in figure 9 alongside their respective R-alkyne reagents that were added.

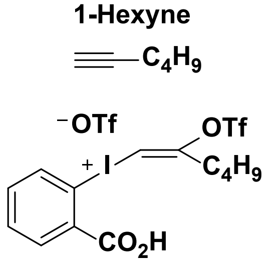


Figure 8, optimized iodonium salt

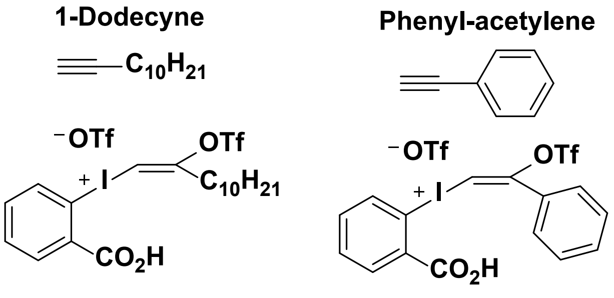


Figure 9, iodonium salt varieties with respective R-alkyne reagents

Earlier one of the reasons given for generating a variety of compounds was to increase the scope of the project; this means that the larger number of novel compounds that can be generated, the more potential there is to synthesize other products from these vinyl iodonium salts. For example, if there was a method discovered to make pharmaceuticals using these vinyl iodonium salts, a wide variety of different salts would equate to a wide variety of pharmaceuticals that could be made. This is where the importance of variety plays a vital role.

Before we can start thinking about the real-life applications of these iodonium salts, we need to understand how they work in a reaction. How a starting material is converted into a desired product is called the *mechanism*, and accordingly the process to uncover the mechanism is referred to as *mechanistic studies*. To best understand a mechanism, it is easiest to look at some previously reported research on structurally similar compounds and hypothesize a method by adjusting for the change in structure. For our mechanistic studies we again looked at the previous research by Kitamura *et al* in 1996[2] that described a nucleophilic substitution reaction in the alkynyliodonium salts mentioned earlier (figure 3). A nucleophilic substitution reaction involves the replacement of one group on a molecule, in this case the triflate/OTf group by a new compound, or nucleophile, which in this case is azide/N_3. This reaction mechanism is described in figure 10.

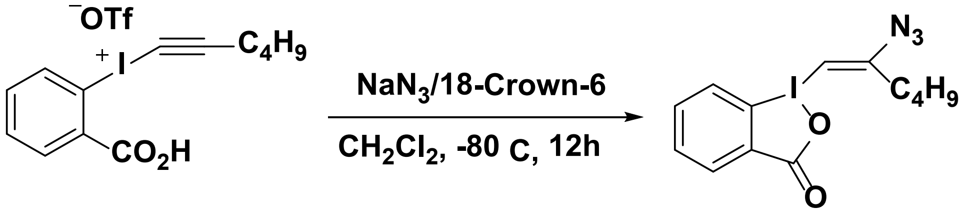


Figure 10: Reaction mechanism suggested by Kitamura *et al.* in 1996

The components of this reaction include the following: NaN_3 is sodium azide, which dissociates into sodium and azide in solution and is the nucleophile that is added to the triple bond in this reaction scheme. 18-crown-6 is crown ether, which serves as a delivery mechanism to bring the azide nucleophile to the salt. The solvent is methylene chloride, CH_2Cl_2 and the reaction is performed in dry ice/acetone (-80°C) and runs for 12 hours. Analysis of this reaction mechanism was essential for our own mechanistic studies to figure out how the vinyl iodonium salts react. Our hypothesis was that if we could synthesize the same product observed by Kitamura in 1996 using the same reaction conditions we could reverse-engineer a reaction mechanism for the vinyl iodonium salt. Based on the product structure in comparison to our starting material, we hypothesized that the reaction mechanism would be an addition-elimination reaction resulting in the replacement of the triflate/OTf group with the azide/N_3 on the vinyl substituent. This reaction mechanism is depicted in figure 11.

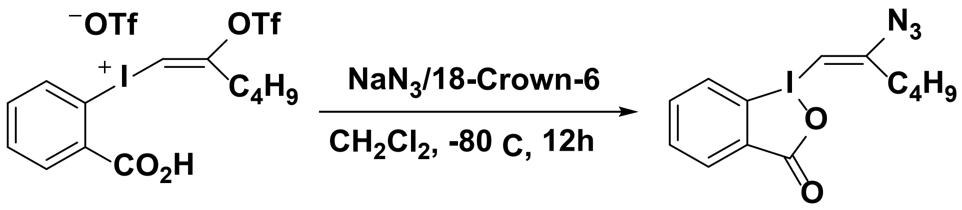


Figure 11: Reaction mechanism hypothesized for nucleophilic substitution

After repeating several trials, we could confirm our hypothesis. We were able to successfully isolate and characterize the final azide product, and now had the information necessary to understand how the vinyl iodonium salt reacts in nucleophilic substitution reactions. Similar to the method that was performed for the synthesis of the iodonium salts, we set out to optimize the reaction conditions to make this azide product and also performed this reaction with a variety of vinyl iodonium salts in order to generate a set of different azide products.

Future Research

The purpose of generating the variety of products was the same as before concerning the vinyl iodonium salts, but there was also another reason this time; these azide compounds have potential to be used as precursors for many biologically active compounds, like pharmaceuticals. Some preliminary investigation suggests that the azide products could undergo reactions with a base to generate a reactive intermediate which could in turn be used to synthesize various *triazoles*. Triazoles are cyclized organic compounds that contain three nitrogen atoms, and they are very common in pharmaceuticals, specifically as antifungal medications. Therefore, since we could synthesize a variety of azide compounds we could then also synthesize a variety of potential pharmaceuticals. Additional research beyond the scope of this project will have to be performed to investigate the conditions necessary to synthesize these triazoles, but there is much promise at this point in the project.

In order to finish this project, a few more versions of the novel compounds need to be investigated; for example, it would be useful to have a vinyl iodonium salt compound that contains a halogen (like chlorine) on the R-group to better understand some of the other reactions that the vinyl iodonium salt can participate in. Additionally, we will need to investigate the use of nucleophiles other than azide/N_3 to make sure that the iodonium salt can participate in several nucleophilic substitution reactions and not just one. The ability to participate in many reactions is desirable since it gives the target compound more potential uses and increase its viability.

Since I will be graduating this spring and there is more than a semester's work to complete for this project, as well as allotting for the time that it will take Dr. Yoshimura to write the publication, the rest of this semester I will be focused on teaching one of our new undergraduate researchers in Dr. Zhdankin's lab this project. I will spend most of the time going over the process of the project thus far, and then explain the future research that needs to be accomplished. I will also need to spend some time working on some techniques with him since some of my reaction conditions are tricky, such as the use of dry ice/acetone to reach low temperatures, but for the most part the student will already be well versed on organic chemistry techniques.

Conclusion

Over the course of my time in Dr. Zhdankin's research lab, we have been able to successfully optimize the conditions necessary for the synthesis of novel vinyl iodonium salts. In addition, we could synthesize a wide variety of these compounds and now have a substantial catalog of compounds that can be generated with our methods. We also determined the reaction mechanism of the vinyl iodonium salts in nucleophilic substitution reactions and were successful in synthesizing a wide variety of azide compounds that have potential applications as pharmaceutical precursors. Some future research will need to be done to complete this project for publication and investigation of pharmaceutical applications will be the basis of a future project.

References

[1]: Kitamura, T.; Nagata, K.; Taniguchi, H. *Tetrahedron Letters* 1995, *36* (7), 1081–1084.

[2]: Kitamura, T.; Fukuoka, T.; Fujiwara, Y. *Synlett* 1996, *1996* (07), 659–660.

General information on iodine and hypervalent iodine from the following textbook:

Zhdankin, V. *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications*;

John Wiley & Sons, 2013