2010

Synthesis and Reactivity of alpha-Azido Acylals

Gretchen Bell
Andrews University, bellg@andrews.edu

John Nevins Andrews Scholars
Andrews University Honors Program

Honors Thesis

Synthesis and Reactivity of α-Azido Acylals

Gretchen Bell

July 27 2010

Advisor: Dr. Desmond Murray

Primary Advisor Signature:_____

Department: _____

Abstract

α-Azido acylals are a novel combination of azide (N_3) and acylal [R-C$(OOCR)_2$] functional groups. Since these compounds are new chemical entities, little is known in the chemical literature about their physical, chemical, and biological properties. This synthetic methodology investigation sought to (1) develop a one-pot, two reaction method for preparing α-azido acylals and (2) investigate the chemical reactivity of α-azido acylals with phosphine reagents.

Progress has been made and will be discussed regarding both the synthesis and reactivity of α–azido acylals. This work developed methods and processes that will have significant impact in our broader objective of exploring the reactivity and determining the synthetic usefulness of novel α-functionalized acylals.

Background and Introduction

α-Azido acylals are a novel combination of azide (N_3) and acylal [R-C$(OOCR)_2$] functional groups in which an azide replaces one of the two acylal ester substituents. Acylals belong to a broad structural class of organic compounds in which two heteroatoms, generally oxygen, sulphur or nitrogen, are attached to the same sp^3 hybridized carbon *via* single bonds. Common examples of this family of organic compounds includes acetals, hemiacetals and aminals as shown below in **Figure 1**.

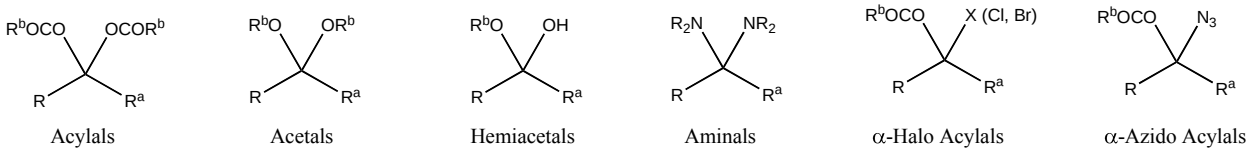


Figure 1: Families of Organic Compounds Related to α-Functionalized Acylals

Due to their 'hybrid' structure, we anticipate that α-azido acylals will exhibit a unique blend of chemical and physical characteristics. In addition, due to their rarity in the chemical literature, little is known about their physical, chemical and biological properties. Therefore, gaining a fundamental understanding of these features is an underlying rationale for this investigation.

The azide functional group has been the topic of an ever-increasing body of research; it has many known applications including explosives, the synthesis of heterocycles, blowing agents and use in the pharmaceutical industry (Bräise). Azides decompose with the release of nitrogen and thus frequently serve as detonators in explosives. For instance, sodium azide is often used to create the nitrogen gas needed for an airbag detonation (Madlung). A famous pharmaceutical application is the azidonucleoside, which in certain forms has been shown to inhibit replication

of the human immunodeficiency virus (HIV) and improve the condition of patients suffering from acquired immunodeficiency virus (AIDS) (Birnbaum).

In organic synthesis, the azide is a common organic functional group utilized extensively and reliably in Staudinger reductions, Staudinger ligations, and aza-Wittig reactions. (Bräise). In all these reactions, an aza-ylide intermediate is formed accompanied by loss of nitrogen upon reaction of the azide with phosphines. In the Staudinger reduction the aza-ylide is hydrolyzed under mild reaction conditions to an amine. In ligations the aza-ylide react (ligate) intramolecularly with an ester to form an amide bond. This process has spawned many useful applications in chemical biology. In the aza-Wittig reaction, aldehydes or ketones reacts with aza-ylide intermediates to form imines.

In contrast to the reactivity of the azide, acylals commonly function in organic synthesis as protective groups for aldehydes. In order to exert selectivity over the reactions of a multifunctional compound, a protective group is used to temporarily block one of the reactive sites so that only the desired part of the molecule participates in the reaction. A protecting group must react selectively in order to give a protected substrate with a high percent yield. It must also be removable in high yield by non-toxic reagents that would not damage the regenerated functional group (Greene). Acylals can be easily obtained by reacting an aldehyde with acetic anhydride and a suitable catalyst at low temperatures. The reverse reaction from acylal to aldehyde is obtained by exposure to high temperature (Guillermo). Our project expands the utility of acylals by shifting its primary function from protective to reactive.

We anticipate that studies such as this project will lay the groundwork for later research involving the applications of α-haloacylals and α-azido acylals. Specifically, this project sought

to (1) develop a one-pot, two reaction method for preparing α-azido acylals and (2) investigate the chemical reactivity of α-azido acylals with phosphine reagents.

The first phase of the study relied on a previously established method for preparation of α–azido acylals. This allowed focus to be placed on establishing a preliminary reactivity trend for α–azido acylals with phosphine reagents. Phosphines were chosen because of their high degree of selectivity, that is, orthogonal chemical reactivity, they were expected to have in reactions with multifunctional α–azido acylals.

Previous chemical literature has established a trend for the reactivity of both the azide and ester functional groups with phosphine reagents. Esters, including acylals, do not react with phosphines, while azides react very readily. This led to the hypothesis that phosphines would react exclusively with the azide functional group in α-azido acylals. This would then form the previously mentioned aza-ylide intermediate as shown in **Figure 2**. From this intermediate it was believed that depending on whether the reaction proceeded intramolecularly or intermolecularly the final products would be an N-acyl imine, an α-acyloxy imine or a mixture of both.

The intramolecular route would involve an unusual variation of the Staudinger ligation. If this pathway occurred, it is predicted that it would involve the formation of a highly strained four-membered ring intermediate that has not been previously reported in Staudinger ligations. In contrast, the intermolecular reaction of the intermediate aza-ylide would involve an aldehyde partner in an aza-Wittig reaction. If this pathway occurred, then α-acyloxy imines would be the predicted product as shown below in **Figure 2**.

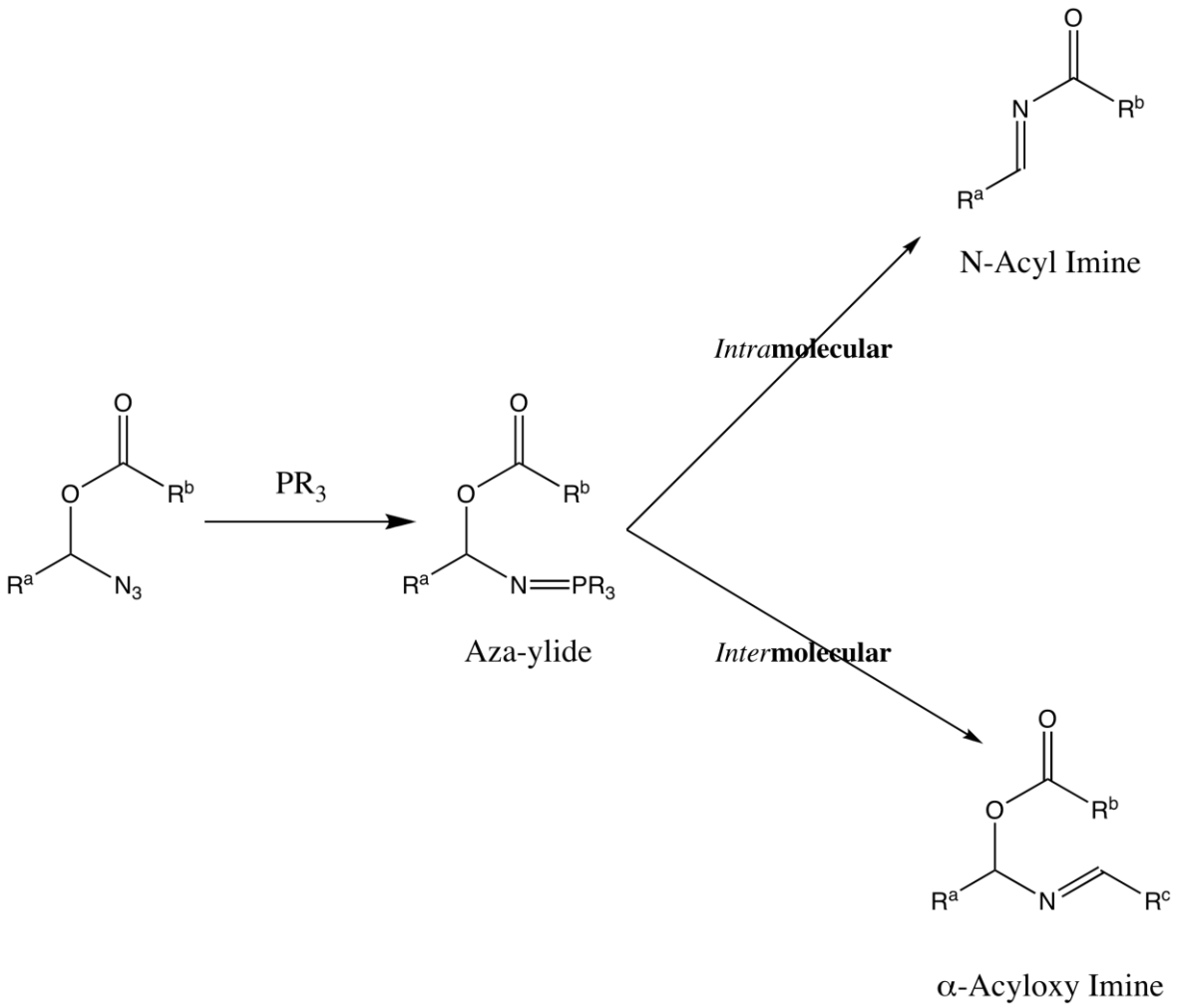


Figure 2: Proposed Phosphine Reaction Pathways for α-Azido Acylals

The second phase of the study focused on refining the synthesis of α–azido acylals. The compound was synthesized by reacting an aldehyde with acetyl bromide to produce an α-bromoacylal. Subsequently, after reaction workup and product isolation, the α-bromoacylal was reacted with sodium azide as shown below in **Figure 3**. This original procedure was a two-step, two-pot process that though effective was time consuming. It involved isolation of unstable α-bromoacylals and often resulted in impure product. To solve this problem, focus was placed on developing a one-pot, two reaction method for preparing α-azido acylals. The goal was not only to make the synthesis more time efficient but also to obtain product that could be easily purified

through standard reaction workup procedure. This would allow for more facile access to large scale quantities of α–azido acylals for subsequent chemical reactivity studies.

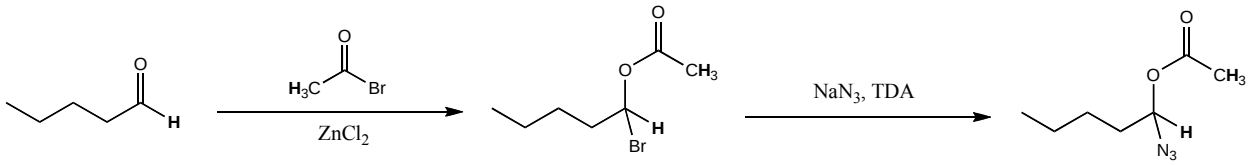


Figure 3: Two-step, Two-Pot Synthesis of α-Azido Acylals from Valeraldehyde

Methodology: Experimental Procedures

Lewis Acid Catalyzed Synthesis of α-Bromoacylal

A 50ml round-bottom flask capped with a $CaCl_2$ drying tube was placed in an ice bath. Anhydrous hexane (20 ml) was added to the round-bottom flask and the magnetic stirrer was turned on. Next zinc chloride (0.0008 mols) was added to the reaction. Then acetyl bromide (0.016 mols) and valeraldehyde (0.016 mols) were slowly syringed into the mixture. The reaction was stirred for 1 hour with the reaction temperature being allowed to rise to room temperature. The reaction flask was removed from the stirrer and the reaction mixture was gravity filtered through anhydrous Na_2SO_4 into a clean oven dried round bottom flask and rotovapped. The product was then collected, weighed and analyzed spectroscopically.

Synthesis of α-Azido Acylal using TDA catalyst

A 25ml round-bottom flask capped with a $CaCl_2$ drying tube was placed in an ice bath over a magnetic stir plate. 20ml acetonitrile was added to the flask. NaN_3 (0.0058 mols), α-bromoacylal (0.005 mols) and TDA (0.000874 mols) were added to flask. The reaction was then stirred for 22 hours and the ice bath warmed to room temperature. The reaction was then quenched in a beaker containing 20 ml $NaHCO_3$ and then washed and extracted 3x using approximately 20 ml CH_2Cl_2

each time. The mixture is then dried using anhydrous Na_2SO_4 and gravity filtered into a clean oven-dried 25ml flask and rotovapped. The product was then collected, weighed and analyzed spectroscopically.

Procedure for Phosphine Reactions

15 ml of fresh dry tetrahydrofuran (THF) were syringed separately into two oven-dried 25 ml round-bottom flasks. The top of each round-bottom flask was fitted with a clean dry condenser capped with a $CaCl_2$ drying tube. To one flask, α-azido acylal (0.00293 mols) and of phosphine reagent (0.00293 mols) were added. To the second flask, α-azido acylal (0.00293 mols), aldehyde (0.00293 mols) and phosphine reagent (0.00293 mols) were added. Both round-bottom flasks were stirred and refluxed for 3 hours. The reaction mixtures were removed from the hot plate and cooled to room temperature. Each mixture was then added to a separatory funnel containing 20ml NaCl solution. The mixture was then extracted 3x using approximately 20ml hexane. The mixture was then dried using Na_2SO_4 and gravity filtered in a clean oven dried 50 ml round-bottom flask and rotovapped. The product was then collected, weighed and analyzed spectroscopically.

Modified Procedure for Phosphine Reactions

15 ml of THF was syringed into an oven-dried 25ml round-bottom flask. The top of the round-bottom flask was fitted with a clean dry condenser capped with a $CaCl_2$ drying tube. The flask were then clamped over a magnetic stir plate. Absolute ethanol (0.004395 mols), α-azido acylal (0.00293 mols), and trimethyl phosphite (0.00293 mols) were added to the flask. The reaction was stirred and refluxed for 3 hours. It was then allowed to cool to room temperature. The reaction was added to a separatory funnel containing 20ml NaCl solution and then extracted 3x using approximately 20ml hexane each time. The reaction was then dried using Na_2SO_4 and

gravity filtered in a clean oven dried 50 ml round-bottom flask and rotovapped. The product was then collected, weighed and analyzed spectroscopically.

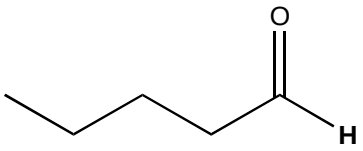
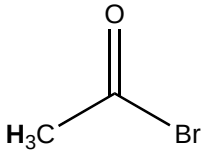
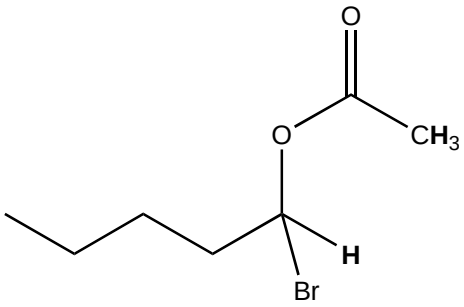
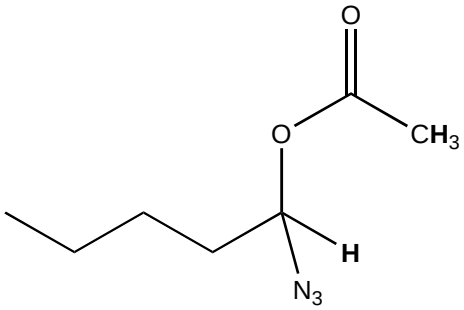
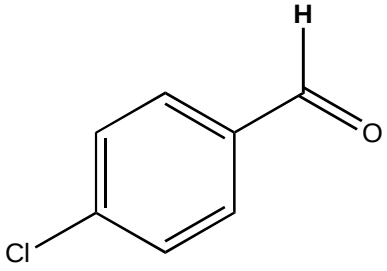
Modified α-Azido Acylal Synthesis (One-Pot, Two Reaction) Procedure

A 50 ml oven dried round-bottom flask was capped with a $CaCl_2$ drying tube and placed in an ice bath over a magnetic stir plate. 15ml cyclohexane followed by ZnO (0.00137 mols) was added to the flask. Acetyl bromide (0.0137 mols) and valeraldehyde (0.0137 mols) were syringed into the round-bottom flask. The reaction was stirred for 2 hours. The reaction was then removed from the stirrer and ZnO was removed by gravity filtration. The reaction was then rotovapped until about 5ml cyclohexane remained. Then 15ml CH_3CN was added followed by TDA (0.00137 mols) and NaN_3 (0.0137 mols) were added to the flask and stirred for 24 hours. 20ml $NaHCO_3$ was used to quench the reaction. The mixture was then extracted 3x using 20ml CH_2Cl each time, dried using Na_2SO_4 and rotovapped. The product was then collected, weighed and analyzed spectroscopically.

Methodology: Spectroscopic Analysis

A very important part of our standard methodology involved spectroscopic analysis of the reaction product. For this, nuclear magnetic resonance (NMR) and infrared (IR) were utilized, with proton (^1H) NMR being the preferred and routinely used method. The ^1H NMR of the starting organic reactants were taken and compared to those of the reaction product. This was a quick method of allowing us to compare and contrast and determine if a reaction occurred or not. It also assisted in determining the structural identity of the reaction product.

Several important diagnostic peaks (**in bold**) in the reactants and products were used in analyzing the ^1H NMR spectra, as shown in the Table below:

Name	Structure	^{1}H NMR Diagnostic Peak (s)
Valeraldehyde		Triplet, 9.7ppm
Acetyl bromide		Singlet, 2.8ppm
α-Bromoacylal		Triplet, 6.6ppm Singlet, 2.1ppm
α-Azido Acylal		Triplet, 5.8ppm Singlet, 2.1ppm
4-Chlorobenzaldehyde		Singlet, 9.9ppm

Results and Discussion

Lewis Acid Catalyzed Synthesis of α-Bromoacylal:

Synthesis of the α-bromoacylal was successful as determined by spectroscopic analysis. The α-bromoacylal was shown to be most effective if used within several days of synthesis due to degradation during long periods of storage. The reaction was run frequently during the project and the relevant data are summarized in **Table 1**.

Table 1: Summary of α-Bromoacylal Synthesis

Experiment Date	**Scale**	**% Yield**	**^{1}H NMR Results**
1/9/10	1x	73.43%	triplet @6.6ppm
1/10/10	5x	90.91%	triplet @6.6ppm
1/25/10	5x	85.20%	triplet @6.6ppm
2/22/10	5x	102.24%	triplet @6.6ppm
5/7/10	5x	82.65%	triplet @6.6ppm

Synthesis of α-Azido Acylal using TDA catalyst:

Synthesis of the α-azido acylal was shown to be most effective if a catalyst was used. The catalyst increased the reaction yield by 'freeing up' the azide from sodium azide which makes the azide more reactive in its' displacement of bromide from the α-bromoacylal. Our catalyst of choice was TDA, which has the ability to surround/solvate/encapsulate the sodium ion and consequently 'free up' the azide nucleophile. The reaction was also successfully scaled up as summarized in **Table 2**.

One of the problems with this method was the difficulty of completely removing the TDA catalyst from the final product mixture.

Table 2: Summary of α-Azidoacylal Synthesis

Expt Date	Scale	Catalyst	% Yield	Results
1/20/10	1x	Absent	68.30%	Mixed. Small 'azide' peak @ 5.8ppm
1/21/10	1x	10% TDA	127.72%	Strong 'azide' peak @ 5.8ppm. TDA peaks b/4-3ppm
1/25/10	5x	10% TDA	90.07%	Strong 'azide' peak @ 5.8ppm. TDA peaks b/4-3ppm
2/17/10	5x	10% TDA	128.33%	Strong 'azide' peak @ 5.8ppm. TDA peaks b/4-3ppm
5/10/10	5x	10% TDA	124.96%	Strong 'azide' peak @ 5.8ppm. TDA peaks b/4-3ppm

Phosphine Reactions of α-Azido Acylals:

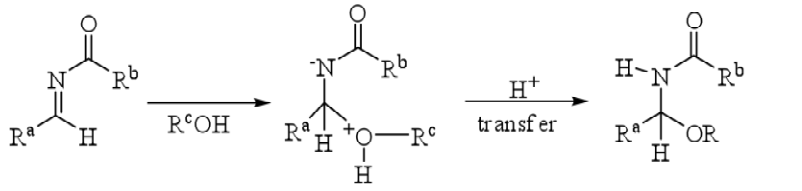
The reaction of α-azido acylals with phosphines were conducted in pairs: with aldehyde and without aldehyde. The aldehyde used was 4-chlorobenzaldehyde. Preliminary results showed that the transformation of the α-azido acylal was occurring in all reactions, with and without aldehyde, as indicated by disappearance of the characteristic azide triplet at 5.8ppm in the ^{1}H NMR (see **Table 3**). It was often difficult to conclusively discern the identity of the products due to contamination by TDA catalyst and phosphine reagents.

The persistent presence of the 9.9ppm diagnostic peak from 4-chlorobenzaldehyde suggested that the intermolecular imine-forming reaction pathway was not occuring. Based on these results we hypothesized that N-acyl imines were forming but because of their well-known reactivity/instability, they were immediately breaking down in the reaction flask or being

Table 3: Summary of Phosphine Reaction Results

Expt Date	Reagent	Aldehyde	Results
2/17/10	Tributylphosphine	Absent	No triplet@ 5.8ppm.TDA peaks b/4-3ppm
2/17/10	Tributylphosphine	4-chlorobenzaldehyde	No triplet@ 5.8ppm.TDA peaks b/4-3ppm
2/18/10	Triphenylphosphine	Absent	No triplet@ 5.8ppm.TDA peaks b/4-3ppm
2/18/10	Triphenylphosphine	4-chlorobenzaldehyde	No triplet@ 5.8ppm.TDA peaks b/4-3ppm
2/22/10	Triethylphosphite	Absent	No triplet@ 5.8ppm.TDA peaks b/4-3ppm
2/22/10	Triethylphosphite	4-chlorobenzaldehyde	No triplet@ 5.8ppm.TDA peaks b/4-3ppm

hydrolyzed in the work-up procedure. So, modified phosphine experiments were designed to 'trap' the predicted unstable N-acyl imine from the intramolecular reaction pathway. We further speculated that identifying the presence or absence of the N-acyl imine could be determined through this proposed mechanism:



N-Acyl Imine
(Unstable
very reactive)

α-alkoxy Amides
(Stable
Isolatable)

Table 4: Summary of Modified Phosphine Reaction Results – Search For N-Acyl Imines

Expt Date	Reactant	Temperature	Solvent	Results
5/6/10	Styrene	Reflux	THF	No triplet@ 5.8ppm
5/6/10	Furan	Reflux	THF	No triplet@ 5.8ppm
5/6/10	Absolute Ethanol	Reflux	THF	No triplet@ 5.8ppm
5/11/10	Absolute Ethanol	20-25°C	THF	Azide triplet @5.8ppm
5/11/10	No	20-25°C	THF	Azide triplet @5.8ppm
5/14/10	Absolute Ethanol	Reflux (24 hour)	THF	undefined azide triplet@5.8ppm
5/14/10	Absolute Ethanol	20-25°C	Toluene	No triplet@ 5.8ppm
5/14/10	No	20-25°C	Toluene	No triplet@ 5.8ppm

The reflux reaction with absolute ethanol showed some evidence of the formation of an N-acyl imine, though due to the impurity of the α-azido acylal these results were not entirely conclusive.

Modified α-Azido Acylal Synthesis (One-Pot, Two Reaction)

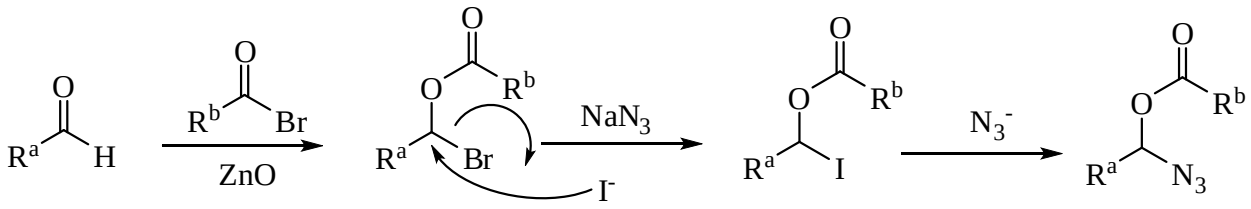
During the second phase of the project α–azido acylal was successfully synthesized by a one-pot, two reaction method. For the reaction to be successful it was necessary for the ZnO to be filtered out between the first and second steps and the cyclohexane evaporated off till only about 5ml remained. Though more time efficient, the product mixture still contained TDA after

workup. Multiple variations of the procedure involving catalyst and workup proved ineffective to resolve this problem. Chromatography also proved unsuccessful, no purified α–azido acylal was obtained. Synthesis of the α–azido acylal from an aldehyde with a smaller chain also proved ineffective, the product was too volatile to 'withstand' the vacuum line.

Table 5: α-Azido Acylal Synthesis (One-pot, Two Reaction) with Organic Catalyst

Expt Date	Catalyst	Workup	% Yield	Results
5/17/10	10% TDA	$NaHCO_3$	42.30%	No triplet @5.8 ppm
5/19/10	10% TDA	$NaHCO_3$	unknown	Azide triplet@ 5.8ppm. TDA peaks b/4-3ppm.
5/24/10	10% TMEDA	$NaHCO_3$	58.97%	Very faint azide triplet@ 5.8ppm; TMEDA present
5/24/10	10% TMPDA	$NaHCO_3$	50.85%	azide triplet@ 5.8ppm; TMPDA present
6/8/10	5% TDA	H_3PO_4	unknown	No triplet @5.8 ppm
6/8/10	10% TDA	H_3PO_4	10.68%	No triplet @5.8 ppm
6/22/10	5% TDA	$NaHCO_3$	56.41%	Mixed: Starting Material. Azide triplet@ 5.8ppm. TDA peaks b/4-3ppm.
6/22/10	2.5% TDA	$NaHCO_3$	47%	Mixed: Starting Material. Small Azide triplet@ 5.8ppm. TDA peaks b/4-3ppm.
6/24/10	20% TDA	H_2O	64.10%	Azide triplet@ 5.8ppm. TDA peaks b/4-3ppm.

In order to solve the problem of the catalyst a different approach was tried replacing TDA catalyst with iodides and carbonates. The preliminary results of these attempts are very promising. The KI and NaI reaction schemes are proposed to have progressed through a double displacement S_N2 mechanism. This is successful because iodide is both a better nucleophile and a better leaving group than bromide as shown below.



In the case of the carbonate synthesis, the Cs and K ions are believed to have exchanged with the sodium from sodium azide forming the more reactive cesium and potassium azides, respectfully. Potassium and Cesium are larger ions, and are less tightly bound to azide, which allows the azide to react more freely.

Table 6: α-Azido Acylal Synthesis (One-Pot, Two Reaction) with Inorganic Catalyst

Expt Date	**Reactant**	**% Yield**	**Results**
7/13/10	K_2CO_3	59.82%	Azide peak @ 5.8ppm
7/13/10	Cs_2CO_3	59.82%	Azide peak @ 5.8ppm
7/13/10	KI	76.92%	Azide peak @ 5.8ppm
7/13/10	NaI	53.41%	Azide peak @ 5.8ppm

Future Directions

The future direction of this research would be to further explore and refine synthesis of the α-azido acylals without the use of an organic catalyst. Since unlike TDA, the excess iodide and carbonate are both inorganic it should be much simpler to purify the α-azido acylals through normal lab techniques. While this work is based on stoichiometric quantities of inorganic salts, future work will focus on the use of catalytic amounts. In addition, tetraalkylammonium iodide may also be an effective and will be tried.

The use of inorganic catalysts will also be applied to α-chloro acylals to determine their effectiveness in these double S_N2 reactions. This methodology will also be extended to other nucleophiles, like, isocyanates and isothiocyanates.

Further phosphine reactions with α-azido acylals would be conducted to determine more conclusively their reactivity and their potential utility in N-acyl imine chemistry.

Annotated bibliography

1.Allison Agnetta, Jihye Ha, Tenesha Patrick, Kimberly Robinson, Carrie Roosenberg, Desmond Murray. "Electrophilic Carbonyl Additions: Synthesis of a-Haloacylals." Undergraduate Research Poster Session, Division of Chemical Education, 233rd American Chemical Society National Meeting, Chicago, IL, March 26, 2007.

This project is useful to the synthesis of α-azido acylals. Dr. Murray and several student researchers compare and contrast electrophilic carbonyl addition using a cationinic trigonal intermediate versus nucleophillic carbonyl addition with a anionic tetrahedral intermediate. The electrophillic carbonyl addition was tested using various aldehydes and acyl halides. Results showed that alkyl aldehydes give a better yield of product than aryl aldehydes. It also showed that there are multiple acid halides that can act effectively in catalyzing the reaction.

2.Bräse, Stefan Carmen Gil, Kerstin Knepper and Viktor Zimmermann. "Organic Azides: An Exploding Diversity of a Unique Class of Compounds" Angewandte Chemie International Edition 44(2005): 5188.

The authors review the fundamental characteristics of azide chemistry as well as reviewing current research being done in the field. They found that despite their difficult characteristics such as explosiveness and toxicity, that organic azides are useful in synthesis particularly in cycloadditions. The Aza-Wittig reaction is most commonly used to synthesize nitrogen heterocycles with the success of the reaction dependent upon the chain length and nitrogen and phosphorous substituents on the precursors

3.Birnbaum, George I, Jerry Giziewicz, Eric J. Gabe, Tai-Shun Lin and William H. Prusoff. "Structure and Conformation of 3-azido-3-deoxythymidine (AZT), an inhibitor of the HIV (AIDS) Virus" Can. J. Chem. 65, 2135 (1987). Web, 19 July 2010.

The article provides necessary and relevant background information on the azide functional group specifically the role of the azidonucleoside in the treatment of AIDS. The authors examine azidonucleosides and the role of AZT in inhibiting the replication of the HIV virus. The primary emphasis of their project was to develop the exact crystalline structure of AZT.

4.Chen, Jiehao and Craig J. Forsyth. "Synthesis of the Apratoxin 2,4-Disubstituted Thiazoline via an Intramolecular Aza-Wittig Reaction" Organic Letters 5 (2003): 1281-1283.

Vicinal azido-thiolesters were converted into 2,4-disubstituted thiazolines using a sequential in pot reaction, the second half of which utilized an intramolecular Aza-Wittig mechanism. They found this type of in pot reaction allowed the reaction to proceed under neutral conditions without the complication of dehydration. The reaction used Ph3P in THF at anhydrous conditions at 50°C which gave them a good percent yield of their target thiazolines. Their

reaction conditions provide more background about setting up similar experiments focused on the Aza-Wittig reaction.

5.Chujo, Yoshik and Junpei Miyake. " The Aza-Wittig Polymerization: An Efficient Method for the Construction of Carbon-Nitrogen Double Bonds-Containing Polymers" Macromolecules 41 (2008): 5671-5673.

The investigators used the Aza-Wittig reaction to attempt the novel synthesis of C=N group containing-polymers. They found that the polymerization was not only possible, but also easily controllable by controlling the steric and and electronic features of the phosphine reagents involved. The phosphine reagents that were sterically hindered by the presence of bulky organic substituents were unable to undergo the polymerization reaction. For example triphenylphosphine (PPh3) a widely used reagent in the Aza-Wittig reaction was found to be inappropriate for the polymerization reaction.

6.Fernando P., Alonso Concepcion, Lecea Begona, Mirari Ayerbe, Gloria Rubiales, and Francisco Palacios. "Mechanism and Stereoselectivty of the Aza-Wittig Reaction between Phosphazenes and Aldehydes, Cossio" Journal of Organic Chemistry 71 (2006): 2839.

The Aza-Wittig reaction was used to synthesize phosphazenes and aldehydes. The experimenters' general description of Aza-Wittig reaction and its products may be applicable to other Aza-Wittig reactions such as my own.

7.Greene, Theodora and Peter G. M. Wuts. "Greene's Protective Groups In Organic Synthesis" Hoboken, John Wiley & Sons Inc. 2007. Print.

Greene's work is a comprehensive review of the role of the protective group in organic synthesis. It was used to provide relevant information since the predominantly known application for the acylal functional group is protective not reactive.

8.Headley, Catherine E and Stephen P. Marsden. "Synthesis and Application of P-Stereogenic Phosphines as Superior Reagents in the Asymmetric Aza-Wittig Reaction" Journal of Organic Chemistry 72 (2007): 7185-7189.

Phospho-boranes were deprotected and used as reagents in the asymmetric aza-Wittig reaction. The phospines that had bulky substituents had to be heated before they could undergo the reaction. It was also discovered that the alkyl substituents on the aryldialkylphosphines are best when maximally differentiated which is important when engineering the phosphine reagents.

9.Madlung, A. "The Chemistry Behind the Air Bag: High Tech in First-Year Chemistry," (1996) *J. Chem. Ed.,* **73** (4), p. 347-348. Print.

The author details the history of airbags and their current role in the modern American automotive Industry. He then details how airbags work, specifically the chemical the involved and their uses. The article culminates with a suggested laboratory exercise geared toward first year chemistry students. This article was useful for establishing specific background knowledge of applied uses for the azide functional group.

10.Murray, Desmond H. "Electrophilic Carbonyl Additions: A Forgotten Class of Carbonyl Reactions." Ninth Tetrahedron Symposium Poster Session, Berkeley, CA, July 22-25, 2008.

This project is useful in the synthesis of α-azido acylals. It reacts aldehydes with chloroformates, chlorocarbamyls, sulphonyl cholorides and other halogenated compounds versus the more common reaction with acid halides. Acylals as well as other compounds were formed. It was determined that 10-20% Lewis acid as well as a simple alkyl or aralkyl halide gave the best yields of product.

11. Negron, Guillermo E. et al . A mild and efficient method for the chemoselective synthesis of acylals from aromatic aldehydes and their deprotections catalyzed by sulfated zirconia. J. Braz. Chem. Soc., São Paulo, v. 16, n. 3a, June 2005 . Web. July 19 2010.

Aldehydes were converted to acylals and then back using heat and a reusable catalyst. Guillermo's work details a specific example of how the acylal functional group can play a protective group in organic chemistry. It was useful to this project because it gave relevant background information about the uses and reactivity of the acylal functional group.

12.Sigma-Aldrich. Web. July 21 2010.

The Sigma-Aldrich website is a well known website for a well-known chemical distribution company. They supplied many of the chemicals used in this project. The website was used to verify information about the chemicals, chemical structure and reaction equations.

13.Ryosuke Matsubara and Shu Kobayashi "Enamides and Enecarbamates as Nucleophiles in Stereoselective C-C and C-N Bond-Forming Reaction"Accounts of Chemical Research 41 (2008): 292.

Enamides and Enecarbonates were used to make a novel type of nucleophile instead of the more common metal enolates and enamines. Revealed that in nucleophillic addition the compounds' hydrogen or nitrogen atom readily form N-protected imines. Specifically the authors reacted enecarbamates with aldeheydes to form N-acylamines. The observed the stereo specificity of this

reaction; E-carbamates gave anti products while Z-carbamates gave syn products. They also found they could decrease the catalyst to as little as 0.1% mols in some cases of the reaction.

14."1,2,3-Triazole" *Museum of Learning* Web. July 19 2010.

The Museum of learning website provides relevant and factual articles on a variety of topics. For this project it was used to verify and specify information on the uses of the 1,2,3-Triazole which is briefly mentioned in Bräse's work as being one of the applications for the azide functional group.