Transamination of Amides Using Azanides

Introduction

Amide bonds are very strong, very stable chemical bonds formed between amines and carbonyl groups. They are found synthetically in polymers such as nylons, where they afford nylon its tensile strength. They are ubiquitous in biological settings, where they are called peptide bonds. Peptide bonds are essential for biological life as they provide kinetic and thermodynamic stability to proteins.

To break peptide bonds, expensive and synthetically limited enzymes are required. [1] Alternatively, polyamides, such as proteins, can be reacted with strong acids or alkali solutions under heat for extended periods of time. The former method can generally only cleave peptide bonds at the ends of a chain or a specific bond in a specific protein, limiting their usage. The latter method has no control over which bonds break as it breaks all of them and is energetically inefficient e.g. requires heating at 300 °C for 24 hours.

Many drugs and medicines are formed using amide bonds to help them interact with biological target sites effectively. Often, this makes them susceptible to *in vivo* degradation by enzymes. Peptoids, N-substituted amides, have been used frequently in drug development to shield medicines from enzyme attack. [2]

Azanides are amino anions i.e. deprotonated amines. They have few known synthetic uses as they are generally too basic to give the control needed for synthetic application. [3]

In short, my proposal is to discover under what reaction conditions azanides can be used to transaminate amides, i.e. to cleave the amide bond and replace the amine part with a substituent amine residue. The likelihood is that to make the amino leaving group stable enough for this reaction to occur, N-substituted amides will need to be used. These reactions will be analogous to the targeted cleavage of peptoids and could be used to develop methods of joining peptide chains together for use in drug development.

Research Questions

1: Under what reaction conditions can the transamination of amides using azanides occur?

2: Can these methods be used to develop synthetic routes to transaminate and/or cleave peptoid bonds?

3: Can peptoid bonds be cleaved or transaminated selectively while they are part of a peptide chain?

4: Can azanide-peptoid pairs be developed to join pairs of peptide chains together?

Methodology

1: Test a series of small amides such as acetamide, N-methylacetamide, etc. with small azanides such as azanide, methylazanide, etc. in various solvents to develop a uniform

approach to experimentation with which to test larger molecules. The success of each reaction will be determined using various analytical methods available in the department: mass spectrometry, NMR and IR spectroscopy.

2: Amides with larger and more complicated leaving groups will likely be needed to stabilise the amine leaving groups and help the reactions progress. This will be done by substituting appropriate stabilising groups such as phenyl groups on to the amine part of the amide. N-substituted amides are also known as peptoids. Some of these will be commercially available but others may need to be developed. The Cobb group has experience in the development of peptoids [4] and Dr. Cobb's field of expertise is peptide and peptoid science. [5] At this stage, I will likely be taking advantage of that expertise to develop the necessary synthetic pathways for my project.

3: Once peptoid transamination has been developed, it may be possible to do so on larger chains of amides, e.g. synthetic peptides with a single peptoid linkage. Peptide chains like this are available commercially and are developed in the Cobb group so a variety of target molecules will be available for testing. It is likely that acutely designed reaction conditions will be needed to prevent side reactions. This will likely include extensive use of protecting groups and solid-phase synthesis, both specialities of the Cobb group.

4: Quasi-peptide-chain pairs will be developed where one chain of the pair has an azanide group at the N-terminal end and the other has a peptoid linkage to see if the methods developed through the course of experimentation can be used to join peptide chains together using azanide transamination.

Outcomes

I am expecting parts 1 and 2 to be successful, if potentially difficult, within the allotted time. After talking to Dr. Cobb, we have agreed that this research may take longer than 6 weeks and have each scheduled 10 weeks into the first summer. Parts 3 and 4 are theoretically possible but I cannot say as to how synthetically successful we will be at this stage.

It should be understood that this research is very novel. The only reactions involving azanides and amides I have been able to find have involved using amides as solvents.[6] If successful, this research will open up a broad series of previously unexplored synthetic pathways.

It is also likely that earlier experimentation may inadvertently yield new synthetic pathways for imidic acids and amide-alkenes too due to possible side reactions during the development of a working practical method.

I am expecting that, although we may not be successful with parts 3 and 4 at this stage, we will be able to provide insight and direction for future experimentation for myself, Dr. Cobb and his team, and other researchers.

References

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