

3.1: Introduction to Neighboring Group Participation, Rearrangements, and Fragmentations

Objectives

After completing this section, you should be able to:

1. Understand the general reaction types classified as neighboring group participation, rearrangements, and fragmentations
2. Spot structural fragments that favor neighboring group participation, rearrangements, and fragmentations

Key Terms

Make certain that you can define, and use in context, the key terms below.

- Neighboring group participation
- Rearrangement
- Fragmentation

Study Notes

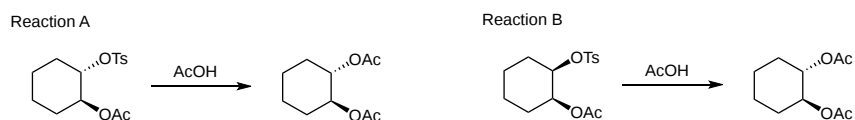
In Intro Orgo, you learned about common substitution and elimination reactions of alkyl halides (and halide equivalents like tosylates) and classified them as S_N1 , S_N2 , E1, and E2. In this section, we are going to introduce you to more interesting reactions that begin with standard R-X or R-OTs starting materials. Our goal in this introductory chapter is to provide an organizational framework that will help guide your more in depth study in the following three chapters. Don't worry about the lack of problems in this chapter, there will be plenty of problems to come when we talk about neighboring group participation, rearrangements, and fragmentations each in their own specific chapter.

Content

As with many topics in Intro Orgo, we only scratched the surface when introducing reactions of alkyl halides. You learned a variety of useful substitution and elimination reactions but likely haven't met reactions that involve neighboring group participation. When studying carbocations formed in S_N1 and E1 reactions, you probably learned about simple carbocation rearrangements like hydride, methyl, and alkyl shifts. However, it's unlikely that you were introduced to fascinating rearrangements like the pinacol, Favorskii, or Wolff rearrangements. Finally, fragmentation reactions, where key structural carbon-carbon bonds are cleaved to generate a new carbon skeleton, were probably not mentioned. Let's spend this chapter briefly introducing each of these reactions before studying them in depth in the following chapters.

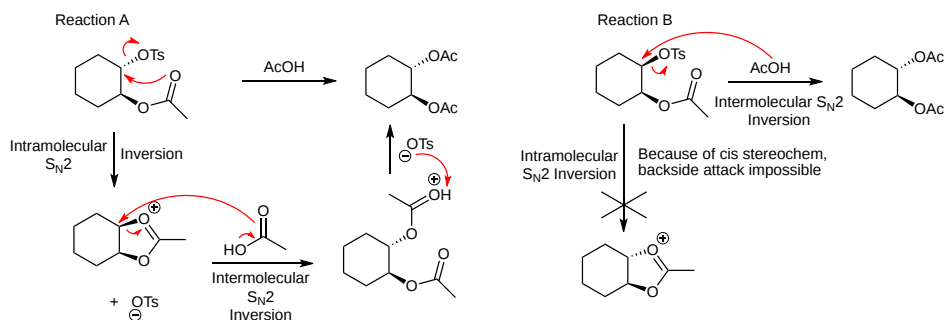
Neighboring Group Participation (NGP)

As the name implies, this class of reactions relies on the influence of a neighboring group to explain what at first seem like incomprehensible reactions. These are generally substitution reactions that have unexpected outcomes. Their mechanisms become clear, however, once you spot the participation of an intramolecular nucleophile on the reaction outcome. Don't forget that intramolecular nucleophiles can be either a lone pair on a heteroatom or an electron rich pi bond. The following pair of reactions illustrates the importance of understanding neighboring group participation. These are substitution reactions of diastereomeric tosylates that yield the identical trans product. These look like straightforward substitution reactions where an acetate nucleophile replaces a tosylate leaving group. Reaction B fits the pattern we learned in Intro Orgo for an S_N2 reaction. The cis starting material reacts with complete inversion to yield the trans product. However, what's happening in Reaction A? This substitution reaction proceeds with complete retention, the trans starting material yields a trans product. This can't be an S_N1 reaction since we learned that will yield a racemic mixture (1:1 mixture of cis and trans products). How do we get only retention? The most straightforward way is if two consecutive S_N2 reactions occur. How is this possible? If the acetate group that starts on the molecule participates in the reaction as the neighboring group, this explains the outcome.



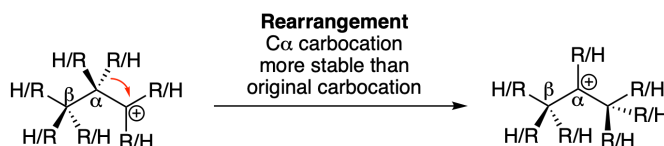
Looking at the mechanisms, we can understand the reactions. In Reaction A, the neighboring acetate group (always draw out the complete functional group structure to spot if NGP is possible) can participate in an intramolecular S_N2 reaction resulting in the first inversion. This is followed by the second S_N2 reaction which is of the intermolecular variety with acetic acid. Deprotonation

yields the trans product. The mechanism demonstrates how retention is possible: an intramolecular S_N2 reaction followed by an intermolecular S_N2 reaction. In Reaction B, due to the cis stereochemistry, an intramolecular S_N2 reaction is impossible. The cis acetate can't participate in a backside attack since it is on the same face as the leaving group. So, this reaction can only undergo a standard intermolecular S_N2 reaction to yield the same trans product.

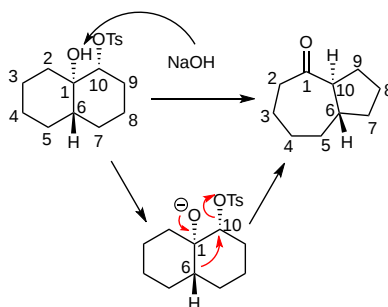


Rearrangements

You have likely already seen carbocation rearrangements in Intro Orgo. When generating a carbocation as part of an S_N1 and/or $E1$ reaction, you were told to "beware of rearrangement". Thus, you analyzed the structure to determine the type of carbocation generated (primary, secondary, tertiary, and/or resonance stabilized) and looked to the adjacent carbons (the alpha carbons) to see if they would be a more stable carbocation (more highly substituted or resonance stabilized). If so, a group on the adjacent carbon "shifted" to make a new bond to the carbocation. The most common rearrangement being a hydride shift, but you likely also saw alkyl shifts.

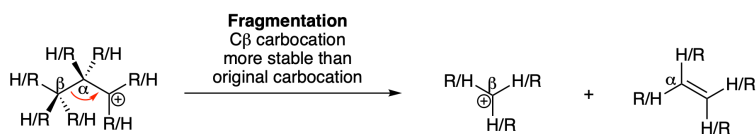


Rearrangements definitely occur from carbocation intermediates (as pictured above); however, the most synthetically useful rearrangements proceed via mechanisms that don't involve true carbocation intermediates. The lack of a carbocation helps control the selectivity of the reaction toward production of only the desired target. To identify a rearrangement that doesn't involve a carbocation, the key is to spot a leaving group next to a group that promotes rearrangement. A common example is an alcohol that can turn into a carbonyl upon rearrangement. For example, the semipinacol rearrangement shown below highlights a rearrangement promoted by the loss of a tosylate and the formation of a carbonyl. Deprotonation by sodium hydroxide generates the negatively charged intermediate that undergoes rearrangement. Formation of the new carbonyl at C1 promotes rearrangement resulting from cleavage of the C1-6 bond to form the new C6-10 bond. This rearranges the original bicyclo[6,6] system into a new bicyclo[5,7] system. We will see many more examples of cationic and anionic rearrangements in an upcoming chapter.

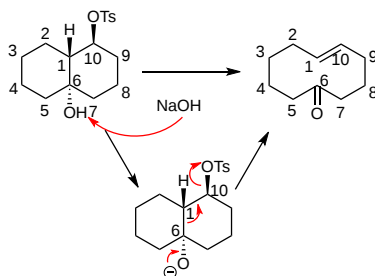


Fragmentations

Fragmentations are related to rearrangements in that the structural fundamentals vary slightly. For cationic intermediates, rearrangements occur when the alpha carbon is a more stable carbocation. Fragmentations occur with the beta carbon is a more stable carbocation. This results in cleavage of the alpha-beta C-C bond, the beta carbon becomes the new carbocation, and formation of a new alkene.



Investigating a substrate similar to our rearrangement example above, we can see that true carbocations aren't necessary for fragmentations either. We just need the fragmentation promoting group, an alcohol in this case, one more bond away from the leaving group. With the OH on C6, formation of the new carbonyl promotes cleavage of the 1-6 bond to form a new alkene upon loss of the tosylate leaving group. This example demonstrates the power of the Grob fragmentation for the production of medium-sized rings, in this case a 10-membered ring, that are often difficult to make.



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