3.4: Fragmentations

Objectives

After completing this section, you should be able to:

1. Spot structural fragments that favor fragmentation reactions
2. Draw mechanisms incorporating fragmentations to explain reaction outcomes

Key Terms

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

- Grob Fragmentation
- Eschenmoser Fragmentation

Study Notes

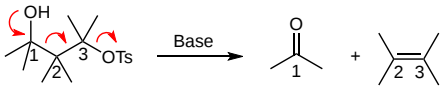
We briefly introduced fragmentations in a previous chapter and you likely did not learn about them in Intro Orgo. We also met the Beckmann fragmentation at the end of the previous chapter on rearrangements. In this chapter, we will focus exclusively on fragmentations that are synthetically useful. Like rearrangements, fragmentations occur readily under strongly acidic conditions, but this leads to uncontrolled decomposition for most substrates. You will see that useful fragmentations occur under conditions similar to rearrangements but with a slightly different arrangement of atoms, one more carbon between the fragmentation promoting atom (generally O or N) and the leaving group. Fragmentations are much less common than rearrangements.

Content

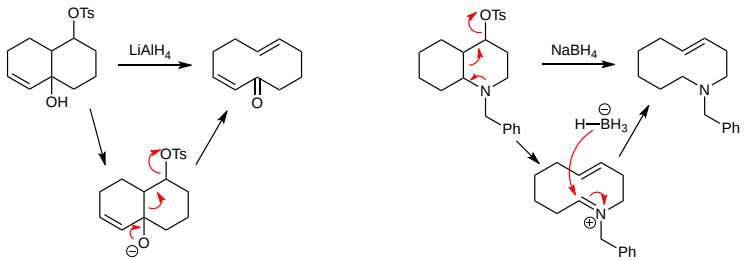
In this chapter, we will introduce the most important fragmentations you will likely encounter in organic synthesis papers. We also know this will provide you with the skills to understand other reactions that you might encounter during your studies. Heteroatom placement in these reactions is critical, with heteroatoms playing the roles of both leaving groups and fragmentation promoting atoms. We will see that substrates fragment to make new C-C bonds and turn cyclic molecules into acyclic targets. Fragmentations also provide a novel method for the synthesis of challenging medium-sized rings upon fragmentation of bicyclic systems.

Grob Fragmentation

The Grob fragmentation is similar to the pinacol rearrangement. Substrates that are 1,2-diols (or 1,2-diol type compounds) undergo the pinacol rearrangement to yield a new ketone or aldehyde. Substrates that are 1,3-diols (or 1,3-diol type compounds) undergo the Grob fragmentation to yield both a new ketone/aldehyde and an alkene, as shown below.

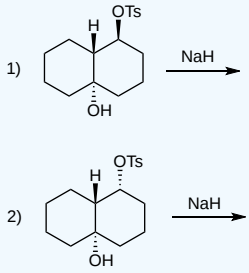


The Grob fragmentation is an excellent method for constructing medium or large rings from bicyclic systems. Two examples for the synthesis of 10-membered rings are shown below. The example on the left is a standard Grob fragmentation. A deprotonated alcohol forms a carbonyl that promotes cleavage of the adjacent C-C bond (the fragmentation) to generate a new alkene and loss of the tosylate leaving group. The example on the right highlights that nitrogen can also function as a fragmentation promoting atom. In this case, fragmentation and loss of tosylate yields a new alkene and an iminium ion. Sodium borohydride reduces the iminium ion to yield the amine product. The example on the left is actually an oversimplification of this reaction because it does not show stereochemistry. Fragmentations are similar to E2 reactions and cyclic pinacol rearrangements in that the reacting groups must be antiperiplanar for constructive orbital overlap to occur. The follow problem explores the importance of stereochemistry for the Grob fragmentation.



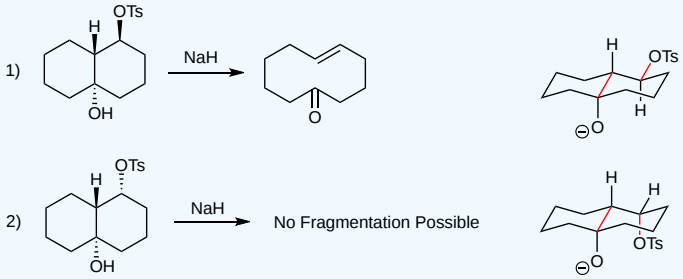
Exercise 3.4.1

Only one of the following two reactions yields a Grob fragmentation. Which reaction is it? Explain. Hint: It is very helpful to draw out these trans decalin molecules in the chair conformation.



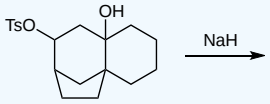
Answer

Reaction #1 undergoes the fragmentation while reaction #2 does not. Focusing on the chair conformation for each molecule, we can explain why. In the first reaction, the fragmenting C-C bond and the bond to the leaving group are anti (both in red). In reaction #2, the fragmenting C-C bond and the leaving group (both in red) are not anti. Instead, a C-H bond is anti to the fragmenting C-C bond so the reaction does not occur.



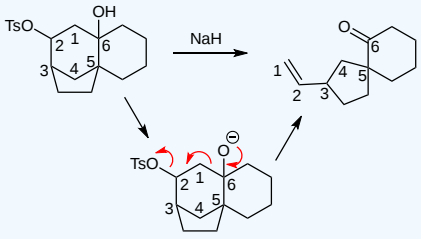
Exercise 3.4.2

Predict the product of the following reaction.



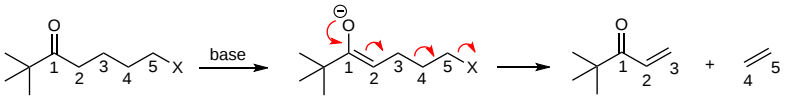
Answer

Following our standard strategy for the Grob fragmentation, we can show how the starting tricycle fragments into the product bicycle. As always, numbering helps keep track of atoms.



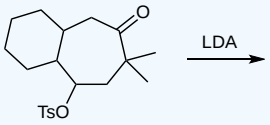
1,5-Fragmentations

Though much less common than Grob fragmentations, 1,5-fragmentations are also possible. These substrates start as ketones or aldehydes and the reaction is promoted by base induced enolate formation. Upon fragmentation, they yield an unsaturated ketone and an alkene, as shown below.



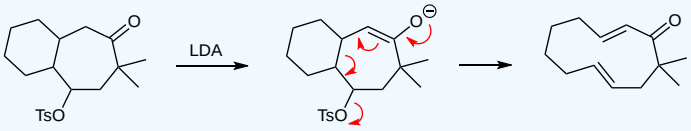
Exercise 3.4.3

Predict the product of the following reaction.



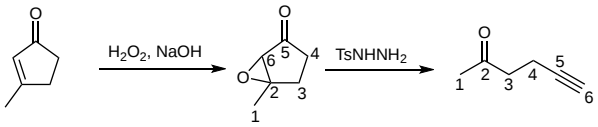
Answer

After formation of the enolate, the molecule can fragment as shown above to yield the 11-membered ring product.

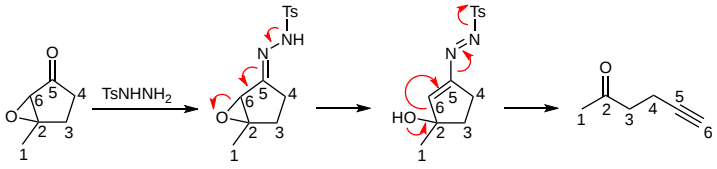


Eschenmoser Fragmentation

The Eschenomser fragmentation (sometimes called the Eschenmoser-Tanabe fragmentation) was discovered in 1967 in the lab of Albert Eschenmoser at the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland. Much of the early work on the scope of this reaction in the Eschenmoser lab was conducted by Dorothee Felix. The reaction begins with the epoxidation of a cyclic conjugated enone to yield an epoxy carbonyl. Treatment of this molecule with tosyl hydrazine promotes fragmentation to remove the ring, generating a new carbonyl and alkyne.

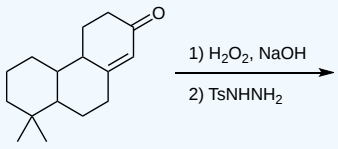


The mechanism of the fragmentation reaction is similar to the Wolff-Kishner reaction (reduction reaction of carbonyls with hydrazine and base) with important differences due to the presence of the epoxide and the tosylate group. After formation of the tosyl hydrazone, the important mechanistic steps begin. Movement of electrons from the nitrogen attached to the tosyl forms a double bond between the nitrogens, creates a C5-C6 alkene, and opens the epoxide. Next, the electrons flow back in the opposite direction. A carbonyl forms which cleaves the C2-C6 bond (the fragmentation) to yield the product alkyne while generating nitrogen gas (N_2) and the tosyl leaving group.



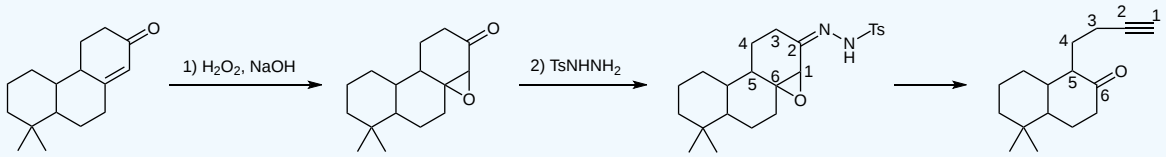
Exercise 3.4.4

What is the product of the following reaction sequence?



Answer

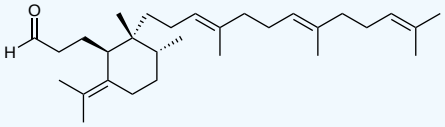
Like all Eschenmoser fragmentations, the reaction will ultimately cleave the alkene bond in the original conjugated enone. The means that the alkene carbon farthest from the carbonyl (the beta carbon) will turn into the product ketone while the other carbon from the alkene and the ketone carbon will turn into the product alkyne. Applying this along with the mechanism show above yields the target, containing one fewer ring than the starting material.



Summary Problems

Exercise 3.4.5

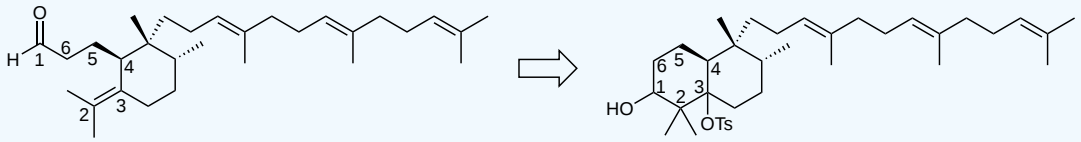
The triterpene shown below was shown to arise biosynthetically via a Grob fragmentation. Propose a reasonable precursor that would participate in this fragmentation to yield the given target.



Answer

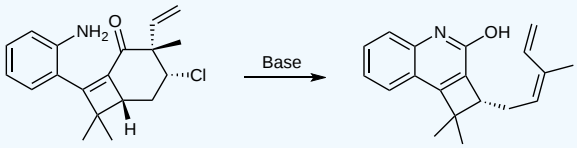
Returning to our introduction of the Grob fragmentation above, we can see that the product has a carbonyl at C1 and an alkene between C2 and C3. This means for our 1,3-diol type starting material, we need the alcohol at C1 and the leaving group at C3. We also need a bond between C1 and C2 that will cleave during the fragmentation reaction. That means our starting material is the bicyclic molecule shown below.

Reference - *Angewandte Chemie* 2006



Exercise 3.4.6

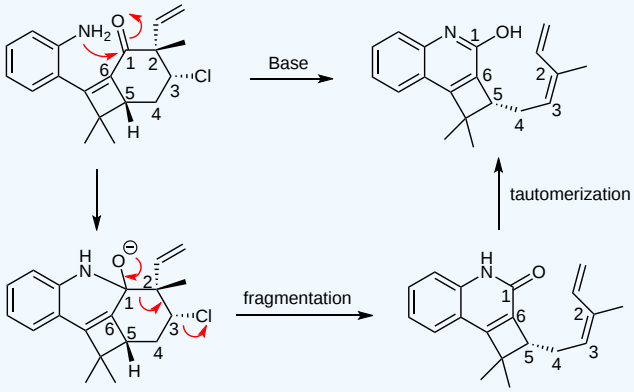
The following undesired reaction occurred during John Wood's synthesis of welwitindolinone. Propose a mechanism to explain this transformation. Hint: The final step of the mechanism is a tautomerization reaction to generate the bicyclic aromatic system from a lactam.



Answer

The mechanism starts with an intramolecular carbonyl addition of the amine to the ketone. (Base removes a proton from the amine after the addition.) The resulting tetrahedral intermediate is set up perfectly for a fragmentation due to the chloride leaving group at the 3-position. So, the carbonyl reforms, the C1-C2 bond cleaves to form the C2-C3 alkene, and chloride leaves. This yields a lactam that tautomerizes to the product quinoline structure.

Reference: *Journal of the American Chemical Society* 2008



Contributors

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