Diels Alder Class 1

March 3, 2011

I want to talk in some detail over the next few classes about Diels-Alder reactions. I am sure that most of you have heard of Diels-Alder reactions before, but we will start with a brief review anyway.

The general scheme for a Diels-Alder reaction is shown below:

\[
\text{diene} \quad + \quad \text{dienophile} \quad \rightarrow \quad \text{cyclohexane}
\]

You have a diene (with two double bonds conjugated to each other) and a dienophile (literally, something that loves a diene) that react in a concerted mechanism. “Concerted” just means that all electrons move simultaneously. We will talk later about how that may not actually be an accurate description of the mechanism, but for now let’s assume concerted. We can represent the concerted mechanism either with three arrows (one for each pair of electrons moving) or with dashed lines to indicate that all bonds are being broken/formed at the same time:

\[
\text{diene} \quad + \quad \text{dienophile} \quad \rightarrow \quad \text{cyclohexane}
\]

Also note here that the product is always a six membered ring with a double bond in it.

In practice, you need to tweak the substituents on the molecules to get complementary reactivity. What I mean by that is, there is no compelling reason for these two unsubstituted hydrocarbons to react. However, if you make one electron-deficient and one electron-rich, now there becomes more of a driving force for the reaction. In the “normal Diels-Alder reaction,” the dienophile is electron deficient and the diene is electron rich. Some examples of Diels-Alder reactions are shown below.
Again, I want to emphasize the electron deficient nature of the dienophile and the relative electron-rich nature of the diene. In 1974, Professor Sam Danishefsky developed an electron-rich diene, which has since become known as “Danishefsky’s diene.”

This diene has two notable features: (1) it is highly electron rich, and (2) the functionalities are easily removed after the addition is complete to generate an alpha-beta-unsaturated ketone in a six-membered ring system. An example using Danishefsky’s diene is shown below:

After you form this product, the TMS ether is readily hydrolyzed under the reaction conditions to generate the enol. This enol then converts into the ketone with simultaneous removal of the methoxy group:
Note that this is the same sort of product that you would obtain via Robinson annihilations. So we should practice disconnecting this compound retrosynthetically via Robinson annihilation and via Danishefsky’s diene:

via Robinson annihilation:

It has come to my attention that some of you are not familiar with a Robinson annihilation reaction, so we are going to do a 2-minute overview:

Robinson reaction is a Michael reaction followed by an Aldol condensation. The overall reaction scheme is shown below:

First you form an enolate, that attacks the alpha,beta-unsaturated ketone. The resulting product then forms another enolate that undergoes an aldol condensation to generate a new six membered ring. The OH group that forms is dehydrated easily to give the alpha,beta unsaturated product.

So retrosynthetically, if you see an alpha, beta unsaturated ketone, you can disconnect it with a Robinson annihilation. The first step is to put an OH at the beta carbon, and then you break the bond from the aldol reaction, and then you go back one more step to a nucleophile and an alpha-beta unsaturated ketone system.

The second time you form an enolate, there are definitely several different enolates that can form – any place where there is an alpha carbon with hydrogens on it, that can enolize. However, all of these steps (until the last dehydration) are reversible – so the likelihood is that any enolate that forms is going to unform until you get to the most stable product, which is the six membered ring system.

I want to talk in some more detail about the following Diels-Alder topics:

(1) selected diene examples; (2) selected dienophile examples; (3) examples of Diels-Alder reactions in total synthesis; and (4) inverse-electron demand Diels-Alder reactions.
(1) Selected dienes – The first new diene is the Danishefsky diene. There are other variants on the Danishefsky diene, shown below:

Here I’ve shown the parent Danishefsky diene as well as three variants. These are all formed from the alpha, beta unsaturated ketones via treatment with trimethyl silyl chloride and zinc chloride (Lewis acid). The mechanism of this transformation is shown below:

The zinc chloride is a Lewis acid that activates the oxygen for reaction with the silicon.

The other major advantage to the Danishefsky diene series (in addition to their high reactivities and easy manipulation into alpha,beta unsaturated enones) is that it promotes regioselective Diels-Alder reactions.

We have not talked about regioselectivity yet in the context of Diels-Alder reactions, but in general it is a major concern. If you consider a generic Diels-Alder reaction, there are four possible regioisomeric products:
The first two products are from the dienophile substituent oriented up (as shown), and the second two products are from the dienophile substituent oriented down (not shown).

Within those two general orientations, the X and the R groups can be on the same side of the newly formed bond, or on opposite sides.

In general, Diels-Alder reactions give regioisomeric product mixtures. Danishefsky's diene has a strong regiochemical preference for the silyl ether to be oriented near the more electron deficient part of the dienophile. Let’s take a particular example. The dienophile shown below is more electron deficient at C-3 than at C2, and therefore it reacts with the silyl ether diene to yield a single regioisomeric product:

The reason these dienes display such regioselectivity is because C-1 of the diene is more electron-rich than C-4. Try to draw resonance forms of both the diene and the dienophile and that will explain this regiochemical preference.

Another class of reactive dienes is ortho-quinone dimethide compounds. The unsubstituted diene is shown below:

where A = generic electron acceptor.

The quinone dimethide is generated from the ring opening reaction of benzocyclobutanes:
You can also draw an arrow-pushing mechanism which doesn’t involve the benzene ring. Either way of looking at the ring opening reaction is equally valid.

These dienes tend to be highly reactive, because the Diels-Alder reaction has the added benefit of restoring aromaticity to the benzene ring:

\[ \text{NOT AROMATIC} \quad \xrightarrow{\text{Diels-Alder}} \quad \text{AROMATIC!} \]

In general, these dienes have been used much more in intramolecular Diels-Alder reactions compared to intermolecular ones.

However, the research group of Danishefsky also developed a new ortho-quinone dimethide (which contains two electron donating silyl ether groups):

which undergoes a wide variety of intermolecular Diels-Alder reaction. Your Diels-Alder problem set contains this diene and a variety of Diels-Alder products. You should practice identifying the dienophile used in all cases.