

Introductory Organic Chemistry - II
Professor Doctor Harinath Chakrapani
Indian Institute of Science Education and Research, Pune
Lecture 51

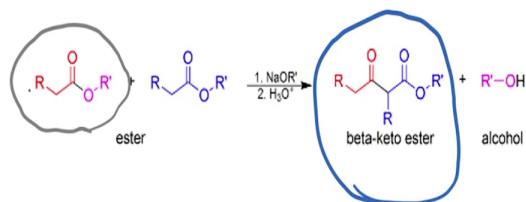
Acylation of Enol/Enolates and Related Name Reactions

So, in this lecture, we are going to look at various aspects of acylation of enolates. And we will also look at a number of what are known as name reactions. And these name reactions are now very widely used in organic synthesis, and organic chemistry, and therefore, they are important. And what we will focus on is the chemistry.

So, the name of the reaction is important, but what is more important is our understanding of the chemistry behind that reaction and the mechanism behind that reaction. So, we do not need to memorize the name of the reaction, per se, it is useful to always remember it, but what we need to understand is how the reaction works, and what is the mechanism of the reaction.

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Claisen Ester Condensation

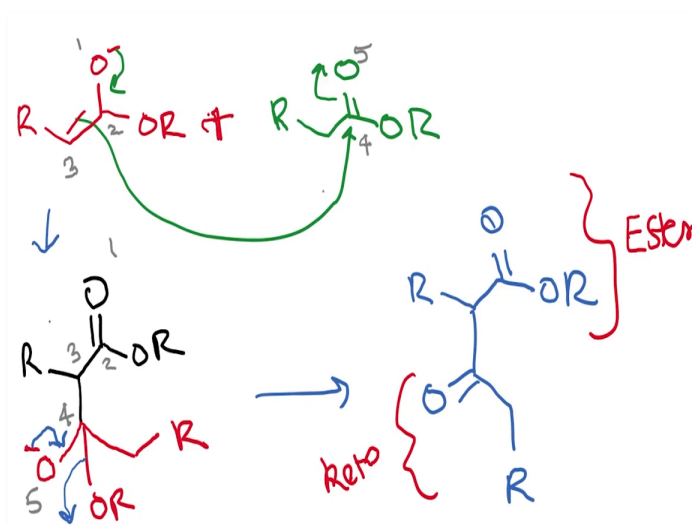


So, the first reaction we are going to look at is the Claisen Ester condensation. And so here in this reaction, you know, basically it is a reaction very much similar to the aldol reaction that we have studied in the past, here it is a reaction between two esters. And if you see here, the product here is a β -keto ester. So, again just to remind you, this is a keto ester. And this is something that we have looked at, during you know, for example, acetoacetic ester or malonic ester, melonic

esters are derivatives which are similar to this and they are very useful intermediates in organic reactions.

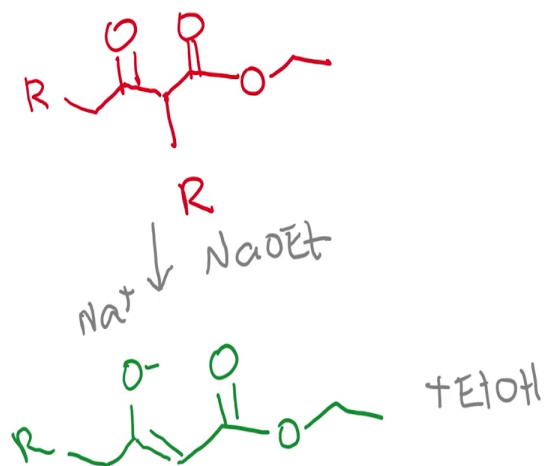
And of course, the byproduct is the alcohol. Now, again, see the name of this reaction is Claisen ester condensation, but if you are given a situation or if you are given these reagents that is these esters and given the product, we should be able to reason out the mechanism. So, the first thing that we need to understand is when we are approaching such reactions is that you know there is a base that we are adding, this is a sodium methoxide or sodium ethoxide. And so, when you have an ester, you know that an enolate is going to be produced.

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So, this is the enolate that will be formed. And once this enolate is produced the enolate can react with the only electrophile in solution which is itself which is the ester. So, when it reacts, we follow the same numbering 1, 2, 3, 4 and 5. So, once this reaction happens, you get a bond that is going to be formed between carbon 3 and carbon 4, which is shown here and you generate this tetrahedral intermediate on oxygen number 5 having a negative charge. And then this tetrahedral intermediate collapse. And of course, you can still think about two options that is it goes back to the starting material or ethoxide is kicked out and you get this β -keto ester. So, in principle these reactions might be reversible.

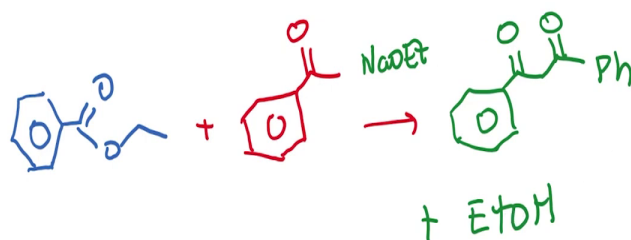
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But the important point here is that the last step of this reaction, you have the deprotonation of this 1,3-Dicarbonyl compound to give you a very stable you know enolate that is formed and this is the driving force for this reaction. So therefore, the reaction becomes irreversible after this point, because it is difficult for the enolate to go back to the keto form and do the retro reaction as we have discussed.

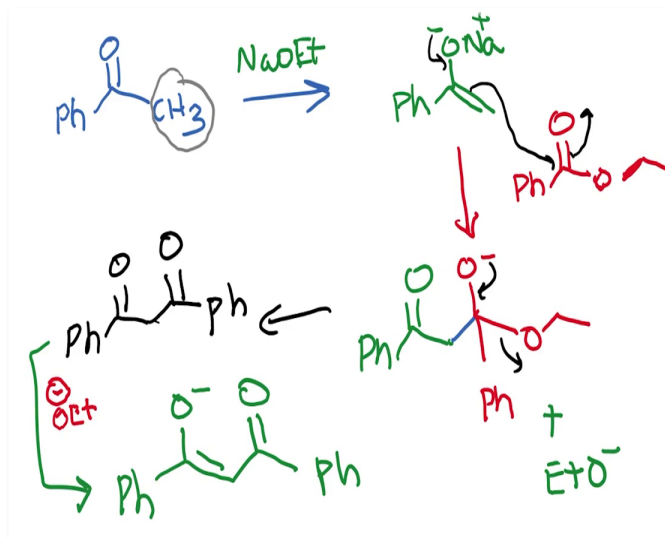
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Crossed-Claisen Ester Condensation



Next is the possibility of doing a Crossed-Claisen Ester condensation, again similar to the crossed aldol reaction. So here what we want to do is we want to react ketone with an ester. So, when we mix this in solution, notice that there is only one enolizable hydrogen which is this and the product that you get is this 1, 3-Dicarbonyl compound again and ethanol.

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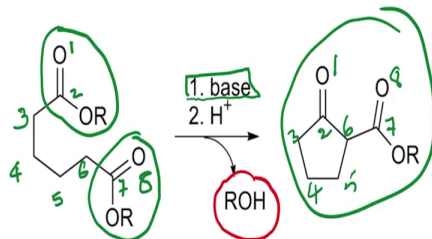


So, the mechanism that we can propose or suggest is the following. So, as I mentioned, this is the only enolizable hydrogen over here and then the sodium ethoxide reaction is going to be quite fast and it is going to give you this enolate and this enolate can then react with the ester to give you this intermediate and then again, the collapse of this intermediate followed by loss of ethoxide gives you this 1,3-Dicarbonyl compound as shown here. And now once the ethoxide is present, it irreversibly reacts with this to give you the highly stable you know enolate system as shown here, 1, 3-Dicarbonyl enolate system.

So now, using this strategy, you can design quite elaborate cross-Claisen reactions. And, you know, there is a lot of interest in this and a lot of reactions can be done. In the interest of time, we will not be able to go into more details than this, we will solve some problems related to this. But suffice to say that a lot of wealth of reactions have been discovered using this kind of strategy.

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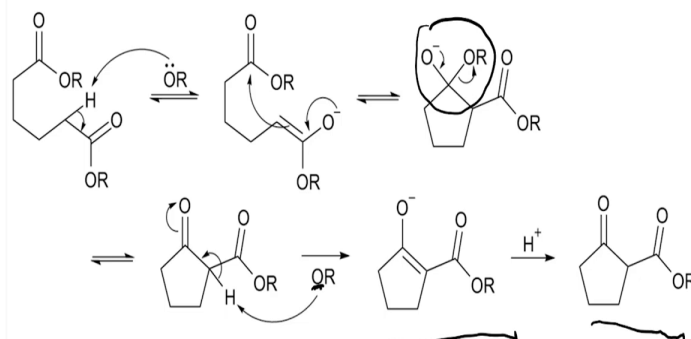
Dieckmann condensation



The next reaction is called the Dieckmann condensation. But again, let us focus on the reaction actually, that is happening. So, here, we should be, you know, very careful and look at the condition. So, the first thing that is given here is a base, and you have a diester system over here. And so, the product here is this 1,3-Dicarbonyl compound. Now, what we will do is, we will just start by just numbering these carbons, so let me just start, maybe we should just start numbering with the oxygen, so this is 1, 2, 3, 4, 5, 6, 7, and let us call this 8.

Now, in the order in which we have written this is 8, 7, and this would be carbon number 6, 5, 4, 3, 2 and 1, so what is being lost here is basically ROH. So, when you are given a reaction such as this, you need to first systematically look at the reaction, and then find out what are the parts that are missing, and what are the parts that are actually combining to give you the product. So, with this background, now let us look at the mechanism, the first obvious thing that we will propose is to form the enolate.

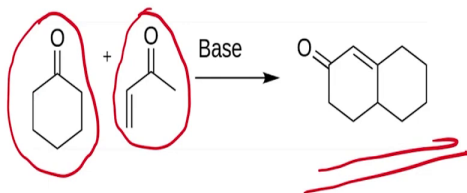
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And so, the enolate can be formed in the following manner. And now to this enolate, you can then do propose an intra-molecular reaction to give you this kind of a tetrahedral intermediate, and then this tetrahedral intermediate, then collapses. And, you know, gives you this keto ester compound. And you can envisage that all of these reactions might be in equilibrium and might actually reverse. However, the last step of this reaction where you know the reaction of RO⁻, which is shown here, with this 1,3-Di carbonyl compound is an irreversible step. So now, if you remember in the second step of the reaction is a work up with acid. And so, you can isolate this compound as the 1,3-Dicarbonyl compound. So, the Dieckmann condensation is nothing but an intramolecular Claisen reaction.

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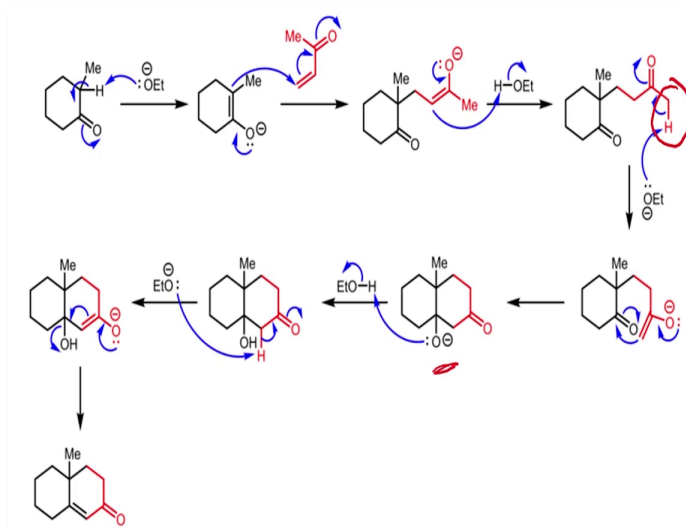
Robinson annulation



Let us move to the next name reaction, which is Robinson annulation. So, again do not get perturbed or worried about the name, the name is important, but what is more important is that you understand the reaction. So here again, it is vital for us to make sure that we are able to see the transformation that happens. So, what you are seeing here is that this is the one of the reacting groups which is cyclohexanone.

And there appears to be fusion with this α,β -unsaturated ketone, to give you this kind of product. Now, you know, I do not have any byproducts written here. But the first obvious thing that I would propose is that in the presence of the base, you are going to have a deprotonation of the carbonyl compound. So, let us start with that and move forward with the mechanism.

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So, you have here that the reaction of the cyclohexanone compound and this is going to, you know, generate this enolate over here, and then the example that I am showing you there is an additional methyl group. So here ethoxide attacks and it forms the enolate as shown here, and then now the enolate can do conjugate addition.

And the conjugate addition is also called a Michael addition. And so here is the attack that happens and it produces the second enolate. And now the second enolate can actually pick up proton from ethanol, which is a solvent to give you back this ketone. So, the interesting part here is that you know, the ketone now can undergo further you know, form this next enolate and in this time, it picks up the hydrogen which is the terminal hydrogen, and ethoxide attacks here and generates this enolate.

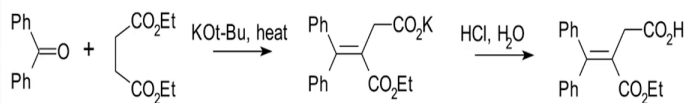
And now the enolate can do a cyclization reaction to give you this tetrahedral intermediate as shown here, which then gets protonated to give you this alcohol. And then we being very familiar with the E1cB mechanism, which is like the next step to the aldol wherein an enolate is produced and then the enolate sort of rearranges, there is an elimination to give you this olefin over here. Now, the question that you can ask is that why not this enolate that is produced here react directly with the ketone.

So, if you number these carbons, you will find that it is going to form a 4-membered ring. So, if there was no option, that is possible that under certain conditions, you can make 4-membered ring. But since you have an option of forming a 6-membered ring; 6-membered ring and 5-membered ring are generally more favored compared to 4-membered ring.

So therefore, this mechanism is quite reasonable that we are proposing. And this is an annulation reaction, because annulation refers to the formation of a ring. And so, during this Robinson reaction, we are actually producing a new ring as shown here. And therefore, this is called the Robinson annulation reaction.

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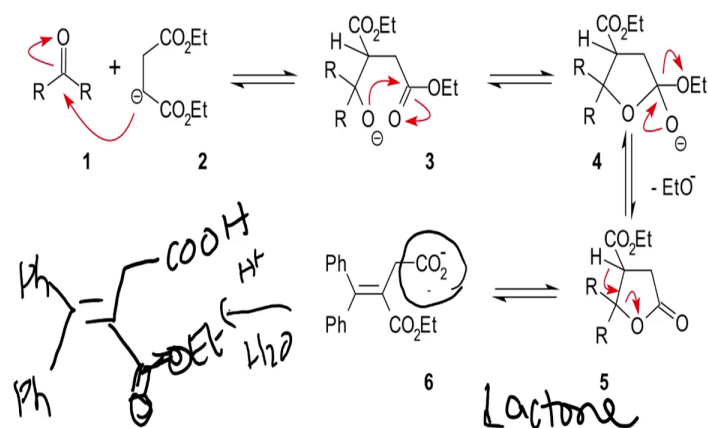
Stobbe condensation



The next reaction we are going to look at is the Stobbe condensation. So, again, the condensation word refers to loss of water, so you are going to see at some point that water is going to be lost. So, again do not get too perturbed by the reactants or the products or by the name of the reaction, we are going to look at it in a very systematic manner. So, if you see here, these two are added in the presence of a base and the base is potassium tertiary butoxide and then you are heating it and you get this kind of a product which then under acid conditions is going to give you the final product.

So, the first thing we should think about is in the presence of a base what is going to happen. So, here clearly there is no possibility of reaction with a base it is more likely that this is undergoing enolate formation. So, with that background, let us look at the mechanism.

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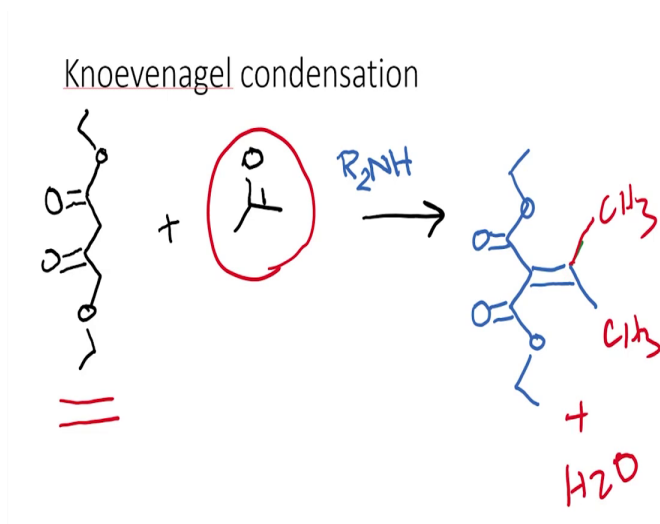
So, as I mentioned the enolate that is produced here is going to then react with the ketone and then what happens is that it forms this tetrahedral intermediate. The interesting thing about this ketone is that the ketone oxygen, O minus is actually an alkoxide ion. And because there is a second ester that is present here, this alkoxide can actually close the ring in principle and produce a second tetrahedral intermediate, which can then collapse and kick out the ethoxide ion. Now, what you are doing is actually you are producing what is known as a lactone.

So, this lactone being the intermediate here is important because that helps us understand why a carboxylate ion is actually formed. So, now what happens is that you can have the second you know rearrangement that can happen where this undergoes an elimination reaction to form a carbon-carbon double bond along with it, there is a loss of carboxylate ion, COO⁻ which is shown here and the final product has an olefin in it as well as a carboxylate. Now, when you add H₃O⁺, H⁺ and water under neutralizing conditions, the product that is formed is this (Ph)₂C=C(CH₂COOH) (COOEt).

So, this is another very interesting reaction. The unique thing about this mechanism is the fact that since the esters are positioned in such a manner, that an intramolecular reaction can actually occur, it leads to the formation of this kind of a tetrahedral intermediate, which then collapses

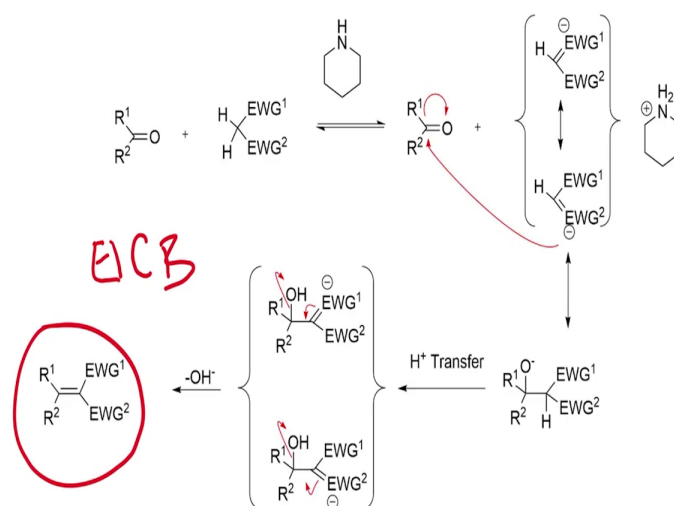
kick out ethoxide and form this lactone. So, other than this, you know the mechanism that is suggested here is quite similar to the previous reactions that we have encountered.

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Moving forward, we are going to look at the next condensation reaction which is the Knoevenagel condensation. So, Knoevenagel condensation is very similar to the previous Stobbe condensation that we looked at, but there are some differences. So, here if you start with this 1,3-Dicarbonyl compounds and react it with a ketone in the presence of secondary amine base, the product that is formed, you know, is actually this olefin as shown here, this would be CH_3 and CH_3 , and the byproduct of course is water. But the interesting thing is that this is a reaction which actually gives you an olefin.

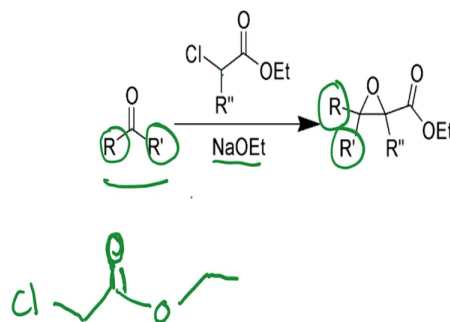
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Again, let us just follow the same principles that we are very much used to, you know, you start with the compound which has 2 electron withdrawing groups. This is a general mechanism and when you add a base such as this, you know you have the formation of the enolate. And once this enolate attacks the carbonyl compound, you get an intermediate like this and then this intermediate undergoes the second enolate formation. And then the second enolate undergoes E1cB, so this is E1cB to give you the olefin. So again, this is a mechanism that you can work out very easily given all the discussion that we have had on enolate formation and E1cB reaction.

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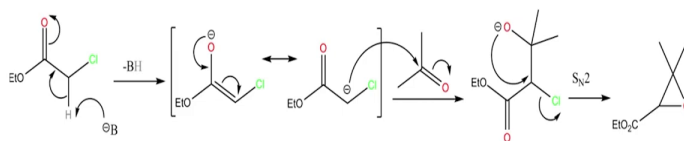
Darzens glycidic ester synthesis



So, moving on. The next name reaction that we are going to deal with is the Darzens glycidic ester synthesis. So, this reaction is you know, the following where you start with the ketone and you react it with this α -chloro ester. So, this is something that we have already looked at previously about how to synthesize for example, α -bromo esters and α -chloro esters. So, this can be fairly easily synthesized.

Now, in the presence of sodium ethoxide, there is a very interesting transformation that occurs. So, this R and R¹ are here R and R¹ and this C double bond O is now going to be you know, sort of now forming an epoxide like this. So, the oxygen here and you know, this carbon here comes from here and the chloro is gone, and you actually form an epoxide. So, basic transformation here is that there is a carbon-carbon bond that is being formed between this carbon and this carbon and the chloride is missing and the oxygen seems to have moved to form an epoxide So, with this, we can propose a mechanism.

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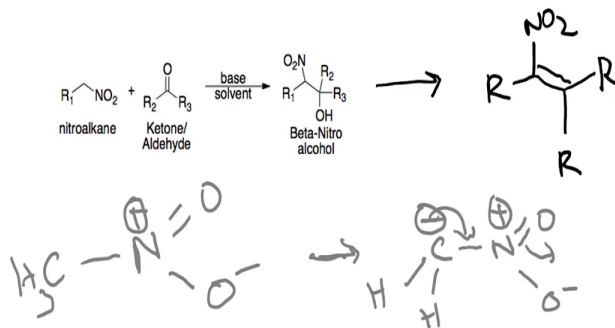
So, the mechanism that we can propose is that the α -chloro ester undergoes the enolate formation. And so, you produce an enolate like this. And this enolate you know, because of the electron withdrawing nature of the chloro might be preferred to be formed here, and then the enolate reacts with the ketone, and the ketone gives you a tetrahedral intermediate. So, the key step in the next transformation is that once you generate this tetrahedral intermediate, you know,

so one of this can get protonated but the other thing it can do is to swing around and react with this carbon you know with this carbon here and do a S_N2 reaction to form the epoxide.

So, this is one of the interesting ways to actually produce an epoxide, and that sort of gives us a method for epoxidation of reactions. And as you can see here, there is no olefin here so you are starting this reaction with a keto or with an ester and you are producing this epoxide as the product. So, this is called the Darzen's reaction.

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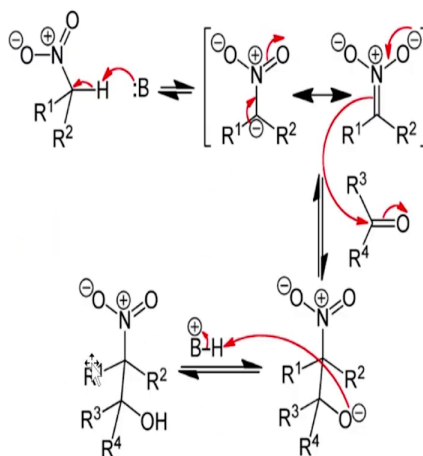
Henry reaction (also known as Nitro-aldol reaction)



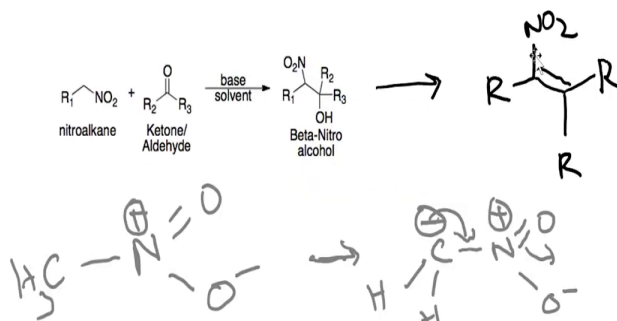
The next reaction is the Henry reaction, which is also known as the nitro-aldol reaction. So, nitro functional group is a very interesting functional group. As you all know, it is quite electron withdrawing and you know, one of the ways in which we can understand this is actually once you generate the C minus, you have hydrogen and you have hydrogen and this can be very nicely sort of stabilized by delocalization as shown here.

So, much like a nitro group on an aromatic ring makes it deactivating towards electrophiles. A nitro group on alkyl carbon actually increases the acidity. So, this exactly is like an aldol reaction where only the difference is that the enolate is produced from a nitro compound and it produces this aldol. And subsequently this β-nitro alcohol can undergo elimination to give you the product as shown here.

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Henry reaction (also known as Nitro-aldol reaction)

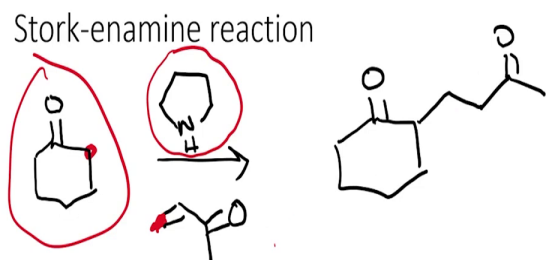


Now, the mechanism is as I mentioned to you is fairly straightforward. The base attacks the alpha position, which is quite activated, and it produces this carbon-based carbanion which can delocalize over here to give you this enolate type anion, which can then react with this ketone and produce the tetrahedral intermediate are shown here.

And subsequently, you know, this can undergo and you know, when this is the reaction but if you have an another enolizable nitro you know, if you have a product which can actually undergo

elimination over here, then you can produce the olefin as shown here. Otherwise, you just end up getting this kind of product.

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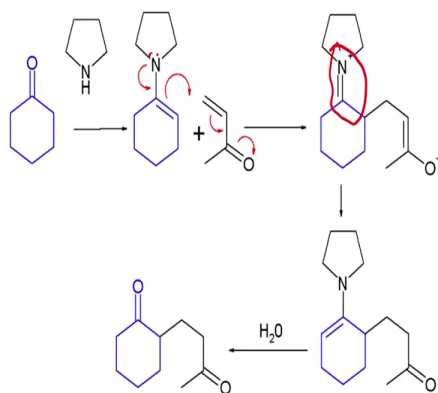
The Stork enamine synthesis:

1. formation of an enamine from a ketone
2. addition of the enamine to an alpha, beta-unsaturated aldehyde or ketone
3. hydrolysis of the enamine back to a ketone

The next reaction is the Stork-enamine reaction. So, the Stork-enamine reaction is actually you know, something that we have looked at in passing. So, it is a combination of two concepts that we already know. So, if you look at the starting material here, it is a ketone, cyclohexanone. It reacts with this α , β -unsaturated carbonyl compound, and gives you this product.

So, the new bond that is formed is between this carbon and this carbon. So, with this, you can actually stitch the pieces, so it is a conjugate addition reaction. And I think one important part here is to understand the role of this secondary amine. So, which is basically as the name of the reaction suggests, it forms an enamine. So, the Stork-Enamine synthesis has the following components, the first step is to form an enamine from a ketone, which is what we will do with this ketone. And then we add the enamine to an α , β -unsaturated aldehyde or ketone, which is shown here. And then what happens is, then the reaction occurs and then you hydrolyze off the enamine back to a ketone.

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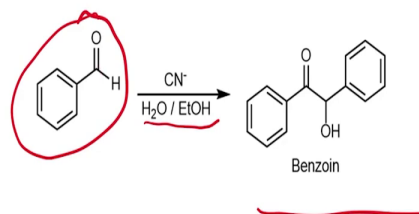


So, the mechanism is as follows. So, you react these two, this ketone and the secondary amine and you get to see an enamine. We have already looked at the mechanism of production of enamine so I am not going to go into the details. And now the lone pair on this nitrogen is going to move in here and react to a conjugate addition to give you this enolate. And then the enolate can then pick up a proton to give you the enol, which can then subsequently do a keto-enol tautomerism to give you this ketone.

And now this intermediate here is now positively charged. So, what it can do is it can just pick up, can just do a tautomerism to give you this enamine again. And now under hydrolysis conditions, you are going to generate back the ketone. So again, this is a very powerful method to form a carbon-carbon bond.

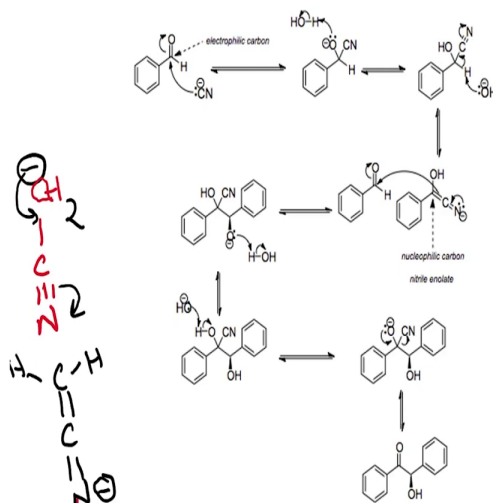
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Benzoin condensation



The next reaction we are going to look at is the Benzoin condensation. So, benzoin is this compound, this as shown here it is 2-hydroxy ketone. And so, the way this reaction happens is that you know, you react benzaldehyde with cyanide, and water and ethanol and you get benzoin. So, as you can see, there is no other reactant here other than benzaldehyde. So, this is very similar to the Cannizzaro type reaction that we have seen previously. And so, what I would expect is that when cyanide and benzaldehyde are reacted together, I would form a cyanohydrin. And now this next step of this reaction is going to be interesting. So, you have a carbon-carbon bond between benzaldehyde and another mole of benzaldehyde.

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So, with that let us look at the mechanism. So, cyanide attacks here it forms a cyanohydrin. And then the cyanohydrin, as shown here, is going to react with water. And it is going to form a cyanohydrin. The alkoxide is going to react and give you the cyanohydrin. And now because you have a cyanide group over here, next to this alpha, this hydrogen is quite acidic. So, just like nitro compounds are acidic, cyano compounds, because cyanide is actually an electron withdrawing group $\text{C}\equiv\text{N}$.

It can give you $^-\text{CH}_2\text{C}\equiv\text{N}$ and this is a fairly good electron withdrawing group. And so, the alpha position to a cyano group is quite acidic. And one of the reasons is you can think about is the ability to delocalize as shown here, $\text{C}=\text{C}=\text{N}$ with a minus over here, and there are 2 hydrogens. So, this is one way to move forward and understand this. So, because you have a base here, this hydrogen here can be pulled out, and you form this nitrile enolate.

And now the nitrile enolate is in a great position to attack the benzaldehyde and here is the carbon-carbon bond forming reaction and you regenerate the nitrile and subsequently you have, basically, picking up of proton to give you this OH . And now the last step of this reaction is to regenerate the ketone because the product does not have the cyanide in it. So, the way the ketone is regenerated is to produce this again, this tetrahedral intermediate, which then kicks out cyanide to give you back the final product.