Principles and Applications of Enolate Alkylation: A Unique Strategy for Construction of C-C (sp3 - sp3) bonds in asymmetric fashion

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Module - 01
Basic introduction of enolates
Lecture - 01
Enolate generation, structure of enolates and related topic - I

Welcome to all of you for this NPTEL course named as Principles and Application of Enolate Alkylation: A Unique Strategy for Construction of Carbon-Carbon (sp^3 - sp^3) bonds in asymmetric fashion.

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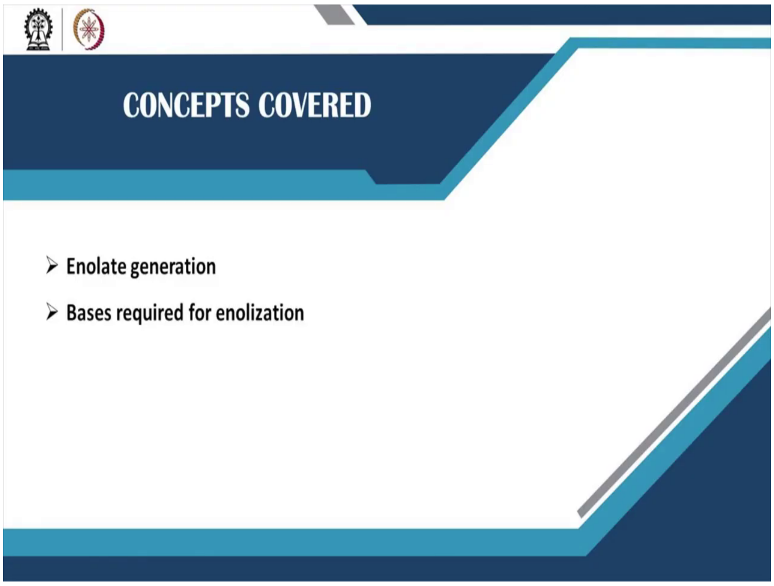

CONCEPTS COVERED

- Enolate generation
- Bases required for enolization

So, today we will be mainly covering this particular two topics, how you can generate the enolates and particular bases required for enolization.

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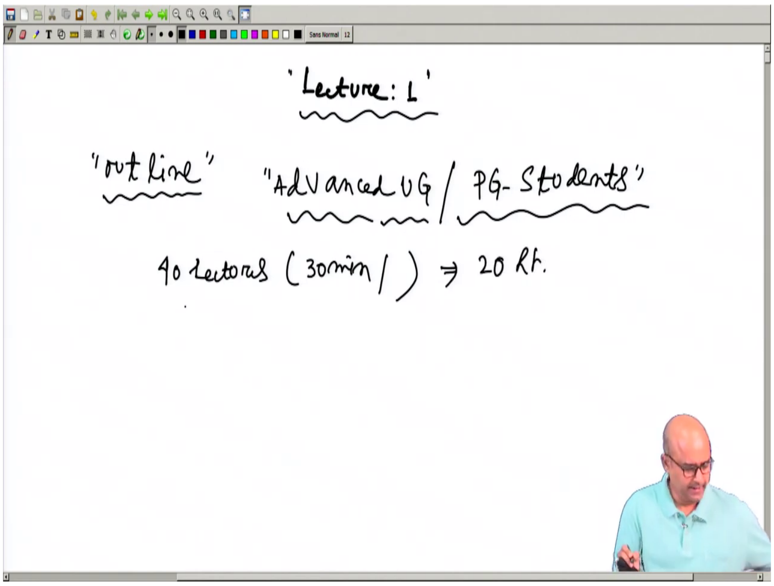

'Lecture: 1'

"out line" "Advanced UG / PG- Students"

40 Lectures (30min /) ⇒ 20 hr.

Before we start, just try to give you a general outline of the entire course and what will be our main objective in this course throughout the entire course work. This course basically meant for a little bit of advanced UG students as well as PG students.

As you can see the name implies particularly enolate alkylation and the main focus is for the construction of new asymmetric center or stereogenic center, in the carbon-carbon bond forming reaction. The entire course work is a 40 hours sorry 40 lectures which consists of 30 minute each and so in principle this is basically a 20 hour course work ok.

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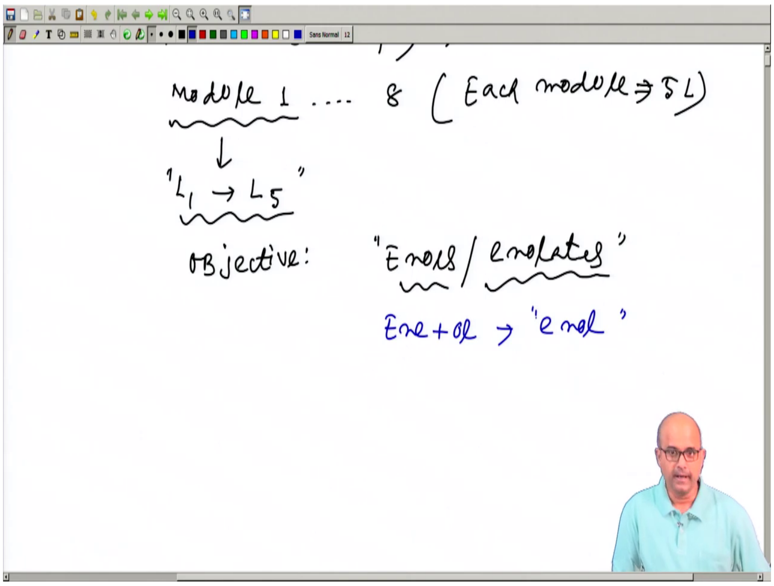

Module 1 .... 8 (Each module ⇒ 5 L)

↓

"$L_1 \rightarrow L_5$"

Objective: "Enols / enolates"

Ene + ol → 'enol'

And the entire coursework we have divided into few modules, we have module 1 to module 8 each module consists of 5 lecture 5 lectures. So, we will start today with module 1 which contains basically 5 lecture and we will try to start or try to begin with the lecture 1.

As I said this course work is implied or named for particularly construction of carbon-carbon bonds. So, the very beginning we would like to give you a demonstration of the main objective that what this course all about. The major objective of this course was mainly based on how you can create enols or enolates which are very useful synthetic intermediates in organic chemistry.

So, in the first lecture which we are going to talk today, we will try to be focused on how you can construct a enolate species or enol species. Now what are enols? If you see by their name enol basically has two components, one is ene another is ol that makes enol. So, enols are basically kind of unsaturated alcohol and we will talk about these things in our course work little bit of detail.

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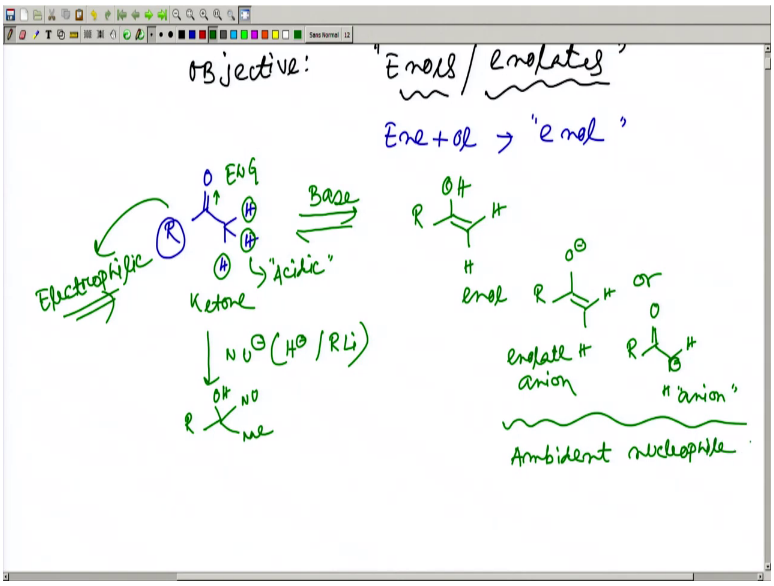

Now, let us try to give you a brief introduction or revision which probably all of us have studied earlier. I am just trying to draw a carbonyl compound and categorically try to put a R group which are not specified and the alpha position of this carbonyl group contains three hydrogen which are basically associated with a electron withdrawing carbonyl group.

So, this carbonyl group as all of us know is electron withdrawing. And that basically means that these three hydrogens are kind of acidic in nature as electron is being pulled out from this hydrogen. So, they if you try to use or apply some suitable base or some other condition it is possible that you generate something like this, after abstraction of one hydrogen, but this hydrogen will come here and you get a species which is called as enols, so this is your enol.

And eventually we will put a double arrow to show that there are in dynamic equilibrium depending on your reaction condition you can switch over the equilibrium. So, this we called a ketone and this we called an enol. Now, normally ketones and enols they have a different chemical reactivity property.

Ketone as you know they are susceptible to nucleophile. So, ketones in principle they are electrophile in nature or electrophilic because this carbonyl can accept some external nucleophile. Now this nucleophile can be of different choice it could be a hydride nucleophile, could be a lithium or a Grignard nucleophile and what basically you get you get a tetrahedral compound, which is a normally this kind of compounds.

Now, enols they do have a different reactivity altogether. If you see the enol usually have a negative charge on oxygen, it could be one of the species or it could have anion which you just abstract it after the initial proton abstraction. So, this is the naked anion we call it and this is the enolate anion.

So, enols in principle this two species if you see it are ambident nucleophile means they have two nucleophilic sites in their structure. So, enols will definitely react in a different way.

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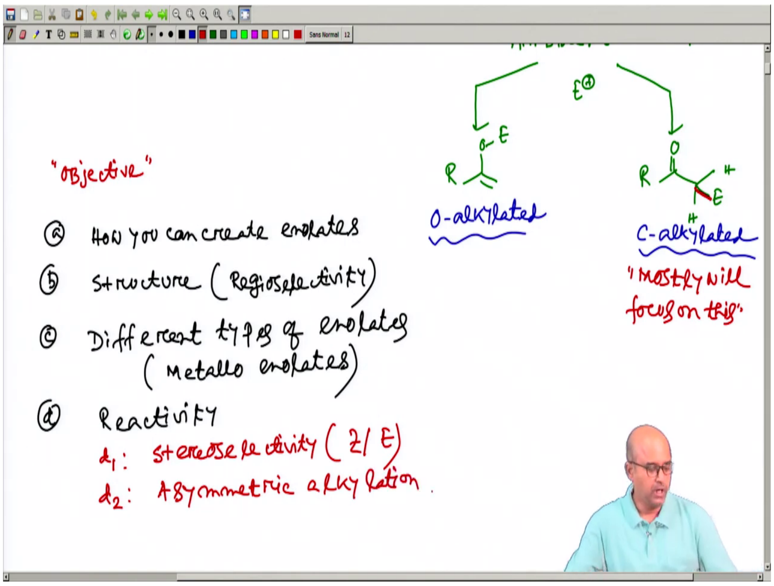

"Objective"

ⓐ How you can create enolates

ⓑ Structure (Regioselectivity)

ⓒ Different types of enolates
(Metallo enolates)

ⓓ Reactivity
d_1: stereoselectivity (Z/E)
d_2: Asymmetric alkylation.

"mostly will focus on this"

Now, how you can react it eventually if you react with suitable electrophile, electrophile or a species which does have a positive charge you usually get an O alkylated product or you can have a C alkylated product E.

So, these two are the main possibility of product formation, we call it O alkylated if your electrophile is alkyl iodide and we call this as a C alkylated thing. Now depending on the condition you can basically control this O alkylated product and C alkylated product, but most precisely in this course work we will actually focus for this C alkylated product mostly we will focus on this.

And eventually if you are trying to get a synthetic chemist's perspective you see you are getting a new carbon electrophile bond at this point. So, you are basically creating a new carbon-carbon bond and if your electrophile is a carbon containing electrophile, you can eventually create a new carbon carbon bond.

Now, before we again start, so we will try to focus the main objective of this particular section that what should be our prime objective in this part. So, the initial objective was how you can create or generate enols or enolate enolates ok and then we will. This basically means that what are the conditions, which will give you enols or enolates in the reaction mixture and then the next one is their structure.

Their structural part is very important. Structure means that once you abstract the hydrogen depending on the available sources or depending on the structure of the starting material. You can basically have some structural aspects and these structural aspects mainly will be focusing on regioselectivity issue.

And then we will talk about different type of enolates, different type of enolate means enolates usually can be stabilized if you are treating with a metal ion for better coordination. So, usually in this part we will be trying to talk about mainly metallo enolates, which are most significantly used in the synthetic organic chemist for long time ok.

And then we will be mainly focused about their reactivity, in this reactivity criteria all our different things will come into picture. So, we will just try to fit it the d1, that the stereo selectivity issue means, once you try to generate the enolate means whether the enol will be *Z* geometry or *E* geometry that is a very important concept. And then we will mainly switch over that asymmetric alkylation which is the main key point of our course work.

Means once you are trying to use a carbon carbon containing electrophile, how you can control those things in different way.

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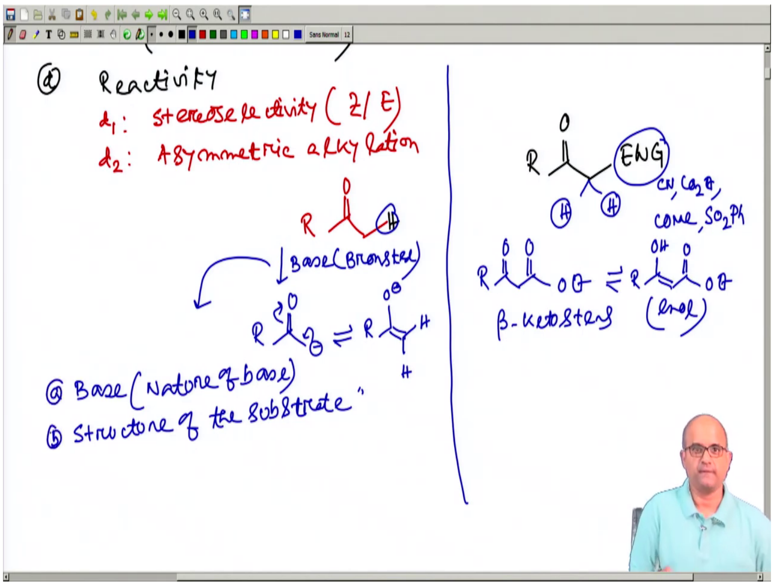

ⓓ Reactivity

d_1: Stereoselectivity (Z/E)

d_2: Asymmetric alkylation

ⓐ Base (Nature of base)

ⓑ Structure of the substrate "

So, then come back to the original discussion that you do have a carbonyl compound or a starting material, where you basically have an abstractable hydrogen.

Now, sometimes it happens that I will try to write a very general structure for this kind of starting material. It has been happened that in addition to the carbonyl compound, you might have some other electron withdrawing group in the vicinity of your carbonyl. And in those cases these hydrogen's are extremely labile or kinetically labile, as this contains two electron withdrawing group at the alpha position.

Now, this electron withdrawing group might be cyanide, might be a CO_2Et might be another carbonyl compound, might be a sulfone and most of the compounds probably you have noticed, that if I draw the structure of this compound. Let us say this is an ethyl acetoacetate, a beta keto ester which usually is found that this compound mostly prefers enol at the room temperature.

You really do not have to do anything else, you will might be observing that these compounds have a appreciable amount of enol tautomer in the room temperature. So, once you open the bottle of ethyl acetoacetate or this kind of beta keto ester. So, this kind of spontaneous keto enol equilibrium or keto enol tautomerism was the major factor in many of the structurally related compound, where you have an extra electron withdrawing group.

But we are not focused about that we are talking about a simple compound where you have an abstractable hydrogen which you can simply picked up by a base, the main thing we will now try to add a base. Now base what we will do normally these bases are usually Bronsted base and they will abstract a proton and they will give you a naked carboanion. This naked curve anion can be then stabilized through conjugation and forms a new pi bond which is the double bond which is we call the enols.

Little bit after that we will basically explaining the molecular orbital picture of this enols, how it would have been generated. Now before that we will now try to switch over that what kind of base and what kind of structural requirement, we need to fix it here. So, two important points we will be now discussing, the base means nature of base which are very helpful for generating the enolate and particularly structure of the substrate.

So, these two components are very important for generation of the enolates in the solution phase.

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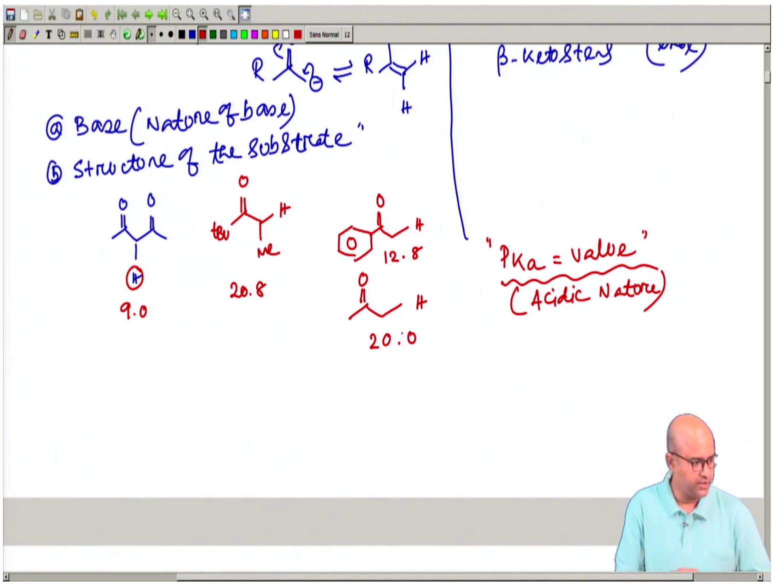

Before we go we will just now try to have a bit of structural information and I will try to write couple of structure, where you can find that this structure usually does have very easily abstractable hydrogen.

Like this compound beta diketone compound, few other compounds like I will say a compound something like, let us say compound like this where you have a tert butyl at the one end. So, no abstractable hydrogen this is the only one hydrogen you can abstract, we can write some simple other carbonyl compound varying their different structure and let me try to deal with these things.

Then in the other series we will have compounds like this. Now I will try to write a numerical thing which basically now explaining this numerical thing basically belongs to the pKa value of those compounds. Now what do you mean by here pKa? pKa is basically a numerical value, which normally stands for the how these compounds can attribute or to donate the hydrogen when exposed under basic condition.

So, pKa value is directly related to acidic nature of those compounds. Probably most of us have been quite familiar with the pKa value we will just try to give you a little bit of idea about the pKa terminology and then we will try to explain that what is pKa.

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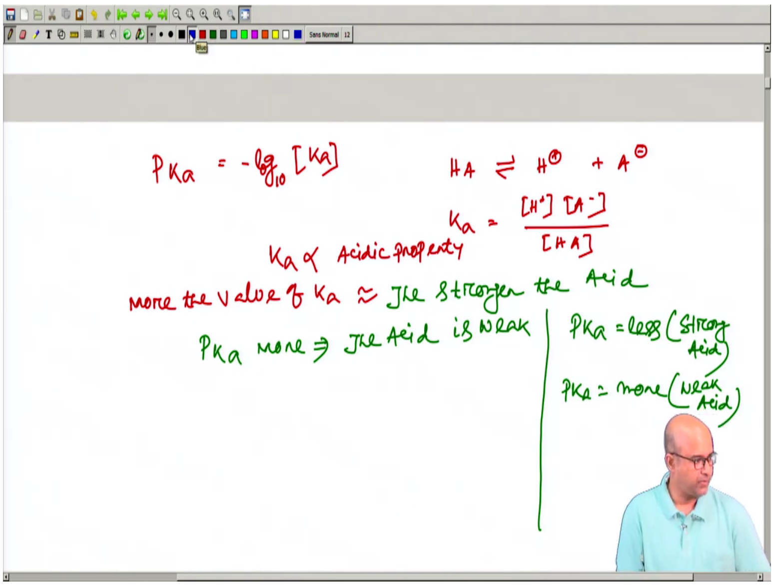

$pKa = -\log_{10}[Ka]$

$HA \rightleftharpoons H^{\oplus} + A^{\ominus}$

$Ka = \frac{[H^+][A^-]}{[HA]}$

$Ka \propto$ Acidic property

more the value of Ka ≈ The stronger the Acid

pKa more ⇒ The Acid is weak

pKa = less (Strong Acid)

pKa = more (Weak Acid)

Now, pKa is eventually is nothing a negative log of nature of natural logarithm of a value Ka.

Now, what is Ka? If a Bronsted acid or proteogenic acid, it tends to dissociate it basically can follow this kind of equilibrium and Ka is basically the equilibrium constraint of this particular reaction. So, which eventually means that the more Ka of an acid means that it is easily dissociable. So, Ka is directly proportionate to the acidic property.

So, more Ka means more the value of Ka more the value of Ka, implies the strongest acid or stronger the acid. This was kind of a directly correlation as pKa is kind of opposite to the Ka, so if pKa is more it implies that the acid is pretty weak just opposite of the Ka.

So, we can say that pKa value less means strong acid, this you can just remember as a rule of thumb. pKa value more, this is weak acid, this can serve you as a normal guideline and you can try to follow this typical thing.

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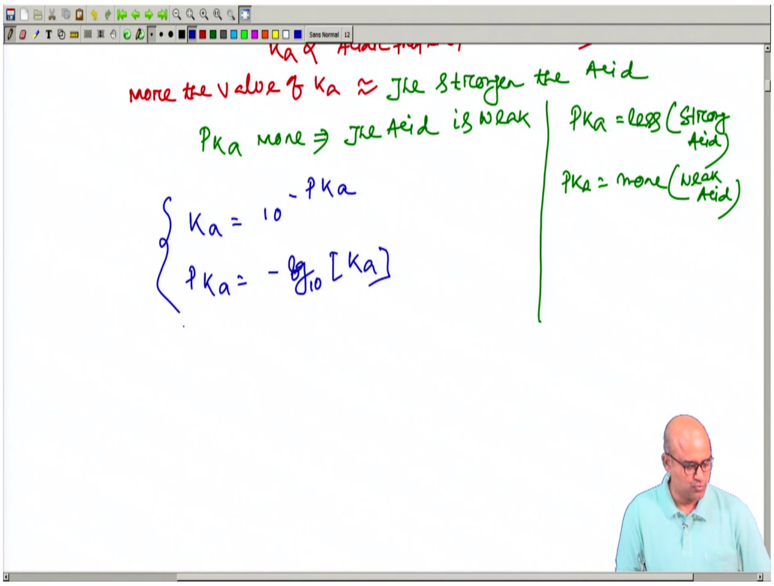
More the value of Ka ≈ The stronger the Acid

pKa more ⇒ The Acid is weak

pKa = less (Strong Acid)

pKa = more (weak Acid)

$K_a = 10^{-pK_a}$

$pK_a = -\log_{10}[K_a]$

So, the conversation of Ka to pKa as I said as you can easily convert these things very easily and this is the conversation way you can do it is a natural logarithm based ten. So, pKa and Ka can easily be convertible ok.

And for synthetic organic chemist we usually prefer to use pKa and pKa is gives you a kind of a qualitative idea that how strong or how weak the acid or base is.

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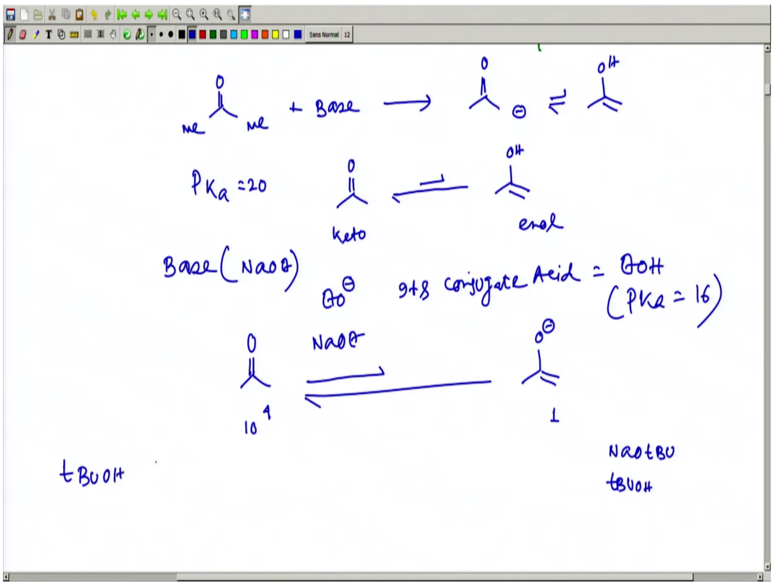

Now, again come back to our original problem that when you are trying to do an enolization what kind of thing is related to with.

We take a simple compound acetone, acetone the pKa value which is reported in the literature its pKa is close to 20 you use a base the base of base nature I am not specifying. You can basically get a carbanion, which then try to give you the corresponding enolate.

Now this particular equilibrium this particular equilibrium, this acetone to this enol or something like this. So, this is the keto form and this is the enol form. Now this I have written something like this means that I want everything should be converted to enol or very little amount should be left for the keto or the other way depending on your choice.

So, this particular equilibrium you can basically control by your let us say I want exclusively ketone and little bit of enol. Now, what kind of a base usually you should choose to control this equilibrium or the keto and enol percentage. The most of the cases we choose something you basically need a base, base means let us say you are using a base sodium ethoxide.

Now sodium ethoxide is a base which basically gives you EtO minus. Now EtO minus its conjugate acid is its conjugate acid is ethanol, ethanol pKa value is 16. So, in terms of acidity acetone and ethanol seems to be at par, there are very little differences for this. Now this can serve you a very good guideline that if you use sodium ethoxide as the base it has been observed that under this condition, if you use sodium ethoxide as a base the equilibrium mostly preferred towards the ketone it is basically preferred.

Ethoxide is not that much stronger base, but it could be switched over to different case. Now the ratio will be quite interesting it will be 10 to the power 4 is to 1. So, very negligible amount of enol will be formed and you will get exclusively ketone product now try to use a little bit of stronger base, sodium tertiary butoxide.

Tertiary butoxide means conjugate acid is tert-butanol ok tert-butanol is a conjugate acid.

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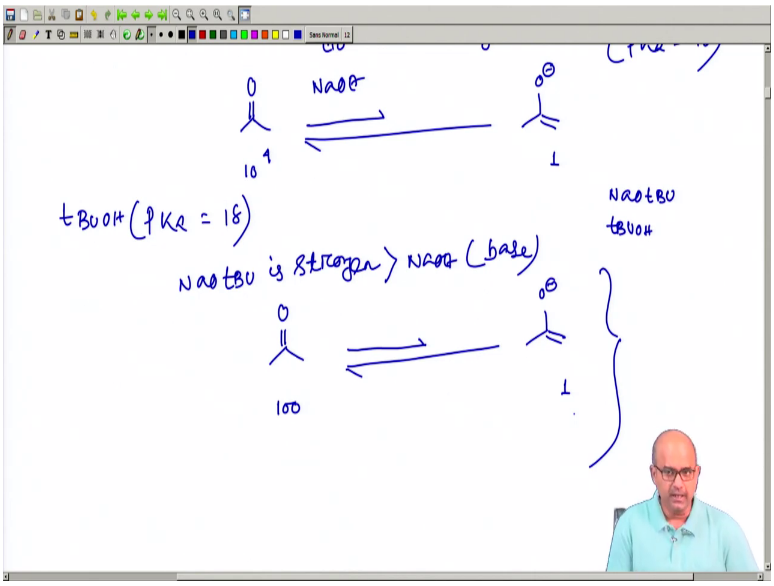

Now, tert-butanol the pKa value is little bit higher than ethanol its 18 and that is why sodium tertiary butoxide is stronger base, than the corresponding ethoxide in terms of basicity.

Now, if you use a tertiary butoxide in this particular reaction equilibrium you will observe that the equilibrium position does not change definitely, but the percentage will be little bit of more in favor of the ketone. So, now, it will be 100 is to 1, so means enol formation has little bit increased. And usually if you try to have that this kind of equilibrium where you want ketone as well as enol though the ratio was not that great, but you can control it. So, alkoxide base was usually preferred.

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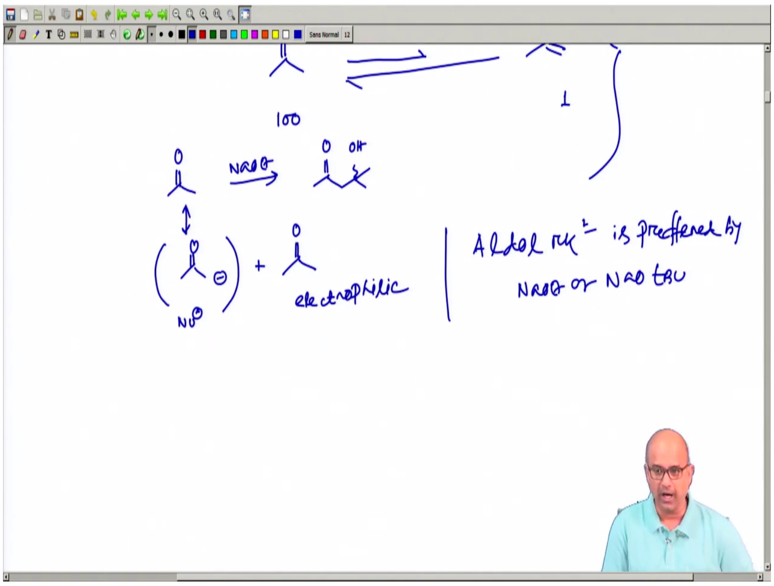

Now, you remember in the aldol reaction often we used alkoxide base, you remember you use acetone with a base like sodium ethoxide. Now acetone can undergo aldol reaction with this your one of this acetone, will be reacting to first give you the carbanion and this carbanion will then react with these things.

Now, why you need this? Basically you need this enol or this carbanion as a nucleophile which can attack to the acetone as the electrophile, this could be your nucleophile partner and this could be your electrophilic partner. So, normally for that reason usually we prefer the alkoxide base for the aldol reaction. So, for aldol reaction alkoxide base was always preferred because usually you get a nice equilibrium.

This equilibrium 100 is to 1 you can keep on adding excess tertiary butoxide and you find that the equilibrium might be close to 50-50. So, aldol reaction is usually preferred by your ethoxide or tertiary butoxide. Now in our case as we are not going to do the aldol reaction, we will be mainly focusing on that how this enol will be exclusively generated.

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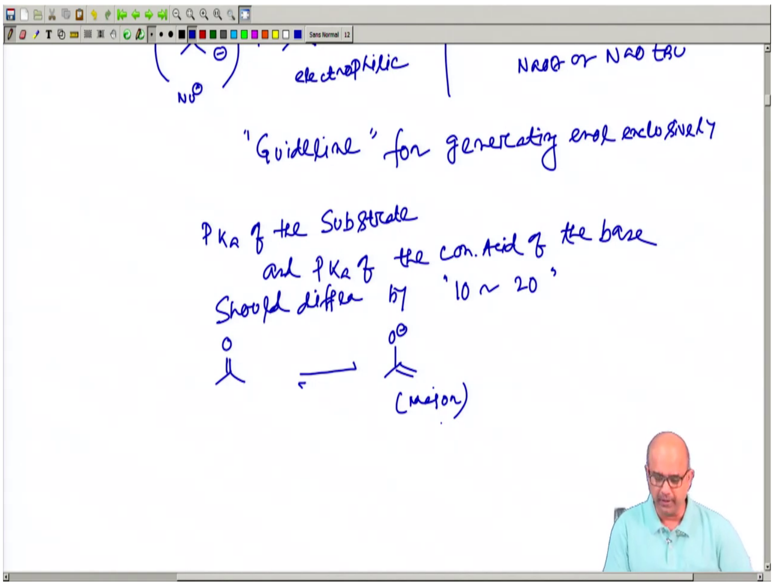

Nu⊖ electrophilic | NaOH or NaO tBu

"Guideline" for generating enol exclusively

pKa of the Substrate and pKa of the con. Acid of the base Should differ by '10 ~ 20'

(major)

Now there is a rule or guideline for generating exclusively enols, exclusively and this could be served as a very good guiding principle. And if usually found that the pKa of the substrate or the precursor and pKa of the conjugate acid of the base, which will be using should differ very high should differ, should differ, so differ by 10 to 20.

And this was can be served as a very good guiding principle for your enol generation exclusively. In those cases, what happen if you try to use and you will find that mostly the enols will be preferred over the ketone. So, this is major product or equilibrium will be mainly shifted towards the enol tautomer and ketone will be exclusively converted to the enols.

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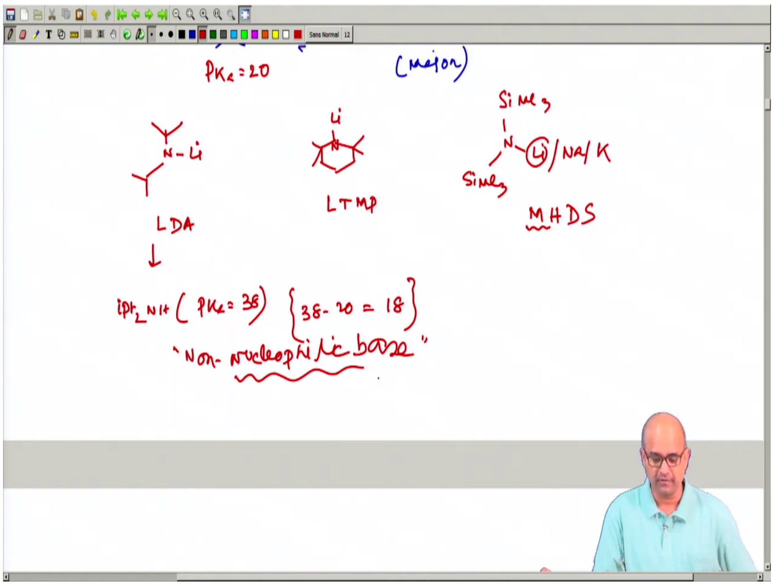

Now, we will be trying to talk about some of those bases in the subsequent section, but definitely just try to give you a brief overview and you can continue in that next lecture. And normally we found that very sterically bulky bases like it is called LDA lithium diisopropylamide.

The bases which are used exclusively for the enolate generation something like this is called LTMP lithium tetramethylpiperidide, it is a very good commercially available bases. And then you have a LDA analog where instead of isopropyl group you use TMS group hexamethyldisilazane and this can be lithium this can be sodium this can be potassium,

These bases are named as MHDS, so M basically stands for the corresponding metal, if you have lithium you called LHDS. So, you can add different metals and these bases are usually very strong because the corresponding pKa value, pKa value of acetone we know. pKa of acetone is 20, but in this case what is the conjugate acid? The conjugate acid is (NH isopropyl)$_2$.

This pKa is 38. So, what is the difference? 38 minus 20 is almost 18. So, and this means that this will basically convert entirely the ketone to the corresponding enol in addition these bases are sterically very bulky and these are called non nucleophilic bases, non-nucleophilic bases.

So, we can try to discuss those bases in later part of our lecture. And I want to stress on this part non nucleophilic means this bases usually does not take part in the nucleophilic reaction because carbonates are electrophilic.

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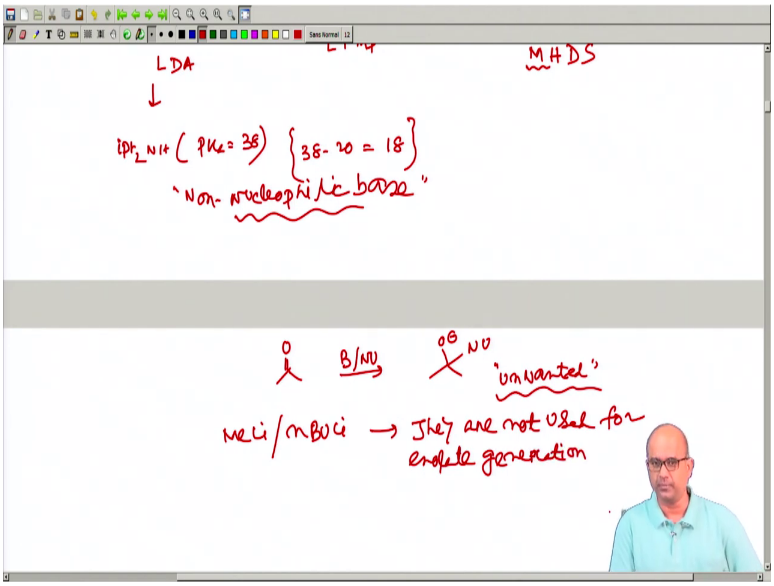

So, if you can find that in some cases these carbonyls do react, so like you have this carbonyl compound.

So, if your base can act as a nucleophile you will definitely do have a side product which you do not want ok. So, this is unwanted product, so normally in for that reason we never use a nucleophilic base. Like sodium ethoxide usually is a nucleophilic bases other bases like methyl lithium, n-butyl lithium is only for that reason we tend to avoid for enolization.

Methyl lithium, n-butyl lithium these are also pretty good bases, but they are not used for enolate generation not used for enolate generation. That is the rule of thumb you can keep it in your mind. And you will always try to use that as a guiding principle when you are trying to do the enolate chemistry ok.

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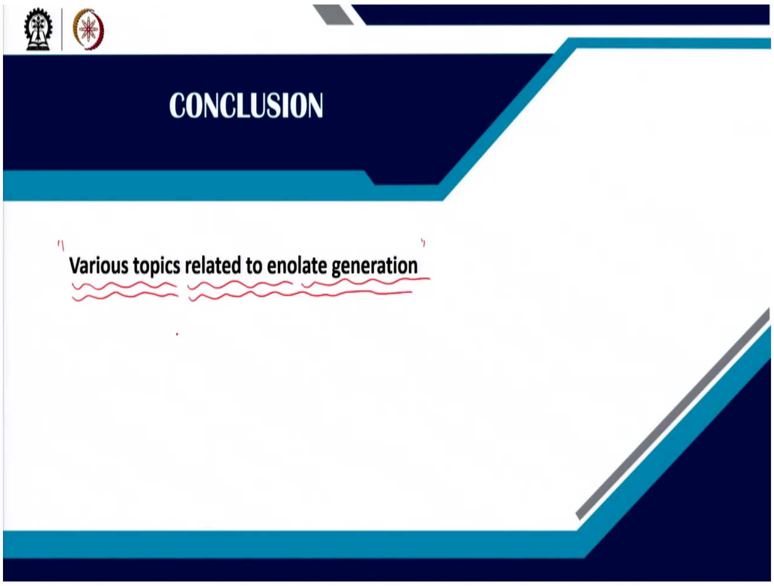

CONCLUSION

Various topics related to enolate generation

Nevertheless, we will try to conclude for today's thing and what we will try to say that, as a concluding remark I would like to say that we have started a very introductory session on enolate generation. We said that how enols could be generated and there are different features, mostly we talked about different kind of bases that what you need to use, so mainly these bases take a very good thing. So, we will continue for next lecture.

Till then have a good time and goodbye.