

Organic Chemistry  
Semester-4, CBCS  
Course: CEMG CC-4/GE-4

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

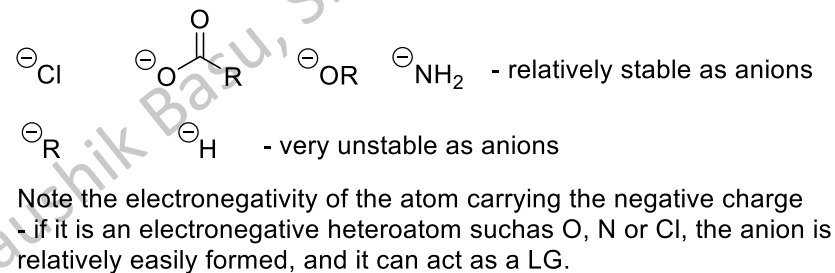
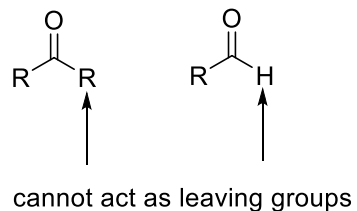
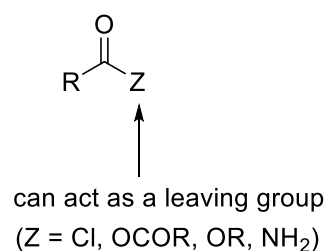
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Lecture Note prepared by Kaushik Basu, SPCMC

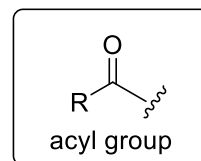
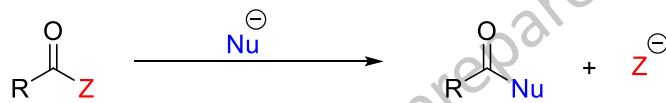
Reactions of carboxylic acid derivatives:

Nucleophilic acyl substitution:

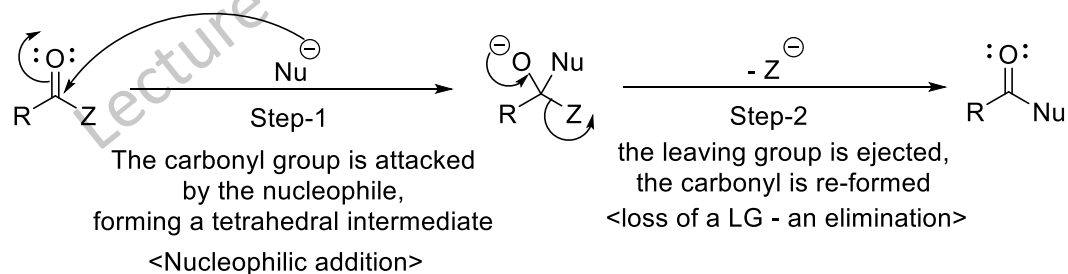
The reactivity of carboxylic acid derivatives is similar to the reactivity of aldehydes and ketones in a number of ways. In both cases, the carbonyl group is electrophilic and subject to attack by a nucleophile. In both cases, the same rules and principles govern the proton transfers that accompany the reactions, as we will soon see. Nevertheless, there is one critical difference between carboxylic acid derivatives and aldehydes/ketones. Specifically, carboxylic acid derivatives possess a heteroatom that can function as a leaving group, while aldehydes and ketones do not.



When a nucleophile attacks a carboxylic acid derivative, a reaction can occur in which the nucleophile replaces the leaving group:



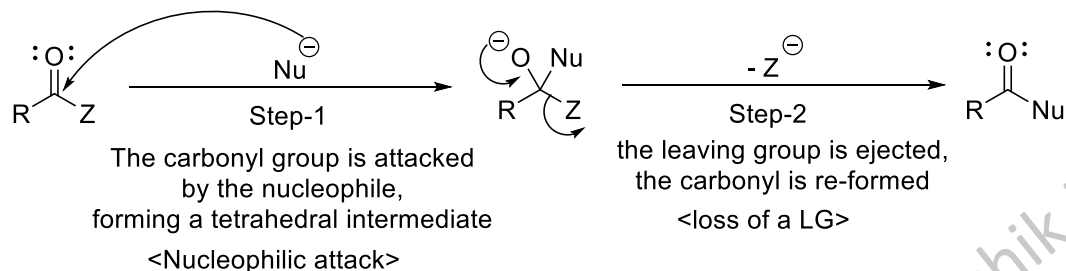
This type of reaction is called a nucleophilic acyl substitution, and the rest of this lesson will be dominated by various examples of this type of reaction. The general mechanism has two core steps.



Reactions of carboxylic acid derivatives:

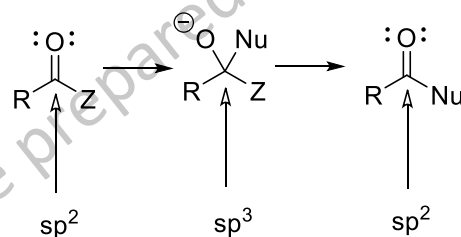
Nucleophilic acyl substitution:

This type of reaction is called a nucleophilic acyl substitution, and the rest of this chapter will be dominated by various examples of this type of reaction. The general mechanism has two core steps.

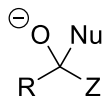


During the first step, in which a nucleophile attacks the carbonyl group, the hybridization state of the carbon atom changes.

In both the starting material and product, the carbon atom is sp<sup>2</sup> hybridized with trigonal planar geometry, but the same atom in the intermediate is sp<sup>3</sup> hybridized with tetrahedral geometry.



In recognition of this geometric change, the intermediate is often called a tetrahedral intermediate.



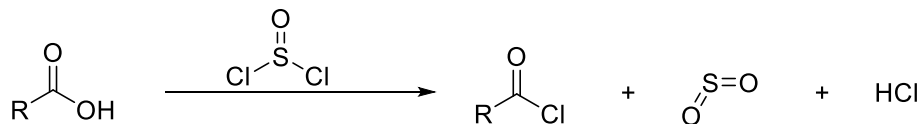
tetrahedral intermediate (TI)

In the second step, the carbonyl group is re-formed via the loss of a leaving group. Re-formation of the C=O double bond is a powerful driving force, and even relatively poor leaving groups (such as alkoxides or amides) can be expelled under certain conditions.

Carboxylic acid derivatives:

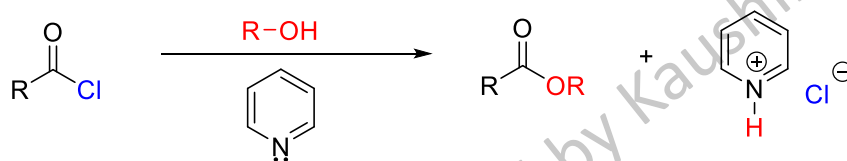
Preparation and Reactions of Acid Chlorides:

Preparation: Acid chlorides can be formed by treating carboxylic acids with thionyl chloride ( $\text{SOCl}_2$ ) or phosphorous pentachloride ( $\text{PCl}_5$ ):



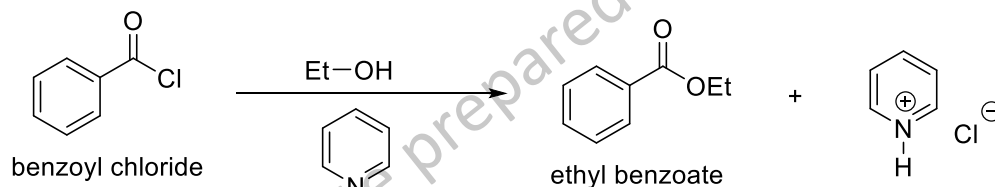
Reactions:

i) Alcoholysis: When treated with an alcohol, acid chlorides are converted into esters.

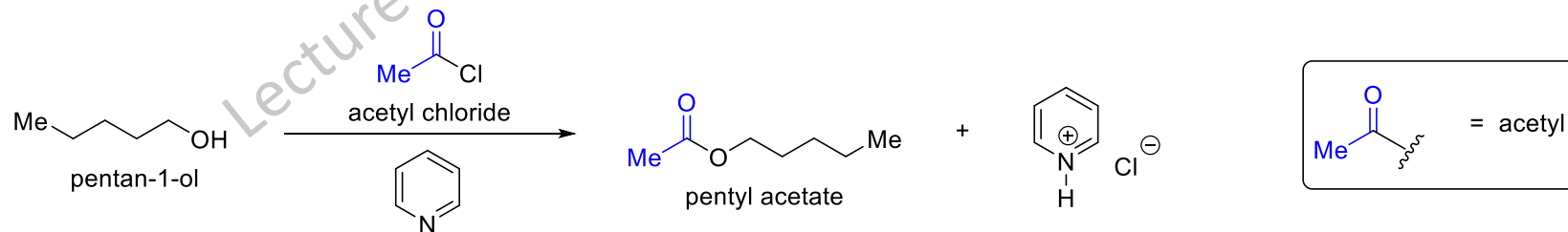


Pyridine is used as a base to neutralize the HCl as it is produced.

For example,



This reaction is viewed from the perspective of the acid chloride, but the same reaction can be written from the perspective of the alcohol.

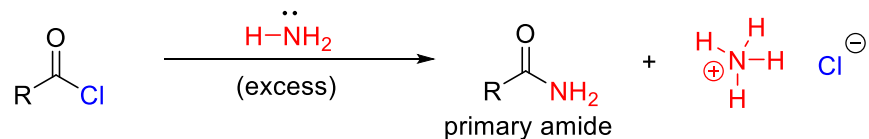


When shown like this, the OH group is said to undergo acylation, because an acyl group has been transferred to the OH group to produce an ester. In this example shown above, pentanol is said to be acetylated, note that acetyl group is "MeCO".

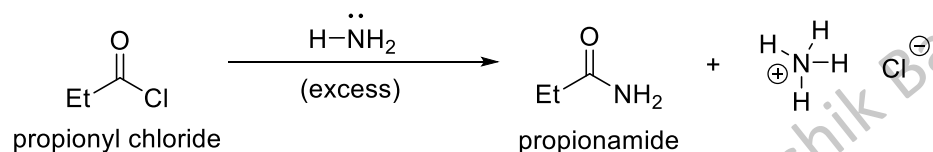
Carboxylic acid derivatives:

Reactions of acid chlorides:

ii) Aminolysis: When treated with ammonia, acid chlorides are converted into amides.



For example,

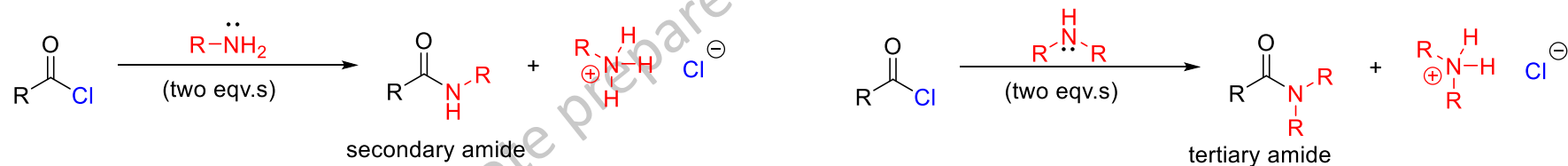


Pyridine is not used in this reaction, because ammonia itself is a sufficiently strong base to neutralize the HCl as it is produced.

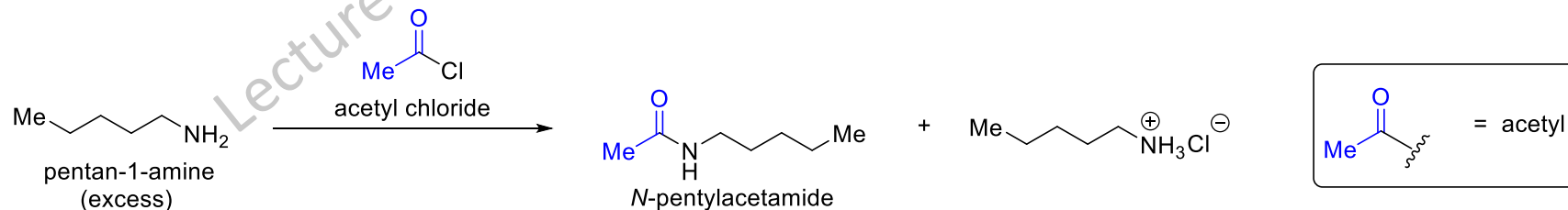
For this reaction, at least two equivalents of ammonia are necessary: one for the nucleophilic attack and the other to neutralize the HCl.

In general, excess ammonia is used.

This reaction also occurs with primary and secondary amines to produce *N*-substituted amides.



This reaction is viewed from the perspective of the acid chloride, but the same reaction can be written from the perspective of the amine.

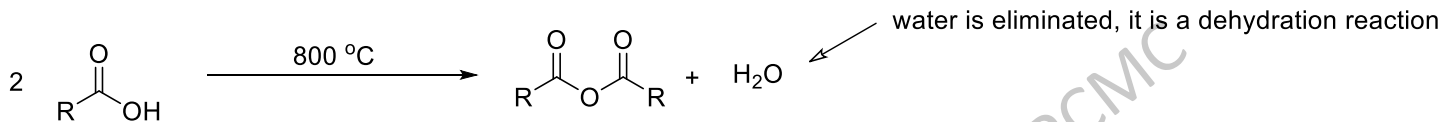


When shown like this, the NH<sub>2</sub> group is said to undergo acylation, because an acyl group has been transferred to the NH<sub>2</sub> group to produce an amide. In this example shown above, pentamine is said to be acetylated, note that acetyl group is "MeCO".

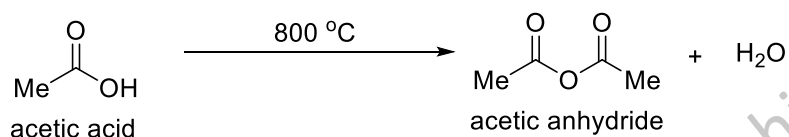
Carboxylic acid derivatives:

Preparation and Reactions of Acid Anhydrides:

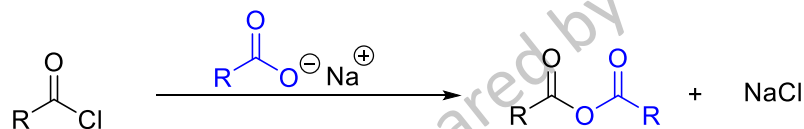
Preparation: Carboxylic acids can be converted into acid anhydrides with excessive heating.



For example,

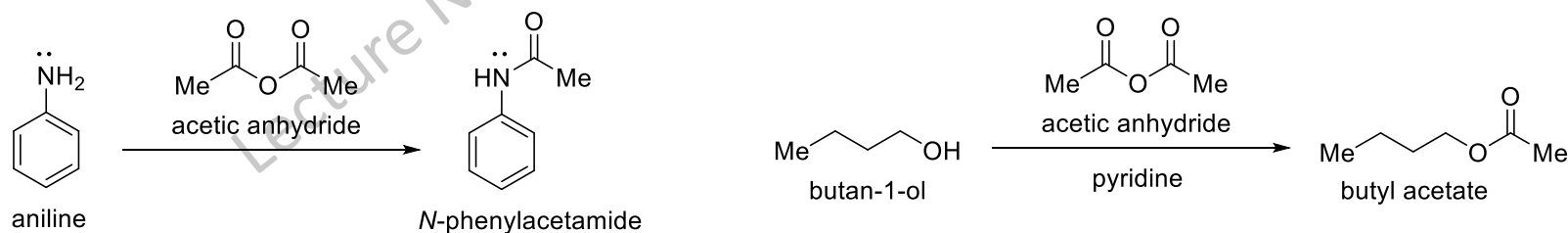


This method is only practical for acetic acid, as most other acids cannot survive the excessive heat. An alternative method for preparing acid anhydrides involves treating an acid chloride with a carboxylate ion, which functions as a nucleophile.



Reaction: Acetylation of an alcohol or an amine:

Acetic anhydride is often used to acetylate an alcohol or an amine. The products are esters and amides:

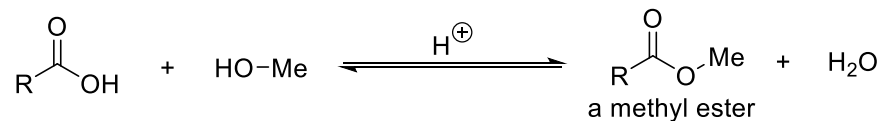


When shown like this, the NH<sub>2</sub> group and the OH group is said to undergo acylation, because an acyl group has been transferred to the NH<sub>2</sub> group / OH group to produce an amide and an ester respectively. In this example shown above, the amine and the alcohol is said to be acetylated, note that acetyl group is "MeCO".

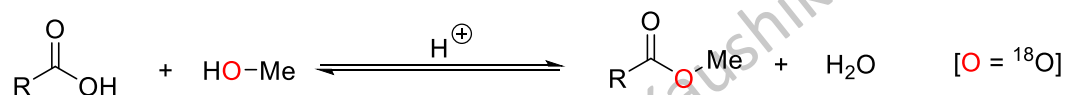
Carboxylic acid derivatives:

Preparation and Reactions of Esters:

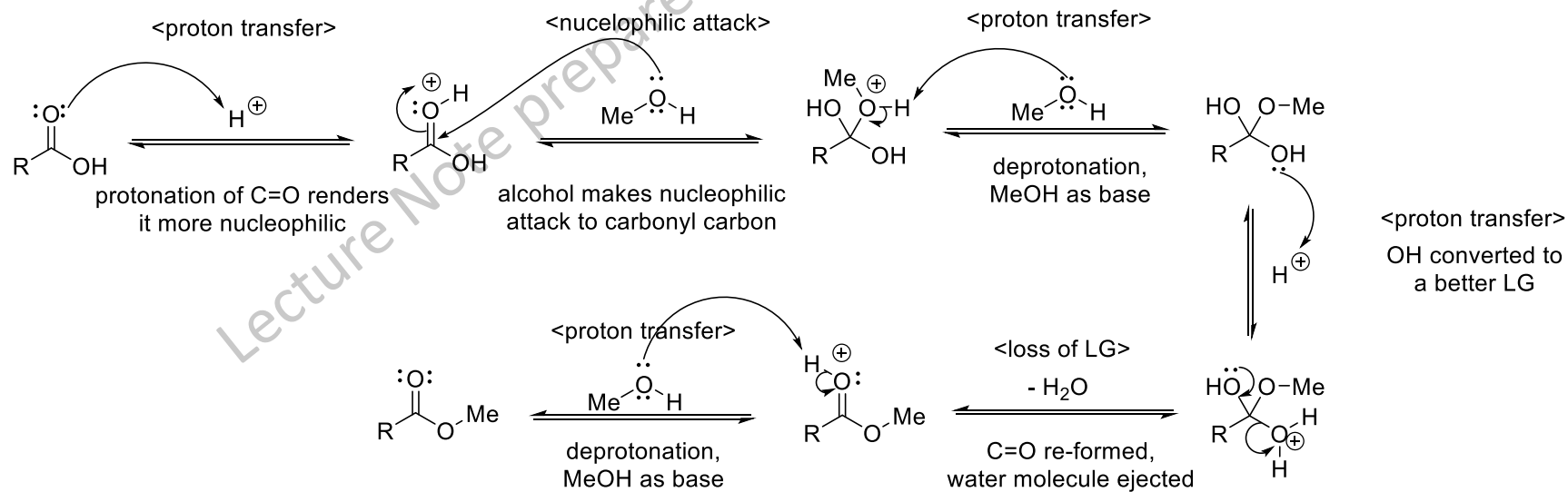
Preparation: Carboxylic acids are converted into esters when treated with an alcohol in the presence of an acid catalyst. This process is called the Fischer esterification.



Mechanism: The accepted mechanism is exactly what we would expect for a nucleophilic acyl substitution that takes place under acidic conditions. Evidence for this mechanism comes from isotopic labelling experiments in which the oxygen atom of the alcohol is replaced with a heavier isotope of oxygen ( $^{18}\text{O}$ ), and the location of this isotope is tracked throughout the reaction.



The location of the isotope in the product (shown in red) supports the mechanism outlined below:



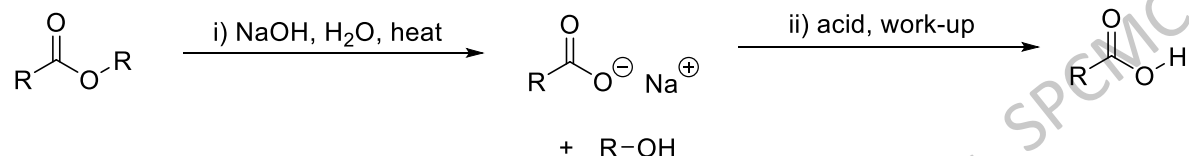




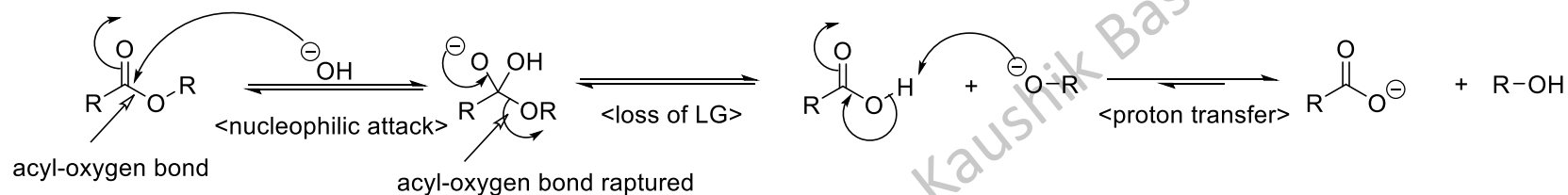
Carboxylic acid derivatives:

Reactions of Esters:

i) Saponification: Esters can be converted into carboxylic acids by treatment with sodium hydroxide followed by an acid. This process is called saponification.



Mechanism:



The first two steps of this mechanism are exactly what we would expect of a nucleophilic acyl substitution reaction occurring under basic conditions:

(1) nucleophilic attack followed by (2) loss of a leaving group. The nucleophilic attack is the slow, rate-determining step of the reaction.

In basic conditions, an alkoxide ion can function as a leaving group and is not protonated prior to its departure.

Although alkoxide ions are not a very good leaving group (as they are strongly basic in nature), they can function as leaving groups in these circumstances because the tetrahedral intermediate is sufficiently high in energy.

The tetrahedral intermediate itself is an alkoxide ion, so expulsion of an alkoxide ion is not very unfavourable.

Under such strongly basic conditions, the carboxylic acid does not survive; it is deprotonated to produce a carboxylate salt. In fact, the formation of a stabilized carboxylate ion is a driving force that pushes the equilibrium to favor formation of products. After the reaction is complete, an acid is required to protonate the carboxylate ion to give the carboxylic acid.

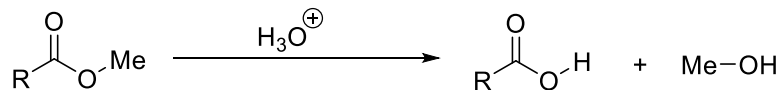
This is called the  $\text{B}_{\text{Ac}}2$  mechanism: Base-induced, Acyl-oxygen cleavage, Bimolecular.

The reaction occurs in base, the  $\text{C}(=\text{O})-\text{OR}$  bond, i.e. the acyl bond is cleaved, and the rate-determining step is the attack of the hydroxide on the ester, so two molecules are involved.

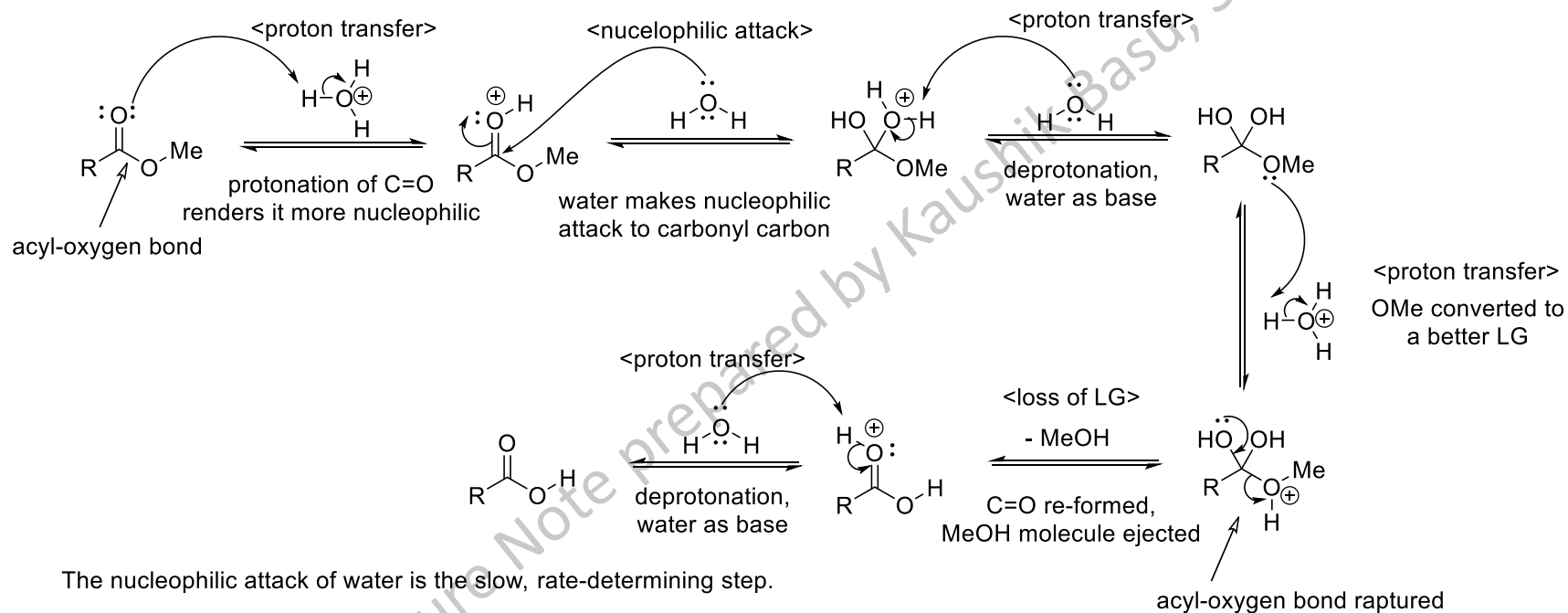
Carboxylic acid derivatives:

Reactions of Esters:

ii) Acid-catalysed hydrolysis of esters: Esters can also be hydrolysed under acidic conditions.



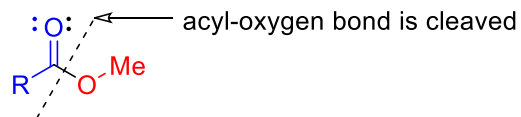
This process is the reverse of a Fischer esterification.



The nucleophilic attack of water is the slow, rate-determining step.

This is called the  $A_{AC}2$  mechanism: Acid-catalysed, Acyl-oxygen cleavage, Bimolecular.

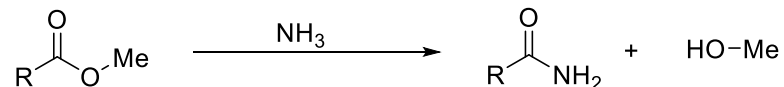
The reaction occurs in acid medium, the  $\text{C}(=\text{O})-\text{OR}$  bond, i.e. the acyl bond is cleaved, and the rate-determining step is the attack of the water, so two molecules are involved.



Carboxylic acid derivatives:

Reactions of Esters:

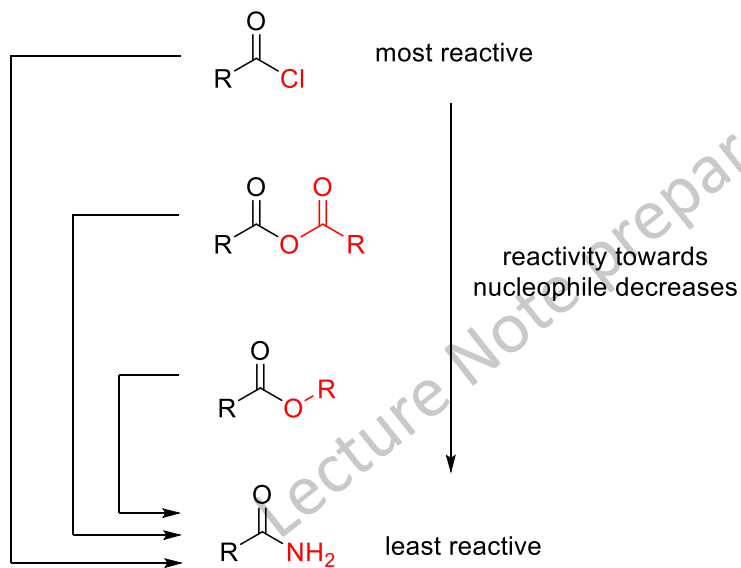
iii) Aminolysis of esters: Esters react slowly with amines to yield amides.



This process has little practical utility, because preparation of amides is achieved more efficiently from the reaction between acid chlorides and ammonia or primary or secondary amines.

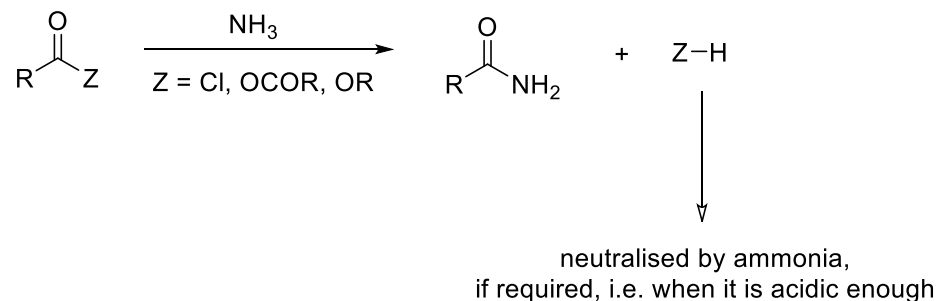
Preparation and Reactions of Amides:

Preparation: Amides can be prepared from any of the carboxylic acid derivatives discussed earlier.



The carboxylic acid derivatives' reactivity ladder

Among these methods, amides are most efficiently prepared from acid chlorides. Acid chlorides are the most reactive of the carboxylic acid derivatives, so the yields are best when an acid chloride is used as a starting material.

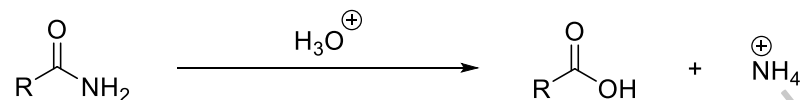


Carboxylic acid derivatives:

Reactions of Amides:

i) Hydrolysis under acid catalysis:

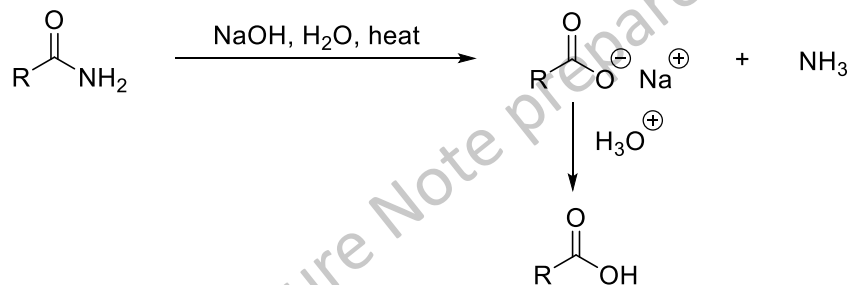
Amides can be hydrolyzed to give carboxylic acids in the presence of aqueous acid, but the process is slow and requires heating to occur at an appreciable rate.



In this reaction, notice that an ammonium ion ( $\text{NH}_4^+$ ) is formed as a by-product. The ammonium ion ( $\text{p}K_{\text{a}} = 9.2$ ) is a much weaker acid than  $\text{H}_3\text{O}^+$  ( $\text{p}K_{\text{a}} = -1.7$ ), and the formation of a weak acid is one of the driving forces for this reaction. Indeed, the equilibrium greatly favours formation of products, and the process is effectively irreversible.

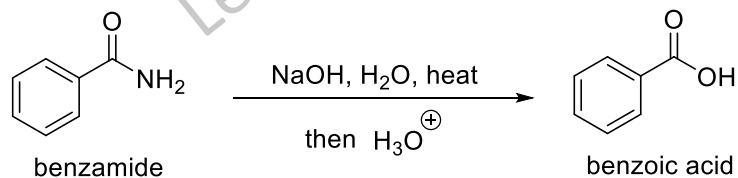
ii) Hydrolysis of amides under basic condition:

Amides are also hydrolysed when heated in basic aqueous solutions, although the process is very slow.

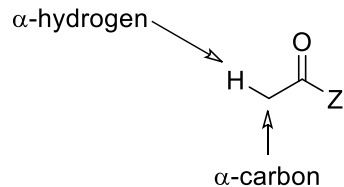


The accepted mechanism for this process is directly analogous to the mechanism that we saw for the saponification of esters. In the last step, formation of the carboxylate ion drives the reaction to completion and renders the process irreversible.

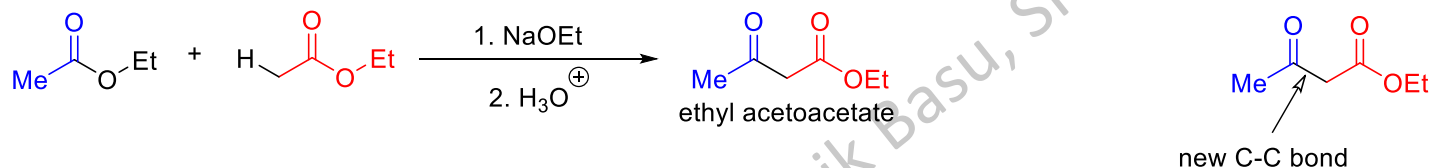
Example,



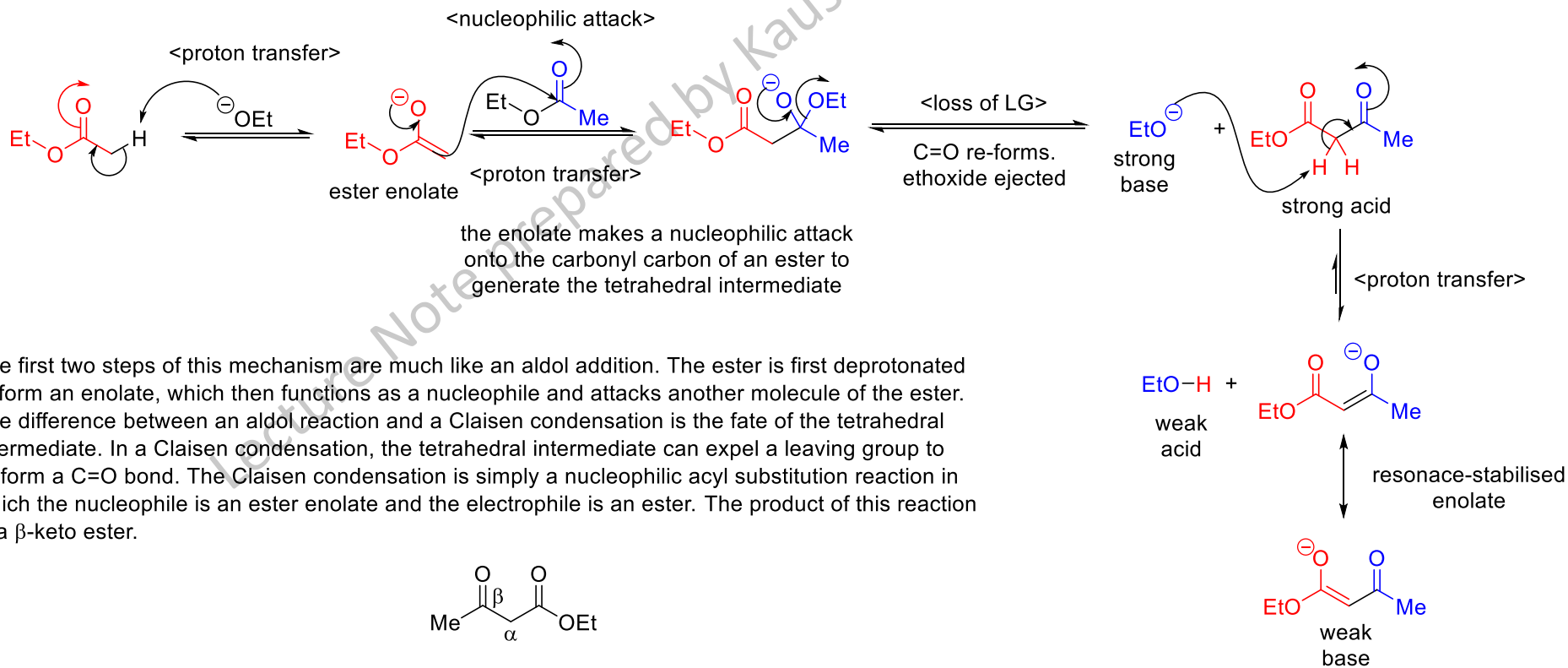
Reactions of carboxylic acid derivative:  
Reactions involving the  $\alpha$ -hydrogen:



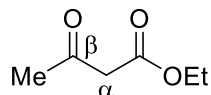
Claisen Condensation: Like aldehydes and ketones, esters also exhibit reversible condensation reactions.



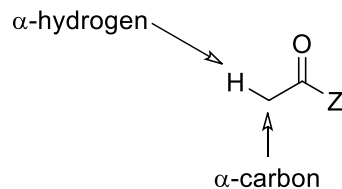
This type of reaction is called a Claisen condensation, and a mechanism for this process is shown:



The first two steps of this mechanism are much like an aldol addition. The ester is first deprotonated to form an enolate, which then functions as a nucleophile and attacks another molecule of the ester. The difference between an aldol reaction and a Claisen condensation is the fate of the tetrahedral intermediate. In a Claisen condensation, the tetrahedral intermediate can expel a leaving group to re-form a C=O bond. The Claisen condensation is simply a nucleophilic acyl substitution reaction in which the nucleophile is an ester enolate and the electrophile is an ester. The product of this reaction is a  $\beta$ -keto ester.

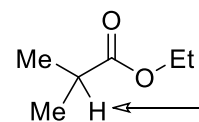


Reactions of carboxylic acid derivative:  
Reactions involving the  $\alpha$ -hydrogen:

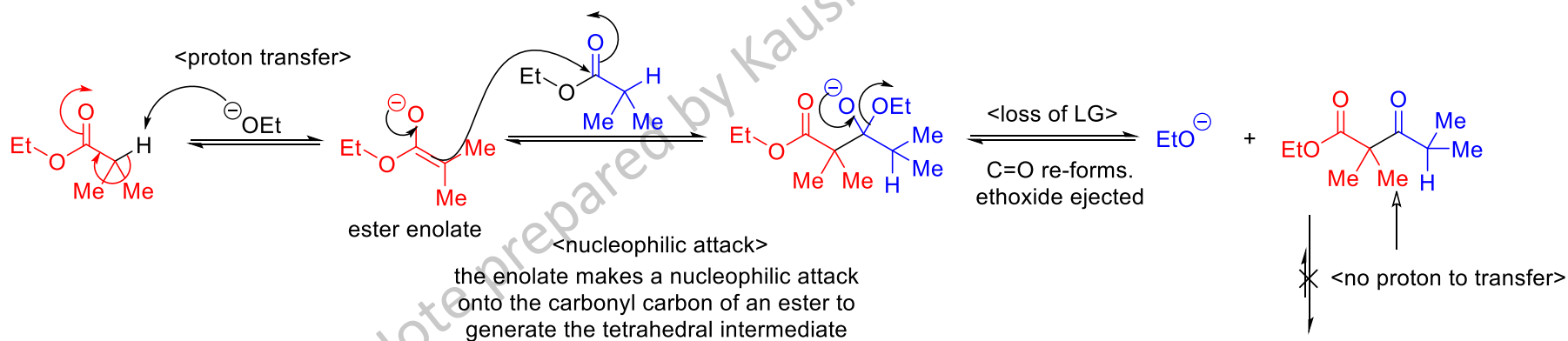


When performing a Claisen condensation, the starting ester must have two  $\alpha$ -protons.

If it only has one  $\alpha$ -proton, then the driving force for condensation is absent (a doubly stabilized enolate of the ketoester product cannot be formed).



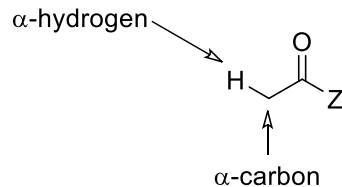
only one  $\alpha$ -proton, cannot take part in Claisen condensation when sodium ethoxide is used as a base.  
ethyl isobutyrate



Notice that the last step in the mechanism, i.e. the deprotonation of the  $\beta$ -keto ester to give a doubly-stabilized ketoester enolate ion cannot proceed here, as there is no proton to pick off at the C between the two  $\text{C}=\text{O}$ .

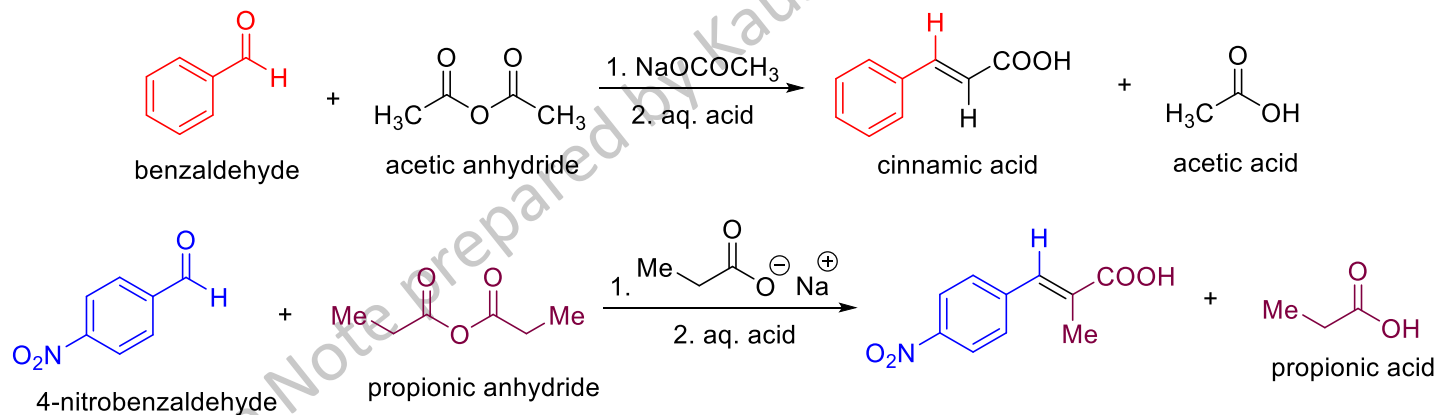
This deprotonation step is essential for the reaction to proceed to completion. As it cannot proceed under this reaction condition, the condensation is a failure.

Reactions of carboxylic acid derivative:  
Reactions involving the  $\alpha$ -hydrogen:



Perkin reaction:

The Perkin reaction is an aldol-condensation type reaction that is used to convert an aromatic aldehyde and a carboxylic acid anhydride to an  $\alpha,\beta$ -unsaturated aromatic carboxylic acid in presence of the sodium salt of the acid (whose anhydride is used). This sodium salt acts as the base catalyst in the condensation. If we use acetic anhydride as the anhydride, we must use sodium acetate as the base catalyst. An aqueous acid work-up is needed to release the final unsaturated carboxylic acid product.



The mechanism of Perkin reaction is too complicated to discuss in detail in this course.

It is the *trans*-isomer that is formed selectively. This is probably driven by the tendency to minimize steric repulsion.

