Esterification

Preparation of β-D-glucose pentaacetate

Dr. Zerong Wang at UHCL

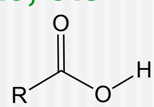
Table of contents

- Ester
- Reaction with carboxylic acids
- Reaction with esters: transesterification
- Reaction with acid anhydrides
- Reaction with acid halides and other acyl derivatives
- Preparation of β-D-glucose pentaacetate

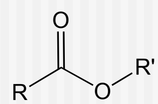
Dr. Zerong Wang at UHCL

Carboxylic Acid and Ester

- Common carboxylic acids are: formic acid, acetic acid, benzoic acid, etc.
- Common esters are formate, acetate, benzoate, etc.



R = H, alkyl, aryl



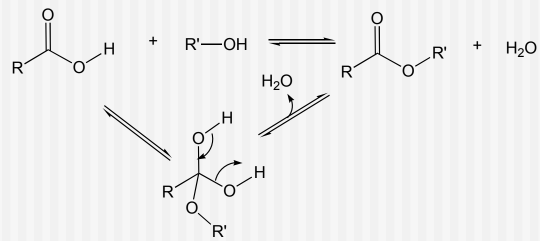
R = H, alkyl, aryl
R' = alkyl, aryl

Reaction with Carboxylic Acids

- Without Activator
- Acid Catalysts
- Carbodiimide Activators
- The Mitsunobu Reaction
- Enzymes

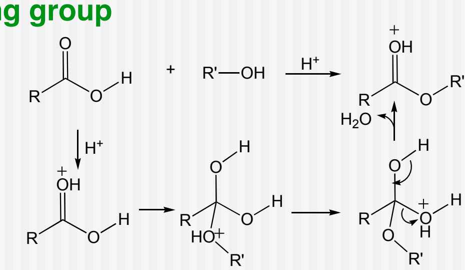
With Acid without Activator

- Hydroxy is not a good leaving group
- Possible for carboxylic acid and alcohols with high boiling points



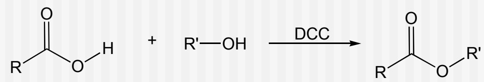
Acid Catalysts

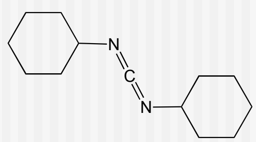
- Acid catalyst protonates the carbonyl group of carboxylic acid and enhances the electrophilicity of carbonyl group
- Acid catalyst help the conversion of hydroxyl group to leave as water, the neutral molecule and a good leaving group



Carbodiimide Activation

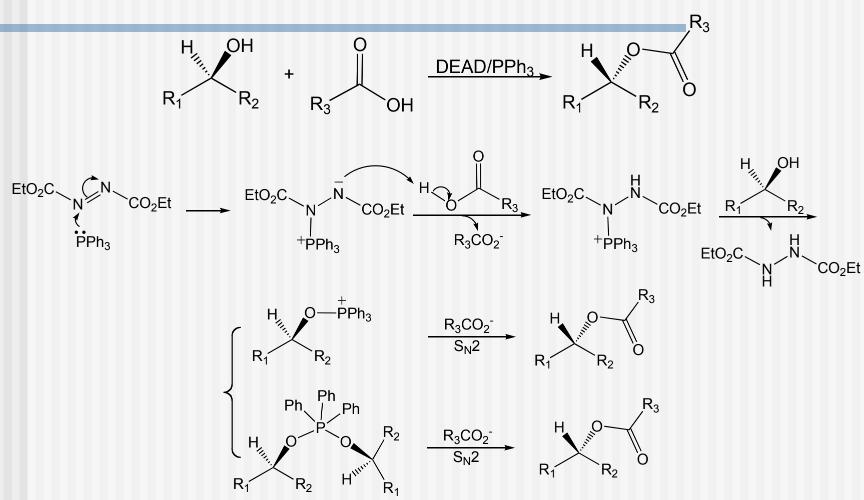
- Dicyclohexyl carbodiimide (DCC) accelerates the esterification by formation of dicyclohexyl urea





Dr. Zerong Wang at UHCL

The Mitsunobu Reaction



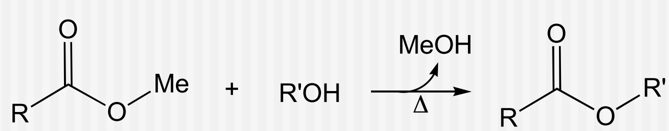
Dr. Zerong Wang at UHCL

Reaction with Esters: Transesterificaiton

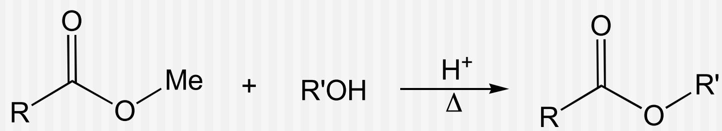
- Without Activator
- Acid Catalysts
- Enzymes

Transesterification without Activator

- Esters from small alcoholic components such as methanol or ethanol can react with other large alcohols to form different esters, as methanol and ethanol are more volatile than water.



Transesterification with Acid Catalysts



Transesterification with Lipases

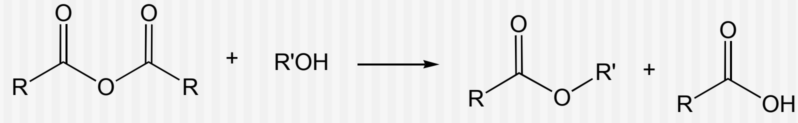
- The enzymes that cleave the ester functional group are known as Lipases
- In the presence of lipases, the alcohols can be easily acylated using other ester as acylating agents
- Especially for the secondary alcohols, only one enantiomer will be acylated, so that enantiomeric pure esters can be prepared from this method
- Reactions are usually carried out at room temperature in non-polar solvent such as toluene

Reaction with Acid Anhydrides

- Without Activator
- Acid Catalysts
- Base Activators
- Mixed Anhydrides

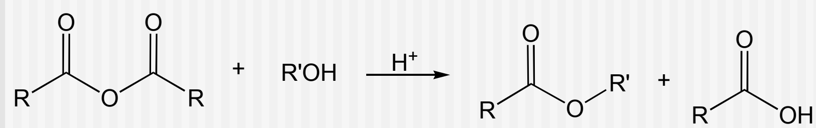
Reaction with Anhydride

- Anhydride is much more electrophilic than carboxylic acid, thus the addition of alcoholic oxygen to carbonyl bond is much faster
- The carboxylic acid cleaved from this esterification is a much better leaving group than hydroxyl group in carboxylic acid



Reaction with Anhydride and Acid Catalyst

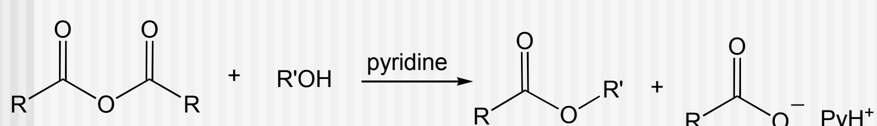
- The presence of acid will protonate the carbonyl group in anhydride, and further enhances the electrophilicity

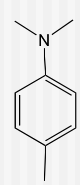


Dr. Zerong Wang at UHCL

Reaction with Anhydride and Base Activator

- The base, usually tertiary amine, presenting in the reaction system will scavenge the formed acid, and shift the equilibrium to ester

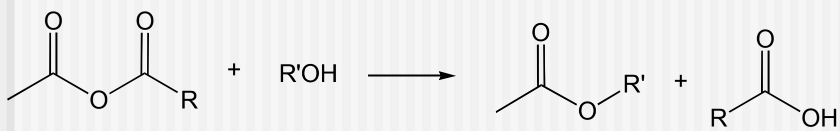


DMAP 

Dr. Zerong Wang at UHCL

Reaction with Mixed Anhydride

- Generally, the reaction with mixed anhydride, the alcohols will be acylated by the smaller carboxylic moiety, because of the electrophilicity



Dr. Zerong Wang at UHCL

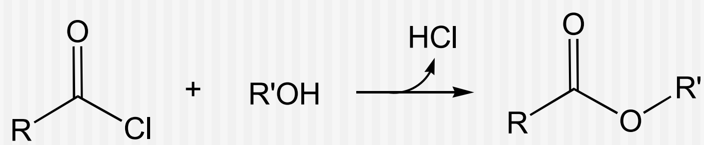
Acyl Halide and Acyl Derivatives

- Without Activator
- Acid Catalysts
- Base Activators
- Enzymes

Dr. Zerong Wang at UHCL

Reaction with Acyl Halides

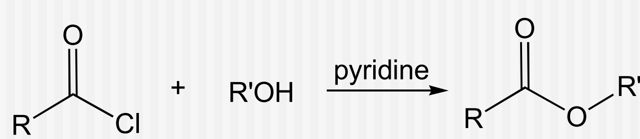
- As halides are good leaving groups, the reaction between alcohol and acyl halides are very fast and exothermic
- The reaction must be carefully carried out with cooling or in dilute solution



Dr. Zerong Wang at UHCL

Reaction with Acyl Halides with Base Activator

- The presence of base (tertiary amines) can neutralize the hydrochloride acid
- Other amines (primary or secondary amines) will further react with ester to form amides



Dr. Zerong Wang at UHCL

Reaction with Other Acyl Derivatives

- Alcohol can react with nitriles to form esters

Acetylation of Glucose

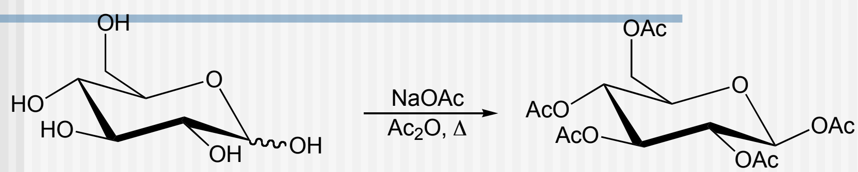
- Glucose is a monosaccharide with five free hydroxyl groups
- It often mutarotates between α- and β-anomer
- The acetylation of glucose is very useful for transformation of glucose into a useful material for carbohydrate synthesis

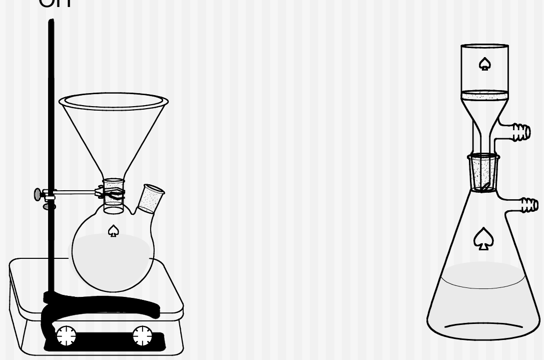
Acetylation of Glucose

- Acetylation of glucose may lead to the formation of kinetic product or thermodynamic product; they are α-D-glucose pentaacetate and β-D-glucose pentaacetate
- The acetylation with acetic anhydride in the presence of pyridine results in the formation of kinetic product
- The acetylation with acetic anhydride in the presence of sodium acetate (base) gives thermodynamic product

Dr. Zerong Wang at UHCL

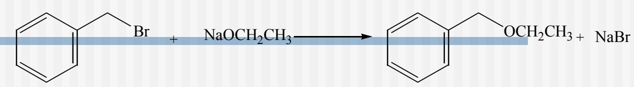
Acetylation of Glucose





Dr. Zerong Wang at UHCL

Atom Economy



	benzyl bromide	sodium ethoxide	benzyl ethyl ether	
MW (g/mol)	171.04	68.05	136.20	102.89
grams used	17.1	10.2		
moles used	0.100	0.150		

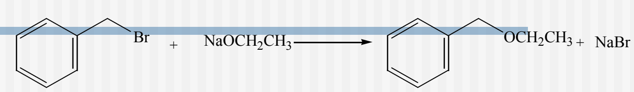
- **Atom economy** is a ratio of the molecular weight of the product vs. the molecular weights of all reactants used in the synthesis.

$$Atomic \quad Economy = \frac{MW_{desired}}{\sum MW_{react.}}$$

$$\frac{136.20 g/mol}{(171.04 g/mol + 68.05 g/mol)} \times 100\% = 57.0\%$$

Dr. Zerong Wang at UHCL

Experimental Atom Economy



	benzyl bromide	sodium ethoxide	benzyl ethyl ether	
MW (g/mol)	171.04	68.05	136.20	102.89
grams used	17.1	10.2		
moles used	0.100	0.150		

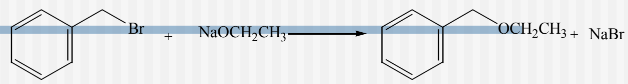
•**Experimental atom economy** compares the theoretically obtainable amount of the desired product to the total amount of reactants used in the synthesis.

$$Experimental \quad Atomic \quad Economy = \frac{Mass_{desired \quad product}}{\sum mass_{react.}}$$

$$\frac{13.62g}{(17.1g + 10.2g)} \times 100\% = 49.9\%$$

Dr. Zerong Wang at UHCL

"E" Product



	benzyl bromide	sodium ethoxide	benzyl ethyl ether	
MW (g/mol)	171.04	68.05	136.20	102.89
grams used	17.1	10.2		
moles used	0.100	0.150		

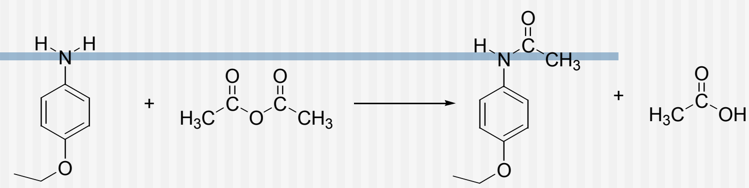
"E" product considers both the chemical yield and the experimental atom economy.

$$E\ Product = \%\ Chemical\ Yield \times \%\ Experimental\ Atom\ Economy$$

e.g., 93% yield, E Product = 93% × 49.9% = 49.4%

Dr. Zerong Wang at UHCL

Cost Analysis



$C_8H_{11}NO$
Acros #: 41716
Cost:
$81.60/250g

$C_4H_6O_3$
Acros #: 42323
Cost:
$23.80/500mL

Cost of Phenetidine used:

1.0 mL * (1.07 g/mL) = 1.07 g used

1.07g * ($81.60/250 g) = $0.35 per synthesis

Dr. Zerong Wang at UHCL

Calculation of Yields

$$Atomic \quad Economy = \frac{MW_{desired}}{\sum MW_{react.}}$$

$$Experimental \quad Atomic \quad Economy = \frac{Mass_{desired \quad product}}{\sum mass_{react.}}$$

$$E\ Product = \%\ Chemical\ Yield \times \%\ Experimental\ Atom\ Economy$$

Dr. Zerong Wang at UHCL