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**CHEM 2212 Promo Packet**

**Chapter 10: Reactions of Alcohols, Ethers, Epoxides and Amines**

**Check out our website for the video tutorial of this packet!**

**Feel free to email us if you have any questions at** [**tutor@scienceguyz.com**](mailto:tutor@scienceguyz.com)

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**Chapter 10: Nucleophilic Substitution of Alcohols, Sulfides, and Thiols**

1. **Nucleophilic Substitution of Alcohols (Generally)**: Alcohols are poor leaving groups in nucleophilic substitution reactions. In order to substitute alcohols, one must turn the alcohol in to a good leaving group (remember weak bases are good leaving groups).
2. **Substitution of Alcohols with HX:** Alcohols can be substituted using HX, where the nucleophile X is replaced for the OH group.
   1. **Halogenating Secondary and Tertiary Alcohols with HX**: When HX is used to halogenate a secondary or tertiary alcohol, the reaction proceeds through SN1 mechanism. HBr and HI are preferred because the Br- and I- halides are much more nucleophilic than Cl-.
      1. **Note**: heat is required for secondary alcohols but not for tertiary alcohols



* 1. **Halogenating Primary Alcohols with HX**: When HX is used to halogenate a primary alcohol, the reaction proceeds through an SN2 mechanism.



* 1. **The Lucas Reagent**: As mentioned previously, the chloride ion is not as good a nucleophile and therefore produces poor yields when undergoing a chlorination reaction with primary and secondary alcohols. Using the Lucas Reagent (ZnCl2) gives much higher yields than simply using HCl because the ZnCl2 Lewis acid makes the alcohol a better leaving group.
     1. Chlorinating a secondary alcohol with the Lucas Reagent will proceed through an SN1 mechanism.



* + 1. Chlorinating a primary alcohol with the Lucas Reagent will proceed through an SN2 mechanism.



* 1. **Beware of Carbocation Rearrangements:** When halogenating secondary and tertiary alcohols in acid, beware of carbocation rearrangements because the reactions will proceed through SN1 mechanism.



* 1. **Avoiding carbocation rearrangements when halogenating an alcohol**: Carbocation rearrangements of alcohols can be avoided if the alcohol is halogenated using PX3 or SOCl2 in pyridine (note that the conditions are now basic). These reagents ONLY halogenate primary and secondary alcohols and the mechanism proceeds via SN2 (Inversion of Stereochemistry).







* 1. Coupling alcohol halogenating agents with an additional SN2 reaction (***Double inversion equals retention***)



1. **Substitution of Alcohols with Sulfonate Esters**: Alcohols can be converted into good leaving groups by converting them into sulfonate esters.
   * 1. Once alcohols are converted into sulfonate esters (good leaving groups) they can undergo substitution and elimination reactions like any alkyl halide.
     2. Simply converting the alcohol into the sulfonate ester does NOT affect the stereochemistry of the alcohol oxygen.





* 1. Coupling Substitution of Alkyl Sulfonates with other Nucleophilic Substitutions (***Single inversion***):



1. **Dehydration of Alcohols**: Alcohols can undergo elimination in strong acid or base.
   1. **Dehydration of Alcohols in Strong Acid**: Secondary and Tertiary Alcohols can undergo dehydration (elimination) in the presence of strong acid. The elimination takes place via E1 mechanism. The elimination follows **Zaitsev’s Rule** meaning the more substituted alkene is formed as the major product.



* 1. **Take care!** Acid catalyzed dehydration reactions can undergo rearrangement due to the formation of the carbocation intermediate.



* 1. When attempting to dehydrate a primary alcohol in strong acid, the mechanism initially proceeds through an E2 mechanism. However, once the alkene is formed, it reacts with residual protons and forms a carbocation which then undergoes an additional elimination step.



* 1. **Dehydration of Alcohols in Base (POCl3 and Pyridine)**: Alcohols can also be dehydrated in POCl3 and pyridine.
     1. POCl3 converts the alcohol into a good leaving group and pyridine acts as a base, removing a proton and creating the double bond via E2 mechanism.
     2. Zaitsev’s Rule applies.
     3. Note: No carbocation rearrangement is observed when using POCl3 and pyridine to dehydrate a primary or secondary alcohol.



1. **Oxidation of Alcohols**: Alcohols can be oxidized to carbonyl compounds. Pay attention to what substitution of alcohol is being oxidized and which reagent is used for the oxidation.
   1. **Primary Alcohols**:
      1. **Strong Oxidants:** H2CrO4/Heat; Na2Cr2O7/H2SO4/Heat; or KMnO4/H2SO4/Heat will oxidize primary alcohols to the corresponding carboxylic acid.
      2. **Mild Oxidants:** PCC/CH2Cl2 or NaOCl/CH3CO2H 0oC or 1. DMSO, Oxallyl Chloride -60°C 2. Triethylamine will oxidize primary alcohols to the corresponding aldehyde.







* 1. **Secondary Alcohols**: Regardless of which oxidant you use, you will only be able to oxidize the secondary alcohol to the corresponding ketone.



* 1. **Tertiary Alcohols**: Regardless of which oxidant is used, tertiary alcohols will NEVER be oxidized.



1. **Additional Nucleophilic Substitution of Alcohols**
   1. **Ester Formation**: Alcohols will undergo deprotonation in strong base to form an alkoxide. The alkoxide can then react in a substitution reaction with an acid halide to form an ester (SN2 mechanism).



* 1. **Williamson Ether Synthesis**: An alkoxide can also react in a substitution reaction with an alkyl halide to form an ether. Works best when a primary or secondary halide is used.



* 1. **Acid Catalyzed Ether Formation**: Alkenes will react with strong acid in the presence of an alcohol to form an ether. Note that the alcohol will attack the more substituted side of the double bond (not the best way to create an ether).



1. **Acid Catalyzed Ether Cleavage**: Ethers can ONLY be cleaved in acid.
   1. The acids typically used are HBr or HI.
   2. When ethers are cleaved, the nucleophile (X-) will attack the most substituted side of the ether because the more stable carbocation intermediate is created.
   3. When an ether having two side with the same substitution is cleaved, the side which is least hindered is attacked by the nucleophile.
   4. Note that when there is a vinyl or aryl ether which is cleaved, the oxygen will ALWAYS remain with the *vinyl* or *aryl* side of the ether.





1. **Formation of the Syn-Diol (Osmylation)**: Alkenes will undergo osmylation to form a syn-diol.



1. **Formation of Epoxides**: Epoxides can be formed in two ways: either by reacting an alkene with a peroxyacid or by reacting a halohydrin with a strong base.



1. **Opening Epoxides**: Epoxides can be opened in acid or base.
   1. **Acid Catalyzed Epoxide Opening**: When epoxides are opened in acid, the nucleophile will always go to the more substituted side of the epoxide. The alcohol formed from the oxygen originally found in the epoxide will point in the same direction that the epoxide previously pointed. The nucleophile will attack opposite the direction that the epoxide originally pointed.
   2. **Base Catalyzed Epoxide Opening (or Neutral Conditions)**: When epoxides are opened in base, the nucleophile will always go to the least substituted side of the epoxide. The alcohol formed from the oxygen originally found in the epoxide will point in the same direction that the epoxide previously pointed. The nucleophile will attack opposite the direction that the epoxide originally pointed.



1. **Formation of the Sulfide, Sulfur Mercury Compounds, and the Sulfonium Cation**:







1. **Nomenclature of Thiols**
   * 1. When naming a thiol, where the thiol takes priority, find the longest chain of carbons which contains the thiol.
     2. Number down through the longest chain giving priority to the SH.
     3. Name the compound as you would normally, alphabetizing the substituents but at the end of the name, you will place the suffix thiol including the locant of the thiol before the name thiol.
     4. If there is a higher priority substituent present (an alcohol) the SH will be named as a substituent called mercapto-.



1. **Hoffman Elimination**:
   1. Amines can be exhaustively methylated to form a quaternary ammonium halide.
   2. The halide of the ammonium halide can be replaced with hydroxide by reacting it with Ag2O.
   3. When the ammonium hydroxide is heated in base, the hydroxide will remove a ***beta-hydrogen*** to from an alkene, displacing an amine.
   4. The Hoffman rearrangement will selectively remove the b-hydrogen which is least hindered, forming the least substituted double bond.



Chapter 10 Table of Reactions







Test your understanding of chapter 10 with these practice problems.

Complete the line reactions below with the missing reactant/reagent(s)/product(s).



Provide a detailed, stepwise mechanism for the following reactions.





Propose a synthesis for the following reactions.



