

Model Answer –Key

Adv Org Chem-MPharm (Pharm Chem)-SEM-I

Q1

- a Resonance stabilization
 - b Opposite side attack in transition phase intermediate and Walden inversion to be explained.
 - c Steric hinderance
 - d Charge delocalisation at these sites to be shown by resonance structures.
 - e Elimination Unimolecular conjugate Base. *Elimination* refers to the fact that the mechanism is an elimination reaction and will lose two substituents. *Unimolecular* refers to the fact that the rate-determining step of this reaction only involves one molecular entity. Finally, *conjugate base* refers to the formation of the carbanion intermediate, which is the conjugate base of the starting material.
 - f. Ozonolysis occurs at the double bond which ultimately breaks and leads to two products from which its location can be predicted.
 - g. The free radical intermediate formed leads to anti-Markovnikoffs rule.
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Q2

a. Discuss various methods of determining reaction mechanisms

There are a number of commonly used methods for determining mechanisms. In most cases, one method is not sufficient and the problem is generally approached from several directions.

Identification of Products

Any mechanism proposed for a reaction must account for all the products obtained and their relative proportions. A proposed mechanism cannot be correct if it fails to predict the products in approximately the observed proportions.

Determination of Presence of an Intermediate

1. **Isolation of an Intermediate:** An intermediate can be isolated from a reaction mixture by stopping the reaction after a short time or by the use of very mild conditions. If the isolated compound gives the same product when subjected to the reaction conditions and at a rate no slower than the starting compound, this gives a strong evidence that the reaction involves that intermediate.
2. **Detection of an Intermediate:** Intermediates can be detected by IR, NMR, or some other spectra. For example, the detection of NO_2^+ by Raman spectra was regarded as strong evidence that this is an intermediate in the nitration of benzene. Free radicals and triplet intermediates can be detected by ESR and by CIDNP.
3. **Trapping of an Intermediate:** In some cases, the intermediates may react with a certain compound in a given way. The intermediate can be trapped by running the reaction in the presence of that compound. For example, benzyne react with dienes in the Diels-Alder reaction. The detection of the Diels-Alder adduct indicate that the benzyne was probably present.

Isotopic Labeling

Informations about the reaction mechanism can be obtained by using molecules that have been isotopically labeled and tracing the path of the reaction in this way. Radioactive isotopes as well as stable isotopes can be used as tracers. O-18 can be detected by mass spectrometry. D can be determined by IR and NMR spectra when used as a substitute for H . Also, C-13 which is non-radioactive can be detected by C-13 nmr.

Stereochemical Evidences

If the products of a reaction are capable of existing in more than one stereoisomeric form, the form that is obtained may give information about the mechanism. For example, *Cis*-2-butene when treated with KMnO_4 gives *meso*-2,3-butane diol and not the racemic mixture is evidence that the two OH groups attack the double bond from the same side.

Kinetic Evidence

Several types of mechanistic informations can be obtained from kinetic studies such as the order of the reaction, the rate determining step etc. The rate constant obtained from kinetic data is most important since it tells the effect of changes in the structure of the reactants, the solvent, ionic strength, addition of catalyst etc. on the reaction rate.

- b. Discuss Elimination Reactions and the Hoffmann and Zaitsev (Saytzeff) rules of elimination with suitable examples..

When an alkyl halide is heated with a nucleophile, substitution takes place. If the nucleophile behaves as a base elimination takes place.

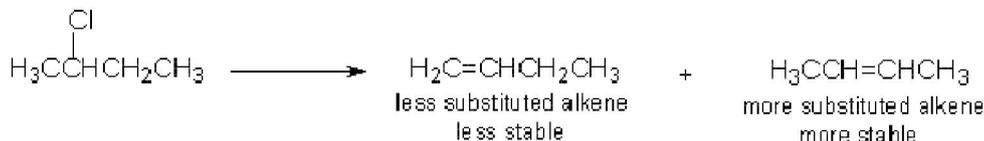
Thus when 2-Chloropropane is heated with KOH nucleophilic substitution takes place resulting in 2-Propanol as the predominate product.

When it is heated with alcoholic KOH elimination takes place resulting in Propene as the predominate product.

Conditions for elimination:

1. KOH / Ethanol
2. NaOEt / Ethanol
3. Potassium t-butoxide / t-butyl alcohol

In eliminations the halogen and the hydrogen atom at the next carbon are lost. There can be more than one adjacent carbons so more than one product is possible.



If the hydrogen at C1 is involved the result is 1-Butene, the less substituted alkene.

If the hydrogen at C3 is involved the result is 2-Butene, the more substituted alkene.

More substituted alkene is more stable therefore should be the major product.

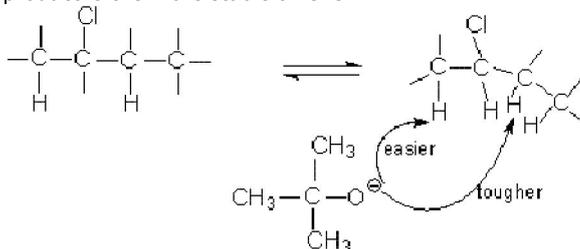
(thermodynamically more substituted alkene is more stable, it gives out less heat of hydrogenation)

With elimination conditions 1 or 2, the more substituted alkene is the major product.

But under reaction condition 3, the less substituted alkene is the major product.

Reason: The t-butoxide anion is large in size, it is a hindered base. It is tougher for this base to reach the interior of the molecule and pull out a proton at C3. (Keep in mind that 2-Chlorobutane is not linear, the carbon atoms are all sp³ hybridised, due to free rotation about the C-C bond axis it assumes many conformations). On the other hand it can pull off a proton at the terminal of the molecule at C1 with comparative ease. Thus leading to 1-Butene as the major product.

Conditions 1 and 2 involve bases much smaller in size, they are capable of reaching the interior of the molecule, so the major product is the more stable alkene.

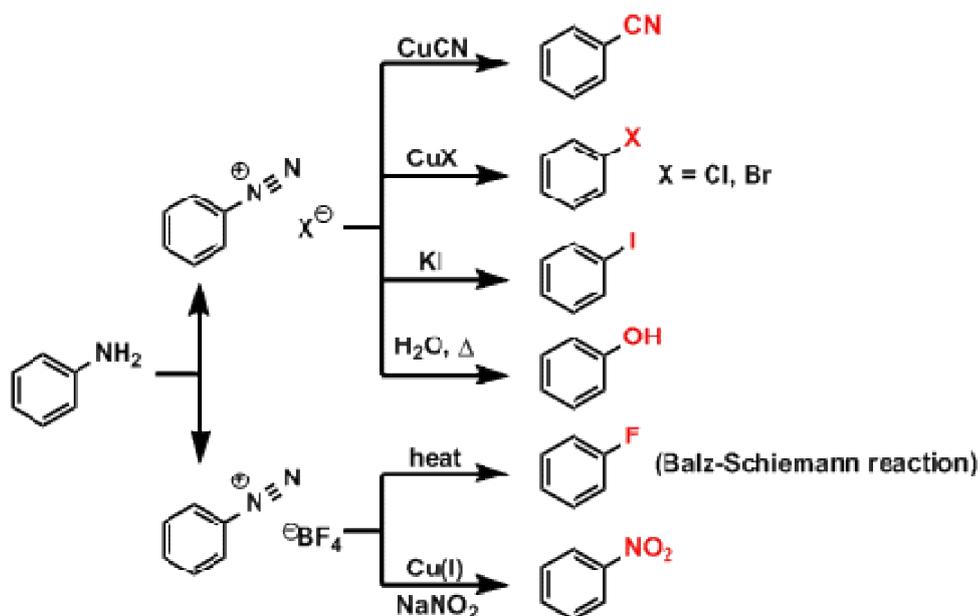


Elimination is more likely in secondary halides than primary halides for the same reason, that is, the base will be sterically more hindered to participate in substitution.

1. When the more substituted alkene is the major product of dehydrohalogenation the reaction is said to follow Zaitsev rule (Saytzeff, Saytseff, or Saytzev). The major product is referred to as **Zaitsev product**.
2. If the major product is the less substituted alkene the reaction is following Hoffmann rule and the product is **Hoffmann product**.

c.) Discuss the Sandmeyer reaction and its synthetic applications to obtain various substituted benzenes.

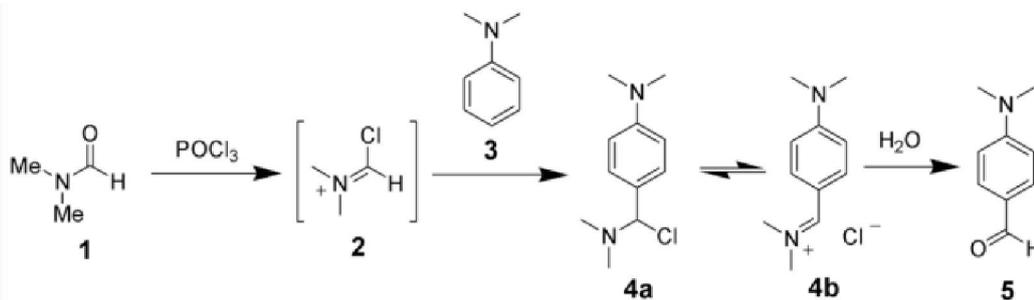
The **Sandmeyer reaction** is a chemical reaction used to synthesize aryl halides from aryl diazonium salts. It is an example of a radical-nucleophilic aromatic substitution. The Sandmeyer reaction provides a method through which one can perform unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation, and hydroxylation.



Q3:

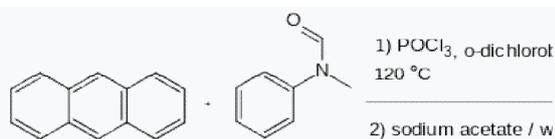
a. **Discuss the Vilsmeier–Haack reaction, its reagent, its mechanism and applications**

The Vilsmeier–Haack reaction (also called the Vilsmeier reaction) is the chemical reaction of a substituted amide (1) with phosphorus oxychloride and an electron-rich arene (3) to produce an aryl aldehyde or ketone (5). The reaction is named after Anton Vilsmeier and Albrecht Haack. The reaction of a substituted amide with phosphorus oxychloride gives a substituted chloroiminium ion (2), also called the Vilsmeier reagent. The initial product is an iminium ion (4b), which is hydrolyzed to the corresponding aromatic ketone or aldehyde during workup.



The Vilsmeier–Haack reaction

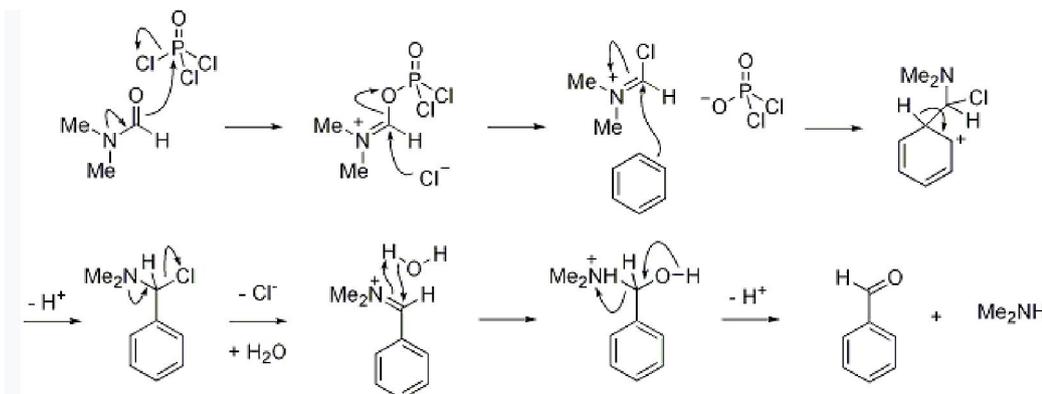
For example, benzanilide and dimethylaniline react with phosphorus oxychloride to produce an unsymmetrical diaryl ketone. Similarly, anthracene can be formylated exclusively at the 9-position. The reaction of anthracene with *N*-methylformanilide, also using phosphorus oxychloride, is shown below:



N-Methylformanilide and anthracene and phosphorus oxychloride

Reaction mechanism

The reaction of the amide with phosphorus oxychloride produces an electrophilic iminium cation. The subsequent electrophilic aromatic substitution produces an iminium ion intermediate, which is hydrolyzed to give the desired aryl ketone or aryl aldehyde.



Vilsmeier-Haack reaction mechanism

Applications

One recent application of this reaction involved a new synthetic route to tris(4-formylphenyl)amine[®] from triphenylamine which by known procedures resulted in a poor chemical yield of 16%. It was found that this low yield was caused by deactivation of the remaining benzene ring by the imine groups on the other two phenyl groups in the third formylation step. The procedure was modified by taking the reaction to a diimine compound followed by hydrolysis to the di-formyl compound and then (with final position reactivated) a separate formylation to the trisubstituted compound.

Q3b. Define molecular rearrangements, classify them and discuss the Baeyer-Villiger oxidation in details.

Definition: Molecular rearrangements are organic reactions which involve migration of an atom or group from its original position to an adjacent atom or near adjacent atom. Most rearrangements are intramolecular processes.

CLASSIFICATION

There are four major types:

1. Rearrangements of electron deficient systems (Nucleophilic rearrangement reactions):

Migrating group is a nucleophile (Nu⁻) and migrated on electrophile (E⁺).

(a) Electron deficient oxygen:

(i) Bayer-Villiger oxidation (ii) Dakin oxidation.

(b) Electron deficient nitrogen: (i) Hoffman rearrangement (ii) Curtius rearrangement (iii) Lossen rearrangement (iv)

Schmidt rearrangement (v) Beckmann rearrangement

(c) Electron deficient carbon:

(i) Wagner Meerwein rearrangement (ii) Pinacol - Pinacolone rearrangement (iii) Benzilic acid rearrangement

2. Rearrangement of electron rich system (Electrophilic rearrangement reactions)

Migrating group is electrophile (E) and migrated on electron rich centre.

(i) Steven's rearrangement (ii) Sommet rearrangement (iii) Favorskii rearrangement (iv) Neber rearrangement

3. Rearrangement to aromatic nucleus (Aromatic rearrangements):

(i) Fries rearrangement (ii) Claisen rearrangement

4. Pericyclic rearrangements: (Migration to double/triple bonds sigma-pi) (i) Cope rearrangement

