REVIEW ON ORGANIC SYNTHETIC MECHANISMS

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ABSTRACT

In this theoretical study, explanation about mechanism of normal and heterocyclic compounds, reactions, preparation, reactivity, examples, protection of functional groups have been nicely narrated.

KEYWORDS: Mechanism, Organic, Synthetic, Cyclization, Closure, Expand

INTRODUCTION

The ability to write an organic reaction mechanism properly is key to success in organic chemistry classes. Organic chemists use a technique called arrow pushing to depict the flow or movement of electrons during chemical reactions. Arrow pushing helps chemists keep track of the way in which electrons and their associated atoms redistribute as bonds are made and broken.

Organic synthesis is the process of building complex molecules from simpler ones, one reaction at a time, through a multistep sequence. In order to propose a synthesis you must be familiar with reactions

- Starting functional group
- Functional group produced (region chemistry, stereochemistry)
- Reactants used
- Limitations

As briefly, a broader terminology is applied to the very common case of reactions in which new sigma bonds form between electron rich and electron poor regions of molecules.

Nucleophiles: (meaning nucleus seeking) are molecules that have relatively electron rich pi bonds or lone pairs that act as electron sources for arrows making new bonds.

Electrophiles: (meaning electron seeking) are molecules with relatively electron poor atoms that serve as sinks for these arrows. Analogously, a molecule, or region of a molecule, that is a source for such an arrow is called nucleophilic, while a molecule or region of a molecule that is a sink for these arrows is referred to as being electrophilic. Based on this description, it should be clear that nucleophiles are analogous to Lewis bases and electrophiles are analogous to Lewis acids. Chemists use these terms interchangeably, although nucleophile and electrophile are more commonly used in kinetics discussions while Lewis acid and Lewis base are more commonly used in discussions about reaction thermodynamics.
Nucleophilicity Rankings:

Within a group of nucleophiles that react with electrophile with the same atom, the nucleophilicity decreases with decreasing basicity of the nucleophile.

Decreasing basicity is equivalent to decreasing affinity of an electron pair for a proton, which to a certain extent, is a model electrophile for the electrophiles since both alkylating agents and protons are Lewis acids.

The nucleophilicity of a given nucleophilic center is increased by attached hetero-atoms i.e., heteroatoms in the a-position—with free electron pairs (the so-called A-effect)

\[
\begin{align*}
\text{HO} & \overset{\ominus}{\rightarrow} \text{O} \ominus > \text{H} \overset{\ominus}{\rightarrow} \text{O} \ominus \\
\text{H}_2\text{N} & \overset{\ominus}{\rightarrow} \text{NH}_2 \rightarrow \text{H} \overset{\ominus}{\rightarrow} \text{NH}_2
\end{align*}
\]

Figure 1

Nucleophilicity decreases with increasing electronegativity of the reacting atom. This is always true in both comparisons of atoms that belong to the same row of the periodic table of the elements

\[
\begin{align*}
\text{R}_2\text{N} & \gg \text{RO} \gg \text{F} \ominus \\
\text{Et}_3\text{N} & \gg \text{Et}_2\text{O}
\end{align*}
\]

Figure 2

\[
\begin{align*}
\text{RS} \ominus > \text{RO} \ominus & > \text{I} \ominus > \text{Br} \ominus > \text{Cl} \ominus > \text{F} \ominus \\
\text{RSH} & > \text{ROH}
\end{align*}
\]

Figure 3

What makes a leaving group good or bad in substrates that react with nucleophiles as alkylating agents?

That a good leaving group is a stabilized species, not a high-energy species. Therefore, good leaving groups are usually weak bases.

Another way of thinking about it: A strong base reacts rapidly with protons (electrophiles) in an energetically favorable process, the reverse of which is necessarily energetically unfavorable.

By analogy we can conclude that a mixture of a strongly basic leaving group with the product of an SN reaction is also relatively high in energy. Very basic leaving groups are produced relatively slowly.

The suitability of halide ions as leaving groups is predicted correctly based on this reasoning alone,

Where \( \text{I} \ominus > \text{Br} \ominus > \text{Cl} \ominus > \text{F} \ominus \).
The Importance of Synthesis

- Total synthesis of interesting and/or useful natural products.
- Industrially important compounds
- Compounds of theoretical interest
- Structure proof
- Development of new synthetic methodology
- Importance to other areas of science and technology

Analysis of Compounds

All organic compounds contain from nucleophile part and electrophile part

According to condition of reaction (type of solvent, catalysis, medium of reaction)

![Figure 4](image)

When learning new mechanisms, first focus on the overall transformation that

Takes place. It might be a reaction in which atoms or groups are added (an addition reaction), a reaction in which atoms or groups are removed (an elimination reaction), a reaction in which atoms or groups replace an atom or group (a substitution reaction), or other processes we will encounter. Often, the overall process is composed of multiple steps. Once you have the overall process in mind, it is time to think about the individual steps that convert starting material(s) into product(s). Predicting complete multi-step

Mechanisms, then, comes down to learning how to predict the individual steps.

Understanding, as opposed to memorizing, mechanisms is critical to mastering organic chemistry. Although the mechanisms you encounter throughout the course may seem entirely different, they are actually related in fundamental ways. In fact, almost all of the organic reaction mechanisms you will learn are composed of only a few different individual elements (steps) that are put together in various combinations.
Mechanism of Alpha- Ester (Heck Reaction):

![Mechanism of Alpha- Ester](image)

**Figure 5**

Mechanism of Reaction with Alpha – Ester:

![Mechanism of Reaction with Alpha – Ester](image)

**Figure 6**

Examples for Anion Reaction

![Examples for Anion Reaction](image)

**Figure 7**

**Proposed Mechanism:**

![Proposed Mechanism](image)

**Figure 8**

**Selectivity of Reaction:** means that one of several reaction products is formed preferentially or exclusively.

In the simplest case, for example, reaction product 1 is formed at the expense of Reaction product 2. Selectivities of this type are usually the result of a kinetically controlled reaction process.
“kinetic control.” This means that they are usually not the consequence of an equilibrium being established under the reaction conditions between the alternative reaction products 1 and 2. In this latter case one would have a thermodynamically controlled reaction process, or “thermodynamic control.”

![Figure 9](image9.png)

**Figure 9**

All the Mechanisms so Far Discussed Take Place at a Saturated Carbon Atom

![Figure 10](image10.png)

**Figure 10**

Example for Dianion Reaction (Prefer What):

By using very strong bases, a dianion can be formed that will preferentially alkylate at the methyl group.

![Figure 11](image11.png)

**Figure 11**

![Figure 12](image12.png)

**Figure 12**

![Figure 13](image13.png)

**Figure 13**
Mechanism of Corey-Kim Oxidation / Corm-Kim Reaction:

Mannich Reaction – Mechanism (Other Type):

Type of product depends on type of solvent and medium, temperature of reaction.
Enamine from Nitrile Compounds

Enamine from Leaving Group

Grundmann Aldehyde Synthesis:

In the related Kostaneck Reaction, the same reagents give a different product. In that case, the attacking species is the phenol oxygen, rather than the enol tautomer of the ketone.

Cyclic Products According to Type Catalysis
Hantiz – Mechanism: By Cyclization (2+3) to Yield Cycle

![Figure 24]

Gabriel-Colman Rearrangement

![Figure 25]

Robinson – Gabriel - Mechanism

![Figure 26]

Schweizer Ally1 Amine Synthesis

A combination of Gabriel and Wittig Reaction (Mix –Reaction):

![Figure 27]
Alkylation on Alpha-Position

![Figure 28](image)

Arndt-Eistert Homologation Reaction

![Figure 30](image)

Nierenstein Reaction: Reaction of carbanion with carbonyl

![Figure 31](image)
Mechanism of Reissert Reaction (Grosheintz-Fischer-Reissert Aldehyde Synthesis):

![Mechanism of Reissert Reaction](image)

**Figure 32**

Mechanism of Nierenstein Reaction:

![Mechanism of Nierenstein Reaction](image)

**Figure 33**

Mechanism of Baker-Venkataraman Rearrangement:

![Mechanism of Baker-Venkataraman Rearrangement](image)

**Figure 34**

Mechanism of Baker-Venkataraman Rearrangement:

![Mechanism of Baker-Venkataraman Rearrangement](image)

**Figure 35**
Mechanism of this Reaction:

\[
\begin{align*}
\text{Mechanism Diagram} & \quad \text{Figure 36} \\
\text{Chemical Reactions} & \quad \text{Figure 37} \\
\text{Chemical Reactions} & \quad \text{Figure 38} \\
\text{Chemical Reactions} & \quad \text{Figure 39}
\end{align*}
\]
Mechanism of Ring Closure:

![Figure 40](image)

Propose a stepwise mechanism for the transformation shown below.

![Figure 41](image)

![Figure 42](image)

![Figure 43](image)

![Figure 44](image)
Cyclization of three components

Formation of thiophene from carbonyl compounds via di anion with di carbonyl compound:

Self - Condensation:
Ring Expansion:

Expansion of the pyrrole ring by heating with chloroform or other halogeno compounds in alkaline solution. The intermediate dichlorocarbene, by addition to the pyrrole, forms an unstable dihalogenocyclopropane which rearranges to a 3-

Halogeno pyridine

Diazotization of amine group then expansion of cycle:

Type of Product Depends on Conditions of Reaction:

On the other hand, if only catalytic amounts of AlCl₃ are added, the acetyl group of the acetophenone is brominated. Under these conditions the carbonyl oxygen of a fraction of acetophenone can be complexed. The bulk of the substrate still contains uncomplexed carbonyl oxygen. The enol is a better nucleophile than the aromatic ring because it is brominated electrophilically without intermediate loss of aromaticity. HBr is the stoichiometric by-product of this substitution. Just like the HCl that is formed initially, it catalyzes the enolization of unreacted acetophenone and thus keeps the reaction going.
Regio Selective Reactions

Methyl groups are on the electrophilic C atom. Therefore, it reacts with phenol regioselectively in the para- and not at all in the less favored ortho-position. The benzyl cation formed thereafter is a poor electrophile, too, and again for both electronic and steric reasons, it reacts with the second phenol molecule with high para-selectivity.

Michael Addition: as cyclization of two compounds to yield cycle.

Rearrangement: Formation of Stable Compounds.
Cyclization Compounds: From Diels-Alder via double bond

Figure 59

Figure 60

Figure 61

Gallagher-Hollander Degradation:

Figure 62

Ring Expansion Mechanism:

Figure 63
Ring Closure Methods:

Several methods for ring closure are reported in the literature. Some of them are given below.

A standard method by H$_2$SO$_4$ for the preparation of 1,3,4-thiadiazoles is dehydrative cyclization of acylthiosemicarbazide.

Different acidic reagents have been used for dehydration like sulfuric acid, phosphoric acid, acetic anhydride and phosphorus halides.

The condensation of thiosemicarbazide with benzoic acid in phosphorus oxy chloride gives 1,3,4-thiadiazole in 94% yield by POCl$_3$ with heating for 1 hr at 70°C.

5-Amino-[1,3,4]-thiadiazole derivatives can be prepared from the reaction of p-anisaldehyde with thiosemicarbazide to give an intermediate, followed by cyclization in the presence of ferric chloride in
Aqueous Solution

The dehydration of thiosemicarbazides with acetyl chloride followed by hydrolysis of the acetamide gives amino-1,3,4-thiadiazoles.

2,5-Disubstituted-1,3,4-thiadiazole has been prepared by the reaction of diacylhydrazide with phosphorus pentasulphide \( \text{P}_2\text{S}_5 \).

Dithiocarbazinic acid derivatives on reaction with carbon disulphide yield 2, 5-dimercapto-1,3,4-thiadiazole.

2-Mercapto-1,3,4-thiadiazoles can also be obtained when dithiocarbazinic acids react with aliphatic aldehydes.
1,3,4-Thiadiazoles are synthesized from $N'$-acylbenzohydrazide

By using **Fluorous Lawesson’s reagent** in THF at 55°C within 6hrs.

The plan which is illustrated by scheme was based on the following known principles:

- Carboxylic acids undergo esterification in acidic medium in the presence of an alcohol.
- Esters of carboxylic acids are converted to their respective hydrazides with hydrazine monohydrate.
- Isothiocyanates are formed from amines involving salts of dithiocarbamate as an intermediate.
- Condensation of carboxylic acid hydrazides with isothiocyanates yields thiosemicarbazides.
- Intramolecular dehydrative cyclization of substituted thiosemicarbazides in basic medium affords the corresponding substituted 3-mercapto-1,2,4-triazoles.
- Cyclization of substituted thiosemicarbazides in acidic medium gives the corresponding substituted 1,3,4-thiadiazoles.
Selective Reactions Via Cleavage

Figure 73

Formation of Bicycles Via movement of bonds:

Using a numbering scheme when writing a m

Figure 74

Self Reaction Mechanism:

Numbering of the atoms in the starting material and product makes it clear that nitrogen-1 becomes attached to carbon-6.

Figure 75

Figure 76

Figure 77
Reduction Mechanism of Ring Size
REFERENCES