Retrosynthesis

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Abstract

The American chemist Elias James Corey was awarded the 1990 Nobel Prize in chemistry for developing the theory and methodology of organic synthesis. He called his method “retrosynthetic analysis,” a technique for simplifying the synthesis of large complex molecules. He worked out and described in detail a new and fruitful systematic approach to synthetic chemistry. He has synthesized over 100 substances, including ginkgolide B (a compound extracted from the ginkgo tree and used experimentally to treat asthma) and prostaglandins (hormone-like compounds used to induce labor and treat infertility). Corey—Nobel Prize for Retrosynthetic Analysis

Keywords: organic synthesis, retrosynthetic analysis, synthetic chemistry

I. Introduction

Since the early beginnings of chemical sciences, organic synthesis has fascinated scientists due to its capability to build challenging molecules from scratch. The quest to create very complex structures efficiently and in fewer steps then in previously reported syntheses is an ongoing challenge in many laboratories around the world. A Retrosynthesis Approach for Biocatalysis in Organic Synthesis[1,2].

Retrosynthetic analysis, also known as the disconnection approach, is the most basic and common method for organic synthesis route design. Inverse synthetic analysis method is a kind of reverse logic thinking method, from the analysis of the chemical structure of target molecules, according to the connection between the atoms in molecules (bonds), the characteristics of the integrated use of method and reaction mechanism of the organic chemistry knowledge, choose the appropriate chemical bonds to cut off, will target molecules into some smaller intermediates; These intermediates are then used as new target molecules and cut into smaller intermediates; And so on until you find a starting material that you can easily buy. Starting from the molecular structure of the synthetic product, the method of “cutting a chemical bond” is used to obtain the required synthetic raw materials (synthons).

First, I would like to start with the simplest aromatic hydrocarbon compound, an organic compound with a benzene ring as the core and connected with a branched alkyl group. In order to study the reversible Friedel-Crafts reaction, scientists created this activated aromatic ring connected with a branched alkyl group and named it TM 82, as shown in Figure 1.

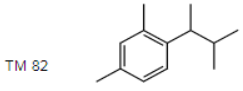

Figure1:TM82

When you think about a retrosynthetic synthesis reaction, you should first look at the product’s structure. Benzene ring is a stable structure and is not easy to react to, so the branched alkyl around it becomes the breakthrough to solve this problem. There are several guidelines for inverse synthesis reactions. The first rule is that disconnection must correspond to known, reliable reactions. Organic Chemistry[3] Therefore, when you disconnect TM 82, the first consideration is to break the alkyl chain. You add a hydroxyl group to the branch chain on the most significant side chain, as shown in the Figure 2:

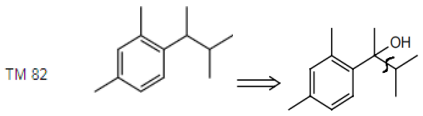

Figure 2: Disconnection of TM82

Adding hydroxyl to break the C -- C bond in the branched-chain will recall the first two substances that synthesized MT 82, as shown in Figure3:

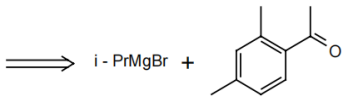

Figure 3: Retrosynthetic products of TM82

Wherein the chemical formula of I-PRMGBR is:

In this case, you will apply guideline 2： for a compound consisting of two parts joined by a heteroatom, disconnect next to the heteroatom.Organic Chemistry[3] In most reverse reactions, you have a heteroatom. In most reverse synthesis, there is a heteroatom (Nitrogen or Oxygen) that holds the rest of the molecule together, and in each case,

you have to make the connection next to the Nitrogen and Oxygen. Using guideline two, you can suggest the Oxygen atomic narrator disconnect. According to guideline 1, the benzene ring is not easy to change, so there must be no reverse synthesis on the benzene side. So in the end, the raw material for the reverse reaction of MT 82 came out: as shown in Figure 4 below:

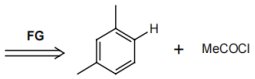

Figure4: another retrosynthesis

Using this method, chemists successfully produced TM 82 by the retrosynthetic reaction shown in Figure 5.

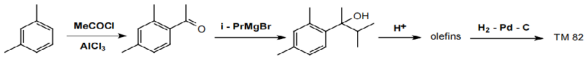

Figure5: producing TM82

II. INTRODUCTION TO DISCONNECTIONS

Before you get into the concepts of retrosynthetic analysis, you need to know what a retrosynthetic analysis is. In chemical knowledge, it is the need to synthesize certain substances through different methods for the new material, many substances have been used on various occasions in life, like the detergents we use, disinfectants commonly used by industries, which all provide convenience for us. However, once any new materials/ molecules are found, especially when they are crucially important and useful to us, how to make it will become the main problem. The solution is people's imagination and creativity, and of course some secured basis of chemical knowledge. You shall create what you desire with all that, starting from the product, and gradually go back to the reactant, for which we call this series of conversion process retrosynthetic analysis.as shown in Figure 6.

Figure 6: Retrosynthesis of an ester

It is an ester,and it can be made from alcohol plus acyl chloride.Draw the mechanism of the imaginary reverse reaction, the formation of ester from the alcohol and acyl chloride. shown in Figure 7.

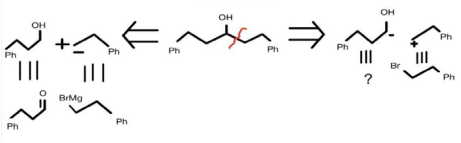

Figure 7: Different retrosynthetic products of the same compound

For this alcohol, you can choose to break it off here, but then you have to think about whether it makes sense, and that is the rationality principle in reverse reactions. shown in Figure 8

Suggest a disconnection for TM 16

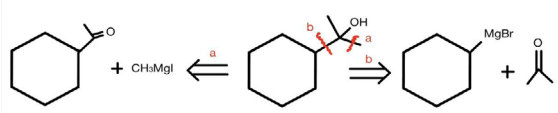

Figure 8: Choosing Disconnection of TM82

Both are reasonable mechanisms,But you prefer (b) because b is simpler, whereas (a) cuts off just one carbon atom, making (a) products as difficult to synthesize as TM 16.Route (b) however breaks the molecule into two more equal pieces.That is the principle of maximum simplification.as shown in Figure 9.

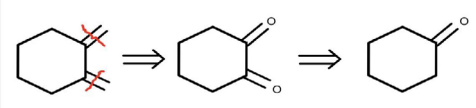

Figure 9: Disconnecting a hydrocarbon

In the case of the aromatic hydrocarbon above, it is surrounded by two functional groups. Therefore, when involving functional groups, it should be cut off in the functional group attachment, if two functional groups form it, the original functional group should be cut off.

A Diels-Alder reaction is an organic reaction (specifically, a cycloaddition reaction). Conjugate diene reacts with substituted alkenes (commonly called dienophiles) to form substituted cyclohexene. The reaction can continue even if some of the atoms in the newly formed ring are not carbon atoms. Some of these reactions are reversible, and such ring decomposition reactions are called retro-Diels-Alder reactions. The Diels-Alder reaction is done in one step, shown in Figures 10 and 11.

And you are going to use this reaction later.

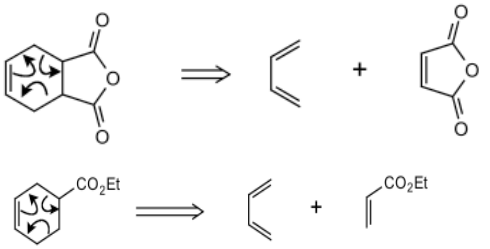

Figure 10: Diels-Alder reaction

All of these problems can be solved by Diels-Alder reaction. Note that the Diels-Alder reaction works best when there is an electron-withdrawing group on the olefinic component.

III. Functional group interconversions (FGI)

What Functional Group Interconversion does? In inverse synthesis analysis, the conversion of one functional group to another by substitution, addition, elimination, oxidation, and reduction reactions. Purpose of Functional Group Interconversion:

Functional group transformation is the necessary preparation for severance, which corresponds exactly to a reaction and thus makes a severance possible. Retrosynthetic Analysis and Organic Synthesis Design [4].

Functional Group Interconversion symbols:(Figure 11)

Figure 11: Functional Group Interconversion

For example, the following aromatic hydrocarbon, you know you need to disconnect the next alkane, but can it go straight to the reverse reaction, shown in Figure 12.

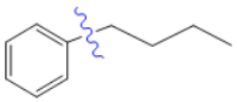

Figure 12: direct disconnection

The answer is no, you need to convert this thing into a branch chain with a functional group to get what you want. So the reverse reaction is here shown in Figure 13:

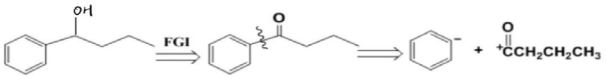

Figure 13: using Functional Group Interconversion

IV. Functional group addition (FGA)

What Functional Group Addition does?An essential operation of inverse synthesis analysis is to introduce different functional groups at different locations to lead to different cleavages. Functional Group Addition applications:

The molecule or a specific position in a molecule that does not contain functional groups - functional group transformation in synthesis. The reaction requires selective control - the introduction of active or protective groups into the synthesis. Retrosynthetic Analysis and Organic Synthesis Design[4]

Functional Group Addition symbols: (Figure 14)

Figure 14: Functional Group Addition

And the following reaction, you know from what you have seen, is to break the carbon-carbon bond next to the functional group, as shown in Figure 15.

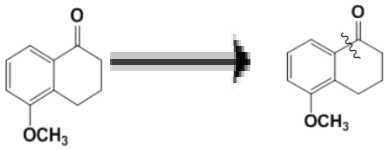

Figure 15: disconnection

In this reverse reaction, you need to add a carbonyl group to the broken ring in order for this reverse reaction to work (Figure 16):

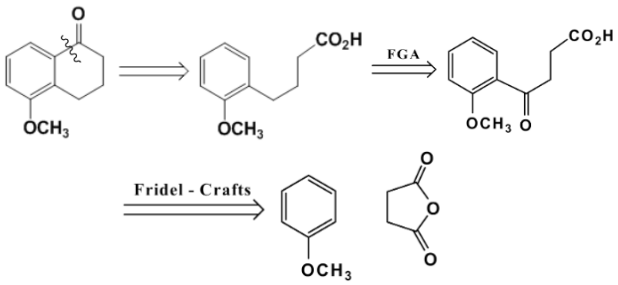

Figure 16: Example of Functional Group Addition

Frdel-crafts reaction is an important method for constructing tetrahydronaphthalene ring system.

V. RECONNECTION

Functions of reconnection:

In inverse synthesis analysis, bonds are joined (rather than cut) within molecules for bonding, selective control and so on.

A. Reconnection occasions

Corresponding to the ring-opening reaction and fragmentation reaction in the synthesis route. A means of stereochemical and chemical selective control, as shown in Figures 17 and 18.

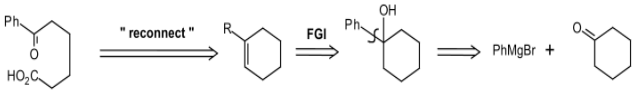

Figure 17: Example of reconnection

Figure 18: Example of reconnection

These reverse reactions reattach the broken rings in preparation for the next step.

B. Retrosynthetic analysis of important compounds

1) Simple alcohols

Select the most stable anion to cut off. Example (Figure 19).

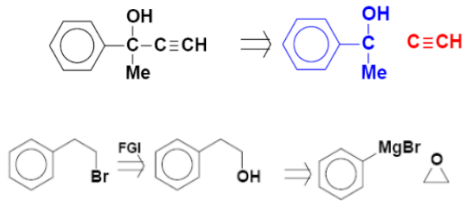

Figure 19: Functional Group Interconversion

2) Derivatives of alcohols

When H- reduction is involved, it can be regarded as a process of functional group interchange (FGD). Functional Group Interconversion to alcohols is a good idea for synthesis with the following structures.

Example (Figure 20).

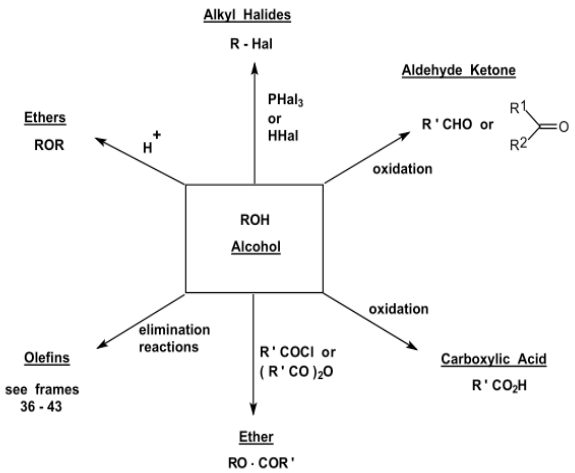

Figure 20: Derivatives of Alcohols

This is a common form of hydroxyl reverse reaction.

C. Disconnection of simple alkene

The most important step in converting olefin is adding water, as shown in Figure 21.

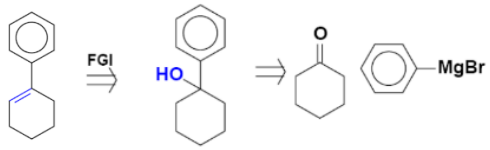

Figure 21: Functional Group Interconversion

You need to add the OH group to something that needs to be broken, not to another carbon that does not need to be broken. (Figure 22)

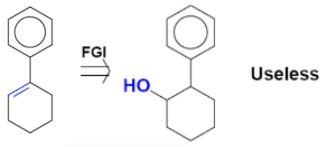

Figure 22: Less useful Functional Group Interconversion

If the addition goes to the wrong place, the subsequent bond-breaking steps cannot proceed.

D. Disconnection of aromatic ketone

Based on aromatic acylation (Figure 23)

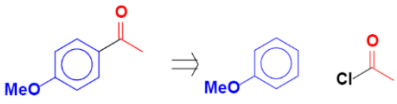

Figure 23: Example1

Based on the substitution of the carboanion(Figure 24)

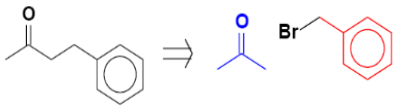

Figure 24: Example2

Disconnection of simple ketone (Figure 25)

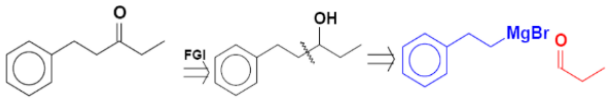

Figure 25: Example3 (Functional Group Interconversion)

In the end it is reasonable to bring all ideas together by using one last example, a useful, and rather proliferating drug- Paracetamol.

E. Paracetamol

This reaction is the retrosynthesis of a renowned compound paracetamol. Paracetamol has proliferated in modern drug productions and analysis, it's usually used as antipyretics,pain suppressants and so on.

To begin with let us take a closer look at its structure- it is a phenol attached to an amide group, and it is plausible to suppose this compound is actually synthesized with a starting material of phenol!

F. The Retrosynthesis of Paracetamol

The bond between nitrogen and carbon is broken to give 4-aminophenol, and acetic anhydride. And these two structures can react through Nucleophilic addition

reaction as they are an amine and a carbonyl compound. And that is why this specific bond is broken and not any other bonds.

The aminophenol can then be broken further on their carbon nitrogen bond and get an NH2 and Phenol(the starting material), as shown in Figure 26.

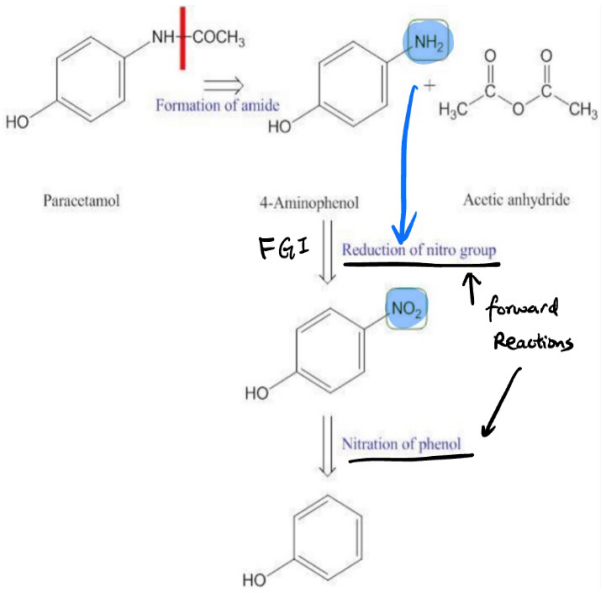

Figure 26: Multi-Step Retrosynthesis of Paracetamol

VI. Conclusion

Through this research report, we learned about the historical background of the reverse reaction, and the purpose of the reverse reaction. First, we used two classic examples of reverse reactions, TM 82 and paracetamol respectively, to introduce the overall introduction of reverse reactions.

After that, we introduced some of the principles that might be used to do the reverse reaction and gave specific examples of each principle for your understanding: The principle of rationality and the principle of maximum simplification. And we shared with you the Diels-Alder reaction. And then we looked at three common ways to reverse reactions: Functional Group Interconversion, Functional Group Addition, and reconnection.

Of course, different functional groups have different ways of reversing reactions. So, we have shown you a few specific things here, and they all have their functional groups. These are just a few of the simplest types of reverse reactions, and there are many more complicated ones, such as bifocals, that require even more complicated steps in reverse reactions, but with this foundation, it would be easier to understand what is going on in reverse reactions.

References

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