The brief introduction and extension to Retrosynthesis

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Abstract

Retrosynthesis is a vital methodology to design a complex molecule through the opposite direction, which is the opposite direction: breaking bonds. Many principles need to follow the rules. This study aims to summarize the rudimentary basis of retrosynthesis and give some outlook on the chemical synthesis of important molecules with important utilization value.

Keywords: background, disconnection, synthon, equivalent, funtional group, dioxygenation, retrosynthesis

1. INTRODUCTION

Retrosynthesis refers to the design of synthetic routes, often from the target molecules or target molecules, step by step to deduce the starting material to be used, the process, and the synthesis process in the opposite direction. In the process of inversion, the complex molecular structure can be simplified by analyzing the structure. As long as each step is reasonable, the reasonable route of drug synthesis can be obtained.

This article introduces retrosynthesis from the following aspects, Disconnection: An analytical operation, which breaks a bond and converts a molecule into a possible starting material. The reverse of a chemical reaction. Symbol \rightarrow and a curved line drawn through the bond being broken.

FGI: Functional Group Interconversion: The operation of writing one functional group for another so that disconnection becomes possible. The reverse of a chemical reaction. Symbol \rightarrow with FGI written over it.

Reagent: A compound that reacts to give an intermediate in the planned synthesis or to give the target molecule itself. The synthetic equivalent of a synthon.

Synthetic equivalent: A reagent carrying out the function of a synthon which cannot itself be used, often because it is too unstable.

Synthon: A generalized fragment, usually an ion, produced by a disconnection. (some people also use synthon for a synthetic equivalent).

Target Molecule: The molecule whose synthesis is being planned.

2. BACKGROUND

I think we can use the analogy of a maze. For example, we try a route to disconnect it but it doesn't work. This is the same principle as running a maze and hitting a wall. Then we'll try another method and keep on going until we find the right route.

The Synthetic Route to a Target Molecule



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FIGURE 1: the synthetic route to a target molecule

The Synthetic Route to a Target Molecule



The breakdown of bonds is the key to retrosynthesis. Return to the appropriate stage of molecules and pay attention to the reaction mechanism to determine the proper cut-off approach. When functional groups are involved, they are either cut off at the connection of functional groups, or the original functional group is cut off if the functional group is generated by two functional groups. If the C-X bond is present in the molecule, it is usually decided to cut it off at the heteroatom, especially when the heteroatom is oxygen, nitrogen, or sulphur [1-3]. Retrosynthetic analysis, which is covered in the benzene and other aromatic compounds electrophilic substitution reactions chapter starts by defining retrosynthetic analysis, or RSA is a technique for planning an organic synthesis by breaking down the target molecule (TM) into simple starting materials, called the readily available starting materials, which are abbreviated as RASMs [4-6].

This is achieved by imaginary breaking bonds, which are called disconnections, and by the conversion of one functional group into another functional group (called functional group into conversions (FGIS) [7].

An RSA is used to the device, on paper, an appropriate forward synthetic route to the target molecule (TM), there is often more than one correct analysis [8].

An Example RSA



FIGURE 3: the first step of the example

Then, using a retrosynthetic analysis as an example showns in figure 3, create a synthesis for this ketone molecule here. This is the target molecule, and the first thing we'll do is recognize that secondary alcohols can be used to make ketones, and then we will do an FGI back to the secondary alcohol, recognizing that we can oxidize the secondary alcohol back to the ketone in the final step of the synthesis, so this secondary alcohol here now becomes a new target molecule, and we will connect it to the carbon-carbon bond shown here to form a set of synthon [9].





There are two possible sets of synthon that can be formed by disconnection of that carbon carbon bond: a positive charge on the left and a minus on the right, or a minus on the left and a plus on the right. These are the two possible sets of synthon that can be obtained by disconnection of that carbon carbon bond [10].





FIGURE 6: the forward synthesis of the example

The challenge now is to assign synthetic equivalents to each of these same synthetic, these are the reactants that act like these synthetic, so the synthetic equivalent for this benzyl cation, one something like benzyl bromide where we have a leaving group for this particular carbon, a synthetic equivalent for the negative charge on the carbon and OH carriers are not obvious, and so cannot easily assign a synthetic equivalent for this, the other set of synthetic equivalents of the synthon gives this negative charge on the carbon next to the benzene ring. For a synthetic, the equivalent might be a Grignard reagent in an organometallic reagent, which behaves like a benzylic, and then the synthetic equivalent for this positively charged synthon is an aldehyde since so the two equivalents synthesize reasonably.

And in the forward reaction, we have these two steps take the Grignard reagents that react it with the aldehyde and then on acidic workup that formed the secondary alcohol and it's this new C-C bond that's formed and the reaction, and then in the second step oxidizing the secondary alcohol to a ketone using an oxidizing agent.



FIGURE 7: RSA and synthesis

Such as pyridinium chlorochromate so take some other instance now and an RSA in the synthesis of this fragrant compound right here wherein we have the methoxyl group and the methyl ketone, and the one, 4 role of a benzene ring, so that is the goal molecule and I am going to understand that this OME group is 2,4-directing, so meaning that I can introduce this ketone group and the 4 role due to the fact the OME group can direct an electrophile to the entire role of the ring, so disconnecting of that ketone citrate, I'm going to examine the set of synthons and positioned a minus at the benzene ring due to the fact that is the nucleophilic group I'm going to position a plus at the carbon bearing the carbon are the artificial equal for those synthons are proven right here, specifically the benzene ring itself and we are going to positioned a chlorine atom now connected to the carbonyl and this withinside the ahead response might be a Friedelcrafts isolation response. Then making ready this new goal molecule and disconnecting the oxygen carbon bond and drawing a synthon, we are going to positioned a minus at the oxygen due to the fact that is especially smooth to achieve, we are going to devise with a plus at the methyl facet chain, so my artificial equal now for those synthons might be phenol itself and positioned a leaving group right here, then positioned a bromine, so that is bromomethane, the ahead response, I can take phenol, and deprotonate it with a base in this case, so that you have hydride that bureaucracy the phenoxide ion and phenoxide ion can then react with bromomethane and substitution response to shape the methyl ether, and this is called after Williamson who devised this form of response and is known as the Williamson ether synthesis, the following step started to do a Friedel crafts isolation, however come to understand that the OME group is 2,4-directing it is able to accurate the ketone and the 4 positions of the ring, and so we will turn out to be with this electricity product with a ketone it's far added on the 4 role on response with ethanol or chloride and aluminium trichloride, and we can additionally get the undesirable legal thing, however the ketone group has been added at the 2 role with appreciate to the OME and we are able to separate those nearby isomers and separating the preferred goal molecule that we require in our synthesis.

3. DISCONNECTION

3.1 Electron pushing arrows

In organic chemistry, much of the time your focus is on bonds, often making bonds or breaking bonds, and what happens to the framework. Now you have to think about what happens when you actually break a bond. 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. There are three fundamental types of electrons pushing processes:

As shown in Figure 8, the first possibility is that by taking the electrons that are in the bond in middle, when you break them, you are gonna give them to the partner righthand side, which left with a positive charge on the left one.



FIGURE 8: elecrtron pushing arrows to the right

Possibility number two is to do exactly the same thing, like figure 9, but to give the electrons to the other partner, so you have a anion on left hand side and an cation on right side.



FIGURE 9: elecrtron pushing arrows to the left

The other alternative is to take one electron on each side. Notice that one thing is different about this kind and the other two kinds is that there is no dipole, because they both have the same electronegativity, so it will give out two free radicals, which is a molecular species capable of independent existence that contains an unpaired electron in an atomic orbital.



FIGURE 10: elecrtron pushing arrows on each side

3.2 Synthons and synthetic equivalent

The terms synthon and synthetic equivalent come under the branch of retrosynthetic analysis. The key difference between synthon and synthetic equivalent is that synthon is a moiety of a chemical compound that can be formed by a known synthetic process, whereas synthetic equivalent is a reagent that carries out the function of a synthon. That means, synthon is a part of a substrate molecule which you are going to change its structure in order to obtain the desired structure, while synthetic equivalent is the molecule that you need to react with the synthon in order to get the desired compound. By considering an example, the synthesis of alcohol, it goes back to a protonated carbonyl group plus an ionic alkyl fragment. These are the direct products of a retrosynthetic step, and these are synthons. But you really need are some synthetic equivalents, and for a protonated carbonyl, you need the Grignard reagent to be the synthetic equivalence which the organic magnesium compound had this covalent bond but it reacted like an anion.



FIGURE 11: sythetic equivalent

3.3 Functional group guided disconnections

When you look at a molecule typically your eyes go towards the functional group and so it's not surprising that for retrosynthesis, a lot of the disconnections will be guided by functional groups.

For the most part, you'll be looking at one functional group and disconnecting that molecule. So again, by using the same example just above, you can think about the fact that this alcohol has two lone pairs and use those lone pairs to help guide the retrosynthesis. As shown in Figure 12, by pushing the lone pair into the adjacent carbon, you can start to form a carbon-oxygen double bond, but as you do that, the carbon on the bottom gain too much electrons, so there may be a bond breaking.



disconnection

This is also true for the 2 group disconnections.



FIGURE 13: two functional group disconnection

And for the third one, which is the electrocyclic disconnections, the retrosynthesis should be guided by electron flows inside the ring, for instance, the Diels-Alder reaction.



FIGURE 14: Example of 13 two functional group disconnection

Disconnections must correspond to known and reliable reactions. As the diagram shows below, getting positive benzene is unusual which means the disconnection is not accessible.

Function group interconversion is being used when the disconnection does not lead to the logical starting material, symbol for functional group interconversion is using a retrosynthetic arrow with the acronym (FGI) above it. the example as the molecule shown below, three bromoanilines cannot be produced by the bromination of aniline because the amino group is ortho para directing, however using functional group interconversion where converting the amino group into a nitro group makes the reaction accessible. Bromide ion can be joined to the nitrobenzene through bromination using iron bromide.

In the analysis, it is essential to find the greatest simplification for the molecule.

Disconnections can be made toward the middle of the molecule. As the diagram shows below, if we disconnect the bond in the middle part of the molecule, therefore two synthons are formed with opposite charges on them. The minus charge can be complemented with a hydrogen atom. And the other synthon with a positive charge can be converted into methyl vinyl ketone, in this case, aldol reaction can be carried out to form the target molecule where the ketone will react with the strong base and form stabilized resonance and it will attack the aldehyde and generate a new bond between them which is aiming product.



FIGURE 15: synthesis of 2-cyclopentylidenec yclopentanone

Disconnections can also be made at the branch point, as the figure shown below, if the bond at the branch point is broken, two synthons with opposite charges are formed, and the negative charge can be complemented by a hydrogen atom which forms an ester, one proton will be abstracted when it reacts with a strong base and a nucleophile will be formed, the other synthon can be replaced by a bromine ion which makes the carbon partially positive charged after that the nucleophile will react with bromoalkane and forming the target molecule.

The other strategy for maximum simplification is looking for symmetry, the molecule in the image has two fivemembered rings, so we can disconnect the bond between them and use the strong base to extract the nucleophile and attack the carbon attaches to ketone forming a new bond between those two rings, and remove water molecule through condensation reaction to obtain the target molecule.

For compounds containing two parts joined by a heteroatom, disconnection should be made next to the heteroatom. heteroatom stands for any atom which is not hydrogen or carbon.



FIGURE 16: Retrosynthesis of benzyl phenyl ether

As the figure shown below. two parts of molecules are joined with an oxygen atom, disconnection next to the oxygen will be made, synthons phenoxide and benzyl cation will be formed. The synthetic equivalence will be phenol and benzyl bromide respectively. The target molecules can be produced when two reagents react in the presence of a strong base.

Consider more than one disconnection and select one that avoids chemoselectivity issue. There are two retrosynthetic pathways shown in the figure, pathway requires the process of chemoselective reduction to form the organic compound however it does not consist chemoselectivity issue which is better to follow.



FIGURE 17: Retrosynthesis of 3-hydroxy-1-phenylbutan-1-one

4. DIOXYGENATION PATTERN

There are various structures of organic molecules, even though we cannot summarize a method to synthesize any type of complex molecules, however, the compound that contain oxygen functional groups with spice less than 6, including carbonyl, hydroxyl group, follows a same rule, which known as "deoxygenation pattern".There are mainly five types of dioxygenation pattern: 1,2 ; 1,3; 1,4: 1,5; 1,6.

4.1 1,2 dioxygenation pattern

Generally, the way to disconnect these compound is to cut the carbon bond that connect two functional groups. Forward reaction may include mainly nucleophilic addition of the carbonyl compound; methylenation; Benzoin condensation; and so on.

For example, diol, diketone, generally they will change to olefin. The first step is to use FGI to change the structure to a standard structure. The forward reaction is to use OsO4, or KMnO4 dihydroxylation, and the product is alkene.



Oxygens add to the same face of the C=C

FIGURE 18: the examples

OsO4 and KMnO4 will form a cyclic intermediate through syn addition, and the intermediates will be hydrolysised, to form the cis-1,2 diol.

4.2 1,3, dioxygenation pattern

1,3 dioxygenation pattern also follows the same pattern as 1,2 dioxygenation. There are three carbon atoms connect to the functional group, they can be two hydroxyl group, carbonyl groups or the combination of hydroxyl or carbonyl group, whether is combination or the double functional group, there is a universal way to deal with them. The forward reaction might include: Aldol condensation, carbonylation, carboxylation and so on.



FIGURE 19: example of1,3 dioxygenation pattern

In this example, we can see that, pentane,2,4diol, acetylacetone, 2, hydroxypentan-4-one, the general way the disconnect the molecule is to let the functional group oxidize to carbonyl group, and reduce the left side to hydroxyl group. This process is FGI in order to produce prototypical structure.

The next step is breaking the C-C bond between the carbonyl and hydroxyl group which is the principle we should follow: cut the bond that connect to the heteroatoms and functional groups.

4.3 1,4 and 1,5 dioxygenation pattern

The main way to break bond is to break the through a forward reaction called "Michael addition". First of all, base will try to get the alpha-hydrogen atom on carbon, produce a enol anion, and the enol anion will react with acceptor 1-4 conjugate addition, the product of the reaction will get one proton in the solution, to form enol, and the target molecule will be gotten from tautomerism.



FIGURE 20: example of Michael addition

Michael addition is a chemical reaction with regioselectivity. Nucleophile will attack the β -carbon atom first, and produce a enolate intermediate. Enolate intermediate will be protonated and produce the final product.

In addition, Michael addition have utilized in Robinson annulation. Robinson annulation is a cascade reaction, it combined three reactions: Michael addition and Aldol addition, and E1cb reaction which is a very important way to construct 6-membered rings and fused rings compound.



FIGURE 21: Robbinson Annealation

4.4 1,6 dioxygenation pattern

For the 1, 6 dicarbonyl compound, a lot of them can be synthesis from a ring opening reaction, the most common one is ozonation.



2-(2-oxoethyl)cyclohexyl]acetaldehyde

FIGURE 22: Ozonation

From this reaction, we can see that the octahydronaphthalene can disconnect bond to form 1, 2-[2-(2-oxoethyl) cyclohexyl] acetaldehyde:



FIGURE 23: the example of 1.6 dioxygenation pattern



FIGURE 24: synthetic route of trioxolane

From this example, we can see that, not only single carbonyl will have the reaction, the reaction will also

happen with carboxylic acid functional group, the final product is dimethylpentene.



FIGURE 25: synthetic route of trioxolane

From the ozonation, a lot of mechanism have been mentioned, the most reliable one is the mechanism mentioned by Rudolf. First of all, for all alkane and alkene, will react with ozone to form a intermediate with the mechanism of 1,3 ozone addition, next step is retro 1,3 cycloaddition. In the next step, the molozonide will break into two intermediates, which is carbonyl and carbonyl oxide and they have special name: Criegee intermediate. In this step, the C-C bond given up a pair of electrons, and move to the C-O bond. This step makes the whole compound break down into two parts. (Please have a see at the rectangle) Carbonyl Oxide has two oxygen atoms and it is a zwitterion. The oxygen atom that has electronegativity will attack the double bond of the carbonyl; it will produce trioxolane through the mechanism of 1,3 cycloaddition. The next step is reductive process or oxidative process.

5.EXTENSION

Retrosynthesis analysis for(3aS,6aS)-3a-

methylhexahydro-4H-cyclopenta[b]furan-4-one



FIGURE 26: Retrosynthesis analysis for(3aS,6aS)-3a-methylhexahydro-4Hcyclopenta[b]furan-4-one

As shown in the figure 26, first the furan ring in compound 1 can be synthesized via the intramolecular substitution of 2. Then the compound 2 may be obtained from 3 through the activation of primary alcohol with MsCl. Next the alcohol functionality in compound 3 should be derived by the reduction of aldehyde group of 4which can be generated by means of oxidation reaction of the double bonds in 5. The compound 5 would be produced by protecting the secondary alcohol group in compound 6 with TMSC. Finally, compound 6 is planned to be synthesized from diketone 7 by implementing a desymmetric enantioselective reduction. The compound 7 can be prepared from the commercially available diketone 8.

6.CONCLUSION

To sum up, retrosynthesis is the process of "deconstructing" a target molecule into readily available starting materials. In the study of chemistry, it is very difficult to make a complex compound from a simple material. The method is widely used to make drugs and other products by thinking backwards, starting with the compound molecule you want to make and then analysing which readily available reagents and reaction sequences can be used to synthesize it.

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