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AN OVERVIEW OF RETROSYNTHETIC METHODS, EVALUATION, AND MECHANISM

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Abstract
One particular area of chemical synthesis in organic chemistry is called organic synthesis. Chemical synthesis is a highly effective tool for humans because it yields a wide range of valuable compounds, particularly those that are either entirely absent from or present in very little amounts in nature. In organic chemistry, the concept of retrosynthesis examines the possibility of creating a complex organic molecule through the process of reverse synthesis. Retrosynthesis is an essential process for creating complicated molecules by going in the other direction—that is, breaking bonds. Rules must be followed by many principles. In order to overcome the difficulties posed by various reaction processes, concepts, and factors in organic synthesis, total synthesis, and asymmetric synthesis, "retrosynthesis" is a crucial strategy. Its synthetic routes are also simpler and easier to develop and construct. Because organic synthesis is influenced by a multitude of reaction mechanisms, concepts, and factors, "retrosynthesis" is a crucial technique for resolving its synthetic routes. It is less complex and easier to design and conceptualize than organic synthesis, total synthesis, and asymmetric synthesis.
Keywords: Retrosynthesis, Synthon, FGI, Bond Disconnection.

Introduction

Organic synthesis is a crucial part of chemistry that can directly lead to scientific and societal benefits by actualizing new molecules that have ideal functions in different disciplines,such as material science and medicine. Retrosynthetic analysis is formalized in E.J. Corey's book The Logic of Chemical Synthesis [1]. Compared with inorganic syntheses, organic syntheses are usually much harder to visualize and design, due to the large complex structures of many organic compounds. 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 functionalgroup 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 [2]. Retrosynthesis is an important method for solving organic synthesis routes and is certainly the most basic way to design organic synthesis. Retrosynthesis is often found in organic chemistry, chemical engineering, and biochemistry. Its role includes the synthesis of natural products, the synthesis of new drugs, and the reduction of products.

Symbol → and a curved line drawn through the bond being broken [3].

FGI: Functional Group Interconversion: The operation of writing one functional group foranother so that disconnection becomes possible. The reverse of a chemical reaction.

Symbol → with 3 FGI written over it.

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

Synthetic equivalent: A reagent carrying out the function of a synthon that cannot itself beused, often because it is too unstable [4].

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

Target Molecule: The molecule whose synthesis is being planned.

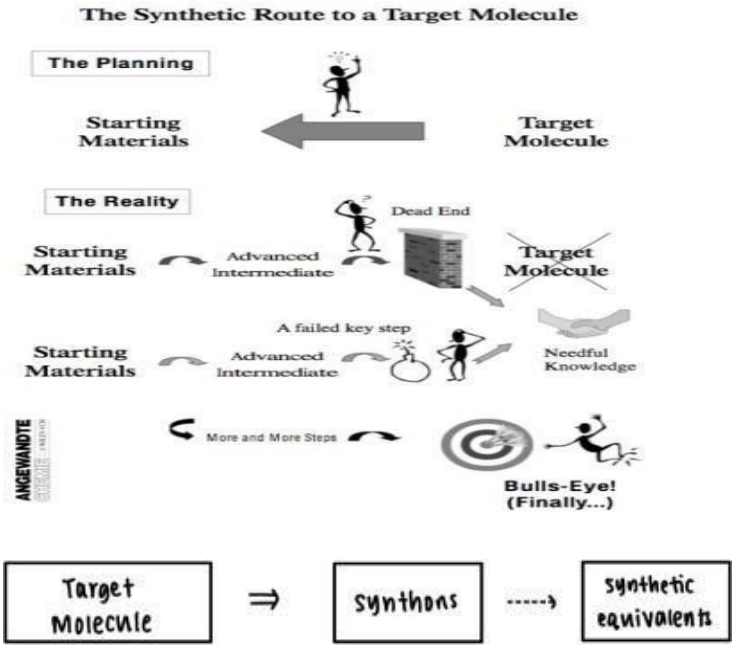


Fig 3: Retrosynthesis

1. What is retrosynthesis

Retrosynthetic analysis [5] is a method and an intellectual tool adopted to help come up with a synthesis for a complex organic molecule. The retrosynthetic analysis allows chemists to conduct the "reverse" synthesis process. Starting from the target molecule, it "deconstructs"the large and complicated target molecule into many simpler and more basicconstituents, known as synthons.

Each step of the retrosynthetic process is represented with a retrosynthetic arrow (different from the arrow used in forward syntheses). The steps in this process chosen may or may not bepossible, but plausible reactions can be predicted with existing knowledge. For example, if onewants to synthesize a molecule (target molecule) from a given starting substance, one can devise a retrosynthetic pathway such as where each step brings us closer from to, that can actas a guide for writing a forward synthetic pathway.

1.1 Benefits of doing retrosynthesis

More economical Conducting retrosynthetic analysis [6] before doing the synthesis straightaway allows different routes to be compared based on feasibility and the cost of related reagents. Thus, the more efficient and effective pathway, particularly cost-effective,can be used for large-scale synthesis.

1.2 Guiding Principles of Retrosynthesis

If one wants to synthesize an ester from an olefin, instead of thinking of how to produce an ester from an olefin, focus can be put on how to design reactions that can generate the olefin. Even though there are thousands of possibilities in each retrosynthetic step, some solutions arebetter than others, with only a few being the best.

1.3 Simplification

The first goal of a retrosynthetic step is simplification. To turn the usually very complicated target molecule into simple and readily accessible starting materials, each step ofthe retrosynthetic process should simplify the molecule as much as possible to resemble the starting materials. An example of a step that simplifies the target molecule may be disconnecting a cyclic structure into linear pieces or disconnecting a functional group thatis absent in the starting materials.

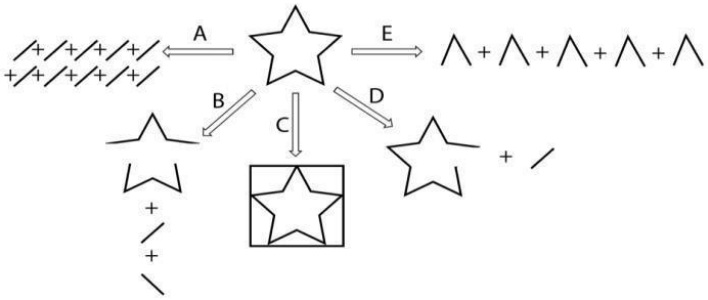


Fig :2.Retrosynthesis of a star

1.4 Minimal Complexity

The second goal of a retrosynthetic step is minimal complexity[7]. Although a step can be envisioned where every bond in the target molecule is disconnected to obtain theseparate organic, such a step is certainly impossible in a forward synthesis where it would require everybond to be formed exactly simultaneously. Disconnecting one bond is generally easier than disconnecting two or more bonds. If the forward reaction is considered — an unimolecular process occurs more easily than a bimolecular process because the unimolecular process is easier to arrange geometrically for a successful collision than the bimolecular process. Similarly, a bimolecular process is much more likely to happen than a trimolecular process.

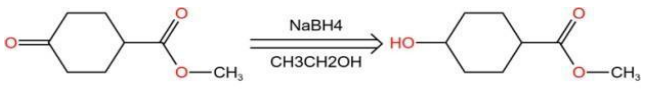
2. Retrosynthesis analysis terms

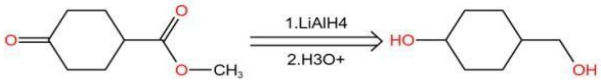
2.1 Reaction selectivity

Chemical selectivity (Chemo selectivity)[8] - The ability of a reagent or intermediate

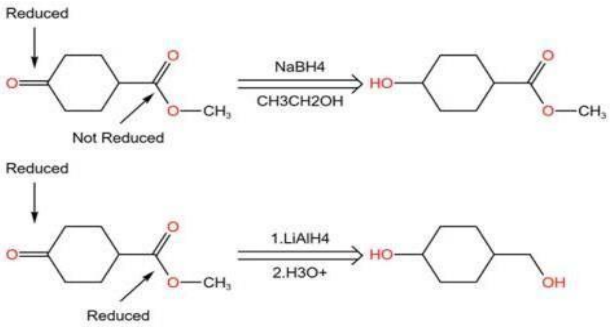
to react with one group or atom in a molecule rather than another group or atom present in the same molecule. Of course, one of the functional groups reacts in preference to the otherone or morefunctional groups.

We focus on the ketone to the left of the cyclohexane while both reactions reduce it, the only difference is that the ester on the right side of the compound does not undergo any change when NaBH4 is the reagent, but when the reagent was LiAlH4, the ester was also reduced.





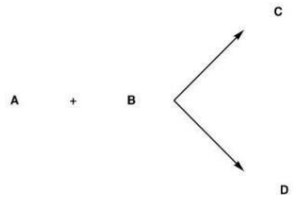
A reaction that acts on only one functional group in the presence of other functionalgroups. Therefore, it is chemo-selective when the reagent is NaBH4. Because the ester is retained. the reaction of LiAlH4 doesn't have chemo selective because both functional groups ketone, and ester are reduced.



2.1.1 Stereo selectivity

Stereo selectivity[9] is if more than one reaction may occur between a group of reactants under thesame conditions, producing stereoisomeric products, and if one product is formed in greater amounts than the others, the whole

reaction is said to be stereoselective. [6,7]



2.1.2 Regioselectivity

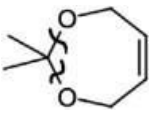
Regioselectivity refers to reactions formed by the selection of an enantiomer, adiastereomer,or a double bond isomer over other isomers. Any process that facilitates the formation of bonds on specific atoms rather than on other possible atoms [10].

2.2 Symbols of retrosynthesis

Retrosynthetic arrow: This represents going backward from the target molecule to simplermolecules.

Synthetic arrow

Bond disconnection: A wavy line () to show where the bond is being broken (disconnected)

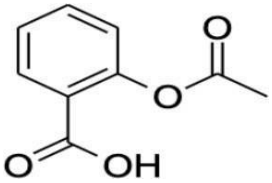


3. Basic Steps of Retrosynthesis

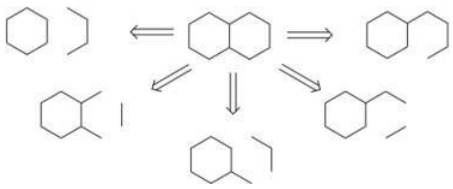
Each step in a retrosynthetic analysis involves one or more disconnections of the bonds in thestructure. One can only disconnect bonds because it is not very practical to slice the atoms themselves. After all, they occupy very limited volumes [11].

3.1 Disconnection

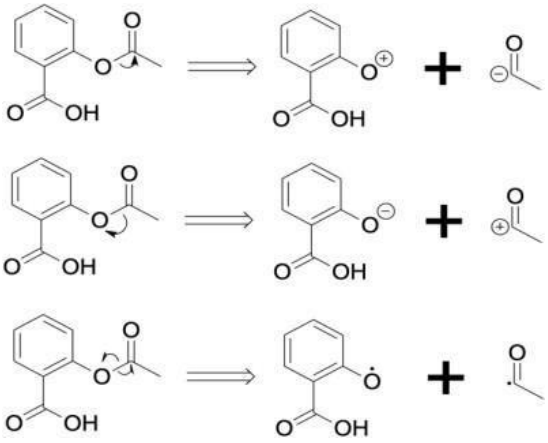
As the consequence of disconnection, one of the three things may happen: both electrons go to the left synthon



(A hypothetical fragment of a compound that is a building block for the target molecule), both electrons go to the right synthon, or the electrons are split between the two synthons -Disconnection is the most important part of the retrosynthesis, which acts in the course of a hypothetical chemical reaction, speculating on possible broken bonds and generating synthons up to the desired target molecule. when considering only bond-breaking, we can break the bond at a tertiary carbon, only one benzene ring and one functional group is retained in the form. Optionally, two tertiary carbons can be broken and one of the benzene rings will be completelyopened to form a ring-opening reaction. When a ring-opening reaction occurs, the disconnection can act on any position of the benzene ring, and when more than two chemical bonds are severed.[12]



Ex- Structure of acetylsalicylic acid (Aspirin)



Three possibilities of a bond disconnection

3.1.1 **Bond disconnections**

3.1.2 **One-group disconnections:**

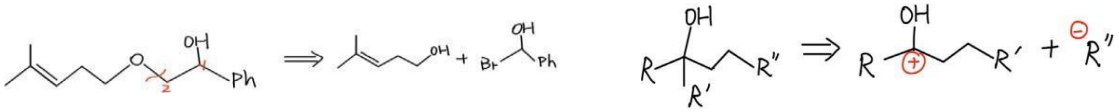
One-bond disconnection is a bond disconnection that can split molecules with a relatively simple structure. The common types are the disconnection of alcohols, olefins, acids, and some carbon compounds. For instance, C-C disconnections are one form. The C-C bond adjacent toan alcohol group can be disconnected, ending with an aldehyde and a Grignard reagent [13].

Two-group disconnections

Apart from one-bond disconnection[14], the other imaginary bond disconnectionmethod is two-bond disconnection. It can be used when target molecules have two functional groups. And it works better than the last method.

1,2-deoxygenation

This approach can be applied when the functional groups are connected with carbonone and carbon 2 in the chain of the target molecule. The bond between the functional group and the oxygenated carbon could be a single bond or a double bond. The general structure ofthe TM might be different, so the first necessary step is converting the molecule back intoits prototypical version by functional group interconversion, which is a diol, and the end product would be an olefin (15).



3.1.3 Electrocyclic Disconnection

Electrocyclic disconnection is the cutting of a cyclic molecule into pieces. In a cyclohexane molecule which contains 6 carbon atoms (), we can cut down a piece of two carbons from the molecule (4+2 disconnection) or we can cut the molecule into twoidentical propane (3+3 disconnection) [16]. We can also break one bond instead of two, to form a straight-chain hexane. In any of the processes, the number of carbon atoms remains the same. In a molecule with doublebonds like cyclohex-1,3-ene, the single bond between carbons 5 and 6 can be disconnected by an electron transfer from the double bond to an adjacent single bond. All these are described as cyclic disconnection for simplifying the target molecule.

3.1.4 Illogical Disconnection

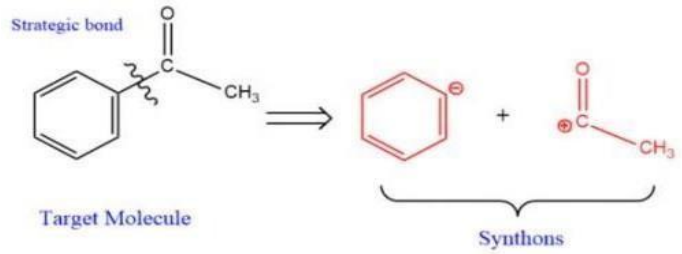
We know the three possible options when we break a C-C sigma bond, but in a more complex molecule, we need to care of the unfavorable 7 E3S Web of Conferences 385 (17), 04008 (2023) https://doi.org/10.1051/e3sconf/202338504008 ISESCE 2023 interaction between like charges as well. In Figure 15, there is a 1, 3 disconnection to form two synthons. The left synthon corresponds to an alcohol after it is converted to its resonance form, while the corresponding starting material of the right synthon contains an

Electronegative halogen.

4. Synthon

The concept of a synthon [11] was introduced by Elias James Corey in 1967. It is a hypothetical unit in the target

compound that represents the potential reagents experienced by the target molecule in the retrosynthesis. When some key chemical bonds in the target molecule are broken, two charged compounds are sometimes formed, which are synthons. The first step is to identify the chemical bonds that have been disconnected in the molecule to form one type of negatively charged and another type of positively charged materials, all collectively referred to as synthons. After predicting as well as understanding the smallest fragment of the target molecule as well as the building blocks, the synthons are combined to form the target molecule, thus synthons are very important substances in the process of retrosynthesis [16] and can lead to the synthetic route that generates the target molecule.



Synthetic equivalents

Synthetic equivalents are reagents that perform the functions contained in the synthetics and, since they can exist directly, do not carry a positive/negative charge.

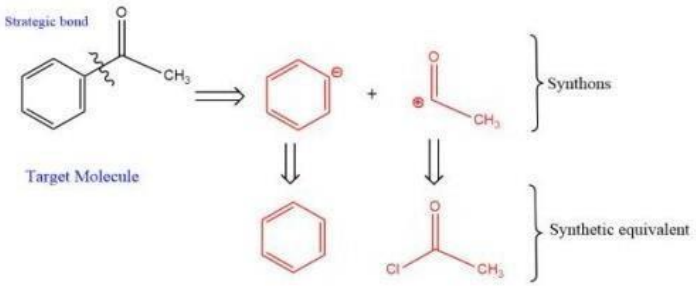
Ex- phenylacetic acid

we were able to find two suitable synthons in designing as well as planning the synthetic route, which can be carboxyl (COOH) and benzyl. With a synthetic substrate, we need to find the corresponding synthetic equivalent to replace it. Usually, the effective synthetic

equivalents for the carboxyl group are cyanide anions and benzyl bromide is a suitable synthetic equivalent[9]for the benzyl group. Their chemical reactions proceed as follows:

$$PhCH2Br + NaCN \rightarrow PhCH2CN + NaBr$$

$$PhCH2CN + 2H2O \rightarrow PhCH2COOH + NH$$

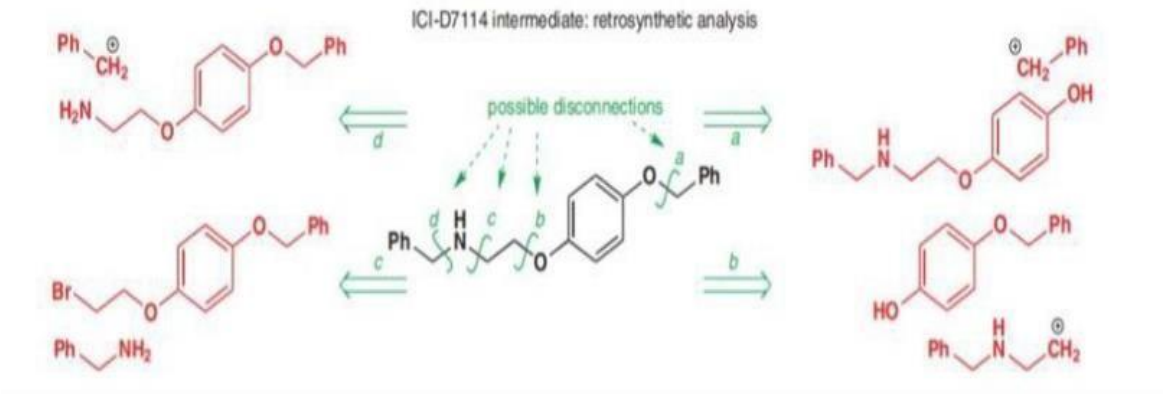


Synthetic equivalent of acetophenoneStrategies

4.1 Functional groups

In the process of retrosynthesis, there are lots of choices to disconnect a bond, but only one or two bonds will be broken. This problem is known as chemo selectivity. Chemo selectivity works when there are more than one functional group that can take a reaction with the reagent and only one functional group can be chosen. [10]

Taking ICI-D7114 (potential anti-obesity drug) as an example, there are many positions that we may consider as a bond disconnection. In this case, the bond in position (d) is where the disconnection will most likely to happen. (a) and (b) can lead to great chemoselectivity problems because it is difficult to alkylate the phenol due to the basic nitrogen atom. As to thedisconnection at (c), the alkylation of is favorable in the presenceof group, so it is better than(d).

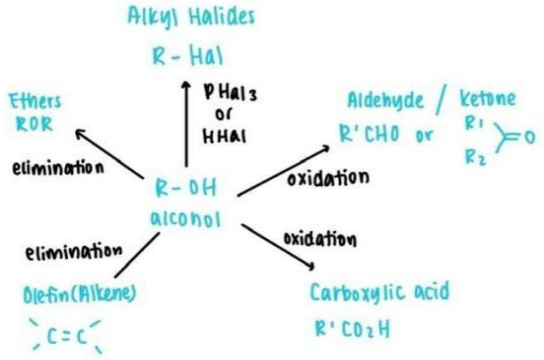


Retrosynthesis of ICI-D7114

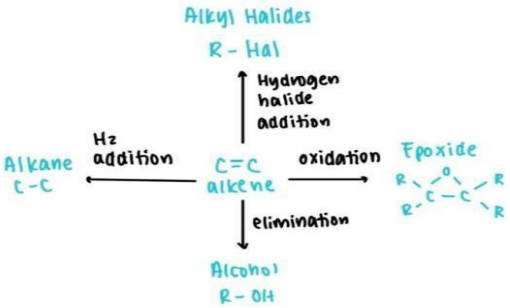
5. Functional group interconversion

FGI stands for functional group interconversions[12]. It describes the process of changingone functional group to another functional group. In a retrosynthetic analysis, FGI forms thefoundation of later bond disconnections.

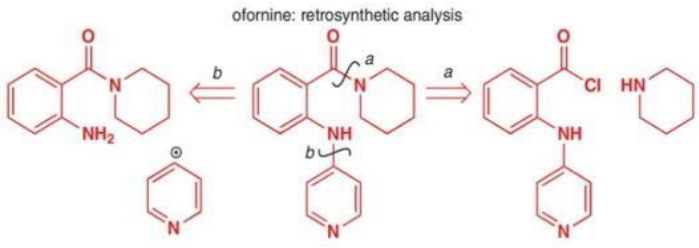
Common FGIs:



Common FGIs related to alcohol



Common FGIs related to olefin Retrosynthetic analysis of Ofornine

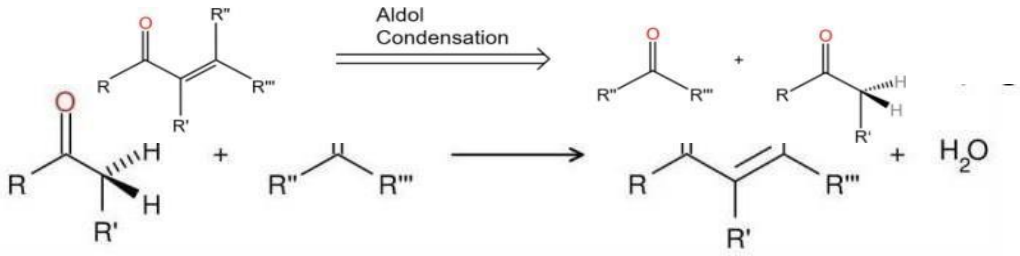


6. Mechanism of reaction

6.1 Aldol condensation

Acid (Base)-catalyzed condensation. In Aldol Condensation[10] reaction enol or enol ion reacts with carbonyl compound to form β-hydroxy aldehyde or β-hydroxy ketone.[12]And the product can sometimes lose a water molecule to form α,β-unsaturated carbonyl compounds.

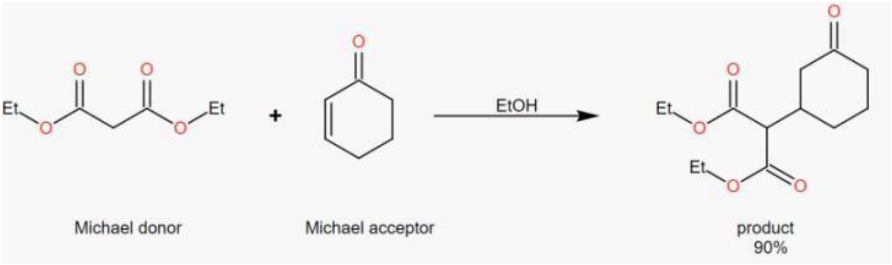
Aldol condensation



Aldol condensation in retrosynthesis

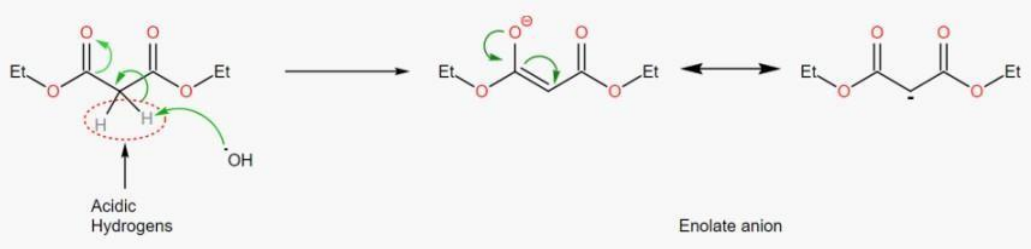
6.2 Michael addition

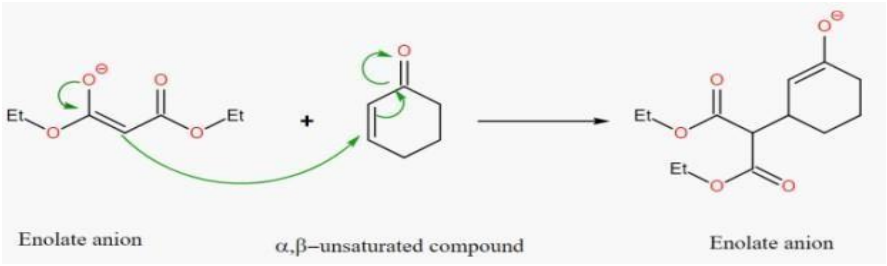
Michael addition[13] is also known as 1,4-addition or conjugate addition. [13] This reaction was first discovered by Arthur Michael in 1887 and is one of the common methodsfor growing carbonchains in organic synthesis. we can see from the resonance structure of the α,β unsaturated carbonyl compound that it has two electrophilic positions, that is, it carries a partial positive charge at its positions 2 and 4. The nucleophilic reagent is usually used as a Michael donor to attack the position 4 of α,β-unsaturated carbonyl compound in Michael addition, and the 1,4 addition reaction is carried out to it under basic conditions.



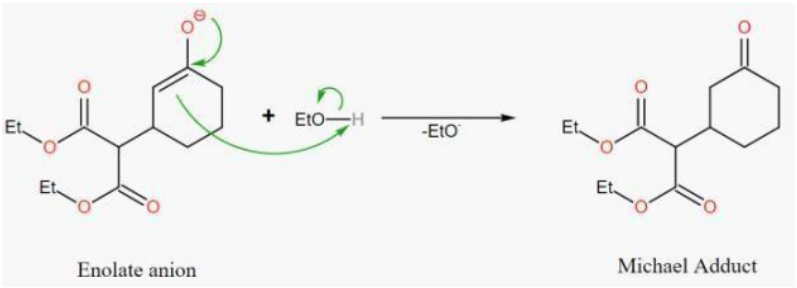
Step 1. Deprotonation: Hydroxide ions in alkaline solutions attack acidic hydrogens, giving rise to carbon negative ions also known as Enolate anion in the Figure. enolate anion in the Figure , has a resonance structure to maintain stability.

Step 2. Attack of nucleophile: The carbon anion acts as a Michael donor, which is electron rich, providing electrons to the Michael acceptor, which is electron-deficient. in the Figure below, the enolate anion obtained from the first step acts as a Michael donor, attacking the α,β-unsaturated carbonyl compound of the β- carbon, resulting in the formation of enolate anion.

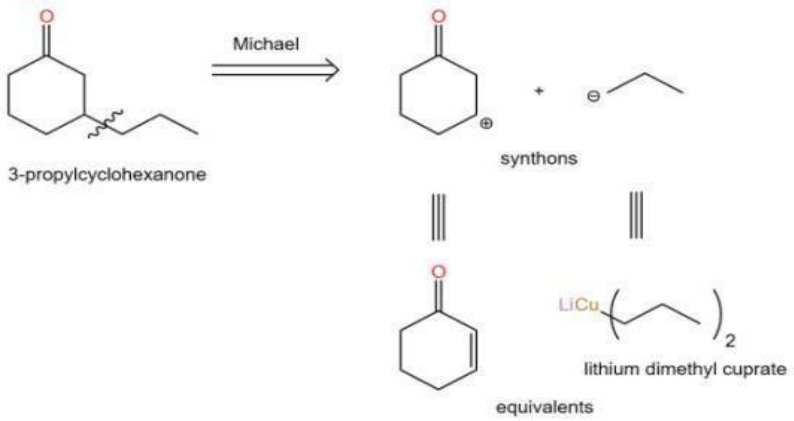




Step 3. Protonation: The carbonyl compound is protonated in the third step by accepting electrons from the solvent or Michael donor and forming the final product called "Michael Adduct".



Michael addition reaction and retrosynthesis



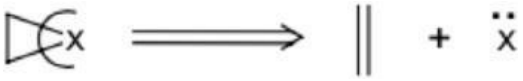
Analysis of retrosynthesis of 3-propylcyclohexanone:

7. Further examples of retrosynthesis

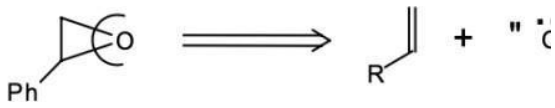
Retrosynthesis of 3 membered rings has mainly two approaches[13]

1. One bond disconnection to make a long carbon chain.
2. Disconnection by removal of an atom. The atom removed can be either oxygen(epoxide)or an R group.

Disconnection by removing an atom



Disconnection by removing an oxygen atom

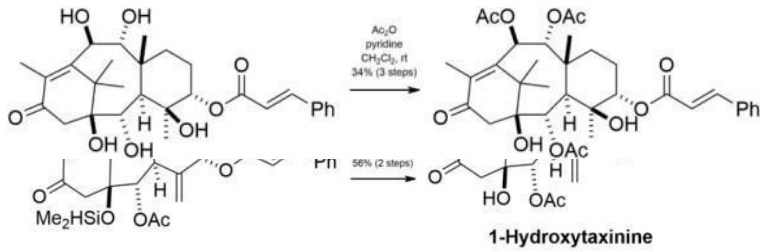


8. Another approach for retrosynthesis

Apart from the common atom approach[14], which is to locate the common atoms in two identicalparts of a molecule, especially between rings, there are other ways to proceed with retrosynthesis.

The work might focus on a step that is currently the easiest and probably disregard some duplicated steps while forming a molecule because they should be accomplished simultaneously.

1- hydroxytasinine[15] which is the procedure of substituting three H+ with Ac+ ionssimultaneously, which is time-efficient.



1-Hydroxytaxinine

Applications of Retrosynthesis-

The applications of retrosynthesis are diverse and impactful in various fields. Retrosynthesis is a method of chemical synthesis that involves breaking down a target molecule into simpler starting materials to determine the best synthetic route. Here are some key applications of retrosynthesis based on the provided sources:

1. Drug Design- Retrosynthesis[18] plays a crucial role in drug design by enabling the discovery of novel synthetic routes for pharmaceutical compounds. It aids in the efficient and cost-effective synthesis of biologically active compounds, facilitating drug development processes.
2. Organic Synthesis- Retrosynthesis is fundamental in organic synthesis, allowing chemists to plan the synthesis of complex organic molecules efficiently. It helps in understanding the complex nature of natural products, providing multiple synthetic routes for selecting the most cost effective and environmentally friendly path.
3. Chemical Research- Retrosynthesis has revolutionized the field of chemical research[21] by providing chemists with a systematic approach to organic chemical synthesis. It allows for the deconstruction of complex target structures into simpler precursors, aiding in the discovery of multiple synthetic routes and the selection of the most favorable and efficient route before industrial- scale synthesis.
4. Sustainable chemistry- Retrosynthesis is also linked to predictive sustainable[19] chemistry and nanotechnology. By simplifying the planning of organic moleculesynthesis, it contributes to the development of sustainable chemical processes and technologies.

Advantages:

1. Efficient Planning: It allows for the transformation of a target molecule into simpler precursor structures, simplifying the planning of organic syntheses
2. Structural Simplification: Retrosynthetic analysis aims to simplify the structure of the target molecule, making the synthesis process more manageable[19].
3. Multiple Synthetic Routes: It enables the discovery of different synthetic routes, providing flexibility in the synthesis process
4. Logical Comparison: By consulting a database at each stage, it facilitates the comparison of different synthetic routes in a logical and straightforward manner
5. Creative Strategies: Offers various strategies like functional group, stereochemical, structure-goal, transform-based, and topological strategies toguide the synthesis process

Disadvantages:

1. Complex Molecules: Powerful transform-based retrons are rarely present in complex molecules, often requiring additional synthetic steps to establish their presence
2. Need for Creativity: Disconnections in retrosynthetic analysis involve creativity,which can be challenging in complex synthesis processes [20].
3. Ring Structures: Disconnections that preserve ring structures are encouraged, while those creating rings larger than 7 members are discouraged, adding complexity to theanalysis.

Conclusion

This paper discusses the fundamental principles and ideas involved in retrosynthesis analysis. Retrosynthesis has generally grown in importance as a method for chemical development. Retrosynthesis provides reliable reactions and starting ingredients for every molecule. To summarize, the retrosynthetic process involves "breaking down" a target molecule into easily obtainable building blocks. Making a complex molecule from a simple material is a particularly challenging task in the study of chemistry. Thinking backwards is a popular strategy for creating medications and other products. You start with the chemical molecule you want to create and then analyze which easily available reagents and reaction sequences can be utilized to synthesize it.

Author contributions

All authors are contributed equally.

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Declaration of Competing Interest

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