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The review of fundamental retrosynthetic analysis and simple practical to hydroxychloroquine

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Abstract. In this paper, we discussed the basic mechanism of retrosynthetic analysis. We start with the idea of disconnection, which is a hypothesis to break the target molecule into some relatively simpler and more common molecules. Then we break bonds to verify our hypothesis made during disconnect. Based on the number and location of the functional groups, we can apply different methods for retrosynthetic analysis. We also apply our research of retrosynthetic analysis on the synthesis of hydroxychloroquine. In the second part of our paper, we discussed which method is more efficient to synthesize hydroxychloroquine, which should simplify the steps as much as possible, reduce the need for special conditions such as temperature, pressure, etc., and reduce waste liquid pollution, to ensure the ultimate industrial production effect.

Keywords: Handbook, Retrosynthetic, Mechanism, Hydroxychloroquine.

1. Introduction

1.1. retrosynthetic analysis

The essence of retrosynthetic analysis is to transform the target molecule into a simple precursor structure, which was proposed in the 1960s [1]. The retrosynthetic analysis is one of the most straightforward approaches to synthetic a target organic molecule. The retrosynthetic analysis does not consider any potential reactivity or interaction with the reagent and continues to decompose the structure until one is reached that can be used industrially [2]. Retrosynthetic consists mainly of two concepts, the disconnection, and the synthon. The disconnection determines the structure of the synthon, and the synthon itself is not a real molecule, but there are some real chemicals that behave like the synthon [3-4].

1.2. hydroxychloroquine

We pick hydroxychloroquine to do retrosynthetic is that hydroxychloroquine was primarily used as an anti-malarial drug. In the early stage of the COVID-19 pandemic, hydroxychloroquine has shown promising inhibitory effects. A recent paper reported an inhibitor effect of remdsivir (a new antiviral drug) and chloroquine (an old anti-malarial drug) on the growth of SARS-CoV-2 in vitro. Hydroxychloroquine will be a promising novel coronavirus Treatment, the supply needed will also rise.

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However, further research results show that hydroxychloroquine is ineffective in stopping the COVID-19 virus [5-6].

1.3. Background

Retrosynthesis is an analytical process in which target organic molecules are deconstructed or fragmented to obtain starting materials or "synthons". For a long time, many people have used this idea to design their own synthesis methods, but there is no clear definition. The concept of "retrosynthesis" was first formalized in 1964 by Professor Elias J. Corey in his book The Logic of Chemical Synthesis. It provides different ideas for the synthesis of single and complex target molecules. For some extremely complex molecules, the basic goal is to generate precursors that correspond to the available starting materials. In other words, retrosynthetic analysis is simplified for molecules. Often, there will be more than one possible synthetic route to the synthesis. Retrosynthesis is ideal for discovering different synthetic routes and making logical and direct comparisons.

Retrosynthetic analysis is a problem-solving technique for converting the structure of a synthetic target molecule into progressively simpler structural sequences along a pathway, ultimately yielding simple or commercially available starting materials for chemical synthesis. Presumably, the synthesis starts with a starting material of a few carbon atoms, and the reaction will add carbon fragments to increase the complexity of the molecule as it transforms into the final target in many steps. Therefore, it is necessary to understand the different reactions and reagents used to form different types of carbon-carbon bonds.

2. Mechanism

2.1. disconnection

Disconnection is a method of breaking up large molecules into smaller molecules with simpler structures. This method is usually used to deduce the target molecule by breaking it into simpler molecules. Disconnection would be the most basic concept of retrosynthetic. It is important to note that the disconnected method is a hypothetical process. People through the known chemical and equations to reasoning target molecules, but sometimes the target molecules split into pieces does not exist, in order to make the molecules of synthetic goes as planned, so people can add material in response to ensure that the reaction carried out in accordance with the plan, or find ways to react with the fragments of the same alternatives.

2.2. breaking the bond

Retrosynthetic trends to break up the single bond in the molecule since the single bond has lower energy than double bond and triple bond, so it would take less energy to break the single bond. There are 2 electrons in the single bond. Therefore, there will be three possibilities when breaking one single bond shown in Figure 1. One the top of Figure 1 is a sample molecule connected by a single bond. The first possibility is that all two electrons in the molecule are given to the right synthon, forming a synthon with a cation to the left and a synthon with an anion to the right. The second possibility is opposite to the first one, all the electrons are given to the left synthon, which makes a synthon with an anion to the right and a synthon with a cation to the right. The third possibility is that two synthons split two electrons in a single bond, forming one synthon with an electron to the left and one synthon with an electron to the right.

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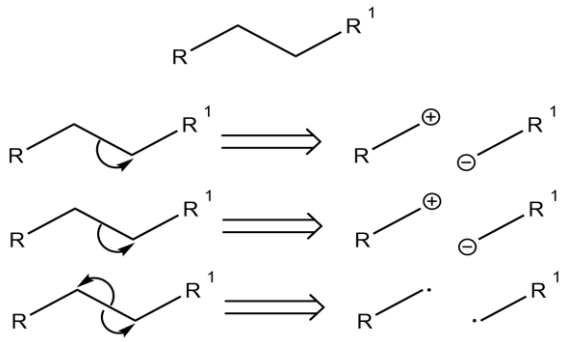

Figure 1. Three possibilities of breaking a single bond and forming synthons.

For every synthon, they have some synthetic, sometimes even multiple ones. This is because every time the disconnection happens, there will be several possibilities that electrons can go, which means different disconnections create different synthetic equivalents.

2.3. functional group

So, starting with one functional group molecule is the most straightforward approach to understanding how the functional group would affect the disconnection. This process is called one functional group disconnection. As Figure 2 shows, the functional group, alcohols, disconnects from the 2-Butanol to form a double bond by giving the one lone pair on the oxygen to the C-O single bond. When we try to make a double bond, one carbon atom does not fit into five bonds by the Octet Rule, so one of three other bonds connected to this carbon must be broken. By breaking different bonds, the target molecule will produce different pairs of synthons. Then we can beginning consider which process is the better way.

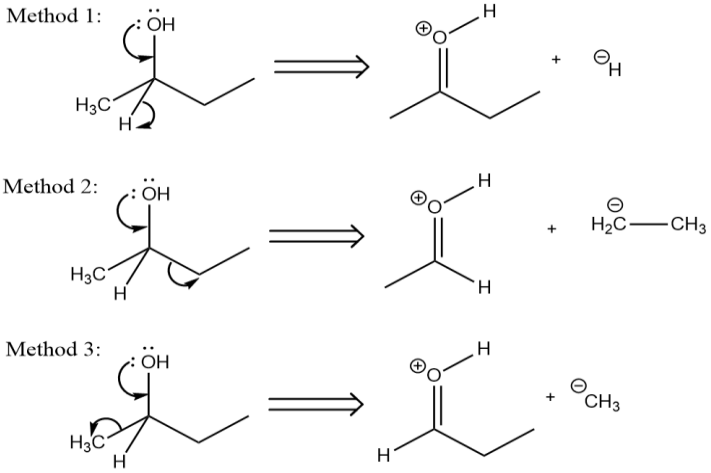

Figure 2. Three possible ways to disconnect alcohol from 2-Butanol.

The best way to disconnect this compound is Method 2 shown in Figure 2, because it divides the four carbons in the compound into two synthons equally have two carbons.

2.4. Two functional group disconnections

The two functional groups' disconnect is that we're gonna use both groups in concert with one of them. As the figure shows below, we push the electron in, and other three bonds on the carbon group where the alcohol is are going to broken, the methyl, the hydrogen, and one bond to another set of equations, and if we pursue the bond that links right functional group's disconnection, the electron on the right groups' oxygen would be forced away from oxygen. The process that pushes electron density out on

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something is called electron negative. That is the way you can use both functional groups together, and all possible bonds that you can disconnect just narrow down to one, even the best one. So we can take both functional groups' advantages at the same time, and actually, two functional groups' disconnection is a kind of strategy, the strategy that helps simply question, and directly get the solution.

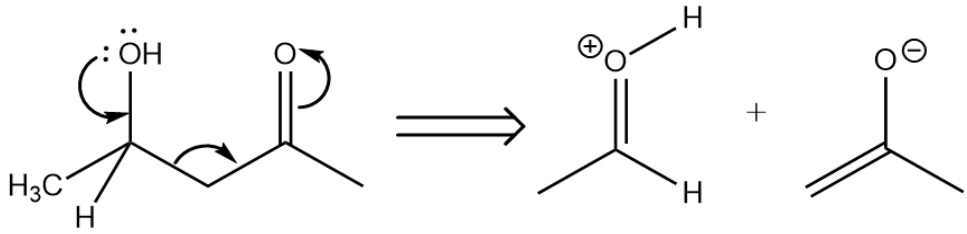

Figure 3. An example of Two functional group disconnections.

2.4.1. Electrocyclic Disconnection. This method is used on six member rings, if we swing the electron around, we have to break another bond and make a double bond several times. This method allows us to break two bonds at the same time and also break six member ring.

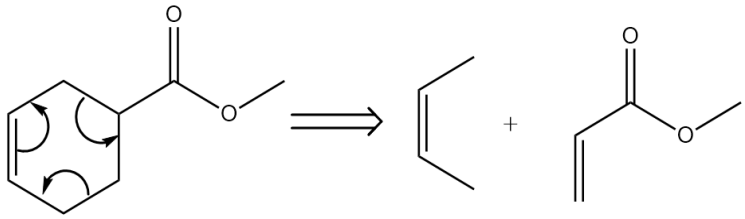

Figure 4. An example of Electrocyclic Disconnection.

2.4.2. Illogical Disconnection. A logical synthesizer that can be formed if the charge interacts favourably with the functional group. In other words, if changes were swapped, synthons would be "illogical" due to adverse interactions. It's used to make new bonds instead of disconnecting bonds, and also it is the one of the most common disconnections in retrosynthetic.

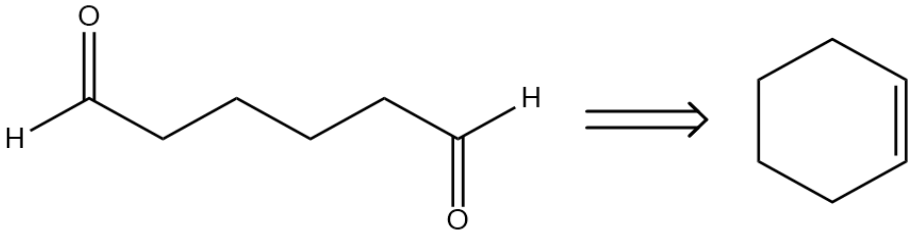

Figure 5. An example of Illogical Disconnection.

2.5. Fine-tuning

Makes a little adjustment to make retrosynthetic easier.

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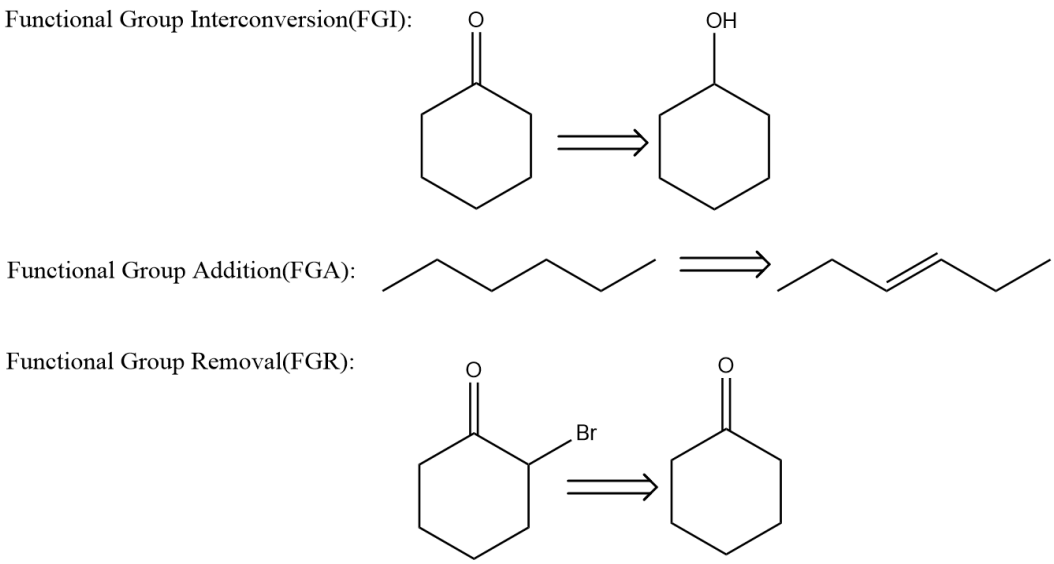

Figure 6. Three ways of fine-tuning.

2.5.1. Functional group interconversion. Trade one functional group with another one, like the figure 1 above, we convert a ketone problem to alcohol, we simplify the problem. This change just changes a tiny part, the main problem is still six member rings.

2.5.2. Functional group Addition. Add something one the compound when you have no idea how to start the problem, like figure 2 above, we have alkan, but no functional groups, so we just add a double bond in the middle.

2.5.3. Functional group removal. If we can't deal with multiple functional groups at the same time, we can choose to get rid of some functional groups to help us disconnect compounds. Like we just clear the bromine from the six member rings at figure 3 above.

2.6. Dioxygenation Patterns

This part is some examples of Dioxygenation Patterns.

2.6.1. Dioxygenation. The classical disconnection for 1,2 dioxygenation is to do interconversion, like the figure below, we take alcohol back to the olefin, because we already know the reaction between these two compounds. So every time when we see a deoxygenation on the jasen carbons, we can immediately consider it's arise from olefin.

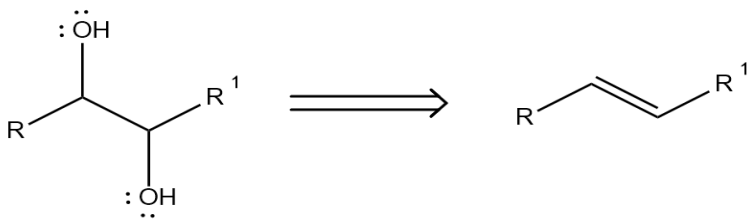

Figure 7. An example of 1,2 Dioxygenation.

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2.6.2. 1,3 Dioxygenation. The disconnection applied on hydroxy dicarboxylic is use hydroxyl and carbonyl concert, we break 2, 3 bonds and it disconnects them to two group.

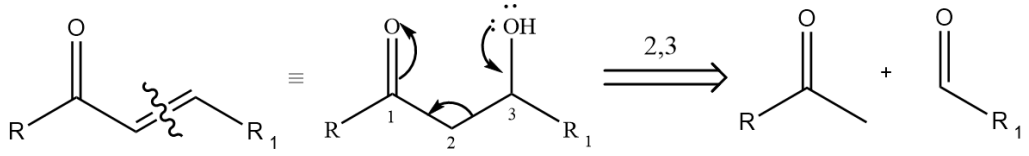

Figure 8. An example of 1,3 Dioxygenation.

2.6.3. 1,4 Dioxygenation. Break 2,3 bond and make treatment carbonyl to be strong base.

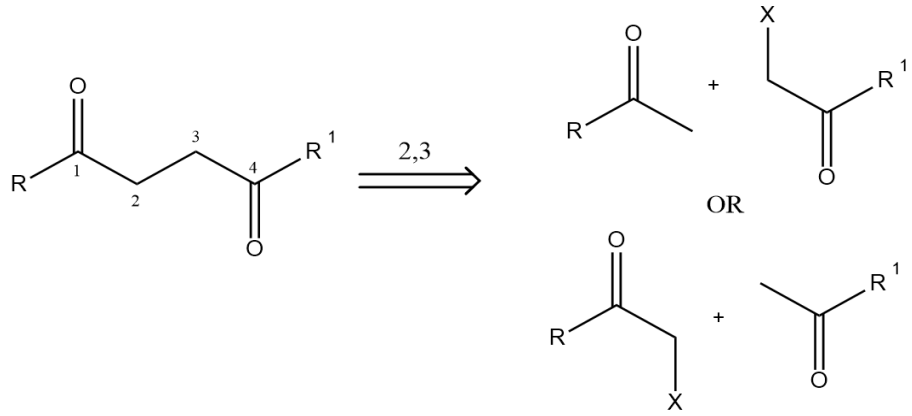

Figure 9. An example of 1,4 Dioxygenation.

2.6.4. 1,5 Dioxygenation. We can break 2,3 bond or 3,4 bond.

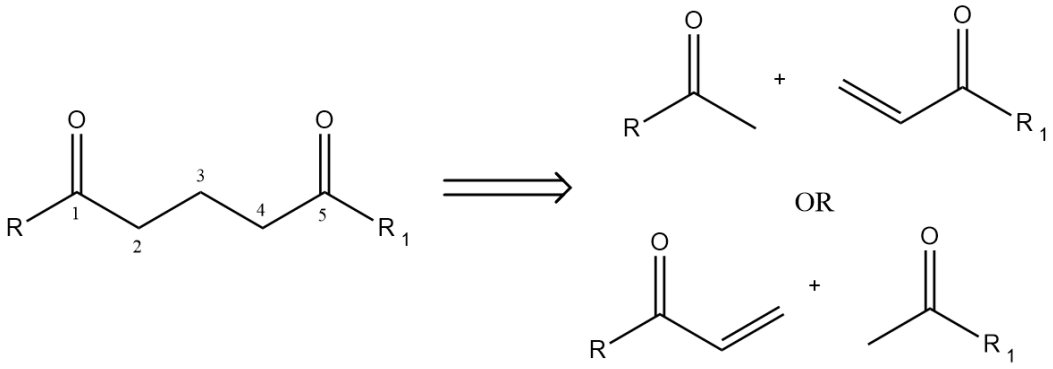

Figure 10. An example of 1,5 Dioxygenation.

2.6.5. 1,6 Dioxygenation. We connect them to a ring just like “illogical disconnection” does. As what Figure 5 shown.

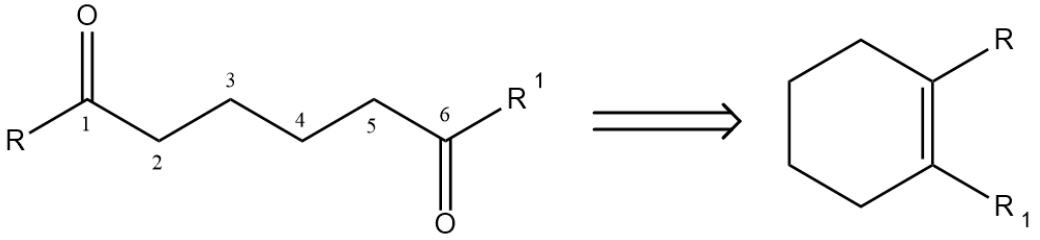

Figure 11. An example of 1,6 Dioxygenation.

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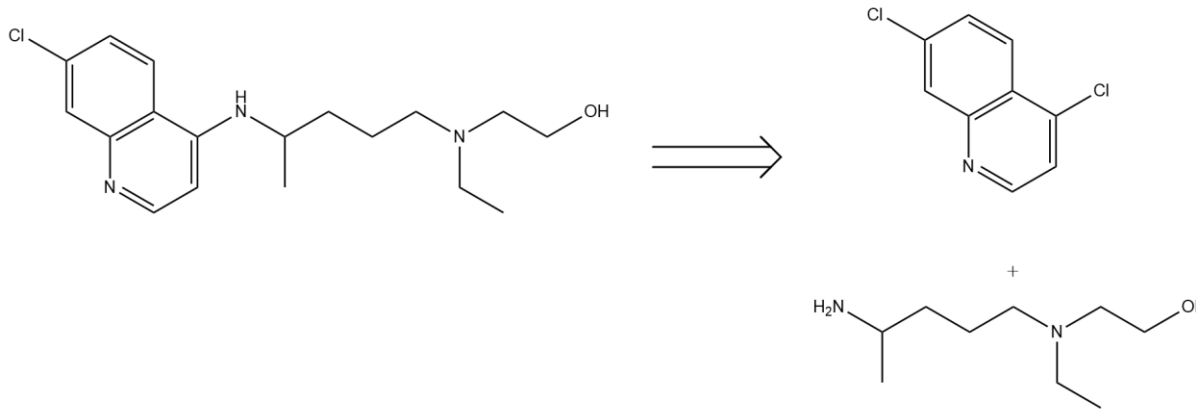

Figure 12. Extension Scheme 1.

When we first look at hydroxychloroquine, the first idea coming up is to detach 7-chloroquinoline from the rest of the complex. So, we break the single bond which connected 7-chloroquinoline and the rest of the complex. The single bond is formed by two electrons, by breaking the single bond, it leaves one to the part of 7-chloroquinoline and one electron to the part of the rest complex, which is the simplest disconnections. To form a stable molecule, we choose a chlorine atom to combine with the free electron on the 7-chloroquine and form a 4,7-dicholoroquinoline. The other free electron on the rest of the complex can connect with a hydrogen atom and create a stable complex, 2-[(4-Aminopentyl) ethylamino] ethanol. This process is our hypothesis to retrosynthetic hydroxychloroquine.

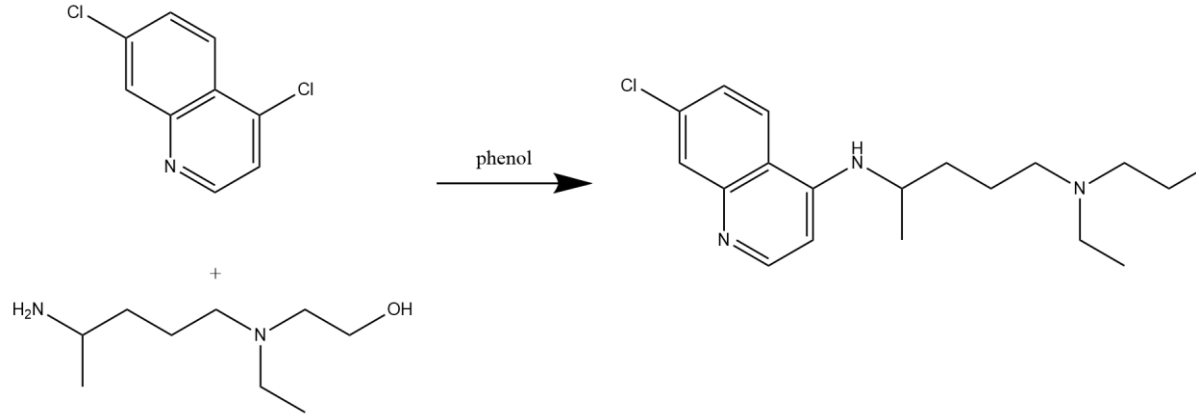

Figure 13. Method A.

To prove our hypothesis of retrosynthetic hydroxychloroquine, we use existing forward reactions to show that Scheme 1 is feasible. Method A used the exact same mechanism with Scheme 1, which was patented in 1951, with patent number US2546658 by Sterling Durg Inc., which is one of the first ways to synthetic hydroxychloroquine. Method A uses 4,7-dicholoroquinoline and 2-[(4-Aminopentyl) ethylamino]ethanol as reactants, as Scheme 1 predicted. And both of the reactants are easy to obtain. However, this Method A is too complicated for mass production, and it takes too many steps to synthesis hydroxychloroquine. Overall, the entire reaction time is more than four days. Even so, the yield of this reaction is poor, which is lower than 20%. Furthermore, the reaction used phenol as the solvent in the synthesis process. Phenol is a toxic substance. 50-500mg/kg of phenol is lethal to humans, which makes disposal of waste solution contention with phenol a very serious problem. But Method A proved that Scheme 1 is feasible.

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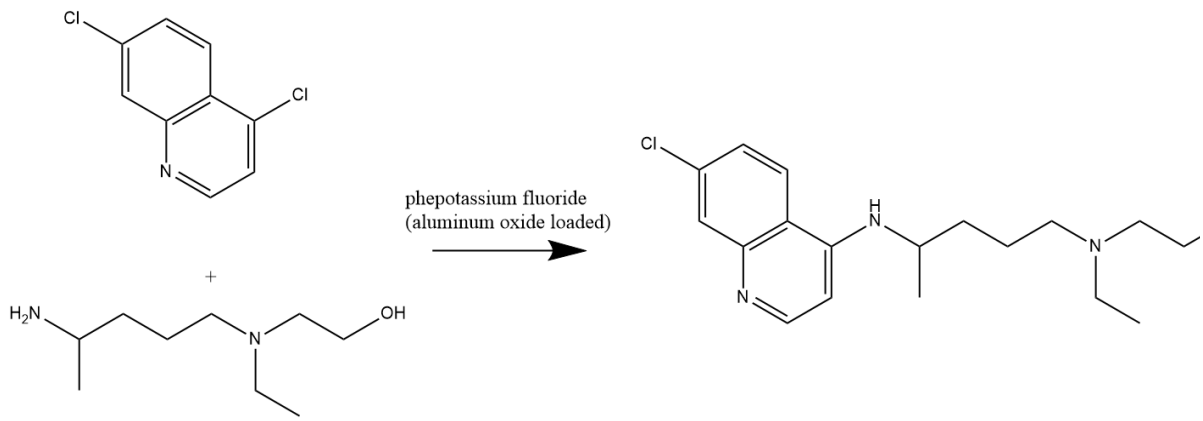

Figure 14. Method B.

There are many improvements developed from Method A and based on retrosynthetic hydroxychloroquine from Scheme 1. For example, Method B is a more efficient reaction compared to Method A, in which both reactions have the same mechanism. Method B is from patent CN109456266 and was published in March 2019. Method B uses potassium fluoride (aluminum oxide loaded) as the catalyst, and the reactant is protected by inert gas. The reaction yield of hydroxychloroquine of Method B is more than 90%, so Method B is an excellent reaction. The improvement on Method B mainly focuses on lowering the cost of the reaction and adapting the reaction for mass production. The reaction reduced the types of organic solvents used, which lowered the cost and made the reaction more environmentally friendly at the same time. Potassium fluoride, as the catalyst, is considerably less toxic. Method B has fewer steps than Method A, which means less time is needed to produce hydroxychloroquine. Furthermore, all steps are processed under normal pressure during the entire reaction, which makes the reaction much easier since it does not require specific conditions. All those improvements made the reaction more suitable for mass production.

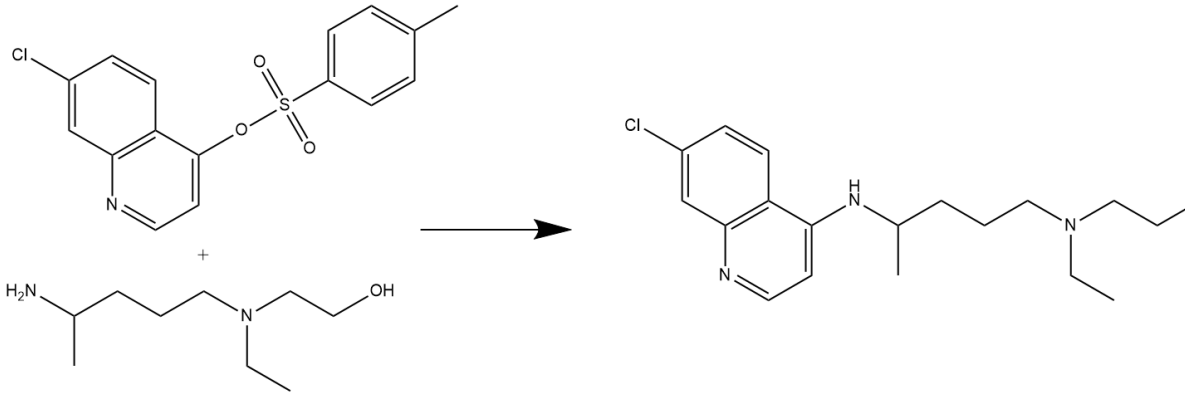

Figure 15. Method C.

Method C used the same mechanism as Method A and Method B. In Method C, the reaction use 4-Quinolinol, 7-chloro-, 4-(4-methylbenzenesulfonate), and 2-[(4-Aminopentyl) ethylamino] ethanol as the reactant. 4-Quinolinol, 7-chloro-, 4-(4-methylbenzenesulfonate) is very similar with 4,7-dicholoroquinoline, instead of connecting a single chlorine atom, as Method A and Method B did. Method C connect p-Toluenesulfonate to the part of 7-chloroquinoline. By using 4-Quinolinol, 7-chloro-, 4-(4-methylbenzenesulfonate), Method C lowered the temperature of the reaction to 95 °C, which is 25 °C lower than Method B. In mass production, lower temperature means the reaction can be processed in a safer condition, making mass production much more accessible. Also, method C

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decreased the time of the reaction. By reducing production time, the cost of production can be lower simultaneously.

3. Conclusion

In this paper, we simply tell the concept of retrosynthetic analysis, also known as the disconnection approach, is the most basic and commonly used method for organic synthesis route design. Retrosynthetic analysis is a reversible logical thinking method. It starts from analyzing the chemical structure of the target molecule, and according to the characteristics of the connection mode (chemical bond) between the atoms in the molecule, comprehensively uses the knowledge of organic chemical reaction methods and reaction mechanisms to select The appropriate chemical bonds are cut to convert the target molecule into some slightly smaller intermediates; these intermediates are used as new target molecules, and they are cut into smaller intermediates until a starting material that can be easily purchased is found. . It starts from the molecular structure of the synthetic product and adopts the analysis method of "cutting a chemical bond" to obtain the required synthetic raw material (synthon).

Retrosynthesis gives us the inspiration of how a molecular can be synthesis. Hydroxychloroquine can be easily broken into two parts. Based on that model, lots of experiment and improvement was done to increase the yield and make mass production more accessible.

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