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Editorial

Retrosynthesis Strategy in Organic Chemistry

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ABSTRACT: Retrosynthetic analysis represents a cornerstone of modern organic synthesis, providing a rational and highly systematic framework for the design and planning of complex molecular architectures. This strategy involves the stepwise disconnection of a target molecule into progressively simpler intermediates and ultimately into commercially available or readily accessible starting materials. By focusing on strategic bond disconnections and functional group interconversions, retrosynthesis facilitates the identification of key synthetic transformations, allowing chemists to navigate backward from the desired product to a feasible synthetic route. The integration of this methodology enables the optimization of reaction sequences in terms of step economy, atom economy, stereoselectivity, and overall synthetic efficiency. Furthermore, retrosynthetic planning is indispensable in the synthesis of biologically active compounds, natural products, and pharmaceutical agents, where the construction of complex frameworks demands both creativity and precision. As such, retrosynthesis not only streamlines the synthetic process but also enhances the reliability, scalability, and reproducibility of organic synthesis, making it an essential tool in both academic research and industrial applications.

KEYWORDS: Biologically; organic; disconnections; molecule; precision

1. INTRODUCTION

The synthesis of complex molecules requires a thorough knowledge of the reactions that form carbon-carbon bonds, as well as those that convert one functional group to another. Most chemical reactions used in synthesis involve the manipulation of functional groups. Furthermore, the synthesis of a molecule is rarely successful unless all aspects of chemical reactivity, functional group interactions, conformation, and stereochemistry are well understood.

Today, the term organic synthesis encompasses a wide variety of chemical reactions. Planning and using organic transformations to construct a molecule is certainly an important aspect of organic synthesis. A thorough understanding of the many organic reactions, reagents, and chemical transformations now known is necessary to achieve this goal. As mentioned, the practice of organic synthesis requires an understanding of the chirality and stereochemistry of molecules, both for developing synthetic strategies and for selecting the reactions and reagents used for the various chemical transformations. The conformational analysis of each molecule, from the starting material to the final product, must be understood because chemical reactivity and stereochemistry are often influenced by conformation (Fawwaz et al., 2024).

The most important component in planning an organic synthesis is a thorough and in-depth knowledge of the chemical reactions and reagents. If one knows only one reagent for converting an alcohol to a ketone, and if that reagent does not work for a particular system, then there is no alternative. On the other hand, if one knows 30 different reagents for that transformation, there are many alternatives if one does not work. Perhaps more importantly, knowing the 30 reagents allows one to better plan a synthesis, using the particular reagent that maximizes the likelihood that the synthetic sequence will proceed as planned. The same is true for carbon-carbon bond formation. Presumably, a synthesis begins with a starting material consisting of a few carbon atoms, and reactions add carbon fragments to increase the complexity of the molecule as it is transformed in many steps toward the final target. Therefore, it is important to understand the various reactions and reagents that form the various types of carbon-carbon bonds (Fawwaz, 2023).

Changing one functional group to another is defined as functional group interchange (FGI). Simple examples are the SN2 reaction of 3-bromopentane with the nucleophilic cyanide ion NaCN to form 2-ethylbutanenitrile, and the E2 reaction of 2-bromo-2-methylpentane by reaction with the base KOH to produce 2-methylpentan-2-ene (**Figure 1**). The first transformation converts the halide to a cyano group (alkyl halide to nitrile), while the second transformation converts the halide to an alkene (alkyl halide to alkene). These functional group interchange reactions are important because they can combine the primary function into the final target, but are also used to "prepare" the molecule to make carbon-carbon bonds (DMF = N,N-dimethylformamide) (Smith, 2017).

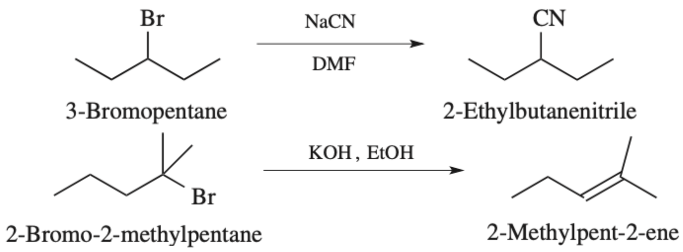

Figure 1. Functional group interchange model

2. RETROSYNTHESIS

Retrosynthesis is an approach used to design a pathway for the synthesis of organic compounds by reversing the synthesis process. In other words, in retrosynthesis, we start with a target compound and try to reverse the reaction to determine the starting materials and steps required to synthesize the compound. Retrosynthetic analysis rarely correlates with an exact reverse pathway with simple reagents to synthesize the target. For molecules with multiple functions, especially complex natural products, the idea of performing a retrosynthetic analysis and simply providing reagents for each cleavage to convert the starting material to the target is usually problematic. Certain cleavages may not be possible unless the functional group is changed or modified. Typically, there are steps that do not work using available reagents or those suggested by the literature. In addition, reactions may give poor results or incorrect stereochemistry. There may also be unexpected functional group interactions and unexpected requirements for protecting groups.

Understanding retrosynthesis is essential in drug synthesis because it allows researchers to design efficient and effective synthesis pathways, starting from the desired drug compound to simpler starting materials. Retrosynthesis involves analyzing the structure of the target compound by breaking it down into smaller, simpler components. Here are some reasons why retrosynthesis is important in drug synthesis (Fawwaz, 2023):

a. Efficient Synthesis Design

   By understanding retrosynthesis, chemists can design more efficient synthesis pathways, eliminating unnecessary steps and avoiding unwanted reactions. This is essential to save time and money in the production of drug compounds.

b. Estimating Starting Material Sources

   Retrosynthesis helps in identifying cheaper and more readily available chemicals that can be used to produce drug compounds. This is especially important for larger scale production, where the availability of raw materials is a concern.

c. Increasing Synthesis Success

   By understanding retrosynthesis, chemists can predict the reactions that may occur during synthesis and avoid potential problems such as the formation of byproducts or uncontrolled reactions. This increases the likelihood of a cleaner and higher-quality drug synthesis.

d. Supporting New Drug Discovery

   In drug development, newly discovered drug compounds often have complex structures. Understanding retrosynthesis allows researchers to design synthetic routes for these compounds, even when they are first discovered in nature or in combination with other compounds.

e. Optimization of Synthesis Pathways

   The retrosynthesis process provides insight into how to optimize synthesis pathways, both in terms of high reaction yields and waste reduction or the use of environmentally friendly solvents. This is very important in the development of drugs that are not only effective but also environmentally friendly.

f. Development of New Synthesis Methods

   Understanding retrosynthesis can also spur innovation in developing new synthesis methods or improvements to existing methods, which may be faster, cheaper, and more efficient. Overall, retrosynthesis is an important tool in the synthesis of drug compounds because it facilitates a more targeted, efficient, and cost-effective synthesis design and execution process, which ultimately contributes to the discovery and development of better new drugs.

3. STEPS OF RETROSYNTHESIS

To begin the synthesis of an organic compound, the first step is to identify the target compound, which refers to the final molecule intended for production. Once identified, a structural analysis of the target compound is carried out to examine its molecular framework and determine which parts can be broken down into simpler, more accessible components. This is followed by the process of retrosynthesis, in which the structure of the target molecule is systematically deconstructed into potential precursors or starting materials. The goal of retrosynthesis is to trace a logical and feasible pathway backward from the final product to readily available or easily synthesized building blocks.

Based on the retrosynthetic analysis, the next step is to select the most efficient and practical synthetic route. This route should be optimized for yield, selectivity, and feasibility in terms of laboratory conditions and available reagents. For instance, in the synthesis of acetylsalicylic acid (aspirin), retrosynthetic analysis involves breaking the molecule down into salicylic acid and acetic acid, followed by the design of a chemical reaction that effectively links these two components.

An example of such an approach is illustrated in **Figure 2**, which presents a synthetic scheme developed using the principles of disconnection and retrosynthesis. The scheme outlines a multistep reaction sequence, with each stage carefully validated and analyzed using modern instrumental techniques. The successful formation of the target compound confirms the effectiveness and reliability of the selected retrosynthetic strategy (Fawwaz et al., 2020).

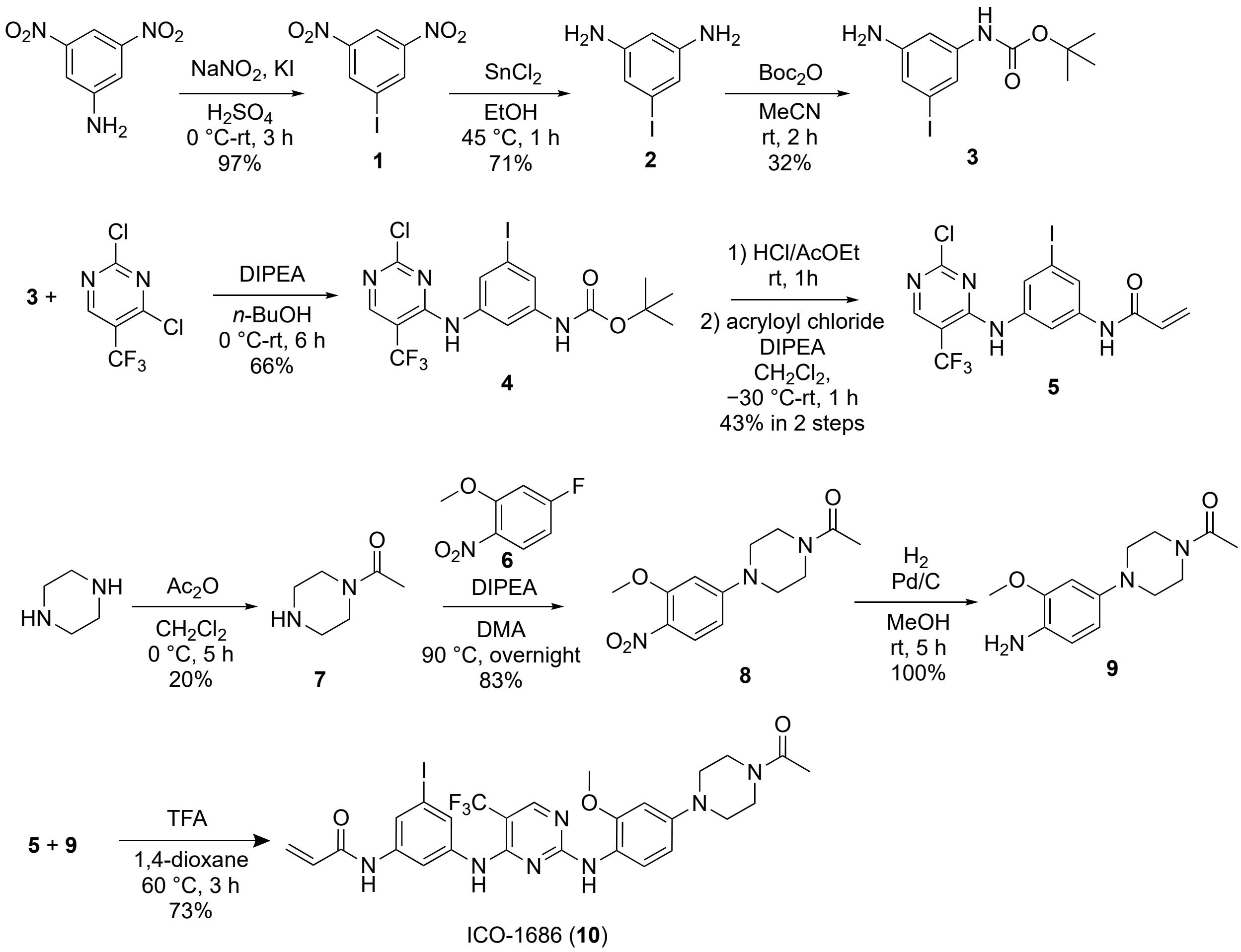

Figure 2. Synthesis scheme of iodinated rociletinib analogue

4. CONCLUSION

Retrosynthetic strategy plays a crucial role in organic chemistry by providing a logical and systematic approach to designing the synthesis of complex molecules. It involves breaking down a target compound into simpler starting materials through a step-by-step analysis known as retrosynthetic analysis. This strategy enables chemists to identify key disconnections, select efficient synthetic pathways, and optimize reaction conditions. By focusing on molecular structure and functional group transformations, retrosynthesis enables the development of practical, cost-effective, and scalable routes for compound synthesis. It is especially valuable in the synthesis of pharmaceuticals, natural products, and advanced materials, where precision and efficiency are essential. Overall, retrosynthetic planning is a foundational tool that enhances creativity, problem-solving, and success in modern organic synthesis.

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REFERENCES

Fawwaz, M. (2023). *Strategi Sintesis Senyawa Organik*. Penerbit NEM.

Fawwaz, M., Mishiro, K., Arwansyah, A., Nishii, R., & Ogawa, K. (2024). Synthesis and initial in vitro evaluation of olmutinib derivatives as prospective imaging probe for non-small cell lung cancer. *Bioimpacts, 14*(1), 27774. https://doi.org/10.34172/bi.2023.27774

Fawwaz, M., Mishiro, K., Nishii, R., Sawazaki, I., Shiba, K., Kinuya, S., & Ogawa, K. (2020). Synthesis and Fundamental Evaluation of Radioiodinated Rociletinib (CO-1686) as a Probe to Lung Cancer with L858R/T790M Mutations of Epidermal Growth Factor Receptor (EGFR). *Molecules, 25*(12), 2914. https://www.mdpi.com/1420-3049/25/12/2914

Smith, M. B. (2017). *Organic Synthesis* (Fourth Edition ed.). Academic Press by Elsivier.