The 2nd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/4/20220666

Formal Synthesis of Morphine Backbone and Its Possible Improvements

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Abstract. Intramolecular interactions between molecules have been reported as the most efficient way of synthesizing morphine molecules. A total of nine-step synthesis using intramolecular cycloaddition, also known as Diels-Alder reaction, has been so far the most successful way of synthesizing morphine. Tandem radical cyclization has also been proved to be efficient. Although both reactions are simple, they might be affected by stereochemistry. Thid paper proposes some possible ways of improving such intramolecular interactions.

Keywords: morphine, Suzuki coupling, Diels-alder reaction, tandem radical cyclization

1. Introduction

1.1. Background of morphine synthesis

Morphine is a widely used analgesic drug isolated from opium. Morphine molecules consist of five rings and are restricted by steric effects. In the twentieth century, morphine was converted from an O-methylated morphine, a common ingredient of opium poppy. This isolation method has a 90% conversion between morphine and codeine. However, when morphine was restricted or inhibited worldwide, a synthesis route was needed. Because of its complex structure, synthesis of morphine with high yield and purity is one of the most difficult challenges for scientists. In the twentieth century, synthesis of morphine involved thirteen steps that could cause a lower yield. During the process of synthesis, availability of starting materials, prices, number of steps needed, and stereochemistry should be considered. Key steps in the synthesis of morphine involve preparing starting cyclic compounds that are commercially available, cyclization reactions that can form basic structures of morphine rings, and ring closing steps and ring completion steps by deprotecting certain groups.

1.2. Property of morphine

Morphine consists of five rings and aromatic groups which are asymmetrically arranged throughout space. Its chemical properties are controlled by both functional groups as well as their stereochemistry. Fig.1 shows the basic structure of morphine. A morphine molecule contains a phenol group, an aromatic ring, an ether group, and an amine. The presence of such polar functional groups generates steric effects that make the synthesis process difficult. In modern days, Tandem radical cyclization strategy, along with Heck coupling reaction, is regarded as one of the most important steps in forming the key structure of morphine.

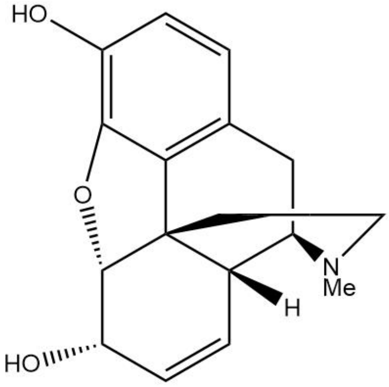

Figure 1. Structure of morphine [1].

1.3. Key methods for morphien synthesis

Nowadays, main improvements of morphine synthesis include increasing yield, minimizing steps, and modifying backbone structure of morphine. Throughout history, morphine became available for synthetic chemistry and did not have to depend on natural products. Also, morphine synthesis was reduced from more than 20 steps to nine steps with a higher yield [2]. Today, we will keep discovering possible ways of modifying structures and making it more pure and commercially available by controlling its conditions and structures.

2. Background of tandem cyclization, Diels-alder reaction, and Suzuki coupling

2.1. Tandem cyclization strategy and its application in morphine synthesis

Tandem radical cyclization strategy is a series of reactions in which each reaction is based on the previous product. Therefore, within tandem reaction, isolation of intermediate is not required, and therefore the condition of each step remains the same. In the context of morphine synthesis, the basic structure is formed within 3 steps with a high yield (71%) during intramolecular tandem reaction shown in Fig 2.a [3]. Within these steps, intramolecular forces will break double bonds and form C rings itself. After proper workup steps, fundamental structures of morphine can be obtained with high yield. Such radical cyclization can also be extended throughout other steps of morphine synthesis. When workup steps are prohibited, the remaining electron will keep attacking double bonds to form new rings shown in Fig 2.b. Even though such a cyclization method can be restricted by steric effects, certain substituents can be found to make the reaction sterically favorable.

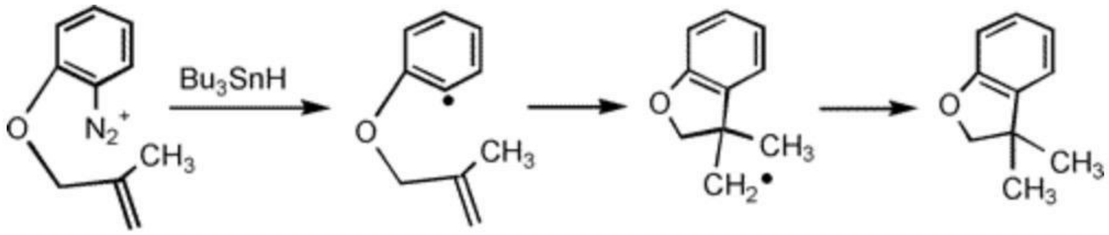

Figure 2. a. Basic mechanism of Tandem radical cyclization strategies [3].

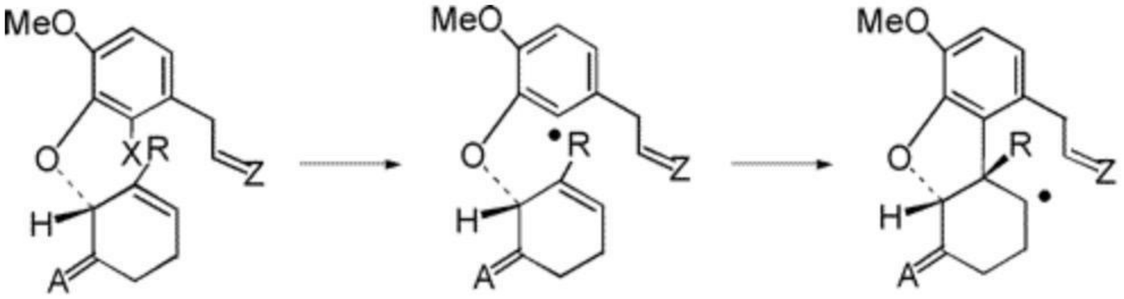

Figure 2. b. Extension of Tandem radical cyclization [4].

2.2. Diels-alder reaction and its application in morphine synthesis

4+2 cycloaddition, also known as Diels-Alder addition, utilizes intramolecular interactions to form carbon rings [5]. As illustrated in Fig 3.a, a Diels-Alder reaction can form two C rings at the same time, which saves a few steps compared to normal cyclization methods. Because the substrates go through intramolecular interactions, the experimental results end up with 73% percent yield in average [4]. Also, an acceleration of reaction rate is reported due to an addition of bromine atoms and decrease in exothermicity. However, such intramolecular reactions might be restricted by steric controls and decreasing aromaticity. In the context of 4+2 cycloaddition, synthesis of the essential structure of morphine from 1 and 2 have been proved to be problematic. Since Diels-Alder reactions do not have steric controls, one will get a 1:1 ratio of endo/exo products. In this case, PTSA was induced under 160 degree Celsius to get the desired stereochemistry for further synthesis to receive a 21% yield [4].

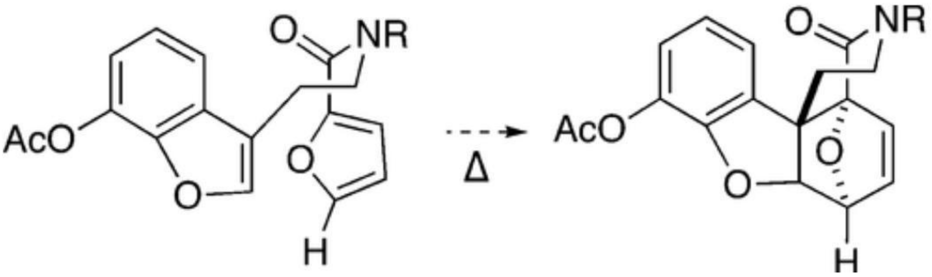

Figure 3. 4+2 cycloaddition of morphine structure [4].

2.3. Basic mechanism of Suzuki coupling and its reactivity in morphine synthesis

Suziki coupling, also know as Plladium-catalyzed reaction, is famous for its reaction rate, relatively simple conditions, and even its possibilities of combining two stericlly hindered groups together. To start with, similar to both Tandem cyclization and 4+2 cycloaddtion, the use of Suzuki coupling can avoid side products and have a less strict condition for chemical reactions. A halogen group (usually bromine) is added to one of the molecule to form a halogen compound. This new molecule is then hydrolized by reacting with a strong base (NaOH). Such process enables the new molecule to further react with Boronic acid and finish the reaction cycle. As shown in Fig 2.c, ring closing process can also be btained by using Suzuki coupling. In this reaction cycle, a ring is closed by by simple oxidative addtion, transmetallation, and reductive elimination. Such steps only require conditions similar to room temperature, and are almost spontaneous reactions, thus giving a faster rate and a more complete reaction. In this case, when the designed reaction has a lower energy barrier, the reaction might go complete, resulting in a higher percent yield in the product. In the reaction of 1,2,7 triene as shown in Fig 3.c, the data reported that the final yield in percentage is 95% and it is independent from the stric effect of chemical groups at the end of the molecule [6]. Bulky as it may be, the percent yield in this ring closing reactions depends only on the electronegativity of halogen atom on the starting molecule [7].

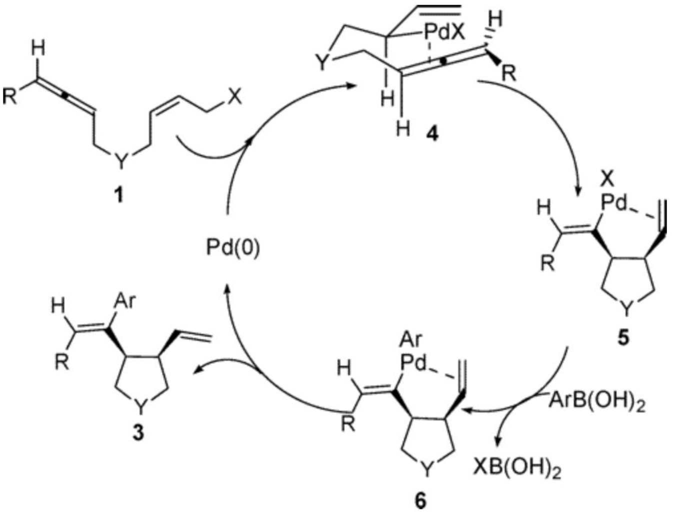

Figure 2. c. Basic mechanism of Palladium-catalyzed reaction in the context of ring closing reactions [6].

3. Discussion

3.1. Problems with existing methods of morphine synthesis

In the context of morphine synthesis, difficulties in forming the main ring structure of morphine due to steric effect and lack of economic procedures will limit the development of such substances. In this case, tandem cyclization strategies and Diels-Alder reactions are introduced. A tandem cyclization is regarded as an effective way of forming C rings of benzene because it utilizes intramolecular interactions, which minimize the loss of final product. The experimental results show that intramolecular tandem cyclization have a high yield (81%) because the former product is directly used in the subsequent reactions without participation of any other substances [3]. When tandem cyclization takes place, a radical form between starting materials is available, and such interactions will follow a 1:1 reaction. This line of reactions has a higher reaction rate and will have a relatively easier control over the conditions of each reaction. Also, tandem cyclization is stereospecific, indicating that we only have to control the stereochemistry of starting materials. The subsequent reactions will follow the same stereochemistry when proceeding the reaction, which makes the condition of molecules extremely easy to control. In addition, without the steps of separating endo/exo mixtures, one will expect a higher yield of the final product. However, the final product still has a low yield because of 13 steps throughout synthesis.

3.2. Improvements and limitations of current methods

An improvement to Tandem cyclization strategies is the use of 4+2 cycloaddition, also known as Diels-Alder reaction. Compared with Tandem cyclization, a 4+2 cycloaddition in morphine synthesis also utilizes intramolecular interactions to form 6–carbon rings as shown in Fig1. Because starting materials of Diels Alder reaction follow a 1:1 ratio during reaction, the former product of the morphine structure can be directly used in following steps of synthesis. Despite the similarities, Diels-Alder reaction in morphine synthesis is regarded as a faster and more efficient way of morphine synthesis. Throughout the formation of the morphine backbone, the reaction rate of Diels-Alder reaction is accelerated due to its decreased exothermicity. Also, when the energy barrier is low enough, a cascade reaction will be obtained since the energy required for each cycloaddition reaction is low (Fig.3). Although Tandem radical cyclization has the same cascade ring-forming steps, 4+2 cycloadditions allow rings to be formed without any intermediates and can allow the synthesis of two rings at the same time. And such interactions can decrease morphine synthesis to only 9 steps. However, Diels-Alder reaction is not stereospecific. A 1:1 ratio of endo/exo products is not desired for the final product of morphine. Instead, we may raise the temperature while treating the starting material with PTSA.

3.3. Possible improvements for synthetic methods

However, even though Diels-alder reactions can reduce the total synthesis of morphine to only nine steps, final yield of both strategies are low. Therefore, minimizing steps of reaction might still be needed. One way of shortening steps can be the use of Suzuki coupling or heck reactions [8]. Heck reaction is the reaction between vinyl halides (or alkyl halide) and alkene under basic conditions [9]. In the context of morphine synthesis, since carbon backbones are aromatic and thus can become good starting materials for morphine synthesis. Comparing to traditional intramolecular interactions, the use suzuki coupling does not require harsh reaction conditions, and its final yield is significantly higher than older methods (95% in comparison to 73%). This comparison reports that the use of catalyze is more likely to complete the reaction, thus generating more products. This makes suzuki coupling a better reaction for morphine because we can avoid the loss of products greatly by applying Suzuki coupling in ring closing steps of morphine synthesis. In comparison, final yields in intramolecular cyclization reactions are restricted by the relatively high energy barrier of the reactions and its incomplete interactions between two ends of the molecule. Such problems can be solved by the utilizations of suzuki coupling.

Another major difficulty that makes intramolecular cyclization problematic is the steric effect. Morphine is constructed by five rings either stacked or firmly connected to each other. Therefore, if the starting material is too bulky, the reaction might be stopped because the energy barrier would be too high to stabilize the intermediate.

In contrast, the suzuki coupling can possibly bypass such difficulty. In the ring closing step, the final yield of Palladium catalyzed reaction is only related to the electronegativity of halogen group in the starting material. This could be reasonably applied in the ring closing step in morphine synthesis [7]. Steric hinderance is mostly due to the high energy required in the form of certain conformations, thus restricting certain structures of reaction. However, in Pd-catalyzed reaction, the activation energy was first lowered by the presence of palladium during reaction cycle, and was then replaced to a relatively high value after catalyzation [6]. Even though the new structure has a relatively high energy and might become unstable, the high energy barrier would prevent the reverse reaction from emerging even though such reaction is strongly favored by reverse reaction [10]. However, the example of bypassing steric effect by applying suzuki coupling is problematic and stays only at theoretical level. Future studies and experiments are required to further test the validity of bypassing steric effect by using suzuki coupling.

4. Conclusion

In conclusion, the use of Aiels-Alder reaction and Tandem cyclization strategies do make morphine synthesis easier and accessible. Compared with traditional synthesis methods, a 23-step process that includes greater amounts of alkylation, the use of intramolecular cycloaddition can decrease steps needed greatly. However, the lack of efficiency in yield remain unsolved. Possible ways of improving yield might be the control over reaction steps and conditions. Another way of improving efficiency of ring closing is the use of palladium-catalyzed reaction. Effective as it may be, the steric hinderance in a complex molecule such as morphine molecule is still problematic, and we only manage to solve this problem in a theoretical level. However, what is promising is that we need to apply catalyst in the process of morphine synthesis in order to increase its percent yield and bypass steric effects from complex molecule/ Future improvements might include a simplified route and more commercial starting materials. Also, more experiments on verifying the validity of suzuki coupling in the context of morphine synthesis should be required. Also, despite of suzuki coupling, the emergence of click chemistry in bio orthogonal chemistry also seems promising. Such methodologies shed light on morphine related drug synthesis and could provide insights on solving energy differences in the process of ring closing steps.

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