

A Proposal for the Synthesis Route of Lyaline

Shuang Wu^{1*}, Xu Han² and Jiedong Li³

¹*Xiwai International School, Shanghai 201600, China*

²*Shenzhen College of International Education, Shenzhen 518043, China*

³*University of California, Santa Barbara, CA 93106, U.S.A.*

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Abstract: Lyaline is a monoterpene indole alkaloid first isolated in 1974. After attempts of proposing a synthesis route of this compound, researchers found its structure to be unstable and that the proposed structure to be incorrect. Later researchers revised the structure and set lyaline as the first naturally occurring nacycline analogue. While most previous research examine the spectroscopic data of lyaline and came up with a structure, this work assess the possibility of retrosynthesizing this compound and propose a theoretical synthesis pathway for the revised structure of lyaline. Through online research and books, we decided to retrosynthesize this molecule by first separating it into a cyclohexene and an indole. And with 3 starting materials—molecule 1 and 2 presented below, and an indole—it is possible to synthesis lyaline through a series of nucleophilic substitutions and Dials-Alder cyclic addition. This proposal will finally make the molecule of lyaline, though not completed. The following researches can be done by experimenting and resolving the stereoselectivity of the specific Dials-Alder reaction and using a better protection to increase the yield of the amine formation.

1 INTRODUCTION

The molecule lyaline was first isolated from the root of the plant named *Pauridiantha paucinervis*. Its structure was proposed by researchers based on limited spectroscopic data and was later proven incorrect through attempts in retrosynthesizing this compound. Significant difference from the original spectroscopic data and the fragile nature of the synthesized compound indicates that the initially proposed structure was incorrect. Through thorough analysis of the ¹H NMR spectrum by analyzing the peaks produced and through comparison with the array of MIA structural variants, a new structure of lyaline was proposed. Though there is possibility that degradation of the sample analyzed may have occurred, which may invalidate the tests done, experiments have been done to proved the stability of MIA collections. Since most research done on lyaline was examination of the spectroscopic data of the sample containing lyaline, this work aims to propose a synthesis route for the revised the structure of lyaline so that this molecular structure can be synthesized and further test can be carried out to examine its property.

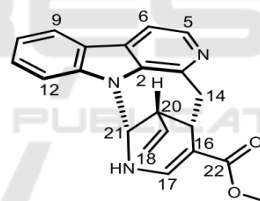


Figure 1: The revised structure of lyaline.

2 GENERAL OUTLINE

As shown in Figure 2, the first step starts with breaking the N-C21 bond and C14-C15 bond to divide the huge molecule into an indole-containing molecule and a cyclohexene containing molecule. Next, a Dials-Alder mechanism to break the cyclohexene into smaller molecules. We believe that the indole containing molecule is purchasable, but in case it cannot, we can synthesize it using a Fischer-Indole mechanism.

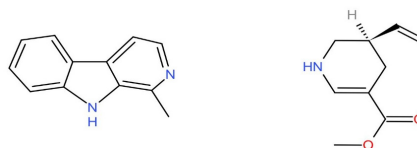


Figure 2: The3 two parts that the original molecule is broken into.

3 METHODS

3.1 Breaking N-C21 Bond and C14-C15 Bond

Upon considering the procedure to connect C-21 and nitrogen in the pentagon, and the connection of C-14 and C-15, the basic logic was to make form the easier bond and then the other bond. This logic allows us to avoid the influence of the problem of choosing the point to connect. This means that with the application of a sequential procedure rather than a spontaneous reaction, we can form the desired bond first.

In this case, the bond between C-21 and that particular nitrogen is considered to be formed through formation of a trisubstituted amine. The reaction starts with the central nitrogen in a substituted indole. We will use a base to deprotonate the nitrogen, producing a nitrogen anion. In the lower part, there are initially two carbons connect with halogens, that are C-21 and C-15. In this case, with the contribution of the lone pair electron from the nearby nitrogen of C-21, the amine formation of C-21 is more likely to perform rather than C-15. The reason is that the lone pair nitrogen is likely to attack C-21 due to the inductive effect of bromine's negativity, which makes C-21 more electropositive. The negatively charged N will then perform a SN2 nucleophilic substitution to connect to C-21, forming the target bond between C-21 and nitrogen in the indole (ABU-SHANAB, 2010).

Attempt to make the C-14, C-15 bond:

With a treatment of a base, a carbon anion could form at C-14 on the indole structure of the upper section. The base deprotonates the methyl group of C-14 and forms a carbon anion. This anion again

performs an SN2 nucleophilic substitution on the electropositive C-15 that is bonded to a Cl. Upon attacking C-15 with the carbon anion and ejecting Cl⁻, the desired C15-C14 bond is formed, so is the desired product (Figure 3).

It is worthy noticing that benefiting from the amine alkylation of the previous step, the strong base added to the reaction in this stage only deprotonates C-14 instead of forming anion on the nitrogen that is to connect with C-21 (Hunt, 2021).

3.2 Breaking the Cyclohexene

To form the cyclohexene, use 2 smaller molecules:

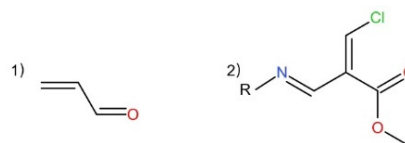


Figure 4: The starting materials to make the cyclohexene.

With the starting ingredients shown in Figure 4, the initializing step here uses a double-bonded O instead of C on molecule 1 because the O can mesomerically withdraw electrons, which makes the left most C more electropositive; the reason why not separate the ester out from part 2 and name it as part 3 is that the ester can also draw electrons toward the O in the ester through resonance, which also helps make C bonded to Cl more electropositive; and connect N to a R-group because it can help stabilize the electrons on N. All of these helps the Diels-Alder reaction proceed (Wilson, 2001; Juhl M, 2009).

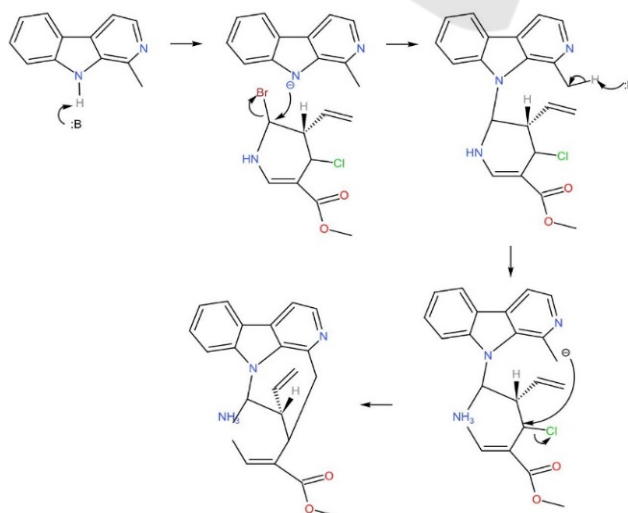


Figure 3: The mechanism for making C-14, C-15 bond.

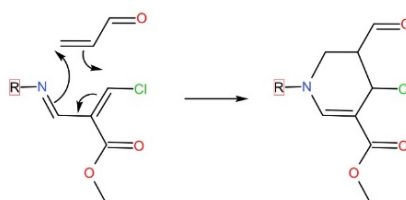


Figure 5: The mechanism for the Diels-Alder reaction to form the cyclohexene.

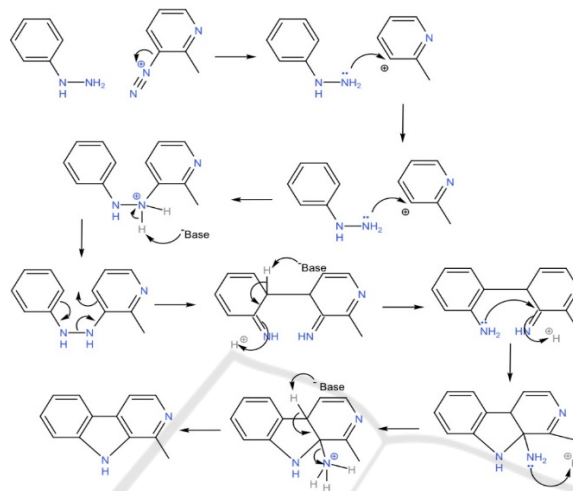


Figure 6: The mechanism for synthesizing the indole using Fischer-Indole Mechanism.

To start synthesis the ring, the electron on N will first attack the carbon connecting to Bromine and start the reaction as shown in Figure 5. The double bond connecting bromine will shift one bond to form new sigma bond with the carbon connecting Chlorine in part 2. Then the double bond near Chlorine will also shift the bond to left to form new double bond. And the double bond originally connecting nitrogen will shift one bond to help form C-N bond and finish to form the final product (Jagora et al., 2021).

After forming the product, change the C=O in molecule 1 back to a C=C using a Wittig mechanism. Unfortunately, there is not a clear way to change the N-R to an N-H in molecule 2, which could be an aim for future research.

So, with molecule 1, molecule 2, and the indole containing molecule as starting materials and with a reliable way to change N-R to NH in molecule 2 after forming the cyclohexene, the above mechanism could be a possible way of synthesizing the molecule lyaline.

3.3 Breaking the Pyradine Structure into Simpler and Easier to Purchase Ingredients

As shown in figure 6, the indole can possibly be

formed with the Fischer-Indole mechanism using the two starting materials shown above and heated in acidic solution. As it is unfavorable to perform an imine formation on a benzene (because benzene is electron dense, it therefore repels the lone pair of electrons on the nucleophile), a N₂ is used. As the N₂ leaves as a gas, it leaves the C it connected to positively charged, which makes it easier for the lone pair on the N of the other starting material to attack.

Then the molecule would perform a [3, 3] sigmatropic rearrangement. This step is favourable because of 2 reasons: 1. From an orbital symmetry perspective, according to the Woodward-Hoffman rules, the reaction is thermally allowed as its total number of (4q+2)s and (4r)a components is odd; 2. From an enthalpy perspective, the original N-N bond has lower bond enthalpy than the new C-C bond while the original C=C has the same bond enthalpy as the new C=N, so the reaction is also enthalpy favoured. The last step is reforming the aromaticity of the benzene, which gives an aminal, then expelling ammonia.

4 CONCLUSIONS

As shown above, the molecule lyaline can possibly be

synthesized through a series of nucleophilic substitutions and Diels-Alder cyclic addition, using the starting materials molecule 1, molecule 2, and the indole. However, most research done in this work are through the internet and books as we were not yet able to experiment on each step of our proposal, thus we could not give the accurate yield of each step at the moment. In future research, we would test this proposal in experimentation and keep making improvements on this synthesis route.

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