Synthesis of 1,1'-Dideaza-Quinine: A Proof of Concept

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Abstract

Quinine is a naturally occurring alkaloid found in the bark of the cinchona tree. Its medicinal relevance cannot be overstated as it is one of the most widely used anti-malarial drugs in the world. While the synthetic pathway to derive quinine is of limited relevance due to its abundance and ease of extraction, the puzzle of engineering reactions to isolate a stereochemically pure product of quinine captivated chemists for generations. The purpose of this study was to prove the conceptual route proposed by Stotter, Friedman, and Minter[1] for the stereochemically pure total synthesis of quinine via a non-nitrogenous analog where the two nitrogen atoms of quinine are substituted with carbon atoms. The product of the analogous route is 1,1'-Dideaza-Quinine. Quinine is stereochemically complex, containing four separate stereocenters, thus the synthesis of quinine opens up the possibility of generating sixteen different isomeric structures. While the total synthesis of quinine with the correct stereochemistry was accomplished in 2001,[2] the proposed route simplifies the process by relying on a stereospecific aldol addition to eliminate potential isomerization.[1] The results of the study are not yet conclusive for the validation of the proposed conceptual route. Future experimentation will occur in order generate the necessary substrate to perform the stereoselective aldol addition reaction. Additionally, due to the analogous nature of the synthetic route utilized, two novel compounds were generated adding to the body of knowledge available to the Chemistry community.

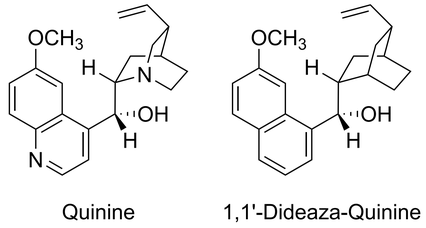

Figure 1. Structures of title compounds

Model System Ongoing Experimentation

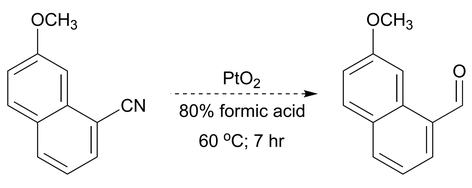

Figure 4. Conversion of nitrile to aldehyde with formic acid and platinum catalyst

Model System Experimentation

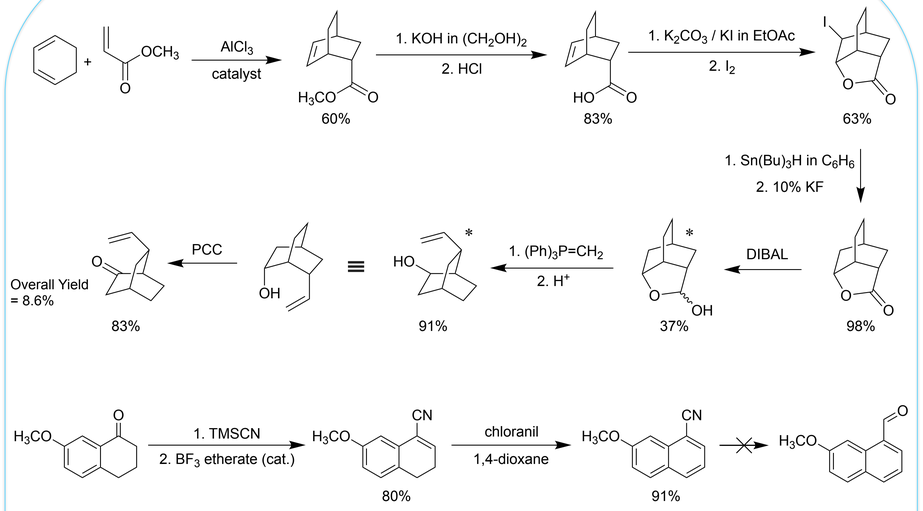

Figure 2. Model System Progress

All reactions were performed on a model system that differed from the target molecule, Quinine, in that the nitrogen atoms of Quinine were substituted with carbons, thereby making the target molecule 1,1'-Dideaza-Quinine. This model system has much more readily available substrates of higher complexity leading to a simpler synthesis of the target molecule which would facilitate the proof of concept much quicker. Future plans for this project include determining a reaction that converts the nitrile to the aldehyde which has not been accomplished as indicated by the crossed out arrow shown above. Yields are reported for all successful transformations. Once proof of concept is determined, experimentation will be done to optimize the yields involved in this pathway.

Model System Future Experimentation

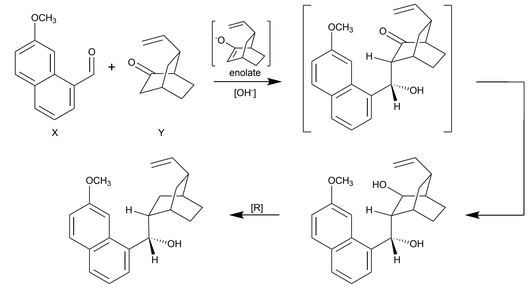

Figure 5. Stereoselective aldol addition reaction for the subsequent reduction to yield 1,1'-Dideaza-Quinine

Once a successful reaction is determined for the conversion of the nitrile to the aldehyde (Compound X), it will be reacted with the ketone (Compound Y), which has already been obtained, in basic solution to result in an aldol addition reaction which will combine both substrates. The product of the reaction has an acidic hydrogen located adjacent to the carbonyl resulting in an epimerizable center and loss of stereochemical control. This issue is alleviated by the quick conversion to the alcohol without isolation of the ketone intermediate in order to remove the epimerizable center. Subsequent reduction of the alcohol will lead to the generation of the target molecule, 1,1'Dideaza-Quinine.

Model System Complications

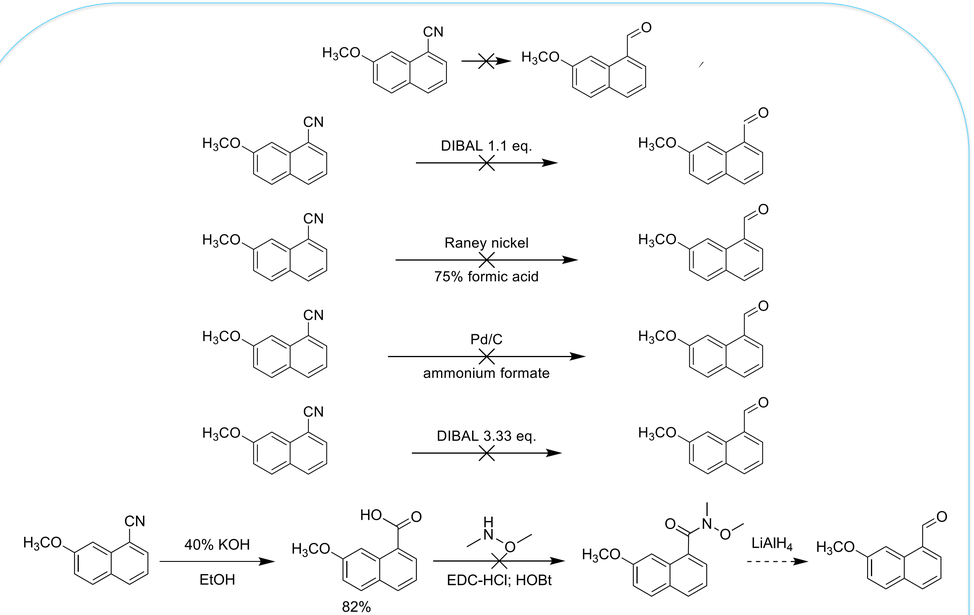

Figure 3. Model System Complications

Our attempts at the conversion of the nitrile to the aldehyde shown above have not yet been successful. The generation of the aldehyde is vital to the synthesis of 1,1'-Dideaza-Quinine because it is one of the two components necessary for the aldol addition reaction shown in Figure 5. As such, a variety of different methods have been employed to produce this molecule, however, none have worked thus far. The most promising route determined experimentally is to first convert the nitrile into a carboxylic acid, then generate the Weinreb amide, and lastly reduce the amide with a hydride source to be left with the aldehyde, as indicated in the last reaction scheme above. Producing the Weinreb amide has also proven difficult, but the reaction will be performed again to ensure this pathway is invalid. Additionally, conversion of the nitrile to the aldehyde is currently being attempted, as shown in Figure 4, using formic acid and a platinum catalyst. While platinum is not cost effective, its efficacy is still worth exploring as most other common nitrile to aldehyde conversions have been attempted.

Conclusions

The aromatic aldehyde, listed as Compound X in Figure 5, has proven to be extremely difficult to produce from the aromatic nitrile precursor, indicated in Figure 3. Without having the aldehyde of interest, the reaction schematic proposed in Figure 5 cannot be carried out. Thus, until the aldehyde, Compound X, is generated, the proof of concept for the stereoselective synthesis of 1,1'-Dideaza-Quinine cannot be completed. Therefore, ongoing and future experimentation will be directed toward finding a viable reaction for the production of the aldehyde and then carrying out the scheme shown in Figure 5. Additionally, along the schematic pathway for the generation of the ketone in Figure 5, Compound Y, two novel compounds were isolated. These two compounds, indicated by an asterisk in Figure 2, will be published and added to the literature of known compounds following combustion analysis and X-ray crystallography.

Acknowledgments

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References

(1) Stotter, P. L.; Friedman, M. D.; Minter, D. E. *J. Org. Chem.* **1985**, *50* (1), 29–31.

(2) Stork, G.; Niu, D.; Fujimoto, R. A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *Journal of the American Chemical Society* **2001**, *123* (35), 3239–3242.