Progress Towards the Synthesis of 4,5-Benzoxepin: Mechanism for Formation of Ring-Opened Metabolites of Cytochrome P450

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Introduction

Naphthalene is a potential carcinogen and an environmental pollutant which is found in crude oils and used in mothballs. In the human body it is metabolized by cytochrome P450 to form naphthalene oxide.

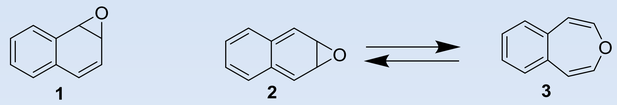
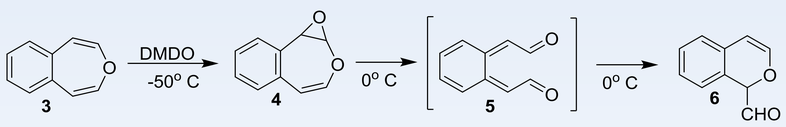


Figure 1. Hypothetical Naphthalene Metabolites

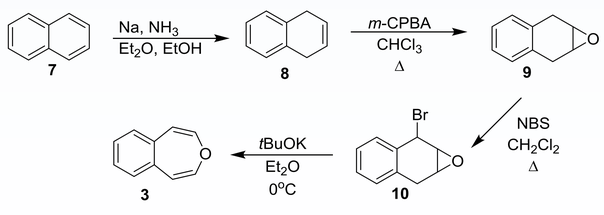
The 1,2 bond in naphthalene is the most reactive and the 1,2-epoxide **1** is formed from the cytochrome P450 metabolism . However, the hypothetical 2,3-epoxide **2** and its oxepin tautomer **3** are useful models in mechanistic studies of naphthalene metabolism.



Scheme 1. Oxidation of 4,5-Benzoxepin with Dimethyl Dioxirane

Experimental Work

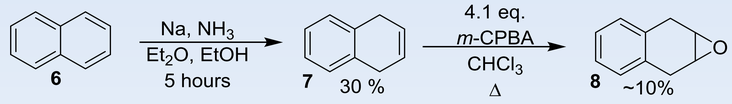
This project worked towards the synthesis of 4,5-dihydro-2,3-epoxynaphthalene **3**. The proposed synthetic route involves a Birch reduction of naphthalene **7** to give the 4,5-dihydronaphthalene **8**. Followed by an epoxidation with *m*-CPBA to give the epoxide **9**. Then a bromination with NBS to give the brominated epoxide **10** and a dehalogenation reaction to give the desired oxepin **3**.



Scheme 2. Proposed Synthetic Route to 4,5-Benzoxepin

Results & Discussion

Naphthalene was reduced via a Birch reduction and both the dihydro and tetrahydro products were formed in a 1:1 ratio with two equivalents of excess starting material. The epoxidation reaction of was attempted twice without purification of **7**. The first attempt produced the epoxide in better yields which was purified via column chromatography. However, not enough epoxide has been isolated to attempt the next reaction.



Scheme 3. Completed Experimental Work Towards Synthesis of 4,5-Benzoxepin

The isolated products were characterized by proton and carbon NMR spectroscopy.

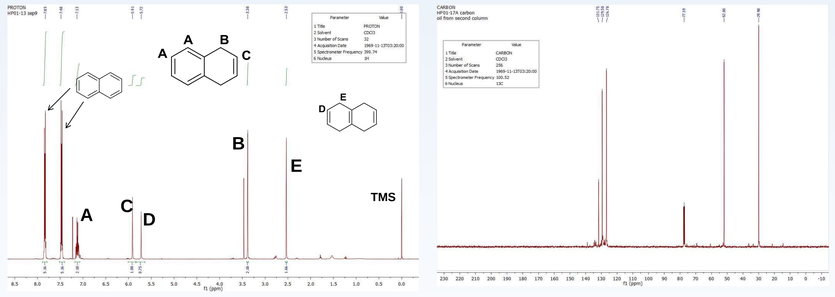


Figure 2. ^{1}H Proton and ^{13}C Carbon NMR Spectra of 4,5-dihydronaphthalene

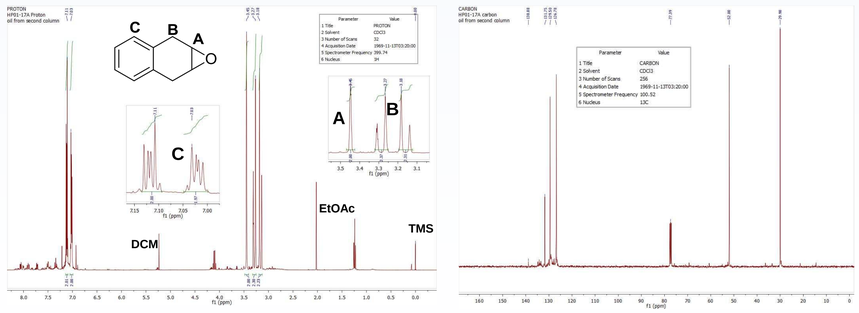
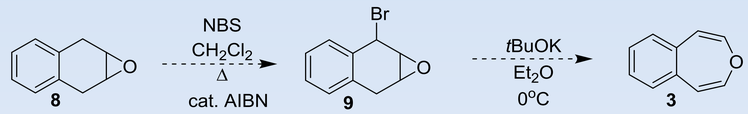


Figure 3. ^{1}H Proton and ^{13}C Carbon NMR Spectra of 4,5-dihydro-2,3-epoxynaphthalene

Future Work

Once more of the 4,5-dihydro-2,3-epoxy naphthalene **8** is isolated, the following reactions will be attempted to complete the synthesis of 4,5-benzoxepin **3**.



Scheme 4. Synthetic Route of 4,5-Benzoxepin

Upon completion of synthesis the 4,5-benzoxepin **3** will be oxidized with dimethyl dioxirane to form the oxidized oxepin **4**. This will be characterized with GC/MS and will be used in enzymatic studies with cytochrome P450.

Conclusions

Progress was made toward the synthesis of 4,5-benzoxepin **3**.

Ethanol is not the best proton source for a Birch Reduction of naphthalene, due to low yields.

Acknowledgements

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References

Harvey, R. G.; *Synthesis*. **1970**, *4*, 161-172

Morgan, J., Greenberg, A., *J. Org. Chem.* **2010,** *75*, 4761-4768

Nauduri, D., Greenberg, A., *Tetrahedron Letters*, **2004,** *45*, 4789-4793

Rabideau, Peter W.; *J. Org Chem.* **1978,** *43*, 4283-4288

Vogel, E. *Angew. Chem. Int. Ed.* **1967,** *6*, 385-401