Trioxaferroquines as Hybrid Antimalarial Drugs
Synthesis and Identification of Trioxaferroquine 8

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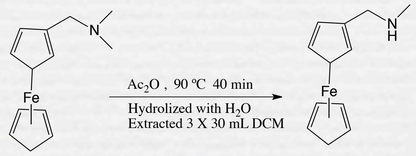
Introduction

The purpose of this experiment was to synthsize one of the trioxaferroquines, trioxaferroquine 8, from aminomethylferrocene and trioxane 6. The trioxaferroquines were used for multi-drug therapy in the 1950's for those first infected with tuberculosis and are still used today for anti-malarial purposes.

Results and Discussion

The first synthesis was the demethylation of N,N-dimethylaminomethylferrocene to methylaminomethylferrocene. This was done by refluxing N,N-dimethylaminomethylferrocene with acetic anhydride then extracting the organic layer.

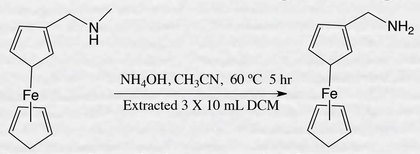


Scheme 1. Demethylation of N,N-dimethylaminomethylferrocene to methylamiomethylferrocene

-Yield 3.501 grams (82.5 %)

-Purity was tested by ^{1}H NMR

The second synthesis was the demethylation of the methylaminomethylferrocene to aminomethylferrocene. This was done by refluxing methylaminomethylferrocene with ammonium hydroxide and acetonitrile then extracting the organic layer.



Scheme 2. Demethylation of methylamiomethylferrocene to aminomethylferrocene

-Yield 0.627 grams (76.4 %)

-Purity was tested by ^{1}H NMR

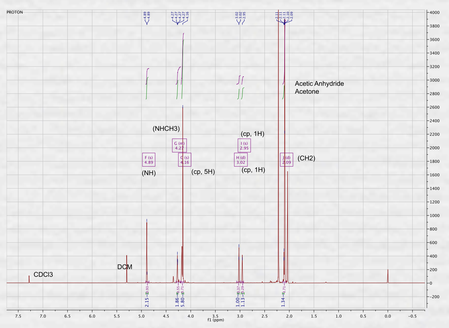


Figure 1. ^{1}H NMR spectrum of the synthesized methylaminomethylferrocene compound.

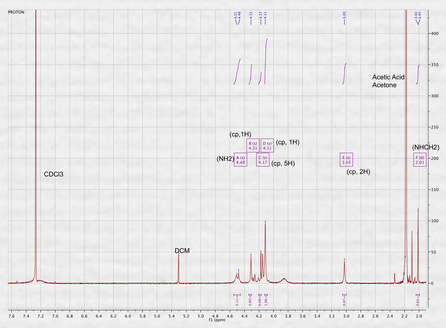
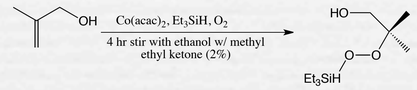


Figure 2. ^{1}H NMR spectrum of the synthesized aminomethylferrocene compound.

The third synthesis was the synthesis of the intermediate of the Trioxane 6 later to be attached to the ferrocene compound. This was done with a stir under oxygen environment for 4 hours.

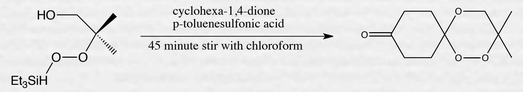


Scheme 3. Synthesis of the trioxane 6 intermediate

-Yield 2.506 grams (25 %) literature yeild of 36 %

-Purity was tested by ^{1}H NMR

The fourth synthesis was the synthesis of the Trioxane 6. This was done by another stir for 45 minutes.



Scheme 4. Synthesis of the trioxane 6

- Purified by column chromatography with ethyl acetate/hexanes 50:50

-Yield 0.050 grams (5.6 %) literature yeild of 57 %

-Purity was tested by ^{1}H NMR -H NMR (400 MHz, CDCl3): δ = 3.79 and 3.52 (2 br. s, 2 H, O-CH2), 2.70-1.95 (m, 8 H, Hcyclohexanone), 1.53 and 1.13 (2 br. s, 6 H, 2 CH3) ppm

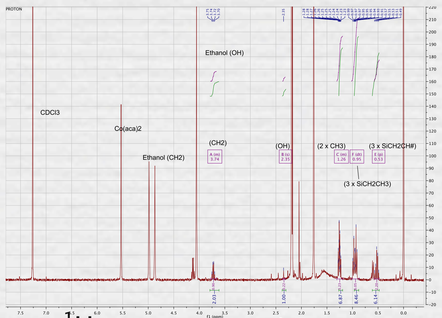


Figure 3. ^{1}H NMR spectrum of the synthesized trioxane 6 intermediate compound.

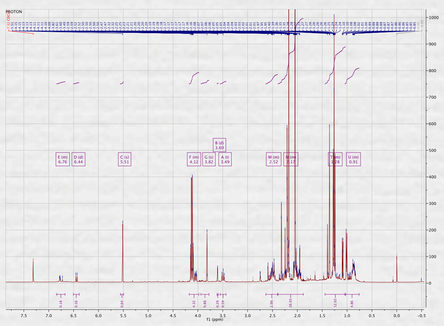
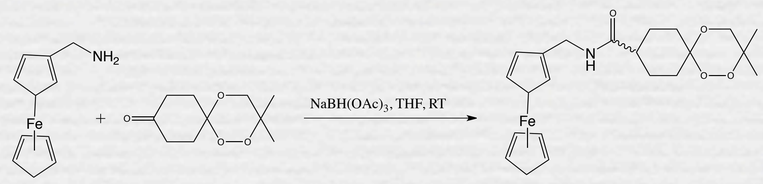


Figure 4. ^{1}H NMR spectrum of the synthesized trioxane 6 compound.

Future Work

For future work I would first like to purify/ identify the trioxane then attach the synthesized trioxane 6 to the synthesized aminomethylferrocene, as shown below in Scheme 5, to form the trioxaferroquine 8 which was the intended product for this experiment.



Scheme 5. Addition of the trioxane 6 to the animomethylferrocene

Conclusions

Overall all reactions went well except the Trioxane 6 which was attempted three times. The final time was attempted using a new paper[4] that had an isolated intermediate before the synthesis of the final product.

Acknowledgments

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References

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