Perfecting a Synthesis Pathway for the Production of a Family of Schiff Base Ligands for Complexing into NN'OS Coordination Spheres

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INTRODUCTION

The relationship between transition metals and surrounding ligand structures in coordination compounds is of high interest in research and commercial chemistry. This research group focused on synthesizing tetradentate NN'OS coordination spheres formed from salicylaldehydes and imines with the addition of a metal ion. Figure 1 demonstrates the generic production goals of the research group.

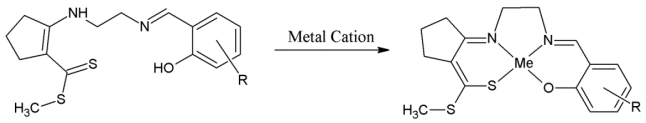
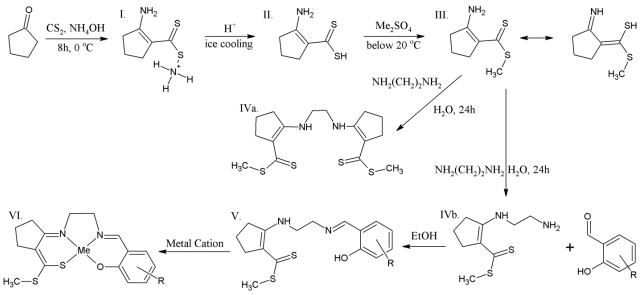


Figure 1: Complexing of a metal ion with a Schiff-base ligand to form an NN'OS coordination sphere. The variable substituent refers to variation in possible salicylaldehyde groups in order to create a family of ligands.

Synthesis of these and similar compounds is helpful in understanding the roles that coordination complexes play in bioinorganic compounds such as hemoglobin, a coordination complex centered about the transition metal iron. This molecule is a critical functional component of blood, and disruption of the ligands surrounding hemoglobin as the result of genetic mutation, lifestyle, environment, or other factors can result in a failure of the swapping of oxygen for carbon dioxide in the blood.[1] An understanding of the chemical nature of such molecules could lead to advances in pharmaceuticals designed to prevent or treat related diseases. Nickel is of interest due to a growing understanding of its role in the redox chemistry of a number of previously poorly understood enzymes.[2] Schiff bases derived from aldehydes and diamines are useful and versatile ligands: functional groups may be easily swapped for steric/electronic variability and they are commonly studied to simulate metalloprotein models.[2] In this research, the swappable functional group(s) of interest is located on the salicylaldehyde substituent. This research intended to generate a family of Schiff-base ligands and eventually NN'OS coordination spheres by varying these functional groups with additions of different salicylaldehydes.

Experimental

All chemical precursors were obtained from the Sigma-Aldrich chemical supply company in reagent grade quality. The following synthesis techniques were gathered, appropriated, adapted, and optimized from the work of previous researchers. Scheme 1 has been adapted from their results as well as the specific interests and results of this project.[5,6,7,8]



Scheme 1: Appropriated synthesis pathway for a family of NN'OS complexed Schiff-base ligands. The products are identified as follows; Compound I: Step 1 ammoniated product, Compound II: Step 2 protonated product, Compound III: Step 3 methylated product, Compound IVa: Step 4 dimer product, Compound IVb: Step 4 aminated product, Compound V: Step 5 Schiff-base ligand, and Compound IV: Step 6 NN'OS coordination sphere. Adapted from Asadi *et al.* (2006).

Step 1, preparation of **{[(2-aminocyclopent-1-en-1-yl)carbothioyl]sulfanyl}ammonium** (I) from cyclopentanone. Cyclopentanone (25.0g, 26.4ml, 0.30mol) was measured into a round bottom flask and cooling to 0°C on ice. To this reaction vessel, ammonium hydroxide (100mL, 33% solution) was added. While the contents of the reaction vessel were stirred, carbon disulfide (34.8g, 27.5ml, 0.45mol) was added dropwise. The reaction mixture was allowed to stir for a total of 8 hours with temperature maintained at 0°C. A yellow precipitate gradually fell out of solution. The product was filtered off and washed with ethyl ether. This salt was not stored for long because of its instability and instead was quickly pushed forward to protonation, yield 33.83, (65%). It is worth noting that greater yields were achieved with smaller reaction scales. Since this is the first step of the pathway, keep in mind the desired amount of product at the end to of the pathway and consider the risks.

Step 2, preparation of **2-aminocyclopent-1-ene-1-carbodithioic acid** (II) from I. Product I (33.34g, 0.19mol) was dissolved in 300mL of water within a 1000mL beaker. To this vigorously stirred solution, 2M HCl was added dropwise until the pH was 4-5. Approximately 80mL of 2M HCl was added. An orange-yellow crystalline product precipitated. The solution was put on ice in order to precipitate a greater amount of product. Because of fairly clean

and desirable NMR results, this product was not recrystallized, but after downstream problems resulted, recrystallization may be advisable. The yield is inflated due to inadequate drying times before the next step. Yield 54.36g, (wet 181%).

Step 3, preparation of **methyl 2-aminocyclopent-1-ene-1-carbodithioate** (III) from II. Compound III was formed by dissolving the above II. product (4.77g, 0.03mol) in aqueous 0.6M NaOH solution (50 mL) in a 100mL round bottom flask and placed on a heavy ice bath with temperature maintained at less than 20°C. The product was then stirred vigorously. After waiting approximately ten minutes for the temperature of this solution to cool completely to bath temperature, dimethyl sulfate (2.9mL, 2.18g, 0.03mol) was added slowly dropwise without reducing the stir rate. Watch the reaction mixture for signs of a black aggregating precipitate, and slow down dimethyl sulfate addition further if it forms. The reaction mixture was stirred with temperature maintained below 20°C for about 2 hours until a powdery brown precipitate dropped out of clear, colorless solution. Filter this precipitate off as soon as it is removed from the ice bath in order prevent irreversible formation of the black tar precipitate. Reaction scales greater than this are not recommended and tend to form more black tar precipitate due to issues with proper cooling. The product was not recrystallized due to satisfactory NMR and IR analysis. Yield 3.45g, (wet 143%).

Step 4, preparation of **dimethyl 2,2'-(ethane-1,2-diyldiimino)biscyclopent-1-ene-1-carbodithioate** (IVa) and methyl **2-[(2-aminoethyl)amino]cyclopent-1-ene-1-carbodithioate** (IVb) from III. Compounds IVa and IVb were formed by dissolving the III product (3.46g, 0.02mol) in methanol (35mL). To this stirred solution, ethylene diamine was added dropwise (6.7 mL, 6.0g, 0.1mol). After 24 hours, the dark red solution turned to a yellowed solution with precipitate. This precipitate, a dimer formed from III, was filtered off and washed with water. As with product I, the dimer was largely insoluble in available deuterated NMR solvents including acetone, dimethyl sulfoxide, water, and chloroform. Yield 0.67g, (9.0%). To the filtrate approximately 120mL of water was added. A fine, yellow precipitate dropped out of solution. The solution was placed into an ice bath. Yellow crystals precipitated from the solution, were filtered off, and washed with water. These were the intended IVb product. Yield 0.49g, (11%). Note that the expected yields for these compounds assume that only one of the two potential products is formed.

Results

Each step's product(s) was analyzed and characterized using a combination of the following methods: physical characteristics such as solubility and appearance, infrared spectroscopy, C-13 NMR spectroscopy, and H-NMR spectroscopy. Additionally, step by step success was determined through expected alteration of IR and NMR results between major reactant and product. The site nmrdb.org was utilized in order to predict aspects of each NMR spectra. In the interest of time, melting point analysis was not conducted. See the appendix for a complete list of all relevant melting points and spectra as gathered from past research. Aside from minor peaks blamed on contamination, the completed steps of the pathway corroborate with past in-house research and the work of initial researchers. The following tables show the NMR data gathered after each step. All NMR samples were run using deuterated DMSO as the solvent.

Table 1: Step 1 C-13 NMR

Functional Group	Predicted Shift (ppm)	Actual Shift (ppm)
Sulfur ester	225	200
Amine/alkene	171	177
Alkene	130	137
Alkane	36	30
Alkane	30	30
Alkane	22	25

I.

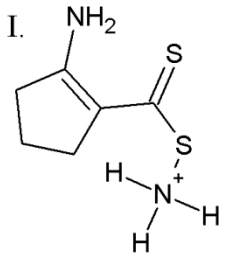


Table 2: Step 1 H-NMR	Expected			Actual		
Functional Group	Splitting	Integral	Shift (ppm)	Splitting	Integral	Shift (ppm)
Alkane	triplet	2	2.77	triplet	~2	2.65
Alkane	triplet	2	2.49	triplet	~2	2.51
Alkane	quintet	2	1.77	quintet	~2	1.55

As shown by Tables 1 and 2, the intended product does appear to be present in the sample. However,

there does appear to be some kind of contamination or multiple product tautomers as evidenced by notable recurring peaks around 9 and 11ppm in H-NMR. C-13 NMR appears to be fairly clean. IR results show a definite presence of amine stretch ~3300wn associated with the added ammonium ion.

Table 3: Step 2 C-13 NMR		
Functional Group	Predicted Shift (ppm)	Actual Shift (ppm)
Sulfur ester	225	200
Amine/alkene	171	171
Alkene	129	118
Alkane	36	36
Alkane	30	35
Alkane	22	20

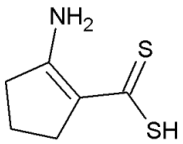
II. 

Table 4: Step 2 H-NMR	Expected			Actual		
Functional Group	Splitting	Integral	Shift (ppm)	Splitting	Integral	Shift (ppm)
Alkane	triplet	2	2.77	triplet	~2	2.91
Alkane	triplet	2	2.49	triplet	~2	2.68
Alkane	quintet	2	1.77	quintet	~2	1.85

As shown by Tables 3 and 4, the intended product does appear to be present in the sample. However there were small additional peaks in the C-13 NMR, likely indicating residual reactant. The same may be said of the H-NMR results, with some carryover of step 1 product peaks. Signal strength for the desired peaks was much stronger than for the undesired ones, indicating acceptable purity. IR results show appearance of the protonated sulfur at ~2500wn.

Table 5: Step 3 C-13 NMR		
Functional Group	Predicted Shift (ppm)	Actual Shift (ppm)
Sulfur ester	209	200
Amine/alkene	169	170
Alkene	118	117
Alkane	36	36
Alkane	32	33
Alkane	20	20
Alkane	18	16

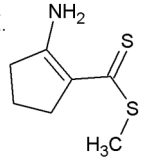
III. 

Table 6: Step 3 H-NMR	Expected			Actual		
Functional Group	Splitting	Integral	Shift (ppm)	Splitting	Integral	Shift (ppm)
Alkane	triplet	2	2.75	triplet	~2	2.65
Alkane	triplet	2	2.54	triplet	~2	2.63
Alkane	quintet	2	1.81	quintet	~2	1.76
Alkane	singlet	3	2.45	singlet	~3	2.45

As shown by Tables 5 and 6, the desired product does appear to present in the sample. C-13 NMR results demonstrated extremely strong and fairly pure signal, indicating high ratio of desired products to contaminants. H-NMR results were similar, indicating that the carryover peaks are more likely structural variation or tautomeric shifts of the product molecules instead of leftover reactants. It should be noted that the black tar byproduct will not show up in NMR using DMSO, so care should be taken to vet samples on the basis of desired physical characteristics. IR results show the addition of the sulfur-associated methyl group at ~2345wn and the disappearance of the sulfur-associated proton from the step II spectra.

Table 7: Step 4 C-13 NMR		
Functional Group	Predicted Shift (ppm)	Actual Shift (ppm)
Sulfur ester	210	193
Amine/alkene	161	170
Alkene	119	117
Amine/alkane	45	49
Amine/alkane	41	42
Alkane	32	34
Alkane	29	33
Alkane	20	21
Alkane	18	16

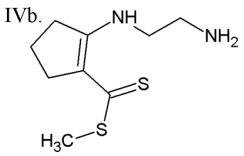
IVb. 

Table 8: Step 4 H-NMR	Expected			Actual		
Functional Group	Splitting	Integral	Shift (ppm)	Splitting	Integral	Shift (ppm)
Alkane	triplet	2	2.8	triplet	~2	2.73
Alkane	triplet	2	2.55	triplet	~2	2.68
Alkane	quintet	2	1.83	quintet	~2	1.81
Alkane	singlet	3	2.45	singlet	~3	2.45
Amine/Alkane	triplet	2	2.77	triplet	~2	2.78
Amine/Alkane	triplet	2	3.33	quartet	~2	3.36

As shown by Tables 7 and 8, the desired product does appear to be present in the sample. The C-13 NMR results demonstrated strong and clean signal, indicating excellent sample purity. The H-NMR results displayed an odd splitting for the newly added Amine/Alkane group associated with the ethylenediamine. This may be an artifact or the result of a tautomer. However, speculative modeling on nmrdb.org did not yield a structure capable of such an overall H-NMR spectra. IR results were inconclusive due to the shrouding of the desired amine stretch by an –OH stretch from the reaction solvent, methanol. Characterization of the dimer compound IVa involved multiple pieces of evidence. Because the compound would not dissolve in the DMSO, it could not be analyzed via NMR; however, this physical characteristic separated it from compounds III and

IVb. When IR was conducted on sample, an –OH stretch from methanol solvent contamination prevented visibility of the expected disappearance of the amine stretch at ~3300wn. The IR spectra was, however, otherwise identical to compound III in every other area of the spectra, including the fingerprint region. This suggests that no other modifications were made to the compound other than those which would be hidden by the –OH stretch. Therefore, the compound must be the dimer as it stongly resembles the successfully characterized dimer from past research and does not behave as the other compounds in the pathway do.

Conclusion

Despite initial successes, we ran into difficulty reproducing the efficient success of the research period. Unfortunately, Step III methylation proved to be more complicated than initially expected. Through trial and error, attention to detail, and carefully analyzing the reaction, a more specific and detailed procedure was developed for the methylation step in order to improve yield and purity while simultaneously avoiding the formation of the undesired tar byproduct. The fact that these issues were not encountered over the summer is suspicious. It is worth noting that all methylation batches were conducted with the same batch of Step II product during this research period. Although spectroscopic analysis of the Step I and II products appeared satisfactory, contaminants may still have avoided detection if they did not completely dissolve in the NMR solvent. Additionally, in the interest of time samples were not allowed to properly dry as they had been over the summer. This would have resulted in an excess of certain reactants and unforeseen downstream complications due to compounded contamination. Future researchers should remain wary of these issues as they continue to utilize and build upon this pathway for ligand-family development. However, synthesis of both compound IVa dimer and IVb aminated product appeared to be successful, albeit in minute quantities of low yield. Future in-house researchers may wish to compare the compiled library of compounds synthesized this semester alongside their own products for each step of the pathway. Overall, even if the methylation issues were purely the result of contamination, the embellished procedure is still applicable and may prove useful in increasing the yield of Step III methylation and therefore the overall yields of downstream steps as well.

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