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Synthesis of Bis(quinoxalino) Ligand for the Removal of Transition Metal Contamination



Honors Thesis

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Department: Chemistry

Advisor: Judit K. Beagle, Ph.D.

April 2017

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Abstract

Transition metal contamination is a constant concern both in the environment and in chemical reaction mixtures. One proposed solution, is the use of peraza-crown macrocycles to selectively bind and remove transition metals. The aim of our project is to determine the novel synthesis of bis(quinoxalino) peraza-crown macrocycles for use as ligands to bind to transition metals. Our proposed molecules incorporate the rigid quinoxaline subunit into an aza-crown macrocycle which can improve binding properties. The synthesis route is novel and overcomes several limitations of the existing methods of aza-crown macrocycle preparation. We have designed the synthesis in such a way that it does not use a metal template and is general enough that new derivatives can be easily obtained.



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Introduction

In an increasingly “green” world, transition metal contamination has become a growing environmental concern. Transition metals can be found in the natural environment and are produced as the result of human activity. They are widely used as industrial catalysts and can persist in reaction mixtures and in final products. Transition metals pose a major threat to both natural ecosystems and human health as a result of their often deleterious effects (Costa, 1997). Therefore, the existing and ongoing contamination must be addressed. Overall, the primary objective of our research project is to find ways to efficiently detect and selectively remove transition metal contamination both from reaction mixtures as well as soil and water samples.

Bis(quinoxalino) ligands are comprised of two quinoxaline groups flanking either side of a peraza-crown subunit as shown in Fig. 1. In literature, these subunits have been synthesized independently; however, the synthesis of this particular arrangement has not yet been shown.

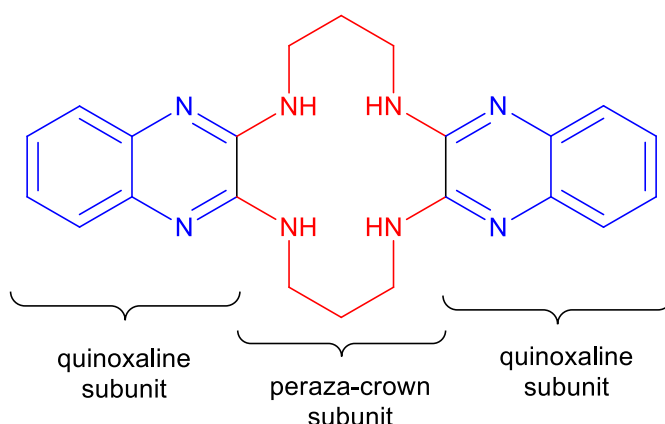
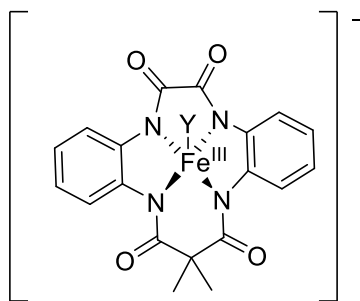


Figure 1: General structure of the bis(quinoxalino) ligand

Quinoxalines are widely expressed in biological systems and as a result, much interest has surrounded their investigation (Patidar, 2011). Quinoxalines provide the building blocks for pharmacological molecules with antibacterial, antifungal, antineoplastic, antitubercular, antileishmanial, antimalarial, and antidepressant properties (Patidar, 2011). Additionally, both peraza-crowns containing at least three nitrogen atoms and their oxygen containing analogs, the crown ethers, have been shown to complex strongly with metal cations (Hancock, 1986). Crown ethers show preference for alkali and

alkaline-earth metals whereas peraza-crown molecules show a particular selectivity for transition and post-transition metals (Hancock, 1986). Additionally, derivatives of the peraza-crowns have been used in redox metalloenzyme mimicking, antibodies for cancer localization and therapy, hydrolytic agents for non-oxidative cleavage of DNA and RNA (Parker, 1990), and oxidative catalysts for various organic transformations. The nitrogen-donating peraza-crown macrocycles have also been shown to selectively bind and remove transition metal cations (Bradshaw, 1989).

Given these properties, we elected to use the nitrogen-containing peraza-crown macrocycle in order to meet the goals of our project. Furthermore, certain 13-membered peraza-crown molecules have been examined for their ability to purify water (Ellis, 2010). The metal complexation exhibited by the 13-membered peraza-crown macrocycle can be improved by adding rigid or voluminous structural fragments. This can be accomplished with the addition of aromatic motifs. These motifs will force the donor-nitrogen atoms into rigid, well-arranged conformations (Holzberger, 2004).



13-membered aliohatic peraza-crown macrocycle for water purification

Figure 2: Selected example of peraza-crown macrocycle

Presently, there are several commonly used methods for synthesis of peraza-crowns that are known from literature. Some of these include ring closure reactions with or without the formation of a Schiff-base (MacDermott, 1967), cyclocondensation to four C-N single bonds (Richman, 1974), condensation of a polyamine with acid chlorides (Dietrich, 1989), activated carboxylic acids (Tabushi, 1976), α , β -unsaturated esters (Kimura, 1986), or “crab-like” cyclization (Krakowiak, 2000).

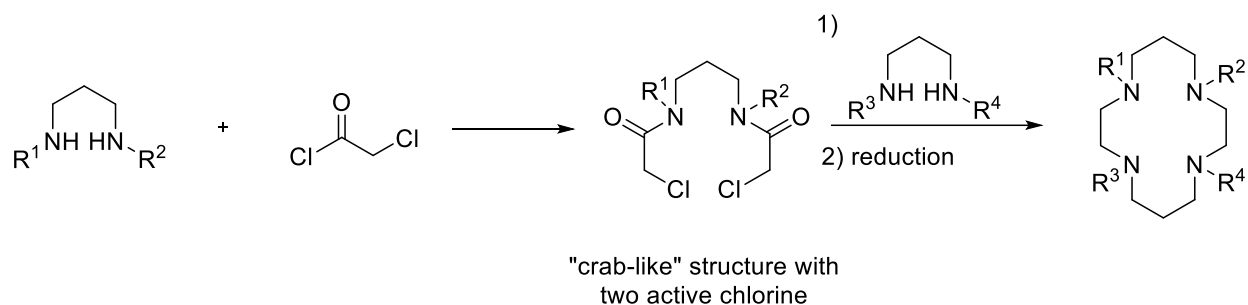


Figure 3: ‘Crab-like’ synthesis of peraza-crown macrocycle

Most notably, all of the methods of synthesis listed above are in competition with polymerization or make use of a transition metal template (Tabushi, 1976). Additionally, it is known that the removal of these metal templates is often difficult and sometimes impossible (Bradshaw, 1993). Since we are seeking to use these ligands to remove transition metal contaminants, this is not a desirable property. As a result, we detail a novel method of synthesis for these ligands which avoids use of a metal template or use of a high dilution conditions.

Specific Aim

Overall, the objective of our project is the synthesis of bis(quinoxalino) ligands which are capable of selectively interacting with transition metals. We hypothesized that by coupling the rigidity of the aromatic quinoxaline and the good, metal-binding properties of the aza-crown macrocycles, we can obtain useful molecules with superior properties compared to existing options. This specific aim, as outlined in Fig. 4, can be further broken down into two main objectives:

Objective 1: Successful synthesis of key intermediate **5**

Objective 2: Successful synthesis of final product **7** with various diamines/R-group substitutions and further optimization of the process.

For our synthesis, we planned to react 2, 3-dichloroquinoxaline (**3**) with protected diamines in order to form the key intermediate **5**. The proposed synthetic route was to achieve this in a one-step reaction, but a two-step reaction was also considered as an alternative. Once intermediate **5** is successfully obtained, we planned to complete the synthesis by the deprotection of **5** to yield **6**. A subsequent coupling with another molecule of **3** would then give us our final product. The synthesis, as outlined in Fig. 4, easily allows

for modifications to be made both in the size of the peraza-crown unit itself as well as the R-groups on the quinoxaline subunit.

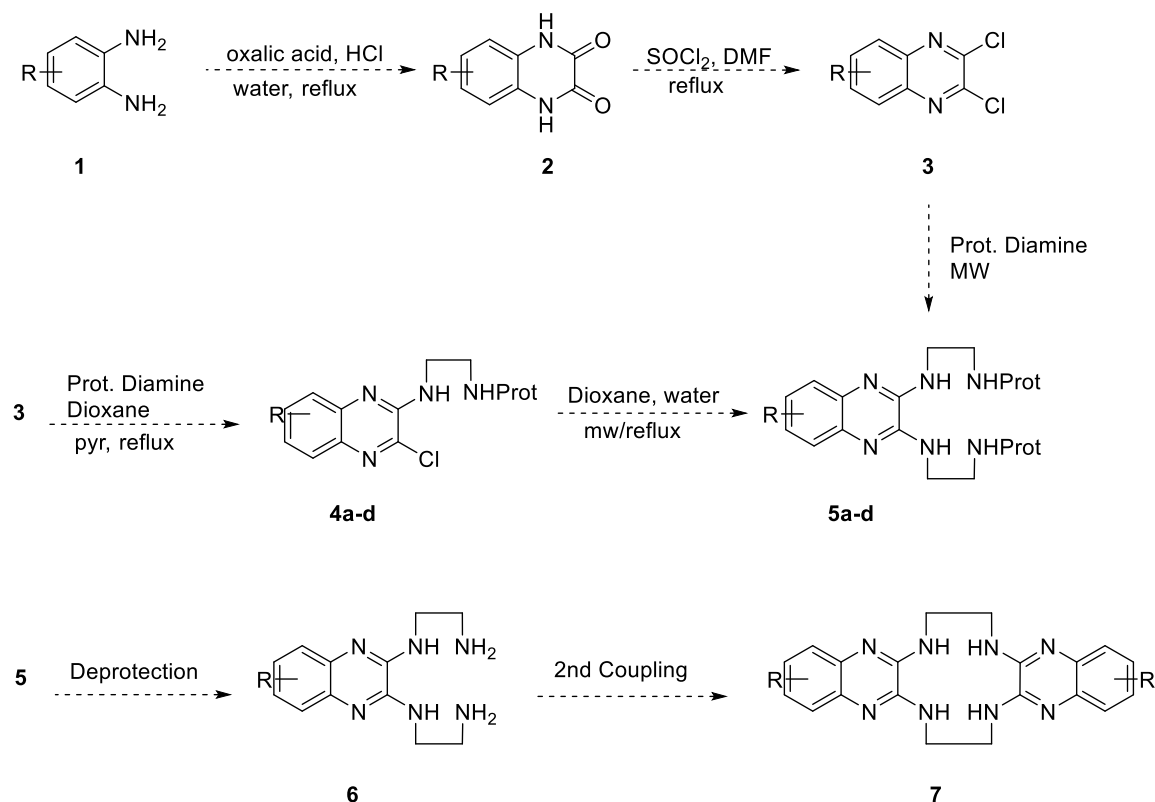


Figure 4: Proposed Synthetic Route

Results and Discussion

Synthesis of the Quinoxaline Subunit

The reagents for the first reaction, *o*-phenylenediamine and oxalic acid, were available commercially. From literature, the synthesis of both **2** and **3** are known to occur both in high yield and in high purity. For our own synthesis, our data were in agreement with known values and proceeded without problem. Additionally, a 4,5-dimethyl variant of the quinoxaline was synthesized using the same procedure.

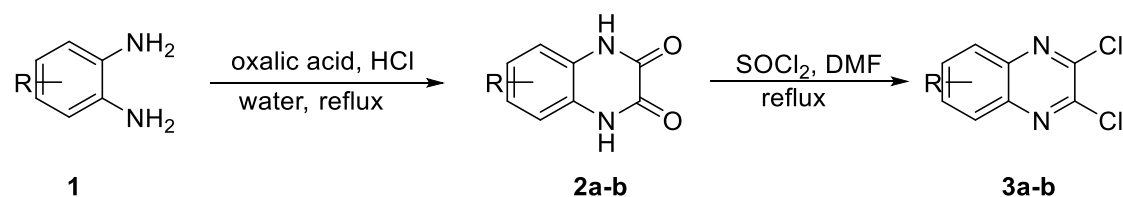


Figure 5: Scheme for synthesis of quinoxaline subunit

| Entry | R-group | Yield (2) | Yield (3) |
|----------|--------------|-----------|-----------|
| a | H | 79% | 83% |
| b | 4,5-dimethyl | 84% | 97% |

Table 1: Yields of quinoxaline and intermediates

Synthesis of Protected Diamines

We elected to use protected diamines to reduce any chance of polymerization resulting from the availability of both nitrogen atoms. We considered to using three different protecting groups. The most important factor in determining which protecting groups to use was the need for basic reaction conditions. This is because the condensation of the protected diamines onto **3** eliminates a molecule of HCl. The first protecting group considered was Cbz (benzylcarboxycarbonyl) as it stable under both the basic conditions and the thermal conditions used in these reactions. Troc (2,2,2-trichloroethoxycarbonyl) was also considered as it can persist through conditions similar to the Cbz (Kocienski, 2004). The main advantage that Troc offers is that it is a smaller molecule than Cbz. Lastly, the Boc (*t*-butoxycarbonyl) protecting group was considered because it is smaller than both Troc and Cbz. Some of the other benefits of the Boc group are that it is extremely resistant to both basic and nucleophilic deprotection schemes (Kocienski, 2004). However, its deprotection conditions are harsher than those for Troc or Cbz.

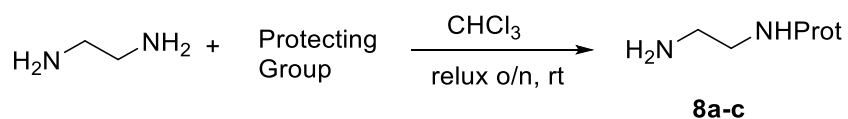


Figure 6: General scheme for protected diamines

| Prot | Cbz (8a) | Troc (8b) | Boc (8c) |
|-------|----------|-----------|----------|
| Yield | 100% | 100% | 66% |

Table 2: Yields of protected diamines

Initially, we worked with the Cbz protecting group as it best fit our needs given its stability under a wide variety of conditions previously detailed. Later, we conducted the synthesis using the Boc and Troc groups as well. All three protected diamines were synthesized following the same general scheme outlined in Fig. 6. The associated yields for the diamines are listed in Table 2.

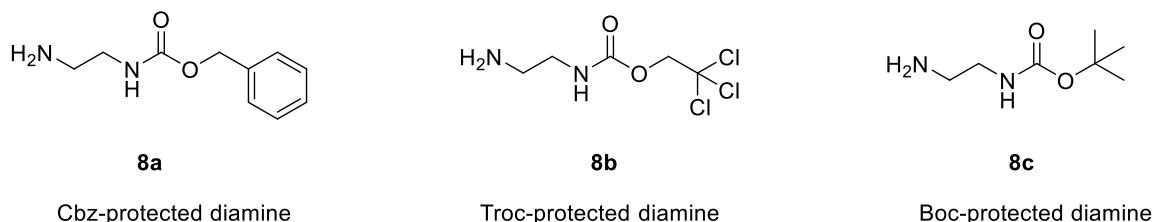


Figure 7: Structures of protected diamines

Synthesis of the Key Intermediate 5

Starting with this step, we began to make use of microwave chemistry. It was our hope that we would be able to replace the traditional method of overnight reflux with microwave irradiation. The advantages of this are that irradiation can be completed on a much more reasonable timescale, often less than one hour, and uses significantly less energy than reflux. Given our goals in green chemistry, as well as for practical purposes, these benefits were extremely desirable.

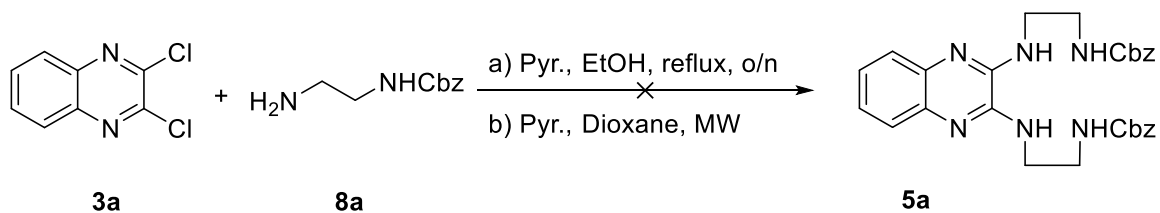


Figure 8: Scheme for double substitution attempt

Our initial synthesis of the key intermediate was attempted using microwave irradiation. The reaction mixture of **3** and the Cbz-protected diamine (**8a**) in dioxane with pyridine was irradiated several different times, at increasing temperature and power settings. After 50 total minutes of irradiation, we ran a column on the reaction mixture, separating only the monosubstituted product, as confirmed by NMR. However, the yield was low at 52%. Further optimization was needed if we wanted to utilize this in the one-step alternate route. Later samples were irradiated only once, but at higher temperature and

power settings (60min, 150°C, 100W), and at a higher concentration of amine relative to **3**. Ultimately, we were unable to achieve consistent results using microwave irradiation for this step. The first microwave run of this reaction produced the highest yield. These low yields were observed because at higher temperatures, decomposition products started to form, instead of driving the reaction to completion for either product.

Then, we attempted in a one-pot reflux using ethanol as the solvent. Attempting both substitutions simultaneously gave us only the mono-substituted molecule **4a** instead of the product **5a** for which we had hoped.

At this point, it became clear that we needed a different approach to the synthesis. Given the fact that we only obtained the mono-substituted product, and the fact that longer reactions led to decomposition, we switched to a step-wise method.

In moving forward with mono-substituted synthesis, we employed the traditional method of overnight reflux to drive the reaction. Using this method, we were able to synthesize the molecules **4a,b,d** in good yields as can be seen in Table 3. The reactions carried out in reflux appeared cleaner on TLC, and proved to be more practical for the synthesis of the mono-substituted products.

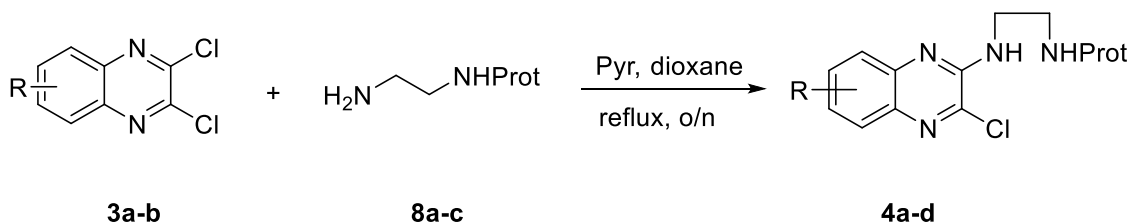


Figure 9: General scheme for the first condensation reaction

| Entry | R-Group | Prot. Group | Yield (4) |
|----------|--------------|-------------|-----------|
| a | H | Cbz | 78% |
| b | 4,5-dimethyl | Cbz | 38% |
| c | H | Troc | 78% |
| d | H | Boc | 88% |

Table 3: Yields for first condensation reaction

Once we had synthesized our mono-substituted product **4a**, we were able to proceed with the second substitution at the site of the remaining chlorine. As we did with the synthesis of **4a**, this reaction was first driven using microwave irradiation. The microwave reaction was not as straightforward this time around. Like the previous reaction, we attempted a variety of settings for temperature, power, and time, but the variation in settings did little to change the resulting mixtures. With the previous reaction, we were at least able to synthesize the mono-substituted product with even a small yield. For the synthesis of **5a**, we produced little, if any product using the microwave. Furthermore, the resulting mixture contained several UV-active decompositions which appeared on TLC. With this in mind, we reasoned that it would not be feasible to attempt a separation of the product. So, overnight reflux was again employed to try to circumvent the problems of the microwave. Unfortunately, reflux was not able to drive the reaction sufficiently. A crude NMR of the product mixture showed that some product was produced, but again the separation of that product was not practical. Here, we also tried the substitutions using the 4, 5-dimethyl quinoxaline subunit under similar conditions. The results for the production of **5b** were similar to those of **5a**.

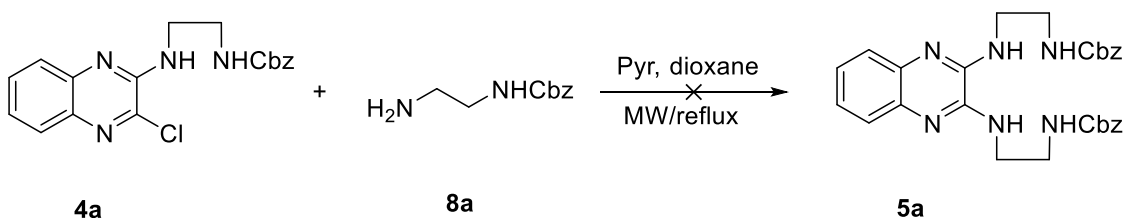


Figure 10: Scheme for second condensation using Cbz-protected diamine

While the Cbz-group is extremely stable under a variety of conditions, it is a bulky protecting group. We hypothesized that it was crowding produced as a result of the first substitution that was keeping the reaction from moving forward with an appreciable yield. With this in mind, we employed the use of the Troc-protected diamines. The Troc group is known to be stable under a range of conditions similar to those of the Cbz group (Kocienski, 2004). However, the Troc group is smaller molecule overall than the Cbz group, which we thought would allow us to avoid the problem of crowding, and drive the synthesis forward. Taking the lessons learned from the synthesis of the Cbz-protected **4a**, we did not attempt the synthesis of the Troc-protected mono-substitution in the microwave.

It was more efficient for us to go directly to overnight reflux as we already knew that the mono-substitution could be completed with a good yield using that method.

Following the successful synthesis of the Troc-protected **4c**, we again moved onto the second substitution. Initially, we attempted to drive this reaction forward by again using microwave irradiation. The hope was that we would be able to avoid the decomposition products that were produced while going from Cbz-protected **4a** to **5a**. As when using the Cbz, we were not able to successfully produce the product molecule **5c** using the microwave. So, we tried this step again using overnight reflux only to find similar results. From here, we decided to try using yet another protecting group.

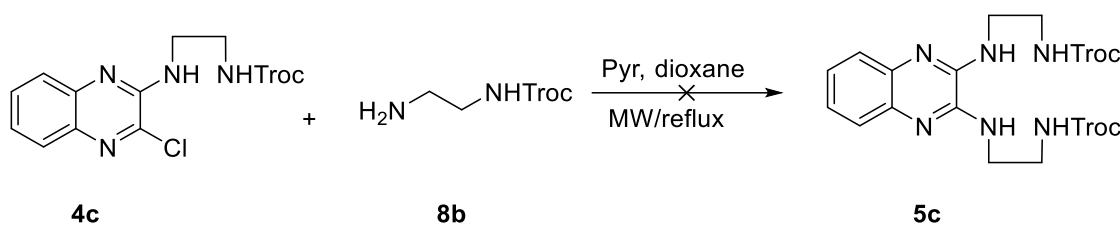


Figure 11: Scheme for second condensation using Troc-protected diamine

For our third protected diamine, we decided to use the Boc protecting group. The Boc protecting group is smaller than both the Cbz and the Troc groups, and is stable under basic conditions. The reason the Boc was not initially used is because the harsh acidic conditions of this reaction were those necessary for deprotection. In spite of this, proceeded using the Boc-protected diamines. For the synthesis of **4d**, the reaction was only done under overnight reflux conditions, which produced the mono-substituted product that we desired in a good yield.

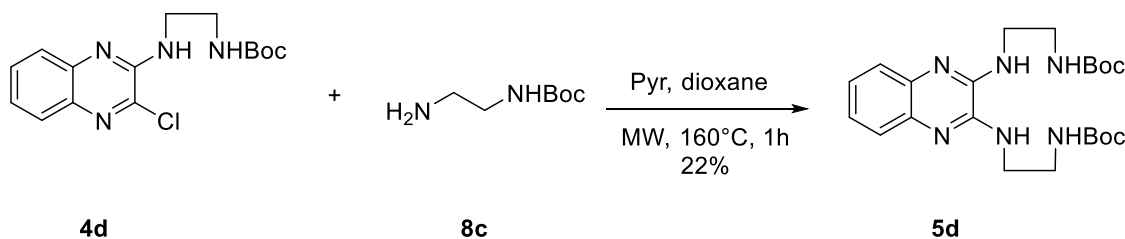


Figure 12: Scheme for second condensation using Boc-protected diamine

For the synthesis of **5d**, we used microwave irradiation to drive the reaction to completion. Converse to what was found in earlier substitutions using Troc/Cbz-protected amines, the reaction was found to go to completion, producing the Boc-protected **5d**.

Additionally, this resulting mixture following irradiation was significantly cleaner for this reaction when compared to earlier trials using Cbz/Troc groups. It is noteworthy that this reaction was not attempted using overnight reflux as was done while using the other protecting groups. So, using the Boc-protected diamine, we were able to synthesize our first di-substituted quinoxaline. In spite of this, the yield which we achieved using this method was low at 22%. This low yield was a result of observed thermal deprotection of the Boc. It became clear that further optimization was still required for this step.

| Entry | R-group | Prot. Group | Yield (5) |
|----------|--------------|-------------|-----------|
| a | H | Cbz | - |
| b | 4,5-dimethyl | Cbz | n.a. |
| c | H | Troc | - |
| d | H | Boc | 22% |

Table 4: Yields for second condensation

During the course of optimization for the previous step, we found that increasing the concentration of the reaction mixture increased the yield of the reaction. Knowing this, we attempted a one-pot double substitution to the molecule **5d** from **3** without any solvent in the microwave (160°C, 10min). After this, we were able to isolate our desired product with a 90% yield. Essentially, this development allows us to completely circumvent the synthesis of the intermediate **4** in the future, avoiding the lengthy and energy intensive overnight refluxes that were previously employed in those intermediate steps. Furthermore, this solvent-less synthesis is more economical than the previously outlined step-wise method.

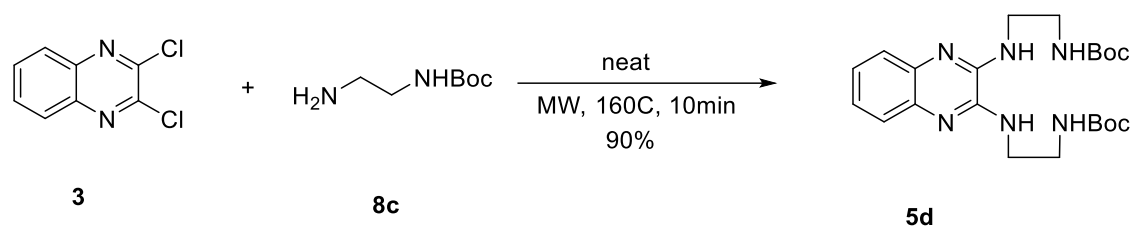


Figure 13: One-pot double condensation using Boc-protected diamines

Future Work

At this point in the research, we have been able to synthesize the key intermediate **5** both in high yield and in high purity. To complete the overall goal of the project, additional work is still needed. The next step to be completed is the deprotection of the molecule **5d**. From there, we can couple an additional quinoxaline subunit to the amines and complete our desired ligand **7** as was previously outlined in Fig. 4. Additional optimization is needed for many of the steps. We can then complete our second objective listed in the introduction involving transition metal binding studies. Furthermore, we can test binding effects caused by different R-group substitutions and varying the length of the diamines. We can then determine if these ligands are indeed suitable for transition metal contamination removal.

Experimental Methods and Data

General Methods

NMR spectra were obtained in CDCl₃ or DMSA-d₆. Operating at 300 MHz with TMS as the internal standard. All microwave assisted reactions were carried out with a single mode cavity CEM Discovery Microwave Synthesizer. Purification was accomplished using Teledyne-Isao Combiflash flash chromatography system. All commercially available materials were used without further purification.

Synthesis of Protected Amines

Ethylene diamine was dissolved in 250mL CHCl₃. Benzyl chloroformate, 2,2,2-trichloroethoxycarbonyl chloride, or Boc anhydride were dissolved separately in 125mL CHCl₃. The protecting group solution was added dropwise into the ethylenediamine, and the resulting mixture was stirred overnight at room temperature in a sealed flask. After stirring overnight, the mixture was extracted three times using water and was dried over sodium sulfate. The product was then dried under a vacuum. The yields can be found in Table 1. Analytical data is consistent with those reported in the literature (Cal, 2013; Holland, 2010)

Synthesis of Compound 2

Oxalic acid (5.4g, 60mmol) was dissolved in water and was heated to 95°C. 10mL of concentrated HCl were added, and then *o*-phenylenediamine (5.4g, 50mmol) was added to the reaction mixture. The temperature was maintained at 98-100°C for 15 minutes. The mixture was taken off heat, and ~60g of ice were added. The precipitate was filtered, washed with water, and then dried over vacuum. The reaction yielded 6.4711g (39.4mmol) of 1,4-dihydroquinoxaline-2,3-dione (**2a**) in a 79% yield (6.4711g, 39.4mmol). 6,7-dimethyl-1,4-dihydroquinoxaline-2,3-dione (**2b**) was synthesized using the same procedure to yield 5.8 g (30.8 mmol) product. Analytical data is consistent with those reported in the literature (Komin, 1976)

Synthesis of Compound 3

Compound **2** (4g, 25mmol) was added to a solution of SOCl₂ and DMF (12.5mL SOCl₂, 172mmol; 0.25mL DMF). The mixture was refluxed until the solid dissolved (2 hours). Ice was added, and the precipitate was filtered using water and dried under vacuum to give 4.13g (20.7mmol) of 2,3-dichloroquinoxaline at a yield of 83%. Synthesis of 2,3-dichloro-6,7-dimethylquinoxaline (**3b**) was carried out under the same conditions to give the product in 97% yield. Analytical data is consistent with those reported in the literature (Komin, 1976)

Synthesis of Compound 4a

The amine (1.166g, 6mmol) was dissolved in 14mL of dioxane, Pyridine (0.484mL, 6mmol) and **3a** (0.398, 2mmol) were added to the solution. The reaction mixture was refluxed (105°C) overnight. The resulting mixture was dried onto silica gel and separated by flash column chromatography using a hexanes/ethyl acetate solvent system. The product benzyl (2-((3-chloroquinoxalin-2-yl)amino)ethyl)carbamate (0.5574g, 1.56mmol) was produced by this method with a 78% yield. The structure was confirmed using H¹ NMR. ¹H-NMR (CDCl₃) δ: 3.50 (q, J = 6 Hz, 2H), 3.67 (q, J = 6 Hz, 2H), 5.09 (s, 2H), 5.75 (br s, 1H), 6.16 (br s, 1H), 7.25-7.30 (m, 5H), 7.34 (t, J = 9 Hz, 1H), 7.52 (t, J = 9 Hz, 1H), 7.64 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H)

Synthesis of Compound 4b

The Cbz-protected amine (1.166g, 6mmol) was dissolved in a small amount of dioxane. Pyridine (0.484mL, 6mmol) was added followed by **3b** (0.454g, 2mmol). The reaction mixture was refluxed overnight at 105°C. This was evaporated onto silica gel and separated by flash column chromatography using a hexanes/ethyl acetate solvent system. This isolate, benzyl (2-((3-chloro-6,7-dimethylquinoxalin-2-yl)amino)ethyl)carbamate was evaporated by rotary evaporation and the structure confirmed by NMR in a 38% yield (0.294g, .765mmol).

¹H-NMR (CDCl₃) δ: 2.39 (s, 6H), 3.57 (q, J = Hz, 2H), 3.74 (q, J = 6Hz, 2H), 5.13 (s, 2H), 5.53 (br s, 1H), 5.96 (br s, 1H), 7.30-7.40 (m, 5H), 7.49 (s, 1H), 7.56 (s, 1H)

Synthesis of Compound 4c

Troc-protected diamine (2.12g, 9mmol) was dissolved in dioxane. Pyridine (0.726mL, 9mmol) was added followed by **3a** (0.597g, 3mmol). The reaction mixture was refluxed overnight at 105°C. The resulting mixture was dried onto silica gel and separated by flash column chromatography using a hexanes/ethyl acetate solvent system. The isolate was evaporated using rotary evaporation and structure of 2,2,2-trichloroethyl (2-((3-chloroquinoxalin-2-yl)amino)ethyl)carbamate (2.35mmol, 78% yield) was confirmed by NMR.

¹H-NMR (CDCl₃) δ: 3.61 (q, J = 6 Hz, 2H), 3.80 (q, J = 6 Hz, 2H), 4.73 (s, 2H), 5.36 (br s, 1H), 6.04 (br s, 1H), 7.42 (t, J = 9 Hz, 1H), 7.59 (t, J = 9 Hz, 1H), 7.73 (d, J = 9 Hz, 1H), 7.81 (d, J = 9 Hz, 1H)

Synthesis of Compound 4d

Boc-protected ethylenediamine (0.48g, 3mmol) was dissolved in dioxane. Pyridine (0.24mL, 3mmol) was added followed by the compound **3a** (0.20g, 1mmol). The reaction mixture was refluxed overnight (110°C). A TLC was run (1:1 Hexanes: Ethyl acetate) which showed primarily the presence of product. Next, the mixture was dried onto silica gel and separated by flash column chromatography using a hexanes/ethyl acetate solvent system. Overall, the product tert-butyl (2-((3-chloroquinoxalin-2-yl)amino)ethyl)

carbamate (0.284g, .879mmol) was produced with a yield of 88%. The structure of **4d** was confirmed using $^1\text{H-NMR}$. Upon scaling up by a factor of three, the compound **4d** was produced in a yield of 84%.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (s, 9H), 3.51 (q, $J = 6$ Hz, 2H), 3.70 (q, $J = 6$ Hz, 2H), 5.08 (br s, 1H), 6.31 (br s, 1H), 7.39 (t, $J = 9$ Hz, 1H), 7.58 (t, $J = 9$ Hz, 1H), 7.70 (d, $J = 9$ Hz, 1H), 7.80 (d, $J = 9$ Hz, 1H)

Synthesis of Compound 5d

The compound **4d** (0.323g, 1mmol) was dissolved in dioxane. The Boc-protected ethylenediamine (0.32g, 2mmol) was added. CsCO_3 (0.652g, 2mmol dissolved in minimal water) was added. The mixture was irradiated in the microwave for 1 hour at $160^\circ\text{C}/100\text{W}$. The mixture was qualitatively analyzed by TLC (1:1 Hexanes: Ethyl acetate) under UV-light. The TLC showed two primary UV-active spots. The reaction mixture was then evaporated using rotary evaporation and redissolved in ethyl acetate. The solution was extracted three times: first with 10% citric acid, second with sodium carbonate, and third with saturated sodium chloride. The extracted solution was dried over sodium sulfate and filtered. The filtered solution was then dried onto silica gel and purified by flash column chromatography using a hexanes/ethyl acetate solvent system to give di-tert-butyl ((quinoxaline-2,3-diylbis(azanediyl))bis(ethane-2,1-diyl))dicarbamate (0.0989g, 0.217 mmol) in a 22% yield. The structure of **5d** was confirmed by $^1\text{H-NMR}$.

For the second method of synthesis, compound **3** (0.199g, 1mmol) was added in a 10mL microwave vessel, and the Boc-protected amine was added (0.96g, 6mmol). The mixture was heated in the microwave at 160°C for 10 minutes. The resulting mixture was dissolved in ethyl acetate and purified by column chromatography (hexanes/ethyl acetate). Di-tert-butyl ((quinoxaline-2,3-diylbis(azanediyl))bis(ethane-2,1-diyl))dicarbamate (**5d**) was isolated in a 90% yield.

$^1\text{H-NMR}$ (CDCl_3) δ : 1.43 (s, 18H), 3.47 (q, $J = 6$ Hz, 4H), 3.68 (q, $J = 6$ Hz, 4H), 5.53 (br s, 2H), 5.66 (br s, 2H), 7.28 (q, $J = 6$ Hz, 2H), 7.58 (q, $J = 6$ Hz, 2H)

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References

- Bradshaw, J. S. et al. (1989). Silica gel-bound aza-crowns for the selective removal and concentration of metal ions. *Pure & Applied Chemistry*, 61(9), 1619-1624.
- Bradshaw, J. S., Krakowiak, K. E., & Izatt, R. M. (1993). *Aza-crown Macrocycles*. John Wiley & Sons.
- Cal, M., Jaremko, M., Jaremko, L., Stefanowicz, P. (2013). Solid phase synthesis of peptide hydroxamic acids on poly(ethylene glycol)-based support. *Journal of Peptide Science*, 19(1), 9-15.
- Costa, D. L., & Dreher, K. L. (1997). Bioavailable Transition Metals in Particulate Matter Mediate Cardiopulmonary Injury in healthy and Compromised Animal Models. *Environmental Health Perspectives*, 105(5), 1053-1060. Retrieved April 6, 2017, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1470172/pdf/envhper00330-0063.pdf>.
- Dietrich, B. (1989). Anion receptor Molecules: Synthesis of an Octaaza-cryptand and Structure of its Fluoride Cryptate. *Tetrahedron Letters*, 30(31), 4125-4128.
- Ellis, W. C. et al. (2010). Designing Green Oxidation Catalysts for Purifying Environmental Waters. *Journal of the American Chemical Society*, 132, 9774-9781.
- Holland, J. P.; Fisher, V., Hickin, J. A., Peach, J. M. (2010). Pyrene-Functionalised Copper Complexes as Potential Dual-Modality Imaging Agents. *European Journal of Inorganic Chemistry*, 1, 48-58.

- Holzberger, A.; Holdt, H. J.; Kleinpeter, E. (2004). Conformational analysis of mixed oxathia crown ethers and their complexational ability towards Ag(I) and Pd(II)-an experimental solution NMR and theoretical molecular modelling studying. *Organic Biomolecular Chemistry*, 2, 1691-1697.
- Hancock, R. D. (1986). Macrocycles and their selectivity for metal ions on the basis of size. *Pure & Applied Chemistry*, 58(11), 1445-1452.
- Kimura, E.; Fujioka, H.; Kodama, M. (1986). A New Ditopic Receptor Molecule for Ionic Guest Molecules. *Journal of the Chemical Society, Chemical Communications*. 1158-1159
- Kocienski, P. J. (2004). *Protecting Groups* (3rd ed.). Stuttgart: Georg Thieme.
- Komin, A. P., Carmack, M. (1976) The chemistry of 1,2,5-thiadiazoles V. Synthesis of 3,4-diamino-1,2,5-thiadiazole and [1,2,5] thiadiazolo[3,4-b]pyrazines. *Journal of Heterocyclic Chemistry*, 13(1), 13-22.
- Krakowiak, K. E., & Bradshaw, J. S. (2000). Synthesis of Azacrown Macrocycles and Related Compounds by a Crablike Cyclization Method: A Short Review. *Industrial and Engineering Chemical Research*, 39, 3499-3507.
- MacDermott, T. E., & Busch, D. H. (1967). Reactions of Coordinated Ligands. *Journal of the American Chemical Society*, 89(23), 5780-5784.
- Parker, D. (1990). Tumour Targeting with Radiolabelled Macrocyclic-Antibody Conjugates. *Chemical Society Reviews*, 19, 271-291.
- Patidar, A. K. (2011). Exploring Potential of Quinoxaline Moiety. *International Journal of PharmTech Research*, 3(1), 386-392.
- Richman, J. E.; Atkins, T. J. (1974). Nitrogen analogs of crown ethers. *Journal of the American Chemical Society*, 96, 2268-2270.
- Silva Miranda, F. et al. (2008). Synthesis of substituted dipyrido[3,2-a:2',3'-c]phenazines and a new heterocyclic dipyrido[3,2-f:2',3'-h] quinoxalino[2,3-b] quinoxaline. *Tetrahedron*, 64, 5410-5415.
- Tabushi, I., Okino, H., & Kuroda, Y. (1976). Convenient Synthesis of Macrocyclic Compounds Containing Two of Nitrogen, Oxygen or Sulfur Atoms. *Tetrahedron Letters*, 48, 4339-4342.