Search for a Convenient One-Pot Procedure for the Synthesis of 2,2’:6’,2”-Terpyridine

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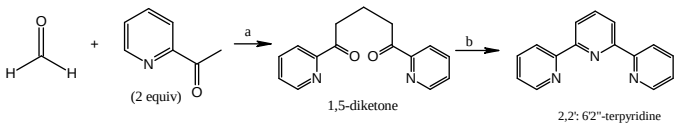
***Abstract*- 2,2’:6’2”-terpyridine is an organic compound that has shown importance in science and technology. During the implementation of a one-pot procedure for the synthesis of 2,2’:6’2”-terpyridine under certain conditions is demonstrated that the desired product is not accomplished instead, new discoveries are made, including two pure isomers.**

Recently, the organic compound 2,2’:6’,2”-terpyridine (TerPy) has been relevant due to its wide use as a metal ligand and its applicability in various fields of science and technology. Ruthenium(II) complexes with TerPy from supramolecular metallopolymers possessing magnetic and conducting properties; Platinum 2,2’:6’,2”-terpyridine metallopolymer electrodes have been proposed as an economically efficient substitute for bulk platinum catalyst in the reduction of oxygen and conversion of hydrogen. The complex TerPy-$CoCl_2$ has been used as an effective catalyst for the Suzuki-Miyaura cross-coupling reaction. Ruthenium(II) and platinum(II) complexes with TerPy and its derivatives showed antitumor activity and luminescence properties.

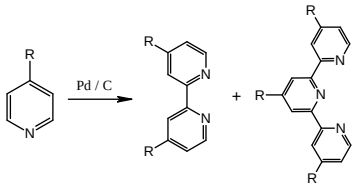
However, there is not a simple one-pot synthesis available in the literature that reported a high percentage yield. That is why commercially, TerPy is very expensive. Consequently, trying to develop a simple methodology for the production of this high-demand organic molecule is relevant.

There have been various approaches to obtaining TerPy. In 2006, it was reported that reacting paraformaldehyde with 2-acetylpyridine in the presence of methanol and potassium hydroxide at room temperature produced a diketone. Then, the mixture was dissolved and heated to reflux in acetic acid and ammonium acetate for 3h. From various conditions, the final percentage yield reported of TerPy was from 5 to 30%. However, the reproducibility is questionable (*See Scheme 1*) [1].



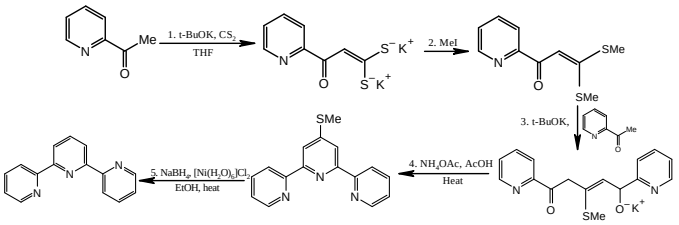
Scheme 1. Synthesis of TerPy from paraformaldehyde and 2-acetylpyridine. Reagents and conditions: a) MeOH, KOH, 16h at room temperature, b) NH_4OAc, AcOH, reflux for 3h.

Another reported method was done in 2014 where 4-picoline was reacted with palladium on carbon, potassium hydroxide, manganese dioxide, and dichloromethane under several techniques such as sublimation, recrystallization, reflux, ^1H and ^{13}C NMR, gas chromatography, flash and column chromatography. In the presence of a methyl group, it was possible to obtain a 3% yield of TerPy (*See Scheme 2*) [2].



Scheme 2. Synthesis of TerPy from 4-picoline. Reagents and conditions: Pd/C. R=Methyl group.

A newly reported method from 2018 demonstrated to achieve of a 70% yield of TerPy [3]. This synthetic procedure had five (5) stages which initially started with 2-acetylpyridine and reacted with reagents such as potassium tert-butoxide, carbon disulfide, THF, and ammonium acetate (*See Scheme 3*). Although this method reported a high percentage yield, it was not a considerable procedure because carbon disulfide (CS_2) is hazardous and its complexity.



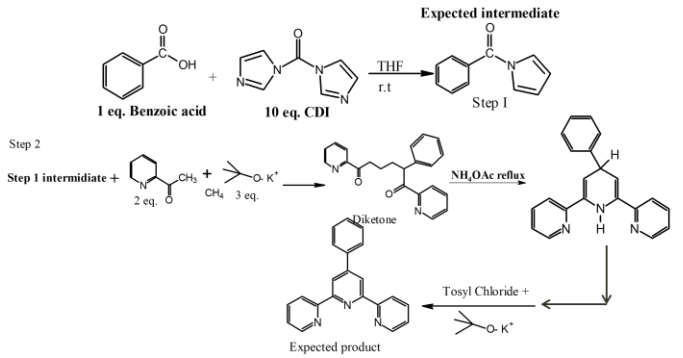
Scheme 3. Synthesis of TerPy from 2-acetylpyridine. Reagents and conditions: 1) t-BuOK, CS_2, THF, 2) MeI, 3) t- BuOK, 2-acetylpyridine, 4) NH_4OAc, AcOH, Δ, 5) $NaBH_4$, $[Ni(H_2O)_6]Cl_2$, EtOH, Δ.

Experimental

Considering the previous reports, our search for developing a new one-pot synthetic procedure for 2,2’:6’,2”-terpyridine was proposed by Dr. Lavey.

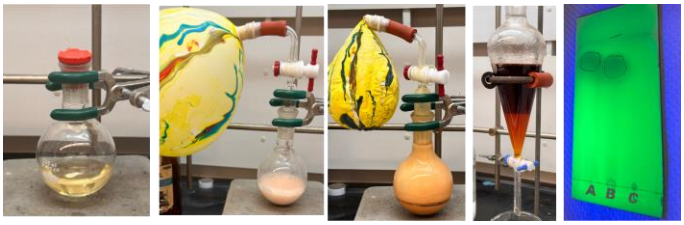
A. Synthetic approach 1.

The initial reaction was made with benzoic acid, THF, and 1,1’-carbonyldiimidazole (*See Scheme 4*) for 30 minutes under room temperature and seal conditions to prevent evaporation.



Scheme 4. Reaction of Benzoic acid with 1,1'-carbonyldiimidazole. Reagents and conditions: 1) THF, 2) 2-acetylpyridine, $KOC(CH_3)_3$, 3) NH_4OAc, reflux, 4) Tosyl Chloride, $KOC(CH_3)_3$.

After the mixing time was complete, 2-acetylpyridne was added to the mixture along with potassium tert-butoxide. This mixture was done under nitrogen gas for a 24h reflux at room temperature (*See Figure 1*). It was a noticeable physical change since the beginning of the reaction.



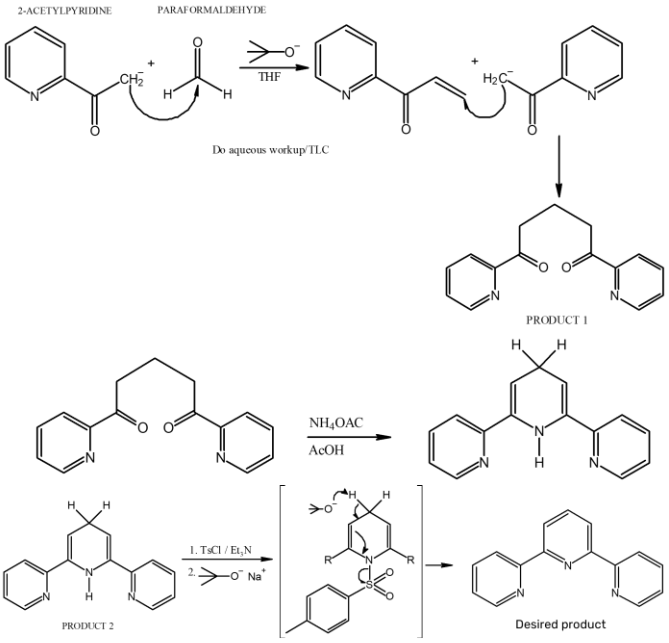
(a) **(b)** **(c)** **(d)** **(e)**

Figure 1. Synthetic approach 1. (a) 30 minutes mixture, (b) beginning of 24h mixture, (c) end of 24h mixture, (d) separation, (e) TLC plate with sample A authentic 2-acetylpyridine, sample B Organic layer, sample C Benzoic acid.

After 24h mixed, there was a separation process using a separatory funnel with Brine solution and Ethyl Acetate. During this step, the reaction showed a small separation where it was evident to see a deep glow red color as shown in ***Figure 1d,*** and it was important to analyze the organic layer in an alumina TLC plate (***Figure 1e***) to identify the compounds we had in the mixture. On the TLC plate, the solvent used was an 8:2 ratio of Hexane:Ethyl Acetate. Although it was not possible to see benzoic acid, authentic 2-acetylpyridine and the organic layer were visible through the mobile phase. At the moment of comparing samples A and B was difficult because it was not common to see organic compounds with that tonality and not similar to the authentic sample A. Additionally, it was not possible to continue isolating the organic product.

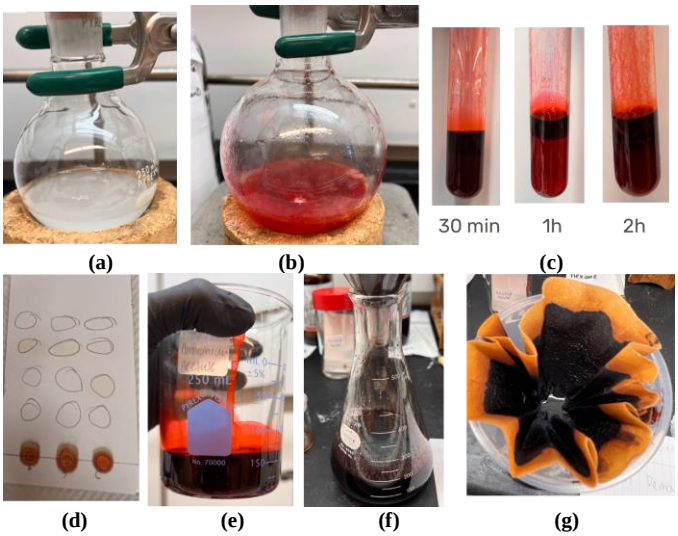
B. Synthetic approach 2.

In this second experiment, the procedure was reacted with paraformaldehyde and THF under sealed conditions (*See Scheme 5*). After 30 minutes, 2-acetylpyridine and potassium tert-butoxide were added to the mixture and refluxed for 2h. In this case, the reaction changed its color from light grey to red.



Scheme 5. Reaction of 2-acetylpyridine and paraformaldehyde. Reagents and conditions: 1) $KOC(CH_3)_3$, and THF, 2) NH_4OAc, AcOH, 3) $TsCl/Et_3N$, $NaOC(CH_3)_3$.

Because of the physical change, the reaction was supervised by taking three (3) samples at 30 minutes, 1h, and 2h of mixing, and then adding a small amount of brine solution, as shown in ***Figure 2c***. Although it was only possible to see a separation at 1h mixed and not in the other two samples, this separation disappeared after a couple of minutes.



(a) **(b)** **(c)** **(d)** **(e)** **(f)** **(g)**

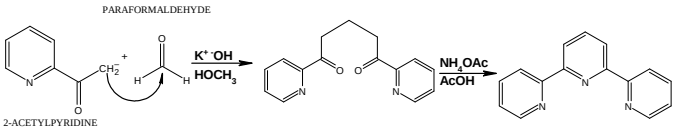
Figure 2. Synthetic approach 2. (a) 30 minutes mixture, (b) mixture of 2h, (c) separation related to time, (d) TLC plate with sample A 30min, sample B 1h, sample C 2h, (e) separated organic layer, (f) and (g) second separation of organic product.

An alumina TLC plate was placed with the three samples in the same order of taking place under a solvent of 7:3 ratio of Hexane:Ethyl Acetate (*See Figure 2d*). Clearly, all samples had the same compounds on them. After 2h of mixing, a separation stage took place with ammonium acetate, but it was

not possible to separate because the final organic product was thick with a very strong color (*See Figure 2e, f, and g*) and unable to compare with any reference compound.

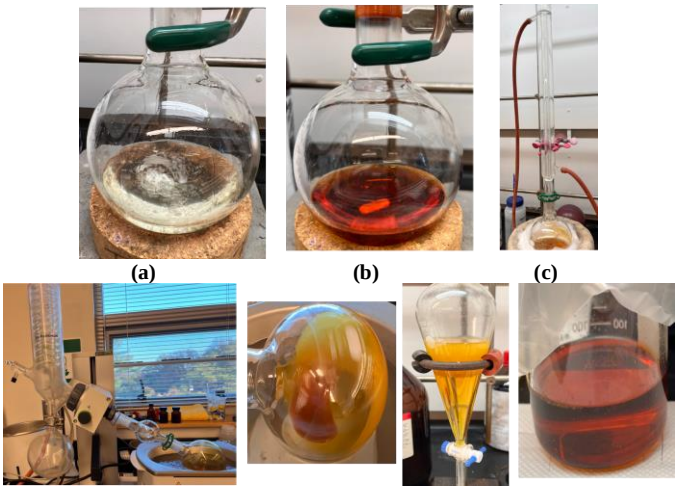
C. Synthetic approach 3.

This approach was similar to approach 2, but THF was replaced with methanol during the initial sealed mixture and potassium tert-butoxide with potassium hydroxide for a 24h mixing (*See Scheme 6*).



Scheme 6. Reaction of 2-acetylpyridine and paraformaldehyde. Reagents and conditions: 1) KOH, and $HOCH_3$, 2) NH_4OAc, AcOH.

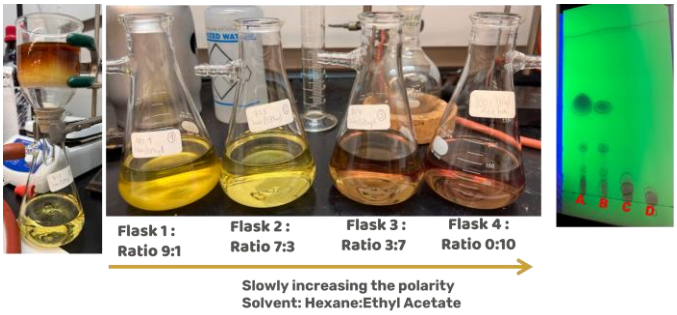
Additionally, the mixture went under a 3h reflux using a water condenser and adding ammonium acetate. The reflux temperature was between 50-70°C, as shown in ***Figure 3c***. When the reflux process was completed, the leftover methanol was removed under reduced pressure in a rotavapor to reduce the organic product as much as possible.



(a) **(b)** **(c)** **(d)** **(e)** **(f)** **(g)**

Figure 3. Synthetic approach 3. (a) 30 minutes mixture, (b) mixture of 24h, (c) addition of NH_4OAc under a reflux for 3h, (d) Reducing under rotavapor, (e) reduced organic product, (f) extraction of organic product, (g) separated organic layer.

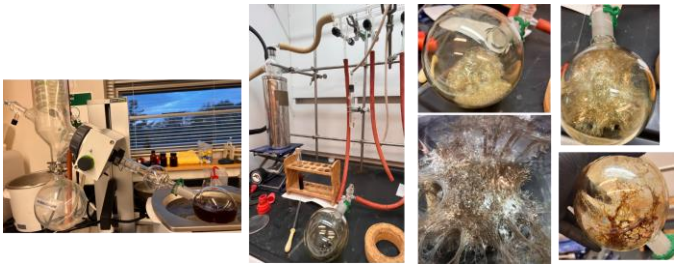
Using the reduced organic product, the extraction process was completed with chloroform until recollected a light red organic layer (*see Figure 3 f and g*). During this process, it was visible that the organic layer needed more testing to determine which compounds were presented on this extracted product. Additionally, a dry column vacuum chromatography was done using silica gel under a low vacuum system and slowly increasing the polarity of the solvent. The solvent used was Hexane:Ethyl Acetate (*see Figure 4*).



(a) **(b)** **(c)**

Figure 4. Dry column vacuum chromatography. (a) set up, (b) samples of extraction, (c) TLC plate, **A.** sample 9:1, **B.** sample 7:3, **C.** sample 3:7, **D.** sample 100% ethyl acetate.

To further analyze each sample and their composition, a silica TLC plate was performed with a 7:3 solvent ratio of Hexane:Ethyl acetate, and it was determined that samples 9:1 and 7:3 contained the same compounds with different proportions as samples 3:7 and 0:10. For this reason, flasks 1 and 2 were combined as flasks 3 and 4.



(a) **(b)** **(c)**

Figure 5. (a) Drying using rotavapor, (b) high pressure vacuum set up, (c) dried product.

The combination of flasks 3 and 4 was dried under reduced pressure using the rotavapor. After, the dried organic product was isolated at a high-pressure vacuum and slowly started to change from a liquid state to a brown solid state, as shown in ***Figure 5c***.

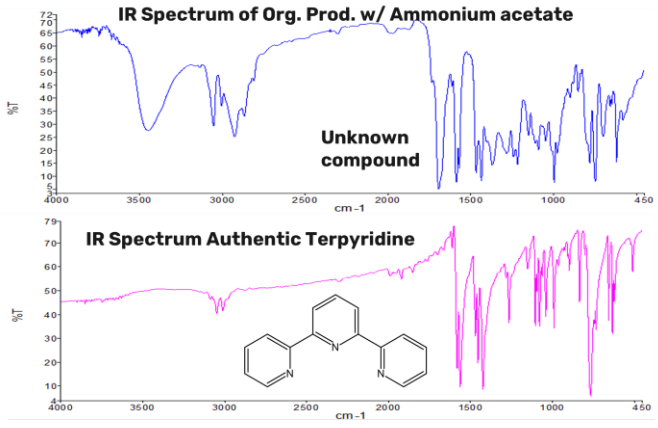


Figure 6. (**top**) IR spectrum of isolated organic product (brown color), (**bottom**) IR spectrum authentic terpyridine.

To recognize the final organic product, it was necessary to perform chemical analyses such as IR and ^{1}H NMR. According to ***Figure 6***, the IR spectrum did not show any similarities related to the authentic Terpyridine. Additionally, the ^{1}H NMR spectrum did not exhibit any similar pattern as indicated in ***Figure 7***. From these data, we were able to conclude that it was a pure unknown product.

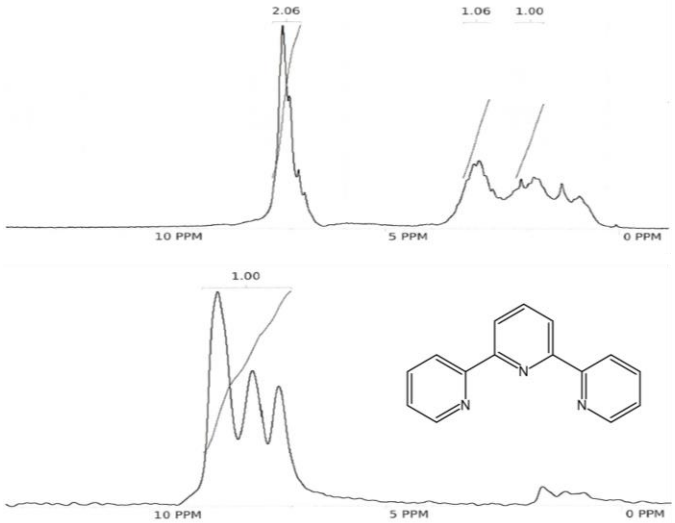
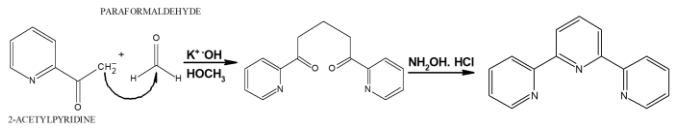


Figure 7. (**top**) ^{1}H NMR spectrum of isolated organic product (brown color) in $CDCl_3$, (**bottom**) ^{1}H NMR spectrum authentic terpyridine in $CDCl_3$.

D. Synthetic approach 4.

During this synthetic approach, the previous methodology was applied with paraformaldehyde and methanol under a sealed mixture and the addition of 2-acetylpyridine and potassium hydroxide. During the reflux process, the ammonium acetate was replaced with hydroxylamine, and the reflux temperature was between 60-70°C (*See Scheme 7*).



Scheme 7. Reaction of 2-acetylpyridine and paraformaldehyde. Reagents and conditions: 1) KOH, and $HOCH_3$, 2) NH_2OH, HCl.

During this phase, there is no visible change during the reaction. After removing the methanol from the mixture in the rotavapor and transferring it to the separatory funnel, it was not possible to identify a separation only using chloroform. In this case, it was necessary to add a small amount of water (*Figure 8f*). The final extracted organic layer had to be dried out again under the rotavapor to reduce the final organic product.

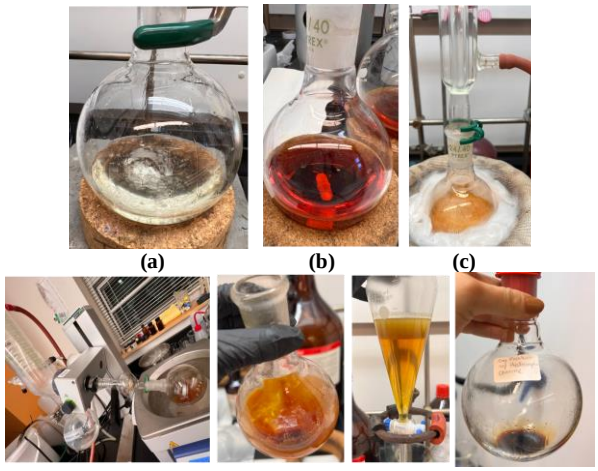


Figure 8. Synthetic approach 4. (a) 30 minutes mixture, (b) mixture of 24h, (c) addition of $NH_2OH.HCl$ under a reflux for 3h, (d) Reducing under rotavapor, (e) reduced organic product, (f) extraction of organic product, (g) separated organic layer.

Using the same methodology applied to the dry vacuum chromatography, the organic product was extracted with different ratios of solvent Hexane:Ethyl Acetate. Comparing the collected samples in ***Figure 9c***, there was a similarity of organic compounds between flasks 1, 2, and 3 that was not able to see in flask 4 throughout the silica TLC plate, which was accomplished in a 7:3 solvent ratio of Hexane:Ethyl acetate.

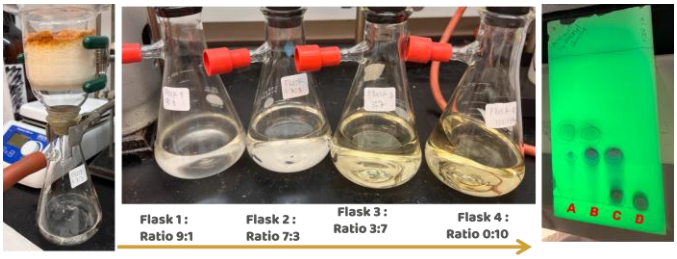


Figure 9. Dry column vacuum chromatography. (a) set up, (b) samples of extraction, (c) TLC plate, **A.** sample 9:1, **B.** sample 7:3, **C.** sample 3:7, **D.** sample 100% ethyl acetate.

According to the previous comparison, similar samples were combined. The combination of flasks 1, 2, and 3 was dried using the rotavapor. Then, it was isolated at a high-pressure vacuum until obtained a white powder product as shown in ***Figure 10***.

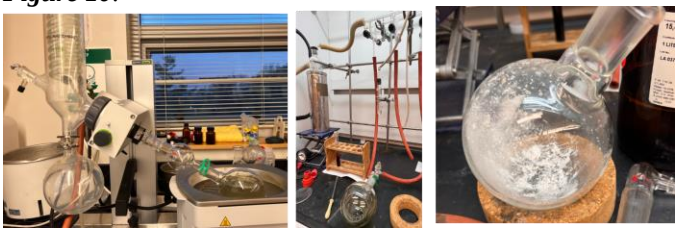


Figure 10. (a) Drying using rotavapor, (b) high pressure vacuum set up, (c) dried product.

On the other hand, flask 4 (sample of 100% ethyl acetate) was analyzed through column chromatography. In this method, there were two attempts with different ratios of the eluent. In trial 1, the eluent used 9:1 Hexane:Ethyl acetate, but there was not any movement of the organic layer (*Figure 11a*). In trial 2, the eluent was 7:3 Hexane:Ethyl acetate and the organic layer slightly moved down (*Figure 11b*). In this trial, there was a collection of 49 samples that were spotted under a TLC plate.

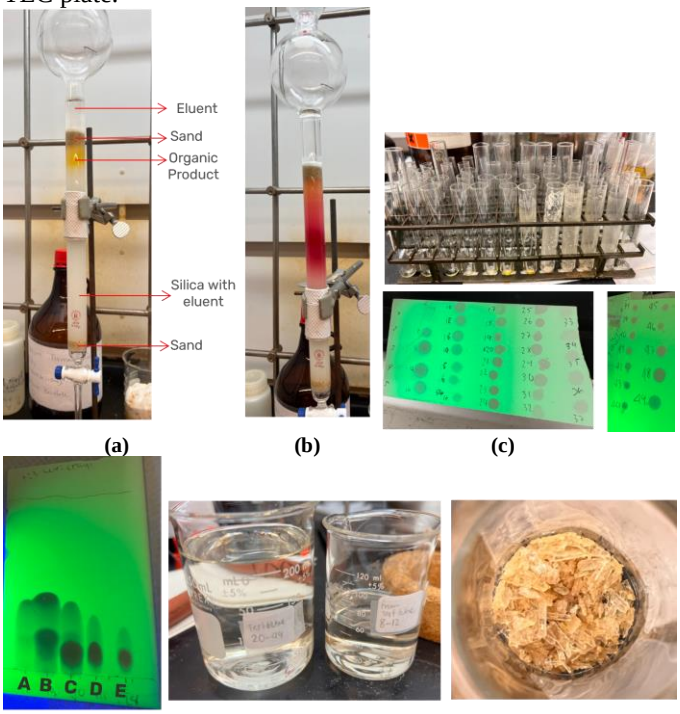


Figure 11. Column Chromatography. (a) Trial 1, (b) Trial 2, (c) collection of samples in test tubes and TLC plate of each sample, (d) TLC plate of test tubes 8, 12, 16, 20, and 24, (e) Dried pure organic products, (f) Crystalized pure organic product from test tube 8-12.

Another TLC plate took place with only test tubes 8, 12, 16, 20, and 24 respectively, with a ratio of 7:3 Hexane:Ethyl acetate as solvent. Although sample A did not have a strong pattern along the mobile face, it was still similar to sample B. While samples C, D, and E, had the same strong compound on them. Thus, all the test tubes between 8 to 12, and 13 to 49, were isolated and mixed with a small amount of ethyl acetate (*Figure 11d and e*). These two organic products were dried out, but it was only possible to continue analyzing the crystal product from test tubes 8 to 12 (*Figure 11f*) because of the short time of the research.

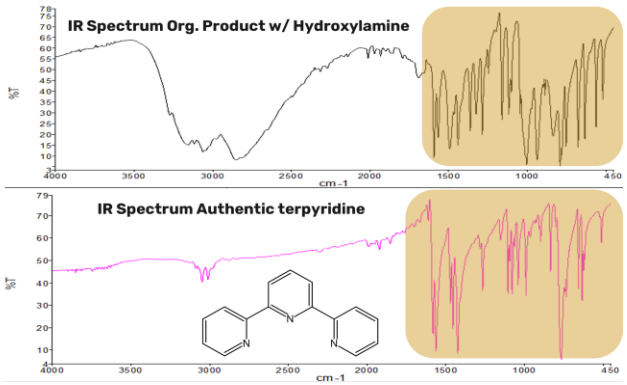


Figure 12. (**top**) IR spectrum of isolated organic product (white color), (**bottom**) IR spectrum authentic terpyridine.

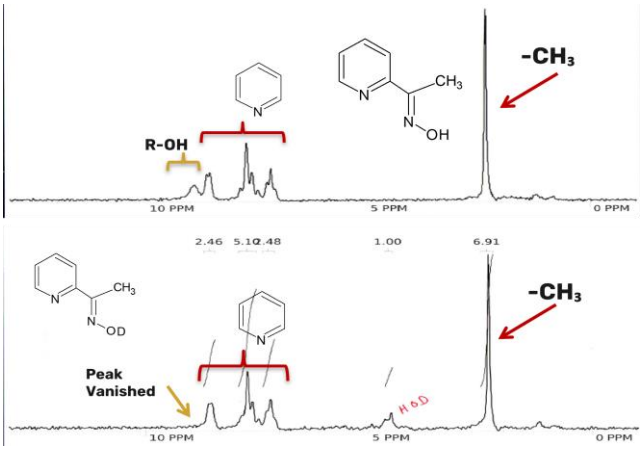


Figure 13. (**top**) ^{1}H NMR spectrum of isolated organic product (white color) in $CDCl_3$, (**bottom**) ^{1}H NMR spectrum of isolated organic product (white color) in $CDCl_3$ with one drop of D_2O.

After synthesizing these organic products, it was applied the same IR and ^{1}H NMR techniques. Initially, the white organic product was compared to the authentic terpyridine sample, and there was a similarity in patterns (*Figure 12*). Furthermore, ^{1}H NMR spectrum was done in $CDCl_3$ only and with one drop of D_2O. In ***figure 13,*** both spectrums indicated that there was a methyl group and an aromatic group presented in the white pure product. Also, there was a peak that vanished when one drop of D_2O was added. Thus, we assigned that it was an O-H peak.

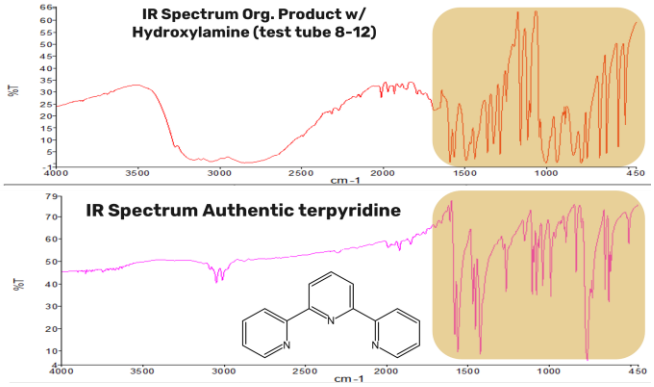


Figure 14. (**top**) IR spectrum of isolated crystal organic product, (**bottom**) IR spectrum authentic terpyridine.

Moreover, the IR spectrum of the crystallized product from test tubes 8 to 12 was related to the authentic terpyridine, which illustrated a similar pattern (*Figure 14*). In ***figure 15***, ^{1}H NMR spectrum was done in $CDCl_3$ only and with one drop of D_2O, which showed a similar spectrum. In this case, both spectrum had a methyl group and an aromatic group. Once again, a peak vanished in presence of one drop of D_2O, which was assigned as an O-H peak

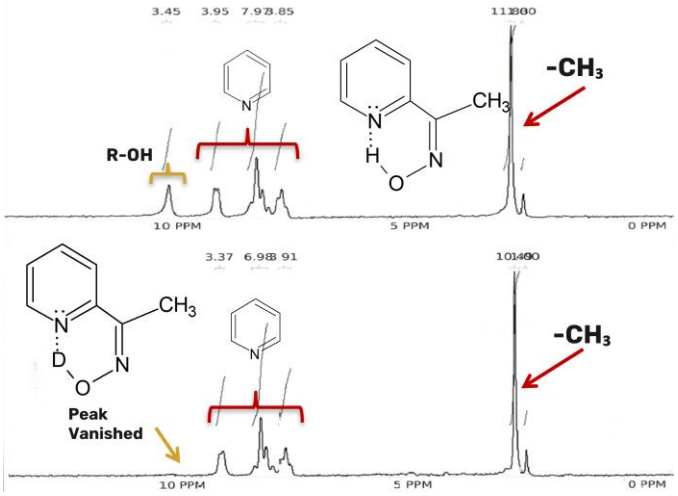


Figure 15. (**top**) ^{1}H NMR spectrum of isolated crystal organic product in $CDCl_3$, (**bottom**) ^{1}H NMR spectrum of isolated crystal organic product in $CDCl_3$ with one drop of D_2O.

Comparing the two previous final products, it is important to recall that these compounds can deb isomers because they showed similar patterns on the spectrums with different percentages of absorption (*figure 16*).

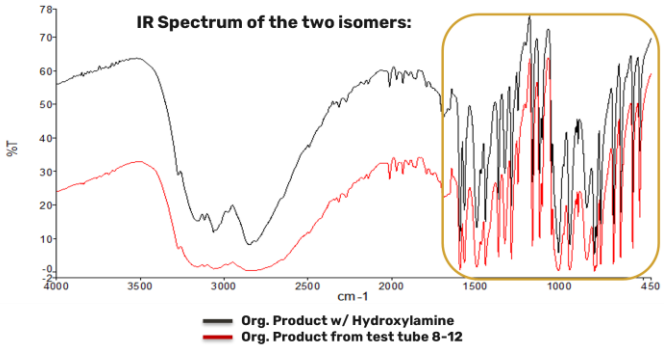


Figure 16. Comparison of the white product and crystal product.

Additionally, it was possible to react both pure compounds with Iron(III) chloride solution. As illustrated in ***figure 17***, $FeCl_3$ solution was reacted with both final products, which formed a deep red color. This type of reaction is strong evidence that both pure compounds are very good chelating agents.

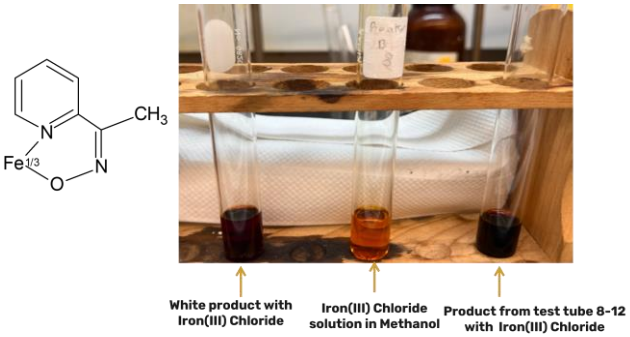
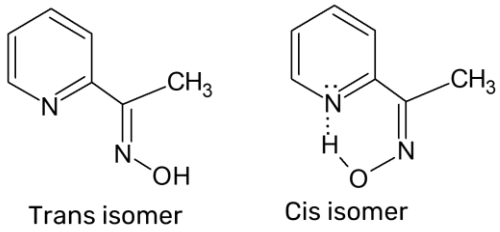


Figure 17. Reaction with $FeCl_3$ solution.

Based on IR and ^{1}H NMR spectrums, D_2O exchange reaction, and deep coloration with $FeCl_3$ solution, we conclude that the oxidation step with hydroxylamine provided two pure products that are capable of chelating metal salts to produce tris coordination complexes. The proposed structures for these two pure products are as follows:



Scheme 8. Proposed structures for the pure products.

These products indicate that the first reaction did not go to completion before the hydroxylamine was added. However, by following the proposed synthetic scheme, we are unable to detect any desired product (2,2':6',2"-terpyridine). We are trying to proceed with various other methods to get the desired products.

E. Conclusions

Using Benzoic acid, 2-acetylpyridine, potassium tert-Butoxide, and THF, we got some new red glowing compound. The structure is yet to be determined.

Following the same procedure in my second attempt, I used paraformaldehyde instead of Benzoic acid and found the same glowing deep red compound. We are trying to isolate that product in pure form.

However, by changing the strong base as potassium tert-butoxide to potassium hydroxide (KOH) and the solvent from THF to CH_3OH, followed by carrying out the oxidation with hydroxylamine hydrochloride ($NH_2OH.HCl$), we ended up isolating three (3) different pure products. Based on 1H-NMR and IR spectrums and reactions with $FeCl_3$, we are confident that those two pure compounds are pyridyl oxime isomers. The structure of the 3rd compound is yet to be established.

When the cyclization process was carried out with Ammonium acetate (NH_4OAc) in the second step, I am able to isolate another pure product, whose 1H-NMR and IR spectrums look very similar to Terpyridine, but its TLC

behavior is different. Its real structure is yet to be determined. Also, it does not complex with $FeCl_3$.

ACKNOWLEDGMENT

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