4,4′,4″-Trimethyl-2,2′:6′,2″-terpyridine by Oxidative Coupling of 4-Picoline

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Abstract:

My research is based on an article published in *The Journal of Organic Chemistry (J. Org. Chem. 2014, 79, 10624-10628)* about a new innovative method of synthesizing terpyridine. The proposed new method is a one-step reaction that takes up to 7 days, followed by sublimation to purify the product. My input to this project was to try and find a different way to purify the product without using sublimation. So far I have managed to actually synthesize the desired products, come up with a desired solvent system for thin layer chromatography(TLC), column chromatography and prep-thin layer chromatography(Prep-TLC). I have also analyzed my results using nuclear magnetic resonance(NMR) spectroscopy and high performance liquid chromatography (HPLC). I have also found a promising method to crystalizing the product.

Introduction

The reason why terpyridine is so important to us is because it is an intermediate in organometallic chemistry and coordination chemistry, which puts it at a very high demand. There is no easy one-step method to synthesize terpyridine at a high yield on a large scale. The best results published by Michael T. Robo and his group was 14% terpyridine and 40% bipyridine. Since terpyridine is so difficult to synthesize, it is commercially unavailable.

My research goal is to reproduce the results that were published and come up with a different way to separate the products from each other. The authors used sublimation to purify the products. Although sublimation gives nice pure products, it is not ideal on a large scale. I explore other methods of separating the two products, bipyridine and terpyridine.

Techniques/Instruments

To separate the products, bipyridine and terpyridine, I used TLC, column chromatography, prep TLC and crystallization. To analyze the products, I used NMR and HPLC.

Experimental results and Discussions

For the first trial I attached a schlenk tube to a schlenk line, alternated between nitrogen gas and vacuum for 10 minutes with external heating. Placed a stirring rod inside the tube. Added 160mg of 10% palladium on carbon(Pd/C) to the tube. Again alternated between nitrogen and vacuum to make sure it was dry. Added 1.79g of Manganese dioxide(MnO_2). Repeated the

drying process. Used a syringe to measure out 2.00mL of 4-Methylpyridine and injected it into the tube through the rubber septum. Placed the sealed tube into a 140℃ oil bath and stirred the reaction for 7 days total.

After 7 days the tube was removed from the oil bath, while hot, poured into a 150mL beaker, the tube was washed out several times with total of 15mL CH_2Cl_2. Once all the soluble materials were dissolved in CH_2Cl_2, it was poured through a thin layer celite, which was washed with 10mL of CH_2Cl_2. Rotor vaporized the CH_2Cl_2 to obtain the first crude.

Separation and Analysis of first crude

The first technique I used to analyze the compound was TLC. I had no given information about the solvent system or stationary phase of TLC components so I did a lot of trials and eventually came up with a solvent system of 4:6 ethyl acetate and hexane with 1 drop of ammonium hydroxide per 10mL of solvent. The ammonium hydroxide is to neutralize the silica gel.

In comparison, I did have standard bipyridine to compare my product with. With this ratio the bipyridine moves up the silica gel and clearly separates as seen in *figure 1.* For the terpyridine to move up the silica gel plate, it requires 100% ethyl acetate with 1 drop of ammonium hydroxide per 10mL of solvent.

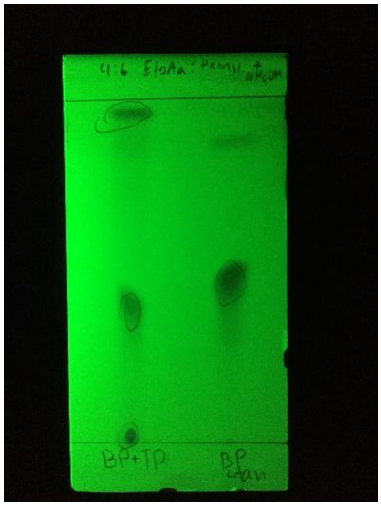
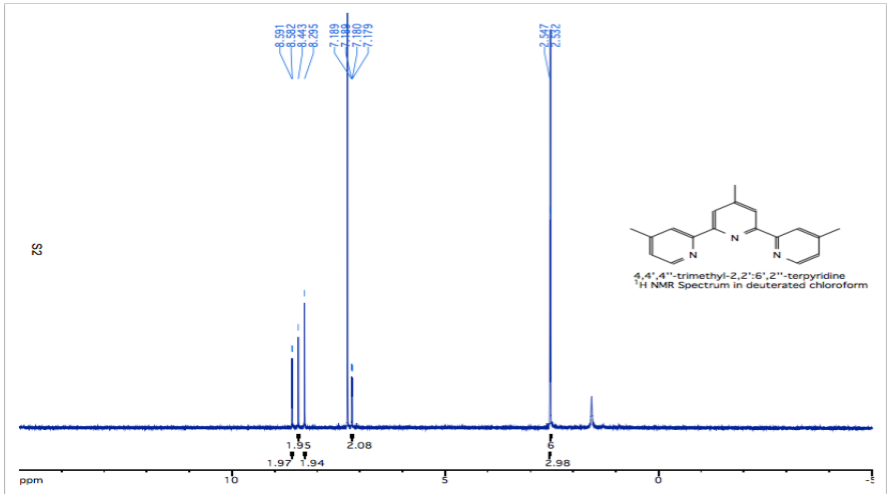
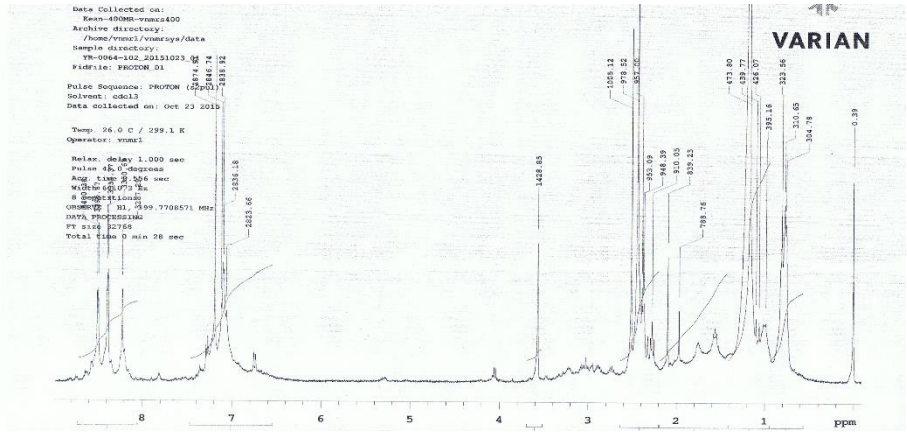


Figure 1: On left bipyridine and terpyridine mixture and on right bipyridine standard in 4:6 ethyl acetate and hexane and 1 drop of ammonium hydroxide

Moving on from TLC to a larger scale, column chromatography, I dissolved the solid crude in pure ethyl acetate and placed it on the column. I used the same solvent ratio as in TLC and got two different fractions. The majority of the product was in test tubes 1-3 and very little was in test tubes 5-10. Took an NMR spectrum of both samples. The high resolution NMR of test tubes 5-10 compared with literature NMR of terpyridine as seen in *figure 2*, show methyl signal at 2.5ppm and four aromatic hydrogen signals at 7.1, 8.1, 8.2, 8.3. In comparison to literature value, this concludes that there is terpyridine in the second fraction along with impurities.

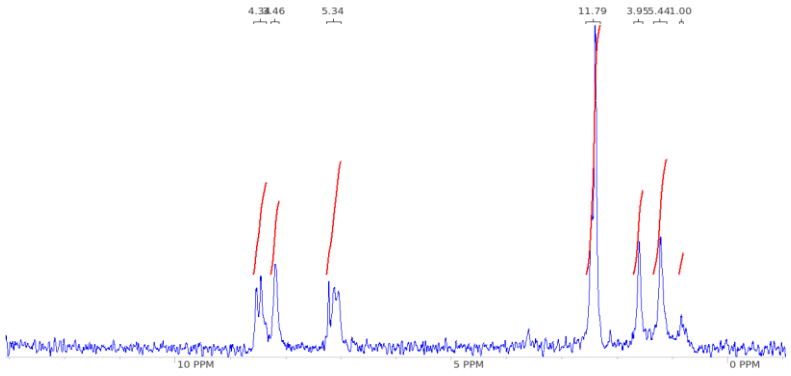
Figure 2: top, published literature NMR terpyridine. Bottom, high resolution NMR from Kean University





Moving forward to the first fraction, test tube 1-3, NMR as seen in *figure 3*, show us similar peaks as the terpyridine spectrum. The NMR spectrum difference between bipyridine and terpyridine is one less hydrogen signal in the aromatic region. Based on this NMR spectrum I concluded that the first fraction test tubes 1-3, had both bipyridine and terpyridine in it, and the second fraction, test tubes 5-10, is just terpyridine.

Figure 3: NMR spectrum of fraction 1, test tubes 1-3.



With this information I resorted back to column chromatography to further separate my first fraction. I tried many variations of column chromatography. I experimented with a gradient solvent system, silica gel plug, low polarity system. Nothing seemed to work because the product would just all at once come out with no separation.

I eventually moved on to prep-TLC. Dissolved my product in ethyl acetate and loaded the prep-TLC plate with it. Used the same solvent system and got a clear separation with only two bands. The bipyridine on top and terpyridine on bottom. I scraped both of the bands from the plate and used 100% ethyl acetate with 1% methanol in flash chromatography to extract my products. After I rotor vaporized the solvents I took the NMR spectrum of both bands. As seen in *figure 4*, The NMR spectrum for both of the samples are very similar with similar peaks along with lots of impurities.

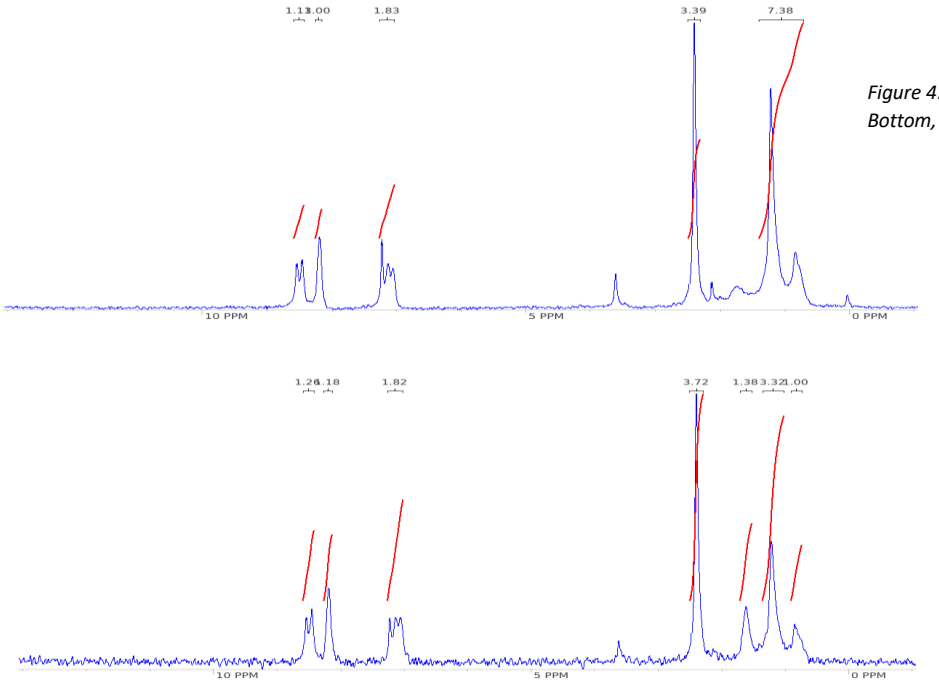


Figure 4: top, lower band of prep TLC, terpyridine. Bottom, higher Rf value band from prep TLC.

Second Reaction

For the second reaction, the procedure is exactly the same as the first one except I doubled the scale of the reaction. Everything was exactly the same up until the workup. After I extracted the product from the celite and rotor vaporized the CH_2Cl_2, I did flash chromatography with it with pure ethyl acetate to remove the impurities. Again I rotor vaporized it and dissolved the solid in just ethyl acetate. After 7 days I saw crystals forming from the mother liquor. I immediately took the NMR spectrum of the crystal as seen in *figure 5* and the TLC of the sample as seen in *figure 6*. The NMR of the sample concludes that it is bipyridine compound and the TLC backs up this claim. Also since I had a pure 4 4'-dimethyl-2 2'-bipyridine compound I ran it through the HPLC. The solvent system used is 50:50 methanol and water and the retention time is about 17 minutes as seen in *figure 7*.

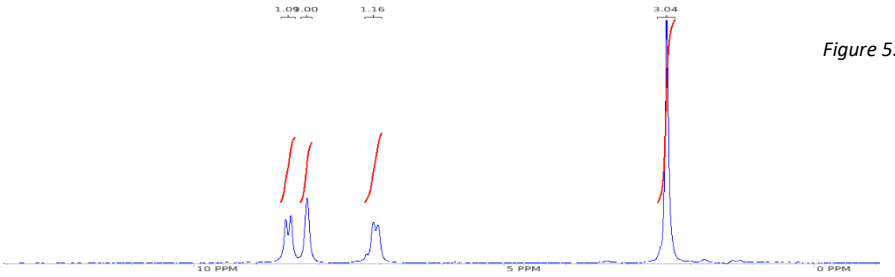


Figure 5: NMR of crystalized product

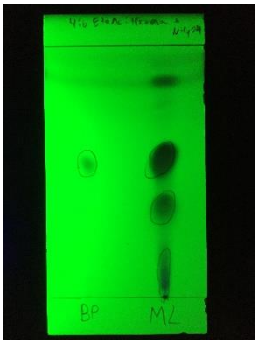


Figure 6: TLC of crystalized product and mother liquor in 4:6 ethyl acetate and hexane solvent with 1 drop of ammonium hydroxide

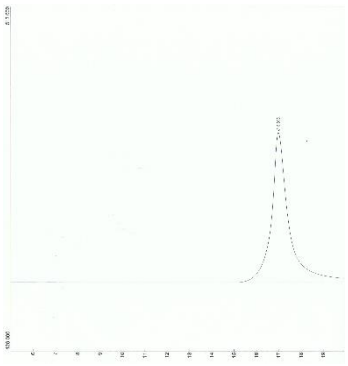


Figure 7: HPLC of crystalized product

Conclusions

One of the biggest results in my experiments was the new method of crystalizing the 4 4'-dimethyl-2 2'-bipyridine. Crystallization has the most potential from all the methods and techniques I have explored. Also its clear that there is a lot more of the product in the mother liquor, which if I had waited longer the crystal would have become bigger and thus I would have

more sample. This can potentially be the course of this research project. Also the bipyridine and the terpyridine crystals could come at different times. Once there is enough sample of terpyridine, HPLC could be done with it and we could get the retention time for both of the products and the ratio of the products from it.

As far as column chromatography goes, the solvent system I have isolated works well but instead of the ammonium hydroxide I should have used triethylamine. The terpyridine might not stick to the column as much if I had used triethylamine. Prep TLC can be done with it again with this compound to get a better separation so when the silica gel is cut out there is less contamination between the bands.

This is as far as I have gone with this project, with more work I am certain there is a better way to separate these products and eventually perform the reaction on a higher scale with high yield.

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