

Development of a Student Lab Experiment: ^1H NMR Characterization and Synthesis of Substituted 2,2'-Bipyridines

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Abstract:

This paper describes an undergraduate research project focused on the creation of a laboratory experiment that crosses the fields of green, biomimetic, inorganic, organic, and organometallic chemistry. Research involved investigation of the synthesis and NMR characterization of a series of Water oxidation catalysts for providing a rich learning experience for students. A goal of this project was to consider the implementation of a greener student laboratory where learning outcomes across multiple years of undergraduate laboratories could be proposed. The experimental progress and results to date will be presented.

INTRODUCTION

Greener sources of energy production are in high demand due to negative global impacts from producing energy through the combustion of fossil fuels. The production of hydrogen-fuel through water splitting is one environmentally friendly energy alternative. In nature, an inorganic oxygen evolution catalyst (OEC), present within photosystem II, can split water into hydrogen and oxygen molecules. Water oxidation catalysts (WOCs) are of great interest due to their ability to mimic this naturally occurring process. The synthesis of ligands is an essential process that occurs during the development of drugs, polymers, and catalysts such as WOCs, that contain a central metal atom. Bipyridines comprise a family of ligands with the formula $(\text{C}_5\text{H}_4\text{N})_2$. Specifically, the 2,2'-bipyridines are popular ligands in coordination chemistry.¹ For example,

the ligand synthesis of 6,6'-dimethoxy-2,2'-bipyridine was an essential process for the development of a copper water oxidation catalyst.² The synthesis of bipyridines involves the coupling of two pyridine rings. Recently, a synthetic approach using nickel-catalyzed reductive couplings of 2-halopyridines without the use of an external ligand for symmetrical 2,2'-bipyridines was reported (Figure 1).¹

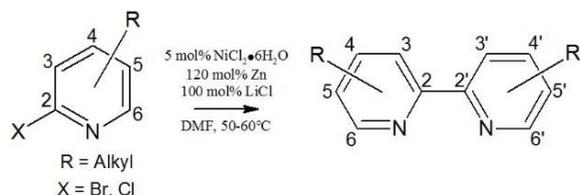
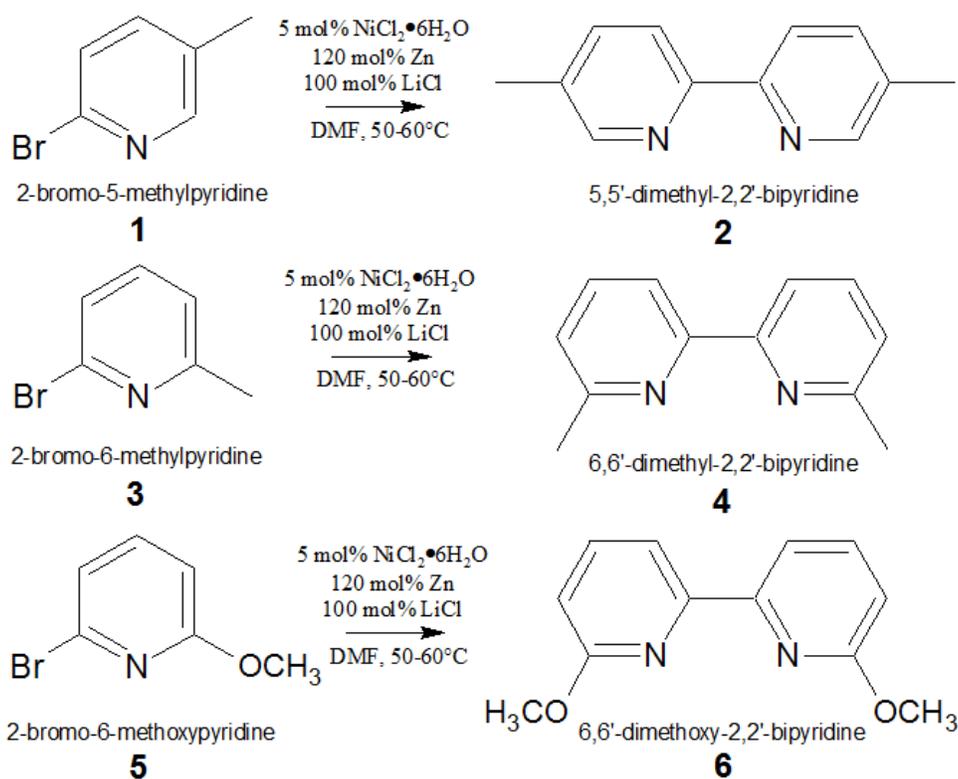


Figure 1. Ni-Catalyzed Reductive Homocoupling of 2-Halopyridines¹

It is important in synthetic studies to be able to support that the correct ligand has been synthesized. One major technique for chemical identification is NMR spectroscopy. NMR spectroscopy is an extremely powerful analytical technique used to determine the structure of a compound by examining the unique environments of each nuclei. Many different nuclei can be observed in an NMR experiment. The majority of studies utilize ¹H nuclei, as it is present in most chemical compounds.

A practical experiment is presented here and in Scheme 1 for the synthesis of symmetrical 2,2'-bipyridines and their characterization by ¹H NMR spectroscopy. The experiment can have two or three parts, which can be performed during two or three lab periods, respectively. The symmetrical 2,2'-bipyridines are synthesized during the first lab. The 2,2'-bipyridines can be purified through flash chromatography during an optional second lab period. The final lab period involves hands-on ¹H NMR spectroscopy experience.



Scheme 1. Relevant substituted 2-bromopyridines reactions and subsequent 2,2'-bipyridine products from this study

EXPERIMENTAL PLAN

The goal of this project was to create a multi-week experiment for students to synthesize a symmetrical 2,2'-bipyridine via reductive cross-coupling and characterize their product by ^1H NMR spectroscopy. This project was part of an undergraduate semester long directed research endeavour, during which seven syntheses, three purifications, and nine ^1H NMR characterizations were performed.

MATERIALS

Reagents

The 2-bromopyridines selected for experimental development included 2-bromo-

5-methylpyridine (**1**), 2-bromo-6-methylpyridine (**3**), and 2-bromo-6-methoxypyridine (**5**). The reagents necessary for experimental development included nickel chloride hexahydrate ($\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$), N,N-dimethylformamide (DMF), anhydrous lithium chloride (LiCl), zinc dust, iodine, acetic acid, hydrochloric acid (HCl), and ammonia. All reagents were of reagent grade.

Products

To help confirm product formation, respective 2,2'-bipyridines were purchased. These included 5,5'-dimethyl-2,2'-bipyridine (**2**) and 6,6'-dimethyl-2,2'-bipyridine (**4**). All products were purchased from Sigma-Aldrich and were of reagent grade.

Other Chemicals

Dichloromethane (CH_2Cl_2) and anhydrous sodium carbonate (Na_2CO_3) were required for liquid-liquid extraction and drying steps in the experimental procedure. To monitor formation of product, by thin layer chromatography (TLC), hexane and ethyl acetate were used as the developing solvent. For the flash chromatography purification, clean sand and silica gel 60 were required in addition to the hexane and ethyl acetate mobile phase.

Required Equipment

This experiment required access to a standard organic chemistry kit, a UV lamp, a rotary evaporator, flash chromatography glass wear, and a ^1H NMR spectrometer.

EXPERIMENTAL OVERVIEW

Synthesis of Symmetrical 2,2'-Bipyridines

A general procedure was modified and utilized.¹ A 25 mL round-bottom flask (RBF) was charged with $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.01g) and DMF (2 mL), and a stir bar. The RBF, with a condenser attached, was stirred and heated to 40 °C on a hot water bath (Figure 2). At 40 °C, the 2-halopyridine (1 mmol), anhydrous LiCl (0.04 g) and zinc dust (0.08 g) were added. When the temperature rose to 50 °C, a grain of iodine and a drop of glacial acetic acid was added. During this addition, a colour change occurred. The reaction mixture went from blue to green to brown to black. The reaction mixture was stirred at 55 to 60 °C for a 2 h period. During this period,

product formation was monitored by TLC using a 5:1 hexane:ethyl acetate solution. The reaction mixture was cooled to room temperature and 1 M HCl aqueous solution (1.5 mL) was added. The mixture was then made alkaline with 25% aqueous ammonia. The alkalinity was monitored by red litmus paper. The mixture was then transferred to a 60 mL addition funnel for liquid-liquid extraction. The mixture was extracted with three 15 mL portions of CH_2Cl_2 . The organic layers were collected, combined, and dried over anhydrous Na_2CO_3 . After drying, the organic layer was filtered into a 100 mL RBF. The organic layer was then concentrated on a rotary evaporator. This procedure was also attempted with the DMF being substituted for acetonitrile.

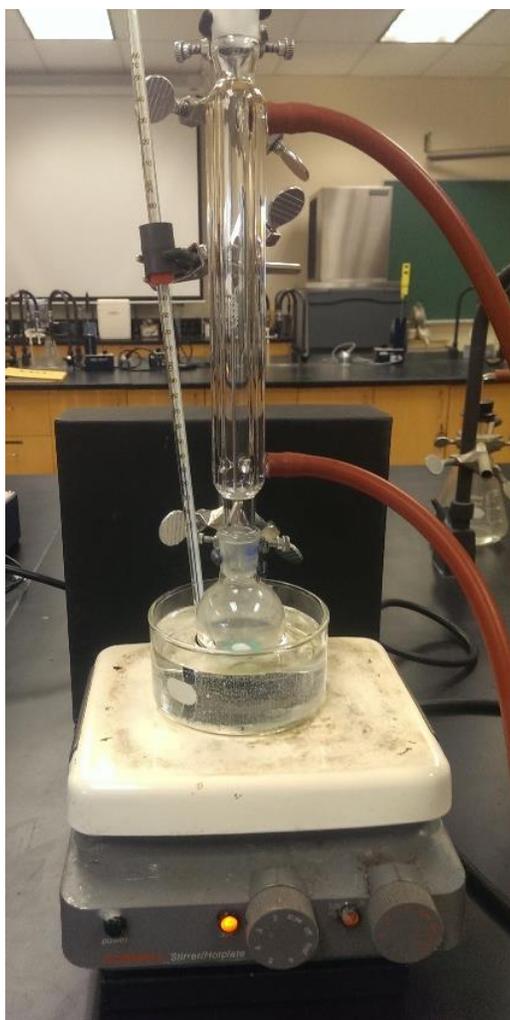


Figure 2. Synthesis apparatus

Purification of Products

Flash chromatography columns were prepared in 60 mL addition funnels (Figure 3). A small piece of cotton wool was added directly above the stopcock of an addition funnel. An approximately 1 cm layer of clean sand was added on top of the cotton wool. In a fume hood, a silica gel slurry was formed with silica (8 g) and a 5:1 hexane:ethyl acetate solution (60 mL). This slurry was stirred until it appeared homogenous and was then added on top of the clean sand. The crude sample was dissolved in a minimum amount of 5:1 hexane:ethyl acetate and added to the top of the silica gel, where it was allowed to soak into the silica. A small layer of sand was then added to the top of the silica gel column. Three elution solutions (60 mL) were then added in the following order: 5:1, 3:1, and 1:1 hexane:ethyl acetate. Fractions were collected in ten 18 mm test tubes. Thin layer chromatography was used to monitor for the presence of product in the fractions. Fractions containing product were combined and the solvent was removed on a rotary evaporator.



Figure 3. Purification apparatus

^1H NMR Measurements

All samples were dissolved in approximately 1 mL of deuterated-chloroform (CDCl_3). The dissolved samples were then transferred into NMR tubes. All ^1H NMR spectra were

acquired with a Bruker AVANCE III 500 MHz NMR spectrometer. Spectra were recorded at room temperature with 160 scans at a spectral width of 20.6 ppm.

HAZARDS

Proper protective equipment should be worn at all times throughout the experiment. The hazards for each compound used, in this experimental development, are located in the current material safety data sheets (MSDS).

RESULTS

Purchased 5,5'-dimethyl-2,2'-bipyridine

The NMR spectra of the purchased product **2** was acquired (Figure S1; figures S1 to S8 are provided below, in the Supporting Material). ¹H NMR (500 MHz, CDCl₃) δ 2.41 (6H, s), 7.63 (2H, d), 8.26 (2H, d), 8.51 (2H, s).

Purchased 6,6'-dimethyl-2,2'-bipyridine

The NMR spectra of the purchased product **4** was acquired (Figure S2). ¹H NMR (500 MHz, CDCl₃) δ 2.67 (6H, s), 7.18 (2H, d), 7.73 (2H, t), 8.22 (2H, d).

Purchased 2-bromo-5-methylpyridine

The NMR spectra of the purchased product **1** was acquired (Figure S3). ¹H NMR (500 MHz, CDCl₃) δ 2.32 (3H, s), 7.34 (2H, m), 8.23 (1H, s).

Reactions

In all, seven reactions were performed using different reagents and reaction conditions to optimize the syntheses. The conditions of each reaction are listed in **Table 1**.

Table 1. Experimental reactions performed

Reaction (#)	Reactant (#)	Solvents	Purification (Y/N)
1	1	<i>DMF</i>	Y
2	3	<i>DMF</i>	N
3	5	<i>DMF</i>	Y
4	1	<i>DMF</i>	N
5	1	<i>Acetonitrile</i>	N
6	1	<i>Acetonitrile</i>	N
7	3	<i>Acetonitrile</i>	Y

Synthesis of 5,5'-dimethyl-2,2'-bipyridine with DMF and purification (Reaction 1)

The ¹H NMR spectrum of the product obtained from the attempted synthesis of **2** from **1** using DMF was acquired (Figure S4). ¹H NMR (500 MHz, CDCl₃) δ 2.44 (6H, s), 7.69 (2H, d), 8.33 (2H, d), 8.55 (2H, s). This attempt included the flash chromatography purification.

Synthesis of 6,6'-dimethyl-2,2'-bipyridine with DMF and no purification (Reaction 2)

The ¹H NMR spectrum of the product obtained from the attempted synthesis of **4** from **3** using DMF was acquired (Figure S5). All peaks observed were due to CDCl₃. This attempt did not include the flash chromatography purification.

Synthesis of 6,6'-dimethoxy-2,2'-bipyridine with DMF and purification (Reaction 3)

The ¹H NMR spectrum of the product obtained from the attempted synthesis of **6** from **5** using DMF was acquired (Figure S6). ¹H NMR (500 MHz, CDCl₃) δ 0.12 (6H, s), 1.30 (6H, m). This attempt included the flash chromatography purification.

Synthesis of 5,5'-dimethyl-2,2'-bipyridine with DMF and LiCl wash (Reaction 4)

The attempted synthesis of **2** from **1** using DMF and a LiCl wash during extraction was acquired (Figure S7). ¹H NMR (500 MHz, CDCl₃) δ 2.40 (6H, br), 7.62 (2H, br), 8.25 (2H, br), 8.51 (2H, br). This attempt did not include the flash chromatography purification.

Syntheses of 5,5'-dimethyl-2,2'-bipyridine with acetonitrile and no purification (Reaction 5 & 6)

The synthesis of **2** from **1** using acetonitrile was attempted twice. The ¹H NMR spectra of the products obtained from the attempts were acquired (Figures S8 & S9). ¹H NMR (500 MHz,

CDCl₃) δ 2.32 (3H, s), 7.39 (2H, m), 8.23 (1H, s). These attempts did not include the flash chromatography purification.

Synthesis of 6,6'-dimethyl-2,2'-bipyridine with acetonitrile and purification (Reaction 7)

The ¹H NMR spectrum of the product was not obtained from the attempted synthesis of **4** from **3** using acetonitrile. No product was recovered during the flash chromatography purification.

DISCUSSION

Synthesis of 5,5'-dimethyl-2,2'-bipyridine with DMF and purification (Reaction 1)

The ¹H NMR spectrum obtained from the attempted synthesis of **2** supported the presence of the desired product (Figure S4). The chemical shifts, coupling, and integration of the peaks in the ¹H NMR spectrum correlated with that of the purchased **2** (Figure S1).

Synthesis of 6,6'-dimethyl-2,2'-bipyridine with DMF and no purification (Reaction 2)

The ¹H NMR spectrum obtained from the attempted synthesis of **4** did not support the presence of the desired product (Figure S5). The ¹H NMR spectrum appears to have only the expected solvent peak.

Synthesis of 6,6'-dimethoxy-2,2'-bipyridine with DMF and purification

The ¹H NMR spectrum obtained from the attempted synthesis of **6** did not support the presence of the desired product (Figure S6). The ¹H NMR spectrum has unexpected peaks at 1.30 and 0.12 ppm. The ¹H NMR spectrum does not contain the peaks expected, from 7 to 9 ppm, for the aromatic hydrogens.

Synthesis of 5,5'-dimethyl-2,2'-bipyridine with DMF and LiCl wash

The ¹H NMR spectrum obtained from the attempted synthesis of **2** supported the presence of the desired product (Figure S7). The chemical shifts and integration of the peaks in the ¹H NMR spectrum correlated with that of the purchased **2** (Figure S1). The coupling in the ¹H NMR spectrum does not correlate to that of the purchased product and the previously

synthesized **2** (Figure S4). The expected splitting was not observed due to the broadness of the peaks.

Syntheses of 5,5'-dimethyl-2,2'-bipyridine with acetonitrile

The ^1H NMR spectra obtained from the attempted syntheses of **2** from **1** using acetonitrile (Figures S8 & S9) suggests that acetonitrile is not a suitable solvent for the reaction. The ^1H NMR spectra (Figure S9) supported the presence of the starting compound **1**.

Synthesis of 6,6'-dimethyl-2,2'-bipyridine with acetonitrile and purification

The ^1H NMR spectrum of the product obtained from the attempted synthesis of **4** from **3** using acetonitrile was not acquired due to the loss of the potential product in the purification process.

Summary

The syntheses of symmetrical 2,2'-bipyridines using DMF were relatively successful. The underlying issue with the syntheses utilizing DMF is the concentration process. DMF may be a suitable solvent for the reactions, but was found to be incredibly difficult to remove due to its high boiling point of 152.8°C^3 . This difficulty is the major problem with possible adoption in an undergraduate lab. The issue with removal of the DMF solvent resulted in attempting the reactions with another polar aprotic solvent, acetonitrile. Acetonitrile was an optimal choice as its boiling point, 81.6°C^4 , was much lower than that of DMF. The lower boiling point of acetonitrile allowed for easier removal during concentration, but its usage did not result in the desired final products. A LiCl wash was used, during a synthesis with DMF, to try and assist with DMF removal, but it did not achieve this goal.

Flash Chromatography Purification

The flash chromatography purification may be a necessary step to remove residual reactant from the product and produce a cleaner NMR spectrum. The flash chromatography purification may not be necessary if the reactions are allowed to occur for a longer period of time.

LAB DEVELOPMENT

Structure of Experiment

The experiment developed here can be performed in one of two versions. The first involves the synthesis of a symmetrical 2,2'-bipyridine, purification by flash chromatography, and characterization by ^1H NMR spectroscopy. This version can be performed over three lab periods. The second version of the lab, which involves the synthesis of a symmetrical 2,2'-bipyridine and characterization by ^1H NMR spectroscopy, can be performed over two lab periods.

Suitability

This experiment is not yet suitable for incorporation during a semester. A method has to be designed to either remove the DMF efficiently, in less time, or to have the reaction occur in a different solvent. One possible method to attempt is to switch the extraction solvent from CH_2Cl_2 to hexane. Substituting this extraction solvent may be ideal, as DMF is immiscible in hexane. Once a method has been devised to solve the DMF issue, the experiment will be suitable for use over two or three laboratory periods, depending on whether the flash chromatography step is desired.

Learning Outcomes and Assessment

The key learning outcomes of this lab experiment are that students acquire knowledge and experience with ligand synthesis and ^1H NMR spectroscopy. Students will be able to acquire, integrate, and manipulate NMR spectra. Students will gain experience in determining compound identity based on interpretation of NMR spectra. Students will also acquire experience in predicting the number of signals, splitting patterns, and integrations from a compound's structure. The learning outcomes will be acquired through an introduction at the beginning of the lab, followed by performance of the experiment. Students will be assessed on the learning outcomes through a formal report. The formal report will examine students' understanding of several important ^1H NMR concepts, such as spin-spin coupling, multiplicity, and integration.

Future work

The most important future work that needs to be accomplished is to resolve the DMF issue. This will allow the laboratory experiment to occur in a suitable period of time. Other future work can include complexing the synthesized 2,2-bipyridines to metals to form catalysts and adapting product ^1H NMR analysis for remote-operation through the British Columbia – Integrated Laboratory Network.

Conclusions

This laboratory experiment would result in a strong learning experience for students. The synthesis of a ligand and the hands-on ^1H NMR experience and knowledge will strengthen students' skills for later undergraduate labs.

References

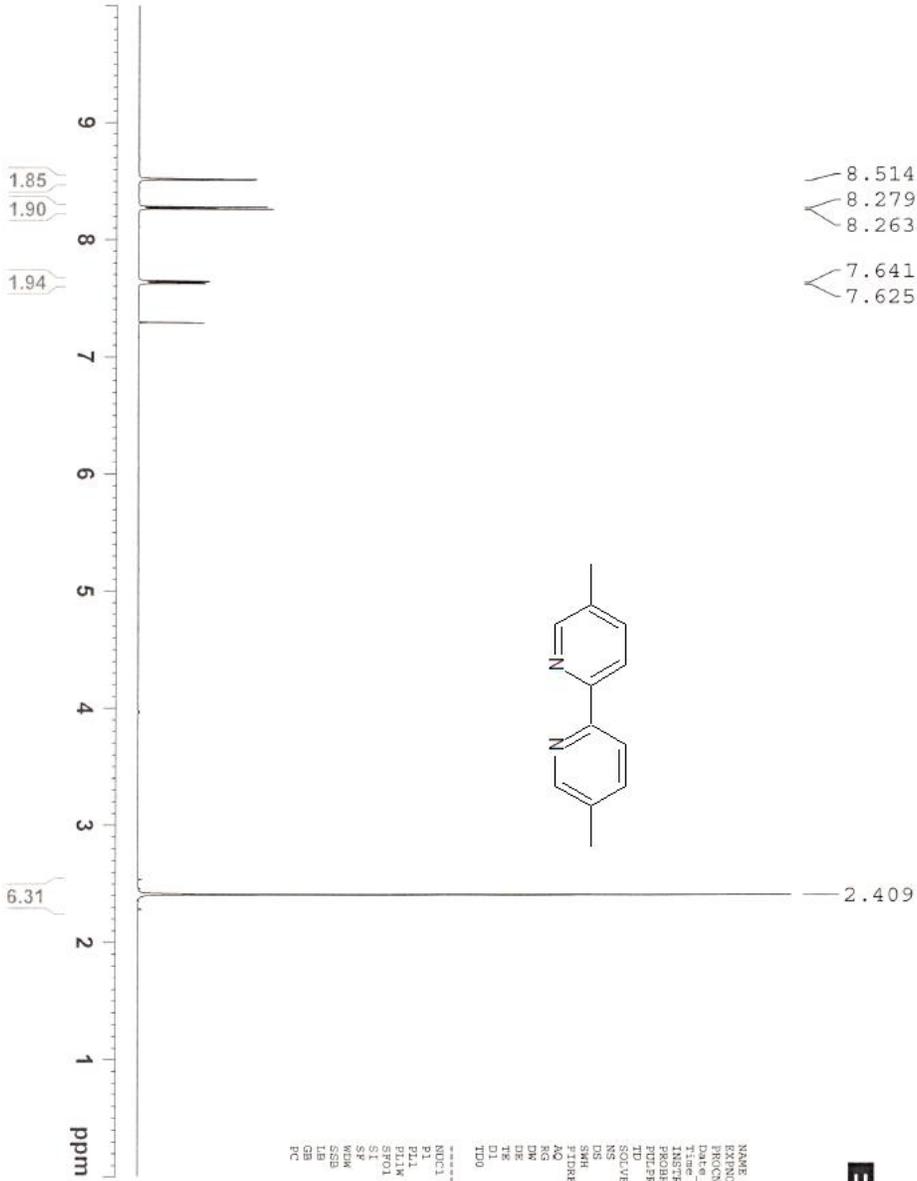
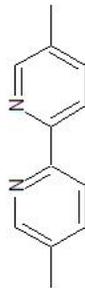
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2. Zhang, T.; Wang, C.; Liu, S.; Wang, J.; Lin, W. *J. Am. Chem. Soc.* **2014**, *136*, 273-281.
3. CRC Handbook of Chemistry and Physics, 95th Edition, 2014-2015. Section 3: Physical Constants of Organic Compounds, DMF. Retrieved from <http://www.hbcpNetbase.com> (Accessed Apr-27-2015).
4. CRC Handbook of Chemistry and Physics, 95th Edition, 2014-2015. Section 3: Physical Constants of Organic Compounds, Acetonitrile. Retrieved from <http://www.hbcpNetbase.com> (Accessed Apr-27-2015).

Supporting Material

The supporting material includes all ^1H NMR spectra acquired.

Purchased 5,5'-dimethyl-2,2'-bipyridine

8.514
8.279
8.263
7.641
7.625



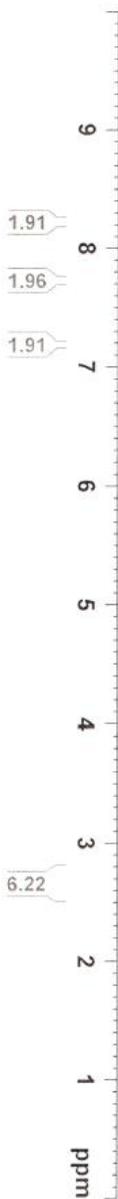
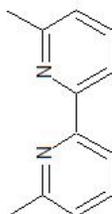
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SSB 0
ZS 0.20 Hz
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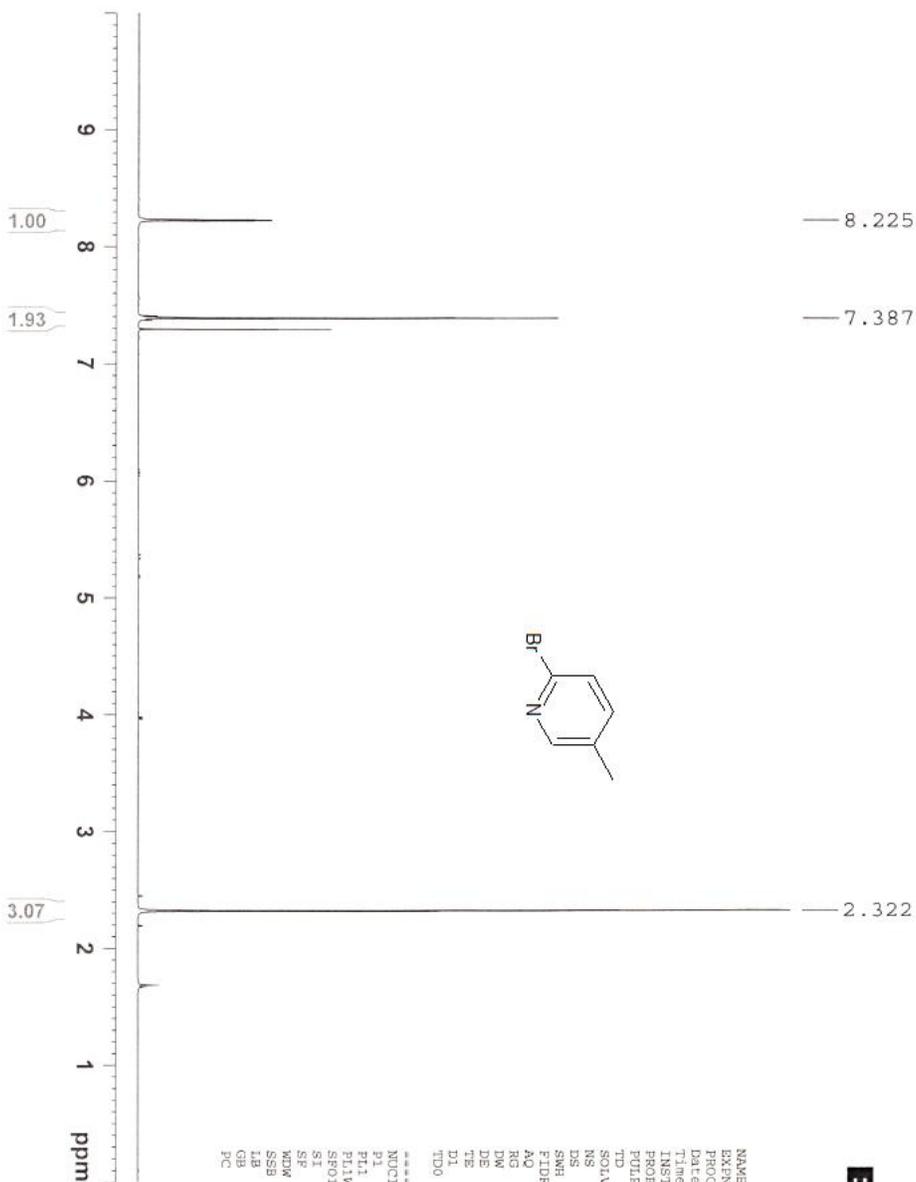
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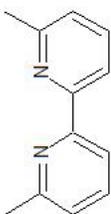
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