Progress toward the Synthesis of a Heteroaromatic Aminium Ion

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Progress toward the Synthesis of a Heteroaromatic Aminium Ion

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Senior Thesis

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Background Information

Electron transfer chemistry is one of the most fundamental processes in chemistry, and is important in inorganic, organic, and physical chemistry as well as biochemistry. In a pure electron transfer process, an electron is transferred from an oxidizing agent to a reducing agent. A variety of electron transfer reagents (both oxidizing and reducing agents) of different strengths have been developed. As will be seen below, stable, isolable reagents are particularly useful, as they can be stored and used when necessary. Otherwise, electrochemical oxidation may be difficult to control if inappropriate reagents are used.

Employing redox reagents to do electron transfer chemistry has both advantages and disadvantages when compared to the unrivaled electrochemical methods (Connelly and Geiger 878). The advantages of chemical redox reagents include the following:

(1) Absence of supporting electrolyte. Abundant electrolyte salts are employed in electrolysis reactions. If the desired product possesses a charge, it will have similar solubility properties to that of the supporting electrolyte, making separation difficult. Chemical redox reagents can be used in stoichiometric amounts and hence do not pose as much of a separation problem in the workup of the reaction solution. This is probably the greatest advantage of chemical redox reagents (Connelly and Geiger 878).

(2) Rapid, large-scale preparations. Redox reactions occur in a shorter time frame and at higher concentrations than most electrolysis reactions to yield the desired product. Some products have limited stability and exist for only a short time and therefore are difficult with which to deal under electrolytic conditions.

(3) Use of nonpolar solvents. The reaction solvent heavily influences electron transfer chemistry. Most nonpolar will not coordinate to a metal and hence seldom displace ligands from a desired coordination compound as a redox product. The use of nonpolar solvents also makes rapid precipitation of highly reactive charged products feasible as they are normally insoluble (Connelly and Geiger 878).

When compared with electrochemical methods, chemical redox reagents have a number of disadvantages. These include the following:

(1) Fixed redox strength. Redox reagents have a fixed redox potential in a given solvent, and hence a selection of reagents must be used to provide a range of redox strengths. While the potential can vary over a large range, individual classes of oxidants often will have a narrow range of potentials. Fixed redox strength is the greatest limitation of chemical redox reagents.

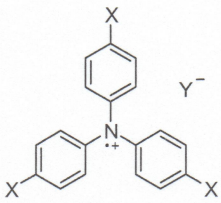
(2) Reagent byproduct in reaction mixture. Redox reactions may produce byproducts that may be reactive. The byproducts may also interfere with other characterization, and namely spectroscopy. It also can interfere with isolation if separation is difficult.

(3) Purity and stability of reagents. Stability must be considered as most redox reagents have a short shelf life and hence cannot be stored for long periods of time. The purity of a reagent may have to be assessed immediately before use, and the reagent may have to be purified.

Chemical redox reagents may be classified into numerous categories. Generally, redox reagents may be categorized as organic and inorganic. Inorganic oxidants include metal and metal complex oxidants such as ferrocenium salts, $[FeCp_2]^+$, oxygen, and acids such as fluoroboric acid, HBF_4, and hexafluorophosphoric acid, HPF_6. Organic reagents include radical cations, such as triarylaminium radical cations, $[N(aryl)_3]^{\bullet +}$, and carbocations such as the trityl cation, $[CPh_3]^+$.

Triarylaminium radical cations are the main focus of this research project. These compounds are mild to very strong one-electron oxidants used widely in organic chemistry and, to far lesser extent, in inorganic chemistry. Since triarylaminium cations are remarkably stable they can be used as stoichiometric oxidation agents, and additionally they act as catalysts in electron transfer chain processes and/or as intermediates in indirect electrosynthesis (Connelly and Geiger 891, 892). They have a wide range of oxidizing potentials that depend on the electron-donating and -withdrawing nature of the substituents. (Reduction potentials of the triarylaminium-triarylamine couples are shown in Table 1, Mayer *et al.* 6080, Connelly and Geiger 891). Electron withdrawing substituents tend to increase the potential and make the triarylaminiums stronger oxidizing agents, whereas electron donating substituents tend to decrease the potential and tend to make the triarylaminiums weaker oxidizing agents. This is a large range compared to metal complexes, which typically vary over ~0.50 by ligand variation (Connelly and Geiger).

Table 1. Potentials of Triarylaminium Oxidants (in acetonitrile, V vs. ferrocene/ferricenium)

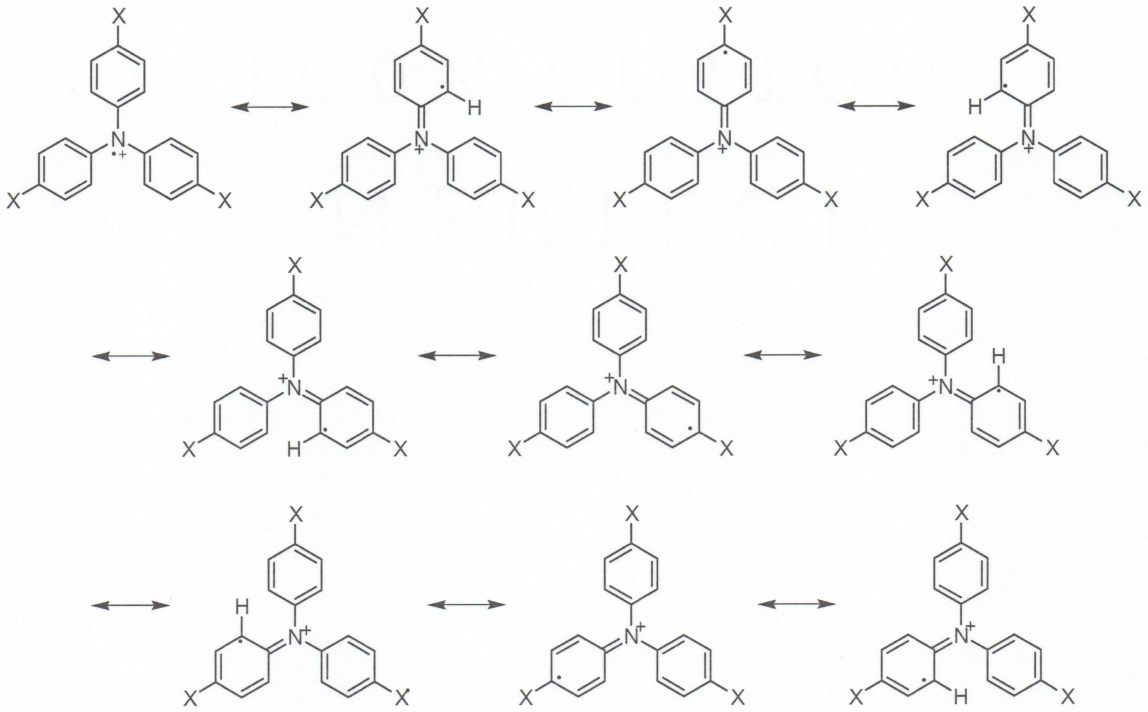


Structure of a triarylaminium ion with para-substituted phenyl rings as aryl groups

Oxidant	$E_{1/2}$	Redox Strength
$[N(p\text{-}C_6H_4OMe)_3]^{\cdot+}$	0.16	Mild
$[N(p\text{-}C_6H_4OMe)_2(p\text{-}C_6H_4Br)]^{\cdot+}$	0.32	Strong
$[N(p\text{-}C_6H_4OMe)(p\text{-}C_6H_4Br)_2]^{\cdot+}$	0.48	Strong
$[N(p\text{-}C_6H_4Br)_3]^{\cdot+}$	0.67	Strong
$[N\ (p\text{-}C_6H_4Br\text{-}4)_3]^{+}$	0.70	Strong
$[N\ (p\text{-}C_6H_4CN\text{-}4)_3]^{+}$	1.08	Very Strong
$[N\ (p\text{-}C_6H_4NO_2\text{-}4)_3]^{+}$	1.20	Very Strong
$[N\ (p\text{-}C_6H_4Br_3\text{-}2,4,6)_3]^{+}$	1.36	Very Strong
$[N\ (C_6Cl_5)_3]^{+}$	1.72	Very Strong

Triarylaminium radical cations are also interesting to organic chemists since they are stable radical cations. Most radical cations are reactive (and hence unstable) for two reasons. First, they contain unpaired electrons; electrons in organic compounds are usually paired to make bonds and hence most radicals will undergo dimerization (Clayden *et al.* 1024). Second, they have a positive charge (that is, are a cation); most radical cations are acidic and readily can lose a proton. The stability of the triarylaminium ion results from the delocalization of the single unpaired electron and the positive charge (Figure 1), and because there is no acidic proton to lose. The persistent, isolable triarylaminiums also have *para*-substituted phenyl rings as the aryl groups that prevent dimerization (Figure 1).

Figure 1. Delocalization of single unpaired electron and positive charge of triarylaminium system.



X = NO_2, Br, Cl, OCH_3, etc.

Triarylaminium salts are formed from the oxidation of the corresponding triarylamines by one of three main preparative procedures:

(1) a silver(I) salt in the presence of iodine

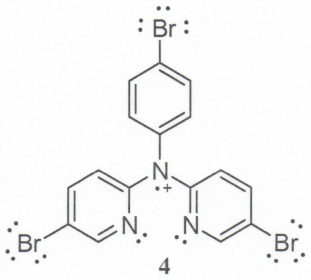
(2) a nitrosonium ion salt, such as $[NO]^+X^-$ ($X^- = [PF_6]^-$, $[BF_4]^-$, etc.)

(3) a higher valent halide, usually antimony pentachloride, $SbCl_5$, as the oxidant.

The chosen method depends upon the oxidation potential of the amine and the counterion desired (Connelly and Geiger 891). We intended to use NO^+ in our synthesis.

We are interested in the investigation of variation of this triarylaminium structural type to determine the stability of related compounds and the effect of structure on oxidation potential. The goal of this research project is to synthesize an aminium ion with heteroaromatic rings and to determine its properties. In our compound, two of the phenyl rings have been replaced with bromine-substituted pyridine rings (compound **4**). By determining the compound's physical properties, such as its UV-Vis spectra (as often as they are colored, absorbing light in the

region of 400-700 nm, Connelly and Geiger), and chemical properties, such as stability and reduction potential, we can expand on the knowledge of aminium ions as radical cations and potential oxidants. The change in aromatic rings is a further variation on structure that can increase the range of possible redox potentials for these compounds. A pyridine compound is more electron deficient than the corresponding phenyl compound, and will be expected to be a stronger oxidizing agent. Furthermore, less is known about heteroatomic radical cations and their stability than for the substituted phenyl analogs.



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Experimental

(2-Pyridyl)phenylamine (Compound **1**).

A mixture of 2-bromopyridine (1.06 mL, 0.0110mol) and aniline (2.00 mL, 0.0219mol) was refluxed for 1 ½ h. The contents of the flask were basified with sodium carbonate and distilled with steam. On cooling the contents in the distillation flask, a thick brown oil formed. The contents of the flask were extracted with ether and the residue from the ethereal solution was twice recrystallized from ethanol. A light yellow solid material was obtained, melting at 106-108 °C. Wibuat and Tilman give a melting point range of 105-108 °C. Additional attempts at this synthesis were employed using 2-bromopyridine (2.65 mL, 0.0274 mol) and aniline (5.00 mL, 0.0548 mol) and 2-bromopyridine (2.65 mL, 0.0274 mol), aniline (5.00 mL, 0.0548 mol) and zinc(II) chloride (5-10% mole ration of limiting reagent). Analysis of the crude reaction mixtures led to inconsistent results with that of proposed product, compound **1**.

Palladium-Catalyzed formation of Di(2-pyridyl)phenylamine (compound **2**)

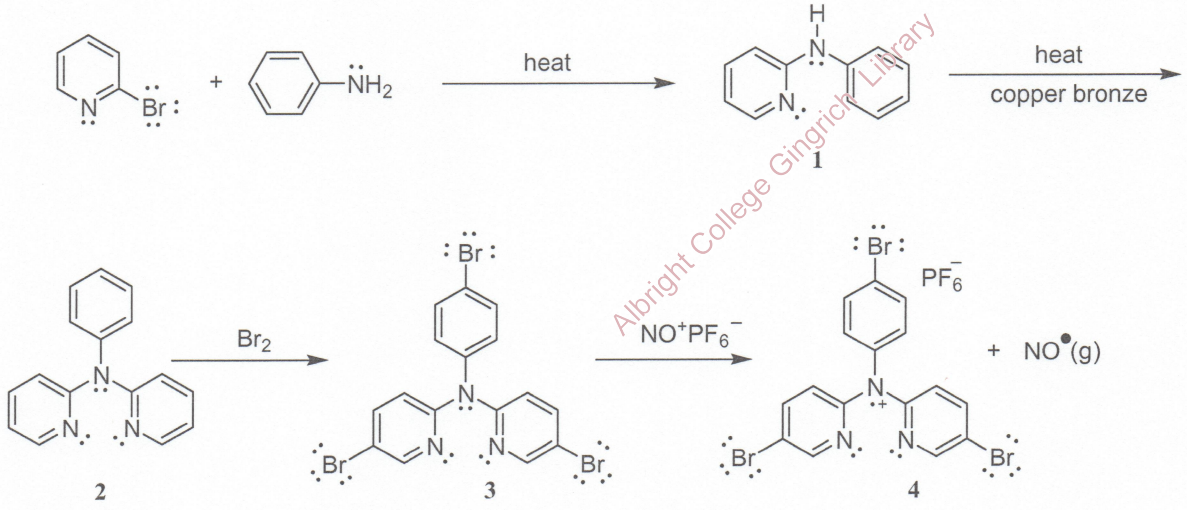
Aniline (66.5 µL, 0.730 mmol), 2-bromopyridine (157 µL, 1.60 mmol), $NaOBu^t$ (0.200 g, 2.04 mmol), DPPF (0.032 g, 0.058 mmol), and $Pd_2(dba)_3$ (0.022 g, 0.024 mmol) were placed in a 50-mL round bottom flask, mixed with anhydrous toluene (3 mL), and heated under nitrogen at 100 °C for 24 hr. The solution was cooled and

then ~30 mL of CH_2Cl_2 was added. The filtrate was concentrated under reduced pressure to afford a brown sludge-like crude product. Further purification was performed by column chromatography using a mixed solvent of ethyl acetate/hexanes (1:5) as the eluent to provide 0.15 g of a light brown oil. A second column with the same eluent produced three fractions, one of which has a ^{1}H NMR suggestive of **1** (DMSO-d_6, 300 MHz): 8.98 (1H, br s), 8.13 (m, 1H), 7.66* (d, 2H, J = 9 Hz), 7.53 (m, 1H), 7.24* (t, 2H, J = 8 Hz), 6.84 (m, 2H), 7.72 (m, 1H) ppm. (The protons with asterisks have further splitting.)

Results

Two general routes for the synthesis of di(2-pyridyl)phenylamine (compound **2**). The first route carried out was taken from Wibuat and Tilman (1933). This synthesis involves the formation of compound **2** by the addition of 2-bromopyridine and aniline under reflux to form a single pyridine-substituted aniline compound **1** (Figure 2). (While this compound was recently available commercially, it can no longer be purchased.) The single substituted aniline compound is then reacted with additional 2-bromopyridine, mesitylene, and copper bronze under reflux to yield compound **2**. Reaction with bromine, followed by $NOPF_6$ would produce the final compound.

Figure 2. Synthesis of a Heterocyclic Aminium Ion



As will be discussed below, Wibuat and Tilman's synthesis of di(2-pyridyl)phenylamine led to complex reaction mixtures that were difficult to separate. Hence, a more recent procedure obtained from Yang, Lin, Lin, and Liao (2004) was attempted. This synthesis involves the formation of compound **2** by way of a palladium-catalyzed organometallic amination reaction. The synthesis leads to compound **2** without having to isolate the intermediate compound **1.** The reaction process involves the addition of aniline and 2-bromopyridine to sodium *tert*-butoxide ($NaOBu^t$), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), and palladium(0) dibenzoylacetoacetate ($Pd_2(dba)_3$) at 100 °C for 24 h.

The first step in the Wibuat and Tilman procedure was attempted where 2-bromopyridine and aniline were heated to reflux as in the published procedure with no unchanged parameters or modifications. A small amount of a yellow solid was obtained after steam distillation and crystallization of the product mixture. The literature value given by Wibuat and Tilman describes a melting point range of 105-108 °C for a white crystalline solid, and the solid obtained in this study had a melting point range of 106-108 °C. A melting point test is a necessary piece of evidence for characterization, but is not sufficient for a full characterization.

After an additional attempt at the procedure, a ^{1}H NMR of the solid was obtained after steam distillation but before crystallization (in spectrum C in the Appendix). The spectrum obtained contains many peaks, with a few peaks in the aromatic region, δ 6 to 8.5 parts per million (ppm) (Gilbert and Martin 249). This would be expected since the desired secondary amine contains all aromatic hydrogen atoms (with the exception of one hydrogen atom which is bound to the nitrogen atom). Comparison to ^{1}H NMR spectra of aniline and 2-bromopyridine (Spectral Database for Organic Compounds, Spectra A and B in the Appendix) indicates a mixture of aniline, 2-bromopyridine, and small amounts of an additional compound or compounds. Hence, the ^{1}H NMR data does not support the presence of (2-pyridyl)phenylamine in high amounts, and therefore it can be concluded that the synthesis was unsuccessful.

Wibuat and Tilman's procedure for (2-pyridyl)phenylamine was taken and modified several times as the first modification involved boiling under reflux for 24 h instead of the listed 1 ½ h. The reaction mixture was checked 24 h later and no product was obtained as the reaction mixture was heated above the specified temperature on error and the mixture became charred. With this situation and little product, if any, formed, the next modification to the (2-pyridyl)phenylamine procedure involved changing the quantities of the starting materials so that there

would be a larger volume and less liquid would be lost to evaporation; hence, the quantities of aniline and 2-bromopyridine were changed.

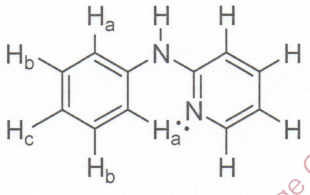
A ^{1}H NMR spectrum of the changed reaction mixture, spectrum D, was obtained. Spectrum D was a little more promising as almost all of the peaks in this spectrum are in the aromatic range. The peaks seemed scattered across the aromatic region and are not consistent with the literature spectrum of (2-pyridyl)phenylamine which shows peaks of δ 6.71 (t, 1H, J = 6.9 Hz), 6.87 (d, 1H, J = 7.8 Hz), 7.02-7.07 (m, 2H), 7.31 (m, 2H), 7.33 (m, 2H), 7.44-7.50 (m, 1H), 8.19 (d, 1H, J = 8.1Hz) (Katritzky *et. al.* 2001). Spectrum D closely resembles that of 2-bromopyridine (Spectral Database for Organic Compounds, Spectrum A in the Appendix) The peak at δ 2.2 ppm of Spectrum D could possibly be the N—H peak, as amine hydrogen atoms typically resonate at δ 1-5 ppm (Gilbert and Martin 249). (The literature NMR spectrum of (2-pyridyl)phenylamine does not show a N—H peak which may be the result of a broad N—H peak.) The literature spectrum of aniline, which has an N—H peak of δ 3.5 ppm, was compared to the possible N—H peak of Spectrum D of the potential (2-pyridyl)phenylamine. The peak is slightly more shielded which is not consistent with the structure of (2-pyridyl)phenylamine as the N—H peak would be further deshielded due to the aromatic rings in the system of (2-pyridyl)phenylamine. A better model of this, *N, N*-diphenylamine has its N—H at 5.6 ppm (Spectral Database for Organic Compounds), which is clearly further downfield. Thus there is a lack of evidence to support the successful synthesis of (2-pyridyl)phenylamine using the modified Wibuat and Tilman procedure.

Because of the lack of success at formation of (2-pyridyl)phenylamine with the method of Wibuat and Tilman, literature research was carried out to determine any solvent or catalysts that may aid in the synthesis of compound **1**. Zinc(II) chloride, $ZnCl_2$, was discovered to be effective in the type of α-substituted pyridine synthesis reaction attempted (Katritzky and Rees 330). $ZnCl_2$ was added in a catalytic amount (5-10% mole ratio of limiting reagent) to the reaction mixture of aniline and 2-bromopyridine. The reaction mixture was allowed to stir for 24 h without boiling under reflux. A ^{1}H NMR spectrum of the product, spectrum F, was obtained. Spectrum F appears to be a combination spectrum of aniline and 2-bromopyridine based on these literature spectra (Spectral Database for Organic Compounds, Spectra A and B in the Appendix). No reaction of the starting materials seems to have occurred. All protons observed in this spectrum are aromatic, but the number of peaks seen in the aromatic region is quite high. Although a small peak at δ 2.2 ppm is visible on spectrum F, it is insignificant in size compared to the other peaks. Refluxing was attempted for this reaction mixture, but the reaction mixture was heated above the

specified temperature and the mixture was charred. This reaction process could be repeated with a different heat source, which will provide better reaction temperature control.

Wibuat and Tilman's procedure was deemed to be an unreliable procedure for the synthesis of compound **1**. Further literature research uncovered a palladium-catalyzed amination synthesis that parallels the synthesis of compound **1** (Yang *et al.* 3525). This procedure differed from Wibuat and Tilman's procedure in the that it makes a tertiary amine from the starting materials in one reaction step through the use of a palladium catalyst, whereas Wibuat and Tilman's makes a secondary amine in one reaction step, followed by further workup to give the tertiary amine.

This procedure was followed, and a product was obtained. After two columns, the component in one fraction had a ^{1}H NMR spectrum (Spectrum G) that was consistent with **1**. While the ^{1}H NMR in $CDCl_3$ does not match that of the literature (Katritzky *et. al.* 2001), the integrations, splitting and chemical shifts in DMSO-d_6 are suggestive. In particular, an unsubstituted phenyl ring is suggested by a double and triplet with integrations of 2:2 are suggestive of protons *a* and *b*. (These protons are further split by small coupling constants with other aromatic protons, and hence are not true doublets or triplets.) The protons of the pyridyl ring are suggested by three absorptions that integrate 1:1:1. The last pyridyl and phenyl peak (*c*) must overlap to give a multiplet with integration 2. Finally, a somewhat broadened peak at 8.99 ppm is consistent with the N–H proton.



This ^{1}H NMR suggests that while the palladium coupling did not yield that desired coupling product, some coupling did occur, and that a future attempt with more careful omission of water and air could lead to a pure, isolated product. .

Conclusion

During my work on this research project I attempted two routes to make pyridine-substituted anilines. . The first procedure resulted in low conversions with questionable products. ^{1}H NMR suggests that the second reaction led to product **1**, but further optimization will be required to yield compound **2**. The remaining steps of the synthesis for a heteroarylaminium ion, compound **4**, seem feasible if a reliable and well established procedure for the synthesis of compound **2** can be accomplished. Other project goals such as the determination of the stability and redox potential of compound **4**, can be pursued at that time.

References

Clayden, J., Nick Greeves, Stuart Warren, and Peter Wothers. *Organic Chemistry*, Oxford University, New York, NY, 2001.

Connelly, Neil G. and William E. Geiger. "Chemical Redox Agents for Organometallic Chemistry." *Chem. Rev.* **1996, *96***, 877-910.

Gilbert, J.C. and S.F. Martin. *Experimental Organic Chemistry: A Miniscale and Microscale Approach*, 3rd ed., Brooks-Code, Pacific Grove, CA, 2002.

Katritzky, Alan, R. and Charles W. Rees. *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds*. Vol. 2: "Six Membered Rings with One N Atom". Pergamon Press, New York, NY, **1984**.

Katritzky, Alan R.; Huang, Tian-Bao; Voronkov, Micahel V. "From Amides to Amidines: Preparations of Imidoylbenzotriazoles and Arylaminoheterocycles." *J. Org. Chem.* **2001**, 66, 1043-1045.

Mayer, James M, Ian J. Rhile, Todd F. Markle, Hirotaka Nagao, Antonio G. DiPasquale, Oanh P. Lam, Mark A. Lockwood, and Katrina Rotter. "Concerted Proton-Electron Transfer Oxidation of Hydrogen-Bonded Phenols." *J. Am. Chem. Soc.* **2006**, *128*, 6075-6088.

Spectral Database for Organic Compounds, SDBS. "Aniline." Accessed 11 November 2006. <http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng>

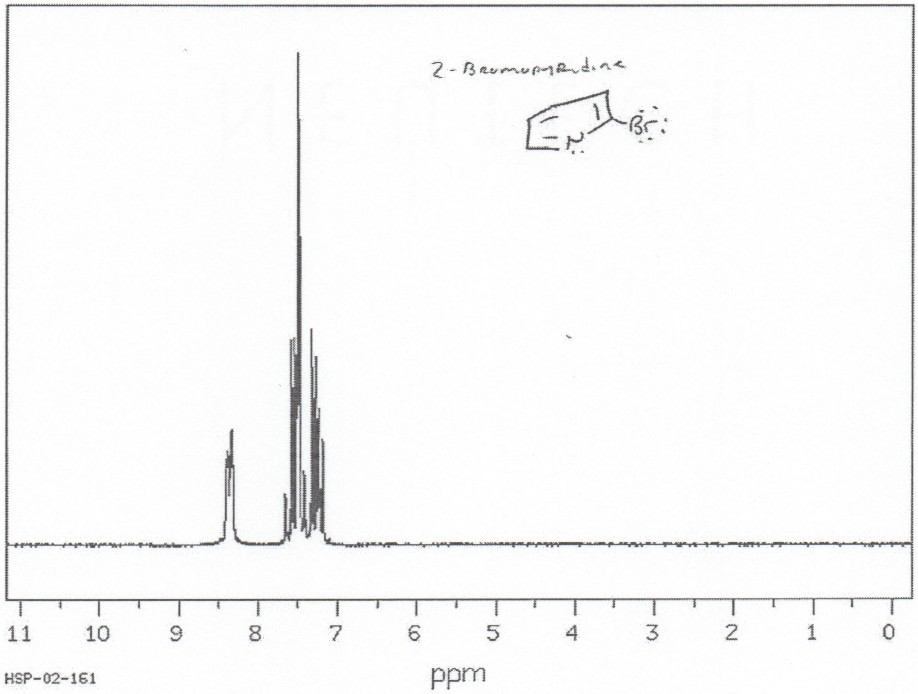
Spectral Database for Organic Compounds, SDBS. "2-Bromopyridine." Accessed 11 November 2006. <http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng>

Spectral Database for Organic Compounds, SDBS. "Diphenylamine" Accessed 25 April 2007. <http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng>

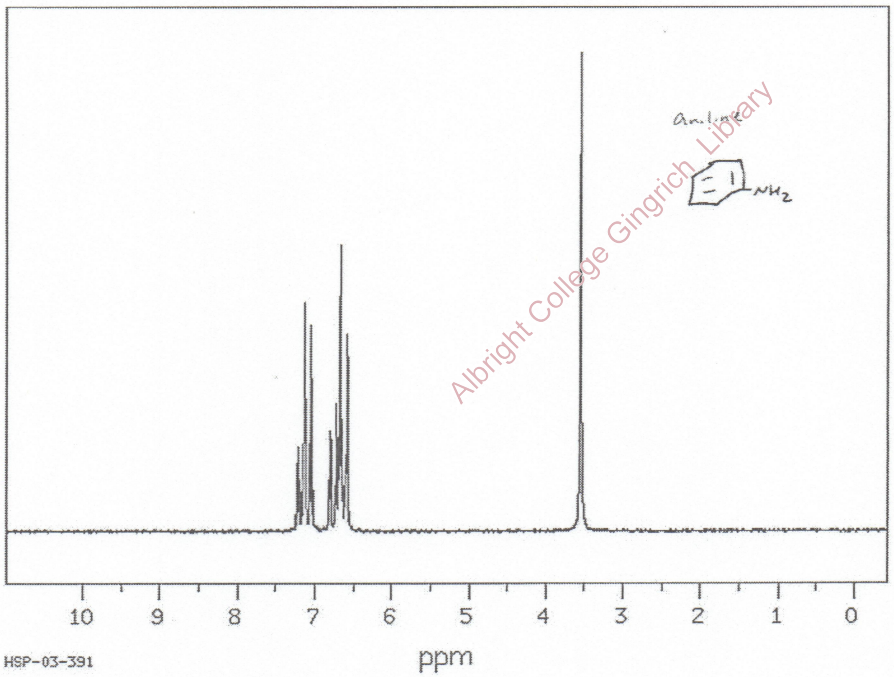
Wibuat, J.P and G. Tilman. "Di(2-pyridyl)phenylamine and N-(2-pyridyl)piperidine." *Rec. Trav. Chim. Pays-Bas Belg.* **1933**, *96*, 987-990.

Yang, Jye-Shane; Yan-Duo Lin, Yu-Hsi Lin, and Fen-Ling Liao. "Zn(II)-Induced Ground-State π-Deconjugation and Excited State Electron Transfer in *N,N*-Bis(2-pyridyl)amino-Substituted Arenes." *J. Org. Chem.* **2004**, *69*, 3517-3525.

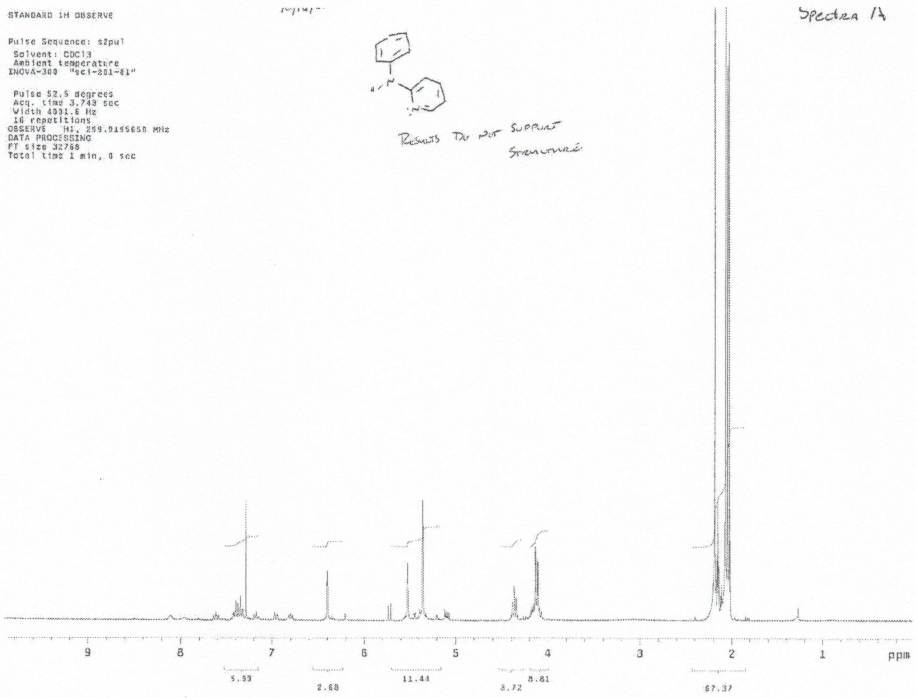
Appendix
Spectrum A (SDBS "2-Bromopyridine")



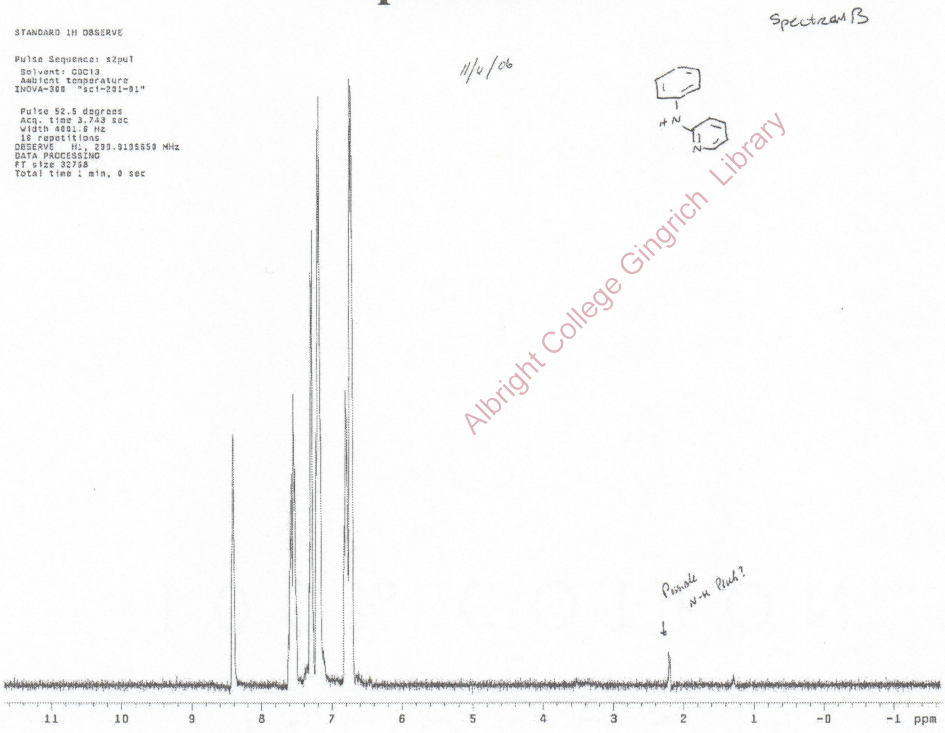
Spectrum B (SDBS "Aniline")



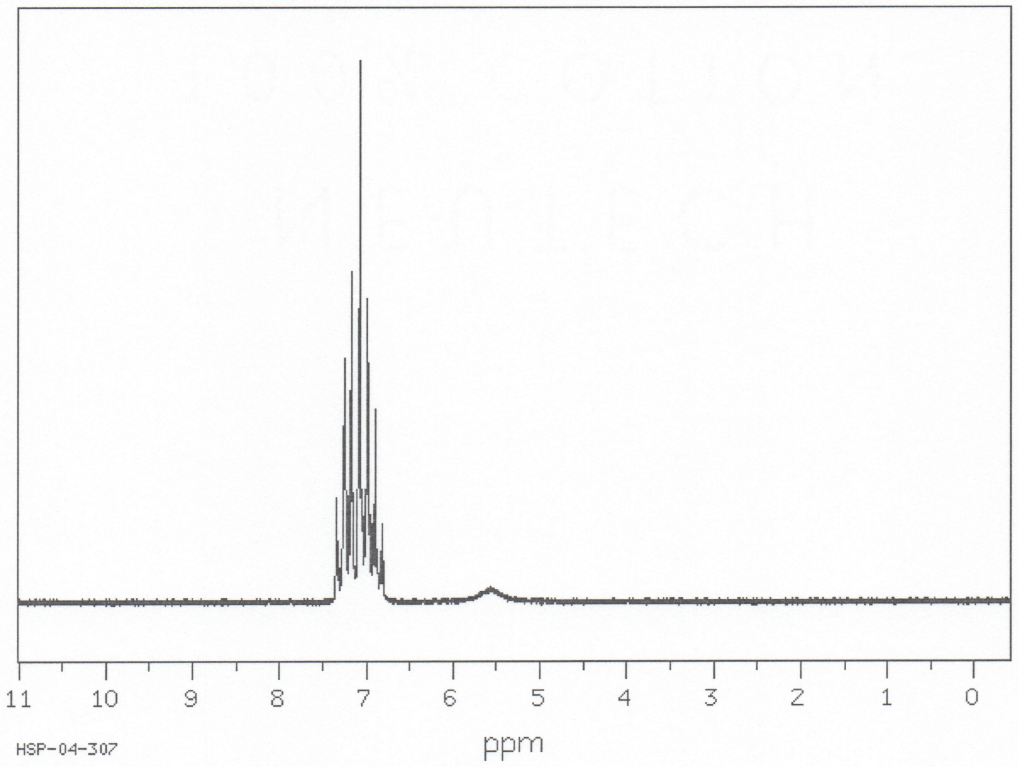
Spectrum C



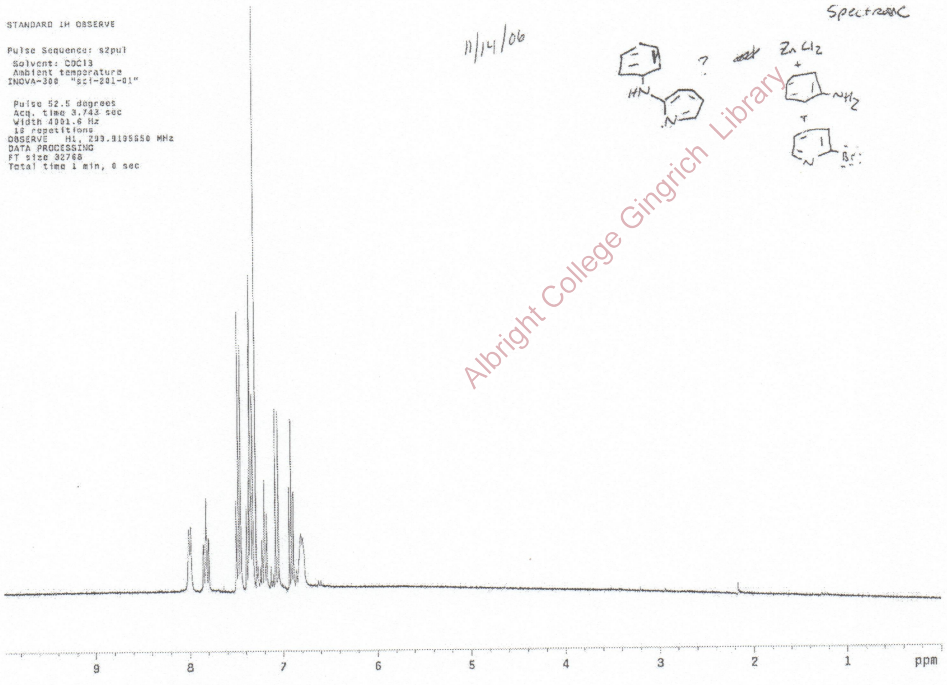
Spectrum D



Spectrum E (SDBS, "Diphenylamine")



Spectrum F



Spectrum G