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Syntheses and Characterizations of 4-Cyano-3-tolylpyrazole and its Metal Complexes

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Syntheses and Characterizations of 4-Cyano-3-tolylpyrazole and its Metal Complexes

Thesis Submitted in Partial Fulfillment of Honors-in-Discipline in Chemistry

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The Honors College

Honors-in-Discipline Program

East Tennessee State University

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Introduction

Coordination chemistry is the study of compounds formed between metal ions and other neutral or negatively charged molecules.[1] Although many coordination compounds have been used for centuries, coordination chemistry did not become a prominent field until Alfred Werner began studying cobalt-ammonia chloride complexes at the beginning of the 20th century.[1] The striking colors of coordination compounds and their color changes upon reaction that were used as pigments and dyes since antiquity provided the incentive for further studies of coordination complexes.[1] Upon interest in coordination chemistry, scientists realized they had to discover a theory to explain the unique bonding that occurs in coordination complexes as existing theories were proved inadequate.

As discussed previously, a coordination compound usually consists of a metal atom or ion and one or more ligands that donate electrons to the metal.[1] Ligands behave as Lewis bases and the central atom acts as a Lewis acid, where Lewis bases are simply electron donors and Lewis acids are known as electron acceptors.[1] Depending on the nature of the metal and the ligands, the metal can have up to 16 ligands attached to it, with four and six being the most common numbers.[1]

There are a wide variety of ligands with more than one donor site to the metal center. Ligands with two or more donor sites are called chelating ligands, and their compounds are termed chelates.[1] Ligands with only one donor site are termed monodentate ligands, whereas bidentate ligands have two donor atoms which allow them to bind to a central metal atom or ion at two points.[1] Ligands that have more than two points of attachment to the metal center are termed polydentate ligands, meaning "multiple teeth".[9]

Alfred Werner's interest in Coordination Chemistry expanded during his work with cobalt-ammonia chloride complexes when he discovered that the current day organic bonding theories failed to explain bonding in coordination compounds. In the compound hexaamminecobalt(III) chloride, $[Co(NH_3)_6]Cl_3$, for example, cobalt only has a valence of three and therefore, based on the organic bonding theories in Werner's time, only three chlorides could bind to cobalt leaving the six ammonias with no means of participating in binding with cobalt.[1] There were multiple theories developed to try and explain the binding of all six ammonias with the most popular one from C.W. Blomstrand and another from Alfred Werner. Blomstrand's theory stated that the nitrogens from ammonia molecules could form chains much like those of carbon, and thus could have a valence of 5.[1] Werner, on the other hand proposed that all six ammonias could bond directly to the cobalt ion and the chloride ions were more loosely bound and considered independent ions.[1] After much debate and extensive research, Werner was able to disprove Bronsted's chain theory, and his theory was considered to be correct.

For each coordination compound, as the coordination number increases the number of possible isomers increases as well.[1] There are two main groups of isomers, stereoisomers and structural isomers. Stereoisomers occur when the ligands have the same bonds, but the bonds are in different orientations relative to one another.[2] On the other hand, the bonds are different in structural isomers as the isomers have the same overall formula but have different ligands attached to the central atom or ion.[1] In square planar coordination complexes where there are two separate sets of ligands with each set containing identical ligands, the molecules can be arranged in two diverse ways.[2] The molecules can either be arranged in a *cis* or *trans* fashion. In molecules with the cis arrangement, the two identical ligands are on the same side of the complex and the bond angle between the two similar ligands is 90 degrees in both the square

planar and octahedral coordination complexes.[2] In molecules that are in the trans arrangement, the similar ligands are on opposite sides of the complex and have a bond angle of 180 degrees between the two similar ligands.[2] An example of cis and trans stereoisomers can be seen below in Figure 1.
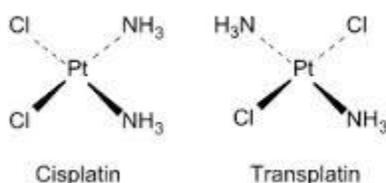
Figure 1. Cis and Trans Stereoisomers for Square Planar Complexes[3]

Aside from *cis* and *trans* geometrical arrangements for octahedral and square planar complexes, the ligands in octahedral complexes can also be arranged geometrically in a different way if the complex contains three identical ligands. Complexes of the formula $ML_3L'_3$, where L and L' are monodentate ligands, can have two isomeric forms called *fac*- facial and *mer*-meridional.[1] *Fac* isomers have three identical ligands on one triangular face, whereas *Mer* isomers have three identical ligands in a plane bisecting the molecule.[1] As a matter of fact, a *Mer* isomer is sometimes considered to be a combination of a trans and cis since it contains both trans and cis pairs of identical ligands. On the other hand, since the *Fac* isomer has any two identical ligands that are adjacent to one another, the ligands are considered to have a cis arrangement.[2] Examples of *Fac* and *Mer* isomers can be seen below in Figure 2.

Figure 2. Meridional and Facial Stereoisomers for Octahedral Complexes[2]

Structural isomers have the same overall formula but have different ligands attached to the central atom. When identifying a structural isomer there are two key aspects to take note of. First, it is pertinent to look at the ligands which are bonded to the central metal, and secondly to note which atom of each ligand attaches to the central metal.[4] There are four main types of structural isomerism, ionization isomerism, hydrate isom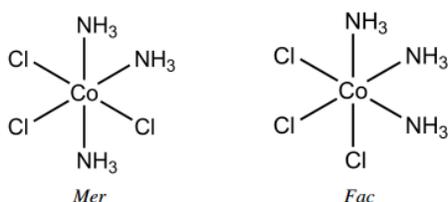erism, linkage isomerism, and coordination isomerism.[5] Ionization isomers are practically identical except one of the ligands exchanges places with an anion or neutral molecule that was originally outside the coordination sphere. For example, in the case of two octahedral ionization isomers, both will have five identical ligands and one different ligand. The dissimilar ligand in the first ionization isomer will exchange places with the anion that was originally outside the coordination sphere, therefore yielding the second ionization isomer.[5] Figure 3 below displays two chemical formulas of ionization isomers and the exchanging process of ligands and ions between the two.
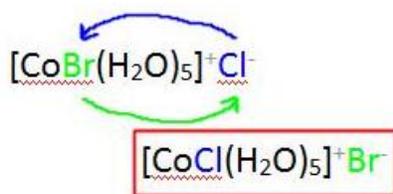
Figure 3. Pentaaquabromocobaltate(II)chloride vs. Pentaaquachlorocobaltate(II)bromide[4]

Hydrate isomers are simply a specialized form of ionization isomers with the main difference being that a water molecule is one of the molecules that exchanges places from inside the coordination sphere to outside the coordination sphere. In coordination isomers such as tetraaminezinc(II) tetrachlorocuprate(II) and tetraaminecopper(II) tetrachlorozincate(II) as shown below in Figure 4, the anion and cation complexes exchange ligands within each ionic complex.[4]

$$[Zn(NH_3)_4]^{+2}[CuCl_4]^{-2} \qquad [Cu(NH_3)_4]^{+2}[ZnCl_4]^{-2}$$

Figure 4. Coordination Isomers[4]

Linkage isomers are another type of structural isomer where each isomer has the same central atom and ligands, but the ligands are attached to the metal at the same locations through different donor sites.[4] In order to have linkage isomers, the molecular ligands have to have more than one donor atoms capable of binding to the ion. It can be seen in Figure 5 below that the ligand NO_2^- is binding to iron through the nitrogen atom in one isomer and through the oxygen atom in the other, thus making the two isomers linkage isomers.

LINKAGE ISOMERS

$$[FeCl_5(NO_2)]^{3-} \qquad [FeCl_5(ONO)]^{3-}$$

Figure 5. Linkage Isomers[6]

The chemistry of pyrazole ligands has been very popular in inorganic and organometallic chemistry for nearly four decades.[7] As seen in Figure 6 below, a pyrazole ligand is a heterocyclic compound which consists of a planar ring of 5 members with two nitrogen atoms in the relative positions 1 and 2, and three carbon atoms in the relative positions 3 to 5.
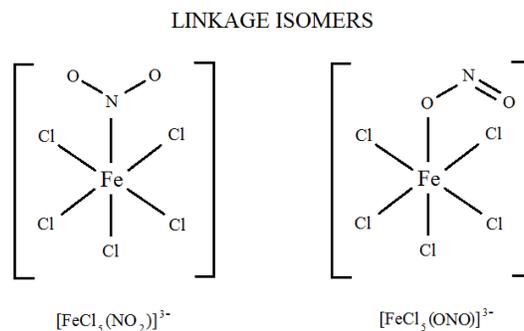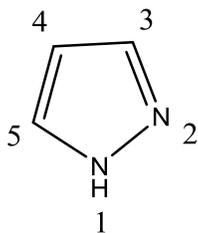
Figure 6. Structue of Pyrazole

Transition metal complexes of pyrazoles and pyrazole-derived ligands have attracted attention

because of their versatile structures and properties.[7] A large variety of pyrazole ligands can be

obtained containing different functional groups that present different affinities for various metal

cations leading to a wide range of application fields in chemistry such as: metal ions extraction,

bioinorganic chemistry, agrochemistry, colorant manufacture, photography field, polymer

development, magnetochemistry studies, and catalysis.[8] The research I was involved in focused

on the addition of a bulky substituent at the third carbon position, a cyano group at the fourth

carbon position, and the bonding of a metal to the second nitrogen position as seen in Figure 7.

R = Bulky Substituent
M = Metal
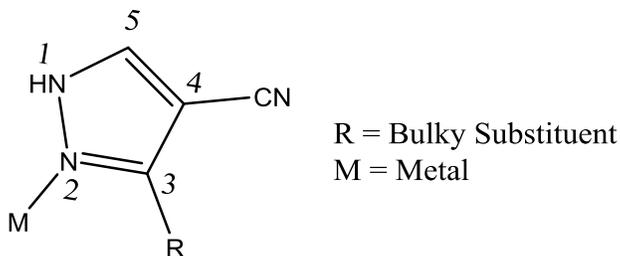
Figure 7. Introduction of Cyano Group, Metal, and Bulky Substituent to Pyrazole

Additions of substituted groups stem from the interest in substituted polypyrazolylborates, also

known as scorpionate ligands, which alter the bonding and electronic structure of the metal

complexes. Basically, once the boron is introduced to the pyrazole rings, the boron will produce

either two, three, or four arms to the pyrazole rings, and each pyrazole ring will coordinate to the

metal. Figure 8 below displays three separate scorpionate ligands where boron has two, three,

and four arms to pyrazole creating a dihydrobispyrazolylborate ligand (Bp),

hydrotrispyrazolylborate ligand (Tp), and a tetrakispyrazolylborate ligand (pzTp) respectively.
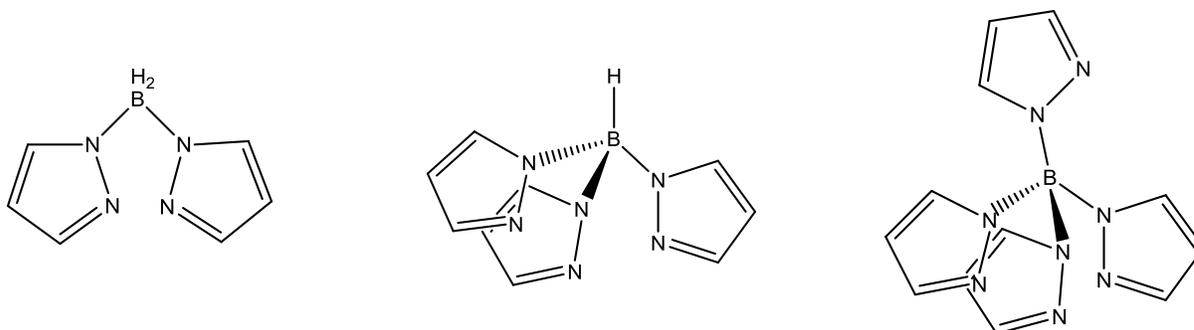
Figure 8. Bp, Tp, and pzTp Pyrazolylborate Ligands

The previous work done relating to this experiment has involved adding both a phenyl

substituent or a *tert*-butyl substituent to the third carbon on the cyano substituted pyrazole ring to

form 4-cyano-3-phenyl pyrazole and 3-*tert*-butyl-4-cyano pyrazole. The previous findings of the

addition of each of these bulky groups to the pyrazole ring have produced two unexpected effects

on the bond between the nitrogen and metal. It was predicted that the bulky substituents such as

tert-butyl groups would block the pathway between the ligand and the metal center, thus

increasing the bond length between metal ion and pyrazole. Instead, the metal-nitrogen bond

may have been facilitated causing a decrease in the bond length when *t*-butyl groups were

introduced as substituents to the pyrazole ring. It was suggested that the more bulky *t*-butyl

groups in the polypyrazolylborate complex may have a wrapping effect around the metal to help

facilitate its bonding to the nitrogen atom of the pyrazole ring, thus creating a shorter bond.

Research on substituted pyrazolylborate ligands could potentially lead to the development

of useful compounds used in applications for the material sciences such as catalysis and metal

ion extraction. A reason for focusing on polypyrazolylborates is that a wide variety of

substituents can be added to the carbons on the pyrazole ring that can modify the ligand metal

properties. One research project completed by Eichhorn, Moore, Mwania, and Zhao focused on creating thallium(I) complexes of cyano-substituted bispyrazolylborate ligands with different bulky substituent groups attached to the third carbon position on the pyrazole ring. They investigated the differences in the electronic and steric properties of the metal complexes containing differing bulky substituents attached to the pyrazole ring. Thallium(I) scorpionate complexes of both dihydrobis 3-phenyl-4-cyanopyrazolylboratothallium(I) (TlBp^{Ph,4CN}) and dihydrobis 3-*tert*-butyl-4-cyanopyrazolylboratothallium(I) (TlBp$^{t-Bu,4CN}$) were prepared and characterized in this research, and can be seen in Figure 9 below.
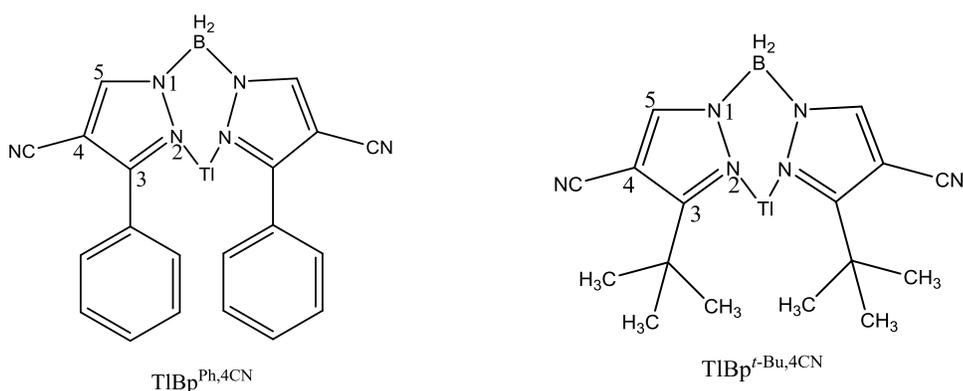
Figure 9. Scorpionate Complexes of TlBp$^{Ph.4CN}$ and TlBp$^{t-Bu,4CN}$

It was found that the Tl-N bond lengths for TlBp^{Ph,4CN} (2.814(3),2.934(3) Å) were longer than the Tl-N bond lengths for TlBp$^{t-Bu,4CN}$ (2.738(2), 2.788(2) Å).[9] The longer Tl-N bond lengths for the phenyl substituted ring is unexpected considering the phenyl group is less bulky than the *t*-butyl group. In order to compare the difference between the effects of the cyano substituent added to the pyrazole ring, the Tl-N bond lengths for TlBp$^{t-Bu,4CN}$ (2.738(2), 2.788(2)Å) and TlBp$^{3t-butyl, 5Me}$ (2.59(3),2.597(16)Å) were determined.[9] The increased Tl-N bond lengths for the cyano substituted pyrazole rings are correlated with the electron-withdrawing nature of the cyano substituents.[9] The electron withdrawing nature of the cyano group will affect the donor property

of the nitrogen bonded to the metal causing an increase in the Tl-N bond distance. This research is related to my research project with the difference being that I will be substituting a bulky tolyl group to the third carbon position of the pyrazole ring. The results of my research will provide an insight to the effects of bulky substituents on Metal-Nitrogen bonds. Specifically, since tolyl groups are more bulky than phenyl and less bulky than *tert*-butyl groups, we hypothesize the same sequence of the Tl-N bond length of corresponding scorpionate complexes. Even though the research is far from over, if this were the discovery by adding the tolyl group to the pyrazole ring, then it may indicate that the more bulky substituents facilitate the bonding of the metal to the nitrogen on the pyrazole ring.

In the two semesters I spent in the research lab, I worked on the addition of a new substituent (a tolyl group) to the third carbon position on the cyano substituted pyrazole ring. The main question of interest was will the addition of another bulky group such as a tolyl group to the third carbon position facilitate the bonding of the metal center to the nitrogen atom? In order to begin the route of determining the answer to this question, I had to first successfully synthesize the ligand: 4-cyano-3-tolylpyrazole as seen below in Figure 10.
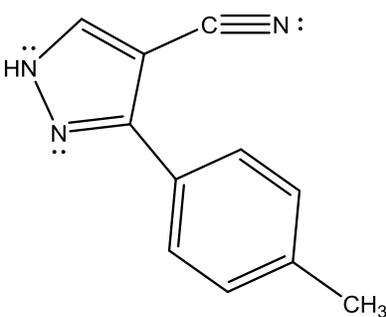

Figure 10. 4-cyano-3-tolylpyrazole Ligand

A successful synthesis of 4-cyano-3-tolylpyrazole was simply one milestone in the overall goal of this research, which is to verify or refute the hypothesis that the bulky tolyl substituent will

facilitate the bonding of the metal center to the nitrogen on the pyrazole after the scorpionate ligand is formed. Another question we hope to eventually answer in the scope of this research is will it be possible for the lone pair on the nitrogen in the cyano group to have short contact or form a real coordination to a second metal center? The group involved in this research is expecting the answer to this question to be yes since previous studies have shown it to be possible.

Before reaching the answer to these questions, it was first necessary to prove the successful synthesis of 4-cyano-3-tolyl pyrazole by running various analytical tests such as ^{1}H NMR, FTIR spectroscopy (which show the cyano peaks within the molecule), and GC-MS. After verification that the ligand 4-cyano-3-tolyl pyrazole was synthesized, next we had to attempt to bind it to a metal. I have attempted to bind the substituted pyrazole ligand to copper-(II), cobalt-(II), and thallium-(I) by growing crystals using the liquid-liquid diffusion and liquid-vapor diffusion methods. Once a successful crystal is formed, we will be able to determine that it is possible to bind a tolyl substituted pyrazole to a metal center and can then go forth in the future to attempt at forming polypyrazolylborate complexes containing tolyl substituents. The successful complexation of a scorpionate ligand to a metal center can then provide answers to the questions we are hoping to answer regarding to bond lengths between the nitrogen and metal in the polypyrazolylborate complexes.

Methods and Materials

I. Materials:

1. Solvents

    a. DMSO- Dimethyl Sulfoxide

      - Used as supplied by Fischer Scientific

    b. Acetone

      - Used as supplied by Fischer Scientific

    c. Methanol

      - Used as supplied by Fischer Scientific

    d. THF- Tetrahydrofuran

      - Used as supplied by Fischer Scientific

    e. Ethyl Acetate

      - Used as supplied by Fischer Scientific

    f. Hexane

      - Used as supplied by Fischer Scientific

    g. Toluene

      - Used as supplied by Fischer Scientific

    h. Methylene chloride

      - Used as supplied by Fischer Scientific

    i. Distilled Water

      - Used as supplied

    j. Diethyl ether

- Used as supplied by Fischer Scientific

2. Reagents

a. Sodium Hydride

- Used as supplied by Fischer Scientific

b. Tert-butyl cyanoacetate

- Used as supplied by Alfa Aesar

c. p-tolylchloride

- Used as supplied by Fischer Scientific

d. Sodium Hydroxide

- Used as supplied by Fischer Scientific

e. Hydrochloric acid

- Used as supplied by Fischer Scientific

f. p-toluenesulfonic acid

- Used as supplied by Acros Organics

g. DMF-dimethylacetal

- Used as supplied by Acros Organics

h. Hydrazine

- Used as supplied by Alfa Aesar

3. Metal Compounds

a. Cobalt(II) nitrate anhydrous

- Used as supplied by Fischer Scientific

b. Cobalt(II) nitrate hexahydrate

- Used as supplied by Fischer Scientific

c. Copper(II) nitrate anhydrous

- Used as supplied by Fischer Scientific

d. Thallium(I) nitrate

- Used as supplied by Fischer Scientific

II. Experimental Methods:

1. Synthesis of 4-cyano-3-tolylpyrazole

2. Vapor Diffusion Crystal Attempt

3. Liquid-Liquid Diffusion Crystal Attempt

4. ^{1}H NMR Spectroscopy

   a. A JEOL NMR Spectrometer was used

5. IR Spectroscopy

   a. A Shimadzu IR Prestige-21 Fourier Transform Spectrometer was used

6. GC-MS Spectrometry

   a. An Agilent GC/MS 5890 A Series II was used

Synthesis of 4-cyano-3-tolylpyrazole

Dry toluene, 150 mL, was first added to a suspension of 2.812 g (70.3 mmol) of sodium hydride (60% dispersion in mineral oil). This solution was placed under nitrogen and cooled in an ice/water bath. Next, 10 mL (70.3 mmol) of tert-butyl cyanoacetate in 10 mL of dry toluene was added dropwise to the solution under nitrogen and stirred for roughly 18 hours.

After approximately 18 hours, 11.95g (70.3mmol) of p-tolylchloride in 10mL of dry toluene was added dropwise into the viscous solution. Upon addition of p-tolylchloride, the solution immediately turned light yellow and became less viscous. The solution was left to stir for three nights.

The solution was placed in a separatory funnel where 100mL of 0.20M sodium hydroxide was added to separate the aqueous layer from the organic layer. The solution was rinsed with 100mL of sodium hydroxide three separate times to extract the aqueous layer from the organic layer. The crude product should be found in the aqueous layer with all remaining byproducts in the organic layer. The aqueous layers were combined together and washed once with ethyl ether to remove any remaining waste and toluene. The aqueous solution was acidified in order to neutralize the sodium hydroxide used during the extraction and to fully protonate the product. The acidification of the aqueous solution was accomplished by adding a solution containing 50% water and 50% saturated HCl until the solution's pH reached about 1. Immediately after the addition of the acidic solution, a white precipitate formed. The acidified aqueous mixture containing the organic, white precipitate was then extracted three times using 100mL of ethyl acetate. The white precipitate was dissolved in ethyl acetate and moved to the top yellow, clear organic layer in the separatory funnel. The organic layers were combined together after the three extractions, dried over magnesium sulfate, and filtered. The solvent in the organic layer containing the desired product was then removed with rotary evaporation to yield 10.77g

(41.6mmol, 59.14%) of the intermediate product p-tolyl-2-cyano-3-oxo-4,4-dimethylpentanoate.

The intermediate product was redissolved in 150mL of toluene and 0.79g (4.16mmol) of p-toluenesulfonic acid. This mixture was heated at reflux for approximately 18 hours. The dark orange solution that remained after reflux was filtered to remove any insoluble materials, and then rotoevaporated to remove any remaining toluene. The resulting yellow/orange product, known as 3-oxo-tolyl-propanenitrile was allowed to cool and then weighed to be 7.183g (45.75mmol, 109.9%). The product was then redissolved in 150mL of toluene and to this, 5.997g (50.3mmol) of DMF-dimethylacetal was added. Upon addition of DMF-dimethylacetal, an immediate color change took place from orange to red/orange clear which indicated the desired reaction occurred. The mixture was stirred for 18 hours under nitrogen.

After 18 hours of stirring, the solvent was removed with rotary evaporation, and the product was separated using silica-gel chromatography. The column was set up using a small amount of glass wool at the bottom tip of the column, followed by a small layer (about 2cm high) of sea sand, followed by 100-200 mesh silica gel. Methylene chloride was used as the mobile phase in the column, and was mixed with the silica gel prior to packing the column to make for an easier column packing process. The column was allowed to drip about 2-3 drops/second for one hour. The impurities adsorbed onto the silica gel very strongly, indicated by a dark red layer in the column that did not travel down the column with the mobile phase. The yellow product eluted down the column at a slow rate and was collected in 22, 10mL test tubes. Thin Layer Chromatography was performed on the products collected in each of the 22 test tubes. The tubes containing the product were added together and the methylene chloride was removed with rotary evaporation, leaving 6.06g (28.3mmol, 61.87%) of 2-oxo-tolyl-3-

dimethylaminoacrylonitrile. The product was then dissolved in 125 mL of methanol and 2.83g

(56.6mmol) of hydrazine was added. The solution was covered and stirred for 18 hours.

The methanol was removed by rotary evaporation and Thin Layer Chromatography was

performed to determine the best ratio of ethyl acetate to hexane which gave optimum separation

between the product and byproducts. It was determined that 25/75 ethyl acetate/hexane was the

best ratio of solvents to use as the mobile phase for silica-gel chromatography as it resulted in

optimum separation. After collection of the eluent, the solvent was removed by rotary

evaporation and as a result, the purified product was 5.08g (27.75mmol, 98.05%) of 4-cyano-3-

tolylpyrazole. The reaction mechanism pathway for the synthesis of 4-cyano-3-tolylpyrazole can
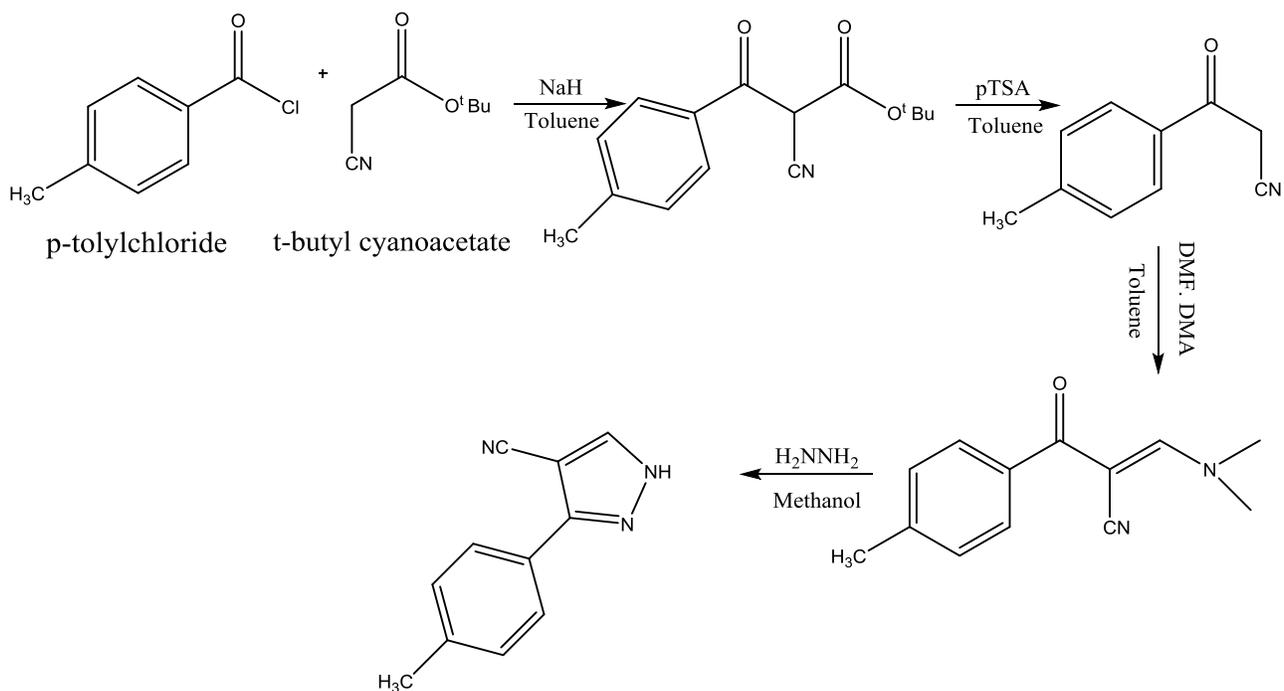
be seen below in Figure 11.

Figure 11. Reaction Mechanism for Synthesis of 4-cyano-3-tolylpyrazole

Vapor Diffusion Crystal Attempt

Initially, a solubility test had to be conducted on various solvents to determine the solubility of 4-cyano-3-tolylpyrazole in each solvent. The solubility of the ligand 4-cyano-3-tolylpyrazole in various solvents was necessary to determine which solvents could be used in vapor diffusion for crystal growth. Table 1 below lists the solubility of the ligand in each solvent tested. The (+) indicates that 4-cyano-3-tolylpyrazole was soluble in the particular solvent indicated and a (-) indicates that 4-cyano-3-tolylpyrazole was insoluble in the indicated solvent.

Table 1. Solubility Tests of Vapor Diffusion

Solvent	Solubility (+) or (-)
DMSO	(+)
Acetone	(+)
Methanol	(+)
THF	(+)
Ethyl Acetate	(-)
Hexane	(-)

After performing the solubility tests on the ligand 4-cyano-3-tolylpyrazole using the various solvents seen in Table 1, twenty attempts were made to grow crystals using the vapor-diffusion method. In each system, about 0.5 -1.0 mg of 4-cyano-3-tolylpyrazole ligand, 1.0 mg of $Co(NO_3)_2$, and about 1 mL of soluble solvent was placed in a 0.5 dram vial. A light pink, clear solution resulted. Each 0.5 dram vial was then placed inside a 3 dram vial containing about 2 mL of insoluble solvent and then capped. The vapor diffusion method is illustrated in Figure 12 below.
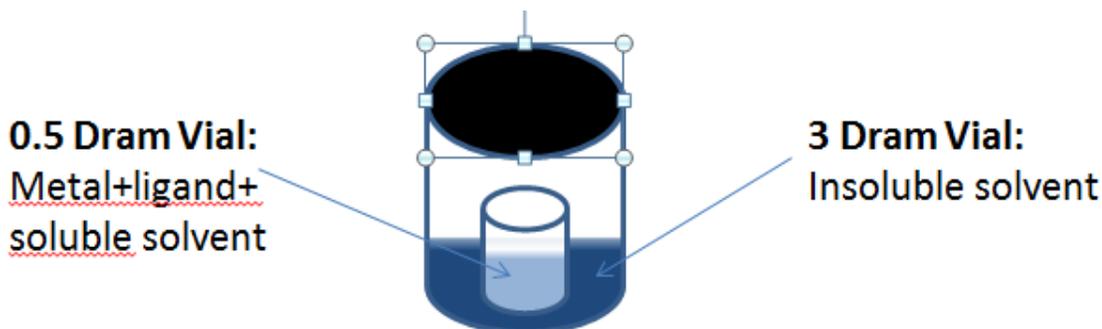
Figure 12. Vapor Diffusion Setup for Crystal Growth

Four different combinations of vapor diffusion systems were constructed, with each combination

containing five identical systems, to give a total of 20 separate vapor diffusion systems. Each of

the four different types of systems contained various combinations of soluble and insoluble

solvents. Each combination can be seen in Table 2 below.

Table 2. Four Solvent Combinations in Vapor Diffusion Crystal Attempt

	Combination 1	Combination 2	Combination 3	Combination 4
0.5 Dram Vial	Acetone	DMSO	THF	Methanol
3 Dram Vial	Ethyl Acetate	Hexane	Ethyl Acetate	Hexane

After each vapor diffusion system was constructed, a cap was placed on each 3 dram vial, and

each vial was placed in the cabinet in hopes of undisturbed crystal growth.

Liquid-Liquid Diffusion Crystal Attempt

Various attempts were made at growing crystals using liquid-liquid diffusion method. In

attempt A, a saturated solution of $Cu(NO_3)_2$ in a 50:50 solution of acetone / DI water mixture

was prepared. Next, $0.5 - 1.0$ mg of 4-cyano-3-tolylpyrazole was dissolved in about 5 mL of

acetone. A long, slender glass tube was filled about half way to the top with the saturated copper

solution, and the pyrazole acetone solution was slowly and gently added on top of the copper

solution. The same procedure for loading each solution in the glass tubes was used to set up

about 6 tubes, each containing the same amount of ligand and metal. Each tube was then covered

and placed in the cabinet in hopes of crystal growth.

In attempt B, a saturated solution of $Co(NO_3)_2 \cdot 6H_2O$ in a 50:50 solution of acetone in DI

water mixture was prepared, resulting in a medium pink colored solution. Next, a separate

solution of 0.01M 4-cyano-3-tolylpyrazole in acetone was created. Finally, 8 separate 13X100

mm test tubes were filled to the half way mark with saturated cobalt solution and the 4-cyano-3-

tolylpyrazole in acetone solution was gently poured on top. Each test tube was then covered

with parafilm and placed in the cabinet in hopes of undisturbed crystal growth.

In attempt C, nine different liquid-liquid diffusion systems were constructed using

various concentrations of 4-cyano-3-tolylpyrazole in methanol and various concentrations of

$Co(NO)_3$ in a 50:50 methylene chloride : methanol mixture. Figure 13 below demonstrates the

pairings of each concentration of metal with each concentration of ligand in each diffusion

system. For example, a 0.01M solution of $Co(NO)_3$ in a 50:50 mixture of methylene chloride

and methanol was prepared and added to the bottom half of a slender, glass tube. A 0.01M

solution of 4-cyano-3-tolylpyrazole in methanol was then prepared and added to the top half of

the same glass tube. The same procedure was repeated eight more times varying the

concentrations of each ligand and metal solution according to Figure 13 below.
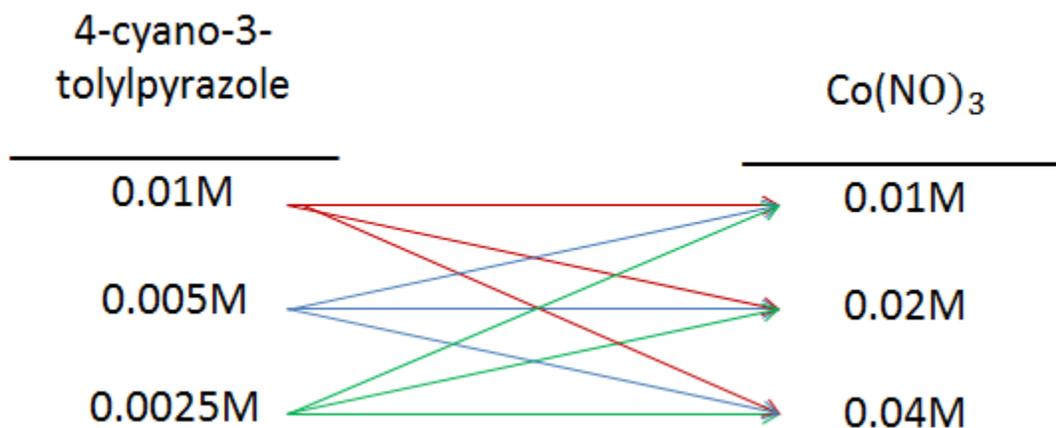
Figure 13. Nine Combinations of Ligand / Metal Concentrations in Liquid-Liquid Diffusion

In attempt D, three different liquid-liquid diffusion systems were prepared by keeping the concentration of 4-cyano-3-tolylpyrazole in methanol constant and varying the concentration of $Tl(NO)_3$ in 50:50 methanol : water solvent mixture. Figure 14 below demonstrates the pairings of each concentration of ligand and metal solutions in each diffusion system.
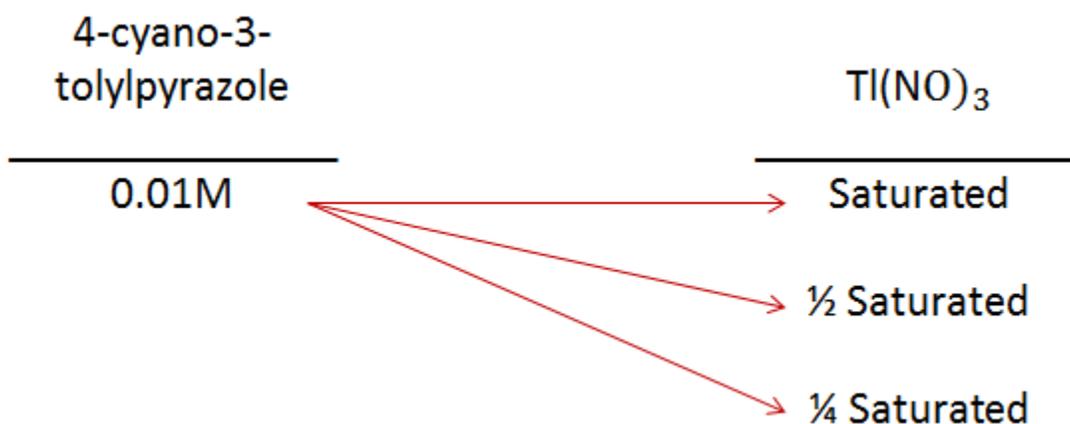

Figure 14. Three Combinations of Ligand / Metal Concentrations in Liquid-Liquid Diffusion

In order to create the half and one-quarter saturated $Tl(NO)_3$ solutions, a large amount of $Tl(NO)_3$ was added to a set volume of the 50:50 methanol : water mixture until visibly saturated. Then, a set volume of the saturated solution was removed and an equal amount of the methanol:

water mixture was added, thus creating a half saturated solution. To create a one-quarter

saturated solution, a set volume of the half saturated solution was removed and an equal amount

of the methanol: water mixture was added.

^{1}H NMR Spectroscopy

A JEOL NMR instrument operating at 400 MHz was used to collect all the ^{1}H NMR data.

For each sample analyzed by NMR spectroscopic analysis, a small amount of sample of about

0.01g was dissolved in d-chloroform and pipetted into an NMR tube. Each NMR tube was filled

about half full with d-chloroform. The NMR was programmed to run 32 scans, and the spectra

were collected and analyzed.

IR Spectroscopy

A Shimadzu IR Prestige-21 spectrometer was used for every FTIR spectroscopic

analysis. The purpose of running an FTIR on the final product, 4-cyano-3-tolylpyrazole was to

determine if all the main functional groups were present in the sample as expected. The main

peaks of interest on the FTIR spectrum were those representing the C≡N stretching of the cyano

group, the N-H stretching representing the presence of the nitrogen's in the pyrazole ring, and

peaks representing stretching from aromatic nuclei. The specific absorption peaks associated

with these indicated functional groups are listed below in the FTIR portion of the results section.

No special sample preparation was necessary prior to running the FTIR machine. A small

amount of each sample was individually placed on the eye of the FTIR for analysis.

GC/MS Spectrometry

An Agilent GC/MS 5890 A Series II spectrometer was used along with a Windows 98

processor for GC/MS analysis of 4-cyano-3-tolylpyrazole. The GC spectrum displays how many

compounds are in a chemical mixture based on the number of peaks that appear in the spectra.

When analyzing the synthesized compound 4-cyano-3-tolylpyrazole, only one peak is expected and any other peak represents the presence of an impurity. The MS spectrum is useful as the molecular weight of the sample can be determined based on the m/z ratio of the molecular weight peak. The main peak of interest on the MS spectrum is the molecular weight peak, which is expected at 183 m/z. Since the molecular weight of 4-cyano-3-tolylpyrazole is 183 g/mol, a molecular weight peak at 183 m/z is a good indication of the successful synthesis of the ligand 4-cyano-3-tolylpyrazole. The sample preparation for running the GC/MS involves placing a small amount of the sample in the GC/MS vial and completely dissolving the sample by filling the vial three-quarters of the way to the top with either acetone, hexane, or methanol. In the case for running the GC/MS for 4-cyano-3-tolylpyrazole, methanol was used as the solvent.

Results and Discussion

1. ^{1}H NMR Data

A proton NMR spectrum was obtained for the ligand, 4-cyano-3-tolylpyrazole in order to determine if successful synthesis of the ligand occurred. When analyzing the proton NMR spectra, it was necessary to pay close attention to the chemical shift of each proton. The peaks near the right side of the spectra are considered to be upfield and more shielded, whereas the peaks near the left side of the spectra are considered to be shifted downfield and are more deshielded. Each proton in a molecule is surrounded by electrons from neighboring atoms, so depending on how dense the electrons are around the nucleus determines how great the magnetic field is. If there is a large electron density surrounding the proton's nucleus, the proton is considered to be shielded and will not feel a strong magnetic field. If a proton experiences the removal of electron density surrounding the nucleus due to induction effects of neighboring atoms, the proton's nucleus is said to be deshielded and will experience a larger magnetic field.

The ^{1}H NMR spectrum for the ligand 4-cyano-3-tolylpyrazole is shown in Figure 16. The chemical shifts of interest can be seen below in Table 3.

Table 3. ^{1}H NMR Shifts of Interest for 4-cyano-3-tolylpyrazole

Peak	Chemical Shift (ppm)	Multiplicity	Integration	Interpretation
A	7.93	Singlet	0.15	Aromatic proton directly on pyrazole ring
B	7.72	Doublet	0.30	Aromatic proton
C	7.28	Doublet	0.31	Aromatic proton
D	2.41	Singlet	0.54	Benzylic protons

Figure 15 below contains the structure of 4-cyano-3-tolylpyrazol. Letters on the hydrogen atoms within the molecule corresponds to the peaks on the ^{1}H NMR shown in Table 3 and on the ^{1}H NMR spectra in Figure 16.
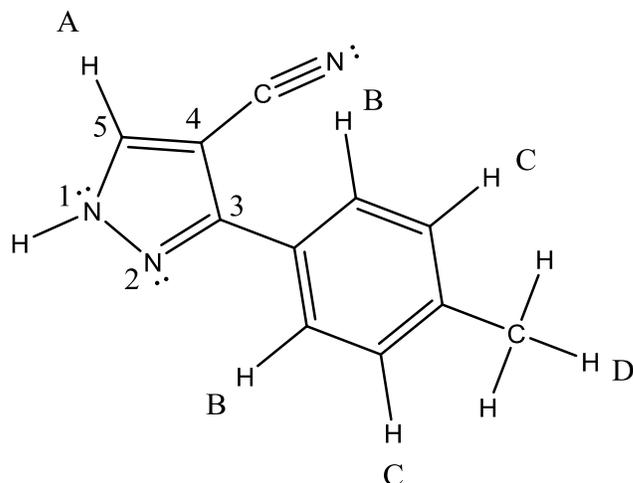

Figure 15. 4-cyano-3-tolylpyrazole Molecule

There are five chemically different hydrogen's on the ligand 4-cyano-3-tolylpyrazole, therefore five peaks on the ^{1}H NMR spectra were expected. When focusing on the aromatic ring attached to the pyrazole, peak D represents the chemical shift for the benzylic hydrogens in the methyl group para to the pyrazole ring. The chemical shifts for both protons in the ortho position on the phenyl ring were represented by peak B, and the chemical shifts for both protons in the meta position on the phenyl ring were represented by peak C. The chemical shift for the aromatic hydrogen directly attached to the pyrazole ring through the carbon atom was represented by peak A, and the hydrogen directly attached to the nitrogen on the pyrazole ring did not have a peak appear on the NMR within the accepted range. The proton at position A experienced the most deshielding with a chemical shift of 7.93 ppm. This deshielding was due largely in part to its attachment to an aromatic ring within close proximity to many electron withdrawing groups, such as the cyano group in position 4 and the two nitrogen's in positions 1 and 2 on the pyrazole ring. Peak A showed up as a singlet since there were no neighboring hydrogen atoms

surrounding the hydrogen attached to the third carbon position on the pyrazole ring. The aromatic protons ortho to the pyrazole ring experienced more deshielding than the aromatic protons meta to the pyrazole ring since the ortho protons have the closest proximity to the nitrogen electron withdrawing groups. This explains the larger chemical shift of 7.72 ppm for the ortho position protons versus 7.28 ppm for the meta position protons, represented by peaks B and C respectively. The aromatic protons that are ortho and meta to the pyrazole ring each have one neighboring proton, and therefore peaks B and C each appear to be doublets. The three benzylic protons are represented by a singlet peak with a chemical shift of 2.34 ppm since there are no neighboring protons, and benzylic protons typically have chemical shifts within 2-3 ppm. The proton connected directly to the nitrogen located in position one on the pyrazole ring did not appear in the ^{1}H NMR spectra as hydrogen's of this type typically do not. If this hydrogen were to appear in the spectra, a doublet would be expected at a chemical shift greater than 13 ppm. By looking at the integration values of 0.15, 0.30, 0.31, and 0.54 for peaks A, B, C, and D respectively, the ratio of protons between each peak can be determined. The integration values for the four peaks A-D in the spectra have a ratio of about 1:2:2:3 respectively. The ratio indicates that there is one hydrogen contributing to the peak labeled A, two hydrogen's contributing to the signals for peaks B and C, and three hydrogen's contributing to the signal for peak D. By looking at the molecule in Figure 15 above, it is clear that there is one hydrogen in position A, two hydrogens in positions B and C, and three hydrogen's in position D. Since the data collected from the ^{1}H NMR spectra matches the expected signals from a ^{1}H NMR spectra of the desired ligand 4-cyano-3-tolylpyrazole, it can be concluded that 4-cyano-3-tolylpyrazole was successfully synthesized. This theory can be further supported based on the results from the other analytical tests run on the synthesized ligand.
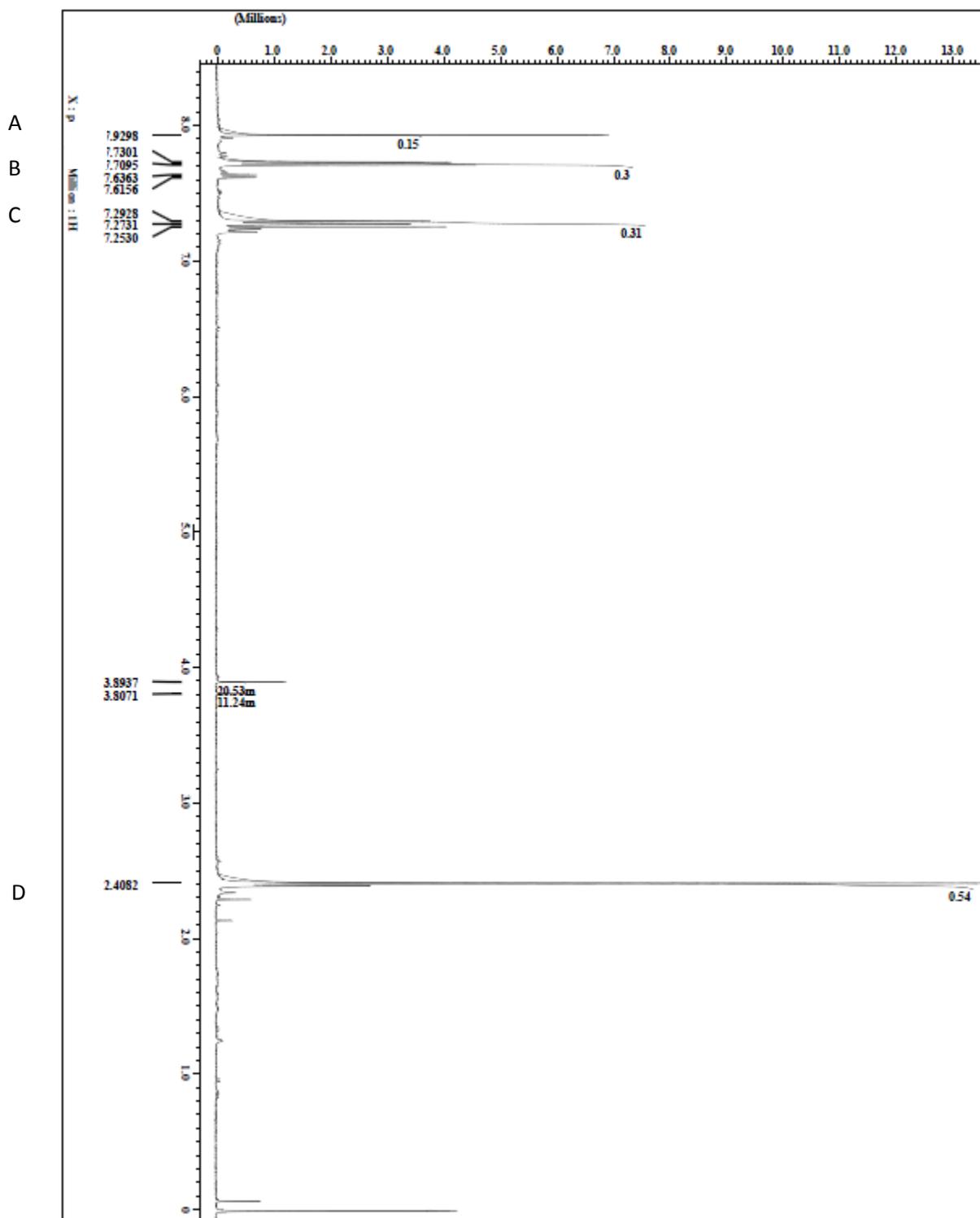
X : p

MHz : HᵃH

(Millions)

A	7.9298
B	7.7301 / 7.7095 / 7.6363 / 7.6156
C	7.2928 / 7.2731 / 7.2530

0.15

0.3

0.31

3.8937
3.8071

20.53m
11.24m

D 2.4082

0.54

Figure 16. ¹H NMR Spectrum of 4-cyano-3-tolylpyrazole

2. FTIR Data

The Fourier Transform Infrared Spectrometer used was a Shimadzu IR Prestige-21, and was used on the molecule 4-cyano-3-tolylpyrazole to help analytically determine if the proposed synthesis of the pyrazole ligand was successful. Although the FTIR spectrum solely cannot determine the complete structure of a molecule, it can be extremely useful when combined with other analytical techniques such as ^{1}H NMR and Mass spectrometry. What the FTIR spectrum can do is determine which functional groups are within the molecule of interest. Based on the functional groups that are expected in the proposed ligand of 4-cyano-3-tolylpyrazole, one can determine if all the expected groups are present or if any unexpected groups are present within the spectra. The main peaks of interest in the FTIR spectrum for 4-cyano-3-tolylpyrazole are the C≡N stretching of the nitrile group, N-H stretching of the secondary amine on the pyrazole ring, and stretching indicating the presence of an aromatic ring.

The major peaks shown in the IR spectrum for 4-cyano-3-tolylpyrazole are shown in Table 4 and correspond with the IR spectrum shown below in Figure 17.

Table 4. IR Data for 4-cyano-3-tolylpyrazole

Frequency (cm^{-1})	Functional Groups
3126.61	N-H Stretching from 2° Amine
2895.15	C-H Stretching
2233.57	C≡N Stretching Nitrile
1620.21	C=N Stretching or C=C Stretching
1498.69	C=C Stretching Aromatic Nuclei
1438.90	C=C Stretching Aromatic Nuclei
1203.58	C-H Bending
1093.64	C-H Bending
952.84	C-H Bending
813.96	C-H Bending
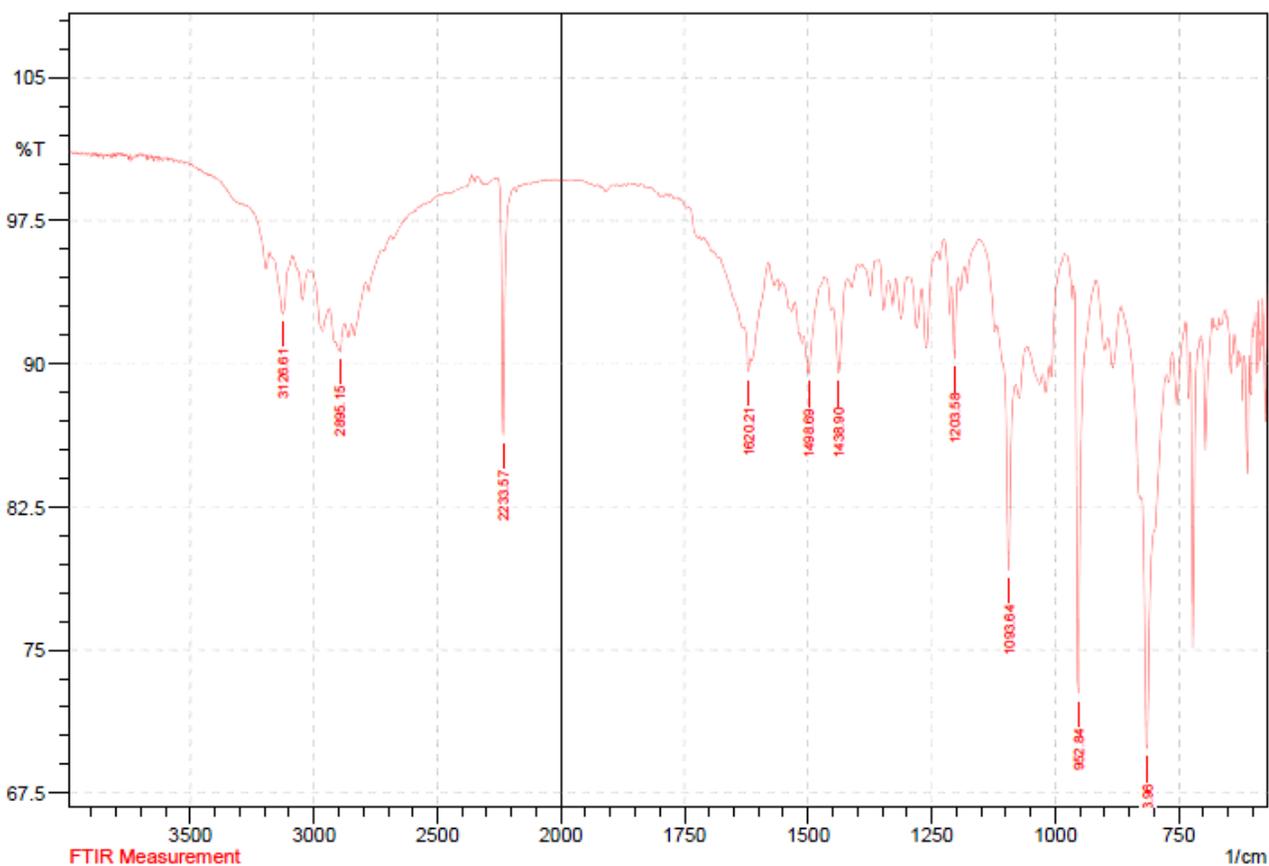
	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	813.96	69.82	14.89	827.46	775.38	4.69	1.33
2	952.84	72.7	21.46	962.48	918.12	2.33	1.18
3	1093.64	79.16	10.85	1118.71	1080.14	2.19	0.52
4	1203.58	90.27	3.99	1209.37	1195.87	0.44	0.1
5	1438.9	89.5	3.95	1448.54	1419.61	1.04	0.22
6	1498.69	89.49	2.71	1508.33	1467.83	1.44	0.16
7	1620.21	89.56	1.2	1629.85	1616.35	0.57	0.02
8	2233.57	86.23	13.34	2256.71	2187.28	1.04	0.89
9	2895.15	90.65	0.96	2912.51	2875.86	1.47	0.08
10	3126.61	92.63	3.13	3178.69	3086.11	2.25	0.52

Figure 17. FTIR Spectrum of 4-cyano-3-tolylpyrazole

The FTIR exhibits peaks for main groups of interest that indicate the attachment of the cyano group, the presence of the nitrogen in the pyrazole ring, and the aromatic ring. The presence of the cyano group is indicated by the fairly strong peak at 2233.57 cm^{-1}. This nitrile C≡N stretch is consistent with the literature value range of 2222-2240 cm^{-1}.[10] The presence of the nitrogen in the pyrazole ring is indicated by the N-H stretching seen at 3126.61 cm^{-1} as well as

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the C=N stretching seen at 1620.21 cm^{-1}. This N-H stretching is consistent with the literature value range of 3200-3500 cm^{-1} and the C=N stretching is consistent with the literature value range of 1471-1689 cm^{-1}.[10] The presence of the aromatic ring is indicated by the C=C stretching of aromatic nuclei seen at 1496.69 cm^{-1} and 1438.9 cm^{-1}. These two values are consistent with the literature value range associated with C=C stretching of aromatic nuclei of 1400-1500 cm^{-1}.[10]

3. Gas-Chromatography Mass Spectrometry

The Gas Chromatography Mass Spectrometry instrument used to analyze the synthesized ligand was an Agilent GC/MS 5890 A Series II along with a Windows 98 processor. This instrument is composed of two parts, the gas chromatographer (GC) and the mass spectrometer (MS). The GC separates the chemical mixture based on each chemical's volatility and the MS identifies and quantifies each separate chemical.[11] Once in the MS, the separated compounds are blasted with electrons, which cause the molecules to break into positively charged ions or fragments.[11] Each of these fragments then travel through an electromagnetic field which filters the fragments based on their masses.[11] Each one of these fragments that is filtered through the MS is detected and a mass spectrum is constructed indicating the mass to charge ratio of the molecule and each of its fragments. Figures 18 and 19 below show the two spectra that resulted from running 4-cyano-3-tolylpyrazole through the GC/MS. Figure 18 indicates the spectrum resulting from the gas chromatographer and Figure 19 is the spectrum resulting from the mass spectrometer.
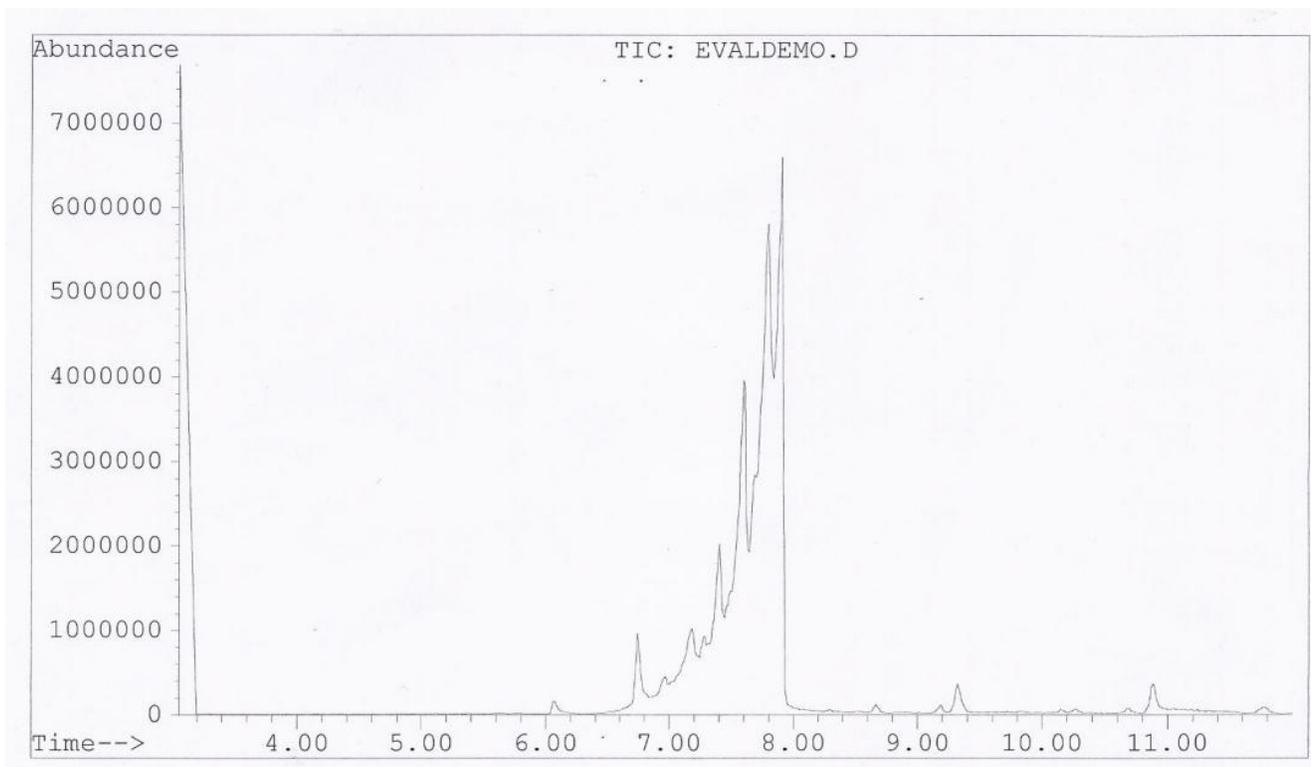
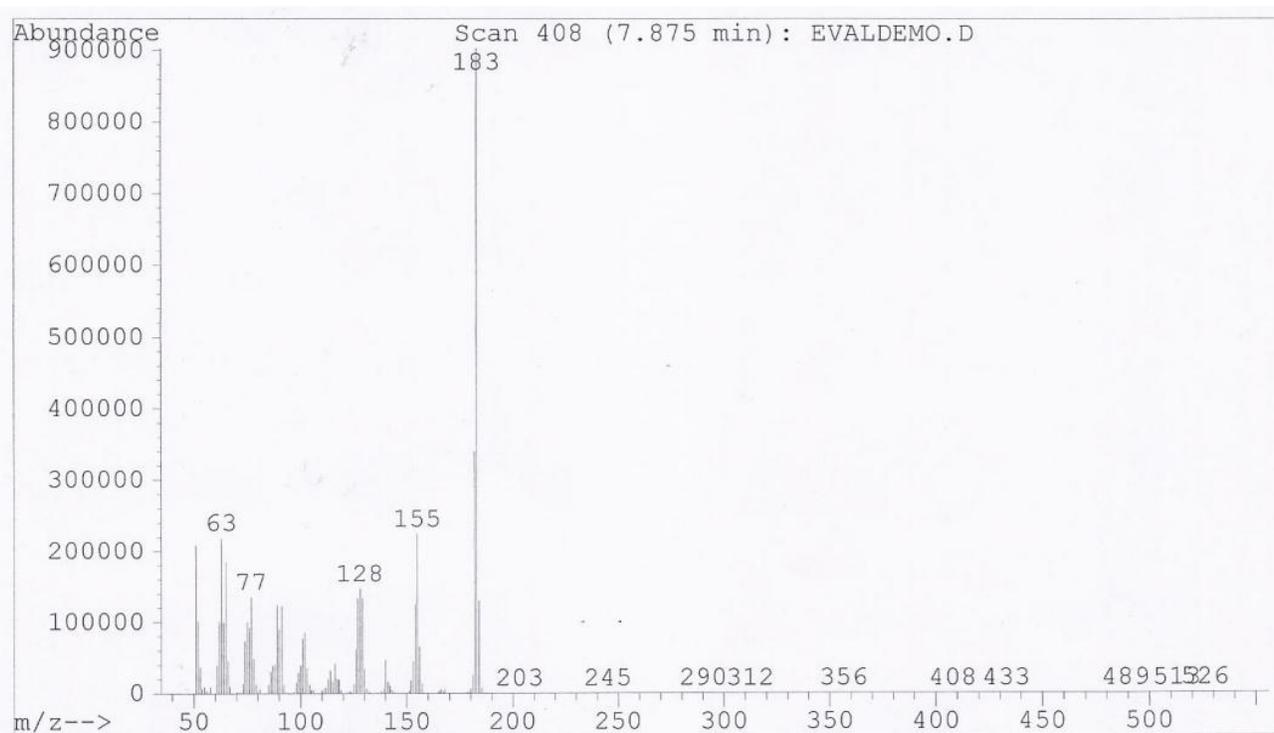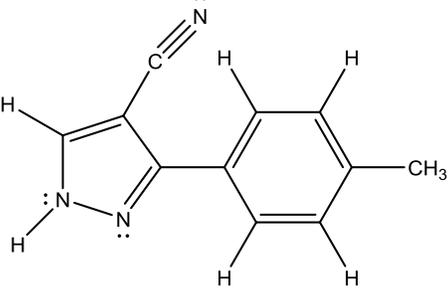Figure 18. Gas Chromatography Spectrum for 4-cyano-3-tolylpyrazole
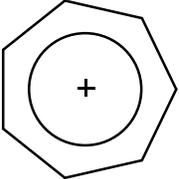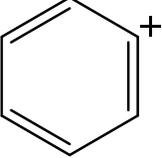

Figure 19. Mass Spectrometry Spectrum for 4-cyano-3-tolylpyrazole

It is evident by looking at the GC spectrum in Figure 18 that there is one main peak with a retention time between 6.5 minutes and 8.0 minutes. Since each peak in the GC spectrum represents a different compound, the single peak seen in the spectrum indicates there are no impurities in the sample. Since the peak on the GC spectrum is fairly broad it was necessary to determine if the entire peak represented the desired compound 4-cyano-3-tolylpyrazole and contained no overlapping impurities. This goal was accomplished by clicking the cursor around various areas of the GC peak to see if a different mass spectrum resulted. Each point in the GC peak from 6.5 minutes to 8.0 minutes resulted in the same MS spectrum, further indicating no impurities.

Table 5 below contains some of the main fragment peaks found from the mass spectrometry spectrum for the synthesized compound along with molecular structure or formula for each fragment.

Table 5. Mass Spectrometry Fragments for 4-cyano-3-tolylpyrazole

m/z	Molecular Fragment
183	
155	$C_{11}H_9N^{+\bullet}$
128	$C_{10}H_8^{+\bullet}$
91	
77	

The MS spectrum in Figure 19 displays a molecular ion peak at 183 m/z, which indicates the sample has a molecular weight of 183 g/mol. The MS spectrum in Figure 19 shows various fragment peaks at 155 m/z, 128 m/z, 91 m/z, and 77 m/z which can all be explained by fragmentation of 4-cyano-3-tolylpyrazole. There is a difference of 28 m/z between the molecular weight peak at 183 m/z and the fragment peak at 155 m/z. This difference indicates the loss of a N_2 molecule from 4-cyano-3-tolylpyrazole. Since there is a difference of 27 m/z between the two fragment peaks at 155 m/z and 128 m/z, the fragment peak at 128 m/z can be explained by the further removal of a CN group and one hydrogen from the fragment at 155 m/z. The MS

peak at 91 m/z is the result of the fragmented seven membered tropylium ion that is a commonly found in mass spectrometry due to the rearrangement of the tolyl group. The MS spectrum in Figure 19 also displays a large peak at 77 m/z, which is the result of the ionic form of benzene that was fragmented from 4-cyano-3-tolylpyrazole. Since the molecular weight of the desired compound 4-cyano-3-tolylpyrazole is 183 g/mol and because the indicated fragment peaks all support fragmentation resulting from 4-cyano-3-tolylpyrazole, it is evident that the desired ligand 4-cyano-3-tolylpyrazole was in fact successfully synthesized.

4. Crystal Growth

4.1 Vapor Diffusion Crystal Attempt

The twenty vapor diffusion systems were allowed to sit undisturbed for about two weeks until some sort of growth was detected in the vials. Out of the four combinations of solvents, the vials with solvent combination 3, containing THF and ethyl acetate, were the only systems that developed any solid. The solid appeared small, green, and somewhat translucent, but it was determined using a light microscope that the solid was in fact not a crystal, only a precipitate. Due to the unsuccessful attempt at growing crystals, I have not determined the complexation of cobalt with 4-cyano-3-tolylpyrazole.

4.2 Liquid-Liquid Diffusion Crystal Attempt

Attempt A: In the first attempt at growing crystals using the liquid-liquid diffusion method, the two solutions prepared were a saturated solution of $Cu(NO_3)_2$ in a 50:50 mixture of DI water and acetone, and a small amount of 4-cyano-3-tolylpyrazole dissolved in acetone. When performing liquid-liquid diffusion, it is important to use two solvents that are miscible with each other, yet the ligand-metal complex has to be insoluble in one of the solvents. Over time when the two layers of solvent diffuse together, the complex can come out of solution and

form crystals with the metal in the insoluble solvent. In this crystal attempt, 4-cyano-3-tolylpyrazole was dissolved in acetone since it was determined in the solubility tests seen in Table 1 that acetone is a soluble solvent for 4-cyano-3-tolylpyrazole. When choosing a solvent to dissolve the metal, the two requirements to be met were that 1) 4-cyano-3-tolylpyrazole had to be insoluble in the solvent and 2) the two solvents used in the system had to be compatible with one another. A 50:50 mixture of acetone and water was chosen to dissolve the metal $Cu(NO_3)_2$ because 4-cyano-3-tolylpyrazole was determined insoluble in water, and a mixture of the acetone and water was more compatible with acetone than simply dissolving the metal in water. After allowing the tubes to sit undisturbed for about two weeks, a white colored precipitate with a green tint filled each slender, glass tube with no crystal growth.

Attempt B: In the second attempt at growing crystals using the liquid-liquid diffusion method, the same procedure was followed as in attempt A using the same solvent solutions, only $Co(NO_3)_2 \cdot 6H_2O$ was used instead of $Cu(NO_3)_2$. After allowing the tubes to sit undisturbed for about two weeks, a white colored preceipitate with a pink tint resulted with no crystal growth.

Attempt C: In the third attempt at growing crystals using the liquid-liquid diffusion method, nine different liquid-liquid diffusion systems containing varying concentrations of 4-cyano-3-tolylpyrazole in methanol and varying concentrations of $Co(NO_3)_2$ in a 50:50 methylene chloride : methanol mixture were prepared. Each of these nine different combinations of varying solution concentrations can be seen in Figure 13 above. The thought process in decreasing the concentration of each solution containing the metal and ligand was to hopefully avoid formation of a precipitate and avoid interference of the precipitate with crystal formation. After each tube was covered and left undisturbed for a month, there was no formation of precipitate and no crystal growth.

Attempt D: In the fourth attempt at growing crystals using the liquid-liquid diffusion method, three different liquid-liquid diffusion systems containing one concentration of 4-cyano-3-tolylpyrazole in methanol and varying concentrations of $Tl(NO_3)$ in a 50:50 methanol: water mixture were prepared. Each of the three types of systems involved a 0.01M solution of 4-cyano-3-tolylpyrazole in methanol with a saturated solution of $Tl(NO_3)$ in the first set, a half saturated solution of $Tl(NO_3)$ in the second set, and a one-quarter saturated solution of $Tl(NO_3)$ in the third set of liquid-liquid diffusion systems. After each tube was covered and left undisturbed for a month, there was no formation of a precipitate and no crystal growth, only a solution with a light yellow tint resulted.

Conclusion

Based on the syntheses and analytical results from ^{1}H NMR, FTIR, and GC/MS, the successful synthesis of 4-cyano-3-tolylpyrazole was proven. The next step of the research was to introduce a metal to 4-cyano-3-tolylpyrazole, in hopes of complexing a metal to the second nitrogen position of the pyrazole ring. Although five separate attempts have been made to bind either cobalt(II), copper(II), or thallium(I) to the second nitrogen position in the pyrazole ring using liquid-liquid diffusion and vapor diffusion techniques, the crystal growth was yet unsuccessful. These attempts will be useful in the future to optimize concentrations of metal and ligand at growing the crystals by looking at what products and precipitates did result from each crystal attempt.

If a crystal had successfully formed, and the X-ray crystallography had proven the metal complex we predicted, this research could be further carried out to answer any underlying questions relating to the larger scope of this research. If one of these metals had complexed to 4-cyano-3-tolylpyrazole, it could lead one to believe when boron were introduced to 4-cyano-3-tolylpyrazole to produce a pyrazolylborate ligand, metal ions would bind and form a metal complex with the scorpionate ligand as well. Future researchers could then be able to determine the metal to nitrogen bond length in the pyrazolylborate complex containing the bulky tolyl substituent and how it compares to the Tl-N bond lengths found in previous research for the two pyrazolylborate complexes TlBp$^{t\text{-Bu, 4CN}}$ and TlBp$^{\text{Ph, 4CN}}$. In the future, hopefully someone will be able to continue on with this research and will be able to successfully bind a metal to the ligand 4-cyano-3-tolylpyrazole so all these unanswered questions can be put to rest.

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