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Synthetic Formal Report #2 - The Synthesis of 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole

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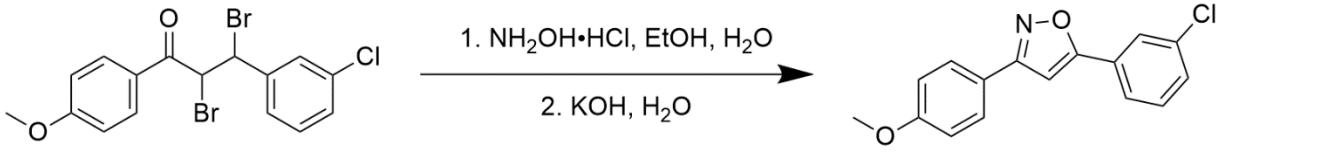
Introduction

The synthesis of the 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole (**2**) from the brominated chalcone (**1**) is a ketone addition reaction resulting in an imine and heterocycle formation. In this reaction, the carbonyl pi bond is broken and a new pi bond forms to nitrogen. The next step is heterocycle formation, which breaks two sigma bonds of leaving groups and forms a sigma bond and pi bond, completing the aromatic heterocycle synthesis. Aromatic heterocycle formation is greatly important because of the wide-ranging biochemical properties and uses of heterocyclic compounds[1]. Ketone addition reactions also have a wide variety of uses, including acting as an electrophile in a nucleophilic addition reaction, allowing for the attachment of a wide variety of substituents, like alcohols, ethers, and more to the carbonyl carbon. Ketone additions reactions can be the final step of a reaction, or be used further in another step, while heterocycle synthesis is useful as the final step because of the high stable aromatic system created.

Isoxazoles are extremely important, primarily because of their potential to act on biological systems. Different isoxazole compounds have been found to have antiviral, antimicrobial, antitumor, anti-inflammatory, and other useful properties[2]. Isoxazole formation allows easy attachment of many different substituents and allow for a wide variety of different large molecules to be synthesized. Because of their stability, modifying other parts of the isoxazole-containing molecule after heterocyclic formation is possible in some cases. In addition to biological properties, isoxazoles can also be used in additional steps of syntheses. Research shoes that isoxazoles can undergo reductive ring cleaving in the presence of copper/diamine catalysts to yield enaminones[3]. These enaminones currently can be used to create a variety of drugs, and other applications are possible[3].

The balanced reaction synthesis of the isoxazole product goes through eight major steps. In the acidic environment, the ketone oxygen is protonated first. Hydroxylamine then nucleophilic attacks the carbonyl carbon and electrons from the carbonyl pi bond are pushed onto the carbonyl oxygen. Solvent mediated proton transfer then occurs between hydroxylamine and carbonyl oxygen, deprotonating nitrogen and turning the alcohol to water, a good leaving group. The water leaves and lone electron pair from nitrogen form a pi bond with the previous carbonyl carbon. The acid catalyst is then regenerated, and nitrogen is deprotonated. Once base is added, hydroxide deprotonated the ketoxime and pushes the electrons onto the oxygen. The anionic oxygen then electrophilic attacks the beta carbon. The bromine on the beta carbon acts as a good leaving group and the cyclic system is formed. Finally, by E1CB mechanism, hydroxide deprotonates the beta carbon and bromine on the alpha carbon acts as a good leaving group. The resulting product is 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole (**2**). While straight forward, this method is not the only way to accomplish the goal of creating the isoxazole. β-dicarbonyl compounds in the presence of hydroxylamine hydrochloride and hetropolyanions, like Preyssler's catalyst, have formed isoxazoles[4]. This method uses a green and reusable catalyst and is a viable method to create 3,5-diphenyl isoxazoles. Disubstituted isoxazoles can also be made from C(α)-*O*-Dilithiooximes treated with lithium diisopropyl-amide, condensed with esters[4]. This method introduces lithium, which poses several dangers and is not the preferred method of synthesis.



1
2,3-dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)propan-1-one
MW: 432.50 g/mol
mp 140°C

2
5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole
MW: 285.72
mp 128°C

Figure 1: Isoxazole synthesis from brominated chalcone

Results, Discussion, and Conclusions

0.25g (0.577mmol) brominated chalcone was added to 12.5ml of absolute ethanol in a round bottom flask and stirred vigorously. 0.08g (1.16mmol) hydroxylamine hydrochloride was added to 1.2mL distilled water and dissolved, and then added to the reaction flask dropwise. The reaction flask was placed in a heating mantle set to 50% and refluxed for 20 minutes. Under acidic conditions, hydroxylamine hydrochloride reacts with the ketone of the brominated chalcone. After 20 minutes, 2.0mL 2M sodium hydroxide solution was added. The excess base in solution pushes the reaction forward by adding hydroxide to deprotonate the ketoxime intermediate, eventually leading to an E1CB reaction, deprotonating the newly formed ring and creating the heterocyclic isoxazole. Reaction was refluxed for 2.5 hours to encourage maximum product formation. Reaction was monitored by TLC (30% ethyl acetate/70% hexanes) every thirty minutes to monitor progress. Product spot (R_f = 0.45) intensity started low and increased over time of reaction. Similarly, starting material spot (R_f = 0.50) intensity started high and decreased over time. Polarity of the isoxazole was slightly higher because of bond dipoles, electronegativity, and polarizability of the heterocyclic system. Reaction mixture turned from cloudy white to transparent when hydroxylamine hydrochloride was added, transparent brown when potassium hydroxide was added, and finally yellow/orange as the reaction refluxed, reflecting reaction progressing. Byproduct formation was marked by a small TLC spot of growing intensity at R_f = 0.25, remaining relatively small.

After completion, the reaction mixture was cooled to room temperature and separated into two layers with 15mL DCM and 20mL distilled water. Layers were seperated and aqueous layer was extracted with 15mL DCM to draw out any organic product. The organic layers were combined and washed with 15ml distilled water to remove molecular ions, followed by 15ml saturated sodium chloride solution to draw out water and further dry organic layer. Organic layer was then dried over anhydrous sodium sulfate for 15 minutes to remove any additional water. Solvent was then evaporated to yield crude product.

After workup, crude product was dissolved in 2ml DCM and loaded into prepared silica column. Column chromatography was ran with 5% ethyl acetate/95% hexanes to 20% ethyl acetate/80% hexanes over 15 fractions. Isoxazole product solely eluted in fractions 1-7, isoxazole and byproducts coeluted 8-11, and byproducts eluted 12-13. The column was mostly successful, but there was coelution and some product was lost because of similar polarities. Product yield was 42%, which was similar to the literature 40%[7]. The white crystalline appearance matched the expected appearance, indicating high purity.

The isoxazole product was successfully synthesized and purified according to 400 mHz ^{1}H-NMR data. Most downfield are hydrogens A, B, and C. Hydrogen A being a singlet integrating to one at 7.809 ppm, hydrogen C is a doublet integrating to two at 7.791 ppm, and hydrogen B is a doublet integrating to one at 7.708 ppm. Hydrogen A is most downfield because it is ortho to the EWG chlorine, hydrogen C is next most downfield because the close-proximity nitrogen is sterically locked and partially deshields hydrogen C, and hydrogen B is most upfield of the three. Hydrogen A-C overlap into a multiplet around 7.72 ppm. Next most upfield, hydrogen D is a doublet integrating to one at 7.413 ppm and hydrogen e is a triplet integrating to one at 7.413. These two hydrogens overlap to a multiplet. Hydrogen F is a doublet integrating to two at 6.995 ppm. Hydrogens F are pushed slightly upfield because they are ortho to the EDG ether. Hydrogen G is a singlet integrating to one at 6.790 ppm. Hydrogen G is the most upfield aromatic hydrogen because of resonance within the heterocyclic system. Finally, hydrogens H form a singlet integrating to three at 3.362 ppm. The lack of two doublet integrating to one in the 2.0-4.1 ppm region prove that the brominated chalcone was successfully converted to the isoxazole product and none remained in the final product. The presence of the singlet integrating to one 6.79 ppm proves product formation, as it is unique to the isoxazole product. All expected peaks were present at expected values[7], the isoxazole product was successfully purified by column chromatography. Hexanes peaks were present at 0.872 and 1.253 ppm, because they were used apart of the column solvent, and water is seen at 1.612 ppm. There is an unknown aromatic contaminant at 6.679 ppm, is small but could have been a byproduct

that co-eluted during column chromatography. The level of contamination is small, and the final product is highly pure. This is reinforced by the expected white crystalline appearance, 128.5 C expected MP, and other spectral data. Overall, according to 400 mHz ^{1}H-NMR, 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole was successfully synthesized and subsequently purified by column chromatography.

The isoxazole product was successfully synthesized and purified according to ^{13}C-NMR data. The starting brominated chalcone and isoxazole product share many peaks but differ in several key, distinct carbons. Both molecules will product signals of fourteen distinct hydrogens, but several will appear at different ppm. The most downfield C=O ketone peak from the starting material in the 190-220 ppm range is noticeably absent in the isoxazole carbon NMR. This indicates starting material conversion from the brominated chalcone. The most downfield carbon 1 is present in the ^{13}C-NMR at 168.624 ppm. This carbon is the isoxazole carbon attached to oxygen. The imine carbon 3 also appears at 161.136 ppm. The presence of carbons 1 and 3 in this region help prove product formation, as they are unique to the isoxazole product and not present in the brominated chalcone. Carbon 5, which was connected to the bromide carbon in the starting material, is now shifted slightly more upfield to 130.372 ppm from ~140 ppm because the EWG bromine is no longer present. Carbons 6-10 also shift slightly in response to the loss of the EWG bromines and ketone. The alkene carbon 13 appears at 98.080 ppm, which is due to isoxazole formation. Most upfield in the product's ^{13}C-NMR is the methoxy carbon at 55.326 ppm. Further proving starting material formation, two bromide peaks are absent in the 30-65 ppm range. There are several, very low intensity peaks in the aromatic region, which could explain the aromatic contaminant in ^{1}H-NMR. All peaks, present and absent, agrees with literature values[7]. ^{13}C-NMR indicates that the isoxazole product was successfully synthesized and purified by column chromatography.

The isoxazole product was successfully synthesized and purified according to IR data. Most down on the IR is the C-H aromatic peak at 3107.98 cm^{-1}. This is closely followed by the C-H alkene peak at

2964.28 cm^{-1} and C-H aliphatic at 2843.53 cm^{-1}. More upfield is the C=N imine peak at 1607.13 cm^{-1}. This is then followed by a C=C trisubstituted alkene peak at 1561.13 cm^{-1}. Both peaks are unique to the isoxazole product and prove product formation. C=C aromatic peaks are observed at 1521.24 and 1476.43 cm^{-1}. C-O ether peaks are seen at 1432.49 and 1241.44 cm^{-1}. CH_3 umbrella peaks are then seen at 1382.15 and 1292.17 cm^{-1}. Next, the C-O ring peak is observed at 1173.60 cm^{-1}, which is also unique to the isoxazole and proves product formation. Most upfield at 1021.43 cm^{-1} is the C-Cl aryl. Lack of a conjugated C=O ketone peak at 1700-1675 cm^{-1} and C-Br aliphatic peak at 650-510 cm^{-1} prove conversion of starting material. There is no visible impurities observed in IR, which lines up with expected white crystalline appearance, expected 128.5 C MP, and other spectral data, indicating high purity and success of synthesis and purification. In conclusion, isoxazole product was successfully synthesized and purified by column chromatography according to IR data.

The experiment was overall successful. The overall goal was to synthesize 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole from the step one brominated chalcone product and purify the isoxazole by column chromatography. This goal was fulfilled, and all data and observations were consistent with expectations[7]. 400 mHz ^{1}H-NMR data returned all expected peaks at appropriate shift values, with only minor contaminants, including water, hexanes, which was a column solvent; and a small intensity aromatic contaminant at 6.679 ppm, which could be a byproduct that coeluted during column chromatography. These peaks had very low intensity and no other contaminants were present, indicating a highly pure isolated product. ^{13}C-NMR returned fourteen distinct hydrogens in the expected shift ranges. Specifically, the isoxazole C-O at 168.624 ppm, imine carbon at 161.136 ppm, and alkene carbon at 98.08 ppm appeared, indicating product formation. The ketone carbon at 220-190 ppm and two C-Br carbons at 65-30 ppm were absent from the isoxazole carbon NMR, proving lack of starting material present. IR data also supported these conclusions. All expected peaks were present, matching expected literature values. C-H alkene peak at 2964.28 cm^{-1}, C=N imine at 1607.46 cm^{-1}, C=C trisub. alkene at 1561.13 cm^{-1}, and C-

O ring at 1173.6 cm^{-1} all supported product formation. Lack of a conjugated C=O ketone peak at 1700-1675 cm^{-1} and C-Br aliphatic at 650-510 cm^{-1} prove conversion from starting material. No contaminants were seen in IR, further proving a highly pure product. The physical appearance of the product was the expected white crystalline power, and MP occurred at 128.5-132.5 C, right around the expected 128-130 C. Pure mass was 0.07 g, which is a 42% yield, and recovery from column chromatography was 49%. Pure yield, while at the expected literature yield is a source of error, as well as the aromatic contaminant seen in ^{1}H-NMR. Possible improvements would be running the reaction longer to encourage more product formation, and exploring reaction conditions to discourage byproduct formation. Considering all available data, 5-(3-chlorophenyl)-3-(4-methoxyphenyl)isoxazole was successfully synthesized from 2,3-Dibromo-3-(3-chlorophenyl)-1-(4-methoxyphenyl)-1-propanone and purified by column chromatography.

References

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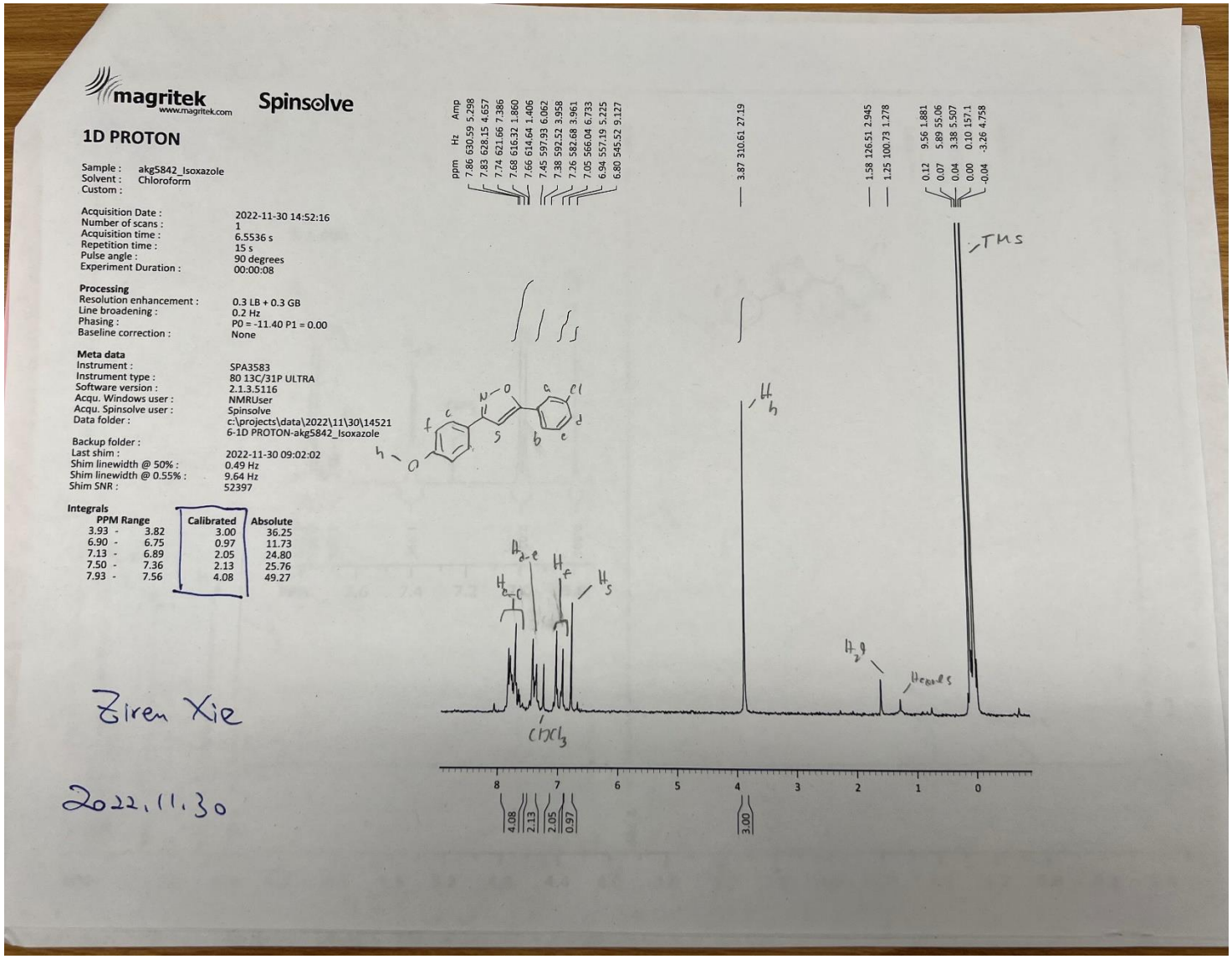
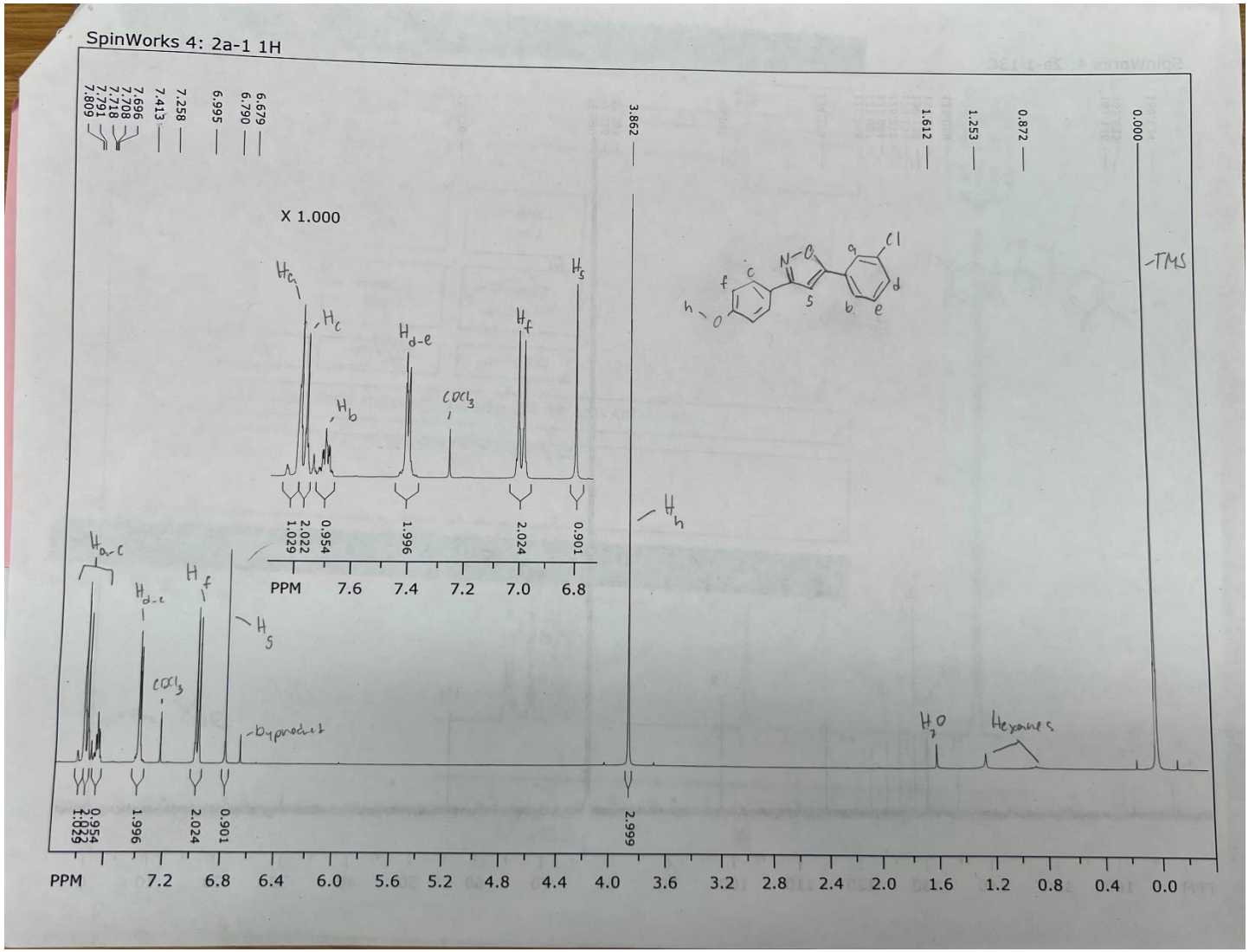
Spectral Data

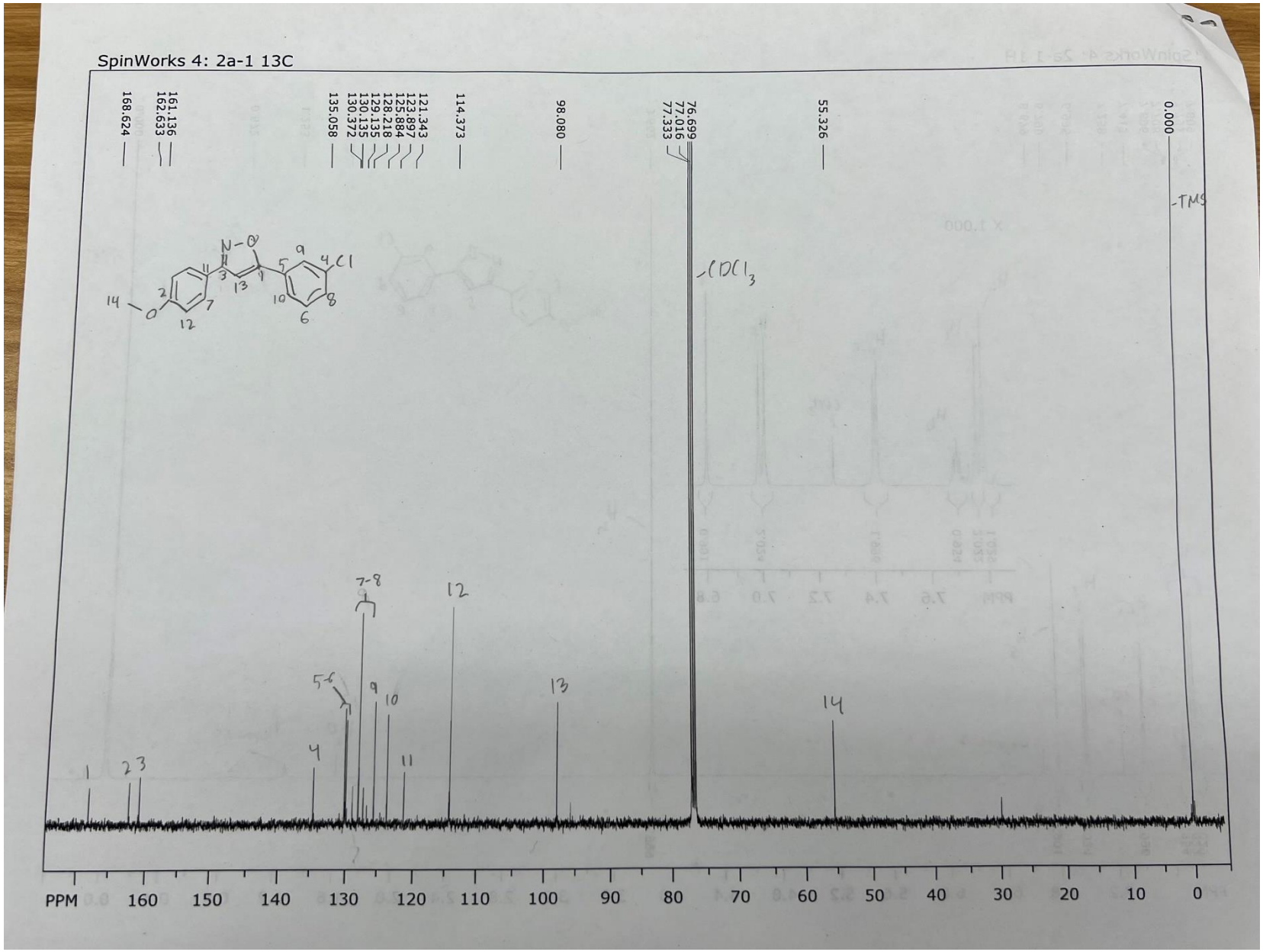
- Proton NMR (60 MHz), annotated



- Proton NMR (400 MHz), annotated



- Carbon-13 NMR (100 MHz), annotated



- IR, annotated