A Multistep Synthesis of Thiopyrimidine Derivatives

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Augustana Honor Code: "*On my honor, I pledge that I have upheld the Honor Code, and that the work I have done on this assignment has been honest, and that the work of others in this class has, to the best of my knowledge, been honest as well."*

Abstract

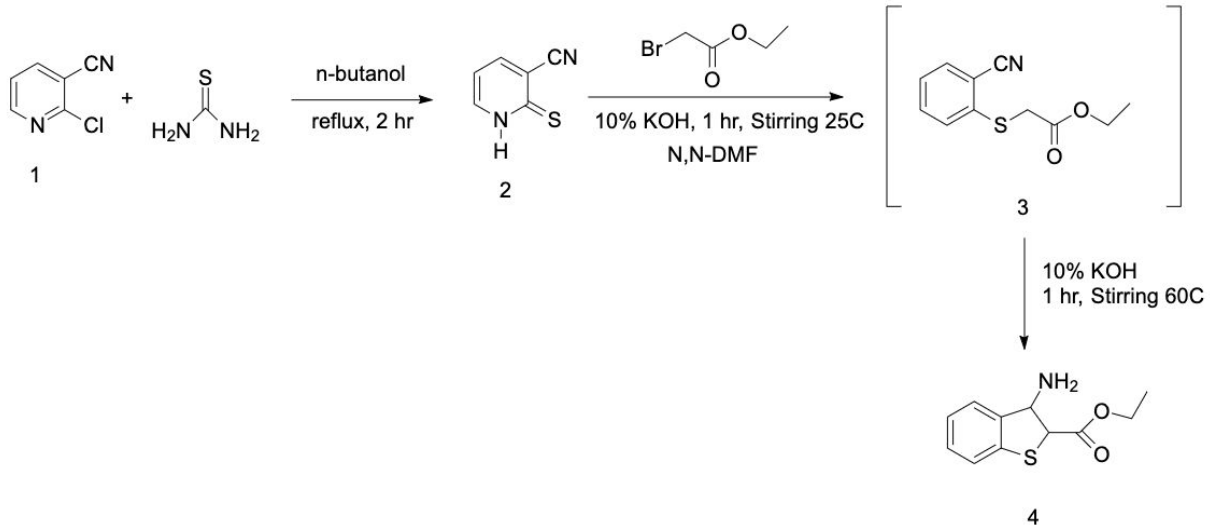


Figure 1: Synopsis of the Synthesis

A multistep synthesis was performed to produce ethyl 3-aminothieno[2,3-b]pyridine-2-carboxylate (4) (Figure 2). A reflux of 2-chloro-3-cyanopyridine (1) and thiourea in n-butanol produced 2-mercaptonicotinonitrile (2) which was characterized using IR, GCMS, and ^{1}H NMR spectroscopy. Performing an alkylation of (2) with ethyl bromoacetate produced an intermediate, ethyl-2-((3-aminopyridin-2-yl)thio)acetate (3) verified by TLC that underwent base-promoted ring-closing to produce the product (4), which was then characterized by FTIR, GCMS, ^{1}H NMR, ^{13}C NMR, COSY, and HMQC spectroscopy. Tautomer ratios of (2) were determined by calculating energies of formation using the Hartree-Fock 6-31G basis set in the Spartan '18 software package.

Introduction

In the undergraduate laboratory, organic chemistry experiments are generally limited in complexity due to time constraints, limiting the amount of synthetic steps able to be performed by students. The synthesis of thieno[2,3-b]pyridine derivatives serve to gain experience with multiple stages of synthesis, purification, and characterization, akin to experiences later in industry or in research capacities. Thiopyrimidine derivatives are prepared under relatively mild conditions using commercially-available reagents. Recent work involves many medicinal applications as anticancer agents[1], regulation of GluR5 receptors, and as an inhibitor of human copper-trafficking proteins.[2] The blood platelet anti-clotting medication, Prasugrel (Figure 3), is based off of the thiopyrimidine structure and is shown to reduce the risk of additional episodes of acute coronary syndrome (ACS) after patients experience a heart attack.[3] Industry uses of thieno[2,3-b]pyridines also include industrial dyes, chemical plant protection in the form of insecticides, and acid corrosion prevention.[4,5]

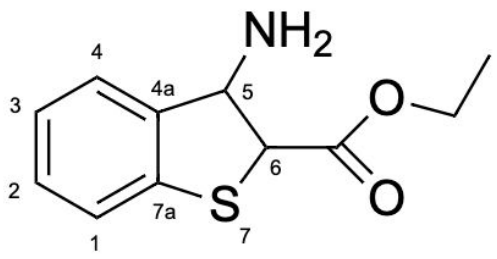
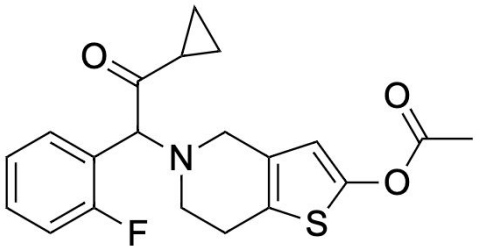
	

Figure 2: 3-aminothieno[2,3-b]pyridine-2-carboxylate (4)	**Figure 3: Prasugrel**

General Experimental

Physical and Spectral Data

- Mass spectra data was acquired on a Hewlett Packard G1800A instrument. The CHEM331 method was used to obtain spectra. The column temperature started at 60°C and ended at 300°C with a ramp of 40°C/min. The solvent delay was 2.0 min and 2.0 min were allowed for final elution. A 0.25 mm diameter silica column at a length of 30.0 m was used with He gas as the mobile phase.
- ^{1}H NMR, ^{13}C NMR, COSY, and HMQC spectra were acquired on a JEOL ECS-400 NMR spectrometer. Proton NMR data are listed in standard JOC formatting, as follows: chemical shift (ppm) (multiplicity, coupling constants, integrated number of protons, proton assignment in structure). Carbon NMR data are also listed in JOC formatting: chemical shift (ppm) (carbon assignment in structure). d_6-DMSO was used as a solvent, referencing ^{1}H NMR spectra to 2.50 ppm and ^{13}C spectra to the septet at 39.5 ppm.
- Infrared spectra were acquired on a Nicolet Avatar 361 FT-IR with Gateway 2000 data system. Solid samples were made using KBr pellets, while liquid samples were placed on NaCl plates after being washed with CCl_4.
- Melting point data were obtained on a Barnstead Thermolyne Mel-Temp Electrothermal 1001D Melting Point Apparatus. Melting point was determined over a range, where the apparatus was started at 150°C at a 5°C/min ramp until 250°C was achieved.
- Spartan '18 calculations on chemical structures were performed in sequence to determine the equilibrium geometry in the gas phase. The iterative run sequence is a molecular mechanics MMFF run, then semi-empirical AM1, PM3, and PM6 runs, and finally a B3LYP/6-31G9d DFT calculation. Enthalpy of formation values for tautomer ratios were obtained from the DFT run output.

Solvents

- 95% EtOH was stored in a brown-glass bottle and was used as a recrystallization solvent.
- 10% KOH was dissolved in deionized water and stored in clear Nalgene bottles.
- N-butanol was stored in a brown-glass bottle and was used as a reaction solvent.

- N,N-dimethylformamide was stored in a brown-glass bottle in a non-anhydrous environment and was used as a reaction solvent.

Reaction Standards

- Glassware was washed and allowed to let dry in ambient air before synthesis work occurred.
- Water used in reactions was purified by the in-house reverse osmosis deionization system.
- Removal of solvent under reduced pressure refers to solvent removal on a Büchi RE 111 rotary evaporator connected to a water aspirator and an ethylene glycol cooling system.
- Unless otherwise stated, all solvents/reagents were reagent grade and used without further purification.

Safety Information/Warnings

- Ethanol is highly flammable and intoxicating, keep away from flames and use in ventilated area.
- KOH is a corrosive base, wear PPE when handling.
- DMSO-d_6 (NMR Solvent) is harmful if swallowed, toxic if inhaled and is a known carcinogen. Use PPE while handling in a well ventilated area.

**Safety Information from Sigma-Aldrich Inc[6].

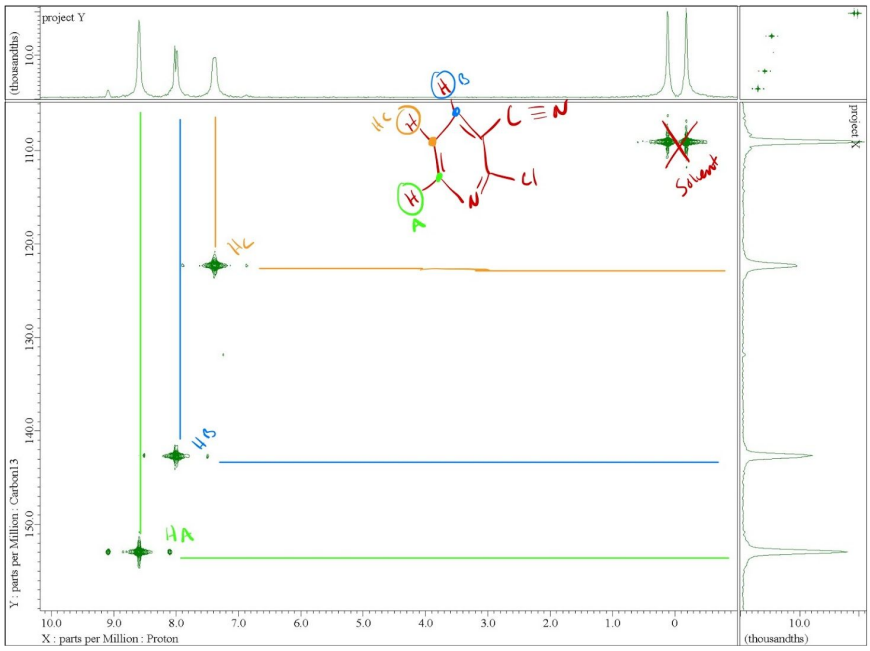
Characterization of Starting Reagents

****SPECTRA REFERENCED ARE CONTAINED IN APPENDIX A****

2-chloro-3-cyanopyridine (1)

FTIR: 3065 cm^{-1} Ar-H stretch, 2235 cm^{-1} nitrile, 1578 cm^{-1} C=N stretch, 1406 cm^{-1} ArC-nitrile stretch 1080 cm^{-1} Ar-Cl, 809 cm^{-1} =C-H oop bend 736 cm^{-1} ArC ring bend

Figure 4: 2-chloro-3-cyanopyridine HMQC Annotated Spectra

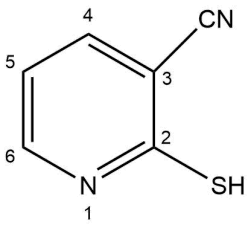


Thiourea

FTIR: 3377 cm^{-1} primary N-H stretch, 3272 cm^{-1} N-H stretch, 1619 cm^{-1} C=N stretch, 1474 cm^{-1} C-N stretching, 1412 cm^{-1} C=S stretching, 1083 cm^{-1} NH_2 rocking, 730 cm^{-1} C-S Stretching

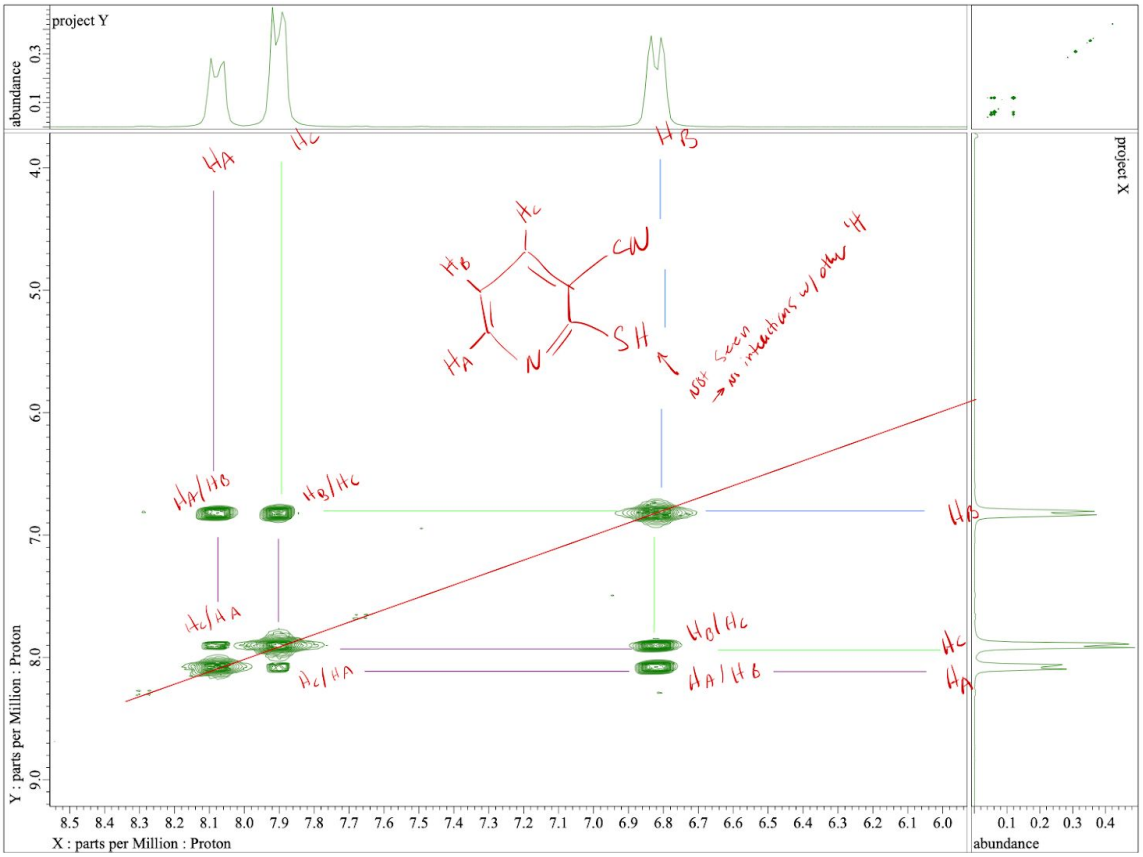
Peak assignments with assistance from Stewart (1957)[7]

Characterization of Intermediate Product (2)



FTIR: 3452 cm^{-1} (C=S)N-H Stretch, 3076 cm^{-1} Ar-H stretch, 2225 cm^{-1} nitrile C-N stretch, 1587 cm^{-1} C=C stretch, 1438 cm^{-1} C=S stretch, 1319 cm^{-1} C=N ring stretch, 1236 cm^{-1} =C-S Stretch, 778 cm^{-1} =C-H oop bend; ^{1}H NMR (dMSO-d_6, 400 MHz): δ 3.33 (s, 1H, N-H), 6.86 (dd, 1H, J=7.3, 6.4 Hz, ArCH-ArCH-ArC-CN), 7.94 (dd, 1H, J=6.4, 1.6 Hz, ArCH-ArC-CN), 8.12 (dd, 1H, J=7.3, 1.6 Hz, ArCH-ArN); ^{13}C NMR (dMSO-d_6, 100 MHz): δ 112.4 (ArC-C-N), 116.6 (*m*-ArN ArCH), 116.9 (*p*-ArN ArCH), 142.8 (ArN-ArC(SH)-ArC-CN), 145.6(ArN-ArCH), 177.3(ArN-ArC-SH); GCMS: M^+ 136, 109, 92, 82, 76, 64, 51, 32, 28, 18 m/z; T_{Decomp}: 250°C]

Figure 5: 2-mercaptonicotinonitrile COSY Annotated Spectra



Synthesis and Characterization of 3-aminothieno[2,3-b]pyridine-2-carboxylate (4)

2-Chloro-3-pyridine (1) (10.0 mmol) and (10.0 mmol) of thiourea was added to a 50 mL round bottom flask containing (20.00 mL) of *n*-butanol. The mixture was refluxed for 2.5 hours, then cooled to room temperature where the resulting solid was vacuum filtered with a Hirsch funnel and washed with additional cold *n*-butanol. The intermediate product was then verified with TLC using a 70:30 acetone:hexanes system and then recrystallized with 100 mL of boiling 95% ethanol before proceeding. (3.7 mmol) of the recrystallized intermediate product (2) was then added to a 50 mL round bottom flask with 0.039 mol) of N,N-dimethylformamide. Once stirring, (6.4 mmol) of 10% KOH was added in the form of 10% KOH solution and then (0.40 mL) of ethyl bromoacetate was added dropwise with a 1.0 mL syringe. Alkylation was confirmed with TLC after stirring for 1.25 hr and an additional (6.4 mmol) of KOH was added. The mixture was then stirred at room temperature for an additional 1 hr before heating with a mantle for 20 min. TLC, using the 70:30 acetone:hexanes system, was used to confirm cyclization of the product (Figure 5.5). Ice cold water (10.5 mL) was added to precipitate the crude product which was then vacuum filtered, washing with ice-cold water. Recrystallization with ~100 mL of boiling 95% ethanol yielded 0.451g of crystals (Figure 7) giving a total synthesis yield of 55.55 %. [FTIR: 3305 cm^{-1} primary amine N-H stretch, 2961 cm^{-1} sp^3 CH_3 sym C-H stretch, 2933 cm^{-1} sp^2 CH_2 sym C-H stretch, 1673 cm^{-1} C=O ester stretch, 1624 cm^{-1} C=C stretch, 1520 cm^{-1} secondary amine N-H bend, 1293 cm^{-1} sp^2 ester C-O stretch, 1242 cm^{-1} sp^2 =C-S stretch, 1060 cm^{-1} C-N stretch, 808 cm^{-1} =C-H oop bend; ^{1}H NMR (dMSO-d_6, 400 MHz): δ 1.29 (t, 3H, J=7.1 Hz, CH_2-C$\underline{H}_3$), 4.27 (q, 2H, J=14.2, 7.0 Hz, C$\underline{H}_2$-CH_3), 7.30 (s, 2H, ArC-N$\underline{H}_2$), 7.46 (q, 1H, J=8.2, 4.6 Hz, ArN-ArCH-ArC-$\underline{H}$), 8.54 (dd, 1H, J=8.2, 1.4 Hz, *p*-ArN ArC-$\underline{H}$), 8.68 (dd, J=4.6, 1.4 Hz, ArN-ArC-$\underline{H}$); ^{13}C NMR (dMSO-d_6, 100 MHz): δ 14.5 (CH_2-C$\underline{H}_3$), 60.0 (C$\underline{H}_2$-CH_3), 119.4 (*m*-ArN Ar$\underline{C}$H), 125.6 (*m*-ArN Ar$\underline{C}$), 131.5 (=$\underline{C}$-NH_2), 147.8 (*p*-ArN Ar$\underline{C}$-H), 150.8 (ArN-Ar$\underline{C}$H), 159.7 (ArN-Ar$\underline{C}$-S), 164.4 ($\underline{C}$=O); GCMS: M^+ 222, 194, 176, 148, 122, 104, 78, 28; T_M: 184.4 - 187.2 °C]

***Identification of impurities in ^{1}H NMR Sample from Fulmer et al.[8]*
++ Reference (Figure 2) for atom label

Figure 5.5: Visualization of TLC Confirmation of Product Cyclization (4)

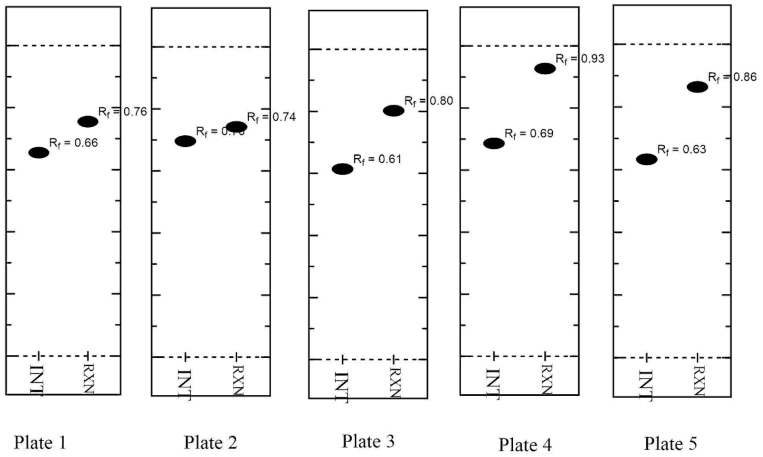


Plate 1 was developed earliest where plate 5 was developed latest. The INT lane is the intermediate (2) in acetone, where the RXN lane is the cyclization progress of (3).

Figure 6: Annotated HMQC Spectra of Thiopyridine Product (4)

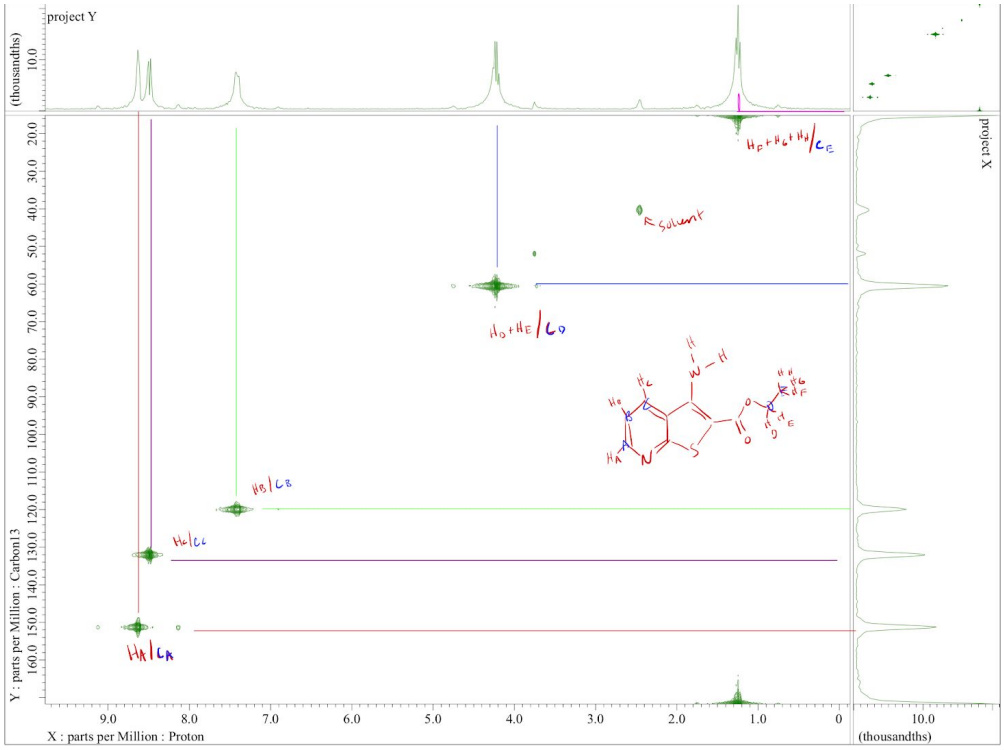


Figure 7: Thiopyridine Product (3) Rectangular Crystals Formed During Recrystallization

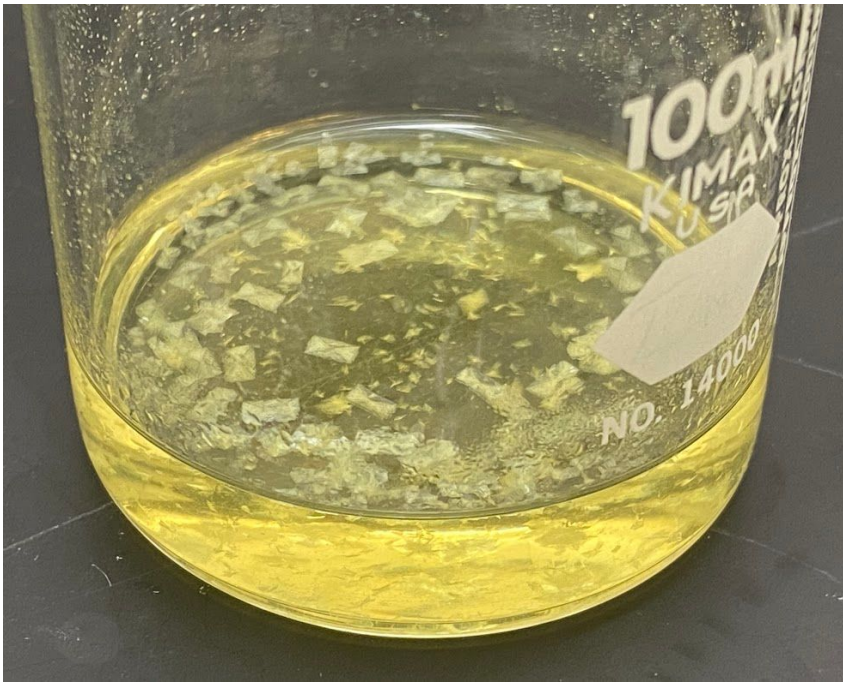
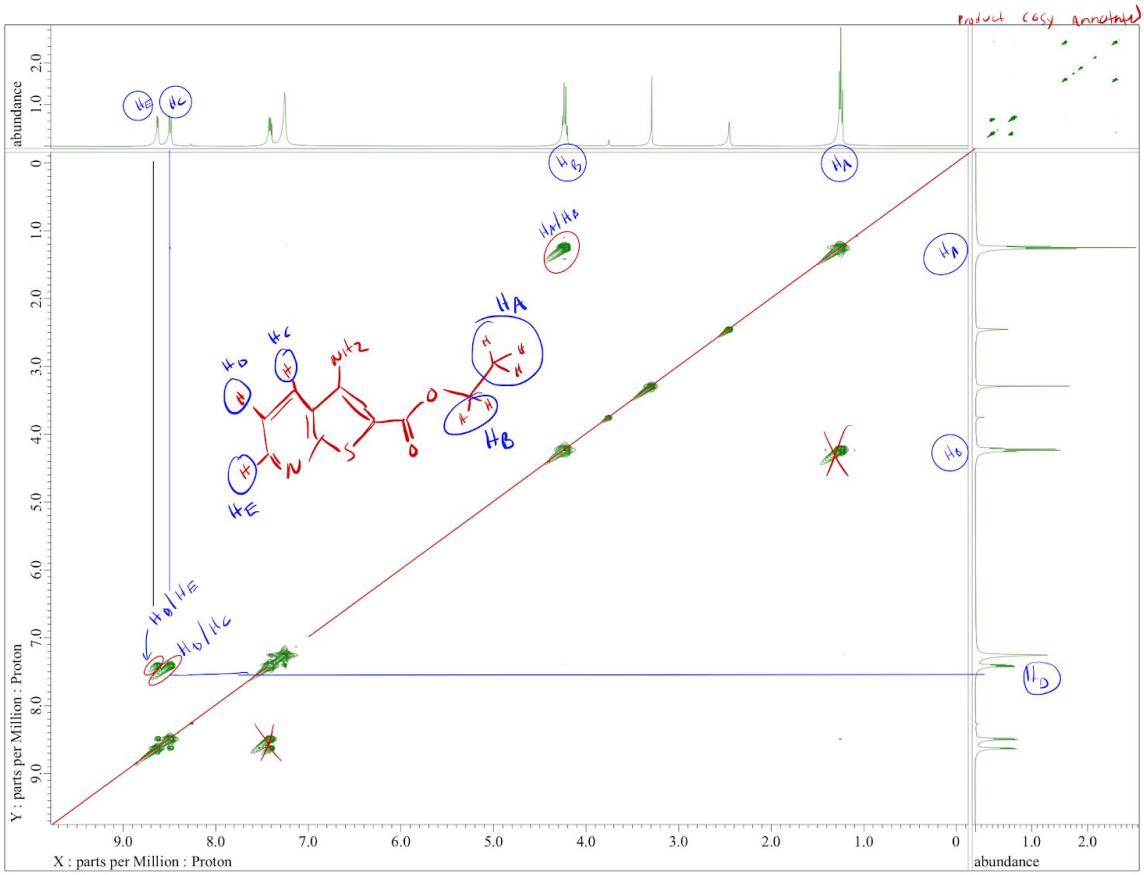


Figure 8: Annotated COSY ^{1}H NMR Spectra of Thiopyridine Product (4)



Discussion

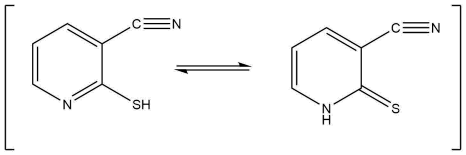
-- SPECTRA REFERENCED IN THIS SECTION ARE CONTAINED IN APPENDIX A--

FTIR Spectroscopy Analysis

The IR spectra of 2-chloro-3-cyanopyridine (1) contains peaks indicative of the present functional groups. A peak at 2235 cm^{-1} is characteristic of a nitrile, where a strong peak at 1578 cm^{-1} indicates C=N stretching. Aromatic heterocycle characteristics are identified by a peak at 3065 cm^{-1} for Ar-H stretching, a peak at 809 cm^{-1} pertaining to =C-H out-of-plane bending, and at 736 cm^{-1} for an Ar ring bending. The Aromatic chlorine substituent is evident from a peak at 1080 cm^{-1}. Another starting reagent, thiourea, was also characterized with IR spectroscopy. Peaks unique to this reagent include primary amine N-H stretching at 3377 cm^{-1}, a C=N stretch at 1619 cm^{-1}, C=S stretching at 1412 cm^{-1} and C-S stretching at 730 cm^{-1}. Other resonance forms may be accounted for in the observed spectra.

IR spectra of the intermediate shows peaks indicative of addition of the starting reagents. Resonance forms of this reagent are also possible, and contribute to multiple peaks in the spectra. These resonance forms are shown in Figure 9 below:

Figure 9: Tautomer Forms of the Intermediate Product (2)



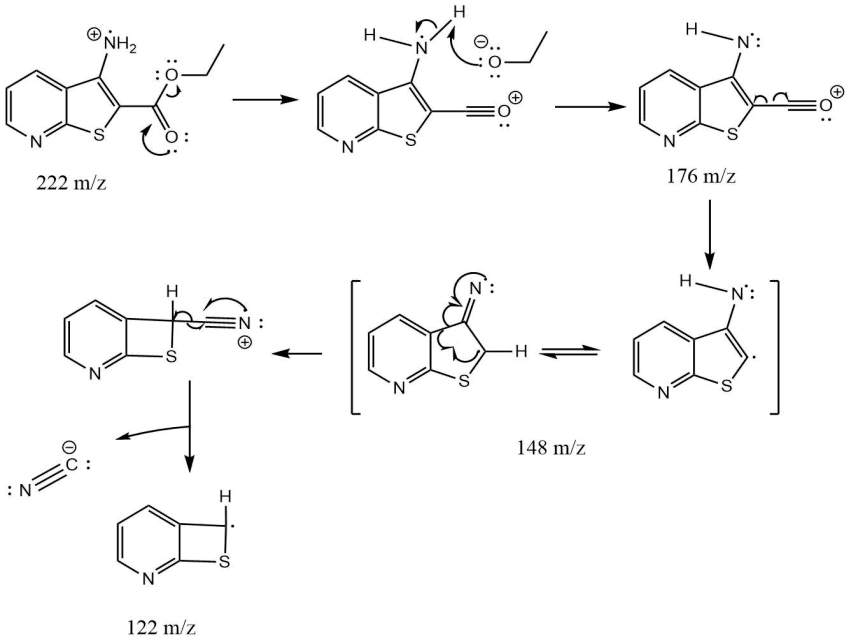
Peaks indicative of the intermediate include a (C=S)N-H stretch at 3452 cm^{-1}, nitrile stretching at 2225 cm^{-1}, C=S stretching at 1319 cm^{-1}, =C-S stretching at 1236 cm^{-1}, and aromatic =C-H out-of-plane bending at 778 cm^{-1}.

The final thiopyrimidine product (3) showed peaks in the IR confirming the occurrence of the subsequent alkylation and cyclization steps in the synthesis. The absence of a nitrile stretch at ~2200 cm^{-1} is replaced with secondary amine N-H stretching at 3305 cm^{-1}. The addition of sym sp^3 and sym sp^2 C-H stretching from the addition of the ethyl ester is also indicated by peaks at 2961 and 2933 cm^{-1} respectively. A carbonyl stretch pertaining to the C=O ester is observed at 1673 cm^{-1}, lower than a typical ester commonly found between 1740 and 1750 cm^{-1}. This is likely due to extended conjugation between the heterocyclic rings. Conjugated C=C alkene stretching is observed at 1624 cm^{-1}, similar to other precursor compounds. At 1520 cm^{-1}, N-H bending of a secondary amine is observed, in parallel to the N-H stretching observed. A peak at 1293 cm^{-1} pertains to sp^2 =C-O ester stretching, due to the addition of ethyl bromo acetate, where =C-S-C= stretching is observed at 1242 cm^{-1}. Out-of-plane bending of =C-H was observed as in previous intermediates at 808 cm^{-1}.

Mass Spectrum Analysis

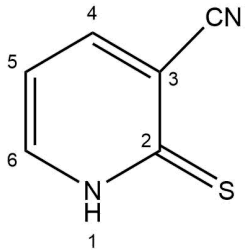
The mass spectrum of the product (4) contains an M^+ peak at 222 m/z. Loss of ethanol gives the peak at 176 m/z. A loss of carbon monoxide gives a peak at 148 m/z. A peak at 122 m/z corresponds to the loss of a cyanide ion. A peak at 18 m/z corresponds to water, where a peak at 28 m/z corresponds to carbon monoxide. The cleavage mechanisms are shown below:

Figure 10: Proposed Cleavage Mechanism of the Product (4)



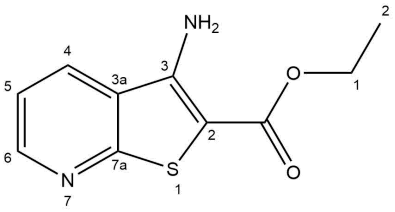
NMR Spectroscopy Analysis

The HMQC spectra of 2-chloro-3-cyanopyridine serve to indicate aromatic proton resonances. These proton resonances are observed in subsequent NMR spectra. At position 4 of the pyridine ring, proton B at 7.98 ppm corresponds to a ^{13}C resonance at 142 ppm, where proton C at position 5 corresponds to a resonance at 7.36 ppm, with a ^{13}C resonance at 122 ppm. Finally, at position 6 of the ring, proton A corresponds to a resonance at 8.59 ppm and a ^{13}C resonance at 153 ppm.



The ^{1}H NMR of the intermediate (2) indicates an N-H resonance at 3.33 ppm in addition to the three aromatic ring protons observed in (1). The addition of the sulfur atom on the ring also shifted the proton resonances slightly upfield, indicative of the replacement of a EWG (Cl atom) with an electron donating group (S). Carbon resonances also indicate this group replacement, where C2 is shifted downfield at 177 ppm, similarly to a carbonyl C=O, yet not to the same degree due to the larger deshielding effect of a sulfur atom.

In the spectra of the erster thiopyridine product (4), The addition of an ester ethyl group is observed in the proton, carbon, COSY, and HMQC spectra. A triplet at 1.29 ppm is indicative of a terminal methyl group, where a quartet at 4.27 ppm is indicative of a CH_2 group. ^{13}C spectra also contains the methyl and methylene resonances at 14.9 and 60.5 ppm as expected. A singlet integrating to ~2H corresponds to the protons on a secondary amine are observed as a singlet at 7.30 ppm in the proton spectra. Due to extended conjugation, protons on an amine that generally have a resonance at ~3-4 ppm on alkenes have a resonance further downfield in this context. Using the ChemNMR prediction tool within ChemDraw, this resonance is predicted at 7.11 ppm, thus giving confidence in this peak assignment. Additionally, Liu and colleagues cite this stretch within the region of 7.00-7.18 ppm as well.[9] The three protons from the starting reagents in (1) and in the intermediate product (2) are found at 7.46, 8.54, and at 8.68 ppm. Assignment of the protons was assisted with HMQC and COSY spectra. The proton at position 5 correlated with the protons at pos. 4 + 6 in the COSY spectra and the HMQC spectra indicated the assignment of the proton at position 5 at 7.46 ppm, where J couplings from ^{1}H spectra were observed in other proton resonances (8.2 Hz) for the proton at position 4 and (4.6 Hz) for the proton at position 6, where geminal ^{2}J couplings of (1.4 Hz) are observed in protons at the 4 and 6 positions on the ring. An ester ^{13}C resonance is observed at 164.9 ppm, upfield from a typical carbonyl carbon region, likely due to extended conjugation of the heterocyclic ring system.



Melting Point Determination Analysis

The melting point of the product (3) was observed to occur within the range of 184.4 - 187.2 °C. This relatively small range indicates a relatively pure product. Boiling point of the base thieno[2,3-b]bipyridine system is reported at 236.5 °C, which would make logical sense in context. A similar compound with differing substituents, 3-amino-N-phenylthieno[2,3-b]pyridine-2-carboxamide, is reported with a melting point in the range of 247-249°C.[10] From other derivatives also reported by Hung et al., melting point of these compounds was shown to vary widely (~70 → ~350°C).

Spartan '18 Molecular Modeling Analysis

Molecular modeling of the tautomers of (2) were conducted using the methodology mentioned above in the experimental section. Values for the enthalpy of formation and entropy were used to calculate ΔG using Gibbs free energy (eq 1, 2) to determine k, the equilibrium constant.

$$\Delta G = \Delta H - T\Delta S \qquad \text{(equation 1)}$$

$$\Delta G = -R*T*\ln(k) \qquad \text{(equation 2)}$$

Table 1: Values from Hartree-Fock 6-31G Calculations

Compound	Enthalpy of Formation (kJ/mol)	Entropy (kJ/mol)	Percent Present
=S tautomer form	312.7497	351.68	37.1
-SH tautomer form	308.3675	356.04	62.9

Using the above equations, k was calculated to be 0.59 and can be interpreted as a ratio of (=S/-SH) tautomers. From this result, the calculations predict that the thiol tautomer of (2) is favorably formed.

Conclusion

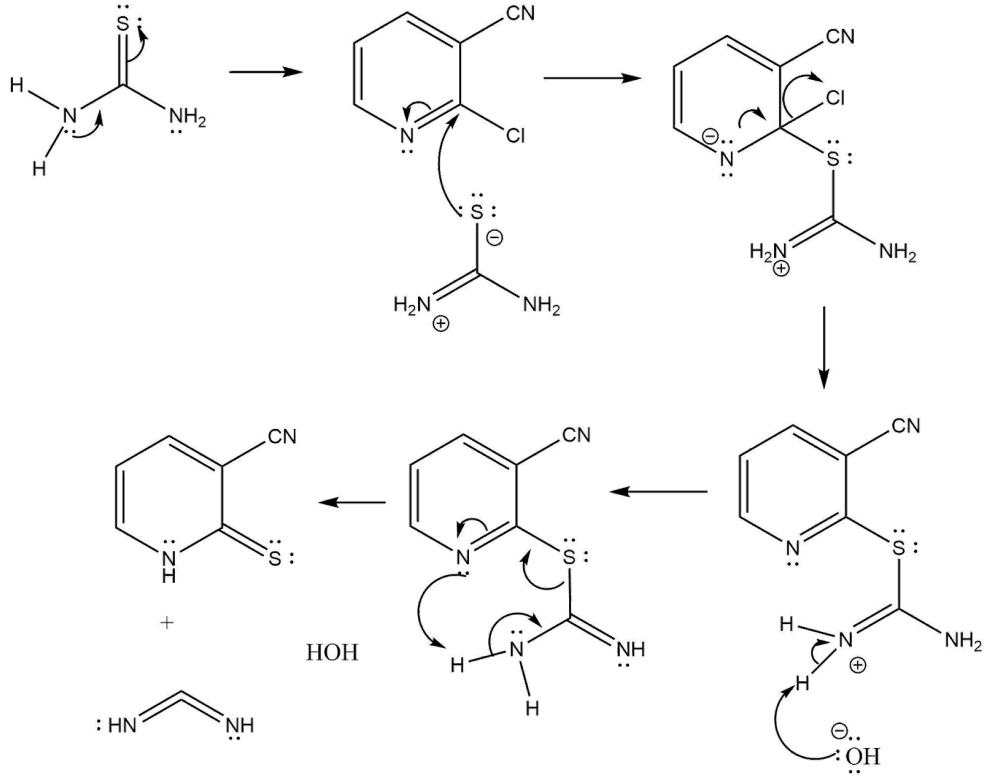
In this laboratory and computer modeling exercise, 3-aminothieno[2,3-b]pyridine-2-carboxylate (3) was synthesized in multiple steps under mild conditions. A reflux of (1) and thiourea produced an intermediate product, which was alkylated with ethyl bromoacetate under basic conditions. Ring-closing was then accomplished with the addition of base. This multistep synthesis produced a yield of 55.55%, well within agreement with literature values (57%).[9] The final product (3) was identified with a M^+ peak of 222 m/z in the mass spectrum, a singlet peak in the ^1H NMR at 7.30 ppm pertaining to the primary amine attached to an aromatic system along with a characteristic quartet and triplet splitting of an ethyl group, ring proton correlation in the COSY spectrum with assignments assisted from HMQC spectra, and N-H stretching of an amine at 3305 cm^{-1}, CH_2 and CH_3 sym stretching at 2961 cm^{-1} and 2933 cm^{-1}, and an ester C-O stretch at 1242 cm^{-1}.

Molecular modeling predicted a tautomer ratio of 62.9% thiol to 37.1% sulfonyl in the intermediate (2). Both forms were observed in the IR spectrum of the intermediate with a =C-S stretch at 1236 cm^{-1}, and a C=S stretch at 1438 cm^{-1}. Overall, this synthesis was excellent in reinforcing multiple step synthesis strategies, and produced product with good yields in excellent purity.

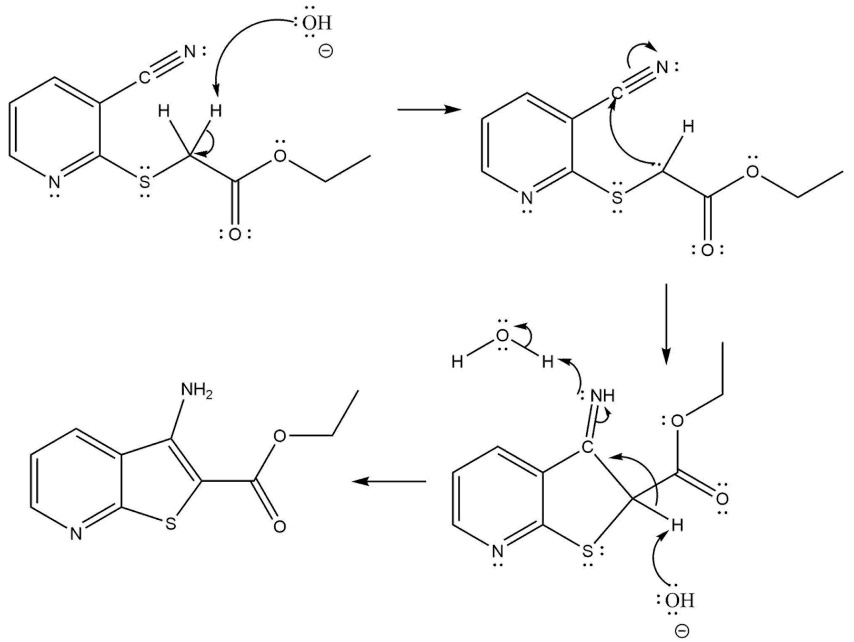
Questions

1. An intermediate with a positive charge is formed during electrophilic aromatic substitution of a typical benzene ring. When the aromatic system is reformed, a proton is abstracted adjacent to the site of substitution. If a nitrogen is in the ring, substitution and reformation on the nitrogen would result in a positive charge on the quaternary-substituted nitrogen, which is far less stable without a counter anion in proximity.

2. The mechanism is a nucleophilic substitution with proton transfers.



3. The structure of (2) has a conjugated pi system that is elongated by the sulfonyl group, therefore, the lambda max of (2) would be higher than (1).
4. In the first addition of KOH, the base promotes the alkylation reaction where the second addition catalyzes the closing of the alkyl tail.

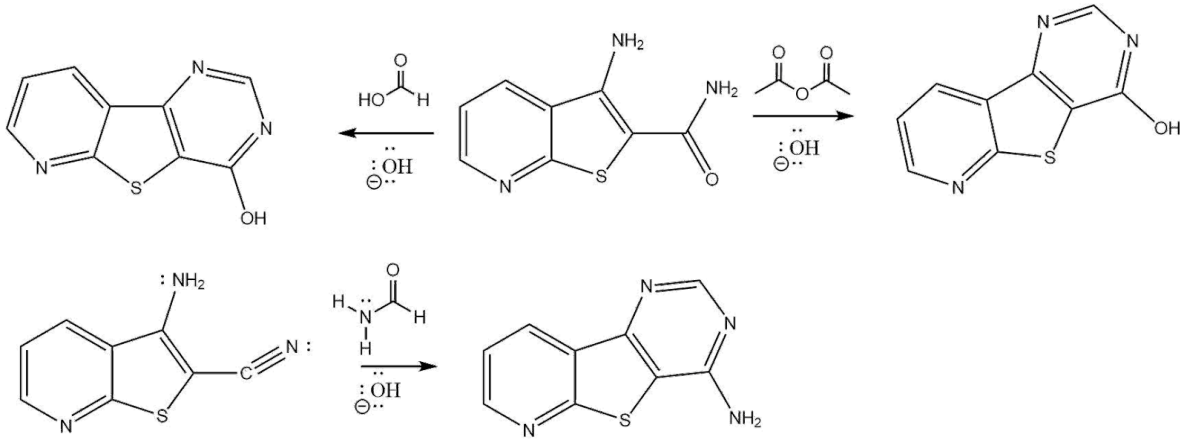


5.

6. Methylene CH_2 pKa Estimations

R Group	pKa Estimate
3	12
4	18
7	7

These pKa's are lower due to a trapped enolate that exists between the sulfur atom and the carbonyl or nitrile carbon.



7.

References

(1) Hung, J. M.; Arabshahi, H. J.; Leung, E.; Reynisson, J.; Barker, D. Synthesis and Cytotoxicity of Thieno[2,3-b]Pyridine and Furo[2,3-b]Pyridine Derivatives. *Eur. J. Med. Chem.* **2014**, *86*, 420–437. https://doi.org/10.1016/j.ejmech.2014.09.001.

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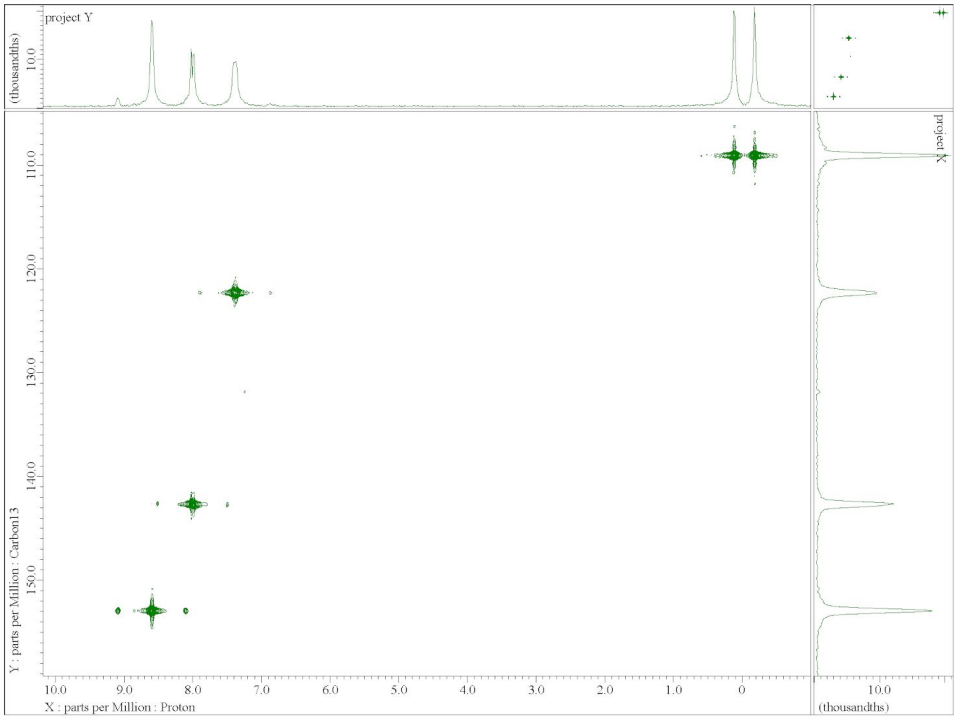
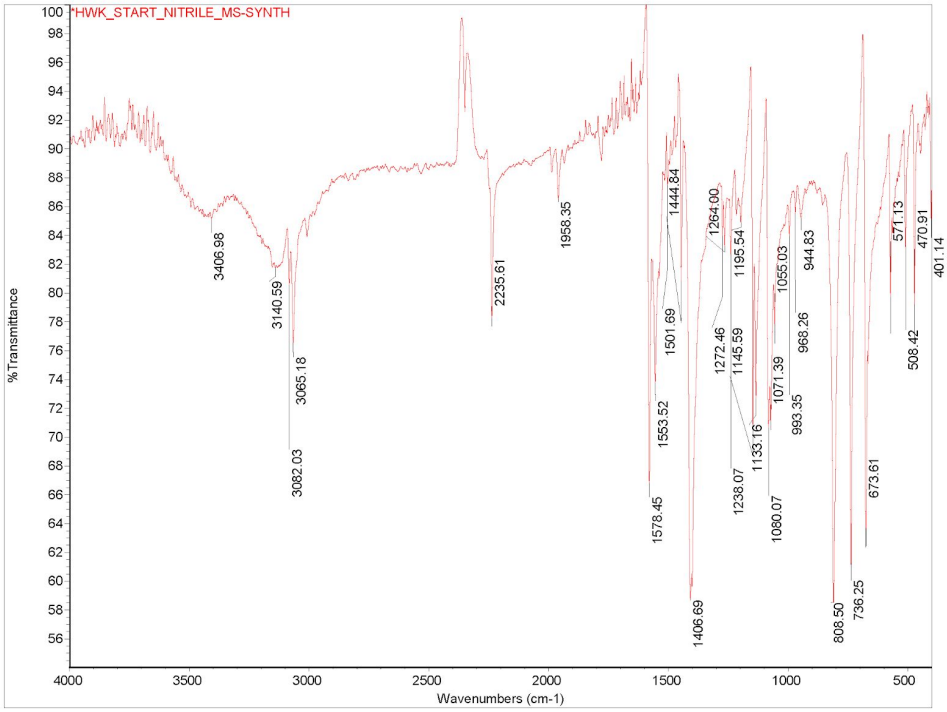
APPENDIX A: SPECTROSCOPY SUPPLEMENTAL DATA

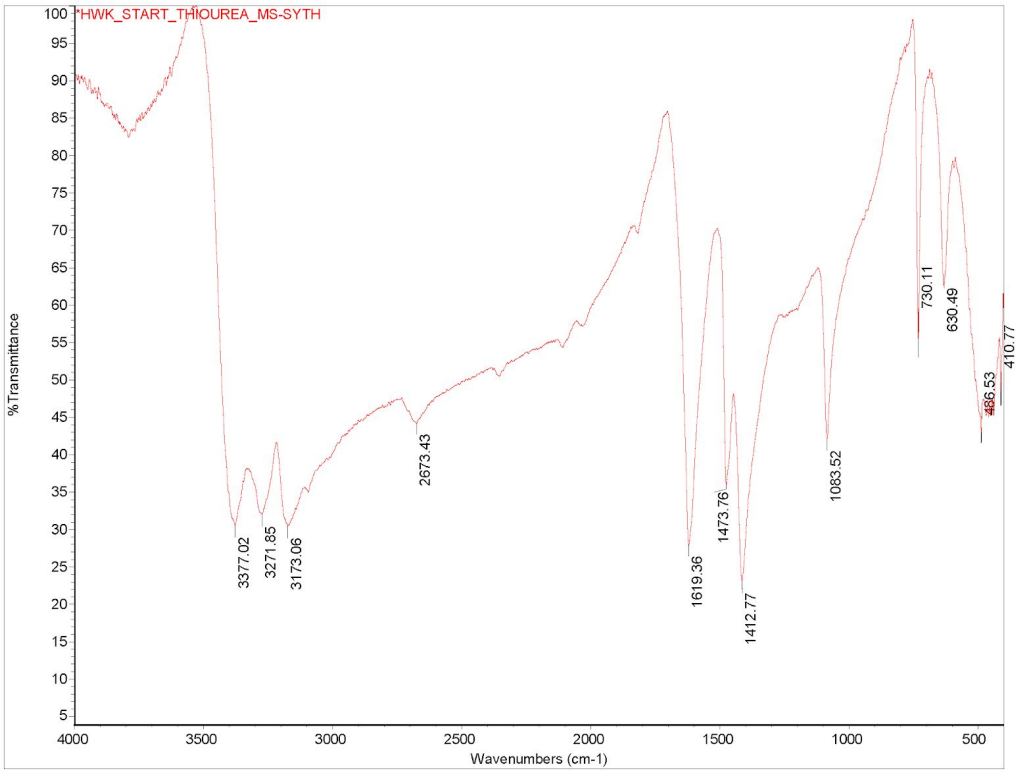
HMQC Spectra of 2-chloro-3-pyrimidine (1)



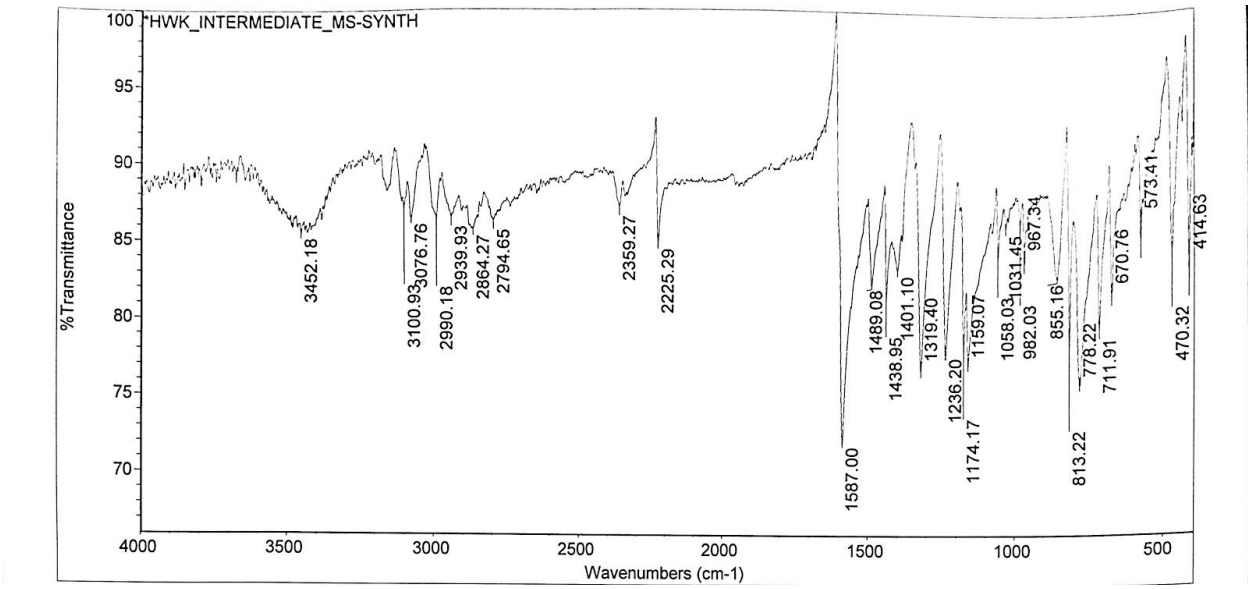
IR Spectra of 2-chloro-3-pyridine (1)



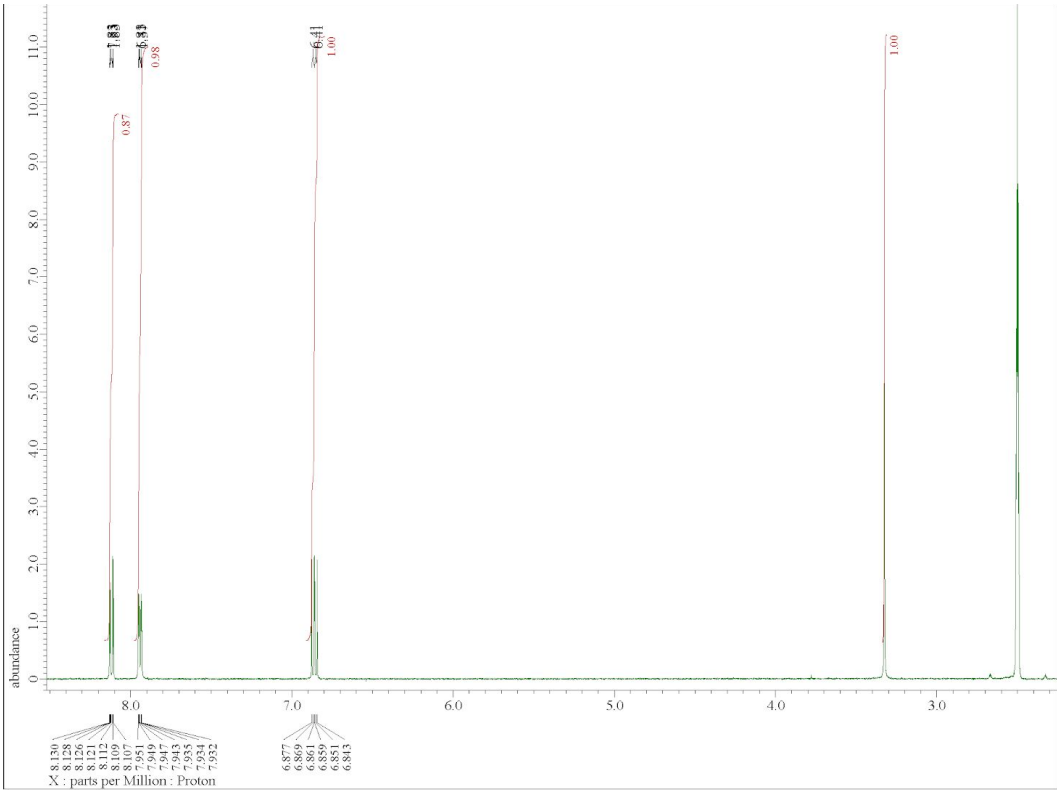
IR Spectra of Thiourea



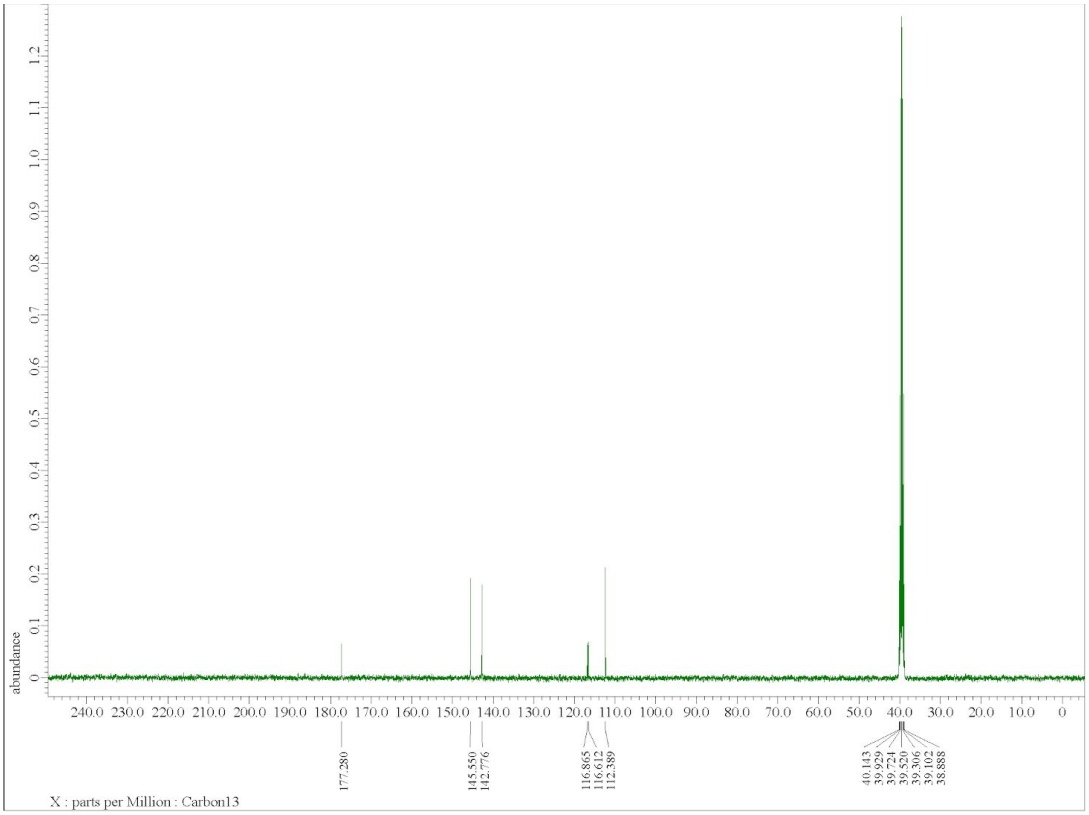
IR Spectra of Intermediate (2)



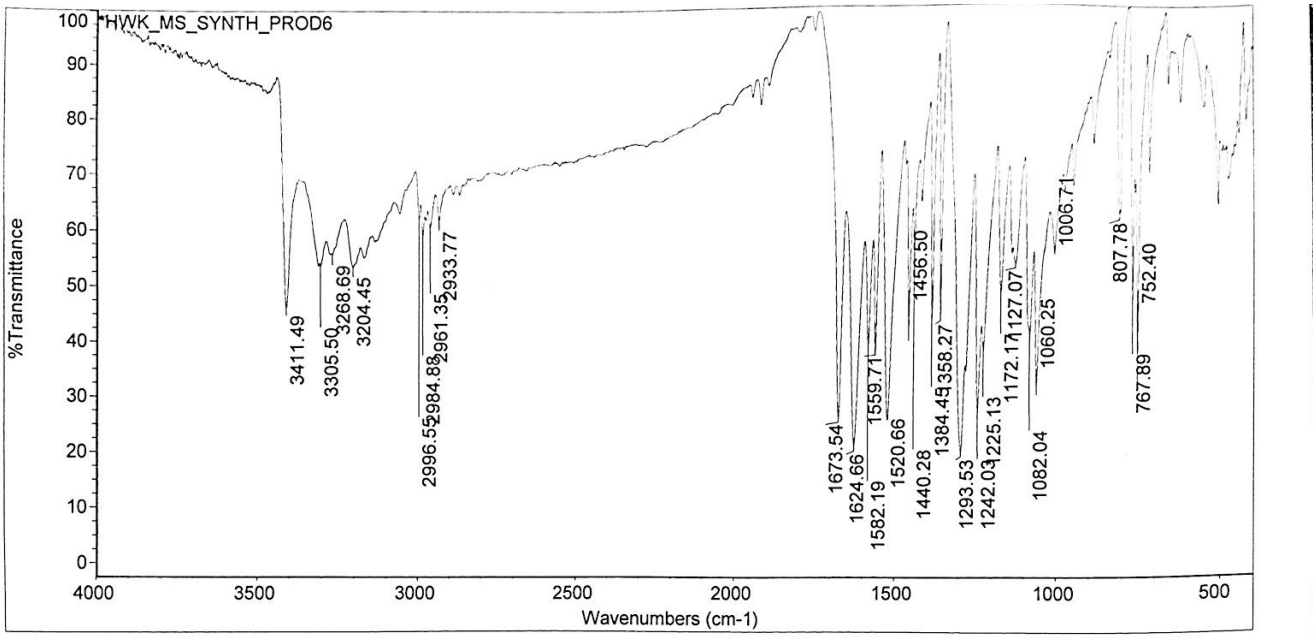
^{1}H NMR Intermediate (2) Spectra



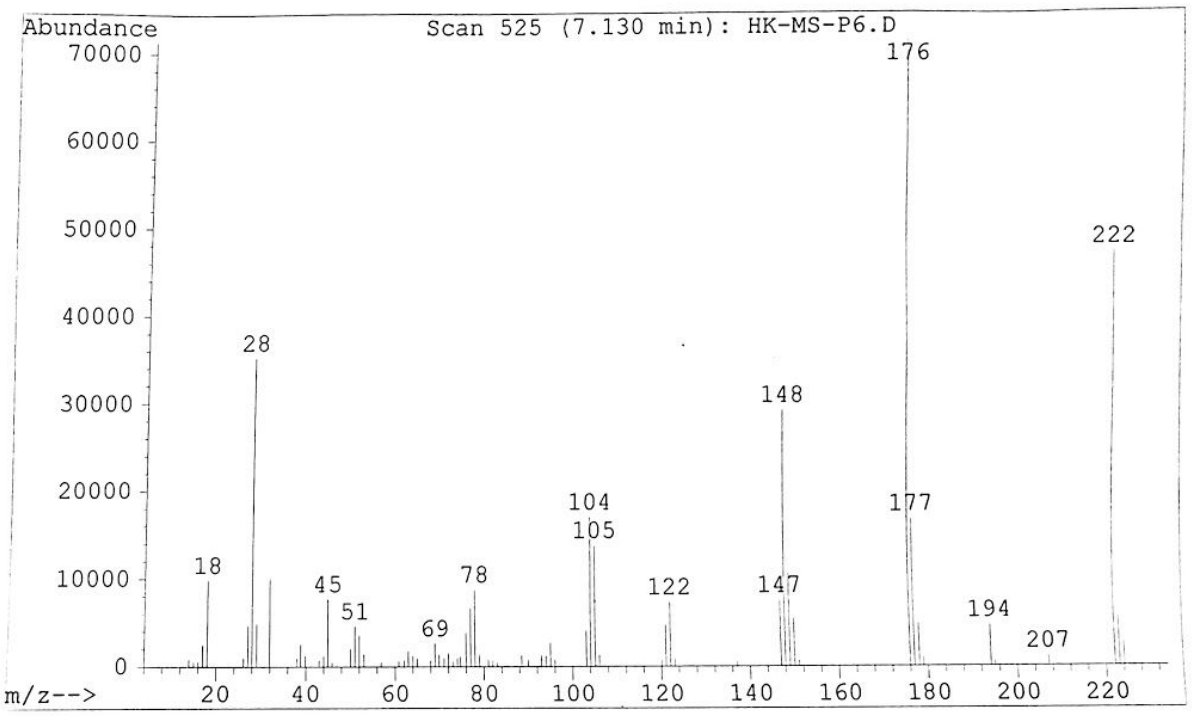
^{13}C NMR Intermediate (2) Spectra



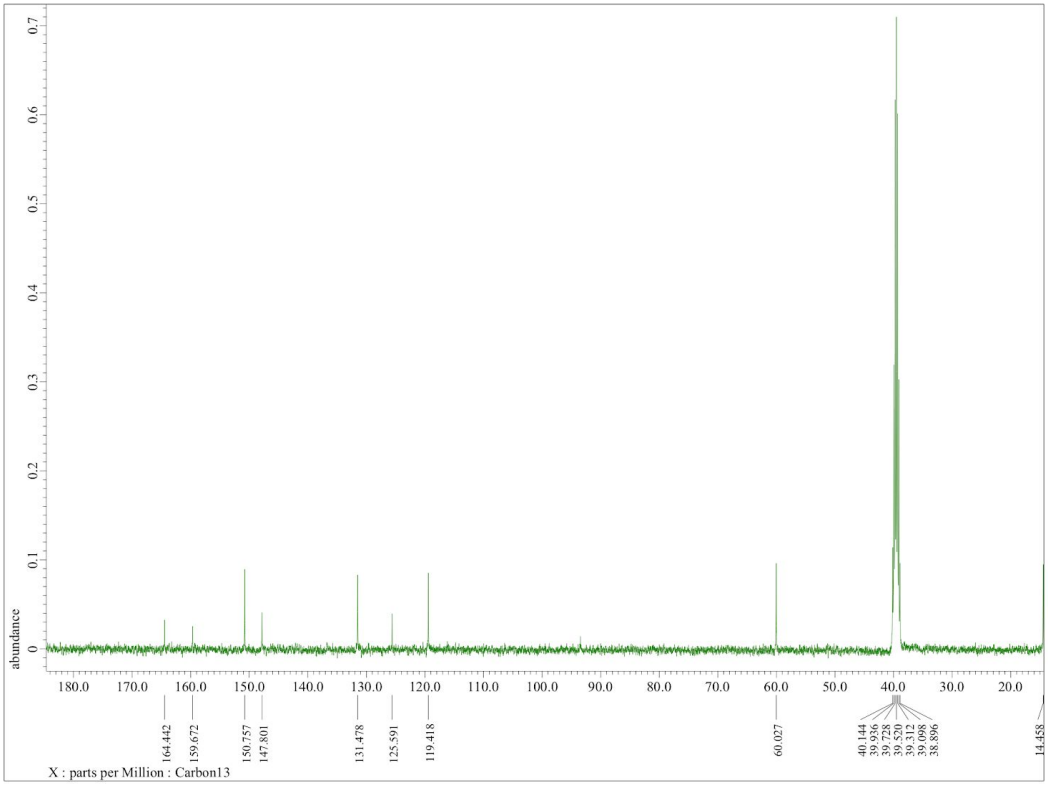
IR Spectra of Product (4)



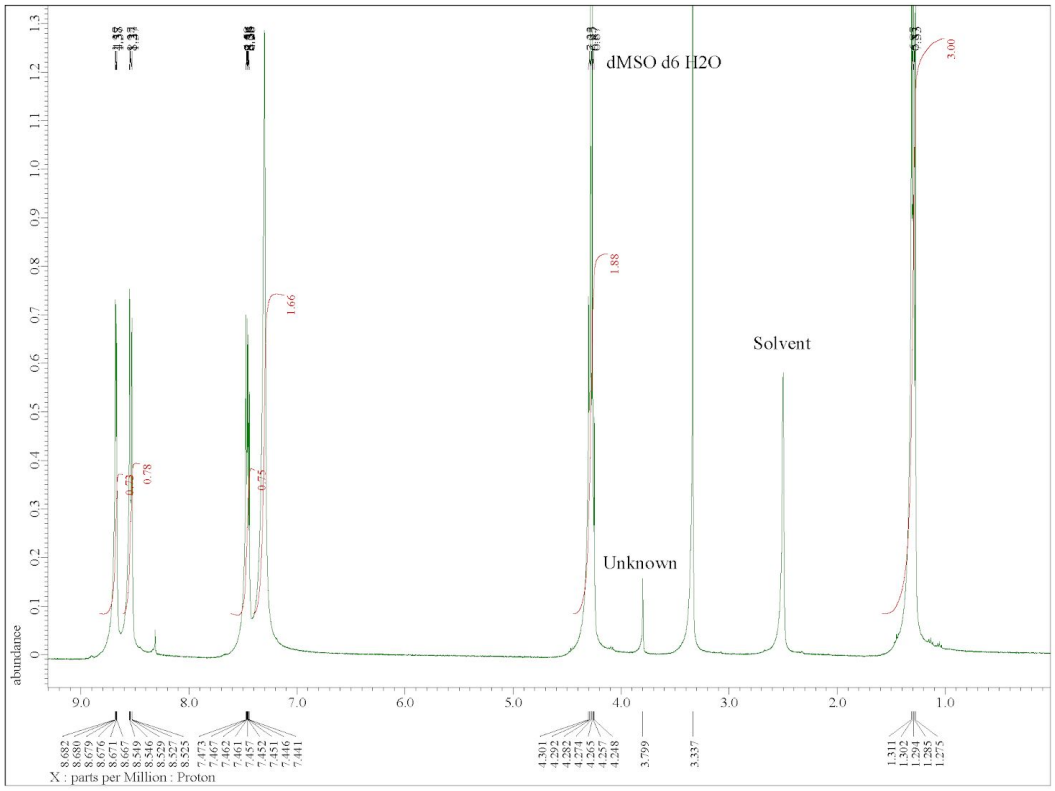
Mass Spectrum of Product (4)



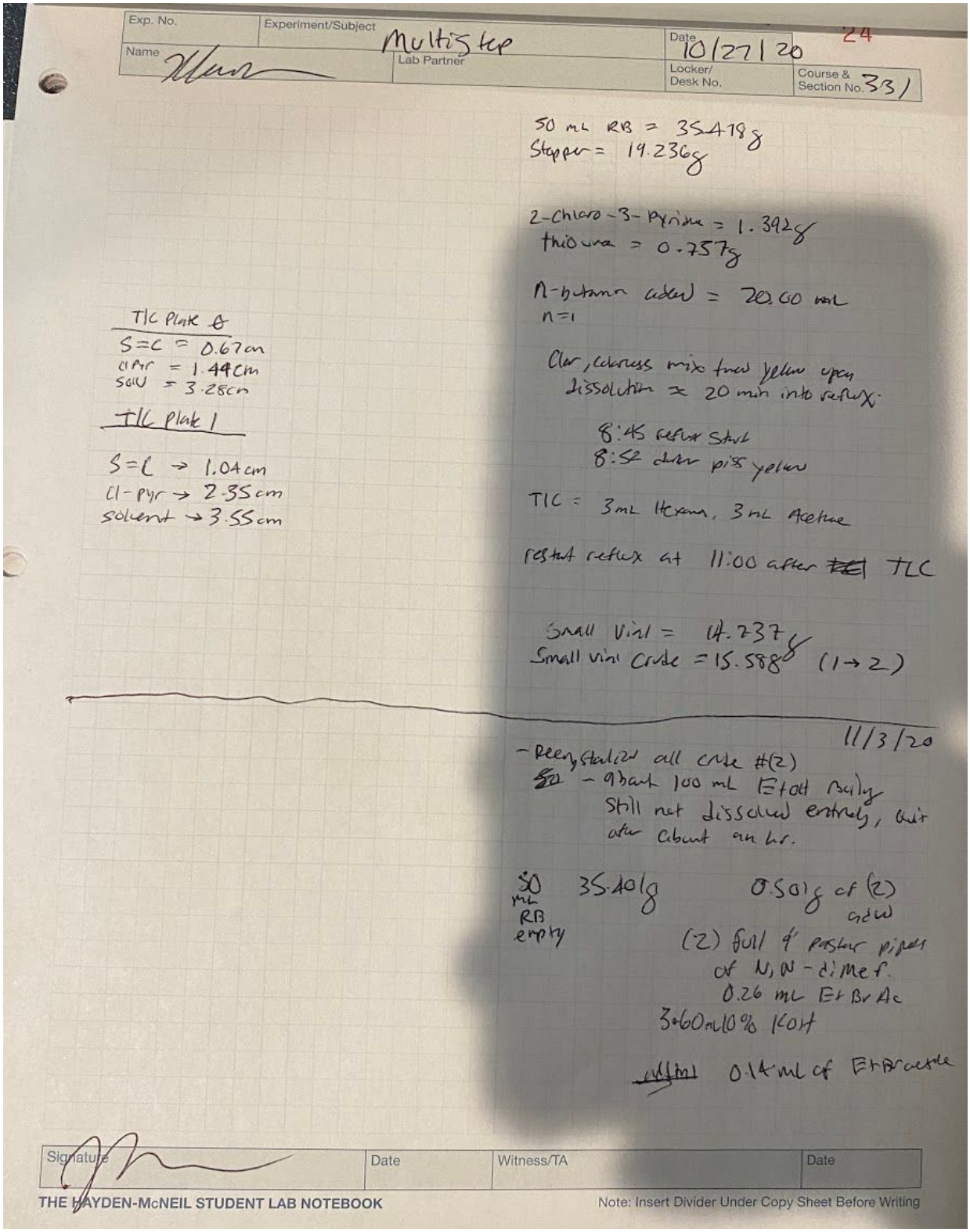
^{13}C NMR Spectra of Product



^{1}H NMR Product Spectra (4)



APPENDIX B: LAB NOTEBOOK PAGES



Exp. No. | Experiment/Subject: Multistep | Date: 10/27/20 | 24
Name: [signature] | Lab Partner | Locker/Desk No. | Course & Section No. 331

50 mL RB = 35.418 g
Stopper = 19.236 g

2-Chloro-3-Pyridine = 1.392 g
thiourea = 0.757 g

N-butanol added = 20.00 mL
n=1

Clear, colorless mix turned yellow upon dissolution ~ 20 min into reflux.

8:45 reflux start
8:52 clear piss yellow

TLC = 3 mL Hexane, 3 mL Acetone

restart reflux at 11:00 after ~~TLC~~ TLC

TLC Plate A
S=C = 0.67 cm
Cl Pyr = 1.44 cm
Solv = 3.28 cm

TLC Plate 1
S=C → 1.04 cm
Cl-pyr → 2.35 cm
solvent → 3.55 cm

Small vial = 14.237 g
Small vial crude = 15.588 g (1→2)

11/3/20

- Recrystallize all crude #(2)
~~50~~ - 9 bar 100 mL EtOH boiling
Still not dissolved entirely, quit after about an hr.

50 mL RB empty 35.401 g

0.501 g of (2) added

(2) full 9" Pasteur pipets of N,N-dimet.
0.26 mL EtBrAc
3.60 mL 10% KOH

~~0.14~~ 0.14 mL of EtBrAcetate

Signature | Date | Witness/TA | Date

THE HAYDEN-McNEIL STUDENT LAB NOTEBOOK — Note: Insert Divider Under Copy Sheet Before Writing

Exp. No.	Experiment/Subject	Date	25
Name HWK	Lab Partner	Locker/ Desk No.	Course & Section No.

Multistep Synth

11/10/20

TLC Plate #4 did not decisively confirm ~~not~~ Alkylation, Therefore, I continued in the procedure...

3.60 mL 10% KOH added to space.

- After stirring & heating for 1 hr and 15 min, Product got thicker + slightly chunky (foamy almost)

Vial = 14.935 g
Vial + product = 15.386 g

Melting points

Intermediate: ~~Start~~: NO melt, just color change for decomposition
Product 6: Start: 184.4°C
Stop: 187.2°C

TLC Plate Values

1. Solv: 3.66cm
   Int: 2.41cm
   rxn: 2.78cm
2. Solv: 3.49cm
   Int: 2.43cm
   rxn2: 2.59cm
3. Solv: 3.39cm
   Int: 2.06cm
   rxn3: 2.72cm
4. Solv: 3.54cm
   Int: 2.43cm
   rxn4: 3.28cm
5. Solv 3.76 cm
   ~~Int~~ 3.76cm
   Int: 2.38 cm
   rxn5 3.25 cm