Alkyllithium synthesis: Attempted synthesis of 2-chloro-4-(thiophen-2-yl)pyrimidine

Glenn Murray

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Department of Chemistry

Georgia State University, Atlanta, GA

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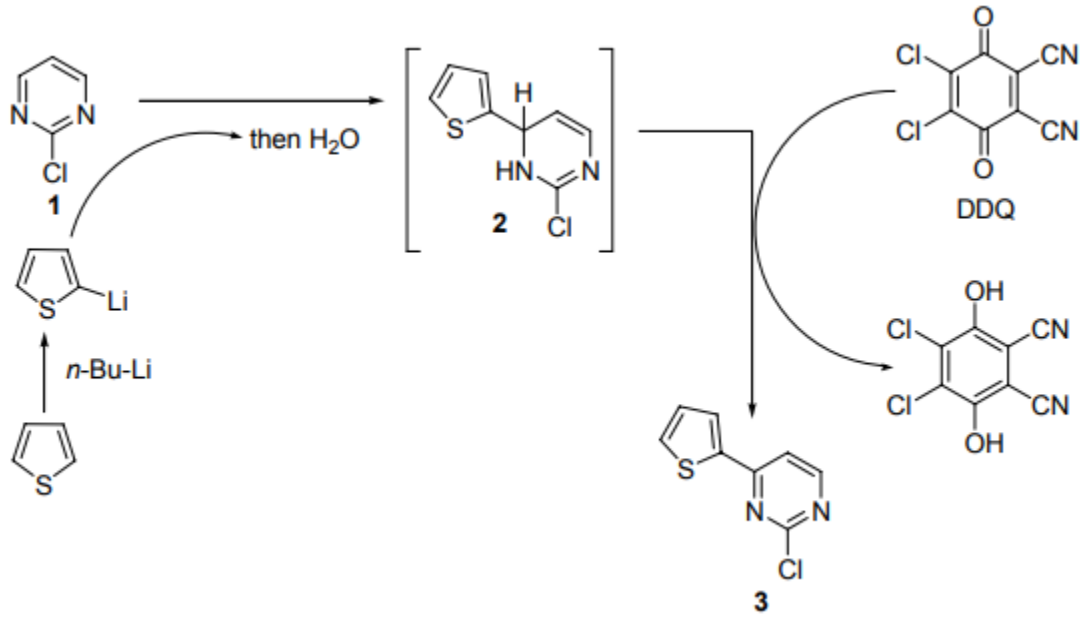
ABSTRACT

Alkyllithium compounds are powerful reagents used in a wide range of synthetic transformations. In addition to functioning as strong bases and potent nucleophiles, they can generate reactive organometallic intermediates that facilitate carbon–carbon bond formation. In this experiment, n-butyllithium was used to lithiate thiophene, with the resulting thiophen-2-yllithium intended to react with 2-chloropyrimidine to form 2-chloro-4-(thiophen-2-yl)pyrimidine following an oxidation step. The synthetic scheme shows in Scheme 1.

Scheme 1 – Synthesis of 2-chloro-4-(thiophene-2-yl)pyrimidine using n-Bu-Li



The synthesis appeared to fail at the combination of the 2-cyclobutadienelithum addition to 2-chloropyrimidine. The TLC run of the product produced showed no product and other groups' attempt at the synthesis failed to show one as well. The ^{1}H and ^{13}C-NMRs showed no good evidence of a successful synthesis. The 2-chloropyrimidine reagent is suspected to have been hydrolyzed. The purified yield is 0.0 g and 0% percent yield.

Keywords: Complex-induced proximity effects,

1.0 INTRODUCTION

Alkyllithium compounds are powerful synthetic reagents that function as strong bases and potent nucleophiles. They are widely used to deprotonate acidic sites, such as terminal alkynes, and to mediate halogen–lithium exchange on aromatic rings, as in the conversion of 3-bromotoluene to a reactive organolithium intermediate.[1] Commonly employed organolithium reagents include n-butyllithium (n-BuLi) and tert-butyllithium (t-BuLi), the latter being particularly pyrophoric and highly reactive. Lithium diisopropylamide (LDA) is also widely used as a strong, non-nucleophilic base.[2]

The reactivity and aggregation state of n-BuLi depend strongly on the solvent environment. In nonpolar solvents, alkyllithium compounds tend to form tetrameric or hexameric aggregates.[3] Coordinating ether solvents, such as tetrahydrofuran (THF) and diethyl ether, interact with lithium through the lone pairs of their oxygen atoms, thereby influencing aggregation and reactivity.[4] In THF, n-butyllithium can exist as a dynamic mixture of aggregated species, including dimers and tetramers.[5] Regioselective lithiation adjacent to directing groups may also be facilitated by the complex-induced proximity effect (CIPE), in which coordination interactions promote deprotonation at a nearby C–H bond.[6]

In this experiment, n-butyllithium was used to lithiate thiophene, generating the intended thiophen-2-yllithium intermediate. This intermediate was then reacted with 2-chloropyrimidine in an attempt to form a new carbon–carbon bond between the thiophene and pyrimidine rings. The pyrimidine ring is electron-deficient, making it susceptible to nucleophilic attack; however, the regioselectivity and mechanism of the reaction depend on the reaction conditions and the specific organolithium species involved.[7] Following aqueous quenching, the reaction mixture was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to promote aromatization of the proposed intermediate. The target compound was 2-

chloro-4-(thiophen-2-yl)pyrimidine. Product formation was assessed by TLC and NMR spectroscopy.

2.0 RESULTS AND DISCUSSION

The reaction of n-butyllithium with thiophene was intended to generate thiophen-2-yllithium. The resulting organolithium intermediate was then reacted with 2-chloropyrimidine to produce the proposed dihydropyrimidine intermediate, which was subsequently intended to undergo oxidation to form 2-chloro-4-(thiophen-2-yl)pyrimidine. However, the 2-chloropyrimidine starting material did not dissolve completely in THF, and its brown-orange coloration differed from the supplier's reported description.[8] TLC analysis did not reveal a spot corresponding to the reference product. Other experimenters using material from the same container also failed to isolate the expected product.

The container of 2-chloropyrimidine had been opened previously, possibly as long as one year before the experiment. Degradation during storage may therefore have contributed to the unsuccessful synthesis. Exposure to moisture could have promoted hydrolysis of 2-chloropyrimidine to 2-hydroxypyrimidine, which exists in tautomeric equilibrium with 2(1H)-pyrimidinone. These species may have contributed to the observed solubility problems.[9,10] Hydrolysis could also have generated HCl, potentially leading to protonation of basic species in the reaction mixture and the formation of poorly soluble salts. However, neither hydrolysis nor salt formation was experimentally confirmed. Other degradation pathways are conceivable, but the available observations do not establish that they occurred. The brown-orange coloration may indicate the presence of impurities or degradation products, although its origin remains unknown.[11]

An additional difficulty was the formation of a residue that was insoluble in both THF and CH_2Cl_2 but readily soluble in water. This behavior suggests that the residue may have contained ionic or highly polar material, although its composition was not determined. One possible explanation is that the reaction or oxidation conditions promoted the formation of side products. Interactions between basic species in the reaction mixture and DDQ-derived byproducts may also have contributed to the residue.[12] However, neither the identity of the residue nor the mechanism of its formation was established. Consequently, these explanations should be regarded as hypotheses rather than confirmed causes of unsuccessful isolation.

The ^{1}H NMR spectrum contained five reported signals in the aromatic region. Although some of the chemical shifts may be consistent with the proposed target structure, the observed multiplicities and chemical shifts require further evaluation.[13] Chemical shifts alone are insufficient to establish the identity of the isolated material, particularly because TLC did not reveal a spot corresponding to the reference product. The ^{13}C NMR spectrum contained eight reported signals, including three signals at 159.44, 161.60, and 161.88 ppm, which may be consistent with carbons in a nitrogen-containing heteroaromatic ring.[14,15] However, these data do not conclusively establish the structure of the isolated material. A pyrimidinone derivative, such as 4-(thiophen-2-yl)pyrimidin-2(1H)-one, could be considered as a possible alternative, but its identity remains unconfirmed.

A product mass spectrum could have determined whether the chlorine on the 2-chloropyrimidine was still present or had been hydrolyzed. Identifying this earlier would have resolved several issues and supported a reason for the loss of product.

3.0 EXPERIMENTAL

3.1 Chemicals

Reagents used were 2—chloropyrimidine – 98%+, Acros Organics, NJ. CAS# 9722-12-9; thiophene – 99.5%, extra pure, Acros Organics, NJ (or Akfa Aeser, Ward Hill, Ma), CAS# 110-02-1; n-butyllithium - 1.6 M solution in hexanes, Sigma-Aldrich, St. Louis, MO. CAS# 109-72-8; 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) – Biosynth Intl., Itasca, IL. CAS# 84-58-2; tetrahydrofuran – certified, Fisher Chemical, Fair Lawn, NJ. CAS# 109-99-9; hexanes – mixture of isomers, 99.9%, Fisher Chemical, Fair Lawn, NJ. CAS# 92112-69-1; dichloromethane – 99.9%, ACS certified, Fisher Chemical, Fair Lawn, NJ. CAS# 75-09-2; Nitrogen – UHP – Pure gas, AirGas, Radnor PA. CAS# 7727-37-9; Silica gel for chromatotron – 60PF_{254} containing gypsum, EMScience, NJ. And Silica gel for column chromatography = ultrapure, 60-200 micron, 60 Å, Acros Organics, NJ. CAS# 7631-86-9. Also used were TLC glass plates – Silica Gel 60 PF_{254}, Merch KGaD, Darmstad, Germany.

3.2 Equipment

The equipment used included rotary evaporator, Rotavap R-114, manufactured by Büchi Labortechnik AG, Meierseggstrasse 40, 9230 Flawil, Switzerland; and Bruker NMR, Bruker Avance 400 MHz, manufactured by Bruker BioSpin, 40 Manning Road, Billerica, MA 01821.

3.3 Procedures

An oven-dried flask containing a magnetic stir bar was fitted with a septum and flushed with N_2. THF (10 mL) and thiophene (0.79 mL) were added, and the stirred mixture was cooled to

0 °C in an ice bath, with n-butyllithium (3.125 mL, 1.6 M) added dropwise and the mixture stirred for 20 min, then cooled to −25 °C. A solution of 2-chloropyrimidine (0.5 g) in dry THF was added dropwise with stirring, and the temperature was maintained at −25 °C for 30 min. The majority of the 2-chloropyrimidine did not dissolve, so was added as a solid. Reaction progress was monitored by thin-layer chromatography (TLC) using hexane/CH_2Cl_2/methanol (10:10:0.1) eluent. After 30 mins the mixture was then allowed to warm to 0 °C and stirred for an additional 30 min. A solution of water (7 mmol, 0.126 mL) in THF (1 mL) was added to quench the reaction, and the mixture was stirred at 25 °C for 10 min.

The reaction was quenched by the addition of water (0.126 mL, 7 mmol) in THF (1 mL), and the mixture was stirred at 25 °C for 10 min. A solution of DDQ (5 mmol) in THF (5 mL) was added slowly via pipette. The mixture was stirred for 10 min and then cooled to 0 °C. Hexane (10 mL) and aqueous NaOH (12 mmol, ~1 mL) were added, and the mixture was stirred for 5 min. 2-chloropyrimidine was the limiting reagent. For reactant information see Table 1.

Table 1 Reactants in synthesis

RMF = relative mole factor - integer

Reactants	RMF	MW (g/mol)	Mole (mmols)	mass (g)	vol (mL)	density (g/mL)
2-chloropyrimidine	1	114.53	4.5	0.515		
thiophene	1	84.14	10.0	0.841	0.79	1.066
DDQ	1	227	5.0	1.135		
n-Bu-Li	2	64.06	5.0	0.320	3.14	

Because no distinct organic layer was observed, additional THF (25 mL) was added, and the mixture was swirled. The mixture was decanted to separate the aqueous layer (less than a mL), leaving a substantial residue in the flask. This solid residue was insoluble in common organic solvents but readily soluble in water, suggesting it was an inorganic salt by-product. The organic layer was isolated, dried over $MgSO_4$, and gravity filtered. The transparent filtrate

was concentrated via rotary evaporation, and the flask was left open to allow any residual solvent to evaporate.

Once evaporated to a solid, the material had a small portion dissolved in a CH_2Cl_2, and used for TLC, in a group with other experimenters. The group for this experiment was labeled DG in the third lane. The first lane contained a product solution prepared from a previous successful experiment (eluted product circled in red). You can see in Figure 1, that lane 3 has no product corresponding to the product, in lane 1.

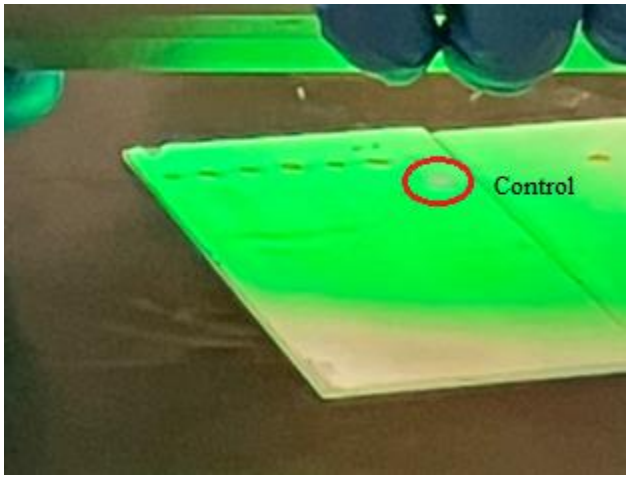


Figure 1 – TLC of crude, dried product

A specimen was sent for ^{1}H NMR and ^{13}C NMR.

3.4 Product Characterization

1. *2-chloro-4-(thiophene-2-yl)pyrimidine:* a dark blue-black solid, pure yield 0 g, percent yield 0%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19-7.21 (d, *J*-coupling 4.0 Hz, 1H), 7.48-7.49 (d, 1H, *J*-coupling 2.5 Hz), 7.60-7.62 (d, 1H, *J*-coupling 5.2 Hz), 7.83-7.84 (d, *J*-coupling 2.6 Hz, 1H), 8.54-8.56 (d, *J*-coupling 5.2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 113.57, 128.76, 129.09, 131.71, 140.33, 159.44, 161.60, 161.88.

4.0 CONCLUSIONS

The synthesis of 2-chloro-4-(thiophen-2-yl)pyrimidine proceeded uneventfully until the addition of 2-chloropyrimidine. The resulting compound failed to dissolve in tetrahydrofuran (THF). Subsequent TLC analysis, performed alongside a known sample of the target product, showed no spot with an R_f value corresponding to that of the reference sample.

The color of the compound produced was extremely dark blue, unlike the light color of the intended product. The ^{1}H NMR and ^{13}C NMR were possible for the product but given the lack of a compound matching the reference compound in the TLC run, confidence in having produced the correct product was not warranted. Had a mass spectrum been run, it could have confirmed that chlorine was in the product. Also, all the other groups executing the same experiment failed in the same pattern. There was suspicion that the previously opened bottle of 2-chloropyrimidine may have hydrolyzed, but there is no clear evidence of that, other than the lack of THF solubility.

5.0 REFERENCES

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6.0 SUPPLEMENTAL INFORMATION

6.1 Formulas

Yield calculations

Product moles as determined by moles of limiting reagent = moles of limiting reagent *x* ratio of product moles to moles of the limiting reagent

Theoretical yield = Product MW *x* (product moles as determined by moles of limiting reagent)

Percent yield = yield / theoretical yield

J coupling constant calculations

J coupling constant = difference in ppm, between two adjacent signals (of a tuplet) *x* operating frequency

Moles calculated from concentration and volume

molarity = moles / liters

moles = liters *x* molarity

6.2 Significant Figures

Significant figures used were the significant figures of the raw data plus one, for all calculation results.

6.3 Acknowledgements

6.3.1 Acknowledged use of AI in this paper

AI was used to check tense, wording, spelling, and grammar. All work in this paper is the author's original work.

6.3.2 Acknowledged use of figures, schemes, and tables

Scheme 1 – Reprinted from INTRODUCTION TO ADVANCED SYNTHESIS Chem 4330/6330 Lab Manual, 2010 Edition by L. Strekowski and M. Henary Department of Chemistry, Georgia State University

6.4 Raw Data

Available on request.

6.5 Tables, Graphs, and Plots

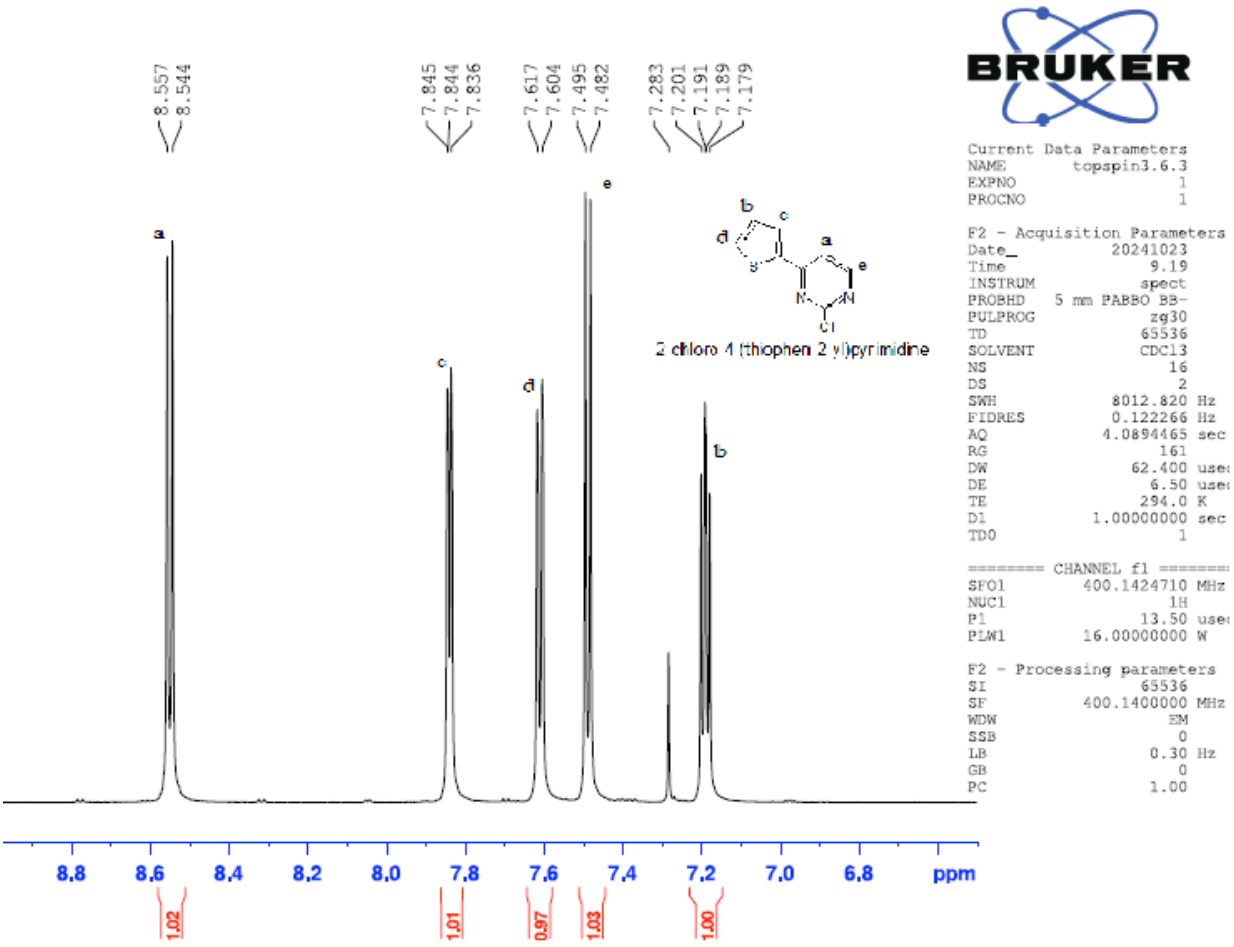

Figure S1 – ^{1}H NMR of Chromotron elution, Aromatic Region

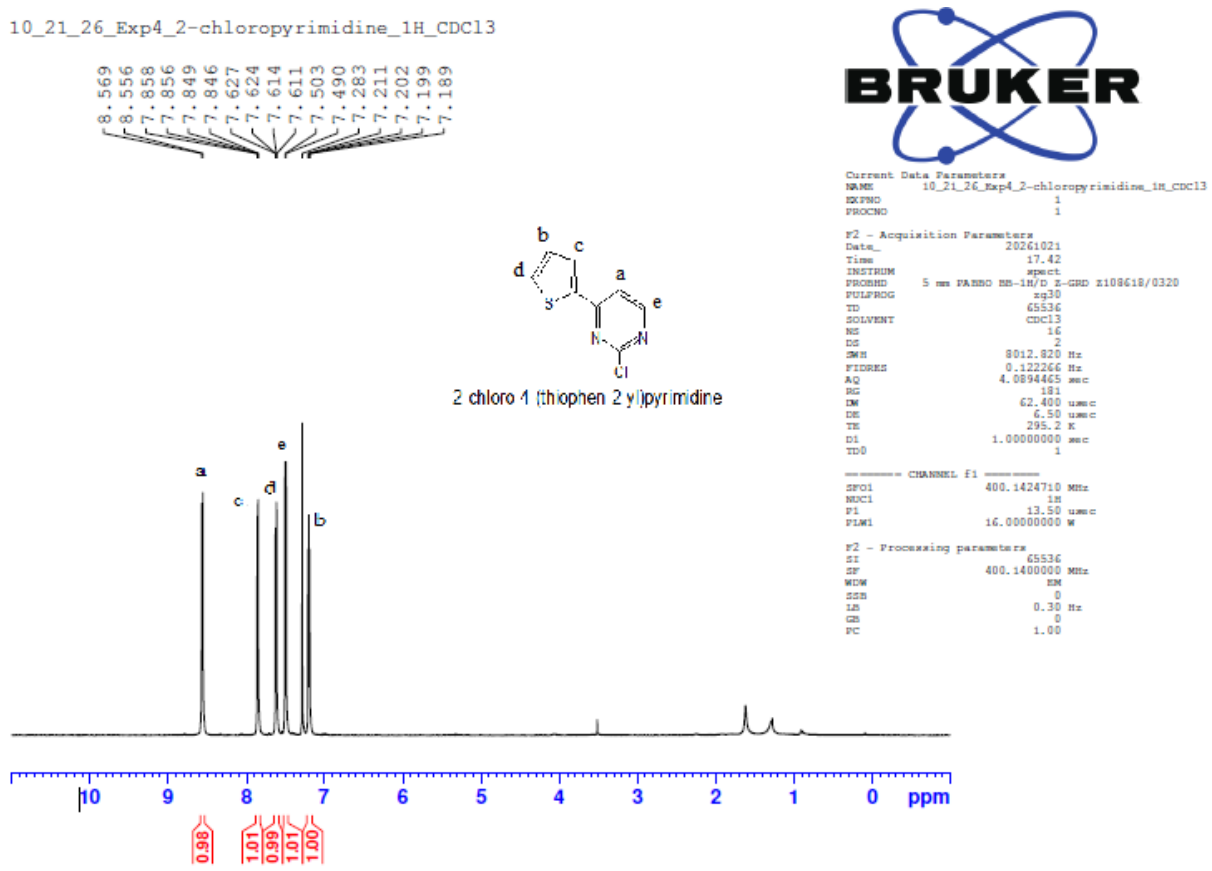

Figure S2 – ^{1}H NMR of Chromatotron elution

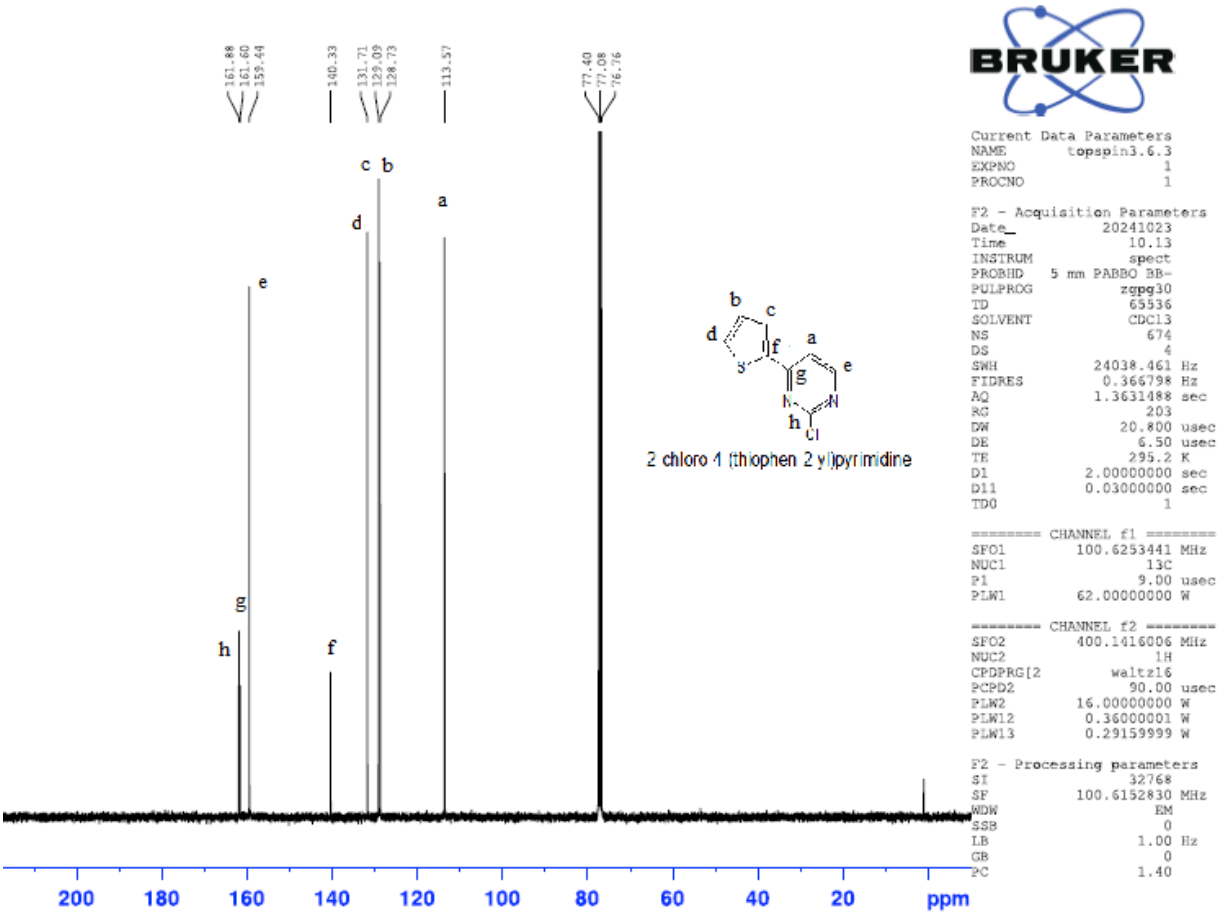

Figure S3 – ^{13}C NMR of Chromatotron elution