Ene Reactions of Methylidene Thiazolidines

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ABSTRACT

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This thesis describes the synthesis of seven new racemic molecules from methylidene thiazolidines reacting with two enophiles, N-phenylmaleimide and ethyl glyoxylate. The synthesis of these molecules was achieved through the ene reaction under thermal conditions, resulting in an adduct containing a single chiral carbon.

This is foundational work in exploration of ene reactions of the methylidiene thiazolidines used in this work with different enophiles and eventually asymmetric catalysis to synthesize chiral compounds, such as non-natural amino acids.

Chapter 1 of this thesis describes the ene reaction and the various molecules that were synthesized via an ene reaction. It also describes very recent chemistry and applications of thiazolidines and their derivatives.

Chapter 2 of this thesis reports the exploratory attempts of the ene reactions with 6 different methylidene thiazolidines and N-phenylmaleimide, which resulted in successful synthesis of the products in low yields. It then describes what experimental changes needed to be made to optimize the yields. Another reaction described is reacting one of methylidene thiazolidines with ethyl glyoxylate, and two different experimental methods were used. One method showed that the product was successfully synthesized using pure ethyl glyoxylate, and another method shows that synthetic ethyl glyoxylate can be used to successfully synthesize the product.

Chapter 3 of this thesis has the experimental procedures used to synthesize each new molecule and the characterization data for each new molecule.

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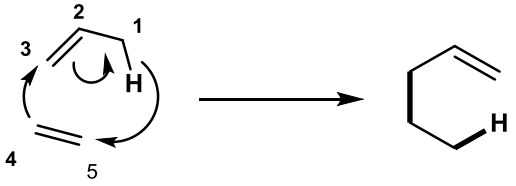
CHAPTER 1- INTRODUCTION

1.1 The Ene Reaction

In an ene reaction, an alkene with an allylic hydrogen (the "ene" component) reacts with a compound containing an electron deficient multiple bond (enophile) to form a new bond with the migration of the ene double bond and a net 1,5-hydrogen shift.[1] This reaction was first discovered by Alder in 1943 and proceeds via a six-electron pericyclic mechanism (Scheme 1) much like the Diels-Alder reaction. It is also carried out thermally like the Diels-Alder reaction.[2]



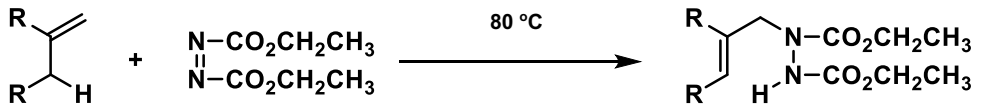
Scheme 1 – Mechanism of Ene Reaction

Since its discovery, ene reactions have been demonstrated in many different settings, where various "enes" and enophiles have been used to synthesize compounds. In addition to experiments where the reactions are carried out thermally, catalysts or additives have been implemented in order to achieve enantioselectivity or to optimize yields.

One of the earlier ene reactions was reported by Thaler in 1964,[3] where he described thermal ene reactions with monoolefins and ethyl azodicarboxylate (Scheme 2). In 1974, Snider introduced using aluminum chloride as a Lewis acid catalyst in ene reactions, where methyl acrylate was used as the enophile because it was less reactive.[4] Later in 1990, catalytic asymmetric ene reactions with prochiral glyoxylates were first developed by Mikami, where the

catalyst was a chiral titanium complex prepared from $(i\text{-PrO})_2TiX_2$ and (*R*)-BINOL in the presence of molecular sieves.[5]

a)



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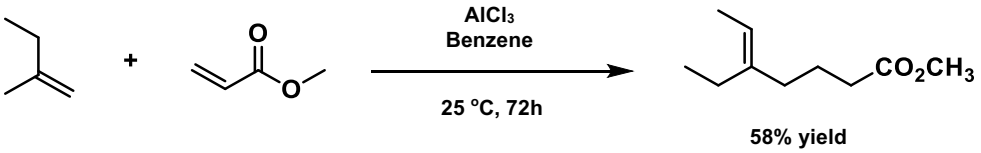

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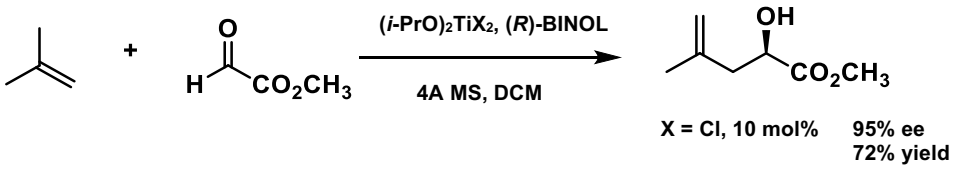
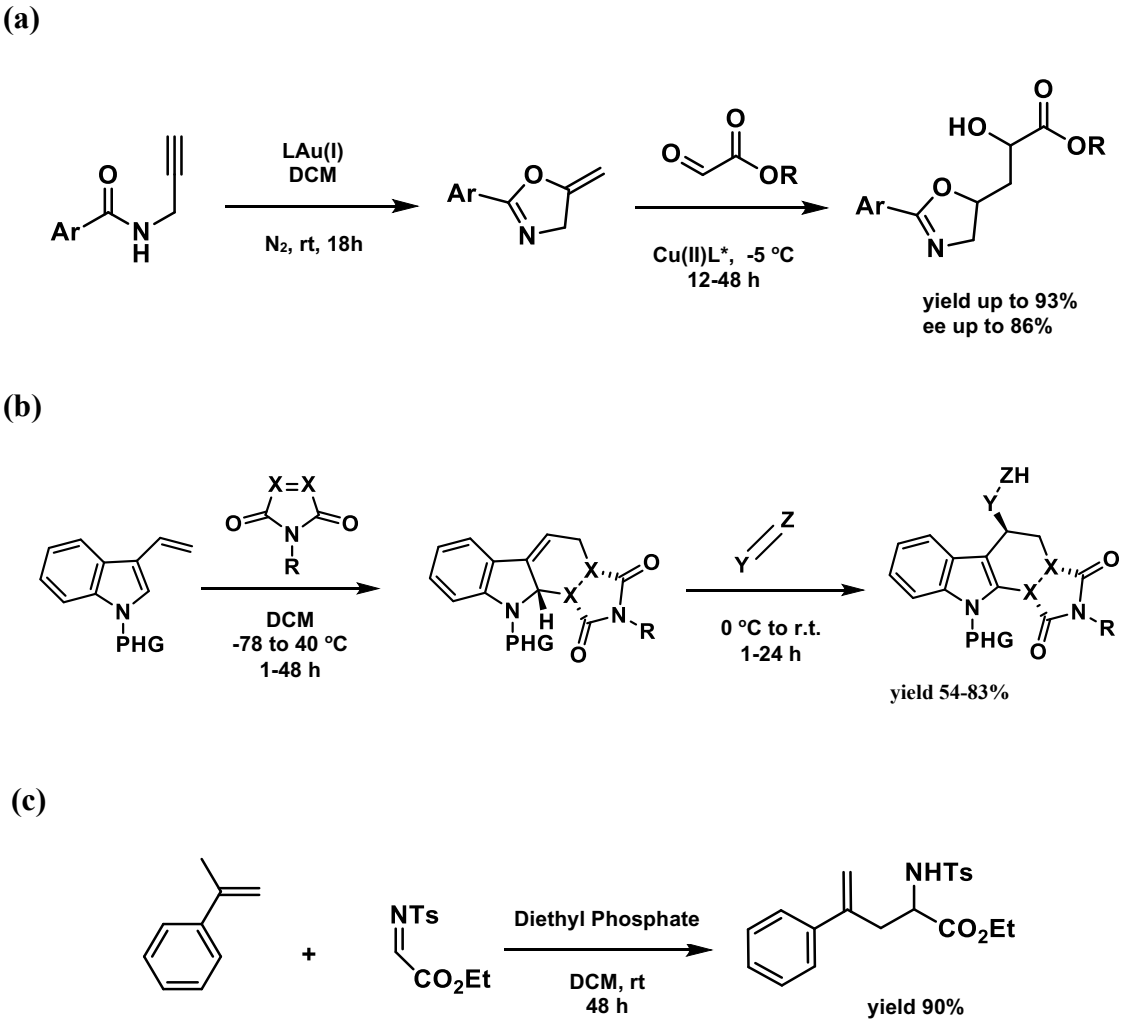


Scheme 2 – Earlier Ene Reactions

In more recent reports, Nalivela synthesized asymmetric oxazole α-hydroxy esters through intramolecular formation of an alkylidene oxazoline followed by reacting it with an alkyl glyoxylate using an asymmetric copper(II)-catalyzed ene reaction (Scheme 3).[6] Cowell synthesized functional carbazoles using thermal Diels-Alder reactions of vinyl indoles followed by thermal intermolecular ene reactions using a one-pot 3 component system.[7] Oliver reported that adding Bronsted acids (particularly diethyl phosphate) to imino-ene reactions of all-carbon olefins with glyoxylate derived imines significantly increased the yields over that of thermal reactions.[8]



Scheme 3 – Recent Ene Reactions

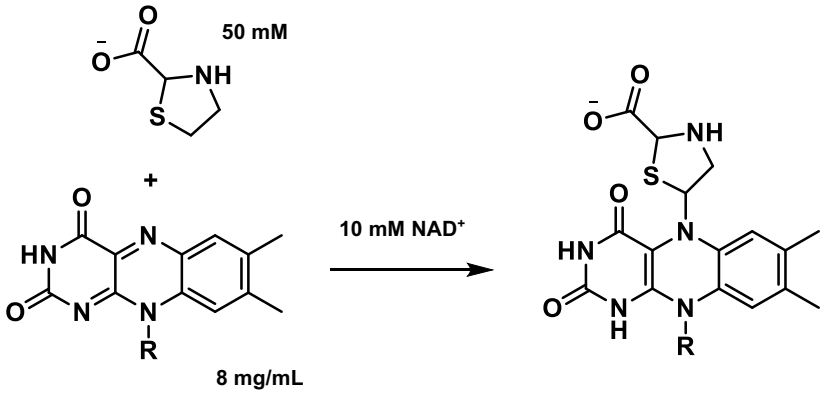
1.2 Thiazolidines

The structure of penicillin includes a thiazolidine ring, which are saturated 5 membered rings with a thio moiety at the 1 position and an amino group at the 3 position. In the last few years, some new applications and chemistry involving thiazolidines have been reported.

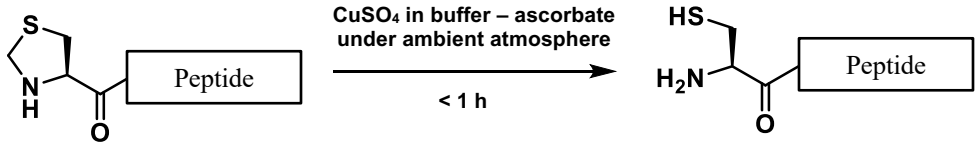
Last year, Campbell reported the use of thiazolidine-2-carboxylate to covalently modify a flavin moiety (Scheme 4) in the enzyme proline dehydrogenase (PRODH), a possible cancer therapy target. The results showed that this covalent modification deactivated PRODH.[9]

In chemical synthesis of peptides, 1,3-thiazolidine-4-carbonyl (Thz) has been used as a protecting group on the N-terminal amino acid. Last year, Naruse reported that cupric sulfate can deprotect these peptides by efficiently opening the thiazolidine ring, producing an N-terminal cysteine without the use of inert gas or solvent.[10]

(a)



(b)



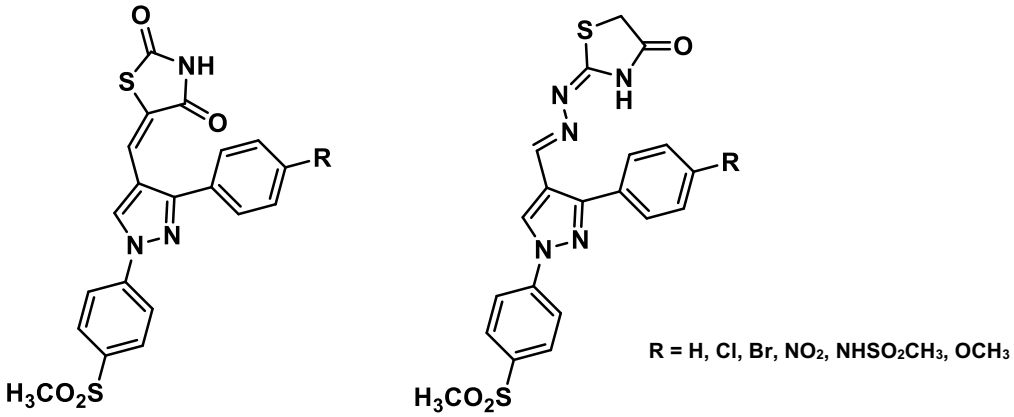
Scheme 4 – Thiazolidine Chemistry

Thiazolidine based compounds have shown promising pharmaceutical applications. Abdellatif synthesized two new series of thiazolidine derivatives with a pyrazole core, one derivative with thiazolidinedione and the other derivative with thiazolidinone. Six compounds in each series were synthesized (Figure 1a) and were tested for anti-inflammatory activity, ulcerogenic liability, and anti-diabetic activity.[11] In-vivo studies comparing effectiveness of these new compounds with commercial drugs showed that one of them had higher anti-inflammatory activity (98%) than celecoxib (89%) 5 hours after treatment. All of these

compounds were significantly less ulcerogenic (ulcer indexes 2.62-5.11) than ibuprofen (ulcer index 20.25) and were comparable with celecoxib, a non-ulcerogenic drug (ulcer index 2.93). For anti-diabetic activity, there was a broad range of 19.32-65.37% when compared with acarbose at 49.5%.

Thiazolidinedione derivatives are very commonly prepared scaffolds and have been tested for antimicrobial activity. Trotsko has conducted these tests with thiazolidine-2,4-dione (TZD) derivatives and last year reported that the TZD-based derivatives with pyridine-4-carbohydrazone (Figure 1b) substituents had very effective antimycobacterial activity (minimum inhibitory concentration = 1 μg/mL) when tested with *Mycobacterium tuberculosis* H37Ra[12].

a)



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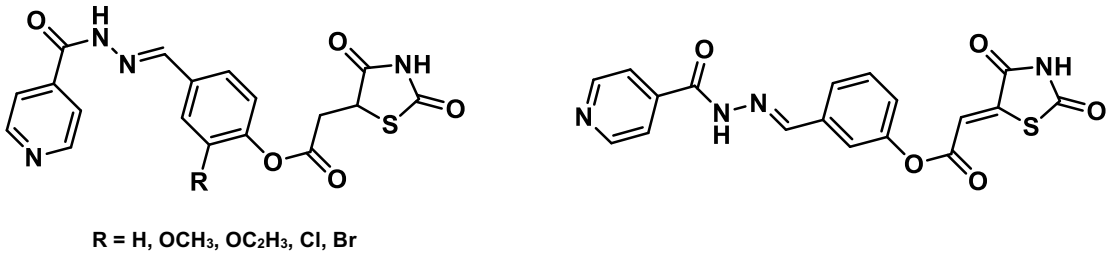
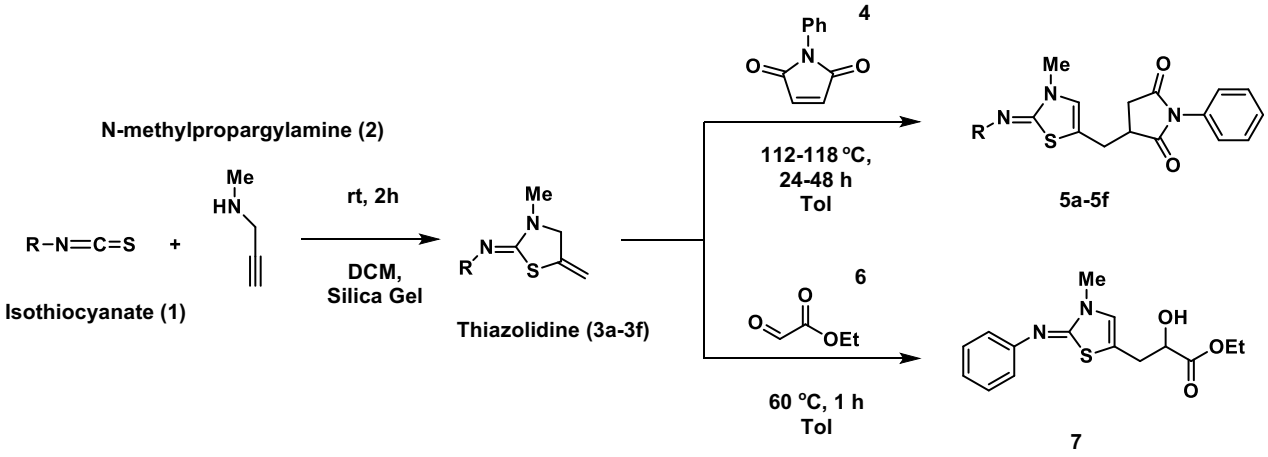


Figure 1 – Thiazolidines Derivatives Used in Pharmaceutical Applications

1.3 Synthesis of New Molecules

In this work, a two-step approach similar to Nalivela was used to synthesize seven new racemic molecules. First, methylidene thiazolidines were synthesized by an intermolecular reaction with an isothiocyanate compound **1** and *N*-methyl propargylamine **2** on silica gel (Scheme 5). The resulting products **3a-3f** served as the "ene components" in this work. **3a-3d** were previously synthesized by Singh[13] (Figure 2), and two additional reactions not reported by Singh were performed, synthesizing compounds **3e** and **3f** (Figure 3). Next, these thiazolidines were evaluated in a thermal ene reaction with two enophiles, N-phenylmaleimide **4** and ethyl glyoxylate **6** to form racemic compounds **5a-5f** and **7**.



Scheme 5 – Synthesis of New Racemic Molecules

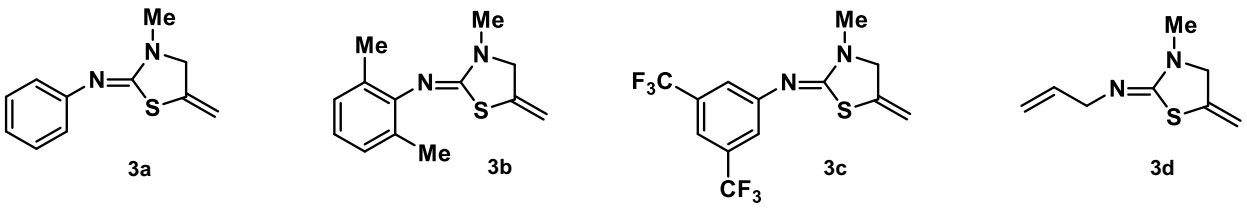


Figure 2 - Previously Synthesized Thiazolidines

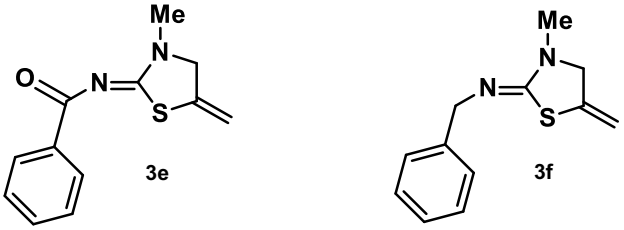
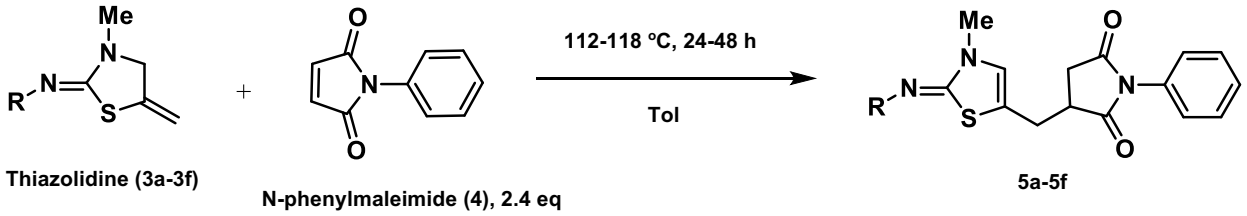


Figure 3 - Newly Synthesized Thiazolidines

CHAPTER 2 - RESULTS AND DISCUSSION

2.1 Reactions with N-phenylmaleimide

The results of the ene reactions with methylidene thiazolidines **3a-3f** and N-phenylmaleimide (**4**) are shown in Figure 4. Toluene was used as the solvent in all reactions to give **3a-3f** solution concentrations of approximately 0.3M. The solutions had to be degassed with nitrogen along with the air in the sealed tube being flushed with nitrogen in order to avoid autoxidation, where O_2 would react with the methylidene to form an aldehyde. In the initial stages of these experiments, **3a-3f** were synthesized and stored at room temperature under normal atmospheric conditions for periods ranging from days to months. When these compounds were reacted with **4**, the reaction proceeded for 24 hours. A few grams of **3a** were previously synthesized and stored at room temperature under normal atmospheric conditions for several months, and when this batch was reacted with **4,** the yield for **5a** was 58%. When **3e** was stored under the same conditions for a month before reacting with **4,** the yield for **5e** was 62%. However, when **3b-3d** and **3f** were reacted with **4** after storage for a period of days to months under the same conditions, the yields ranged between 14% and 35%. Another observation from these initial sets of reactions is that the TLC analysis showed spots in addition to the starting materials and the products, which indicates the possibility of side reactions occurring.



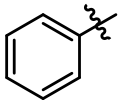
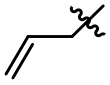
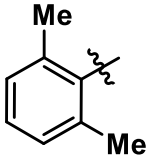
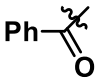
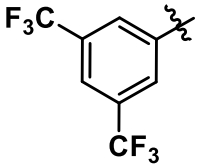
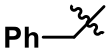
R Group on Product		Yield	R Group on Product		Yield
5a		66%	5d		78%
5b		61%	5e		67%
5c		58%	5f		79%

Figure 4 – Summary of Methylidene Thiazolidine Reactions with N-phenylmaleimide

Addressing the challenge of these low yields came about through further experimentation with the new methylidene thiazolidine **3f**. When this molecule was successfully synthesized, a 5-fold scale up reaction was done, resulting in 551 mg of **3f** that could be used for repeating the reaction with **4** and finding ways to optimize the yields. The first successful reaction of **3f** and **4** resulted in only a 14% yield of **5f**, which was done after 3 months **3f** was stored at room temperature under normal atmospheric conditions. ^{1}H NMR analysis of the isolated products showed a possible side product (Figure 5) and **5f** with significant contamination (Figure 6).

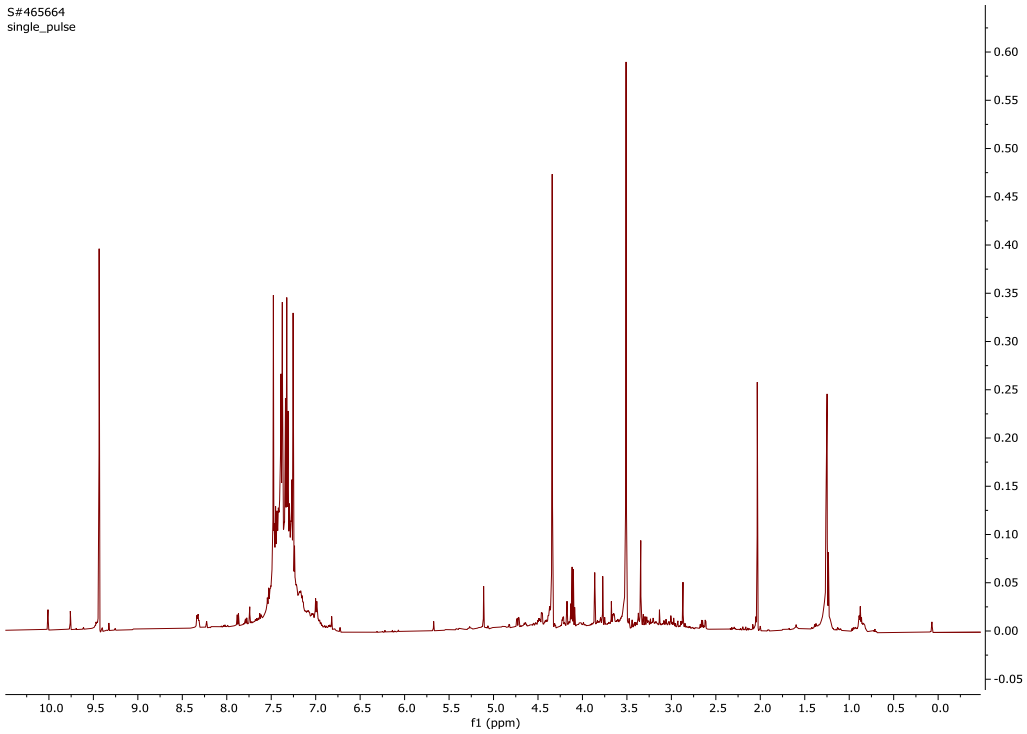


Figure 5 – ^{1}H NMR Spectrum of Possible Side Product From Initial Reaction

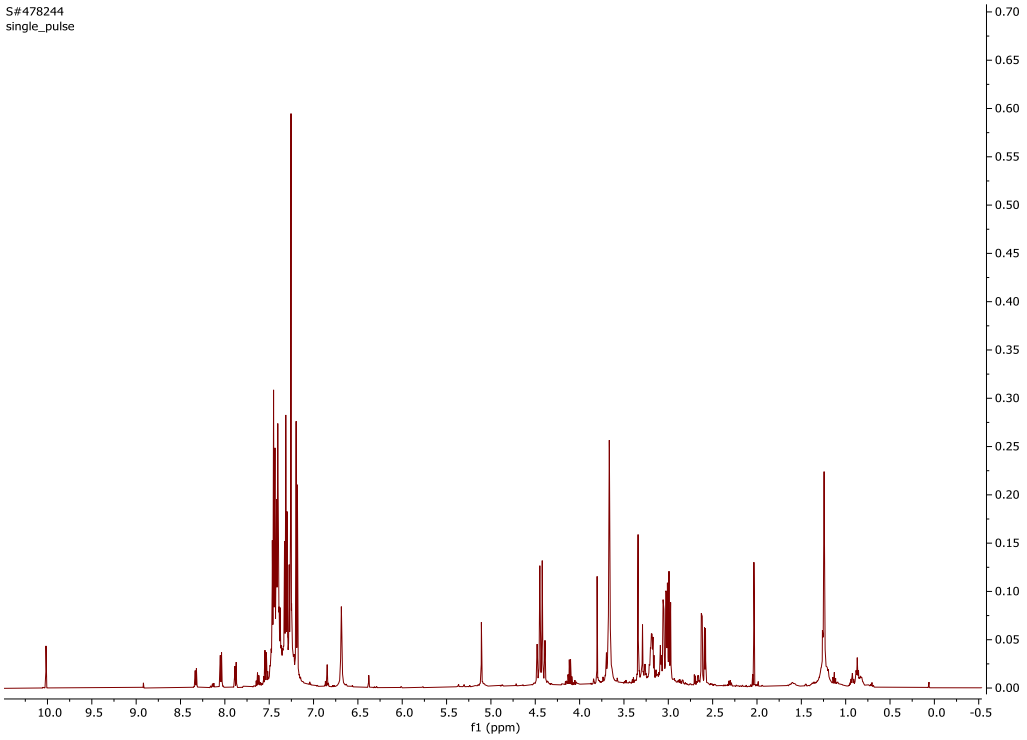


Figure 6 – ^{1}H NMR Spectrum of 5f with Significant Contamination

When this reaction was repeated 6 months after **3f** was synthesized, the ^{1}H NMR analysis of the products in this reaction (Figure 7 and 8) were possibly **5f**; however, they were inconclusive because there appears to be significant decomposition.

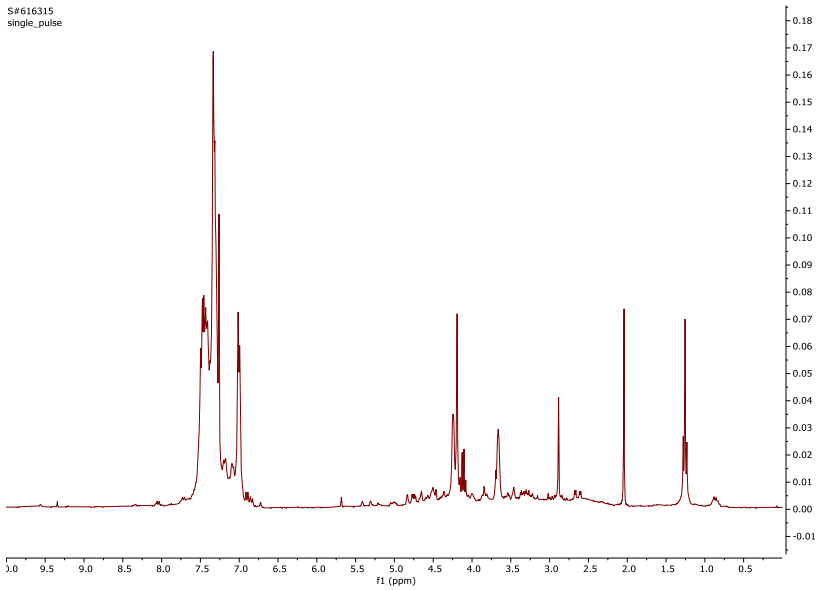


Figure 7 – ^{1}H NMR Spectrum of Possible 5f When Reaction Was Repeated

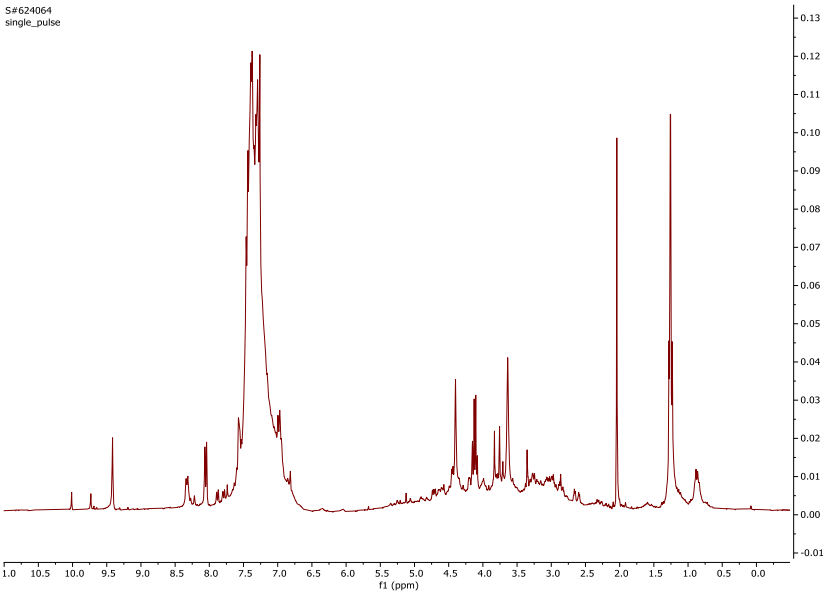


Figure 8 – ^{1}H NMR Spectrum of Possible 5f When Reaction Was Repeated

3f was then synthesized again at its regular scale, and when it reacted with **4** the following week, the yield of **5f** improved to 35%. However, TLC and ^{1}H NMR analysis of the isolated products showed a possible side product of the reaction (Figure 9).

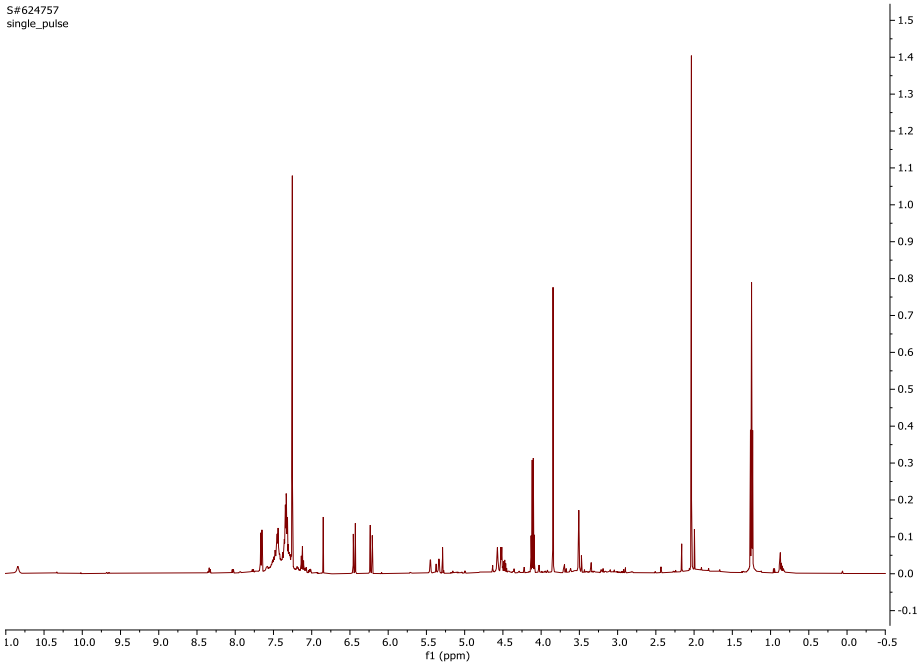


Figure 9 – ^{1}H NMR Spectrum of Possible Side Product After a Third Reaction Attempt

More of **3f** needed to be synthesized for full characterization, and when this sample was analyzed by ^{1}H and ^{13}C NMR just two days after its synthesis, it clearly showed that **3f** started degrading (Figures 10-13) with the appearance of additional peaks. As mentioned previously, the **3a-3f** solutions need to be degassed with N_2 to avoid autoxidation, where the methylidene would react with O_2 to form an aldehyde with the double bond migrating inside the ring between C3 and C4. Additionally, the aldehyde can be oxidized further to a carboxylic acid. The ^{1}H NMR spectrum in Figure 11 shows an aldehyde peak at 9.4 ppm, and a carboxylic acid peak at 10.0 ppm. There is also a vinylic hydrogen peak at 6.9 ppm resulting from the double bond migration. Likewise,

the ^{13}C NMR in Figure 13 shows an aldehyde peak at 192.6 ppm and a possible carboxylic acid peak at 179.1 ppm.

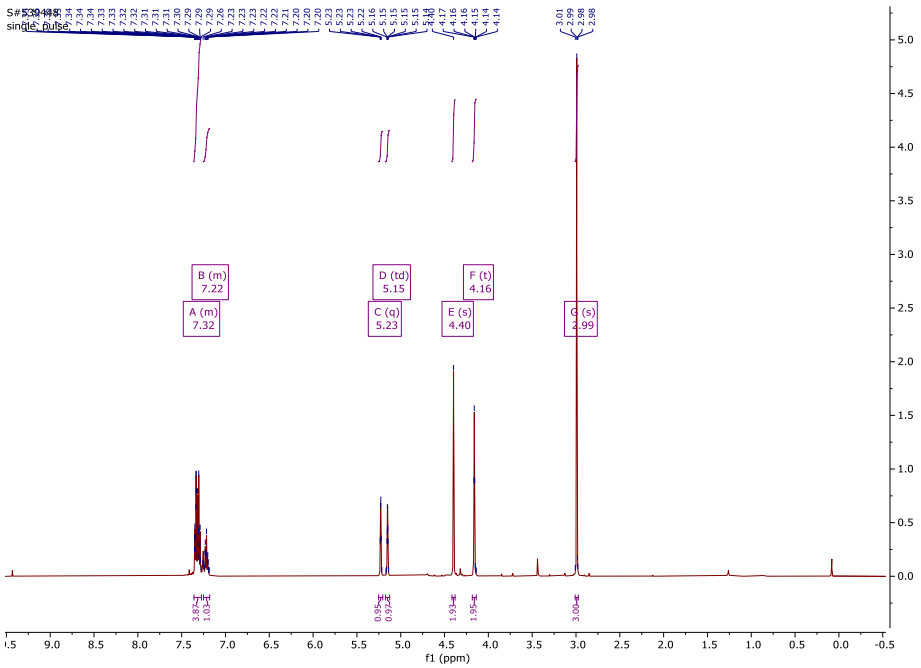


Figure 10 – ^{1}H NMR Spectrum of Pure 3f

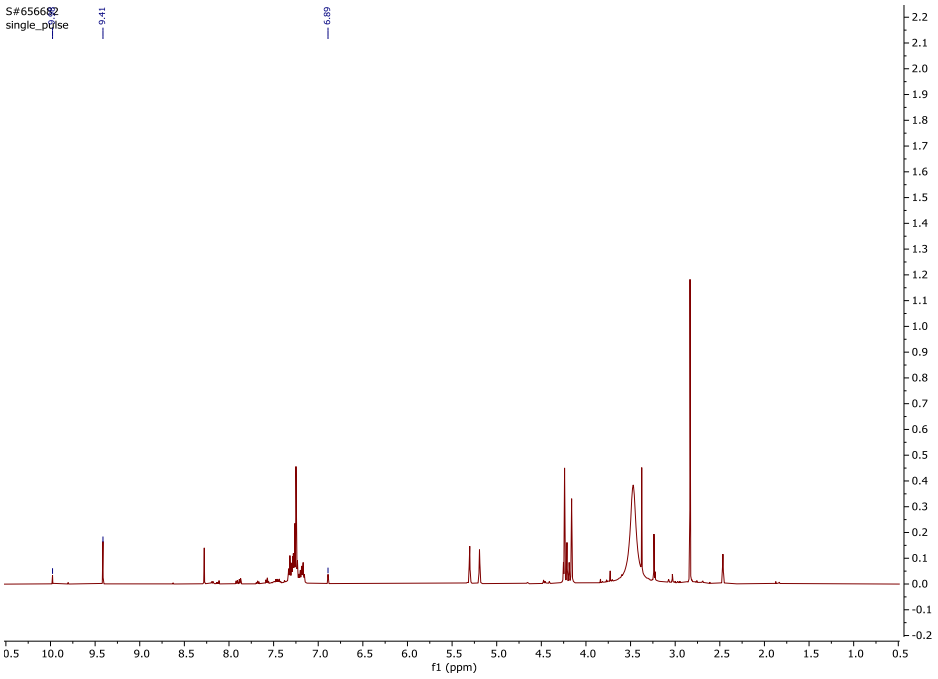


Figure 11 – ^{1}H NMR Spectrum of Contaminated 3f

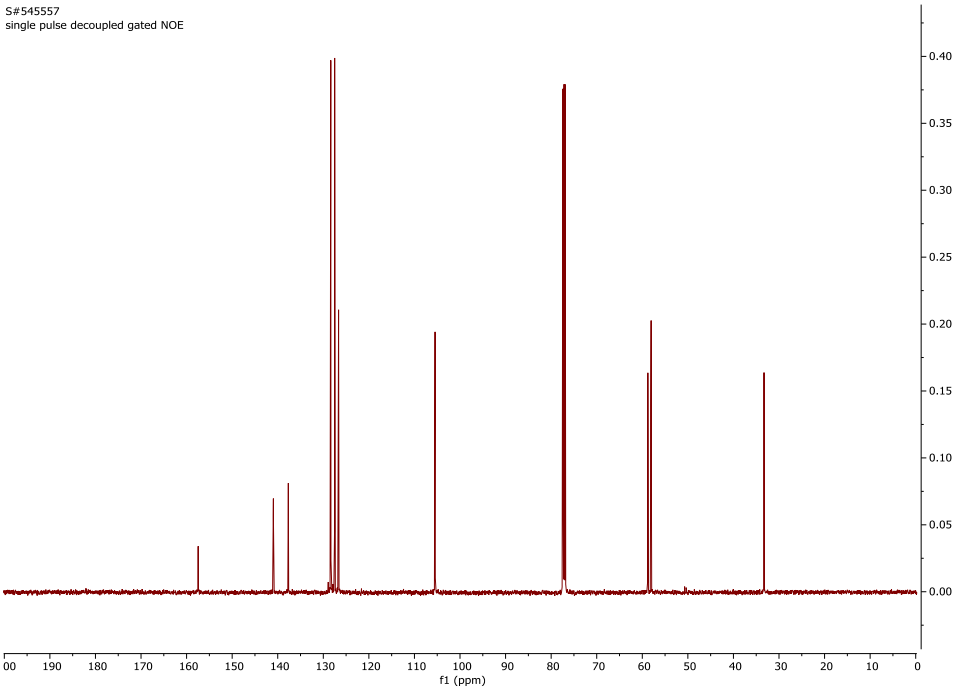


Figure 12 – ^{13}C NMR Spectrum of Pure 3f

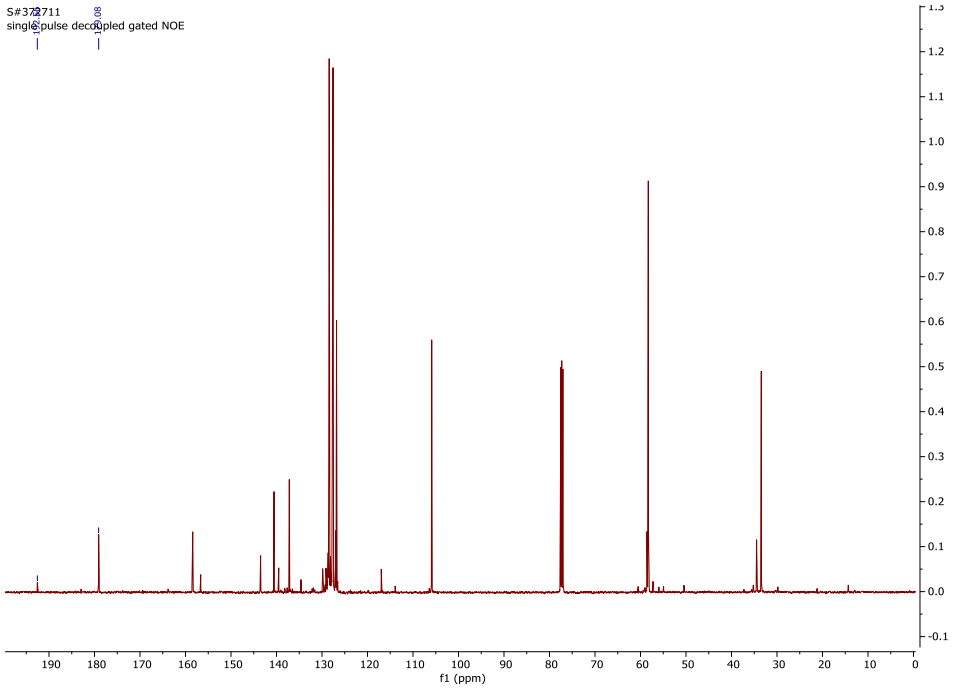


Figure 13 – ^{13}C NMR of Spectrum of Contaminated 3f

Other observations noted of **3f** after having been stored at room temperature under normal atmospheric conditions included changes in color, texture, and solubility. Immediately after synthesis, **3f** would be soluble in toluene and chloroform, but after storage, it would no longer be soluble in toluene and chloroform.

These findings with **3f** indicates that the compound is not very stable, and similar findings were made for **3b-3d**. This led to a change in the procedure from storing **3a-3f** at room temperature and normal atmospheric conditions prior to reaction with **4** to conducting the reaction with **4** immediately following synthesis of **3a-3f**. TLC and ^{1}H NMR spectroscopic analysis of the crude reaction mixtures following this new procedure showed just the two starting materials and the product, indicating no side reactions for 5 of the compounds, while the reaction with **3e** showed some rearomatization. This new procedure increased the yield of **5f** to 79% after a 24-hour reaction, confirmed by ^{1}H NMR (Figure 14). This also explains that the additional spots found in the TLC analysis of the initial experiments was due to the degrading thiazolidines.

In the first reaction with **3b** and **4,** the yield of **5b** was 33%. When the new procedure was used, the yield of **5b** increased to 52% after a 24-hour reaction. The reaction was repeated for 48 hours, and the yield of **5b** increased to 61%. The first two reactions with **3c** and **4** had yields of **5c** at 34% and 30%. When the new procedure was used, the yield of **5c** increased to 42%, then when the reaction was repeated for 48 hours and increased the yield of **5c** to 69%. These yields of **5c** resulted from a **3c** concentration of around 0.2M. When the **3c** concentration was increased to around 0.3M, the yield was 58%. The reaction with **3d** and **4** was done 3 times before the new procedure was used, and the yields of **5d** were 15%, 35%, and 25%. When the new procedure was used, the yield of **5d** increased to 78% after a 24-hour reaction.

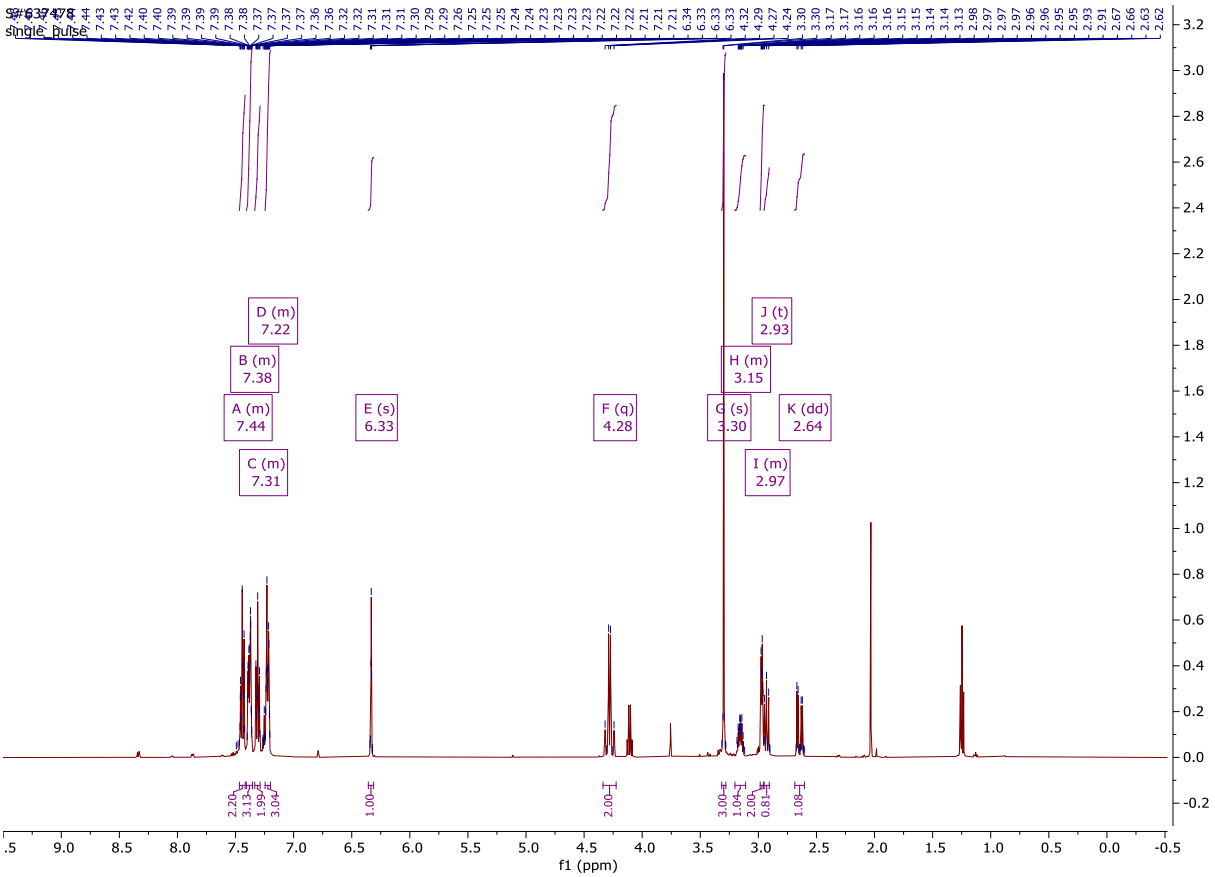


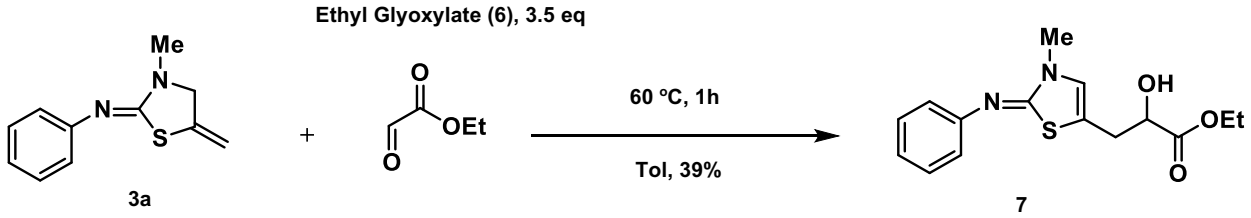
Figure 14 – ^{1}H NMR Spectrum of 5f with Residual Ethyl Acetate

Although the yield for **5a** was decent at 58% after **3a** was stored for several months before it was reacted with **4**, the new procedure was used resulting in an increased yield 66% after the reaction ran for 24 hours. The yield for **5e** was also decent at 62% after **3e** was stored for a month before it was reacted with **4**. When the new procedure was used, the yield increased to only 67% after the reaction ran for 24 hours. This could be due to the rearomatization of **3e** during the reaction, where the double bond of the exocyclic alkene migrates to inside the thiazolidine ring. The TLC analysis of the crude reaction mixture showed a single spot in addition to the two starting materials and the product. When this spot was isolated and analyzed by ^{1}H NMR, it confirmed rearomatization.

This work showed that optimal yields for ene reactions with thiazolidine methylidene compounds **3a-3f** with N-phenylmaleimide **4** were achieved when the ene reaction is done immediately following the synthesis of **3a-3f**, due to their relative instability. Any subsequent ene reactions with **3a-3f** and other enophiles should be done using the same procedure in order to achieve optimal results. Since the ene reactions of **3a** and **3e** after long term storage at room temperature and under normal atmospheric conditions had decent yields, this suggests that these two compounds may be more stable than **3b-3d** and **3f**.

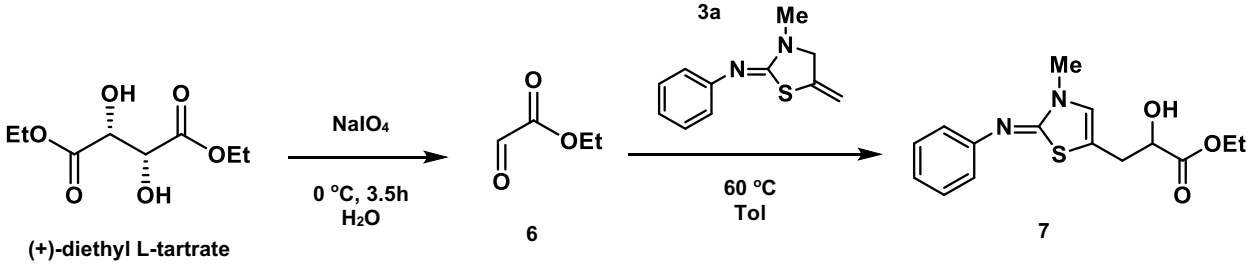
2.2 Reactions with Ethyl Glyoxylate

A series of ene reactions with **3a** and pure ethyl glyoxylate **5** (50% w/w in toluene) were done using the same batch of previously synthesized **3a** mentioned in section 2.1. Toluene was used as the solvent in these reactions, but it was not degassed with N_2. When **3a** reacted with 2.4 equivalents of **5** for 1 hour at 60 °C, the yield was only 20%. When the reaction was repeated and ran for 24 hours at 60 °C with 2.4 equivalents of **5**, the yield increased to only 29%, and the TLC analysis showed several spots in addition to the starting material and the product. When 3.5 equivalents of **5** was used and the reaction run for 1 hour at 60 °C, the yield increased to 39% (Scheme 6), and ^{1}H NMR confirmed the formation of product **7**.



Scheme 6 – Ene Reaction of 3a with Pure Ethyl Glyoxylate

Subsequent reactions with methylidene thiazolidines **3a-3f** and **5** will use a procedure where ethyl glyoxylate is synthesized from (+)-diethyl L-tartrate. Li reported a procedure where sodium periodate was used the convert (+)-diethyl L-tartrate to ethyl glyoxylate, and the crude product was used immediately in the next reactions.[14] This same procedure with the same scale as reported by Li was used, where the crude ethyl glyoxylate product was immediately reacted with **3a** (Scheme 7). The yield of this reaction was very low at 5%, and the ^{1}H NMR showed that product **7** had impurities. Future reactions to optimize the yield will use the same methods in the N-phenylmaleimide reactions. This includes using the same reactant concentrations in those reactions, degassing toluene with N_2, flushing the air in the sealed tube with N_2, and varying the reaction time.



Scheme 7 – Ene Reaction of 3a with Synthetic Ethyl Glyoxylate

CHAPTER 3 - EXPERIMENTAL

3.1 General Procedures

Compounds **3a-d** were synthesized according to a literature procedure reported by Singh.[13]

NMR spectra were recorded on JEOL ECX 300 MHz and Eclipse+ 500 MHz Spectrometers. ^{1}H NMR spectra were recorded in $CDCl_3$ at a spectrometer frequency of 300.53 MHz or 500.13 MHz using $CHCl_3$ (δ = 7.26 ppm) as an internal reference. ^{13}C NMR were recorded in $CDCl_3$ at a spectrometer frequency of 75.57 MHz or 125.76 MHz using $CHCl_3$ (δ = 77.2 ppm) as an internal reference.

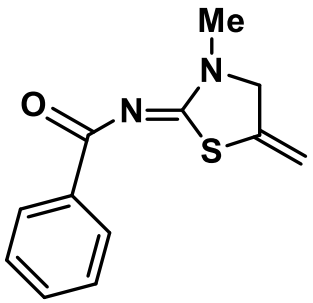
Infrared (IR) spectra were recorded using a Brucker Alpha FT-IR Spectrometer using neat samples.

High resolution mass spectra (HRMS) were recorded by electrospray ionization mass spectrometry (ESI-MS) and was conducted by The Shimadzu Center for Advanced Analytical Chemistry at The University of Texas at Arlington.

Melting point was measured using a Laboratory Devices Inc. Mel Temp apparatus.

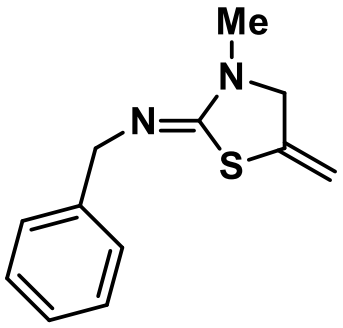
3.2 Synthesis

Synthesis of (Z)-*N*-Benzoyl-5-methylidene-3-methylthiazolidin-2 imine (3e):



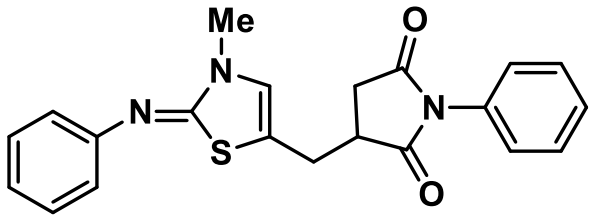
A solution of N-methyl propargylamine (0.72 mmol, 50 mg) and benzoyl isothiocyanate (0.72 mmol, 118 mg) in 0.2 mL of CH_2Cl_2 was added dropwise to 1.26 g of silica gel (1.75 g/mmol) and stirred vigorously for 3 h. Compound was purified by silica gel column chromatography using 10% and 15% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a pale solid (106 mg, 63% yield). ^{1}H NMR: (500 MHz, Chloroform-d) δ 8.31 – 8.26 (m, 2H), 7.55 – 7.49 (m, 1H), 7.49 – 7.40 (m, 2H), 5.34 – 5.28 (m, 2H), 4.40 (t, J = 2.7 Hz, 2H), 3.41 (s, 3H). ^{13}C NMR: 175.7, 169.5, 139.1, 136.6, 132.1, 129.7, 128.1, 106.3, 56.0, 34.3. FT-IR (neat, cm^{-1}): 3286, 3047, 2919, 1699, 1625, 1611, 1551, 1390, 1334, 1246, 965, 851, 704, 673. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{12}H_{12}N_2SO$ 233.0743, found 233.0743. m.p. 100-104 ^{o}C

Synthesis of (Z)-*N*-Benzyl-5-methylidene-3-methylthiazolidin-2 imine (3f):



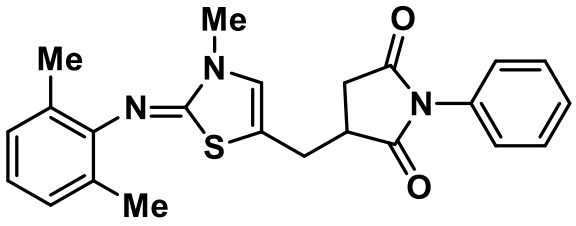
A solution of N-methyl propargylamine (0.72 mmol, 50 mg) and of benzyl isothiocyanate (0.72 mmol, 107 mg) in 0.2 mL of CH_2Cl_2 was added dropwise to 1.26 g of silica gel (1.75 g/mmol) and was stirred vigorously overnight. Compound was purified by silica gel chromatography using 20% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a pale yellow gum (115 mg, 73%). ^{1}H NMR: (500 MHz, Chloroform-d) δ 7.37 – 7.27 (m, 4H), 7.27 – 7.17 (m, 1H), 5.23 (q, J = 2.0 Hz, 1H), 5.15 (td, J = 2.4, 1.6 Hz, 1H), 4.40 (s, 2H), 4.16 (t, J = 2.3 Hz, 2H), 2.99 (s, 3H). ^{13}C NMR: 157.5, 141.0, 137.7, 128.4, 127.5, 126.7, 105.5, 58.8, 58.1, 33.3. FT-IR (neat, cm^{-1}): 3083, 3060, 3025, 2867, 2813, 1647, 1618, 1580, 1378, 1349, 1286, 1238, 1073, 1026, 695, 654, 601. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{12}H_{14}N_2S$ 219.0950, found 219.0929

Synthesis of (Z)-*N*-Phenyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5a):



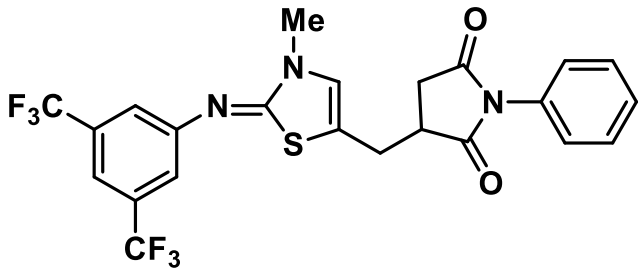
Immediately following synthesis of the thiazolidine, 100 mg (0.49 mmol, 1.0 eq) of **3a** and 203 mg (1.17 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.3 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~112 ^oC for 24 h. Compound was purified by silica gel chromatography using 20%, 40%, 60%, 80%, and 100% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a yellow gum (122 mg, 66%). ^1H NMR: (500 MHz, Chloroform-d) δ 7.45 – 7.40 (m, 2H), 7.40 – 7.35 (m, 1H), 7.34 – 7.29 (m, 2H), 7.22 – 7.16 (m, 2H), 7.09 – 7.00 (m, 3H), 6.34 (s, 1H), 3.36 (s, 3H), 3.12 – 3.03 (m, 1H), 2.93 – 2.89 (m, 2H), 2.87 (t, J = 9.1 Hz, 1H), 2.57 (dd, J = 18.4, 5.1 Hz, 1H). ^{13}C NMR: 177.8, 175.1, 158.6, 151.7, 131.9, 129.6, 129.3, 128.9, 126.5, 126.4, 123.4, 121.6, 108.9, 40.0, 33.8, 33.2, 29.4. FT-IR (neat, cm^{-1}): 3467, 3048, 2916, 1777, 1705, 1610, 1555, 1383, 1334, 1246, 1177, 965, 852, 697, 674. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{21}H_{19}N_3O_2S$ 378.1271, found 378.1264

Synthesis of (Z)-*N*-(2,6-Dimethylphenyl)-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5b):



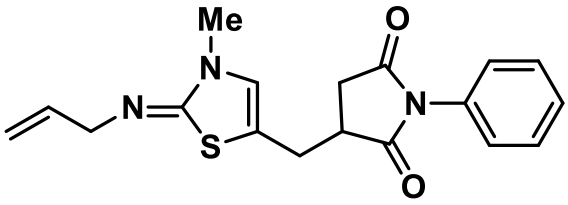
Immediately following synthesis of the thiazolidine, 112 mg (0.48 mmol, 1.0 eq) of **3b** and 200 mg (1.16 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.5 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~117 ^oC for 48 h. Compound was purified by silica gel chromatography using 20%, 40%, and 60%, EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a brown gum (119 mg, 61%). ^1H NMR: (500 MHz, Chloroform-d) δ 7.46 – 7.35 (m, 3H), 7.18 – 7.10 (m, 2H), 7.06 – 7.01 (m, 2H), 6.95 – 6.88 (m, 1H), 6.34 (s, 1H), 3.41 (s, 3H), 3.13 – 3.05 (m, 1H), 2.97 – 2.84 (m, 3H), 2.59 (dd, J = 18.4, 4.9 Hz, 1H), 2.10 (s, 6H). ^{13}C NMR: 177.9, 175.1, 158.2, 149.4, 131.8, 129.5, 129.3, 128.9, 128.6, 126.6, 126.5, 123.5, 109.1, 39.9, 33.6, 33.0, 29.8, 29.4, 17.8. FT-IR (neat, cm^{-1}): 3065, 3014, 2916, 2850, 1776, 1707, 1584, 1382, 1178, 947, 866, 753, 697. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{23}H_{23}N_3O_2S$ 406.1584, found 406.1567

Synthesis of (Z)-*N*-(3,5-Bis-(trifluoromethyl)phenyl)-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5c):



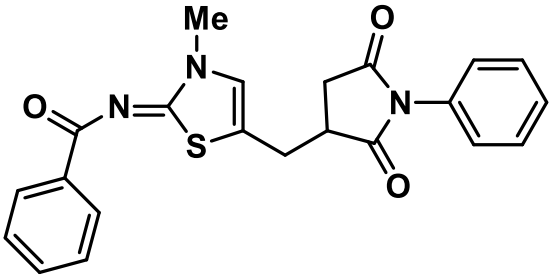
Immediately following synthesis of the thiazolidine, 172 mg (0.51 mmol, 1.0 eq) of **3c** and 210 mg (1.21 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.3 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~117 ^oC for 48 h. Compound was purified by silica gel chromatography using 20%, 40%, and 60% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a yellow gum (153 mg, 58%). ^1H NMR: (500 MHz, Chloroform-d) δ 7.54 – 7.48 (m, 3H), 7.47 – 7.42 (m, 2H), 7.41 – 7.37 (m, 1H), 7.24 – 7.15 (m, 2H), 6.48 (s, 1H), 3.42 (s, 3H), 3.22 – 3.14 (m, 1H), 3.09 – 2.94 (m, 3H), 2.63 (dd, J = 18.3, 5.3 Hz, 1H). ^{13}C NMR: 177.4, 174.8, 159.7, 152.3, 132.7 (q, J = 33.0 Hz), 131.7, 129.4, 129.0, 126.5, 126.3, 123.5 (q, J = 273.7 Hz). 121.8, 116.2, 110.1, 40.1, 34.1, 33.3, 29.2. FT-IR (neat, cm^{-1}): 3086, 3021, 2924, 1780, 1708, 1620, 1563, 1383, 1332, 1274, 1122, 955, 879, 751, 697. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{23}H_{17}F_6N_3O_2S$ 514.1018, found 514.1018

Synthesis of (Z)-*N*-Allyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5d):



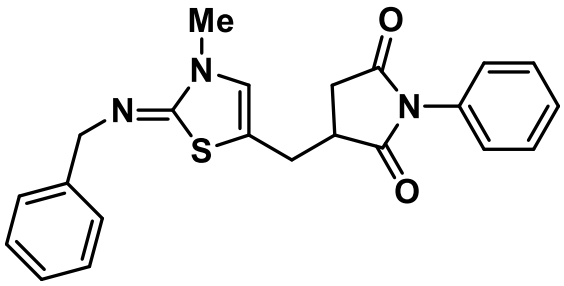
Immediately following synthesis of the thiazolidine, 86 mg (0.51 mmol, 1.0 eq) of **3d** and 212 mg (1.23 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.3 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~115 ^oC for 24 h. Compound was purified by silica gel chromatography using 20%, 50%, and 100% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a dark brown gum (135 mg, 78%). ^1H NMR (500 MHz, Chloroform-d) δ 7.52 – 7.40 (m, 3H), 7.24 – 7.20 (m, 2H), 6.31 (s, 1H), 5.94 (ddt, J = 17.0, 10.2, 5.5 Hz, 1H), 5.25 (dq, J = 17.0, 1.8 Hz, 1H), 5.09 (dq, J = 10.1, 1.6 Hz, 1H), 3.76 – 3.64 (m, 2H), 3.24 (s, 3H), 3.19 – 3.10 (m, 1H), 2.97 – 2.94 (m, 2H), 2.92 (t, J = 9.5 Hz, 1H), 2.62 (dd, J = 18.4, 5.1 Hz, 1H). ^{13}C NMR: 177.9, 175.2, 159.0, 135.7, 131.9, 129.3, 128.8, 126.8, 126.5, 115.4, 108.4, 57.4, 40.2, 33.5, 33.3, 29.6. FT-IR (neat, cm^{-1}): 3077, 3013, 2977, 2917, 2803, 1776, 1703, 1598, 1499, 1380. 1316, 1288, 1176, 911, 751, 732, 695. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{18}H_{19}N_3O_2S$ 342.1271, found 342.1250

Synthesis of (Z)-*N*-Benzoyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5e):



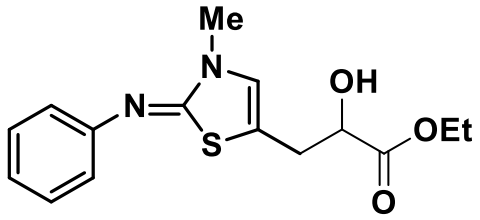
Immediately following synthesis of the thiazolidine, 104 mg (0.45 mmol, 1.0 eq) of **3e** and 186 mg (1.07 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.4 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~117 ºC for 24 h. Compound was purified by silica gel chromatography using 10%, 40%, 60%, and 100% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a pale solid (122 mg, 67%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.37 – 8.30 (m, 2H), 7.52 – 7.41 (m, 5H), 7.41 – 7.35 (m, 1H), 7.31 – 7.21 (m, 2H), 6.81 (s, 1H), 3.78 (s, 3H), 3.30 – 3.21 (m, 2H), 3.10 – 2.94 (m, 2H), 2.65 (dd, J = 18.4, 5.2 Hz, 1H). ^{13}C NMR: 177.4, 174.6, 173.9, 167.1, 136.7, 131.8, 129.4, 129.3, 128.9, 128.2, 126.5, 124.9, 121.2, 40.5, 35.8, 33.8, 28.9. FT-IR (neat, cm^{-1}): 3070, 2920, 2851, 1777, 1704, 1592, 1559, 1382, 1357, 1253, 1168, 995, 863, 716, 690. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{22}H_{19}N_3O_3S$ 406.1220, found 406.1211. m.p. 192-194 ºC

Synthesis of (Z)-*N*-Benzyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine (5f):



Immediately following synthesis of the thiazolidine, 111 mg (0.51 mmol, 1.0 eq) of **3f** and 211 mg (1.22 mmol, 2.4 eq) of N-phenylmaleimide (**4**) were dissolved in 1.4 mL of toluene in a sealed tube. The solution was degassed with N_2 for over 5 minutes followed by 5 minutes of flushing the air in the sealed tube with N_2. The reaction was stirred at ~116 ºC for 24 h. Compound was purified by silica gel chromatography using 25%, 50%, 70%, and 100% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford a dark brown gum (158 mg, 79%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.42 (m, 2H), 7.41 – 7.35 (m, 3H), 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 3H), 6.33 (s, 1H), 4.28 (q, J_{AB} = 15.2 Hz, $\nu_{AB} = 17.5$, 2H), 3.30 (s, 3H), 3.20 – 3.11 (m, 1H), 2.98 – 2.95 (m, 2H), 2.93 (t, J = 9.1 Hz, 1H), 2.64 (dd, J = 18.4, 5.1 Hz, 1H). ^{13}C NMR: 177.9, 175.2, 159.1, 140.4, 131.9, 129.3, 128.9, 128.4, 127.6, 126.8, 126.8, 126.5, 108.4, 58.6, 40.2, 33.6, 33.3, 29.6. FT-IR (neat, cm^{-1}): 3019, 2915, 2847, 1776, 1707, 1627, 1608, 1382, 1331, 1285, 1179, 867, 755, 697, 666. HR-MS (m/z): calcd. for $[M + H]^+$ $C_{22}H_{21}N_3O_2S$ 392.1427, found 392.1400

Synthesis of (Z)-*N*-Phenyl-5-(Ethyl 2-hydroxy-propanoyl)-3-methyl-4-thiazolin-2 imine (7):



100 mg (0.49 mmol, 1.0 eq) of **3a** and 175 mg (3.5 eq) of **6** (ethyl glyoxylate 50% w/w in toluene) were dissolved in 4 mL of toluene in a sealed tube. The reaction was stirred at ~60° C for 1 h. Compound was purified by silica gel chromatography using 20% EtOAc:Hexanes. The fractions containing the product were evaporated in vacuo to afford an amber gum (58.4 mg, 39%). ^{1}H NMR (301 MHz, Chloroform-d) δ 7.36 – 7.23 (m, 2H), 7.09 – 6.97 (m, 3H), 6.39 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.41 (s, 3H), 3.21 – 3.09 (m, 1H), 2.91 (dd, J = 12.1, 3.9 Hz, 1H), 2.78 (dd, J = 15.2, 6.3 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H).

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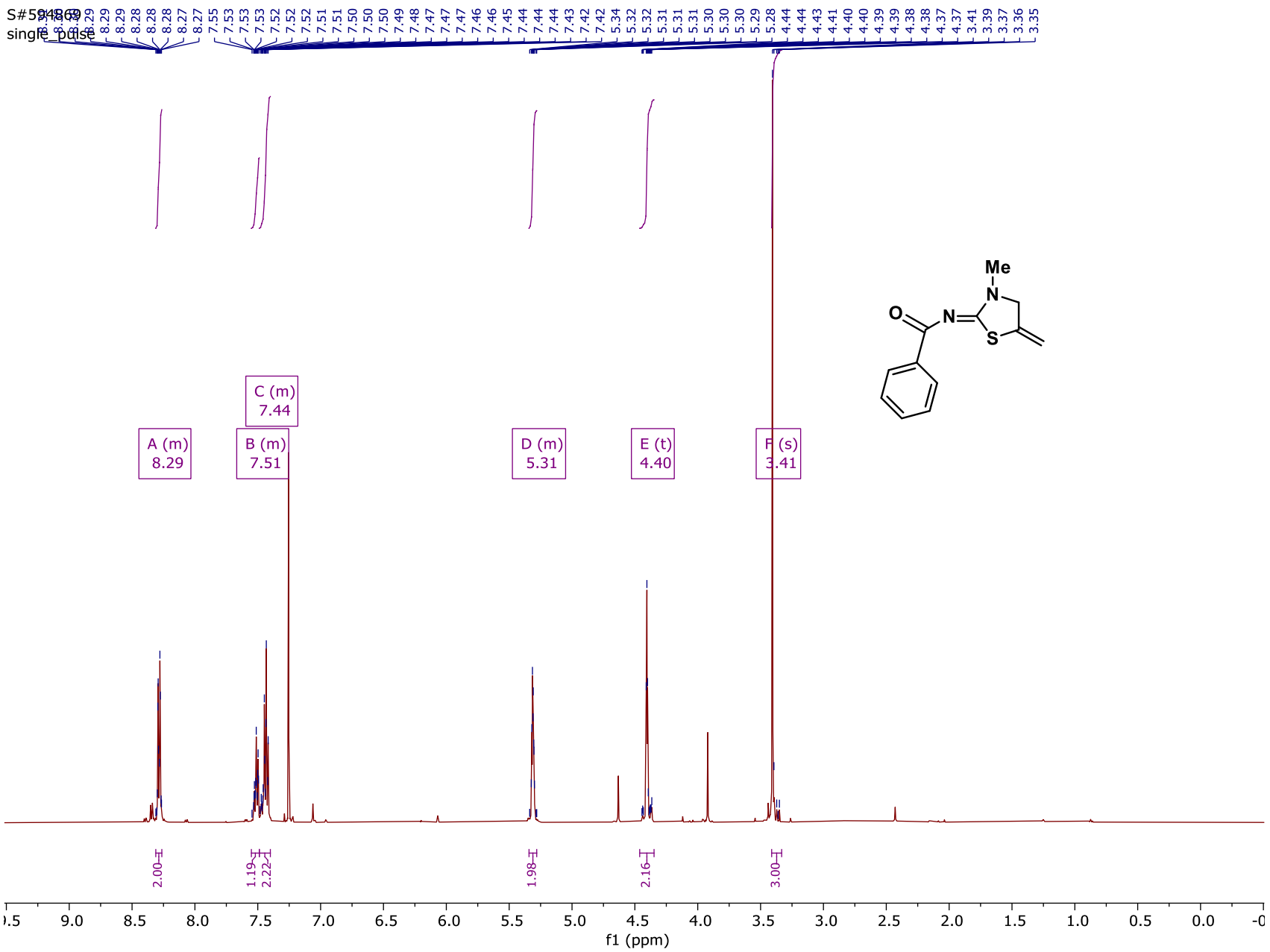
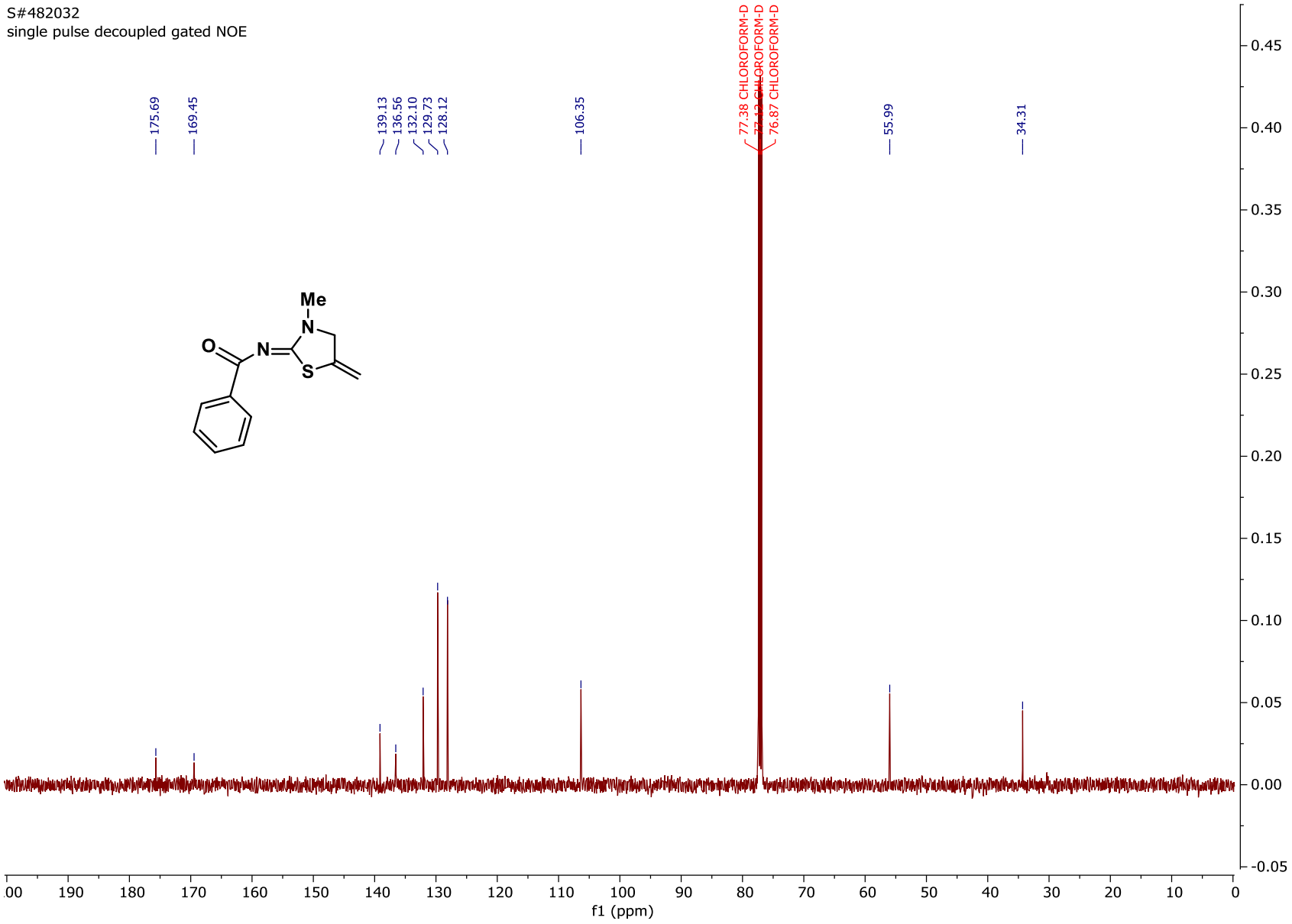
APPENDIX 1 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Benzoyl-5-methylidene-3-methylthiazolidin-2 imine **3e**

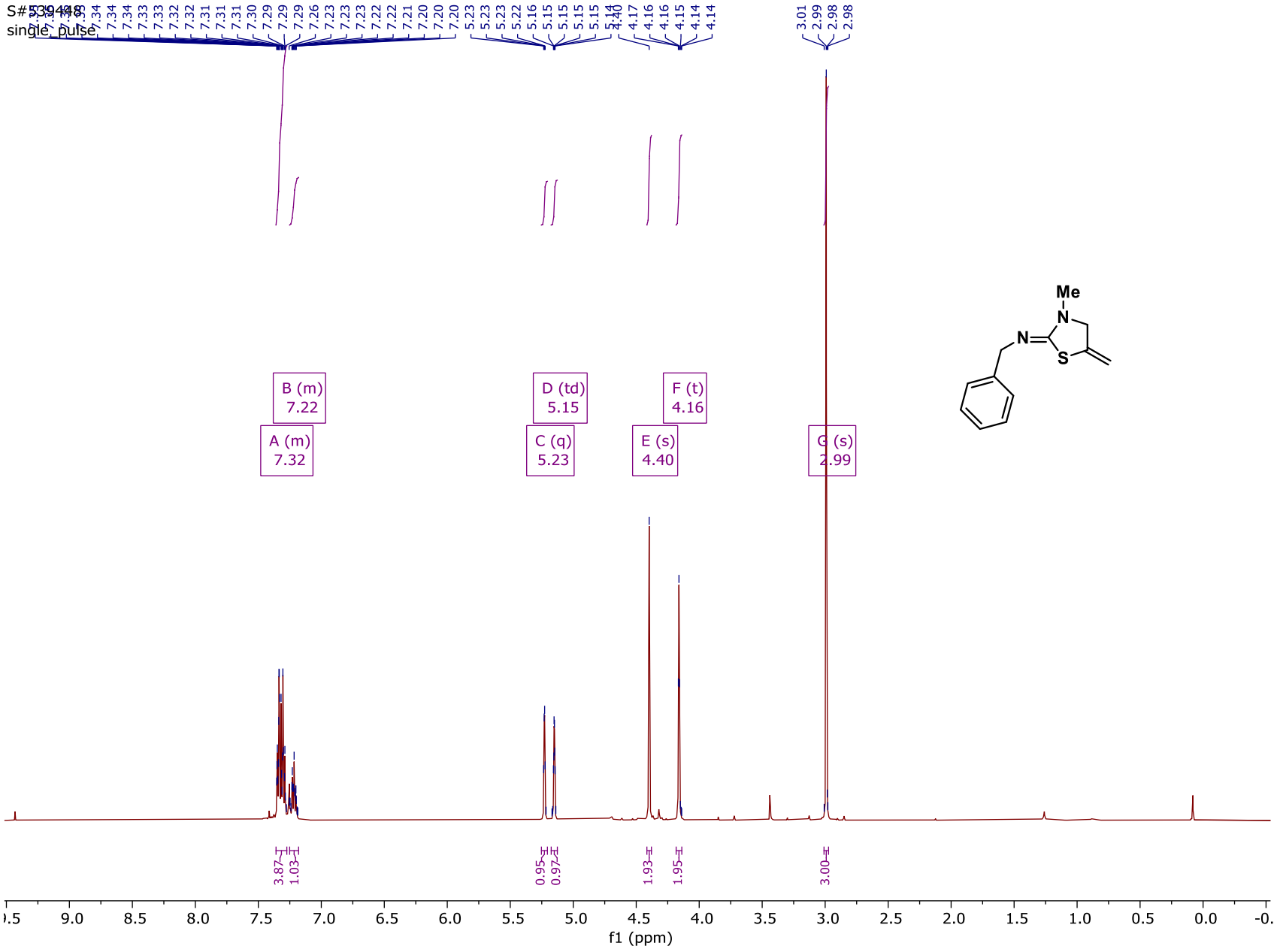
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

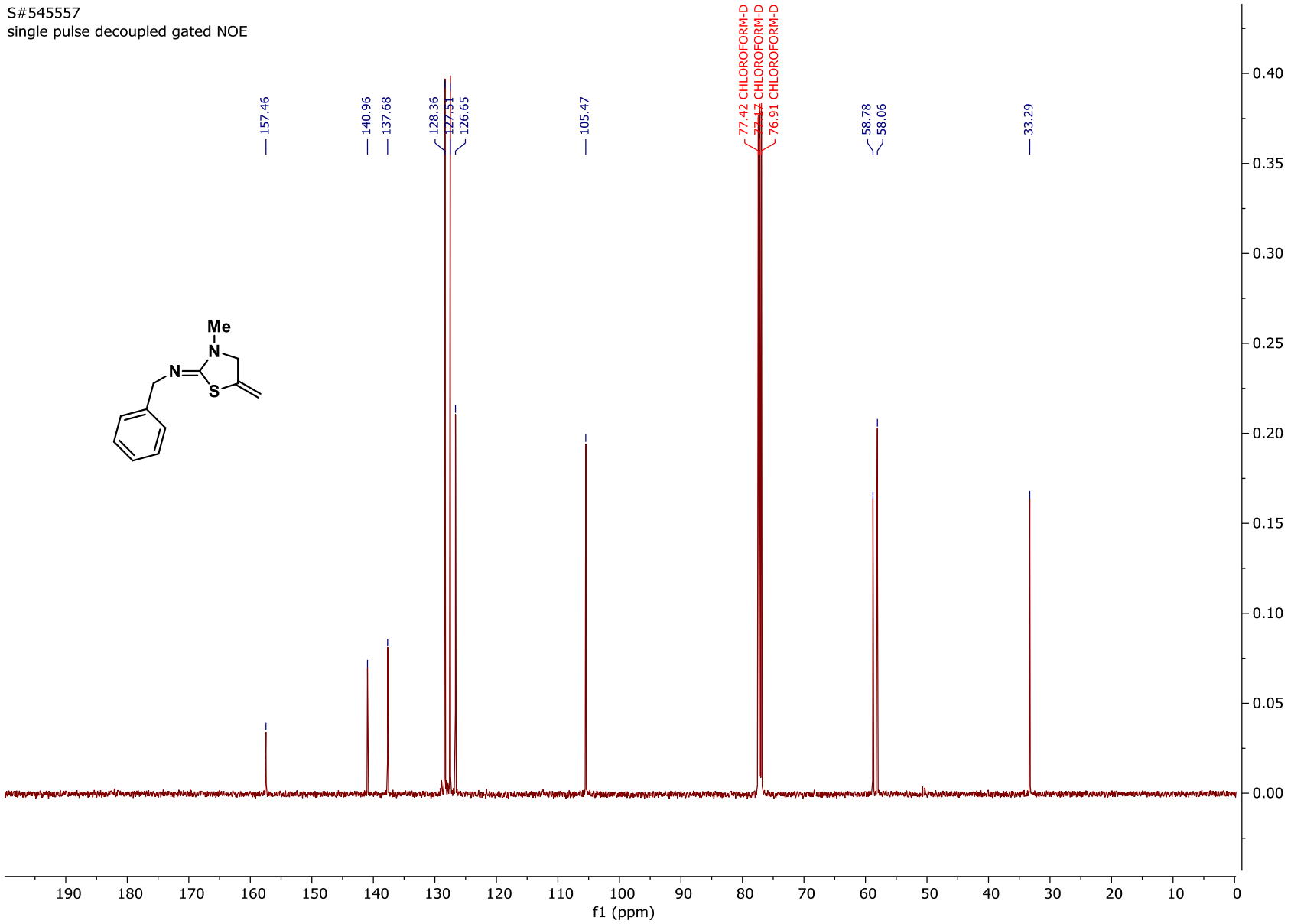

S#594869
single_pulse
A (m)
8.29
B (m)
7.51
C (m)
7.44
D (m)
5.31
E (t)
4.40
F (s)
3.41
2.00
1.19
2.22
1.98
2.16
3.00
f1 (ppm)


S#482032
single pulse decoupled gated NOE
175.69
169.45
139.13
136.56
132.10
129.73
128.12
106.35
77.38 CHLOROFORM-D
77.13 CHLOROFORM-D
76.87 CHLOROFORM-D
55.99
34.31
Me
N
O
N
S
f1 (ppm)

APPENDIX 2 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Benzyl-5-methylidene-3-methylthiazolidin-2 imine **3f**

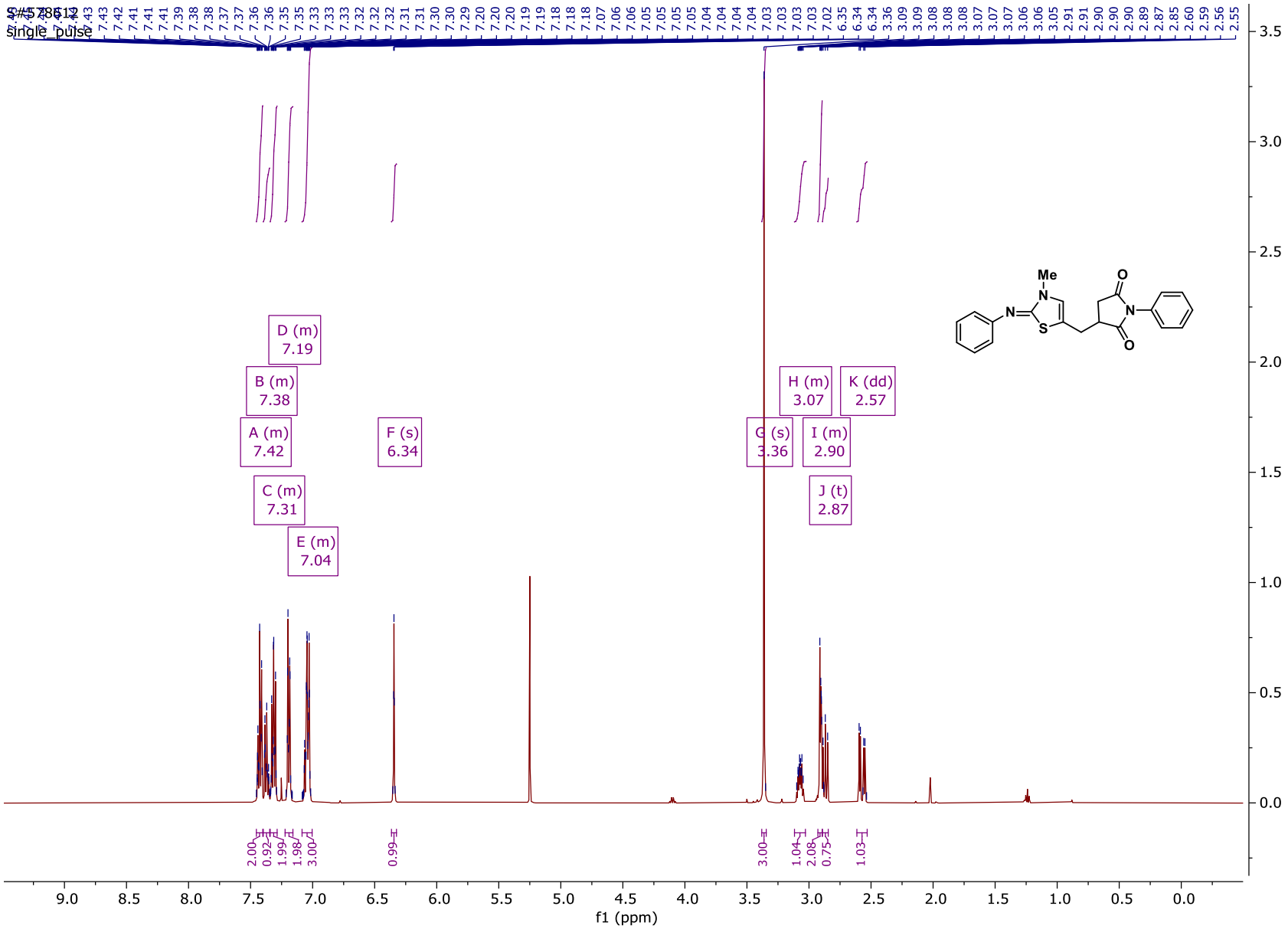
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

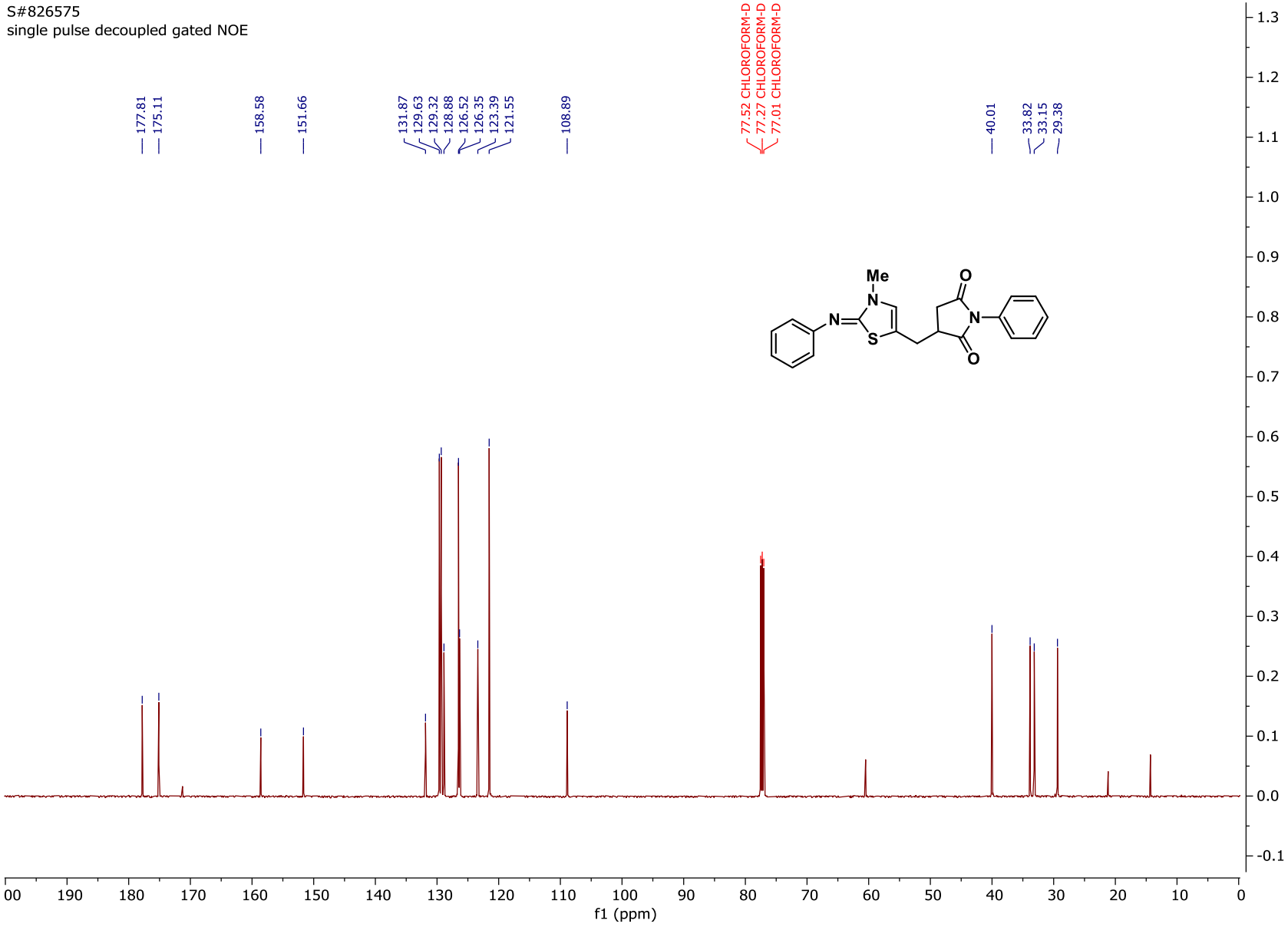

single_pulse
B (m)
7.22
A (m)
7.32
D (td)
5.15
C (q)
5.23
F (t)
4.16
E (s)
4.40
G (s)
2.99
Me
N
N
S
3.87
1.03
0.95
0.97
1.93
1.95
3.00
f1 (ppm)


S#545557
single pulse decoupled gated NOE
157.46
140.96
137.68
128.36
127.51
126.65
105.47
77.42 CHLOROFORM-D
77.17 CHLOROFORM-D
76.91 CHLOROFORM-D
58.78
58.06
33.29
Me
N
N
S
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

APPENDIX 3 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Phenyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5a**

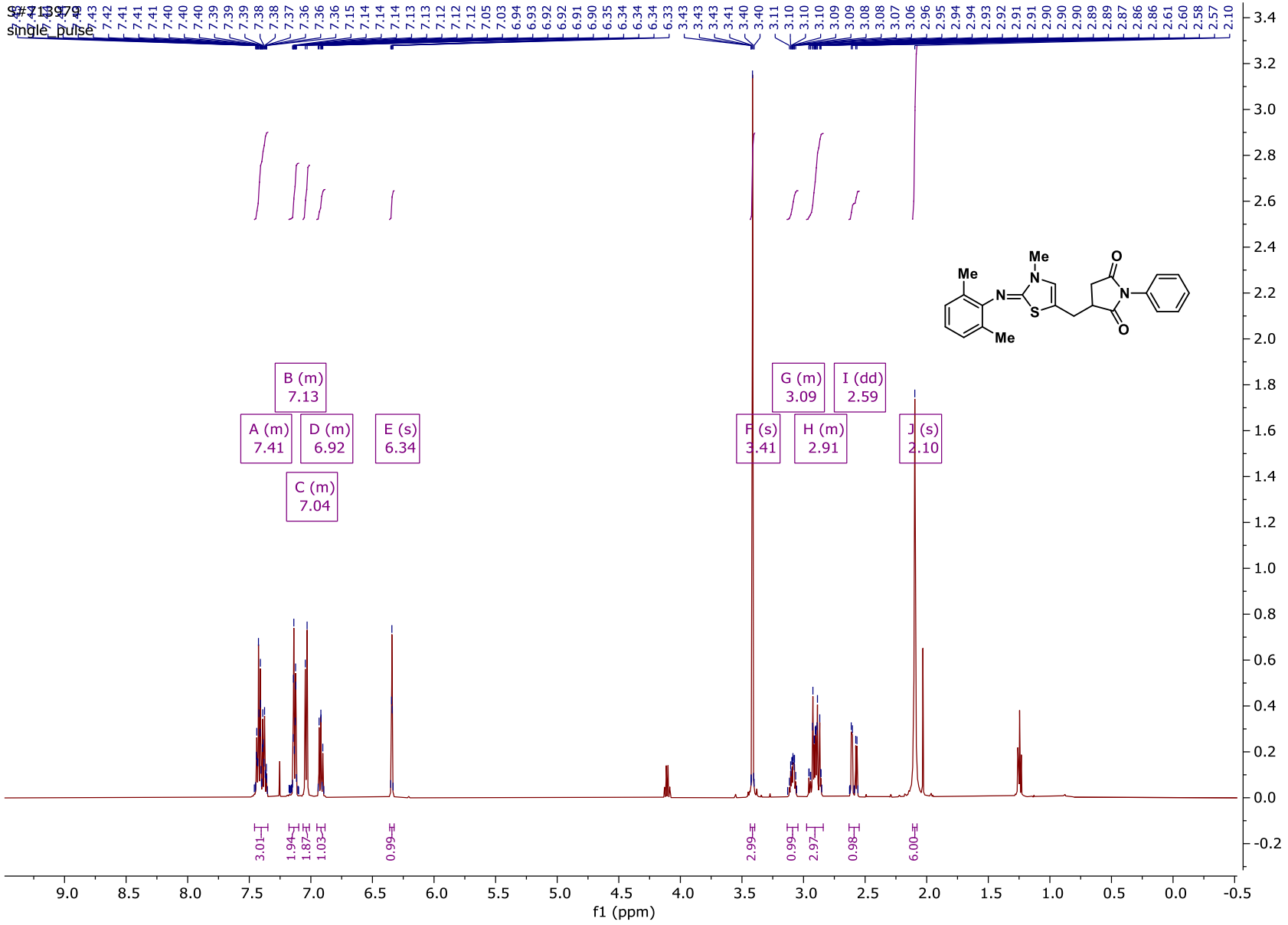
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

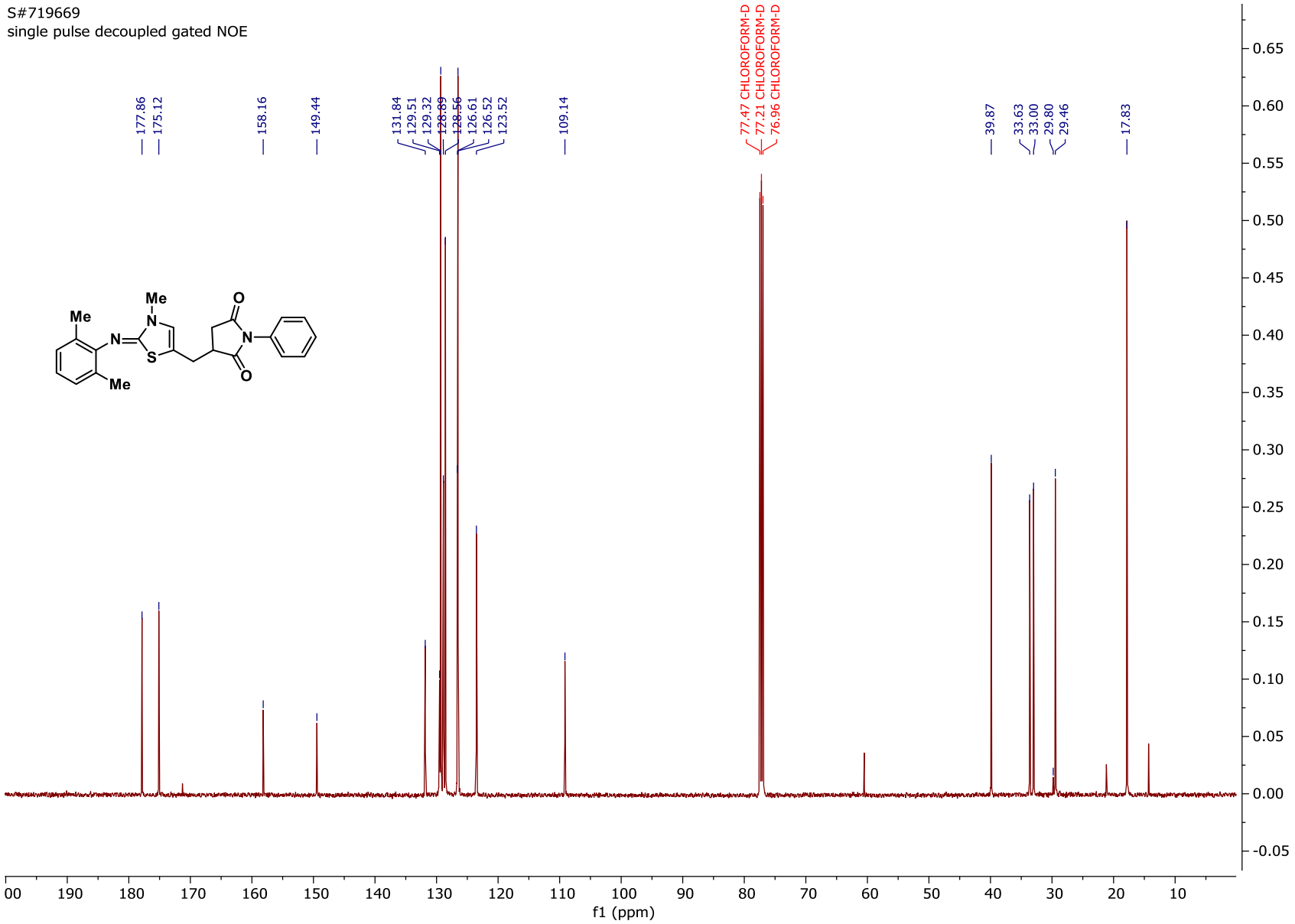

S#578612
single_pulse
D (m)
7.19
B (m)
7.38
A (m)
7.42
C (m)
7.31
E (m)
7.04
F (s)
6.34
G (s)
3.36
H (m)
3.07
I (m)
2.90
J (t)
2.87
K (dd)
2.57
Me
N
S
O
2.00
0.92
1.99
1.98
3.00
0.99
3.00
1.04
2.08
0.75
1.03
f1 (ppm)


S#826575
single pulse decoupled gated NOE
177.81
175.11
158.58
151.66
131.87
129.63
129.32
128.88
126.52
126.35
123.39
121.55
108.89
77.52 CHLOROFORM-D
77.27 CHLOROFORM-D
77.01 CHLOROFORM-D
40.01
33.82
33.15
29.38
Me
N
S
O
f1 (ppm)

APPENDIX 4 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-(2,6-Dimethylphenyl)-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5b**

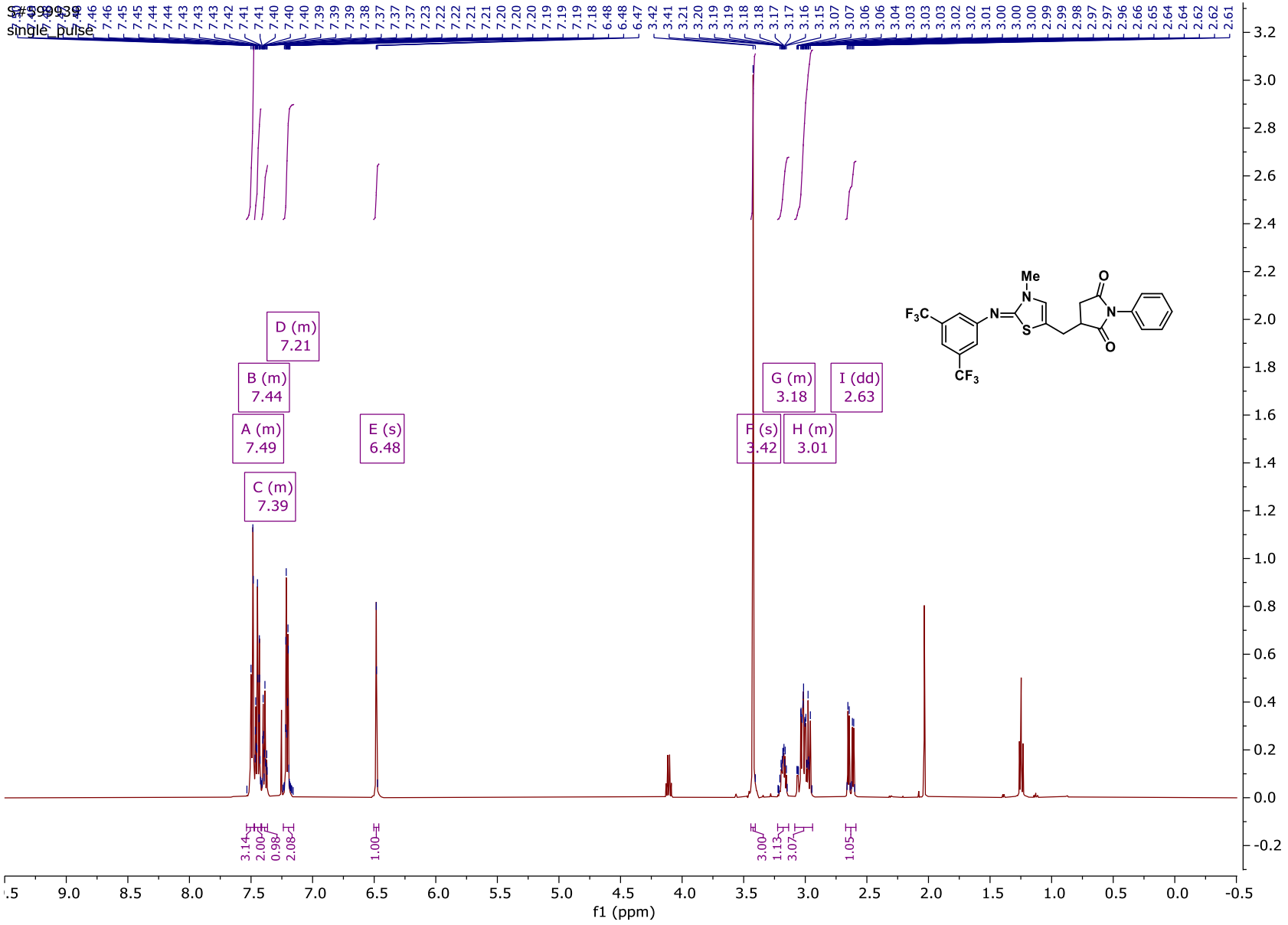
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

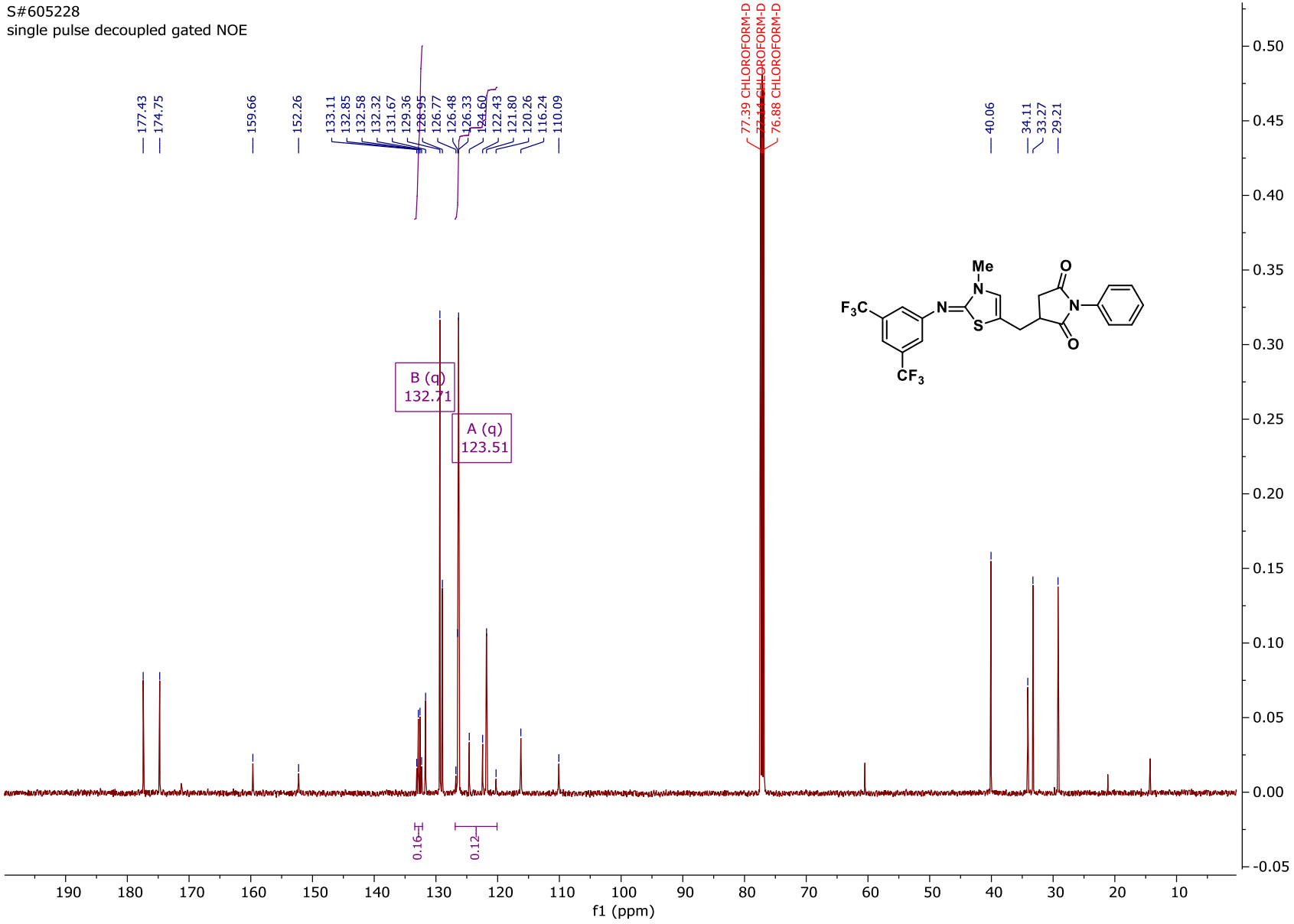

S#13979
single_pulse
B (m)
7.13
A (m)
7.41
D (m)
6.92
E (s)
6.34
C (m)
7.04
G (m)
3.09
I (dd)
2.59
F (s)
3.41
H (m)
2.91
J (s)
2.10
Me
N
S
O
f1 (ppm)


S#719669
single pulse decoupled gated NOE
177.86
175.12
158.16
149.44
131.84
129.51
129.32
128.89
128.56
126.61
126.52
123.52
109.14
77.47 CHLOROFORM-D
77.21 CHLOROFORM-D
76.96 CHLOROFORM-D
39.87
33.63
33.00
29.80
29.46
17.83
Me
Me
Me
N
N
S
O
O
N
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

APPENDIX 5 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-(3,5-Bis-(trifluoromethyl)phenyl)-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5c**

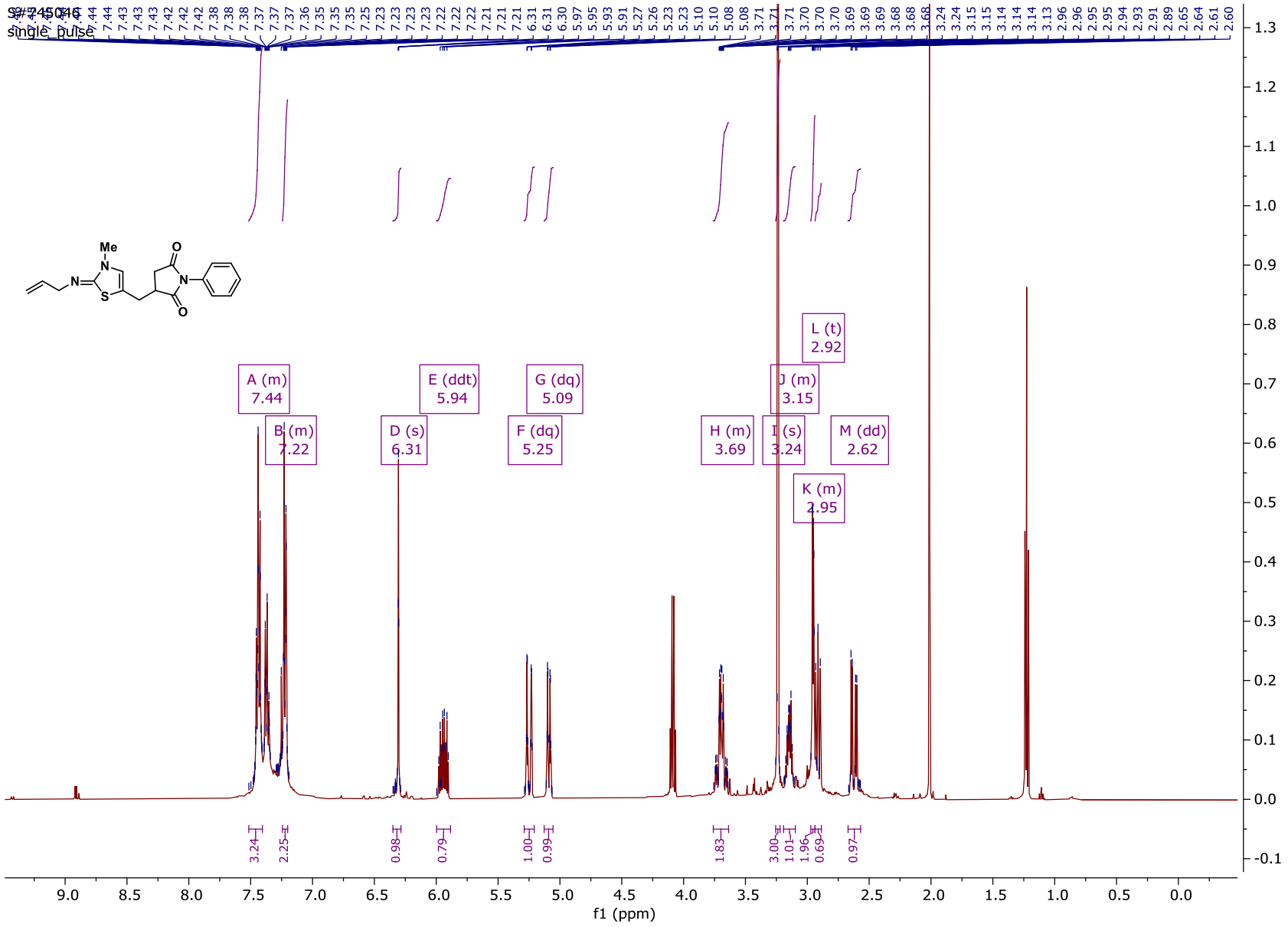
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

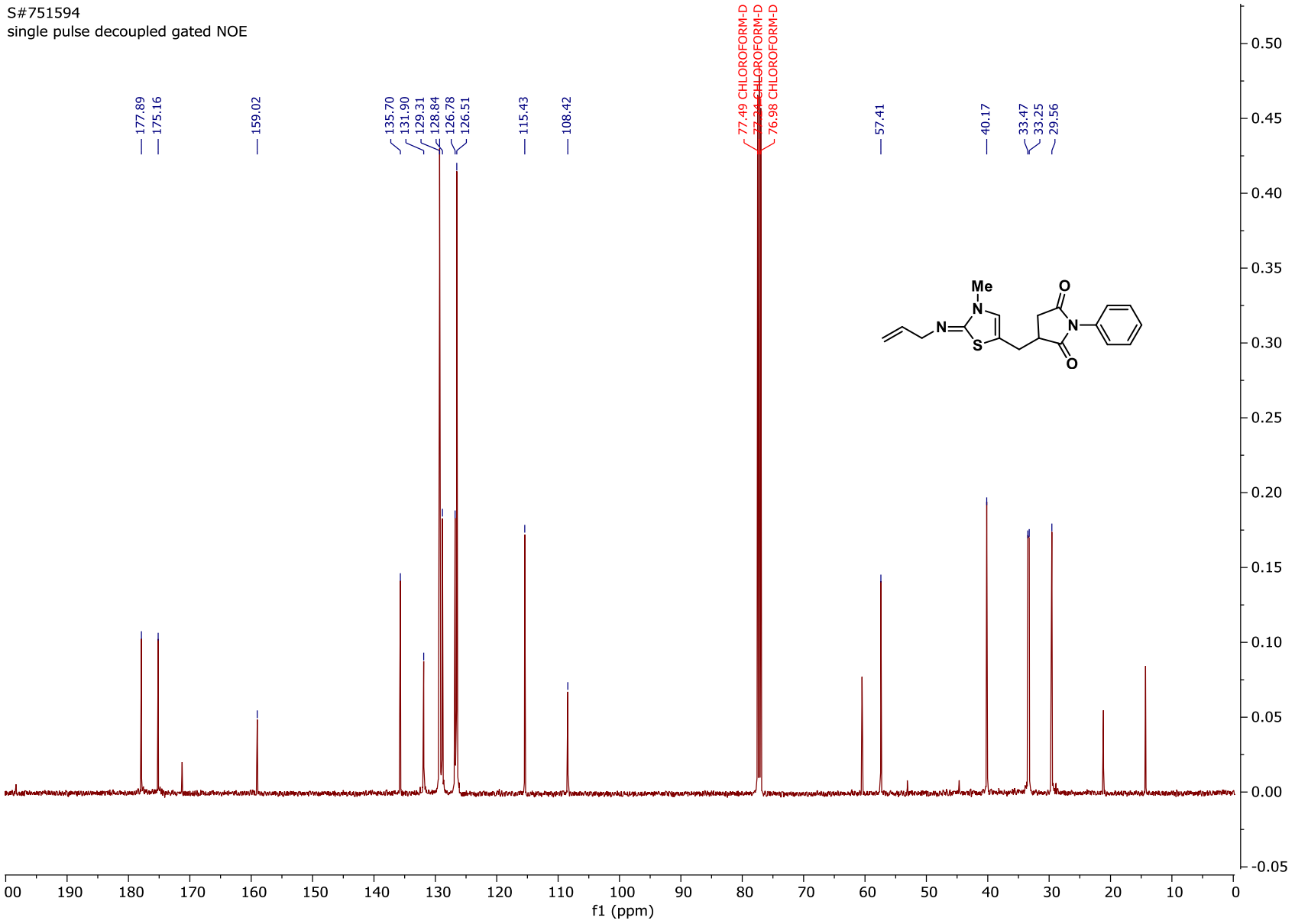

single_pulse
D (m)
7.21
B (m)
7.44
A (m)
7.49
C (m)
7.39
E (s)
6.48
G (m)
3.18
I (dd)
2.63
F (s)
3.42
H (m)
3.01
Me
N
S
O
F3C
CF3
f1 (ppm)


S#605228
single pulse decoupled gated NOE
177.43
174.75
159.66
152.26
133.11
132.85
132.58
132.32
131.67
129.36
128.95
126.77
126.48
126.33
124.60
122.43
121.80
120.26
116.24
110.09
77.39 CHLOROFORM-D
77.14 CHLOROFORM-D
76.88 CHLOROFORM-D
40.06
34.11
33.27
29.21
B (q)
132.71
A (q)
123.51
0.16
0.12
Me
N
F3C
N
S
O
N
O
CF3
f1 (ppm)

APPENDIX 6 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Allyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5d**

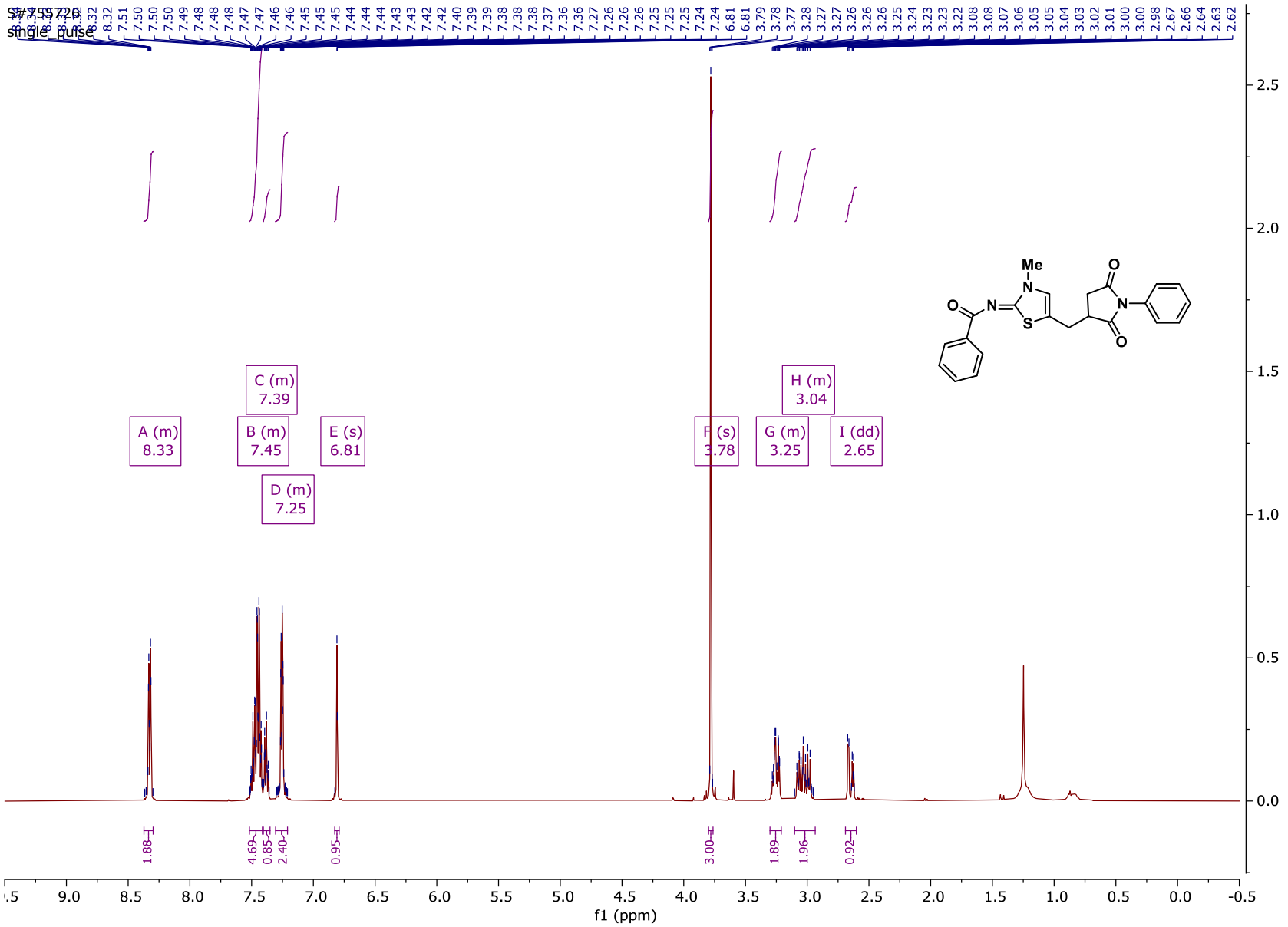
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

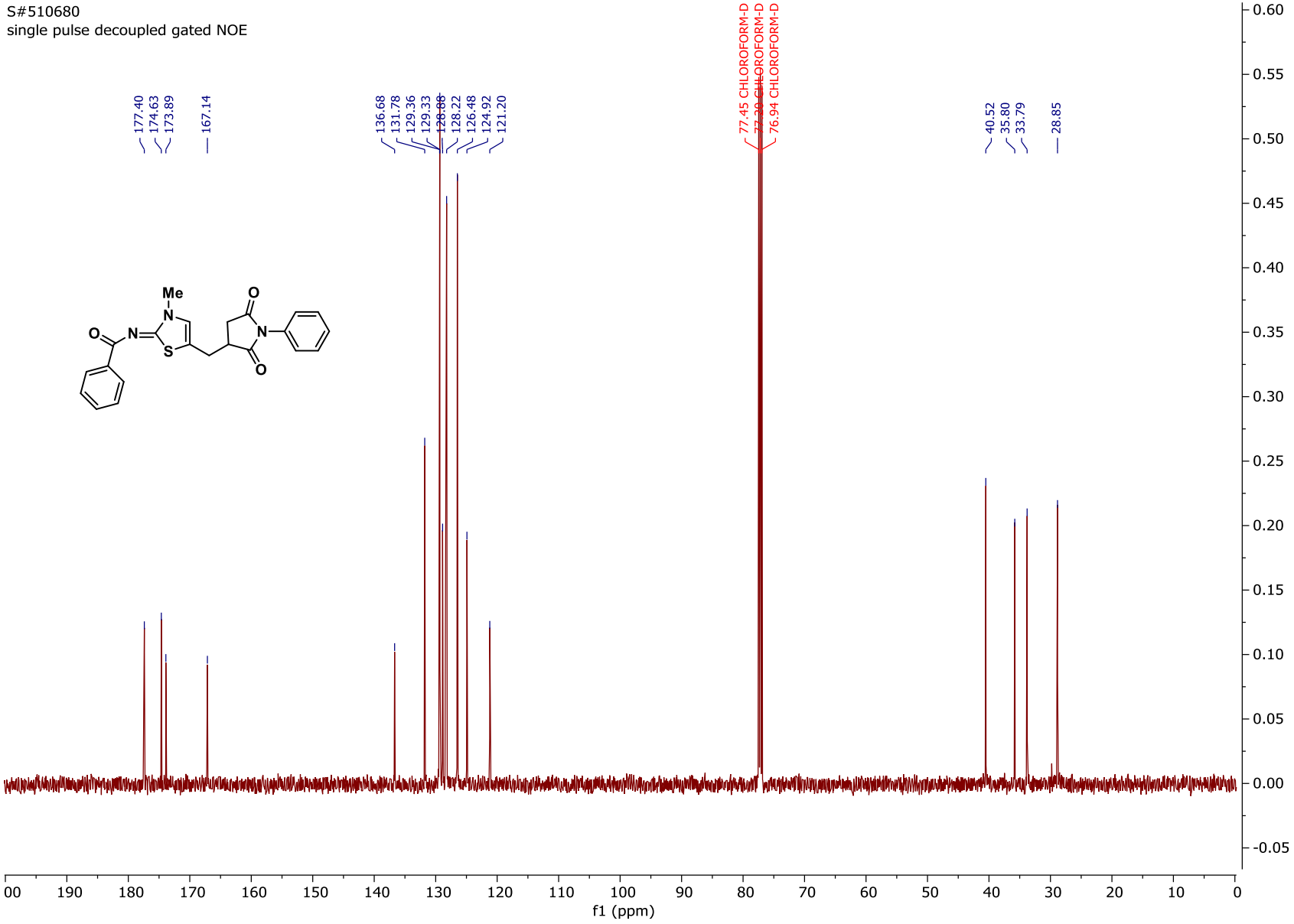

S#745046
single_pulse
A (m)
7.44
B (m)
7.22
D (s)
6.31
E (ddt)
5.94
F (dq)
5.25
G (dq)
5.09
H (m)
3.69
I (s)
3.24
J (m)
3.15
K (m)
2.95
L (t)
2.92
M (dd)
2.62
3.24
2.25
0.98
0.79
1.00
0.99
1.83
3.00
1.01
1.96
0.69
0.97
f1 (ppm)


S#751594
single pulse decoupled gated NOE
177.89
175.16
159.02
135.70
131.90
129.31
128.84
126.78
126.51
115.43
108.42
77.49 CHLOROFORM-D
77.24 CHLOROFORM-D
76.98 CHLOROFORM-D
57.41
40.17
33.47
33.25
29.56
Me
N
O
S
f1 (ppm)

APPENDIX 7 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Benzoyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5e**

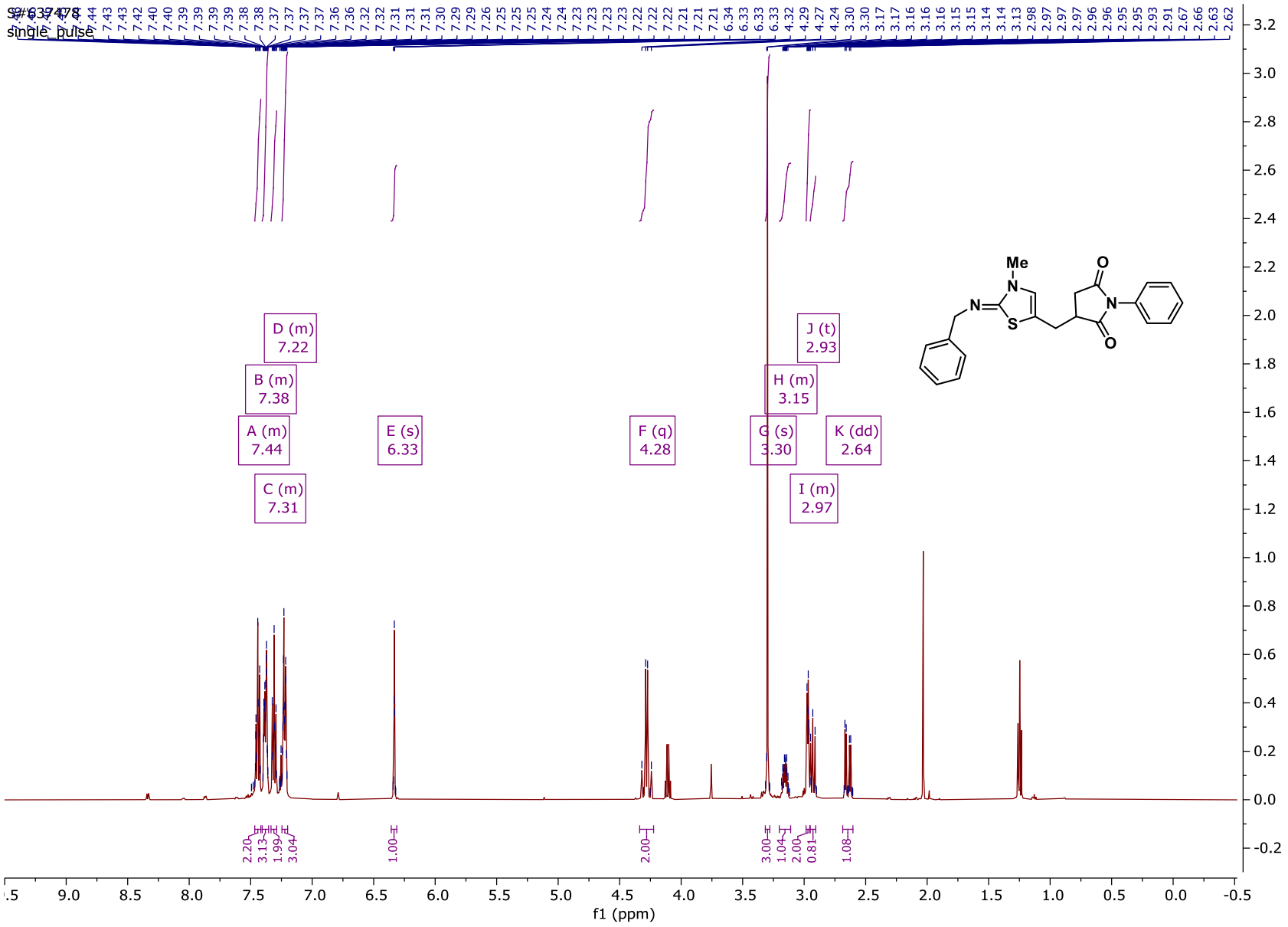
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform

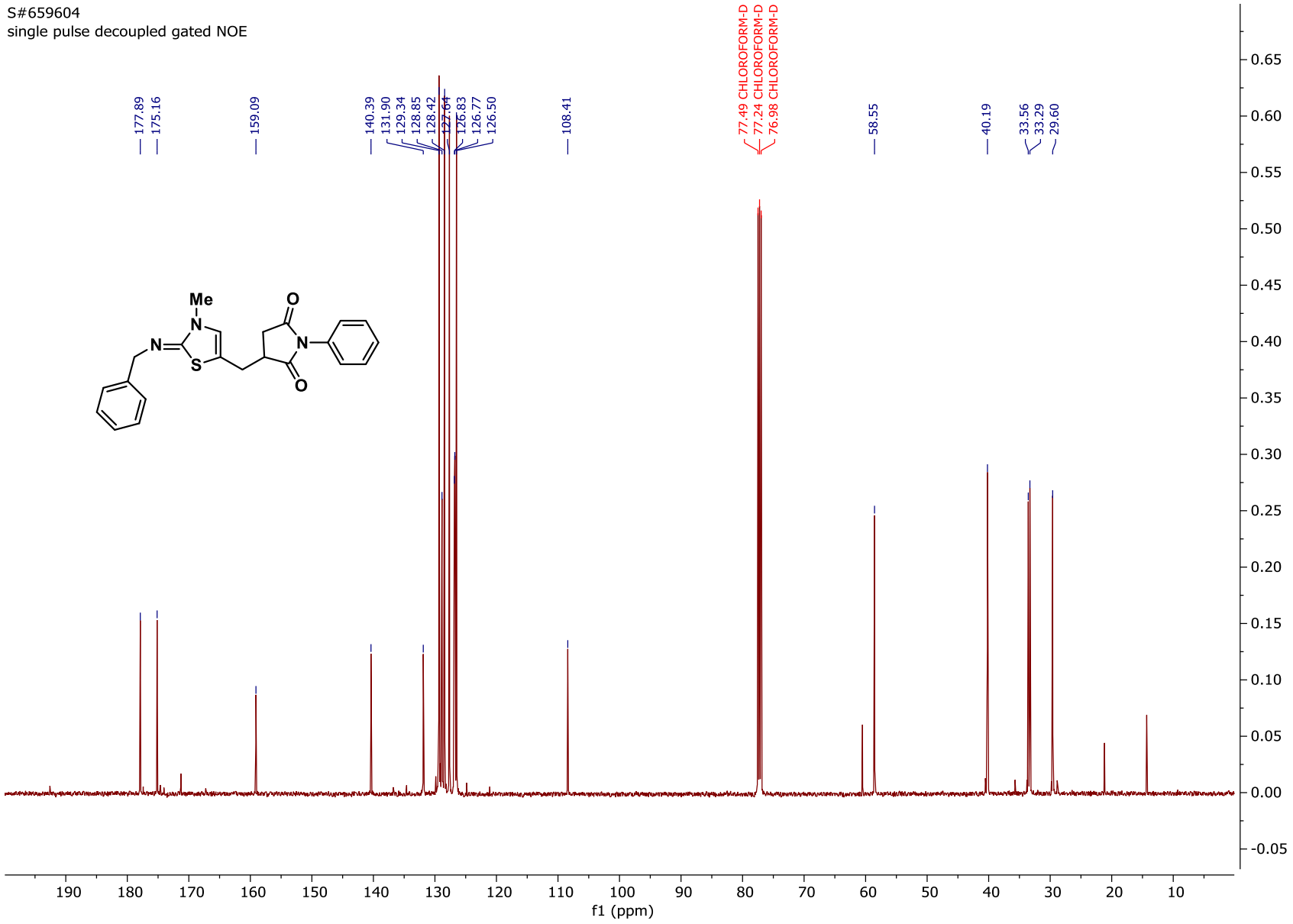

single_pulse
A (m)
8.33
B (m)
7.45
C (m)
7.39
D (m)
7.25
E (s)
6.81
F (s)
3.78
G (m)
3.25
H (m)
3.04
I (dd)
2.65
Me
N
O
O
N
S
N
O
O
1.88
4.69
0.85
2.40
0.95
3.00
1.89
1.96
0.92
f1 (ppm)


S#510680
single pulse decoupled gated NOE
177.40
174.63
173.89
167.14
136.68
131.78
129.36
129.33
128.88
128.22
126.48
124.92
121.20
77.45 CHLOROFORM-D
76.94 CHLOROFORM-D
40.52
35.80
33.79
28.85
Me
N
O
N
S
O
N
O
O
f1 (ppm)

APPENDIX 8 - ^{1}H NMR and ^{13}C NMR Spectra of (Z)-*N*-Benzyl-5-(2-methylidene-N-phenylsuccinimidyl)-3-methyl-4-thiazolin-2 imine **5f**

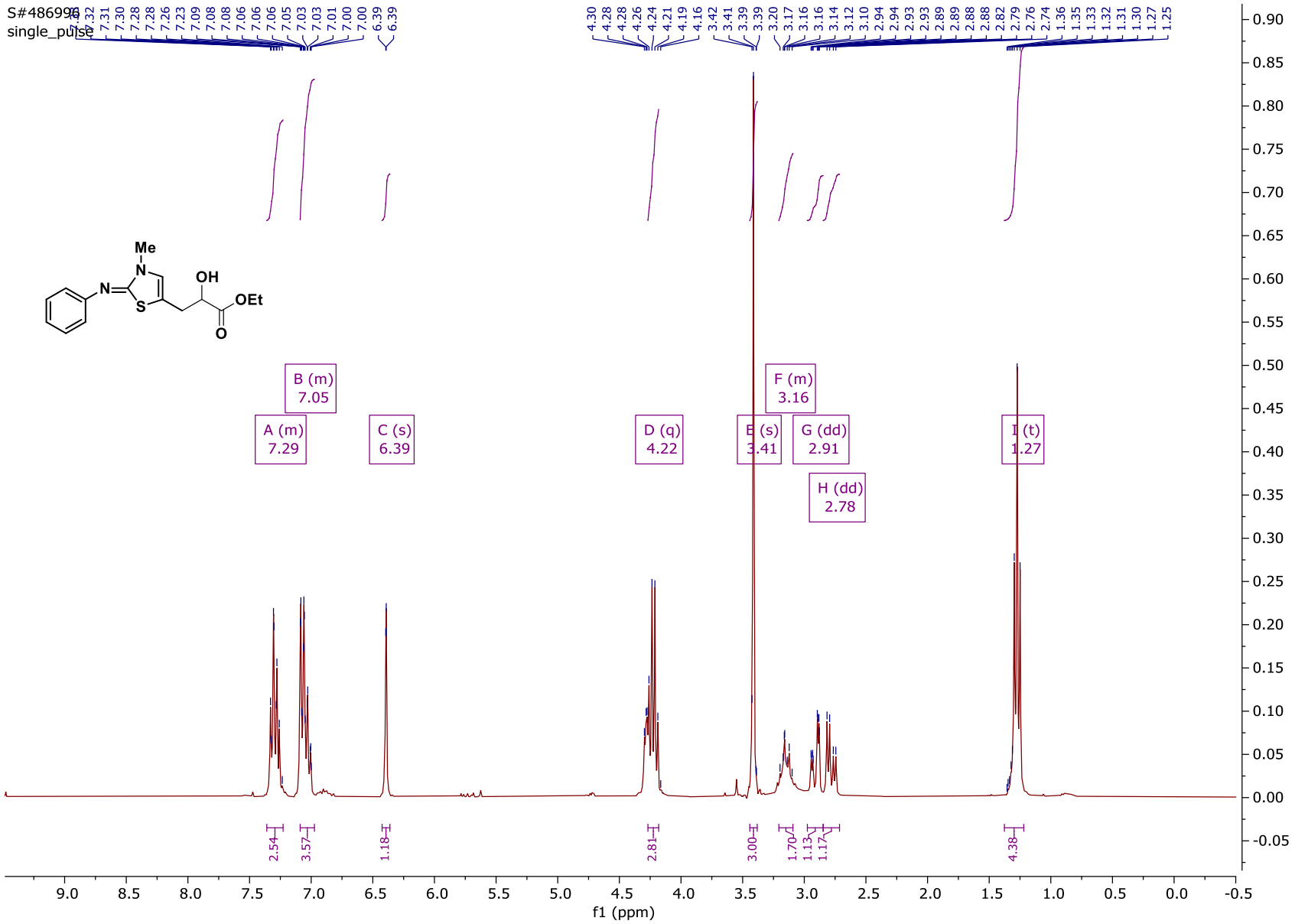
Measured on JEOL Eclipse+ 500 MHz Spectrometer in Deuterated Chloroform


S#637478
single_pulse
D (m)
7.22
B (m)
7.38
A (m)
7.44
C (m)
7.31
E (s)
6.33
F (q)
4.28
J (t)
2.93
H (m)
3.15
G (s)
3.30
K (dd)
2.64
I (m)
2.97
Me
N
S
O
f1 (ppm)


S#659604
single pulse decoupled gated NOE
177.89
175.16
159.09
140.39
131.90
129.34
128.85
128.42
127.64
126.83
126.77
126.50
108.41
77.49 CHLOROFORM-D
77.24 CHLOROFORM-D
76.98 CHLOROFORM-D
58.55
40.19
33.56
33.29
29.60
Me
N
N
S
O
N
O
f1 (ppm)

APPENDIX 9 - ^{1}H NMR Spectra of (Z)-*N*-Phenyl-5-(Ethyl 2-hydroxy-propanoyl)-3-methyl-4-thiazolin-2 imine **7**

Measured on JEOL ECX 300 MHz Spectrometer in Deuterated Chloroform


S#486996
single_pulse
Me
N
OH
N
S
OEt
O
B (m)
7.05
A (m)
7.29
C (s)
6.39
D (q)
4.22
F (m)
3.16
E (s)
3.41
G (dd)
2.91
H (dd)
2.78
I (t)
1.27
2.54
3.57
1.18
2.81
3.00
1.70
1.13
1.17
4.38
f1 (ppm)