Title
New Reactions and Synthetic Strategies: Radical Functionalization and Transnitrosation

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New Reactions and Synthetic Strategies: Radical Functionalization and Transnitrosation

By

Jordan Galloway

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

In

Chemistry and Chemical Biology

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The Dissertation of Jordan Galloway is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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University of California, Merced

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Dedication

This is dedicated to my brother Jeffrey.

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LIST OF ABBREVIATIONS

°C – degrees Celsius

Ac – acetyl

AcOH – acetic acid

$AgNO_3$ – silver Nitrate

aq – aqueous

Bn – benzyl

BNTS – *N*-Benzyl-*N*-nitroso-*p*-toluenesulfonamide

DCE – 1,2-dichloroethane

DCM – dichloromethane

DMBS – dimethylbenzylsulfonamide

EtOAc – ethyl acetate

EtOH – ethanol

g – grams

GCMS – gas chromatography–mass spectrometry

h – hours

HAT – hydrogen atom transfer

hv – Planck constant

Hz – Hertz

MeCN – acetonitrile

MeOH – methanol

min – minute

$NaNO_2$ – sodium nitrite

NFSI – *N*-Fluorobenzenesulfonimide

nm – nanometer

NMR – Nuclear Magnetic Resonance

NMTS – *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide

NO – nitric oxide

PC – photocatalyst

Ph – phenyl

Py – pyridine

SET – single-electron transfer

TBN – *tert*-butyl nitrite

tBu-ONO – *tert*-butyl nitrite

TFA – trifluoroacetic acid

TFT – α,α,α-trifluorotoluene

THF – tetrahydrofuran

TLC – thin layer chromatography

U.S. FDA – United States Food and Drug Administration

UV-vis – ultraviolet–visible spectroscopy

LIST OF FIGURES

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I would like to express my deepest gratitude to my advisor, Professor Ryan Baxter. Your supervision and support has made this experience a spirited journey that has led to some very cool discoveries. It has been a privilege to be in your lab.

Thank you to all the members of my committee, Professor Erik Menke, Professor Benjamin Stokes, Dr. Archana Kumar, and Professor Rebeca Arevalo, for your support and guidance.

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PUBLICATIONS

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ABSTRACT OF THE DISSERTATION

New Reactions and Synthetic Strategies: Radical Functionalization and Transnitrosation

By

Jordan Galloway

Doctor of Philosophy in Organic Chemistry

University of California, Merced, 2020

Professor Erik Menke, Chair

Professor Ryan Baxter, Advisor

The following dissertation discusses the development of Selectfluor mediated Minisci reactions leading to functionalized heterocycles and quinones. These investigations include a wide variety of heterocycles and quinones that can be functionalized in one step allowing for access to more complex structures while retaining the essential backbone. Mechanistic investigations and direct comparisons to other harsher oxidants are considered. Novel transnitrosating reagents were developed allowing for nitroso compounds in one step when thermally initiated. Considerations for other applications for this novel reagent are discussed as well.

Chapter 1. Overview of Minisci reactions

Abstract. Overview of Minisci reactions, limitations and new developments are described. Our in-house method for silver-catalyzed Minisci reactions using Selectfluor as a mild oxidant is discussed.

Background

Heterocycles and quinones are chemical motifs present in many biologically active compounds targeted by pharmaceutical and agrochemical industries.[1] The pyridine core is the second most common nitrogen heterocycle found in U.S. FDA approved pharmaceuticals.[1] Examples include antihistamines for the treatment of hay fever, and papaverine for the treatment of visceral spasm and vasospasm. Simple quinone structures have cytotoxic properties useful in anticancer treatments, while heterocycles have been useful in mesenteric ischemia treatments (Figure 1-1).

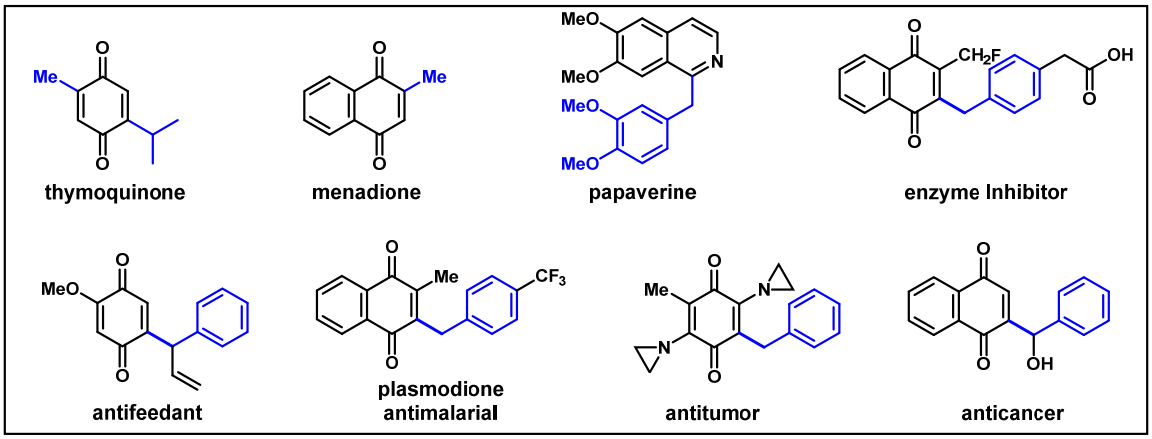

Figure 1-1. Examples of biologically active heterocycles and quinones

Functionalized quinones are well-established as oxidants for organic and organometallic transformations, and are also important structural motifs in

biologically active molecules.[2] Simple quinone structures have shown potent biological activity and have been utilized by pharmaceutical and agrochemical industries.[3-5] Thymoquinone has been used to treat cardiovascular diseases, while Menadione has previously been used as a nutritional supplement. Benzylated quinones have demonstrated enzyme inhibition,[6] antitumor,[7] anticancer,[8] and antifeedant[9] properties (Figure 1-1). A benzylated adduct of menadione is responsible for the high potency and antimalarial properties of plasmidione towards blood-stage parasites.[10,11]

Importance of the Minisci Reaction in Heteroarene and Quinone Functionalization

A simple, one-step synthetic method leading to a diverse array of heteroarenes and quinone derivatives from a common precursor is continuously sought after.[12] Currently, the modification of these molecules, especially quinones, is not trivial. In an ideal scenario, numerous derivatives would be accessible through the manipulation of a common substrate structure at any stage of a synthesis using mild and economically viable reagents. One method for direct functionalization of these compounds is the Minisci reaction, developed in 1971 by Francesco Minisci (Figure 1-2A).[13] This reaction involves stoichiometric Ag(I) radical, an excess alkyl carboxylic acid as the radical precursor, and inorganic persulfates ($S_2O_8^{2-}$) as the oxidant. The reaction is run at elevated temperatures in fuming sulfuric acid. Once the alkyl radical is generated, this radical adds to the substrate to afford an aminyl radical cation, which is oxidized to afford the alkylated compound (Figure 1-2B).

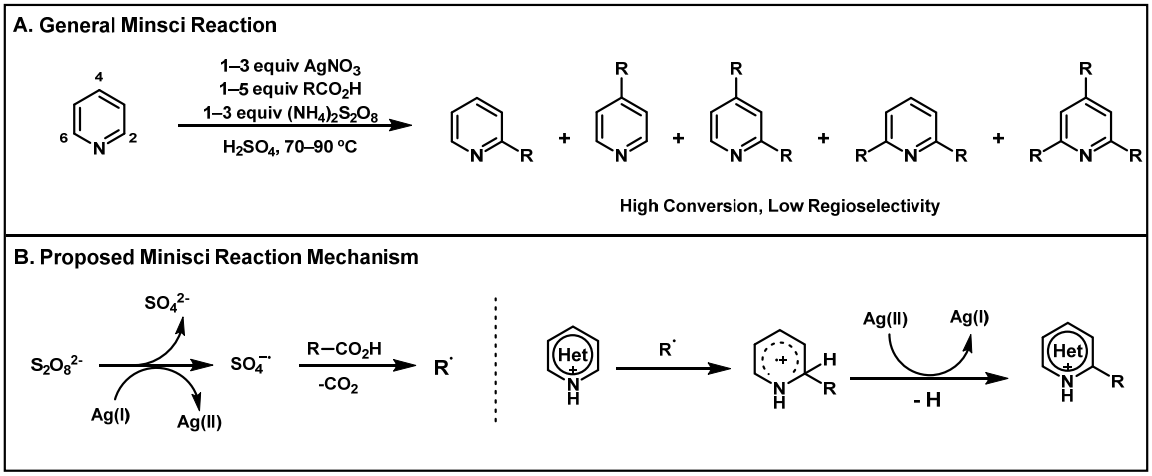

Figure 1-2. A. General conditions for the Minisci reaction. B. Mechanism for the Minisci reaction.

A few drawbacks of this method described in Figure 1-2A include harsh conditions, likely over-oxidation and decomposition of sensitive functional groups, and the requirement of carboxylic acid as the radical precursor. This motivated research groups to pursue other radical precursors and metals as well as milder conditions to increase the synthetic utility (Figure 1-3).[14]

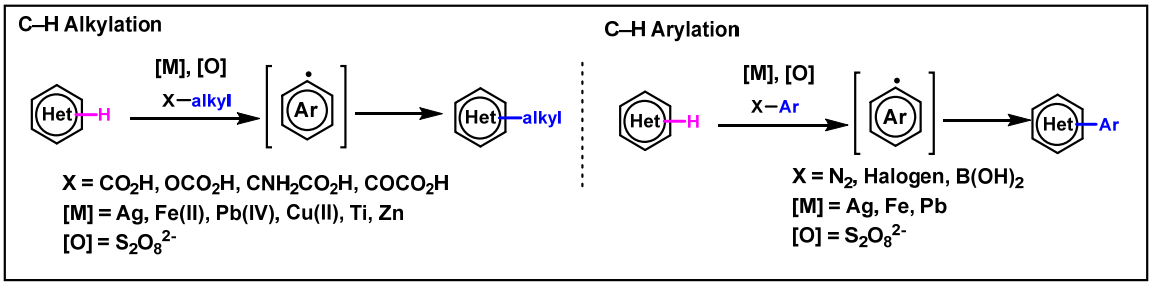

Figure 1-3. Summary of general conditions for Minisci reactions.

Some of the recent advances in the Minisci reaction were reported by the Baran group, who discovered that boronic acids and trifluoroborate salts could serve as aryl, allyl and some alkyl radicals.[14] A variety of heterocycles were functionalized in good yields across a broad range of boronic acids and trifluoroborate salts.

However, the requirement for persulfate salts as oxidants did not allow for the functionalization of heterocycles such as caffeine. Primary alkyl carboxylic acid and boronic acids typically provided low conversion and yields.

Drawing inspiration from Langlois,[15] the Baran group recognized that zinc and sodium sulfonates could readily be expanded as bench-stable radical precursors to access standard alkyl and alkyl fluorinated radicals for heterocycle functionalization.[16] The Baran Diversinates™ are sulfinate reagents that are used as alkylating reagents in the functionalization of (hero)arenes. They react with a variety of (hetero)arene cores, greatly expanded the Minisci reaction toolkit medicinal chemists to access (Figure 1-4). The proposed mechanism follows a single-electron transfer from the peroxide, releasing alkyl radicals and SO_2 gas.

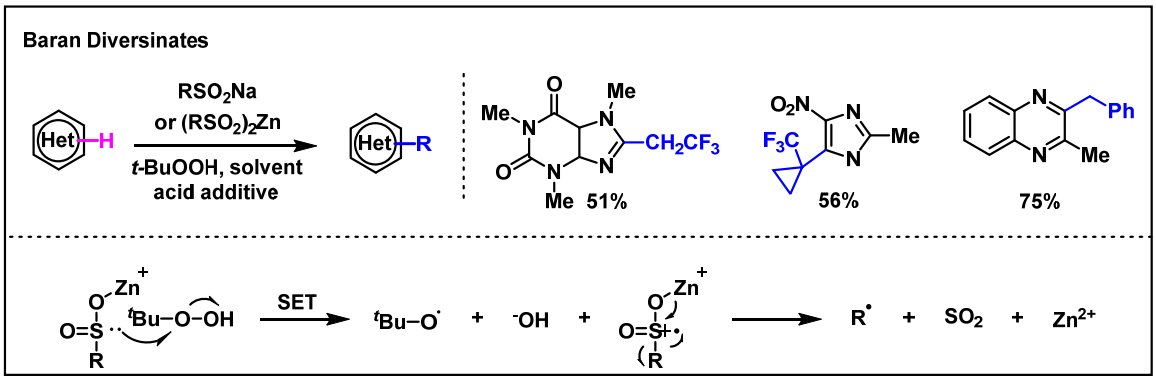

Figure 1-4. Select examples of Baran Diversinates.

Ongoing Challenges of the Minisci Reaction

The Minisci reaction tends to produce mixtures of isomers and byproducts as a result of the generation of highly reactive radicals resulting in multiple radical additions. Understanding reactivity, regioselectivity, and rates under different reaction conditions is ongoing to improve this important reaction. The issue of

regioselectivity still remains one of the outstanding challenges in Minisci chemistry; reactivity studies have been described by Minisci and further investigated in 2013 by Baran and Blackmond.[17] Initial mechanistic studies by Minisci suggested that the combination of silver and persulfate rapidly generated a high concentration alkyl radicals. Baran and Blackmond further investigated and summarized the findings of Minisci with new mechanistic studies focused on the Borono-Minisci reaction with persulfate and came to the conclusions that the selectivity is guided by innate and conjugate reactivity (‘see below’) of heterocycle used.

As shown in Figure 1-5A, aromatic C–H reactivity is dependent on electron density. The more electron deficient the heterocycle, the better it will couple to the nucleophilic radials generated on aryl and alkyl partners. In Figure 1-5B, conjugate reactivity is observed when π delocalization is present with electron withdrawing groups. This contributes to electron deficiency at the positions *ortho* and *para* to the substituent on a heterocyclic ring. The reactivity of 4-methoxypyridine, an electron rich pyridine shown in Figure 1-5C, reacts at the C-3 and C-5 position of the pyridine ring with electrophilic radicals. This is not observed with 4-cyanopyridine, which only reacts with nucleophilic radicals. Lastly, as shown in Figure 1-5D, an acid additive protonates the nitrogen creating a positive charge and accentuates the electrophilicity of heterocycles at the C-2 and C-5 position. In addition to these findings, the Baran and Blackmond group describes how the changes in pH, solvent, functional groups, and the nature of the radical generated all influence the product distribution in these reactions (Figure 1-5).

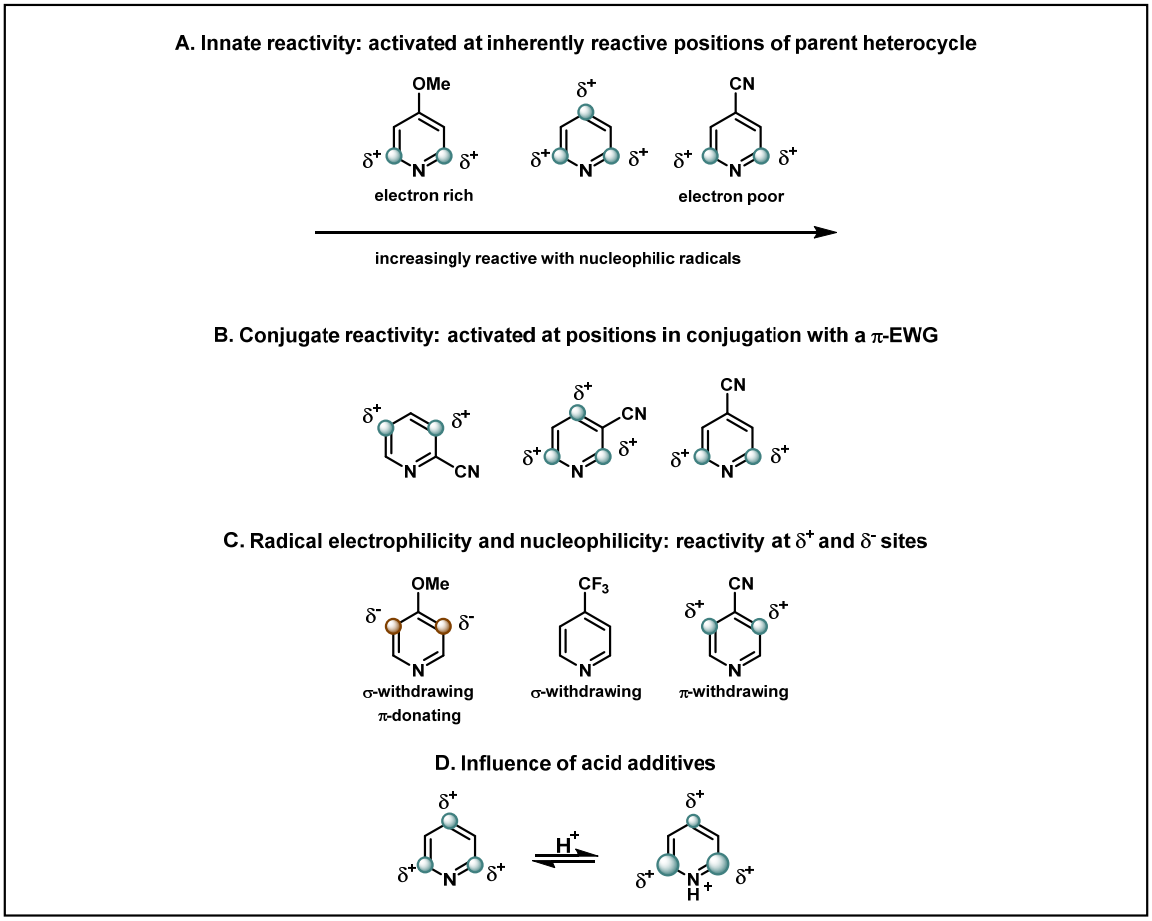

Figure 1-5. The regioselectivity of the Minisci reaction.

The reactivity for Minisci-type reactions is increased when the substrate is electron deficient bearing substituents that delocalize electron density from the ring. This builds up partial positive charge at select areas within the ring allowing them to couple with nucleophilic radicals. Under acidic conditions, the regioselectivity can favor and in some cases override innate reactivity of the heterocycle. The regioselectivity and reactivity can also change in quinones depending on inductive and resonance effects built into the substrate with electron withdrawing substituents. Substituents can, in some cases, override innate regioselectivity and provide predictable product distribution in acidic media.

These mechanistic studies have either focused on persulfate oxidants. However, other oxidants such as Selectfluor have not been studied in-depth or employed in the Minisci reactions.

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Chapter 2. Selectfluor-Mediated Minisci Reactions

Abstract. Silver-catalyzed Minisci reactions using Selectfluor as a mild oxidant is discussed. Heteroarenes and quinones both participate in radical C–H alkylation and arylation from a variety of carboxylic and boronic acid radical precursors. This method was extended to other radical precursors via a C–H abstraction mechanism leading to benzylated quinones using Selectfluor and catalytic Ag(I) initiators. This reaction occurs under mild conditions and is effective for a variety of quinones and radical precursors bearing primary benzylic carbons. The use of pre-formed $Ag(4–OMePy)_2NO_3$ as a catalyst proved effective in desired product formation. A survey of radical additions to quinones is reported with different oxidants being compared. Carboxylic acids, aldehydes, and unprotected amino acids are compared as alkyl radical precursors for the mono- or bis- C–H alkylation of several quinones. Different methods for kinetic analysis were considered and the data reveals dramatic differences in the rate of radical initiation depending on the identity of the radical precursor and oxidant. A metal initiator free method for the radical alkylation of quinones is discussed. Lewis basic nitrogen additives increase the efficacy of quinone alkylations from carboxylic acids using catalytic $AgNO_3$ and Selectfluor as a mild oxidant. Electrochemical data suggests that certain Lewis basic additives are capable of directly reducing Selectfluor through a single-electron transfer, presumably via a charge-transfer complex. This process yields intermediates capable of promoting oxidative decarboxylation of alkyl carboxylic acids, and hydrogen atom abstraction of C–H radical precursors without an added metal initiator.

Background

Selectfluor is a free-flowing, virtually non-hygroscopic, white solid used in electrophilic fluorination. In the past 5 years, Selectfluor has found synthetic utility as a transition-metal oxidant, fluorinated intermediate initiator, Lewis-acid catalyst and a radical initiator.[1] Li et al. reported the first silver-catalyzed decarboxylative radical fluorination of aliphatic carboxylic acids with Selectfluor in aqueous solution in the middle of 2012 (Figure 2-1).[2] This led to a series of novel radical fluorination reactions with Selectfluor or NFSI.[3] This demonstrated that a Ag(I)-Selectfluor system was capable of decarboxylating alkyl carboxylic acids under mild conditions, and this radical could be intercepted for use in a Minisci reaction.

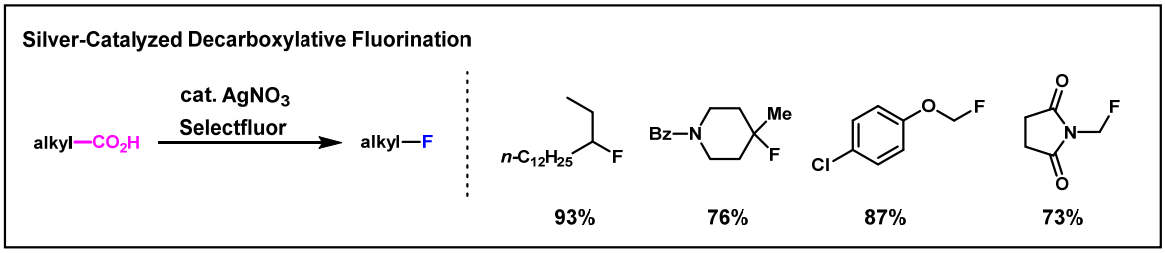


Figure 2-6. Chaozhong Li's method for decarboxylative fluorination.

Silver Catalyzed Minisci Reactions with Selectfluor

A focus of the Baxter lab was to identify alternative oxidants to promote oxidative decarboxylation or deborylation for heterocycle and quinone functionalization. We have found that Selectfluor (E^o = -0.04 V) served as a suitable replacement for the traditionally used inorganic persulfate oxidants ($S_2O_8^{2-}$, E^o = 2.01 V), although diminished reactivity generally accompanied the milder reaction conditions. We believed that the use of a mild oxidant like Selectfluor could be used as an oxidant

in the functionalization of heterocycles and quinones. The Baxter Group was interested in identifying and developing a single Minisci reaction that would allow for heterocycle and quinone functionalization using alkyl and aryl radical precursors. Often considered as just an electrophilic source of fluorine, Selectfluor has been shown to be a versatile functional reagent, serving as transition metal oxidant, fluorine cation initiator and radical initiator. The Baxter group believed that Selectfluor could serve as an excellent and mild oxidant for the Minisci reaction.

Minisci Reactions Using Selectfluor as a Mild Oxidant

As shown in Figure 2-2, the use of Selectfluor and catalytic $AgNO_3$ in the presence of one equivalent of TFA allowed for the functionalization of several heterocycles and carboxylic radical precursors.[4] In most cases, unreacted heterocycle accounted for the mass balance of incomplete reactions. Pyridines, quinoline, isoquinoline, pyridazines, quinoxaline, and quinazoline were all suitably alkylated. Secondary alkyl radicals typically provide the highest yield, although primary (**3**, **9**, **10**, **14**), tertiary (**8**), and acyl (**11**) radicals are also effective. Notably, *N*-protected amino acids are suitable radical precursors (**10**), in spite of α-aminoalkyl radicals being highly reducing and prone to over-oxidation.[5] It has been reported that fluorinated carboxylic acids are traditionally unsuccessful as radical precursors for Minisci reactions with heterocycles, a shortcoming that has recently been addressed using custom fluorinated sulfinate salts or alkyltrifluoroborates as alternative radical precursors.[6] However, we found that 4,4,4-trifluorobutyric and

4,4-difluorocyclohexane carboxylic acid are effective radical precursors under our reaction conditions, producing **14** and **16** in moderate to good yields.

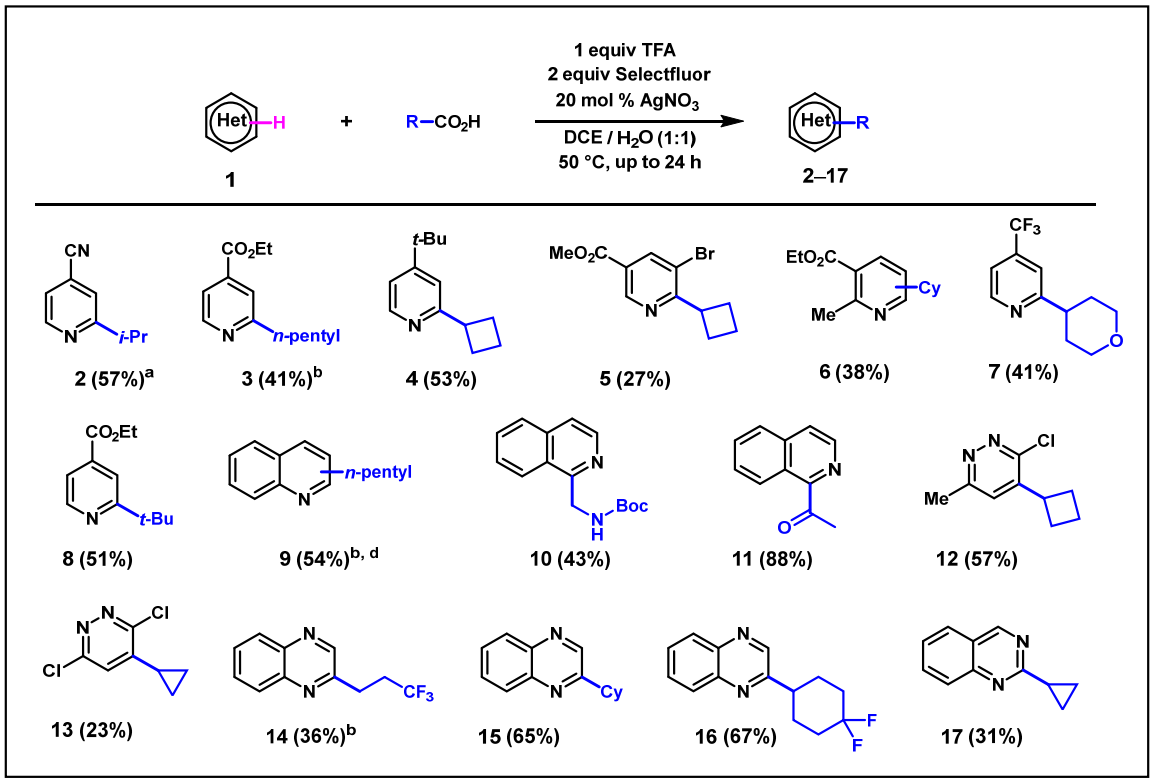


*Figure 2-7. Selectfluor mediated factualization of heterocycles. General reaction conditions: heterocycle (0.2 mmol), carboxylic acid (0.4 mmol), trifluoroacetic acid (0.2 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol), 2 mL DCE : H_2O (1:1), 50 °C for up to 24 hours. Yields refer to chromatographically pure material unless otherwise noted. Regioisomeric ratios determined by crude ^1H NMR. [a]4% of 2,6-bis alkylated product **2a** observed. [b]1.0 mmol of carboxylic acid used.*

In addition to alkyl carboxylic acids, aryl boronic acids served as excellent radical precursors for heterocycle arylation (Figure 2-3). Aryl boronic acids are utilized because a the aryl carbon-carbon bond in benzoic acid is far stronger than the aryl carbon boron bond present in a boronic acid. Aryl boronic acids are the only suitable radical precursors for the formation of aryl radicals under Minisci conditions. Pyridines, quinoxaline, and quinolines are all successfully arylated using phenylboronic acid as a radical precursor. Consistent with previous reports,

heterocycles possessing electron-withdrawing groups are good electrophiles for reaction with nucleophilic aryl radicals (**18**, **19**). However, we were pleased to find that electron-rich heterocycles are also suitably arylated (**20**–**22**). In addition to boronic acids, radical arylation is effective for boronic acid pinacol esters and trifluoroborate salts (**18**).

A variety of arylboronic acids and esters are suitable radical precursors for heterocycle arylation. Substitution with either electron-withdrawing (**32**–**37**) or electron-donating (**38**, **39**) groups is tolerated. Previous reports have shown that tolyl- and methoxyboronic acids are highly reactive towards radical arylation of heterocycles, although competing C–H fluorination under our reaction conditions is observed. Alkynyl (**40**) and alkenyl (**41**, **42**) radical precursors do not appear to be effective, yielding only trace products with 4-cyanopyridine. Interestingly, although linear alkyl carboxylic acids are suitable radical precursors for heterocycle alkylation (**3**), *n*-hexyl boronic acid did not yield alkylated products with 4-cyanopyridine (**43**).

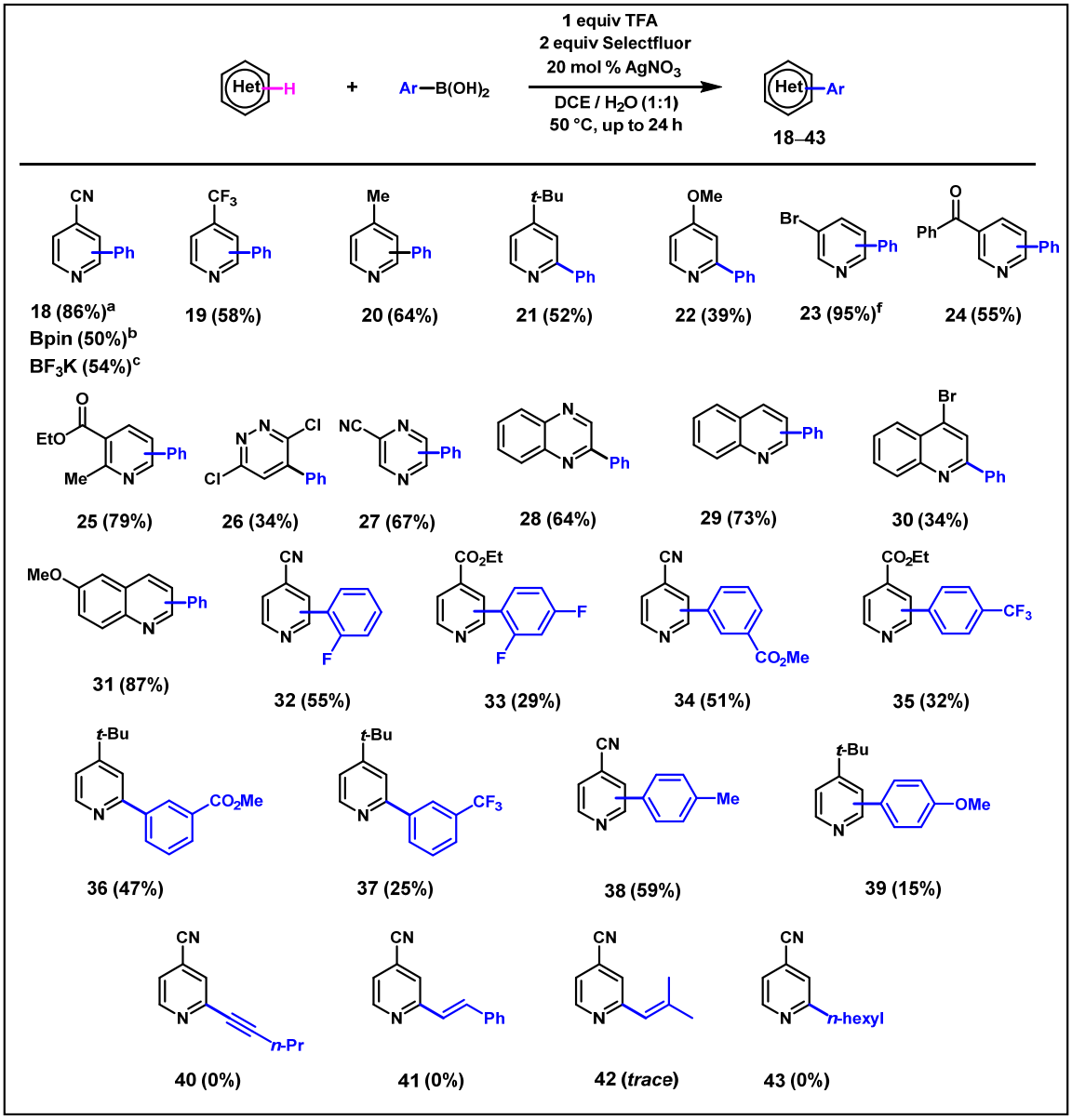


Figure 2-8. Scope of heterocycle radical arylation. General reaction conditions: heterocycle (0.2 mmol), phenylboronic acid (0.4 mmol), trifluoroacetic acid (0.2 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol), 2 mL DCE:H_2O (1:1), 50 °C for up to 24 hours. Yields refer to chromatographically pure material unless otherwise noted. Regioisomeric ratios determined by crude ^1H NMR. [a]50% yield (C2:C3 1.5:1) when pinacol ester used. [b]54% yield when trifluoroborate salt used (C2:C3 2.5:1). [c]Pinacol ester used.

Moderate to good yields are also observed for Ag(I)-catalyzed quinone alkylation and arylation at room temperature (Figure 2-4). Secondary radicals are effective for alkylating *p*-benzoquinone (**44**–**47**), although tertiary (**48**) and primary (**49**) alkyl

radicals led to poor conversion. Naphthoquinones (**50**) are successfully alkylated, and thymoquinone (**51**) can be readily accessed in one step from methyl-*p*-benzoquinone using isobutyric acid as a radical precursor. Whereas high levels of mono-alkylation are observed using Selectfluor as an oxidant, we found alkylation using traditional Minisci conditions led to low yields of **44** in addition to bis-alkylated products.[7] Quinones have shown high levels of reactivity towards aryl radicals for C–H functionalization. In competition studies, quinones outcompete electron-deficient heterocycles for trapping tolyl radicals, and high yields of C–H arylated products have been observed for borono-Minisci reactions.[8] Phenylboronic acid is an efficient radical precursor for *p*-benzoquinone arylation (**52**), and similar to heterocycle arylation, boronic acid pinacol esters and trifluoroborate salts are also effective aryl radical precursors. Substituted arylboronic acids are also successful radical precursors for *p*-benzoquinone arylation (**53**–**55**).

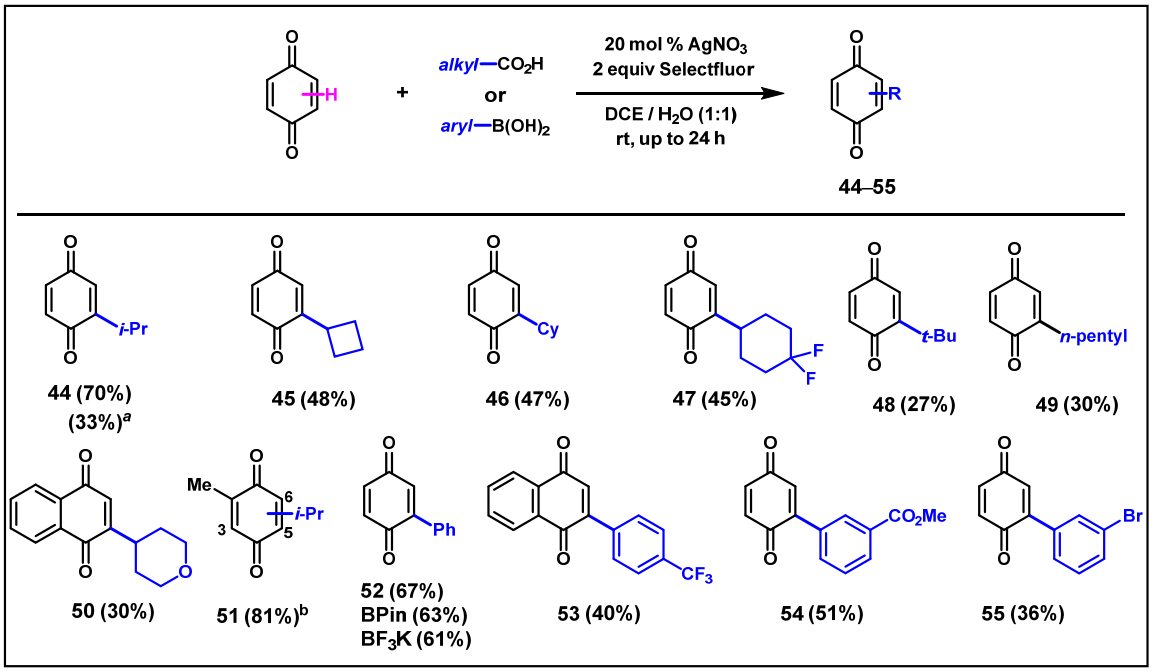
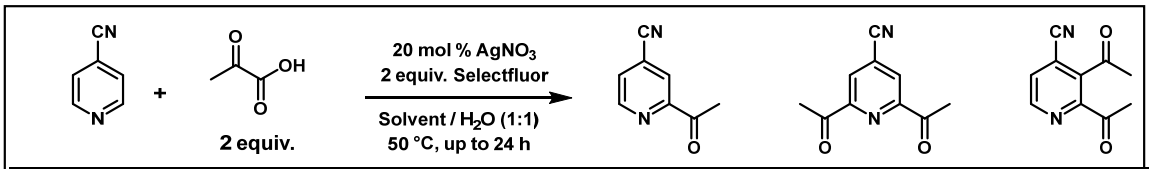


Figure 2-9. C–H Alkylation and Arylation of Quinones. General reaction conditions: quinone (0.2 mmol), radical precursor (0.4 mmol), Selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol), 2 mL DCE:H_2O (1:1), up to 24 hours. Yields refer to chromatographically pure material unless otherwise noted. [a]$(NH_4)S_2O_8$ (0.4 mmol) used as an oxidant. See supporting information for details. [b]63% yield when pinacol ester used. [c]61% yield when trifluoroborate salt is used.

There were attempts to optimize a protocol for the acylation of heterocycles and quinones from alpha-keto acids. When the acylation conditions were considered, we noticed an interesting product distribution from preliminary NMR studies (Figure 2-5). In all these cases there was full conversion of the starting material 4-cyanopyridinde, but the product distribution follows that of sp^3-carbon centered radical and a sp^2-carbon radical. This is observed by the presence of two bis-acylated regioisomers at the C-2, C-6 and C-2, C-3-positions. This result suggests that Selectfluor may be able to directly decarboxylate alpha-keto acids without the presence of silver. A solvent screened revealed that n-hexane was a suitable and unconventional solvent for this reaction. The starting material and product are insoluble at room temperature, but as the reaction proceeds at elevated temperatures, the reagents go into solution. Biphasic solvent mixtures have been shown to be effective at increasing yields of radical reactions.



Entry	TFA	Solvent			
1	-	DCE	37%	1%	2%
2	-	TFT	45%	1%	3%
3	-	n-hexane	51%	1%	5%
4	1 equiv	DCE	55%	1%	4%
5	1 equiv	n-hexane	42%	2%	6%

Figure 2-10. Screen of conditions to acylate heterocycles. 1,3,5-triemthoxybenzene was used as internal standard.

Comparison of Silver-Catalyzed Minisci Reactions: Selectfluor vs Persulfate

In the presence of silver, one equivalent of Selectfluor is capable of forming a reactive intermediate **SF-I** for single-electron transfer (SET) processes (Figure 2-6). A SET is the radical process of moving a single electron from one substrate (electron rich) to another (electron poor). This intermediate can facilitate the SET of a carboxylic acid functional group to produce the radical (R = alkyl). For amino acids, the radical decarboxylation produces an alpha-amino radical, which can undergo oxidation to the aldehyde and decarbonylation to provide the radical. Finally, **SF-1** can be used to decarbonylate to produce the same radical. To further develop Selectfluor-mediated reactions, we compared these radical precursors with quinone as the substrate.

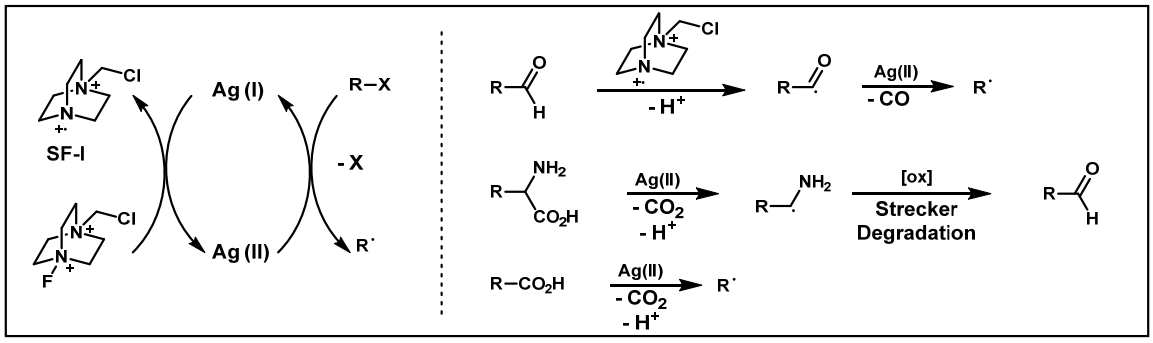


Figure 2-11. Mechanism of silver catalyzed radical formation.

With these radical precursors, we systematically investigated their reactivity and effectiveness in Minisci reactions mediated by Selectfluor. In addition, we also ran the same set of experiments using persulfate as the oxidant. We hypothesized that formation of an isopropyl radical from valine would limit the rate of C–H alkylation

due to a multi-step initiation process, allowing unfavorable termination pathways to compete with a second alkylation. Whereas carboxylic acids or aldehydes theoretically only require one equivalent of oxidant for alkylation, the Strecker degradation of unprotected amino acids presumably consumes several equivalents of oxidant per alkyl radical generated, minimizing the likelihood of bis-alkylation.

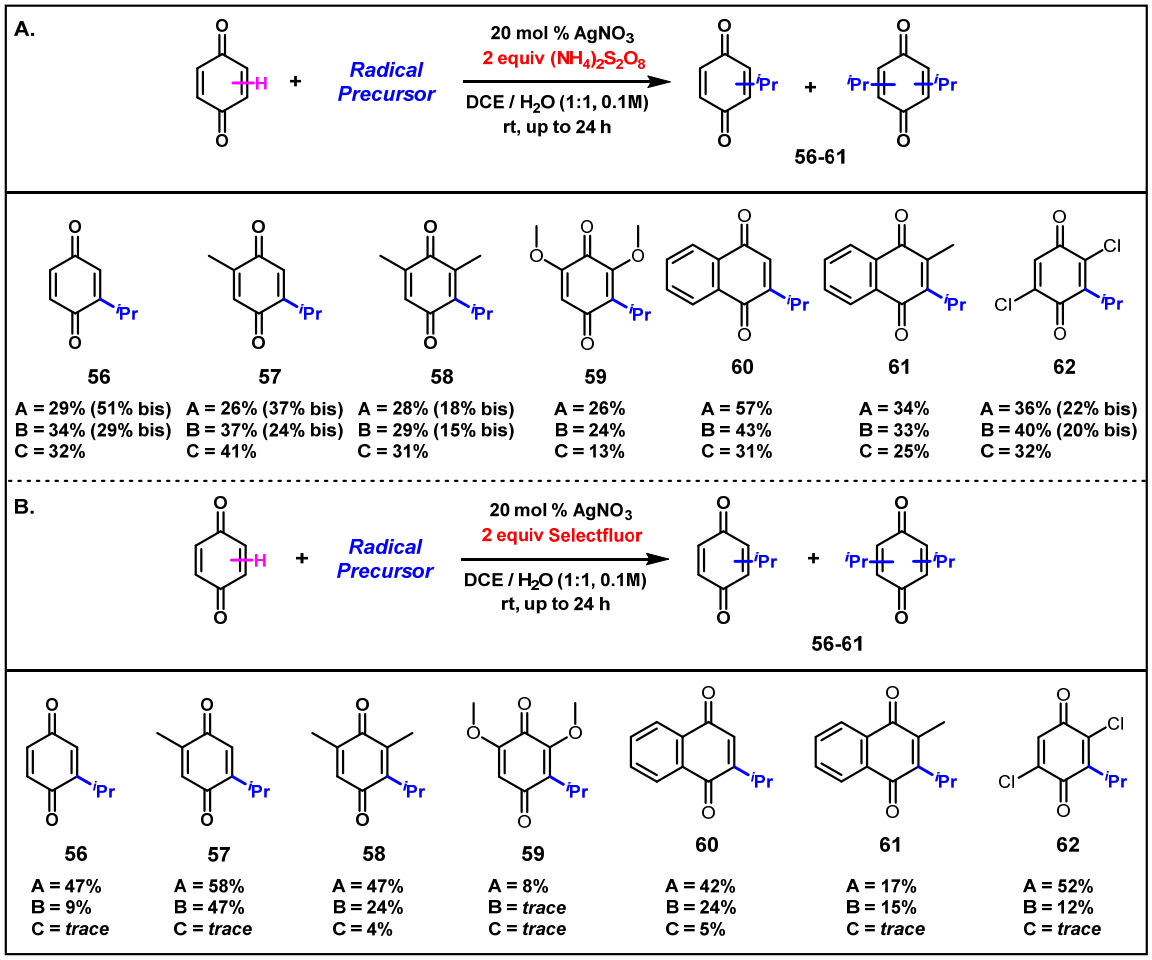


Figure 2-12. Direct comparison of alkylated quinones. General reaction conditions: quinone (0.2 mmol), radical precursor (0.4 mmol), ammonium persulfate or selectfluor (0.4 mmol), $AgNO_3$ (0.04 mmol) in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Method 'A' radical precursor is isobutyric acid. Method 'B' radical precursor is isobutyraldehyde. Method 'C' radical precursor is valine.

In the presence of persulfate as the oxidant, we observed bis-alkylation. Although the use of valine provided lower yields, the multi-step sequence required to produce the isopropyl radical resulted in selective formation of the mono-alkylated product (Figure 2-7A). Comparing the same set of isopropyl radical precursors under identical experimental conditions with Selectfluor as the stoichiometric oxidant, only mono-alkylated products were observed in all cases (Figure 2-7B). Across the range of quinones studied, isobutyric acid was shown to be the superior radical precursor whereas valine is essentially ineffective. These results suggested that highly reactive quinones are more effectively mono-alkylated using Selectfluor as an oxidant with carboxylic acids as radical precursors. This is contrary to the observed bis-alkylated products present when using persulfates. To further study these reactions, we monitored the temporal changes in concentrations of the reactants and products. Heterogeneous reaction conditions resulted in partial solubility of active reagents products formed (Figure 2-8).

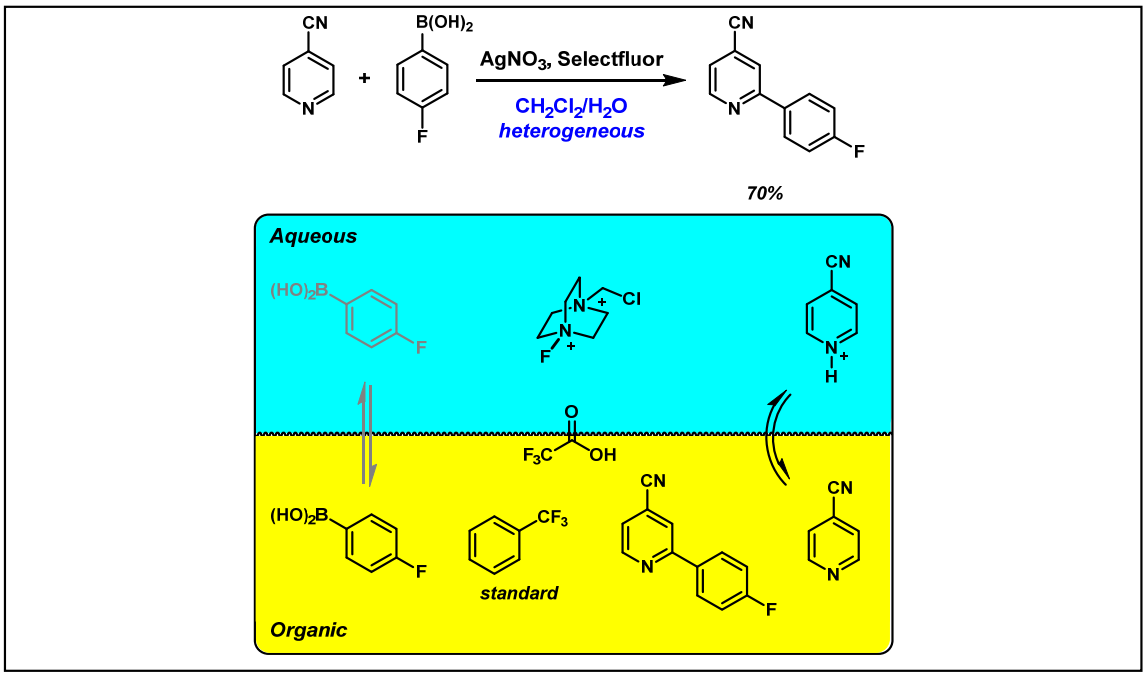


Figure 2-13. Monitoring of the reaction with Selectfluor and heterocycles.

The Baxter lab has utilized several techniques to monitor starting materials and product formation in biphasic systems. At the time, there were two options to study these reactions: manual sampling of the organic layer or utilizing the Mettler-Toledo EasySampler for automated sampling of both the aqueous and organic phases simultaneously. Samples would be diluted in a homogenizing deuterated solvent and analyzed via ^{19}F-NMR. This strategy was utilized because low sample concentration is a concern for NMR analysis, but the enhanced sensitivity and spectral window of ^{19}F led allows for quantitative data to be acquired. The EasySampler allowed us to monitor Selectfluor consumption as the reaction progressed without compromising the reaction. We compared product formation, boronic acid consumption and Selectfluor consumption, and both sampling techniques are compared in Figure 2-9.

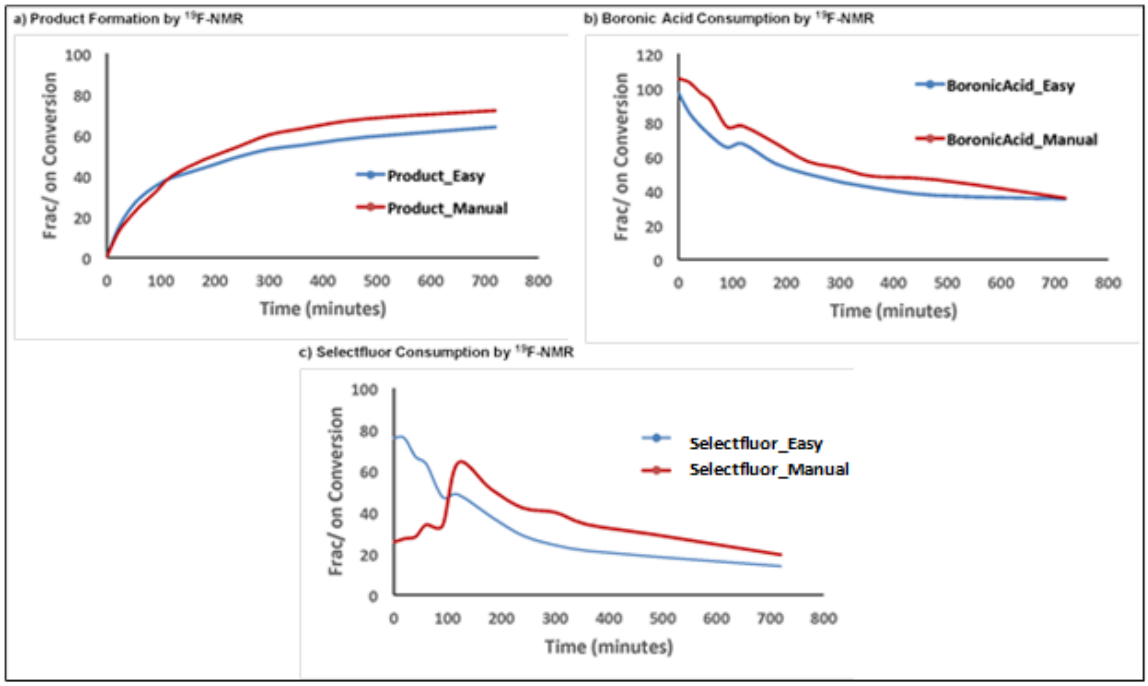


Figure 2-14. Comparison of Sampling Techniques for Reaction Monitoring. Fraction Conversion. Blue curves: automated sampling of reaction mixture using EasyMax. Red curves: manual sampling of reaction mixture. General reaction conditions; 4-cyanopyridine (0.1 M), 4-fluorophenyl boronic acid (0.15 M), Selectfluor (0.15 M), trifluoroacetic acid (0.1 M), trifluorotoluene (0.1 M, internal standard), $AgNO_3$ (0.02 M), 5 ml H_20, 5 ml dichloroethane.

Although automated sampling using the Mettler-Toledo EasySampler provided reliable reaction progress data in a straightforward manner, manual sampling was determined to be easier and equally effective for assessing concentration of product formed. We also assessed a different substrate 1,4-benzoquinone, to ensure that the starting material was not prone to noticeable solubility in aqueous solvents.

As shown in Figure 2-9, 1,4-benzoquinone is consumed within three hours with ammonium persulfate as an oxidant (plot ‘a’). Under these conditions, the rate of product formation is higher using isobutyric acid as a radical precursor compared to isobutyraldehyde (plot ‘b’). This result suggests that oxidative decarboxylation

is faster than decarbonylation as all elementary mechanistic steps are expected to be identical after formation of the isopropyl radical.[a]

It is interesting to note that for isobutyric acid, formation of the bis-alkylated product is not observed until nearly all of the 1,4-benzoquinone starting material is consumed when persulfate is used (the point indicated by the arrow in plot 'b'). This suggests that the slightly electron-rich 2-isopropyl-1,4-benzoquinone is a less effective electrophile, consistent with the 1,4-Benzoquinone alkylation data shown in Figure 2-9.

[a] Radical formation is believed to occur via a hydrogen-atom abstraction/decarbonylation sequence rather than an oxidation/decarboxylation sequence. Evidence for this mechanism is provided via the presence of acylated products from aldehydes in reference 22.

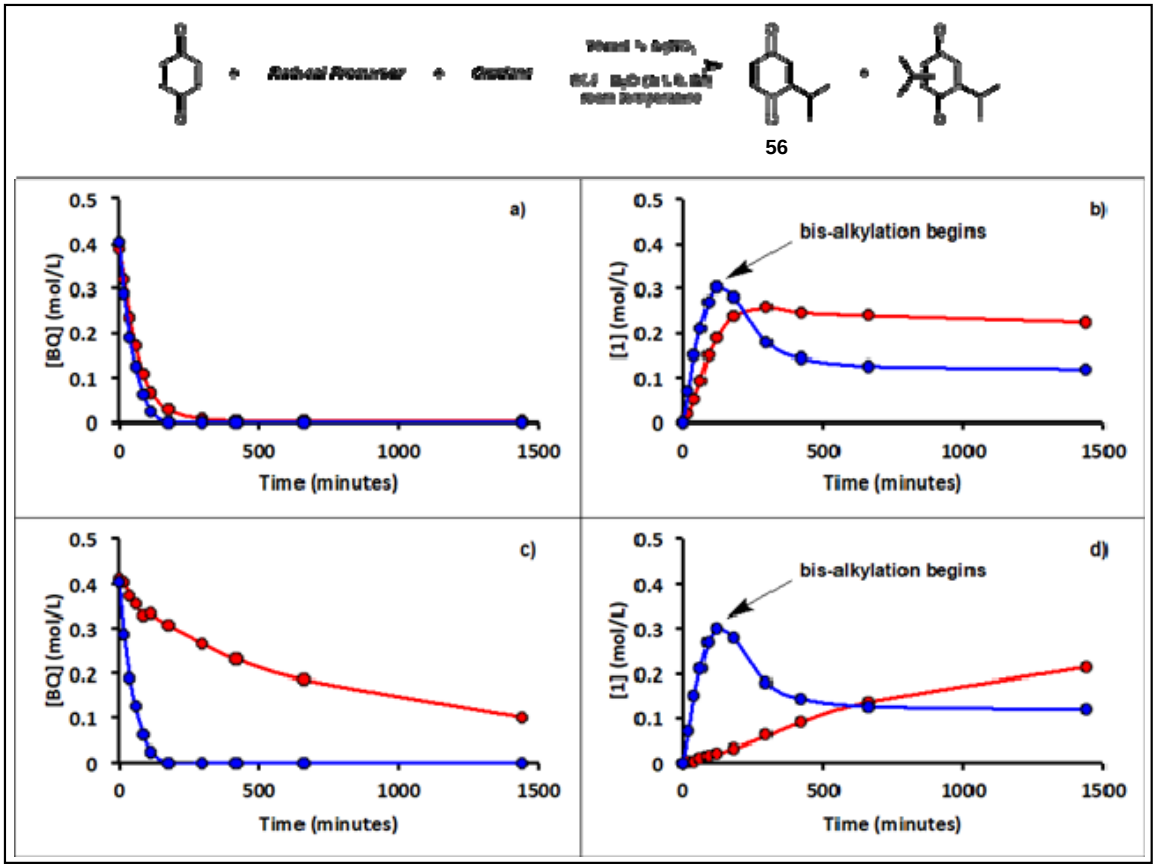


Figure 2-15. Rate comparisons for isobutyric acid and isobutyraldehyde using ammonium persulfate and Selectfluor. General reaction conditions: 1,4-benzoquinone (0.4 mmol), radical precursor (0.8 mmol), oxidant (0.8 mmol), and $AgNO_3$ (0.08 mmol) in 4 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Using a glass micro syringe 10 µL aliquots were taken from the organic phase at specified time points. Conversions were determined by GCMS against 4-tert-butylbenzene as an internal standard. Each data point represents the average value of three runs under identical conditions. Plots a) and b); $(NH_4)_2S_2O_8$ as oxidant, blue data is isobutyric acid as radical precursor, red data is isobutyraldehyde as radical precursor. Plots c) and d); isobutyric acid as radical precursor, blue data is $(NH_4)_2S_2O_8$ as oxidant, red data is Selectfluor as oxidant.

Because the conversions shown in Figure 2-10 were generally lower with isobutyraldehyde, we compared the rates of C–H alkylation with ammonium persulfate or Selectfluor using isobutyric acid as the sole radical precursor. Dramatic differences in the rate of C–H alkylation were observed between the two oxidants. Whereas persulfate-mediated initiation consumes 1,4-benzoquinone in approximately three hours, the Selectfluor-mediated reaction still contains 25%

unreacted starting material after 24 hours (plot ‘c’). Comparing the initial rates of product formation for the two methods reveals that persulfate-mediated alkylation occurs approximately 30x faster than when using Selectfluor as an oxidant (plot ‘d’). This data is consistent with our hypothesis that the formation of bis-alkylation products is largely controlled by the rate of alkyl radical formation, which is directly related to the strength of the stoichiometric oxidant.

We have shown in Figure 2-11, that several alkyl carboxylic acids are suitable radical precursors for quinone alkylation using Selectfluor as an oxidant. In many cases, the stability and nucleophilicity of the generated alkyl radical play determines reaction efficiency, and the choice of oxidant depends on predicting the efficacy of the nucleophilic radical generated. As shown in Figure 2-11, for highly reactive quinones like 1,4-benzoquinone, simple secondary alkyl radicals (**63**) produce higher yields of mono-alkylation when using Selectfluor as an oxidant. The poor stability of primary radicals (**64**) renders them inefficient with either oxidant, but the stable *t*-butyl radical (**65**) is more efficient with a stronger oxidant likely due to steric effects slowing the nucleophilic addition. Because of their decreased nucleophilicity, deactivated secondary radicals (**66, 67**) are more efficient when rapidly formed using ammonium persulfate. Stabilized benzylic radicals (**68**) are reactive enough to produce bis-alkylation with ammonium persulfate, but still yield a suitable amount of the mono-alkylated product.

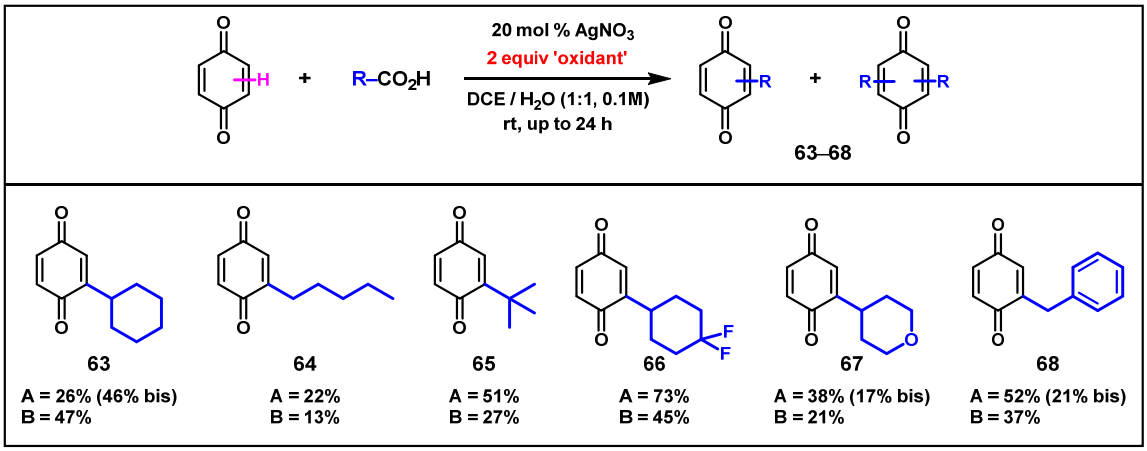


Figure 2-16. 1,4-Benzoquinone alkylation from various carboxylic acids. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), oxidant (0.4 mmol), $AgNO_3$ (0.04 mmol) in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as a standard. Method 'A' oxidant is $(NH_4)_2S_2O_8$. Method 'B' oxidant is Selectfluor.

Figure 2-12 shows the proposed mechanism for radical addition into quinones. The mechanism is mediated by the use of an oxidant to generate Ag(II). It is then rationalized that Ag(II) interacts with the carboxylate group leading to a radical decarboxylation and generation of an alkyl radical. This alkyl radical then couples with the quinone resulting in a functionalized quinone structure.

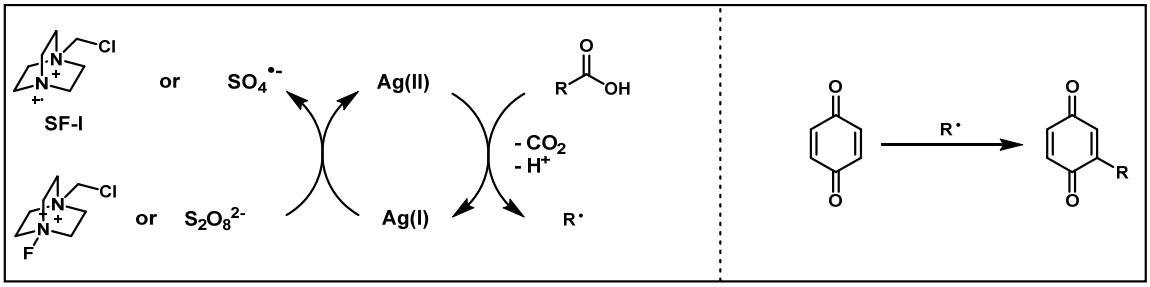


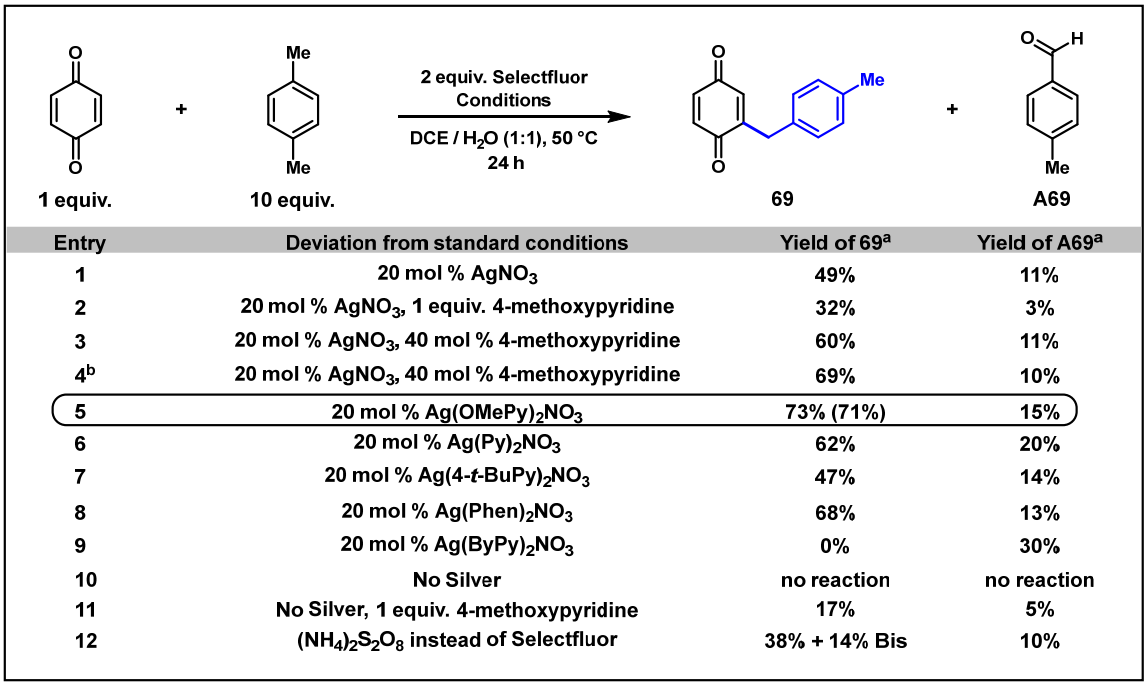
Figure 2-17. Proposed mechanism for quinone alkylation.

Minisci Reactions Using Selectfluor as HAT Reagent

As previously discussed, Selectfluor in the presence of silver forms an intermediate for SET processes (Figure 2-13). This intermediate facilitates decarboxylation,

decarbonylation and deborylation to produce radicals. This radical cation intermediate has been shown to undergo hydrogen-atom transfer (HAT). HAT is the process of transferring a proton coupled with an electron from the same orbital of a H–C or H–O bond. The radical generated from selectfluor has been shown to participate in intermolecular HAT from activated and in some cases of unactivated C–H bonds under visible light.[9-15] After establishing the feasibility of Selectfluor as an oxidant for Minisci reactions, we decided to examine alkyl radicals generated via C–H abstraction as an opportunity for additional synthetic pathways.

Our optimization studies using quinone and p-xylene revealed that 20 mol% $Ag(OMePy)_2NO_3$ provided desired product in good yield with minor amounts of aldehyde **A69** formed. The formation of the aldehyde can be minimized by using degassed solvents and allowing the reaction to run under an inert atmosphere. It is known that oxygen quenches benzylic radical to form benzaldehydes.



Entry	Deviation from standard conditions	Yield of 69[a]	Yield of A69[a]
1	20 mol % $AgNO_3$	49%	11%
2	20 mol % $AgNO_3$, 1 equiv. 4-methoxypyridine	32%	3%
3	20 mol % $AgNO_3$, 40 mol % 4-methoxypyridine	60%	11%
4[b]	20 mol % $AgNO_3$, 40 mol % 4-methoxypyridine	69%	10%
5	20 mol % $Ag(OMePy)_2NO_3$	73% (71%)	15%
6	20 mol % $Ag(Py)_2NO_3$	62%	20%
7	20 mol % $Ag(4\text{-}t\text{-}BuPy)_2NO_3$	47%	14%
8	20 mol % $Ag(Phen)_2NO_3$	68%	13%
9	20 mol % $Ag(ByPy)_2NO_3$	0%	30%
10	No Silver	no reaction	no reaction
11	No Silver, 1 equiv. 4-methoxypyridine	17%	5%
12	$(NH_4)_2S_2O_8$ instead of Selectfluor	38% + 14% Bis	10%

Figure 2-18. Optimization of quinone functionalization. [a] NMR yields wit 1,3,5-trimethoxybenzne. [b] run under argon.

A variety of quinones and methyl arene reaction partners were examined (Figure 2-14). Para substituted toluenes with electron donating groups (**70–71**) benzylated benzoquinone in moderate to good yield. Electron-withdrawing methylarene (**72**) was less effective resulting in poor yields with the isolation of unreacted benzoquinone accounting for mass balance. Ortho-substituted arenes with methyl substitution (**73**) furnished product in moderate yield. Meta-methylated (**74**) and tetramethylated (**75**) arenes were also effective partners in generating desired products. A variety of quinones were screened to determine the scope of electrophiles suitable for this reaction. Benzylated 1,4-benzoquinone (**76**) was synthesized in moderate yield. Using solvent quantities of the radical precursor results in largely similar reaction conversions. An increase in yield is also observed when the equivalents of Selectfluor are raised from 2 to 5 equivalents. Both

methylated (**77–78**) and halogenated (**79–80**) benzoquinones were effective coupling partners and resulted in moderate yields of benzylated products with no bis-benzylated products observed. Finally, functionalized naphthoquinone (**81**) and associated analogs such as juglone (**82**) and menadione (**83**) can also be produced.

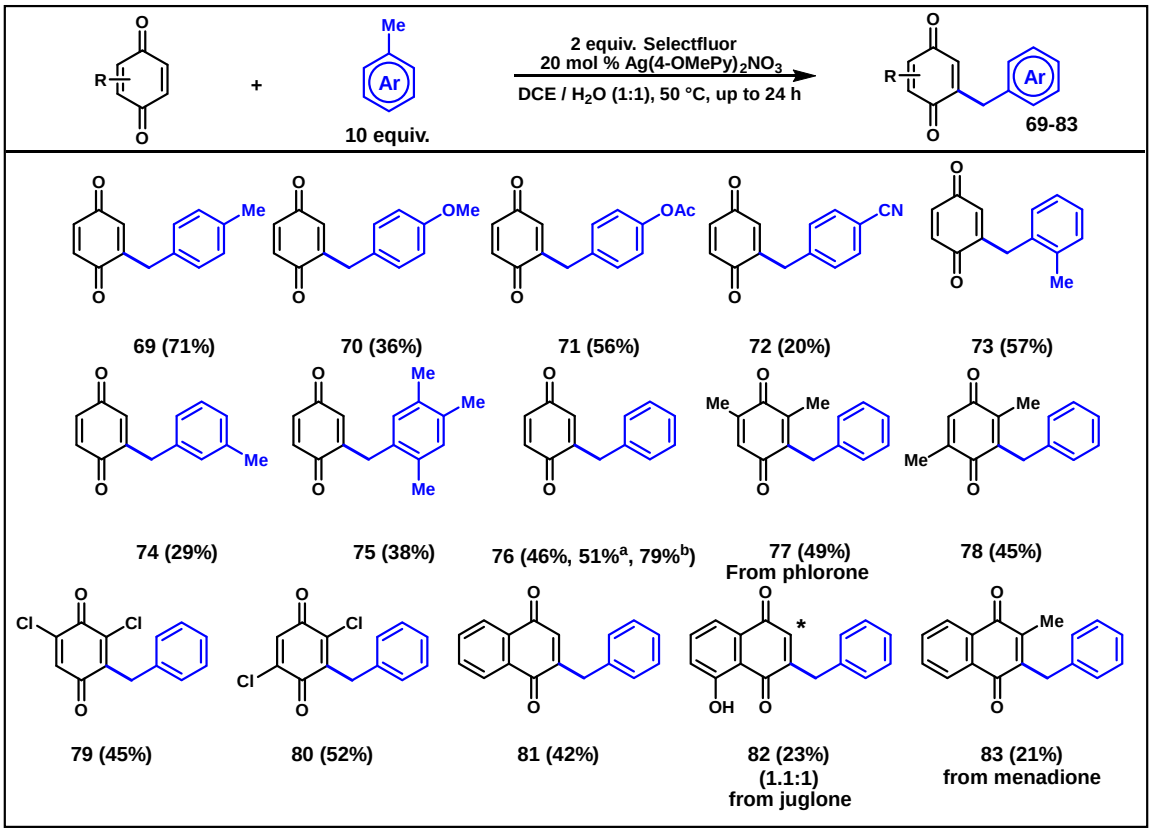


Figure 2-19. Scope of quinone benzylation. Yields refer to chromatographically pure compounds. [a]Toluene was used instead of DCE as organic solvent. [b]5 equivalents of Selectfluor used instead of 2 equivalents.

Efforts to extend this method towards other C–H radical precursors and heterocyclic substrates resulted in poor yields (Figure 2-15).

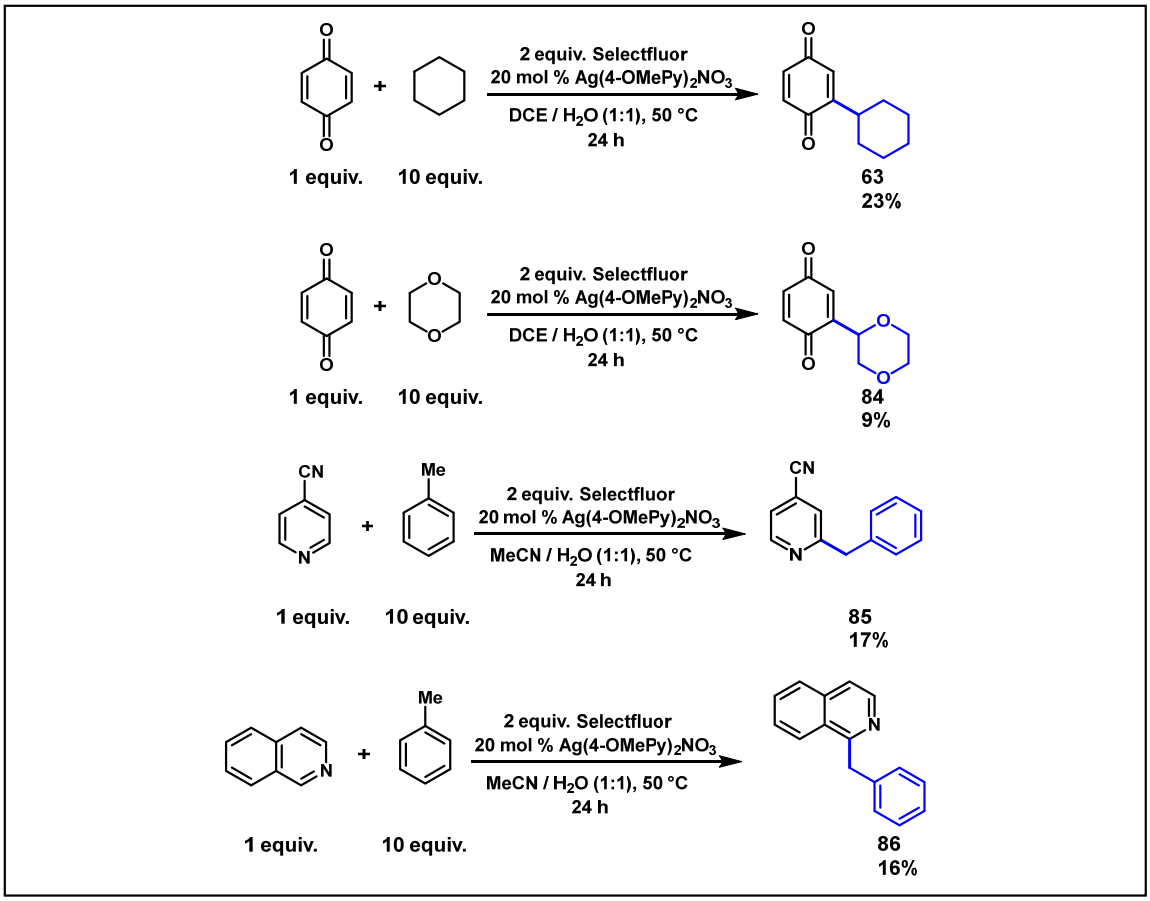


Figure 2-20. Efforts to extend HAT mediated reactions to other substrates and coupling partners. Yields refer to chromatographically pure compounds.

To better understand the effect of 4-methoxypyridine as a ligand for Ag(I), we tracked the concentration of Selectfluor by ^{19}F-NMR over the course of a typical experiment. Due to the biphasic nature of the reaction, *in situ* reaction monitoring posed a challenge. Instead, small aliquots were removed from the aqueous phase of the reaction to determine Selectfluor concentration against an external standard over the course of 24 hours. Figure 2-16, entry B suggested that excess 4-methoxypyridine had a negative effect on reaction conversion. Previous work in our group had established that electron-rich pyridines can directly consume

Selectfluor in an unproductive manner, an observation that is now extended to this biphasic solvent system.[14]

We were interested in comparing the use of $AgNO_3$ and catalytic 4-methoxypyridine to $Ag(4\text{-}OMePy)_2NO_3$ to establish the benefit of the pre-formed catalyst. A catalytic amount of $AgNO_3$ consumed approximately 80% of Selectfluor within 24 hours, confirming that a nitrogen additive is not required for the Ag(I)/(II) redox cycle under these conditions (Figure 2-16A). A Ag(I)/(II) redox cycle is proposed because following the oxidation of Ag(I) by Selectfluor to generate Ag(II); aqueous solutions of Ag(II) are unstable and readily oxidize water to oxygen at room temperature regenerating Ag(I). A catalytic amount of 4-methoxypyridine consumes Selectfluor in an apparent 1:1 stoichiometry with an initial rate that is on par with the $AgNO_3$-mediated reaction (Figure 2-16B). Under these conditions only trace amounts of product are formed, confirming that free 4-methoxypyridine has a deleterious effect on the desired transformation even in catalytic quantities. Finally, reaction with pre-formed $Ag(4\text{-}OMePy)_2NO_3$ produces the highest overall reaction rate for consumption of Selectfluor, while providing the desired product in the highest overall conversion (Figure 2-16C). This data suggest that the pre-formed catalyst circumvents unfavorable interactions between 4-methoxypyridine and Selectfluor, presumably because strong association to Ag(I) precludes the occurrence of free pyridine in solution. Free pyridine in solution interacts unfavorably with selectfluor and ultimately shuts down the reaction.

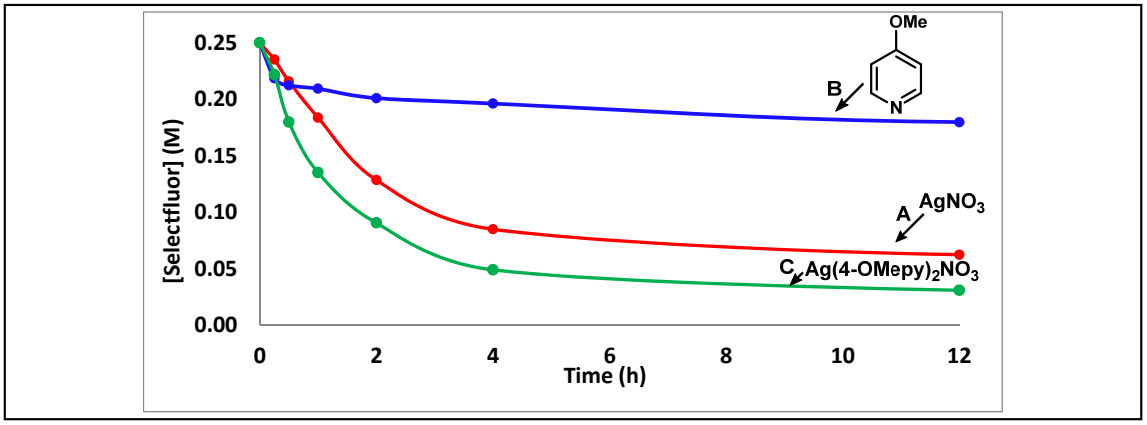


Figure 2-21. ^{19}F-NMR monitoring of the consumption of Selectfluor (1.0 mmol) with either (A) 0.1 mmol of $AgNO_3$, (B) 0.2 mmol of 4-methoxypyridine, or (C) 0.1 mmol of $Ag(4\text{-}OMePy)_2NO_3$. Reaction conditions: Selectfluor (1.0 mmol) in DCE/H_2O (4 mL, 1:1) at 50 °C for up to 24 h. Using a glass micro syringe, 200 µL aliquots were taken from the aqueous phase at specified time points. Conversions were determined by ^{19}F-NMR using trifluorotoluene as an external standard.

A plausible mechanism for the benzylation of quinone is shown in Figure 2-16. Single-electron transfer between $Ag(4\text{-}OMePy)_2NO_3$ and Selectfluor generates **SF-I** and the Ag(II)-complex with concomitant generation of fluoride anion (Figure 2-17A). Hydrogen atom abstraction of a methylarene via **SF-I** leads to a nucleophilic benzyl radical that is trapped by an electrophilic quinone substrate. The resulting radical intermediate is then oxidized, either by Selectfluor or Ag(II), and deprotonated to produce the expected C–H benzylated product (Figure 2-17B). This is a robust catalyst system for generating benzylic radicals via C–H abstraction and combining these radicals with various electrophilic quinones.

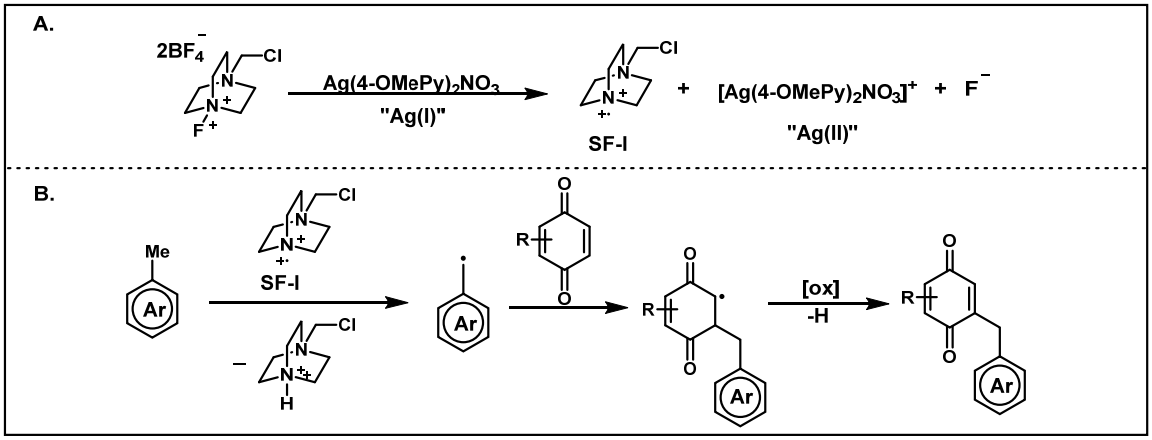


Figure 2-22. Proposed mechanism for quinone benzylation.

Metal Free Minisci Reactions Using Selectfluor

During the course of our studies, we were confident Selectfluor was capable as a radical initiator for the Minisci reaction in the absence of metal. Metal-free Minisci reactions are ideal because recent investigations into Minisci reactions described previously require expensive metal salts which require harsh conditions to initiate, or expensive photocatalysts that require high energy UV light for good yields. We envisioned by developing a metal-free minisci reaction we would be able to achieve a cheap mild reaction with conditions that could be utilized in the late-stage functionalization of compounds in a cheap and environmentally friendly manor. This chapter focuses on our efforts and success toward applying a metal-free variant for the synthesis of substituted quinones. Progress towards this goal has been achieved by promoting single-electron reduction of Selectfluor using Hünig's base (Figure 2-18).

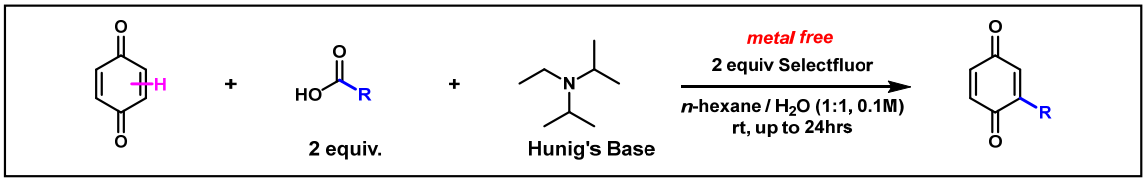


Figure 2-23. General conditions for metal free Minisci reaction.

Through our previous work on radical fluorination, we showed that Selectfluor was capable of promoting Ag(I) to Ag(II) oxidation (E^o = 1.71 V) when unprotected amino acids, such as glycine, served as electron-donating ligands for Ag(I).[15] This effect could be reproduced with various pyridines, which altered the oxidation potential of Ag(I) to an even greater extent (Figure 2-19).

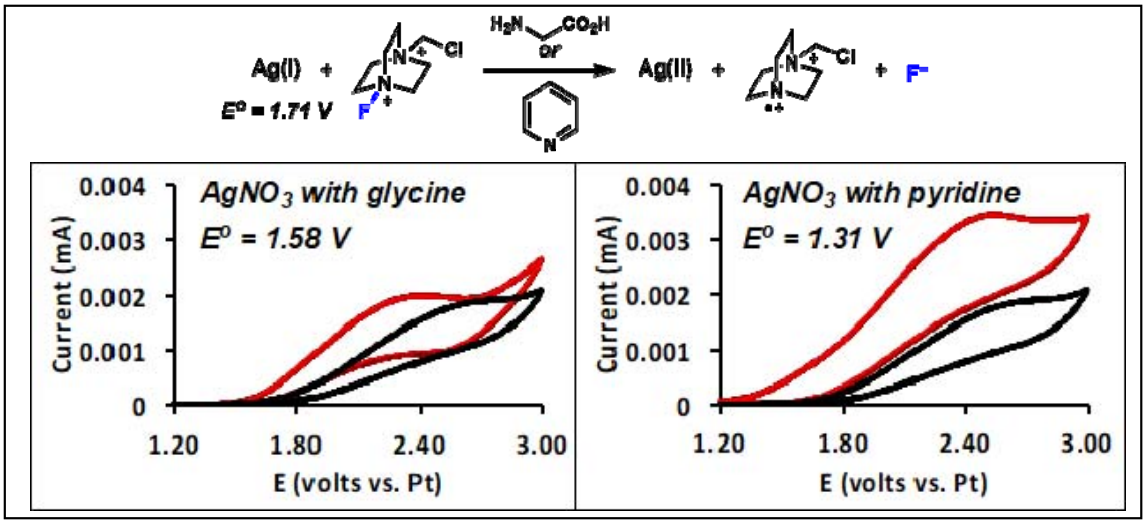


Figure 2-24. Ligand-dependent oxidation potentials for Ag(I). Electrochemical experimental conditions: $AgNO_3$ (0.4 mmol) in 5 mL CH_3CN, tetrabutylammonium tetrafluoroborate supporting electrolyte (0.1 M), additive, where applicable, (0.4 mmol). Left: $AgNO_3$ alone (black curve), $AgNO_3$ with glycine added (red curve). Right: $AgNO_3$ alone (black curve), $AgNO_3$ with pyridine added (red curve). E^o values are determined as the minimum voltage producing 100 mA of current in the oxidizing direction (left-to-right).

Because the Ag(I)/Ag(II) couple is implicated in radical decarboxylation and deborylation, we used the electrochemical information above to guide our development of a Minisci reaction that uses Selectfluor as a mild oxidant. We

believed the presence of a heterocyclic substrate would be sufficient to promote Ag(I) oxidation, as even electron-deficient heterocycles yielded Ag(I) species with lower oxidation potentials than $AgNO_3$ alone (*vide infra*). During the development of that previous work, we were surprised to discover that quinone alkylation and arylation was also possible with Selectfluor in the absence of any suitable heterocyclic ligands for Ag(I).

Because we observed enhanced reactivity using pre-complexed Ag(I)-initiators leading to benzylated quinones, we wondered whether a similar strategy could be used to describe any interactions with only Selectfluor to initiate the radical alkylation reactions.

There have been many recent reports where a proposed single-electron transfer event between electron-rich pyridines and Selectfluor via a charge-transfer intermediate can lead to productive fragmentation of Selectfluor. An analogous electron-transfer between Hünig's base and Selectfluor seemed reasonable based on the precedence of using trialkylamines as reductive quenchers in photocatalysis due to their favorable redox potentials compared to $Ru(bpy)_3^{2+}$ ($E1/2^{II*/I}$ = 0.77 V vs SCE).[16] Electrochemical analysis confirmed that Hünig's base possessed an onset oxidation potential lower than that of $AgNO_3$ (Figure 2-20).

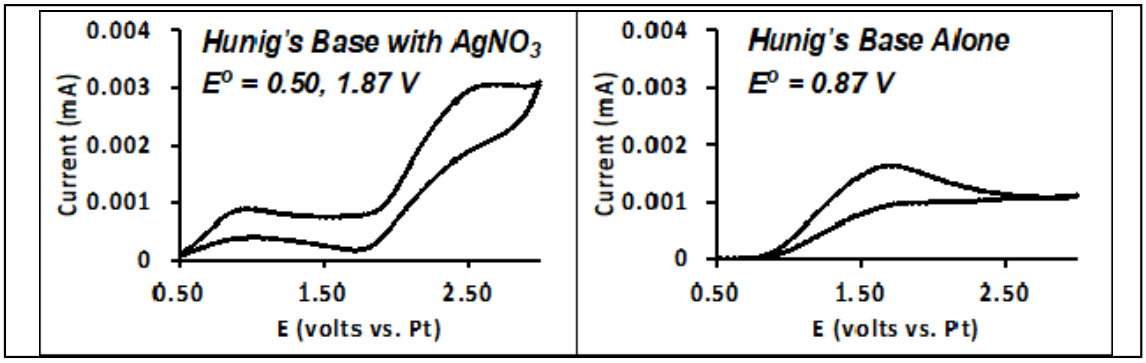
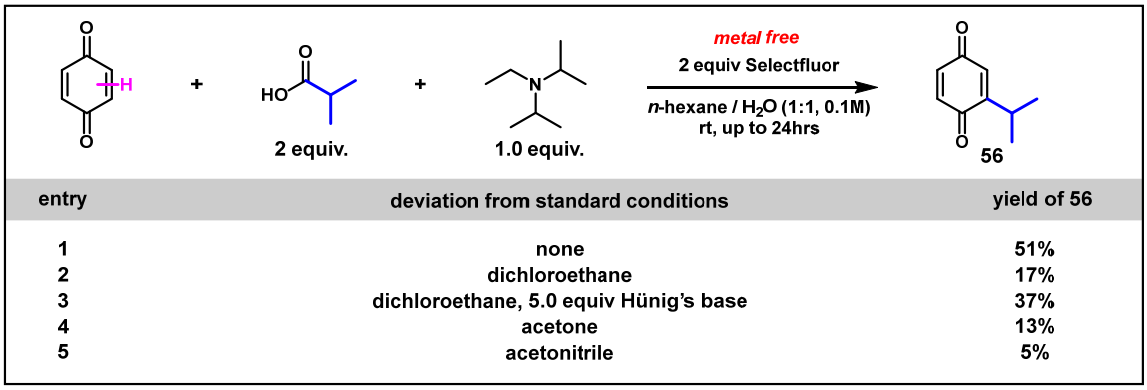


Figure 2-25. Cyclic voltammetry of Hünig's base. Electrochemical experimental conditions: $AgNO_3$, where applicable, (0.4 mmol) in 5 mL CH_3CN, tetrabutylammonium tetrafluoroborate supporting electrolyte (0.1 M), Hünig's base, where applicable, (0.4 mmol). Left: $AgNO_3$ alone (black curve), $AgNO_3$ with Hünig's base added (red curve). Right: $AgNO_3$ alone (black curve), Hünig's base alone (red curve). E^o values are determined as the minimum voltage producing 100 mA of current in the oxidizing direction (left-to-right).

We sought to optimize metal-free alkylations of quinones using Hünig's base as a single-electron reductant for Selectfluor. As shown in Figure 2-20, dichloroethane is the optimum co-solvent when using Hünig's base, although only moderate yields can be achieved with just one equivalent of the additive (Figure 2-21, entry 1). Increasing the equivalents of Hünig's base led to higher conversion, suggesting that the protocol may be amenable to further optimizations. New stir bars and disposable glassware were used to minimize the possibility of trace metal contaminants initiating the radical reaction. No desired product is observed in the absence of Hünig's base, and trace metal analysis of this reagent suggests the reaction is occurring without metal-initiators.



entry	deviation from standard conditions	yield of 56
1	none	51%
2	dichloroethane	17%
3	dichloroethane, 5.0 equiv Hünig's base	37%
4	acetone	13%
5	acetonitrile	5%

Figure 2-26. Metal-free radical addition to 1,4-benzoquinone. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), Hünig's base (0.2–1.0 mmol), in 2 ml of organic solvent/H_2O (1:1) at room temperature for up to 24 hours. Isolated yields of chromatographically pure material are shown.

Although this work is in its early stages, these preliminary results show promise for developing a general strategy for Minisci-type reactions that do not rely on metal initiators. A brief screen of quinones and carboxylic acids showed that modest conversion to the alkylated quinone could be achieved for a variety of carboxylic acid radical precursors (Figure 2-22).

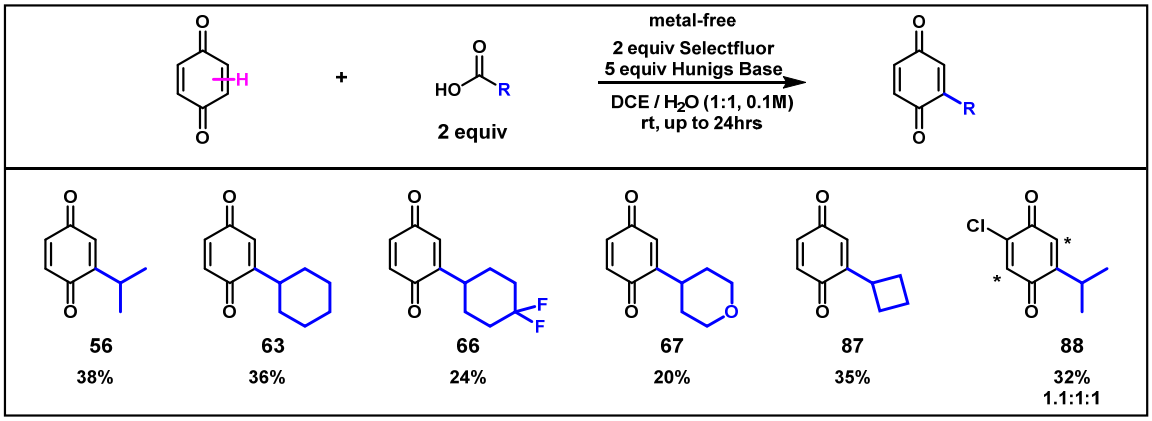


Figure 2-27. Metal-free radical addition to 1,4-benzoquinone. General reaction conditions: quinone (0.2 mmol), carboxylic acid (0.4 mmol), Selectfluor (0.4 mmol), Hünig's base (1.0 mmol), in 2 ml of DCE/H_2O (1:1) at room temperature for up to 24 hours. Isolated yields of chromatographically pure material are shown.

Conclusions

Minisci reactions mediated by Selectfluor can be utilized to functionalize both heterocycles and quinones. Alkyl carboxylic acids are preferred sources of alkyl radicals when using Selectfluor compared to aldehydes and amino acids. Methyl arenes can be utilized to for the benzylation of quinones in good yields and low yields were observed with other activated and unactivated C–H bonds. The arylation of heterocycles and quinones can be achieved by using aryl boronic acids, tetrafluoroborate salts, and boronic acid pinacol esters. The reactivity of silver catalyzed Minisci reactions can be modified by using a precomplexed Ag(I) catalyst with pyridine ligands. Lastly, Selectfluor can be reduced by Lewis basic nitrogen leading to the generation of an intermediate capable of decarboxylating alkyl carboxylic acids leading to alkylated quinones. Continued work in this area will lead to the access to a truly mild and metal-free Minisci reaction.

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Chapter 3. Nitroso Compounds and The Development of a Novel Transnitrosation Reagent

Abstract. Nitroso compounds are reviewed, and their synthesis is detailed. We describe the limitations to the methods to access nitroso compounds. We discuss the development of novel N-nitrososulfonamides that are capable of transnitrosation without decomposition. N-nitrososulfonamides have been regarded as transnitrosating reagents but are prone to decomposition when acting in certain media. Our design and synthesis covers the unique features of our reagent that is ideal for accessing nitroso compounds in one-step.

Background

Nitrosated compounds have highly unique characteristics in biological systems (Figure 3-1). *N*-nitrosonicotine, a tobacco-specific nitrosated amine produced during the curing and processing of tobacco, is linked to cancerous activity and development of tumors in the body.[1] Cupferron, a nitrosated hydroxylamine, is used in analytical chemistry and for the detection of uranium.[2] Lomustine, a nitrosated urea is uses as a chemotherapeutic due to its ability to cross the blood-brain barrio and alkylate DNA.[3] *S*-nitroso-*N*-acetylphenicillamine (SNAP), an *S*-nitrosothiol, has seen applications as a signaling molecule in studies involving vasodilation.[4] *S*-nitrosoglutathione is another example of a known endogenous nitric oxide source that plays a role in signaling in biological systems.[5] Interestingly, *N*-nitrosoglutathione is one of the few *S*-nitrosothiols that are isolatable.[6] Amyl nitrite, an organic nitrite, is employed as an antidote for cyanide positing and used in the treatment of heart disease.[7]

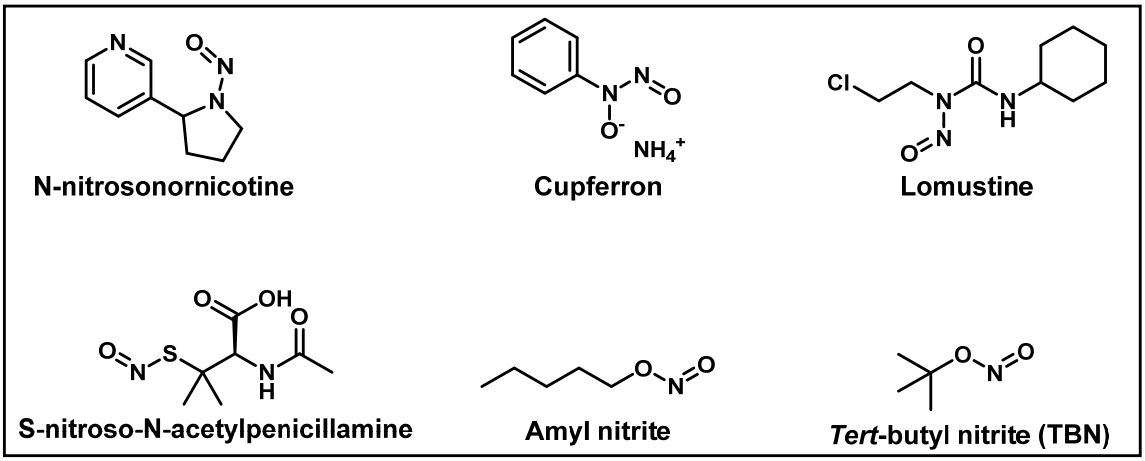


Figure 3-28. Nitrosated organic compounds.

Many NO bonded compounds act as endogenous nitric oxide donating compounds. The structural diversity of NO compounds translates well into the varied pathways involved with NO generation within the body. Many reviews have highlighted some of these compounds with application-based studies included.[8] The structure-activity relationships for nitrosated compounds are not well understood and continue to be investigated; the access to a range of diverse NO compounds is needed.

N-Nitroso Compounds

N-nitroso compounds can be synthesized from a wide variety of nitrogen functional groups with many implications and applications(Figure 3-2). Nitrosamines serve as precursors for the formation of carbon–nitrogen through the generation and formation of ammonium radicals within a solvent change.[9] *N*-nitrosodimethylamine are present in water sources and has been heavily investigated as a carcinogen.[10] Nitrosamines are also often used to generate hydrazine in the presence of zinc and can be used to enrich amines with deuterium

while refluxing in aqueous sodium methoxide in D_2O solutions.[11–12] *N*-nitrosamides have been found to be carcinogenic materials, but also serve as precursors for the formation of amidyl radicals with reports of HAT transfer capabilities.[13–14] *N*-nitrosohydrazines have specific utility as NO donors in biological systems.[15] *N*-nitrosoureas are capable of DNA repair and used in chemotherapeutic treatments for lung cancer. [16] *N*-nitroso derivatives of guanidine has been shown to be an effective antioxidant,[17] and as synthetic precursor to azomethane.[18] *N*-nitroimines have been shown to be masked carbonyl analogues that reveal themselves upon thermal decomposition with the liberation of molecular nitrogen as the by-product.[19] *N*-nitrosohydroxylamines have seen many applications as NO donors and as inhibitors of enzymes like in the case of tropolone.[20] *N*-nitrososulfonamides such as Diazald's reagent is commonly used as a precursor to generate diazomethane under basic conditions or with mild heat.[21] *N*-nitrosocarbamates possess mutagenic properties, with subtle structural variations playing a direct role on the mutagenicity of the compound. [22]

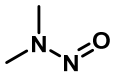
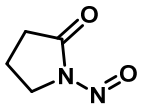
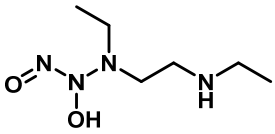
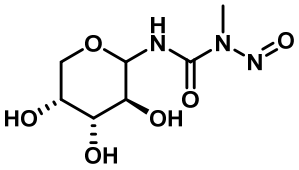
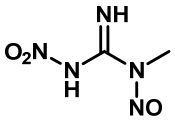
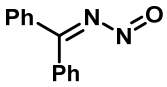
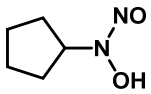
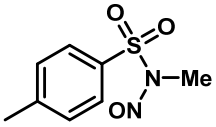
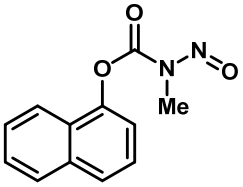
Class	Example	Comments	Reference
Amine		Animal Carcinogen	10
Amide		Animal Carcinogen	13,14
Hydrazine		NO Donor	15
Urea		Chemotherapeutic Drug	16
Guanidine		Mutagen and Precursor to diazomethane	17, 18
Imine		Precursor to Molecular Nitrogen	19
Hydroxylamine		Mushroom Tyrosinase Inhibitor	20
Sulfonamide		Precursor to Diazomethane	21
Carbamate		Mutagen	22

Figure 3-29. Examples of N-nitroso compounds.

Synthesis of *N*-Nitroso Compounds

The synthesis of nitroso compounds is typically achieved in one step under hard Bronsted or Lewis acidic conditions in the presence of nitrite anions (Figure 3-3A).[23]

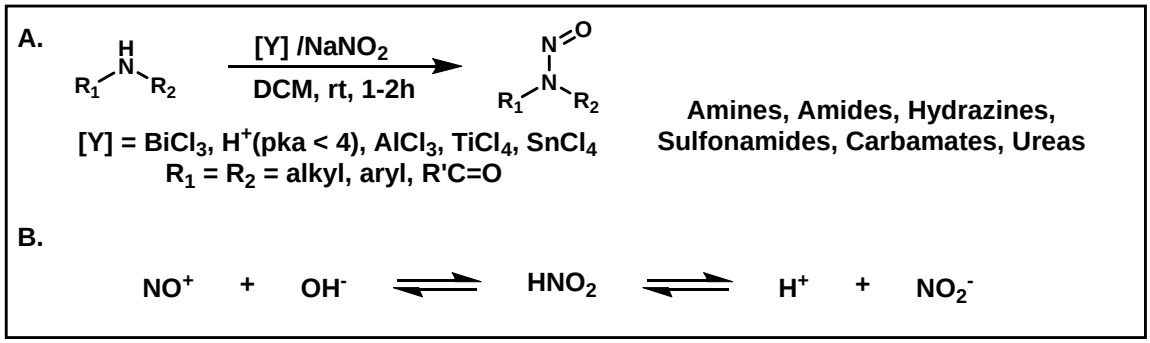


Figure 3-30. Synthesis of N-nitroso compounds.

The combination of Lewis or Bronsted acid and nitrite anions generate a nitronium cation, which can then be trapped by nitrogen nucleophile to produced desired N-nitroso compounds (Figure 3-3B). However, these reactions do not always produce stable and isolable compounds under reported reaction conditions. For example, cyclic amides rearrange to form lactones while releasing N_2 (Figure 3-4).[24]

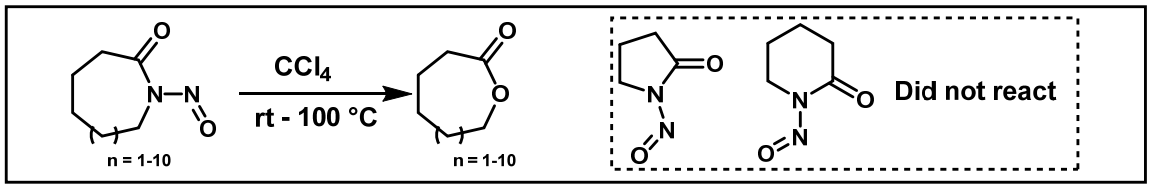


Figure 3-31. Rearrangement from N-nitrosolactams to lactones.

The isolation of *N*-nitroso compounds is nontrivial. As shown in Figure 3-5A, *N*-nitrosolactams rearrange to lactones. The formation of a zwitterion can occur between the nucleophilic oxygen of the nitroso functional group and carbonyl. Although the zwitterion in Figure 3-5A is similar to Figure 3-5B, the acyclic nature

and α-sp^2 carbon found in *N*-nitrosated anilides leads to the formation of aryl radical and carbocations (Figure 3-5B).[25] Figure 3-5C shows that sulfonyl groups can also be attacked by the NO group to form azo compounds and sulfonic acid.[26] In Figure 3-5D, *N*-nitrosoimines are also prone to this rearrangement leading to the formation of ketones in an analogous fashion described previously.[27]

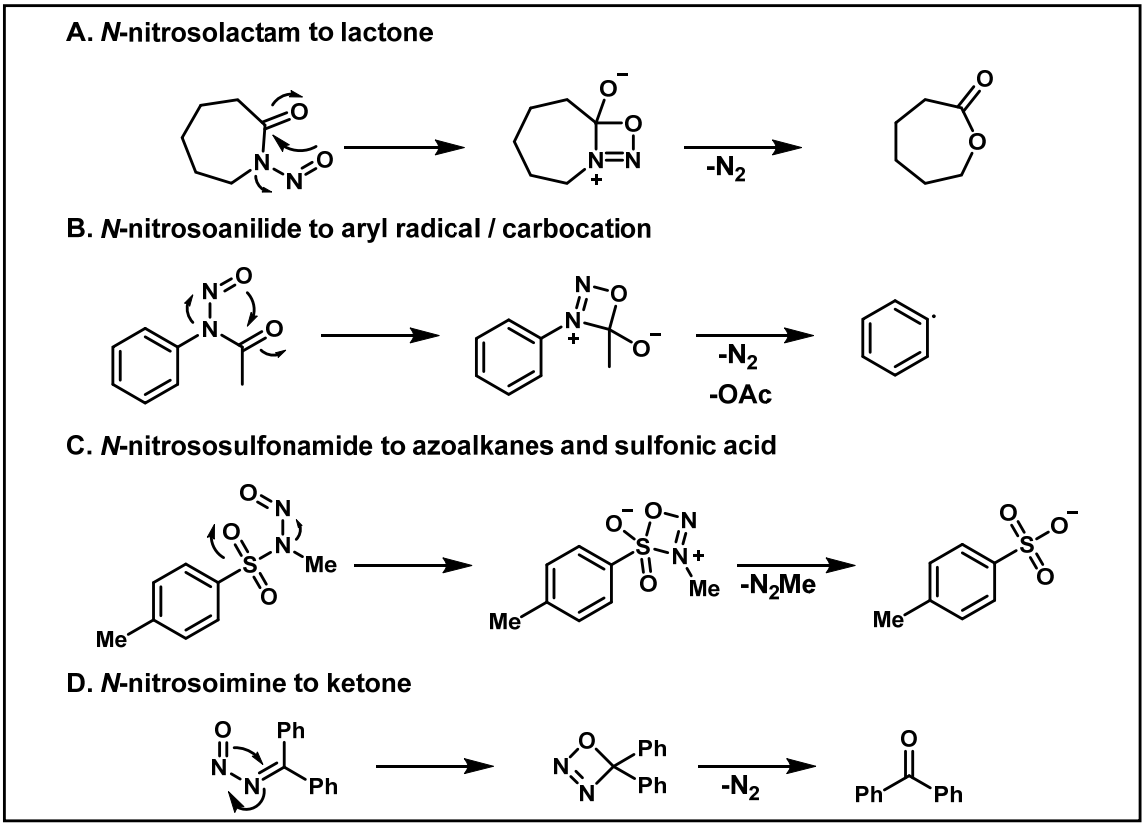


Figure 3-32. Rearrangements of N-Nitroso compounds.

In addition to rearrangements, cleavage of N–NO bond often occurs under harsh reaction conditions. There is a need for mild methods to generate nitrosated compounds prone to rearrangement and provide additional opportunities to isolate

compounds that have been thought to not be stable or exist under current reaction conditions.

O-Nitroso Compounds ("Alkyl Nitrites")

O-nitroso compounds or alkyl nitrites are relatively stable compounds that have many applications in biology. [28] As shown in Figure 3-6, alkyl nitrites have been used as rocket propellent, recreational substances and as a synthetic nitrosation reagent (Figure 3-6).

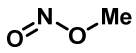
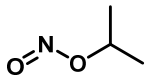
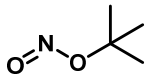
Class	Example	Comments	Reference
Primary Alcohol		Rocket Propellant	29
Secondary Alcohol		Recreational Substance of Abuse	30
Tertiary Alcohol		Synthetic Reagent	31

Figure 3-33. Select examples of alkyl nitrites.

Primary alkyl nitrites like methyl nitrite are highly flammable and been used as fuel for rockets. In high concentrations, methyl nitrite is toxic and classified as a narcotic. [29] Secondary alcohols like isopropyl nitrite are also explosive and been used as a narcotic and recreational inhalant. This compound in large doses is known to cause methemoglobinuria and cyanosis which results in shock that can be fatal.[30] Tertiary alcohols like *tert*-butyl nitrite have seen many synthetic applications mostly known as a diazotization and nitrosating agent. [31]

Synthesis of *O*-nitroso compounds

The synthesis of alkyl nitrites is done with reagents and conditions analogous to the formation of *N*-nitroso compounds (Figure 3-7).

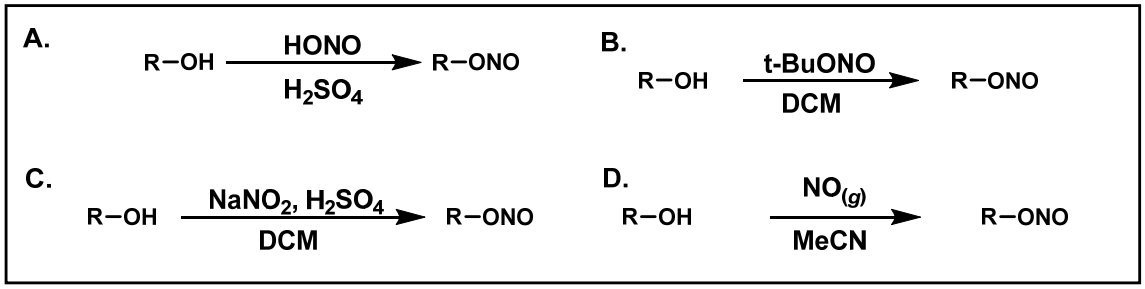


Figure 3-34. Synthesis of alkyl nitrites.

This transformation was first reported in 1943 with nitrous acid in sulfuric acid, resulting in the first reported formation of 1-butyl nitrite (Figure 3-7A). [32] *Tert*-butyl nitrite can be used as a nitrosating reagent for primary and secondary alcohols to generate alkyl nitrites in good yields (Figure 3-7b).[33] Alkyl nitrites can also be formed with nitrate salts under acidic conditions (Figure 3-7C). [34] Lastly, alkyl nitrites can be formed by bubbling in nitric oxide gas into a solution of acetonitrile (Figure 3-7D). [35]

Utility of *O*-nitroso compounds

One of the earliest synthetic uses of alkyl nitrites was reported in 1960 by Sir Derek Barton in the Barton Reaction (Figure 3-8). [36]

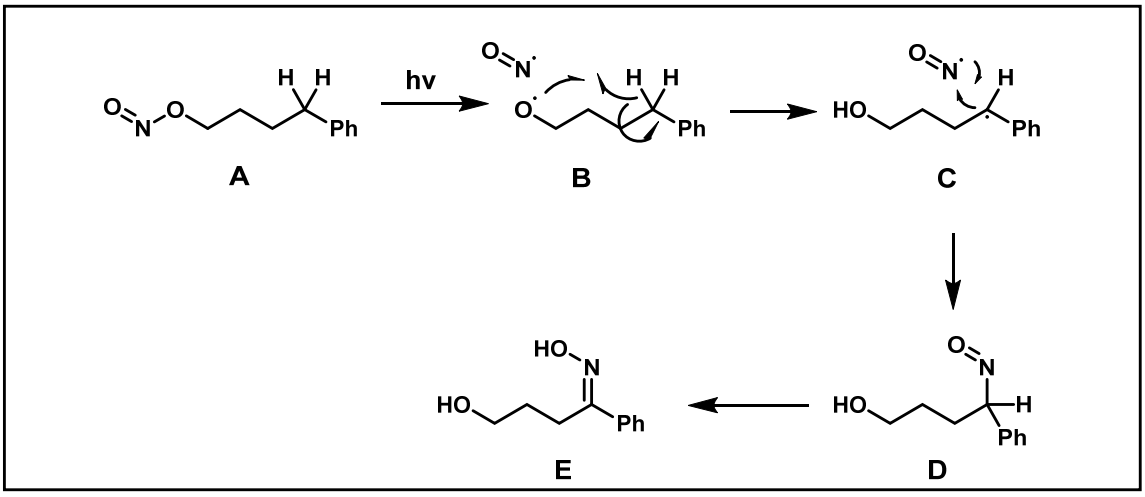


Figure 3-35. General mechanism of the Barton reaction.

This reaction involves a long chain alkyl nitrite (**A**) that is photolyzed under UV light. Under irradiation, the RO–NO bond is homolytically cleaved generating an alkoxy radical (**B**). This alkoxy radical is capable of 1,5-hydrogen-atom transfer generating an alcohol with a localized carbon radical (**C**). The alkyl radical combines with the nitrosyl radical to form compound **D**, which then tautomerizes into an oxime **E**. The Barton reaction was one of the first examples of alkyl nitrite in organic synthesis.

The alkyl nitrite *tert*-butyl nitrite (*t*-BuONO) has been used extensively in the development of novel methods for the reactions between chemical compounds (Figure 3-9). *Tert*-butyl nitrite has been used to nitrosate amines and amides in good to excellent yield with high selectivity. [37] Under basic conditions, reactions between *t*-BuONO and carbonyl substrates with available α-protons undergo enolization leading to the formation of α-oximinoketones.[38] Reactions with primary amines lead to the diazotization of these compounds as shown in Figure 3-9C. The diazotization leads to the formation of an aryl radical and in the presence of a

suitable electrophile like trimethylsilyl azide ($TMSN_3$) results in for formation of phenyl azide.[39]

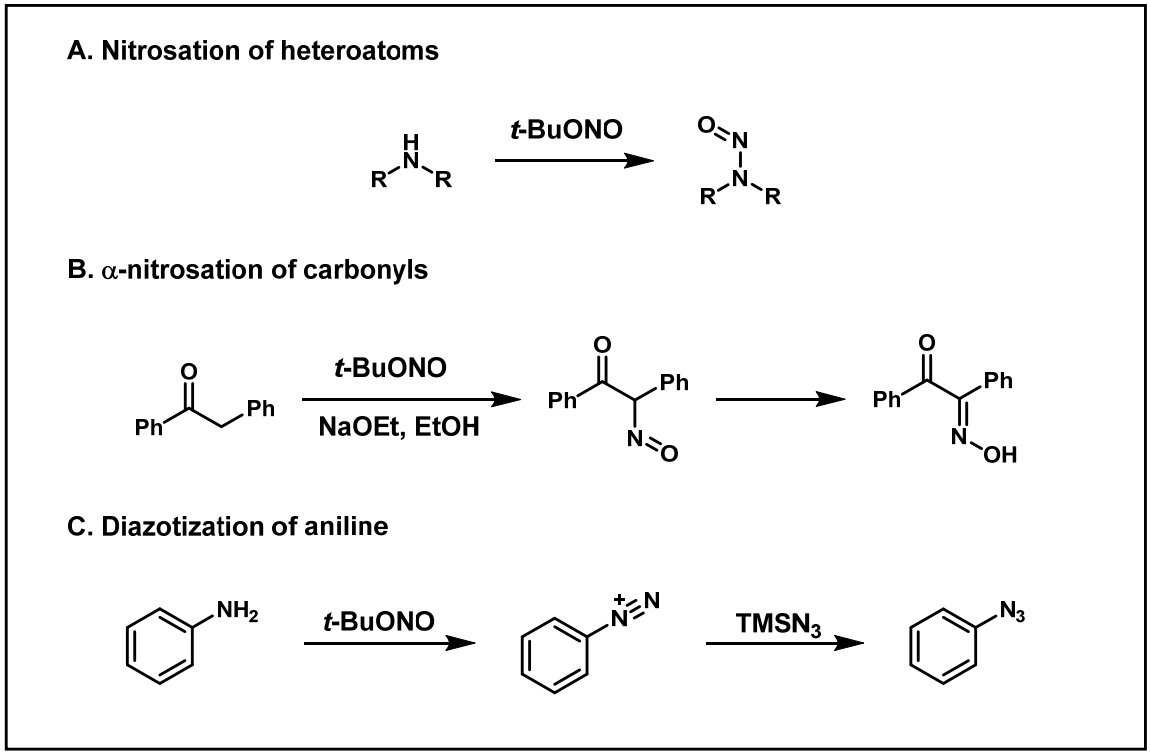


Figure 3-36. t-BuONO used in synthesis.

S-Nitroso compounds

S-Nitroso compounds are unique nitrosated heteroatoms that are commonly observed as thiol nitrites and sulfonyl nitrites (Figure 3-10). Thiol nitrites were first noted in the literature as a result of tissues and cells generating nitric oxide (NO).[40] They were thought to provide stabilization and transport of the highly reactive NO, which has been shown to provide an effect on proteins involved with muscle contractility, apoptosis, and circulation.[41]

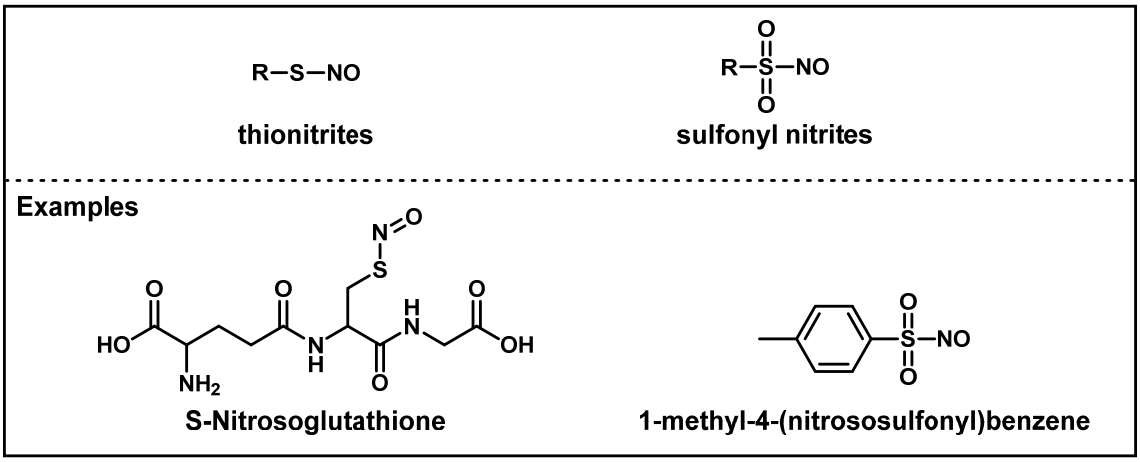


Figure 3-37. General structures of S-nitroso compounds with select examples.

Synthesis of S-nitroso compounds

Recently, a method for synthesizing thiol nitrites with N_2O_4 with 18-crown-6 ether has been published, showing the formation of thiol nitrites in solution, which decompose to produce disulfides (Figure 3-11).[42]

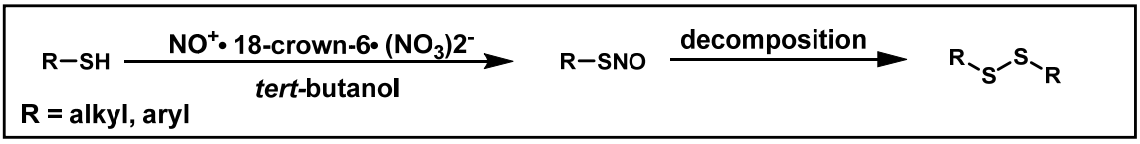


Figure 3-38. Synthesis of thiol nitrites and their decomposition into disulfides.

Thiol nitrites readily decompose into disulfides and are typically characterized by their UV and IR absorbance. When steric hindrance is present, thiol nitrites are less prone to decomposition and isolation of thiol nitrites as stable compounds are possible. The first reported synthesis of thiol nitrites were *S*-nitrosocysteine and *S*-nitrosoglutathione, accomplished though utilizing iron ions in a buffer solution containing nitric oxide gas. [43] The primary biological compounds used to synthesize RSNO compounds were glutathione, cysteine, homocysteine, *N*-acetylpenicillamine, *N*-ethyl maleimide, mercaptopropionic acid, and bovine serum

albumin. [44] To further understand these compounds, research focused on the synthesis of stable thiol nitrites, outside of the protein predecessors, was needed. The synthesis of thiol nitrite compounds bearing bowl-like substituents allow for the stabilization of the compounds at room temperature with $NaNO_2$ under acidic conditions (Figure 3-12).[45]

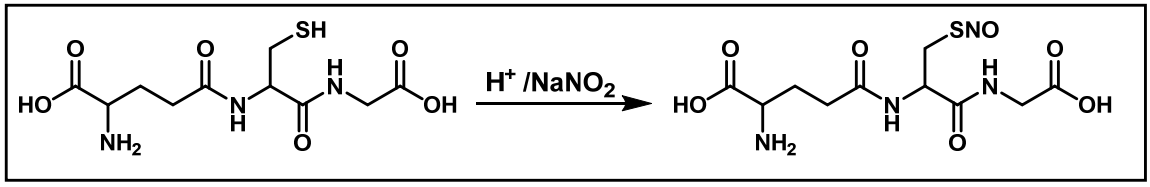


Figure 3-39. Synthesis of N-nitrosoglutathione using sodium nitrite.

In addition to *S*-nitroglutathione, it was found that substituent groups such as triaryl-methyl were sterically bulky enough to stabilize the weak sulfur to nitrogen bond, which allowed the crystal structure determination to be done (Figure 3-13).[46]

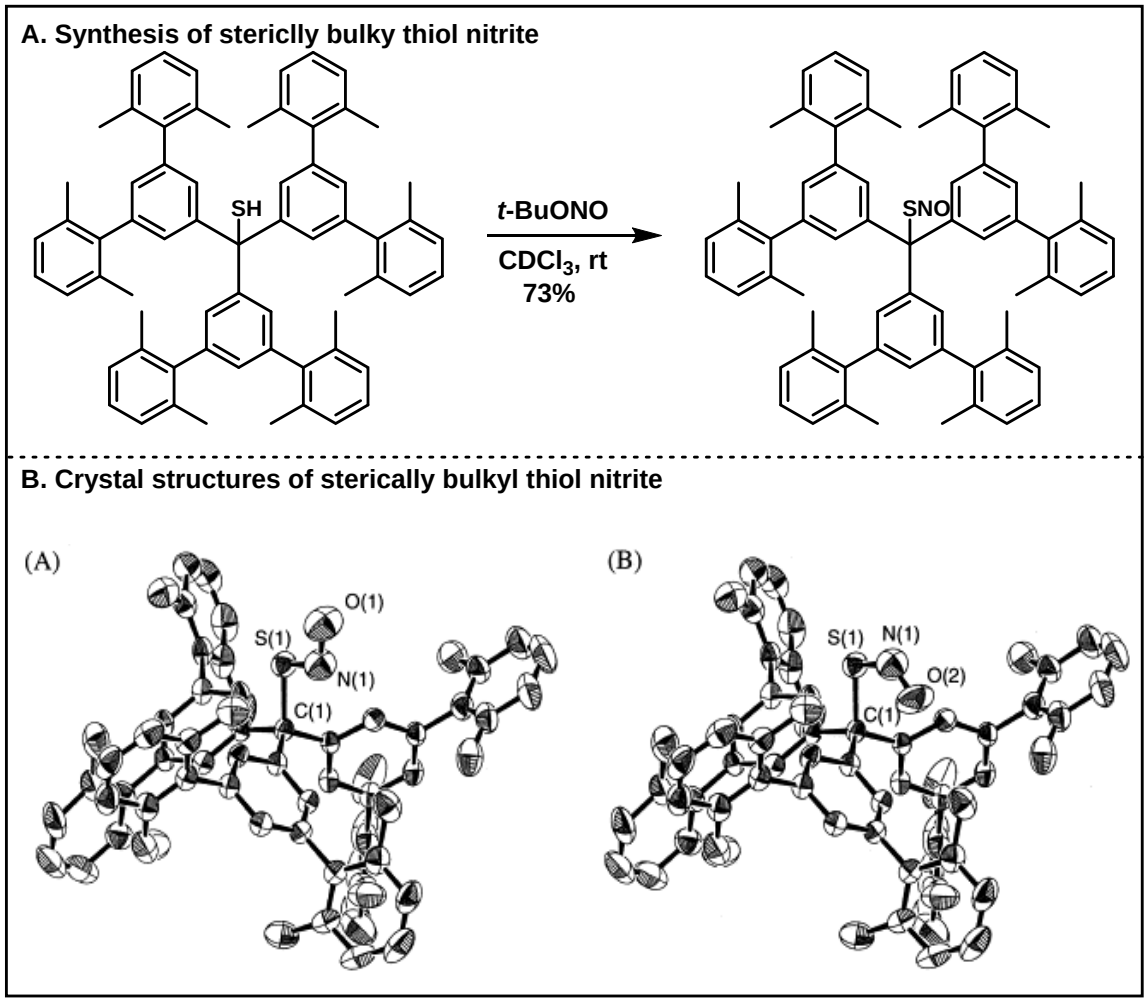


Figure 3-40. A. Synthesis and crystal structure of sterically bulky thiol nitrite. B. Crystal structures of the anti (A) and syn (B) isomers isolated.

Sulfonyl nitrites are potent nitrosating and diazotizating reagents that thermally decompose at elevated temperatures (Figure 3-14).[47]

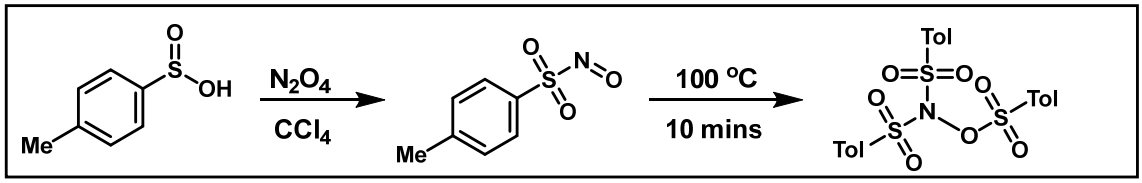


Figure 3-41. Synthesis and decomposition of sulfonyl nitrites.

Most research on sulfonyl nitrites are focused on their utility in deamination reactions that proceed via a diazotization reaction pathway (Figure 3-15).[48]

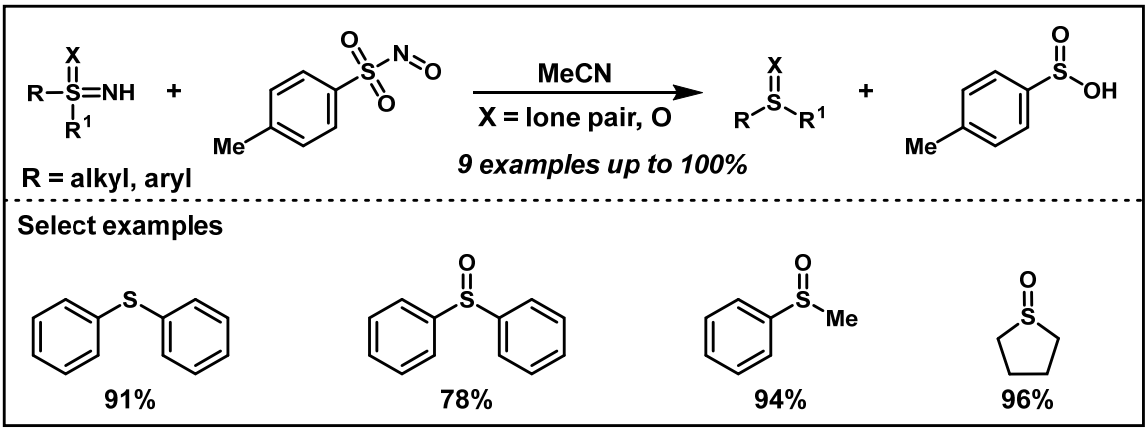


Figure 3-42. Example of deamination reaction.

Transnitrosation of Nitroso Compounds

Transnitrosation is the process of transferring the nitroso functional group from one compound to another. As described previously, nitrosation is commonly performed with metal nitrites in the presence of acid allowing for the access to nitroso compounds. The ability to transnitrosate depends on the heteroatom and functional group the nitroso group is bound to. This determines the reactivity profile of these nitroso reagents in the presence other organic compounds. This has huge implications in the human body and prompted studies of the decomposition of nitroso compounds under several conditions. This also opened the door for nitro compounds to be utilised in the synthesis of nitroso compounds through a transnitrosation mechanism.

Transnitrosation of Sulfonamides

N-nitrososulfonamides are organic nitroso compounds that are highly capable of transnitrosation. There are several studies that describe the decomposition or transnitrosation of sulfonamides in the presence of other organic substrates, but the products formed are never the focal point of the study.[49] The *N*-

nitrososulfonamide used in these studies is *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (**MNTS**) with several investigative reports published demonstrating its transnitrosation ability (Figure 3-16).[49, 50]

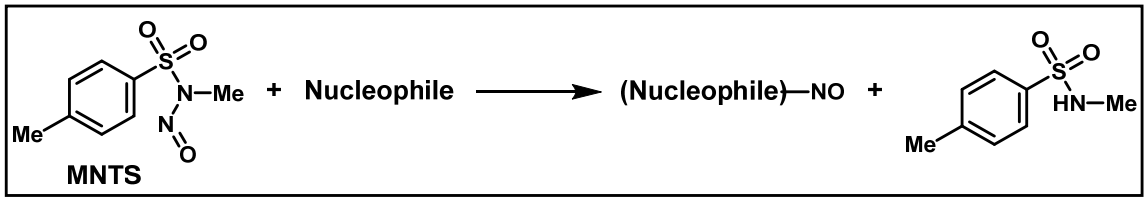


Figure 3-43. General scheme for transnitrosation from MNTS to an organic nucleophile

MNTS was studied with several nucleophiles to understand the kinetics of transnitrosation. Reactions with carbanions were studied and showed that transnitrosation to carbon atoms is possible. Although the products are not characterized in the publication, it is likely the resulting nitrosated compound tautomerizes into an oxime as the isolatable product (Figure 3-17).[50e]

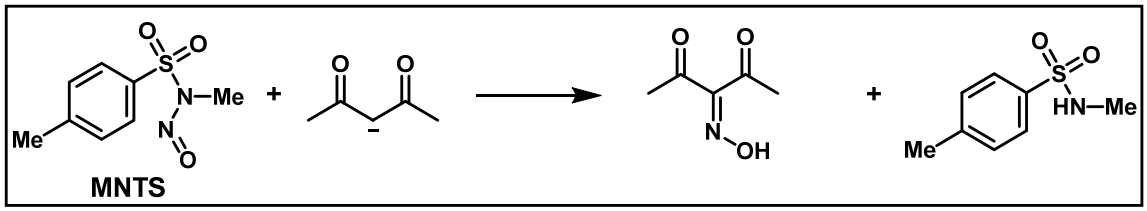


Figure 3-44. General scheme for the transnitrosation from MNTS to a carbanion.

The kinetic study demonstrated that the reactivity of the carbanions correlated with their gas phase acidity. Efforts to link reactivity to characteristics present in these substrates led to a non-perfect synchronization consideration to thermodynamic quantity pK_a and rate constants for structurally diverse carbanions. This means that there was not a clear correlation between the nucleophilicity of nucleophiles towards the rate of product formation.

A study on sulphur nucleophiles demonstrated that thiolates react with **MNTS** to form thiol nitrites in an asynchronous mechanism (Figure 3-18). [50d]

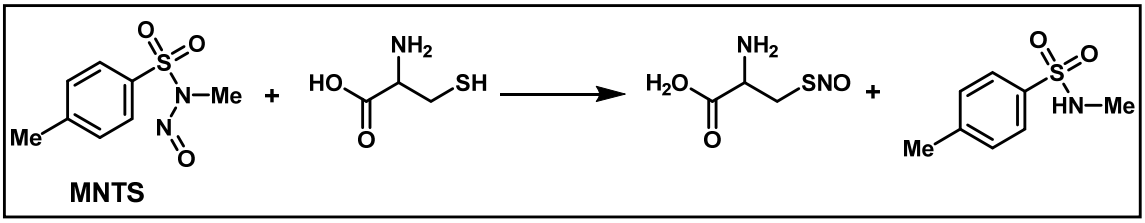


Figure 3-45. Transnitrosation from MNTS to thiols.

In a comparison with secondary amines, it was found that nitrosation at the sulfur atom is 2000 times more likely to occur than at nitrogen atom. When a compound such as cystine is nitrosated, nitrosation occurs exclusively at the sulfur atom, even when other oxygen and nitrogen nucleophilic sites are present.

Transnitrosation to form *N*-nitroso compounds from **MNTS** has been reported with a variety of nitrogen nucleophiles ranging from primary, secondary and tertiary amines (Figure 3-19).[49]

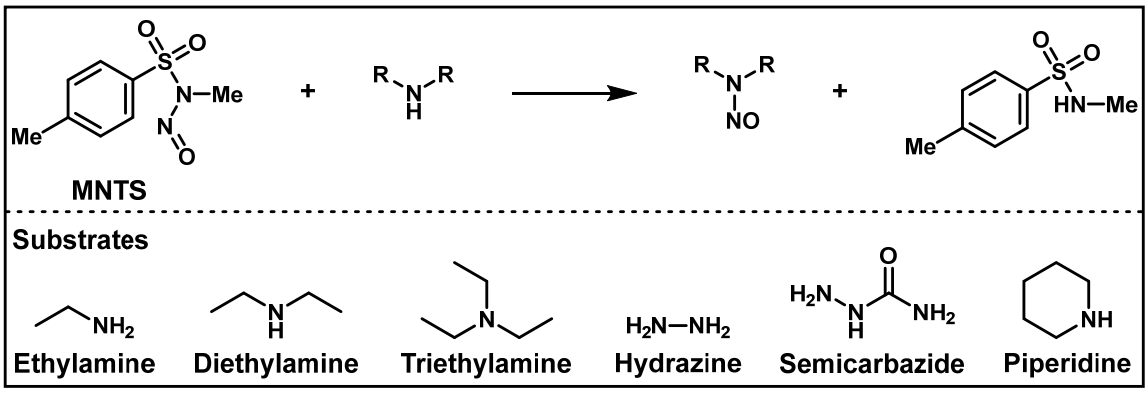


Figure 3-46. Transnitrosation from MNTS to nitrogen nucleophiles.

This extensive study examines a wide range of nucleophiles focused on amines, hydrazines, carbazides in various medias to determine the kinetics of transnitrosation from **MNTS**. In all of these cases the reactions afforded full

conversion of **MNTS** to the sulfonamide byproduct. Their rates were found to be in good correlation with Richie's N_+ scale. N_+ is originally used as a parameter depending on the identity of the nucleophile and the solvent for the following equation:

$$\log k = log k_0 + N_+$$

where log k_0 is a parameter dependent on the identity of the cation.[51] Considering transnitrosation from **MNTS** to an amine is an ionic covalent bond forming transformation, this equation and scale was an effective way to characterize these substrates nitrosated. The conclusions showed that there was a very close correlation between the reactions between the nucleophile and electrophile fulfilling Ritchie's equation and that it was a concerted reaction of nucleophiles with the nitroso group. The rate of transnitrosation is governed by the nucleophilicity of the atom and the solvent used in the reaction. Another factor to consider are vertical ionization potentials relative to a standard nucleophile. Using N_+ allows for an accurate depiction of nucleophilicity and the reactivity of this ionic transition state.

Unfortunately, at elevated temperatures, **MNTS** has a unfavorable pathway available where it decomposes to form diazomethane under basic conditions.[52] **MNTS** has a shelf life of 1–2 years in addition to being both toxic and mutagenic.[53] **MNTS** shows thermal instability in temperatures as low as 60 °C.[54] This presents a challenge when attempting to use **MNTS** to nitrosate compounds that require elevated temperatures. In addition, **MNTS** is sensitive to pH in solution

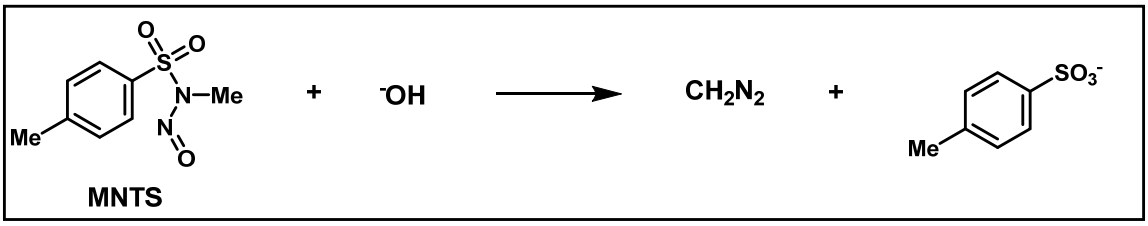


Figure 3-47. MNTS catalyzed by alkali hydroxide to form diazomethane.

Despite these issues, MNTS is effective at forming diazomethane under basic conditions (Figure 3-20). Diazomethane is a highly desired versatile reagent that can behave as a methylene precursor.[55]

Transnitrosation of Alkyl Nitrites

Alkyl nitrites are effective transnitrosation reagents and have been studied, showing the transnitrosation capability between alcohol substrates in solution (Figure 3-21).[56] As shown in Figure 3-21, there is an equilibrium between alkyl nitrites and alcohols, where nitrosyl exchange accorus rapidly between the two.

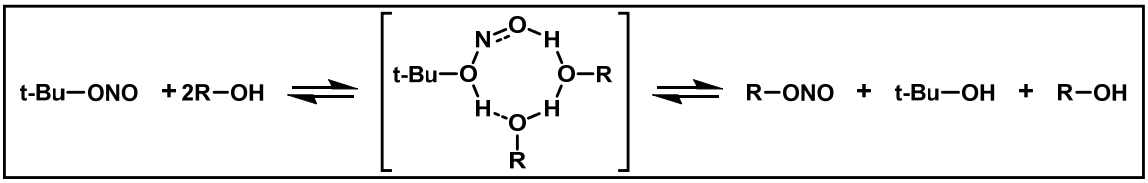


Figure 3-48. Transnitrosation in equilibrium with alcohols.

Primary alkyl nitrites are formed from TBN with an equilibrium constant near 10 with no beta substituents affecting the observed equilibrium. Secondary alcohols ave an observed equilibrium constant of 4. This equilibrium constant is minimized even further when tertiary alcohols are used as substrates. This indicates that TBN ability to transnitrosate decreases significantly moving from primary alcohols to tertiary alcohols.

The synthesis of tertiary alkyl nitrites remains difficult and access of these compounds are nontrivial with methods currently presented. By our search of the literature we were only able to identify a methods paper that featured the synthesis with emphasis on the access to tertiary alkyl nitrites from alchohols in one step. There are some papers that use sodium nitrite[57] and glycerol nitrite[58] to synthesize tert-amyl nitrite with no reported yields determined. Novel methods to generate alkyl nitrites is of increasing interests for the chemistry community.

Development of next generation nitrosating reagent

After evaluation of transnitrosation and previous work on MNTS, we decided to pursue the synthesis and evaluation of novel *N*-nitrososulfonamides as transnitrosation reagents and potential HAT reagents (see Chapter 4). A variety of *N*-substituted-*N*-nitrososulfonamides were targeted using a two-step synthetic sequence (Figure 3-22).

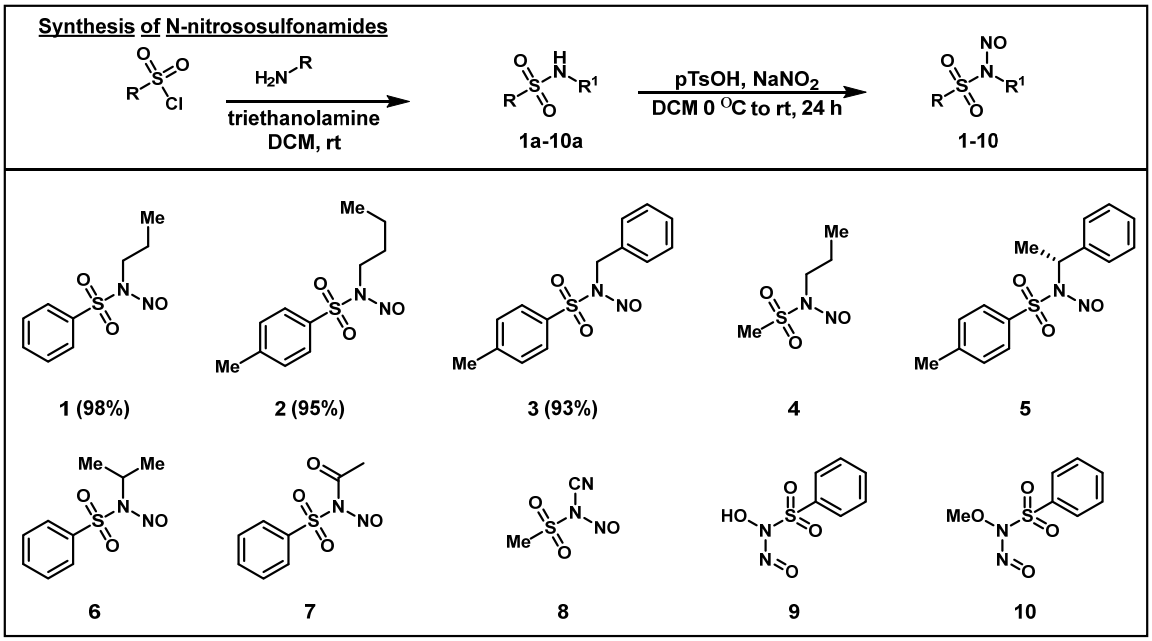


Figure 3-49. Scope of N-nitrososulfonamide synthesis.

Our efforts to synthesize compounds **1–10** proved to reveal a lot about the accessibility and stability of *N*-nitrososulfonamides. Compounds **1–2** were synthesized and isolated, but unfortunately, they readily decompose upon standing. Compound **3** (**BNTS**) was able to be synthesized as a solid material with no signs of decomposition upon standing under ambient conditions. Compounds **4–10** were unable to be synthesized despite several attempts to isolate converted substrates. Compound **7** with the *N*-acyl group was unable to be isolated, likely due to an in-situ decomposition after the nitroso group was installed.

Because of the observed bench stability of **BNTS** and its physical state as a solid, we investigated this compound as a transnitrosation reagent. We reacted amide **11** with **BNTS** for the synthesis of nitrosated compound **12** (Figure 3-23). At room

temperature, no reaction was observed. At elevated temperatures, **12** was formed in 77% yield.

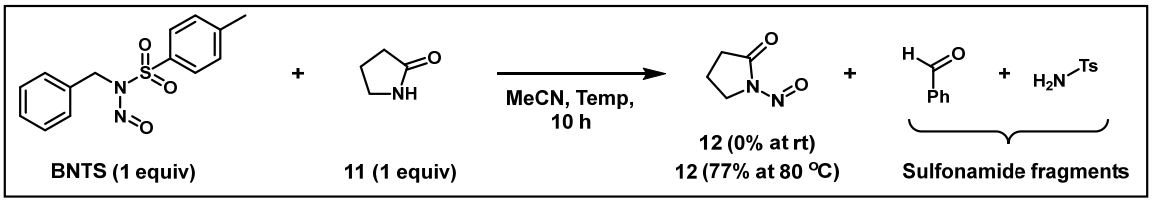


*Figure 3-50. Initial transnitrosation reaction between **BNTS** and **12**.*

Over the course of the reaction, we also observed and isolated benzaldhyde and *N*-tosylamine, as a result of BNTS decomposition. These byproducts could be deleterious to others substrate scope. *N*-Benzyl-*N*-nitrososulfonamide (**BNTS**) has been shown to decompose rapidly at higher temperatrues into a nitrogenous entity-separated ion pair, forming nitrogen gas, benzyl carbocation, and sulfonic acid.[59]

For this reason, we decided to evaluate other *N*-nitrososulfonamides shown in Figure 3-24 that we believed were not prone to rearrangements and decomposition.

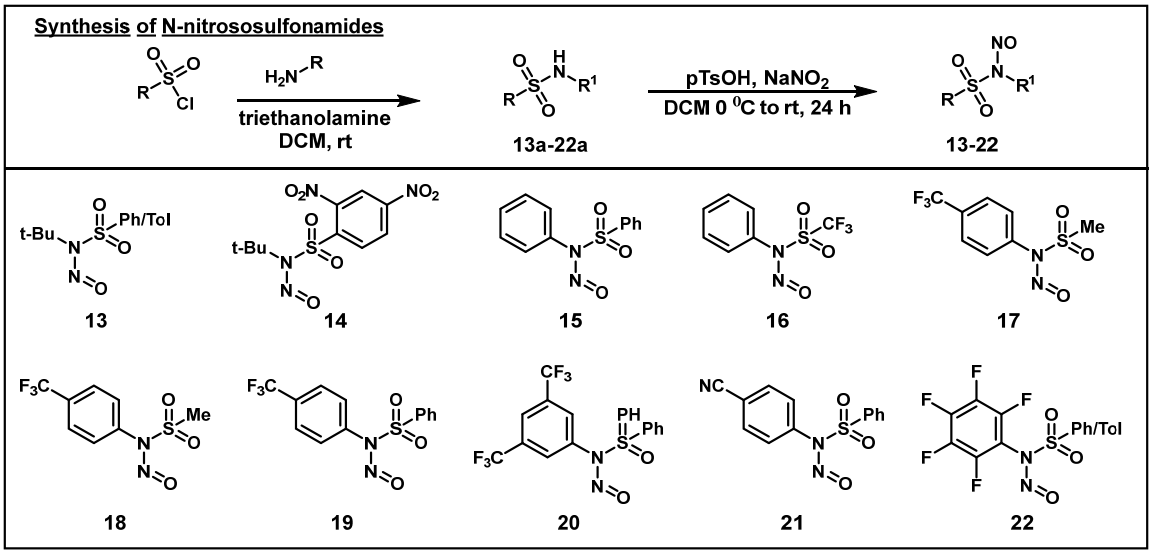


Figure 3-51. Attempts to synthesize N-nitrososulfonamides without α-protons.

Our strategy was to use bulky substituents and the lack of α-hydrogens to generate a transnitrosating reagent that could be recovered and reconverted back into the reagent. Despite our best efforts we were unable to synthesize compounds **13–22**. Compounds **13–14** with *N-tert*-butyl substituents resulted in zero conversion from **13a–14a**. Compounds **15–21** with N-aryl substituents exclusively nitrated the *N*-aryl ring regardless of how electron deficient (**17–21**) the aryl group was. When the *N*-aryl group was perfluorophenyl (**22**) the reaction failed to yield the desired product with zero conversion from **22a.** Our next strategy was to examine cyclic sulfonamides.

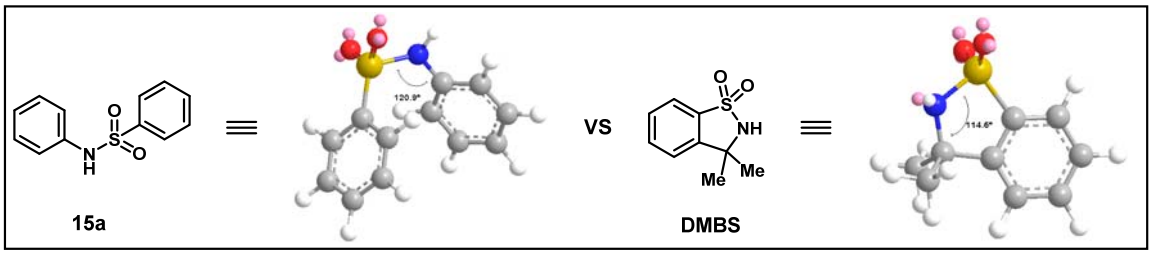


Figure 3-52. Chem3D models of an acyclic and cyclic sulfonamide.

Chem3D models shown in Figure 3-25, of acyclic and cyclic sulfonamides reveals a a noticeable change to the dihedral angle when modeling an acyclic compound **12** (120.9º) vs an cyclic compound **DMBS** (114.9º). We believe that this change in dihedral angle is enough to allow for the nitrosation of **DMBS**.

Compound **NO-1** was synthesized in four steps from saccharin (Figure 3-26).

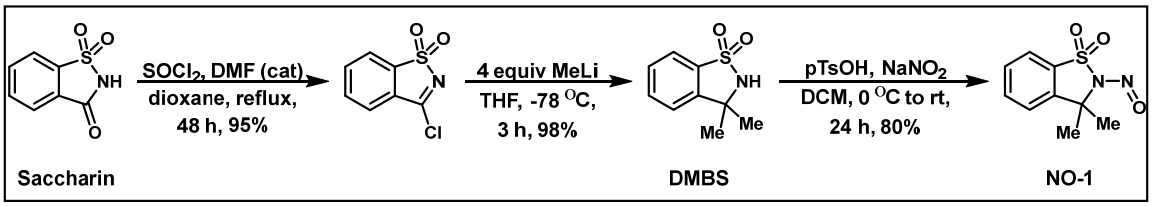


*Figure 3-53. Synthesis of novel reagent **NO-1***

Saccharin is a relatively inexpensive chemical commonly used as an artificial sweetener commonly sold as “Sweet’n Low”.[60] The synthetic sequence was developed using previous reports for the synthesis of **DBMS**.[61] After optimization, **DBMS** could be converted to **NO-1** in good yields with high reproducibility and scale (10 g).

Compound **NO-1** is a crystalline solid with no signs of thermal instability under ambient conditions. A crystal structure revealed rotamers around the N-N bond in the 0.87:0.13 ratio (Figure 3-27).

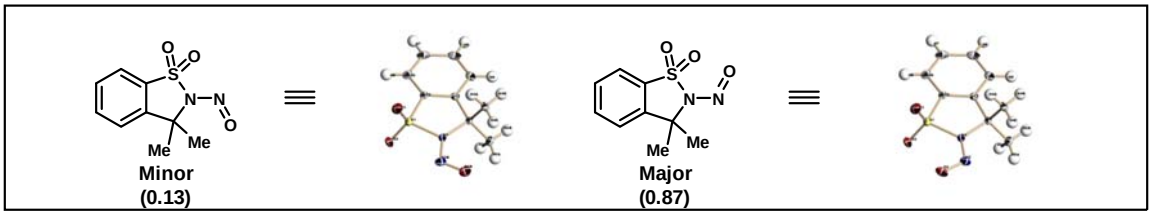
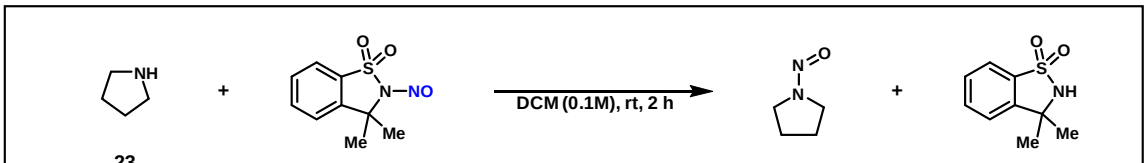


*Figure 3-54. Crystal rotamers of **NO-1**.*

Transnitrosation with Novel Reagent NO-1

For our initial screen, we evaluated secondary amine pyrrolidine (**23**) and **NO-1** (Figure 3-28).



23
1 equiv

1 equiv

24

DMBS

entry	deviation from standard conditions	yield of 14
1	none	93%
2	EtOAc	89%
3	Acetone	72%
4	MeCN	89%
5	H_2O	36%

*Figure 3-55. Optimization of transnitrosation reaction using **NO-1**.*

This reaction worked well in a variety of different solvents at room temperature to produce nitrosamine **24** and **DMBS,** being the only remaining compounds after the reaction was analyzed (Figure 3-25, entry 1). We observed that chlorinated solvents (CH_2Cl_2 or DCE) working best across a wide group of substrates.

Transnitrosation to Nitrogen nucleophiles Substrate Scope

With optimized conditions in hand, we examined a variety of nitrogen nucleophiles to determine how well the transnitrosation worked across a broad substrate scope (Figure 3-29).

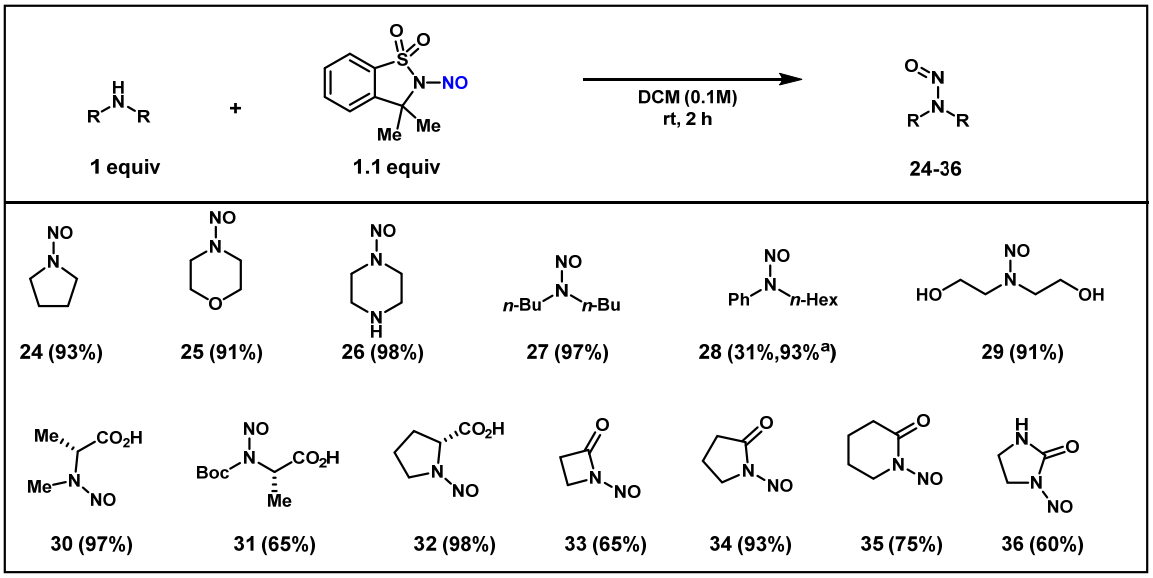
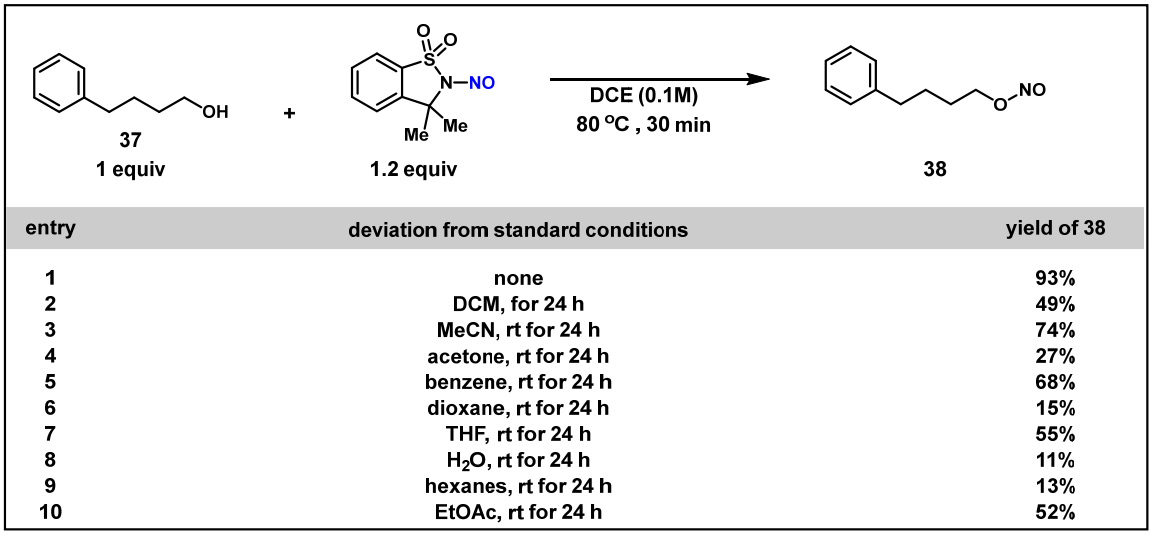


Figure 3-56. Substrate scope for transnitrosation reaction. Reaction conditions: substrate (0.2 mmol), NO-1 (0.22 mmol), 2 mL of CH_2Cl_2, rt for 2 h. Yields refer to chromatographically pure material unless otherwise noted. [a] Dichloroethane used as solvent and reaction conducted at 80 ^oC.

As shown in Figure 3-29, secondary amines (**24–29**) are able to be nitrosated in excellent yields. The reaction proceeded smoothly in the presence of other heteroatoms (**25**–**26**). Acyclic alkyl amine (**27**) proceeded smoothly, while *N*-alkylated aniline (**28**) was sluggish at room temperature. At elevated temperatures in dichloroethane, **28** was produced in high yield. Amines with hydroxyl groups present (**29**) are selectively nitrosated at the nitrogen in the compound. In addition to amines, amino acids are also able to be nitrosated in good to excellent yield (**30–32**). Lastly amides (**33–35**) and urea (**36**) are able to be synthesized in good to excellent yield.

Transnitrosation to Oxygen nucleophiles Substrate Scope

We performed an optimization study on NO-1 for the synthesis of alkyl nitrites. Using 4-phenylbutan-1-ol (**37**) as the substrate, a variety of conditions were examined (Figure 3-30).



entry	deviation from standard conditions	yield of 38
1	none	93%
2	DCM, for 24 h	49%
3	MeCN, rt for 24 h	74%
4	acetone, rt for 24 h	27%
5	benzene, rt for 24 h	68%
6	dioxane, rt for 24 h	15%
7	THF, rt for 24 h	55%
8	H_2O, rt for 24 h	11%
9	hexanes, rt for 24 h	13%
10	EtOAc, rt for 24 h	52%

*Figure 3-57. Optimization for the synthesis of alkyl nitrites using **NO-1**.*

We discovered that this reaction works across a broad range of solvents. High yield of alkyl nitrite was achieved in 30 minutes at 80 °C in dichloroethane. We determined elevated temperatures were needed to get over any rotational barriers in NO-1 so that transnitrosation can occur. When the reaction time was extended, we noticed decrease in yield and the formation of 4-phenylbutanal. This indicates that alkyl nitrites are prone to decompose and oxidize to the aldehyde, as observed in previous reports on alkyl nitrites.[56] In general, DCE and MeCN providing the highest yields of the desired products.

With optimized conditions in hand, we examined alcohol substrate scope to determine the effectiveness of this reagent to form alkyl nitrites (Figure 3-31).

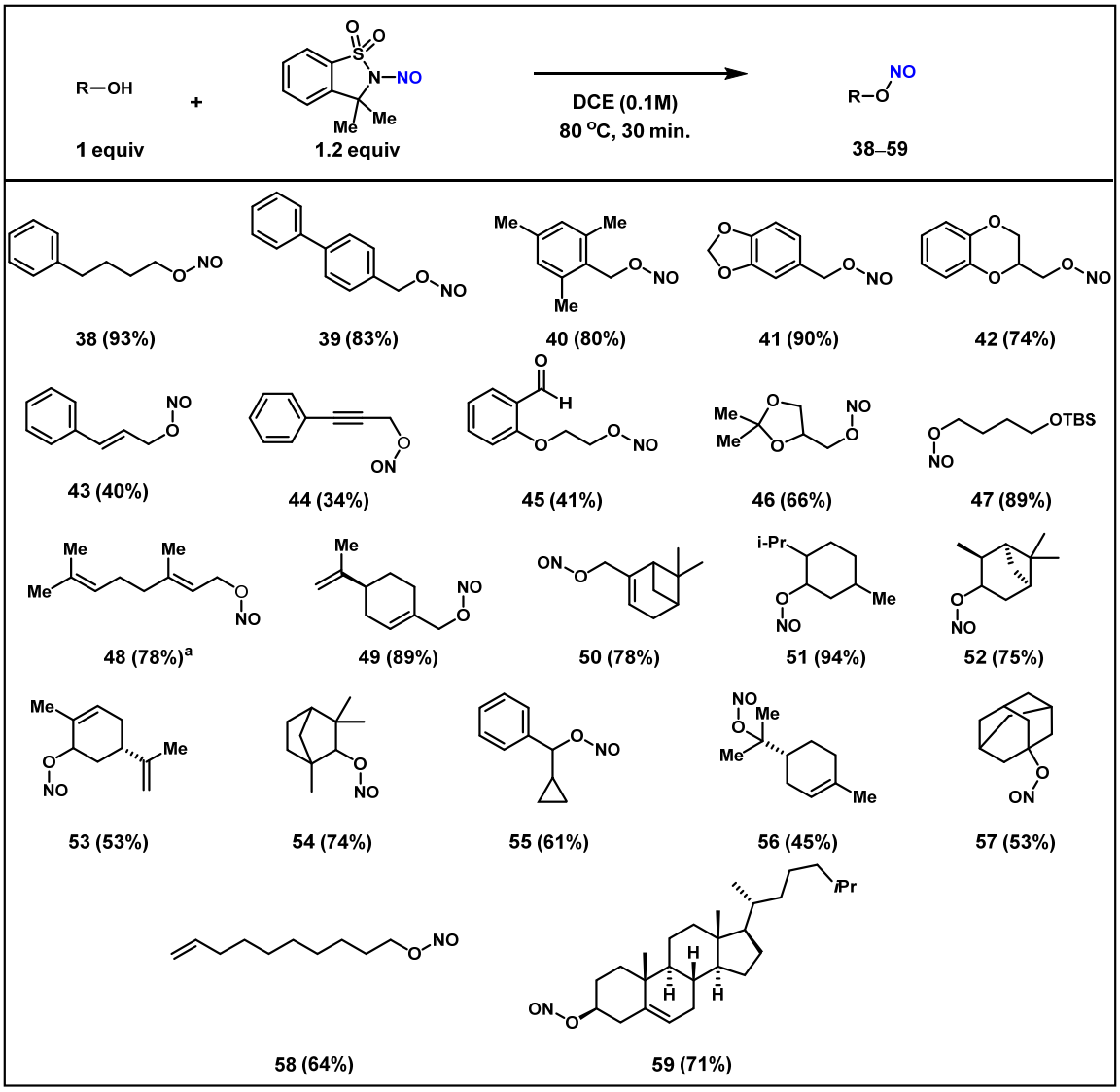


Figure 3-58. Substrate scope for the transnitrosation to form alkyl nitrites. Reaction conditions: Reaction conditions: substrate (0.2 mmol), NO-1 (0.24 mmol), 2 mL of DCE, rt for 30 min. Yields refer to chromatographically pure material unless otherwise noted. [a] Reaction conducted at 50 °C.

The synthesis of these alkyl nitrites from a wide range of alcohols is shown in Figure 3-31. Primary alkyl nitrites (**38–50**) were achieved in good to excellent yields. Long chain alcohols **38** and **58** were achieved in excellent yields. Benzylic alkyl nitrites **39–41** was shown to be effective in formation under standard conditions. Allylic alkyl nitrite **43**, **48–50** was achieved in good yields demonstrating

the mild nature of this reaction. Additionally, compounds with protecting groups (**41**, **42**, **46**, and **47**) proceeded smoothly and demonstrate the versatility of this reaction. Secondary alkyl nitrites **51–55** were achieved in good to excellent yields. Tertiary alcohols **56** and **57** proceeded smoothly as well. The nitrosation of cholesterol into the alkyl nitrite analog **59** was achieved in good yield. In certain cases, lower temperatures proved to be better to to reduce decomposition of the product to the aldehyde. Initial reactIR studies shows that there are no signs of decomposition in solution and more studies are forthcoming.

Conclusions

Through developing novel reagent **NO-1** we have demonstrated it as an effective nitrosating reagent to form *N*-nitroso and *O*-nitroso compounds. This is marked by the recoverability of the NH-sulfonamide **DMBS** after the reaction is complete. This presents a mild and effective methods to the synthesis and isolation of nitroso compounds. The recyclability and avoided decomposition of the sulfonamide demonstrates the effectiveness of this reagent in an economically and green alternative to methods published. Additionally, the eliminated need for acids and nitrite salts makes this a neutral pH reaction that has good functional group tolerability. The development of novel reagent **NO-1** has been shown to demonstrate a wide variety of utility in our hands. We have demonstrated it can be utilized in clean nitrosation reactions affording nitroso compounds with no decomposition of the sulfonamide. Additionally, we have demonstrated that novel reagent **NO-1** can undergo deconstructive-transnitrosation reactions affording a variety of unique reaction. Further work examining the utility of the reagent can led

to a truly versatile reagent where conditions can be pushed to more mild and desired reaction conditions.

Interesting Results and Future Work

During our substrate scope, we observed unique reactivity depending on the nucleophile used. The following examples are unique to the functional group we initially were interested in nitrosating. For example, in the presence of a tertiary amine triethylamine, we observed a secondary nitrosamine **61** as the final product in 31% yield (Figure 3-32).

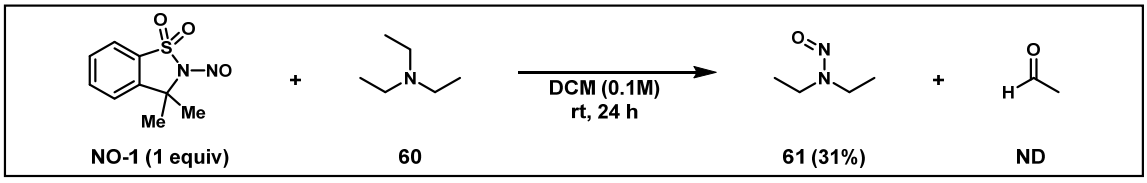


Figure 3-59. Dealkylated N-nitroso compounds from tertiary amines.

The possible pathways to this product follows the formation of acetaldehyde and *N*,*N*-diethylamine occurs first, which then reacts with **NO-1** to form **61**.[62] In previous reports, it is suggested that the tertiary amine is nitrosated to form a cationically charged nitrogen, which then decomposes to cleave an alkyl group to generate acetaldehyde. In theory, this reaction pathway could only produce up to 50% yield with 1 equivalent of **NO-1**.

When anilides were used as substrates it was interesting to observe the product not as a nitrosamide but as cholorobenzene when the crude mixture was analyzed by GCMS (Figure 3-33).

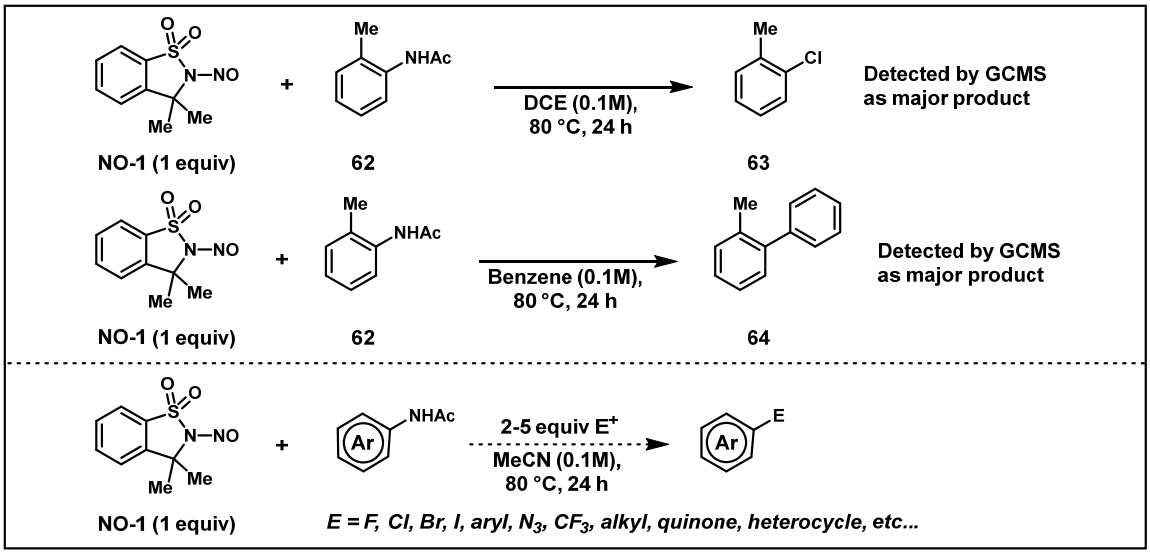


Figure 3-60. Anilides as latent radical precursor to form aryl radicals.

Nitrosating reactions conditions have previously led to the generation of aryl radical from anilides, which can form covalent bonds with electrophiles in solution.[63] Examples have shown that nitrosating reagents such as alkyl nitrites, and nitrite salts in aromatic solvents or in the presence of halides like Cl and I lead to their coupled product after liberating N_2 and acetic acid. When reacting anilide **62** was used as substrate it was interesting to observe the product not as a nitrosoamide but as *o*-chlorotoluene **63** when DCE was used and *o*-methylbiphenyl **64** when benzene was used as the solvent after the crude mixture was analyzed by GCMS (Figure 3-33). Further development of this reaction can lead to the development of a reaction where a variety of electrophiles can be used to arrive at functionalized arenes.

Reactions between **NO-1** and anilines led to the formation of azobenzene **66** in 84% yield after 2 hours at room temperature (Figure 3-34).

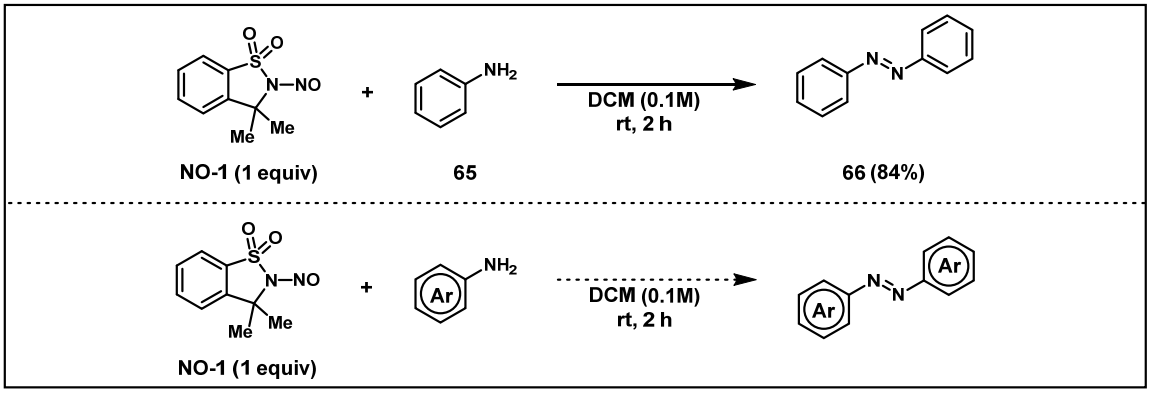


Figure 3-61. Diazotization of Anilines to Form Azoarenes.

This reaction is belived to be a diazonation of aniline to form azo-compounds.[64] It is belived that the primary amine is nitrosated then decomposes into an aryl radical and in the presence of a diazonizing aniline formes azo-benzene as the product. Typically, these compounds proceed uncer acidic conditions with nitrite salts. Further development of this method would be the first diazoniation reaction from a *N*-nitrososulfonamide.

In the presence of phenol **67**, we observed regioisomers of para- **68** and ortho- **69** nitrophenols as the product (Figure 3-35).

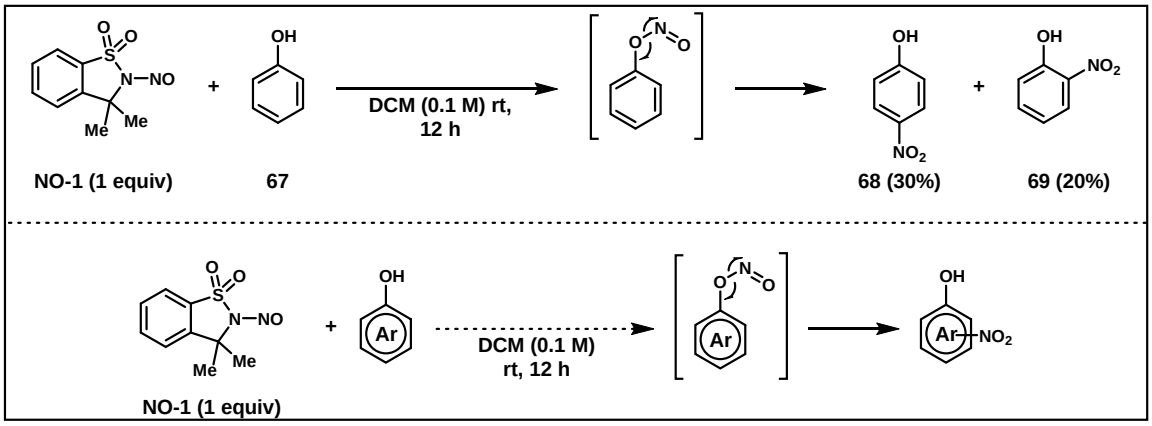


Figure 3-62. Nitration of phenols.

The nitration of phenols under nitrosating conditions has been previously reported.[65] It is believed that phenol is nitrosated first and decomposes to form nitrophenol under an air atmosphere. Development of this reaction will lead to the acess of nitrophenols in one pot.

Finally, the ipso-nitration **72** or nitrosation **71** of aryl bornic acid **70** was observed when reacting **NO-1** with aryl boronic acids (Figure 3-36).

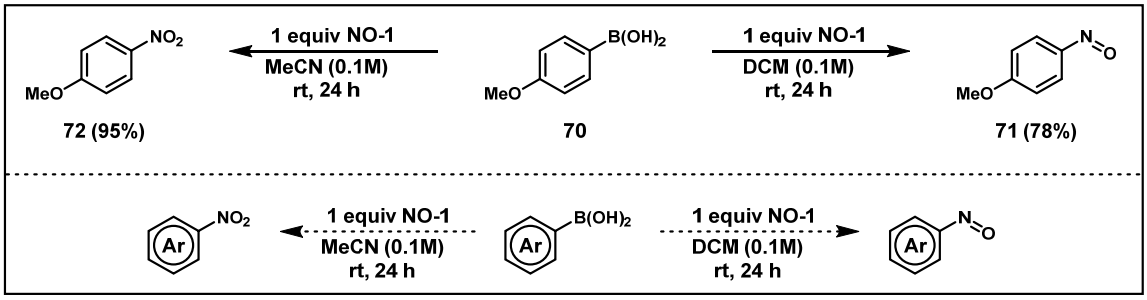


Figure 3-63. Ipso-Nitration or nitrosation of aryl boronic acids.

The products observed largely depended on the solvent used for the reaction. Efforts to fully understand this are ongoing. Ipso-nitration has been reported to occur to aryl boronic acids under nitrosating conditions.[66] Findings have shown that there is selective nitrosation or nitration depending on the reaction conditions. In some cases, this has been shown by the Molander group that this can be extended to aryl tetrafluoroborates in the presence of $NOBF_4$ arriving at nitroso arenes.[67] Developments on these compounds would have significant value in the ease of access for nitroarenes and nitrosoarenes.

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Chapter 4. Progress Towards a Novel Reagent for Hydrogen-atom Abstraction

Abstract. Preliminary results with novel reagent developed in chapter 3 as a mediator for radical reactions is covered. A background on Hydrogen-atom abstraction (HAT) is covered as well as the limitation. The application of a novel HAT reagent developed within the Baxter lab is presented. A variety of oxidative and radical single-electron transfer (SET) reactions that allow for the simple reaction conditions can be utilized to access target molecules via thermal and light initiated techniques. Future work with this reagent is outlined demonstrating the utility and usefulness further investigation into this research can reward.

Background

Hydrogen atom abstraction is a direct method to generate carbon–carbon and carbon–heteroatom bonds. It is a chemical transformation that features concerted movement of a proton and electron in a single step.[1] In the presence of a radical initiator, a reactive radical intermediate is generated, which can then abstract unactivated and activated carbon–hydrogen bonds to form various carbon–carbon and carbon–heteroatom bonds (Figure 4-1).

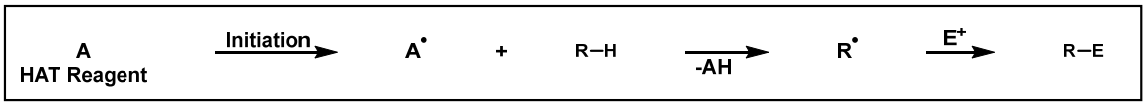


Figure 4-64. General mechanism for stoichiometric HAT reagent for C–H reactions.

This approach is ideal for functionalizing substrates without the need to preinstall a functional group. The first examples of these HAT reactions featured nitrogen-

centered radicals from a variety of *N*–halogenated amines. Initial HAT reactions were focused on intramolecular amination. The first synthetic application of haloamines was shown by Hofmann, Loffler and Freytag (HLF reaction) in 1883. In the presence of acid and at elevated temperatures, 1,5-hydrogen atom transfer from *N*-chloroamines and *N*-bromoamines generates aminium radical. Base-mediated cyclization generates heterocycles shown in Figure 4-2.[2]

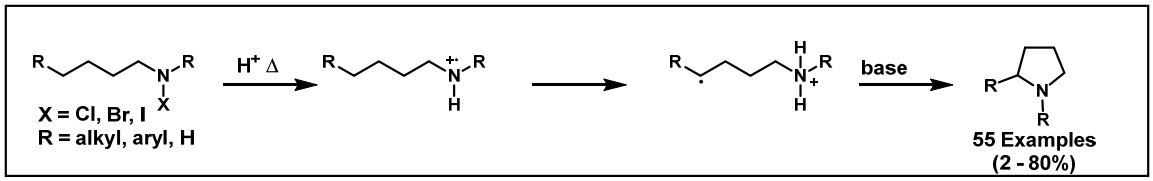


Figure 4-65. General scheme for the HLF reaction.

Since this report, various research groups have shown that nitrogen-centered radicals are effective at hydrogen-atom abstraction and can be formed from a variety of N–halogen radical precursors for both intramolecular and intermolecular HAT reactions.[3] In general there are three reactivity profiles observed for aminyl radical, which have different reactivity profiles dependent on reaction conditions such as acidic media or reagents used to initiate radical formation from *N*-haloamines (Figure 4-3).[4]

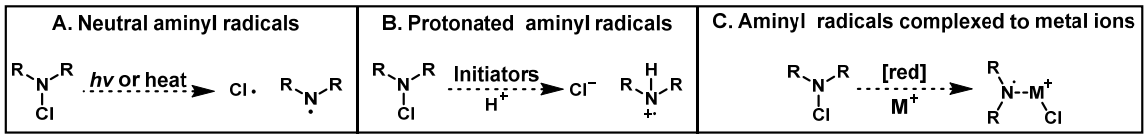


Figure 4-66. Generation of aminyl radicals of different types from N-chloroamines.

A neutral aminyl radical (Figure 4-3A) can be generated via radical, thermal, or photochemical conditions. However, neutral aminyl radical often dimerizes to form

hydrazines and disproportionate into Schiff bases and amines. In addition, neutral aminyl radicals prefer intramolecular hydrogen atom abstraction over radical additions to alkenes and arenes.

A protonated aminyl radical (Figure 4-3B) can be generated via homolytic decomposition of N-chloroamines in acidic media. Protonated aminyl radical prevents dimerization or disproportionate into Schiff bases and amines.[5] The protonated radical is reported to preferentially add to unsaturated hydrocarbons and arenes over C–H abstraction of activated allylic or benzylic hydrogen atoms. Potential side reactions in the amination of alkenes and are competitive electrophilic chlorination.

As shown in Figure 4-3C, aminyl radicals can be formed using a metal complex. Metal-complexed aminyl radicals do not tend to undergo HLF, intermolecular C–H abstractions, dimerize or disproportionate, but can react with dienes, acetylenes, and alkenes. Moreover, use of a non-acidic medium in many cases prevents electrophilic chlorination.[6]

The major drawbacks to of these methods are that *N*–halogen bonds are susceptible to bond cleavage or elimination and require additional precaution to keep these reagents stable. They are not considered a bench stable reagent and are commonly generated *in situ*.

Alternatively, the use of amidyl radicals have been investigated as alternative HAT reagents because of their intrinsic *π*-delocalization. This *π*-delocalization allows for a high electrophilic character once the amidyl radical is formed offering the

advantage of an umpolung reactivity complementing the nucleophilic character of N-species in classical polar reaction modes.[7]

Amidyl radicals can be formed from a variety of *N*–heteroatom, *N*–halogen or directly from N–H compounds (Figure 4-4). How amidyl radicals initiated are formed provide different reactivity profiles.[3]

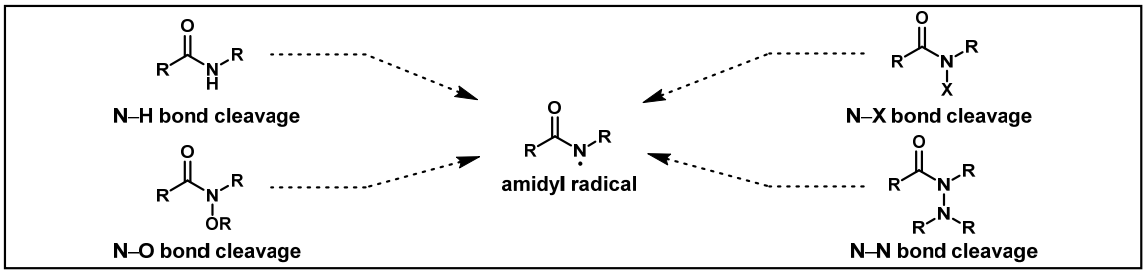


Figure 4-67. Strategies for the formation of amidyl radical.

There have been recent reports of *NH*-amides being used in the presence of a photo redox catalyst such as iridium or ruthenium to initiate nitrogen center radical to form. The Knowles group showed that an *NH*-amide can participate in intramolecular HAT reactions in the presence of a photocatalyst (Figure 4-5).[8]

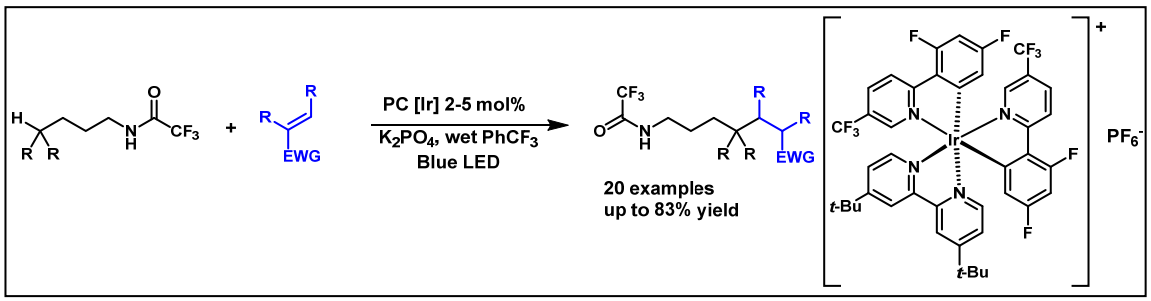


Figure 4-68. Photoredox-catalysed C–C bond formation at unactivated sp^3 C–H bonds.

While this was an excellent demonstration of the capabilities that amides have at intramolecular HAT reactions, the use of a photocatalyst can significantly

complicate the ease of set-up required for reactivity. Often these photocatalysts are unstable under ambient conditions and require rigorous set-up conditions for reactions to perform optimally. Our desire was to pursue reactivity that was achievable without the need for a photocatalyst or metal initiators that would require inert conditions to proceed.

N-Nitrosoamides

One unique class of organic compounds as radical precursors are *N*-nitrosoamides. As shown in Figure 4-6A, *N*-nitrosoamides have delocalized electrons due to the presence of a carbonyl group alpha to the N–N bond in the molecule. In addition to electron delocalization present in the molecule, these compounds have further disorder present due to the presence of rapidly exchanging rotamers as shown in Figure 4-6B.

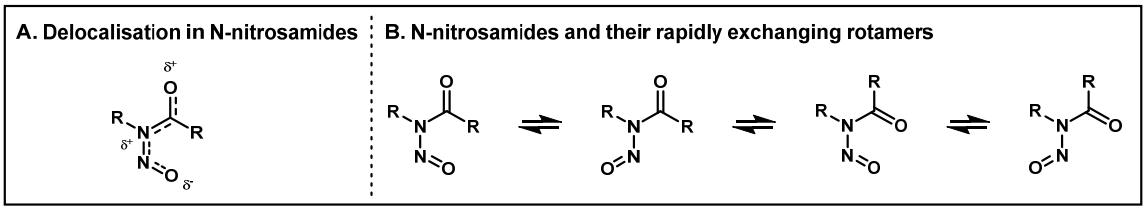


Figure 4-69. A. Electron delocalization present in N-nitrosamides. B. Rotamers present in acyclic N-nitrosamides.

This information demonstrates how the identity of the substituents determines the stability and properties of these molecules. A wide range of stability have been reported with N-nitrosamides decomposing at room temperature or elevated temperatures (100 °C).[9] Rotamers can be observed with ^{1}H-NMR, while electron diffraction analysis can be used to determine the length of the N–N bond to

determine the electronic properties. Theoretical calculations can be utilized to determining the site for highest electron density and predict the reactivity when in the presence of an acid or base. More importantly, photochemical studies have revealed that *N*-nitrosamides can be irradiated upon to generate free radicals in solution capable of participating in synthetically desirable transformations (Figure 4-7).[10]

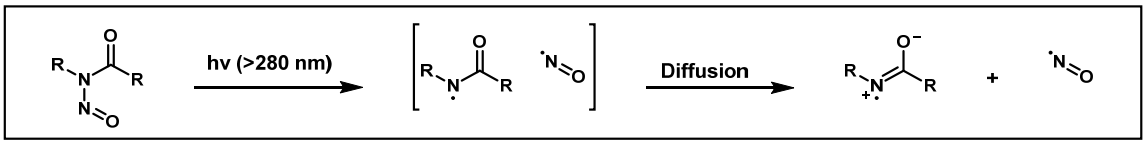


Figure 4-70. General reaction pathway for form amidyl and nitric oxide radicals.

There are three pathways an amidyl radical can proceed after it has been generated. Shown in Figure 4-8A is the most favorable pathway, an intramolecular 1,5-hydrogen-atom abstraction to produce oximes that follows the mechanism of the Hofmann–Löffler–Freytag (HLF) reaction using *N*-haloamides.[11] Depending on the conditions, this reaction pathway can produce functionalized amides with broad functional group tolerance. Shown in Figure 4-8B is intermolecular hydrogen atom transfer (HAT) from a proton containing substrate which is then functionalized to produce compounds with NO functional groups. The last mechanism shown in Figure 4-8C is β-elimination and can occur when 1,5-HAT is unfavorable, a poor H-donating solvent is used or there is lack of a δ-hydrogen in the alkyl chain. β-elimination pathways can be favorable in the presence of elevated temperatures.

In the presence of light, *N*-nitrosoamide **1** can be photochemically cleaved to produce an amidyl (**2**) and nitric oxide radicals (Figure 4-8). This is due to the n→π*

transition bands present at ~ 373, 387, 403, and 421 nm.[12] Irradiation at these wavelengths allows for a radical cleavage of the N-N bond allowing for amidyl and nitric oxide free radicals to be present in solution. The amidyl (**2**) radical can undergo intramolecular 1,5-HAT to produce **3** in moderate yield. However, *N*-nitrosamide **6** does not undergo intramolecular 1,5-HAT because there are no δ-hydrogens present; intermolecular C–H abstraction and β-elimination becomes the mechanistic pathways observed. As shown in Figure 4-8B, intermolecular HAT becomes favorable and C–H abstraction of the solvent and recombination with nitroso radical generates **7**. This is especially observed when a large excess of hydrolytic compounds are present which is the case when the hydrolytic substrate is the solvent. If intermolecular C–H abstraction is not favorable, or the hydrolytic substrate is in low concentration then β–elimination generating oxidized imine **9** becomes the favorable pathway (Figure 4-8C).

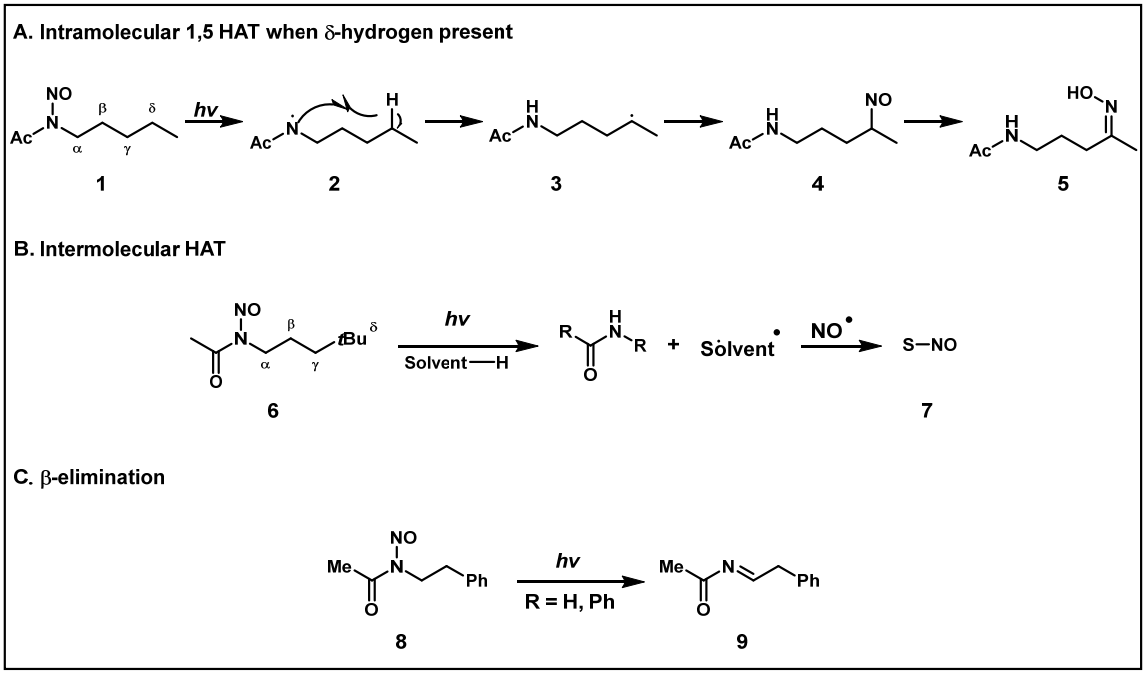


Figure 4-71. Reaction pathways for N-nitrosamides being photolyzed. A. Shows the intramolecular HAT pathway. B. Shows the intermolecular pathway. C. Shows β-elimination leading to imine formation.

As shown in Figure 4-9, subtle change in reaction conditions determine product observed.[12b] When *N*-nitrosamide **10** is irradiated at 0 °C in benzene it is in the presence of a poor hydrolytic solvent. This allows for intramolecular 1,5-HAT to predominate the reaction. This indicated that a carbon centered radical is formed on the amidyl chain and combines with free NO radical for form a nitrosated compound which tautomerized into the oximinamide **11**. The observed 11 after the reaction was quenched indicates that some HAT from the solvent occurs but is not the major pathway under these conditions. This is further confirmed in Figure 4-9B when the solvent is changed to carbon tetrachloride. Carbon tetrachloride acts as a radical scavenger competing with the free NO radical in solution. Because of its large concentration as the solvent is exclusively reactions with the carbon radical

generated after 1,5-HAT forming chlorinated amide **13**. When MeOH is used as the solvent in Figure 4-9C, the hydrolytic nature of the solvent causes a competition between intermolecular HAT and intramolecular HAT. This results in a lower concentration of oximinamide **12** and a much higher concentration of formaldehyde **14**. Formaldehyde is formed after the H–OMe bond is radically cleaved forming formaldehyde **14** as the final product of the radical HAT between nitrosamide **11** and MeOH. In all cases β-elimination is not discussed, most likely due to the lowered temperature preventing this least favorable competing reaction to occur or due to the lack of investigation into their existence once the reaction was quenched.

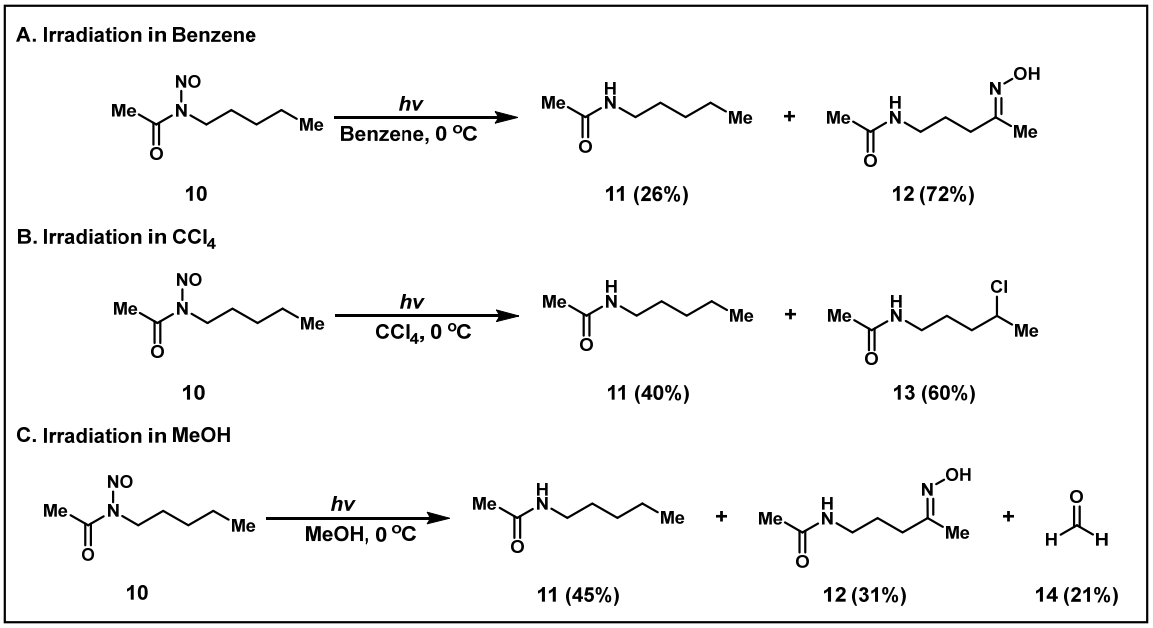


Figure 4-72. Reaction pathways in different solvents affording different product distribution. A. reaction in benzene. B. Reaction done in carbon tetrachloride. C. Reaction done in methanol.

The scope of *N*-nitrosoamides as intermolecular HAT reagents have been under explored and their role as an overall effective HAT reagent could be the key to accessing highly desired compounds under mild conditions.

Initial Research Strategy

We initially explored *N*-nitrosoamide reagents for intermolecular HAT transformations. To increase bench and thermal stability, we focused on synthesizing cyclic *N*-nitrosoamides without δ-protons (Figure 4-10). In our initial studies, cyclic amides were examined because of previous literature precedent on stability at elevated temperatures when the ring size is seven atoms or less.[13]

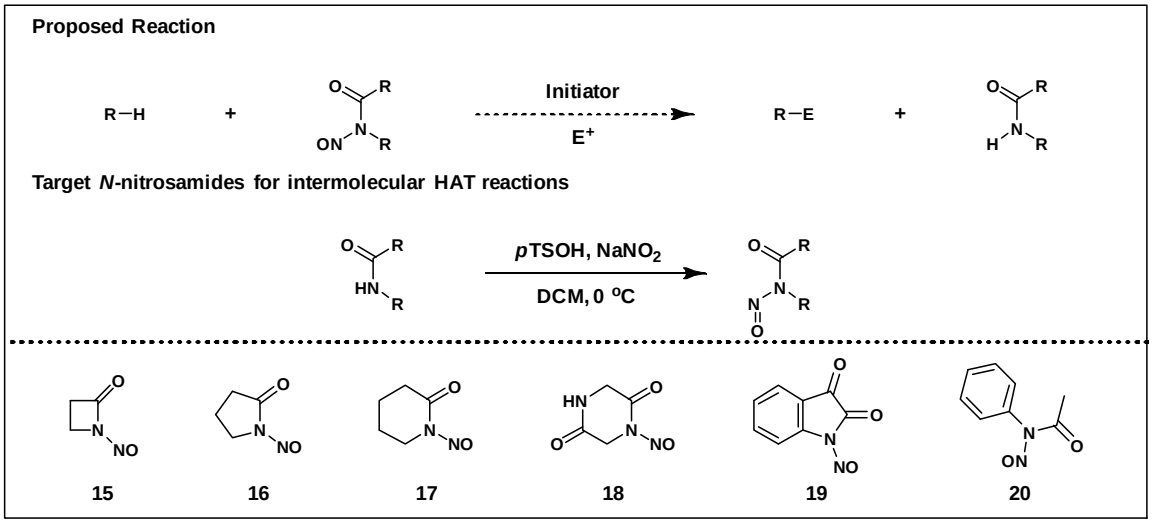


Figure 4-73. Target compounds and the proposed HAT reactions we aimed to investigate.

Efforts to synthesize compounds **15–20** using nitrate salts under acidic conditions were unsuccessful. All these compounds with the exception of **20** showed full conversion from their amide substrate but no characteristics of the desired compounds under NMR and GC/MS. This might be due to the presence of acid in

the reactions condition which is known to decompose *N*-nitrosamides.[14] *N*-nitrosamide **20** was isolated after reaction under acidic conditions, but rapid and violent decomposition occurred upon standing at room temperature shortly after purification.[15]

Research Strategy Using *N*-Sulfonamides

In Chapter 2, we synthesized a variety of *N*-nitrososulfonamides specifically for nitrosation of a variety of different alcohols, amines, etc. We hypothesized if the *N*-nitrososulfonamide could be homolytically cleaved, the resulting nitrogen-centered radical could abstract a variety of C–H bonds. We needed to identify if: (1) *N*-nitrososulfonamides could serve as HAT; (2) conditions to facilitate N–NO cleavage; (3) methods to prevent unwanted side reactions like β-elimination.

More recently, Knowles[16] and Kanai[17] developed a photocatalyzed HAT reaction using *N*-sulfonamides as the radical precursor (Figure 4-11). In the presence of an iridium photocatalyst and ammonium salts, the Knowles group showed that nitrogen centered radical could be generated from sulfonamide **21** to facilitate intramolecular 1,5-HAT followed by radical addition to conjugate acceptors producing alkylated sulfonamides like **22** in good yields. Alternatively, Kanai showed that under iridium-catalyzed photocatalysis, a radical could be generated from sulfonamide **23** to facilitate an intermolecular C–H abstraction and radical addition to electron-deficient arenes to generate functionalized arenes.

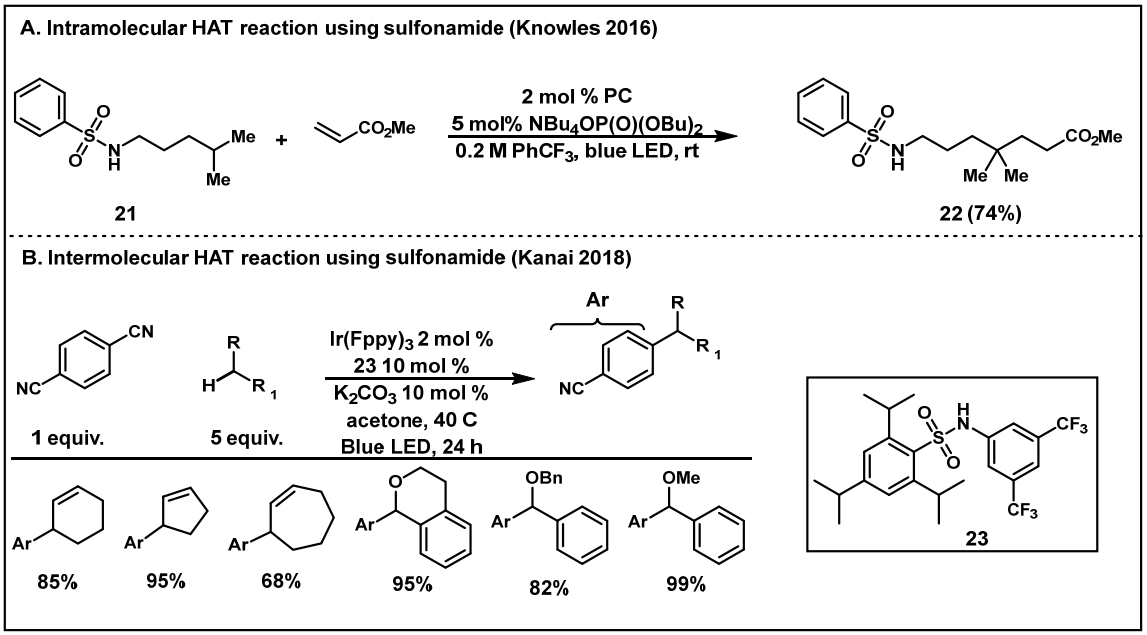


Figure 4-74. A. Sulfonamides used for intramolecular HAT. B. Sulfonamides used for intermolecular HAT.

These results suggest that homolytic cleavage of *N*-nitrososulfonamides will generate a nitrogen-centered radical that could engage in hydrogen atom transfer to facilitate radical transformations.

In addition to *NH*-sulfonamides acting as precursors to HAT reagents, *N*-halosulfonamides have also been studied and shown to abstracting hydrogens after photolysis.[18] The Nagib group showed that a cyclic sulfonamide is capable of intramolecular HAT. When initiated photochemically, a sulfonyl radical is believed to be formed from *N*-bromosulfonamide, which then initiates an intramolecular HAT pathway and forming bicyclic sulfonamides under basic conditions (Figure 4-12).[19]

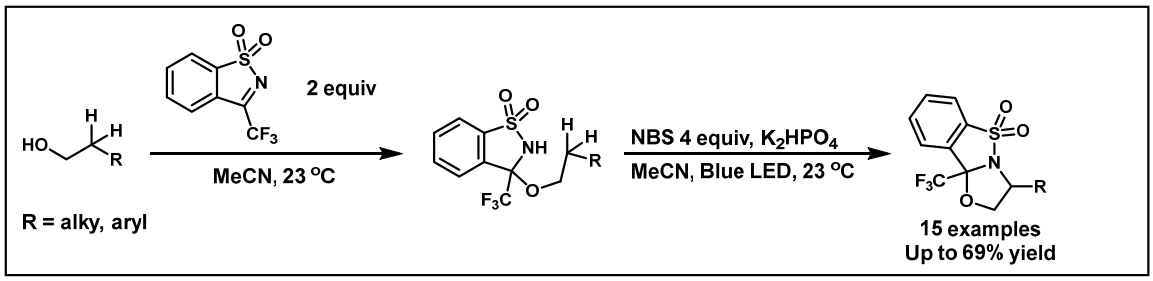


Figure 4-75. Intramolecular cyclization via intramolecular HAT.

Additionally, the Wang group has studied 1,5-HAT reactions with chiral copper catalyst that lead to enantiomerically enriched functionalized sulfonamides from *N*-fluorosulfonamides (Figure 4-13).[20]

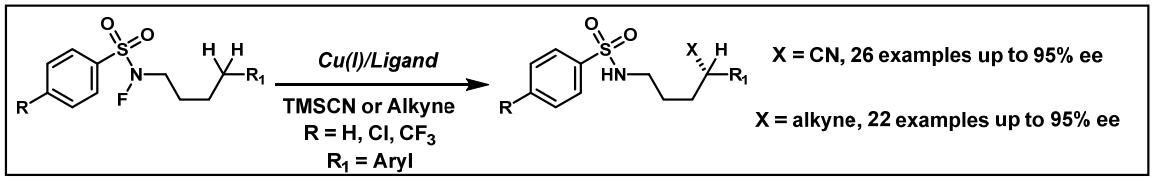


Figure 4-76. Intramolecular HAT from N-fluorosulfonamides.

There are many examples using *N*-halosulfonamides as a radical HAT precursor, but to the best of our knowledge, only three publications utilizing *N*-nitrososulfonamides as a radical precursor for HAT reactions have been reported.

The Boer group studied the photolysis and degradation pathways of N-nitrososulfonamide (Figure 4-14).[21] As shown in Figure 4-14A, *N*-nitrososulfonamides photolytically decompose to generate sulfonimine **25** and after hydrolysis, produces sulfonamide **26** and carbonyl compounds **27**. This mechanism occurs through β-elimination and in the presence of a variety of hydrogen donating solvents. In a study of temperature effects, different products were observed. As shown in Figure 4-14B, homolytic cleavage of N–NO bond

followed by ring opening and recombination with NO radical produces imine intermediates **29** or **31**. Hydrolysis of this intermediate then generates sulfonamide **26** and ketone **30** or aldehyde **32**. Because there are no protons available for intramolecular HAT reactions and the solvent is not hydrolytic, β-elimination is favorable. An interesting observation was the temperature dependent rupture of the cyclic sulfonimine and at -80 °C there is no rupture of the imine forming **29** as the main intermediate while at higher temperatures (-10 °C) the ruptured imine intermediate **31** is proposed based on the observed formation of **32** upon hydrolysis. This study was the first detailed investigation into photochemical reactions of *N*-nitrososulfonamides and indicates that homolytic cleavage can generate a *N*-sulfonamide radical and nitroso radical while still possessing similar reaction pathways as *N*-nitrosamides.

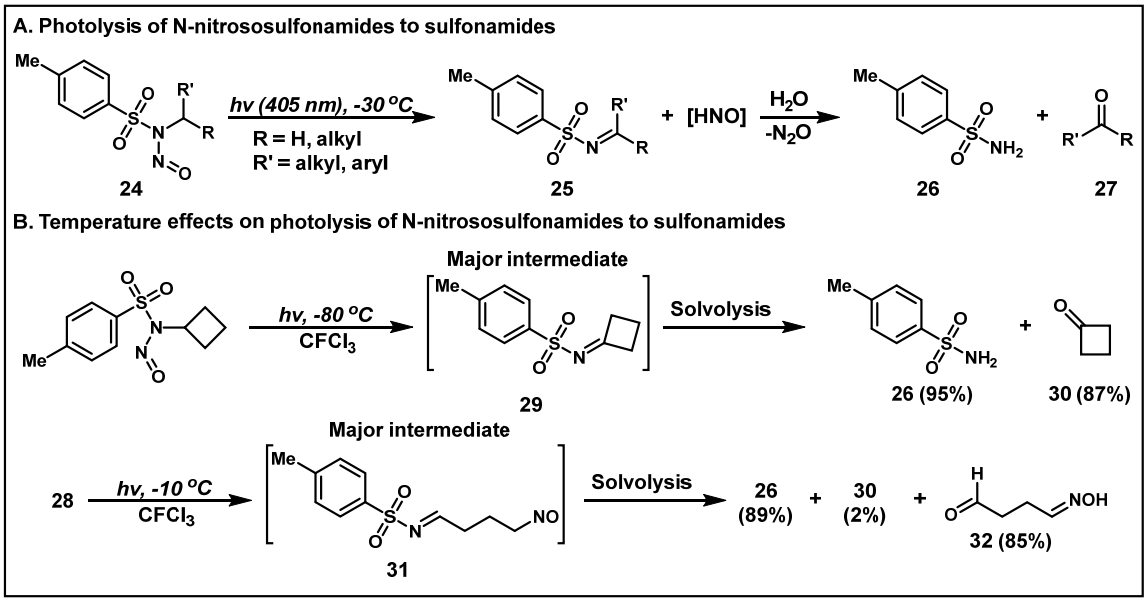


Figure 4-77. Photochemical reactions using N-nitrososulfonamides.

Novel Reagent NO-1 for Radical Reactions

After developing *N*-nitrososulfonamide **NO-1** as a transnitrosating reagent, we considered **NO-1** as a HAT reagent for intermolecular HAT reaction (Figure 4-15).

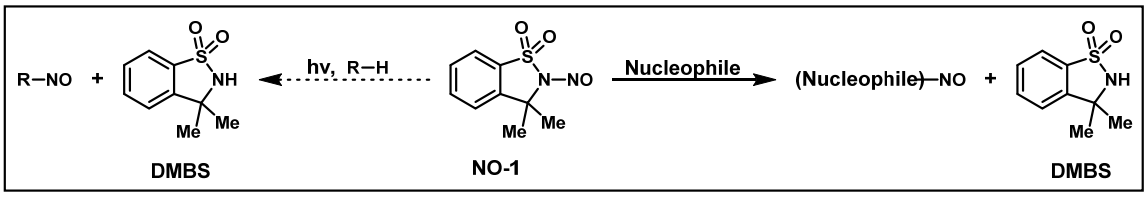


*Figure 4-78. Proposed reactivity of **NO-1** to act as a transnitrosating reagent or HAT reagent.*

As shown in Figure 4-15, if the N–NO bond could be cleaved homolytically under mild conditions, this would provide a nitrogen radical capable of hydrogen atom abstraction. Then, radical combination with the NO radical would provide R–NO and **DMBS**. The following features of **NO-1** made it a highly desirable radical precursor:

[1] The synthesis of **NO-1** is simple in sequence and set-up, non-hazardous with tolerance to moisture and air, and scalable to synthesize large quantities of the reagent.

[2] Recoverability of **DMBS** to regenerate **NO-1** in a single step. This occurs because **NO-1** *nor* ***DMBS*** can undergo β-elimination or fragmentation because there are no α-hydrogen to the sulfonamide nitrogen.

[3] Intramolecular and β-elimination cannot occur because reaction pathways are not able to proceed under photochemical or thermally initiated conditions.

[4] **NO-1** has physical and photochemical properties that are favorable for a mild photochemical intermolecular HAT reaction to proceed.

Photochemical Reactions with NO-1

The photochemical properties of **NO-1** are ideal for photochemical properties with near visible light. A UV-vis of **NO-1** shows an absorbance at 408 nm representing the n→π* excitation pathway (Figure 4-16).

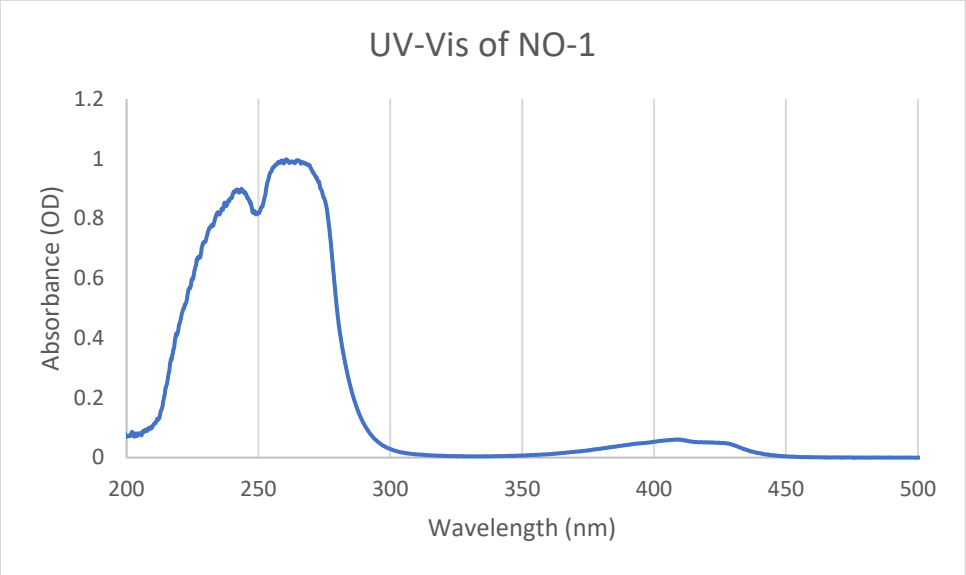


*Figure 4-79. UV-Vis of **NO-1** in MeOH.*

It was observed by Boer that this excitation wavelength was responsible for the observed HAT reactions from these type of reagents.[18] Photolysis can be described as homolytic cleavage of the N–N bond in *N*-nitrososulfonamide to form free radicals in solution (Figure 4-17).

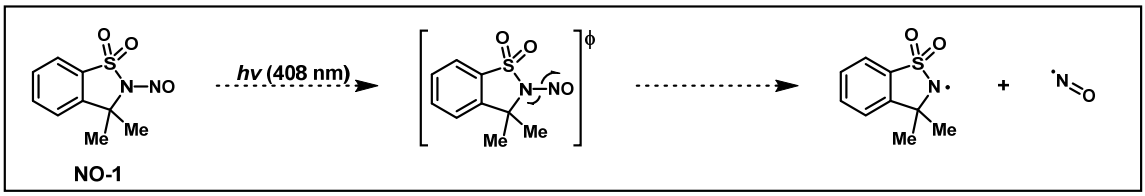


*Figure 4-80. Hypothesized photolysis of **NO-1**.*

The photochemical properties suggest that irradiation at 408 nm the optimal light source required to generate the sulfonamidyl radical in solution.

Investigations Into HAT Reactions Initiated by Light

We investigated a simple reaction of **NO-1** in the presence of excess toluene to evaluate the feasibility of a benzylic C–H functionalization reaction. (Figure 4-18).

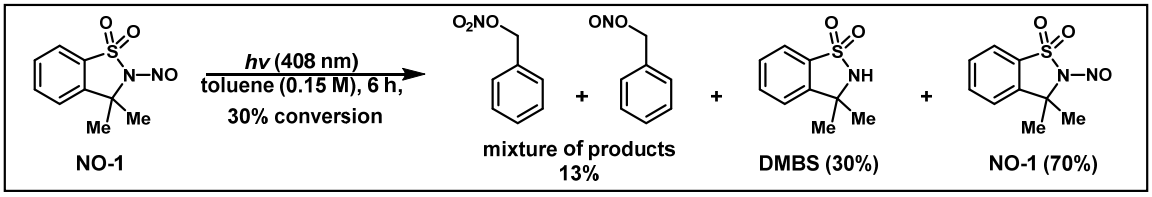


*Figure 4-81. Reactivity of **NO-1** in solvent after irradiation at 405 nm.*

Our hypothesis was that if irradiation occurred in a hydrolytic solvent, the nitrogen-centered radical should be able to abstract a proton from toluene at the benzylic position and react with a free radical to generate a new bond. Examination of the crude reaction mixture by NMR showed that benzylic functionalization was observed. However, the reaction was not air-free and with the presence of O_2, the products produced were a result of quenching of the radical with a O_2 followed by nitrosation. The can e avoided by running the reaction under and inert atmosphere. With this preliminary result, we plan to develop a variety of methods that utilize **NO-1** for C–H radical abstraction across a variety of substrates and functionalization with electrophiles.

Future Work With NO-1 as HAT Reagent

The following schemes are a summary of proposed projects stemming from **NO-1** for C–H radical functionalization (Figure 4-19).

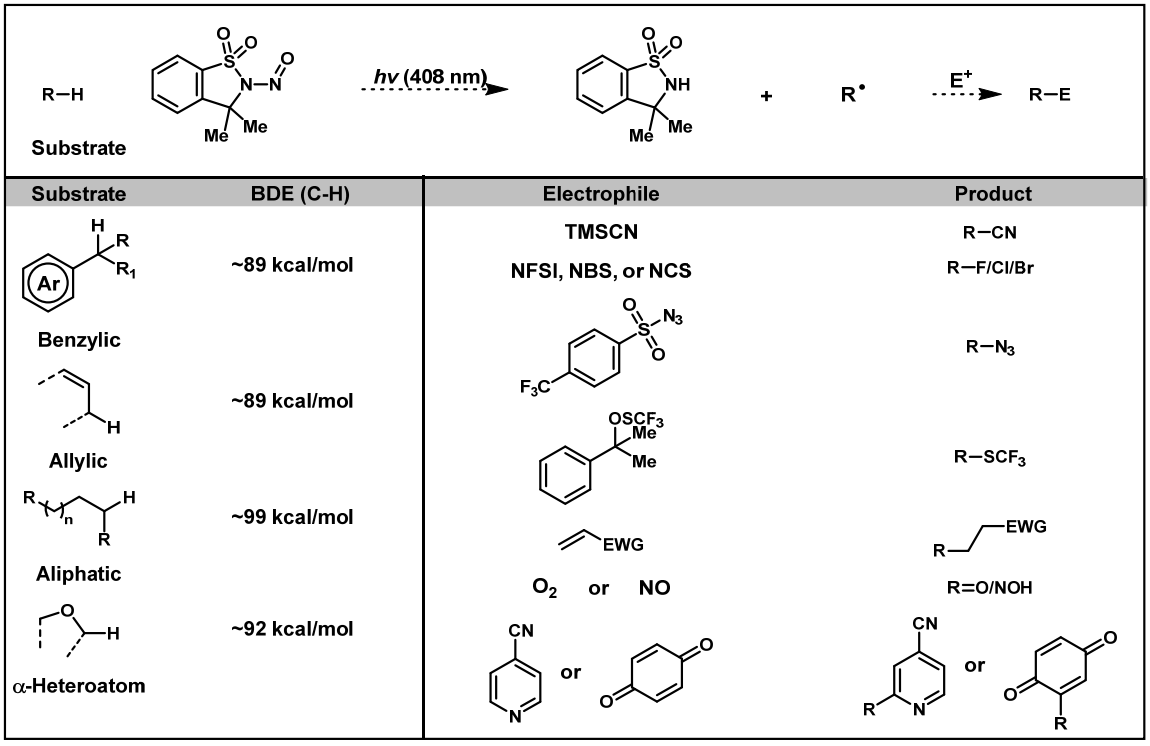
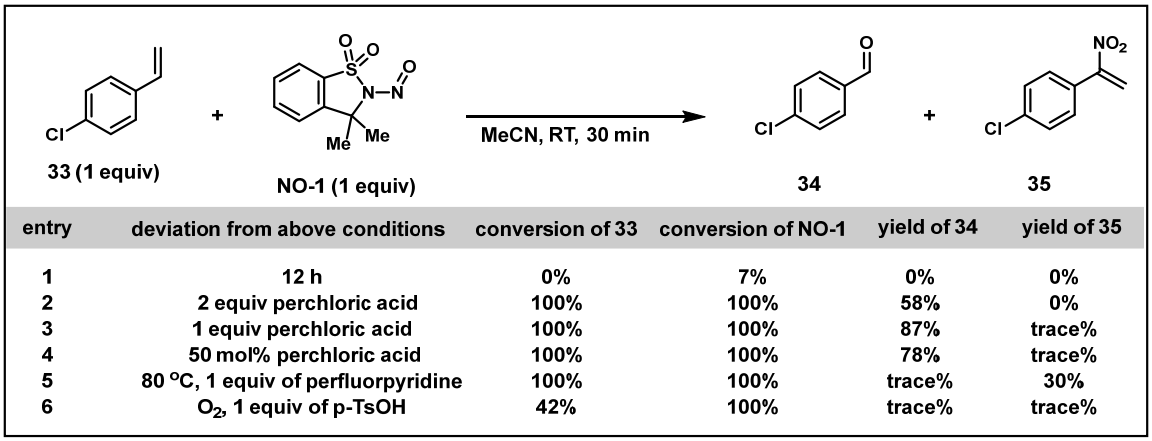


*Figure 4-82. Proposed future work to evaluate **NO-1** as a HAT reagent.*

A variety of substrates bearing C–H bonds will be examined with a variety of electrophiles. We anticipate that the installation of nitriles, halogens, thiols, alkyl groups, carbonyls, oximes, and heteroaromatic and quinone structures can be achieved.

Chemically Initiated Radical Reactions With NO-1

We are also examining chemically-initiated reactions with NO-1. Under carefully controlled pH, we are able to facilitate an interesting oxidative cleavage reaction of styrene **33** and **NO-1** (Figure 4-20).



entry	deviation from above conditions	conversion of 33	conversion of NO-1	yield of 34	yield of 35
1	12 h	0%	7%	0%	0%
2	2 equiv perchloric acid	100%	100%	58%	0%
3	1 equiv perchloric acid	100%	100%	87%	trace%
4	50 mol% perchloric acid	100%	100%	78%	trace%
5	80 ^{o}C, 1 equiv of perfluorpyridine	100%	100%	trace%	30%
6	O_2, 1 equiv of p-TsOH	42%	100%	trace%	trace%

*Figure 4-83. Preliminary investigation into **NO-1** reactions with alkene.*

Under neutral conditions, no reaction was observed (Figure 4-20, entry 1). We rationalized that the addition of an acid such as perchloric acid (pKa = -10), would protonate the **NO-1** and help facilitate the radical decomposition of **NO-1**. As shown in entry 2–5, the addition of acid helped facilitate the formation of aldehyde **34.** Interestingly, when pentafluoropyridine was added, we observed the formation of nitroalkene **35** (entry 5). While the mechanism for the formation of these compounds needs further examination, we do know that pKa plays a significant role here. When *p*-toluenesulfonic acid (pKa = -2.3) we observed only trace formation of both **34** and **35**.

We also observed interesting effects on product distribution with changes of pH for indole substrate **36** (Figure 4-21).

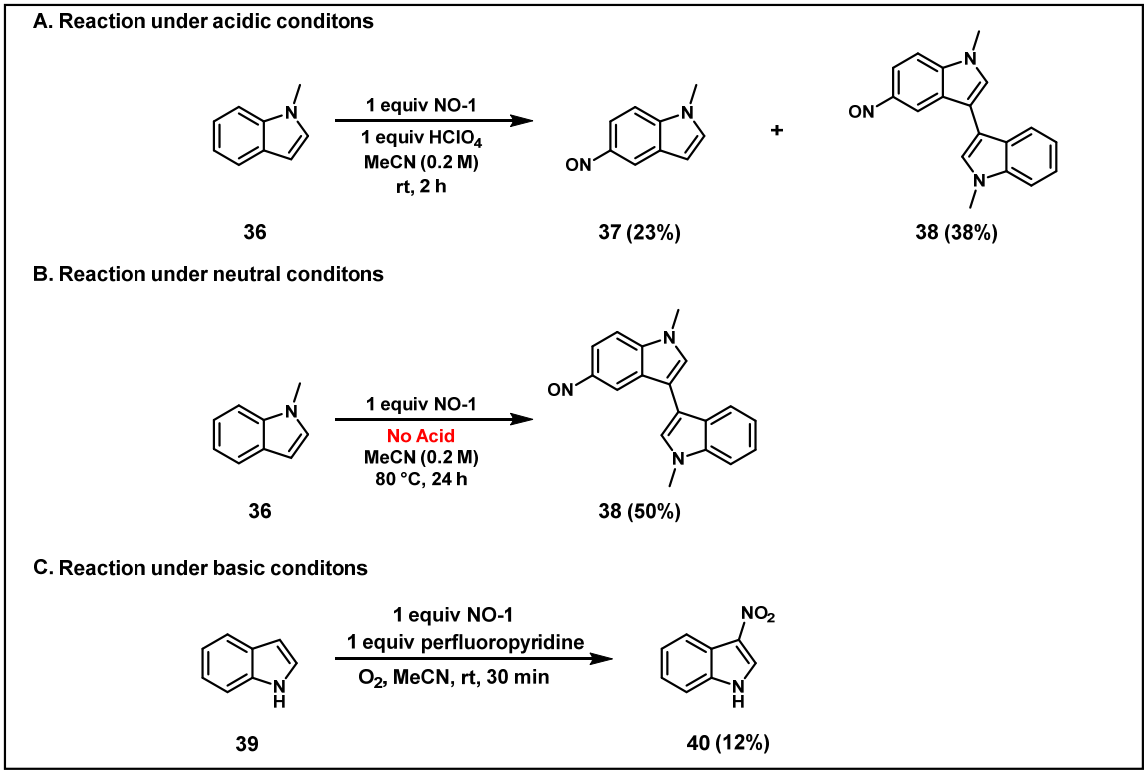


*Figure 4-84. Reaction with **NO-1** with indoles under various pH conditions.*

As shown in Figure 4-21, we examined the reaction of **NO-1** in the presence of N-methyl indole **36** and indole **39**. When perchloric acid is used, a mixture of a nitrosated indole **37** and a nitrosated dimer **38** are the observed products (Figure 4-21A). Interestingly, when no acid is used at room temperature, no reaction was observed. However, at elevated temperatures only **38** is present once the reaction is complete. This result demonstrates that the pH and temperature have an effect on the product distribution (Figure 4-21B). Under basic conditions, *N*-methyl indole **36** provided no reaction. When we reacted indole **39** with **NO-1** in the presence of perfluoropyridine, we observed nitroindole **40** as the major product (Figure 4-21C). This last result suggests that nitrosation can occur with electron-rich arenes.

Further work on these projects is needed to elucidate the mechanism and explain product distribution and reactivity.

Next Generation HAT Reagents

While efforts are ongoing to determine the reactivity of **NO-1**, a variety of compounds similar to **NO-1** can be synthesized understand subtle structural changes has on HAT (Figure 4-22).

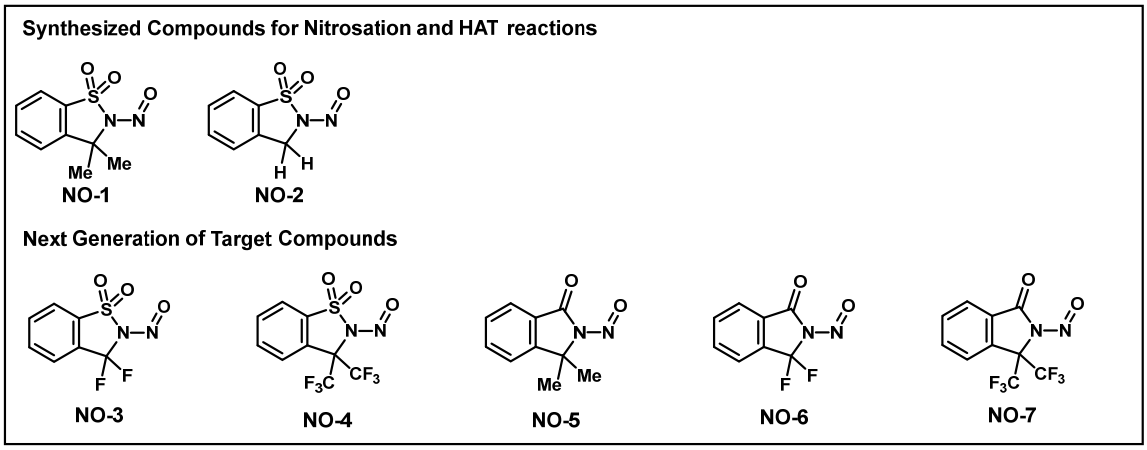


Figure 4-85. Target compounds for the next generation of transnitrosation and HAT reagents.

We have synthesized **NO-1** and **NO-2** in an efficient manner but are interested in expanding our analogs to feature difluoro (**NO-3**) and ditrifluoromethyl (**NO-4**) alpha to the nitrogen. These compounds would present the opportunity to track the reaction by ^{19}F–NMR. Additionally, the presence of electron withdrawing substituents could prove to be beneficial in the ease of access to the sulfonamidyl radical because of the reduced electron density on the sulfonamide nitrogen through inductive effects.

In addition to the *N*-nitrososulfonamides (**NO-1–NO-4**) we are interested in synthesizing and examining *N*-Nitrosamides (**NO-5–NO-7**). We want to understand the importance of the sulfonamide vs amide on HAT reactivity. Ongoing work in this area will reveal how effective these compounds can be in future work.

Conclusions

We have been able to synthesize a novel compound **NO-1** that shows promise as a photochemical HAT reagent under mild conditions. This novel reagent is bench stable and can be recycled after subjected to reaction conditions because of the design to prevent fragmentation. We have demonstrated that it can be thermally initiated to react with unsaturated compounds forming a variety of unique products. Future work with novel reagent **NO-1** will be exceptionally useful in radical reactions to arrive at a diverse range of analogs from a substrate in one step.

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Supporting Information

Experimental Section

General Considerations. Reagents and solvents were purchased and used without purification. Yields refer to homogenous material that is purified by silica-gel chromatography and spectroscopically pure (>95%) by ^{1}H NMR and ^{13}C NMR. Reactions were monitored by thin-layer chromatography using 0.25 mm E. Merck silica gel plates (60F-254) or ReactIR 15. NMR spectra were recorded on a Varian-INOVA 400 Mhz or 500 Mhz spectrometer, calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ – ^{1}H NMR 7.26 ppm, ^{13}C NMR 77.16 ppm). The following abbreviations were used to explain multiplicities (s–singlet, d–doublet, t–triplet, q–quartet, m–multiplet).

Chapter 2. Supporting Information.

The Supporting Information for the data featured in Chapter 2 are all published and available in the referenced published work:

[1] Galloway, J. D.; Mai, D. N.; Baxter, R. D. Silver-Catalyzed Minisci Reactions Using Selectfluor as a Mild Oxidant. *Org. Lett.* **2017**, *19*, 5772–5775.

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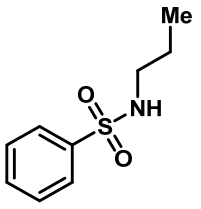
[4] Galloway, J. D.; Baxter, R. D. Towards the Development of Metal-Free Minisci Reactions Under Mild Conditions *Tetrahedron*, **2019**, *76(46),* 130665.

Chapter 3. Supporting Information.

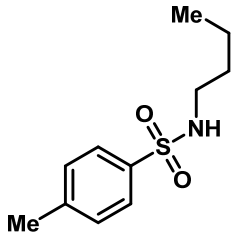
[A] General Procedure for sulfonamides. To a 250 mL round bottom fitted with a stir bar 25 mmol of sulfonyl chloride (25.0 mmol), and 100 mL of DCM was added. The reaction was cooled in an ice back to 0 ^{o}C. Then, primary amine (37.5 mmol), and triethanolamine (50.0 mmol) were added slowly while stirring was engaged. The reaction was allowed to stir for 3 h. Once the reaction was complete the reaction was diluted with saturated $NaCl_{(aq)}$ (500 mL) and extracted with DCM. The solvent was removed under reduced pressure was then rotovated down if considered too impure reaction was further purified through column chromatography with EtOAc/hexanes mixtures to yield the desired product.



1a

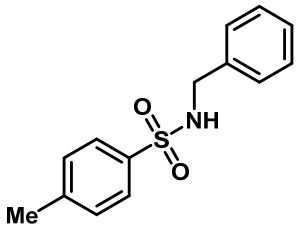
***N*-propylbenzenesulfonamide (1a)**. General procedure A was employed using benzenesulfonyl chloride (3.2 mL, 25.0 mmol) and propan-1-amine (3.1 mL, 37.5 mmol). The reaction afforded **1a** (4.901 g, 98% yield) as a pale yellow oil. The data matches those previously reported.[1] **^{1}H NMR (500 MHz, $CDCl_3$):** 7.87 (d, *J*

= 8.0 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.07 (s, 1H), 2.89 (s, 2H), 1.54 – 1.40 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H).



2a

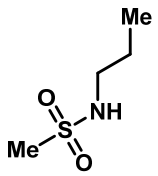
N-butyl-4-methylbenzenesulfonamide (2a). General procedure A was employed using 4-Toluenesulfonyl chloride (4.8 g, 25.0 mmol) and butan-1-amine (3.7 mL, 37.5 mmol). The reaction afforded **2a** (5.280 g, 93% yield) as a pale yellow oil. The data matches those previously reported.[1] **^{1}H NMR (500 MHz, $CDCl_3$):** 7.74 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 4.99 (s, 1H), 2.89 (dd, *J* = 10.3, 3.8 Hz, 2H), 2.40 (s, 3H), 1.46–1.37 (m, 2H), 1.31 – 1.17 (m, 3H), 0.81 (dd, *J* = 7.7, 6.9 Hz, 3H).



3a

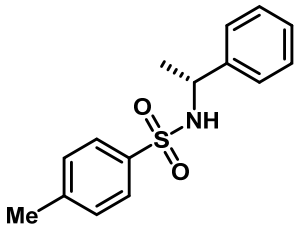
N-benzyl-4-methylbenzenesulfonamide (3a). General procedure A was employed using 4-Toluenesulfonyl chloride (4.8 g, 25.0 mmol) and phenylmethanamine (4.1 mL, 37.5 mmol). The reaction afforded **3a** (5.28 g, 93%

yield) as a pale yellow oil. The data matches those previously reported.[2] **^{1}H NMR (500 MHz, $CDCl_3$):** 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.20 (m, 4H), 7.13–7.09 (m, 1H), 7.07 (dd, *J* = 5.3, 3.3 Hz, 2H), 6.70 (s, 1H), 2.37 (s, 3H).



4a

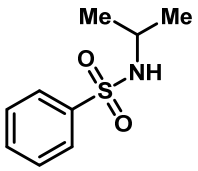
***N*-propylmethanesulfonamide (4a)**. General procedure A was employed using methanesulfonyl chloride (2 mL, 25.0 mmol) and propan-1-amine (3.1 mL, 37.5 mmol). The reaction afforded **4a** (3.102 g, 90% yield) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** 4.65 (bs, 1H), 3.07 (dd, *J* = 13.4, 7.0 Hz, 2H), 2.94 (s, 3H), 1.68 – 1.48 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 45.1, 40.3, 23.5, 11.2.



5a

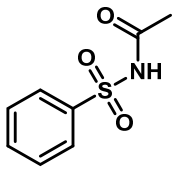
N-benzyl-4-methylbenzenesulfonamide (5a). General procedure A was employed using 4-Toluenesulfonyl chloride (4.8 g, 25.0 mmol) and (S)-1-phenylethan-1-amine (4.8 mL, 37.5 mmol). The reaction afforded **5a** (6.523 g, 95% yield) as a pale yellow oil. The data matches those previously reported.[3] **^{1}H**

NMR (500 MHz, $CDCl_3$): 7.62 (d, *J* = 8.3 Hz, 2H), 7.21 – 7.13 (m, 5H), 7.13 – 7.07 (m, 2H), 5.24 (s, 1H), 4.53 – 4.38 (m, 1H), 2.38 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 3H).



6a

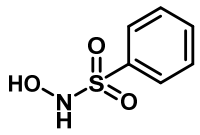
N-isopropylbenzenesulfonamide (6a). General procedure A was employed using benzenesulfonyl chloride (3.2 mL, 25.0 mmol) and propan-2-amine (3.2 mL, 37.5 mmol). The reaction afforded **6a** (5.200 g, 97% yield) as a colorless oil. The data matches those previously reported.[4] **^{1}H NMR (500 MHz, $CDCl_3$):** 7.88 – 7.82 (m, 2H), 7.50 – 7.45 (m, 1H), 7.44 – 7.38 (m, 2H), 5.47 (d, *J* = 7.4 Hz, 1H), 3.36 (dq, *J* = 13.3, 6.6 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 6H).



7a

N-(phenylsulfonyl)acetamide (7a). General procedure A was modified, and the following procedure was used. To a 250 mL round bottom fitted with a stir bar benzenesulfonyl chloride (3.2 mL, 25.0 mmol), and 200 mL of DCM was added. The reaction was cooled in an ice back to 0 °C. Then, saturated ammonium hydroxide (24.1 mL, 180 mmol) was added slowly to maintain the temperature was at 0 °C. After thirty minutes of stirring the reactions was allowed to warm to room

temperature and suited for an additional 6 h. After cooling, the solid was filtered off, dried to give benzenesulfonamide as white powder. The resulting compounds was then used without further purification. To a solution of the free sulfonamide (2.5 g, 16 mmol) was added Ac_2O (12.0 mL, 126 mmol) and $Zn(II)Cl_2$ (190.8 mg, 1.4 mmol) at 23 °C. The residue was dissolved in EtOAc (25 mL) and washed with saturated NH4Cl (25 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuo, and then purified by silica gel chromatography as title compound **7a** (2.952 g, 98%) a colorless solid. The data matches those previously reported.[5] **^{1}H NMR (400 MHz, $CDCl_3$):** 8.84 (s, 1H), 8.11 – 8.01 (m, 2H), 7.70 – 7.63 (m, 1H), 7.61 – 7.52 (m, 2H), 2.08 (s, 3H).

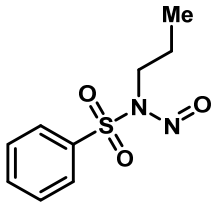


9a

N-hydroxybenzenesulfonamide (9a). General procedure A was modified employing hydroxylamine hydrochloride (3.5 g, 50.0 mmol), and potassium carbonate (6.9 g, 50 mmol) in 50 mL of water maintained at 0 ºC. The reaction as stirred for 15 mins and then 120 mL of THF and 30 mL of MeOH was added to the mixture. Then benzenesulfonyl chloride (3.2 mL, 25.0 mmol) was added dropwise with stirring. The reaction was allowed to stir for 4 h at room temperature. The solvent was removed under reduced pressure and extracted with EtOAc. The reaction afforded **9a** (1.417 g, 33% yield) as a white solid. The data matches those

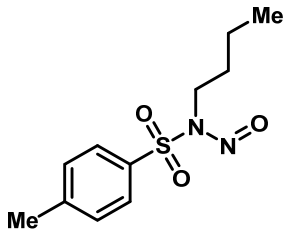
previously reported.[6] **^{1}H NMR (500 MHz, DMSO):** 9.65 (dd, *J* = 17.2, 3.3 Hz, 2H), 7.91 – 7.84 (m, 2H), 7.68 (ddd, *J* = 6.6, 3.8, 1.3 Hz, 1H), 7.65 – 7.58 (m, 2H).

[B] General Procedure for N-nitrososulfonamides. To a 1L round bottom fitted with a stir bar, sulfonamide (~ 25.0 mmol) was dissolved in 250 mL of DCM. The reaction was cooled to 0 °C. Then NaNO2 (50.0 mmol) and *p*TsOH (50.0 mmol) were added portion wise and allowed to stir overnight slowly warming to RT. The reaction was filtered to remove the *p*-Toluenesulfonic acid, sodium salt and precipitates. The solvent was removed under reduced pressure or absorbed onto silica and purified though column chromatography column chromatography with EtOAc/hexanes mixtures to yield the desired product.



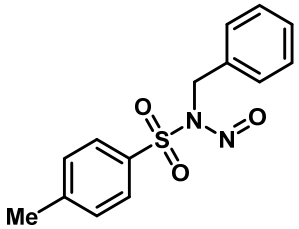
1

N-nitroso-N-propylbenzenesulfonamide (1). General procedure B was employed. The reaction afforded **1** (5.36 g, 94% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.99 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.71 – 7.65 (m, 1H), 7.60 – 7.54 (m, 2H), 3.66 (t, *J* = 7.0 Hz, 2H), 1.51 – 1.40 (m, 2H), 0.80 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 138.1, 134.7, 129.7, 128.1, 44.9, 21.3, 11.3.



2

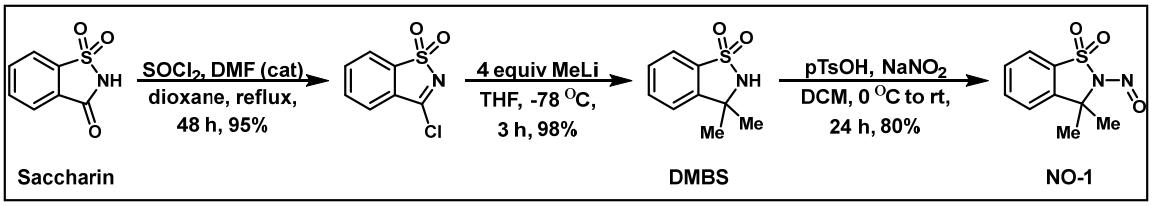
N-butyl-4-methyl-N-nitrosobenzenesulfonamide (2). General procedure B was employed. The reaction afforded **2** (4.86 g, 90% yield) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.87 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 8.3 Hz, 2H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.46 – 1.33 (m, 2H), 1.26 – 1.13 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 146.1, 135.1, 130.3, 128.2, 43.2, 29.8, 21.8, 20.2, 13.6.



3

N-benzyl-4-methyl-N-nitrosobenzenesulfonamide (3 or BNTS). General procedure B was employed. The reaction afforded **3 or BNTS** (6.32 g, 95% yield) as a pale yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.73 (d, J = 8.3 Hz, 2H), 7.29 – 7.22 (m, 5H), 7.13 (dd, J = 6.4, 2.8 Hz, 2H), 4.94 (s, 2H), 2.43 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 146.0, 135.2, 133.6, 130.2, 128.7, 128.5, 128.2, 128.2, 46.1, 21.8.

[C] Procedure for synthesis of NO-1.

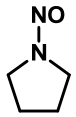


3-chlorobenzo[d]isothiazole 1,1-dioxide. To a 2 L round bottom with a stir bar atop a heating mantle 54.9 g (0.3 mol) of saccharin, 90.0 ml (0.45 mol) of SOCI, and a catalytic amount of DMF (4 ml) was added. The reaction was heated in 250 ml of dioxane for 48 hours at reflux. The clear brown solution was concentrated in vacuo in a rotary evaporator in a heating bath. The residue was used in the next step without further purification.

3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (DMBS). To a 250 mL round bottom 100 mL of dry diethyl ether was added to 20 g of 3-chlorobenzo[d]isothiazole 1,1-dioxide (0.1 mol). The reaction was cooled to -10 °C. Slowly added to the chilled solution was 4 equivalents of 1.6 M MeLi. The reaction was stired for 30 min at -10 °C. The reaction was warmed to RT and allowed to stir for 2.5 h. Once reaction is complete pour into 150 mL of dilute HCL (5%). The organic layer was seperated and washed with water until neutral. The crude reaction was absorbed onto silica and purified with 50/50 EtOAc/Hexanes. Rf = 0.4. The product isolated as a colorless solid in 19.4 g (98% yield). **^{1}H NMR (500 MHz, $CDCl_3$):** 7.63 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.44 – 7.38 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 5.42 (s, 1H), 1.56 (s, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** 146.0, 134.8, 133.3, 128.9, 122.8, 120.8, 60.8, 29.4.

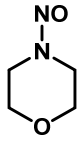
3,3-dimethyl-2-nitroso-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (NO-1). To a large 1L round bottom 9.865 g (0.10 mol) of 3,3-dimethyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide was added with 500 mL of DCM and 17.2 g (0.14 mol) of pTsOH. The mixture was stirred and cooled to 0 °C. Slowly added was 10.2 g (0.15 mol) $NaNO_2$. The reaction was left to warm to room temperature and stirred overnight. The was filtered through a Büchner funnel to remove the insoluble material. The filtrate was then absorbed onto silica and purified with column chromatography using only DCM (Rf = 0.4) as the mobile phase. Isolated was 18.1 g (80% yield) of greenish yellow material. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.88 – 7.75 (m, 2H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 1.99 (s, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** 135.5, 130.3, 123.5, 122.0, 65.5, 29.6.

[D] General Procedure for Nitrosation. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22 mmol, 1 equiv). Dichloromethane (2 mL) was then added and the reaction was stirred at room temperature until completed (thin-layer chromatography or React IR 15). In some reactions, heating is required (80 ºC) and dichloroethane (2 mL) was used in replacement of dichloromethane. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.



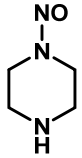
24

1-nitrosopyrrolidine (24). General procedure D was employed using pyrrolidine (17 µL, 0.2 mmol). The reaction afforded **24** (18.6 mg, 93 % yield) as a pale yellow oil. The data matches those previously reported.[7] **^{1}H NMR (500 MHz, $CDCl_3$):** 4.34 – 4.21 (m, 2H), 3.66 – 3.53 (m, 2H), 2.14 – 1.95 (m, 4H).



25

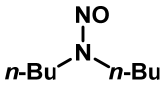
4-nitrosomorpholine (25). General procedure D was employed using morpholine (17 mg , 0.2 mmol). The reaction afforded **25** (21.1 mg, 91 % yield) as a pale yellow oil. The data matches those previously reported.[7] **^{1}H NMR (500 MHz, $CDCl_3$):** 4.33 – 4.25 (m, 1H), 3.92 – 3.83 (m, 2H), 3.65 (t, *J* = 5.2 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** 67.4, 66.0, 50.1, 40.5.



26

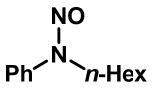
1-nitrosopiperazine (26). General procedure D was employed using piperazine (17 µl, 0.2 mmol). The reaction afforded **26** (22.5 mg, 98 % yield) as a pale yellow oil. The data matches those previously reported.[8] **^{1}H NMR (500 MHz, $CDCl_3$):**

4.27 – 4.18 (m, 1H), 3.85 – 3.78 (m, 1H), 3.11 – 3.03 (m, 1H), 2.87 – 2.78 (m, 1H), 2.67 (s, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** 51.1, 46.6, 45.1, 40.8.



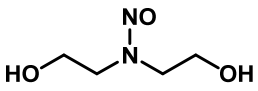
27

N,N-dibutylnitrous amide (27). General procedure D was employed using N,N-dibutylamine (36 ul , 0.2 mmol). The reaction afforded **27** (30.7 mg, 97 % yield) as a yellow oil. The data matches those previously reported.[7] **^{1}H NMR (500 MHz, $CDCl_3$):** 4.06 (t, *J* = 7.3 Hz, 2H), 3.58 – 3.48 (m, 2H), 1.77 – 1.66 (m, 2H), 1.49 – 1.41 (m, 2H), 1.41 – 1.33 (m, 2H), 1.32 – 1.23 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 52.1, 43.6, 30.4, 28.2, 20.5, 19.9, 13.8, 13.7.



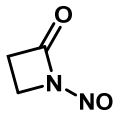
28

N-hexyl-N-phenylnitrous amide (28). General procedure D was employed using *N*-hexylaniline (40 µl, 0.2 mmol). The reaction afforded **28** (41.0 mg, 93 % yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.53 (d, *J* = 7.6 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 6.9 Hz, 1H), 4.08 – 3.95 (m, 2H), 1.54 (s, 2H), 1.27 (s, 6H), 0.86 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 141.8, 129.6, 127.4, 119.8, 44.1, 31.4, 26.8, 26.6, 22.6, 14.1.



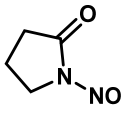
29

N,N-bis(2-hydroxyethyl)nitrous amide (29). General procedure D was employed using diethanolamine (19 ul , 0.2 mmol). The reaction afforded **29** (24.4 mg, 91 % yield) as a pale yellow oil. The data matches those previously reported.[7] **^{1}H NMR (500 MHz, $(CD_3)_2SO$):** 4.92 (t, *J* = 5.5 Hz, 1H), 4.85 (t, *J* = 5.5 Hz, 1H), 4.18 (t, *J* = 5.6 Hz, 2H), 3.72 (q, *J* = 5.5 Hz, 2H), 3.66 (t, = 6.0 Hz, 2H), 3.44 (q, *J* = 5.8 Hz, 2H). **^{13}C NMR (125 MHz, $(CD_3)_2SO$):** 58.7, 56.8, 55.1, 46.5.



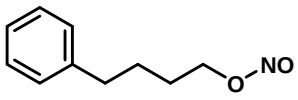
33

1-nitrosoazetidin-2-one (33). General procedure D was employed using azetidin-2-one (15 mg , 0.2 mmol). The reaction afforded **33** (13.0 mg, 65% yield) as a pale yellow oil. The data matches those previously reported.[9] **^{1}H NMR (400 MHz, $CDCl_3$):** 3.65 (t, *J* = 5.9 Hz, 2H), 3.18 (t, *J* = 5.9 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 160.8, 40.7, 33.9.



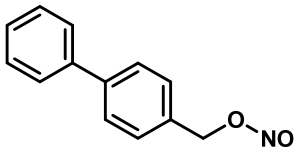
34

1-nitrosopyrrolidin-2-one (34). General procedure D was employed using pyrrolidin-2-one (17 uL , 0.2 mmol). The reaction afforded **35** (21.2 mg, 95 % yield) as a pale yellow oil. The data matches those previously reported.[9] **^{1}H NMR (500 MHz, $CDCl_3$):** 3.73 – 3.63 (m, 2H), 2.79 (t, *J* = 8.1 Hz, 2H), 2.25 – 2.09 (m, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** 173.1, 42.7, 31.0, 15.9.



38

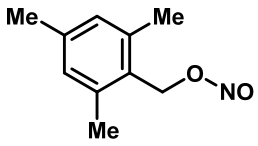
4-phenylbutyl nitrite (38). General procedure A was employed using 4-phenylbutan-1-ol (31 µL, 0.2 mmol). The reaction afforded **38** (30.9 mg, 94% yield) as a pale yellow oil. The data matches those previously reported.[10] **^{1}H NMR (500 MHz, $CDCl_3$):** 7.31 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.15 (m, 3H), 4.73 (s, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 1.84–1.69 (m, 4H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 141.9, 128.5, 128.5, 126.0, 68.3, 35.5, 28.7, 27.8.



39

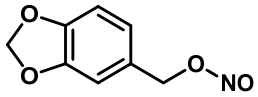
[1,1'-biphenyl]-4-ylmethyl nitrite (39). General procedure A was employed using [1,1'-biphenyl]-4-ylmethanol (37.0 mg, 0.2 mmol). The reaction afforded **39** (35.7 mg, 93% yield) as a colorless solid. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.61 (t, *J* = 7.4

Hz, 4H), 7.41 (qd, *J* = 14.9, 7.3 Hz, 5H), 5.76 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 141.5, 140.5, 134.5, 128.8, 128.6, 127.6, 127.5, 127.1, 69.7.



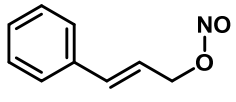
40

2,4,6-trimethylbenzyl nitrite (40). General procedure A was employed using 2,4,6-trimethylbenzyl alcohol (30 mg, 0.2 mmol). The reaction afforded **40** (26.3 mg, 80% yield) as a colorless solid. The data matches those previously reported.[11] **^{1}H NMR (400 MHz, $CDCl_3$):** 6.91 (s, 2H), 5.72 (s, 2H), 2.34 (s, 6H), 2.30 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 138.9, 138.2, 129.3, 128.4, 64.8, 21.2, 19.7.



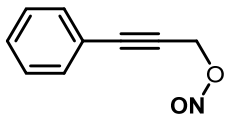
41

benzo[d][1,3]dioxol-5-ylmethyl nitrite (41). General procedure A was employed using benzo[d][1,3]dioxol-5-ylmethanol (31 mg, 0.2 mmol). The reaction afforded **41** (32.7 mg, 90% yield) as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 6.86 – 6.73 (m, *J* = 7.7 Hz, 3H), 5.97 (s, 2H), 5.61 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** 148.1, 148.0, 129.4, 122.3, 109.0, 108.5, 101.4, 70.2.



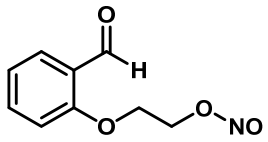
43

cinnamyl nitrite (43). General procedure A was employed using cinnamyl alcohol (27 µL, 0.2 mmol). The reaction afforded **43** (12.6 mg, 40% yield) as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.40 (t, *J* = 9.3 Hz, 2H), 7.34 (dd, *J* = 16.5, 8.9 Hz, 2H), 7.31 – 7.26 (m, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.32 (dt, J = 15.7, 6.3 Hz, 1H), 5.35 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** 136.1, 134.9, 128.8, 128.4, 126.8, 122.8, 68.7.



44

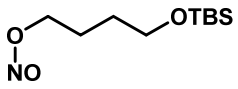
3-phenylprop-2-yn-1-yl nitrite (44). General procedure A was employed using 3-phenylprop-2-yn-1-ol (27 µL, 0.2 mmol). The reaction afforded **44** (11.0 mg, 34% yield) as a colorless oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 7.47 – 7.44 (m, 2H), 7.36–7.30 (m, 3H), 5.49 (s, 2H). **^{13}C NMR (125 MHz, $CDCl_3$):** 132.0, 131.8, 129.0, 128.5, 122.1, 87.0, 51.9.



45

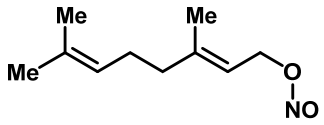
2-(2-formylphenoxy)ethyl nitrite (45). General procedure A was employed using 2-(2-hydroxyethoxy)benzaldehyde (23 µl, 0.2 mmol). The reaction afforded **45** (16.1 mg, 41% yield) as a yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** 10.42 (s, 1H), 7.84 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.97

(d, J = 8.4 Hz, 1H), 5.20 (s, 2H), 4.44 – 4.32 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 189.6, 160.7, 136.1, 128.7, 125.2, 121.6, 112.5, 66.8, 66.3.



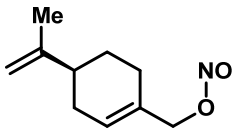
47

4-[(*tert*-butyldimethylsilyl)oxy)]butyl nitrite (47). General procedure A was employed using 4-[(*tert*-butyldimethylsilyl)oxy]butan-1-ol (48 mg, 0.2 mmol). The reaction afforded **47** (41.6 mg, 89% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 4.73 (s, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 1.86 – 1.76 (m, 2H), 1.62 – 1.55 (m, 2H), 0.89 (s, *J* = 6.8 Hz, 9H), 0.04 (s, 6H).



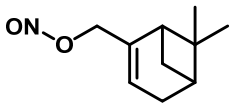
48

(*E*)-3,7-dimethylocta-2,6-dien-1-yl nitrite (48). General procedure A was employed using geraniol (35 µL, 0.2 mmol). The reaction afforded **48** (28.7 mg, 78% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 5.37 (t, *J* = 6.5 Hz, 1H), 5.21 – 5.02 (m, *J* = 22.4, 16.7 Hz, 3H), 2.17 – 1.99 (m, 4H), 1.74 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H).



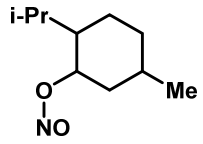
49

(S)-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl nitrite (49). General procedure A was employed using (S)-(4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methanol (38 µL, 0.2 mmol). The reaction afforded **49** (32.2 mg, 89% yield) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** 5.80 (s, 1H), 5.08 (s, J = 53.9 Hz, 2H), 4.72 (d, J = 9.1 Hz, 2H), 2.21 – 1.95 (m, 5H), 1.90 – 1.81 (m, J = 12.0 Hz, 1H), 1.74 (s, 3H), 1.55 – 1.44 (m, J = 28.8, 10.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** 149.6, 132.5, 127.1, 109.0, 72.7, 40.9, 30.6, 27.4, 26.6, 20.9.



50

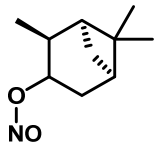
(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl nitrite (50). General procedure A was employed using (6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methanol (38 µL, 0.2 mmol). The reaction afforded **50** (28.2 mg, 78% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 5.60 (s, 1H), 5.05 (s, 2H), 2.41 (dt, *J* = 8.7, 5.6 Hz, 1H), 2.29 (q, *J* = 18.1 Hz, 2H), 2.11 (d, *J* = 5.2 Hz, 2H), 1.28 (s, 3H), 1.18 (d, *J* = 8.7 Hz, 1H), 0.81 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 142.9, 122.8, 71.3, 43.7, 40.8, 38.3, 31.6, 31.5, 26.2, 21.2.



51

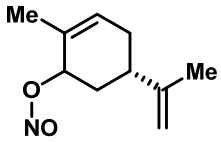
2-isopropyl-5-methylcyclohexyl nitrite (51). General procedure A was employed using (±)-menthol (31 mg, 0.2 mmol). The reaction afforded **51** (34.8

mg, 94% yield) as a pale yellow oil. The data matches those previously reported.[12] **^{1}H NMR (400 MHz, $CDCl_3$):** 5.34 – 5.17 (m, 1H), 2.07 – 1.98 (m, 1H), 1.85 – 1.72 (m, 2H), 1.69 – 1.55 (m, 1H), 1.52 – 1.42 (m, 1H), 1.30 – 1.12 (m, 2H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 80.1, 46.7, 42.2, 34.2, 31.9, 25.9, 23.6, 22.2, 20.9, 15.9.



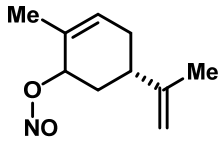
52

(1S,2S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl nitrite (52). General procedure A was employed using (1*R*,2*R*,3*R*,5*S*)-(−)-Isopinocampheol (31 mg, 0.2 mmol). The reaction afforded **52** (27.6 mg, 74 % yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 5.69 (s, 1H), 2.71 – 2.57 (m, 1H), 2.46 – 2.36 (m, 1H), 2.22 – 2.12 (m, 1H), 2.04 – 1.95 (m, 1H), 1.93 – 1.88 (m, 1H), 1.88 – 1.81 (m, 1H), 1.27 (s, 3H), 1.14 (d, *J* = 7.4 Hz, 3H), 1.08 – 1.01 (m, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 79.3, 47.5, 43.8, 41.4, 38.7, 35.9, 33.9, 27.6, 24.0, 20.1.



53 (trans)

1

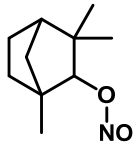


53 (cis)

1.25

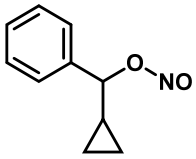
(1R,5S)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl nitrite (53 trans) and (1S,5S)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl nitrite (53 cis). General

procedure A was employed using (-)-carveol (32 µL, 0.2 mmol). The reaction afforded **53 (trans)** and **53 (cis)** as a mixture of inseparable isomers (19.1 mg, 53% yield) as a pale yellow oil. **(53 trans) and (53 cis) ^{1}H NMR (500 MHz, $CDCl_3$):** 6.06 – 5.95 (m, 1H), 5.83 – 5.79 (m, 1H), 5.77 (s, 1H), 5.73 – 5.65 (m, 1H), 4.78 – 4.69 (m, 4H), 2.52 – 2.41 (m, 1H), 2.35 – 2.11 (m, 5H), 2.06 – 1.99 (m, 2H), 1.95 – 1.88 (m, 2H), 1.79 – 1.67 (m, 11H), 1.61 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 148.7, 148.2, 132.4, 123.0, 128.9, 127.0, 109.7, 109.5, 40.8, 35.7, 35.2, 35.0, 30.9, 30.9, 21.0, 20.6, 20.6, 19.3.



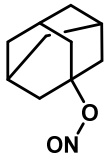
54

1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl nitrite (54). General procedure A was employed using 1,3,3-trimethylbicyclo[2.2.1]heptan-2-ol (32 mg, 0.2 mmol). The reaction afforded **54** (27.3 mg, 74% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 4.93 (s, 1H), 1.81 (d, *J* = 3.0 Hz, 1H), 1.70 (d, *J* = 10.8 Hz, 2H), 1.65 – 1.57 (m, 1H), 1.53 – 1.44 (m, 1H), 1.29 (d, *J* = 10.6 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H), 0.73 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 91.3, 48.7, 48.3, 41.8, 40.3, 30.3, 26.7, 26.0, 21.2, 19.2.



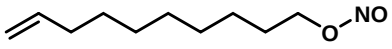
55

cyclopropyl(phenyl)methyl nitrite (55). General procedure A was employed using cyclopropyl(phenyl)methanol (29 µL, 0.2 mmol). The reaction afforded **55** (21.5 mg, 61% yield) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** 7.47 – 7.28 (m, 5H), 5.68 (d, *J* = 8.8 Hz, 1H), 1.54 – 1.41 (m, 1H), 0.75 – 0.68 (m, 2H), 0.52 (dt, *J* = 14.1, 9.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** 140.0, 128.7, 128.3, 126.8, 85.7, 16.7, 4.5, 3.9.



57

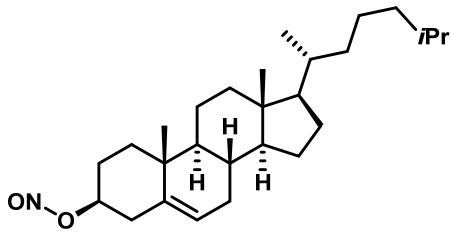
adamantan-1-yl nitrite (57). General procedure A was employed using adamantanol (31 mg, 0.2 mmol). The reaction afforded **57** (19.2 mg, 53% yield) as a colorless solid. **^{1}H NMR (500 MHz, $CDCl_3$):** 2.29 (s, 3H), 2.13 (s, 6H), 1.76 (s, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** 82.3, 42.9, 36.2, 30.9.



58

dec-9-en-1-yl nitrite (58). General procedure A was employed using dec-9-en-1-ol (36 ul , 0.2 mmol). The reaction afforded **58** (23.8 mg, 54% yield) as a pale yellow oil. **^{1}H NMR (500 MHz, $CDCl_3$):** 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.99 (d, *J* = 17.1 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 4.69 (s, 2H), 2.04 (dd, *J* = 14.0, 6.9

Hz, 2H), 1.79 – 1.65 (m, 2H), 1.42 – 1.22 (m, 10H). **^{13}C NMR (125 MHz, $CDCl_3$):** 139.3, 114.3, 114.3, 68.6, 33.9, 29.5, 29.3, 29.1, 29.0, 26.0.



59

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl nitrite (59). General procedure A was employed using cholesterol (83 mg, 0.2 mmol). The reaction afforded **59** (59.0 mg, 71 % yield) as a white solid. **^{1}H NMR (500 MHz, $CDCl_3$):** 5.49 – 5.42 (m, 1H), 5.29 – 5.19 (m, 1H), 2.52 (t, *J* = 11.6 Hz, 1H), 2.41 (dd, *J* = 13.1, 3.3 Hz, 1H), 2.09 – 1.92 (m, 4H), 1.90 – 1.68 (m, 3H), 1.65 – 1.45 (m, 6H), 1.43 – 1.24 (m, 6H), 1.23 – 0.98 (m, 12H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.88 (dd, *J* = 6.5, 1.9 Hz, 6H), 0.70 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$):** 139.6, 123.2, 79.6, 56.9, 56.3, 50.3, 42.5, 39.9, 39.7, 38.9, 37.3, 36.8, 36.4, 36.0, 32.1, 32.0, 28.5, 28.4, 28.2, 24.5, 24.0, 23.0, 22.7, 21.2, 19.5, 18.9, 12.0.

[E] Procedure for dealkylated N-nitroso compounds from tertiary amines. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22 mmol, 1 equiv). Dichloromethane (2 mL) was then

added and the reaction was stirred at room temperature for 24 h. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.

[F] General procedure for anilides as latent radical precursor to form aryl radicals. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22 mmol, 1 equiv). Dichloromethane (2 mL) was then added and the reaction was stirred at 80 ^{o}C for 24 h. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.

[G] General procedure for diazotization of anilines to form azoarenes. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22 mmol, 1 equiv). Dichloromethane (2 mL) was then added and the reaction was stirred at room temperature for 2 h. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.

[H] General Procedure for nitration of phenols. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22

mmol, 1 equiv). Dichloromethane (2 mL) was then added and the reaction and a rubber septa was added on top of the vial with the insertion of an O_2 balloon. The mixture was stirred at room temperature for 24 h. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.

[I] General Procedure for ipso-nitration or nitrosation of aryl boronic acids. The threads of a 3 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added substrate (0.2 mmol, 1 equiv), **NO-1** (45.0 mg, 0.22 mmol, 1 equiv). Dichloromethane (2 mL) for nitrosation and MeCN for nitration was then added and the reaction was stirred at room temperature for 2 h. Upon completion, the solvent was removed under reduced pressure, crude mixture was directly absorbed onto silica and purified by silica gel chromatography to yield the desired product.

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Butanol, and 3-Phenyl-1-Propanol with Ceric Ammonium Nitrate. *J. Org. Chem.* **1975**, *40*, 1454–1456.

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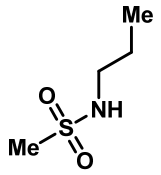
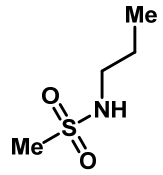
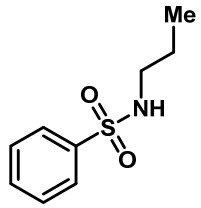
Chapter 3. Characterized Compound Spectra



1a ^{1}H NMR (400 MHz, $CDCl_3$)



1a ^{13}C NMR (100 MHz, $CDCl_3$)



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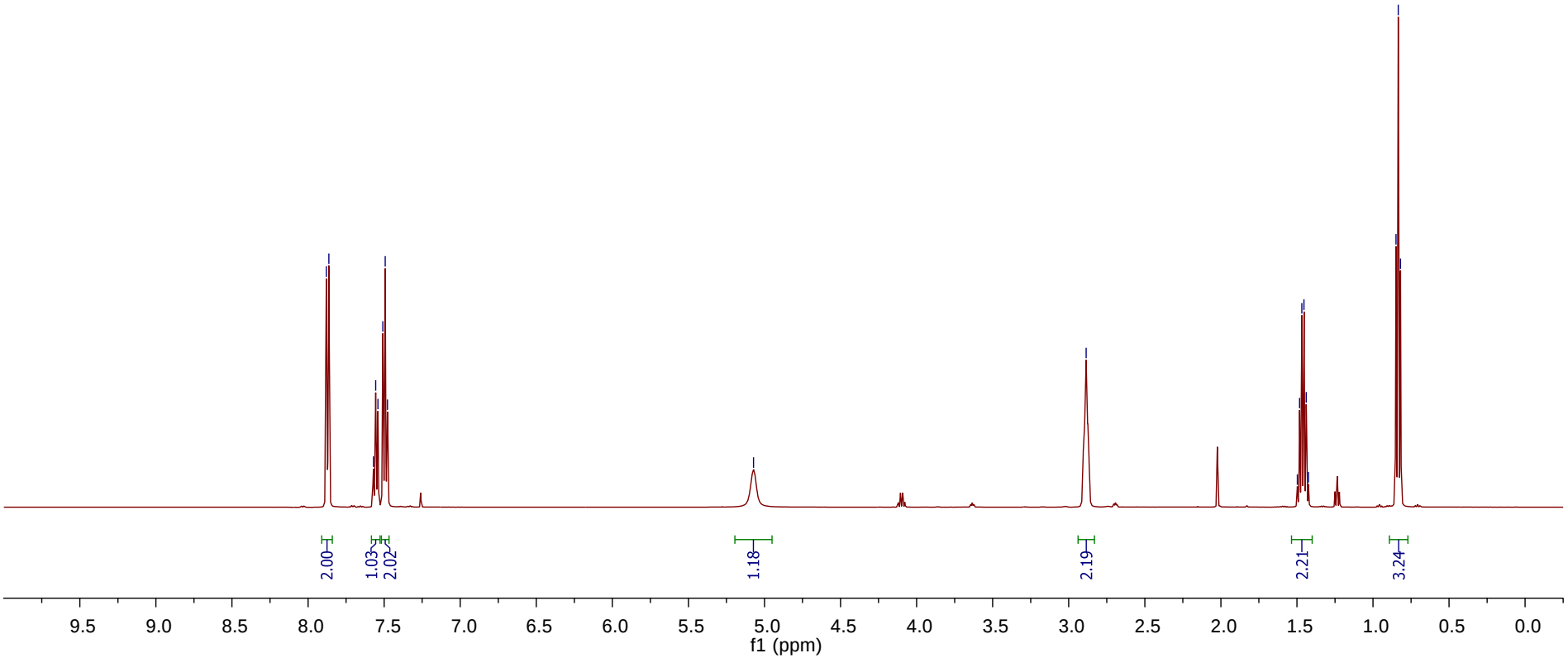
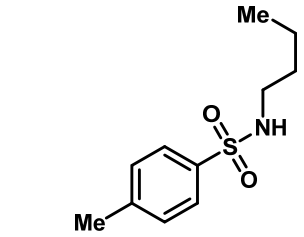
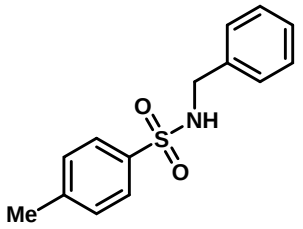




3a ^{1}H NMR (400 MHz, $CDCl_3$)



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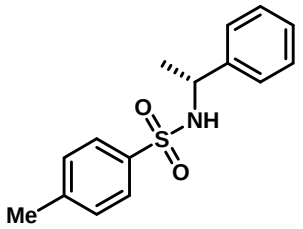
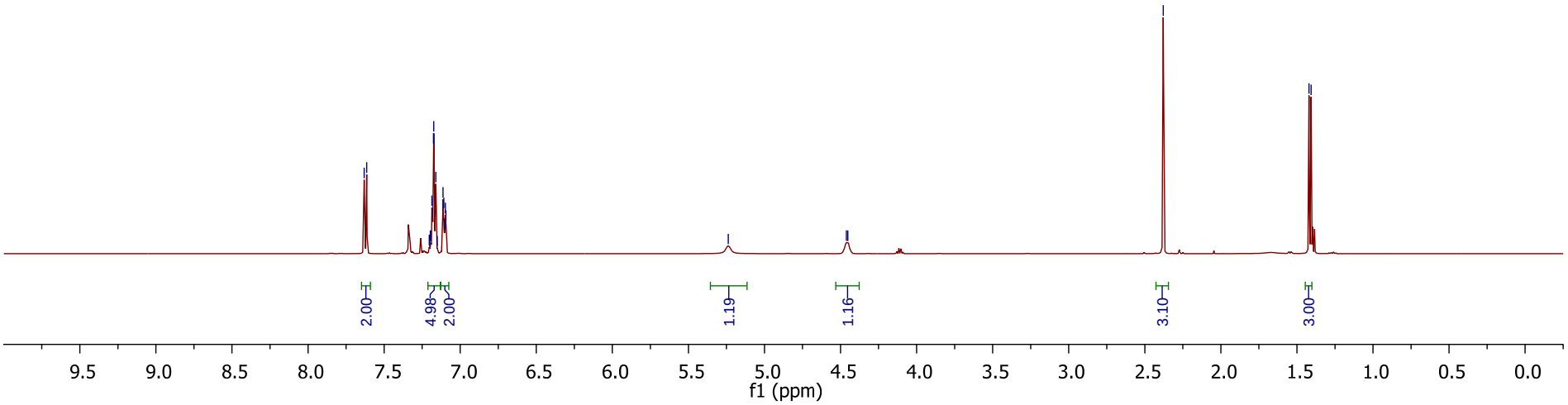
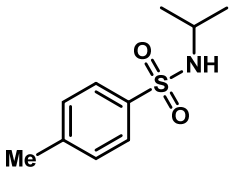


5a ^{1}H NMR (500 MHz, $CDCl_3$)





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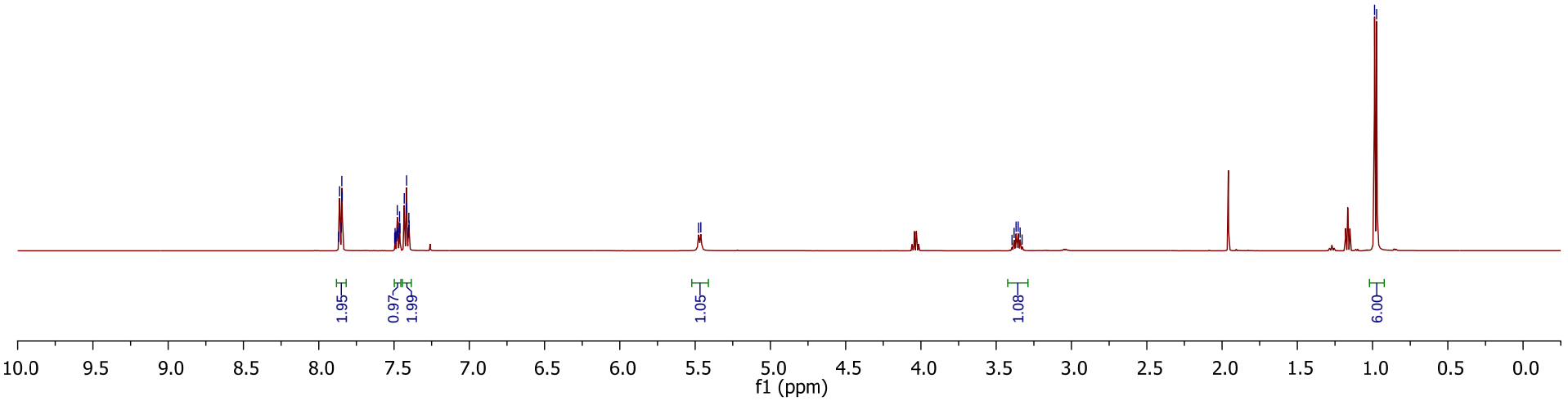
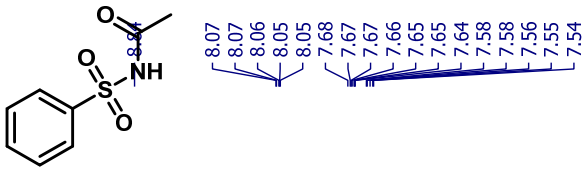
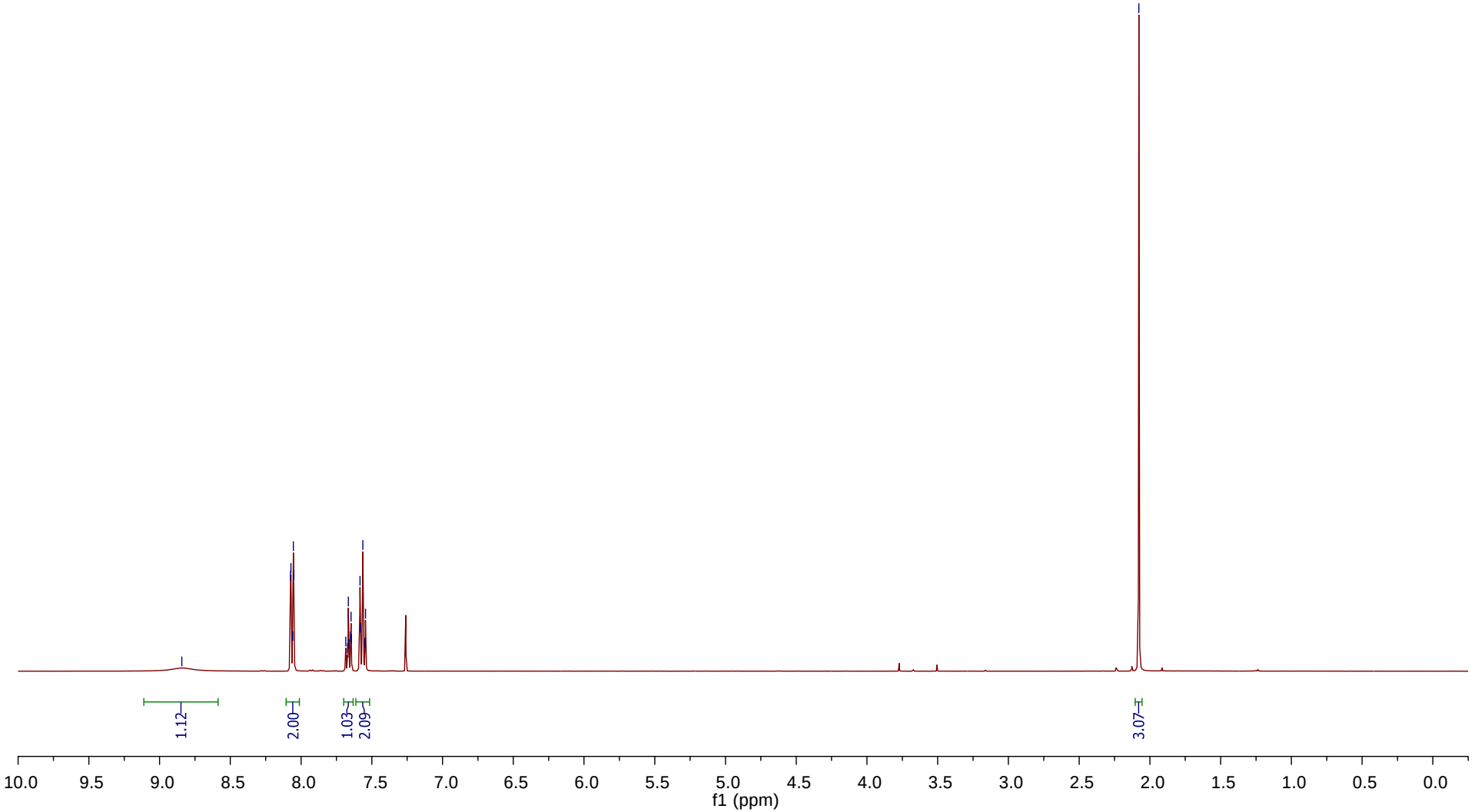
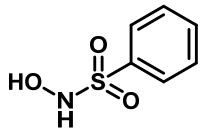


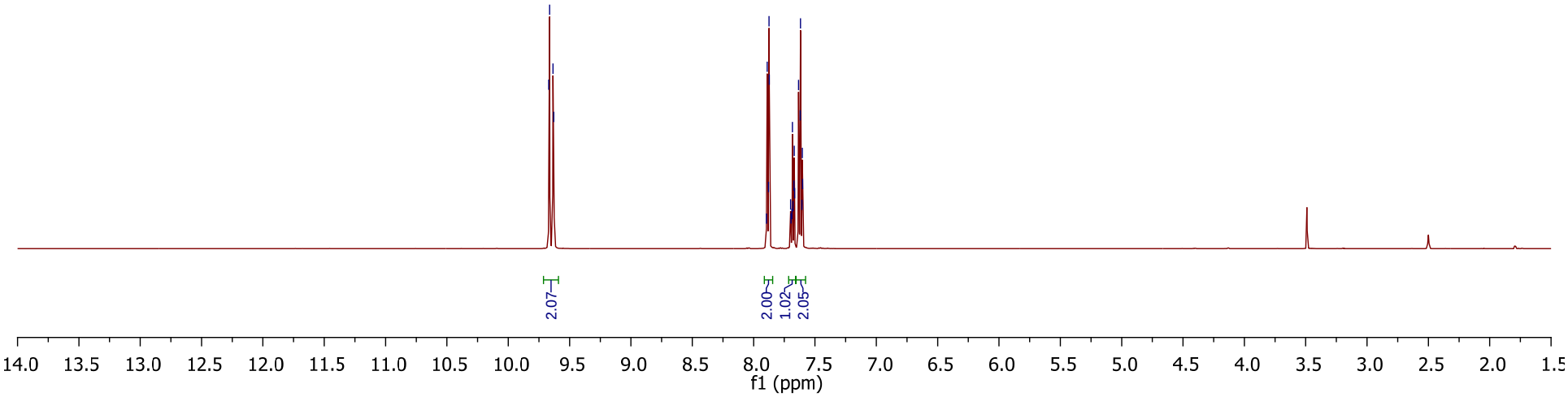


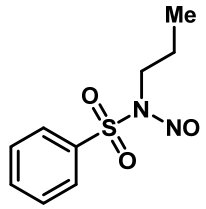
7a ^{1}H NMR (400 MHz, $CDCl_3$)





9a ^{1}H NMR (500 MHz, DMSO)





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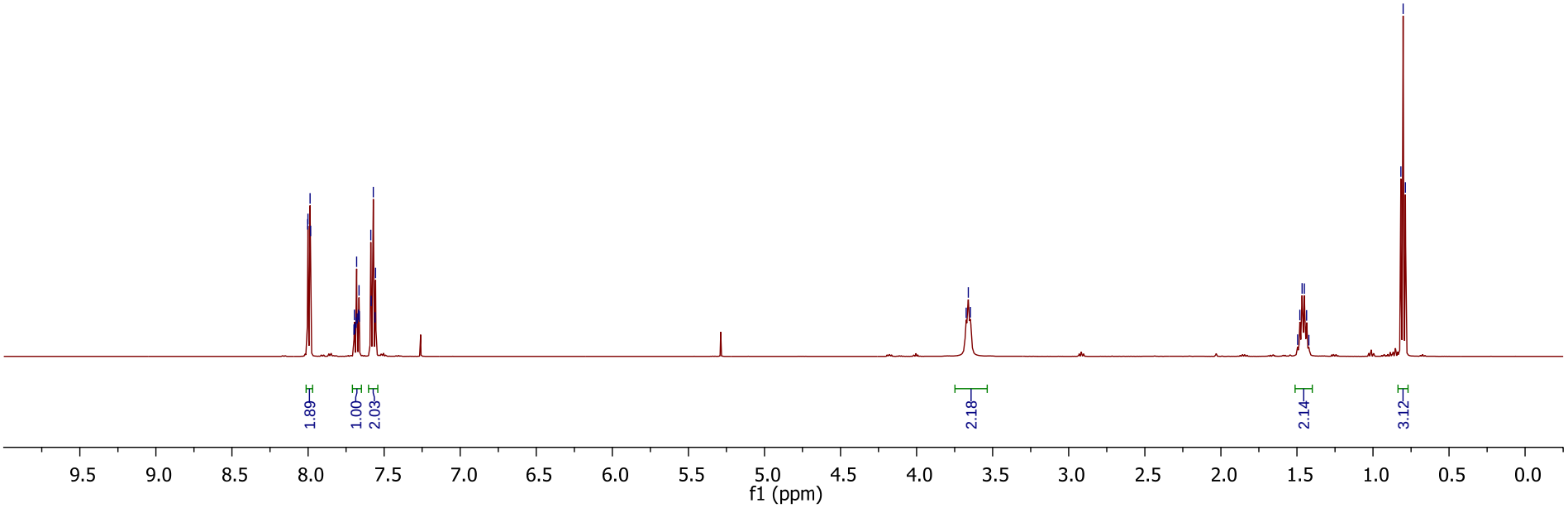
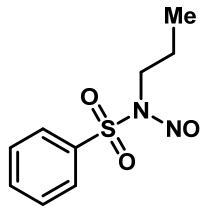
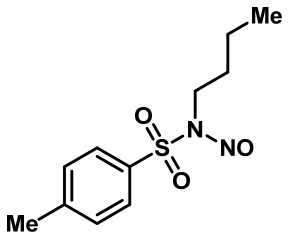




1 ^{13}C NMR (125 MHz, $CDCl_3$)



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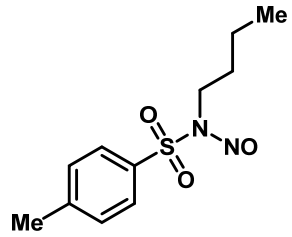

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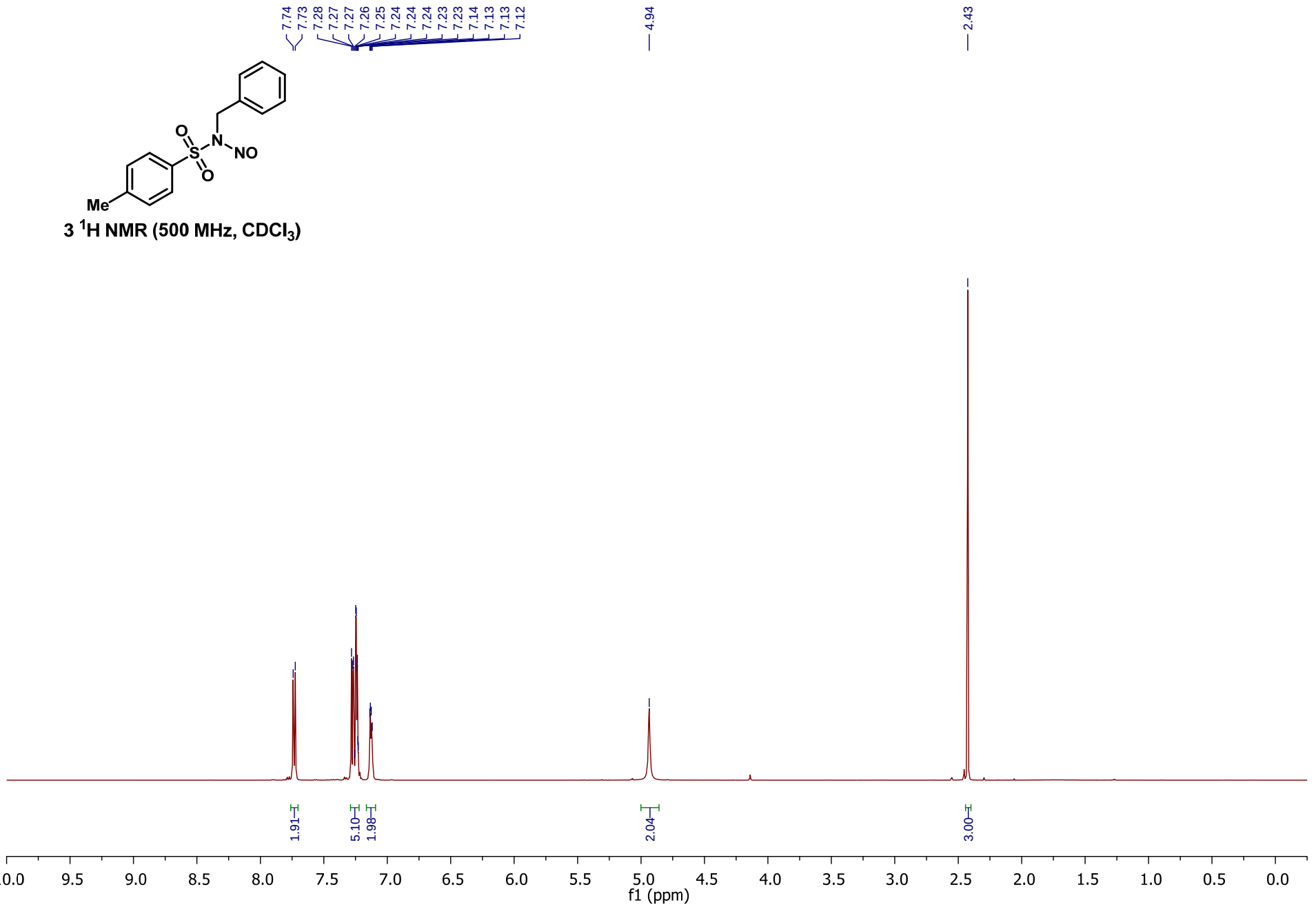

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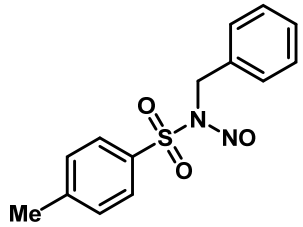

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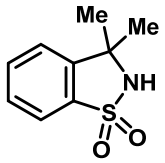
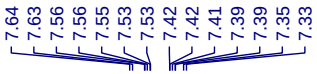
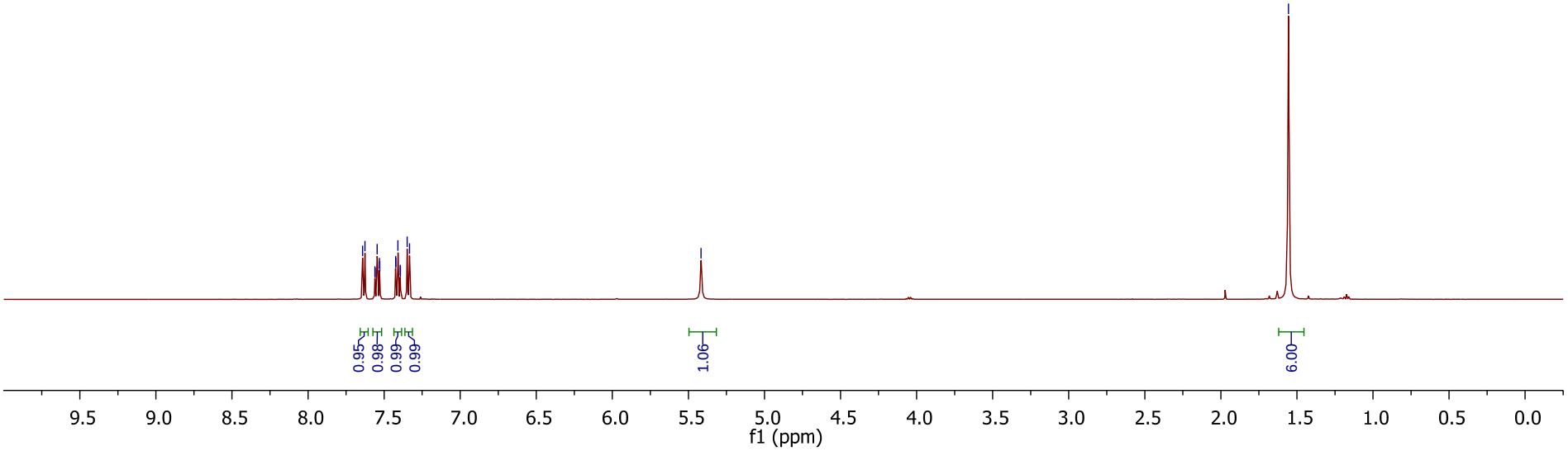
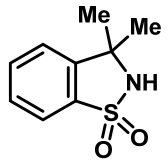


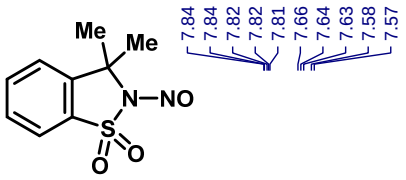


DMBS ^{1}H NMR (500 MHz, $CDCl_3$)

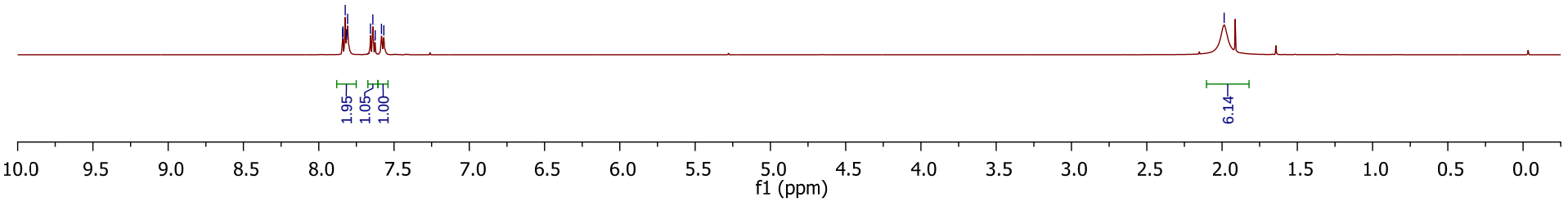


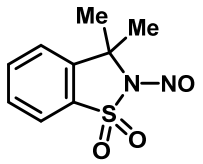


DMBS ^{13}C NMR (125 MHz, $CDCl_3$)

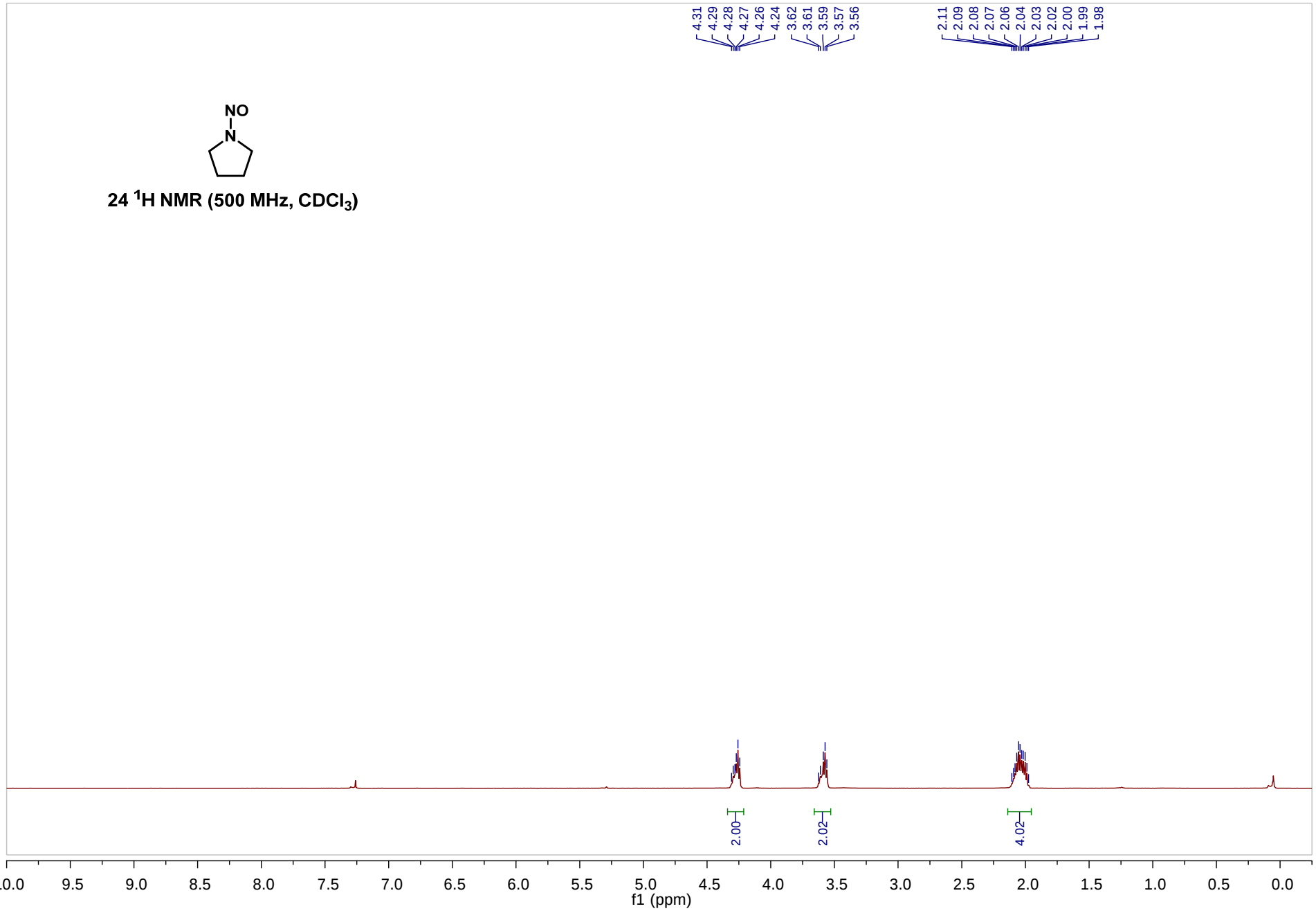


NO-1 ^{1}H NMR (500 MHz, $CDCl_3$)

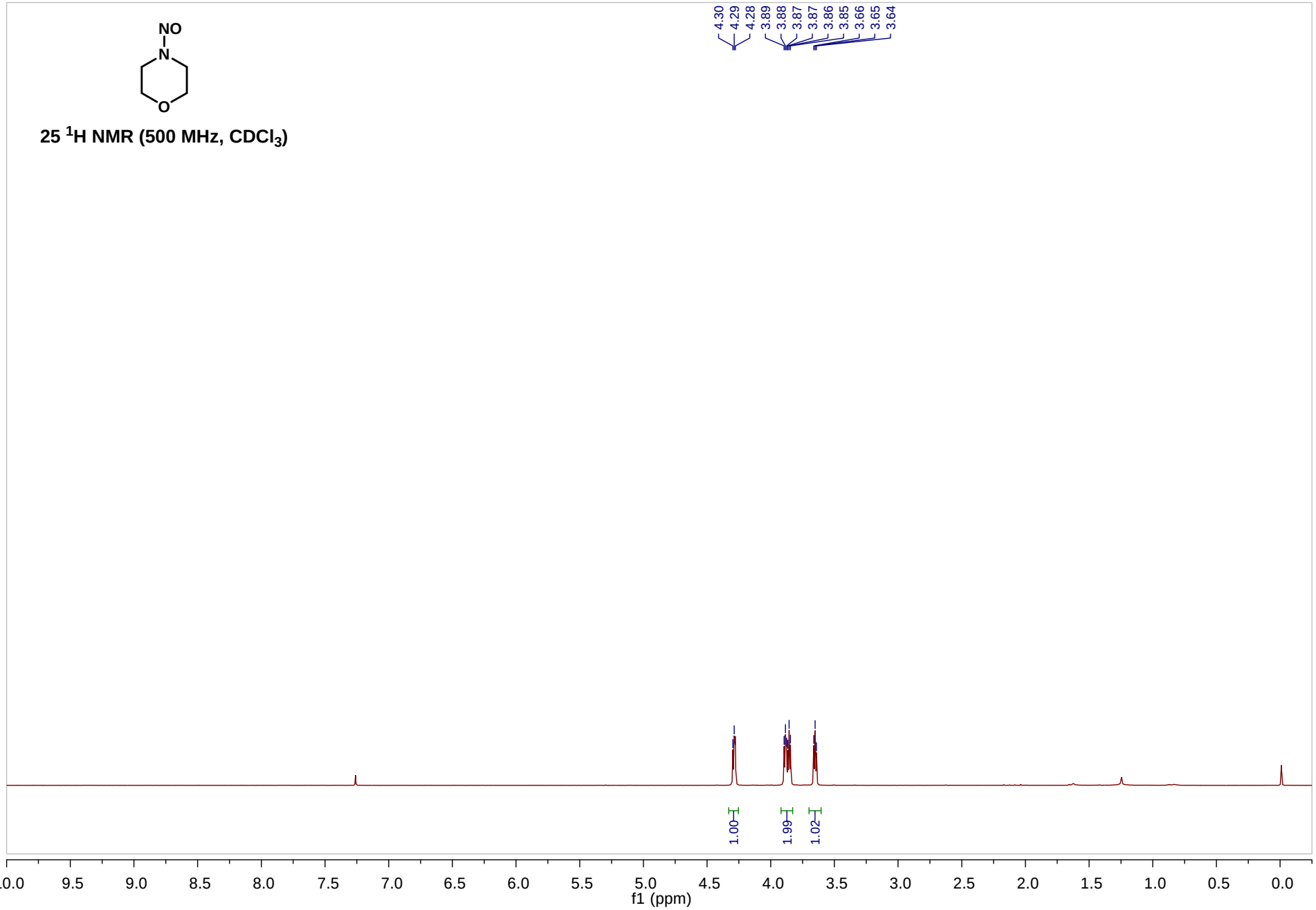


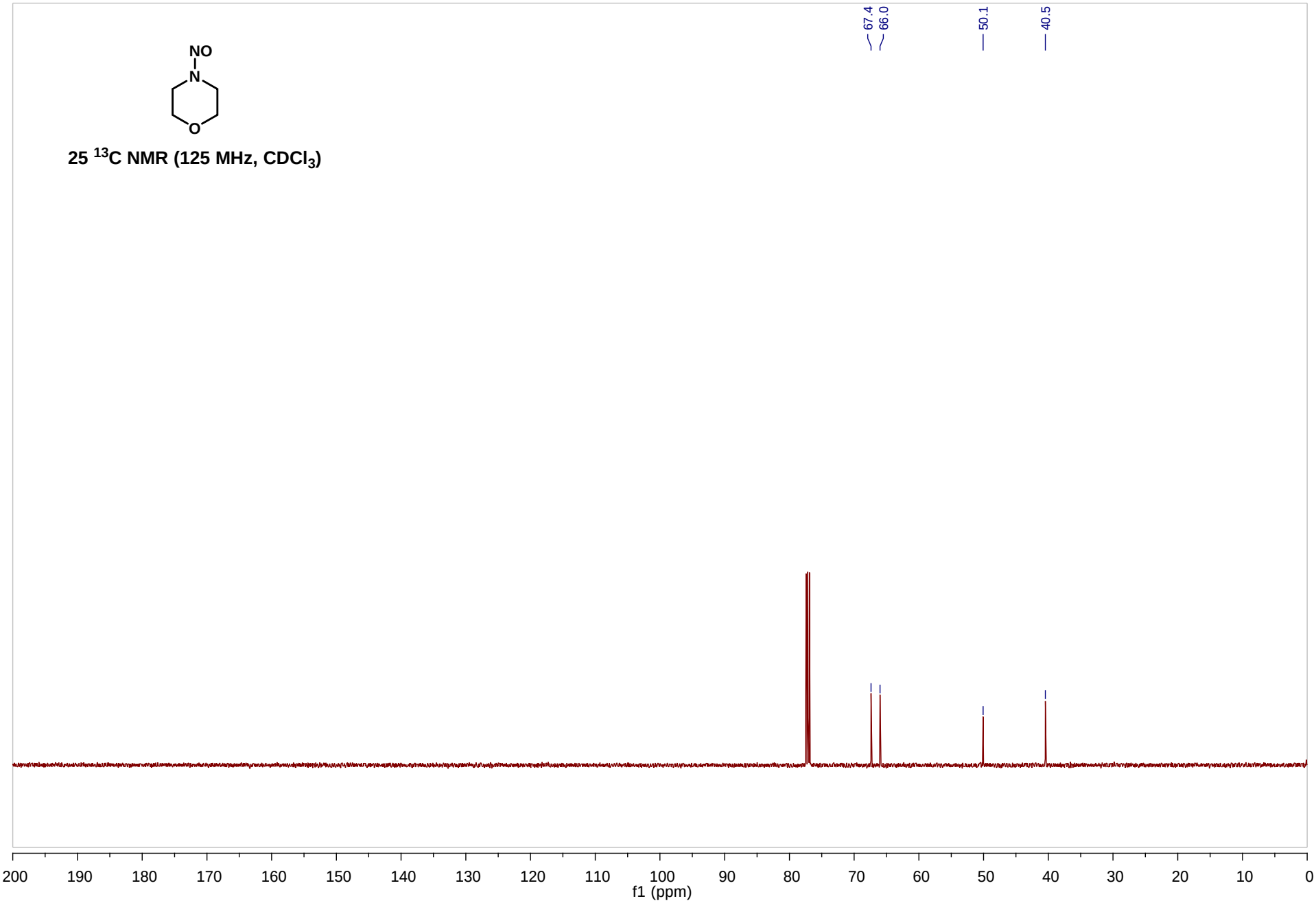


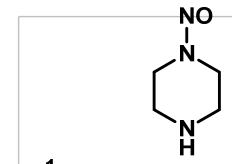
NO-1 ^{13}C NMR (125 MHz, $CDCl_3$)



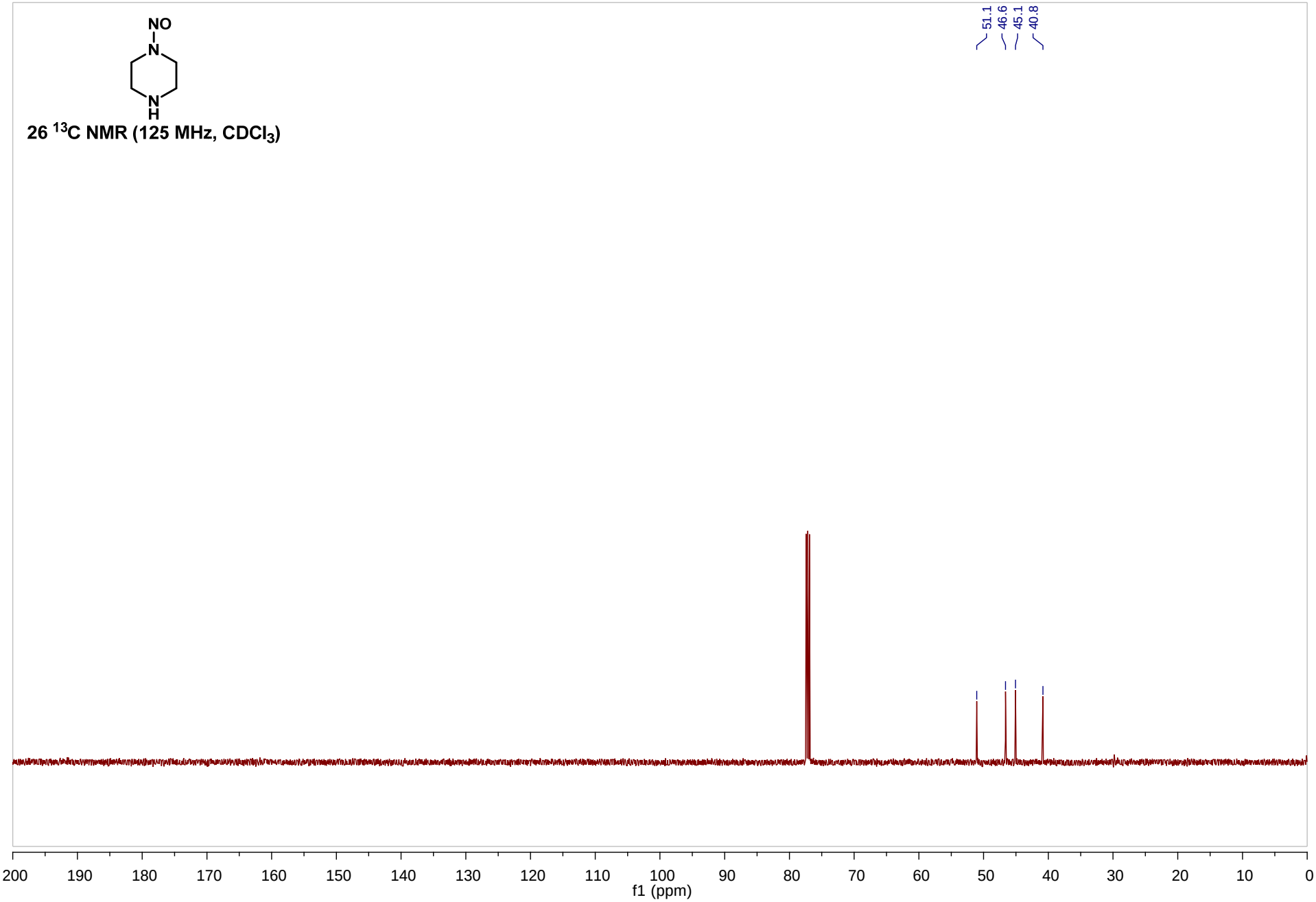
24 ^{1}H NMR (500 MHz, $CDCl_3$)

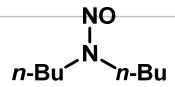

NO
N
O
25 1H NMR (500 MHz, CDCl3)
4.30
4.29
4.28
3.89
3.88
3.87
3.87
3.86
3.85
3.66
3.65
3.64
1.00
1.99
1.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


NO
N
O
25 13C NMR (125 MHz, CDCl3)
67.4
66.0
50.1
40.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

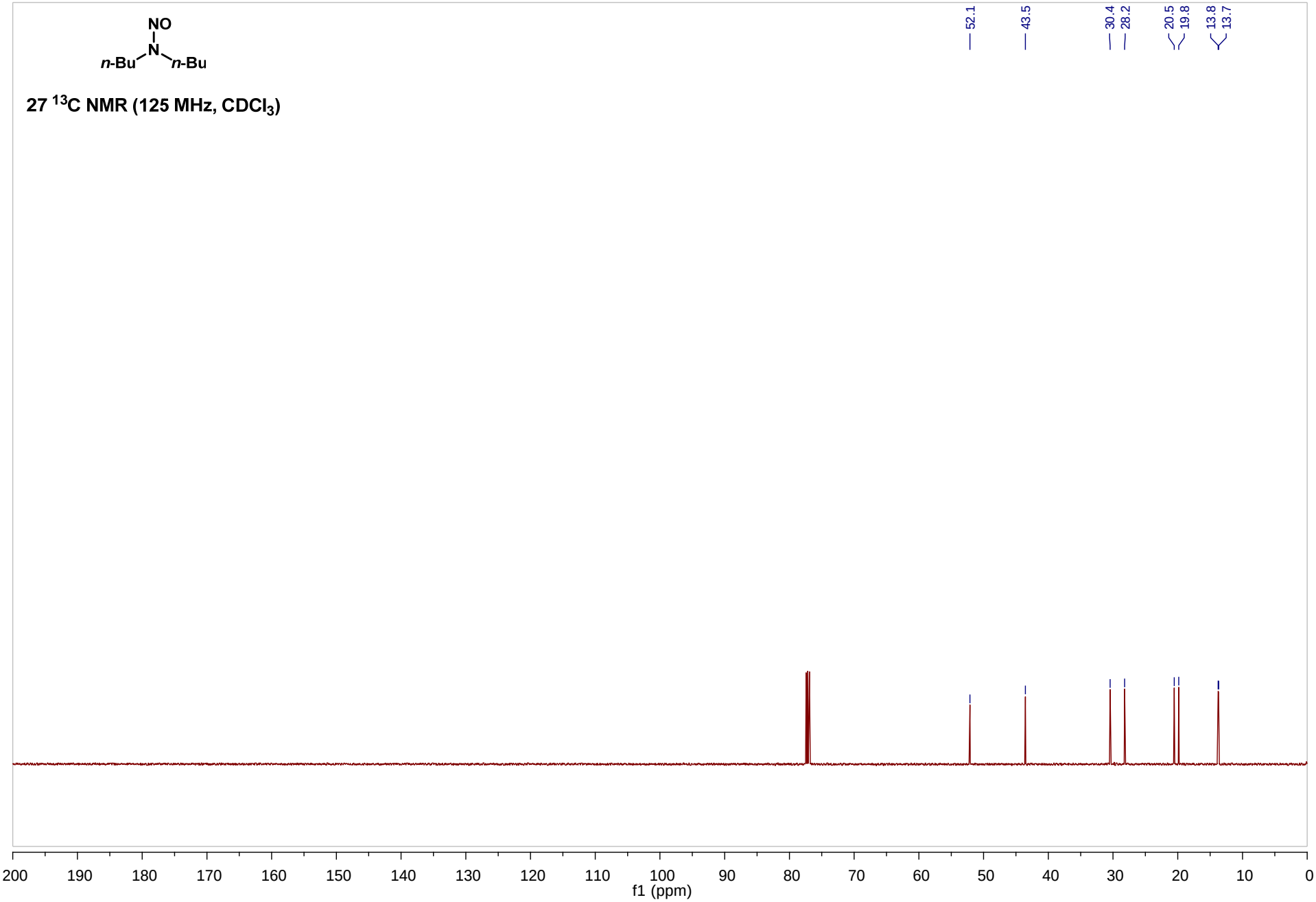


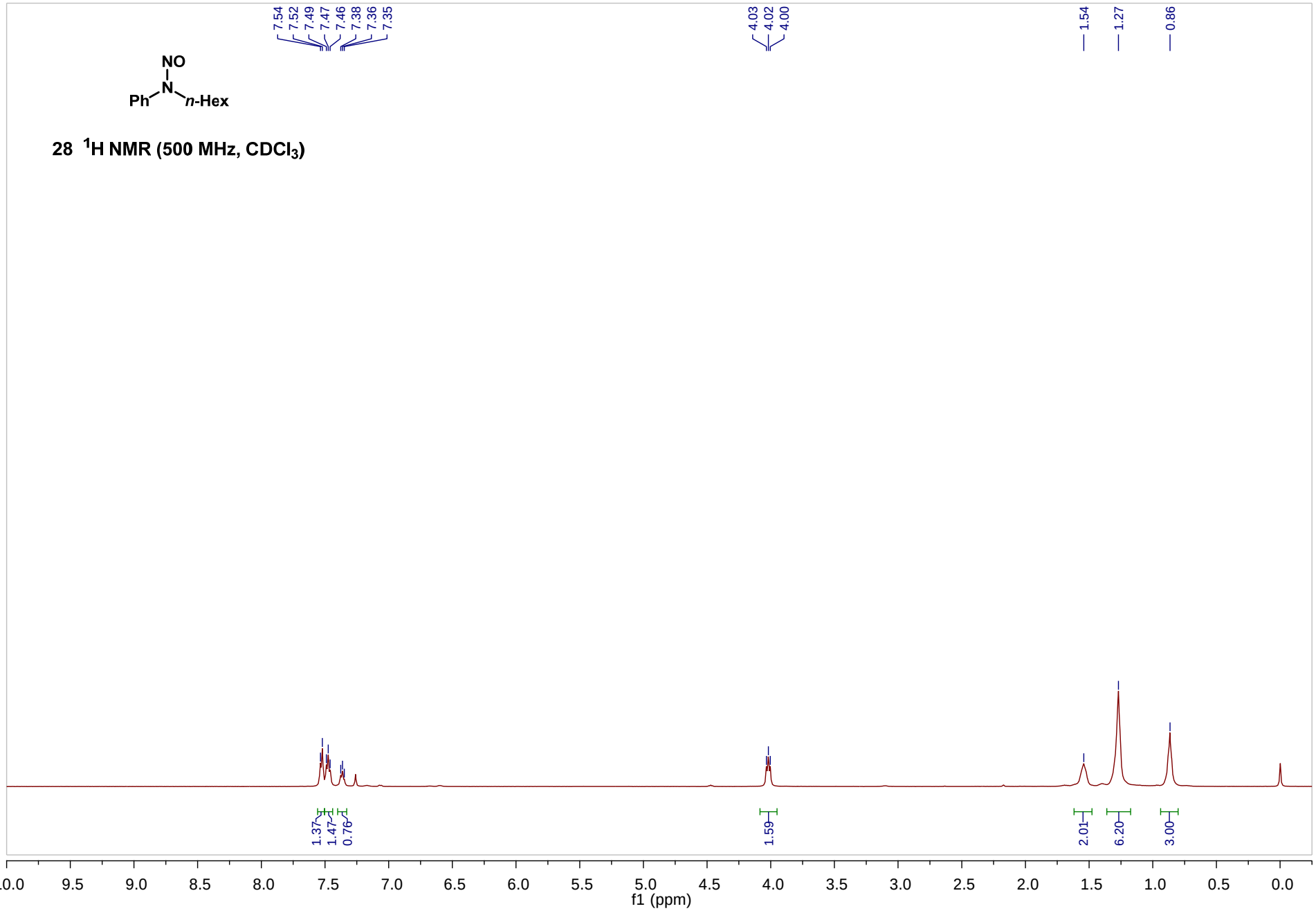
26 ^{1}H NMR (500 MHz, $CDCl_3$)

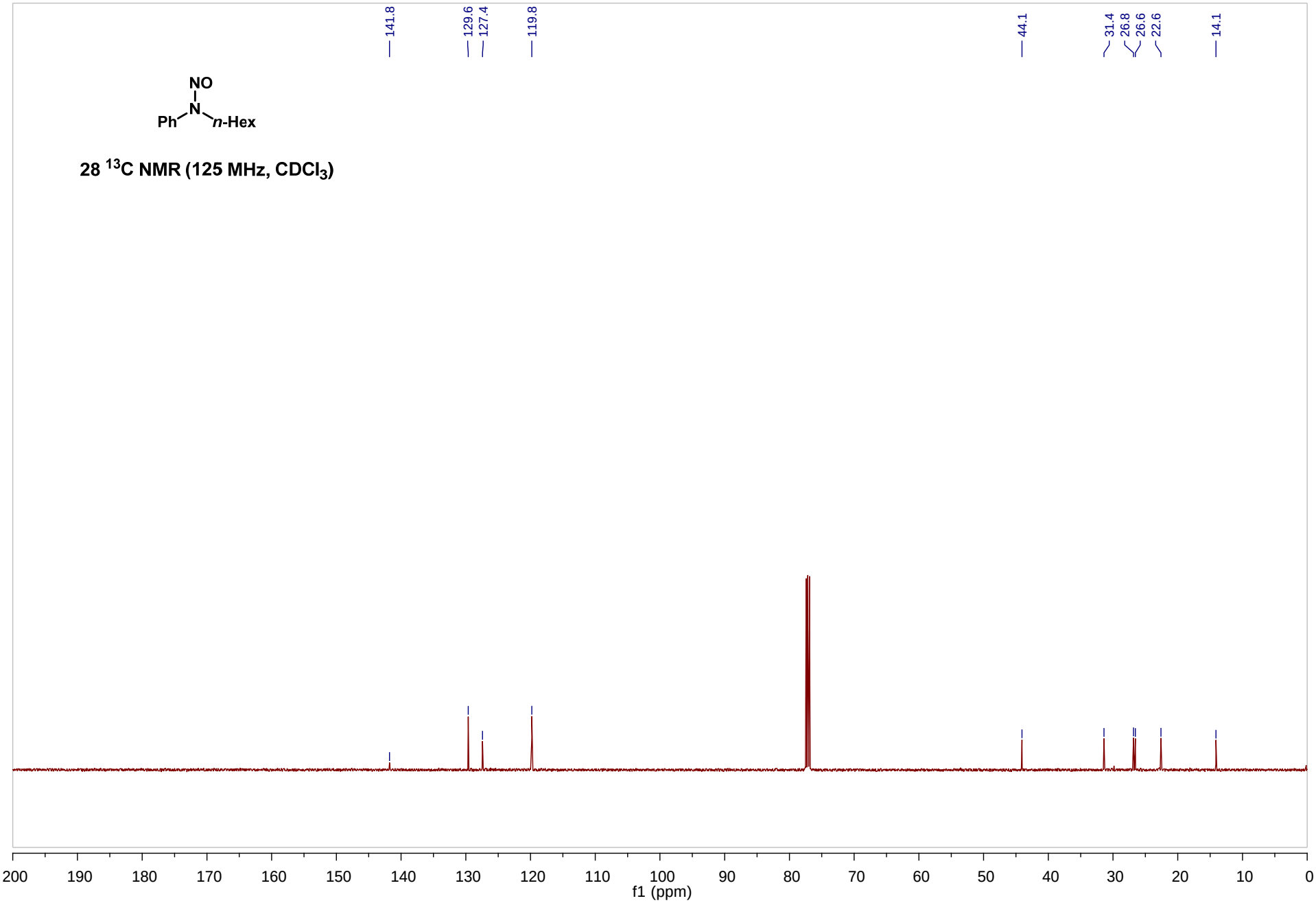

NO
N
N
H
26 ^{13}C NMR (125 MHz, $CDCl_3$)
51.1
46.6
45.1
40.8
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

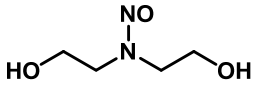


27 ^{1}H NMR (500 MHz, $CDCl_3$)

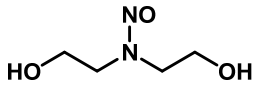

NO
N
n-Bu
n-Bu
27 13C NMR (125 MHz, CDCl3)
52.1
43.5
30.4
28.2
20.5
19.8
13.8
13.7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.54
7.52
7.49
7.47
7.46
7.38
7.36
7.35
4.03
4.02
4.00
1.54
1.27
0.86
NO
N
Ph
n-Hex
28 1H NMR (500 MHz, CDCl3)
1.37
1.47
0.76
1.59
2.01
6.20
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

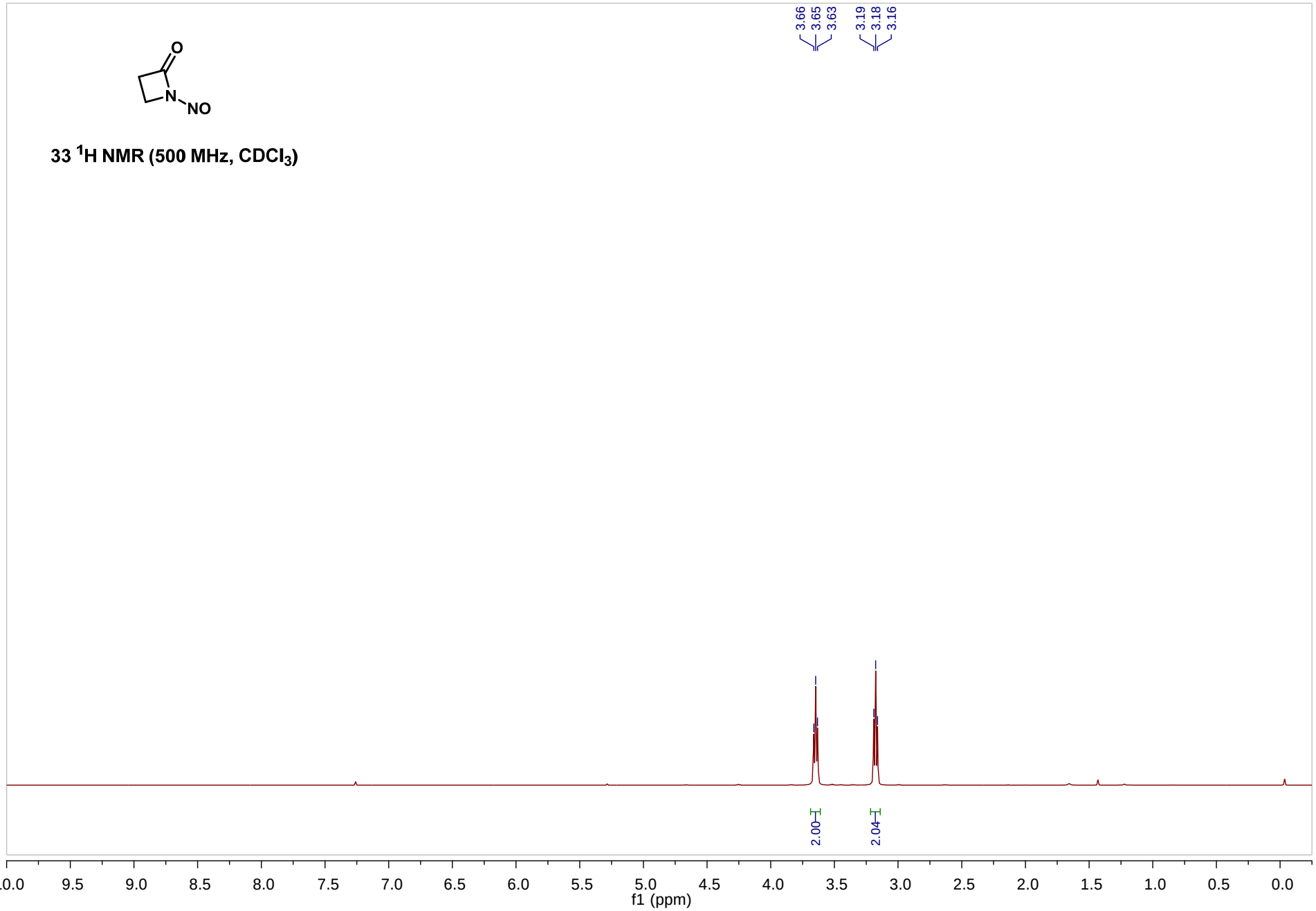

141.8
129.6
127.4
119.8
44.1
31.4
26.8
26.6
22.6
14.1
NO
N
Ph
n-Hex
28 13C NMR (125 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



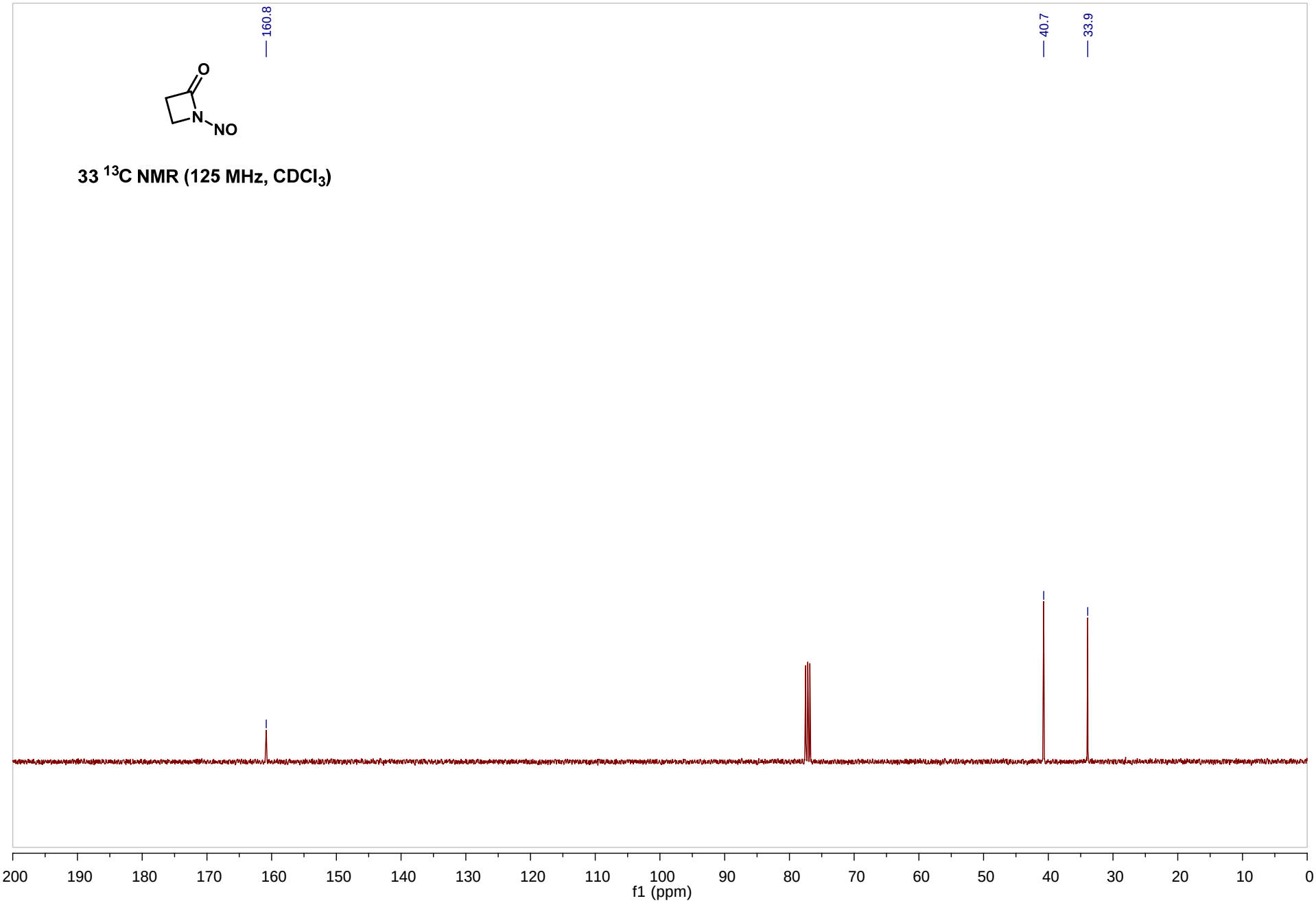
29 ^{1}H NMR (500 MHz, $(CD_3)_2SO$)



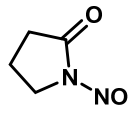
29 ^{13}C NMR (125 MHz, $(CD_3)_2SO$)



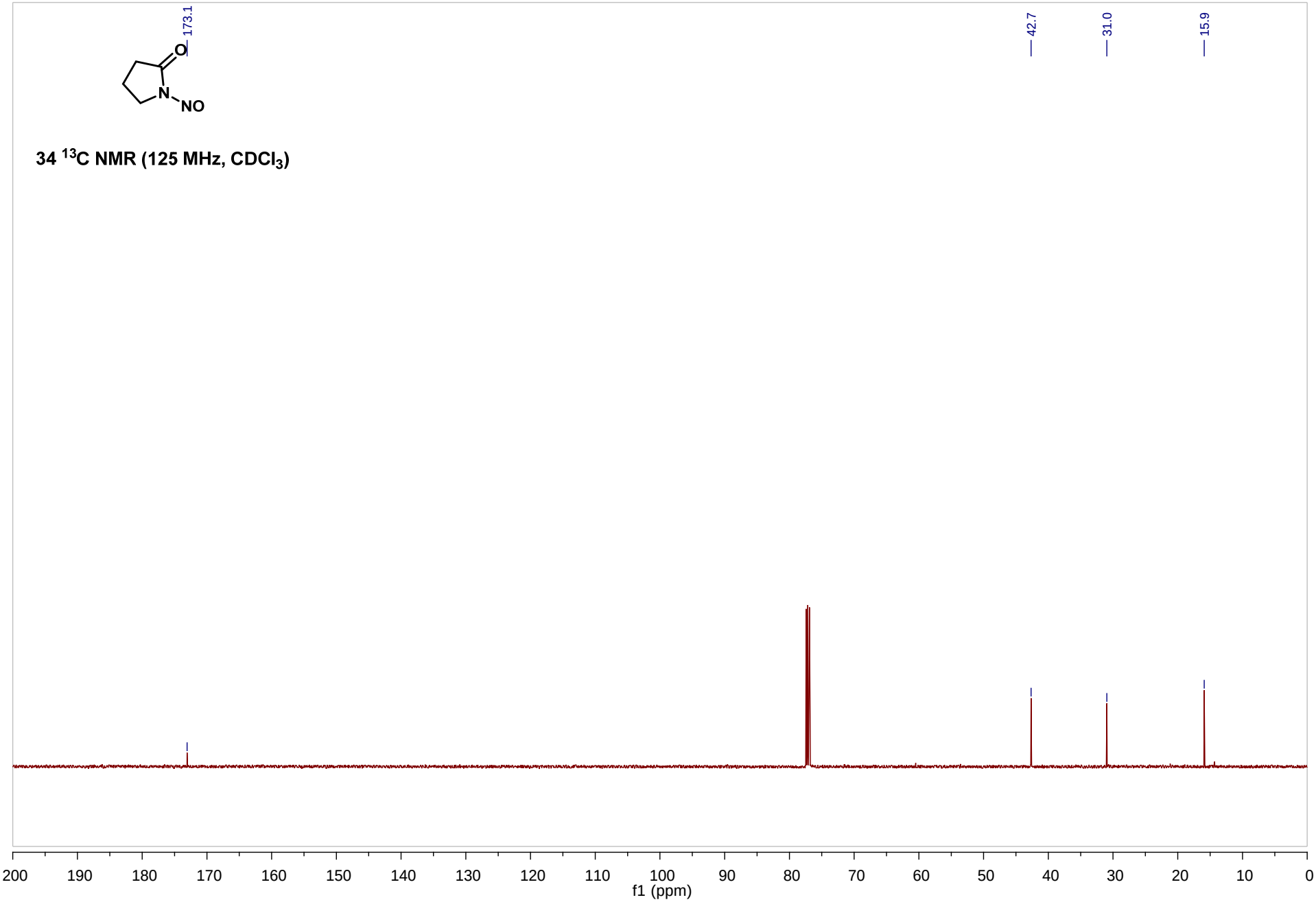
33 ^{1}H NMR (500 MHz, $CDCl_3$)



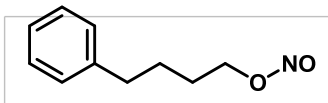
33 ^{13}C NMR (125 MHz, $CDCl_3$)



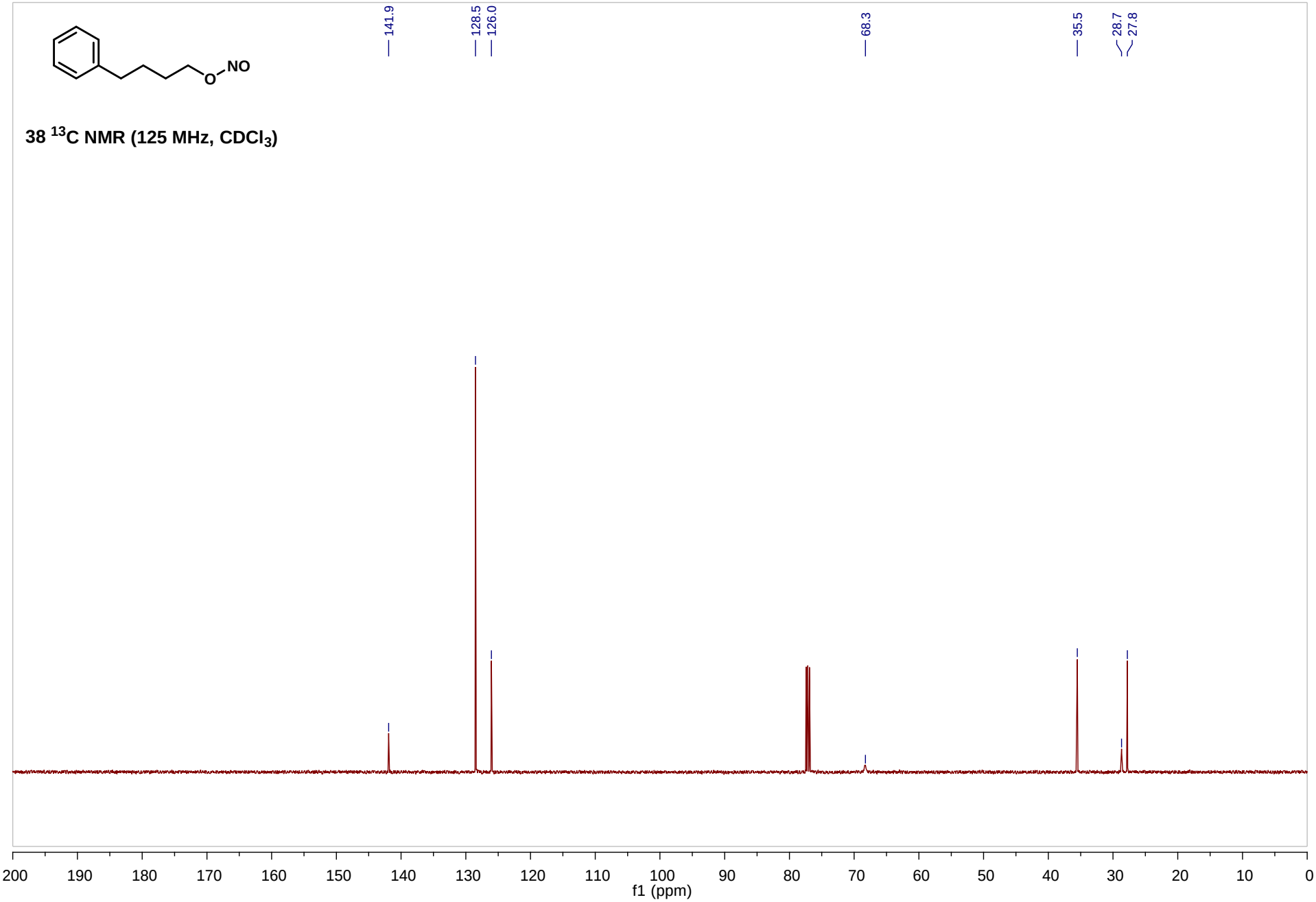
34 ^{1}H NMR (500 MHz, $CDCl_3$)



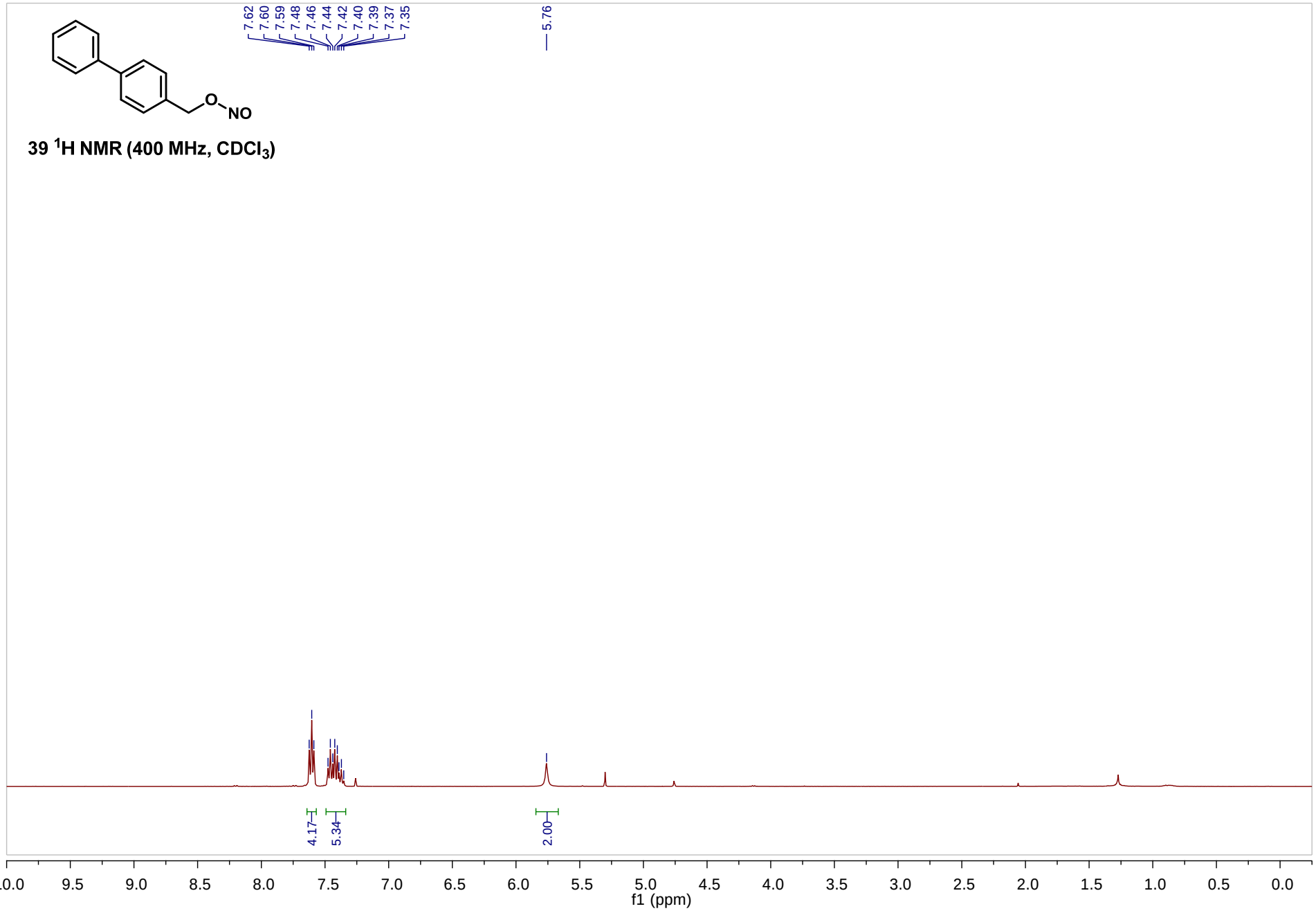
34 ^{13}C NMR (125 MHz, $CDCl_3$)

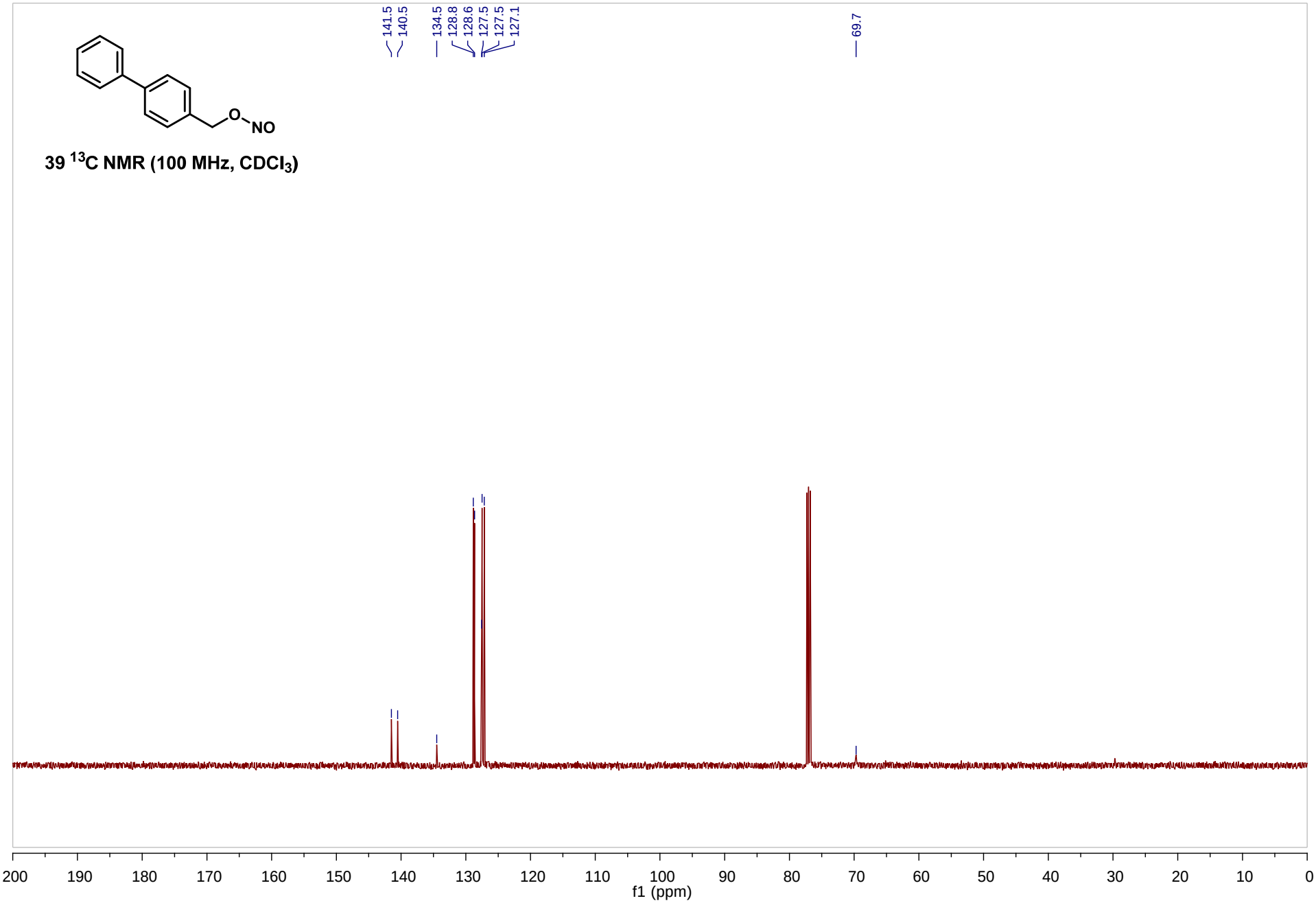


38 ^{1}H NMR (500 MHz, $CDCl_3$)

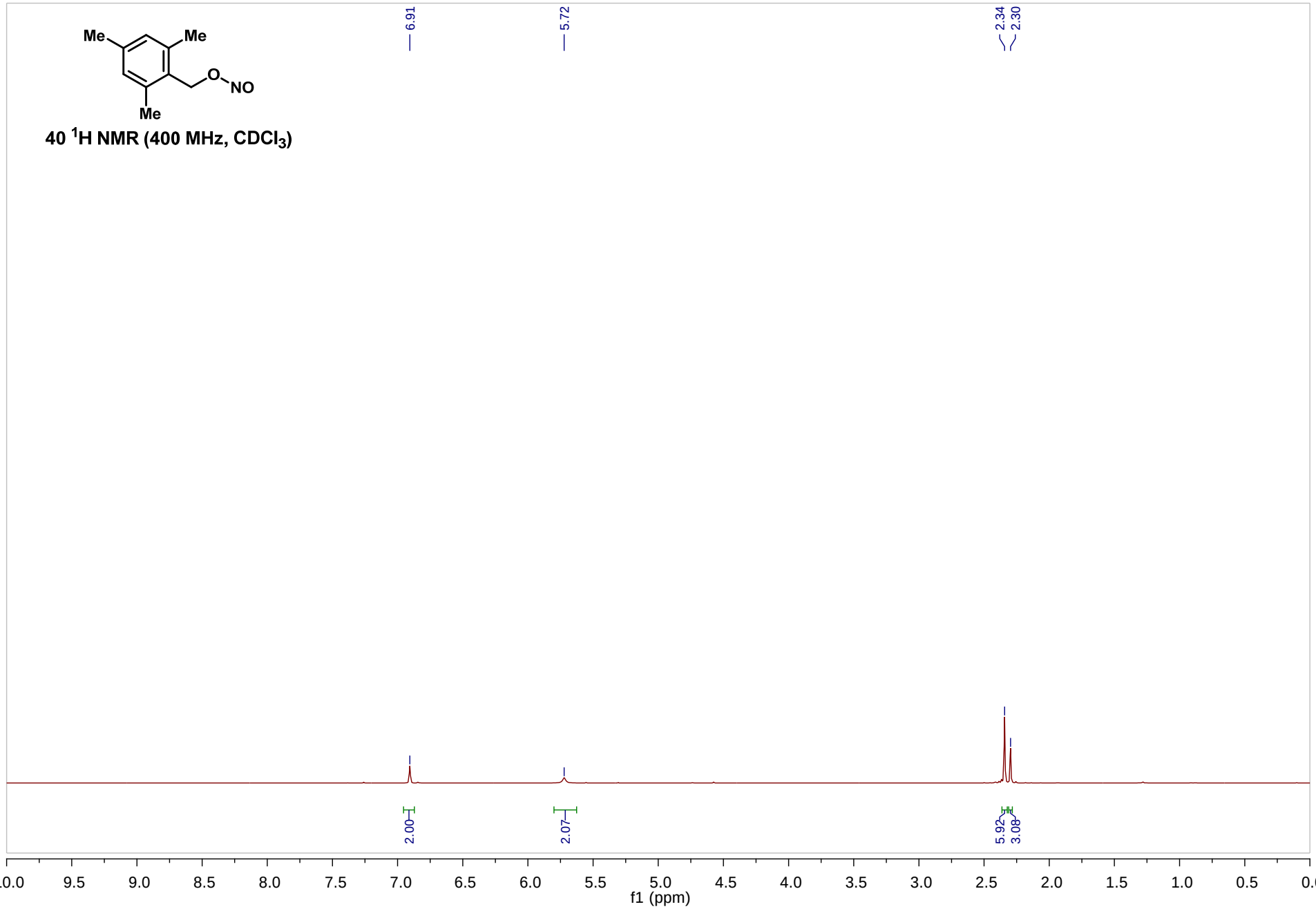


38 ^{13}C NMR (125 MHz, $CDCl_3$)

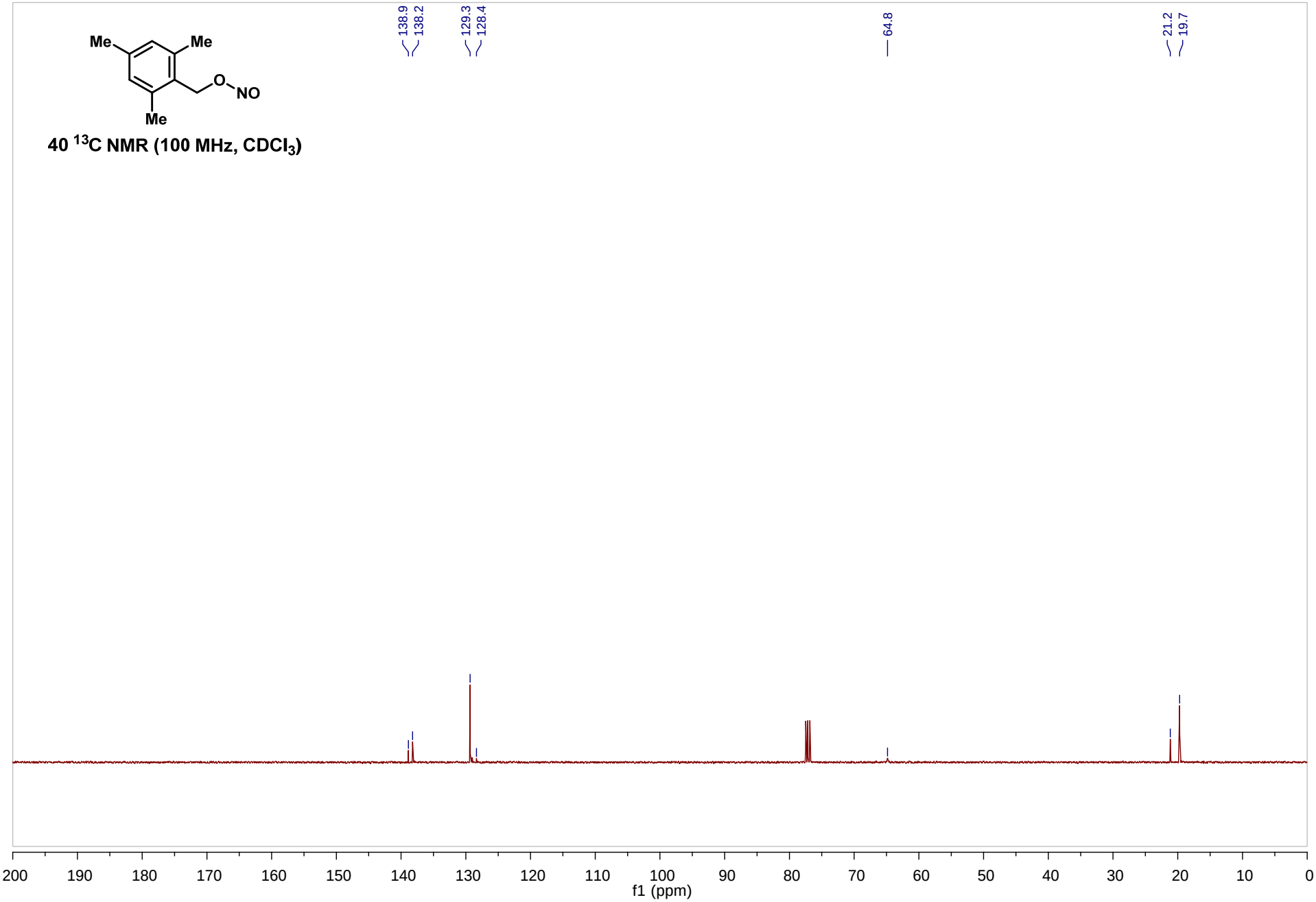

7.62
7.60
7.59
7.48
7.46
7.44
7.42
7.40
7.39
7.37
7.35
5.76
O
NO
39 ^{1}H NMR (400 MHz, $CDCl_3$)
4.17
5.34
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



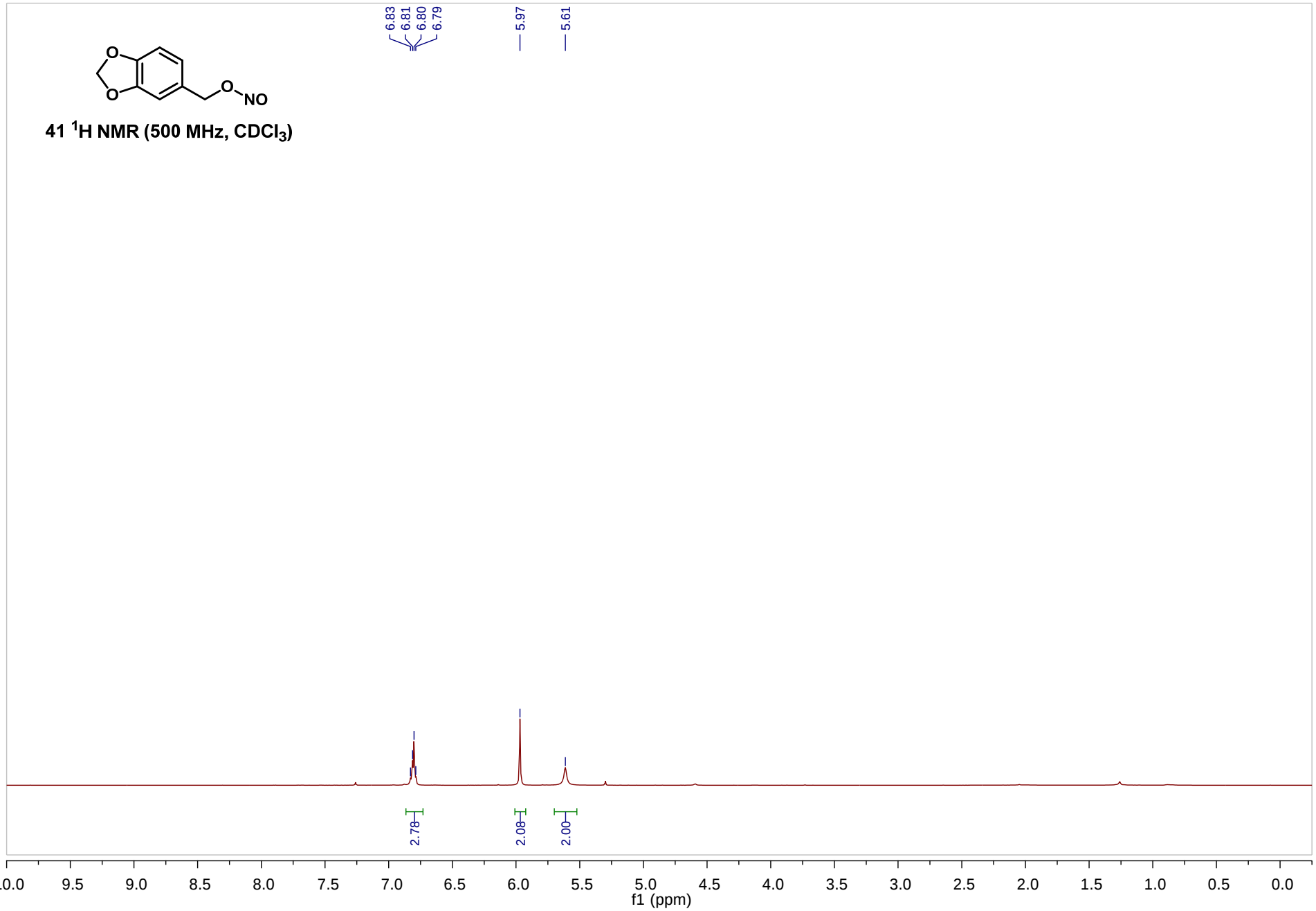
39 ^{13}C NMR (100 MHz, $CDCl_3$)

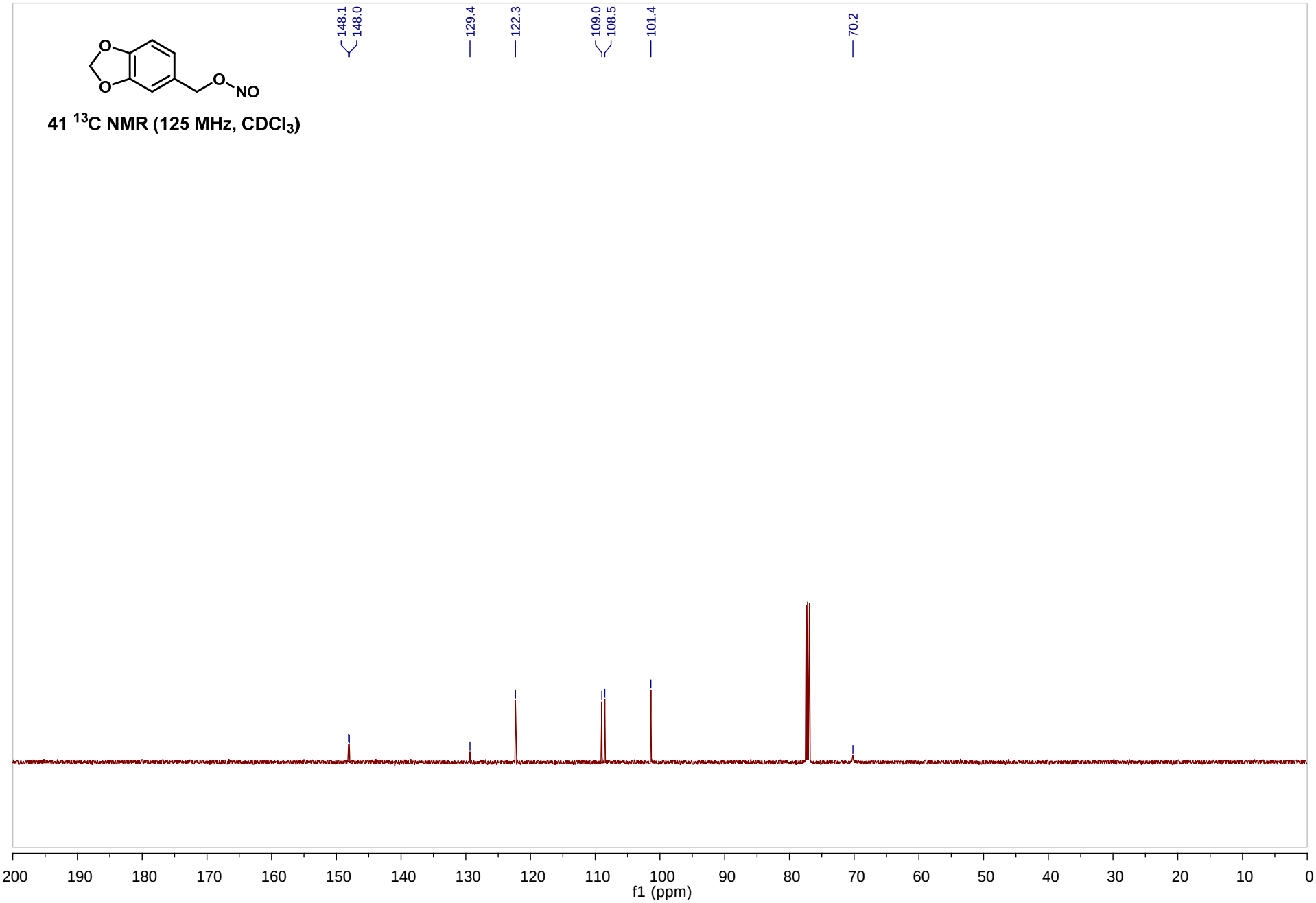


40 ^{1}H NMR (400 MHz, $CDCl_3$)

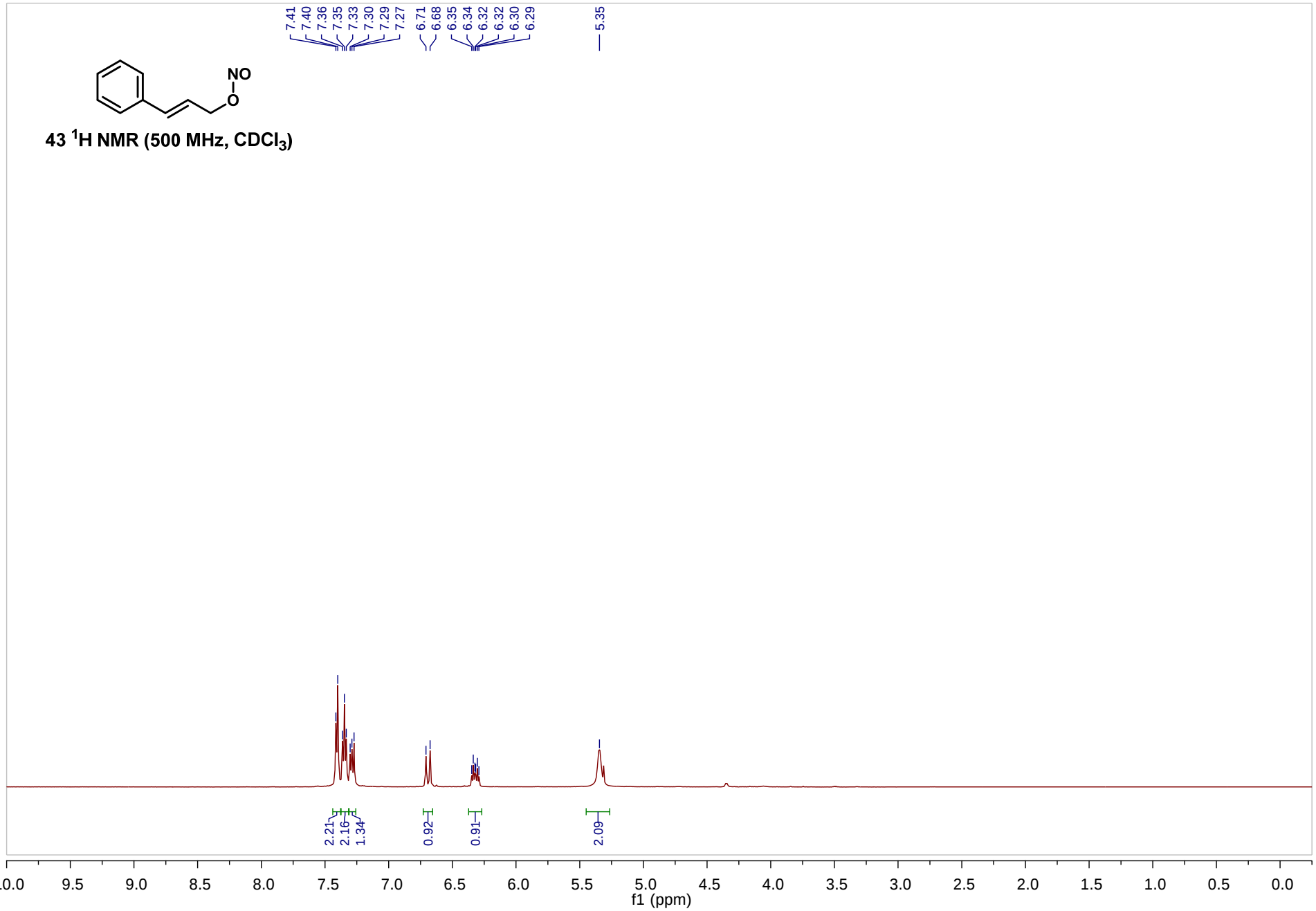


40 ^{13}C NMR (100 MHz, $CDCl_3$)

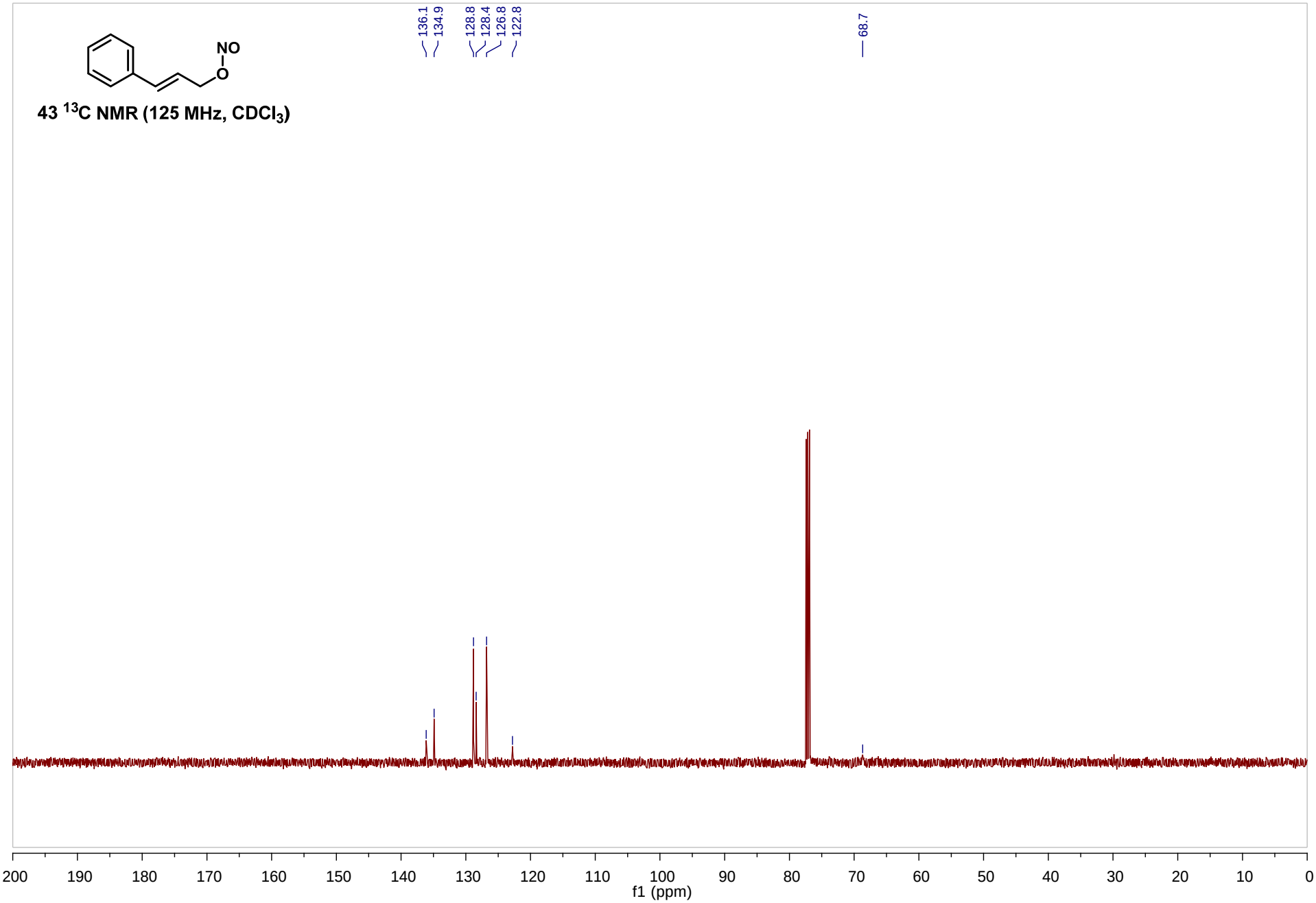

6.83
6.81
6.80
6.79
5.97
5.61
O
O
O
NO
41 ^{1}H NMR (500 MHz, CDCl$_3$)
2.78
2.08
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



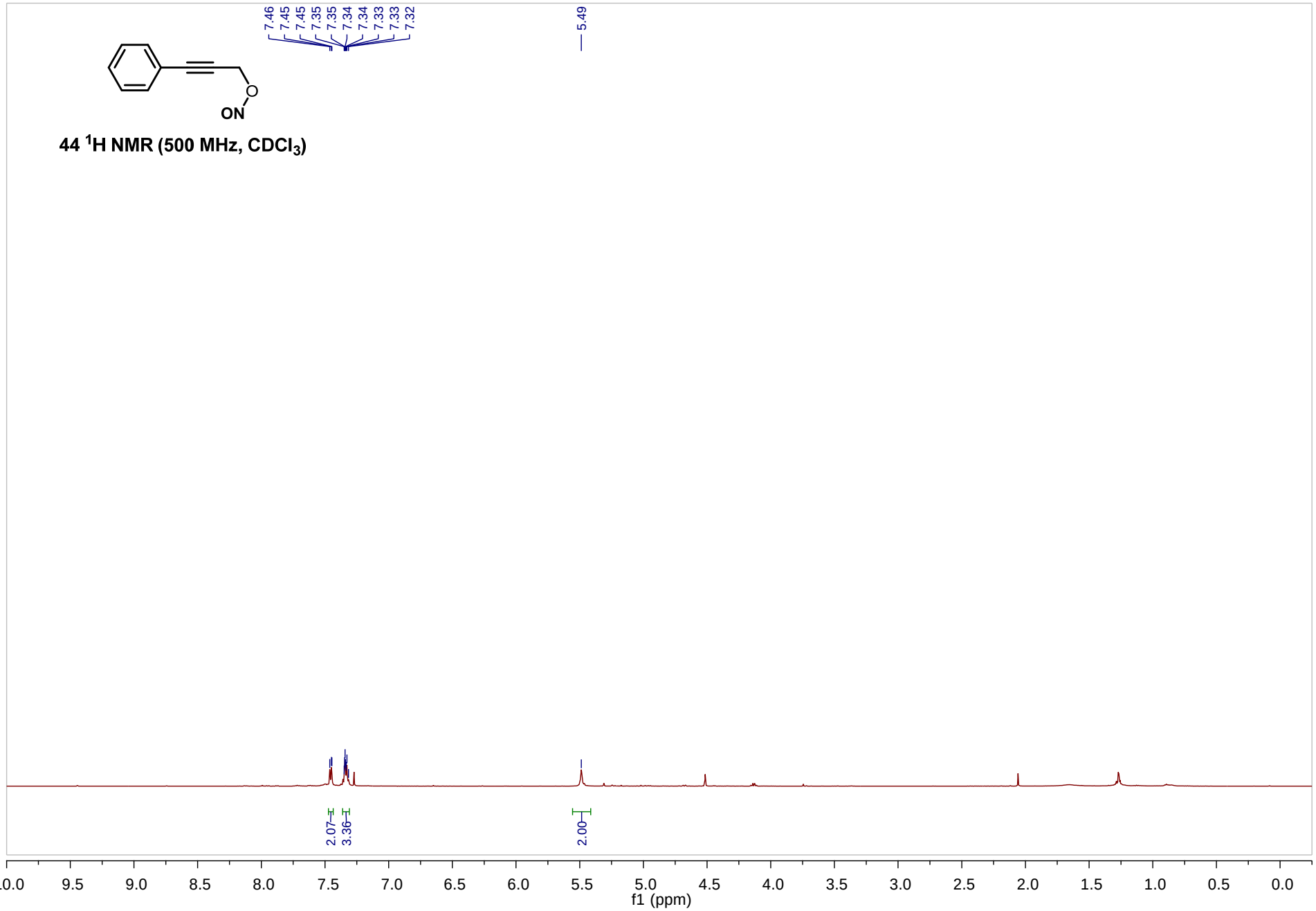
41 ^{13}C NMR (125 MHz, $CDCl_3$)



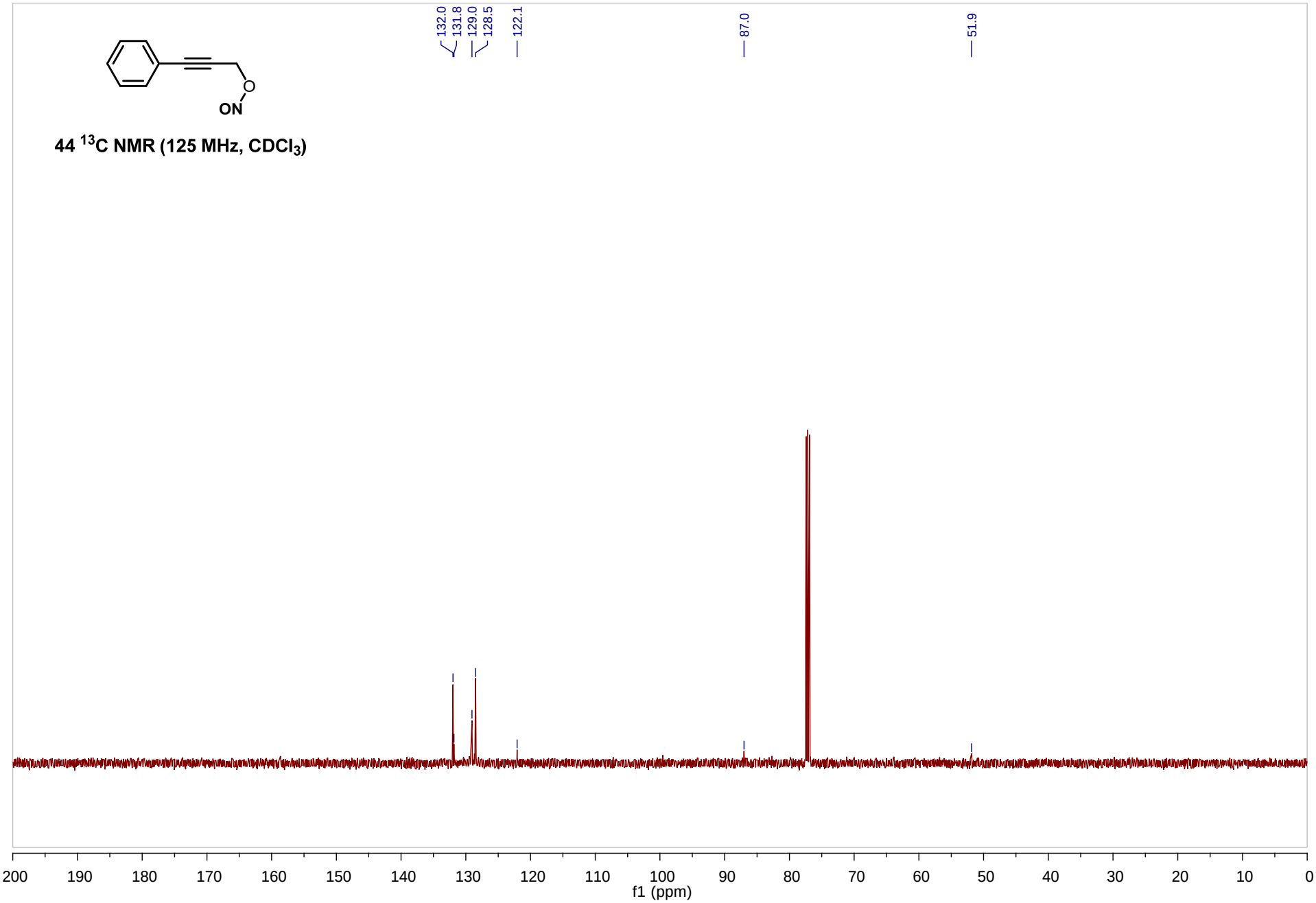
43 ^{1}H NMR (500 MHz, $CDCl_3$)

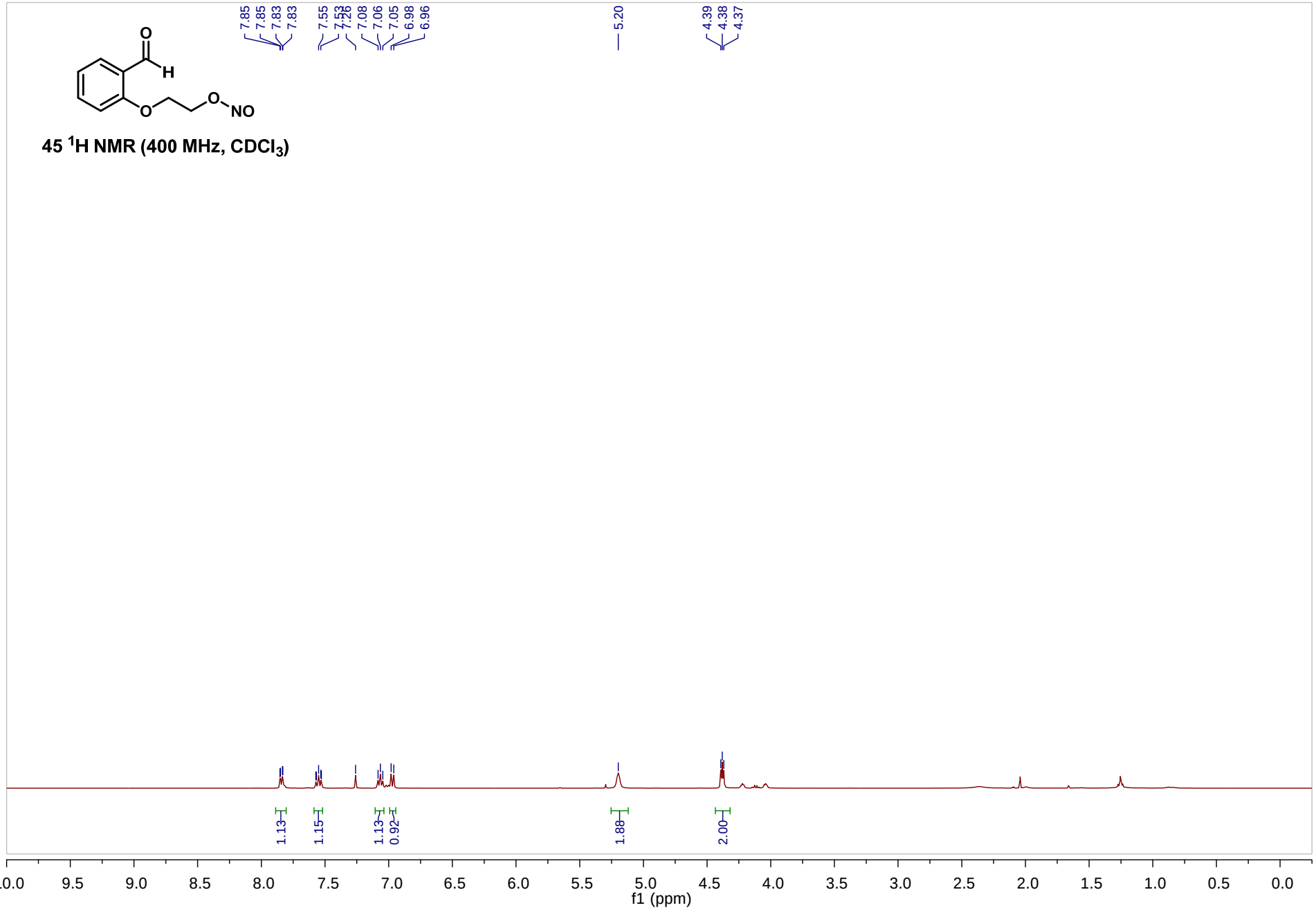


43 ^{13}C NMR (125 MHz, $CDCl_3$)

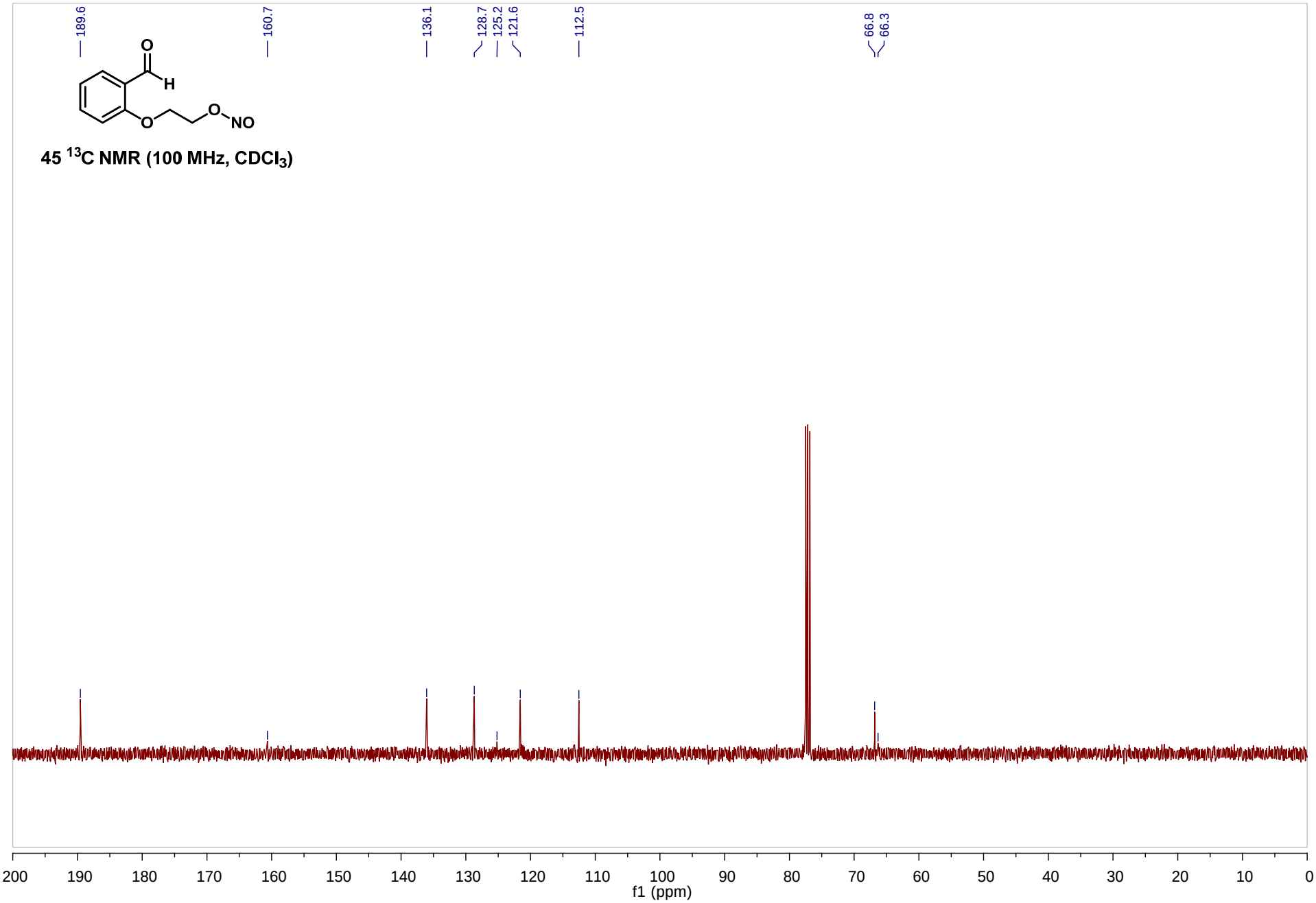


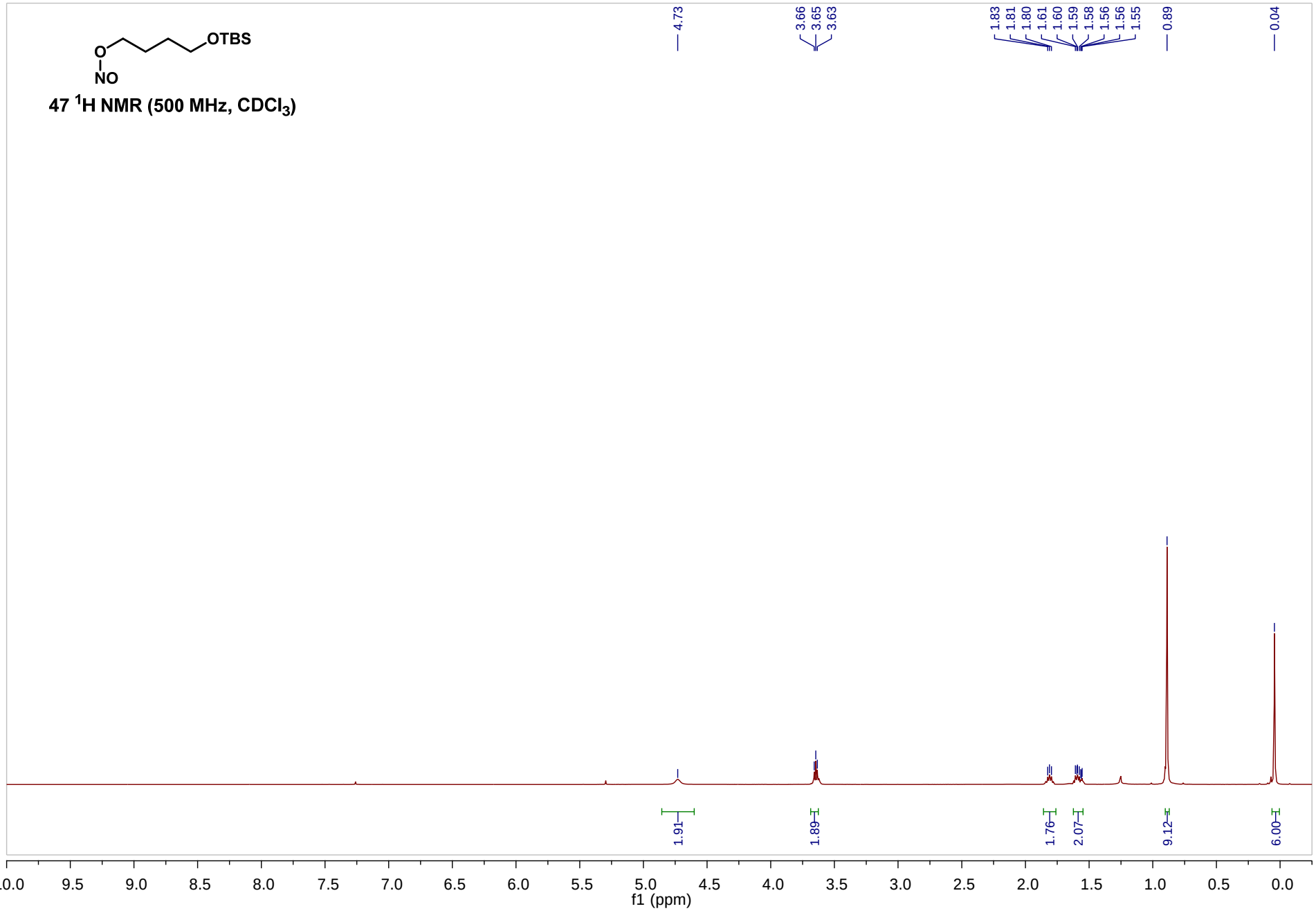
44 ^{1}H NMR (500 MHz, $CDCl_3$)

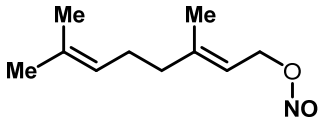

132.0
131.8
129.0
128.5
122.1
87.0
51.9
ON
44 ^{13}C NMR (125 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



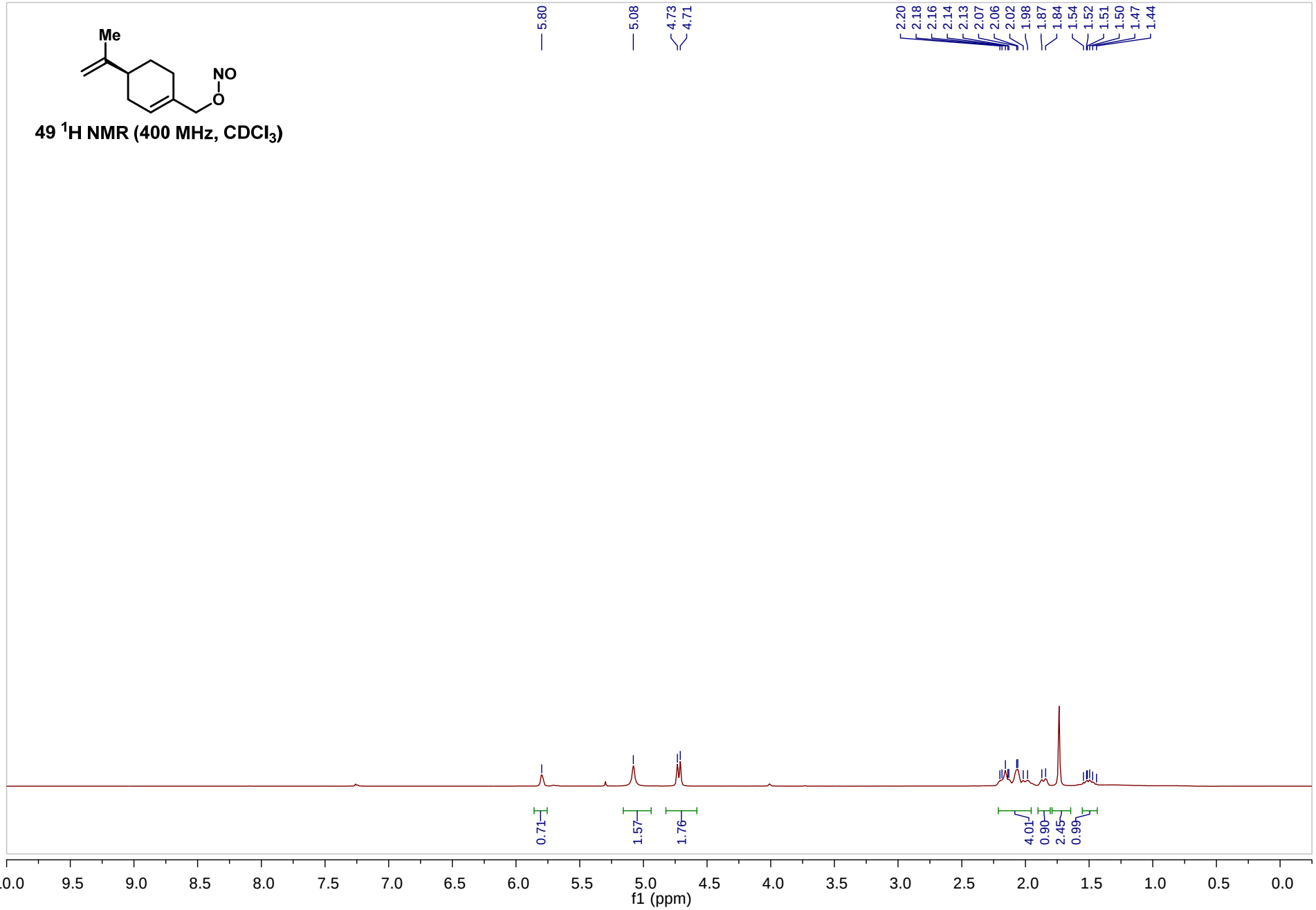
45 ^{1}H NMR (400 MHz, $CDCl_3$)

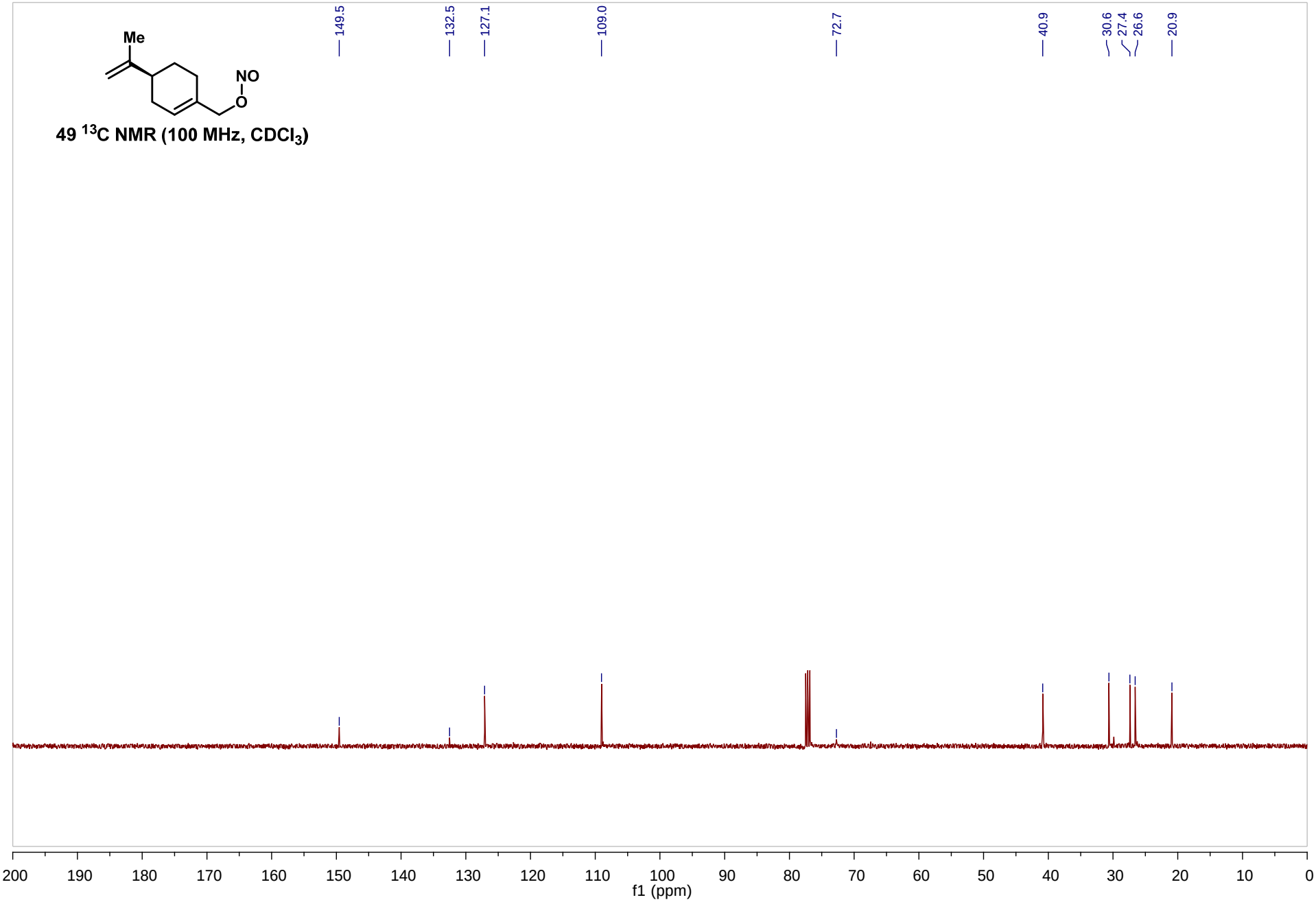

189.6
160.7
136.1
128.7
125.2
121.6
112.5
66.8
66.3
O
H
O
O
NO
45 13C NMR (100 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OTBS
O
NO
47 ^{1}H NMR (500 MHz, $CDCl_3$)
4.73
3.66
3.65
3.63
1.83
1.81
1.80
1.61
1.60
1.59
1.58
1.56
1.56
1.55
0.89
0.04
1.91
1.89
1.76
2.07
9.12
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

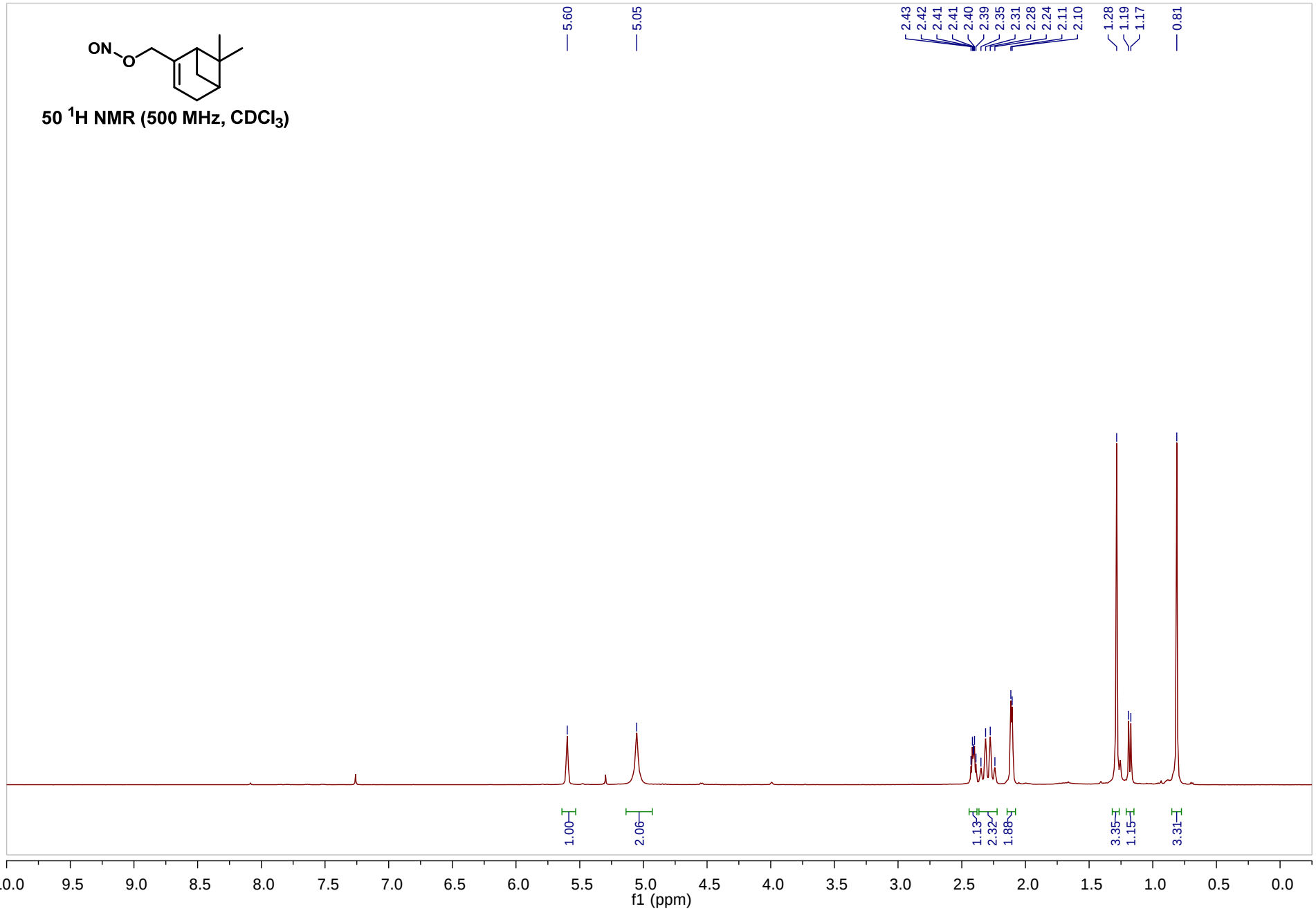


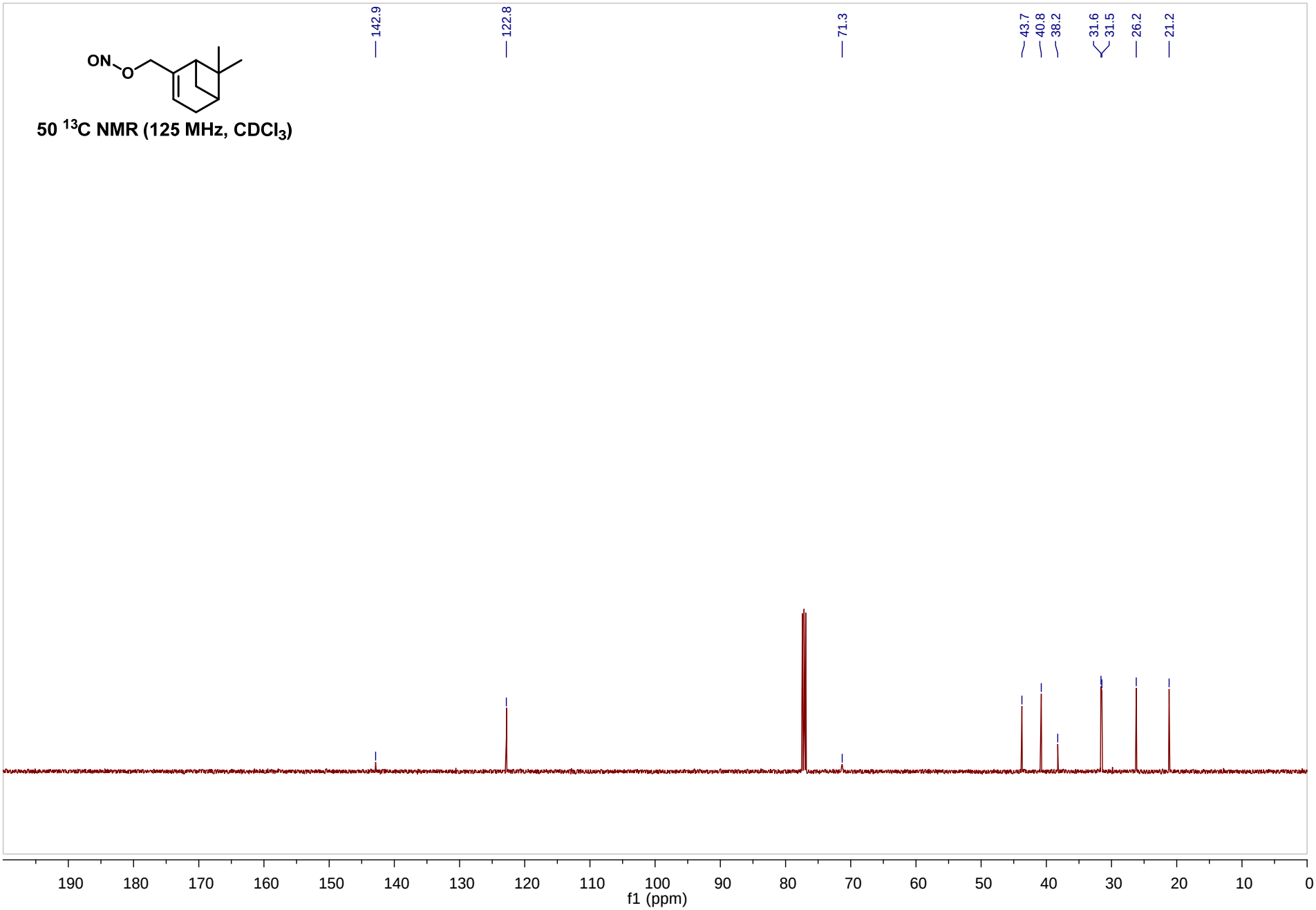
48 ^{1}H NMR (500 MHz, $CDCl_3$)

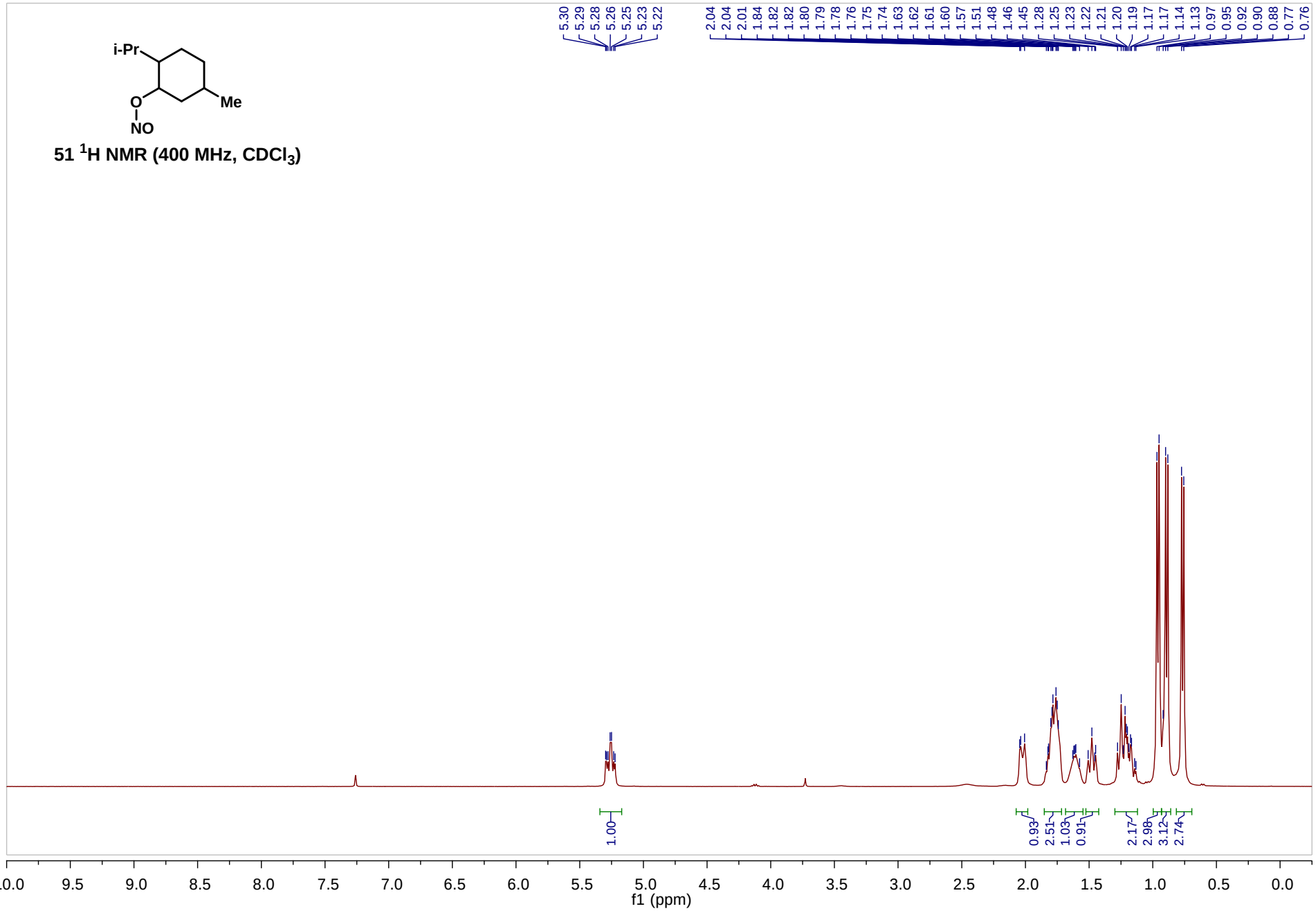

Me
NO
O
49 ^{1}H NMR (400 MHz, $CDCl_3$)
5.80
5.08
4.73
4.71
2.20
2.18
2.16
2.14
2.13
2.07
2.06
2.02
1.98
1.87
1.84
1.54
1.52
1.51
1.50
1.47
1.44
0.71
1.57
1.76
4.01
0.90
2.45
0.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



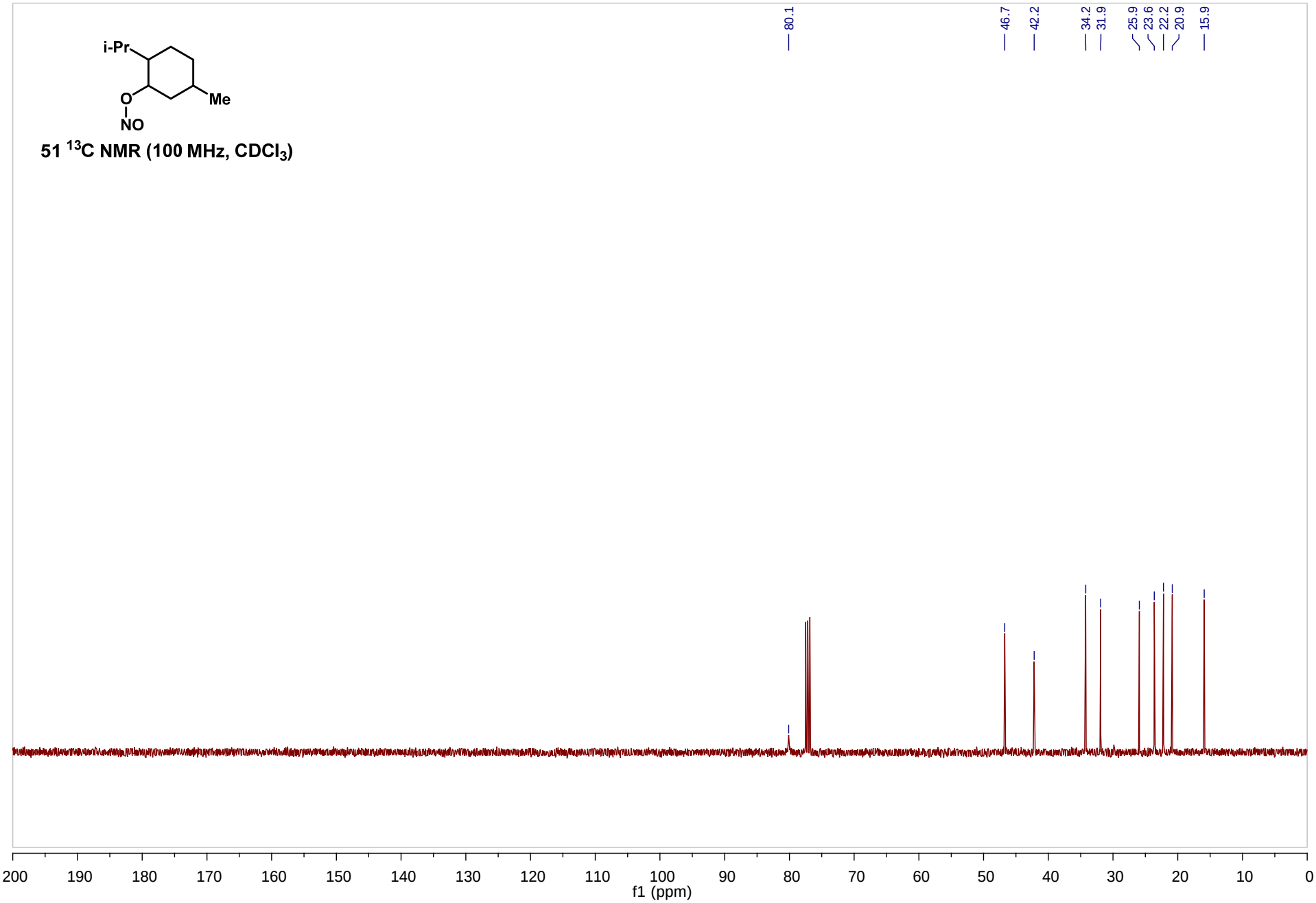
49 ^{13}C NMR (100 MHz, $CDCl_3$)


ON
O
50 ^{1}H NMR (500 MHz, $CDCl_3$)
5.60
5.05
2.43
2.42
2.41
2.41
2.40
2.39
2.35
2.31
2.28
2.24
2.11
2.10
1.28
1.19
1.17
0.81
1.00
2.06
1.13
2.32
1.88
3.35
1.15
3.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

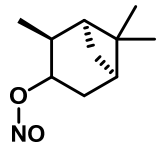

ON
O
142.9
122.8
71.3
43.7
40.8
38.2
31.6
31.5
26.2
21.2
50 13C NMR (125 MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



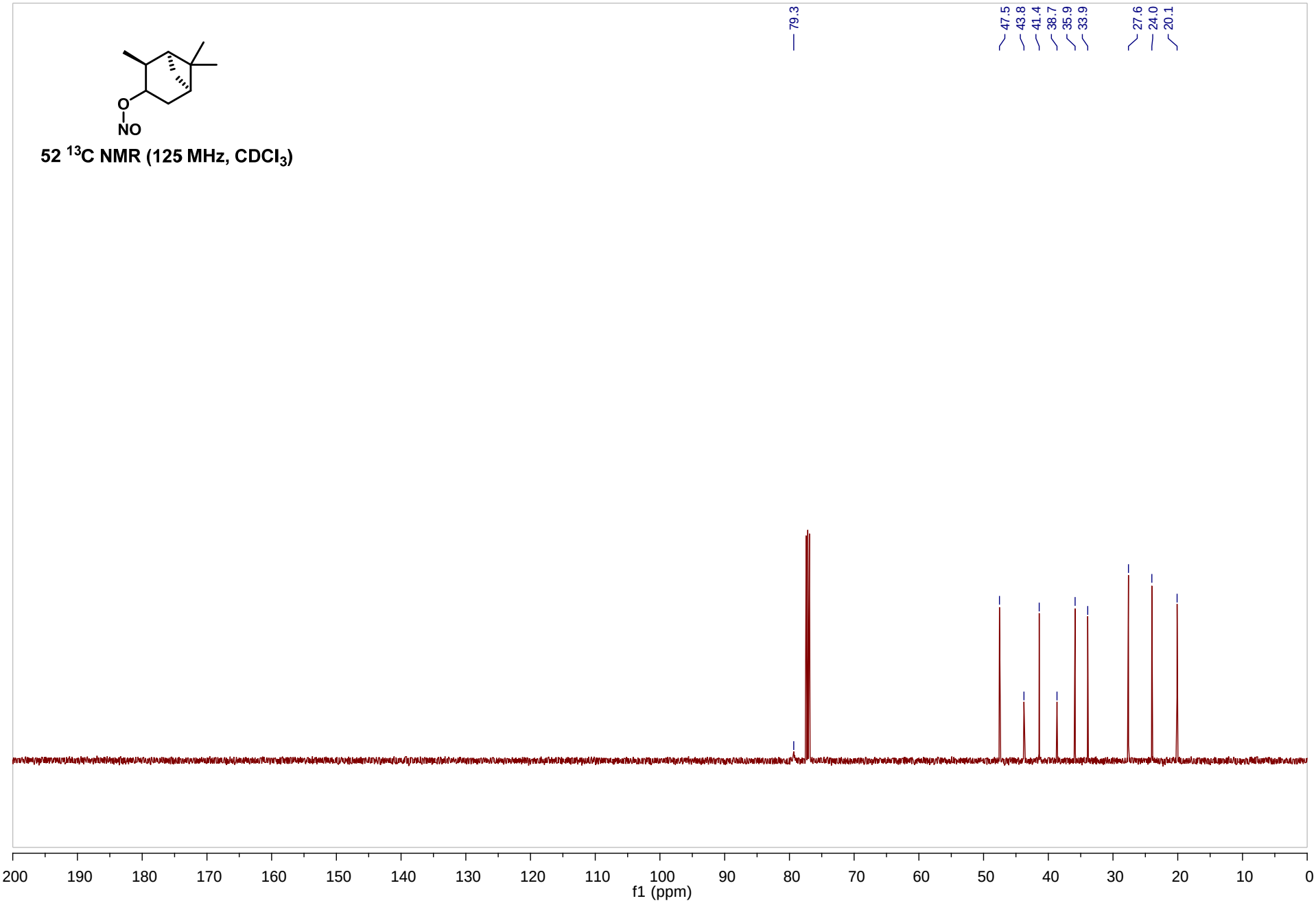
51 ^{1}H NMR (400 MHz, $CDCl_3$)

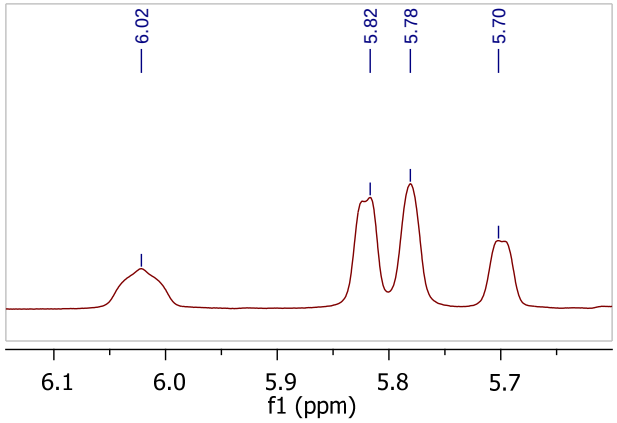


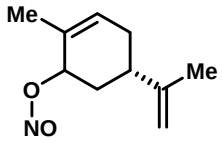
51 ^{13}C NMR (100 MHz, $CDCl_3$)

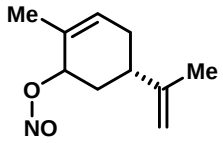


52 ^{1}H NMR (500 MHz, $CDCl_3$)


79.3
47.5
43.8
41.4
38.7
35.9
33.9
27.6
24.0
20.1
O
NO
52 ^{13}C NMR (125 MHz, $CDCl_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



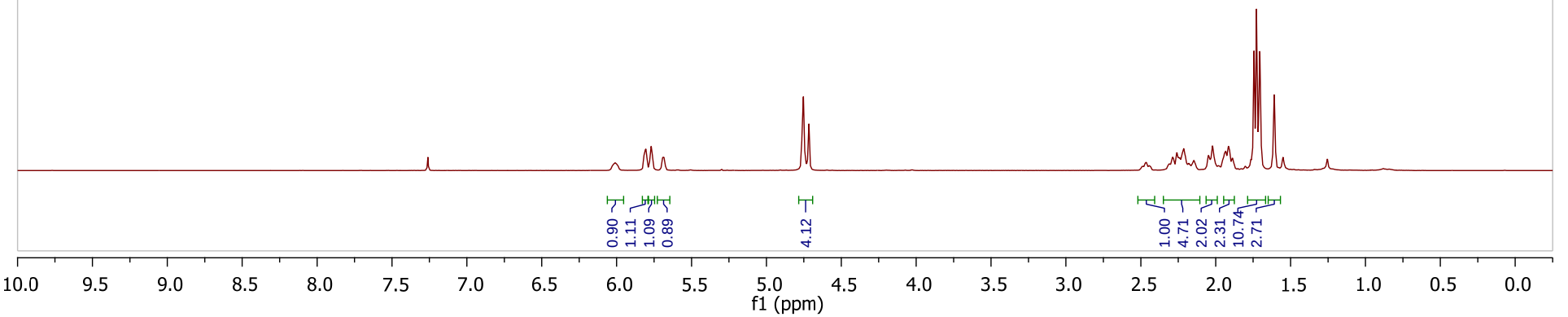


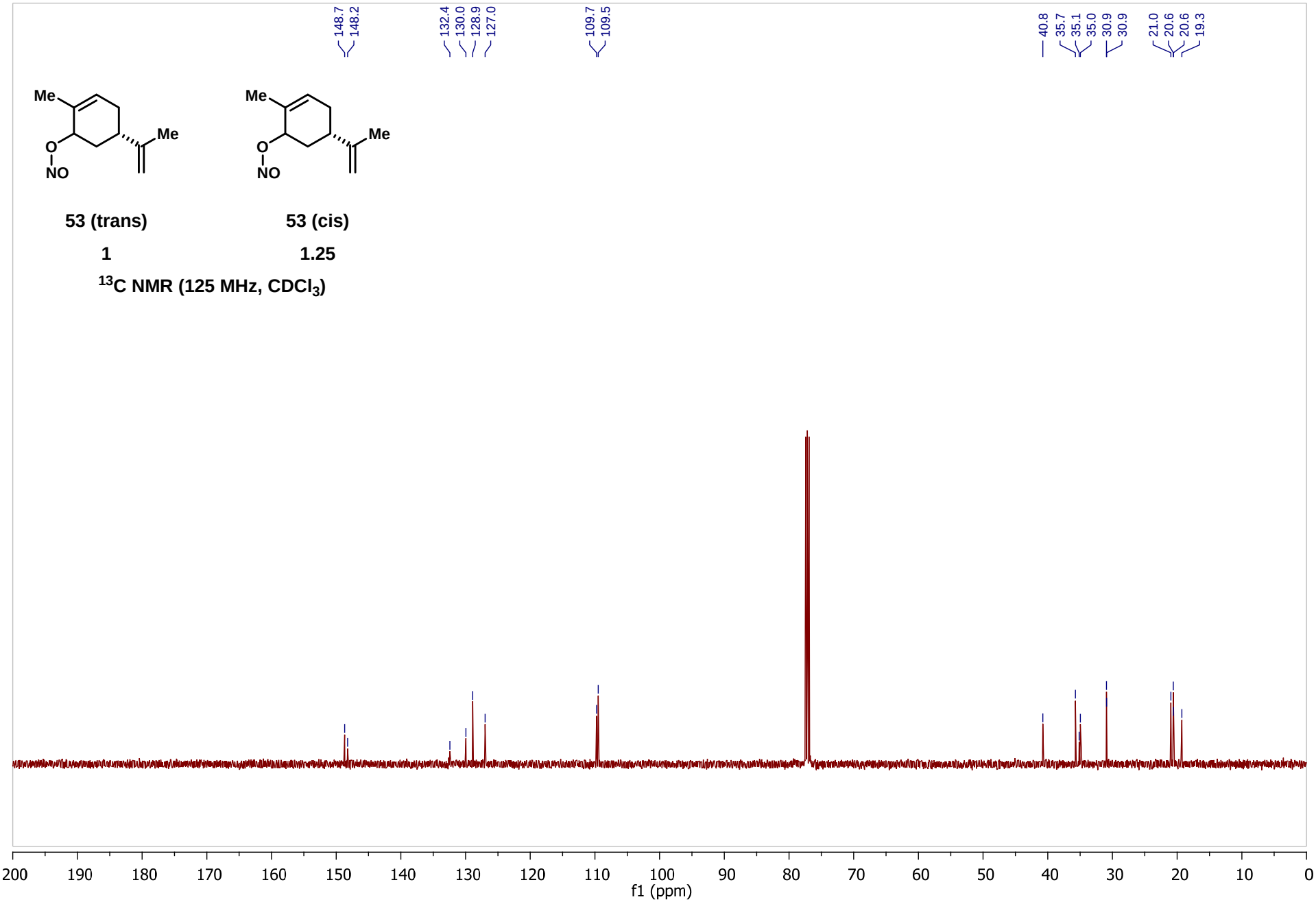


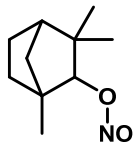
53 (trans) **53 (cis)**

1 **1.25**

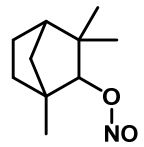
^{1}H NMR (500 MHz, $CDCl_3$)



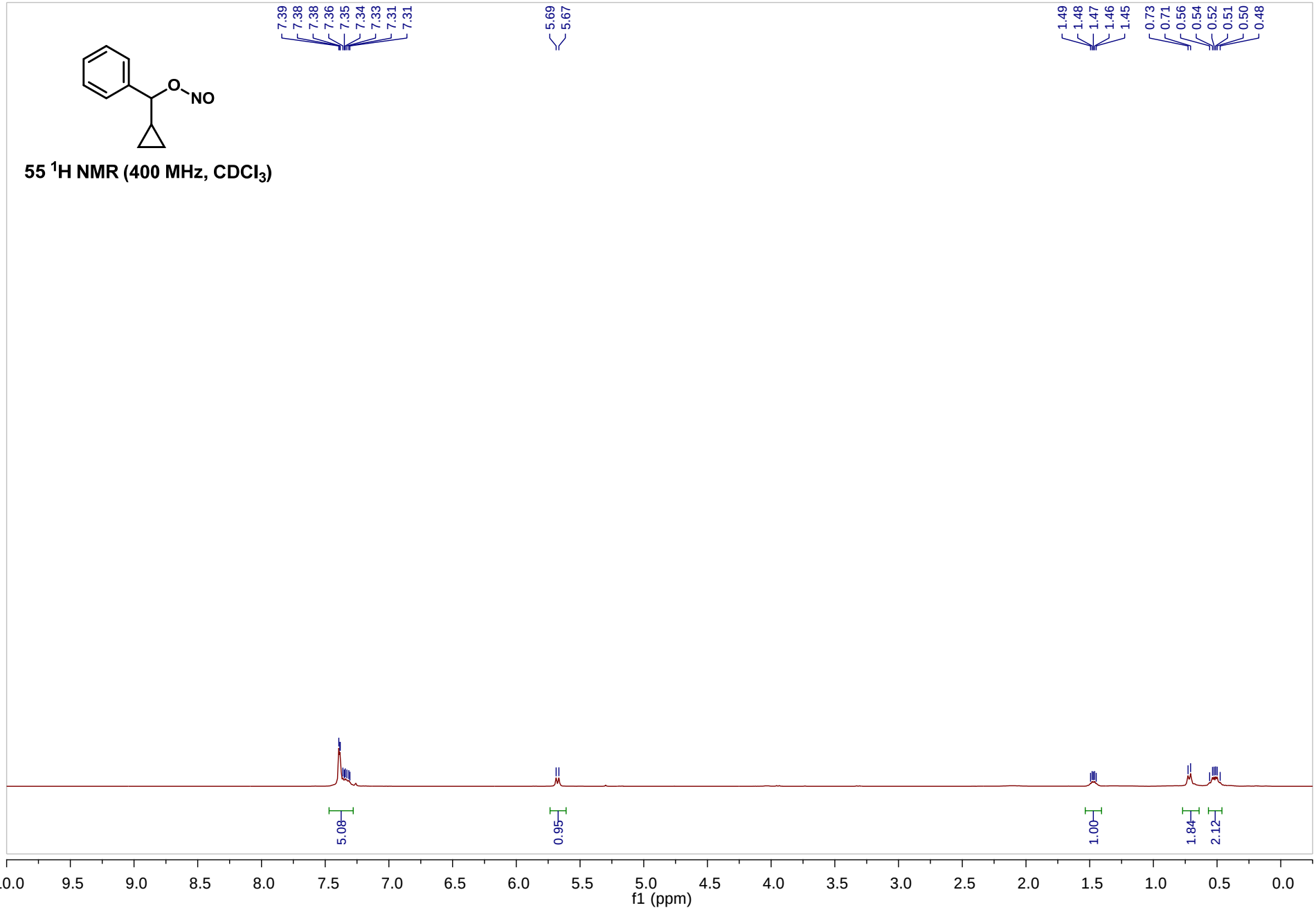

148.7
148.2
132.4
130.0
128.9
127.0
109.7
109.5
40.8
35.7
35.1
35.0
30.9
30.9
21.0
20.6
20.6
19.3
Me
Me
O
NO
Me
Me
O
NO
53 (trans)
53 (cis)
1
1.25
13C NMR (125 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

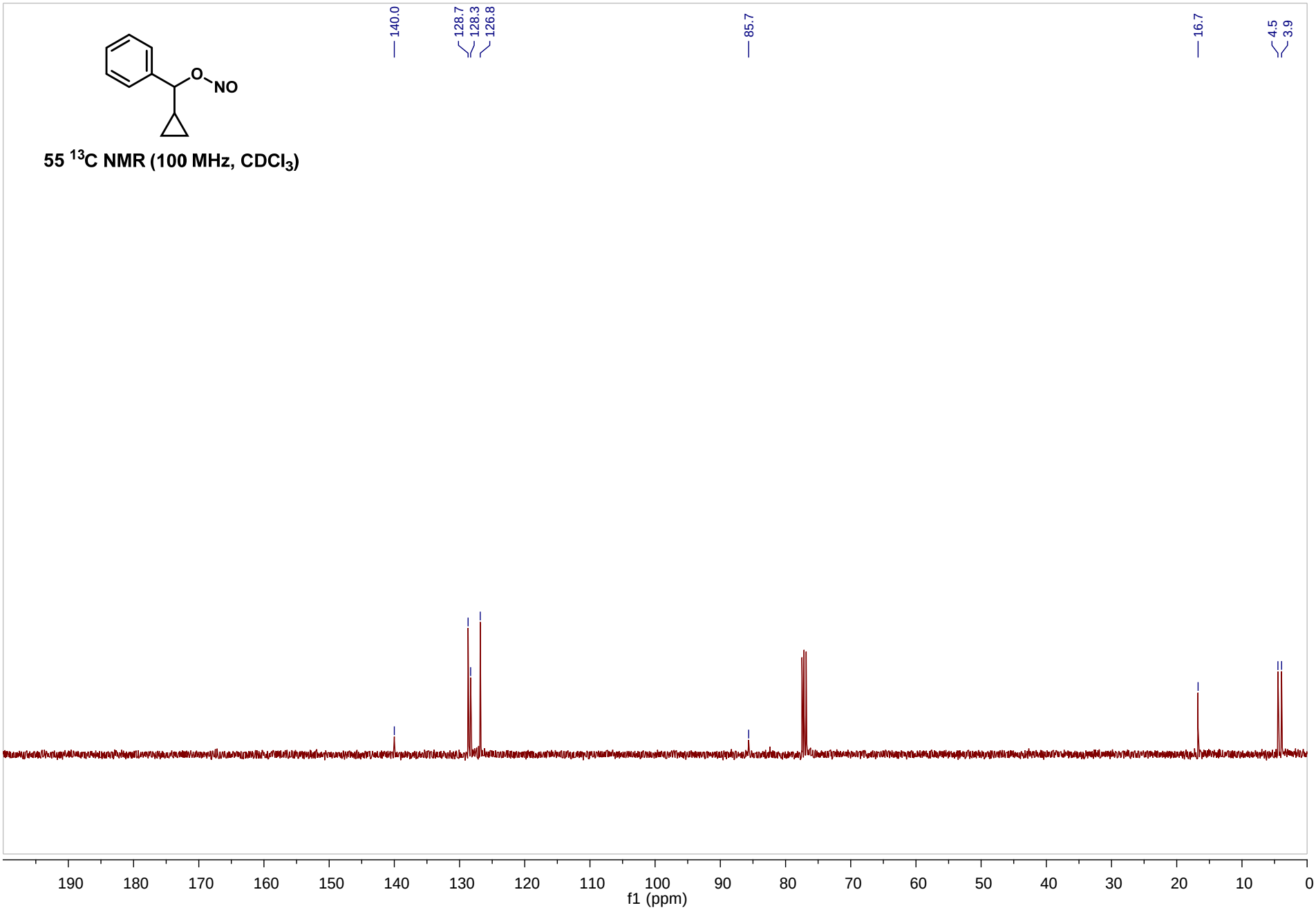


54 ^{1}H NMR (500 MHz, $CDCl_3$)

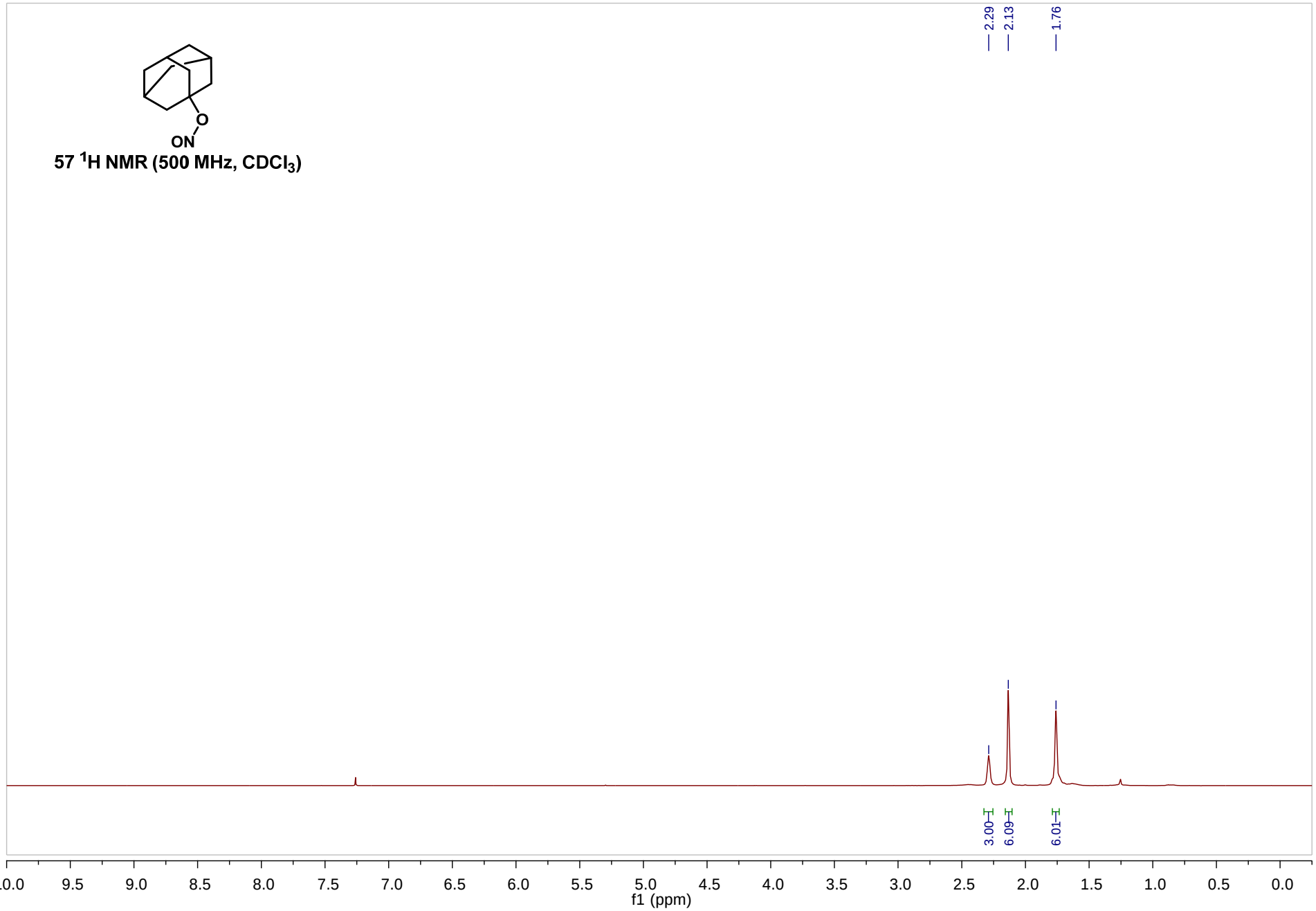


54 ^{13}C NMR (125 MHz, $CDCl_3$)

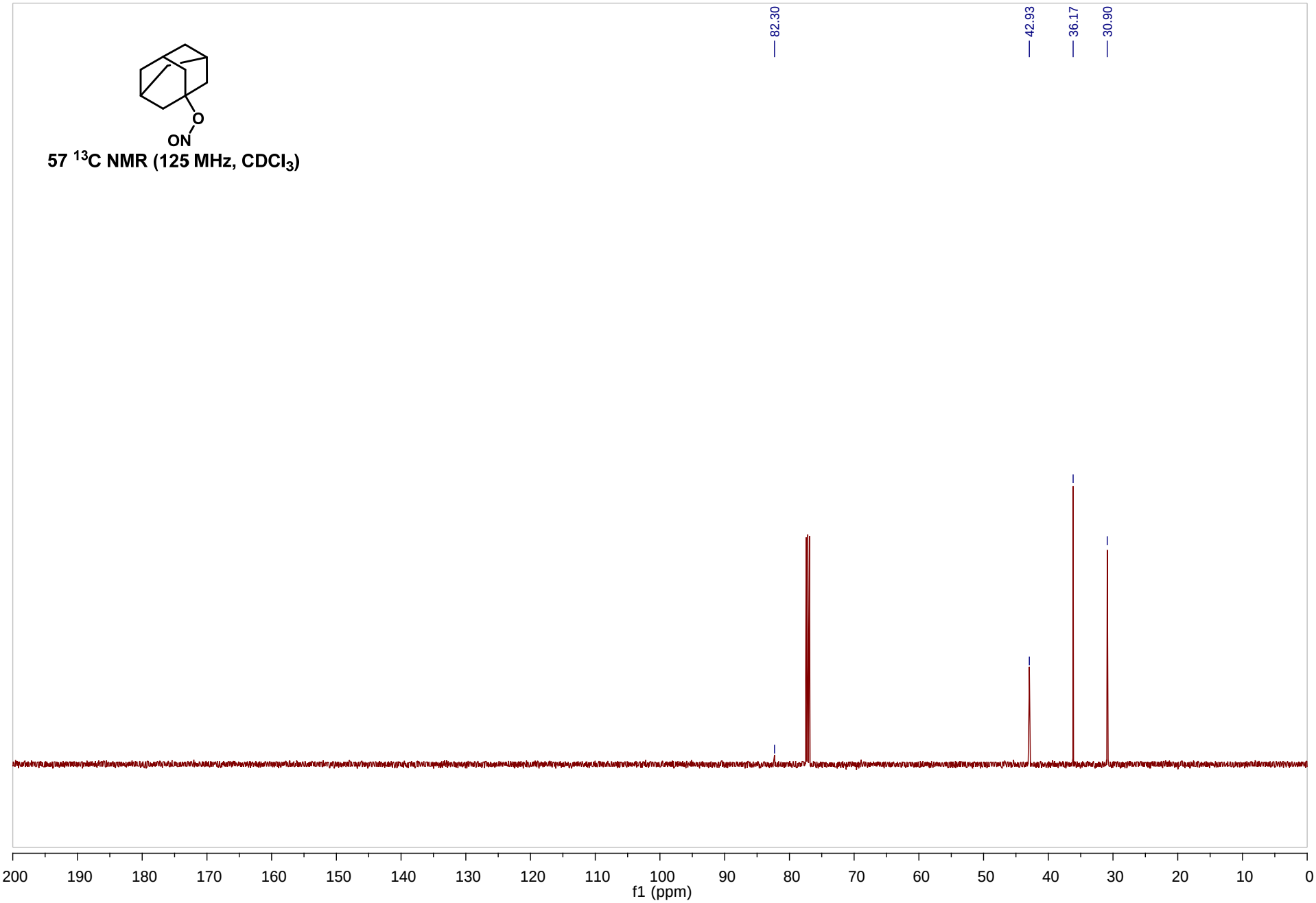

7.39
7.38
7.38
7.36
7.35
7.34
7.33
7.31
7.31
5.69
5.67
1.49
1.48
1.47
1.46
1.45
0.73
0.71
0.56
0.54
0.52
0.51
0.50
0.48
O
NO
55 ^{1}H NMR (400 MHz, CDCl$_3$)
5.08
0.95
1.00
1.84
2.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

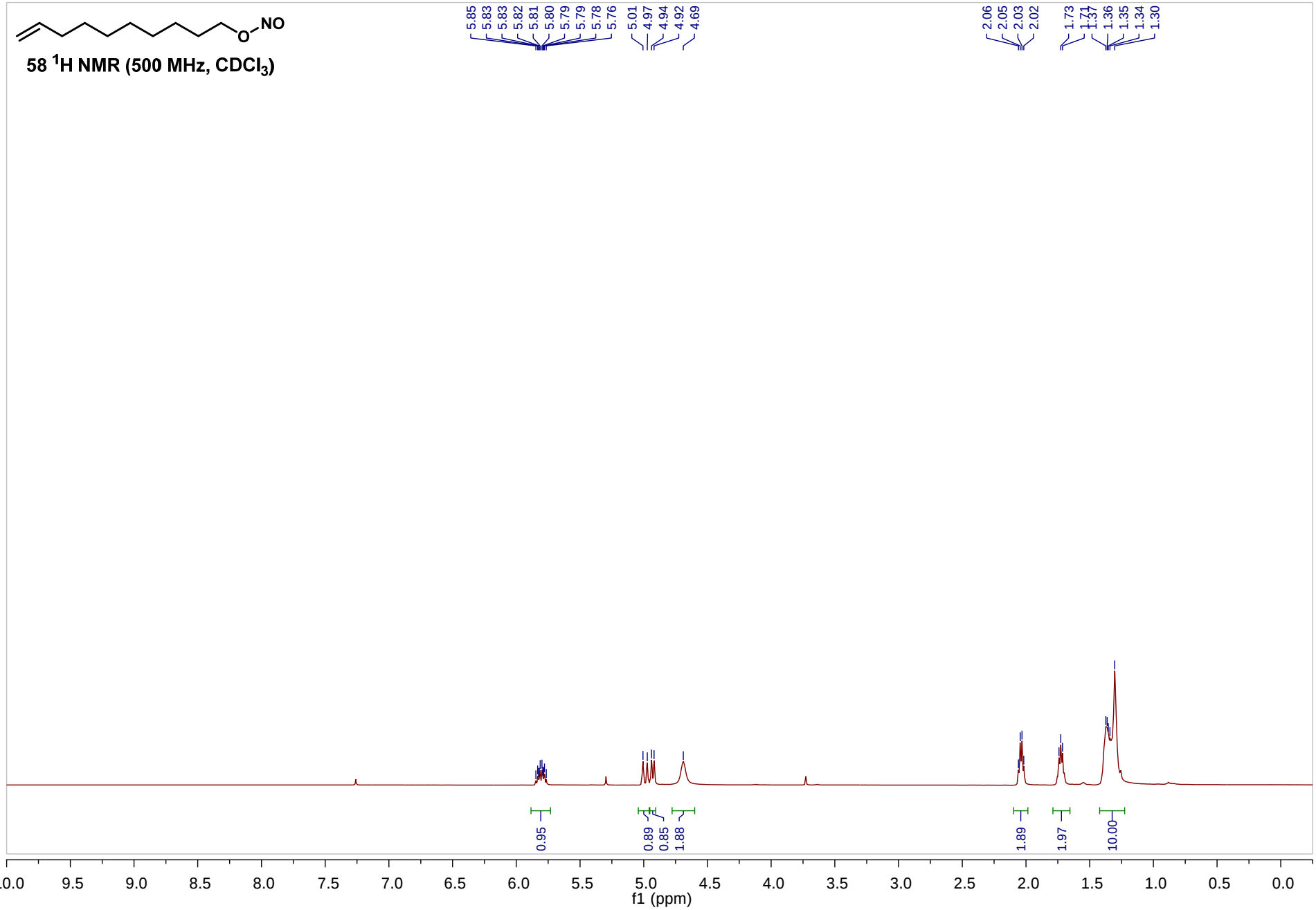


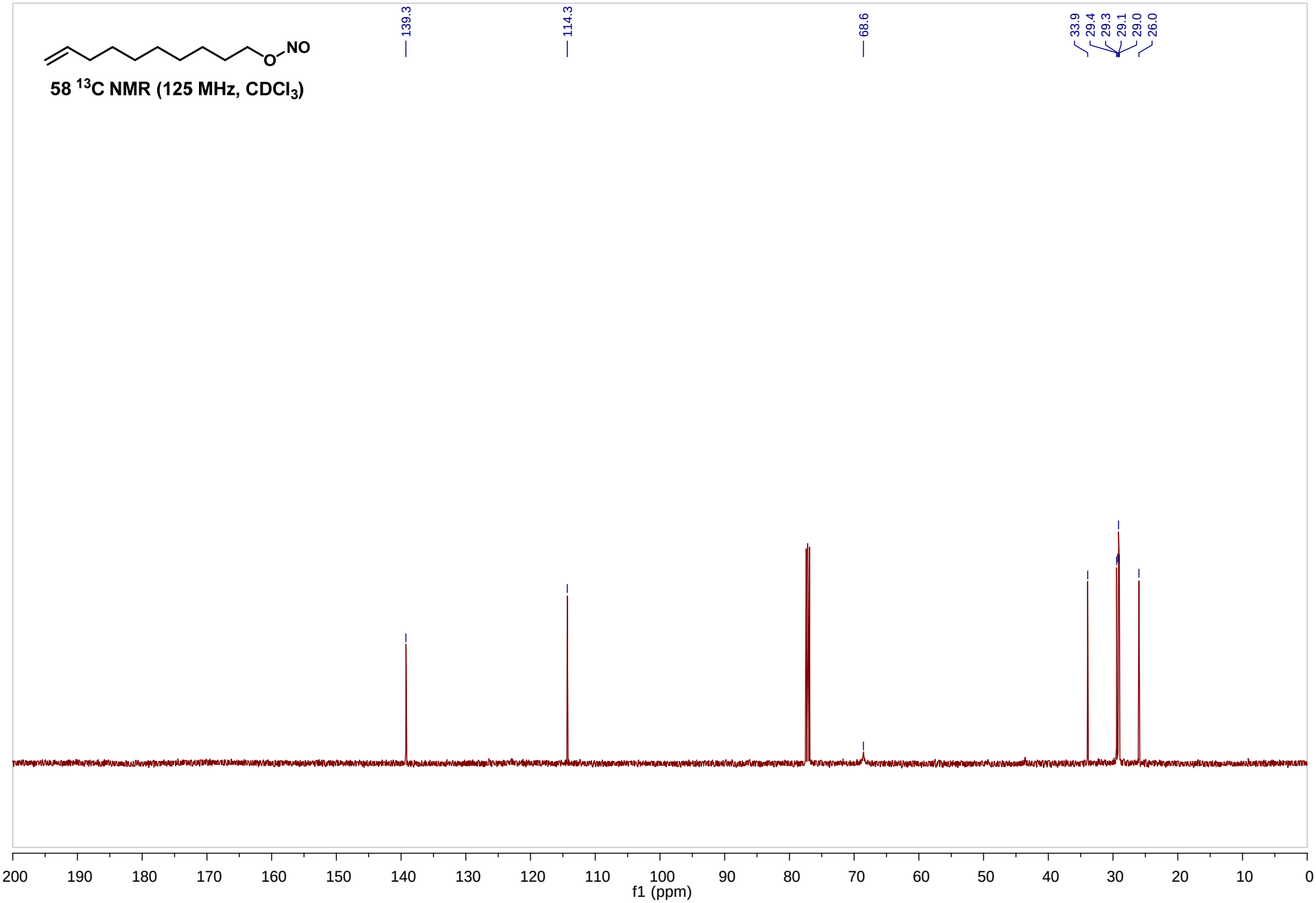
55 ^{13}C NMR (100 MHz, $CDCl_3$)

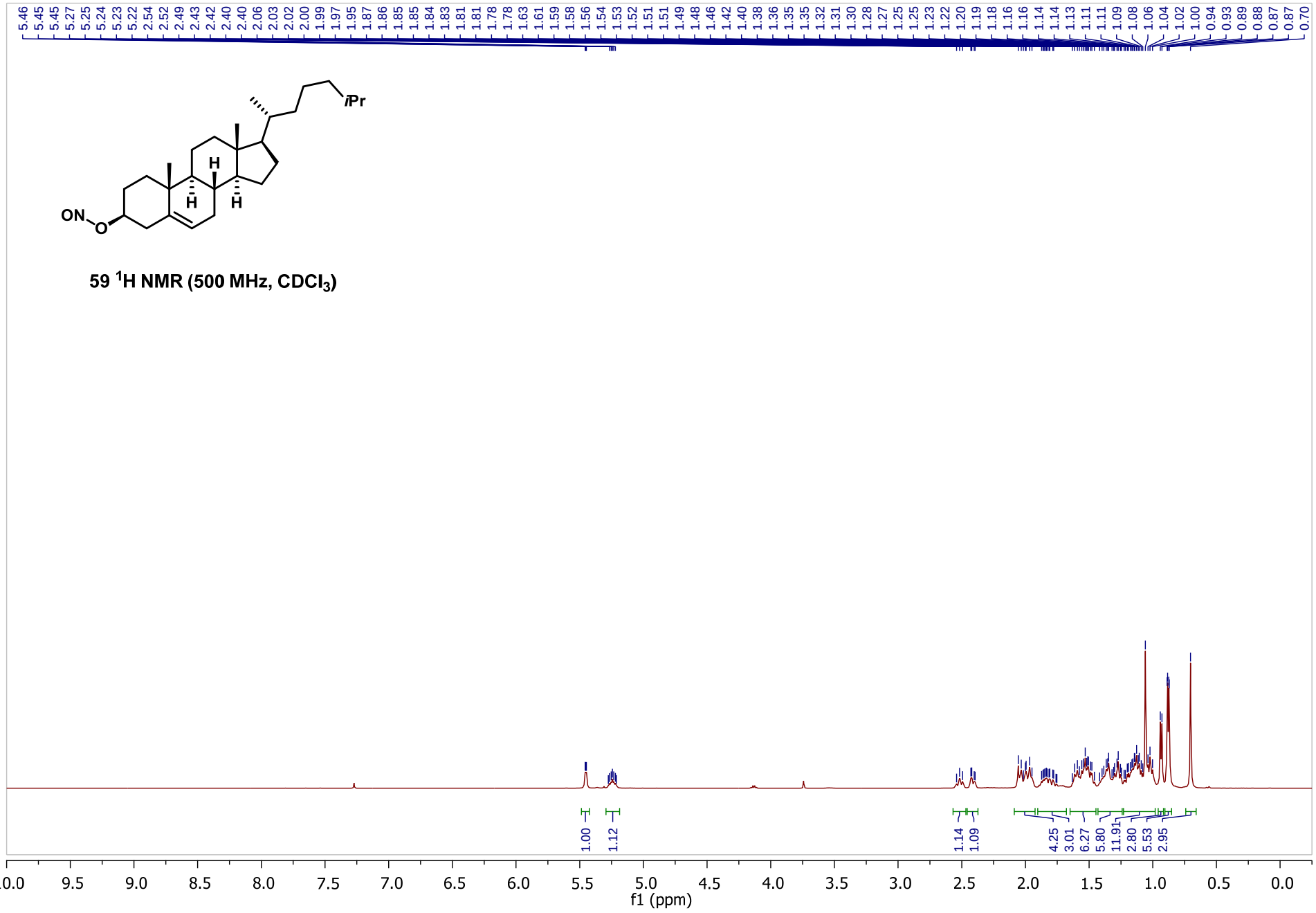


57 ^{1}H NMR (500 MHz, $CDCl_3$)

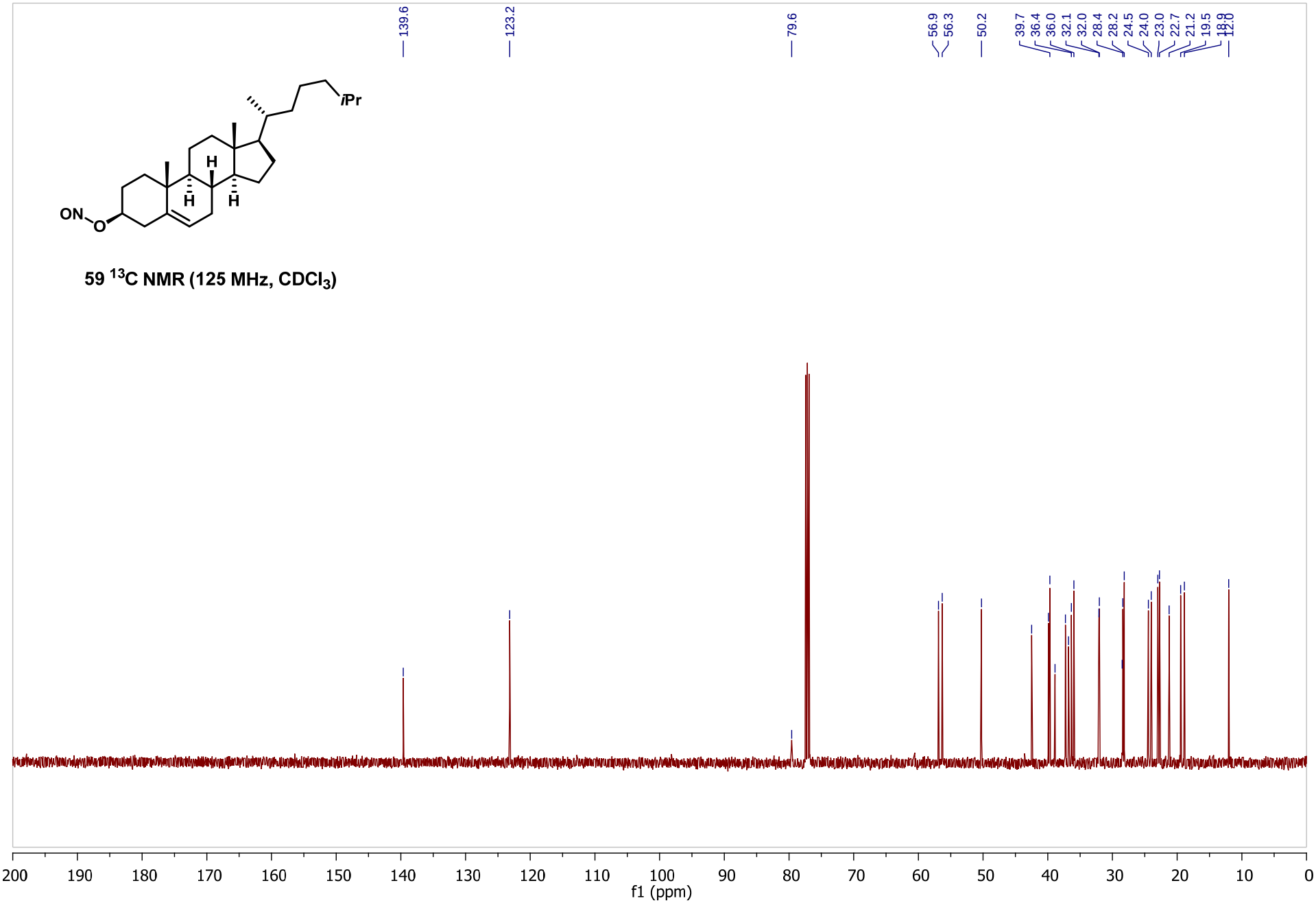

82.30
42.93
36.17
30.90
O
ON
57 13C NMR (125 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


58 ^{1}H NMR (500 MHz, $CDCl_3$)
NO
5.85
5.83
5.83
5.82
5.81
5.80
5.79
5.79
5.78
5.76
5.01
4.97
4.94
4.92
4.69
2.06
2.05
2.03
2.02
1.73
1.71
1.37
1.36
1.35
1.34
1.30
0.95
0.89
0.85
1.88
1.89
1.97
10.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


NO
139.3
114.3
68.6
33.9
29.4
29.3
29.1
29.0
26.0
58 13C NMR (125 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



59 ^{1}H NMR (500 MHz, $CDCl_3$)


139.6
123.2
79.6
56.9
56.3
50.2
39.7
36.4
36.0
32.1
32.0
28.4
28.2
24.5
24.0
23.0
22.7
21.2
19.5
18.9
12.0
iPr
H
H
H
ON
O
59 13C NMR (125 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)