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Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one derivatives by electrophilic aromatic substitution

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SYNTHESIS OF 5-METHYL-3-PHENYL-1,3,4-OXADIAZOL-2(3H)-ONE DERIVATIVES BY ELECTROPHILIC AROMATIC SUBSTITUTION

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

By

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B.S., Central State University, 2013

2018
Wright State University

WRIGHT STATE UNIVERSITY

GRADUATE SCHOOL

December 13th, 2018

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Amanda Solis Conde ENTITLED Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one derivatives by electrophilic aromatic substitution BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science.

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Abstract

Conde, Amanda Solis. M.S. Department of Chemistry, Wright State University, 2018. Synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one derivatives by electrophilic aromatic substitution

An important research element in the Turnbull laboratory has been the one-pot synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one from sydnone. The present study reexamined the reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one with electrophiles and optimized methods for synthesis of oxadiazolinone derivatives. Further the oxadiazolinone derivatives were reacted with electrophiles to better comprehend the donating ability of the oxadiazolinone ring system in general with the expectation that the oxadiazolinone ring system is a slightly donating system. Additionally, when the structure assignment of the oxadiazolinone derivative was ambiguous, the corresponding oxadiazolinone or it's isomer was synthesized from the appropriate sydnone to validate or refute the suggested structure.

The results of the present study showed the reproducibility of experiments done by previous interns in the Turnbull laboratory. The procedure for nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one could be optimized. Extension of nitration to *para* substituted oxadiazolinones resulted in *di*-substituted derivatives. Through these nitration studies, the oxadiazolinone ring system is shown to be a moderate donor.

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Acknowledgements

It is by God's grace that I am here.

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I would to acknowledge the support of the chemistry department and professors at Wright State University and Central State University.

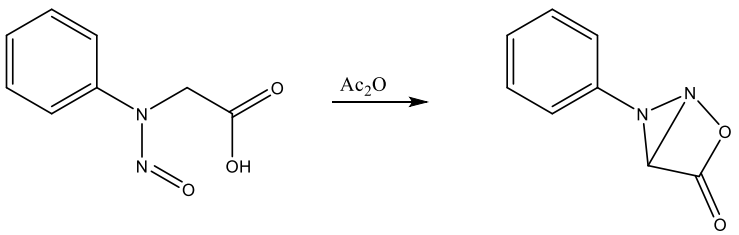
Introduction

I. Sydnones

While the work reported in this thesis is not devoted specifically to the area of sydnones, the following introduction includes a synopsis of sydnone background and properties since in this research the oxadiazolinones studied were derived from sydnones.

i. Historical

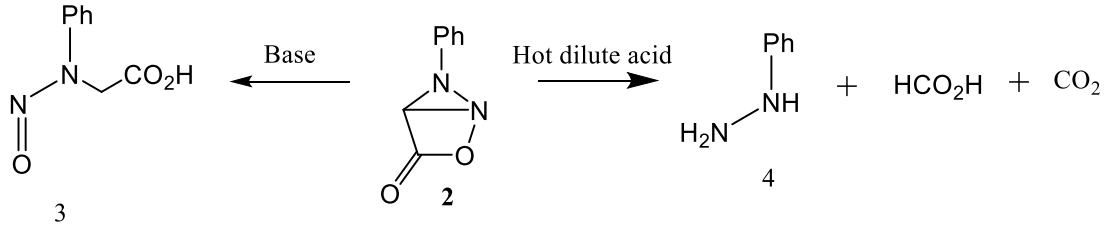
Sydnones are members of a unique class of organic molecules categorized as mesoionic. They are valued for the pharmacological activities that they possess; since mesoionic compounds are neutral, dipolar hybrids of many contributing ionic resonance structures, it is rationalized that the dipolar nature of the sydnone facilitates interactions with biological molecules <2003BMCL2899>. The bromidic name sydnone is derived from their site of discovery, *viz*. Sydney, Australia. In 1935, Earl and Mackney first synthesized 3-phenylsydnone, shown as a bicyclic structure **2**, by reacting N-nitroso-N-phenyl glycine (**1**) with acetic anhydride (Scheme 1) <1935JACS899>.



1 **2**

Scheme 1: Synthesis of 3-phenylsydnone

Much controversy arose about the bicyclic representation of the sydnone, principally due to the considerable strain that should thus be exhibited but was not in evidence for any example prepared. To further strengthen the claim that the sydnone was not a bicyclic structure, Baker and Ollis showed that treatment of **2** with hot dilute acid gave phenyl hydrazine **4**, formic acid, and carbon dioxide and, conversely, treatment of **2** with base resulted in formation of the original N-nitroso acid **3** (Scheme 2) <1957QCS15>; conditions far more vigorous than would be expected for a very strained bicyclic molecule.



Scheme 2: Reaction of 3-phenylsydnone with acid or base

From these and later studies, it was clear that the structure of the sydnone moiety was more complex than represented by the bicyclic structure **2**. Thus, in 1949, Baker, Ollis, and Poole introduced the term, mesoionic, a combination of the two words mesomeric (meaning resonating) and ionic (relating to an ion or, in this case, charge), to describe the bonding situation in sydnones and, by extrapolation, similar molecules. A mesoionic compound must be a five or six membered planar heterocyclic compound with both positive and negative charges delocalized, possess considerable resonance energy, and contain an exocyclic group or atom capable of bearing considerable negative charge density <1949JC307>. The sydnone, then, is a monocyclic, dipolar species with no one true representation. Thus, many resonance forms are associated with the sydnone and all twelve, *viz.* **5a-5l**, are shown in Figure 1.

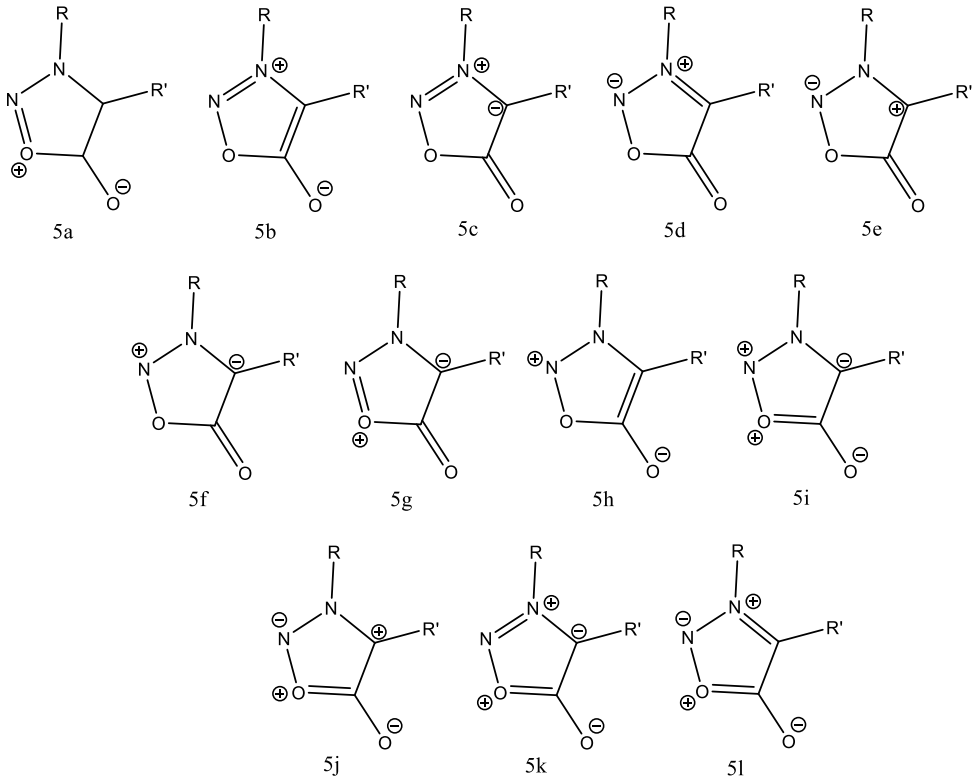
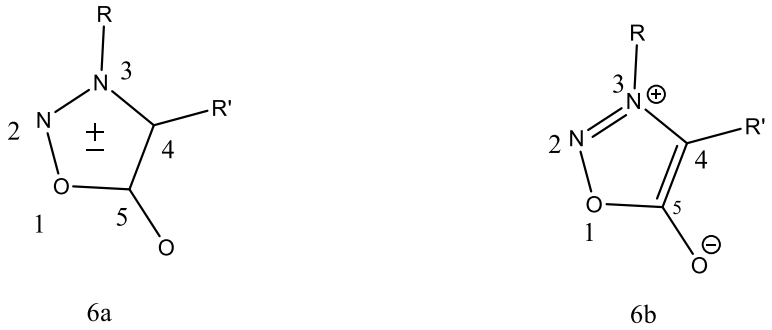


Figure 1: The resonance forms of sydnone

ii. Physical Properties of Sydnones

The many resonance forms of the sydnone are typically represented by a hybrid



structure **6a** including both a plus and minus sign inside the sydnone ring**.** While this is the preferred representation, nonetheless, many sydnone chemists, including those in the Turnbull

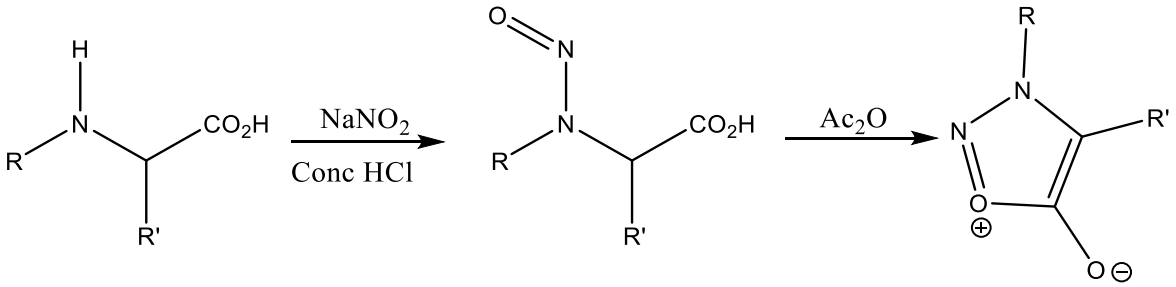
laboratory, use an alternative structure **6b**, which emphasizes the aromaticity of the molecule. The numbering system begins with the atom of highest atomic number (O) and continues, in this case clockwise, through the remaining heteroatoms. The substituent R can be alkyl or aryl but not hydrogen. R' substituents can be members of rings and can have a wide variety of attached functional groups such as carboxyl, ester, ether, nitrile, or hydroxyl. Currently, there has not been a sydnone prepared with a strong donating group in the C-4 position. Structurally, sydnones are generally crystalline solids though those with small alkyl groups attached to the N-3 position are liquids. Most sydnones are fairly soluble in organic compounds including benzene but, despite their polar appearance, the vast majority are insoluble in water <1949JC307>. Despite having a lactonic character, sydnones are generally stable due to the high resonance energy they possess. They are, however, unstable to vigorous conditions such as high heat and acidic environments.

The IR spectra of sydnones show a characteristic C=O stretching band at approximately 1760 cm^{-1} and a C-H stretching band (if an H is present at the C-4 position) at approximately 3150 cm^{-1}. Similarly, if an H is present at C-4, the ^{1}H-NMR spectrum exhibits a singlet at approximately 6.80 ppm. Compared to an alkenyl group, this shift of the C-4 proton downfield is due to the polar and aromatic nature of the sydnone ring. Sydnone ^{13}C-NMR spectra show the carbon at the C- 4 position at about 95 ppm and the C-5 position at about 165 ppm. These latter positions are relatively unusual and, accordingly, can be very helpful in assessing whether or not a sydnone ring has been formed.

iii. Synthesis of Sydnones

The synthetic method developed by Earl and Mackney is still the only useful avenue to sydnones. Thus, if the appropriate N-substituted amino acid is available, a sydnone can be

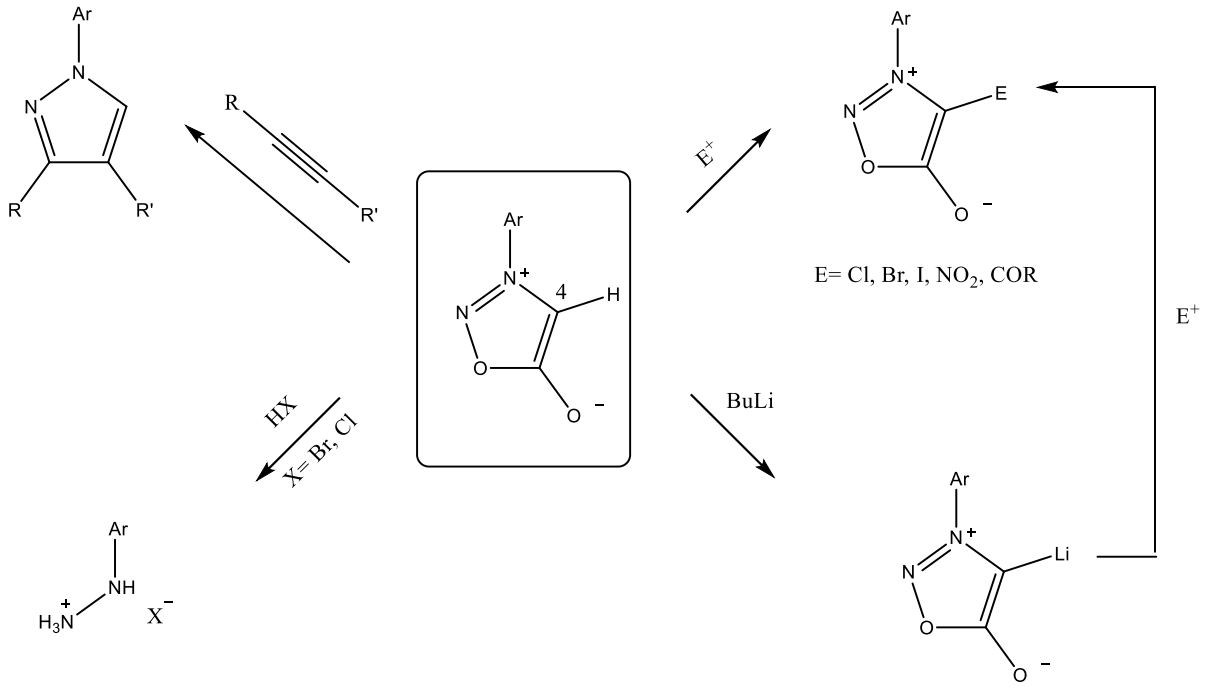
synthesized easily in just two steps, *viz*. N-nitrosation with sodium nitrite in acid followed by cyclodehydration with acetic anhydride (Scheme 3). Over the years, some improvements to this basic protocol have been forthcoming. Thus, instead of using acetic anhydride, which often requires many days at room temperature or considerable heat, trifluoroacetic anhydride has been employed to increase the rate of cyclization <1950JC1542>. Further, as an alternative pathway for acid-sensitive starting materials, Turnbull et al. *N*-nitrosated various *N*-substituted glycines with isoamyl nitrite. <1988S1011> For more complex sydnones, it may be necessary to synthesize the glycine from the appropriate, substituted aniline prior to using the procedure shown in Scheme 3.



Scheme 3: Classical synthesis of sydnone

iv. Reactions of Sydnones

Sydnones can undergo a variety of reactions, many of which take place at the C-4 position (see Scheme 4).



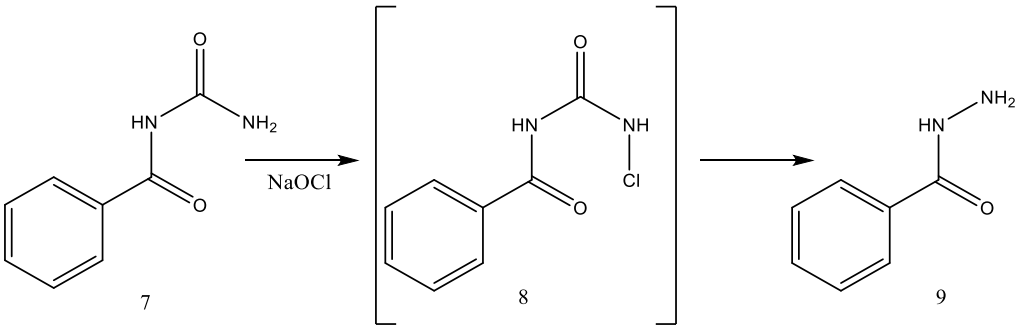
Scheme 4: Common reactions of 3-arylsydnones

The C-4 hydrogen on the sydnone ring has a pKa between 18 and 20 thus classifying it as acidic and the C-4 carbon is also nucleophilic due to a considerable partial negative charge at that location. Accordingly, two main types of reaction can be performed at the C-4 position: 1) electrophilic aromatic substitution or 2) deprotonation followed by nucleophilic substitution <1970JHC1433>. The ring can also undergo 1,3-dipolar cycloaddition or be cleaved under acidic conditions to afford a hydrazine or a hydrazine derivative, as shown in Scheme 4.

II. Oxadiazolinones

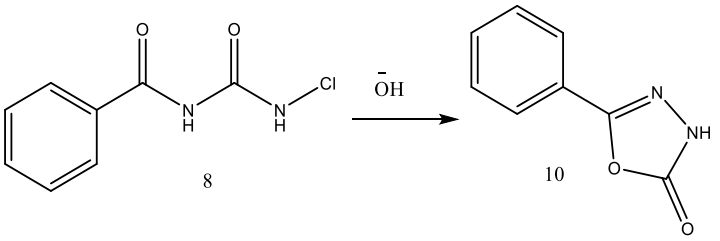
i. Background

In 1912, Schestakoff reacted N-benzoylurea (**7**) with sodium hypochlorite to yield benzoylhydrazide (**9**). N-Benzoyl-N'-chlorourea (**8**) was proposed as the likely intermediate that underwent a Hoffman rearrangement to give **9** (Scheme 5). <1912ber3273>



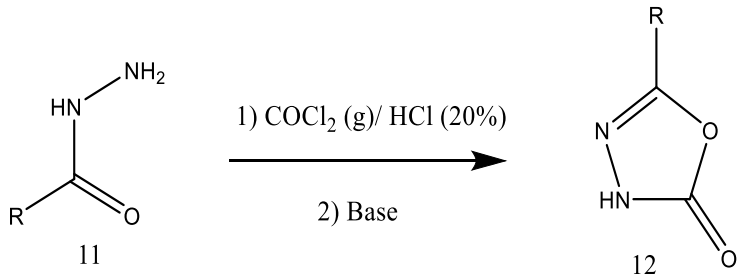
Scheme 5: Schestakoff's reaction of Benzoylurea with Sodium Hypochlorite

To extend the research of Schestakoff, Diels and Okada reacted **8** with base in the anticipation that the corresponding hydrazide would result (Scheme 6). <1912ber2437> However, instead of the hydrazide, an unknown ring structure was obtained, which was identified by Stolle et al. in 1913 as 5-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**10**). <1913ber4076>



Scheme 6: First synthesis of 1,3,4-oxadiazol-2(*3H*)-one (**10**)

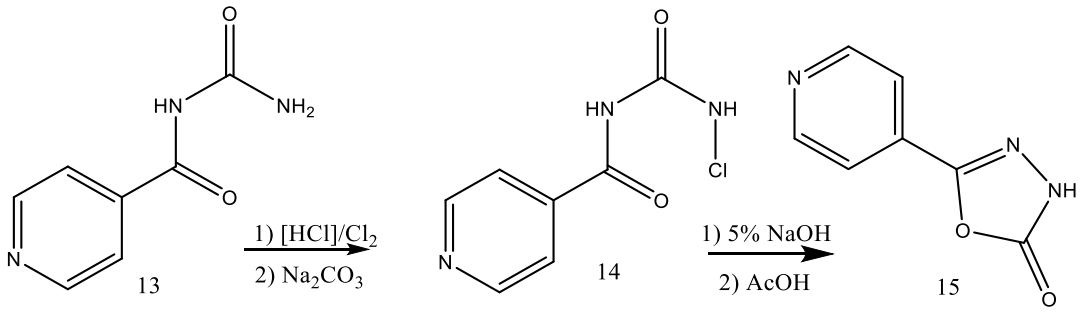
In 1949, Dornow and Bruncken reinvestigated the reaction of hydrazides with phosgene, first reported by Freund and Goldsmith in 1888 <1888Ber1240>, as a possible avenue to oxadiazolinones. Thus, substituted hydrazides **11** were reacted with phosgene gas in dilute HCl to yield 5-substituted 1,3,4-oxadiazol-2*(3H)*-ones **12** (Scheme 7). <1949ber121> While this approach appeared to be quite general, the dangers associated with phosgene reduced its attractiveness.



Scheme 7: Reaction of hydrazides and phosgene

Since hydrazides had proven to be valuable starting materials for oxadiazolinone synthesis it became apparent that, with the limited resources of hydrazine (the usual reactant for hydrazide preparation) available at the time, a different route to synthesize hydrazides was imperative. With this in mind, Stemple et al. explored the synthesis of isonicotinic acid hydrazides, with oxadiazolinones as intermediates, that did not require hydrazine as a reagent. Thus, a mini series of substituted isonicotinylureas was synthesized, with the intention that the

latter would be employed as the starting materials in the synthesis of substituted isonicotinic acid hydrazides. Accordingly, isonicotinylurea (**13**) was chlorinated with chlorine in concentrated hydrochloric acid to form the N-chloro intermediate **14**. The latter was unstable and, when treated with dilute base, resulted in a rearrangement and cyclization. Upon neutralization, the product obtained was 5-(4-pyridyl)-1,3,4-oxadiazol-2(*3H*)-one (**15**) with a 45% yield (Scheme 8).



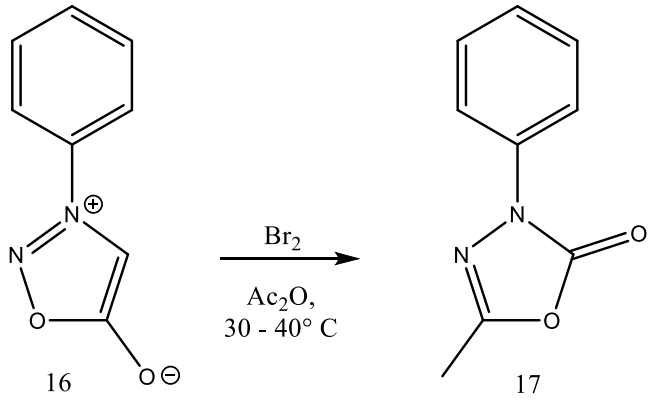
Scheme 8: Synthesis of 5-(4-pyridyl)-1,3,4-oxadiazol-2(*3H*)-one (**15**)

Similarly, the 3-isopropyl substituted hydrazide was transformed into the corresponding oxadiazolinone and the preparation of the 3-ethyl substituted hydrazide was attempted but was unsuccessful.

Since the preparation of **15** resulted in a low product yield and the procedure was difficult to repeat, and the product difficult to purify, Grunberg and Schnitzer elected to adapt the procedure reported by Dornow and Bruncken to synthesize the same isonicotinyl mini-series from hydrazides by treatment with phosgene gas. The products were obtained in greater percent yield (85%) and purity and they were used as standards against the compounds synthesized from substituted ureas (as shown in Scheme 8). It was shown that under similar reactions conditions, when bulky substituents were added to the hydrazide, percent yields were drastically lowered to around 39%. <1955JOC412> Nevertheless, further studies of the oxadiazolinone ring system were performed and, from the work of Grunberg and Schnitzer, it

was shown that **15** and the 3-isopropyl derivative, both synthesized using the method of Dornow and Bruncken, were active *in vivo* against *M. tuberculosis.* The compound derived from the nicotinic acid was inactive. With a lack of studies of the metabolic fate of the newly synthesized compounds available at the time, it was concluded that the activity likely resulted from a cleavage of the oxadiazolinone ring producing isonicotinic acid hydrazide.

In 1958, Stansfield re-explored the bromination of 3-phenylsydnone (**16**). <1958ACS4781> With modifications to the reaction conditions, 3-phenylsydnone (**16**) was transformed into 5-methyl-3-phenyl-1,3,4-oxadiazo-2(*3H*)-one (**17**) instead of the corresponding 4-Br species (Scheme 9).

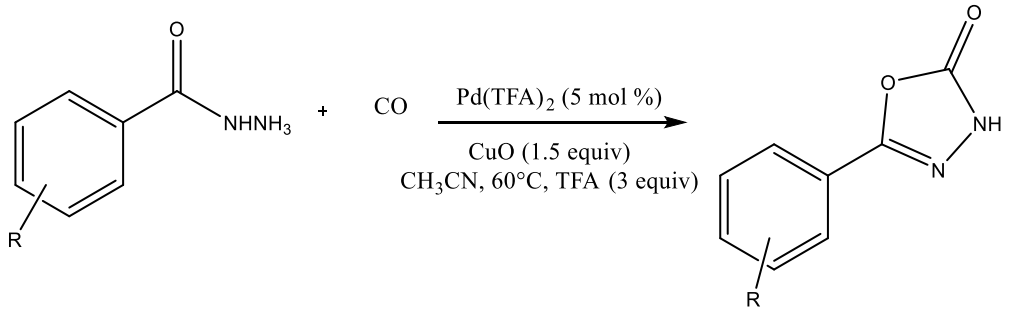


Scheme 9: Stansfield synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

This method was extended by Badami in 2000 to a variety of substituted sydnones, which were transformed to the corresponding substituted oxadiazolinones. <2000IF65> Both Stansfield and Badami's research will be discussed in greater detail at a later point in this thesis.

In 2015, Jiang et al. explored a more facile synthetic route to 1,3,4-oxadiazolinones from hydrazides without the use of toxic reagents and harmful organic solvents. <2015JOC5713> Carbocyclic and heterocyclic compounds had been synthesized previously by way of oxidative

carbonylation and, thus, Jiang et al. optimized the reaction of aryl substituted hydrazides **18** with carbon monoxide and a palladium catalyst to yield the corresponding aryl substituted oxadiazolinones **19** in good yields (Scheme 10).

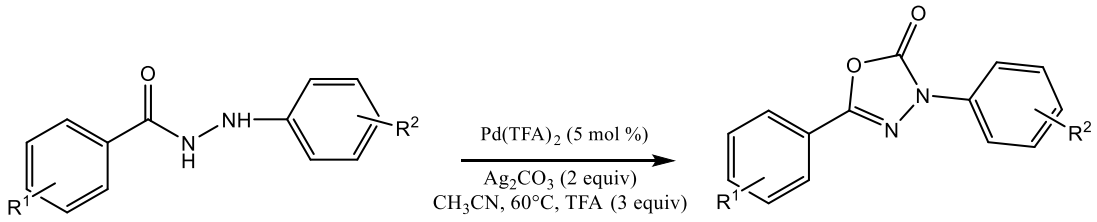


18 19

R: H, Me, t-butyl, Ph, CF_3, NO_2, F, Cl, Br, 3-Me, 2-Me, 3-Cl, 3,5-Cl_2, -C_4H_4

Scheme 10: Synthesis of oxadiazolinones **19** using CO and a Pd catalyst

Many different functional groups can be tolerated using this protocol, even substrates containing a heterocyclic ring. To further extend the study, N'-phenyl-benzohydrazide was subjected to the same reaction conditions, however, the resulting product was obtained in low yield. To combat this, N-aryl substituted derivatives **20** were reacted with Ag_2CO_3, instead of CuO, to yield the appropriate N- substituted 1,3,4-oxadiazolinones **21** (Scheme 11).



20 21

Scheme 11: Synthesis of N-substituted 1,3,4-oxadiazolinones **21**

The most notable compound synthesized using this method is BMS-191011 (Figure 2), a large-conductance calcium activated potassium channel opener, which can be used in a wide variety of medical applications.

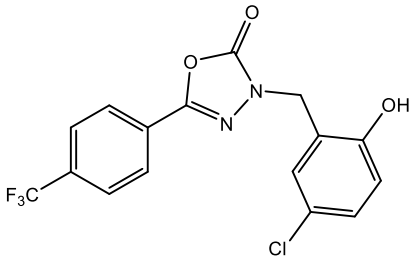
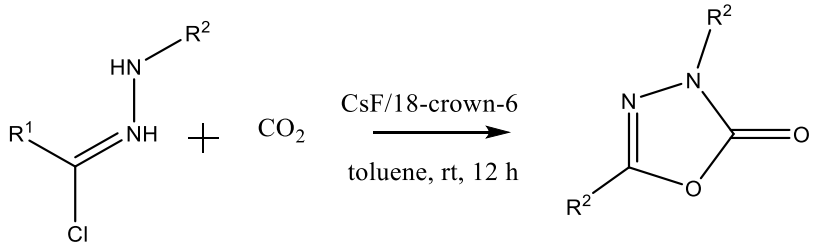


Figure 2: BMS-191011

In an attempt to develop a more efficient and facile synthesis of 1,3,4-oxadiazol-2(*3H*)-ones, without the use of a palladium catalyst as reported by Jiang et al. <2015JOC5713>, in 2017, Zhang et al. re-explored the 1,3-dipolar cycloaddition of nitrile imines with carbon dioxide, first reported by Pfoertner and Foricher using the photo-reaction of 3-methyl-4-phenylsydnone. <1980HCA653> Zhang et al. reacted substituted hydrazonyl chlorides **22** with carbon dioxide and CsF/18-crown-6 to yield the appropriate 1,3,4-oxadiazol-2(*3H*)-ones **23** (Scheme 12).



22 23

Scheme 12: 1,3-dipolar cycloaddition using carbon dioxide to yield oxadiazolinones **23**

Further studies were performed to determine how the use of Cs_2CO_3 or CsF/18-crown-6 altered the system. When Cs_2CO_3 was reacted with a substituted hydrazonyl chloride without the addition of CO_2, NMR data showed the formation of the nitrile imine intermediate and the resultant dimer, while the use of CsF without addition of CO_2, did not show the presence of either. The addition of 18-crown-6 with either base readily formed both the nitrile intermediate and the dimer. Though reaction of the substituted hydrazonyl chloride and CsF/18-crown-6, or Cs_2CO_3/18-crown-6, showed formation of the desired intermediate, CsF/18-crown-6 exhibited a higher efficiency for the 1,3-dipolar cycloaddition, thus enabling the increased reactivity of CO_2 as a 1,3-dipolarophile. <2017JOC7637> Though, generally, carbon dioxide has a low reactivity towards 1,3-dipoles and there is a fast dimerization of the imines formed *in situ*, this method was applied successfully to the synthesis of a commercial herbicide Oxadiazol, and a MAO B inhibitor, shown in Figure 3.

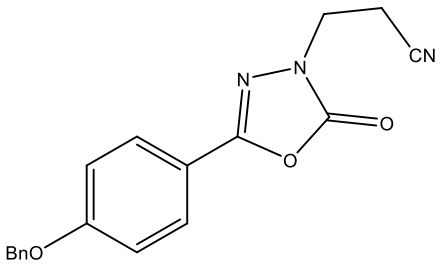
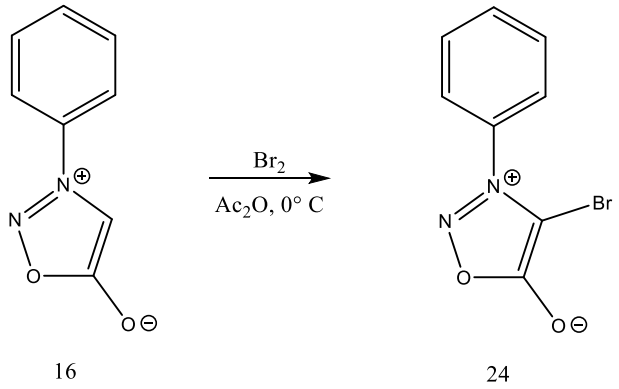


Figure 3: MAO B inhibitor

ii. Synthesis of 5-methyl-3-aryl-1,3,4-oxadiazol-2(3H)-ones from sydnones

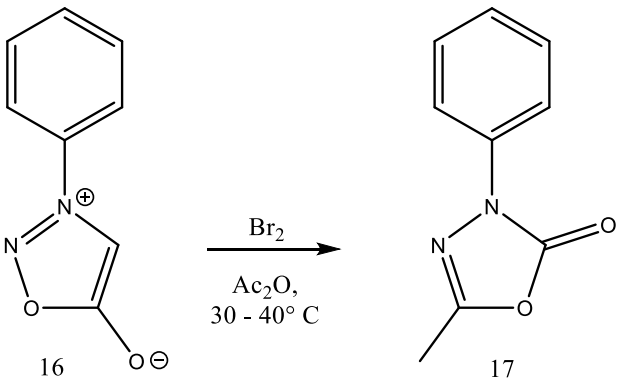
The standard preparation of an oxadiazolinone from 3-phenylsydnone follows the procedure discovered by Stansfield and shown previously in Scheme 9. Since this transformation is an important part of the research work reported in this Thesis it is valuable to provide more background to Stansfield's findings. Thus, in 1958, Stansfield attempted to repeat the work of

Baker, Ollis, and Poole <1958ACS4781> by brominating 3-phenylsydnone (**16**) with bromine in acetic anhydride at 0°C to form 4-bromo-3-phenylsydnone (**24**) [Scheme 13].



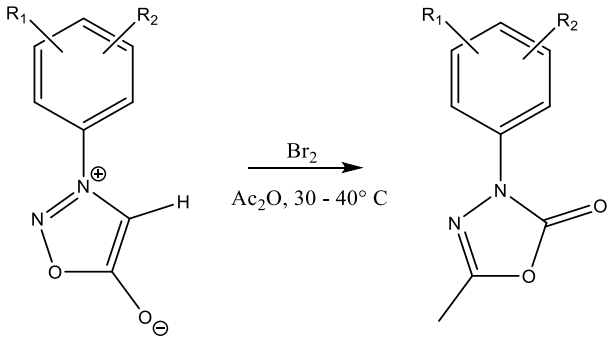
Scheme 13: Baker et al. bromination of 3-phenylsydnone (**16**)

However, perhaps inadvertently, the reaction was heated to 30-40°C and evolution of carbon dioxide was observed. Upon work-up, rather than the expected 4-bromo sydnone **24**, 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) was formed (Scheme 9, as previously seen). Stansfield suggested that the acidic conditions may have cleaved the sydnone ring to a hydrazine but he did no further follow-up studies.



Scheme 9: Stansfield synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**)

In 2000, Badami extended the study to a variety of 3-aryl-substituted sydnones **25** and transformed them successfully into the corresponding aryl-substituted oxadiazolinones **26** (Scheme 14) <2000IF65>. All the compounds were tested for antimicrobial activity against two pathogenic bacteria, viz.,



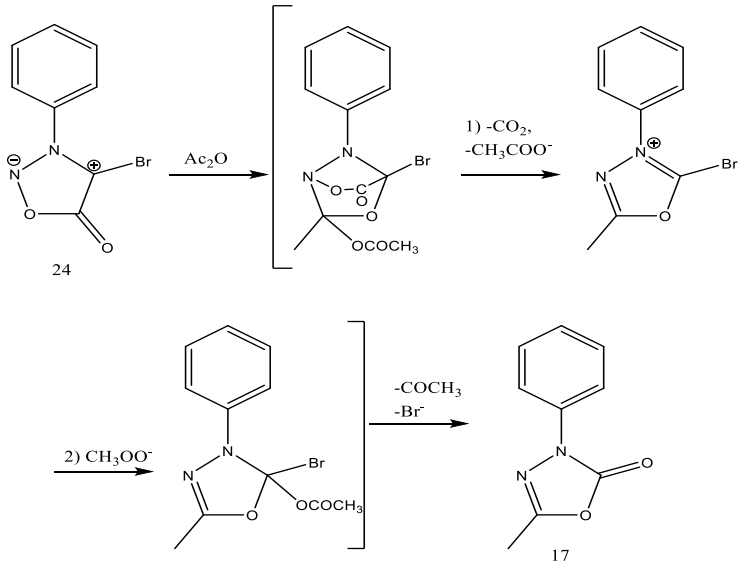
25 26

R_1= H, 3-CH_3, 2-CH_3, 2-OCH_3, 4-CH_3, 4-Cl
R_2 = H, 3-CH_3, 2-CH_3, 2-OCH_3, 4-CH_3, 4-Cl, 4-Br, 4-NO_2, 2-NO_2, 2-COOH, 4-$COCH_3$, 2-$COCH_3$, 4-$COOCH_3$, 4-$COOCH_2H$, 4-CH_3, 5-CH_3, 4-Cl, 3-Cl, 3-F

Scheme 14: Badami's synthesis of oxadiazolinones **26** from arylsydnones

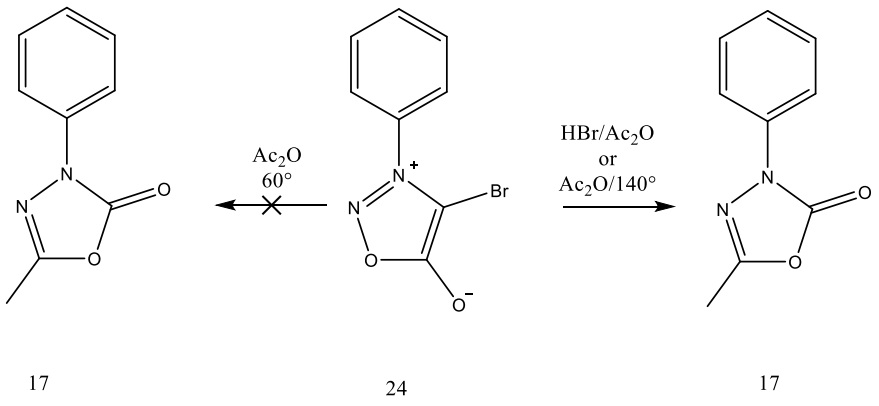
Escherichia coli and *Pseudomonas pyocyanous*. The 3-chloro- and 4-chloro- aryl oxadiazolinone derivatives exhibited growth inhibition only against *Pseudomonas pyocyanous* whereas the 4-bromoaryl derivative exhibited growth inhibition against *Escherichia coli.* Additionally, these compounds demonstrated greater antifungal activity than the standard drug. Further, a chloro fluoroaryl substituted derivative exhibited growth inhibition against both strains with equal intensity to the standard,

Mallur and Badami <2000IF65> suggested that the mechanism for the formation of **17** from **24** was a 1,3-dipolar cycloaddition between the sydnone and a carbonyl group in the anhydride (Scheme 15).



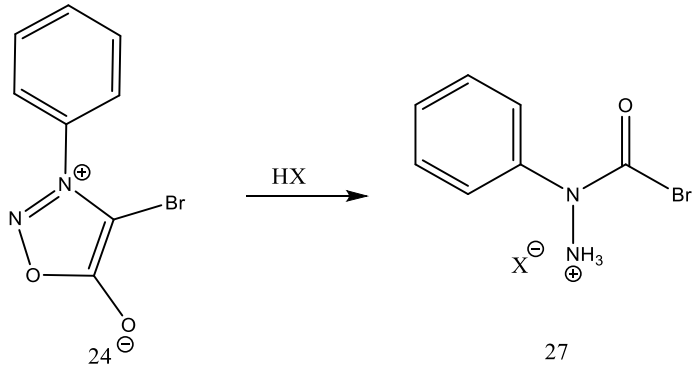
Scheme 15: Badami's proposed mechanism for sydnone to oxadiazolinone conversion

To further support the above mechanisim, Badami later suggested that HBr, formed in situ during the preparation of **24** from 3-phenylsydnone, acted as a catalyst for the 1,3-dipolar cycloaddition. When **24** was subjected to reaction with acetic anhydride at high temperatures, or with acetic anhydride and HBr, **17** was produced, but with acetic anhydride and moderate heat, no reaction was observed (Scheme 16).



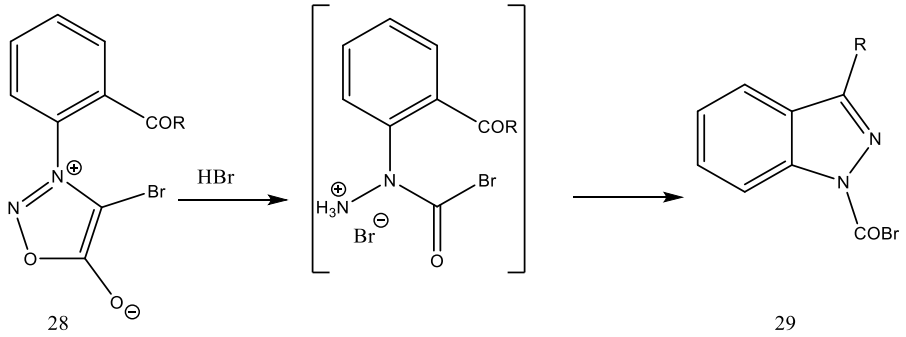
Scheme 16: Badami's reaction of 4-bromo-3-phenylsydnone (**24**) with HBr or Ac_2O

This led Badami to conclude that HBr did not hydrolyze the sydnone ring <2002JICS629>. However, research done by Yeh et al. and, separately, Turnbull and Marx suggested that Badami's proposed mechanism was highly unlikely. Yeh et al. <1994JCCS8499> showed that the 4-bromo sydnone **24** reacted with HX (X=Cl , Br) to yield a moderately stable carbonyl hydrazine salt **27** (Scheme 17).



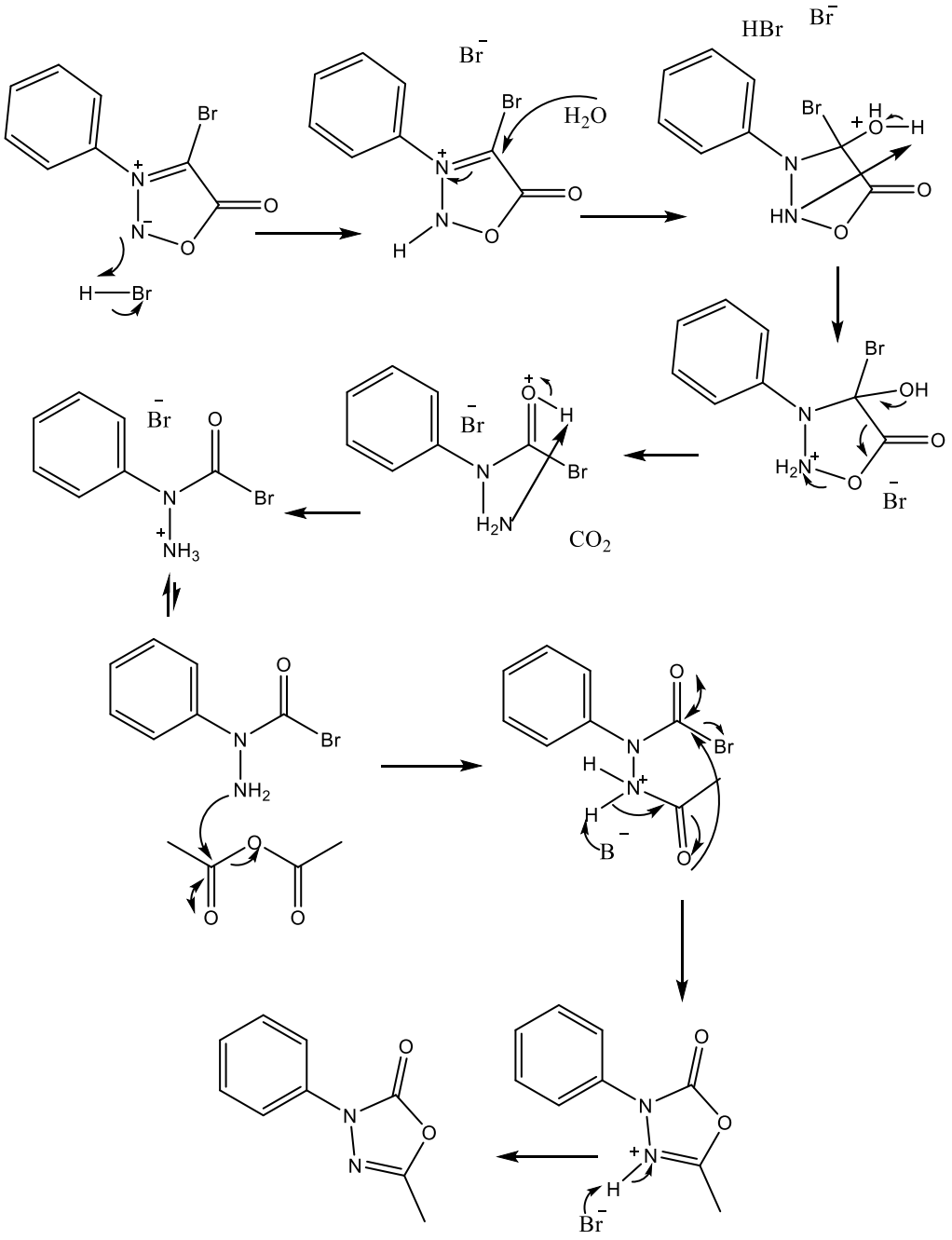
Scheme 17: Yeh et al. synthesis of bromocarbonyl hydrazine salt

Additionally, in previous work reported by Turnbull and Marx <1993TL239>, it was proposed that bromocarbonyl hydrazine derivatives were intermediates in the reactions of 4-bromo *o*-carbonyl substituted aryl sydnones **28** with HBr (Scheme 18). These intermediates, though not isolated, were presumed to lead to the formation of bromocarbonylindazoles **29**.



Scheme 18: Formation of bromocarbonylindazoles

Both Yeh and Turnbull's work led to the conclusion that Badami's mechanism (Scheme 15) could not be correct and that sydnone ring cleavage by HBr is a key step in the process. Indeed, further study of the process by Thijs Gerritsen in the Turnbull lab showed with a high degree of certainty that the synthesis of **17** could not be a 1,3-dipolar cycloaddition with **24** but was instead an HBr induced ring cleavage of the latter to form a bromocarbonyl hydrazine salt followed by cyclization of the latter with acetic anhydride, as shown in Scheme 19. This new mechanism provides further insight into the reactions of sydnones, especially the one pot synthesis of **17** from 3-phenylsydnone (**16**)

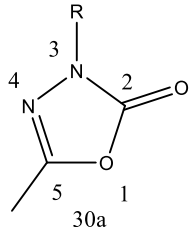


Scheme 19: Turnbull proposed mechanism for oxadiazolinone formation

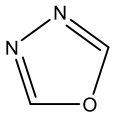
iii. Properties of Oxadiazolinones

Oxadiazolinone (**30**a) has the skeletal structure of 1,3,4-oxadiazole (**30**b) with a carbonyl functionality attached to the 2-position. The numbering system begins with the atom

of highest atomic number (O) and continues, in this case counter clockwise, through the remaining heteroatoms.



30a



30b

IR spectra of oxadiazolinones show two characteristic peaks, *viz.* a band around 1775 cm^{-1} for C=O stretch and a band around 1630 cm^{-1} due to C=N stretch. Further, the lack of a signal at 3100 cm^{-1} (sydnone C-H stretch) can be useful in assessing the success of the transformation from a sydnone to an oxadiazolinone.

The ^{1}H-NMR spectra of 5-methyl oxadiazolinones (as used in this thesis) show the signal for the C-5 methyl protons at approximately 2.35 ppm. If the oxadiazolinone is *para*-substituted on the aryl ring at the 3-position (as used in this thesis) two doublets are observed in the aromatic region, the exact position being dependent upon the substituent. In each case the methyl protons of the C-5 position remain around 2.35 ppm.

Oxadiazolinone ^{13}C-NMR spectra show a C-2 peak at 153-155 ppm and a C-5 peak at 150-152 ppm and these values change very little with substituent variation. The carbons on the aryl ring are affected by any substituents that may be present and the methyl group connected to the C-5 (if present) appears about 12 ppm.

Mass spectrometry provides a very characteristic breakdown for oxadiazolinones. First, the loss of a fragment of 44 m/z is observed, which corresponds to the expulsion of CO_2 to leave mass fragment 132. Next, CH_3CN is cleaved leaving mass fragment 91 (Figure 4).

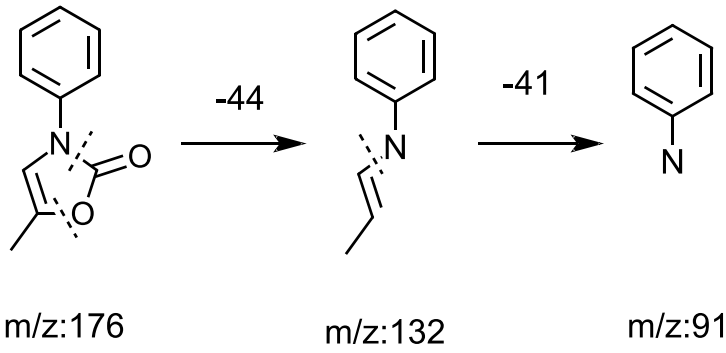
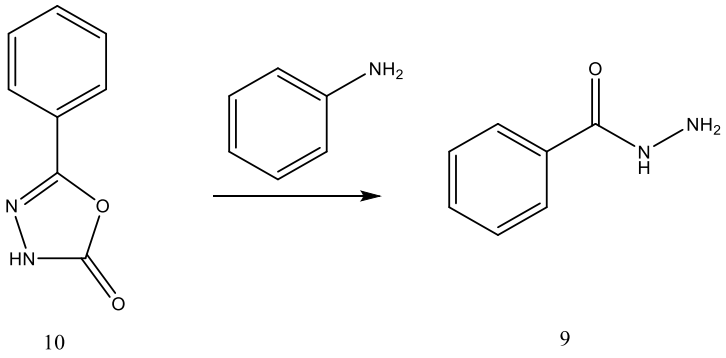


Figure 4: Mass spectral breakdown of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

If a halogen is attached to what would have been the 5-methyl group then, in the mass spectrum, the former will break off first and the resultant oxadiazolinone will continue to break down as normal. If the aryl ring is halo substituted, the halogen remains attached to the aryl ring until the oxadiazolinone ring breaks down completely.

iv. Reactions of oxadiazolinones

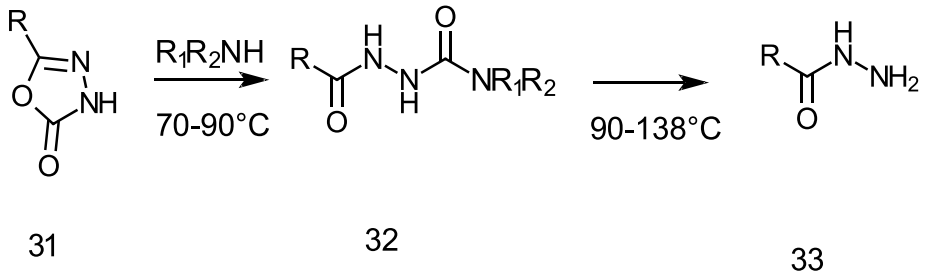
Diels and Okada refluxed oxadiazolinone **10** with aniline and obtained benzoyl hydrazide (**9**) [Scheme 20].



Scheme 20: Diels' conversion of oxadiazolinone to benzoyl hydrazide

This transformation happens by way of nucleophilic attack at the C2 position followed by ring opening to form a semicarbazide that decomposes further upon heating. <1912ber2437>

Stemple et al. successfully synthesized 5-substituted-1,3,4-oxadiazol-2(*3H*)-ones **31** and extended Diels and Okada's work by reacting them with substituted amines to yield either hydrazides **33** or semicarbazides **32**, the latter being the intermediates to the hydrazides (Scheme 21). <1955JOC412>

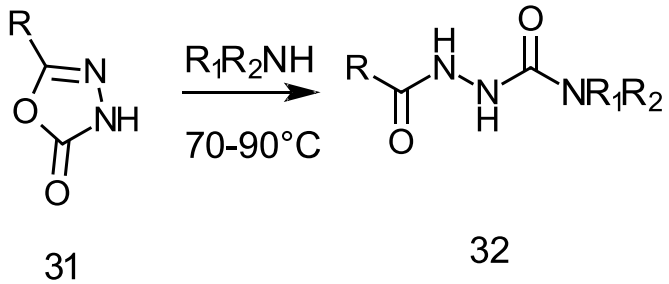


31 32 33

Scheme 21: Formation of hydrazides from 5-substituted oxadiazolinones

In general, oxadiazolinones were found to be attractive starting materials for the preparation of substituted semicarbazides since the substituents could be readily introduced at the 3 and 5 positions of the oxadiazolinone ring.

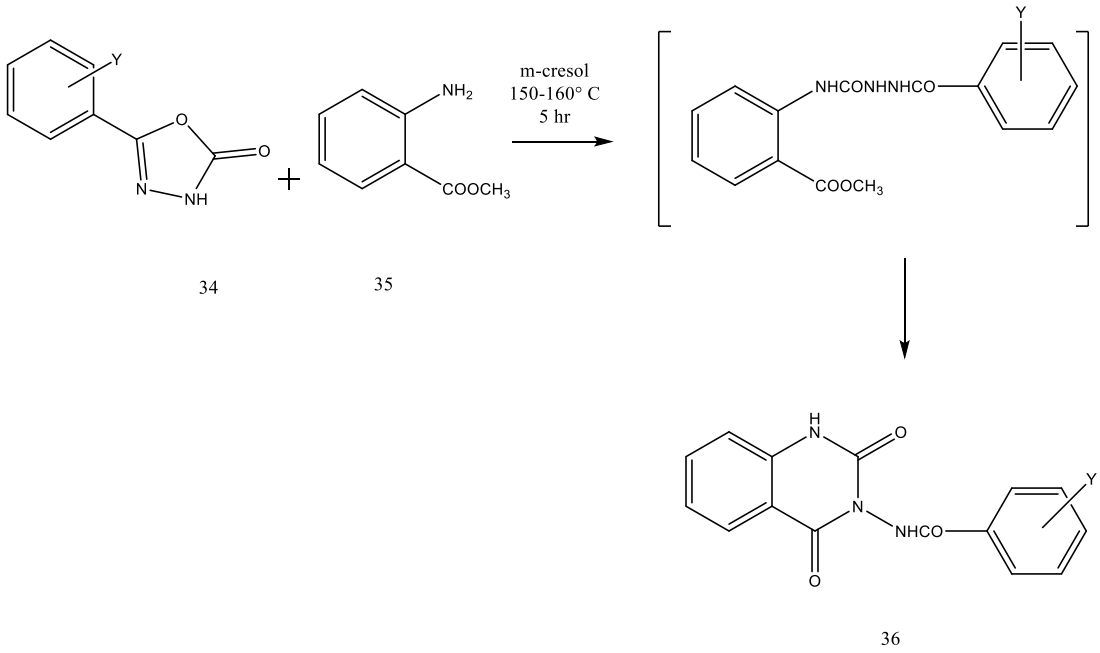
An analysis of oxadiazolinone ring stability was performed by Stemple et al. by reacting 5-substituted oxadiazolinones **31** with amines at various temperatures. At room temperature, no reaction was observed, however, with heating, the appropriate substituted semicarbazide **32** was formed (Scheme 22). <1955JOC412>



31 32

Scheme 22: Reaction of oxadiazolinones with amines

In 1981, Saegusa et al. reported the one-pot synthesis of substituted N-(2,4-dioxo-1,3,4-tetrahydro-quinazolinyl)benzamides **36** by reaction of 2-aryl-1,3,4-oxadiazol-2-ones **34** with methyl anthranilate (**35**) [Scheme 23]. <1982JHC541> Mechanistically, the methyl anthranilate acts as a nucleophile and attacks the carbonyl of **34** to yield the ring-opened semicarbazide, which undergoes subsequent ring closure with the elimination of methanol to yield **36**. This reaction showcased the synthetic utility of the 1,3,4-oxadiazolinones since a variety of aryl-substituted 1,3,4-oxadiazolinones could be transformed easily into more complex heterocyclic compounds such as quinazolines. 1,3,4-oxadiazolin-2-thiones were also studied but the main emphasis was on 1,3,4-oxadiazol-2-ones **34** (Scheme 23).



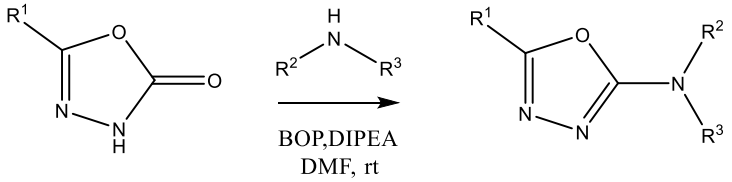
34 35 36

Y= H, 2-Cl, 4-Cl, 4-CH_3, 2-NO_2, 3-NO_2, 4-NO_2

Scheme 23: Synthesis of N-(2,4-oxo-1,3,4-tetrahydroquinazolinyl)benzamides **36**

N,N-Disubstituted 2-amino-1,3,4-oxadiazolinones have been difficult to prepare from oxadiazolinones, however, in 2008, Wan and Levins explored direct amination of

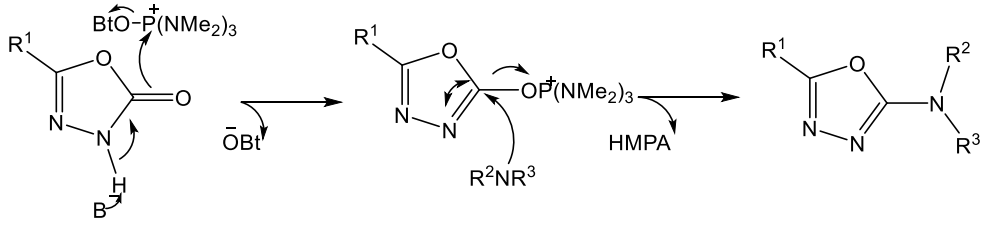
oxadiazolinones in the presence of phosphonium reagents as a potential avenue to such species.<2008OL1755>. Previous research by these authors had shown that direct amination could occur on ureas and cyclic amides with the use of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), a commercially available peptide coupling reagent <2006OL2425>, and, accordingly, it was opted to apply this protocol to the 1,3,4-oxadiazol-2(*3H*)-one system. Thus, 5-substituted 1,3,4-oxadiazol-2(*3H*)-ones **37** were reacted with 2° amines in the presence of BOP to yield the corresponding N,N-disubstituted 2-amino-1,3,4-oxadiazolinones **38** (Scheme 24).



37 38

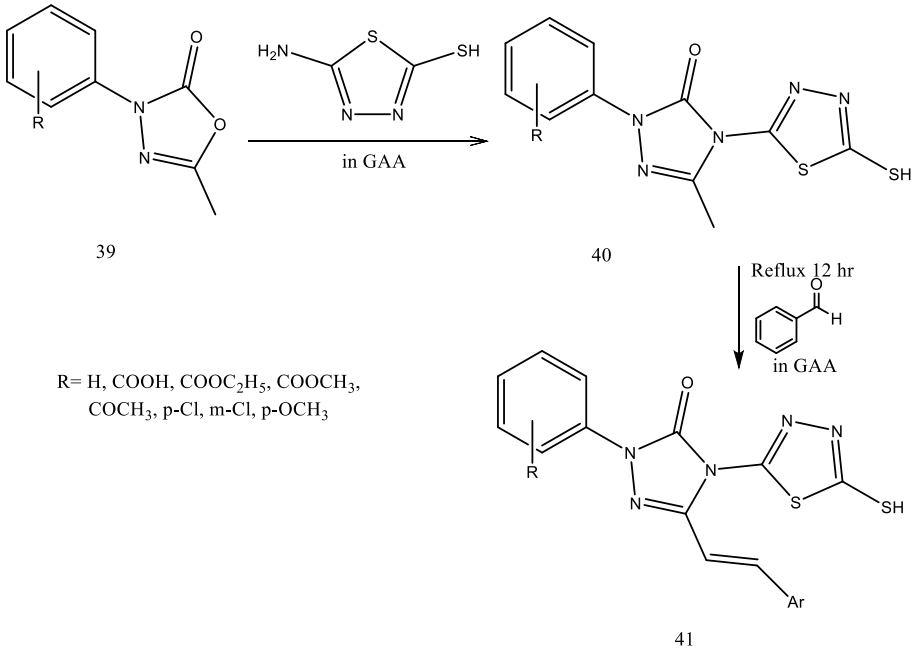
Scheme 24: Synthesis of N,N-disubstituted 2-amino-1,3,4-oxadiazolinones **38**

As opposed to a ring opening nucleophilic attack, this process occurs by way of a mechanism in which the base removes a proton from the carbamate NH in the oxadiazolinone ring allowing resonant attack by the carbonyl oxygen upon the phosphonium reagent with release of the ⁻OBt group. The amine then attacks the newly formed imine carbon, which ultimately leads to expulsion of hexamethylphosphoramide and formation of the 2-amino oxadiazole (Scheme 25).



Scheme 25: Proposed synthesis mechanism of N,N-disubstituted 2-amino-1,3,4-oxadiazolinones **38**

In 2009, publication in 2010, Kotresh et al. synthesized a variety of 1,2,4-triazol-3-ones **41** from 3-aryl substituted oxadiazolinones **39**. <10EJC545> Triazoles containing other heterocyclic rings have many diverse applications such as treatment against bacteria and viruses and use in dyes and pesticides. <01IF919> Synthesis of **41** occurred in a two-step process that used glacial acetic acid (GAA) as solvent. <03JCR275> First, **39** was reacted with 5-amino-1,3,4-thiadiazole-2-thiol to form the intermediate triazolone **40** through attack of the amino group on the carbonyl to open the ring, followed by recyclization. Subsequent reflux with benzaldehyde afforded a variety of substituted 1,2,4-triazol-3-ones **41** (Scheme 26).



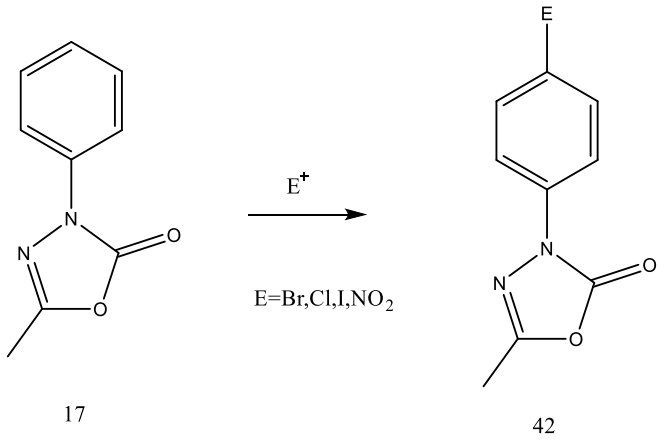
Scheme 26: Reaction of aryl substituted oxadiazolinones **39** with 5-amino-1,3,4-thiadiazole-2-thiol

Biological testing of the newly synthesized compounds was performed against *E. coli*, *B. substilis*, *A. niger*, and *C. Albicans*. While all the derivatives prepared exhibited antibacterial and

antifungicidal properties, the p-acetyl, p-chloro, and p-methoxy substituted aryl derivatives were the most biologically active.

v. Aims

Previous work in the Turnbull laboratory has shown that 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**17**) undergoes electrophilic aromatic substitution with electrophiles to yield the corresponding para-substituted compounds **42** <MI2014A> [Scheme 27].

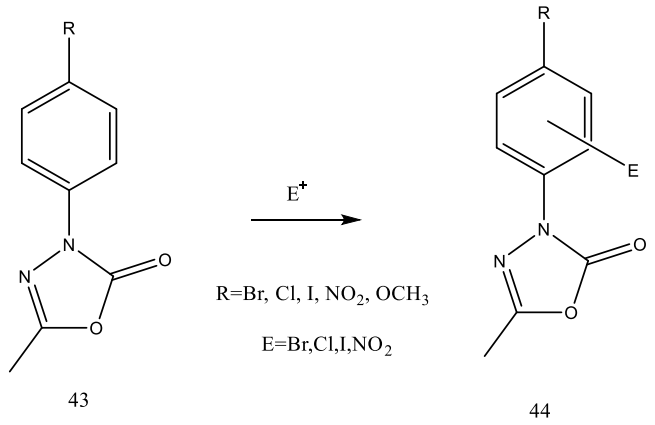


Scheme 27: Reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with electrophiles

While this was a novel finding, and offered interesting possibilities for further study, the initial work was limited and resulted in low product yields for only two examples, *viz.* bromination and nitration. To further this study, it was opted to prepare the starting oxadiazolinone **17** from 3-phenylsydnone (**16**) [as described in the Introduction, Scheme 9] and extend the range of electrophiles and reagents examined with a view to providing better product yields and a larger variety of interesting products for subsequent modification.

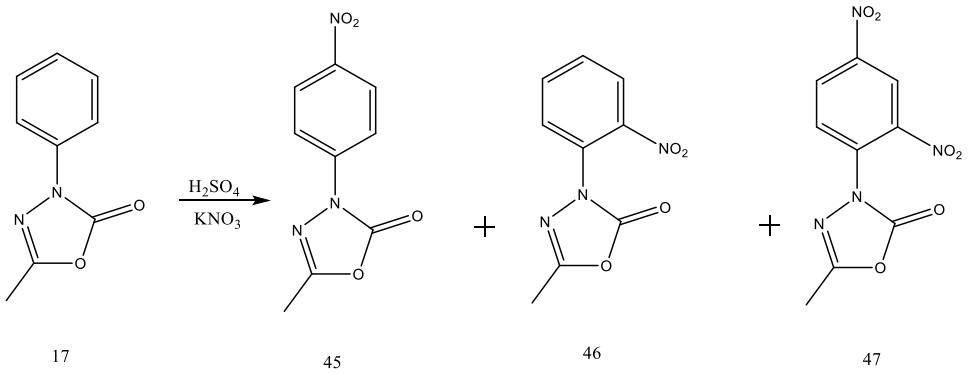
Further, though the oxadiazolinone ring appears to be a relatively weak ortho-para director, it has yet to be determined how strongly activating the system behaves when another

substituent is present on the aryl ring. Accordingly, it was planned to prepare a series of *para*-substituted oxadiazolinones 43, from the corresponding sydnones or by the reactions of electrophiles with oxadiazolinone 44, and investigate the sites of reaction on the aryl ring upon further reaction with electrophiles (Scheme 28).



Scheme 28: Reaction of 5-methyl-3-(4-substituted phenyl)-1,3,4-oxadiazol-2(*3H*)-ones **43** with electrophiles

In addition, during the previous synthesis of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**45**) by nitration of **17**, various by-products were also formed. These by-products were thought to be 5-methyl-3-(2-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**46**) and 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**47**) [Scheme 29] and it was planned in the present work to explore the potential optimization of this process for each of these species individually by modifications to the reaction temperature, concentration, and reaction time.



Scheme 29: Nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

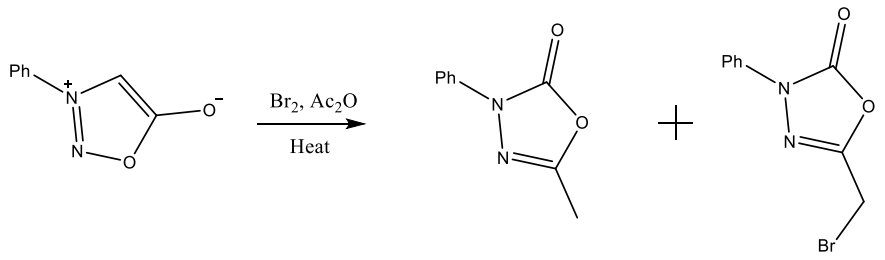
As mentioned previously, Badami synthesized a wide variety of aryl-substituted oxadiazolinones (Scheme 12) <00IF65>. The 4-chloroaryl and 4-bromoaryl derivatives were shown to have biological activity against *Pseudomonas pyocyanous* and *Escherichia coli*, respectively, and the 4-chloro-3-fluoro-aryl derivative had biological activity against both strains of bacteria.

III. Results and discussion

i. Preparation of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17)

The synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) was adapted from Badami's procedure <00IF65> in which 3-phenylsydnone (**16)** was reacted with bromine in acetic anhydride at 0°C. Accordingly, 2 molar equivalents (instead of 1.5 as it was difficult to weigh the bromine accurately on the small scale employed) of cold bromine in acetic anhydride were added to a suspension of the sydnone in acetic anhydride with stirring and cooling. The mixture was then gradually heated to 50-60°C for 1 hr, after which time the solution was poured into water and the resulting precipitate was filtered, washed with cold water and recrystallized from ethanol.

While the procedure employed did give the desired product **17**, as evidenced by its spectral characteristics (*vide infra*), the most obvious differences from Badami's report were the yield and purity of the product. In Badami's work, she reported the isolation of pure **17** in >80% yield without recrystallization but, in the present work, the initial purity of the product was low and two major products were obvious from TLC analysis. Accordingly, multiple recrystallizations were necessary to obtain pure samples of **17** and this led to product yields no higher than 25%. The low percent yields were attributed to the formation of a major impurity, which was later identified as 5-(bromomethyl)-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**48**) [Scheme 30].



16 17 48

Scheme 30: Turnbull synthesis of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**)

Even though no such impurity was mentioned by Badami, this compound was present in every reaction performed in the present work. Indeed, **48** was such a significant contaminant when two equivalents of bromine were used that it was elected to try Badami's conditions exactly, *viz*. with 1.5 equivalents of bromine. While this modification did reduce the amount of by-product (TLC evidence), it was still a major contaminant and the recrystallized percent yield of the desired product **17** was still not satisfactory, with 35% being the best yield obtained. Around this time, this aspect of the research was delegated for further study to Jimmy Klaasen, a newly arrived Dutch intern, and the focus in the present research was shifted elsewhere. The optimized procedure developed by Klaasen after a thorough study included adding neat bromine to the reaction pot without cooling and raising the subsequent reaction temperature to 70°C rather than 50-60°C. Accordingly, this adapted procedure was utilized in the present work and yields of the methyl phenyl oxadiazolinone **17** were drastically increased, with the best recrystallized yield being 53 %**.** The pure product had a sharp melting point (85- 86°C) but displayed a lower melting point compared to Badami's reported results (95-96°C). However, the structure and purity were confirmed by GC-MS (Appendix A) and $^{1}H/^{13}C$-NMR analyses. The mass spectrum showed a molecular ion peak at 176 m/z, which is the molecular mass of the

expected product **17**. Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed (Figure 5).

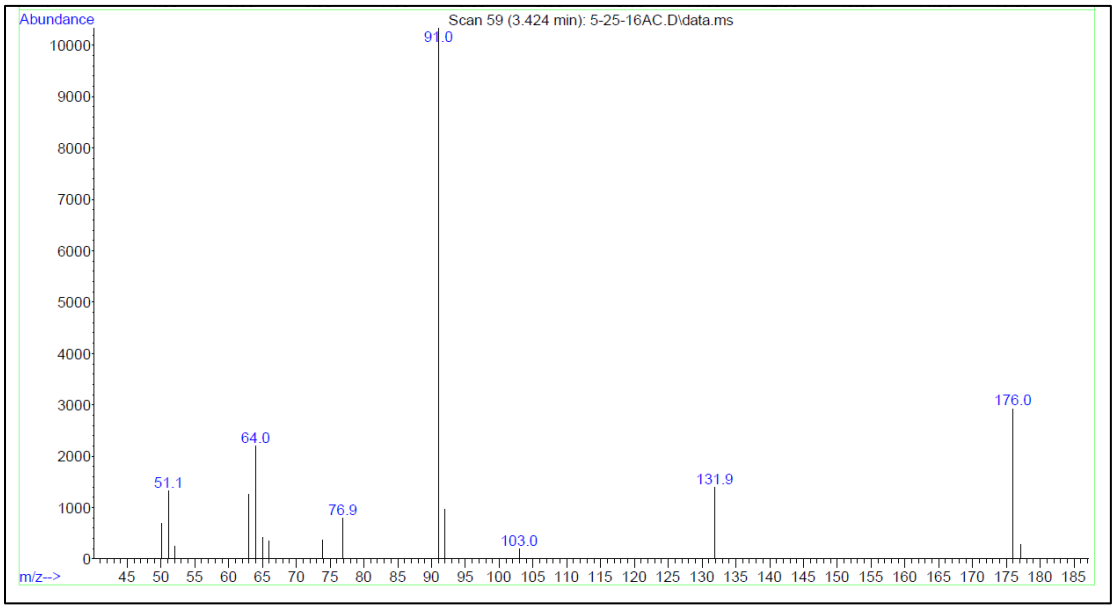


Figure 5**:** Mass spectrum of 5-methyl-3-phenyl-1,3,4-oxadiazo-2(*3H*)-one (**17**)

The IR-spectrum showed the expected C=O absorption at 1773 cm^{-1}, which is shifted slightly higher than a typical carbonyl due to the strain of the oxadiazolinone ring system and because of its carbamate-like functionality (Appendix B).

The ^{1}H-NMR spectrum showed 4 signals, a singlet (3H) at 2.34 ppm for the methyl protons and, in the aromatic region, a triplet (1H) at 7.25 ppm, a triplet (2H) at 7.42 ppm, and a double doublet (2H) at 7.82 ppm (Figure 6).

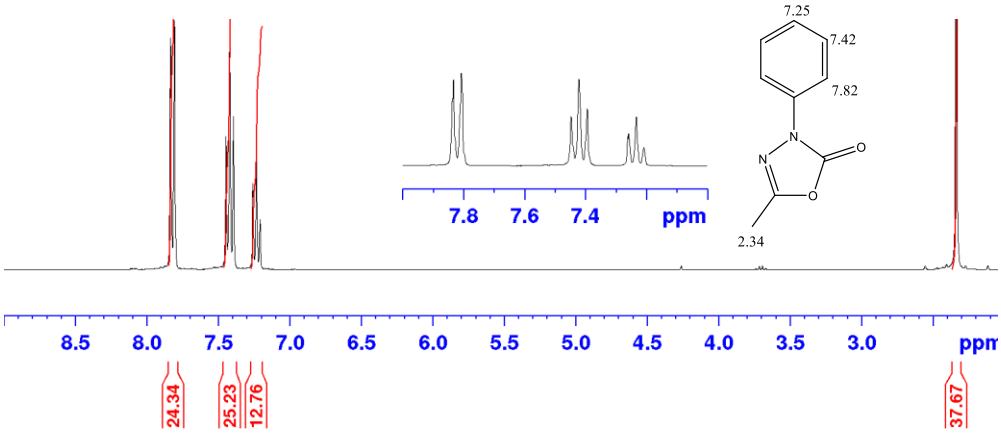


Figure 6: Proton NMR spectrum and proton assignments for 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

The ^{13}C-NMR spectrum showed 6 signals, 1 signal for the methyl group, 4 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine (Figure 7).

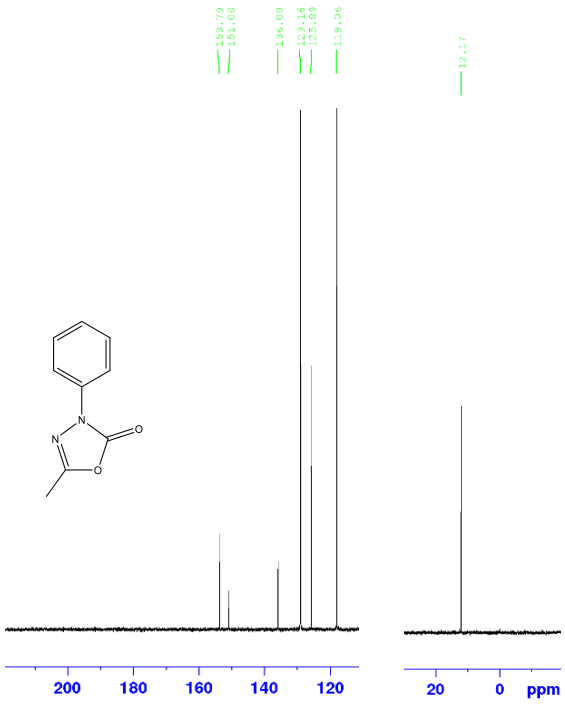


Figure 7: C^{13} NMR spectrum of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

Though the carbon NMR spectrum exhibits very clear signals for the methyl group (12.17 ppm) and the oxadiazolinone carbonyl and imine carbon atoms (153.79 ppm and 151.08 ppm, respectively), the carbons in the aromatic region cannot be assigned with certainty. Therefore, these assignments were determined from the heteronuclear single quantum correlation (HSQC) spectrum (Figure 8), in which proton signals (on the x-axis) are correlated with carbon signals (on the y-axis).

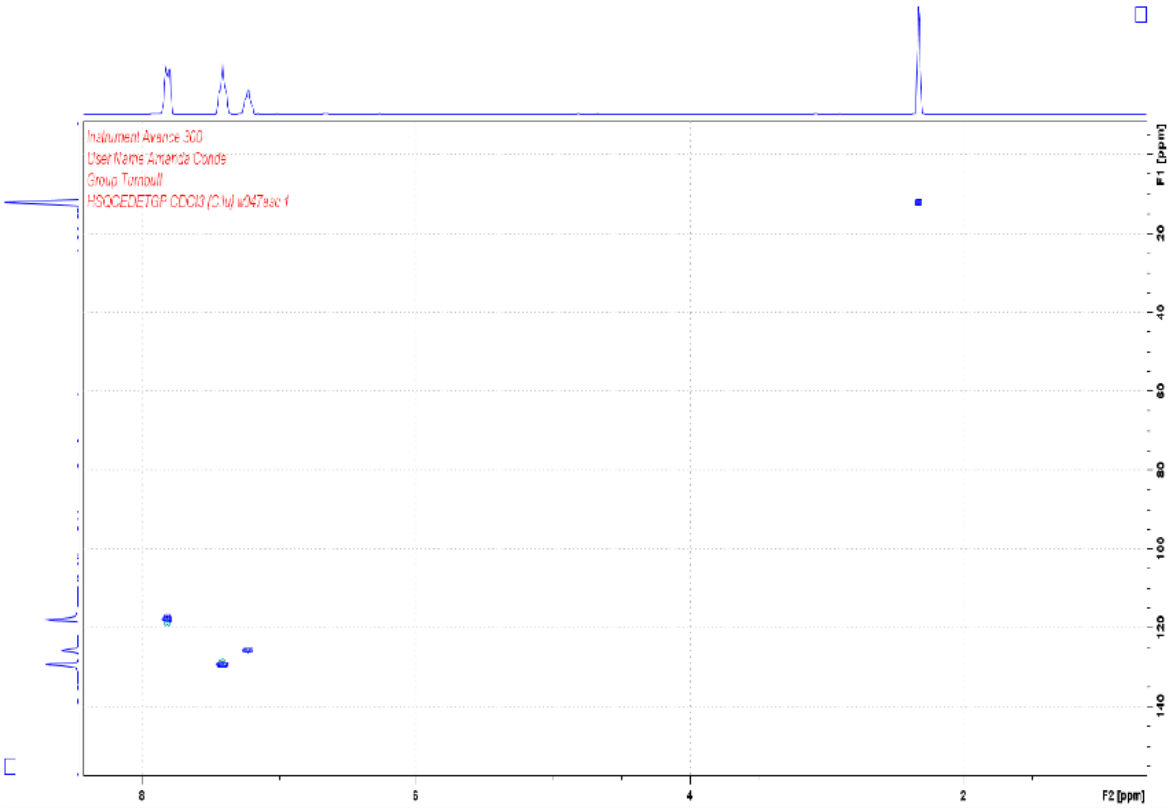


Figure 8: HSQC spectrum of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**)

Figure 8 indicates that the (2H) double doublet correlates to the carbon at 118.06 ppm, the (2H) triplet to the carbon at 129.16 ppm and the (1H) triplet to the carbon at 125.89 ppm. These data permit assignment as shown in Figure 9 and extrapolation to derivatives discussed later.

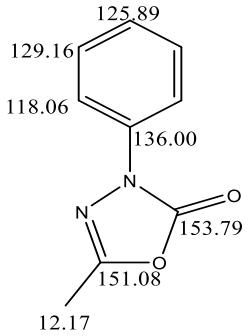


Figure 9: Aromatic ring carbon assignments for 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

Further, just as with any other substituent, the carbon shifts on the benzene ring are naturally affected by the oxadiazolinone ring system. However, there are no known literature values for the effects of the oxadiazolinone ring system on a benzene ring and therefore calibration is necessary to determine the magnitudes of these values. Calibration was performed by using the following equation: $^{\delta}c_i = 128.5 + x_i$ (Equation 1) <83SD120> where 128.5 represents the carbon of an unsubstituted benzene and $^{\delta}c_i$ represents the ^{13}C NMR determined values in the aromatic region of **17**. By substituting the appropriate values into equation 1, the effects of the oxadiazolinone ring system were calculated as shown below in Table 1.

Parent ring system	Ipso	Ortho	Meta	Para
Oxadiazolinone ring	7. 5	-10.44	0.66	-2.61

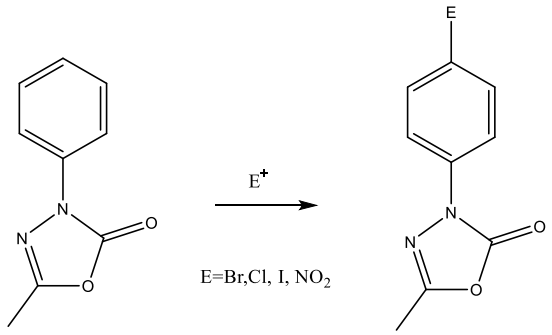
Table 1: Electronic effects of the oxadiazolinone ring system upon an attached benzene ring

It is evident that the greatest effect of the oxadiazolinone ring system is on the ortho position of the attached phenyl ring, with a shift of -10.44 ppm. The negative value denotes an upfield shift, thus supporting the notion that the oxadiazolinone ring system is an electron donating substituent when attached through the N-3 position. Further support for the resonance

donating effect of the oxadiazolinone is the observation that the *para* position also is shielded relative to benzene.

ii. Reactions of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with electrophiles

With an adequate amount of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) prepared, the reactions of **17** with electrophiles were explored with a view to extending the scope of the processes examined briefly in the Turnbull laboratory previously (Scheme 31). These modifications will be discussed in the following subsections.

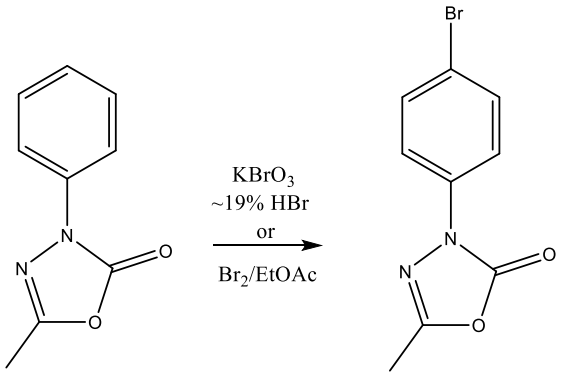


Scheme 31: Reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**) with electrophiles

a. Bromination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17)

The synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) from **17** with potassium bromate or bromine in ethyl acetate had been explored previously by two Dutch interns, Gerritsen and Klaasen, in 2014 and 2015, respectively [Scheme 32]. <MI14A;MI15B> However, with the time constraints under which they operated, they were unable to fully optimize the reaction conditions. In addition, while the *para*-bromo species was the major product in these cases, it was of interest to determine whether or not it was possible to effect halogenation at the *ortho*- position or at multiple sites on the phenyl ring. It was therefore

elected to re-explore these reactions with modifications to various reaction parameters, as well as try an alternative method for bromination using N-bromosuccinimide (NBS).

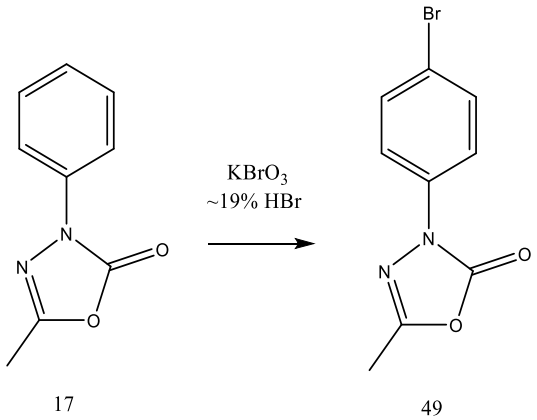


17 49

Scheme 32: Synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**)

b. Bromination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17) with potassium bromate and ~19% HBr

In Gerritsen and Klaasen's procedure, 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) in ~19% hydrobromic acid was reacted with 2 equivalents of potassium bromate for 1 hour (Scheme 33).



17 49

Scheme 33: Synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**) with $KBrO_3$ in ~19% HBr

Entry	Equivalents of $KBrO_3$ used	Time (hour)	Total Yield %*	GC % ratio of product to starting material (Crude)	Melting point (°C)
1	1	0.5	59 %(crude)	36:64	–
2	1.1	1	40	88:12	125-126
3	1.1	2	62	93:7	125-126
4	1.5	0.5	41	76:24	118-120
5	5	0.5	64	97:3	125-126

*Purified yield unless otherwise noted

*Table 2: Results of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**) with KBrO3 and ~19% HBr*

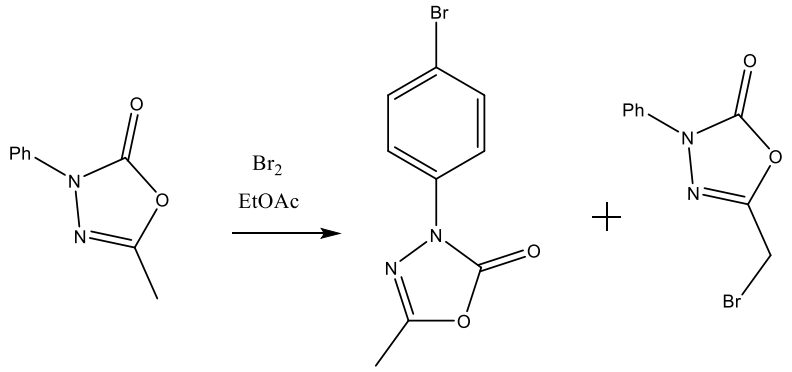
After workup and recrystallization from ethanol, 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) was isolated with a trace amount of starting material present. However, in the present work, when this process was repeated, the initial purity of the product was low due to the presence of a significant amount of starting material, **17** (observed by GC-MS). It was therefore elected to modify the amounts of reagent and reaction times employed in an attempt to obtain full conversion to the desired product **49** and the results of these studies are shown above in Table 2.

As seen in Table 2, it should be noted that the total percent yields are for the recrystallized products, unless otherwise specified, and the GC-MS studies were performed on the crude products. Further, it is clear from the results obtained that the amount of $KBrO_3$ used in the reaction has a direct effect upon the purity of the product formed. When the reaction

time was kept constant at 0.5 h and the equivalents of potassium bromate used were adjusted (Entries 1, 4 and 5), the relative amount of the para-bromo product **49** increased and that of the starting material **17** decreased. Thus, with 5 equivalents of $KBrO_3$ the crude product was composed of 97% of the desired product and the latter was isolated in 64% yield after recrystallization. Despite this success, other changes to the conditions were examined. For example, when, 1.1 equivalents of $KBrO_3$ were used a slight difference was observed in the ratio of product/starting material obtained when the time was varied (Entries 2 and 3). With a 1-hour reaction time there was an 88% conversion to **49** (the rest being starting material), while with a 2-hour reaction time there was a 93% conversion to **49** (the rest being starting material).

Thus, it is evident from the reactions performed that the use of 5 equivalents of $KBrO_3$ for 0.5 hours provided the best conditions for the preparation of the desired product, **49**. However, the differences in purity and overall yield obtained using 1.1 equivalents of reagent for 2 hours and 5 equivalents for 0.5 hours (Entries 3 and 5, respectively) are relatively minor and, for large-scale reactions, it might be possible to save reagent costs by using lesser amounts of potassium bromate. Some of the variations in product yield and purity (especially relative to the previous results from the Turnbull laboratory) are undoubtedly due to the heterogeneous nature of the reaction, which would certainly explain why greater amounts of reagent or longer reaction times had positive effects. While the recrystallized percent yields could have been better, a sufficient amount of pure product was obtained to use in further studies.

c. Bromination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17) with bromine in ethyl acetate

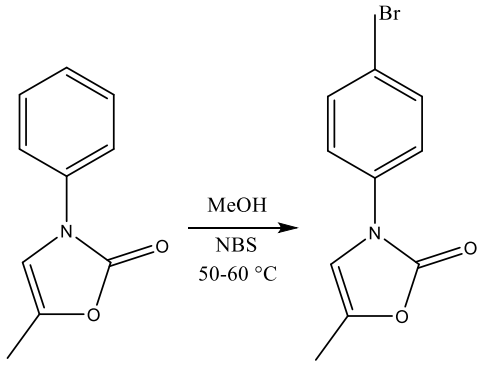


Scheme 34: Synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**) using bromine in ethyl acetate

For the reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with bromine in ethyl acetate shown in Scheme 34, it was opted to start with the same amount of bromine used by Klaasen, *viz.* 3 equivalents. The reaction was monitored by TLC and stopped after 2 hours when it appeared that all of the starting material had been converted to a major product. After work up and recrystallization from ethanol, the *para*-bromo product **49** was obtained as colorless crystals in a 68**%** yield. While not quite as high a yield as reported by Klaasen (76**%**), nevertheless, it was a satisfactory starting point for further exploration. For the latter, it was elected to try fewer equivalents of bromine, since bromine is an expensive, hazardous chemical that can be difficult to handle. Unfortunately, when 2 equivalents of bromine were used in the standard procedure, even after a reaction time of 24 hours, full conversion to **49** was not observed (monitored by TLC). GC-MS analysis of the crude product showed a product distribution consisting of 52% of the desired *para*-bromo species **49**, 47% of the starting material **17**, and 1% of 5-bromomethyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**48**). It was clear that reducing the amount of bromine, even for longer reaction times, did not have the desired

effect and, accordingly, 3 equivalents of bromine were used whenever this approach was employed subsequently.

d. **Bromination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one** (**17**) **with N-bromosuccinimide**



17 49

Scheme 35: Synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**) using NBS

For the reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with NBS (as shown in Scheme 35), initially, 2 equivalents of reagent were employed for 24 hours at room temperature. However, the product obtained had a crude yield of approximately 35% with only a 26% conversion to the desired product **49**, and the rest comprising unreacted starting material **17** (as evidenced by GC-MS). Accordingly, it was elected to employ 4 equivalents of NBS (added over a 4-hour period). After 24 hours and appropriate workup, an oil was obtained, which proved to be a multiple component mixture containing the *para*-bromo species **49** (28%), unreacted starting material **17** (4%), and multiple other unidentifiable components (GC / MS evidence). Since bromination with $KBrO_3$ and Br_2 proved to be more efficient routes to **49**, no further study of the reaction of **17** with NBS was pursued.

The pure *para*- bromo product **49** had a sharp melting point (125-126°C), which was considerably higher than that reported by Badami (111-112°C). However, the structure and purity were confirmed by GC-MS and $^{1}H/^{13}C$-NMR analyses. The IR-spectrum showed the expected C=O absorption at 1796 cm^{-1}, which is shifted slightly higher than a typical carbonyl

due to the strain of the oxadiazolinone ring system and because of its carbamate-like functionality (Appendix C).

Further, the mass spectrum showed the expected molecular ion peaks at 254/256 m/z (signifying the presence of a bromine atom) and the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed (Figure 10).

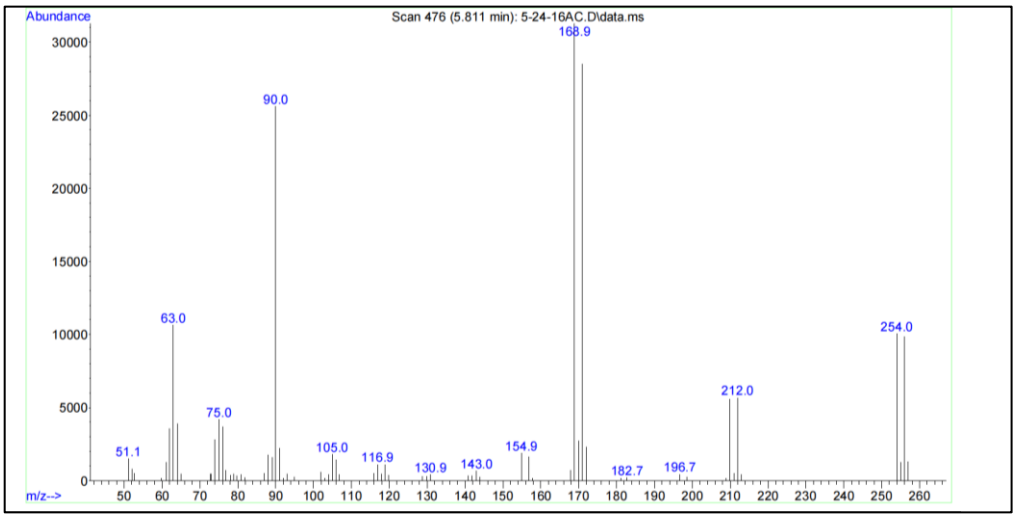


Figure 10: Mass spectrum of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**)

The ^{1}H-NMR spectrum of **49** showed 4 signals, a singlet (3H) at 2.36 δ for the methyl protons and, in the aromatic region, a (2H) doublet at 7.73 δ and another (2H) doublet at 7.53 δ; a clear indication of *para*-substitution (Appendix D). Comparison of this ^{1}H-NMR spectrum with that of the parent 3-phenyl oxadiazolinone **17** indicates that the presence of a bromine atom on the aromatic ring has little effect on the system. In general, since the halogen is both inductively withdrawing and resonance donating these two characteristics counterbalance each other and provide little effect on the aryl ring.

As expected for **49** the ^{13}C-NMR spectrum showed 7 signals, 1 signal for the methyl group, 4 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine (Figure 11).

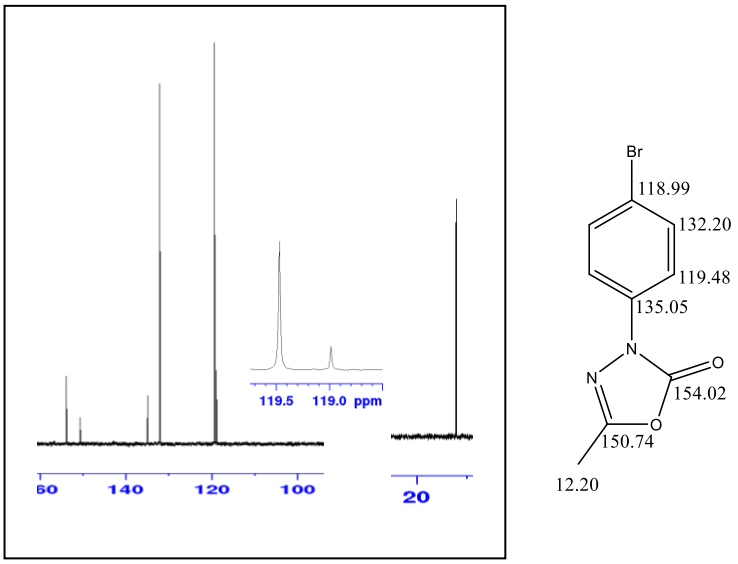
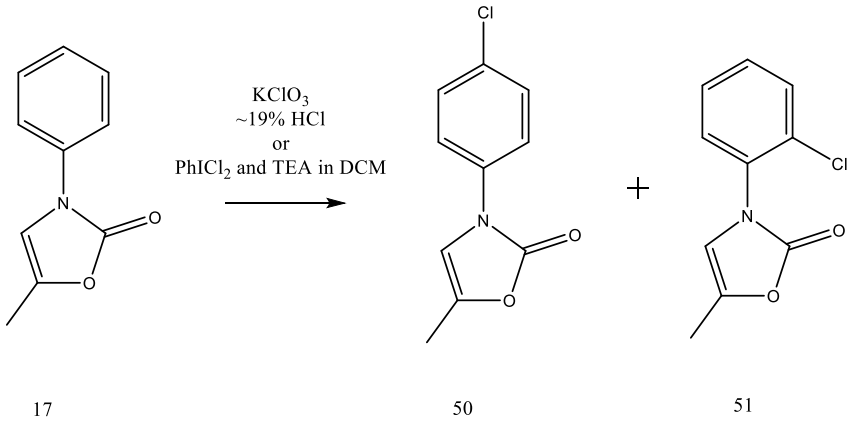


Figure 11: Carbon NMR spectrum of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**)

iii. Chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17)

The attempted synthesis of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**) from **17** using potassium chlorate in ~19% hydrochloric acid or $PhICl_2$ and TEA in DCM (Scheme 36) had been explored previously by two Dutch interns, Gerritsen and Klaasen, in 2014 and 2015, respectively. In each case their results were unsatisfactory in that a mixture of mono-chloro products was obtained. These were assumed to be the *para*-chlorophenyl- and *ortho*-chlorophenyl- oxadiazol-2(*3H*)-one products **50** and **51**, respectively. <MI2014A; MI2015B>



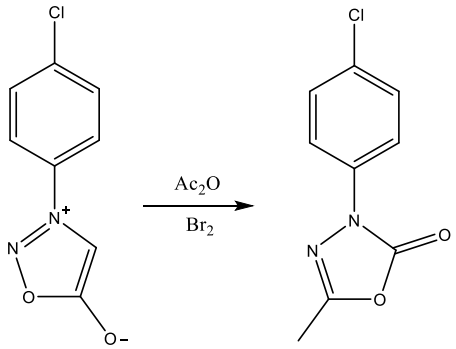
Scheme 36: Gerritsen and Klaasen's chlorination of 5-methyl-1,3,4-oxadiazol-2(*3H*)-one(**17**)

However, even though the *para*-chloro species **50** appeared to be the major product in these cases, it could not be isolated successfully since significant amounts of both starting material and what was presumed to be the *ortho*-chloro species (GC / MS evidence) were present in each sample. In the present work it was therefore elected to re-explore these reactions with modifications to various reaction parameters as well as try alternative methods for chlorination *e.g*. N-chlorosuccinimide (NCS) and iodine monochloride (ICl).

a. Synthesis of 5-methyl-3 (4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (50) from 4-chloro-3-phenylsydnone (52)

Before attempting chlorination reactions with **17** it was deemed important to have an authentic sample of the *para*-chloro species **50** available for comparison purposes. Accordingly,

it was decided to utilize the modification of the Stansfield / Badami procedure developed previously in the Turnbull laboratory (Scheme 30 and corresponding discussion) for the conversion of 3-(4-chlorophenyl)sydnone (**52**) to 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**) using bromine in acetic anhydride at room temperature (Scheme 37). Thus, 3-(4-chlorophenyl)sydnone (**52**) [readily available in the Turnbull laboratory] was treated with 1.5 equivalents of bromine in acetic anhydride and refluxed at 70°C for 2 hours. Subsequently, the cooled solution was poured slowly into cold water and the resulting precipitate was dried and then recrystallized from ethanol to yield the desired *para*-chloro oxadiazolinone **50** in 69% yield. This purified material was used also for further nitration studies to be discussed later.



52 50

Scheme 37: Synthesis of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**) from 3-(4-chlorophenyl)sydnone (**52**)

The pure product had a sharp melting point (122-123°C) but displayed a higher melting point compared to Badami's reported result (98-99°C). However, the identity of the compound is not in question since the structure and purity were confirmed by GC-MS and $^{1}H/^{13}C$-NMR analyses. The mass spectrum showed molecular ion peaks at 210/212 m/z (the m/z and peak heights signifying a chlorine present), the expected molecular mass for the chloro compound **50**. Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44

m/z) then $CH_3C{=}N$ (41 m/z)] were observed, in which the chlorine remained present on the aryl ring until after the loss of both carbon dioxide and the imine (Appendix E).

The IR-spectrum showed the expected C=O absorption at 1799.87 cm^{-1}, which is shifted higher than a typical carbonyl due to the strain of the oxadiazolinone ring system and because of its carbamate-like functionality (Appendix F).

The ^{1}H-NMR spectrum showed 3 signals, a singlet (3H) at 2.36 ppm for the methyl protons and, in the aromatic region, a double doublet (2H) at 7.38 ppm, and a double doublet (2H) at 7.79 ppm, indicative of *para*-substitution (Appendix G).

Further, as expected for the chloro compound **50**, the ^{13}C-NMR spectrum showed seven signals, one for the methyl group, four for the aromatic carbons, and two signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine (Figure 12). The carbon connected to the chlorine is further downfield compared to the comparable carbon atom in the unsubstituted oxadiazolinone **17** due to the electronegative disposition of the attached chlorine atom.

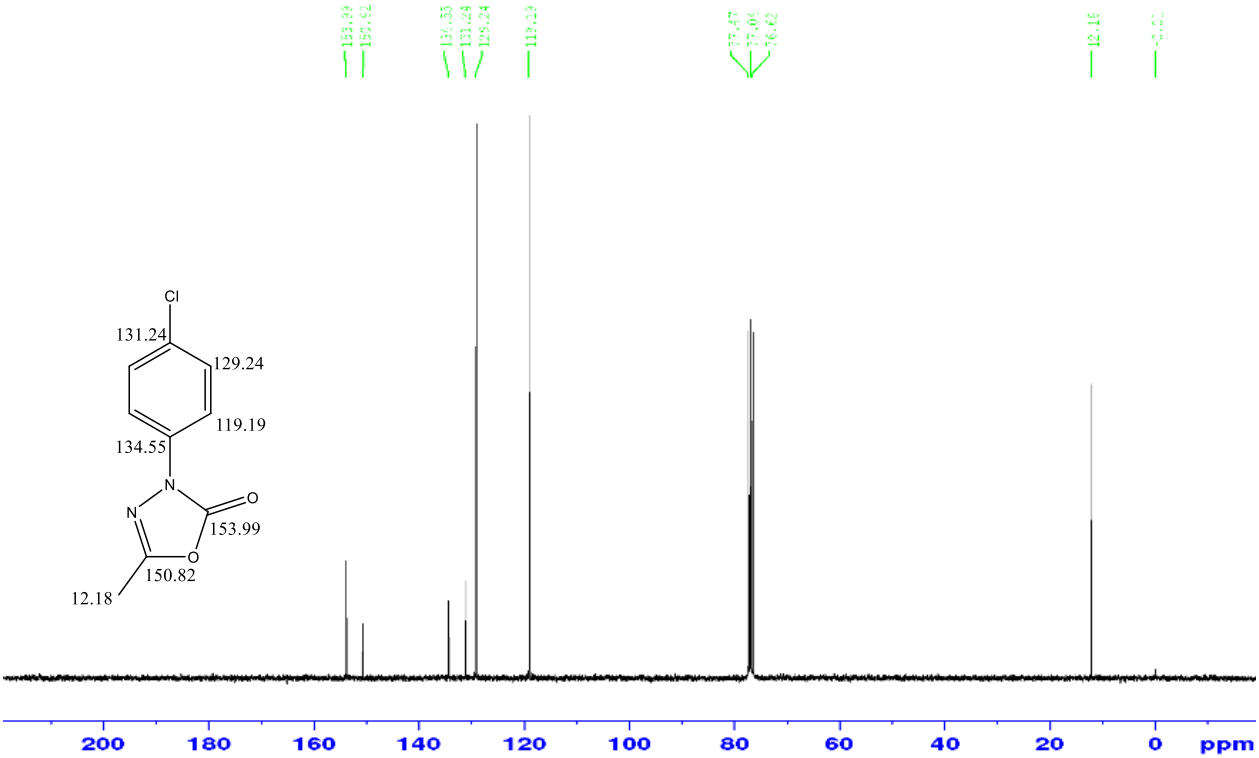
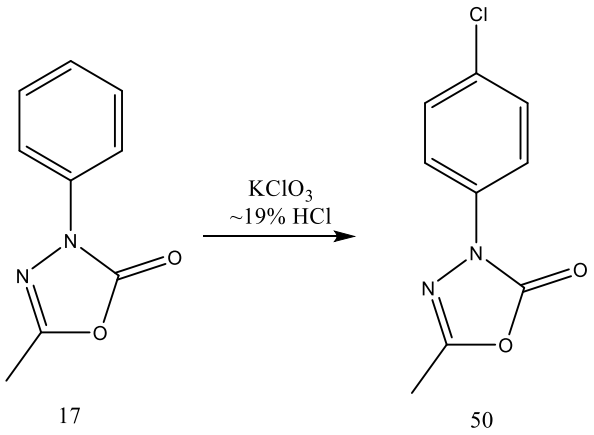


Figure 12: Carbon NMR spectrum for 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**)

b. Chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17) with potassium chlorate in ~19% HCl

In Klaasen's procedure, 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) in ~19% hydrochloric acid was reacted with 5 equivalents of potassium chlorate for 24 hours (Scheme 38). After workup, a mixture of products was obtained, with 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**), 5-methyl-3-(2-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**51**) [presumably] and unreacted starting material **17** all present. The major product was the *para*-chloro product **50** (GC / MS evidence and TLC comparison with an authentic sample prepared herein).



Scheme 38: Attempted synthesis of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(3H)-one (**50**) with $KClO_3$ in ~19% HCl

In the present work, using Klaasen's conditions, the initial yields were extremely low, however, only a very small amount of unreacted starting material **17** was present (observed by GC-MS). Accordingly, these results seemed to offer the possibility for isolation of **50** if the yield and conversion could be improved as a first step. To achieve the latter, it was elected to try various amounts of reagent and various reaction times as shown below in Table 3.

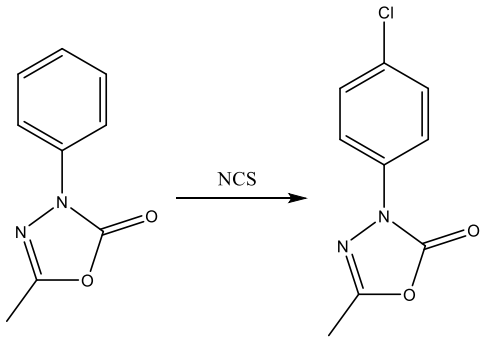
Entry	Equivalents of $KClO_3$ used	Time (h)	Crude % yield of 50	GC ratio of 50 to starting material
1	1.1	1	41	95:5
2	1.1	1.5	24	93:7
3	1.1	2	45	92:8
4	5.0	0.5	<20	97:3

Table 3: Results of chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (17) with $KClO_3$

As seen in Table 3, in the chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**) with $KClO_3$ in ~19% HCl, crude product yields did not exceed 45%. Using 1.1 equivalents of $KClO_3$ (Entries 1, 2, and 3) and varying the reaction time did little to enhance the process. Oddly

enough, more starting material was present as the reaction time was increased, however, it should be noted that the amounts of starting material present were small and are likely to be within the margin of error. Using five equivalents of $KClO_3$ (Entry 4) and a 0.5-hour reaction time did reduce the amount of unreacted starting material to around 3%, however, the crude reaction product was recovered in extremely low yield. The lack of formation of the *ortho*-chloro species (GC evidence) is in stark contrast to Klaasen's findings and may be due to the changes in reaction times. Klaasen used a reaction time of 24 hours, as opposed to the maximum time of 2 hours used in the current research. It is possible that the longer reaction time allowed for the formation of the *ortho*-chloro species, while the major product was the *para*-chloro species due to the less hindered nature of the *para*-position. Though there was no evidence for the formation of the *ortho*-chloro species in the present work, this was scant consolation since the *para*-chloro species was still not successfully isolated due to the very poor, crude yields obtained. It was therefore elected to continue exploration of chlorination with other reagents.

c. Chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with N-chlorosuccinimide (NCS)

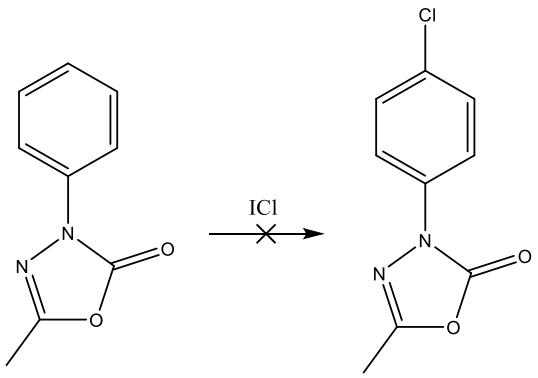


17 50

Scheme 39: Attempted synthesis of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(3H)-one (**50**) using NCS

For the reaction of the oxadiazolinone **17** with N-chlorosuccinimide it was elected to employ 2 equivalents of the reagent, initially at room temperature (Scheme 39). When no reaction was observed (TLC evidence), the mixture was refluxed, ultimately for 24 hours. TLC examination indicated that there was a significant amount of starting material present and, accordingly, another equivalent of NCS was added and the reaction was continued for 1 hour more. Upon workup, the oil which was obtained was shown by GC / MS analysis to contain only 7% of the desired product, a trace amount of starting material and a substantial amount of other unidentified compounds. It was concluded that this method of chlorination would not be amenable to further study and, accordingly, it was decided to move on to the use of an alternative reagent.

d. Attempted chlorination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17) with ICl in DCM



17 50

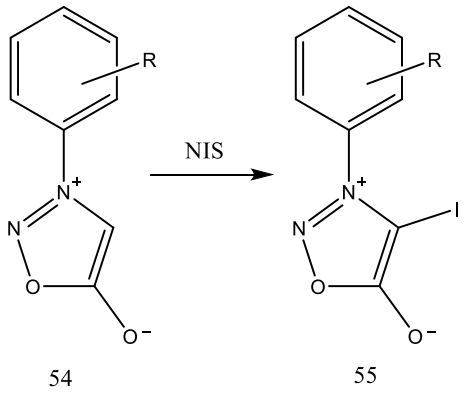
Scheme 40: Attempted synthesis of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**) with ICl

While the iodination of sydnones with iodine monochloride (ICl) in acetic acid was reported by Dumitrascu in 1997 <1997LA2613>, it was only very recently that Tumey and Owens in the Turnbull laboratory demonstrated that chlorination could be effected with the same

reagent, simply by modifying the solvent to dichloromethane (DCM) <2017OPP59>. The latter result presented an opportunity for the present research and it was opted therefore to employ ICl in DCM as an avenue for the chlorination of the phenyl ring in the oxadiazolinone species **17** (Scheme 40). Unfortunately, using the optimized conditions reported by Tumey and Owens, *viz*. 3 equivalents of ICl for 30 minutes at room temperature under nitrogen, with **17** showed no sign of conversion to the chloro species **50** and only unreacted starting material was recovered. Clearly, the phenyl ring in **17** is only modestly activated by the attached oxadiazolinone and the ICl reagent is not polarized sufficiently in DCM to permit reaction. Further, given the instability of the ICl reagent, it was not deemed feasible to heat the reaction mixture in an attempt to drive the chlorination process and, accordingly, the reaction was not examined further.

iv. Iodination of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (17) with N-iodosuccinimide

In addition to previously synthesized halogenated oxadiazolinones viz., 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) and 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**), it was opted to also synthesize 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**). As discussed earlier, previous halogenated oxadiazolinones were prepared by electrophilic aromatic substitution in a manner similar to that for the synthesis of halogenated sydnones. Therefore, it was decided to adapt the optimized procedure for iodination of a variety of *3*-arylsydnones **54** with N-Iodosuccinimide to yield the corresponding iodosydnones **55** [Scheme 41], developed in 2013 by Dan Brown from the Turnbull laboratory <2013SC3233>.

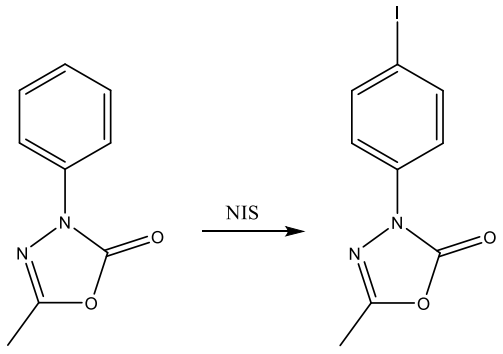


54 55

Scheme 41: Iodination of *3*-arylsydnones (**54**) with NIS

Thus, 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) [previously synthesized as discussed earlier] in acetic acid was treated with 3.5 equivalents of N-Iodosuccinimide and refluxed at 70°C for 24 hours. Subsequently, the cooled solution was poured slowly into ice**,** extracted with dichloromethane and the combined extracts dried and evaporated to yield a brown solid that

was recrystallized from ethanol to yield the desired *para*-iodo oxadiazolinone (**53**) as beige needles in 36% yield (Scheme 42). Despite the low yield, this purified material was used also for further nitration studies to be discussed later.



17 53

Scheme 42: Synthesis of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**) using NBS

The pure *para*- iodo product **53** had a sharp melting point (98-99°C) and the structure and purity were confirmed by GC-MS and $^{1}H/^{13}C$-NMR analyses. The mass spectrum showed the expected molecular ion peaks at 302 m/z and the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed (Figure

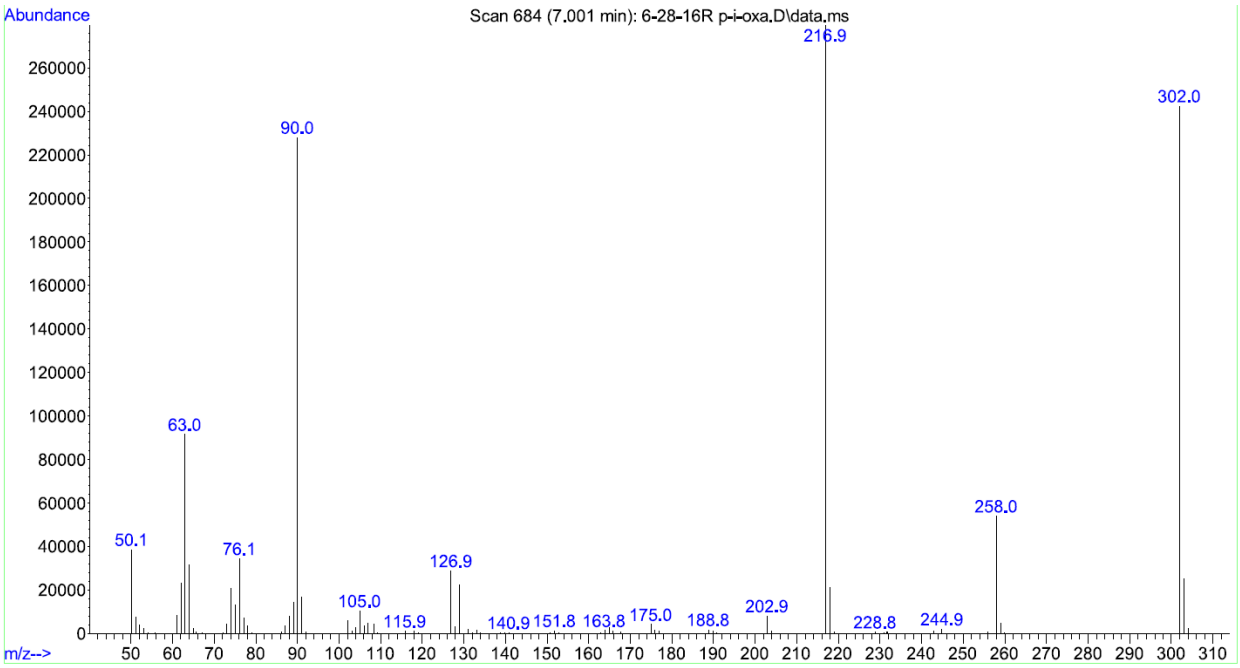


Figure 13: Mass spectrum of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**)

The ^{1}H-NMR spectrum showed 4 signals, a singlet (3H) at 2.36 δ for the methyl protons and, in the aromatic region, a (2H) doublet at 7.73 δ and another (2H) doublet at 7. 61 δ; a clear indication of *para*-substitution (Appendix H). Comparison of this ^{1}H-NMR spectrum with that of the parent 3-phenyl oxadiazolinone **17** indicates that the presence of an iodine atom on the aromatic ring has little effect on the system. In general, since the halogen is neither particularly inductively withdrawing or resonance donating these two characteristics counterbalance each other and provide little effect on the aryl ring.

As expected for **53** the ^{13}C-NMR spectrum showed 7 signals, *viz*., 1 signal for the methyl group at 12.21 ppm, 4 signals for the aromatic carbons at 89.89 ppm, 119.71 ppm, 135.78 ppm and 138.25 (the significantly shielded signal at 89.89 is the C with the iodine attached), and 2 signals for the characteristic oxadiazolinone ring carbons at 150.74 ppm and 154.02 ppm, representing the carbonyl and the imine carbon atoms (Figure 14).

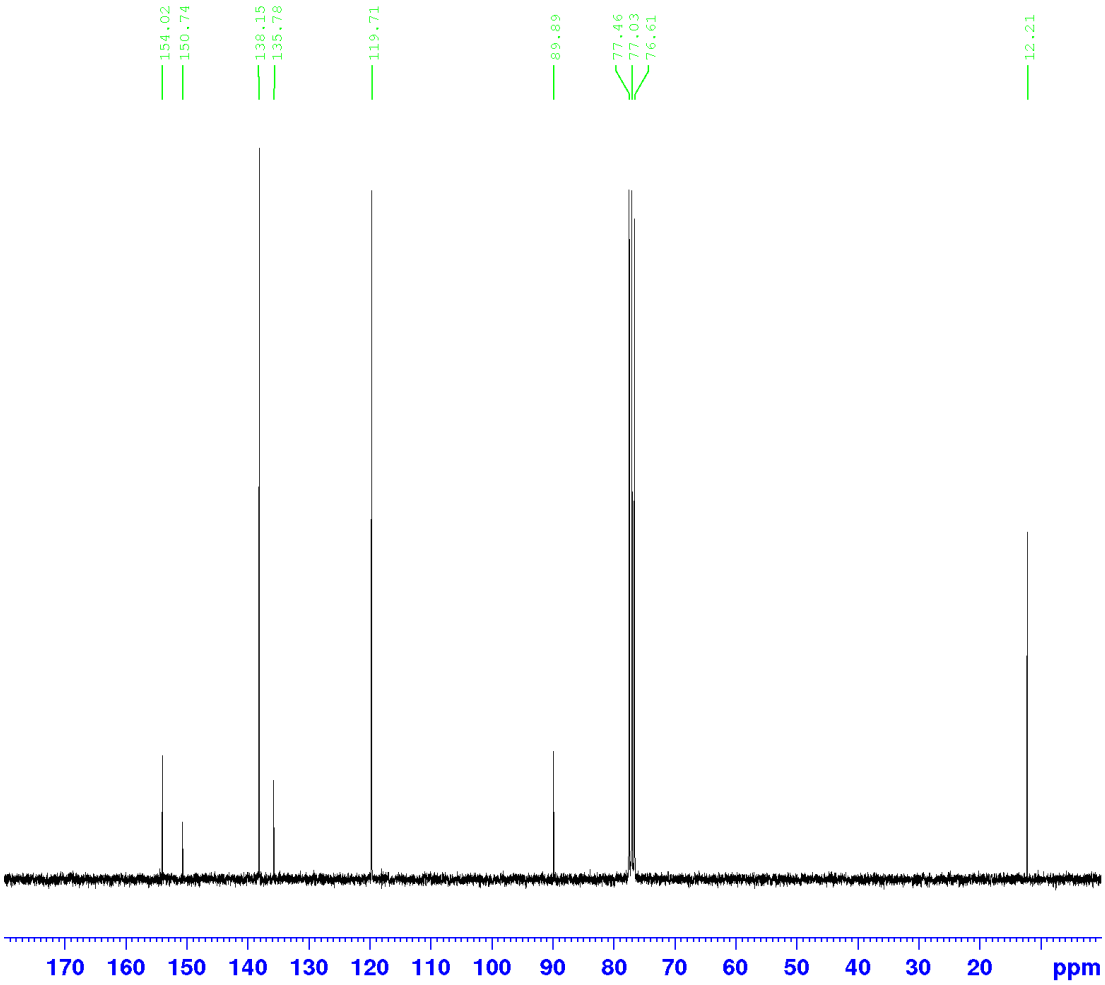
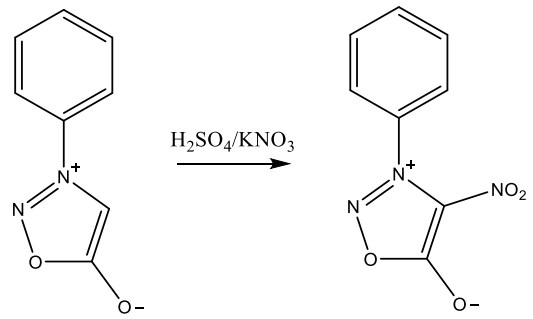


Figure 14: Carbon NMR spectrum of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**)

v. Nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with potassium nitrate and sulfuric acid

The method employed for the nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) was adapted from previous nitration studies of sydnones. Nitration of 3-phenylsydnone (**16**) was first reported by Baker et al. in 1950 <50JC1542>, in which reaction occurred at the C-4 position to generate 4-nitro-3-phenylsydnone (**56**) [Scheme 43]. In this procedure, 3-phenylsydnone (**16**) in concentrated sulfuric acid at −10 °C was reacted with a mixture of concentrated sulfuric and nitric acids added dropwise. After 0.5 hour, the reaction was quenched by pouring it onto ice, the precipitate collected and washed with base and then water. The product, 4-nitro-3-phenylsydnone (**56**), was recrystallized from dioxane and isolated as light-yellow plates in 24% yield.



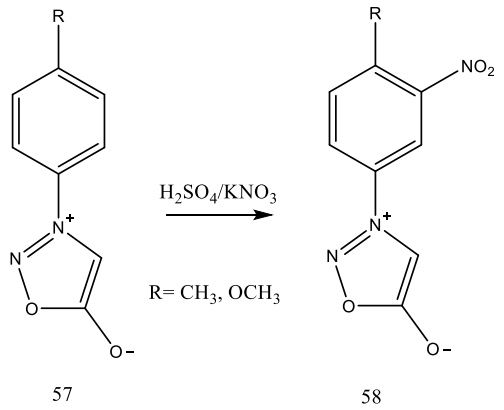
16 56

Scheme 43: Baker et al. nitration of 3-phenylsydnone (**16**)

In contrast to the 3-(ortho-, meta-, or para- nitrophenyl) sydnones, 4-nitro-3-phenylsydnone (**56**) is unstable, cannot be recrystallized in alcohol and decomposes when heated with dilute

acid. Though electrophilic aromatic substitution with other electrophiles also occurs at the C-4 position of **16**, the nitration reaction is unique because the nitro group is an extremely strong electron-withdrawing group.

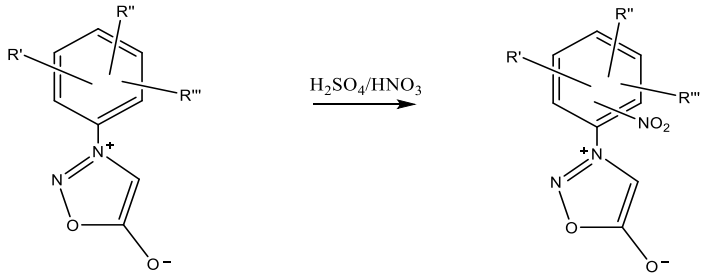
In 1969, Weintraub and Bambury <69TL579> repeated the work of Baker et al. and achieved the same results. However, upon extension to activated aryl sydnones (**57**, R = Me, OMe), contrary to the situation with 3-phenylsydnone (**16**), nitration took place on the aryl ring to yield the corresponding *meta*-nitro compounds **58 <**Scheme 44>. This was the first report of electrophilic aromatic substitution on the attached aryl ring in competition with the open sydnone C-4 position.



57 58

Scheme 44: Weintraub and Bambury nitration of 3-arylsydnones **57**

In 1995, Turnbull et al. <96JHC486> further extended the sydnone nitration studies to a variety of di- and tri- methylphenylsydnones **59** <Scheme 45>. Once again, there was no evidence of nitration at the C-4 position and all of the products were aryl ring substituted, mono-nitro compounds **60**.



59, a, R'= 2-CH_3 R"= 4-CH_3
b, R'= 3-CH_3 R"= 4-CH_3
c, R'= 2-CH_3 R"= 5-CH_3
d, R'= 2-CH_3 R"= 3-CH_3
e, R'= 2-CH_3 R"= 6-CH_3
f, R'= 2-CH_3 R"= 5-CH_3
g, R'= 2-CH_3 R"= 4-CH_3

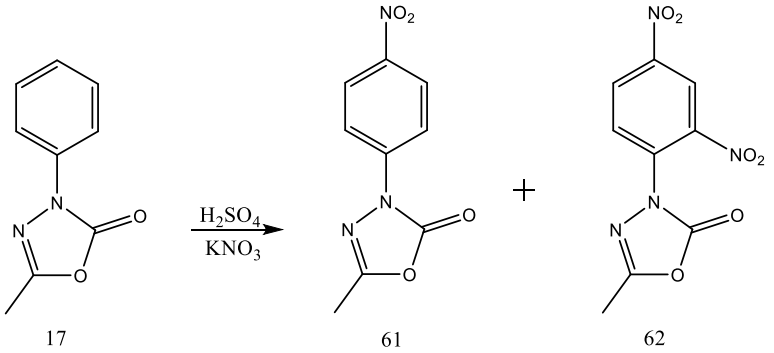
60, a, R'= 2-CH_3, R"= 4-CH_3, 5-NO_2
b, R'= 3-CH_3, R"= 4-CH_3, 5-NO_2
c, R'= 2-CH_3, R"= 5-CH_3, 3-NO_2
d, R'= 2-CH_3, R"= 3-CH_3, 5-NO_2
e, R'= 2-CH_3, R"= 6-CH_3, 3-NO_2
f, R'= 2-CH_3, R"= 5-CH_3, 2-NO_2
g, R'= 2-CH_3, R"= 4-CH_3, 3-NO_2

Scheme 45: Turnbull nitration of substituted 3-arylsydnones **59**

The methyl groups are inductively donating, thus, activating the aryl ring and, depending on the position of the methyl groups on the aryl ring, electron density appears to be increased mainly at the meta positions relative to the sydnone ring (as determined by the sites of nitration). The sydnone ring is both weakly resonance withdrawing and strongly inductively withdrawing upon the attached aryl ring. Accordingly, the aryl ring is deactivated to reaction with electrophiles and, given the substantial activation at the sydnone C-4 position, in general, this deactivation prevents reaction on the aryl ring, even when weakly activating groups are attached to the 3-aryl substituent. However, the conditions for nitration appear unique in this regard, providing nitroaryl species rather than 4-nitro sydnones, possibly because the presumed nitronium intermediate is a “harder”, more reactive species than those involved in halogenation or acylation of sydnones. This intriguing switch in reactivity offers a valuable avenue to otherwise difficultly accessible sydnones.

As mentioned earlier, the general sydnone nitration procedure using H_2SO_4/KNO_3 was extended to the present oxadiazolinone study. Thus, in 2015, a Dutch intern, Jimmy Klaasen, examined the nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**). <2015MI(B)>

However, with the time constraints inherent in his intern period, he was not able to fully optimize the reaction conditions. In addition, while the *para*-nitro species **61** was the major product, 3-(2,4-dinitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**62**) was also observed in small quantities (Scheme 46).



Scheme 46: Nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (17)

Again, due to time constraints, the latter was not isolated for characterization, but its presence was inferred from the GC/MS analysis. Accordingly, it was a major goal in this thesis work to re-examine the process with the intention of optimizing the preparation of both the *para*-nitro compound 61 and di-nitro species **62**. With this in mind, it was elected to make modifications to various reaction parameters, *viz*., reaction time and equivalents of KNO_3 employed. These modifications and results are explicitly shown later in Table 4.

To establish a baseline for further work, it was important to repeat the nitration experiment using the conditions reported previously. Accordingly, 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) was treated with 1.1 eq. of KNO_3 in sulfuric acid at 0°C for 1.5 h. After the standard work-up it was clear from GC analysis of the crude product (Fig. 15) that there were 4 components, unreacted starting material, with a retention time of 3.42 minutes, 3-(4-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**61**), with a retention time of 7.3 minutes, by comparison with authentic samples, and 2 others to be discussed below.

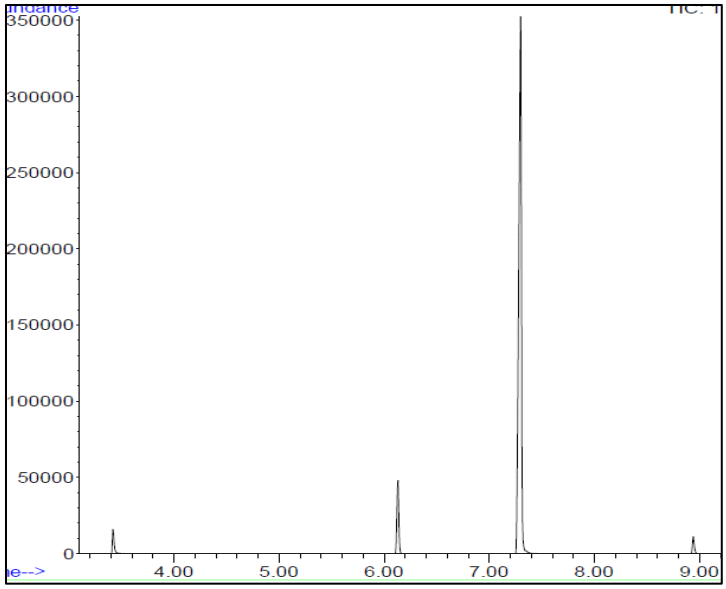


Figure 15: GC of a crude sample of 5-methyl-3-(4-nitrophenyl)- 1,3,4-oxadiazol-2(3H)-one (61)

Based on the molecular mass peaks, MS analysis suggested that the other 2 product components were 5-methyl-3-(2-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**61**) and 3-(2,4-dinitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**62**). Both **62** and **63** have identical parent ions (221 m/z), however, their GC retention times are sufficiently different to allow distinction between them, *viz*. 7.3 and 6.2 minutes, respectively. The di-nitro species elutes from the GC at 8.9 minutes and shows a molecular ion peak at 265.9 m/z, as expected. Further support for these findings will be discussed in more detail later.

As mentioned above, using Klaasen's reaction conditions to nitrate 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (**17**), viz., 1.1 eq. of KNO_3 in sulfuric acid at 0°C for 1.5 hr, gave three products [including the targeted 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(3*H*)-one (**61**)]. Table 4, shown below, charts the changes in product ratio with modifications to the reaction conditions.

Entry	Eq. KNO_3 / addition time (min)	Time (Hr)	Temp (°C)	GC % of 61	GC % of 63	GC % of 62	GC % of 17
1	1.1/10	1.5	0	86	8	2	4
2	1.1/10	1.5	-10 to -5	95	<1.5	<1	3
3	1.05/10	1.5	-10 to -5	93	5.5	<1	<1
4	1.05/10	3	-15 to -10	94	5	<1	----
5	1.1/20	1.5	-15 to -10	100	----	----	----

Table 4: Reaction conditions and crude yields from nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (17)

When comparing entry 1 to entry 2, it is apparent that the lower reaction temperature impacted the product distribution, viz., an increase of the para-nitro species **61** by 9**%**. It is logical to assume that the lower temperature shifts the equilibrium to the desired product since the reaction is exothermic (nitric acid is generated when the sulfuric acid and the potassium nitrate are reacted). When the equivalents of nitrating reagent were slightly decreased, as is the case in entry 3 (compared to entry 2), not surprisingly there was little difference in the final product distribution. In entry 4, with the equivalents and the reaction temperature the same as entry 3, the reaction time was doubled from 1.5 hours to 3 hours in the expectation that more time would allow for more collisions between the nitronium ions (made in situ) and the oxadiazolinone **17** molecules, thus ensuring that all the starting material would be reacted to yield the desired product **61**. However, even with an extended reaction time, the product distribution was not greatly affected. Finally, in entry 5, when the nitrating reagent was added over a period twice as long, in an attempt to further control the heat content of the system,

there was a complete conversion to the desired para-nitro species **61**. Therefore, the optimized procedure involved use of a reaction temperature between -15 to -10 °C and 1.1 equivalents of nitrating reagent adding over 20 minutes with a reaction time of 1.5 hours. The best, pure yield obtained using this optimized procedure was 78%.

The pure product **61** had a sharp melting point of 123-124°C, which was significantly higher compared to Badami's reported results (86-87°C). Despite the lack of congruency of the melting points, the structure was confirmed by GC-MS, ^{1}H-NMR, and ^{13}C-NMR analysis. Thus, the mass spectrum showed a molecular ion peak of 221 m/z, which is the molecular mass of the *p*-nitro species **61**. The characteristic breakdown of the oxadiazolinone ring (*viz*. loss of CO_2 then $CH_3C{=}N$) was also observed. As evidenced by the gas chromatogram, the retention time for **61** was 7.3 minutes, easily distinguishing it from any other analogs (Appendix H).

The IR-spectrum showed a C=O absorption at 1818.87 cm^{-1} which is shifted to a higher wave wavelength compared to 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one **17** presumably due to the strong electron-withdrawing effect of the nitro group, thus causing shortening of the carbonyl group. The spectrum also showed absorptions at 1335.83 and 1500.75 cm^{-1} characteristic of a nitro group (Appendix I).

The ^{1}H-NMR spectrum of **61** showed 3 signals, a singlet (3H) for the methyl protons and 2 doublets (2H) in the aromatic region, which are shifted downfield compared to those in the parent compound **17** due to the strong electron withdrawing effect of the nitro group. The 2 doublets in the aromatic region are a clear indication of *para*-substitution (Appendix J).

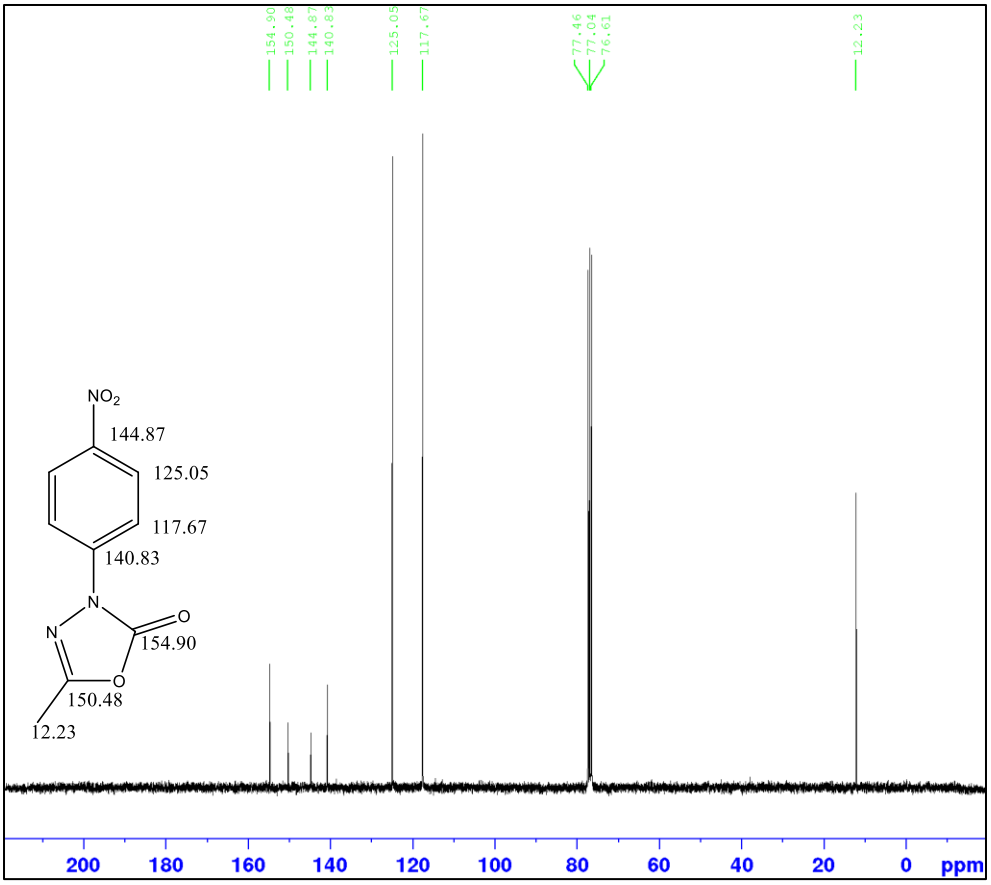


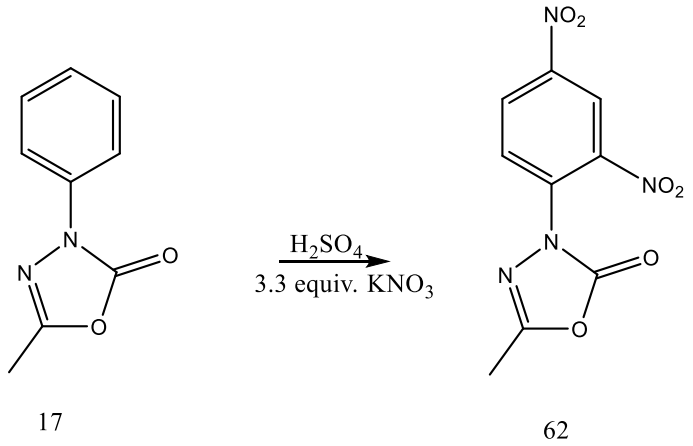
Figure 16: ^{13}C-NMR spectrum of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**61**)

The ^{13}C-NMR spectrum for **61** (Figure 16 above) showed 7 signals, 1 signal for the methyl group (12.23 ppm), 2 signals for the characteristic oxadiazolinone ring carbons (154.90 and 150.48 ppm), and 4 total aromatic carbons (117.67, 125.05, and 144.87 ppm) with the carbon at 144.87 ppm [in comparison with 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**)] being significantly shifted further downfield because of the strong electron withdrawing effect of the nitro group attached to it (Figure 14). The carbons were given assignments based on calculations. The carbons from 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) were used as a baseline and the effect of the nitro group was added <1983MI(C)>. For example, the calculation for the carbon with the nitro group attached, the 4-position, was performed by adding (+19.6), the effect of having a nitro on the ipso carbon <1983MI(C)>, and 125.89 [the value for the 4-

position from 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**)] resulting in 145.49 ppm. The assignments are not definite, however, the calculations are compelling evidence.

vi. Dinitration of 3-phenyl-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (17)

As previously discussed, 3-(2,4-dinitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**62**) was thought to be a by-product from the synthesis of 3-(4-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**61**). Accordingly, it was hoped to synthesize **62** to use as a standard. Extensive literature research uncovered only one previous reference to **62**, *viz*. a German patent <1989GPat>, in which the target molecule was prepared from starting materials already containing the dinitro motif. In addition, the only characterization data reported in the patent were from an IR spectrum. Accordingly, it seemed that our nitration approach from the parent oxadiazolinone **17** would provide a novel avenue to 62 (if successful). Indeed, when the reaction was conducted using 3.3 equivalents of the nitrating reagent, the desired product was obtained in 78% yield as pale-yellow needles after recrystallization from 95% ethanol.



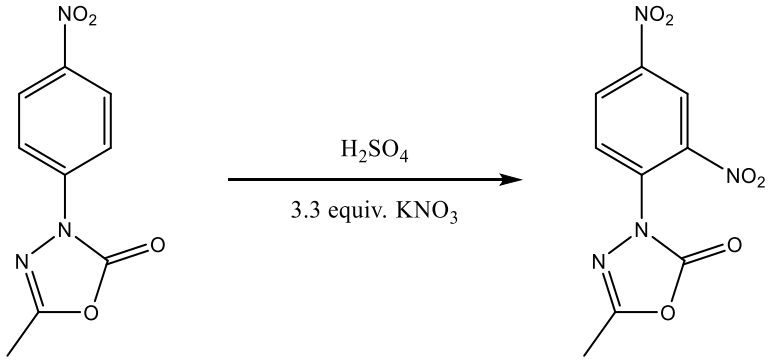
17 62

Scheme 47: Dinitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(3H)-one (**17**)

As discussed earlier in the mono nitration of **17**, **62** was believed to have formed as one of the by-products in that process; therefore, the product from the dinitration of **17** (Scheme 47)

was used as a comparison standard against the by-products from the mono nitration of **17**. Both GC-MS results and thin layer chromatography (TLC) analysis showed the products from both processes to be the same (*viz*. **62**).

In the assumption that the dinitration process involves initial nitration of **17** on the aromatic ring *para* to the oxadiazolinone ring system, the *para-nitro species* **61** was treated with 1.1 equivalents or 3.3 equivalents of nitrating reagent with the expectation that this approach would lead easily to the dinitro species **62**. Accordingly, keeping the same reaction conditions (temperature and time) as those for mono-nitration, **61** was treated with 1.1 equivalents of nitrating reagent. Surprisingly, upon analysis of the product mixture using GC/MS, only 7% conversion to the dinitro species **62** had occurred and the remaining 93% consisted of unreacted starting material. In contrast, when 3.3 equivalents of nitrating reagent were used (Scheme 48), conversion to **62** was100% (GC/MS evidence) and the product was isolated as a yellow solid in 76 % yield.



61 62

Scheme48: Nitration of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**61**)

When comparing the amount of nitrating reagent used in mono nitration of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) versus dinitration, perhaps it is not surprising that the dinitration

would require 3.3 equivalents of nitrating reagent, as the energy required to put on the second nitro group is presumably much greater due to the electron-withdrawing effect of the first nitro group. In addition, with both the oxadiazolinone ring and nitro group present on the benzene ring, it was initially unclear which substituent would take precedence as a directing group. Figure 17 depicts the 2 different arrangements that could result from the nitration of **61**: *viz*. 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**62**) and 5-methyl-3-(3,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**64**). To determine the correct structure resulting from both the dinitration of **17** and the nitration of **61**, the splitting patterns from the ^{1}H-NMR were analyzed. However, it became apparent that both structures (**62**) and (**64**) could fit the observed pattern.

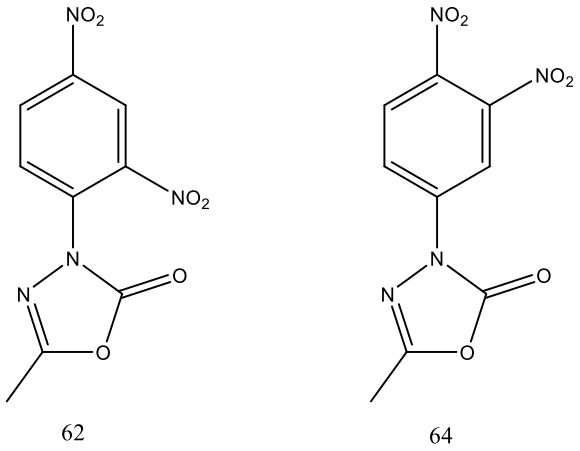
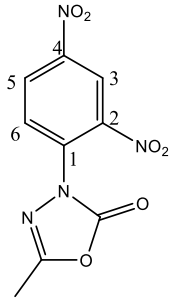


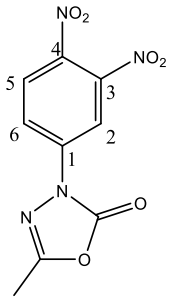
Figure 17: Possible dinitration products from nitration of para nitro oxadiazolinone

Accordingly, the ^{13}C-NMR shifts of both **62** and **64,** with focus on the aromatic region, were extrapolated using the equation, $^{\delta}c_i = {}^{\delta}z_i + x_i$ where $^{\delta}z_i$ represents carbons from the aromatic region of **61** and x_i represents the effect of the nitro group <1983SD120>. For example, the calculation of the 2- position in 5-methyl-3-(3,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**64**) would be: $^{\delta}c_i$ = 112.37= 117. 67 + (- 5.3). The calculated values for **62** and **64** were compared to the ^{13}C-NMR values obtained for the dinitro compound from the nitration of **61**, as seen in Table

5, where the calculated carbons are arranged based on the carbon position while the determined values are organized in ascending order and labeled either quaternary or C-H, based on the degree of attachment on the carbon.



62



64

Carbon position	Calculated ^{13}C-NMR values of **62**	Calculated ^{13}C-NMR values of **64**		Determined ^{13}C-NMR values (dinitration of 17)
1	135.53	140.91		121.37 (C-H)
2	137.27	112.37		125.46 (C-H)
3	119.75	144.65		127.78 (C-H)
4	145.67	139.57		132.68 (quaternary)
5	131.05	125.13		142.03 (quaternary)
6	118.67	123.67		145.59 (quaternary)

Table 5: Comparison of calculated and determined data for dinitro oxadiazolinone **62**

With emphasis on the calculated values of the quaternary carbons of **62** and **64**, viz. 1,2, and 4 or 1,3, and 4 (structures seen with Table 5) the determined ^{13}C-NMR values correlated to both structures. When comparing **64** to the determined values, in the 2- position there is an outlier at 112.37 ppm (the closest corresponding determined value is 121.37 ppm). With calculated values within 5 ppm of the determined values, **62** best represents the correct structure. To further strengthen the latter interpretation, in **62** the positions of the 4-nitro group and oxadiazolinone ring system would make carbon 2 a more electron rich site and therefore, reaction could occur

easily at the 2 position as opposed to carbon 3. Thus, the expected structure would be 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(3H)-one (**62**), in line with the ^{13}C-NMR results. Accordingly, it became of interest to explore the nitration of other substituted aryl oxadiazolinones (detailed later in this thesis) since having multiple points of functionalization could offer valuable avenues to otherwise difficultly accessible oxadiazolinones.

The pure dinitro product **62** had a sharp melting point (127-128°C) and the structure and purity were confirmed by GC-MS and ^{1}H/^{13}C-NMR analyses. The gas chromatogram showed a retention time of 8.9 minutes and the mass spectrum showing a mass peak at 266 m/z, the molecular mass of the expected product **62**. The elution time correlates with the elution time of the by-product from the mono-nitration process.

Further, the characteristic breakdowns of the oxadiazolinone ring (loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z) were also observed, in which the nitro group remained present on the aryl ring until after the loss of carbon dioxide and the imine (Figure 18; Appendix K)

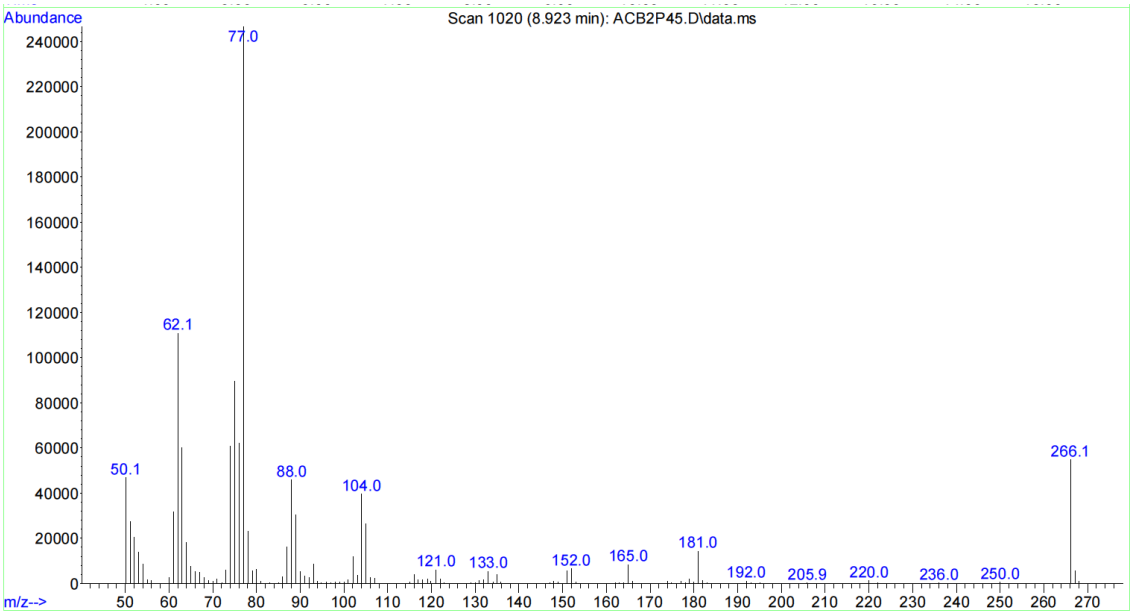


Figure 18: Mass spectrum of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**62**)

The IR-spectrum showed the expected carbonyl absorption at 1785.44 cm^{-1}, which is a slightly higher frequency than a typical carbonyl due to the carbamate-like functionality in the oxadiazolinone ring system and because the nitro groups have a withdrawing effect on the system, thus shortening the C=O bond compared to that of the unsubstituted oxadiazolinone **17** (Appendix L).

The ^{1}H-NMR spectrum (Figure 19) showed 4 signals, a singlet (3H) at 2.41 δ for the methyl protons and, in the aromatic region, a doublet (1H) at 8.05 δ, a double doublet (1H) at 8.55 δ, and a doublet (1 H) at 8.79 δ. The latter are shifted slightly more downfield when compared to the aromatic proton signals in the para-nitro compound **61** due to the strong electron withdrawing effect of the additional nitro group.

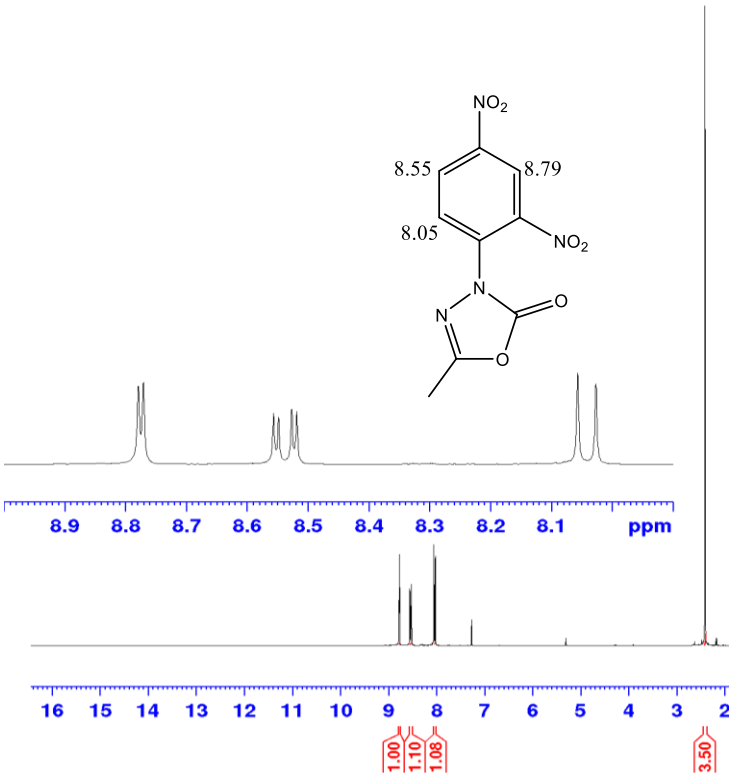


Figure 19: ^{1}H-NMR spectrum of 3-(2,4-dinitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**62**)

As expected for structure **62**, the ^{13}C-NMR spectrum showed 9 signals, 1 signal for the methyl group, 6 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine moieties (Appendix M). As expected, each carbon with a nitro substituent was significantly further downfield compared to those in the unsubstituted oxadiazolinone **17** due to the electronegative disposition of the nitro groups. Initially, rigorous assignment of the individual aromatic carbons proved to be difficult and, therefore, HSQC was performed (Appendix N). The HSQC spectrum determined that the carbon at 121.37 ppm correlated with the proton at 8.79 δ, the carbon at 125.4*6 ppm* correlated with the proton at 8.05 δ, and the carbon at 127.78 ppm correlated to the proton at 8.55 δ. The assignments for the remaining aromatic carbons were made by extrapolation from previously discussed oxadiazolinones. Table *6* shows the carbon assignments and the correlated protons (where appropriate).

Carbon Position	**Proton Shift**	**Carbon Shift**
1		132.*68*
2		142.03
3	8.79	121.37
4		145.59
5	8.55	127.78
6	8.05	125.4*6*
7		150.34
8		15*6.17*
9	2.41	12.31

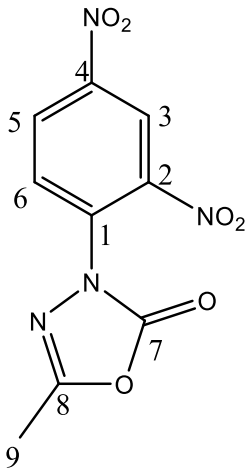
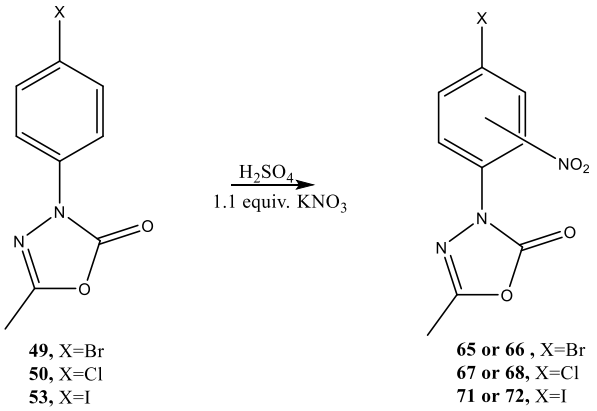


Table *6*: Carbon assignments for 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**62**)

vii. Nitration of 5-methyl-3-(4-bromophenyl)-1,3,4-oxadiazol-2(*3H*)-one (49)

As previously discussed in this thesis, nitration of 3-(4-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**61**) and dinitration of 3-phenyl-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) were explored with satisfactory results. Accordingly, it became of interest to investigate the nitration of various halogen substituted oxadiazolinones with the expectation that the nature of the halogen might affect the location of the attached nitro group (Scheme 49).

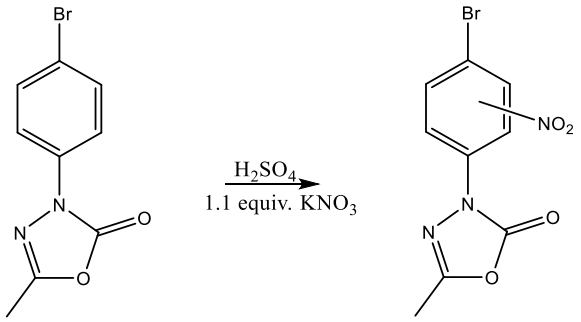


49, X=Br
50, X=Cl
53, X=I

65 or 66 , X=Br
67 or 68, X=Cl
71 or 72, X=I

Scheme 49: Nitration of halo substituted oxadiazolinones

Therefore, the optimized procedure for nitration of 3-phenyl-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) [*viz*. reaction temperature between -15 to -10 °C with 1.1 equivalents of nitrating reagent added over 20 minutes and a reaction time of 1.5 hours] was applied to the nitration of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**). (Scheme 50). After workup the pure product **65** or **66** was obtained as colorless needles in 72**%** yield.



49 65 or 66

Scheme 50: Nitration of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**)

In this case, it was unclear from the outset, which product (**65** or **66**), nitro *ortho* to the oxadiazolinone ring (2-position) or *ortho* to the Br (3-position), respectively, would be favored since both the oxadiazolinone ring and the bromine atom are *ortho* /*para* directors. The 2-position on the aryl ring is more electron dense and therefore more available for reaction as opposed to the 3- position aryl ring. Indeed, upon analysis of the aromatic region in the ^{1}H-NMR of the product, Figure 20, this dilemma was evident from the splitting pattern, viz. a doublet (1H) at 7.61 (ortho split as indicated with a J value of 8.62 Hz), a double doublet (1H) at 7.83 (ortho and meta split as indicated with the J values , 8.63 Hz and 2.21 Hz respectively) and a doublet (1H) at 8.12 (meta split as indicated with a J value of 2.16 Hz) . Either structure **65** or **66** could satisfactorily correspond with this splitting pattern.

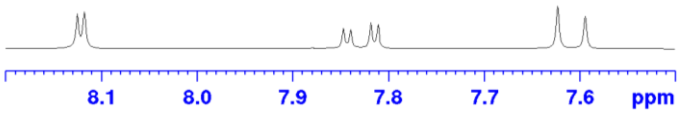


Figure 20: ^{1}H-NMR aromatic region of nitrated 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**61**)

Based on the relative positions of the substituents the splitting pattern of the protons could be predicted and thus, the protons of both structures, viz. 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**65**) and 3-(4-bromo-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-

one (**66**), were assigned ^{1}H-NMR values based on the splitting patterns mentioned above (below in Figure 21).

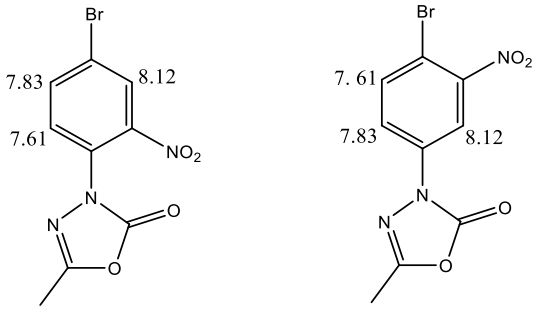
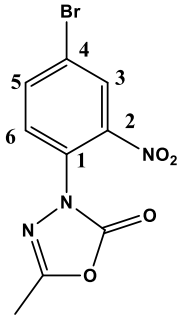


Figure 21: Comparison of proton chemical shift assignments for nitro bromophenyl oxadiazolinones

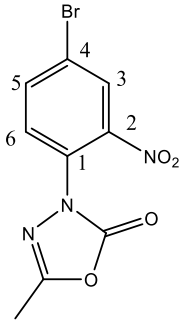
When looking at structure **65** (as seen in figure 20), it is expected that the proton closest to the bromine would be more deshielded due to the electron withdrawing nature of bromine, and the proton closest to the oxadiazolinone ring would be more shielded due to the donating nature of the ring. Indeed, in the ^{1}H-NMR, the proton *ortho* to the oxadiazolinone ring in **65** is further upfield and the proton in **65** *ortho* to the bromine is further downfield.

Furthermore, the carbon values, with an emphasis on the aromatic region, were calculated in a similar manner. The carbon values for **65** and **66** were calculated (with (4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) used as the baseline) and then compared to the actual values obtained by ^{13}C-NMR, shown further below in Table 6. The calculated values were placed in order of carbon position while the determined values were grouped in numerical order and labeled by degree of carbon attachment. The calculated values of for the carbon positions 2, 3, and 4, viz., 114.18 ppm, 151.80 ppm, and 113.69 respectively, do not correlate to the experimentally determined values as such, the validity of structure **66** cannot be corroborated. In contrast, the calculated values for **65** correlate to the experimental

values. Based on the calculations, 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**65**) is the correct structure from the nitration of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**).



65



66

Carbon position	Calculated ^{13}C-NMR values of 65	Calculated ^{13}C-NMR values of 66		Determined ^{13}C-NMR values (dinitration of 49)
1	128.75	135.85		121.68 (quaternary)
2	139.08	114.18		127.21 (quaternary)
3	126.90	151.80		127.40 (C-H)
4	119.79	113.69		128.50 (C-H)
5	138.20	133.00		136.60 (C-H)
6	120.28	125.48		143.46 (quaternary)

Table 7: Comparison of calculated and determined data for bromo nitro oxadiazolinone

Based on the calculations presented in Table 7, 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**65**) is the correct structure from the nitration of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**).

The pure product had a good melting point (127-129°C) and the structure and purity were confirmed by GC-MS and ^{1}H/^{13}C-NMR analyses. The GC/MS analysis showed a signal at 8.13 minutes with a parent ion peak of 298 m/z, **t**he molecular mass of the expected product **65**. In the mass spectrum, two peaks of equal height were observed, signifying a bromine present

on the molecule. Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed, in which the nitro and bromine atoms remained present on the aryl ring until after the loss of carbon dioxide and the imine (Appendix O).

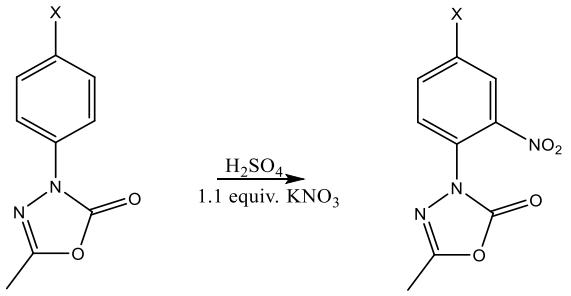
The IR-spectrum showed the expected C=O absorption at 1789.50 cm^{-1}, which is shifted slightly higher than a typical carbonyl due to the strain of the oxadiazolinone ring system and because of its carbamate-like functionality. Further, the nitro group has a slight withdrawing effect on the system (Appendix P).

As described earlier, the ^{1}H-NMR spectrum showed four signals, a singlet (3H) at 2.41 δ for the methyl protons and, in the aromatic region, a doublet (1H) at 7.61 δ, a double doublet (1H) at 7.83 δ, and a doublet (1 H) at 8.12 δ (Appendix Q).

The ^{13}C-NMR spectrum showed 9 signals, 1 signal for the methyl group, 6 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine (Appendix R). As expected the carbon with a nitro substituent is significantly further downfield compared to the corresponding carbon atom in the unsubstituted oxadiazolinone due to the electronegative disposition of the nitro group.

viii. Nitration of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (50)

As previously discussed, 3-(4-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**61**) and 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) undergo nitration in a facile manner to yield the corresponding 2-nitrophenyl species **62** and **65**, respectively (Scheme 51).

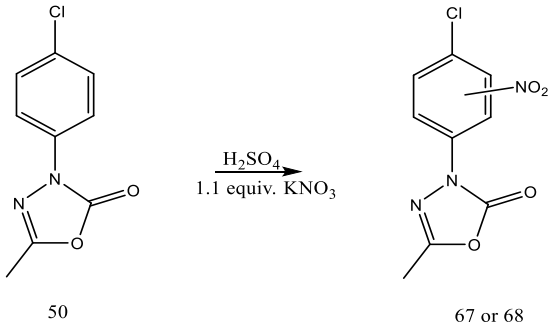


61 X= NO_2
49 X= Br

62 X=NO_2
65 X= Br

Scheme 51: Nitration of *para*-nitro- and *para*-bromo- phenyloxadiazolinones

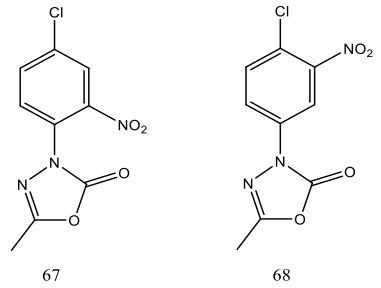
With sufficient quantities of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**) prepared, as discussed earlier in this thesis, it became possible to investigate further the nitration of another halogen substituted oxadiazolinone. Thus, **50** was stirred in sulfuric acid at a temperature between -15 to -10 °C and treated with 1.1 equivalents of potassium nitrate for 1.5 hours. The suspension was slowly poured into ice, the resulting precipitate was filtered, dried and then recrystallized from ethanol to yield **67** or **68** in 70% yield (Scheme 52).



50 67 or 68

Scheme 52: Nitration of para-chlorophenyl oxadiazolinone **50**

Just as for the other previously discussed *para*-substituted oxadiazolinones ,**49** and **61**, nitration of **50** could lead to the possibility of two product arrangements, *viz*. 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**67**) or 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) [Figure 22].



67 68

Figure 22: Possible reaction products from the nitration of para-chlorophenyloxadiazolinone (**50**)

Similar to the nitration of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**49**) it was unclear which site on the aryl ring, *viz*. the 2- or 3- position, would be most activated since both the chlorine and the oxadiazolinone ring are electron donating groups. Accordingly, the ^{1}H-NMR spectrum was recorded and is shown below in Figure 23. There are 3 signals (instead of the expected 4), *viz*., a singlet (3 protons) at 2.39 δ, 2 protons at 7.68 δ, and 1 proton at 7.98 δ, both unexpectedly represented as a singlet. With the apparent overlap of two signals at 7.68 δ, which

did not clarify with expansion of the scale, there was still a lack of evidence to support either structure **67** or **68**).

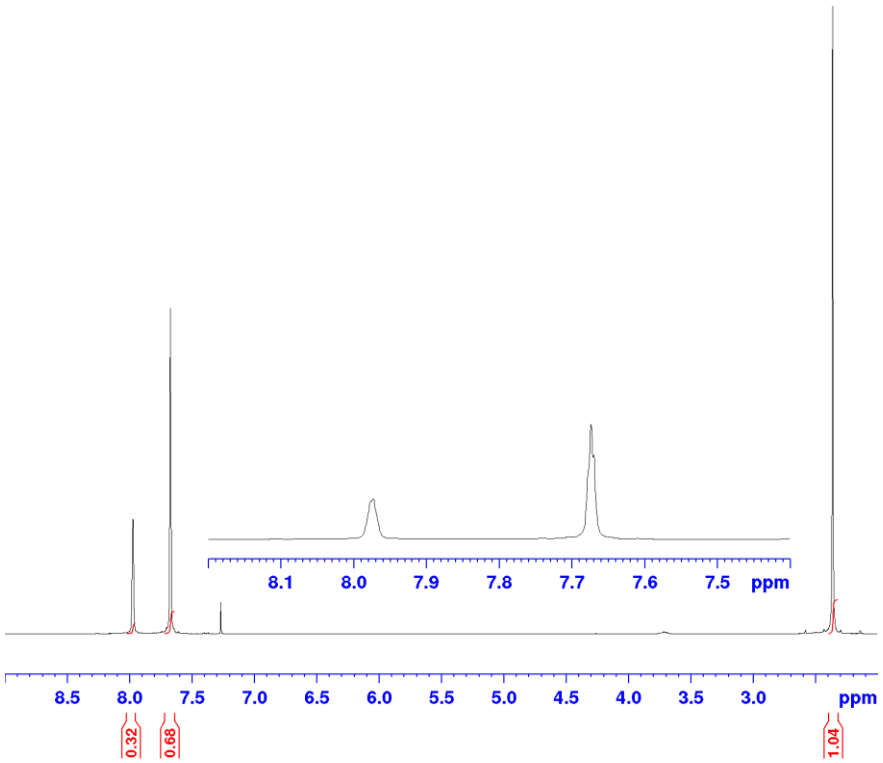
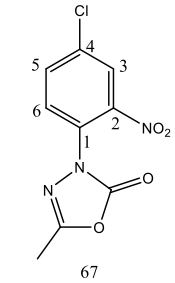
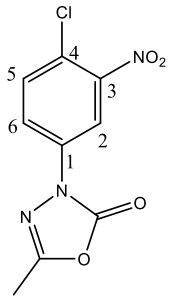


Figure 23: ^{1}H-NMR spectrum of nitrated 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**)

Therefore, just as described previously for other such compounds, the carbon nmr values for the various carbons in **67** and **68** were calculated (using the values for 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**) as the baseline) and then compared to the experimentally determined values obtained from the ^{13}C-NMR spectrum for nitration of **50**, shown in Table 8. The calculated values were placed in order of carbon position while the determined values were grouped in numerical order and labeled by degree of carbon attachment.



67



68

Carbon position	Calculated values for (67)	Calculated values for (68)		Determined ^{13}C-NMR Nitration of 50
1	129.00	135.35		125.66 (C-H)
2	139.06	113.88		126.72 (quaternary)
3	124.36	148.84		127.35 (C-H)
4	132.69	125.94		133.66 (C-H)
5	135.36	130.04		134.46 (quaternary)
6	119.86	125.18		143.43 (quaternary)

Table 8: Comparison of calculated and experimental values for nitrated para chloro oxadiazolinone **50**

Based on analysis from the values for the previous nitrated oxadiazolinone derivatives and the values calculated, the structure was believed to be 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**67**). However, the inability to distinctly identify the protons and due to the discrepancies in the calculated values compared to the determined values, carbon assignments could not definitely be made, especially with the carbons being in such close proximity. Since the structure could not be validated it was opted to synthesize 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**). If successful, the results would potentially help reinforce the above observations as the structure 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**67**) [to be discussed further in this thesis].

The pure product **67** had a sharp melting point (135-136°C) and the structure and purity were confirmed by GC-MS and $^{1}H/^{13}C$-NMR analyses. The mass spectrum showed a parent molecular ion peak at 255 m/z, the molecular mass of the expected product **67**, with a GC elution time of 7.2 minutes. The parent molecular ion exhibited a pattern for a molecule with chlorine, *viz*. 2 peaks with a 3:1 height ratio. Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed, in which the chlorine remained present on the aryl ring until after the loss of carbon dioxide and the imine (Appendix S).

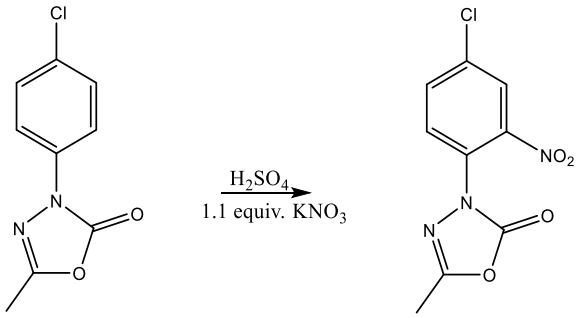
The IR-spectrum showed the expected C=O absorption at 1782.08 cm^{-1}, which is shifted considerably higher than a typical carbonyl due to the strain of the oxadiazolinone ring system and because of its carbamate-like functionality. Further, the nitro groups have a withdrawing effect on the system and thus shift the system to a higher frequency compared to the unsubstituted oxadiazolinone. In addition, two peaks, viz. 1541.12 cm^{-1} and 1350.84 cm^{-1}, were observed for the nitro group (Appendix T).

The ^{1}H-NMR spectrum showed 3 signals, a singlet (3H) at 2.39 δ for the methyl protons and, in the aromatic region, a 2H singlet at 7.68 δ, and an unresolved 1H singlet at 7.89 δ (Figure 23).

The ^{13}C-NMR spectrum showed 9 signals, 1 signal for the methyl group at 12.23 ppm, 6 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons at 150.39 ppm and 154.87 ppm, representing the carbonyl and the imine functionalities (Appendix U).

ix. Synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (68)

As previously discussed, it was conjectured that 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**67**) had been synthesized in 70% yield from the nitration of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**) using sulfuric acid and sodium nitrate (Scheme 53).



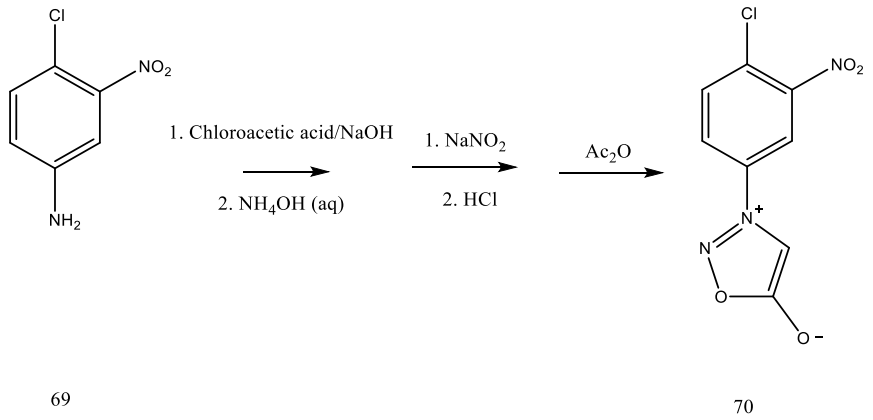
50 67

Scheme 53: Expected product from the nitration of para chloro oxadiazolinone **50**

However, as mentioned earlier, the expected arrangement of structure **67** could not be confirmed by common spectral methods such as ^{1}H-NMR and ^{13}C-NMR. Synthesis of **67** would entail preparation of the corresponding sydnone in a similar manner described earlier in Scheme 3. The precursor to the appropriate glycine, 4-chloro-2-nitroaniline, was available for purchase, however, research in the Turnbull laboratory indicated that when a nitro substituent was *ortho* to the amino group, as in the case of 2-nitroaniline, the amino group was non-reactive to electrophiles. Therefore, it was opted to synthesize the congeneric 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) in anticipation that the properties and data collected

would allow comparison with the compound isolated from the nitration of **50**. Two possibilities existed, *viz*. that the newly synthesized **68** would be identical or different from the nitration product from **50**. The former situation would unequivocally identify the product as structure **68** while the latter scenario would not identify the product unequivocally as **67** but would further strengthen its assignment as such. While 3-(4-chloro-3-nitro-phenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) is a known compound, synthesized by Badami et al., no characterization data were provided and, accordingly, it was important to prepare the compound in our laboratory. <2000IF406>

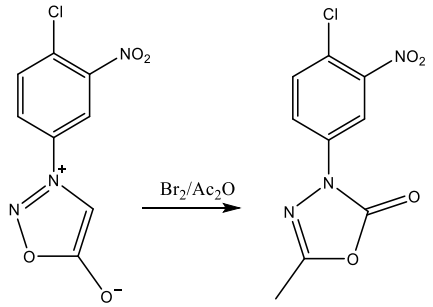
In preparation for the synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**), 3-(4-chloro-3-nitrophenyl)sydnone (**70)**, commercially unavailable, was first synthesized. In 1964, Stansfield et al. first reported the synthesis of **70** from 4-chloro-3-nitroaniline (**69**) <64CRV129>. Further in 2003, Dunkley and Thoman reported a slightly modified synthesis of (**70**), in which an amalgamation was used in the preparation of **70.** <2003BMCL2899>. Accordingly, synthesis of **70** [Scheme 54] began with treatment of the aniline **69** with chloroacetic acid and sodium hydroxide under reflux for 48 hours. Workup included treatment of the filtrate with hot aqueous ammonium hydroxide to yield the corresponding glycine. The aryl substituted glycine was nitrosated, using sodium nitrite in hydrochloric acid, and then cyclized with acetic anhydride to yield 3-(4-chloro-3-nitrophenyl)sydnone (**70**).



69 70

Scheme 54: Synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**)

The sydnone was then transformed into 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one structure (**68**) according to the previously described method (Scheme 55), viz., 3-(4-chloro-3-nitrophenyl)sydnone (**70**) was stirred and cooled with acetic anhydride and 1.1 equivalents of bromine mixed in acetic anhydride were added dropwise with stirring and cooling. The mixture was then gradually heated to 70°C for 30 minutes, after which time the solution was poured into cold water and the isolated oil was subjected to column chromatography, resulting in a low yield of the desired product **68** as a colorless solid.



70 68

Scheme 55: Synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**68**)

The ^{1}H-NMR spectrum showed a singlet at 2.40 δ methyl protons, compelling evidence of the formation of the oxadiazolinone ring system. In the aromatic region, as expected there

were 3 distinct signals, viz., a 1H signal at 7.61 δ, a 1H signal at 8.08 δ and a 1H signal at 8.37 δ (Figure 24).

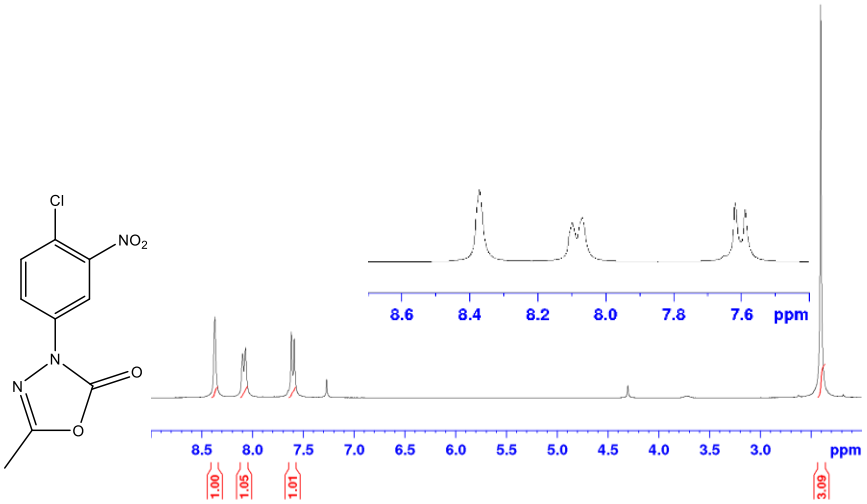


Figure 24: ^{1}H-NMR spectrum of nitrated 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**)

While the proton signals in the aromatic region are distinguishable, the splitting patterns are not evident and, therefore, in order to assign the protons, HSQC was utilized, as explained later.

As earlier discussed, synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**68**) and characterization would either validate or refute the structure suggested for the product isolated from the reaction of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**) with potassium nitrate in sulfuric acid. Accordingly, the^{1}H-NMR spectrum of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**68**) was compared to that for the putative 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**67**) obtained by nitration of **17**, with emphasis on the aromatic regions, left and right, respectively (Figure 25).

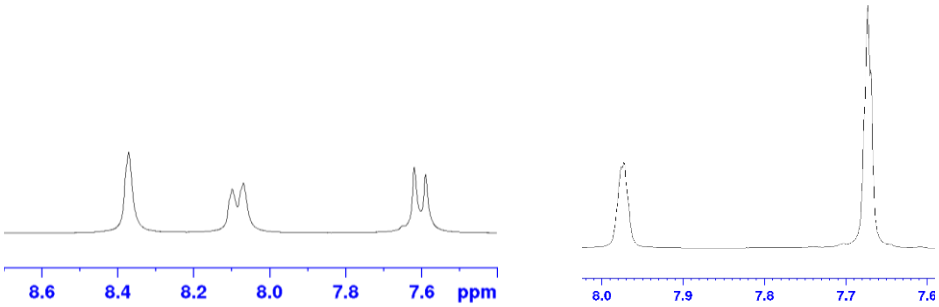
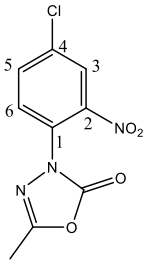


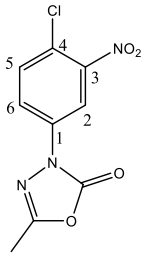
Figure 25: ^{1}H-NMR spectrum of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) and ^{1}H-NMR spectrum of 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**67**)

It is evident, from Figure 24, that the two structures are not the same. While the evidence is compelling, it is not sufficient to make an absolute claim in the identification of the isolated product from the nitration of **50**. Even though the structures are not identical, it is unclear why both spectra are poorly resolved. Since there is no overlap in the aromatic region of **68**, pictured to the left in Figure 26, HSQC could be used to determine the positions of the protons, discussed in more detail later.

Further, the calculated carbon values for both **67** and **68** were compared to the experimentally derived values for **68** [Table 9] in a similar manner as discussed in previous sections. The calculated values are placed in order by the carbon position, as shown in Table 9. The experimentally determined values were placed in numerical order and labeled based on the degree of carbon attachment.



67



68

Carbon position	Calculated values for (67)	Calculated values for (68)		Determined ^{13}C-NMR values for 68
1	129.00	135.35		114.67 (C-H)
2	139.06	113.88		121. 53 (C-H)
3	124.36	148.84		123.35 (quaternary)
4	132.69	125.94		132.59 (C-H)
5	135.36	130.04		135.22 (quaternary)
6	119.86	125.18		148.17 (quaternary)

Table 9: Calculated values for **67** and **68** compared to the experimental values of **68**

As expected, the experimentally determined values best correlated to the calculated values for 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**68**). The specific carbon assignments were determined from Table 9 in conjunction with the results from HSQC (see later). Since the carbon values did not correlate as well to those for structure **67**, this is compelling evidence that the isolated product from the nitration of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**) has structure **68**.

The pure product **68** had a sharp melting point of 124-125°C, compared to 135-136°C for **67**, and the structure and purity were confirmed by MS and ^{1}H-NMR analyses. The mass spectrum showed a parent molecular ion peak at 255 m/z with a GC elution time of 8.25 minutes, contrasting to 7.2 minutes for **67**. The parent molecular ion peak exhibited a pattern

for a molecule with chlorine viz., 2 peaks with a 3:1 height ratio. Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed, in which the chlorine remained present on the aryl ring until after loss of carbon dioxide and the imine functionality (Figure 26).

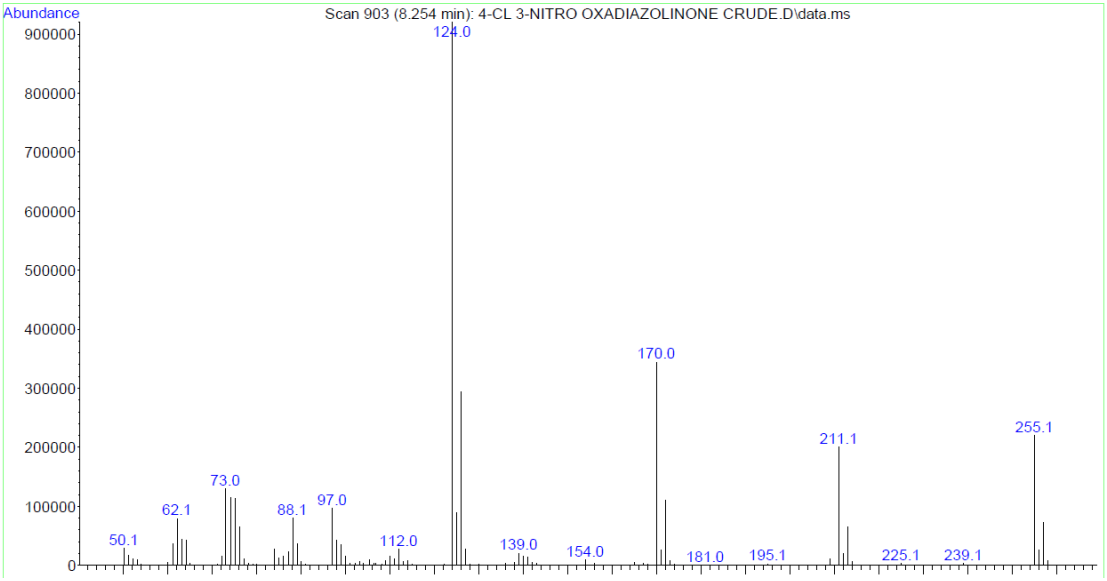


Figure 26: Mass spectrum of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**)

The IR-spectrum showed the expected C=O absorption at 1786.04 cm^{-1}, which is shifted slightly higher than a typical carbonyl due to the strain of the oxadiazolinone ring system, the carbamate-like functionality. Also, observed were 2 peaks at 1532.10 cm^{-1} and 1369.73 cm^{-1}, signifying the presence of a nitro group (Figure 27).

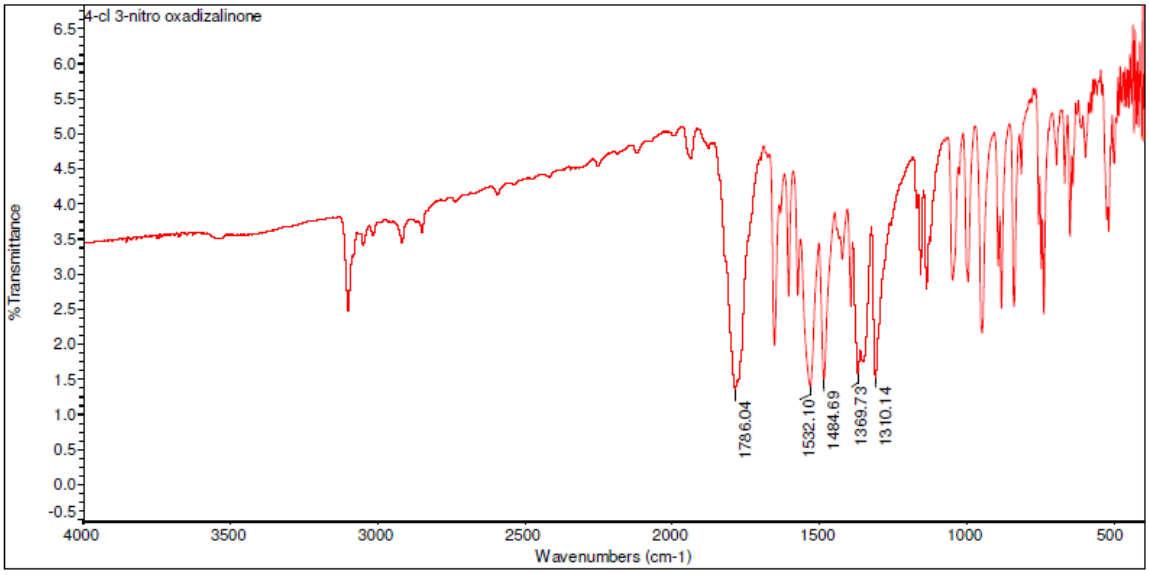


Figure 27: IR spectrum of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**68**)

The ^{1}H-NMR spectrum of **68** showed 3 signals, a singlet (3H) at 2.40 δ for the methyl protons and, in the aromatic region, a 1H signal at 7.61 δ, a 1H signal at 8.08 δ and a 1H signal at 8.37 δ (Figure 23).

The ^{13}C-NMR spectrum of **68** showed 9 signals, 1 signal for the methyl group, 6 signals for the aromatic carbons, and 2 signals for the characteristic oxadiazolinone ring carbons, representing the carbonyl and the imine.

Initially, rigorous assignment of the individual aromatic protons in **68** proved to be difficult and, therefore, HSQC was performed (Appendix X). The HSQC spectrum determined that the carbon at 114.67 ppm correlated with the proton at 8.37 δ, the carbon at 121.53 *ppm* correlated with the proton at 8.08 δ, and the carbon at 132.59 ppm correlated to the proton at 7.61 δ. The assignments for the remaining aromatic carbons were made by extrapolation from previously discussed oxadiazolinones (*vide infra*). Table 10, shown below, shows the carbon assignments and the correlated protons (where appropriate).

Carbon Position	Proton Shift δ	Carbon Shift ppm
1		135.22
2	8.37	114.67
3		148.17
4		123.35
5	7.61	132.59
6	8.08	121. 53
7		15*4.87*
8		150.39
9	2.41	12.23

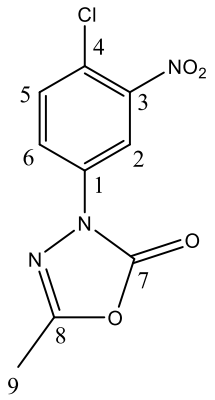
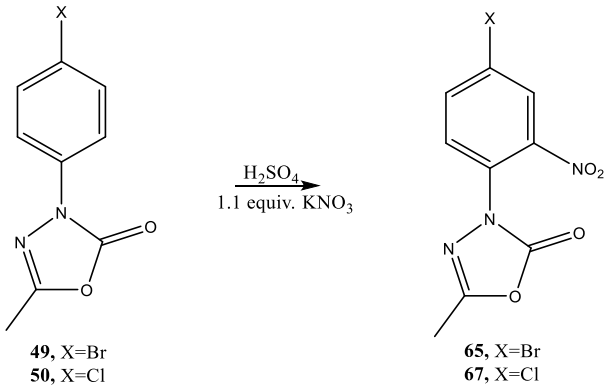


Table 10: Carbon and proton assignments for 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**)

x. **Nitration of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (53)**

As previously discussed, 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one (**49**) and 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**50**) undergo nitration in a facile manner to yield the corresponding 2-nitrophenyl species **65** and **67**, respectively (Scheme 56).

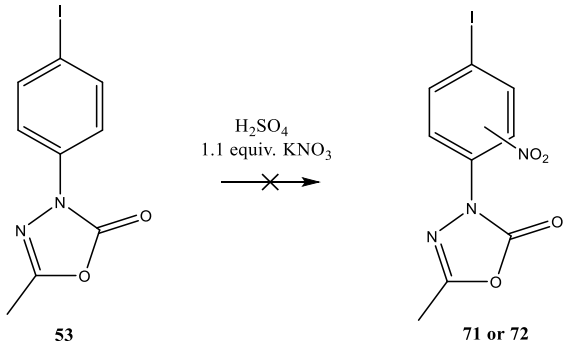


49, X=Br
50, X=Cl

65, X=Br
67, X=Cl

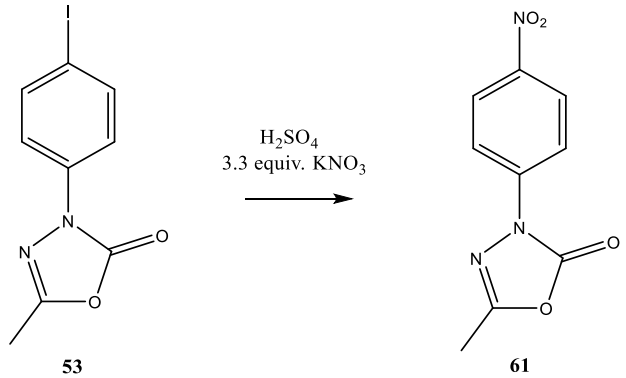
Scheme 56: Nitration of 3-(4-bromophenyl)oxadiazolinone **65** and 3-(4-chlorophenyl)oxadiazolinone **67**

With sufficient 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**) prepared, as discussed earlier in this thesis, it became possible to investigate further nitration on a halogen substituted oxadiazolinone. Thus, the *p*-iodo species **53** was stirred in sulfuric acid at a temperature between -15°C to -10 °C and treated with 1.1 equivalents of potassium nitrate for 1.5 hours. After work up and attempted characterization, there was no indication of the formation of the iodonitro- species **71** or **72** [Scheme 57].



Scheme 57: Attempted nitration of 5-methyl-3-(4-iodophenyl)-1,3,4-oxadiazol-(3H)-one (**53**)

However, according to GC –MS analysis and comparison with authentic samples, there was a 7 % conversion to 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**61**) and the remaining 93% consisted of unreacted starting material. Accordingly, the *p*-iodo species **53** was stirred in sulfuric acid at a temperature between -15°C to -10 °C and treated with 3.3 equivalents of potassium nitrate for 1.5 hours. The mixture was poured into 20 mL of ice to and extracted with methylene chloride to yield a tan solid. TLC, GC-MS, and melting point were consistent with its identification as 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**61**) [Scheme 58].



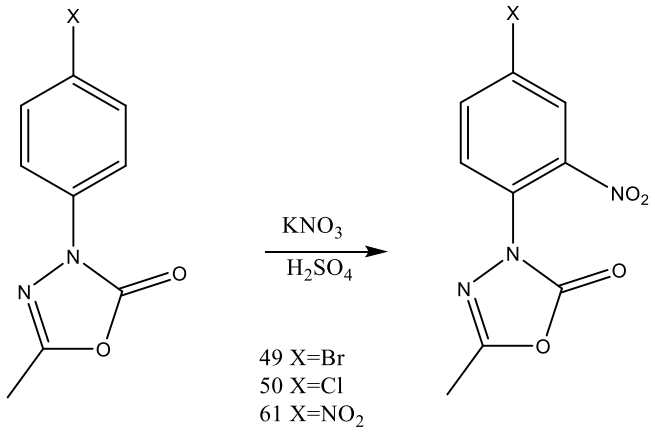
Scheme 58: Nitration of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**53**)

The obvious question that arises from the nitration of 5-methyl-3-(4-iodophenyl)-1,3,4-oxadiazol-2(*3H*)-one (**53**) is why *ipso* nitration takes place rather than placement of the nitro

group at the position *ortho* to the oxadiazolinone ring. The answer is unclear but, undoubtedly, the longer C-I bond length (compared to those of C-Br and C-Cl) plays a role, as does iodine's excellent leaving group ability. While this discovery was intriguing, the reaction was not examined further.

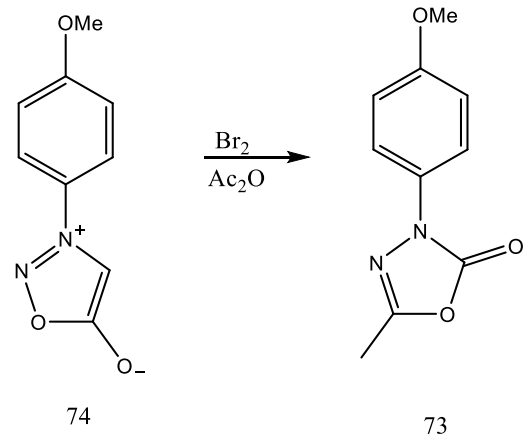
xi. Nitration of 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (73)

As previously discussed, nitration of a variety of *para*- substituted aryloxadiazolinones took place on the attached aromatic ring and it was determined that in all of these cases (except *para*-iodo) reaction with the nitronium electrophile occurred *ortho* to the oxadiazolinone ring (Scheme 59).



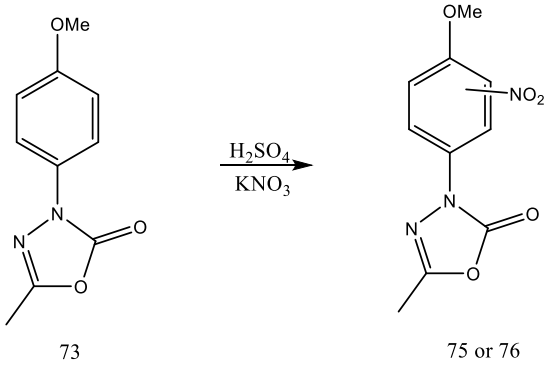
Scheme 59: Nitration of *para* substituted oxadiazolinones

Since these nitration studies were performed on oxadiazolinones with attached withdrawing substituents, it was elected to examine the nitration of an oxadiazolinone with a strong donating group attached to the aryl ring. Accordingly, 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**73**) was selected, largely because the likely precursor, 3-(4-methoxyphenyl)sydnone (**74**), was readily available in the Turnbull laboratory. In the event, sydnone **74** was transformed into the desired product **73** by the previously described method using acetic anhydride and 1.1 equivalents of bromine. (Scheme 60) The product was characterized by comparison with the reported melting point and spectral characteristics.



Scheme 60: Synthesis of 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**73**)

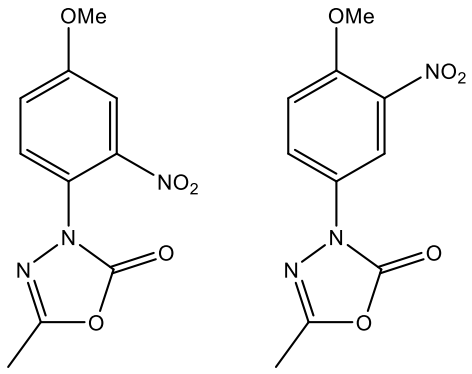
With sufficient quantities of 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**73**) prepared, it became possible to investigate further the nitration of a oxadiazolinone with a strong donating substituent. Thus, **73** was stirred in sulfuric acid at a temperature between -15 to -10 °C and treated with 1.1 equivalents of potassium nitrate for 1.5 hours. The suspension was poured slowly onto ice, the resulting precipitate was filtered and dried to yield the nitrated product **73** in poor yield, undoubtedly due to working on such a small scale. (Scheme 61).



Scheme 61: Nitration of 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**73**)

Similar to the nitration of other oxadiazolinone derivatives, it was initially unclear at which site on the aryl ring, *viz*. the 2- or 3- position, the nitration had occurred. However, even

though both the methoxy group and the oxadiazolinone ring are electron donating groups, observations from our previous nitration studies strongly suggested that the oxadiazolinone ring system is only slightly donating and, therefore, the structure was believed to be 3-(4-methoxy-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**75**) rather than the isomeric structure **76** (Figure 28) **.**

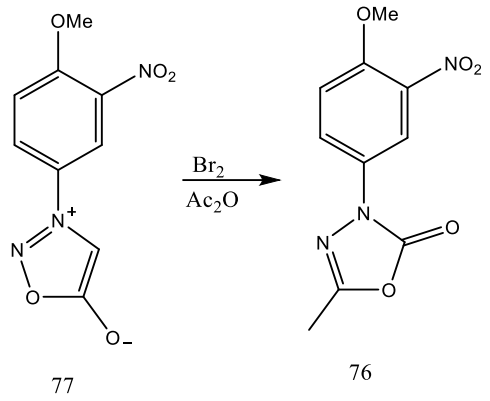


75 76

Figure 28: Possible structures from the nitration of **73**

In order to facilitate identification of the structure of the product from the nitration of **73**, it was opted to synthesize 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**), from the parent sydnone **77**, since the latter was available in the Turnbull lab. It was anticipated that the properties and data collected for **76** would allow comparison with the compound isolated from the nitration of **73**. Two possibilities existed, *viz*. that the newly synthesized **76** would be identical or different from the nitration product from **73**. The former situation would unequivocally identify the product as structure **76**.

The sydnone **77** was then transformed into 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**) according to the previously described method, viz., treatment of **77** with acetic anhydride and 1.1 equivalents of bromine in acetic anhydride, followed by heating to 70°C, pouring into cold water and isolation of the product as a tan solid. (Scheme 62)



Scheme 62: Synthesis of 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**) from sydnone

The pure product had a sharp melting point (141-142°C) and the structure and purity were confirmed by GC-MS and $^{1}H/^{13}C$-NMR analyses. The mass spectrum showed a parent molecular ion at 251 m/z (the molecular mass of the expected product **76**) and a GC peak at 9.3 minutes Further, the characteristic breakdowns of the oxadiazolinone ring [loss of carbon dioxide (44 m/z) then $CH_3C{=}N$ (41 m/z)] were also observed, in which the substituents remained present on the aryl ring until after the loss of carbon dioxide and the imine (Figure 29**).**

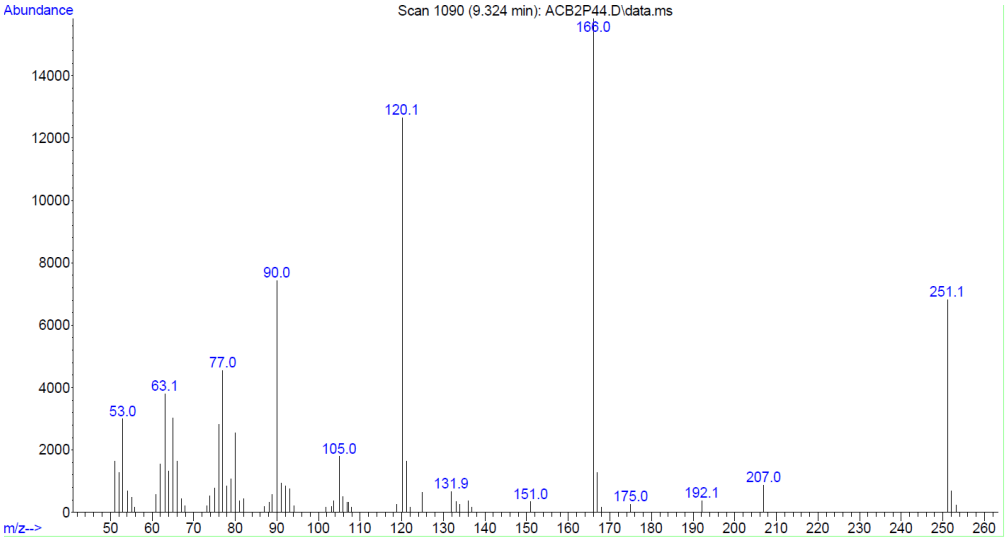


Figure 29: Mass spectrum of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**)

The IR-spectrum showed the expected C=O absorption at 1765 cm^{-1}. Also, observed were 2 peaks at 1535 cm^{-1} and 1369.73 cm^{-1}, signifying the presence of a nitro group.

The ^{1}H-NMR spectrum showed 5 signals, a singlet (3H) at 2.36 δ for the methyl protons on the oxadiazolinone ring, a singlet (3H) at 4.01 δ representative of the methoxy protons and in the aromatic region, a doublet (1H) at 7.16 δ, a double doublet (1H) at 8.09 δ, and a doublet (1 H) at 8.30 δ (Figure 30).

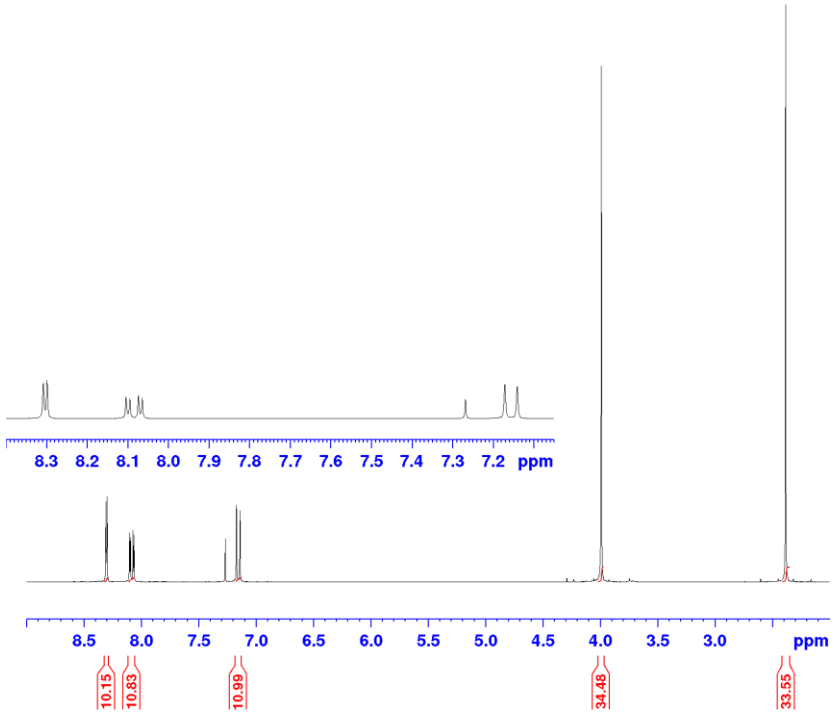


Figure 30: ^{1}H-NMR spectrum of 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**)

The ^{13}C-NMR spectrum showed 10 signals, 2 signals at 12.19 ppm and 56.87 ppm for the two methyl groups, 6 signals for the aromatic carbons at 114.24 ppm, 115.59, 123.17 ppm, 128.88 ppm, 139.51 ppm, and ~150 ppm, and 2 signals for the characteristic oxadiazolinone ring carbons at 154.30 ppm and ~150 ppm (Figure 31). Due to the close proximity of the carbons at 150.54 ppm and 150.77 ppm it was not possible to classify either as an aromatic carbon or

oxadiazolinone carbon and, accordingly, full carbon assignments could not be made for the molecule as a whole.

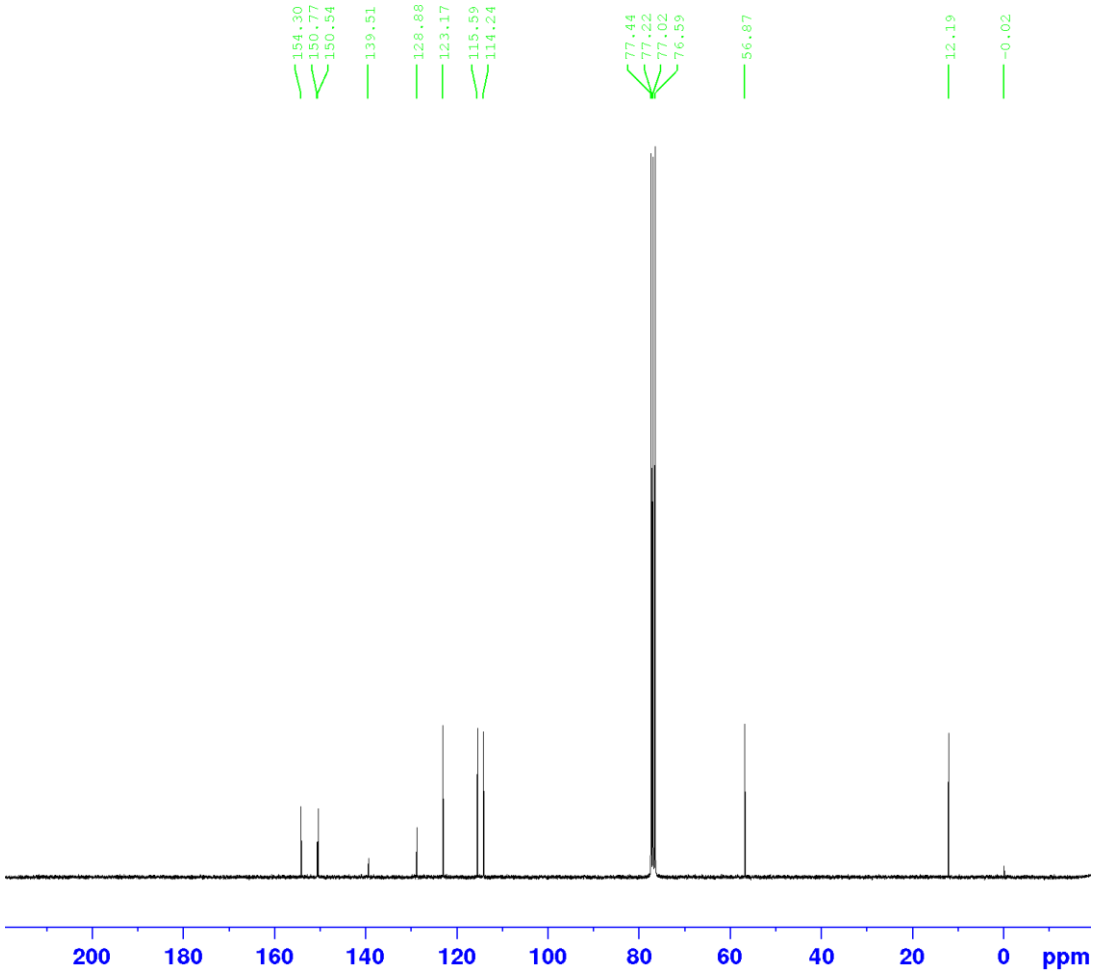


Figure 31: ^{13}C-NMR spectrum of 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**)

When comparing the data collected from nitration of 3-(4-methoxyphenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**73**) to 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**) viz., TLC analysis, melting point, ^{1}H-NMR spectrum, validate that both compounds are identical. While these findings are not absolute, it is evident from this study that the methoxy group is a stronger donor than the oxadiazolinone ring system.

IV. Conclusion

5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) was synthesized successfully in moderate yield, using the optimized procedure reported by Klaasen. The purified product was tan needles and, while it had a lower melting point than published in the literature the melting point was sharp and the structure was confirmed by IR, GC-MS, ^{1}H-NMR, and ^{13}C-NMR analyses. In line with the aims, reaction of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**17**) with electrophiles was reexplored.

Bromination of **17** with potassium bromate in~19% HBr was modified from Klassen's reported procedure. The desired purified bromo product **49**, white needles, was obtained in modest yield. While enough material was available to pursue further reactions, other bromination avenues were investigated also. Thus, bromination of **17** with bromine in ethyl acetate or N-bromosuccinimide, in each case resulted in a small amount of the desired para bromo species **49** in conjunction with unreacted starting material. Also formed in the reaction of **17** with bromine in ethyl acetate was a small amount of the bromomethyl species **48**. Due to these inadequate results, the latter two methods were not investigated further.

Chlorination of **17** with N-chlorosuccinimide resulted in a small amount of the desired para chloro species **50** in conjunction with other unidentified products while attempted chlorination by treatment with iodine monochloride led to no reaction. Due to these inadequate results, these methods were not further investigated. Reexploration of the chlorination of **17** with potassium chlorate in ~19% HCl did result in a low yield of the desired chloro product **50** as colorless needles, however, to prepare larger quantities it was elected to utilize 3-(4-chlorophenyl)sydnone (**52**) in the optimized procedure developed by Klassen from 3-

phenylsydnone (**16**). This approach provided enough material to allow further reactions with electrophiles as described in this thesis.

Iodination of **17** with N-Iodosuccinimide was examined according to Klassen's method. The resulting 4-iodophenyl oxadiazolinone product **53** was obtained in poor yield, nevertheless, enough pure material was available for other studies with electrophiles as described in this thesis.

Reexploration of nitration of **17** with potassium nitrate and sulfuric acid initially resulted in four products. The major product was the para-nitro species **61**, however, there was indication of the dinitro species **62** and unreacted starting material. It was assumed, but not proven that the ortho nitro analog **63** was formed also. The procedure was successfully optimized to yield **71** as yellow needles in good yield. With enough material available, further reactions of **71** with electrophiles were explored, as described in this thesis.

Nitration of **17** to form only **62** was realized using an increased amount of nitrating reagent, with all other reaction conditions the same. It was initially unclear which sites on the aryl ring were most reactive toward the electrophile, however, ^{13}C-NMR calculations were correlated to experimental values. These correlations, in conjunction with ^{1}H-NMR, ^{13}C-NMR, and HSQC analyses, highly suggest that the structure is 3-(2,4-dintrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**62**).

Nitration of **49** paralleled the nitration of the *para* nitro species **61.** Again, it was initially unclear which site on the aryl ring was most reactive toward the electrophile. However, ^{13}C-NMR calculations were correlated to experimental values. These correlations in conjunction with ^{1}H-NMR, ^{13}C-NMR, and HSQC analyses highly suggest the structure as 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**65**).

In the nitration of 3-(4-chloro-phenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**50**), **50** was also reactive toward the electrophile. ^{13}C-NMR calculations were correlated to experimental values. However, with poor resolution of the ^{1}H-NMR spectrum and overlap of protons in the aromatic region, the correct structure could not be validated. As such it was opted to synthesis 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) as a means of comparison, as described in this thesis.

Synthesis of **68** began with the corresponding aniline. ^{13}C-NMR calculations were compared to experimental values from the nitration of **50**. As these did not match, the unique ^{1}H-NMR, ^{13}C-NMR, and HSQC spectra highly suggest the structure as 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**) and therefore, give validity the structure of from the nitration of **50** as 3-(4-chloro-3-ntrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**68**).

Nitration of **53** to form only **61** was realized using an increased amount of nitrating reagent, with all other reaction conditions the same. While it is unclear why *ipso* nitration takes place rather than placement of the nitro group at the position *ortho* to the oxadiazolinone ring, factors include the longer C-I bond length (compared to those of C-Br and C-Cl) and iodine's excellent leaving group ability.

Nitration of **73** paralleled nitration of previously discussed analogues. Yet, with a high degree of certainty, the structure was thought to be 3-(4-metho-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (**76**) since the methoxy substituent is likely a much stronger donor than the oxadiazolinone ring. Therefore, for comparison, it was opted to synthesize **76** from the corresponding sydnone.

Synthesis of **76** from the corresponding sydnone was successful. The data obtained was compared to the data of nitration of **75**. As such, it was evident the reaction products were

identical. While these findings are not absolute, there is a high degree of certainty that the methoxy group is a stronger donor than the oxadiazolinone ring system.

Further work would include optimization of procedures where appropriate. A collaboration with Central State University would extended the research to test for antimicrobial activity of the synthesized compounds. Also, further nitration studies would encompass a wider variety of oxadiazolinone derivatives.

V. Experimental

All starting materials were purchased from commercial sources and used without further purification unless otherwise stated. For reactions with ICl, all glassware was flame dried under an atmosphere of nitrogen prior to the use of dry reagents. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared (IR) spectra were acquired on a Nicolet 6700 FT-IR. Carbon (^{13}C) and proton (^{1}H) Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker Advance 300 MHz NMR. Deuterated chloroform ($CDCl_3$) was used as solvent. Elemental analyses were performed by Midwest Microlab LLC, Indianapolis, Indiana.

Synthesis of 3-phenyl-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (17)

To a stirred mixture of 3-phenyl sydnone (1.00 g, 0.062 mol) in 5 mL of acetic anhydride was added bromine (0.109 g, 0.068 mol) slowly with stirring. The reaction mixture was refluxed for 1 h at 70°C whereupon the mixture was cooled to room temperature and poured slowly onto 40 mL of ice. The resulting precipitate was filtered *in vacuo* and recrystallized from ethanol to yield the title compound as light tan needles, 0.0449 g, m.pt. 86-87 °C. IR (KBr): 1773.70 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.34 (s, 3H), 7.25 (t, 1H), 7.42(t, 2H), 7.82 (dd, 2H) δ; ^{13}C-NMR ($CDCl_3$): 12.17, 118.06, 125.89, 129.16, 136.00, 151.08 (C=N), 153.79 (C=O) ppm.

Synthesis of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (49)

To a stirred mixture of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (0.05g, 0.000285 mol) in 3 mL of ~19% HBr was added crushed $KBrO_3$ (0.238 g, 0.00143 mol) over a period of 5 minutes. T

he reaction continued at room temperature for 30 minutes after which the precipitate was filtered *in vacuo* to yield a fluffy yellow solid, 0.359 g, m.pt. 125-126 °C. IR (KBr): 1796 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.36 (s, 3H), 7.53 (d, 2H), 7.73(d, 2H) δ; ^{13}C-NMR ($CDCl_3$): 12.20, 118.99, 119.48, 132.20, 135.05, 150.74 (C=N), 154.02 (C=O) ppm.

Synthesis of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (50)

To a stirred mixture of 3-(4-chlorophenyl)sydnone (0.200 g, 0.00102 mol) in 5 mL of acetic anhydride was added bromine (0.1835 g, 0.001148 mol) slowly with stirring**.** The reaction mixture was refluxed for 2 hr at 70°C whereupon the mixture was cooled to room temperature and poured slowly onto 80 mL of ice cold water. the reaction mixture was extracted with DCM, followed by a base wash and water wash. The organic layer was dried and then roto evaporated to yield a white solid that was recrystallized from ethanol to yield the title compound as pink needles, 0.12484 g, m.pt. 122-123 °C. IR (KBr): 1796 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.36 (s, 3H), 7.53 (d, 2H), 7.73(d, 2H) δ; ^{13}C-NMR ($CDCl_3$): 12.20, 118.99, 119.48, 132.20, 135.05, 150.74 (C=N), 154.02 (C=O) ppm.

Synthesis of 3-(4-iodophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (53)

To a mixture of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (0.100 g, 0.000571 mol) in 3 mL of acetic acid was added N-Iodosuccinimide (0.4495 g, 0.00199 mol). The reaction mixture was refluxed at 70°C for 24 hours whereupon the mixture was cooled to room temperature and poured slowly onto 20 mL of ice. Once the ice was melted, the reaction mixture was extracted 3 times with methylene chloride. The combined organic layers were washed with of sat. sodium bicarbonate and water. The organic layer was dried with magnesium sulfate. It was then filtered and roto evaporated. The product was transferred to a tarred vial and blown down with nitrogen to yield a brown solid that was recrystallized in EtOH to yield beige needles 0.0624 g,

m.pt. 98-99 °C. ^{1}H-NMR ($CDCl_3$): 2.36 (s, 3H), 7.61 (d, 2H), 7.73 (d, 2H) δ; ^{13}C-NMR ($CDCl_3$): 12.21, 89.89 (C-I), 119.71, 135.78, 138.25, 150.02 (C=N), 154.02 (C=O) ppm.

Synthesis of 3-(4-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (61)

To a stirred mixture of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (0.05g, 0.000285 mol) in 3 mL of cold sulfuric acid was added over a period of 20 minutes crushed KNO_3 (0.0317 g, 0.000314 mol). The reaction continued at -15 to -10 °C for 1 hour 30 minutes whereupon the mixture was slowly poured onto 20 mL of ice. The resulting precipitate was filtered *in vacuo* to yield a yellow solid 0.0456 g, m.pt. 123-124 °C. IR (KBr): 1818.87 (C=O), 1335.83 (C-NO_2), 1500.75 (C-NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.36 (s, 3H), 8.03 (d, 2H), 8.31 (d, 2H) δ; ^{13}C-NMR ($CDCl_3$): 12.23, 117.67, 125.05, 135.78, 140.83, 144.87 (C-NO_2), 150.48 (C=N), 154.90 (C=O) ppm.

Synthesis of 3-(2,4-dinitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (62)

To a stirred mixture of 5-methyl-3-phenyl-1,3,4-oxadiazol-2(*3H*)-one (0.05g, 0.000285 mol) in 3 mL of cold sulfuric acid was added over a period of 10 minutes crushed KNO_3 (0.298 g, 0.00284 mol). The reaction continued at 0 °C for 1 hour 30 minutes whereupon the mixture was slowly poured onto 20 mL of ice. The reaction mixture was extracted 3 times with methylene chloride. The combined organic layers were washed with of sat. sodium bicarbonate and water. The organic layer was dried with magnesium sulfate. It was then filtered, and roto evaporated. The product was transferred to a tarred vial and blown down with nitrogen. The product was recrystallized with ethanol sharp pale-yellow needles 0.0873 g, m.pt. 127-128° C; 1785.44 (C=O), 1552.17 (C-NO_2), 1347.84(C-NO_2) cm^{-1};^{1}H-NMR ($CDCl_3$): 2.41 (s, 3H), 8.05 (d 1H) 8.55 (dd,1H), 8.79 (d, 1H) δ; ^{13}C-NMR ($CDCl_3$): 12.31, 121.37, 125.46, 127.78, 132.68, 142.03(C-NO_2), 145.59 (C-NO_2), 150.30 (C=O), 156.17 (C=O) ppm Analysis calculated for $C_9H_6N_4O_6$: C, 40.61; H, 2.27; N, 21.05. Found: C, 40.30; H, 2.32; N, 20.95.

Synthesis of 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (65)

To a stirred mixture of 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (0.05g, 0.000197 mol) in 3 mL of cold sulfuric acid was added over a period of 20 minutes crushed KNO_3 (0.0219 g, 0.000216 mol). The reaction continued at -15 to -10 °C for 1 hour 30 minutes whereupon the mixture was slowly poured onto 20 mL of ice. The resulting precipitate was filtered *in vacuo* and recrystallized in EtOH to yield white fluffy needles 0.0359g, m .pt. 127-129 °C; 1789.50 (C=O), 1537 (C-NO_2), 1312 (C-NO_2) cm^{-1};^{1}H-NMR ($CDCl_3$): 2.41 (s, 3H), 7.61 (d 1H) 7.83 (dd,1H), 8.12 (d, 1H) δ;^{13}C-NMR ($CDCl_3$): 12.27, 121.68, 127.21, 127.78, 127.39, 128.50, 136.59, 143.59 (C-NO_2), 150.30 (C=O), 156.17 (C=O) ppm

Synthesis of 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (67)

To a stirred mixture of 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (0.05g, 0.000238 mol) in 3 mL of cold sulfuric acid was added over a period of 5 minutes crushed KNO_3 (0.0265 g, 0.000262 mol). The reaction continued at -15 to -10 °C for 1 hour 30 minutes whereupon the mixture was slowly poured onto 20 mL of ice. The reaction mixture was extracted 3 times with methylene chloride. The combined organic layers were washed with of sat. sodium bicarbonate and water. The organic layer was dried with magnesium sulfate. It was then filtered, and roto evaporated. The product was transferred to a tarred vial and blown down with nitrogen. The product was recrystallized with ethanol sharp pale-white needles 0.0416 g, m .pt. 135-136 °C; 1789.50 (C=O), 1541 (C-NO_2), 1351(C-NO_2) cm^{-1};^{1}H-NMR ($CDCl_3$): 2.39 (s, 3H), 7.61 (s 2H) 7.98 (s 1H), δ;^{13}C-NMR ($CDCl_3$): 12.23, 125.66, 126.72, 127.35, 133.66, 134.46, 143.43 (C-NO_2), 150.39 (C=O), 156.87 (C=O) ppm. Analysis calculated for $C_9H_6ClN_3O_4$: C, 42.29; H, 2.37; N, 16.44. Found: C, 42.55; H, 2.63; N, 16.24.

Synthesis of 3-(4-chloro-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (68)

To a stirred mixture of 3-(4-chloro-3-nitrophenyl)sydnone (0.1 g, 0.000391 mol) in 5 mL of acetic anhydride was added bromine (0.068 g, 0.00043 mol) slowly with stirring**.** The reaction mixture was refluxed for 2 h at 70°C whereupon the mixture was cooled to room temperature and poured slowly onto 20 mL of ice cold water. The resulting precipitate was filtered *in vacuo* and recrystallized from ethanol to yield the title compound as white needles, 0.052 g, m.pt. 124-125 °C; 1789.50 (C=O), 1369.73 (C-NO_2), 1532.10 (C-NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$): 2.40 (s, 3H), 7.61 (1H), 8.08 (1H), 8.37 (1H) δ; ^{13}C-NMR ($CDCl_3$): 12.23, 114.67, 121.53, 123.35, 132.59, 135.22, 148.17 (C-NO_2), 150.39 (C=O), 154.87 (C=O) ppm

Synthesis of 3-(4-methoxy-3-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one (68)

To a stirred mixture of 3-(4-MeO-3-nitrophenyl)sydnone (0.020 g, 0.00000843 mol) in 2 mL of acetic anhydride was added bromine (0.0118 g, 0.000105 mol) slowly with stirring**.** The reaction mixture was refluxed for 1 h at 70°C whereupon the mixture was cooled to room temperature and poured slowly onto 20 mL of ice cold water. The reaction mixture was extracted 3 times with methylene chloride. The combined organic layers were washed with of sat. sodium bicarbonate and water. The organic layer was dried with magnesium sulfate. It was then filtered, and roto evaporated. The product was transferred to a tarred vial and blown down with nitrogen and recrystallized to yield tan needles, 0.0118 g, m .pt. 141-142°C; 1765 (C=O), 1370 (C-NO_2), 1535 (C-NO_2) cm^{-1};^{1}H-NMR ($CDCl_3$): 2.36 (s, 3H), 4.01 (s, 3H), 7.16 (d 1H), 8.09 (dd 1H), 8.30 (d H) δ;^{13}C-NMR ($CDCl_3$): 12.19, 56.87, 114.24, 115.59, 123.17, 128.88, 139.51, 150.54, 150.77, 154.30 (C=O) ppm.

VI. References

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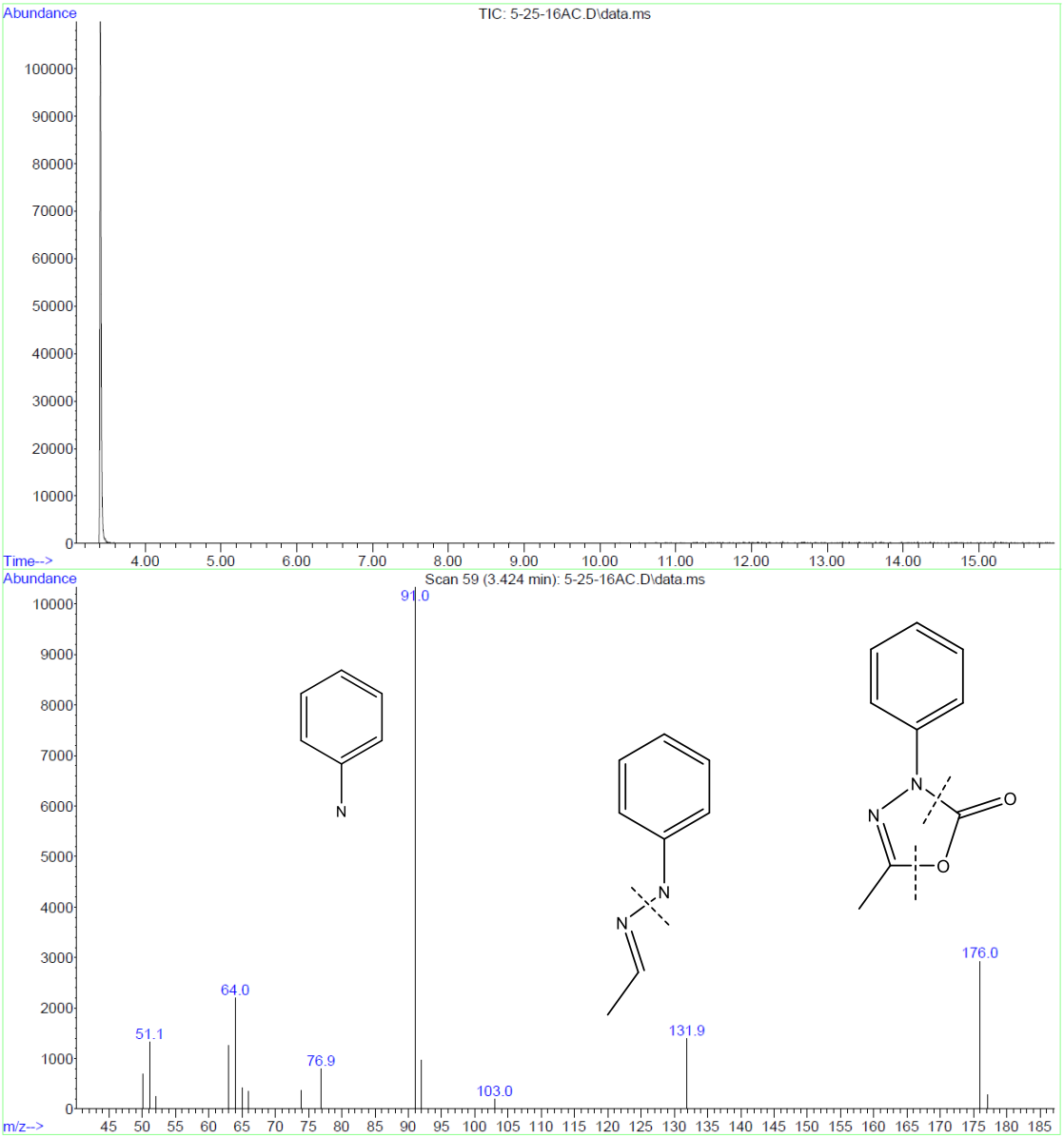
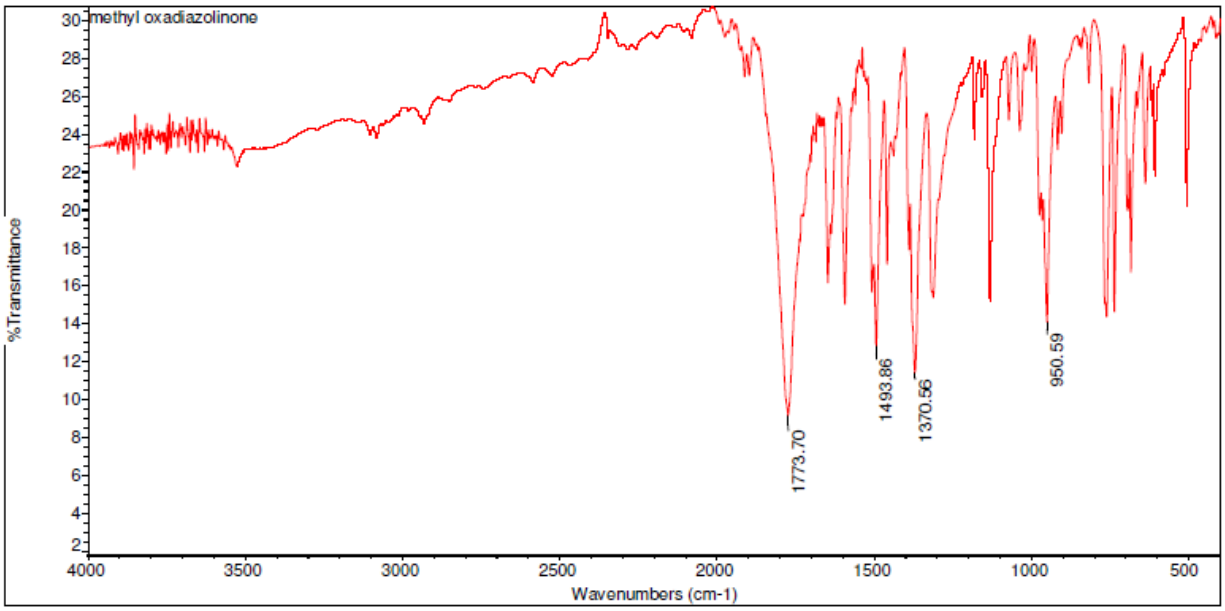
VII. **Appendix**

File :D:\Turnbull\Amanda\5-25-16AC.D
Operator : Amanda
Acquired : 26 May 2016 9:39 using AcqMethod AMANDA.M
Instrument : 5975C MSD
Sample Name: Pure Oxa 5-25-15
Misc Info :
Vial Number: 10



A: TOP: Chromatogram of 5-methyl-1,3,4-oxadiazol-2(*3H*)-one BOTTOM: Mass spectrum of 5-methyl-1,3,4-oxadiazol-2(*3H*)-one



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Spectrum:	methyl oxadiazolinone	
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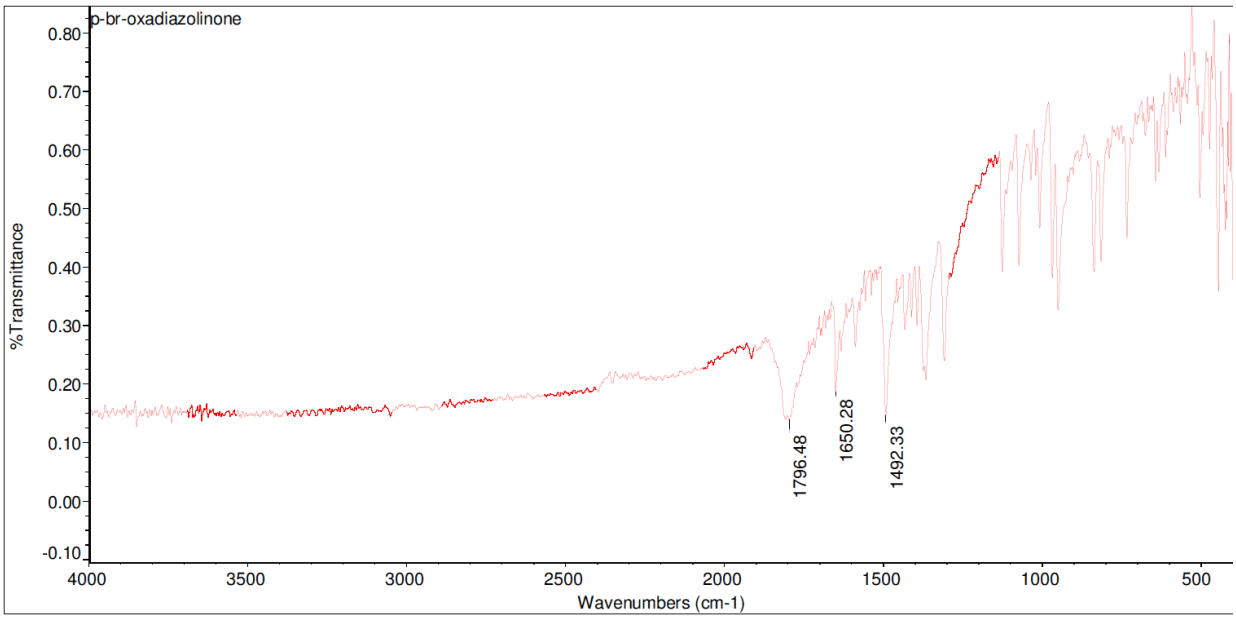
Sensitivity:	50	
Peak list:		

Position:	950.59	Intensity:	14.098
Position:	1370.56	Intensity:	11.449
Position:	1493.86	Intensity:	12.876
Position:	1773.70	Intensity:	9.195

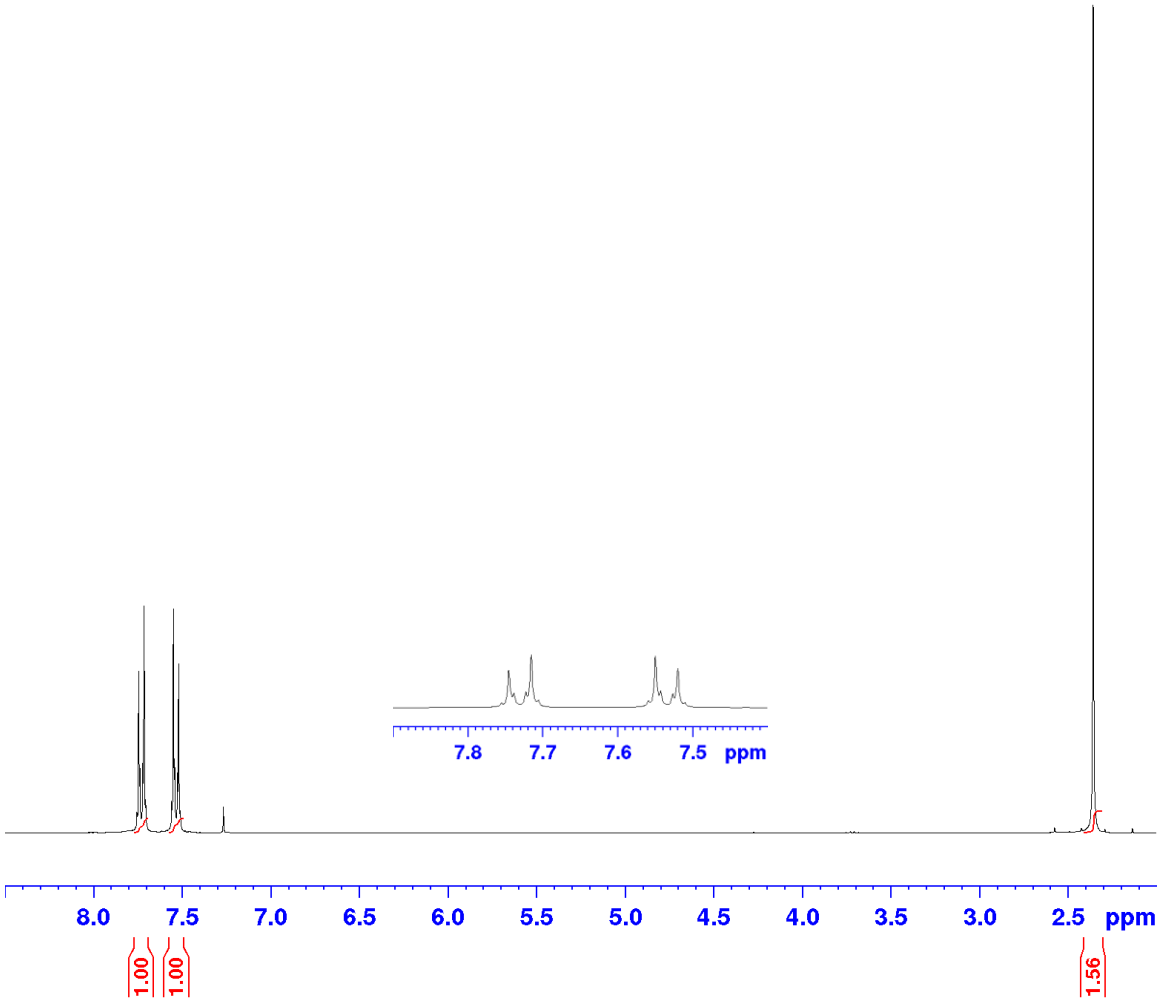
B: IR spectrum of 5-methyl-1,3,4-oxadiazol-2(*3H*)-one



Mon Apr 03 12:21:17 2017 (GMT-04:00)
FIND PEAKS:
Spectrum: p-br-oxadiazolinone
Region: 4000.00 400.00
Absolute threshold: 0.206
Sensitivity: 19
Peak list:

Position:	1492.33	Intensity:	0.146
Position:	1650.28	Intensity:	0.187
Position:	1796.48	Intensity:	0.139

C: IR spectrum 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one



D: ^{1}H-NMR spectrum 3-(4-bromophenyl)-5-methyl-1,3,4-oxadiazol-2(3H)-one

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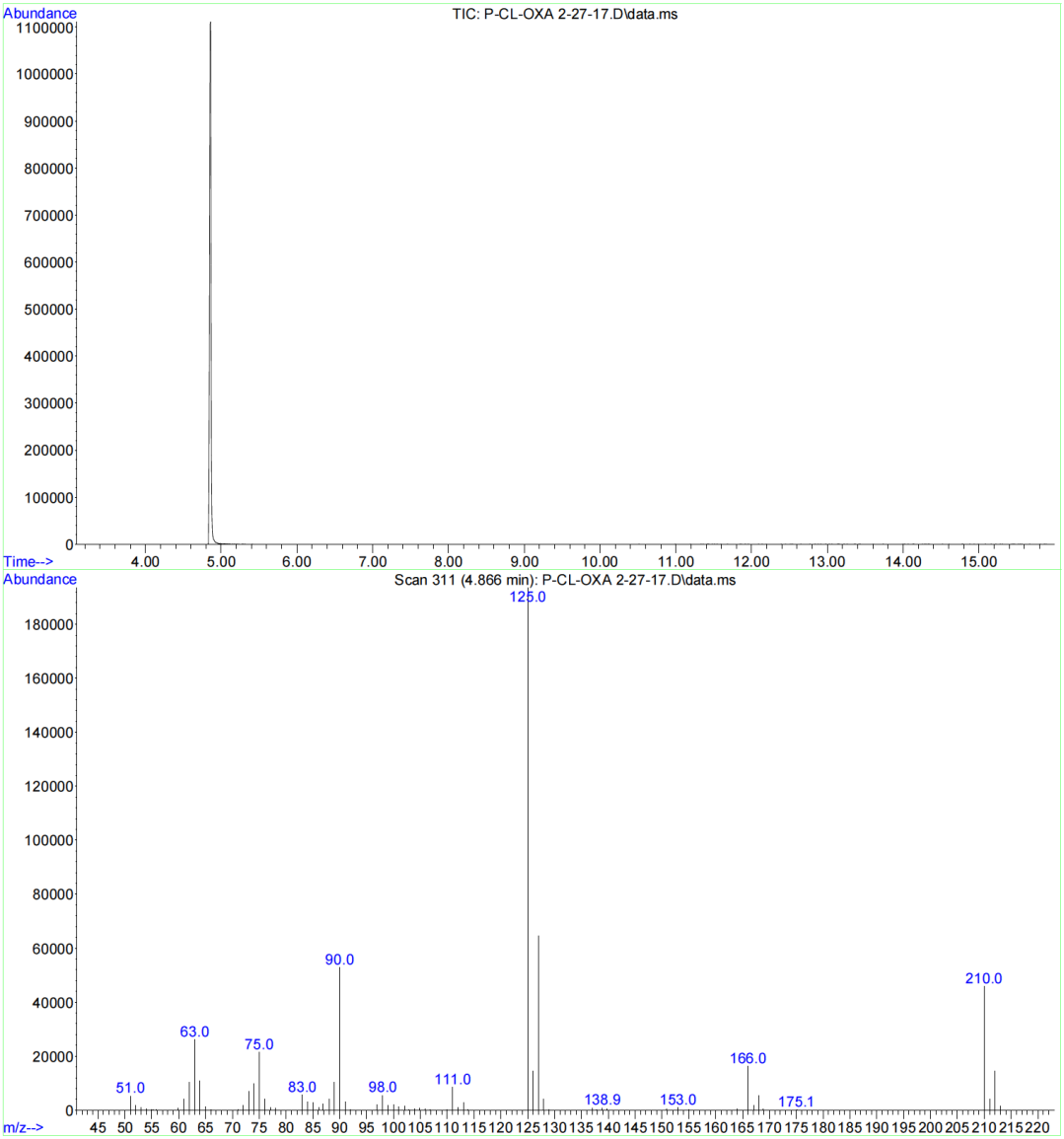
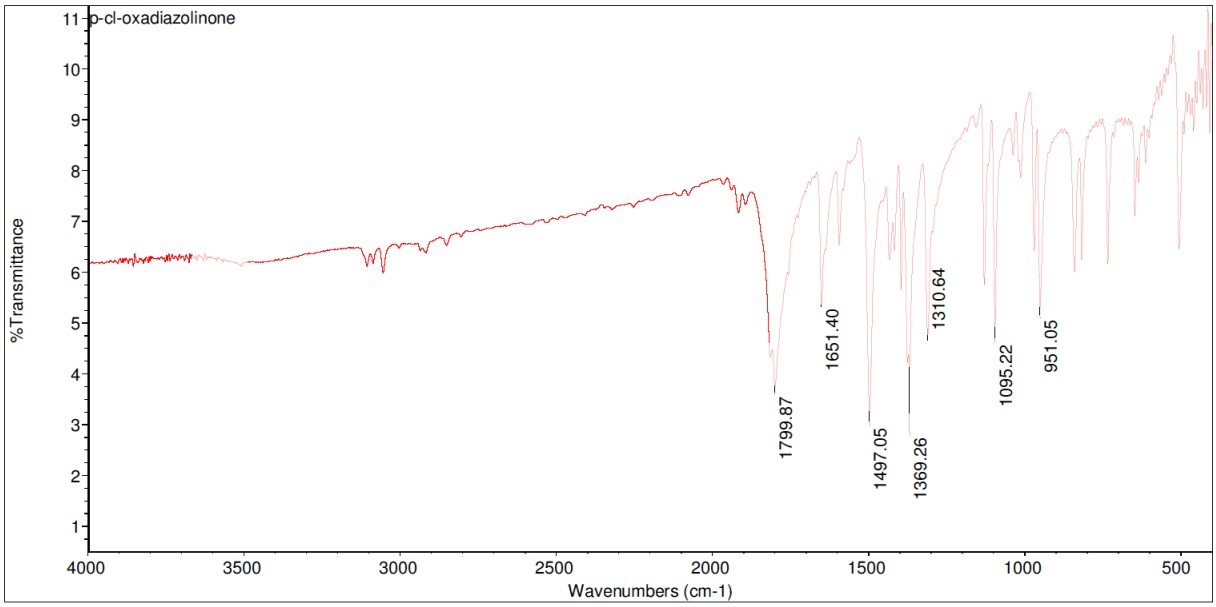
Misc Info :
Vial Number: 9



E: TOP: Chromatogram of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one

BOTTOM: Mass spectrum of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one



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Position:	1310.64	Intensity:	4.748
Position:	1369.26	Intensity:	4.115
Position:	1497.05	Intensity:	3.254
Position:	1651.40	Intensity:	5.353
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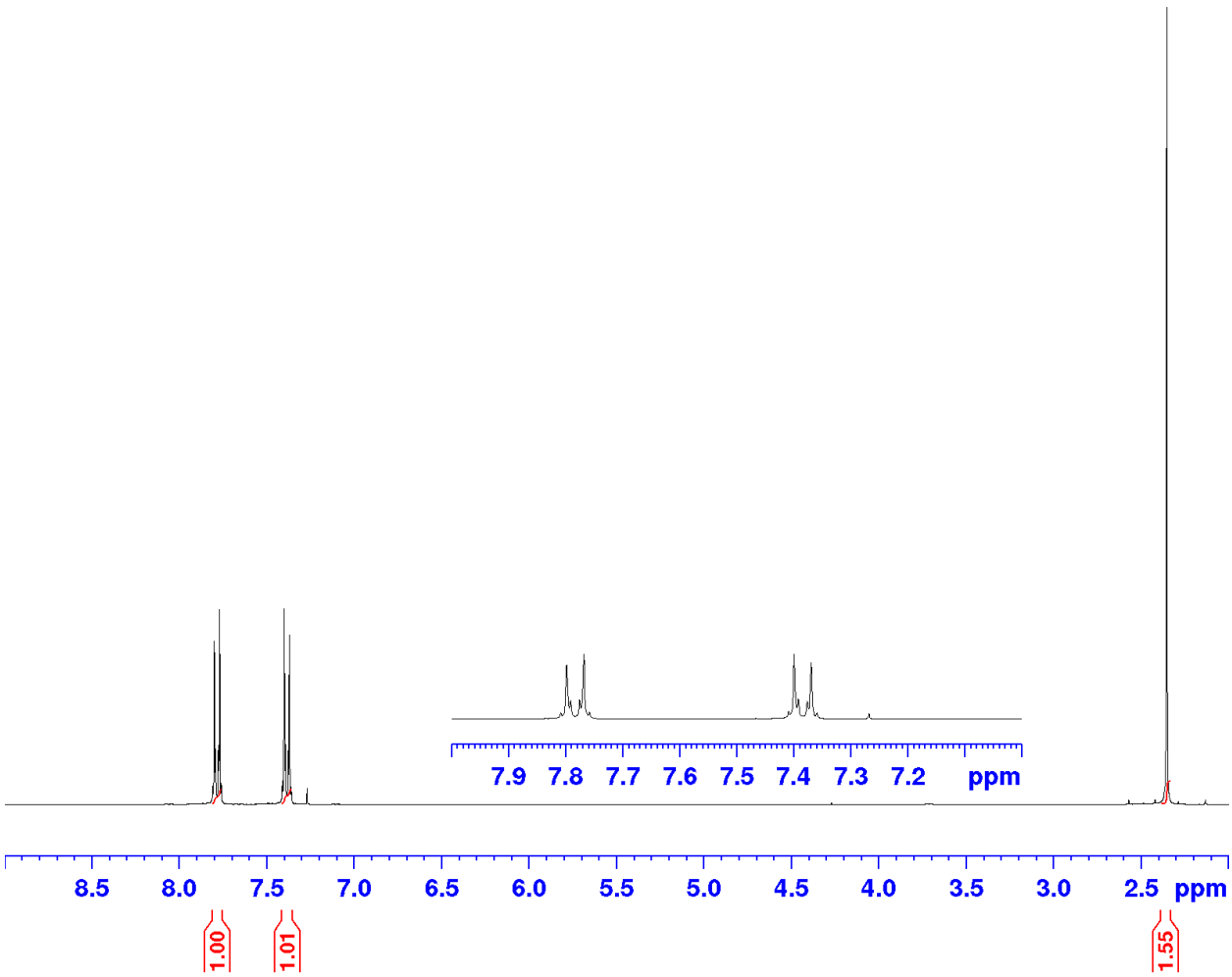
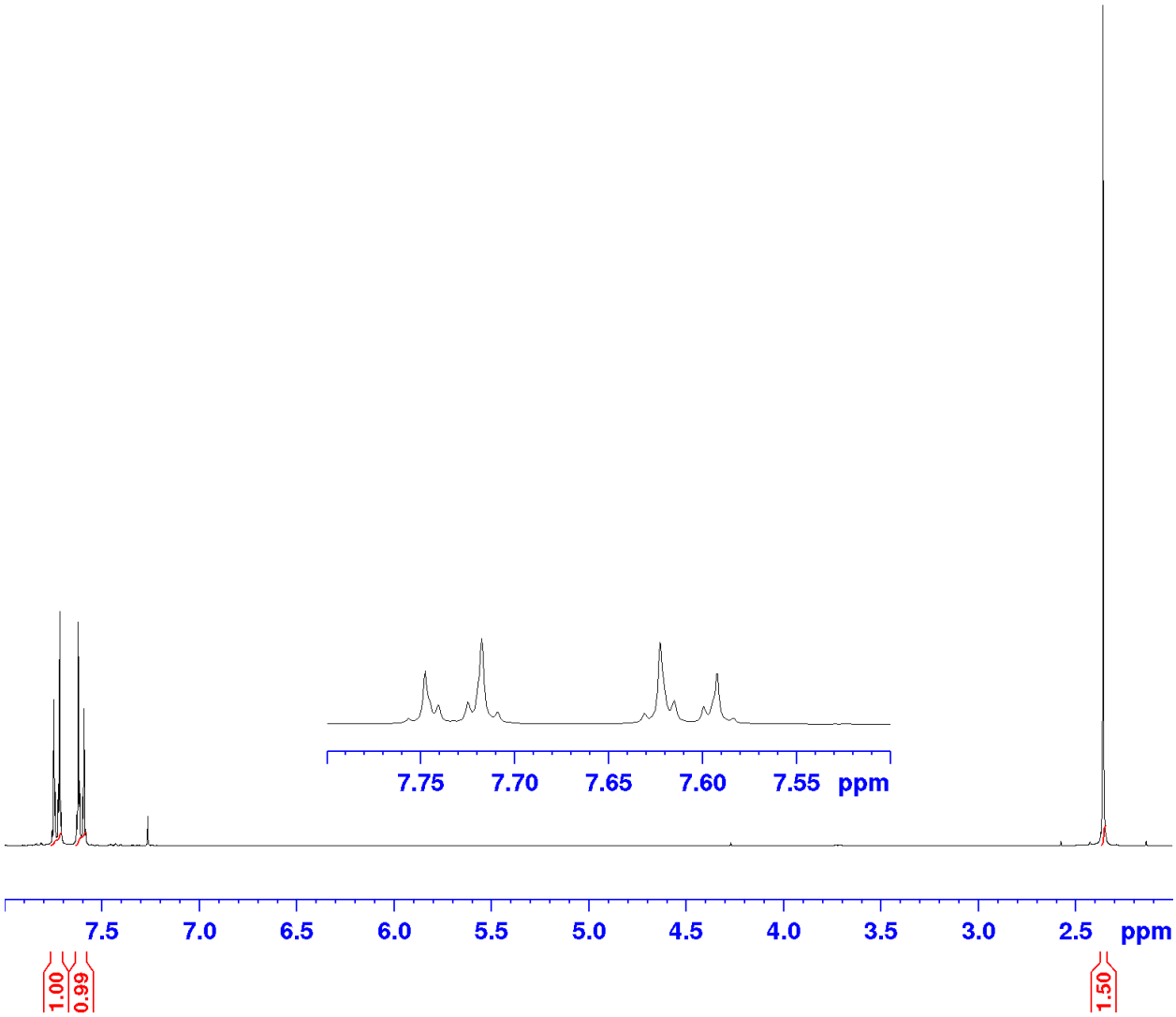
F: IR spectrum of 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one



G: ^{1}H-NMR spectrum 5-methyl-3-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3H*)-one



H: ^{1}H-NMR spectrum 5-methyl-3-(4-iodorophenyl)-1,3,4-oxadiazol-2(*3H*)-one

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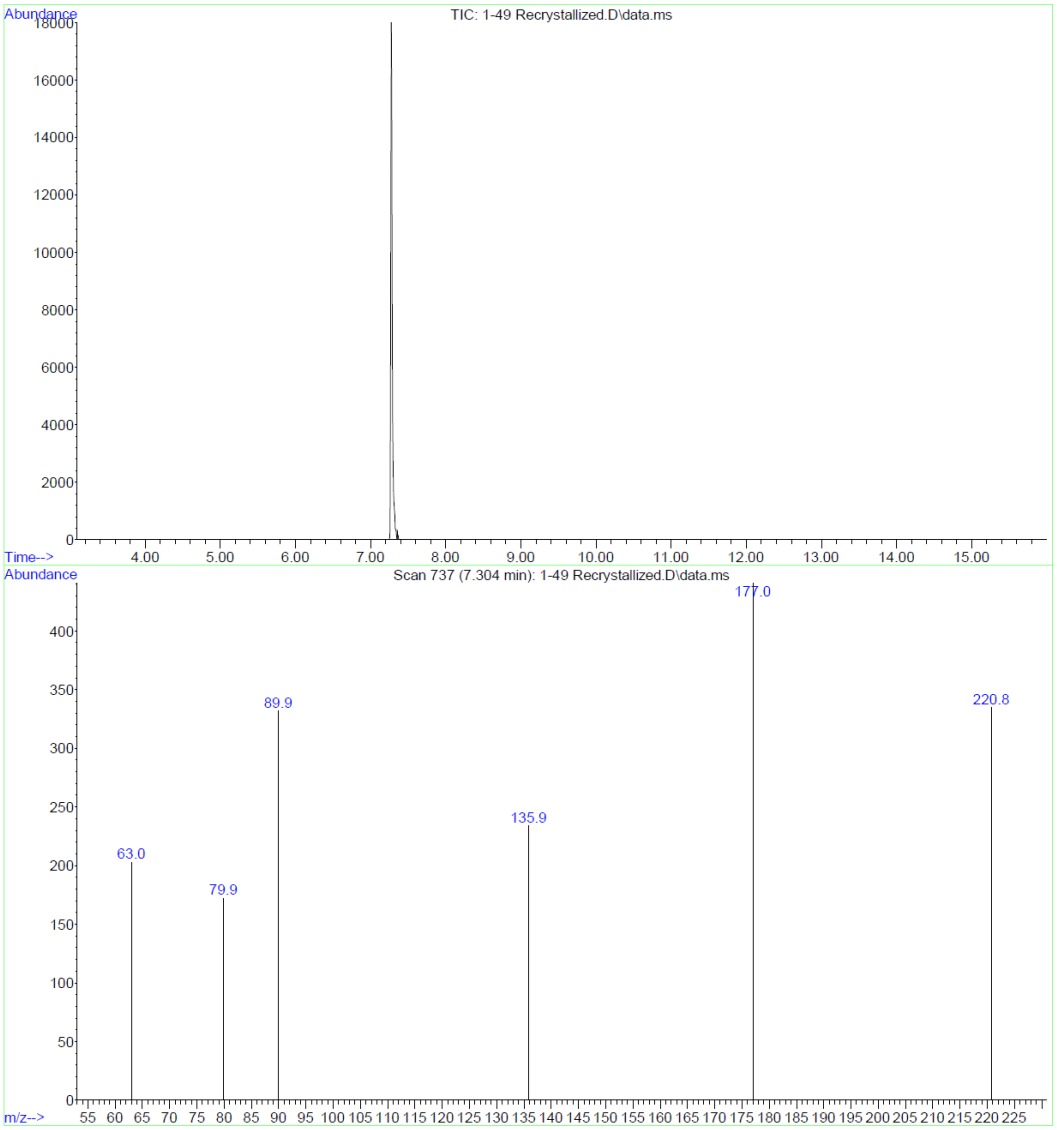
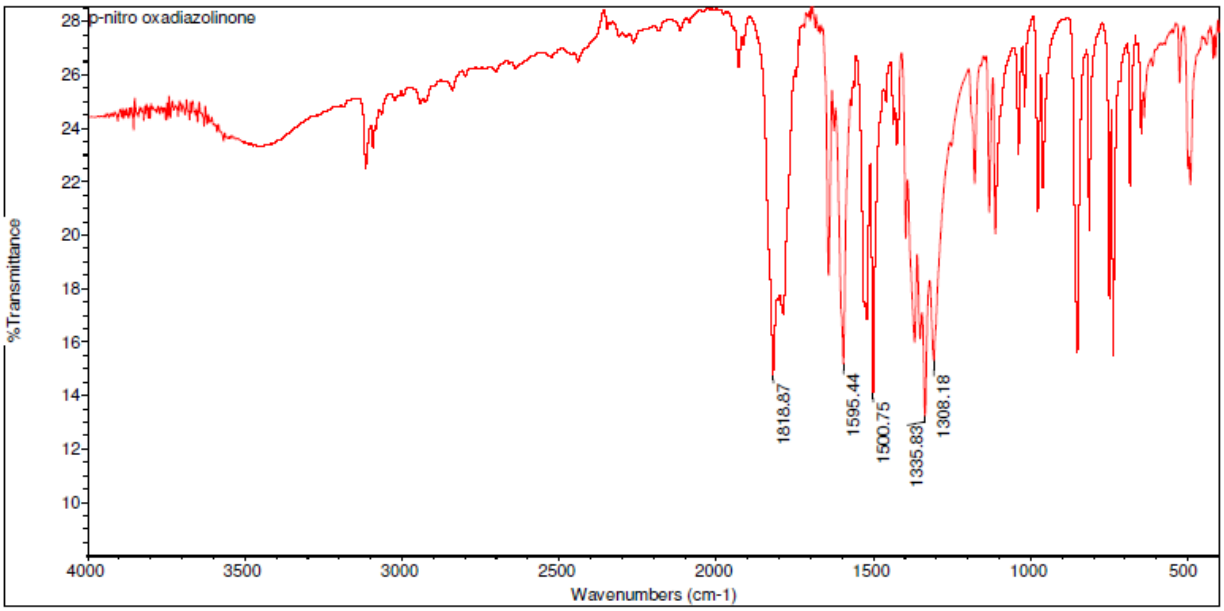
Misc Info :
Vial Number: 5



I: TOP: Chromatogram of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

BOTTOM: Mass spectrum of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one



Tue Jul 11 04:44:34 2017 (GMT-04:00)
FIND PEAKS:
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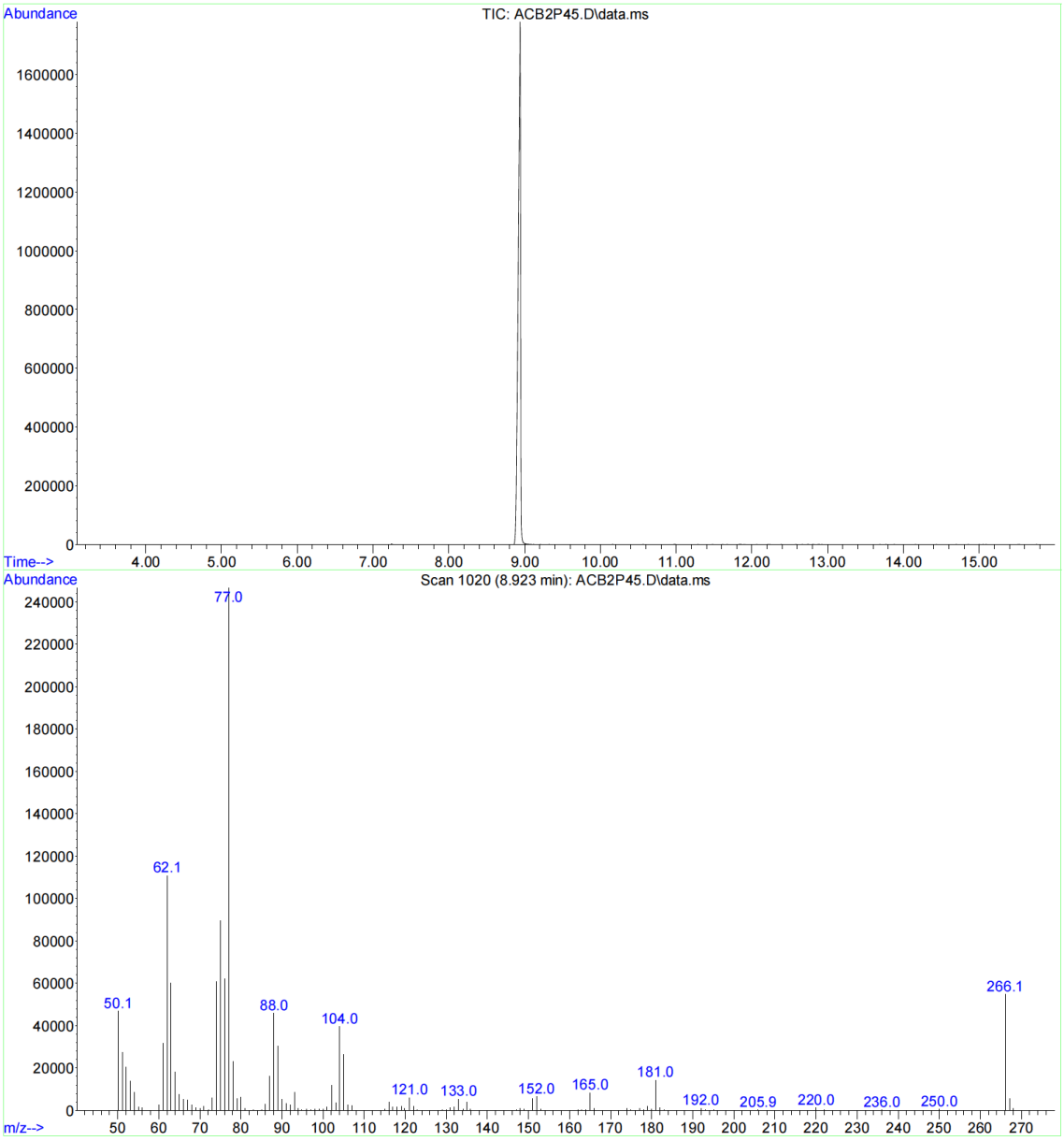
Absolute threshold: 15.456
Sensitivity: 50
Peak list:

Position:	1308.18	Intensity:	15.333
Position:	1335.83	Intensity:	13.259
Position:	1500.75	Intensity:	14.144
Position:	1595.44	Intensity:	15.187
Position:	1818.87	Intensity:	14.799

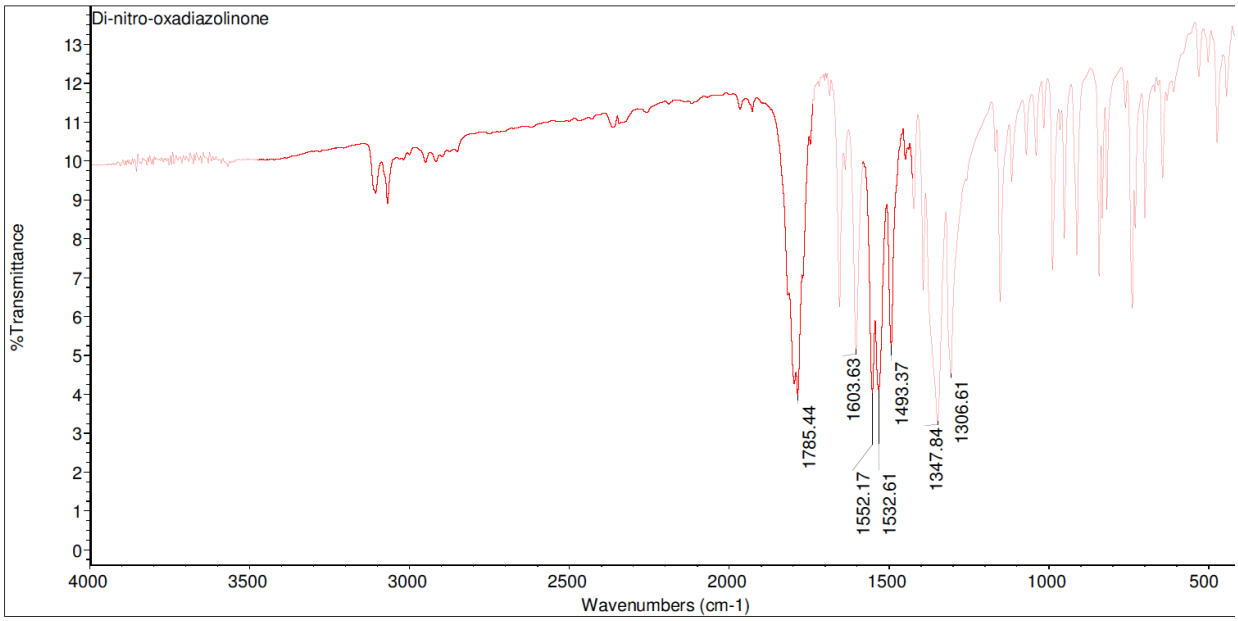
J: IR spectrum of 5-methyl-3-(4-nitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

File :D:\Turnbull\Amanda\ACB2P45.D
Operator : Amanda
Acquired : 22 Mar 2017 11:58 using AcqMethod AMANDA.M
Instrument : 5975C MSD
Sample Name: p-nitro-oxa 3.3 eq nitrated
Misc Info :
Vial Number: 5



K: TOP: Chromatogram of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

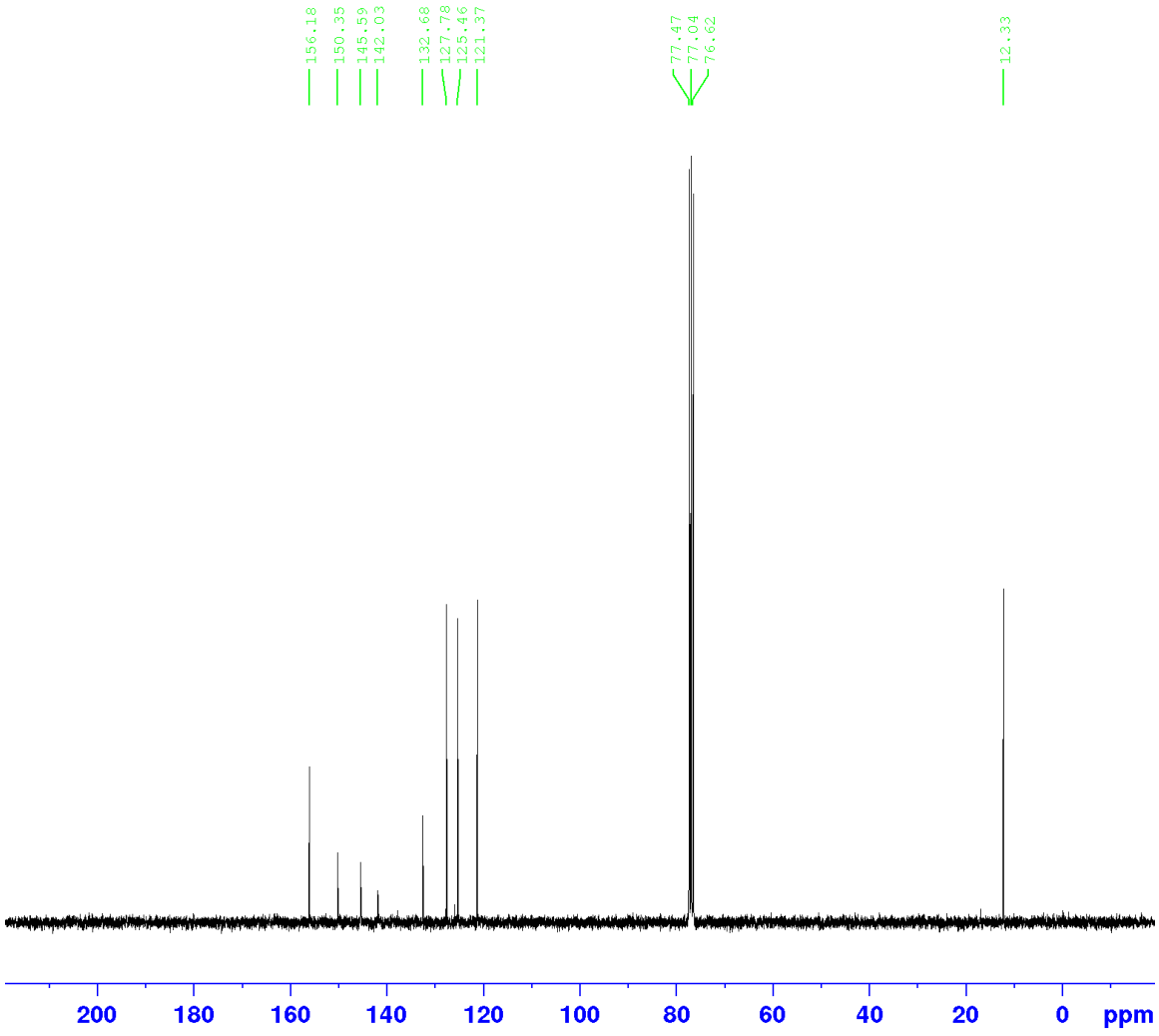
BOTTOM: Mass spectrum of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one



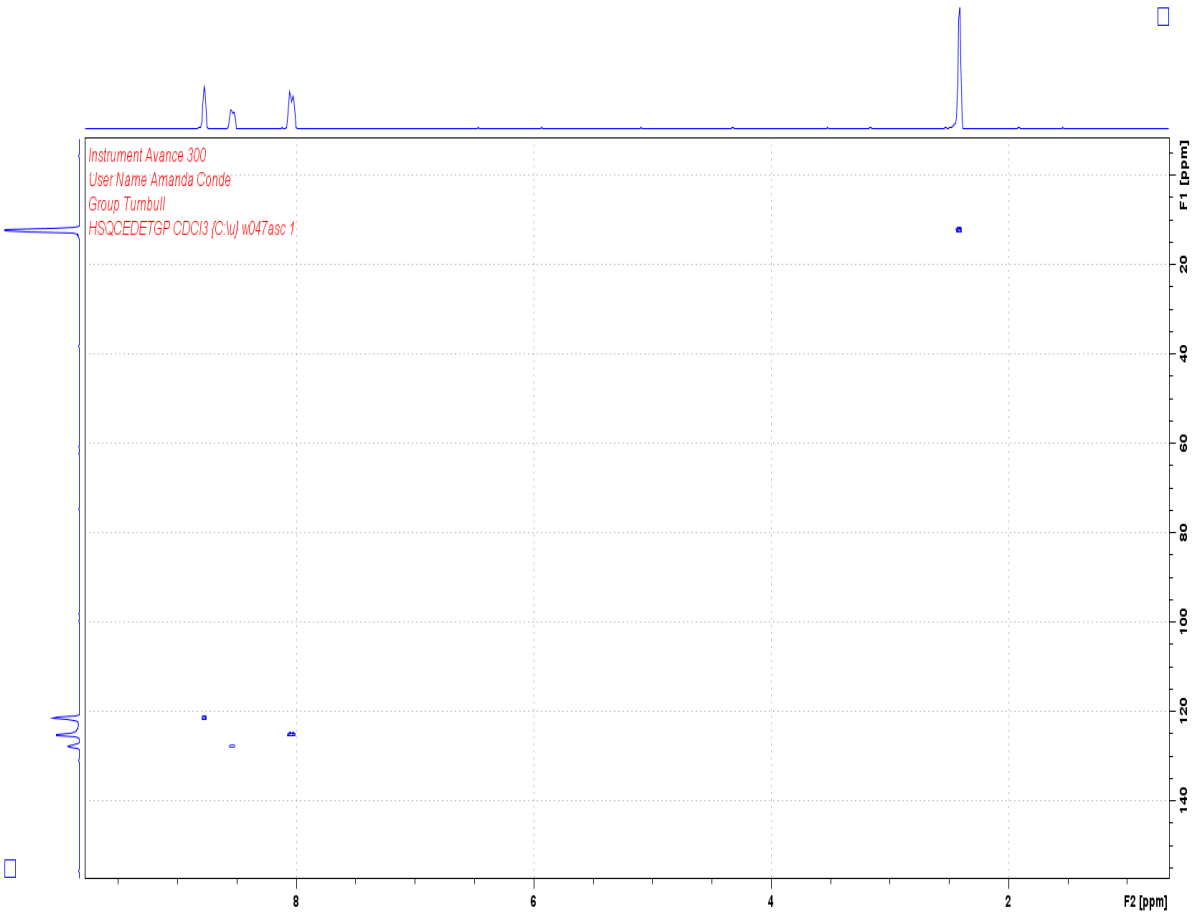
Mon Apr 03 12:10:26 2017 (GMT-04:00)
FIND PEAKS:
Spectrum: Di-nitro-oxadiazolinone
Region: 4000.00 400.00
Absolute threshold: 6.084
Sensitivity: 50
Peak list:

Position:	1306.61	Intensity:	4.517
Position:	1347.84	Intensity:	3.297
Position:	1493.37	Intensity:	5.266
Position:	1532.61	Intensity:	4.128
Position:	1552.17	Intensity:	4.033
Position:	1603.63	Intensity:	5.146
Position:	1785.44	Intensity:	3.988

L: IR spectrum of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

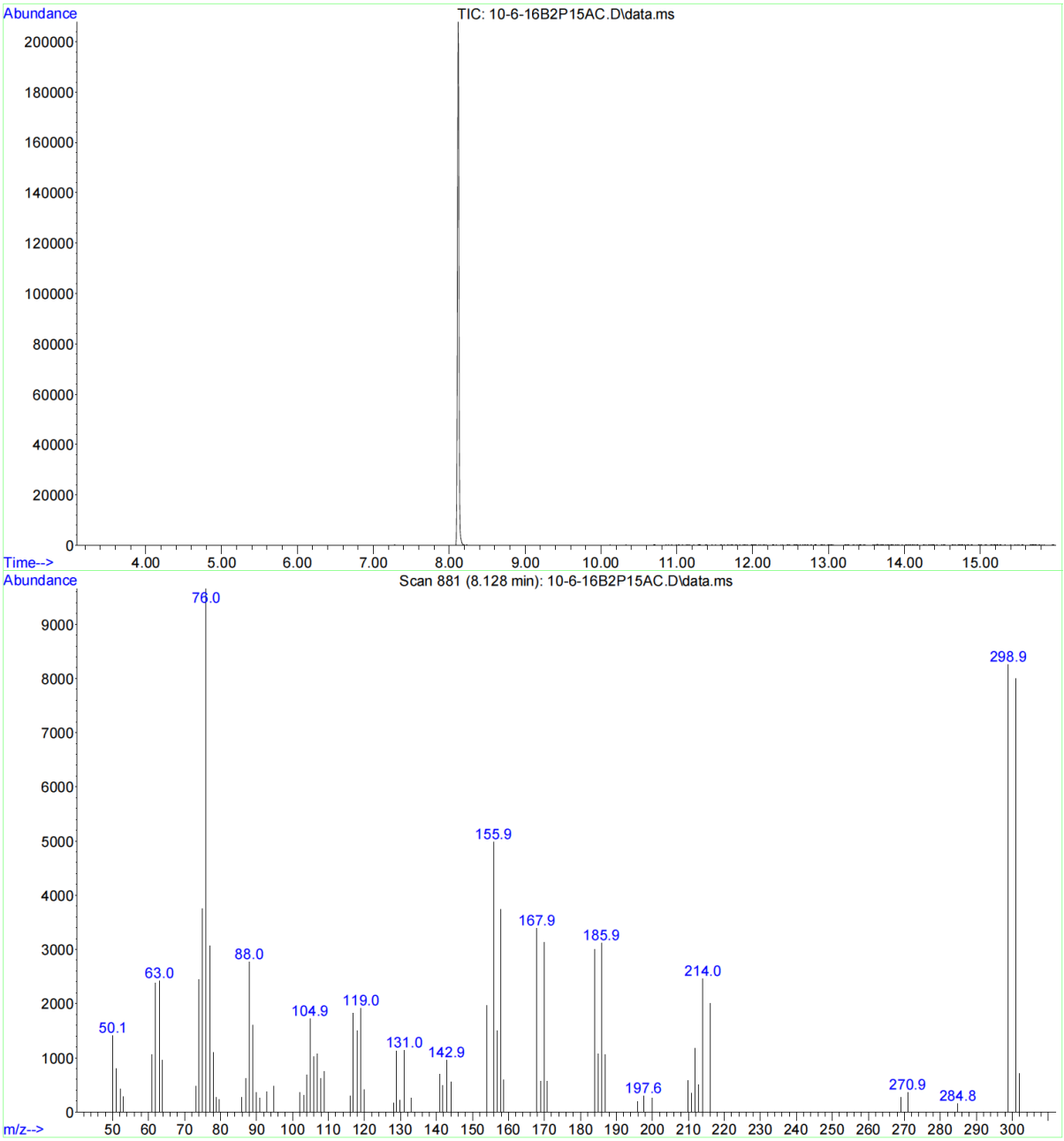


M: ^{13}C-NMR spectrum of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

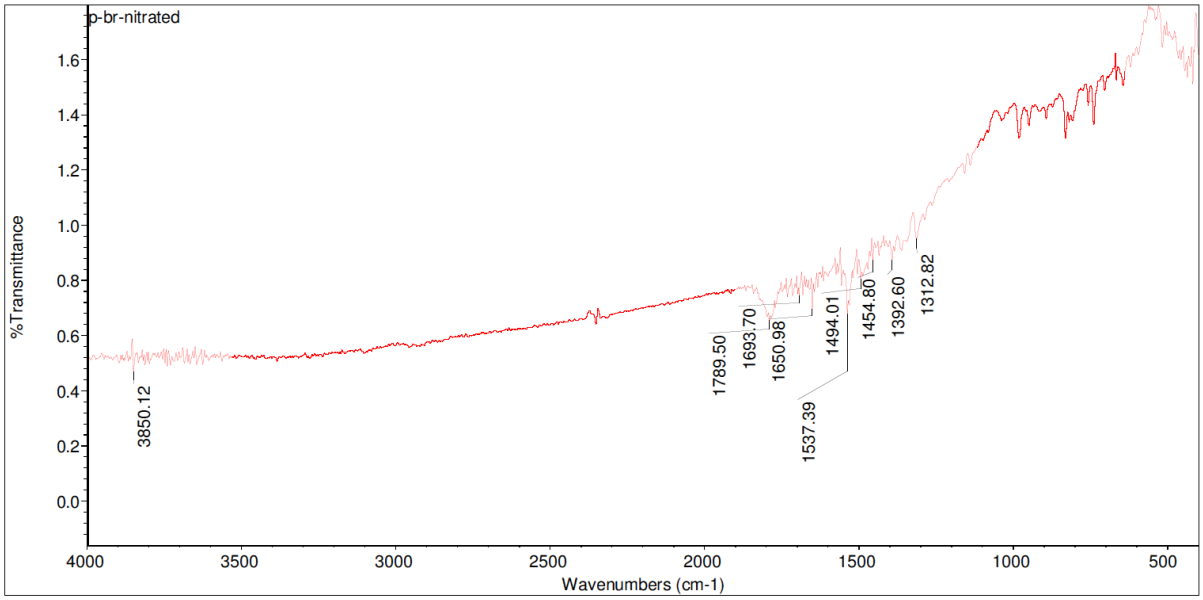


N: HSQC of 5-methyl-3-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2(*3H*)-one

File :D:\Turnbull\Amanda\10-6-16B2P15AC.D
Operator : Amanda
Acquired : 7 Oct 2016 15:08 using AcqMethod AMANDA.M
Instrument : 5975C MSD
Sample Name: p-br-oxa nitrated
Misc Info :
Vial Number: 8



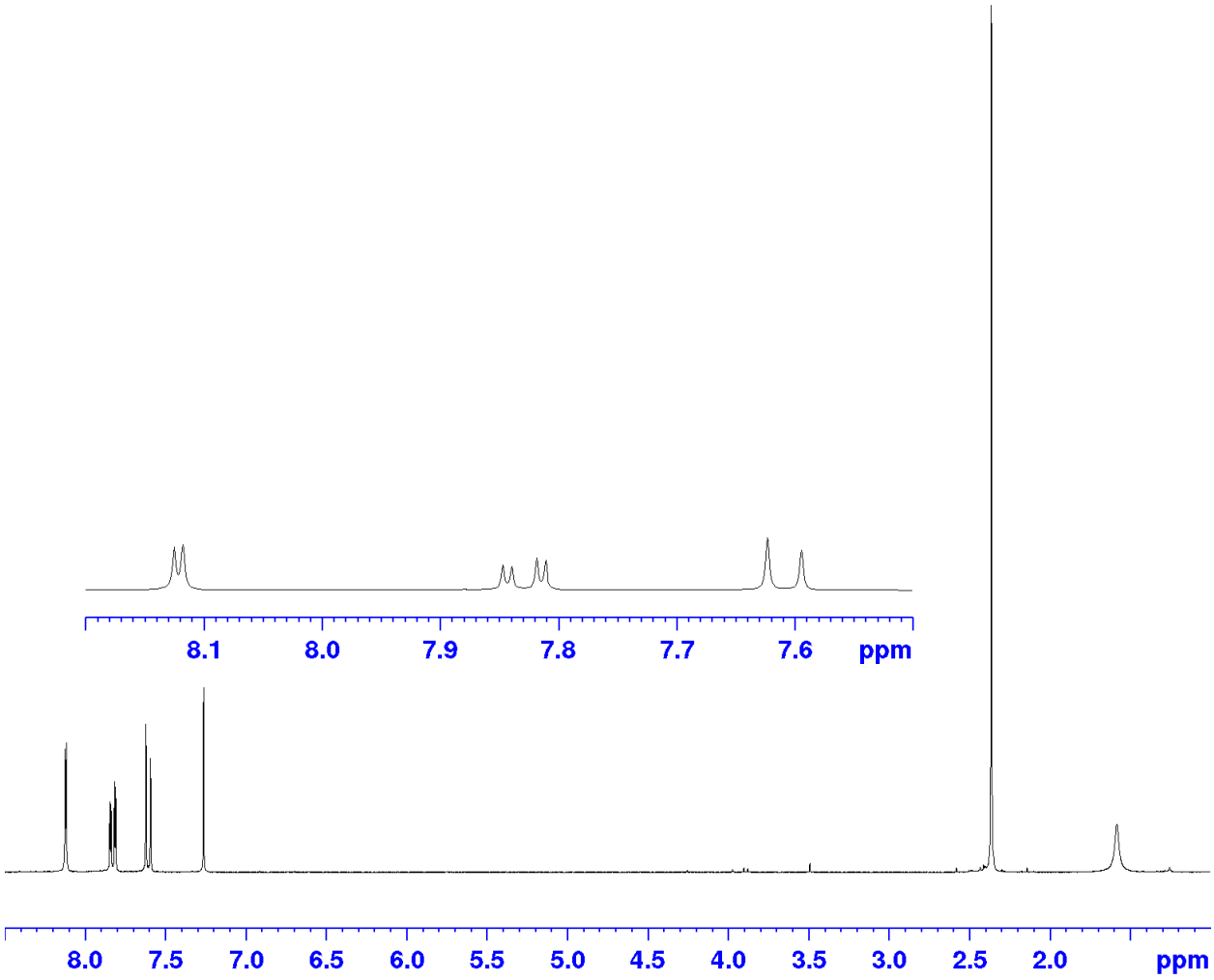
O: TOP: Chromatogram of 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one
BOTTOM: Mass spectrum of 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one



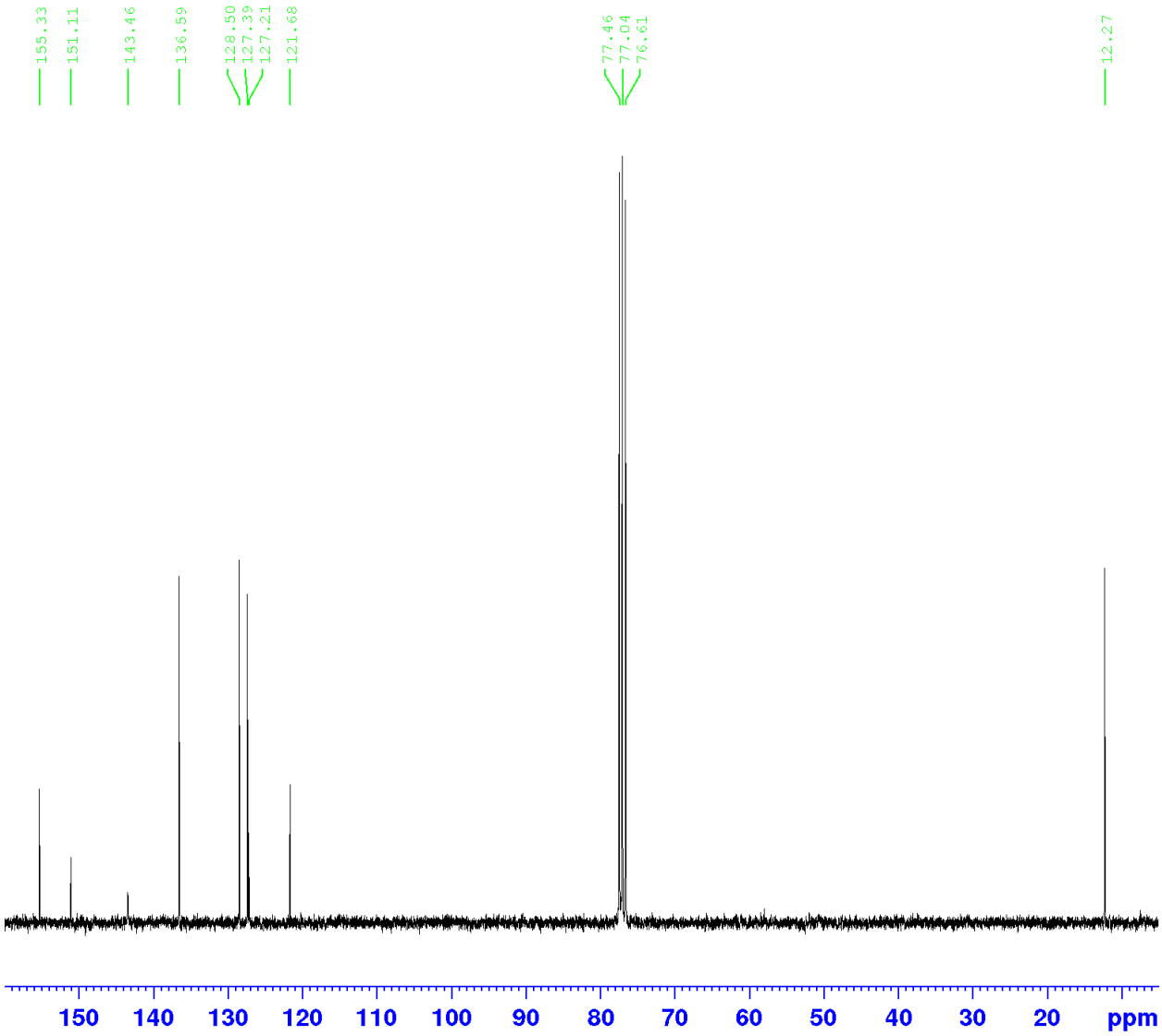
Tue Feb 21 03:55:18 2017 (GMT-05:00)
FIND PEAKS:

Spectrum:	p-br-nitrated		
Region:	4000.00	400.00	
Absolute threshold:	1.131		
Sensitivity:	42		
Peak list:			
Position:	1312.82	Intensity:	0.949
Position:	1392.60	Intensity:	0.873
Position:	1454.80	Intensity:	0.871
Position:	1494.01	Intensity:	0.803
Position:	1537.39	Intensity:	0.676
Position:	1650.98	Intensity:	0.694
Position:	1693.70	Intensity:	0.743

P: IR spectrum of 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one

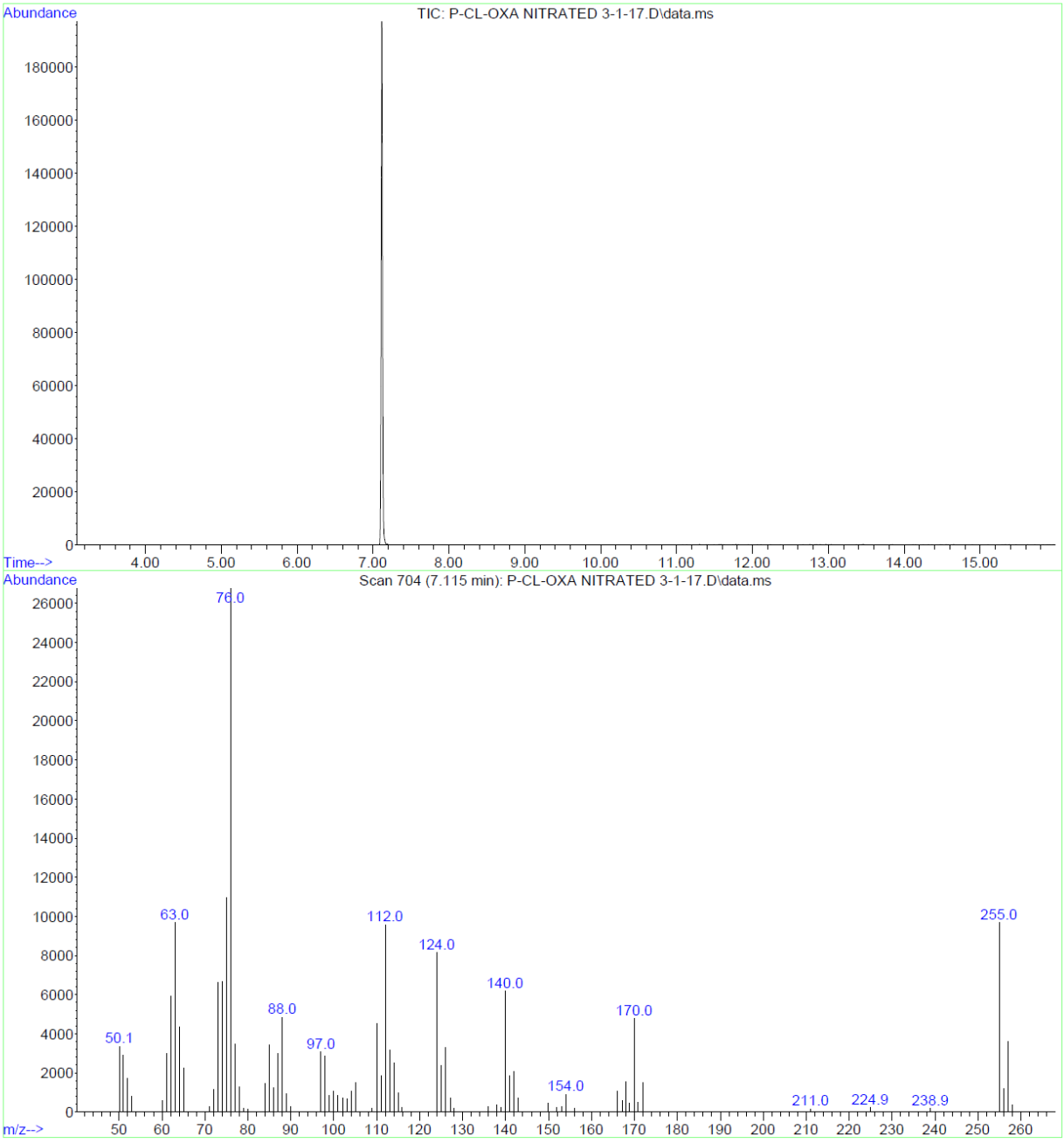


Q: ^{1}H-NMR spectrum 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one



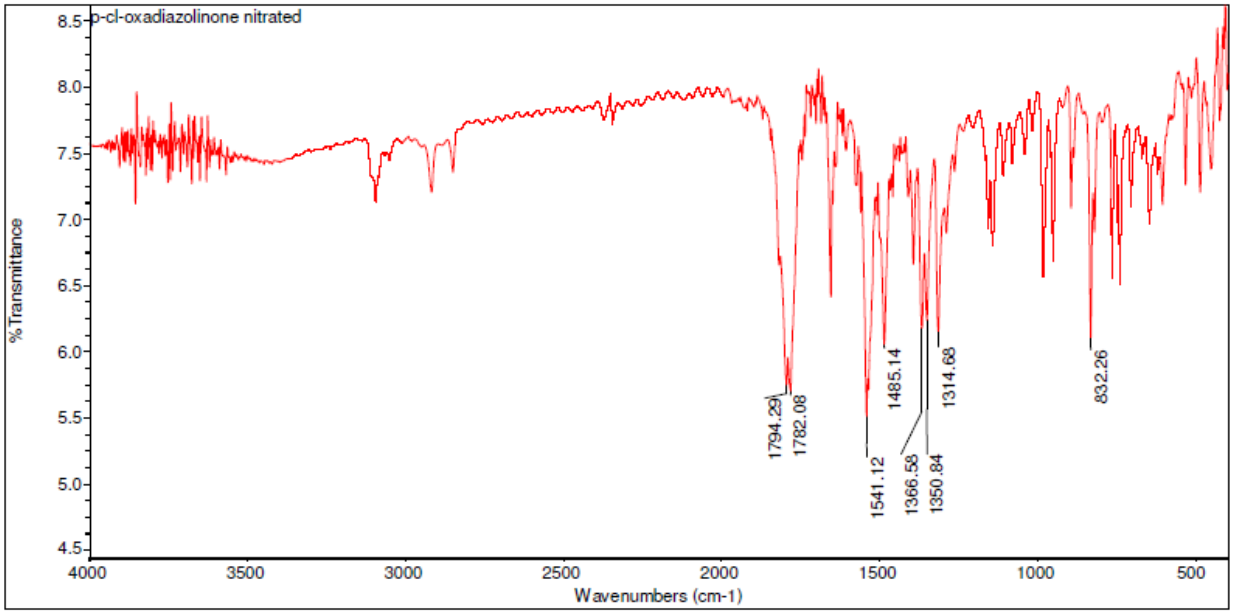
R: C^{13}-NMR 3-(4-bromo-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one

File :D:\Turnbull\Amanda\P-CL-OXA NITRATED 3-1-17.D
Operator : Amanda
Acquired : 1 Mar 2017 15:43 using AcqMethod AMANDA.M
Instrument : 5975C MSD
Sample Name: p-cl-oxa nitrated
Misc Info :
Vial Number: 9



S: TOP: Chromatogram of 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one

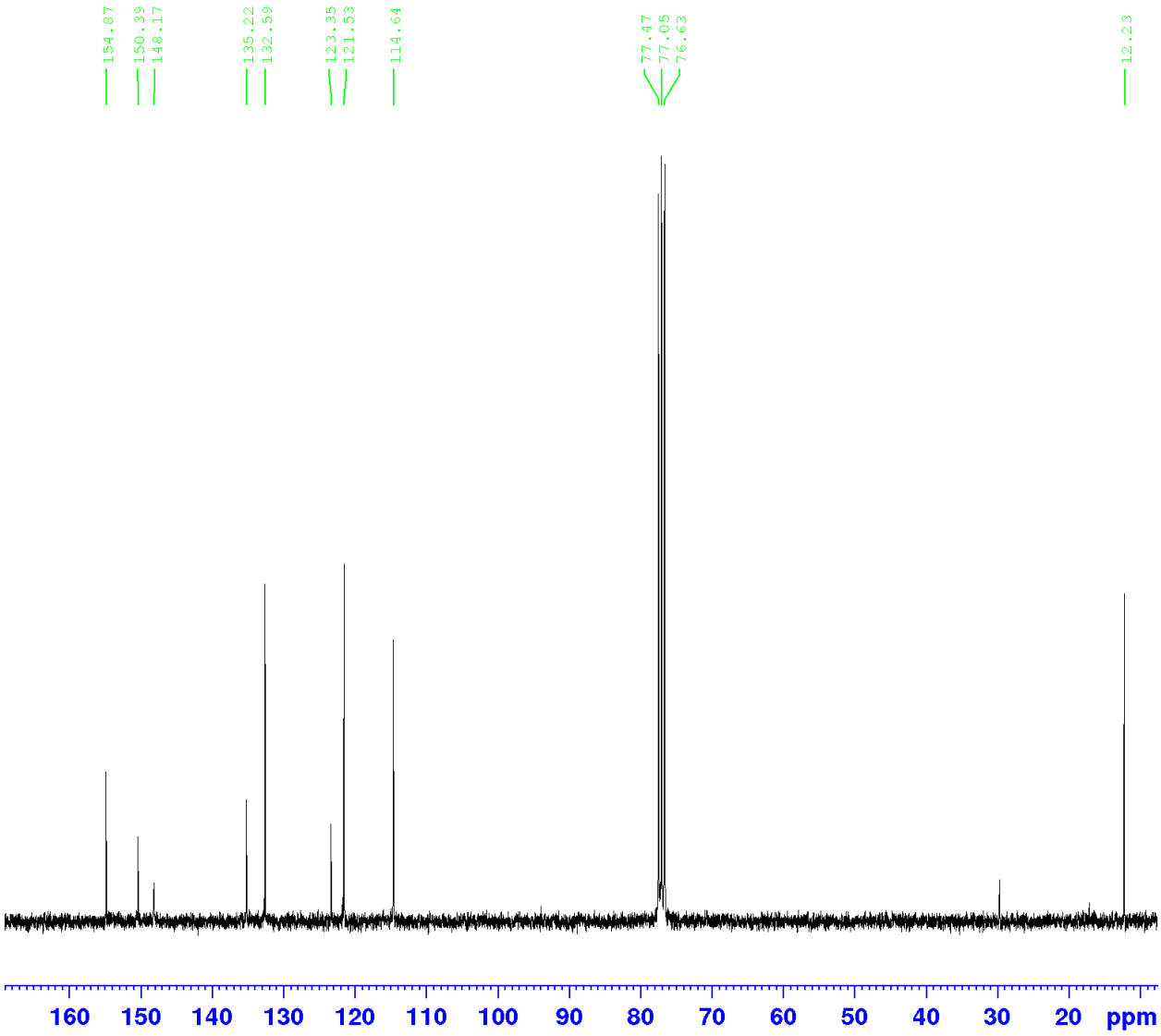
BOTTOM: Mass spectrum of 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one



Mon Apr 03 12:12:55 2017 (GMT-04:00)
FIND PEAKS:
Spectrum: p-cl-oxadiazolinone nitrated
Region: 4000.00 400.00
Absolute threshold: 6.263
Sensitivity: 50
Peak list:

Position:	832.26	Intensity:	6.108
Position:	1314.68	Intensity:	6.155
Position:	1350.84	Intensity:	6.240
Position:	1366.58	Intensity:	6.178
Position:	1485.14	Intensity:	6.058
Position:	1541.12	Intensity:	5.514
Position:	1782.08	Intensity:	5.706

T: IR spectrum of 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one



U: C^{13}-NMR 3-(4-chloro-2-nitrophenyl)-5-methyl-1,3,4-oxadiazol-2(*3H*)-one