REGIOSELECTIVE SYNTHESIS OF ISOXAZOLES BY HYPERVALENT IODINE(III) REAGENT MEDIATED OXIDATIVE CYCLOADDITION

A THESIS
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This thesis is dedicated to my

mom, dad, and sister Ally.

They have been there for me through every

obstacle and success in my life.

I could not have done this without their loving support.

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LIST OF SYMBOLS AND ABBREVIATIONS

HTIB: Hydroxy(tosyloxy)iodobenzene (Koser's reagent)

IBA: 2-Iodosylbenzoic acid

IBA-OTf: 2-[Hydroxy(trifluoromethanesufonyloxy)]iodobenzoic acid

DIB: (Diacetoxyiodo)benzene

PhIO: iodosylbenzene

PIFA: Bis(trifluoroacetoxy)iodobenzene

DCM: Dichloromethane

NMR: Nuclear Magnetic Resonance

ESI-MS: Electrospray Ionization Mass Spectrometry

HR-MS: High-Resolution Mass Spectrometry

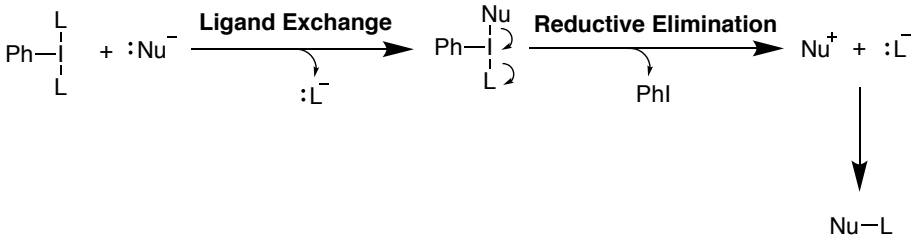
IR: Infrared

ABSTRACT

Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen atoms in the 1,2 positions. Isoxazole rings are found in natural products, such as ibotenic acid and muscimol. The isoxazole structure is incorporated in a variety of pharmaceutical agents. Substitution on different positions on the nucleus of the isoxazole results in various pharmacological effects. Specifically, isoxazole compounds are used in various types of pharmaceutical compounds to treat bacterial infections and pain relief. Oxidative cycloaddition of aldoximes with unsaturated substrates provides an efficient approach to the formation of heterocyclic compounds. More specifically, various isoxazoles can be easily prepared by the oxidative cycloaddition of aldoximes with unsaturated substrates in the presence of hypervalent iodine(III) reagents. Oxidation of aldoximes by hypervalent iodine(III) compounds produces nitrile oxides which further react with respective unsaturated substrates through a 1,3-dipolar cycloaddition reaction resulting in various isoxazole products. This technique is an efficient process that utilizes green chemistry. Here, we report an efficient synthetic approach for preparation of various regioselective 3,4-substituted isoxazoles and 3,4,5-substituted isoxazoles using [hydroxy(tosyloxy)iodo]benzene, commonly known as Koser's reagent. To our knowledge, this is the first time the 3,4-substituted isoxazole has been prepared. The oxidative cycloaddition proceeds at room temperature resulting in moderate to high yields. Structures of several isoxazole derivatives were established by X-ray crystallography. These isoxazole derivatives are stable compounds that have the potential to be useful for biologically active molecules and pharmaceutical reagents.

CHAPTER 1: Hypervalent Iodine

Iodine is known as the heaviest atom in the Periodic Table classified as a non-radioactive element and nonmetal.[1] One of the most important aspects of iodine is its ability to become hypervalent. Iodine is commonly seen in organic compounds as trivalent and pentavalent hypervalent iodine compounds.[1] Hypervalent iodine is used for many organic synthesis reactions such as halogenation reactions, oxidations, rearrangements, bond-forming reactions, and catalytic reactions.[1-2] Specifically, hypervalent iodine reagents are used for various oxidative transformations as they have characteristics that are similar to metals, while being non-toxic, environmentally friendly, commercially available, and relatively inexpensive.[1-3] Furthermore, they offer heteroatom ligands, mild reaction conditions, and rapid synthesis.[3-4] Hypervalent iodine(III) is known for its strong electrophilic characteristics and very high leaving group ability.[1,3] Hypervalent iodine reagents are commonly known for oxidative addition, ligand exchange, reductive elimination, ligand coupling, and catalyst.[1] More specifically, many reactions with hypervalent iodine reagents involve the two-step oxidative process of ligand exchange and reductive elimination (Scheme 1). The process starts with an external nucleophilic attack on hypervalent iodine(III) atom resulting in a ligand displacement followed by the reductive elimination of iodobenzene.[1,3]. This process is energetically favorable as it is associated with an increase in entropy.[3] Hypervalent iodine(III) is at the forefront of "green chemistry" for oxidative transformations.



Scheme 1. Ligand exchange and reductive elimination using hypervalent iodine(III)

CHAPTER 2: Isoxazole Compounds

Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen atoms in the 1,2-positions. Isoxazole rings are found in natural products, such as ibotenic acid and muscimol found in mushrooms (Figure 1).[5-6]

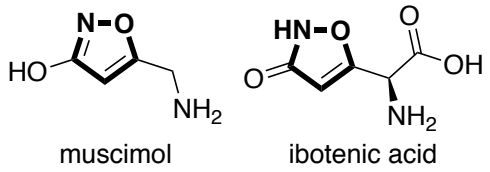


Figure 1. Natural products containing the isoxazole ring

Isoxazole compounds are incorporated in a variety of biologically active molecules and pharmaceutical reagents.[7] Specifically, the isoxazole ring is found in a variety of β-lactamase-resistant antibiotics, such as oxacillin, cloxacillin, and dicloxacillin, as well as in COX-2 inhibitors, such as valdecoxib (Figure 2).[8] Substitution to different positions of the isoxazole ring results in varied pharmaceutical effects. For example, these pharmaceutical reagents can treat bacterial infections as well as pain relief.[8]

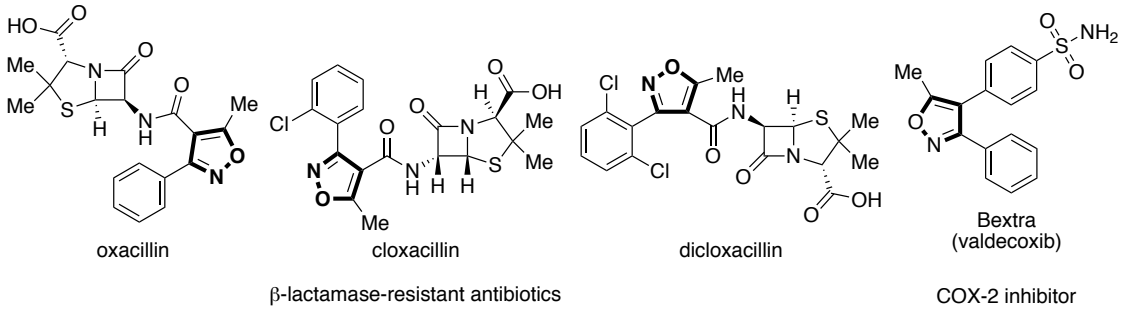


Figure 2. Isoxazole structure incorporated in pharmaceutical agents

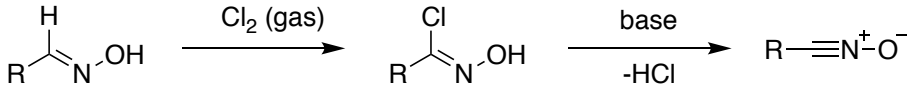
CHAPTER 3: Reactions Involving Nitrile Oxide

The chemistry of nitrile oxides has been studies in great detail over many years.[9] Particularly, aldoximes are good precursors for the generation of nitrile oxide species in situ with hypervalent iodine(III). Oxidative cyclization of aldoximes using hypervalent iodine(III) reagents provides an efficient synthetic approach to many five-membered heterocyclic systems.[9] Hypervalent iodine(III) mediated oxidation of aldoximes generates nitrile oxides which can further react with respective substrates via intermolecular or intramolecular 1,3-dipolar cycloaddition reactions resulting in various heterocyclic compounds.[10-11] Intermolecular nitrile oxide cycloadditions have been known for a very long time.[10-12] Specifically, nitrile oxide can react with alkenes, alkynes, nitriles, and aldehydes through the intermolecular 1,3-dipolar cycloaddition to give the respective heterocyclic products such as isoxazolines, isoxazoles, oxadiazoles, and dioxazoles.[13] Currently, the generation of isoxazoles and isoxazolines from nitrile oxides for various natural products and analogues has been a major focus.[14]

3.1. Common methods to obtain nitrile oxide

3.1.1. From aldoxime

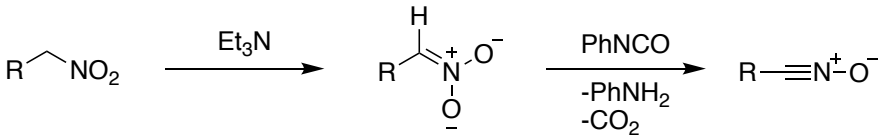
Nitrile oxide was first discovered in 1894 by Werner by the dehydrogenation of aldoxime. The nitrile oxide species was prepared by chlorination of benzaldoxime followed by base-mediated dehydrochlorination of the resulting benzohydroximoyl chloride (Scheme 2).[14] This two-phase method is still widely used today.



Scheme 2. Generation of nitrile oxide from aldoxime through chlorination

3.1.2. From aliphatic nitro compounds

Nitrile oxide can also be generated from nitro compounds utilizing Mukaiyama's procedure. From the procedure, the generation of nitrile oxide is produced by the dehydration of primary nitroalkanes with an aryl isocyanate, usually in the presence of Et_3N as a base (Scheme 3).[9]

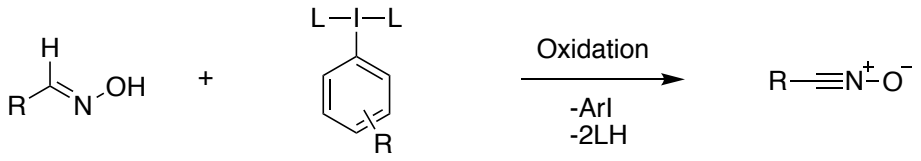


Scheme 3. Generation of nitrile oxide from nitro species

3.1.3. From hypervalent iodine(III)

Nitrile oxide can also be generated using hypervalent iodine(III) by direct oxidation of aldoxime into nitrile oxide species (Scheme 4). Various hypervalent iodine(III)

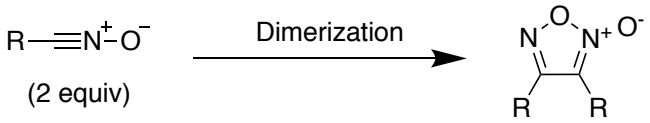
compounds, such as iodobenzene dichloride, iodosylbenzene, (diacetoxyiodo)benzene have been used as oxidants.[9]



Scheme 4. Generation of nitrile oxide from aldoxime using hypervalent iodine(III).

3.2. Nitrile oxide dimerization reaction

The nitrile oxide species is an unstable and highly reactive compound. While nitrile oxides are valuable for 1,3-dipolar cycloaddition reactions, their ability to undergo spontaneous dimerization can be used to prepare furoxans.[14] Nitrile oxides, especially for lower aliphatic and acyl nitrile oxides, can easily dimerize to form 1,2,5-oxadiazole-2-oxides (Scheme 5).[10]



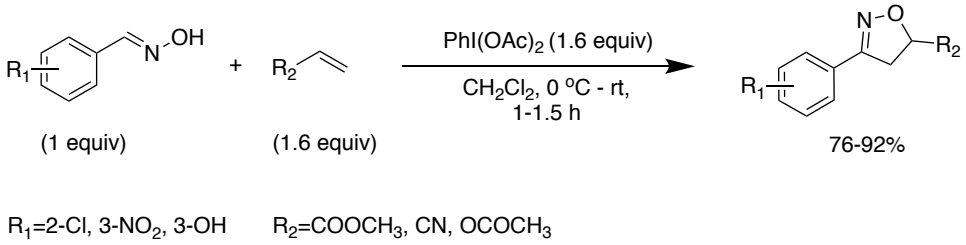
Scheme 5. Generation of furoxan species from nitrile oxide dimerization

3.3. Reactions with aldoximes and hypervalent iodine(III)

3.3.1. Oxidative cycloaddition of aldoxime and alkene

The generation of nitrile oxide in the presence of alkenes results in the intermolecular 1,3-dipolar cycloaddition leading to isoxazolines. In 2004, Das *et al*. reported the reaction of substituted benzaldoximes with (diacetoxyiodo)benzene and alkenes to give the corresponding isoxazolines in good yields (Scheme 6).[15] The presence of an electron-

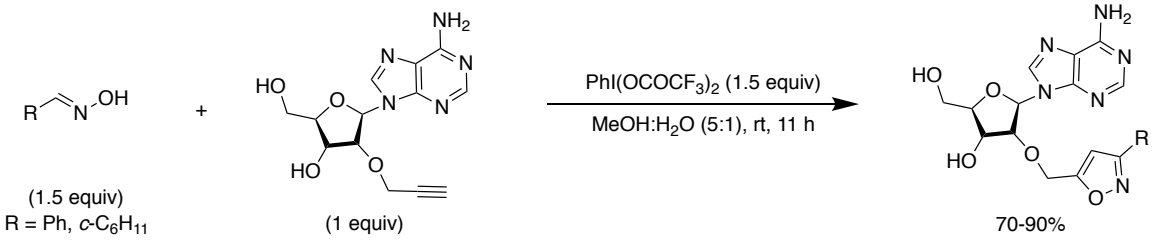
donating or an electron-withdrawing group on the aromatic ring of the aldoximes did not affect the reaction.[15]



Scheme 6. Oxidative cycloaddition of aldoxime and alkene

3.3.2. Oxidative cycloaddition of aldoxime and alkyne

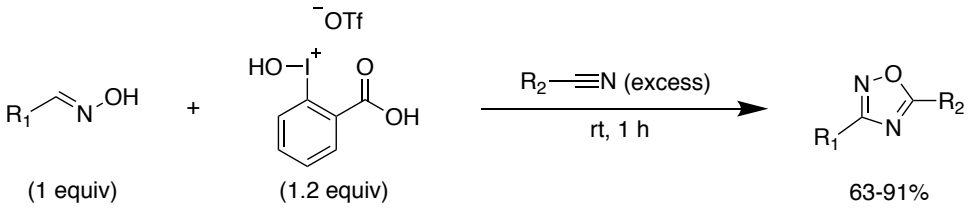
The generation of nitrile oxide in the presence of alkynes results in the intermolecular 1,3-dipolar cycloaddition leading to isoxazoles. In 2011, Jawalekar *et al*. reported the reaction of aromatic or aliphatic aldoximes with various alkynes using [bis(trifluoroacetoxy)iodo]benzene affording the corresponding isoxazole products in good yields (Scheme 7).[16] The hypervalent iodine(III) induced heterocyclization has been used for the efficient synthesis of nucleoside-substituted isoxazoles from aldoximes and nucleosides.[16]



Scheme 7. Oxidative cycloaddition of aldoxime and alkyne

3.3.3. Oxidative cycloaddition of aldoxime and nitrile

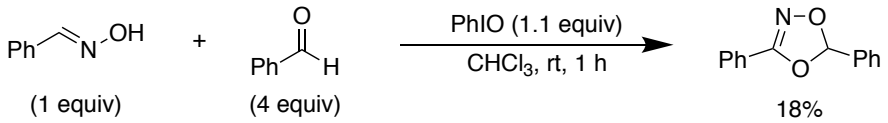
The generation of nitrile oxide in the presence of nitriles results in the intermolecular 1,3-dipolar cycloaddition leading to oxadiazoles. In 2016, Yoshimura *et al*. reported the treatment of aliphatic and aromatic aldoximes with IBA-OTf in acetonitrile solution to form the corresponding oxadiazoles in moderate to good yields (Scheme 8).[17] The reaction also proceeds smoothly in solutions of other nitriles under similar conditions affording 1,2,4-oxadiazoles in moderate to good yields.[17]



Scheme 8. Oxidative cycloaddition of aldoxime and nitrile

3.3.4. Oxidative cycloaddition of benzaldoxime and benzaldehyde

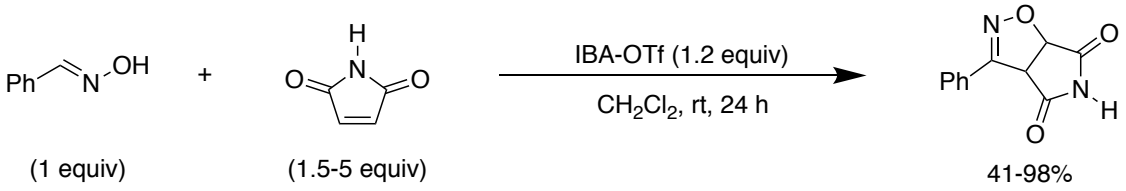
The generation of nitrile oxide in the presence of aldehydes results in the intermolecular 1,3-dipolar cycloaddition leading to dioxazoles. In 2002, Tanaka *et al*. reported the oxidative cycloaddition reaction of aldoxime with aldehyde using hypervalent iodine(III).[18] For example, the reaction of benzaldoxime with benzaldehyde using iodosylbenzene (PhIO) results in the product 3,5-diphenyl-1,2,4-dioxazole in low yield (Scheme 9).



Scheme 9. Oxidative cycloaddition of benzaldoxime and benzaldehyde

3.3.5. Oxidative cycloaddition of benzaldoxime and maleimide

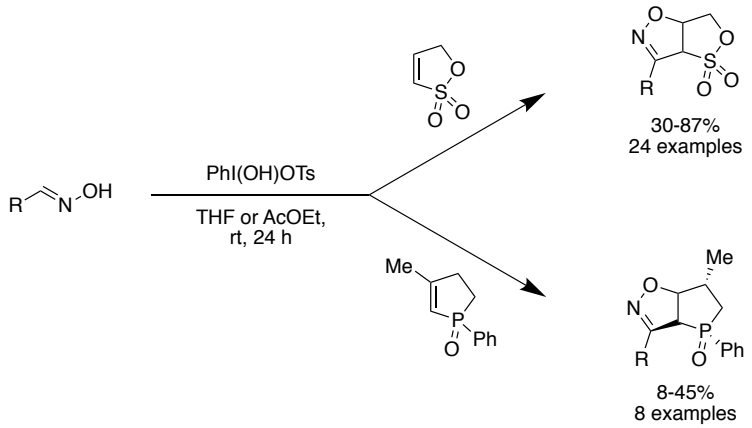
Nitrile oxides can further react with symmetrical heterocyclic alkenes to obtain pyrrolo-isoxazoles. In 2016, Yoshimura, Nguyen, *et al*. developed an efficient cycloaddition of heterocyclic alkenes with nitrile oxide species in situ from aldoximes using IBA-OTf (Scheme 10).[19] The corresponding heterocycles were obtained in moderate to high yields. This method was also developed in catalytic conditions.[19]



Scheme 10. Oxidative cycloaddition of benzaldoxime and maleimide

3.3.6. Oxidative cycloaddition of aldoxime with sultone and phospholene

Nitrile oxides can further react with asymmetrical heterocyclic alkenes to obtain isoxazoline-ring-fused heterobicyclic and heterobicyclic phospholene oxide products. In 2017, Yoshimura, Nguyen, *et al*. developed an efficient regioselective cycloaddition of heterocyclic alkenes with nitrile oxide species in situ from aldoximes using [hydroxy(tosyloxy)iodo]benzene (Scheme 11).[20] First, the oxidative cycloaddition of various aldoximes with 1-propene-1,3-sultone resulted in the respective isooxazoline-ring-fused heterobicyclic products in moderate to good yields.[20] Next, the reaction of aldoxime with 3-methyl-1-phenyl-2-phospholene-1-oxide under similar conditions resulted in the corresponding heterobicyclic phospholene oxides in moderate yields.[20]



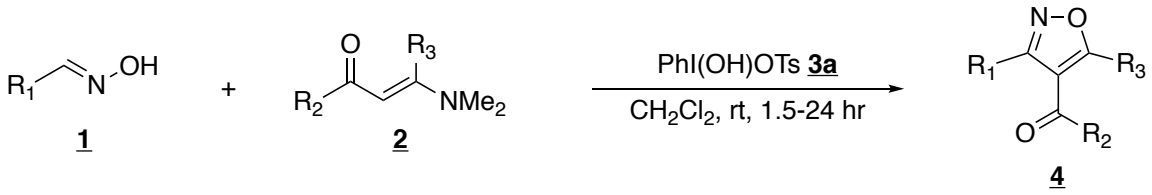
Scheme 11. Oxidative cycloaddition of aldoxime with sultone and phospholene

The generation of the 3,4,5-substituted isoxazoles from oximes and asymmetrical heterocyclic alkenes reported by our group in 2017 inspired us to synthesize the first 3,4-substituted isoxazole regioselectively by hypervalent iodine(III) using aliphatic unsaturated substrates. From the idea that the high electron withdrawing nature of the sultone and phospholene created a dipole within the unsaturated substrate allowing for regioselectivity in the electrostatic attraction with nitrile oxide, we hypothesized that we could modify an aliphatic unsaturated substrate to react with nitrile oxide. This idea inspired us to create the 3,4-substituted isoxazole by reacting the hypervalent iodine(III) mediated nitrile oxide with an aliphatic unsaturated substrate that possessed a dipole.

Chapter 4: Results and Discussion

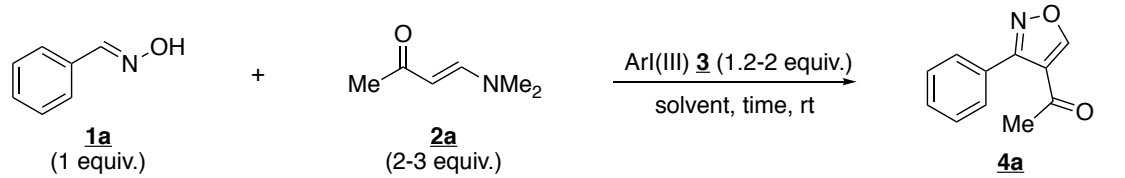
4.1. The aim of research

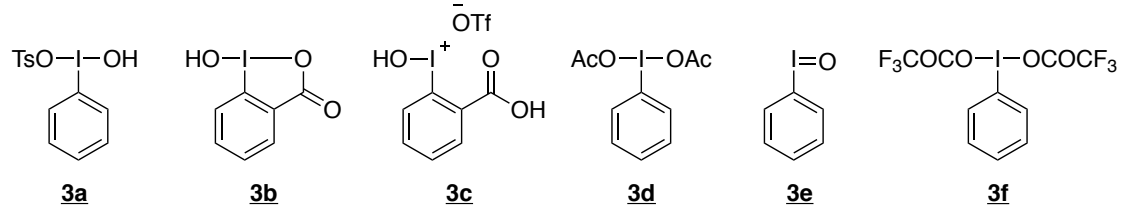
The aim of this research is to prepare 3,4-substituted isoxazoles and 3,4,5-substituted isoxazoles **4** regioselectively by hypervalent iodine(III)-mediated 1,3-dipolar cycloaddition of aldoximes **1** with enaminones **2**. The hypervalent iodine(III) species [hydroxy(tosyloxy)iodo]benzene **3a** was used in the reaction to oxidize aldoxime into nitrile oxide. To our knowledge, this is the first time that hypervalent iodine(III) could be utilized with aldoximes to create the regioselective 3,4-substitued isoxazoles.



Scheme 12. Koser's reagent mediate oxidative cycloaddition of aldoxime with enaminone

Table 1. Optimization of oxidative cycloaddition of (*E*)-benzaldehyde oxime **1a** with *trans*-4-dimethylamino-3-buten-2-one **2a** using iodine(III) reagents **3**[a]





Entry	Time (h)	Solvent	Enaminone **2a** (equiv)	ArI(III)	**4a** (%) [a,b]
1	3h	CH_2Cl_2	2	DIB **3d** (2)	34
2	3h	CH_2Cl_2	2	IBA **3b** (2)	none
3	3h	CH_2Cl_2	2	IBA-OTf **3c** (2)	trace
4	3h	CH_2Cl_2	2	HTIB **3a** (2)	76
5	6h	CH_2Cl_2	2	HTIB **3a** (2)	55
6	24h	CH_2Cl_2	2	HTIB **3a** (2)	64
7	3h	CH_2Cl_2	3	HTIB **3a** (2)	94 (92)
8	3h	CH_2Cl_2	3	DIB **3d** (2)	49
9	3h	CH_2Cl_2	3	PhIO **3e** (2)	16
10	3h	CH_2Cl_2	3	PIFA **3f** (2)	8
11	3h	$CHCl_3$	3	HTIB **3a** (2)	90
12	3h	$ClCH_2CH_2Cl$	3	HTIB **3a** (2)	76
13	3h	Heptane	3	HTIB **3a** (2)	11
14	3h	MeCN	3	HTIB **3a** (2)	80
15	3h	AcOEt	3	HTIB **3a** (2)	32
16	3h	MeOH	3	HTIB **3a** (2)	91
17[c]	3h	CH_2Cl_2	3	HTIB **3a** (2)	(85)
18	3h	CH_2Cl_2	3	HTIB **3a** (1.2)	82 (67)

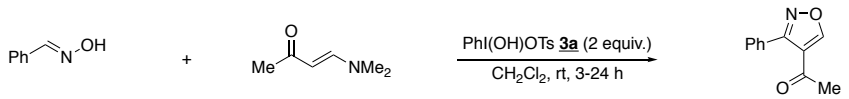
[a]Reaction conditions: (E)-Benzaldehyde oxime **1a** (0.250 mmol; 1 equiv) and *trans*-2-dimethylamino-3-buten-2-one **2a** (0.500-0.750 mmol; 2-3 equiv) with iodine(III) reagent **3** (0.500-0.600 mmol; 1.2-2 equiv) in various solvents were stirred for 3-24 h at room temperature. [b]Yields of product **4a** determined from ^1H spectra of reaction mixtures are shown (numbers in parentheses show yields of **4a** after column chromatography). [c]Large scale experiment: (*E*)-Benzaldehyde oxime **1a** (1.00 mmol; 1 equiv), *trans*-4-

dimethylamino-3-buten-2-one **2a** (3 mmol; 3 equiv), and Koser's reagent **3a** (2 mmol; 2 equiv) in DCM were stirred for 3 h at room temperature.

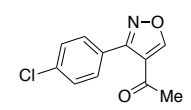
4.2. Optimization study using *trans*-4-dimethylamino-3-buten-2-one

First, we have tested the oxidative cycloaddition of (*E*)-benzaldehyde oxime **1a** (1 equiv) with *trans*-4-dimethylamino-3-buten-2-one **2a** (2-3 equiv) in several solvents using Koser's reagent **3a** (2 equiv). We have found that dichloromethane is the best solvent for the formation of the desired product **4a** using reagent **3a** (Table 1, entries 7, 11−16). Screening of the other hypervalent iodine(III) reagents **3b−3f** has demonstrated that Koser's reagent **3a** is the most efficient oxidant in this cycloaddition (entries 1-4, 7-10). Decreasing the amount of Koser's reagent **3a** verified that 2 equivalence gave the best yield for this reaction (entries 7, 18). For the reactions of Koser's reagent **3a** in dichloromethane, 3 hours gave the best yields for the reaction and increasing the reaction time resulted in lower yields of product **4a** (entries 4-6). Increasing the amount of *trans*-4-dimethylamino-3-buten-2-one **2a** resulted in a higher yield of product **4a** (entries 4, 7). This oxidative cycloaddition is also applicable on a larger scale using millimolar quantities of reagents. Specifically, the reaction of (*E*)-benzaldehyde oxime **1a** (1 mmol) with *trans*-4-dimethylamino-3-buten-2-one **2a** (3 mmol) using Koser's reagent **3a** (2 mmol) under optimized conditions afforded product **4a** in 85% yield (entry 17).

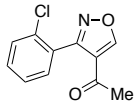
Table 2. Oxidative cycloaddition of aldoximes **1** with *trans*-4-dimethylamino-3-buten-2-one **2a** using Koser's reagent **3a**[a,b]



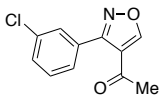
1a (1 equiv.) + **2a** (3 equiv.) → **4a** 92% (85%)[d] (X-ray)



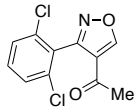
4b 85%



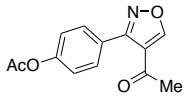
4c 81%



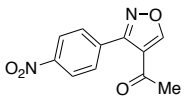
4d 97%



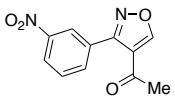
4e 91%



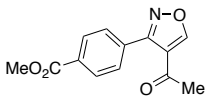
4f 81%



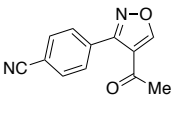
4g 76%



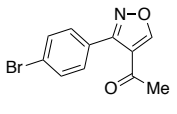
4h 98%



4i 82%



4j 94%



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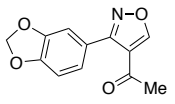

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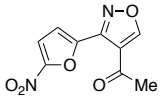
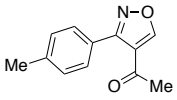
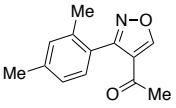


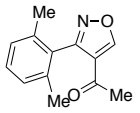
4m 93%



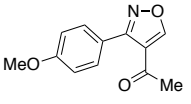
4n 74%



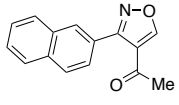
4o 95%



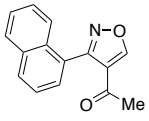
4p 59%



4q 72%



4r 88%



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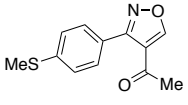
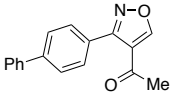
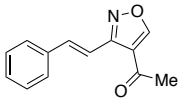


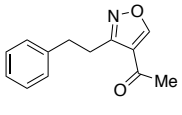
4t 34% (X-ray)



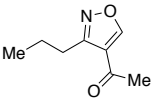
4u 74% (X-ray)



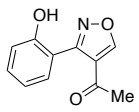
4v 62%



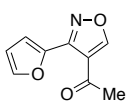
4w 56%



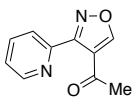
4x 46%



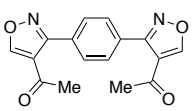
4y (15%)[c]



4z (13%)[c]



4aa (23%)[c]



4am (24%)[c,e]

[a]Reaction conditions: Aldoxime **1** (0.250 mmol; 1 equiv) and *trans*-2-dimethylamino-3-buten-2-one **2a** (0.750 mmol; 3 equiv) with Koser's reagent **3a** (0.500 mmol; 2 equiv) in

DCM were stirred for 3-24 h at room temperature. [b]Yields of products after column chromatography. [c]NMR yields of products. [d]Large scale experiment: (*E*)-benzaldehyde oxime **1a** (1.00 mmol; 1 equiv), *trans*-4-dimethylamino-3-buten-2-one **2a** (3 mmol; 3 equiv), and Koser's reagent **3a** (2 mmol; 2 equiv) in DCM were stirred for 3 h at room temperature. [e]Reaction conditions: 1,4-benezedicarboxaldehyde **1am** (0.125 mmol; 1 equiv) and *trans*-2-dimethylamino-3-buten-2-one **2a** (0.750 mmol; 6 equiv) with Koser's reagent **3a** (0.500 mmol; 4 equiv) in DCM were stirred for 24 h at room temperature.

4.3. Substrate scope study using *trans*-4-dimethylamino-3-buten-2-one

Using the optimized conditions with Koser's reagent **3a**, we have investigated the reaction of various substituted aldoximes **1** with *trans*-4-dimethylamino-3-buten-2-one **2a** leading to the respective isoxazole products **4** (Table 2). The structures of products **4a**, **4t**, and **4u** were established by X-ray crystallography (see Figures S1, S2, and S3 in the experimental section). In general, substitution of (*E*)-benzaldehyde oxime **1a** with either electron-donating or electron-withdrawing groups, under optimized reaction conditions, afforded target products **4a**−**x** in moderate to good yields with excellent regioselectivity.

The reactions of sterically hindered aldoximes, such as 2,6-dimethyl-benzaldoxime **1p** or 2,6-dicholorobenzaldoxime **1e**, gave the corresponding products **4p** and **4e** in moderate to good yields. Interestingly, the presence of bulky chlorine groups in **1e** and **1c** corresponding to products **4e** and **4c** were still isolated in good yields of 91% and 81%, respectively. This result is likely due to the domination of electrostatic effect over steric effect.

The reactions of electron rich aldoximes, such as 4-(methylthio)benzaldehyde oxime **1t**, 2-hydroxybenzaldehyde oxime **1y**, (*E*)-furan-2-carbaldehyde oxime **1z**, and (*E*)-picolinaldehyde oxime **1aa**, resulted in the corresponding products **4t, 4y, 4z, 4aa** in moderate to low yields. In particular, the yield of product **4t** was low (34%), probably due to competitive oxidation on sulfur.[21] However, we were not able to detect the corresponding sulfoxides in the reaction mixture. Product **4y** was not isolated as this product produced a complex mixture that could not be isolated as a clean product. From Raymond *et al*. 2015, it is known that Boulton-Katritzky rearrangement and Neber rearrangement can occur on *O*-hydroxy isoxazole compounds.[22] Therefore, we believe this product may have decomposed or rearranged into an unstable derivative. Interestingly, when the reaction with (*E*)-furan-2-carbaldehyde oxime **1z** was modified with an additional nitro group, (*E*)-5-nitrofuran-2-carbaldehyde oxime **1m**, the corresponding products **4z** and **4m** increased from (13%) to 93%. This can be attributed to the high electron withdrawing properties of nitro pulling electron density off furan, therefore ceasing oxidative competition between furan and Koser's reagent and allowing the reaction to proceed. If we were able to modify the pyridine reactant **1aa** with a nitro, we would hypothesize that the yield would increase, but the reaction was not further studied.

The reactions of aliphatic aldoximes, such as (1*E*, 2*E*)-cinnamaldehyde oxime **1v**, (*E*)-3-phenylpropanal oxime **1w**, and butyraldoxime **1x**, gave the corresponding products **4v**, **4w**, **4x** in moderate to low yields. This lowered yield can be attributed to the relatively low stability of the aliphatic nitrile oxides towards oxidation. Specifically,

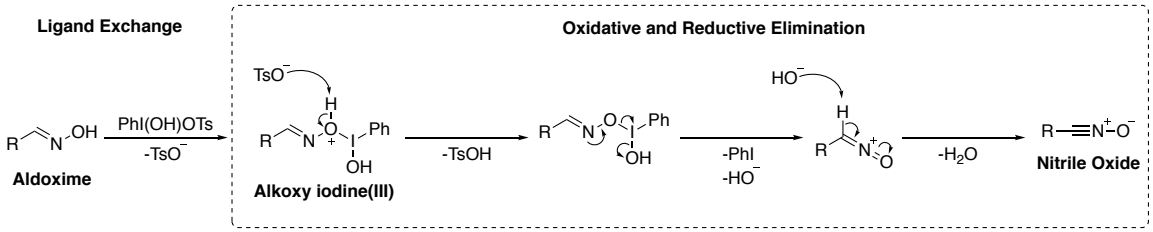
aliphatic nitrile oxides can easily dimerize into the furoxan species[6], which was observed in the case of butyraldoxime **1x.**

The reaction of 1,4-Benzenedicarboxaldeyde **1am** gave the corresponding detected product **4am** in low yield but was not isolated cleanly. This lowered yield could be attributed to the need for an increased amount of oxidative reagent, but this reaction was not further studied.

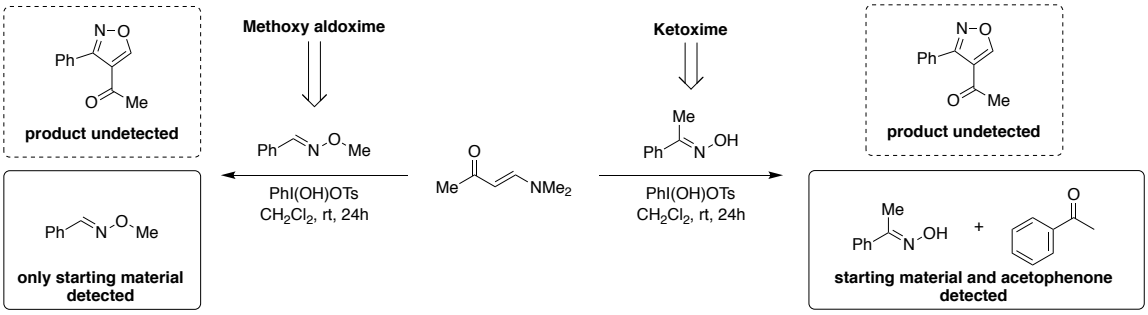
4.4. Reaction mechanism study: Generation of nitrile oxide

Control experiments were performed to study the mechanism of the 1,3-dipolar cycloaddition of benzaldoximes with enaminones. In the proposed mechanism, the generation of nitrile oxide proceeds by a two-step method consisting of ligand exchange and reductive elimination (Scheme 13). In order to confirm the ligand exchange step of the oxidation mechanism proceeds, a methoxy aldoxime was used in place of the aldoxime reagent. The methoxy aldoxime provides a protecting group in place of the hydroxy group on (*E*)-benzaldehyde oxime **1a**. After the blank study was ran, the desired product was not detected and the methoxy aldoxime was recovered (Scheme 14). This confirms that the ligand exchange step is important for the reaction mechanism for the generation of nitrile oxide. Next, in order to confirm the reductive elimination step of the oxidation mechanism proceeds, a ketoxime was used in place of the aldoxime reagent. The ketoxime provides a protecting group in place of the α-hydrogen on (*E*)-benzaldehyde oxime **1a**. After the blank study was ran, the desired product was not detected and ketoxime and the side product acetophenone were recovered (Scheme 14).

This confirms that the reductive elimination step is important in the reaction mechanism for the generation of nitrile oxide. These blank studies helped confirm that the generation of nitrile oxide from aldoxime using hypervalent iodine(III) proceeds first by ligand exchange and reductive elimination.



Scheme 13. Proposed reaction mechanism for the generation of nitrile oxide from aldoxime using Koser's reagent



Scheme 14. Blank experiments for mechanistic studies for the generation of nitrile oxide

4.5. 1,3-Dipolar cycloaddition mechanism

Generation of the unstable nitrile oxide species results in the reaction with unsaturated compounds by 1,3-dipolar cycloaddition to create heterocyclic rings. Due to the resonance structures observed within the unsaturated enaminone substrate, the cycloaddition of nitrile oxide with enaminone occurs regioselectivity. By observing the

resonance structures between **A**, **B**, and **C** of *trans*-4-dimethylamino-3-buten-2-one **2a** (Figure 3), the electron donating amine and electron withdrawing ketone can effectively

delocalize the negative charge by the resonance effect. This resonance creates a dipole within the enaminone substrate that allows for a partial postitive and partial negative within the double bond of the enaminone structure. This dipole then favors the attractive electrostatic interaction with nitrile oxide. Therefore, cycloaddition of nitrile oxides with enaminones is more favored if the negatively charged oxygen of nitrile oxide attacks the partial positive carbon, within the alkene. In this transition state, it is easier for the enaminone to approach towards nitriles oxides as the forces are attractive (Scheme 15). In contrast, the nucleophilic attack of the negatively charged oxygen of nitrile oxide onto the partially negative carbon, within the alkene, is not favored due to the repulsive electrostatic force between the dipole of enaminone and nitrile oxide. In this transition state, it is harder for the enaminone to approach towards nitrile oxide as the forces are repulsive (Scheme 16). Upon beta elimination of the amine group leaving we then obtain our regioselective 3,4-substitued isoxazole.

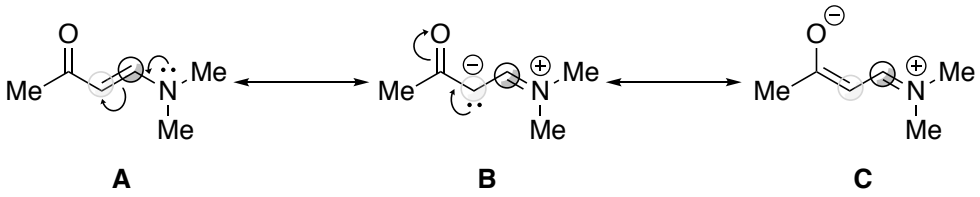
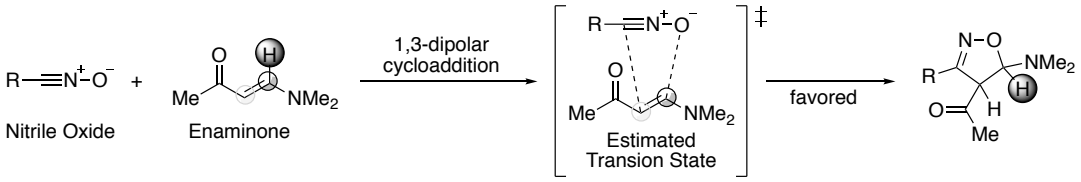
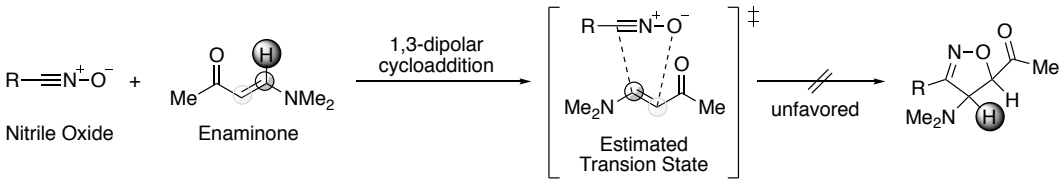


Figure 3. Resonance contributors of enaminone structure, *trans*-4-dimethylamino-3-buten-2-one **2a**

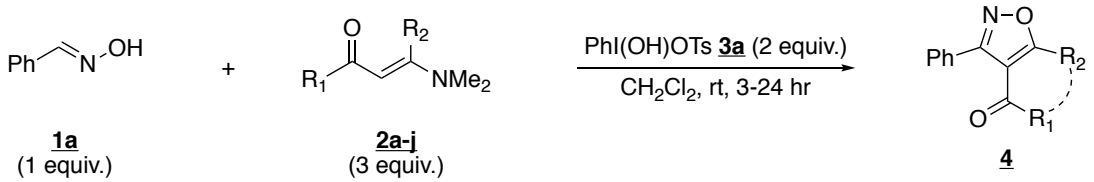


Scheme 15. 1,3-Dipolar cycloaddition favored reaction

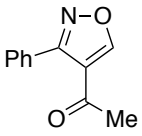
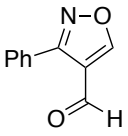
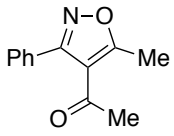
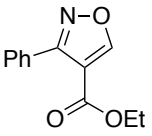
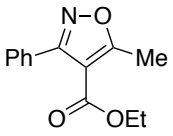
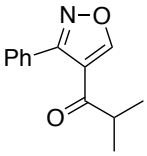
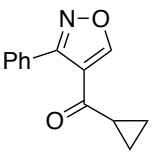
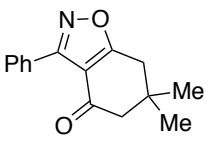
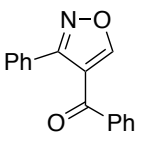
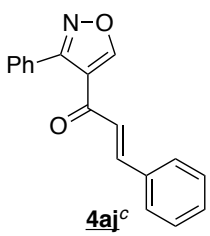


Scheme 16. 1,3-Dipolar cycloaddition unfavored reaction

Table 3. Oxidative cycloaddition of benzaldehyde oxime **1a** with enaminones **2a-i** using Koser's reagent **3a**[a,b]



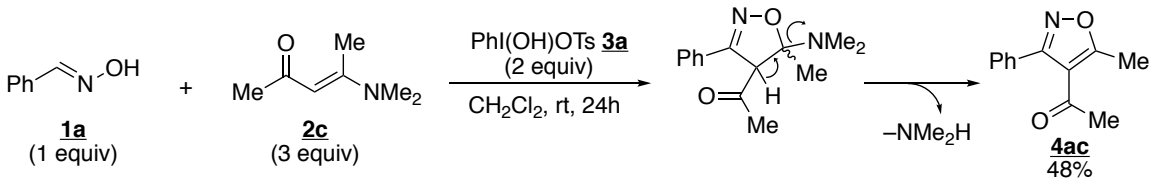
1a (1 equiv.) + **2a-j** (3 equiv.) → **4**

				
4a 92% (X-ray)	**4ab** 46%	**4ac** 48%	**4ad** 72%	**4ae** 59%[d] 36%[e]
				
4af 84%	**4ag** 99%	**4ah** 22%	**4ai**[c] (73%)	**4aj**[c] (72%)

[a]Reaction conditions: (*E*)-Benzaldehyde oxime **1a** (0.250 mmol; 1 equiv) and enaminone **2a-j** (0.750 mmol; 3 equiv) with Koser's reagent **3a** (0.500 mmol; 2 equiv) in DCM were stirred for 3-24 h at room temperature. [b]Yields of products after column chromatography. [c]NMR yields of products. [d]Reaction conditions: Utilizing (*E)* enaminone, ethyl-(*E*)-3-(pyrrolidine-1-yl)but-2-enoate **2e(*E*)**. [e]Reaction conditions: Utilizing (*Z)* enaminone, ethyl-(*Z*)-3-(pyrrolidine-1-yl)but-2-enoate **2e(*Z*)**.

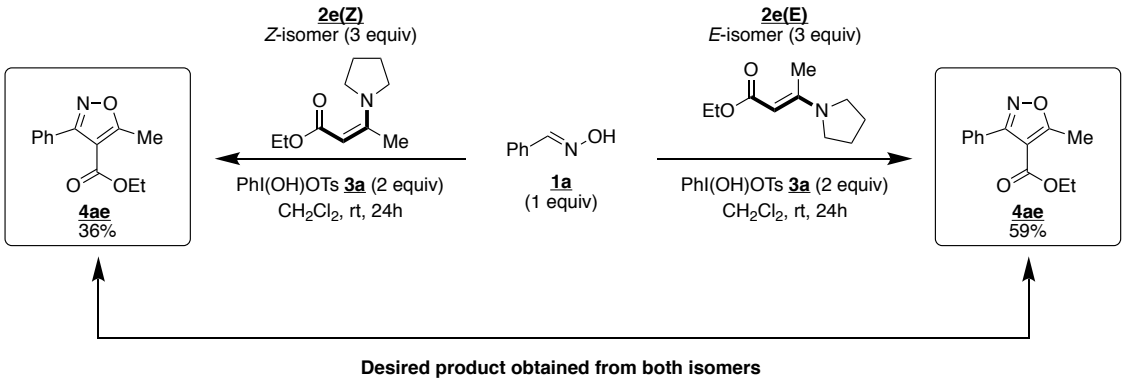
4.6. Substrate scope and reaction mechanism study using various enaminones

At the next step, we attempted to prepare the isoxazole product **4** by the reaction of (*E*)-benzaldehyde oxime **1a** with varied enaminone substrates **2a-j** using hypervalent iodine(III) under similar conditions (Table 3). The reaction of 3-(dimethylamino)acrolein **2b** gave the corresponding product **4ab** in 46% yield. The reaction of (*E*)-4-(dimethylamino)pent-3-en-2-one **2c** gave the corresponding product **4ac** in 48% yield. The lowered yield of product **4ac** can be attributed to the steric hindrance of the methyl group on the point of attack on the enaminone substrate, when comparing the reaction to the similar unhindered product **4a** at 92% yield, but it does not affect the β-elimination step of the reaction mechanism (Scheme 17).



Scheme 17. Blank studies with sterically hindered enaminone

The reaction corresponding to product **4ae** was performed with both (*E*)- and (*Z*)-β-methyl substituted enaminones with cyclic amino groups to determine if the stereochemistry of the enaminone substrate affected the reaction and to see the scope of the amine leaving group. The reaction of ethyl-(*E*)-3-(pyrrolidine-1-yl)but-2-enoate **2e(*E*)** gave the corresponding product **4ae** in 59% and the reaction of ethyl-(*Z*)-3-(pyrrolidine-1-yl)but-2-enoate **2e(*Z*)** gave the corresponding product **4ae** in 36%. Desired product was obtained from both stereoisomer reagents in similar yields. Due to resonance, these molecules could be rotating during the reaction meaning the stereochemistry does not play an important factor (Figure 4). From this result, we can conclude that the stereochemistry of the enaminone substrate does not play an important role in the attack of nitrile oxide or the β-elimination step of the 1,3-cycloaddition mechanism (Scheme 18). We can also conclude that this reaction can proceed with various amine leaving groups. The lowered yield corresponding to product **4ae** can be attributed to the steric hindrance of the methyl on the enaminone substrate, as also seen with product **4ac.** The lowered yield of product **4ae** can also be compared to the reaction of the similar unhindered product **4ad** at 72% yield when comparing A-values of these functional groups.[23]



Scheme 18. Blank studies with sterically hindered stereoisomers

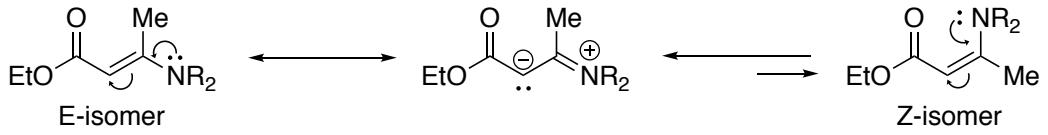


Figure 4. Resonance of stereoisomer enaminones

We also attempted to prepare the isoxazole product **4** with isoxazole fused bicyclic heterocycles by the reaction of aldoximes with cyclic enaminones using hypervalent iodine(III) reagent under similar conditions. The reaction of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one **1ah** gave the corresponding product **4ah** in 22% yield. This lowered yield can be due to the steric hindrance of the cyclic enaminone reacting with nitrile oxide.

The reaction of (1*E*, 4*E*)-1-(dimethylamino)-5-phenylpenta-1,4-dien-3-one **1aj** corresponding to the desired product **4aj** was not obtained cleanly as the dimerized form of the compound was detected within the compound, from GC-MS confirmation.

4.7. Experimental Section

4.7.1. General Experimental Remarks

All reactions were performed under dry argon atmosphere with flame-dried glassware. Dichloromethane was distilled immediately prior to use. All commercial reagents were ACS reagent grade and used without further purification. Melting points were determined in an open capillary tube with a Mel-temp II melting point apparatus. Infrared spectra were recorded as a NaCl pellet on a PerkinElmer 1600 series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Inova 500 and 300 MHz NMR spectrometer. ^{13}C NMR spectra were recorded on a Varian Inova 500 and 300 MHz NMR

spectrometer, at 125 and 75 MHz. Chemical shifts are reported in parts per million (ppm). ^{1}H and ^{13}C chemical shifts are referenced relative to the tetramethylsilane. The known hypervalent iodine(III) compound, Koser's reagent, was prepared according to the reported procedures.[24]

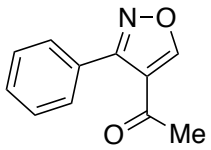
4.7.2. General procedure for generation of aldoxime

Benzaldehyde (5 mmol), $NH_2OH{\bullet}HCl$ (10 mmol), and pyridine (20mmol) were added in dichloromethane (25 mL). The reaction was stirred at room temperature for 20 hours. After completion of the reaction, water and HCl were added and the reaction was extracted in dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of column chromatography (hexane-ethyl acetate = 9:1 to 1:1) afforded analytically pure products.

4.7.3. General procedure for oxidative cycloaddition of aldoximes using Koser's reagent

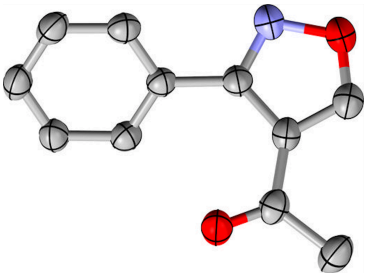
Aldoxime **1** (0.250 mmol) and *trans*-4-dimethylamino-3-buten-2-one **2a** (85 mg, 0.750 mmol) were added to a solution of Koser's reagent **3a** (196 mg, 0.500 mmol) in dry dichloromethane (2 mL). The reaction was stirred at room temperature for 1.5-24 h. After completion of the reaction, 5% aqueous $Na_2S_2O_3$ (5 mL) was added, and the mixture was extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (hexane−ethyl acetate = 9:1 to 1:1) afforded analytically pure products.

1-(3-Phenylisoxazol-4-yl)ethan-1-one, **4a**



Reaction of (*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) according to the general procedure afforded 43 mg (92%) of product **4a**, isolated as a white solid: mp 78.0-78.8 °C, (lit mp[25]: 83.0°C); IR (neat) cm^{-1} 3366, 3127, 3091, 3006, 2923, 2852, 1685, 1560, 1445, 1387; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.72-7.65 (m, 2H), 7.54-7.42 (m, 3H), 2.44 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 190.4, 163.4, 160.8, 130.3, 129.4, 128.4, 127.4, 120.9, 29.7; HRMS (APCI-positive ionization): calcd for $C_{11}H_{10}NO_2$ ($[M+H]^+$): 188.0712, found: 188.0727.

S1: 1-(3-Phenylisoxazol-4-yl)ethan-1-one, **4a**

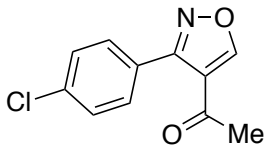


X-ray crystallography was obtained by slow evaporation of dichloromethane.

Large scale: Reaction of (*E*)-benzaldehyde oxime **1a** (121 mg, 1 mmol) and *trans*-4-dimethylamino-3-buten-2-one (339 mg, 3 mmol) were added to a solution of Koser's reagent (784 mg, 2 mmol) in dichloromethane (9 mL) affording 159 mg (85%) of product **4a**, isolated as a white solid: mp 78.0-78.8 °C (lit mp[25]: 83.0°C); IR (neat) cm^{-1} 3366, 3127, 3091, 3006, 2923, 2852, 1685, 1560, 1445, 1387; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.72-7.65 (m, 2H), 7.54-7.42 (m, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz,

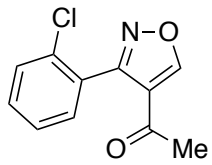
$CDCl_3$): δ 190.4, 163.4, 160.8, 130.3, 129.4, 128.4, 127.4, 120.9, 29.7; HRMS (APCI-positive ionization): calcd for $C_{11}H_{10}NO_2$ ($[M+H]^+$): 188.0712, found: 188.0727.

1-(3-(4-Chlorophenyl)isoxazol-4-yl)ethan-1-one[26], **4b**



Reaction of (*E*)-4-chlorobenzaldehyde oxime **1b** (39 mg, 0.250 mmol) according to the general procedure afforded 47 mg (85%) of product **4b**, isolated as a white solid: mp 111.7-112.1 °C; IR (neatl) cm^{-1} 3345, 3113, 3077, 2923, 2856, 1691, 1577, 1413, 1383, 1095; ^1H NMR (300 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.68 (d. J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 163.6, 159.9, 136.5, 130.8, 128.6, 125.8, 120.5, 29.7; HRMS (APCI-positive ionization): calcd for $C_{11}H_9{}^{35}ClNO_2$ ($[M+H]^+$): 222.0322, found: 222.0332.

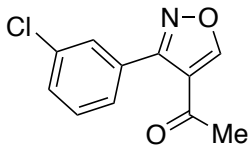
1-(3-(2-Chlorophenyl)isoxazol-4-yl)ethan-1-one, **4c**



Reaction of (*E*)-2-chlorobenzaldehyde oxime **1c** (39 mg, 0.250 mmol) according to the general procedure afforded 45 mg (81%) of product **4c**, isolated as a white solid: mp 62.1-62.6 °C; IR (neat) cm^{-1} 3365, 3139, 3095, 2924, 2854, 1685, 1563, 1437, 1387, 1118; ^1H NMR (300 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.55-7.34 (m, 4H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 162.1, 158.9, 133.8, 131.2, 131.0, 129.7, 127.4, 126.8,

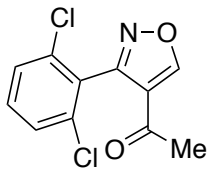
122.1, 28.9; HRMS (APCI-positive ionization): calcd for $C_{11}H_9{}^{35}ClNO_2$ ($[M+H]^+$): 222.0322, found: 222.0331.

1-(3-(3-Chlorophenyl)isoxazol-4-yl)ethan-1-one, **4d**



Reaction of (*E*)-3-chlorobenzaldehyde oxime **1d** (39 mg, 0.250 mmol) according to the general procedure afforded 54 mg (97%) of product **4d**, isolated as a white solid: mp 118.3-119.6 °C; IR (neat) cm^{-1} 3351, 3123, 3092, 2924, 2853, 1689, 1557, 1409, 1390, 1121; ^1H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.72 (d. J=1.5 Hz, 1H), 7.60 (dd, J=7.5 Hz, 1.5 Hz, 1H), 7.49-7.45 (m, 1H), 7.42-7.37 (m, 1H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 163.7, 159.7, 134.2, 130.3, 129.6, 129.5, 129.1, 127.7, 120.6, 29.7; HRMS (APCI-positive ionization): calcd for $C_{11}H_9{}^{35}ClNO_2$ ($[M+H]^+$): 222.0322, found: 222.0333.

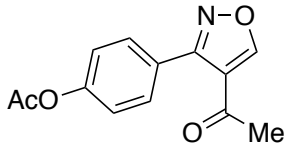
1-(3-(2,6-Dichlorophenyl)isoxazol-4-yl)ethan-1-one, **4e**



Reaction of (*E*)-2,6-dichlorobenzaldoxime **1e** (48 mg, 0.250 mmol) according to the general procedure afforded 58 mg (91%) of product **4e**, isolated as a white solid: mp 107.4-108.8°C, (lit mp[27]: 118-120°C); IR (neat) cm^{-1} 3350, 3134, 3091, 3066, 2925, 2857, 1688, 1567, 1424, 1391, 1095; ^1H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.44

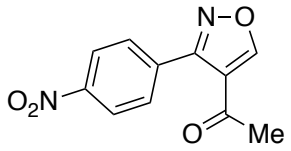
(d. J=7.5 Hz, 1H), 7.41-7.36 (m, 2H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.4, 162.7, 156.8, 135.3, 131.5, 128.0, 127.1, 121.8, 28.8; HRMS (APCI-positive ionization): calcd for $C_{11}H_8{}^{35}Cl_2NO_2$ ($[M+H]^+$): 255.9932, found: 255.9945.

4-(4-Acetylisoxazol-3-yl)phenyl acetate, **4f**



Reaction of (*E*)-4-((hydroxyimino)methyl)phenyl acetate **1f** (45 mg, 0.250 mmol) according to the general procedure afforded 50 mg (81%) of product **4f**, isolated as a white solid: mp 83.5-84.3 °C; IR (neat) cm^{-1} 3366, 3131, 3091, 2926, 2854, 1748, 1685, 1560, 1419, 1365, 1165, 1111; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.77 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.8 Hz, 2H), 2.47 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 190.2, 169.1, 163.7, 160.0, 152.2, 130.8, 124.9, 121.6, 120.6, 29.7, 21.2; HRMS (APCI-positive ionization): calcd for $C_{13}H_{12}NO_4$ ($[M+H]^+$): 246.0766, found: 246.0774.

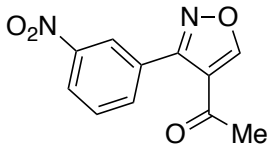
1-(3-(4-Nitrophenyl)isoxazol-4-yl)ethan-1-one[27], **4g**



Reaction of (*E*)-4-nitrobenzaldehyde **1g** (42 mg, 0.250 mmol) according to the general procedure afforded 44 mg (76%) of product **4g**, isolated as a white solid: mp 182.5-183.3 °C; IR (neat) cm^{-1} 3365, 3137, 3083, 3066, 2845, 1691, 1562, 1510, 1420, 1350,

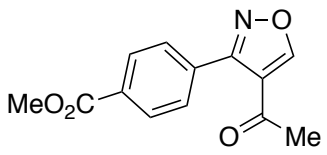
856; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.33 (d, J=9.5 Hz, 2H), 7.94 (d, J=9.5 Hz, 2H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.8, 163.9, 159.2, 148.9, 133.7, 130.7, 123.4, 120.5, 29.7; HRMS (APCI-positive ionization): calcd for $C_{11}H_9N_2O_4$ ($[M+H]^+$): 233.0562, found: 233.0567.

1-(3-(3-Nitrophenyl)isoxazol-4-yl)ethan-1-one, **4h**



Reaction of (*E*)-3-nitrobenzaldehyde oxime **1h** (42 mg, 0.250 mmol) according to the general procedure afforded 57 mg (98%) of product **4h**, isolated as a light yellow solid: mp 118.7-119.3 °C; IR (neat) cm^{-1} 3359, 3094, 2927, 2854, 1685, 1560, 1539, 1428, 1390, 1349, 861; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.65 (t, J=1.5 Hz, 1H), 8.35 (dd, J=8.4 Hz, 1.5 Hz, 1H), 8.09 (d, J=7.5 Hz, 1H), 7.70-7.61 (m, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 163.9, 159.0, 147.9, 135.3, 129.2, 129.0, 124.8, 124.6, 120.2, 29.5; HRMS (APCI-positive ionization): calcd for $C_{11}H_9N_2O_4$ ($[M+H]^+$): 233.0562, found: 233.0576.

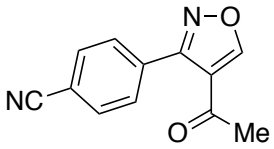
Methyl 4-(4-acetylisoxazol-3-yl)benzoate, **4i**



Reaction of methyl(*E*)-4-((hydroxyimino)methyl) benzoate **1i** (45 mg, 0.250 mmol) according to the general procedure afforded 50 mg (82%) of product **4i**, isolated as a

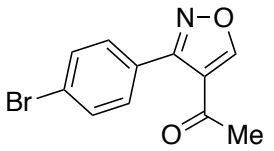
white solid: mp 116.2-117.4 °C; IR (neat) cm^{-1} 3371, 3093, 3005, 2916, 2849, 1705, 1689, 1559, 1413, 1119; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.13 (d, J=8.3 Hz, 2H), 7.79 (d, J=8.3 Hz, 2H), 3.94 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.0, 166.5, 163.8, 160.1, 131.8, 131.6, 129.5, 129.5, 120.7, 52.3, 29.7; HRMS (APCI-positive ionization): calcd for $C_{13}H_{12}NO_4$ ($[M+H]^+$): 246.0766, found: 246.0779.

4-(4-Acetylisoxazol-3-yl)benzonitrile, **4j**



Reaction of (*E*)-4-((hydroxyamino)methyl) benzonitrile **1j** (37 mg, 0.250 mmol) according to the general procedure afforded 50 mg (94%) of product **4j**, isolated as a white solid: mp 181.3-181.7 °C; IR (neat) cm^{-1} 3370, 3134, 3090, 3057, 2922, 2232, 1689, 1577, 1421, 1386; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.87 (d, J=7.1 Hz, 2H), 7.75 (d, J=7.1 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.8, 163.9, 159.4, 131.9, 130.2, 120.4, 118.3, 113.9, 29.6; HRMS (APCI-positive ionization): calcd for $C_{12}H_9N_2O_2$ ($[M+H]^+$): 213.0664, found: 213.0667.

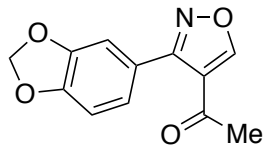
1-(3-(4-Bromophenyl)isoxazol-4-yl)ethan-1-one, **4k**



Reaction of (*E*)-4-bromobenzaldehyde oxime **1k** (50 mg, 0.250 mmol) according to the general procedure afforded 60 mg (90%) of product **4k**, isolated as a white solid: mp

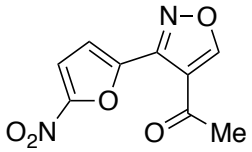
111.5-112.1 °C; IR (neat) cm^{-1} 3348, 3111, 3082, 3068, 2925, 2854, 1692, 1575, 1408, 1380; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.64-7.58 (m, 4H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 163.9, 160.2, 131.8, 131.2, 126.5, 125.1, 120.7, 29.9; HRMS (APCI-positive ionization): calcd for $C_{11}H_9{}^{79}BrNO_2$ ($[M+H]^+$): 265.9817, found: 265.9828.

1-(3-(Benzo[*d*][1,3]dioxol-5-yl)isoxazol-4-yl)ethan-1-one, **4l**



Reaction of Piperonaldoxime **1l** (41 mg, 0.250 mmol) according to the general procedure afforded 48 mg (83%) of product **4l**, isolated as a white solid: mp 133.2-133.6 °C; IR (neat) cm^{-1} 3339, 3091, 3025, 2908, 1673, 1562, 1466, 1397, 1260, 1242, 1150; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.25 (dd, J=7.8 Hz, 1.8 Hz, 1H), 7.19 (d, J=1.8 Hz, 1H), 6.89 (d, J=7.8 Hz, 1H), 6.03 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.4, 163.6, 160.3, 149.4, 147.6, 123.9, 120.8, 120.6, 109.8, 108.3, 101.5, 29.8; HRMS (APCI-positive ionization): calcd for $C_{12}H_{10}NO_4$ ($[M+H]^+$): 232.0610, found: 232.0626.

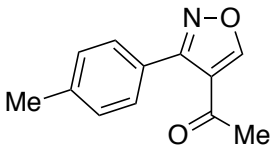
1-(3-(5-Nitrofuran-2-yl)isoxazol-4-yl)ethan-1-one, **4m**



Reaction of (*E*)-5-nitrofuran-2-carbaldehyde oxime **1m** (39 mg, 0.250 mmol) according to the general procedure afforded 52 mg (93%) of product **4m**, isolated as a yellow solid:

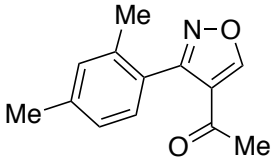
mp 133.7-135.9 °C; IR (neat) cm^{-1} 3363, 3165, 3120, 2926, 2854, 1687, 1557, 1542, 1406, 1359, 1346; ^1H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.81 (d, J=3.9 Hz, 1H), 7.42 (d, J=3.9 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.3, 164.2, 150.1, 143.9, 120.5, 118.2, 112.1, 29.6 (1 peak overlap); HRMS (APCI-positive ionization): calcd for $C_9H_7N_2O_5$ ($[M+H]^+$): 223.0355, found: 223.0366.

1-(3-(*p*-Tolyl)isoxazol-4-yl)ethan-1-one, **4n**



Reaction of (*E*)-4-methylbenzaldehyde oxime **1n** (34 mg, 0.250 mmol) according to the general procedure afforded 37 mg (74%) of product **4n**, isolated as a white solid: mp 86.3-88.0 °C; IR (neat) cm^{-1} 3372, 3057, 2918, 2849, 1690, 1556, 1417, 1381; ^1H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.58 (d, J=7.5 Hz, 2H), 7.27 (d, J=7.5 Hz, 2H), 2.43 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 163.3, 160.7, 140.4, 129.2, 129.0, 124.3, 120.8, 29.7, 21.4; HRMS (APCI-positive ionization): calcd for $C_{12}H_{12}NO_2$ ($[M+H]^+$): 202.0868, found: 202.0876.

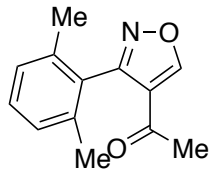
1-(3-(2,4-Dimethylphenyl)isoxazol-4-yl)ethan-1-one, **4o**



Reaction of (*E*)-2,4-dimethylbenzaldehyde oxime **1o** (37 mg, 0.250 mmol) according to the general procedure afforded 51 mg (95%) of product **4o**, isolated as a white solid: mp

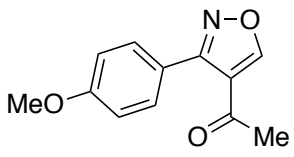
86.0-86.9 °C; IR (neat) cm^{-1} 3363, 3094, 3008, 2924, 2859, 1696, 1563, 1385, 1361; ^1H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.17 (d, J=7.8 Hz, 1H), 7.13 (s, 1H), 7.09 (d, J=7.8 Hz, 1H), 2.37 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 162.7, 160.6, 139.9, 136.9, 133.2, 129.6, 126.5, 124.3, 122.2, 29.2, 21.3, 19.7; HRMS (APCI-positive ionization): calcd for $C_{13}H_{14}NO_2$ ($[M+H]^+$): 216.1025, found: 216.1036.

1-(3-(2,6-Dimethylphenyl)isoxazol-4-yl)ethan-1-one, **4p**



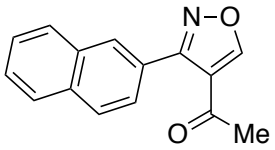
Reaction of 2,6-dimethylbenzaldehyde oxime **1p** (37 mg, 0.250 mmol) according to the general procedure afforded 32 mg (59%) of product **4p**, isolated as a white solid: mp 96.7-97.9 °C; IR (neat) cm^{-1} 3359, 3093, 2955, 2925, 2858, 1685, 1565, 1466, 1386; ^1H NMR (500 MHz, $CDCl_3$): δ 9.09 (s, 1H), 7.28 (d, J=7.8 Hz, 1H), 7.14 (d, J=7.8 Hz, 2H), 2.13 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 163.1, 159.7, 137.1, 129.6, 127.6, 127.2, 122.1, 28.7, 20.2; HRMS (APCI-positive ionization): calcd for $C_{13}H_{14}NO_2$ ($[M+H]^+$): 216.1025, found: 216.1032.

1-(3-(4-Methoxyphenyl)isoxazol-4-yl)ethan-1-one, **4q**



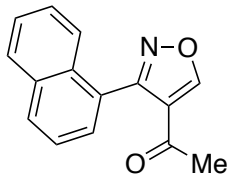
Reaction of (*E*)-4-methoxybenzaldehyde oxime **1q** (38 mg, 0.250 mmol) according to the general procedure afforded 39 mg (72%) of product **4q**, isolated as a white solid: mp 95.4-96.7 °C; IR (neat) cm^{-1} 3371, 3056, 2965, 2917, 2849, 1693, 1613, 1425, 1383, 1255, 1036; ^1H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H), 7.68 (d, J=9.0 Hz, 2H), 6.98 (d, J=9.0 Hz, 2H), 3.86 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.4, 163.4, 161.1, 160.3, 130.8, 120.6, 119.4, 113.7, 55.3, 29.7; HRMS (APCI-positive ionization): calcd for $C_{12}H_{12}NO_3$ ($[M+H]^+$): 218.0817, found: 218.0825.

1-(3-(Naphthalen-2-yl)isoxazol-4-yl)ethan-1-one, **4r**



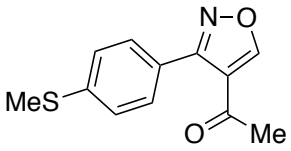
Reaction of (*E*)-2-napthaldehyde oxime **1r** (43 mg, 0.250 mmol) according to the general procedure afforded 52 mg (88%) of product **4r**, isolated as a white solid: mp 93.5-95.1 °C; IR (neat) cm^{-1} 3373, 3091, 3056, 2925, 2854, 1691, 1561, 1434, 1394, 862, 831, 822; ^1H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.26 (s, 1H), 7.94-7.89 (m, 2H), 7.87 (d, J=8.0 Hz, 1H), 7.74 (d, 8.0 Hz, 1H), 7.57-7.48 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 163.6, 160.7, 133.9, 132.8, 129.5, 128.6, 127.9, 127.7, 127.2, 126.5, 126.2, 124.7, 120.9, 29.7; HRMS (APCI-positive ionization): calcd for $C_{15}H_{12}NO_2$ ($[M+H]^+$): 238.0868, found: 238.0879.

1-(3-(Naphthalen-1-yl)isoxazol-4-yl)ethan-1-one, **4s**



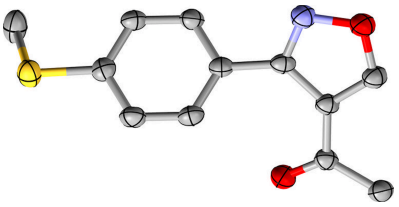
Reaction of (*E*)-1-napthaldehyde oxime **1s** (43 mg, 0.250 mmol) according to the general procedure afforded 52 mg (88%) of product **4s**, isolated as a white solid: mp 139.8-141.1 °C; IR (neat) cm^{-1} 3364, 3090, 3060, 2923, 2854, 1685, 1564, 1423, 1383, 803; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.13-7.97 (m, 1H), 7.92 (d, J=8.0 Hz, 1H), 7.62-7.54 (m, 3H), 7.52 (t, J=7.3 Hz, 1H), 7.49-7.44 (m, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 162.0, 159.7, 133.4, 131.8, 130.5, 128.5, 128.1, 127.1, 126.4, 125.2. 125.0, 124.7, 123.0, 29.1; HRMS (APCI-positive ionization): calcd for $C_{15}H_{12}NO_2$ ($[M+H]^+$): 238.0868, found: 238.0869.

1-(3-(4-(Methylthio)phenyl)isoxazol-4-yl)ethan-1-one, **4t**



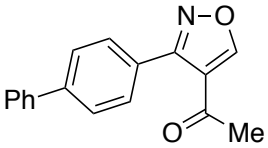
Reaction of (*E*)-4-(methylthio)benzaldehyde **1t** (42 mg, 0.250 mmol) according to the general procedure afforded 20 mg (34%) of product **4t**, isolated as a white solid: mp 93.1-94.8 °C; IR (neat) cm^{-1} 3363, 3099, 2924, 2854, 1685, 1573, 1411, 1379, 736; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.65 (d, J=8.5 Hz, 2H), 7.31 (d, J=8.5 Hz, 2H), 2.52 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 163.5, 160.3, 141.8, 129.7, 125.6, 123.6, 120.7, 29.8, 15.2; HRMS (APCI-positive ionization): calcd for $C_{12}H_{12}NO_2S$ ($[M+H]^+$): 234.0589, found: 234.0592.

S2: 1-(3-(4-(methylthio)phenyl)isoxazol-4-yl)ethan-1-one, **4t**



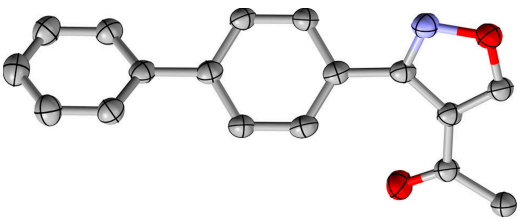
X-ray crystallography was obtained by slow evaporation of dichloromethane.

1-(3-([1,1'-Biphenyl]-4-yl)isoxazol-4-yl)ethan-1-one, **4u**



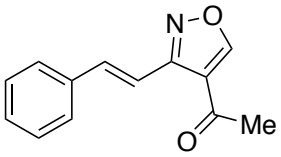
Reaction of (*E*)-([1,1'-biphenyl]-4-carbaldehyde oxime **1u** (49 mg, 0.250 mmol) according to the general procedure afforded 49 mg (74%) of product **4u**, isolated as a white solid: mp 146.8-147.7 °C; IR (neat) cm^{-1} 3353, 3126, 3083, 2926, 2856, 1692, 1572, 1446, 1411; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.79 (d, J=7.8 Hz, 2H), 7.68 (d, J=7.8 Hz, 2H), 7.63 (d, J=8.1 Hz, 2H), 7.50-7.42 (m, 1H), 7.37 (t, J=6.9 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.5, 163.7, 160.6, 143.2, 140.4, 130.0, 129.0, 127.9 127.3, 127.2, 126.3, 120.9, 29.9; HRMS (APCI-positive ionization): calcd for $C_{17}H_{14}NO_2$ ($[M+H]^+$): 264.1025, found: 264.1032.

S3: 1-(3-([1,1'-biphenyl]-4-yl)isoxazol-4-yl)ethan-1-one, **4u**



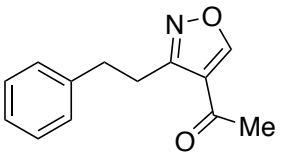
X-ray crystallography was obtained by slow evaporation of dichloromethane.

(*E*)-1-(3-Styrylisoxazol-4-yl)ethan-1-one, **4v**



Reaction of (1*E,* 2*E*)-cinnamaldehyde oxime **1v** (37 mg, 0.250 mmol) according to the general procedure afforded 33 mg (62%) of product **4v**, isolated as a white solid: mp 94.9-96.3 °C; IR (neat) cm^{-1} 3345, 3068, 3026, 2925, 2854, 1682, 1565, 1408, 1362, 854; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.91 (s, 1H), 7.68 (d, J=16.8 Hz, 1H), 7.58 (d, J=7.5 Hz, 1H), 7.47 (d, J=16.8 Hz, 1H), 7.41-7.36 (m, 2H), 7.33 (t, J=7.3 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 162.9, 158.2, 137.3, 135.9, 129.1, 128.8, 127.4, 120.0, 113.6, 29.4; HRMS (APCI-positive ionization): calcd for $C_{13}H_{12}NO_2$ ($[M+H]^+$): 214.0808, found: 214.0879.

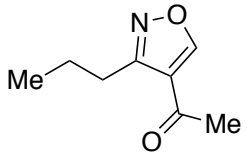
1-(3-Phenethylisoxazol-4-yl)ethan-1-one, **4w**



Reaction of (*E*)-3-phenylpropanal oxime **1w** (37 mg, 0.250 mmol) according to the general procedure afforded 30 mg (56%) of product **4w**, isolated as a white solid: mp 52.8-53.9 °C; IR (neat) cm^{-1} 3353, 3104, 3064, 3028, 2934, 2865, 1685, 1578, 1412, 1363; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.33-7.25 (m, 4H), 7.23-7.18 (m, 1H), 3.24 (dd, J=10.5 Hz, 8.3 Hz, 2H), 3.01 (dd, J=10.5 Hz, 8.3 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.8, 162.6, 161.4, 140.8, 128.5, 128.4, 126.2, 120.4, 33.6,

29.1, 27.6; HRMS (APCI-positive ionization): calcd for $C_{13}H_{14}NO_2$ ([M+H]$^+$): 216.1025, found: 216.1032.

1-(3-Propylisoxazol-4-yl)ethan-1-one, **4x**

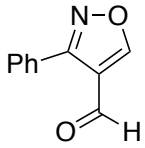


Reaction of butyraldoxime **1x** (24 mg, 0.250 mmol) according to the general procedure afforded 18 mg (46%) of product **4x**, isolated as a clear oil; IR (neat) cm^{-1} 3356, 3101, 2966, 2936, 2876, 1680, 1577, 1413, 1363; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 2.91 (t, J=7.5 Hz, 2H), 2.48 (s, 3H), 1.72 (sext, J=7.5 Hz, 2H), 0.99 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.3, 162.0, 161.5, 119.9, 29.9, 28.8, 20.3, 13.3; HRMS (APCI-positive ionization): calcd for $C_8H_{12}NO_2$ ([M+H]$^+$): 154.0868, found: 154.0880.

4.8.4. General procedure for oxidative cycloaddition of (*E*)-benzaldehyde oxime and enaminones using Koser's reagent.

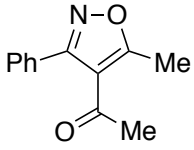
(*E*)-benzaldehyde oxime **1a** (30 mg, 0.250 mmol) and enaminone **2** (0.750 mmol) were added to a solution of Koser's reagent **3a** (196 mg, 0.500 mmol) in dry dichloromethane (2 mL). The reaction was stirred at room temperature for 3-24 h. After completion of the reaction, 5% aqueous $Na_2S_2O_3$ (5 mL) was added, and the mixture was extracted with dichloromethane. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (hexane−ethyl acetate = 9:1 to 1:1) afforded analytically pure products.

3-Phenylisoxazole-4-carbaldehyde, **4ab**



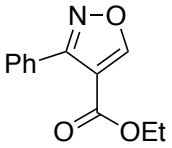
Reaction of 3-(dimethylamino)acrolein **2b** (74 mg, 0.750 mmol) according to the general procedure afforded 20 mg (46%) of product **4ab**, isolated as a white solid: mp 45.5-46.9 °C (lit mp: 41-42°C)[28] ; IR (neat) cm^{-1} 3375, 3125, 3093, 2926, 2854, 2751, 1696, 1559, 1448, 1384; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.0 (s, 1H), 9.09 (s, 1H), 7.80 (dd, J=7.5 Hz, 2.0 Hz, 2H), 7.57-7.50 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.7, 165.2, 160.5, 130.8, 129.1, 129.0, 126.7, 121.0; HRMS (APCI-positive ionization): calcd for $C_{10}H_8NO_2$ ($[M+H]^+$): 174.0555, found: 174.0573.

1-(5-Methyl-3-phenylisoxazol-4-yl)ethan-1-one, **4ac**



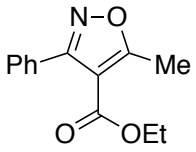
Reaction of (*E*)-4-(dimethylamino)pent-3-en-2-one **2c** (95 mg, 0.750 mmol) according to the general procedure afforded 24 mg (48%) of product **4ac**, isolated as a white solid: mp 57.9-58.7 °C (lit mp[29]: 61.3-61.7 °C); IR (neat) cm^{-1} 3345, 3004, 3065, 2927, 2854, 1683, 1570, 1409, 1360; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.47 (m, 5H), 2.71 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 193.3, 174.7, 161.9, 130.0, 129.1, 129.0, 128.7, 117.3, 30.6, 13.6; HRMS (APCI-positive ionization): calcd for $C_{12}H_{12}NO_2$ ($[M+H]^+$): 202.0868, found: 202.0879.

Ethyl-3-phenylisoxazole-4-carboxylate[30], **4ad**



Reaction of ethyl-N,N-dimethylamino-acrylate **2d** (107 mg, 0.750 mmol) according to the general procedure afforded 42 mg (72%) of product **4ad**, isolated as a yellow oil; IR (neat) cm^{-1} 3450, 3066, 3101, 2984, 2940, 1719, 1565, 1448, 1387; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.77 (dd, J=8.0 Hz, 2.0 Hz, 2H), 7.52-7.43 (m, 3H), 4.29 (q, J=7.0 Hz, 2H), 1.30 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.1, 161.3, 160.9, 130.2, 129.5, 128.2, 127.3, 113.0, 61.1, 14,1; HRMS (APCI-positive ionization): calcd for $C_{12}H_{12}NO_3$ ($[M+H]^+$): 218.0817, found: 218.0827.

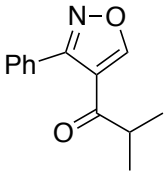
Ethyl 5-methyl-3-phenylisoxazole-4-carboxylate, **4ae**



Reaction of ethyl-(*E*)-3-(1-pyrrolindinyl)crotonate **2e(*E*)** (137 mg, 0.750 mmol) and ethyl-(*Z*)-3-(1-pyrrolindinyl)crotonate **2e(*Z*)** (137.4 mg, 0.750 mmol) according to the general procedure afforded 34 mg (59%) and 21 mg (36%)of product **4ae** respectively, isolated as a white solid: mp 46.6-47.6 °C (lit mp[31]: 49 °C); IR (neat) cm^{-1} 3413, 3064, 2984, 2934, 2873, 1715, 1604, 1448, 1425, 1150; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64-7.59 (m, 2H), 7.48-7.39 (m, 3H), 4.23 (q, J=7.0 Hz, 2H), 2.73 (s, 3H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 175.8, 162.6, 162.0, 129.7, 129.4, 128.5, 127.9,

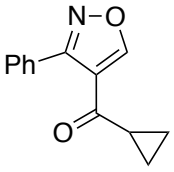
108.5, 60.7, 14.0, 13.6; HRMS (APCI-positive ionization): calcd for $C_{13}H_{14}NO_3$ ($[M+H]^+$): 232.0974, found: 232.0990.

2-Methyl-1-(3-phenylisoxazol-4-yl)propan-1-one, **4af**



Reaction of (*E*)-1-(dimethylamino)-4-methylpent-1-en-3-one **2f** (106 mg, 0.750 mmol) according to the general procedure afforded 45 mg (84%) of product **4af**, isolated as a light yellow oil; IR (neat) cm^{-1} 3361, 3090, 2974, 2934, 2875, 1688, 1558, 1444, 1387; ^1H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.67 (dd, J=8.3 Hz, 1.8 Hz, 2H), 7.51-7.43 (m, 3H), 3.06 (sept, J=7.0 Hz, 1H), 1.18 (d, J=7.0 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 197.7, 162.4, 161.3, 130.2, 129.3, 128.3, 127.5, 119.3, 39.9, 18.8; HRMS (APCI-positive ionization): calcd for $C_{13}H_{14}NO_2$ ($[M+H]^+$): 216.1025, found: 216.1032.

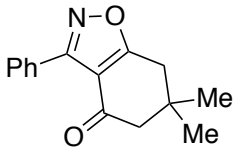
Cyclopropyl(3-phenylisoxazol-4-yl)methanone, **4ag**



Reaction of 1-cyclopropyl-3-(dimethylamino)-2-propen-1-one **2g** (104 mg, 0.750 mmol) according to the general procedure afforded 52.7 mg (99%) of product **4ag**, isolated as a yellow oil; IR (neat) cm^{-1} 3337, 3090, 3011, 2926, 2854, 1685, 1557, 1448; ^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.72-7.67 (m, 2H), 7.51-7.43 (m, 3H), 2.18-2.11 (m, 1H), 1.23 (dt, J-7.5 Hz, 3.5 Hz, 2H), 0.96 (dt, J=8.0 Hz, 3.5 Hz, 2H); ^{13}C NMR (500

MHz, $CDCl_3$): δ 193.5, 162.6, 160.7, 130.2, 129.4, 128.3, 127.6, 121.5, 20.8, 12.1; HRMS (APCI-positive ionization): calcd for $C_{14}H_{14}NO_2$ ($[M+H]^+$): 214.0868, found: 214.0881.

6,6-Dimethyl-3-phenyl-6,7-dihydrobenzo[*d*]isoxazol-4(5*H*)-one, **4ah**



Reaction of 3-(dimethylamino)-5,5-dimethyl-2-cyclohexen-1-one **2h** (125 mg, 0.750 mmol) according to the general procedure afforded 13 mg (22%) of product **4ah**, isolated as a white solid mp: 88.2-90.6 °C (lit mp[32]: 101-103°C); ^{1}H NMR (500 MHz, CDCl3): δ 8.11-8.06 (m, 2H), 7.50-7.43 (m, 3H), 2.92 (s, 2H), 2.47 (s, 2H), 1.19 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 191.5, 181.7, 159.8, 130.6, 129.1, 128.4, 127.4, 113.1, 53.2, 37.1, 28.3; HRMS (APCI-positive ionization): calcd for $C_{15}H_{16}NO_2$ ($[M+H]^+$): 242.1181, found: 242.1188.

4.8. Conclusion and Recommendation

We developed a strategy to prepare 31 isoxazoles through hypervalent iodine(III) cycloaddition of aldoximes with enaminones. In this procedure, Koser's reagent was used as the oxidant to convert aldoximes to their respective nitrile oxide species. Further study on the reaction mechanism showed the that formation of reactive nitrile oxide species proceeds by ligand exchange and reductive elimination. The active nitrile oxide species then reacts with respective enaminone substrates by 1,3-dipolar cycloaddition to create 5-membered ring isoxazole compounds. Aldoximes with electron-donating and electron-withdrawing groups reacted with the enaminone substrates to afford the 3,4 isoxazole in moderate to good yields with minimal limitation by steric hindrance. Furthermore, aldoximes containing functional group that were susceptible to oxidation competitive had lower yields of desired product as side reactions competed with the 1,3-dipolar cycloaddition reaction. The identity and characterization of all compounds were validated by ^{1}H NMR and ^{13}C NMR. FT-IR and ESI-MS were also recorded for all compounds. Structures of 3 isoxazole derivatives were established by X-ray crystallography. For future research, the generation of new isoxazole derivatives will be further studied utilizing hypervalent iodine(III).

CHAPTER 5: Supporting Information

5.1. Bibliography

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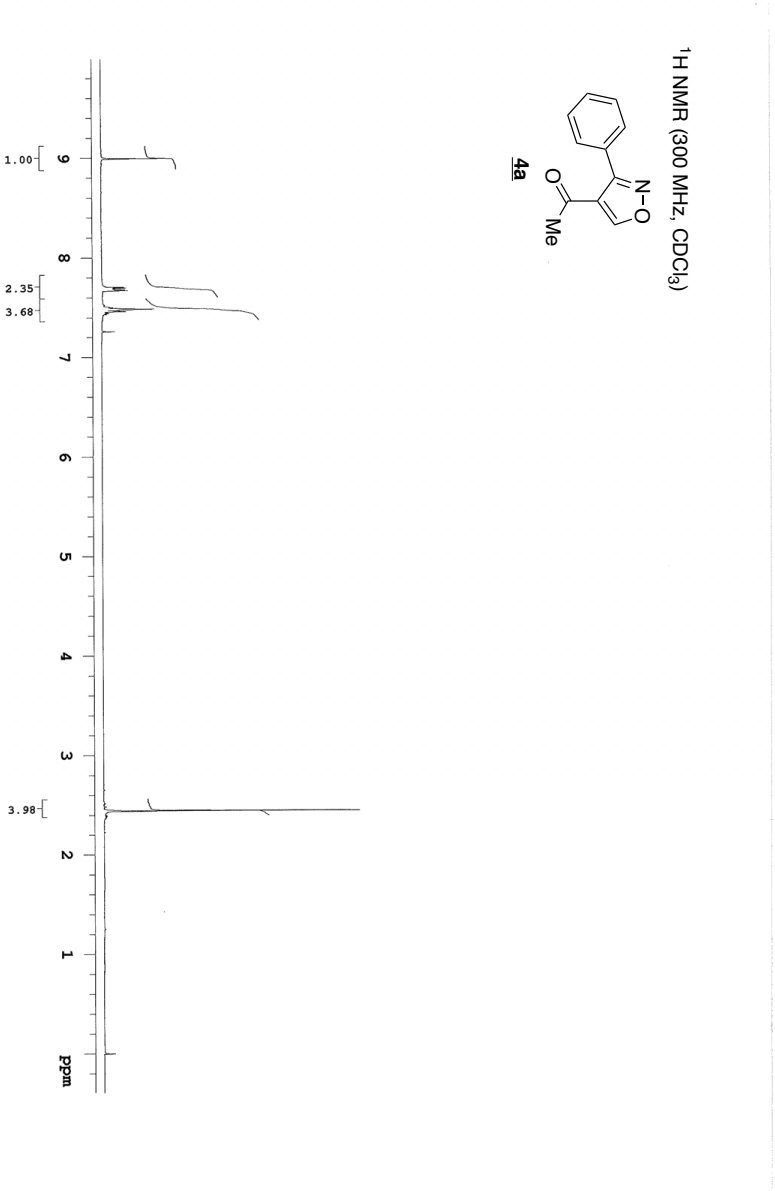
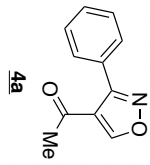
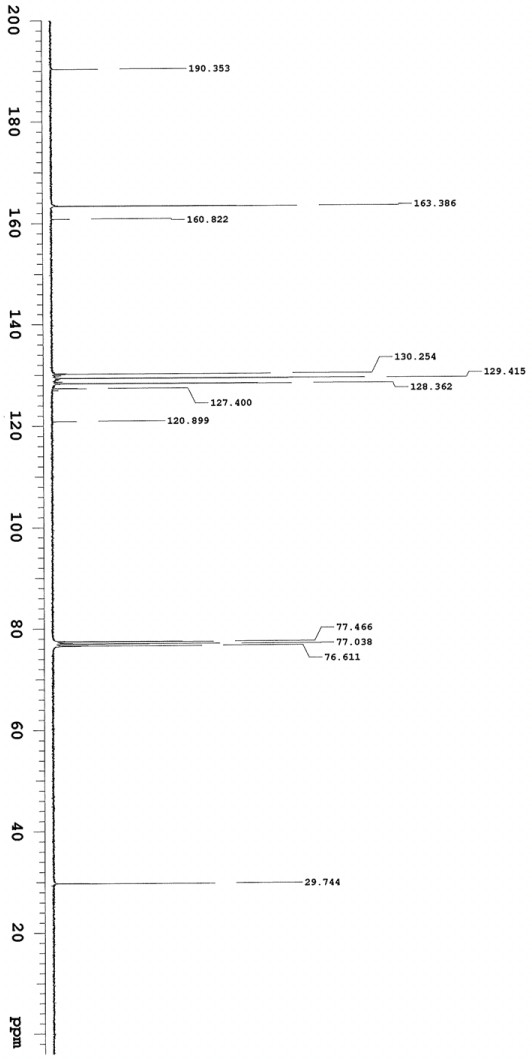
5.2. Appendices



^{13}C NMR (75 MHz, $CDCl_3$)



4a



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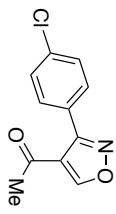

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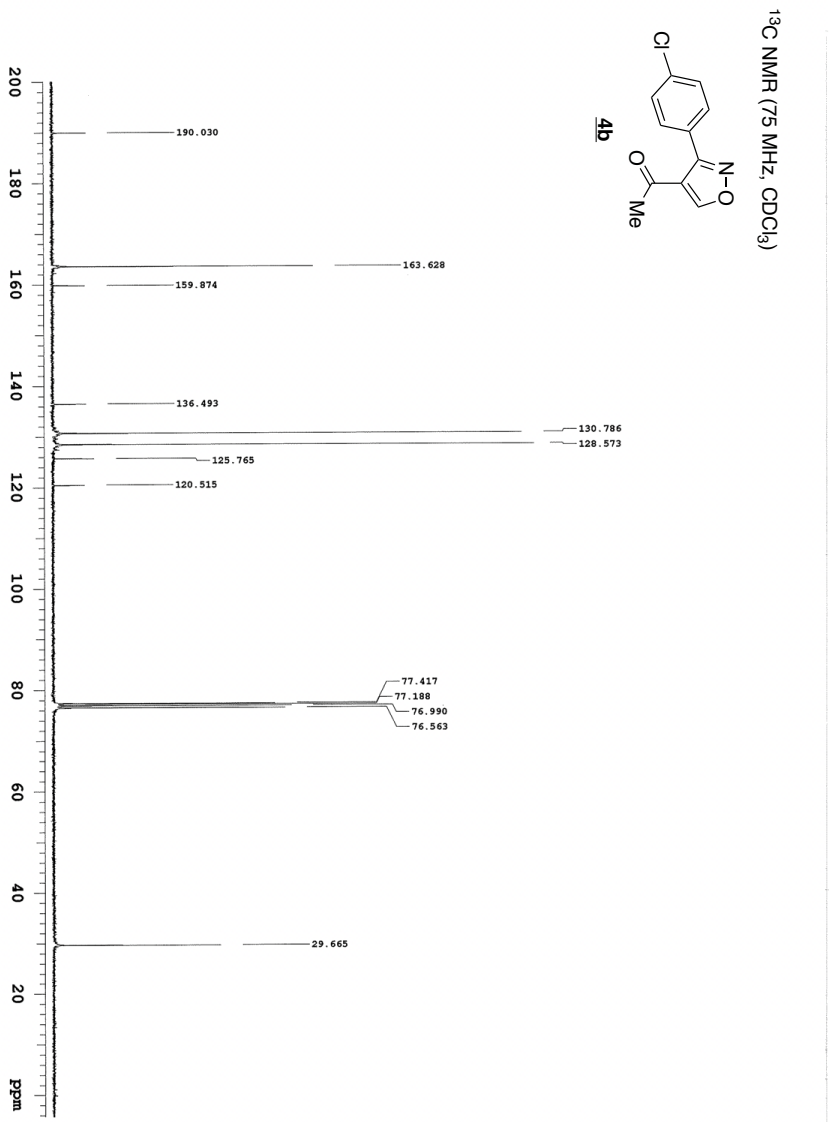
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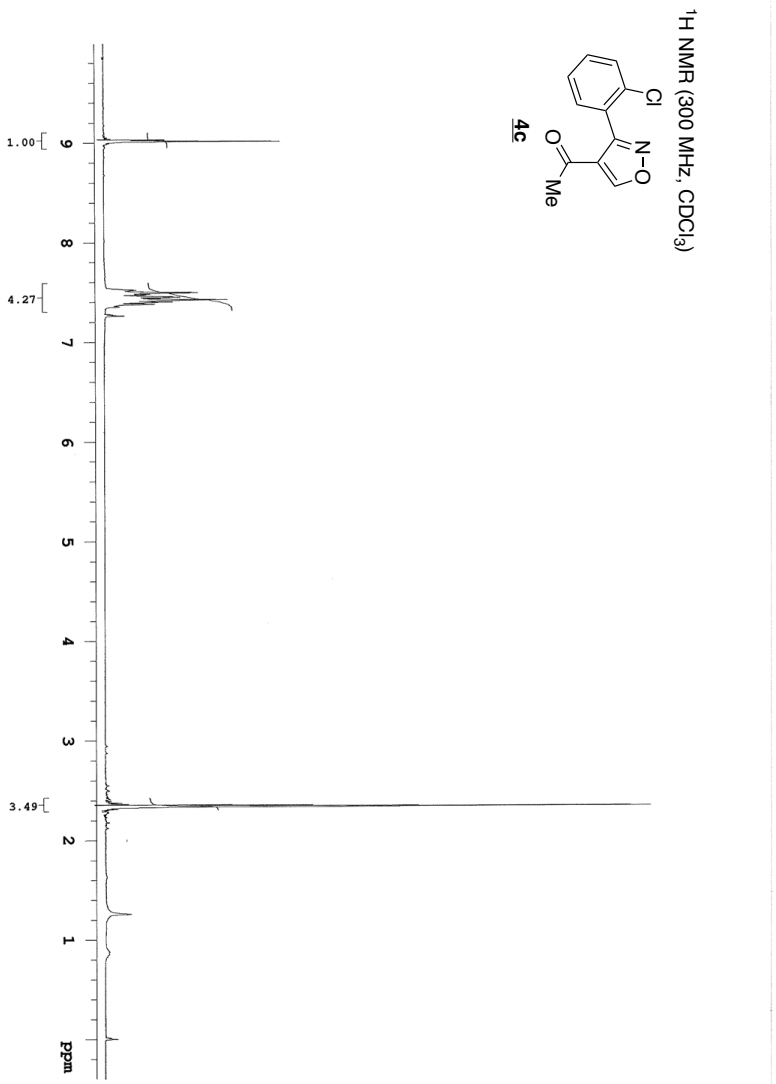
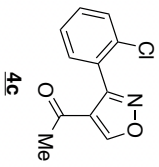
Cl
N–O
O
Me
4b
190.030
163.628
159.874
136.493
130.786
128.573
125.765
120.515
77.417
77.188
76.990
76.563
29.665
200
180
160
140
120
100
80
60
40
20
ppm


1H NMR (300 MHz, CDCl3)
Cl
N–O
O
Me
4c
1.00
4.27
3.49
9
8
7
6
5
4
3
2
1
ppm

^{13}C NMR (75 MHz, $CDCl_3$)



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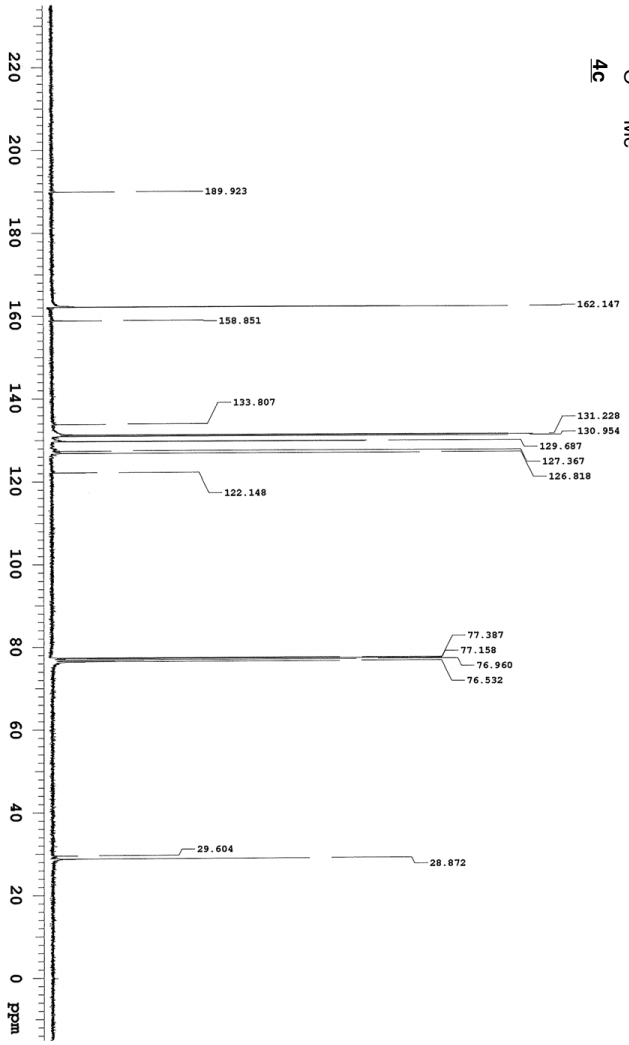

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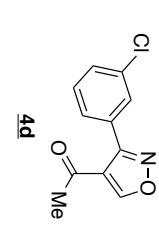

4d

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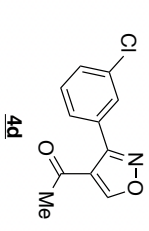
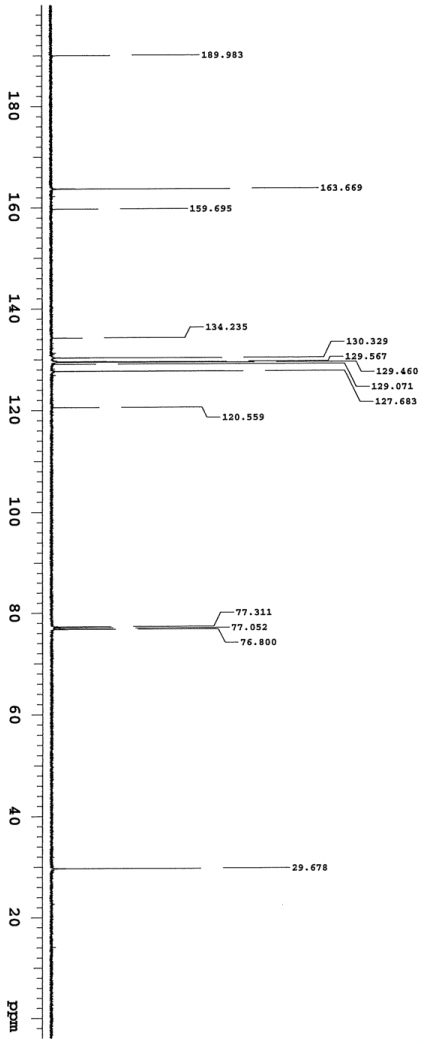


4d



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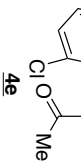

4e

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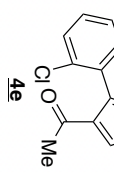

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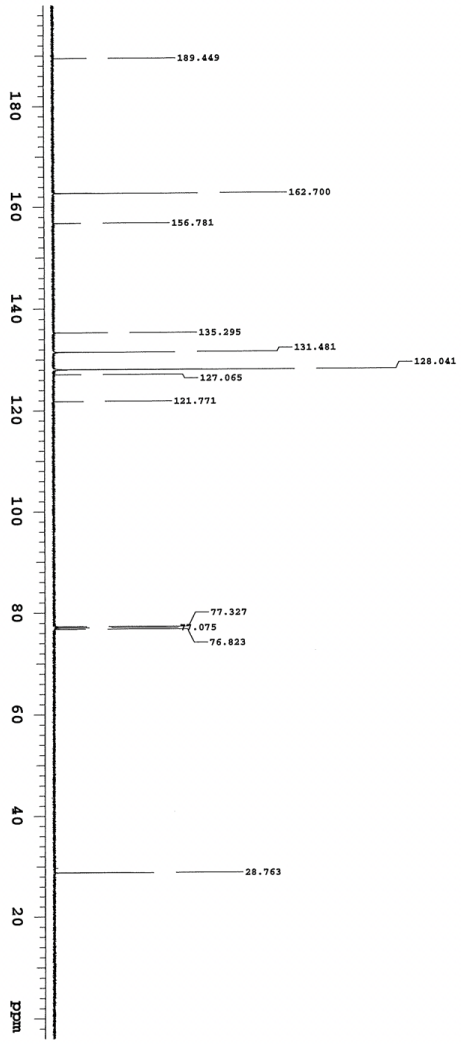

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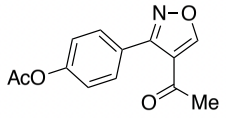

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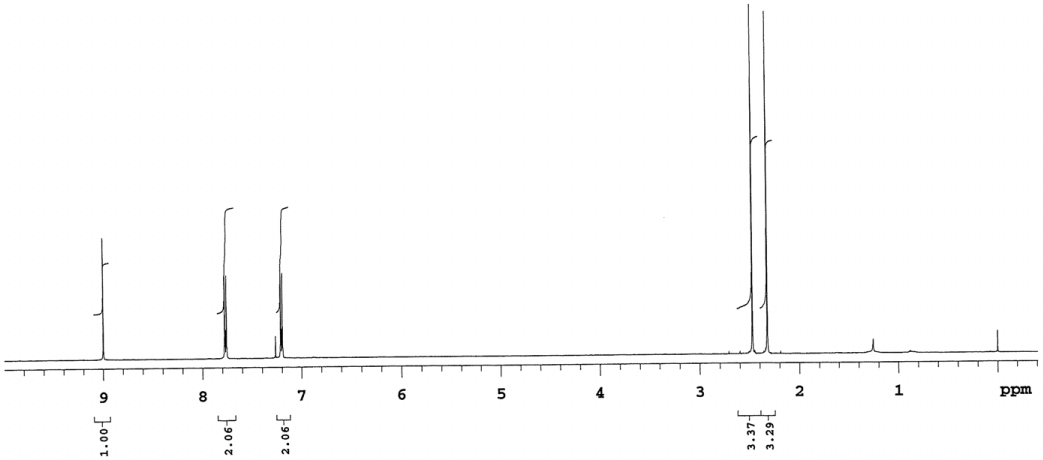

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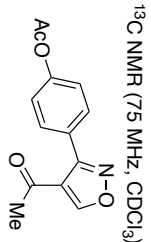

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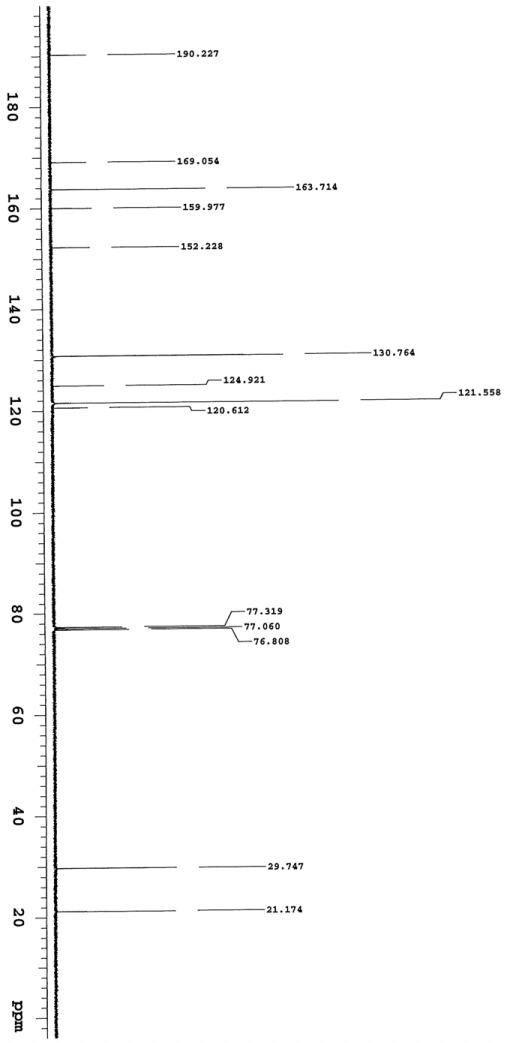
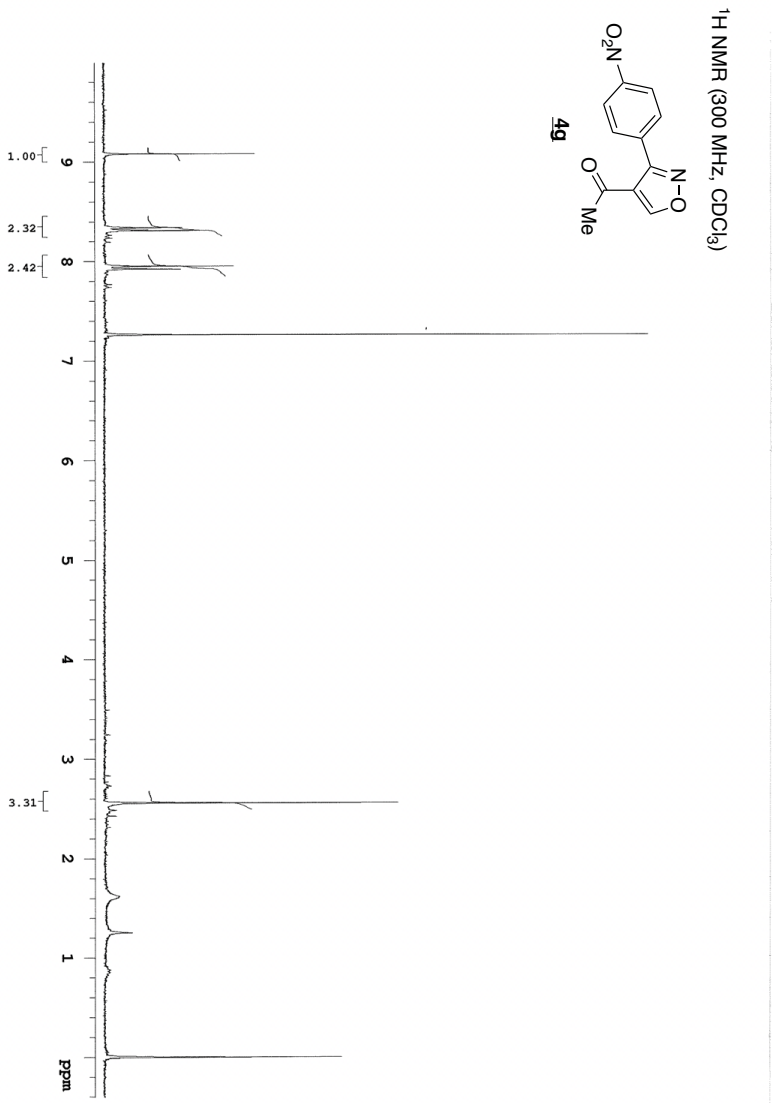
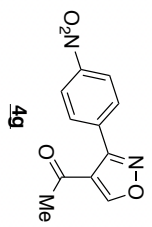
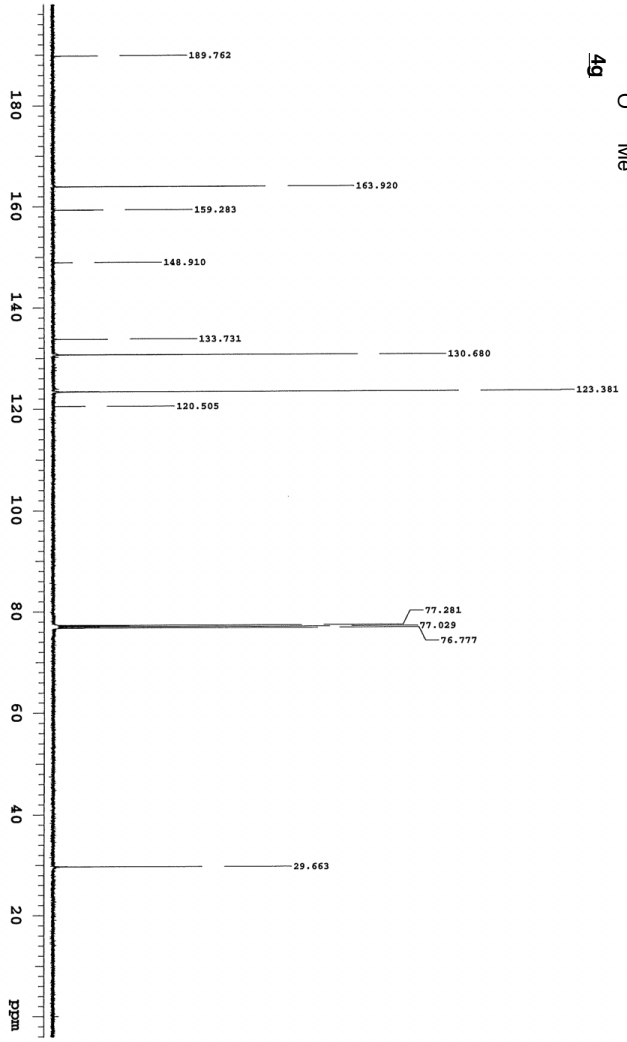



^{1}H NMR (300 MHz, $CDCl_3$)
O_2N
N–O
O
Me
4g
1.00
2.32
2.42
3.31
9
8
7
6
5
4
3
2
1
ppm

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



4g



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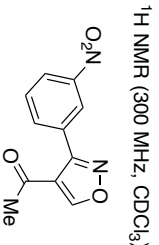
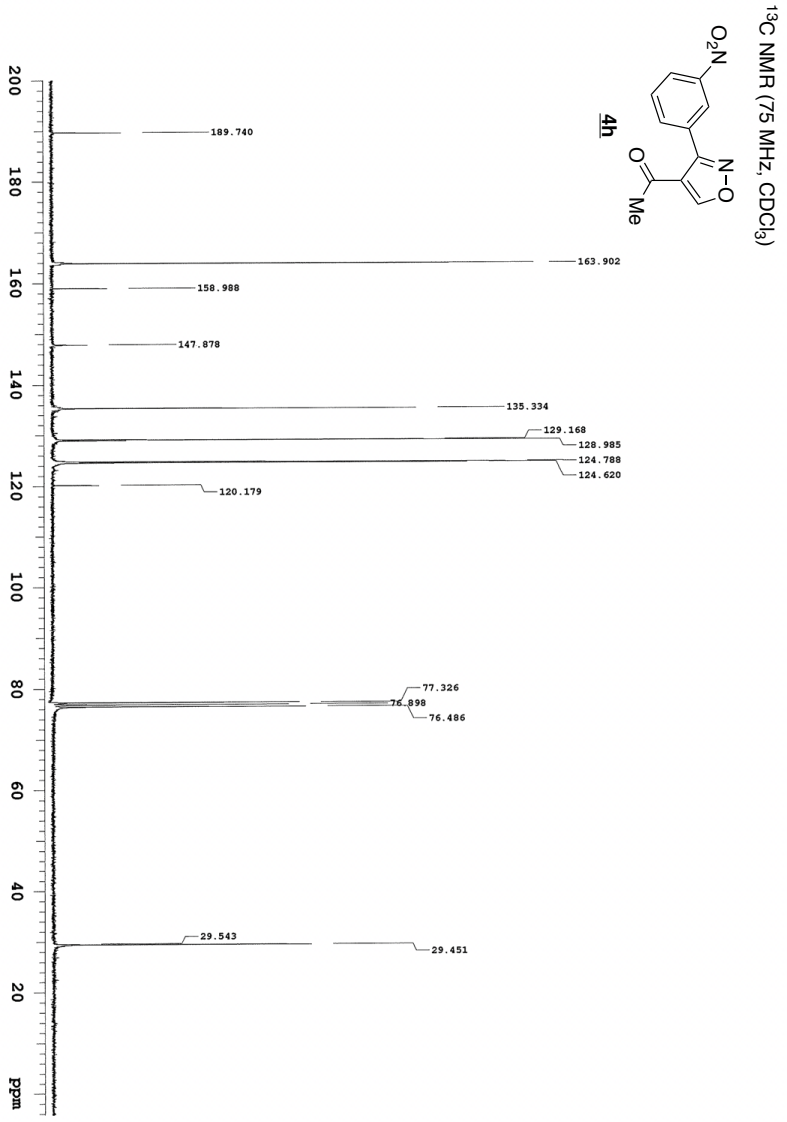


4h


^{13}C NMR (75 MHz, CDCl$_3$)
O_2N
N–O
O
Me
4h
189.740
163.902
158.988
147.878
135.334
129.168
128.985
124.788
124.620
120.179
77.326
76.898
76.486
29.543
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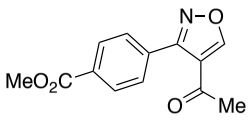
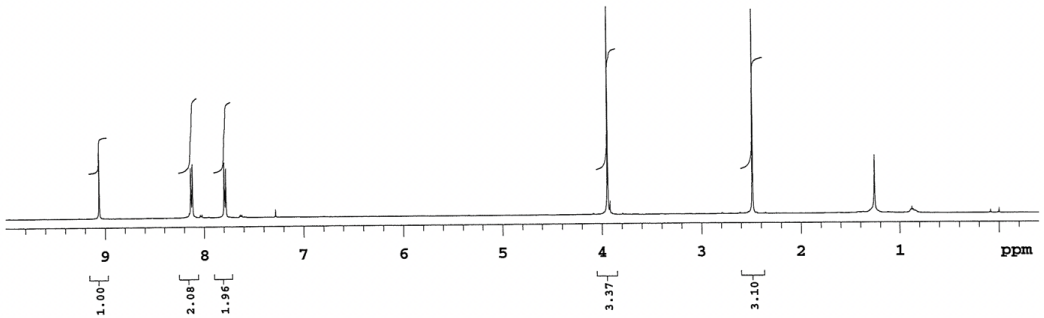
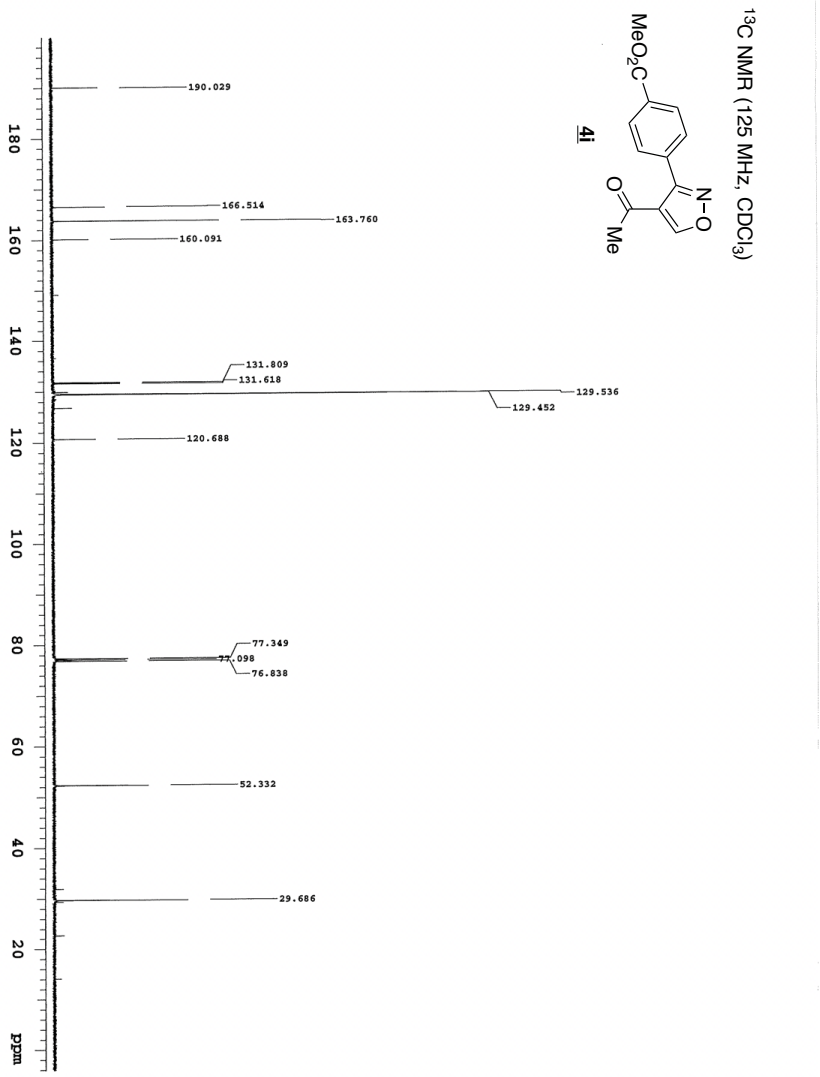
200
180
160
140
120
100
80
60
40
20
ppm

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

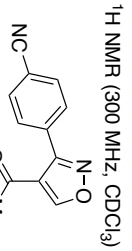


4i




13C NMR (125 MHz, CDCl3)
MeO2C
N–O
O
Me
4i
190.029
166.514
163.760
160.091
131.809
131.618
129.536
129.452
120.688
77.349
77.098
76.838
52.332
29.686
180
160
140
120
100
80
60
40
20
ppm

^{1}H NMR (300 MHz, $CDCl_3$)



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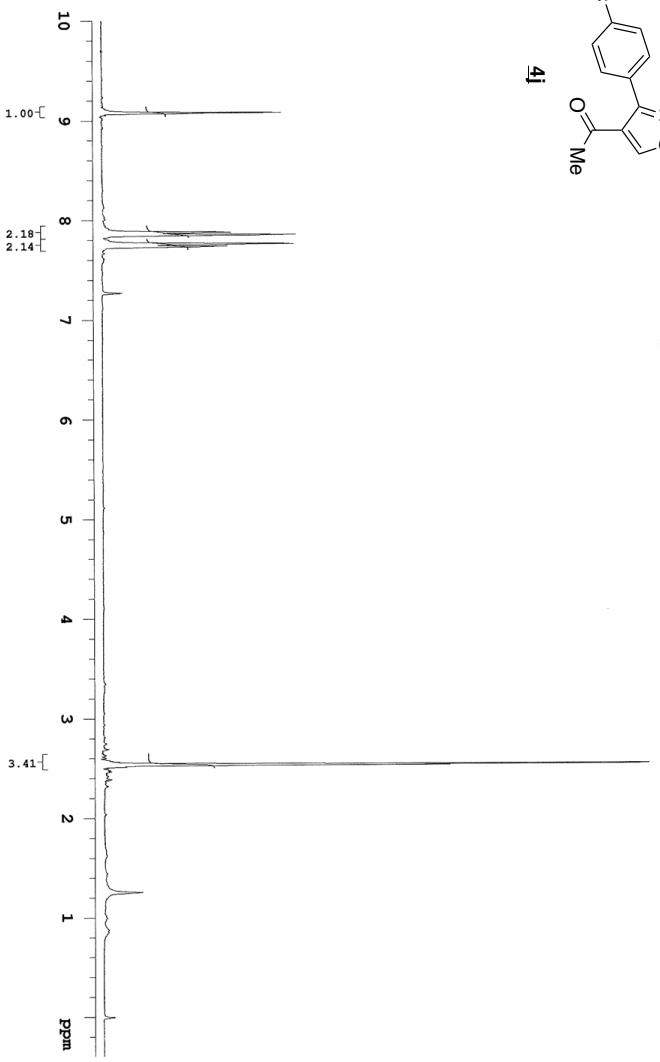
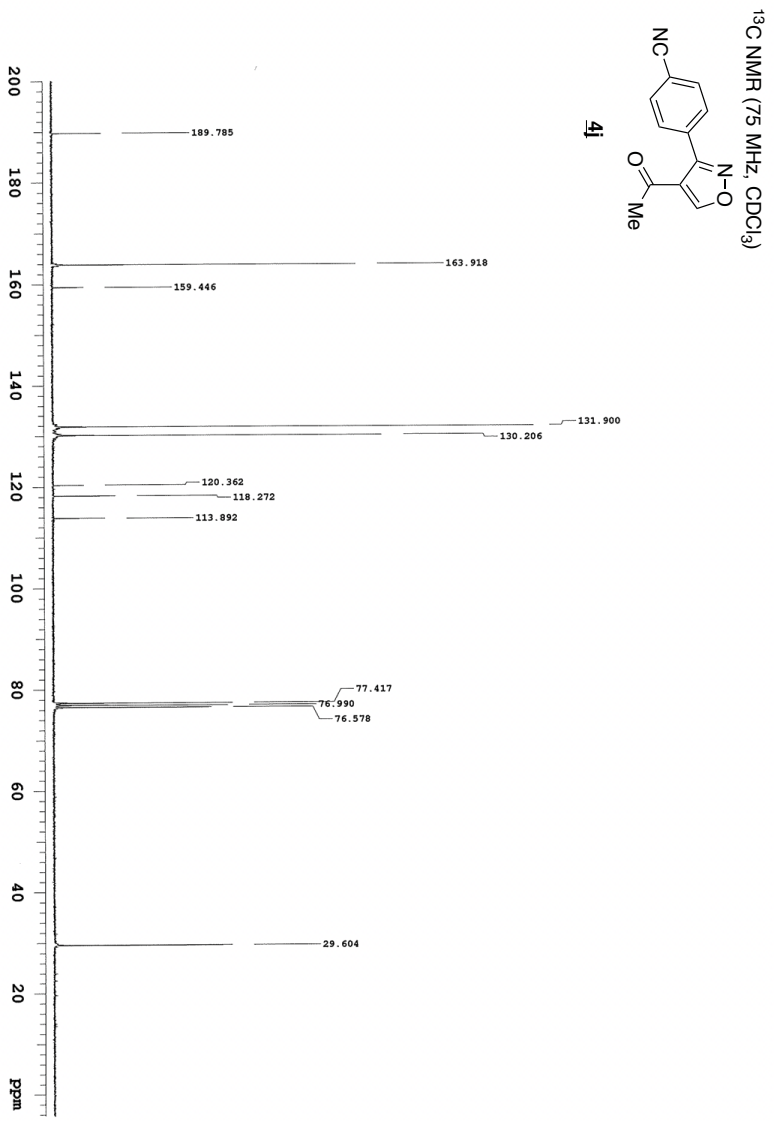
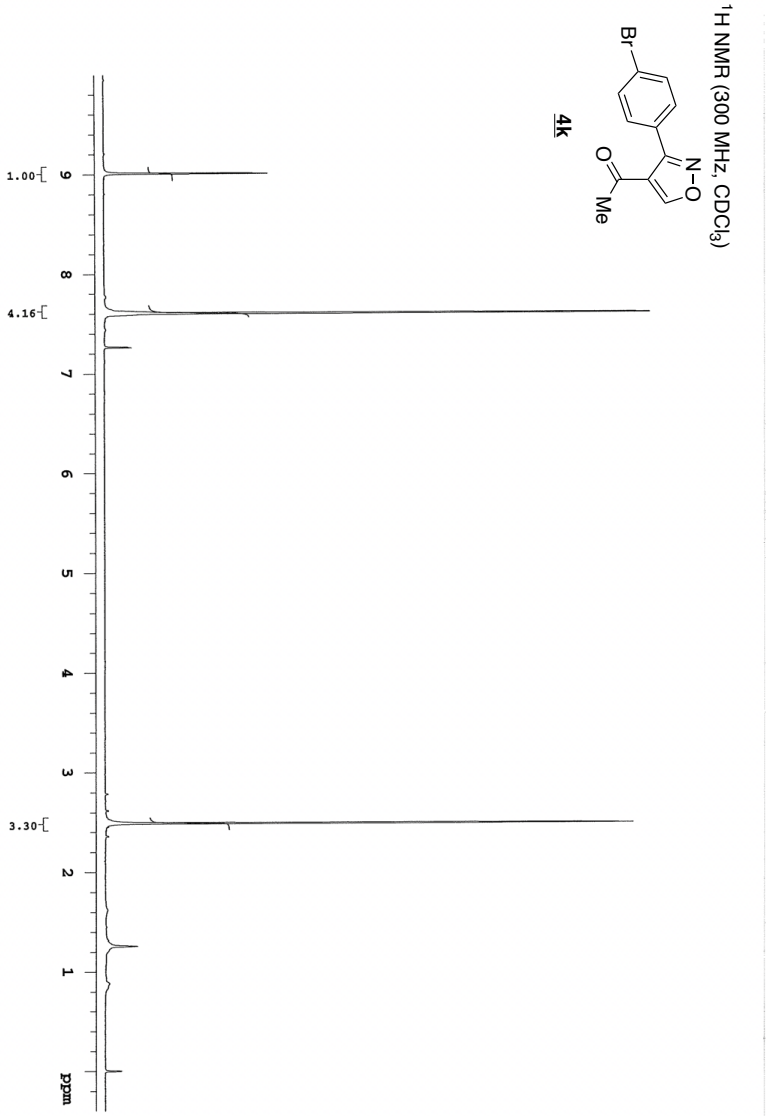
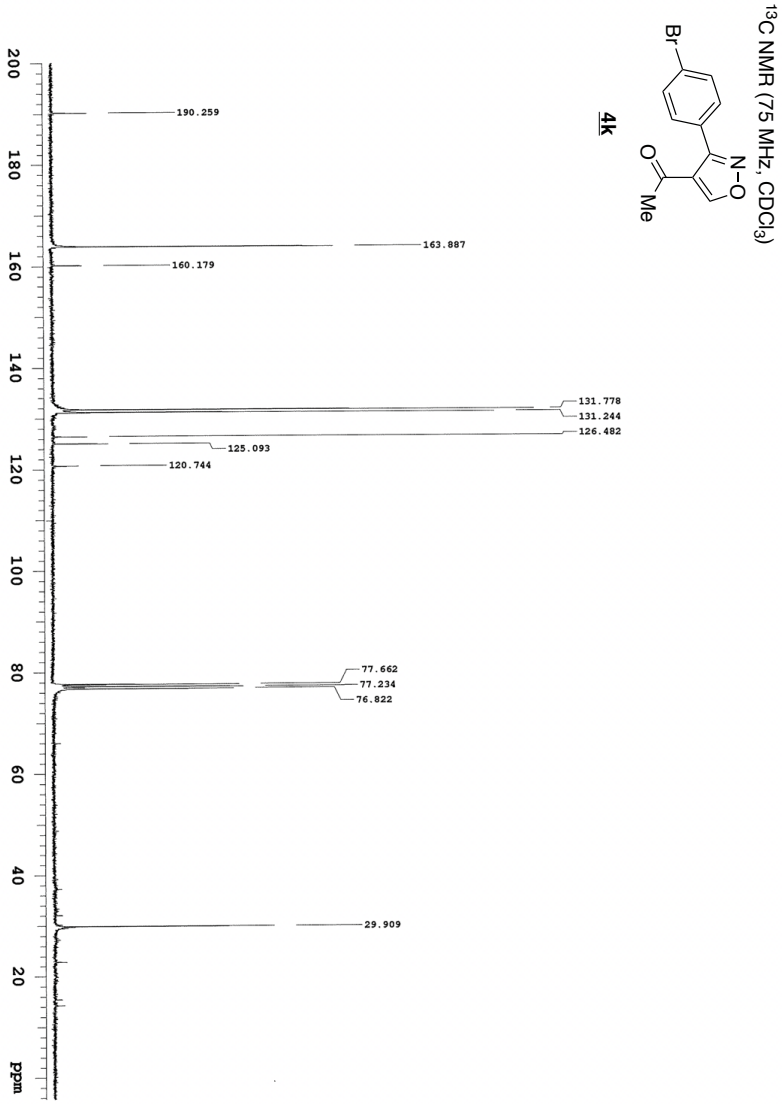
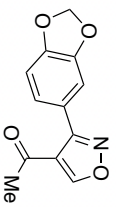



13C NMR (75 MHz, CDCl3)
4j
NC
N–O
O
Me
189.785
163.918
159.446
131.900
130.206
120.362
118.272
113.892
77.417
76.990
76.578
29.604
200
180
160
140
120
100
80
60
40
20
ppm


^{1}H NMR (300 MHz, CDCl$_3$)
Br
N–O
O
Me
4k
1.00
4.16
3.30
9
8
7
6
5
4
3
2
1
ppm

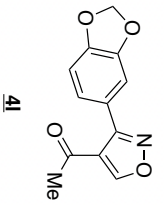

^{13}C NMR (75 MHz, $CDCl_3$)
Br
N–O
O
Me
4k
190.259
163.887
160.179
131.778
131.244
126.482
125.093
120.744
77.662
77.234
76.822
29.909
200
180
160
140
120
100
80
60
40
20
ppm

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

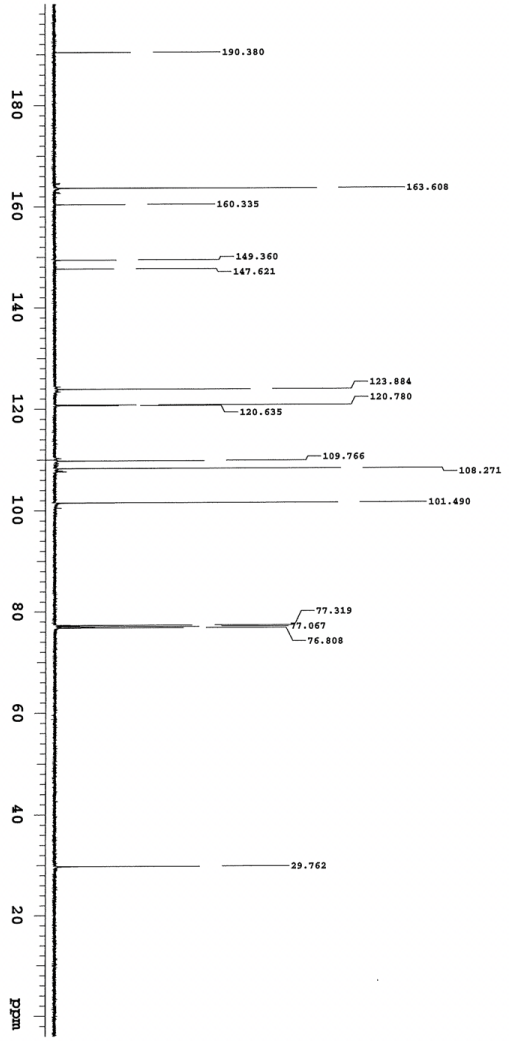


4l

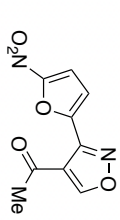
^{13}C NMR (125 MHz, $CDCl_3$)



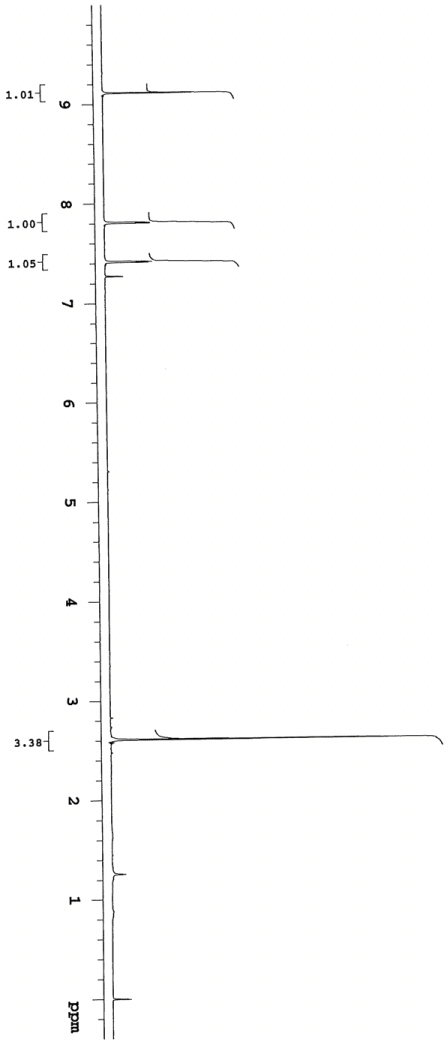
41



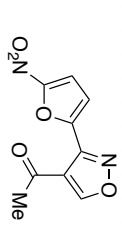
^{1}H NMR (500 MHz, $CDCl_3$)



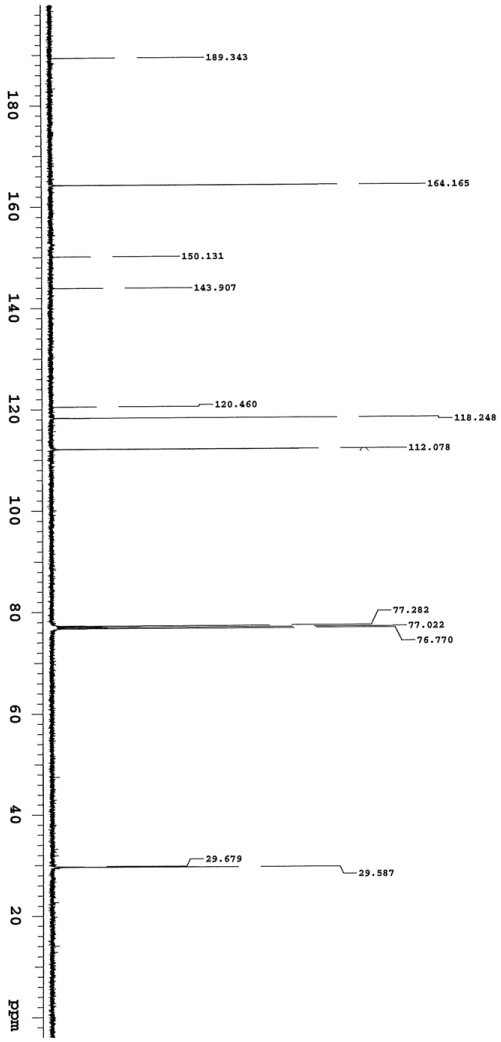
4m

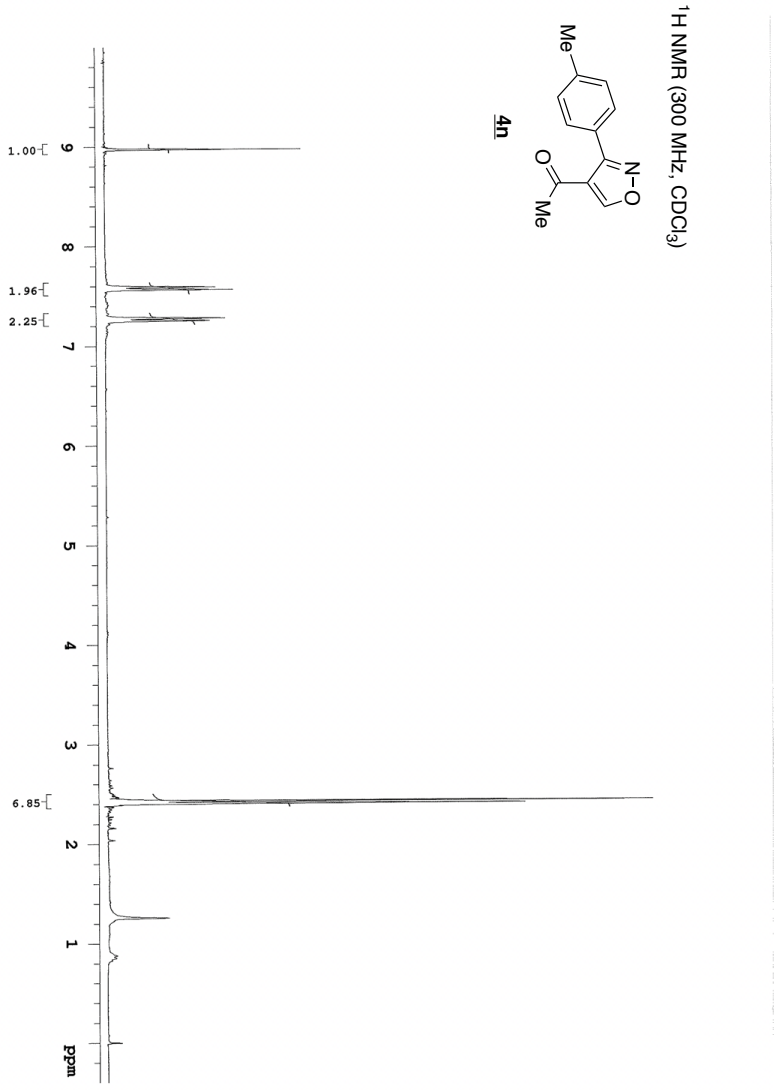


^{13}C NMR (125 MHz, $CDCl_3$)

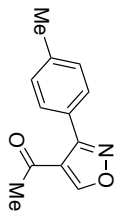


4m

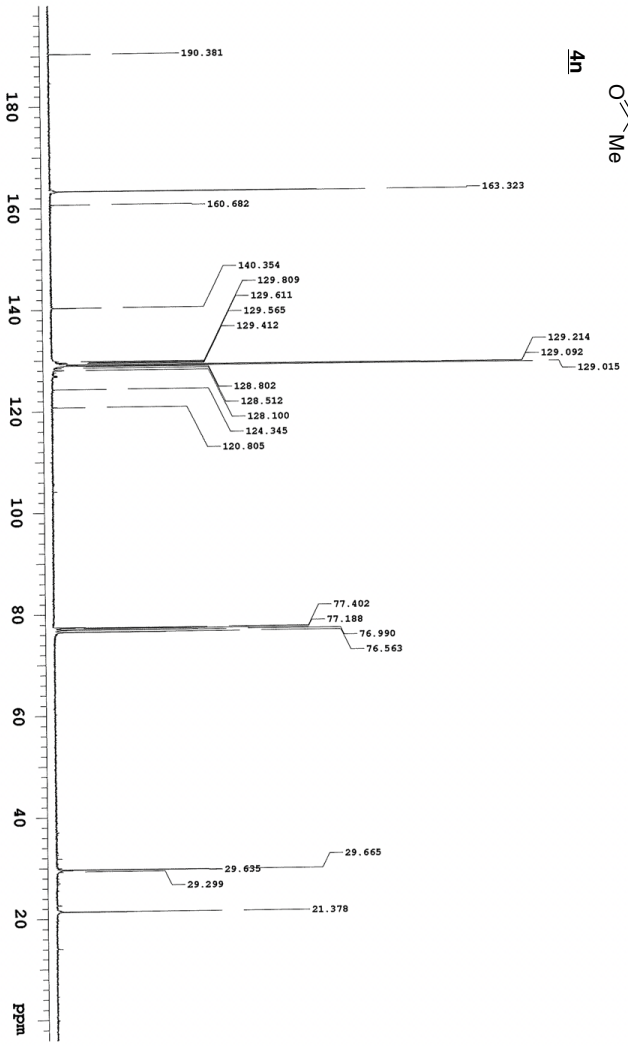



^{1}H NMR (300 MHz, $CDCl_3$)
Me
N–O
O
Me
4n
1.00
1.96
2.25
6.85
9
8
7
6
5
4
3
2
1
ppm

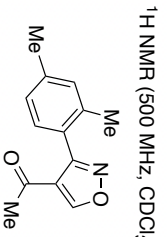
^{13}C NMR (75 MHz, $CDCl_3$)



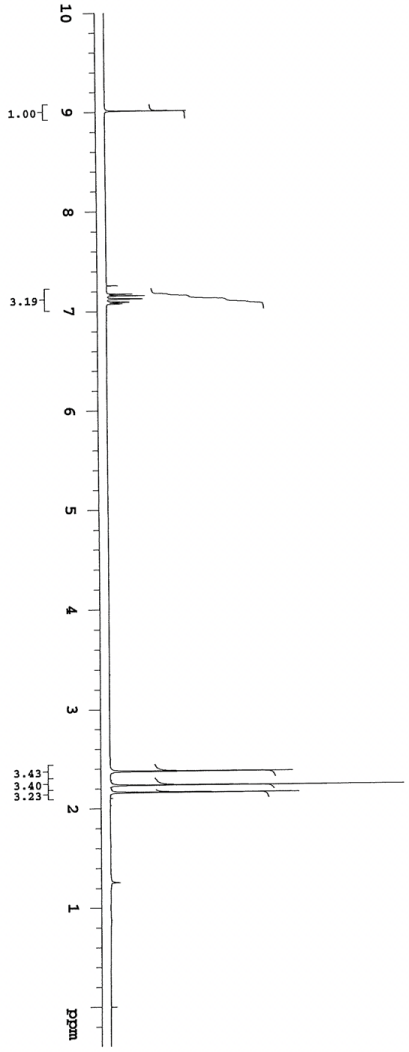
4n



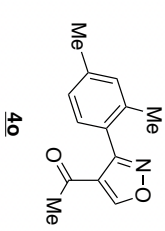
^{1}H NMR (500 MHz, $CDCl_3$)



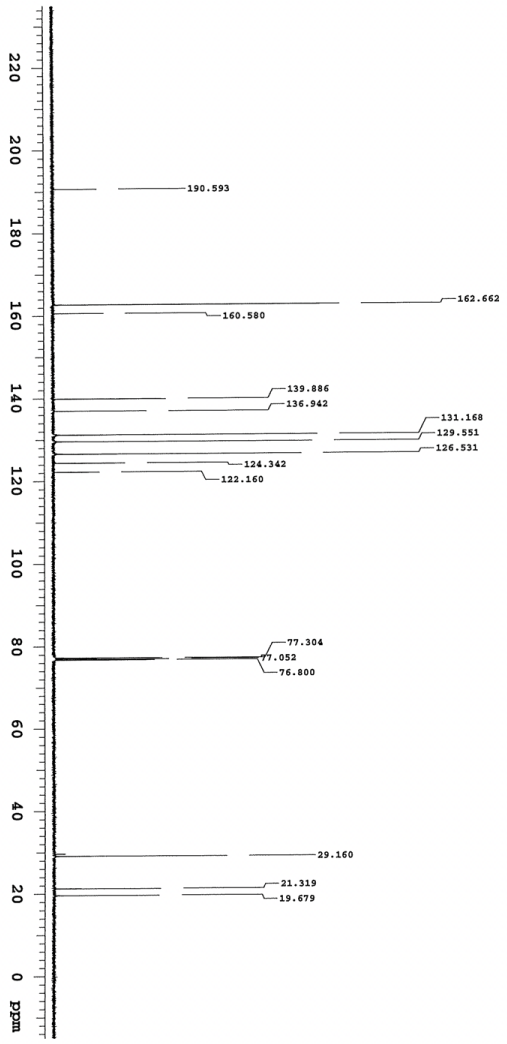
4o



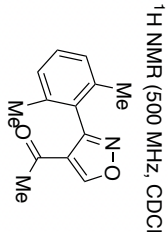
^{13}C NMR (125 MHz, $CDCl_3$)



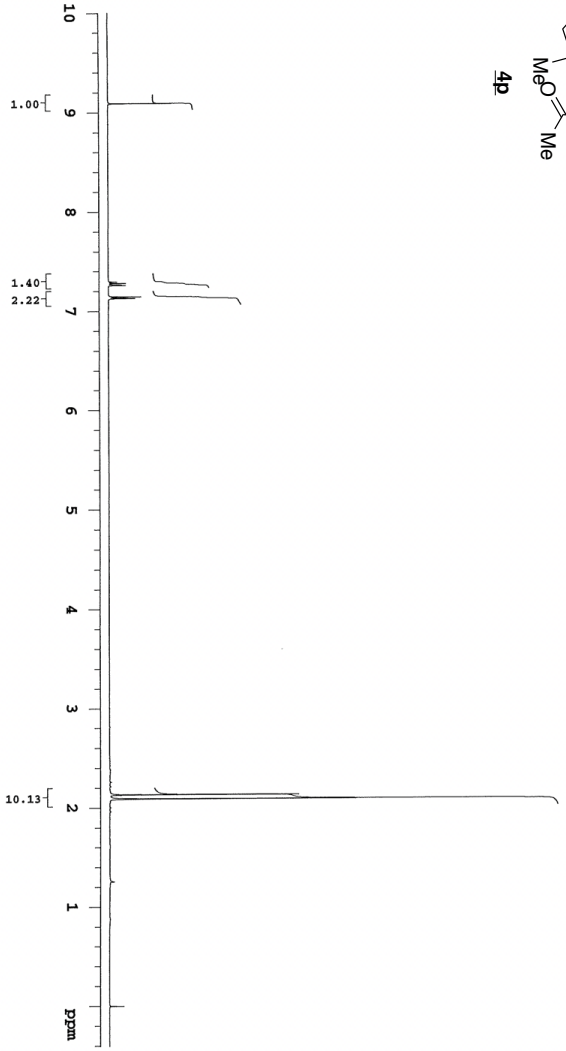
4o

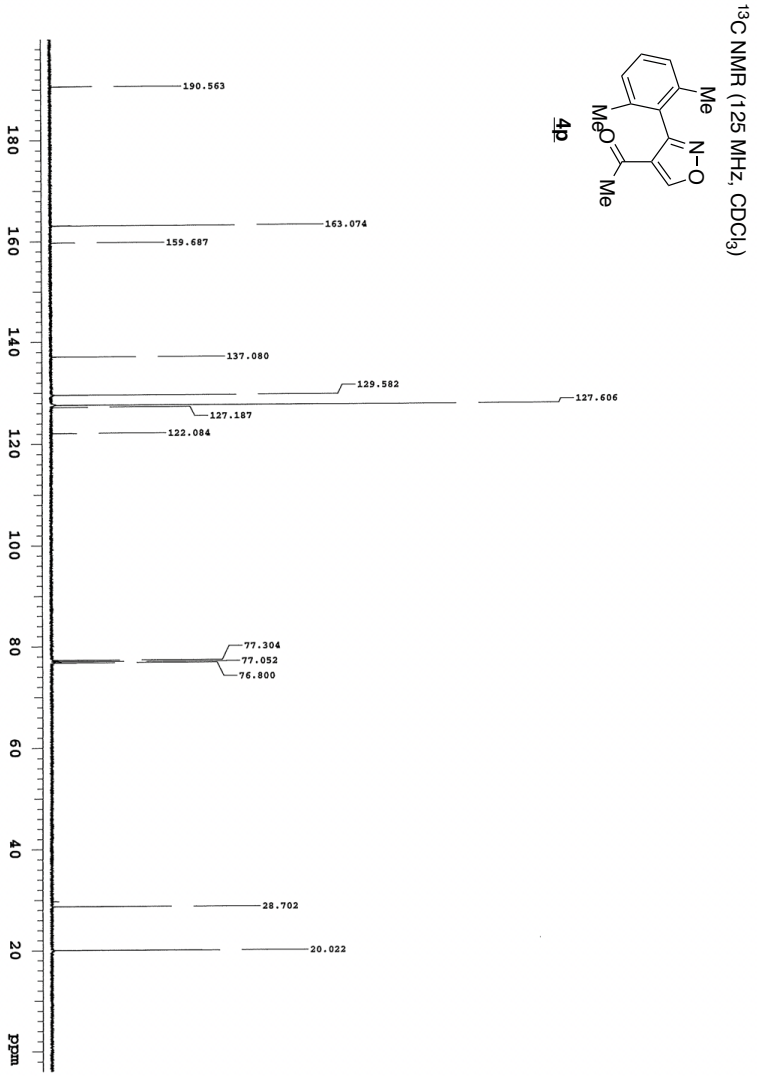


^{1}H NMR (500 MHz, $CDCl_3$)

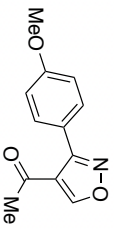


4p



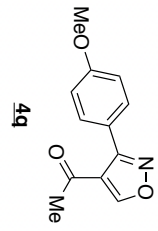

^{13}C NMR (125 MHz, $CDCl_3$)
Me
N–O
MeO
Me
4p
190.563
163.074
159.687
137.080
129.582
127.606
127.187
122.084
77.304
77.052
76.800
28.702
20.022
180
160
140
120
100
80
60
40
20
ppm

^{1}H NMR (300 MHz, $CDCl_3$)

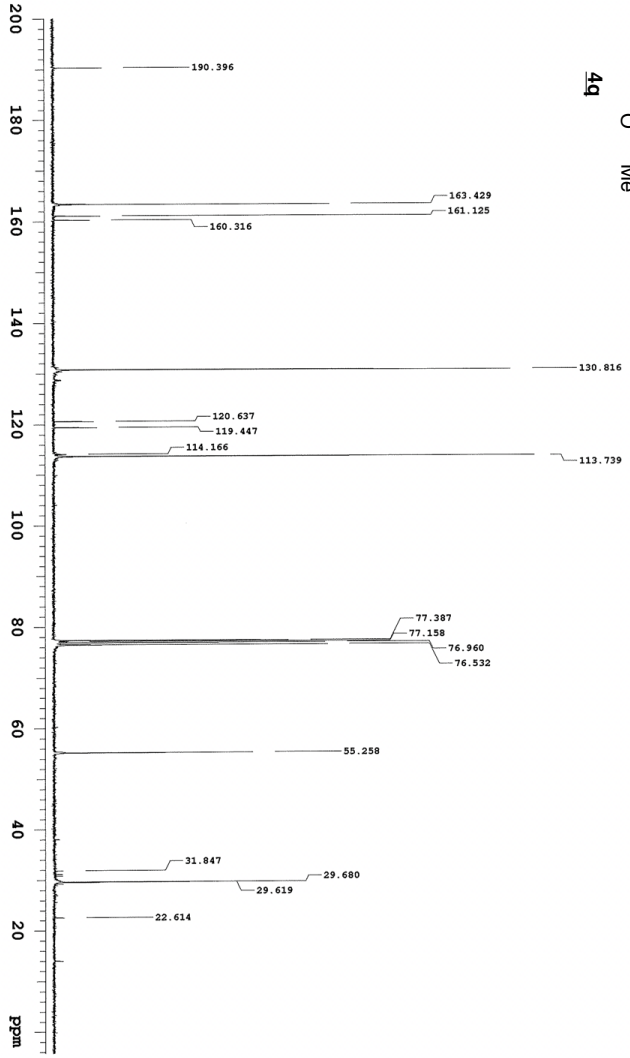


4q

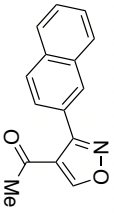
^{13}C NMR (75 MHz, $CDCl_3$)



4q

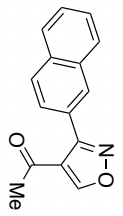


^{1}H NMR (500 MHz, $CDCl_3$)

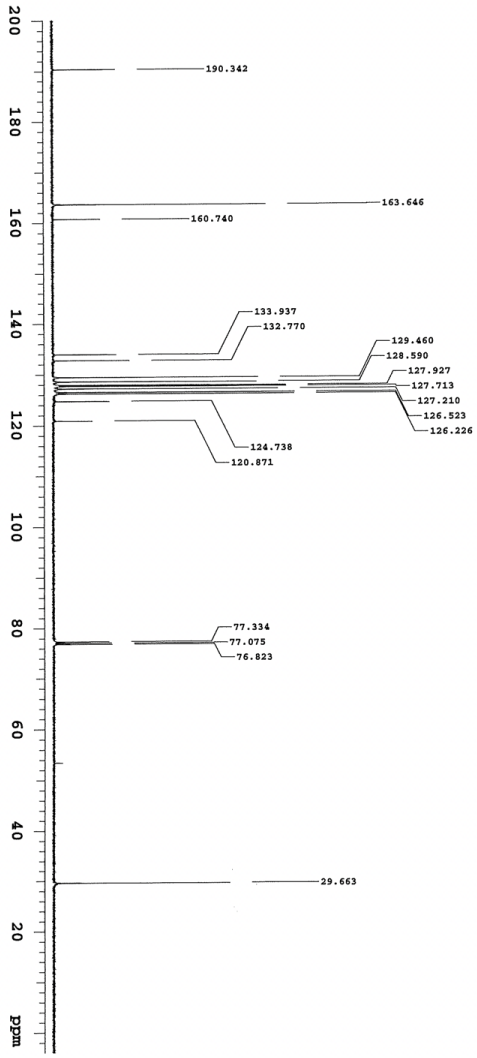


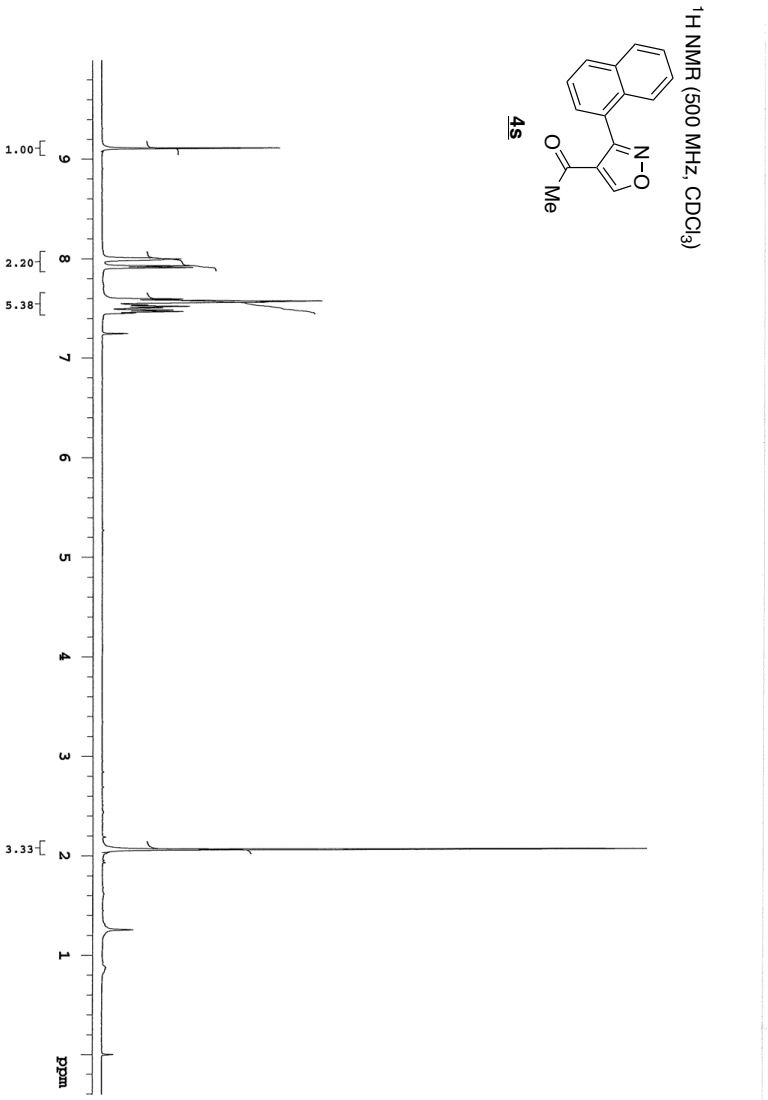
4r

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

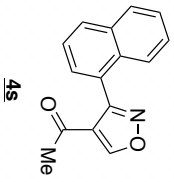


4r

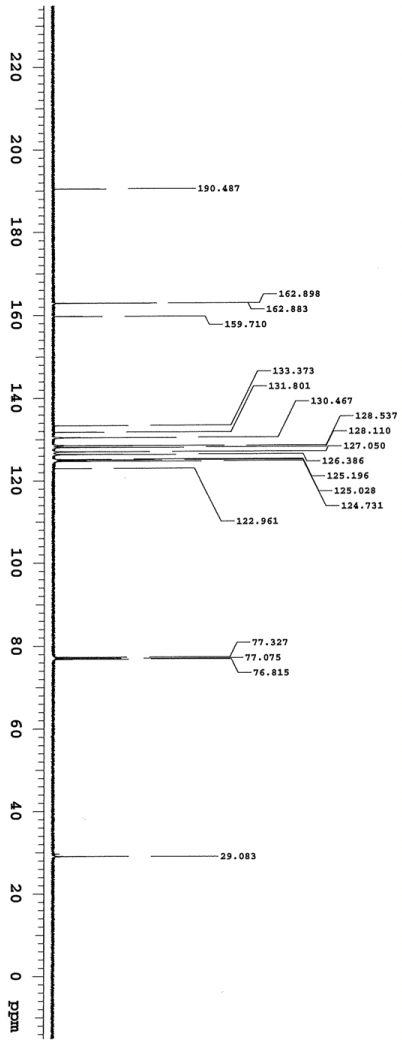



1H NMR (500 MHz, CDCl3)
N–O
O
Me
4s
1.00
2.20
5.38
3.33
9
8
7
6
5
4
3
2
1
ppm

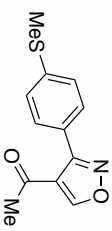
^{13}C NMR (125 MHz, $CDCl_3$)



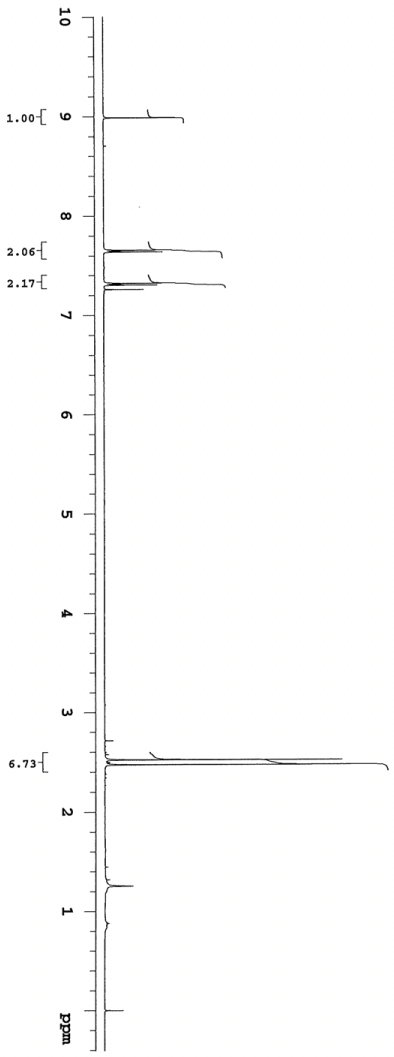
4s



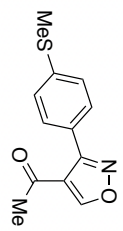
^{1}H NMR (500 MHz, $CDCl_3$)



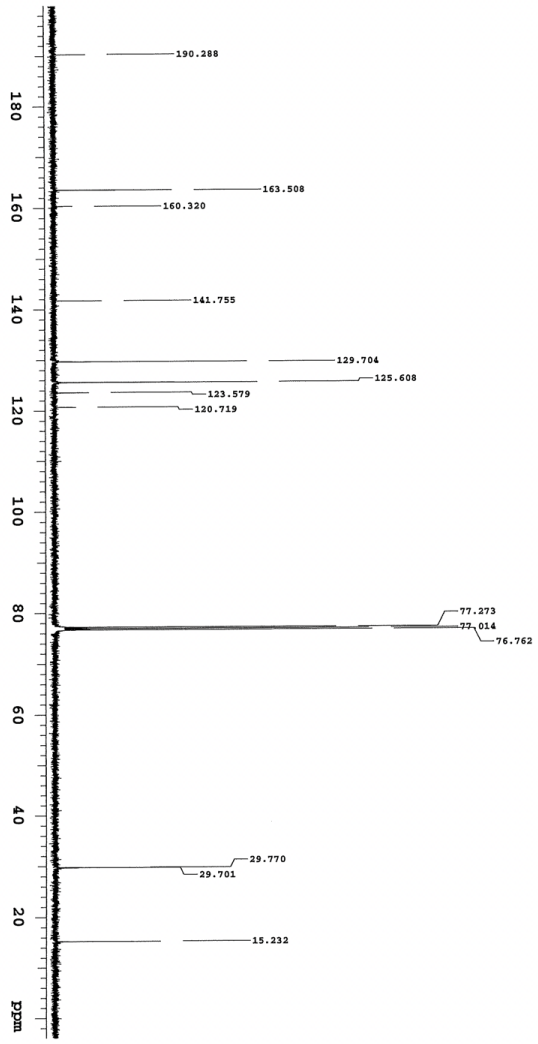
4t



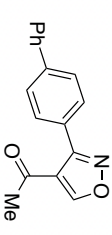
^{13}C NMR (125 MHz, $CDCl_3$)



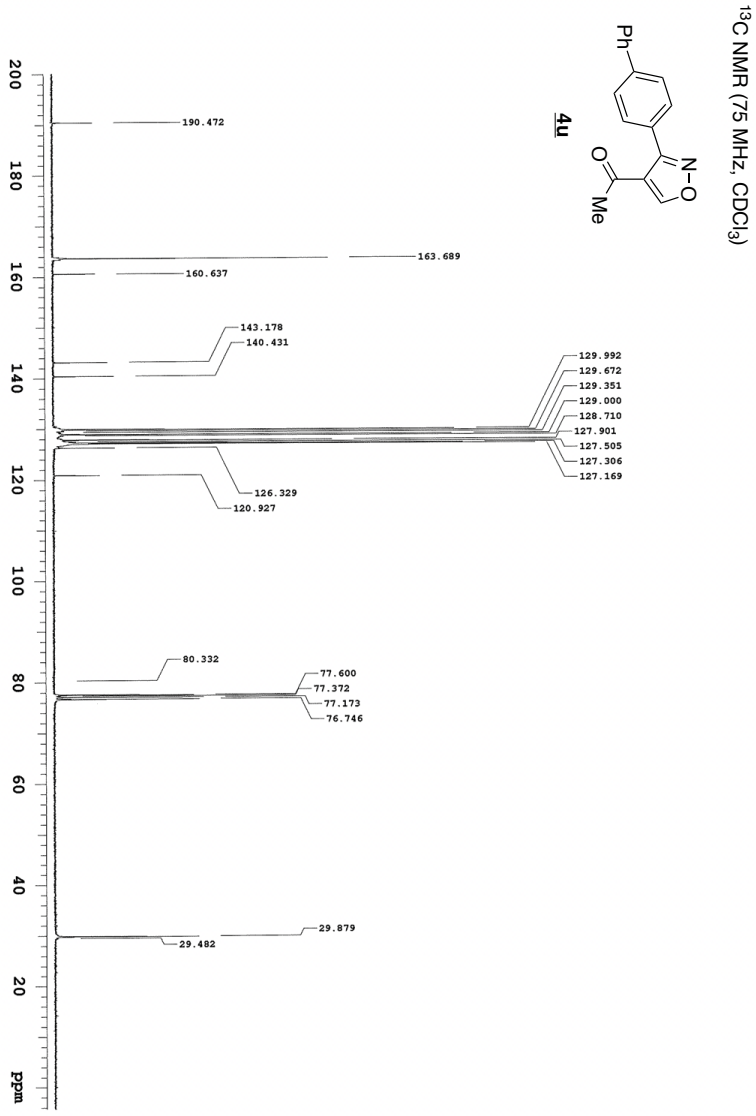
4t



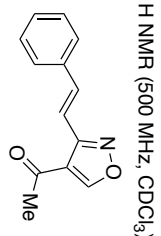
^{1}H NMR (300 MHz, $CDCl_3$)



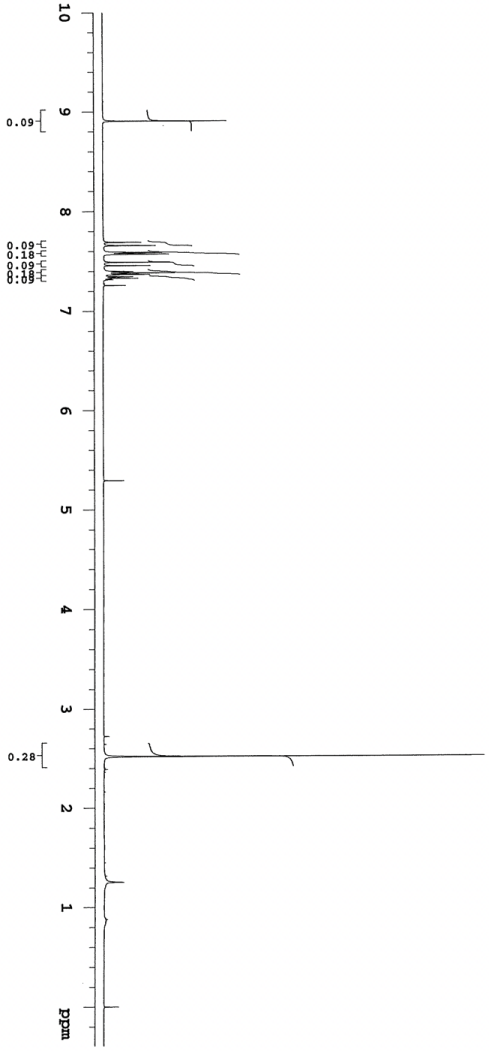
4u

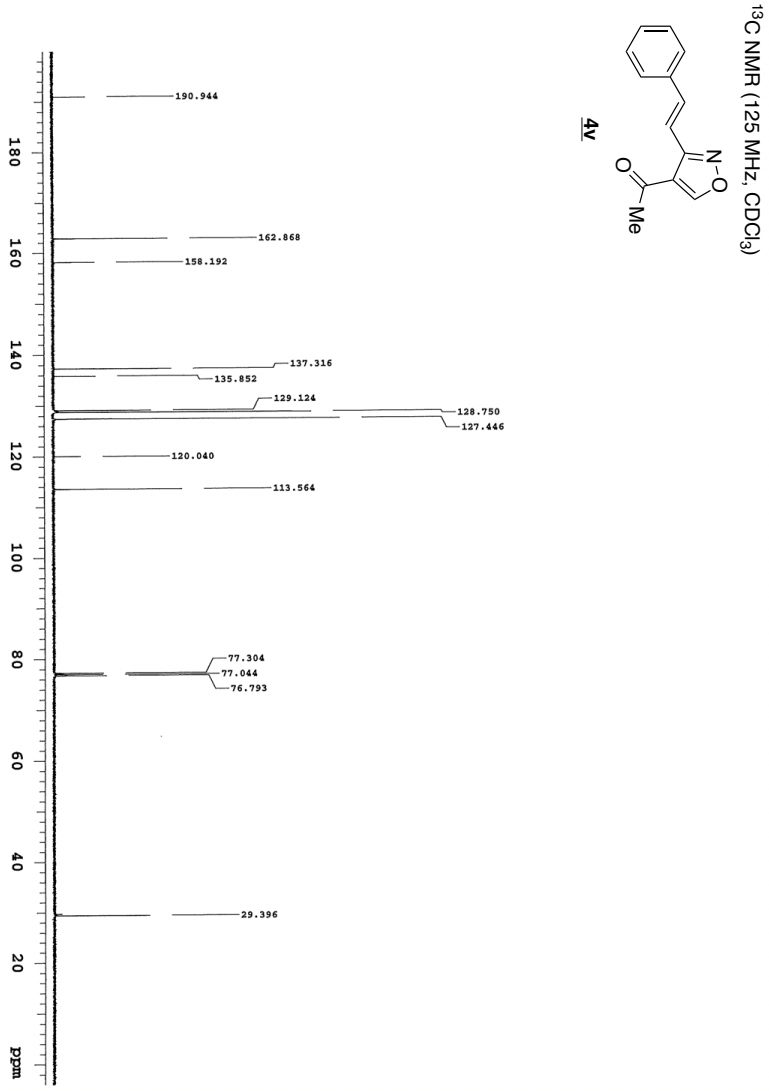

^{13}C NMR (75 MHz, $CDCl_3$)
Ph
N–O
O
Me
4u
190.472
163.689
160.637
143.178
140.431
129.992
129.672
129.351
129.000
128.710
127.901
127.505
127.306
127.169
126.329
120.927
80.332
77.600
77.372
77.173
76.746
29.879
29.482
200
180
160
140
120
100
80
60
40
20
ppm

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

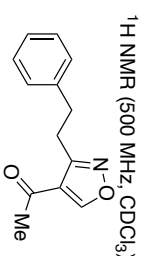


4v

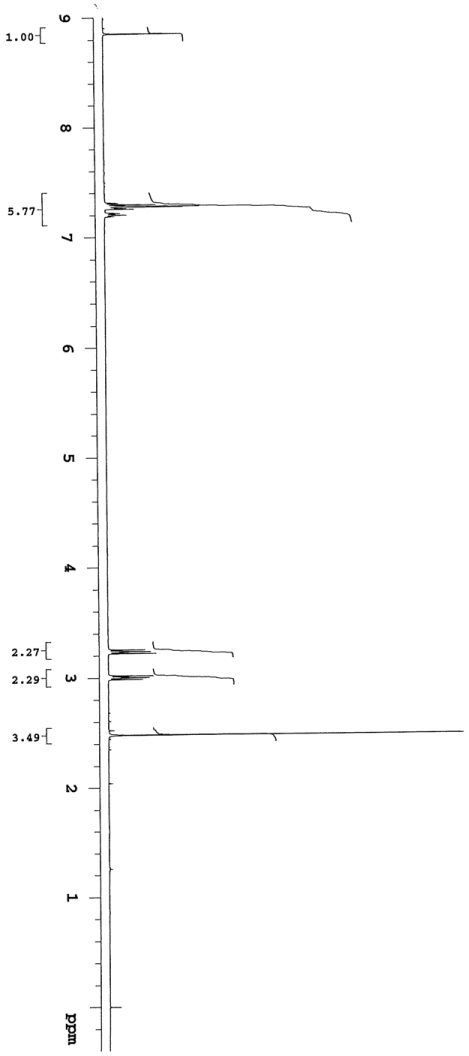


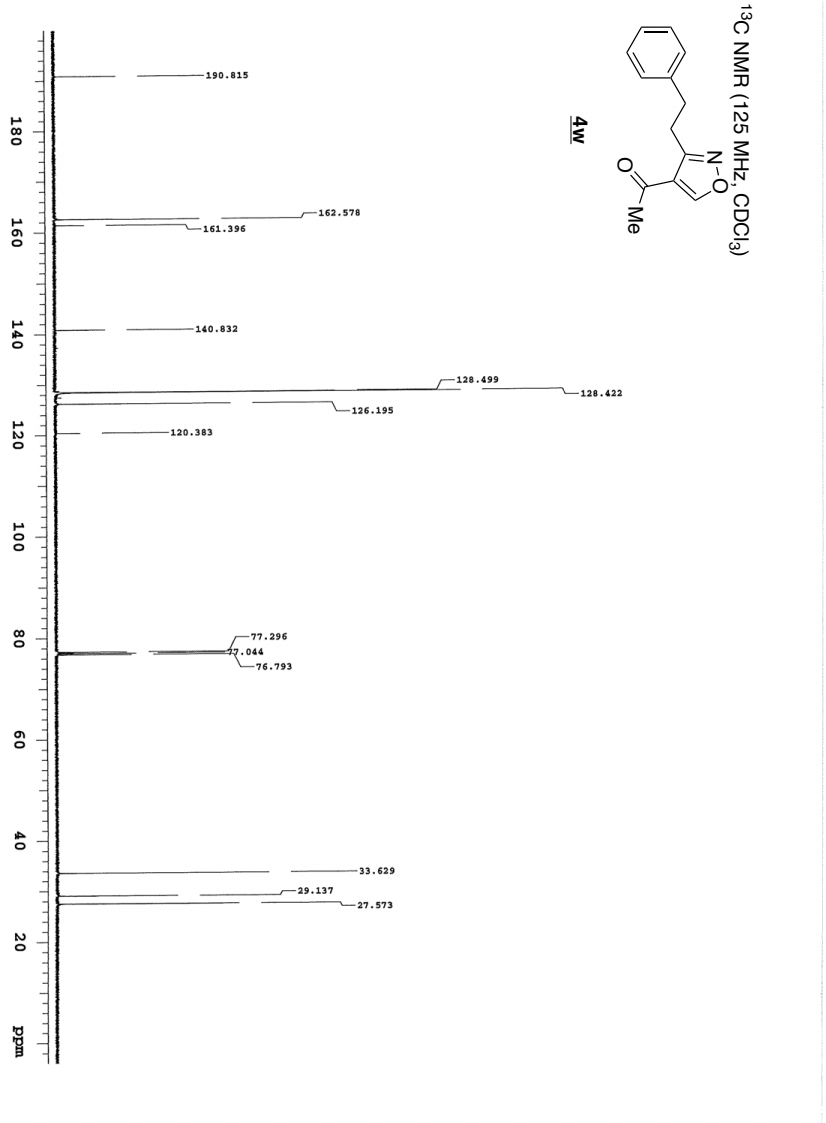

^{13}C NMR (125 MHz, CDCl$_3$)
4v
N
O
O
Me
190.944
162.868
158.192
137.316
135.852
129.124
128.750
127.446
120.040
113.564
77.304
77.044
76.793
29.396
180
160
140
120
100
80
60
40
20
ppm

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

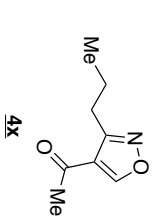


4w

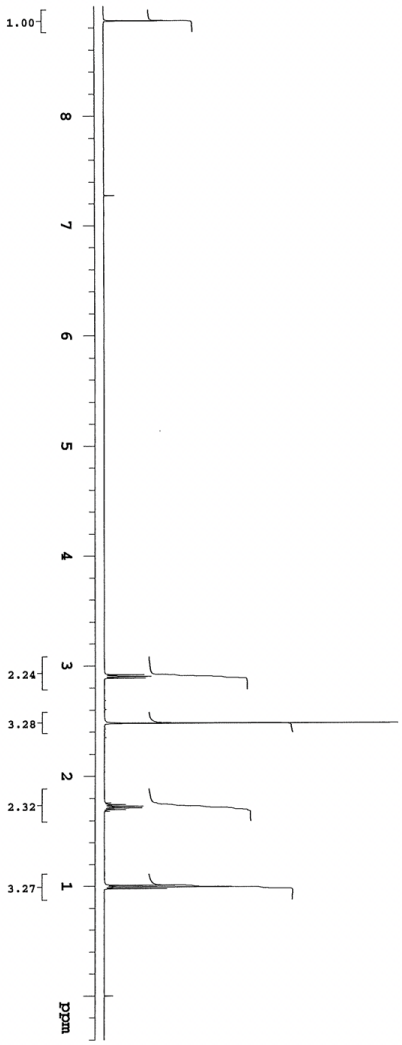



13C NMR (125 MHz, CDCl3)
4w
Me
190.815
162.578
161.396
140.832
128.499
128.422
126.195
120.383
77.296
77.044
76.793
33.629
29.137
27.573
ppm

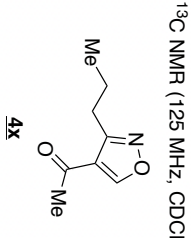
^{1}H NMR (500 MHz, $CDCl_3$)



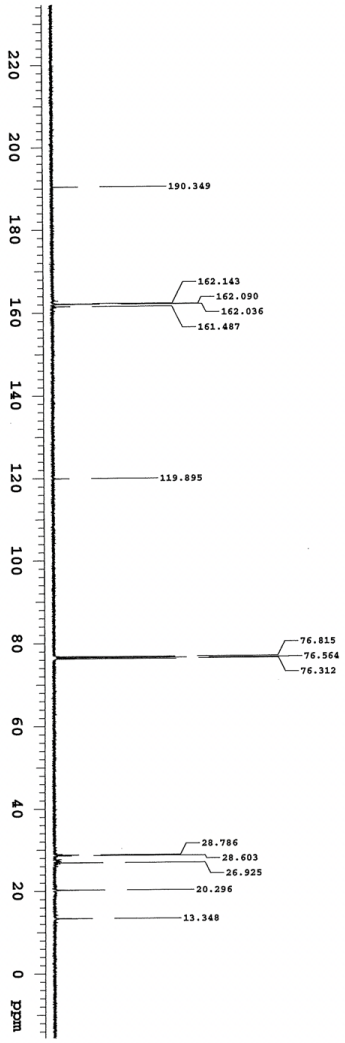
4x



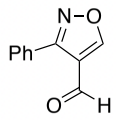
^{13}C NMR (125 MHz, $CDCl_3$)



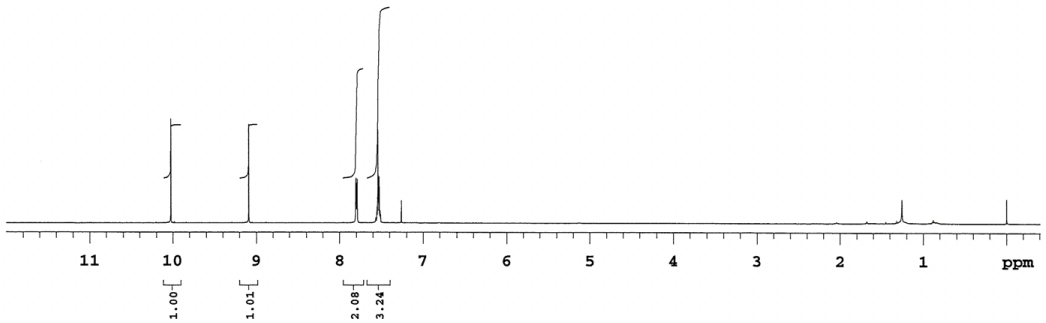
4x



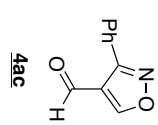
^{1}H NMR (500 MHz, $CDCl_3$)



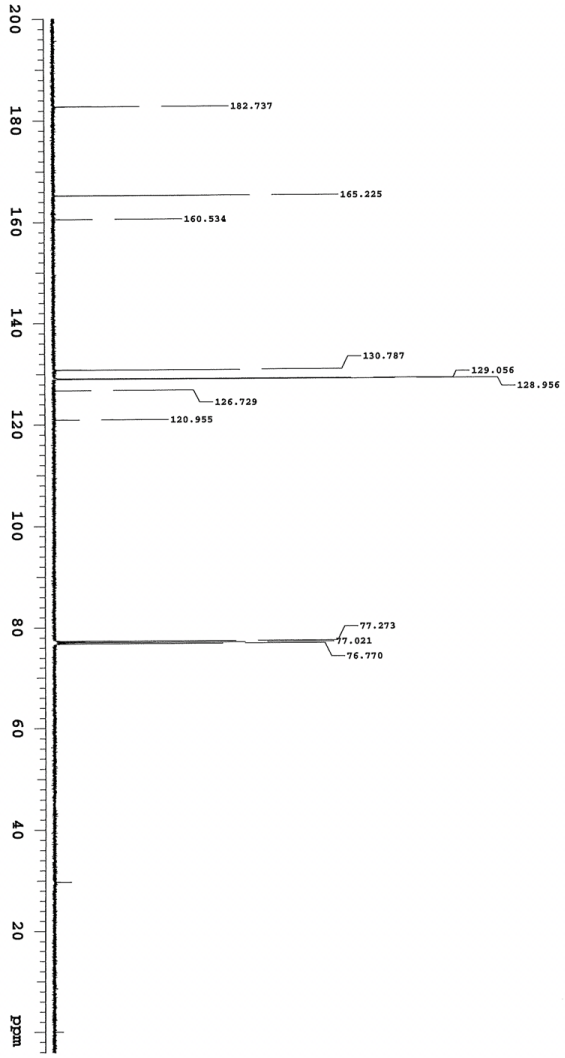
4ac



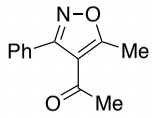
^{13}C NMR (125 MHz, $CDCl_3$)



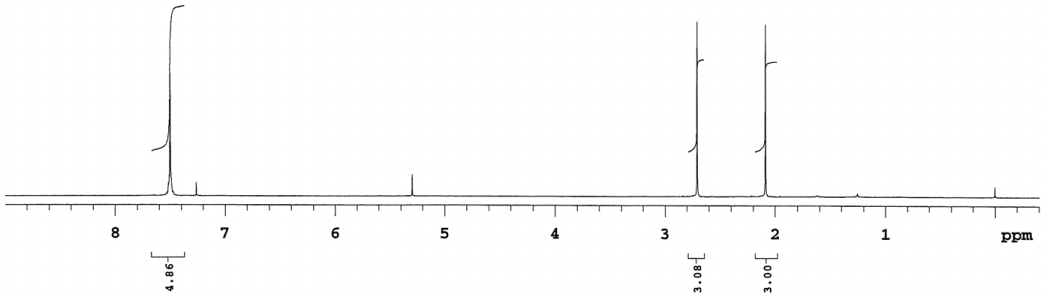
4ac



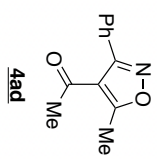
^{1}H NMR (500 MHz, $CDCl_3$)



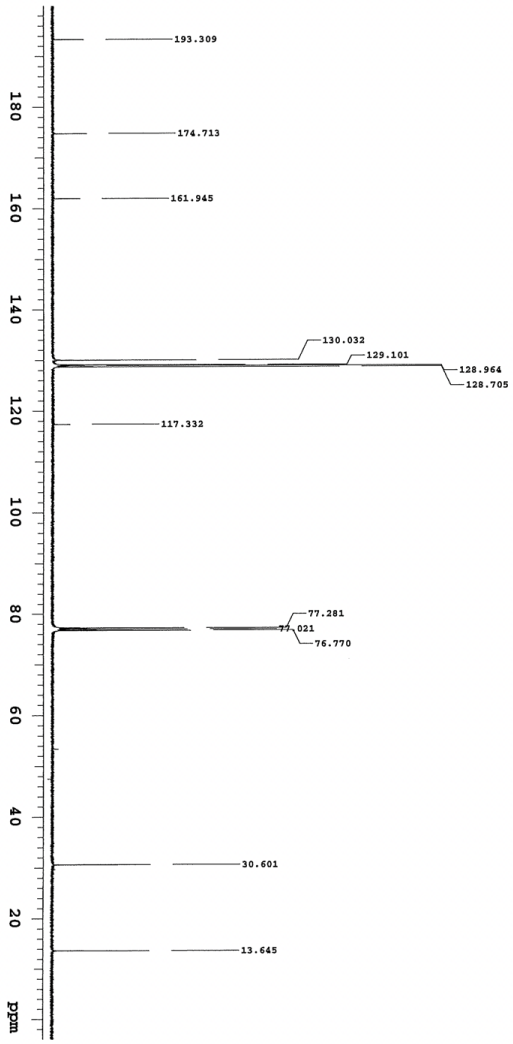
4ad



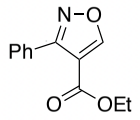
^{13}C NMR (125 MHz, $CDCl_3$)



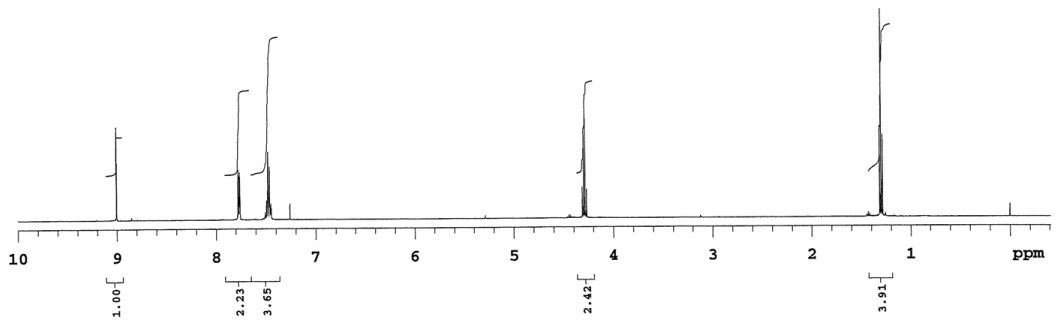
4ad



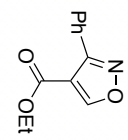
^{1}H NMR (500 MHz, $CDCl_3$)



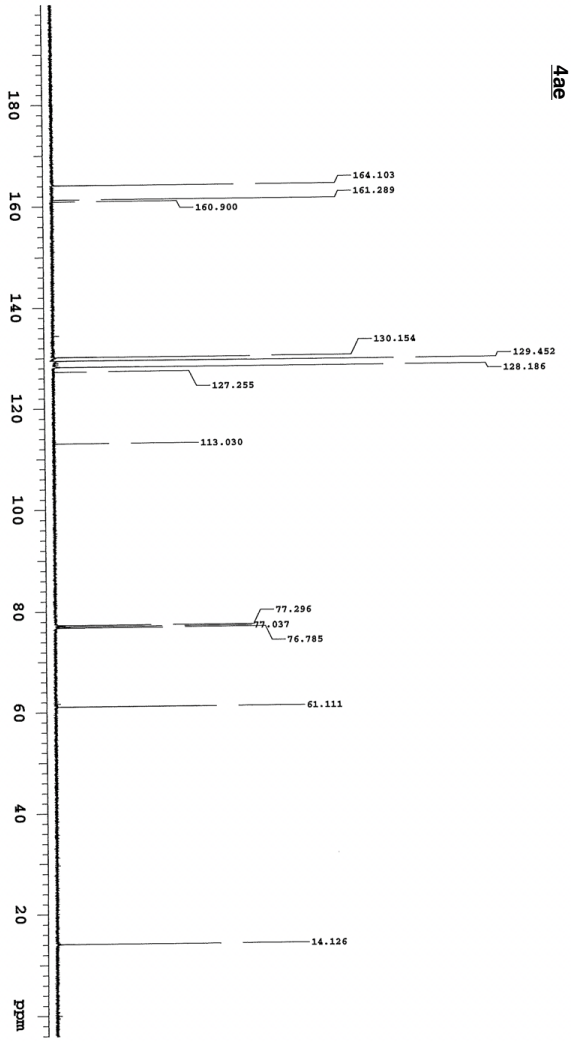
4ae



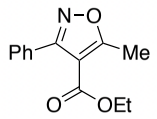
^{13}C NMR (125 MHz, $CDCl_3$)



4ae



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



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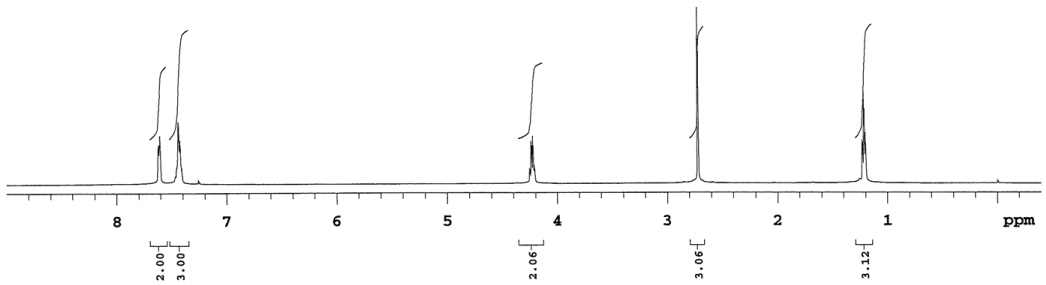
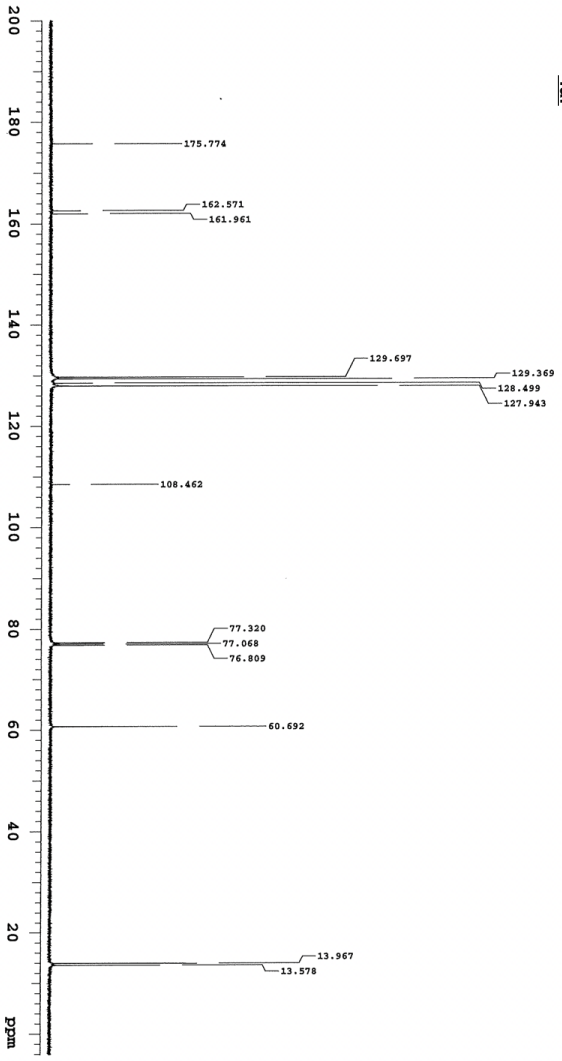
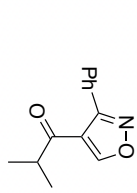


^{13}C NMR (125 MHz, $CDCl_3$)



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



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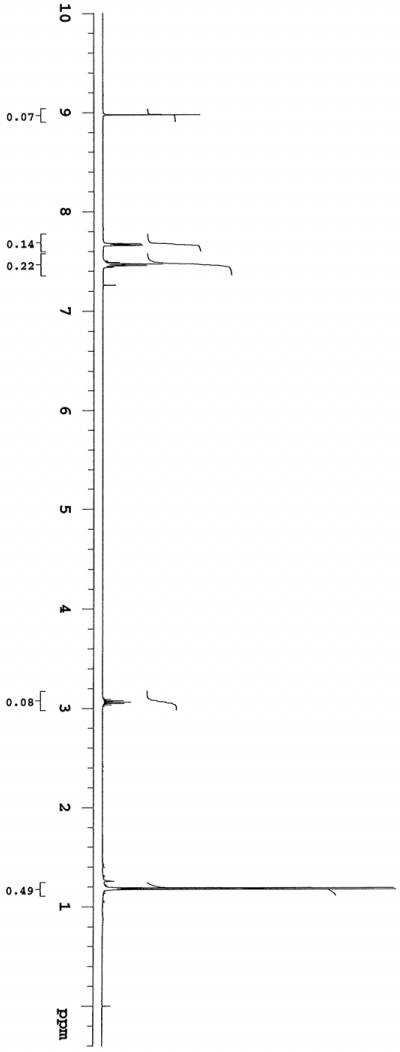
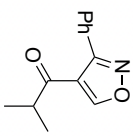


^{13}C NMR (125 MHz, $CDCl_3$)



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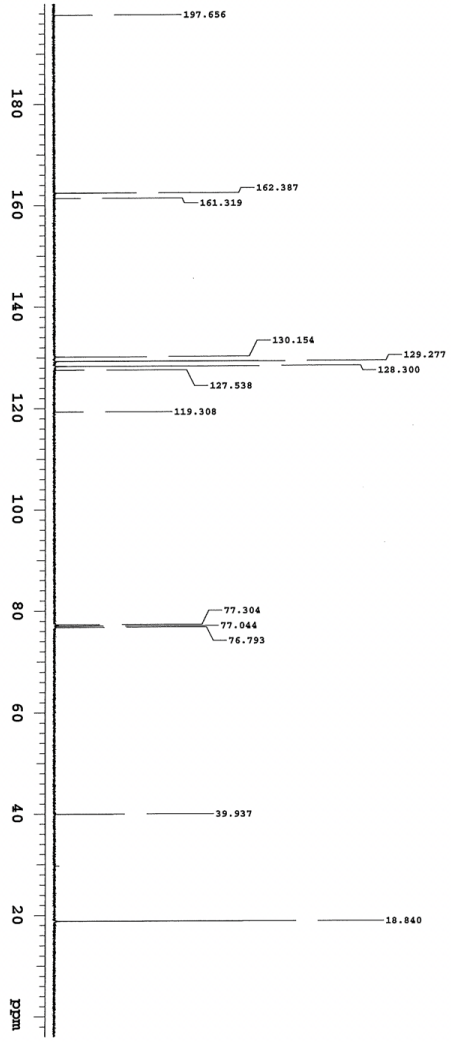
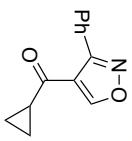


^{1}H NMR (500 MHz, $CDCl_3$)



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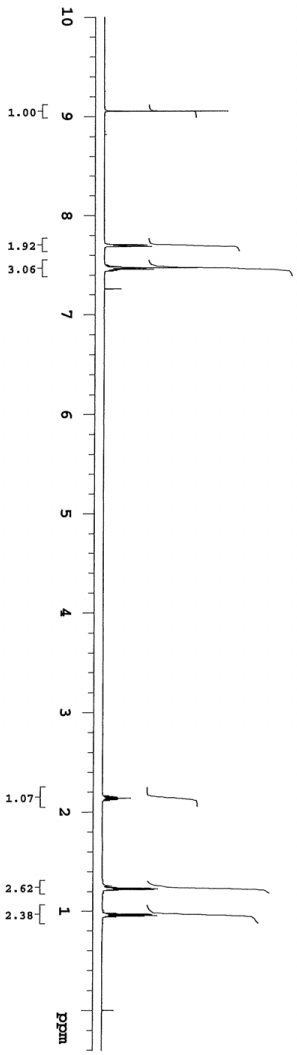
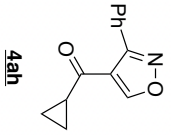


^{13}C NMR (125 MHz, $CDCl_3$)



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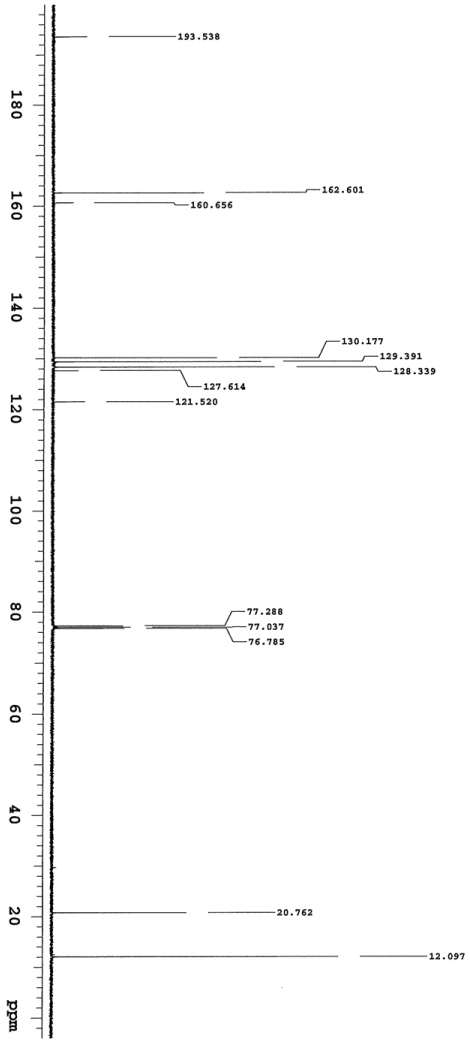
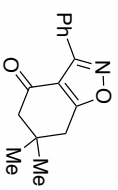


^{1}H NMR (500 MHz, $CDCl_3$)



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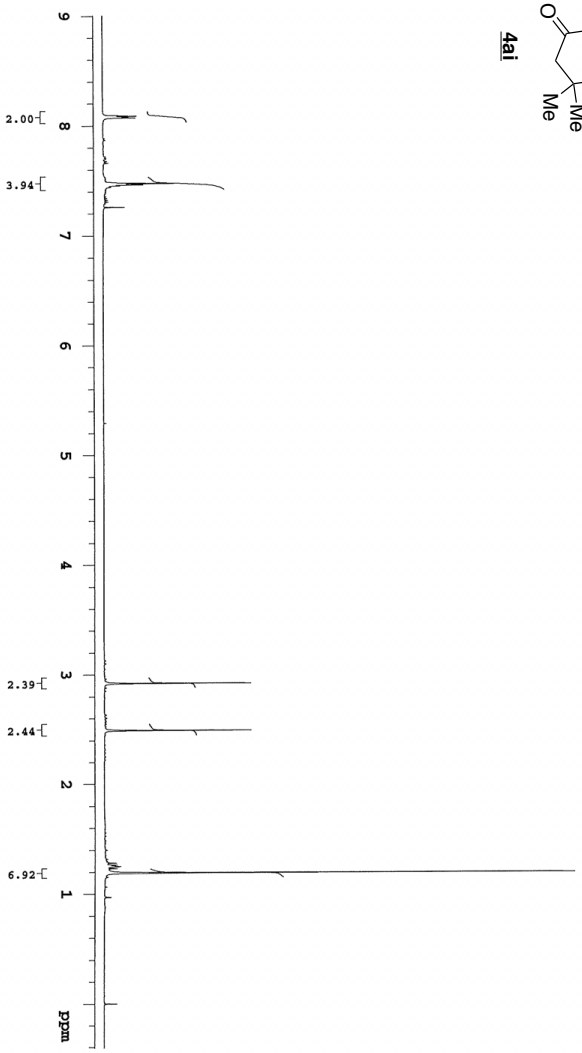
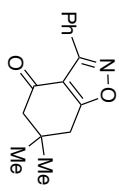


^{13}C NMR (125 MHz, $CDCl_3$)



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