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Efforts towards the discovery of novel methods for the synthesis of pharmacologically relevant molecular scaffolds

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EFFORTS TOWARDS THE DISCOVERY OF NOVEL METHODS FOR THE SYNTHESIS OF PHARMACOLOGICALLY RELEVANT MOLECULAR SCAFFOLDS

by

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Abstract

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2017-2018
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With the introductions of pharmaceuticals into modern day society many people have been using them to improve their lives. Due to this high increase in demand along with the ever-growing concern of environmental impact pharmaceutical companies have been pressed to synthesis new and existing drugs at a higher rate. This increased rate can cause low yield drugs or have a heavy environmental impact. As the use of pharmaceuticals becomes more widespread the need for greener and simpler organic synthesis methods to make these pharmaceuticals becomes more needed.

Herein is reported the methodological development of different pharmacologically relevant scaffolds. This work shows Titanium Dioxide (TiO_2, rutile) as well as Hydroxylamine-O-Sulfonic Acid (HOSA) can be employed to make a scaffold that is commonly used for the synthesis of amino acids. This work also presents two methods for the formation of heterocyclic compounds that have been found to have antibacterial properties. These works highlight the value of simple methodology to achieve relevant scaffolds for pharmaceuticals.

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Chapter 1

Sulfonylamidonitriles

1.1 Introduction to the Strecker Reaction and Titanium Dioxide

Scaffolds that contain an aminonitrile are of significant importance in organic chemistry[1, 2], and are typically prepared through a nucleophilic addition of a cyanide to an imine known as the Strecker reaction.[3-5] The Strecker reaction allows for the formation of pharmaceutically relevant molecular scaffolds such as α-amino acids (Figure 1).[6-8]

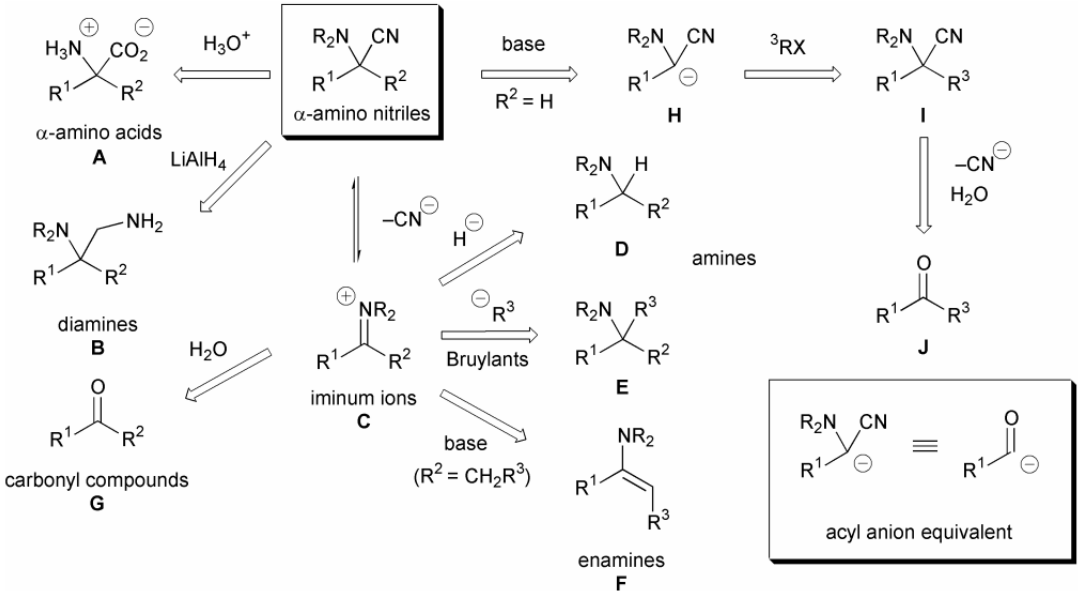


Figure 1. Various modes of α-aminonitrile activity

Traditionally the Strecker reaction is carried out with the use of bulky and expensive catalysts[9-11] (Figure 2) that are efficient but tend to be toxic and are the cause of wasteful and tedious workups.[12, 13] Ti-catalyzed Strecker reactions are commonly run in toluene using 10% mol of the Ti-catalyst. These conditions allow for the increase of enantioselectivity and stereoselectivity, at -20˚C, of the nitrile formed. The stereoselectivity was also seen to decrease upon heating usually around 0-10˚C. Different heterogenous catalysts in the presence of polymeric sulfuric acid[14], molecular sieves[15], nanosized material[16], heteropolyacids, and supported complexes have all shown to improve the efficiency of this reaction in terms of cost, recovery, and separation but the toxicity and waste management still persist.[17-20]

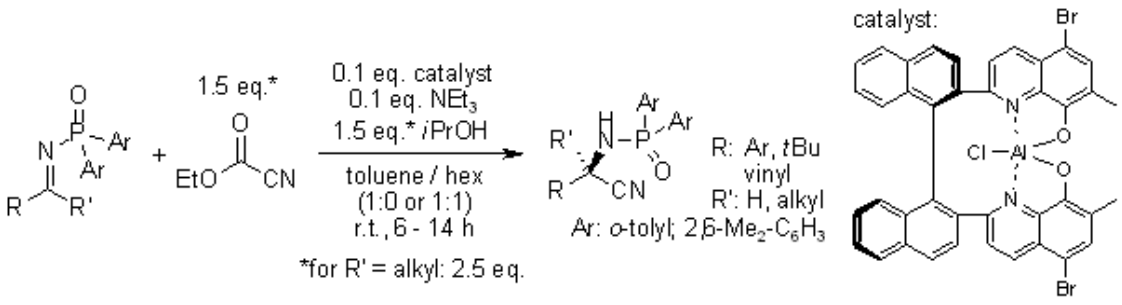


Figure 2. Nitrile Synthesis Using an Aluminum Catalyst

The synthesis of sulfonylamidonitriles relies on the nucleophilic addition of cyanide to a sulfonylimine (Figure 3) which is an important Strecker-type reaction.[21-23]

Other methods for the synthesis of these scaffolds have relied on organic sources of cyanide and transition metals in order to achieve higher levels of selectivity and efficiency.[24-26] These transition metals included an La-catalyst using HCN as the cyanide source. The La-catalyst dissolved more in EtCN than toluene while still providing the same enantioselectivity. This lead to high enantioselectivity of the nitrile with α,β-Unsaturated aldimines while aliphatic aldimines gave poor enantioselectivity. These reactions ran the catalyst in 10 mol percent while the reaction ran at -20˚C for 20 hours. The La-catalyst was also poorly activated and needed upwards of 50 mol percent of an additive to achieve the desired enantioselectivity. Due to the high cost and toxicity of these reagents attention has shifted to the development of cyanide sources that are less expensive and toxic while being easy to dispose of.[27-29]

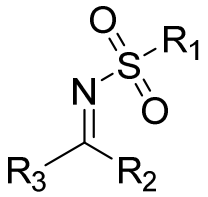


Figure 3. General Structure of a Sulfonylimine

It has been shown that titanium dioxide (TiO_2, rutile) can be used as a catalyst support[30] and allows for the modulation of catalytic activities such as dehydrogenation and hydrodesulfurization.[31-33] Rutile nanoparticles have been used as a catalyst to

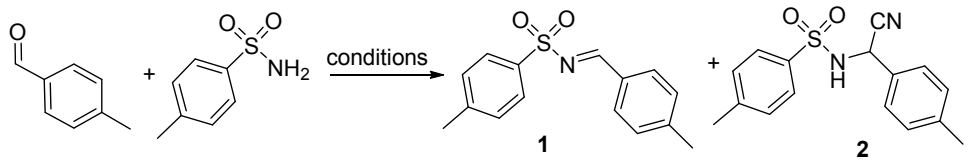
synthesize quinolinones via a domino hydrolysis/ aldol condensation/ Michael addition reaction.[34] Rutile is the mineral form of titanium dioxide, which is the most abundant natural source of titanium.[35, 36] The nontoxic nature as well as the high physical and chemical stability have led to rutile being researched in a wide variety of fields.[37]

1.2 Results and Discussion

With the knowledge that sulfonylamidonitriles formation is usually not a green reaction, we set out to find optimal conditions in which this reaction would be a one pot green reaction. Optimization began with the addition of excess sulfonamide (Table 1, Entry 1). This showed high conversion to the imine but a low conversion to the product. Phase transfer catalysts have commonly been used in Strecker reactions and through the addition of tetrabutylammonium iodide (TBAI) in the solvent tetrahydrofuran (THF) the yield of the reaction increased significantly (Table 1, Entry 5). Lewis acids have also been known to promote Strecker reactions and found that decreasing the strength of the Lewis acid promoted the reaction further showing that rutile was the best promoter (Table 1, Entry 7, 9 ,10-11). Other metal oxides were than tested and it was observed that rutile was the best promoter (Table 1, Entry 13-16). Upon changing the stoichiometric amounts of rutile, the optimal conditions were arrived upon (Table 1, Entry 19).

Table 1

Sulfonylamindonitrile Synthesis Optimization Studies



Entry	Solvent	Promoter	molar ratio[a]	CN	Conversion[b]	Yield **2**[c]
1	H_2O	-	1:2:1:2	NaCN	90%	64%
2	$CHCl_3$	-	1:2:1:2	cyanohydrin	88%	50%
3	$CHCl_3$	-	1:2:1:2	TMSCN	84%	55%
4	THF/H_2O	-	1:2:1:2	NaCN	95%	68%
5	THF	TBAI	1:2:1:2	NaCN	93%	66%
6	THF/H_2O	TBAI	1:1:1:2	NaCN	71%	59%
7	THF	$TiCl_4$	1:1:1:2	cyanohydrin	78%	40%
8	THF	$Ti(EtO)_4$	1:1:1:2	cyanohydrin	89%	62%
9	THF	$Ti(EtO)_4$/TBAI	1:1:1:2	NaCN	95%	75%
10	THF	TiO_2[c]	1:1:1:2	NaCN	90%	90%
11	THF	TiO_2/TBAI[c]	1:1:1:2	NaCN	95%	89%
12	H_2O	TiO_2[d]	1:1:1:2	NaCN	99%	97%
13	H_2O	ZrO_2	1:1:1:2	NaCN	88%	75%
14	H_2O	Fe_2O_3	1:1:1:2	NaCN	82%	55%
15	H_2O	ZnO	1:1:1:2	NaCN	80%	71%
16	H_2O	MgO	1:1:1:2	NaCN	88%	64%
17	H_2O	TiO_2[e]	1:1:1:2[f]	NaCN	95%	82%
18	H_2O	TiO_2[d]	1:1:0.5:2	NaCN	99%	92%
19	H_2O	TiO_2[d]	1:1:0.2:2	NaCN	99%	93%
20	H_2O	TiO_2[d]	1:1:0.1:2	NaCN	80%	71%
21	H_2O	TiO_2[d]	1:1:0.2:1[f]	NaCN	80%	62%

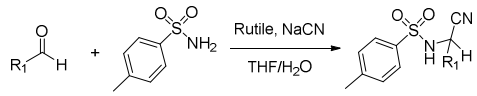
Reaction conditions: tolualdehyde (0.1 mmol), toluenesulfonamide (0.1 mmol) and rutile (0.02 mmol) were mixed in H_2O and then NaCN (0.2 mmol) was added as a 4M H_2O solution.
a) Molar ratio: Aldehyde:Sulfonamide:Rutile:NaCN. b)Reaction conversion measured by ^1H NMR.
c) Isolated yield. d) TiO_2 as Rutile. e) TiO_2 as Anatase. f) Reaction with 1 equiv. of $NaHCO_3$.

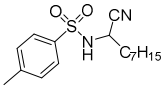
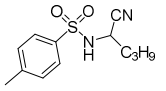
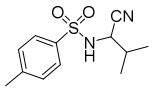
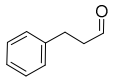
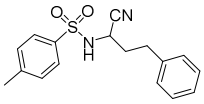
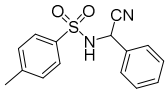
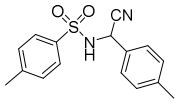
With the optimal conditions in hand we moved on to test the scope of this reaction. It was found that aliphatic aldehydes converted to the nitrile in excellent yields

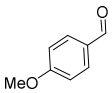
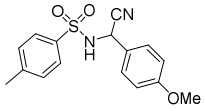
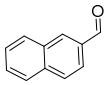
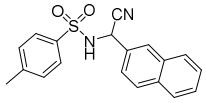
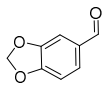
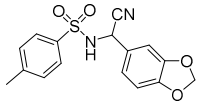
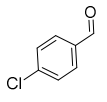
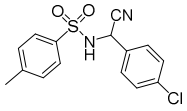
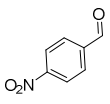
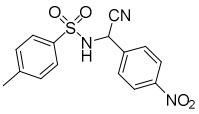
(Table 2, Entry 1-3). Aromatic aldehydes also proved to have excellent yields including cinnamaldehyde (Table 2, Entry 4-11). As expected electron donating groups proved to have excellent yields with this method (Table 2, Entry 6-7). Electron withdrawing groups also proved to have good yields (Table 2, Entry 10-11). Molecules with electron withdrawing groups were observed to perform background reactions and required purification through a silica gel column.

Table 2

Sulfonylamindonitrile Synthesis Scope



Entry	Aldehyde	Sulfonylamidonitrile	Conversion[a]	Yield[b]
1			93%	88%
2			95%	90%
3			99%	99%
4			99%	92%
5			95%	88%
6			98%	97%

Entry	Aldehyde	Sulfonylamidonitrile	Conversion[a]	Yield[b]
7			99%	91%[c]
8			90%	85%
9			95%	90%
10			95%	75%[c]
11			96%	80%[c]

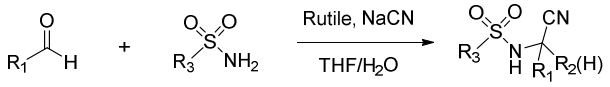
a) Reaction conversion measured by ^{1}H NMR. b) Isolated yield. c) Isolated through automated silica gel chromatography.

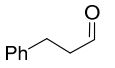
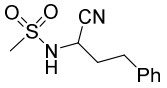
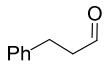
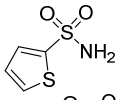
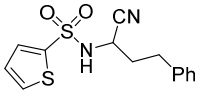
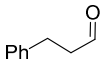
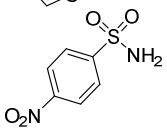
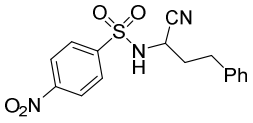
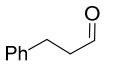
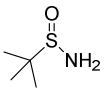
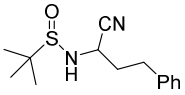
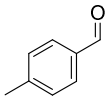
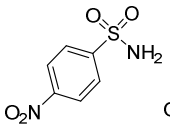
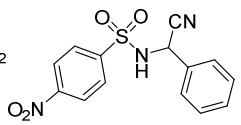
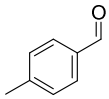
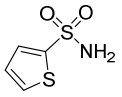
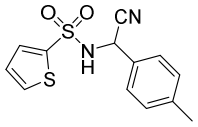
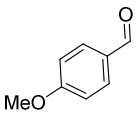
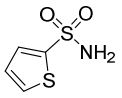
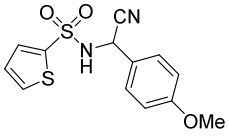
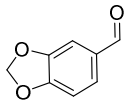
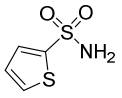
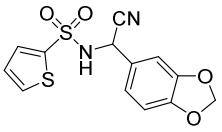
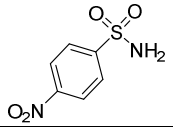
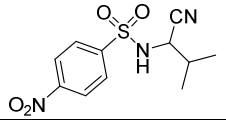
Tests to determine the scope of sulfonamides were done using cinnamaldehyde due to them having the greatest yields. Pharmacologically relevant sulfonamides were tested and found to have excellent yields (Table 3, Entry 2-3). High chirality transfer was testing using t-buytlsulfonamide and the reaction showed poor yields (Table 3, Entry 4).

Tests were done on other aldehydes with the test sulfonamides to see if the reactions would still proceed in high yields (Table 3, Entry 5-9).

Table 3

Sulfonylamidonitrile Sulfonamide Synthesis Scope



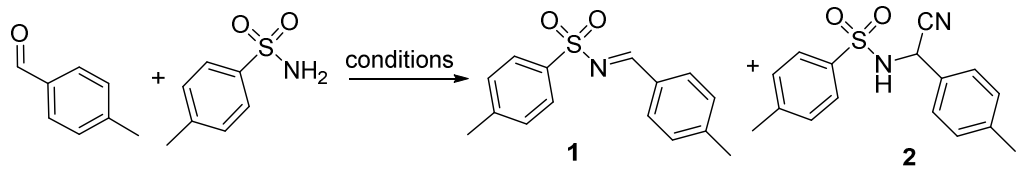
Entry	Aldehyde	Sulfonamide	Sulfonylamidonitrile	Conversion[a]	Yield[b]
1				93%	88%
2				95%	90%
3				99%	99%
4				93%	<5%
5				95%	88%
6				98%	90%
7				99%	95%
8				95%	75%[c]
9				90%	86%

a) Reaction conversion measured by ^{1}H NMR. b) Isolated yield.
c) Isolated through automated silica gel chromatography.

The recyclability of the rutile as a catalyst was tested and was found that after four cycles of reuse the time required for the reaction to complete increased (Table 4, Entry 4). After six cycles the yield of the reaction decreased slightly (Table 4, Entry 6) while, by cycle ten the reaction was no longer viable (Table 4, Entry 10).

Table 4

Sulfonylamidonitrile Rutile Recyclability Study



	Cycle 1[e]	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10
Conversion[a]	100%	100%	100%	100%	100%	100%	95%	95%	95%	95%
Yield of **2**[b]	92%	91%	92%	94%	90%	90%	86%	84%	66%	48%
Amount of TiO_2[c]	80 mg	80 mg	79 mg	73 mg	73 mg	75 mg	71%	68 mg	65 mg	64 mg
Time[d]	3 h	3 h	3 h	3 h	6 h	6 h	6 h	6 h	12 h	12 h

a. Reaction conversion was measured by ^{1}H-NMR. b. Isolated yields.
c. Reaction scale was 5 mmol (20 mol% of TiO_2, 80 mg). d. Reaction was monitored by TLC.
e. TiO_2 was allowed to settle and was then filtered. This operation was repeated with 10 mL of H_2O to remove traces of NaCN.

The reaction mechanism starts with the chelation of rutile to each oxygen molecule (Figure 4). After this the primary amine of the sulfonamide attacks the carbonyl carbon and pushes the electrons up to the oxygen. After proton transfer the lone pair on the amine pushes toward the carbon-nitrogen bond and displaces water. This forms an

imine that can now be attacked by the cyanide which, after proton transfer and an aqueous workup forms the final sulfonylamidonitrile product.

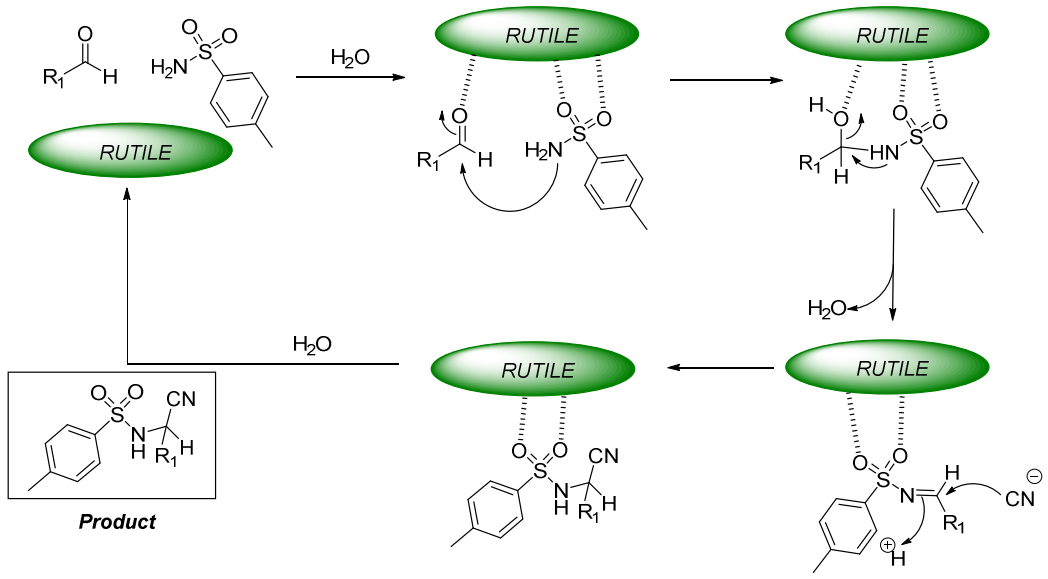


Figure 4. Proposed Mechanism of the Sulfonylamidonitrile Reaction

1.3 Conclusion

This method shows the development of an efficient and novel synthesis of sulfonylamidonitriles in the presence of rutile as a catalyst. The data provided shows that aliphatic and aromatic aldehydes undergo this reaction in excellent yields with complete conversion. Moreover, the presented data shows that a variety of substituted sulfonamides are ideal for this reaction. Rutile has also been shown through these experiments to be

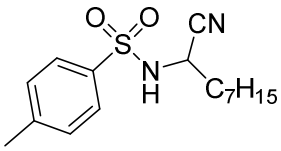
easily recovered and reused for 8 cycles with no significant loss of productivity. The proposed mechanism also postulates that rutile provides a Lewis acidic environment that allows for multiple interaction sites on the rutile, enhancing the rate of cyanide addition across the imine intermediate.

1.4 Experimental

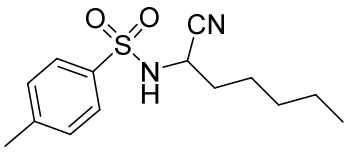
Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4-mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$). Silica flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Automated chromatography was performed on an ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0- 30% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 9 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.23 ppm; ^{13}C, 77.0 ppm; coupling constants are expressed in Hz.

1.4.1. General method for the synthesis of Sulfonylamidonitriles. In a 4-mL reaction vial, aldehyde (0.1 mmol, 1.0 equiv), sulfonaamide (0.1 mmol, 1.0 equiv.), ruitle (0.02 mmol, 0.2 equiv) were dissolved in a 4 mL solution of de-ionized H_2O with (0.2 mmol, 2 equiv) NaCN. The solution was stirred at RT for 3 h or until complete conversion, determined by TLC. The reaction was concentrated by rotary evaporation to afford the crude product. The product was directly characterized unless traces of impurities required purification by automated silica gel flash chromatography (few examples).

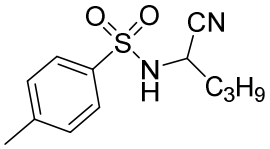
1.4.2. Synthesis of Sulfonylamidonitriles from Table 2.



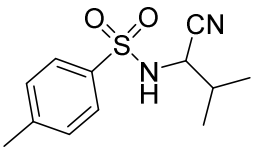
***N*-(1-cyanooctyl)-4-methylbenzenesulfonamide (2a):** Sulfonylamidonitrile **2a** was obtained (27 mg, 88%) as a pale-yellow oil. **TLC**: R_f 0.64 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.76 (d, J = 7.5 Hz, 2H), 7.28 (d, J = 7.5 Hz, 2H), 4.22 (t, J = 7.1 Hz, 1H), 2.48 (s, 3H), 1.75 (ddd, J = 7.3, 6.9, 6.4 Hz, 2H), 1.48-1.44 (m, 2H), 1.27-1.23 (m, 8H), 0.82 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.6, 136.0, 130.1, 127.2, 117.5, 44.4, 34.0, 31.6, 28.8, 28.5, 25.0, 22.6, 21.6, 14.0 ppm. **ESI-MS** *m/z* (rel int): (pos) 309.1 ($[M+H]^+$, 100); (neg) 307.1 ($[M-H]^-$, 100).



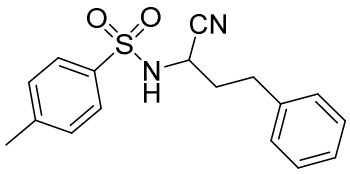
***N*-(1-cyanohexyl)-4-methylbenzenesulfonamide (2b):** Sulfonylamidonitrile **2b** was obtained (25 mg, 91%) as a colorless oil. **TLC**: R_f 0.64 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.78 (d, J = 7.3 Hz, 2H), 7.26 (d, J = 7.3 Hz, 2H), 6.02 (bs, 1H), 4.17 (t, J = 6.8 Hz, 1H), 2.48 (s, 3H), 1.78 (ddd, J = 7.5, 7.0, 6.4 Hz, 2H), 1.42-1.25 (m, 4H), 0.75 (t, J = 6.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.3, 135.8, 129.8, 127.0, 117.5, 44.1, 33.1, 26.8, 21.5, 21.4, 13.4 ppm. **ESI-MS** *m/z* (rel int): (pos) 267.1 ($[M+H]^+$, 100); (neg) 265.1 ($[M-H]^-$, 100).



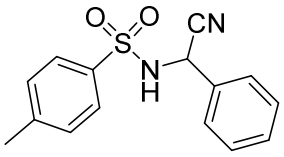
***N*-(1-cyanobutyl)-4□methylbenzenesulfonamide (2c):** Sulfonylamidonitrile **2c** was obtained (22 mg, 90%) as a colorless oil. **TLC**: R_f 0.64 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.81 (d, J = 7.2 Hz, 2H), 7.28 (d, J = 7.2 Hz, 2H), 5.78 (bs, 1H), 4.20 (bs, 1H), 2.48 (s, 3H), 1.78 (dt, J = 7.3, 6.9 Hz, 2H), 1.52-1.49 (m, 2H), 0.98 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.6, 135.9, 130.0, 127.2, 117.5, 44.1, 35.9, 21.6, 18.4, 13.0 ppm. **ESI□MS** *m/z* (rel int): (pos) 253.2 ($[M+H]^+$, 100); (neg) 251.2 ($[M-H]^-$, 100).



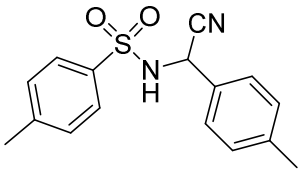
***N*-(1-cyano-2□methylpropyl)-4-methylbenzenesulfonamide (2d):** Sulfonylamidonitrile **2d** was obtained (25 mg, 99%) as a pale□yellow oil. **TLC**: R_f 0.64 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.75 (d, J = 7.1 Hz, 2H), 7.29 (d, J = 7.1 Hz, 2H), 5.58 (d, J = 5.7 Hz, 1H), 4.02 (d, J = 6.2 Hz, 1H), 2.48 (s, 3H), 1.78 (sd, J = 7.3, 6.8 Hz, 1H), 1.03 (d, J = 7.3 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.3, 135.9, 129.9, 127.0, 116.6, 50.5, 32.2, 21.5, 18.3, 17.6 ppm. **ESI-MS** *m/z* (rel int): (pos) 253.2 ($[M+H]^+$, 100); (neg) 251.2 ($[M□H]^-$, 100).



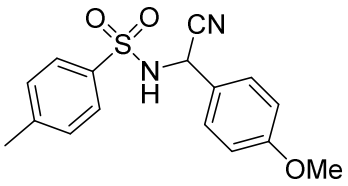
***N*□(1□cyano□3□phenylpropyl)□4-methylbenzenesulfonamide (2e):** Sulfonylamidonitrile **2e** was obtained (29 mg, 92%) as a pale□yellow oil. **TLC**: R_f 0.68 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.76 (d, J = 7.3 Hz, 2H), 7.28-7.24 (m, 5H), 7.09 (d, J = 7.3 Hz, 2H), 6.11 (bs, 1H), 4.22 (t, J = 7.1 Hz, 1H), 2.77 (t, J = 6.6 Hz, 2H), 2.48 (s, 3H), 2.06 (tt, J = 7.1, 6.6 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.3, 138.7, 135.6, 129.8, 128.5, 128.1, 127.0, 126.4, 117.3, 43.4, 34.9, 30.8, 21.3 ppm. **ESI-MS** *m/z* (rel int): (pos) 315.1 ($[M+H]^+$, 100); (neg) 313.1 ($[M□H]^-$, 100).



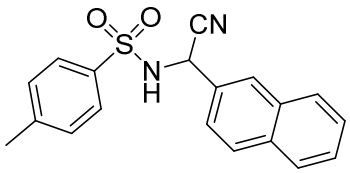
***N*-(cyano(phenyl)methyl)-4□methylbenzenesulfonamide (2f):** Sulfonylamidonitrile **2f** was obtained (25 mg, 89%) as a colorless oil. **TLC**: R_f 0.60 (2:1 heptanes/EtOAc). **^{1}H□NMR** (400 MHz, $CDCl_3$): d 7.72 (d, J = 7.1 Hz, 2H), 7.25-7.22 (m, 5H), 7.01 (d, J = 7.1 Hz, 2H), 6.28 (bs, 1H), 4.28 (s, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.7, 139.1, 135.2, 129.6, 128.3, 128.0, 127.5, 126.3, 116.0, 43.4, 21.3 ppm. **ESI□MS** *m/z* (rel int): (pos) 287.2 ($[M+H]^+$, 100); (neg) 285.2 ($[M-H]^-$, 100).



***N*-(cyano(*p*-tolyl)methyl)-4-methylbenzenesulfonamide (2):** Sulfonylamidonitrile was obtained (29 mg, 97%) as a pale-yellow oil. **TLC**: R_f 0.62 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.76 (d, J = 7.1 Hz, 2H), 7.29 (d, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.19 (d, J = 7.1 Hz, 2H), 5.43 (s, 1H), 2.48 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.5, 139.9, 136.0, 130.0, 129.6, 129.1, 127.3, 127.0, 116.5, 47.9, 21.6, 21.1 ppm. **ESI-MS** *m/z* (rel int): (pos) 301.1 ($[M+H]^+$, 100); (neg) 299.1 ($[M□H]^-$, 100).

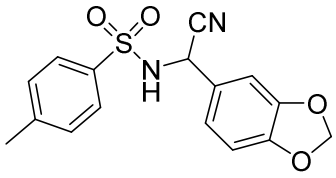


***N*-(cyano(4□methoxyphenyl)methyl)-4-methylbenzenesulfonamide (2g):** Purification by automated silica gel flash chromatography (10 g cartridge, 12 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded sulfonylamidonitrile **2g** (29 mg, 91%) as a white solid. **TLC**: R_f 0.42 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.76 (d, J = 7.1 Hz, 2H), 7.34□7.32 (m, 4H), 7.28 (d, J = 7.1 Hz, 2H), 5.32 (s, 1H), 3.76 (s, 3H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 160.4, 144.5, 135.9, 129.9, 128.5, 127.2, 124.0, 116.5, 114.5, 55.3, 47.6, 21.6 ppm. **ESI-MS** *m/z* (rel int): (pos) 317.2 ($[M+H]^+$, 100); (neg) 315.2 ($[M-H]^-$, 100).



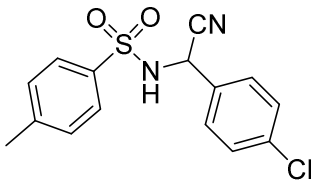
***N*□(cyano(naphthalen-2-yl)methyl)-4-methylbenzenesulfonamide (2h):**

Sulfonylamidonitrile **2h** was obtained (28 mg, 85%) as a colorless oil. **TLC**: R_f 0.55 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.99 (d, J = 7.1 Hz, 1H), 7.81 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 7.1 Hz, 1H), 7.54 (t, J = 7.1 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 7.2 Hz, 2H), 6.02 (bs, 1H), 5.49 (bs, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 144.6, 135.6, 133.9, 131.1, 129.9, 129.0, 127.8, 127.3, 126.9, 126.6, 126.5, 124.9, 122.3, 116.4, 46.3, 21.6 ppm. **ESI-MS** *m/z* (rel int): (pos) 337.2 ($[M+H]^+$, 100); (neg) 335.2 ($[M□H]^-$, 100).

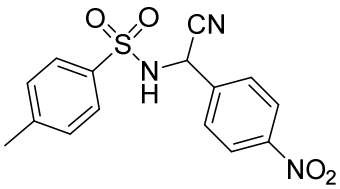


***N*-(benzo[*d*][1,3]dioxol-5-yl(cyano)methyl)-4-methylbenzenesulfonamide (2i):**

Sulfonylamidonitrile **2i** was obtained (30 mg, 90%) as a pale-yellow oil. **TLC**: R_f 0.35 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.74 (d, J = 7.1 Hz, 2H), 7.43 (d, J = 7.1 Hz, 2H), 7.21 (s, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.73 (d, J = 7.3 Hz, 1H), 5.82 (s, 2H), 5.34 (s, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 149.2, 146.3, 142.5, 141.0, 128.7, 128.3, 126.5, 121.4, 118.6, 110.8, 107.8, 101.6, 54.7, 22.6 ppm. **ESI-MS** *m/z* (rel int): (pos) 331.1 ($[M+H]^+$, 100); (neg) 329.1 ($[M-H]^-$, 100).

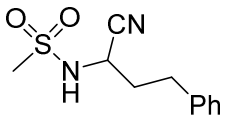


***N*-((4-chlorophenyl)(cyano)methyl)-4-methylbenzenesulfonamide (2j):** Purification by automated silica gel flash chromatography (10 g cartridge, 12 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded sulfonylamidonitrile **2j** (24 mg, 75%) as a colorless oil. **TLC**: R_f 0.69 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.76 (d, J = 7.3 Hz, 2H), 7.36-7.33 (m, 6H), 5.75 (bs, 1H), 5.45 (s, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 140.8, 135.9, 135.7, 130.6, 130.0, 129.5, 128.4, 127.2, 116.0, 47.5, 21.6 ppm. **ESI-MS** *m/z* (rel int) (pos) 321.1 ($[M+H]^+$, 100); (neg) 319.1 ($[M-H]^-$, 100).

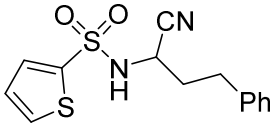


***N*-(cyano(4-nitrophenyl)methyl)-4-methylbenzenesulfonamide (2k):** Purification by automated silica gel flash chromatography (10 g cartridge, 12 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded sulfonylamidonitrile **2k** (26 mg, 80%) as a white solid. **TLC**: R_f 0.58 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 8.24 (d, J = 7.0 Hz, 2H), 7.78 (d, J = 7.0 Hz, 2H), 7.19 (d, J = 7.0 Hz, 2H), 7.49 (d, J = 7.0 Hz, 2H), 5.34 (s, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 148.5, 142.1, 141.2, 138.4, 129.6, 128.1, 118.0, 54.1, 22.6 ppm. **ESI-MS** *m/z* (rel int): (pos) 332.2 ($[M+H]^+$, 100); (neg) 330.2 ($[M-H]^-$, 100).

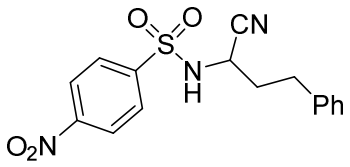
1.4.3. Synthesis of Sulfonylamidonitriles from Table 3.



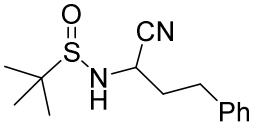
***N*-(1□cyano-3-phenylpropyl)methanesulfonamide (2l):** Purification by automated silica gel flash chromatography (10 g cartridge, 12 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded indole **2l** (22 mg, 92%) as a colorless oil. **TLC**: R_f 0.51 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.28-7.20 (m, 5H), 5.61 (bs, 1H), 4.26 (t, *J* = 7.1 Hz, 1H), 3.05 (s, 3H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.17 (tt, *J* = 7.1, 6.6 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 138.6, 128.8, 128.4, 126.8, 118.2, 43.8, 41.3, 35.0, 31.1 ppm. **ESI-MS** *m/z* (rel int): (pos) 239.1 ($[M+H]^+$, 100); (neg) 237.1 ($[M-H]^-$, 100).



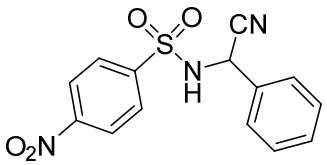
***N*-(1-cyano□3-phenylpropyl)thiophene□2-sulfonamide (2m)** Sulfonylamidonitrile **2m** was obtained (27 mg, 90%) as a pale-yellow oil. **TLC**: R_f 0.40 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.65 (d, *J* = 7.3 Hz, 2H), 7.28□7.16 (m, 6H), 4.26 (t, *J* = 6.5 Hz, 1H), 2.75 (t, *J* = 6.2 Hz, 2H), 2.15 (tt, *J* = 6.6, 6.2 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 138.6, 133.6, 133.4, 128.9, 128.4, 127.8, 126.8, 117.0, 44.0, 35.4, 31.1 ppm. **ESI□MS** *m/z* (rel int): (pos) 307.2 ($[M+H]^+$, 100); (neg) 305.2 ($[M□H]^-$, 100).



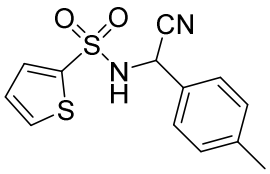
***N*-(1-cyano□3-phenylpropyl)-4-nitrobenzenesulfonamide (2n):** Sulfonylamidonitrile **2n** was obtained (33 mg, 97%) as a white solid. **TLC**: R_f 0.57 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 8.35 (d, J = 7.1 Hz, 2H), 8.04 (d, J = 7.1 Hz, 2H), 7.28-7.16 (m, 5H), 4.22 (t, J = 6.4 Hz, 1H), 2.79 (t, J = 6.6 Hz, 2H), 2.20 (tt, J = 6.9, 6.4 Hz, 2H), 1.27 (bs, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 150.4, 144.5, 138.3, 128.9, 128.8, 128.5, 128.4, 128.3, 127.0, 124.6, 116.9, 43.8, 35.1, 31.0 ppm. **ESI□MS** *m/z* (rel int): (pos) 346.2 ($[M+H]^+$, 100); (neg) 344.2 ($[M-H]^-$, 100).



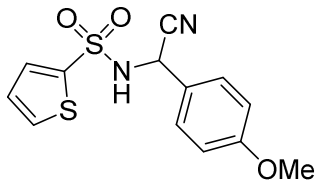
***N*-(1-cyano□3-phenylpropyl)trifluoromethanesulfonamide (2o):** Sulfonylamidonitrile **2o** was obtained (26 mg, 91%) as a pale-yellow oil. **TLC**: R_f 0.58 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.32-7.27 (m, 5H), 4.42 (t, J = 6.8 Hz, 1H), 2.77 (t, J = 6.6 Hz, 2H), 2.24 (tt, J = 6.9, 6.5 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 138.0, 128.9, 128.4, 127.1, 126.6, 120.8 (q, J = 250 Hz, CF_3), 116.6, 45.0, 35.6, 31.0 ppm. **ESI-MS** *m/z* (rel int): (pos) 293.1 ($[M+H]^+$, 100); (neg) 291.1 ($[M□H]^-$, 100).



***N*-(cyano(4-methoxyphenyl)methyl)-4-nitrobenzenesulfonamide (2q):** Purification by automated silica gel flash chromatography (10 g cartridge, 12 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded sulfonylamidonitrile **2q** (30 mg, 86%) as a white solid. **TLC**: R_f 0.40 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 8.42 (d, J = 7.3 Hz, 2H), 8.08 (d, J = 7.3 Hz, 2H), 7.28 (d, J = 7.1 Hz, 2H), 6.88 (d, J = 7.1 Hz, 2H), 5.52 (s, 1H), 3.78 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 160.9, 150.2, 144.9, 128.7, 128.6, 128.3, 124.6, 123.1, 116.0, 114.5, 55.4, 47.9 ppm. **ESI-MS** *m/z* (rel int): (pos) 348.2 ($[M+H]^+$, 100); (neg) 346.2 ($[M-H]^-$, 100).

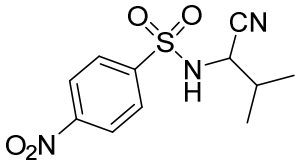


***N*-(cyano(*p*-tolyl)methyl)thiophene-2-sulfonamide (2r):** Sulfonylamidonitrile **2r** was obtained (26 mg, 90%) as a pale-yellow oil. **TLC**: R_f 0.45 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 7.70 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 7.1 Hz, 2H), 7.16 (d, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.41 (s, 1H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 140.1, 139.8, 133.6, 133.4, 130.0, 128.7, 127.8, 127.0, 116.2, 48.1, 21.1 ppm. **ESI-MS** *m/z* (rel int): (pos) 293.1 ($[M+H]^+$, 100); (neg) 291.1 ($[M-H]^-$, 100).



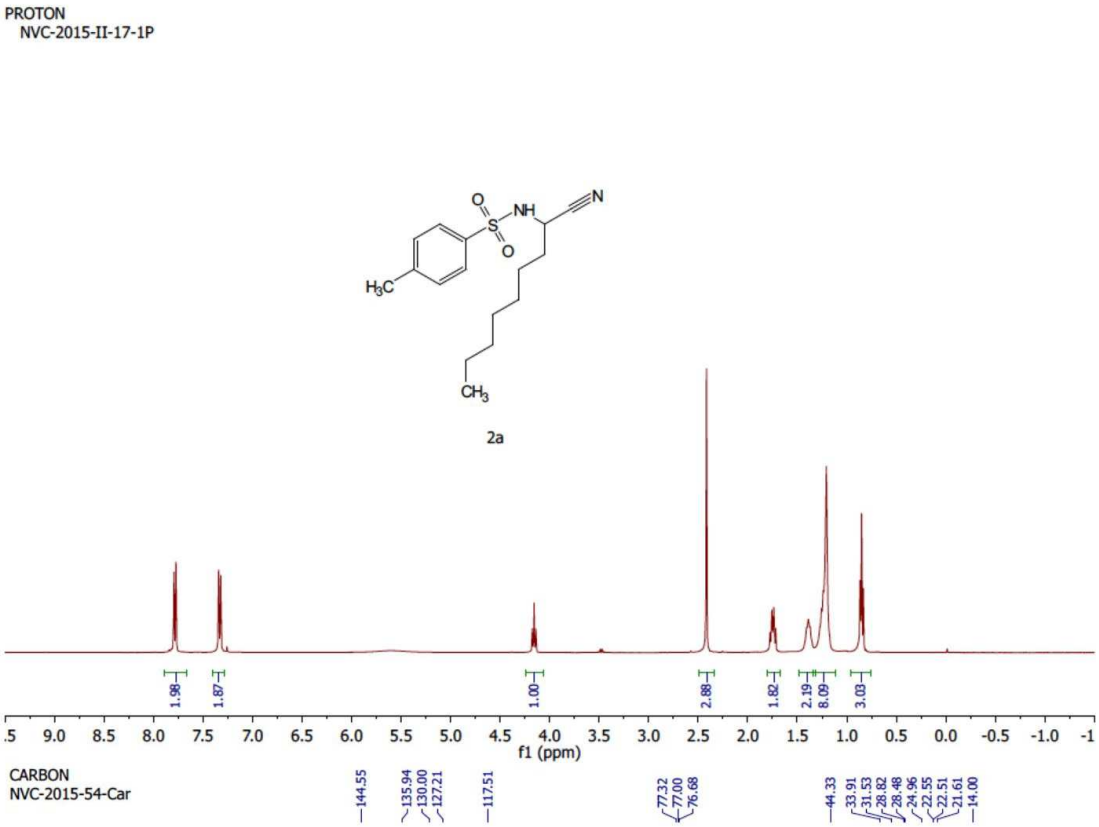
***N*-(1-cyanobutyl)-4-nitrobenzenesulfonamide (2s):** Sulfonylamidonitrile **2s** was obtained (26 mg, 93%) as a pale□yellow oil. **TLC**: R_f 0.62 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 8.42 (d, J = 7.1 Hz, 2H), 8.08 (d, J = 7.1 Hz, 2H), 4.26 (t, J = 6.2 Hz, 1H), 1.76 (dt, J = 7.3, 6.9 Hz, 2H), 1.54-1.50 (m, 2H), 0.99 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 150.4, 144.8,

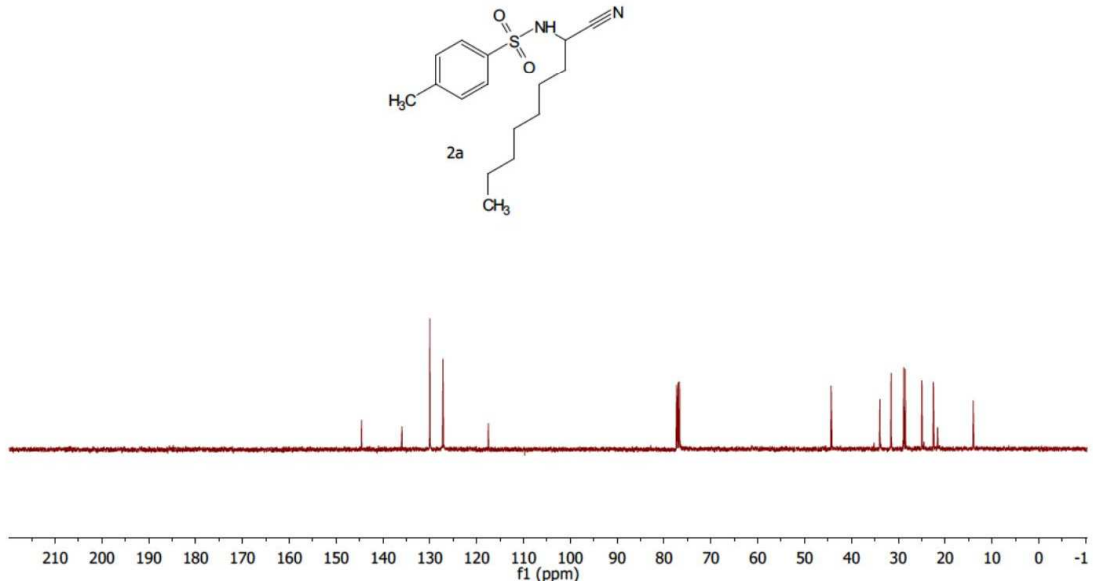
130.6, 128.6, 124.6, 117.2, 44.3, 35.6, 18.4, 13.0 ppm. **ESI-MS** *m/z* (rel int): (pos) 284.1 ($[M+H]^+$, 100); (neg) 282.1 ($[M-H]^-$, 100).



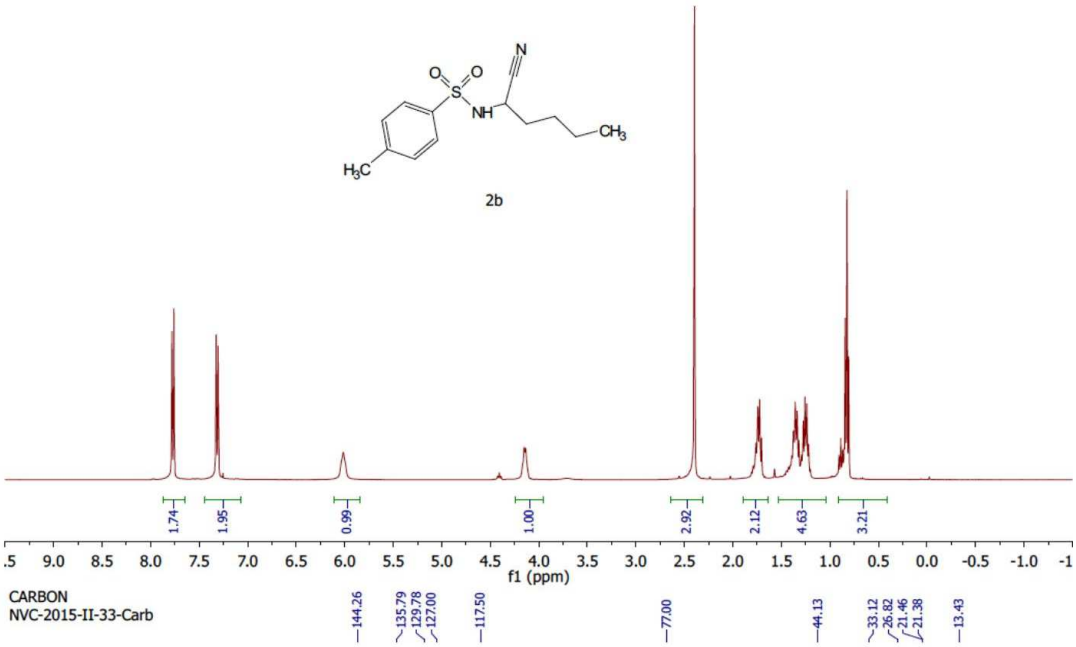
***N*-(1-cyanooctyl)-4-nitrobenzenesulfonamide (2t):** Sulfonylamidonitrile **2t** was obtained (31 mg, 90%) as a pale□yellow oil. **TLC**: R_f 0.66 (2:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$): d 8.48 (d, J = 7.3 Hz, 2H), 8.12 (d, J = 7.1 Hz, 2H), 4.26 (t, J = 6.4 Hz, 1H), 1.80 (dt, J = 7.3, 6.9 Hz, 2H), 1.52-1.48 (m, 2H), 1.32□1.25 (m, 8H), 0.84 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): d 150.4, 144.8, 128.5, 124.6, 117.2, 44.5, 33.7, 31.5, 28.8, 28.8, 25.0, 22.5, 14.0 ppm. **ESI-MS** *m/z* (rel int): (pos) 340.1 ($[M+H]^+$, 100); (neg) 338.1 ($[M-H]^-$, 100).

1.4.4. ^{1}H NMR and ^{13}C NMR of Sulfonylamidonitriles.

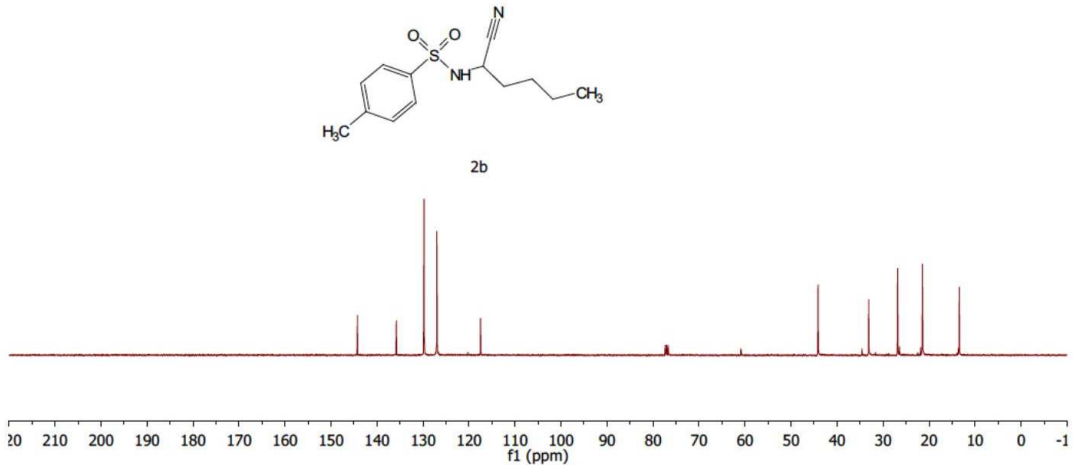




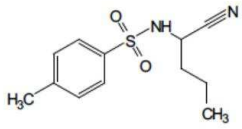
PROTON
NVC-2015-II-33-1P



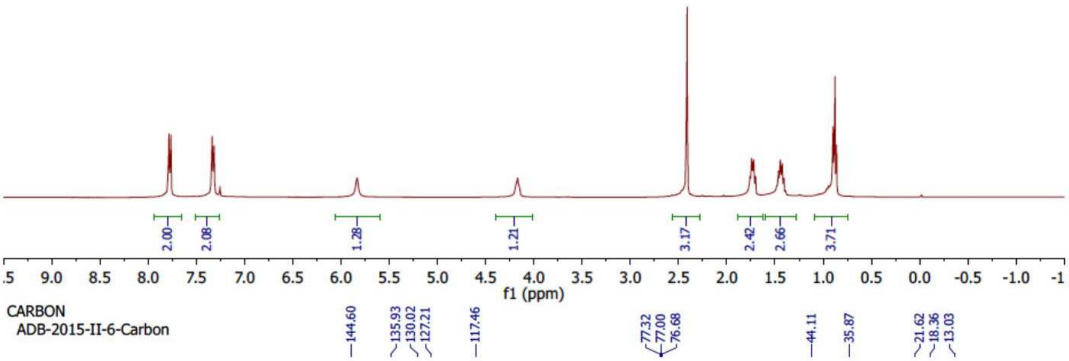
CARBON
NVC-2015-II-33-Carb



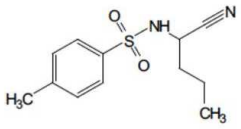
PROTON
ADB-2015-II-6-P



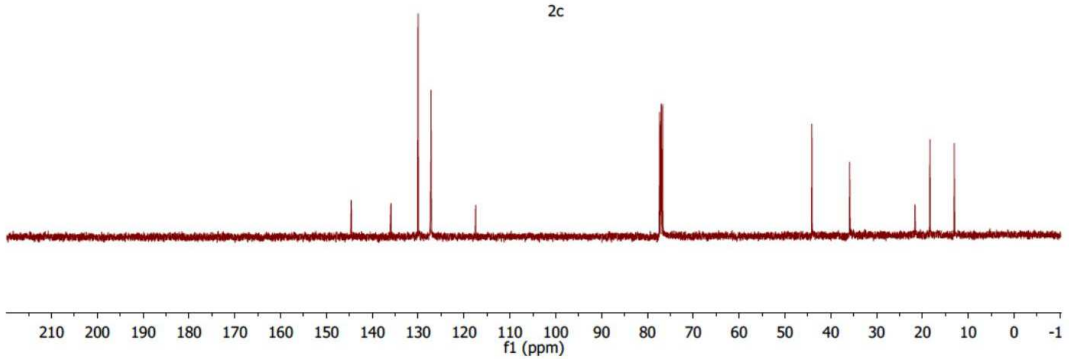
2c



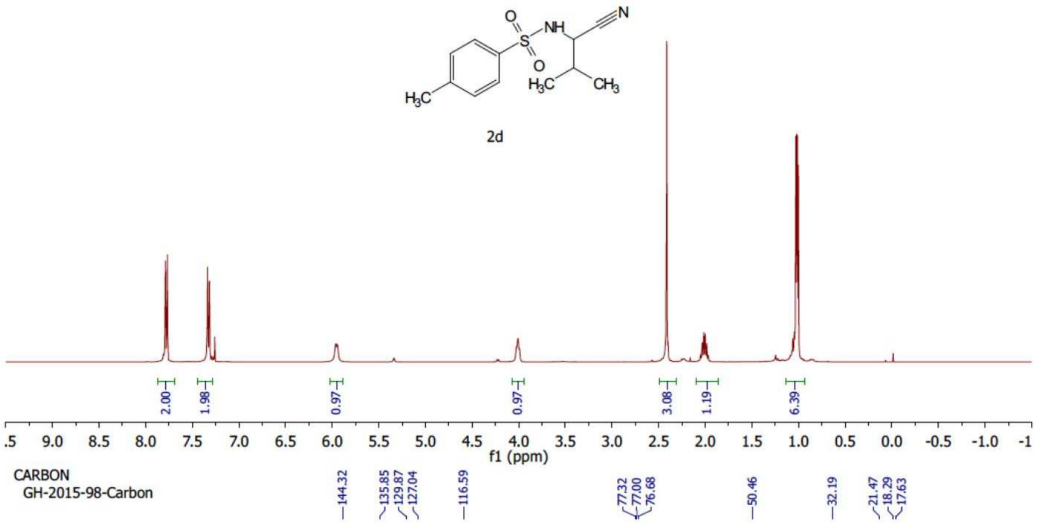
CARBON
ADB-2015-II-6-Carbon



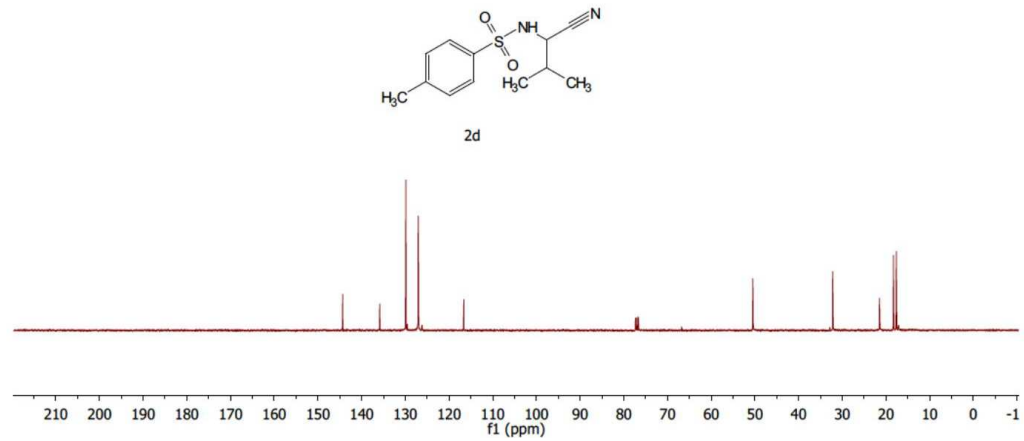
2c



PROTON
GH-2015-98-1P

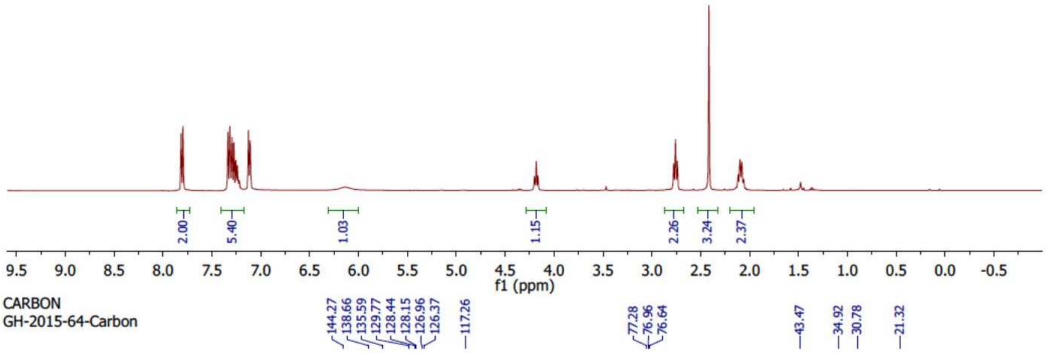


CARBON
GH-2015-98-Carbon



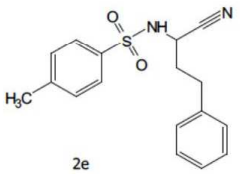
PROTON
GH-2015-64-P2

2e

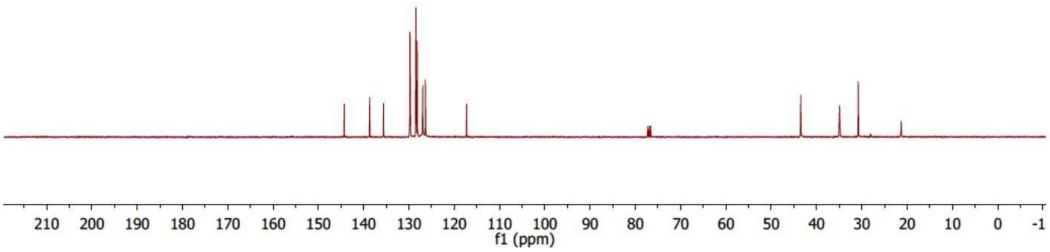


CARBON
GH-2015-64-Carbon

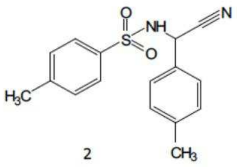
144.27
138.66
135.59
129.77
128.44
128.15
126.96
126.37
117.26
77.28
76.96
76.64
43.47
34.92
30.78
21.32

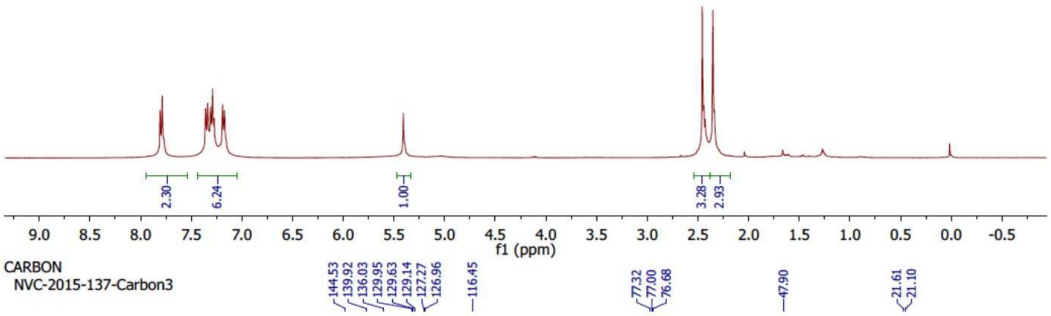


2e



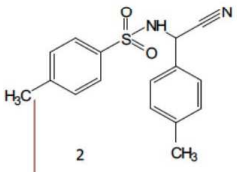
PROTON
ADB-2015-137-2P

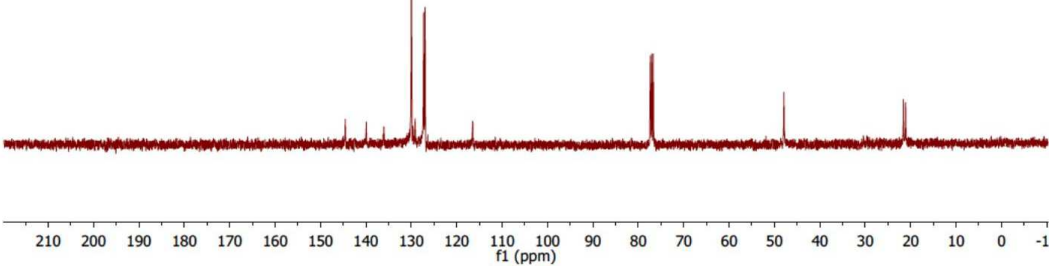




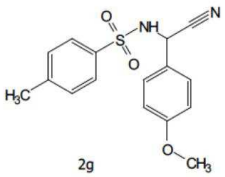
CARBON
NVC-2015-137-Carbon3

144.53
139.92
136.03
129.95
129.63
129.14
127.27
126.96
116.45
77.32
77.00
76.68
47.90
21.61
21.10

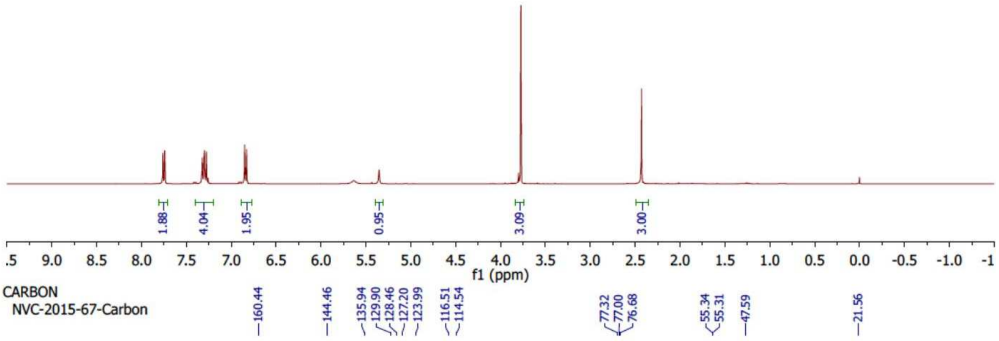




PROTON
NVC-2015-67-2P



2g



CARBON
NVC-2015-67-Carbon

160.44
144.46
135.94
129.90
128.46
127.20
123.99
116.51
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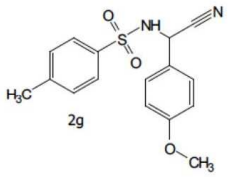
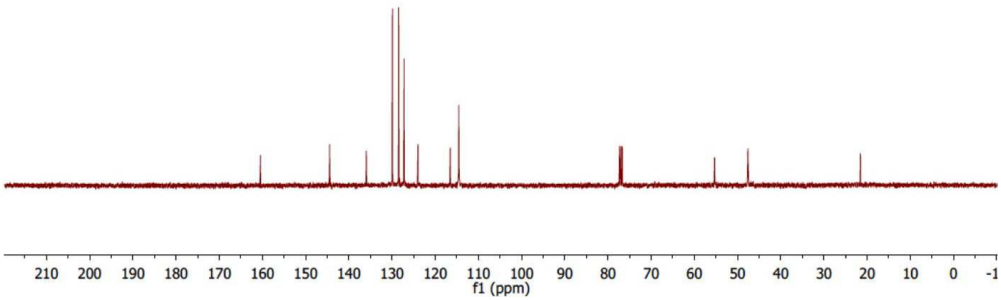
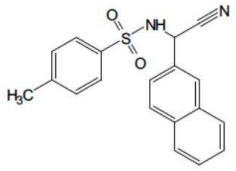
77.32
77.00
76.68
55.34
55.31
47.59
21.56



2g



PROTON
ADB-2015-II-1-Pure



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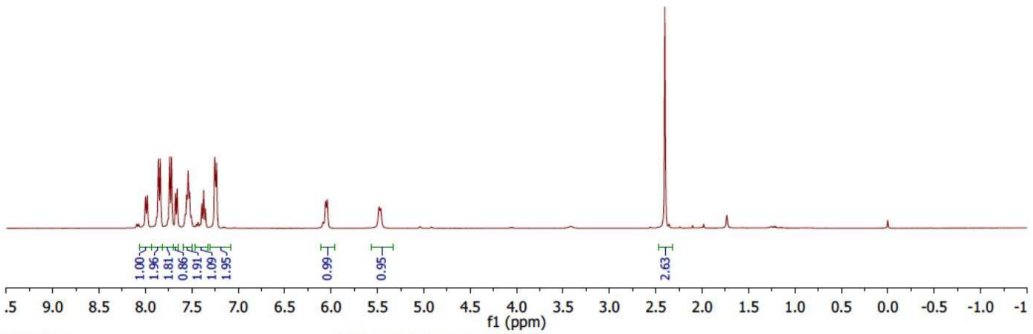

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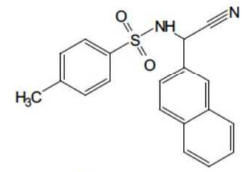

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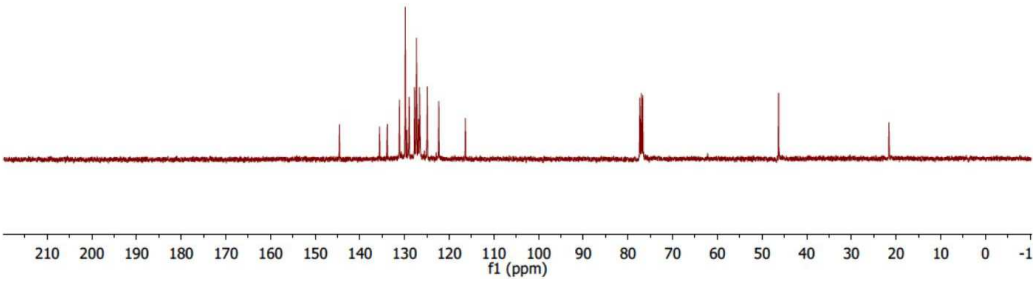

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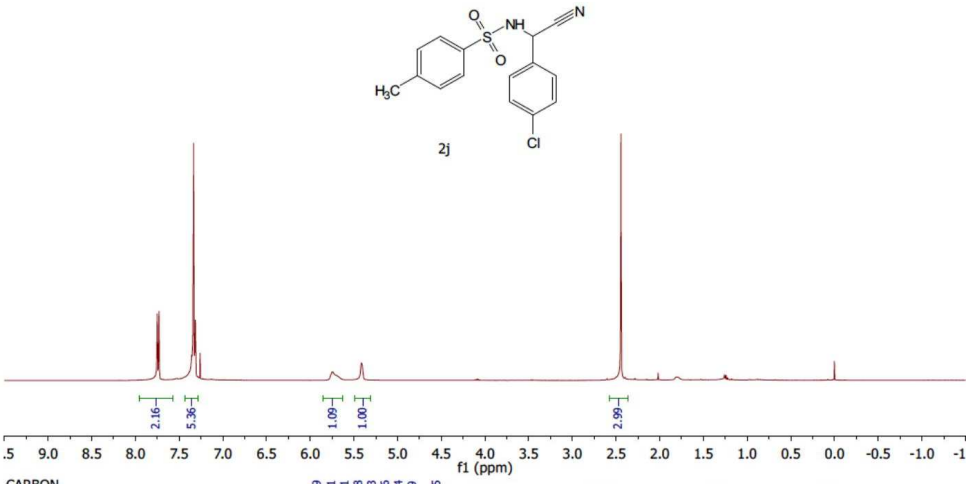

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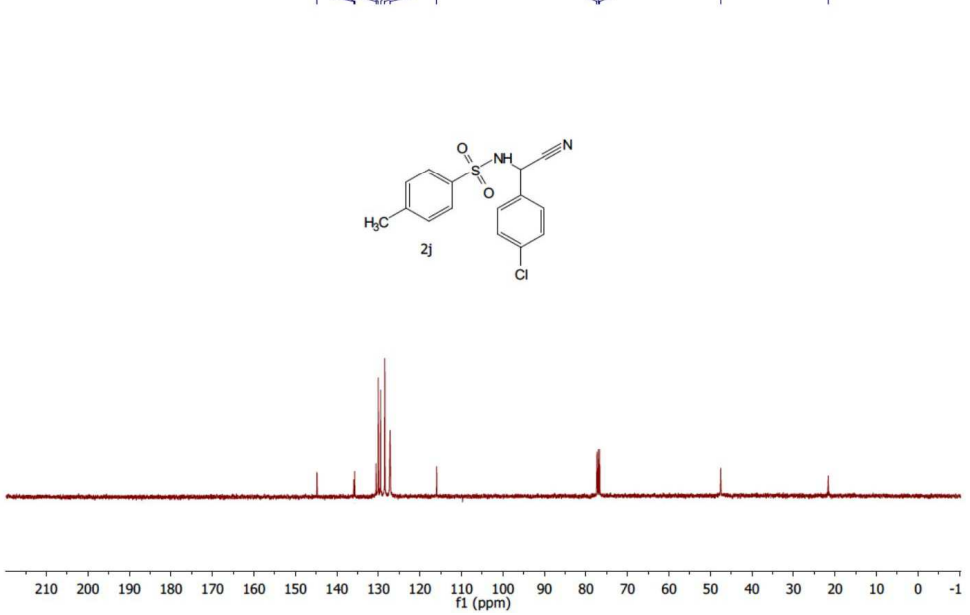

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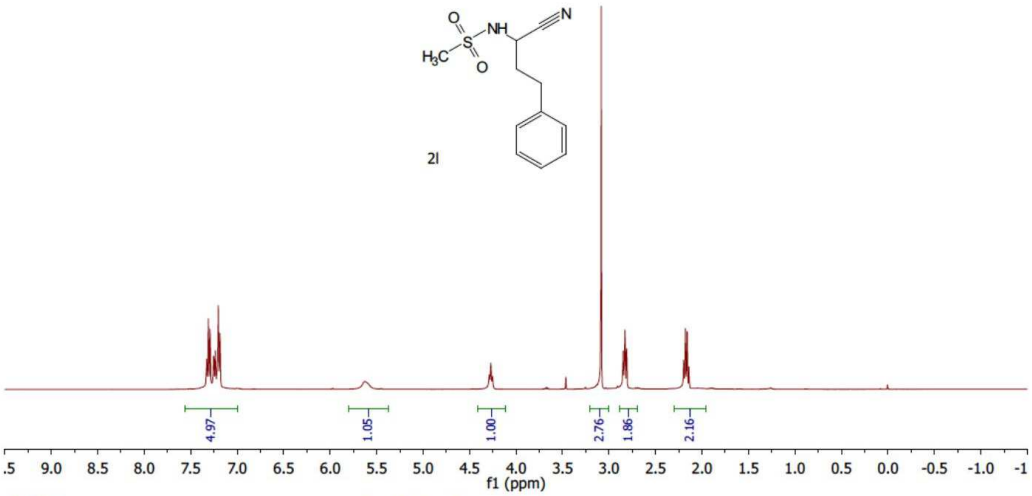

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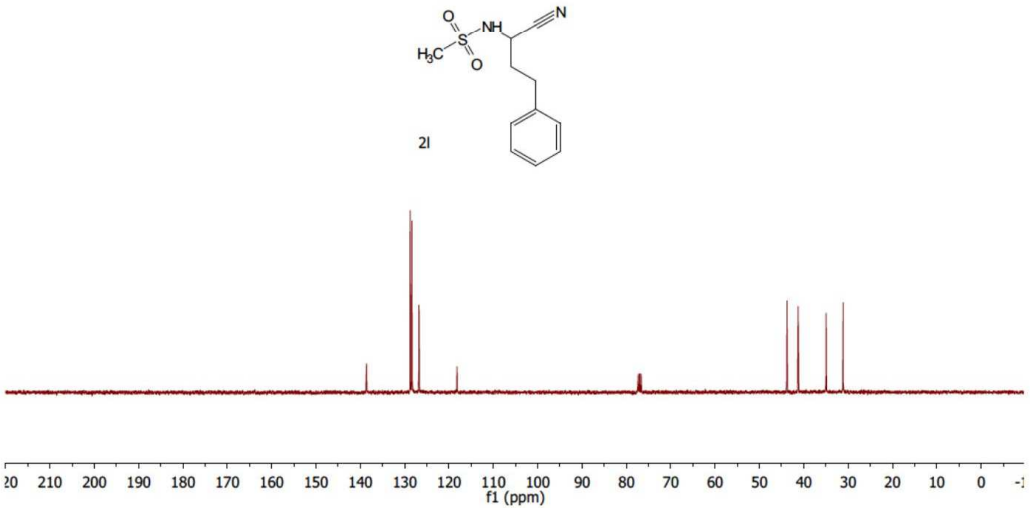

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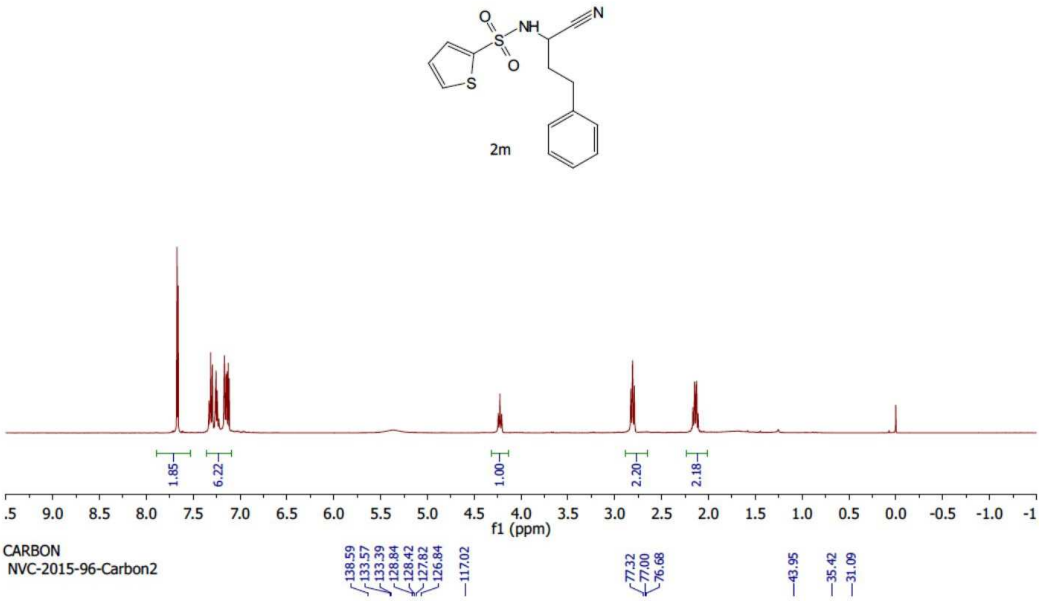

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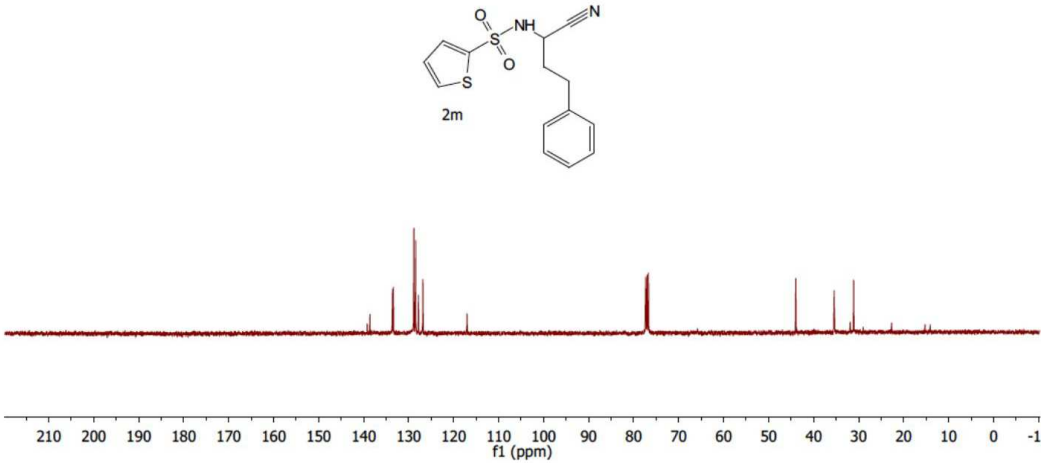

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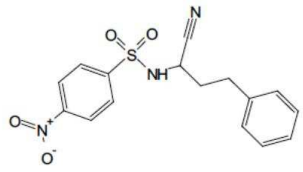

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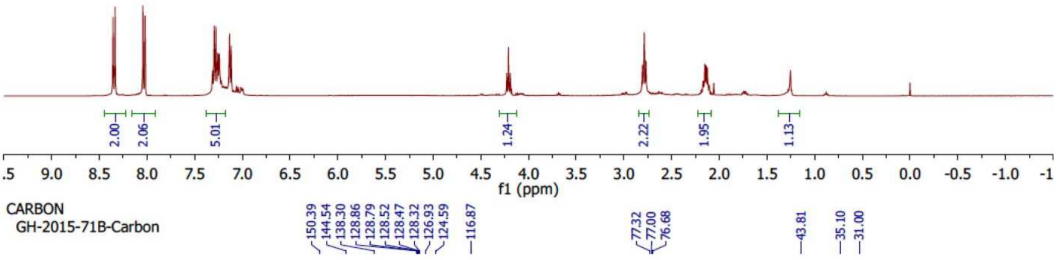

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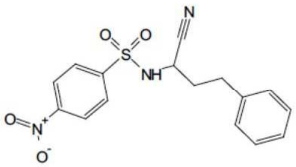

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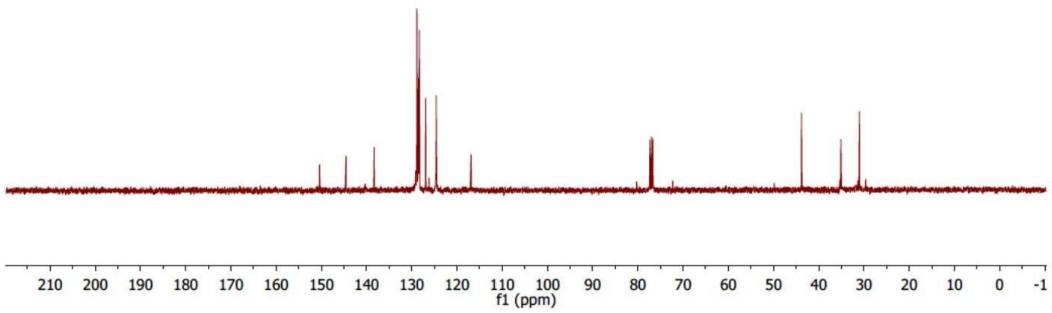

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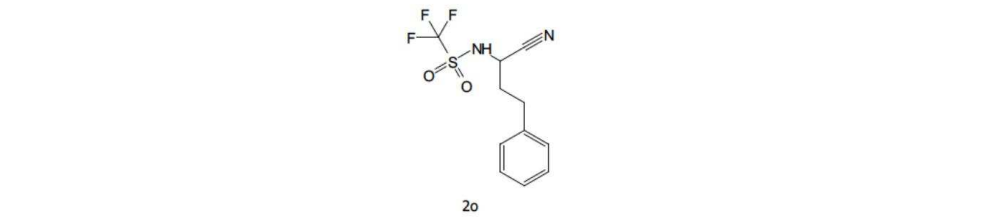

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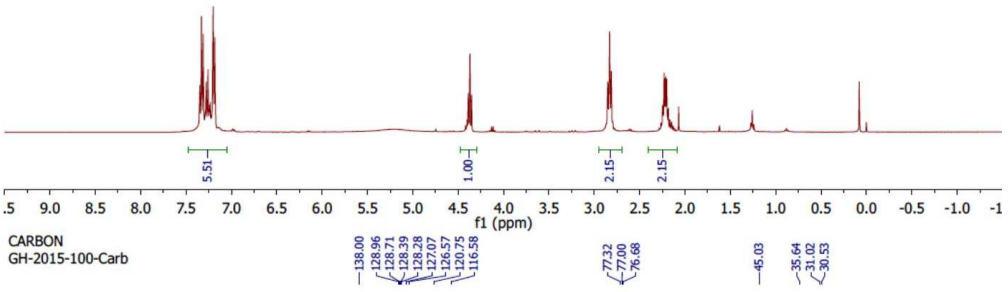

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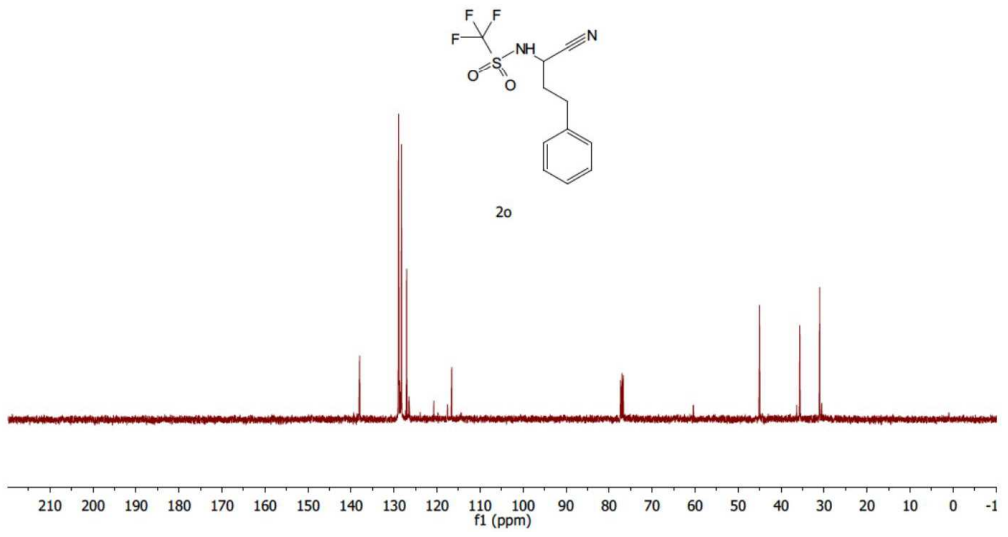

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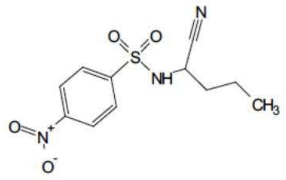

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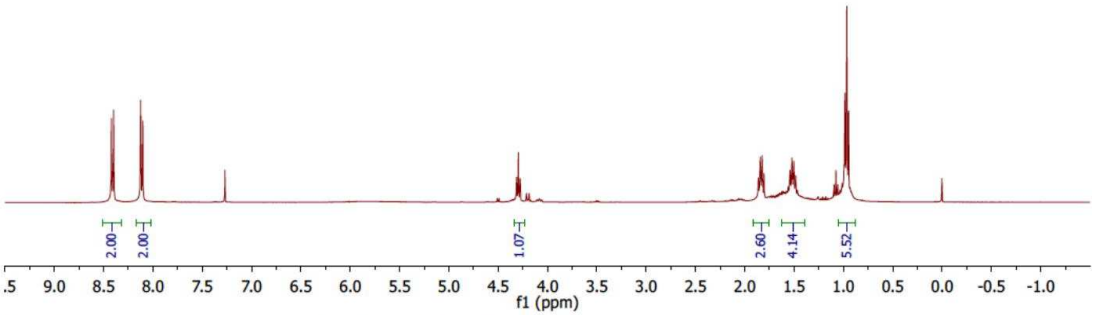

CARBON
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124.62
117.04
82.14
77.32
77.00
76.68
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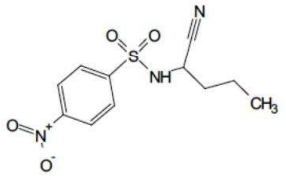

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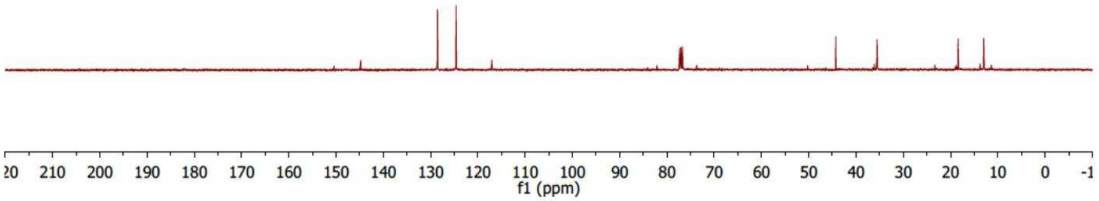

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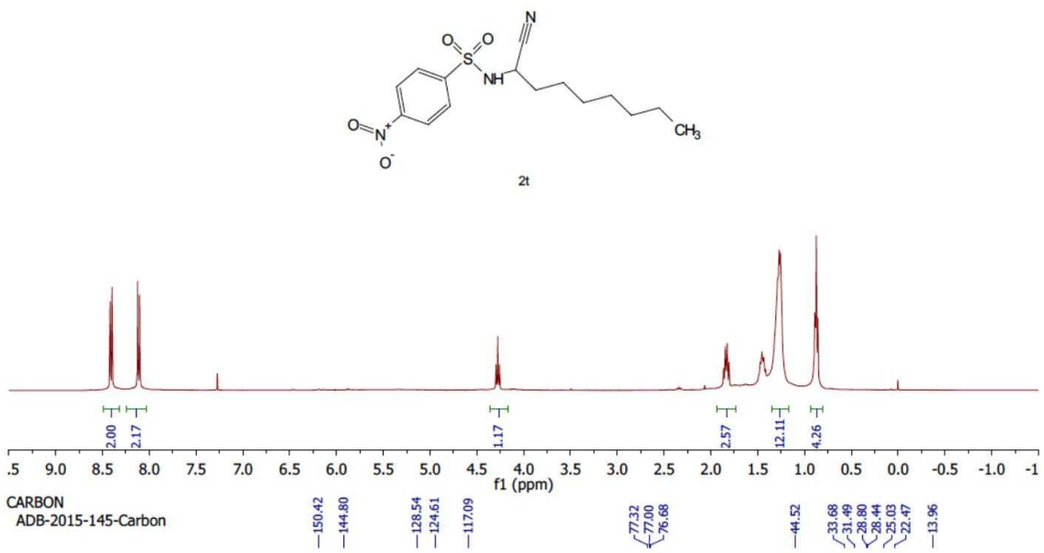

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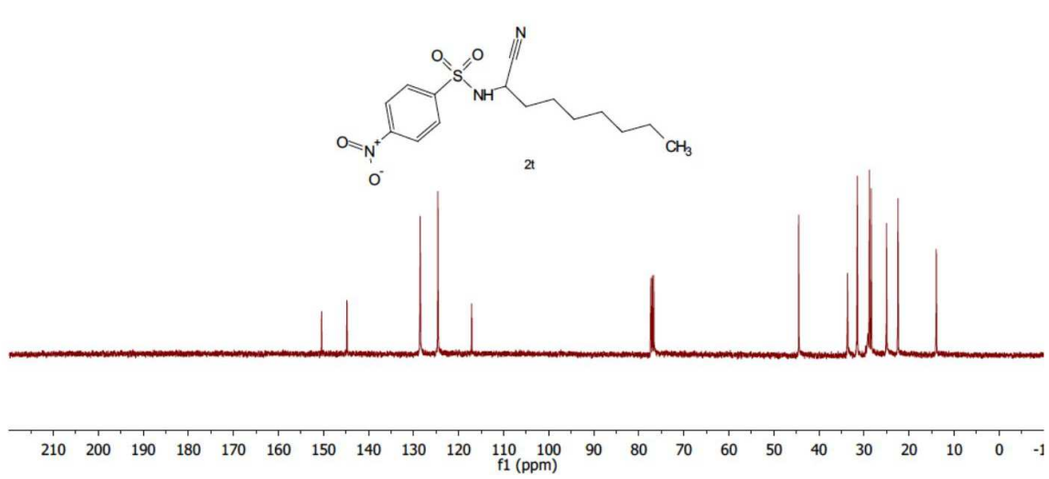


Chapter 2

Nitriles

2.1 Introduction to the Synthesis of Nitriles

Nitriles (Figure 5) are seen as key molecular scaffolds in organic chemistry and are used for the preparation of other functional groups, dyes, materials, and natural products.[38] Nitriles have also been seen as a reoccurring pharmacophore in some commercially available drugs causing a need for a more efficient method of their synthesis to be developed.[39-52]

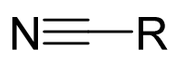


Figure 5. General Structure of a Nitrile

Most synthesis of nitriles rely on the displacement of a good leaving group by toxic cyanide sources such as potassium cyanide (KCN) and copper cyanide (CuCN).[53-60] One method that uses CuCN relies on a three-step process to achieve the desired nitrile. In this method an aromatic primary amine is added with sulfuric acid at 0˚C. After stirring for 30 minutes sodium nitrite is dissolved in water and added to the reaction still at 0˚C. This reaction mixture was then filtered, and the filtrate was combined with sodium carbonate, copper cyanide, and sodium cyanide in water. This method requires harsh reagents that are then separated, filtered, and washed with hot water. Other methods for the synthesis of these molecules involve the dehydration of amides and oximes under high temperature or harsh reagents.[61-65] An example of these harsh reagents is a Uranium catalyzed reaction using N-methyl-N-(trimethylsiyl)trifluoroacetamide (MSTFA) as a dehydration reagent. In the presence of 3 equivalence of MSTFA and 5 mol percent $UO_2(NO_3)_2$ hexahydrate in toluene at 100˚C excellent chemoselectivity and yield were

observed. Without these two reagents the reaction to the nitrile is not observed. Diminishing the amount of MSTFA produced lower yields while lowering the temperature had the same result. These methods generally suffer in poor substrate scope, difficulty of purifications, low yields, toxicity of reagents, generation of large amounts of organic waste, and use of expensive and sensitive catalysts.[66-71] Through a variety of different labs it has been shown that Cu(II) and TEMPO with NH_4OAc and Ag nanoparticles with $K_4Fe(CN)_6$ effectively promote the formation of nitriles from aldehydes[72-74] while, O-(4-CF3-benzoyl)-hydroxylamine and CSA being used as an organic catalyst have been shown to promote the same reaction with a larger scope.[75, 76] Due to these factors a metal free, general synthesis method for nitriles from aldehydes was in need of development.[77]

2.2 Nitrile Discovery

Early work in the Moura-Letts research group was able to highlight the diastereoselective synthesis of diaziridines using Hydroxylamine O-Sulfonic Acid (HOSA) as the source of nitrogen from ketones and aldehydes.[78] When optimizing this reaction, the researchers discovered a competing pathway that was analyzed and found to be a nitrile. After optimization this competing nitrile pathway led to obtaining nitriles in good to excellent yields with high chemoselectivity.

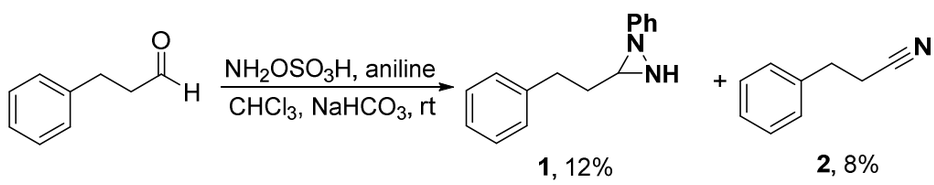


Figure 6. Discovery of Competing Nitrile Pathway

The competition between these two pathways comes from the initial condensation step which allows for both products to be formed (Figure 6). The heterocyclic diaziridine

is formed from the initial condensation of the aldehyde and aniline. Whereas the nitrile condensation requires an initial Aldehyde-HOSA condensation.

After optimization of both pathways it becomes clear that the reaction media is the cause for forming the desired chemoselectivity of the desire products (Figure 7).

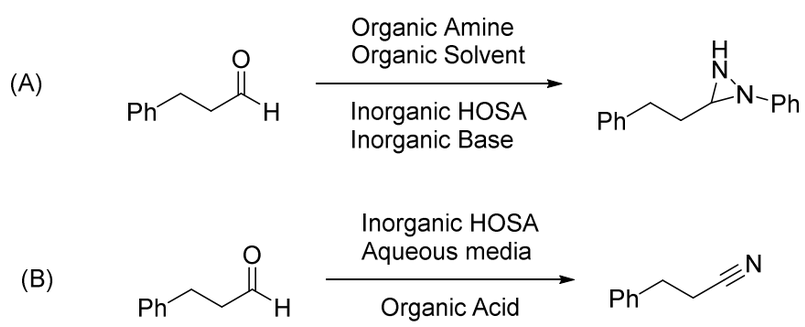


Figure 7. Exploiting Heterogeneous Composition to Control Reaction

By using polar organic solvent (Figure 7A), the diaziridine is obtained in good to excellent yields. This reaction media promotes the condensation of the aldehyde and aniline through a heterogeneous reaction mixture. The inorganic HOSA is slowly introduced to the reaction which allows for the aldehyde-aniline condensation which prompts the diaziridine formation. Using aqueous media promotes the nitrile pathway allowing for the aldehyde-HOSA condensation to take place (Figure 7B).

2.3 Results and Discussion

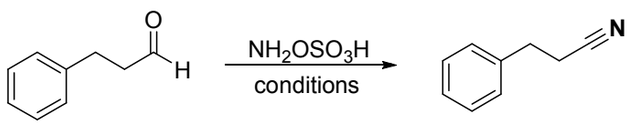
The Optimization studies looked at a large range of organic solvents, additives, and temperature to determine the best conditions for this reaction to proceed accordingly. It was found that the reaction yield was increased significantly by increasing the stoichiometric ratio of hydroxylamine to aldehyde. By increasing this ratio to 2:1 the yield for the reaction was 45% (Table 5, Entry 1). Upon further testing it was found that the

molar equivalence of hydroxylamine could be lowered while not affecting the yield of the reaction while under thermal conditions (Table 5, Entry 6).

A large array of solvents were used to better understand this reaction including several ionic liquids (Table 5, Entry 14-17). Despite this large array of solvents, the best results were found to be in aqueous medium with water as the solvent (Table 5, Entry 18-22). Upon mild heating and an exogenous acid (1 molar equivalent, acetic acid) the reaction was found to produce the nitrile in excellent yields (Table 5, Entry 19). Upon discovering the optimal conditions for this reaction, we sought to determine the scope by looking into the effects of different functional groups on the aldehyde.

Table 5

Nitrile Synthesis Optimization Studies



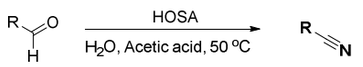
Entry	Stoichiometry[a]	Solvent	Additive[b]	Temperature	Yield[c]
1	1:2	$CHCl_3$	none	rt	45%
2	1:1.5	$CHCl_3$	none	rt	44%
3	1:1.5	H_2O	none	rt	38%
4	1:1.5	ACN	none	rt	25%
5	1:1.5	$CHCl_3$	none	40 °C	48%
6	1:1.5	$CHCl_3$	none	50 °C	64%
7	1:1.5	$ClCH_2CH_2Cl$	none	60 °C	58%
8	1:1.5	$ClCH_2CH_2Cl$	none	80 °C	60%
9	1:1.5	H_2O	none	50 °C	58%
10	1:1.5	ACN	none	50 °C	60%
11	1:1.5	DMSO	none	50 °C	40%
12	1:1.5	$ClCH_2CH_2Cl$	PTSA	50 °C	75%
13	1:1.5	$ClCH_2CH_2Cl$	TFA	50 °C	79%
14	1:1.5	[TMG][LA]	none	50 °C	53%
15	1:1.5	[TMG][LA]	TFA	50 °C	84%
16	1:1.5	[TMGPS][TFA]	none	50 °C	80%
17	1:1.5	[TMGPS][TFA]	H_2O	50 °C	82%
18	1:1.5	H_2O	TFA	50 °C	91%
19	1:1.5	H_2O	acetic acid	50 °C	95%
20	1:1.5	Vinegar	none	50 °C	94%
21	1:1.25	H_2O	acetic acid	50 °C	93%
22	1:1.1	H_2O	acetic acid	50 °C	94%

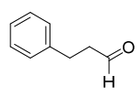
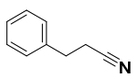
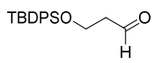
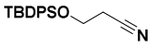
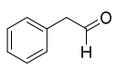
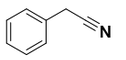
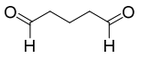
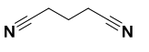
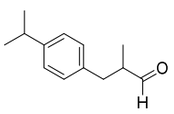
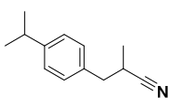
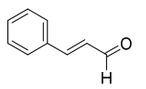
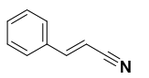
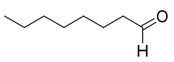
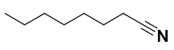
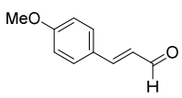
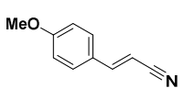
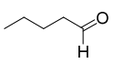
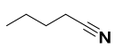
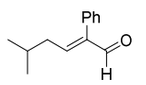
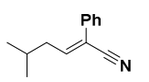
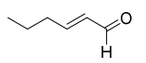
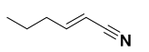
a. Aldehyde:NH_2OSO_3H. *b*.1 equiv. of additive. *c*. Isolated yields.

Aliphatic aldehydes reacted to the nitrile in good to excellent yields under the optimized reaction conditions (Table 6, Entry 1-6). The alpha-beta unsaturated aldehydes also reacted to the nitrile in good to excellent yields (Table 6, Entry 8-11). In some cases, trace impurities were detected by proton NMR and were purified by standard silica gel column to isolate the product (Table 6, Entry 9).

Table 6

Aliphatic and Alpha-beta unsaturated Nitrile Synthesis Scope



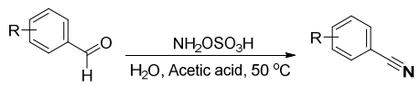
Entry	Aldehyde	Nitrile	Yield[a,b]	Entry	Aldehyde	Nitrile	Yield[a,b]
1			95%	6			80%[c,d]
2			92%	7			80%[c]
3			94%	8			89%
4			90%[c]	9			87%
5			88%	10			86%
				11			92%

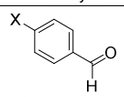
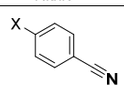
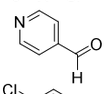
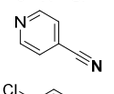
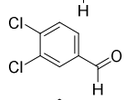
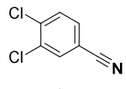
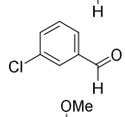
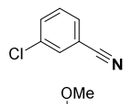
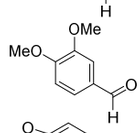
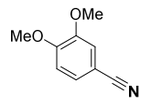
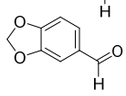
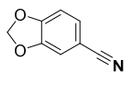
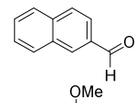
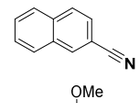
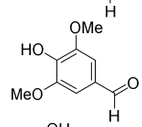
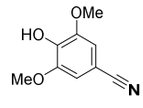
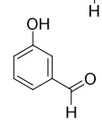
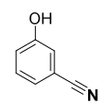
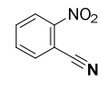
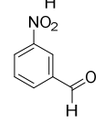
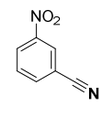
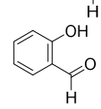
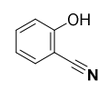
a. Reaction conditions: Aldehyde (1 mmol), Acetci acid (1 mmol), 1 mL of H_2O and HOSA (1.5 mmol) were mixed and heated to 50 °C for 6h. *b.* Isolated yields. *c.*Reaction crude was purified by standard silica gel chromatography. *d.* Reaction in $ClCH_2CH_2Cl$ and PTSA.

Similar to the nitriles in Table 6 the aromatic aldehydes under the optimized reaction conditions afforded good to excellent yields. Different functionalization was added to the benzene ring, such as, electron withdrawing groups (Table 7, Entry 14-15). These groups showed a slight decrease in percent yield but upon further stirring for 16 hrs. instead of the standard 6 hrs. the reaction went to completion. The aromatic nitriles along with the aliphatic and alpha-beta unsaturated nitriles all were obtained in high purity with no purification required except for one compound (Table 7, Entry 14).

Table 7

Aromatic Nitrile Synthesis Scope



Entry[a]	Aldehyde	Nitrile	Yield[b]
			
	1 = X = Br 2 = X = Me 3 = X = OMe 4 = X = H 5 = X = Cl	1 = X = Br 2 = X = Me 3 = X = OMe 4 = X = H 5 = X = Cl	92% 97% 93% 95% 94%
6			91%
7			89%
8			89%
9			93%
10			97%
11			85%
12			98%
13			91%
14			86%[d]
15			82%[c,d]
16			95%

a. Reaction conditions: Aldehyde (1 mmol), Acetci acid (1 mmol), 1 mL of H_2O and NH_2OSO_3H (1.1 mmol) were mixed and heated to 50 °C for 6h. *b.* Isolated yields. *c.*Reaction crude was purified by standard silica gel chromatography. *d.* Reaction achieved 100% conversion after 16h.

There are two proposed mechanisms for this reaction (Figure 8). Mechanism A involves a condensation to get the sulfonylimine. The oxygen attached to nitrogen attacks a proton which then allows water to attack the imine hydrogen and kick off the sulfonyl group allowing for the formation of the nitrile. Mechanism B also starts with a condensation to the sulfonylimine but then performs a syn-elimination to form the nitrile.

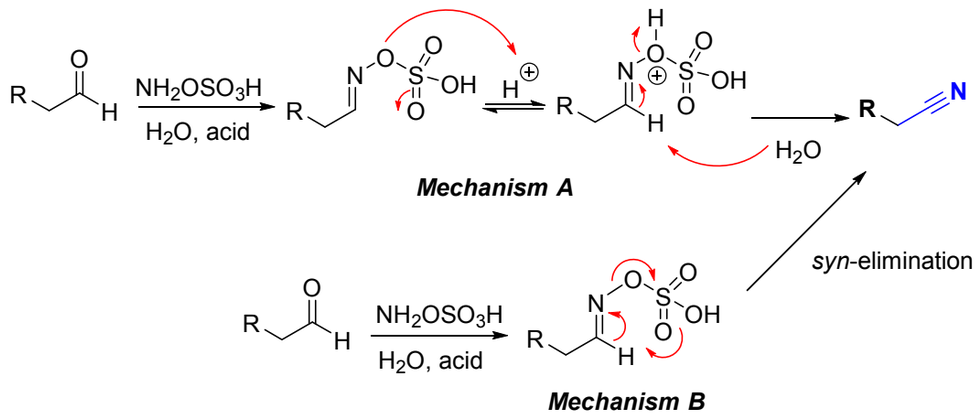


Figure 8. Proposed Mechanism for the Synthesis of Nitriles

2.4 Conclusion

This method provides a robust and versatile way to access the nitrile functional group in good to excellent yields. The scope of this method extends to aromatic, conjugated, and aliphatic aldehydes without the need for purification. Substitution along the aromatic ring does not have any effect on the efficiency of the reaction. The mild conditions of this reaction also allow for the incorporation of a variety of functional groups. The mechanisms proposed for this reaction rely on an elimination step to form the nitrile instead of going through an oxime or amide formation.

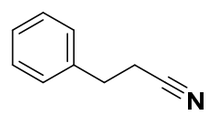
2.5 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4- mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$). Silica flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Automated chromatography was performed on an ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0- 30% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra

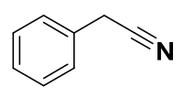
were recorded on Varian Mercury II 400 MHz Spectrometer at 9 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.23 ppm; ^{13}C, 77.0 ppm; coupling constants are expressed in Hz.

2.5.1. General method for the synthesis of Nitriles. In a 4-mL reaction vial, aldehyde (1.0 mmol, 1.0 equiv) and HOSA (1.1 mmol, 1.1 equiv.) were dissolved in 3 mL of de-ionized H_2O with (1 mmol, 1 equiv) acetic acid. The solution was stirred at 50 °C for 6 h or until complete conversion, determined by TLC. The reaction was quenched with aqueous 10% $NaHCO_3$ (1 mL) and the resulting mixture was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to afford the crude product. The product was directly characterized unless traces of impurities required purification by automated silica gel flash chromatography (few examples).

2.5.2. Synthesis of Nitriles from Table 6.

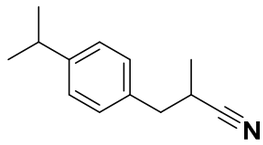


3-Phenylpropanenitrile (T2A): Aldehyde (100mg, 0.75mMol) produced nitrile **2a** (93mg, 95%) as a clear oil. TLC: R_f 0.47 (3:1 Heptanes/EtOAc). **IR** (thin film) 2250 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.38-7.29 (m, 5H), 2.99 (t, J = 7.3 Hz, 2H), 2.64 (t, J= 7.3Hz, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$): 138.0, 128.8, 128.2, 127.1, 119.1, 31.4, 19.2 ppm. **ESI-MS** m/z (re lint): (pos) 132.1 ($[M+H]^+$, 100); (neg) 130.1 ($[M-H]^-$,100).

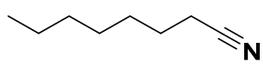


2-Phenylacetonitrile (T2B): Aldehyde (100mg, 0.83mMol) produced nitrile **2b** (89mg, 92%) as a clear oil. TLC: R_f 0.48 (3:1 Heptanes/EtOAc). **IR** (thin film) 2255 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.43-7.38 (m, 5H), 3.76 (s, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$)

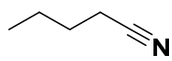
129.8, 128.9, 127.8, 127.8, 117.8, 23.4 ppm. **ESI-MS** m/z (re lint): (pos) 118.1 ($[M+H]^+$, 100); (neg) 116.1 ($[M-H]^-$,100).



3-(4-Isopropylphenyl)-2-methylpropanenitrile (T2C): Aldehyde (100mg, 0.53 mMol) produced nitrile **2c** (93mg, 94%) as a clear oil. TLC: R_f 0.68 (3:1 Heptanes/EtOAc). **IR** (thin film) 2290 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.23 (q, J = 6.8 Hz, 4H), 2.91-2.73 (m, 4H), 1.31 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 6H). **^{13}C-NMR** (100MHz, $CDCl_3$) 147.8, 134.1, 128.9, 126.7, 122.7, 39.6, 33.7, 27.6, 23.9, 17.6 ppm. **ESI-MS** m/z (re lint): (pos) 188.1 ($[M+H]^+$, 100); (neg) 186.1 ($[M-H]^-$,100).

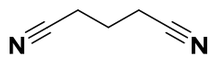


Octanenitrile (T2D): Aldehyde (100mg, 1.16 mMol) produced nitrile **2e** (85 mg, 88%) as a light-yellow oil. TLC: R_f 0.58 (3:1 Heptanes/EtOAc). **IR** (thin film) 2240 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 2.28 (t, J = 7.1 Hz, 2H), 1.65 (quintet, J = 6.9 Hz, 2H), 1.47 (sextet, J = 6.9 Hz, 2H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 119.7, 26.6, 22.0, 16.7, 13.1 ppm. **ESI-MS** m/z (re lint): (pos) 84.1 ($[M+H]^+$, 100); (neg) 82.1 ($[M-H]^-$,100).

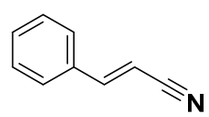


Pentanenitrile (T2E): Aldehyde (100mg, 1.16 mMol) produced nitrile **2e** (85 mg, 88%) as a light-yellow oil. TLC: R_f 0.58 (3:1 Heptanes/EtOAc). **IR** (thin film) 2240 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 2.28 (t, J = 7.1 Hz, 2H), 1.65 (quintet, J = 6.9 Hz, 2H), 1.47 (sextet, J = 6.9 Hz, 2H), 0.88 (t, J = 6.9 Hz, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 119.7, 26.6,

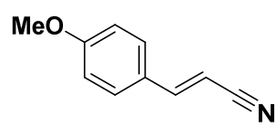
22.0, 16.7, 13.1 ppm. **ESI-MS** m/z (re lint): (pos) 84.1 ($[M+H]^+$, 100); (neg) 82.1 ($[M-H]^-$,100).



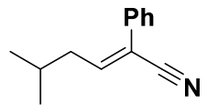
Glutaronitrile (T2F): Aldehyde (100mg, 1.03 mMol) produced nitrile **2f** (83 mg, 86%) as a clear oil. TLC: R_f 0.71 (3:1 Heptanes/EtOAc). IR (thin film) 2250 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 2.51 (t, J = 7.3 Hz, 4H), 3.74 (quintet, J = 7.3 Hz, 2H). **^{13}C-NMR** (100MHz, CDCl3) 117.7, 21.6, 16.2 ppm. **ESI-MS** m/z (re lint): (pos) 95.1 ($[M+H]^+$, 100); (neg) 93.1 ($[M-H]^-$,100).



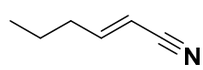
Cinnamonitrile (T2G): Aldehyde (100mg, 0.76 mMol) produced nitrile **2g** (83 mg, 89%) as a light-yellow oil. TLC: R_f 0.75 (3:1 Heptanes/EtOAc). **IR** (thin film) 2210 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.41-7.32 (m, 6H), 5.78 (d, J = 16.1 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 150.4, 133.3, 131.0, 128.9, 127.2, 118.0, 96.1 ppm. **ESI-MS** m/z (re lint): (pos) 130.1 ($[M+H]^+$, 100); (neg) 128.1 ($[M-H]^-$,100).



(*E*)-3-(4-Methoxyphenyl)-acrylonitrile (T2H): Aldehyde (100mg, 0.62 mMol) produced nitrile **2h** (86 mg, 87%) as a white solid. TLC: R_f 0.42 (3:1 Heptanes/EtOAc). **IR** (thin film) 2215 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.29 (d, J = 6.6 Hz, 2H), 7.25 (d, J = 16.5 Hz, 1H), 6.93 (d, J = 6.6 Hz, 2H), 5.83 (d, J = 16.3 Hz, 1H), 3.89 (s, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 162.0, 150.0, 129.0, 126.3, 118.7, 114.5, 93.3, 55.4 ppm. **ESI-MS** m/z (re lint): (pos) 160.1 ($[M+H]^+$,100); (neg) 158.1 ($[M-H]^-$,100).

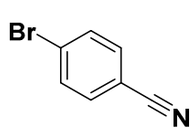


(*E*)-5-Methyl-2-phenylhex-2-enenitrile (T2I): Aldehyde (100mg, 0.53 mMol) produced nitrile **2i** (84 mg, 86%) as a clear oil. TLC: R_f 0.69 (3:1 Heptanes/EtOAc). **IR** (thin film) 2205 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.49-7.43 (m, 5H), 6.71 (t, J = 6.8 Hz, 1H), 2.25 (dd, J = 7.5, 6.8 Hz, 2H), 1.79-1.75 (m, 1H), (d, J = 7.1 Hz, 6H). **^{13}C-NMR** (100MHz, $CDCl_3$) 148.9, 136.4, 129.4, 128.8, 125.5, 116.2, 107.5, 37.5, 28.8, 22.4 ppm. **ESI-MS** m/z (re lint): (pos) 186.1 ($[M+H]^+$, 100); (neg) 184.1 ($[M-H]^-$,100).

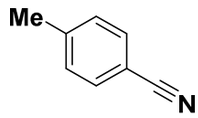


(*E*)-Hex-2-enenitrile (T2J): Aldehyde (100mg, 1.02 mMol) produced nitrile **2j** (89 mg, 92%) as a clear oil. TLC: R_f 0.66 (3:1 Heptanes/EtOAc). **IR** (thin film) 2210 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.91 (dt, J = 16.1, 7.1 Hz, 1H), 5.27 (d, J = 16.1Hz, 1H), 2.24 (dt, J = 7.3, 7.1 Hz, 2H), 1.47 (sextet, J = 7.3 Hz, 2H), 0.82 (t, J = 6.9 Hz, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 155.8, 117.4, 99.6, 35.1, 20.8, 13.3 ppm. **ESI-MS** m/z (re lint): (pos) 96.1 ($[M+H]^+$, 100); (neg) 94.1 ($[M-H]^-$,100).

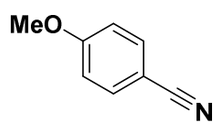
2.5.3. Synthesis of Nitriles from Table 7.



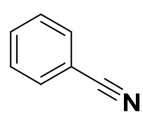
4-Bromobenzonitrile (T3A): Aldehyde (100mg, 0.54 mMol) produced nitrile **3a** (90mg, 92%) as a white solid. TLC: R_f 0.70 (3:1 Heptanes/EtOAc). **IR** (thin film) 2215 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.62 (d, J = 7.1 Hz, 2H), 7.49 (d, J = 7.1 Hz, 2H). **^{13}C-NMR** (100MHz, CDCl3) 133.4, 132.6, 128.0, 118.0, 111.2 ppm. **ESI-MS** m/z (re lint): (pos) 182.0 ($[M+H]^+$, 100); (neg) 180.0 ($[M-H]^-$,100).



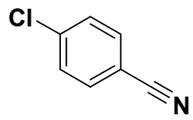
4-Methylbenzonitrile (T3B): Aldehyde (100mg, 0.83 mMol) produced nitrile **3b** (94mg, 97%) as a clear oil. TLC: R_f 0.66 (3:1 Heptanes/EtOAc). **IR** (thin film) 2210 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.54 (d, J = 7.0 Hz, 2H), 7.27 (d, J = 7.1Hz, 2H), 2.44 (s, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 143.6, 132.0, 129.8, 119.1, 109.2, 21.8 ppm. **ESI-MS** m/z (re lint): (pos) 118.1 ($[M+H]^+$, 100); (neg) 116.1 ($[M-H]^-$,100).



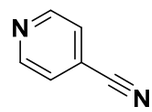
4-Methoxybenzonitrile (T3C): Aldehyde (100mg, 0.74mMol) produced nitrile **3c** (94mg, 93%) as a white solid. TLC: R_f 0.44 (3:1 Heptanes/EtOAc). **IR** (thin film) 2210 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.52 (d, J = 7.3 Hz, 2H), 6.91 (d, J = 7.3 Hz, 2H), 3.78 (s, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 162.8, 133.9, 119.2, 114.7, 103.9, 55.5 ppm. **ESI-MS** m/z (re lint): (pos) 134.1 ($[M+H]^+$, 100); (neg) 132.1 ($[M-H]^-$,100).



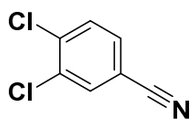
Benzonitrile (T3D): Aldehyde (100mg, 0.94 mMol) produced nitrile **3d** (92mg, 95%) as a clear liquid. TLC: R_f 0.68 (3:1 Heptanes/EtOAc). **IR** (thin film) 2220 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.52-7.32 (m, 5H). **^{13}C-NMR** (100MHz, $CDCl_3$) 132.3, 131.5, 128.6, 118.3, 111.7 ppm. **ESI-MS** m/z (re lint): (pos) 104.1 ($[M+H]^+$, 100); (neg) 102.1 ($[M-H]^-$,100).



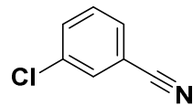
4-Chlorobenzonitrile (T3E): Aldehyde (100mg, 0.71 mMol) produced nitrile **3e** (91mg, 94%) as a white solid. TLC: R_f 0.75 (3:1 Heptanes/EtOAc). **IR** (thin film) 2220 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.58 (d, J = 7.1 Hz, 2H), 7.47 (d, J = 7.1 Hz, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$) 139.5, 133.4, 129.7, 118.0, 110.7 ppm. **ESI-MS** m/z (re lint): (pos) 138.0 ($[M+H]^+$, 100); (neg) 136.0 ($[M-H]^-$,100).



Isonicotinonitrile (T3F): Aldehyde (100mg, 0.93 mMol) produced nitrile **3f** (88mg, 91%) as a white solid. TLC: R_f 0.14 (3:1 Heptanes/EtOAc). **IR** (thin film) 2225 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.53 (d, J = 6.8 Hz, 2H), 7.52 (d, J = 6.8 Hz, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$) 150.7, 125.2, 120.4, 116.3 ppm. **ESI-MS** m/z (re lint): (pos) 105.1 ($[M+H]^+$, 100); (neg) 103.1 ($[M-H]^-$,100).

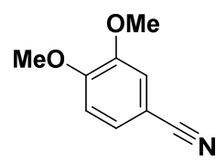


3,4-Dichlorobenzonitrile (T3G): Aldehyde (100mg, 0.57 mMol) produced nitrile **3g** (86mg, 89%) as a white solid. TLC: R_f 0.56 (3:1 Heptanes/EtOAc). **IR** (thin film) 2224 cm^{-1}. **1H-NMR** (400 MHz, $CDCl_3$): 7.63 (d, J = 6.6 Hz, 1H), 7.50 (s, 1H), 7.29 (d, J = 6.6 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 140.0, 137.7, 134.5, 130.2, 127.8, 115.2, 111.8 ppm. **ESI-MS** m/z (re lint): (pos) 172.0 ($[M+H]^+$, 100); (neg) 170.0 ($[M-H]^-$,100).

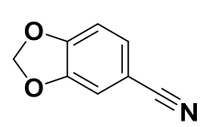


3-Chlorobenzonitrile (T3H): Aldehyde (100mg, 0.71 mMol) produced nitrile **3h** (87 mg, 89%) as a white solid. TLC: R_f 0.54 (3:1 Heptanes/EtOAc). **IR** (thin film) 2225 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.63 (s, 1H), 7.58-7.51 (m, 2H), 7.41 (t, J = 6.9 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 135.1, 133.1, 131.8, 130.4, 130.2, 117.3, 113.8 ppm. **ESI-MS** m/z (re lint): (pos) 138.0 ($[M+H]^+$, 100); (neg) 136.0 ($[M-H]^-$,100).

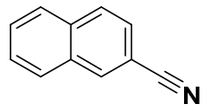
.



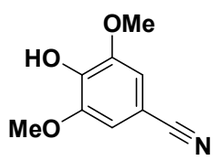
3,4-Dimethoxybenzonitrile (T3I): Aldehyde (100mg, 0.60 mMol) produced nitrile **3i** (91 mg, 93%) as a white solid. TLC: R_f 0.29 (3:1 Heptanes/EtOAc). **IR** (thin film) 2215 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.25 (d, J = 6.8 Hz, 1H), 7.03 (s, 1H), 6.82 (d, J = 6.8 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H). **^{13}C-NMR** (100MHz, $CDCl_3$) 152.7, 149.1, 126.4, 119.1, 113.8, 111.1, 103.8, 56.1, 56.0 ppm. **ESI-MS** m/z (re lint): (pos) 164.1 ($[M+H]^+$, 100); (neg) 162.1 ($[M-H]^-$,100).



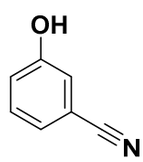
Benzo[*d*][1,3]dioxole-5-carbonitrile (T3J): Aldehyde (100mg, 0.67 mMol) produced nitrile **3j** (96 mg, 97%) as a white solid. TLC: R_f 0.38 (3:1 Heptanes/EtOAc). **IR** (thin film) 2210 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 7.21 (d, J = 6.8 Hz, 1H), 6.99 (s, 1H), 6.77 (d, J = 6.8 Hz, 1H), 6.02 (s, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$) 151.5, 147.9, 128.1, 118.8, 111.3, 109.0, 104.8, 102.2 ppm. **ESI-MS** m/z (re lint): (pos) 148.1 ($[M+H]^+$, 100); (neg) 146.1 ($[M-H]^-$,100).



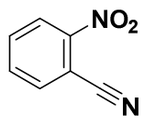
4-Naphtonitrile (T3K): Aldehyde (100mg, 0.67 mMol) produced nitrile **3k** (96 mg, 85%) as a tan solid. TLC: R_f 0.77 (3:1 Heptanes/EtOAc). **IR** (thin film) 2205 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.19 (d, J = 6.6 Hz, 1H), 8.04 (d, J = 6.6 Hz, 1H), 7.87 (t, J = 6.9 Hz, 2H), 7.65 (d, J = 6.8 Hz, 1H), 7.58 (d, J = 6.8 Hz, 1H), 7.47 (d, J = 6.8 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 133.2, 132.8, 132.5, 132.2, 128.6, 128.5, 127.4, 125.0, 124.8, 117.7, 110.0 ppm. **ESI-MS** m/z (re lint): (pos) 154.1 ($[M+H]^+$, 100); (neg) 152.1 ($[M-H]^-$,100).



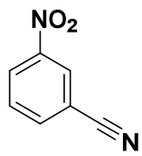
4-Hydroxy-3,5-dimethoxybenzonitrile (T3L): Aldehyde (100mg, 0.55 mMol) produced nitrile **3l** (96 mg, 98%) as a white solid. TLC: R_f 0.12 (3:1 Heptanes/EtOAc). **IR** (thin film) 3450, 2240 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 6.82 (s, 2H), 3.87 (s, 6H). **^{13}C-NMR** (100MHz, $CDCl_3$) 147.1, 139.2, 119.3, 109.1, 102.2, 56.5 ppm. **ESI-MS** m/z (re lint): (pos) 180.1 ($[M+H]^+$, 100); (neg) 178.1 ($[M-H]^-$,100).



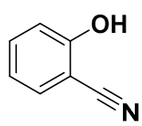
3-Hydroxybenzonitirle (T3M): Aldehyde (100mg, 0.66mMol) produced nitrile **3n** (84 mg, 86%) as a light yellow solid. TLC: R_f 0.53 (3:1 Heptanes/EtOAc). **IR** (thin film) 2240 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.33-8.31 (m, 1H), 7.92-7.89 (m, 1H), 7.84- 7.82 (m, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$) 135.5, 134.3, 133.7, 125.5, 114.9, 108.0 ppm. **ESI-MS** m/z (re lint): (pos) 149.1 ($[M+H]^+$, 100); (neg) 147.1 ($[M-H]^-$,100).



2-Nitrobenzonitrile (T3N): Aldehyde (100mg, 0.66mMol) produced nitrile **3n** (84 mg, 86%) as a light yellow solid. TLC: R_f 0.53 (3:1 Heptanes/EtOAc). **IR** (thin film) 2240 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.33-8.31 (m, 1H), 7.92-7.89 (m, 1H), 7.84- 7.82 (m, 2H). **^{13}C-NMR** (100MHz, $CDCl_3$) 135.5, 134.3, 133.7, 125.5, 114.9, 108.0 ppm. **ESI-MS** m/z (re lint): (pos) 149.1 ($[M+H]^+$, 100); (neg) 147.1 ($[M-H]^-$,100).

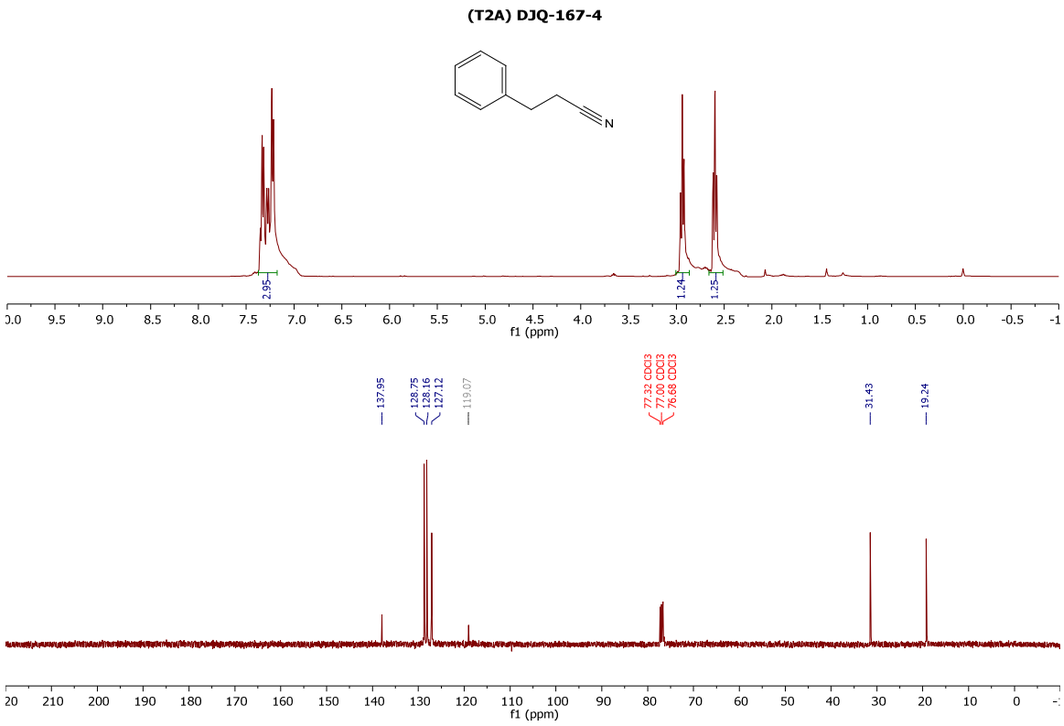


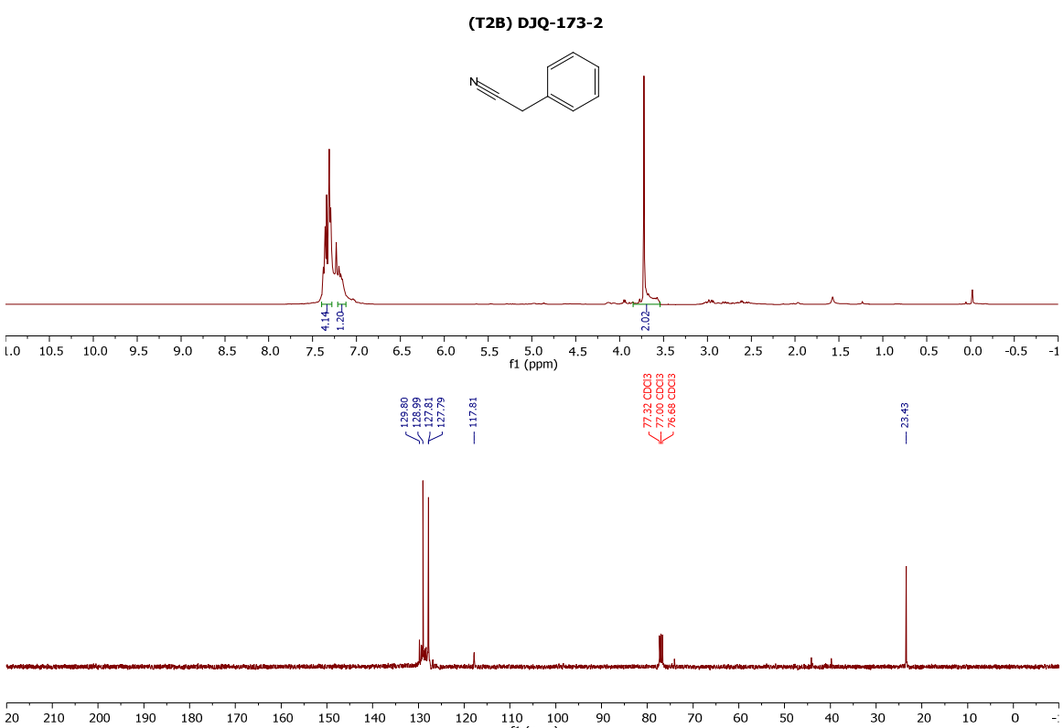
3-Nitrobenzonitrile (T3O): Aldehyde (100mg, 0.66 mMol) produced nitrile **3o** (80 mg, 82%) as a light yellow solid. TLC: R_f 0.55 (3:1 Heptanes/EtOAc). **IR** (thin film) 2235 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$): 8.51 (s, 1H), 8.44 (d, J = 6.6 Hz, 1H), 7.96 (d, J = 6.6 Hz, 1H), 7.74 (dt, J = 6.6 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 137.6, 130.6, 127.5, 127.4, 127.2, 116.5, 114.1 ppm. **ESI-MS** m/z (re lint): (pos) 149.1 ($[M+H]^+$, 100); (neg) 147.1 ($[M-H]^-$,100).

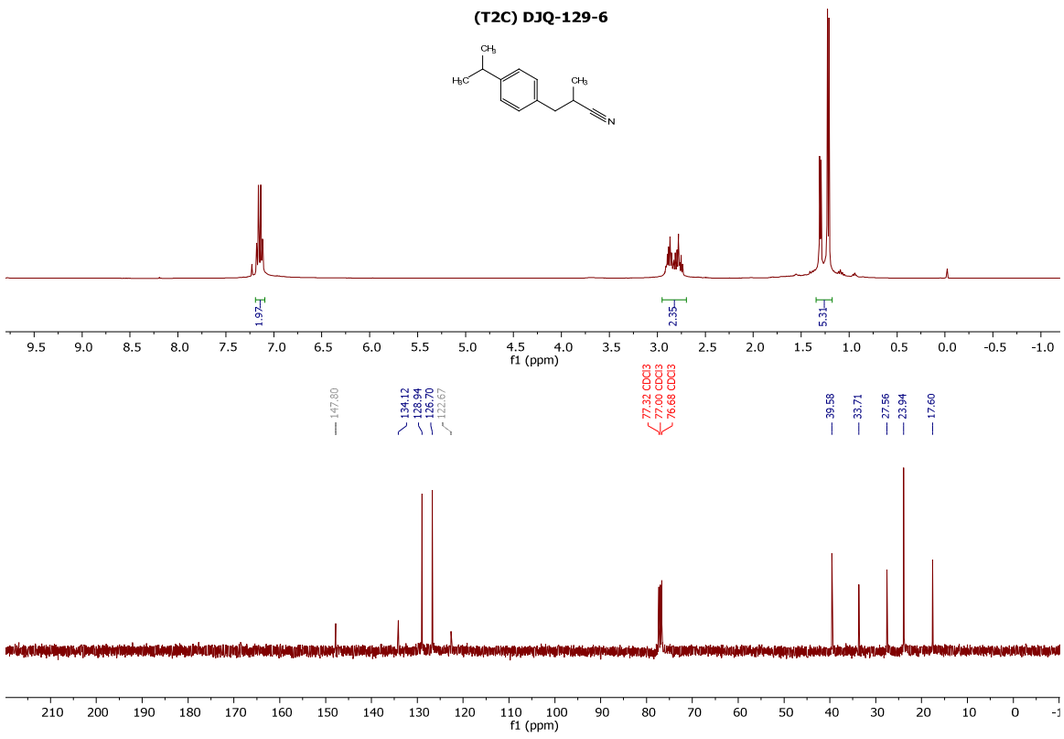


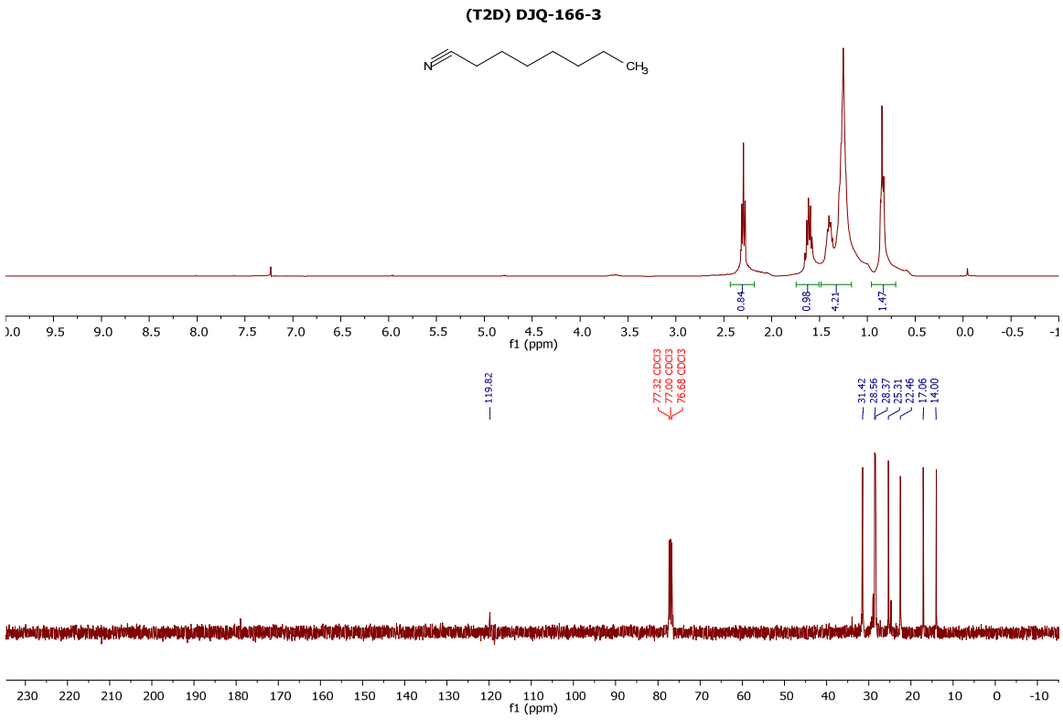
2-Hydroxybenzonitrile (T3P): Aldehyde (100mg, 0.82 mMol) produced nitrile **3p** (93mg, 95%) as a white solid. TLC: R_f 0.29 (3:1 Heptanes/EtOAc). **IR** (thin film) 3460, 2250 cm^{-1}. **1H-NMR** (400 MHz, $CDCl_3$): 7.52-7.44 (m, 2H), 7.39 (bs, 1H), 7.07 (d, J = 7.1 Hz, 1H), 6.97 (t, J = 7.1 Hz, 1H). **^{13}C-NMR** (100MHz, $CDCl_3$) 159.4, 135.3, 135.2, 133.3, 120.9, 116.9, 99.3 ppm. **ESI-MS** m/z (re lint): (pos) 120.1 ($[M+H]^+$, 100); (neg) 118.1 ($[M-H]^-$,100).

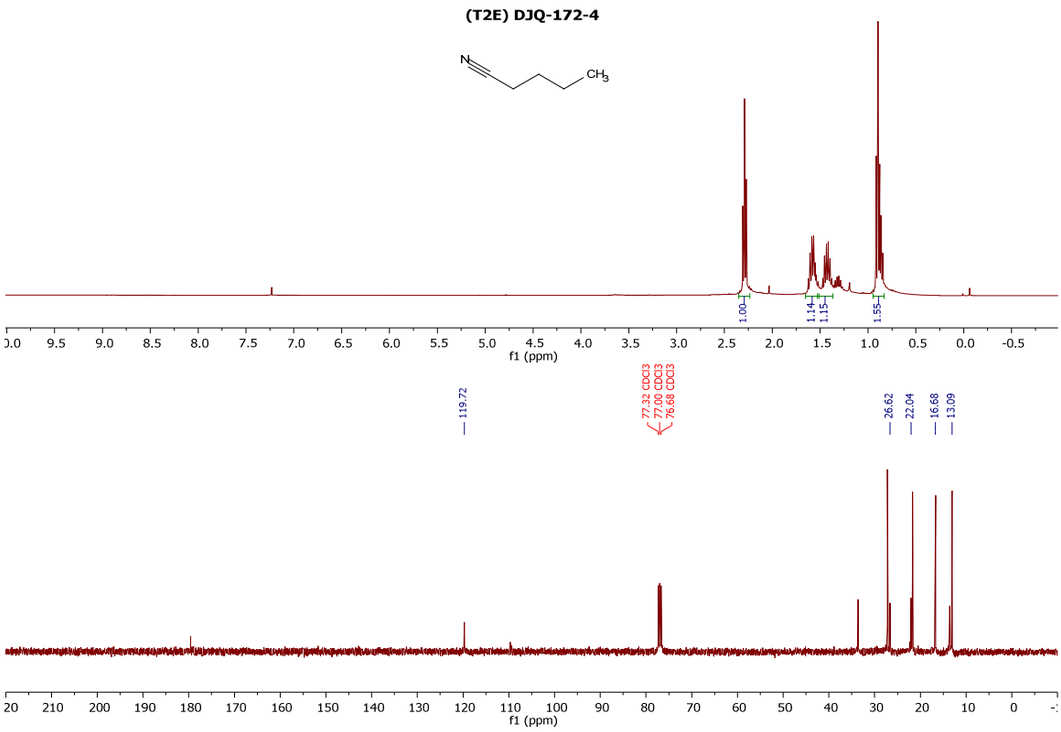
2.5.4. ^{1}H NMR and ^{13}C NMR of Nitriles.

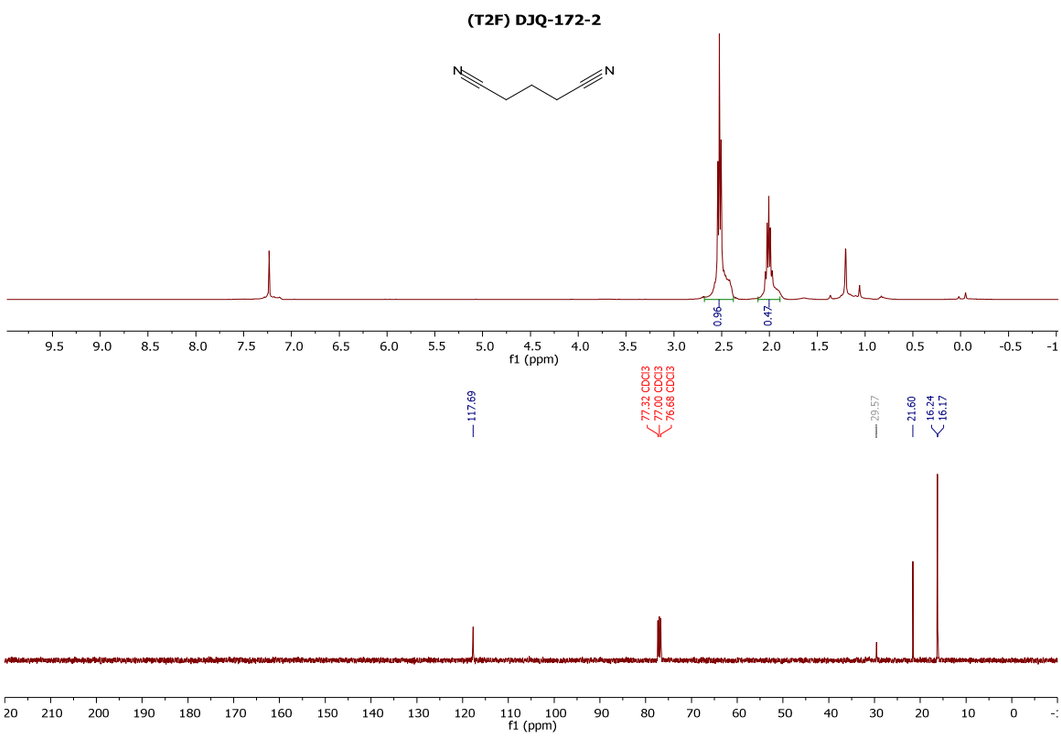


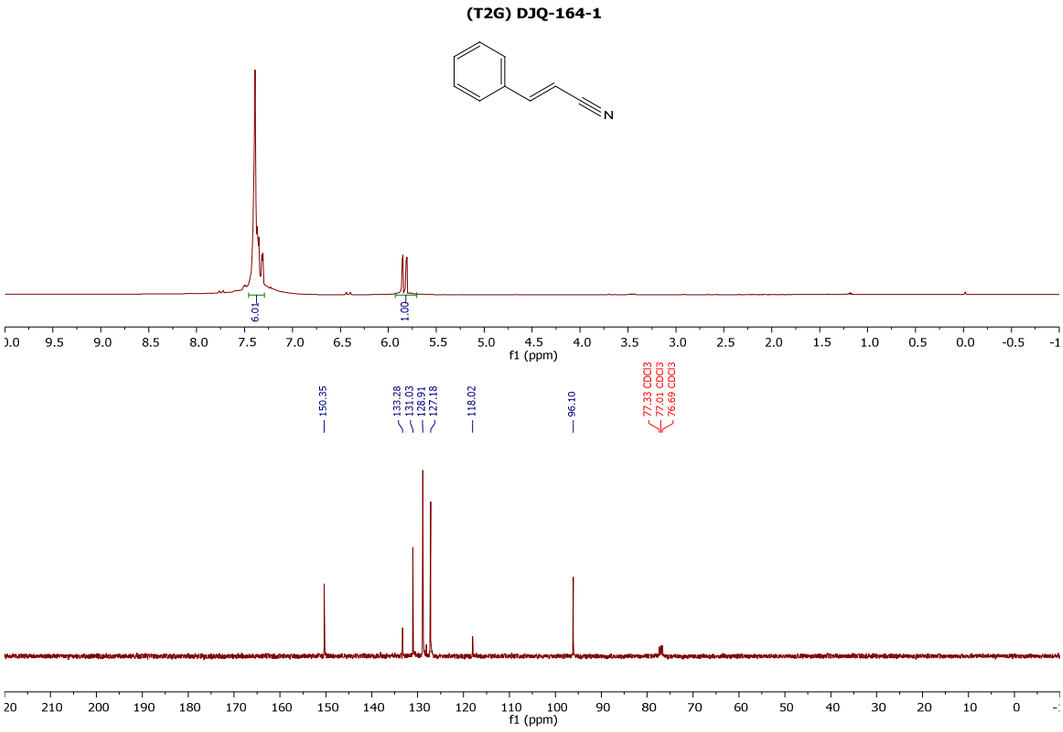


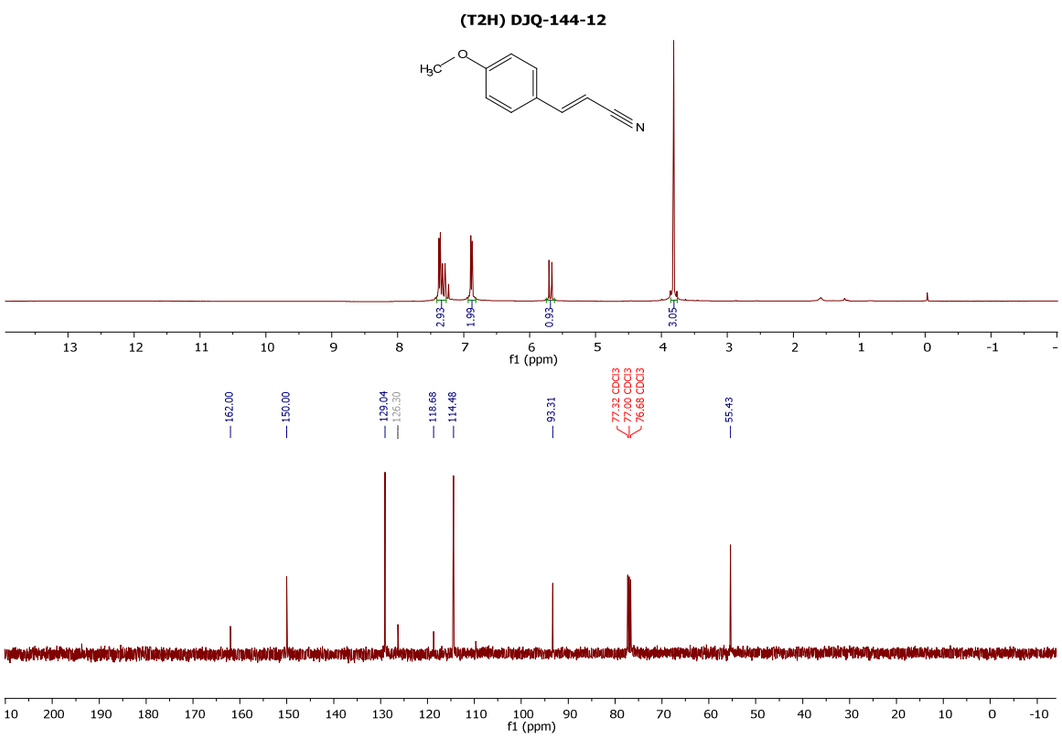












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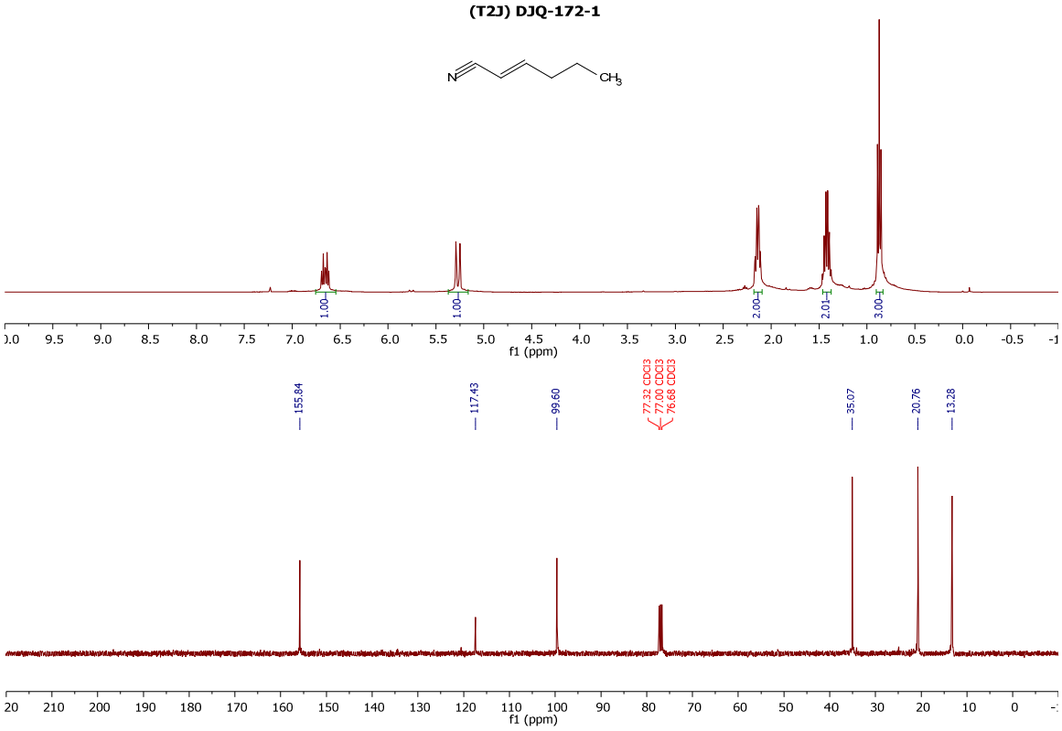
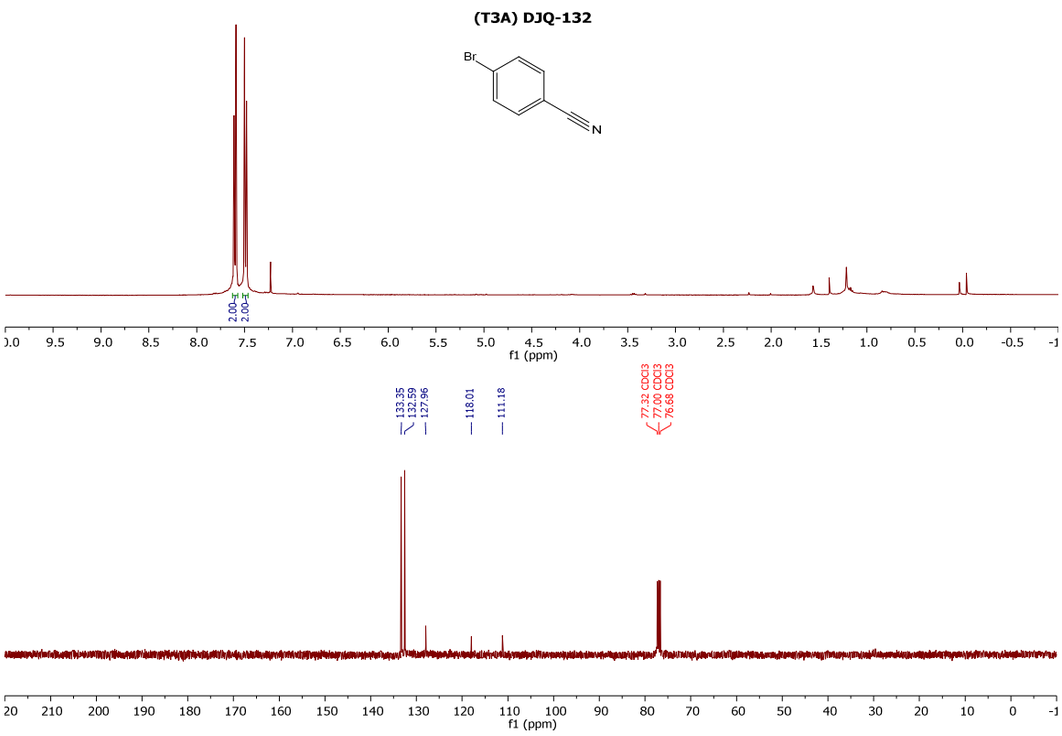
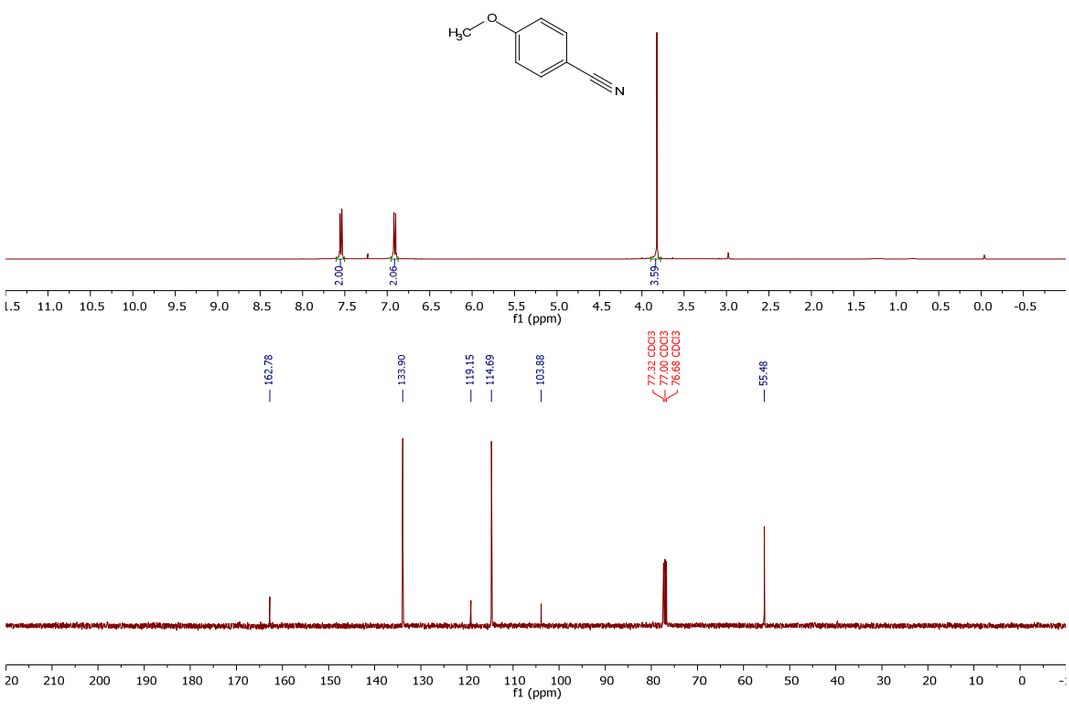


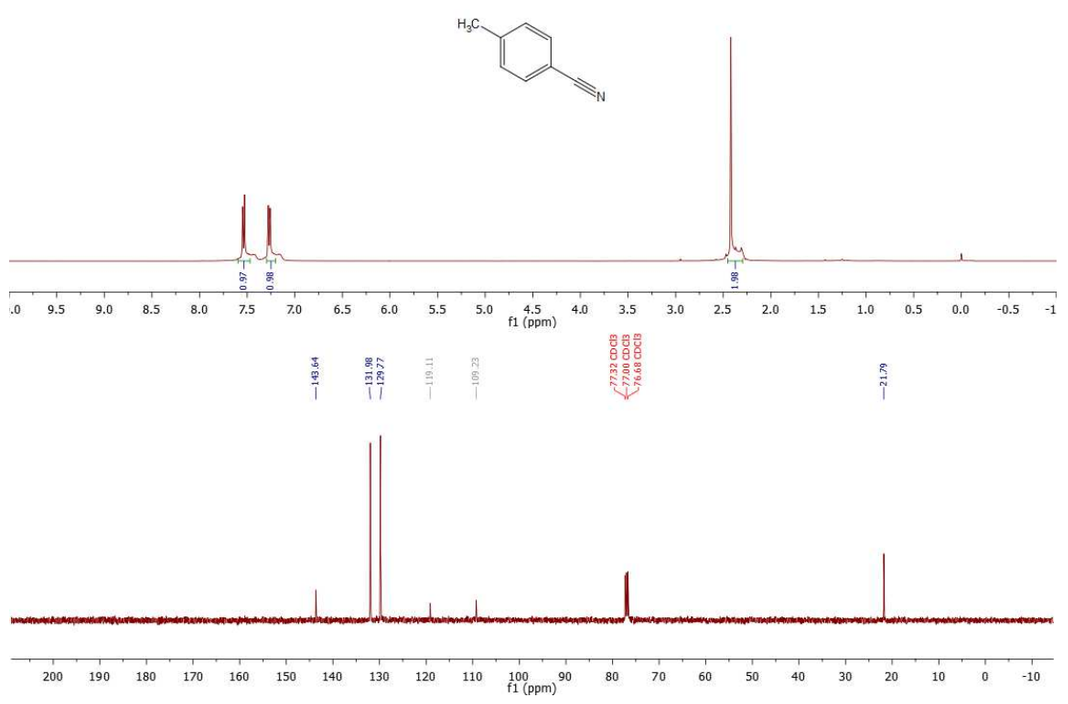
(T3A) DJQ-132



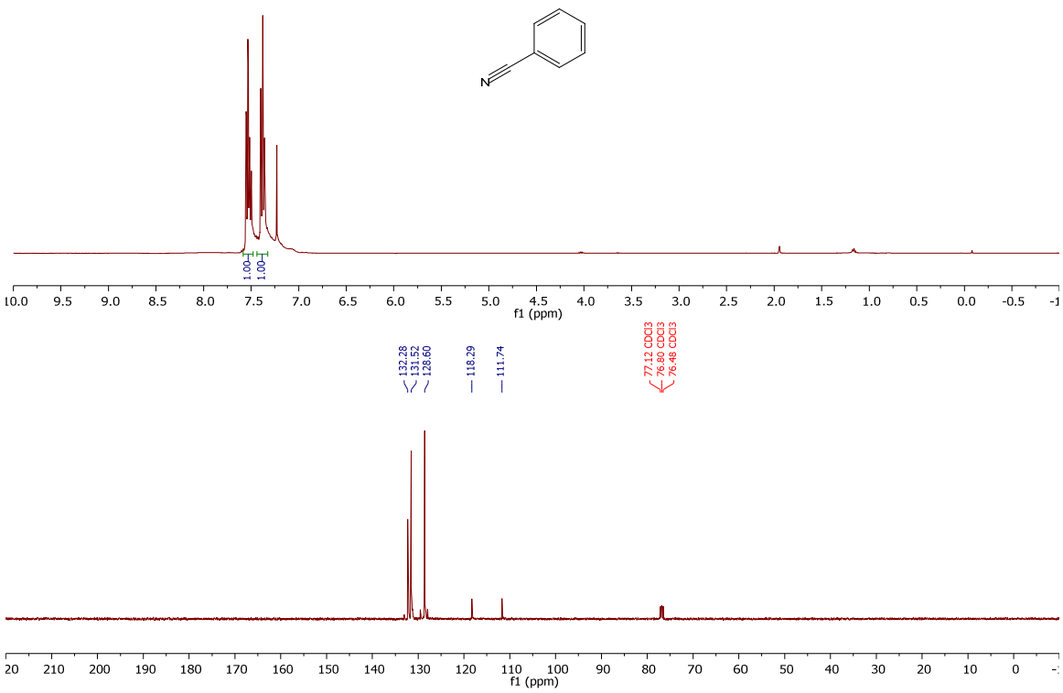
(T3C) DJQ-143-5



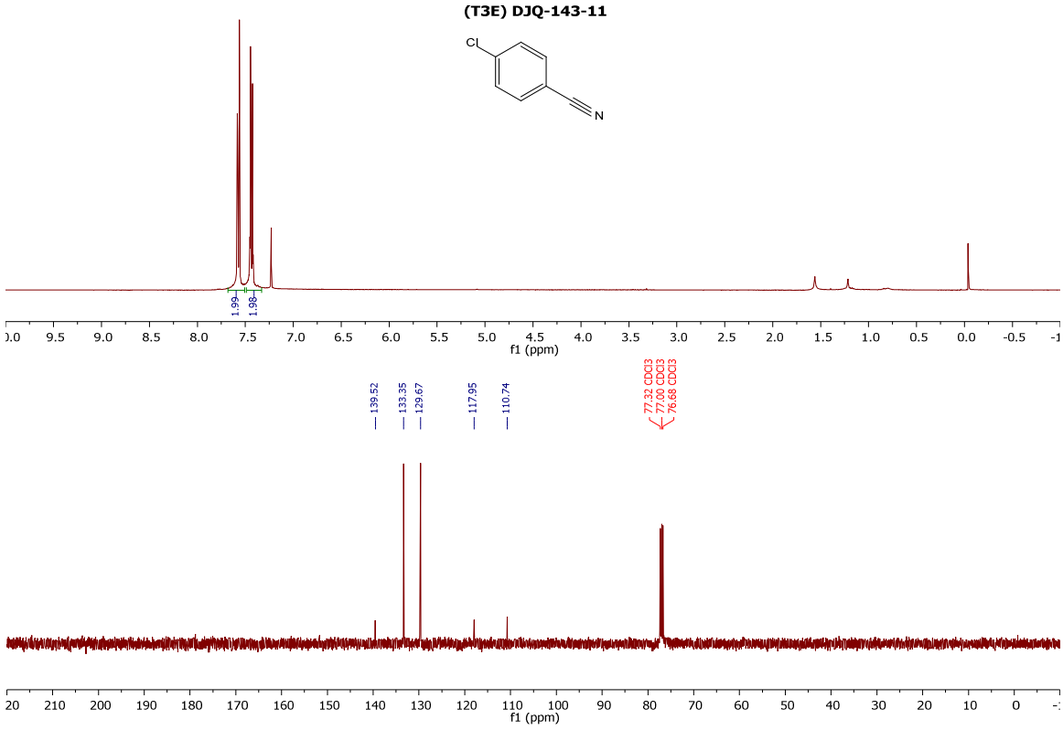
(T3B) DJQ-147



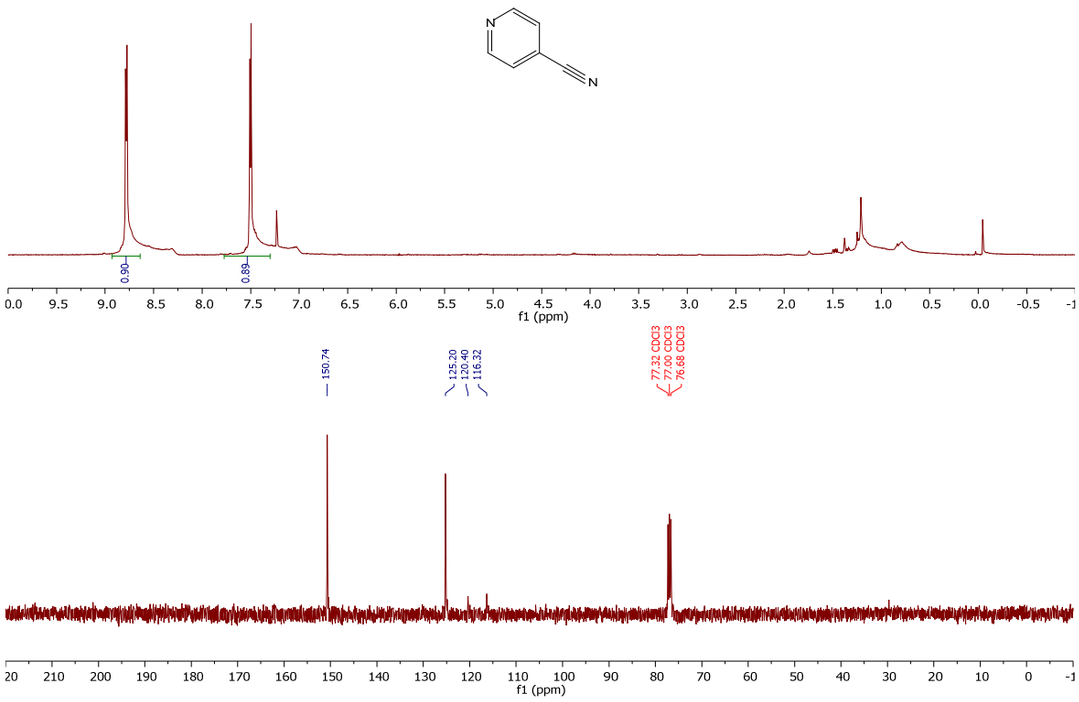
(T3D) DJQ-173-1



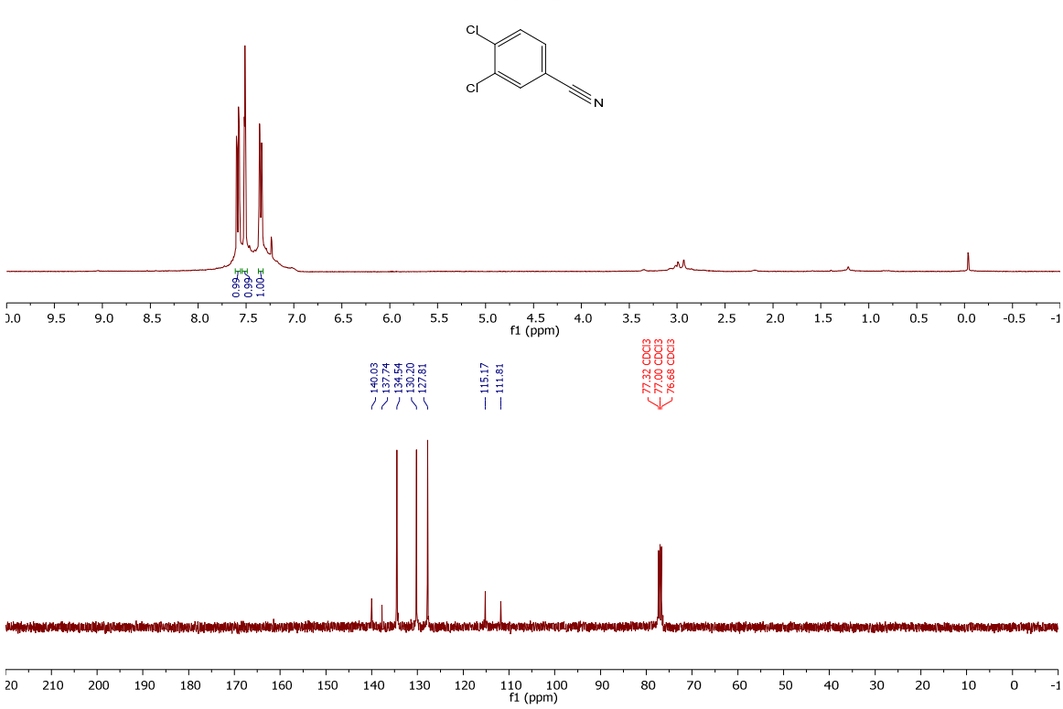
(T3E) DJQ-143-11

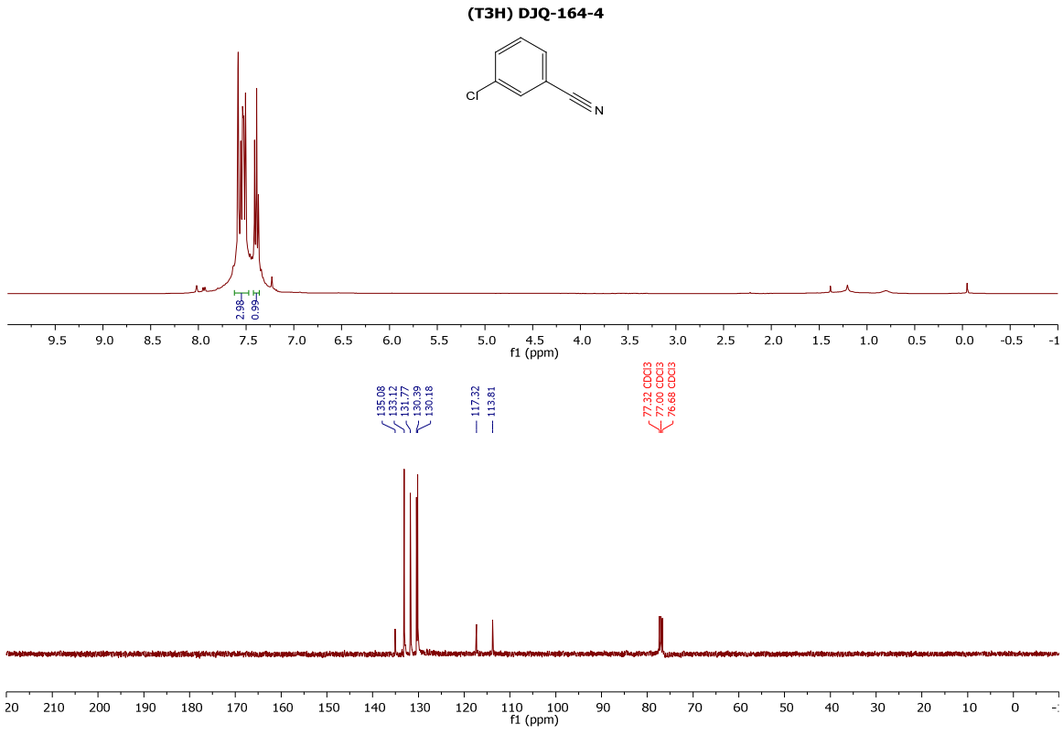


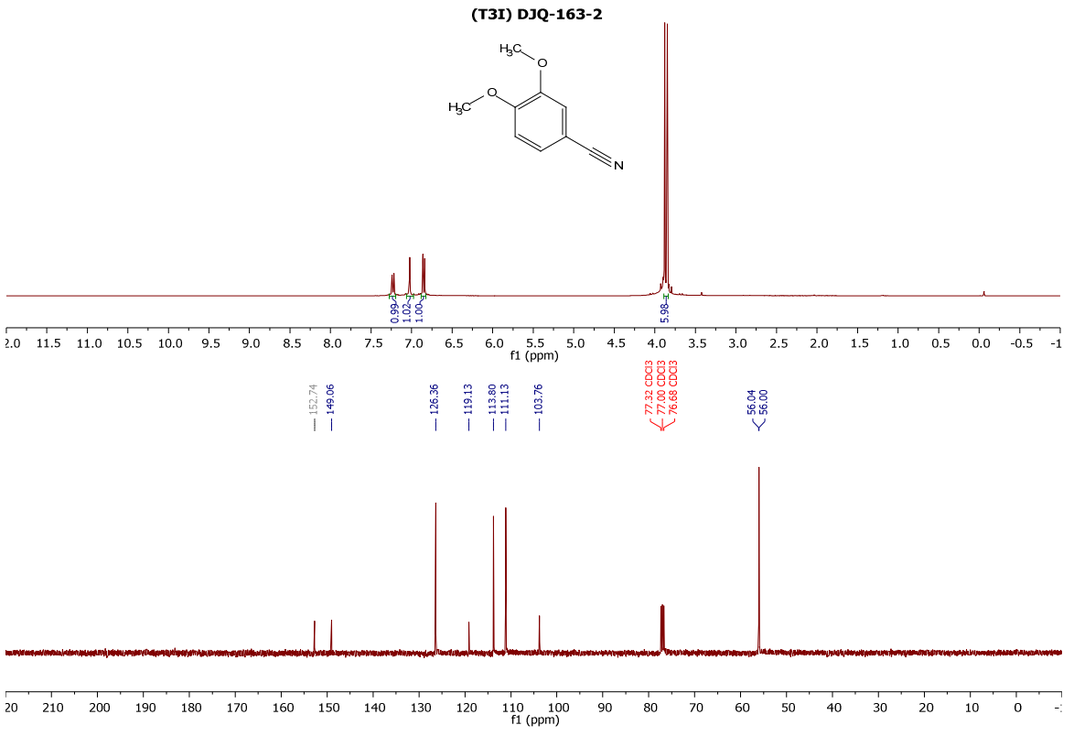
(T3F) DJQ-133-1



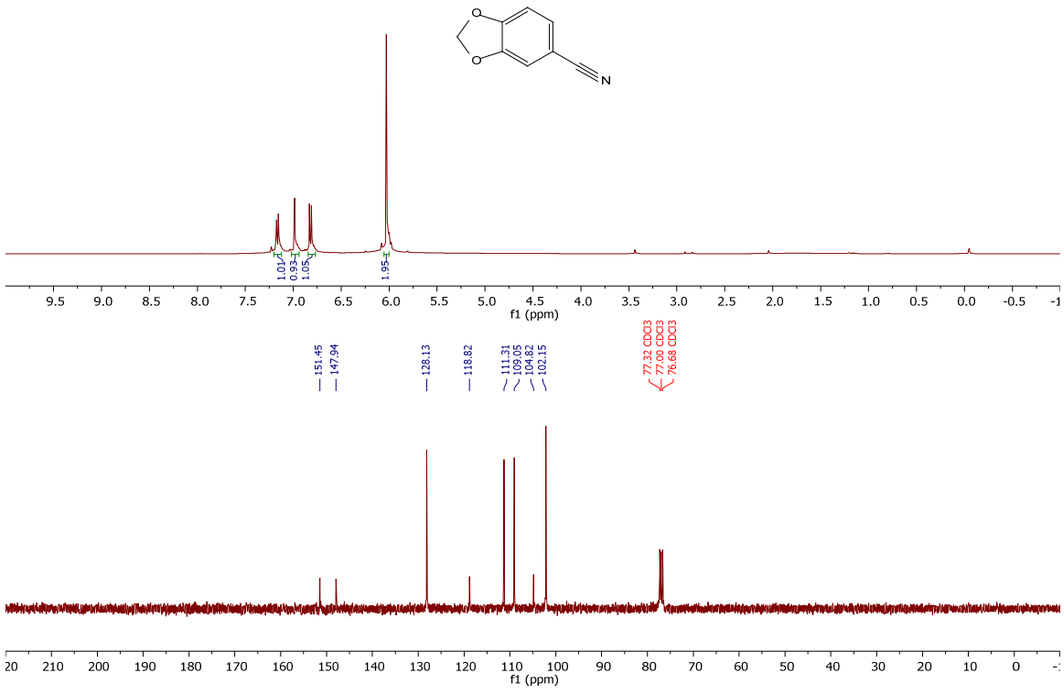
(T3G) DJQ-149



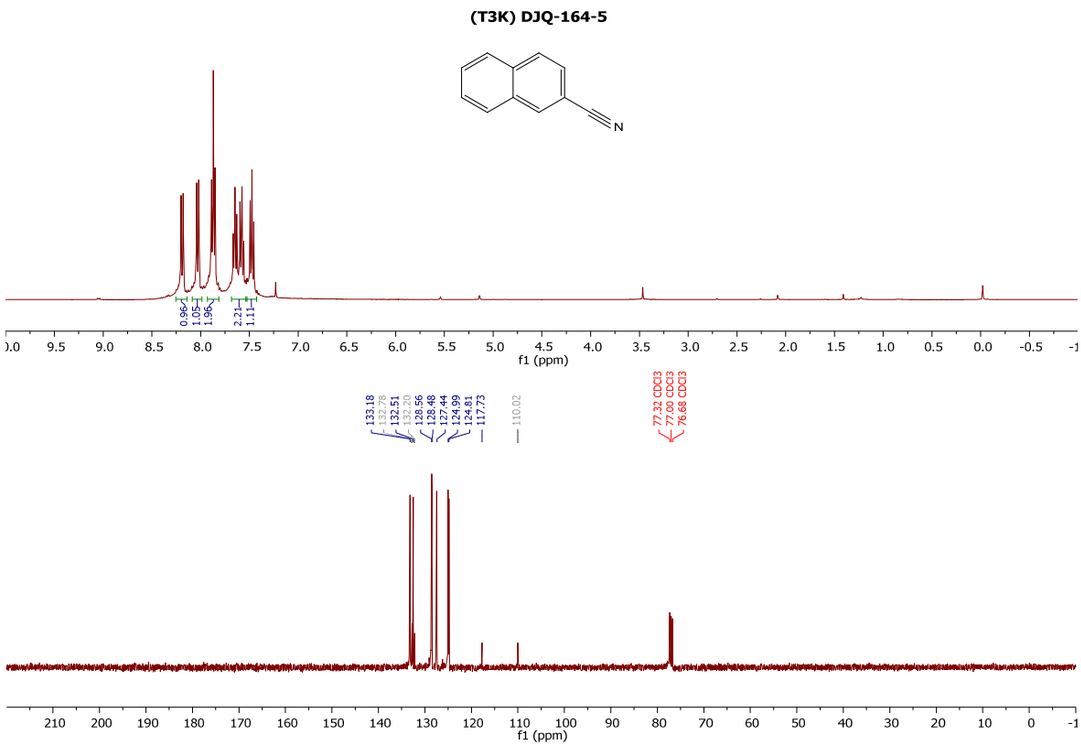




(T3J) DJQ-163-1



(T3K) DJQ-164-5



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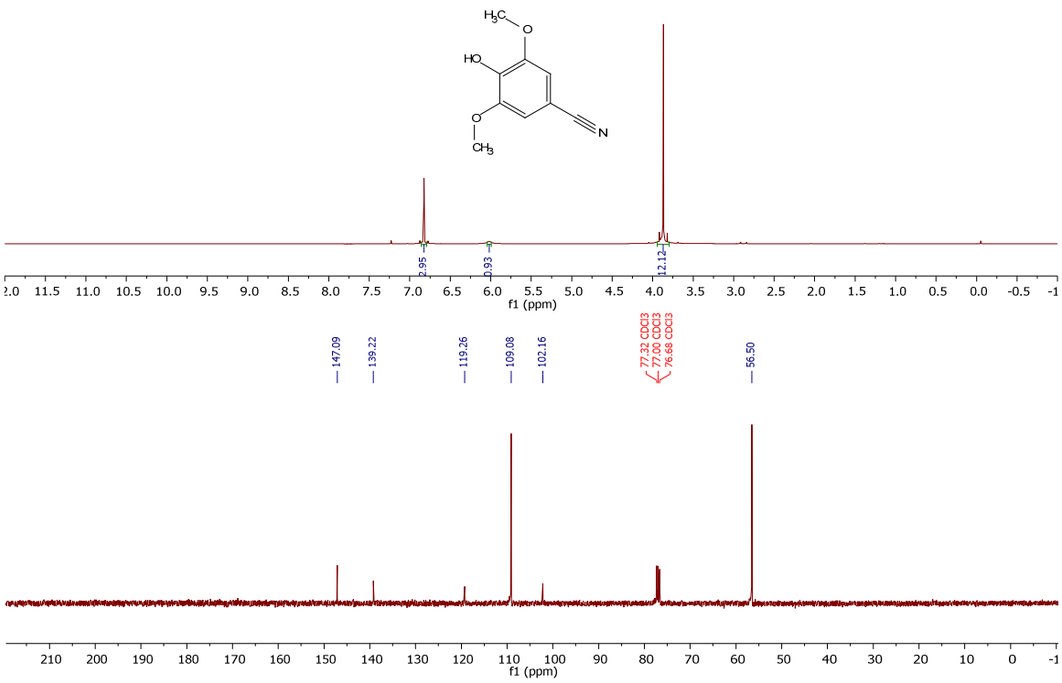

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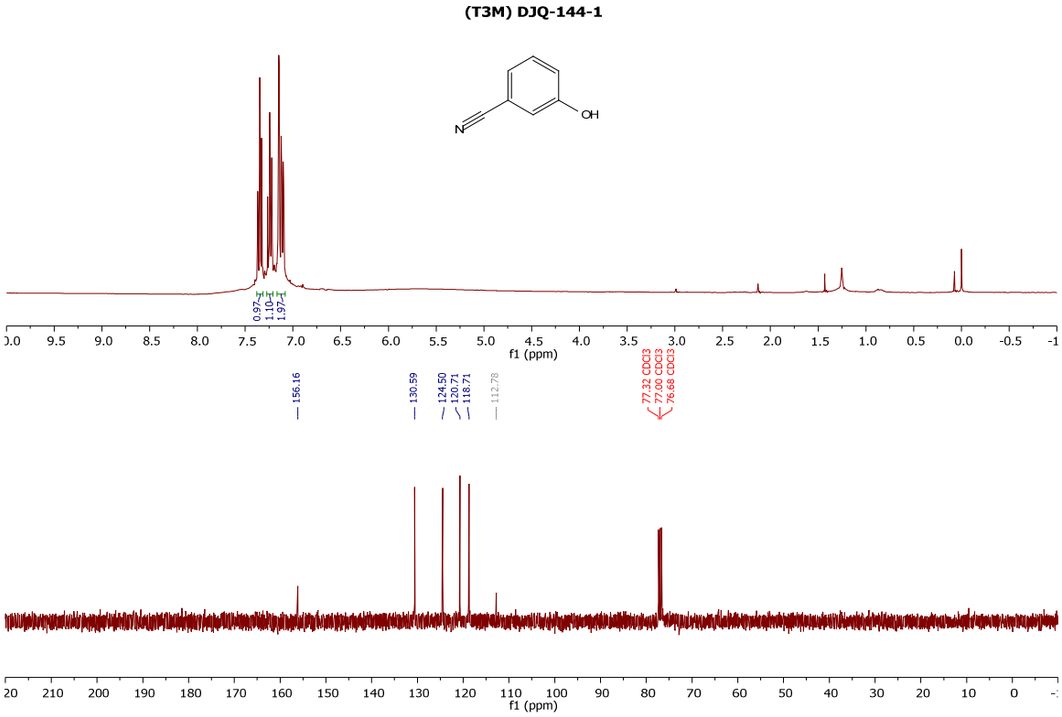
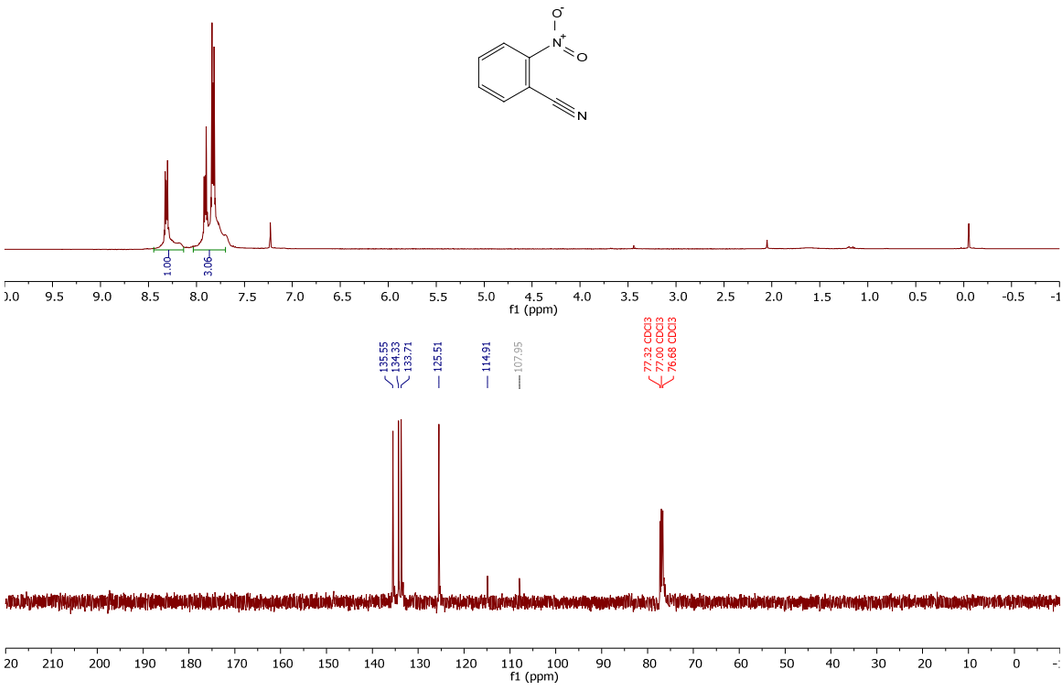
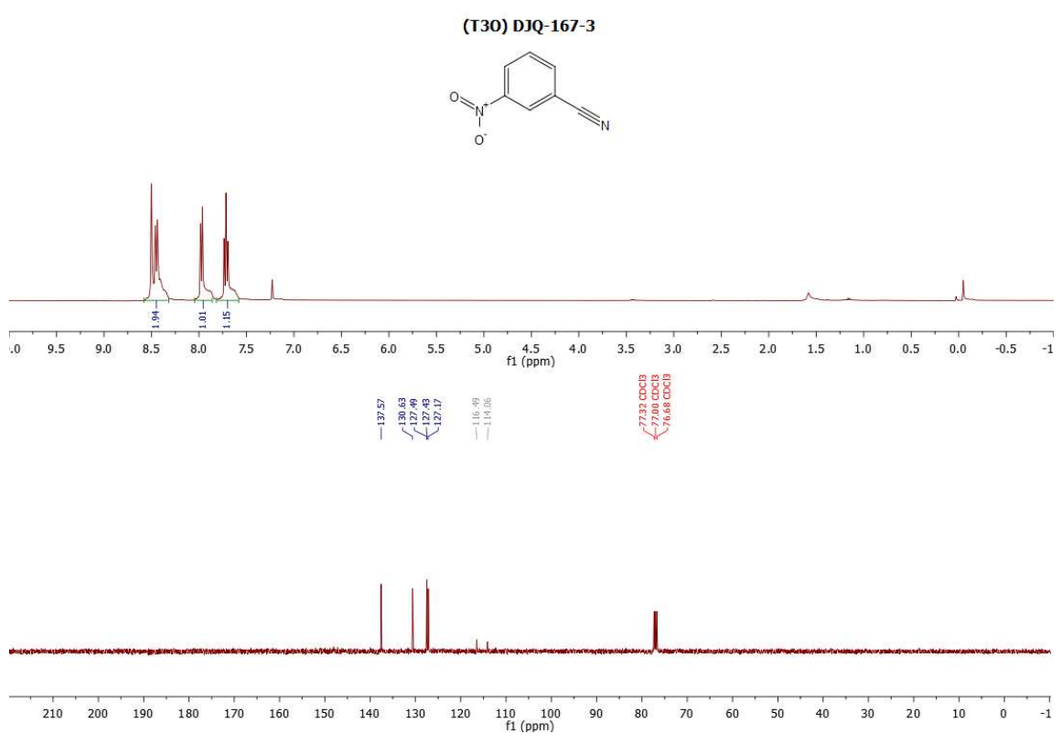


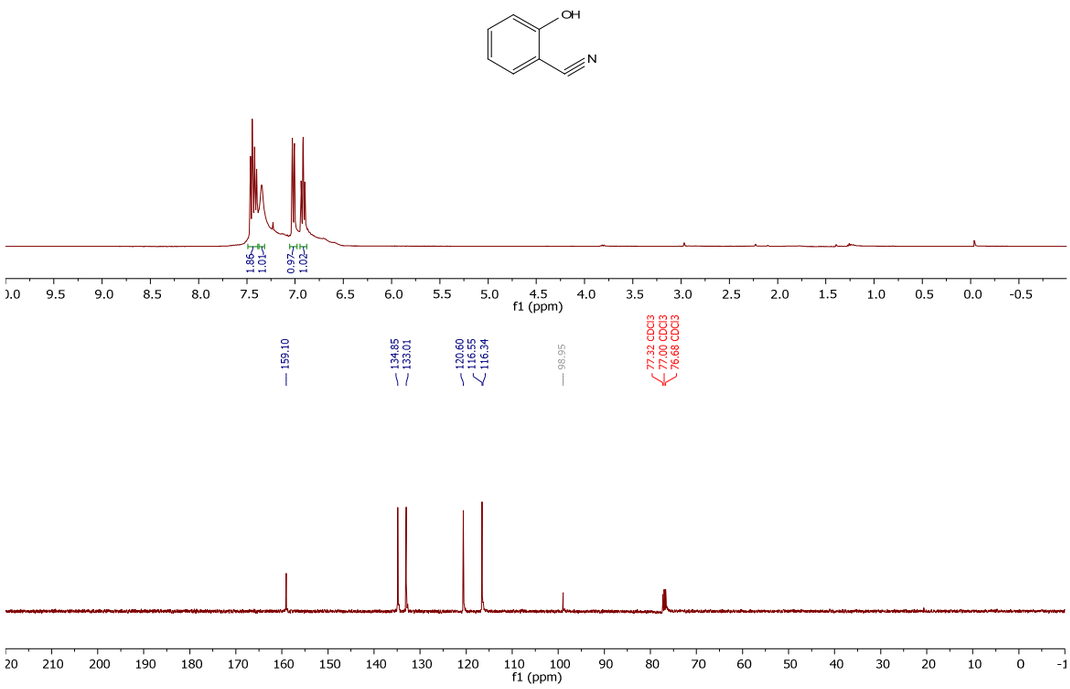
(T3N) DJQ-163-3



(T3O) DJQ-167-3



(T3P) DJQ-152



Chapter 3

Nitrone Dipolar Cycloaddition

3.1 Introduction to the Nitrone Dipolar Cycloaddition

Isoxazolidines (Figure 9) have been a relevant pharmaceutical scaffold for the last 50 years and even appear in many commercially available drugs.[79-83] This scaffold has also been found to have biological activity while also mimicking a wide range of natural building blocks.[84-88] The synthesis of this scaffold has been an important part of organic chemistry for these reasons.

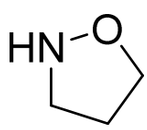


Figure 9. General Structure of an Isoxazolidine

The most successful reaction for the synthesis of isoxazolidines has been the 1, 3-dipolar cycloaddition of nitrones (Figure 10) with an α, β-unsaturated aldehyde.[89-93] This reaction has a high energetic demand[94] that is usually countered through Lewis acid catalysis that is able to enhance the conversion, scope, reaction rates, and the different types of selectivites such as regio-, enantio-, and diastero-.[95-99]

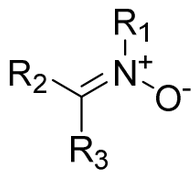


Figure 10. General Structure of a Nitrone

Previous research has shown that when a nitrone is reacted in the presences of an Fe or Ru Lewis acid catalyst produced the endo product of the [3+2] cycloaddition. This high preference for the endo product as seen by the Kündig group did not allow for an exo selective Ru catalyst to be used. The low solubility of nitrones also caused a different set of nitrones to be considered due to the long reaction times and the low stability of the Fe catalyst. Using a cyclic set of nitrones Kündig was able to use the Fe or Ru catalysts which led to excellents yields and moderate stereoselectivity. When compared it was seen that the Fe catalyst was better than the Ru catalyst in terms of selectivity due to the Fe catalyst having a larger catalyst site while, the Ru catalyst was a slightly weaker Lewis acid.

Even though these Lewis acid catalyzed reactions do enhance the regio- and diastereoselectivities there are no clear trends that allow for the prediction of these outcomes.[100, 101] Some computational studies have shown that there exists an electronic bias for the 3, 5-isoxazolidine when carbonyls and cyano groups are on the dipolarophile. These studies have also shown that the 3, 4-isoxazolidine is favored with other electron withdrawing groups on the dipolarophile.[102] Similar calculations show a clear preference for the endo product (Figure) while, also predicting that thermal or Lewis acid promoted nitrone dipolar cycloadditions have similar regioselective tendencies.[103-115] There are no reported efforts to rationalize these tendencies.

There are a variety of methods to obtain substituted nitrones for cycloadditions depends upon the added functionality of the nitrone.[90, 116-122] Vinyl nitrones are a specific type of nitrone that allow for the synthesis of highly complex heterocycles. These nitrones

are synthesized through the condensation of conjugated carbonyls and hydroxylamines.[123-125] With these two substrates a highly functionalized isoxazolidine can be synthesized.[126]

3.2 Pharmaceutical Relevance

Resistant antibiotic bacterial strains have resulted in a large demand for small molecule antibiotics. Beta Lactams have historically filled this rule since the advent of penicillin due to their powerful antibacterial properties.

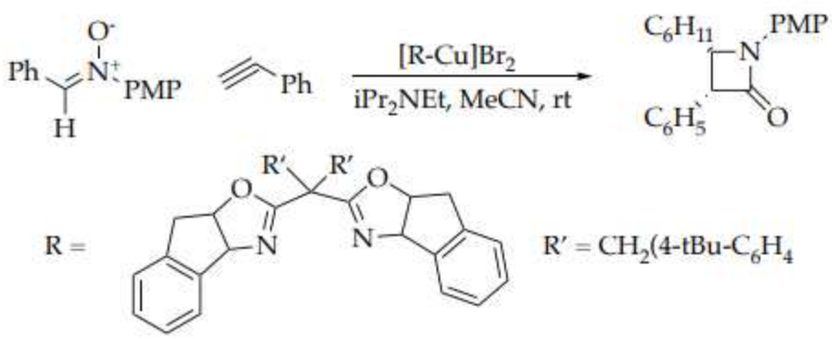


Figure 11. Enantioselective Synthesis of Beta Lactams

Using nitrones an enantioselective synthesis of beta lactams (Figure 11) has significant applications in the pharmaceutical industry.[127] Even though lactams have been historically used for bacterial infection treatment, new structural motifs are becoming more required to fight bacterial evolution. One motif can be synthesized from the isoxazolidine scaffold.

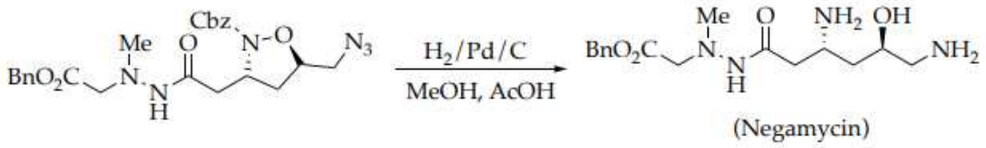


Figure 12. Reductive Cleavage of N-O Bond to Afford Negamycin

Through reductive cleavage of the nitrogen-oxygen bond pharmaceutically relevant amino acids can be formed (Figure 12). With the conformation of the isoxazolidine preserved the total synthesis of the natural product, Negamycin can be achieved.[128] This natural product has several functional groups that can be modified to produce novel antibacterial pharmaceuticals.

3.3 Results and Discussion

With the importance of highly structured isoxazolidines, a library of 3-Vinyl-4-Carbonyl-Isoxazolidines from conjugated carbonyls and simple hydroxylamines was synthesized. This synthesis followed the mechanism of a traditional [3+2] cycloaddition.

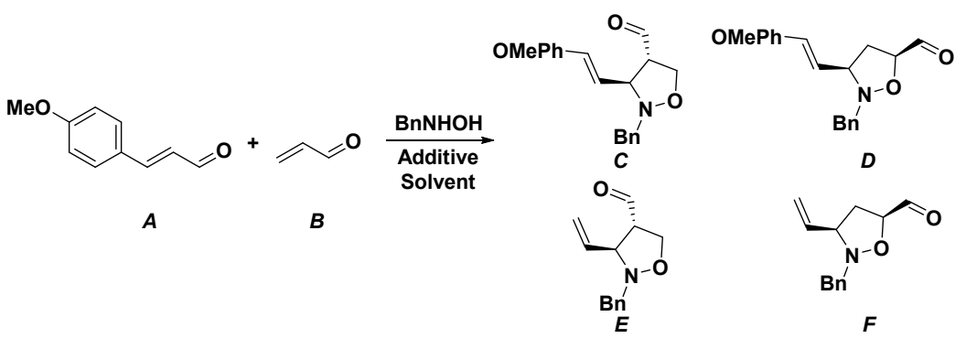
During optimization studies after acrolein (Table 8 -B) underwent a condensation with N-Benzylhydroxylamine, the resulting product underwent a dipolar cycloaddition with unreacted acrolein instead of the dipolarphile (Table 8 - A). This reaction led us to hypothesis the optimal enal - dipolarphile pair. This hypothesized pair made the reaction able to proceed as a one pot conversion without losing chemoselectivity.

Temperature was screened next to determine if the yield of the reaction would increase. It was found that increasing the temperature to 80˚C afforded the highest percent yield while going past this point reduced the diastereoselective of the reaction (Table 8, Entry 7 and 8). Decreasing the temperature did not help improve the diastereoselectivity and decreased the conversion to the desired cycloadduct (Table 8, Entry 6).

While trying to lower the energetic requirement for this reaction several Lewis acid metal catalysts were tested. The rates of the reaction were noticed to increase along with a modest increase in diasteroselectivity, while the percent yield of the reaction decreased (Table 8, Entry 12). The small increase in diasteroselectivity with the Lewis acid metal catalysts did not make up for the loss in percent yield and so thermal conditions remained the most optimal.

Table 8

3-Vinyl-4-Carbonyl-Isoxazolidine Reaction Optimization



A ***B*** ***C*** ***D*** ***E*** ***F***

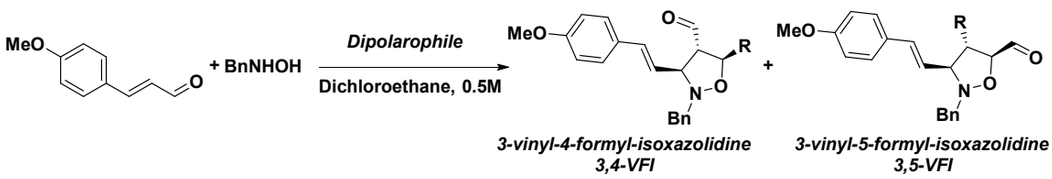
Entry[a]	Enal	Dipolarophile	Additive[e]	Solvent	Time	Temperature	%Yield of ***C:D:E:F***[b]	d.r[c]
1	***B***	***B***	none	DCE	48h	rt	0:0:20:2	8:1
2	***B***[d]	***A***	none	DCE	48h	rt	5:1:10:2	8:1
3	***B***	***A***	none	DCE	48h	rt	8:2:6:2	6:1
4	***A***	***B***	none	DCE	48h	rt	40:4:0:0	10:1
5	***A***	***B***	none	DCE	48h	40 °C	53:6:0:0	15:1
6	***A***	***B***	none	DCE	16h	60 °C	64:9:0:0	15:1
7	***A***	***B***	none	DCE	16h	80 °C	88:4:0:0	15:1
8	***A***	***B***	none	DCE	18h	90 °C	80:16:0:0	10:1
9	***A***	***B***	none	dioxane	16h	80 °C	80:4:0:0	15:1
10	***A***	***B***	none	Acetonitrile	16h	80 °C	73:8:0:0	15:1
11	***A***	***B***	none	DMF	16h	80 °C	64:12:0:0	15:1
12	***A***	***B***	$Cu(OTf)_2$	DCE	6h	rt	64:28:0:0	20:1
13	***A***	***B***	$Cu(OAc)_2$	DCE	6h	rt	35:24:0:0	20:1
14	***A***	***B***	AgOTf	DCE	6h	rt	53:22:0:0	20:1
15	***A***	***B***	AuOTf	DCE	6h	rt	48:20:0:0	15:1
16	***A***	***B***	$Fe(OTf)_3$	DCE	6h	rt	46:32:0:0	15:1

a. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. b. Isolated yields. c. Ratio for the major isomer, measured by ^{1}H-NMR. d. ratio of enal:dipolarophile is 1:1. e. Lewis acid were added in 20 mol%.

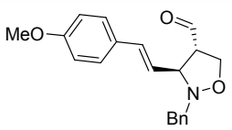
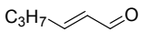
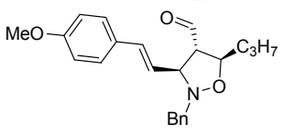
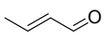
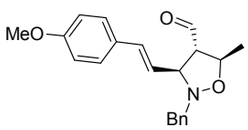
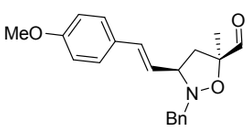
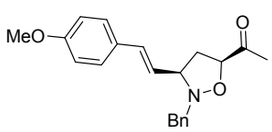
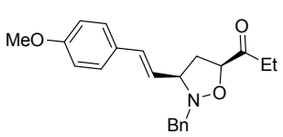
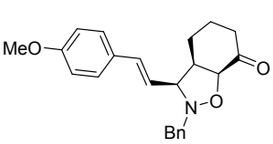
With the optimal conditions we set out to determine the scope of this reaction. Cinnamaldehyde was reluctant to perform the cycloaddition as a dipolarphile so para-methoxy cinnamaldehyde was used instead. This prevented any side cycloadditions as previously seen with cinnamaldehyde allowing the reaction to be a one pot reaction. Simple enals and enones were observed to be suitable dipolarphiles. Straight enal alkyl chains showed traces of regioexcess (Table 9, Entry 1-3), while enal alkyl chain branching afforded complete regioselectivity as observed in methacrolein (Table 9, Entry 4). Similar regioselectivity was seen in both cyclic and acyclic ketones. This similarity did see a drop in diasteroselectivity (Table 9, Entry 4-7).

Table 9

Dipolarphile Scope: Aldehydes and Ketones



3-vinyl-4-formyl-isoxazolidine 3,4-VFI ***3-vinyl-5-formyl-isoxazolidine 3,5-VFI***

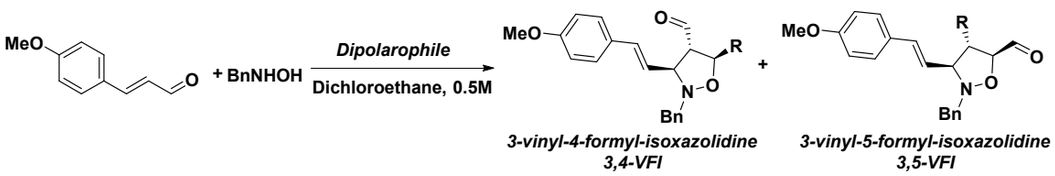
Entry[1]	Dipolarophile	Product	%Yield of ***3,4-VCI***[2]	%Yield of ***3,5-VCI***[2]	d.r.[3]
1			88	4	15:1
2			90	2	16:1
3			84	4	15:1
4			0	91	12:1
5			0	90	12:1
6			0	92	12:1
7			0	73	12:1

1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Ratio for the major isomer, measured by ^{1}H-NMR.

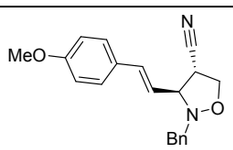
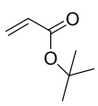
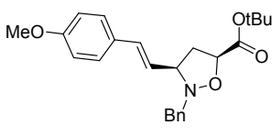
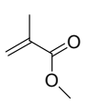
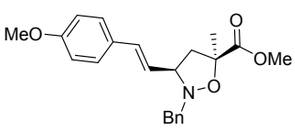
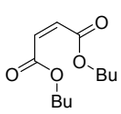
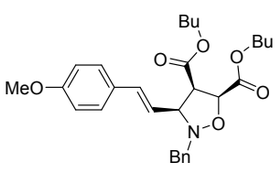
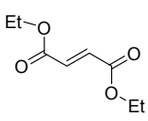
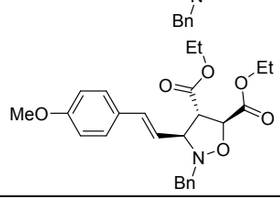
The scope was expanded further by changing the functional group of the enal. Acrylonitrile was used as a dipolarphile and afforded the 3-Vinyl-4-Formyl-Isoxazolidine (Table 10, Entry 1). Bulkier esters were found to produce the 3-Vinyl-5-Formyl-Isoxazolidine (Table 10, Entry 4 & 5).

Table 10

Dipolarphile Scope: Nitriles and Esters



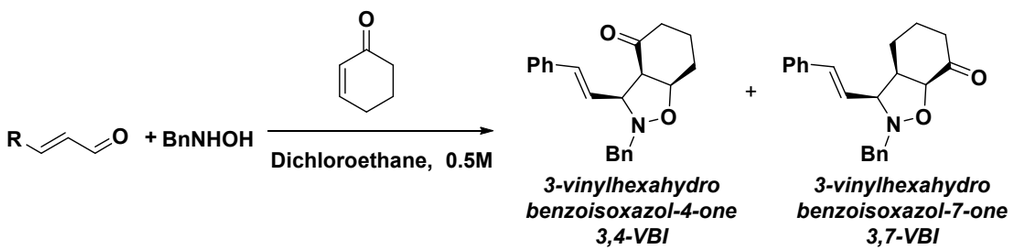
3-vinyl-4-formyl-isoxazolidine 3,4-VFI ***3-vinyl-5-formyl-isoxazolidine 3,5-VFI***

Entry[1]	Dipolarophile	Product	%Yield of ***3,4-VFI***[2]	%Yield of ***3,5-VFI***[2]	d.r.[3]
1			95	0	15:1
2			0	91	16:1
3			0	84	15:1
4			88		18:1
5			89		18:1

1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Measured by ^{1}H-NMR.

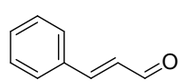
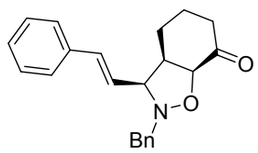
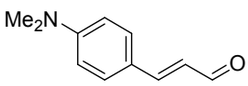
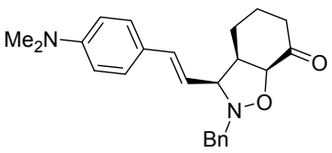
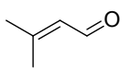
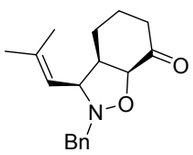
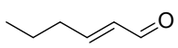
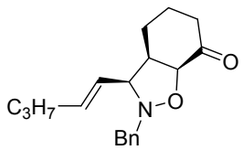
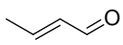
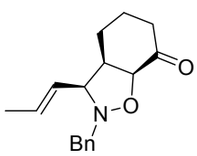
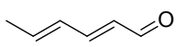
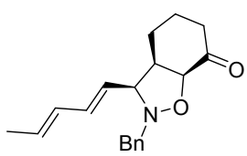
Table 11

Dipole Scope



3-vinylhexahydro benzoisoxazol-4-one 3,4-VBI

3-vinylhexahydro benzoisoxazol-7-one 3,7-VBI

Entry[1]	Enal	Product	% of ***3,4-VBI***[2]	% of ***3,7-VBI***[2]	d.r.[3]
1			0	73	15:1
2			0	79	16:1
3			0	88	15:1
4			0	84	12:1
5			0	86	12:1
6			0	80	14:1

1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Measured by ^{1}H-NMR.

3.4 Conclusion

This method shows the regioselectivity of conjugated dipolarphiles to produce either the 3-Vinyl-4-Formyl-Isoxazolidine or the 3-Vinyl-5-Formyl-Isoxazolidine selectively. The scope of this reactions extends to aliphatic enals, conjugated nitriles and esters, and enones with a diverse substitution with no need for cumbersome purifications

while maintaining excellent yields. The high selectivity can be attributed to the orthogonal reactivity of bulky substituted conjugated carbonyls as enals and unsubstituted conjugated carbonyls as dipolarophiles. The regioselectivity of the diplolar cycloaddition is determined through the substitution pattern of the dipolarophile. The above-mentioned selectivity inhibits the formation of background products making the overall method simple and highly efficient.

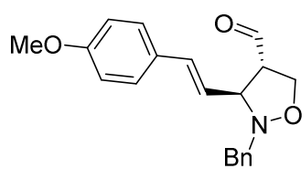
3.5 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4- mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$). Silica flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Automated chromatography was performed on a ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0- 20% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.23 ppm; ^{13}C, 77.0 ppm; coupling constants are expressed in Hz).

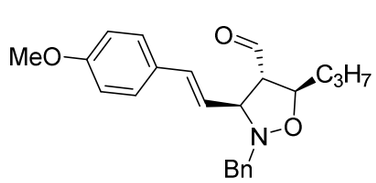
3.5.1. General method for the synthesis of Vinyl Isozazolidines. In a 4- mL glass vial, 1 mMol enal and 1.1 eq. hydroxylamine were dissolved in 1 mL acetonitrile. The mixture was stirred at room temperature for five minutes after which 3 molar equivalents dipolarphile was added. The reaction was stirred vigorously at 80°C for 16 hours. The organic was extracted with 150 mL diethyl ether. The organic layer was washed with 3-25 mL aliquots of (10%) aqueous sodium bicarbonate. The organic layer was dried with 3-25 mL aliquots of saturated aqueous brine solution (NaCl). The organic layer is finally isolated and dried over anhydrous sodium sulfate, filtered, and

concentrated by rotary evaporation to afford the crude product. The crude product is filtered through silica gel over a gradient of 4:1 Heptanes/EtOAc over 12 column volumes to obtain the respective isoxazolidine in good to excellent yields.

3.5.2. Synthesis of Vinyl Isoxazolidines from Table 9 and 11.

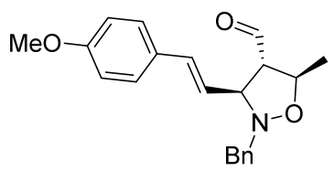


(3S,4S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidine-4-carbaldehyde (T2A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2a** (115mg, 90%) as a yellow oil. **TLC:** R_f 0.20 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.74 (dd, J = 2.4, 0.7 Hz, 1H), 7.41 - 7.26 (m, 7H), 6.89 - 6.82 (m, 2H), 6.60 (d, J = 15.8 Hz, 1H), 6.08 (dd, J = 15.8, 8.5 Hz, 1H), 4.23 (dd, J = 8.9, 4.0 Hz, 1H), 4.15 - 4.07 (m, 2H), 3.80 (d, J = 0.7 Hz, 3H), 3.77 (d, J = 14.0 Hz, 1H), 3.61 (t, J = 8.3 Hz, 1H), 3.31 (dddd, J = 8.3, 7.1, 3.9, 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.82, 159.67, 137.14, 134.53, 128.78, 128.26, 127.82, 127.30, 123.05, 114.03, 65.45, 61.61, 55.27.

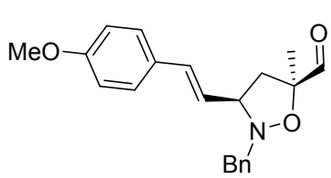


(3S,4S,5R)-2-benzyl-3-((E)-4-methoxystyryl)-5-propylisoxazolidine-4-carbaldehyde (T2B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2b** (100mg, 70%) as a yellow oil. **TLC:** R_f 0.20 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (dd, J = 2.7, 0.7 Hz, 1H),

7.52 - 7.24 (m, 7H), 6.96 - 6.84 (m, 2H), 6.54 (d, J = 15.8 Hz, 1H), 6.06 (dd, J = 15.7, 8.5 Hz, 1H), 4.51 - 4.17 (m, 1H), 4.13 (d, J = 14.3 Hz, 1H), 3.81 (d, J = 0.7 Hz, 3H), 3.77 - 3.61 (m, 1H), 3.01 (ddd, J = 7.8, 5.4, 2.7 Hz, 1H), 1.87 (dddd, J = 13.4, 9.7, 7.8, 5.6 Hz, 1H), 1.60 (ddt, J = 13.5, 9.6, 5.9 Hz, 1H), 1.47 - 1.30 (m, 2H), 0.93 (td, J = 7.4, 3.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.89, 159.62, 137.34, 133.85, 128.55, 128.16, 127.81, 127.08, 123.69, 114.03, 76.92, 76.46, 67.75, 55.30, 37.26, 19.16, 13.87.

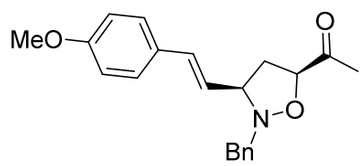


(3S,4S,5R)-2-benzyl-3-((E)-4-methoxystyryl)-5-methylisoxazolidine-4-carbaldehyde (T2C): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2c** (85mg, 70%) as a plae oil. **TLC**: R_f 0.31 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (t, J = 2.0 Hz, 1H), 7.39 - 7.25 (m, 9H), 6.88 - 6.85 (m, 2H), 6.53 (d, J = 15.9 Hz, 1H), 6.13 - 6.05 (m, 1H), 4.52 - 4.47 (m, 1H), 4.13 (d, J = 14.2 Hz, 1H), 3.85 (d, J = 14.3 Hz, 1H), 3.81 (d, J = 1.5 Hz, 3H), 3.75 (d, J = 6.7 Hz, 1H), 2.97 (s, 1H), 1.43 (dd, J = 6.2, 1.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.76 , 133.80 , 128.56 , 128.23 , 127.81 , 127.15 , 123.75 , 114.04 , 73.10 , 68.94 , 59.37 , 55.30 , 20.72 .

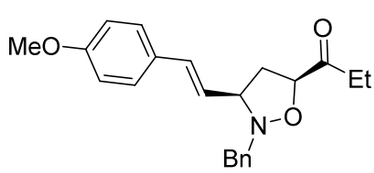


(3R,5S)-2-benzyl-3-((E)-4-methoxystyryl)-5-methylisoxazolidine-5-carbaldehyde (T2D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2d** (165mg, 90%) as a yellow oil. **TLC:** R_f 0.35 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.39 (d, J = 7.1

Hz, 2H), 7.35 - 7.29 (m, 4H), 7.25 (tt, J = 6.0, 1.6 Hz, 1H), 6.93 - 6.78 (m, 2H), 6.53 (d, J = 15.8 Hz, 1H), 5.89 (ddd, J = 15.8, 8.8, 0.6 Hz, 1H), 4.19 (d, J = 14.8 Hz, 1H), 3.81 (d, J = 0.6 Hz, 3H), 3.76 (d, J = 14.8 Hz, 1H), 3.43 (q, J = 8.3 Hz, 1H), 2.52 (dd, J = 12.7, 7.8 Hz, 1H), 2.25 (dd, J = 12.7, 8.4 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 205.12, 133.59, 128.35, 128.18, 127.72, 127.08, 124.71, 114.02, 69.67, 59.15, 55.30, 44.00, 19.07.

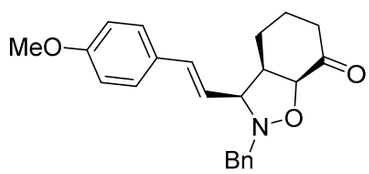


1-((3R,5S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidin-5-yl)ethan-1-one (T2E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2e** (180mg, 80%) as a yellow oil. **TLC:** R_f 0.45 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, J = 7.1 Hz, 2H), 7.33 (ddd, J = 4.3, 2.5, 1.3 Hz, 4H), 7.28 - 7.22 (m, 1H), 6.91 - 6.81 (m, 2H), 6.55 (d, J = 15.8 Hz, 1H), 5.91 (dd, J = 15.8, 8.6 Hz, 1H), 4.28 (dd, J = 9.5, 4.7 Hz, 1H), 4.17 (d, J = 14.1 Hz, 1H), 3.80 (d, J = 0.8 Hz, 3H), 3.69 (d, J = 14.1 Hz, 1H), 3.34 (q, J = 8.3 Hz, 1H), 2.71 (ddd, J = 12.8, 9.4, 7.8 Hz, 1H), 2.38 (ddd, J = 13.0, 8.5, 4.7 Hz, 1H), 2.10 (d, J = 0.8 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 133.77, 128.88, 128.11, 127.68, 127.18, 124.50, 114.00, 80.46, 69.38, 59.72, 55.27, 38.97, 25.35.

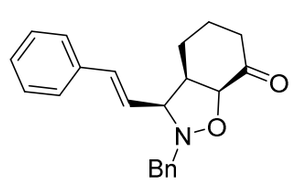


1-((3R,5S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidin-5-yl)propan-1-one(T2F): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2f** (105mg, 70%) as a pale oil. **TLC:** R_f 0.50 (3:1

heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 - 7.21 (m, 8H), 6.89 - 6.83 (m, 2H), 6.54 (d, J = 15.8 Hz, 1H), 5.91 (dd, J = 15.9, 8.5 Hz, 1H), 4.33 (dd, J = 9.4, 4.9 Hz, 1H), 4.16 (d, J = 14.1 Hz, 1H), 3.81 (d, J = 0.7 Hz, 3H), 3.69 (d, J = 14.1 Hz, 1H), 3.35 (q, J = 8.3 Hz, 1H), 2.75 - 2.68 (m, 1H), 2.65 - 2.56 (m, 1H), 2.46 (ddd, J = 11.5, 7.2, 4.4 Hz, 1H), 2.42 - 2.36 (m, 1H), 0.95 (td, J = 7.3, 0.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.51 , 137.57 , 133.73 , 128.89 , 128.10 , 127.70 , 127.19 , 124.59 , 114.02 , 69.45 , 59.76 , 55.30 , 39.09 , 30.54 , 7.13 .

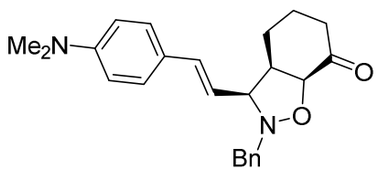


(3S,3aR,7aS)-2-benzyl-3-((E)-4-methoxystyryl)hexahydrobenzo[d]isoxazol-7(4H)-one (T2G): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **2g** (110mg, 65%) as a yellow oil. **TLC:** R_f 0.15 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.34 (m, 2H), 7.34 - 7.26 (m, 4H), 7.24 - 7.20 (m, 1H), 6.87 - 6.81 (m, 2H), 6.58 (d, J = 15.8 Hz, 1H), 6.09 - 6.00 (m, 1H), 4.56 (dt, J = 7.7, 4.3 Hz, 1H), 4.09 (d, J = 14.1 Hz, 1H), 3.87 - 3.78 (m, 5H), 2.99 (t, J = 6.7 Hz, 1H), 2.50 (dt, J = 17.0, 5.1 Hz, 1H), 2.33 (ddd, J = 16.6, 10.2, 6.1 Hz, 1H), 2.06 - 1.96 (m, 1H), 1.95 - 1.87 (m, 2H), 1.86 - 1.78 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.44 , 133.07 , 128.91 , 128.16 , 127.70 , 127.15 , 125.01 , 113.90 , 70.47 , 60.77 , 55.24 , 39.88 , 26.43 , 19.01 .

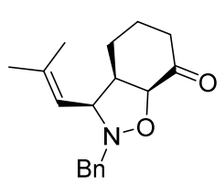


(3S,3aR,7aS)-2-benzyl-3-((E)-styryl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4a** (165mg, 92%) as a white solid. TLC: R_f 0.25 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.2, 6.5 Hz, 4H), 7.32 (t, J

= 7.4 Hz, 4H), 7.28 - 7.23 (m, 2H), 6.67 (d, J = 15.9 Hz, 1H), 6.22 (dd, J = 15.9, 7.9 Hz, 1H), 4.59 (dt, J = 7.8, 4.3 Hz, 1H), 4.10 (d, J = 14.0 Hz, 1H), 3.93 (dd, J = 7.9, 5.9 Hz, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.01 (t, J = 6.6 Hz, 1H), 2.52 (dt, J = 16.8, 5.0 Hz, 1H), 2.36 (ddd, J = 16.5, 10.2, 6.2 Hz, 1H), 2.09 - 1.99 (m, 1H), 1.93 (dq, J = 9.8, 4.4 Hz, 2H), 1.84 (ddd, J = 14.0, 7.1, 3.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.20, 137.41, 136.48, 133.49, 128.99, 128.55, 128.23, 127.82, 127.49, 127.25, 126.54, 76.77, 70.16, 60.75, 60.50, 40.02, 26.42, 19.17.

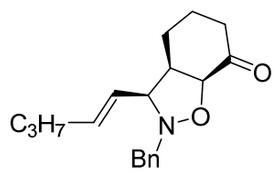


(3S,3aR,7aS)-2-benzyl-3-((E)-4-(dimethylamino)styryl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4b** (178mg, 70%) as a red oil. TLC: Rf 0.19 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 - 7.28 (m, 6H), 7.25 - 7.22 (m, 1H), 6.67 (dd, J = 8.9, 2.6 Hz, 2H), 6.56 (d, J = 15.8 Hz, 1H), 5.98 (ddd, J = 15.7, 8.1, 1.0 Hz, 1H), 4.57 (dt, J = 7.6, 4.2 Hz, 1H), 4.12 (d, J = 14.1 Hz, 1H), 3.80 (d, J = 10.6 Hz, 1H), 3.01 (t, J = 6.9 Hz, 1H), 2.96 (d, J = 1.0 Hz, 6H), 2.54 - 2.30 (m, 3H), 2.09 - 1.92 (m, 2H), 1.91 - 1.82 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.42, 150.26, 137.60, 133.80, 128.98, 128.17, 127.56, 127.13, 122.60, 122.53, 112.32, 76.72, 70.95, 60.91, 60.13, 40.49, 39.81, 26.54, 18.96.

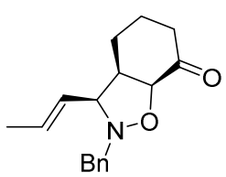


(3S,3aR,7aS)-2-benzyl-3-(2-methylprop-1-en-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4d** (100mg, 88%) as a yellow oil. **TLC:** R_f 0.40 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 4H), 7.25 - 7.21

(m, 1H), 5.19 (ddd, J = 9.4, 2.5, 1.3 Hz, 1H), 4.55 - 4.48 (m, 1H), 3.98 (d, J = 14.1 Hz, 1H), 3.87 (s, 1H), 3.76 (d, J = 14.1 Hz, 1H), 2.88 (t, J = 7.3 Hz, 1H), 2.47 (dt, J = 17.0, 5.1 Hz, 1H), 2.36 - 2.28 (m, 1H), 2.08 - 1.98 (m, 1H), 1.88 - 1.78 (m, 3H), 1.71 (dd, J = 16.9, 1.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.84, 137.68, 136.10, 128.81, 128.13, 127.08, 76.57, 66.73, 61.00, 39.49, 26.65, 26.05, 18.67, 18.47.

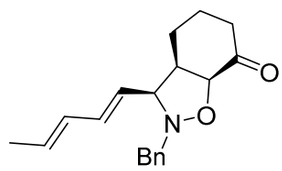


(3S,3aR,7aS)-2-benzyl-3-((E)-pent-1-en-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4e** (110mg, 80%) as a yellow oil. **TLC:** R_f 0.42 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 5.9, 1.9 Hz, 3H), 7.31 (d, J = 7.1 Hz, 2H), 5.70 (dt, J = 15.3, 6.8 Hz, 1H), 5.46 - 5.39 (m, 1H), 4.50 (dt, J = 8.0, 4.2 Hz, 1H), 4.05 (d, J = 14.1 Hz, 1H), 3.75 (d, J = 14.1 Hz, 1H), 3.58 (t, J = 7.6 Hz, 1H), 2.92 (t, J = 7.2 Hz, 1H), 2.50 - 2.45 (m, 1H), 2.31 (ddd, J = 16.7, 10.1, 6.2 Hz, 2H), 2.01 (d, J = 7.3 Hz, 2H), 1.90 - 1.81 (m, 3H), 1.38 (d, J = 7.3 Hz, 2H), 0.87 (d, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.49, 137.56, 135.84, 128.92, 128.87, 128.16, 127.12, 76.37, 70.71, 60.66, 59.94, 39.64, 34.39, 26.56, 22.13, 18.77, 13.59.



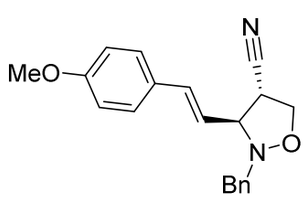
(3S,3aR,7aS)-2-benzyl-3-((E)-prop-1-en-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4F): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4f** (209mg, 70%) as a yellow oil. **TLC:** R_f 0.38 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.25 - 7.20 (m, 1H), 5.78 - 5.65 (m, 1H), 5.45 (ddd, J = 15.2, 8.4, 2.0

Hz, 1H), 4.48 (dt, J = 8.1, 4.2 Hz, 1H), 4.09 - 4.00 (m, 1H), 3.76 (dd, J = 19.8, 14.1 Hz, 1H), 3.56 (t, J = 7.5 Hz, 1H), 2.90 (t, J = 7.3 Hz, 1H), 2.46 (dt, J = 16.5, 5.1 Hz, 1H), 2.34 - 2.23 (m, 1H), 2.03 - 1.95 (m, 1H), 1.88 - 1.76 (m, 3H), 1.70 (dd, J = 6.5, 1.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.51, 137.51, 130.50, 128.82, 128.06, 127.07, 76.26, 70.68, 60.42, 39.54, 26.44, 18.63, 17.86.



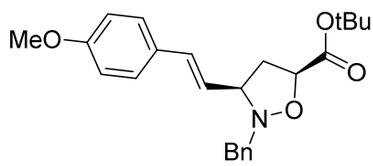
(3S,3aR,7aS)-2-benzyl-3-((1E,3E)-penta-1,3-dien-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4I): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4i** (104mg, 80% yield) as a yellow oil. **TLC:** R_f 0.49 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 - 7.23 (m, 5H), 6.25 (dd, J = 15.2, 10.4 Hz, 1H), 6.08 - 5.96 (m, 1H), 5.80 - 5.65 (m, 1H), 5.52 (dd, J = 15.2, 8.1 Hz, 1H), 4.51 (ddt, J = 11.5, 7.7, 4.2 Hz, 1H), 4.04 (d, J = 14.1 Hz, 1H), 3.74 (d, J = 14.1 Hz, 1H), 3.66 (t, J = 7.2 Hz, 1H), 2.92 (dd, J = 8.7, 5.2 Hz, 1H), 2.51 - 2.43 (m, 1H), 2.35 - 2.27 (m, 1H), 2.03 - 1.95 (m, 1H), 1.91 - 1.84 (m, 2H), 1.80 (ddd, J = 6.9, 5.4, 2.5 Hz, 1H), 1.77 - 1.73 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.31, 137.49, 134.26, 130.62, 130.53, 128.85, 128.13, 127.11, 76.49, 70.31, 60.74, 39.73, 26.46, 18.84, 18.07.

3.5.3. Synthesis of Vinyl Isoxazolidines from Table 10.

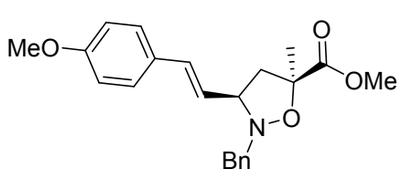


(3S,4R)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidine-4-carbonitrile (T3A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **3a** (80mg, 90%) as a pale oil. **TLC:** R_f 0.20 (3:1

heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 - 7.38 (m, 2H), 7.36 - 7.24 (m, 5H), 6.95 - 6.83 (m, 2H), 6.68 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 8.9 Hz, 1H), 4.30 (t, J = 8.6 Hz, 1H), 4.18 (d, J = 14.3 Hz, 1H), 4.08 (dd, J = 8.4, 6.7 Hz, 1H), 3.82 (d, J = 0.5 Hz, 3H), 3.71 (d, J = 14.3 Hz, 1H), 3.61 (td, J = 8.5, 6.7 Hz, 1H), 3.51 (t, J = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.95 , 136.61 , 128.74 , 128.44 , 128.30 , 128.22 , 127.46 , 119.86 , 114.09 , 69.99 , 68.68 , 55.33 , 38.48.

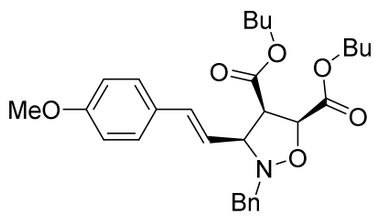


tert-butyl-(3R,5S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidine-5-carboxylate (T3B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **3b** (90mg, 90%) as a pale oil. **TLC:** R_f 0.56 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.40 (m, 2H), 7.31 (dd, J = 8.3, 6.0 Hz, 4H), 7.26 - 7.22 (m, 1H), 6.89 - 6.84 (m, 2H), 6.56 (d, J = 15.9 Hz, 1H), 5.99 (dd, J = 15.8, 8.2 Hz, 1H), 4.50 (dd, J = 8.2, 5.2 Hz, 1H), 4.14 - 4.01 (m, 2H), 3.81 (d, J = 0.8 Hz, 3H), 3.67 - 3.59 (m, 1H), 2.57 (t, J = 8.4 Hz, 2H), 1.51 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.23, 159.47, 137.79, 133.31, 128.98, 128.24, 127.67, 127.12, 124.40, 114.02, 81.69, 75.64, 68.04, 60.68, 55.29, 40.66, 28.04.

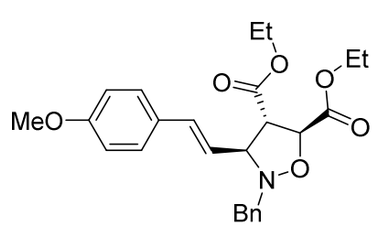


Methyl-(3R,5S)-2-benzyl-3-((E)-4-methoxystyryl)-5-methylisoxazolidine-5-carboxylate (T3C): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **3c** (105mg, 90%) as a yellow oil. **TLC**: R_f 0.50 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 - 7.37 (m,

2H), 7.30 (ddd, J = 8.2, 4.4, 1.5 Hz, 4H), 7.25 - 7.19 (m, 1H), 6.93 - 6.79 (m, 2H), 6.50 (d, J = 15.9 Hz, 1H), 5.95 (ddd, J = 15.8, 8.7, 1.3 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.86 - 3.74 (m, 7H), 3.44 (q, J = 8.4 Hz, 1H), 2.82 (ddd, J = 12.8, 8.6, 1.3 Hz, 1H), 2.31 (ddd, J = 12.9, 8.0, 1.4 Hz, 1H), 1.57 (s, 1H), 1.50 (d, J = 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.45, 137.53, 133.50, 129.08, 128.18, 128.01, 127.68, 126.77, 124.72, 113.98, 81.10, 69.44, 58.71, 55.28, 52.32, 46.07, 23.71.



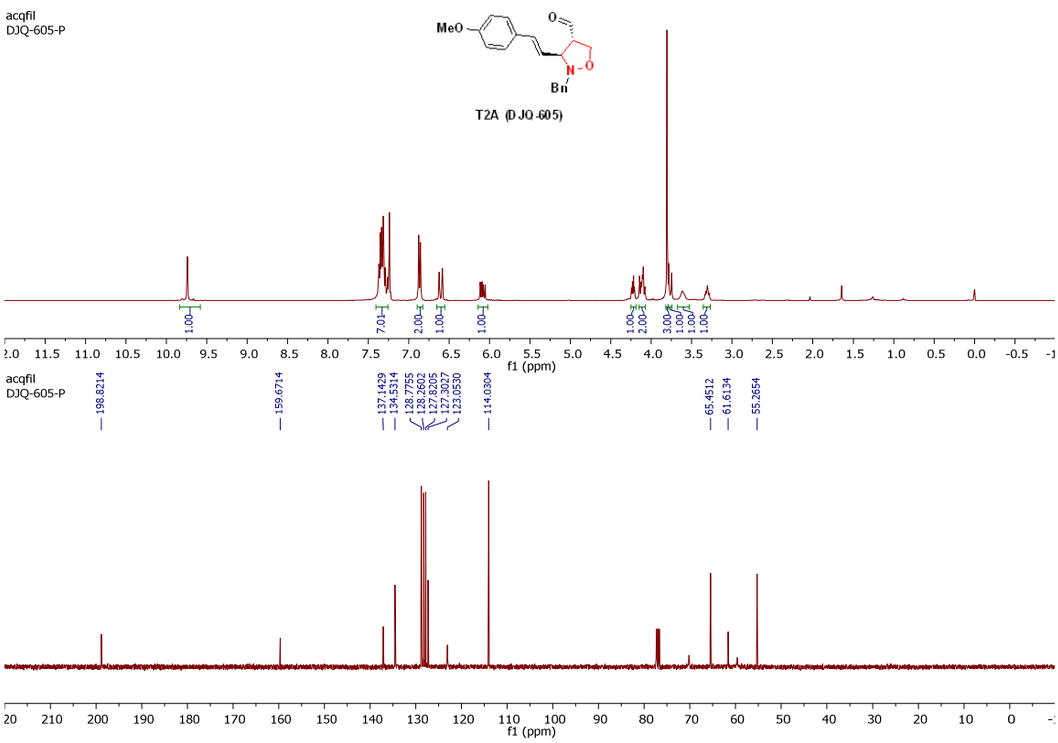
dibutyl (3S,4R,5S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidine-4,5-dicarboxylate (T3D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **3d** (120mg, 90%) as a white solid. **TLC:** R_f 0.62 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 - 7.37 (m, 2H), 7.34 - 7.28 (m, 4H), 7.26 - 7.21 (m, 1H), 6.91 - 6.83 (m, 2H), 6.63 (d, J = 15.8 Hz, 1H), 5.97 (dd, J = 15.8, 8.5 Hz, 1H), 4.21 - 4.14 (m, 2H), 4.12 - 4.02 (m, 4H), 3.91 (t, J = 9.0 Hz, 1H), 3.81 (d, J = 0.6 Hz, 3H), 3.67 - 3.60 (m, 1H), 1.67 - 1.54 (m, 4H), 1.44 - 1.30 (m, 4H), 0.91 (ddd, J = 29.9, 7.6, 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.22, 159.68, 137.34, 135.24, 128.99, 128.83, 128.25, 127.87, 127.27, 122.01, 114.01, 76.67, 72.19, 65.23, 60.25, 56.97, 55.31, 30.45, 19.07, 13.68.

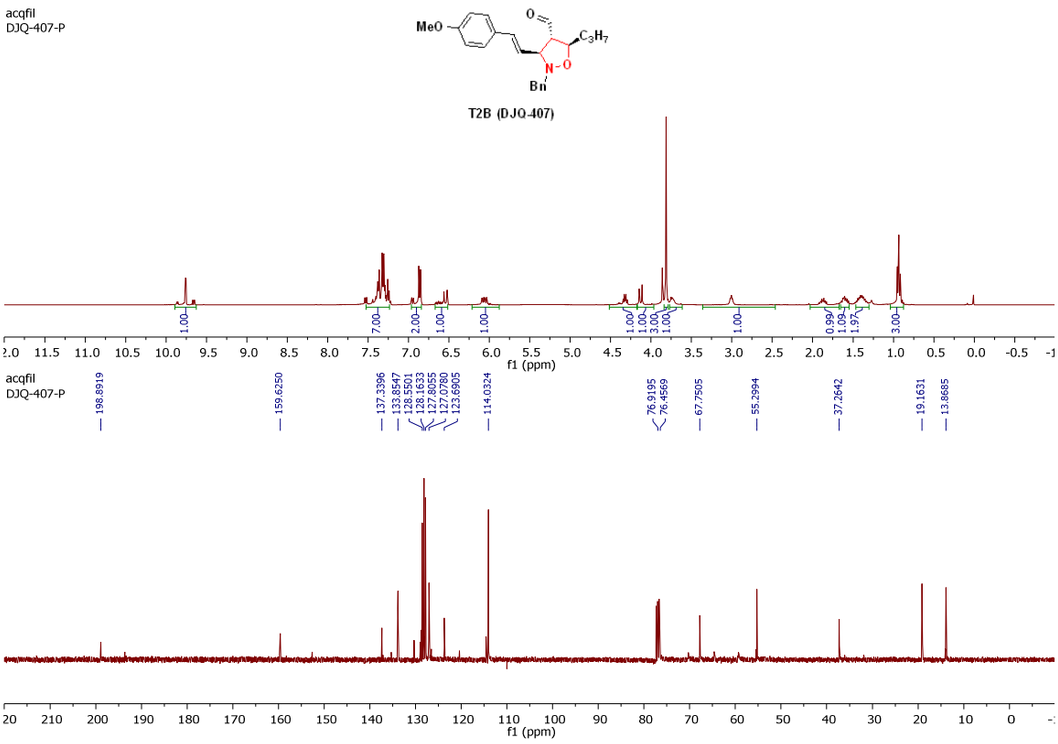


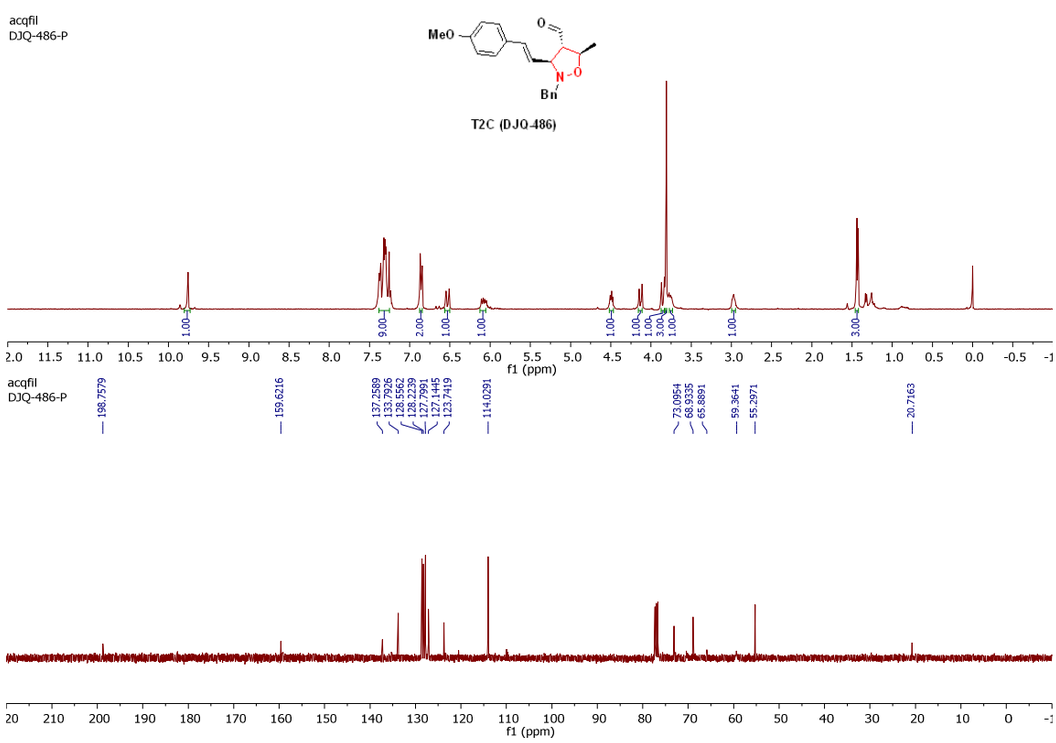
diethyl (3S,4S,5S)-2-benzyl-3-((E)-4-methoxystyryl)isoxazolidine-4,5-dicarboxylate (T3E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **3e** (118mg, 90%) as a white solid. **TLC:** R_f 0.35 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 - 7.43 (m, 2H), 7.33 (dq,

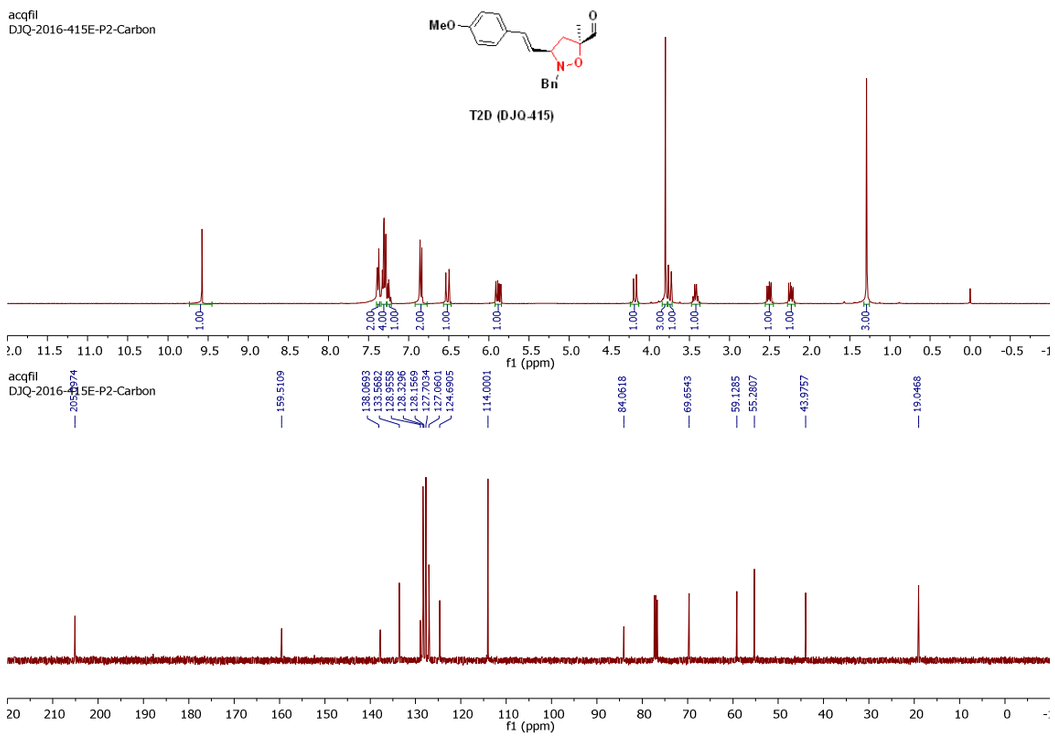
J = 8.7, 2.3, 1.5 Hz, 4H), 7.29 (d, J = 1.5 Hz, 1H), 6.88 - 6.85 (m, 2H), 6.62 (d, J = 15.8 Hz, 1H), 6.02 (dd, J = 15.9, 8.6 Hz, 1H), 4.87 (d, J = 4.3 Hz, 1H), 4.24 (tdd, J = 15.0, 7.5, 3.7 Hz, 5H), 3.86 (d, J = 15.2 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, J = 8.2, 4.3 Hz, 1H), 3.65 - 3.58 (m, 1H), 1.31 (d, J = 7.1 Hz, 3H), 1.25 (d, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.35, 171.04, 159.67, 137.22, 135.12, 128.85, 128.10, 128.08, 127.87, 126.96, 122.64, 114.02, 77.16, 73.48, 61.59, 61.50, 58.74, 57.28, 55.30, 14.19, 14.12.

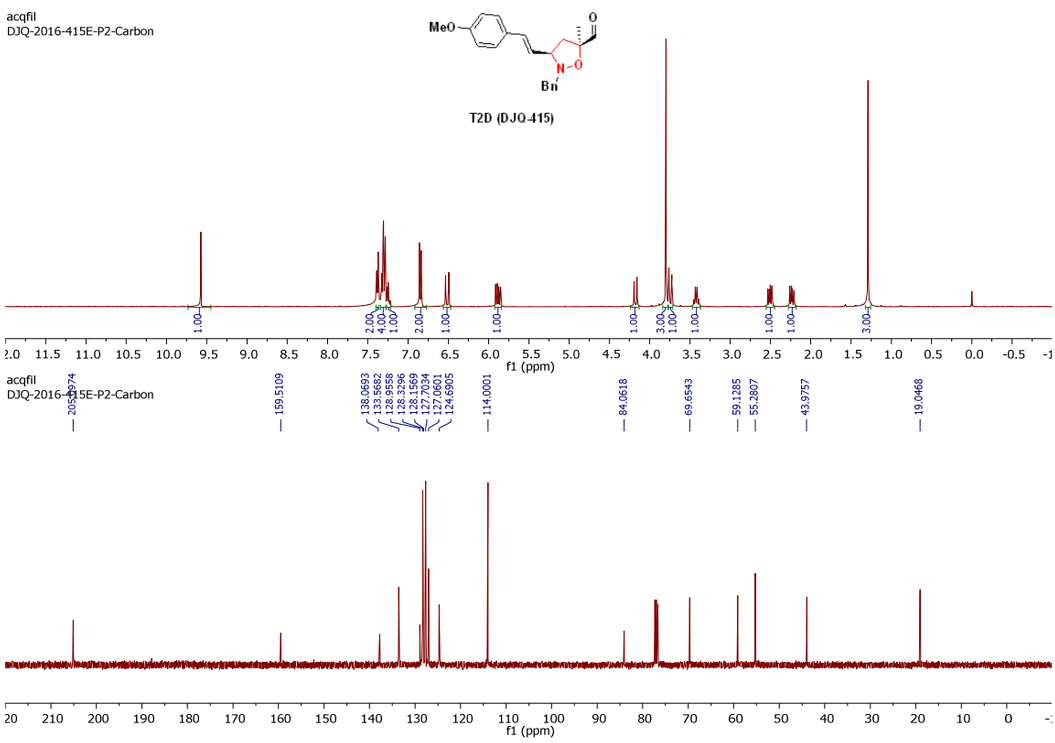
3.5.4. ^{1}H NMR and ^{13}C NMR of Vinyl Isoxazolidines.

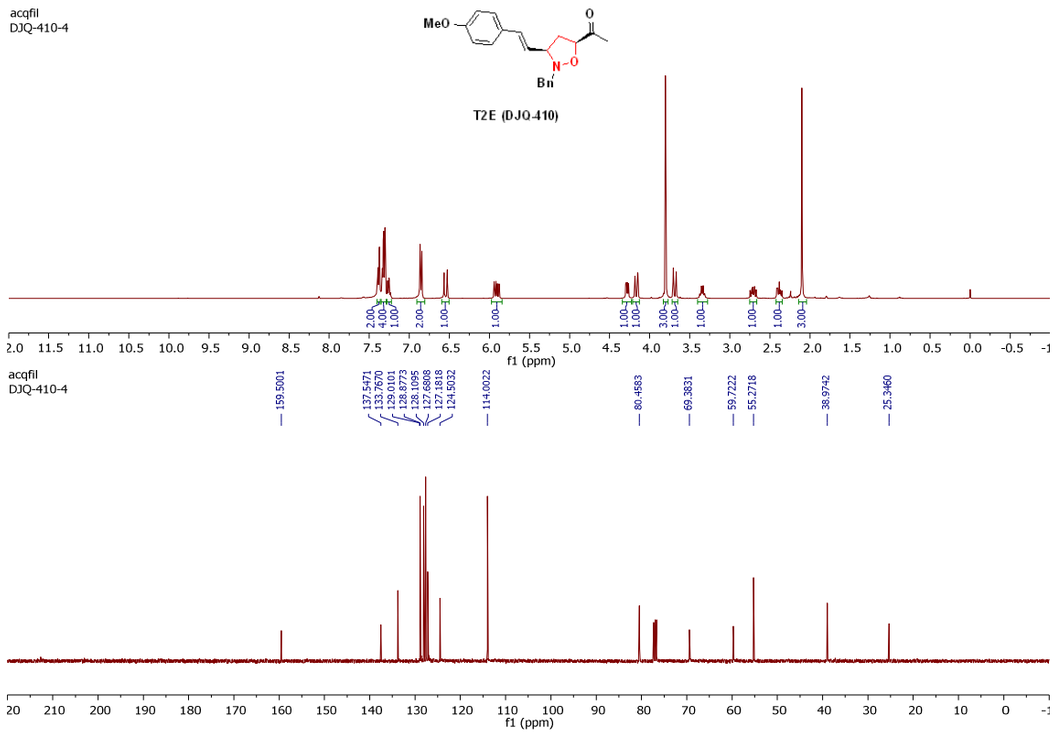


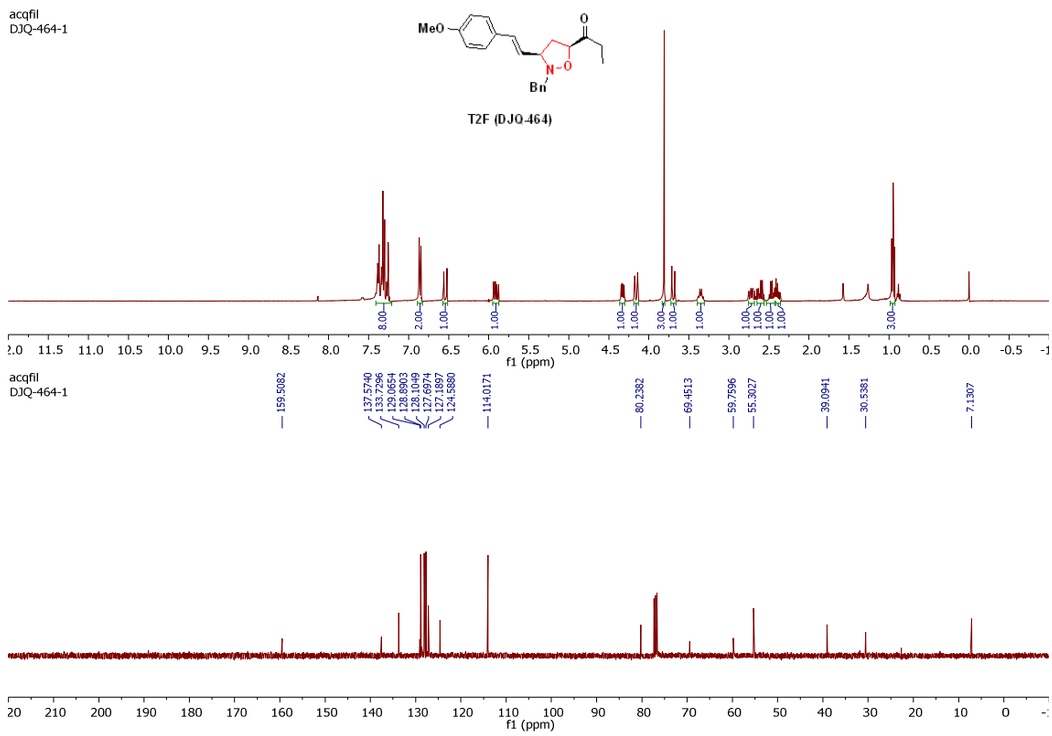


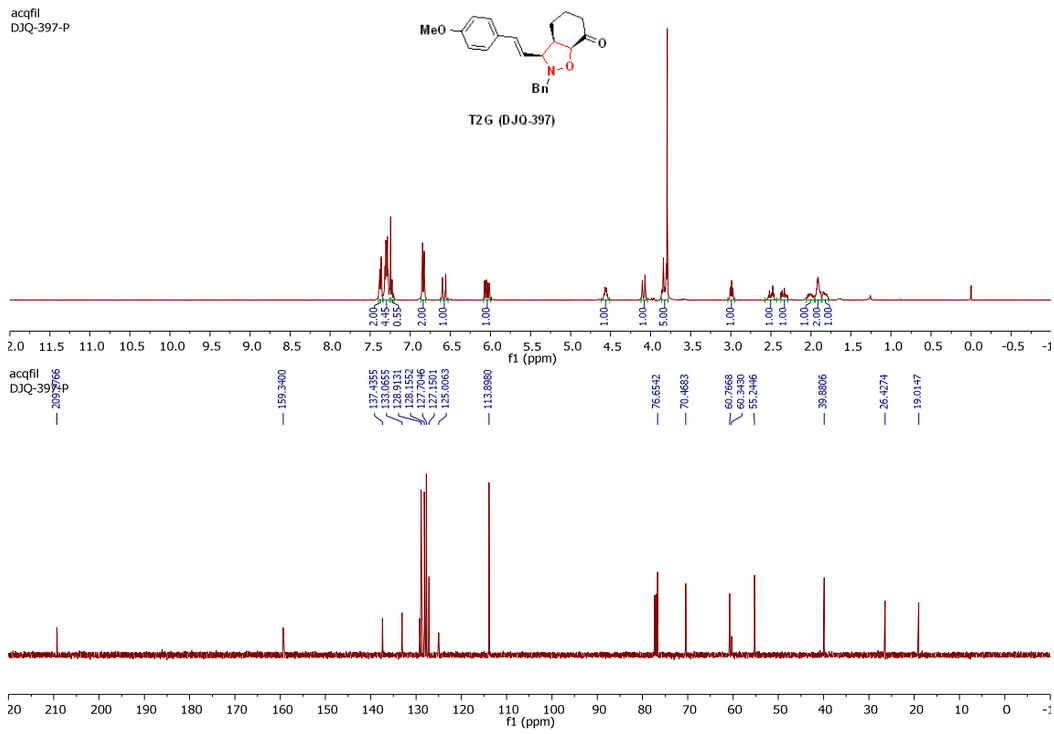


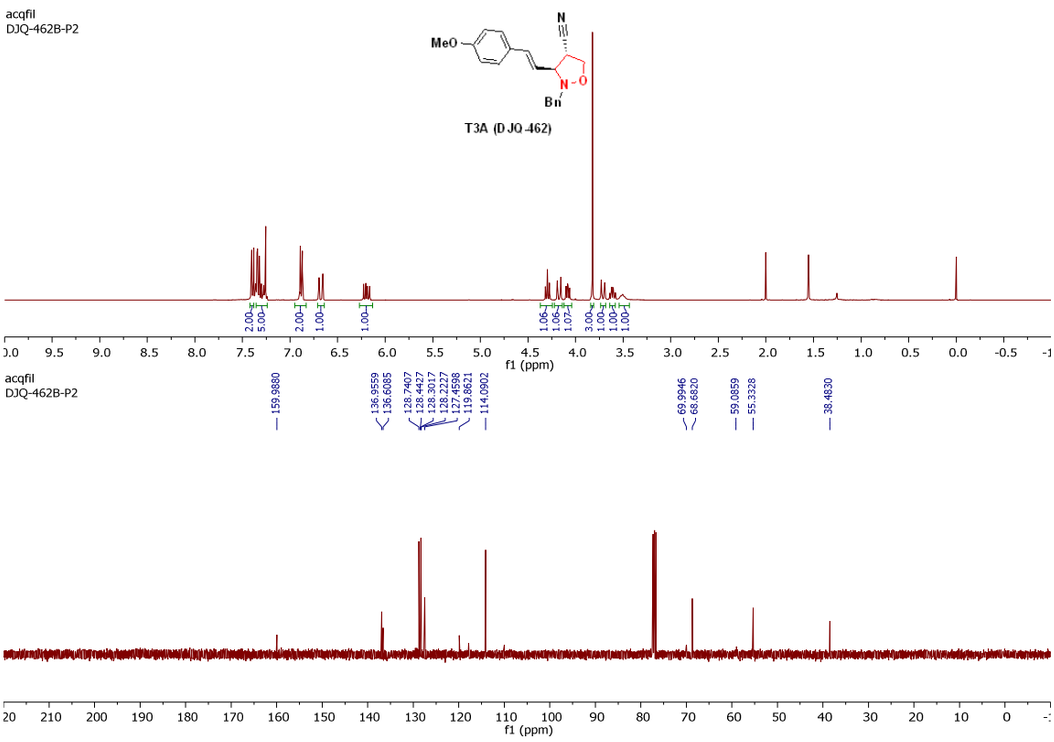


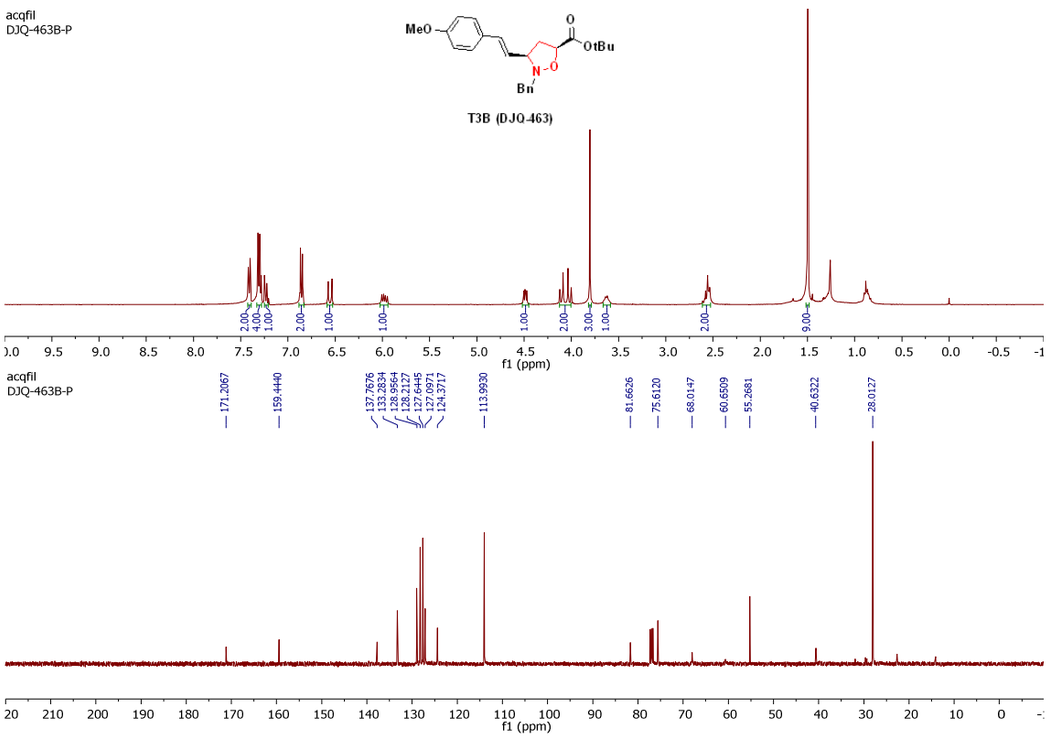


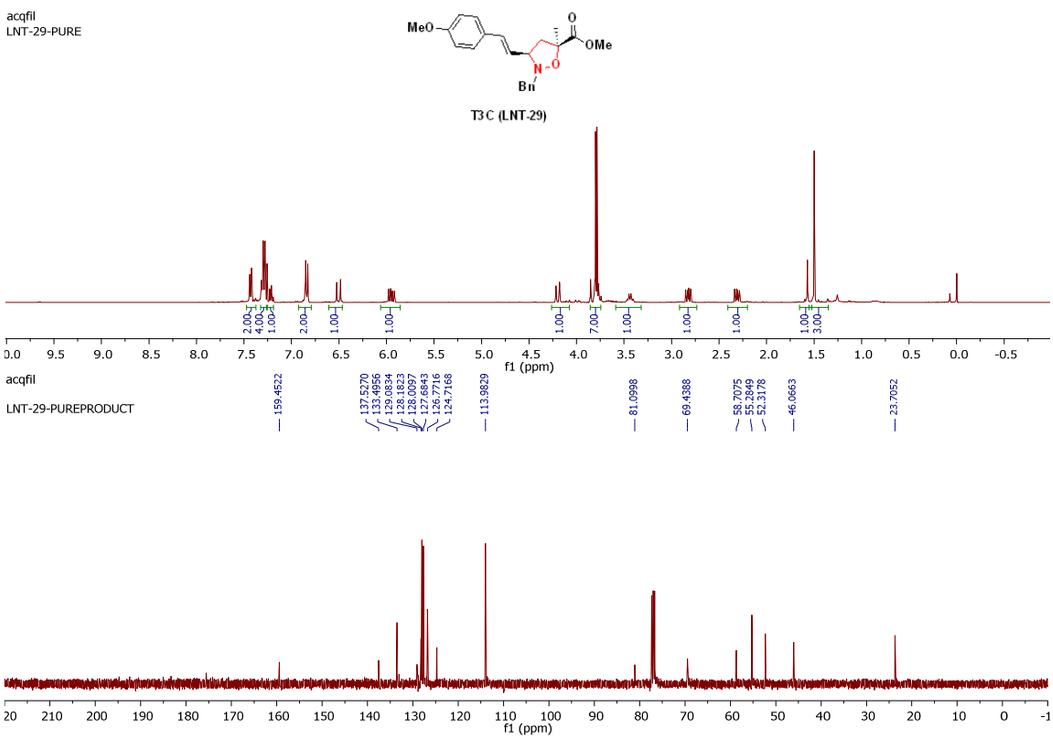


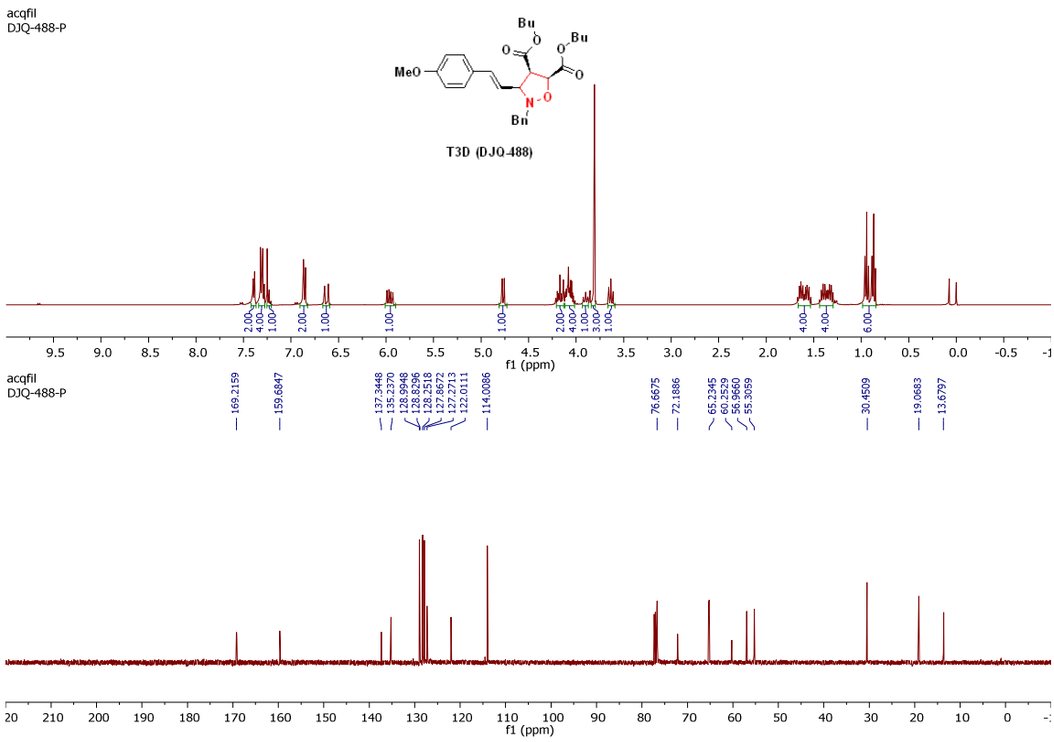


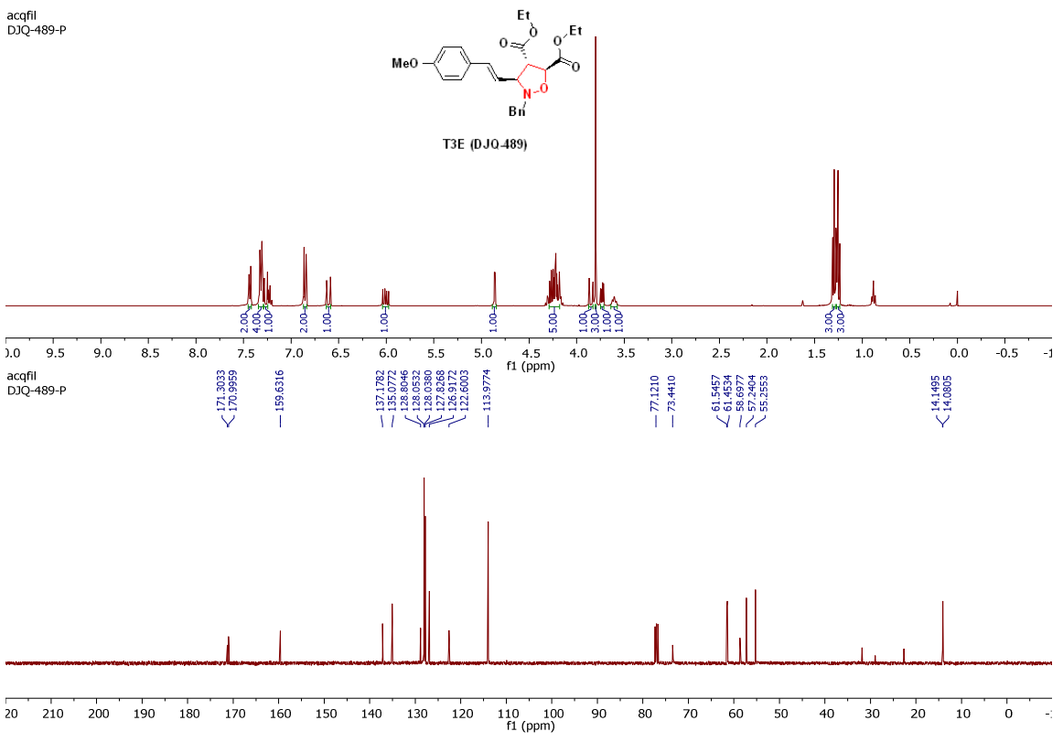


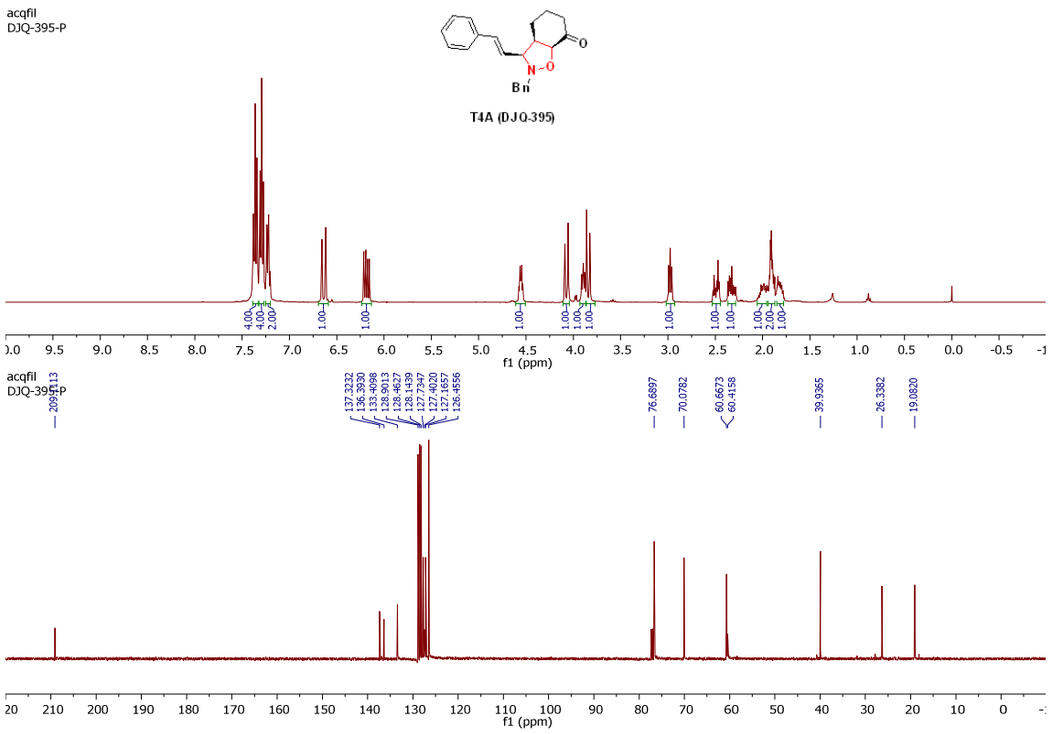


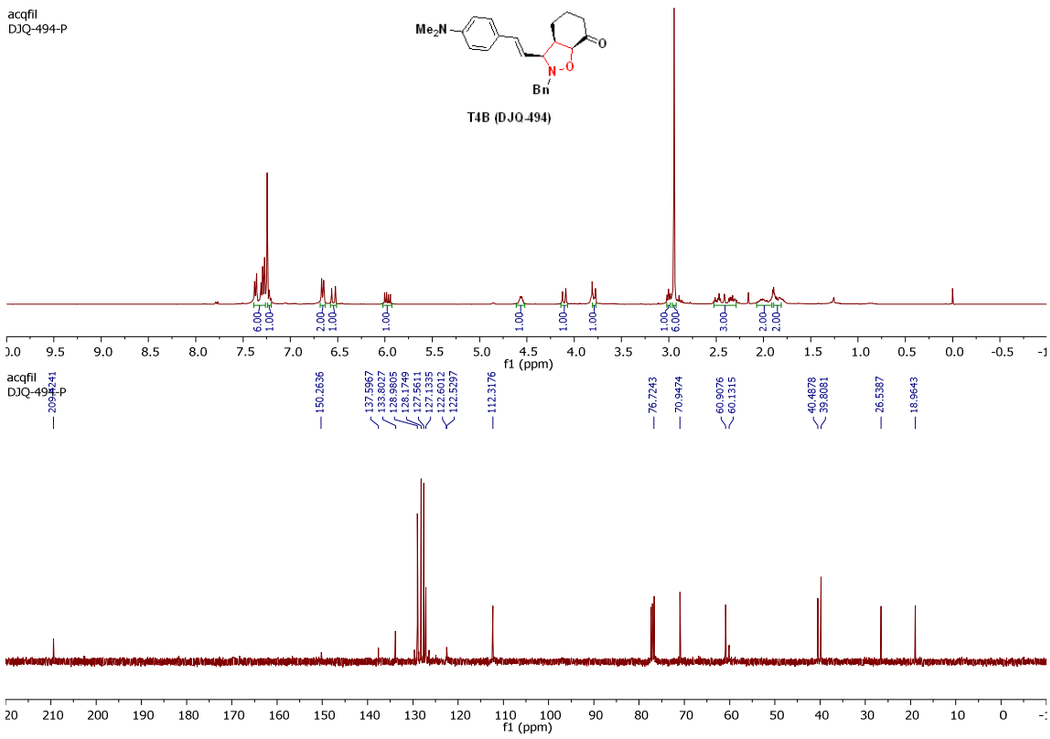


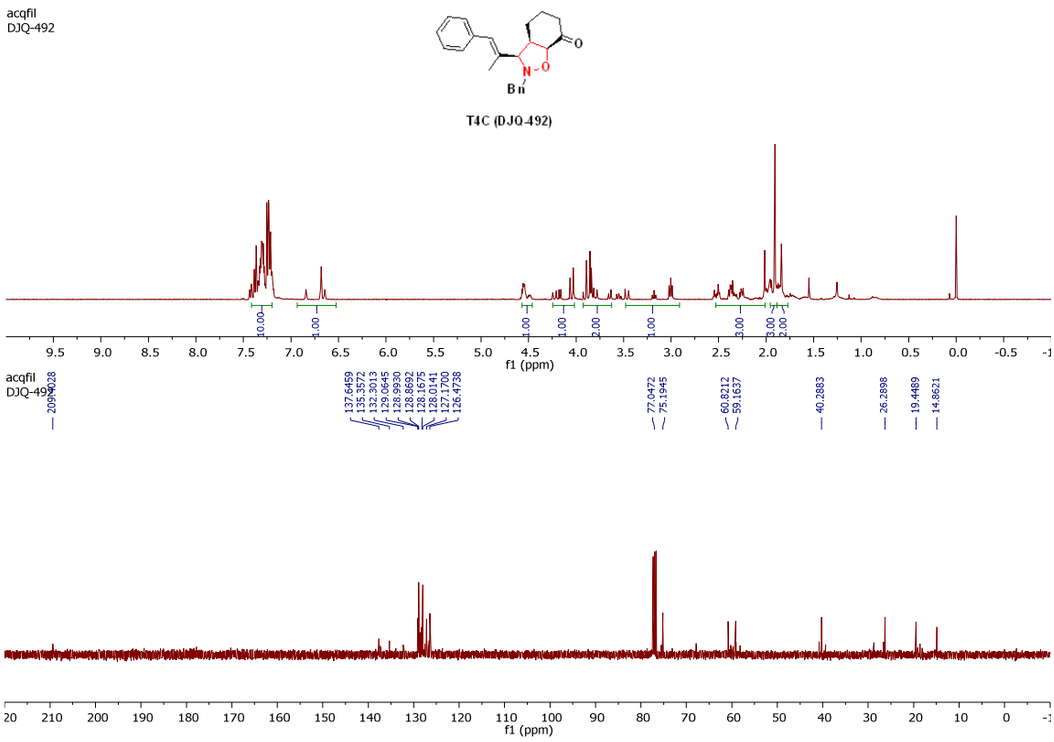


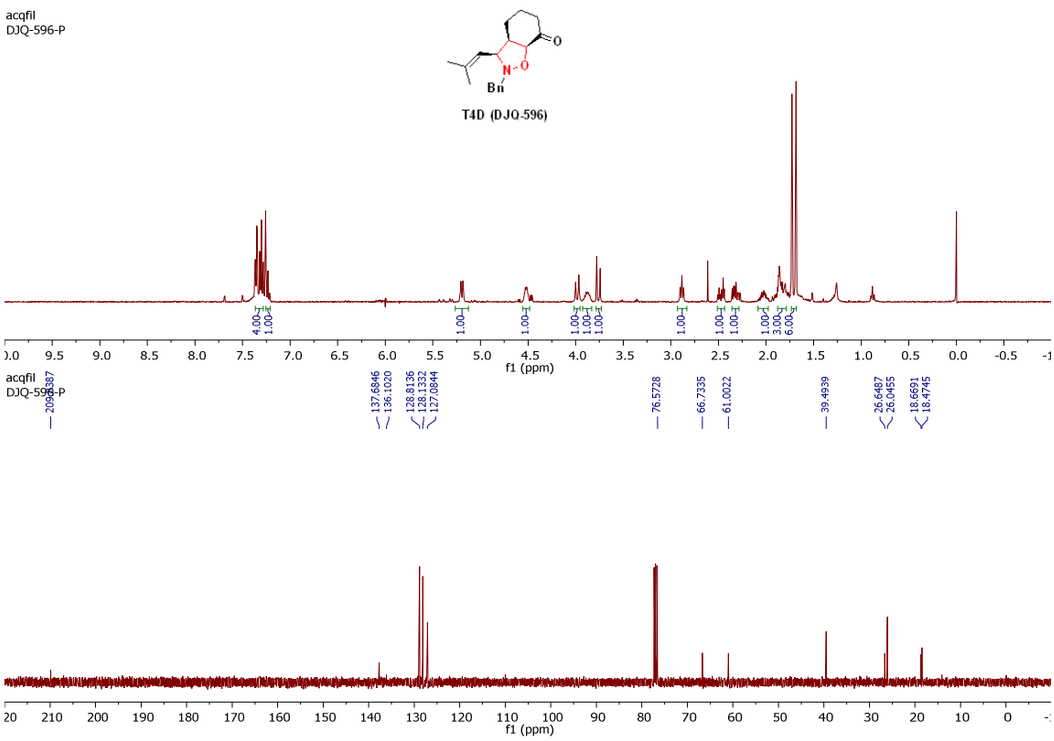


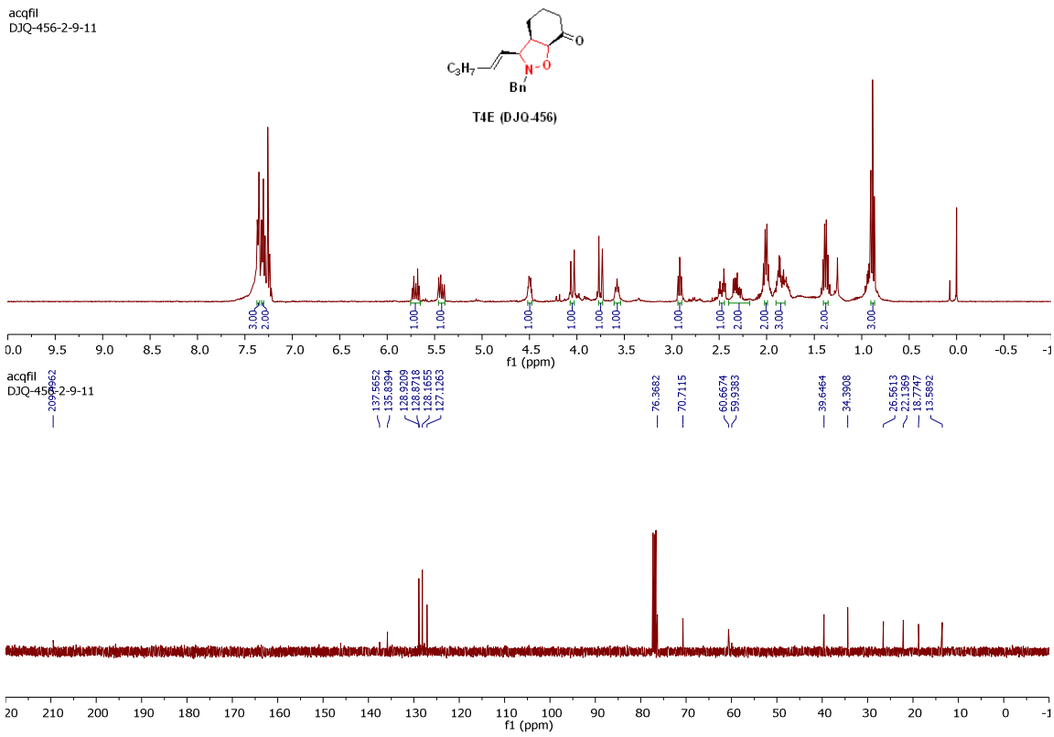


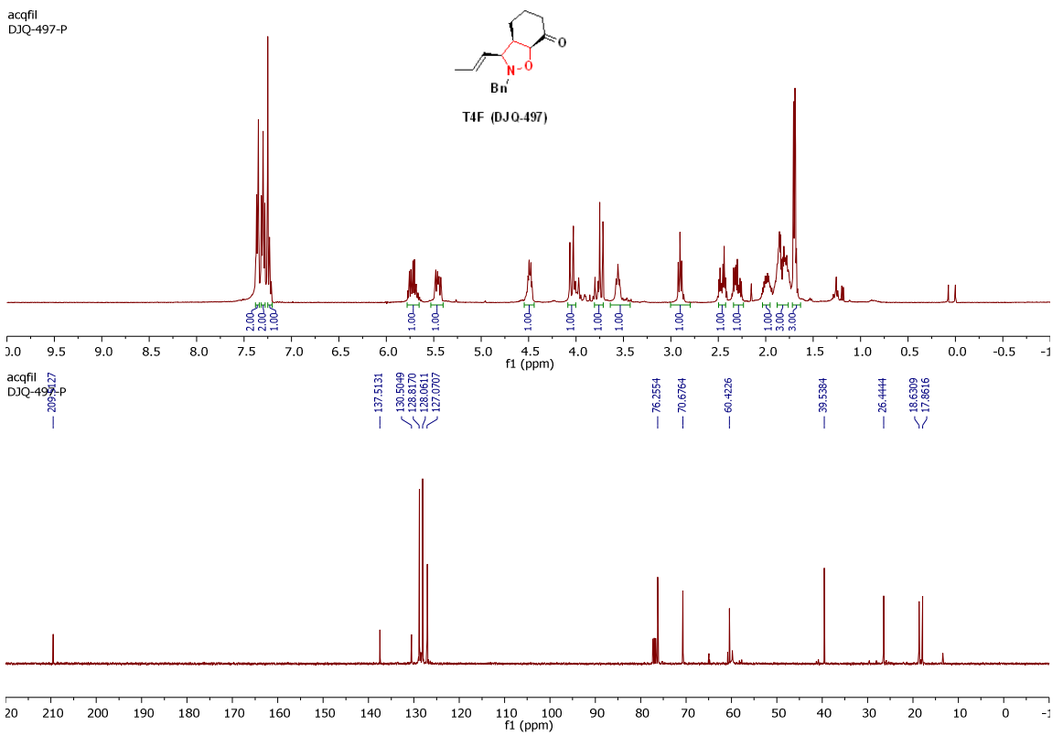


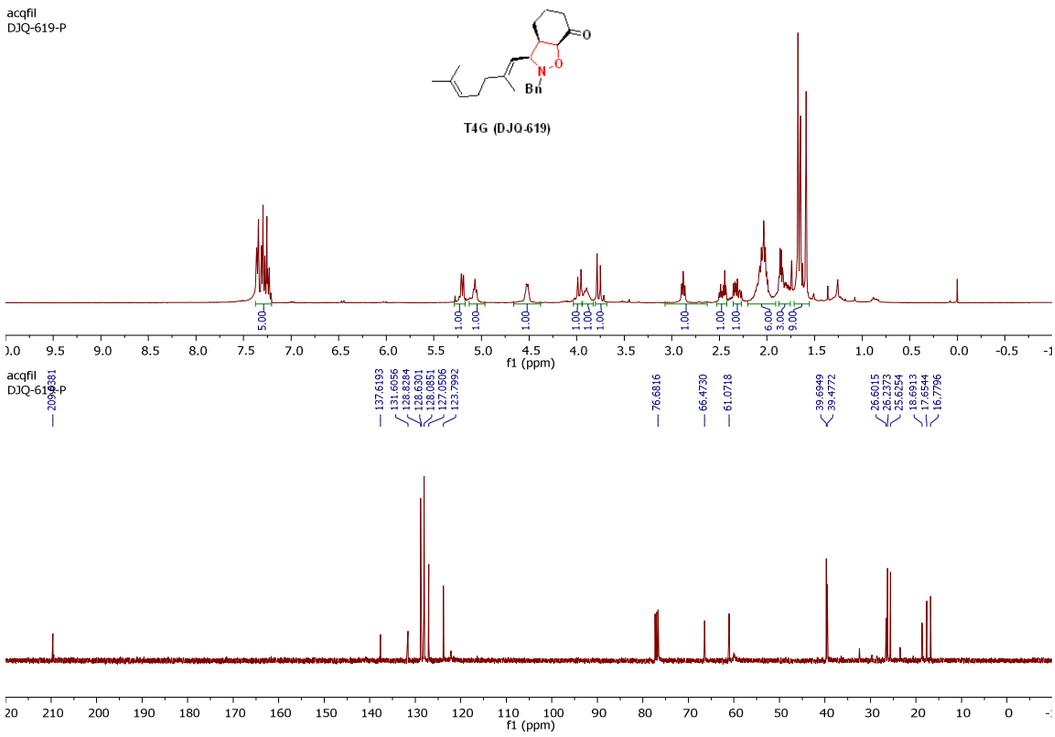


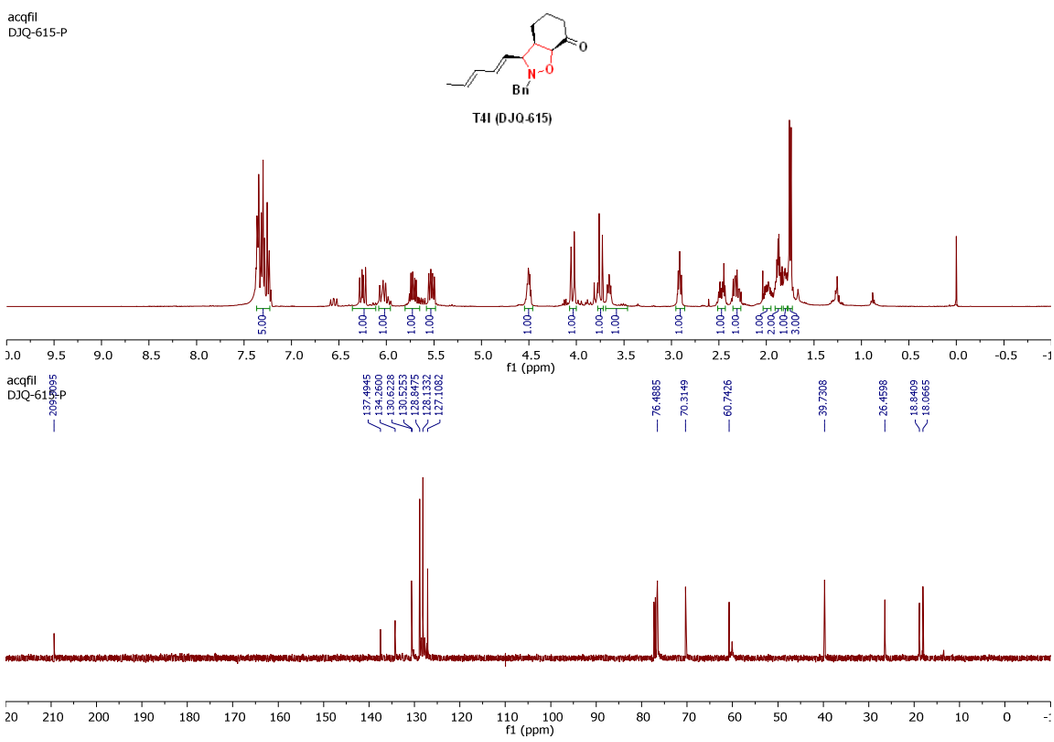












Chapter 4:

Nitrone Intramolecular Cycloaddition

4.1 Pharmaceutical Relevance

Proposed by Smith[129], the 1,3-dipolar cycloaddition reaction is an outstanding methodology for the synthesis of five-membered-ring-containing heterocycles.[116, 117, 130-133] This reaction involves the combination of a 1,3-dipole with a dipolarophile. The methodology of this reaction found widespread application in a variety of fields like materials science, natural product synthesis, and biological chemistry. This methodology gained recognition in the 1960s through seminal work by Huisgen.[134-136] Among the 1,3-dipoles the nitrone stands out as the most widely employed in dipolar cycloadditions.[137-143] Their high stability along with their ease of access and biological significance may be why nitrones are so widely used. Depending on the dipolarophile and isoxazole or isoxazolidine skeletons are formed in their reactions with alkenes or alkynes, respectively. These heterocycles are found in a variety of natural products and can be converted into 1,3-amino alcohols, which are precursors of β-amino acids and β-lactams, through reductive ring opening.[144]

4.2 Chromeoisoxazole Methodology

Formation of the chromeoisoxazole (Figure 13) has been limited to methods using heat[145] and grinding.[146] These methods while affective are often times tedious and wasteful. The use of photocatalysts has become widely used in organic chemistry to facility reactions that would either never happen or would be extremely slow[147, 148]

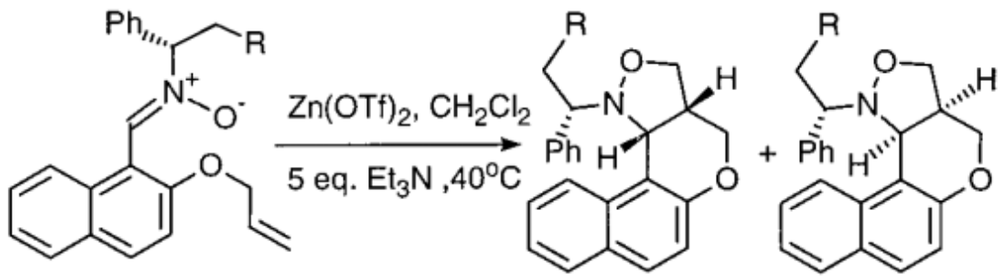


Figure 13. Formation of Chromeoisoxazole Using a Zinc Catalyst Under Mild Conditions

Zhao was able to form the chromeoisoxazoles in good yields as a mixture of diastereomers. These chromeoisoxazoles were formed using a nitrone, this was formed through the condensation of a hydroxylamine and an aldehyde using 5% mol glacial acetic acid. This was able to lead to the nitrone (Figure 14). With the nitrone Zhao was then able to form the chromeoisokxazole by refluxing the nitrone in chloroform for 48 hours at 40˚C (Figure 15). This reaction lead to a mixture of diastereomers in good yields.[145]

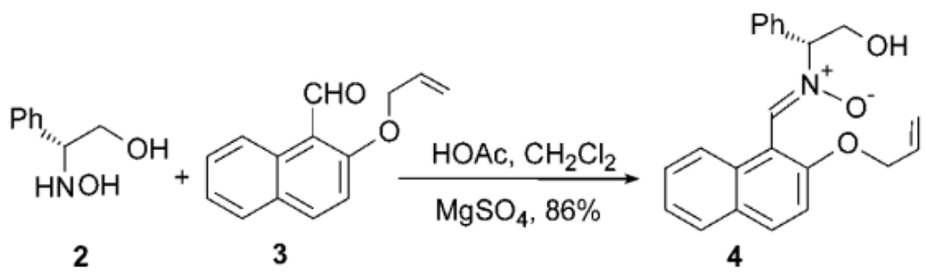


Figure 14. Nitrone formation from Zhao

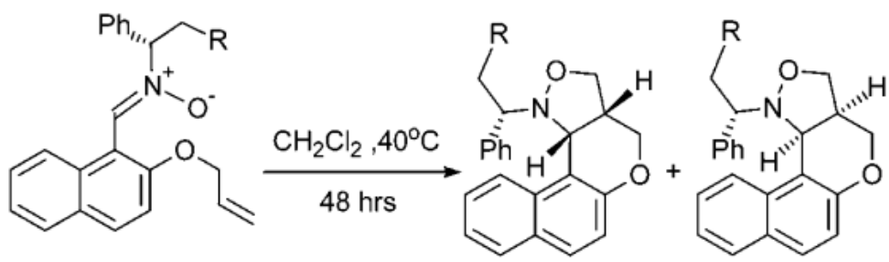


Figure 15. Chromeoisoxazole formation from Zhao

Compared to using heat for this reaction another method that is employed is grinding[149, 150]. Bhutia used two types of grinding tests to determine the best method for the formation of chromeoisoxazoles. The first method was a gentle grinding where they found that after 15 minutes the nitrone was formed while gentle heating was required for the formation of the chromeoisoxazole instead of intermediate grinding for 12 hours at room temperature. The other method employed was liquid assisted grinding (LAG).[151] This method compared three solvents: chloroform, ethanol, and acetonitrile. These three solvents showed similar speeds for the formation of the nitrone compared to the gentle grinding method. The chromeoisoxazole formation was low yielding and so Bhutia stuck with the gentle grinding method.

Photocatalyzed reactions have become a major field in organic chemistry over the past few years, mainly due to visible light being in natural abundance, environmentally benign, renewable, and easy to handle.[147, 152-157] The rapid development of this field has led to the development of new and simpler organic reactions. These reactions range from coupling reactions[158], alkyl-vinyl product formation[159], sulfur ylides formation[160], and ring closing reactions[161, 162] to name a few. Tris(2,2′-bipyridyl)dichlororuthenium(II) hexahydrate ($Ru(bpy)_3Cl_2•6H_2O$) has been used in an oxidative cross-dehydrogenative coupling (CDC).[163]

The CDC method used glycine and styrene as substrates to explore the reaction conditions.[163] The screening began with the use of $Ru(bpy)_3(PF_6)_2$ in 1 mol percent in combination with 10 mol percent of a Lewis acid cocatalyst $Cu(OTf)_2$ in acetonitrile under irradiation of a 3W blue LED bulb for 4 hours. Upon further screening $Ru(bpy)_3Cl_2•6H_2O$ was found to be the best photocatalyst under these conditions and gave a yield of 75% after 4 hours. With further testing it was found that the best Lewis acid cocatalyst was $Cu(OTf)_2$ while acetonitrile proved to be the best medium and the photocatalyst could be reduced to 1 mol percent. Further testing of the light source showed that under a 26W fluorescent lamp the reaction was able to proceed to completion but was slower to complete at 15 hours. Under the irradiation of direct

sunlight, the reaction was able to proceed in 6 hours affording a 74% yield which helped to show the utility of the protocol. Zhang also found that molecular oxygen played a role in the system upon finding that the reaction did not yield the desired product under argon. The conditions were able to show that substituted styrenes, naphtyl ethylenes, 1,2-disubstituted alkenes, aliphatic alkenes, and conjugated dienes. It was noted by Zhang that the aliphatic alkenes had reduced yields compared to their styrene counter parts. Alkenes with strong electron-withdrawing groups were also noted to not be suited for this reaction.

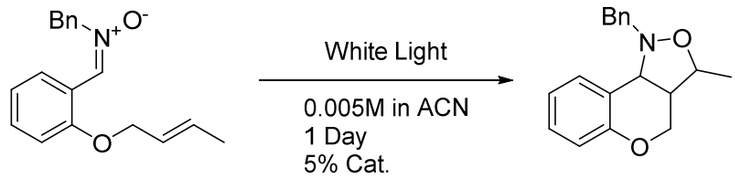
The scope of the glycine esters were also explored by Zhang and were found to give relatively good yields. Para-substituted glycine's were found to give the best yields for these conditions, it was also noted that 3,5-dimethyl substituted glycine was also able to obtain a relatively lower yield of the product. The ester fragment was also explored by Zhang and found that small, large, and bulky ester were suitable for this reaction along with glycine amide and glycine derived dipeptide. Other substrates tried were α-amino carbonyls species such as ketones and amino nitriles, but these were found to give trace products or no reaction respectively.

4.3 Results and Discussion

Since a photocatalyst was being used for this transformation multiple catalysts were tested to see which was the best. These tests were run in the solvent acetonitrile due to some of the catalysts not dissolving in other medium. These catalysts tended to allow the product to undergo hydrolysis back to the starting aldehyde or they caused no reaction at all. $Ru(Bpy)_3$ is a common photocatalyst used in many different organic synthesis methods and provided an 82% yield of the product (Table 12, Entry 1). Other metal catalysts were used that are found in light mediated organic synthesis and they were found to give good to moderate yields (Table 12, Entry 2-4). Two organic photocatalysts were also used and were found to give poor yields or no reaction (Table 12, Entry 5-6).

Table 12

Catalyst Optimization Table



Entry	Catalyst	Yield
1	$Ru(Bpy)_3$	82%
2	$Ir(p\text{-}F\text{-}ppy)_3$	75%
3	$[Ru(bpz)_3][PF_6]_2$	87%
4	$[Ir\{dFcF_3ppy\}_2(bpy)]PF_6$	51%
5	Tetrabromofluorescein	19%
6	Hematoxylin	0%

The formation of chromeoisoxazoles has been traditionally done using high heats. During the optimization process of these compounds the existing methods were tested to observe the viability of this reaction (Table 13, Entry 3). Optomization then focused on visible light after a nitrone was placed on the windowsill to react overnight (Table 13, Entry 5). It was observed that by decreasing the concentration of the reaction the yields would increase significantly (Table 13, Entry 8-11). Upon the addition of a photocatalyst the yields are observed to increase even further when added in five molar percent (Table 13, Entry 12). Through the addition of triethylamine, it was observed that the reaction yields became excellent. This is due to a possible radical mechanism involving the triethylamine (Figure 16).

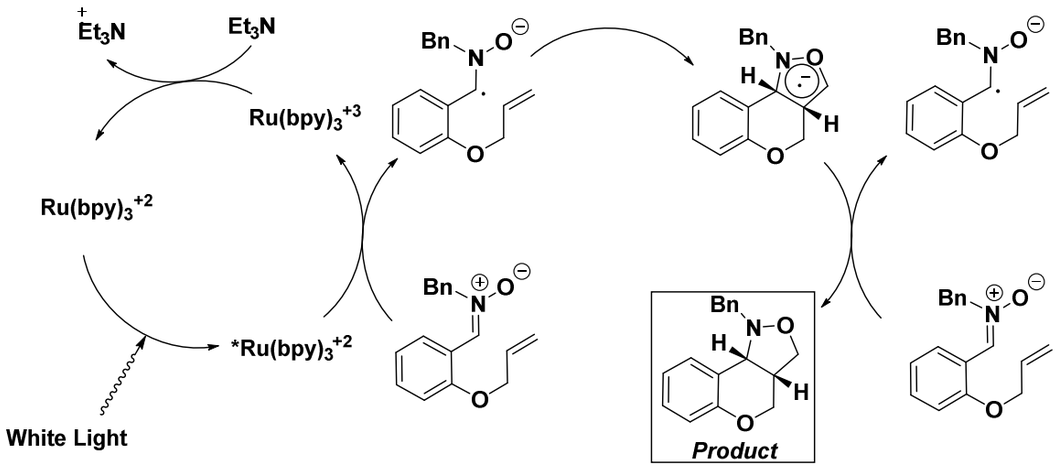
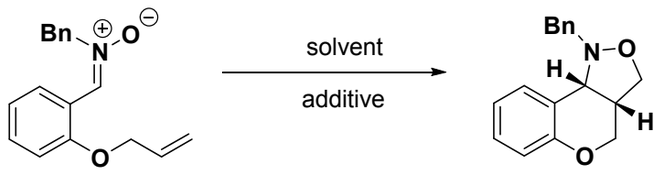


Figure 16. Proposed Mechanism for the Formation of Chromenoisoxazoles

Table 13

Chromeoisoxazole Synthesis Optomization



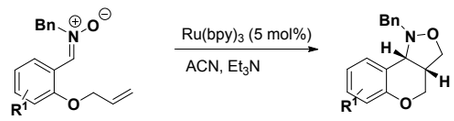
Entry	Additive	Solvent	T	Concentration	Yield[a]
1	none	Benzene	rt	0.01M	0%
2	none	Benzene	60° C	0.01M	32%
3	None	Benzene	80° C	0.01M	91%
4	visible light	Benzene	rt	0.01M	18%
5	visible light	ACN	rt	0.01M	20%
6	visible light	CH_2Cl_2	rt	0.01M	32%
7	visible light	MeOH	rt	0.01M	28%
8	visible light	ACN	rt	0.02M	18%
9	visible light	ACN	rt	0.03M	15%
10	visible light	ACN	rt	0.05M	32%
11	visible light	ACN	rt	0.005M	42%
12	$Ru(bpy)_3Cl_2$ 5mol%	ACN	rt	0.005M	64%
13	$Ru(bpy)_3Cl_2$ 1mol%	ACN	rt	0.005M	44%
14	$Ru(bpy)_3Cl_2$ 10mol%	ACN	rt	0.005M	55%
15	$Ru(bpy)_3Cl_2$ 5%/Et_3N 1 equiv	ACN	rt	0.005M	98%
16	$Ru(bpy)_3Cl_2$ 5%/Et_3N 1.5equiv	ACN	rt	0.005M	95%

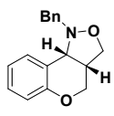
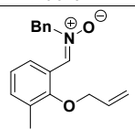
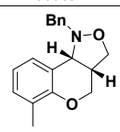
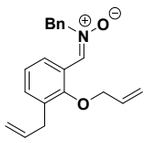
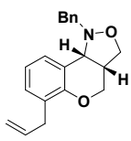
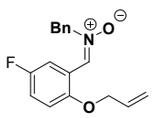
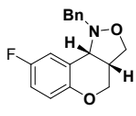
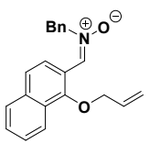
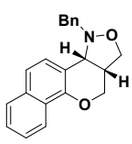
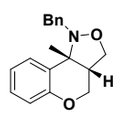
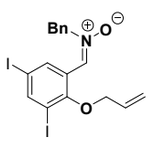
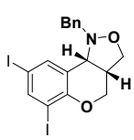
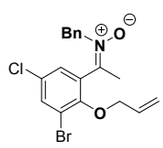
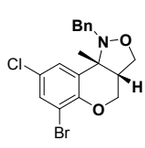
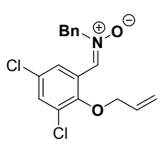
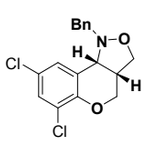
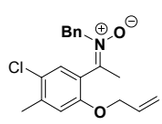
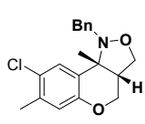
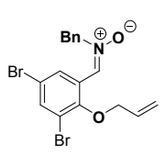
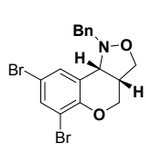
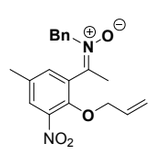
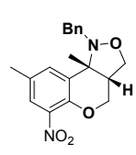
a.Isolated yields.

With the optimal condition in hand for this reaction we sought to determine the scope. Different substitution around the aromatic ring was tested for these reactions such as the meta position which showed excellent yields (Table 14, Entry 2). A fused ring was also test and was found to have excellent yields as well (Table 14, Entry 3). Multiple substitutions around the aromatic ring were tested all found to produce excellent yields (Table 14, Entry 4-6 and 10-12). Electron donating groups were also found to give excellent yields (Table 14, Entry 2 and 7). Electron withdrawing groups were tested as well and no difference between the donating and withdrawing groups were noticed (Table 14, Entry 4-6, 8, 10-12). As expected ketones were found to produce excellent yields as well (Table 14, Entry 10-12).

Table 14

Chromeoisoxazole Synthesis Aromatic Scope



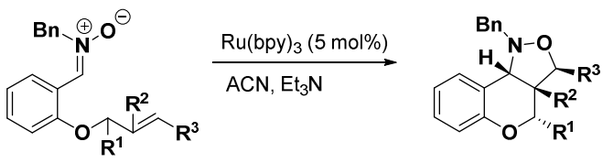
Entry	Nitrone	Product[c]	Yield[a,b]	Entry	Nitrone	Product[c]	Yield[a,b]
1			98%	7			92%
2			97%	8			96%
3			92%	9			93%
4			95%	10			95%
5			94%	11			96%
6			91%	12			90%

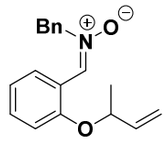
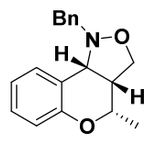
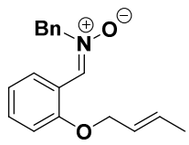
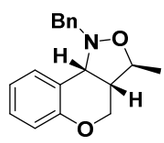
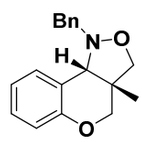
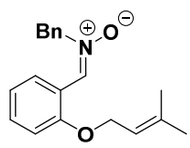
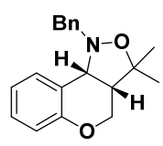
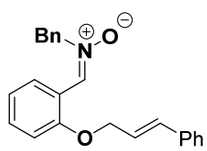
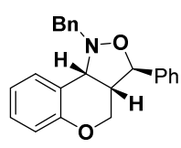
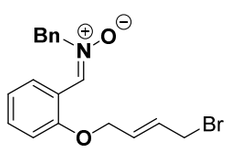
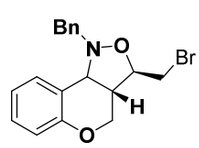
a. Reaction conditions: Nitrone (1 mmol), $Ru(bpy)_3$ (0.05 mmol), Et_3N (1 mmol) in ACN for 12h. *b*. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography.

We also wanted to test if changed the allyl ether group in the ortho position would have any effect on the reaction. When placing methyl groups on the 1, 2, and 3 positions the yields all trended towards excellent and did not deviate from each other to any significant degree (Table 15, Entry 1-3). Bulky groups were tested to determine if there would be any significant effects on the yields and upon testing were found to also be excellent yielding (Table 15, Entry 4-5).

Table 15

Chromeoisoxazole Synthesis Allyl Ester Scope



Entry	Nitrone	Product[c]	Yield[a,b]
1			96%
2			97%
3			94%
4			92%
5			96%
6			93%

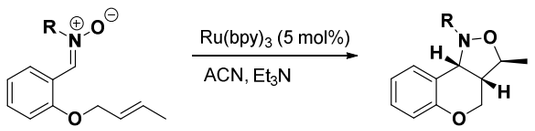
a. Reaction conditions: Nitrone (1 mmol), $Ru(bpy)_3$ (0.05 mmol), Et_3N (1 mmol) in ACN for 12h. *b*. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography.

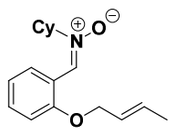
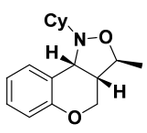
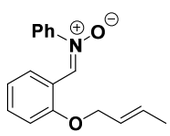
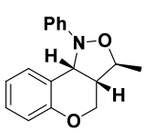
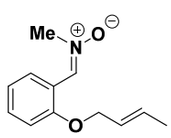
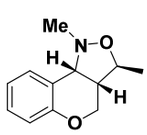
The robustness of this reaction was also attested by changing the hydroxylamine used during the nitrone formation. Small groups were tested and found to form the cycloadduct in excellent yields (Table 16, Entry 3). Likewise, bulky groups were tested and found to oxidize back to the aldehyde and did not form the desired product. Finally,

two different types of rings were tested an aromatic and a nonaromatic both of which formed the chromeoisoxazole in excellent yields (Table 16, Entry 4 and 1).

Table 16

Chromeoisoxazole Synthesis Hydroxylamine Scope



Entry	Nitrone	Product[c]	Yield[a,b]
1			96%
2			95%
3			94%

a. Reaction conditions: Nitrone (1 mmol), $Ru(bpy)_3$ (0.05 mmol), Et_3N (1 mmol) in ACN for 12h. *b*. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography.

4.4 Conclusion

Using visible light and a photocatalyst the formation of chromeoisoxazole has been shown without requiring harsh conditions. Multiple substitutions on the aromatic ring have shown no difference in yield while providing diverse substitutions of the aromatic ring. Changing the allyl ether has also shown to form the chromeoisoxazole in excellent yields. The mechanism for the formation of the chromeoisoxazoles has been proposed via a catalytic mechanism involving a radical.

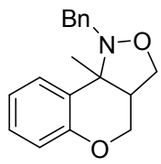
4.5 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4- mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate ($KMnO_4$). Silica flash chromatography was performed on E. Merck 230-400 mesh silica gel 60. Automated chromatography was performed on a ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0- 20% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm relative to solvent signals: $CDCl_3$ (^1H, 7.23 ppm; ^{13}C, 77.0 ppm; coupling constants are expressed in Hz).

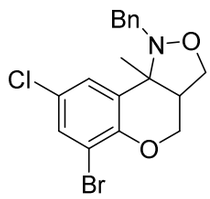
4.5.1. General method for the synthesis of Chromeoisoxazoles.

In a 20- mL glass vial, 1 eq. nitrone and 0.05 eq. $Ru(Bpy)_3$ were dissolved in 7mL acetonitrile. The reaction was stirred vigorously under white light for 22 hours at room temperature. The substrate is concentrated by rotary evaporation to afford the crude product. The crude product is filtered through silica gel over a gradient of 9:1 Heptanes/EtOAc over 12 column volumes to obtain the respective chromeoisoxazole in good to excellent yields.

4.5.2. Chromeoisoxazoles from Table 14.

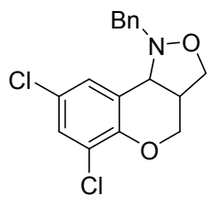


1-benzyl-9b-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.6mg, 93%) as a white solid. **TLC:** R_f 0.20 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 - 7.44 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.33 - 7.27 (m, 2H), 7.27 - 7.15 (m, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 4.28 - 4.14 (m, 3H), 4.01 - 3.82 (m, 3H), 2.84 - 2.76 (m, 1H), 1.56 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 128.59 , 128.49 , 128.37 , 128.21 , 126.94 , 121.21 , 117.07 , 67.05 , 65.28 , 54.95 .

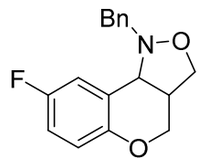


1-benzyl-6-bromo-8-chloro-9b-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19mg, 95%) as a yellow solid. **TLC:** R_f 0.40 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.44 - 7.37 (m, 4H), 7.32 (td, *J* = 7.5, 1.8 Hz, 2H), 7.28 - 7.24 (m, 1H), 4.43 - 4.37 (m, 1H), 4.30 - 4.20 (m, 2H), 4.02 - 3.85 (m, 3H), 2.85 (dddd, *J* = 9.0, 6.0, 4.4, 2.8 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.63 , 131.68 , 128.40 , 128.38 , 128.33 , 128.31 , 127.70 , 127.68 , 127.21 , 127.19 , 66.87 , 65.34 , 64.22 , 55.02 , 29.69 , 23.65 .

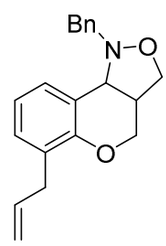
1-benzyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.6mg, 98%) as a yellow solid. **TLC:** R_f 0.52 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.40 (m, 2H), 7.34 (td, *J* = 7.5, 6.9, 1.1 Hz, 2H), 7.30 - 7.25 (m, 1H), 7.19 (dd, *J* = 8.4, 6.5 Hz, 2H), 6.95 - 6.87 (m, 2H), 4.32 (td, *J* = 8.2, 0.9 Hz, 1H), 4.25 (d, *J* = 13.2 Hz, 1H), 4.19 - 4.16 (m, 2H), 4.04 (d, *J* = 13.1 Hz, 1H), 3.95 (d, *J* = 6.9 Hz, 1H), 3.83 (dd, *J* = 8.1, 4.7 Hz, 1H), 3.14 - 3.05 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.84 , 129.05 , 128.95 , 128.39 , 127.42 , 121.21 , 117.01 , 67.57 , 65.70 , 61.70 , 60.44 , 39.84 .



1-benzyl-6,8-dichloro-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.8mg, 94%) as a yellow solid. **TLC:** R_f 0.38 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 - 7.36 (m, 4H), 7.33 (d, *J* = 7.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 4.35 (t, *J* = 8.3 Hz, 1H), 4.27 - 4.19 (m, 2H), 4.10 (d, *J* = 2.1 Hz, 2H), 4.01 (d, *J* = 7.3 Hz, 1H), 3.90 (dd, *J* = 8.3, 5.1 Hz, 1H), 3.21 - 3.11 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.63 , 129.16 , 129.11 , 129.07 , 128.93 , 128.63 , 127.83 , 67.44 , 66.26 , 61.03 , 60.69 , 39.66 .

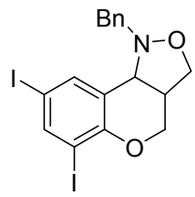


1-benzyl-8-fluoro-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.2mg, 96%) as a brown solid. **TLC:** R_f 0.3 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 2H), 7.37 (td, *J* = 7.7, 7.3, 1.6 Hz, 2H), 7.32 (dd, *J* = 7.0, 1.6 Hz, 1H), 6.91 - 6.80 (m, 3H), 4.35 (td, *J* = 8.3, 1.3 Hz, 1H), 4.16 - 4.11 (m, 4H), 4.01 (d, *J* = 7.3 Hz, 1H), 3.89 (ddd, *J* = 8.1, 5.1, 1.3 Hz, 1H), 3.19 - 3.10 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.95 , 129.11 , 128.56 , 127.68 , 118.07 , 117.99 , 116.50 , 116.27 , 115.99 , 115.76 , 67.63 , 65.75 , 61.26 , 60.71 , 39.88 .

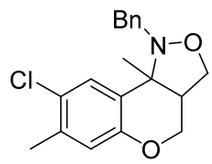


6-allyl-1-benzyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.4mg, 97%) as a yellow solid. **TLC:** R_f 0.56 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 - 7.41 (m, 2H), 7.37 - 7.33 (m, 2H), 7.31 - 7.26 (m, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.00 (ddt, *J* = 17.8, 9.5, 6.5 Hz, 1H), 5.08 - 5.03 (m, 2H), 4.34 - 4.25 (m, 2H), 4.18 (d, *J* = 5.9 Hz, 2H),

4.03 (d, *J* = 13.2 Hz, 1H), 3.95 (d, *J* = 7.0 Hz, 1H), 3.83 (dd, *J* = 8.1, 4.6 Hz, 1H), 3.39 (dd, *J* = 6.7, 2.1 Hz, 2H), 3.13 - 3.04 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.78 , 129.34 , 128.96 , 128.89 , 128.37 , 127.38 , 120.79 , 115.45 , 67.63 , 65.90 , 62.09 , 60.46 , 40.04 , 34.07 .

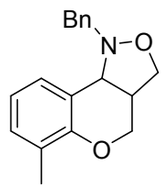


1-benzyl-6,8-diiodo-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.0mg, 95%) as a yellow solid. **TLC:** R_f 0.37 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.1 Hz, 1H), 7.44 - 7.29 (m, 6H), 4.34 (td, *J* = 8.2, 0.8 Hz, 1H), 4.25 - 4.22 (m, 2H), 4.10 (s, 2H), 3.97 (d, *J* = 7.1 Hz, 1H), 3.88 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.18 - 3.09 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.82 , 139.60 , 136.61 , 129.09 , 128.61 , 127.84 , 124.35 , 83.96 , 67.44 , 66.55 , 61.20 , 60.75 , 39.92 .

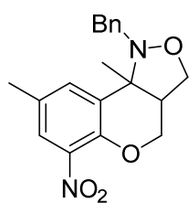


1-benzyl-6,8-diiodo-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.2mg, 96%) as a brown solid. **TLC:** R_f 0.4 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 - 7.52 (m, 1H), 7.38 (d, *J* = 5.6 Hz, 3H), 7.34 - 7.29 (m, 2H), 7.26 - 7.21 (m, 1H), 6.76 (s, 1H), 4.26 - 4.19 (m, 2H), 4.11

(dd, J = 11.5, 3.1 Hz, 1H), 3.91 - 3.83 (m, 2H), 2.77 (dtd, J = 8.9, 5.4, 3.2 Hz, 1H), 2.30 (s, 3H), 1.57 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.08 , 129.94 , 128.72 , 128.57 , 128.45 , 128.41 , 128.24 , 127.05 , 126.99 , 119.09 , 66.97 , 63.32 , 54.90 , 29.69 , 19.80 .

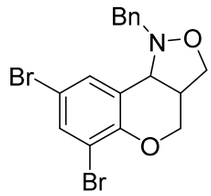


1-benzyl-6-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.4mg, 92%) as a brown-yellow solid. **TLC:** R_f 0.48 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 - 7.45 (m, 1H), 7.42 - 7.36 (m, 2H), 7.34 - 7.29 (m, 1H), 7.10 (t, J = 8.4 Hz, 2H), 6.89 (td, J = 7.5, 1.3 Hz, 1H), 4.35 - 4.29 (m, 2H), 4.25 - 4.20 (m, 2H), 4.05 (d, J = 13.3 Hz, 1H), 3.95 (d, J = 6.9 Hz, 1H), 3.85 (dd, J = 8.1, 4.6 Hz, 1H), 3.08 (qt, J = 6.5, 4.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.65 , 130.23 , 128.98 , 128.46 , 128.40 , 127.39 , 120.56 , 120.01 , 67.62 , 65.88 , 62.16 , 60.44 , 39.98 , 16.13 .



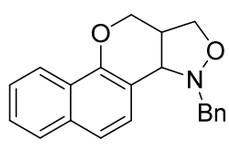
1-benzyl-6-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.0mg, 90%) as a yellow solid. **TLC:** R_f 0.24 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 - 7.50 (m, 2H), 7.39 (d, J = 7.3 Hz, 2H), 7.35 - 7.30 (m, 2H), 7.28 - 7.23 (m, 1H), 4.42 (dd, J = 11.7, 4.5 Hz, 1H), 4.34 - 4.24 (m, 2H), 4.04 - 3.87 (m, 3H), 2.93 - 2.86 (m, 1H), 2.34 (s, 3H), 1.61 (s, 3H). **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 133.93 , 130.12 , 128.45 , 128.34 , 127.23 , 124.95 , 66.92 , 65.27 , 63.93 , 54.99 , 45.90 , 23.79 , 20.59 .



1-benzyl-6,8-dibromo-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole:

Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.2mg, 91%) as a yellow solid. **TLC:** R_f 0.33 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.3 Hz, 1H), 7.44 - 7.35 (m, 4H), 7.34 - 7.29 (m, 1H), 7.15 (d, *J* = 2.3 Hz, 1H), 4.35 (t, *J* = 8.3 Hz, 1H), 4.26 (d, *J* = 5.1 Hz, 2H), 4.10 (s, 2H), 4.01 (d, *J* = 7.2 Hz, 1H), 3.90 (dd, *J* = 8.3, 4.9 Hz, 1H), 3.16 (td, *J* = 7.7, 5.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.59 , 134.67 , 132.59 , 129.10 , 128.76 , 128.62 , 127.84 , 67.45 , 66.38 , 61.13 , 60.71 , 39.74 .

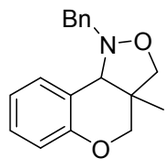


3-benzyl-3,3a,11,11a-tetrahydro-1H-benzo[7,8]chromeno[4,3-c]isoxazole:

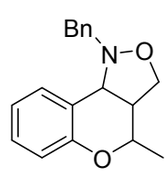
Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.4mg, 92%) as a yellow solid. **TLC:** R_f 0.28 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 - 7.66 (m, 3H), 7.40 (dhept, *J* = 20.6, 7.3 Hz, 7H), 7.10 (d, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 7.7 Hz, 1H), 4.47 (t, *J* = 8.6 Hz, 1H), 4.30 - 3.94 (m, 5H), 3.37 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.48 ,

129.86 , 129.41 , 128.43 , 128.35 , 127.60 , 126.46 , 123.69 , 118.61 , 68.01 , 66.26 , 59.02 , 58.93 , 40.62 .

4.5.3. Chromeoisoxazoles from Table 15.

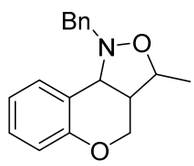


1-benzyl-3a-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.8mg, 94%) as a brown-orange solid. **TLC:** R_f 0.63 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 - 7.38 (m, 2H), 7.31 (ddd, *J* = 7.6, 6.3, 1.4 Hz, 2H), 7.27 - 7.20 (m, 3H), 6.97 - 6.89 (m, 2H), 4.37 (d, *J* = 13.6 Hz, 1H), 4.25 - 4.14 (m, 2H), 4.05 - 3.95 (m, 2H), 3.87 (d, *J* = 6.8 Hz, 1H), 2.49 (tt, *J* = 7.4, 5.0 Hz, 1H), 1.38 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.97 , 129.26 , 128.77 , 128.39 , 128.21 , 127.17 , 121.01 , 117.16 , 74.84 , 65.44 , 62.32 , 60.53 , 46.68 , 29.69 .

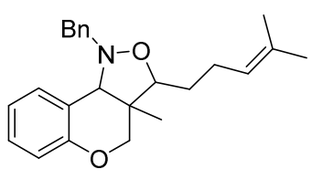


1-benzyl-4-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.2mg, 96%) as a white solid. **TLC:** R_f 0.45 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 - 7.41 (m, 2H), 7.36 (ddt, *J* = 7.4, 5.7, 1.2 Hz, 2H), 7.31 - 7.23 (m, 3H), 6.99 - 6.93 (m, 2H), 4.43 (d, *J* = 13.6 Hz, 1H), 4.29 (ddd, *J* = 8.5, 7.6, 1.2 Hz, 1H), 4.20 (dq, *J* = 12.0, 6.6 Hz, 1H), 3.97 (d, *J* = 13.4 Hz, 1H),

3.85 - 3.73 (m, 2H), 2.63 (dtdd, *J* = 9.8, 6.3, 3.5, 1.1 Hz, 1H), 1.43 (dd, *J* = 6.3, 1.3 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.71 , 130.79 , 129.29 , 128.83 , 128.35 , 127.31 , 120.77 , 117.09 , 71.76 , 67.83 , 62.62 , 60.41 , 46.08 , 19.44 .

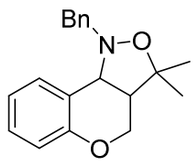


\1-benzyl-3-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.4mg, 97%) as a white solid. **TLC:** R_f 0.43 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 12.1 Hz, 2H), 7.37 - 7.30 (m, 2H), 7.29 - 7.21 (m, 3H), 6.95 (td, *J*= 8.3, 3.9 Hz, 2H), 4.39 (dd, *J* = 13.6, 4.1 Hz, 1H), 4.27 - 4.14 (m, 2H), 4.06 - 3.96 (m, 2H), 3.88 (t, *J* = 5.2 Hz, 1H), 2.50 (dt, *J* = 9.8, 4.8 Hz, 1H), 1.42 - 1.37 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.01 , 129.28 , 128.80 , 128.79 , 128.23 , 127.18 , 121.03 , 117.18 , 74.85 , 65.47 , 62.35 , 60.57 , 46.70 , 20.10 .

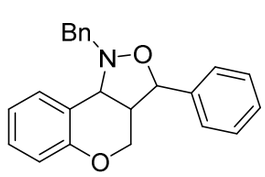


1-benzyl-3a-methyl-3-(4-methylpent-3-en-1-yl)-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.6mg, 93%) as a white solid. **TLC:** R_f 0.63 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39

(d, *J* = 7.3 Hz, 2H), 7.26 (ddd, *J* = 13.0, 9.3, 2.8 Hz, 5H), 6.95 - 6.90 (m, 2H), 5.10 (td, *J* = 7.2, 3.5 Hz, 1H), 4.48 (d, *J* = 14.1 Hz, 1H), 4.31 (td, *J* = 10.2, 9.7, 3.1 Hz, 1H), 4.21 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.95 (dd, *J* = 14.5, 3.0 Hz, 1H), 3.85 (d, *J* = 5.8 Hz, 1H), 2.57 (dt, *J* = 10.3, 5.3 Hz, 1H), 2.07 (dt, *J* = 11.9, 6.8 Hz, 2H), 1.69 (d, *J* = 3.3 Hz, 3H), 1.61 (d, *J* = 3.6 Hz, 3H), 1.26 (d, *J* = 4.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.14 , 129.31 , 128.33 , 128.05 , 126.80 , 123.87 , 120.62 , 116.97 , 64.75 , 62.89 , 59.86 , 45.83 , 42.81 , 25.67 , 23.12 , 20.42 .



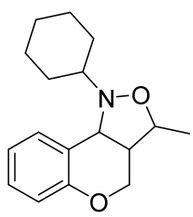
1-benzyl-3,3-dimethyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.4mg, 92%) as a white solid. **TLC:** R_f 0.55 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 2H), 7.31 - 7.20 (m, 5H), 6.95 - 6.89 (m, 2H), 4.49 (dd, *J* = 14.3, 2.7 Hz, 1H), 4.37 - 4.20 (m, 2H), 4.02 - 3.91 (m, 2H), 2.49 (tt, *J* = 7.7, 2.9 Hz, 1H), 1.38 (d, *J* = 2.7 Hz, 3H), 1.30 (d, *J* = 2.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.03 , 129.31 , 128.30 , 128.08 , 126.84 , 120.63 , 116.98 , 64.55 , 62.68 , 60.01 , 47.50 , 30.12 , 22.71 .



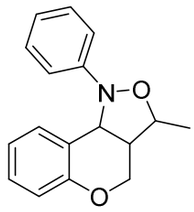
1-benzyl-3-phenyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column

volumes) yielded the isoxazolidine (19.2mg, 96%) as a white solid. **TLC:** R_f 0.5 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 6.5, 1.6 Hz, 5H), 7.41 - 7.29 (m, 6H), 7.29 - 7.21 (m, 3H), 6.98 - 6.92 (m, 2H), 4.42 (d, *J* = 13.5 Hz, 1H), 4.34 (dd, *J* = 11.3, 7.0 Hz, 1H), 4.25 (dd, *J* = 11.3, 4.3 Hz, 1H), 4.20 (d, *J* = 13.5 Hz, 1H), 4.12 (d, *J* = 7.0 Hz, 1H), 2.87 (qd, *J* = 6.8, 4.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.85 , 129.33 , 129.07 , 128.66 , 128.61 , 128.29 , 128.08 , 127.32 , 126.53 , 121.24 , 117.22 , 80.96 , 65.24 , 62.44 , 60.95 , 48.29 .

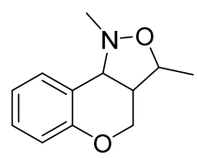
4.5.4. Chromeoisoxazoles from Table 16.



1-cyclohexyl-3-methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.2mg, 96%) as a yellow solid. **TLC:** R_f 0.5 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 8.8, 7.2 Hz, 1H), 7.15 (ddd, *J* = 8.6, 7.5, 1.7 Hz, 1H), 6.94 (td, *J* = 7.5, 1.3 Hz, 1H), 6.82 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.30 (d, *J* = 7.2 Hz, 1H), 4.19 (d, *J* = 4.3 Hz, 2H), 4.07 (p, *J* = 6.3 Hz, 1H), 2.83 (tt, *J* = 10.9, 3.4 Hz, 1H), 2.43 (tt, *J* = 7.2, 4.3 Hz, 1H), 2.25 - 2.19 (m, 1H), 1.86 (d, *J* = 12.1 Hz, 2H), 1.70 - 1.62 (m, 2H), 1.53 - 1.46 (m, 2H), 1.37 (d, *J* = 6.2 Hz, 3H), 1.32 - 1.23 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.57 , 128.60 , 121.31 , 116.82 , 64.33 , 62.57 , 57.22 , 46.75 , 32.27 , 27.31 , 26.12 , 25.54 , 25.20 , 19.81 .

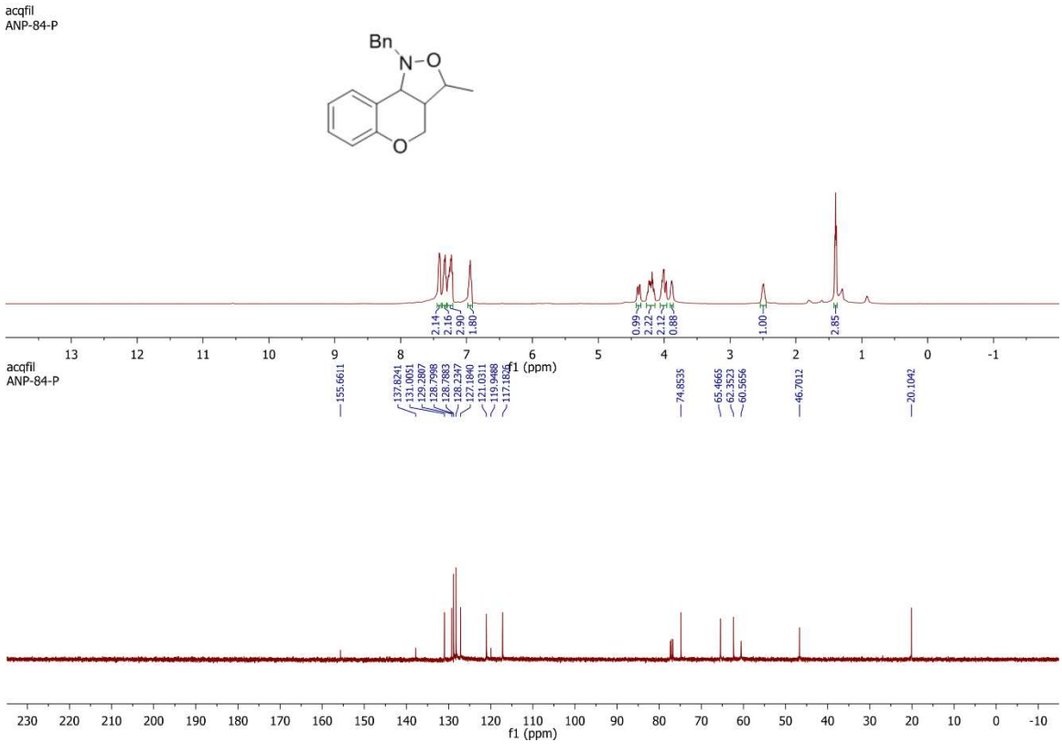


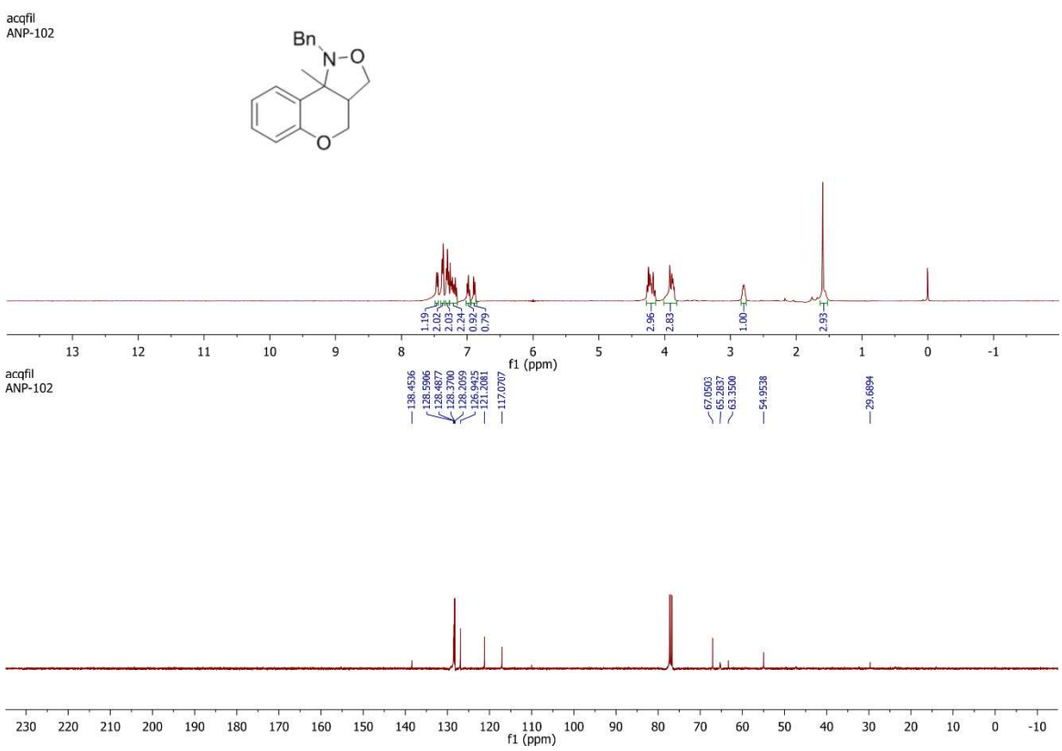
3-methyl-1-phenyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (19.0mg, 95%) as a brown solid. **TLC:** R_f 0.45 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.6, 7.1 Hz, 2H), 7.25 (dd, *J* = 7.1, 1.6 Hz, 2H), 7.22 - 7.17 (m, 1H), 7.10 (dq, *J* = 7.2, 1.6 Hz, 2H), 6.92 - 6.86 (m, 2H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.35 - 4.29 (m, 1H), 4.26 (d, *J* = 3.6 Hz, 1H), 4.20 (dd, *J* = 11.6, 5.5 Hz, 1H), 2.54 (tdd, *J* = 7.0, 5.4, 3.6 Hz, 1H), 1.52 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.62 , 129.18 , 128.75 , 128.70 , 123.68 , 121.24 , 118.08 , 116.87 , 75.91 , 64.48 , 64.19 , 46.51 , 19.90 .

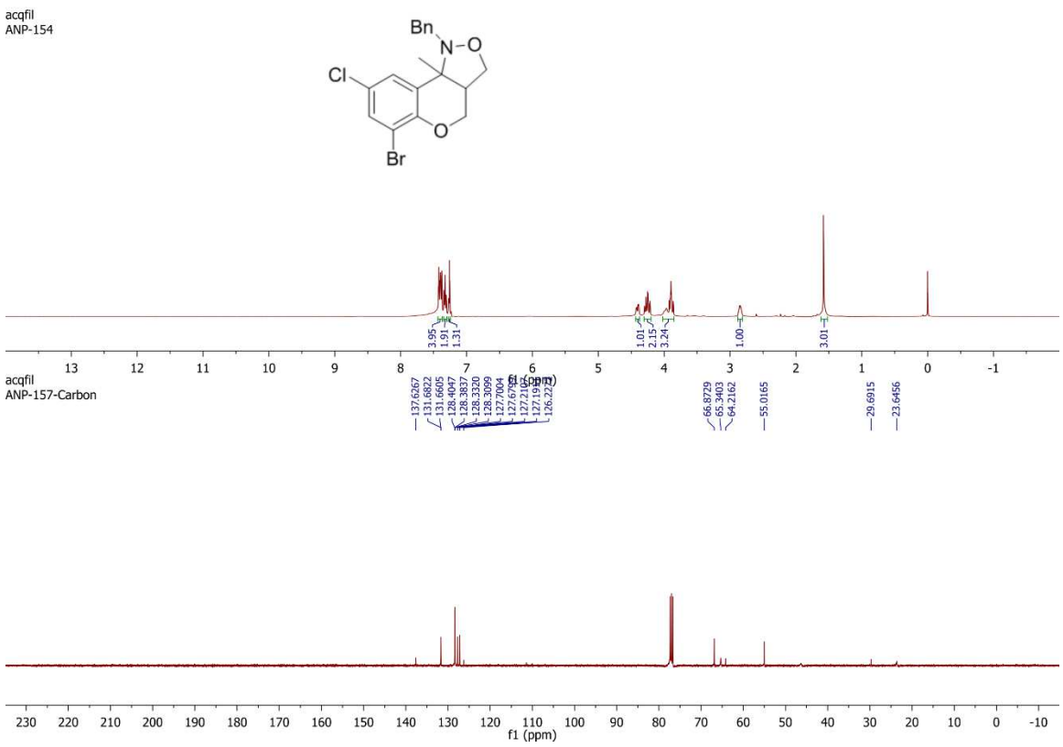


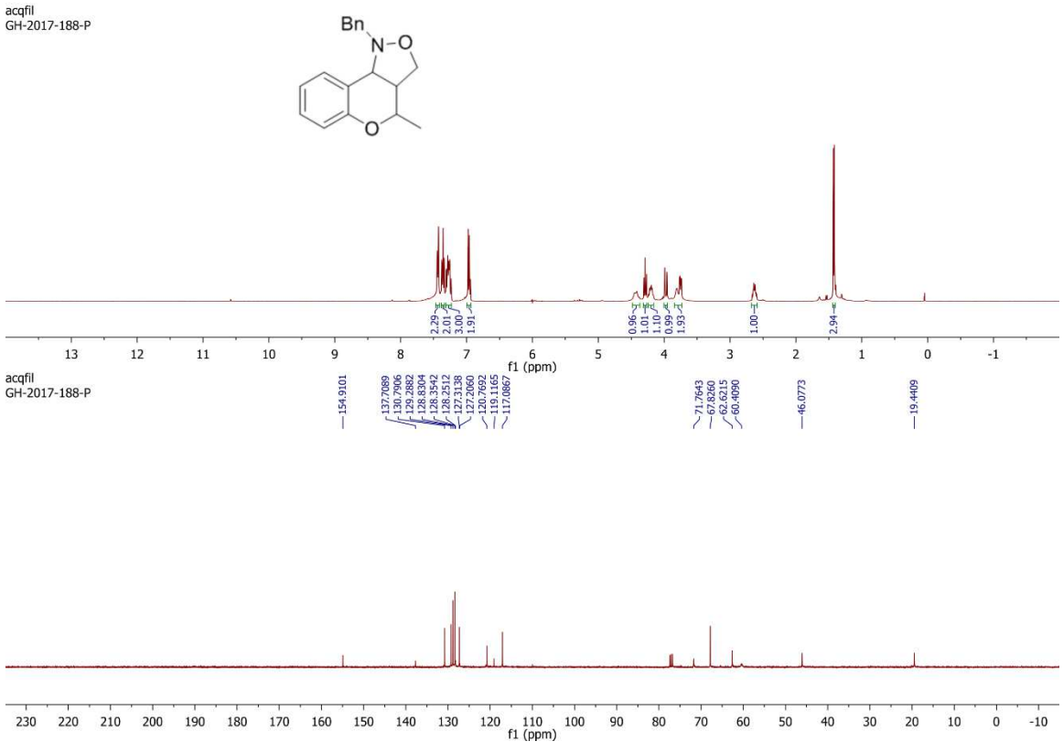
1,3-dimethyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole: Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-15% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine (18.8mg, 94%) as a white solid. **TLC:** R_f 0.33 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 - 7.19 (m, 2H), 6.97 - 6.90 (m, 2H), 4.15 - 4.06 (m, 2H), 4.00 - 3.92 (m, 1H), 3.48 (s, 1H), 2.85 (s, 3H), 2.45 (td, *J* = 7.9, 7.4, 3.5 Hz, 1H), 1.39 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.66 , 129.42 , 121.01 , 117.34 , 74.71 , 65.88 , 64.93 , 47.45 , 43.35 , 19.72

4.5.5. ^{1}H NMR and ^{13}C NMR of Chromeoisoxazoles.









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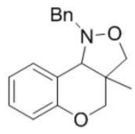
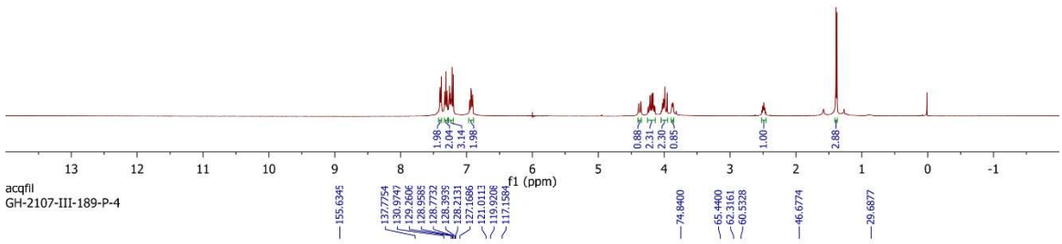
GH-2017-III-189-P





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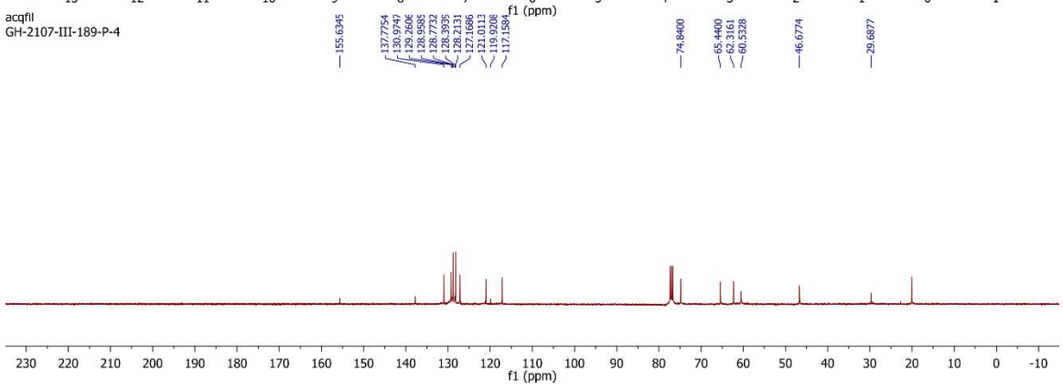

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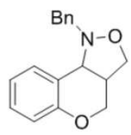

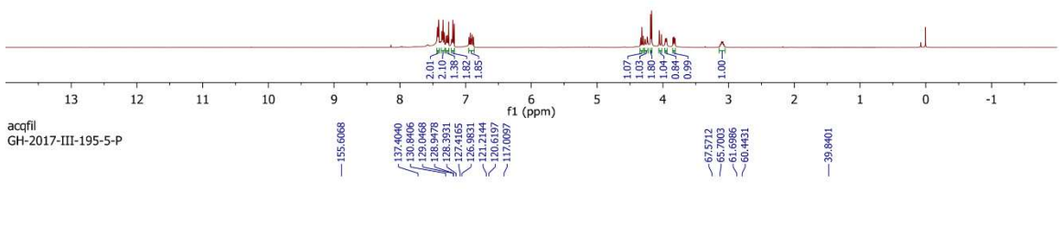

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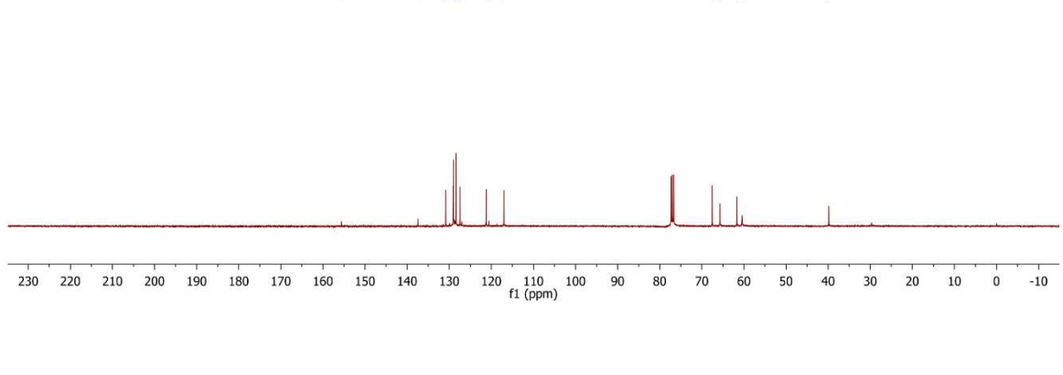

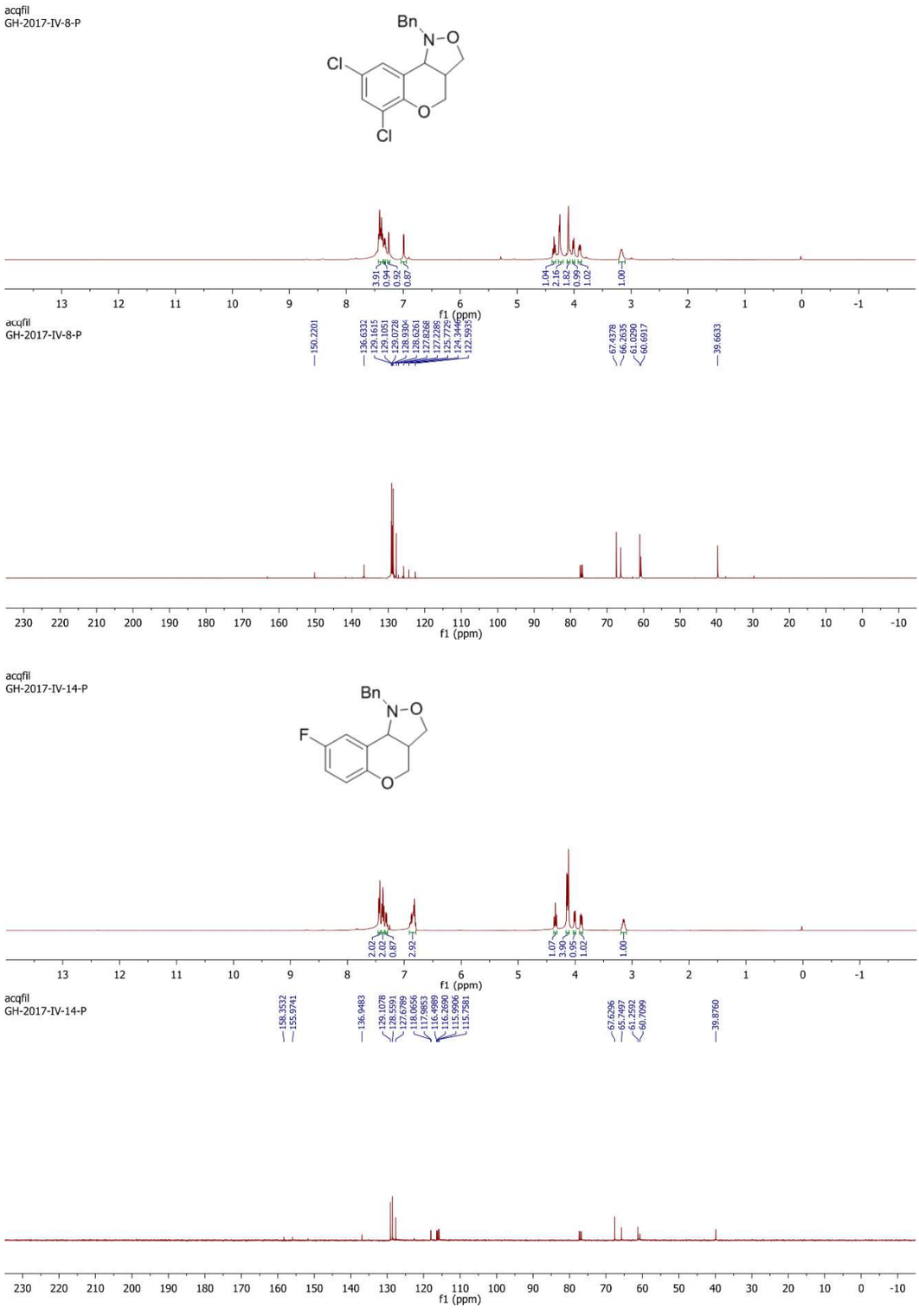

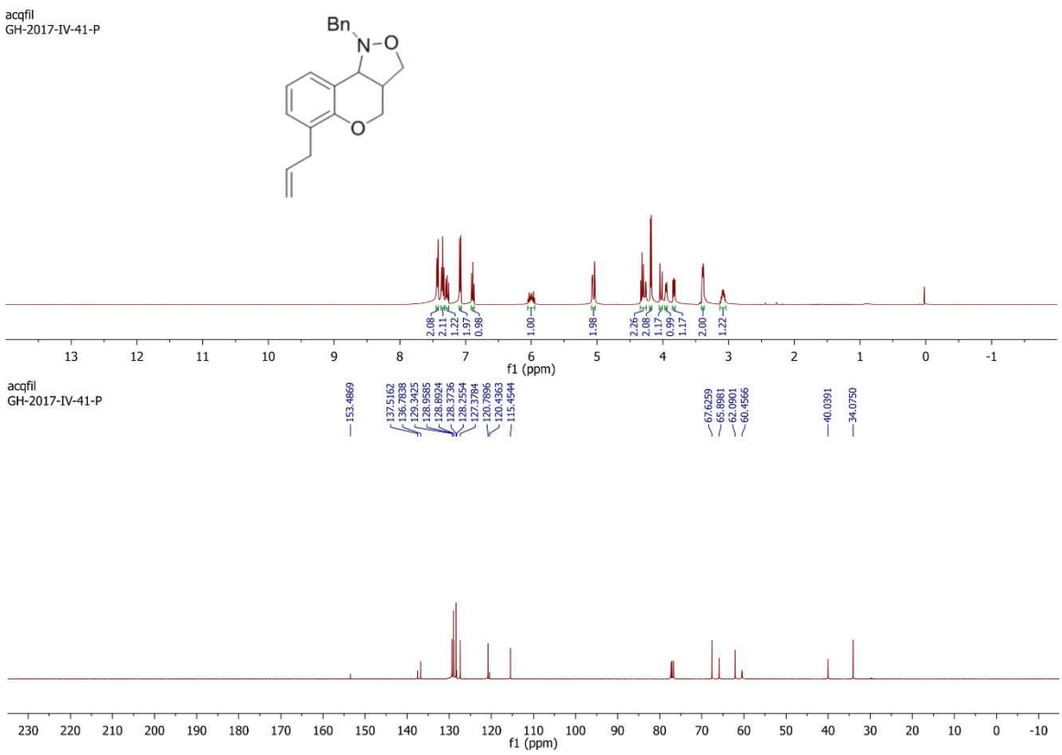

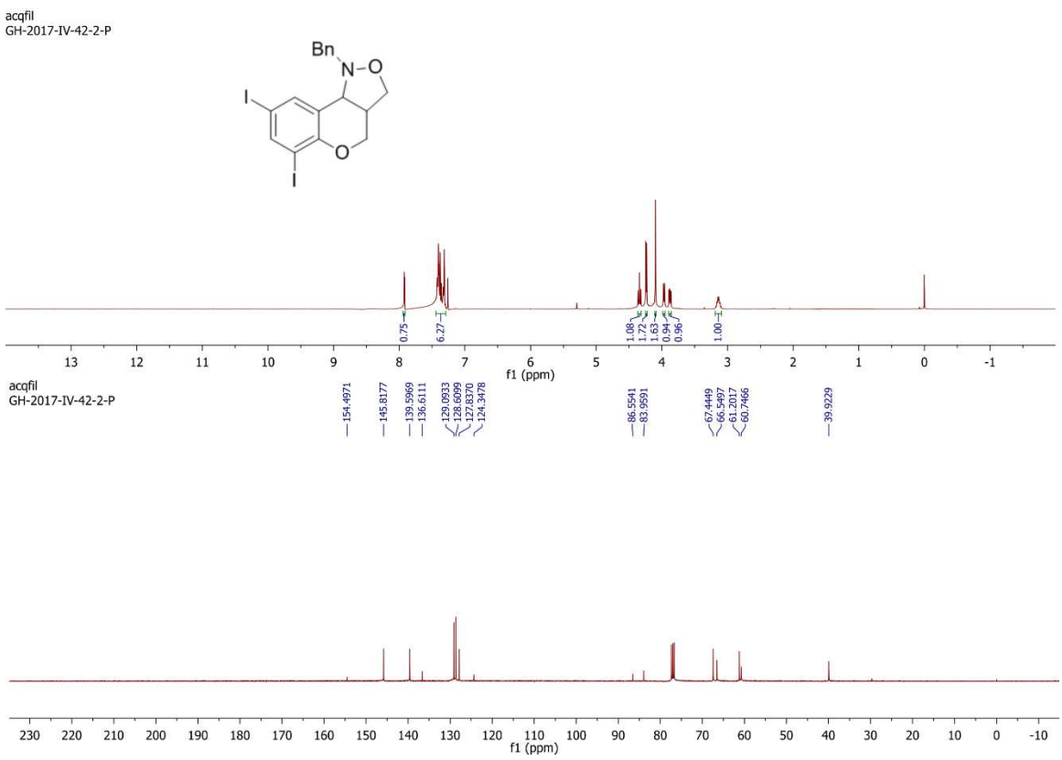

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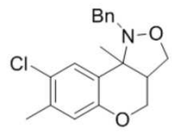

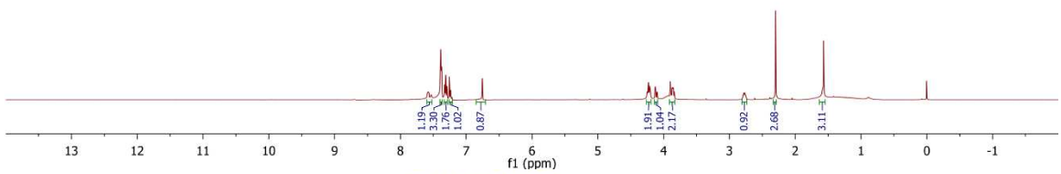

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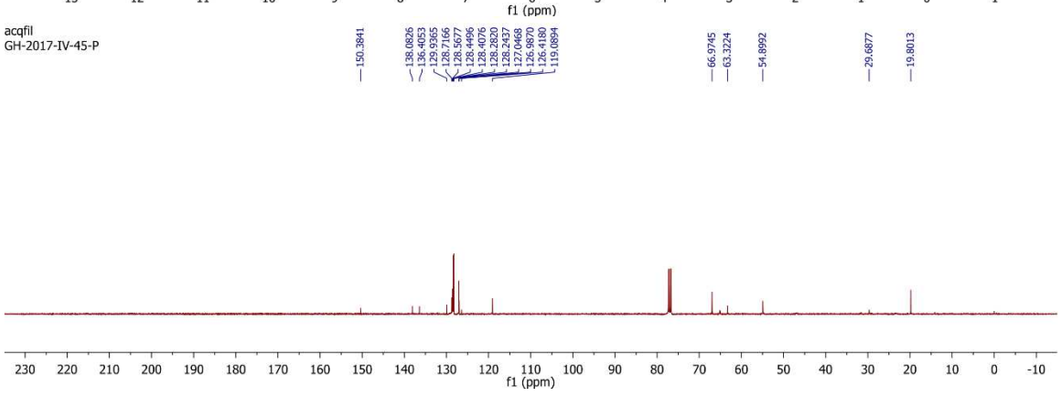

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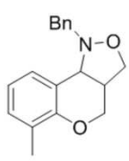

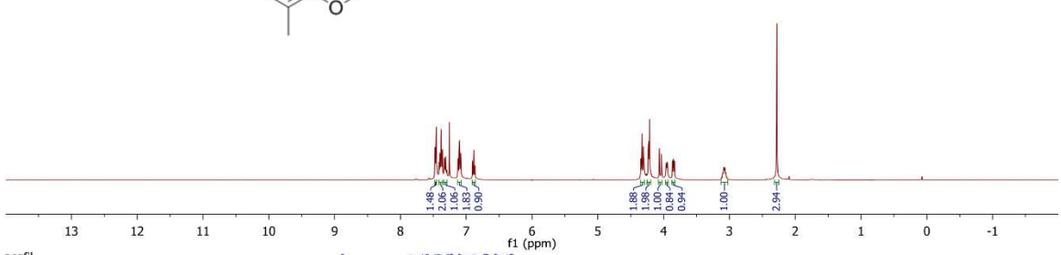

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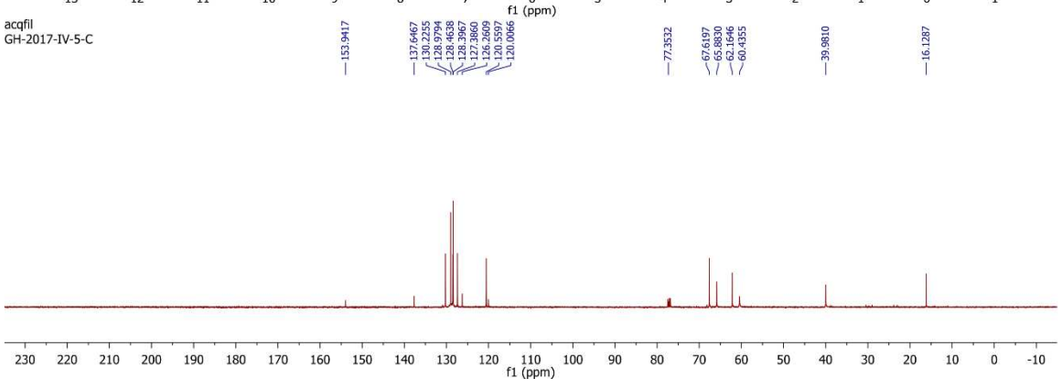

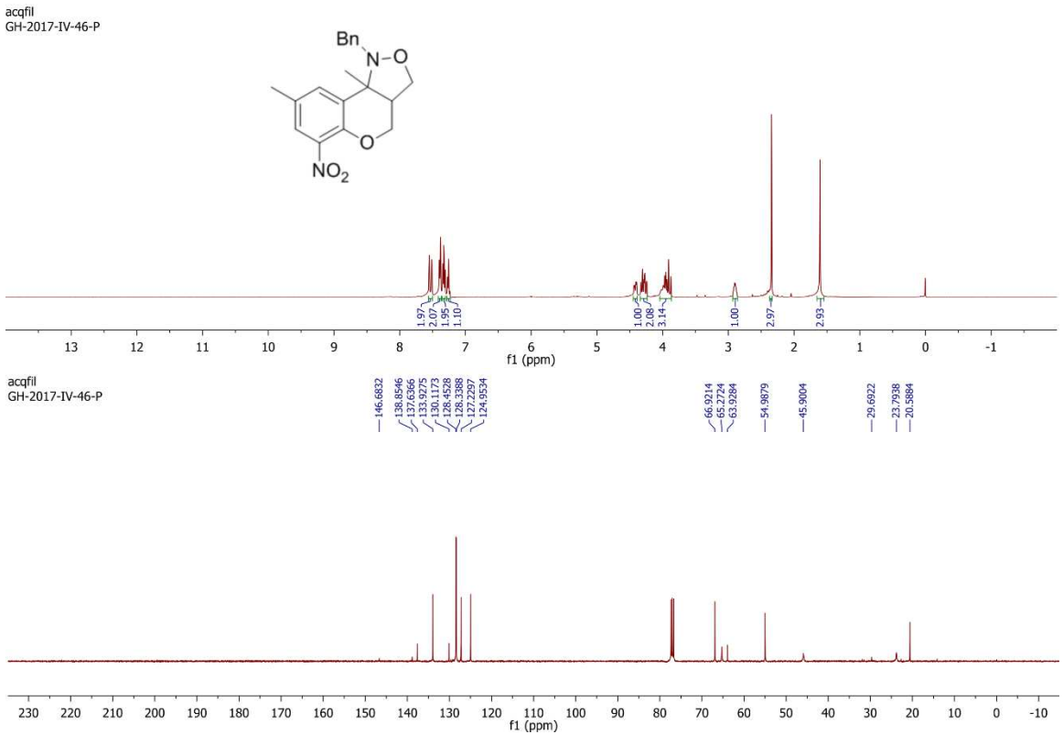

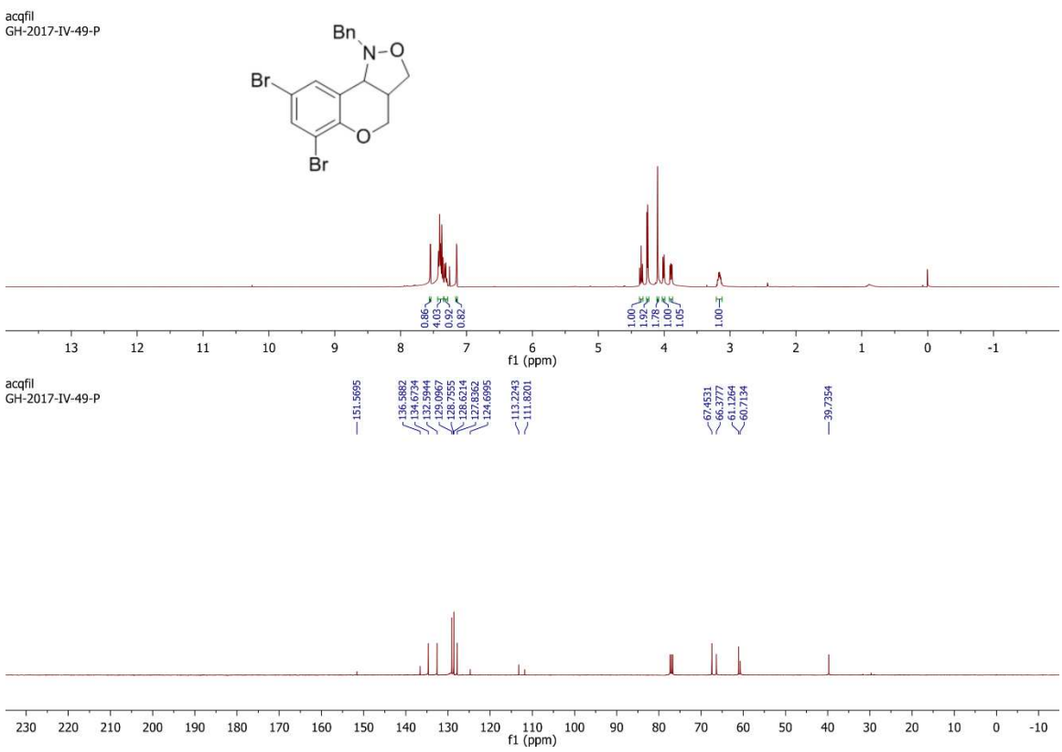

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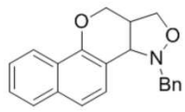

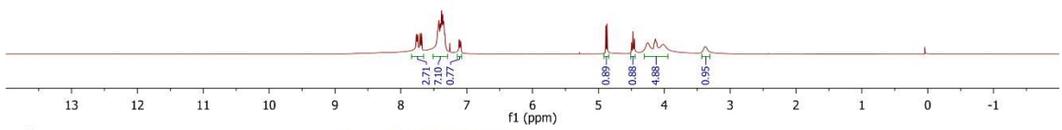

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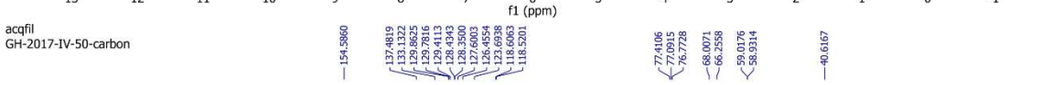

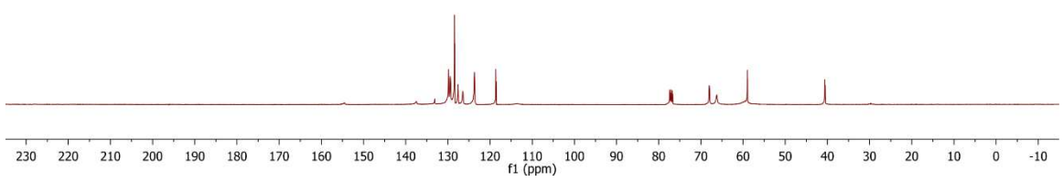

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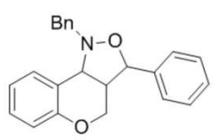

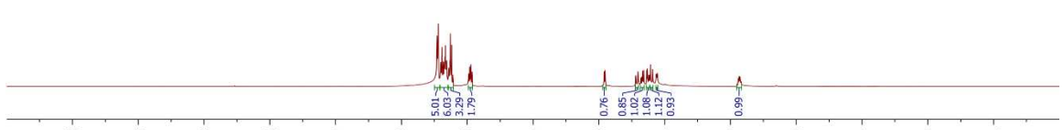

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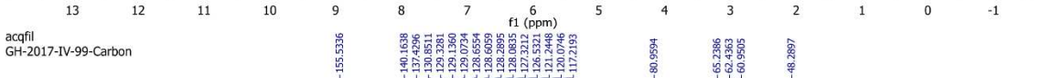

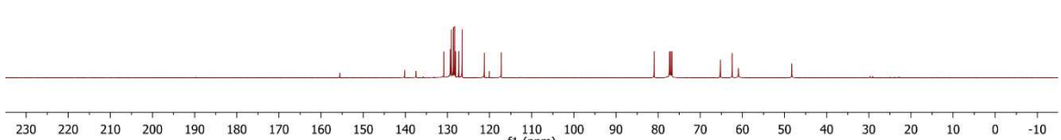

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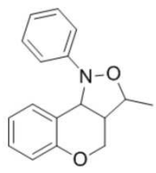

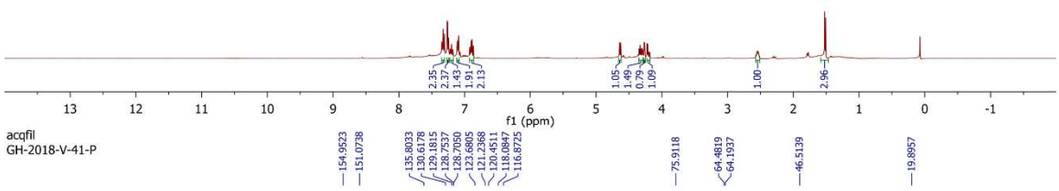

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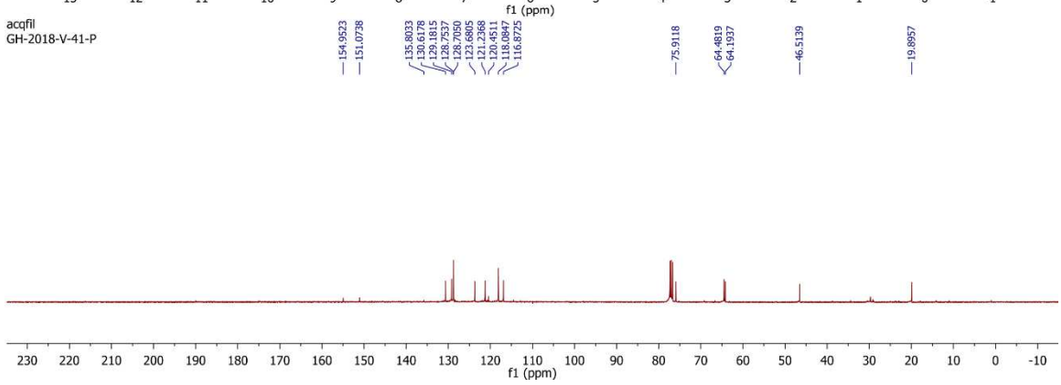

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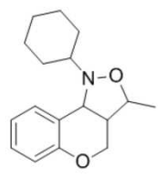

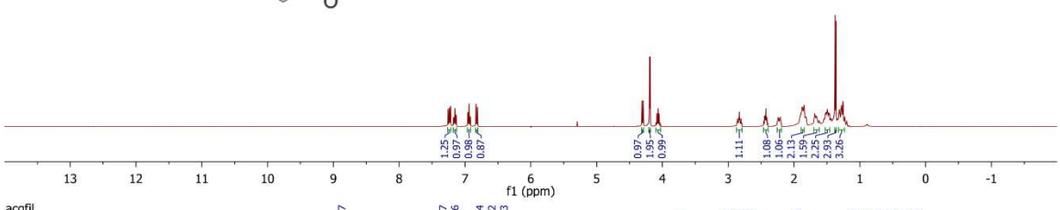

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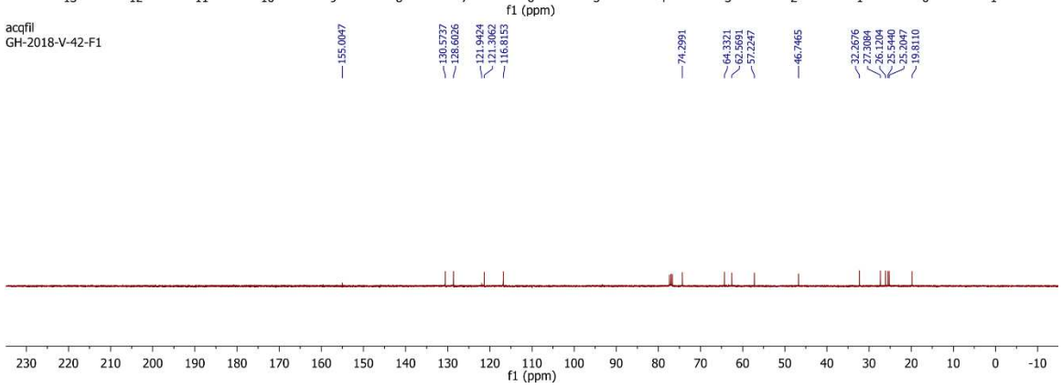

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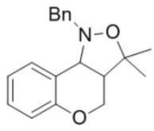

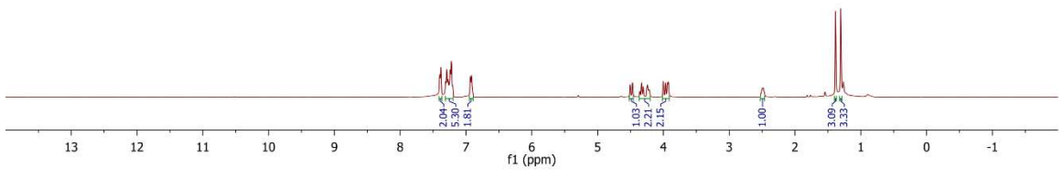

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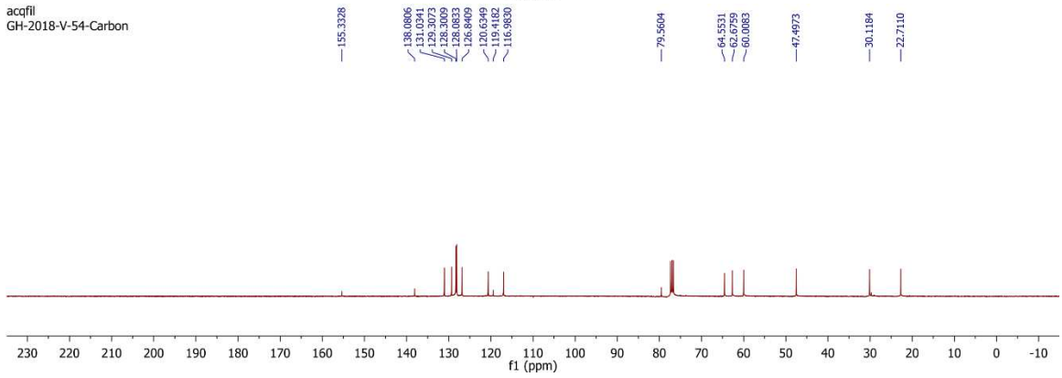

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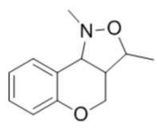

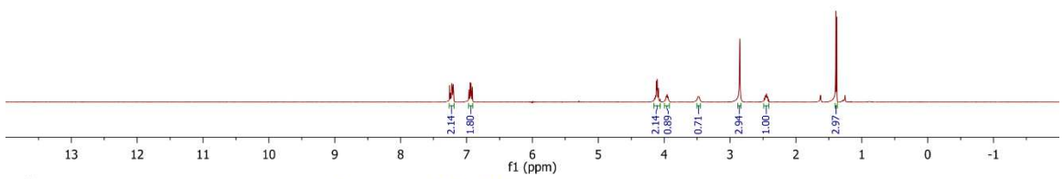

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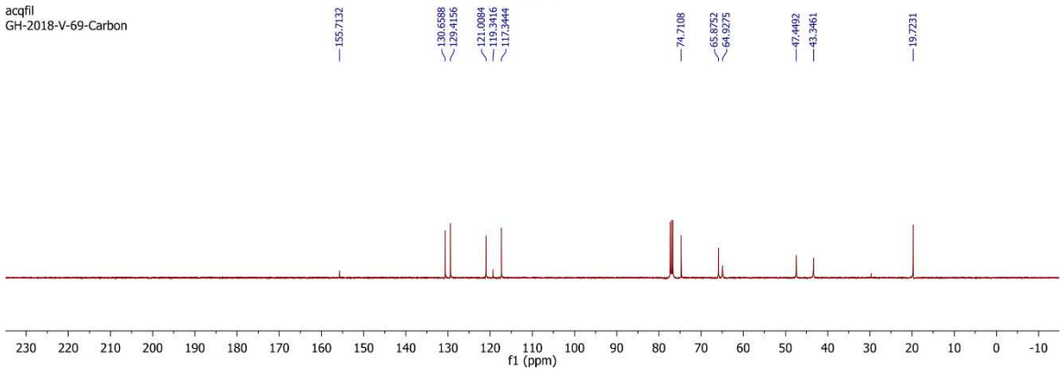

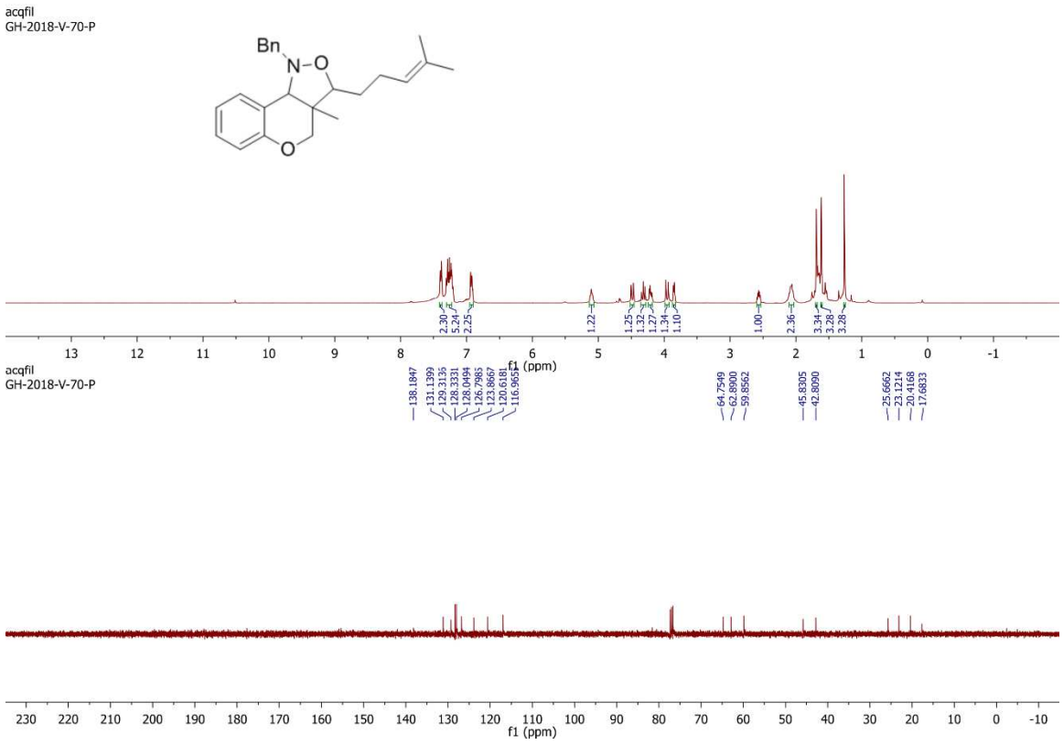

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