Supporting Information

TEMPO-catalyzed Synthesis of 5-Substituted Isoxazoles from Propargylic Ketones and $TMSN_3$

Yan He, [+a] Yu-yang Xie, [+a] Ying-chun Wang,[ab] Xiao-min Bin,[a] Da-chao Hu,[a] Heng-Shan Wang*[a] and Ying-Ming Pan*[a]

[a] State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People's Republic of China. E-mail: whengshan@163.com, panym2013@hotmail.com

[b] College of Chemistry and Chemical Engineering, Jishou University, Jishou 416000, People's Republic of China

*Correspondence authors

Phone: (+86)-773-5846279; fax: (+86)-773-5803930;

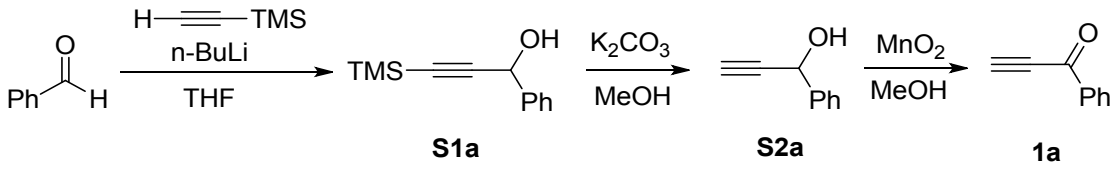
E-mail: whengshan@163.com; panym2013@hotmail.com

General remarks

Melting points were measured with a SGW X-4 melting point instrument (uncorrected). Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as reference standard (δ 7.26 ppm) for ^{1}H NMR and (δ 77 ppm) for ^{13}C NMR. HRMS (ion trap) were recorded using ESI. Precoated silica gel plates GF-254 were used for thin-layer analytical chromatography. Column chromatography was performed on silica gel (300-400 mesh). Starting materials azidomethyl aromatics were readily prepared according to literature procedures. Unless otherwise noted, all reagents were obtained commercially and used without further purification.

General preparation of propargylic ketones substrates

The following synthesis procedure is the general procedure used to prepare all substrates.



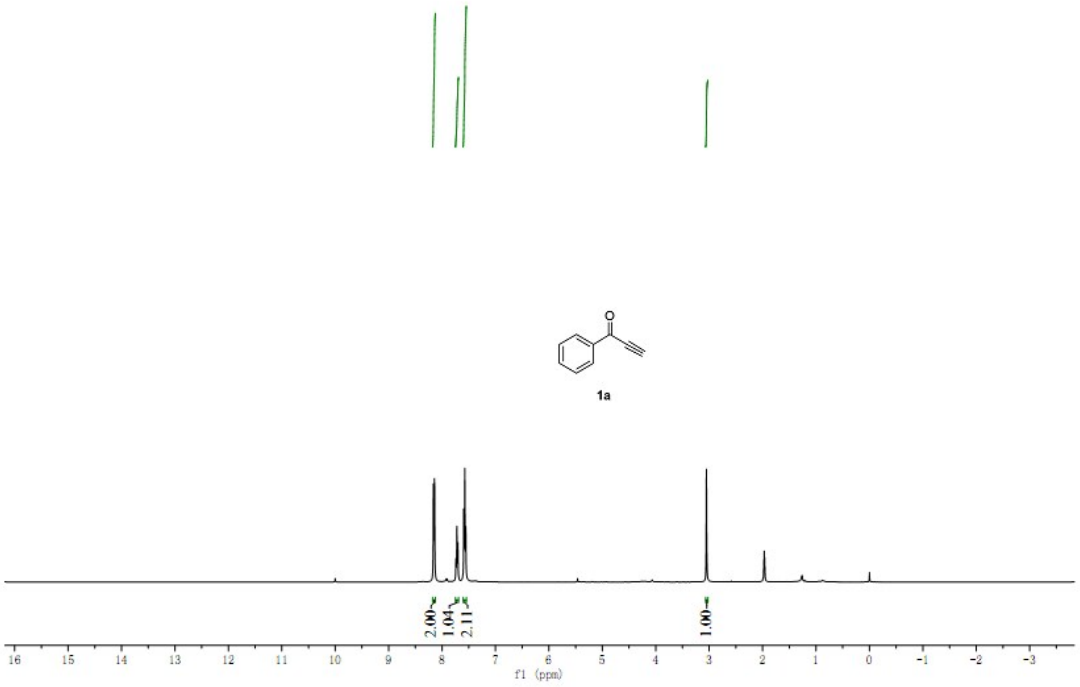
Under an Ar atmosphere, to a solution of trimethylsilylacetylene (1.5 mL, 10.00 mmol) in THF (20.0 mL) were added dropwise *n*-BuLi (9.38 mL, 1.6 M in hexane) at –78 °C, and the mixture was stirred for 30 min at the same temperature. To the above reaction mixture was added benzaldehyde (1.02 ml, 10.00 mmol) at –78 °C, and the mixture was stirred with slowly warming to room temperature. After stirring for 2 h at the same temperature, the reaction was quenched with sat. NH_4Cl aq., and the mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (CH_2Cl_2: hexane = 4:1) to afford 1-phenyl-3-trimethylsilanylprop-2-yn-1-ol (**S1a**) (2.01 g, 9.82 mmol) as colorless oil.

To a solution of **S1a** (2.01 g, 9.82 mmol) in MeOH (20.0 mL) were added K_2CO_3 (1.38 g, 10.00 mmol) at room temperature, and the mixture was stirred for 2 h at the same temperature, and monitored periodically by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The crude residue was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 1:20 to 1:10) to afford propargyl alcohols **S2a** (1.30 g, 9.8mmol).

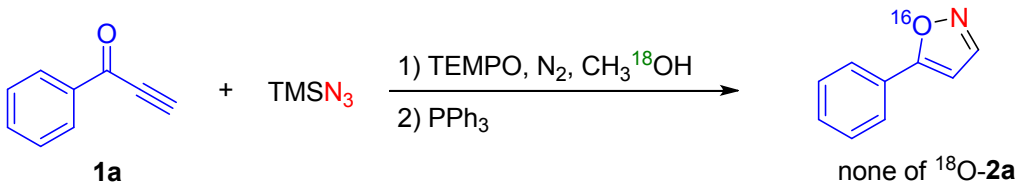
The crude alcohol was dissolved in dichloromethane and treated with MnO_2 (15 equiv.). After stirring at room temperature for 2h, the reaction was complete as

determined by TLC. Excess MnO_2 was removed by filtration of the reaction mixture through a pad of celite. The filtrate was washed sequentially with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford a yellow residue that was purified by flash column chromatography. The crude residue was purified by flash silica gel column chromatography (ethyl acetate/petroleum ether = 1:20 to 1:10) to afford propargylic ketones **1a** (1.04 g, 8.00mmol).

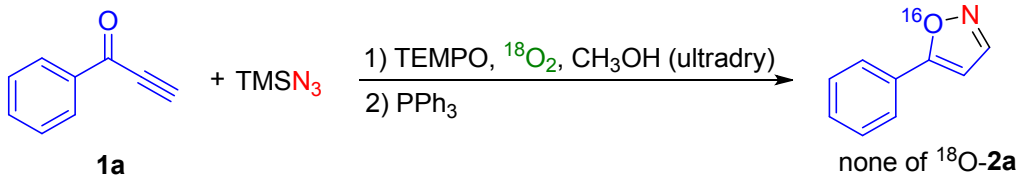
Propargylic ketones (**1a**) ^{1}H NMR (400 MHz, CD_3CN): δ 8.15–8.09 (m, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 3.02 (s, 1H).



Labeling experiments:

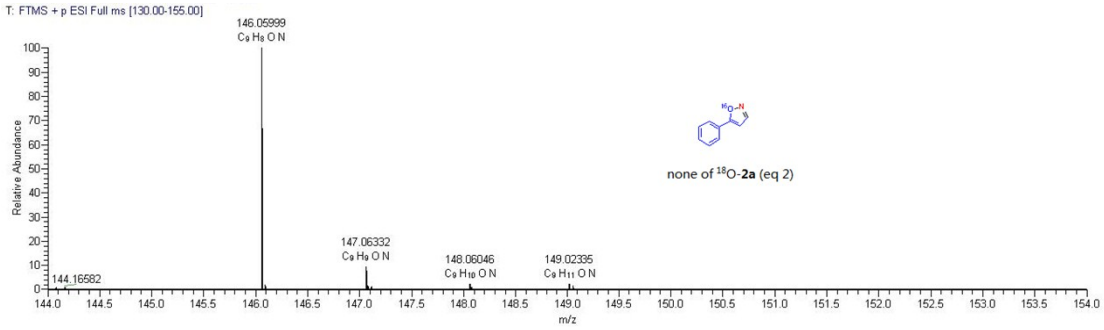


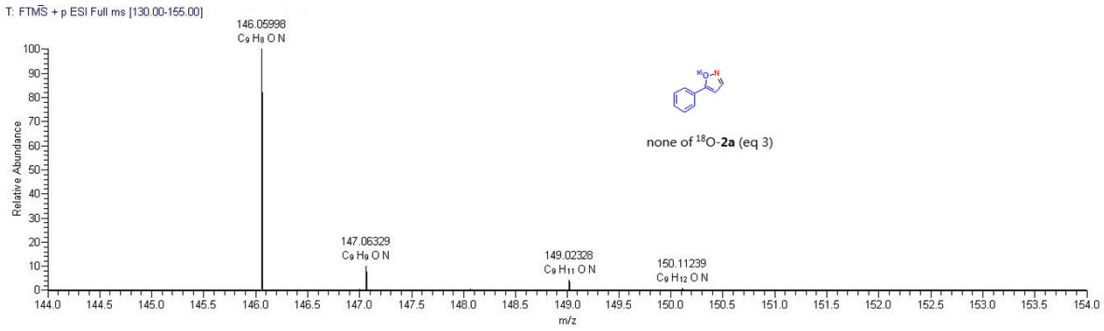
Reaction conditions: **1a** (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in $CH_3{}^{18}OH$ (2 mL) under argon atmosphere at room temperature. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The **^{18}O-2a** was determined by HRMS.

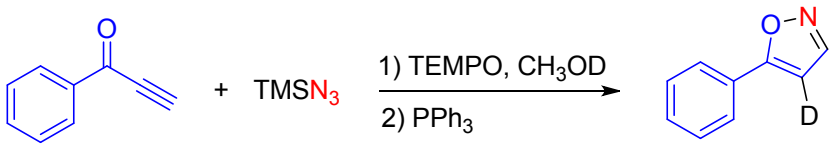


Reaction conditions:**1a** (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in CH_3OH (2 mL) under $^{18}O_2$ atmosphere at room temperature. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The **^{18}O-2a** was determined by HRMS.

HRMS analysis of 2a

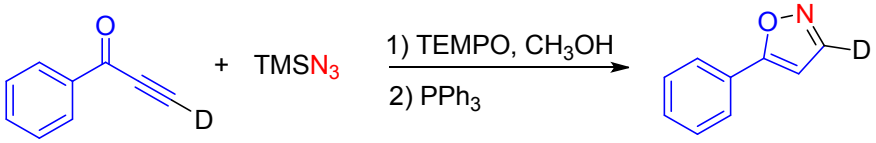






1a **2a-*d*** 78% yield (96%-*d*)

Reaction conditions:**1a** (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in CH_3OD (2 mL) under $^{18}O2$ atmosphere at room temperature. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The **2a-*d*** was determined by ^1H NMR.

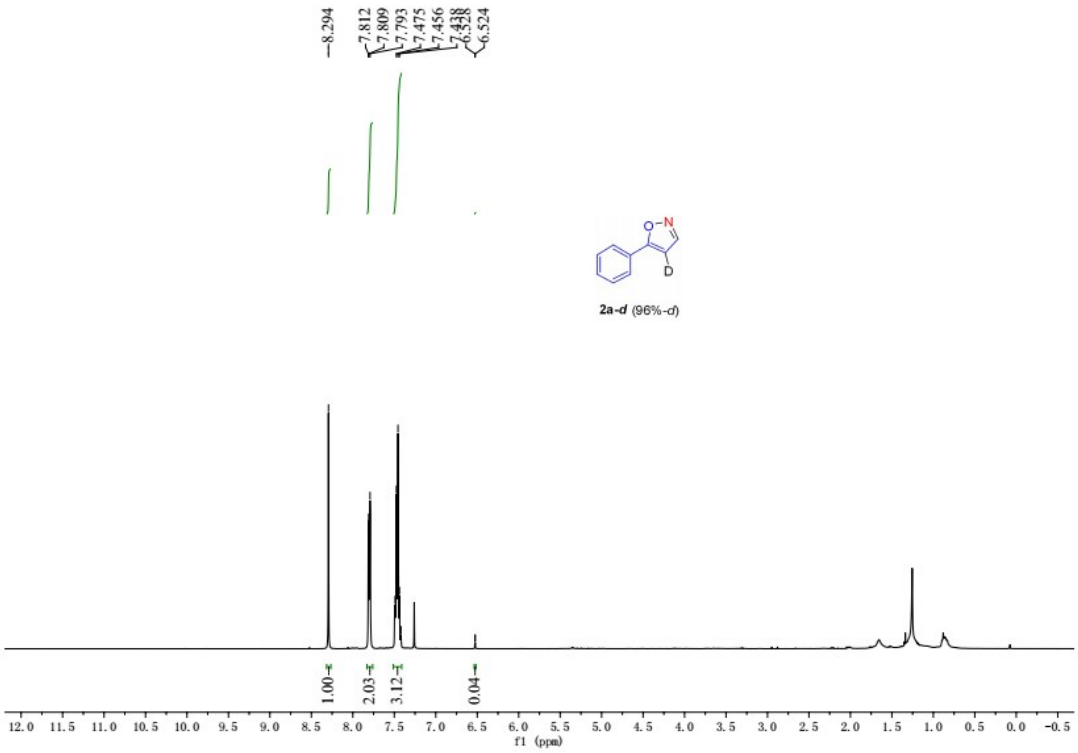


1a-*d*`** (91%-*d*) **2a-*d*` 77% yield (90%-*d*)

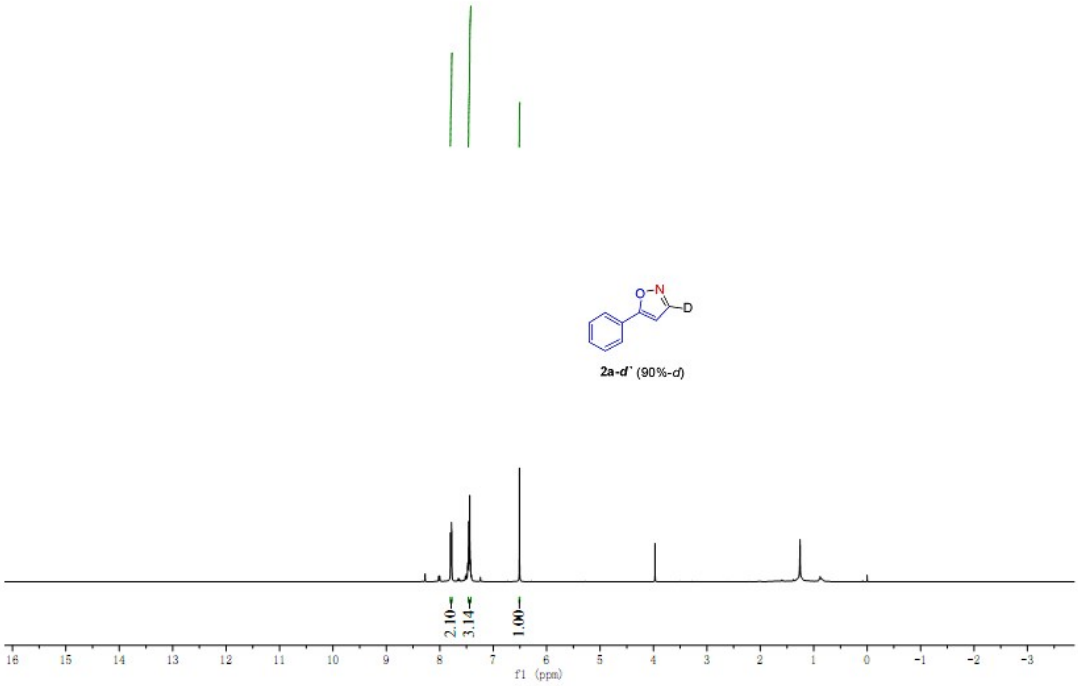
Reaction conditions:**1a-*d*`** (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in $CH_3OH$ (2 mL) under air atmosphere at room temperature. $PPh_3$ (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h. The **2a-*d*`** was determined by ^1H NMR.

Spectral data of 2a-d and 2a-*d*`

2a-*d* ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.83–7.76 (m, 2H), 7.51–7.41 (m, 3H) ppm.



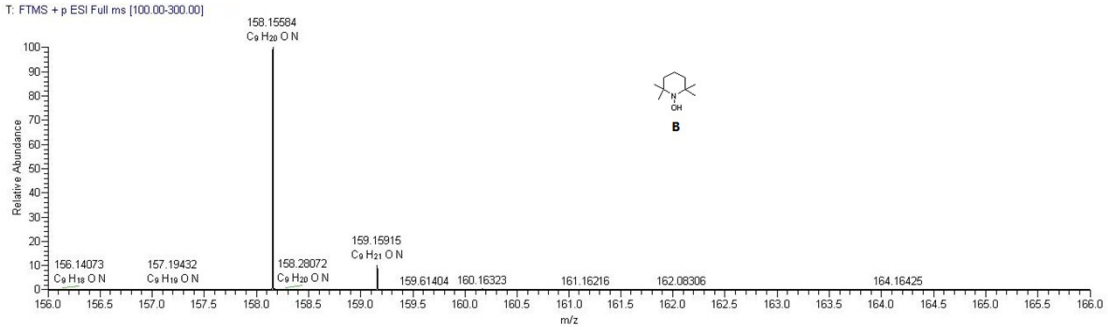
2a-*d`* ^{1}H NMR (400 MHz, CDCl3) δ 7.81 (dd, J = 7.9, 1.6 Hz, 2H), 7.47 (d, J = 7.7 Hz, 3H), 6.53 (s, 1H)



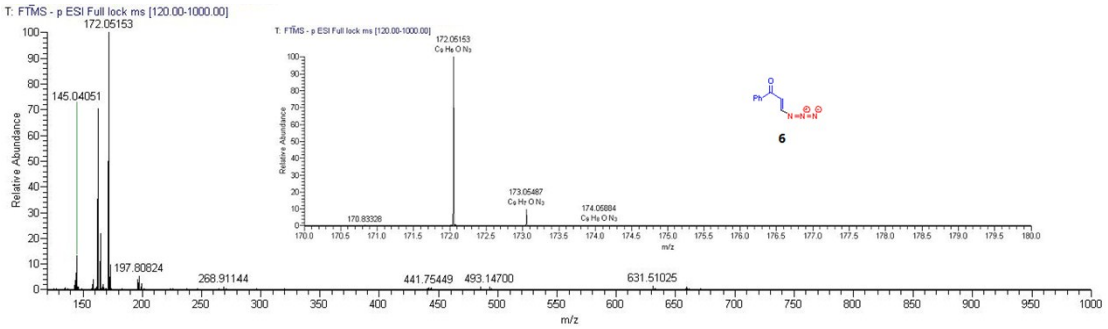
ESI/MS experiments:

1 (0.3 mmol), $TMSN_3$ (0.45 mmol), TEMPO (15 mol%) in CH3OH (2 mL) under air at room temperature. PPh_3 (1.0 equiv.) was added after 12 h and the mixture was stirred for another 1 h and 50 μL of the mixture was used for the ESI analysis in CH_3OH.

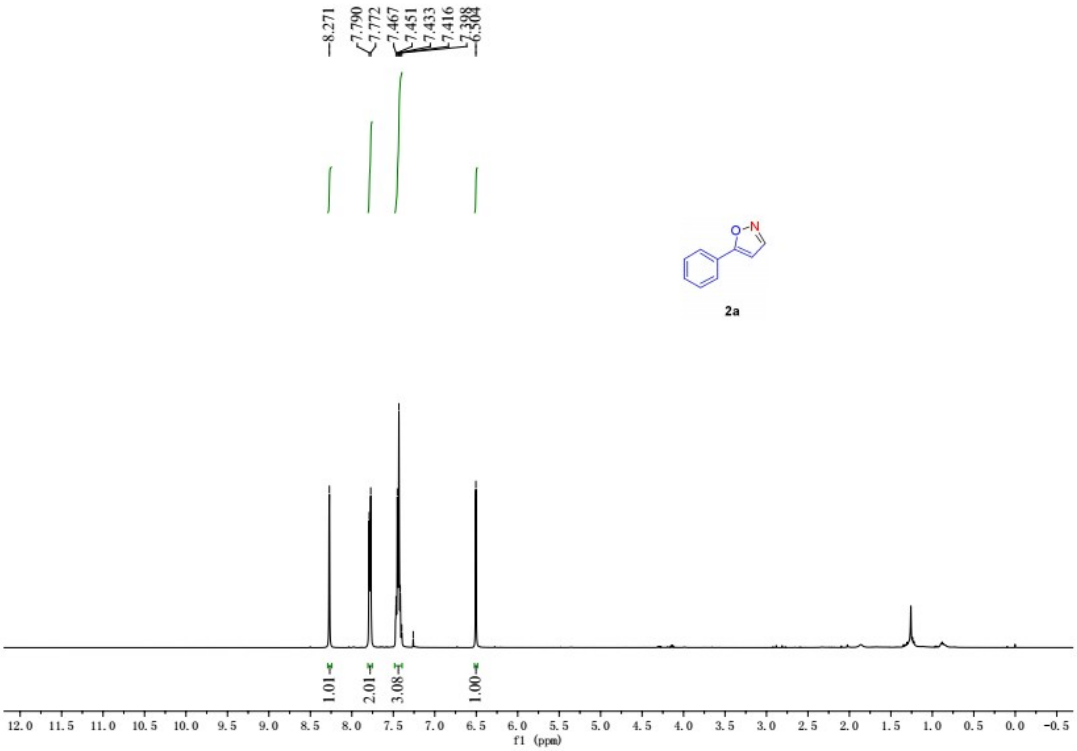
The species **B** in the reaction mixture was identified by HRMS.

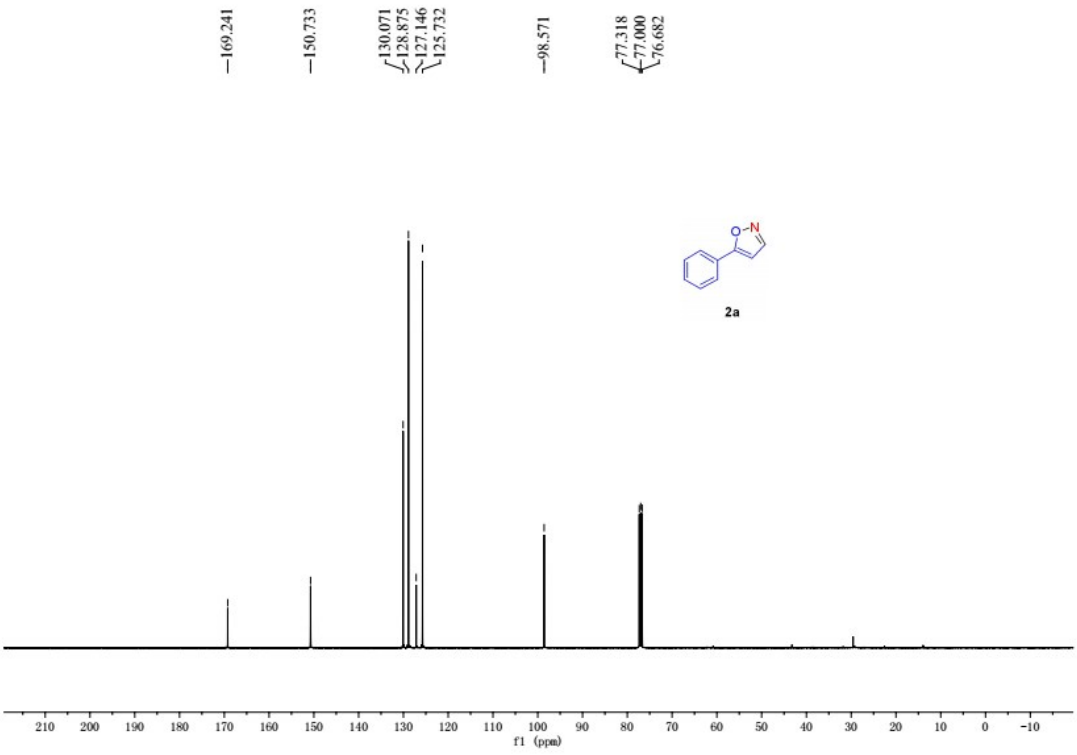


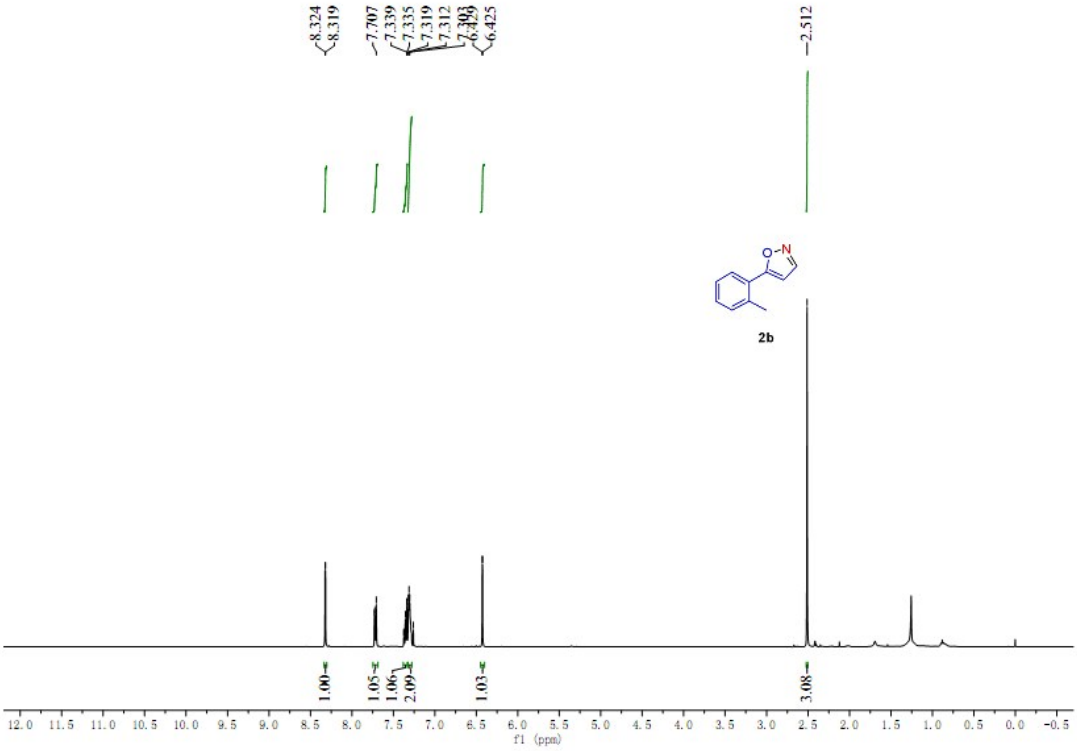
The intermediate **8** in the reaction mixture was identified by HRMS.



^{1}H NMR and ^{13}C NMR spectra for products



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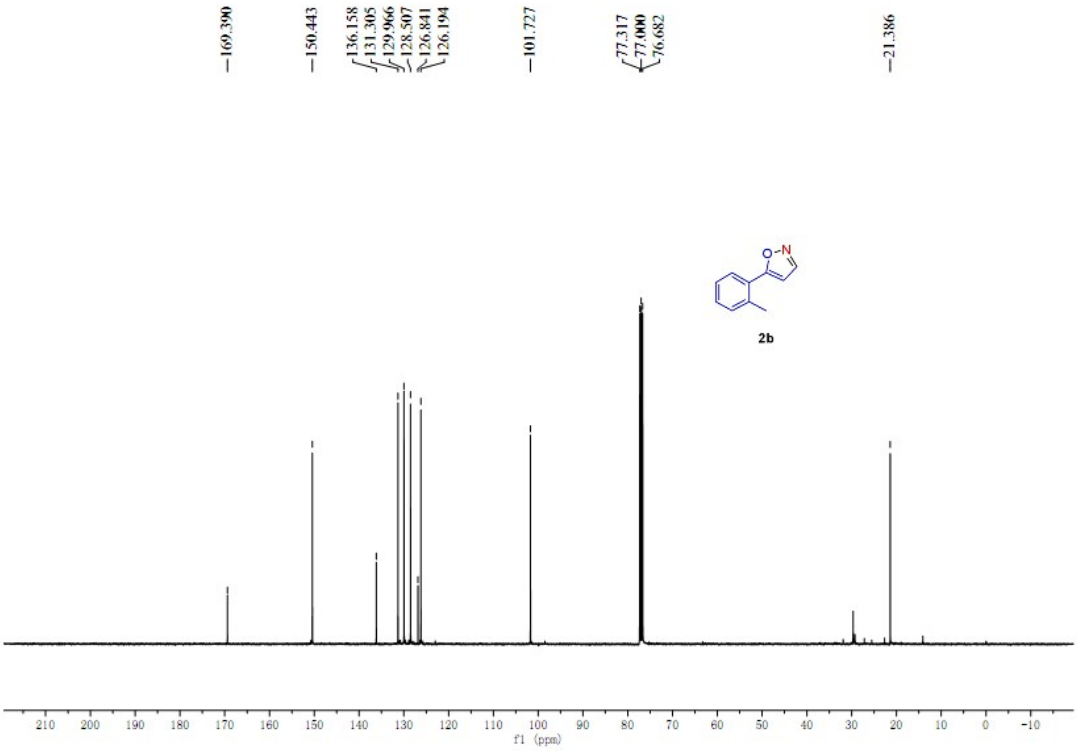
1.05
1.06
2.09
1.03
3.08
f1 (ppm)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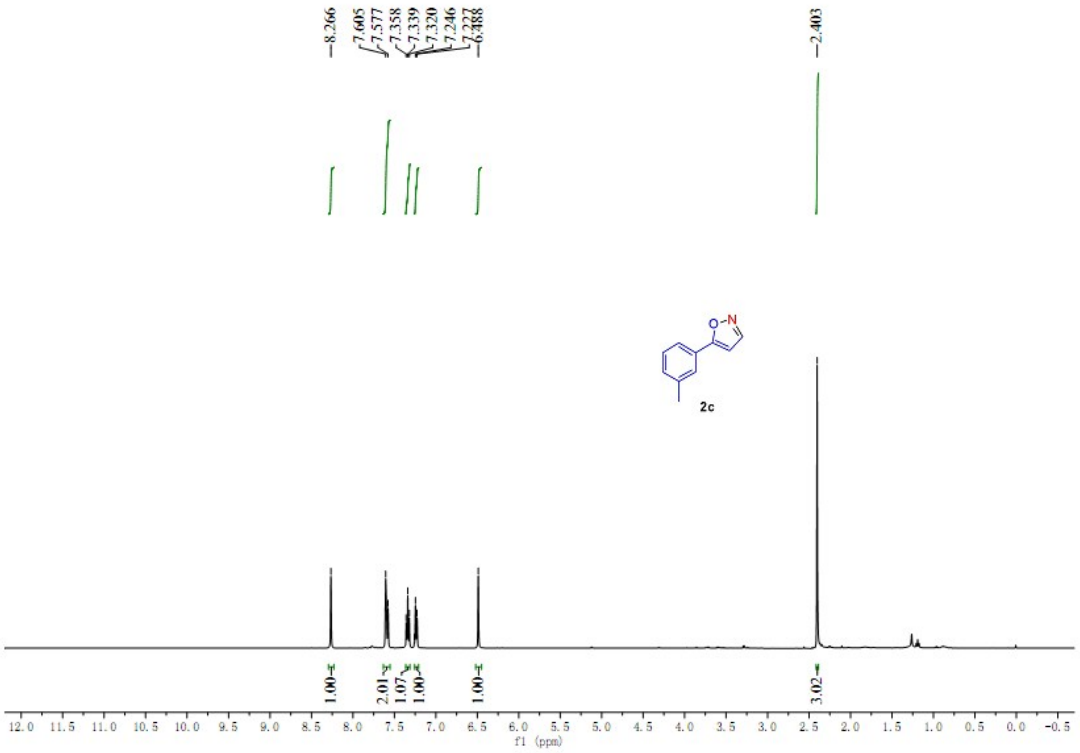
f1 (ppm)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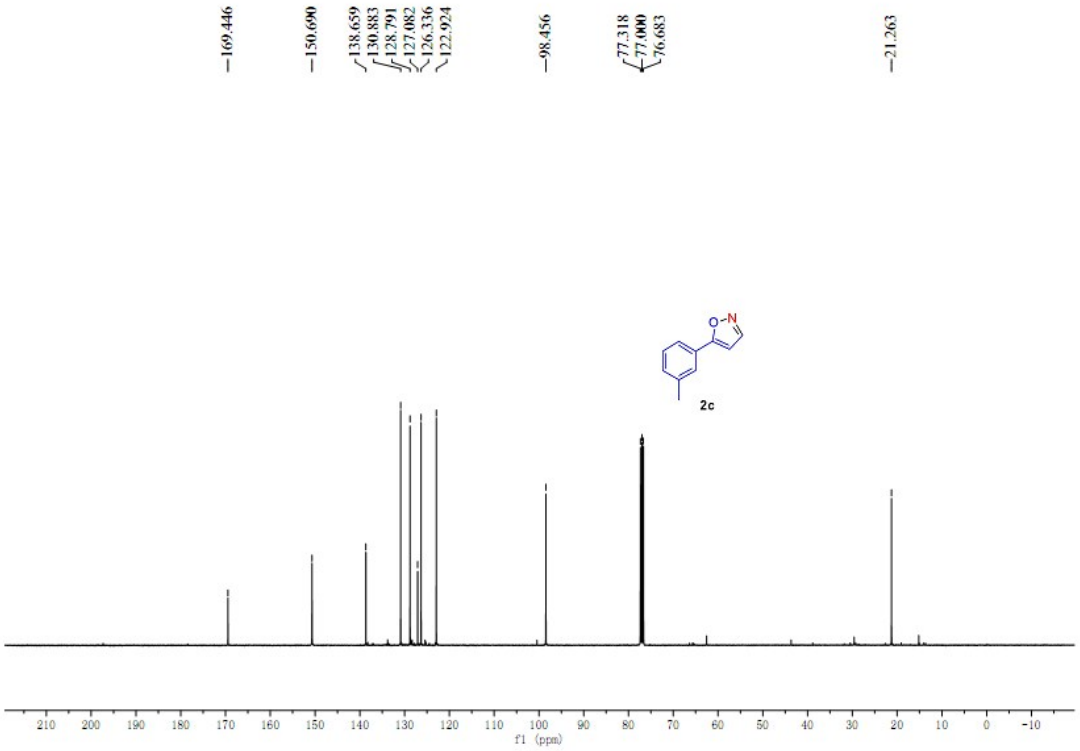
1.07
1.00
1.00
3.02
f1 (ppm)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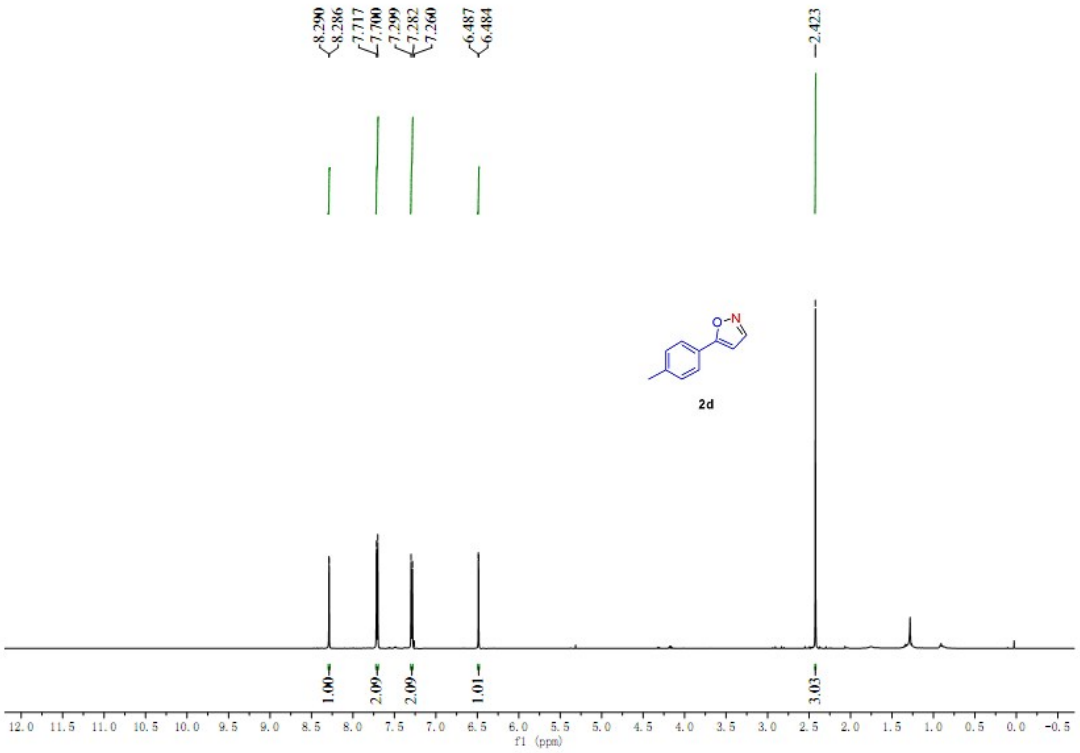
f1 (ppm)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2.09
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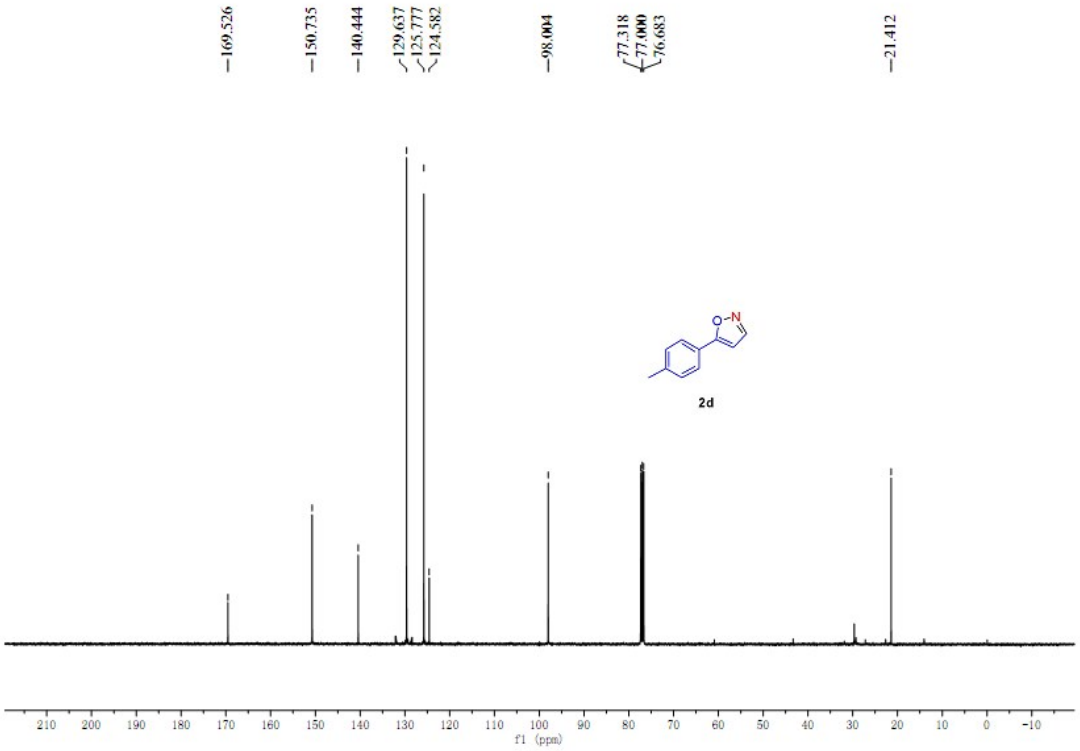
3.03
f1 (ppm)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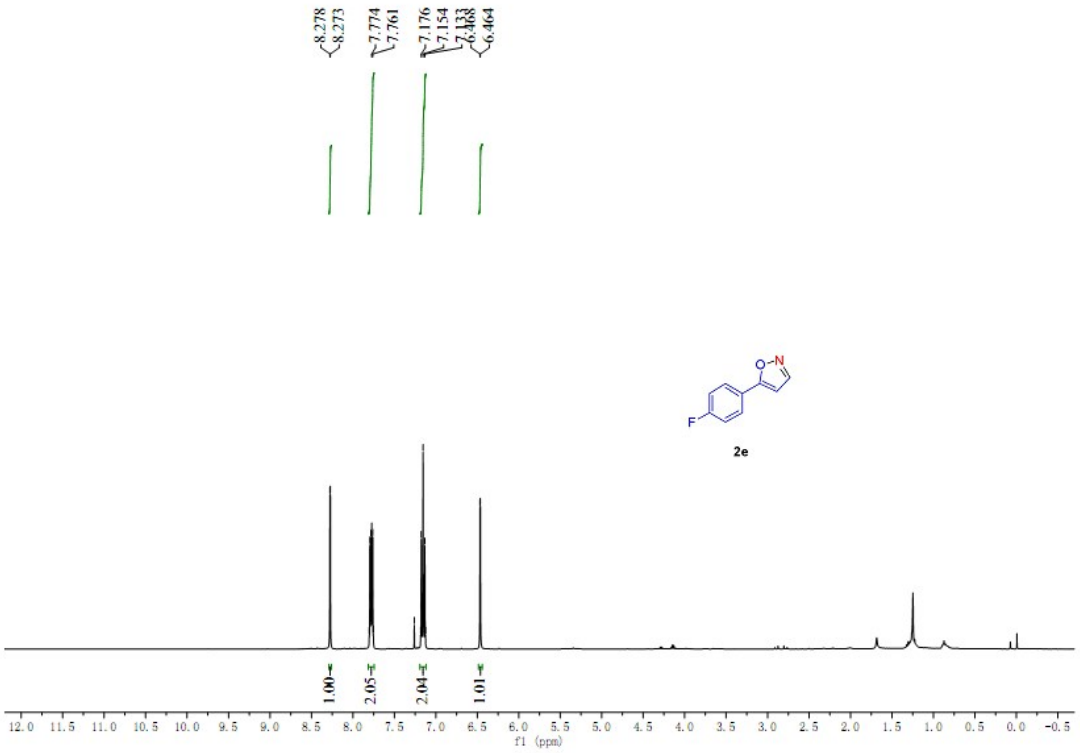
f1 (ppm)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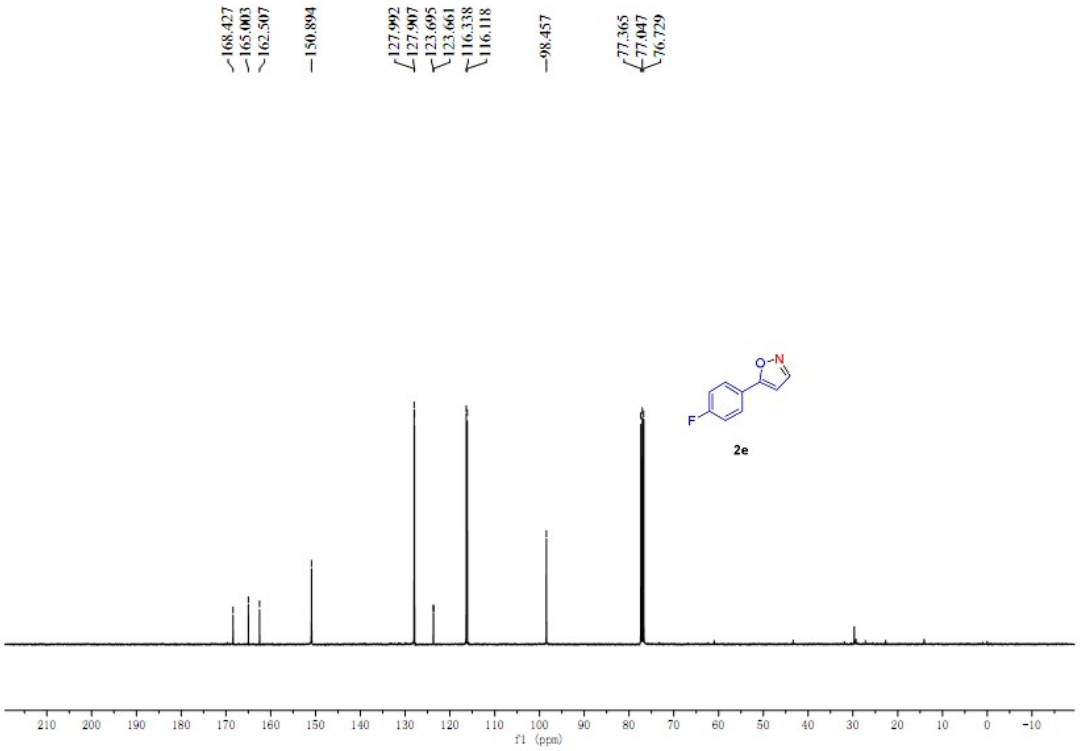
f1 (ppm)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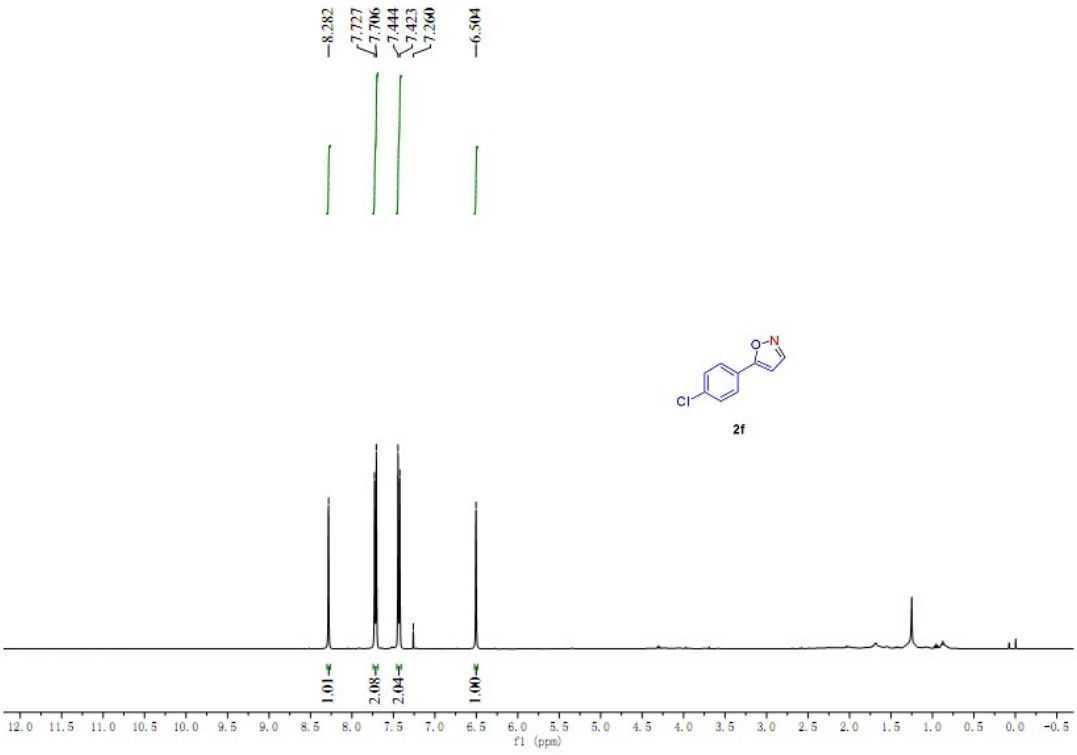
f1 (ppm)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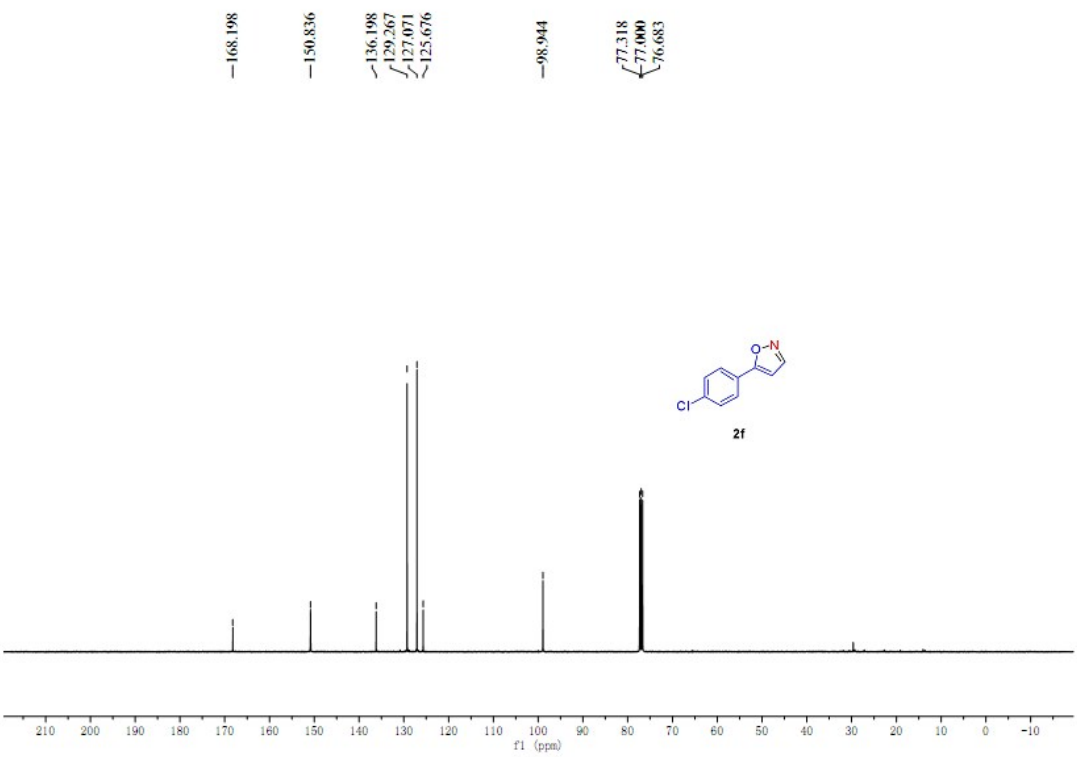
f1 (ppm)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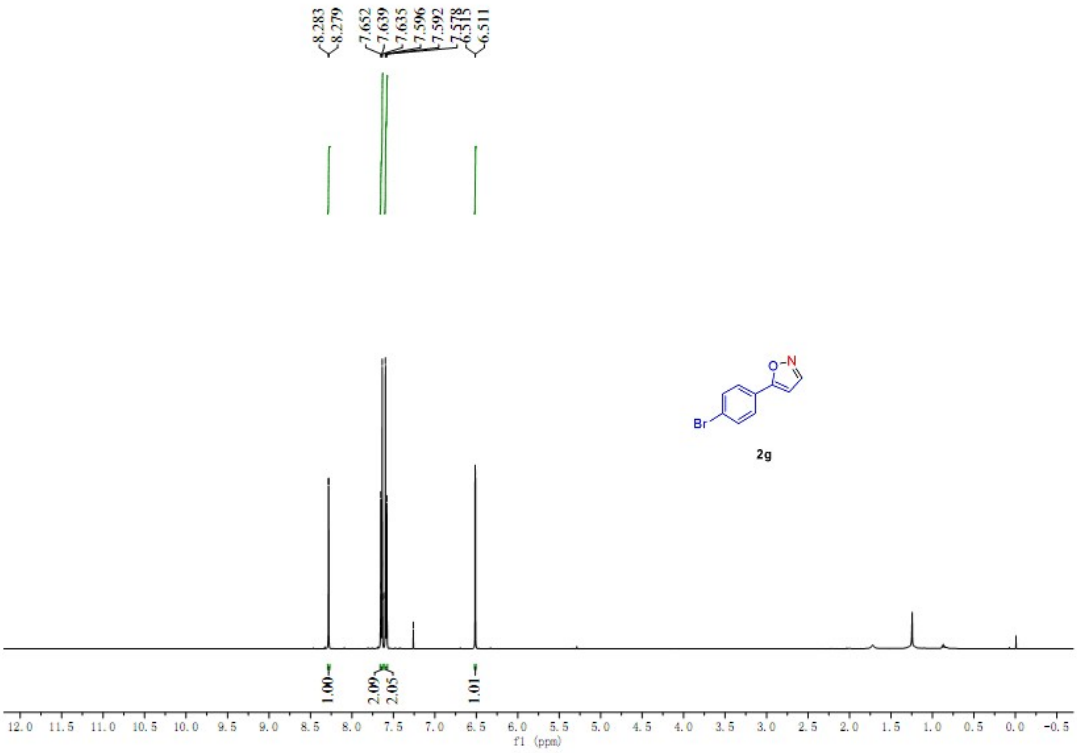
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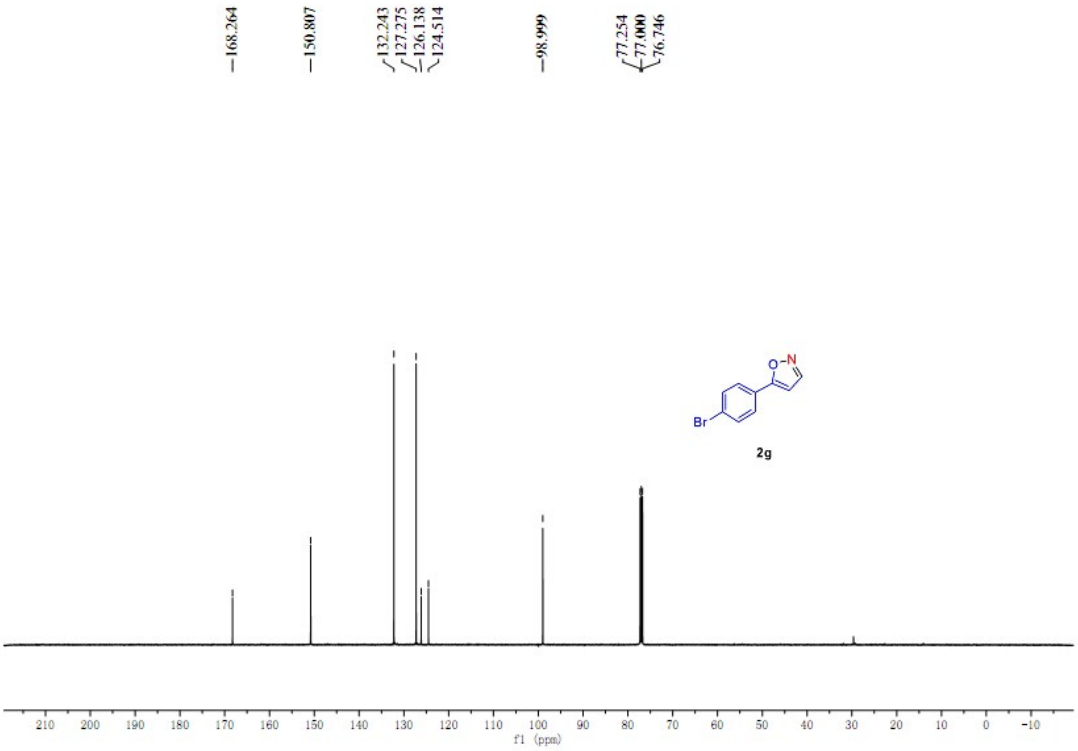
1.01
f1 (ppm)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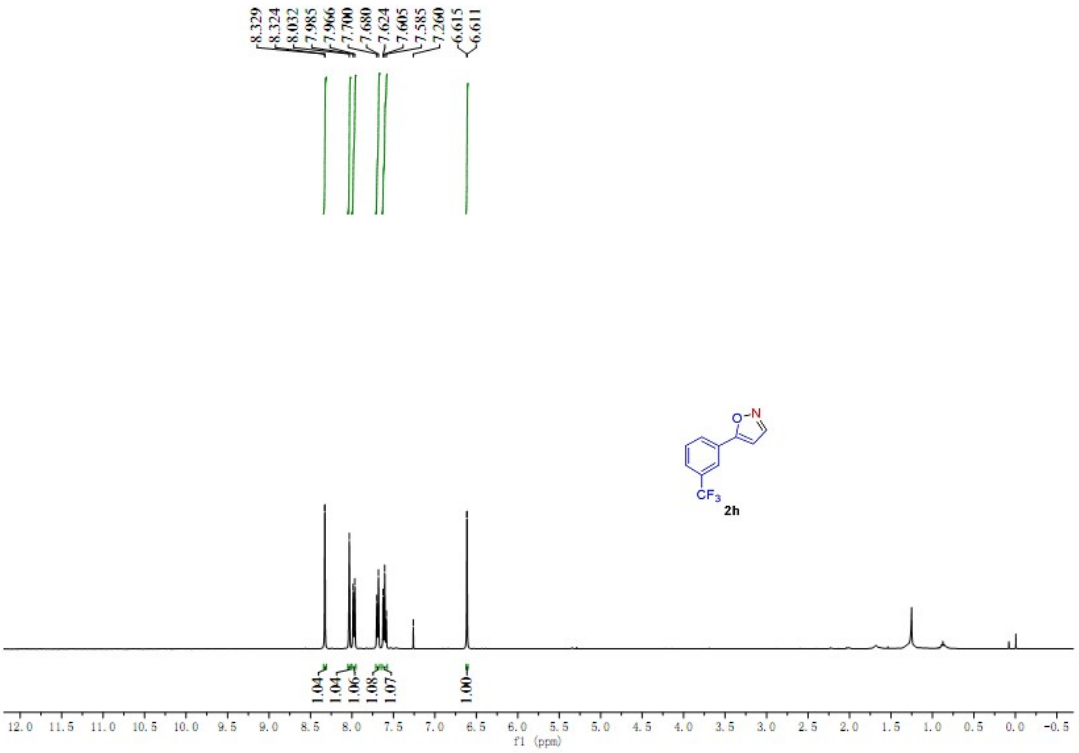
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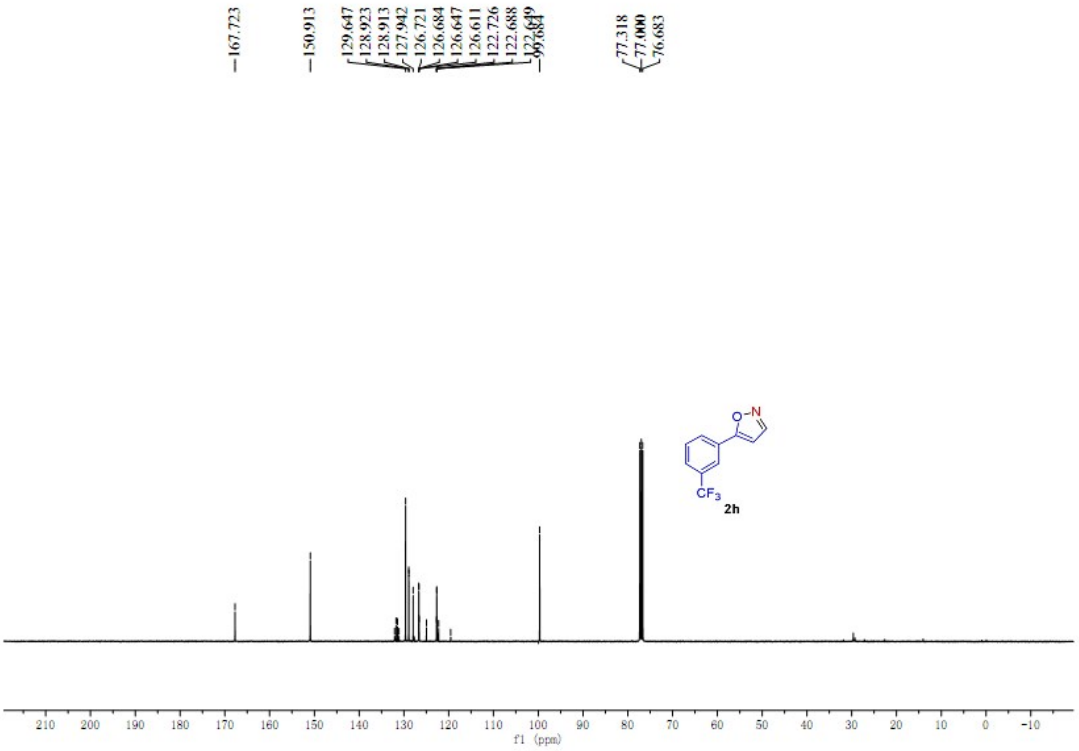
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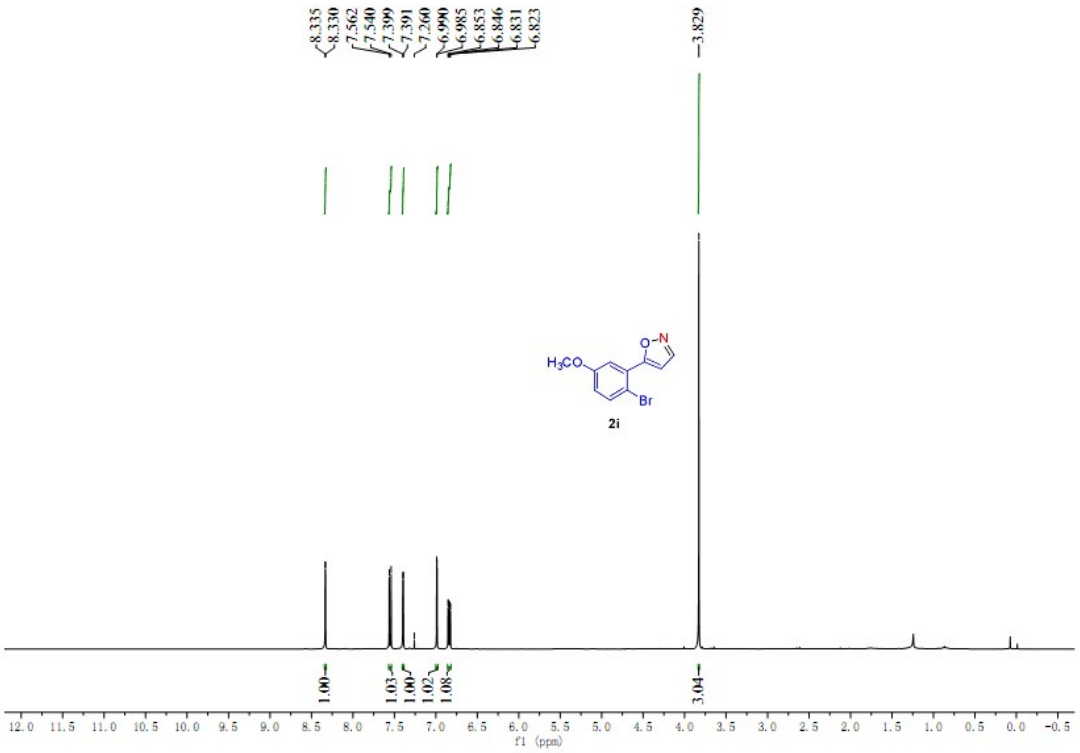
f1 (ppm)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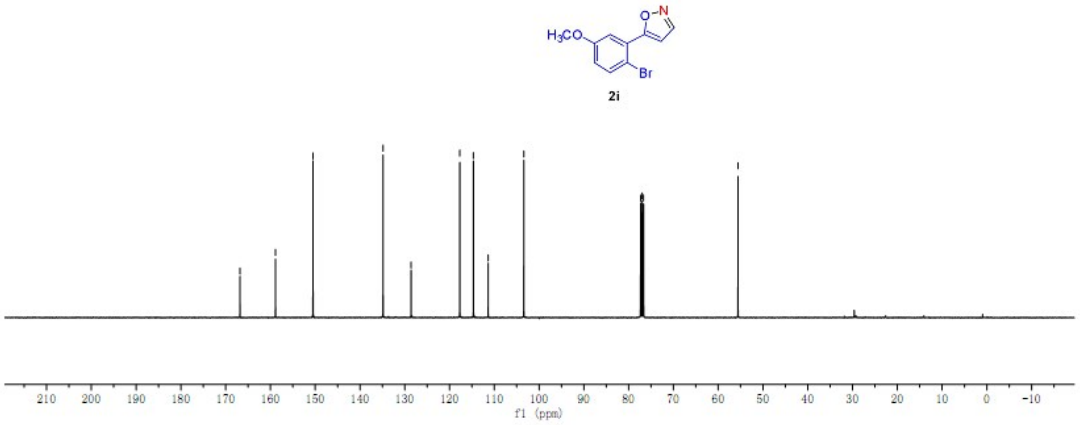
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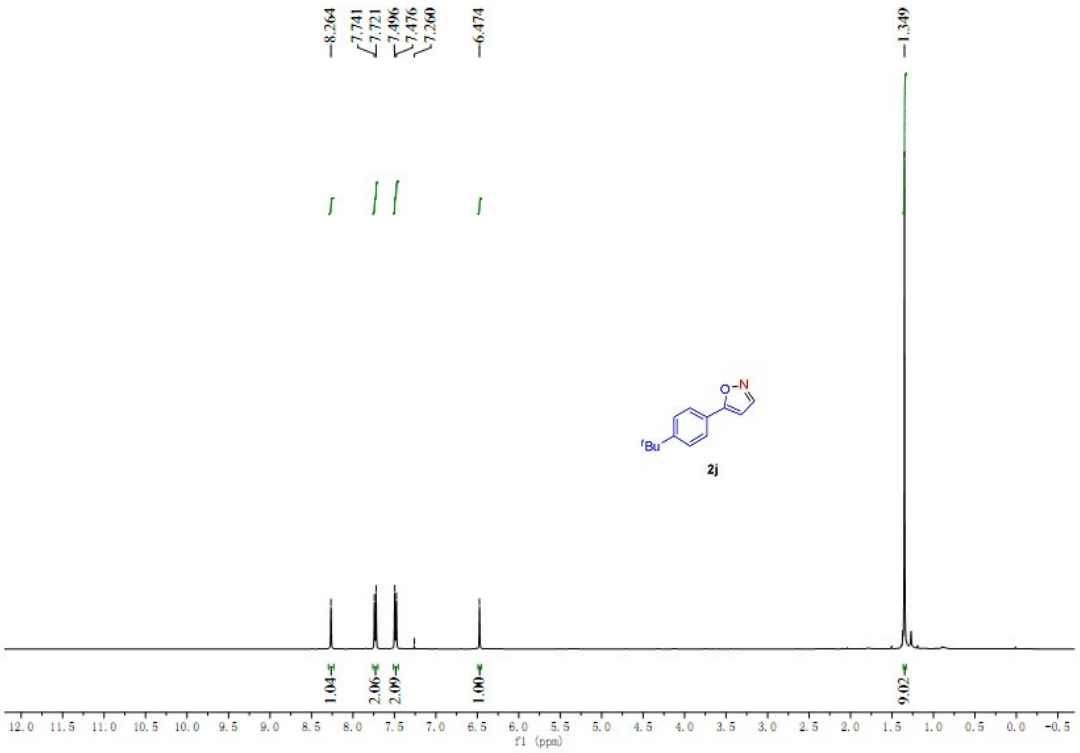
f1 (ppm)

H3CO
O
N
Br

2i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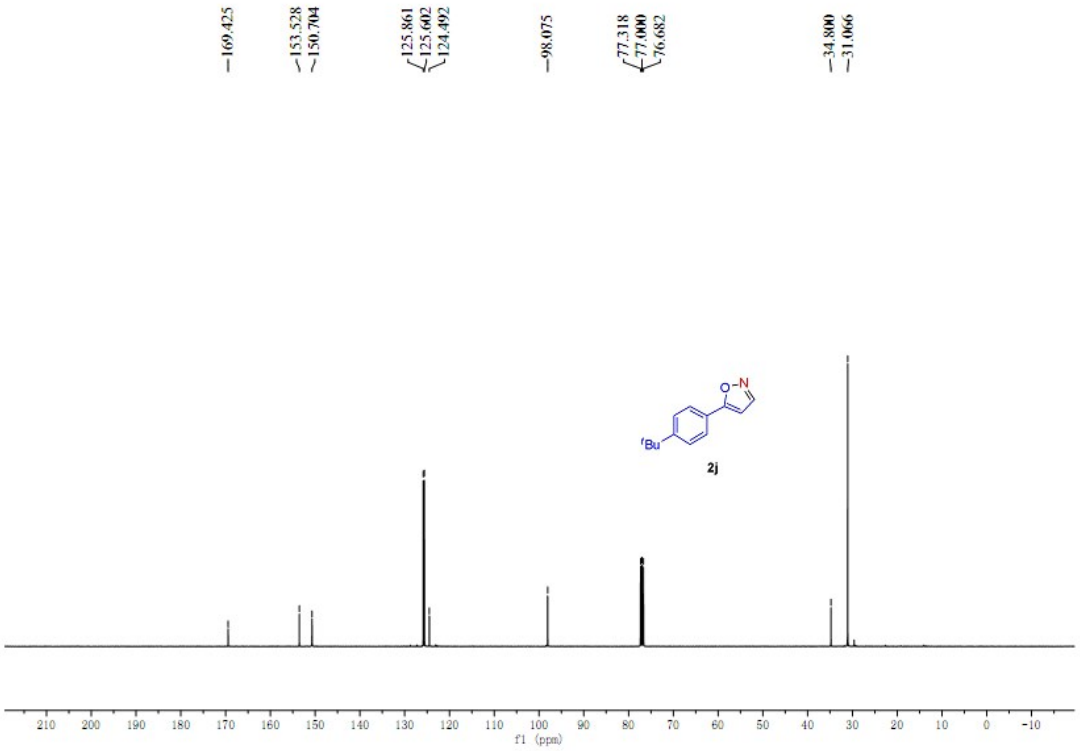
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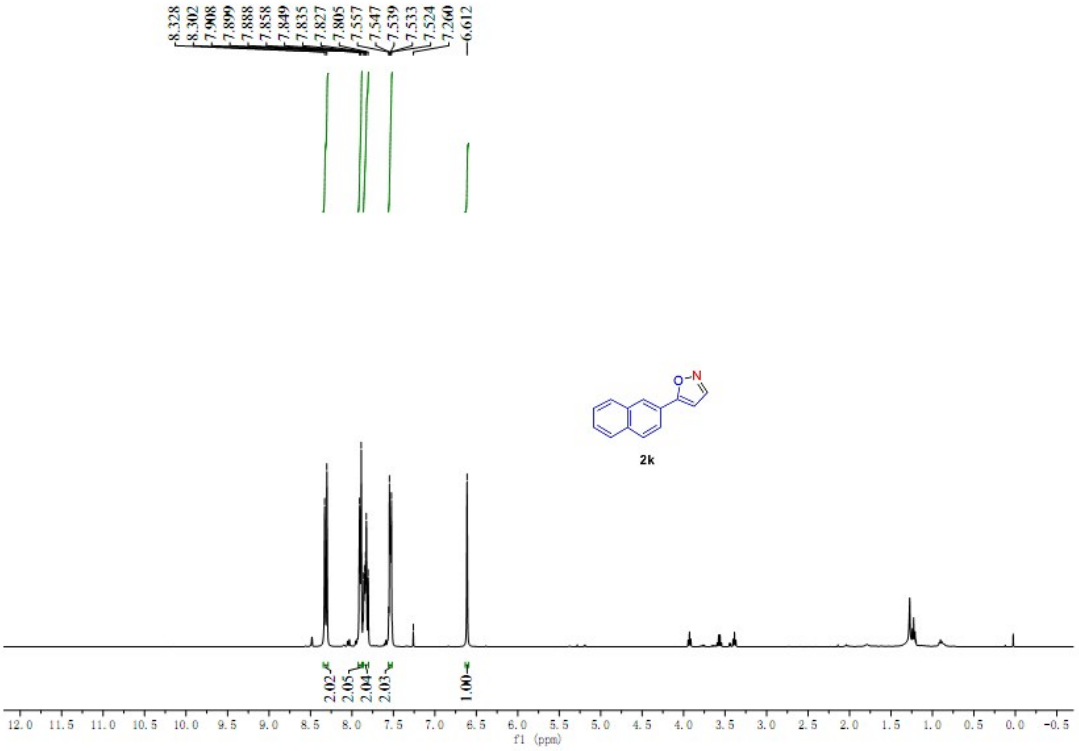
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2.04
2.03
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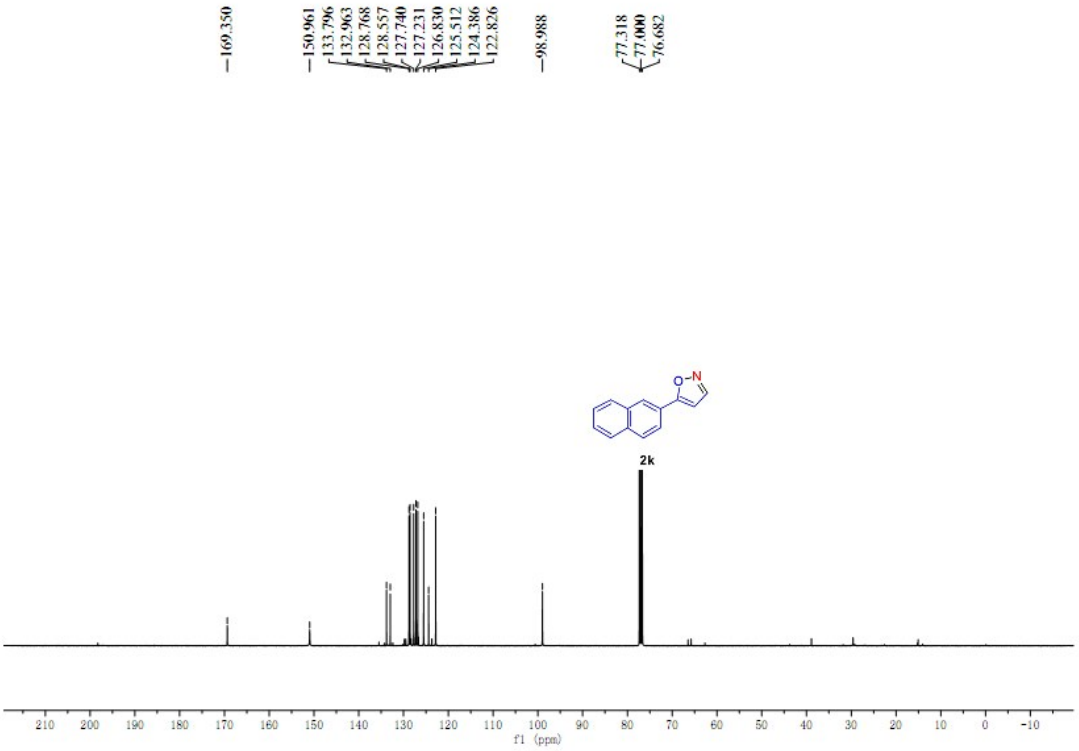
f1 (ppm)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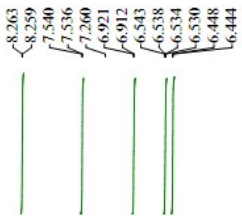
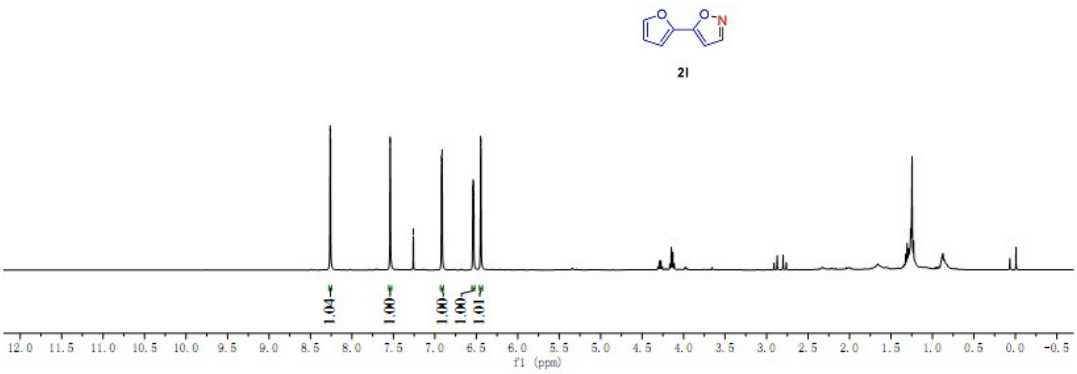
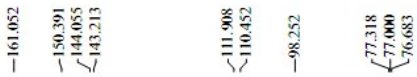
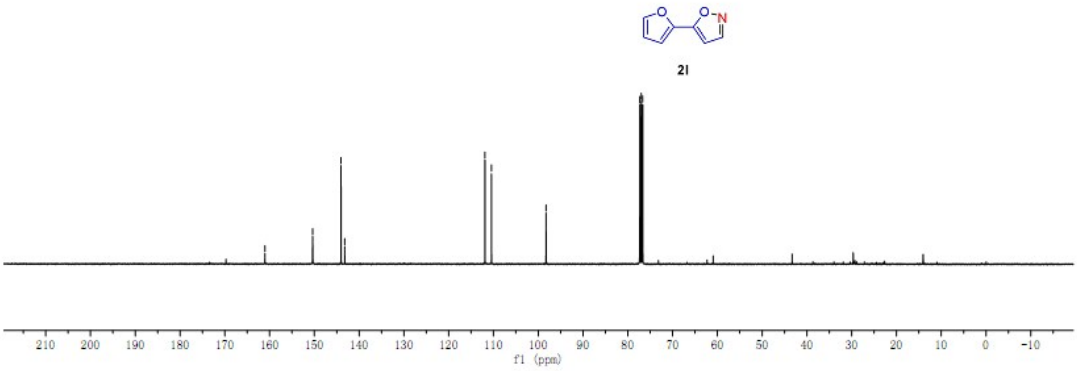
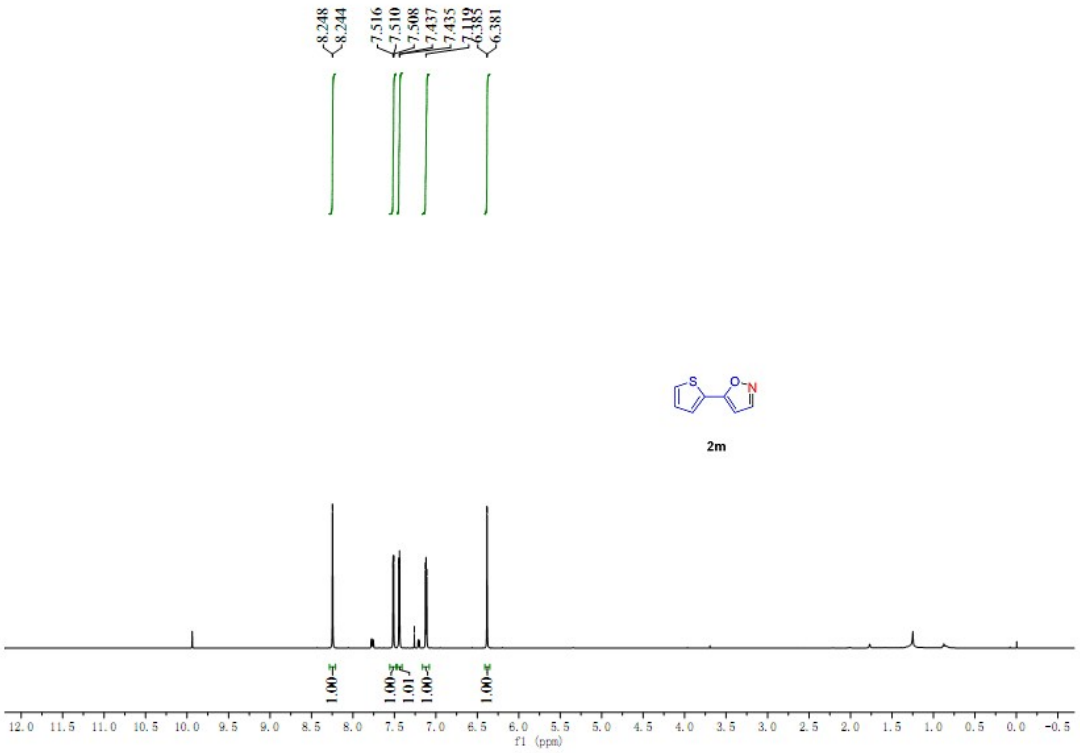
77.318
77.000
76.682
2k
f1 (ppm)

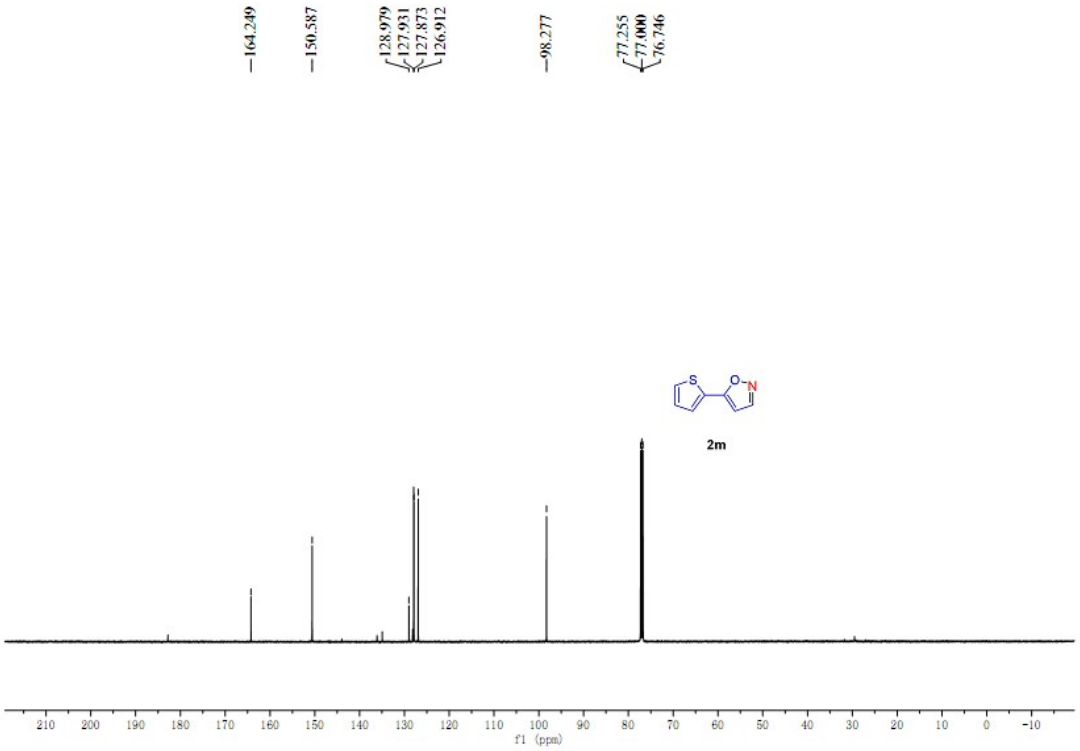

8.263
8.259
7.540
7.536
7.260
6.921
6.912
6.543
6.538
6.534
6.530
6.448
6.444

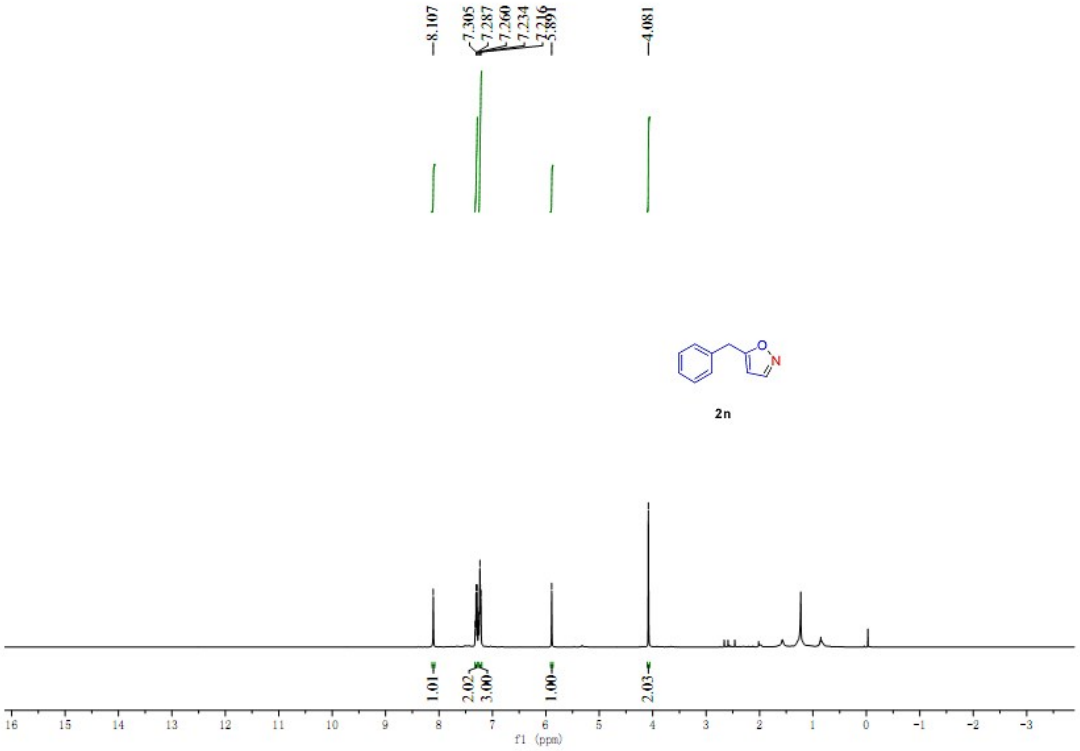

21
1.04
1.00
1.00
1.00
1.01
f1 (ppm)

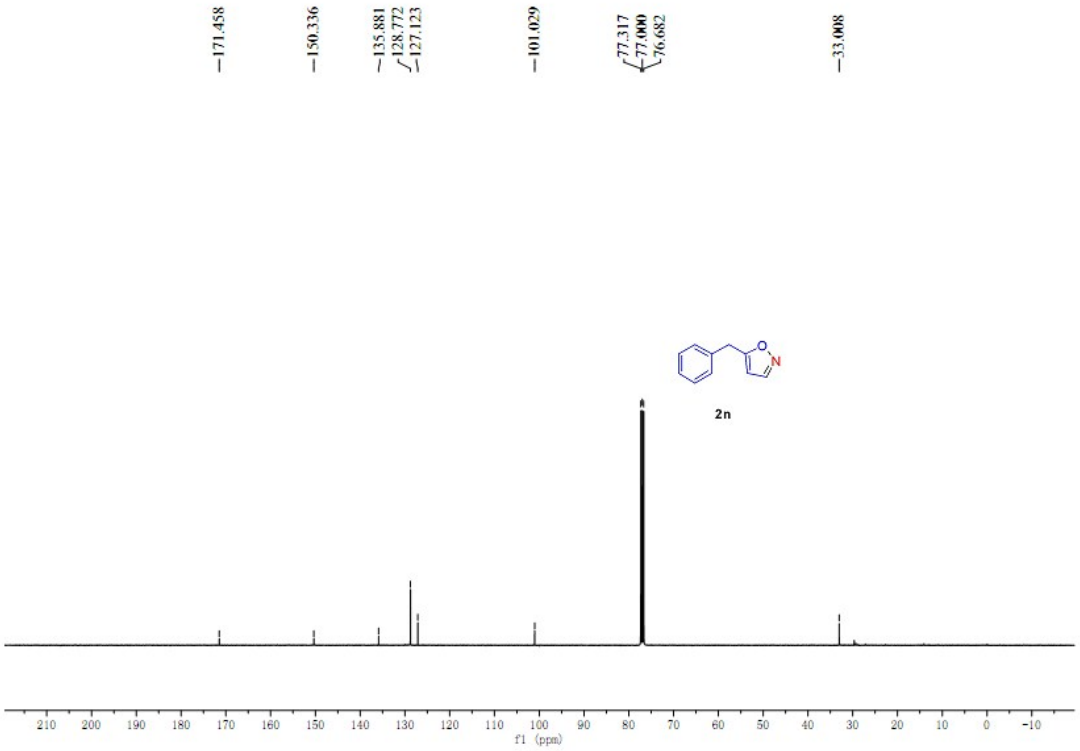

161.052
150.391
144.055
143.213
111.908
110.452
98.252
77.318
77.000
76.683

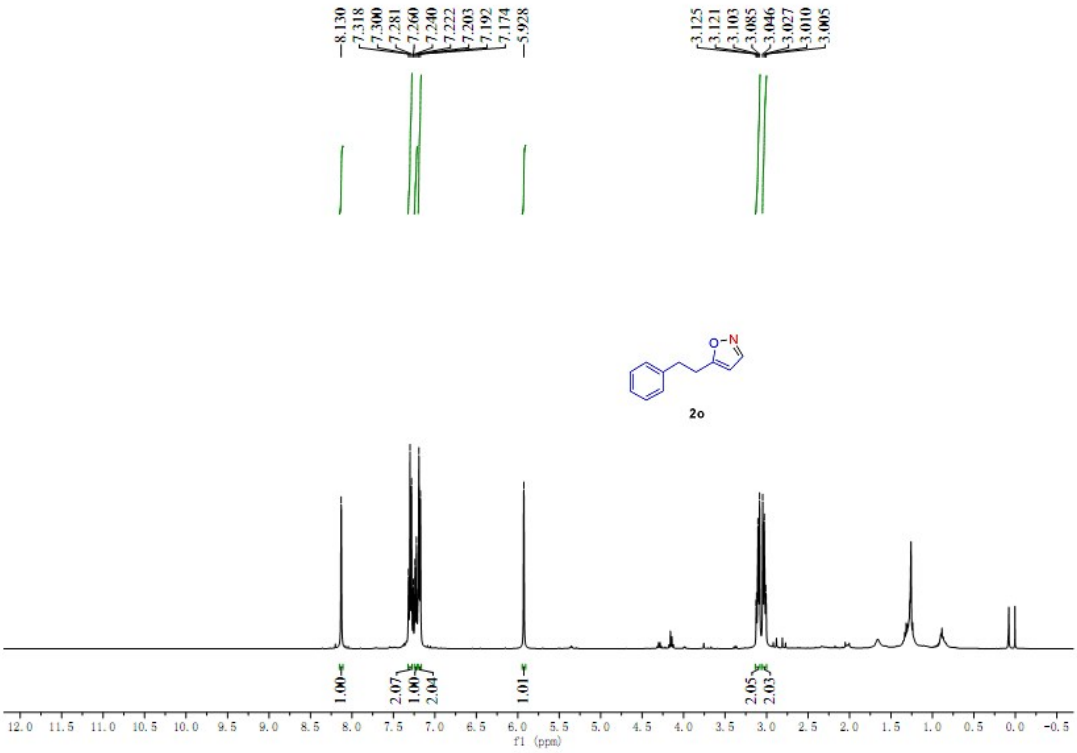

21
f1 (ppm)

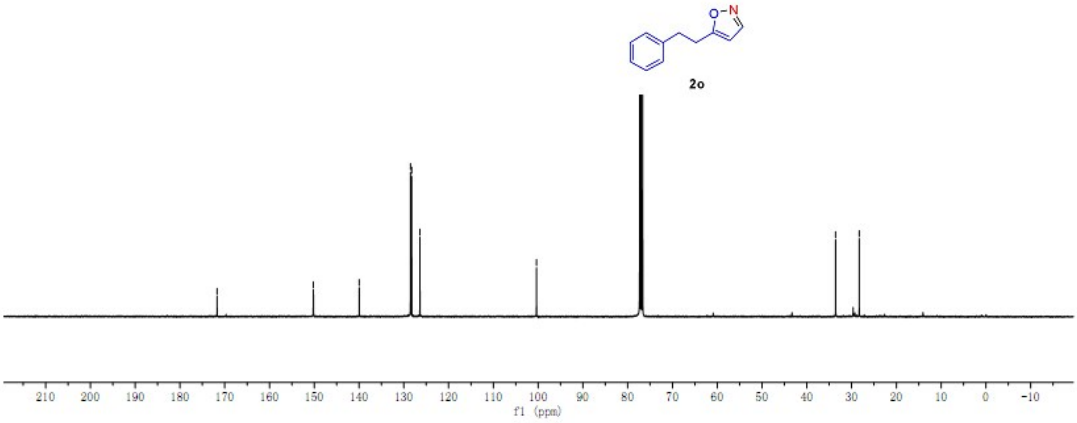

8.248
8.244
7.516
7.510
7.508
7.437
7.435
7.119
6.385
6.381
2m
1.00
1.00
1.01
1.00
1.00
f1 (ppm)

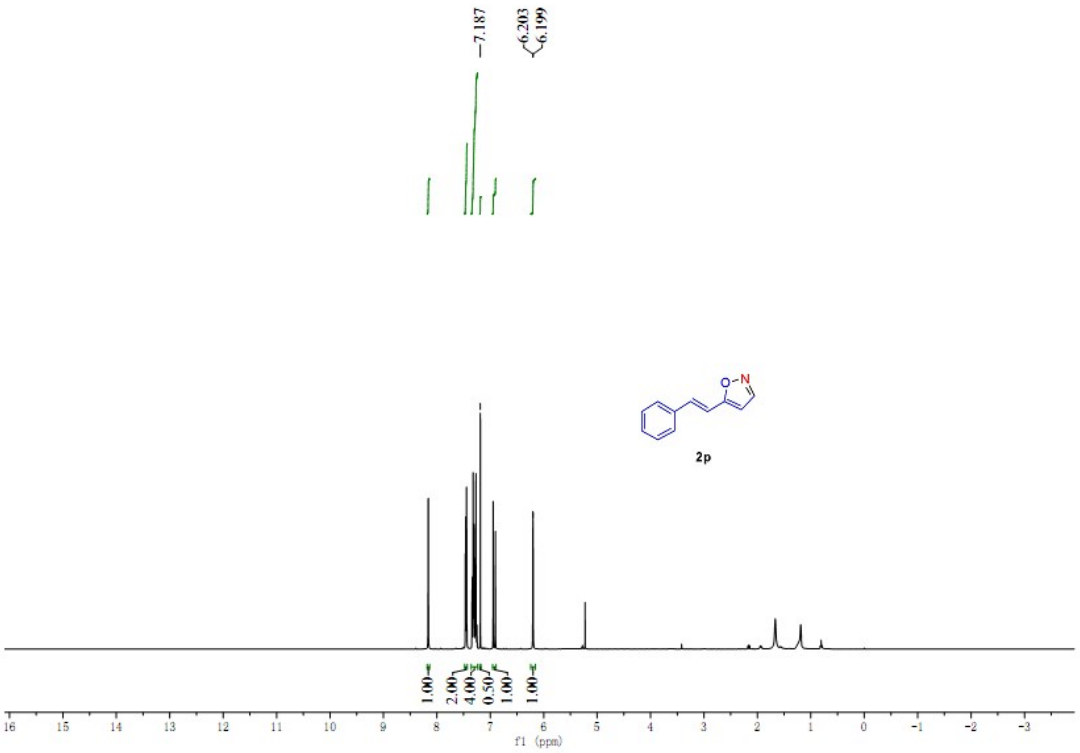

164.249
150.587
128.979
127.931
127.873
126.912
98.277
77.255
77.000
76.746
2m
f1 (ppm)

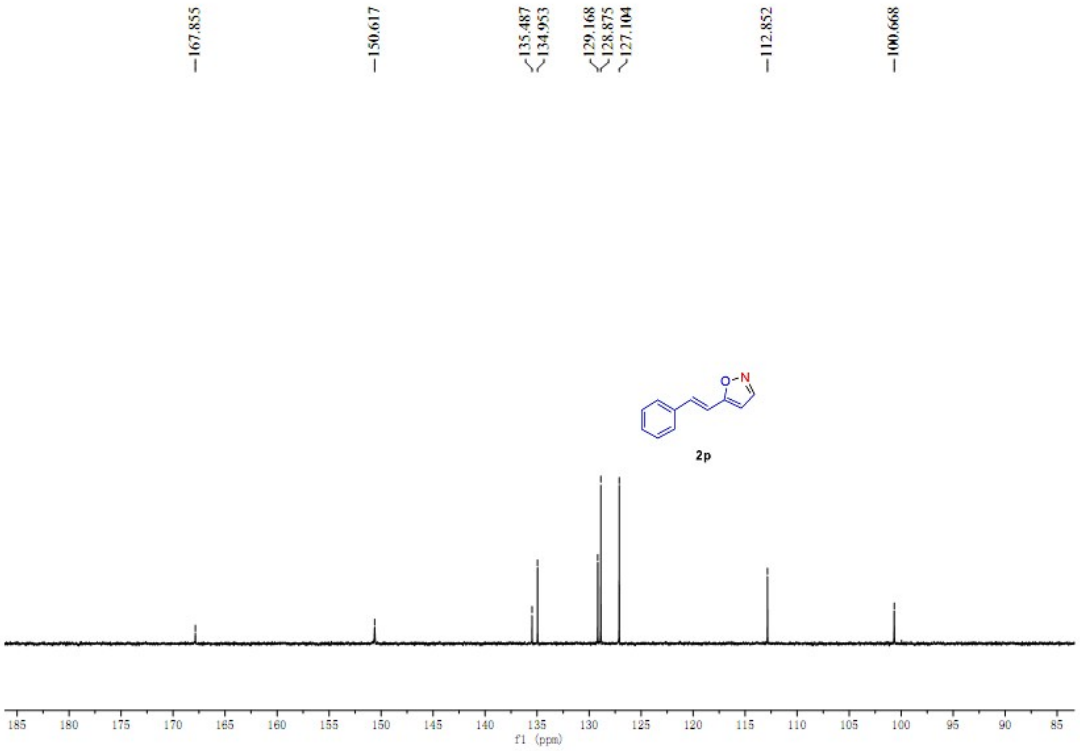

8.107
7.305
7.287
7.260
7.234
7.216
5.891
4.081
2n
1.01
2.02
3.00
1.00
2.03
f1 (ppm)

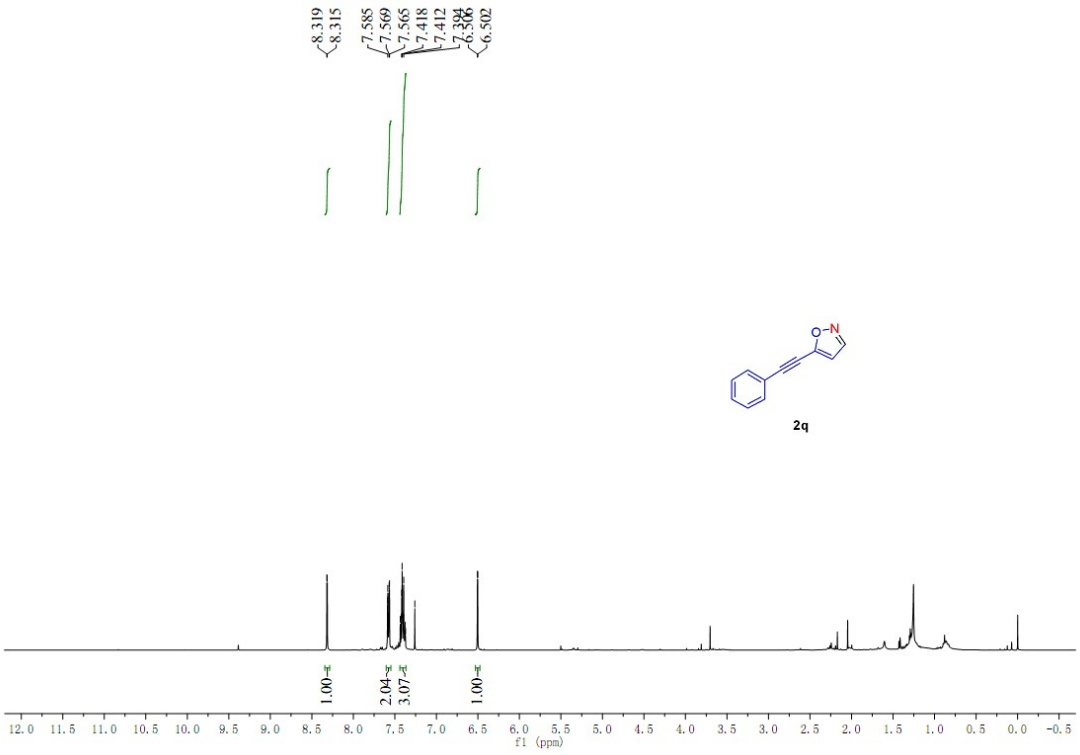

171.458
150.336
135.881
128.772
127.123
101.029
77.317
77.000
76.682
33.008
2n
f1 (ppm)

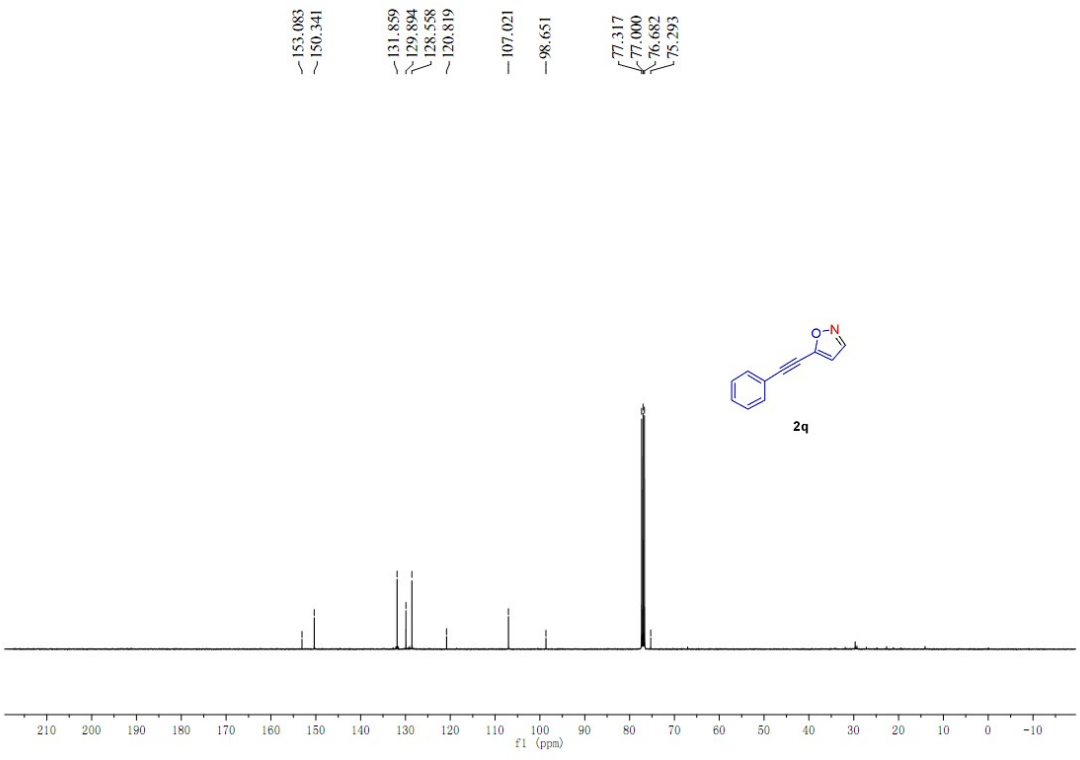

8.130
7.318
7.300
7.281
7.260
7.240
7.222
7.203
7.192
7.174
5.928
3.125
3.121
3.103
3.085
3.046
3.027
3.010
3.005
2o
1.00
2.07
1.00
2.04
1.01
2.05
2.03
f1 (ppm)

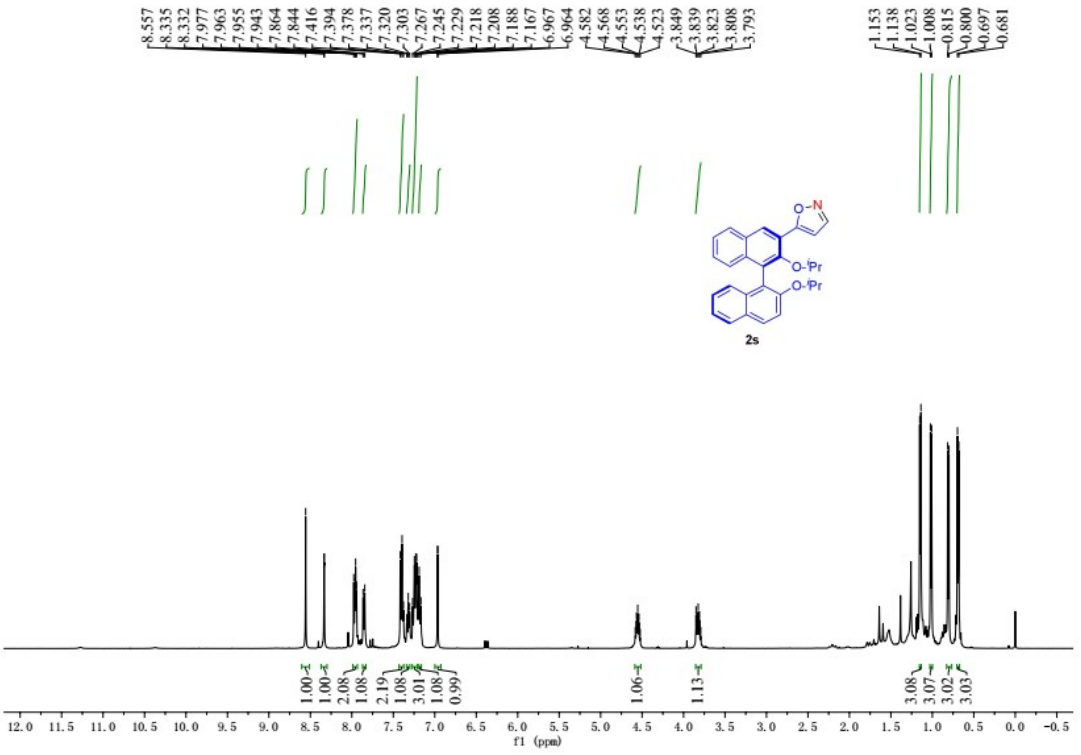

171.709
150.205
139.952
128.506
128.240
126.409
100.367
77.318
77.000
76.683
33.563
28.290
2o
f1 (ppm)

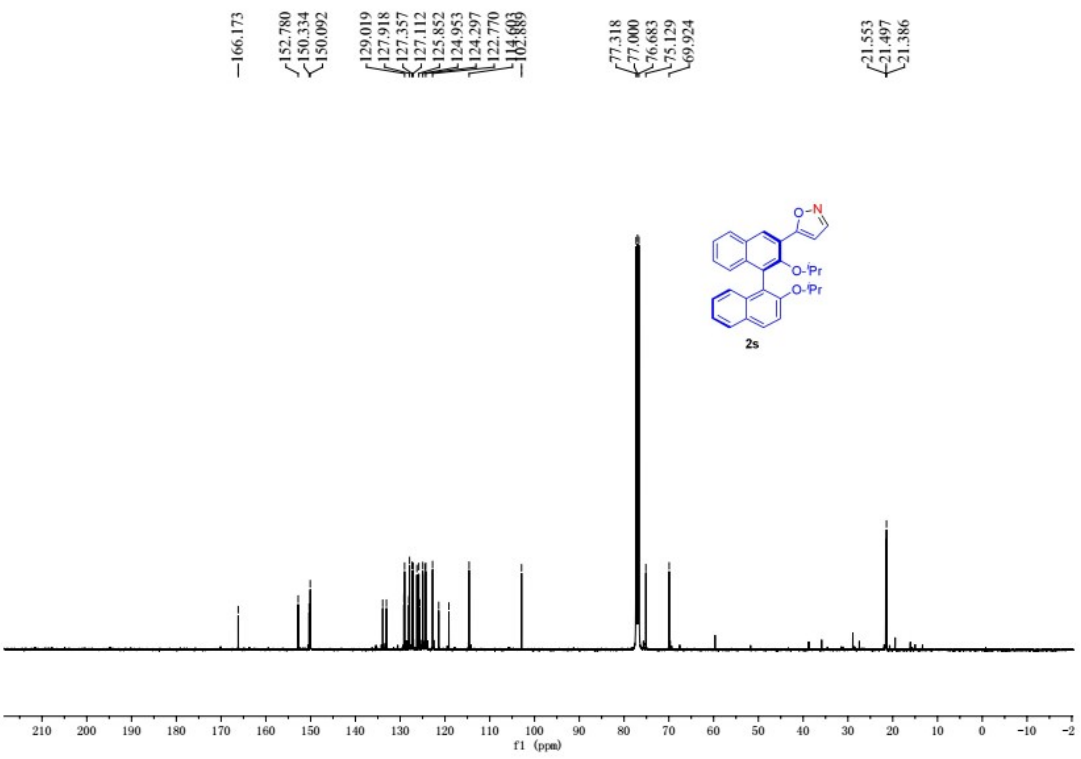

7.187
6.203
6.199
2p
1.00
2.00
4.00
0.50
1.00
1.00
f1 (ppm)


167.855
150.617
135.487
134.953
129.168
128.875
127.104
112.852
100.668
2p
f1 (ppm)


8.319
8.315
7.585
7.569
7.565
7.418
7.412
7.394
6.506
6.502
2q
1.00
2.04
3.07
1.00
f1 (ppm)


153.083
150.341
131.859
129.894
128.558
120.819
107.021
98.651
77.317
77.000
76.682
75.293
2q
f1 (ppm)


8.557
8.335
8.332
7.977
7.963
7.955
7.943
7.864
7.844
7.416
7.394
7.378
7.337
7.320
7.303
7.267
7.245
7.229
7.218
7.208
7.188
7.167
6.967
6.964
4.582
4.568
4.553
4.538
4.523
3.849
3.839
3.823
3.808
3.793
1.153
1.138
1.023
1.008
0.815
0.800
0.697
0.681
O-N
O-iPr
O-iPr
2s
1.00
1.00
2.08
1.08
2.19
1.08
3.01
1.08
0.99
1.06
1.13
3.08
3.07
3.02
3.03
f1 (ppm)


166.173
152.780
150.334
150.092
129.019
127.918
127.357
127.112
125.852
124.953
124.297
122.770
114.603
102.889
77.318
77.000
76.683
75.129
69.924
21.553
21.497
21.386
O-N
O-iPr
O-iPr
2s
f1 (ppm)