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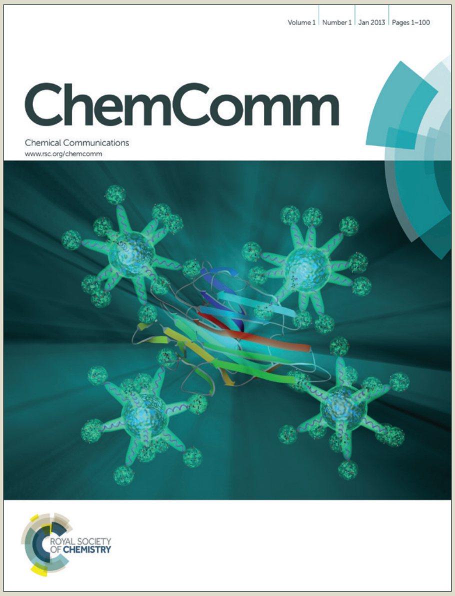

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Copper-Catalyzed Intermolecular Azidocyanation of Aryl Alkenes

Cite this: DOI: 10.1039/x0xx00000x

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Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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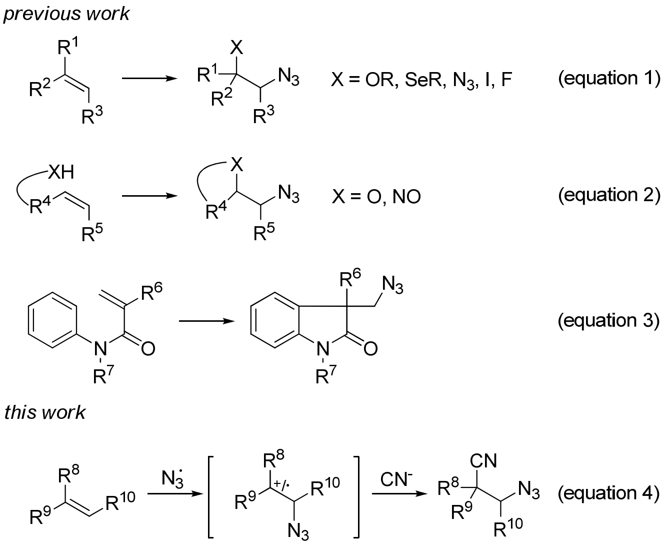
A copper-catalyzed Markovnikov-type intermolecular azidocyanation of aryl alkenes has been developed to give a series of α-azido-propanenitrile in moderate to good yields. This method might provide a potential strategy for the synthesis of corresponding 3-amino-2-arylpropanoic acid.

In the field of organic synthesis, pursuing of the "ideal synthesis" is always one of the major evergreen topics.[1] As a result, tandem reactions and multicomponent reactions, which allow efficient achievement of more than one chemical transformation within one-step operation, have attracted broad attentions of synthetic chemistry community.[2] Accordingly, a large number of corresponding methodologies have been developed and are still constantly emerging. Generally, consecutive functionalizations and/or reorganization of molecular skeletons are involved in such processes. Among those procedures leading to the multi-functionalization of the related starting materials, the difunctionalization of alkenes, which could introduce two functional groups through a single operation, is always a hot topic.[3] In particular, under the impetus of rapid development in C-H functionalization field, transition-metal catalyzed difunctionalization of alkenes has made great progress in recent years.[4] Normally, such a process is initiated by an electrophilic reagent and terminated either intermolecularly or intramolecularly by a nucleophilic step. Among the difunctionalization of alkenes developed in recent years, those initiated with an azide reagent has drawn our attention.[5] On one hand, since the azide group, as an important nitrogen source and versatile functional group, can participate in various chemical transformations, organic azide compounds have shown their broad applications in synthetic chemistry as well as some other interdiscipline.[6] On the other hand, although the difunctionalization of alkenes using azide reagent has been known for long time,[7] and the corresponding carboazidation and hydroazidation of alkenes have been well documented, the terminating patterns of azide reagent-initiated difunctionalization of alkenes are still underexplored. For the procedures terminated by an intermolecular nucleophilic step, most of them are focused on the consecutive construction of C-N_3 and C-hetero bond (Scheme 1, equations 1 and 2).[8,9] While for the consecutive construction of C-N_3 and C-C bond, to our knowledge, only four examples are available via intramolecular terminating step (Scheme 1, equation 3).[10] Especially, there has been no report about such a process terminated by an intermolecular C-C bond formation. Therefore, it is still highly desirable to further investigate under this topic. Based on the background information and our interest in the

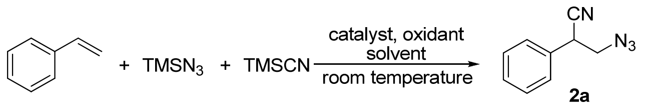


Scheme 1 Difunctionalization of alkenes initialized by an azide reagent.

radical initiated transformations,[11] we envisioned that under proper reaction conditions such an intermediate generated by the reaction between an alkene and azide radical[12] might be trapped with a cyanide source to give synthetically useful α-azido-propanenitrile compounds, which could provide broad range of possibilities for further derivatization (Scheme 1, equation 4). In this paper, we wish to present our preliminary results under this topic.

Following our initial hypothesis, we firstly tested the feasibility of the designed multi-component transformation by using styrene, $TMSN_3$ and TMSCN as the substrates. To our delight, under the catalysis of $Cu(OTf)_2$, the desired Markovnikov-type addition product **2a** could be obtained in 25% yield with the use of $PhI(OAc)_2$ as oxidant in CH_2Cl_2 (Table 1, entry 1). Next, the reaction was further carried out under different solvents, which lead to the observation of clear solvent effect for this transformation. In the similar type solvent, i.e., DCE, almost the same result was obtained (Table 1, entry 2). In contrast, when more polar solvents, such as CH_3CN, DMSO and MeOH, were employed, the reaction could afford the **2a** in higher yields (Table 1, entries 3 to 5). Among them, the use of MeOH could give the highest yield of 52% (Table 1, entry 5). While in the case of other polar solvent like DMF and 1,4-dioxane, no desired product could be detected (Table 1, entries 6 and 7). Additionally, the reaction was performed with different amount of metal catalyst and oxidant, and the combination of 0.1 equiv $Cu(OTf)_2$ and 1.3 equiv $PhI(OAc)_2$ could further increase the yield of **2a** to 72% (Table 1, entry 10). Besides, it was found that increasing the reaction temperature to 50 ºC didn't affect the yield of the product much (For detailed information, please see the ESI). Furthermore, other common oxidants, like PhIO and TBHP, were also evaluated, however, either lower yield of **2a** or no reaction was observed (Table 1, entries 12 to 16). Based on the information above, various metal catalysts were also screened, and we were pleased to find that the yield of **2a** could be further improved to 84% with the use of $Cu(TFA)_2$. It should be noted that although the reaction could be conducted without catalyst, much lower yield was obtained (Table 1, entry 23).

Table 1 Optimization of reaction conditions[a]



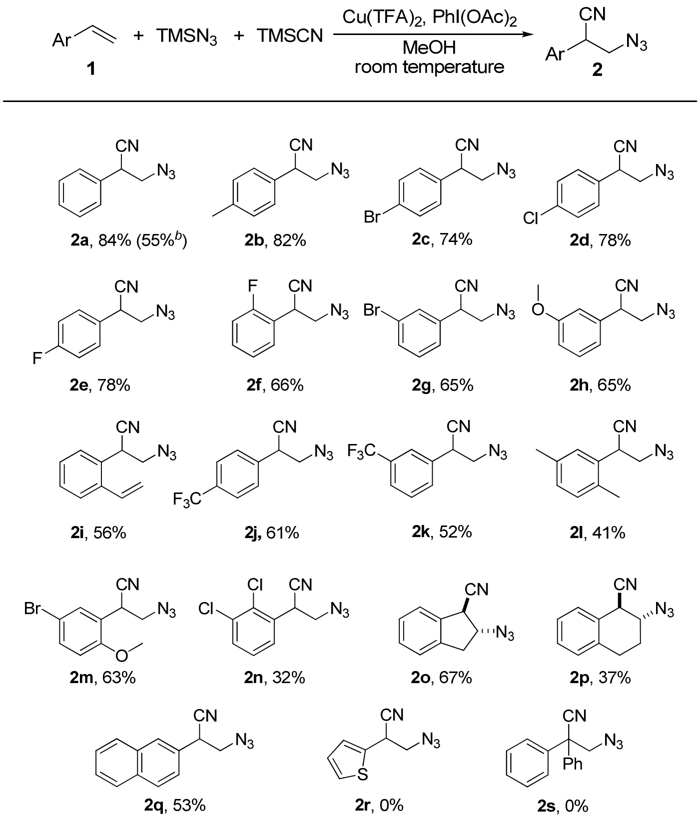
2a

Entry	Catalyst （mol%）	Oxidant （equiv）	Solvent	Yield[b]
1	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	CH_2Cl_2	25%
2	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	DCE	23%
3	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	CH_3CN	45%
4	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	DMSO	35%
5	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	MeOH	52%
6	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	DMF	n.d.[c]
7	$Cu(OTf)_2(5)$	$PhI(OAc)_2(1.1)$	dioxane	n.d.[c]
8	$Cu(OTf)_2(10)$	$PhI(OAc)_2(1.1)$	MeOH	65%
9	$Cu(OTf)_2(20)$	$PhI(OAc)_2(1.1)$	MeOH	63%
10	$Cu(OTf)_2(10)$	$PhI(OAc)_2(1.3)$	MeOH	72%
11	$Cu(OTf)_2(10)$	$PhI(OAc)_2(2)$	MeOH	67%
12	$Cu(OTf)_2(10)$	PhIO(1.3)	MeOH	43%
13	$Cu(OTf)_2(10)$	$PhI(TFA)_2(1.3)$	MeOH	36%
14	$Cu(OTf)_2(10)$	TBHP(1.3)	MeOH	n.d.[c]
15	$Cu(OTf)_2(10)$	$K_2S_2O_8(1.3)$	MeOH	n.d.[c]
16	$Cu(OTf)_2(10)$	CAN(1.3)	MeOH	n.d.[c]
17	CuOTf(10)	$PhI(OAc)_2(1.3)$	MeOH	25%
18	$Cu(TFA)_2(10)$	$PhI(OAc)_2(1.3)$	MeOH	84%
19	$Cu(OAc)_2(10)$	$PhI(OAc)_2(1.3)$	MeOH	38%
20	CuBr(10)	$PhI(OAc)_2(1.3)$	MeOH	46%
21	CuCl(10)	$PhI(OAc)_2(1.3)$	MeOH	40%
22	$FeCl_3(10)$	$PhI(OAc)_2(1.3)$	MeOH	20%
23	No catalyst	$PhI(OAc)_2(1.3)$	MeOH	25%

[a] Reaction condition: without other notification, all of the reactions were performed with styrene (0.3 mmol), $TMSN_3$ (1.1 equiv), TMSCN (2 equiv), catalyst and oxidant in solvent (1 mL) at room temperature under Ar for 10 min. [b] Isolated yield; [c] n.d. = not detected.

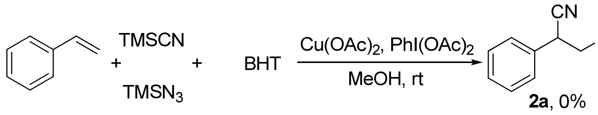
With the optimized reaction conditions in hand (Table 1, entry 19), we turned our attention to the generality of this multi-component reaction. Accordingly, a variety of aryl alkenes (**1a-1q**) were tested for this reaction, and most of them could give corresponding products in moderate to good yields. As shown in Table 2, it was clear that the yield was affected by the substituent on the phenyl ring. For mono-substituted styrene, the existence of a methyl group at *para*-position didn't affect the yield much. Although the existence of a halogen substituent did lead to slightly decrease of the related products' yields, the corresponding halogen atom all survived from the reaction, which provided additional reaction site for further derivatization. Similarly, the use of 1-methoxy-3-vinylbenzene also led to the product **2h** in 65% yield. Interestingly, subjection of 1,2-divinylbenzene to this difunctionalization reaction could selectively afford the product **2i**, of which a vinyl group was intact. Thus, except the azido and cyano groups, such a product **2i** also possesses the additional site for further transformations. Additionally, when the substituent was replaced by an electron-withdrawing group, i.e., CF_3, the yields of the corresponding products **2j** and **2k** were decreased to 52% and 61% respectively. Furthermore, the reaction was also applicable to a series of disubstituted styrene, albeit in moderate yields in most cases. Other than the styrene type of substrates above, some other aryl alkenes were also subjected to this reaction. Among them, 2-vinylnaphthalene could give the desired products **2q** in 53% yield. For the cyclic aryl alkenes, such as 1*H*-indene and 1,2-dihydronaphthalene, the expected azidocyanation could go through diastereoselectively to give the desired product **2o** and **2p** respectively in 67% and 37% yield under the optimized conditions. The relative configuration of the above two products was confirmed by the X-ray crystallography of **2p** (CCDC 1008927, for detailed information, please see the ESI**).** However, the use of 2-vinylthiophene and ethene-1,1-diyldibenzene didn't afford the expected products. And it should be admitted that this difunctionalization was not effective for aliphatic alkenes, which might affect its further application and worth subsequent investigation. Since the product contains N_3 and CN group, it might be used as precursor for the synthesis of related amino acids. Therefore, it is necessary to carry out a large-scale reaction to support its potential synthetic utility. To our delight, under the optimized conditions, close to gram-scale synthesis of product **2a** could be successfully achieved in 55% yield.

Table 2. Copper-catalyzed difunctionalization of arylalkenes[a]



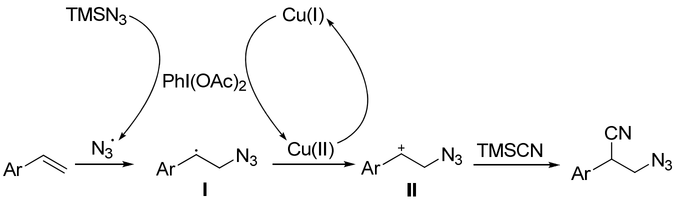
[a] Reaction condition: without other notification, all of the reactions were performed with alkene (0.3 mmol), $TMSN_3$ (1.1 equiv), TMSCN (2 equiv), $Cu(TFA)_2$ (0.1 equiv) and $PhI(OAc)_2$ (1.3 equiv) in MeOH (1 mL) at room temperature under Ar for 10 min; [b] The reaction was carried out with styrene (1 mL) in MeOH (10 mL).

In order to better understand the mechanism of this transformation, additional experiment was carried out. When the reaction of styrene was set up in the presence of 1 equiv of BHT, a common radical scavenger, no product **2a** could be detected except a messy reaction system. This result indicated that an azide radical was possibly involved during the initial stage of this reaction.



Scheme 2 Preliminary mechanistic studies.

Based on above results, a plausible reaction mechanism was proposed (Scheme 3). Firstly, the reaction between $TMSN_3$ and $PhI(OAc)_2$ would generate the azide radical, which could react with arylethylene **1** to give the intermediate **I**. In the presence of copper(II) catalyst, the intermediate **I** would be further oxidized to form the intermediate **II** with a carbocation center, which was trapped with TMSCN to give the final product **2**. At the same time, the copper(I) was reoxidized back to copper(II) by $PhI(OAc)_2$ to complete a catalytic cycle.



Scheme 3 Plausible mechanism of the reaction.

In summary, a copper-catalyzed Markovnikov-type intermolecular azidocyanation of aryl alkenes has been successfully developed. Through the use of this method, regioselective construction of C-N_3 and C-CN bonds was completed within one step to give a series of 3-azido-2-arylpropanenitriles in moderate to good yields. This method not only further enriches the content of azide radical-participated transformations, but also provides a potential strategy for the synthesis of 3-amino-2-arylpropanoic acid.

This work was supported by the NSFC (No. 21202073 and 21372104), and the Project of MOST (2012ZX 09201101-003), the fundamental research funds for the central universities (lzujbky-2014-k20).

Notes and references

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† Patent pending, Chinese Patent Application (No. 201410293166.7).

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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Supporting Information

Copper-Catalyzed Intermolecular Azidocyanation of Aryl Alkenes

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Contents:

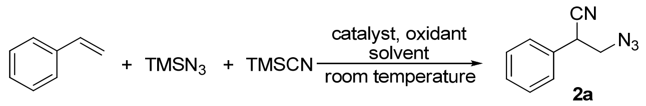
General Information:

All reactions under standard conditions were carried out under argon, dry atmosphere and monitored by thin-layer chromatography (TLC) on gel F254 plates. All reaction solvents were distilled according to the standard method before use. All products were purified through silica gel (200~300 mesh) column chromatography with light petroleum ether (bp. 60~90° C), ethyl acetate as eluent. ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on 400 MHz and 300 MHz instruments, and spectral data were reported in ppm. The MS data were obtained with SHIMADZU GCMS-QP2010 SE by means of EI (70 eV) technique and signals were given in m/z with relative intensity in brackets. High-resolution mass spectral analysis (HRMS) data were measured on the Bruker ApexII by means of the ESI technique. Melting point was measured with SGW-X4B instrument (uncorrected). The substrates 1a, 1b, 1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j, 1k, 1l, 1m, 1n are known compounds purchased form Energy Chemical.

1. Experimental details for new compounds

1.1 Optimization of reaction conditions:

Table S1 Optimization of reaction conditions[a]

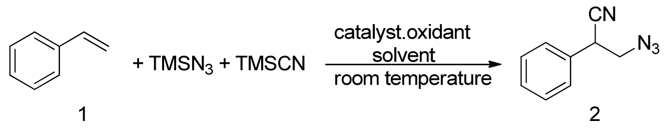


Entry	Catalyst（mol%）	Oxidant（equiv）	Solvent	Yield[b]
1	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	CH_2Cl_2	25%
2	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	DCE	23%
3	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	CH_3CN	45%
4	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	DMSO	35%
5	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	MeOH	52%
6	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	DMF	n.d.[c]
7	$Cu(OTf)_2$(5)	$PhI(OAc)_2$(1.1)	dioxane	n.d.[c]
8	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(1.1)	MeOH	65%
9	$Cu(OTf)_2$(20)	$PhI(OAc)_2$(1.1)	MeOH	63%
10	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	72%
11	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(2)	MeOH	67%
12	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(2.5)	MeOH	52%
13	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(3.0)	MeOH	41%
14[d]	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	72%
15[e]	$Cu(OTf)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	69%
16	$Cu(OTf)_2$(10)	PhIO(1.3)	MeOH	43%
17	$Cu(OTf)_2$(10)	$PhI(TFA)_2$(1.3)	MeOH	36%
18	$Cu(OTf)_2$(10)	TBHP(1.3)	MeOH	n.d.[c]
19	$Cu(OTf)_2$(10)	$K_2S_2O_8$(1.3)	MeOH	n.d.[c]
20	$Cu(OTf)_2$(10)	CAN(1.3)	MeOH	n.d.[c]
21	CuOTf(10)	$PhI(OAc)_2$(1.3)	MeOH	25%
22	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	84%
23[f]	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	74%
24[g]	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	55%
25[h]	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	65%
26[i]	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	46%
27	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(0.8)	MeOH	72%
28	$Cu(TFA)_2$(10)	$PhI(OAc)_2$(2)	MeOH	78%
29	$Cu(OAc)_2$(10)	$PhI(OAc)_2$(1.3)	MeOH	38%
30	CuBr(10)	$PhI(OAc)_2$(1.3)	MeOH	46%
31	CuCl(10)	$PhI(OAc)_2$(1.3)	MeOH	40%
32	$FeCl_3$(10)	$PhI(OAc)_2$(1.3)	MeOH	20%

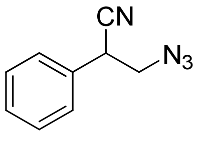
33	No catalyst	PhI(OAc)$_2$(1.3)	MeOH	25%
34	Cu(MeCN)$_4$PF$_6$(10)	PhI(OAc)$_2$(1.3)	MeOH	52%
35	Pd(OAc)$_2$(10)	PhI(OAc)$_2$(1.3)	MeOH	n.d.
36	PdCl$_2$(10)	PhI(OAc)$_2$(1.3)	MeOH	n.d.
37	Pd(PPh$_3$)$_4$(10)	PhI(OAc)$_2$(1.3)	MeOH	45%
38	Au(PPh$_3$)Cl(10)	PhI(OAc)$_2$(1.3)	MeOH	n.d.
39	AgTFA(10)	PhI(OAc)$_2$(1.3)	MeOH	n.d.

[a] Reation condition: without other notification, all of the reactions were performed with styrene (0.3 mmol), TMSN$_3$ (1.1 equiv), TMSCN (2 equiv), catalyst and oxidant in solvent (1 mL) at room termperature under Ar for 10 min. [b] Isolated yield; [c] n.d. = not detected. [d] The reaction was carried out at 50 ºC; [e] The reaction was carried out at 100 ºC in seal tube; [f] TMSN$_3$ (1.5 equiv) and TMSCN (2 equiv) were used; [g] TMSN$_3$ (2 equiv) and TMSCN (2 equiv) were used; [h] TMSN$_3$ (1.1 equiv) and TMSCN (3 equiv) were used; [i] TMSN$_3$ (1.1 equiv) and TMSCN (4 equiv) were used.

1.2 General procedure 2a:

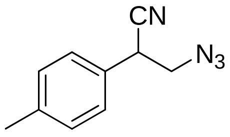


To a stirred solution of the styrene (35ul, 0.3mmol) in MeOH (1 mL) was successively added TMSN$_3$ (52ul, 0.33 mmol), TMSCN (82ul, 0.6 mmol), Cu(TFA)$_2$ (9mg, 0.03mmol) and PhI(OAc)$_2$ (147mg，0.46mmol) at room temperature. After stirred for 10 min, the mixture was concentrated under vacuum. The residue was purified by column chromatography (EtOAc: petroleum ether = 1:80) to give product **2a** (44mg, 84 %) as a yellow oil.



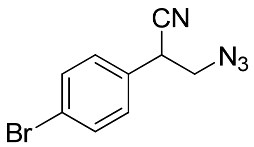
3-azido-2-phenylpropanenitrile (**2a**)

Pale yellow oil; 84% yield; **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.42-7.37 (m, 5H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.71-3.67 (m, 7.5 Hz, 2H); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 131.8, 129.1, 128.8, 127.4, 118.3, 54.4, 37.2; MS m/z (%): 172 (M$^+$, 10), 144 (M$^+$-28, 60), 116 (100) ; **HRMS** (ESI) Calcd. for C$_9$H$_9$N$_2$ [M-N$_2$+H]$^+$: 145.0766, Found 145.0762.



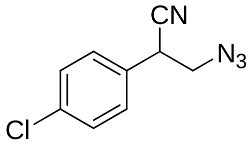
3-azido-2-(p-tolyl)propanenitrile (**2b**)

Pale yellow oil; 82% yield; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.99 (t, *J* = 6.8 Hz, 1H), 3.74-3.65 (m, 2H), 2.40 (s, 3H); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 139.0, 130.1, 129.2, 127.5, 118.8, 54.7, 37.8, 21.1; MS m/z (%): 186 (M$^+$, <1), 143 (M$^+$-43, 1), 130 (100), 116 (100) ; **HRMS** (ESI) Calcd. for C$_{10}$H$_{11}$N$_2$ [M-N$_2$+H]$^+$: 159.0922, Found 159.0917.



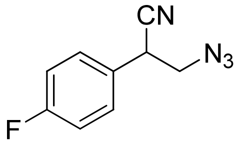
3-azido-2-(4-bromophenyl)propanenitrile (**2c**)

Pale yellow oil; 74% yield; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 3.97 (t, *J* = 6.8 Hz, 1H), 3.70-3.67 (m, 2H); ^{13}**C NMR**(100 MHz, $CDCl_3$): δ 132.6, 131.2, 129.4, 123.3, 118.1, 54.3, 37.6; MS m/z (%): 252 ($[M+2]^+$, <1), 250 (M^+, <1), 224 (1), 222 (1), 196 (100), 194 (98) ; **HRMS** (ESI) Calcd. for $C_9H_8BrN_2$ $[M-N_2+H]^+$: 222.9871, Found 222.9869.



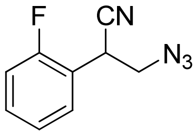
3-azido-2-(4-chlorophenyl)propanenitrile (**2d**)

Pale yellow oil; 78% yield; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.35-7.33 (m, 2H), 4.01 (t, *J* = 6.6 Hz, 1H), 3.76-3.67 (m, 2H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 135.2, 130.7, 129.6, 129.1, 118.1, 54.4, 37.5; MS m/z (%): 163 ($[M-43]^+$, 3), 150 ($[M-56]^+$, 100), 124 (30), 117 (60) ; **HRMS** (ESI) Calcd. for $C_9H_8ClN_2$ $[M-N_2+H]^+$: 179.0376, Found 179.0372.



3-azido-2-(4-fluorophenyl)propanenitrile (**2e**)

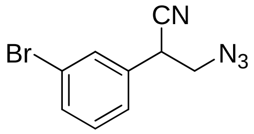
Pale yellow oil; 78% yield; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.37 (m, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 4.02 (t, *J* = 6.6 Hz, 1H), 3.76-3.66 (m, 2H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 161.7 (d, *J* = 248 Hz), 129.5 (d, *J* = 9 Hz), 128.0 (d, *J* = 4 Hz), 118.4, 116.5 (d, *J* = 22 Hz), 54.6, 37.4; MS m/z (%): 147 ($[M-43]^+$, 5), 134 ($[M-56]^+$, 100), 108 (90) ; **HRMS** (ESI) Calcd. for $C_9H_8FN_2$ $[M-N_2+H]^+$: 163.0672, Found 163.0668.



3-azido-2-(2-fluorophenyl)propanenitrile (**2f**)

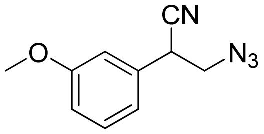
Pale yellow oil; 66% yield; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.44 (m, 1H), 7.34-7.30 (m, 1H), 7.19-7.15 (m, 1H), 7.08-7.04 (m, 1H), 4.26 (t, *J* = 6.4 Hz, 1H), 3.66-3.64 (m, 2H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 158.8 (d, *J* = 247 Hz), 130.1 (d, *J* = 8 Hz), 128.6 (d, *J* = 3 Hz), 124.1 (d, *J* = 3 Hz), 118.4 (d, *J* = 14 Hz), 116.7, 115.0 (d, *J* = 21 Hz), 51.9 (d, *J* = 1 Hz), 31.2 (d, *J* = 3 Hz); MS m/z

(%): 162 ([M-28]$^+$, 3), 134 ([M-56]$^+$, 100), 108 (90) ; **HRMS** (ESI) Calcd. for $C_9H_8FN_2$ [M-N_2+H]$^+$: 163.0672, Found 163.0668.



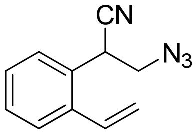
3-azido-2-(3-bromophenyl)propanenitrile (**2g**)

Pale yellow oil; 65% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.37-7.28 (m, 2H), 3.99 (t, *J* = 6.6 Hz, 1H), 3.76-3.69 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.3, 132.3, 130.9, 130.8, 126.4, 123.4 117.9, 54.4, 37.6; MS m/z (%):252 ([M+2]$^+$, <1), 250 (M$^+$, <1), 224 (1), 222 ([M-28]$^+$, 1), 209 ([M-43]$^+$, 3), 207 ([M-43]$^+$, 3), 196 (50), 194 (50), 116 (100) ; **HRMS** (ESI) Calcd. for $C_9H_8BrN_2$ [M-N_2+H]$^+$: 222.9871, Found 222.9867.



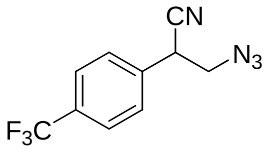
3-azido-2-(3-methoxyphenyl)propanenitrile (**2h**)

Pale yellow oil; 65% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26-7.22 (m, 1H), 6.87-6.82 (m,3H), 3.88 (t, *J* = 6.8 Hz, 1H), 3.73 (s, 3H), 3.61-3.58 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.1, 133.4, 130.3, 119.6, 118.4, 114.2, 113.4, 55.2, 54.4, 37.9; MS m/z (%): 202 (M$^+$, 60), 174 (M$^+$-28, 20), 159 (M$^+$-43, 10), 146 (100) ; **HRMS** (ESI) Calcd. for $C_{10}H_{11}N_2O$ [M-N_2+H]$^+$: 175.0871, Found 175.0867.



3-azido-2-(3-vinylphenyl)propanenitrile (**2i**)

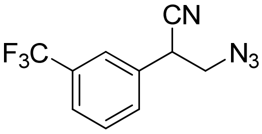
Pale yellow oil; 56% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45-7.24 (m, 4H), 6.74-6.67 (m,1H), 5.82-5.76 (m, 1H), 5.34-5.30 (m, 1H), 4.00-3.96 (m, 1H), 3.73-3.64 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.7, 138.3, 135.7, 135.6, 132.4, 131.3, 129.5, 127.8, 127.0, 126.8, 126.6, 125.4, 118.4, 115.3, 115.2, 54.44, 54.41, 38.0, 37.7; MS m/z (%): 198 (M$^+$, 4), 170 (M$^+$-28, 4), 142 (100) ; **HRMS** (ESI) Calcd. for $C_{11}H_{11}N_2$ [M-N_2+H]$^+$: 171.0922, Found 171.0919.



3-azido-2-(4-(trifluoromethyl)phenyl)propanenitrile (**2j**)

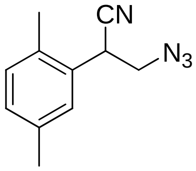
Pale yellow oil; 61% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 4.11 (t, *J* = 6.6 Hz, 1H), 3.78-3.76 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 136.1, 131.4

(q, *J* = 33 Hz), 128.3, 126.4 (q, *J* = 3 Hz), 123.7 (q, *J* = 271 Hz), 117.8, 54.2, 37.8; MS m/z (%): 240 (M^+, <1), 212 (M^+-28, 1), 197 (M^+-43, 3), 184 (100) ; **HRMS** (ESI) Calcd. for $C_{10}H_8F_3N_2$ $[M-N_2+H]^+$: 213.0640, Found 213.0634.



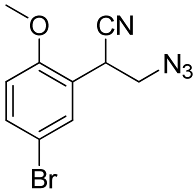
3-azido-2-(3-(trifluoromethyl)phenyl)propanenitrile (**2k**)

Pale yellow oil; 52% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68-7.56 (m, 4H), 4.08 (t, *J* = 6.6 Hz, 1H), 3.76-3.74 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 133.3, 131.9 (q, *J* = 33 Hz), 130.1, 126.0 (q, *J* = 4 Hz), 124.6 (q, *J* = 4 Hz), 123.6 (q, *J* = 271 Hz), 117.8, 54.3, 37.8; MS m/z (%): 240 (M^+, <1), 197 (M^+-43, 2), 184 (25), 84 (100) ; **HRMS** (ESI) Calcd. for $C_{10}H_8F_3N_2$ $[M-N_2+H]^+$: 213.0640, Found 213.0636.



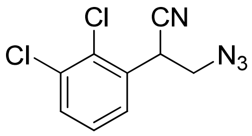
3-azido-2-(2,5-dimethylphenyl)propanenitrile (**2l**)

Pale yellow oil; 41% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.13 (s, 2H), 4.18 (q, *J* = 6.0 Hz, 1H), 3.73-3.62 (m, 2H), 2.38 (s, 3H), 2.34 (s, 3H); **^{13}C NMR**(100 MHz, $CDCl_3$): δ 136.9, 132.2, 131.2, 130.2, 129.8 , 128.5, 119.1, 53.6, 34.9, 20.9, 18.6; MS m/z (%): 200 (M^+, 4), 172 ($[M-28]^+$, 3), 157 ($[M-43]^+$, 2), 144 ($[M-56]^+$, 100), 117 (60) ; **HRMS** (ESI) Calcd. for $C_{11}H_{13}N_2$ $[M-N_2+H]^+$: 173.1079, Found 173.1075.



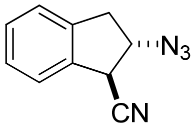
3-azido-2-(5-bromo-2-methoxyphenyl)propanenitrile (**2m**)

Pale yellow oil; 63% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 2 Hz, 1H), 7.39 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.27 (q, *J* = 5.6 Hz, 1H), 3.79 (s, 3H), 3.64-3.54 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.2, 133.1, 131.8, 122.3, 118.2, 113.2, 112.6, 55.9, 52.3, 32.6; MS m/z (%): 282 ($[M+2]^+$, 23), 280 (M^+, 23), 226 (69), 224 ($[M-56]^+$, 69), 84 (100) ; **HRMS** (ESI) Calcd. for $C_{10}H_{10}BrN_2O$ $[M-N_2+H]^+$: 252.9977, Found 252.9974.



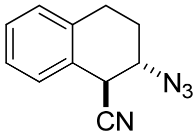
3-azido-2-(2,3-dichlorophenyl)propanenitrile (**2n**)

Pale yellow oil; 32% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56-7.53 (m, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 4.58 (dd, *J*= 4.8, 7.2 Hz, 1H), 3.81 (dd, *J* = 4.8, 12.4 Hz, 1H), 3.71 (dd, *J* = 7.2, 12.4 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 134.1, 132.0, 131.2, 131.2, 128.1, 127.9, 117.7, 52.3, 36.3; MS m/z (%): 212 ($[M-28]^+$, 2), 197 ($[M-43]^+$, 15), 184 (100); **HRMS** (ESI) Calcd. for $C_9H_7Cl_2N_2$ $[M-N_2+H]^+$: 212.9986, Found 212.9983.



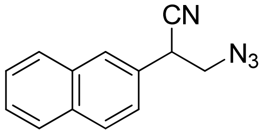
2-azido-2,3-dihydro-1H-indene-1-carbonitrile (**2o**)

Pale yellow oil; 67% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.17 (m, 4H), 4.45 (q, *J* = 7.6 Hz, 1H), 3.98 (d, *J* = 7.6 Hz, 1H), 3.32 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.94 (q, *J* = 7.6, 16.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 138.8, 134.5, 129.4, 128.1, 125.1, 124.3, 118.5, 65.6, 41.3, 37.5; MS m/z (%): 184 (M^+, <1), 156 ($[M-28]^+$, 4), 141 ($[M-43]^+$, 4), 129 (100) ; **HRMS** (ESI) Calcd. for $C_{10}H_9N_2$ $[M-N_2+H]^+$: 157.0766, Found 157.0762.



2-azido-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (**2p**)

White solid, mp 73-75 ºC; 37% yield; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.37 (m, 1H), 7.25-7.20 (m, 2H), 7.13-7.10 (m, 1H), 4.07-4.00 (m, 1H), 3.86 (d, *J* = 9 Hz, 1H), 2.96-2.90 (m, 2H), 2.36-2.01 (m, 1H), 1.95-1.82 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 134.4, 129.2, 128.6, 128.5, 127.3, 127.1, 119.4, 59.2, 37.6, 26.9, 26.4; MS m/z (%): 169 ($[M-29]^+$, 25), 155 ($[M-43]^+$, 6), 142 ($[M-56]^+$, 50), 116 (100) ; **HRMS** (ESI) Calcd. for $C_{11}H_{11}N_2$ $[M-N_2+H]^+$: 171.0922, Found 171.0918.

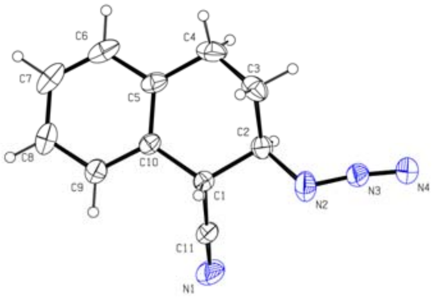


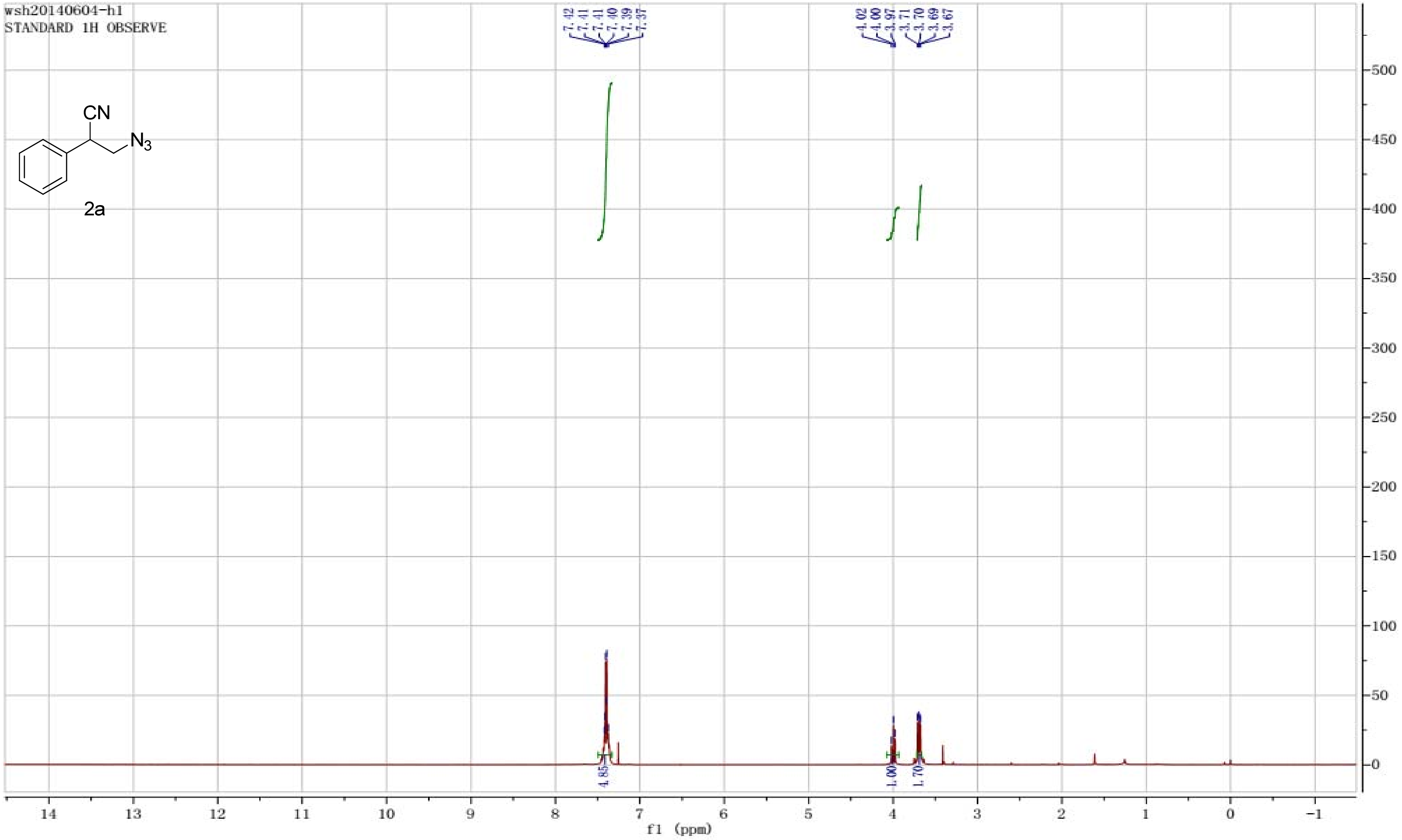
3-azido-2-(naphthalen-2-yl)propanenitrile (**2q**)

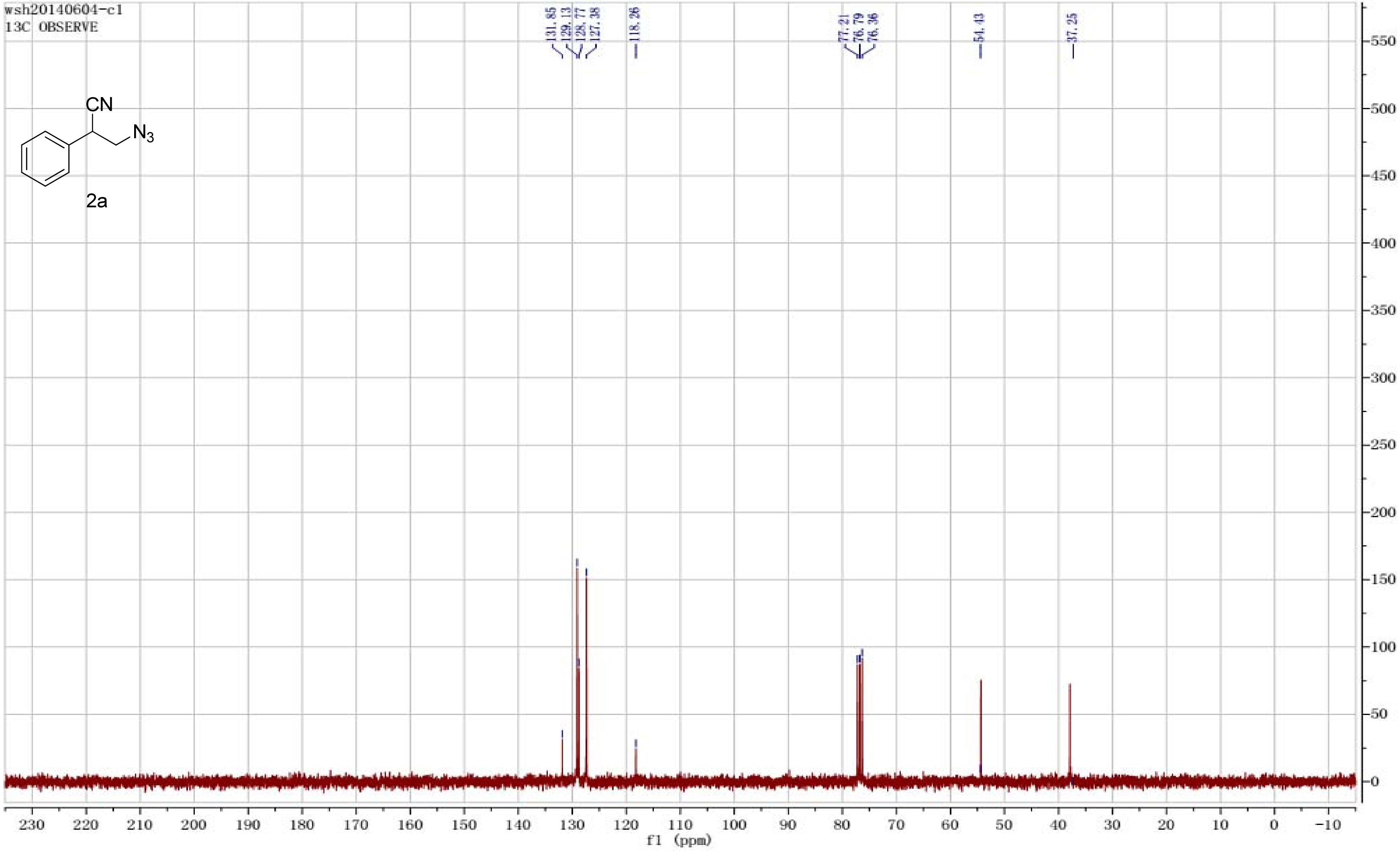
Pale yellow oil; 53% yield; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93-7.88 (m, 4H), 7.58 (dd, *J* = 3.2, 8.4 Hz, 2H), 7.45 (dd, *J* = 2.0, 8.4 Hz, 1H), 4.16 (t, *J* = 6.8 Hz, 1H), 3.80-3.78 (m, 2H); **^{13}C NMR**

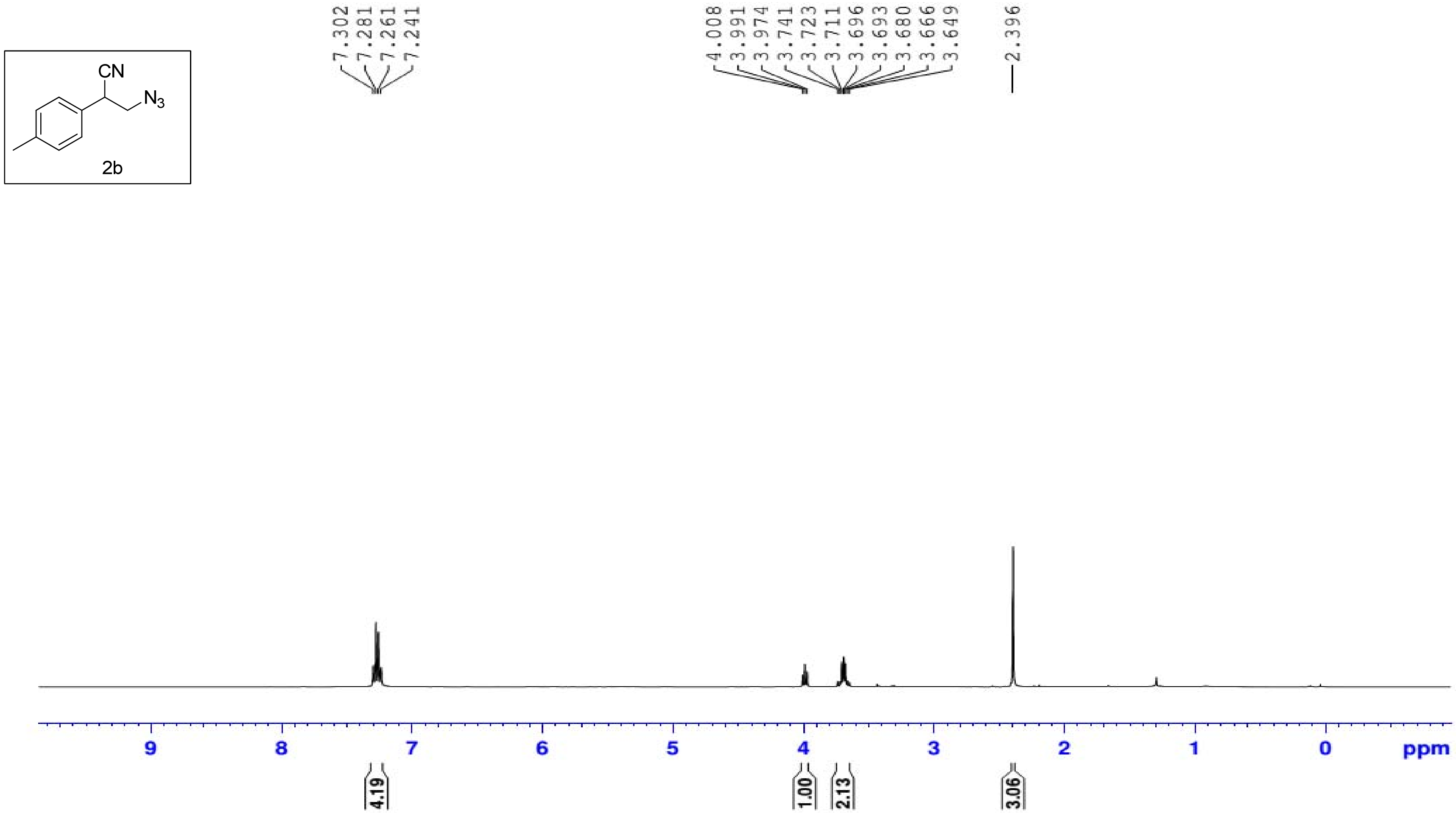
(100 MHz, $CDCl_3$): δ 133.3, 133.2, 129.5, 129.4, 128.0, 127.8, 127.3, 127.1, 127.0, 124.6, 118.7, 54.5, 38.3; MS m/z (%): 222 (M^+, 10), 194 ($[M-28]^+$, 4), 179($[M-43]^+$, 4), 166 ($[M-56]^+$, 100) ; **HRMS** (ESI) Calcd. for $C_{13}H_{11}N_2$ $[M-N_2+H]^+$: 195.0922, Found 195.0918.

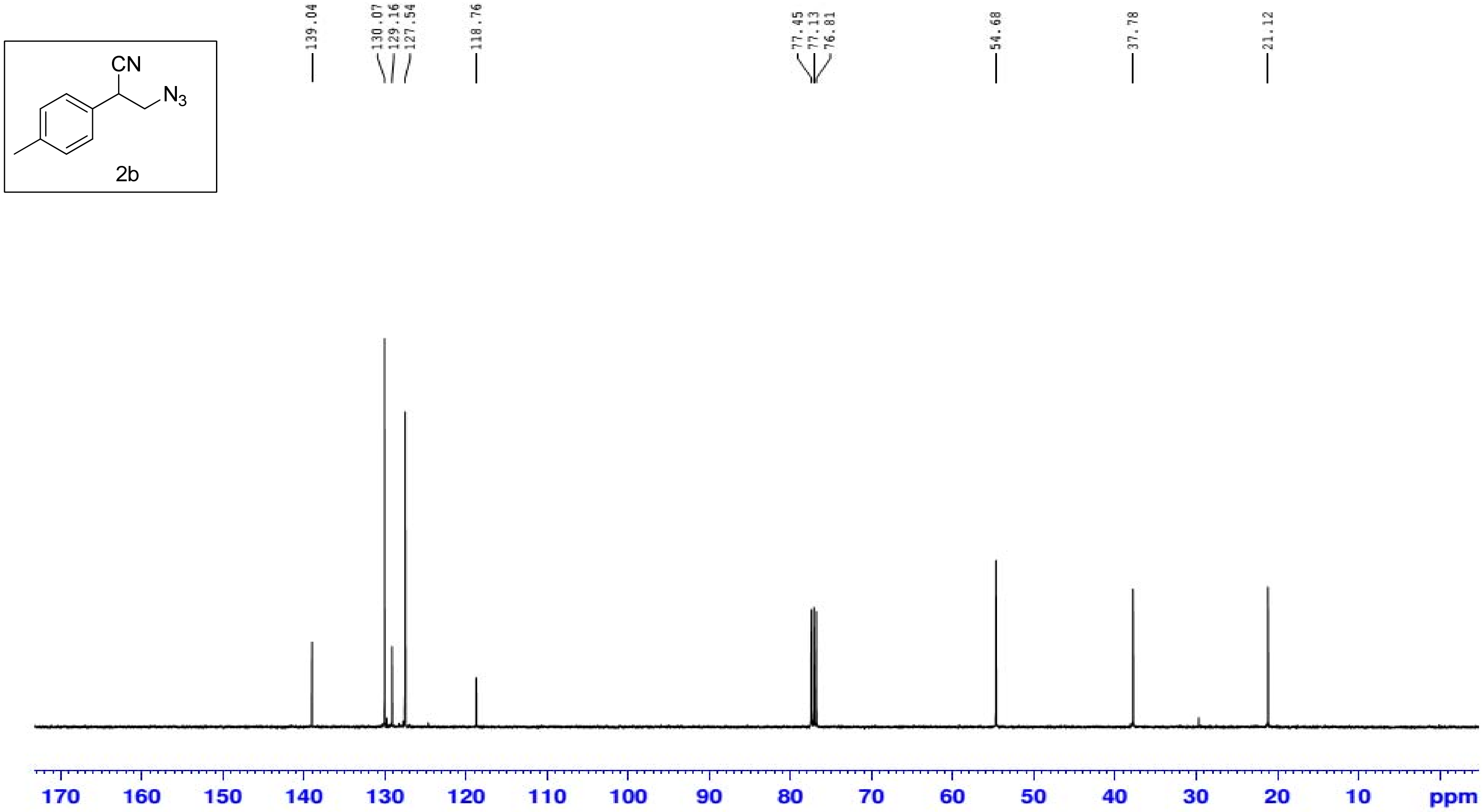
2. X-Ray ellipsoid plots of 2p (CCDC: 1008927)

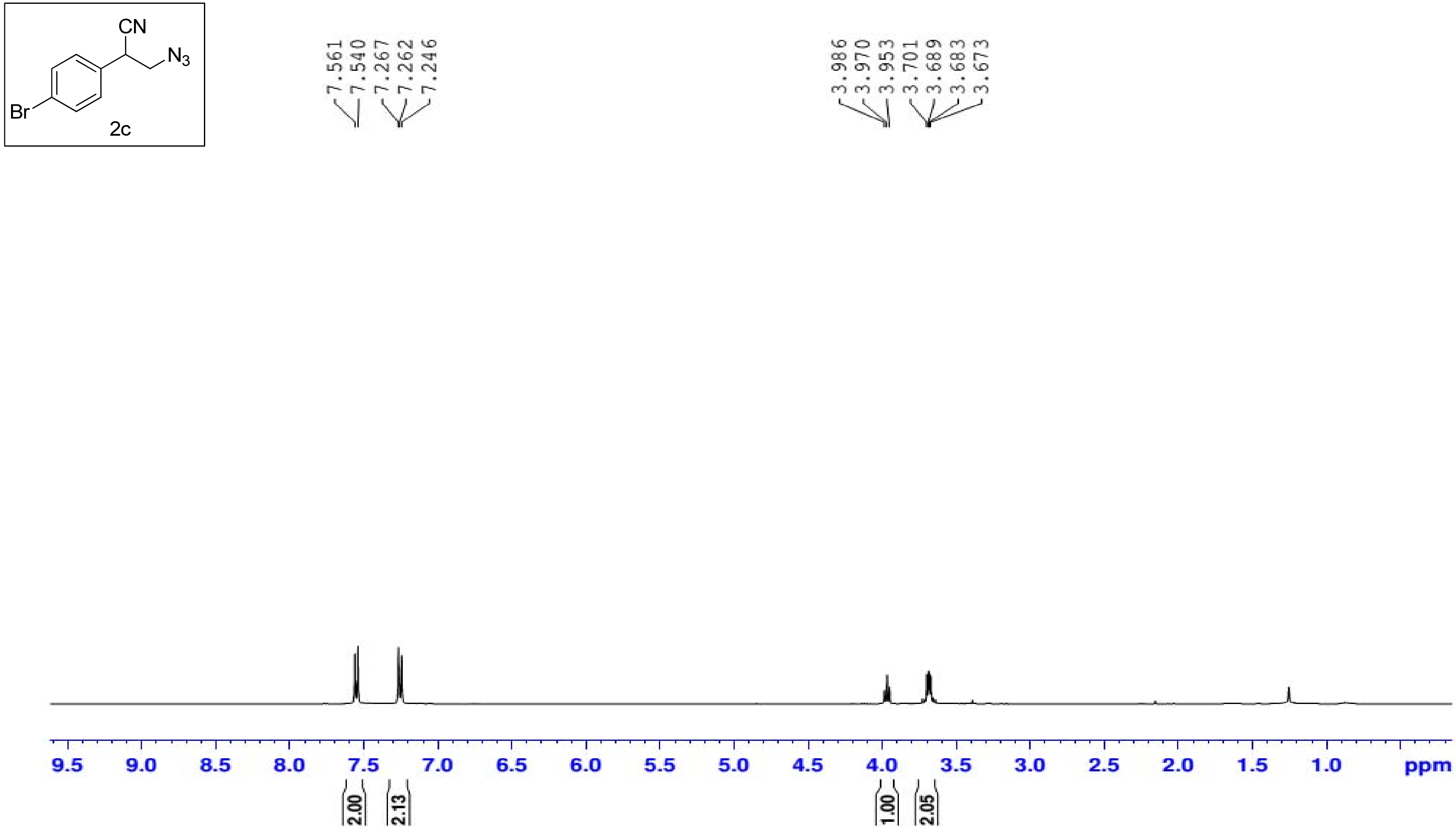



wsh20140604-h1
STANDARD 1H OBSERVE
CN
N3
2a
7.42
7.41
7.41
7.40
7.39
7.37
4.02
4.00
3.97
3.71
3.70
3.69
3.67
4.85
1.00
1.70
500
450
400
350
300
250
200
150
100
50
0
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
f1 (ppm)


wsh20140604-c1
13C OBSERVE
131.85
129.13
128.77
127.38
118.26
77.21
76.79
76.36
54.43
37.25
CN
N_3
2a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)
550
500
450
400
350
300
250
200
150
100
50
0

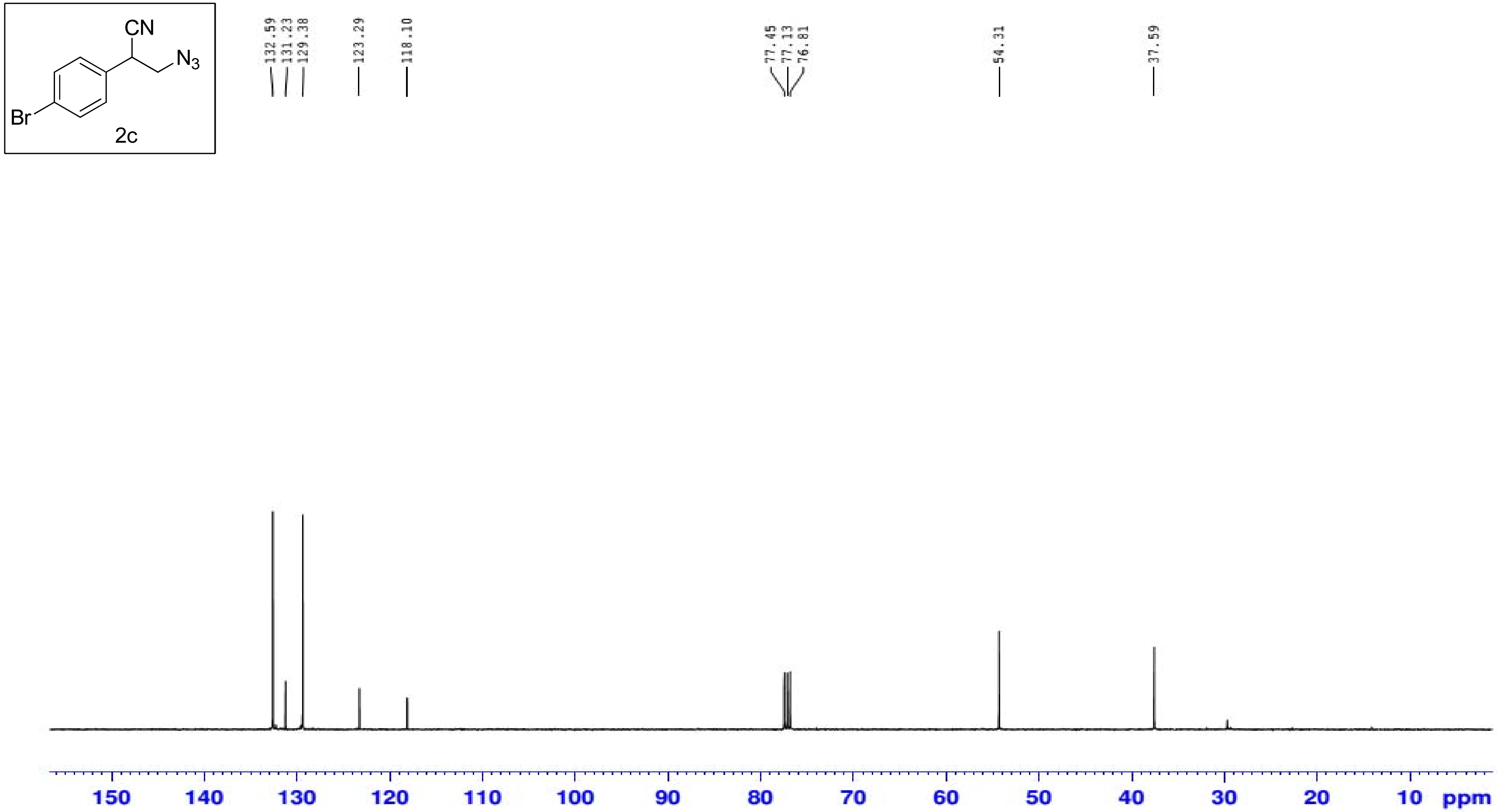

CN
N3
2b
7.302
7.281
7.261
7.241
4.008
3.991
3.974
3.741
3.723
3.711
3.696
3.693
3.680
3.666
3.649
2.396
9
8
7
6
5
4
3
2
1
0
ppm
4.19
1.00
2.13
3.06


CN
N3
2b
139.04
130.07
129.16
127.54
118.76
77.45
77.13
76.81
54.68
37.78
21.12
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

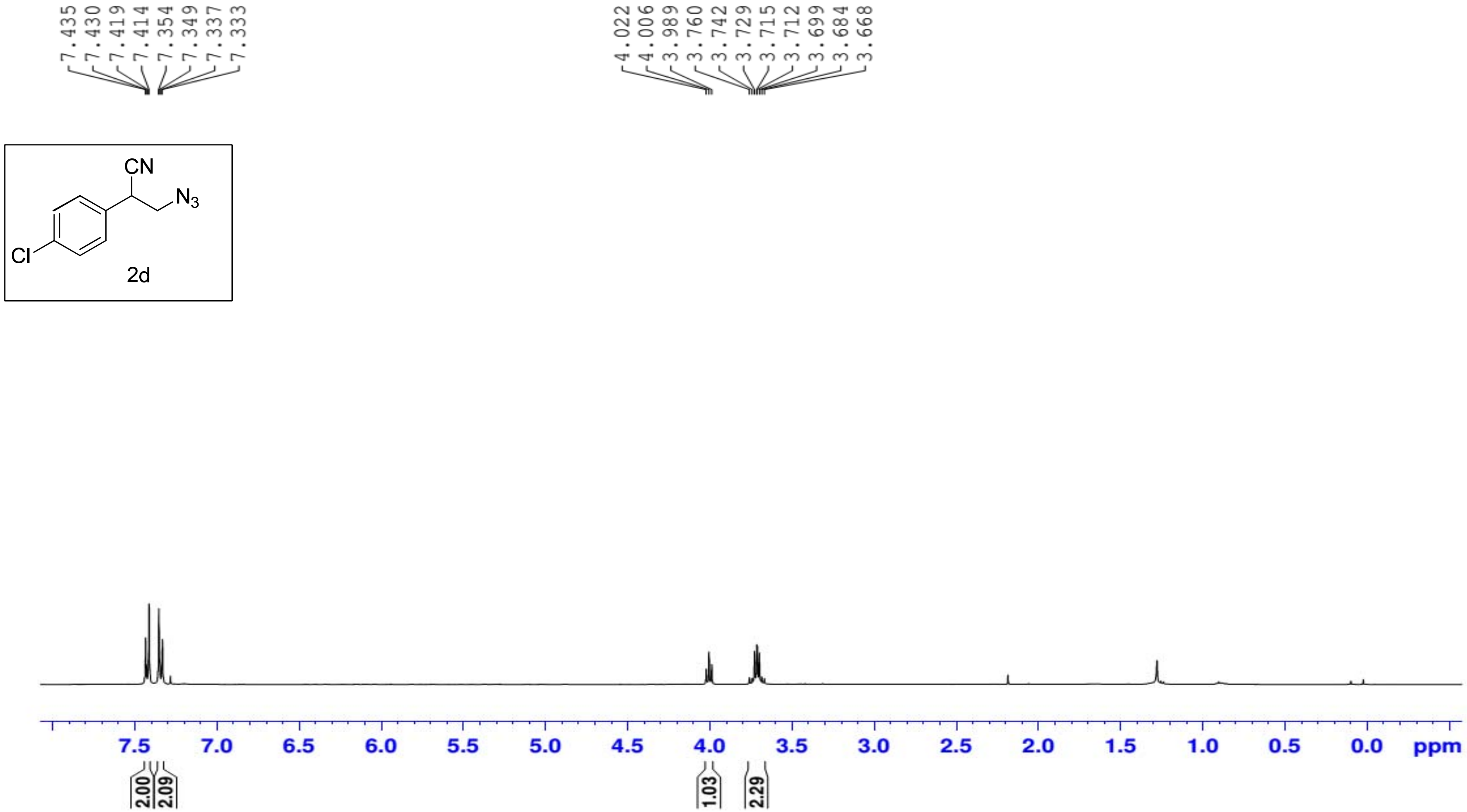

CN
N3
Br

2c

7.561
7.540
7.267
7.262
7.246
3.986
3.970
3.953
3.701
3.689
3.683
3.673
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
2.13
1.00
2.05


CN
N3
Br
132.59
131.23
129.38
123.29
118.10
77.45
77.13
76.81
54.31
37.59
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2c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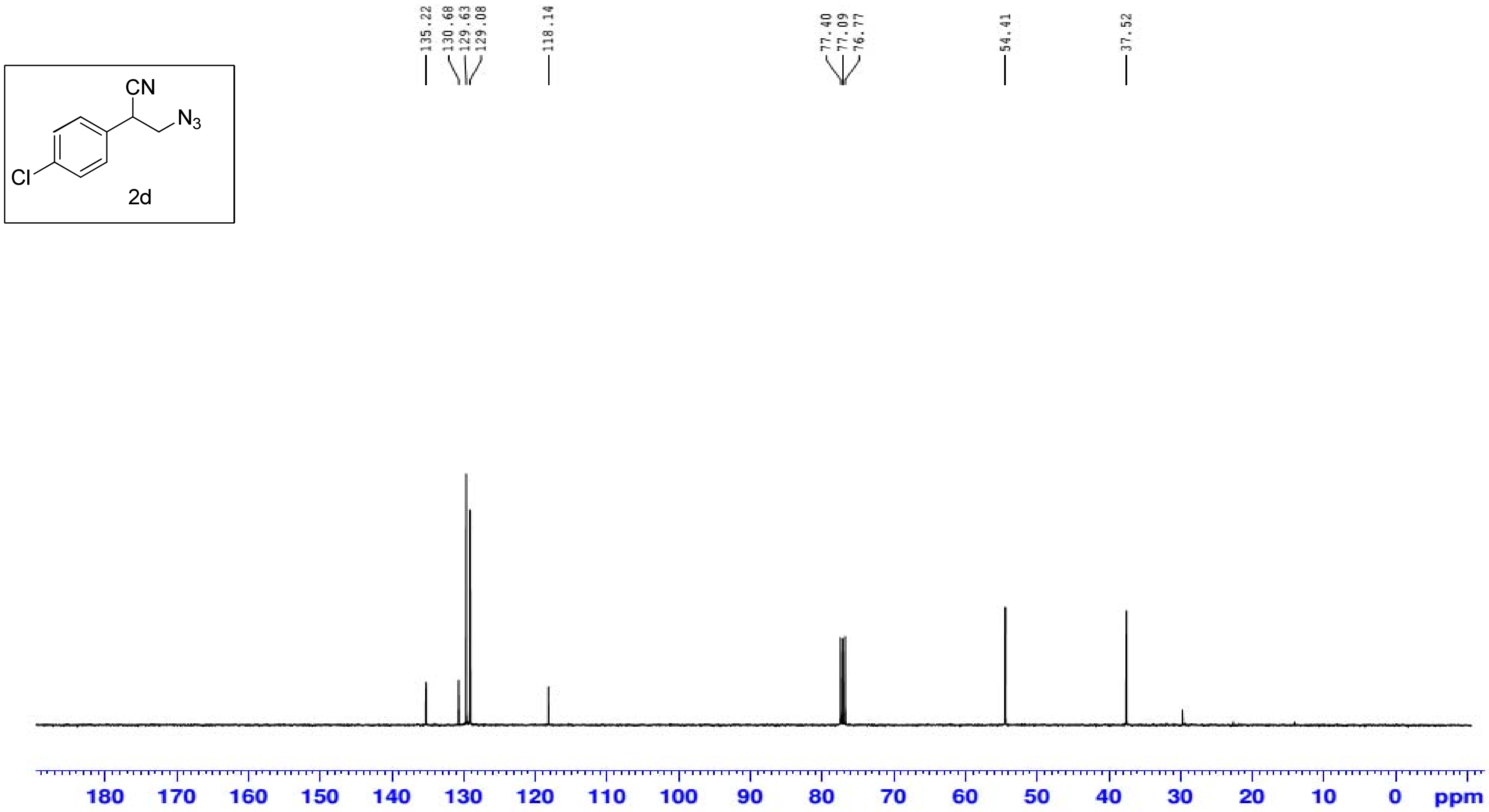
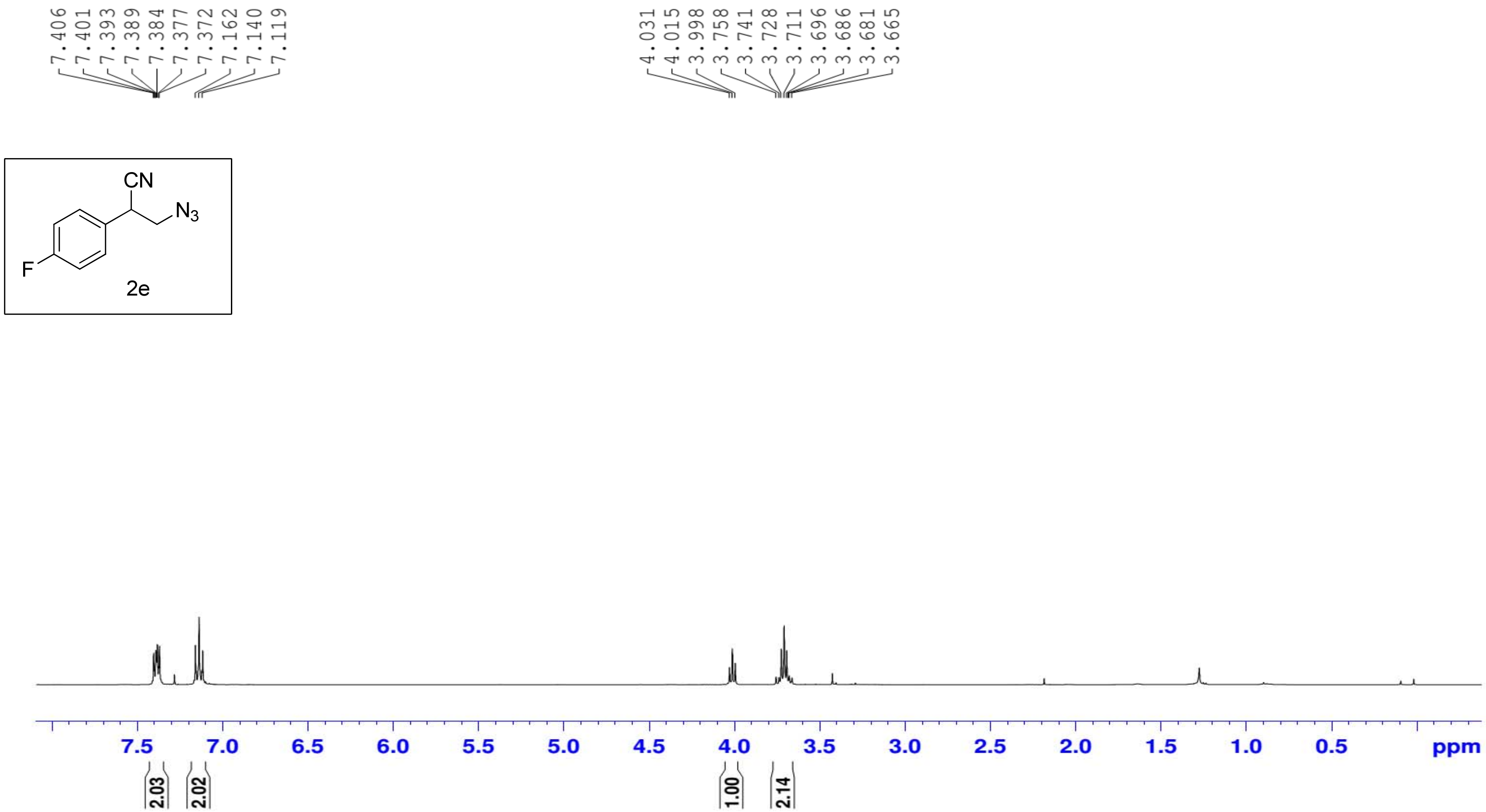
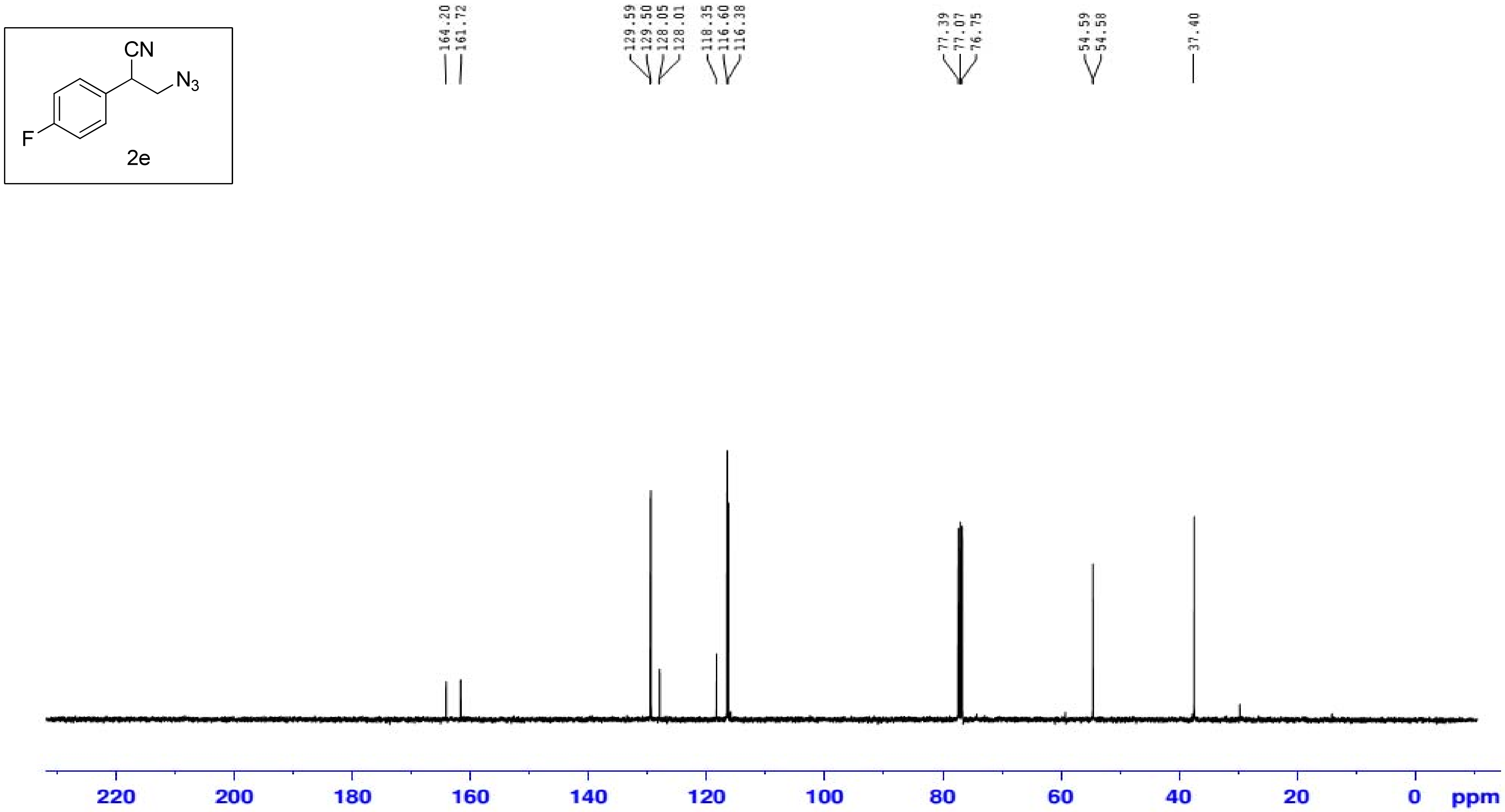
7.430
7.419
7.414
7.354
7.349
7.337
7.333
4.022
4.006
3.989
3.760
3.742
3.729
3.715
3.712
3.699
3.684
3.668
CN
N3
Cl
2d
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.00
2.09
1.03
2.29

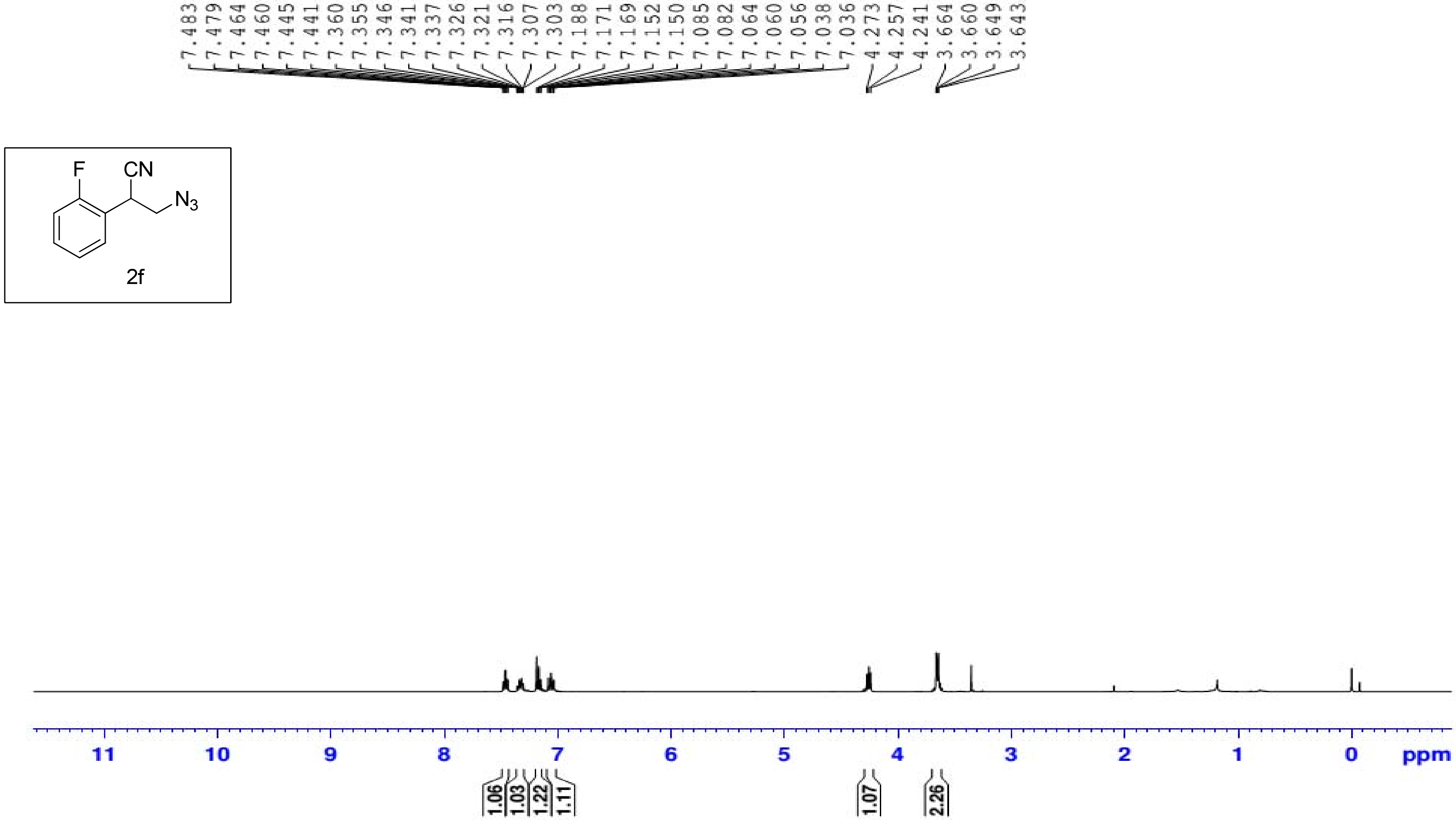

CN
N$_3$
Cl
2d
135.22
130.68
129.63
129.08
118.14
77.40
77.09
76.77
54.41
37.52
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.406
7.401
7.393
7.389
7.384
7.377
7.372
7.162
7.140
7.119
4.031
4.015
3.998
3.758
3.741
3.728
3.711
3.696
3.686
3.681
3.665
CN
N3
F
2e
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
2.02
1.00
2.14


CN
N3
F

2e

164.20
161.72
129.59
129.50
128.05
128.01
118.35
116.60
116.38
77.39
77.07
76.75
54.59
54.58
37.40
220
200
180
160
140
120
100
80
60
40
20
0
ppm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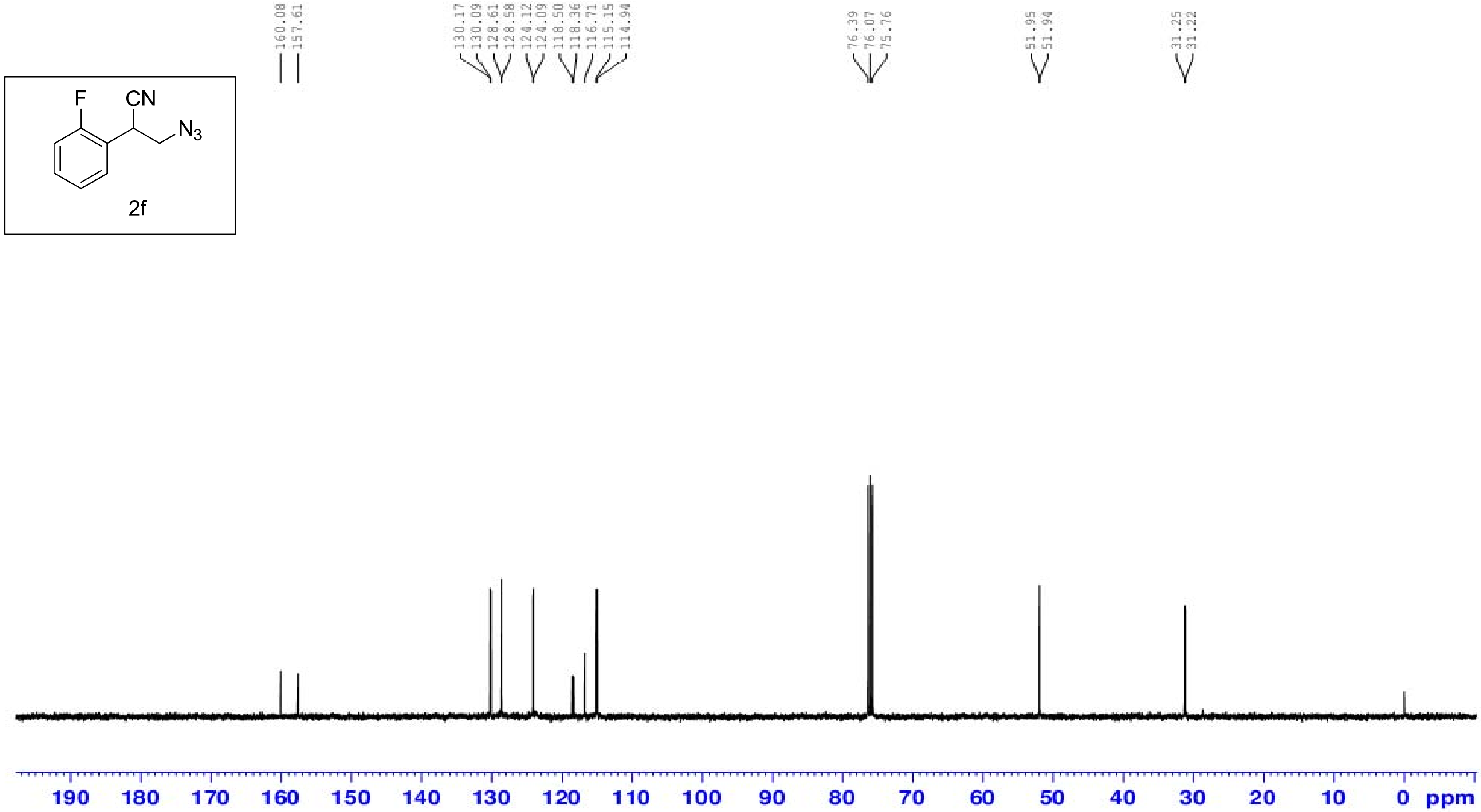
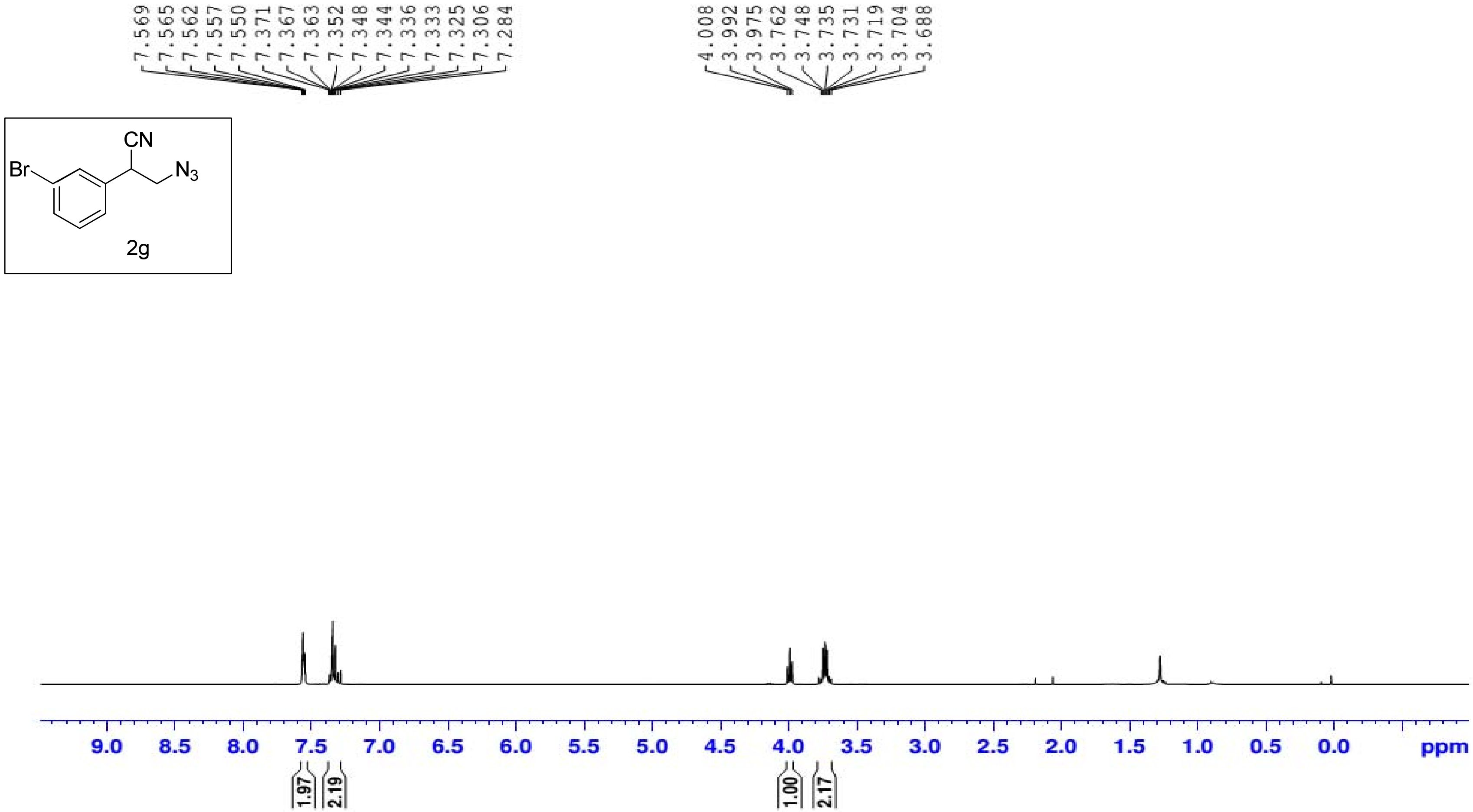
7.460
7.445
7.441
7.360
7.355
7.346
7.341
7.337
7.326
7.321
7.316
7.307
7.303
7.188
7.171
7.169
7.152
7.150
7.085
7.082
7.064
7.060
7.056
7.038
7.036
4.273
4.257
4.241
3.664
3.660
3.649
3.643
F
CN
N3
2f
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.06
1.03
1.22
1.11
1.07
2.26


F
CN
N_3
2f
160.08
157.61
130.17
130.09
128.61
128.58
124.12
124.09
118.50
118.36
116.71
115.15
114.94
76.39
76.07
75.76
51.95
51.94
31.25
31.22
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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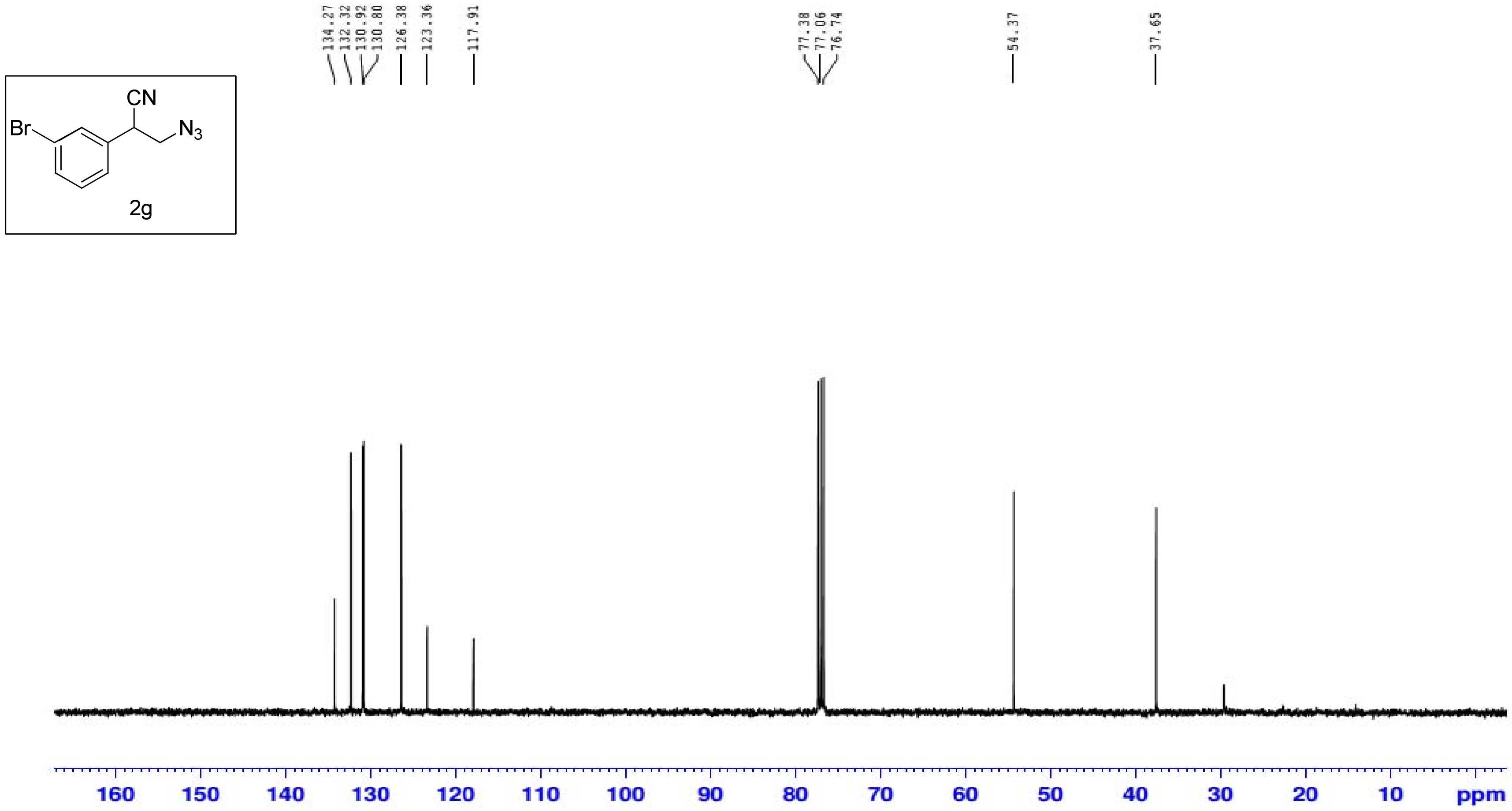
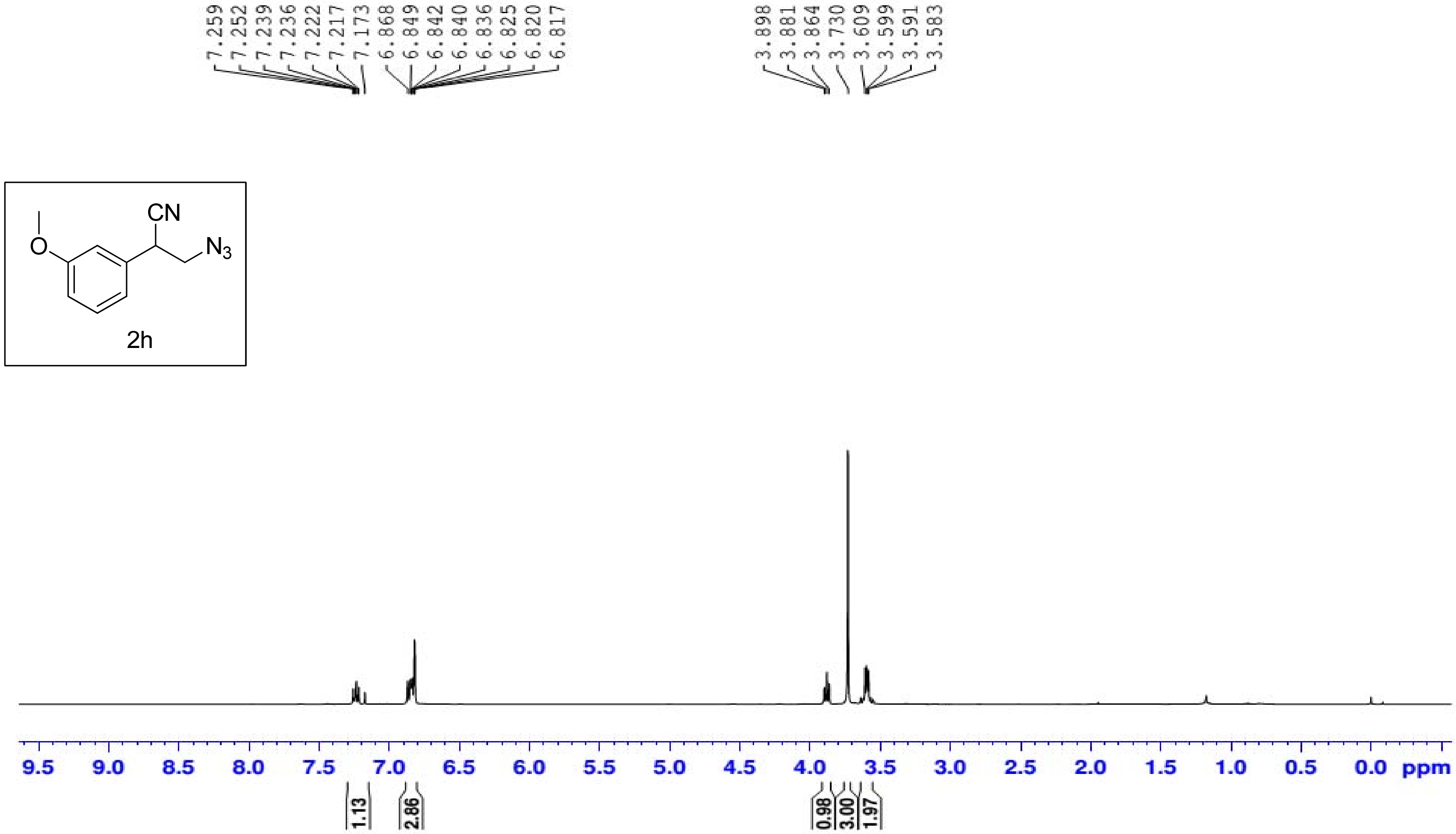
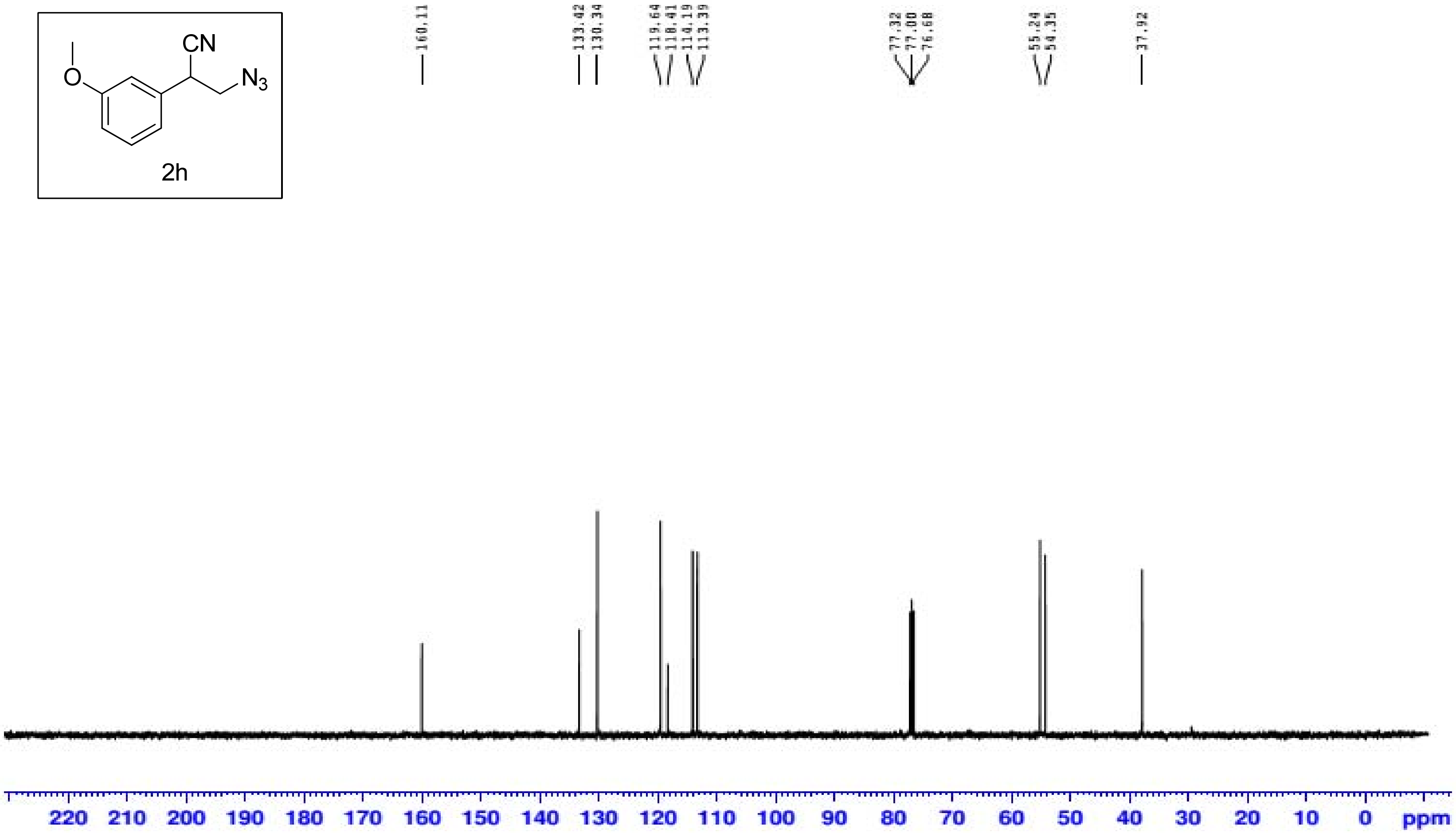
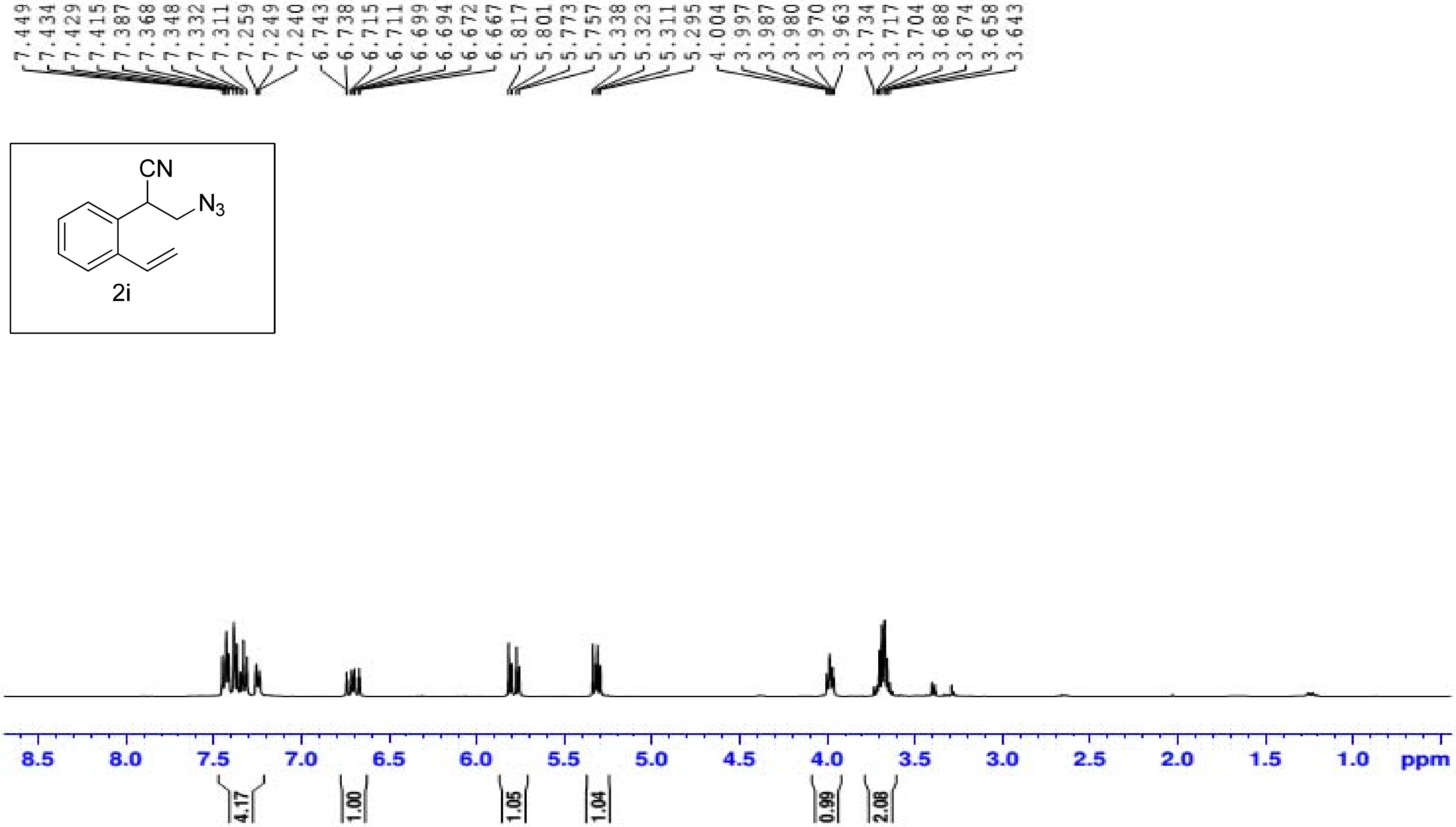
7.562
7.557
7.550
7.371
7.367
7.363
7.352
7.348
7.344
7.336
7.333
7.325
7.306
7.284
4.008
3.992
3.975
3.762
3.748
3.735
3.731
3.719
3.704
3.688
CN
Br
N3
2g
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.97
2.19
1.00
2.17


2g

134.27
132.32
130.92
130.80
126.38
123.36
117.91
77.38
77.06
76.74
54.37
37.65
CN
Br
N_3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.259
7.252
7.239
7.236
7.222
7.217
7.173
6.868
6.849
6.842
6.840
6.836
6.825
6.820
6.817
3.898
3.881
3.864
3.730
3.609
3.599
3.591
3.583
CN
O
N3
2h
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.13
2.86
0.98
3.00
1.97


CN
O
N_3
2h
160.11
133.42
130.34
119.64
118.41
114.19
113.39
77.32
77.00
76.68
55.24
54.35
37.92
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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7.429
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7.332
7.311
7.259
7.249
7.240
6.743
6.738
6.715
6.711
6.699
6.694
6.672
6.667
5.817
5.801
5.773
5.757
5.338
5.323
5.311
5.295
4.004
3.997
3.987
3.980
3.970
3.963
3.734
3.717
3.704
3.688
3.674
3.658
3.643
CN
N3
2i
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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2.0
1.5
1.0
ppm
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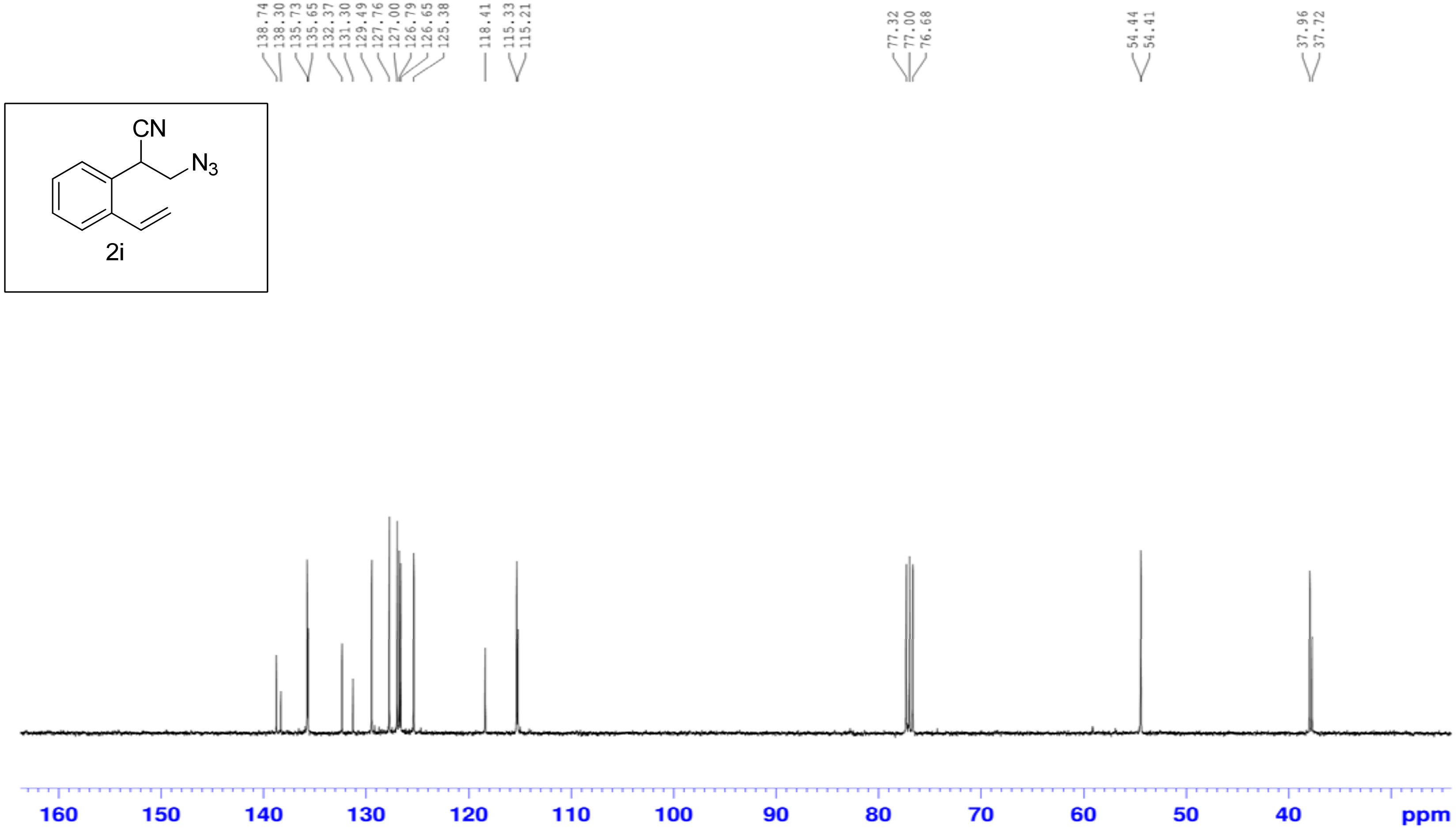
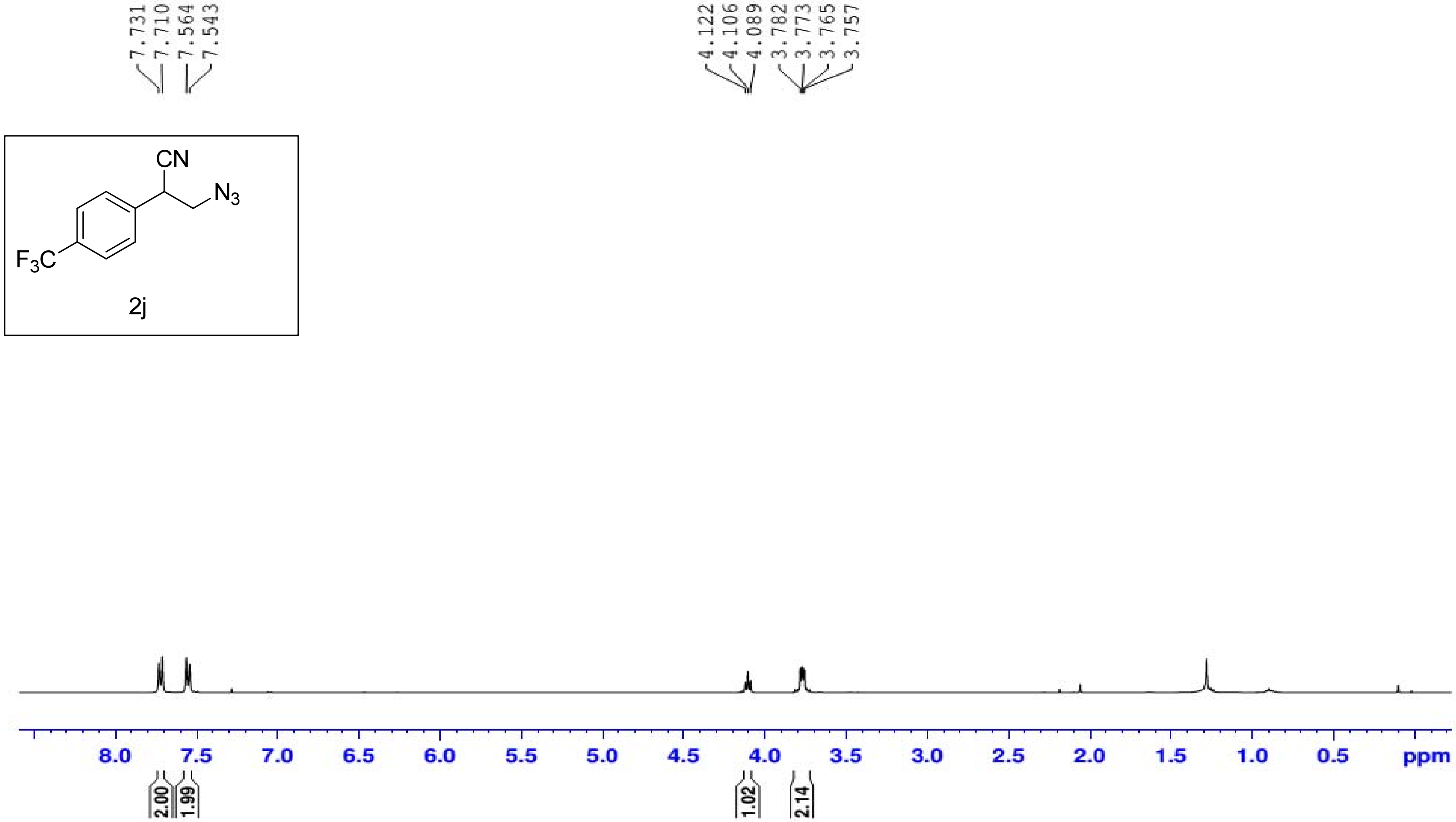
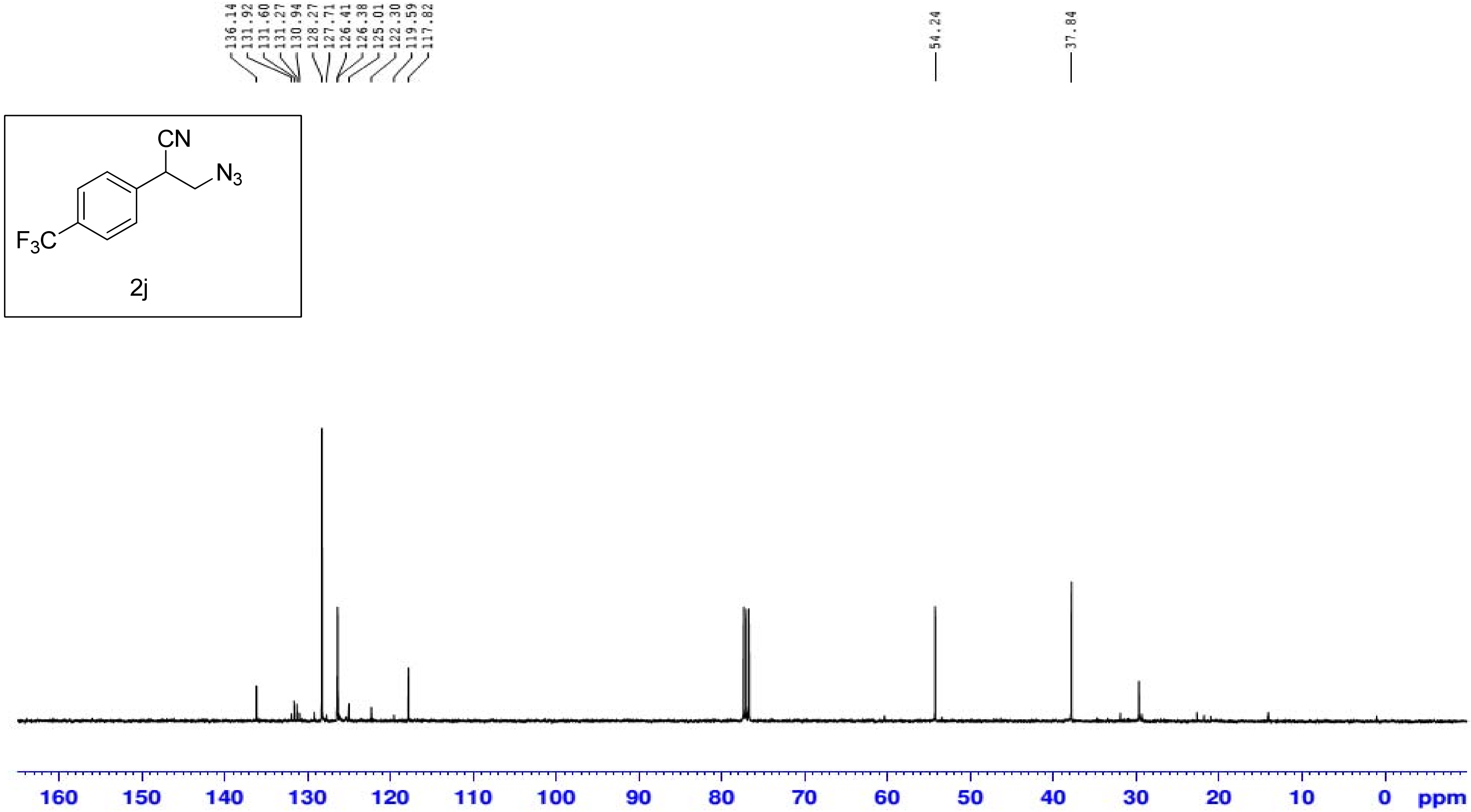
1.05
1.04
0.99
2.08

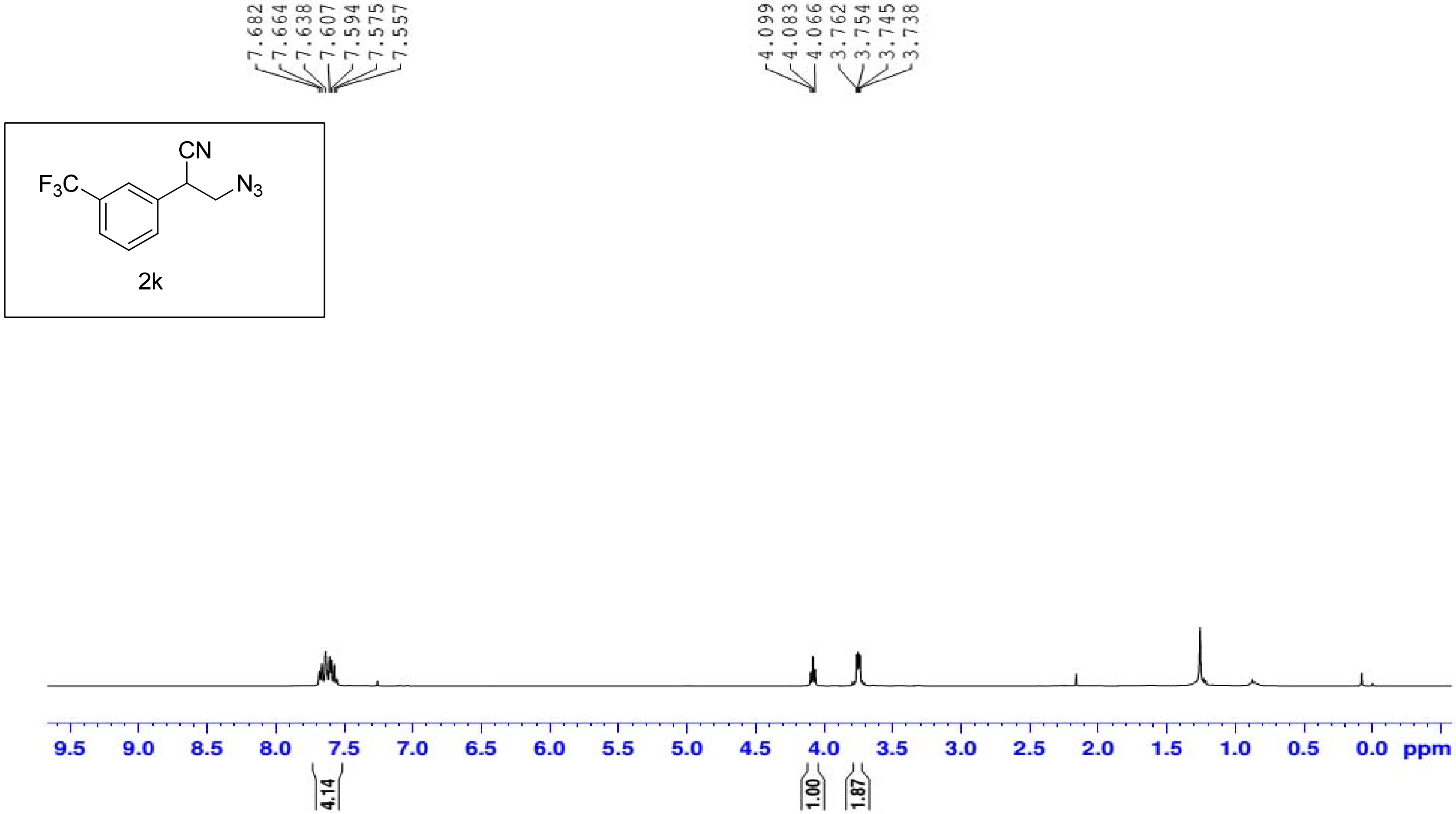

138.74
138.30
135.73
135.65
132.37
131.30
129.49
127.76
127.00
126.79
126.65
125.38
118.41
115.33
115.21
77.32
77.00
76.68
54.44
54.41
37.96
37.72
CN
N3
2i
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


7.731
7.710
7.564
7.543
4.122
4.106
4.089
3.782
3.773
3.765
3.757
CN
N3
F3C
2j
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
1.99
1.02
2.14


CN
N3
F3C

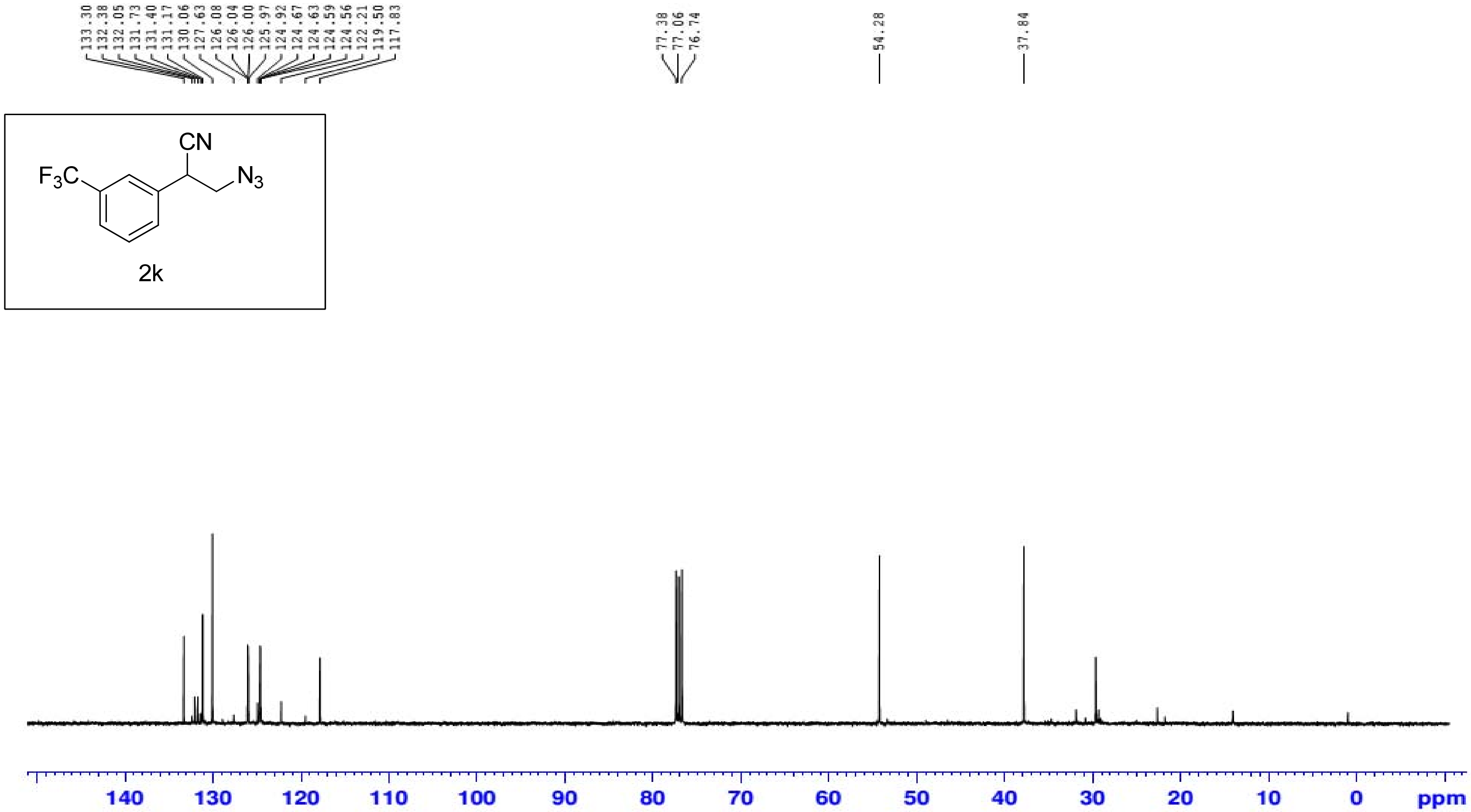
2j

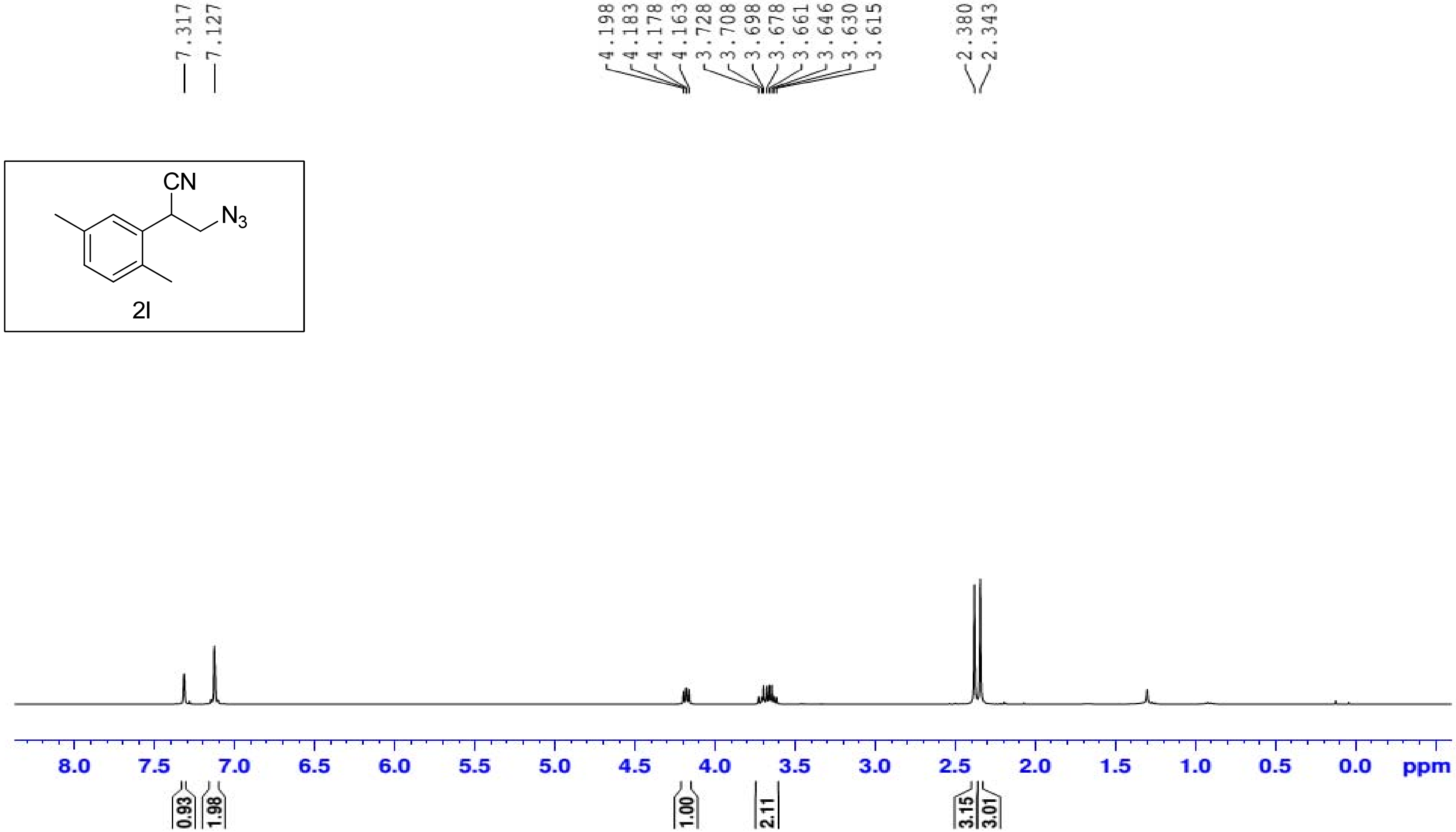
136.14
131.92
131.60
131.27
130.94
128.27
127.71
126.41
126.38
125.01
122.30
119.59
117.82
54.24
37.84
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


CN
F3C
N3

2k

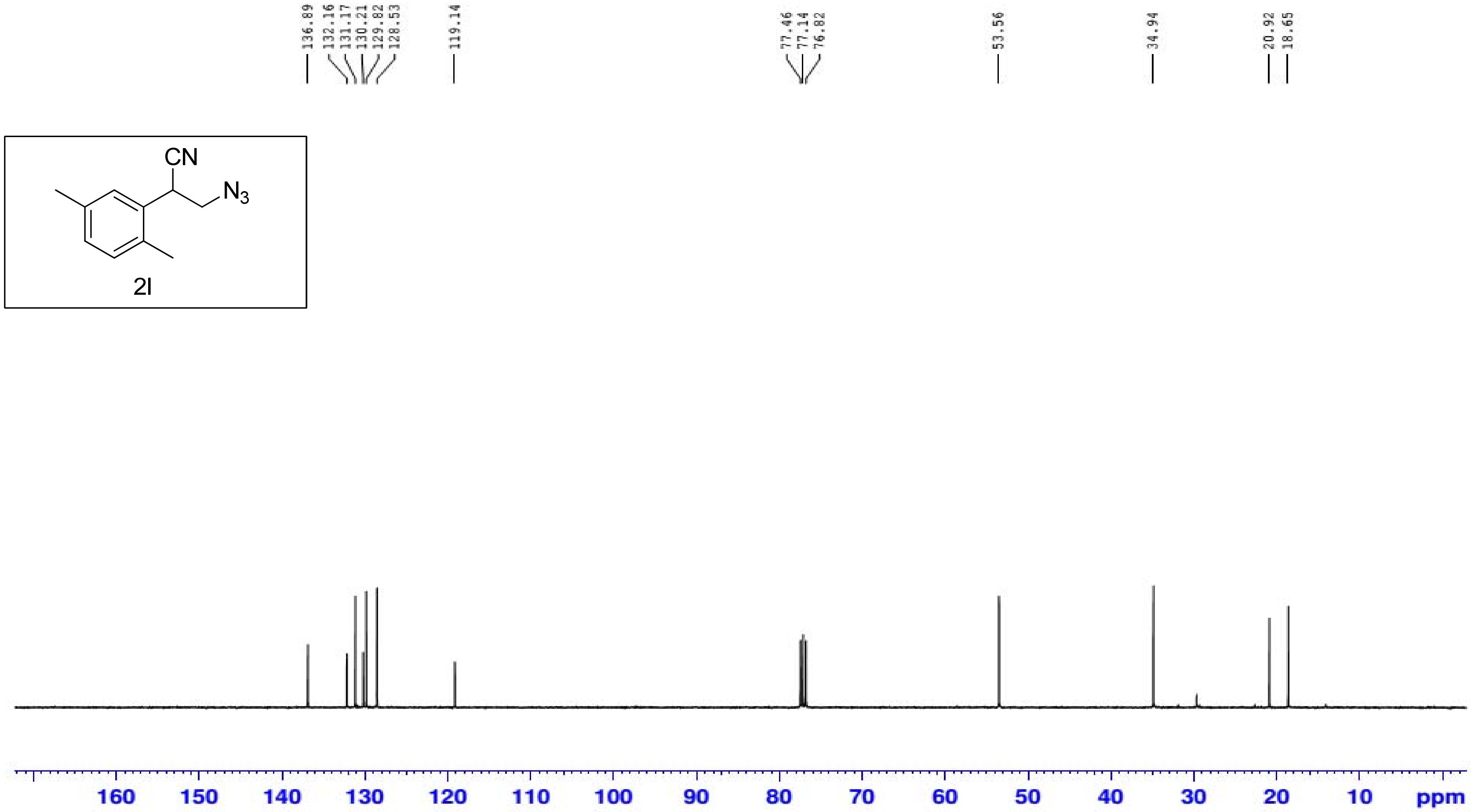
7.682
7.664
7.638
7.607
7.594
7.575
7.557
4.099
4.083
4.066
3.762
3.754
3.745
3.738
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.14
1.00
1.87

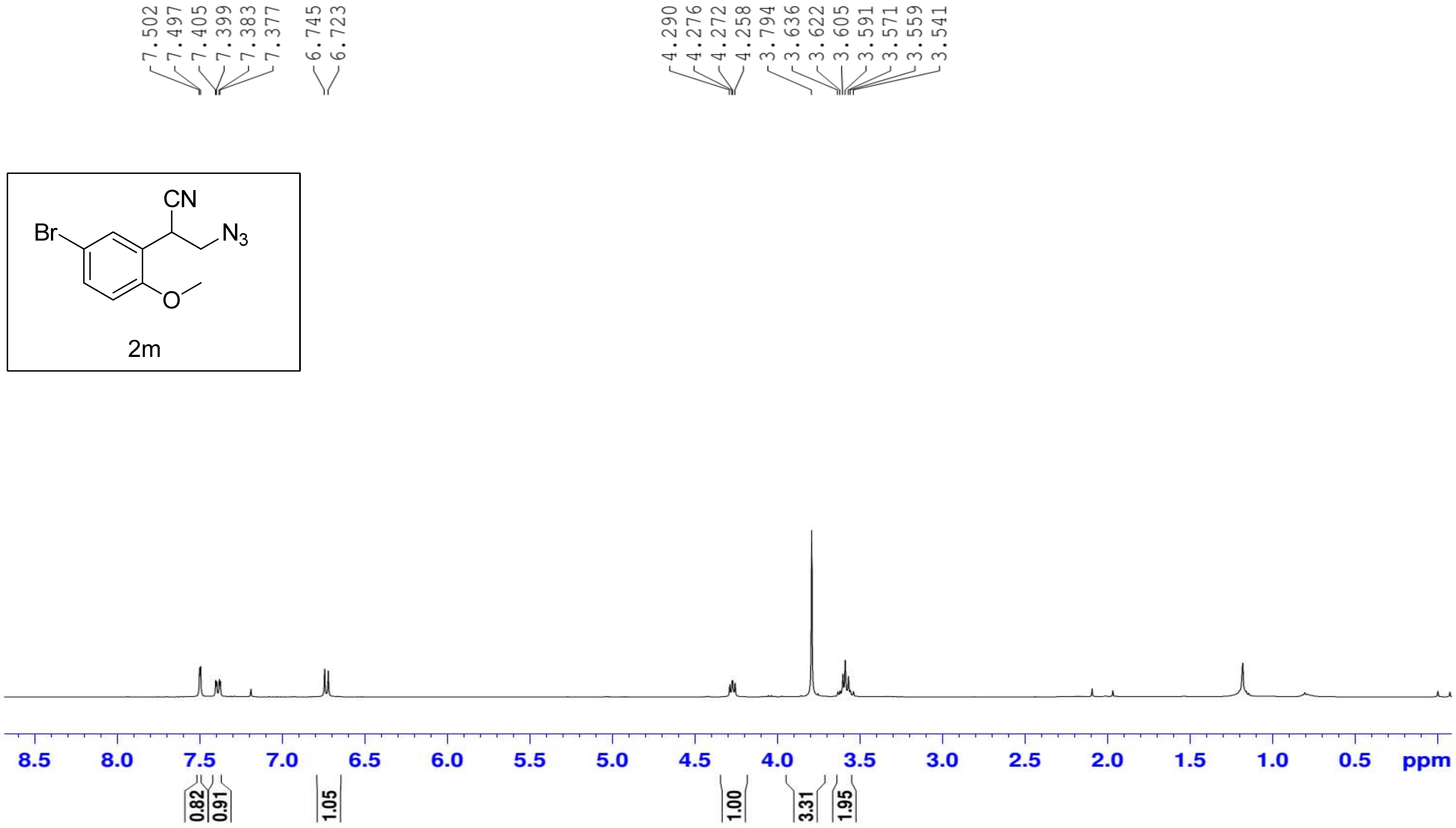

133.30
132.38
132.05
131.73
131.40
131.17
130.06
127.63
126.08
126.04
126.00
125.97
124.92
124.67
124.63
124.59
124.56
122.21
119.50
117.83
77.38
77.06
76.74
54.28
37.84
CN
F3C
N3
2k
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


CN
N3

2l

7.317
7.127
4.198
4.183
4.178
4.163
3.728
3.708
3.698
3.678
3.661
3.646
3.630
3.615
2.380
2.343
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.93
1.98
1.00
2.11
3.15
3.01


136.89
132.16
131.17
130.21
129.82
128.53
119.14
77.46
77.14
76.82
53.56
34.94
20.92
18.65
CN
N3
2l
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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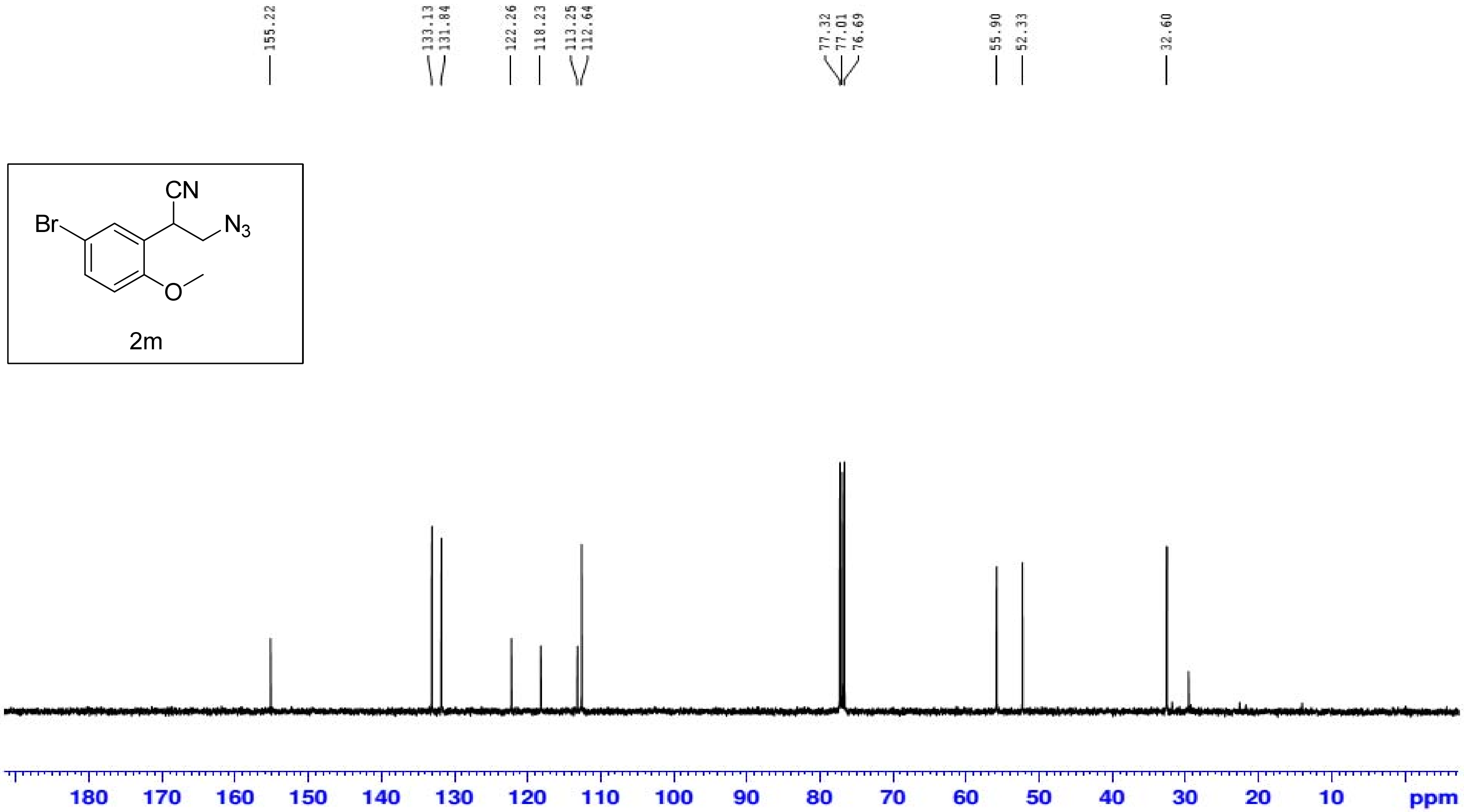
7.405
7.399
7.383
7.377
6.745
6.723
4.290
4.276
4.272
4.258
3.794
3.636
3.622
3.605
3.591
3.571
3.559
3.541
CN
Br
N3
O
2m
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
0.82
0.91
1.05
1.00
3.31
1.95


155.22
133.13
131.84
122.26
118.23
113.25
112.64
77.32
77.01
76.69
55.90
52.33
32.60
CN
Br
N3
O
2m
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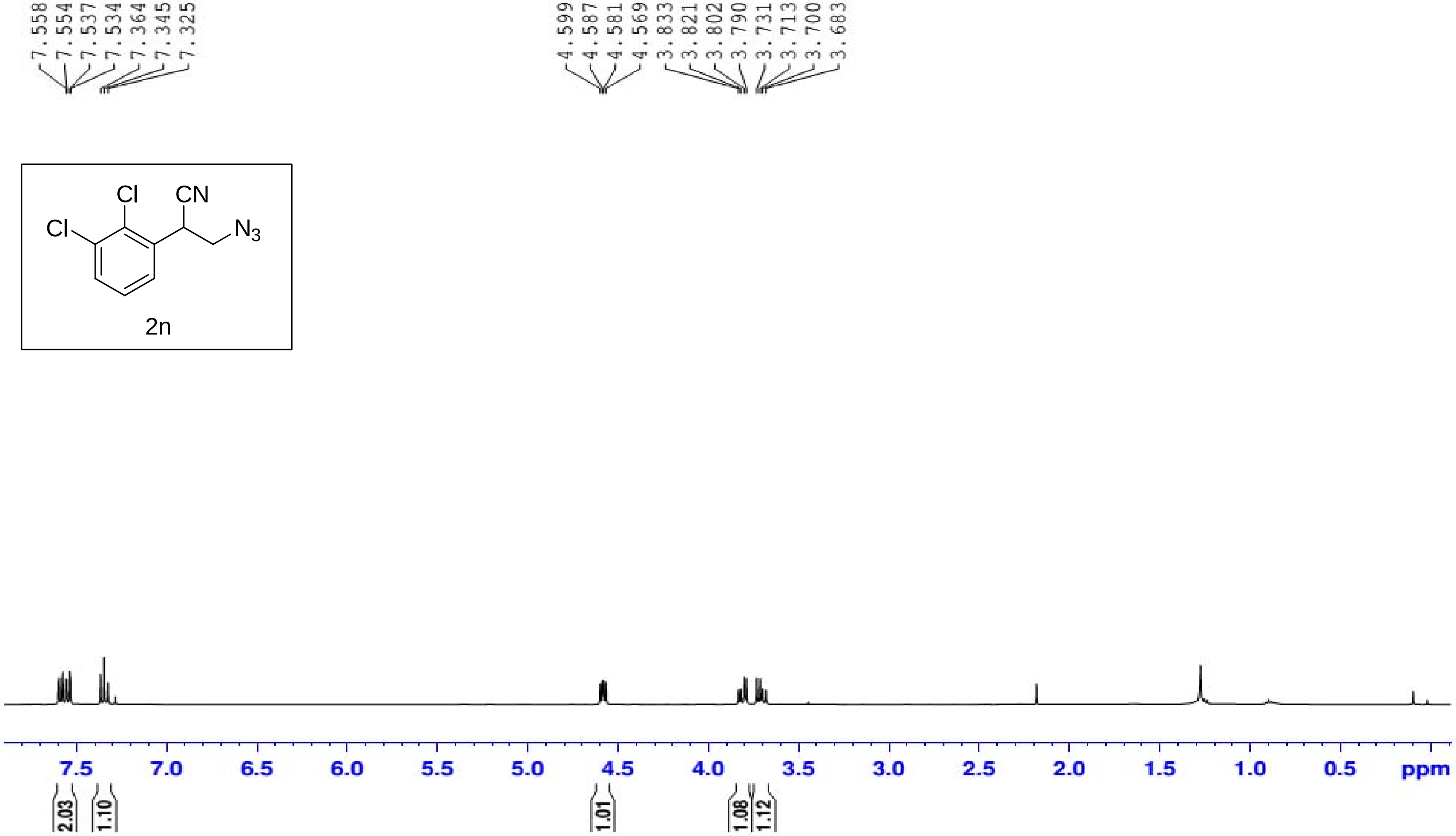
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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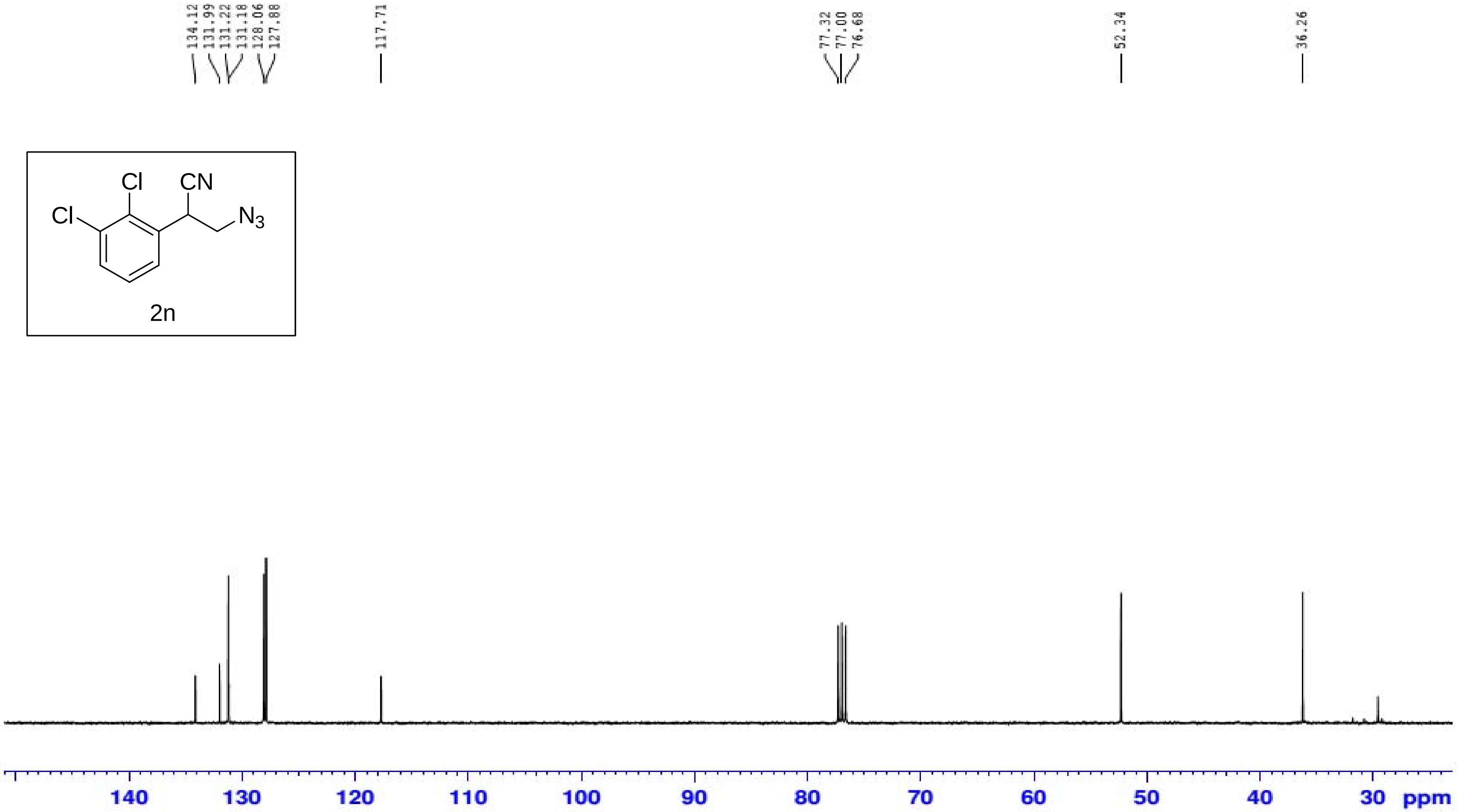
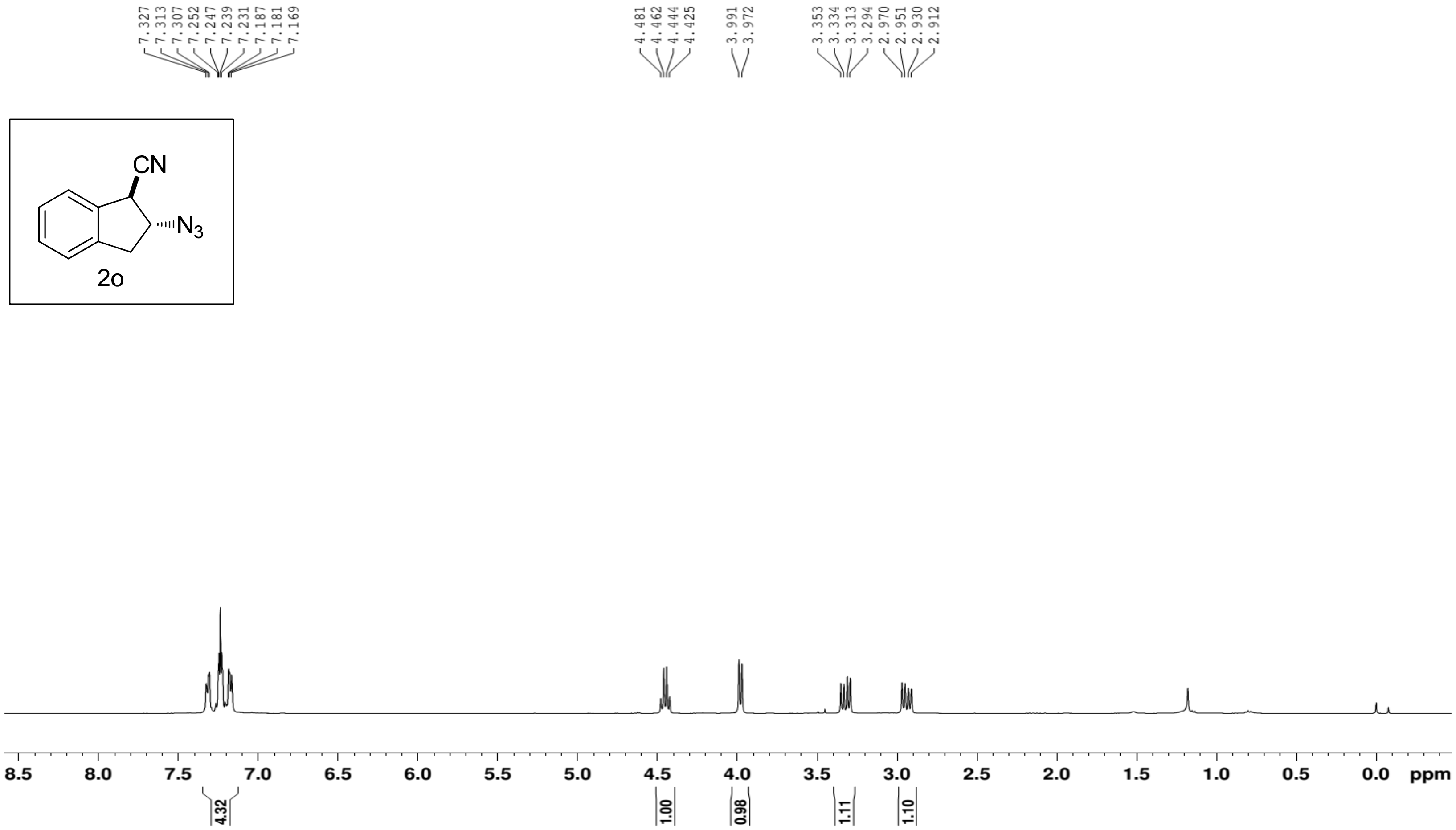
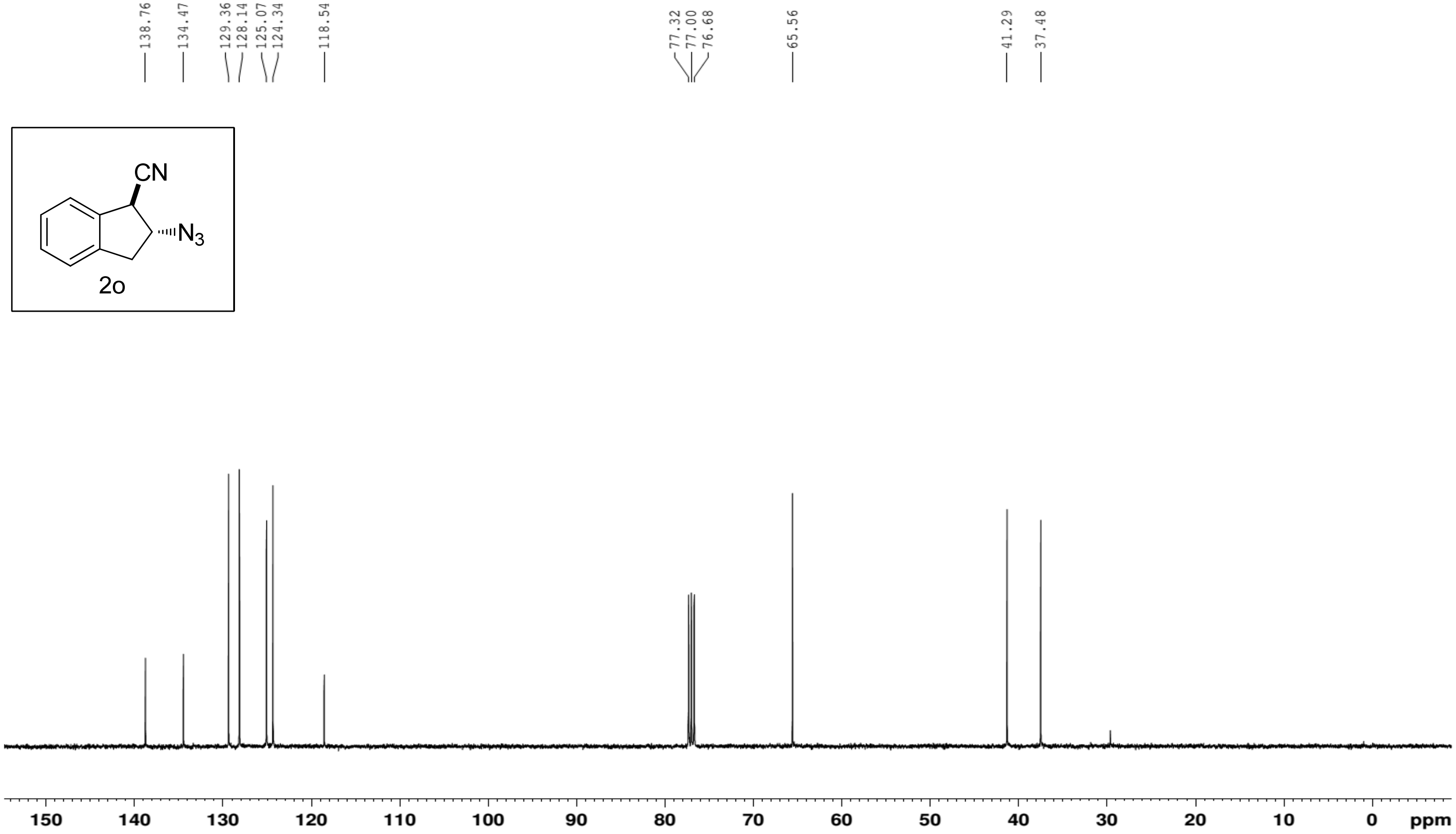
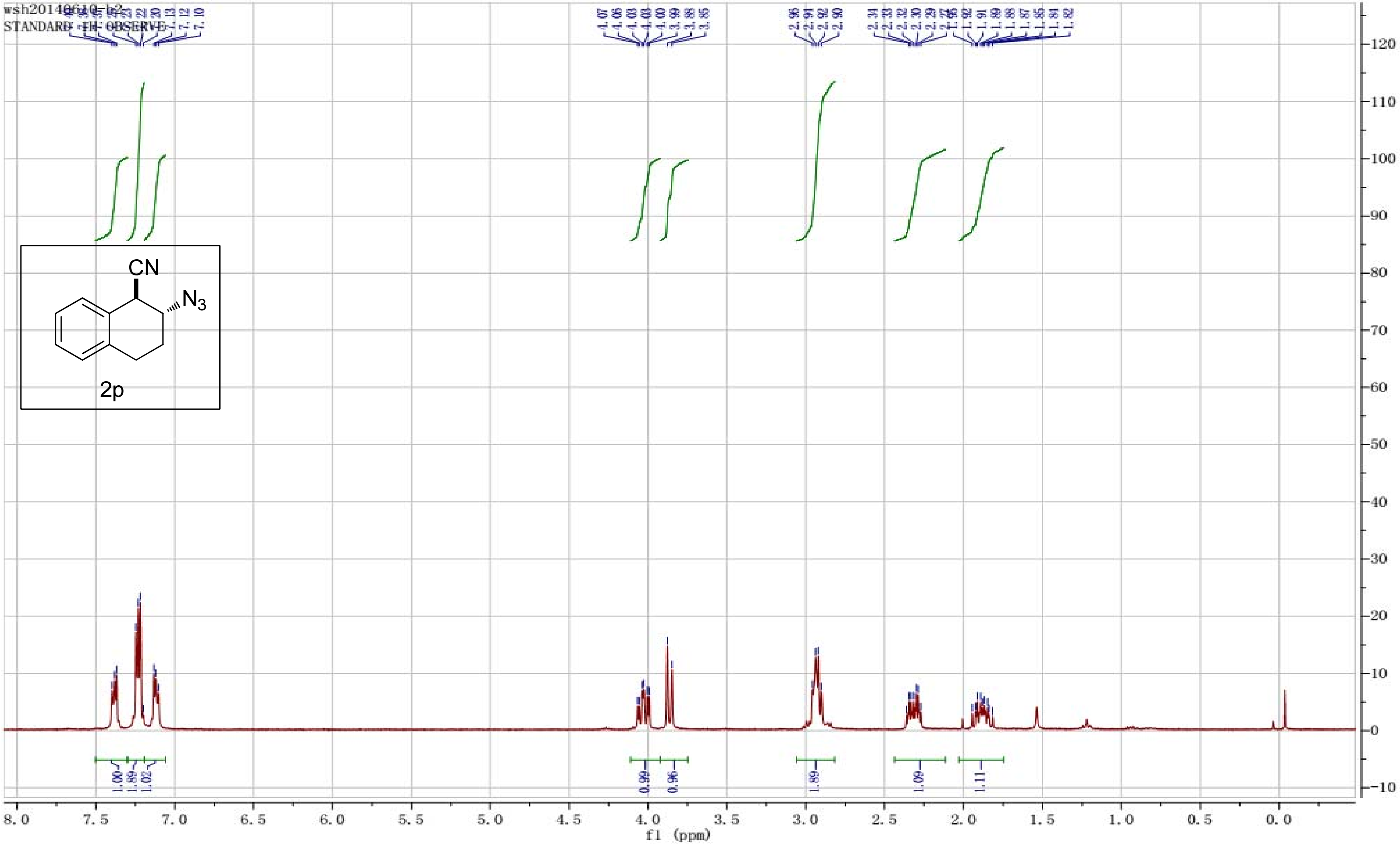
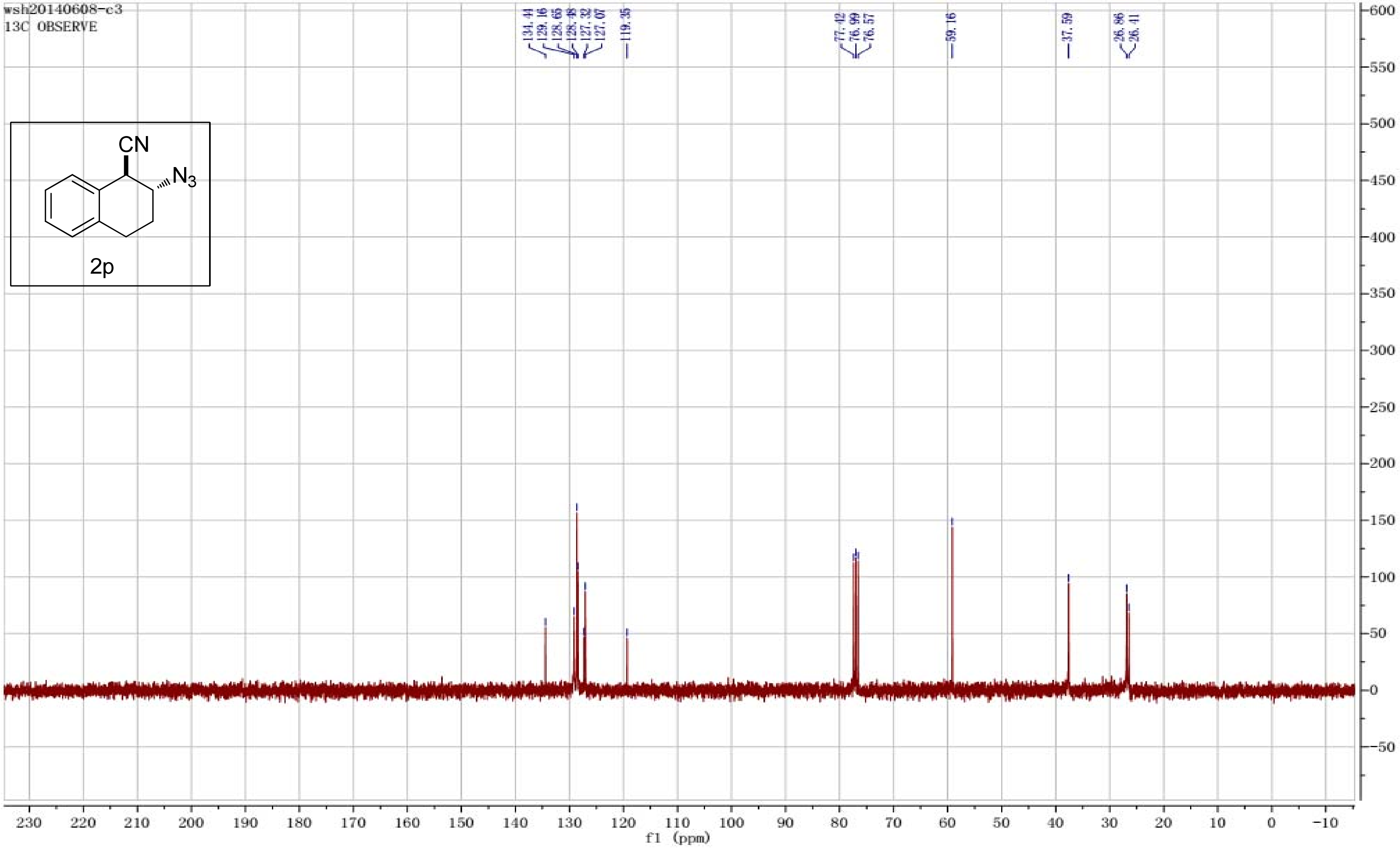
7.554
7.537
7.534
7.364
7.345
7.325
4.599
4.587
4.581
4.569
3.833
3.821
3.802
3.790
3.731
3.713
3.700
3.683
Cl
CN
Cl
N3
2n
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.03
1.10
1.01
1.08
1.12

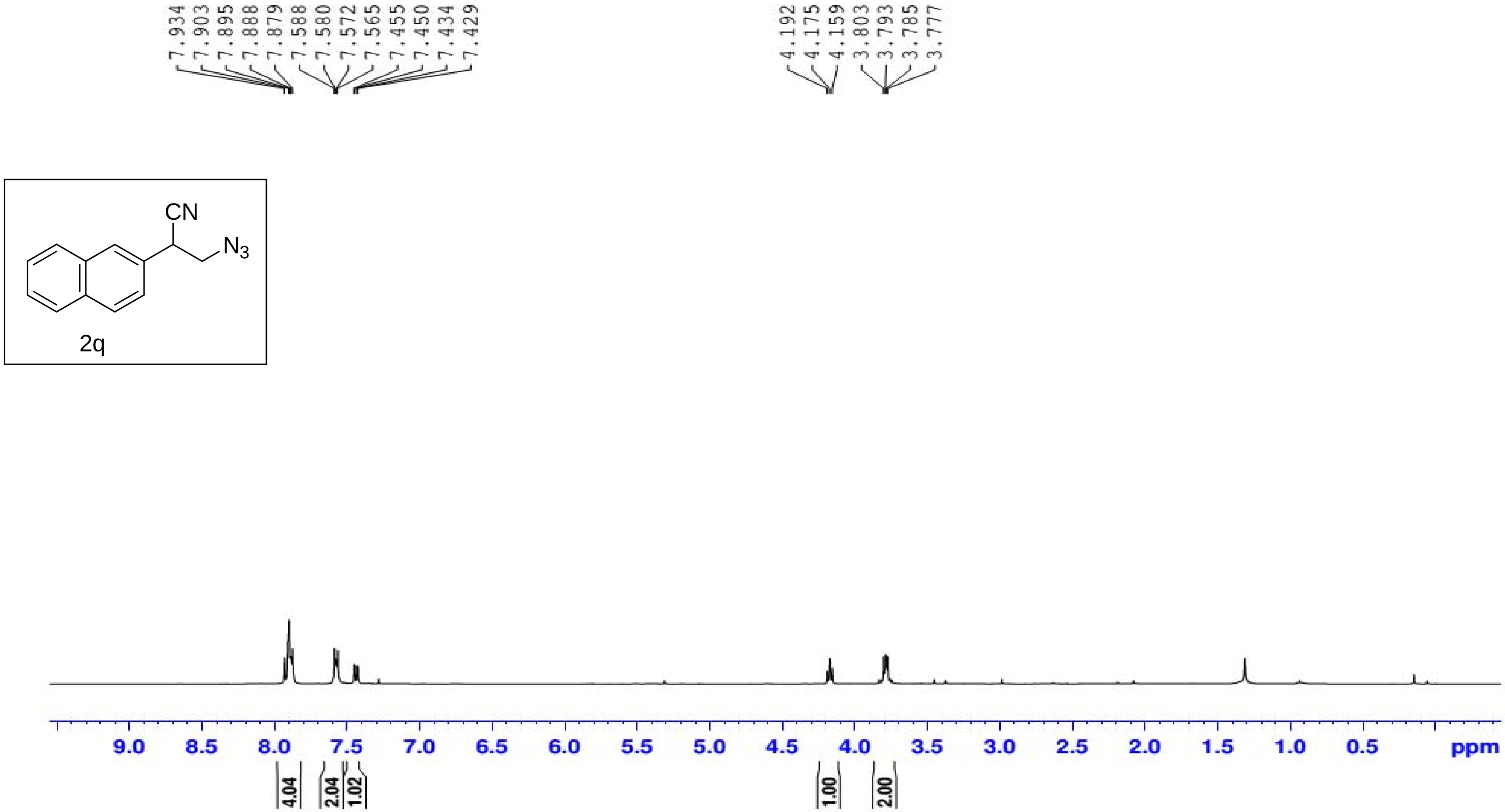

134.12
131.99
131.22
131.18
128.06
127.88
117.71
77.32
77.00
76.68
52.34
36.26
Cl
Cl
CN
N3
2n
140
130
120
110
100
90
80
70
60
50
40
30
ppm


7.327
7.313
7.307
7.252
7.247
7.239
7.231
7.187
7.181
7.169
4.481
4.462
4.444
4.425
3.991
3.972
3.353
3.334
3.313
3.294
2.970
2.951
2.930
2.912
CN
N3
2o
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
4.32
1.00
0.98
1.11
1.10


138.76
134.47
129.36
128.14
125.07
124.34
118.54
77.32
77.00
76.68
65.56
41.29
37.48
CN
N3
2o
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

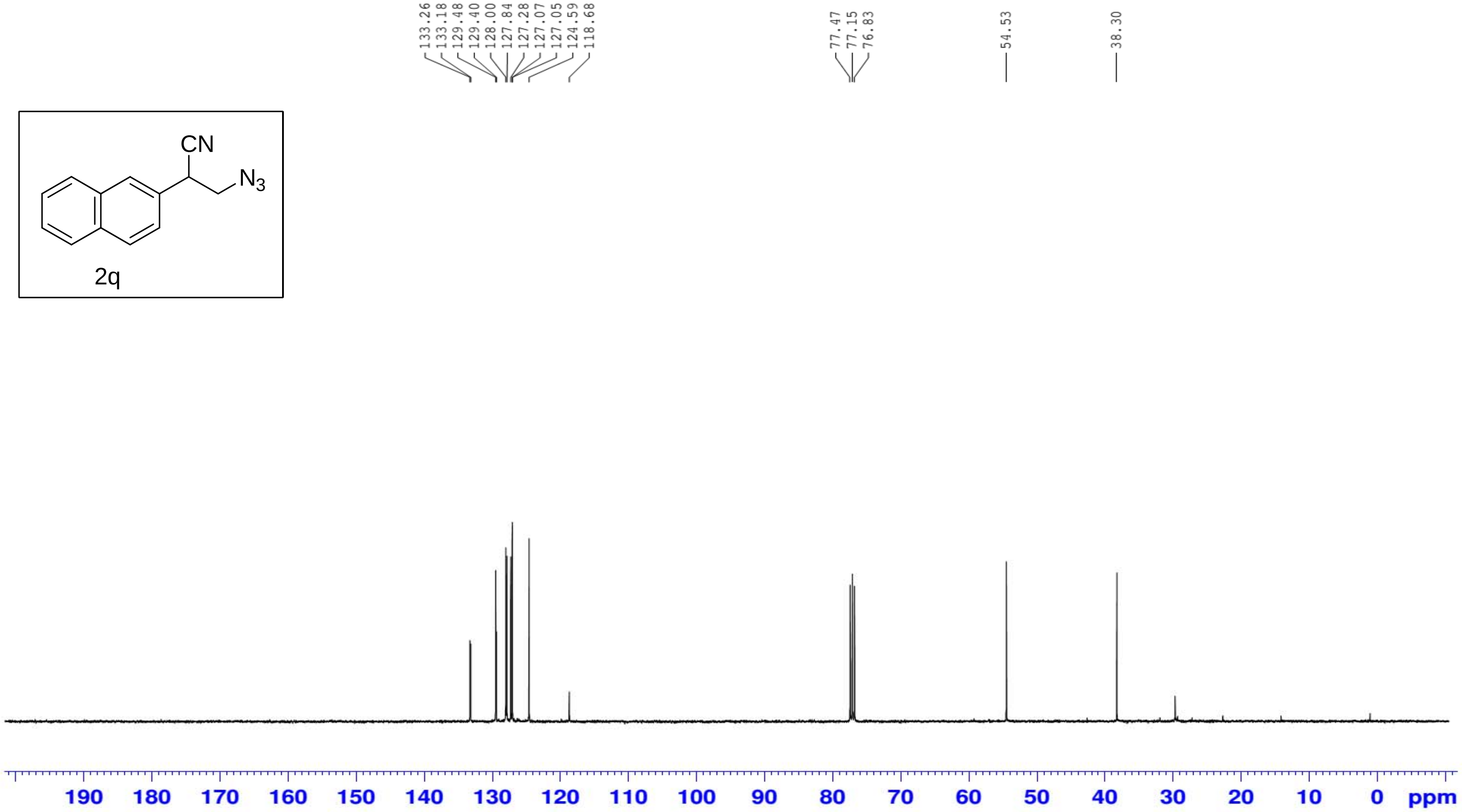

wsh20140610-b2
STANDARD 1H OBSERVE
7.23
7.22
7.20
7.13
7.12
7.10
4.07
4.06
4.03
4.01
4.00
3.99
3.88
3.85
2.96
2.94
2.92
2.90
2.34
2.33
2.32
2.30
2.29
2.27
1.92
1.91
1.89
1.88
1.87
1.85
1.81
CN
N3
2p
1.00
1.89
1.02
0.99
0.96
1.89
1.09
1.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


wsh20140608-c3
13C OBSERVE
134.44
129.16
128.65
128.48
127.32
127.07
119.35
77.42
76.99
76.57
59.16
37.59
26.86
26.41
CN
N3
2p
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.934
7.903
7.895
7.888
7.879
7.588
7.580
7.572
7.565
7.455
7.450
7.434
7.429
4.192
4.175
4.159
3.803
3.793
3.785
3.777
CN
N3
2q
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.04
2.04
1.02
1.00
2.00

CN
N3

2q


133.26
133.18
129.48
129.40
128.00
127.84
127.28
127.07
127.05
124.59
118.68
77.47
77.15
76.83
54.53
38.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm