

Copper-Catalyzed Intermolecular Chloroazidation of α,β -unsaturated amides

Long Chen, Haotian Xing, Huaibin Zhang, Zhong-Xing Jiang* and Zhigang Yang*

E-mail: zxjiang@whu.edu.cn; zgyang@whu.edu.cn

*Hubei Province Engineering and Technology Research Center for Fluorinated
Pharmaceuticals and Wuhan University School of Pharmaceutical Sciences, Wuhan 430071,
P. R. China.*

Index of Content:

I. General.....	S-2
II. Synthesis of substrates	S-2
III. Condition optimization for chloroazidation	S-3
IV. Mechanistic Studies	S-7
V. Isolation of chloroazidation	S-9
VI. Transformation of the product	S-16
VII. References	S-18
VIII. Copies of the NMR spectra.....	S-19

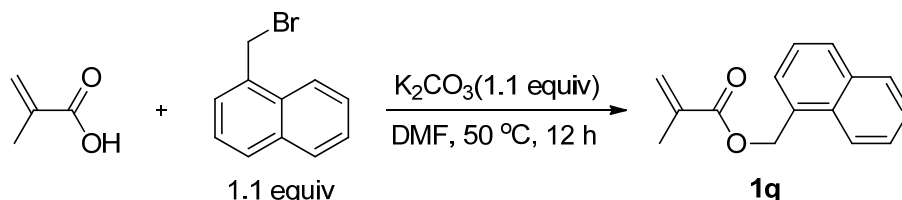
I. General

^1H , ^{19}F and ^{13}C NMR spectra were recorded on a Bruker 400 MHz. ^1H NMR spectra were referenced to tetramethylsilane (d, 0.00 ppm) using CDCl_3 as solvent, ^{13}C NMR spectra were referenced to solvent carbons (77.16 ppm for CDCl_3).

Glassware was dried at 120 °C for at least 3 hours and cooled under an argon atmosphere before used. Unless otherwise indicated, all reagents were obtained from commercial supplier and used without prior purification. CHCl_3 , DCM, DCE, MeOH, DMSO, DMF, and dioxane were dried and freshly distilled prior to use. SOCl_2 , $(\text{COCl})_2$, and PCl_3 was distilled prior to use. Flash chromatography was performed on silica gel (200-300 mesh) with either EtOAc/petroleum ether (PE, 60-90 °C). All reactions were performed under an argon atmosphere. High-resolution mass spectrometry (HRMS) were recorded on a LTQ Orbitrap Elite or Agilent 1100-MSD instrument. GC-MS spectra were recorded on a Asilent 5975-MSD spectrometer. LC-MS spectra were recorded on a Asilent LCMS-1100 spectrometer. Zhdankin's 2a and 2b were prepared according to reported procedures.^[1]

II. Synthesis of substrates

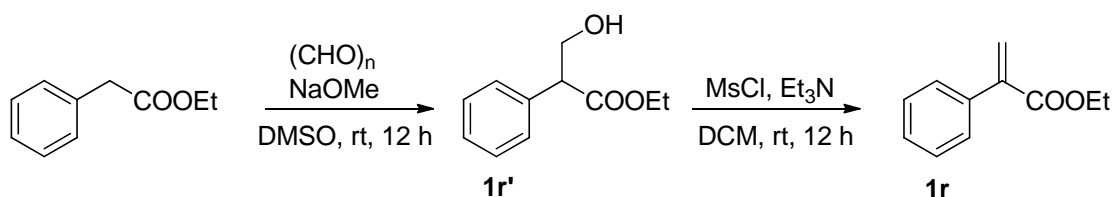
The preparation of unsaturated amide **1a-1p** were followed by reported procedures.^[2-4]



Naphthalen-1-ylmethyl methacrylate (**1q**)

To a solution of methacrylic acid (0.8 g, 9.4 mmol, 1.0 equiv) and K_2CO_3 (1.5 g, 11.0 mmol, 1.1 equiv) in 50 mL anhydrous DMF was slowly added a solution of 1-naphthylmethyl bromide (2.3 g, 11.0 mmol, 1.1 equiv, in 20 mL anhydrous DMF) at room temperature. After addition, the mixture was heated at 50 °C and stirring for 12 hours. After the reaction was completed, 100 mL EtOAc was added to the mixture and the organic layer was washed with brine (3 x 100 mL), dried with anhydrous Na_2SO_4 , filtrated, concentrated under vacuum. The residue was purified by flash chromatography on silica gel with EtOAc/PE=1/5 to give the desired product as yellow oil (2.0 g, 8.8 mmol, 94% yield).

^1H NMR (400 MHz, CDCl_3) δ 8.02 (d, $J = 8.2$ Hz, 1H), 7.87-7.81 (m, 2H), 7.53 (t, $J = 8.5$ Hz, 2H), 7.51-7.40 (m, 2H), 6.12 (s, 1H), 5.63 (s, 2H), 5.53 (s, 1H), 1.94 (s, 3H).



Ethyl 2-phenylacrylate (**1r**)

To a solution of ethyl phenylacetate (5.0 g, 30.5 mmol, 1.0 equiv), paraformaldehyde (2.7 g, 91.4 mmol, 3.0 equiv) and sodium methoxide (0.33 g, 6.09 mmol, 0.2 equiv) in 100 mL DMSO was stirred for 12 hours at room temperature. After the reaction was completed, 200 mL EtOAc was added to the mixture and the organic layer was washed with brine (3 x 100 mL), dried with anhydrous Na_2SO_4 , filtrated, concentrated under vacuum. The residue was purified by flash chromatography on silica gel with EtOAc/PE=1/3 to give the desired product **1r'** as colorless oil (4.8 g, 24.7 mmol, 81% yield).

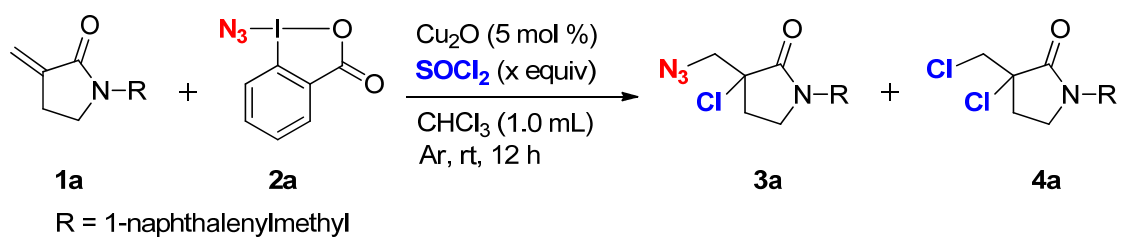
To a solution of alcohol **1r'** (4.8 g, 24.7 mmol, 1.0 equiv) and triethylamine (8.9 mL, 61.8 mmol, 2.5 equiv) in 100 mL anhydrous DCM was slowly added mesyl chloride (1.9 mL, 24.7 mmol, 1.0 equiv) at 0 °C. The mixture was then warm up to room temperature and kept stirring for 12 hours. After the reaction was completed, the solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel with EtOAc/PE=1/10 to give the desired product as colorless oil (4.1 g, 23.5 mmol, 95% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.43-7.41 (m, 2H), 7.36-7.34 (m, 3H), 6.35 (s, 1H), 5.89 (s, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H).

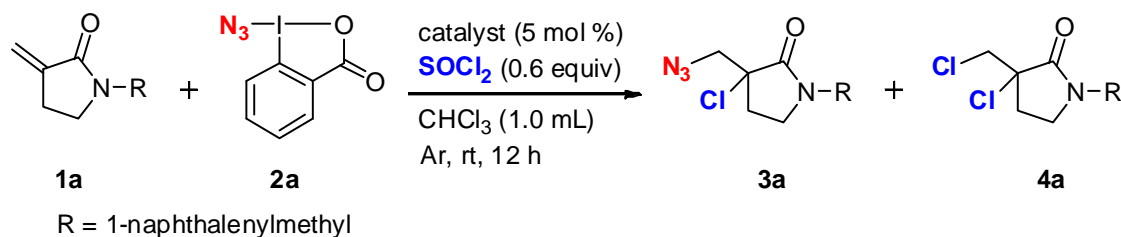
III. Condition optimization for chloroazidation

Typical Procedure for condition optimization:

Under the argon atmosphere, a dry reaction tube was charged with 1-naphthalenylmethyl-3-methylene-2-pyrrolidinon **1a** (0.2 mmol, 1.0 equiv), reagent **2a** (0.3 mmol, 1.5 equiv), catalyst Cu_2O (5 mol %), and EA (0.5 mL). Thionyl chloride (0.12 mmol, 0.6 equiv) was added to the reaction mixture at the room temperature in the end. The mixture kept stirring at the same temperature for 12 hours. Then the mixture quenched with saturated K_2CO_3 (0.5 mL). The yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene (11.2 mg, 0.67 mmol) as an internal standard.

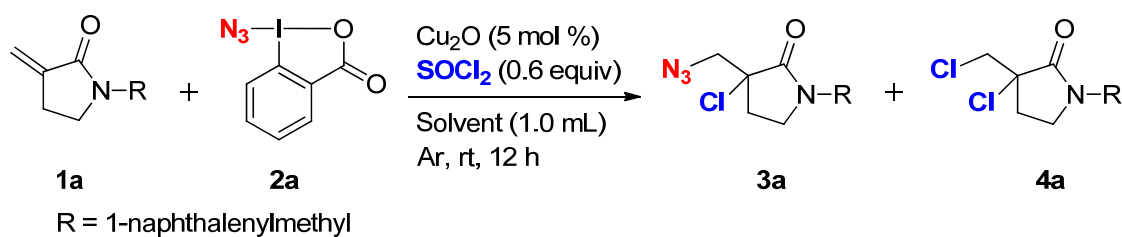
Table S1. Effect of amount of thionyl chloride

Entry	x [equiv]	Yield[%]	3a/4a
1	0.5	42	>20:1
2	0.6	47	>20:1
3	0.75	37	7:2
4	1.0	35	3:2
5	1.5	40	1:1
6	2.0	34	1:2

Table S2. Effect of catalyst

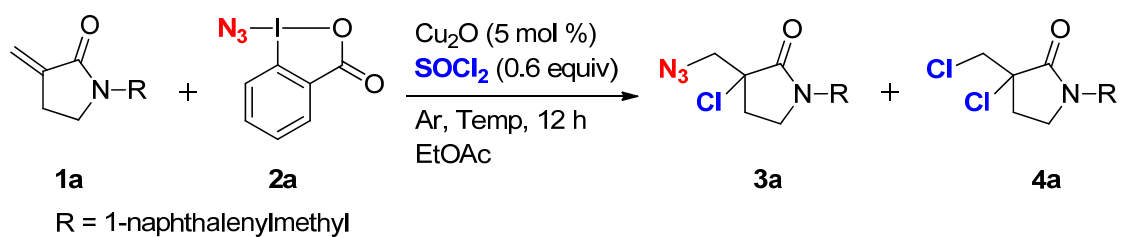
Entry	Catalyst	Yield[%]	3a/4a
1	none	--	--
2	Cu	30	2:1
3	CuCl	45	>20:1
4	CuBr	41	>20:1
5	CuI	36	>20:1
6	Cu ₂ O	46	>20:1
7	CuSCN	10	>20:1
8	CuCl ₂	41	>20:1
9	CuBr ₂	43	>20:1
10	Cu(OAc) ₂ ·H ₂ O	8	>20:1
11	FeCl ₂	22	>20:1
12	FeCl ₃	32	1:2
13	NiCl ₂ ·6H ₂ O	16	1:1
14	PdCl ₂	32	1:1
15	BPO	11	>20:1
16	AIBN	8	>20:1
17	Bu ₄ NCl	13	>20:1

Table S3. Effect of solvent



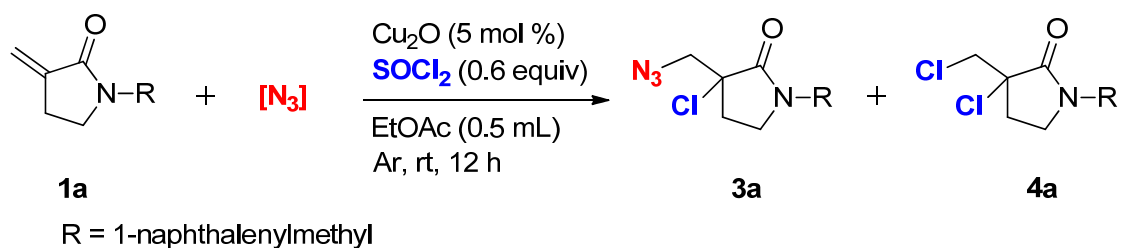
Entry	Solvent	Yield[%]	3a/4a
1	CHCl ₃	45	>20:1
2	DCM	34	>20:1
3	EtOAc	52	>20:1
4	MeOH	40	>20:1
5	THF	45	1:4
6	dioxane	46	1:3
7	DMF	46	1:1
8	CH ₃ CN	52	>20:1
9	Acetone	--	--
10	Et ₂ O	25	>20:1

Table S4. Effect of temperature and concentration



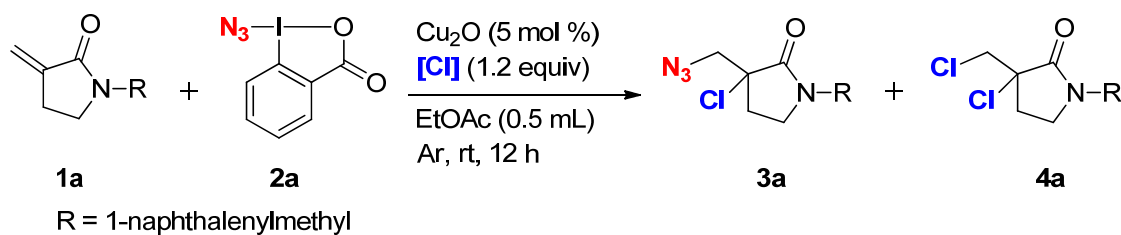
Entry	Temperature[°C]	EtOAc[mL]	Yield[%]	3a/4a
1	10	1.0	20	>20:1
2	rt	1.0	51	>20:1
3	45	1.0	34	>20:1
4	rt	0.3	53	>20:1
5	rt	0.5	73	>20:1
6	rt	1.0	51	>20:1
7	rt	2.0	25	>20:1

Table S5. Effect of azido source



Entry	Azido source	Yield[%]	3a/4a
1	2a	77	>20:1
2	2b	48	>20:1
3	TMSN ₃	--	--
4	TMSN ₃ + PhI(OAc) ₂	62	3:2

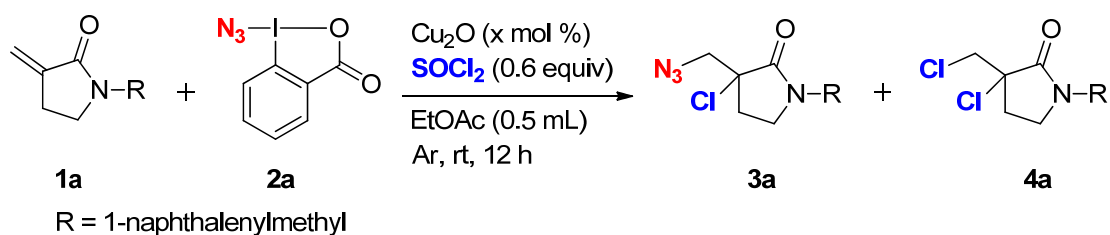
Table S6. Effect of chlorine source



Entry	Chlorine source	Yield[%]	3a/4a
1	SOCl ₂	77	>20:1
2	(COCl) ₂	25	>20:1
3	TMSCl	83	>20:1
4	PCl ₃	90	>20:1
5	AlCl ₃	54	>20:1
6	FeCl ₃	72	>20:1
7	SnCl ₄	53	>20:1
8	CuCl	64	>20:1
9	LiCl	--	--
10	SOCl ₂ with 0.5 eq. Et ₂ NH	88	>20:1
11	Chloramine (T)	75	>20:1
12	NCS	--	--

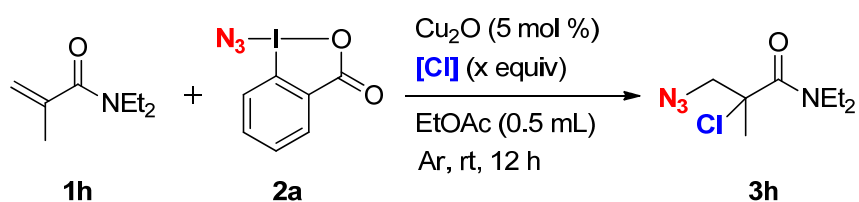
1.2 equiv Cl⁻ was used based on chlorine atomic number

Table S7. Effect of catalyst loading



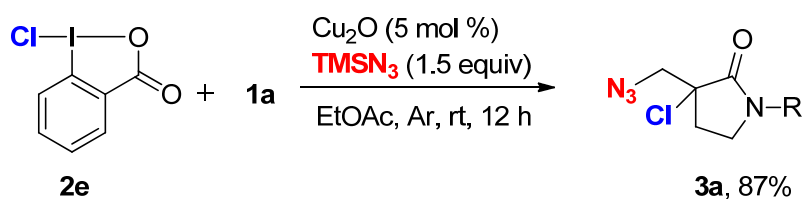
Entry	Catalyst loading[mol %]	Yield[%]	3a/4a
1	0.5	73	>20:1
2	1.0	86	>20:1
3	2.0	86	>20:1
4	5.0	88	>20:1
5	10.0	81	>20:1

Table S8. Optimization of the reaction condition for linear substrate



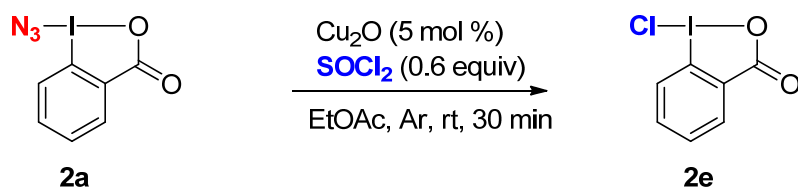
Entry	2a[equiv]	Chlorine source[equiv]	Yield[%]
1	1.5	SOCl ₂ (0.6 equiv)	64
2	1.5	PCl ₃ (0.4 equiv)	72

IV. Mechanistic Studies



R=1-naphthalenylmethyl

The mixture of **2a**, SOCl₂ and Cu₂O.



To a solution of **2a** (86.7 mg, 0.3 mmol) and Cu₂O (1.4 mg, 0.01 mmol) in 0.5 mL EtOAc was added SOCl₂ (8.6 uL, 0.12 mmol) at room temperature. After stirring for 30 min, the mixture was analyzed by ¹H NMR.

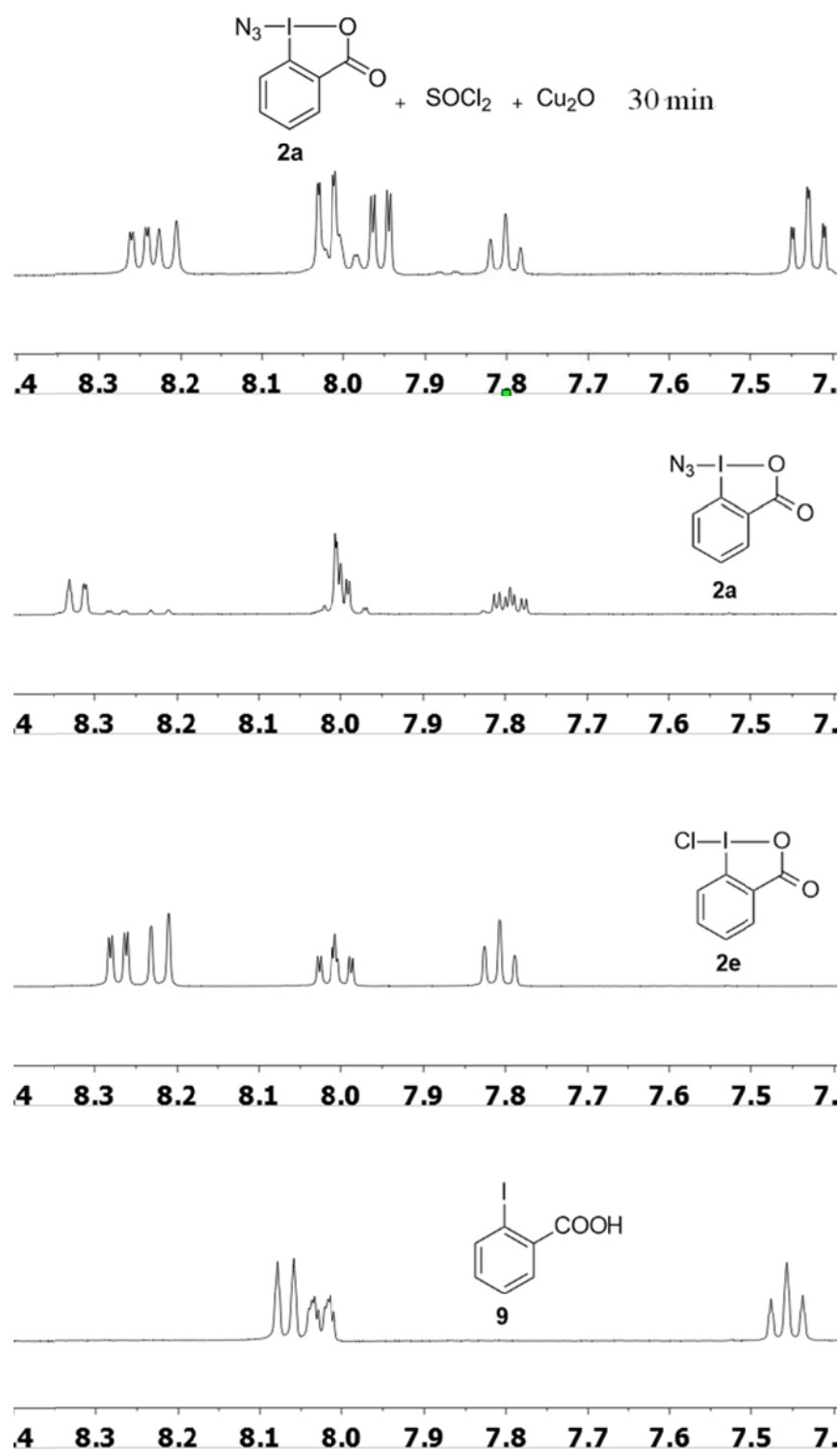
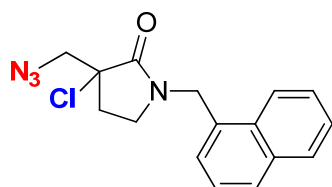


Figure 1. ¹H NMR studies of chloroazidation

V. Isolation of chloroazidation product

General Procedure for Chloroazidation Reaction

In a dry reaction tube, 1-naphthalenylmethyl-3-methylene-2-pyrrolidinon **1a** (0.4 mmol, 1.0 equiv), reagent **2a** (0.6 mmol, 1.5 equiv) and Cu₂O (5 mol %) were mixed in 1 mL anhydrous EA under the argon atmosphere. Thionyl chloride (0.24 mmol, 0.6 equiv) was added to the flask dropwise, followed by addition of diethylamine (0.2 mmol, 0.5 equiv) in the end. After stirring for 12 h at the room temperature, saturated K₂CO₃ (1 mL) was added and followed by extraction with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was directly subjected to silica gel flash chromatography (eluent: petroleum ether/ethyl acetate =10/1) to afford the desired product **3a** in 88% yield.



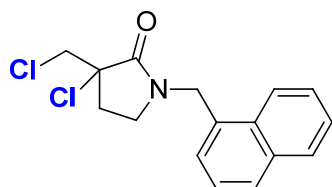
3-(Azidomethyl)-3-chloro-1-(naphthalen-1-ylmethyl)pyrrolidin-2-one (**3a**)

The product (111 mg, 88% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.81 (dd, *J* = 10.9 Hz, 8.4 Hz, 2H), 7.54 (td, *J* = 6.8 Hz, 1.6 Hz, 1H), 7.47 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.43-7.35 (m, 2H), 4.99 (d, *J* = 14.6 Hz, 1H), 4.82 (d, *J* = 14.6 Hz, 1H), 3.91 (d, *J* = 12.5 Hz, 1H), 3.60 (d, *J* = 12.5 Hz, 1H), 3.22-3.15 (m, 1H), 3.03-2.98 (m, 1H), 2.32 (dt, *J* = 14.2 Hz, 8.4 Hz, 1H), 2.14-2.08 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 168.7, 133.5, 131.1, 130.6, 128.9, 128.4, 127.3, 126.6, 126.0, 124.9, 123.3, 67.3, 55.5, 45.3, 42.5, 31.5.

HRMS calcd for C₁₆H₁₆ClN₄O⁺ [M+H]⁺: 315.1007; found:315.1007.



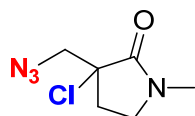
3-Chloro-3-(chloromethyl)-1-(naphthalen-1-ylmethyl)pyrrolidin-2-one (**4a**)

¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.88-7.83 (m, 2H), 7.56-7.49 (m, 2H), 7.45-7.39 (m, 2H), 5.05 (d, *J* = 14.6 Hz, 1H), 4.89 (d, *J* = 14.6 Hz, 1H), 4.14 (d, *J* = 11.2 Hz,

1H), 3.84 (d, $J = 11.2$ Hz, 1H), 3.29-3.23 (m, 1H), 3.13-3.08 (m, 1H), 2.59 (dt, $J = 14.3$ Hz, 8.4 Hz, 1H), 2.26-2.20 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 133.9, 131.5, 130.9, 129.3, 128.7, 127.7, 127.0, 126.4, 125.2, 123.8, 68.2, 47.0, 45.9, 42.8, 31.6.

HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{Cl}_2\text{NO}^+$ $[\text{M}+\text{H}]^+$: 308.0603; found:308.0604.



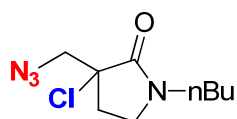
3-(Azidomethyl)-3-chloro-1-methylpyrrolidin-2-one (3b)

The product (56 mg, 74% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 5/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.87 (d, $J = 12.6$ Hz, 1H), 3.67 (d, $J = 12.6$ Hz, 1H), 3.60-3.53 (m, 1H), 3.36-3.31 (m, 1H), 2.95 (s, 3H), 2.53 (dt, $J = 14.2$ Hz, 8.3 Hz, 1H), 2.37-2.31 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 67.2, 56.1, 45.8, 32.2, 30.7.

LC-MS calcd for $\text{C}_6\text{H}_{10}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 189.1; found:189.1.



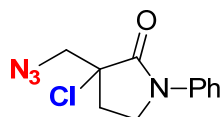
3-(Azidomethyl)-1-butyl-3-chloropyrrolidin-2-one (3c)

The product (81 mg, 88% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.87 (d, $J = 12.6$ Hz, 1H), 3.65 (d, $J = 12.6$ Hz, 1H), 3.59-3.52 (m, 1H), 3.46-3.39 (m, 1H), 3.35-3.25 (m, 2H), 2.50 (dt, $J = 14.1$ Hz, 8.3 Hz, 1H), 2.36-2.30 (m, 1H), 1.59-1.52 (m, 2H), 1.39-1.30 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 67.6, 56.0, 43.6, 43.1, 32.3, 29.1, 19.9, 13.8.

HRMS calcd for $\text{C}_9\text{H}_{16}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 231.1007; found: 231.1009.



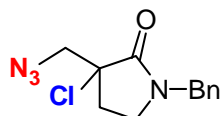
3-(Azidomethyl)-3-chloro-1-phenylpyrrolidin-2-one (3d)

The product (90 mg, 90% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.66 (dd, $J = 8.7$ Hz, 0.9 Hz, 2H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.22 (t, $J = 7.4$ Hz, 1H), 4.09-4.30 (m, 1H), 4.00 (d, $J = 12.7$ Hz, 1H), 3.86-3.81 (m, 1H), 3.73 (d, $J = 12.7$ Hz, 1H), 2.66 (dt, $J = 14.1$ Hz, 8.6 Hz, 1H), 2.84-2.43 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.4, 138.7, 129.2, 125.7, 120.2, 68.3, 55.9, 45.1, 31.7.

HRMS calcd for $\text{C}_{11}\text{H}_{12}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 251.0694; found: 251.0696.



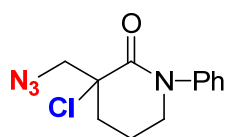
3-(Azidomethyl)-1-benzyl-3-chloropyrrolidin-2-one (3e)

The product (94 mg, 89% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.38-7.28 (m, 3H), 7.25-7.23 (m, 2H), 4.52 (q, $J = 14.7$ Hz, 2H), 3.94 (d, $J = 12.6$ Hz, 1H), 3.69 (d, $J = 12.6$ Hz, 1H), 3.45-3.38 (m, 1H), 3.23-3.18 (m, 1H), 2.49 (dt, $J = 14.2$ Hz, 8.4 Hz, 1H), 2.32-2.27 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.6, 135.4, 129.0, 128.1, 128.0, 67.3, 55.9, 47.4, 43.1, 32.1.

HRMS calcd for $\text{C}_{12}\text{H}_{14}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 265.0851; found: 265.0854.



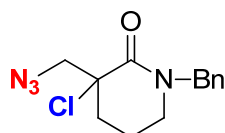
3-(Azidomethyl)-3-chloro-1-phenylpiperidin-2-one (3f)

The product (79 mg, 75% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.40 (t, $J = 7.7$ Hz, 2H), 7.29-7.23 (m, 3H), 4.17 (d, $J = 12.2$ Hz, 1H), 3.81-3.74 (m, 1H), 3.67-3.64 (m, 1H), 3.61 (d, $J = 12.2$ Hz, 1H), 2.47-2.41 (m, 2H), 2.28-2.24 (m, 1H), 1.98 (td, $J = 5.4$ Hz, 1.9 Hz, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.1, 142.5, 129.3, 127.3, 125.9, 66.1, 58.3, 51.8, 33.5, 19.0.

LC-MS calcd $\text{C}_{12}\text{H}_{14}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 265.1; found: 265.1.



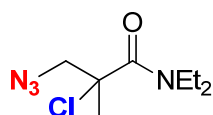
3-(Azidomethyl)-1-benzyl-3-chloropiperidin-2-one (3g)

The product (83 mg, 74% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.36-7.28 (m, 3H), 7.26-7.24 (m, 2H), 4.68 (d, $J = 14.6$ Hz, 1H), 4.54 (d, $J = 14.6$ Hz, 1H), 4.21 (d, $J = 12.1$ Hz, 1H), 3.58 (d, $J = 12.1$ Hz, 1H), 3.31-3.27 (m, 2H), 2.36-2.22 (m, 2H), 2.16-2.12 (m, 1H), 1.85-1.80 (m, 1H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 136.4, 128.8, 128.0, 127.7, 65.7, 58.5, 51.0, 47.4, 33.3, 18.42.

HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 279.1007; found: 279.1011.



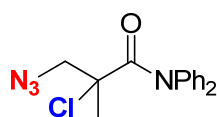
3-Azido-2-chloro-N,N-diethyl-2-methylpropanamide (3h)

The product (63 mg, 72% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 3.74 (q, $J = 12.7$ Hz, 2H), 3.67 (bs, 2H), 3.37 (d, $J = 5.8$ Hz, 2H), 1.80 (s, 3H), 1.25 (bs, 3H), 1.14 (bs, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.0, 67.33, 61.4, 42.6, 41.7, 25.7, 13.9, 12.4.

LC-MS calcd $\text{C}_8\text{H}_{16}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 219.1; found: 219.1.



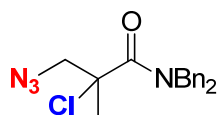
3-Azido-2-chloro-2-methyl-N,N-diphenylpropanamide (3i)

The product (60 mg, 48% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a white solid.

^1H NMR (400 MHz, CDCl_3) δ 7.39-7.33 (m, 8H), 7.29-7.25 (m, 2H), 3.80 (d, $J = 12.2$ Hz, 1H), 3.61 (d, $J = 12.2$ Hz, 1H), 1.58 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.4, 143.2, 129.4, 128.4, 127.8, 67.6, 61.7, 27.3.

LC-MS calcd $\text{C}_{16}\text{H}_{16}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 315.1; found: 315.1.



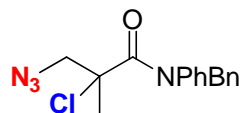
3-Azido-N,N-dibenzyl-2-chloro-2-methylpropanamide (3j)

The product (97 mg, 71% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.39-7.32 (m, 6H), 7.22-7.14 (m, 4H), 4.90 (dd, $J = 33.1$ Hz, 16.3 Hz, 2H), 4.65 (d, $J = 14.9$ Hz, 1H), 4.43 (d, $J = 14.7$ Hz, 1H), 3.86 (s, 2H), 1.85 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 136.5, 135.9, 129.0, 128.8, 127.9, 127.6, 67.3, 61.4, 50.9, 48.9, 25.9.

LC-MS calcd $\text{C}_{18}\text{H}_{20}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 343.1; found: 343.1.



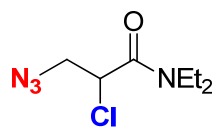
3-Azido-N-benzyl-2-chloro-2-methyl-N-phenylpropanamide (3k)

The product (89 mg, 68% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.35-7.30 (m, 3H), 7.29-7.23 (m, 3H), 7.19-7.17 (m, 2H), 7.12 (bs, 2H), 4.96 (d, $J = 14.2$ Hz, 1H), 4.84 (d, $J = 14.2$ Hz, 1H), 3.79 (d, $J = 12.3$ Hz, 1H), 3.54 (d, $J = 12.2$ Hz, 1H), 1.45 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.2, 141.4, 136.7, 129.9(m), 129.0, 128.6, 127.7, 67.1, 61.5, 57.0, 27.0.

LC-MS calcd $\text{C}_{17}\text{H}_{18}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 329.1; found: 329.1.



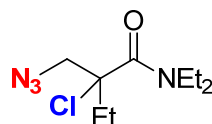
3-Azido-2-chloro-N,N-diethylpropanamide (3l)

The product (52 mg, 63% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 10/1) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 4.38 (dd, $J = 7.8$ Hz, 6.1 Hz, 1H), 3.98 (dd, $J = 12.4$ Hz, 7.8 Hz, 1H), 3.58 (dd, $J = 12.5$ Hz, 6.1 Hz, 1H), 3.54-3.47 (m, 2H), 3.38-3.28 (m, 2H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.16 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.9, 53.5, 50.6, 42.3, 41.1, 14.8, 12.7.

LC-MS calcd $\text{C}_7\text{H}_{14}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 205.1; found: 205.1.



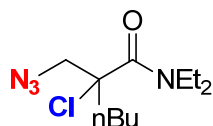
2-(Azidomethyl)-2-chloro-N,N-diethylbutanamide (3m)

The product (65 mg, 70% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 3.80 (dd, $J = 27.0$ Hz, 13.1 Hz, 2H), 3.73 (br, 1H), 3.62 (br, 1H), 3.46 (br, 1H), 3.29 (br, 1H), 2.26-2.17 (m, 1H), 2.15-2.05 (m, 1H), 1.24 (bs, 3H), 1.15 (bs, 3H), 0.95 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.3, 72.1, 58.1, 42.6, 41.8, 30.7, 13.9, 12.4, 9.4.

LC-MS calcd $\text{C}_9\text{H}_{18}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 233.1; found: 233.1.



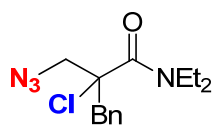
2-(Azidomethyl)-2-chloro-N,N-diethylhexanamide (3n)

The product (77 mg, 74% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 30/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 3.80 (dd, $J = 31.6$ Hz, 13.1 Hz, 2H), 3.76 (br, 1H), 3.62 (br, 1H), 3.45 (br, 1H), 3.29 (br, 1H), 2.25-2.10 (m, 1H), 2.19-2.12 (m, 1H), 2.07-2.00 (m, 1H), 1.40-1.31 (m, 3H), 1.24 (bs, 3H), 1.14 (bs, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.4, 71.6, 58.7, 51.0, 42.5, 41.7, 37.4, 27.0, 22.8, 13.9, 12.4.

HRMS calcd for $\text{C}_{11}\text{H}_{22}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 261.1477; found: 261.1471.



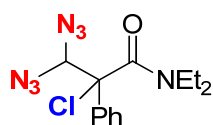
3-Azido-2-benzyl-2-chloro-N,N-diethylpropanamide (3o)

The product (90 mg, 76% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.31-7.28 (m, 3H), 7.20-7.18 (m, 2H), 3.81 (d, $J = 12.9$ Hz, 1H), 7.79 (br, 1H), 3.60 (d, $J = 12.9$ Hz, 1H), 3.51 (br, 1H), 3.38 (q, $J = 14.0$ Hz, 2H), 3.32 (br, 1H), 3.21 (br, 1H), 1.25 (bs, 3H), 1.15 (bs, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.0, 134.2, 130.6, 130.5, 128.6, 128.5, 127.9, 59.1, 43.4, 42.6, 42.1, 13.8, 12.3.

LC-MS calcd $\text{C}_{14}\text{H}_{20}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 295.1; found: 295.1.



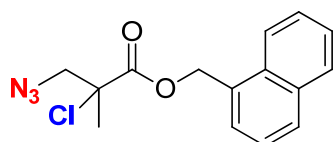
3,3-Diazido-N-benzyl-2-chloro-N,2-diphenylpropanamide (3p)

The product (31 mg, 32% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a colorless oil.

^1H NMR (400 MHz, CDCl_3) δ 7.52-7.50 (m, 2H), 7.44-7.41 (m, 3H), 5.55 (s, 1H), 3.54-3.45 (m, 1H), 3.33-3.25 (m, 1H), 3.17-3.08 (m, 1H), 2.91-2.82 (m, 1H), 1.16 (t, $J = 7.1$ Hz, 3H), 0.84 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 167.2, 134.1, 129.4, 128.7, 127.0, 82.3, 74.9, 42.4, 40.8, 12.5, 12.0.

HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{ClN}_7\text{NaO}^+$ $[\text{M}+\text{Na}]^+$: 344.0997; found: 344.0945.



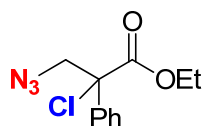
Naphthalen-1-ylmethyl 3-azido-2-chloro-2-methylpropanoate (3q)

The product (85 mg, 70% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 40/1) as a yellow oil.

^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, $J = 8.4$ Hz, 1H), 7.88 (t, $J = 8.4$ Hz, 2H), 7.59-7.51 (m, 3H), 7.46 (dd, $J = 8.1$ Hz, 7.1 Hz, 1H), 5.68 (d, $J = 2.8$ Hz, 2H), 3.78 (d, $J = 12.5$ Hz, 1H), 3.62 (d, $J = 12.5$ Hz, 1H), 1.75 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 169.3, 133.9, 131.7, 130.4, 129.9, 128.9, 127.9, 126.9, 126.2, 125.4, 123.5, 66.9, 66.3, 59.4, 25.3.

GC-MS calcd for $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_2$ $[\text{M}]$: 303.0775; found: 303.0775.



Ethyl 3-azido-2-chloro-2-phenylpropanoate (3r)

The product (74 mg, 73% yield) was purified with silica gel chromatography (petroleum ether/ethyl acetate = 20/1) as a colorless oil.

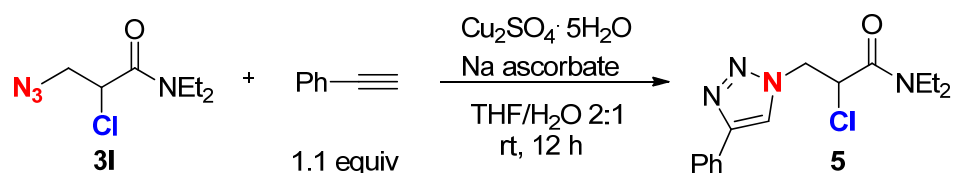
^1H NMR (400 MHz, CDCl_3) δ 7.49 (dd, $J = 8.0, 1.6$ Hz, 2H), 7.43-7.36 (m, 3H), 4.31 (q, $J = 7.2$ Hz, 2H), 4.09 (d, $J = 12.9$ Hz, 1H), 3.95 (d, $J = 12.9$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 136.5, 129.2, 128.8, 128.7, 126.6, 126.4, 73.3, 63.2, 60.37, 14.0.

LC-MS calcd for $\text{C}_{11}\text{H}_{13}\text{ClN}_3\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 254.1, found: 254.1; $\text{C}_{11}\text{H}_{13}\text{ClNO}_2^+$

$[\text{M}-\text{N}_2+\text{H}]^+$: 226.1 found: 226.1.

VI. Transformation of the product



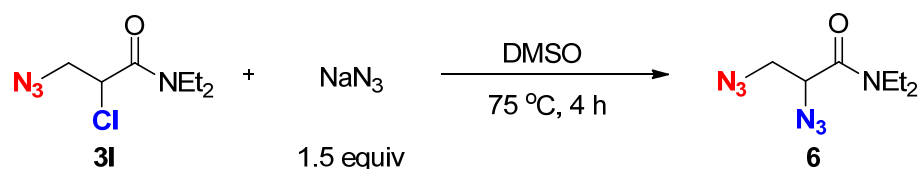
2-Chloro-N,N-diethyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanamide (**5**)

To a solution of azide **3I** (0.4 mmol, 82 mg) and phenylacetylene (0.44 mmol, 48 μL) in 1 mL of THF were added $\text{Cu}_2\text{SO}_4 \cdot 5\text{H}_2\text{O}$ (0.2 mmol, 0.2 mL, 1 mol/L) and sodium ascorbate (0.4 mmol, 0.4 mL, 1 mol/L) at room temperature, and the mixture was stirred for 12 hours until the disappearance of azide **3I** (monitored by TLC). The reaction mixture was filtrated through Celite, extracted with ethyl acetate, dried over anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography (petroleum ether/AcOEt 1:1) to afford the product **5** (119 mg) as a white solid in 97% yield.

^1H NMR (400 MHz, CDCl_3) δ 7.91 (s, 1H), 7.83-7.71 (m, 2H), 7.43 (t, $J = 7.5$ Hz, 2H), 7.36-7.32 (m, 1H), 5.07 (dd, $J = 13.4$ Hz, 7.8 Hz, 1H), 4.95 (dd, $J = 7.8$ Hz, 5.9 Hz, 1H), 4.80 (dd, $J = 13.4$ Hz, 5.9 Hz, 1H), 3.46-3.37 (m, 2H), 3.34-3.22 (m, 2H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.08 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 165.5, 130.3, 129.0, 128.4, 125.8, 121.9, 52.6, 50.6, 42.5, 41.2, 14.6, 12.6.

LC-MS calcd for $\text{C}_{15}\text{H}_{20}\text{ClN}_4\text{O}^+$ $[\text{M}+\text{H}]^+$: 307.1; found: 307.1.



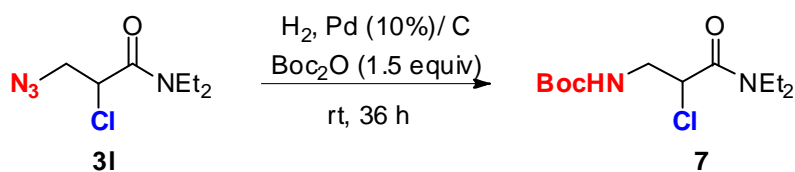
2,3-Diazido-N,N-diethylpropanamide (**6**)

To a solution of **3I** (0.4 mmol, 82 mg) and sodium azide (0.6 mmol, 39 mg) in 1 mL of dimethyl sulfoxide were heated to 75 °C, and the mixture stirred for 4 hours until **3I** was completely transformed. The mixture was cooled and then diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo to afford the product **6** (80 mg) as a colorless oil in 95% yield.

^1H NMR (400 MHz, CDCl_3) δ 3.90 (t, $J = 6.8$ Hz, 1H), 3.79 (dd, $J = 12.3$ Hz, 6.8 Hz, 1H), 3.65 (dd, $J = 12.3$ Hz, 6.9 Hz, 1H), 3.49-3.32 (m, 4H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.17 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 166.3, 57.3, 51.5, 42.3, 41.1, 14.9, 13.1.

HRMS calcd for $\text{C}_7\text{H}_{14}\text{N}_7\text{O}^+$ $[\text{M}+\text{H}]^+$: 212.1254; found: 212.1264.



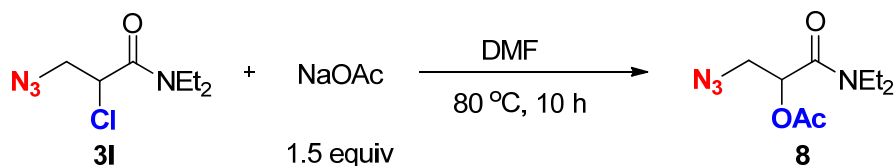
Tert-butyl (2-chloro-3-(diethylamino)-3-oxopropyl)carbamate (7)

In a dry reaction tube, **31** (0.4 mmol, 82 mg), Boc₂O (0.6 mmol, 131 mg) and palladium 10% on carbon (80 mg) was mixed in 2 mL of dry THF, and the mixture stirred at room temperature for 36 h under a H₂ atmosphere. The mixture was filtered through Celite that was thoroughly washed with EtOAc, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/AcOEt 1:1) to afford the product **8** (71 mg) as a colorless oil in 64% yield.

¹H NMR (400 MHz, CDCl₃) δ 5.19 (s, 1H), 4.56 (t, *J* = 6.8 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.56-3.46 (m, 2H), 3.34-3.23 (m, 2H), 1.43 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 167.1, 156.0, 79.8, 50.4, 43.9, 42.2, 40.9, 28.4, 28.4, 14.7, 12.7.

HRMS calcd for C₁₂H₂₃ClN₂NaO₃⁺ [M+Na]⁺: 301.1289; found: 301.1298.



3-Azido-1-(diethylamino)-1-oxopropan-2-yl acetate (8)

To a solution of **31** (0.4 mmol, 82 mg) and sodium acetate (0.6 mmol, 49 mg) in 1 mL of DMF were heated to 80 °C, and the mixture stirred for 10 hours until **31** was completely transformed (monitored by TLC). Then the mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography (petroleum ether/AcOEt 3:1) to afford the product **8** (79 mg) as a colorless oil in 86% yield.

¹H NMR (400 MHz, CDCl₃) δ 5.40 (dd, *J* = 8.1, 4.6 Hz, 1H), 3.69 (dd, *J* = 13.0, 8.1 Hz, 1H), 3.50-3.42 (m, 3H), 3.40-3.28 (m, 2H), 2.17 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.3, 166.3, 69.5, 51.4, 42.0, 41.0, 20.8, 14.4, 12.9.

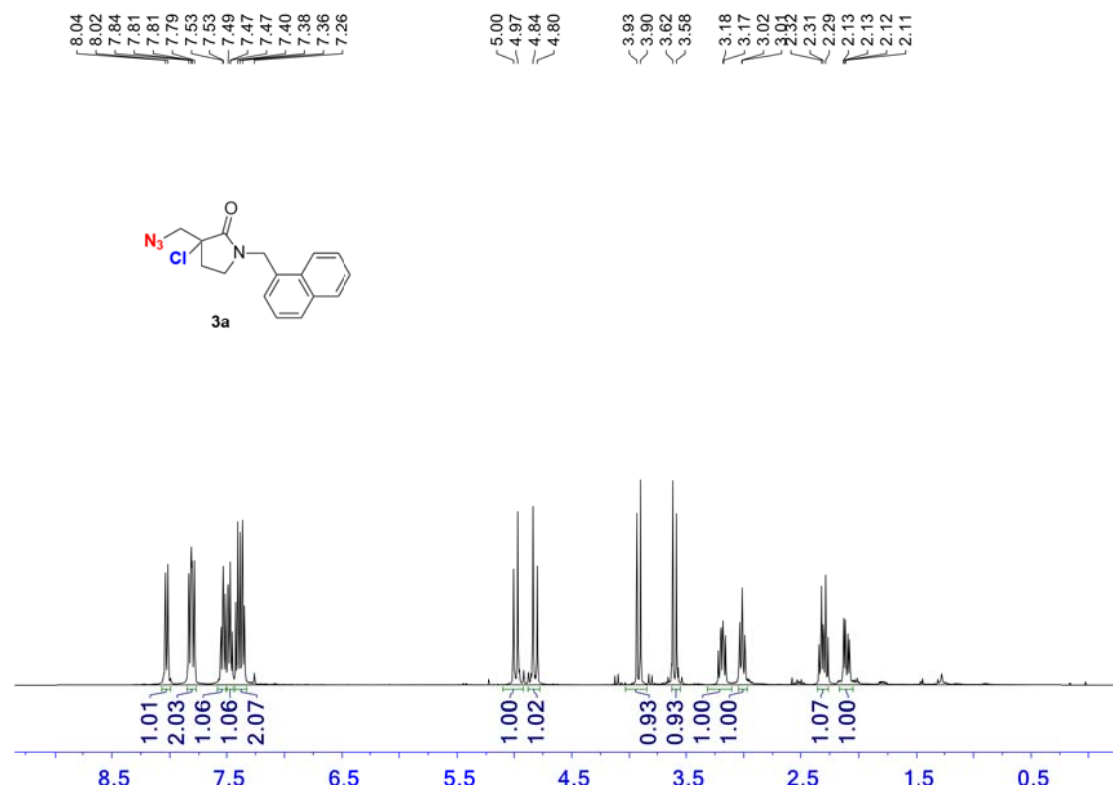
LC-MS calcd for C₉H₁₇N₄O₃⁺ [M+H]⁺: 229.1; found: 229.1.

VII. References

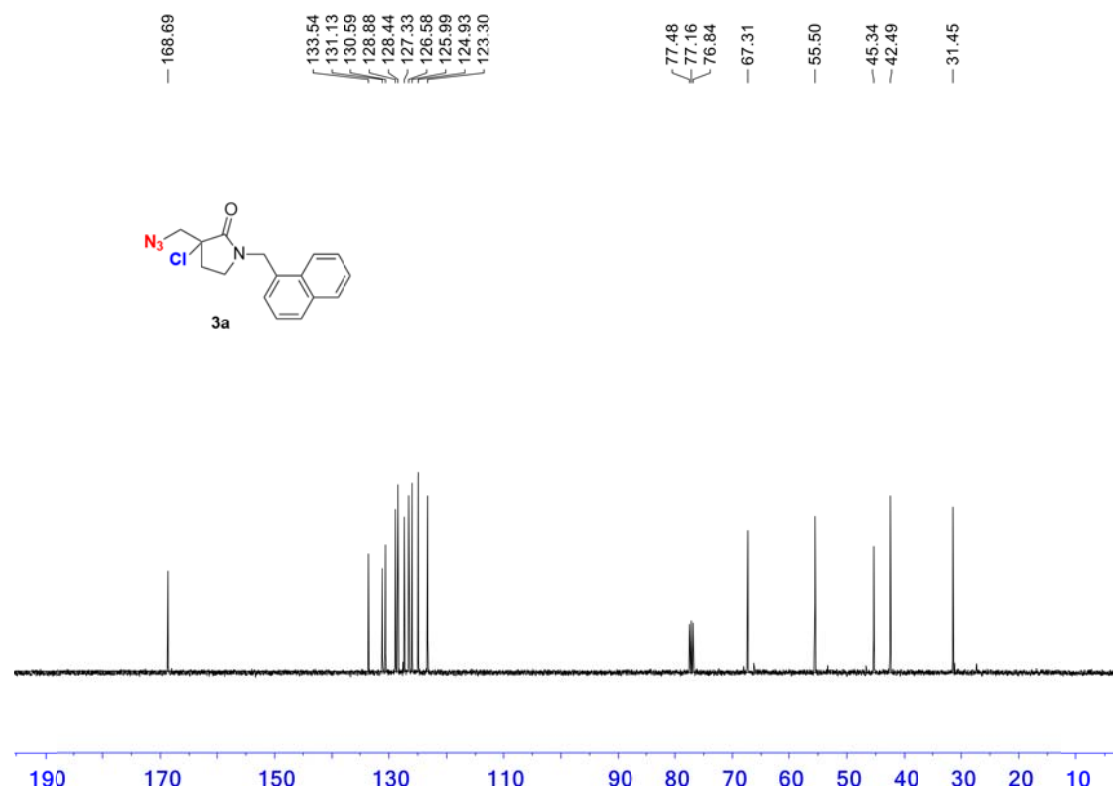
- [1] M. V. Vita, J. Waser, *Org.Lett.* 2013, **15**, 3246.
- [2] M. Fu, L. Chen, Y. Jiang, Z.-X. Jiang, Z. Yang, *Org.Lett.* 2016, **18**, 348.
- [3] M. A. Loreto, A. Migliorini, P. A. Tardella, A. Gambacorta, *Eur. J. Org. Chem.* 2007, **14**, 2365.
- [4] D. A. Kummer, W. J. Chain,; M. R. Morales, O. Quiroga, A. G. Myers, *J. Am. Chem. Soc.* 2008, **130**, 13231.

VIII. Copies of the NMR spectra of compound 3a-3r, 5-8

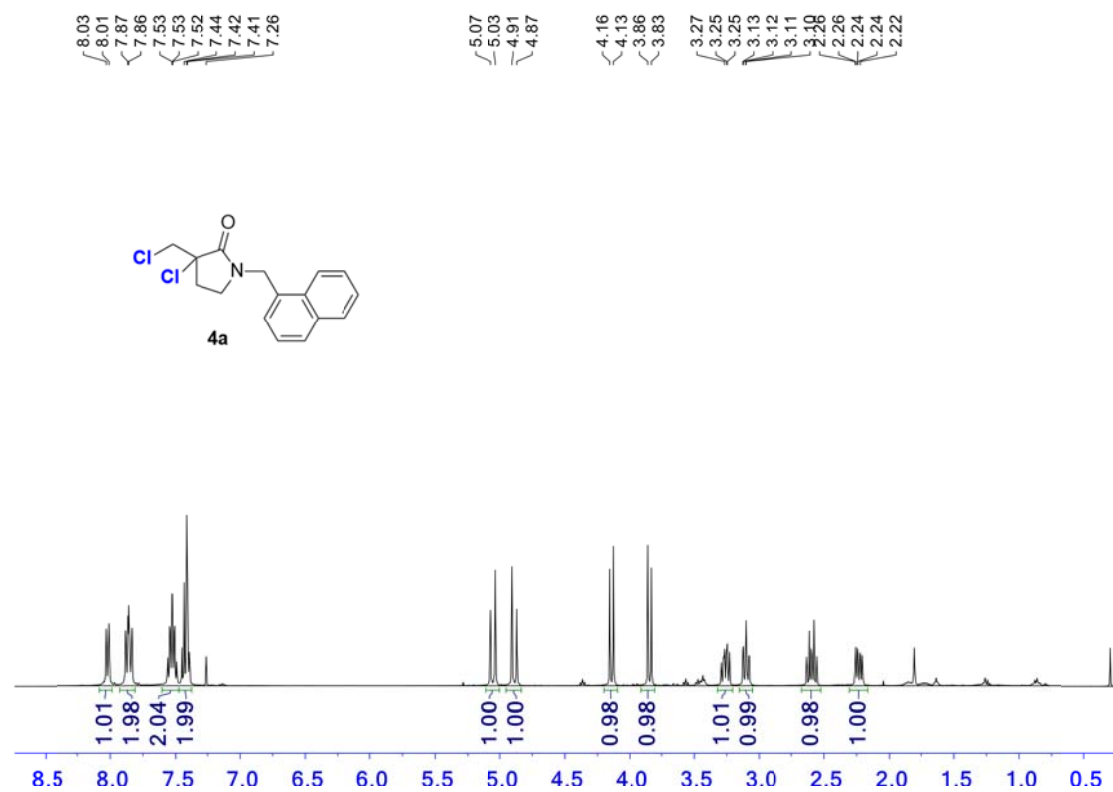
Compound 3a ¹H NMR



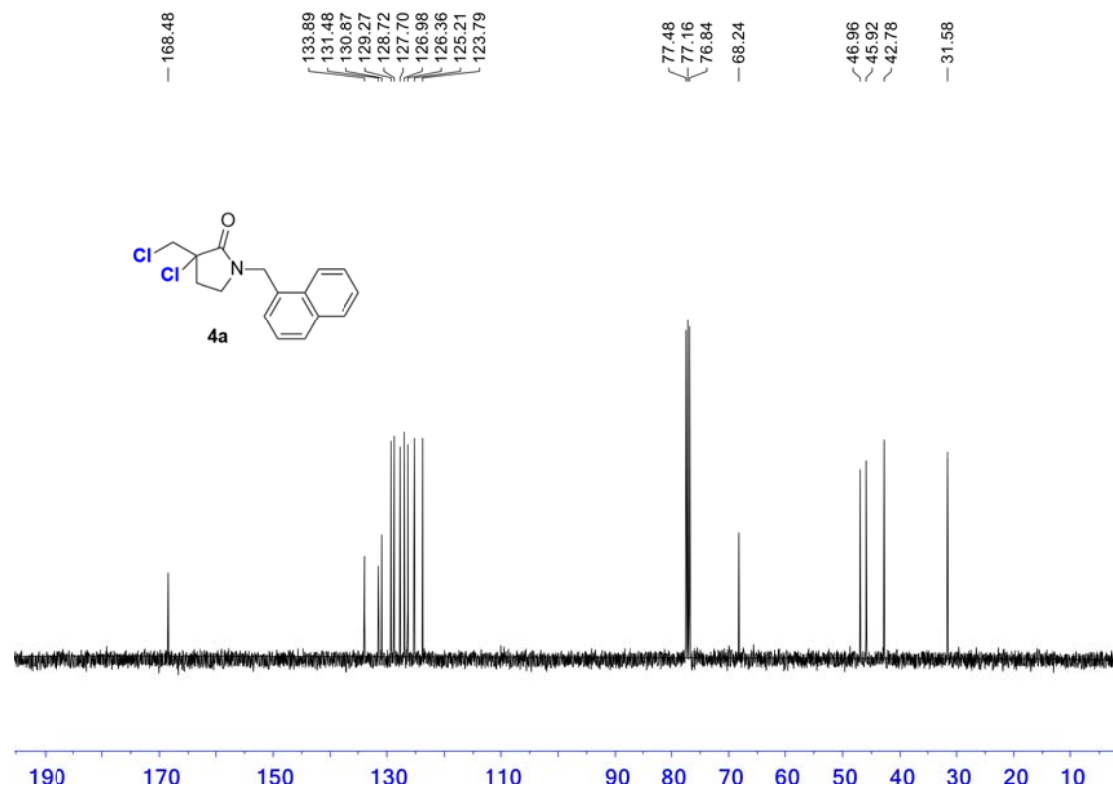
Compound 3a ¹³C NMR



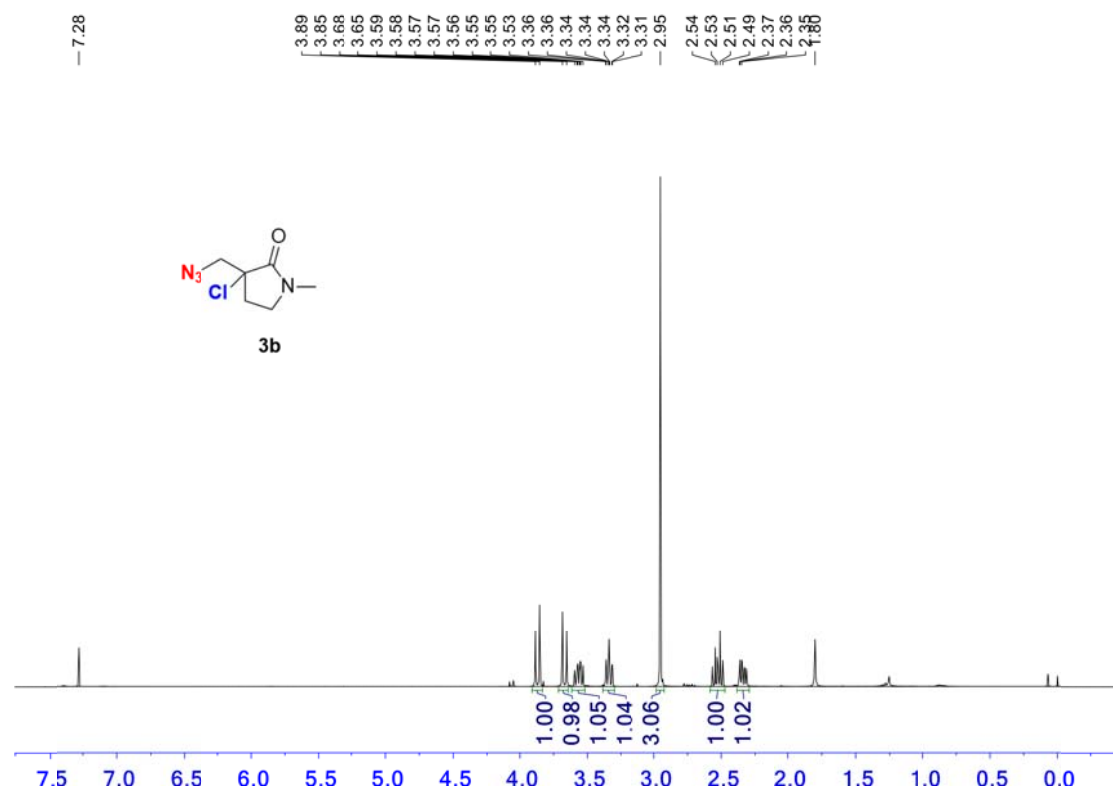
Compound **4a** ^1H NMR



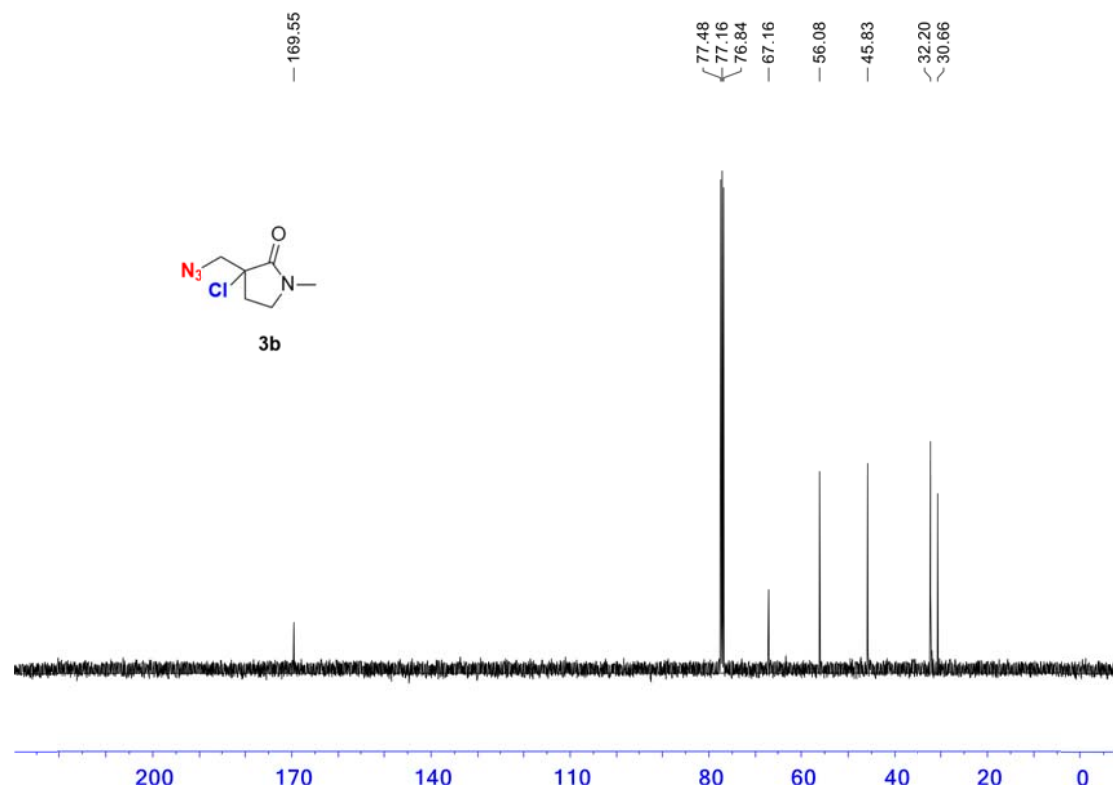
Compound **4a** ^{13}C NMR



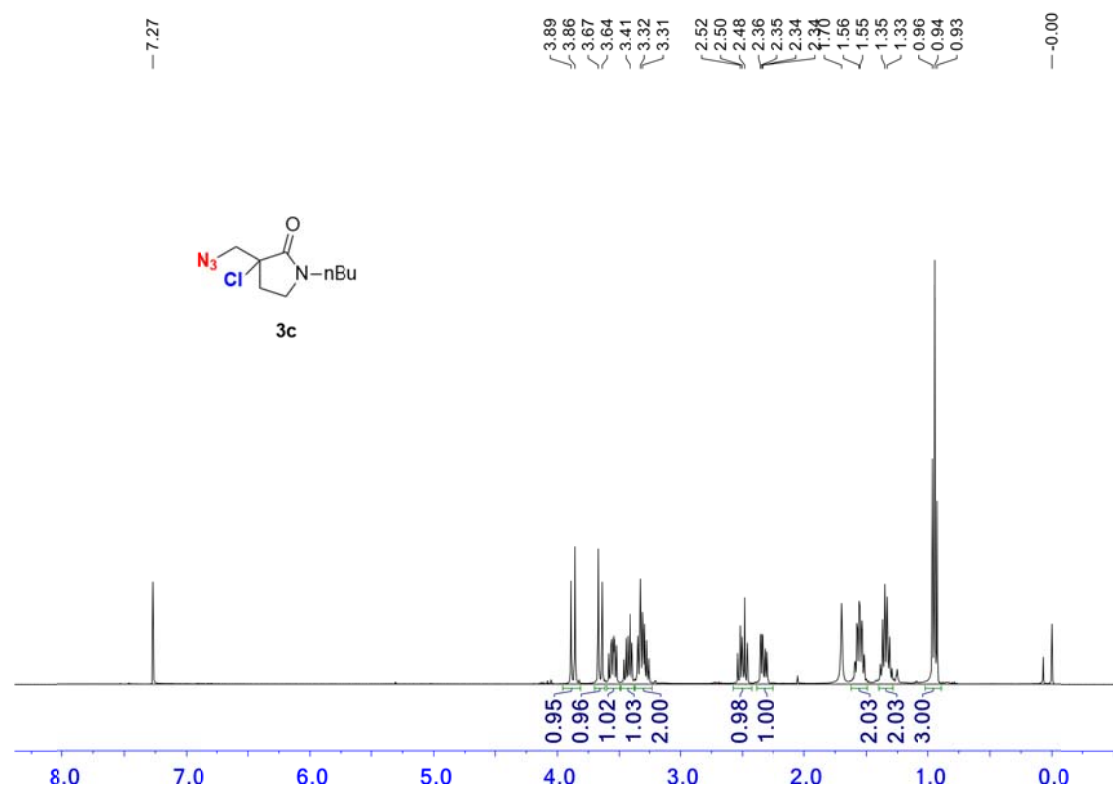
Compound **3b** ^1H NMR



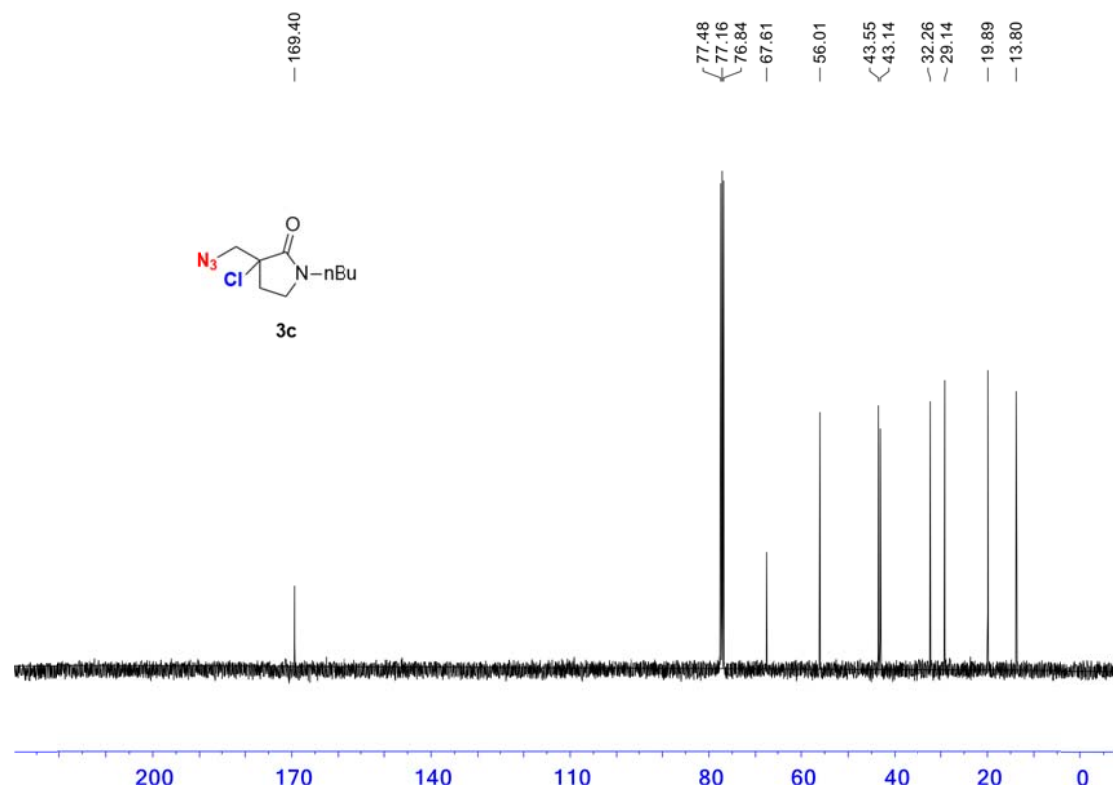
Compound **3b** ^{13}C NMR



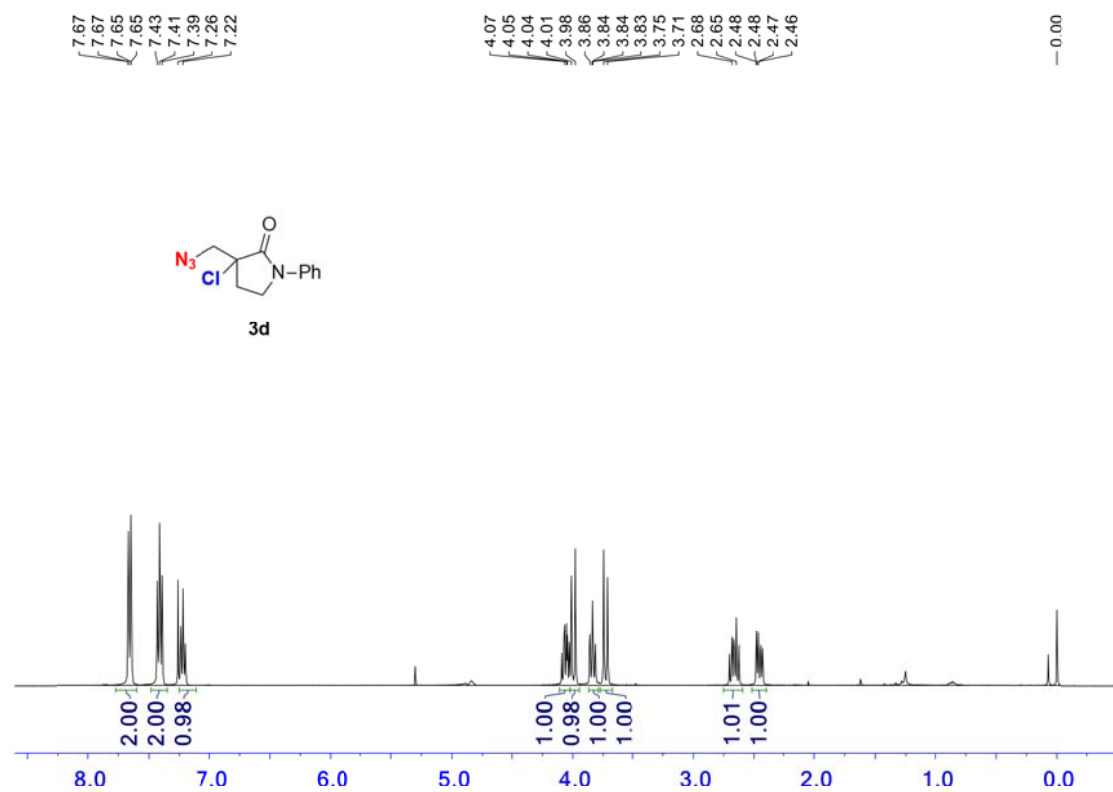
Compound **3c** ^1H NMR



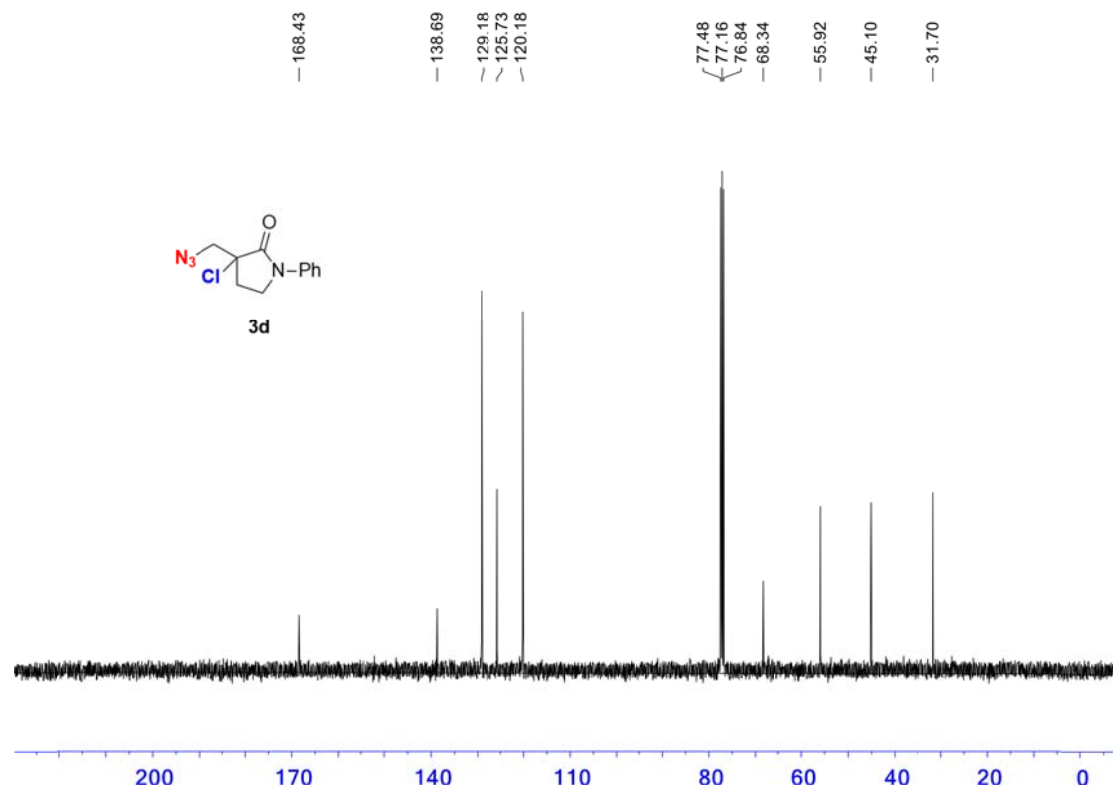
Compound **3c** ^{13}C NMR



Compound 3d ^1H NMR



Compound 3d ^{13}C NMR



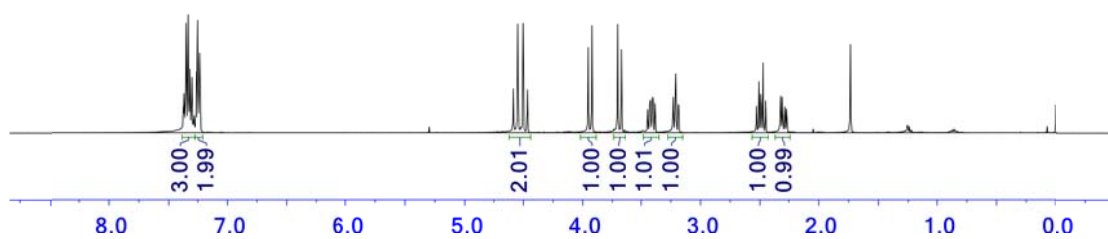
Compound **3e** ^1H NMR

7.36
7.34
7.25
7.25
7.23

4.58
4.55
4.50
4.47

3.95
3.92
3.71
3.67
3.40
3.23
3.21
3.21
2.49
2.47
2.32
2.32
2.30

-0.00



Compound **3e** ^{13}C NMR

169.61

135.44
128.97
128.08
128.03

77.48
77.16
76.84

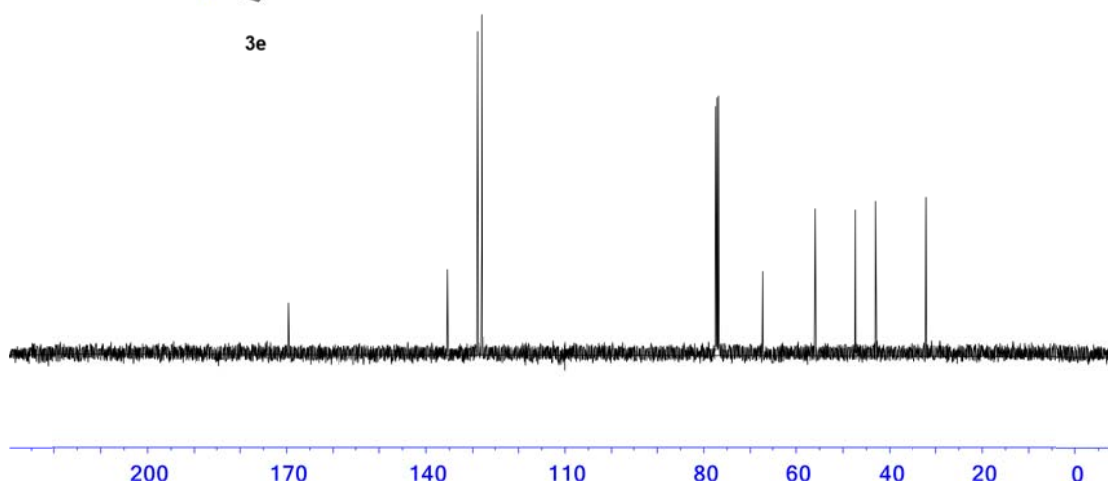
67.33

55.94

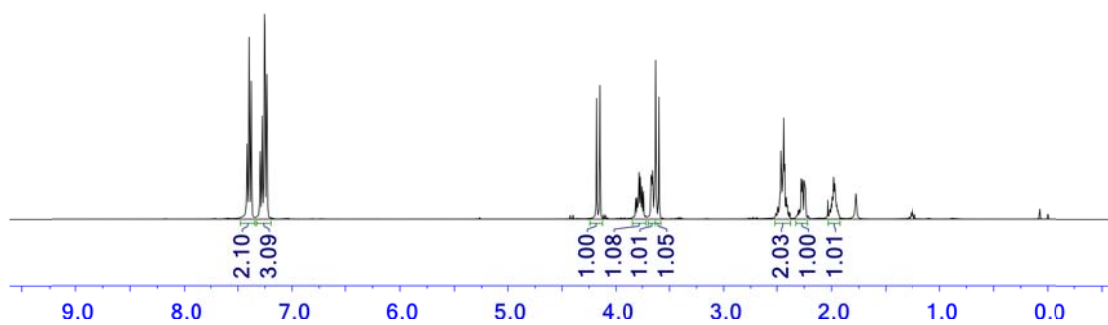
47.38

43.07

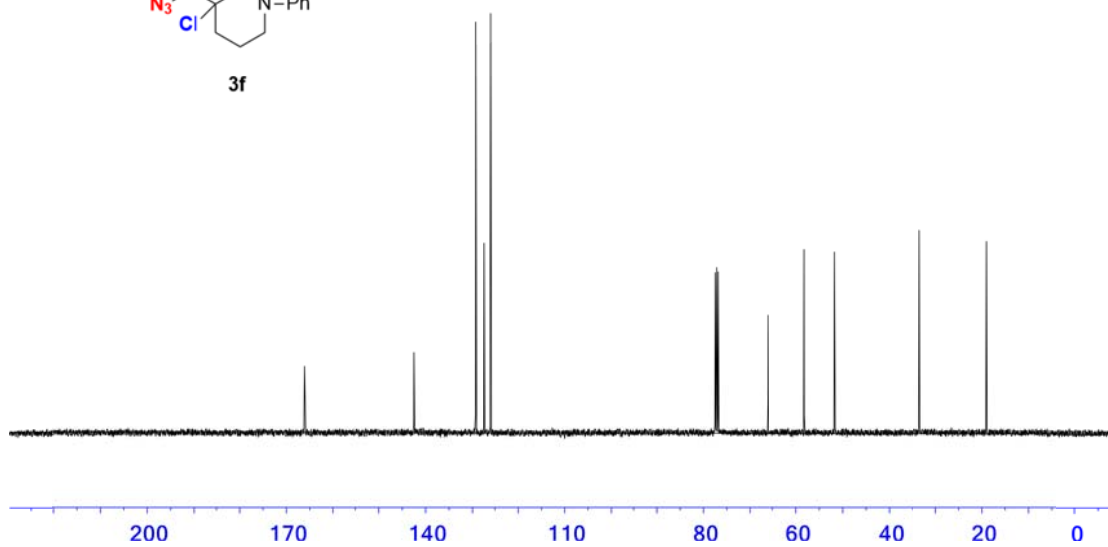
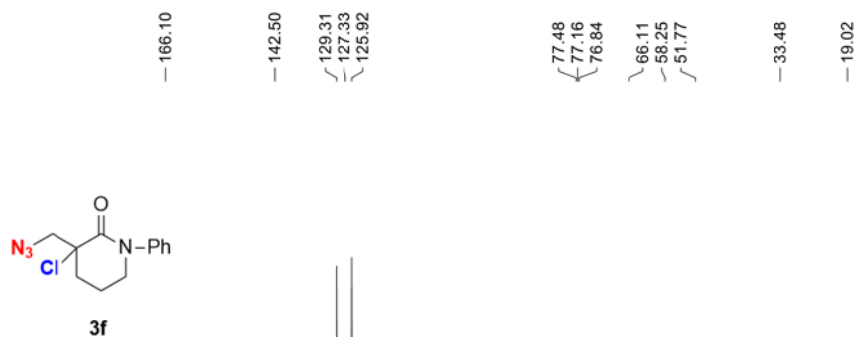
32.07



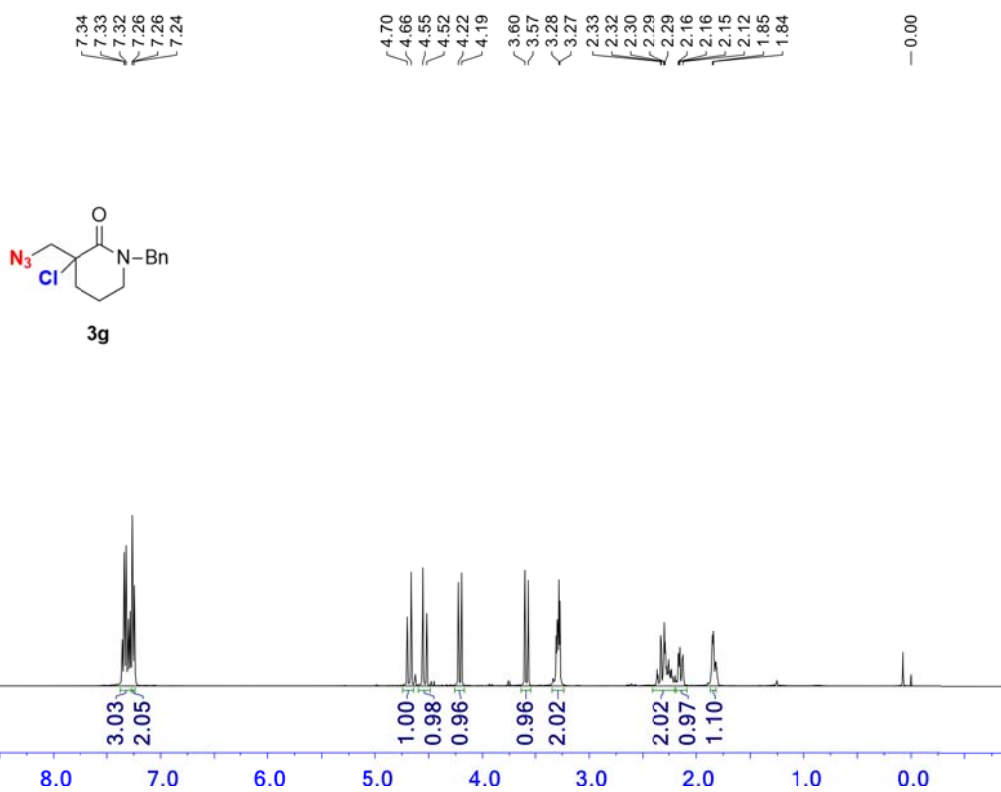
Compound **3f** ^1H NMR



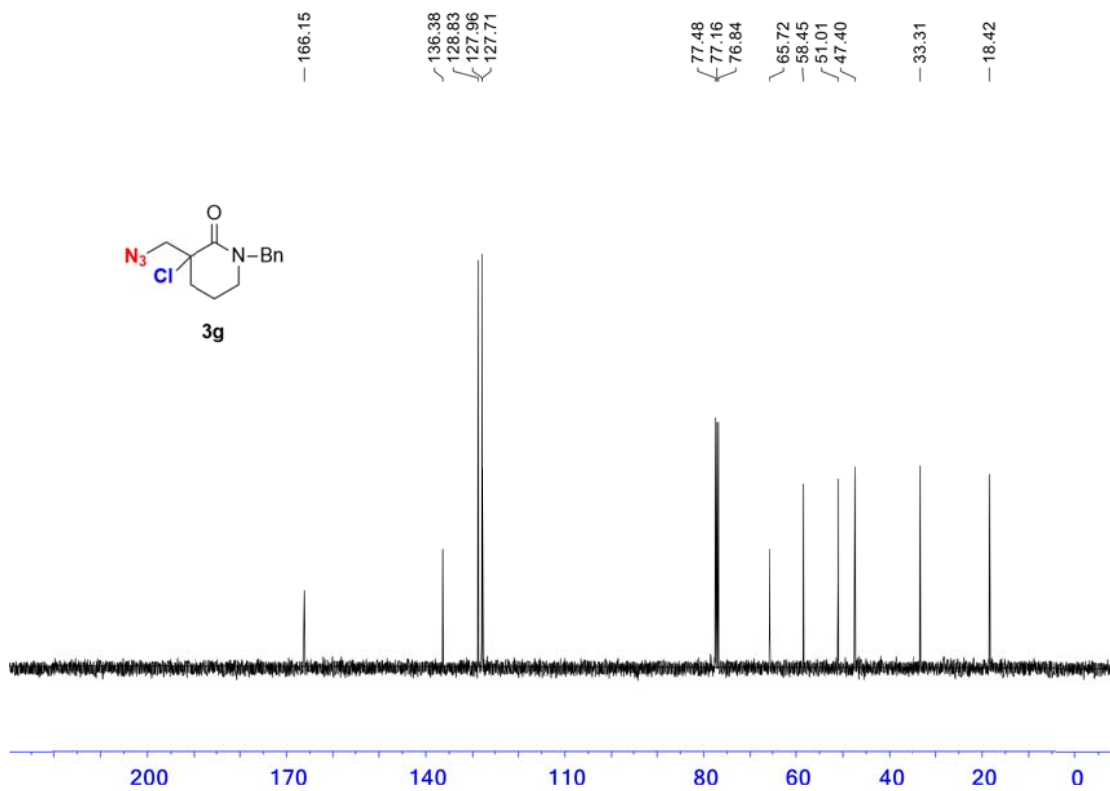
Compound **3f** ^{13}C NMR



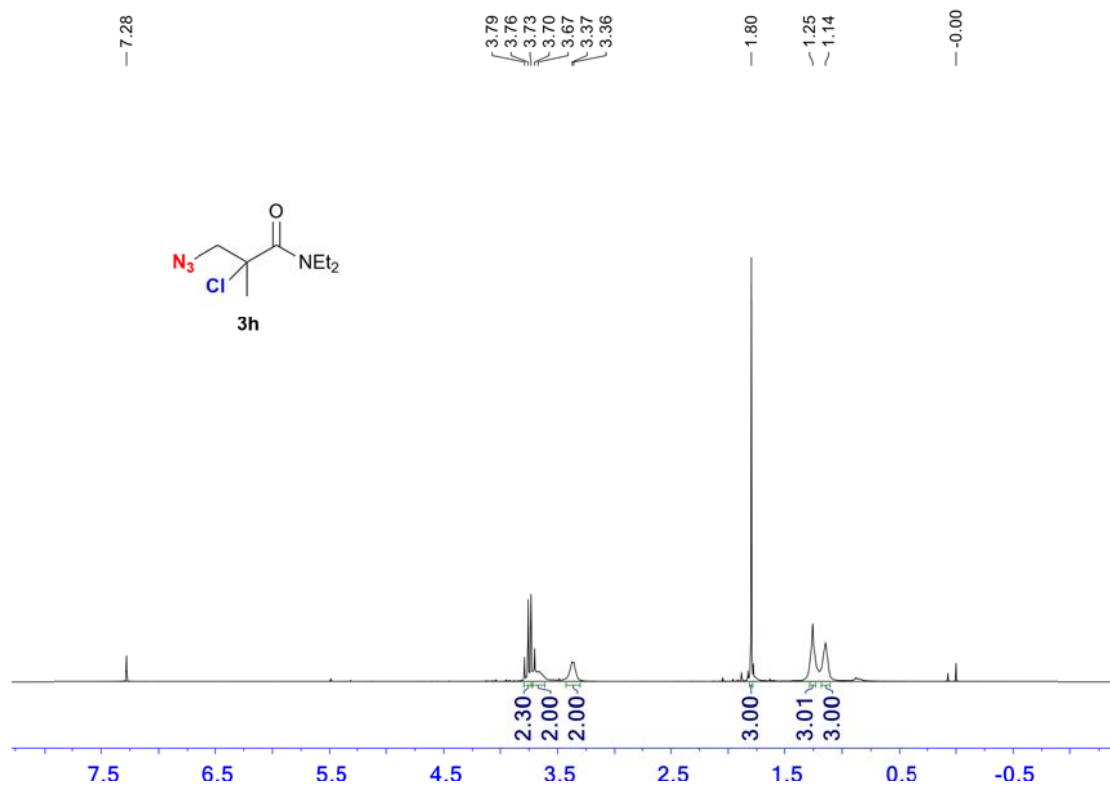
Compound **3g** ^1H NMR



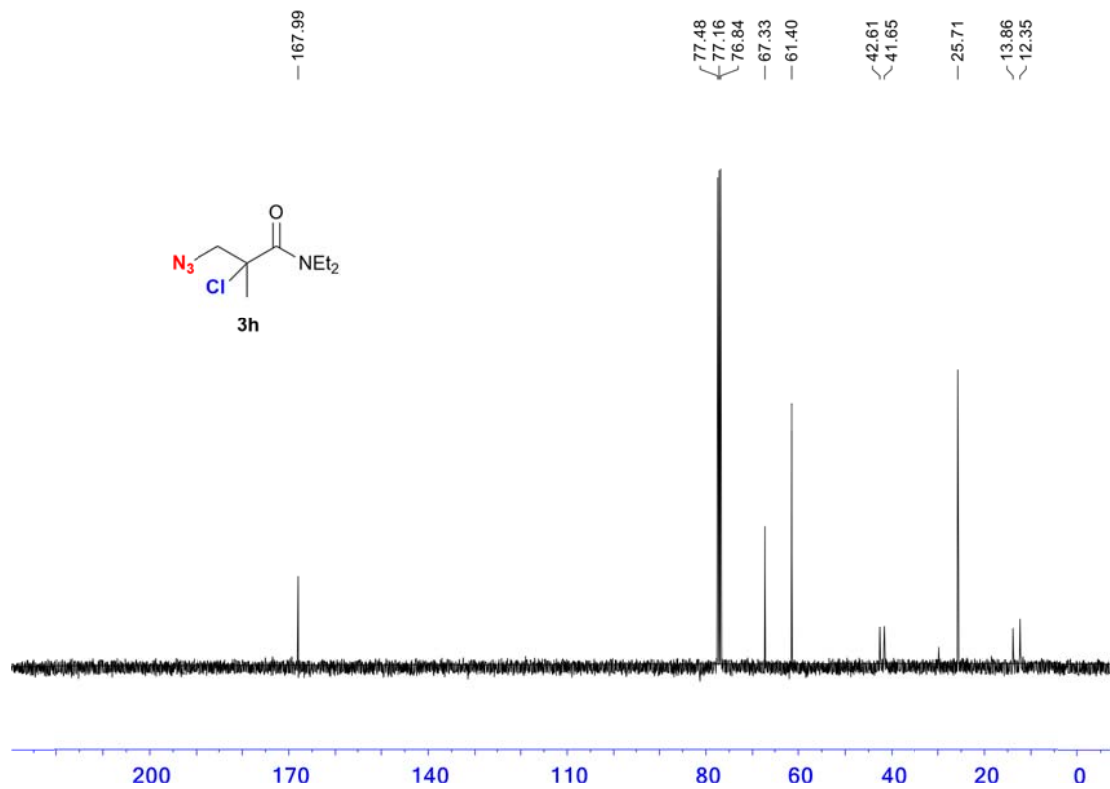
Compound **3g** ^{13}C NMR



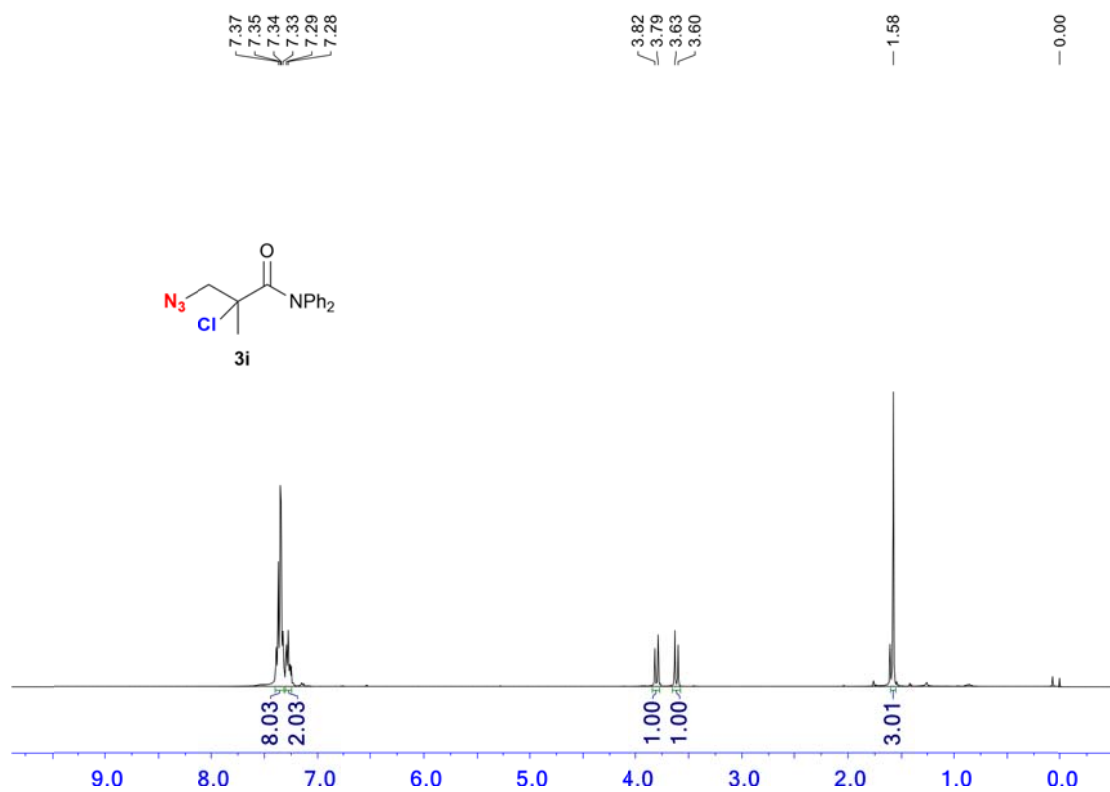
Compound **3h** ^1H NMR



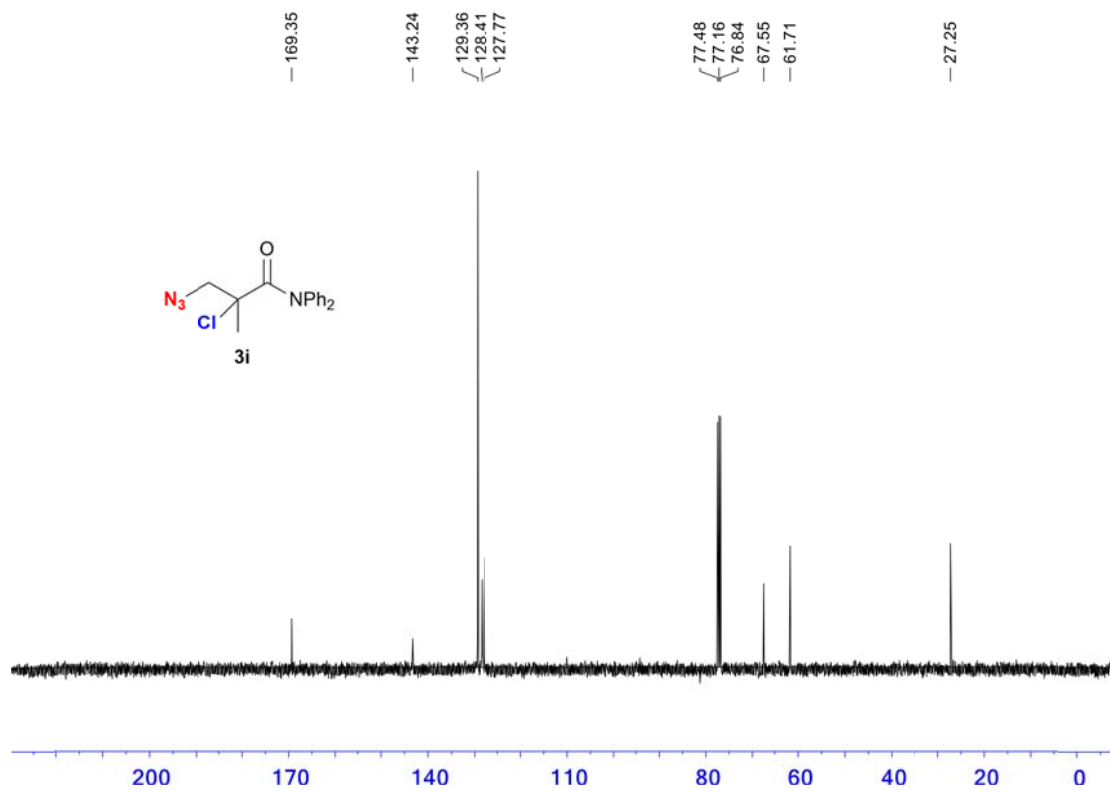
Compound **3h** ^{13}C NMR



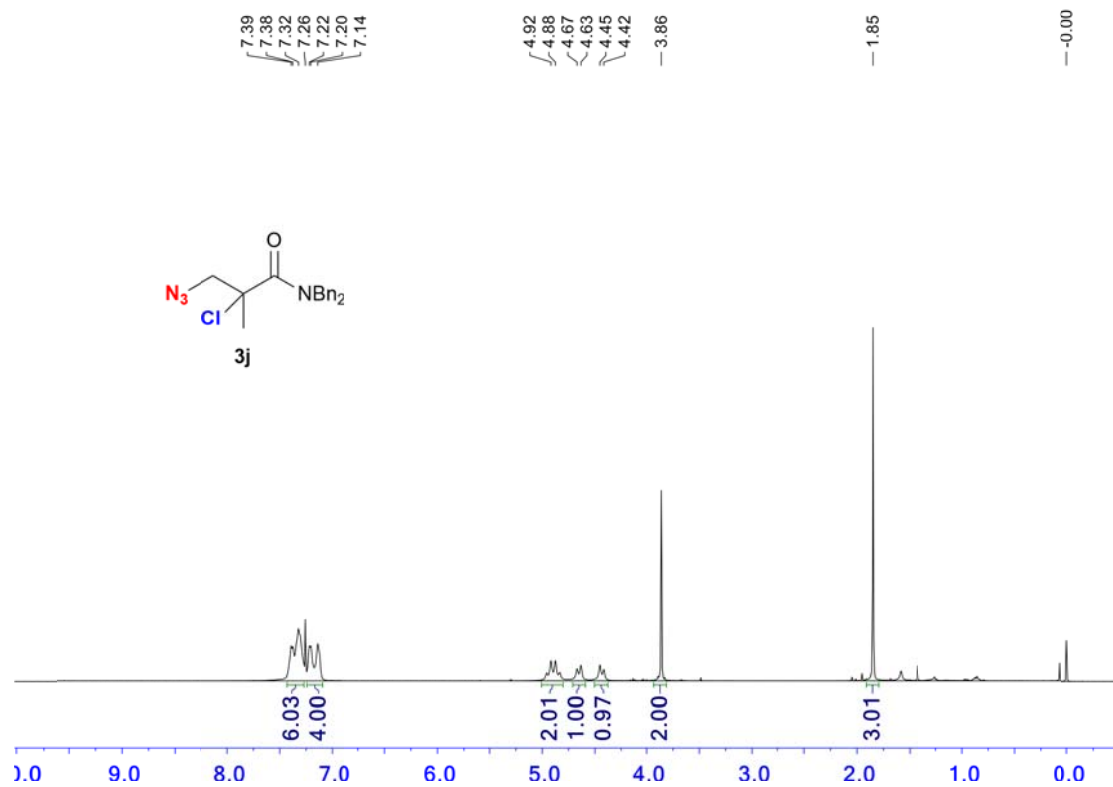
Compound **3i** ^1H NMR



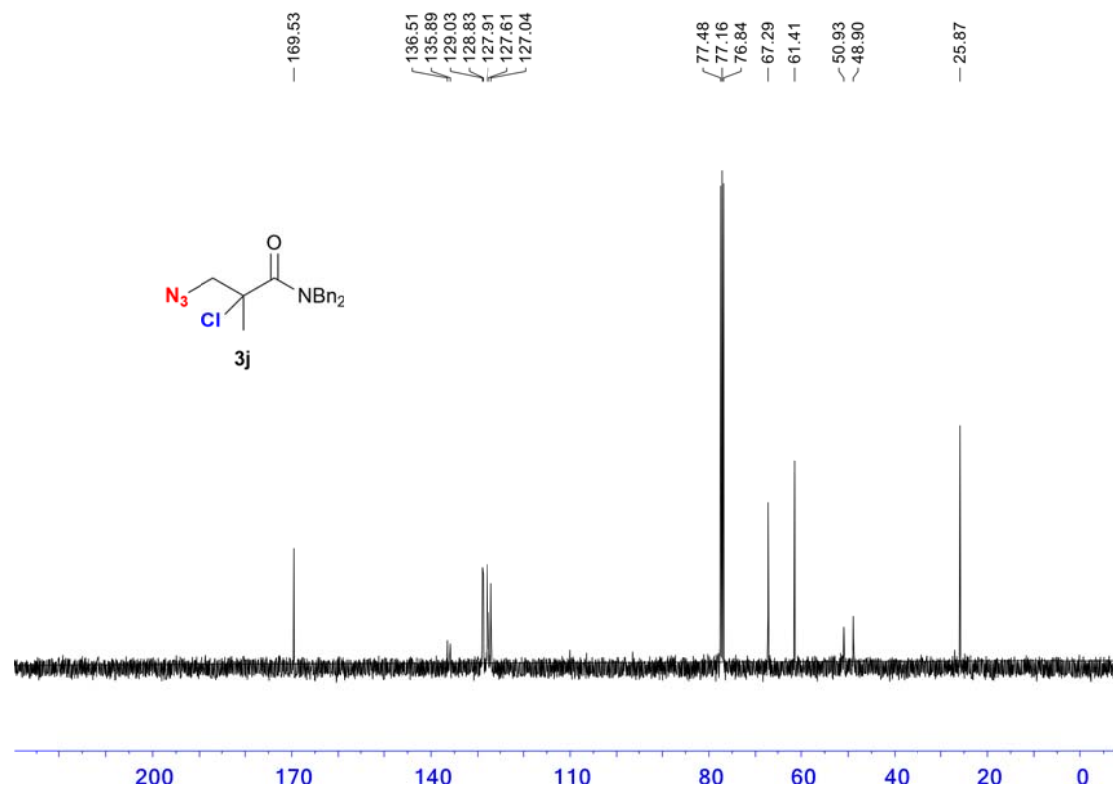
Compound **3i** ^{13}C NMR



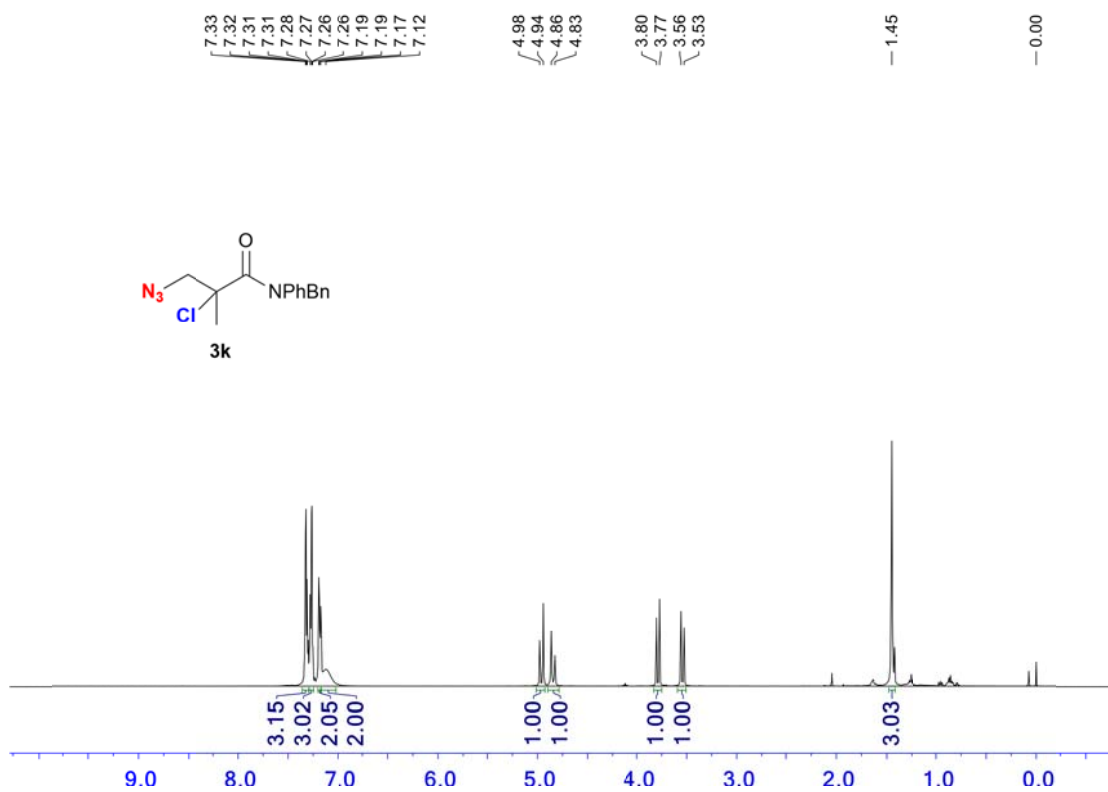
Compound **3j** ^1H NMR



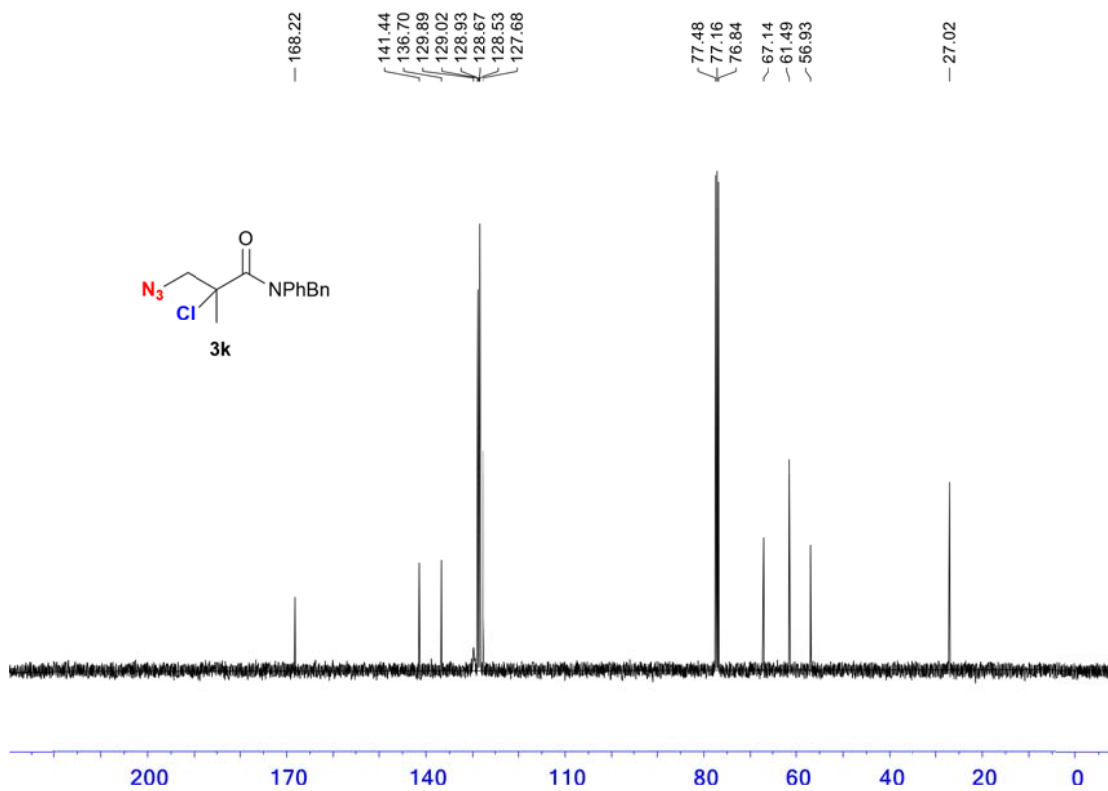
Compound **3j** ^{13}C NMR



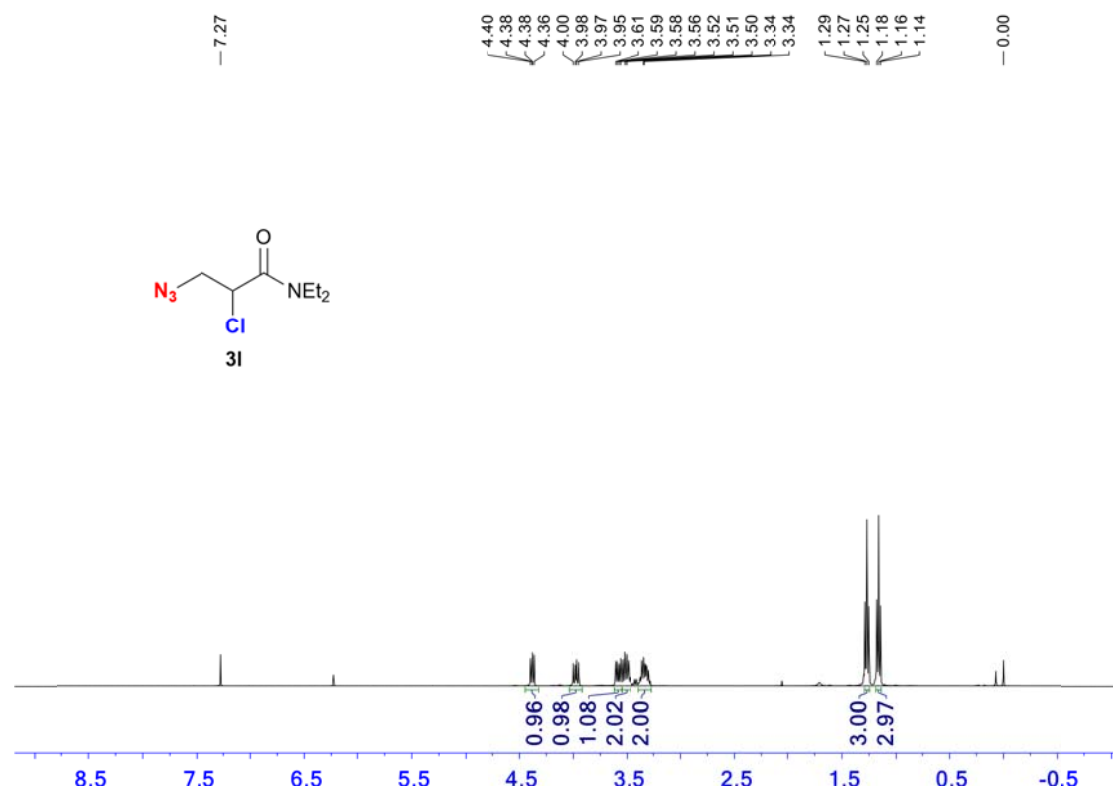
Compound **3k** ^1H NMR



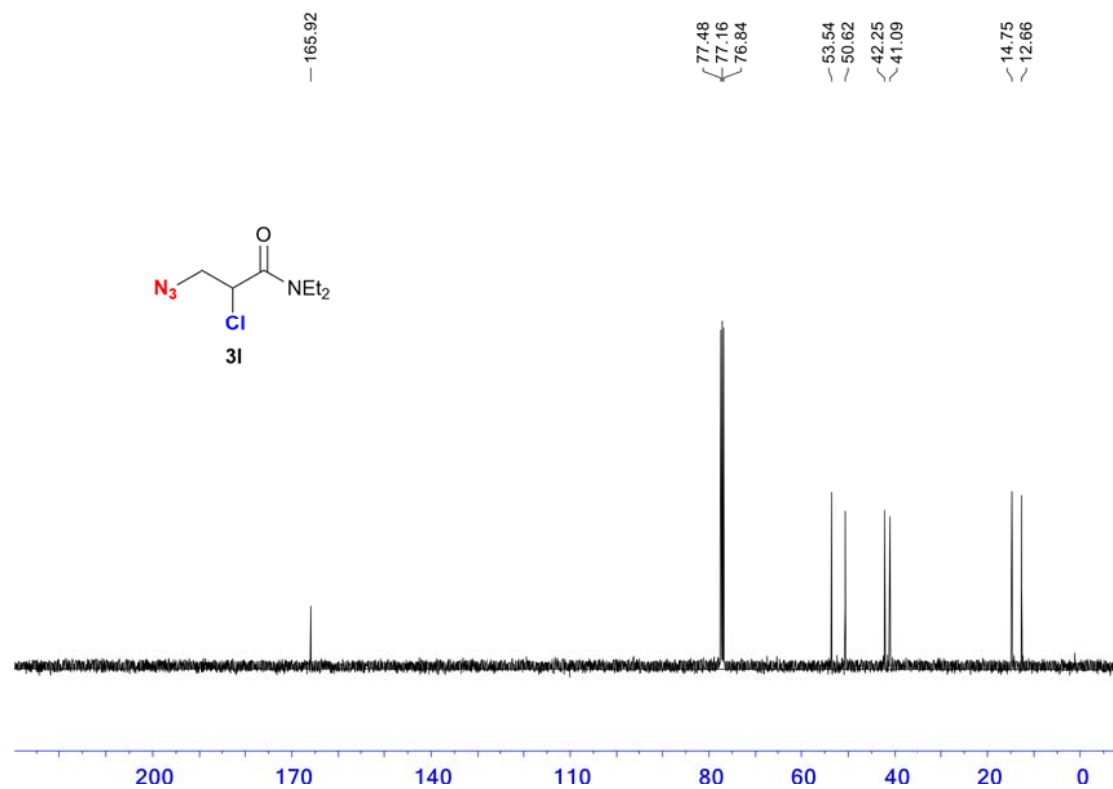
Compound **3k** ^{13}C NMR



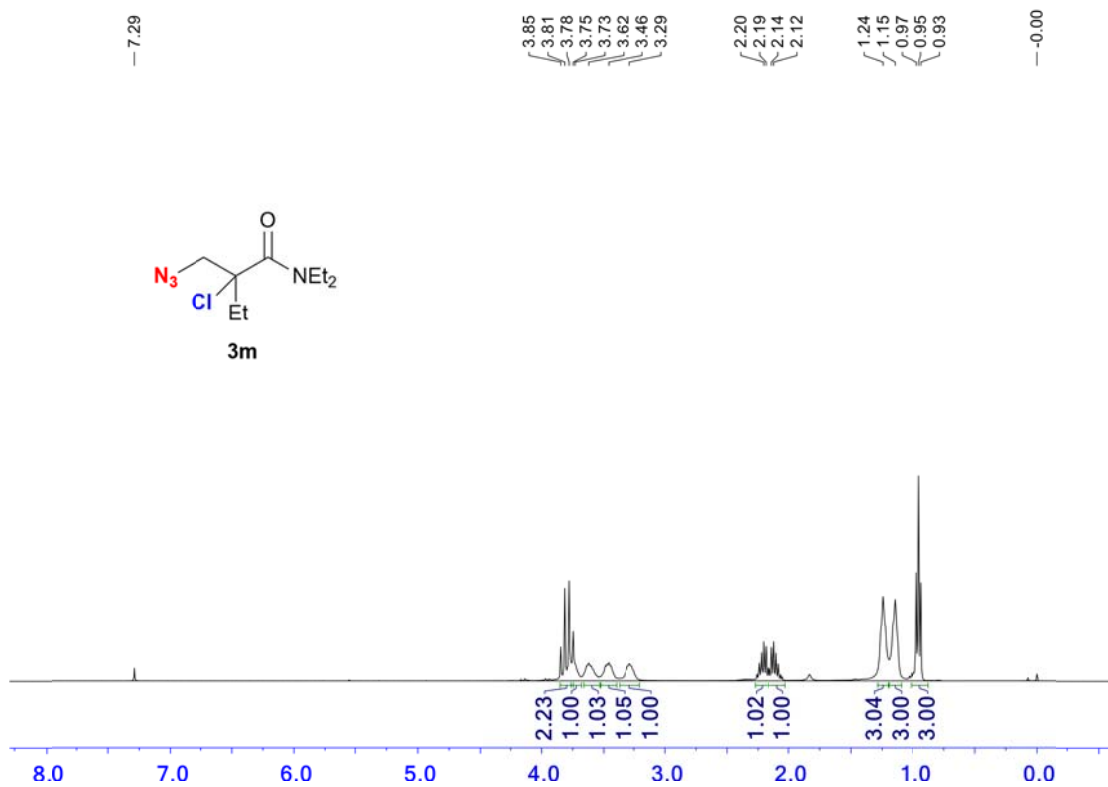
Compound **31** ^1H NMR



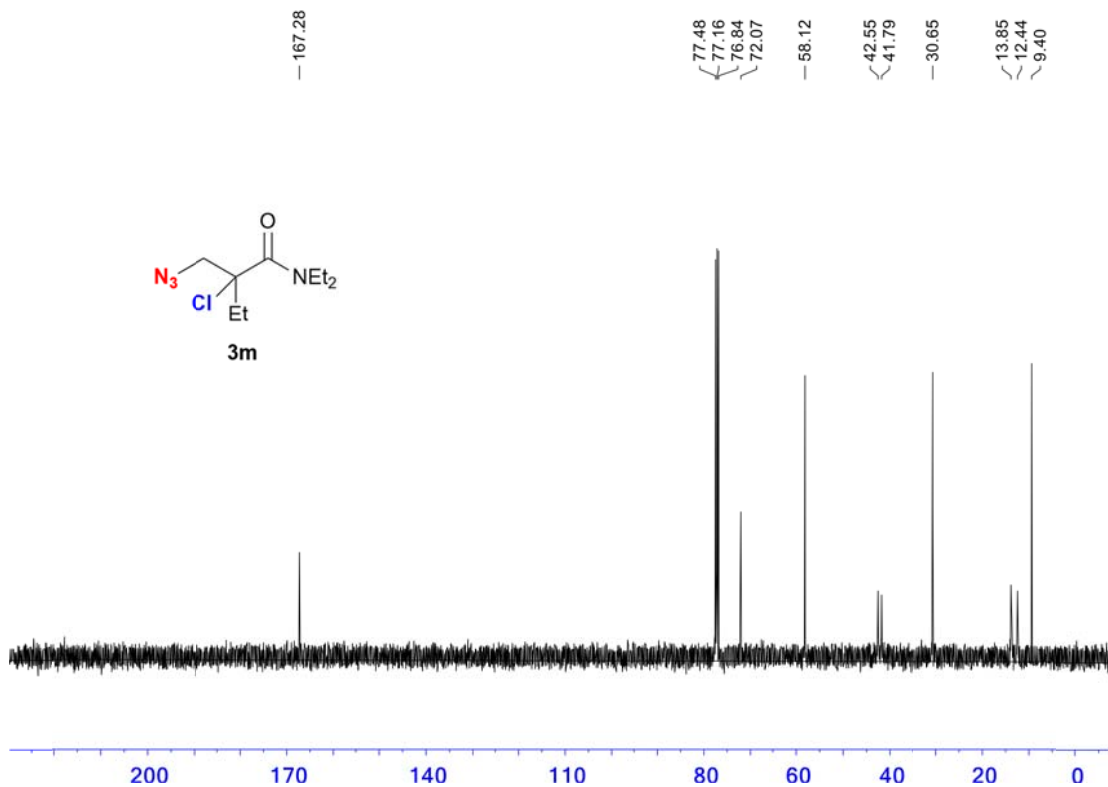
Compound **31** ^{13}C NMR



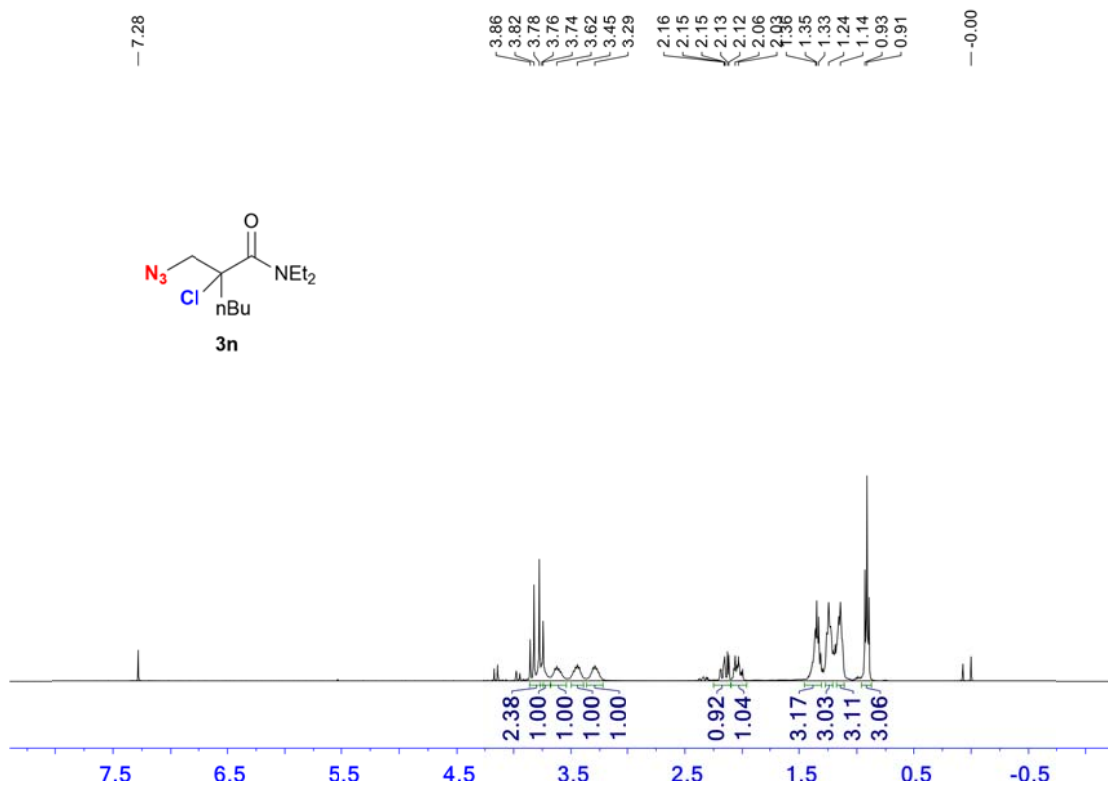
Compound **3m** ^1H NMR



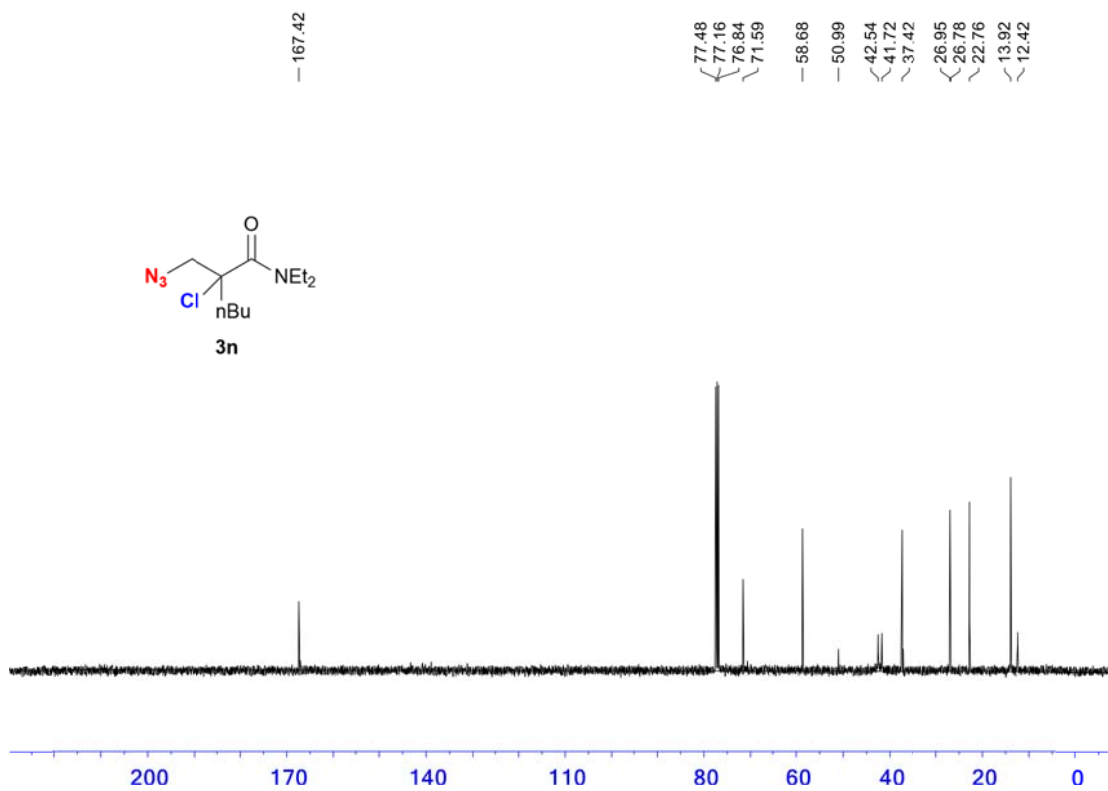
Compound **3m** ^{13}C NMR



Compound **3n** ^1H NMR



Compound **3n** ^{13}C NMR



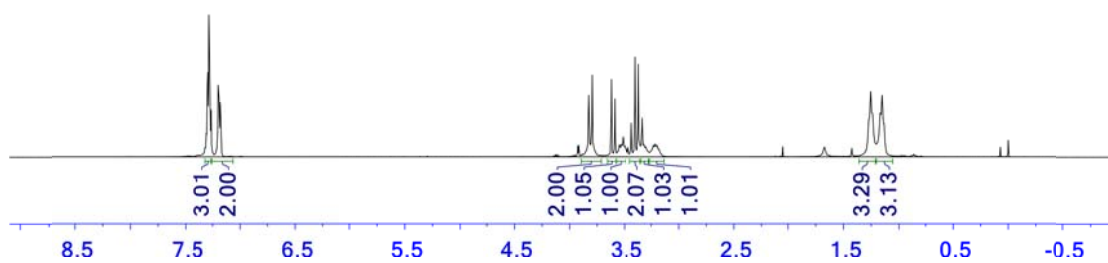
Compound **3o** ^1H NMR

7.30
7.29
7.28
7.28
7.26
7.20
7.19
7.18
7.18

3.83
3.79
3.62
3.59
3.51
3.43
3.40
3.37
3.33
3.32
3.21

1.25
1.15

0.07
0.00



Compound **3o** ^{13}C NMR

166.99

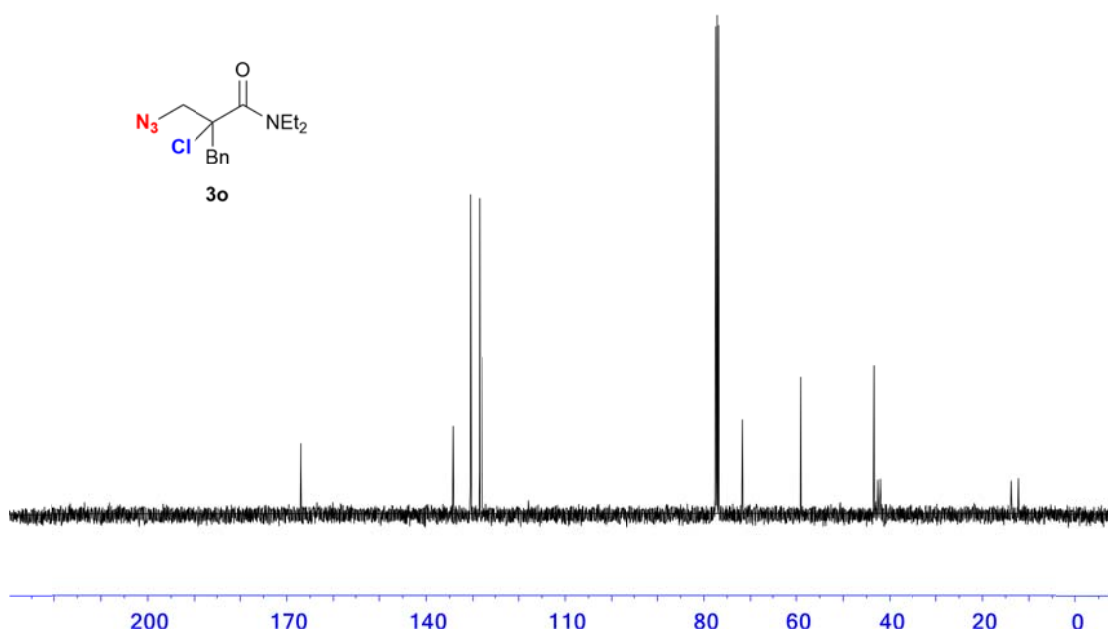
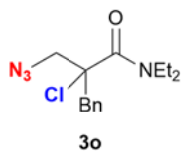
134.23
130.63
130.52
128.55
128.51
127.86

77.48
77.16
76.84
71.75

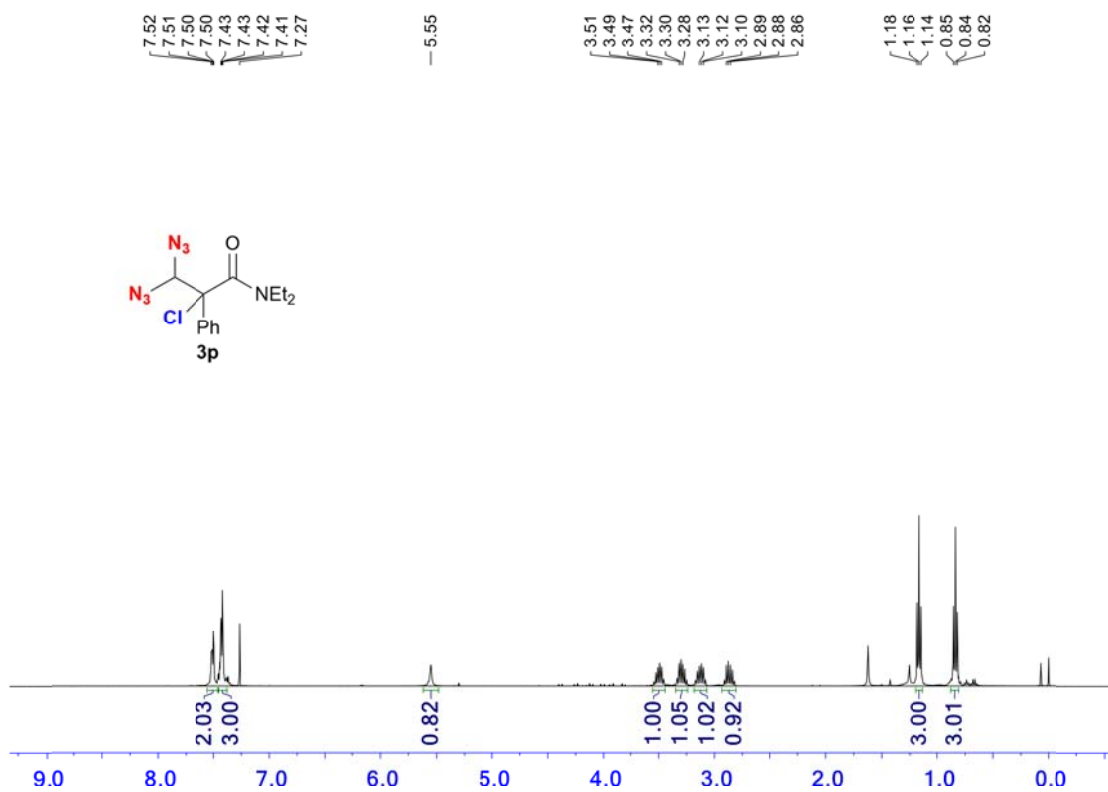
59.05

43.41
42.60
42.06

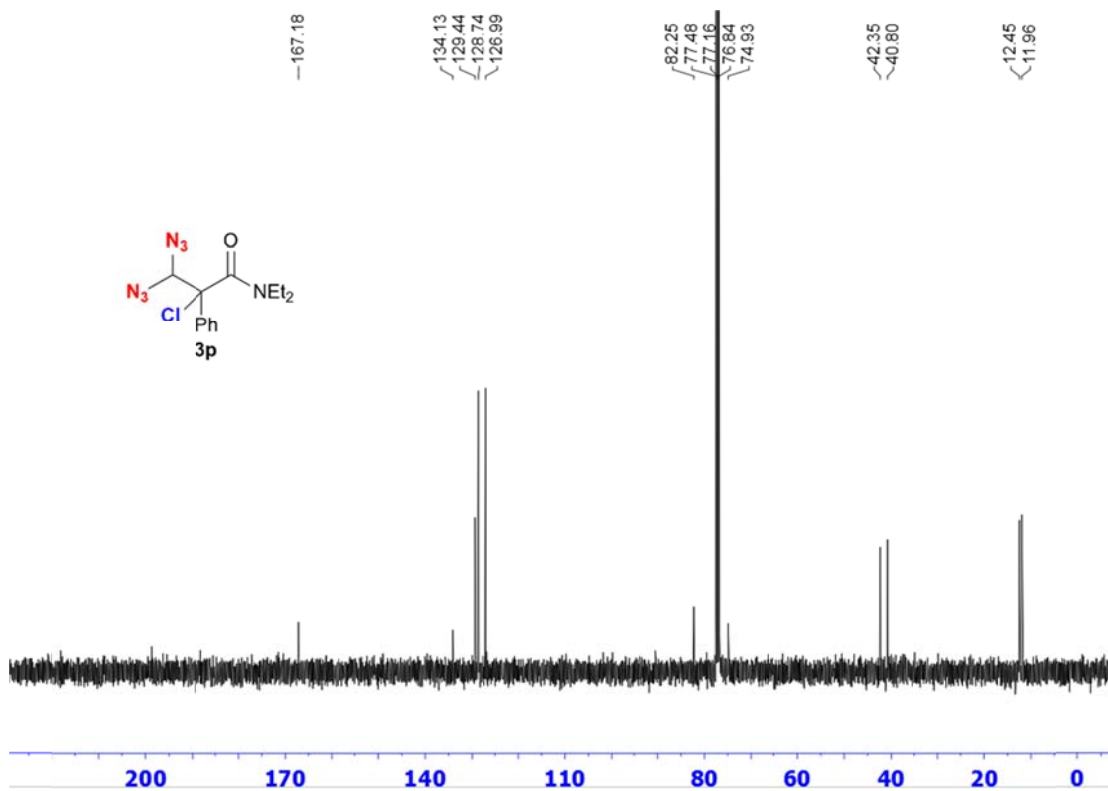
13.82
12.26



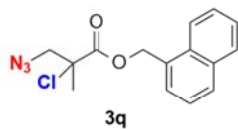
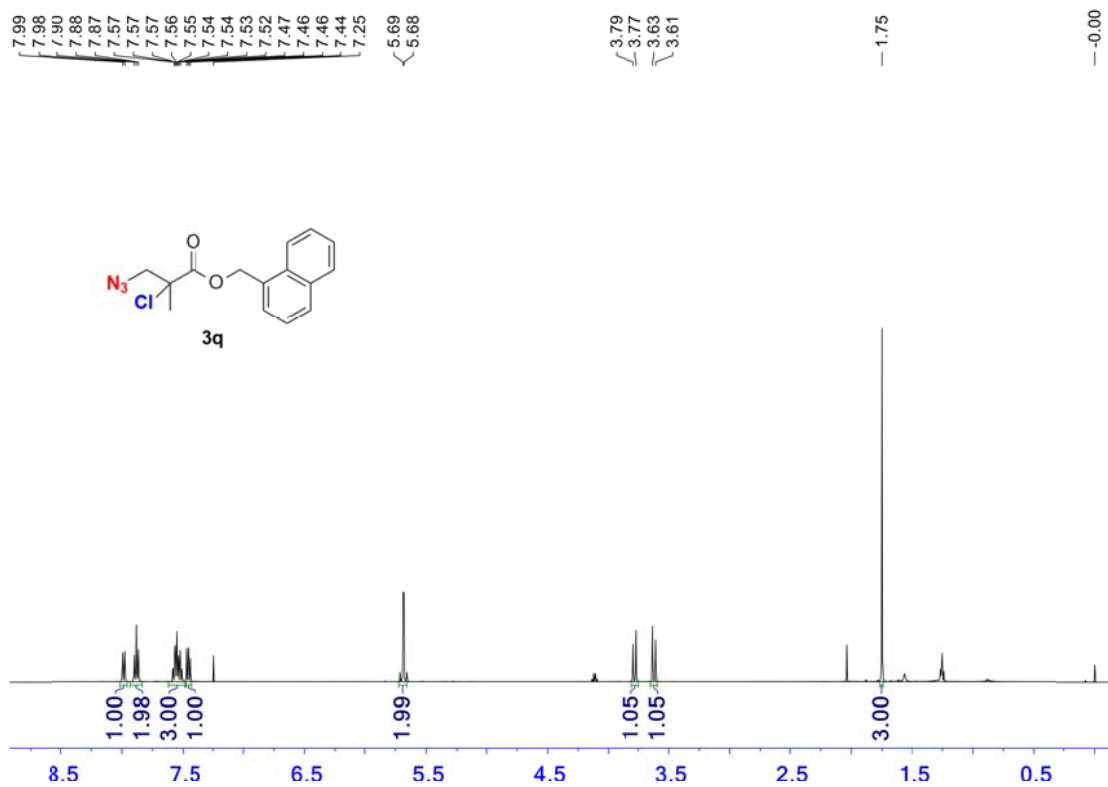
Compound **3p** ^1H NMR



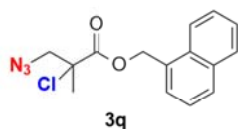
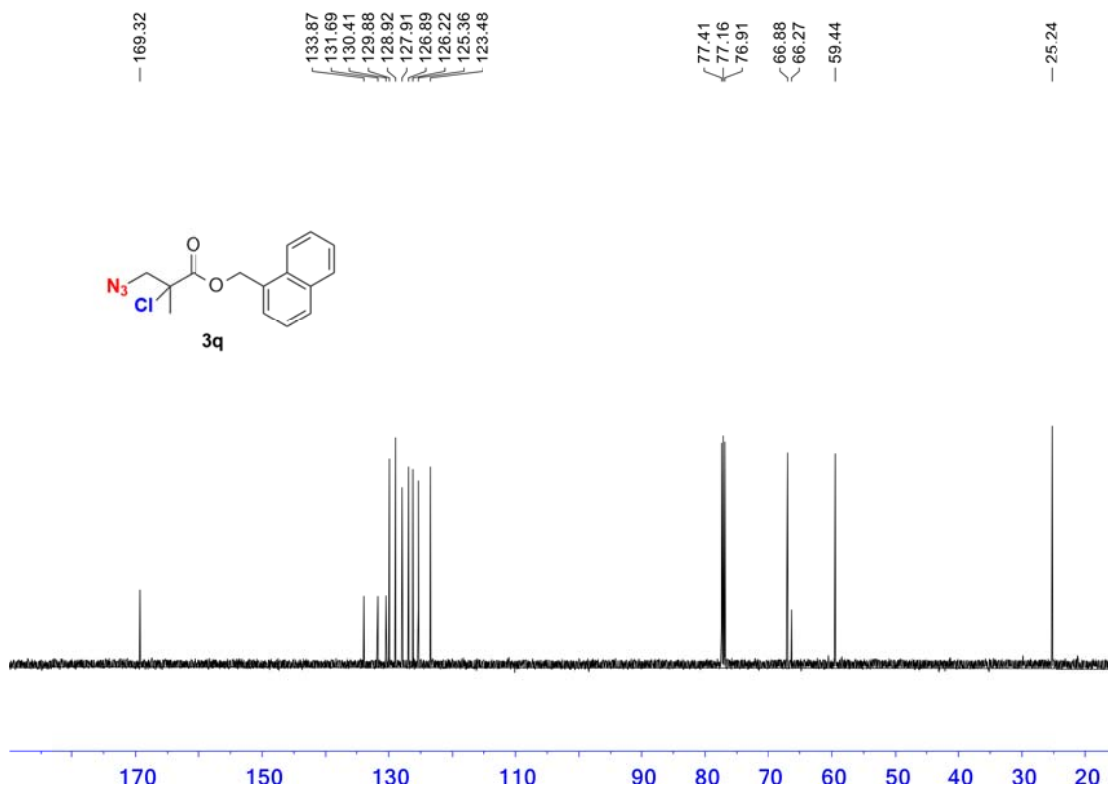
Compound **3p** ^{13}C NMR



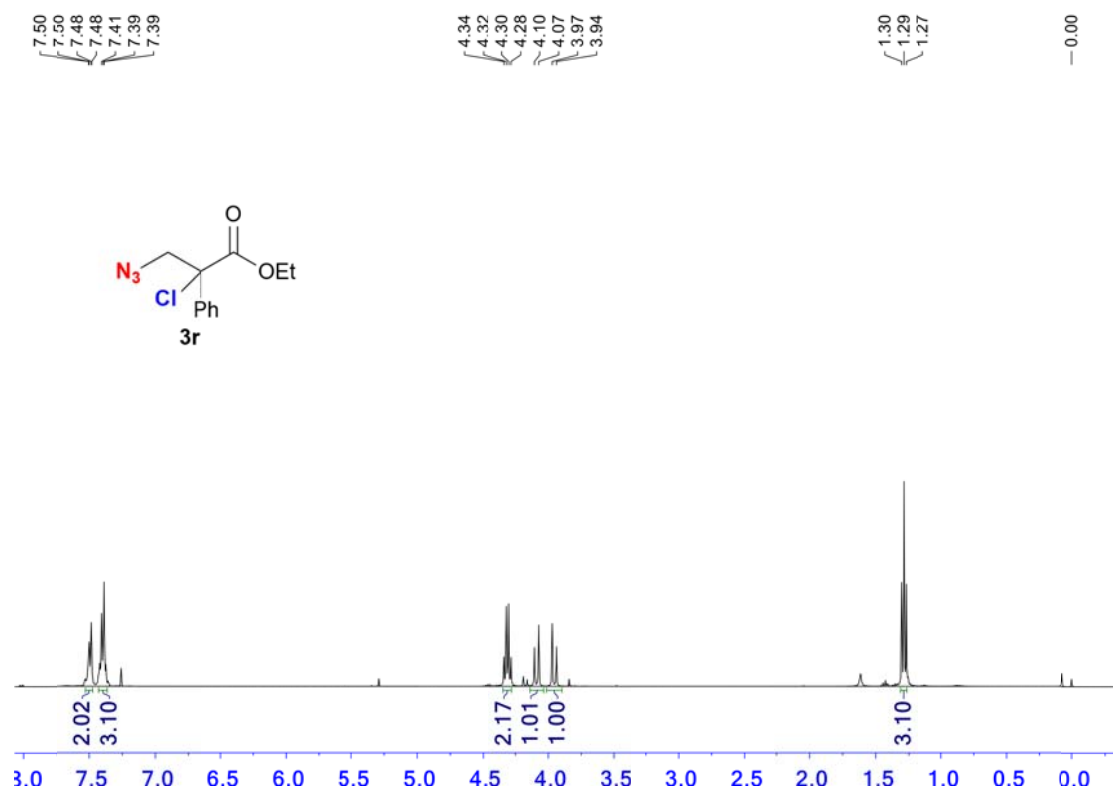
Compound **3q** ^1H NMR



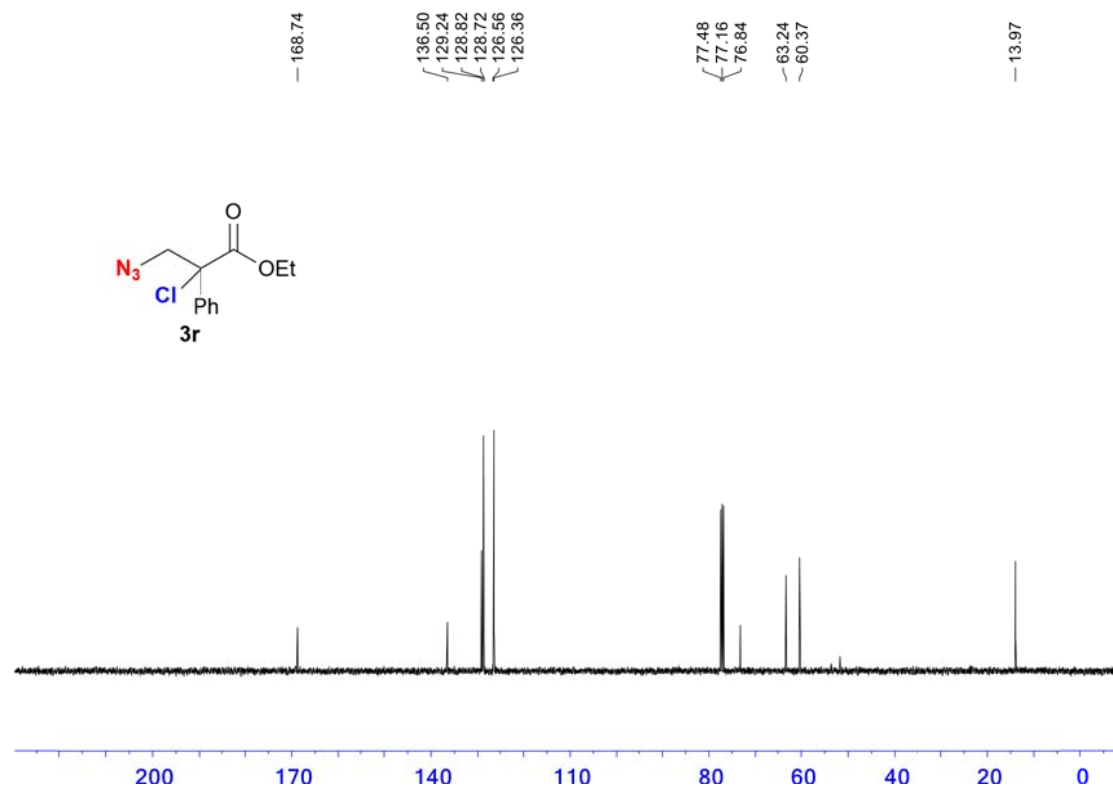
Compound **3q** ^{13}C NMR



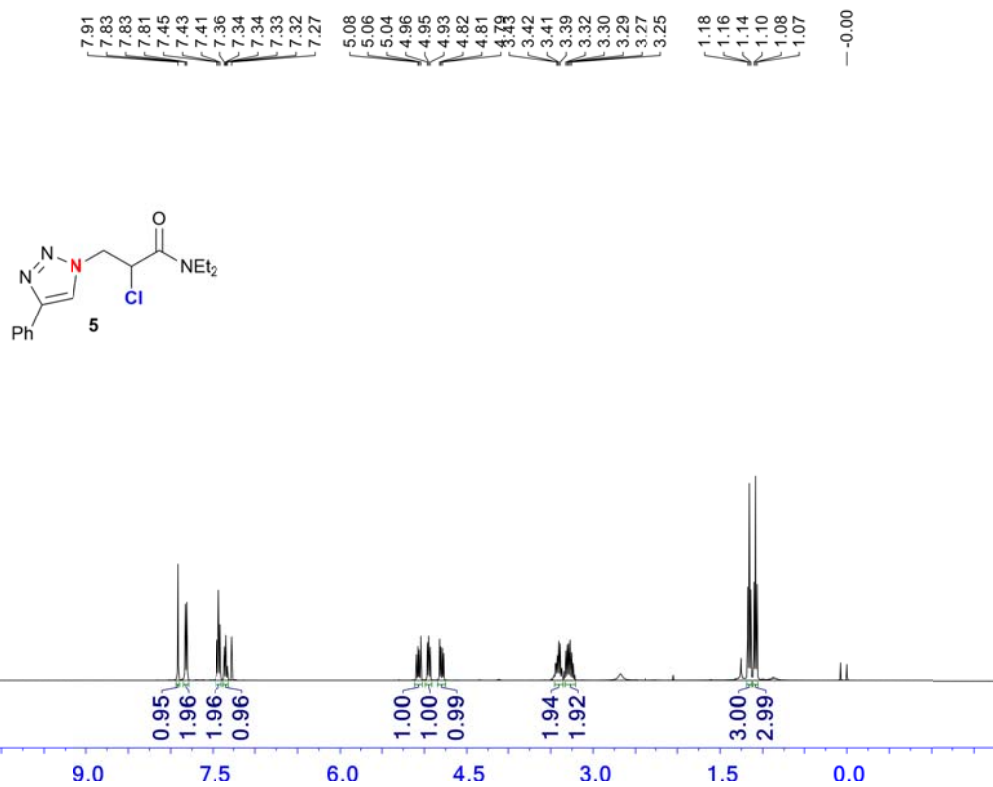
Compound **3r** ^1H NMR



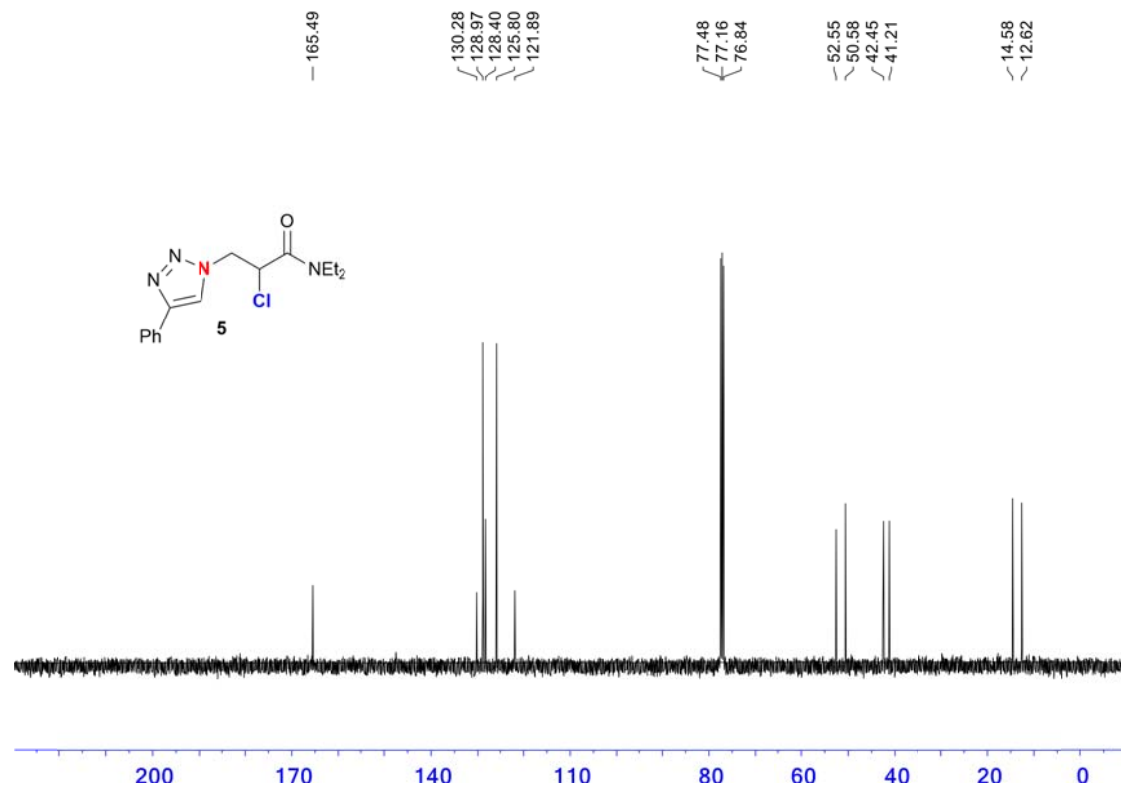
Compound **3r** ^{13}C NMR



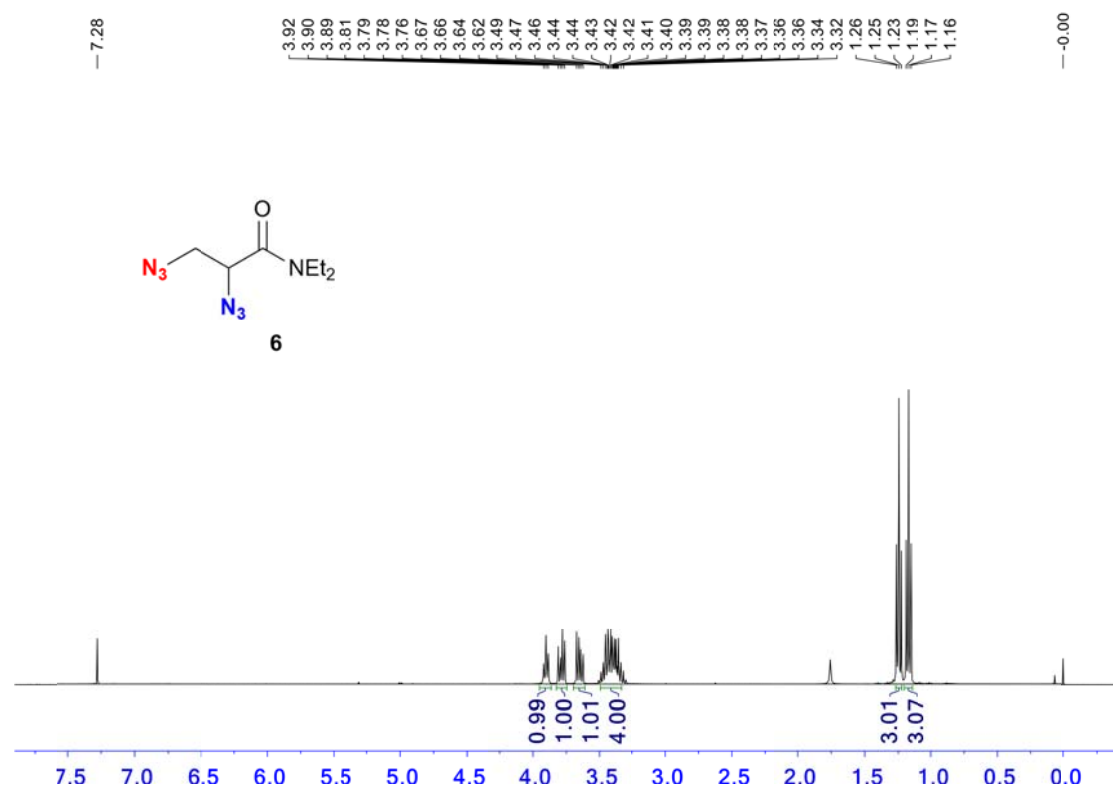
Compound **5** ^1H NMR



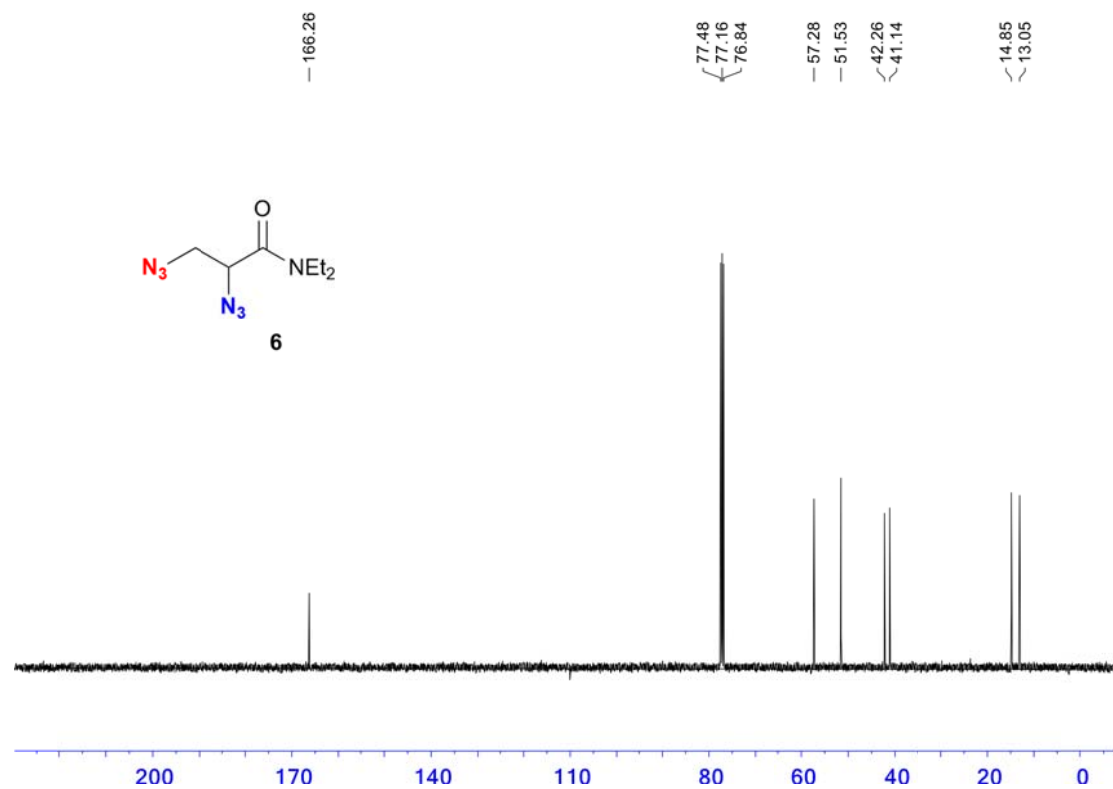
Compound **5** ^{13}C NMR



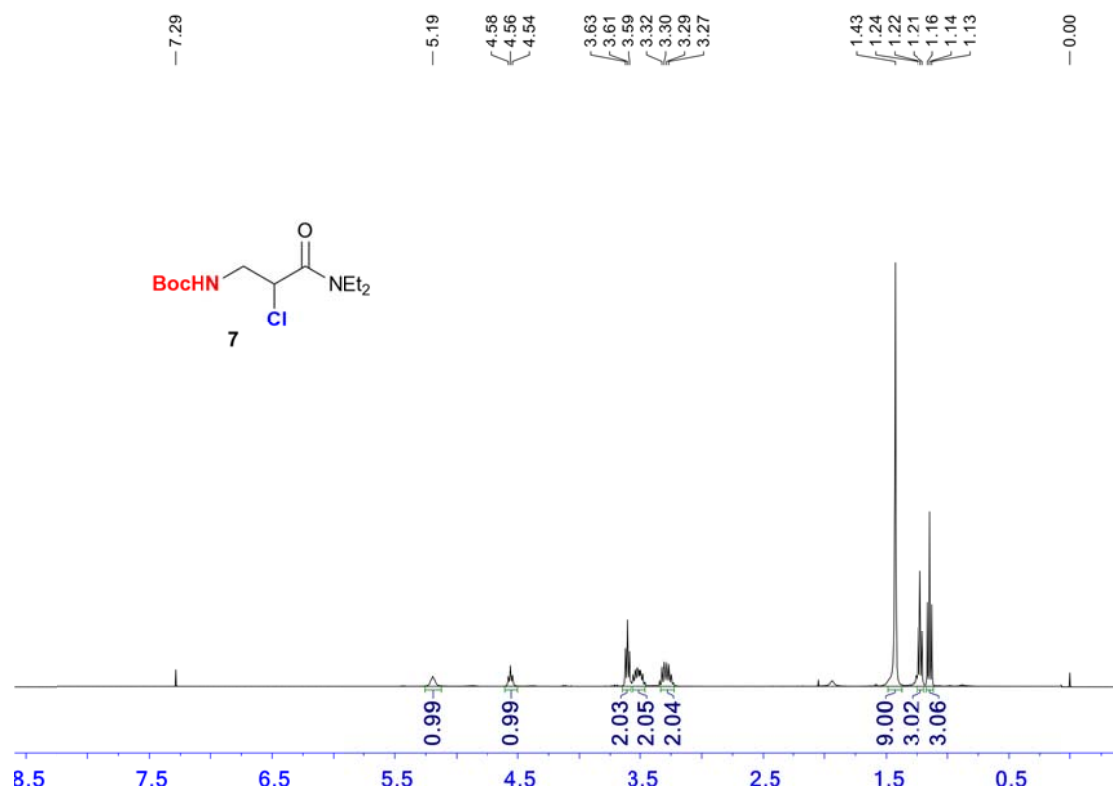
Compound **6** ^1H NMR



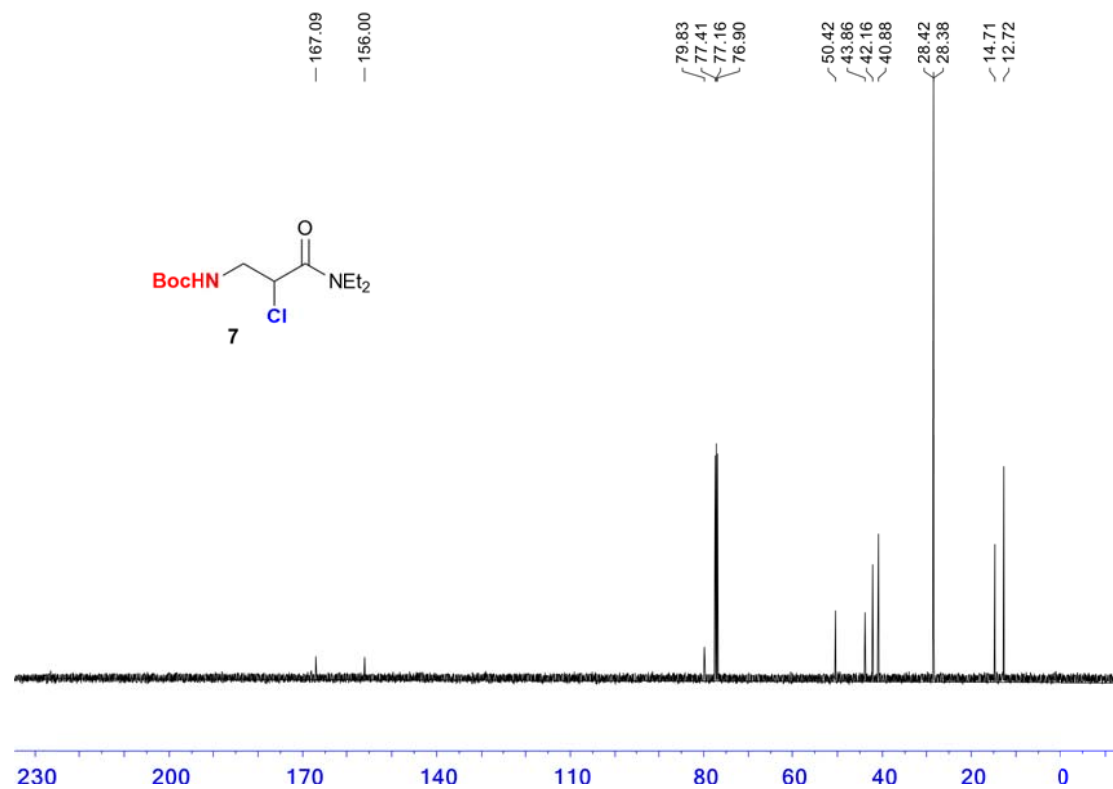
Compound **6** ^{13}C NMR



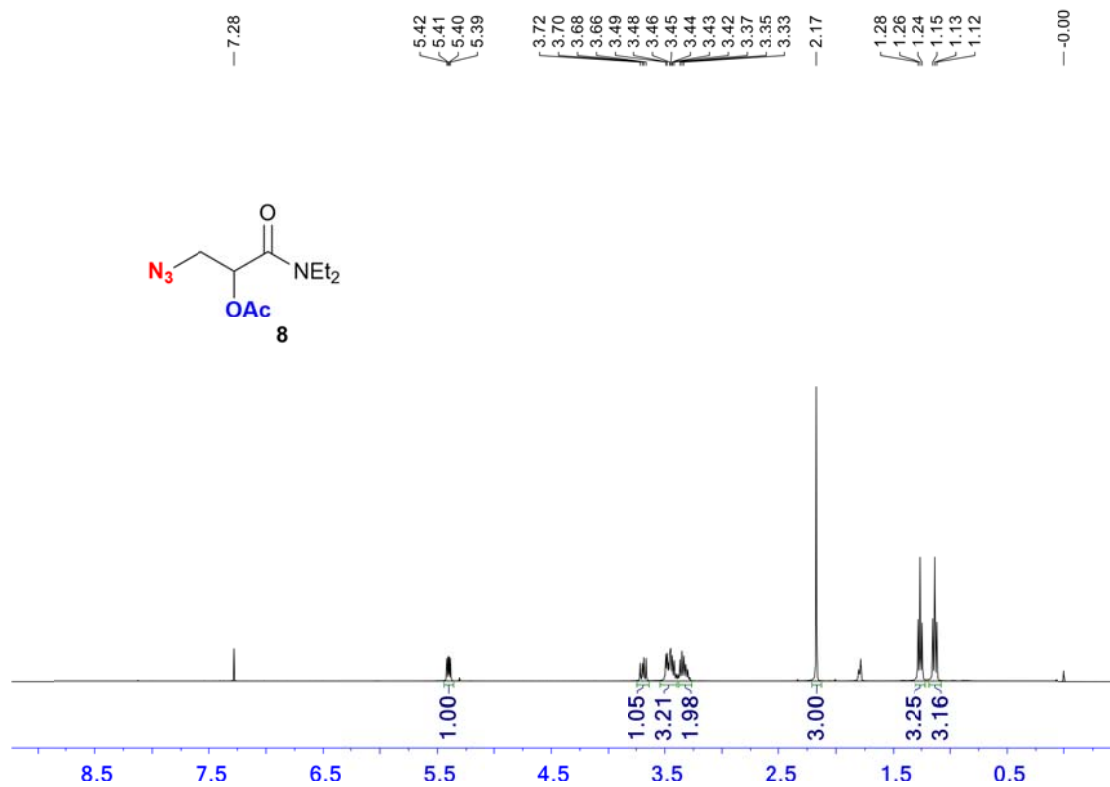
Compound 7 ¹H NMR



Compound 7 ¹³C NMR



Compound **8** ^1H NMR



Compound **8** ^{13}C NMR

