Supporting Information

Copper catalysed alkynylation of tertiary amines with CaC_2 via sp^3 C-H activation

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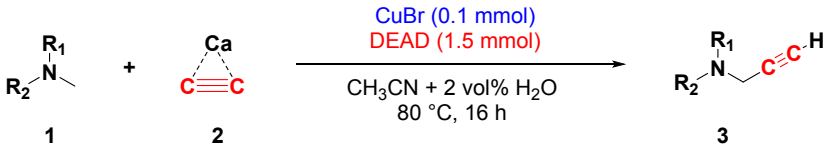
General Information

All solvents and chemicals used were obtained from commercial suppliers and used directly without any pre-treatment, unless otherwise indicated. All reactions were set up under argon atmosphere unless otherwise stated.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F-254 silica gel plates with visualization by ultraviolet light (254 nm) and/or I_2 stain. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV-400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) with the residual solvent peak of tetramethylsilane used as the internal standard at 0.00 ppm. ^1H NMR data are reported in the following order: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constants (J, Hz), integration and assignment. High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-QII spectrometer.

General Experimental Procedure

Preparation of Propargylamines



In a 8 mL pressure vial, CaC_2 (2.5 mmol) and CuBr (0.1 mmol) were added. The vial was then purged and refilled with argon thrice before CH_3CN + 2 vol% H_2O (5 mL), aliphatic amine (0.5 mmol) and DEAD (1.5 mmol) were added to the vial using a syringe. The reaction was stirred at 80 °C for 16 h, cooled to room temperature before it was diluted with H_2O (10 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was further purified by column chromatography on silica gel to afford the corresponding aliphatic propargylamine. For aromatic amines, CH_3CN (5 mL) and t-BuOOH (2 mmol) were used instead. The NMR spectra data of compounds **3b**[1], **3f**[2], **3g**[3] and **5b**[4] are available in the literature and are referenced accordingly.

***N*-methyl-*N*-(prop-2-yn-1-yl)cyclohexanamine (3a)**

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/8) to give the product as a light yellow liquid (139 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.42 (d, *J* = 2.4 Hz, 2H, CH_2), 2.39 – 2.31 (m, 1H, CH), 2.35 (s, 3H, CH_3), 2.19 (t, *J* = 2.5 Hz, 1H, C≡CH), 1.92 – 1.90 (m, 2H, CH_2), 1.78 – 1.75 (m, 2H, CH_2), 1.62 – 1.59 (m, 1H, CH_2), 1.31 – 1.08 (m, 5H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 79.8, 72.6, 60.7, 42.9, 38.5, 29.8, 26.0, 25.5; HRMS (EI) *m/z* calcd. for $C_{10}H_{17}N$ 151.1361; found 151.1358

***N*-cyclohexyl-*N*-(prop-2-yn-1-yl)cyclohexanamine (3b)[1]**

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/10) to give the product as a light yellow liquid (104 mg, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.47 (d, *J* = 2.4 Hz, 2H, CH_2), 2.78 – 2.72

(tt, J = 10.8, 3.3 Hz, 2H, CH), 2.12 (t, J = 2.4 Hz, 1H, C≡CH), 1.85 – 1.75 (m, 8H, CH_2), 1.62 – 1.59 (m, 2H, CH_2), 1.34 – 1.05 (m, 10H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 83.9, 71.0, 57.3, 34.8, 31.2, 26.3, 26.2

***N*-methyl-*N*-(prop-2-yn-1-yl)hexan-1-amine (3e)**

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/10) to give the product as a light yellow liquid (54 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.34 (d, J = 2.4 Hz, 2H, CH_2), 2.39 (t, J = 7.6 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.21 (t, J = 2.4 Hz, 1H, C≡CH), 1.47 – 1.40 (m, 2H, CH_2), 1.32 – 1.26 (m, 6H, CH_2), 0.91 – 0.85 (m, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 78.7, 73.0, 55.8, 45.5, 41.8, 31.8, 27.6, 27.1, 22.7, 14.1; HRMS (EI) *m/z* calcd. for $C_{10}H_{19}N$ 153.1518; found 153.1511

***N*-benzyl-*N*-methylprop-2-yn-1-amine (3f)[2]**

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/16) to give the product as a light yellow liquid (63 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 5H, Ar-H), 3.57 (s, 2H, CH_2), 3.31 (d, J = 2.4 Hz, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.28 (t, J = 2.4 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.3, 129.2, 128.3, 127.3, 78.5, 73.5, 60.0, 44.8, 41.8

3-(methyl(prop-2-yn-1-yl)amino)propanenitrile (3g)[3]

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/5) to give the product as a light yellow oil (45 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.42 (d, J = 2.4 Hz, 2H, CH_2), 2.78 (t, J = 6.9 Hz, 2H, CH_2), 2.51 (t, J = 7.0 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.27 (t, J = 2.4 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 118.6, 77.5, 73.9, 50.8, 45.4, 41.4, 16.6

1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (3h)

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/6) to give the product as an orange oil (68 mg, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.10 (m, 4H, Ar-H), 4.51 (br s, 1H, CH),

3.02 – 2.92 (m, 2H, CH_2), 2.89 – 2.80 (m, 1H, CH_2), 2.74 – 2.65 (m, 1H, CH_2), 2.56 (s, 3H, CH_3), 2.41 (d, *J* = 2.3 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.8, 133.4, 129.0, 127.4, 127.1, 126.0, 81.6, 74.2, 56.1, 48.2, 43.5, 28.7; HRMS (EI) *m/z* calcd. for $C_{12}H_{13}N$ 171.1048; found 171.1042

1-(prop-2-yn-1-yl)piperidine (3i)

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/4) to give the product as a light yellow liquid (44 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.28 (d, *J* = 2.5 Hz, 2H, CH_2), 2.58 – 2.43 (m, 4H, CH_2), 2.23 (t, *J* = 2.4 Hz, 1H, C≡CH), 1.65 – 1.59 (m, 4H, CH_2), 1.48 – 1.39 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 79.3, 72.8, 53.2, 47.6, 25.9, 23.9; HRMS (EI) *m/z* calcd. for $C_8H_{13}N$ 123.1048; found 123.1048

Ethyl 1-(prop-2-yn-1-yl)piperidine-4-carboxylate (3j)

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/2) to give the product as a light yellow liquid (76 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H, CH_2), 3.31 (d, *J* = 2.4 Hz, 2H, CH_2), 2.91 – 2.83 (dt, *J* = 11.9, 3.8 Hz, 2H, CH_2), 2.32 – 2.22 (m, 3H, overlapping CH_2, CH), 2.25 (t, *J* = 2.4 Hz, 1H, C≡CH), 1.99 – 1.90 (m, 2H, CH_2), 1.85 – 1.73 (m, 2H, CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0, 78.8, 73.2, 60.4, 51.6, 47.1, 40.7, 28.2, 14.2; HRMS (EI) *m/z* calcd. for $C_{11}H_{17}NO_2$ 195.1259; found 195.1253

4-chloro-1-(prop-2-yn-1-yl)piperidine (3k)

This compound was prepared according to general procedure and isolated by column chromatography (ethyl acetate/hexane = 1/2) to give the product as a light yellow liquid (55 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.04 (br s, 1H, CH), 3.29 (d, *J* = 2.5 Hz, 2H, CH_2), 2.81 – 2.78 (m, 2H, CH_2), 2.46 – 2.41 (m, 2H, CH_2), 2.25 (t, *J* = 2.5 Hz, 1H, C≡CH), 2.14 – 2.10 (m, 2H, CH_2), 1.97 – 1.90 (m, 2H, CH_2); **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 78.7, 73.3, 56.7, 49.9, 46.9, 35.4; HRMS (EI) *m/z* calcd. for $C_8H_{12}ClN$ 157.0658; found 157.0654

_N_-methyl-_N_-(prop-2-yn-1-yl)aniline (5a)

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/4) to give the product as a yellow oil (54 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H, Ar-H), 6.90 – 6.79 (m, 3H, Ar-H), 4.06 (d, *J* = 2.3 Hz, 2H, CH_2), 2.98 (s, 3H, CH_3), 2.17 (t, *J* = 2.4 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0, 129.1, 118.4, 114.3, 79.3, 72.0, 42.5, 38.6; HRMS (EI) *m/z* calcd. for $C_{10}H_{11}N$ 145.0892; found 145.0887

_N_,4-dimethyl-_N_-(prop-2-yn-1-yl)aniline (5b)[4]

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/1) to give the product as a yellow oil (48 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.79 (d, *J* = 8.4 Hz, 2H, Ar-H), 4.01 (d, *J* = 2.3 Hz, 2H, CH_2), 2.93 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.15 (t, *J* = 2.3 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.0, 129.7, 127.9, 114.9, 79.3, 72.1, 43.0, 38.9, 20.4

4-(tert-butyl)-_N_-methyl-_N_-(prop-2-yn-1-yl)aniline (5c)

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/2) to give the product as a yellow oil (48 mg, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.84 (d, *J* = 8.9 Hz, 2H, Ar-H), 4.04 (d, *J* = 2.4 Hz, 2H, CH_2), 2.97 (s, 3H, CH_3), 2.19 (t, *J* = 2.4 Hz, 1H, C≡CH), 1.31 (s, 9H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.8, 141.1, 126.0, 114.2, 79.5, 72.1, 42.6, 38.8, 33.9, 31.5; HRMS (EI) *m/z* calcd. for $C_{14}H_{19}N$ 201.1518; found 201.1510

2,6-diisopropyl-_N_-methyl-_N_-(prop-2-yn-1-yl)aniline (5d)

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/2) to give the product as a yellow oil (58 mg, 51%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 1H, Ar-H), 7.10 – 7.08 (m, 2H, Ar-H),

3.82 (d, J = 2.5 Hz, 2H, CH_2), 3.34 (m, 2H, CH), 2.90 (s, 3H, CH_3), 2.23 (t, J = 2.5 Hz, 1H, C≡CH), 1.21 (dd, J = 6.9, 1.8 Hz, 12H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.3, 145.9, 126.7, 124.0, 81.6, 71.2, 45.6, 41.1, 28.4, 24.5; HRMS (EI) *m/z* calcd. for $C_{16}H_{23}N$ 229.1831; found 229.1825

2-bromo-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline (5e)

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/3) to give the product as a yellow oil (77 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 1H, Ar-H), 7.30 – 7.21 (m, 2H, Ar-H), 6.96 – 6.92 (m, 1H, Ar-H), 3.94 (d, J = 2.4 Hz, 2H, CH_2), 2.88 (s, 3H, CH_3), 2.24 (t, J = 2.4 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 133.8, 128.0, 125.0, 122.7, 119.7, 78.9, 73.2, 45.3, 40.1; HRMS (EI) *m/z* calcd. for $C_{10}H_{10}BrN$ 222.9997; found 222.9991

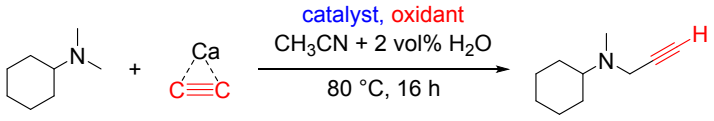
2-chloro-*N*-methyl-*N*-(prop-2-yn-1-yl)aniline (5f)

This compound was prepared according to general procedure and isolated by column chromatography (toluene/hexane = 1/2) to give the product as a yellow oil (54 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 1H, Ar-H), 7.26 – 7.20 (m, 2H, Ar-H), 7.02 – 6.98 (m, 1H, Ar-H), 3.96 (d, J = 2.4 Hz, 2H, CH_2), 2.89 (s, 3H, CH_3), 2.23 (t, J = 2.4 Hz, 1H, C≡CH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.8, 130.6, 128.7, 127.3, 124.3, 122.1, 78.9, 73.2, 44.8, 39.9; HRMS (EI) *m/z* calcd. for $C_{10}H_{10}ClN$ 179.0502; found 179.0495

Procedure for Sonogashira Coupling of Propargylamine

In a 8 mL pressure vial, CuI (0.09 mmol, 17 mg) and $Pd(PPh_3)_4$ (0.03 mmol, 34.7 mg) were added. The vial was then purged and refilled with argon thrice before CH_3CN (3 mL), propargylamine **3a** (1.0 mmol, 151 mg), Et_3N (5 mmol, 0.7 mL) and PhI (1 mmol, 0.11 mL) were added to the vial using a syringe. The reaction was stirred at 60 °C for 17 h and cooled to room temperature. The resulting mixture was concentrated *in vacuo* and the residue was further purified by column chromatography on silica gel (EA/hexane = 1/8) to afford the corresponding *N*-methyl-*N*-(3-phenylprop-2-yn-1-yl)cyclohexanamine[4] as a yellow oil (188 mg, 83 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H, Ar-H), 7.33 – 7.27 (m, 3H, Ar-H), 3.64 (s, 2H, CH_2), 2.49 – 2.39 (m, 1H, CH), 2.42 (s, 3H, CH_3), 2.01 – 1.93 (m, 2H, CH_2), 1.85 – 1.76 (m, 2H, CH_2), 1.67 – 1.58 (m, 1H, CH_2), 1.34 – 1.07 (m, 5H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.7, 128.3, 127.9, 123.5, 85.7, 84.8, 61.0, 43.7, 38.6, 29.9, 26.1, 25.6 The NMR spectrum data of this compound is available in the literature and referenced accordingly.

Table S1. Catalysts and oxidants screening [a]



Entry	Catalyst	Oxidant	Yield[b] (%)
1	CuBr	*t*-BuOOH in decane	47
2	CuBr	*t*-BuOOH in water	40
3	CuBr	Cumene hydroperoxide	44
4	CuBr	Di-*t*-butyl peroxide	trace
5	CuBr	H_2O_2	trace
6	CuBr	$KMnO_4$ / NBS / I_2	NR

[a] Reaction conditions: Amine (1 mmol), CaC_2 (2.5 mmol), catalyst (10 mol%), oxidant (1.5 eq.), CH_3CN + 2 vol% H_2O (5 mL), 80 °C, 16 h. [b] NMR yield.

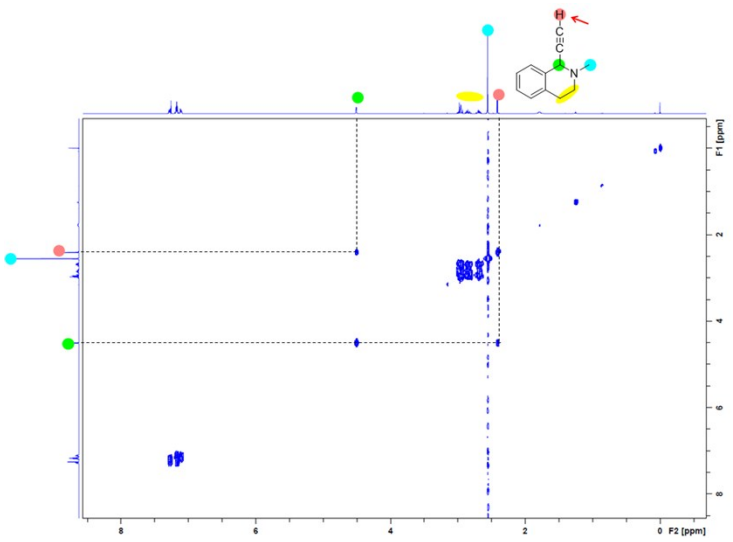
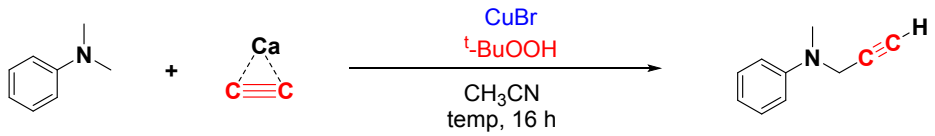


Figure S1. COSY NMR of **3h**

Table S2. Optimization of reaction conditions for *N,N*-dimethylaniline



Entry	Amine (mmol)	t-BuOOH (mmol)	CuBr (mmol)	H_2O added (vol%)	Additive (eq.)	Temp (°C)	Yield[a] (%)
1	0.5	2	0.10	-	-	80	70
2	0.5	2	0.10	0.25	-	80	66
3	0.5	2	0.10	1	-	80	45
4	0.5	2	0.10	2	-	80	5
5	0.5	2	0.10	-	TBAB (1)	80	20
6	0.5	2	0.15	-	-	80	59
7	0.5	2	0.20	-	-	80	50
8	0.5	1	0.10	-	-	80	43
9	0.5	2.5	0.10	-	-	80	60
10	0.5	3	0.10	-	-	80	57

11	**0.5**	**2**	**0.10**	**-**	**-**	**90**	**79**
12	0.5	2	0.10	-	-	100	60

[a] NMR yield.

Table S3. Optimization of reaction conditions for 4,4'-trimethylenebis(1-methylpiperidine) **6**

Entry	DEAD (mmol)	Temp (°C)	Time (h)	Total Yield[a] (%)	Mono- : Di-product[a] (%)
1	3	120	16	77	62 : 15
2	4	120	16	87	58 : 29
3	4	140	16	75	41 : 34
4	4	120	32	65	35 : 30

[a] NMR yield.

References

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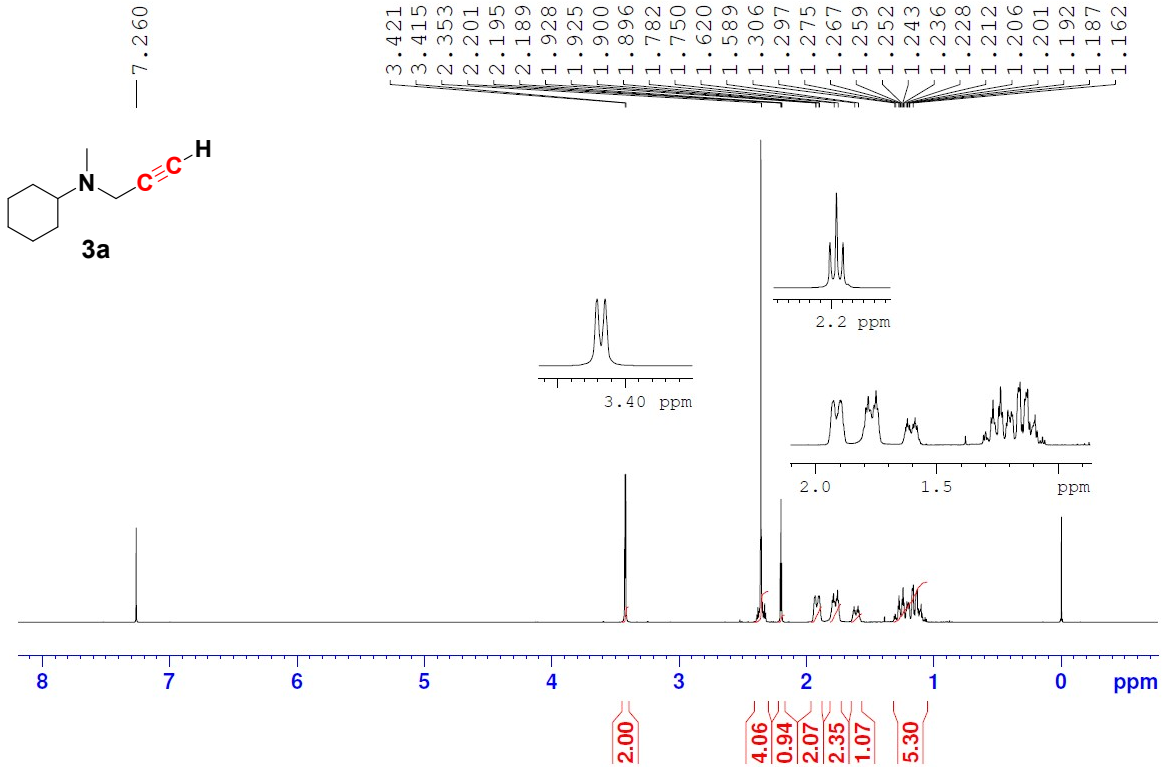
[3] Y. Zhou, J. A. Porco, Jr., J. K. Snyder , *Org. Lett.*, **2007**, 9, 393

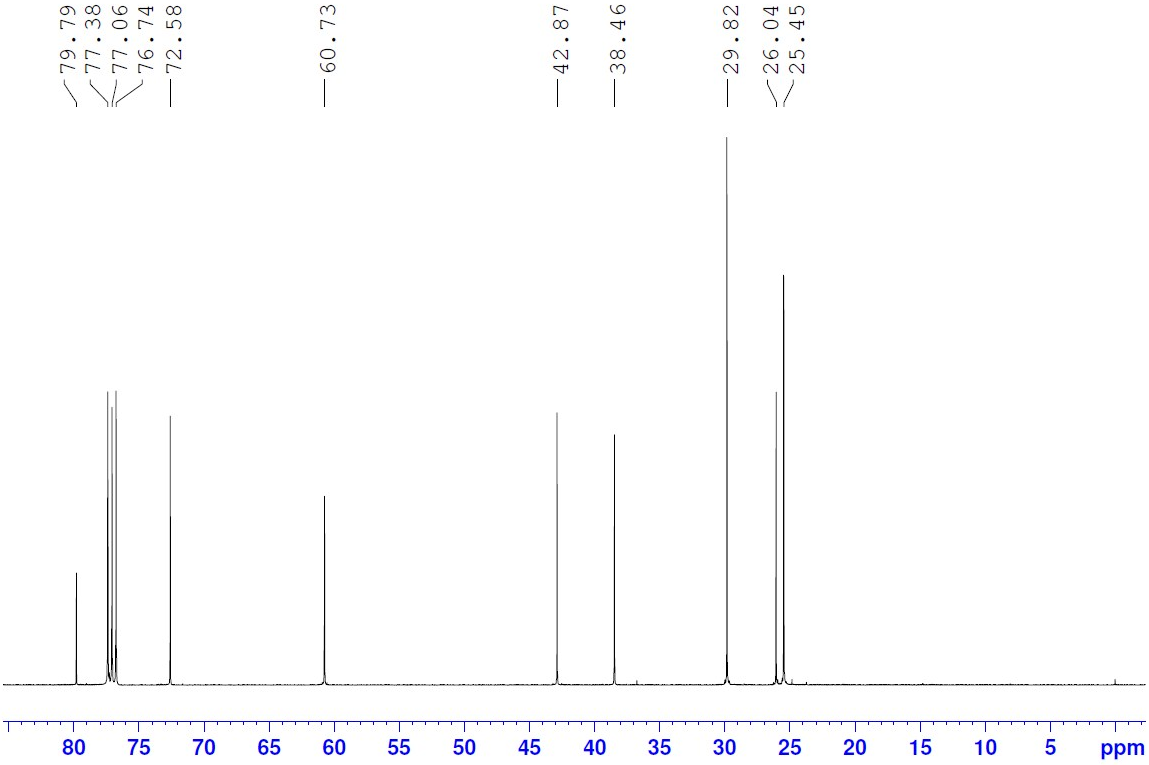
[4] C. M. R. Volla, P. Vogel, *Org. Lett.*, **2009**, 11, 1701

^{1}H and ^{13}C NMR Spectra of Propargylamines

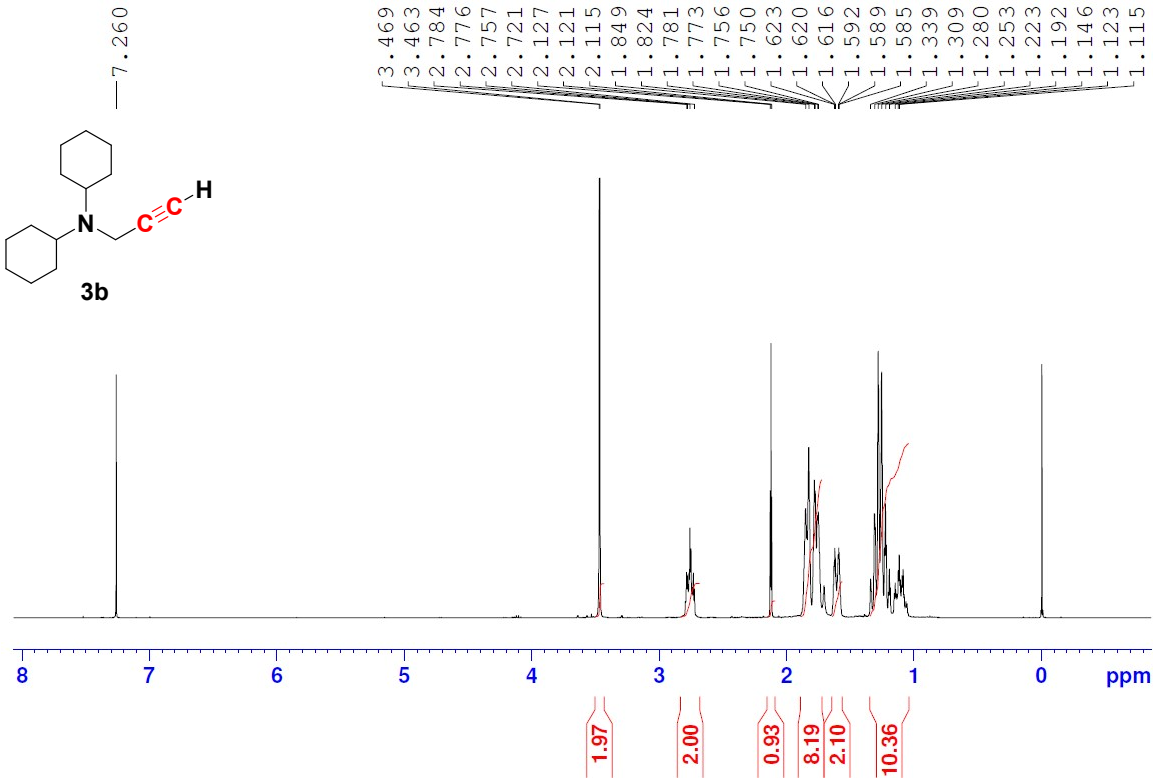
^{1}H NMR, $CDCl_3$, 400 MHz



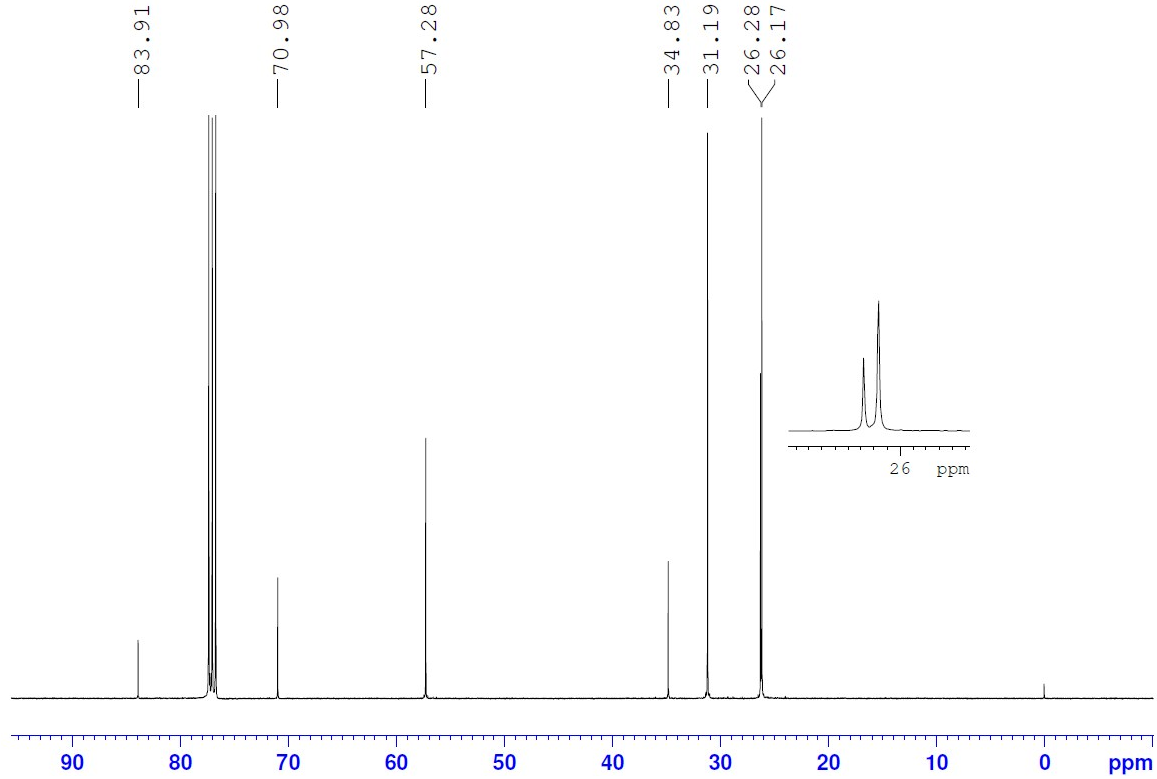
^{13}C NMR, $CDCl_3$, 101 MHz



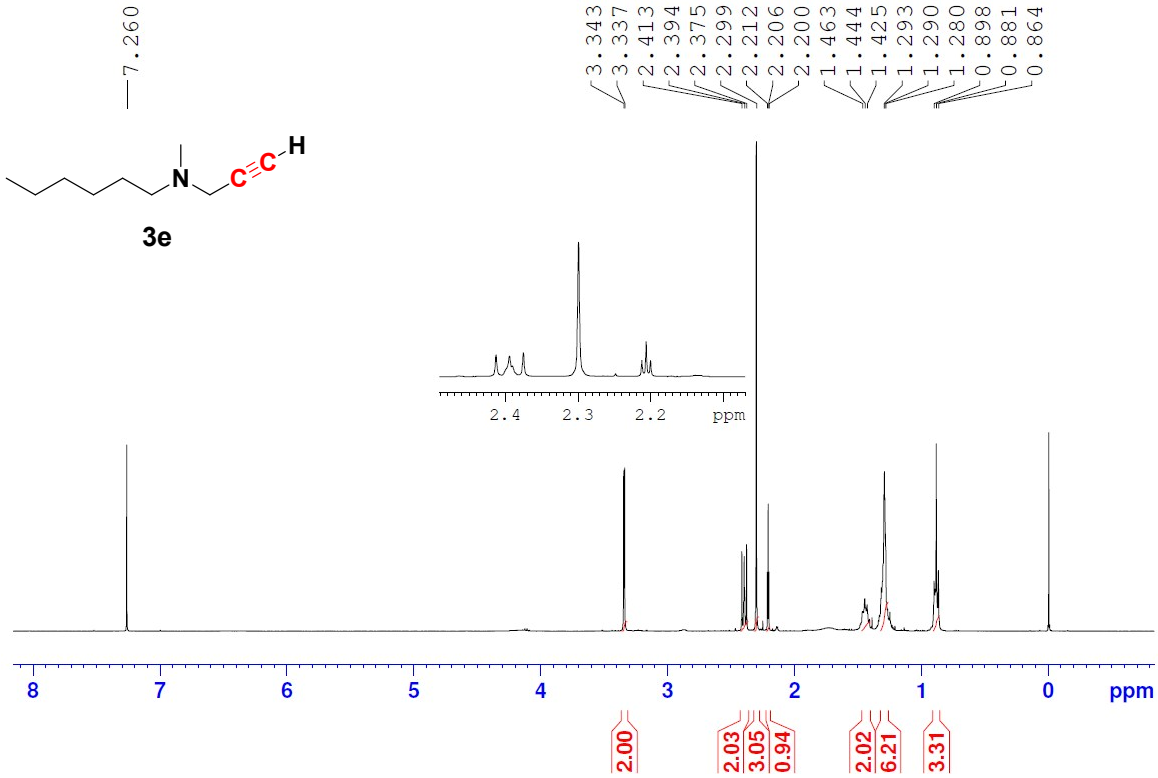
^{1}H NMR, $CDCl_3$, 400 MHz



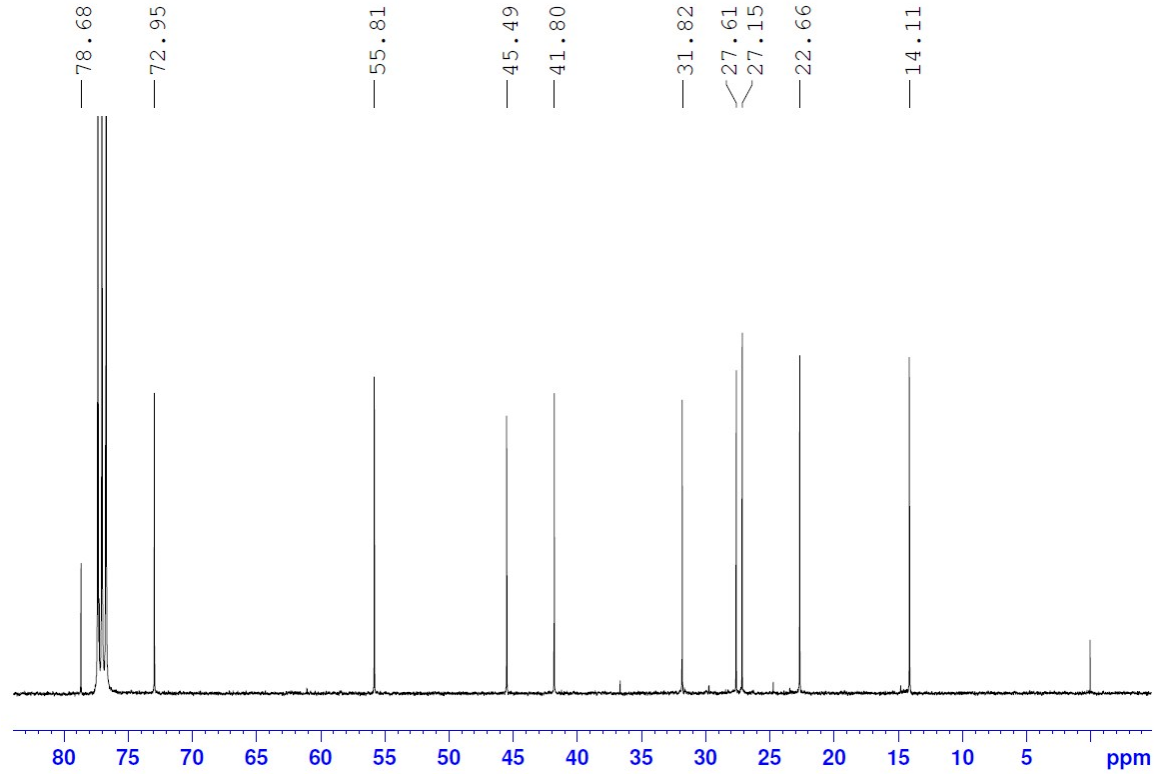
^{13}C NMR, $CDCl_3$, 101 MHz



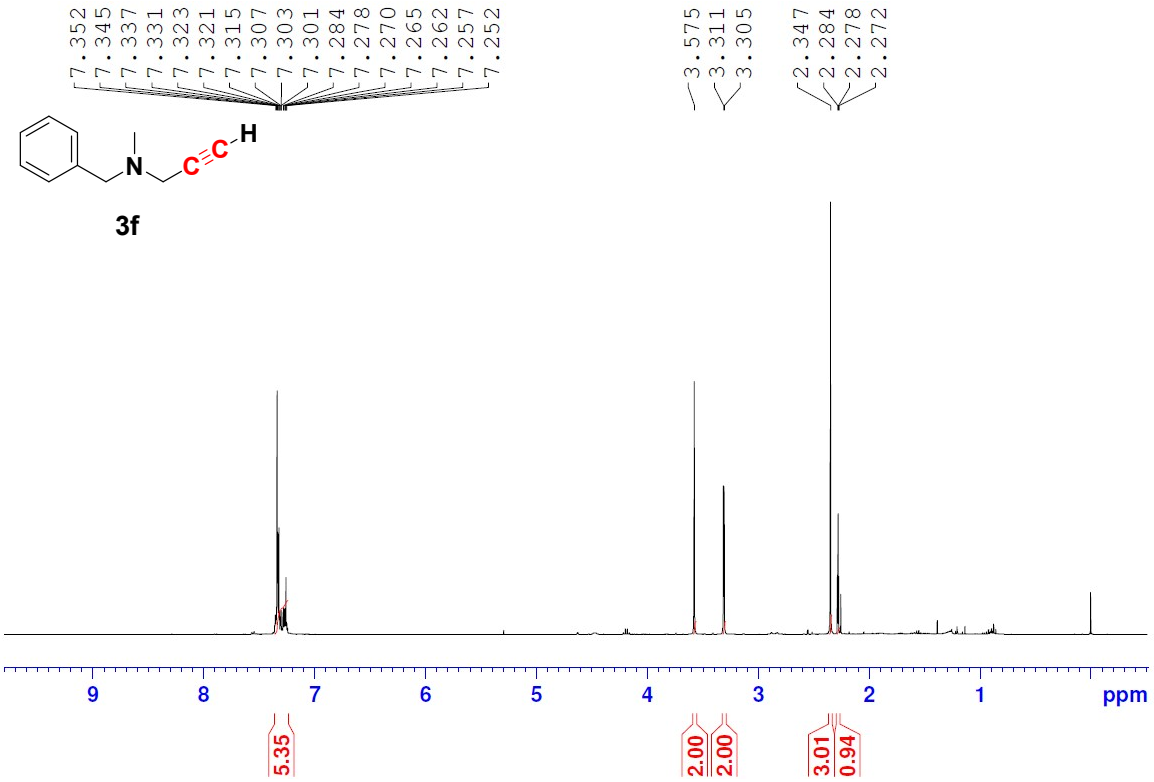
^{1}H NMR, $CDCl_3$, 400 MHz



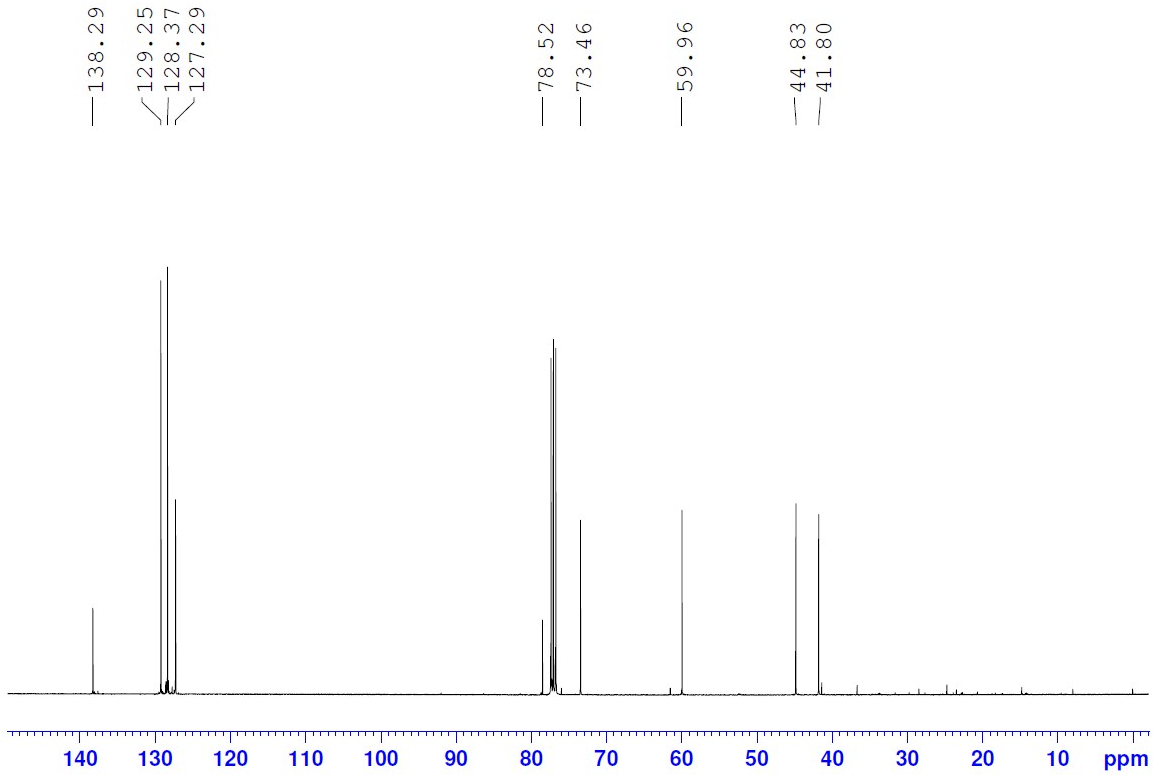
^{13}C NMR, $CDCl_3$, 101 MHz



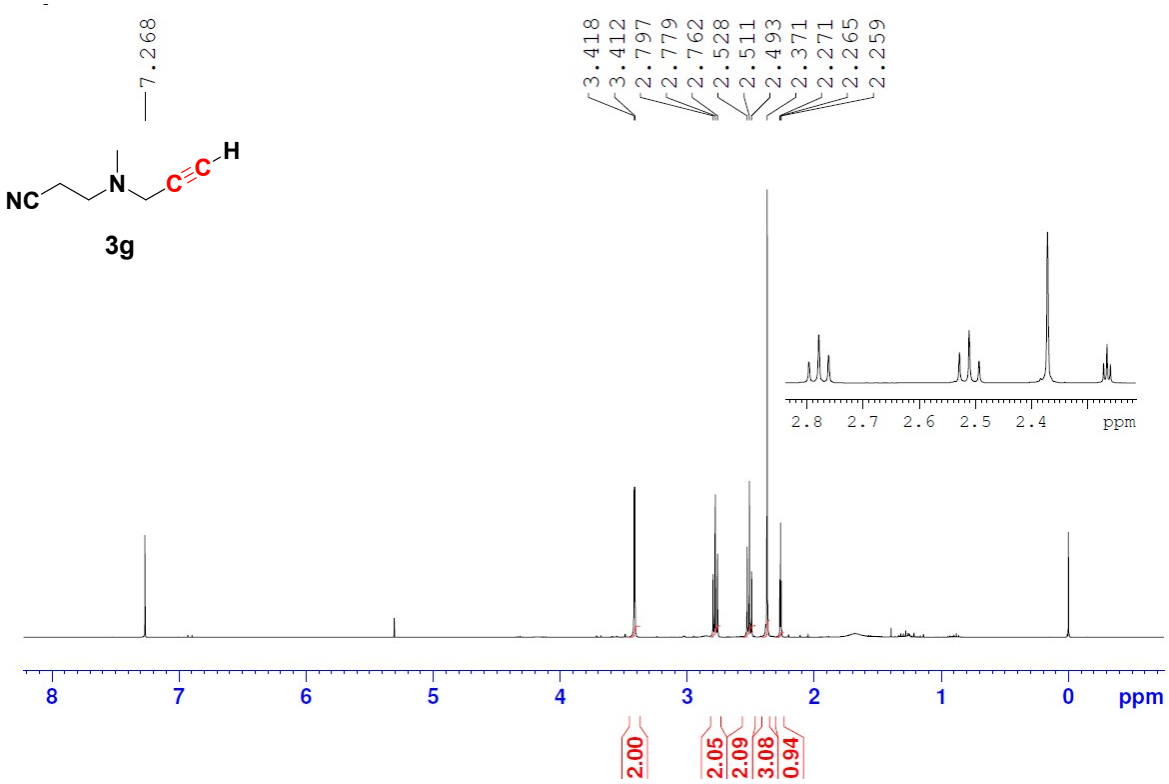
^{1}H NMR, $CDCl_3$, 400 MHz



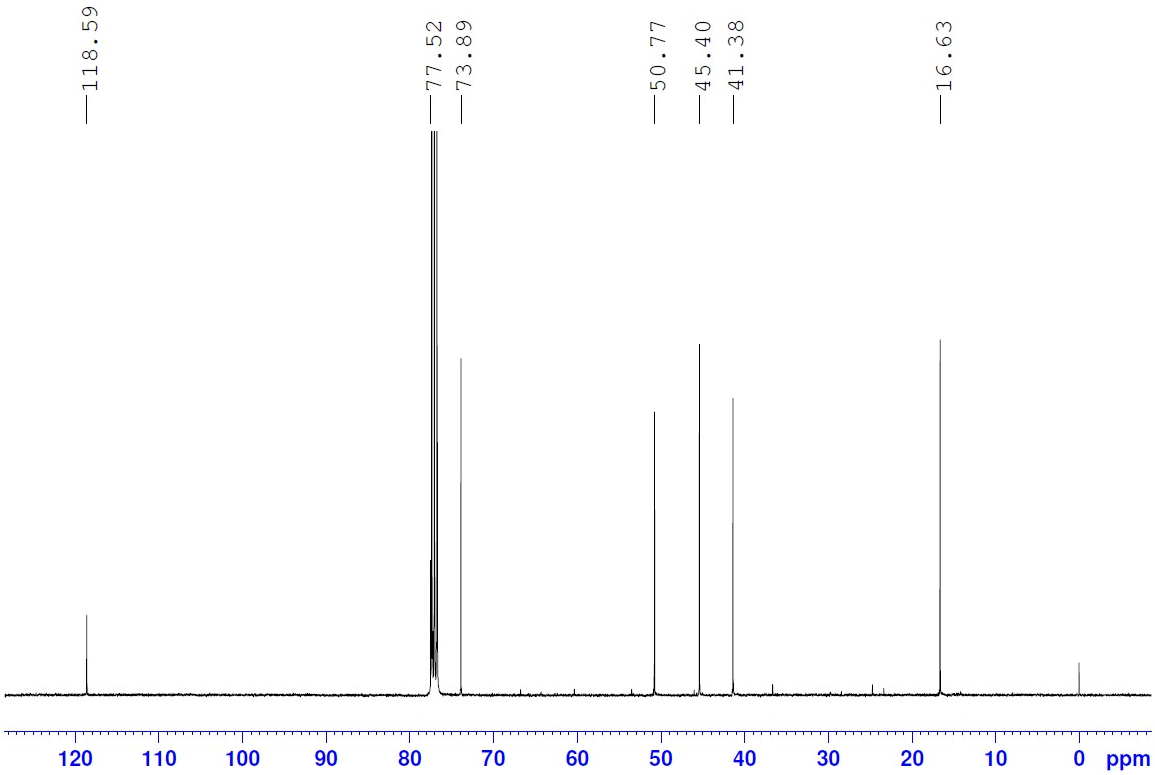
^{13}C NMR, $CDCl_3$, 101 MHz



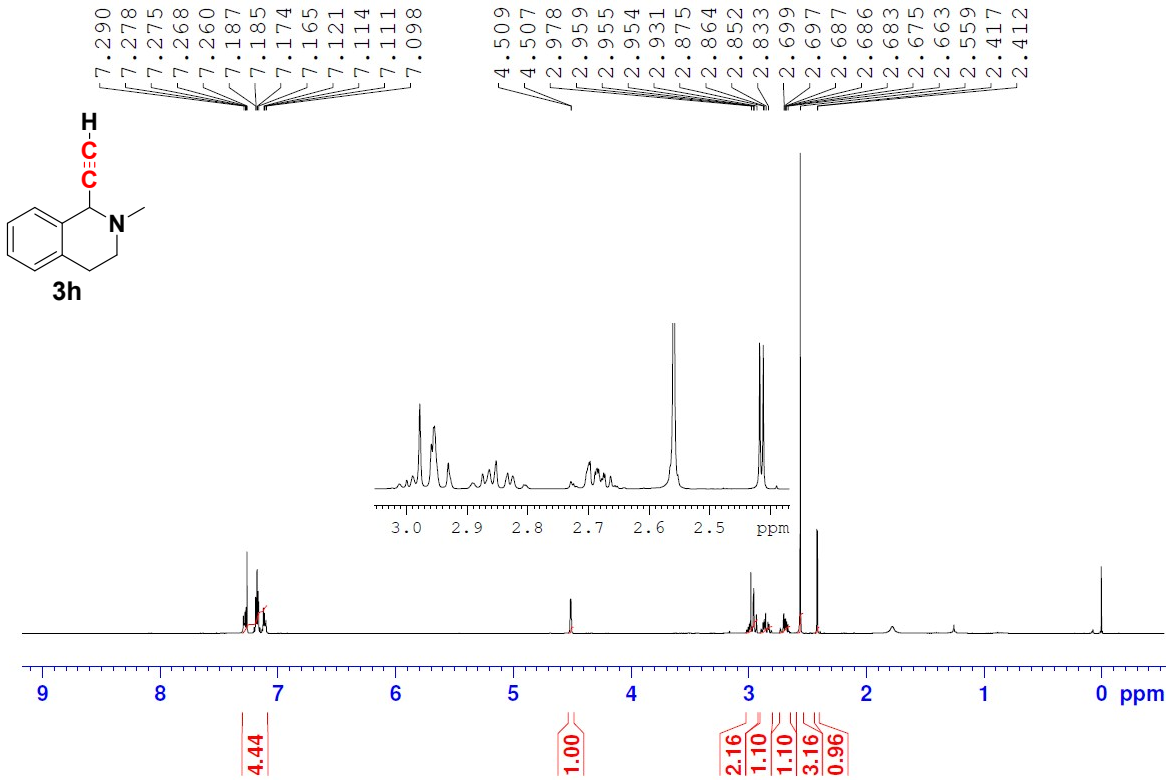
^{1}H NMR, $CDCl_3$, 400 MHz



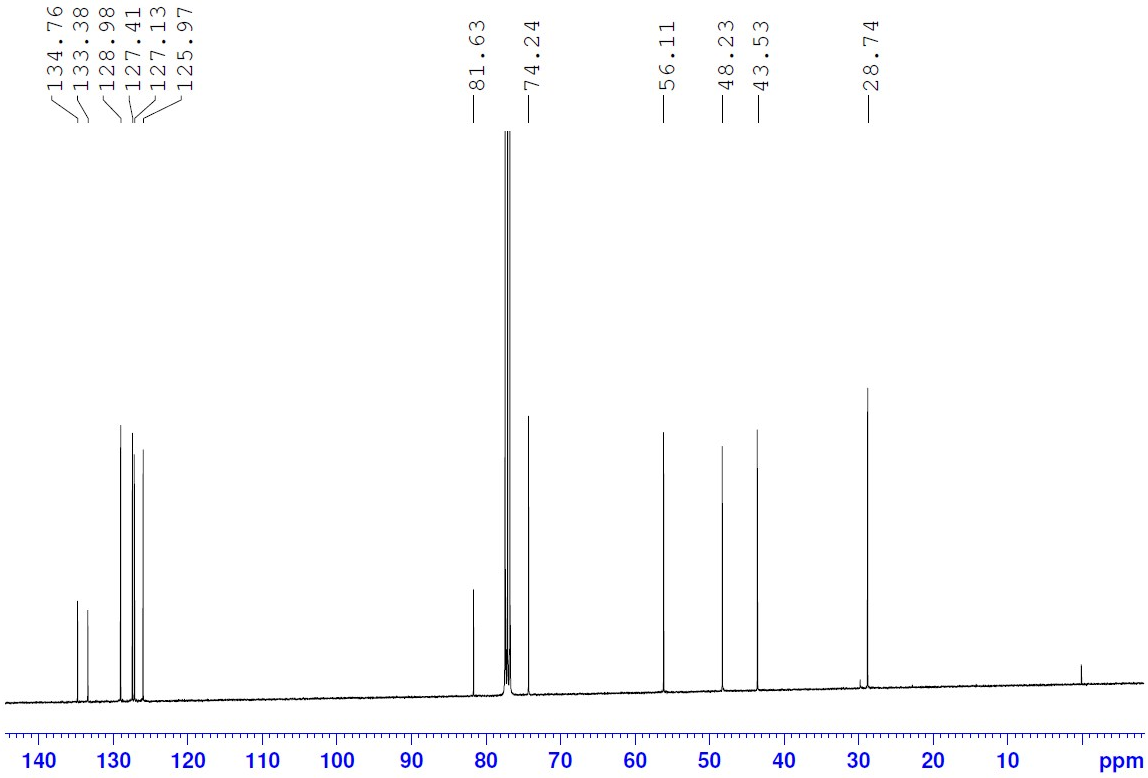
^{13}C NMR, $CDCl_3$, 101 MHz



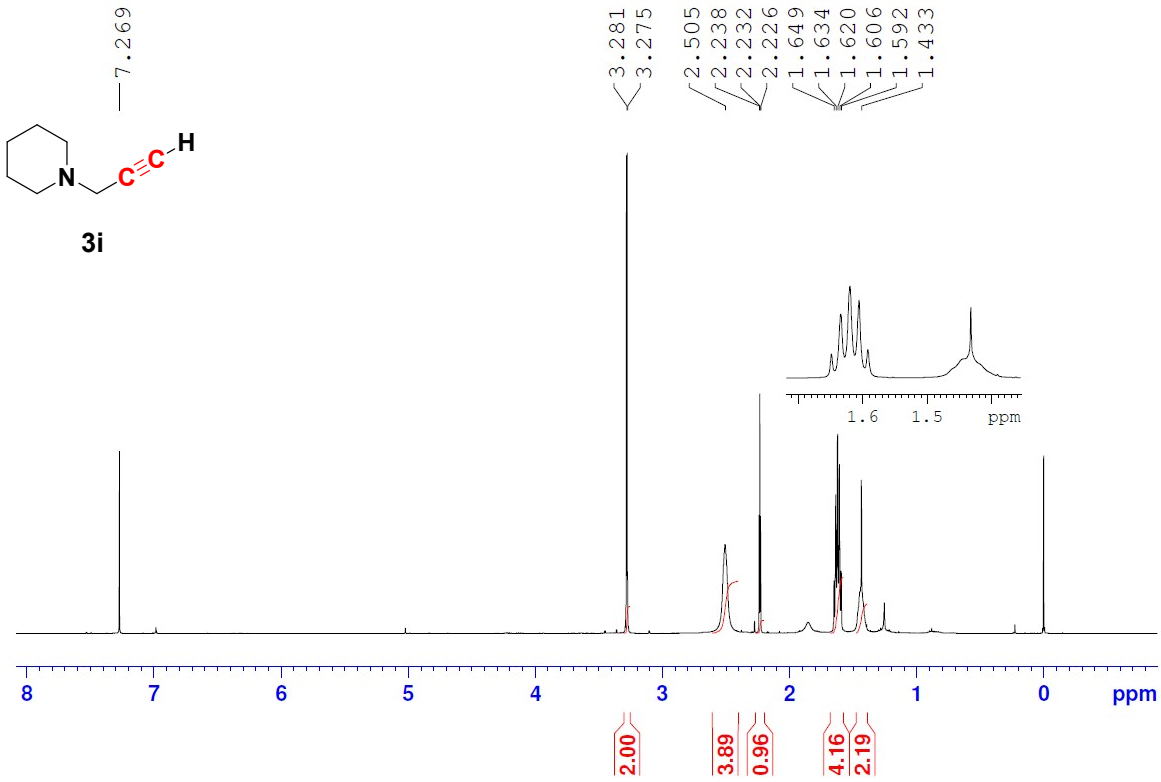
^{1}H NMR, $CDCl_3$, 400 MHz



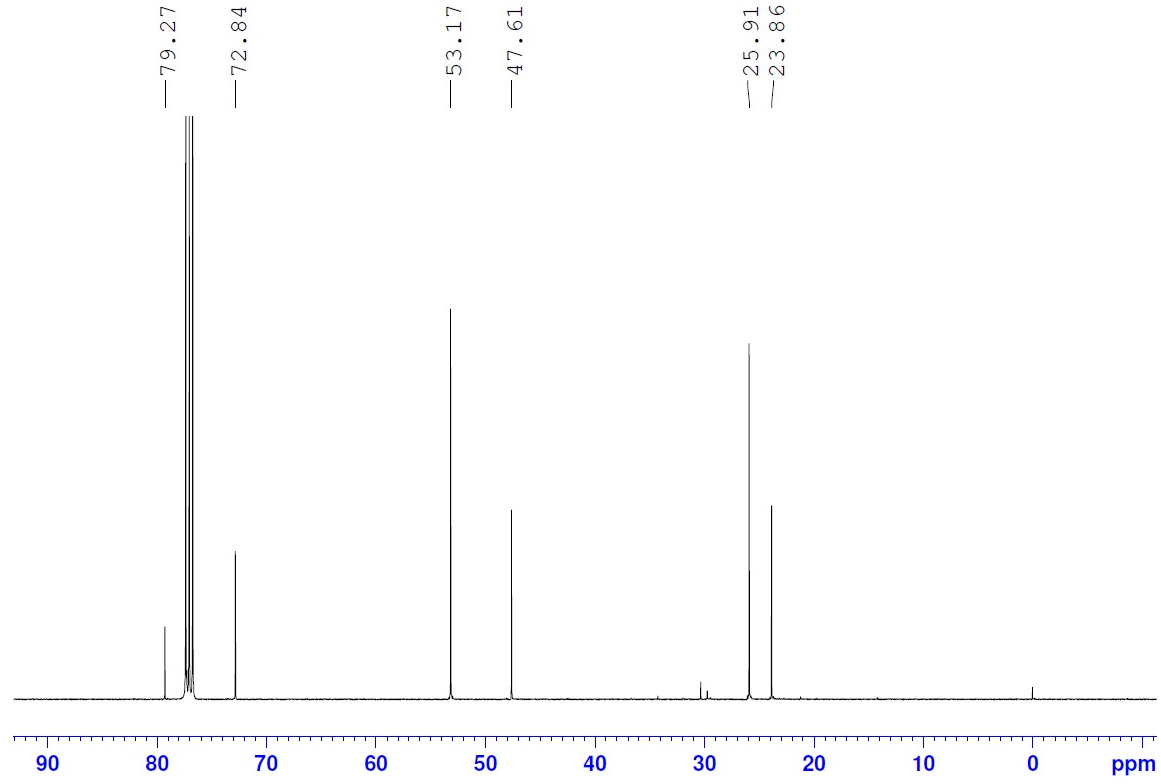
^{13}C NMR, $CDCl_3$, 101 MHz



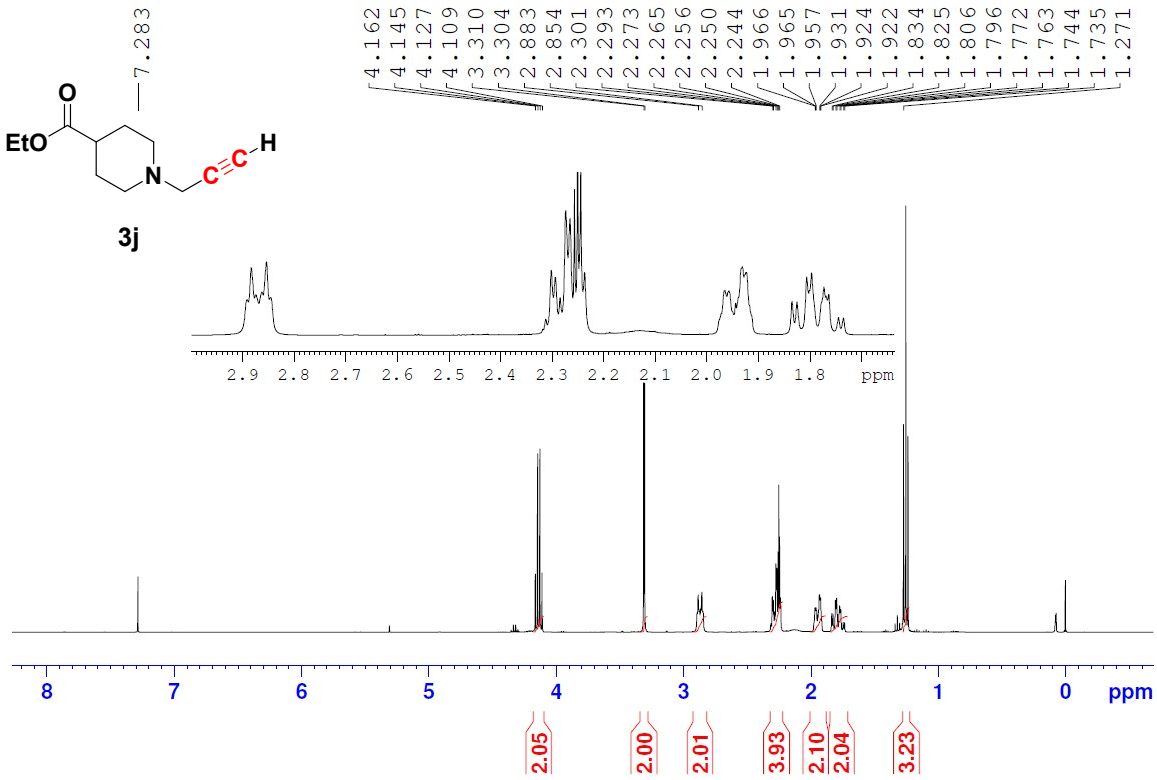
^{1}H NMR, $CDCl_3$, 400 MHz



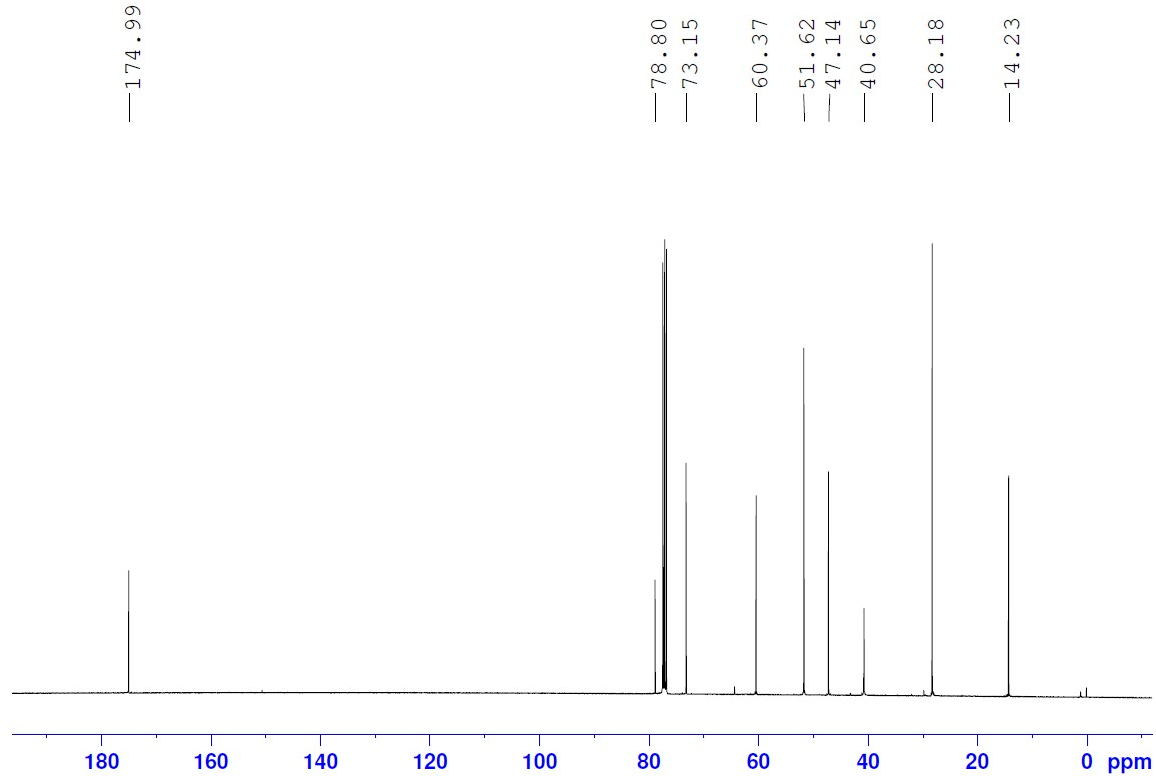
^{13}C NMR, $CDCl_3$, 101 MHz



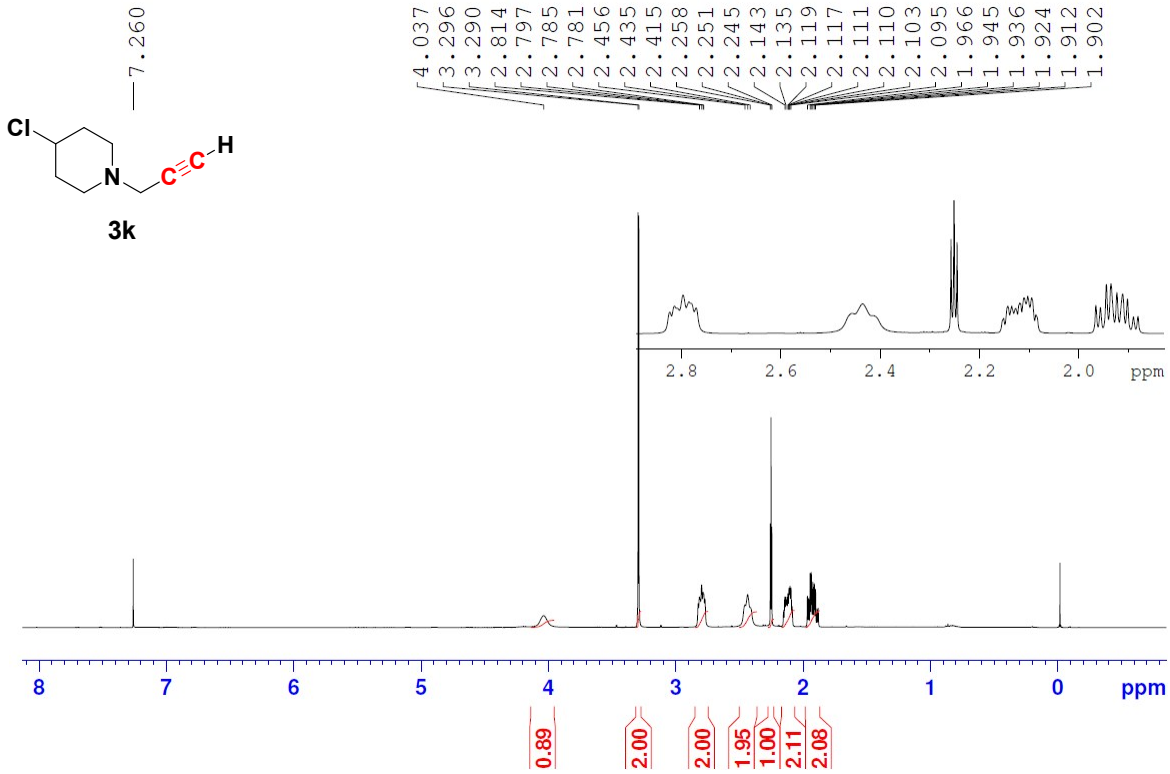
^{1}H NMR, $CDCl_3$, 400 MHz



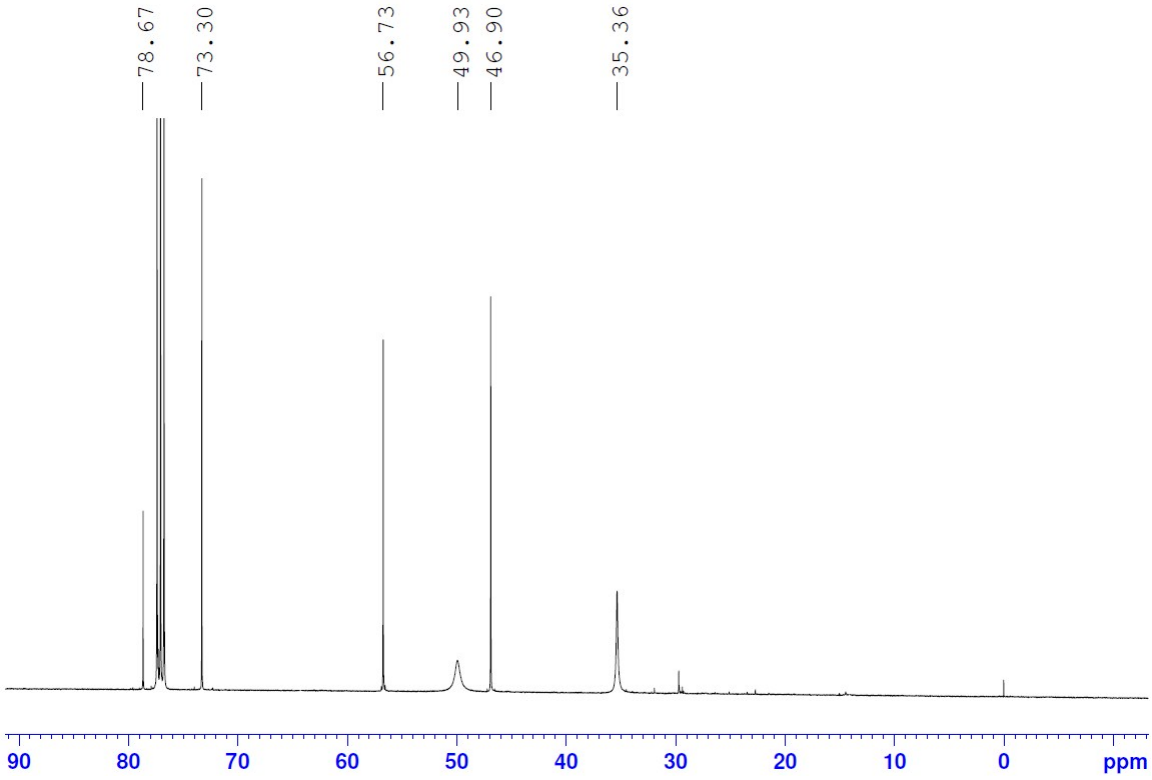
^{13}C NMR, $CDCl_3$, 101 MHz



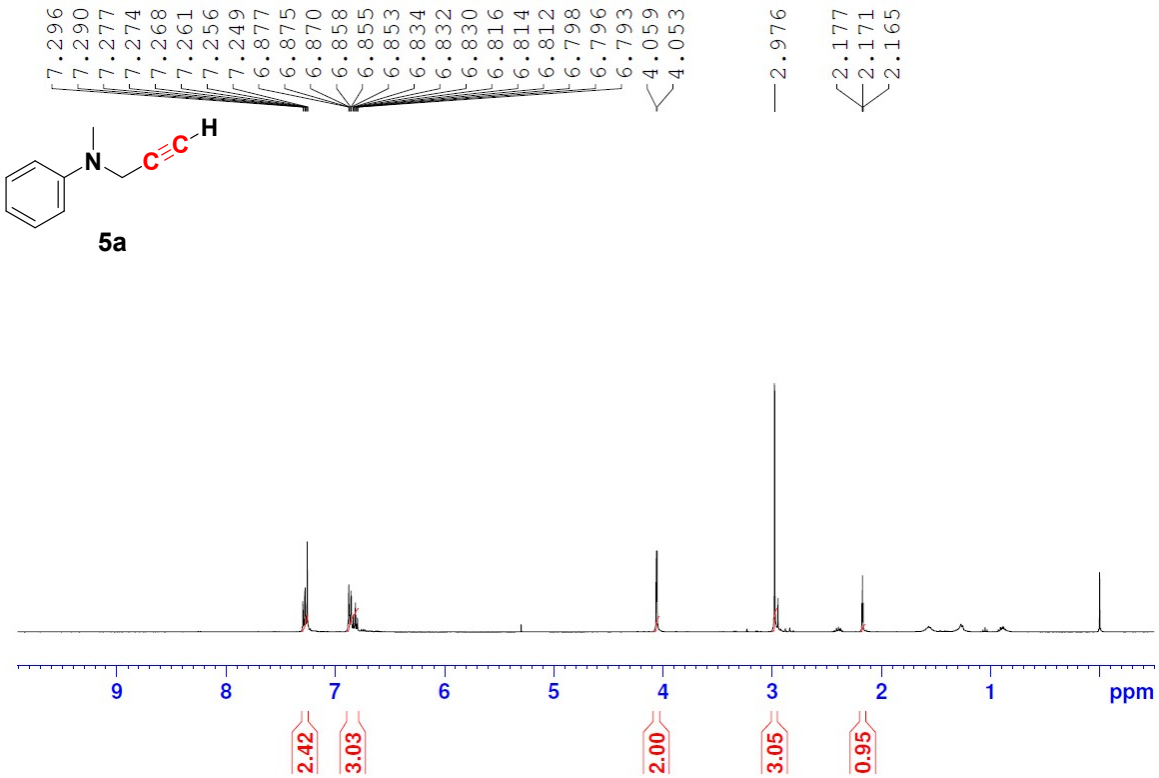
^{1}H NMR, $CDCl_3$, 400 MHz



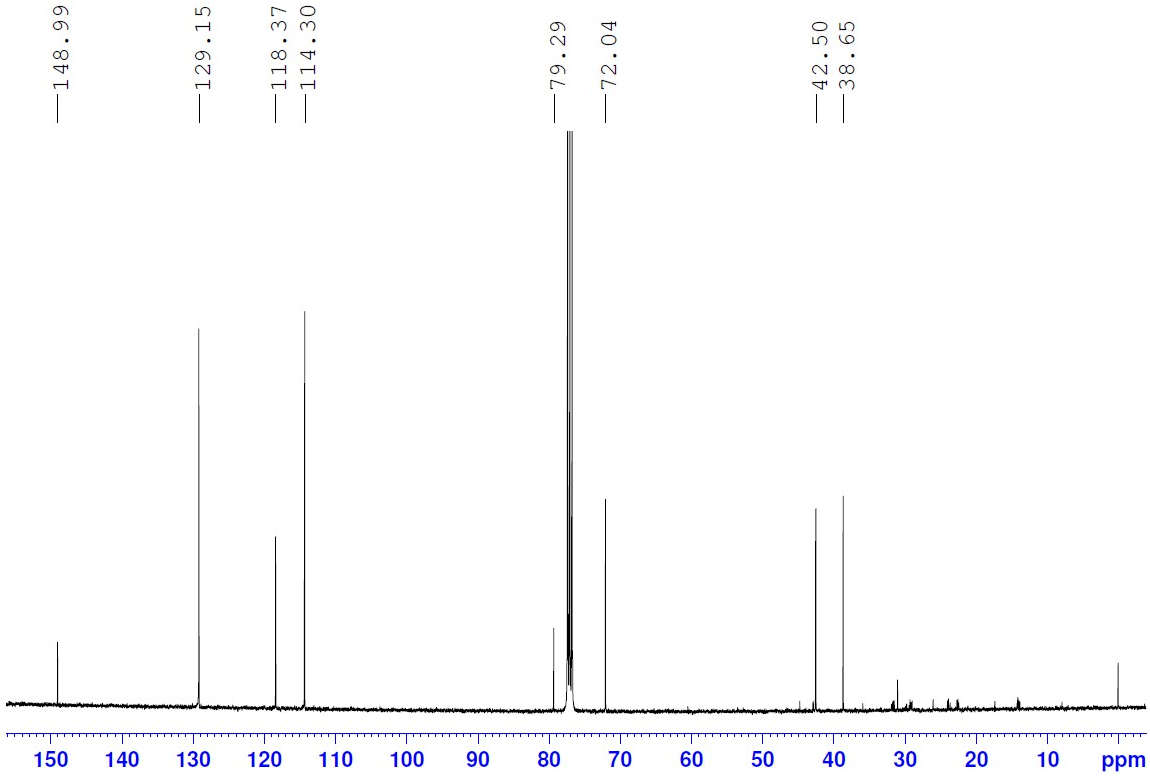
^{13}C NMR, $CDCl_3$, 101 MHz



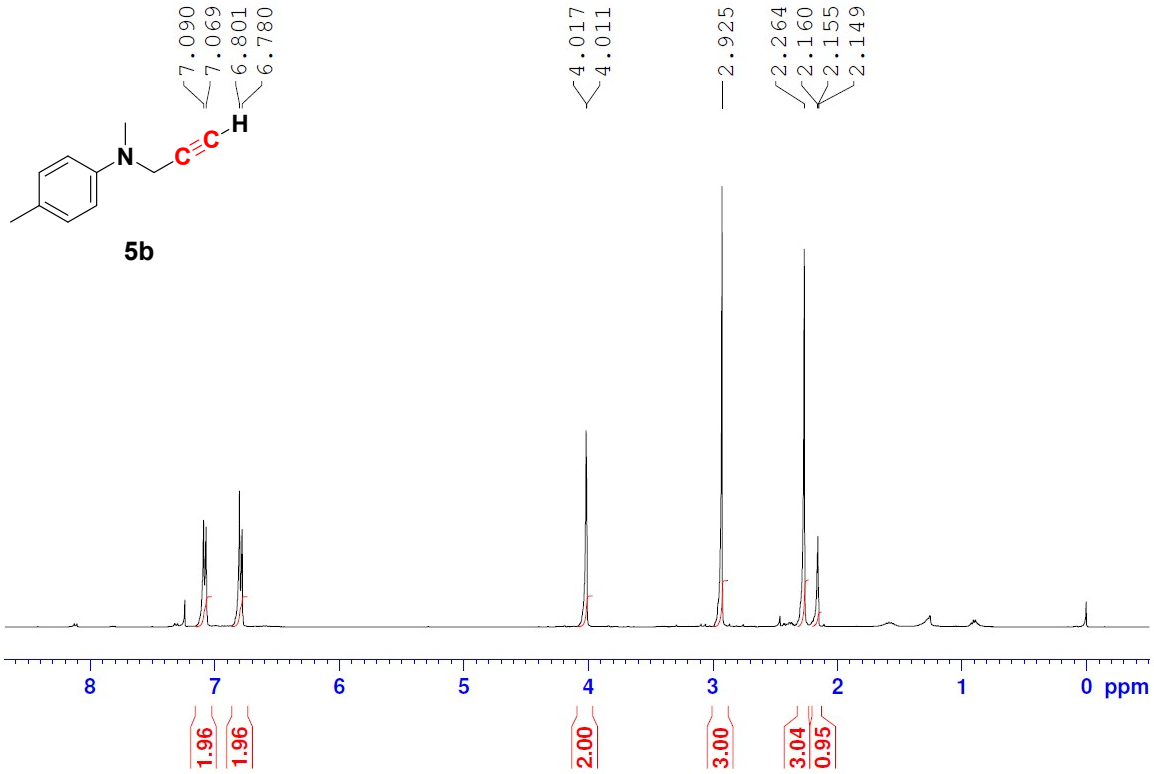
^{1}H NMR, $CDCl_3$, 400 MHz



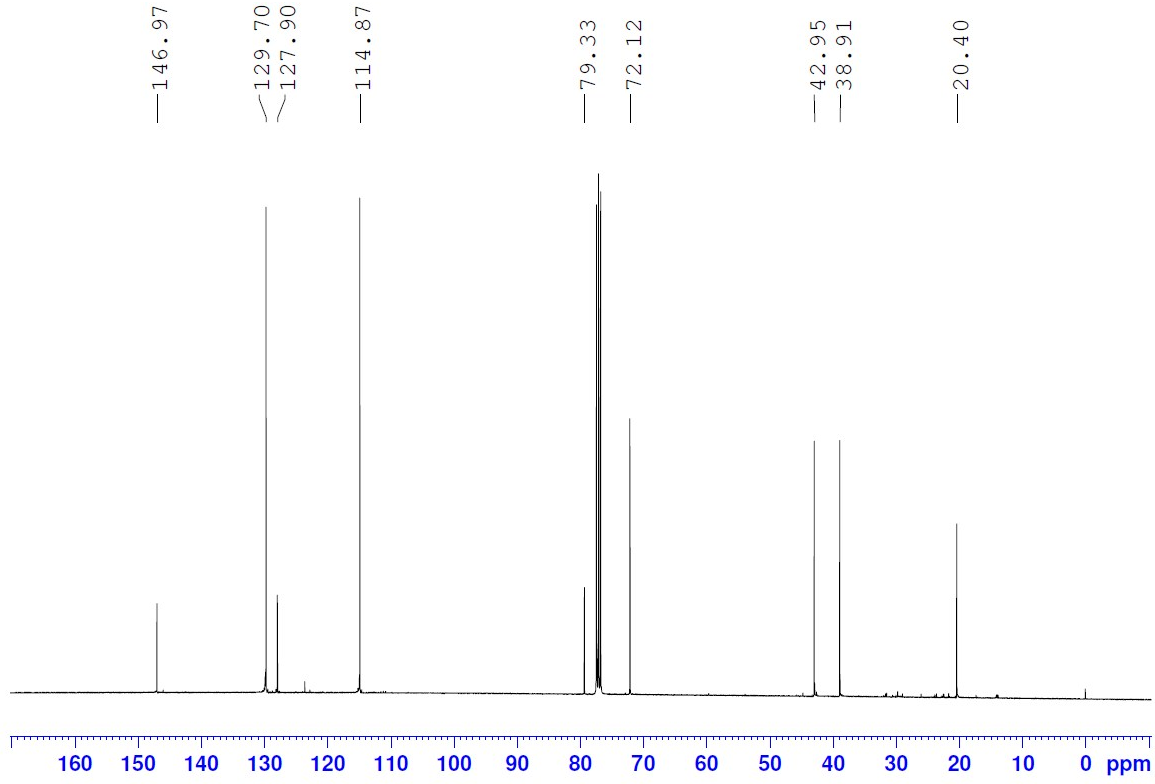
^{13}C NMR, $CDCl_3$, 101 MHz



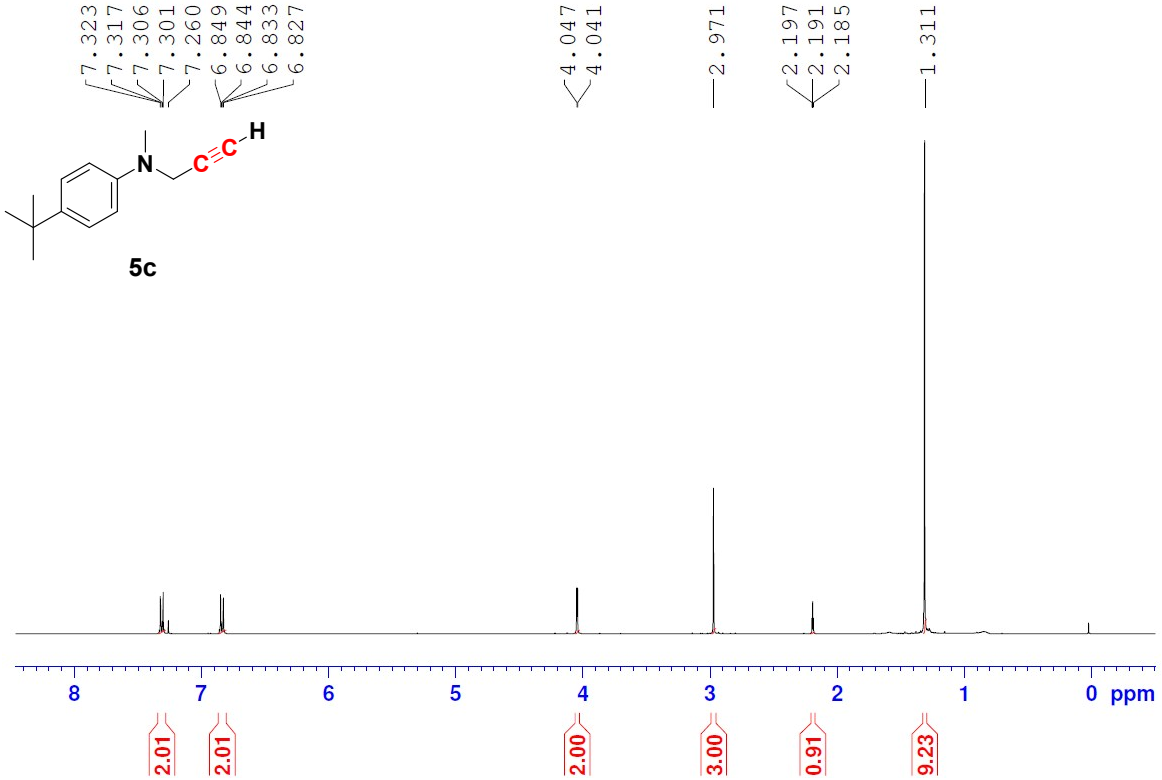
^{1}H NMR, $CDCl_3$, 400 MHz



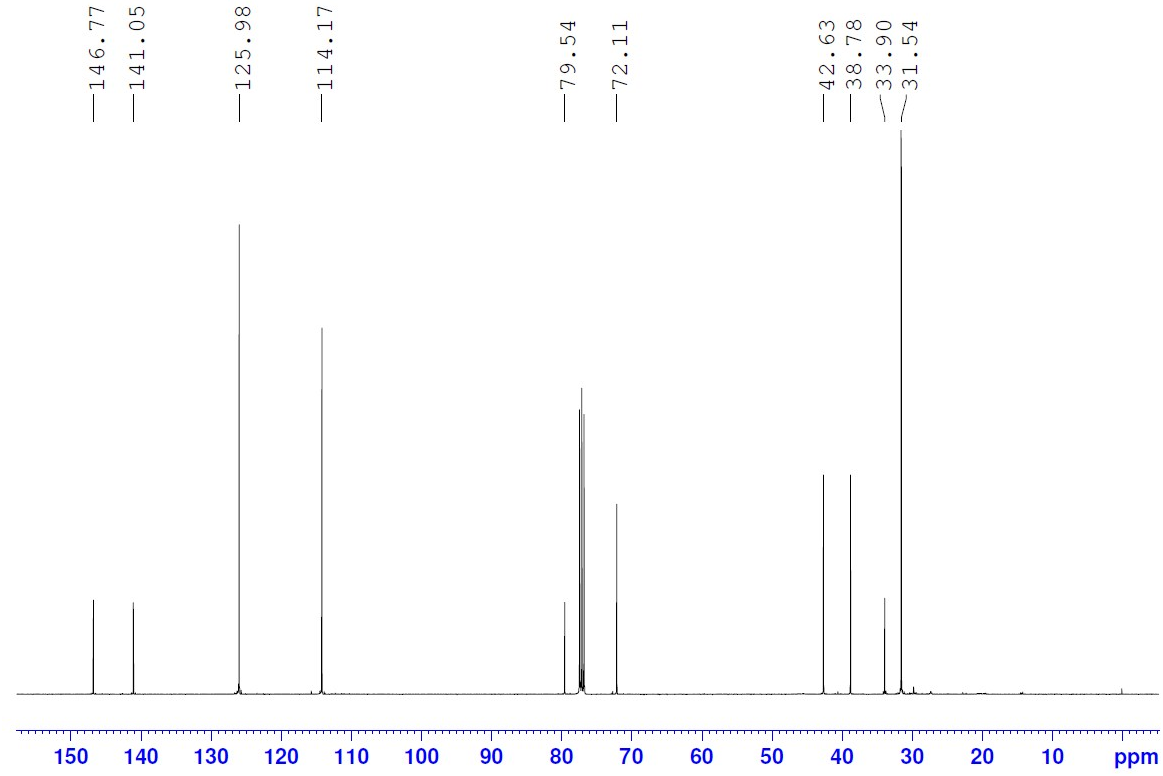
^{13}C NMR, $CDCl_3$, 101 MHz



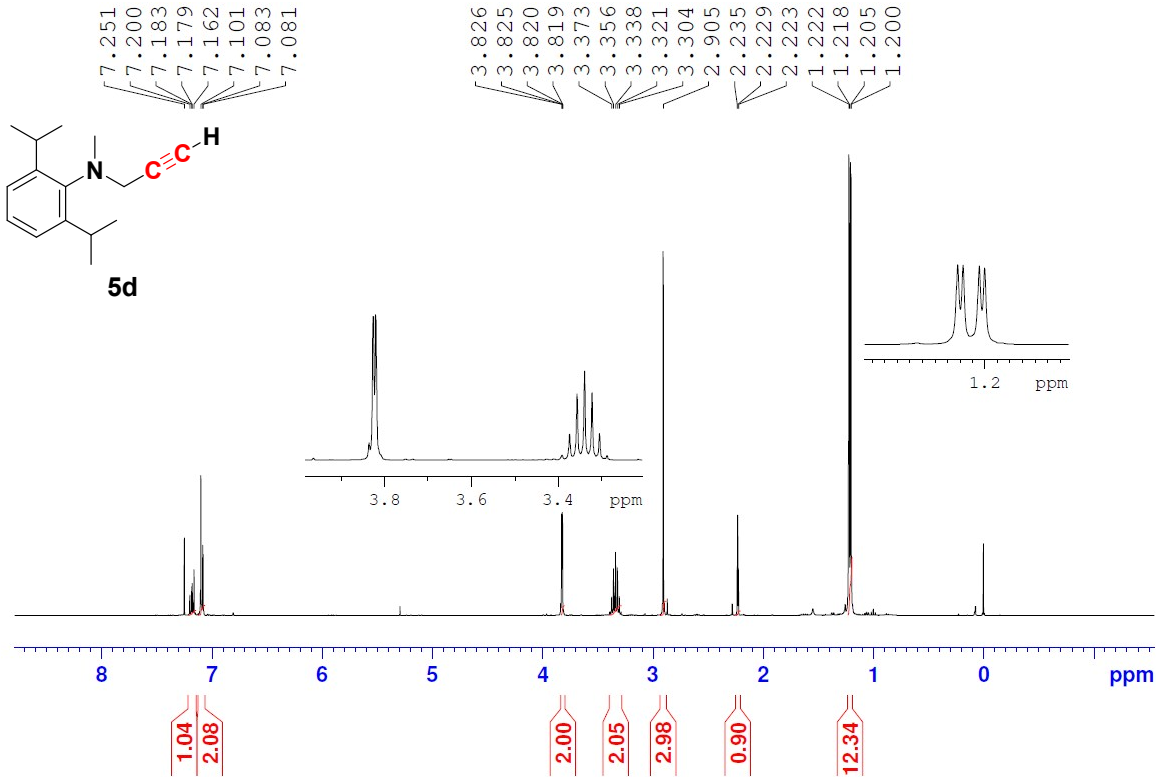
^{1}H NMR, $CDCl_3$, 400 MHz



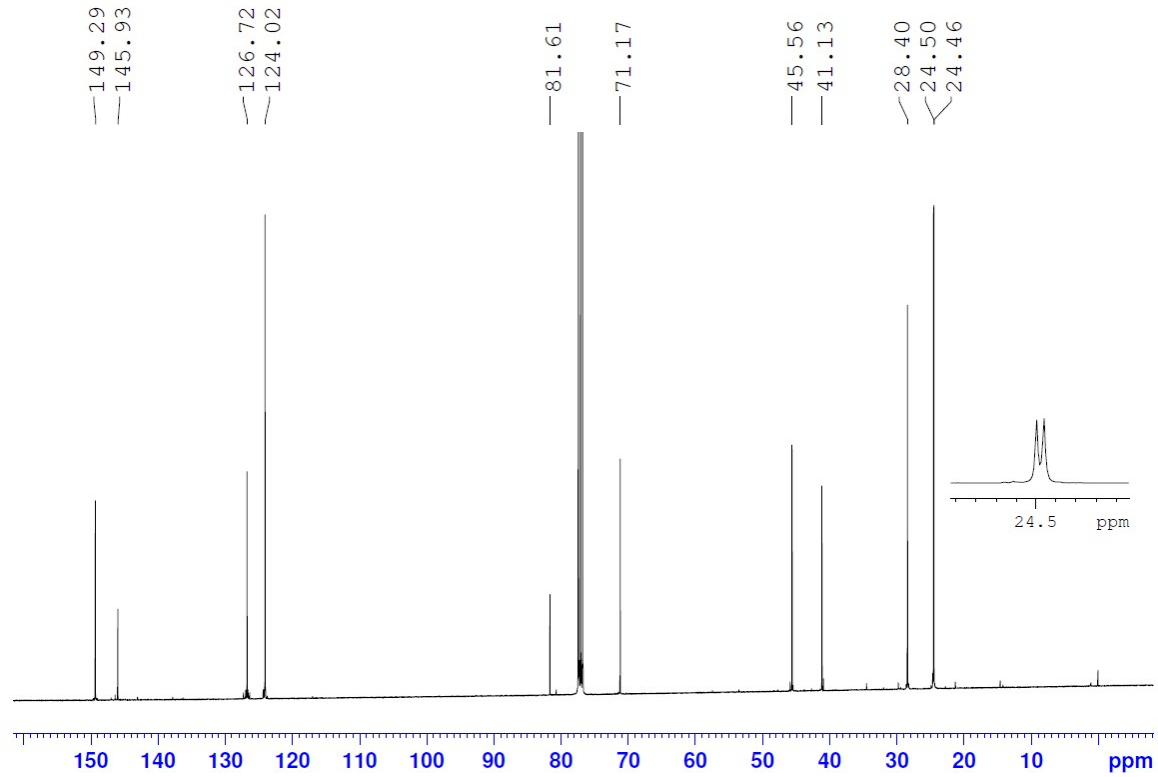
^{13}C NMR, $CDCl_3$, 101 MHz



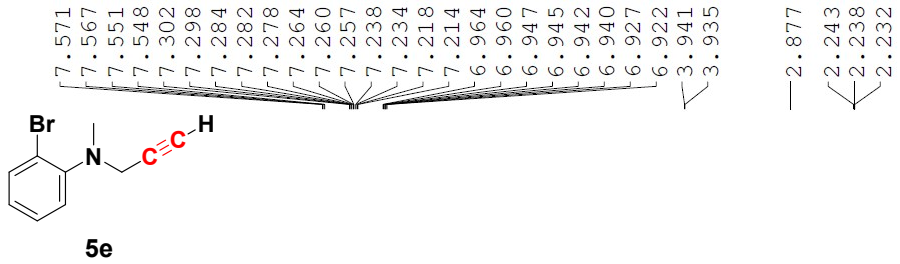
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



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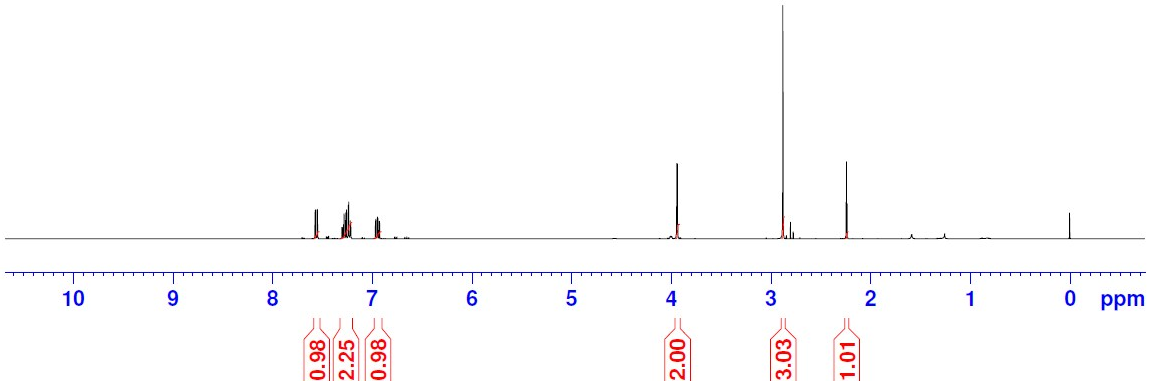
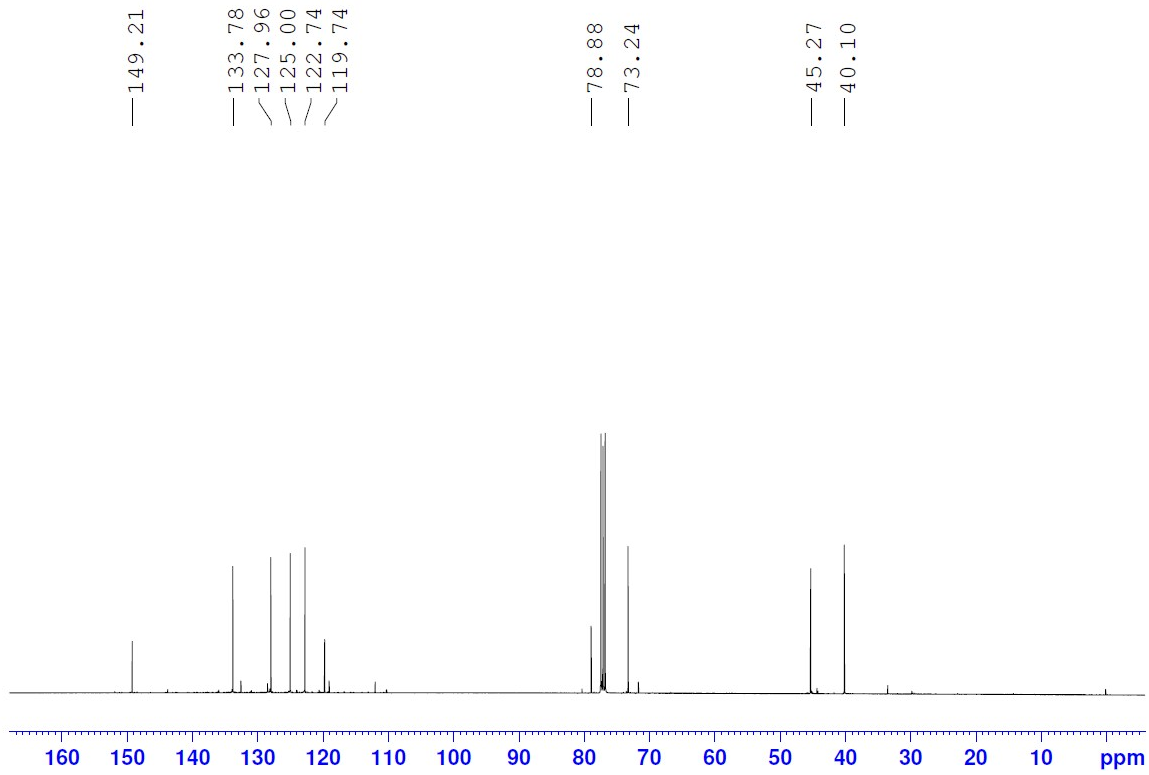
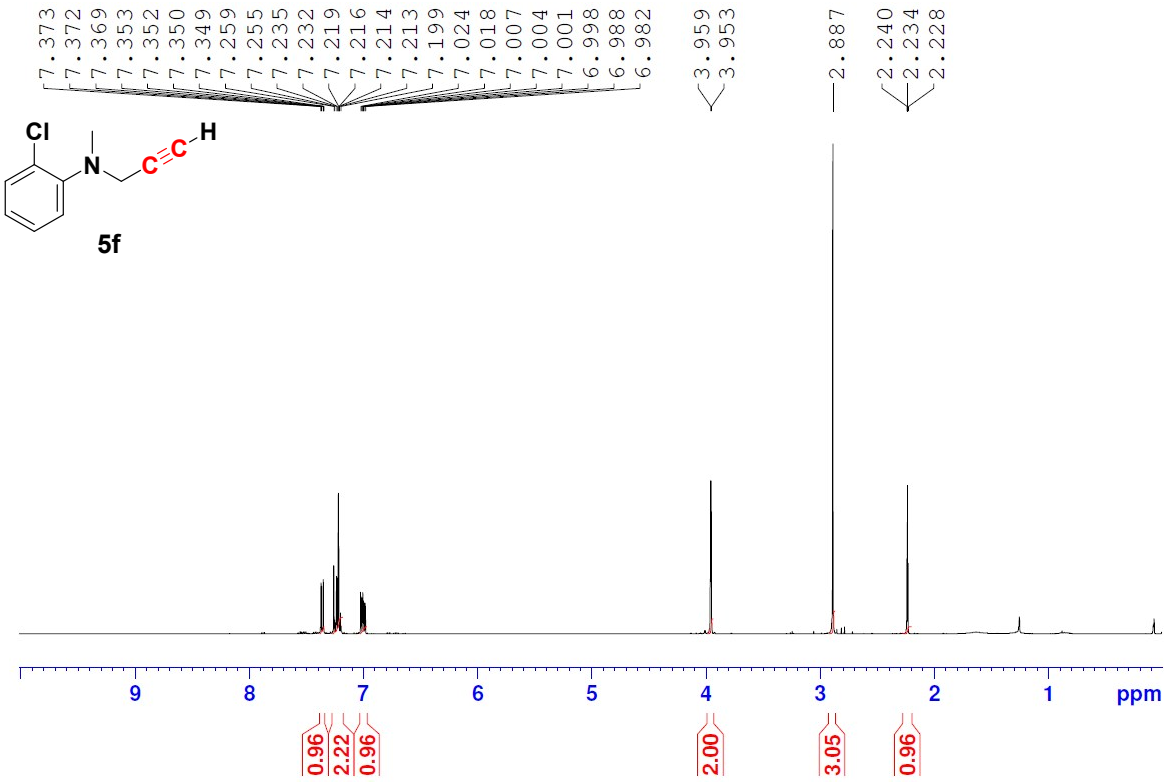


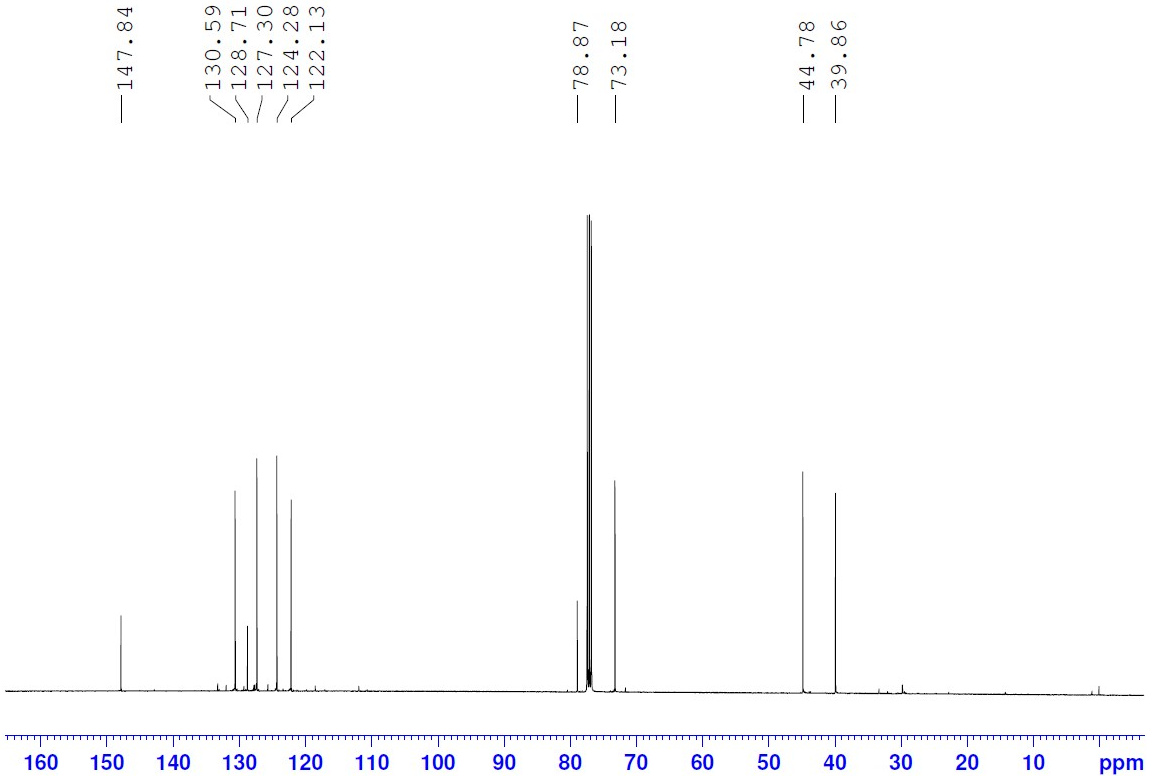
^{13}C NMR, $CDCl_3$, 101 MHz



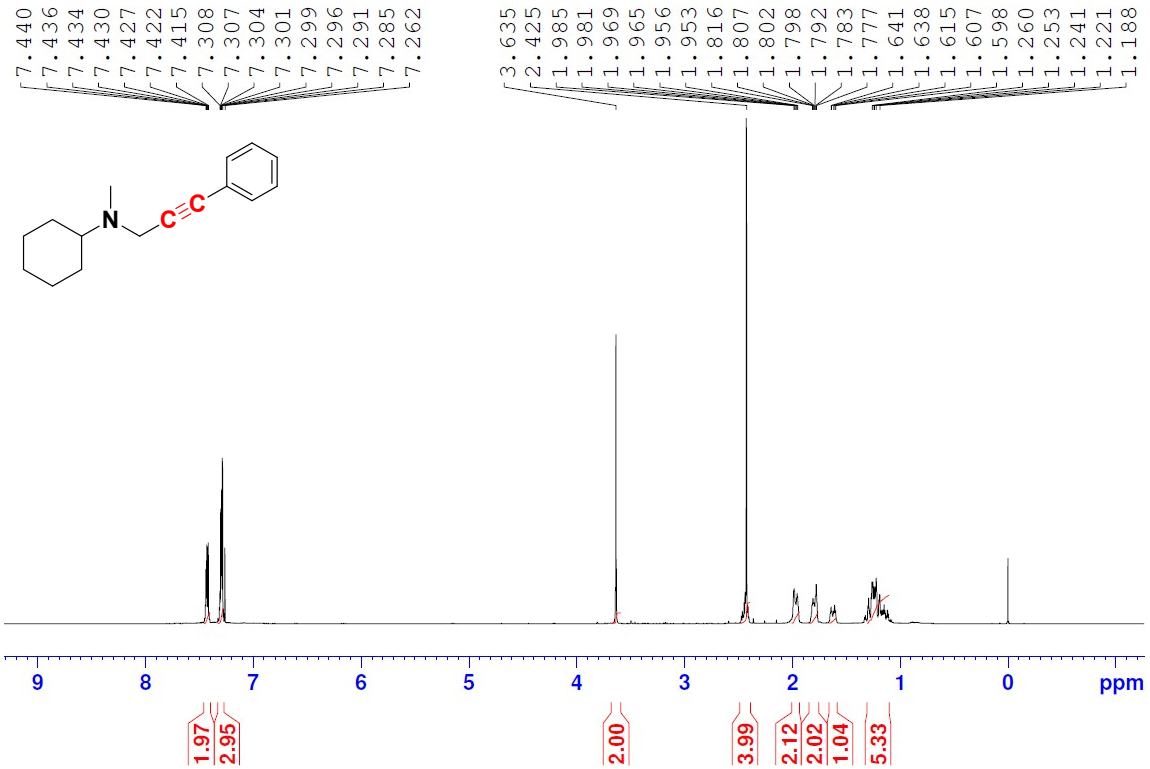
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 101 MHz