# Alkynation of α-Halocarbonyl Compounds—A Stille-Type Cross-Coupling for the Formation of C(sp)–C($sp^3$) Bonds

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Supporting Information

## Experimental Details

**Reagents:** All reactions were carried out under inert atmosphere. All glasswares were oven dried, heated by electrical gun under vacuum, and cooled under nitrogen prior to use. All common reagents were prepared in our lab or from commercial suppliers and were purified following general procedure except methyl bromoacetate, which was obtained from Acros and was directly used without further purification. Tributyl(hept-1-ynyl)stannane **1b** and tributyl(phenylethynyl)stannane **1a** were prepared as reported. $PdCl_2$(dppf) and $PdCl_2(PhCN)_2$ were prepared following general methods. All ligands were obtained from Solvias AG and Strem Chemicals and used without further purification. THF was distillated from sodium under nitrogen, and other solvents were purified following known procedures.

**Analytical Methods:** All new compounds were characterized by $^1$H NMR, $^{13}$C NMR, GC-MS, and HRMS. The known compounds were characterized by $^1$H NMR and GC-MS. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Mercury 300 MHz. GC-MS spectra were recorded on a Varian GC-MS 3900-2100T. All $^1$H NMR experiments are reported in parts per million (ppm) downfield of TMS. All $^{13}$C NMR

spectra were reported in ppm and were obtained with $^1$H decoupling. Gas chromatographic analyses were preformed on Varian GC 2000 gas chromatography instrument with a FID detector and naphthalene was added as internal standard.

The yields in Table 4 refer were isolated yields from column chromatography and estimated to be ≥ 95% pure determined by $^1$H NMR except Entries 3 and 4, which estimated to be about 94%.

**Table 1:** General Procedure for the reactions using different solvents: $PdCl_2$(dppf) (3.4 mg, 0.0045 mmol), Solvent (15 ml), internal standard (naphthalene), Methyl bromoacetate **2a**(15 μL , 0.15 mmol) and tributyl(phenylethynyl)stannane **1a** (59 mg, 0.15 mmol) was added to a Schlenk tube. The mixture was stirred at 66 $^o$C for 7-20 h till the concentration of aimed product reaches the maximum and remains constant, and then passed through a short plug of silica (eluent: ethyl acetate), and prepared for GC analyze.

**Table 2. Entry 1**: $PdCl_2$(dppf) (5.7 mg, 0.0075 mmol), THF (2.5 ml), internal standard (naphthalene), Methyl bromoacetate **2a** (24 μL , 0.25 mmol) and tributyl(phenylethynyl)- stannane **1a** (98 mg, 0.25 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^o$C for 20 hours and then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

**Entries 2-3**: $PdCl_2$(dppf) (3.4 mg, 0.0045 mmol), THF (4 ml for entry 2 and 15 ml for

entry 3), internal standard, Methyl bromoacetate **2a** (15 μL , 0.15 mmol) and tributyl(phenylethynyl)stannane **1a** (59 mg, 0.15 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 20 hours and then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

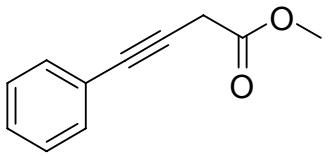
**Entry 4**: $PdCl_2$(dppf) (2.2mg, 0.003 mmol), THF (6 ml) and Methyl bromoacetate **2a** (10 μL , 0.1 mmol) and internal standard (naphthalene) were added to a Schlenk tube. tributyl(phenylethynyl)stannane **1a** (39 mg, 0.1 mmol) was dissolved in another 4 ml THF, and was added to the mixture dropwise over 2 hours and stirred under 66 $^{o}$C for another 18 hours. The mixture was then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

**Table 3**. **Entries 1-10, 14 and 15**: $PdCl_2(PhCN)_2$ (3 mol%, 0.003 mmol), Ligands (1 equiv. to Pd catalyst for bidentate ligands and 2.2 eqiv. for monodentate ligands), THF (5 ml), methyl bromoacetate **2a** (0.1 mmol, 15.3 mg), internal standard (naphthalene) and tributyl(phenylethynyl)stannane **1a** (0.1 mmol, 39.1 mg) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 20 hours and then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

**Entries 11, 13**: Pd catalyst (3 mol% , 0.003 mmol), THF (5 ml), methyl bromoacetate **2a** (0.1 mmol, 15.3 mg), internal standard (naphthalene) and tributyl(phenylethynyl)stannane **1a** (0.1 mmol, 39.1 mg) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 20 hours, and then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

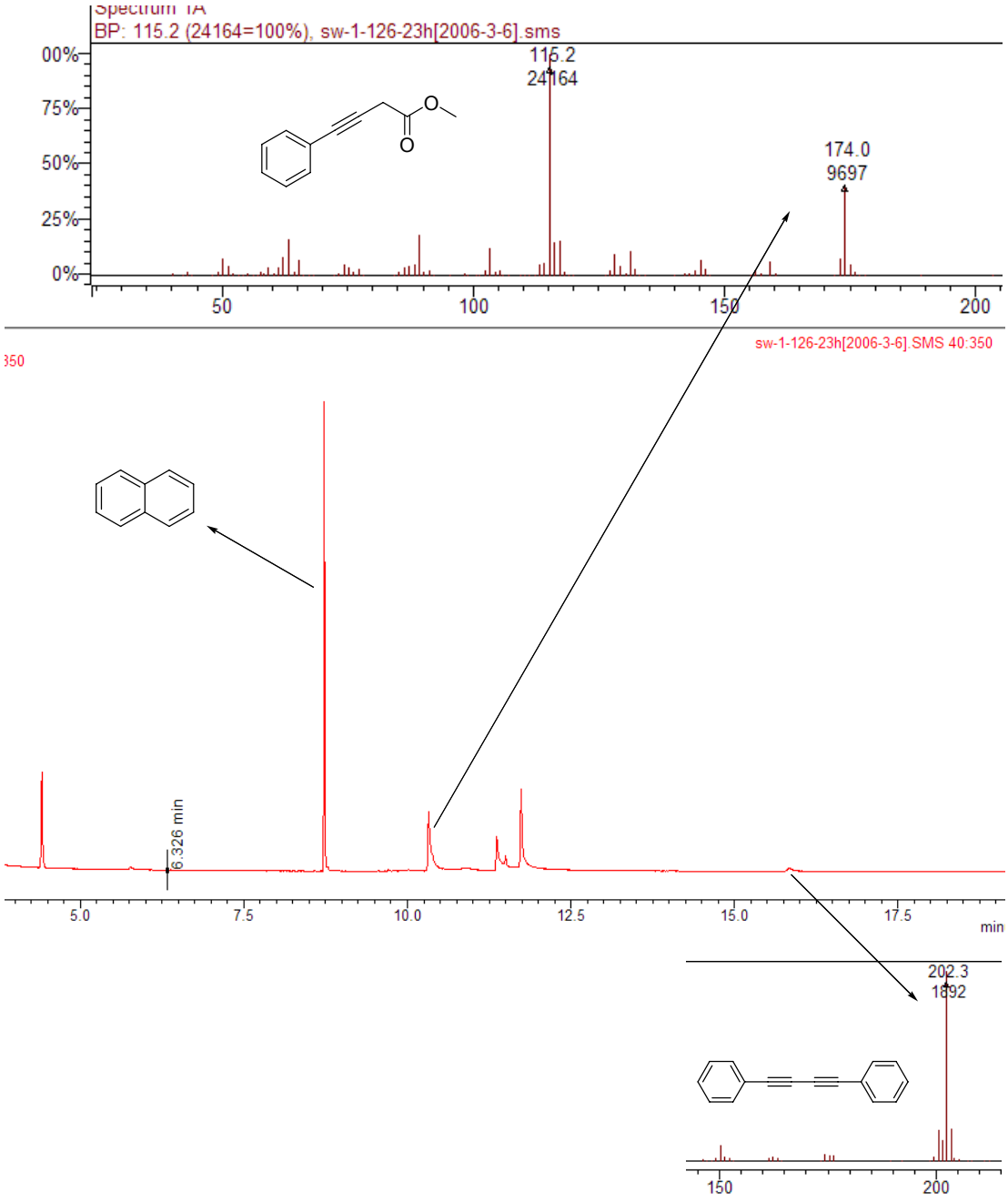
**Entries 12**: $Pd(dba)_2$ (3 mol% , 0.003 mmol, 1.7 mg), THF (5 ml), methyl bromoacetate **2a** (0.1 mmol, 15.3 mg), xantphos (1 equiv to Pd, 0.003 mmol, 1.7 mg), internal standard (naphthalene) and tributyl(phenylethynyl)stannane **1a** (0.1 mmol, 39.1 mg) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 20 hours, and then passed through a short plug of silica (eluent: ethyl acetate), and prepare for GC analyze.

**Table 4, entry 1**: Methyl-4-phenyl-3-butynoate **3a** CAS: (107939-51-5)[1]




Xantphos (5.8 mg, 0.01 mmol), $PdCl_2(PhCN)_2$ (3.8 mg, 0.01 mmol), methyl bromoacetate **2a** (95 μL, 1 mmol), THF (2 ml), and tributyl(phenylethynyl)stannane **1a** (196 mg, 0.5 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 20 hours. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was then removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:50), which afforded the desired product as a colorless oil (54.0 mg, 62%).

$^{1}$H NMR ($CDCl_3$): δ 7.37-7.34 (m, 2H), 7.19-7.22 (m, 3H), 3.67 (s, 3H), 3.42 (s, 2H); MS (EI) *m/e*: 174.0, 159.2, 115.2, 89.3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24164
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O
50
100
150
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sw-1-126-23h[2006-3-6].SMS 40:350
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min
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200

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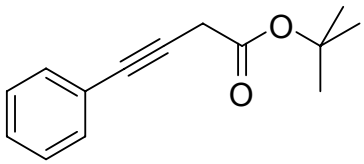
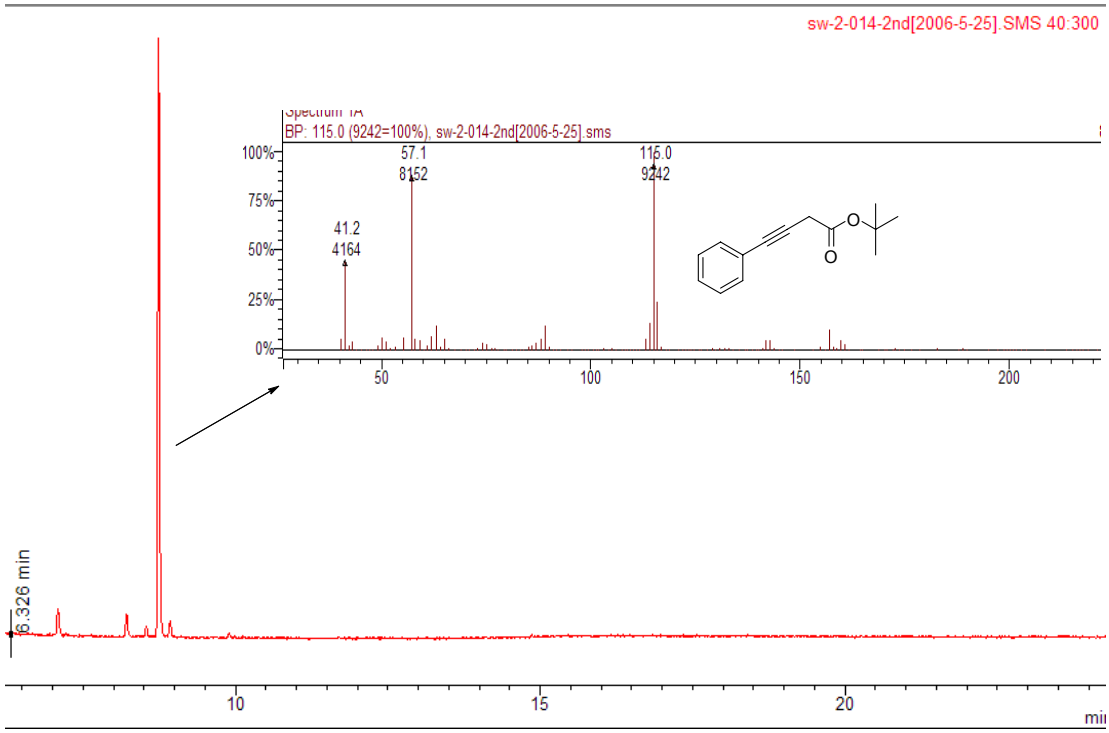
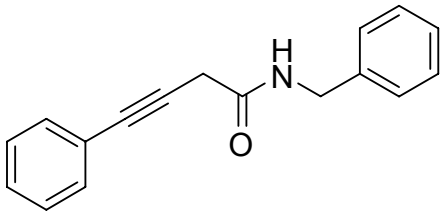


Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), *t*-butyl bromoacetate **2c** (48.8 mg, 0.25 mmol), THF (2 ml), and tributyl(phenylethynyl)stannane **1a** (117 mg, 0.30 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^oC$ overnight. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was then removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:50), which afforded the desired product as a colorless oil (24.6 mg, 46%).

$^1H$ NMR ($CDCl_3$): δ 7.40-7.30 (m, 2H), 7.25-7.19 (m, 3H), 3.35 (s, 2H), 1.43 (s, 9H); MS (EI) *m/e*: 216.2, 159.8, 115.0, 57.1; HRMS ( EI ): $C_{14}H_{16}O_2$ Calcd.: 216.1150, found: 216.1166

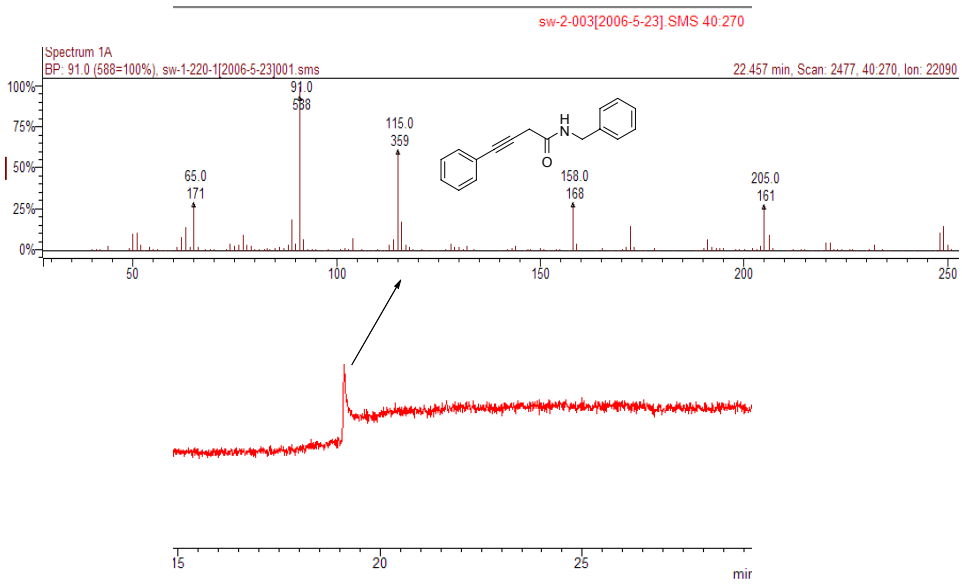



**Entry 3**: N-benzyl-4-phenyl-3-butynamide **3d** CAS: (518061-69-3)[2]

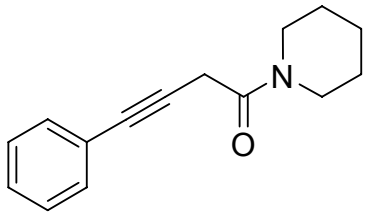



Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), N-benzyl-2-bromoacetamide **2d** (57 mg, 0.25 mmol), THF (2 ml), and tributyl(phenylethynyl)stannane **1a** (108 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 11h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:10), which afforded the desired product as a yellow oil (57 mg, 92%).

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.41-7.26 (m, 10H), 6.86 (br, 1H), 4.51 (d, $J$ = 6.0 Hz, 2H), 3.50 (s, 2H); MS (EI) *m/e*: 248.9, 158.0, 115.0, 91.0



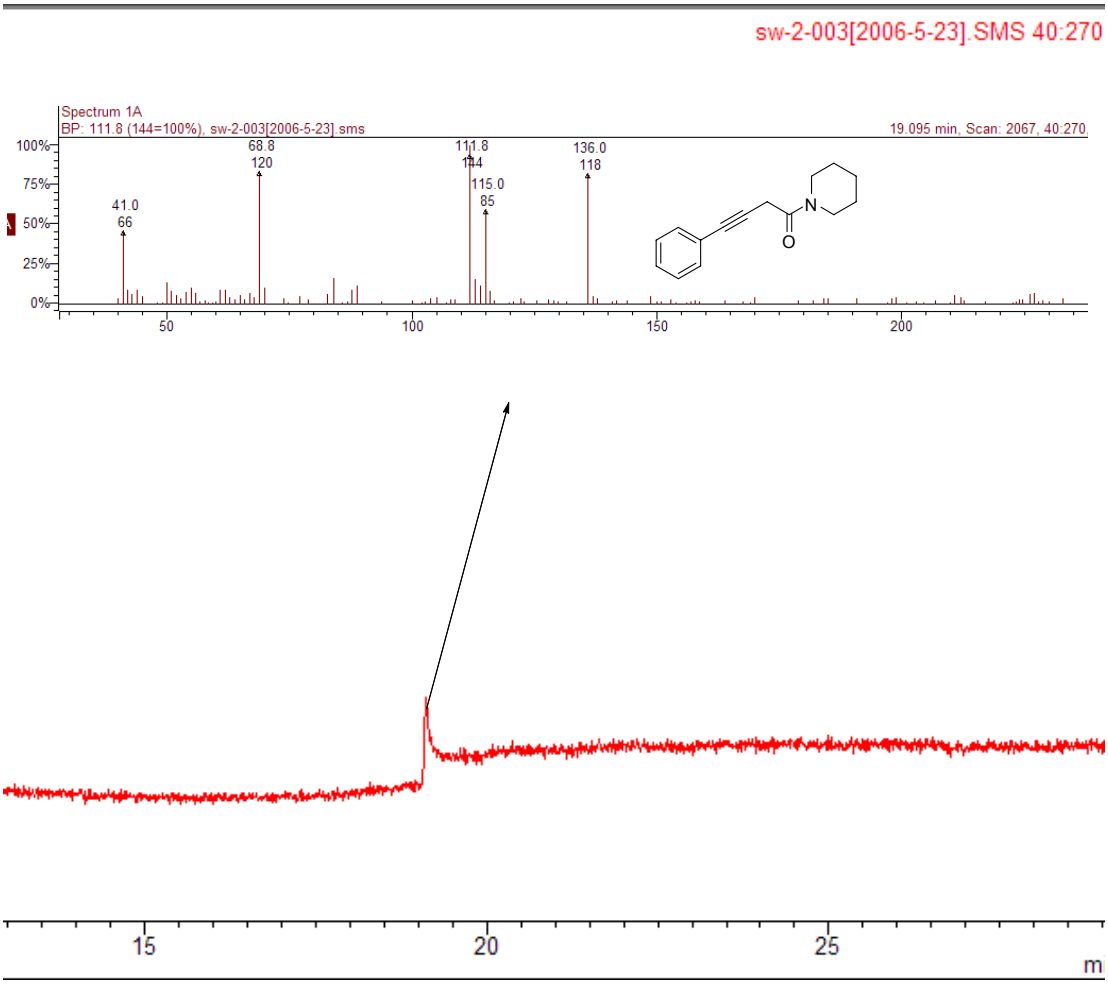

**Entry 4**: Piperidine, 1-(1-oxo-4-phenyl-3-butynyl)- (9CI) **3e** CAS: (52956-07-7)[3]




Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), 2-bromo-1-(piperidin-1-yl)ethanone **2e** (27 mg, 0.13 mmol), THF (2 ml), and tributyl(phenylethynyl)stannane **1a** (108 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^o$C for 12h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:15), which afforded the desired product as a yellow oil

(28.5 mg, 95%).

$^1$H NMR ($CDCl_3$): δ 7.41-7.38 (m, 2H), 7.30-7.27 (m, 3H), 3.56 (t, $J$ = 5.3 Hz, 4H), 3.49 (s, 2H), 1.70-1.60 (m, 4H), 1.60-1.50 (m, 2H); MS (EI) *m/e*: 227.0, 136.0, 115.0, 111.8; HRMS (EI): $C_{15}H_{17}NO$, Calcd.: 227.1310, Found: 227.1319

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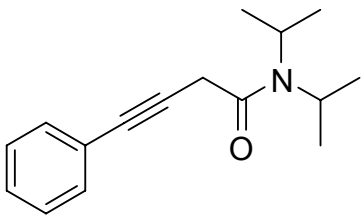
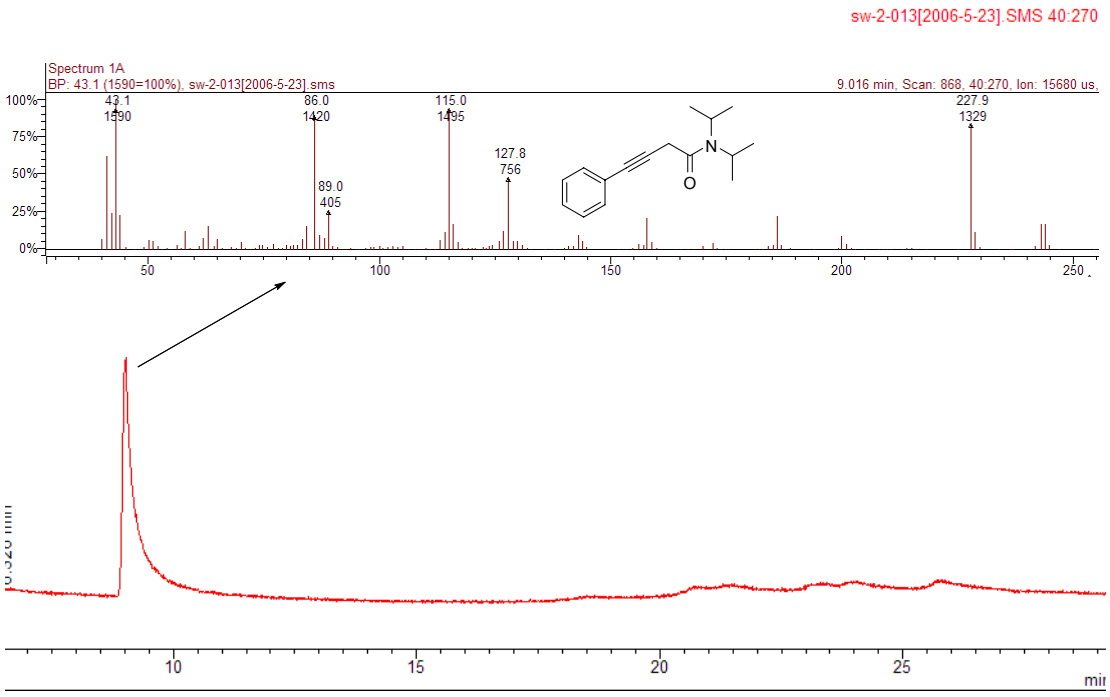


Xantphos (2.9 mg, 0.005mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), 2-bromo-N,N-diisopropylacetamide **2f** (56 mg, 0.25 mmol), THF (2 ml), and tributyl(phenylethynyl)stannane **1a** (108 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C overnight. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:15), which afforded the desired product as a yellow powder (50.1 mg, 83%).

$^{1}$H NMR ($CDCl_3$): δ 7.34-7.30 (m, 2H), 7.18-7.24 (m, 3H), 4.15-4.05 (m, 1H), 3.37 (s, 2H), 3.35-3.25 (m, 1H), 1.34 (d, $J$ = 6.6 Hz, 6H), 1.17 (d, $J$ = 6.6 Hz, 6H); $^{13}$C NMR ($CDCl_3$): δ 166.0, 131.8, 128.5, 128.3, 123.5, 84.1, 83.1, 50.2, 46.4, 29.8, 20.9, 20.6; MS (EI) *m/e*: 243.0, 127.8, 115.0, 86.0; HRMS( EI): $C_{16}H_{21}NO$, Calcd.: 243.1623, Found: 243.1595

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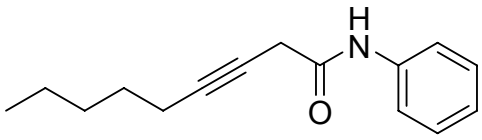
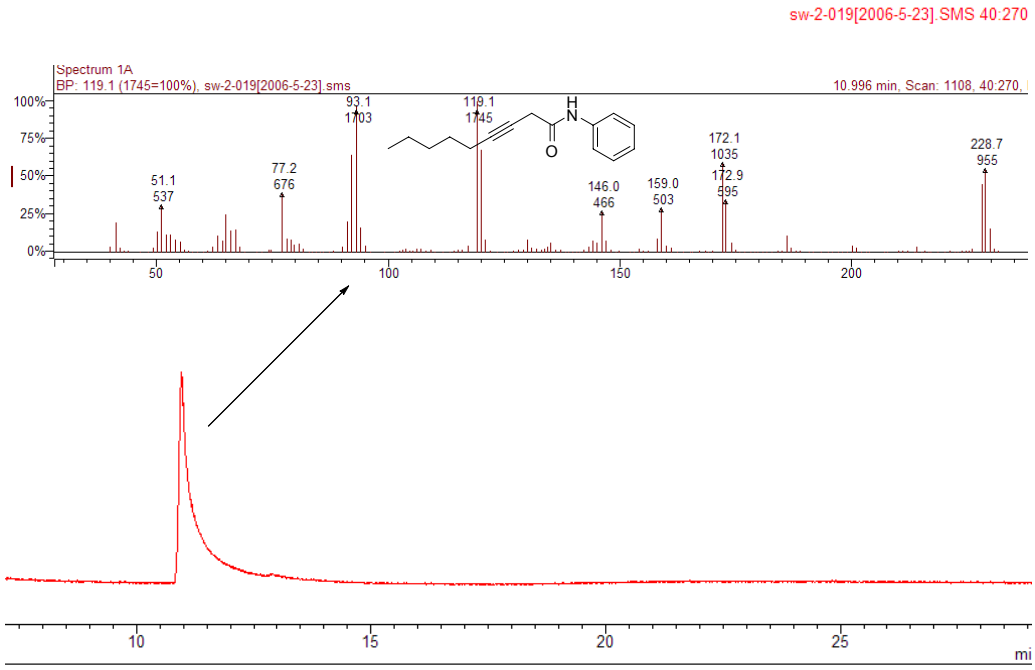


Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), 2-bromo-N-phenylacetamide **2g** (54 mg, 0.25 mmol), THF (2 ml), and Tributyl(hept-1-ynyl)stannane **1b** (106 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 11h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:15), which afforded the desired product as a pale solid (56.7 mg, 94%).

$^{1}$H NMR($CDCl_3$): δ 8.31 (br, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 3.30 (t, *J* = 2.8 Hz, 2H), 2.28-2.22 (m, 2H), 1.55 (q, *J* = 7.2 Hz, 2H), 1.44-1.27 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$): δ 165.8, 137.6, 129.2, 124.8, 120.0, 87.7, 73.2, 31.4, 29.1, 28.6, 22.4, 19.0, 14.2; MS (EI) *m/e*: 228.7, 172.9, 120.0, 93.1; HRMS ( EI ): $C_{15}H_{19}NO$ Calcd.: 229.1467, Found: 229.1471

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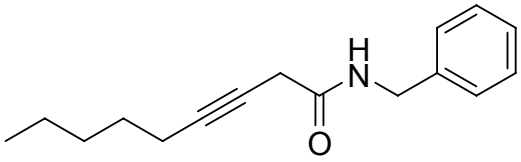
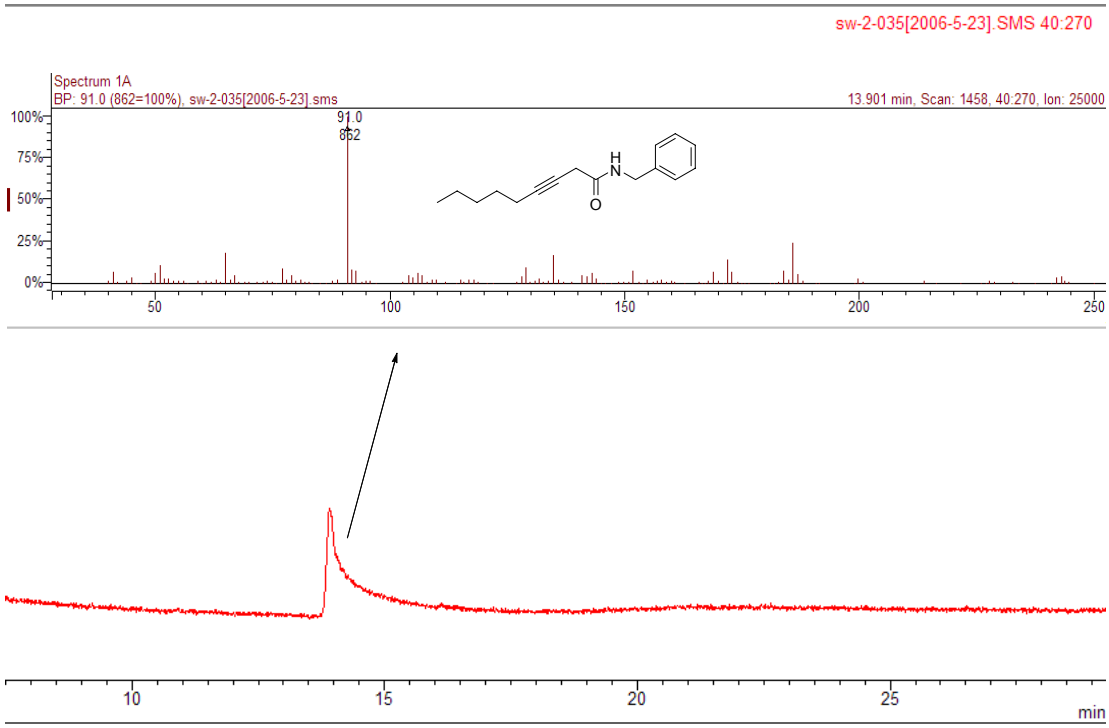



Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), N-benzyl-2-bromoacetamide **2d** (57 mg, 0.25 mmol), THF (2 ml), and Tributyl(hept-1-ynyl)stannane **1b** (106 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 11h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:10), which afforded the desired product as a yellow oil (57.8 mg, 95%).

$^{1}$H NMR ($CDCl_3$): δ 7. 38-7. 26 (m, 5H), 6.85 (br, 1H), 4.48 (d, $J$ = 5.4 Hz, 2H), 3.24 (s, 2H), 2.20-2.15 (m, 2H), 1.49-1.40 (m, 2H), 1.35-1.27 (m, 4H), 0.95-0.84 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 167.7, 138.2, 128.9(2C), 127.8(2C), 86.8, 73.2, 43.9, 31.2, 28.4,

28.0, 22.4, 18.9, 14.1; MS (EI) *m/e*: 243.0, 185.9, 171.9, 91.0; HRMS (EI): $C_{16}H_{21}NO$, Calcd.: 243.1623, Found: 243.1602

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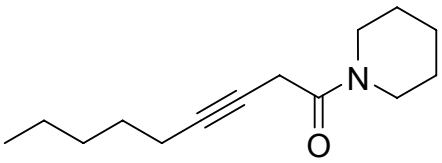
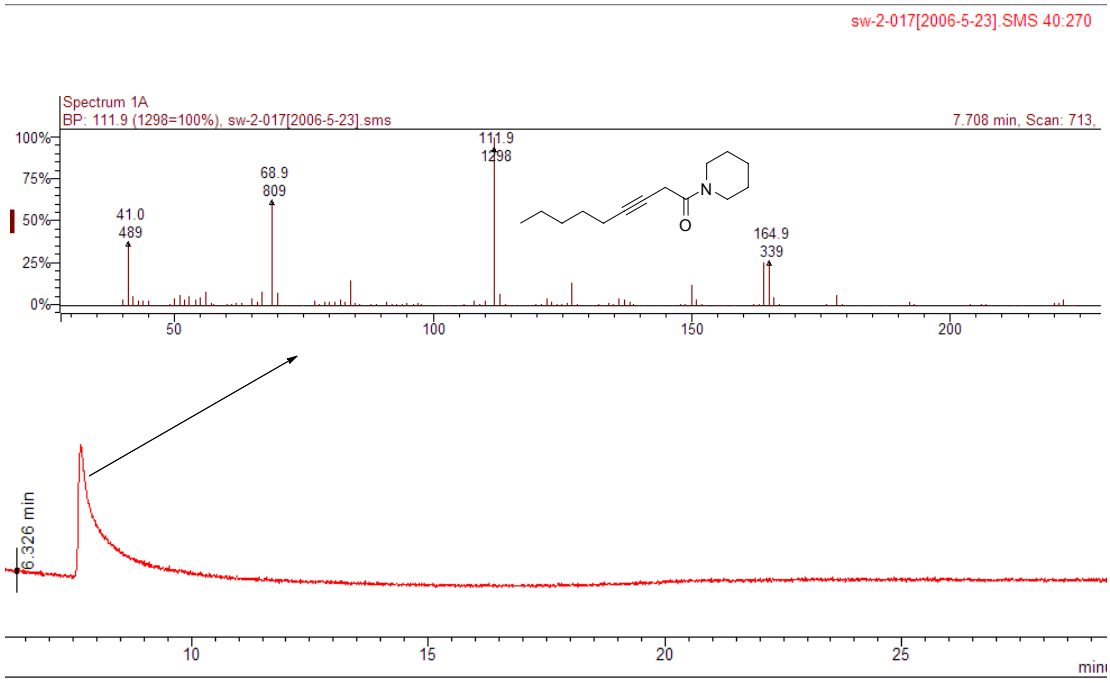



Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), 2-bromo-1-(piperidin-1-yl)ethanone **2e** (51.5 mg, 0.25 mmol), THF (2 ml), and Tributyl(hept-1-ynyl)stannane **1b** (106 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 11h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum ether, 1:15), which afforded the desired product as a yellow oil (52.8 mg, 95%).

$^{1}$H NMR ($CDCl_3$): δ 3.48-3.43 (m, 4H), 3.16 (t, $J$ = 2.4 Hz, 2H), 2.19-2.14 (m, 2H), 1.65-1.46 (m, 8H), 1.42-1.25 (m, 4H), 0.83 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$): δ 166.4, 84.2, 72.7, 47.7, 43.2, 31.2, 28.6, 26.9, 26.4, 25.6, 24.6, 22.4, 18.9, 14.2; MS (EI) *m/e*: 221.8, 164.9, 111.9, 68.9; HRMS (EI): $C_{14}H_{23}NO$, Calcd.: 221.1780; Found: 221.1819

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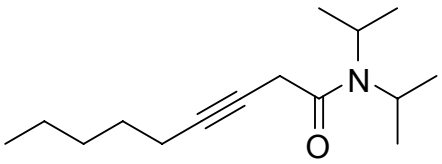
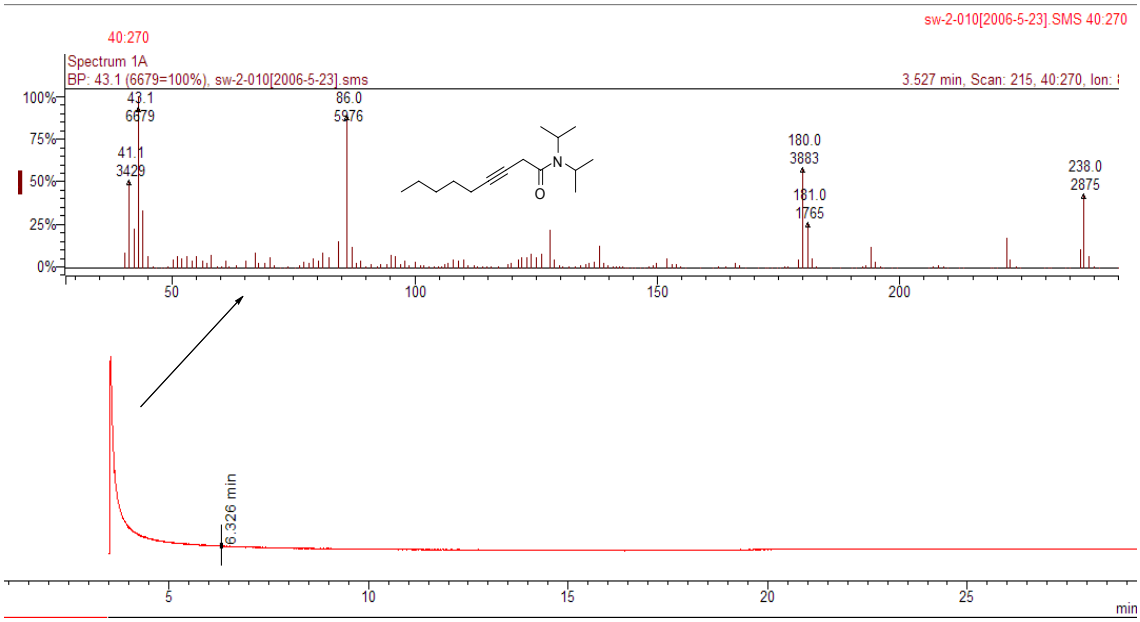


Xantphos (2.9 mg, 0.005 mmol), $PdCl_2(PhCN)_2$ (1.9 mg, 0.005 mmol), 2-bromo-N,N-diisopropylacetamide **2f** (56 mg, 0.25 mmol), THF (2 ml), and Tributyl(hept-1-ynyl)stannane **1b** (106 mg, 0.275 mmol) were added to a Schlenk tube. The mixture was stirred under 66 $^{o}$C for 7 h. 4 ml KF (1.0 M) solution was then added and pale precipitate appeared. The precipitate was removed, and the solution

was evaporated under vacuum. The residue was purified by chromatography (ethyl acetate/petroleum, 1:15), which afforded the desired product as a yellow oil (48.7 mg, 82%).

$^{1}$H NMR ($CDCl_3$): δ 4.10-3.98 (m, 1H), 3.38-3.22 (m, 1H), 3.12 (s, 2H), 2.11 (t, $J$ = 6.6 Hz, 2H), 1.44-1.39 (m, 2H), 1.34-1.22 (m, 12H), 1.14 (d, $J$ = 6.3 Hz, 4H), 0.82 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$): δ 166.8, 84.2, 73.1, 49.9, 46.1, 31.2, 29.0, 28.6, 22.4, 20.8, 20.6, 19.0, 14.1; MS (EI) *m/e*: 238.0, 222.0, 194.0, 180.0, 86.0; HRMS (EI): $C_{15}H_{27}NO$, Calcd.: 237.2093, found: 237.2123



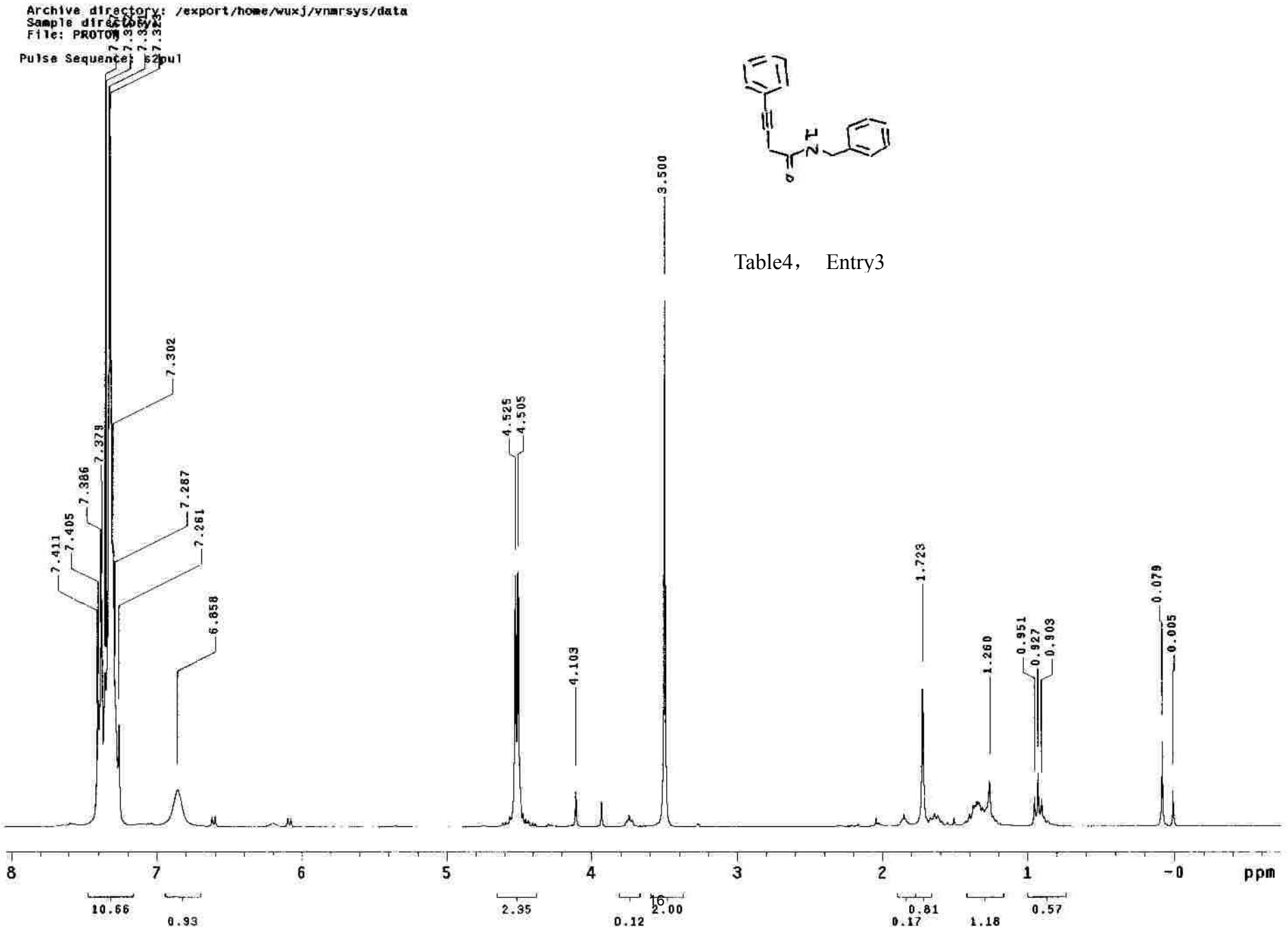



Table4， Entry3

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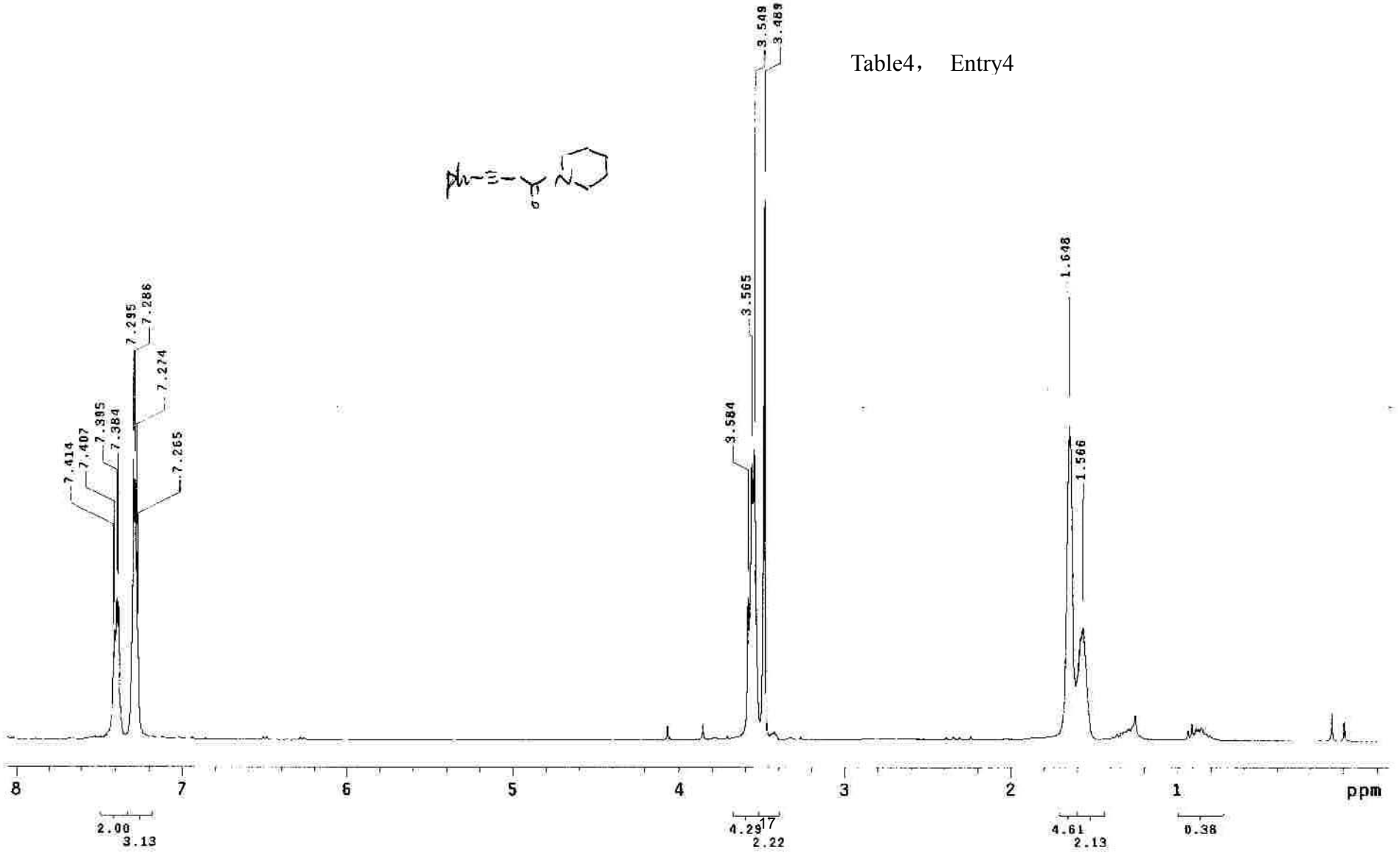
Table4， Entry4



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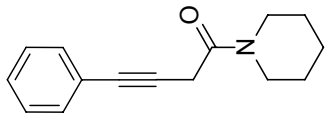

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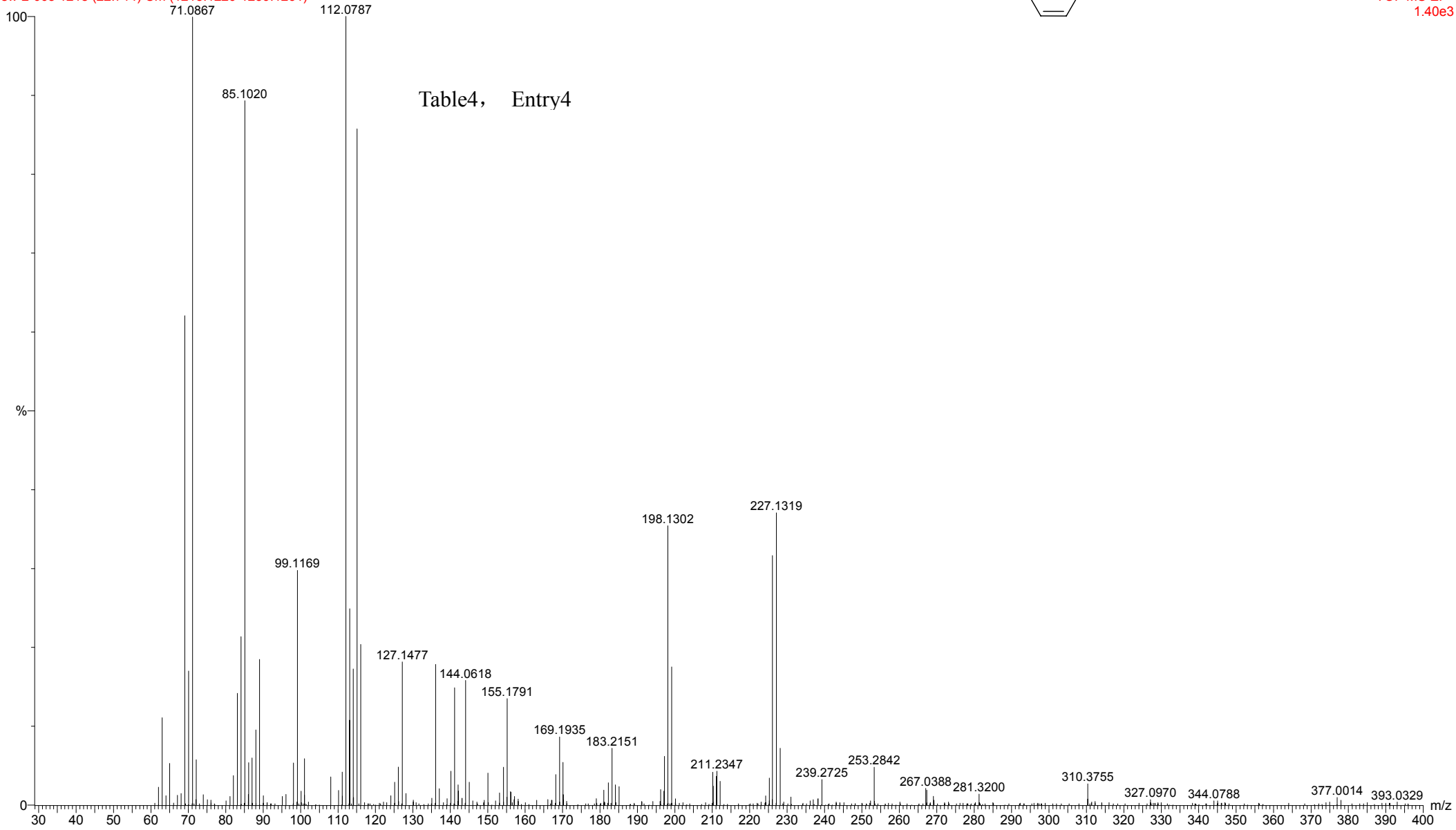
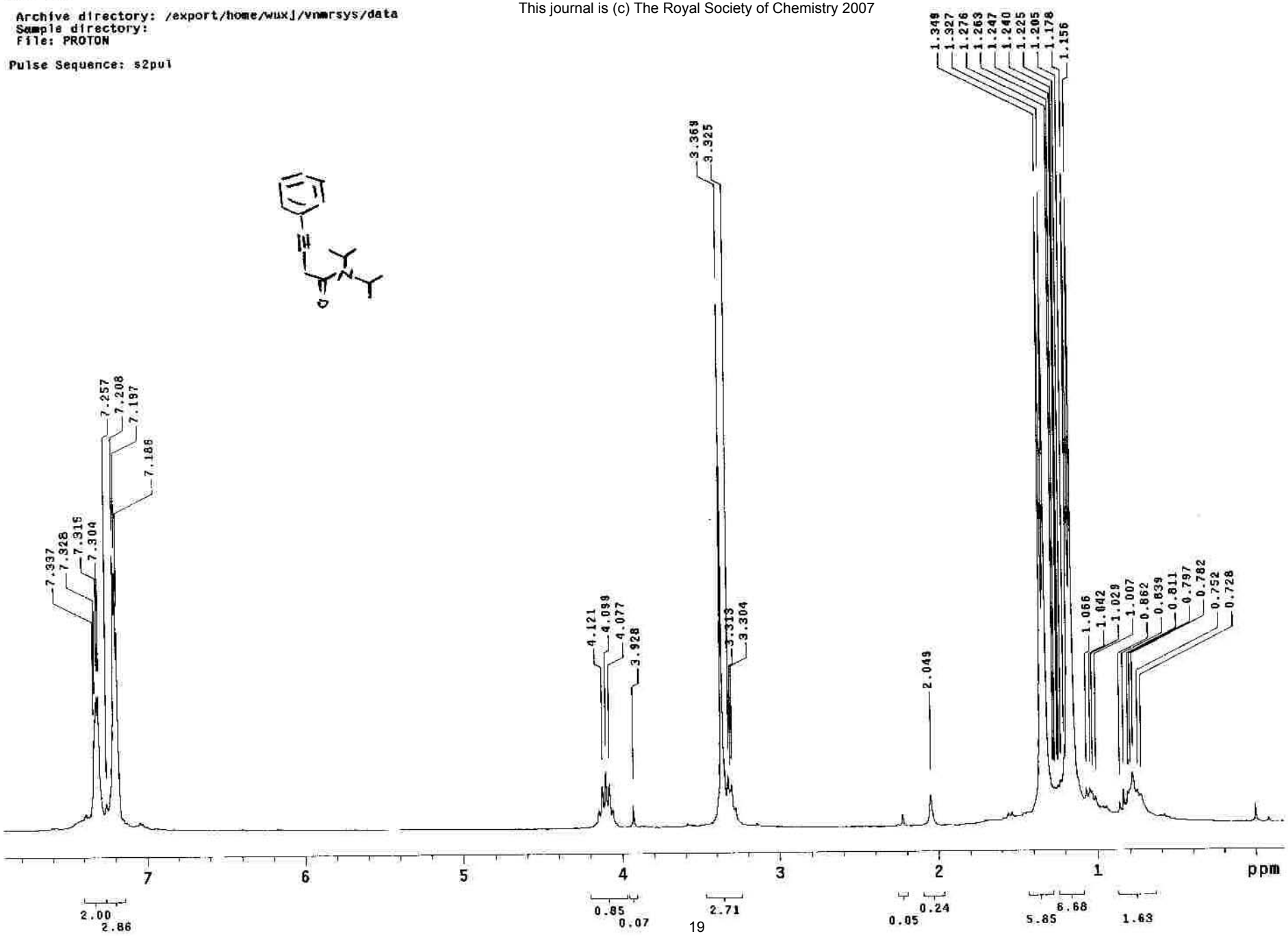
sw-2-003 1218 (22.714) Cm (1213:1220-1239:1261)

Table4， Entry4




sw-2-013
Archive directory: /export/home/wuxj/vnmrsys/data
Sample directory:
File: PROTON
Pulse Sequence: s2pul
7.337
7.328
7.315
7.304
7.257
7.208
7.197
7.186
4.121
4.099
4.077
3.928
3.369
3.325
3.313
3.304
2.049
1.349
1.327
1.276
1.263
1.247
1.240
1.225
1.205
1.178
1.156
1.066
1.042
1.029
1.007
0.862
0.839
0.811
0.797
0.782
0.752
0.728
ppm
2.00
2.86
0.85
0.07
2.71
0.05
0.24
5.85
6.68
1.63

sw-2-013-C

Archive directory: /export/home/wuxj/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-300BB "mercury300"

Relax. delay 1.000 sec
Pulse 43.6 degrees
Acq. time 0.500 sec
Width 18867.9 Hz
2048 repetitions
OBSERVE C13, 75.4552576 MHz
DECOUPLE H1, 300.0814285 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 32768
Total time 55 min, 7 sec

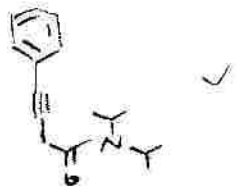
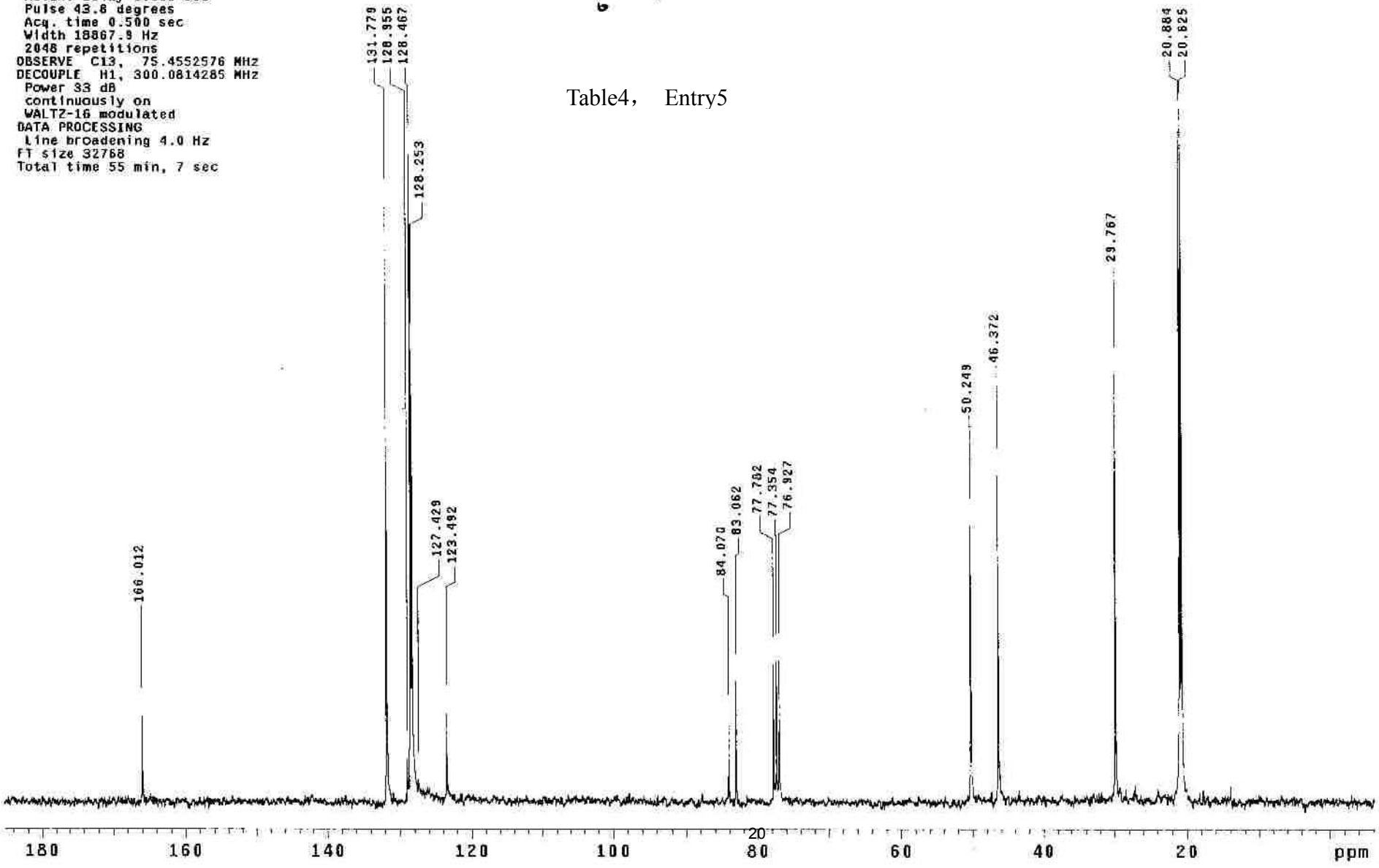
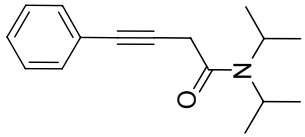


Table4， Entry5



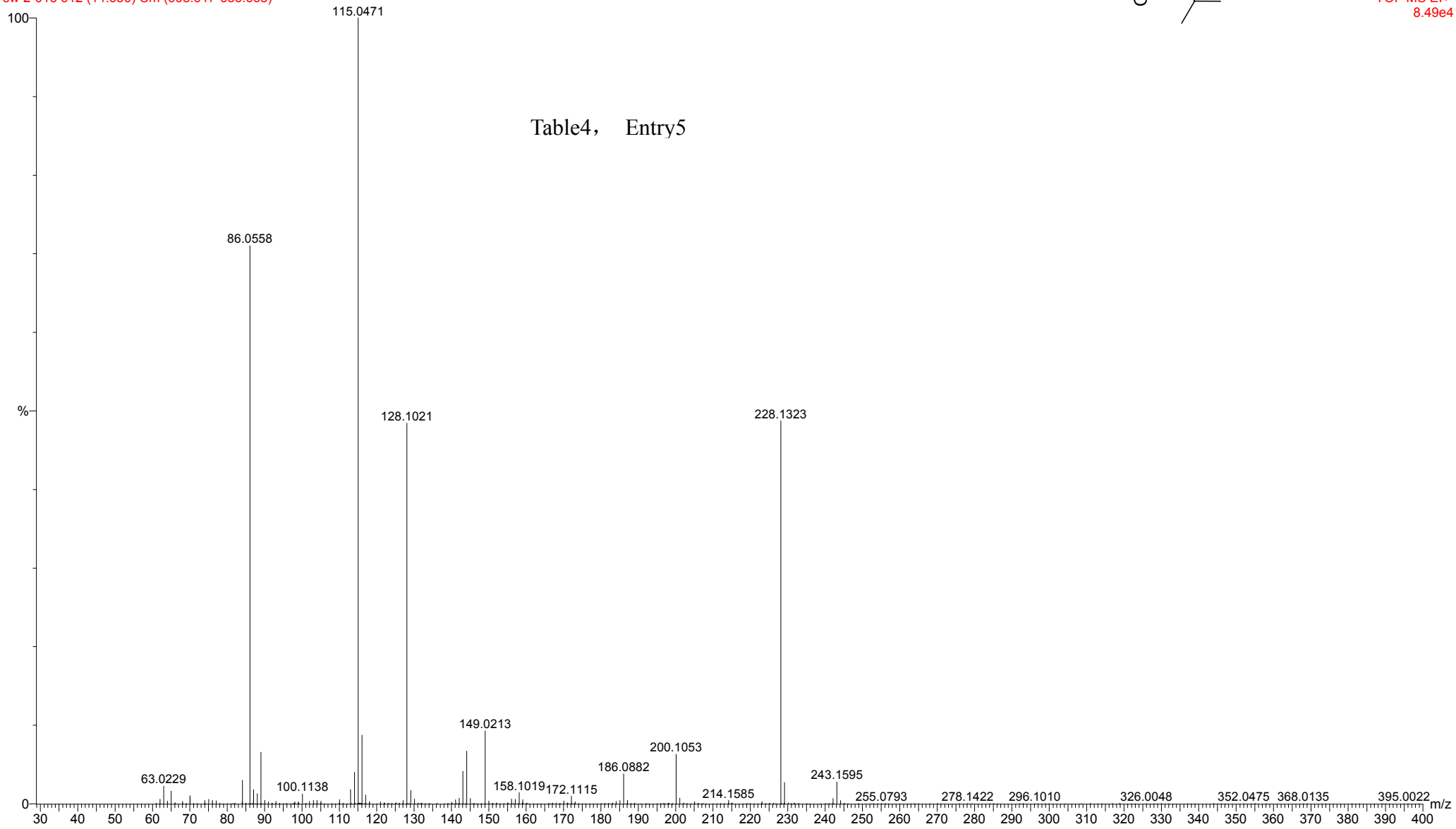
GCT CA100



13:12:58
30-May-2006
TOF MS EI+
8.49e4

sw-2-013 612 (14.650) Cm (608:617-636:665)

Table4， Entry5

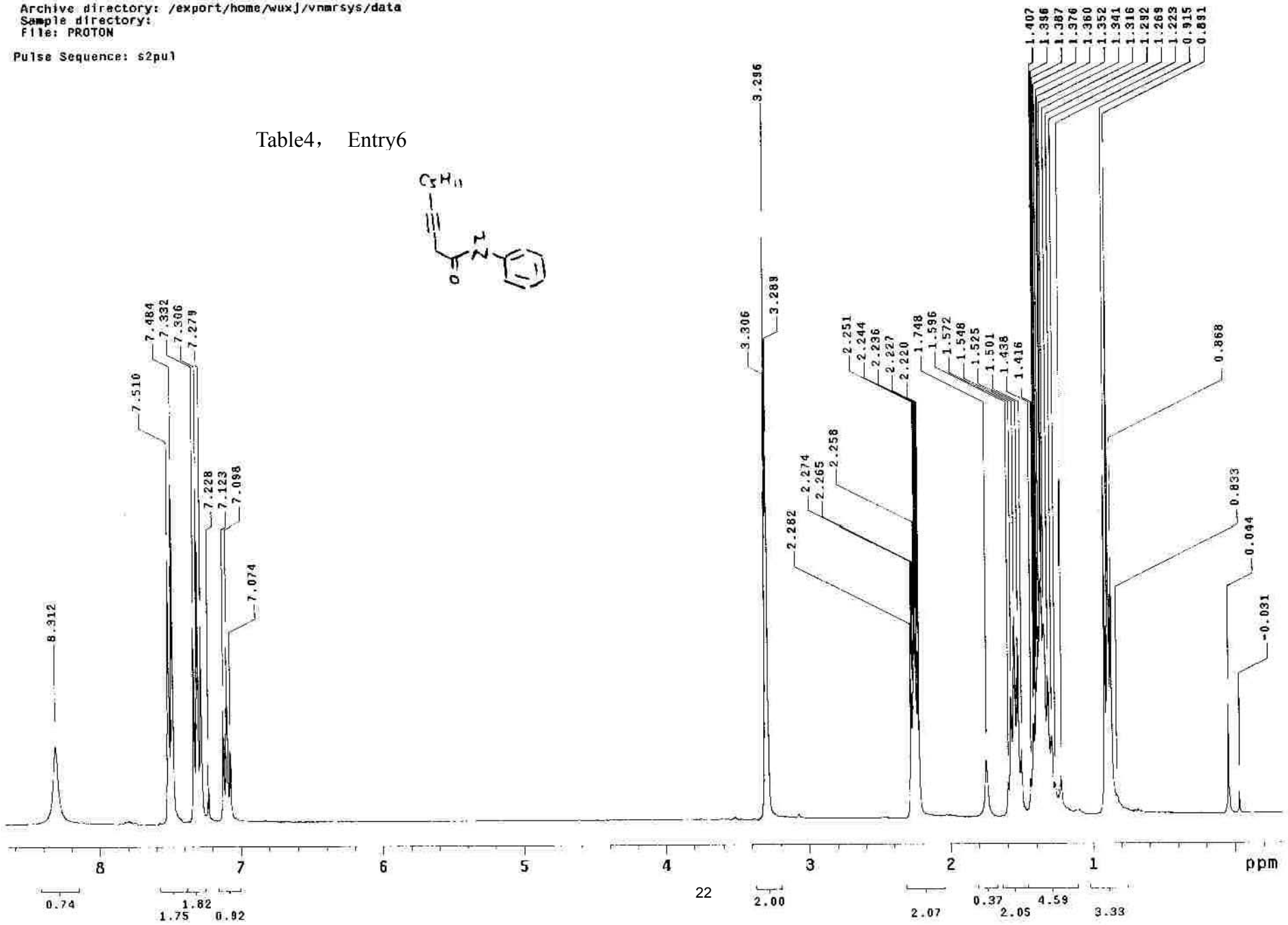


sw-2-012

Archive directory: /export/home/wuxj/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Table4， Entry6

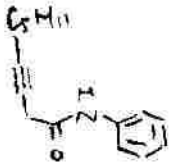


sw-2-012-C

Archive directory: /export/home/wu/vrmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Table4， Entry6



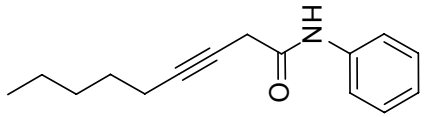



Table4， Entry6

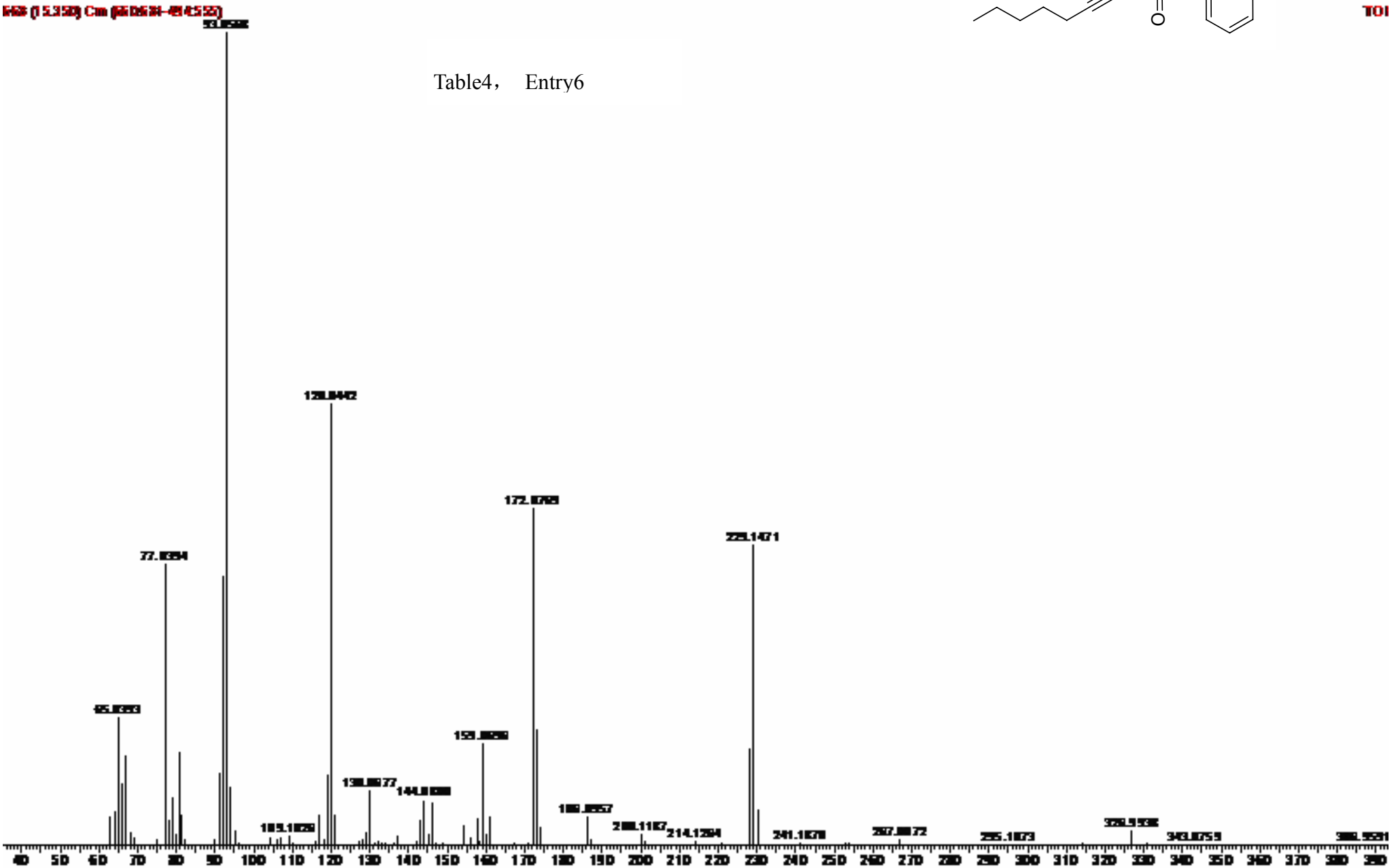
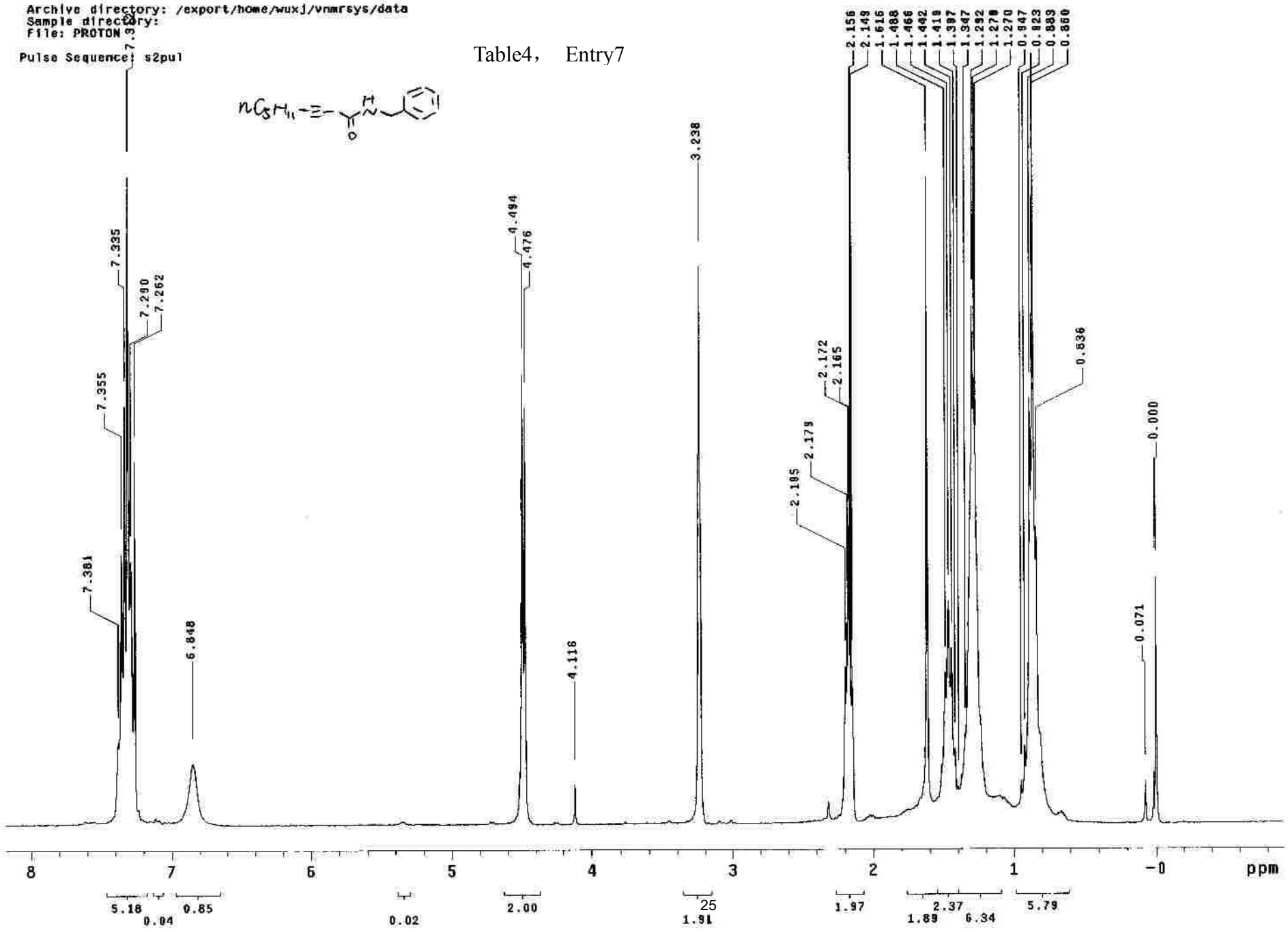


Table4， Entry7



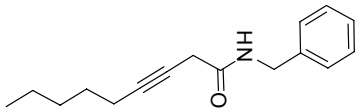
SW5.22-C

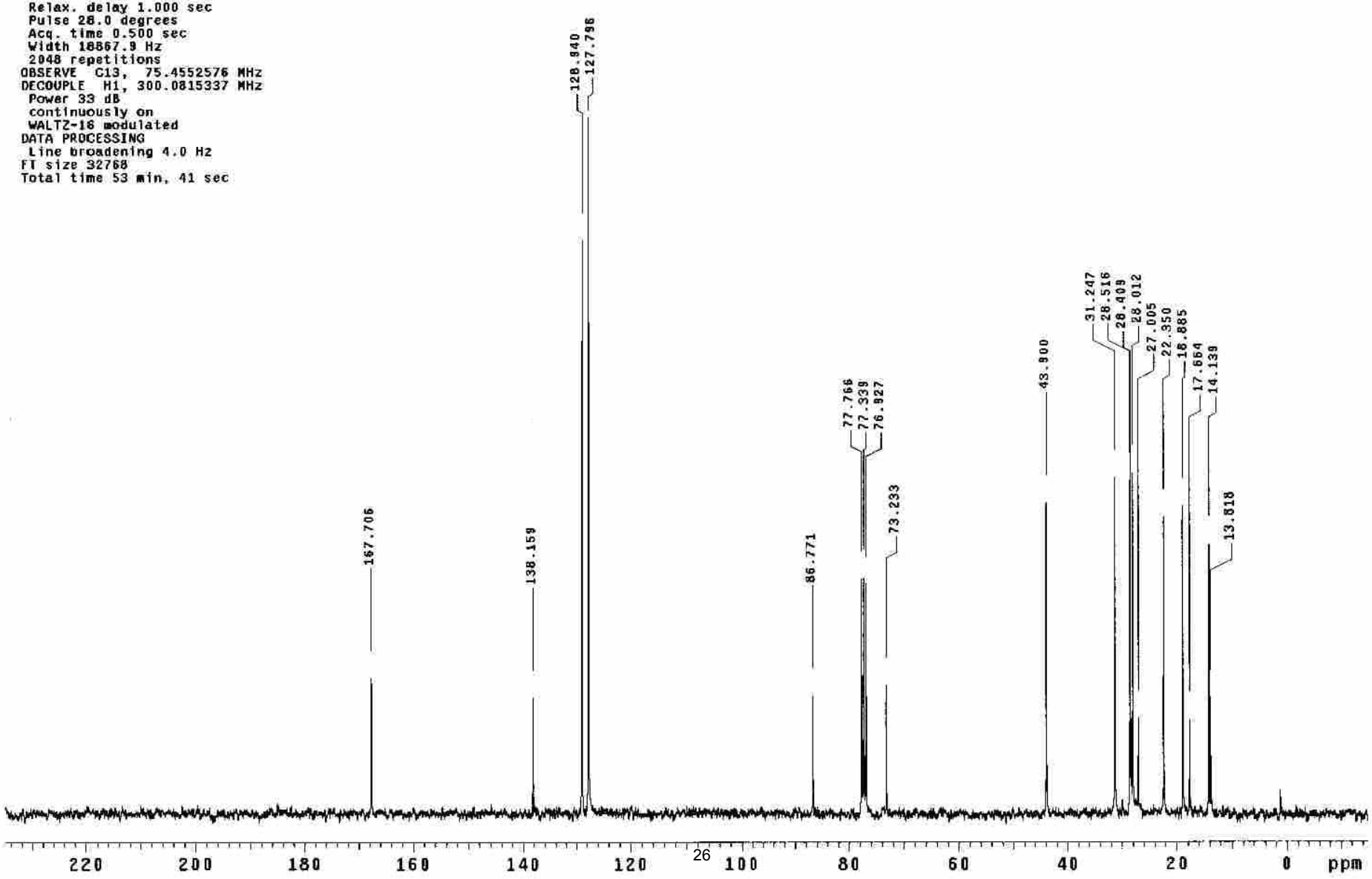
Archive directory: /export/home/wuxj/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-300BB "mercury300"

Relax. delay 1.000 sec
Pulse 28.0 degrees
Acq. time 0.500 sec
Width 18867.9 Hz
2048 repetitions
OBSERVE C13, 75.4552576 MHz
DECOUPLE H1, 300.0815337 MHz
Power 33 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 4.0 Hz
FT size 32768
Total time 53 min, 41 sec

Table4， Entry7



sw-2-004

Archive directory: /export/home/wwxj/wwersys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

Table4， Entry8

Table4， Entry8

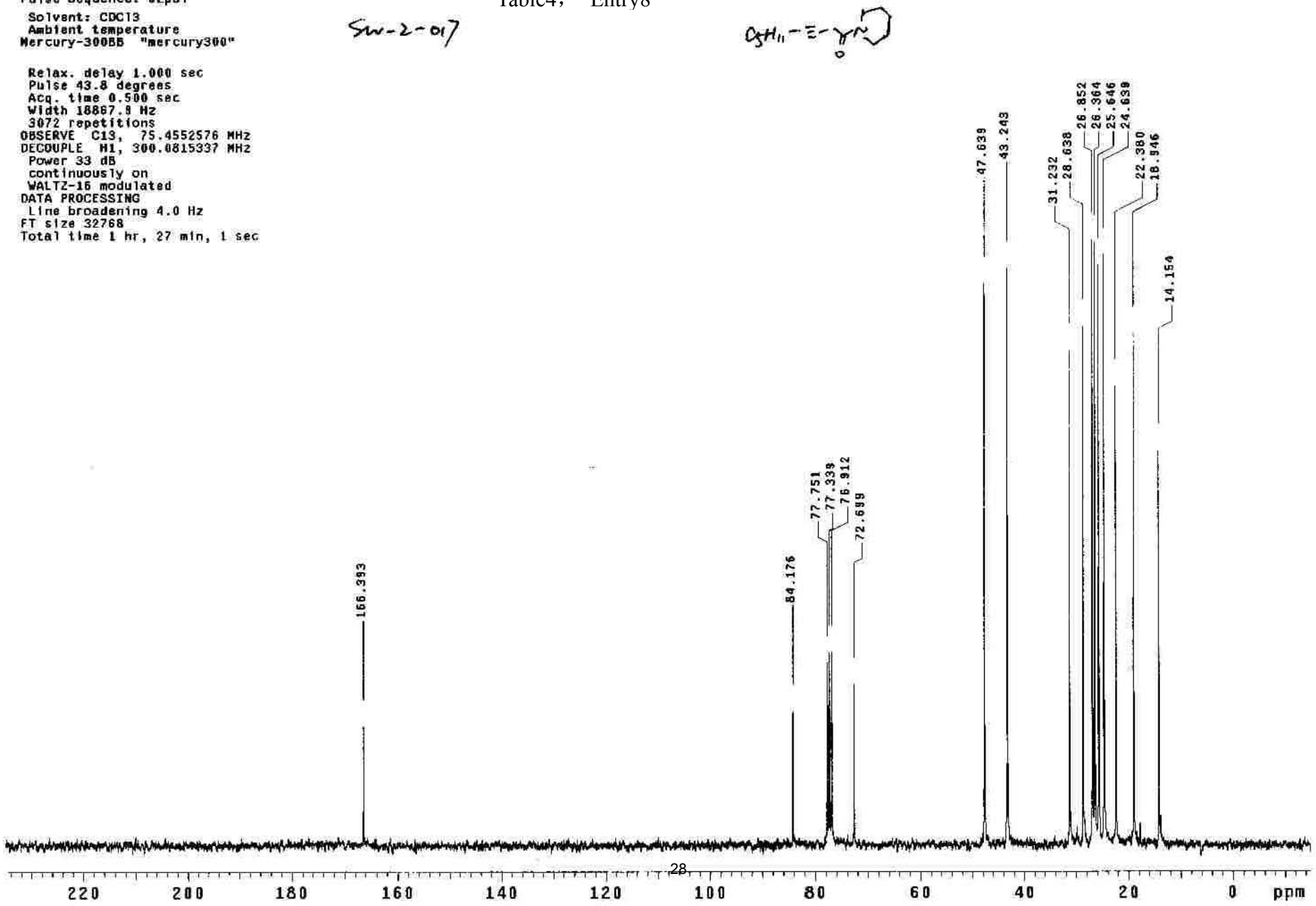
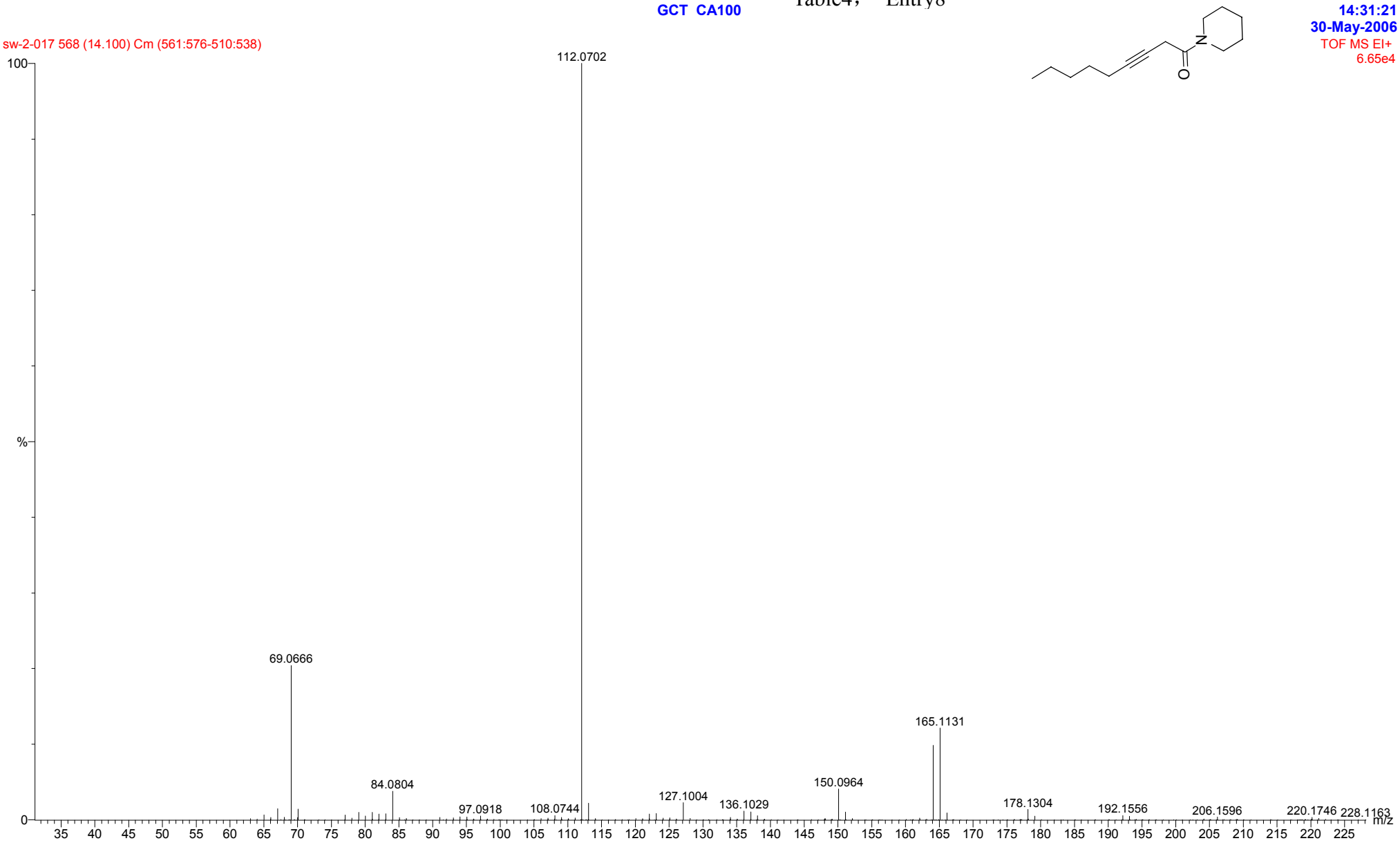


Table4， Entry8



sw-2-010

Archive directory: /export/home/wuxj/vnmrsys/data
Sample directory:
File: PROTON

Pulse Sequence: s2pul

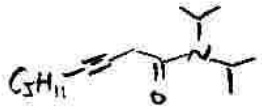


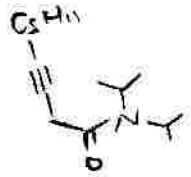
Table4， Entry9

sw-2-010-C

Archive directory: /export/home/wu/vnmrsys/data
Sample directory:
File: CARBON

Pulse Sequence: s2pul

Table4， Entry9



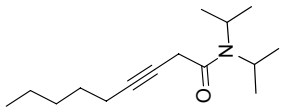

166.788
84.190
77.495
77.283
77.072
73.080
49.855
46.147
31.249
28.997
28.640
22.368
21.035
20.554
18.966
14.128
13.757
180
160
140
120
100
80
60
40
20
ppm

GCT CA100

10:24:27
30-May-2006
TOF MS EI+
1.43e5

sw-2-010 408 (12.103) Cm (402:416-452:513)

Table4， Entry9



1. Davies, H. M. L.; Boebel, T. A., *Tetrahedron Letters* **2000,** 41, 8189-8192.

2. Usugi, S.-I.; Yorimitsu, H.; Shinokubo, H.; Oshima, K., *Bulletin of the Chemical Society of Japan* **2002,** 75, 2687-2690.

3. Kruglikova, R. I.; Kalinina, G. R., *Khim. Khim. Tekhnol., Tr. Yubileinoi Konf., Posvyashch. 70-Letiyu Inst. (Mosk. Inst. Tonkoi Khim. Tekhnol.)*. 1972; p 156-158.