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Supplementary Information

Microwave-Assisted Clean Synthesis of Amides via Aza-Wittig Reaction under Solvent-Free Condition

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Experimental

General

All chemicals, reagents and solvents were of commercially high purity grade purchased from Avra Synthesis Pvt. Ltd. and Merck Ltd. India. Silica gel (60-120 mesh) was used for column chromatographic isolation and purification of the amides synthesized. Organic azides used in the investigation were prepared according to the literature procedures. Melting points were noted on electro-thermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Avance 300 MHz spectrometer and the chemical shifts are reported as δ values in parts *per* million (ppm) relative to tetramethylsilane, with *J* values in Hertz. The splitting patterns in ^{1}H NMR spectra are reported as follows: s = singlet; d = doublet; t = triplet; q = quartet; br s = broad singlet; br d = broad doublet; m = multiplet. ^{13}C NMR data are reported with the solvent peak ($CDCl_3$ = 77.0) as the internal standard. Elemental analyses were performed by CNRS (Vernaison, Lyon) and were in agreement with the calculated values within ±0.4%.

Experimental procedure for the preparation of azides used in the synthesis of amides

Benzyl azide[1]

To a stirred solution of the benzyl bromide (1 g, 5.84 mmol) in water/acetone mixture (1:4 v/v, 10 mL), sodium azide (0.57 g, 8.77 mmol) was added. The resulting suspension was stirred at room temperature for 24 h. Dichloromethane was added to the mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL) and the combined organic layers were dried over anhydrous magnesium sulphate. Solvent was removed under reduced pressure, and the azide was obtained in quantitative yield sufficiently pure to use without further work up.

1-Azido-3-phenyl-2-cyclohex-2-ene[2]

To 20% ethanolic potassium hydroxide (10 mL), 1a-azido-2a-iodo-1e-phenylcyclohexane (1.0 g, 3.0 mmol) was added and the mixture refluxed for 1 h in water bath. Then the mixture after cooling to room temperature was added to excess water and extracted with ether (3 × 20 mL). The organic extract was washed repeatedly with water, dried over anhydrous magnesium sulphate to give the allyl azide contaminated with 1-phenylcyclohexene. Column chromatographic purification on silica with pet ether/ethyl acetate as the eluant afford 1-azido-3-phenyl-2-cyclohex-2-ene in good yield.

Phenyl azide[3]

These azides were prepared by the diazotization procedure similar to that used for the preparation of iodobenzene from aminobenzene by diazotization followed by treatment of aqueous potassium iodide at low temperature. Herein, by the same procedure diazotized solution of aminobenzene and 1-amino-4-bromobenzene were treated with aqueous sodium azide to afford the corresponding organic azides, respectively, which was used without further purification for the synthesis of amides in our investigation.

N-(3-phenylcyclohex-2-enyl)acetamide (Table 1, entry 11)

To an intimate mixture of triethylphosphite (166 mg, 1 mmol) and 1-azido-3-phenyl-2-cyclohexene (200 mg, 1 mmol) in a micro-wave vial (10 mL) equipped with a magnetic stirring bar, acetic anhydride (134 mg, 1.3 mmol) was added in drops while stirring. Stirring was continued until liberation of nitrogen ceased and the reaction vessel

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was sealed with a septum. It was then placed into the cavity of a focused monomode micro-wave reactor (CEM Discover, benchmate) and operated for 15 min at 150 °C (temperature monitored by a built-in IR sensor). The reaction temperature was maintained by modulating the power level of the reactor. The reaction vessel was then cooled to room temperature and the residue was dissolved in ethylacetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amide as white solid. Experimental 85%, mp 118 ºC; IR (KBr) ν_{max}/cm^{-1}: 3445 (–NH), 1671 (–C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.20-7.40 (m, 5H, ArH), 5.96 (pseudo triplet, 1H, C=CH), 5.60 (br d, 1H, *J* 7.5 Hz, –NH), 4.70 (br s,1H, CHN), 1.99 (s, 3H, $-COCH_3$), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H, alicyclic proton), 1.65-1.77 (m, 2H, alicyclic protons), 1.39-1.53 (m, 1H, alicyclic proton); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.4, 148.1, 139.9, 138.7, 126.2, 125.0, 123.6, 45.5, 29.0, 27.1, 23.2, 20.1. Anal. calc. (%) for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found (%) C, 78.25; H, 7.95; N, 6.51.

N-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12)

The reaction mixture obtained from triethylphosphite (166 mg, 1 mmol), 1-azido-3-phenyl-2-cyclohexene (200 mg, 1 mmol) and propionic anhydride (170 mg, 1.3 mmol) was irradiated with microwave for the indicated time and temperature in Table 1 (vide supra); then, it was cooled to room temperature and the residue was dissolved in ethylacetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amide as white solid. Yield 85%, mp 97 ºC; IR (KBr) ν_{max}/cm^{-1}: 3444 (–NH), 1682 (–C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.20-7.50 (m, 5H, ArH), 5.96 (pseudo triplet, 1H, C=CH), 5.62 (br d, 1H, *J* 6.9 Hz, –NH), 4.70 (br s, 1H, CHN), 2.21 (q, 2H, *J* 7.5 Hz, $COCH_2$) 1.16 (t, 3H, *J* 7.5 Hz,$-CH_3$), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H, alicyclic proton), 1.65-1.77 (m, 2H, alicyclic protons), 1.39-1.53 (m, 1H, alicyclic proton); ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 173.0, 141.2, 140.1, 128.2, 127.3, 125.1, 124.6, 45.3, 29.8, 29.1, 27.1, 20.3, 9.8. Anal. calc. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.46; H, 8.36; N, 6.10.

N-(3-phenylcyclohex-2-enyl)butyramide (Table 1, entry 13)

The reaction mixture obtained from triethylphosphite (166 mg, 1 mmol), 1-azido-3-phenyl-2-cyclohexene (200 mg, 1 mmol) and butyric anhydride (200 mg, 1.3 mmol) was irradiated with microwave for the indicated time and temperature in Table 1 (vide supra); then, it was cooled to room temperature and the residue was dissolved in ethylacetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amide as white solid. Experimental 85%, mp 128-129 ºC; IR (KBr) ν_{max}/cm^{-1}: 3447 (–NH), 1692 (–C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.25-7.39 (m, 5H, ArH), 5.96 (s, 1H, C=CH), 5.50 (br d, *J* 6.4 Hz, 1H, NH), 4.71 (br s, 1H, CHN), 2.36-2.40 (m, 2H), 2.16 (m, 2H), 1.95-1.97 (m, 1H, alicyclic protons), 1.81-1.83 (m, 2H, alicyclic protons), 1.68 (m, 2H, alicyclic protons), 1.55-1.57 (m, 1H, alicyclic protons), 0.95 (t, *J* 14.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 172.9, 141.2, 140.2, 128.2, 127.3, 125.1, 124.6, 45.3, 29.8, 29.1, 27.2, 20.3, 18.3, 9.8. Anal. calc. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.88; H, 8.72; N, 5.77.

N-(3-phenylcyclohex-2-enyl)acetamide (entry 14)

The reaction mixture obtained from triethylphosphite (166 mg, 1 mmol), 1-azido-3-phenyl-2-cyclo-hexene (200 mg, 1 mmol) and acetyl chloride (110 mg, 1.3 mmol) was irradiated with microwave for the indicated time and temperature in Table 1 (vide supra); then, it was cooled to room temperature and the residue was dissolved in ethylacetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amide as white solid. Yield: 166 mg (77%).

N-(3-phenylcyclohex-2-enyl)benzamide (entry 15)

The reaction mixture obtained from triethylphosphite (166 mg, 1 mmol), 1-azido-3-phenyl-2-cyclo-hexene (200 mg, 1mmol) and benzoyl chloride (185 mg, 1.3 mmol) was irradiated with microwave for the indicated time and temperature in Table 1 (vide supra); then, it was cooled to room temperature and the residue was dissolved in ethylacetate and washed repeatedly with water followed by saturated sodium bicarbonate solution to afford the amide as white solid. Yield 79%, mp 154 ºC; IR (KBr) ν_{max}/cm^{-1}: 3451 (–NH), 1670 (–C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29-7.75 (10H, m, ArH), 6.00 (br s, 1H, C=CH), 5.60 (br d, 1H, *J* 8.4Hz, NH), 4.60 (br s, 1H, CHN), 2.20-2.42 (m, 2H, alicyclic protons), 1.95-2.07 (m, 1H , alicyclic proton), 1.65-1.77 (m, 2H, alicyclic protons), 1.39-1.53 (m, 1H, alicyclic proton); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.7, 148.2, 140.4, 138.6, 134.7, 131.3, 128.4, 126.9, 126.4, 125.1, 123.6, 45.0, 29.1, 27.2, 20.4. Anal. calc. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 4.05. Found: C, 82.13; H, 6.91; N, 5.06.

N-benzylacetamide (Table 1, entry 1)

Yield 74%, mp 58 ºC (Lit. 59-60 ºC);[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33-7.36 (m, 5H, ArH), 5.10 (s, 2H, CH_2N), 2.09 (s, 3H, CH_3).

N-benzylpropionamide (Table 1, entry 2)

Yield 78%; mp 47 ºC (Lit.48-49 ºC);[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.12-7.33 (m, 5H, ArH), 4.99 (s, 2H, CH_2N), 2.75 (q, *J* 7.2 Hz, 2H, CH_2), 1.14 (t, *J* 7.2 Hz, 3H, CH_3).

N-benzylbutyramide[6] (Table 1, entry 3)

Yield 84%; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.12-7.35 (m, 5H, ArH), 4.98 (s, 2H, CH_2–N), 2.69 (t, *J* 7.2Hz, 2H, CH_2), 1.69 (sextet, *J* 7.2Hz, 2H, CH_2), 0.93 (t, *J* 7.2Hz, 3H, CH_3).

N-benzylbenzamide (Table 1, entry 5)

Yield 76%; mp 103 ºC (Lit.103-104 ºC);[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32-8.18 (10H, m, ArH), 6.61(1H, br s, NH), 4.65 (2H, d, *J* 5.7 Hz, CH_2–N).

N-phenylacetamide (Table 1, entry 6)

Yield 75%; mp 115 ºC (Lit.115-116 ºC);[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.08-7.50 (5H, m, ArH), 2.18 (s, 3H, CH_3).

N-phenylpropionamide (Table 1, entry 7)

Yield 80%; mp 105 ºC (Lit. 105-106 ºC);[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06-7.56 (m, 5H, ArH), 2.38 (q, *J* 7.5Hz, 2H, CH_2), 1.24 (t, *J* 7.5Hz, 3H, CH_3).

N-phenylbutyramide[6] (Table 1, entry 8)

Yield 83%; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06-7.52 (m, 5H, ArH), 2.32 (t, *J* 7.5Hz, 2H, CH_2), 1.75 (sextet, *J* 7.5Hz, 2H, CH_2), 0.99 (t, *J* 7.5Hz, 3H, CH_3).

N-phenylbenzamide (Table 1, entry 10)

Yield 77%; mp 164 ºC (Lit. 162ºC);[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.15-7.88 (m, 10H, ArH).

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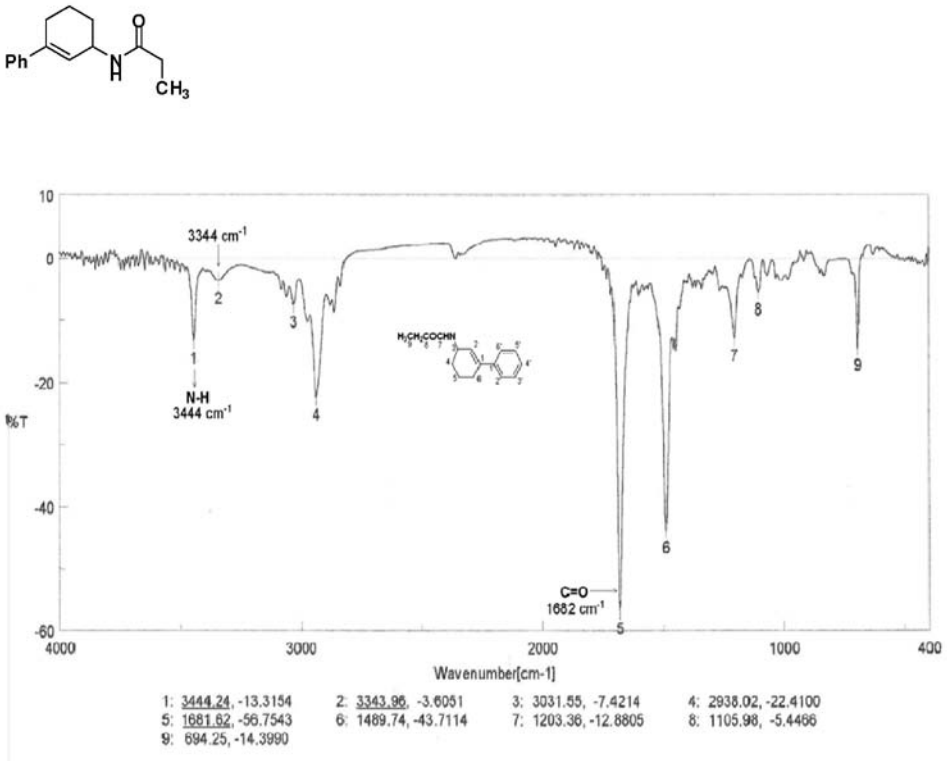
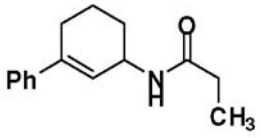


Figure S1. IR spectrum of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

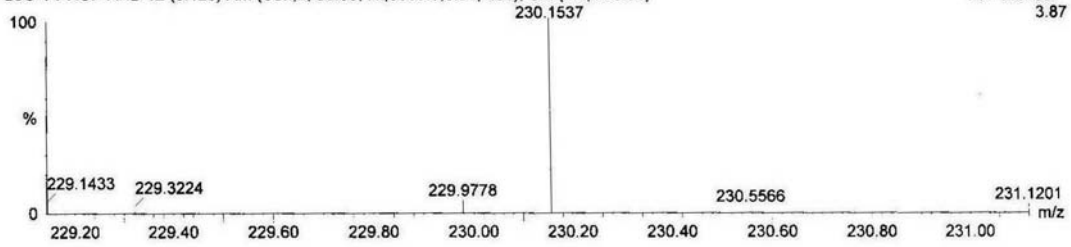


Elemental Composition Report

Single Mass Analysis
Tolerance = 200.0 mDa / DBE: min = -1.5, max = 50.0
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions
2 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)

QTOF MICRO Dept of chemistry - IITM - Chennai 11-Dec-2010 14:27:44
SJG-1-PROP-AND 12 (0.120) AM (Cen,2, 80.00, Ht,5000.0,0.00,1.00); Sm (Mn, 2x3.00) TOF MS ES+ 3.87



Minimum:				-1.5		
Maximum:		200.0	5.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	Score	Formula
230.1537	230.1545	-0.8	-3.6	6.5	1	C15 H20 N O

Figure S2. HRMS of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

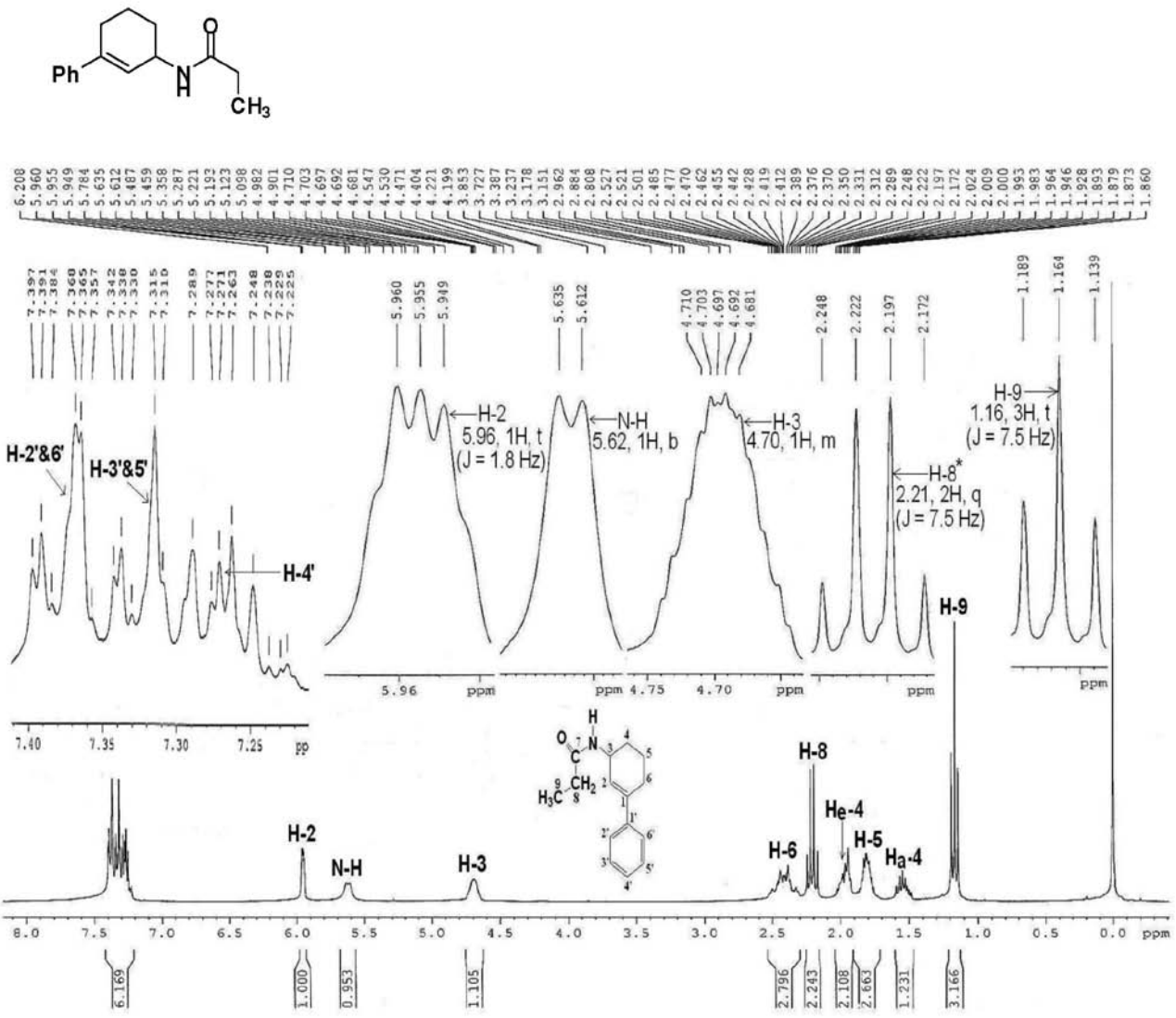


Figure S3. ^{1}H NMR (300 MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

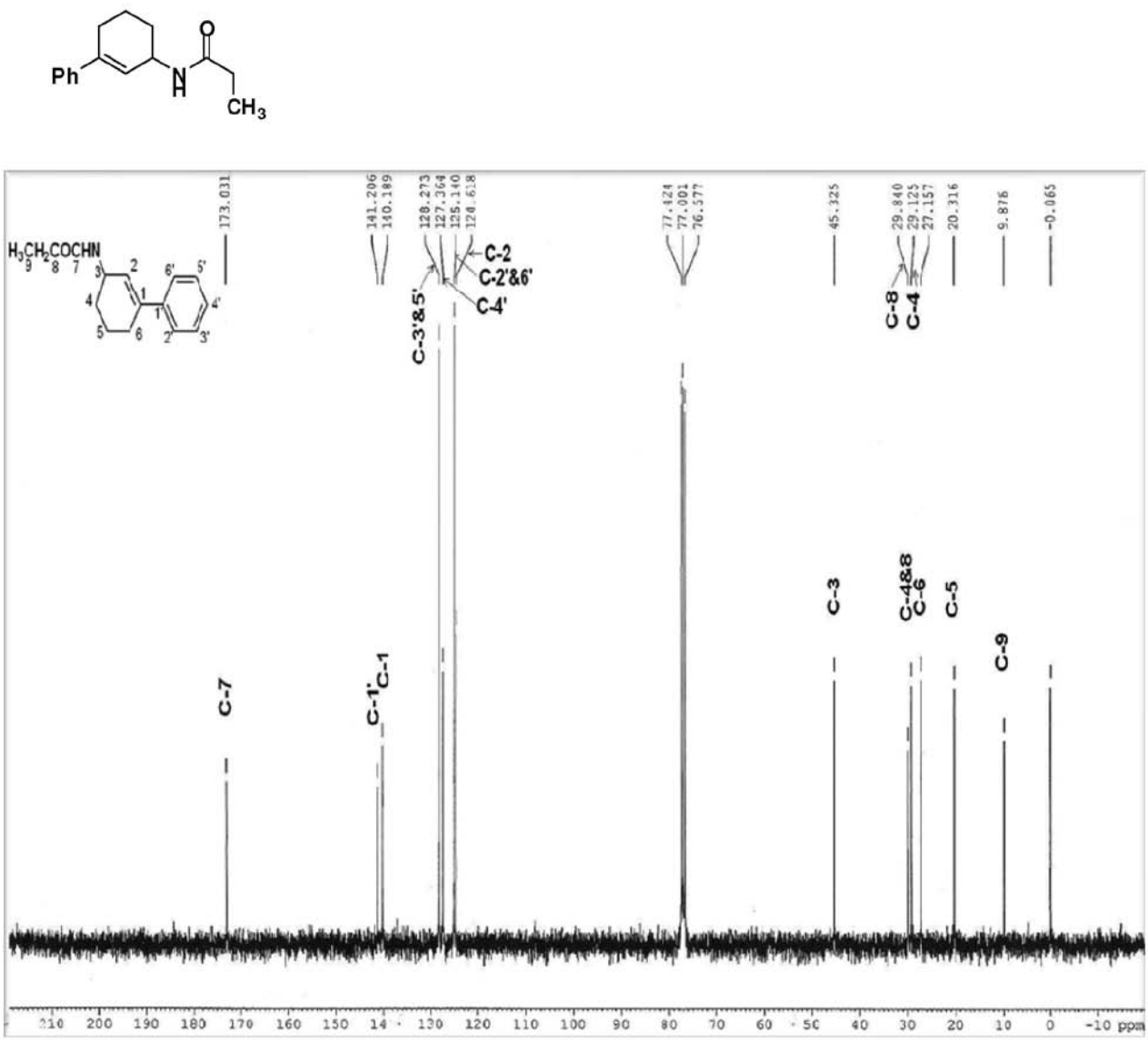


Figure S4. ^{13}C NMR (75 MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

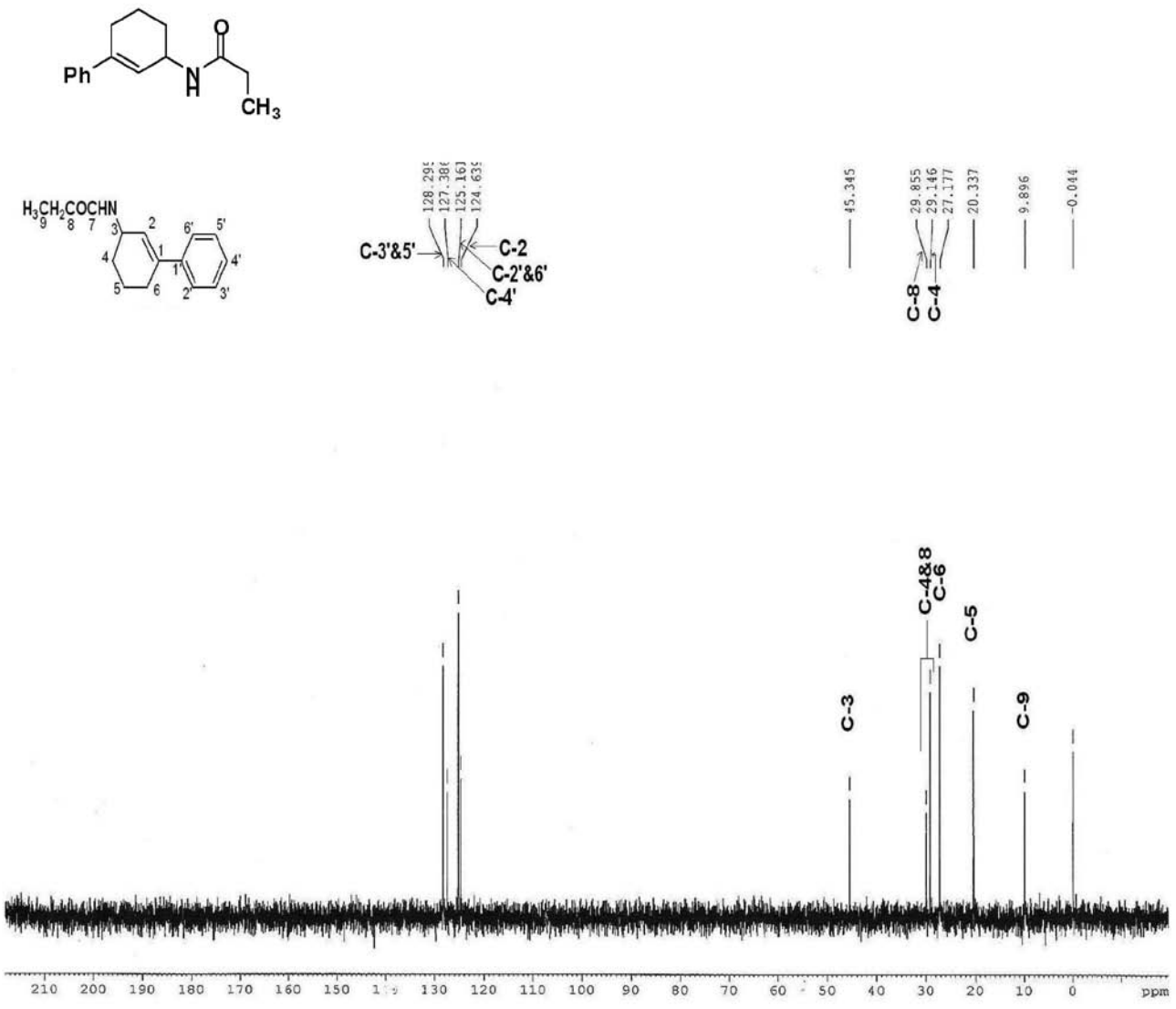


Figure S5. DEPT- 45 of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

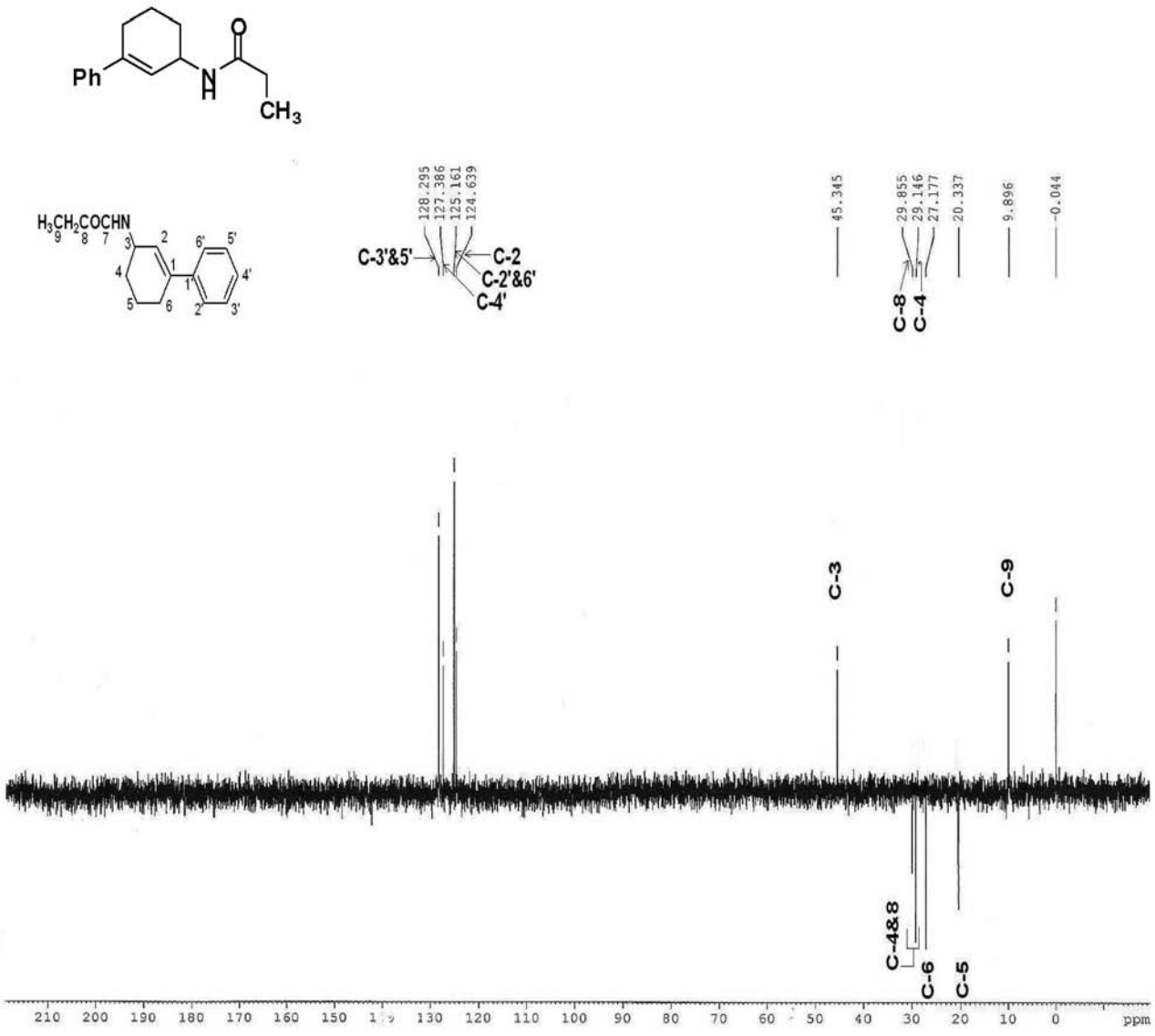


Figure S6. DEPT-135 of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

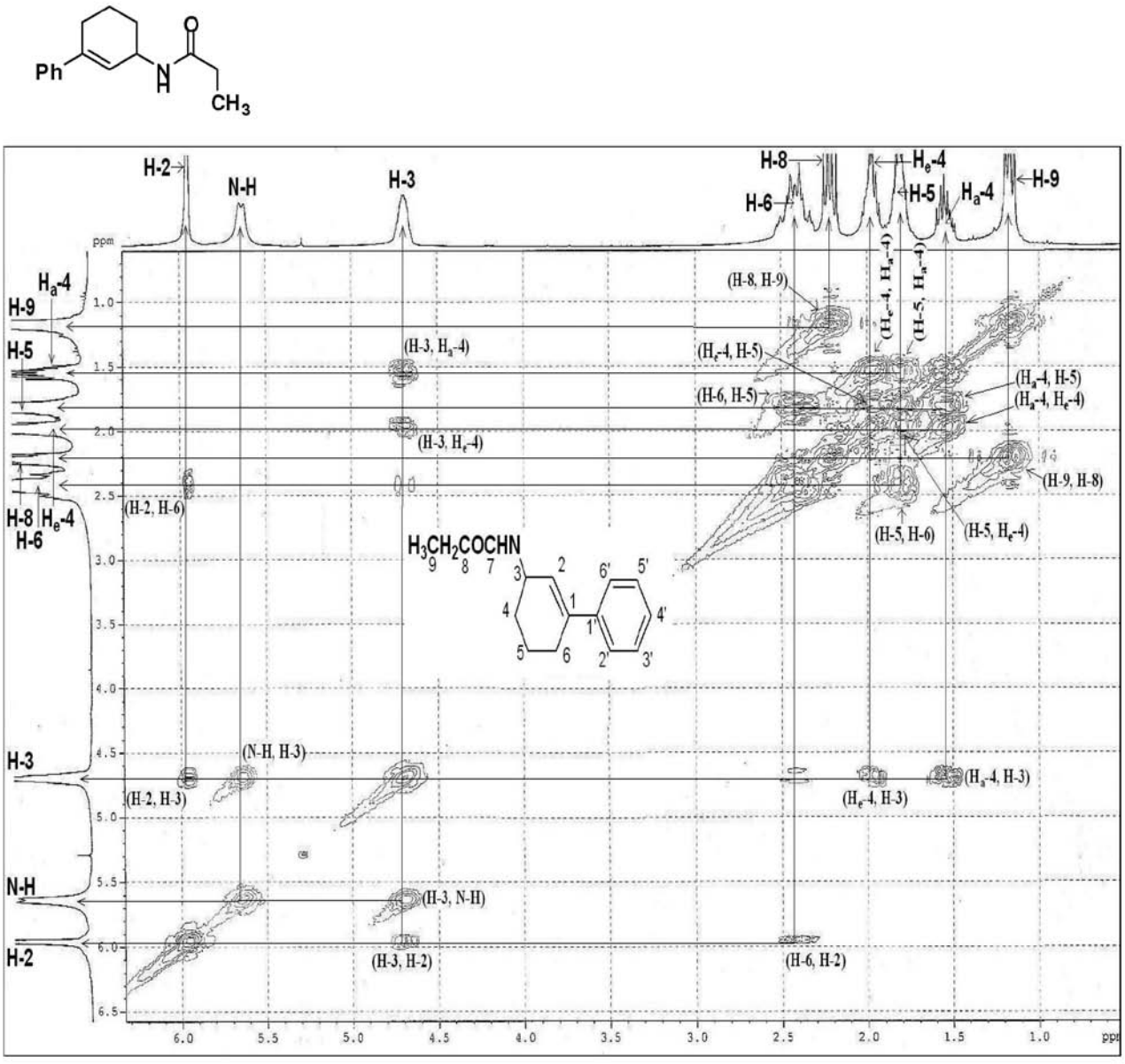


Figure S7. (H, H) COSY of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

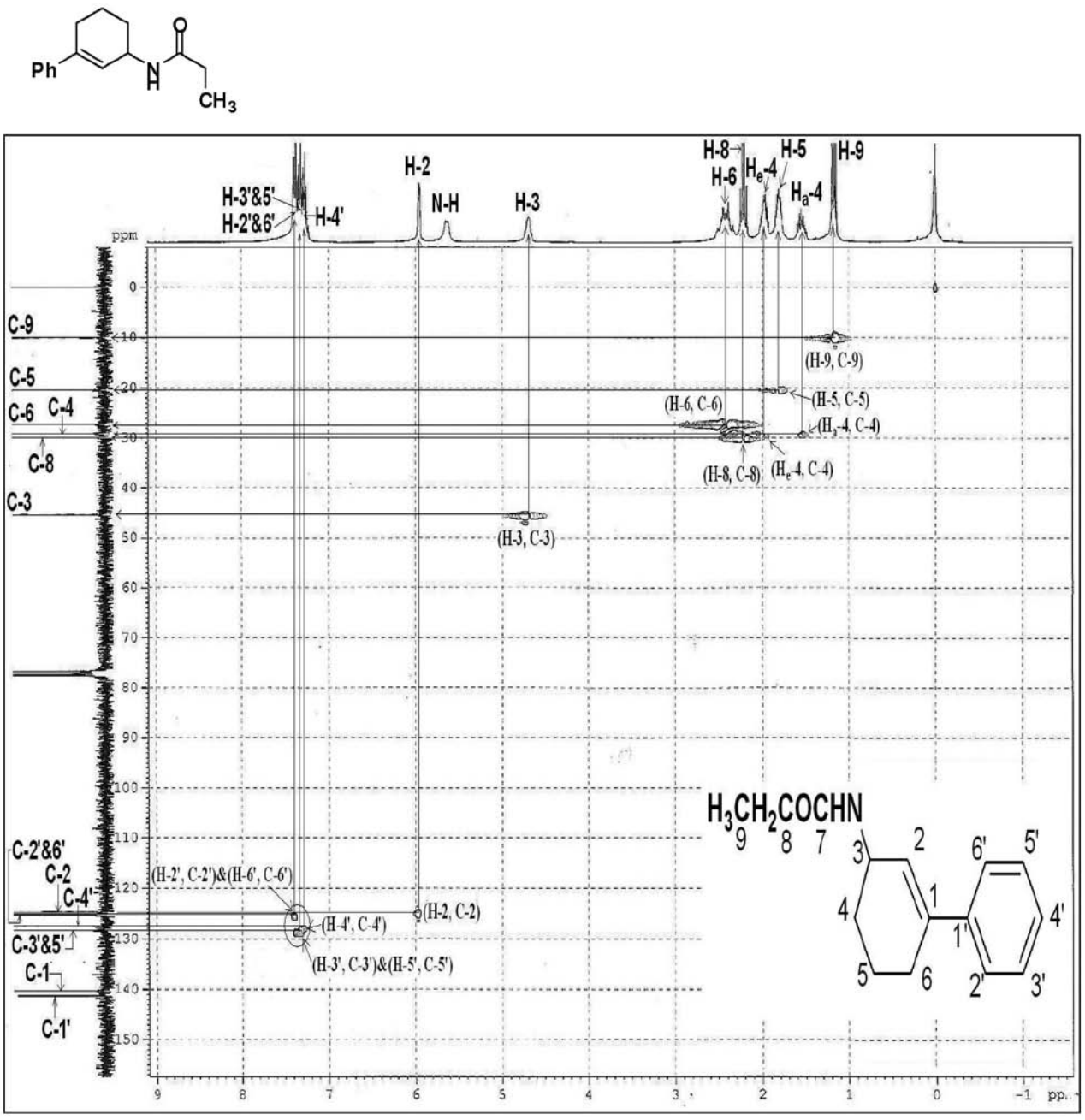


Figure S8. (C, H) COSY of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

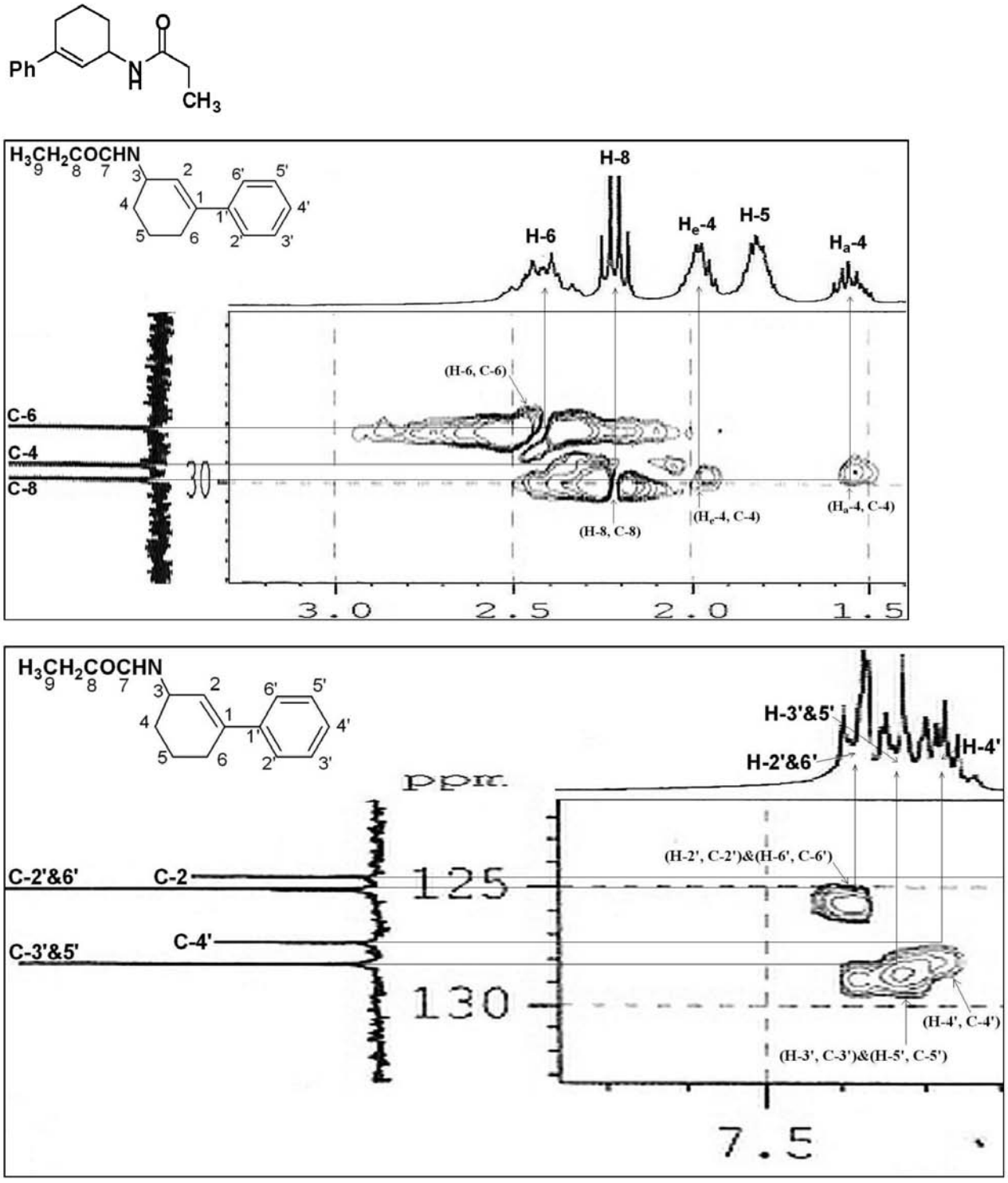


Figure S9. (C, H) COSY of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12) (expansion).

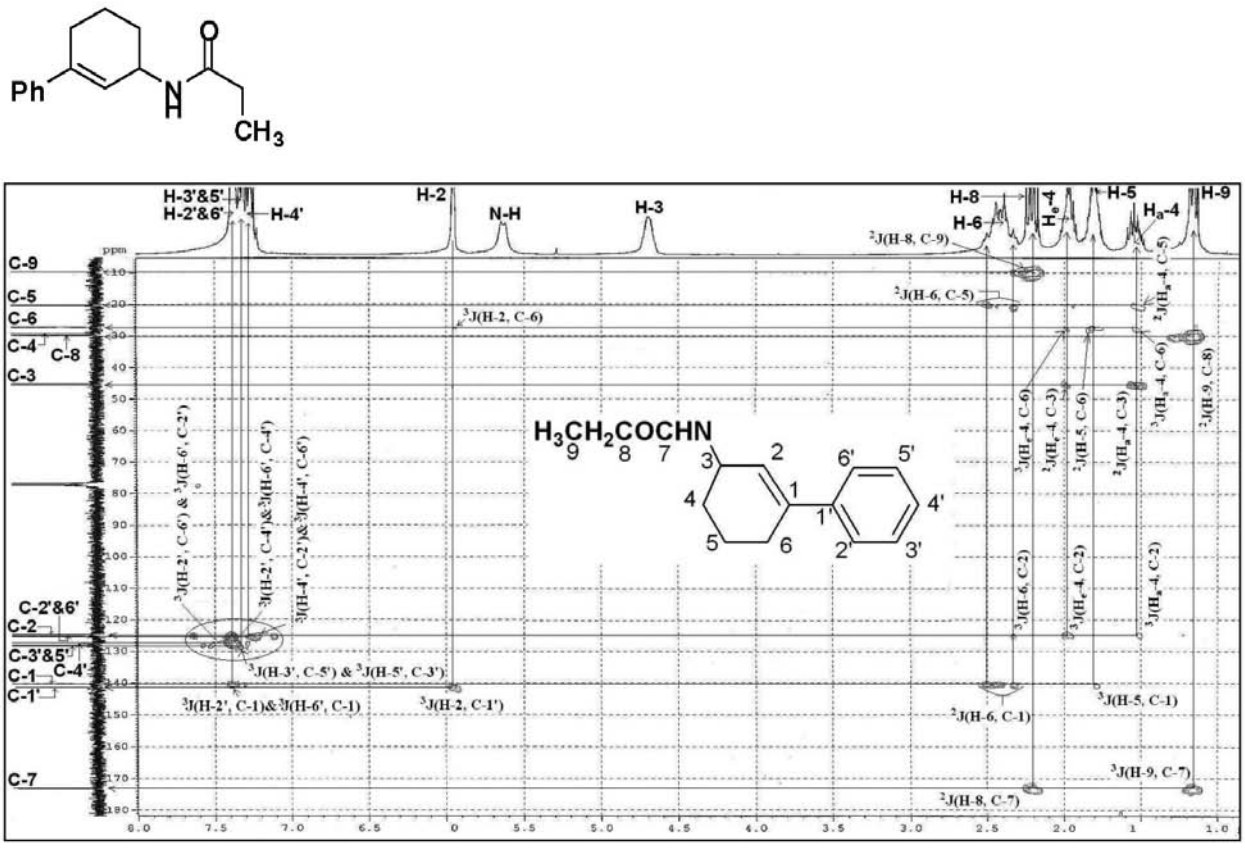


Figure S10. HMBC of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12).

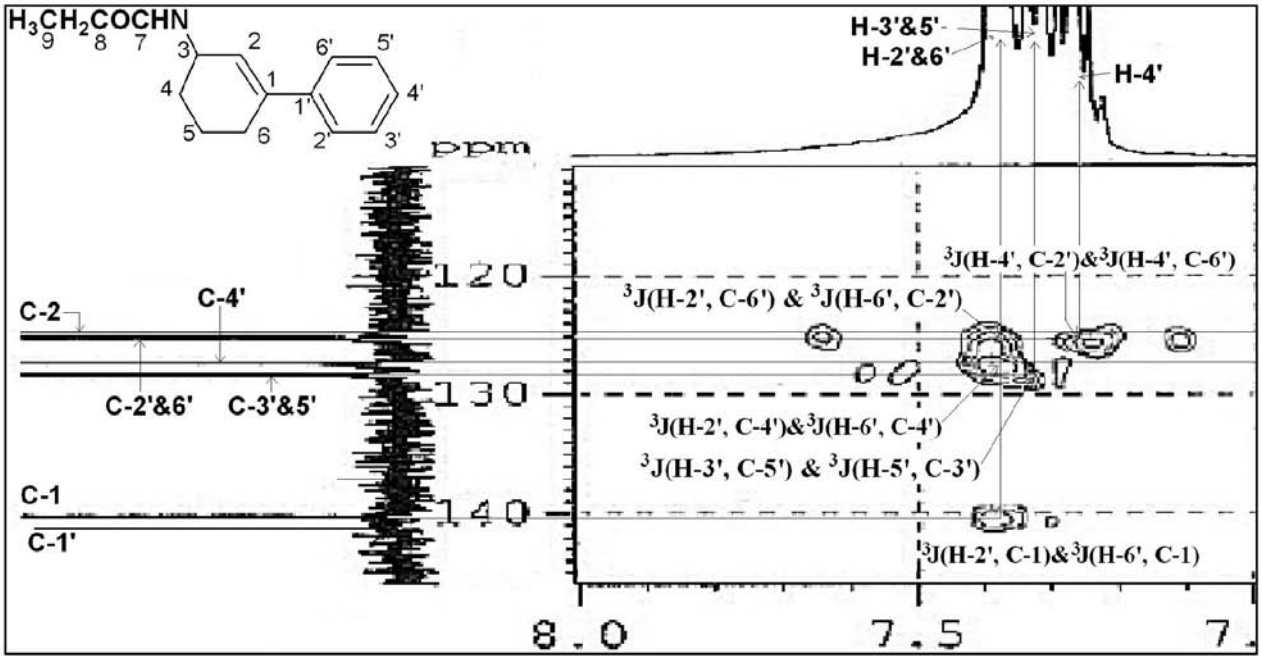


Figure S11. HMBC of *N*-(3-phenylcyclohex-2-enyl)propionamide (Table 1, entry 12) (expansion).

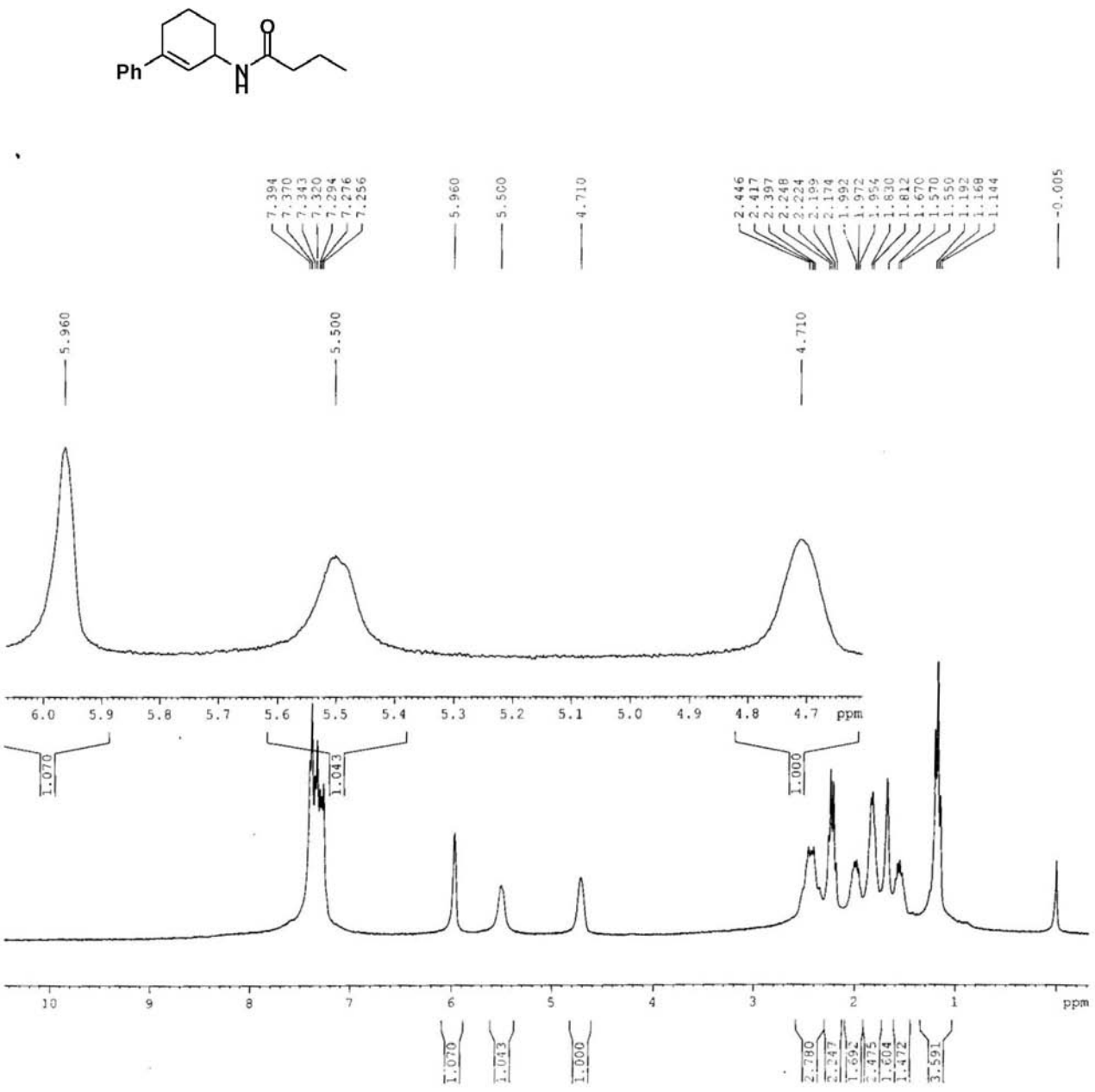


Figure S12. ^{1}H NMR (300MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)butyramide (Table 1, entry 13).

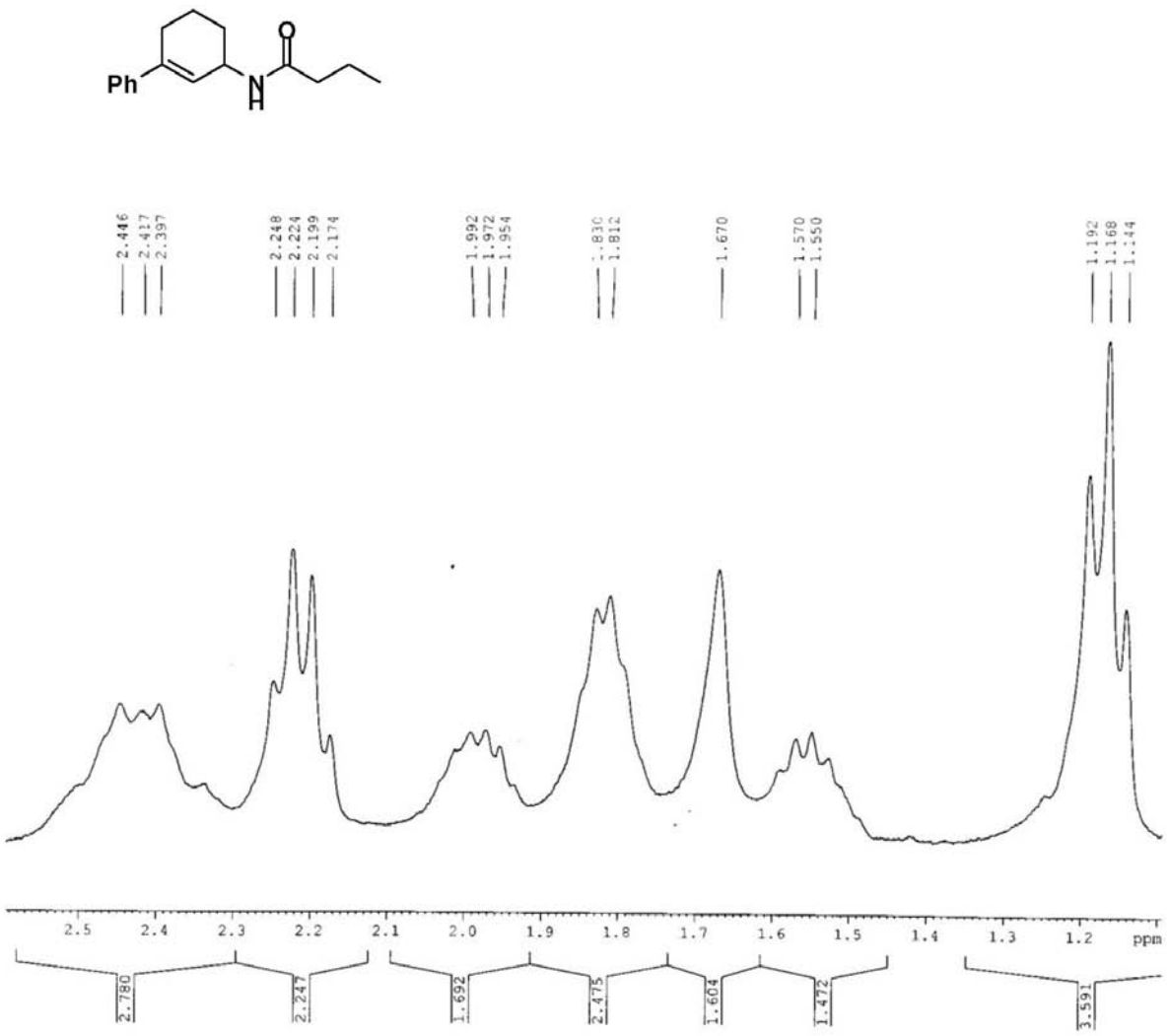


Figure S13. ^{1}H NMR (300MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)butyramide (Table 1, entry 13) (expansion).

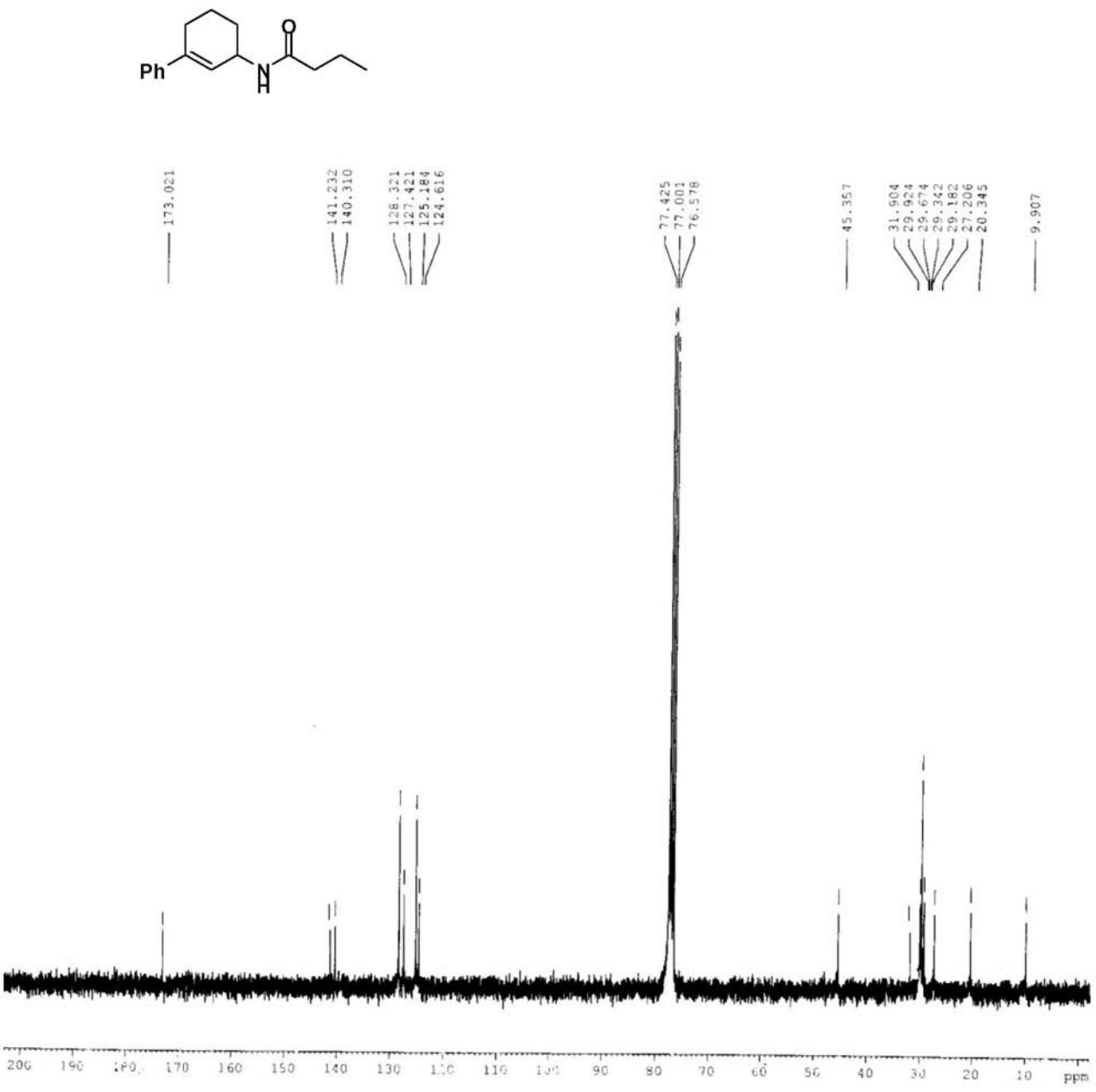


Figure S14. ^{13}C NMR (75MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)butyramide (Table 1, entry 13).

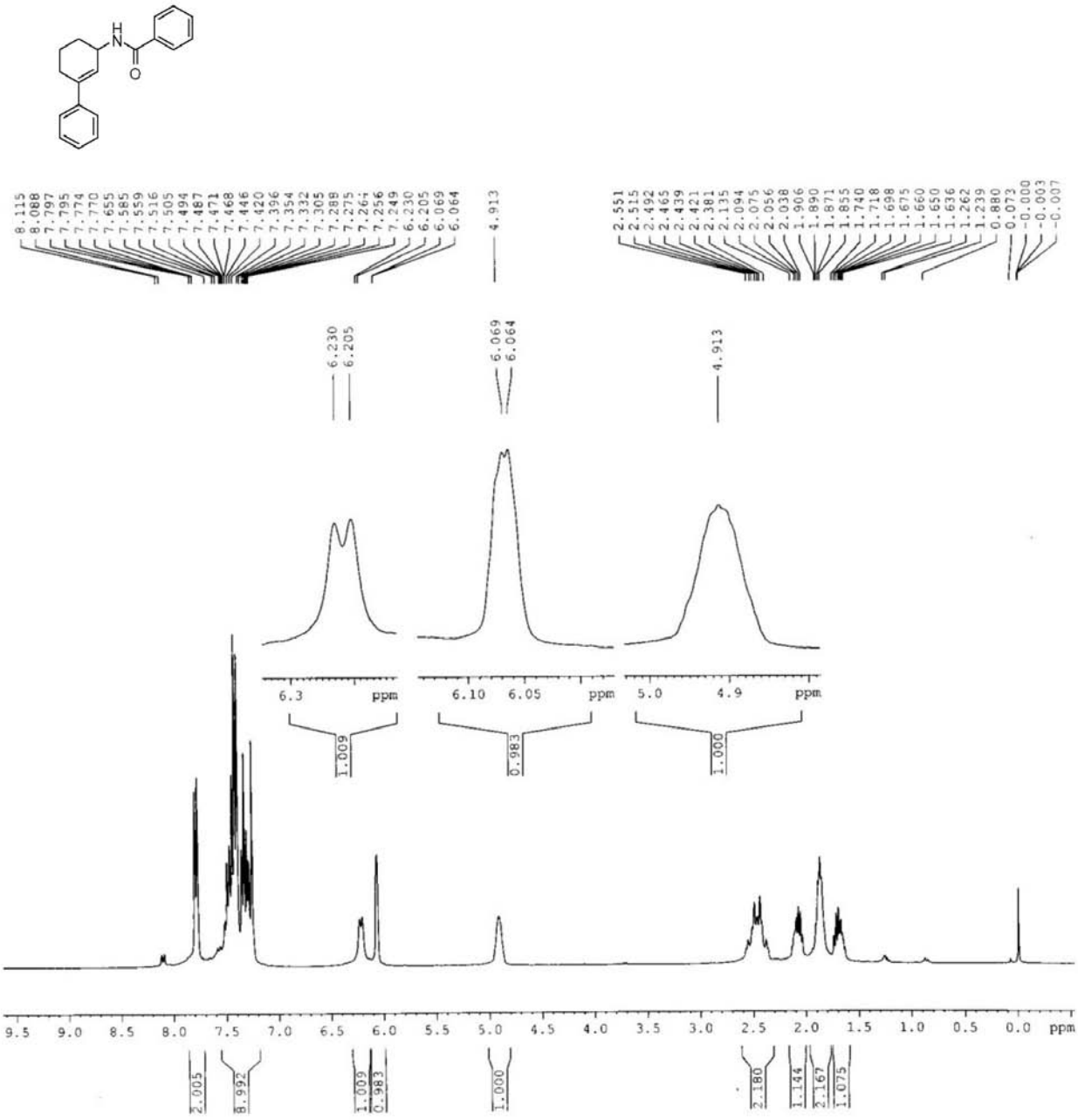


Figure S15. ^{1}H NMR (300MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)benzamide (Table 1, entry 15).

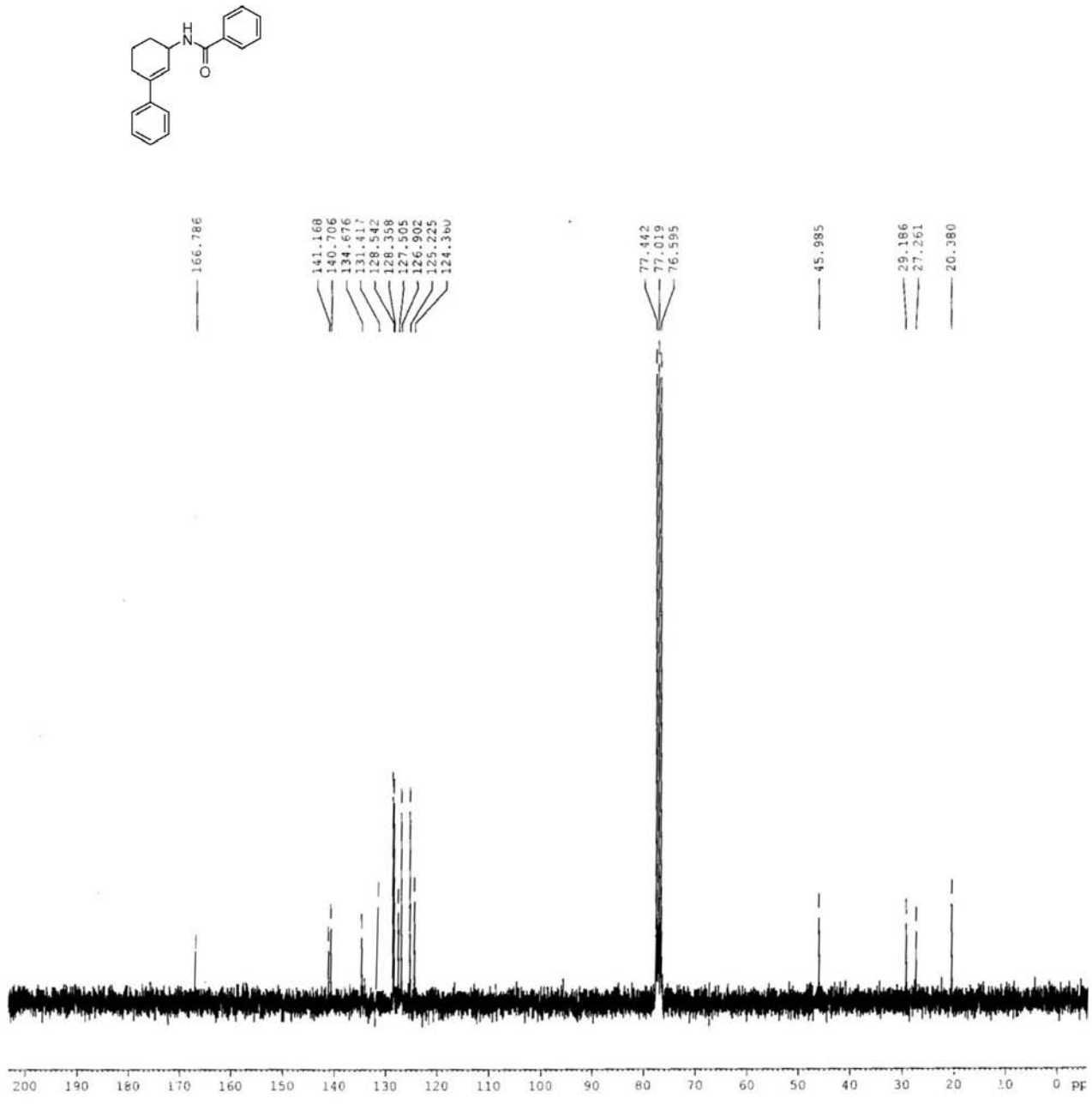


Figure S16. ^{13}C NMR (75MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)benzamide (Table 1, entry 15).

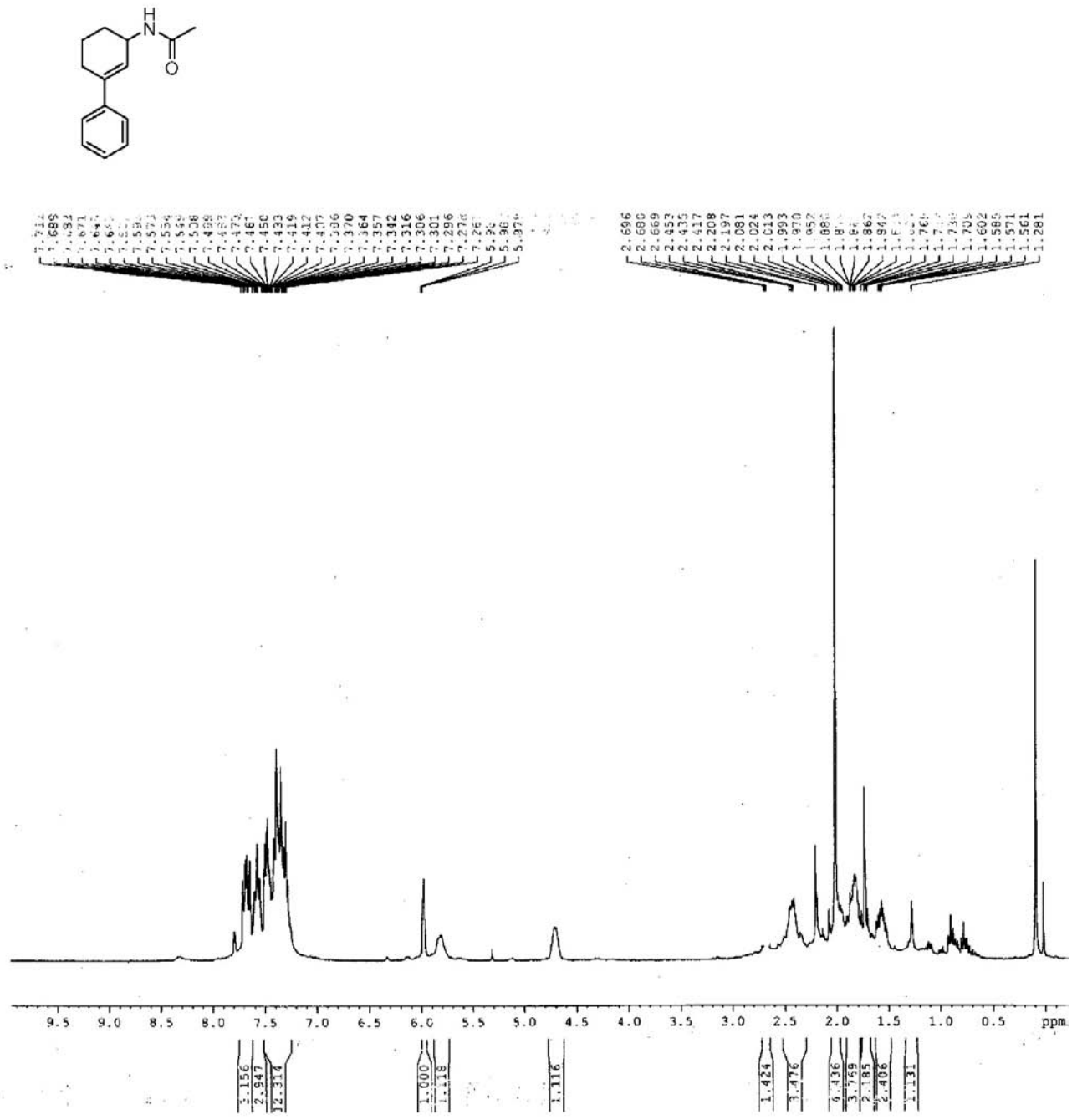


Figure S17. ^{13}C NMR (75MHz, $CDCl_3$) of *N*-(3-phenylcyclohex-2-enyl)acetamide (Table 1, entry 11 and 14).