Supplementary Information for:

Skeletal remodelling of α-substituted cyclic eneformamides to α-ketonyl cyclic amines

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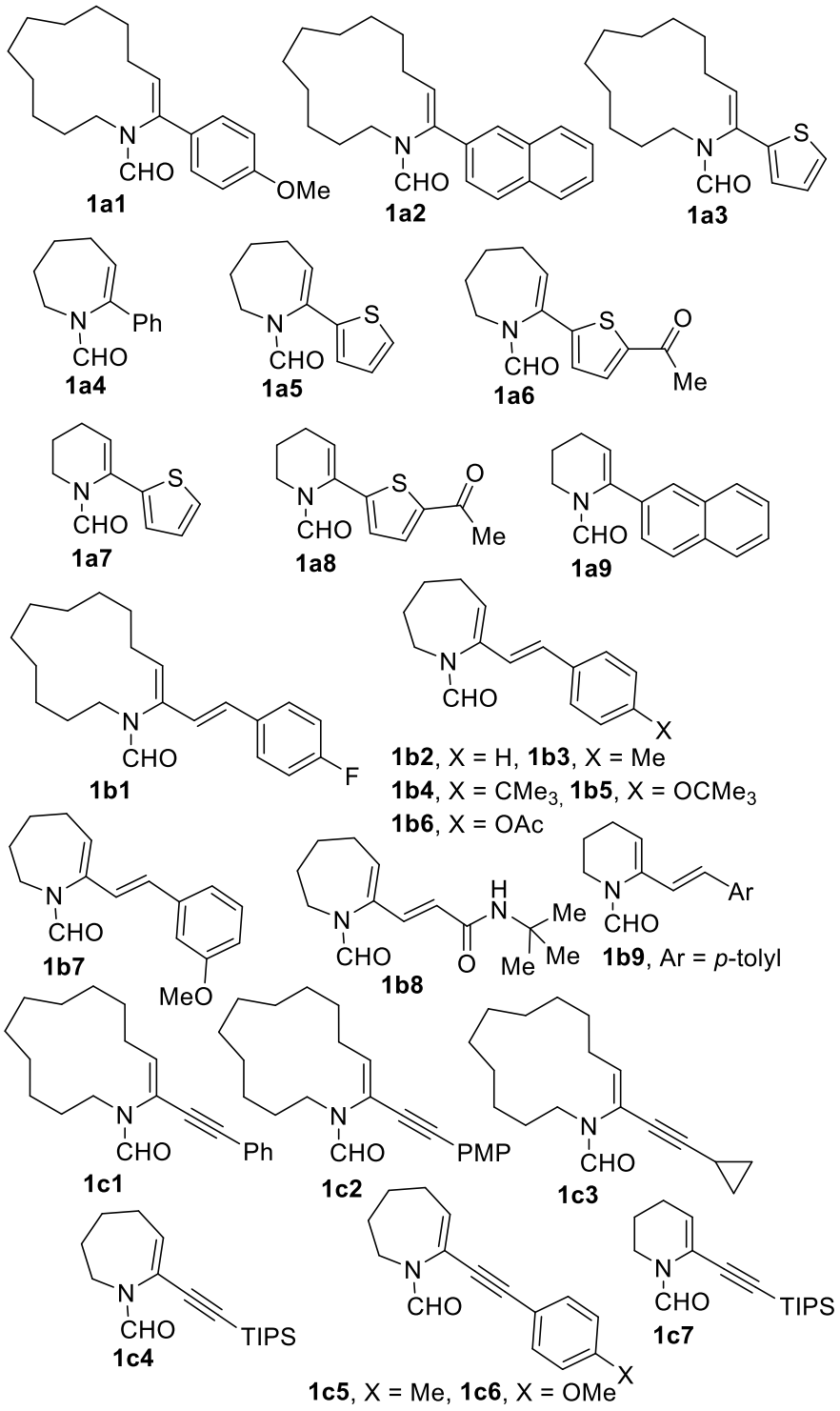
Contents:

2. Experimental Section

All experiments involving air and moisture sensitive reagents such as organolithium reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or $KMnO_4$ stain. Unless otherwise indicated, ^{1}H, ^{13}C, and DEPT-135 NMR spectra were acquired using $CDCl_3$ at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electronspray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).



Alpha-substituted eneformamides utilized in these studies.[1-3]

General Procedure A: Deconstructive oxo-halogenation and substitutive amination

A 10 mL screw-cap vial equipped with a stir bar was charged with a solution of the eneformamide (1.0 mmol), dissolved in 2-MeTHF (5 mL) at room temperature. *N*-iodosuccinimide (1.1 mmol, 1.1 equiv) and deionized water (0.5 mL) were added. After complete consumption of the eneformamide (as judged by TLC and GC-MS), the mixture/suspension was diluted with EtOAc (20 mL). It was washed with *sat*. $Na_2S_2O_3$(aq) and then with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product, which was dissolved in MeOH (5 mL) and Cs_2CO_3 (651.6 mg, 2 equiv) was added. The suspension was stirred at room temperature for 12 h (TLC and GC-MS monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired cyclic formamide, which was purified by flash chromatography on silica.

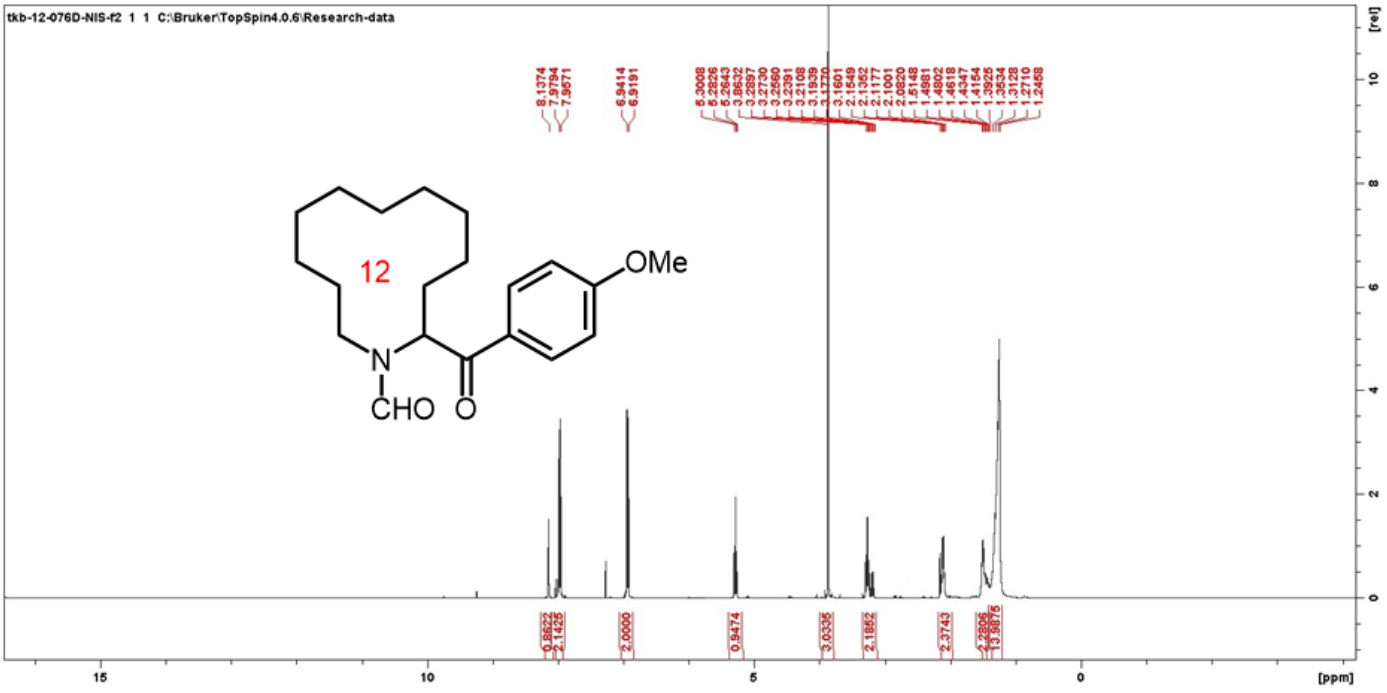
General Procedure B: Hydration and intramolecular C(sp^3)–H amination

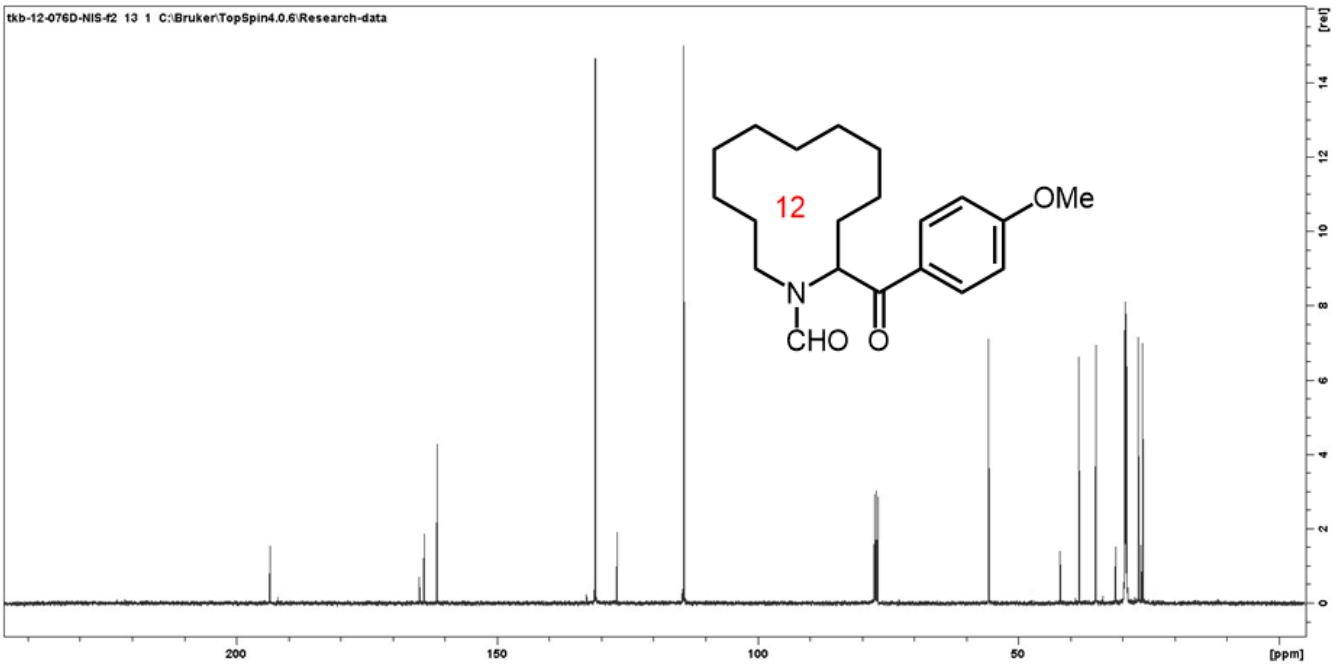
A 10 mL screw-cap vial equipped with a stir bar was charged with a 0.1 M H_3PO_4 (5 mL) solution and the eneformamide (1.0 mmol), dissolved in a small amount of EtOAc (0.5 mL). After stirring for 5 min at room temperature, the contents were transferred to a separatory funnel and EtOAc (10 mL) was added. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with *sat.* $NaHCO_3$ and with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude product was dissolved in MeOH (5 mL) then *N*-iodosuccinimide (1.1 mmol, 1.1 equiv) and K_2CO_3 (2.2 equiv) were added. The suspension was stirred at room temperature (TLC and GC-MS monitoring). After complete conversion, it was diluted with water and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired cyclic formamide, which was purified by flash chromatography on silica.

Compound 4a

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Pale-yellow oil. Yield = 261.8 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.14 (s, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 2H), 5.28 (t, *J* = 7.3 Hz, 1H), 3.86 (s, 3H), 3.29 – 3.16 (m, 2H), 2.15 – 2.08 (m, 2H), 1.51 – 1.24 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 193.4, 193.4, 164.8, 163.9, 161.4, 131.3, 131.1, 130.9, 126.9, 114.3, 114.1, 55.7, 41.9, 38.3, 35.1, 31.3, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 26.9, 26.0. HRMS calc for $C_{20}H_{29}NO_3$ 331.2147, found 331.2151. FTIR (KBr): 2925, 1712, 1495, 1449, 1427, 1393, 1362, 1329, 1289, 1223, 1199, 1130, 1074, 1030, 989, 966, 925, 742, 693.

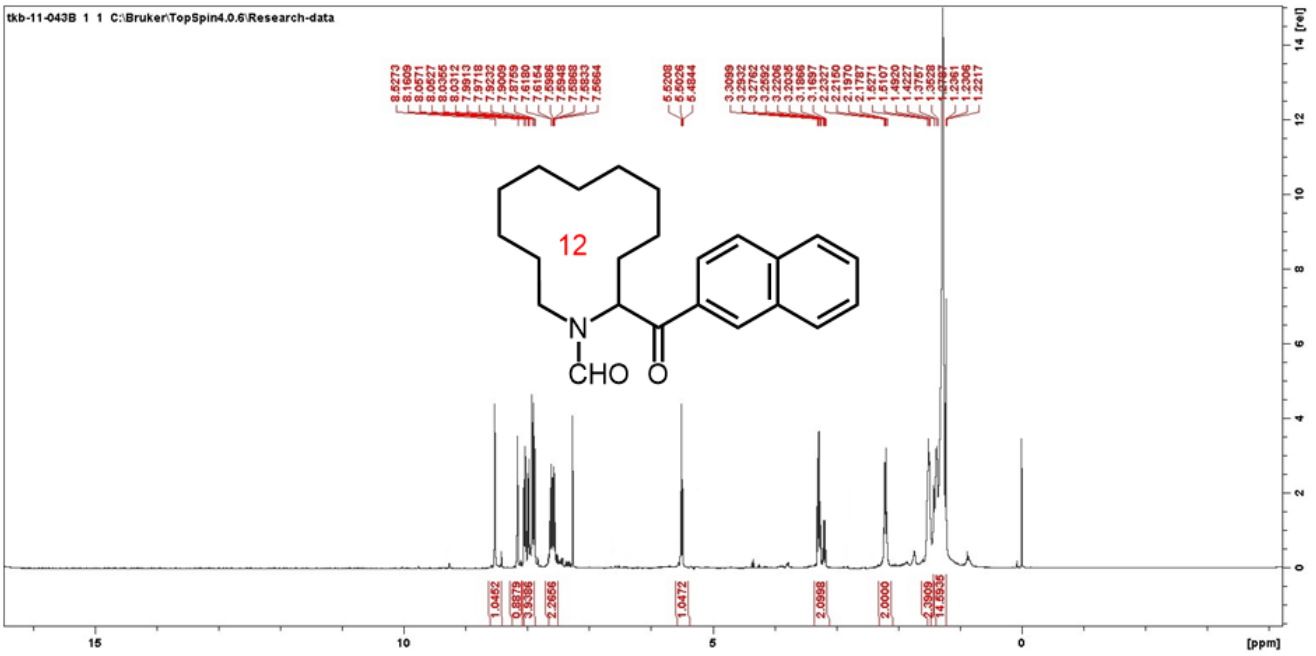
Note: Using **General Procedure B**, formamide **4a** was obtained in 60% yield.

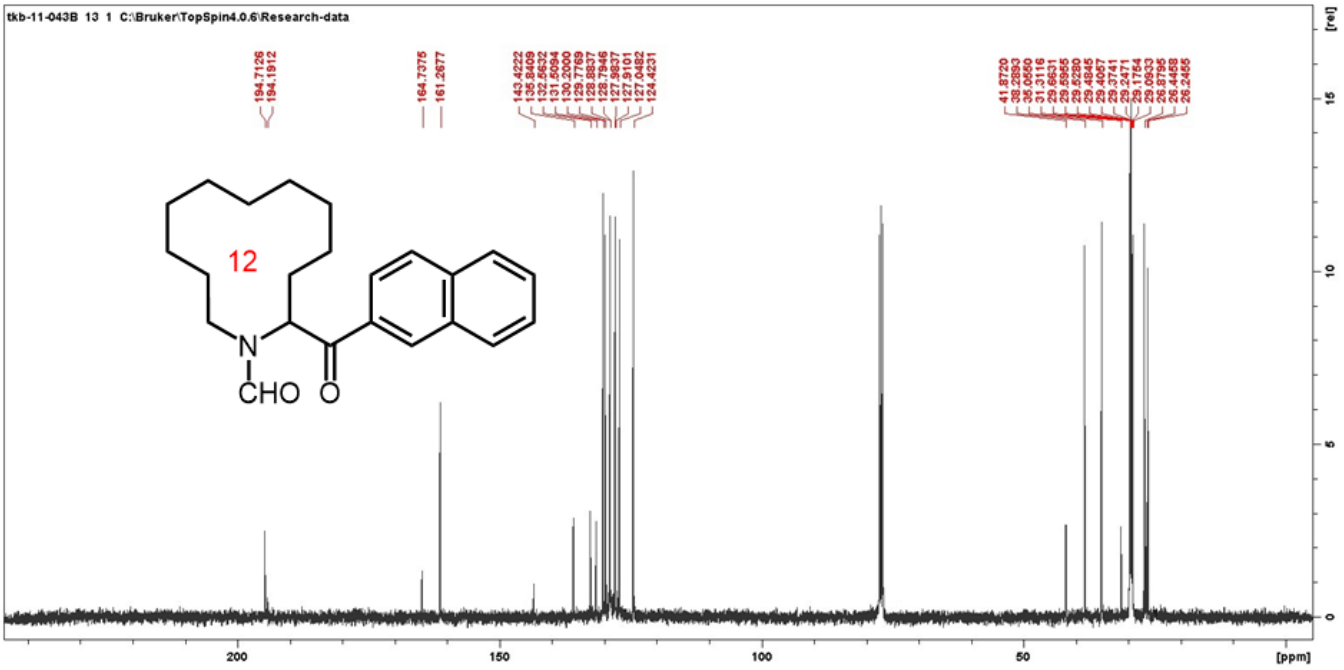




Compound 4b

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (90:10). Viscous oil. Yield = 284.7 mg, 81%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.52 (s, 1H), 8.16 (s, 1H), 8.05 – 7.87 (m, 4H), 7.62 – 7.57 (m, 2H), 5.50 (t, *J* = 7.3 Hz, 1H), 3.30 – 3.17 (m, 2H), 2.23 – 2.18 (m, 2H), 1.53 – 1.22 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$, *rotamers*) δ 194.7, 164.7, 161.3, 143.4, 135.9, 132.6, 131.5, 130.2, 129.8, 128.9, 128.8, 127.9, 127.0, 124.4, 41.9, 38.3, 35.1, 31.3, 29.7, 29.7, 29.6, 29.5, 29.4, 29.2, 29.1, 26.9, 26.4, 26.3, 26.2. HRMS calc for $C_{23}H_{29}NO_2$ 351.2198, found 351.2195.

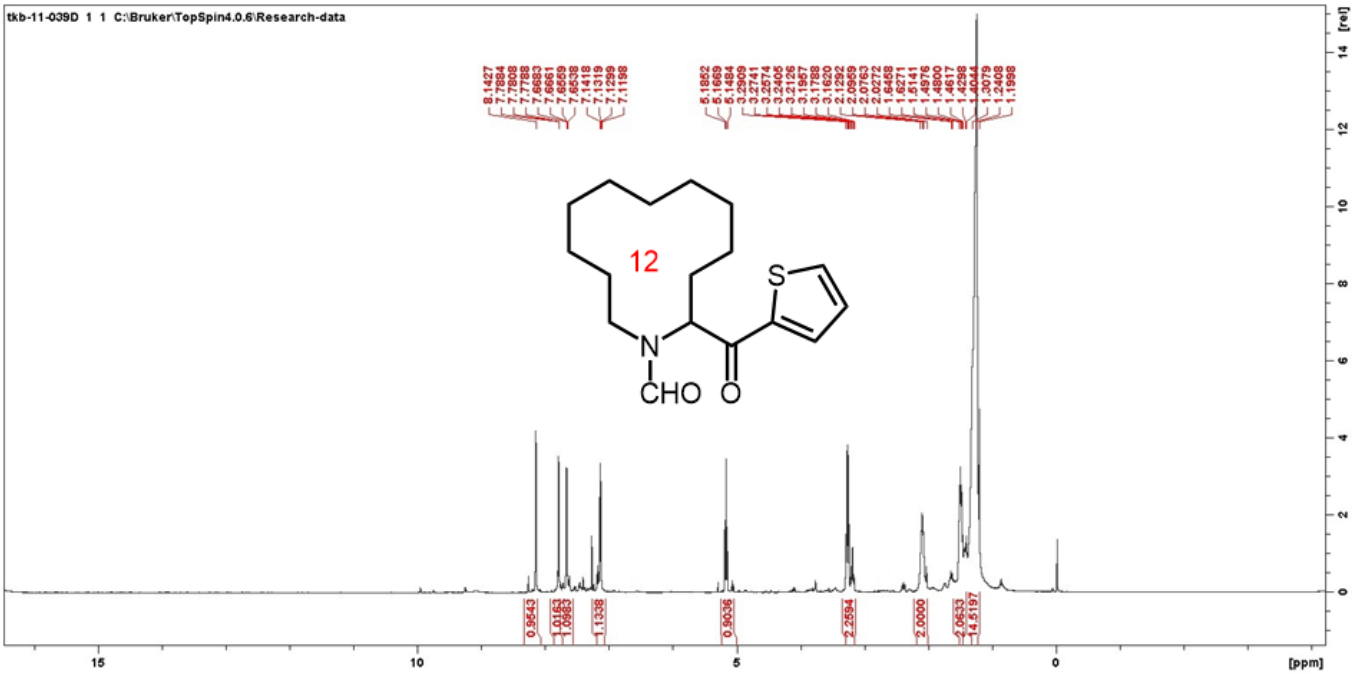


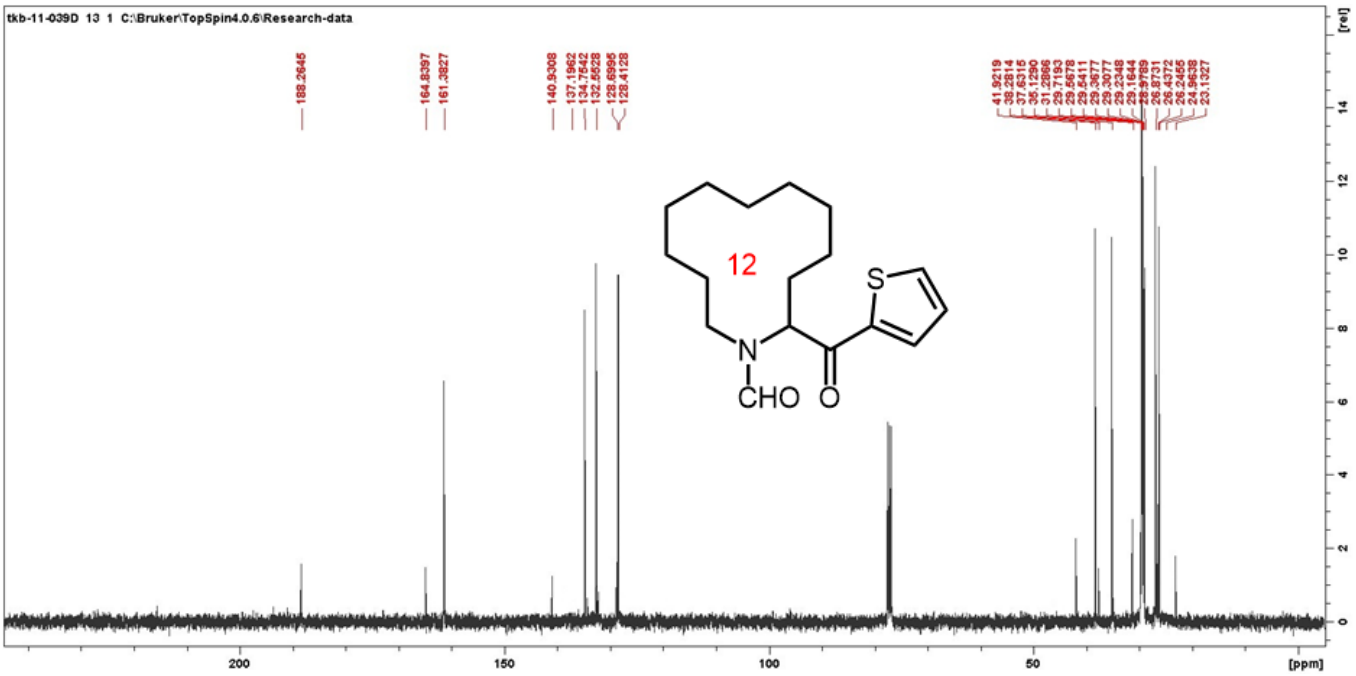


Compound 4c

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yellowish oil. Yield = 236.8 mg, 77%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.14 (s, 1H), 7.78 (d, *J* = 4.4 Hz, 1H), 7.66 (d, *J* = 13.0 Hz, 1H), 7.13 (dd, *J* = 13.0, 4.4 Hz, 1H), 5.18 (t, *J* = 7.4 Hz, 1H), 3.29 – 3.16 (m, 2H), 2.12 – 2.02 (m, 2H),

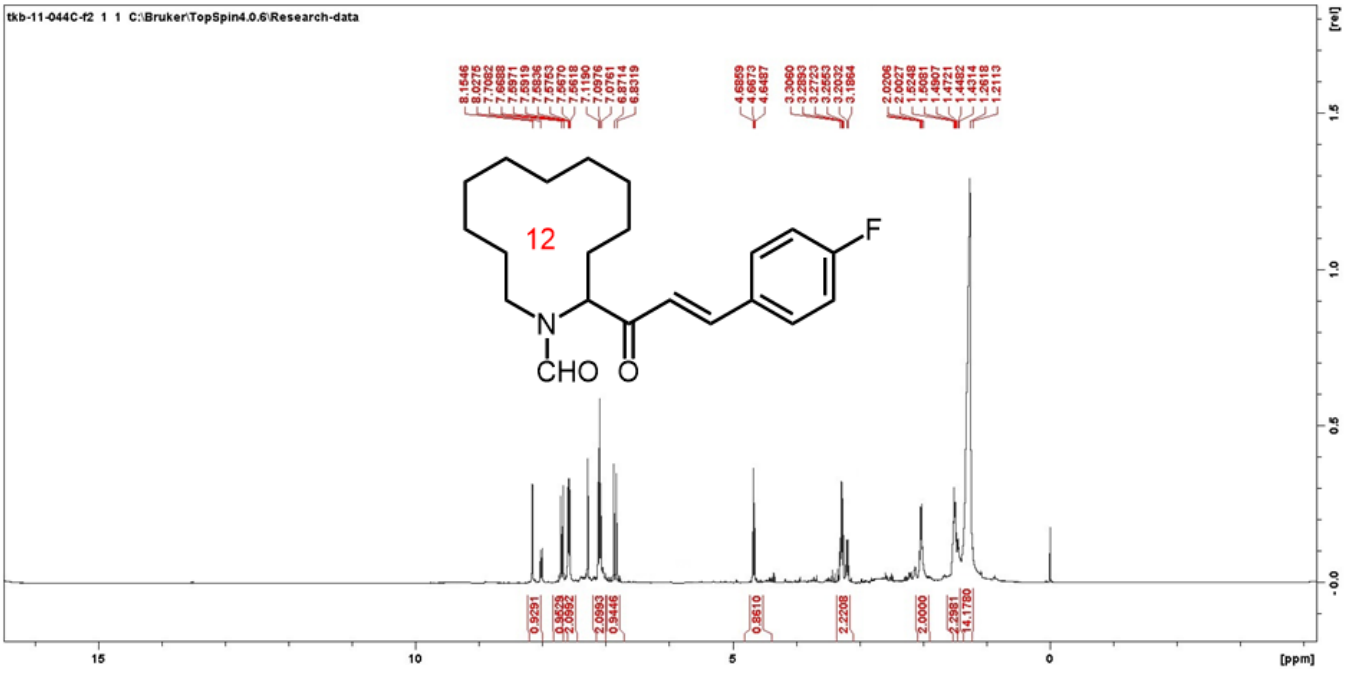
1.64– 1.20 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 188.3, 164.8, 161.4, 140.9, 138.3, 137.6, 137.2, 134.8, 132.6, 128.4, 41.9, 38.3, 37.6, 35.1, 31.3, 29.7, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 26.9, 26.4, 26.2, 23.1. HRMS calc for $C_{17}H_{25}NO_2S$ 307.1606, found 307.1600.

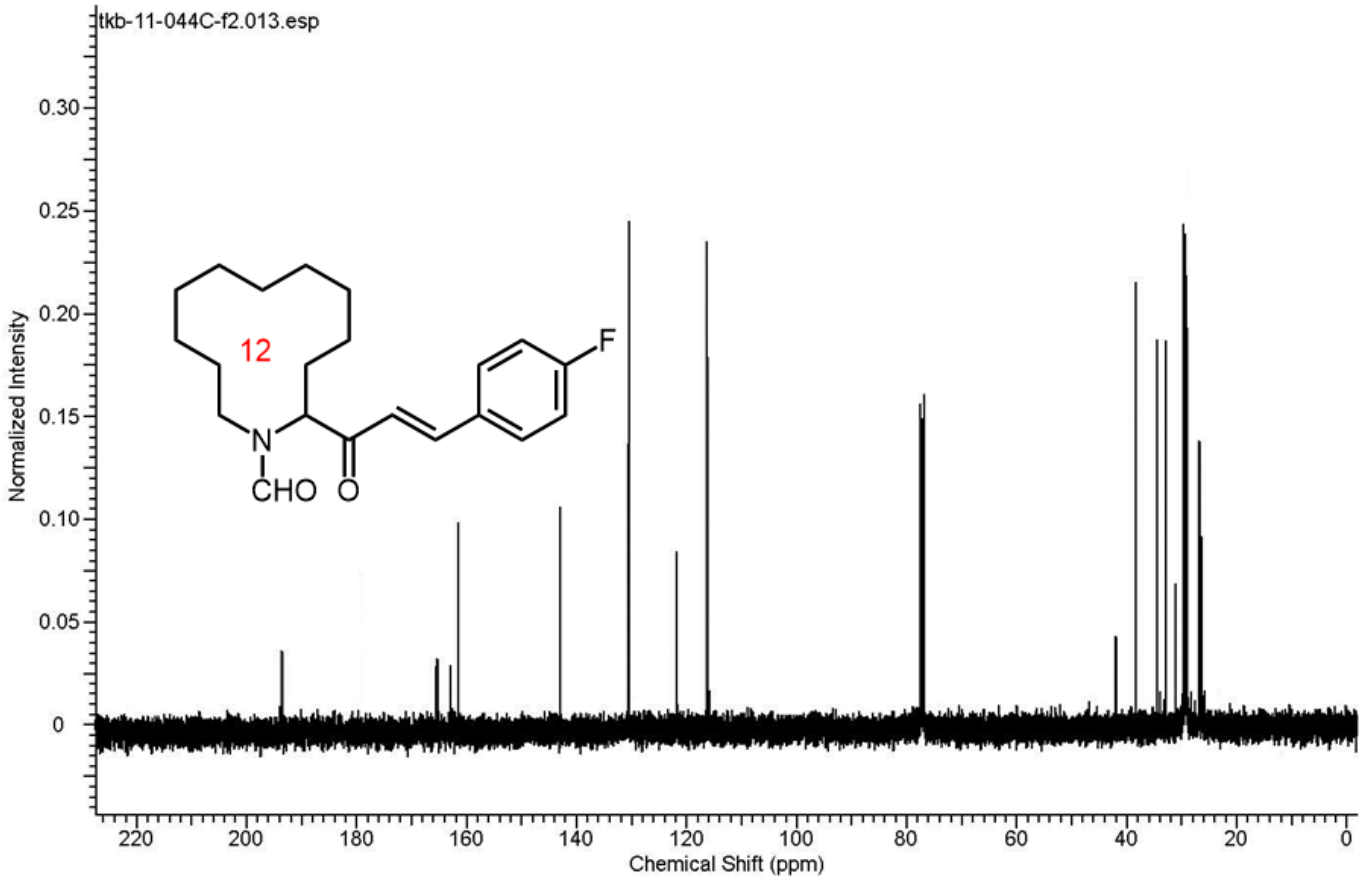




Compound 4d

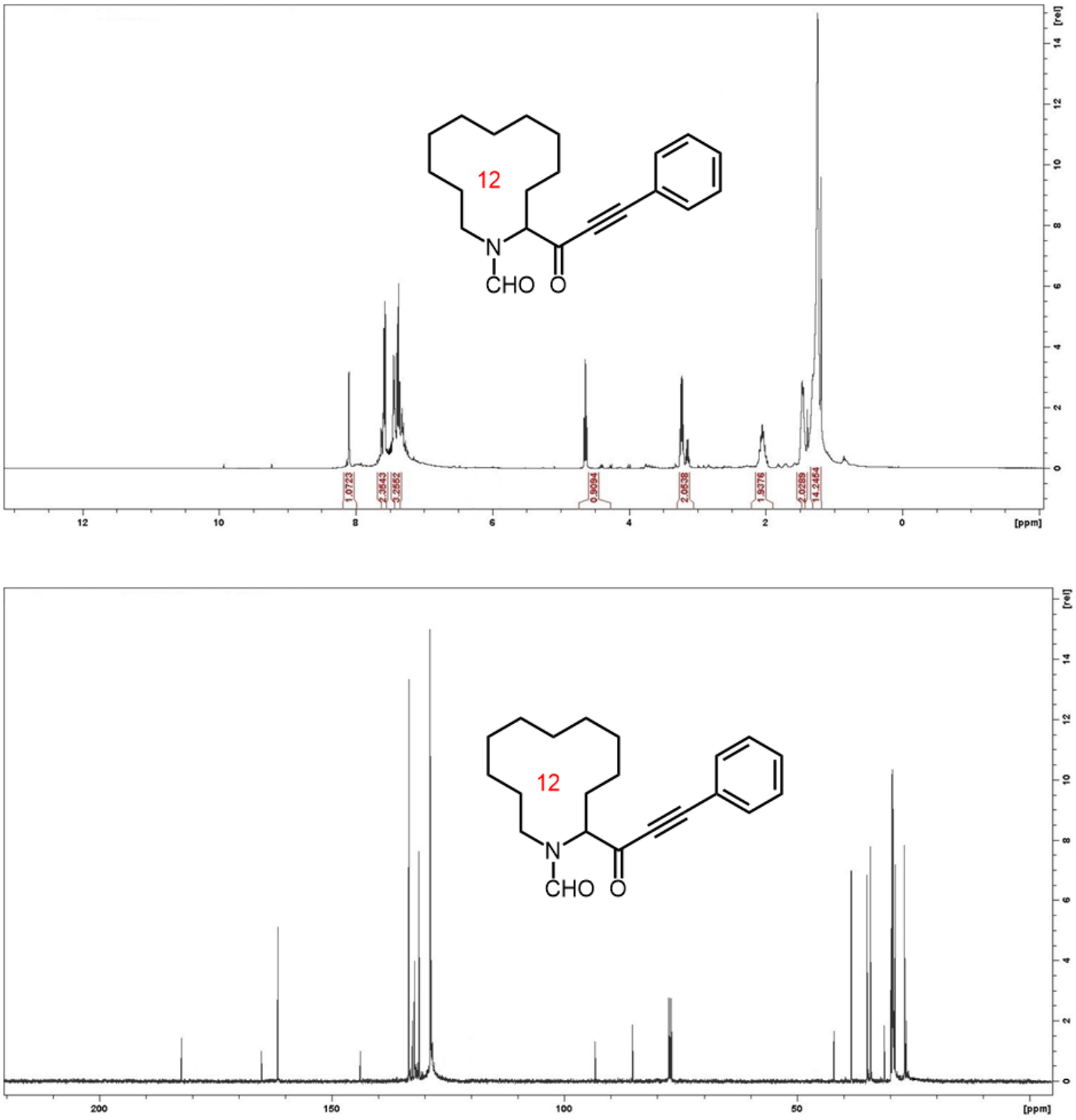
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Yellowish oil. Yield = 255.7 mg, 74%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.15 (s, 1H), 7.69 (d, *J* = 15.8 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 15.8 Hz, 1H), 4.67 (t, *J* = 7.4 Hz, 1H), 3.30 – 3.19 (m, 2H), 2.00 (q, *J* = 7.1 Hz, 2H), 1.52 – 1.21 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.6, 165.5, 165.3, 163.0, 161.5, 143.0, 130.7, 130.6, 121.8, 121.8, 116.3, 116.1, 42.1, 38.3, 34.5, 32.8, 31.2, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 26.9, 26.4. HRMS calc for $C_{21}H_{28}FNO_2$ 345.2104, found 345.2107.





Compound 4e

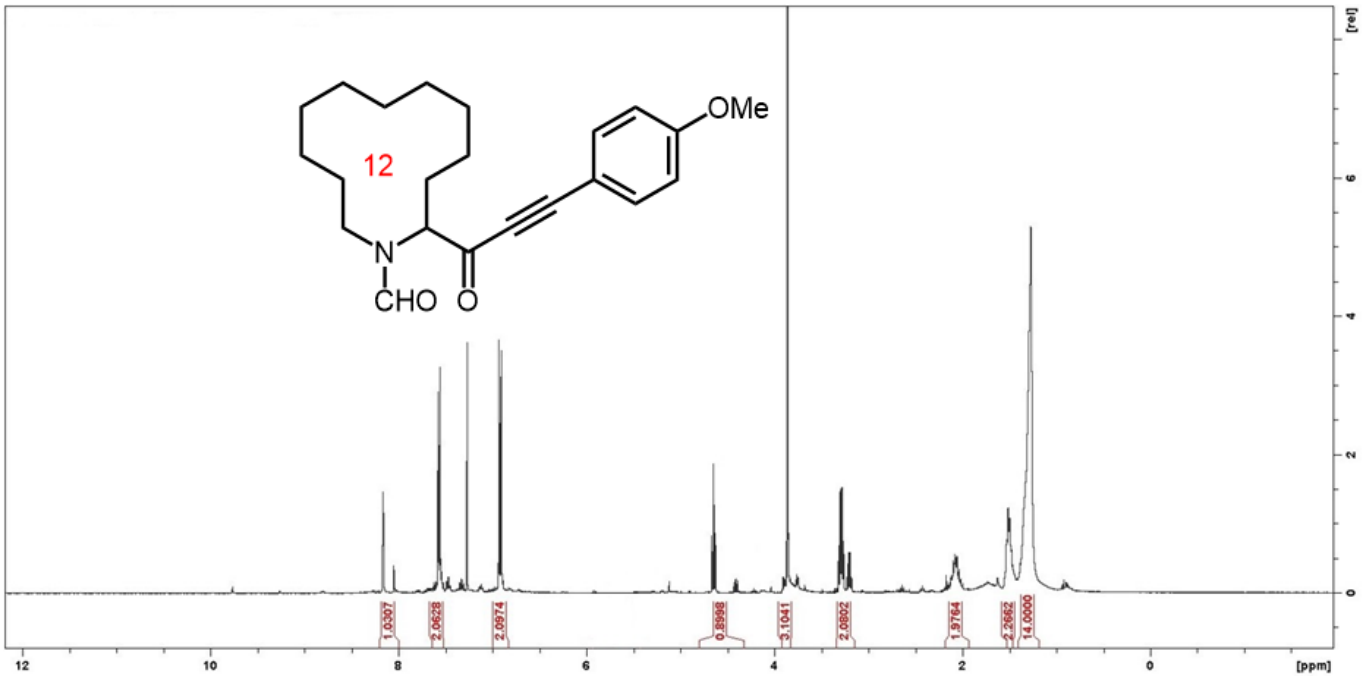
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Yellowish oil. Yield = 227.8 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.18 (s, 1H), 7.60 – 7.51 (m, 2H), 7.42 – 7.32 (m, 3H), 4.62 (t, J = 7.7 Hz, 1H), 3.33 – 3.25 (m, 2H), 2.16 – 1.93 (m, 2H), 1.49 – 1.24 (m, 16H).^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 182.3, 165.0, 161.5, 145.1, 143.8, 133.3, 132.2, 131.2, 128.8, 128.7, 128.6, 93.3, 85.3, 42.0, 38.3, 34.9, 34.3, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 26.9. HRMS calc for $C_{21}H_{27}NO_2$ 325.2042, found 325.2045.

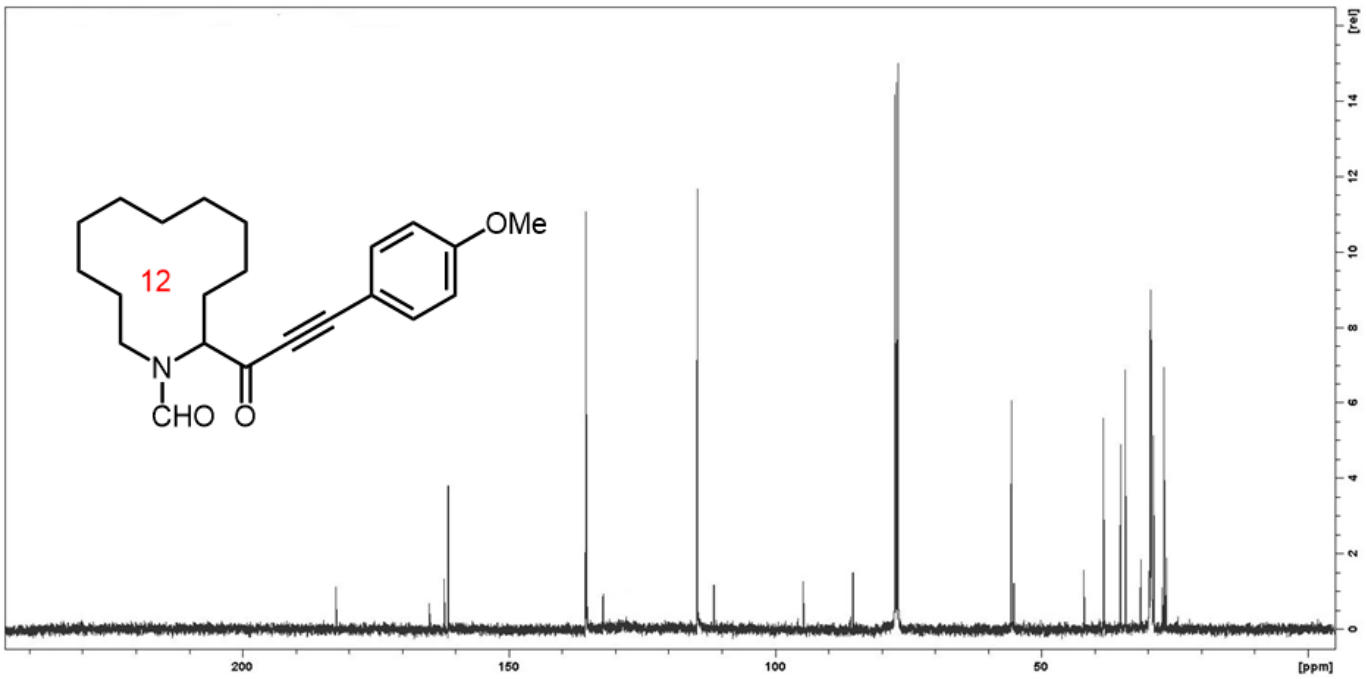


Compound 4f

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yellowish oil. Yield = 259.5 mg, 73%.^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.22 (s, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 7.4 Hz,

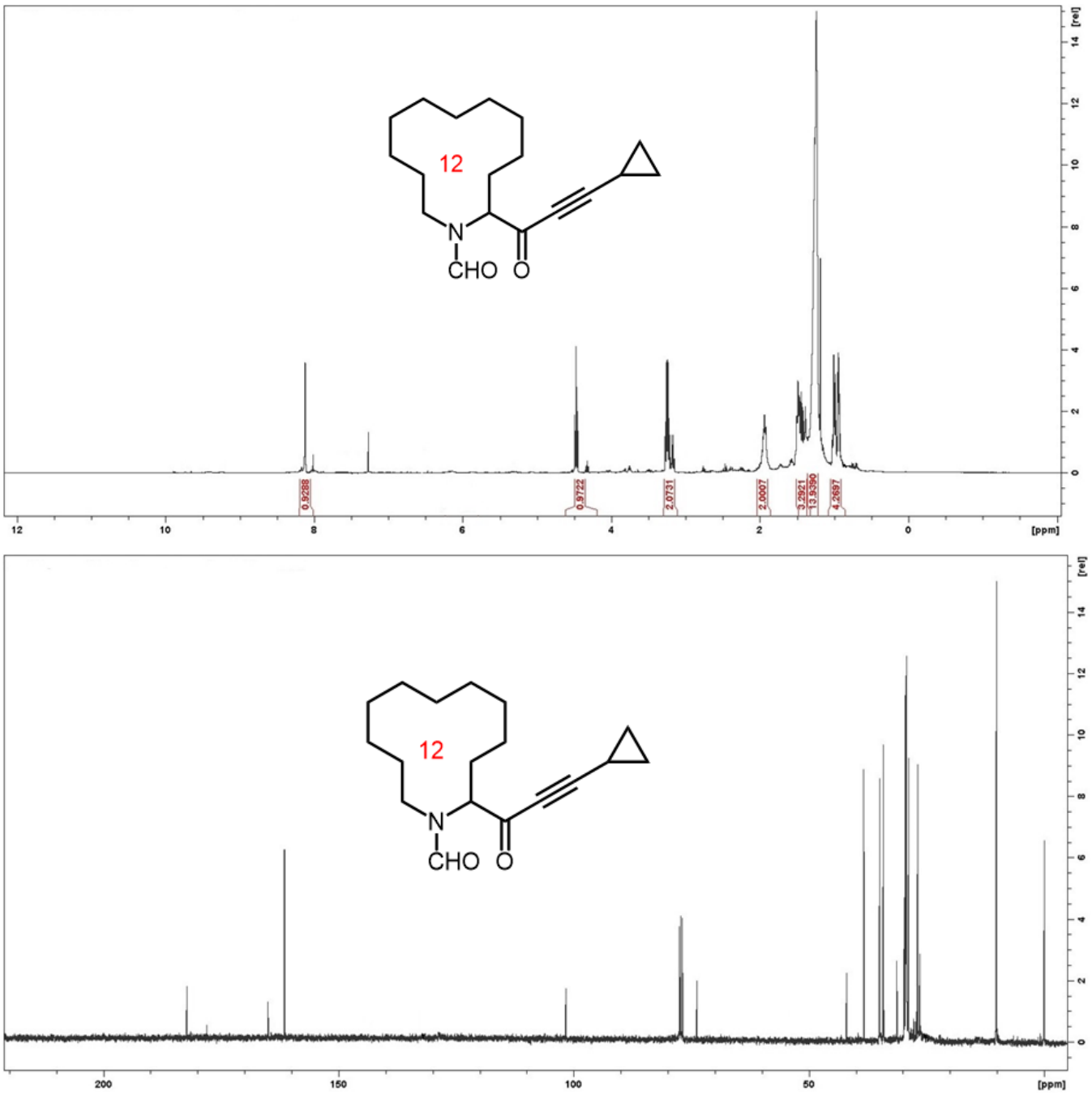
2H), 4.66 (t, *J* = 7.7 Hz, 1H), 3.82 (s, 3H), 3.35 – 3.22 (m, 2H), 2.11 – 1.95 (m, 2H), 1.56 – 1.34 (m, 2H). 1.32 – 1.28 (m, 14H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 182.4, 164.8, 162.0, 161.3, 135.6, 135.5, 132.2, 132.1, 132.0, 114.6, 114.5, 111.4, 94.6, 85.7, 85.3, 55.6, 55.1, 41.9, 39.0, 38.3, 35.1, 34.2, 34.2, 31.3, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 26.9, 26.4. HRMS calc for $C_{22}H_{29}NO_3$ 355.2147, found 355.2144. FTIR: 2977, 1705, 1618, 1583, 1453, 1367, 1339, 1298, 1269, 1228, 1163, 1126, 911, 866.





Compound 4g

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (90:10). Yellowish oil. Yield = 214.2 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.22 (s, 1H), 4.44 (t, J = 7.6 Hz, 1H), 3.27 – 3.18 (m, 2H), 1.89 (m, 2H), 1.49 – 1.30 (m, 17H), 0.96 – 0.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 182.2, 178.0, 164.9, 161.5, 101.6, 73.8, 41.9, 38.3, 34.9, 34.2, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.8, 26.8, 10.2, 10.1, 0.0, -0.1. HRMS calc for $C_{18}H_{27}NO_2$ 289.2042, found 289.2045.

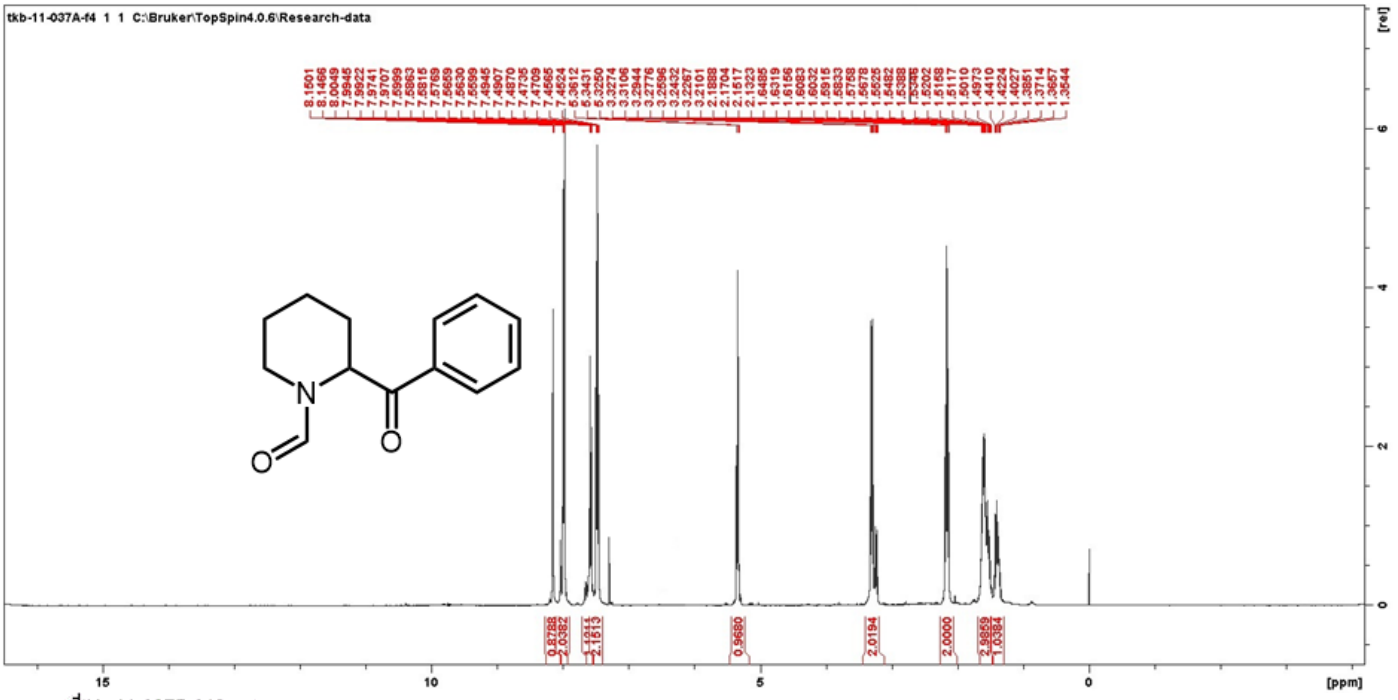


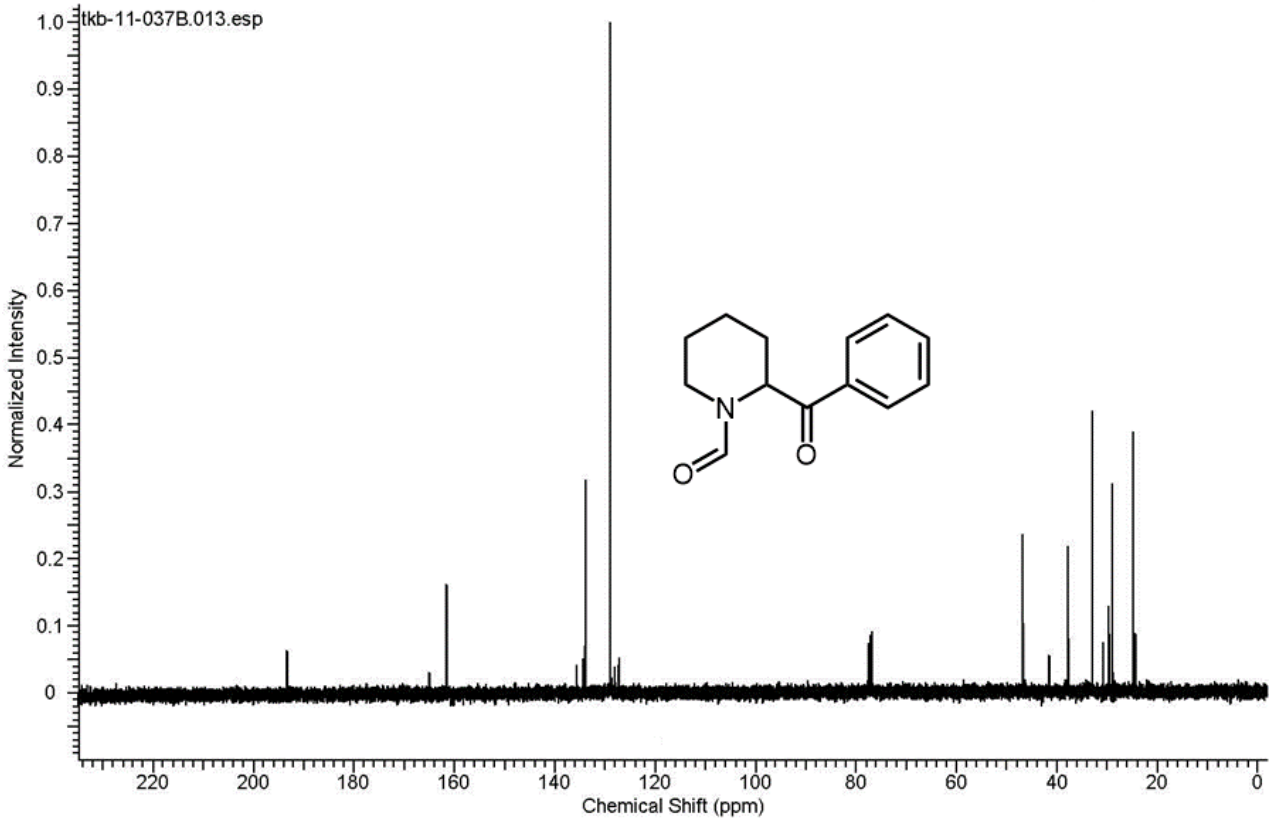
Compound 4h

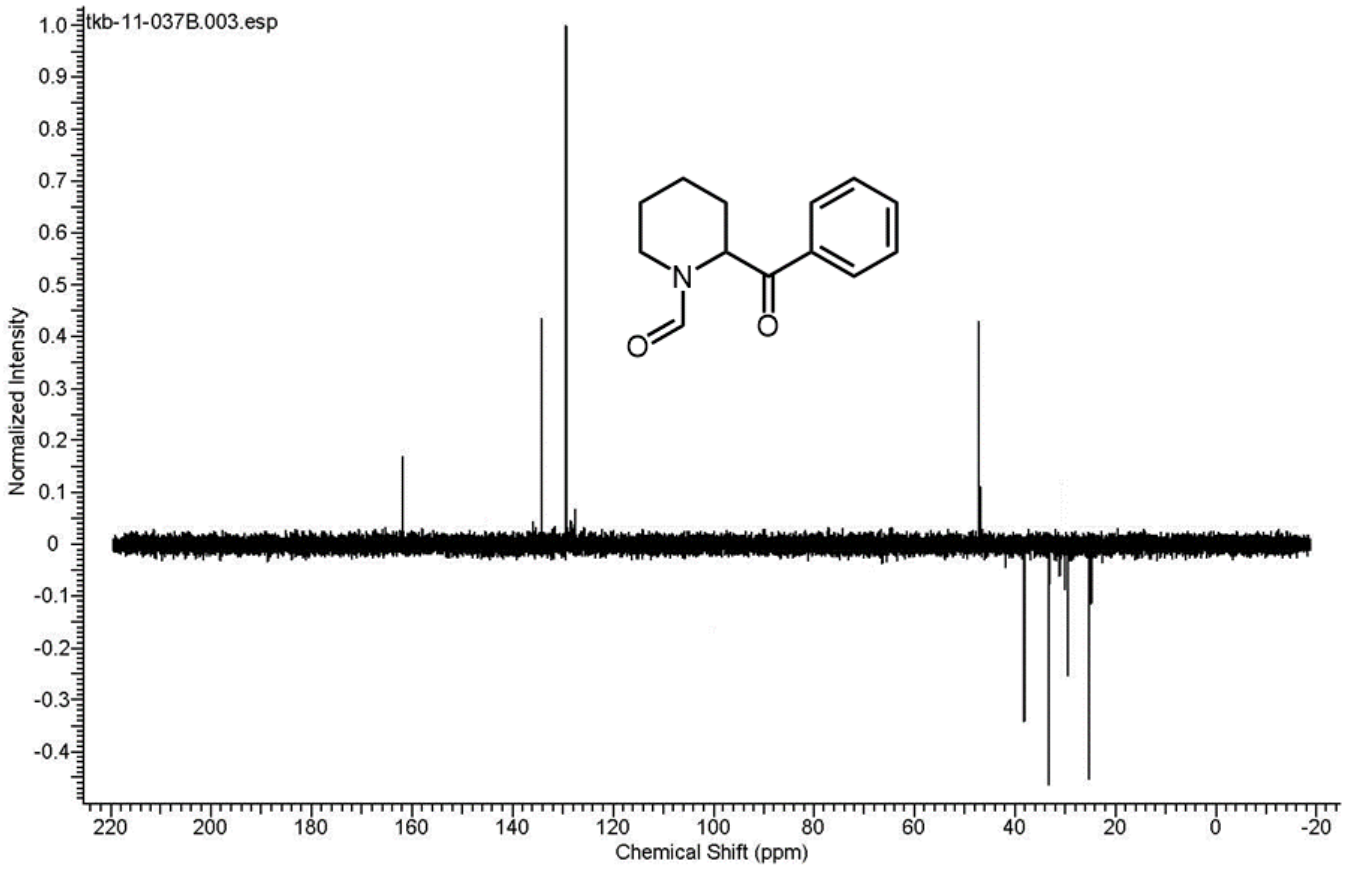
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Yellowish oil. Yield = 195.6 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.15 (s, 1H), 7.99 – 7.97 (m, 2H), 7.59 – 7.56 (m, 1H), 7.45 (t, *J* = 7.3 Hz, 2H), 5.34 (t, *J* = 7.2 Hz, 1H), 3.29 (q, *J* = 6.6 Hz, 2H), 2.17 (q, *J* = 7.4 Hz, 2H), 1.64 – 1.35 (m, 4H) ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 193.3, 165.0, 161.6, 161.5, 134.3,

134.0, 133.9, 129.0, 128.9, 128.9, 128.1, 127.2, 46.9, 46.7, 41.6, 37.9, 37.7, 33.0, 32.9, 30.8, 29.7, 29.5, 29.1, 29.0, 24.8, 24.4. HRMS calc for $C_{13}H_{15}NO_2$ 217.1103, found 217.1106.

Note: Using **General Procedure B**, formamide **4h** was obtained in 73% yield.

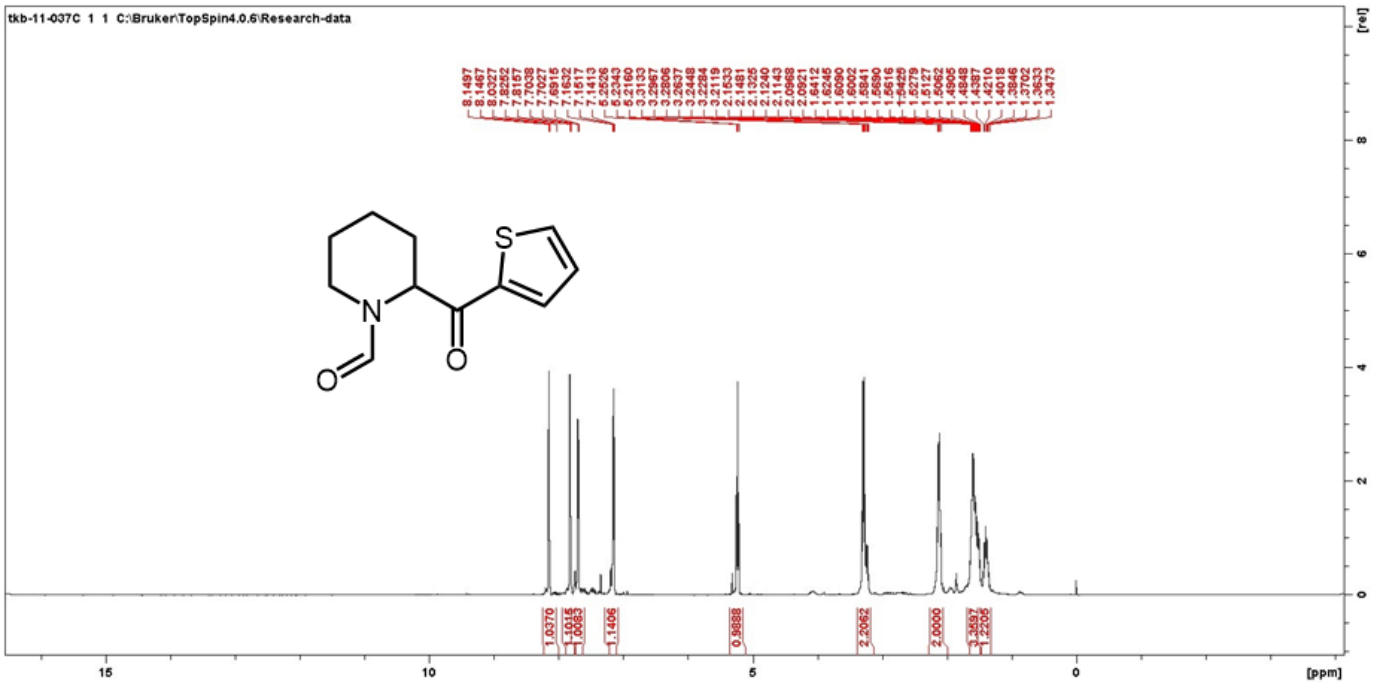


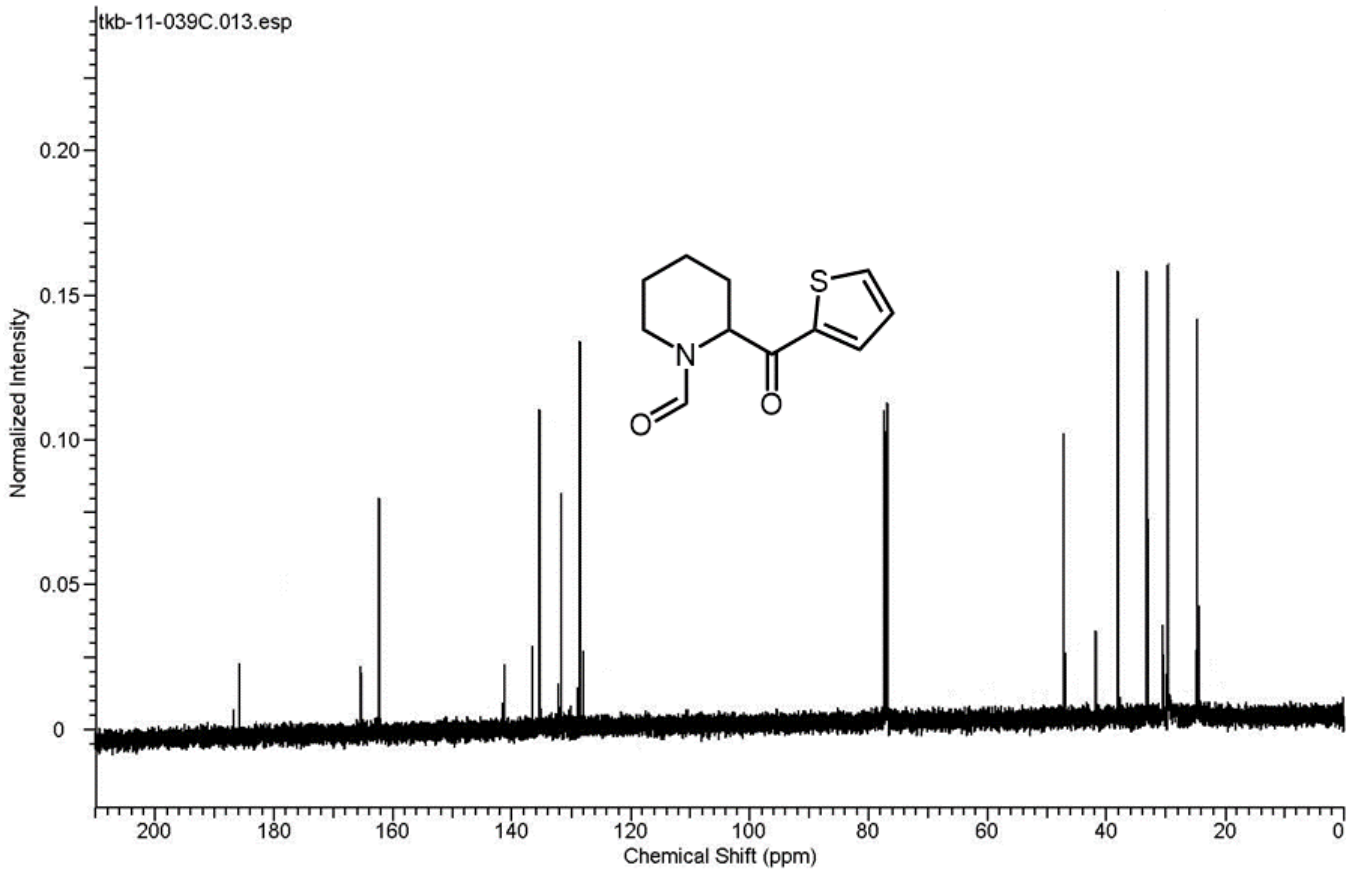




Compound 4i

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Yellowish oil. Yield = 194.3 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.14 (s, 1H), 7.82 (d, *J* = 9.5 Hz, 1H), 7.70 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.14 (t, 1H), 5.23 (t, *J* = 7.5 Hz, 1H), 3.31 – 3.21 (m, 2H), 2.15 – 2.09 (m, 2H), 1.64 – 1.35 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 186.8, 185.7, 165.5, 162.3, 162.2, 141.2, 136.5, 135.4, 135.3, 133.6, 133.6, 133.4, 133.4, 131.7, 131.6, 128.6, 128.5, 128.0, 47.9, 47.7, 47.1, 45.9, 41.8, 38.2, 38.1, 33.3, 33.2, 33.1, 33.0, 28.8, 28.7, 24.7, 24.6. HRMS calc for $C_{11}H_{13}NO_2S$ 223.0667, found 223.0664.

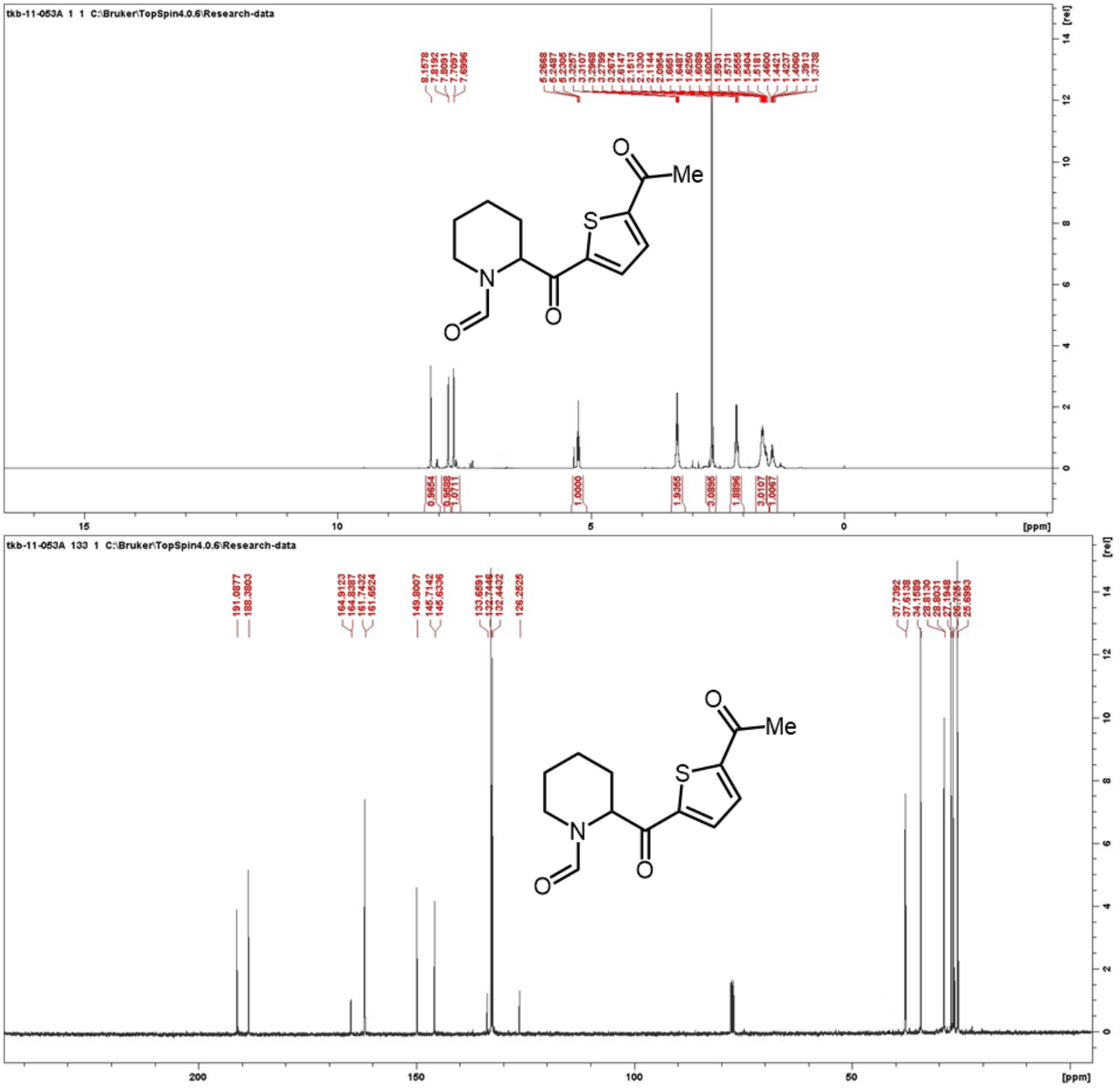




Compound 4j

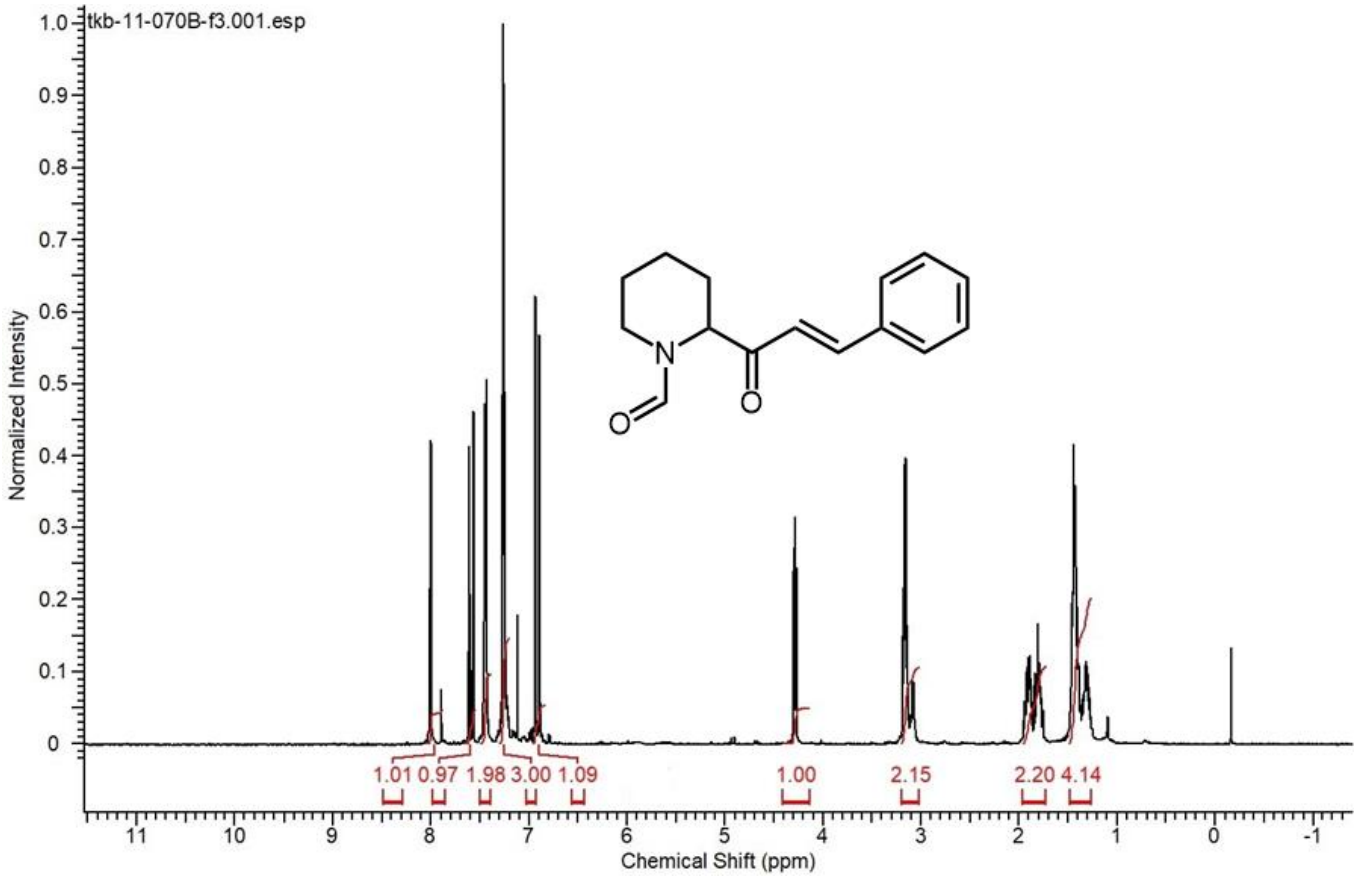
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Viscous oil. Yield = 225.5 mg, 85%. ^{1}H NMR (400

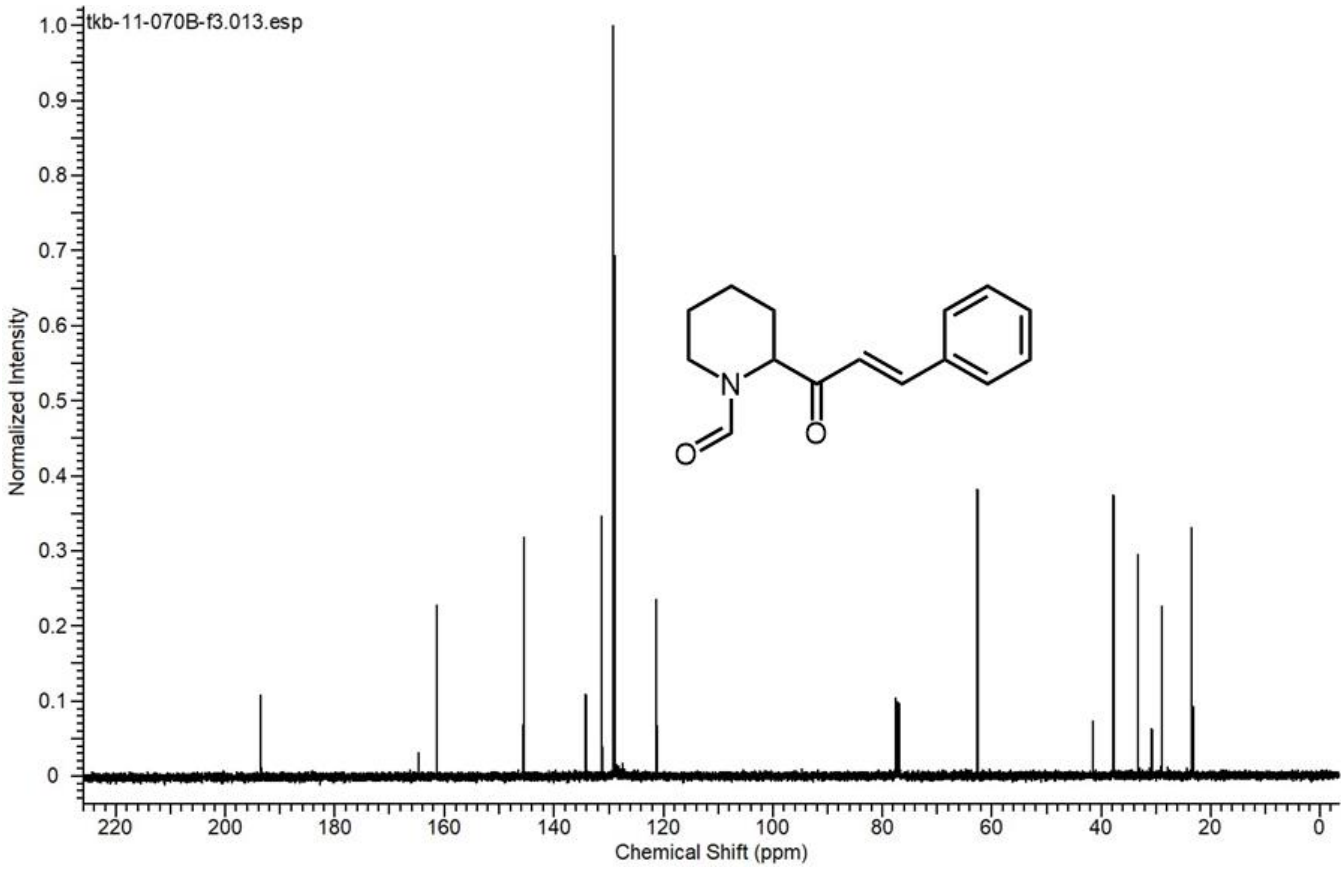
MHz, Chloroform-*d, rotamers*) δ 8.16 (s, 1H), 7.81 (d, *J* = 9.3 Hz, 1H), 7.70 (d, *J* = 9.3 Hz, 1H), 5.25 (t, *J* = 7.5 Hz, 1H), 3.32 – 3.27 (m, 2H), 2.61 (s, 3H), 2.15 – 2.09 (m, 2H), 1.67 – 1.37 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 191.1, 188.4, 164.9, 164.8, 161.7, 161.6, 149.8, 145.7, 145.6, 133.6, 132.7, 132.4, 166.3, 37.7, 37.6, 34.2, 28.8, 28.7, 27.1, 26.7, 25.7. HRMS calc for $C_{13}H_{15}NO_3S$ 265.0773, found 265.0777.



Compound 4k

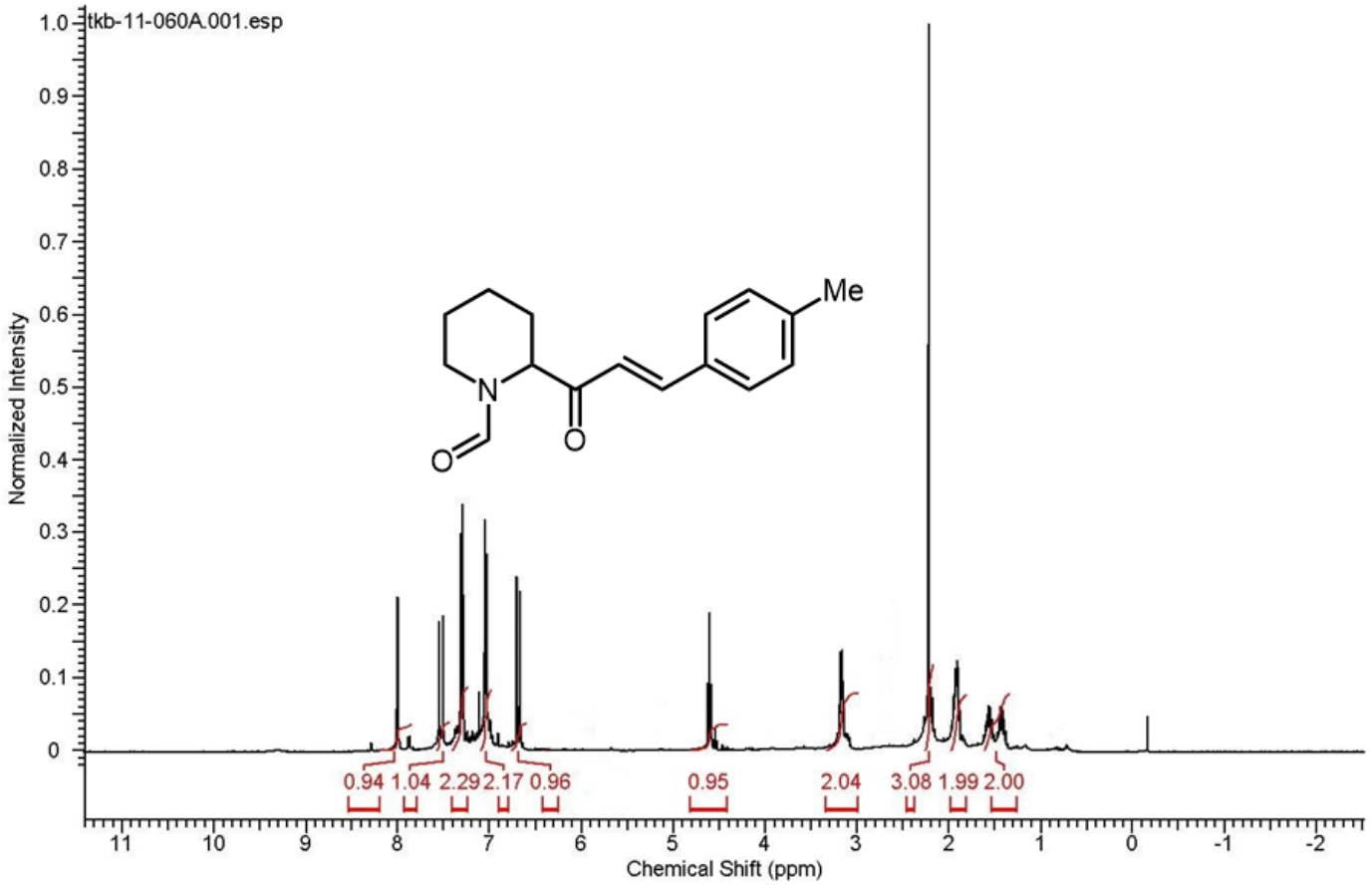
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Pale-yellow oil. Yield = 211.7 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.01 (s, 1H), 7.57 (d, *J* = 15.8, 1H), 7.51 – 7.38 (m, 2H), 7.33 – 7.21 (m, 2H), 6.75 (d, *J* = 15.8 Hz, 1H), 4.54 (td, *J* = 7.3, 2.5 Hz, 1H), 3.22 – 3.13 (m, 2H), 2.02 – 1.83 (m, 2H), 1.41 – 1.22 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.5, 164.7, 161.4, 144.6, 144.5, 134.2, 131.1, 131.0, 129.1, 128.7, 122.2, 41.5, 37.8, 33.9, 33.8, 31.8, 31.5, 30.7, 28.9, 26.8, 26.5. HRMS calc for $C_{15}H_{17}NO_2$ 243.1259, found 243.1262.





Compound 4l

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Pale-yellow oil. Yield = 218.7 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (s, 1H), 7.53 (d, *J* = 15.8 Hz, 1H), 7.46 (d, 2H), 7.17 (d, 2H), 6.68 (d, *J* = 15.8 Hz, 1H), 4.60 (t, *J* = 7.3 Hz, 1H), 3.25 – 3.04 (m, 2H), 2.22 (s, 3H), 2.01 – 1.79 (m, 2H), 1.56 (ddq, *J* = 13.2, 8.5, 6.7 Hz, 1H), 1.41 (ddq, *J* = 13.4, 9.3, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 164.9, 161.8, 161.7, 144.7, 141.7, 131.4, 129.8, 128.8, 121.3, 37.2, 37.1, 31.6, 31.2, 29.4, 21.7, 19.3. HRMS calc for $C_{16}H_{19}NO_2$ 257.1416, found 257.1410.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Normalized Intensity
Chemical Shift (ppm)
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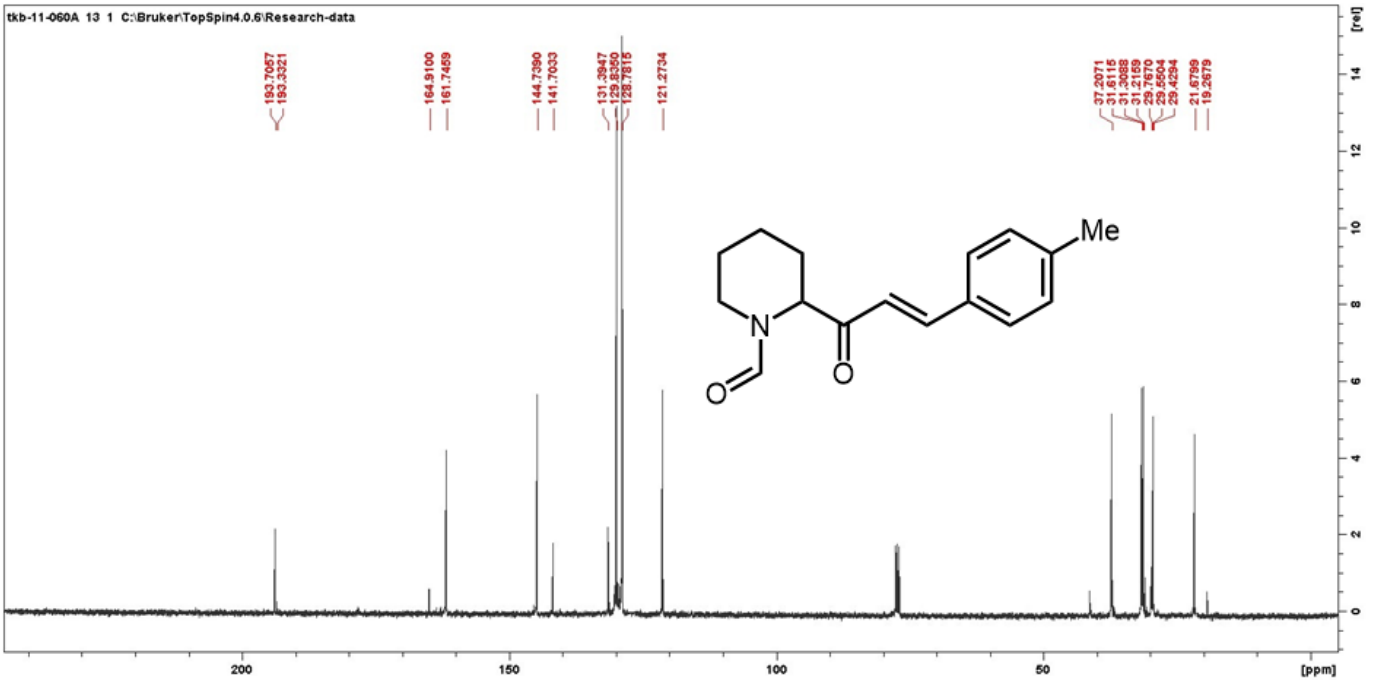
O
O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31.2169
29.7670
29.5504
29.4294
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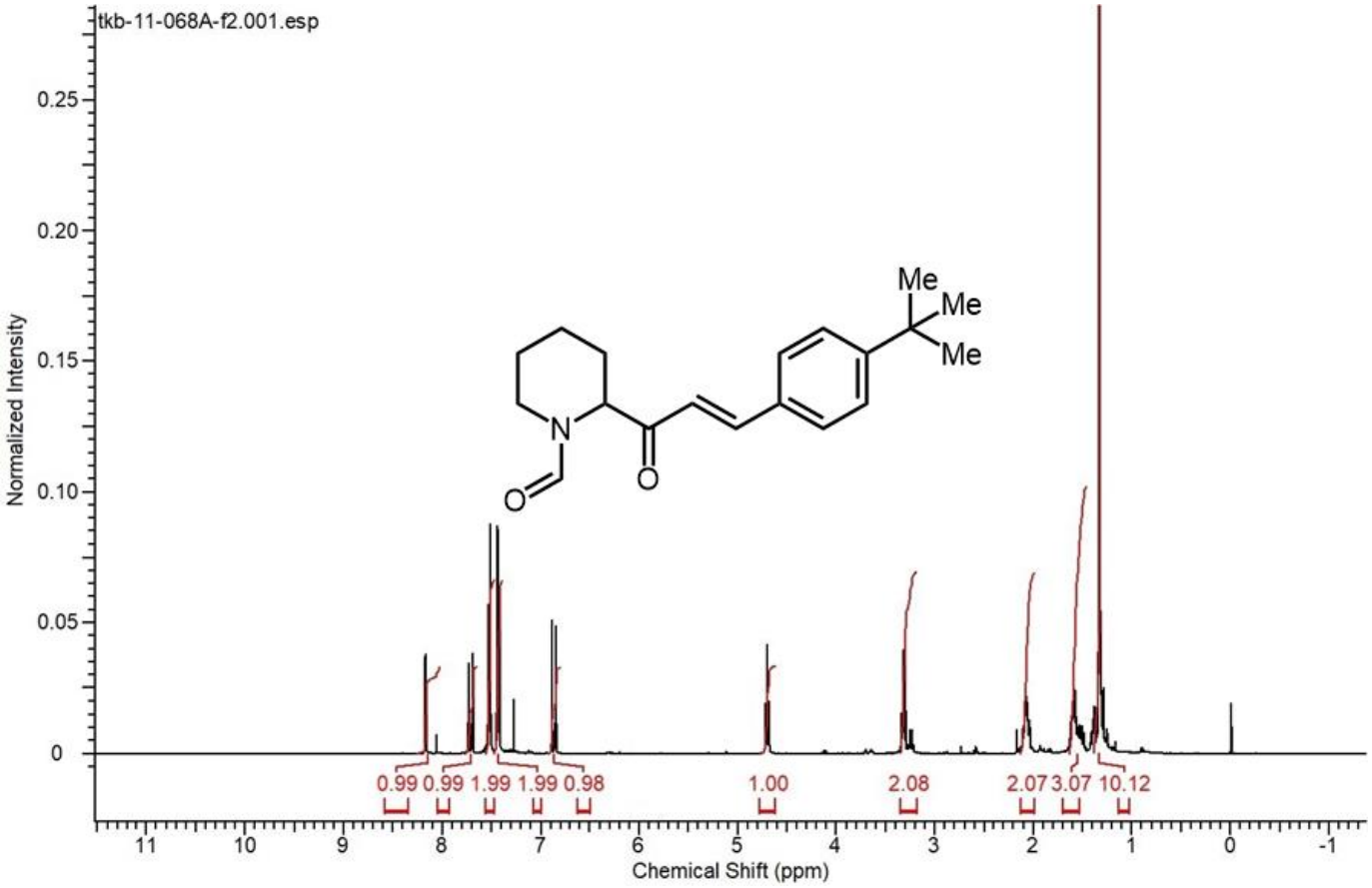
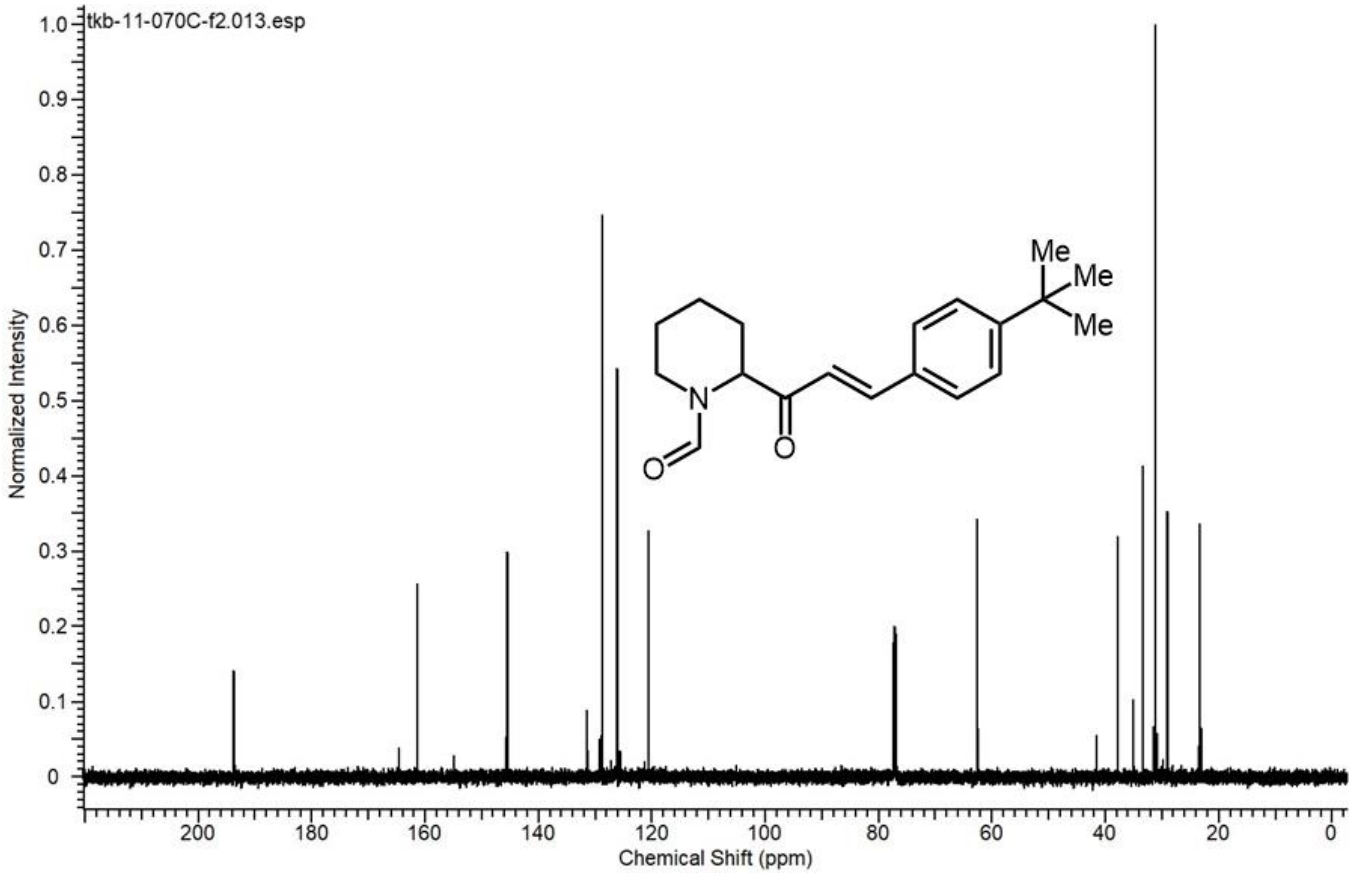
19.2679
Me
N
O
O
[ppm]
[rel]

Compound 4m

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (90:10). Pale-yellow oil. Yield = 263.5 mg, 88%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.01 (s, 1H), 7.56 (d, *J* = 15.9 Hz, 1H), 7.52 (d, 2H), 7.45 (d, 2H), 6.71 (d, *J* = 15.8 Hz, 1H), 4.54 (t, *J* = 7.3 Hz, 1H), 3.13 – 3.06 (m, 2H), 1.99 – 1.86 (m, 2H), 1.45 – 1.33 (m, 3H), 1.28 – 1.16 (m, 1H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$, *rotamers*) δ 193.7, 164.7, 161.4, 154.9, 145.7, 145.5, 131.5, 128.71, 126.1, 120.5, 62.6, 41.5, 37.8, 35.1, 33.4, 31.2, 30.8, 29.0, 23.4, 23.1. HRMS calc for $C_{19}H_{25}NO_2$ 299.1885, found 299.1889.

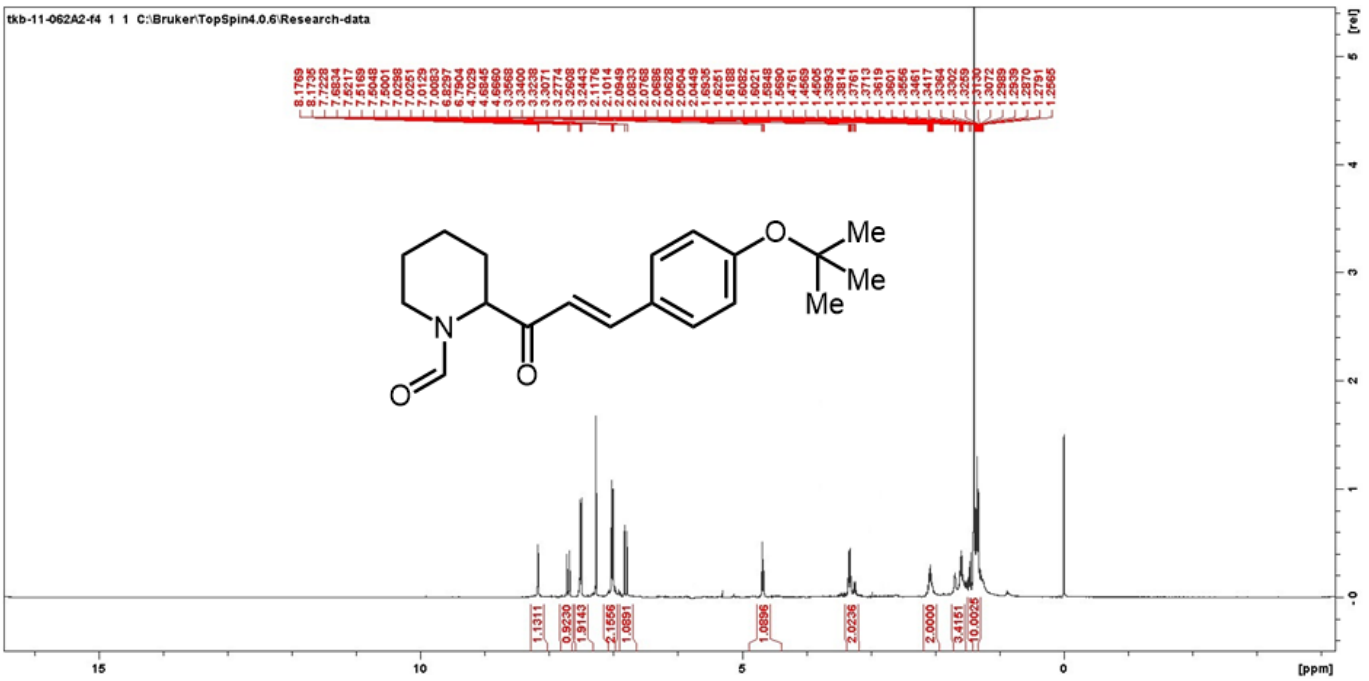
Note: Using **General Procedure B**, formamide **4m** was obtained in 74% yield.

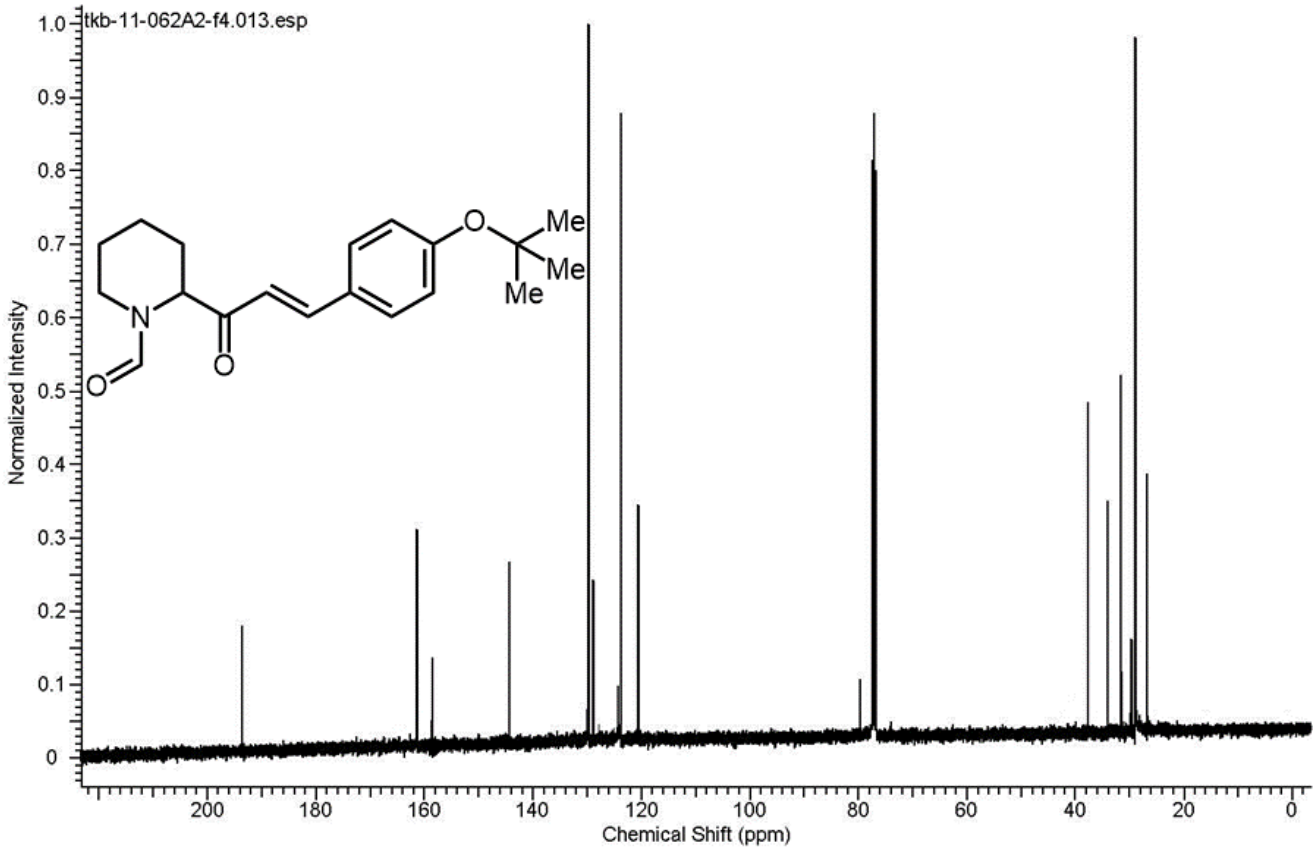




Compound 4n

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Pale-yellow oil. Yield = 268.1 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.18 (s, 1H), 7.71 (d, *J* = 15.8 Hz, 1H), 7.57 – 7.47 (d, 2H), 7.11 – 6.99 (d, 2H), 6.81 (d, *J* = 15.8 Hz, 1H), 4.68 (t, *J* = 7.4 Hz, 1H), 3.40 – 3.32 (m, 2H), 2.16 – 2.01 (m, 2H), 1.63 – 1.47 (m, 2H), 1.39 – 1.28 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 164.7, 161.3, 158.6, 144.4, 144.3, 129.8, 128.9, 123.7, 120.6, 79.7, 37.8, 34.0, 31.7, 29.0, 28.9, 28.8, 28.7, 26.8. HRMS calc for $C_{19}H_{25}NO_3$ 315.1834, found 315.1837.

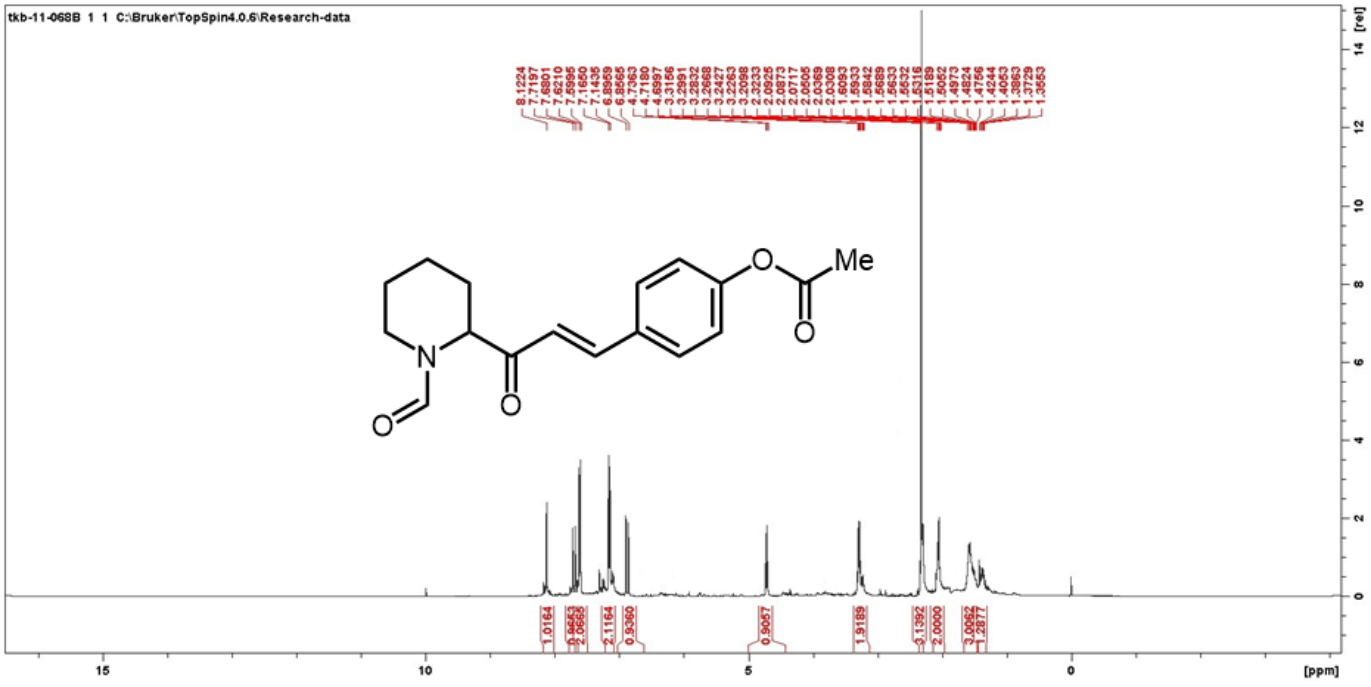


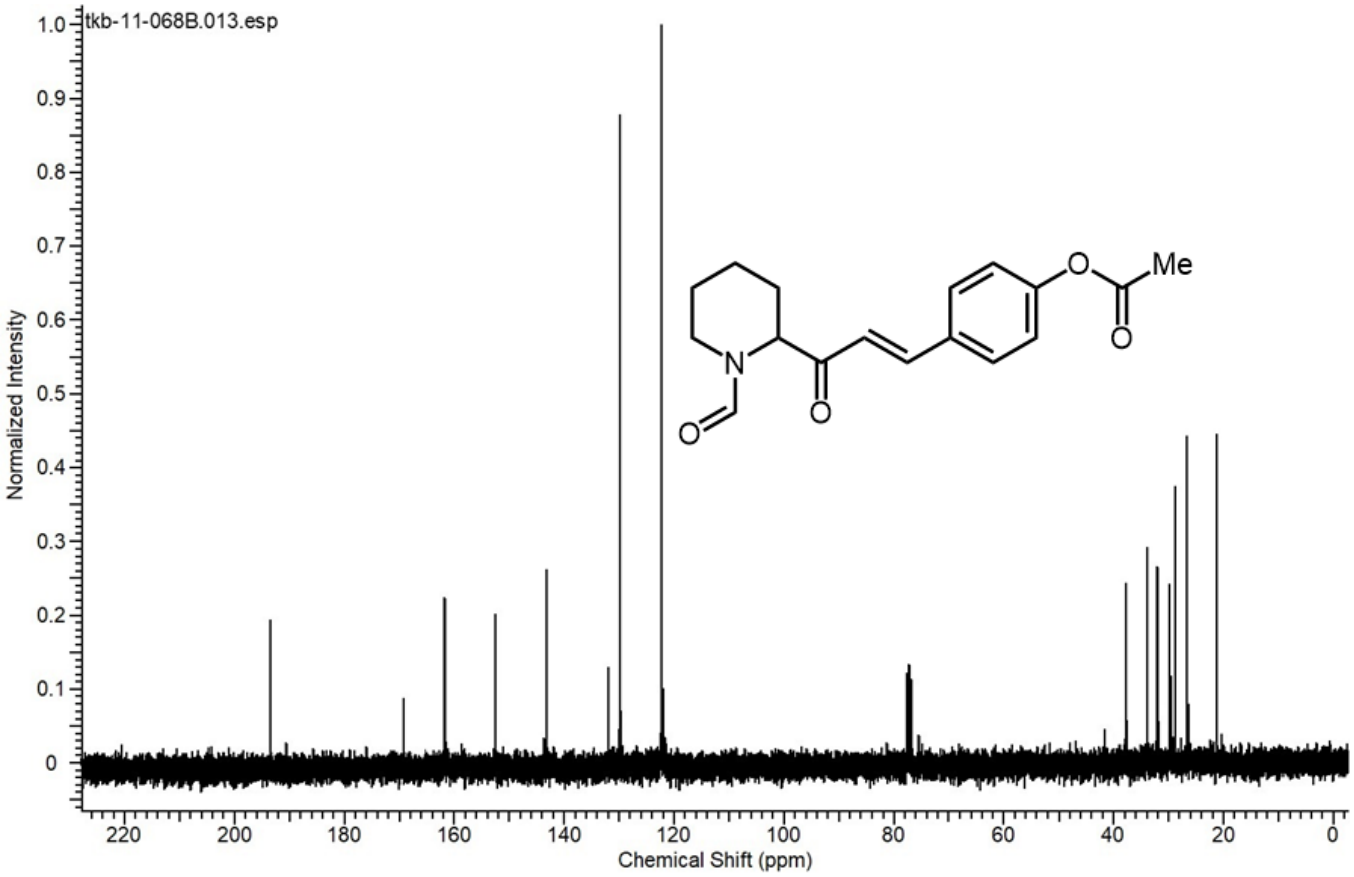


Compound 4o

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Pale-yellow oil. Yield = 247.1 mg, 82%. ^{1}H NMR (400

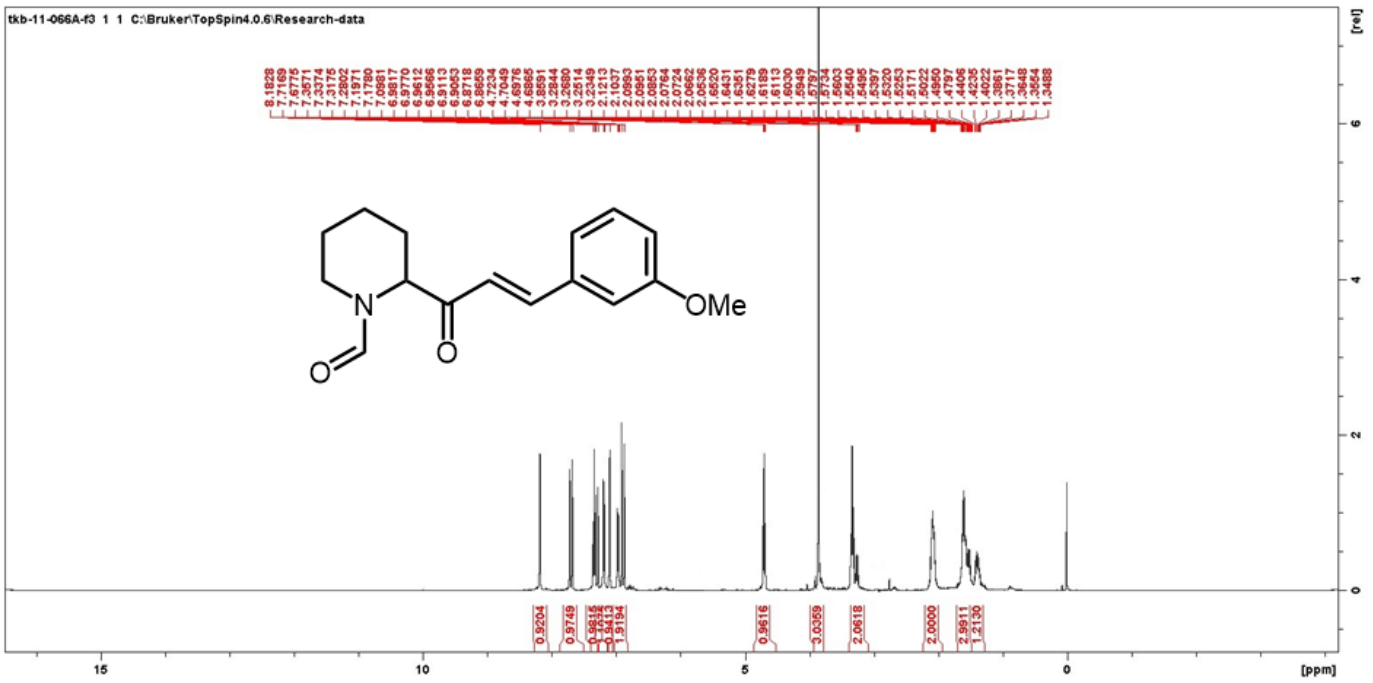
MHz, Chloroform-*d, rotamers*) δ 8.12 (s, 1H), 7.67 (d, *J* = 15.8 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 2H), 6.78 (d, *J* = 15.8 Hz, 1H), 6.23 (s, 1H), 4.53 (t, *J* = 7.3 Hz, 1H), 3.29 – 3.10 (m, 2H), 2.33 (s, 3H), 2.10 (d, *J* = 4.3 Hz, 2H), 1.71 – 1.35 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.4, 193.3, 169.3, 161.8, 152.6, 143.3, 131.9, 129.9, 122.4, 121.9, 41.6, 37.8, 33.9, 32.1, 29.8, 29.5, 28.8, 26.8, 21.3. HRMS calc for $C_{17}H_{19}NO_4$ 301.1314, found 301.1318.





Compound 4p

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Pale-yellow oil. Yield = 243.2 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.18 (s, 1H), 7.74 (d, *J* = 15.8 Hz, 1H), 7.42 (t, 1H), 7.29 (s, 1H), 7.13 (t, *J* = 2.1 Hz, 1H), 6.99 (dd, *J* = 8.3, 2.6Hz, 1H), 6.82 (d, *J* = 15.8 Hz, 1H), 4.74 (t, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.33 – 3.10 (m, 2H) 2.03 – 1.96 (m, 2H), 1.63 – 1.30 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.4, 164.7, 161.4, 160.0, 144.5, 144.4, 135.5, 130.1, 122.5, 121.4, 116.8, 113.6, 113.6, 55.5, 41.4, 37.8, 33.9, 33.9, 31.7, 31.4, 30.7, 28.9, 26.8, 26.4. HRMS calc for $C_{16}H_{19}NO_3$ 273.1365, found 273.1368.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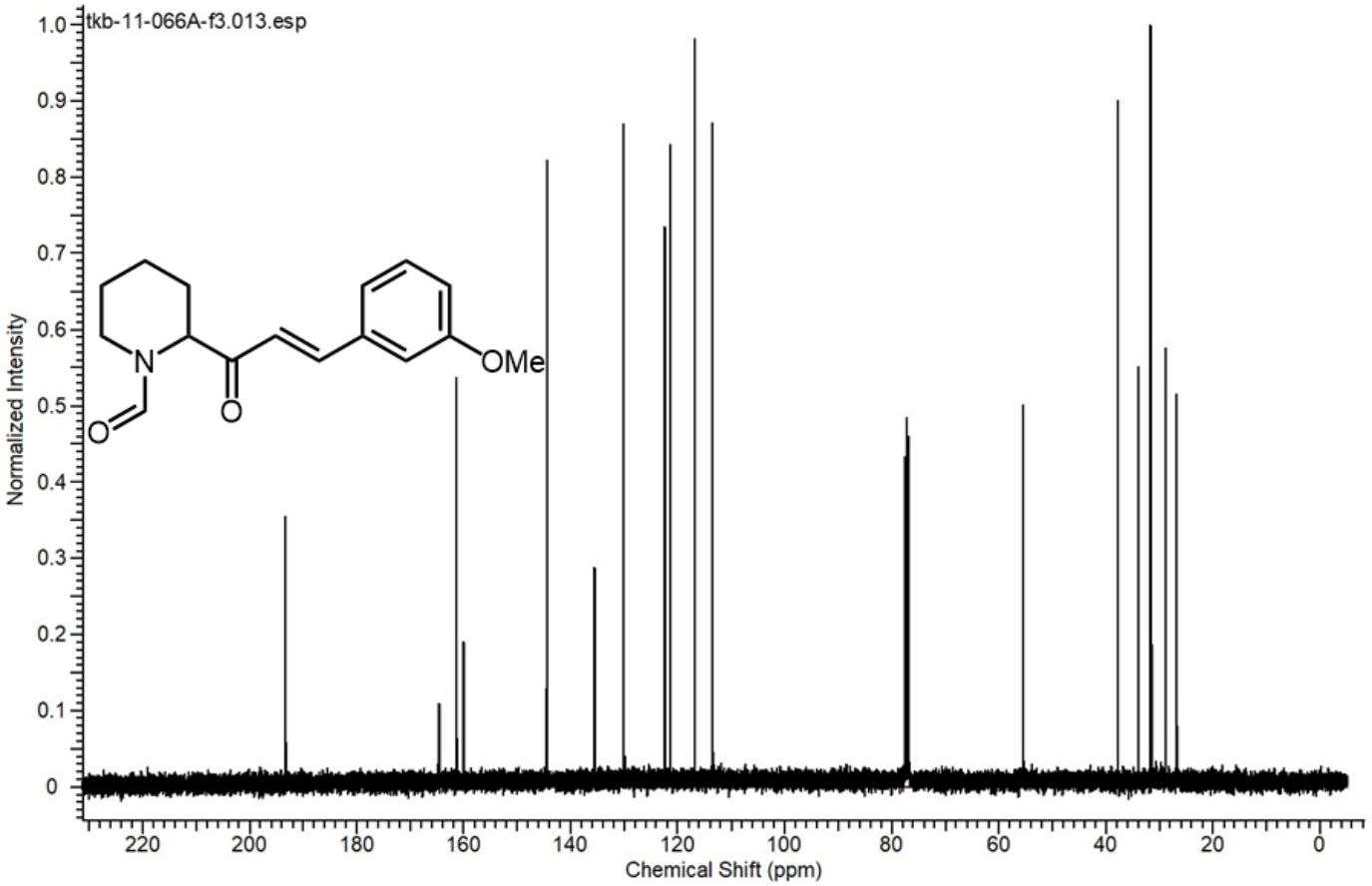
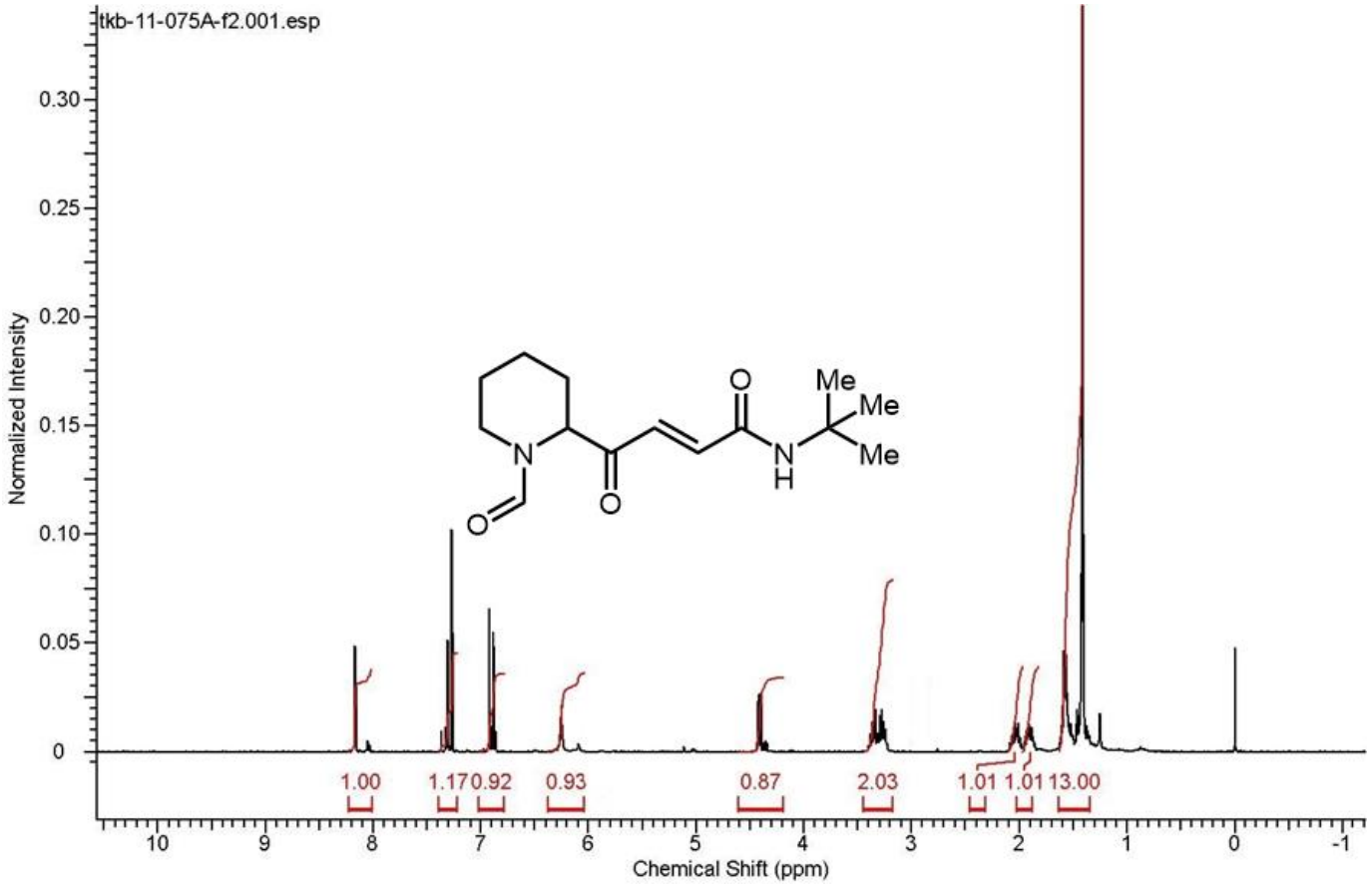
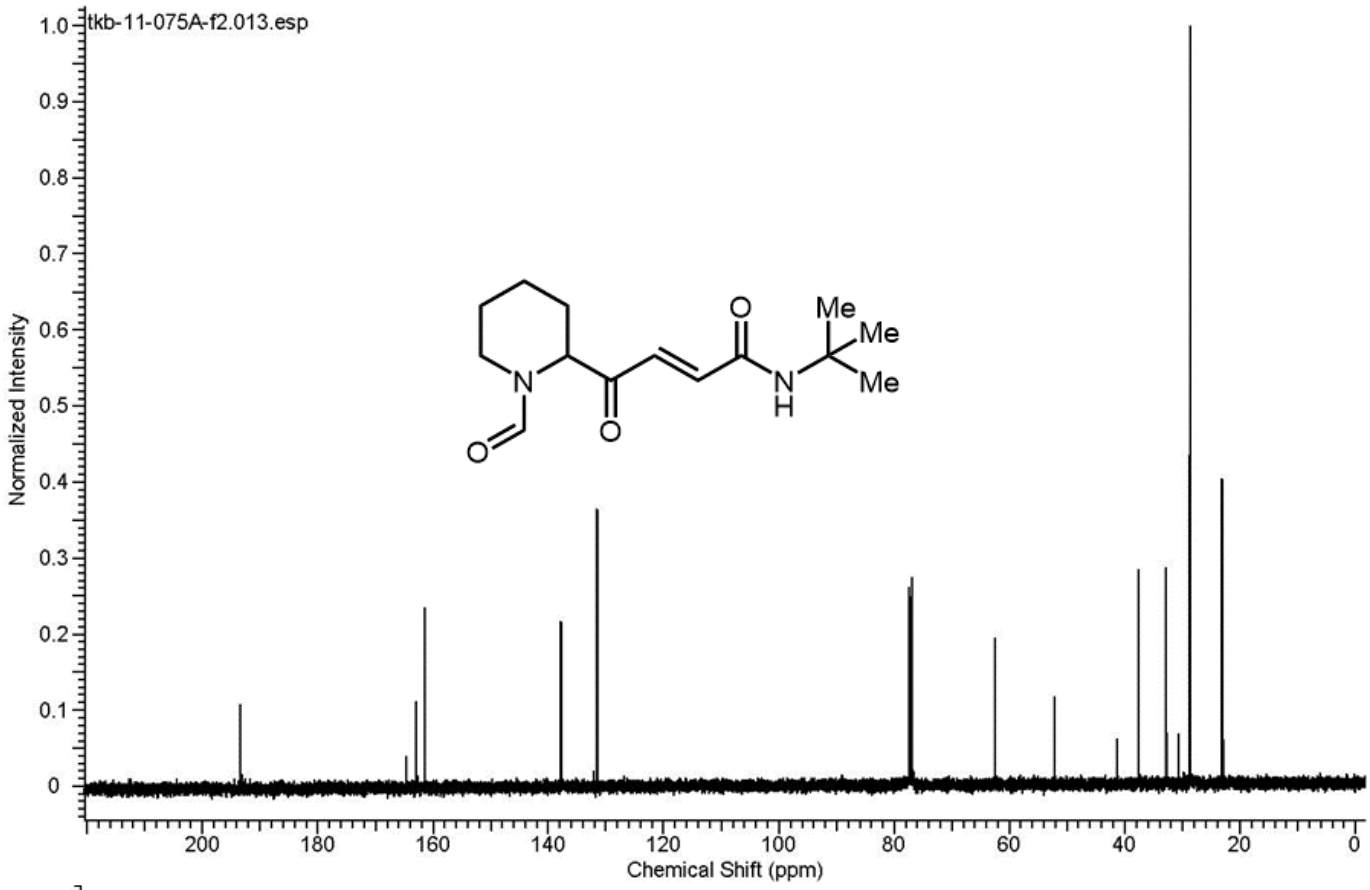
[rel]
[ppm]


tkb-11-066A-f3.013.esp
OMe
Normalized Intensity
Chemical Shift (ppm)

Compound 4q

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Pale-yellow oil. Yield = 215.7 mg, 81%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (s, 1H), 7.24 (d, *J* = 15.2 Hz, 1H), 6.84 (d, *J* = 15.2 Hz, 1H), 6.30 (s, 1H), 4.23 (t, *J* = 8.2 Hz, 1H), 3.37 – 3.25 (m, 2H), 2.05 – 1.97 (m, 1H), 1.93 – 1.88 (m, 1H), 1.49 – 1.25 (m, 13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 164.6, 162.9, 161.5, 137.9, 131.6, 62.6, 62.4, 52.2, 41.4, 37.6, 32.9, 32.7, 30.7, 28.8, 28.7, 28.6, 23.1, 22.9. HRMS calc for $C_{14}H_{22}N_2O_3$ 266.1630, found 266.1635.

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Normalized Intensity
Chemical Shift (ppm)
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Me
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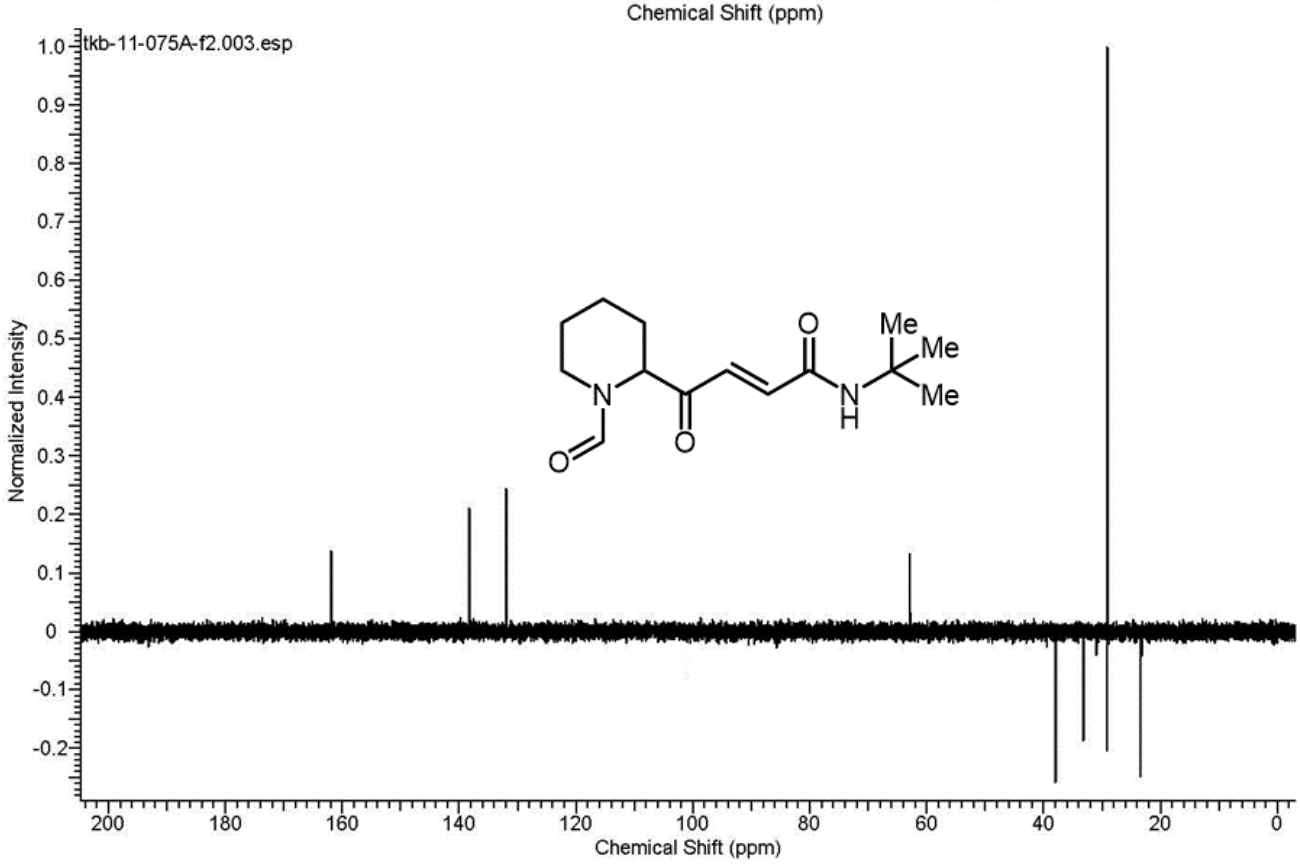
H
O
O
N


tkb-11-075A-f2.003.esp
Normalized Intensity
Chemical Shift (ppm)
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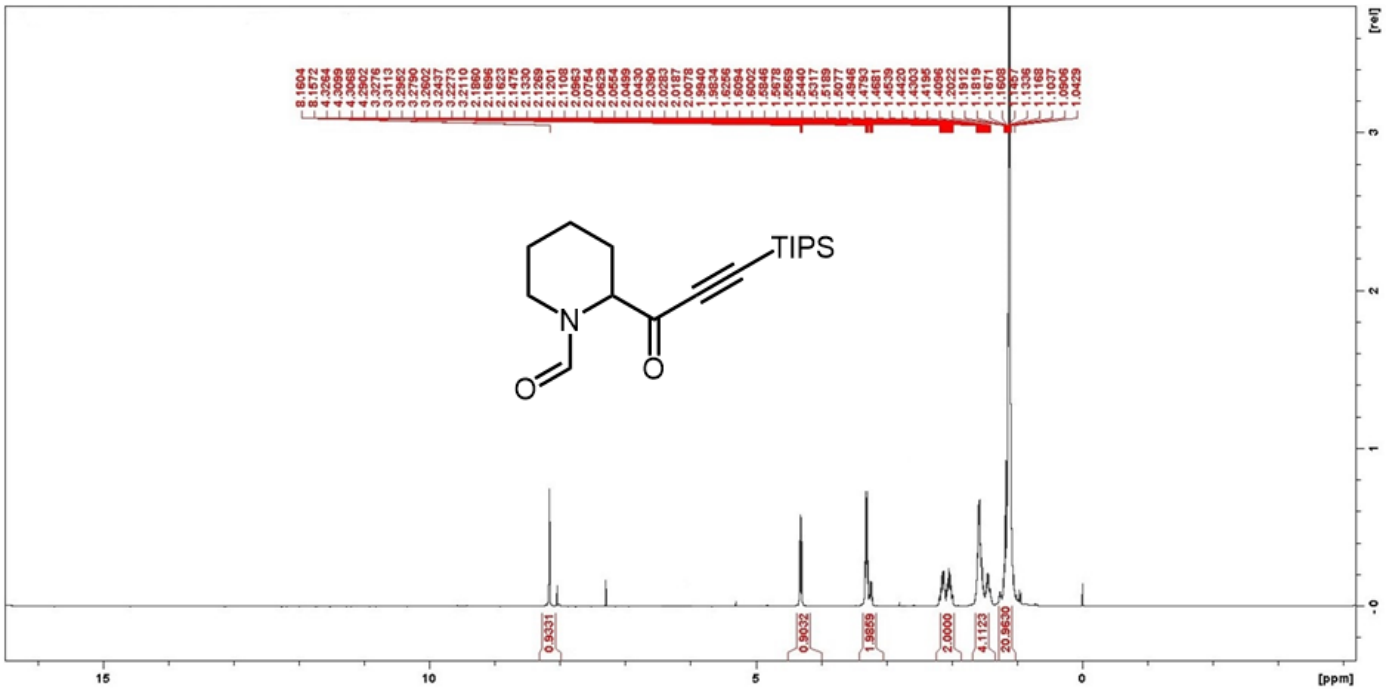
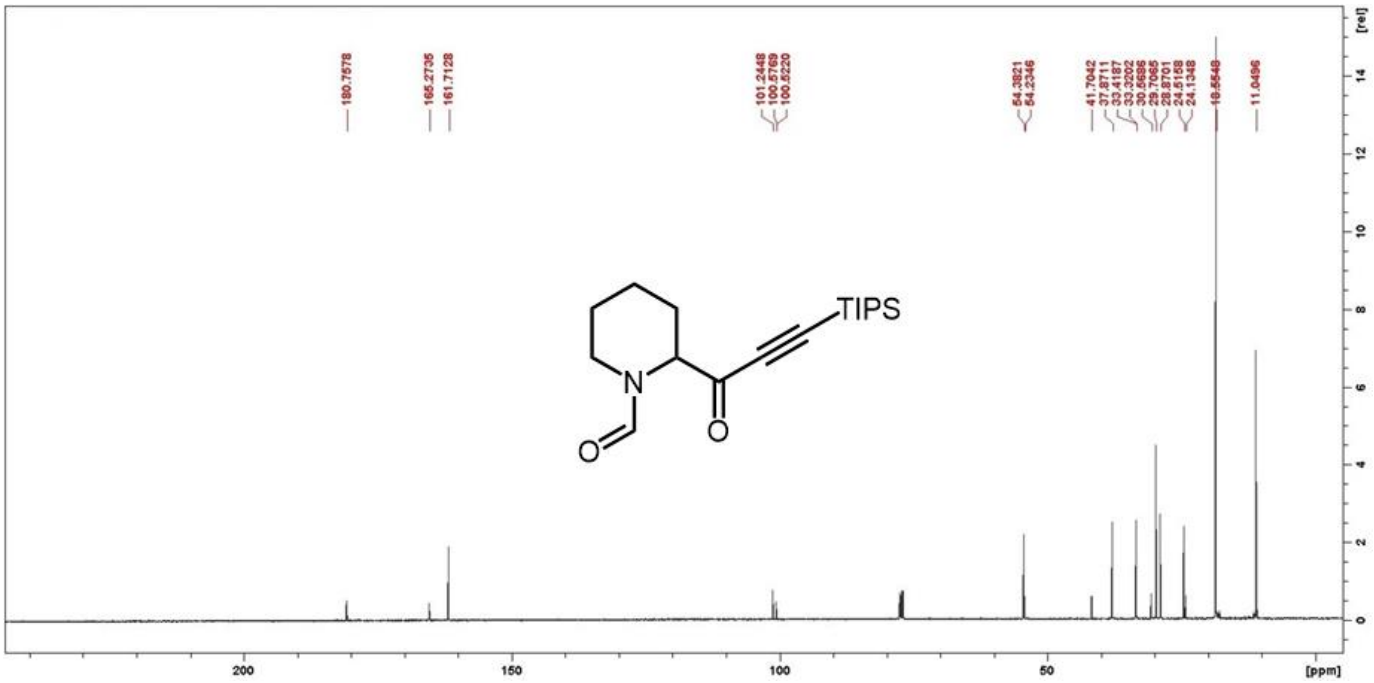
Me
Me
Me
N
H
O
O
N

Compound 4r

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (90:10). Yellowish oil. Yield = 270.1 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.16 (s, 1H), 4.32 (t, *J* = 7.1 Hz, 1H), 3.32 – 3.21 (m, 2H), 2.18 – 1.98 (m, 2H), 1.62 – 1.41 (m, 4H), 1.20 – 1.04 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 180.8, 180.6, 178.2, 164.9, 161.5, 101.2, 100.5, 54.4, 54.2, 41.6, 37.8, 33.4, 33.3, 30.6, 29.7, 28.9, 24.5, 24.1, 18.5, 11.1. HRMS calc for $C_{18}H_{31}NO_2Si$ 321.2124, found 321.2127.

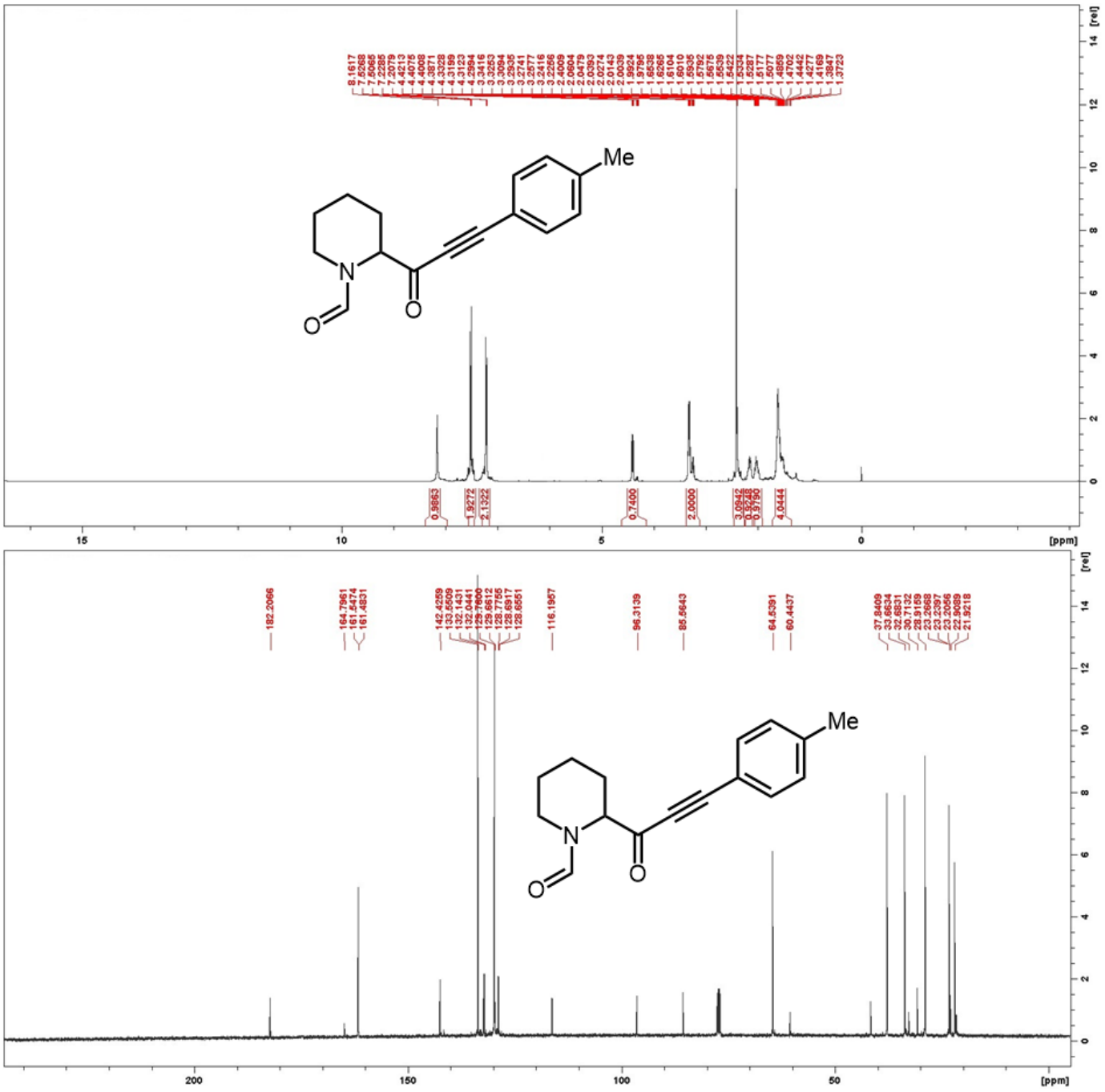
Note: Using **General Procedure B**, formamide **4r** was obtained in 69% yield.





Compound 4s

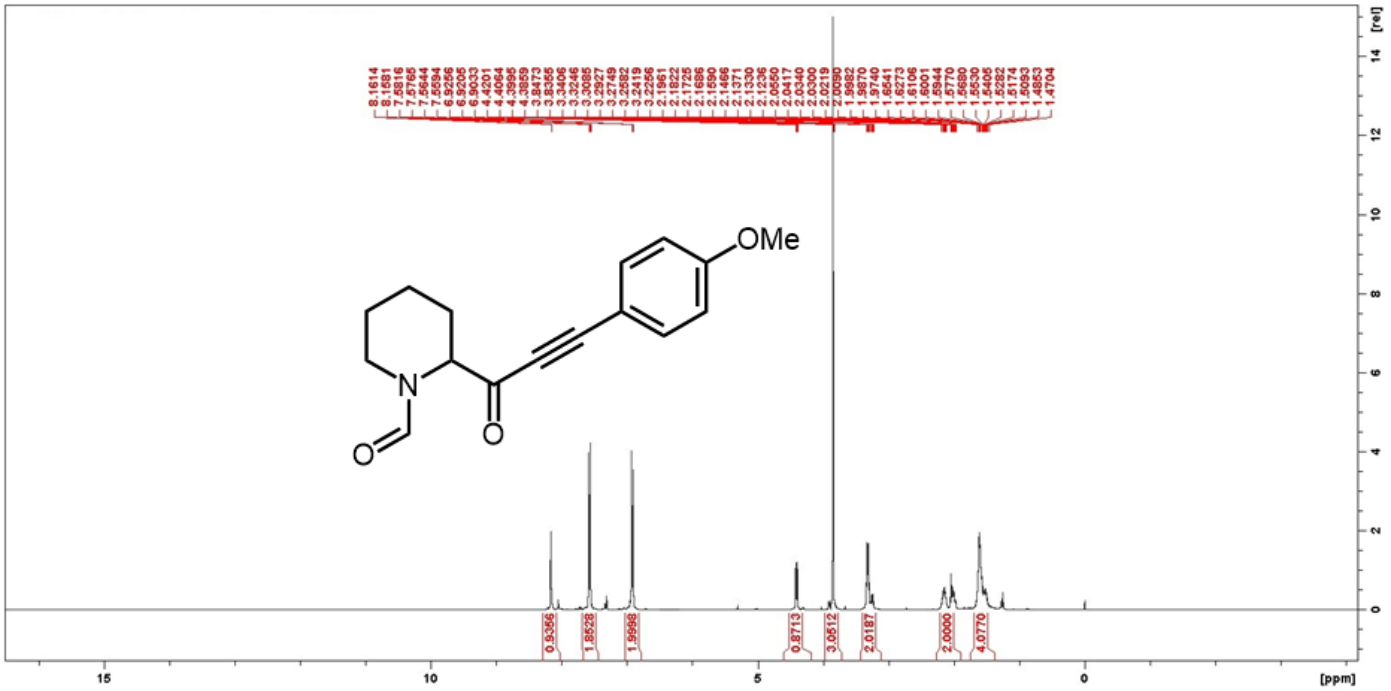
Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Yellowish oil. Yield = 222.1 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.16 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 2H) 7.20 (d, *J* = 7.8 Hz, 2H), 4.40 (t, *J* = 8.2 Hz, 1H), 3.14 (q, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 2.06 – 1.97 (m, 2H), 1.65 – 1.37 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 164.8, 161.5, 161.4, 142.4, 133.5, 132.1, 132.0, 129.7, 129.6, 128.8, 128.7, 128.6, 116.2, 96.3, 85.6, 64.5, 64.4, 60.4, 41.6, 37.8, 37.8, 33.7, 33.6, 33.5, 30.7, 28.9, 28.8, 23.3, 23.2, 22.9, 21.9. HRMS calc for $C_{16}H_{17}NO_2$ 255.1259, found 255.1255.

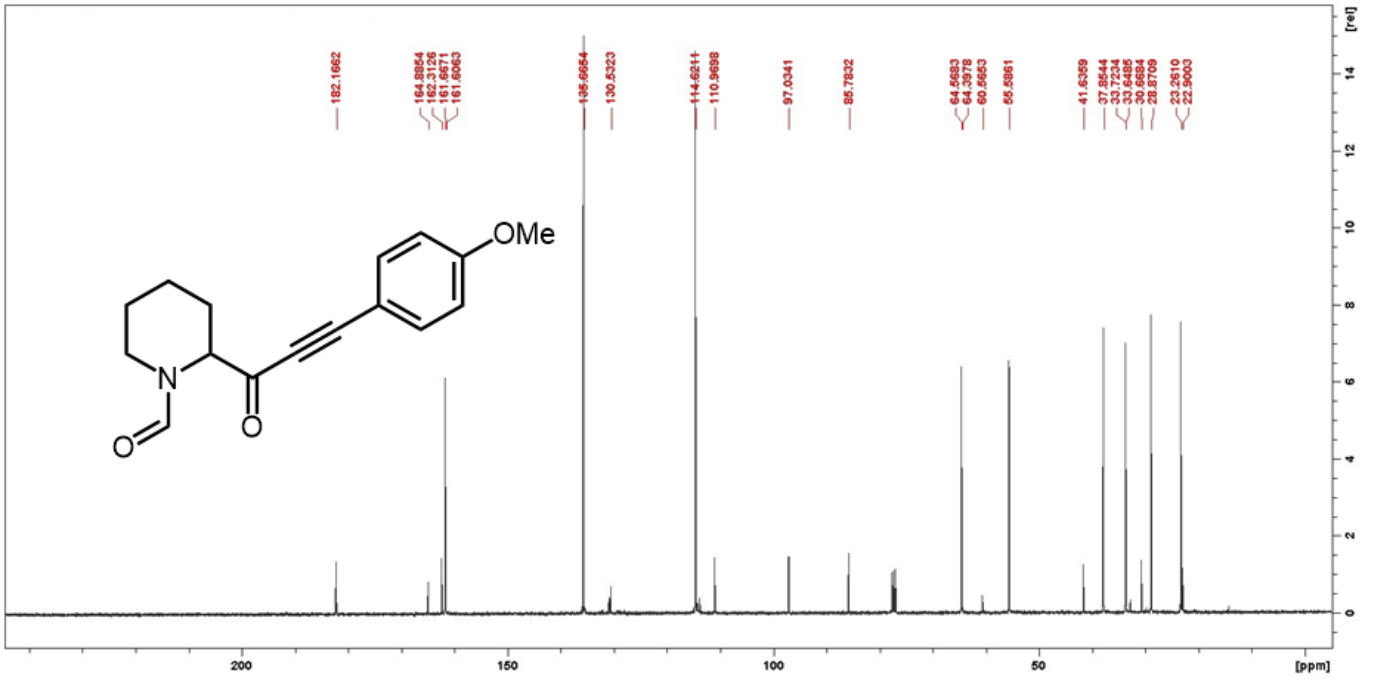


Compound 4t

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Yellowish oil. Yield = 244.2 mg, 90%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.16 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.25 (t, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 3.13 (q, *J* = 6.4 Hz, 2H), 2.06 – 1.86 (m, 2H), 1.50 – 1.36

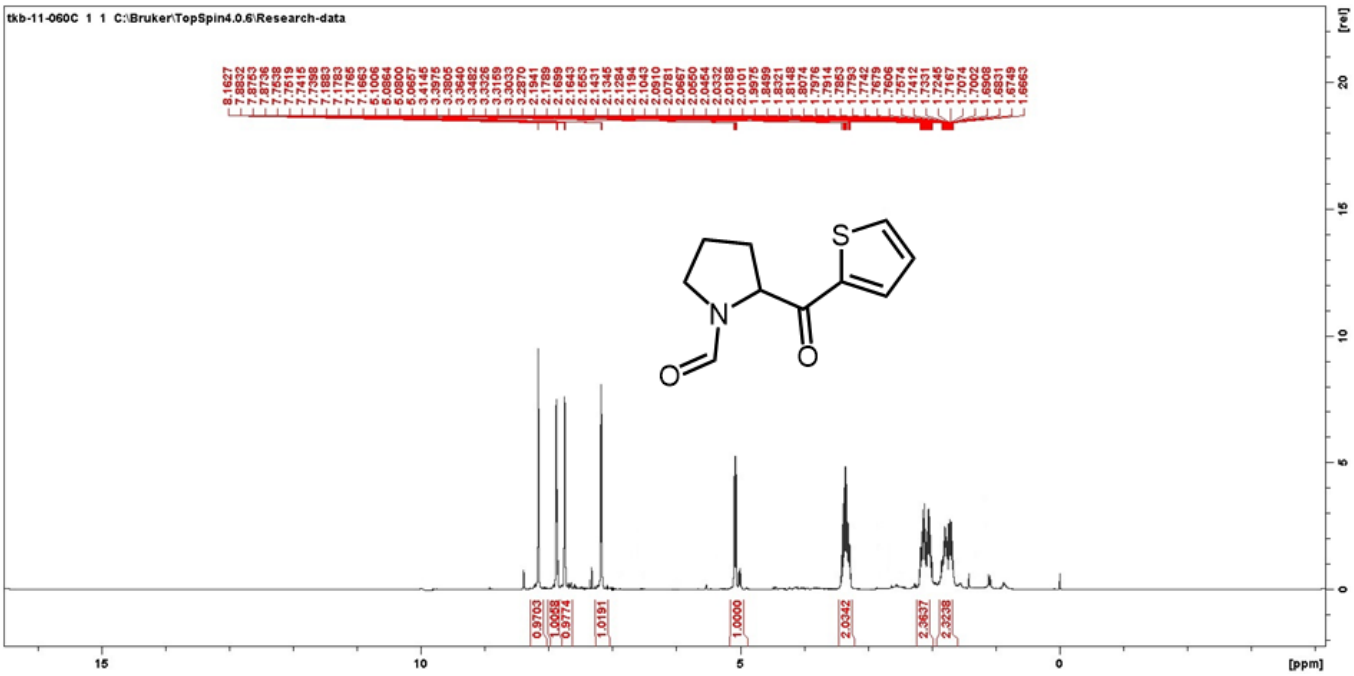
(m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 164.9, 162.3, 161.7, 135.8, 114.6, 110.9, 97.0, 85.8, 64.6, 64.4, 55.6, 41.6, 37.9, 33.7, 33.6, 30.7, 28.9, 23.3, 23.2, 22.9. HRMS calc for $C_{16}H_{17}NO_3$ 271.1208, found 271.1204.

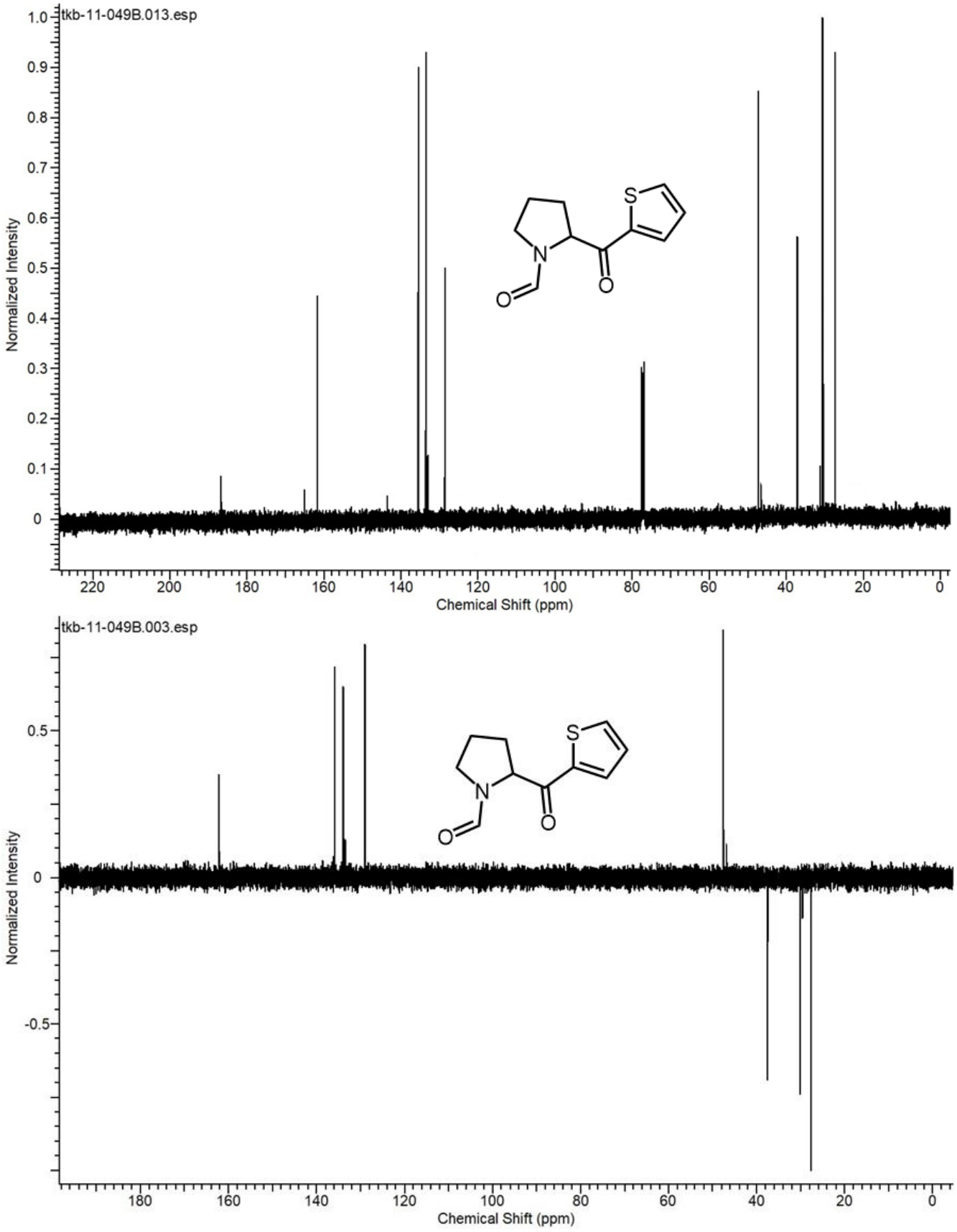




Compound 4u

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Pale-yellow oil. Yield = 171.6 mg, 82%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) 8.16 (s, 1H), 7.87 (d, *J* = 5.0 Hz, 1H), 7.75 (d, *J* = 5.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 3.8 Hz, 1H), 5.08 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.41 – 3.28 (m, 2H), 2.19 – 1.99 (m, 2H), 1.83 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 186.8, 165.1, 161.8, 143.6, 141.2, 135.5, 133.7, 133.5, 133.4, 133.1, 132.2, 131.8, 128.7, 128.6, 47.3, 46.5, 37.2, 37.1, 30.7, 29.5, 27.4, 27.3. HRMS calc for $C_{10}H_{11}NO_2S$ 209.0510, found 209.0514.

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160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)
S
N
O
O
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160
140
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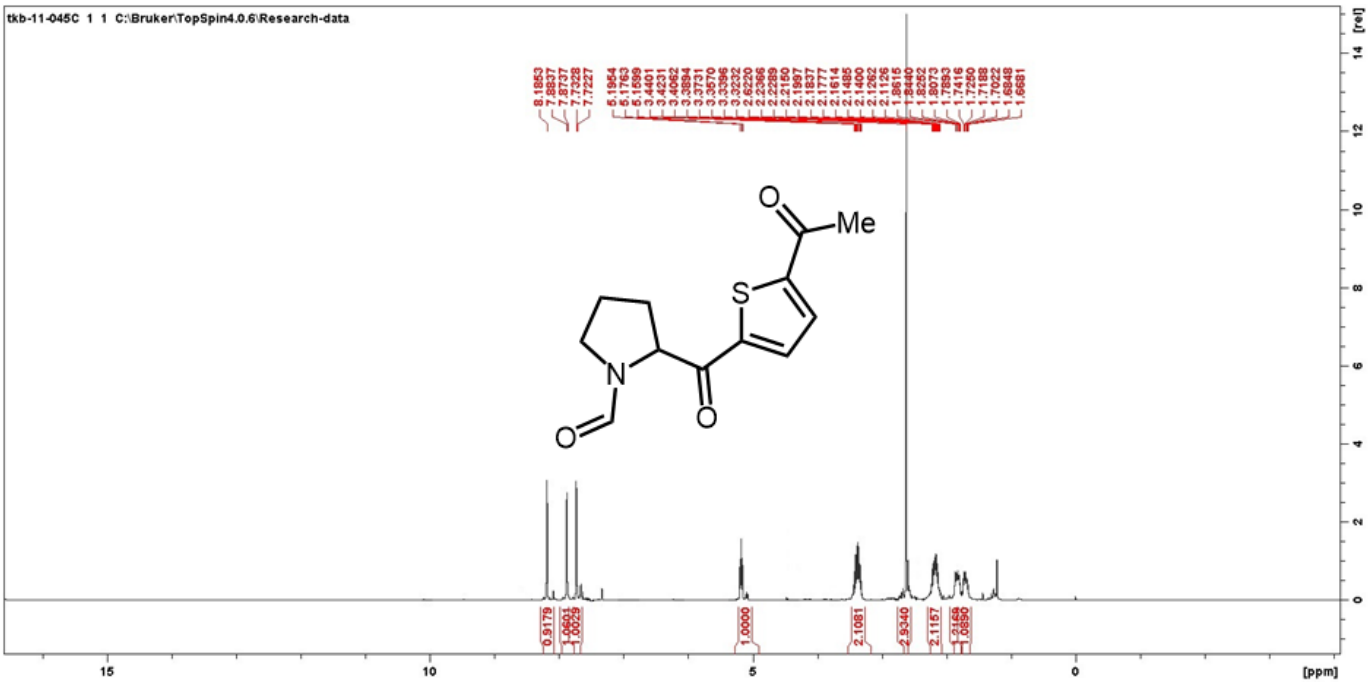
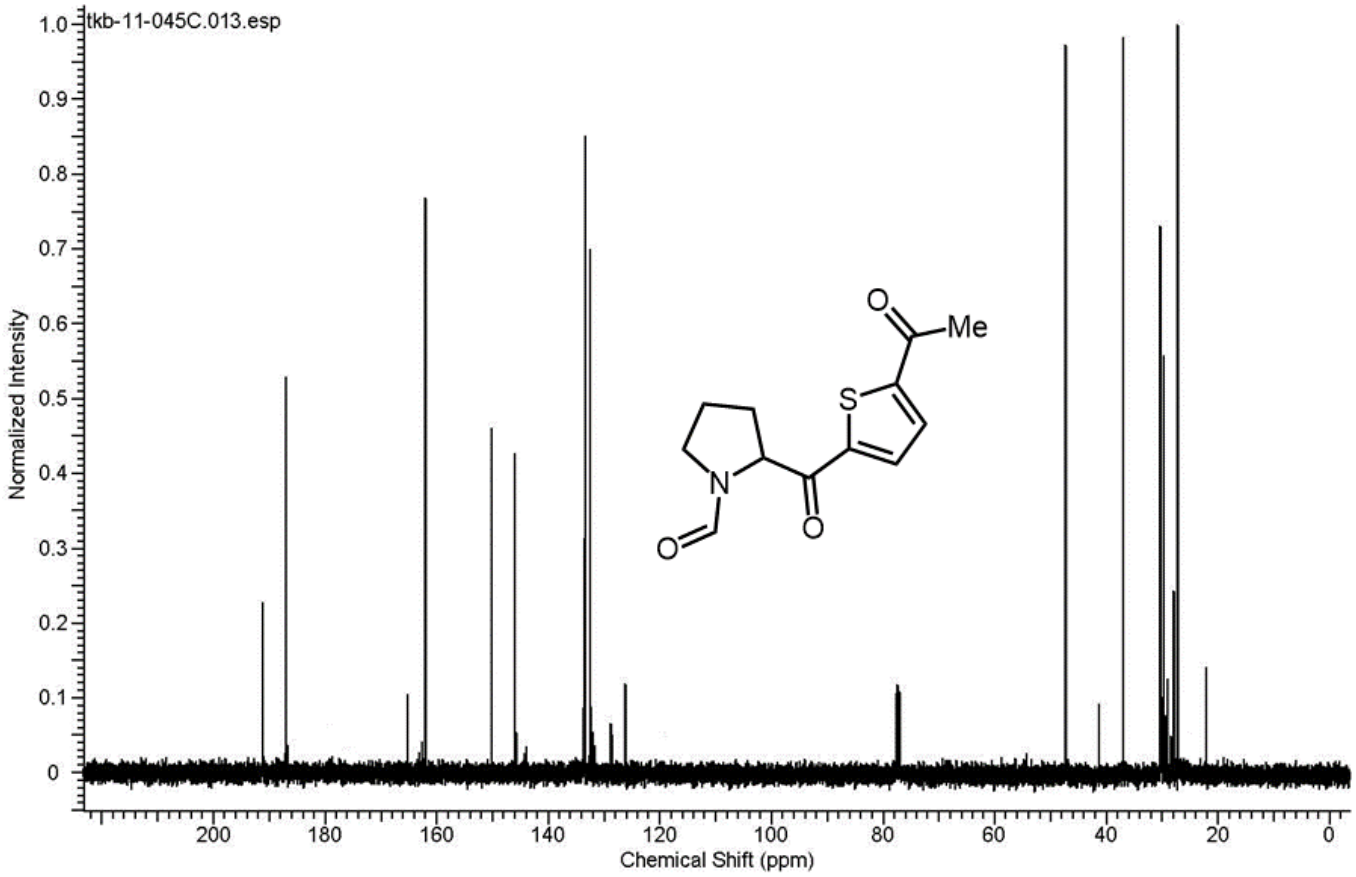
100
80
60
40
20
0
Chemical Shift (ppm)
S
N
O
O

Compound 4v

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (75:25). Pale-yellow oil. Yield = 198.5 mg, 79%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.19 (s, 1H), 7.87 (d, *J* = 5.8 Hz, 1H), 7.72 (d, *J* = 5.8 Hz, 1H), 5.17 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.44 – 3.32 (m, 2H), 2.62 (s, 3H), 2.24 – 2.11 (m, 2H), 1.86 – 1.79 (m, 1H), 1.74 – 1.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 191.2, 187.1, 165.1, 162.0, 150.2, 145.9, 133.5, 133.4, 132.5, 128.8, 128.7, 126.3, 47.3, 41.3, 37.0, 30.3, 29.7, 27.9, 27.2, 27.1, 22.2. HRMS calc for $C_{12}H_{13}NO_3S$ 251.0616, found 251.0619.

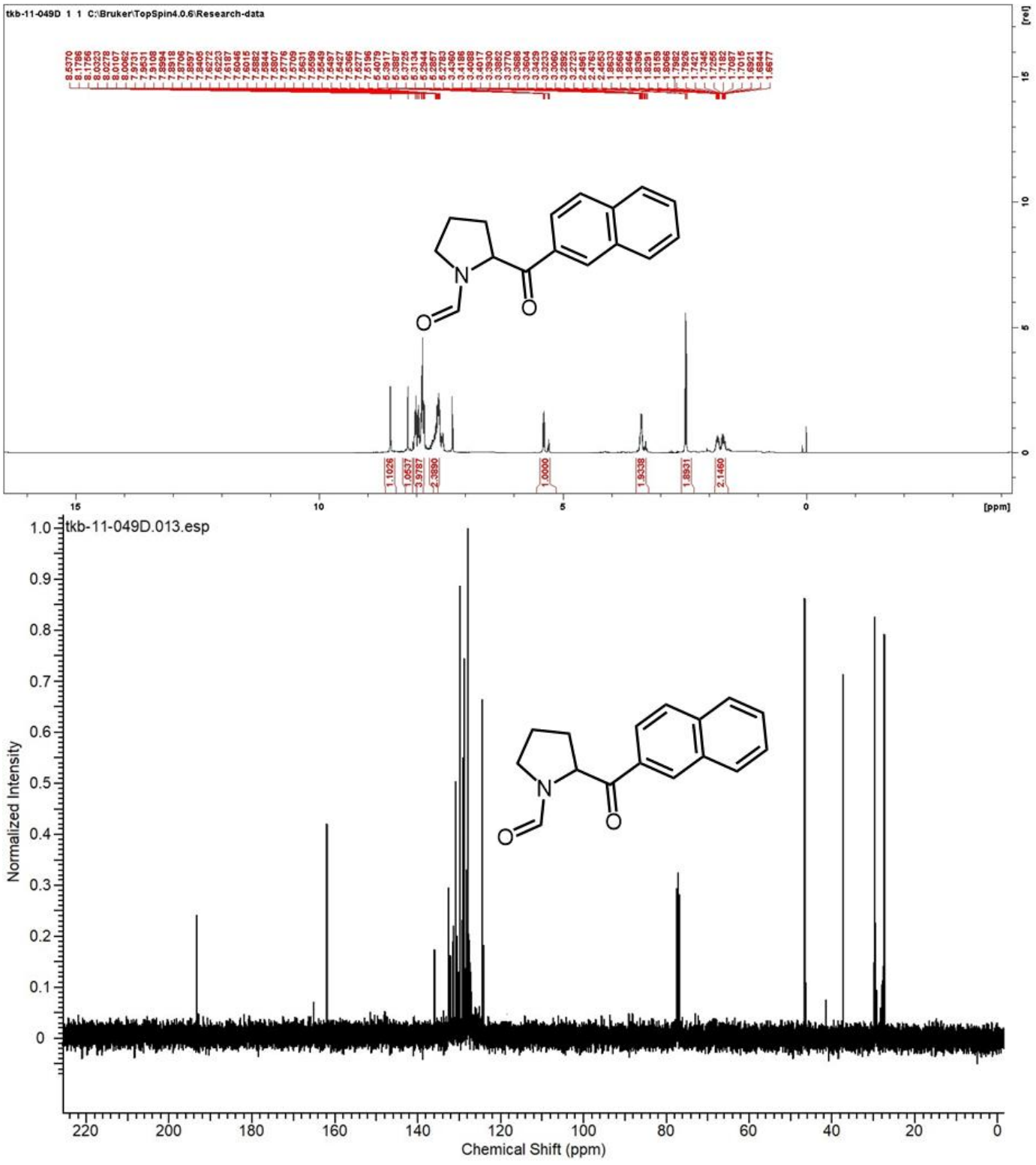




Compound 4w

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (70:30). Pale-yellow oil. Yield = 215.3 mg, 85%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 8.53 (s, 1H), 8.17 (s, 1H), 8.02 – 7.84 (m, 4H), 7.62 – 7.51 (m, 2H), 5.40 (t, *J* = 7.2 Hz, 1H), 3.41 – 3.27 (m, 2H), 2.50 – 2.45 (m, 2H), 1.86 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.3, 161.9, 130.9, 130.9, 129.9, 129.1, 128.9, 128.3, 127.9, 127.1, 124.4, 46.6, 37.4, 30.6, 29.7, 27.4. HRMS calc for $C_{16}H_{15}NO_2$ 253.1103, found 253.1100.

Note: Using **General Procedure B**, formamide **4w** was obtained in 72% yield.

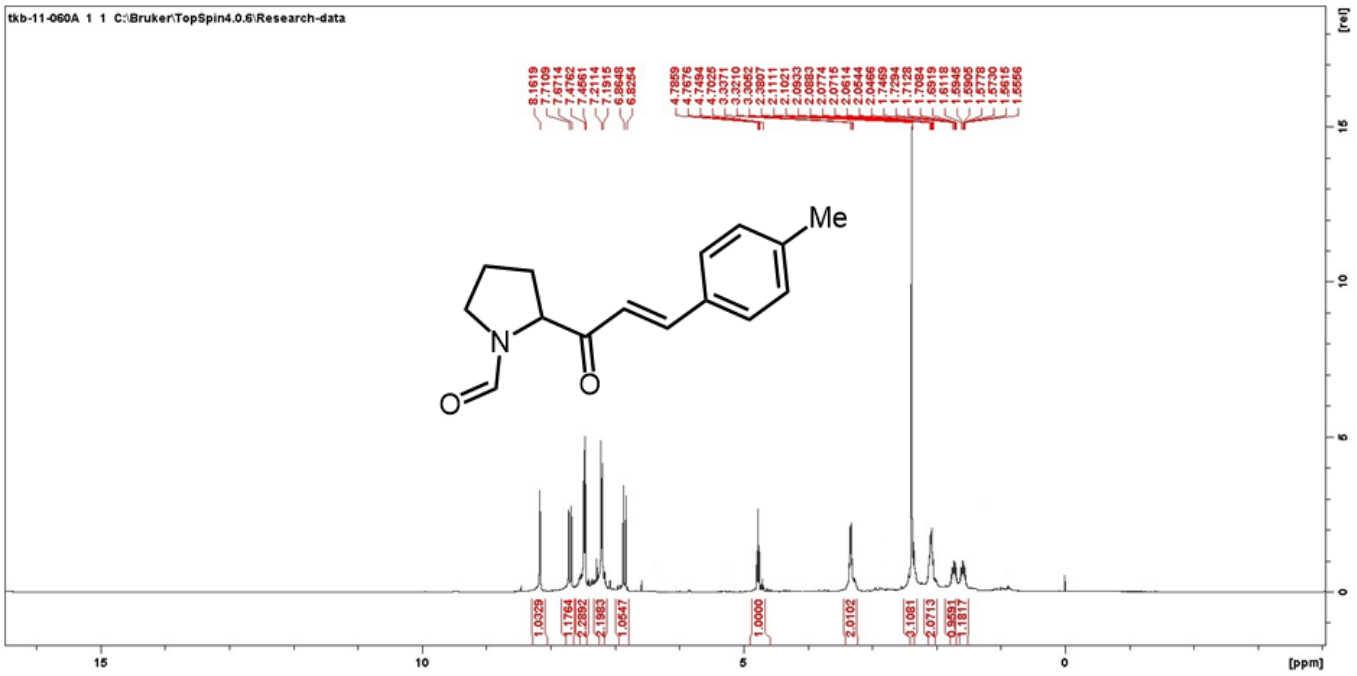


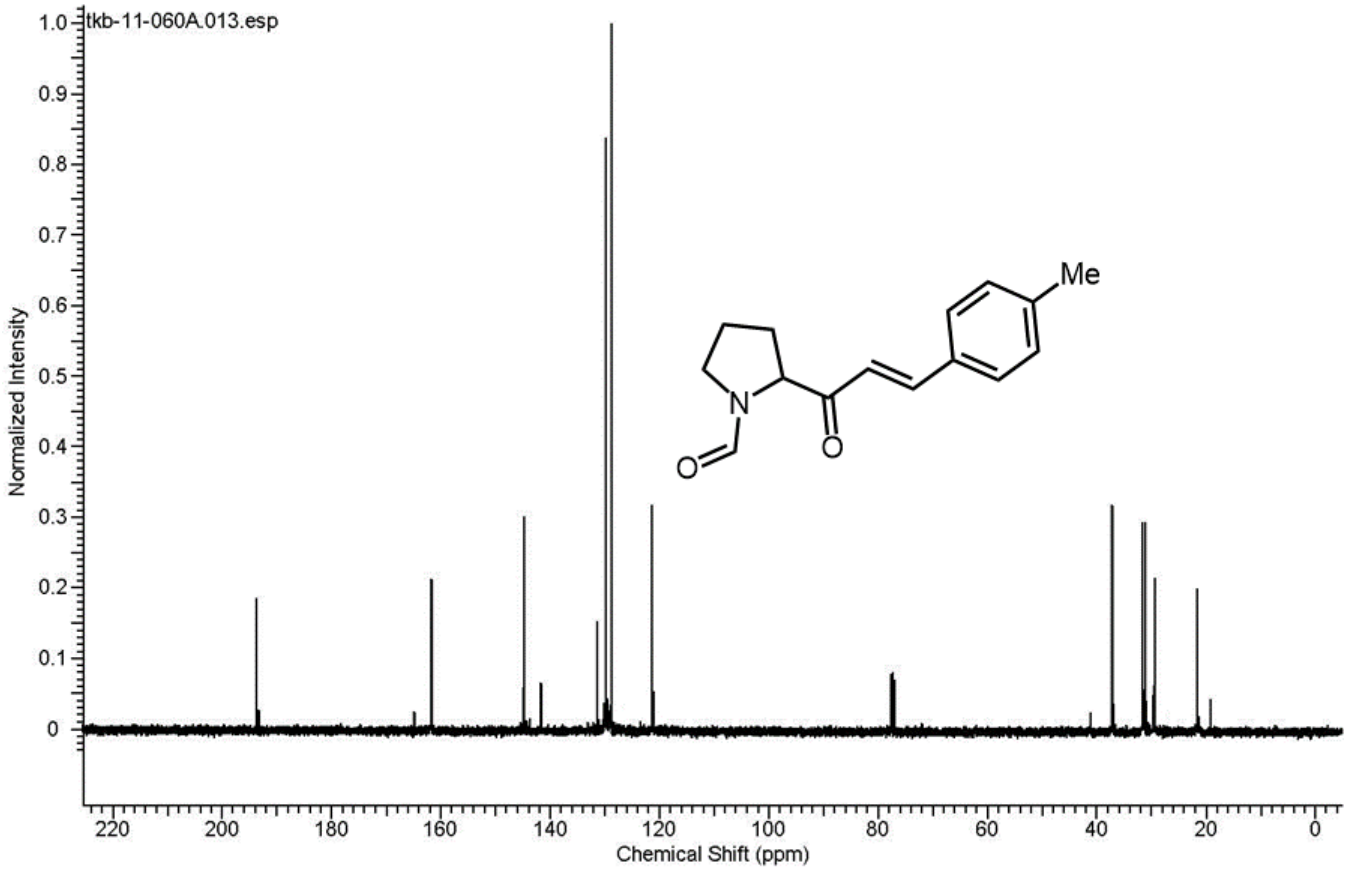
Compound 4x

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Pale-yellow oil. Yield = 194.6 mg, 80%. ^{1}H NMR (400

MHz, Chloroform-*d*) δ 8.16 (s, 1H), 7.71 (d, *J* = 15.8 Hz, 1H), 7.47 (d, *J* = 6.8 Hz, 2H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.86 (d, *J* = 15.8 Hz, 1H), 4.60 (t, *J* = 7.3 Hz, 1H), 3.33 – 3.30 (m, 2H), 2.38 (s, 3H), 2.11 – 2.04 (m, 2H), 1.74 – 1.69 (m, 1H), 1.61 – 1.56 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 193.7, 164.9, 161.8, 161.6, 144.7, 141.7, 131.4, 129.8, 128.8, 121.3, 37.2, 37.1, 31.6, 31.2, 29.4, 21.7, 19.3. HRMS calc for $C_{15}H_{17}NO_2$ 243.1259, found 243.1255.

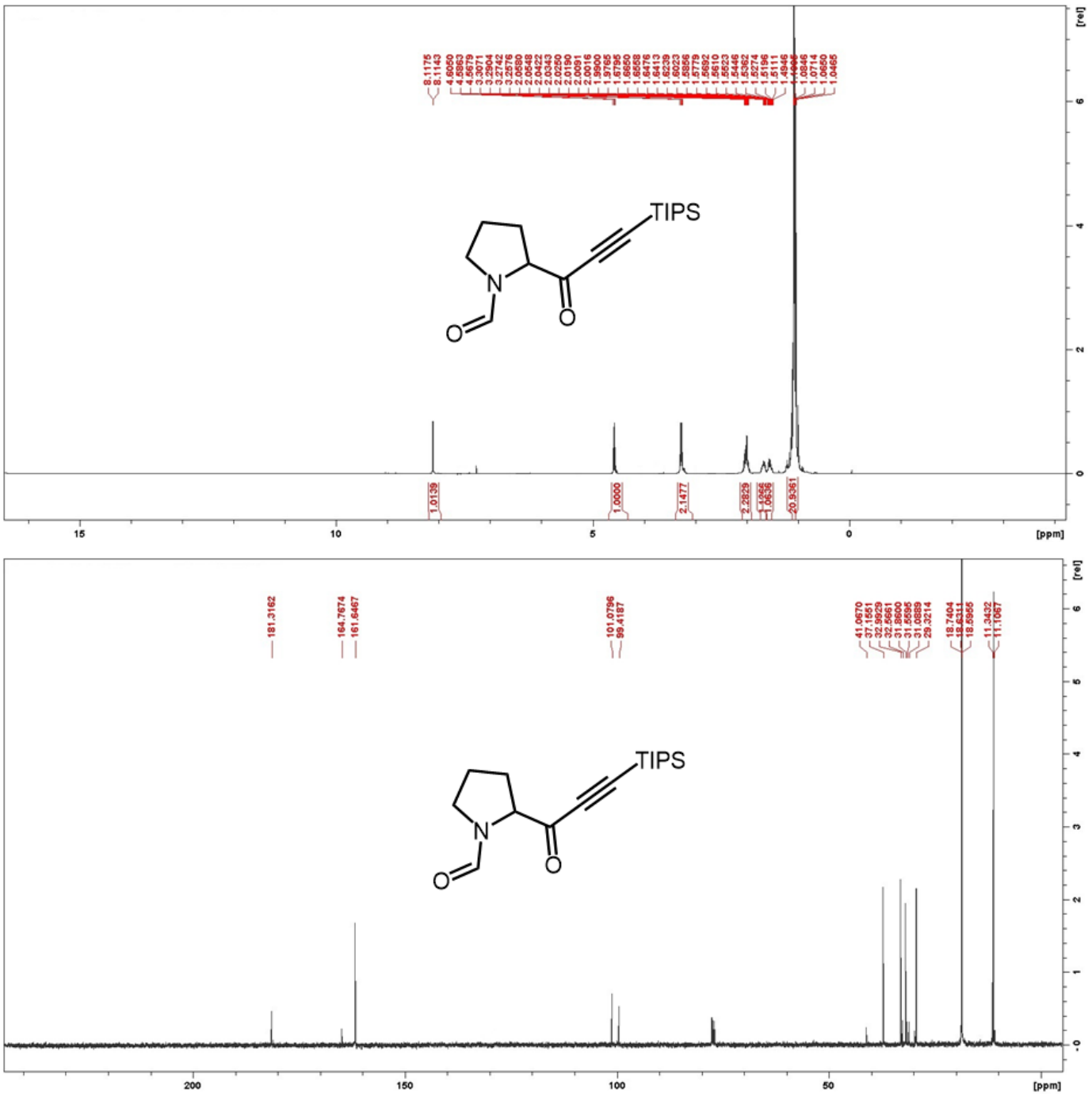
Note: Using **General Procedure B**, formamide **4x** was obtained in 65% yield.





Compound 4y

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (80:20). Pale-yellow oil. Yield = 255.2 mg, 83%. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 8.11 (s, 1H), 4.57 (t, *J* = 7.8 Hz, 1H), 3.31 – 3.26 (m, 2H), 2.06 – 1.97 (m, 2H), 1.68 – 1.59 (m, 1H), 1.56 – 1.49 (m, 1H), 1.10 – 1.04 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 181.3, 164.8, 161.6, 101.1, 99.4, 41.1, 37.2, 33.0, 32.6, 31.9, 29.3, 18.7, 18.6, 18.5, 11.3, 11.1. HRMS calc for $C_{17}H_{29}NO_2Si$ 307.1968, found 307.1972.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TIPS
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164.7674
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18.5945
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11.1067
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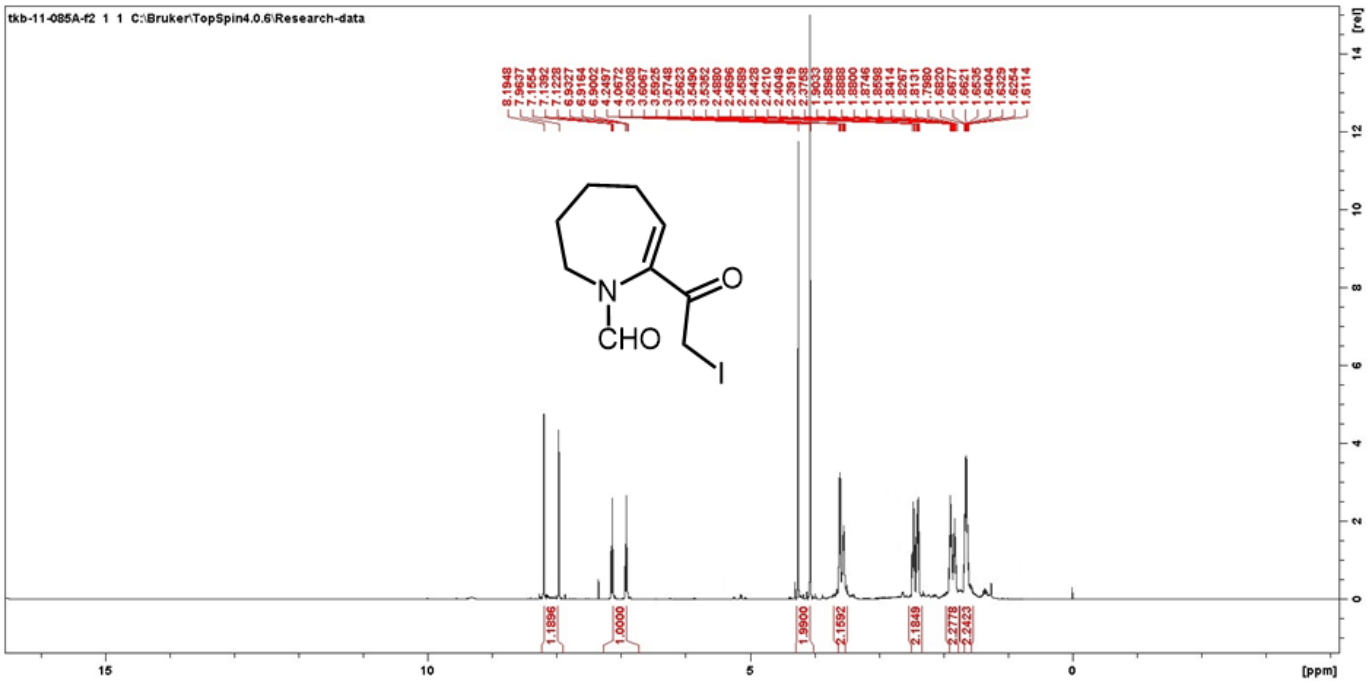
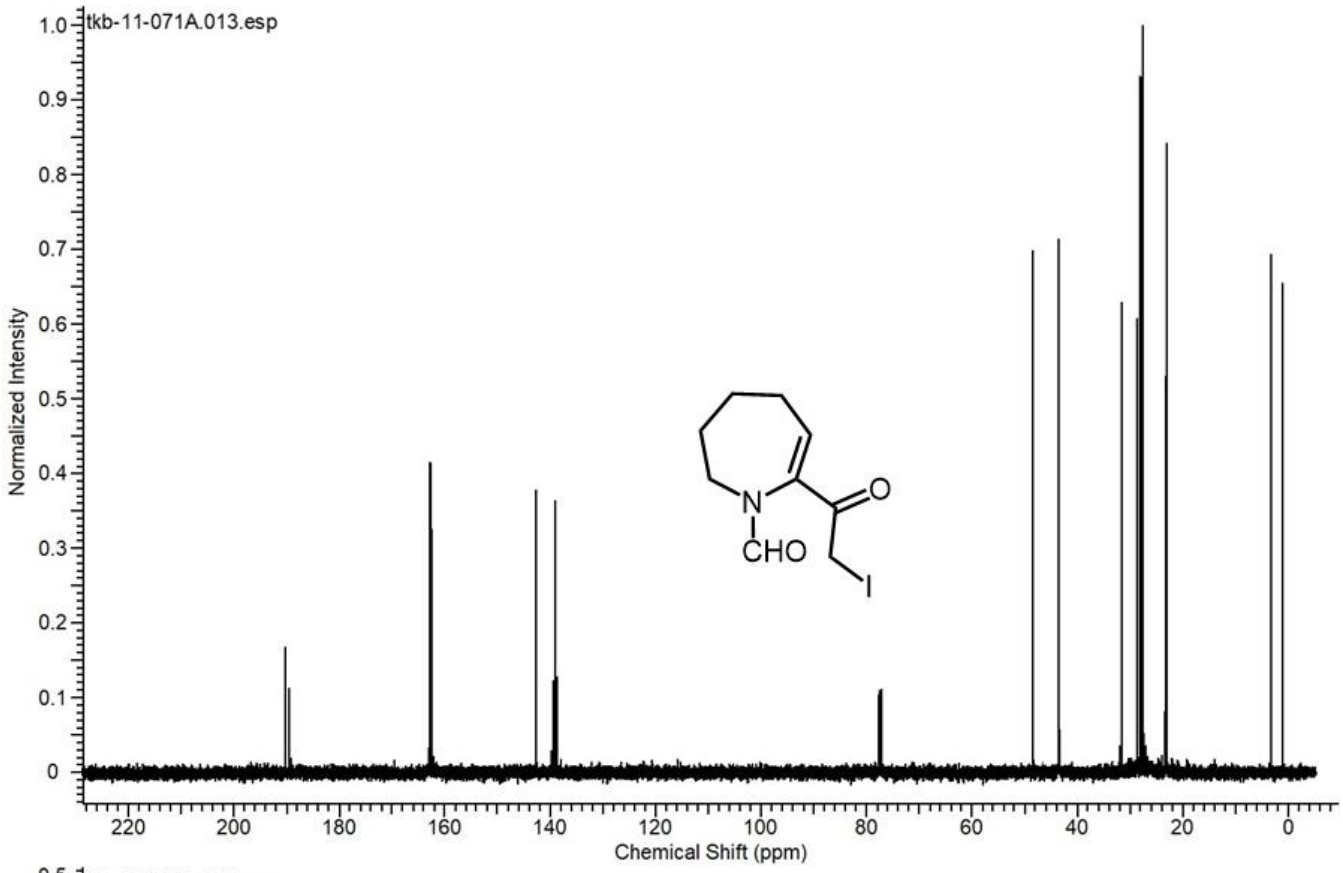
[ppm]
200
150
100
50

Compound 9

Prepared in 1 mmol scale using **General Procedure A** but without subsequent addition of the base. Yield = 281 mg, 96%. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 7.96 (s, 0.5H), 7.94 (s, 1H), 6.91 (t, *J* = 6.5 Hz, 0.5H), 6.69 (t, *J* = 6.5 Hz, 0.5H), 4.02 (s, 1H), 3.92 (s, 1H), 3.52 – 3.22 (m, 2H), 2.44 – 2.32 (m, 2H), 1.75 – 1.60 (m, 2H), 1.45 – 1.28 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 190.2, 189.6, 162.8, 162.5, 142.7, 139.4, 139.0, 138.6, 48.4, 43.5, 31.6, 28.6, 28.0, 27.6, 23.2, 23.0, 3.2, 1.1. HRMS calc for $C_9H_{12}INO_2$ 292.9913, found 292.9916.

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Chemical Shift (ppm)
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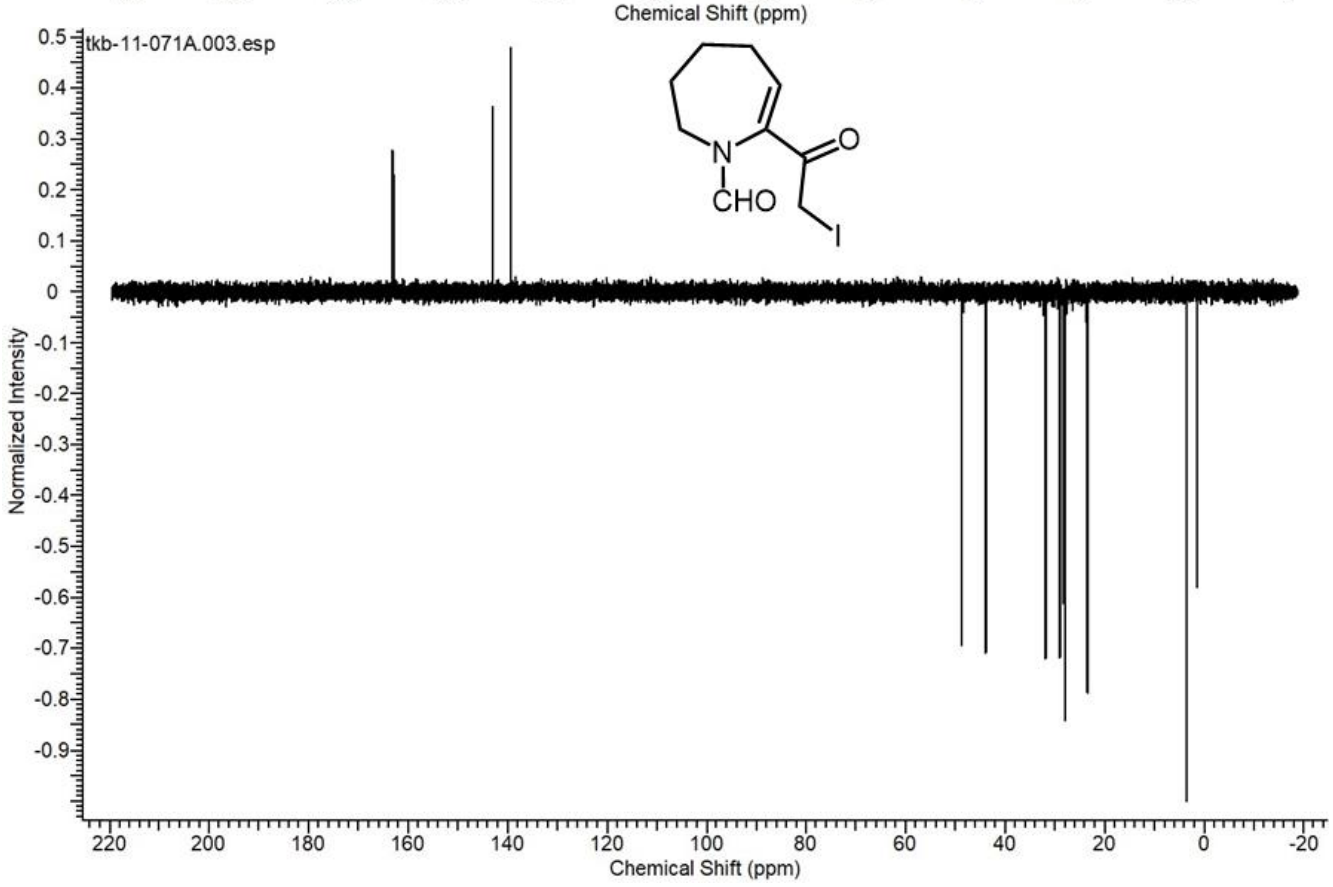
CHO
O
I


tkb-11-071A.003.esp
Normalized Intensity
Chemical Shift (ppm)
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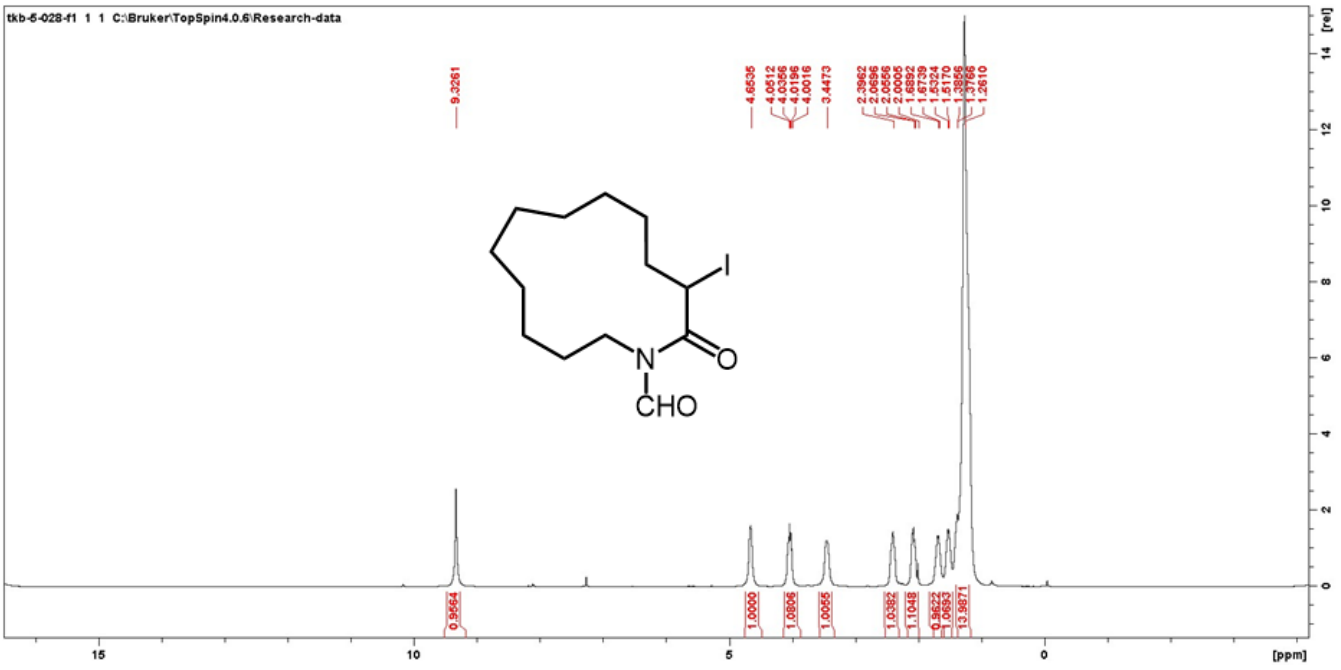
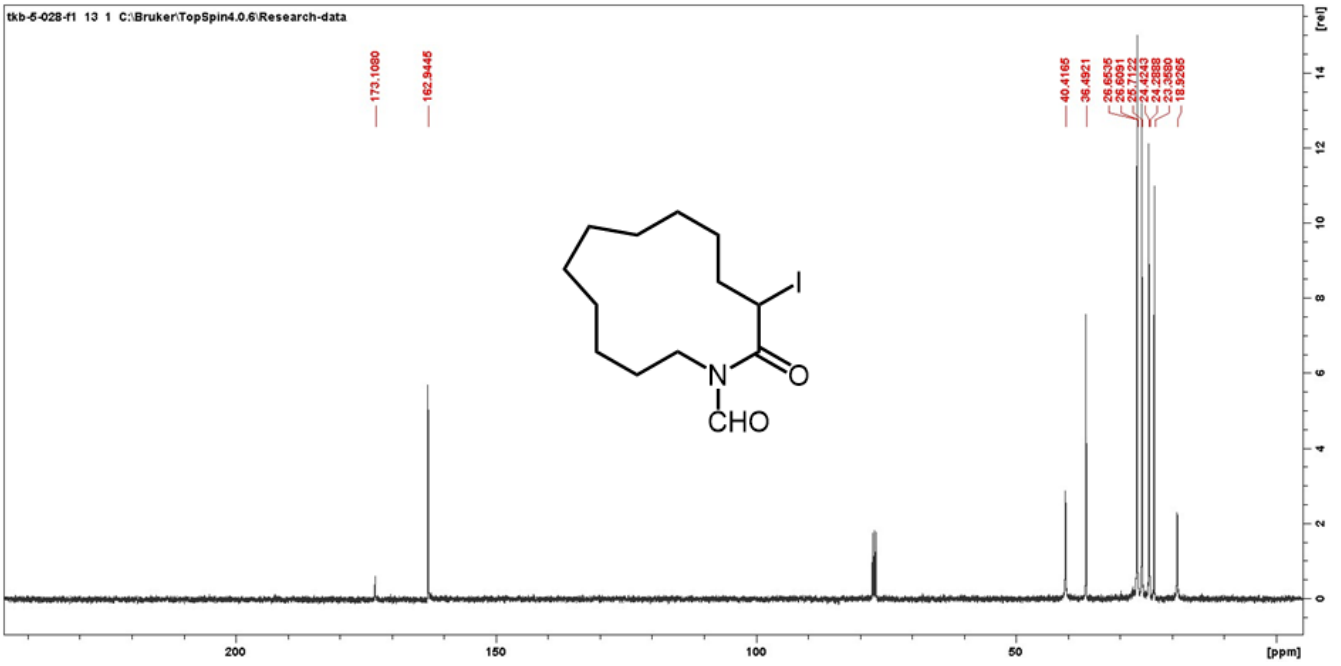
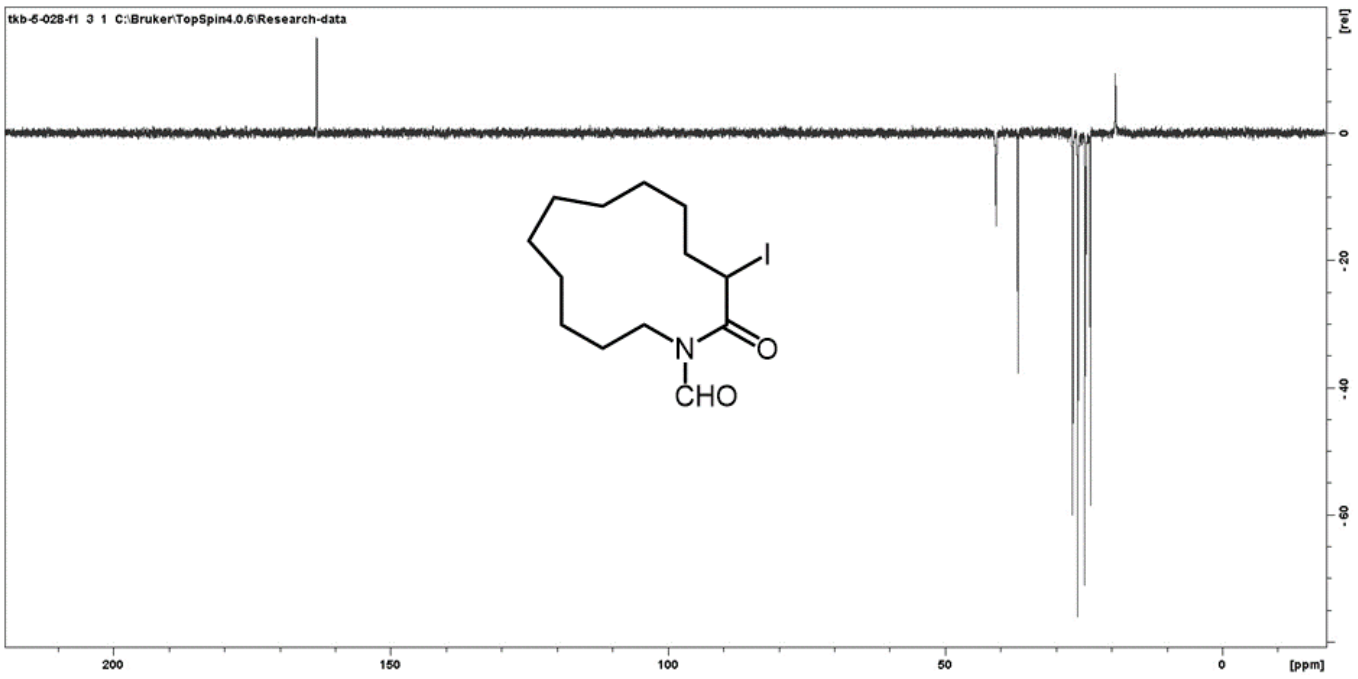
CHO
O
I

Compound 11a

Prepared in 1 mmol scale using **General Procedure A** but without subsequent addition of the base. Yield = 302.0 mg, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 4.70 – 4.62 (m, 1H), 4.04 (dt, *J* = 14.2, 6.7 Hz, 1H), 3.45 (dd, *J* = 14.9, 7.5 Hz, 1H), 2.41 (dt, *J* = 14.0, 7.6 Hz, 1H), 2.13 – 2.01 (m, 1H), 1.69 – 1.26 (m, 16H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 162.9, 40.4, 36.5, 26.7, 26.6, 25.8, 25.7, 24.4, 24.3, 23.4, 18.9. HRMS calc for $C_{13}H_{22}INO_2$ 351.0695, found 351.0692.





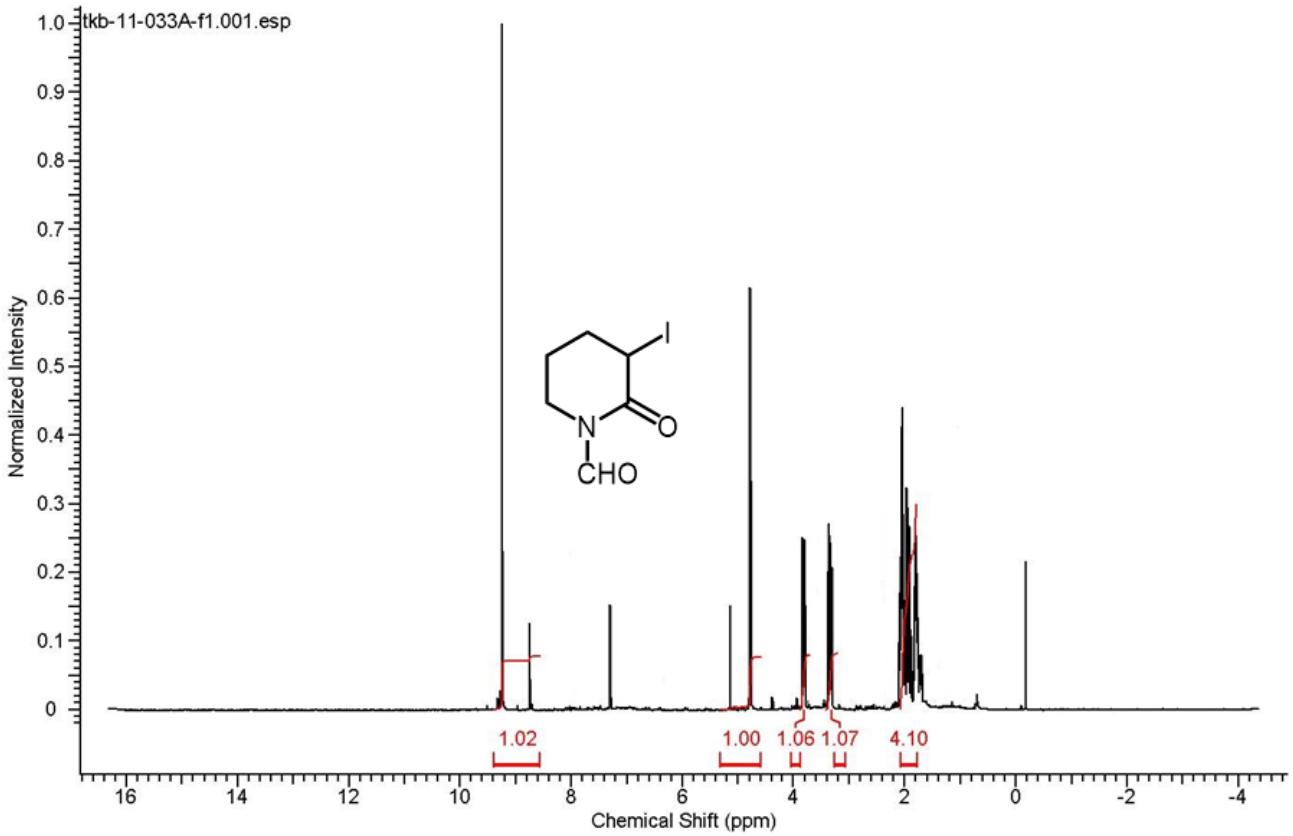


Compound 11b

Prepared in 1 mmol scale using **General Procedure A** but without subsequent addition of the base. Yield = 240.3 mg, 90%. Data as previously reported.[3]

Compound 11c

Prepared in 1 mmol scale using **General Procedure A** but without subsequent addition of the base. Yield = 225.2 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 9.24 + 8.82 (s, 1H), 5.17 + 4.78 (dd, *J* = 5.0, 3.5 Hz, 1H), 3.82 (dd, *J* = 13.4, 5.5 Hz, 2H), 3.35 (dd, *J* = 13.5, 5.1 Hz, 2H), 2.04 – 1.91 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 171.0, 163.2, 161.3, 41.6, 39.1, 32.1, 31.5, 22.8, 21.4, 19.7. HRMS calc for $C_6H_8INO_2$ 252.9600, found 252.9602.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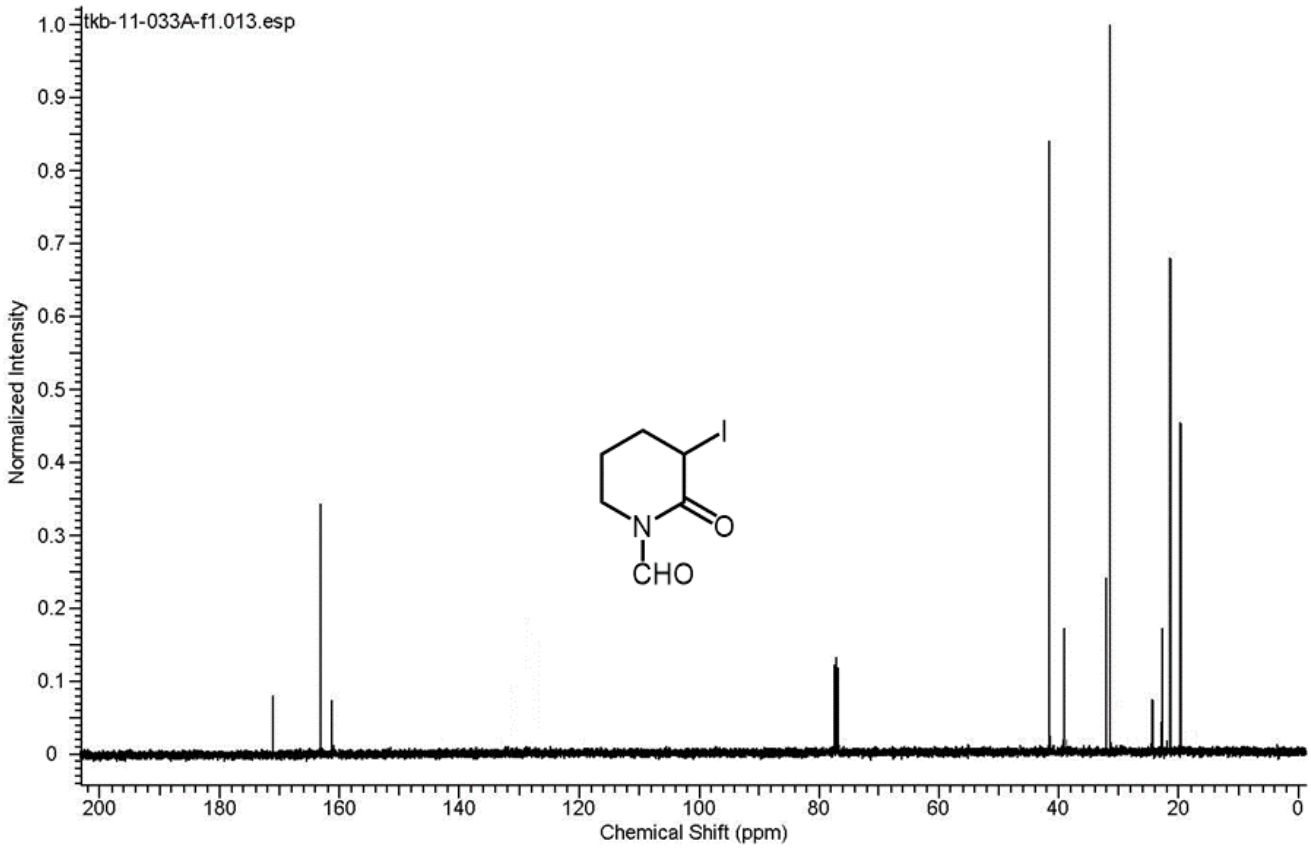
CHO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Normalized Intensity
Chemical Shift (ppm)
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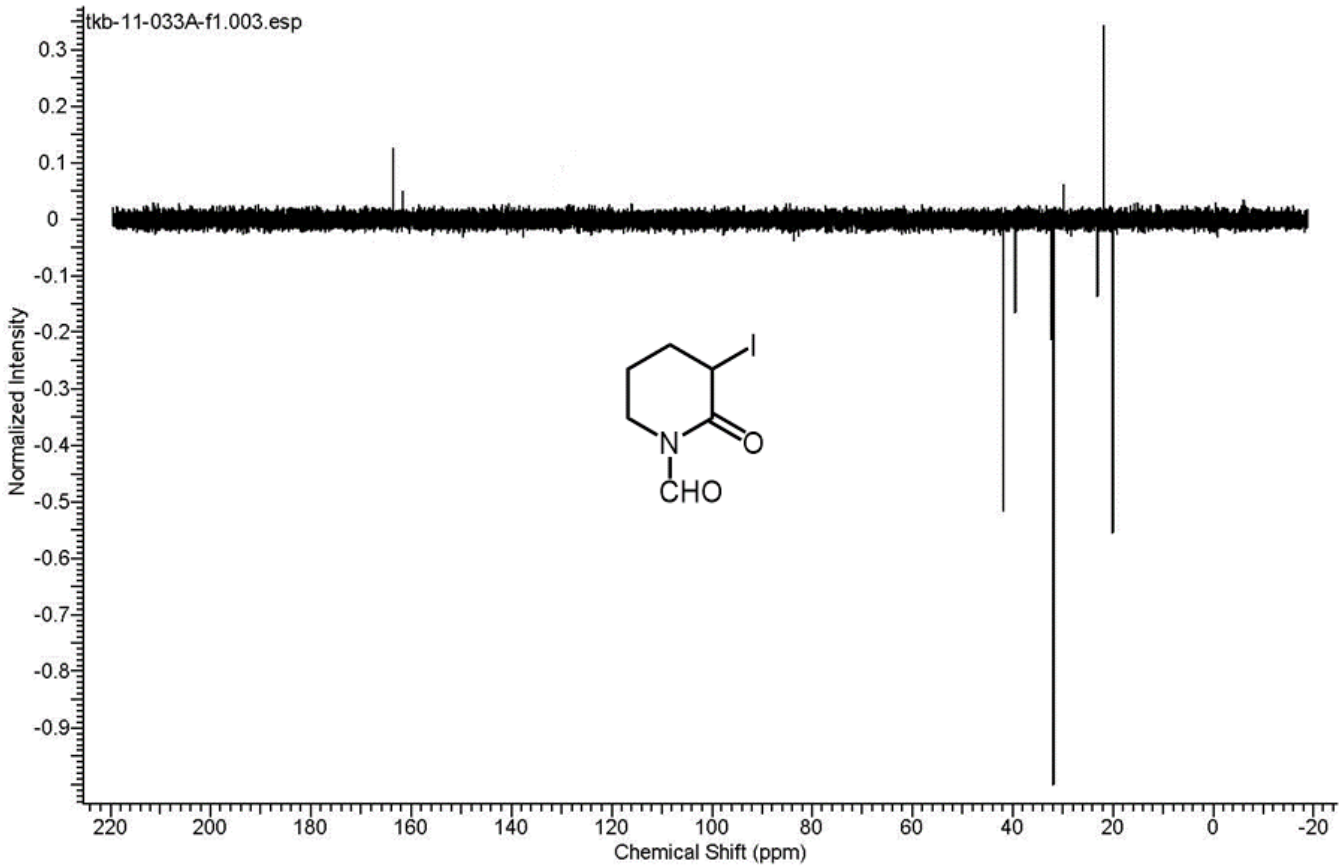
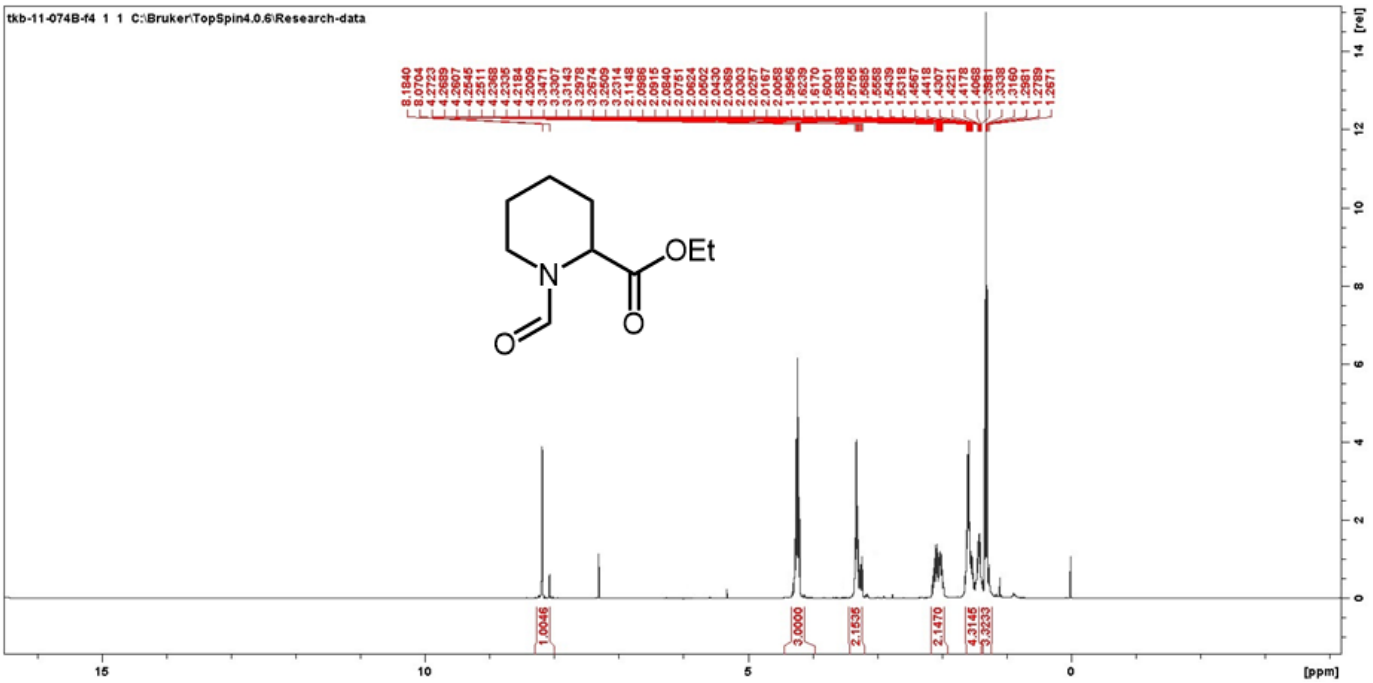
O
CHO



Compound 13a

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Pale-yellow oil. Yield = 161.1 mg, 87%. ^{1}H NMR (400 MHz, Chloroform-*d, mixture of rotamers*) δ 8.18 (s, 1H), 4.27 – 4.20 (m, 3H), 3.34 – 3.23 (m, 2H), 2.11 – 1.99 (m, 2H), 1.62 – 1.39 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 169.8, 164.7, 161.4, 62.2, 62.1, 45.9, 45.6, 41.4, 37.8, 34.4, 34.3, 30.6, 28.8, 24.6, 24.2, 14.0, 8.2. HRMS calc for $C_9H_{15}NO_3$ 185.1052, found 185.1055.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[ppm]
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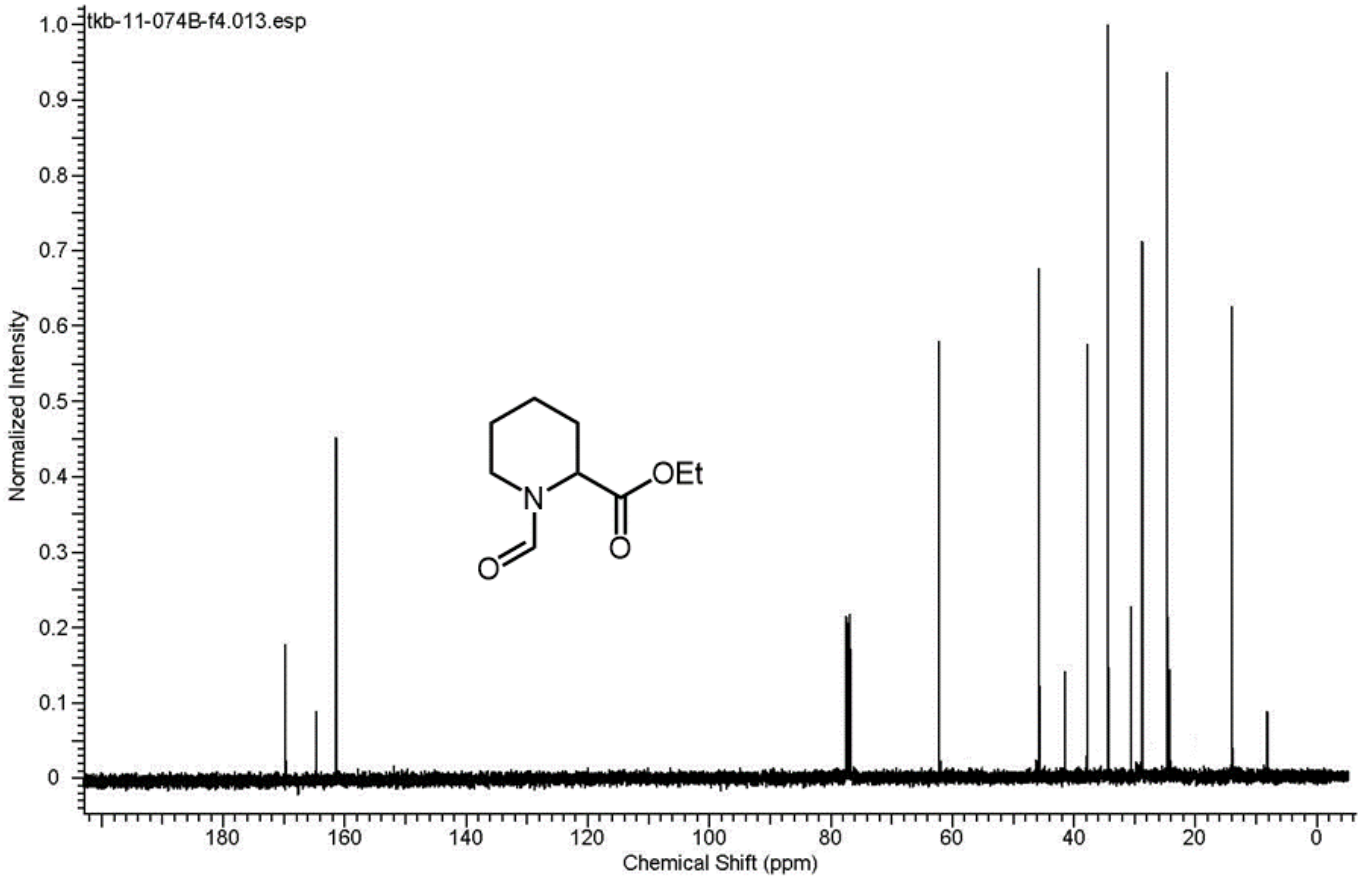
3.3233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Normalized Intensity
Chemical Shift (ppm)
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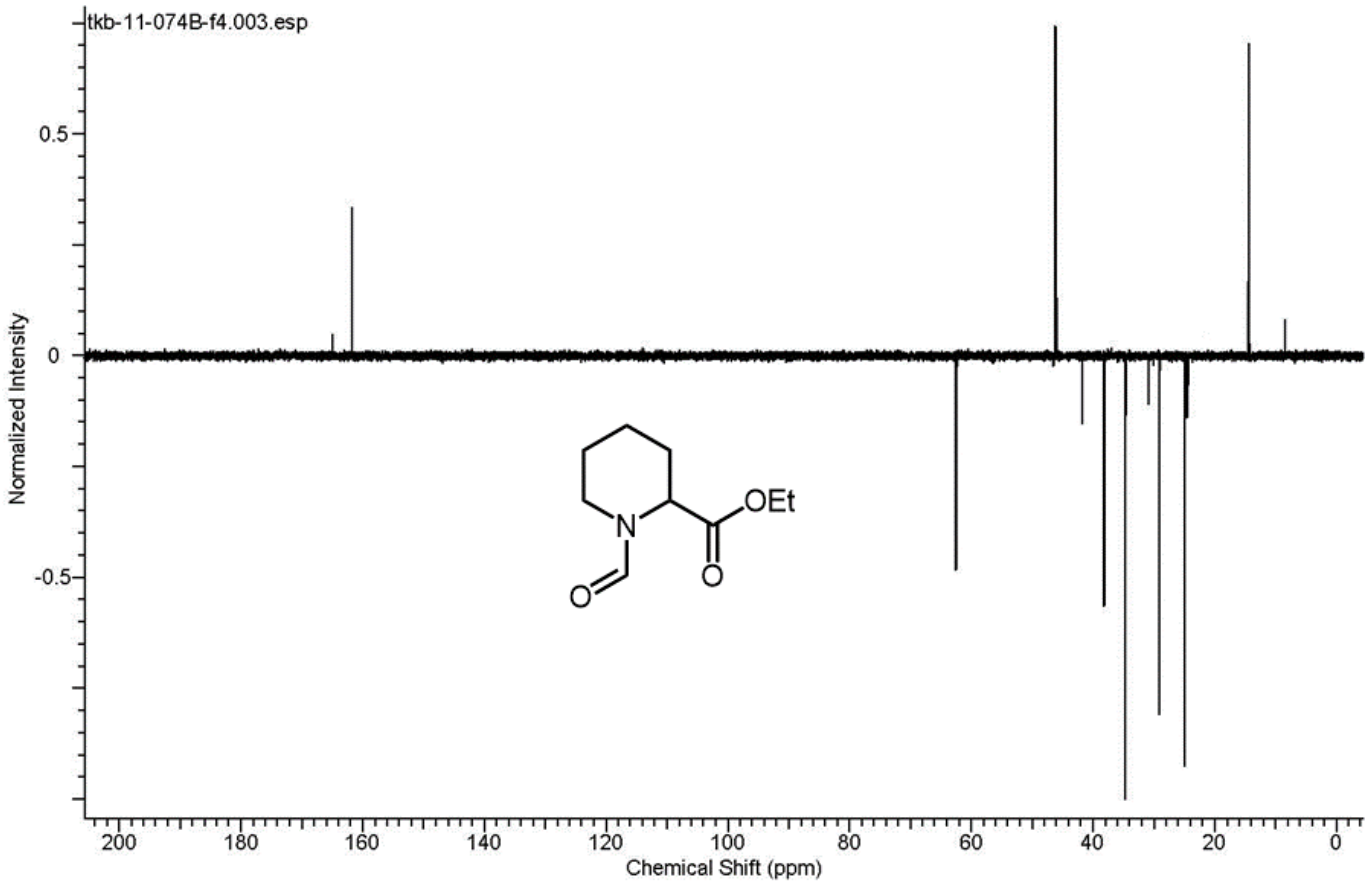
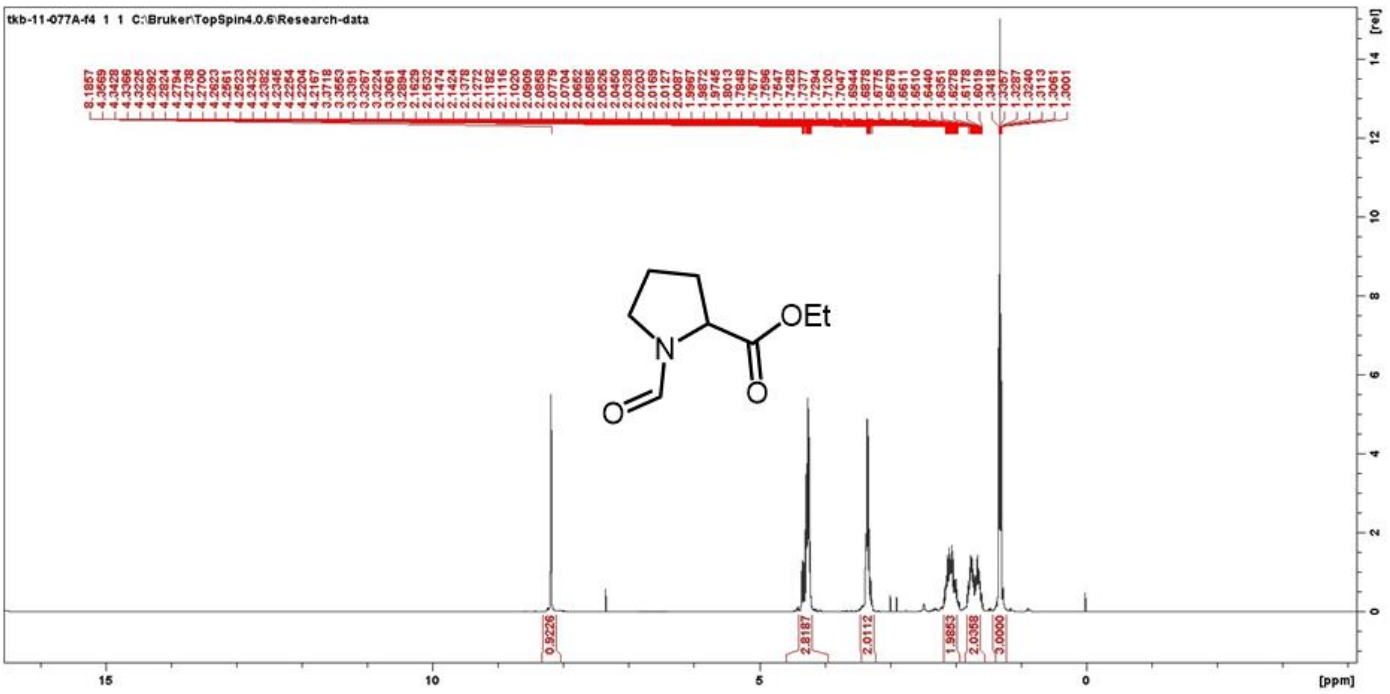
N
O
O



Compound 13b

Prepared in 1 mmol scale using **General Procedure A.** Purification: Flash chromatography on silica eluting with hexane/EtOAc (50:50). Pale-yellow oil. Yield = 143.8 mg, 84%. ^{1}H NMR (400 MHz, Chloroform-*d, rotamers*) δ 7.95 (s, 1H), 4.35 – 4.21 (m, 3H), 3.37 – 3.29 (m, 2H), 2.16 – 1.97 (m, 2H), 1.80 – 1.60 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 169.8, 169.6, 164.8, 161.7, 62.3, 62.2, 57.0, 45.5, 41.1, 37.2, 37.2, 32.1, 32.0, 29.0, 27.3, 27.2, 26.1, 14.1, 14.0. HRMS calc for $C_8H_{13}NO_3$ 171.0895, found 171.0891.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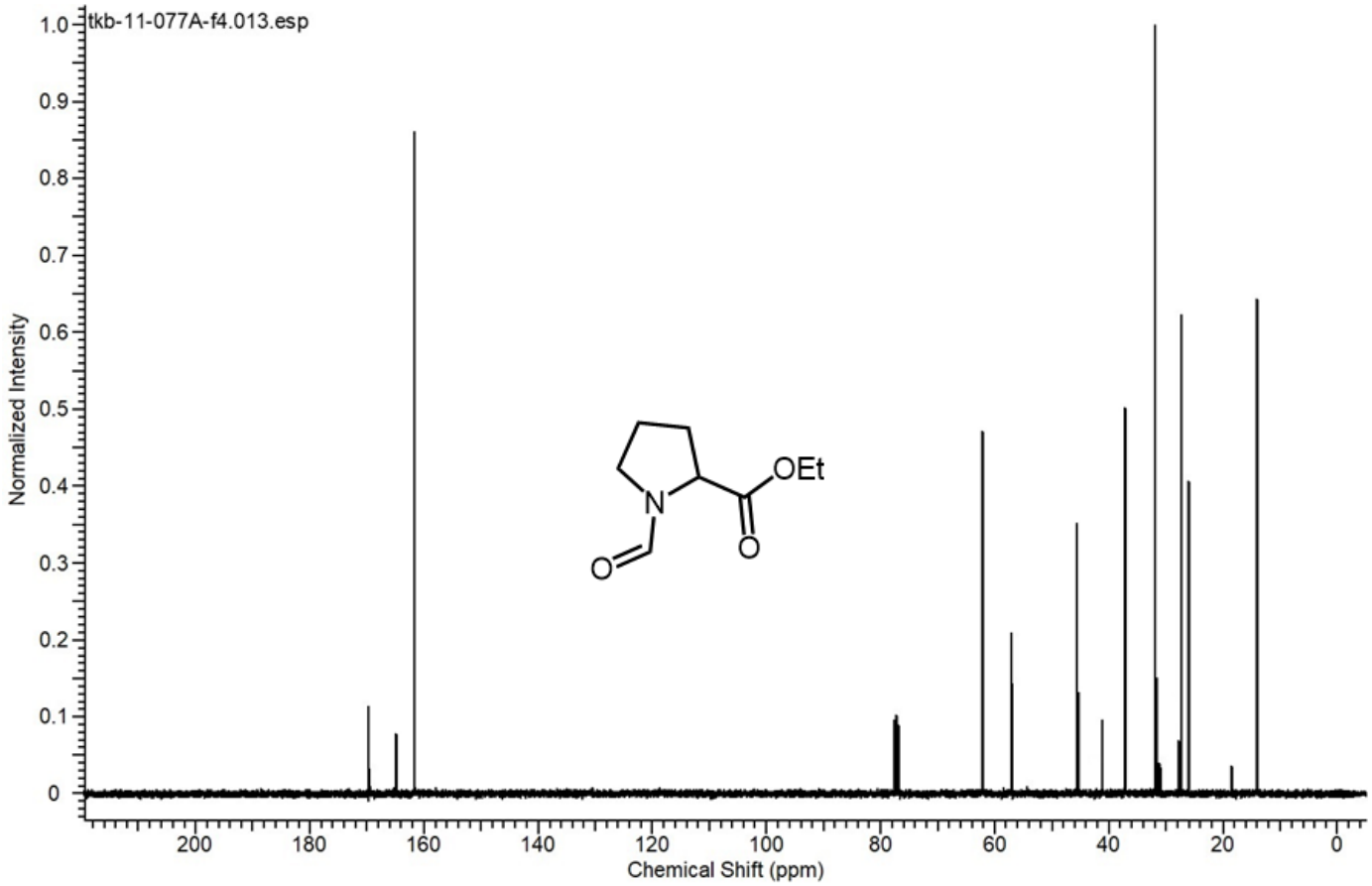
tkb-11-077A-f4.013.esp
Normalized Intensity
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0.5
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O
O
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140
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100
80
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40
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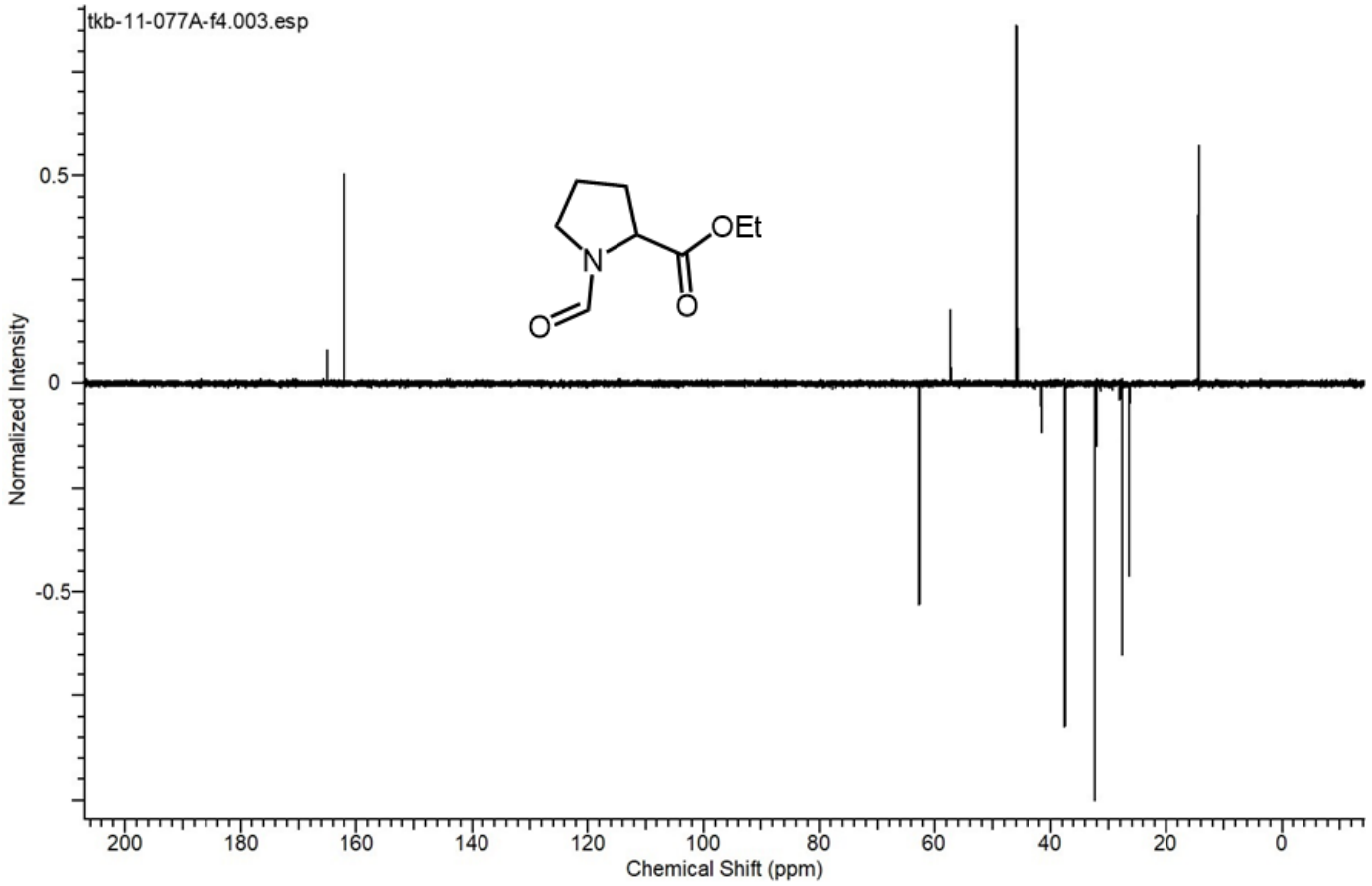
Chemical Shift (ppm)



References

1. Beng, T. K.; Langevin, S.; Braunstein, H.; Khim, M., Regiocontrolled synthesis of (hetero)aryl and alkenyl dehydropyrrolidines, dehydropiperidines and azepenes by Ru-catalyzed, heteroatom-directed α-C-H activation/cross-coupling of cyclic enamides with boronic acids. *Org. Biomol. Chem.* **2016,** *14* (3), 830-834.

2. Bassler, D. P.; Alwali, A.; Spence, L.; Beale, O.; Beng, T. K., Cobalt-catalyzed arylation and alkenylation of alpha-bromo eneformamides and enecarbamates by cross-coupling with organic bromides: Application to the synthesis of functionalized piperidines and azepanes. *J. Organomet. Chem.* **2015,** *780*, 6-12.

3. Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R., Direct Access to Functionalized Azepanes by Cross-Coupling with α-Halo Eneformamides. *Org. Lett.* **2014,** *16* (3), 916-919.