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Telescoped diazo transfer and rhodium-catalysed S–H insertion in continuous flow

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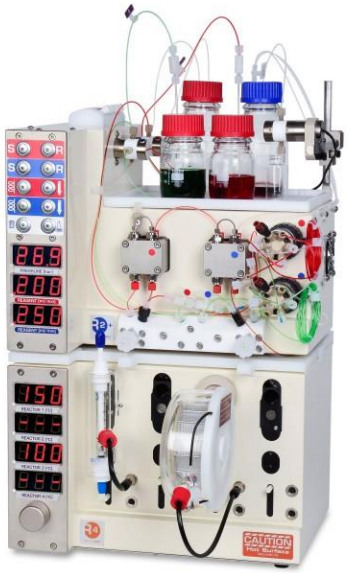
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1. Details of Continuous Flow Platforms

Continuous processes were performed using flow chemistry platforms, as previously described,[1] consisting of a Vapourtec R-Series flow system consisting of four piston (HPLC) pumps and a Vapourtec E-Series flow system consisting of three peristaltic pumps. Where peristaltic pumps were used, the Vapourtec 'red' peristaltic tubing was used for aqueous solutions or toluene solutions and the Vapourtec 'blue' peristaltic tubing was used for dichloromethane or toluene solutions.

Table S1. General specifications for Vapourtec R-Series system



General specifications for continuous-flow system	
Material of tubing	PFA
Diameter of tubing	1 mm
Working flow rates	0.05 mL/min – 9.99 mL/min
Tubular reactor working volume	10 mL
Temperature range	–70 °C to 250 °C

Table S2. General specifications for Vapourtec E-Series system



General specifications for continuous-flow system	
Material of tubing	PFA
Diameter of tubing	1 mm
Working flow rates	0.02 mL/min – 10.0 mL/min
Tubular reactor working volume	10 mL
Temperature range	–70 °C to 250 °C

2. Experimental

2.1 General Procedures

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorous pentoxide, ethyl acetate was distilled from potassium carbonate, and hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification. Activated pyrrolidinones **1** and **5** were prepared according to a literature method.[2]

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at either 300 K (27 °C) or room temperature (*ca.* 20 °C) in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), or m (multiplet). ^{13}C NMR signals were assigned with the aid of DEPT experiments and are identified by the carbon type (CH_3, CH_2, CH or C). Assignment of ^{1}H NMR and ^{13}C NMR signals was aided using 2D NMR experiments (including ^{1}H–^{1}H COSY, HSQC and HMBC).

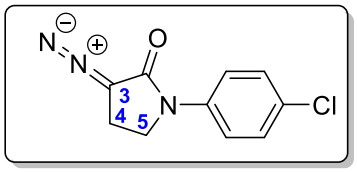
Infrared spectra were measured using universal ATR sampling accessories on a Perkin Elmer Spectrum Two spectrometer. Flash chromatography was performed using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254 nm) light detection.

Nominal mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionisation (ESI) mode using 50% water/acetonitrile containing 0.1% formic acid as eluent, or on an Agilent 6530B Accurate Mass Q-TOF LC/MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were also recorded on a Waters Vion IMSinstrument (SAA055 K) with Waters Acquity I-class UPLC inelectrospray ionization (ESI) mode using 50% acetonitrile−water containing 0.1% formic acid as eluent and Leucine Enkephalin as reference solution. All samples were made up in acetonitrile.

Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

2.2 Synthesis of α-diazolactams 3 and 4 in batch

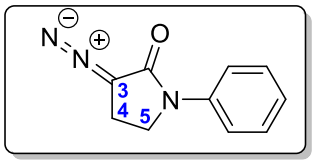
1-(4-Chlorophenyl)-3-diazopyrrolidin-2-one 3[2]



A solution of trifluoromethanesulfonyl azide **2** [prepared from trifluoromethanesulfonic anhydride (1.02 g, 0.6 mL, 3.6 mmol)] in toluene (15 mL) was added dropwise to a stirring solution of ethyl-2-[1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene]-2-hydroxyacetate **1** (0.89 g, 3 mmol, eq) and 1,8-diazabicyclo[5.4.0]unec-7-ene (0.5 g, 0.49 mL, 3 mmol, 1 eq) in dichloromethane (15 mL) at room temperature under nitrogen. The solution was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the resulting residue was applied directly to a plug column of silica gel (neutralised with 1% by weight triethylamine) using hexane:chloroform:ethanol (50:49:1) as eluent to give the pure α-diazolactam **3** (0.44 g, 66%) as a bright orange crystalline solid, 131–135 °C. υ_{max}/cm^{-1} (neat) 2089 (C=N_2), 1664 (C=O); δ_H (400 MHz, $CDCl_3$): 3.22 [2H, dd appears as t, *J* 8.2, 7.2, C(4)H_2 or C(5)H_2], 3.80 [2H, dd appears as t, *J* 7.6, 7.0, C(4)H_2 or C(5)H_2], 7.29 [2H, d, *J* 9.0, aromatic *H*], 7.53 [2H, d, *J* 9.0, aromatic *H*]; δ_c (100.6 MHz, $CDCl_3$): 17.9 [2H, *C*(4)H_2 or *C*(5)H_2], 44.8 [2H, *C*(4)H_2 or *C*(5)H_2], 54.0 [C, *C*(3)], 119.9 (CH, aromatic *C*H), 128.7 [C, *C*(1′) or *C*(4′)], 128.8 (CH, aromatic *C*H), 138.6 [C, *C*(1′) or *C*(4′)], 166.9 (C, *C*O); HRMS(ES+): Exact mass calculated for $C_{10}H_8{}^{35}ClN_3O$ $[M+Na]^+$ 244.0248. Found 244.0218. $^{35}Cl/^{37}Cl$ pattern visible at 224.0246 and 246.0218 in a 3:1 ratio.

Spectroscopic characteristics were consistent with those previously reported.[1,2]

3-Diazo-1-phenylpyrrolidin-2-one 4[2]



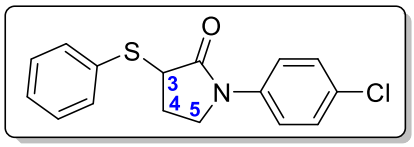
Trifluoromethanesulfonyl azide **2** [prepared from trifluoromethanesulfonic anhydride (0.39 g, 0.23 mL, 1.4 mmol)], in toluene (15 mL) was added dropwise to a stirring solution of ethyl-2-hydroxy-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate **5** (0.30 g, 1.2 mmol, 1 eq) and 1,8-diazabicyclo[5.4.0]unec-7-ene (0.18 g, 0.17 mL, 1.2 mmol, 1 eq) in dichloromethane (15 mL) at room temperature under nitrogen. The solution was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the resulting residue was applied directly to a plug column of silica gel (neutralised with 1% by weight triethylamine) using hexane:chloroform:ethanol (50:49:1) as eluent to give the pure α-diazolactam **4** (0.20 g, 90%) which was isolated as a bright orange crystalline solid (material degraded during mp determination). υ_{max}/cm^{-1} (neat) 2064 (C=N_2), 1661 (C=O); δ_H (400 MHz, $CDCl_3$): 3.21 [2H, dd appears as t, *J* 7.8, 7.4, C(4)H_2 or C(5)H_2], 3.85 [2H, dd appears as t, *J* 7.9, 7.4, C(4)H_2 or C(5)H_2], 7.10 [1H, t, *J* 7.4, aromatic *H*], 7.35 [2H, dd appears as t, *J* 7.9, 7.5,

aromatic *H*], 7.55 – 7.63 [2H, m, aromatic *H*]; δ_c (100.6 MHz, $CDCl_3$): 18.0 [CH_2, *C*(4)H_2 or *C*(5)H_2], 44.9 [CH_2, *C*(4)H_2 or *C*(5)H_2], 54.0 [C, *C*(3)], 118.9, 123.8, 128.9 (3 x CH, aromatic *C*H), 140.0 [C, *C*(1')], 166.9 (C, *C*O); HRMS (ES+): Exact mass calculated for $C_{10}H_9N_3O$ $[M+Na]^+$ 210.0638. Found 210.0637.

Spectroscopic characteristics were consistent with those previously reported.[2]

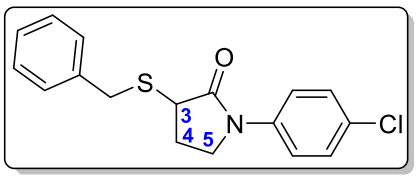
2.3 Synthesis of α-thiolactams 6–15 in batch

1-(4-Chlorophenyl)-3-(phenylthio)pyrrolidine-2-one 6



Rhodium acetate (0.007 g, 0.014 mmol, 1 mol%) was added to a vigorously stirring solution of 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (0.30 g, 1.4 mmol, 1 eq) and thiophenol (0.17 g, 0.16 mL, 1.6 mmol, 1.1 eq) in dichloromethane:toluene (50:50, 15 mL). The reaction mixture was stirred at room temperature for 20 min. The solvent was then removed under reduced pressure and the resulting residue was applied directly to a column of silica gel using chloroform:ethanol (99:1) as eluent to give the α-thiolactam **6** (0.33 g, 87%) as a white solid, mp 97–98 °C. υ_{max}/cm^{-1} (neat) 1682 (C=O); δ_H (300 MHz, $CDCl_3$): 2.12 – 2.25 [1H, m, one of C(4)H_2 or C(5)H_2], 2.52 – 2.68 [1H, m, one of C(4)H_2 or C(5)H_2], 3.50 – 3.60 [1H, m, one of C(4)H_2 or C(5)H_2], 3.62 – 3.71 [1H, m, one of C(4)H_2 or C(5)H_2], 3.97 [1H, dd, *J* 8.7, 5.8, C(3)*H*], 7.27 – 7.33 [5H, m, aromatic *H*], 7.49 – 7.59 [4H, m, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 26.2 [CH_2, *C*(4)H_2 or *C*(5)H_2], 46.5 [CH_2, *C*(4)H_2 or *C*(5)H_2], 49.2 [CH, *C*(3)H], 121.0, 128.3, 128.9, 129.1 (4 x CH, aromatic *C*H), 130.0, 132.6 (C, aromatic *C*), 133.4 (CH, aromatic *C*H), 137.7 (C, aromatic *C*), 171.5 (C, *C*O); m/z (ES-) 302.2 [$C_{16}H_{14}{}^{35}ClNOS$-H^+], 100%. $^{35}Cl/^{37}Cl$ pattern visible at 302.2 and 304.3 in a 3:1 ratio. HRMS (ES+): Exact mass calculated for $C_{16}H_{14}{}^{35}ClNOS$ $[M+H^+]$ 304.0557. Found 304.0550.

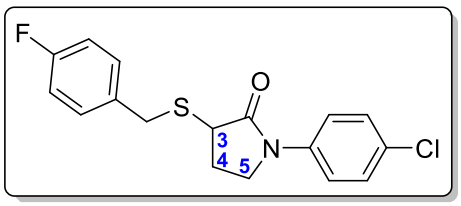
3-(Benzylthio)-1-(4-chlorophenyl)pyrrolidine-2-one 7



Compound **7** was prepared following the method described above for **6** using 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (0.42 g, 1.9 mmol, 1 eq), benzyl mercaptan (0.26 g, 0.24 mL, 2.1 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.009 g, 0.019 mmol, 1 mol%) in dichloromethane (20 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as brown solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **7** (0.52 g, 87%) as a white solid, mp 101–102°C; υ_{max}/cm^{-1} (neat) 1675 (C=O); δ_H (300 MHz, $CDCl_3$): 1.88 – 2.02 [1H, m, one of C(4)H_2 or C(5)H_2], 2.37 -2.52 [1H, m, one of C(4)H_2 or C(5)H_2], 3.46 [1H, dd, *J* 8.6, 4.8, C(3)*H*], 3.65 - 3.75 [1H, m, one of C(4)H_2 or C(5)H_2], 3.80 - 3.91 [2H, m, containing (1H, A of AB system, one of SCH_2) and (1H, m,

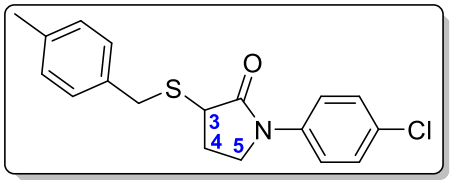
one of C(4)H_2 or C(5)H_2)], 4.21 [1H, B of AB system, J_{AB} 13.4, one of SCH_2], 7.21 – 7.37 [5H, m, aromatic *H*], 7.39 – 7.46 [2H, m, aromatic *H*], 7.58 [2H, d, *J* 9.0, aromatic *H*] ; δ_c (75.5 MHz, $CDCl_3$): 25.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 35.3 (CH_2, S*C*H_2), 42.6 [CH, *C*(3)*H*], 46.7 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 121.1, 127.2, 128.5, 128.9, 129.3 (5 x CH, aromatic *C*H), 129.9, 137.7, 137.9 (3 x C, aromatic *C*), 172.5 (C, *C*O); m/z (ES-) 318.2 [$C_{17}H_{16}{}^{35}ClNOS$-H^+], 34%. $^{35}Cl/^{37}Cl$ pattern visible at 318.2 and 320.3 in a 3:1 ratio. HRMS (ES+): Exact mass calculated for $C_{17}H_{16}{}^{35}ClNOS$ [M+H^+] 318.0714. Found 318.0714.

1-(4-Chlorophenyl)-3-[(4-fluorobenzyl)thio]pyrrolidine-2-one 8



Compound **8** was prepared following the method described above for **6** using 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (0.21 g, 0.9 mmol, 1 eq), 4-fluorobenzyl mercaptan (0.14 g, 0.12 mL, 0.99 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.004 g, 0.009 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as purple oily solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **8** (0.25 g, 81.5%) as a white solid, mp 113–115°C; υ_{max}/cm^{-1} (neat) 1691 (C=O); δ_H (300 MHz, $CDCl_3$): 1.87 – 2.03 [1H, m, one of C(4)H_2 or C(5)H_2], 2.38 – 2.56 [1H, m, one of C(4)H_2 or C(5)H_2], 3.43 [1H, dd, *J* 8.7, 4.6, C(3)*H*], 3.78 - 3.93 [2H, m, containing (3.82, 1H, A of AB system, J_{AB} 13.8, one of SCH_2) and (1H, m, one of C(4)H_2 or C(5)H_2)], 4.20 [1H, B of AB system, J_{AB} 13.8, one of SCH_2], 7.00 [2H, dd appears as t, *J* 8.6, aromatic *H*], 7.33 [2H, d, *J* 9.0, aromatic *H*], 7.37 – 7.45 [2H, m, aromatic *H*] 7.57 [2H, d, *J* 9.0, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 25.4 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 34.5 [CH_2, S*C*H_2], 42.3 [CH, *C*(3)*H*], 46.7 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 115.4 (CH, d, $^2J_{CF}$ 21.5, aromatic *C*H), 121.1, 128.9 (2 x CH, aromatic *C*H), 130.0 (C, aromatic *C*), 130.9 (CH, d, $^3J_{CF}$ 8.1, aromatic *C*H), 133.4 (C, d, $^4J_{CF}$ 3.3, aromatic *C*), 137.8 (C, aromatic *C*), 162.0 (C, d, $^1J_{CF}$ 247.3, aromatic *C*), 172.4 (C, *C*O); m/z (ES+) 336.2 [$C_{17}H_{14}{}^{35}ClFNOS$)+$H^+$], 10%. HRMS (ES+): Exact mass calculated for $C_{17}H_{15}{}^{35}ClFNOS$ [M+H^+] 336.0619. Found 336.0618.

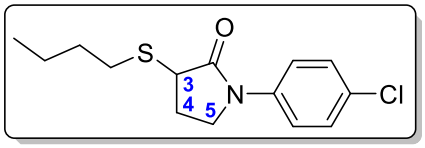
1-(4-Chlorophenyl)-3-[(4-methylbenzyl)thio]pyrrolidine-2-one 9



Compound **9** was prepared following the method described above for **6** using 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (0.20 g, 0.9 mmol, 1 eq), 4-methylbenzylmercaptan (0.14 g, 0.13 mL, 0.99 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.004 g, 0.009 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as purple oily solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **9**

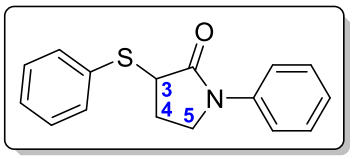
(0.23 g, 76%) as a white solid, mp 104–106°C; υ_{max}/cm^{-1} (neat) 1674 (C=O); δ_H (300 MHz, $CDCl_3$): 1.87 – 2.02 [1H, m, one of C(4)H_2 or C(5)H_2], 2.33 [3H, s, aromatic CH_3], 2.37 – 2.54 [1H, m, one of C(4)H_2 or C(5)H_2], 3.46 [1H, dd, *J* 8.6, 4.7, C(3)*H*], 3.69 [1H, td, *J* 8.6, 4.3, one of C(4)H_2 or C(5)H_2], 3.77 - 3.92 [2H, m, containing (3.82, 1H, A of AB system, J_{AB} 13.3, one of SCH_2) and (1H, m, one of C(4)H_2 or C(5)H_2)], 4.17 [1H, B of AB system, J_{AB} 13.3, one of SCH_2], 7.12 [2H, d, *J* 8.1, aromatic *H*], 7.26 – 7.37 [4H, m, aromatic *H*] 7.58 [2H, d, *J* 9.0, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 21.1 (CH_3, aromatic *C*H_3), 25.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 35.0 (CH_2, S*C*H_2), 42.6 [CH, *C*(3)*H*], 46.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 121.0, 128.9, 129.15, 129.23 (4 x CH, aromatic *C*H), 129.8, 134.5, 136.9, 137.9 (4 x C, aromatic *C*), 172.6 (C, *C*O); m/z (ES-) 332.1 [$C_{18}H_{18}{}^{35}ClNOS$)+H^+], 5%. HRMS (ES+): Exact mass calculated for $C_{18}H_{18}{}^{35}ClNOS$ [M+H^+] 332.0870. Found 332.0870.

3-(Butylthio)-1-(4-chlorophenyl)pyrrolidine-2-one 10



Compound **10** was prepared following the method described above for **6** using 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (0.12 g, 0.52 mmol, 1 eq), *n*-butylmercaptan (0.05 g, 0.06 mL, 0.57 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.003 g, 0.005 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as purple solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **10** (0.12 g, 83%) as a white solid, mp 49–50°C; υ_{max}/cm^{-1} (neat) 1682 (C=O); δ_H (300 MHz, $CDCl_3$): 0.92 [3H, t, *J* 7.3, CH_3], 1.43 [2H, sextet, *J* 7.4, CH_2CH$_3$], 1.65 [2H, sextet, *J* 7.4, CH_2CH$_2$CH$_3$], 1.98 – 2.10 [1H, m, one of C(4)H_2 or C(5)H_2], 2.49 – 2.65 [1H, m, one of C(4)H_2 or C(5)H_2], 2.67 – 2.82 [1H, m, one of CH_2CH$_2$CH$_2$CH$_3$], 2.82 – 2.95 [1H, m, one of CH_2CH$_2$CH$_2$CH$_3$], 3.59 – 3.66 [1H, m, C(3)*H*], 3.69 – 3.79 [1H, m, one of C(4)H_2 or C(5)H_2], 3.87 – 3.98 [1H, m, one of C(4)H_2 or C(5)H_2], 7.32 [2H, d, *J* 9.1, aromatic *H*], 7.58 [2H, d, *J* 9.1, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 13.7 (CH_3, *C*H_3), 22.0 (CH_2, *C*H_2CH$_3$), 26.1 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 31.0 (CH_2, *C*H_2CH$_2$CH$_2$CH$_3$), 31.4 (CH_2, *C*H_2CH$_2$CH$_3$), 44.2 [CH, *C*(3)*H*], 46.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 121.0, 128.9 (2 x CH, aromatic *C*H), 129.8, 138.0 (2 x C, aromatic *C*), 172.5 (C, *C*O); m/z (ES-) 282.3 [$C_{14}H_{18}{}^{35}ClNOS$)-H^+], 10%. $^{35}Cl/^{37}Cl$ pattern visible at 282.3 and 284.2 in a 3:1 ratio. HRMS (ES+): Exact mass calculated for $C_{14}H_{18}{}^{35}ClNOS$ [M+H^+] 284.0870. Found 284.0873.

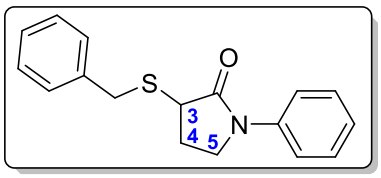
1-Phenyl-3-(phenylthio)pyrrolidine-2-one 11[3]



Compound **11** was prepared following the method described above for **6** using 3-diazo-1-phenylpyrrolidin-2-one **4** (0.12 g, 0.64 mmol, 1 eq), thiophenol (0.08 g, 0.1 mL, 0.70 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.003 g, 0.006 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as brown solid which was purified by column chromatography using hexane:chloroform (50:50, 1% ethanol) as eluent to give the pure α-thiolactam **11** (0.16 g, 92%) as a white solid mp 71–73°C (lit[4] 83.5–85.3°C); υ_{max}/cm^{-1} (neat) 1679 (C=O); δ_H (300 MHz, $CDCl_3$): 2.13 – 2.25 [1H, m, one of C(4)H_2 or C(5)H_2], 2.54 – 2.66 [1H, m, one of C(4)H_2 or C(5)H_2], 3.56 – 3.66 [1H, m, one of C(4)H_2 or C(5)H_2], 3.67 – 3.76 [1H, m, one of C(4)H_2 or C(5)H_2], 4.00 [1H, dd, *J* 8.7, 6.0, C(3)*H*], 7.16 [1H, t, *J* 7.6, aromatic *H*], 7.27 – 7.32 [3H, m, aromatic *H*], 7.36 [2H, t, *J* 7.7, aromatic *H*], 7.52 – 7.61 [4H, m , aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 26.3 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 46.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 49.4 (CH, *C*(3)H), 120.1, 124.9, 128.1, 128.9, 129.0 (5 x CH, aromatic *C*H), 132.8 (C, aromatic *C*), 133.3 (CH, aromatic *C*)], 139.1 (C, aromatic *C*), 171.4 (C signal, *C*O);m/z (ES+) 270.3 [$C_{16}H_{15}NOS$)+H^+], 12%. HRMS (ES+): Exact mass calculated for $C_{16}H_{15}NOS$ [M+H^+] 270.0947. Found 270.0942.

Spectroscopic characteristics were consistent with those previously reported.[3]

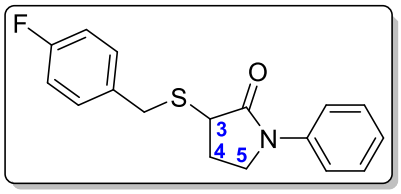
3-(Benzylthio)-1-phenylpyrrolidin-2-one 12[3]



Compound **12** was prepared following the method described above for **6** using 3-diazo-1-phenylpyrrolidin-2-one **4** (0.40 g, 2.14 mmol, 1 eq), benzyl mercaptan (0.29 g, 0.28 mL, 2.35 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.010 g, 0.021 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as brown solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **12** (0.27 g, 45%) as a white solid, mp 106–107°C (lit[4] 109.6–110.7°C); υ_{max}/cm^{-1} (neat) 1675 (C=O); δ_H (300 MHz, $CDCl_3$): 1.86 – 2.00 [1H, m, one of C(4)H_2 or C(5)H_2], 2.36 – 2.51 [1H, m, one of C(4)H_2 or C(5)H_2], 3.47 [1H, dd, *J* 8.6, 4.7, C(3)*H*], 3.72 [1H, td, *J* 8.3, 4.2, one of C(4)H_2 or C(5)H_2], 3.81 – 3.95 [2H, m, containing (3.85, 1H, A of AB system J_{AB} 13.4, one of SCH_2) and one of C(4)H_2 or C(5)H_2], 7.16 [1H, t, *J* 7.3, aromatic *H*], 7.20 – 7.49 [7H, m, aromatic *H*], 7.62 [2H, d, *J* 7.8, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 25.7 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 35.3 (CH_2, SCH_2), 42.7 [CH, *C*(3)*H*], 46.8 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 120.0, 124.8, 127.1, 128.5, 128.9, 129.3 (6 x CH, aromatic *C*H), 137.8, 139.3 (2 x C, aromatic *C*), 172.5 (C, *C*O); m/z (ES+) 284.3 [$C_{17}H_{17}NOS$)+H^+], 10%. HRMS (ES+): Exact mass calculated for $C_{17}H_{17}NOS$ [M+H^+] 284.1104. Found 284.1106.

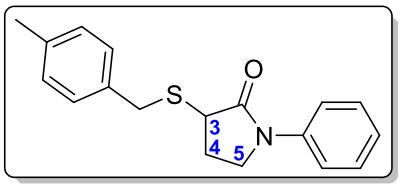
Spectroscopic characteristics were consistent with those previously reported.[3]

3-[(4-Fluorobenzyl)thio]-1-phenylpyrrolidin-2-one 13



Compound **13** was prepared following the method described above for **6** using 3-diazo-1-phenylpyrrolidin-2-one **4** (0.20 g, 1.07 mmol, 1 eq), 4-fluorobenzyl mercaptan (0.17 g, 0.15 mL, 1.18 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.005 g, 0.011 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as purple/brown solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **13** (0.25 g, 77%) as a white crystalline solid, mp 111–112°C; υ_{max}/cm^{-1} (neat) 1675 (C=O); δ_H (300 MHz, $CDCl_3$): 1.88 – 2.01 [1H, m, one of C(4)H_2 or C(5)H_2], 2.38 – 2.55 [1H, m, one of C(4)H_2 or C(5)H_2], 3.44 [1H, dd, *J* 8.6, 4.7, C(3)*H*], 3.69 – 3.79 [1H, m, one of C(4)H_2 or C(5)H_2], 3.82 [1H, A of AB system, J_{AB} 13.5, one of SCH_2], 3.86 – 3.97 [1H, m, one of C(4)H_2 or C(5)H_2], 4.22 [1H, B of AB system, J_{AB} 13.5, one of SCH_2], 7.00 [2H, dd appears as t, *J* 8.8, aromatic *H*], 7.17 [1H, t, *J* 7.5, aromatic *H*], 7.33 – 7.45 [4H, m, aromatic *H*], 7.61 [2H, d, *J* 8.8, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 25.6 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 34.5 (CH_2, S*C*H_2), 42.5 [CH, *C*(3)H], 46.8 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 115.4 (CH, d, $^2J_{CF}$ 21.3, aromatic *C*H), 120.1, 124.9, 128.9 (3 x CH, aromatic *C*H), 130.9 (1 x CH, d, $^3J_{CF}$ 8.3, aromatic *C*H), 133.5 (C, d, $^4J_{CF}$ 3.3, aromatic *C*), 139.2 (C, aromatic *C*), 162.0 (C , d, $^1J_{CF}$ 245.6, aromatic *C*), 172.4 (C, *C*O); m/z (ES+) 324.1 [$C_{17}H_{16}FNOS$)+Na^+], 24%. HRMS (ES+): Exact mass calculated for $C_{17}H_{16}FNOS$ [M+H^+] 302.1009. Found 302.1008.

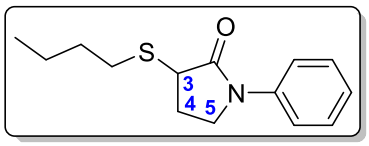
3-[(Methylbenzyl)thio]-1-phenylpyrrolidin-2-one 14



Compound **14** was prepared following the method described above for **6** using 3-diazo-1-phenylpyrrolidin-2-one **4** (0.20 g, 1.08 mmol, 1 eq), 4-methylbenzyl mercaptan (0.16 g, 0.16 mL, 1.19 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.005 g, 0.011 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as purple solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **14** (0.20 g, 64%) as a white crystalline solid, mp 97–99°C; υ_{max}/cm^{-1} (neat) 1675 (C=O); δ_H (300 MHz, $CDCl_3$): 1.87- 2.00 [1H, m, one of C(4)H_2 or C(5)H_2], 2.33 [3H, s, aromatic CH_3], 2.37 – 2.52 [1H, m, one of C(4)H_2 or C(5)H_2], 3.47 [1H, dd, *J* 8.6, 4.8, C(3)*H*], 3.68 – 3.78 [1H, m, one of C(4)H_2 or C(5)H_2], 3.83 [1H, A of AB system, J_{AB} 13.3, one of SCH_2], 3.85 – 3.95 [1H, m, one of C(4)H_2 or C(5)H_2], 4.19 [1H, B of AB system, J_{AB} 13.3, one of SCH_2], 7.08 – 7.20 [3H, m, aromatic *H*], 7.27 – 7.43 [4H, m, aromatic *H*], 7.61 [2H, d, *J* 8.6, aromatic *H*];

δ_c (75.5 MHz, $CDCl_3$): 21.1 (CH_3, aromatic *C*H_3), 25.7 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 35.0 (CH_2, S*C*H_2), 42.7 [CH, *C*(3)H], 46.8 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 120.0, 124.8, 128.9, 129.18, 129.21 (5 x CH, aromatic *C*H), 134.7, 136.8, 139.3 (3 x C, aromatic *C*), 172.5 (C , *C*O); m/z (ES+) 298.2 [$C_{18}H_{19}NOS$)+H^+], 6%. HRMS (ES+): Exact mass calculated for $C_{18}H_9NOS$ [M+H^+] 298.1260. Found 298.1255.

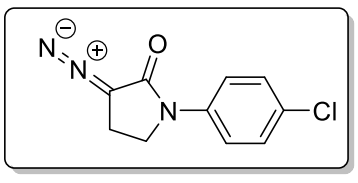
3-(Butylthio)-1-phenylpyrrolidin-2-one 15



Compound **15** was prepared following the method described above for **6** using 3-diazo-1-phenylpyrrolidin-2-one **4** (0.20 g, 1.06 mmol, 1 eq), *n*-butylmercaptan (0.11 g, 0.13 mL, 1.17 mmol, 1.1 eq) and $Rh_2(OAc)_4$ (0.005 g, 0.011 mmol, 1 mol%) in dichloromethane (15 mL). The reaction solution was stirred at room temperature for 1h and the crude α-thiolactam was isolated as a purple oily solid which was purified by column chromatography using chloroform:ethanol (99:1) as eluent to give the pure α-thiolactam **15** (0.11 g, 41%) as a white crystalline solid, mp 44–45°C; υ_{max}/cm^{-1} (neat) 1676 (C=O); δ_H (300 MHz, $CDCl_3$): 0.92 [3H, t, *J* 7.3, CH_2CH_3], 1.43 [2H, sextet, *J* 7.3, CH_2CH_3], 1.63 [2H, sextet, *J* 7.3, $CH_2CH_2CH_3$], 1.97 – 2.10 [1H, m, one of C(4)H_2 or C(5)H_2], 2.49 – 2.65 [1H, m, one of C(4)H_2 or C(5)H_2], 2.68 – 2.82 [1H, m, one of $CH_2CH_2CH_2CH_3$], 2.83 – 2.97 [1H, m, one of $CH_2CH_2CH_2CH_3$], 3.62 [1H, dd, *J* 8.5, 4.5, C(3)*H*], 3.72 – 3.83 [1H, m, one of C(4)H_2 or C(5)H_2], 3.89 – 4.00 [1H, m, one of C(4)H_2 or C(5)H_2], 7.15 [1H, t, *J* 7.4, aromatic *H*], 7.37 [2H, t, *J* 7.5, aromatic *H*], 7.62 [2H, d, *J* 7.8, aromatic *H*]; δ_c (75.5 MHz, $CDCl_3$): 13.7 (CH_3, CH_2CH_3), 22.0 (CH_2, CH_2CH_3), 26.3 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 31.0 (CH_2, $CH_2CH_2CH_2CH_3$), 31.4 (CH_2, $CH_2CH_2CH_3$), 44.4 [CH, *C*(3)H], 46.7 [CH_2, one of *C*(4)H_2 or *C*(5)H_2], 119.9, 124.7, 128.9 (3 x CH, aromatic *C*H), 139.4 (C, aromatic *C*), 172.4 (C, *C*O); m/z (ES+) 250.3 [$C_{14}H_{19}NOS$)+H^+], 8%. m/z (ES+) 249.8 [$C_{14}H_{19}NOS$)-H^+], 8%. HRMS (ES+): Exact mass calculated for $C_{14}H_{19}NOS$ [M+H^+] 250.1260. Found 250.1267.

2.4 Synthesis of α-diazolactams 3 and 4 in continuous flow

1-(4-Chlorophenyl)-3-diazopyrrolidin-2-one 3[2]

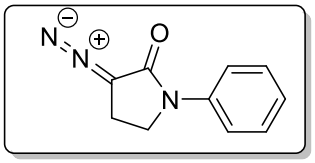


An aqueous solution of sodium azide (10 mL, 3.0 M, 10 equiv, 3.0 mL min^{-1}) was pumped through a micromixer T-piece where it met a toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M, 1.67 equiv, 3.0 mL min^{-1}); the combined stream passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.2 mL min^{-1} to give a residence time of 1 h. The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% w/v, 0.9 mL min^{-1}). The reaction stream was passed through a back-pressure regulator (8 bar). The biphasic effluent was then separated by an

in-line liquid–liquid separator. The organic effluent (25 mL) was directly fed to another pump. The pump delivered the separated triflyl azide **2** solution (25 mL, 2.0 mL min^{-1}) to a T-piece where it met a solution of ethyl-2-[1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene]-2-hydroxyacetate **1** and DBU in dichloromethane (25 mL, 0.12 M, [DBU] 0.128 M, 1.1 equiv relative to **1**, 2.0 mL min^{-1}) and was then passed through a reactor coil (4 × 10 mL, rt). When both reagent solutions had been charged, the combined flow rate was reduced to 0.5 mL min^{-1} to give a residence time of 1 h, after which the reactor effluent subsequently passed through a back pressure regulator (8 bar). The reactor effluent was analysed by IR spectroscopy and concentrated under reduced pressure to give the crude product which was subsequently purified by chromatography on silica gel (treated by adding 1% weight of triethylamine to the dry silica prior to packing) using hexane:chloroform:ethanol (50:49:1) as eluent affording α-diazolactam **3** as a bright orange crystalline solid (0.48 g, 73%).

Spectral characteristics were consistent with those reported above in **Section 2.2** and previously reported.[1]

3-Diazo-1-phenylpyrrolidin-2-one 4[2]

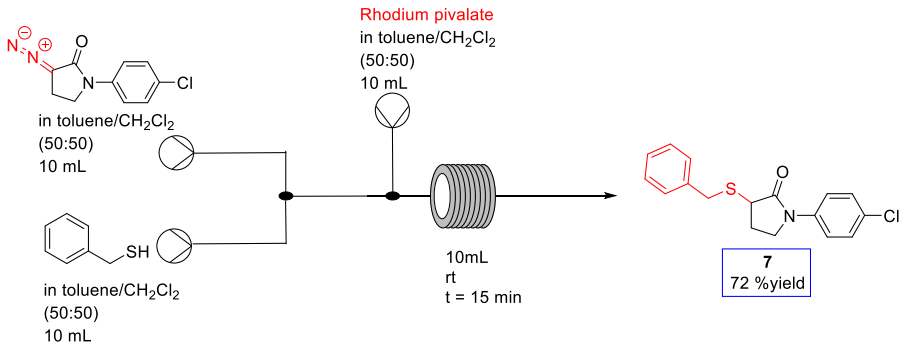


A toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M, 1.67 equiv) was loaded into a 10 mL reagent loop using a peristaltic pump (3.0 mL min^{-1}) before being pumped forward (0.333 mL min^{-1}) to meet a pumped aqueous solution of sodium azide (10 mL, 3.0 M, 10 equiv, 3.0 mL min^{-1}) in a micromixer T-piece (200 µL); the combined stream passed through a reactor coil (4 × 10 mL, rt, 1 h residence time). The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% w/v, 0.9 mL min^{-1}). The biphasic effluent was then separated by an in-line liquid–liquid separator and 25 mL of organic effluent was collected, containing triflyl azide **2** in toluene. This organic effluent (25 mL) was loaded into a reagent loop (25 mL) using a peristaltic pump (2.0 mL min^{-1}) and pumped forward (0.5 mL min^{-1}) to meet a pumped solution of ethyl-2-hydroxy-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate **5** and DBU in dichloromethane (25 mL, 0.12 M, [DBU] 0.128 M, 1.1 equiv relative to **5**, 0.5 mL min^{-1}) at a T-piece and the combined solution was then passed through a reactor coil (4 × 10 mL, rt, 40 min residence time). The reactor effluent was subsequently passed through a back pressure regulator (8 bar). The reactor effluent was analysed by IR spectroscopy and concentrated under reduced pressure to give the crude product which was subsequently purified by chromatography on silica gel (treated by adding 1% weight of triethylamine to the dry silica prior to packing) using hexane:chloroform:ethanol (50:49:1) as eluent affording α-diazolactam **4** as a bright orange crystalline solid (0.31 g, 56%)

Spectral characteristics were consistent with those reported above in **Section 2.2**.

2.5 Synthesis of α-thiolactams 7 and 12 in continuous flow

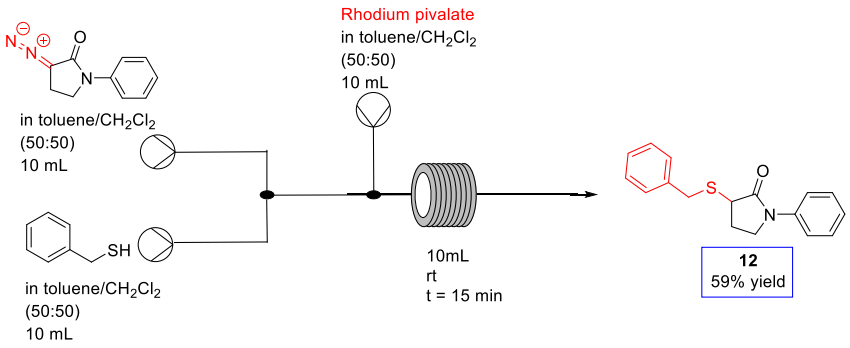
3-(Benzylthio)-1-(4-chlorophenyl)pyrrolidine-2-one 7



A solution of α-diazolactam 1-(4-chlorophenyl)-3-diazopyrrolidin-2-one **3** (10 mL, 0.18 g, 0.08 M, 1 eq, 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) was pumped to meet a solution of benzyl mercaptan (10 mL, 0.1 mL, 0.089 M, 1.1 eq, 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) at a T-piece; the combined stream met a solution of rhodium pivalate (10 mL, 0.005 g, 0.0008 M, 1 mol%, 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) at a second T-piece. The resulting reagent stream passed through a 10mL reactor coil at room temperature for a residence time of 15 min. The outflow from the reactor coil passed through a back pressure regulator (8 bar) before being collected in a round-bottomed flask and concentrated to remove solvent. The crude reaction mixture was purified by column chromatography using chloroform:ethanol (99:1) as eluent to afford the desired α-thiolactam **7** (0.16 g, 72%) as an off-white solid.

Spectral characteristics were consistent with those reported above in **Section 2.3**.

3-(Benzylthio)-1-phenylpyrrolidin-2-one 12[3]



A solution of α-diazolactam 3-diazo-1-phenylpyrrolidin-2-one **4** (10 mL, 0.19 g, 0.1 M, 1 eq., 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) was pumped to meet a solution of benzyl mercaptan (10

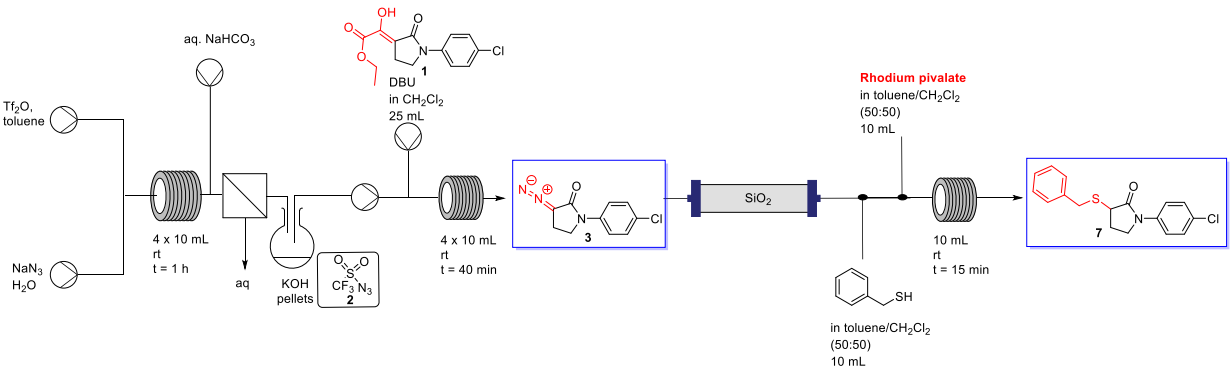
mL, 0.14 g, 0.13 mL, 0.1 M, 1.1 eq 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) at a T-piece; the combined stream met a solution of rhodium pivalate (10 mL, 0.006 g, 0.001 M, 1 mol%, 0.222 mL min^{-1}) in toluene:dichloromethane (50:50) at a second T-piece. The resulting stream passed through a 10mL reactor coil at room temperature for a residence time of 15 min. The outflow from the reactor coil passed through a back pressure regulator (8 bar) before being collected in a round-bottomed flask and concentrated to remove solvent. The crude reaction mixture was purified by column chromatography using chloroform:ethanol (99:1) as eluent to afford the desired α-thiolactam **12** (0.17 g, 59%) as an off-white solid.

Spectral characteristics were consistent with those reported above in **Section 2.3** and previously reported.[3]

2.6 Telescoped reaction sequence including TfN_3 2 generation, diazo transfer and S–H insertion to form α-thiolactams 7 and 12 in continuous flow.

3-(Benzylthio)-1-(4-chlorophenyl)pyrrolidine-2-one 7

Procedure when reaction was carried out at 0.12M concentration



A toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M, 1.67 equiv) was loaded into a 10 mL reagent loop using a peristaltic pump (3.0 mL min^{-1}) before being pumped forward (0.333 mL min^{-1}) to meet a pumped aqueous solution of sodium azide (10 mL, 3.0 M, 10 equiv, 0.333 mL min^{-1}) in a micromixer T-piece (200 µL); the combined stream was passed through a reactor coil (4 × 10 mL, rt, 1 hr residence time). The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% w/v, 0.9 mL min^{-1}). The biphasic effluent was then separated by an in-line liquid–liquid separator and 25 mL of organic effluent was collected, containing triflyl azide **2** in toluene. The organic effluent (25 mL) was collected over 7-10 KOH pellets. This organic effluent (25 mL) was loaded into a reagent loop (25 mL) using a peristaltic pump (2.0 mL min^{-1}) and pumped forward (0.5 mL min^{-1}) to meet a pumped solution of ethyl-2-[1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene]-2-hydroxyacetate **1** and DBU in dichloromethane (25 mL, 0.12 M, [DBU] 0.128 M, 1.1 equiv relative to **1**, 0.5 mL min^{-1}) at a T-piece and the combined solution was then passed through a reactor coil (4 × 10 mL, rt, 40 min residence time). The reactor effluent was passed through a glass column packed with silica gel (pore size 60) (6.6 mm × 150 mm) and was collected (50 mL). The effluent was separated into two portions; one portion (33 mL) to quantify reaction efficiency and a second portion (17 mL) for forward processing to the S–H insertion step. Of the solution forward processed, 14 mL of this was pumped (0.306 mL min^{-1}) forward to a T-piece where it met a solution of benzyl mercaptan (10 mL, 0.11 M, 1.1 equiv relevant to **5**, 0.18 mL min^{-1}) in toluene:dichloromethane (50:50). The combined stream was pumped to a second T-piece where it met a solution of rhodium pivalate (10 mL, 1 mol%, 0.18 mL min^{-1}) in toluene:dichloromethane (50:50) and the resulting stream was passed through a reactor coil (1 x 10 mL, rt, 15 min residence time). The reactor effluent was passed through

a back-pressure regulator (8 bar) and collected in a round-bottomed flask and concentrated to remove solvent. The crude α-thiolactam **7** was purified by column chromatography on silica gel using chloroform:ethanol (99:1) as eluent to give the desired α-thiolactam **7** (0.11 g, 43% yield over 2 steps from **1**) as an off-white solid.

From the portion of the diazolactam solution isolated, the yield of the diazo transfer step was estimated to be 78% and the yield of the S–H insertion step is calculated as 55%.

Spectral characteristics were consistent with those reported above in **Section 2.3.**

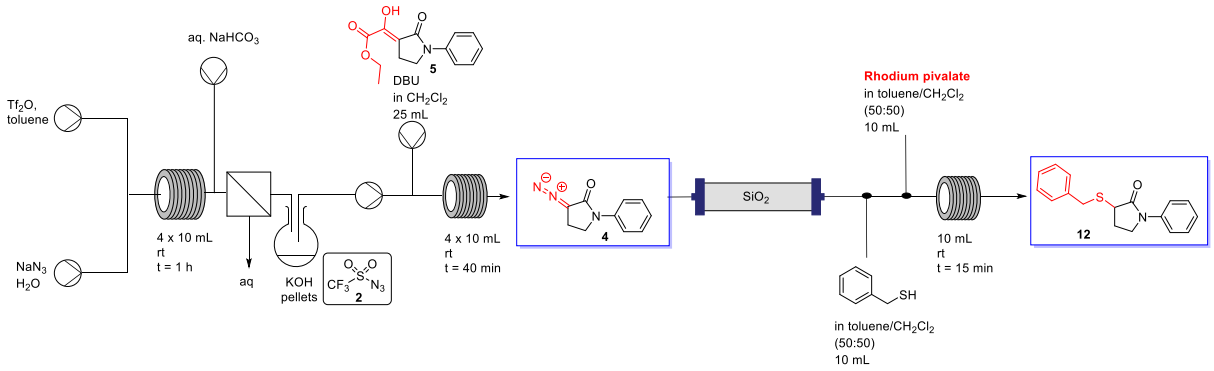
Procedure when reaction was carried out at 0.08M concentration

An aqueous solution of sodium azide (10 mL, 2.0 M, 10 equiv, 3.0 mL min^{-1}) was pumped through a micromixer T-piece where it met a toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.3 M, 1.67 equiv, 3.0 mL min^{-1}); the combined stream was passed through a reactor coil (4 × 10 mL, rt). After all reagent solutions had been charged, the combined flow rate was changed to 0.666 mL min^{-1} to give a residence time of 1 h. The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% w/v, 0.9 mL min^{-1}). The biphasic effluent was then separated by an in-line liquid–liquid separator. The organic effluent (25 mL) was collected over 7-10 KOH pellets and directly fed to another pump. The pump delivered the separated triflyl azide **2** solution (25 mL, 2.0 mL min^{-1}) to a T-piece where it met a solution of ethyl-2-[1-(4-chlorophenyl)-2-oxopyrrolidin-3-ylidene]-2-hydroxyacetate **1** and DBU in dichloromethane (25 mL, 0.08 M, [DBU] 0.088 M, 1.1 equiv relative to **1**, 2.0 mL min^{-1}) and was then passed through a reactor coil (4 × 10 mL, rt). When both reagent solutions had been charged, the combined flow rate was reduced to 1.0 mL min^{-1} to give a residence time of 40 min. The reactor effluent was passed through a glass column packed with silica gel (pore size 60) (6.6 mm × 150 mm) and collected (40 mL). The effluent was separated into two portions; one portion (20 mL) to quantify reaction efficiency and a second portion (20 mL) for forward processing to the S–H insertion step. The portion forward processed (20 mL, 0.355 mL/min) was pumped forward to a T-piece where it met a solution of benzyl mercaptan (10 mL, 0.1 M, 1.1 equiv relevant to **5**, 0.156 mL min^{-1}) in toluene:dichloromethane (50:50). The combined stream was pumped to a second T-piece where it met a solution of rhodium pivalate (10 mL, 1 mol%, 0.156 mL min^{-1}) in toluene:dichloromethane (50:50) and the combined stream was passed through a reactor coil (1 x 10 mL, rt) for a residence time of 15 min. The reactor effluent was passed through a back-pressure regulator (8 bar) and collected in a round-bottomed flask and concentrated to remove solvent. The crude α-thiolactam **7** was purified by column chromatography on silica gel using chloroform:ethanol (99:1) as eluent to give the desired α-thiolactam **7** (0.07 g, 25% over 2 steps from **1**) as an off-white solid.

From the portion of the diazolactam solution isolated, the yield of the diazo transfer step was estimated to be 27% and the yield of the S–H insertion step is calculated as 92%.

Spectral characteristics were consistent with those reported above in **Section 2.3.**

3-(Benzylthio)-1-phenylpyrrolidin-2-one 12[3]



A toluene solution of trifluoromethanesulfonic anhydride (10 mL, 0.5 M, 1.67 equiv) was loaded into a 10 mL reagent loop using a peristaltic pump (3.0 mL min^{-1}) before being pumped forward (0.333 mL min^{-1}) to meet a pumped aqueous solution of sodium azide (10 mL, 3.0 M, 10 equiv, 0.333 mL min^{-1}) in a micromixer T-piece (200 µL); the combined stream was passed through a reactor coil (4 × 10 mL, rt, 1 hr residence time). The reactor effluent passed through a T-piece where it met a stream of aqueous sodium bicarbonate (5% w/v, 0.9 mL min^{-1}). The biphasic effluent was then separated by an in-line liquid–liquid separator and 25 mL of organic effluent was collected, containing triflyl azide **2** in toluene. The organic effluent (25 mL) was collected over 7-10 KOH pellets. This organic effluent (25 mL) was loaded into a reagent loop (25 mL) using a peristaltic pump (2.0 mL min^{-1}) and pumped forward (0.5 mL min^{-1}) to meet a pumped solution of ethyl-2-hydroxy-2-(2-oxo-1-phenylpyrrolidin-3-ylidene)acetate **5** and DBU in dichloromethane (25 mL, 0.12 M, [DBU] 0.128 M, 1.1 equiv relative to **5**, 0.5 mL min^{-1}) at a T-piece and the combined solution was then passed through a reactor coil (4 × 10 mL, rt, 40 min residence time). The reactor effluent was passed through a glass column packed with silica gel (pore size 60) (6.6 mm × 150 mm) and was collected (50mL). The effluent was separated into two portions; one portion (33 mL) to quantify reaction efficiency, and a second portion (17 mL) for forward processing to the S–H insertion step. Of the solution forward processed, 14 mL of this was pumped (0.306 mL min^{-1}) to a T-piece where it met as solution of benzyl mercaptan (10 mL, 0.11 M, 1.1 equiv relevant to **3**, 0.18 mL min^{-1}) in toluene:dichloromethane (50:50). The combined stream was pumped to a second T-piece where it met a solution of rhodium pivalate (10 mL, 1 mol%, 0.18 mL min^{-1}) in toluene:dichloromethane (50:50) and the resulting stream was passed through a reactor coil (1 x 10 mL, rt, 15 min residence time). The reactor effluent was passed through a back-pressure regulator (8 bar) and collected in a round-bottomed flask and concentrated to remove solvent. The crude α-

thiolactam **12** was purified by column chromatography on silica gel using chloroform:ethanol (99:1) as eluent to give the desired α-thiolactam **12** (0.11 g, 36% yield over 2 steps from **2**) as an off-white solid.

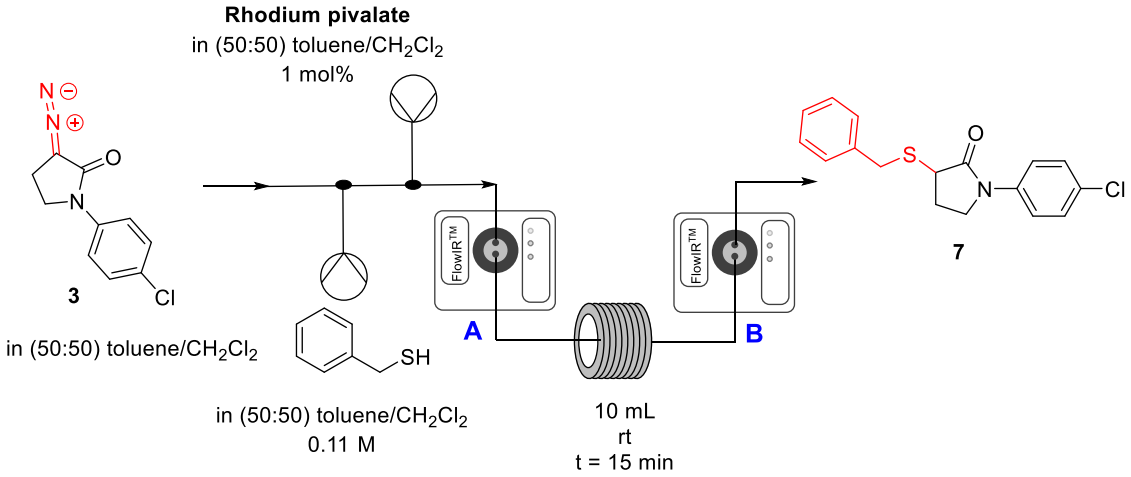
From the portion of the diazolactam solution isolated, the yield of the diazo transfer step was estimated to be 47% and the yield of the S–H insertion step is calculated as 76%.

Spectral characteristics were consistent with those reported above in **Section 2.3** and previously reported.[3]

3. Reaction monitoring by in-line IR

3.1 Experimental Procedure

In-line IR analysis was conducted using a Mettler–Toledo FlowIR™ unit fitted with a SiComp (silicon) probe head and processed using iC IR 7.0 software; IR spectra were recorded at a rate of 1 spectrum min^{-1}.



Scheme S1. Configuration of S–H insertion process step including in-line analysis by FlowIR™ at Positions A or B; spectra were recorded for 15 min at Position A, followed by 15 min at Position B at an acquisition rate of 1 spectrum min^{-1}.

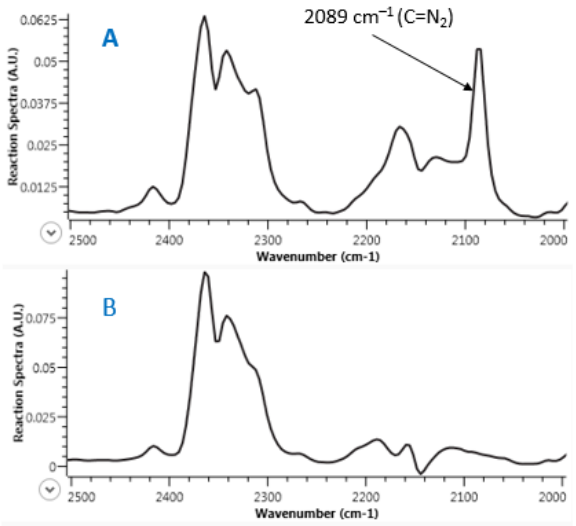


Figure S1: Sample IR spectra, in the region 2500–2000 cm^{-1}, recorded for S–H insertion process step. The spectrum of the substrate stream (shown to contain **3**, as indicated by the band at 2089 cm^{-1}), was recorded at Position A (in Scheme S1), while the spectrum of the product stream (showing consumption of **3**, as indicated by the absence of the band at 2089 cm^{-1}) was recorded at Position B (in Scheme S1).

4. ^{1}H NMR and ^{13}C NMR Spectra

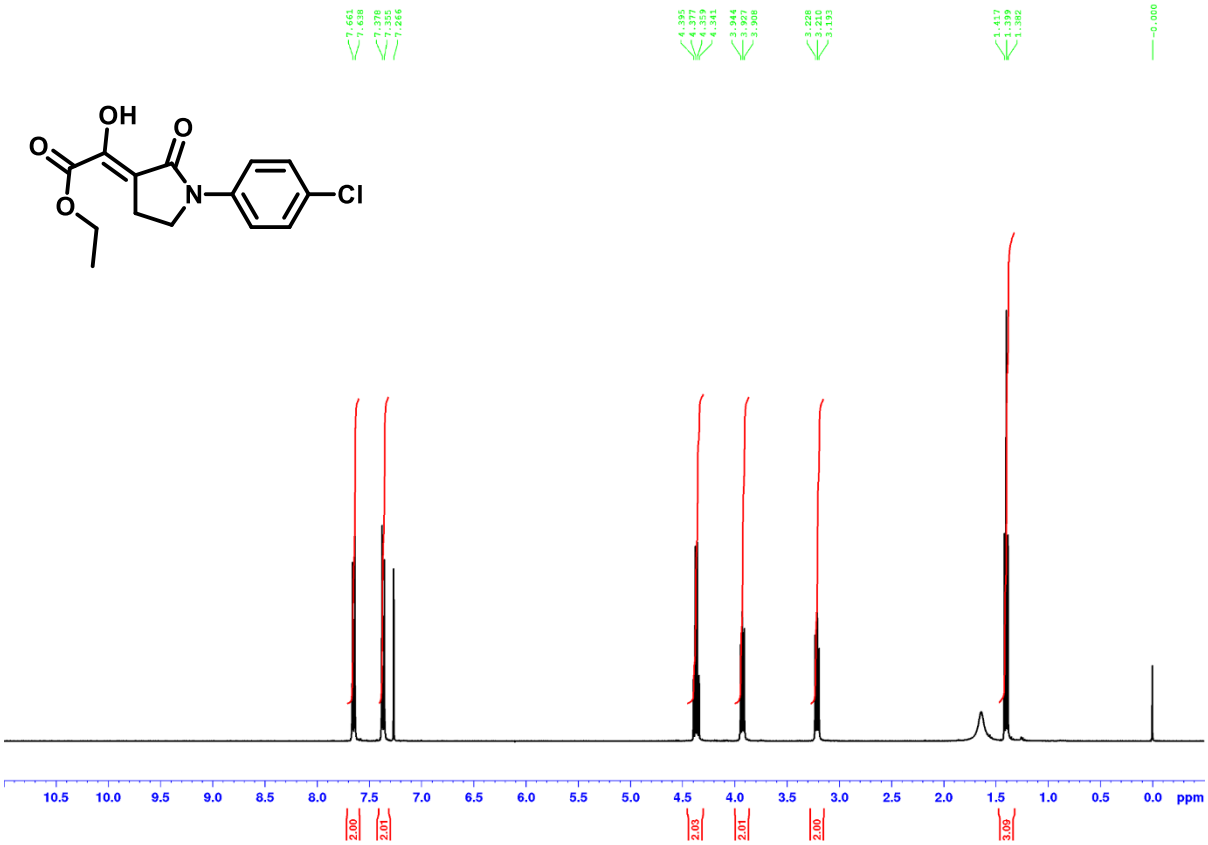


Figure S2: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1**.[2]

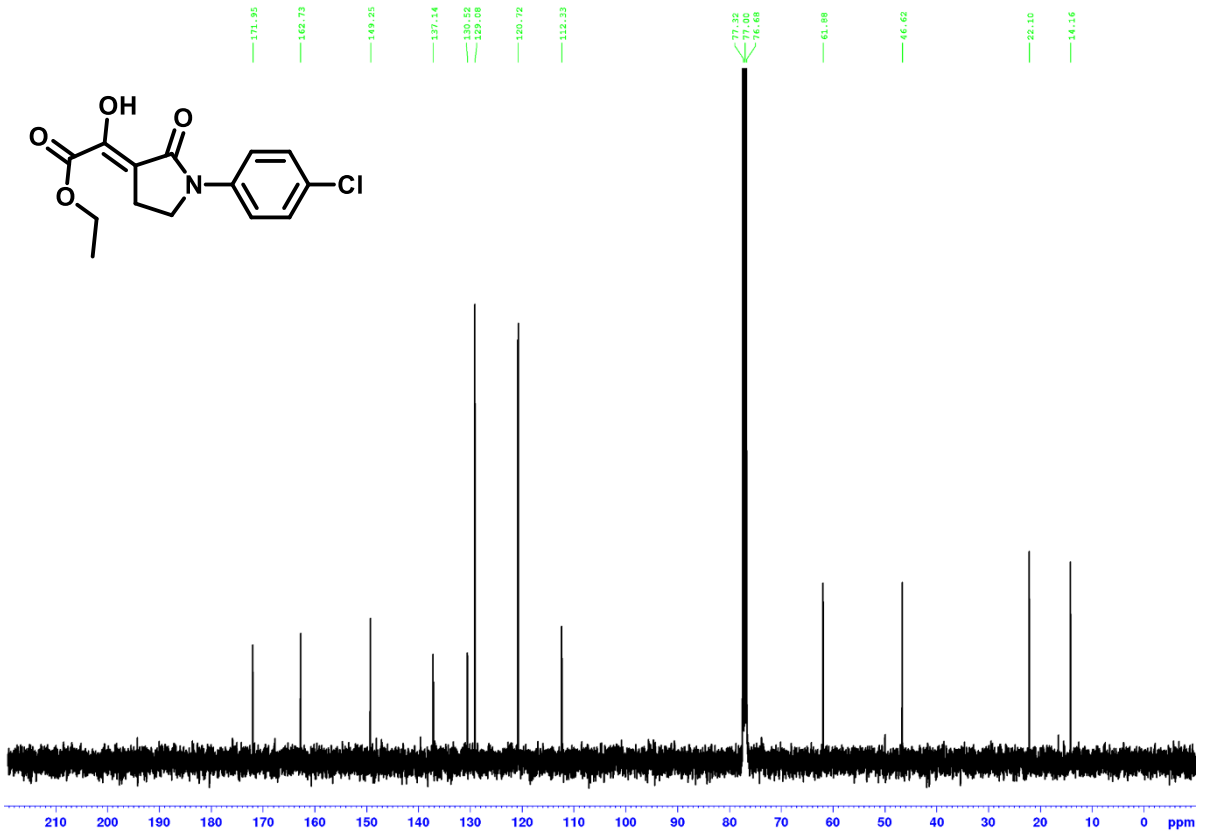


Figure S3: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of **1**.[2]

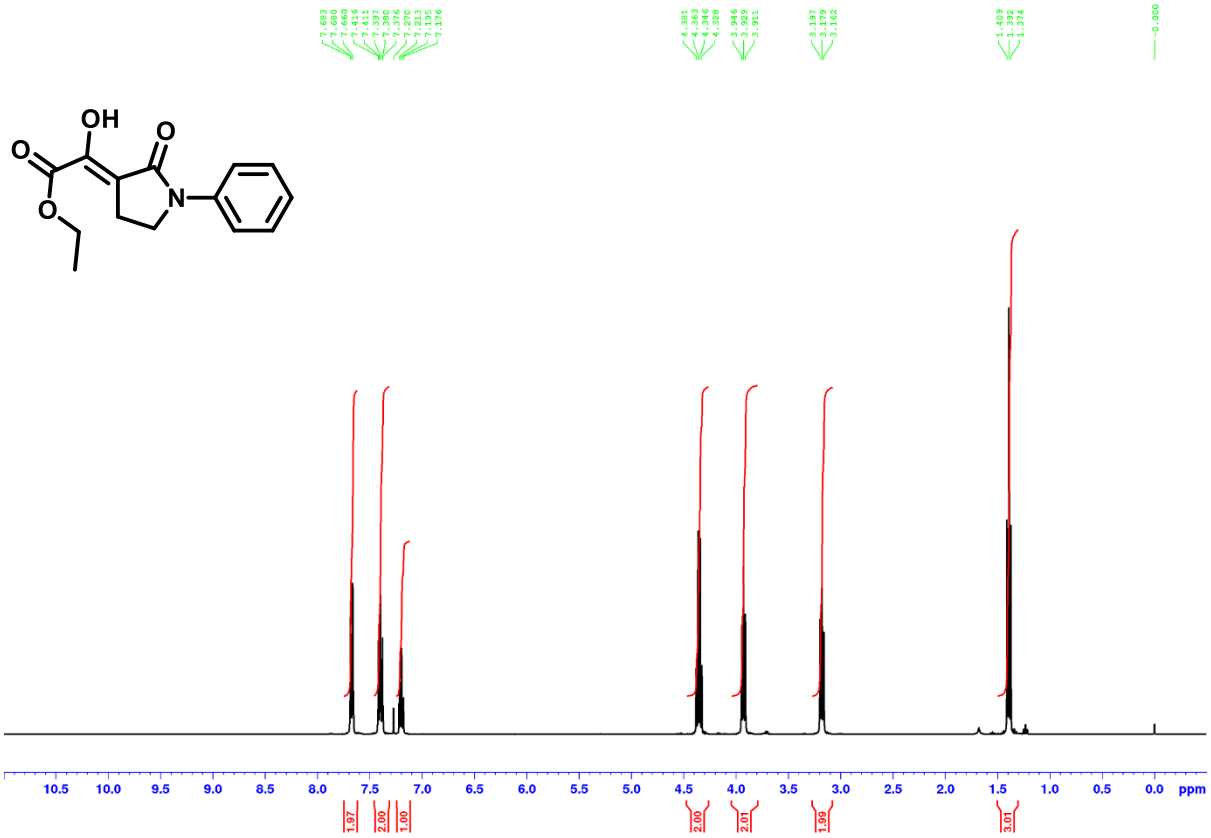


Figure S4: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **5**.[2]

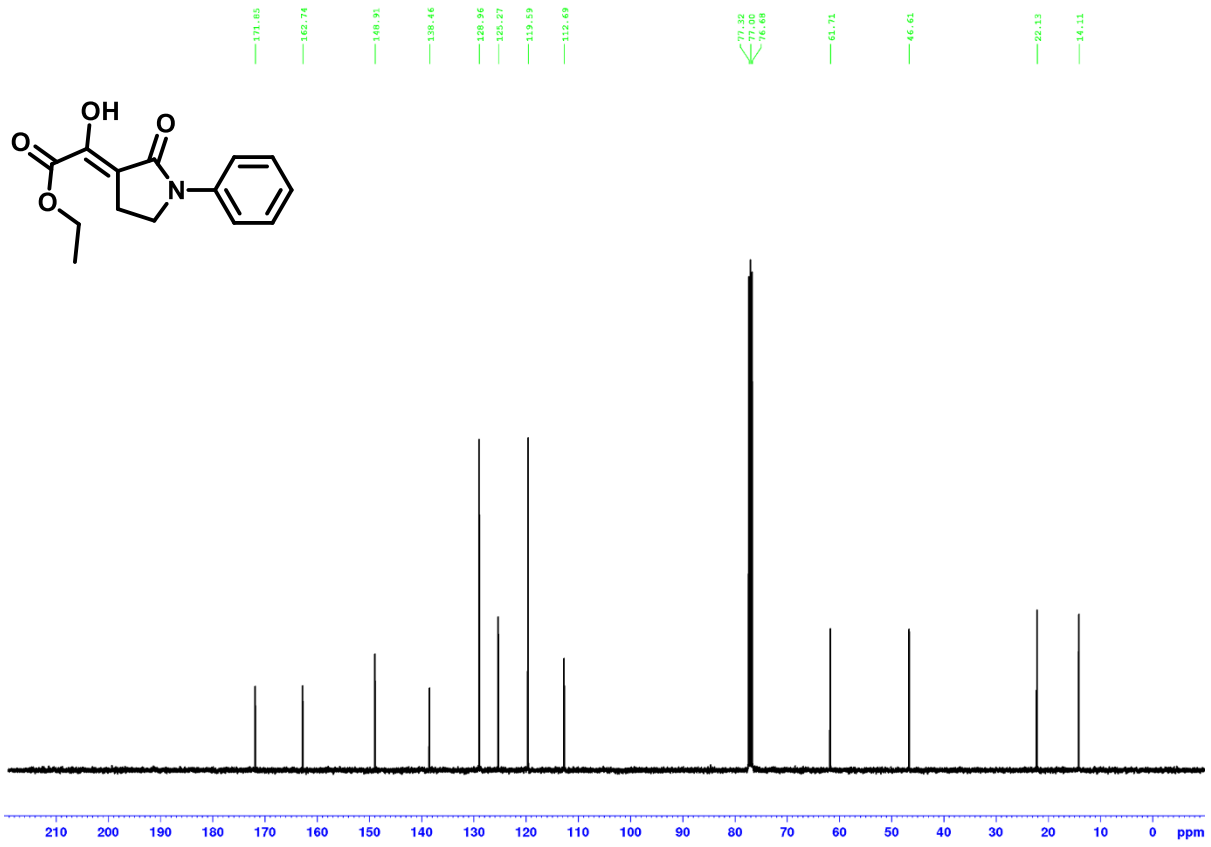


Figure S5: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of **5**.[2]

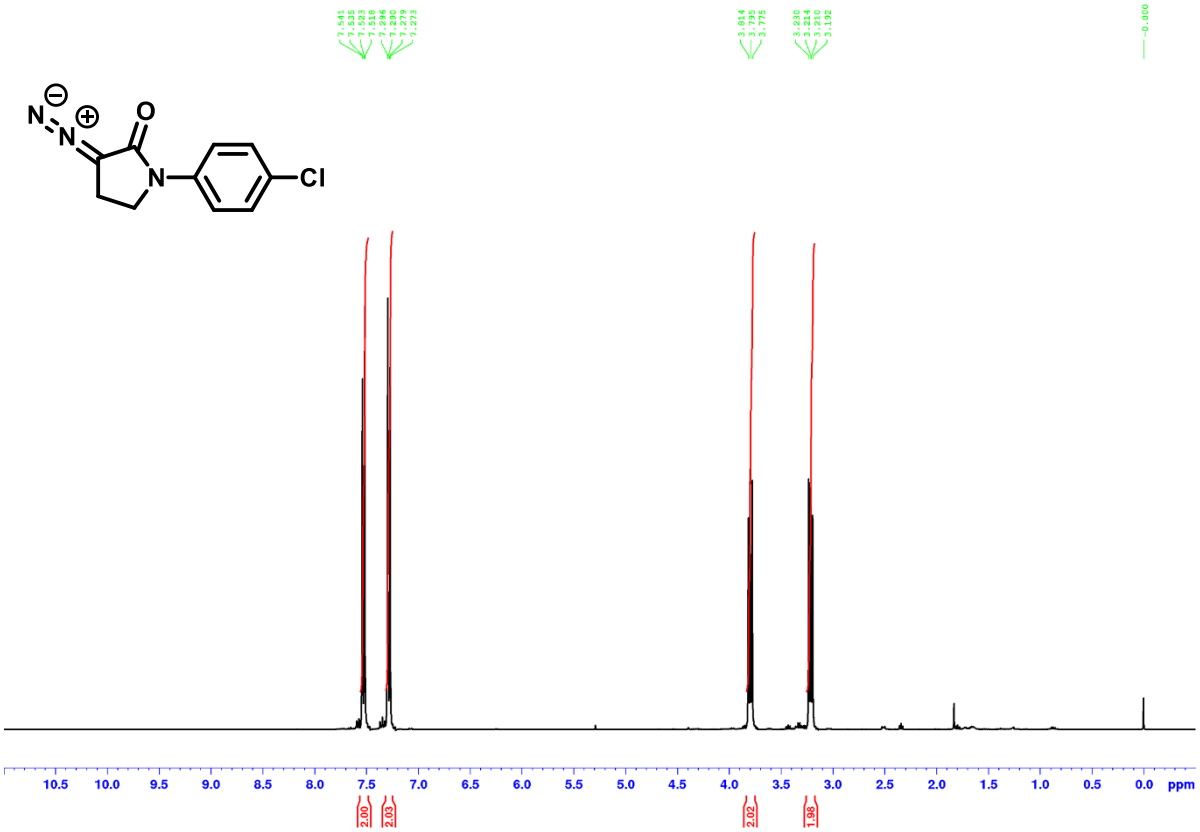


Figure S6: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **3**.[1,2]

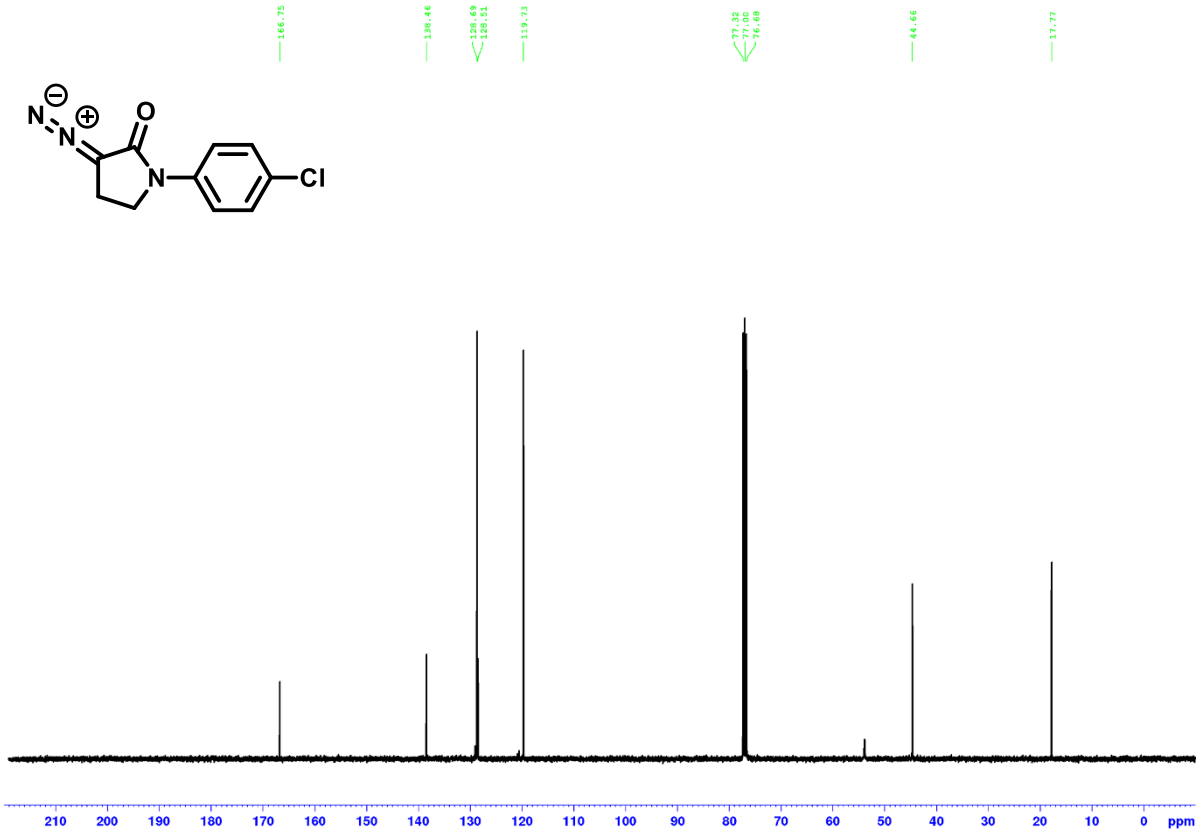


Figure S7: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of **3**.[1,2]

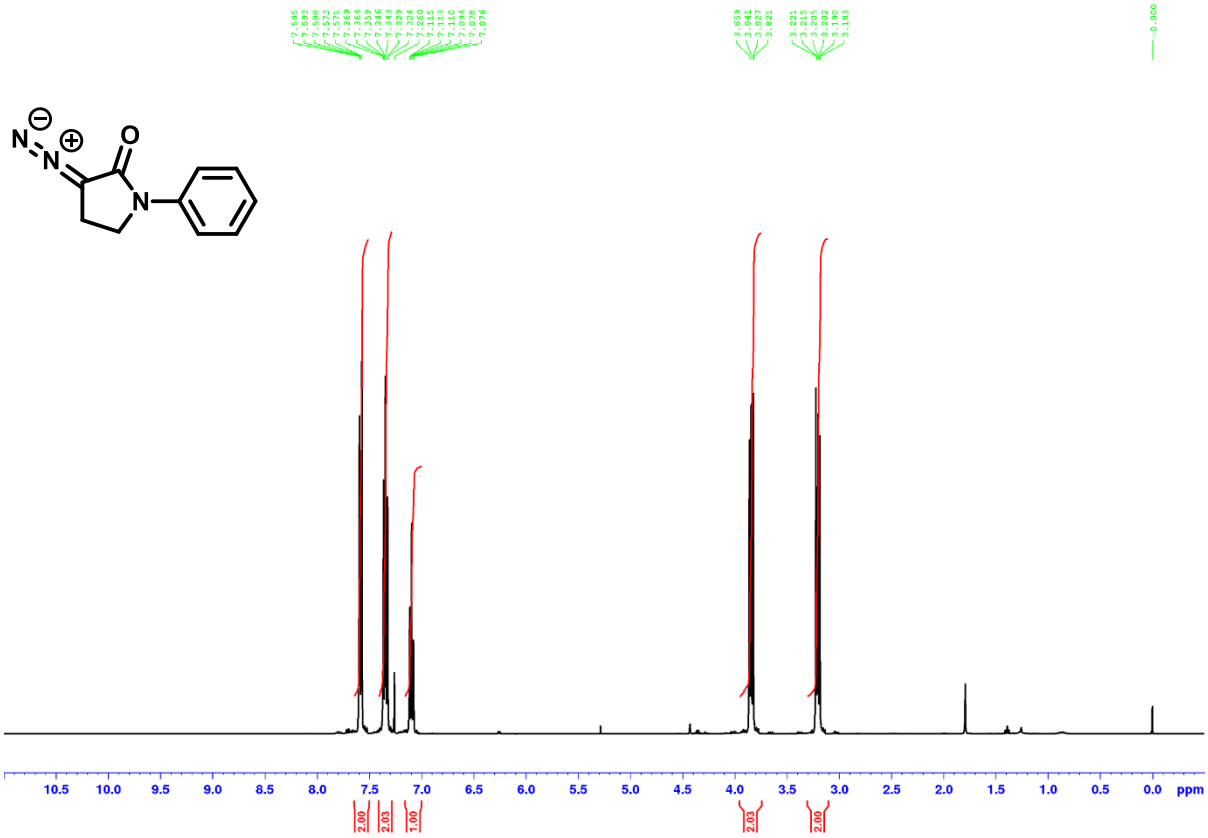


Figure S8: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4.**[2]

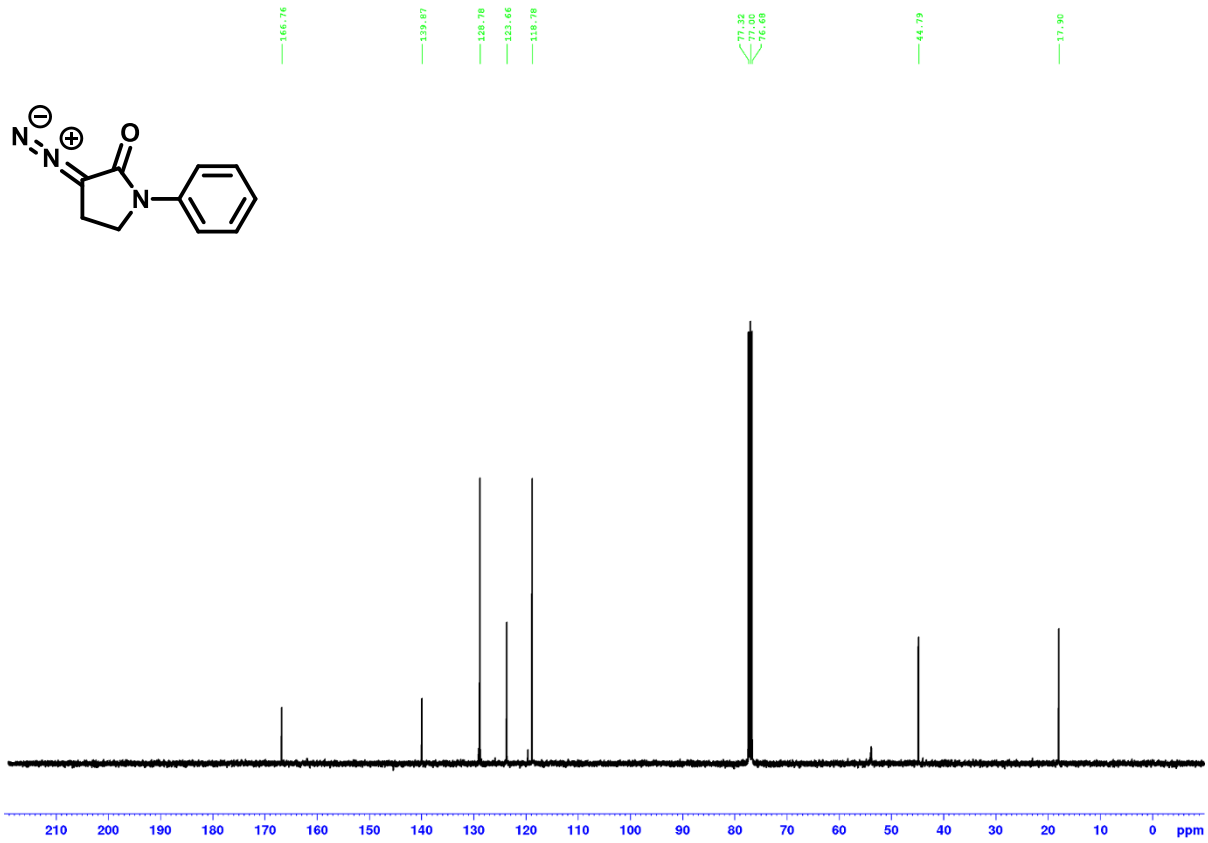


Figure S9: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of **4**.[2]

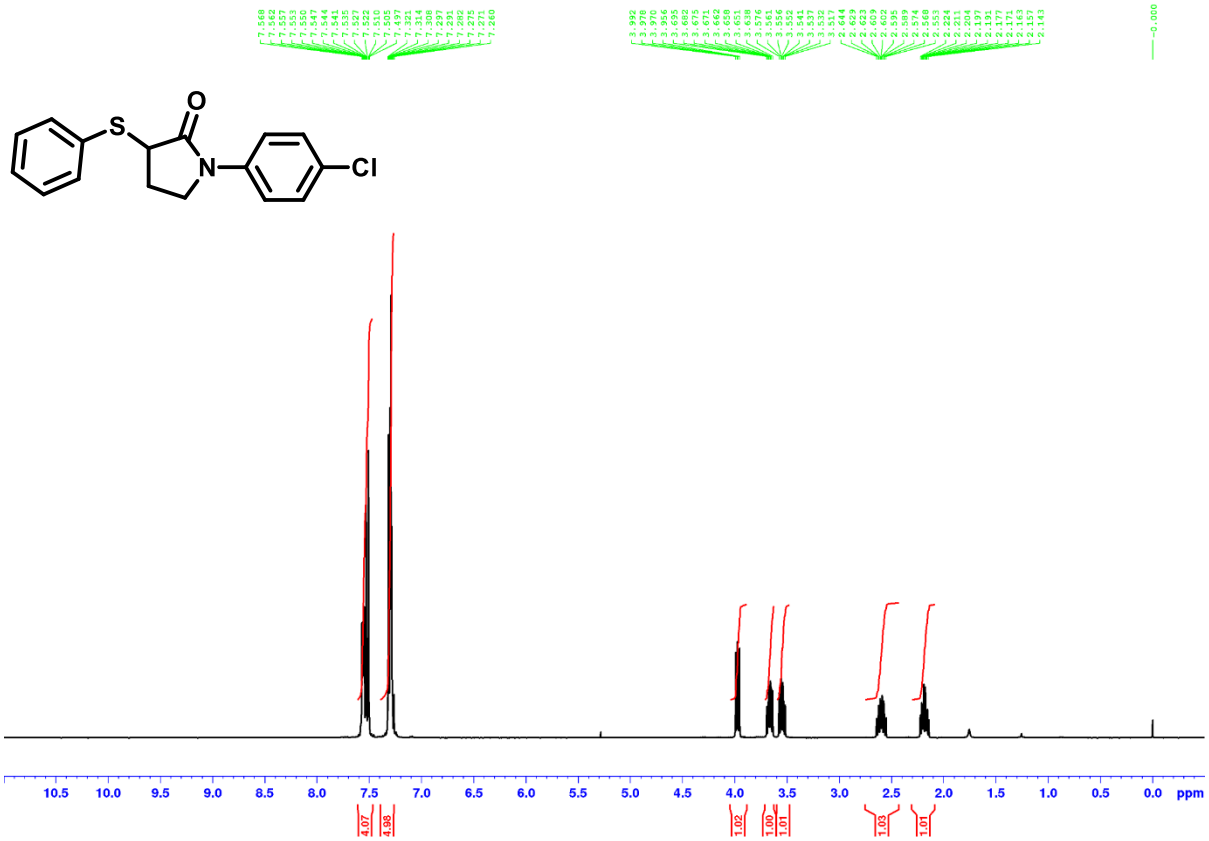


Figure S10: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6**.

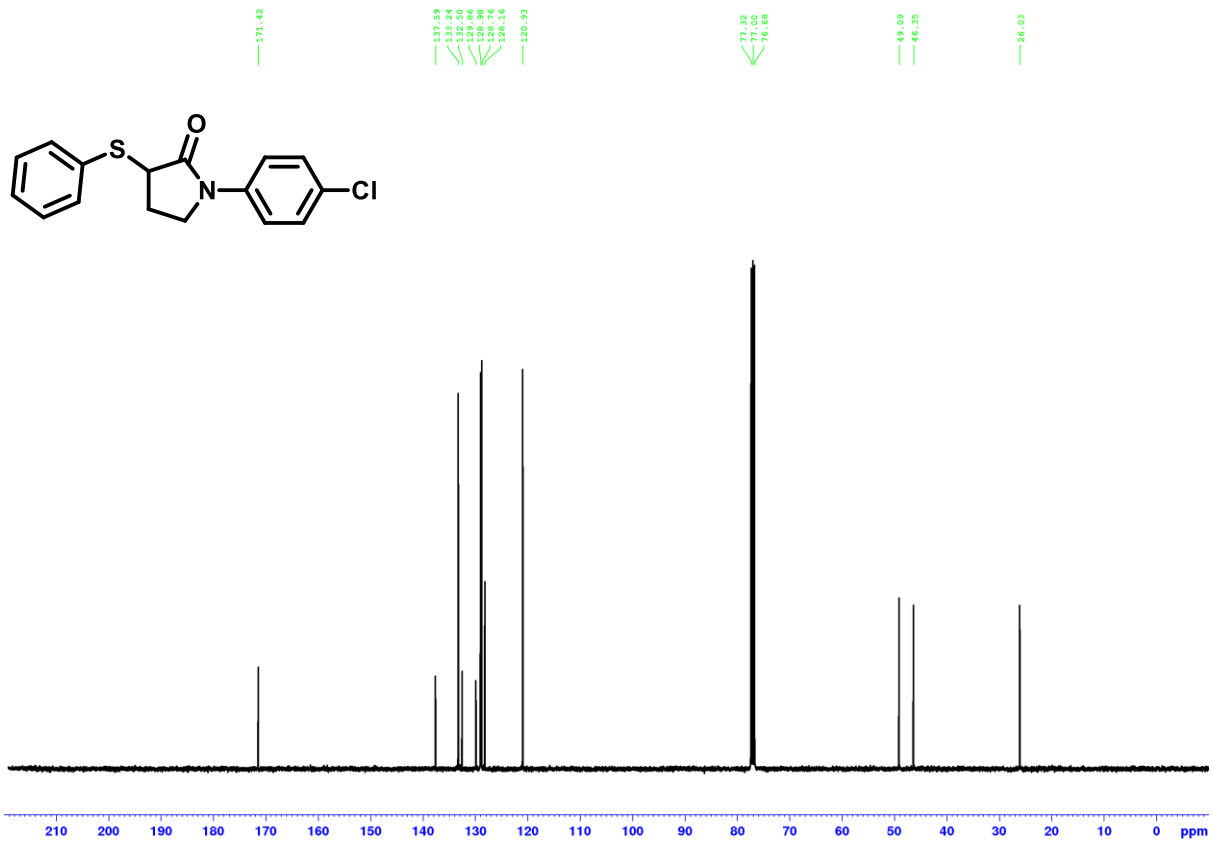


Figure S11: ^{13}C NMR (100.6 MHz, $CDCl_3$) spectrum of **6**.

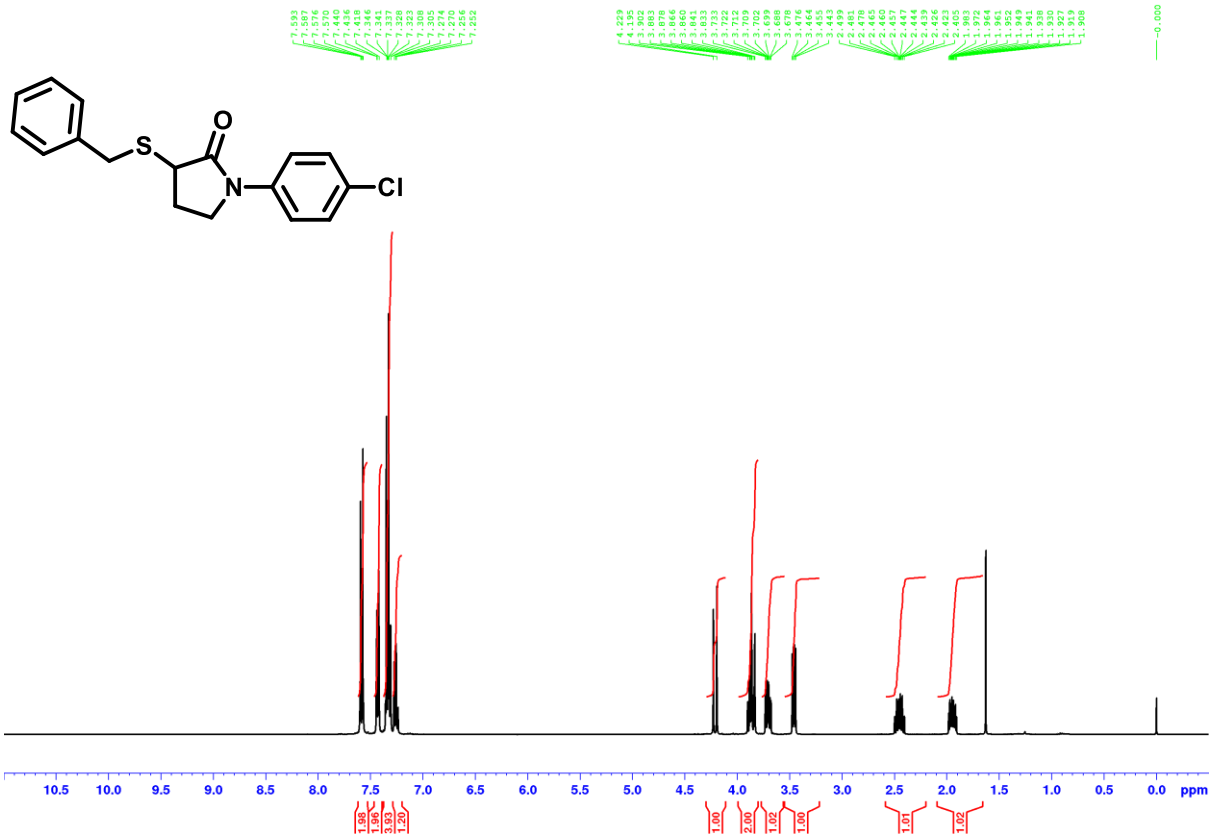


Figure S12: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **7**.

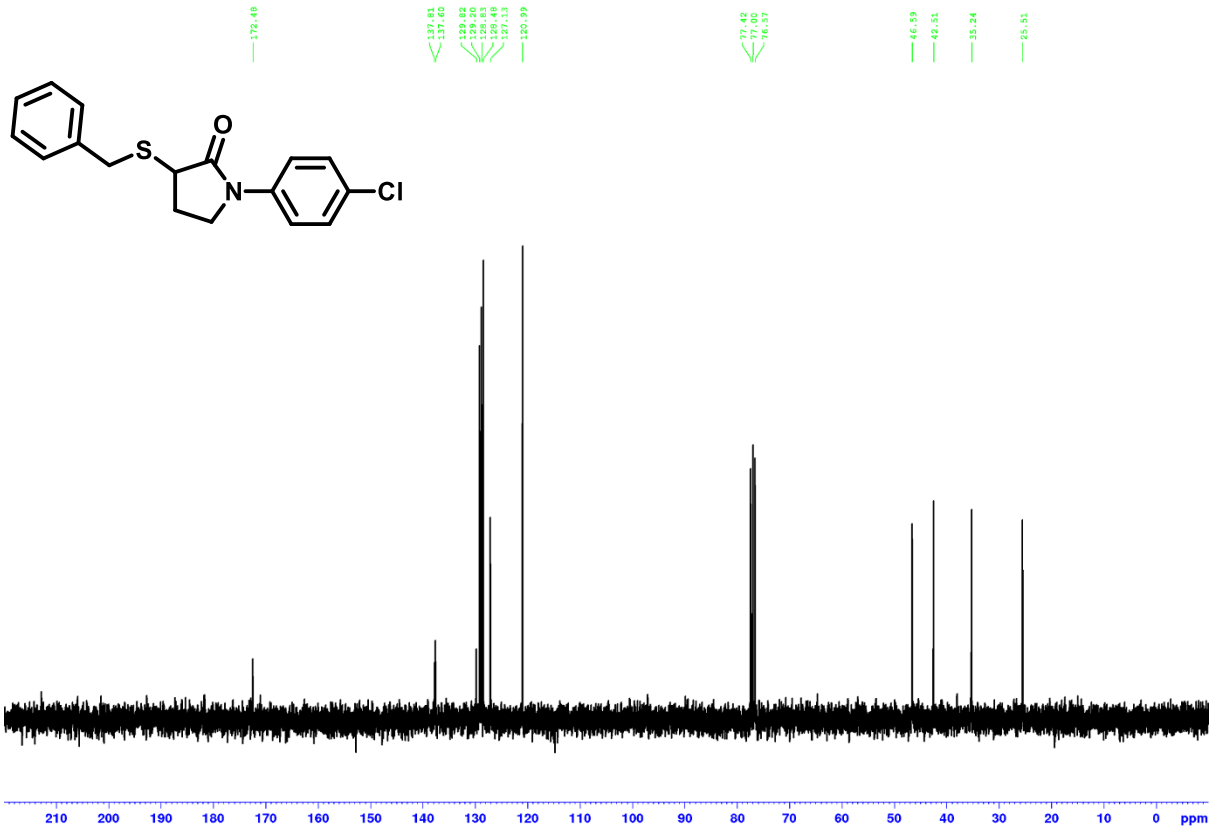


Figure S13: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **7**.

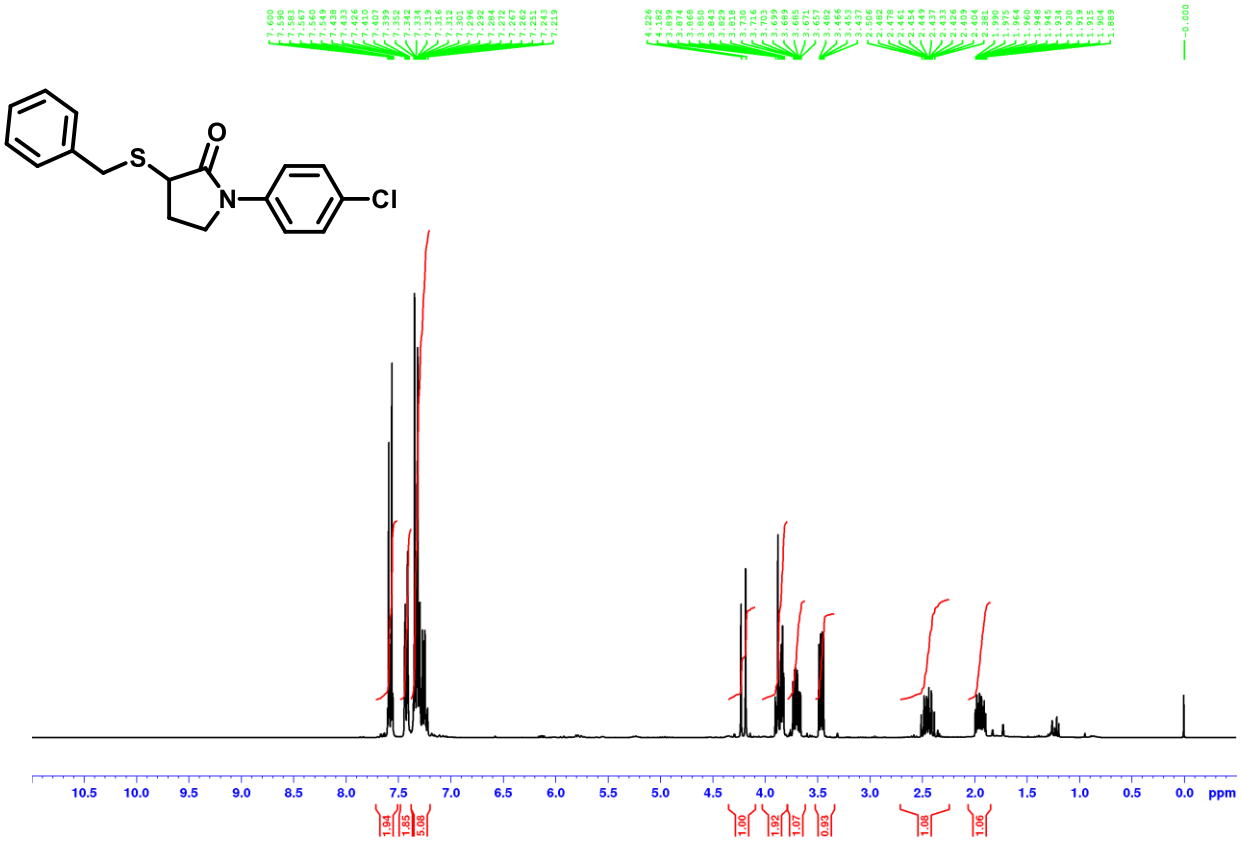


Figure S14: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **7** from telescoped flow process at 0.12 M (Scheme 6).

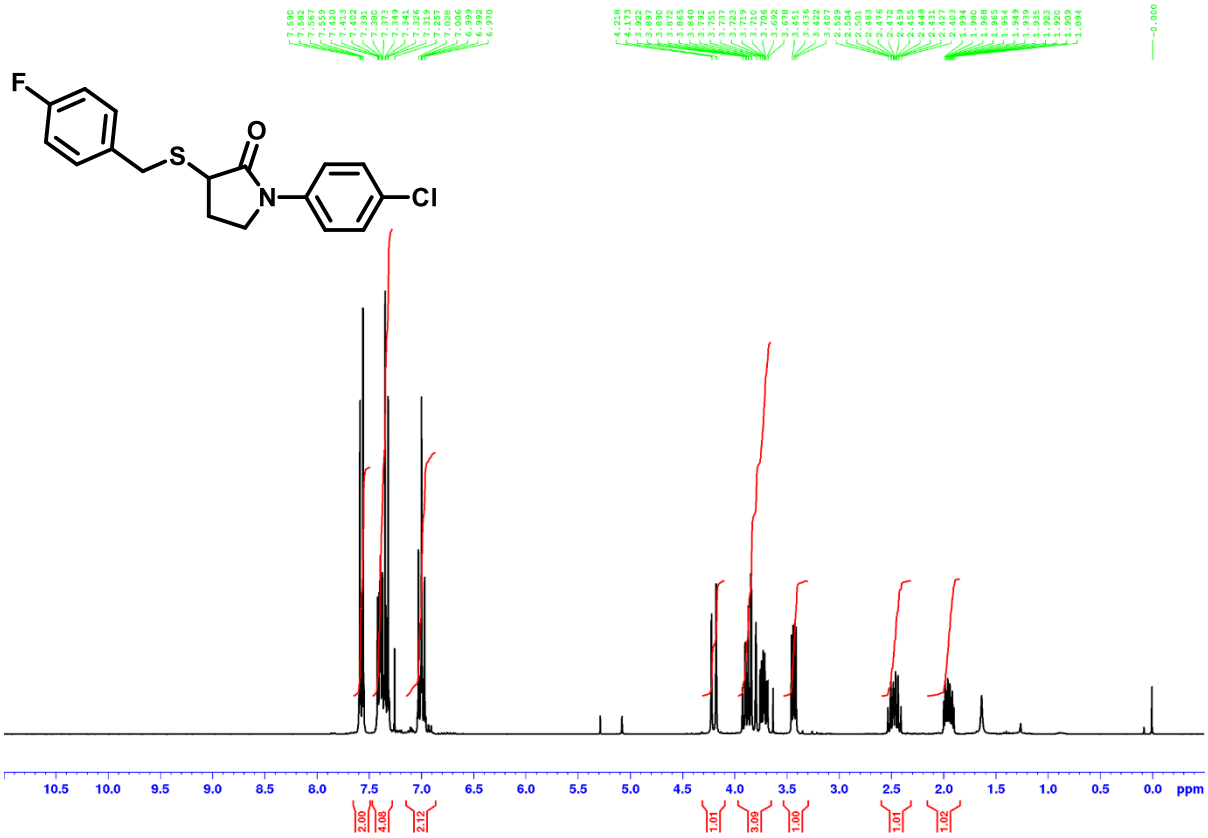


Figure S15: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **8**.

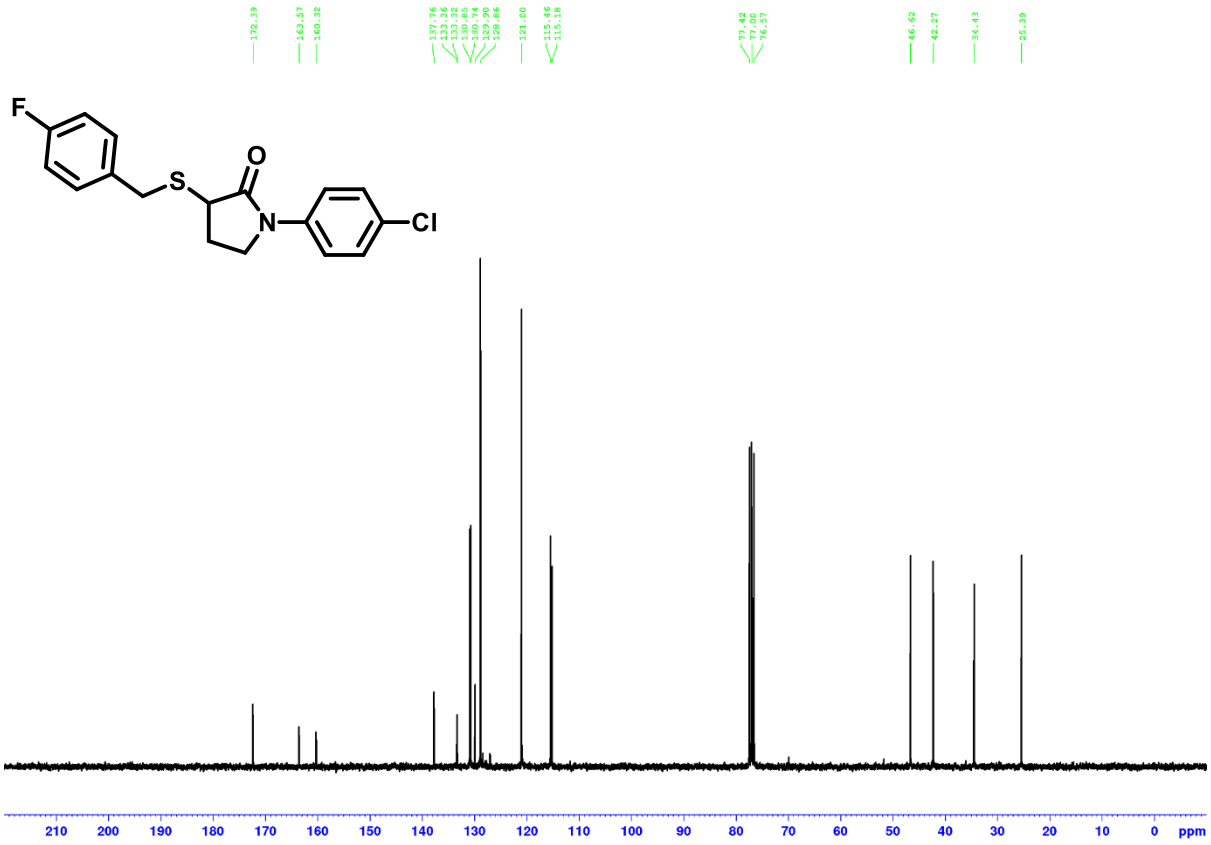


Figure S16: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **8**.

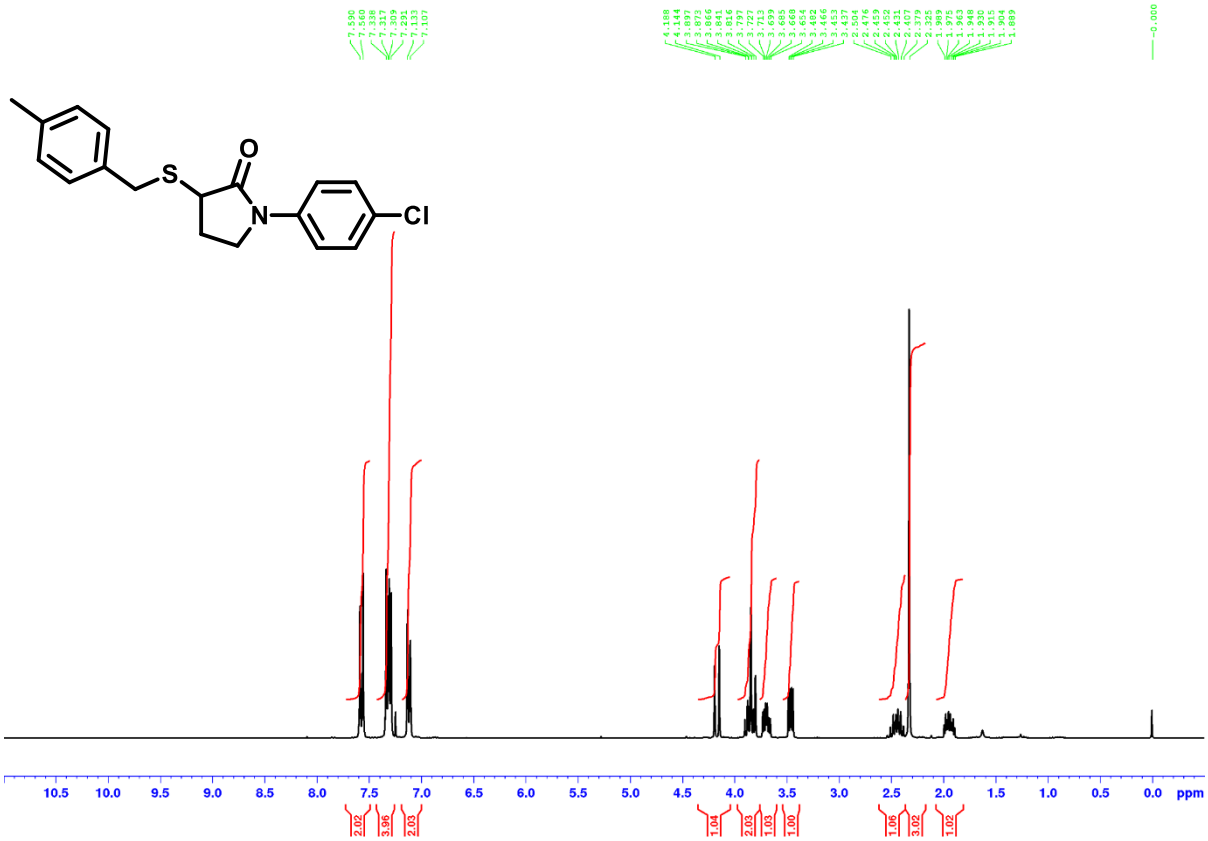


Figure S17: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **9**.

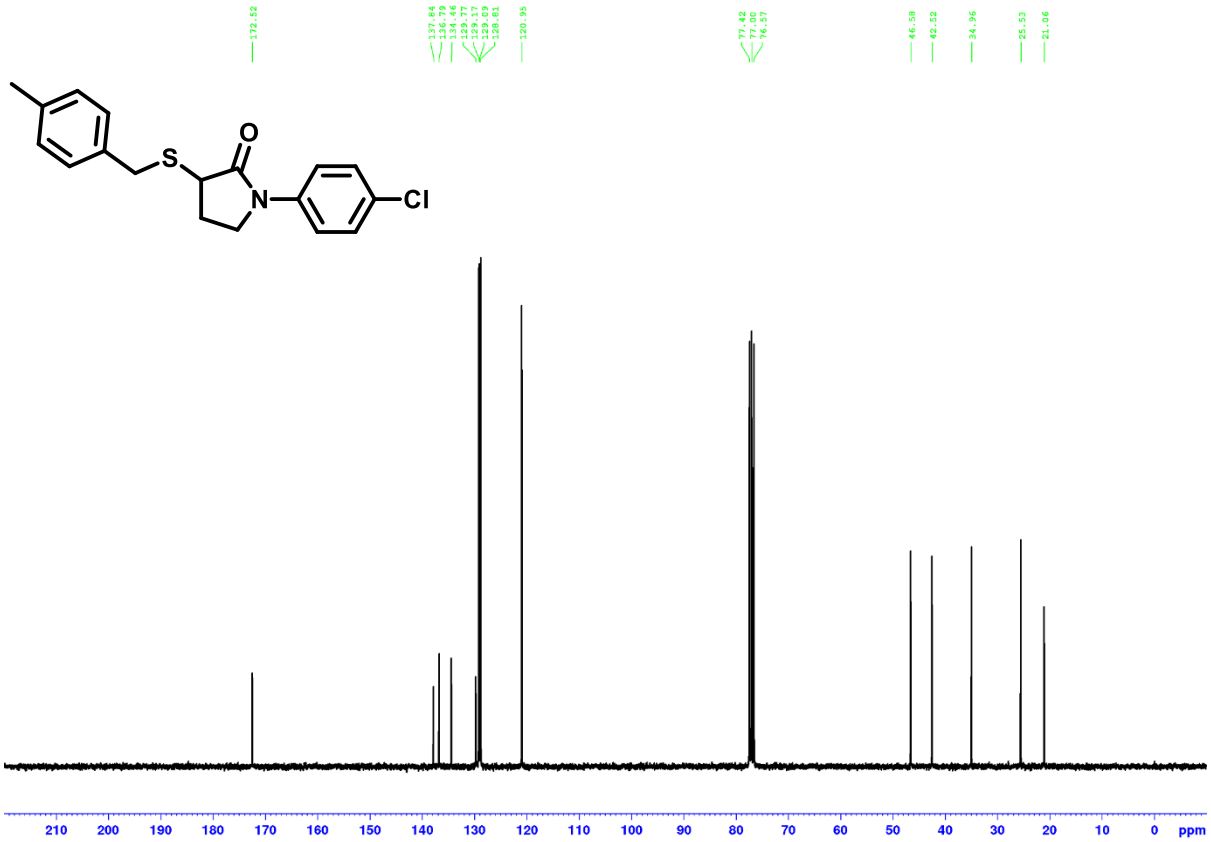


Figure S18: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **9**.

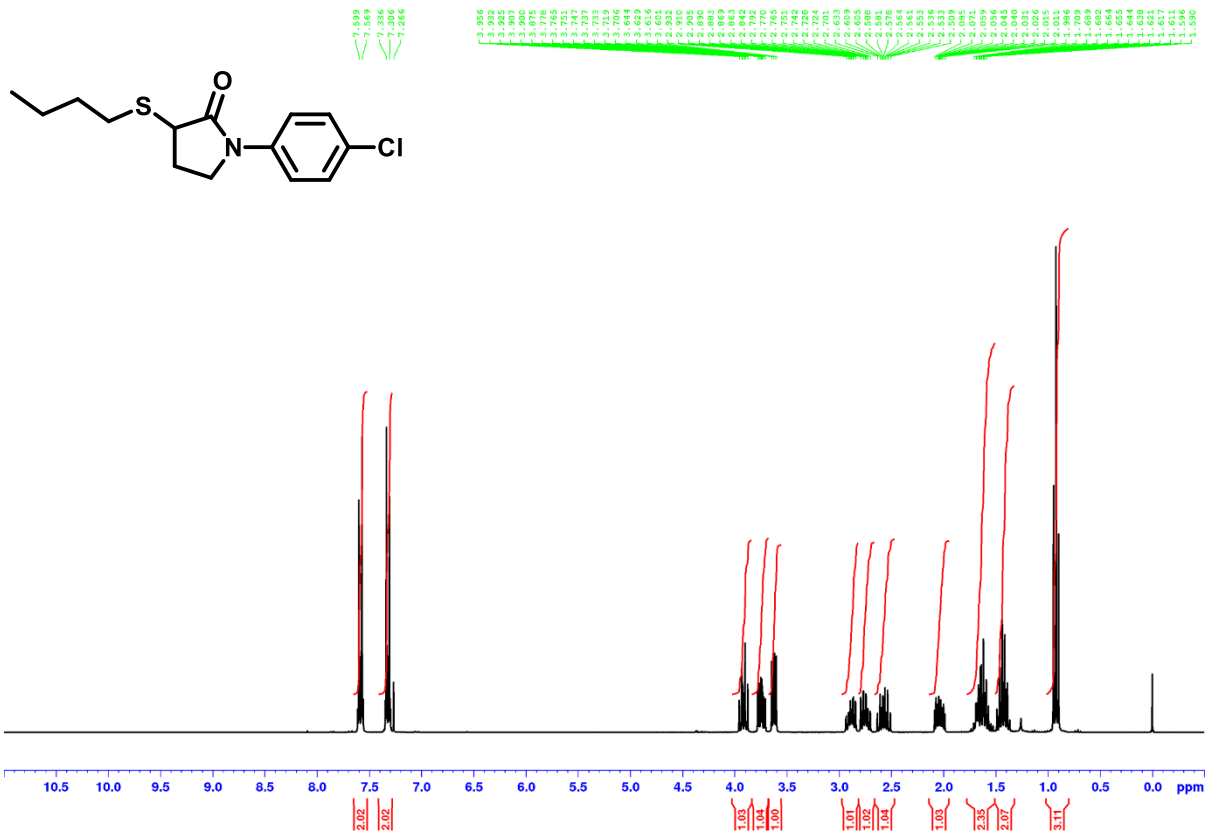


Figure S19: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10**.

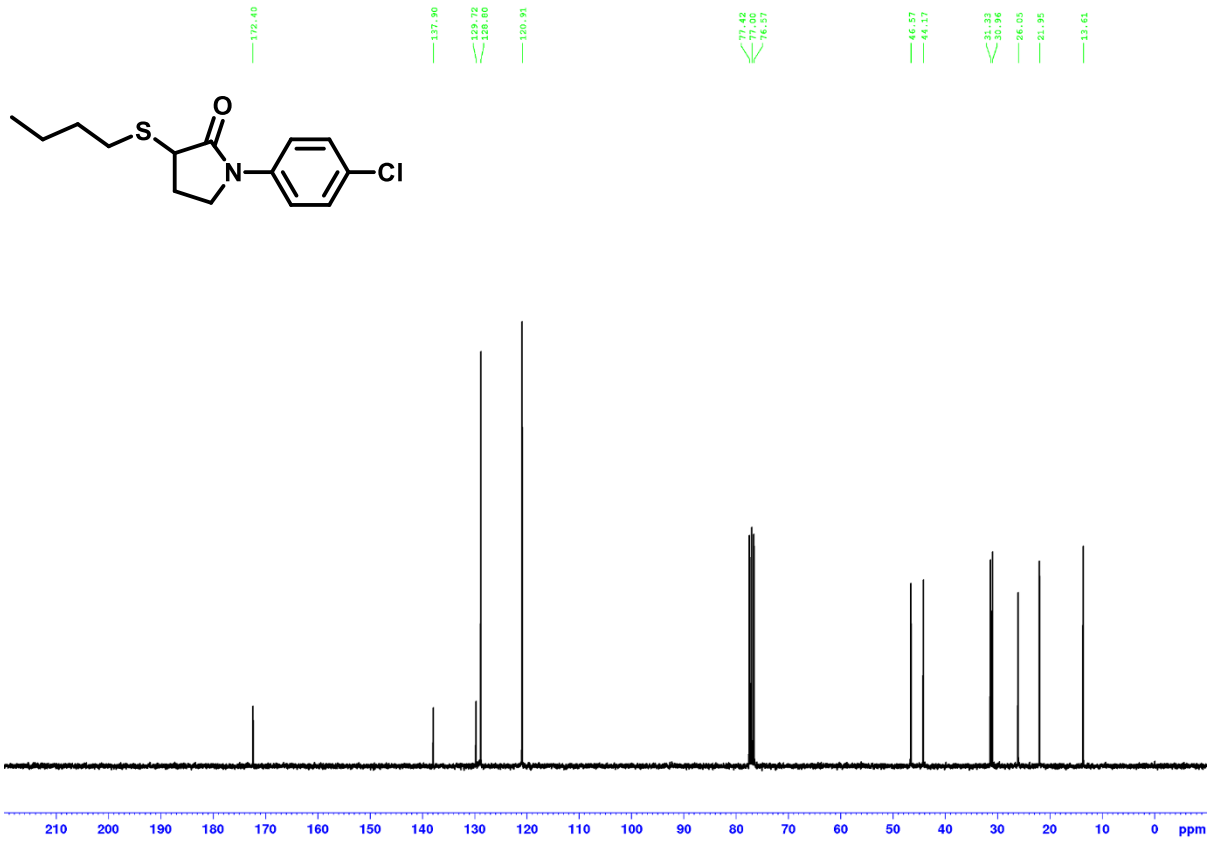


Figure S20: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **10**.

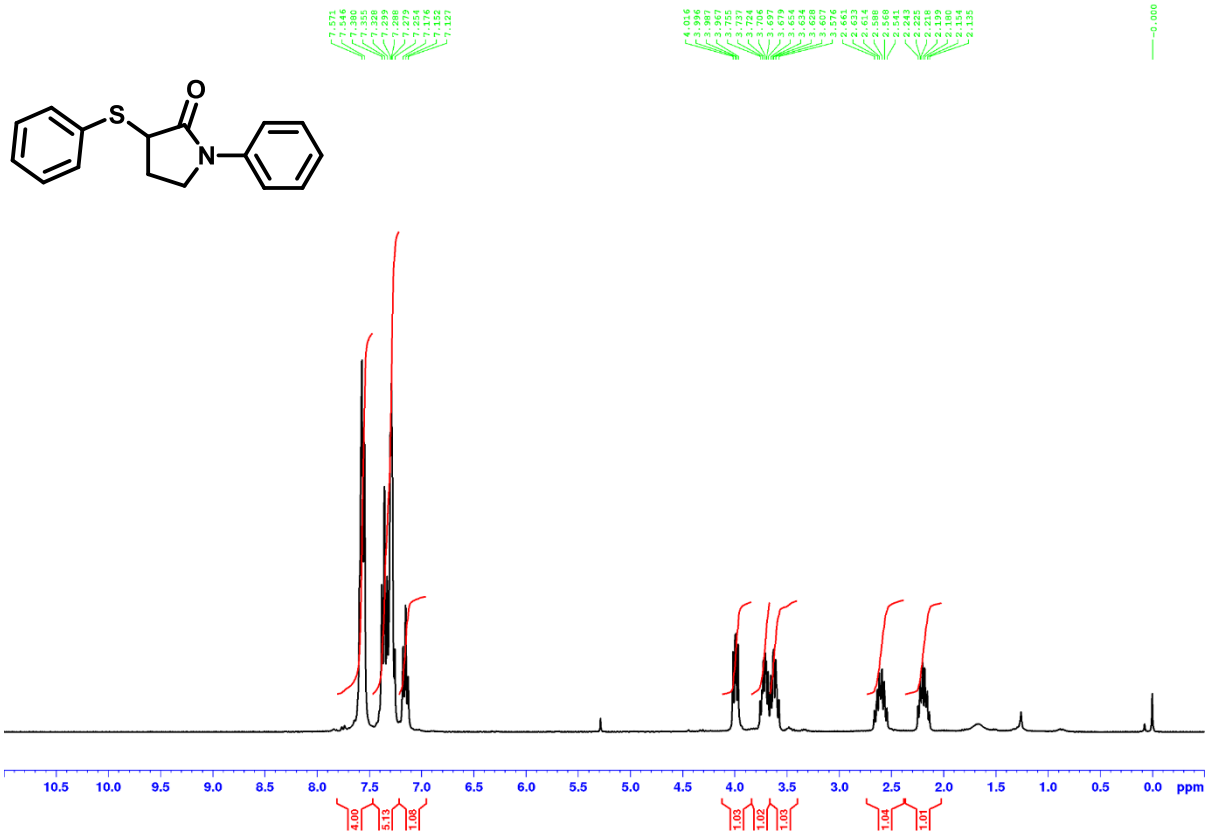


Figure 21: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **11**.[3]

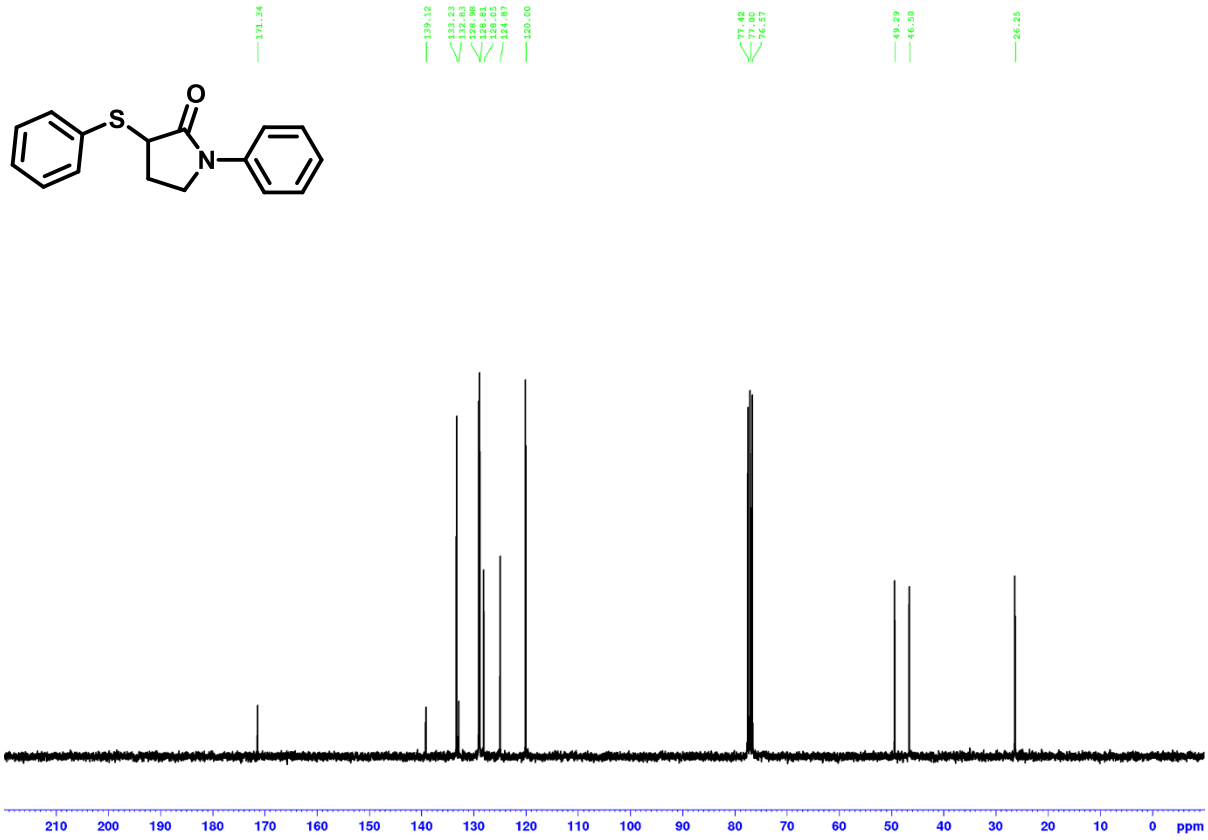


Figure S22: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **11**.[3]

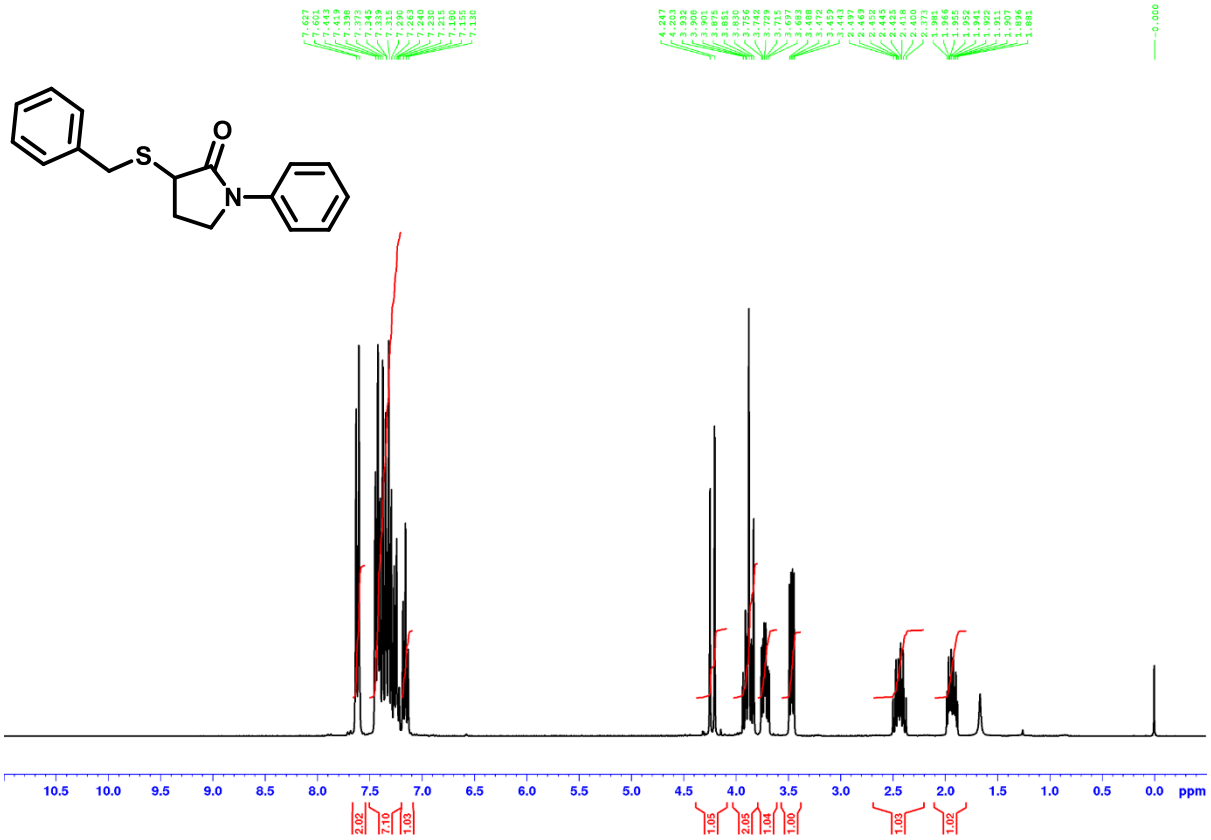


Figure S23: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **12**.[3]

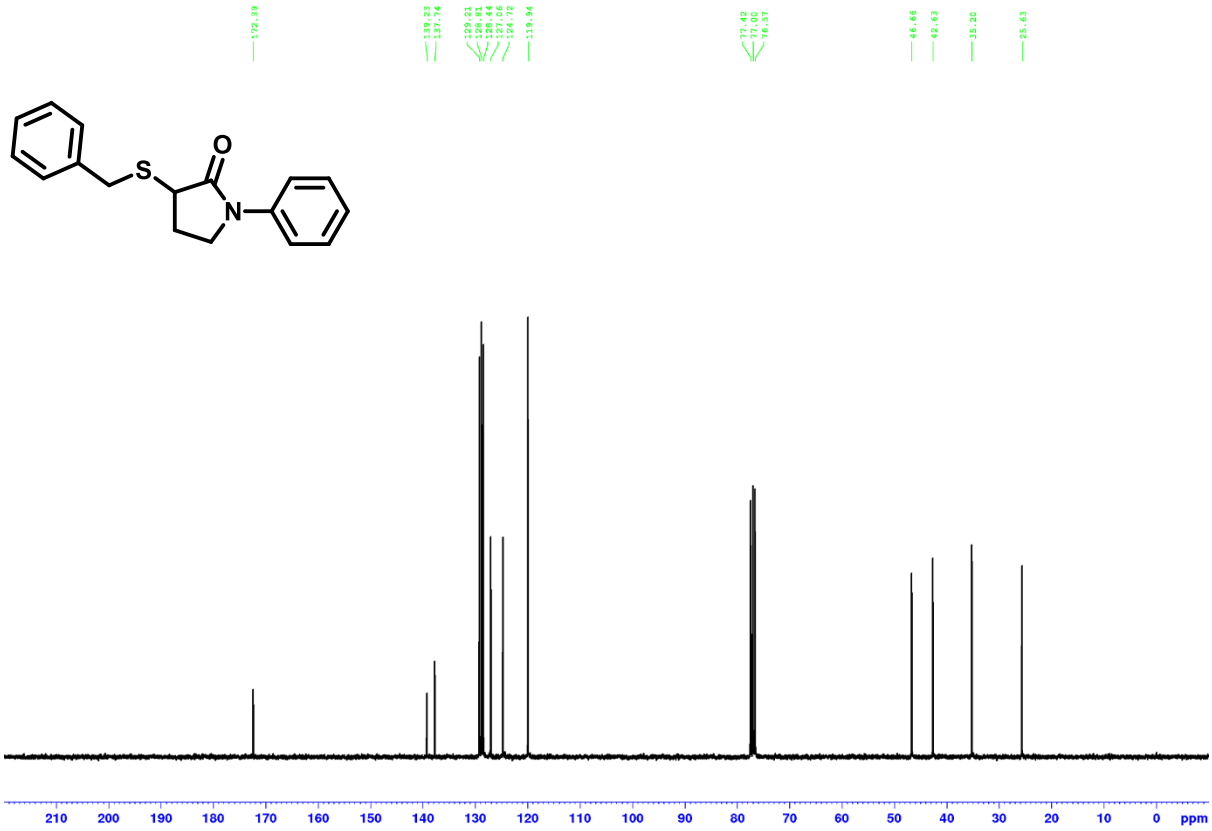


Figure S24: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **12**.[3]

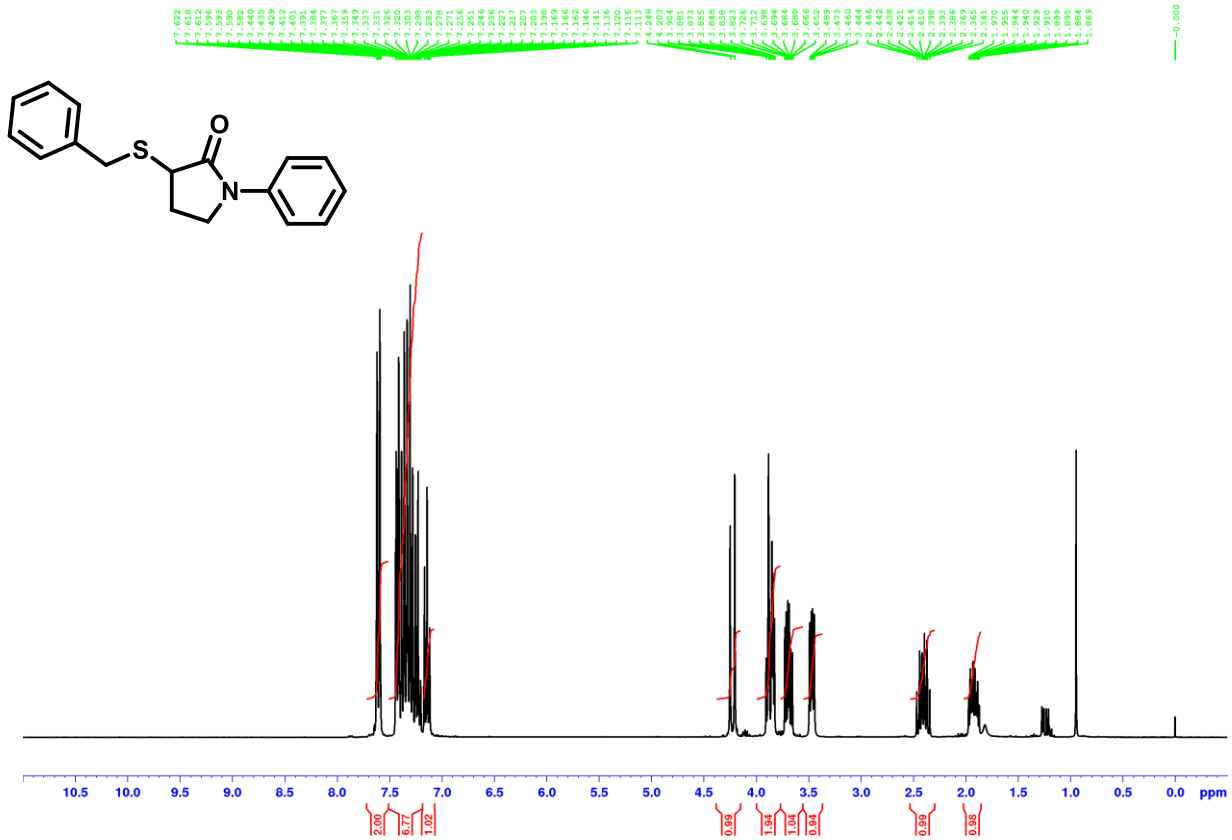


Figure S25: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **12** from telescoped flow process (Scheme 6).[3]

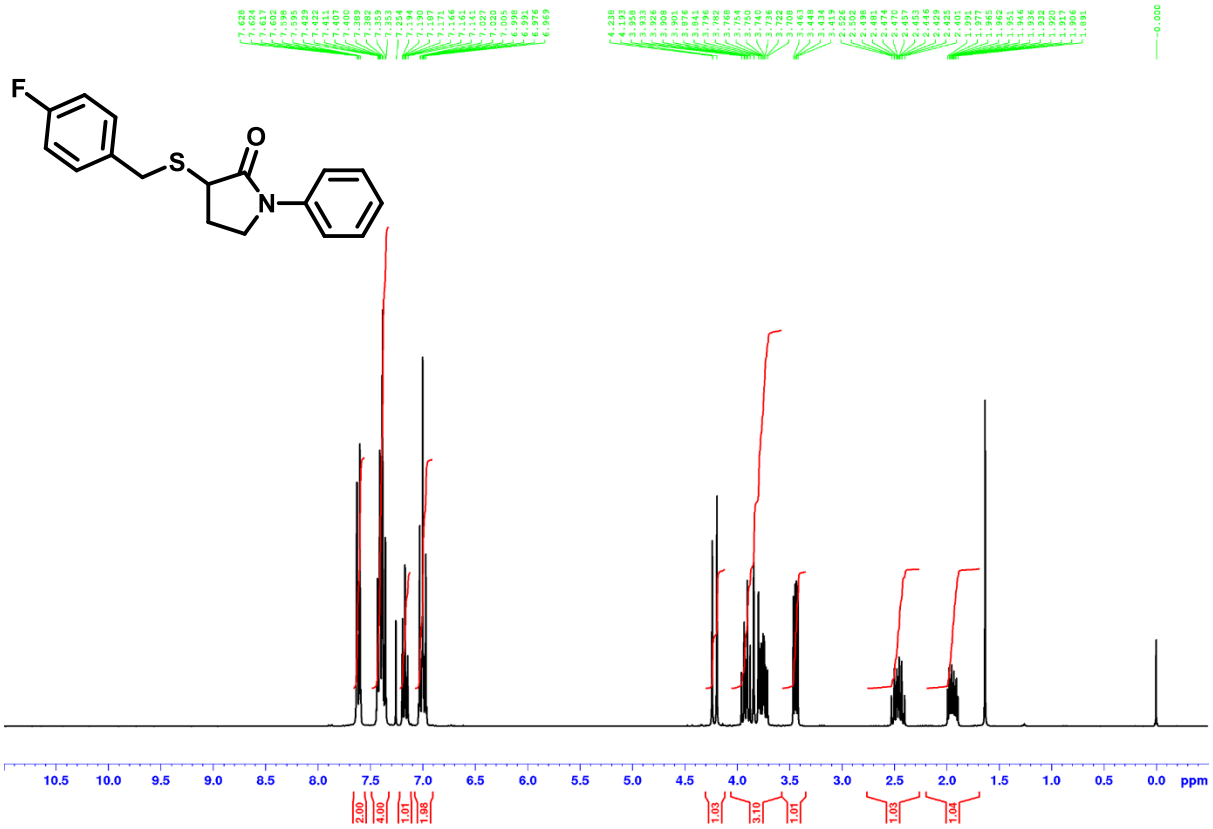


Figure S26: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13**.

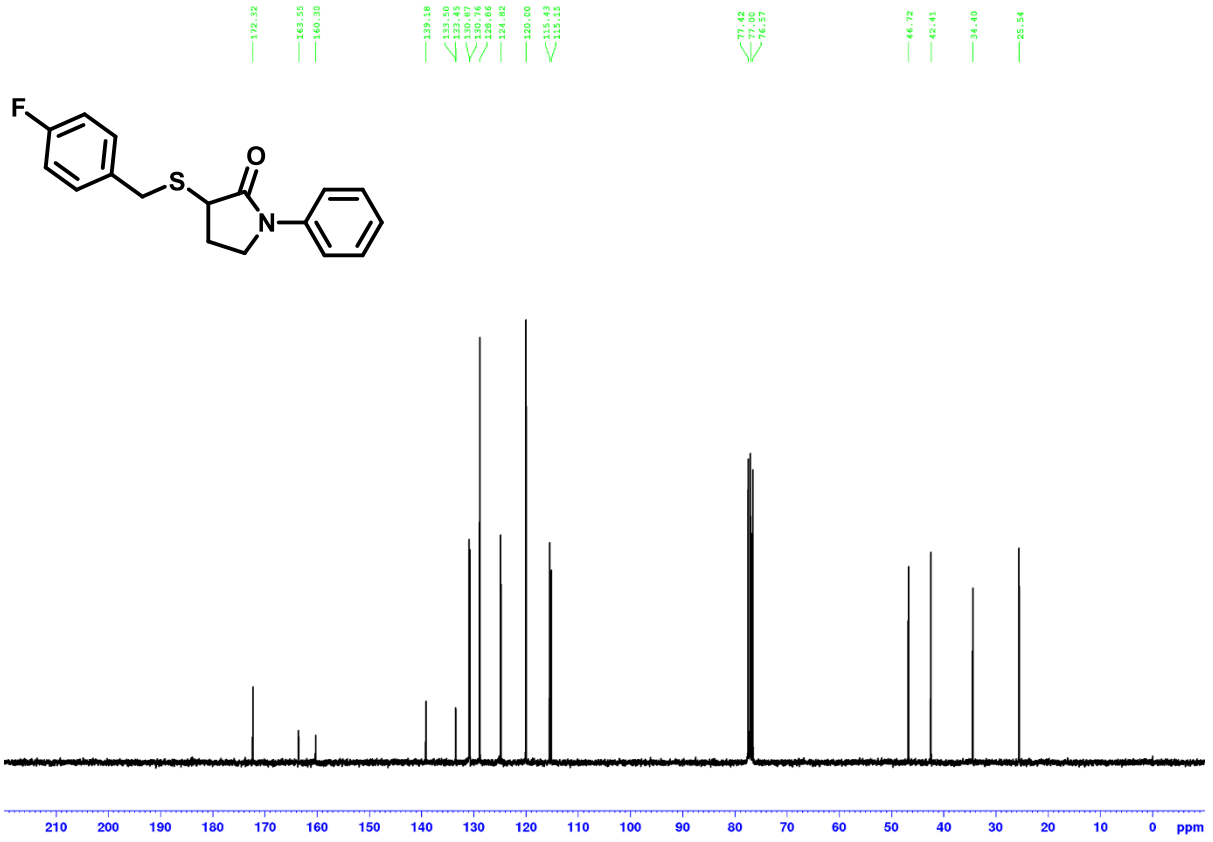


Figure S27: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **13**.

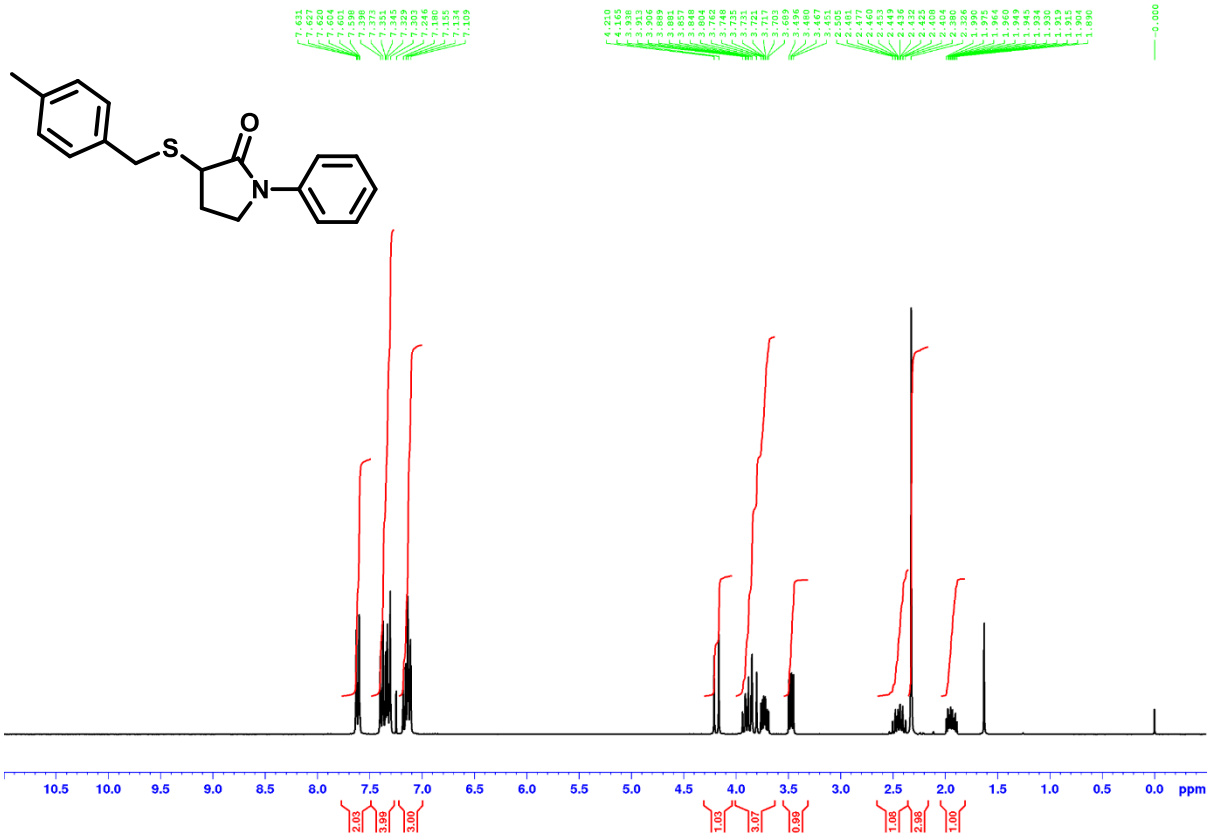


Figure S28: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **14**.

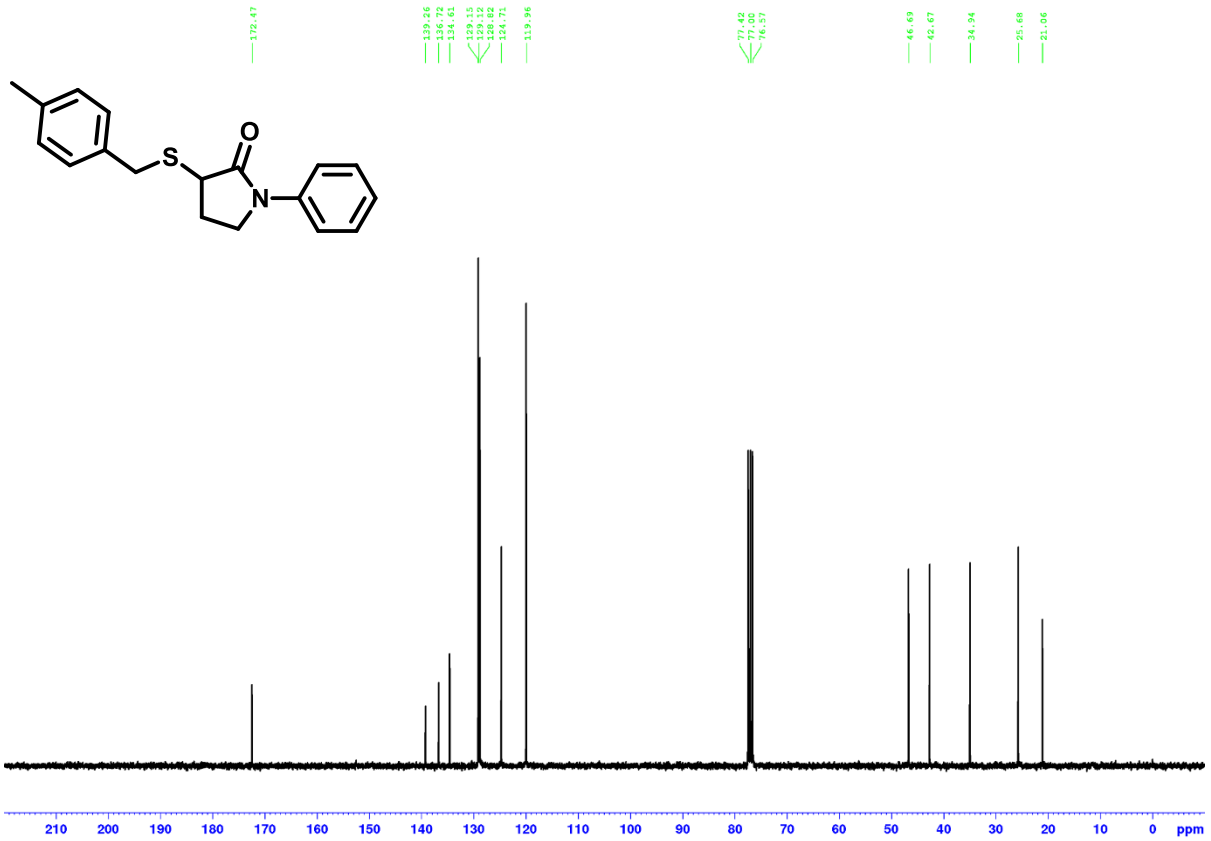


Figure S29: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **14**.

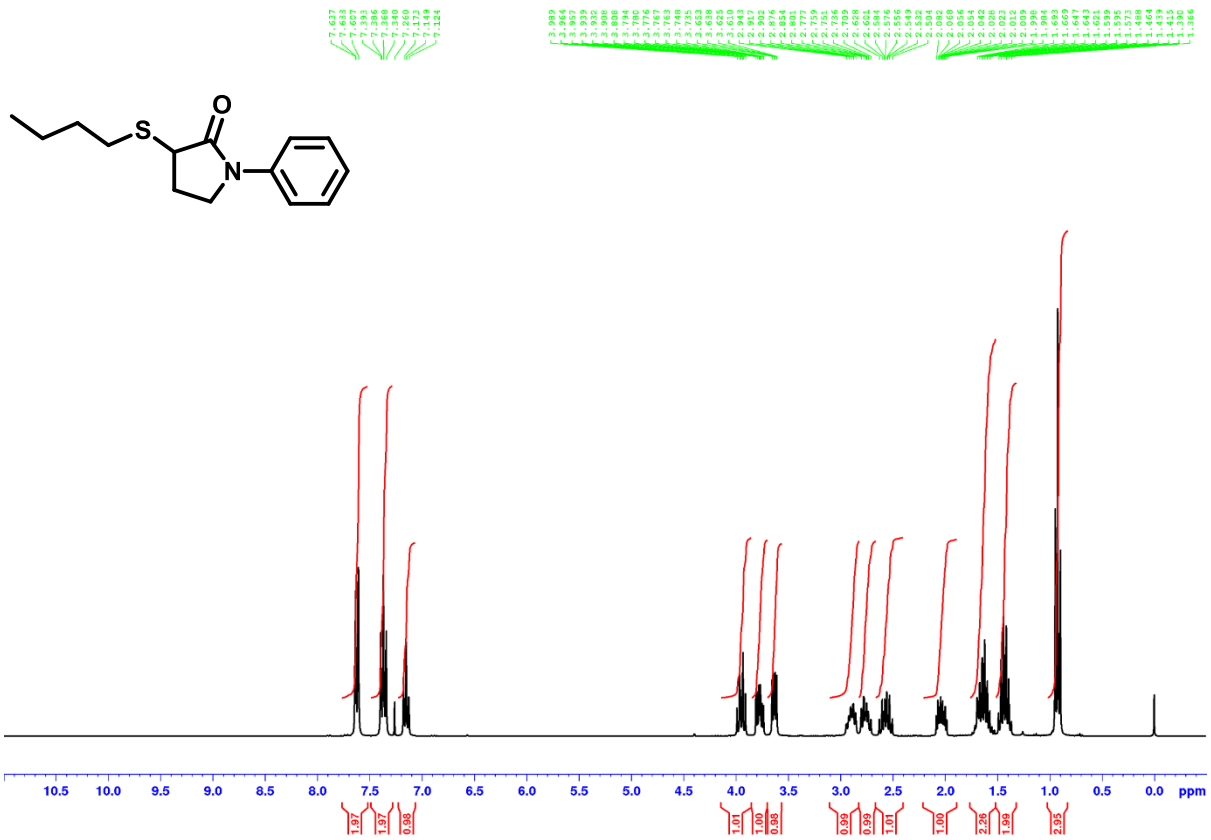


Figure S30: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **15**.

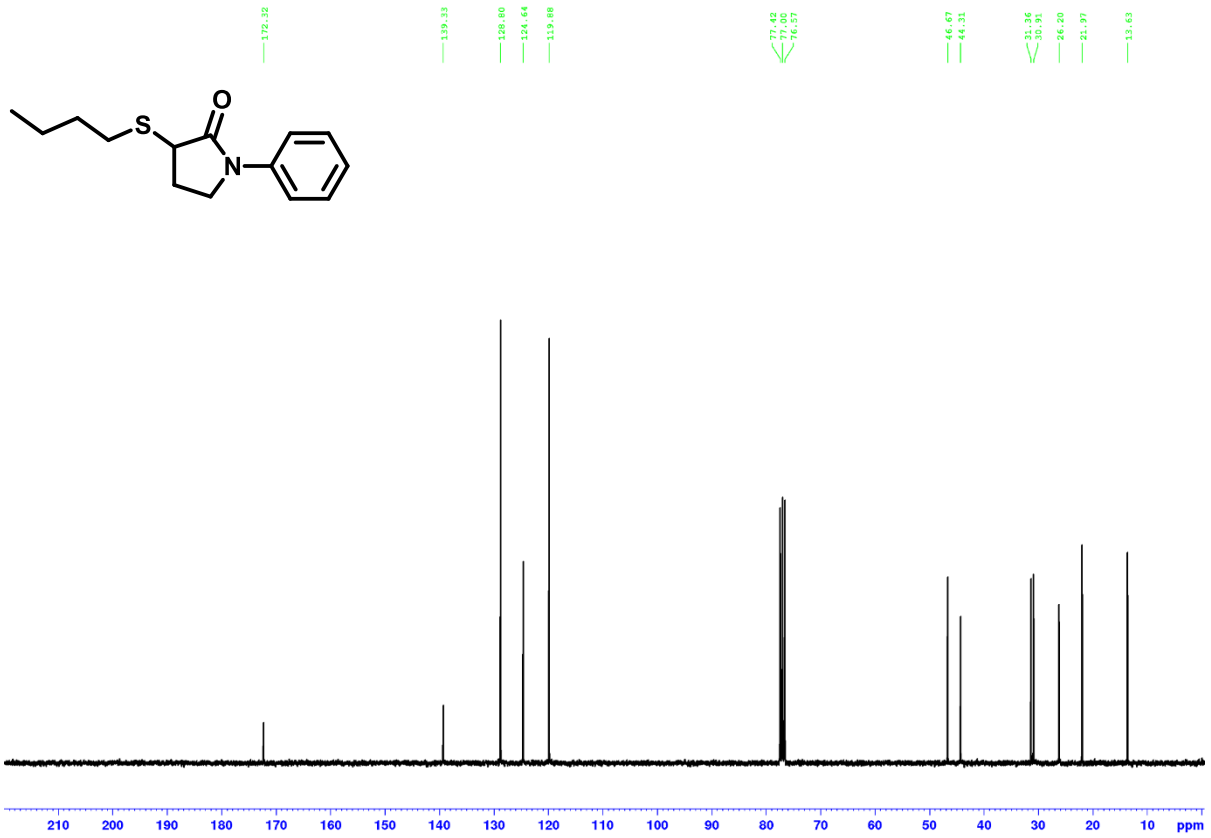


Figure S31: ^{13}C NMR (75.5 MHz, $CDCl_3$) spectrum of **15**.

5. References

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