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Cu(I) mediated Kinugasa Reactions of α,β-unsaturated Nitrones: A Facile, Diastereoselective Route to 3-(Hydroxy/bromo)methyl-1-aryl-4-(-styryl)azetidin-2-ones

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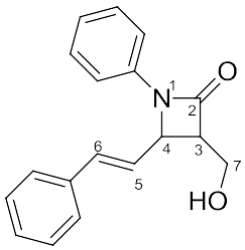
Supplementary Information:

General

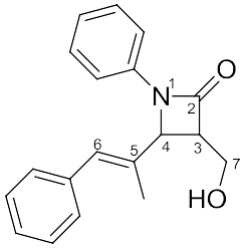
Oxygen- and moisture-sensitive reactions were carried out under nitrogen atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents and solvents (purchased from Aldrich, Merck, Spectrochem, Acros) were used without further purification unless otherwise noted. Analytical thin layer chromatography (tlc) was conducted on Merck Kieselgel 60 F254. Compounds were visualized with both short- and long-wavelength UV light. Column chromatography was performed on silica gel (60-120 mesh). Melting points were determined in capillary tubes using a Mel-Temp apparatus and are not corrected. ^{1}H NMR spectra were obtained with $CDCl_3$ at 300 and 500 MHz, using Bruker spectrometers (residual chloroform referenced to 7.25 ppm). Chemical shifts are reported as δ values. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded with $CDCl_3$ at 75 MHz, using Bruker spectrometers (residual chloroform referenced to 77.0 ppm). IR spectra were recorded on a Shimadzu D-8001 spectrophotometer. Mass spectra were recorded on Shimadzu GCMS-QP-2000 mass spectrometer. Elemental analyses were performed on a Heraus CHNO-Rapid Elemental Analyzer.

EXPERIMENTAL PROCEDURES

General procedure for the synthesis of 3-But-2-enyliden-1,4-diaryl-azetidin-2-one (3): To a solution of propargyl alcohol (10 mmol) in dry DMF, triethyl amine (10 mmmol) was added under Argon. The mixture was stirred for 30 min. at 0^{o}C. Copper (I) iodide (10 mmmol) was added and stirring was continued for 5 min. at room temperature. Solution of individual nitrones (3 mmol) in DMF was added *via* syringe continuously in about 15 mins interval. The reaction mixture was stirred for 24 hrs at *rt* after which it was poured into water and filtered through celite. The celite bed was thoroughly washed with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. Filtration followed by removal of solvent gave a solid mixture. The β-1actams **5** were isolated by column chromatography over Silica gel using hexane- EtOAc (1:1) as eluent. The products were crystallised from CH_2Cl_2/petroleum ether.

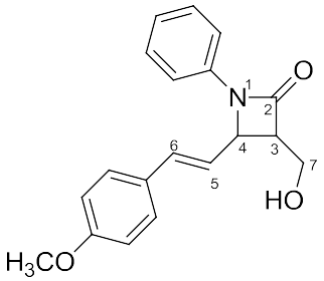


(E)-3-(hydroxymethyl)-1-phenyl-4-styrylazetidin-2-one **5a**: Yield 82%; White solid; m.p. 143-144 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.49 (m, 4H, ArH), 7.28-7.37 (m, 5H, ArH), 7.10 (t, J = 7.5 Hz, 1H, ArH), 6.84 (d, J = 16.0 Hz, 1H, H^6), 6.53 (dd, J = 8.5, 16.0 Hz, 1H, H^5), 4.86 (dd, J = 6.0, 8.5 Hz, 1H, H^4), 4.09 (dd, J = 7.0, 12.0 Hz, 1H, H^7), 4.00 (dd, J = 4.5, 12.0 Hz, 1H, H^7), 3.76 (ddd, J = 4.5, 6.0, 12.5 Hz, 1H, H^3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 56.6, 56.9, 57.9, 116.9, 124.0, 124.3, 126.7, 128.4, 128.7, 129.1, 135.6, 135.8, 138.0, 165.4. MS *m/z* 280 (M+1); Anal. Calc. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01; found: C, 77.44; H, 6.19; N, 4.98.

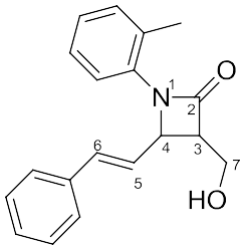


(E)-3-(hydroxymethyl)-1-phenyl-4-(1-phenylprop-1-en-2-yl)azetidin-2-one **5b**: Yield 75%; White solid; m.p. 153-155 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.46 (m, 9H, ArH), 7.10 (m, 1H,

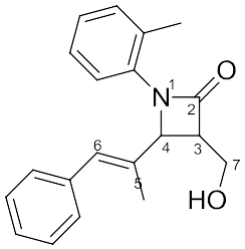
ArH), 6.83 (s, 1H, H^6), 4.86 (dd, *J* = 6.0, 8.5 Hz, 1H, H^4), 3.95-4.12 (m, 2H, H^7), 3.73-3.78 (m, 1H, H^3), 2.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 15.5, 56.7, 56.9, 57.9, 116.8, 124.2, 124.3, 126.7, 128.1, 128.5, 129.1, 135.5, 136.7, 138.6, 164.7. MS *m/z* 294 (M+1); Anal. Calc. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; found: C, 77.86; H, 6.57; N, 4.71.



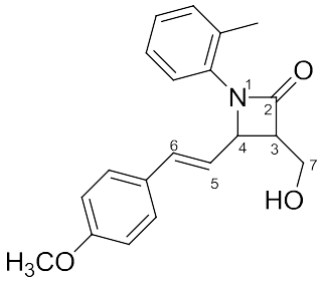
(E)-3-(hydroxymethyl)-4-(4-methoxystyryl)-1-phenylazetidin-2-one **5c**: Yield 75%; White solid; m.p. 197-199 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.51 (m, 8H, ArH), 7.09 (m, 1H, ArH), 6.90 (d, *J* = 16 Hz, 1H, H^6), 6.59 (dd, *J* = 8.5, 16.0 Hz, 1H, H^5), 4.91 (dd, *J* = 6.0, 8.5 Hz, 1H, H^4), 4.14 (dd, *J* = 7.0, 12.0 Hz, 1H, H^7), 4.07 (dd, *J* = 4.5, 12.0 Hz, 1H, H^7), 3.87 (s, 3H, -OCH_3); 3.75 (ddd, *J* = 4.5, 6.0, 12.5 Hz, 1H, H^3),; ^{13}C NMR ($CDCl_3$, 75Hz): δ 51.5, 56.8, 57.3, 58.1, 116.2, 124.2, 124.7, 125.0, 127.9, 128.3, 129.1, 137.3, 137.8, 138.9, 166.8. MS *m/z* 310 (M+1); Anal. Calc. for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53; found: C, 73.81; H, 6.28; N, 4.45.



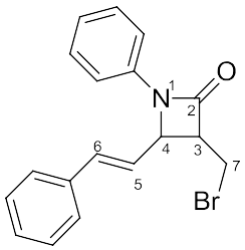
(E)-3-(hydroxymethyl)-4-styryl-1-(o-tolyl)azetidin-2-one **5d**: Yield 70%; White solid; m.p. 170-171 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.79 (m, 3H, ArH), 7.28-7.45 (m, 6H, ArH), 6.92 (d, *J* = 15.5 Hz, 1H, H^6), 6.53 (dd, *J* = 8.5, 16.0 Hz, 1H, H^5), 4.86 (dd, *J* = 6.0, 8.5 Hz, 1H, H^4), 4.01-4.10 (m, 2H, H^7), 3.70-3.82 (m, 1H, H^3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 18.8, 54.9, 55.5, 56.8, 118.9, 123.0, 125.3, 126.5, 127.7, 128.4, 128.7, 129.1, 132.3, 136.7, 136.9, 139.1, 165.9. MS *m/z* 294 (M+1); Anal. Calc. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; found: C, 77.82; H, 6.60; N, 4.71.



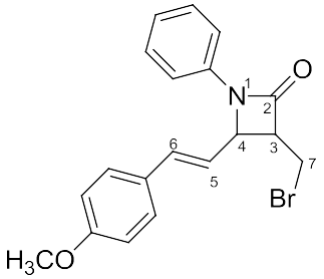
(E)-3-(hydroxymethyl)-4-(1-phenylprop-1-en-2-yl)-1-(o-tolyl)azetidin-2-one **5e**: Yield 70%; White solid; m.p. 179-181 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.52 (m, 5H, ArH), 7.28-7.33 (m, 4H, ArH), 6.98 (s, 1H, H^6), 4.86 (d, J = 6.0 Hz, 1H, H^4), 3.09-4.07 (m, 2H, H^7), 3.75 (m, 1H, H^3), 2.41 (s, 3H, CH_3), 2.11 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 15.7, 18.9, 56.7, 57.2, 57.8, 116.9, 124.0, 124.3, 125.5, 126.7, 128.4, 128.7, 129.1, 130.8, 133.9, 134.5, 136.9, 164.0. MS *m/z* 308 (M+1); Anal. Calc. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56; found: C, 78.19; H, 6.95; N, 4.52.



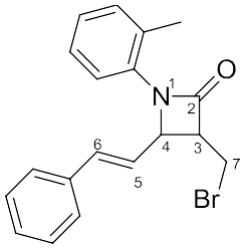
(E)-3-(hydroxymethyl)-4-(4-methoxystyryl)-1-(o-tolyl)azetidin-2-one **5f**: Yield 70%; White solid; m.p. 215-217 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.51 (m, 4H, ArH), 7.16-7.34 (m, 5H, ArH), 6.90 (d, J = 15.5 Hz, 1H, H^6), 6.59 (dd, J = 8.0, 16.0 Hz, 1H, H^5), 4.91 (dd, J = 6.0, 8.5 Hz, 1H, H^4), 4.07-4.13 (m, 2H, H^7), 3.85 (s, 3H, -OCH_3); 3.80 (m, 1H, H^3), 2.41 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 18.7, 51.7, 57.3, 58.1, 58.9, 116.8, 124.1, 124.7, 125.3, 127.9, 128.3, 129.2, 134.7, 135.1, 137.3, 137.7, 138.9, 167.1. MS *m/z* 324 (M+1); Anal. Calc. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33; found: C, 74.36; H, 6.59; N, 4.28.



(E)-3-(bromomethyl)-1-phenyl-4-styrylazetidin-2-one **5g**: Yield 45%; White solid; m.p. 185-188 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.51 (m, 10H, ArH), 7.00 (d, J = 16.0 Hz, 1H, H^6), 6.77 (dd, J = 8.5, 16.0 Hz, 1H, H^5), 4.86 (dd, J = 6.0, 8.5 Hz, 1H, H^4), 3.80-3.92 (m, 2H, H^7), 3.72-3.76 (m, 1H, H^3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 30.4, 53.1, 54.5, 116.7, 123.7, 125.1, 126.8, 128.5, 128.7, 129.1, 135.2, 135.8, 137.0, 161.6. MS *m/z* 342 (M+1); Anal. Calc. for $C_{18}H_{16}BrNO$: C, 63.17; H, 4.71; N, 4.09; found: C, 63.25; H, 4.74; N, 4.01.

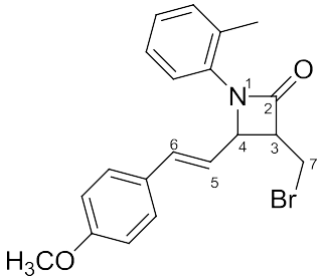


(E)-3-(bromomethyl)-4-(4-methoxystyryl)-1-phenylazetidin-2-one **5h**: Yield 50%; White solid; m.p. 220-222 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.50 (m, 4H, ArH), 7.28-7.33 (m, 5H, ArH), 7.15 (m, 1H, ArH), 6.88 (d, J = 16.0 Hz, 1H, H^6), 6.69 (dd, J = 8.0, 16.0 Hz, 1H, H^5), 4.86 (dd, J = 6.0, 8.5 Hz, 1H, H^4), 3.80-3.92 (m, 5H, OCH_3 + H^7), 3.73 (m, 1H, H^3), ; ^{13}C NMR ($CDCl_3$, 75Hz): δ 31.0, 52.7, 53.9, 55.1, 117.5, 124.2, 125.0, 127.3, 128.9, 129.6, 129.8, 134.9, 135.5, 138.3, 162.4. MS *m/z* 372 (M+1); Anal. Calc. for $C_{19}H_{18}BrNO_2$: C, 61.30; H, 4.87; N, 3.76; found: C, 61.34; H, 4.96; N, 3.71.



(E)-3-(bromomethyl)-4-styryl-1-(o-tolyl)azetidin-2-one **5i**: Yield 40%; White solid; m.p. 198-199 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.44 (m, 4H, ArH), 7.16-7.35 (m, 5H, ArH), 6.85 (d, J = 16.0 Hz, 1H, H^6), 6.70 (dd, J = 8.5, 16.0 Hz, 1H, H^5), 4.85 (dd, J = 6.5, 8.5 Hz, 1H, H^4), 3.78-3.93 (m, 2H, H^7), 3.71 (m, 1H, H^3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 19.0, 30.4, 54.0, 55.9, 118.1, 123.5, 124.5, 126.1, 126.7, 127.3, 128.0, 129.3, 131.8, 133.6, 134.3, 138.9,

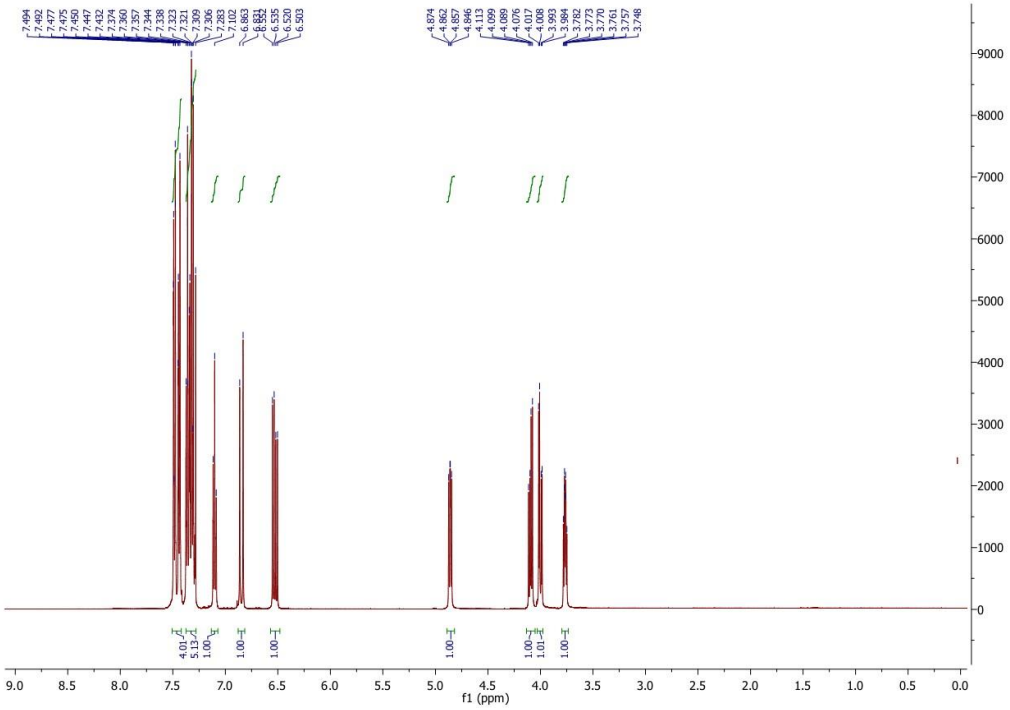
161.1. MS *m/z* 356 (M+1); Anal. Calc. for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93; found: C, 64.11; H, 5.18; N, 3.88.



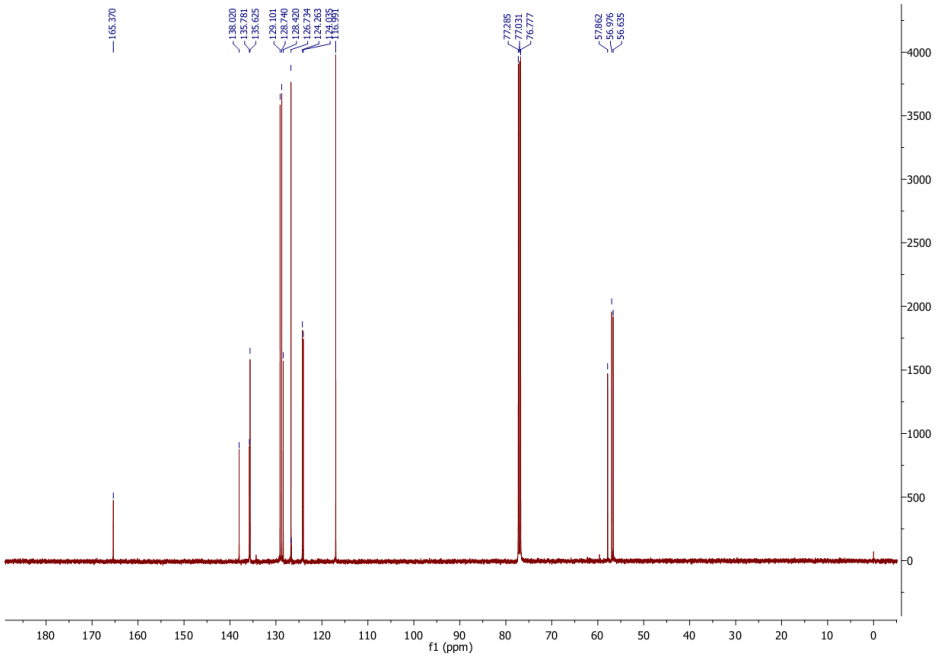
(E)-3-(bromomethyl)-4-(4-methoxystyryl)-1-(o-tolyl)azetidin-2-one **5j**: Yield 42%; White solid; m.p. 241-242 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.50 (m, 4H, ArH), 7.18-7.33 (m, 4H, ArH), 6.92 (d, J = 15.5 Hz, 1H, H^6), 6.64 (dd, J = 8.5, 16 Hz, 1H, H^5), 4.83 (m, 1H, H^4), 3.80-3.96 (m, 5H, OCH_3 + H^7), 3.76 (m, 1H, H^3), 2.39 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75Hz): δ 18.3, 30.9, 52.5, 57.1, 57.5, 116.4, 124.1, 124.5, 125.6, 126.9, 128.3, 128.7, 129.3, 130.8, 135.4, 135.7, 138.9, 164.9. MS *m/z* 386 (M+1); Anal. Calc. for $C_{20}H_{20}BrNO_2$: C, 62.19; H, 5.22; N, 3.63; found: C, 62.23; H, 5.27; N, 3.54.

^{1}H and ^{13}C NMR spectra of representative compounds:

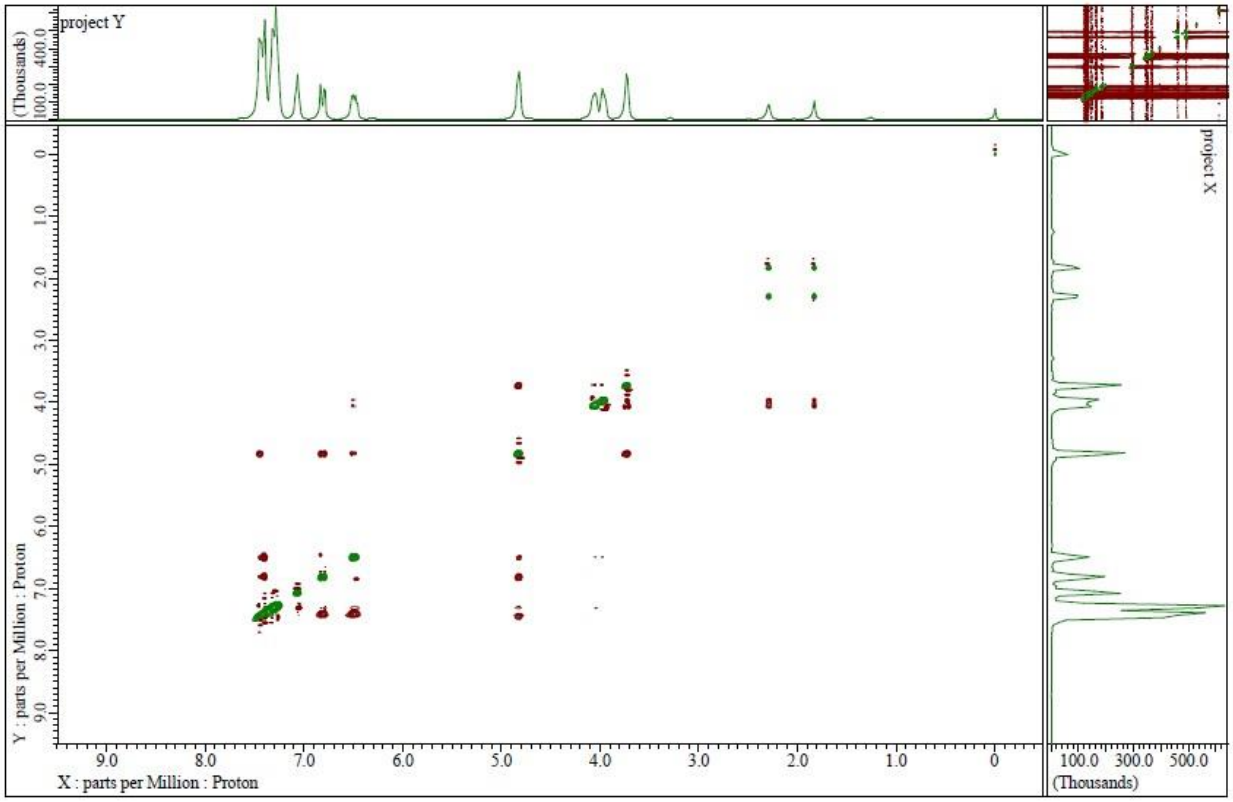
^{1}H NMR spectrum of **5a**:



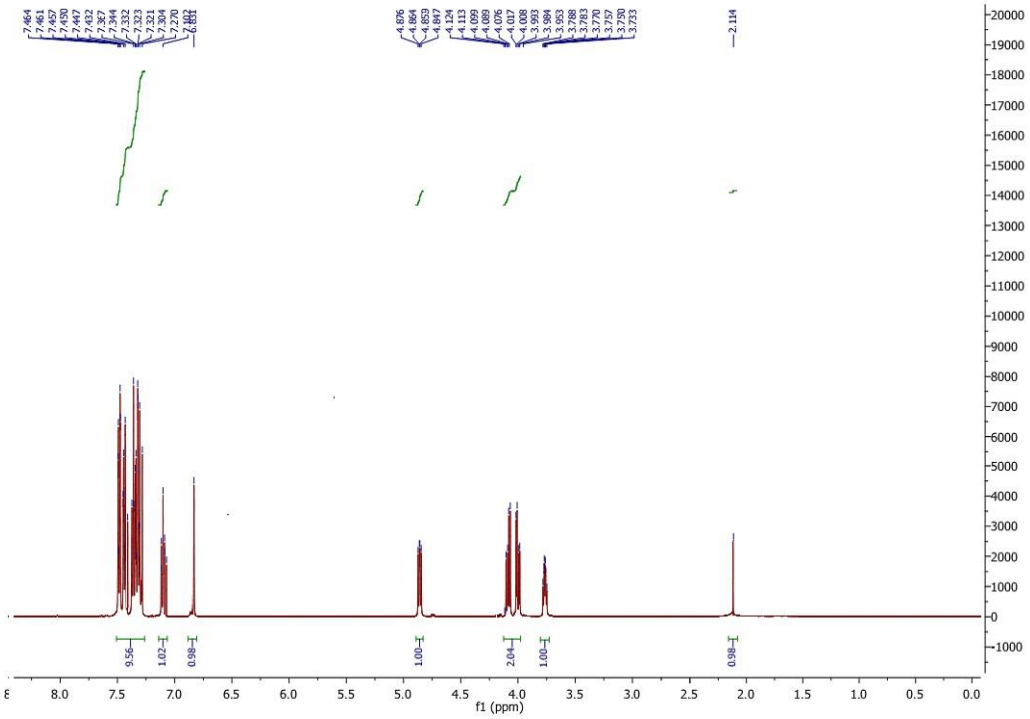
^{13}C NMR spectrum of **5a**:



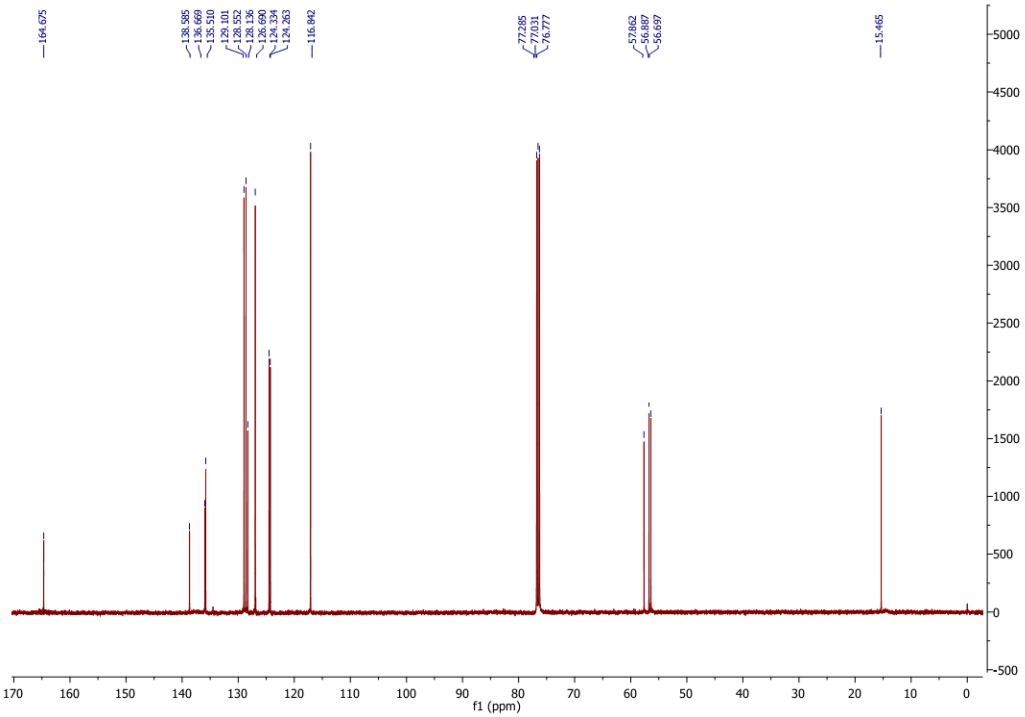
NOE data of **5a**



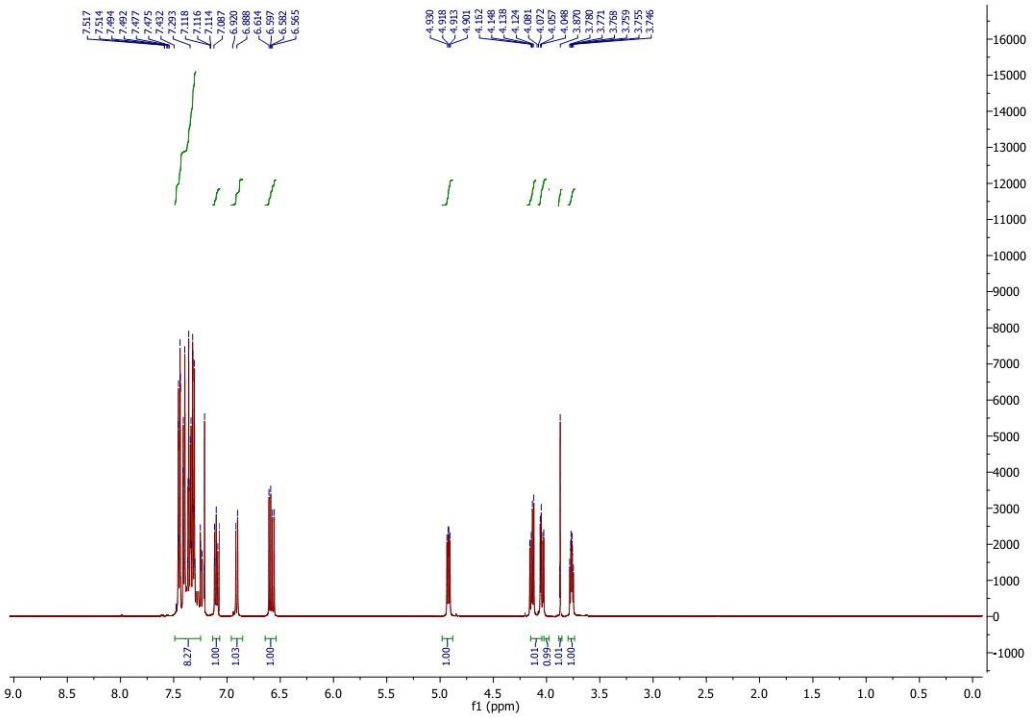
^{1}H NMR spectrum of **5b**:



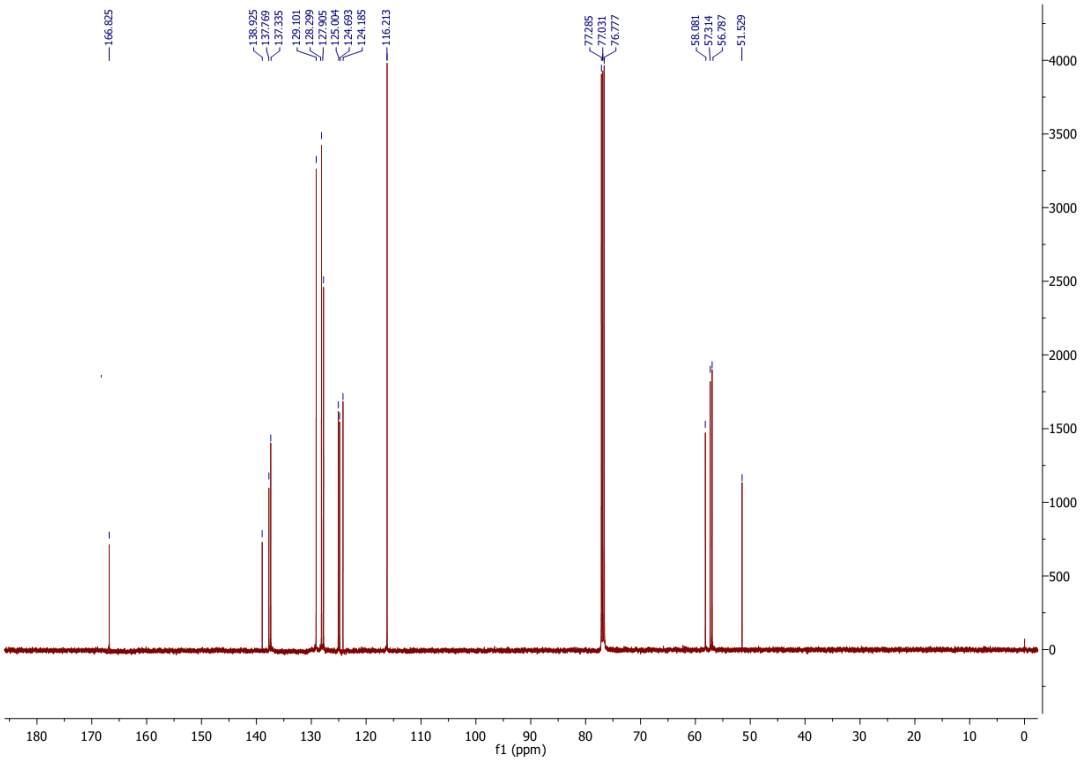
^{13}C NMR spectrum of **5b**:



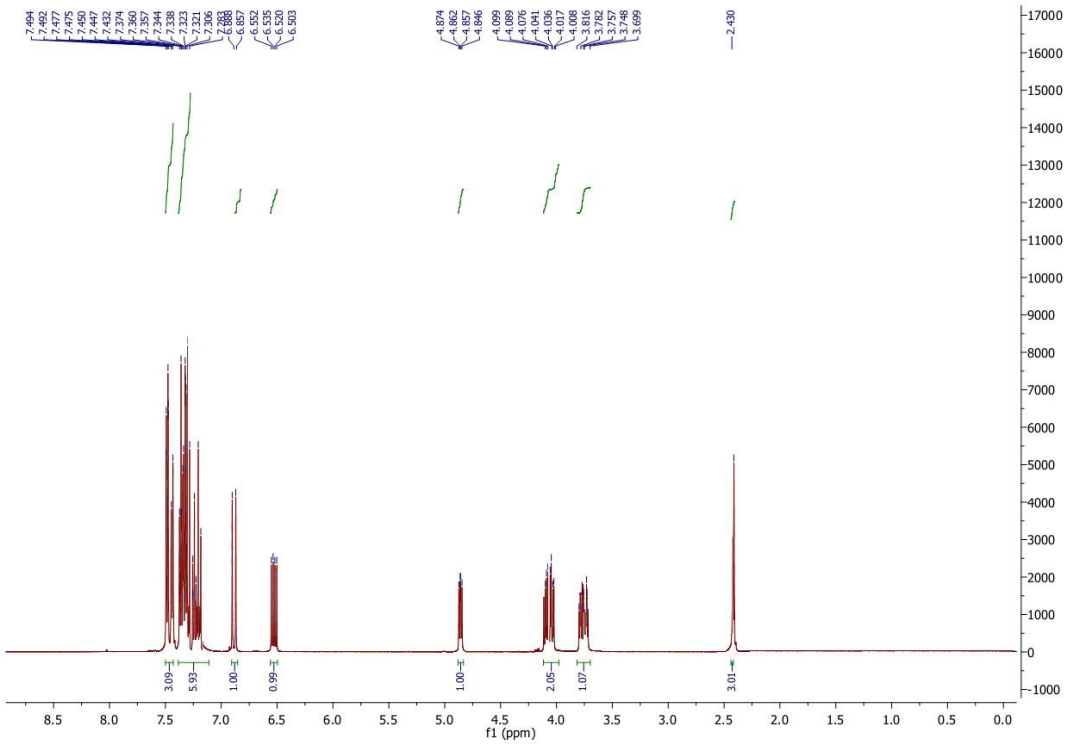
^{1}H NMR spectrum of **5c**:



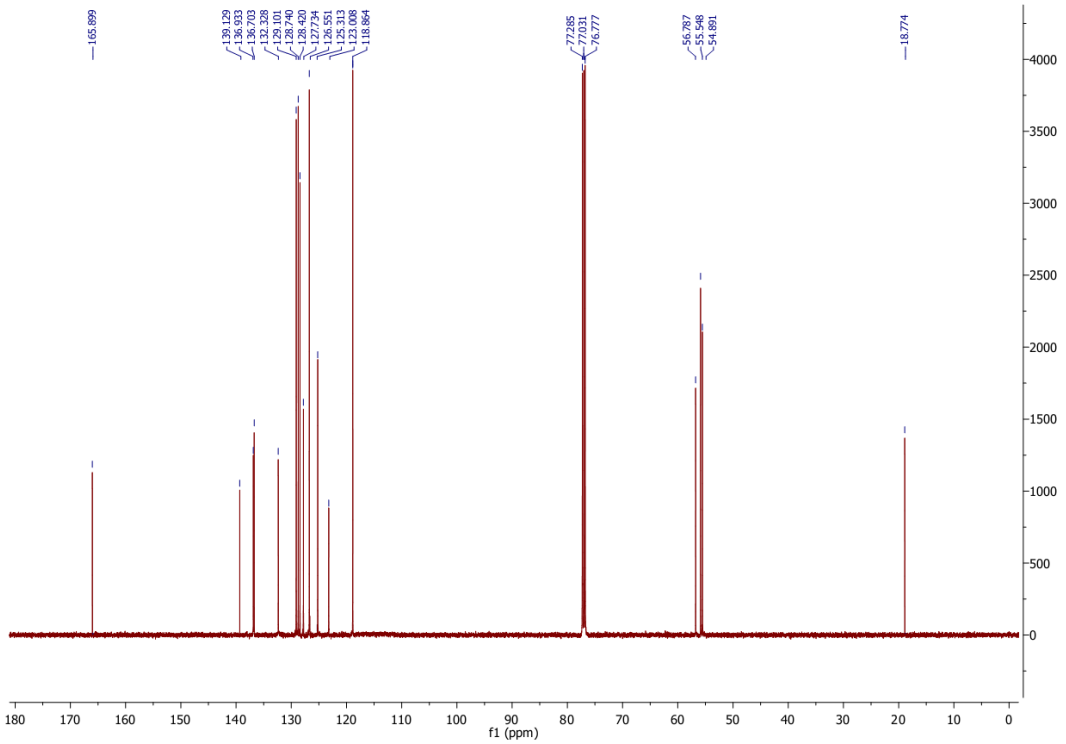
^{13}C NMR spectrum of **5c**:



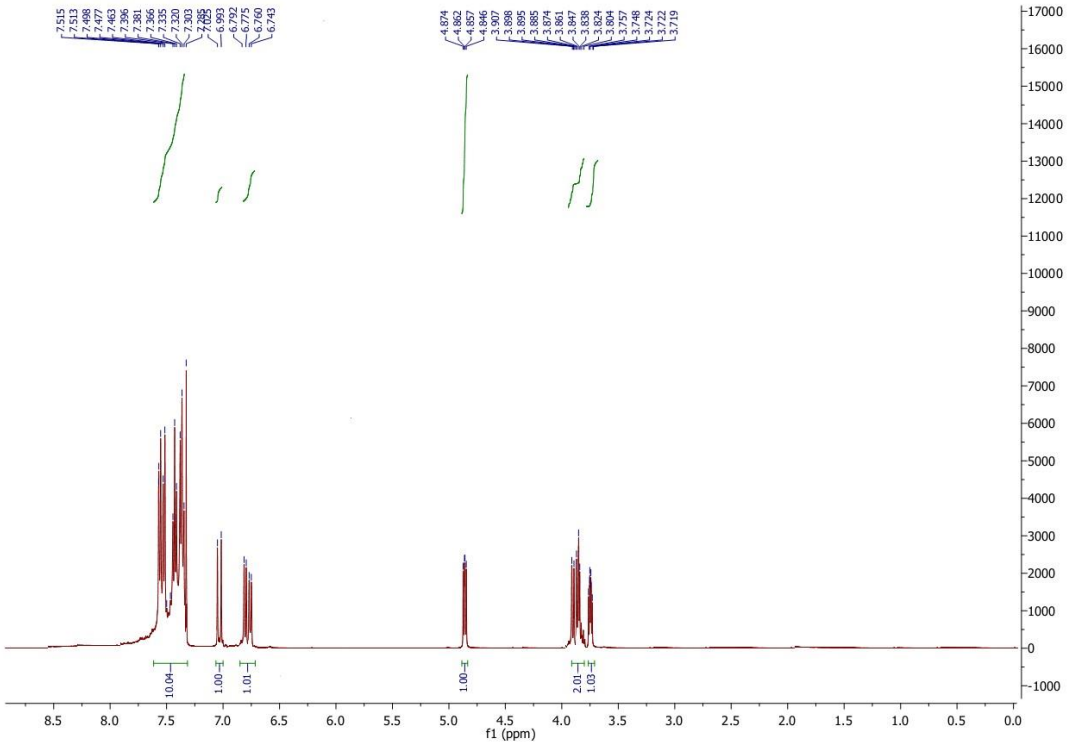
^{1}H NMR spectrum of **5d**:



^{13}C NMR spectrum of **5d**:



^{1}H NMR spectrum of **5g**:



^{13}C NMR spectrum of **5g**: