Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supplementary Information

Indium catalyzed Microwave-accelerated pot economic C-C bond formation process towards 'dry-media' synthesis of pyrimidine derivatives

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General information

All the commercially available reagents were used as received. Melting points were measured with a Buchi M-560 melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given from TMS (0 ppm) and coupling constants are expressed in Hertz (Hz). ^{13}C NMR spectra were recorded on an Avance DPX 75 MHz FT-NMR spectrometer and Chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm). Mass spectra were recorded on ESQUIRE 3000 Mass spectrometer. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on a pre-coated silica gel plates (Merck). After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by stating $KMnO_4$ and warming in a hot air oven. Column chromatography was performed on silica gel (100-200 mesh, Merck) using ethyl acetate-hexane as eluent.

Microwave instrumentation

All microwave reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor. The multitude microwave has a twin magnetron (2.45 GHz) with maximum output power of 1400 W. The output power can be controlled in unpulsed control mode over whole power which is adjustable in 1 W increment. A Motorola 68xxx series microprocessor system control is used to measure power, pressure, time and temperature during the reaction. The temperature and pressure were monitored throughout the reaction by an infrared detector. The temperature can be measured from 0 to 280 ^{o}C with uncertainty ±1%. The pressure can be measured from 0 to 86 bar with uncertainty ±0.2 bar. The MW power is initially set at 720 W and the reaction is run. However, during the course of the reaction, once the set temperature and pressure limit is reached, the reactor automatically adjusts the power by lowering it.

Complete optimization studies for the preparation of quinazoline 3a

Entry	Solvent	Catalyst (mol%)	Reaction condition	Yield(%)
1	Water	-		NR
2	DCM	-		NR
3	DCE	-		NR
4	MeOH	-		NR
5	EtOH	-		NR
6	MeCN	-		NR
7	Dioxane	-		NR
8	Toluene	-		NR
9	*o*-Xylene	-		NR
10	DMF	-		NR
11	Water	$In(OTf)_3$ (5)	Reflux	NR
12	DCE	$In(OTf)_3$ (5)		NR
13	EtOH	$In(OTf)_3$ (5)		NR
14	MeCN	$In(OTf)_3$ (5)		NR
15	Dioxane	$In(OTf)_3$ (5)		Trace
16	Toluene	$In(OTf)_3$ (5)		Trace
17	*o*-Xylene	$In(OTf)_3$ (5)		Trace
18	DMF	$In(OTf)_3$ (5)		Trace
19	Dioxane	$In(OTf)_3$ (10)		Trace
20	Toluene	$In(OTf)_3$ (10)		Trace
21	*o*-Xylene	$In(OTf)_3$ (15)		Trace
22	DMF	$In(OTf)_3$ (15)		Trace
23	Water	$In(OTf)_3$ (5)		NR
24	EtOH	$In(OTf)_3$ (5)		NR
25	MeCN	$In(OTf)_3$ (5)		NR
26	Toluene	$In(OTf)_3$ (5)		Trace
27	*o*-Xylene	$In(OTf)_3$ (5)		Trace
28	Neat	$In(OTf)_3$ (5)		70
29	Neat	$In(OTf)_3$ (10)		89
30	Neat	AgOTf (10)		85
31	Neat	$Cu(OTf)_2$ (10)	MW	85
32	Neat	$Sc(OTf)_3$ (10)		84
33	Neat	$Yb(OTf)_3$ (10)		80
34	Neat	$Zn(OTf)_2$ (10)		85
35	Neat	$In(OTf)_3$ (15)		85
36	Neat	$InCl_3$ (10)		40
37	Neat	$InBr_3$ (10)		40
38	Neat	$CuCl_2$ (10)		Trace
39	Neat	$ZnCl_2$ (10)		Trace

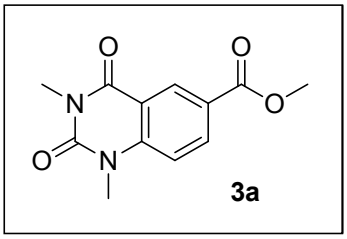
General procedure for the synthesis of products under microwave conditions

A mixture of uracil (**1**, 1.0mmol), acetylene carboxylate (**2**, 1.2mmol) and indium triflate (10 mol%)was irradiated with microwaves (720 W) for appropriate time in a Synthos 3000 microwave reactor at 120 ^{o}C and 10 bar. After reaction the crude product mixture was dissolved in ethyl acetate which was directly purified by column chromatography eluting with ethyl acetate/hexane to obtain pure products(**3**).

General procedure for the synthesis of products under thermal conditions

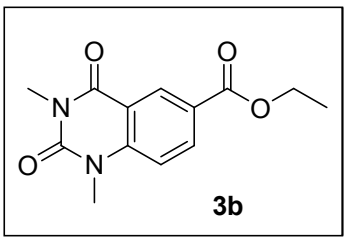
A mixture of uracil (**4**, 1.0mmol), acetylene carboxylate (**2**, 1.2mmol) and indium triflate (10 mol%)was well-homogenized in a Coors alumina mortar (Sigma-Aldrich) and the gummy mixture was heated at 120 ^{o}C for 10 hours. After completion, as indicated by TLC, the crude product mixture was dissolved in ethyl acetate which was directly purified by column chromatography eluting with ethyl acetate/hexane to obtain pure products(**3**).

Characterization data of the Products



*Methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**3a***

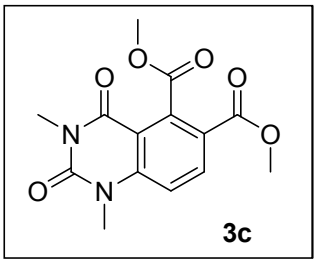
Yield: 89%.m. p. 223-224^{o}C; Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.89 (d,1 H, C*H*=CCOOCH$_3$, $J_{5,7}$= 2.0 Hz), 8.34(dd, 1 H, CH=C*H*-CCOOCH$_3$, $J_{5,7}$ = 2.0 Hz, $J_{7,8}$ = 8.7 Hz), 7.28 (d, 1 H, C*H*=CH-CCOOCH$_3$, $J_{7,8}$ = 8.7 Hz), 3.95 (s, 3 H, COOCH$_3$), 3.65 (s, 3 H, NCH$_3$),3.50 (s, 3 H, NCH$_3$). ^{13}C NMR (75MHz,$CDCl_3$): δ = 165.6, 161.2, 150.9, 143.3, 135.7, 130.8,124.8,115.0, 113.7, 52.3, 31.0, 28.6.IR ($CHCl_3$): 1718.2, 1672.7, 1625.0 cm^{-1}. MS(GC-MS): *m/z*= 248[M]$^{+}$. Anal. Calcd for$C_{12}H_{12}N_2O_4$: C,58.06; H,4.87; N,11.29. Found:C, 58.02; H, 4.85;N, 11.21.



*Ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-6-carboxylate**3b***

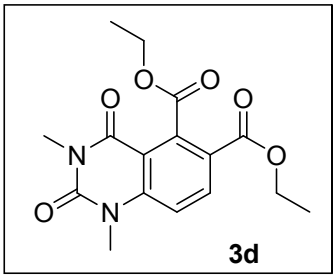
Yield: 89%. m. p. 184-186 ^{o}C; Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.88 (d, 1 H, C*H*=CCOOC$_2$H$_5$, $J_{5,7}$= 2.0 Hz), 8.34 (dd, 1 H, CH=C*H*-CCOOC$_2$H$_5$, $J_{5,7}$ = 2.0 Hz, $J_{7,8}$ = 9.0 Hz), 7.30 (d, 1 H, C*H*=CH-CCOOC$_2$H$_5$, $J_{7,8}$ = 9.0 Hz), 4.42 (q, 2 H, COOCH$_2$, J = 7.1 Hz), 3.65 (s, 3 H, NCH$_3$), 3.46 (s, 3 H, NCH$_3$), 1.42 (t, 3 H, COOCH$_2$C*H*$_3$, J = 7.1 Hz). ^{13}C NMR (75MHz,$CDCl_3$): δ = 165.1, 161.3, 151.0, 143.3, 135.8, 130.8, 125.2, 115.0, 113.6, 61.4, 31.0, 28.6, 14.3. IR ($CHCl_3$): 1713.4,

1671.3, 1625.3 cm^{-1}. MS(GC-MS): *m/z*= 262$[M]^+$. Anal. Calcd for$C_{13}H_{14}N_2O_4$: C, 59.54; H,5.38; N, 10.68. Found:C, 59.51; H,5.30;N, 10.59.



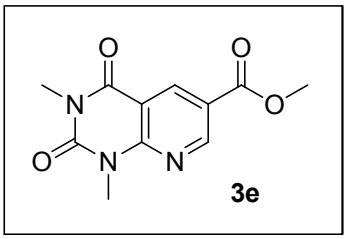
*Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-5,6-dicarboxylate**3c***

Yield: 88%. m. p. 209-211^oC; Off-white solid; ^1H NMR (300 MHz, $CDCl_3$): δ= 8.35 (d, 1 H, CH=C*H*-$CCOOCH_3$, $J_{7,8}$ = 7.0 Hz), 7.30 (d, 1 H, C*H*=CH-$CCOOCH_3$, $J_{7,8}$= 7.0 Hz), 4.01 (s, 3 H, $COOCH_3$), 3.71 (s, 3 H, $COOCH_3$), 3.65 (s, 3 H, NCH_3), 3.50 (s, 3 H, NCH_3).^{13}C NMR (75MHz,$CDCl_3$): δ = 167.8, 163.7, 160.2, 151.0, 143.5, 138.2, 136.5, 121.9, 114.1, 112.4, 52.3, 52.1, 31.0, 28.6. IR ($CHCl_3$): 1728.7, 1721.5, 1655.1 cm^{-1}. MS(GC-MS): *m/z*=306$[M]^+$. Anal. Calcd for$C_{14}H_{14}N_2O_6$: C, 54.90; H,4.61; N,9.15. Found:C, 54.88; H,4.60;N, 9.11.



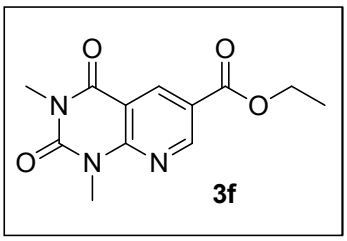
*Diethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazoline-5,6-dicarboxylate**3d***

Yield: 87%. m. p. 150-152^oC; Off-white solid; ^1H NMR (300 MHz, $CDCl_3$): δ= 8.37 (d, 1 H, CH=C*H*-$CCOOC_2H_5$, $J_{7,8}$ = 8.9 Hz), 7.31 (d, 1 H, C*H*=CH-$CCOOC_2H_5$, $J_{7,8}$= 8.9 Hz), 4.54-4.51 (q, 2 H, $COOCH_2$, J = 7.1 Hz), 4.41-4.34 (q, 2 H, $COOCH_2$, J = 7.1 Hz), 3.58 (s, 3 H, NCH_3), 3.35 (s, 3 H, NCH_3), 1.42 (t, 3 H, OCH_2CH_3, J = 7.1 Hz), 1.36 (t, 3 H, OCH_2CH_3, J = 7.1 Hz). ^{13}CNMR (75MHz,$CDCl_3$): δ= 167.7, 163.8, 160.0, 150.5, 143.5, 138.1, 136.5, 122.7, 114.2, 112.4, 62.0, 61.8, 31.4, 28.7, 14.1, 13.8. IR ($CHCl_3$): 1727.3, 1712.2, 1669.3 cm^{-1}. MS(GC-MS): *m/z*= 334$[M]^+$. Anal. Calcd for$C_{16}H_{18}N_2O_6$: C, 57.48; H,5.43; N,8.38. Found:C, 57.40; H,5.39;N, 8.31.



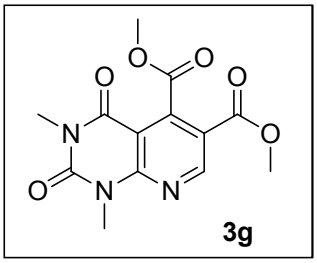
*Methyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate**3e***

Yield: 91%. m. p. 125-126^oC; Off-white solid; ^1H NMR (300 MHz, $CDCl_3$): δ= 8.66 (d, 1 H, N=CH, $J_{5,7}$= 2.1 Hz), 8.47 (d, 1 H, CH=C-$CCOOCH_3$, $J_{5,7}$= 2.1 Hz),3.98 (s, 3 H, OCH_3), 3.70 (s, 3 H, NCH_3), 3.49 (s, 3 H, NCH_3). ^{13}C NMR (75MHz,$CDCl_3$): δ = 164.5, 161.3, 160.6, 156.3, 153.2, 137.5, 121.4, 109.8, 52.5, 29.9, 28.7. IR ($CHCl_3$): 1742.5, 1720.1, 1681.1 cm^{-1}. MS(GC-MS): *m/z*= 249$[M]^+$. Anal. Calcd for$C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N,16.86. Found:C, 53.04; H, 4.41;N, 16.79.



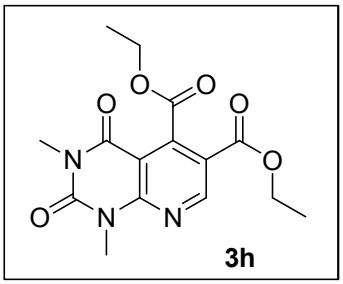
*Ethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate**3f***

Yield: 91%. m. p. 145-146 ^{o}C; Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.13 (d, 1 H, N=CH, $J_{5,7}$ = 2.1 Hz), 8.43 (d, 1 H, CH=C-CCOOCH$_3$, $J_{5,7}$ = 2.1 Hz), 4.42 (q, 2 H, $COOCH_2$, J = 7.1 Hz), 3.65 (s, 3 H, NCH_3), 3.48 (s, 3 H, NCH_3), 1.42 (t, 3 H, $COOCH_2CH_3$, J = 7.1 Hz).^{13}C NMR (75MHz,$CDCl_3$): δ = 165.1, 161.4, 158.9,151.0, 143.9, 138.0, 120.1,111.5, 61.4, 31.0, 28.6, 14.2. IR ($CHCl_3$): 1764.7, 1720.3, 1679.3 cm^{-1}. MS(GC-MS): *m/z*= 263[M]$^{+}$. Anal. Calcd for$C_{12}H_{13}N_3O_4$: C,54.75; H,4.98; N,15.96. Found:C, 54.71; H,4.88;N, 15.88.



*Dimethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5,6-dicarboxylate **3g***

Yield: 90%. m. p. 161-163 ^{o}C; Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.22 (s, 1 H, N=C*H*), 4.01 (s, 3 H, $COOCH_3$), 3.90 (s, 3 H, $COOCH_3$), 3.62 (s, 3 H, NCH_3), 3.44 (s, 3 H, NCH_3). ^{13}C NMR (75MHz,$CDCl_3$): δ = 168.2, 163.2, 160.3, 152.5, 145.1, 139.2, 131.2, 114.7, 112.8, 52.3, 52.1, 31.0, 28.5. IR ($CHCl_3$): 1756.2, 1723.1, 1675.7 cm^{-1}. MS(GC-MS): *m/z*= 307[M]$^{+}$. Anal. Calcd for$C_{13}H_{13}N_3O_6$: C,50.82; H,4.26; N,13.68. Found:C, 49.77; H,4.19;N, 13.50.



*Diethyl 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5,6-dicarboxylate **3h***

Yield: 89%. Off-white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 9.29 (s, 1 H, N=C*H*), 4.53-4.51 (q, 2 H, $COOCH_2$, J = 7.0 Hz), 4.39-4.34 (q, 2 H, $COOCH_2$, J = 7.0 Hz), 3.61 (s, 3 H, NCH_3), 3.45 (s, 3 H, NCH_3), 1.39 (t, 3 H, OCH_2CH_3, J = 7.0 Hz), 1.36 (t, 3 H, OCH_2CH_3, J = 7.0 Hz).IR ($CHCl_3$): 1733.8, 1722.2, 1677.1 cm^{-1}.. MS(GC-MS): *m/z*= 307 [M]$^{+}$. Anal. Calcd for$C_{15}H_{17}N_3O_6$: C,53.73; H,5.11; N,12.53. Found:C, 52.91; H,5.00;N, 12.46.

NMR Spectra of the Products

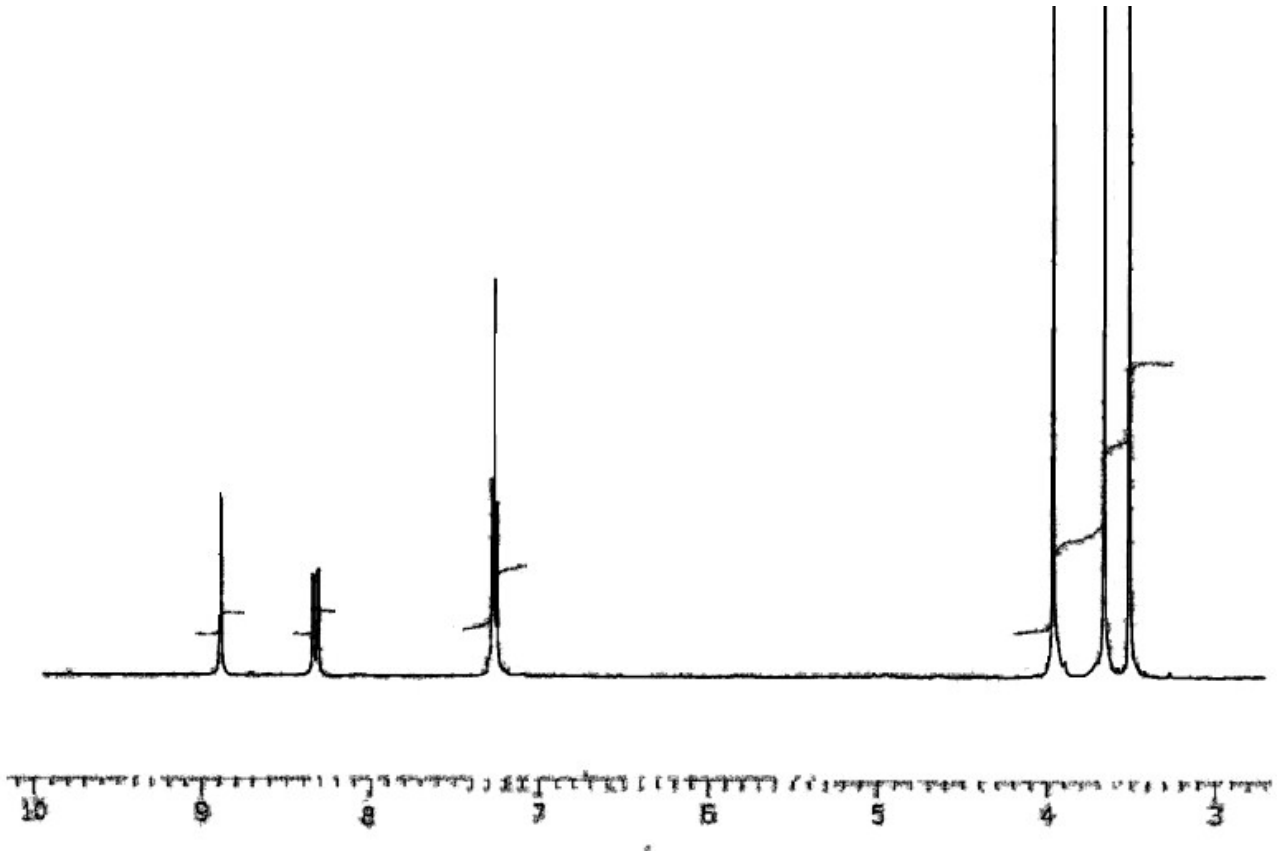


Fig SI-1: ^{1}H NMR Spectrum of Product **3a**

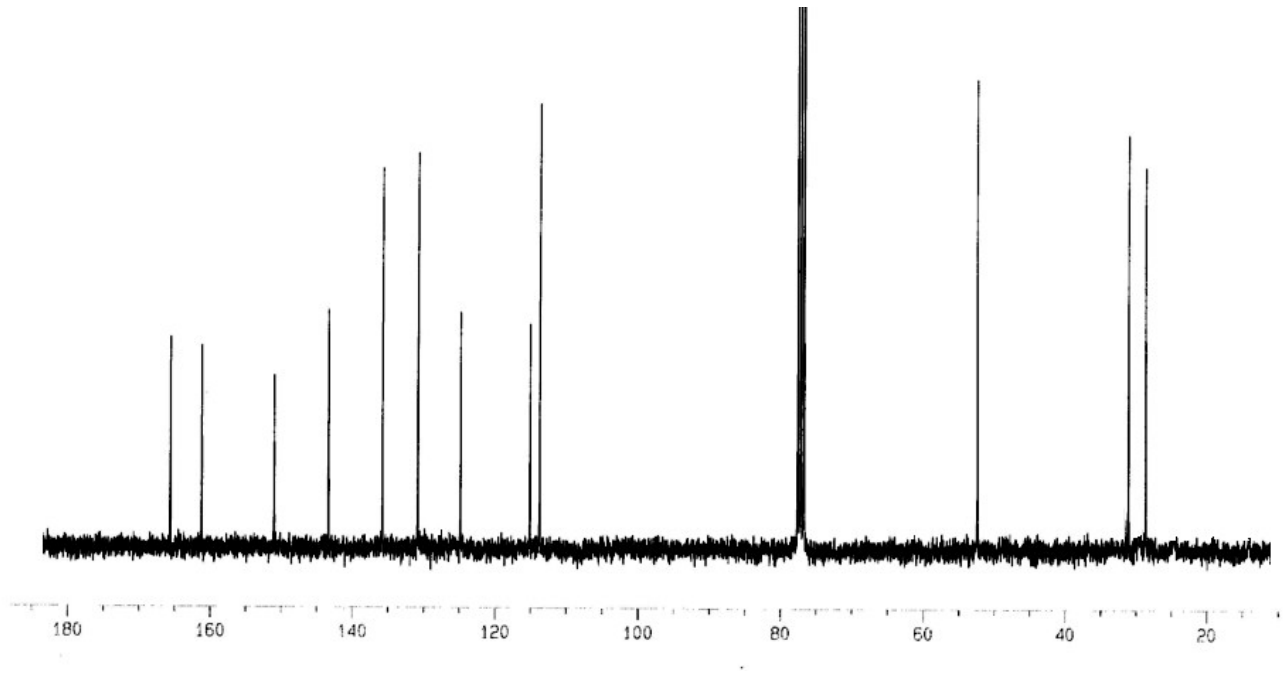


Fig SI-2: ^{13}C NMR Spectrum of Product **3a**

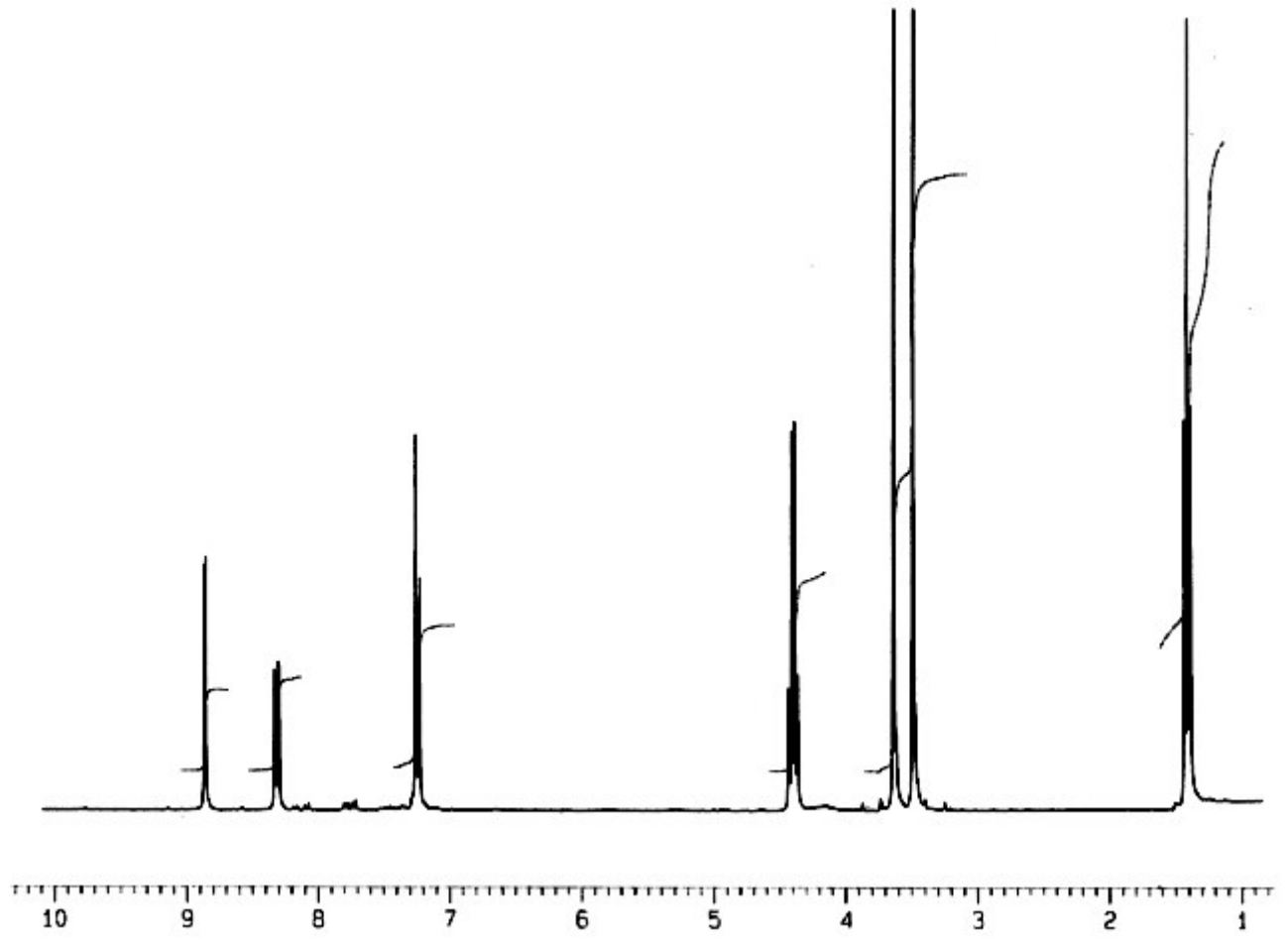


Fig SI-3: ^{1}H NMR Spectrum of Product **3b**

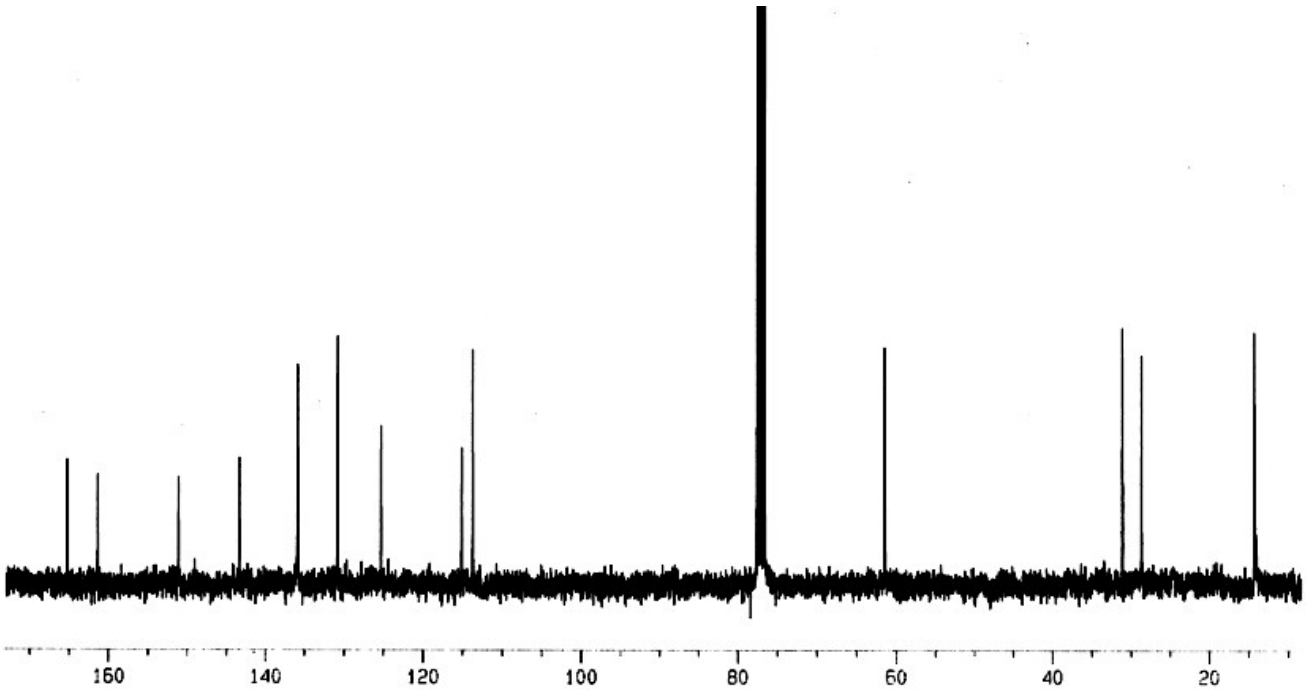


Fig SI-4: ^{13}C NMR Spectrum of Product **3b**

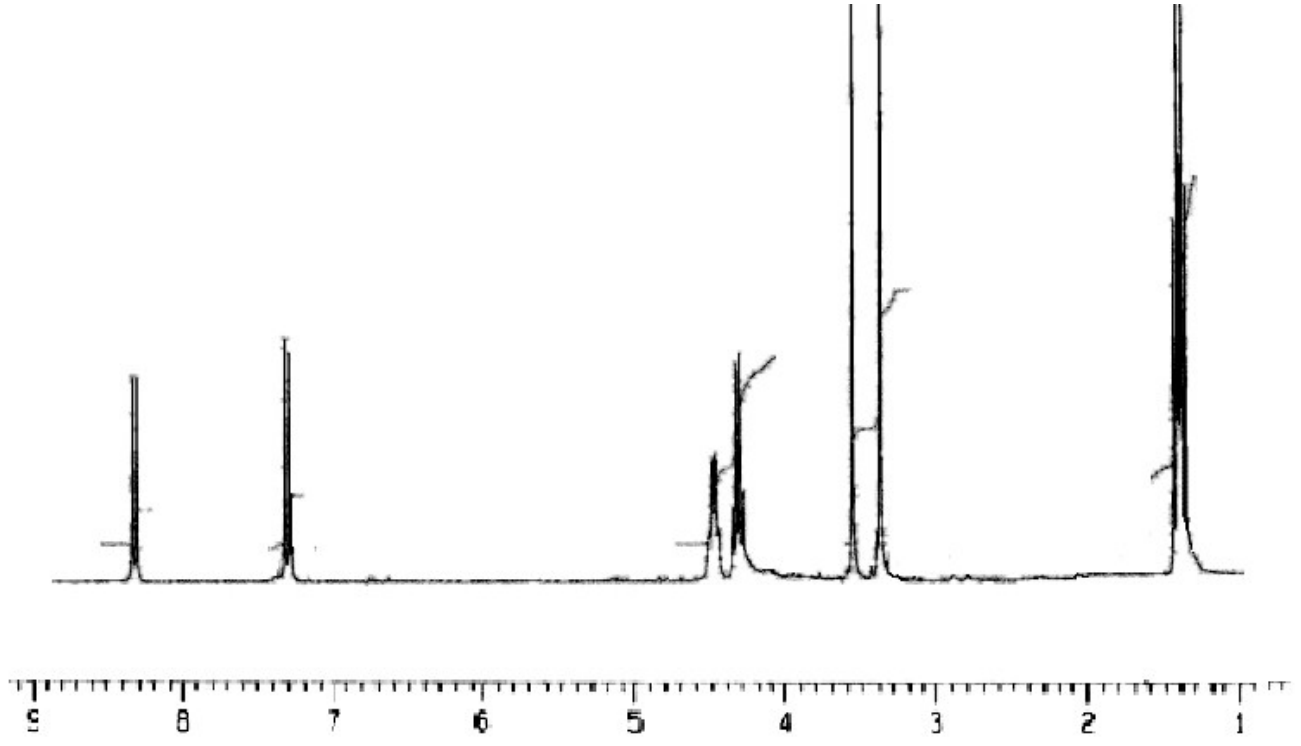


Fig SI-5: ^{1}H NMR Spectrum of Product **3d**

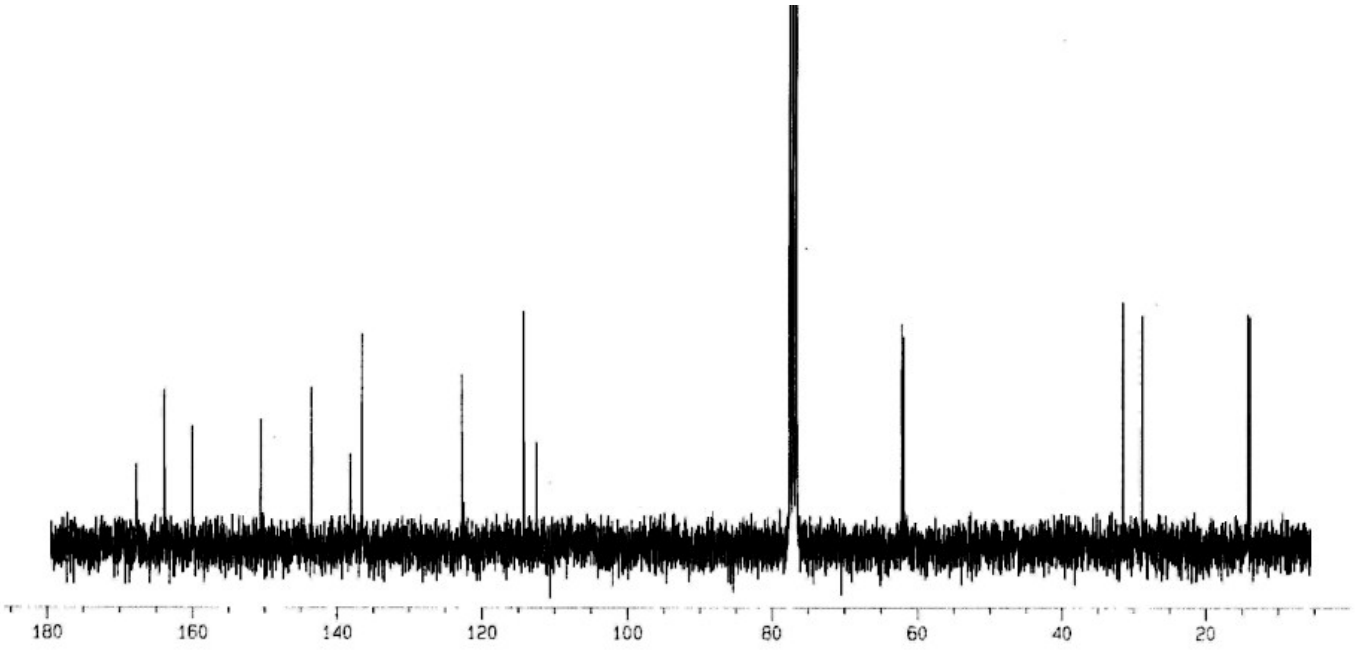


Fig SI-6: ^{13}C NMR Spectrum of Product **3d**

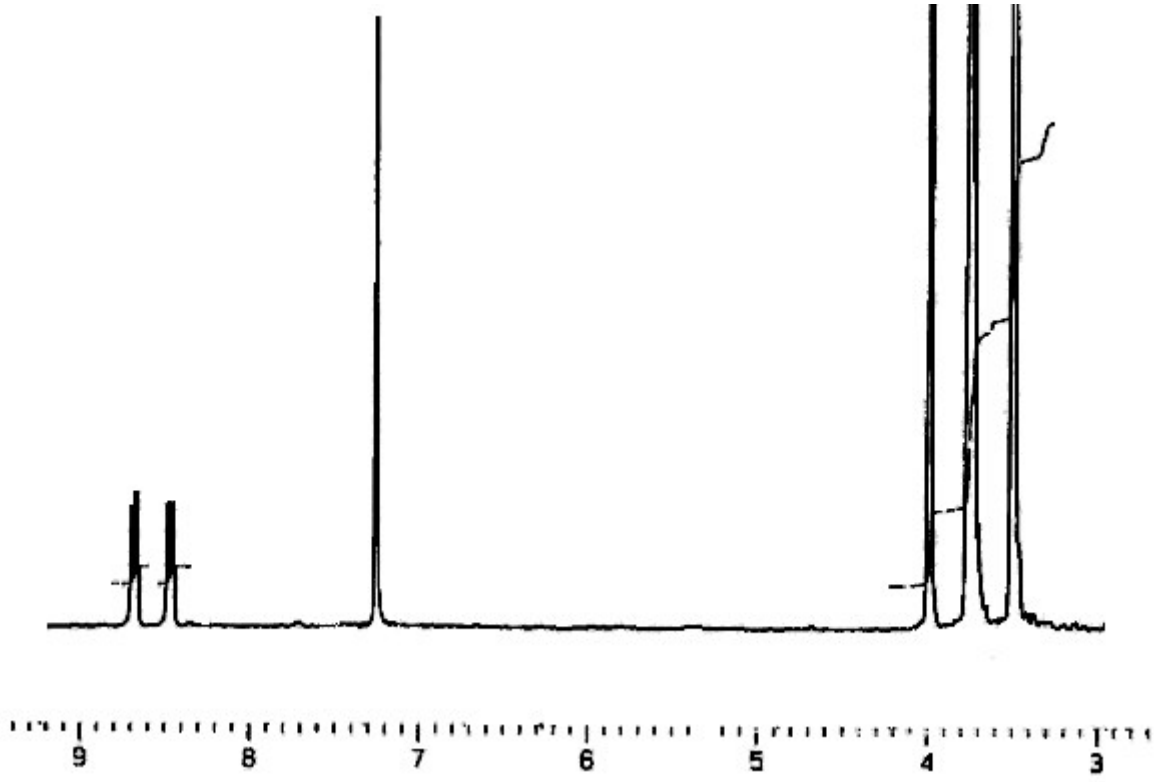


Fig SI-7: ^{1}H NMR Spectrum of Product **3e**

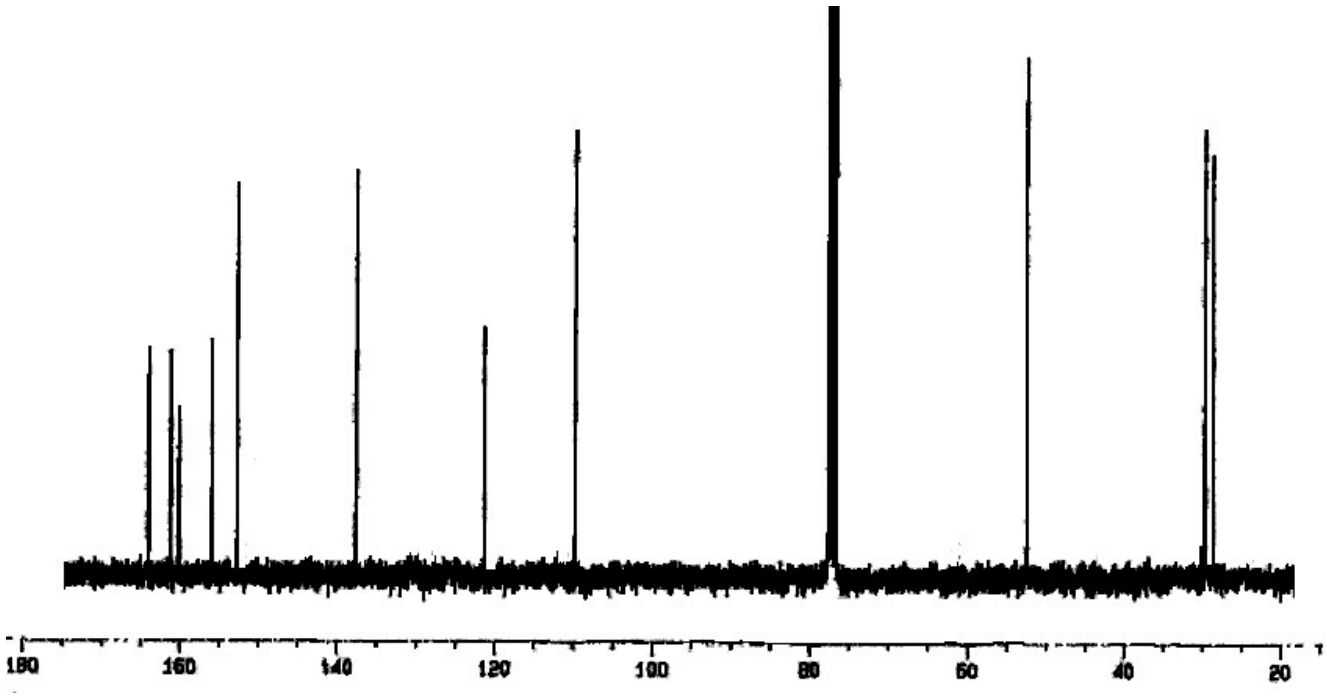


Fig SI-8: ^{13}C NMR Spectrum of Product **3e**

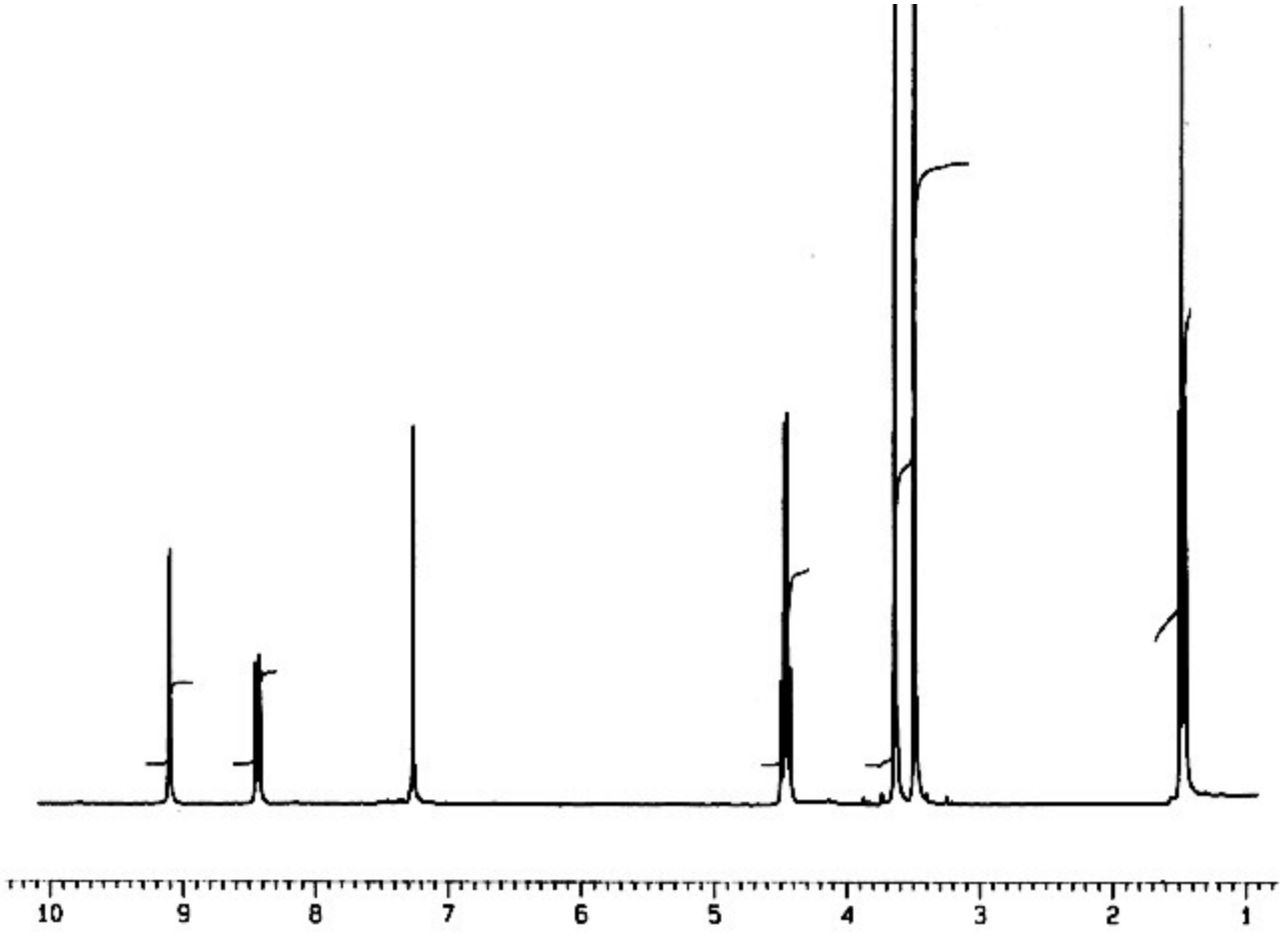


Fig SI-9: ^{1}H NMR Spectrum of Product **3f**

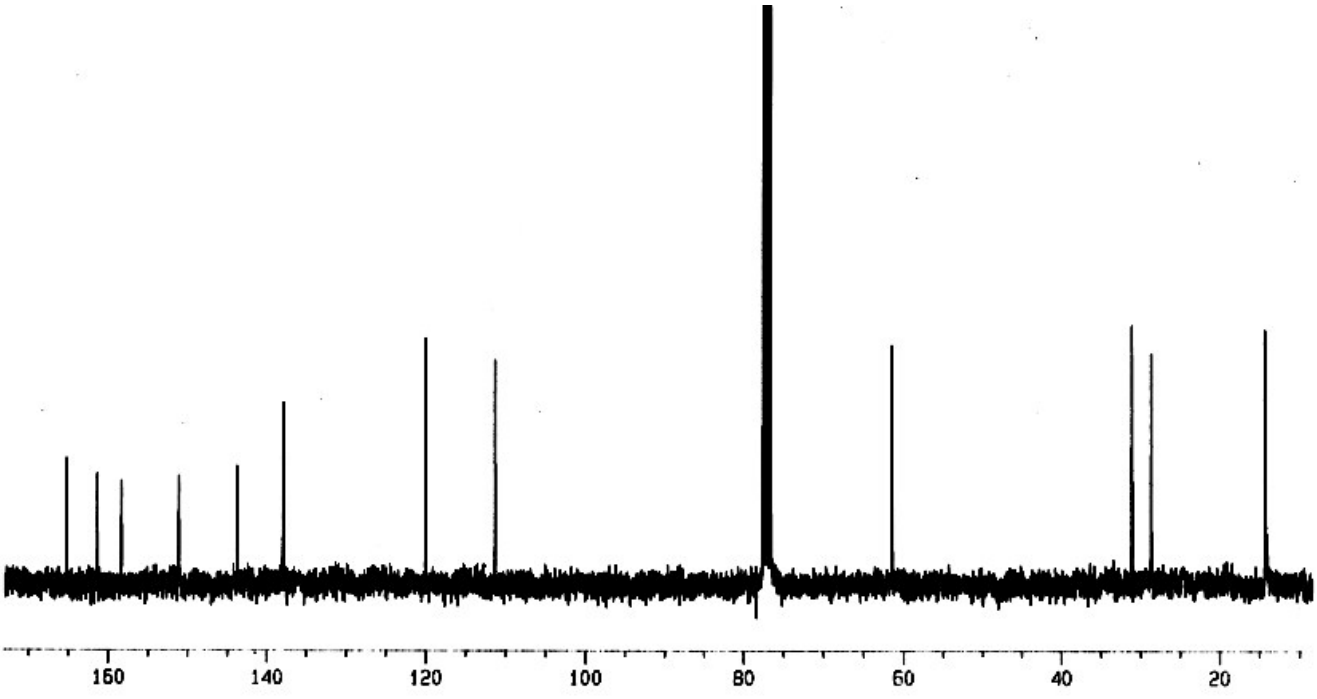


Fig SI-10: ^{13}C NMR Spectrum of Product **3f**

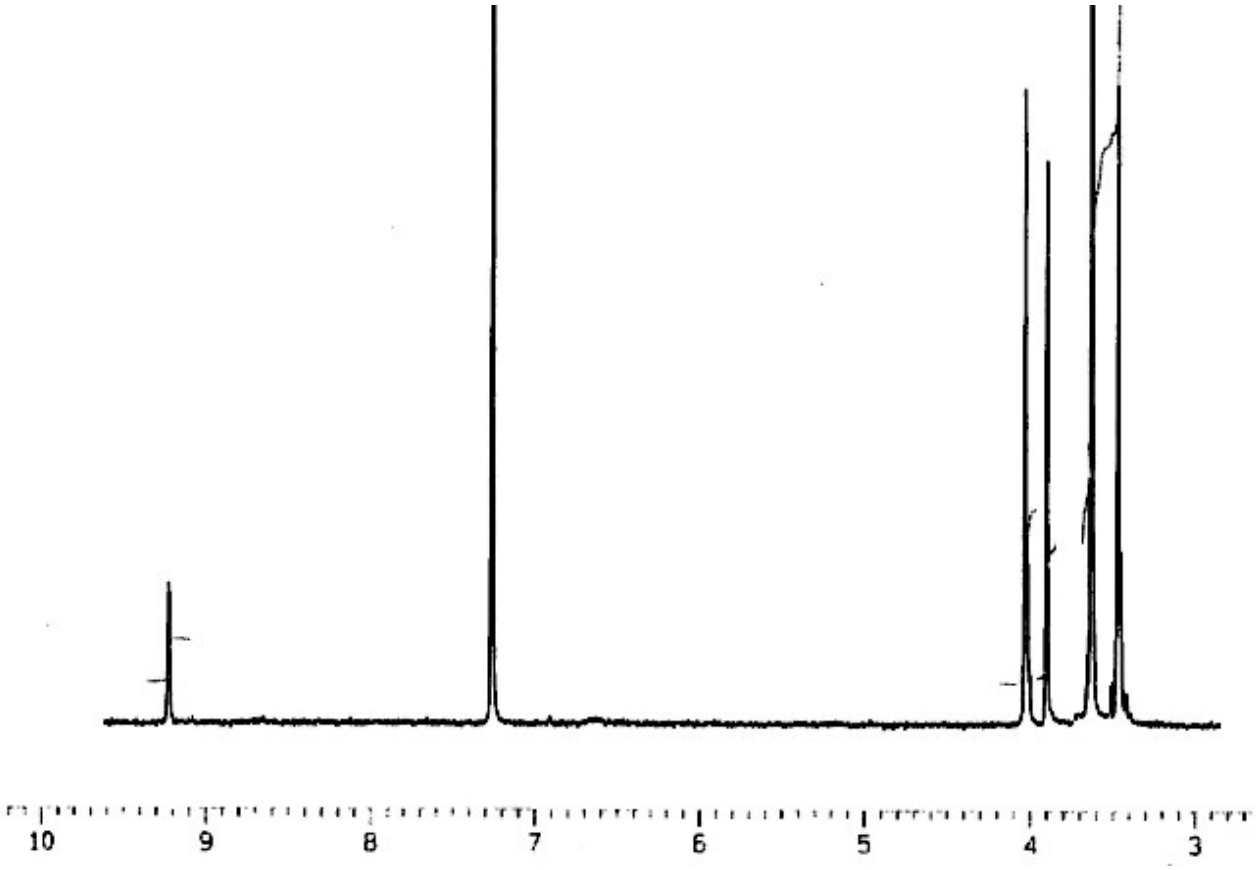


Fig SI-11: ^{1}H NMR Spectrum of Product **3g**