Supporting Information

for

Improved Arndt-Eistert Synthesis of α-Diazoketones Requiring Minimal Diazomethane in the Presence of Calcium Oxide as Acid Scavenger

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Table of contents

1. Materials and instrumentation.

All ^{1}H NMR and ^{13}C NMR were recorded at 250 or 300 MHz and at 62.5 or 100 MHz respectively using a convenient deuterated solvent (reported in the characterization charts) and the residual peak as internal standard or TMS in the case of $CDCl_3$. Chemical shifts are reported in δ (ppm). Spin-spin coupling constants (*J*) are given in Hz. Carbon multiplicities were obtained from DEPT experiments. All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$; the spots were visualized under UV light (λ=254 nm) and/or $KMnO_4$ (aq.) was used as revealing system Diethyl ether was purified by distillation immediately before use. Calcium oxide was dried before use with P_2O_5.

2. Preparation and titration of free-ethanol Diazomethane[1]

Since the known toxicity and potential explosive behavior of diazomethane, special devices were taken. The use of glass apparatus with ground joints and sharp surfaces was avoided. Additionally, silicon grease was spread on connection parts.

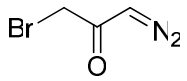
In a 250-mL distilling flask provided with a dropping funnel and an efficient downward condenser, a solution of KOH (6.0 g) in 20 mL of distilled water and 35 mL of 2-methoxyethanol was placed. The condenser was connected to two conical Erlenmeyer flasks in series containing each 20 mL of diethyl ether and cooled in an ice-salt bath. The stirred mixture was heated using a preheated water bath at 50ºC and, as soon as the ether began to distil, a solution of 21.5 g of *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide (Diazald®) in 130 mL of diethyl ether was added dropwise through a dropping funnel during a period of about 20 minutes. After the addition of the Diazald®, an additional amount (60 mL) of diethyl ether was added and distillation was continued until the distillate was colorless. The ethereal solution of diazomethane (*ca.* 200 mL) was dried with 20.0 g of KOH pellets and stored at -20ºC. 500.0 mg (the exact amount was carefully weighed using a microbalance, 4.0970 mmol) of benzoic acid (recrystallized from water and dried overnight over P_2O_5) in 25 mL of anhydrous diethyl ether was allowed to react with the aforementioned solution of diazomethane (11.6 mL). The colorless solution was diluted with distilled water (20 mL) and the excess of benzoic acid was determined by titration using a standard solution 0.10 M of NaOH and phenolphthalein as the indicator. Titration was complete by adding 9.73 mL [medium

value of the three titrations: 1) 9.66 mL; 2) 9.72 mL; 3) 9.80 mL], thus allowing the exact determination of the above prepared ethereal solution of diazomethane (0.27 M).

3. General Procedure for Diazoketones Preparation in the presence of CaO

The above mentioned freshly prepared and titrated ethereal solution of diazomethane (0.27 M, 2.00 mmol, 7.41 mL, 1.0 equiv.) was added to a cooled suspension (0ºC) of calcium oxide (123 mg, 2.20 mmol, 1.1 equiv.) in dry diethyl ether (10 mL). After 5 min, a solution of the corresponding acyl halide (2.00 mmol) **5a-b**, **7a-i** in anhydrous diethyl ether (5 mL) was added dropwise. The reaction mixture was stirred at 0ºC for a period of 3 h. The crude reaction mixture was filtered in vacuo and the remaining solids were washed with diethyl ether (3 x 20 mL). The resulting solution was concentrated under reduced pressure, affording diazoketones **6a-b, 8a-i** which were purified, whenever necessary, by column chromatography or recrystallization, as reported below.

1-Bromo-3-diazopropan-2-one (6a).[2]



Following the general procedure above described, using bromoacetyl bromide **5a** (407 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 326 mg of **6a** (quant. yield) as a yellow viscous oil that did not require any further purification.

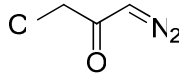
^{1}H NMR (250 MHz, $CDCl_3$) δ 3.75 (s, 2H), 5.77 (s, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 32.3, 56.0, 187.6.

IR (KBr, cm^{-1}) 2106, 1627, 1357.

Elemental Analysis (%) for $C_3H_3BrN_2O$. Calcd.: C, 22.11; H, 1.86; N, 17.19. Found: C, 22.21; H, 1.89; N, 17.12.

1-Chloro-3-diazopropan-2-one (6b).[3]



Following the general procedure above described, using chloroacetyl bromide **5b** (226 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 236 mg of **6b** (quant. yield) as a yellow viscous oil that did not require any further purification.

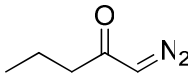
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 2H), 5.88 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 45.7, 55.1, 188.3.

IR (KBr, cm^{-1}) 2108, 1623, 1359.

Elemental Analysis (%) for $C_3H_3ClN_2O$. Calcd.: C, 30.40; H, 2.55; N, 23.67. Found: C, 30.46; H, 2.58; N, 23.71.

1-Diazopentan-2-one (8a).[4]



Following the general procedure above described, using butyryl chloride **7a** (213 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 200 mg of **8a** (89% yield) as a yellow oil after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 8:2).

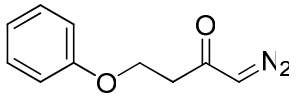
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (tt, J = 2.2 Hz, J = 7.7 Hz, 3H), 1.72-1.60 (m, 2H) 2.37-2.25 (m, 2H), 5.32 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 18.7, 42.9, 54.4, 195.4.

IR (KBr, cm^{-1}) 2110, 1649, 1343.

Elemental Analysis (%) for $C_5H_8N_2O$. Calcd.: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.30; H, 7.26; N, 24.89.

1-Diazo-4-phenoxybutan-2-one (8b).[5]



Following the general procedure above described, using phenoxypropionyl chloride **7b** (369 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 354 mg of **8b** (93% yield) as a yellow oil after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 9:1).

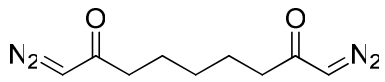
^{1}H NMR (250 MHz, $CDCl_3$) δ 2.80 (m, 2H), 4.29 (t, *J* = 5.0 Hz, 2H), 5.43 (s, 1H), 6.92-7.02 (m, 3H), 7.31 (m, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 40.9, 55.94, 63.8, 114.95, 121.5, 129.9, 158.8, 192.6.

IR (NaCl, cm^{-1}) 3099, 2110, 1790, 1654, 1645, 1600, 1494, 1360, 1325, 1245, 1173, 1036, 888, 790, 756.

Elemental Analysis (%) for $C_{10}H_{10}N_2O_2$. Calcd.: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.24; N, 14.84.

1,9-Didiazononane-2,8-dione (8c).[6]



Following the general procedure above described, using pimeloyl chloride **7c** (394 mg, 2.00 mmol) and diazomethane (0.27 M, 4.00 mmol, 14.82 mL, 2.0 equiv.), provided 396 mg of **8c** (95% yield) as a yellow oil after purification of the crude by column chromatography (dichlorometane / ethyl acetate, 8:2).

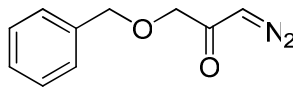
^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31-1.43 (m, 2H), 1.59-1.71 (m, 4H), 2.31 (t, *J* = 6.3 Hz, 4H) 5.27 (s, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 25.2, 29.2, 41.3, 55.4, 195.8.

IR (NaCl, cm^{-1}) 3080, 2927, 2100, 1734, 1700.

Elemental Analysis (%) for $C_9H_{12}N_4O_2$. Calcd.: C, 51.92; H, 5.81; N, 26.91. Found: C, 52.01; H, 5.85; N, 26.86.

1-(Benzyloxy)-3-diazopropan-2-one (8d).[7]



Following the general procedure above described, using benzyloxyacetyl chloride **7d** (369 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 380 mg of **8d** (90% yield) as a yellow oil after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 9:1).

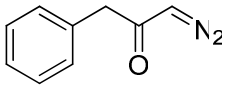
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.06 (s, 2H), 4.59 (s, 2H), 5.82 (s, 1H), 7.34-7.40 (m, 5H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 54.2, 74-0, 74.2, 128.2, 128.6, 129.0, 137.4, 194.4.

IR (NaCl, cm^{-1}) 3032, 2867, 2111, 1732, 1654, 1634, 1497, 1455, 1361, 1272, 1208, 1104, 1028, 821, 740, 699.

Elemental Analysis (%) for $C_{10}H_{10}N_2O_2$. Calcd.: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.26; H, 5.34; N, 14.79.

1-Diazo-3-phenylpropan-2-one (8e).[8]



Following the general procedure above described, using phenylacetyl chloride **7e** (309 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 295 mg of **8e** (92% yield) as a yellow oil after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 9:1).

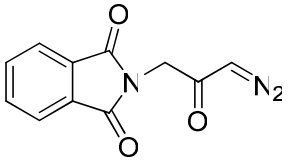
^{1}H NMR (250 MHz, $CDCl_3$) δ 3.64 (s, 2H), 5.17 (s, 1H), 7.25-7.39 (m, 5H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 48.5, 55.6, 127.7, 129.3, 129.8, 135.4, 193.4.

IR (NaCl, cm^{-1}) 3082, 2934, 2103, 1711, 1654, 1626, 1420.

Elemental Analysis (%) for $C_9H_8N_2O$. Calcd.: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.56; H, 5.08; N, 17.54.

2-(3-Diazo-2-oxopropyl)isoindoline-1,3-dione (8f).[9]



Following the general procedure above described, using phthalimidoacetyl chloride **7f** (447 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 458 mg of **8f** (quantitative yield) as a light yellow solid (mp 167-169ºC, lit.[10] 168ºC) after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 8:2).

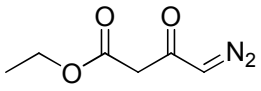
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.46 (s, 2H), 5.44 (s, 1H), 7.76-8.81 (m, 2H), 7.87-7.92 (m, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 44. 6, 54.6, 124.1, 132.4, 134.7, 168.0, 187.3.

IR (NaCl, cm^{-1}) 3078, 2128, 1775, 1734, 1629.

Elemental Analysis (%) for $C_{11}H_7N_3O_3$. Calcd.: C, 57.65; H, 3.08; N, 18.33. Found: C, 57.72; H, 3.11; N, 18.25.

Ethyl 4-diazo-3-oxobutanoate (8g).[11]



Following the general procedure above described, using ethylmalonyl chloride **7g** (301 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 272 mg of **8g** (87% yield) as a yellow oil, after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 7:3).

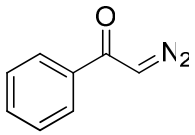
^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.35 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.55 (s, 1H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 47.0, 55.9, 61.6, 167.2, 186.2.

IR (NaCl, cm^{-1}) 2110, 1736, 1639.

Elemental Analysis (%) for $C_6H_8N_2O_3$. Calcd.: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.05; H, 5.21; N, 18.01.

2-Diazo-1-phenylethanone (8h).[12]



Following the general procedure above described, using benzoyl chloride **7h** (281 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 292 mg of **8h** (quantitative yield) as a yellow crystalline solid (mp 47-48ºC, lit.[12] 48ºC) after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 8:2).

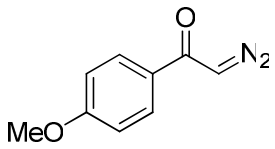
^{1}H NMR (250 MHz, $CDCl_3$) δ 5.94 (s, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7. 56 (t, *J* = 7.5 Hz, 1H), 7.79 (d, 2H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 54.6, 127.1, 129.1, 133.1, 137.1, 186.9.

IR (NaCl, cm^{-1}) 3066, 2104, 1605, 1573, 1448, 1379, 1289, 871, 698.

Elemental Analysis (%) for $C_8H_6N_2O$. Calcd.: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.83; H, 4.19; N, 19.25.

2-Diazo-1-(4-methoxyphenyl)ethanone (8i).[13]



Following the general procedure above described, using 4-methoxybenzoyl chloride **7i** (341 mg, 2.00 mmol) and diazomethane (0.27 M, 2.00 mmol, 7.41 mL), provided 328 mg of **8i** (93% yield) as a yellow solid (mp 81ºC; lit.[14]80ºC), after purification of the crude by column chromatography (petroleum ether / ethyl acetate, 8:2).

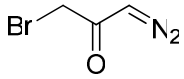
^{1}H NMR (250 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.88 (s, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H).

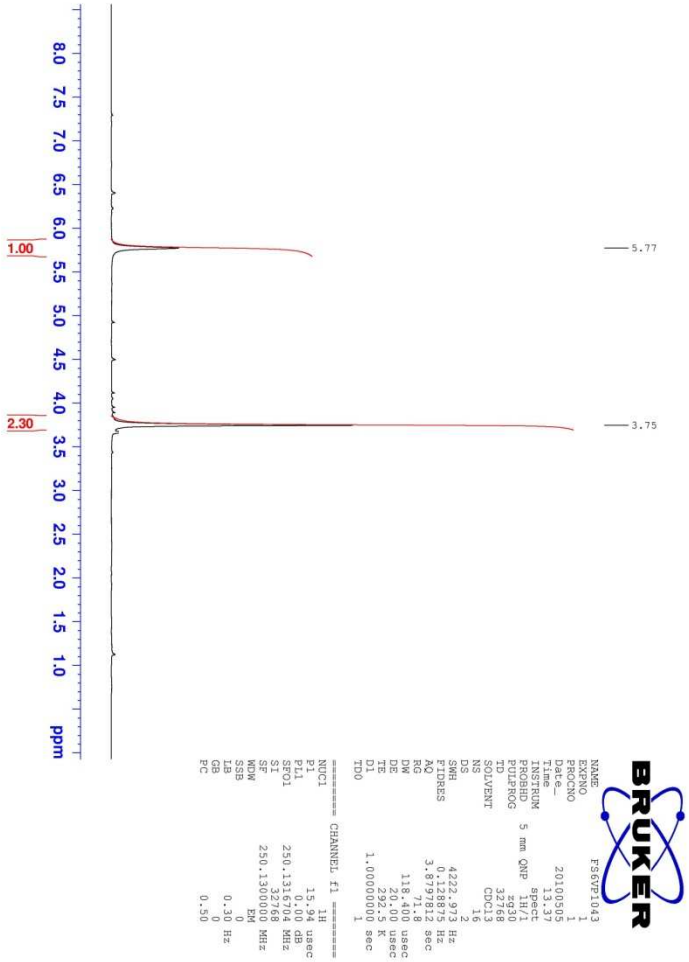
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 53.9, 58.8, 114.2, 129.2, 132.2, 163.7, 185.6.

IR (NaCl, cm^{-1}) 3099, 2938, 2115, 1711, 1610, 1591, 1566, 1512, 1454, 1420, 1390, 1372, 1258, 1170, 1120, 1021, 874, 844, 754.

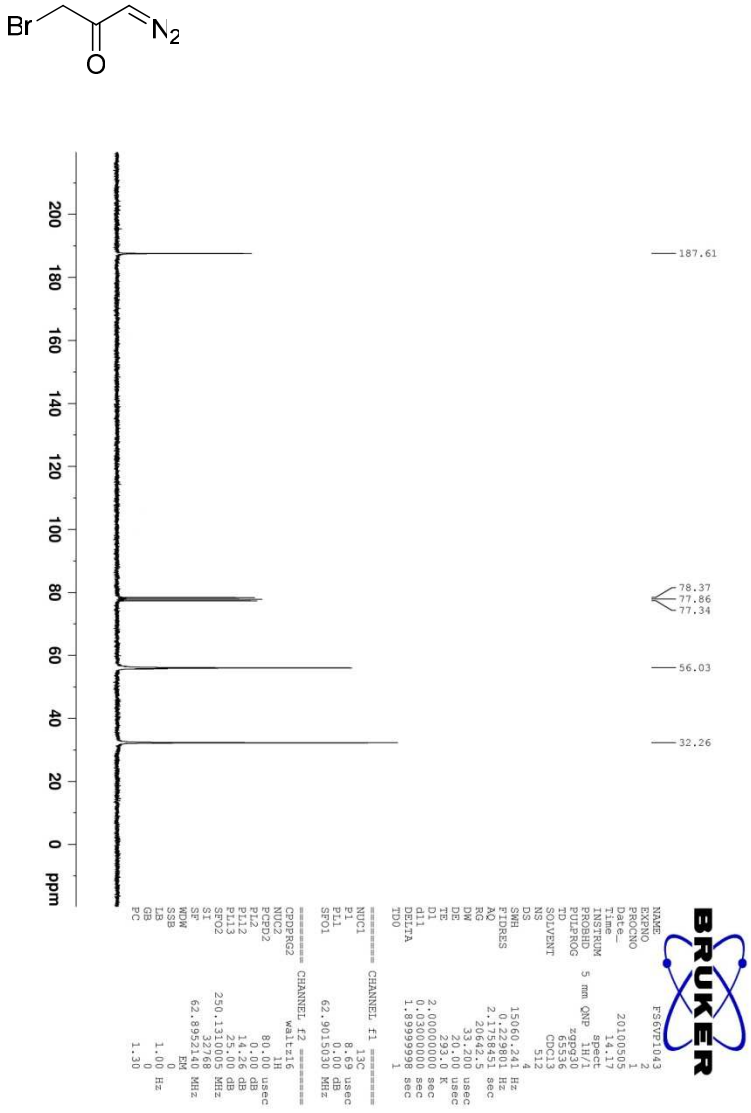
Elemental Analysis (%) for $C_9H_8N_2O_2$. Calcd.: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.41; H, 4.66; N, 15.95.

^{1}H Spectrum of compound **6a**

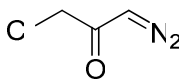


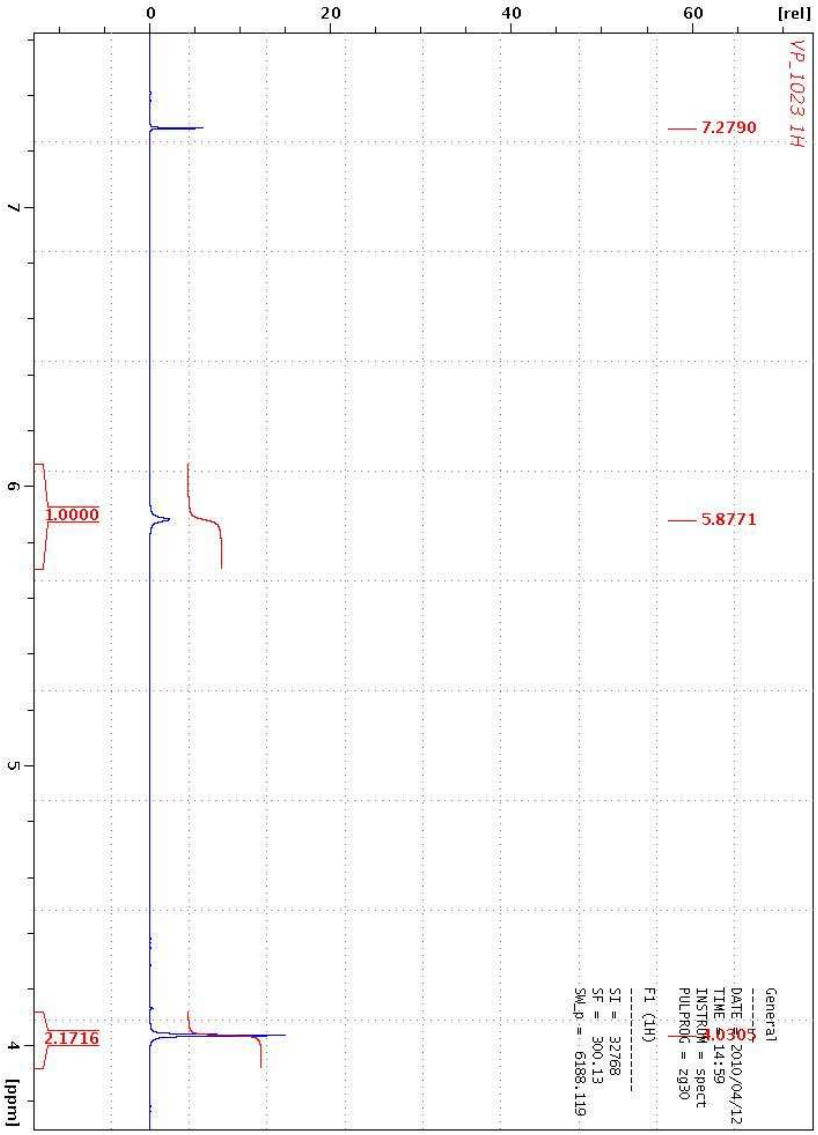


^{13}C Spectrum of compound **6a**

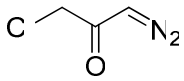


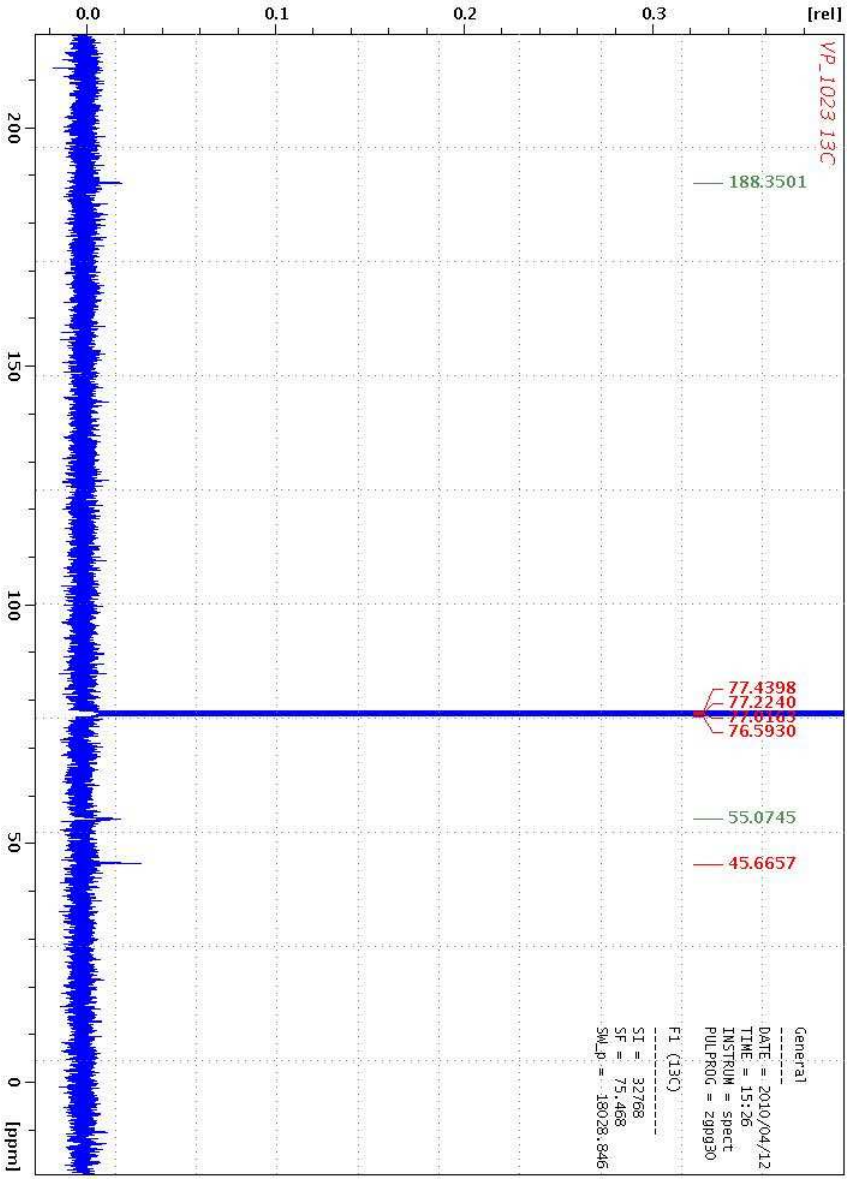
^{1}H Spectrum of compound **6b**



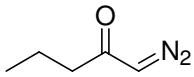


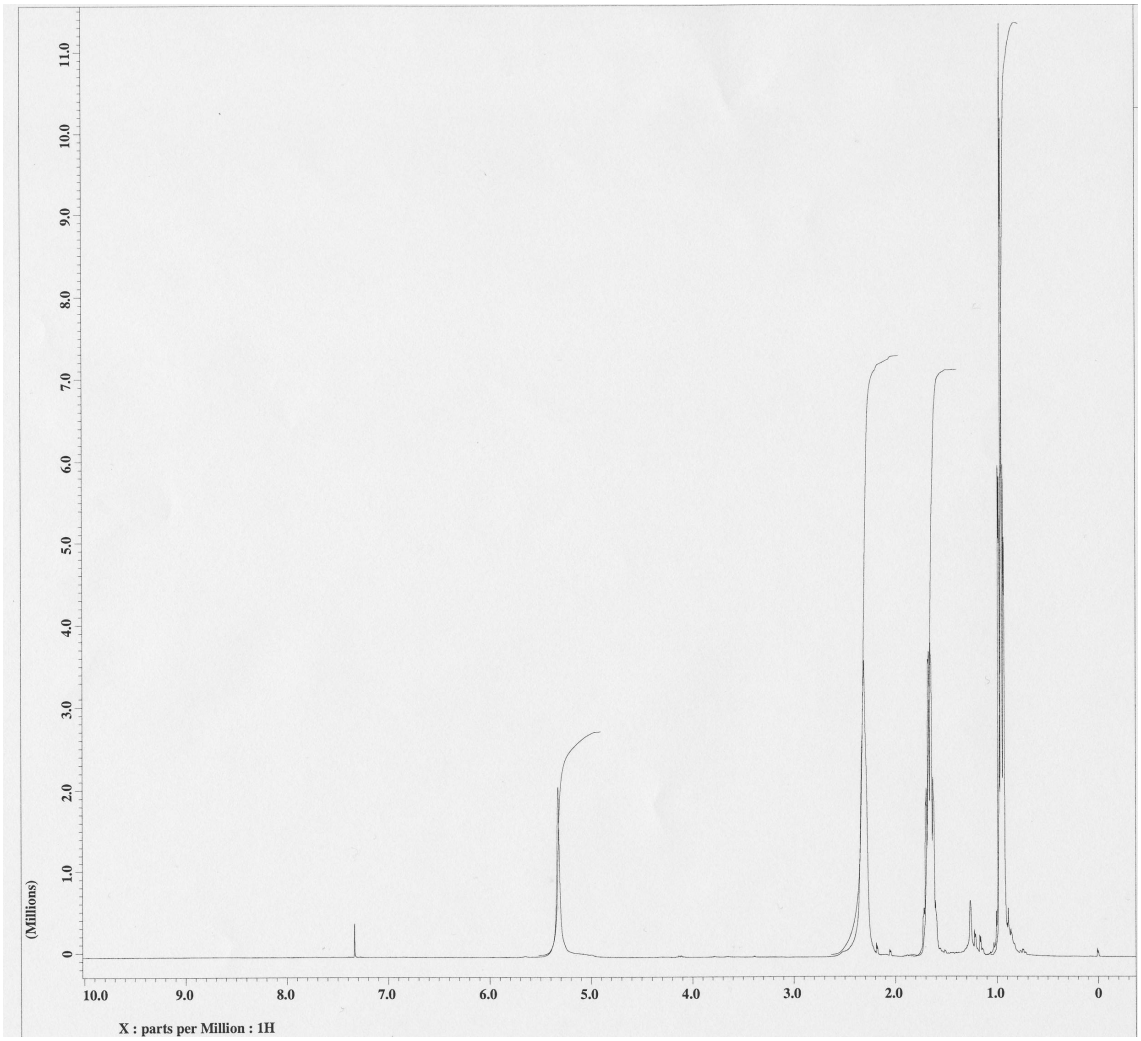
^{13}C Spectrum of compound **6b**



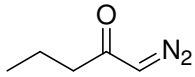


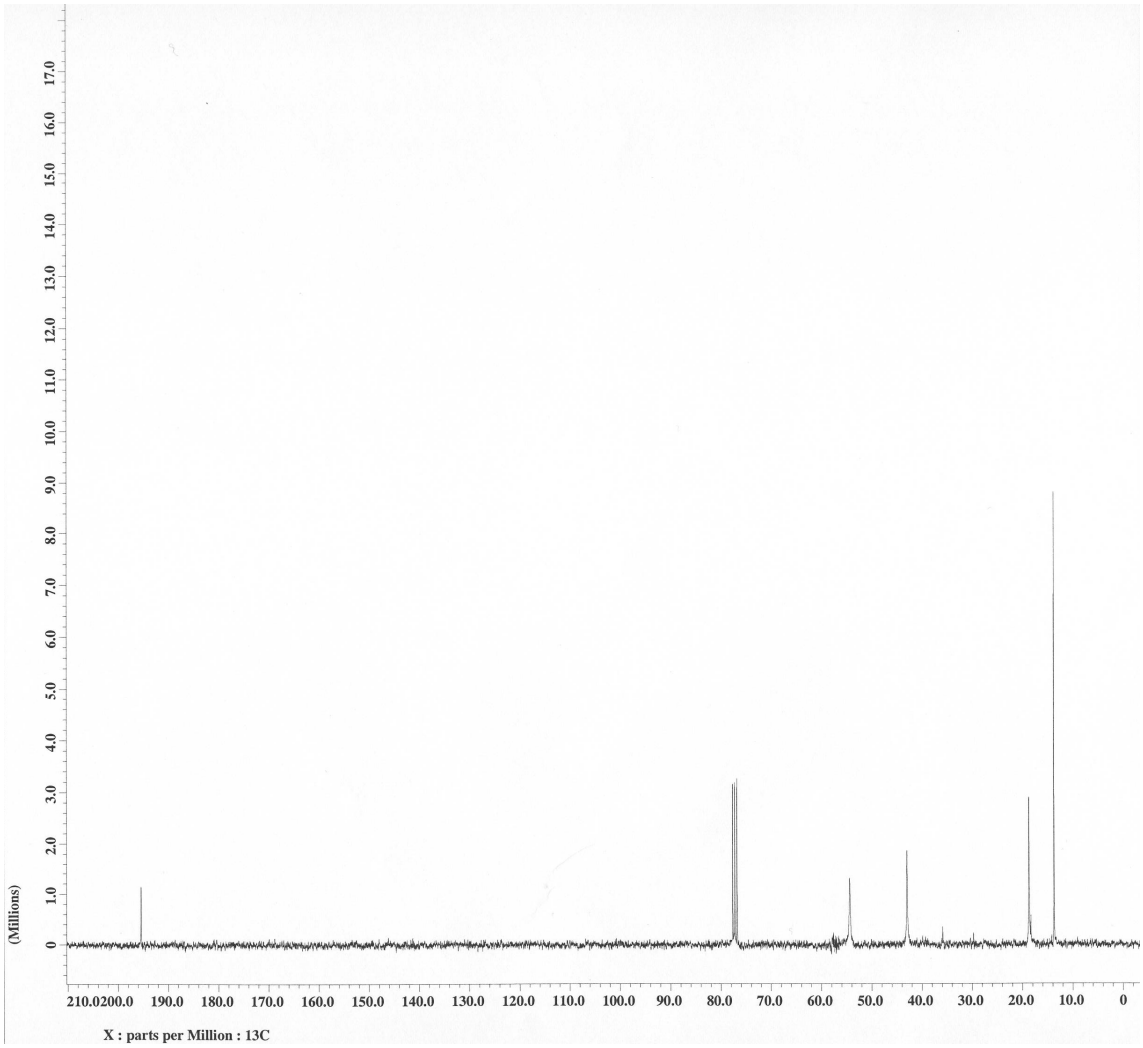
^{1}H Spectrum of compound **8a**



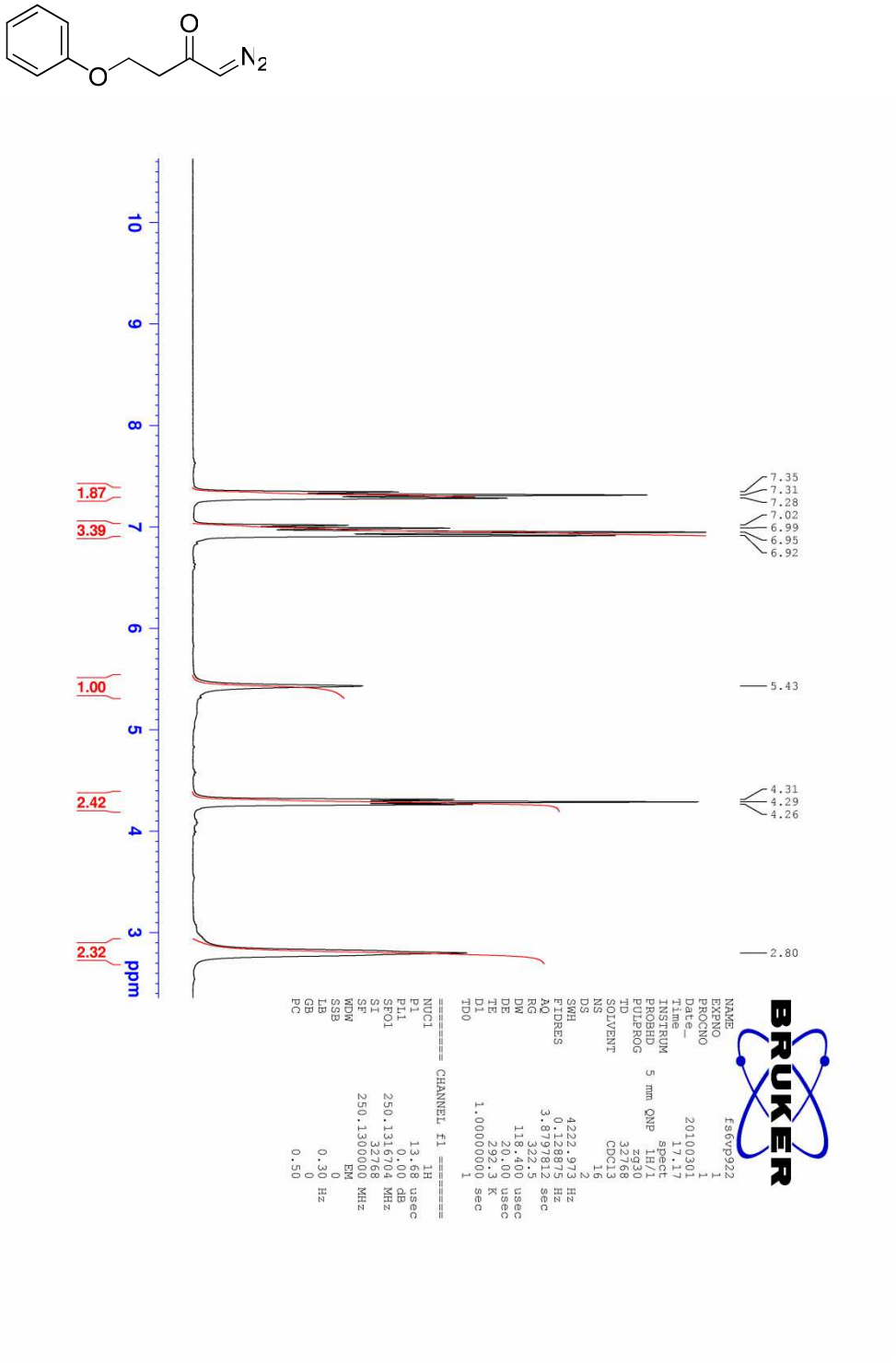


^{13}C Spectrum of compound **8a**

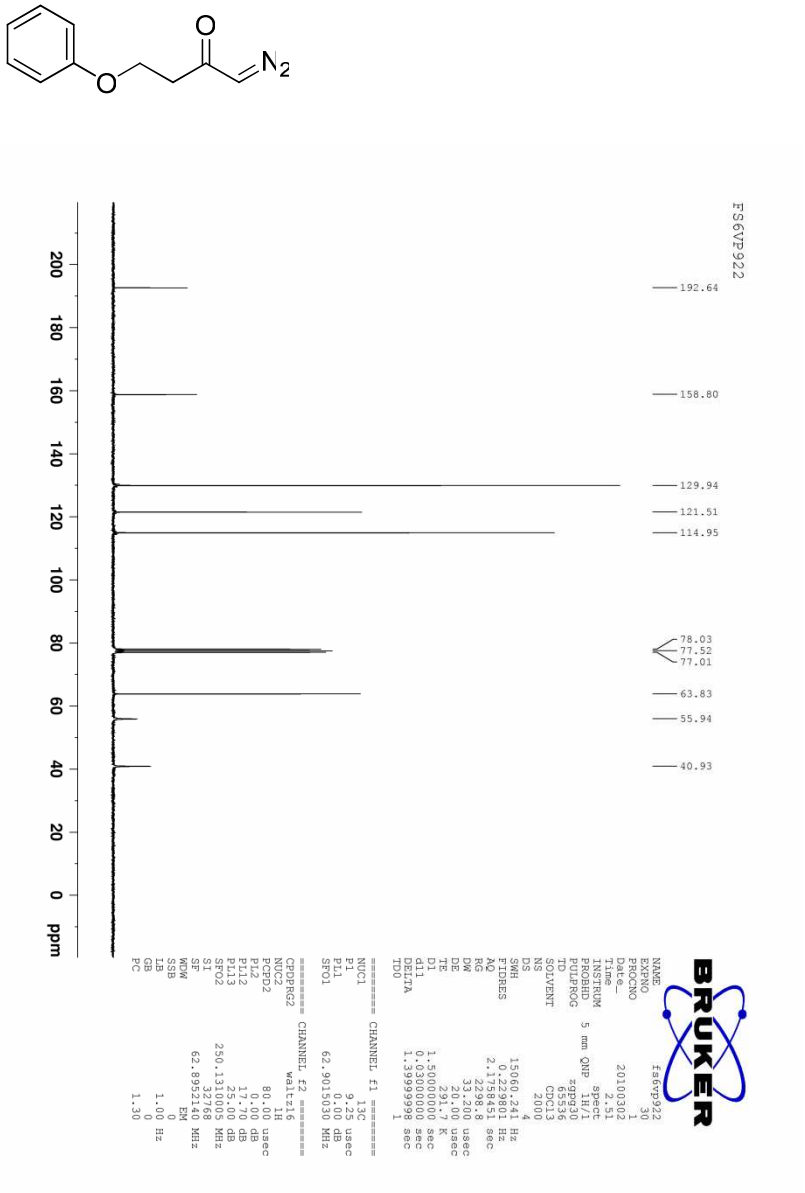




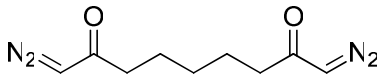
^{1}H Spectrum of compound **8b**

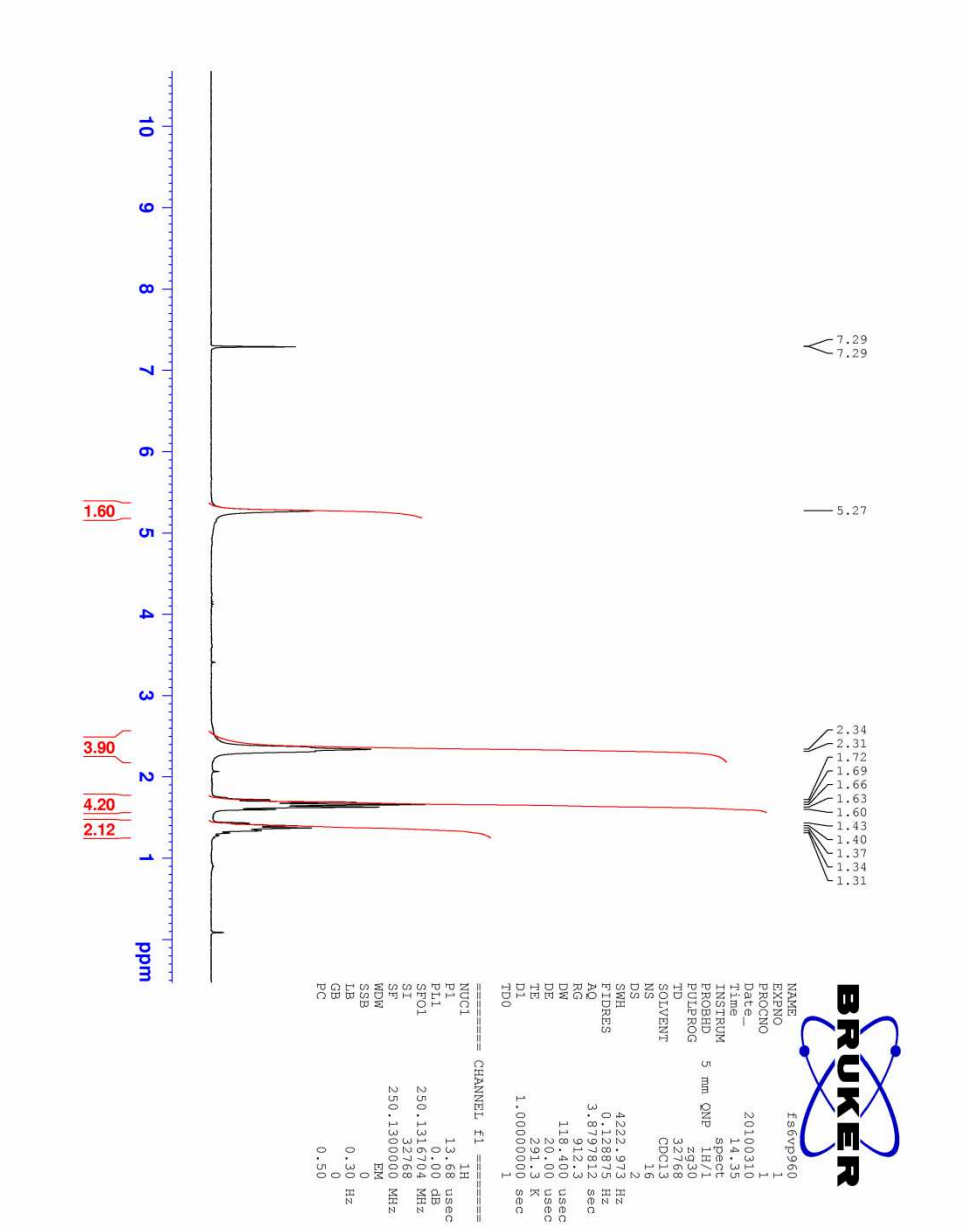


^{13}C Spectrum of compound **8b**

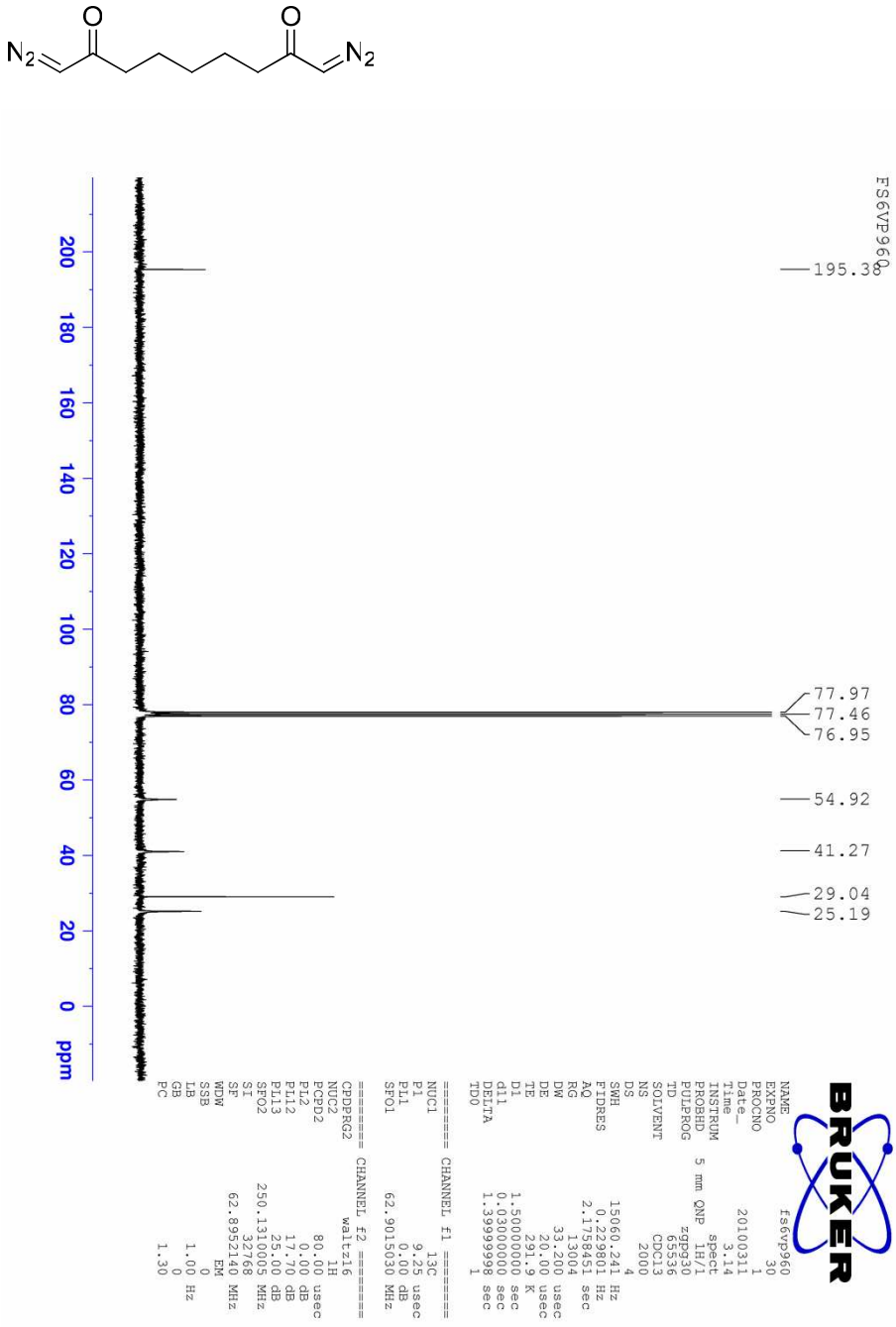


^{1}H Spectrum of compound **8c**

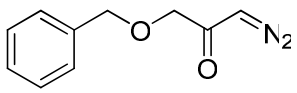


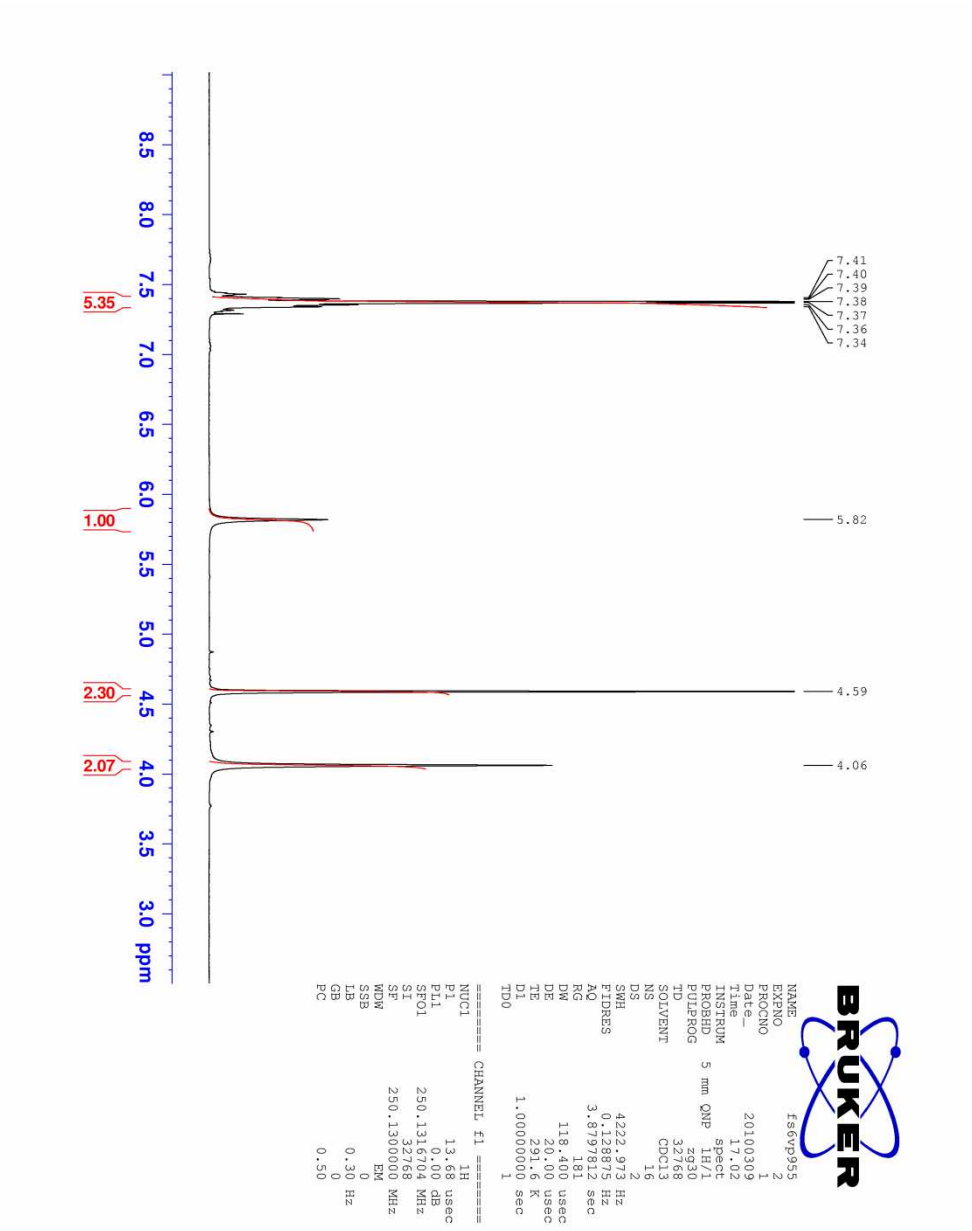


^{13}C Spectrum of compound **8c**

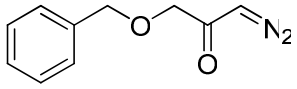


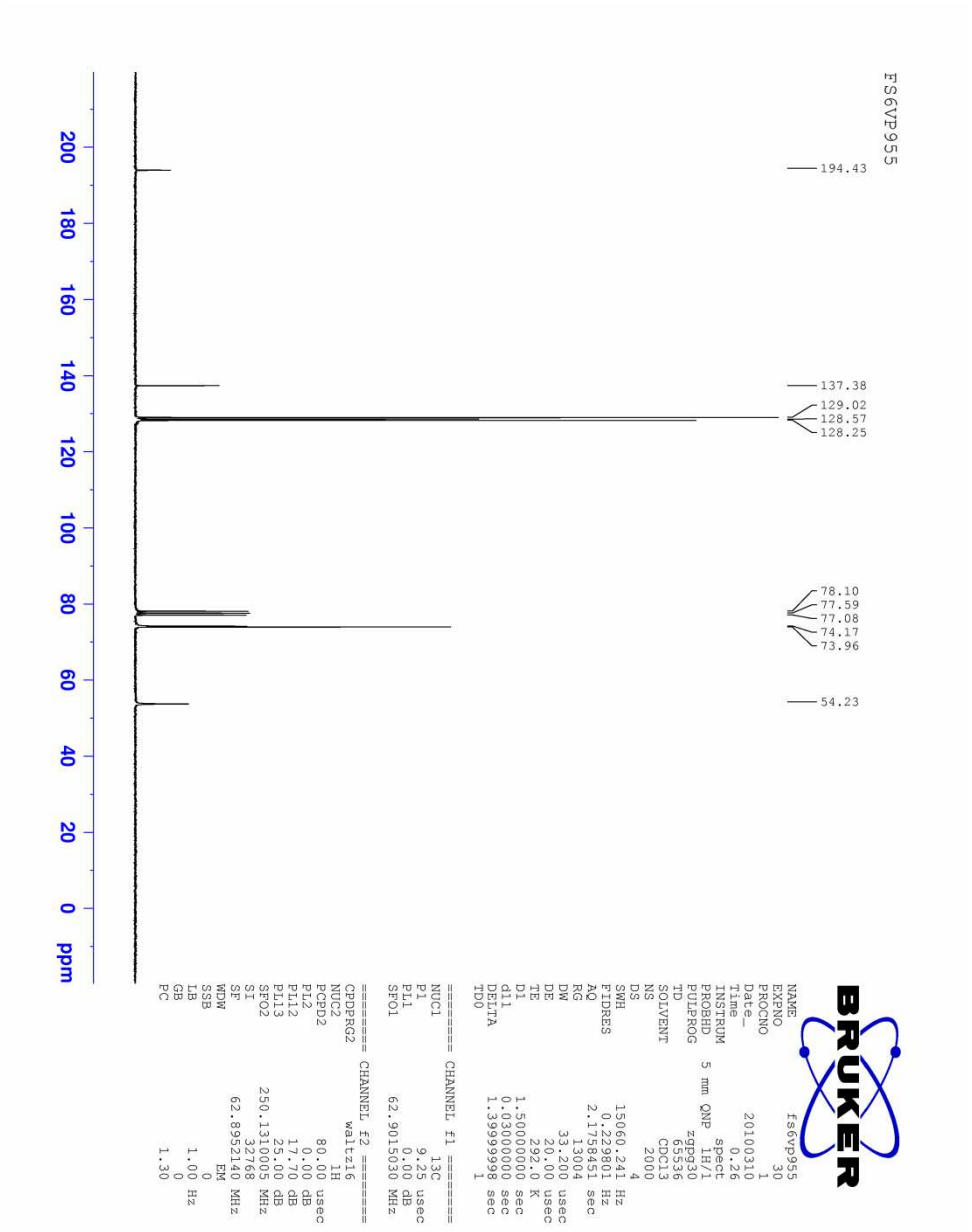
^{1}H Spectrum of compound **8d**



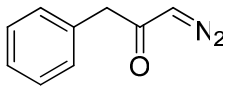


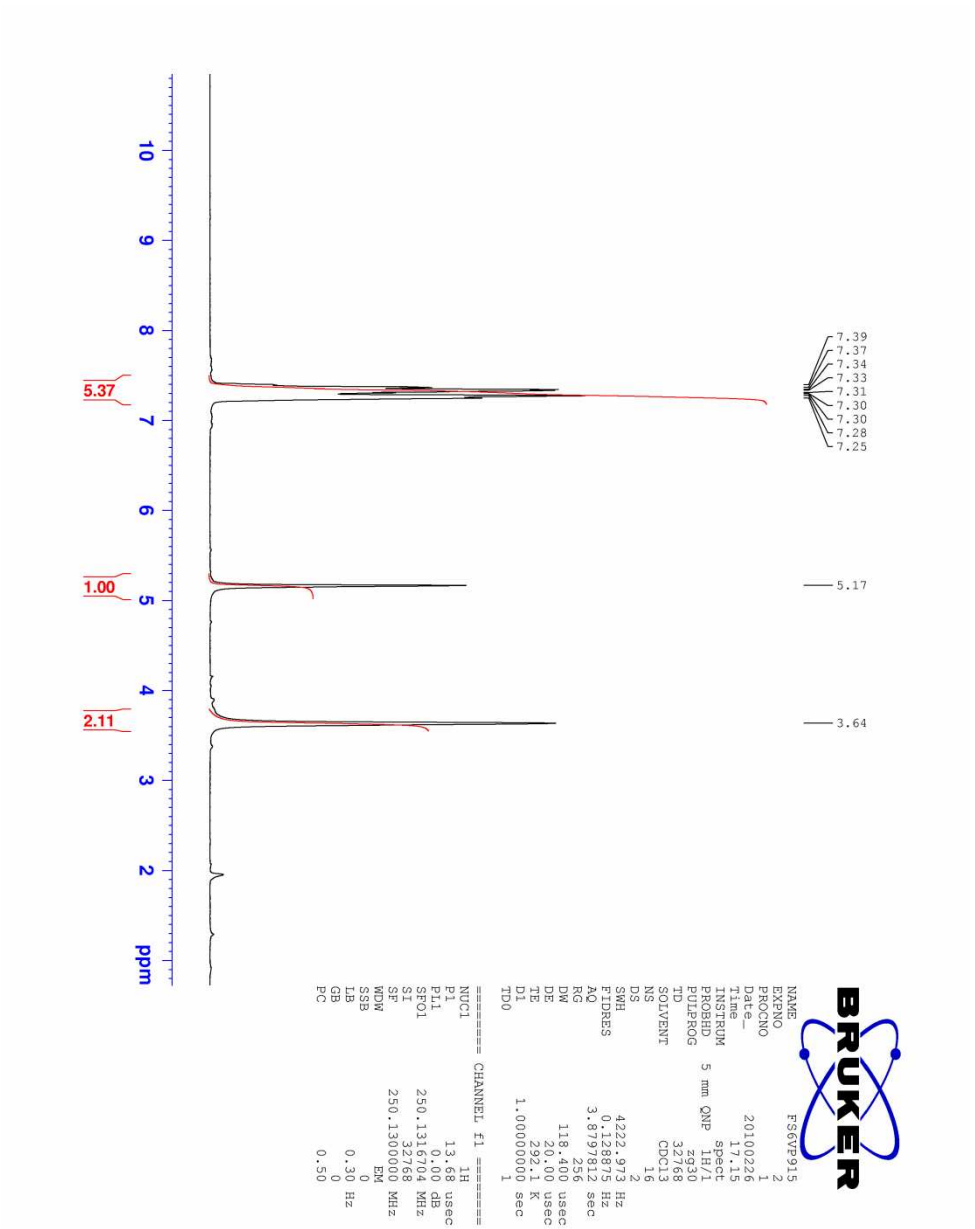
^{13}C Spectrum of compound **8d**



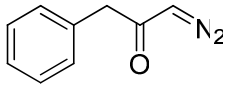


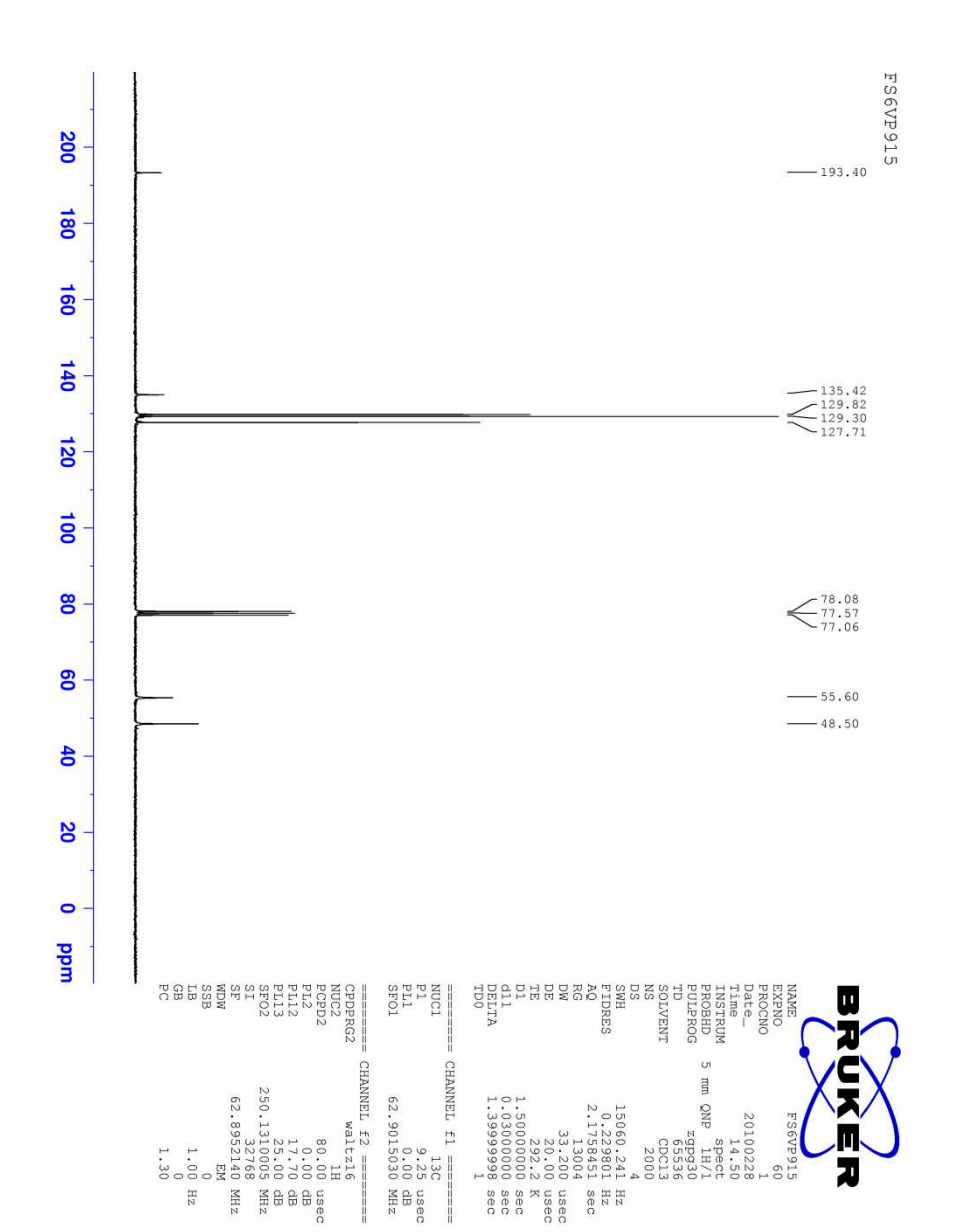
^{1}H Spectrum of compound **8e**



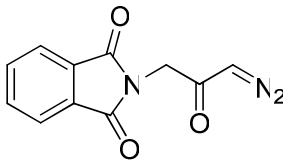


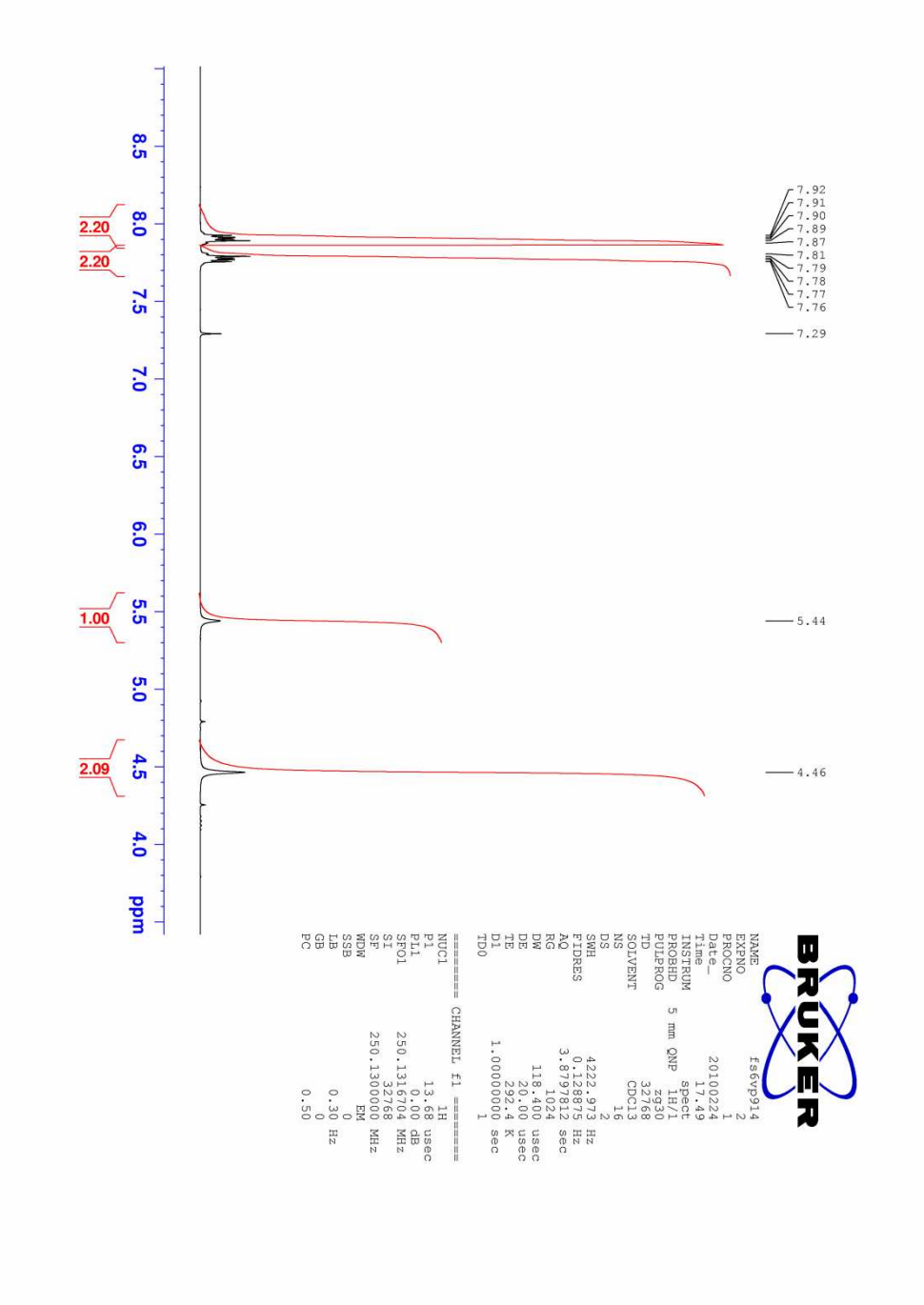
^{13}C Spectrum of compound **8e**



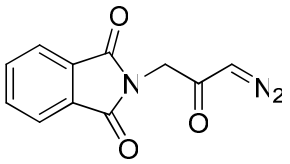


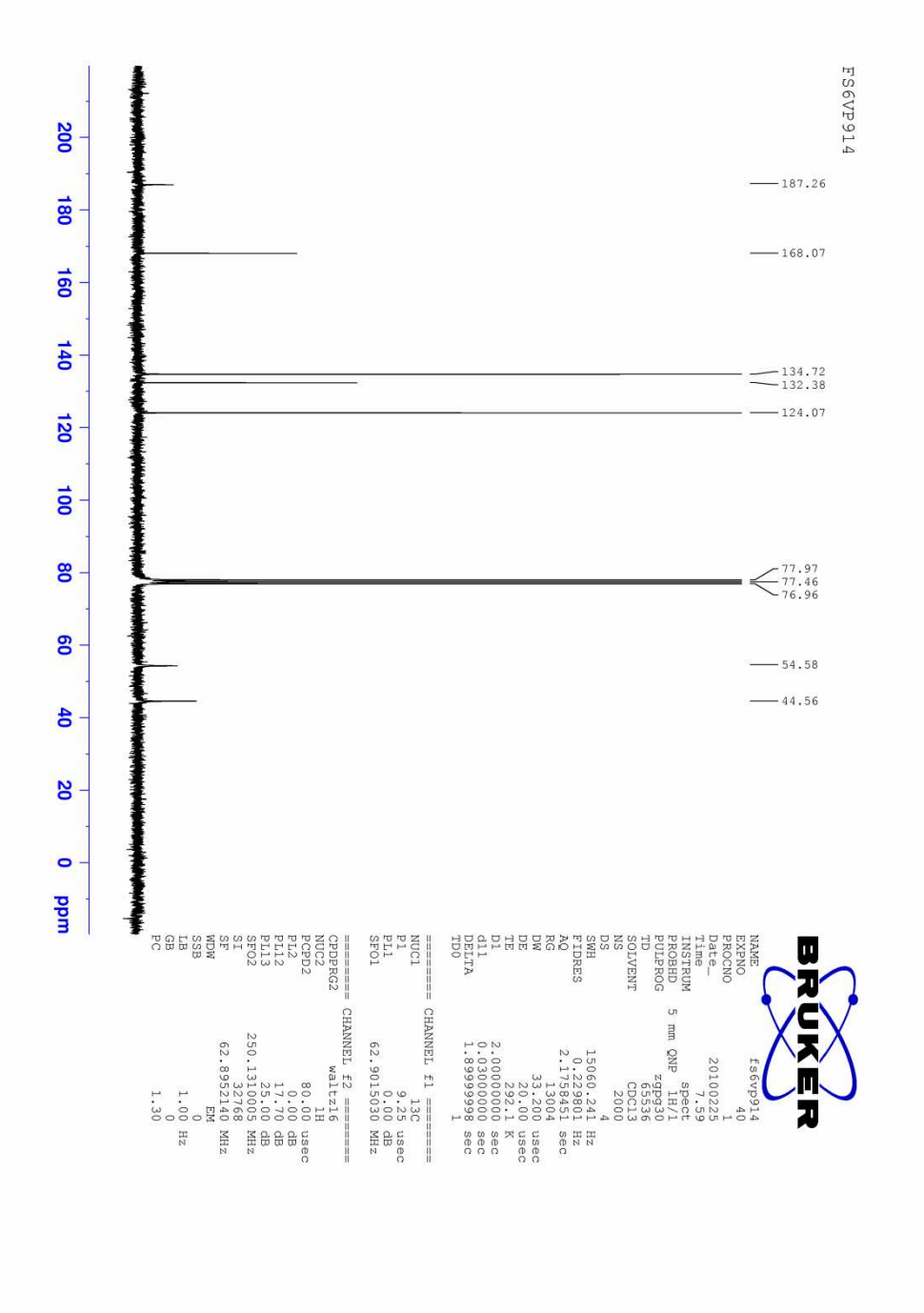
^{1}H Spectrum of compound **8f**



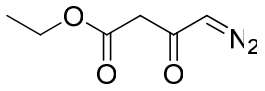


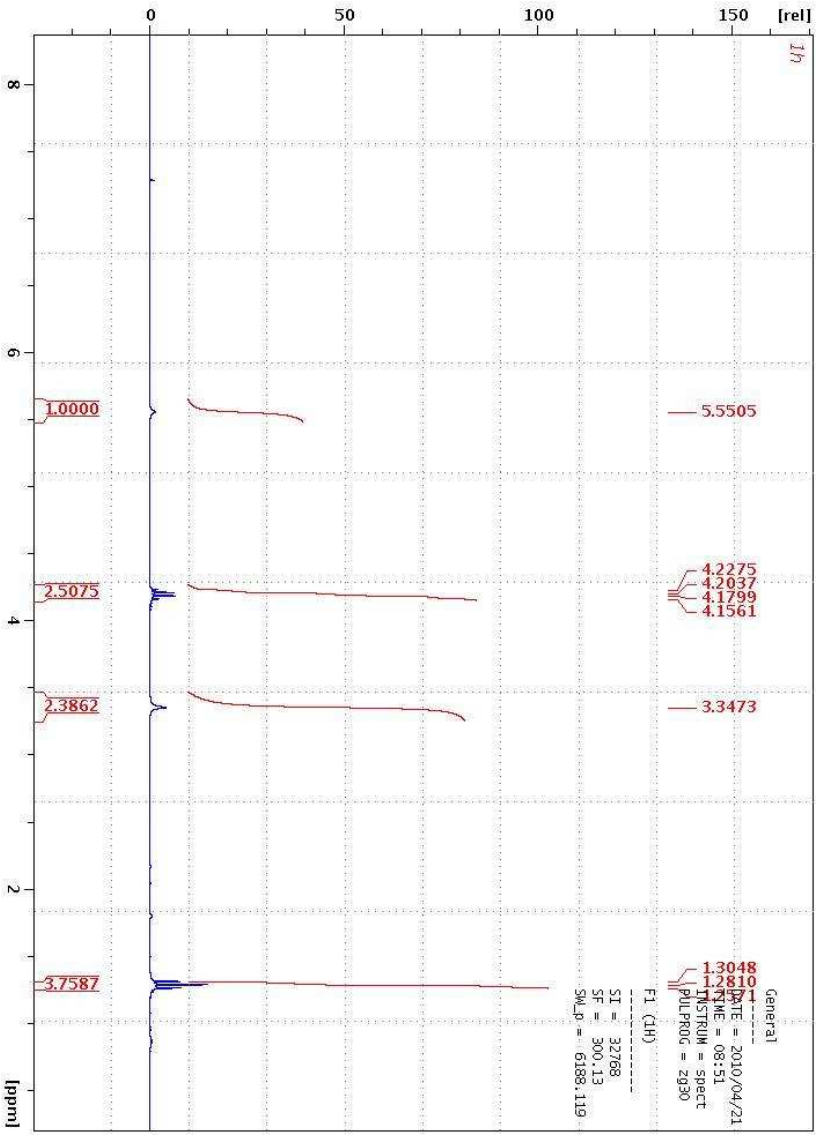
^{13}C Spectrum of compound **8f**



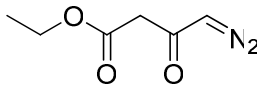


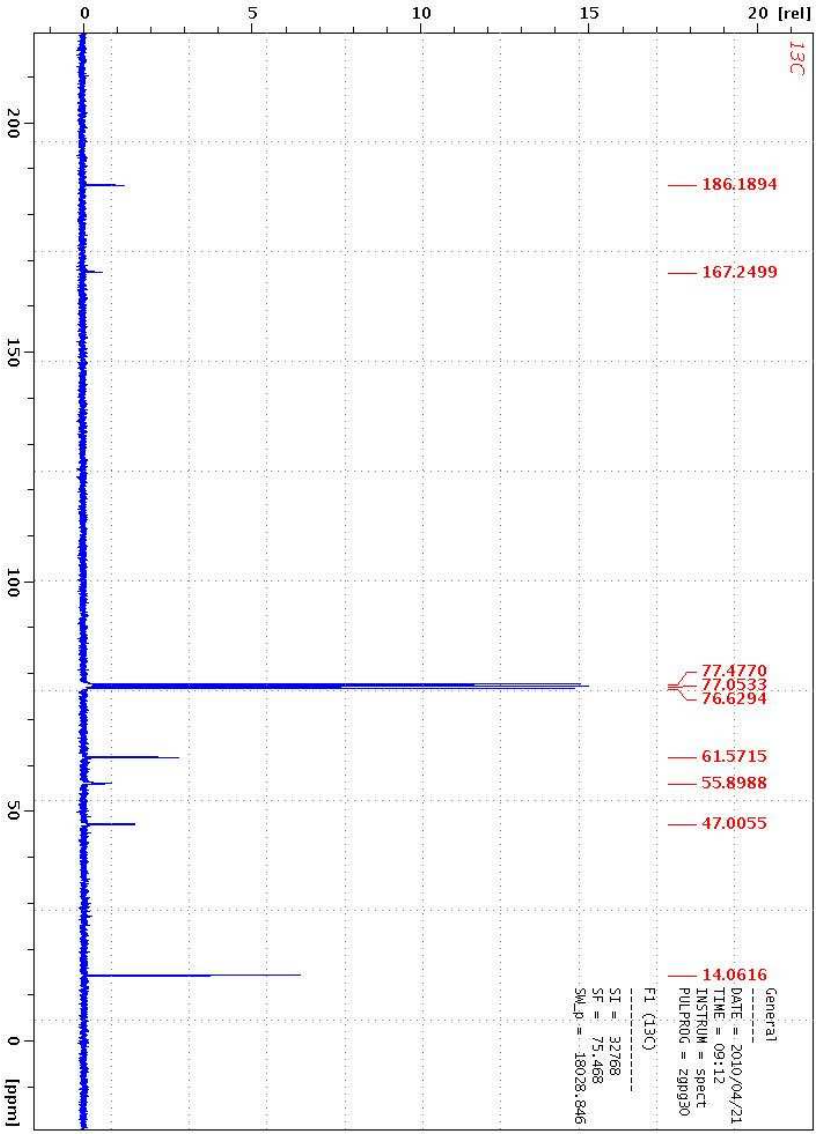
^{1}H Spectrum of compound **8g**



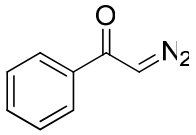


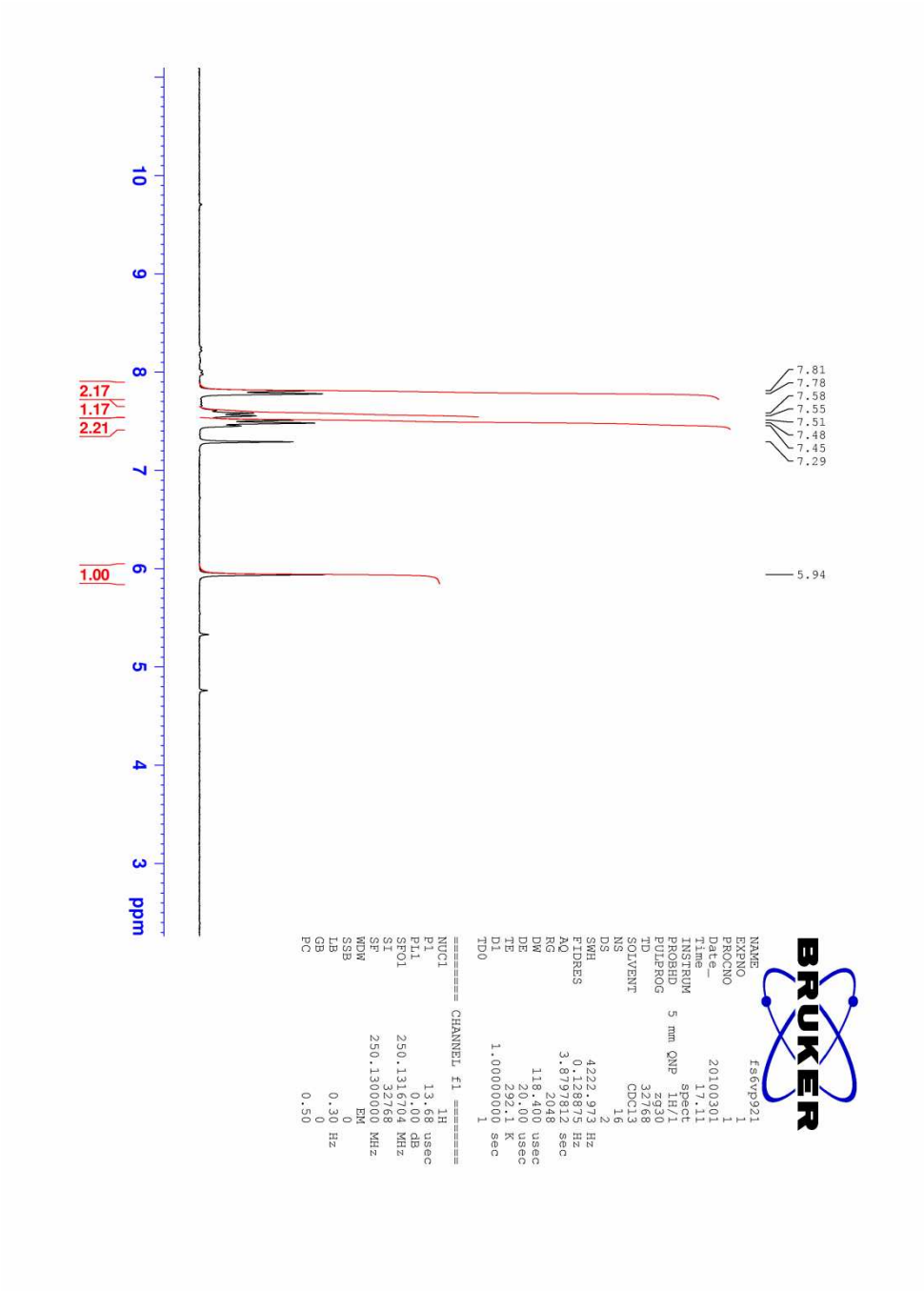
^{13}C Spectrum of compound **8g**



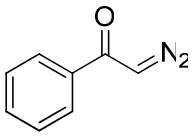


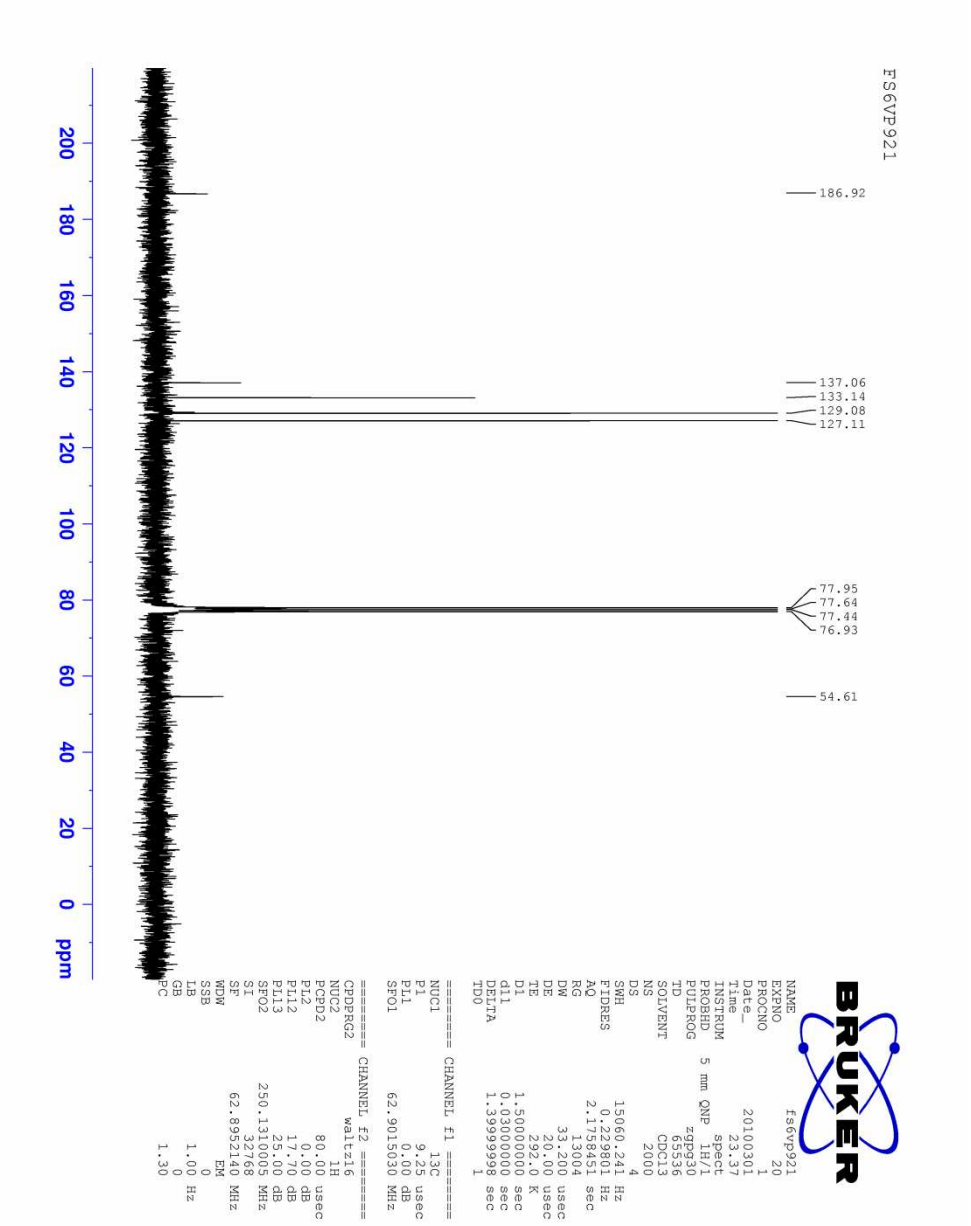
^{1}H Spectrum of compound **8h**



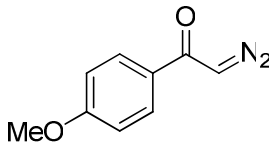


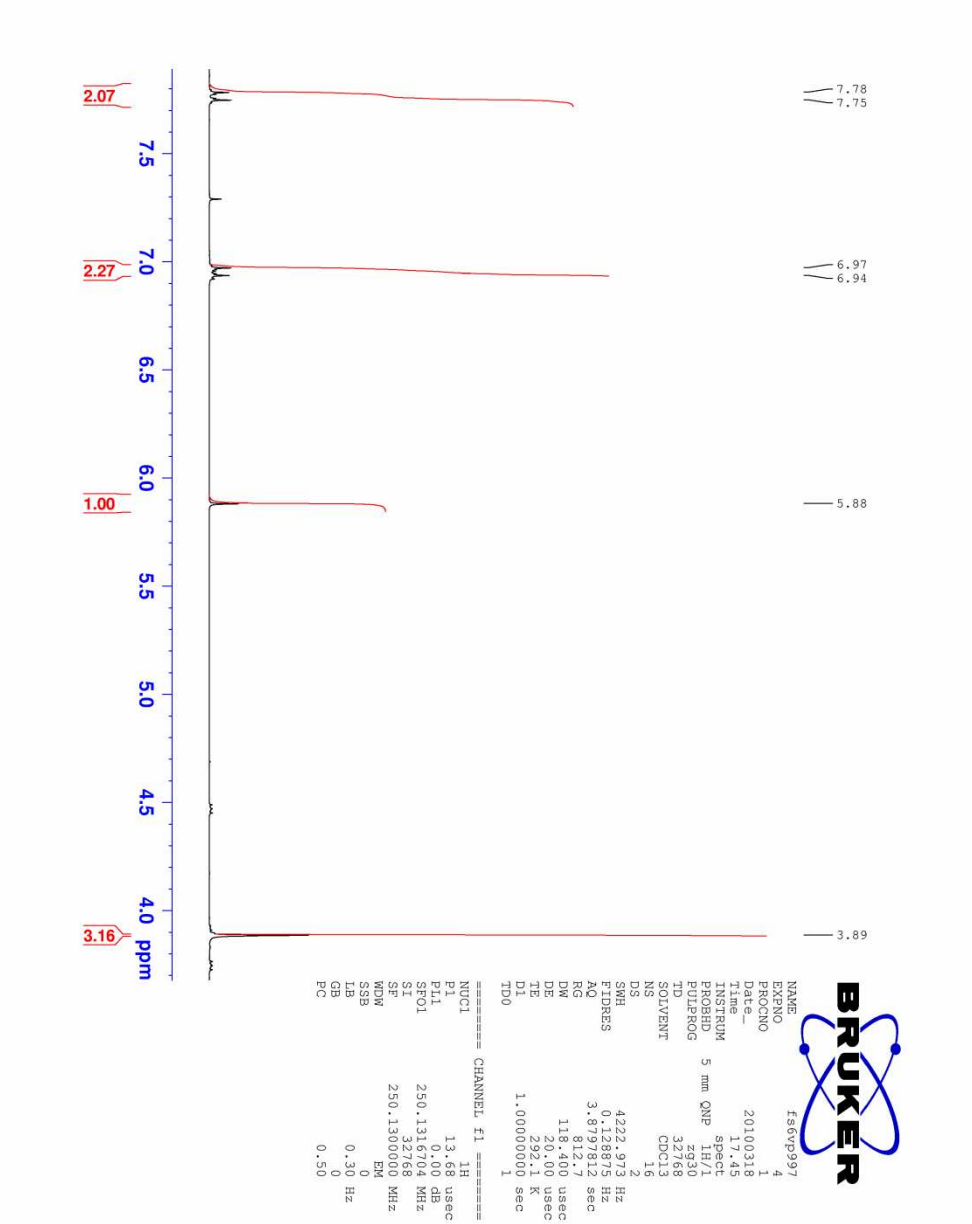
^{13}C Spectrum of compound **8h**



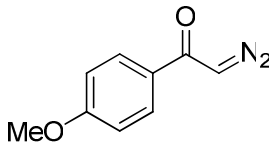


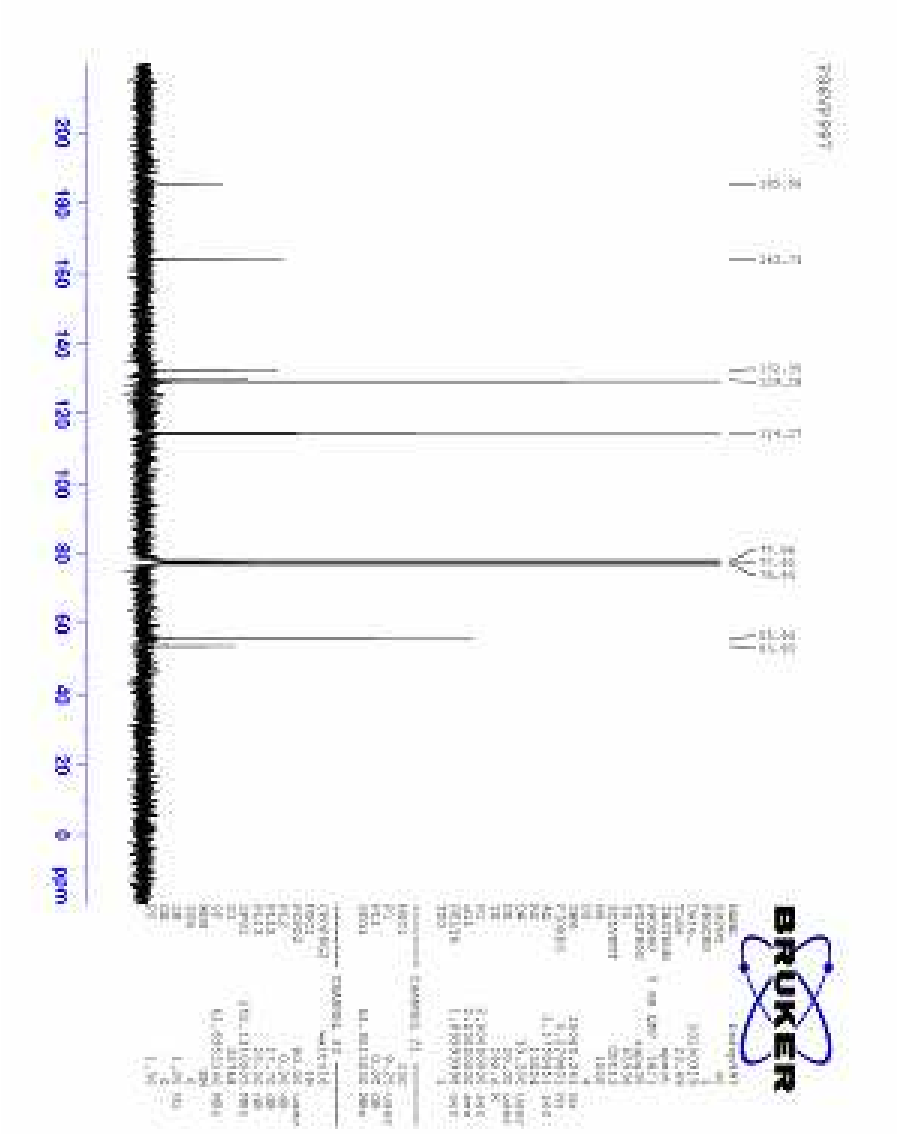
^{1}H Spectrum of compound **8i**





^{13}C Spectrum of compound **8i**





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