Continuous Platform to Generate Nitroalkanes On-Demand (in situ) using Peracetic Acid-Mediated Oxidation in a PFA Pipes-in-Series Reactor

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1. Preparation of starting materials

Materials.

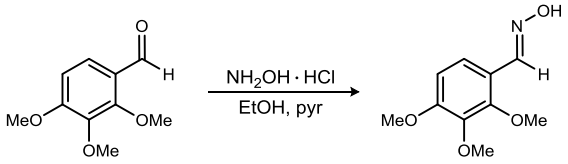
All reagents and solvents were commercial grade and purified prior to use when necessary. Flash column chromatography was performed using Acros 40-60 μm, pore size 60 Å silica gel with solvent systems indicated. Analytical thin layer column chromatography was performed using Merck KGaA 25 x 75 mm glass-backed DC-Kieselgel 60 F_{254} silica gel plates, and were visualized by fluorescence upon 250 nm radiation and/or the by use potassium permanganate. Solvent removal was effected by rotary evaporation under vacuum (~ 20-40 mm Hg). All extracts were dried with $MgSO_4$ unless otherwise noted.

Nuclear magnetic resonance spectra (NMR) were acquired on a 400 MHz Varian spectrometer. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.00 ($CDCl_3$), unless otherwise specified. Mass spectra were recorded on a Thermo Scientific Q-Exactive mass spectrometer. IR spectra were recorded on a Nicolet 6700 FT-IR and are reported in wavenumbers (cm^{-1}).

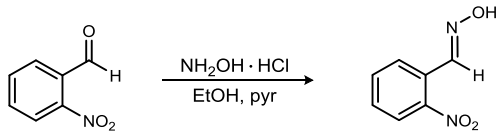
Oxime substrates were prepared according to the description provided in section "Synthesis of Starting Materials and Catalyst" and following previously published procedures. Acetic acid, ethanol, and toluene were purchased and used without further purification.

General procedure for oxime preparation:

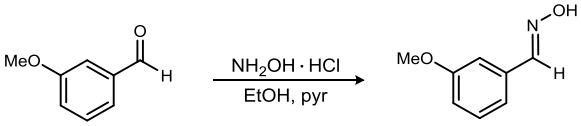
The aldehyde (1.0 equiv), pyridine (1.8 equiv), ethanol (~10 equiv) and hydroxylamine hydrochloride (1.4 equiv) were combined (in order) in in 250 mL round-bottomed flask at room temperature. The mixture was stirred overnight (at least 16 h) at room temperature. Ethanol was removed under reduced pressure. The resulting mixture was dissolved in EtOAc (100 mL), washed twice with 1 M aq HCl (100 mL), once with satd aq $NaHCO_3$ (100 mL) and brine (100 mL). The organic layer was separated and dried, filtered and concentrated under vacuum. The resulting oxime was used in the next step without additional purification.



2,3,4-Trimethoxybenzaldehyde oxime. Prepared according to the general procedure using 25.0 g of 2,3,4-Trimethoxybenzaldehyde (127 mmol). Concentration under vacuum resulted in a white solid (25.4 g, 120 mmol, 94%). The analytical data is identical to that reported.[1]

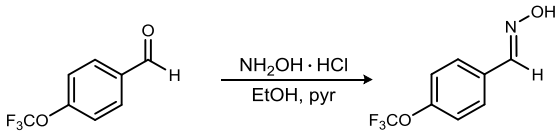


2-Nitrobenzaldehyde oxime. Prepared according to the general procedure using 22.6 g of 2-Nitrobenzaldehyde (150 mmol). Concentration under vacuum resulted in a light yellow solid (24.2 g, 146 mmol, 97%, 10:1 E/Z ratio). The analytical data is identical to that reported. [2]

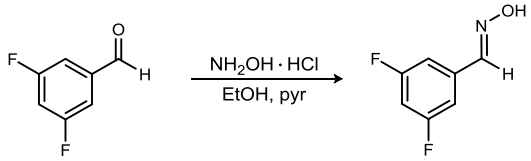


3-Methoxybenzaldehyde oxime. Prepared according to the general procedure using 18.3 mL of 3-Methoxybenzaldehyde (150 mmol). Concentration under vacuum resulted in a colorless oil (22.2 g, 147 mmol, 97%). The analytical data is identical to that reported. **Error! Bookmark not defined.**

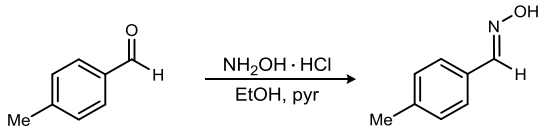
2-(Trifluoromethyl)benzaldehyde oxime. Prepared according to the general procedure using 19.7 mL of 2-(Trifluoromethyl)benzaldehyde (149 mmol). Concentration under vacuum resulted in a white crystalline solid (26.3 g, 139 mmol, 93%). The analytical data is identical to that reported. [3]



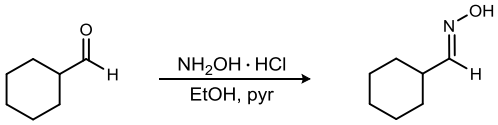
4-(Trifluoromethoxy)benzaldehyde oxime. Prepared according to the general procedure using 21.4 mL of 4-(Trifluoromethoxy)benzaldehyde (150 mmol). Concentration under vacuum resulted in a white solid (27.5 g, 134 mmol, 90%). The analytical data is identical to that reported.[4]



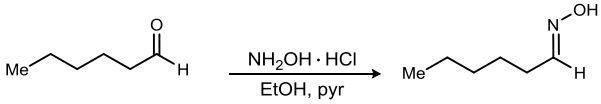
3,5-Difluorobenzaldehyde oxime. [5] Prepared according to the general procedure using 16.5 mL of 3,5-Difluorobenzaldehyde (150 mmol). Concentration under vacuum resulted in white crystalline solid (22.3 g, 142 mmol, 94%, 20:1 *E/Z* ratio). *E*-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.09 (br s, 1H), 7.10 (d, J = 5.6 Hz, 1H), 7.23 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (dd, J_{CF} = 12.5, 248 Hz), 148.5 (d, J_{CF} = 3 Hz), 135.1 (t, J_{CF} = 10 Hz), 109.8 (dd, J_{CF} = 7.6, 19.0 Hz), 105.3 (t, J_{CF} = 25.5 Hz).



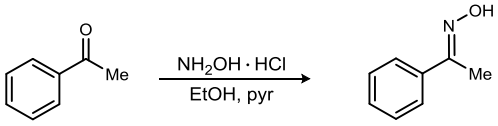
4-Methylbenzaldehyde oxime. Prepared according to the general procedure using 17.7 mL of 4-methylbenzaldehyde (150 mmol). Concentration under vacuum resulted in a white solid (19.6 g, 145 mmol, 97%, 10:1 *E/Z* ratio). The analytical data is identical to that reported. [6]



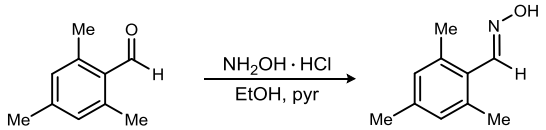
Cyclohexanecarbaldehyde oxime. Prepared according to the general procedure using 18.2 mL of cyclohexanecarbaldehyde (150 mmol) Concentration under vacuum resulted in colorless oil (17.7 g, 139 mmol, 93%, 2.3:1 *E/Z* ratio). The analytical data is identical to that reported. [7]



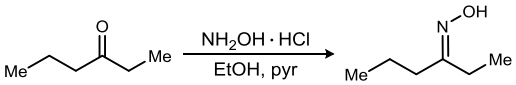
Hexanal oxime. Prepared according to the general procedure using 18.0 mL of hexanal (150 mmol), Concentration under vacuum resulted in a white solid (16.4 g, 142 mmol, 95.0%, 1.2:1 *E/Z* ratio).). The analytical data is identical to that reported.[8]



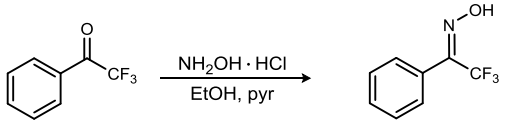
1-Phenylethanone oxime. Prepared according to the general procedure using 17.5 mL of 1-Phenylethanone (150 mmol). Concentration under vacuum resulted in a white solid (18.3 g, 135 mmol, 90%). The analytical data is identical to that reported. [9]



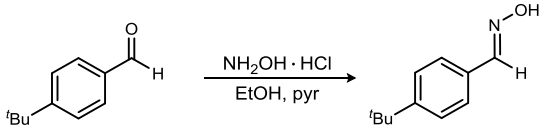
2,4,6-Trimethylbenzaldehyde oxime. Prepared according to the general procedure using 22.1 mL of 2,4,6-Trimethylbenzaldehyde (150 mmol). Concentration under vacuum resulted in a white solid (23.7 g, 145 mmol, 97%). The analytical data is identical to that reported. [10]



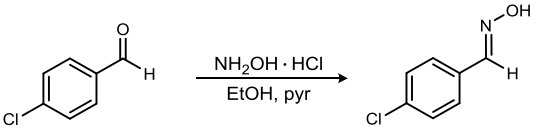
Hexan-3-one oxime.[11] Prepared according to the general procedure using 18.4 mL of Hexan-3-one (150 mmol). Concentration under vacuum resulted in a white solid (13.5 g, 117 mmol, 78%, 1:1 E/Z ratio). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br s, 1H), 2.42-2.31 (m, 2H), 2.24-2.14 (m, 2H), 1.63-1.50 (m, 2H), 1.11-1.03 (m, 3H), 0.98-0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.4, 162.3, 35.6, 29.4, 27.3, 20.7, 19.5, 19.0, 14.2, 13.7, 10.6, 9.9; HRMS (ESI): Exact mass calcd for $C_6H_{14}NO_2$ $[M+H]^+$ 116.1070, found 116.1071.



2,2,2-Trifluoro-1-phenyl-ethanone oxime. Prepared according to the general procedure using 21.0 mL of 2,2,2-Trifluoro-1-phenyl-ethanone (150 mmol). Concentration under vacuum resulted in a white solid (20.3 g, 107 mmol, 72%, 1:1 *E/Z* ratio). The analytical data is identical to that reported. [12]



4-tert-Butylbenzaldehyde oxime. Prepared according to the general procedure using 206 mL of 4-*tert*-Butylbenzaldehyde (1.20 mol). Concentration under vacuum resulted in a white crystalline solid (208.2 g, 1175 mmol, 95%). The analytical data is identical to that reported. [13]



4-Chlorobenzaldehyde oxime. Prepared according to the general procedure using 200 g of 4-Chlorobenzaldehyde (1.42 mol). Concentrated under vacuum resulted in a white crystalline solid (204.5 g, 1314 mmol, 92%). The analytical data is identical to that reported. **Error! Bookmark not defined.**

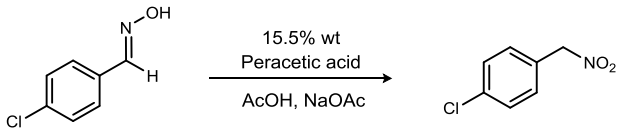
***N*-[4-[hydroxyiminomethyl]phenyl]acetamide**. Prepared according to the general procedure using 9.90 g of *N*-(4-Formylphenyl)acetamide (60.7 mmol). Due to its insolubility in EtOAc the oxime was filtered using a Buchner funnel after the first wash with 1 M aq HCl (100 mL). The filter cake was washed with water (2x30 mL) and 20% EtOAc in hexanes (30 mL), and then dried to provide a yellow solid. The EtOAc solution underwent standard extraction procedure and its concentrated under vacuum provided additional 800 mg of the solid. After NMR analysis confirming that both fractions (filtered solid and EtOAc extract) were identical, they were combined to provide the desired product (10.2 g, 57.2 mmol, 94%, 8:1 *E/Z* ratio). The analytical data is identical to that reported. **Error! Bookmark not defined.**

2. Oxidation of oximes: nitroalkane synthesis.

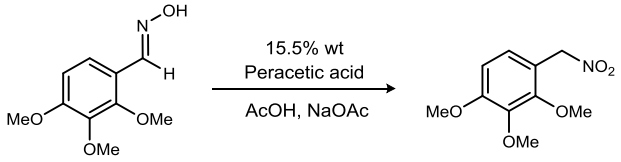
General procedure for oxime oxidation:

The oxime (20.0 mmol, 1.0 equiv) was dissolved in glacial acetic acid (7.0 equiv, 140 mmol). The mixture was heated to 90-92 °C. Sodium acetate (500 mg, 0.18 equiv) was dissolved in a solution of peracetic acid (2.0-4.0 equiv) and the mixture was added in dropwise manner over 20-30 min. The overall reaction time was 30-40 min

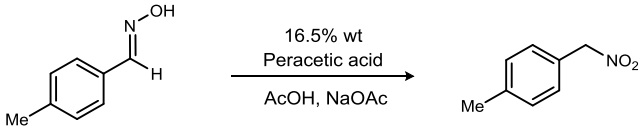
while the temperature of the reaction was maintained carefully at 92-97 °C. The reaction was diluted with water (100 mL) and cooled to room temperature. The resulting solution was extracted with methylene chloride (2x50 mL). The combined organic layers were washed with water (75 mL), satd $NaHCO_3$ (75 mL), satd Na_2SO_3 (75 mL), and brine (75 mL). The resulting solution was dried, filtered, and concentrated. Purification by flash column chromatography (ethyl acetate in heptane) provided the desired product.



1-Chloro-4-(nitromethyl)benzene. 4-Chlorobenzaldehyde oxime (3.11 g, 20.0 mmol) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 40 min reaction time to give the desired product (1.18 g, 6.88 mmol, 34%) as a light yellow oil after flash chromatography (0-8% ethyl acetate in heptane). The benzoic acid was isolated in 29% yield (903 mg). All spectral data were in agreement with literature values.[14]



1,2,3-Trimethoxy-4-(nitromethyl)benzene. 2,3,4-Trimethoxybenzaldehyde oxime (4.22 g, 20.0 mmol) and peracetic acid (17.50 mL, 39.9 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (1.43 g, 6.29 mmol, 32%) as a yellow oil after flash chromatography (0-16% ethyl acetate in heptane). R_f = 0.32 (20% EtOAc/heptane); IR (film) 2969, 2936, 1603, 1555, 1498, 1473, 1372, 1280, 1263, 1099, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.40 (s, 2H), 3.93 (s, 3H). 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 155.5, 152.5, 141.8, 126.1, 116.1, 106.8, 74.3, 60.8, 60.6, 55.8; HRMS (ESI) exact mass calcd for $C_{10}H_{14}NO_5$ $[M+H]^+$ 228.0867, found 228.0864.

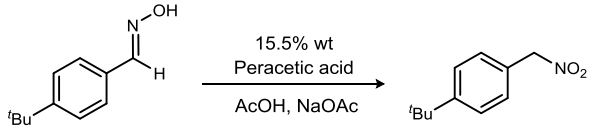


1-Methyl-4-(nitromethyl)benzene.

A. 4-Methylbenzaldehyde oxime (2.70 g, 20.0 mmol, 100 mass%) and peracetic acid (17.50 mL, 39.9 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (1.87 g, 12.4 mmol, 62%, containing ~1% aldehyde) as a yellow oil after flash chromatography (0-5% ethyl acetate in heptane). Benzoic acid was also isolated 240 mg (9%).

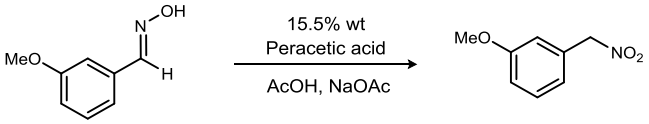
B. 4-Methylbenzaldehyde oxime (2.70 g, 20.0 mmol) and peracetic acid (11.00 mL, 25.1 mmol, 15.5 mass%) were used according to the general procedure with 10 min addition time and overall 15 min reaction time to provide the desired product (1.47 g, 9.69 mmol, 49%) as a yellow oil after flash chromatography (0-10% ethyl acetate in heptane). Benzoic acid was isolated in 5% yield (144 mg) and started material was recovered in 33% yield (896 mg).

All spectral data are in agreement with literature values. [15]

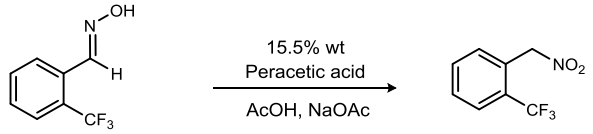


1-*tert*-Butyl-4-(nitromethyl)benzene. 4-*tert*-Butylbenzaldehyde oxime (3.55 g, 20.0 mmol) and peracetic acid (17.50 mL, 39.9 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (2.56 g, 13.2 mmol, 66%, containing ~1% aldehyde) as

a yellow oil after flash chromatography (0-4% ethyl acetate in heptane). Starting material oxime was also recovered (286 mg, 8% recovery) and benzoic acid by-product isolated (240 mg, 7%). All spectral data are in agreement with literature values. [16]



1-methoxy-3-(nitromethyl)benzene. 3-Methoxybenzaldehyde oxime (3.03 g, 20.0 mmol) and peracetic acid (17.50 mL, 39.9 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (1.23 g, 7.36 mmol, 37%) as a yellow oil after flash chromatography (0-8% ethyl acetate in heptane). Acid extracted into bicarbonate layer was isolated in 9% yield (280 mg) and sm was also recovered (417 mg, 14%). All spectral data are in agreement with literature values. [17]

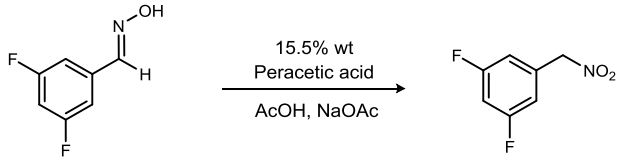


1-(Nitromethyl)-2-(trifluoromethyl)benzene.

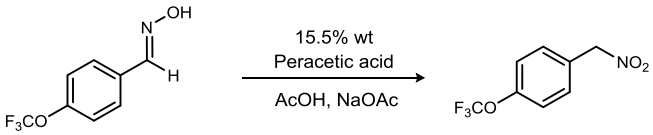
A. 2-(Trifluoromethyl)benzaldehyde oxime (3.78 g, 20.0 mmol,) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 40 min reaction time to give the desired product (1.33 g, 6.48 mmol, 32%) as a yellow oil after flash chromatography (0-8% ethyl acetate in heptane). Acid extracted into bicarbonate layer was isolated in 11% yield (420 mg) and starting oxime was recovered (1.1 g, 29%).

B. 2-(trifluoromethyl)benzaldehyde oxime (3.78 g, 20.0 mmol) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 50 min reaction time to give the desired product (1.52 g, 7.43 mmol, 37%) as a yellow oil after flash chromatography (2-16% ethyl acetate in heptane). Benzoic acid was isolated in 15% yield (582 mg) and starting oxime was recovered (700 mg, 19 %).

All spectral data are in agreement with literature values. [18,20]

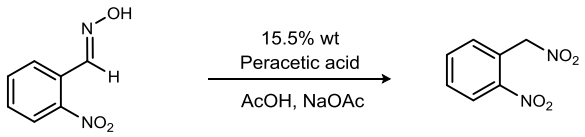


1,3-Difluoro-5-(nitromethyl)benzene.[19] 3,5-Difluorobenzaldehyde oxime (3.15 g, 20.0 mmol) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 40 min reaction time to give the desired product (1.10 g, 6.33 mmol, 32%) as a white solid after flash chromatography (0-5% ethyl acetate in heptane). Also 744 mg (24% yield) of benzoic acid was isolated, 435 mg (14%) of starting oxime was recovered. R_f = 0.37 (20% EtOAc/heptane); IR (film) 3099, 1663, 1598, 1537, 1498, 1466, 1435, 1383, 1329, 1122, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (m, 2H), 6.92 (tt, J = 2.4, 8.8 Hz, 1H), 5.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.1 (dd, J_{CF} = 12.5, 250 Hz), 132.4 (t, J_{CF} = 10 Hz), 113.2 (dd, J_{CF} = 7.4, 18.8 Hz), 105.7 (t, J_{CF} = 24.8 Hz), 78.7; HRMS (ESI): Exact mass calcd for $C_7H_4F_2NO_2$ $[M-H]^-$ 172.0216, found 172.0211.

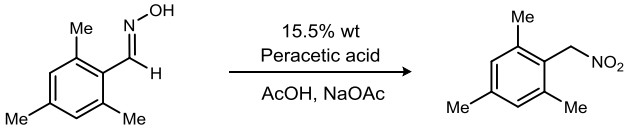


1-(Nitromethyl)-4-(trifluoromethoxy)benzene. 4-(Trifluoromethoxy)benzaldehyde oxime (4.10 g, 20.0 mmol) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 50 min reaction time to give the desired product (2.30 g, 10.4 mmol, 52%) as a white

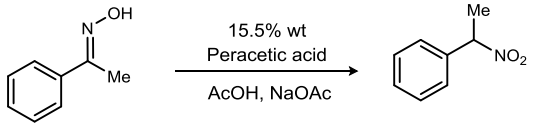
solid after flash chromatography (0-6% ethyl acetate in heptane). Acid isolated in 31% yield (1.27 g). All spectral data are in agreement with literature values.[20]



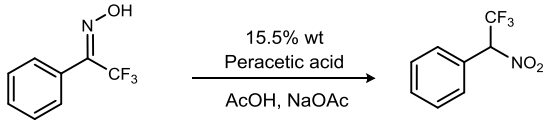
1-Nitro-2-(nitromethyl)benzene. 2-Nitrobenzaldehyde oxime (3.32 g, 20.0 mmol) and peracetic acid (35.0 mL, 79.9 mmol, 15.5 mass%) were used according to the general procedure with 30 min addition time and overall 50 min reaction time to give the desired product (1.58 g, 8.67 mmol, 43%) as a white solid after flash chromatography (0-10% ethyl acetate in heptane). 280 mg (8% yield) of benzoic acid was isolated. Also 630 mg (19%) of starting oxime was recovered. All spectral data are in agreement with literature values. [21]



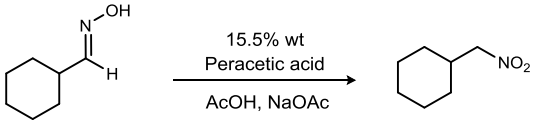
1,3,5-Trimethyl-2-(nitromethyl)benzene. 2,4,6-Trimethylbenzaldehyde oxime (3.27 g, 20.0 mmol) and peracetic acid (17.50 mL, 39.9 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (620 mg, 3.46 mmol, 82 mol%, 17%) as a yellow oil after flash chromatography (0-8% ethyl acetate in heptane). Acid was isolated in 13.5% yield (443 mg). All spectral data are in agreement with literature values. [17b]



1-Nitroethylbenzene. 1-Phenylethanone oxime (2.70 g, 20.0 mmol,) and peracetic acid (17.35 mL, 39.6 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (1.70 g, 11.2 mmol, 56%) as a yellow oil after flash chromatography (0-8% ethyl acetate in heptane). Starting material was also recovered 216 mg (8%). All spectral data are in agreement with literature values. [22]



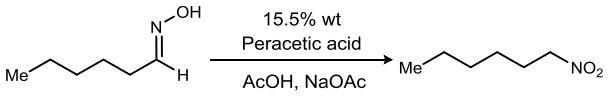
(2,2,2-Trifluoro-1-nitro-ethyl)benzene. 2,2,2-Trifluoro-1-phenyl-ethanone oxime (3.78 g, 20.0 mmol) and peracetic acid (17.35 mL, 39.6 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (1.99 g, 9.70 mmol, 49%) as a white solid after flash chromatography (0-8% ethyl acetate in heptane). R_f = 0.37 (20% EtOAc/heptane); IR (film) 3285, 1559, 1460, 1440, 1336, 1207, 1190, 1183, 1160, 1131, 1015, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (m, 1H), 7.53-7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 147.6 (q, J_{CF3} = 32.3 Hz), 130.7, 128.6, 128.5, 1258, 120.6 (q, J_{CF3} = 274 Hz); HRMS (ESI): Exact mass calcd for $C_8H_7F_3NO_2$ $[M+H]^+$ 206.0423, found 206.0430.



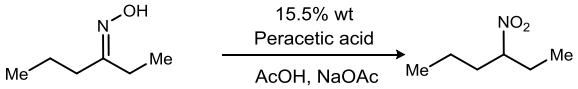
(Nitromethyl)cyclohexane.

A. Cyclohexanecarbaldehyde oxime (2.54 g, 20.0 mmol) and peracetic acid (17.35 mL, 39.6 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give

the desired product (1.15 g, 8.03 mmol, 40%) as a transparent oil after flash chromatography (0-4% ethyl acetate in heptane). Carboxylic acid was isolated in 18% yield (469 mg).
B. Cyclohexanecarbaldehyde oxime (2.54 g, 20.0 mmol) and peracetic acid (11.0 mL, 25.1 mmol, 15.5 mass%) were used according to the general procedure with 11 min addition time and overall 15 min reaction time to give the desired product (947 mg, 6.61 mmol, 33%) as a transparent oil after flash chromatography (0-4% ethyl acetate in heptane). Carboxylic acid was isolated in 16% yield (419 mg).
All spectral data are in agreement with literature values. [23]

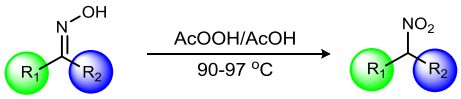


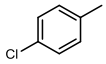
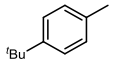
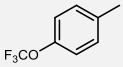
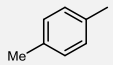
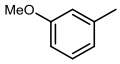
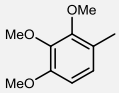
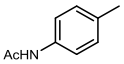
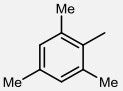
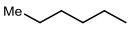
1-Nitrohexane.
A. Hexanal oxime (2.30 g, 20.0 mmol) and peracetic acid (17.35 mL, 39.6 mmol, 15.5 mass%) were used according to the general procedure with 20 min addition time and overall 30 min reaction time to give the desired product (0.800 g, 6.10 mmol, 31%) as a transparent oil after flash chromatography (0-4% ethyl acetate in heptane). Carboxylic acid was isolated in 27% yield (628 mg).
B. Hexanal oxime (2.30 g, 20.0 mmol) and peracetic acid (11.00 mL, 25.1 mmol, 15.5 mass%) were used according to the general procedure with 11 min addition time and overall 15 min reaction time to give the desired product (606 mg, 4.62 mmol, 23%) as a transparent oil after flash chromatography (0-4% ethyl acetate in heptane). Carboxylic acid was isolated 27% yield (616 mg).
All spectral data are in agreement with literature values. [24]



3-Nitrohexane. Hexan-3-one oxime (2.30 g, 20.0 mmol) and peracetic acid (11.00 mL, 25.1 mmol, 15.5 mass%) were used according to the general procedure with 10 min addition time and overall 15 min reaction time to give the desired product (552 mg, 4.21 mmol, 21%) as a transparent oil after flash chromatography (0-8% ethyl acetate in heptane). The product is volatile and can be easily distilled over under reduced pressure upon solvent removal (91 °C at 50 mm Hg).
All spectral data are in agreement with literature values. [25]

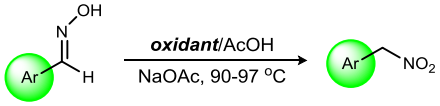
Table S1. Substrate scope for the oxime oxidation with peracetic acid

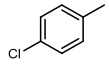
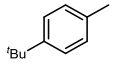
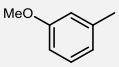
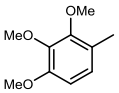
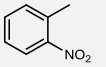
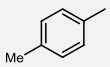
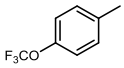


R1	R2	Conditions	yield	sm	acid	R1	R2	conditions	yield	sm	acid
	H	A’	34%	-	29%		H	B	66%	8%	7%
	H	A	52%	-	31%		H	B B’	62% 49%	- 33%	9% 5%
	H	A A’	38% 32%	15% 29%	19% 11%		H	B	37%	14%	9%
	H	A	43%	19%	8%		H	B	32%	8%	-
	H	A’	32%	14%	24%		H	B	<5%	-	-
	H	B B’	40% 33%	- -	18% 16%		H	B	<15%	-	13%
	H	B B’ B”	31% 23% 24%	- - 17%	27% 27% 22%			B	56%	6%	-
		B B’	<15% 21%	- -	- -			B	49%	-	-

[a]Conditions: all reactions employed 20 mmol nitroalkane in 7 mL of AcOH (2.86 M) initiated at 92°C, 15-16 % wt AcOOH was added dropwise maintaining temperatures in 90-97 °C range. Conditions A: 4.0 equiv of AcOOH over 30 min with 50 min overall reaction time. Conditions A’: 4.0 equiv of AcOOH over 30 min with 40 min reaction time. Conditions B: 2.0 equiv of AcOOH over 20 min with 30 min reaction time. Conditions B’: 1.2 equiv of AcOOH over 10 min with 15 min reaction time. Conditions B”: 1.05 equiv of AcOOH over 9 min with 10 min reaction time.

Table S2. Substrate scope for the oxime oxidation using 39 mass% AcOOH



Ar	AcOOH equiv	scale	yield	Ar	AcOOH equiv	scale	yield
	1.2 1.2 1.2	30.0 g 30.0 g 30.0 g	46% 48% 48%		2.1 2.1 2.1	6.0 g 12.0 g 30.0 g	78%, 7% sm 68%, 12% sm 63%
	3.0 4.3 3.3	3.0 g 3.0 g 3.0 g	37%, 20% sm 44% 40%		1.5 2.9 2.3	3.0 g 3.0 g 3.0 g	28%, 43% sm 30% 38%
	3.3 5.9 3.7	3.0 g 3.0 g 3.0 g	41%, 16% sm 49% 51%		1.6	3.0 g	28%
	5.1	3.0 g	46%		2.1	3.0 g	57%
	5.2	3.0 g	59%				

3. Literature summary of oxidants in oxime oxidations

The summary of the methods utilizing a range of oxidants to transform oximes into nitroalkanes are summarized in the table S3.

Table S3. Oxime oxidation

#	equiv	oxidant	additive	time	temperature	yield	reference
1	1.1	AcOOH	NaOAc	3.5 h	80-90 °C	84%	*26*
2	2.0	CF_3COOOH	$NaHCO_3/Na_2HPO_4$	1-2 h	80 °C	50-70%	*27*
3	5.0	Oxone	Phosphate buffer	4-10 h	45 °C	60-70%	*22a*
4	12-20	UHP, TFAA	Na_2HPO_4	5-7 h	0 °C	60-80%	*28*
5	6.0	$NaBO_3 \cdot 4H_2O$, AcOH	-	20 h	55 °C	40%	*15*
6	8.0	MTO (Re), UHP	-	days	23 °C	35-50%	*29*
7	0.5	$[BzOMoO(O_2)_2]^- Bu_4N^+$	-	3 h	40 °C	90%	*30*

4. Port connectors

Figure S1. Port connectors

Port connector reactors were used in two sizes and made from the following Swagelok parts:

1/2 in. version:

Entry	Name	Material	Part number
1.	Cap for 1/2 in. OD Tubing	316 Stainless Steel	SS-810-C
2.	Tube Fitting, Port Connector, 1/2 in. Tube OD	316 Stainless Steel	SS-811-PC

3/8 in. version:

Entry	Name	Material	Part number
1.	Cap for 3/8 in. OD Tubing	316 Stainless Steel	SS-600-C
2.	Tube Fitting, Port Connector, 1/2 in. Tube OD	316 Stainless Steel	SS-601-PC

5. Continuous set up and procedure

Equipment specification:

Description	Part Number	Supplier
Peristaltic Pump	7523-80	Cole-Palmer
Peristaltic tubing size 35	EW9619-35	Cole-Palmer

Reagent solutions.

Oxime solution feed:

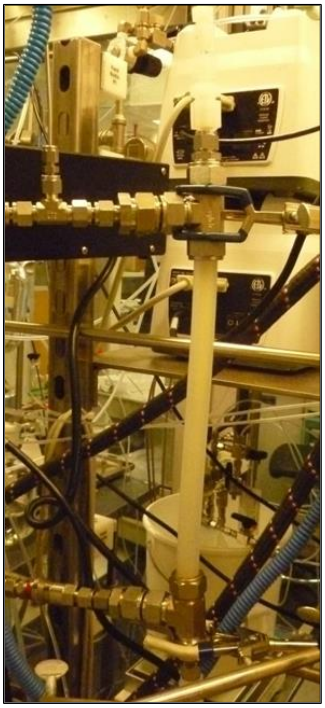
- 96.0 g of oxime and 16.00 g of NaOAc were dissolved in AcOH in volumetric flask to prepare 400 mL of the resulting solution (d = 1.055 mg/mL and C = 1.354 mmol/mL).

Peracetic acid feed:

- Solution of peracetic acid generated using packed column reactor with Amberlite IR-120 resin

Amberlite IR-120 (strongly acidic, hydrogen form, CAS 39381-26-3) purchased from Aldrich (064280-1kg). Resulting solution: 16.5 mass%, (determined by integration of ^{13}C NMR spectroscopic data, d = 1.120 mg/mL, C = 2.200 mmol/ml)

Reactors.



Jacketed PFA tube packed bed reactor:
Dimensions: length 20", heated/packed zone 15" (381 mm), inner diameter 1/4" (6.35 mm)
Estimated reactor volume: 6 mL. This is 12 mL empty column volume in the packed section, and about 50% void space, thus liquid volume in the packed section was about 6 mL.
Residence time: ~7 min
Operational temperature: 50.0 - 52.5 °C
Mass of the packed resin: 18.1 g
Feeding solution: 3.5:1 mixture of glacial AcOH (700 mL) and 50% H_2O_2 (200 mL)
Hydrogen peroxide: pure, 50 wt%, water solution purchased from Acros (lot #302865000)
Flow rate: 0.86 mL/min solution
Solution of peracetic acid flowed into a surge tank which continuously pumped into the next reaction once an operating level was reached.

Figure S2. PFA packed bed reactor

Pipes-in-series reactor characteristics:
Reactor volume including 1/16 inch inner diameter PFA tubing jumpers: about 58 mL
Reactor material of construction: PFA.
Pipes: 16 (d = 0.8 cm, L = 6.4 cm, 3.2-3.3 mL each) Experimental liquid filled volume = 42 mL (measured under reaction conditions)
Jumpers: d = 1/16 inch inner diameter PFA tubing, contains negligible amounts of solution and observed to be mostly gas filled
Mean liquid residence time: 33 min
Operation temperature: 88.7-89.5 °C
Stoichiometry: 3 equiv of AcOOH
The oxime feed added from the 1L feed bottle using peristaltic pump with flow rate: 0.45 mL/min.

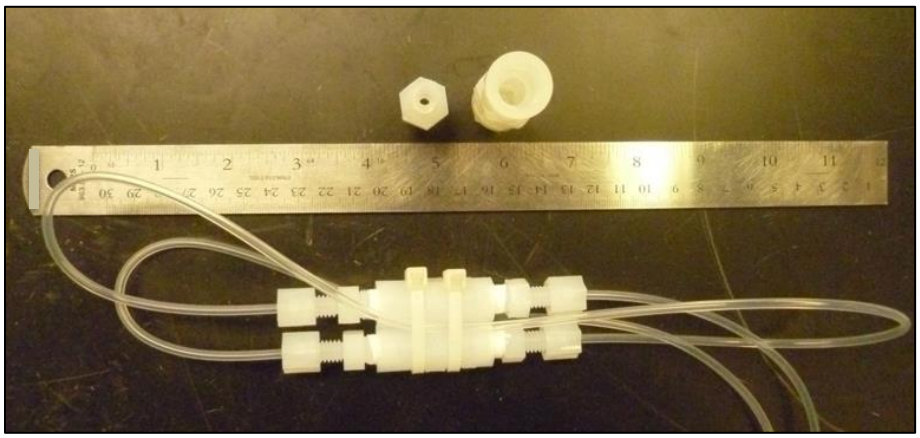
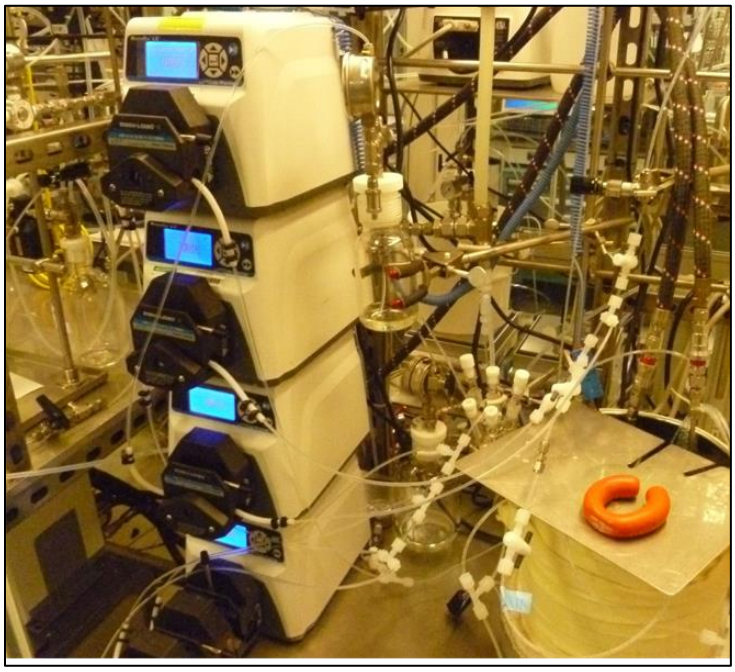
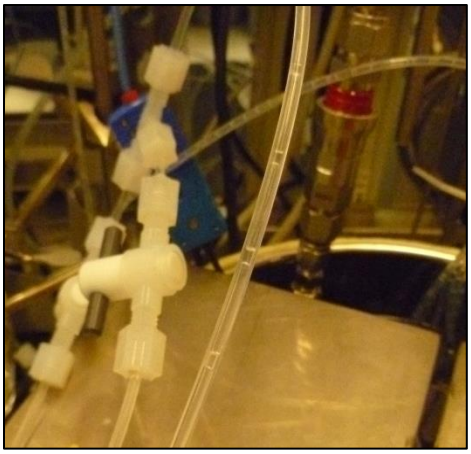


Figure S3. Pipes-in-series reactor



The AcOOH feed added from the surge tank using two peristaltic pumps and was split into four streams.
Pump #1:
a) 0.50 mL/min, 1.8 equiv of AcOOH was added at the beginning
Pump #2 with three heads:
b) 0.11 mL/min, 0.4 equiv of AcOOH in between 4th and 5th pipes
c) 0.11 mL/min, 0.4 equiv of AcOOH in between 8th and 9th pipes
d) 0.11 mL/min, 0.4 equiv of AcOOH in between 12th and 13th pipes

Figure S4. Complete equipment setup



Nitrogen gas was mixed with the starting feed. The nitrogen pressure was controlled *via* regulator and was set up empirically to approximately 7-10:1 ratio of the gas to the feed solution (ratio of gas and liquid slugs inside the PFA tubing for the feeding solution going to the reactor). The solution from the reactor flowed directly into the continuous extraction stage.

Figure S5. Ratio of gas to liquid in the tubing

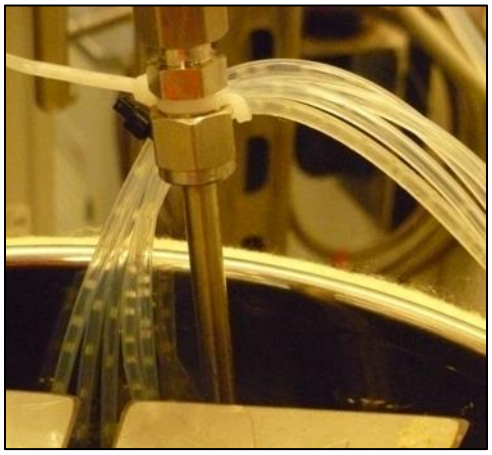


Figure S6. Ratio of gas to liquid in the reactor

Continuous counter-current extraction: 3 stage process, with crude reaction mixture and water streams continuously flowed into the 2nd stage. The resulting product solution was removed and collected from the 3rd stage. The 1st stage was run with continuous back-extraction of product from the aqueous waste stream into toluene. The 3rd stage was extraction of product solution with 1.5 M NaOH.

Table S4. Continuous extraction

stage	water phase		organic phase	
	solution	volume flow rate	solution	Volume flow rate
1st	2nd stage water extract	43 mL	fresh toluene	15 mL 1.5 mL/min
2nd	fresh water reaction mixture	30 mL 3.0 mL/min 13 mL 1.27 mL/min	1st stage toluene	15 mL
3rd	1 M NaOH solution	15 ml 1.5 mL/min	2nd stage toluene	15 mL

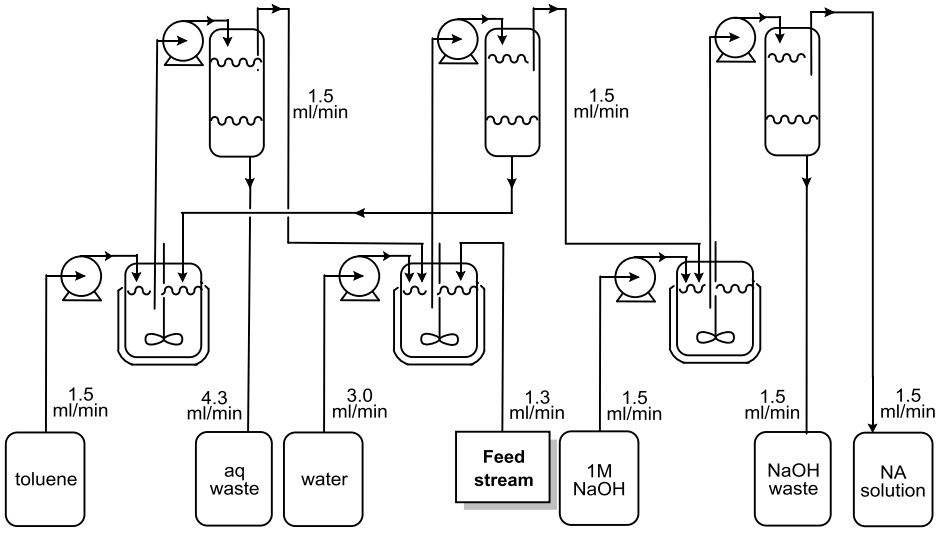
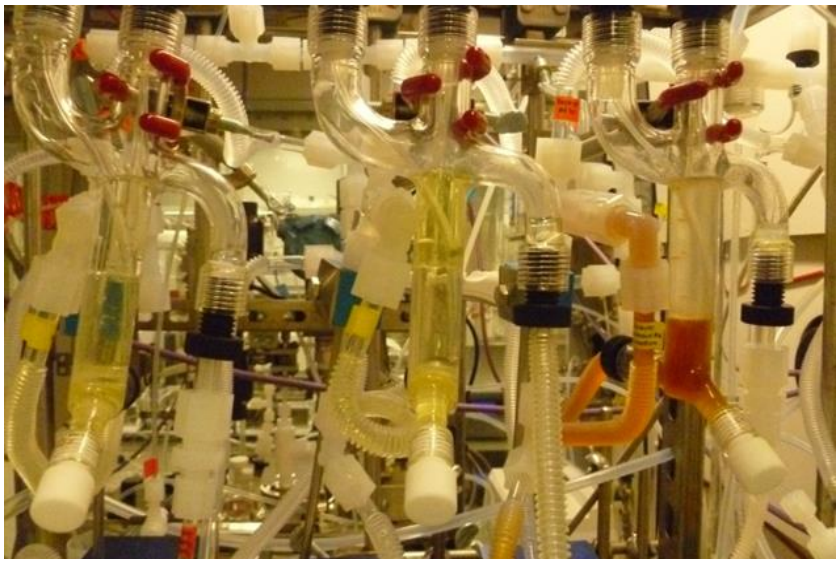


Figure S7. Extraction flow rates



All the processes are insensitive to brief exposure to the residual moisture from the air. No special precautions were taken to avoid air or atmospheric moisture during preparation of the feed solution.

Figure S8. Settlers for continuous extraction

3-stage flow experiment.

The following steps were performed to start the cycle:

1. Both circulators were turned on and set to the appropriate temperatures (50 °C for the packed bed and 90 °C for the pipes-in-series reactor).
2. Once packed bed reactor reached the desired temperature, addition of the hydrogen peroxide solution was initiated by starting the feed pump.
3. 30-50 mL of the peracetic solution was collected in the surge tank; a sample of the solution was characterized by ^{13}C NMR to confirm the desired concentration. Then peristaltic pump responsible for peracetic acid addition was turned on and all the addition lines were filled with the solution up to the T-connectors to the reactor.
4. When oil bath for the pipes-in-series reactor reached 88-89 °C, addition of the oxime and peracetic acid was initiated by starting the feed pumps. The nitrogen supply was turned on and regulated to ensure the correct ratio of the gas to feeding solution.
5. While the pipes-in-series reactor was filling with the reaction mixture the extraction set up was prepared. The feeding bottles were filled with solutions (2 L toluene, 2 L water, 2 L 1 M NaOH solution). The mixers were filled with appropriate volumes of pure water, base solution and organic solvent and stirring was initiated.
6. When the reaction mixture reached the extraction stage (~45 min - 1 h), all the pumps for the extraction were turned on. The product solution was collected into a small surge tank, and an additional pump was used to transfer it to the collection bottle.
7. The 96 g of oxime (400 mL of solution) was processed through the reactor. Samples of the crude solutions after the reactor, and toluene solutions after extraction, were collected manually and analyzed by HPLC.
8. After 15 h when all the oxime feed was completely processed the feeding bottle was substituted with glacial AcOH. The product was collected for an additional hour. At 15.5 h the pump feeding hydrogen peroxide solution was stopped and the packed bed circulator was turned off to ensure consumption of all residual peracetic acid from the surge tank by the end of the run. At 16 h the pipe-in-series circulator was turned off, the pumps for the peracetic acid/acetic acid and extraction set up were stopped and the feed from the reactor was disconnected and all the residual reaction mixture was removed from the reactor using nitrogen gas. All the resulting reaction mixture/excessive peracetic solution were collected, diluted with water, neutralized using base (NaOH) and quenched with the reductant.

Overall reaction time: 16 h

Material collection: 30 min - 16 h.

Sample collection and analysis

1. Concentration of peracetic acid solution was determined by taking samples from the surge tank after the packed bed reactor.
2. Manual samples of the reaction mixture were taken from a sample point between the continuous reactor and the 2nd stage extraction vessel every 30 min and then analyzed to determine the ratio of main components in the crude reaction mixture.
3. NMR analysis of crude reaction mixture was conducted by collection 15-20 sec sample of the reaction mixture followed by quench and extraction. These samples were quenched with water (10.0 mL), cooled to room temperature. The resulting solution was extracted with methylene chloride (2x25 mL). Organic layer was washed with water (2x20 mL). The resulting solution was dried, filtered, and solvent was removed in vacuo.
4. Samples of extracted material were taken from the collection vessels.

Table S5. 16 h continuous run data

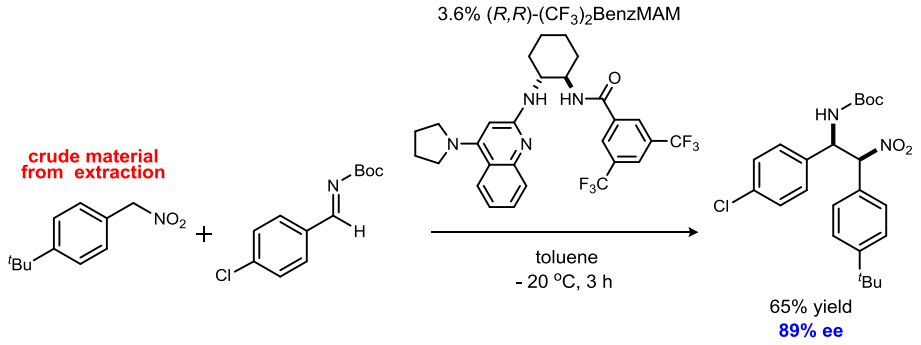
time	T_{column}, °C	$T_{reactor}$, °C	AcOOH	Crude	Crude NMR SM:NA:acid ratio	Tol extract HPLC NA/oxime	Tol extract NMR SM:NA ratio	$M_{tol\ sol}$, g
0.5 h	52.3-52.5	86.2-87.7				-		25.54
1 h	52.3-52.3	87.7-88.5				92.73 4.45		37.81
1.5 h	52.3-52.4	88.3-88.5				86.58 8.14		34.04
2.0 h	52.2-52.4	88.3-88.5				89.24 6.34	3:100	76.16
2.5 h								
3.0 h	52.0-52.2	88.5-88.7	16.2%			84.72 9.86		80.81
3.5 h								
4.0 h	51.8-52.0	88.5-88.7				85.20 8.62		81.41
4.5 h								
5.0 h	51.8-52.0	88.7-88.7				86.41 7.81	4:100	80.74
5.5 h								
6.0 h	51.8-52.0	88.7-88.7	16.2%			85.08 8.54		76.36
6.5 h								
7.0 h	52.0-52.5	88.6-88.7			4:100:19	85.81 7.97		80.93
7.5 h								
8.0 h	52.5-52.5	88.7-88.7				85.86 8.19	4:100	81.37
8.5 h								
9.0 h	52.5-52.5	88.7-88.7	14.9%			85.67 8.23		82.94
9.5 h					5:100:20			

10.0 h	52.4-52.5	88.4-88.7					
10.5 h					85.34 8.69		84.69
11.0 h	52.2-52.4	88.4-88.6					
11.5 h					84.45 8.73	4:100	82.05
12.0 h	52.2-52.4	88.6-88.6	16.2%	9:100:20			
12.5 h					83.97 9.48		83.94
13.0 h	52.4-52.6	88.6-88.6					
13.5 h					86.54 8.19		84.82
14.0 h	52.6-52.6	88.6-88.6					
14.5 h					84.48 9.17	4:100	75.66
15.0 h	52.2-52.6	88.5-88.6	16.2%	6:100:18			
15.5 h					86.32 8.46		

Collected fractions:

After 16 h 1.4 L of solution was collected.

6. aza-Henry reaction using crude extracted material



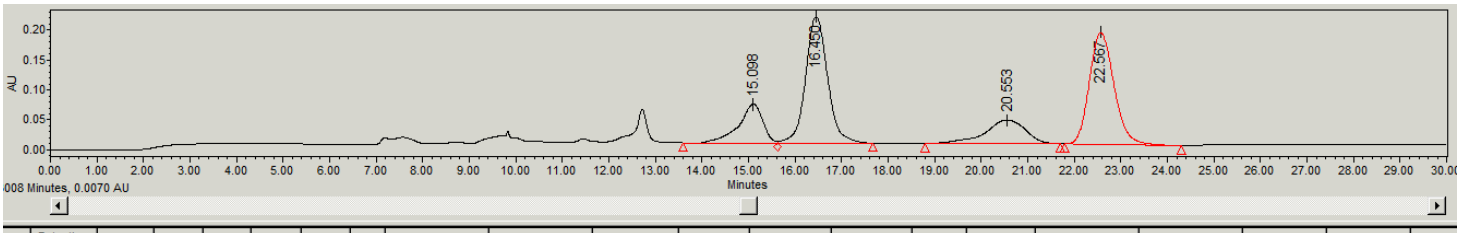
The vacuum-dried round bottom flask was filled with toluene (1.5 mL, 14 mmol) then 1-*tert*-butyl-4-(nitromethyl)benzene (90.0 mg, 0.466 mmol), *N*-[(1*R*,2*R*)-2-[(4-pyrrolidin-1-yl-2-quinolyl)amino]cyclohexyl]-3,5-bis(trifluoromethyl)benzamide (2.5 mg, 0.0045 mmol,) were introduced. After the catalyst was dissolved, the reaction mixture was cooled to -20 °C. Solid imine *tert*-butyl (*E*)-*N*-[(4-chlorophenyl)methylene]carbamate (59.0 mg, 0.246 mmol) was added to the reaction. The resulting mixture was stirred for an additional 3 h at -20 °C. The reaction was warmed to room temperature and solvent was removed in vacuo. The resulting crude product was purified using column chromatography (SiO_2, 4-15% ethyl acetate in hexanes) to provide the aza-Henry adduct as a white solid (110 mg, 52%).

Enantiomeric excess was found to be 89% ee by chiral HPLC (Chiralcel IA, 20% iPrOH/hexanes, 0.4 mL/min, t_r(*anti*, major) 15.3 m, t_r(*anti*, minor) 20.6 m, t_r(*syn*, major) 16.4 m, t_r(*syn*, minor) 22.6 m; R_f = 0.38 (20% EtOAc/heptane); IR (film) 3408, 2972, 1689, 1549, 1503, 1366, 1290, 1162 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.68 (m, 1H), 5.63 (m, 1H), 4.74 (d, *J* = 8.8 Hz, 1H), 1.31 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

ppm 154.1, 153.7, 136.2, 134.6, 129.1, 128.6, 128.4, 128.1, 125.9, 93.9, 80.5, 56.1, 34.8, 31.2, 28.0; HRMS (ESI) exact mass calcd for $C_{23}H_{30}ClN_2O_4$ $[M+H]^+$, 433.1889, found 433.1881.

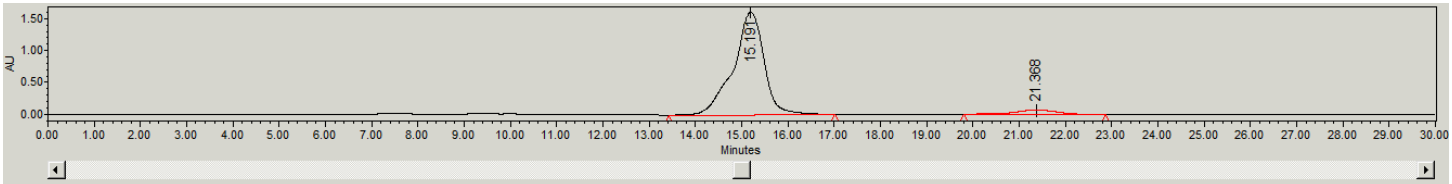
All spectral data are in agreement with literature values.[31]

Racemate:



Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Dissolved Amount	Dissolved Percent	Peak Type	Peak Codes	ActivityFactor	ActivityResult	AdjArea	AdjAreaPct	CCompRef1_Area	CCompRef2_Area	CConst2Value	CConst5Value
15.098	2358186	12.70	64756	bV					Unknown	C06			2358186	12.695457				
16.450	6932666	37.32	210880	Vb					Unknown	C06			6932666	37.322495				
20.553	2399643	12.92	39374	bb					Unknown	C06			2399643	12.918647				
22.567	6884540	37.06	186270	bb					Unknown	C06			6884540	37.063401				

Purified material:



Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Dissolved Amount	Dissolved Percent	Peak Type	Peak Codes	ActivityFactor	ActivityResult	AdjArea	AdjAreaPct	CCompRef1_Area	CCompRef2_Area	CConst2Value	CConst5Value
15.191	75330899	94.61	1616440	bb					Unknown	C06			75330899	94.611100				
21.368	4290730	5.39	66470	bb					Unknown	C06			4290730	5.388900				

7. NMR data

Figure S9. ^{1}H NMR data for 1-chloro-4-(nitromethyl)benzene (400 MHz, $CDCl_3$)

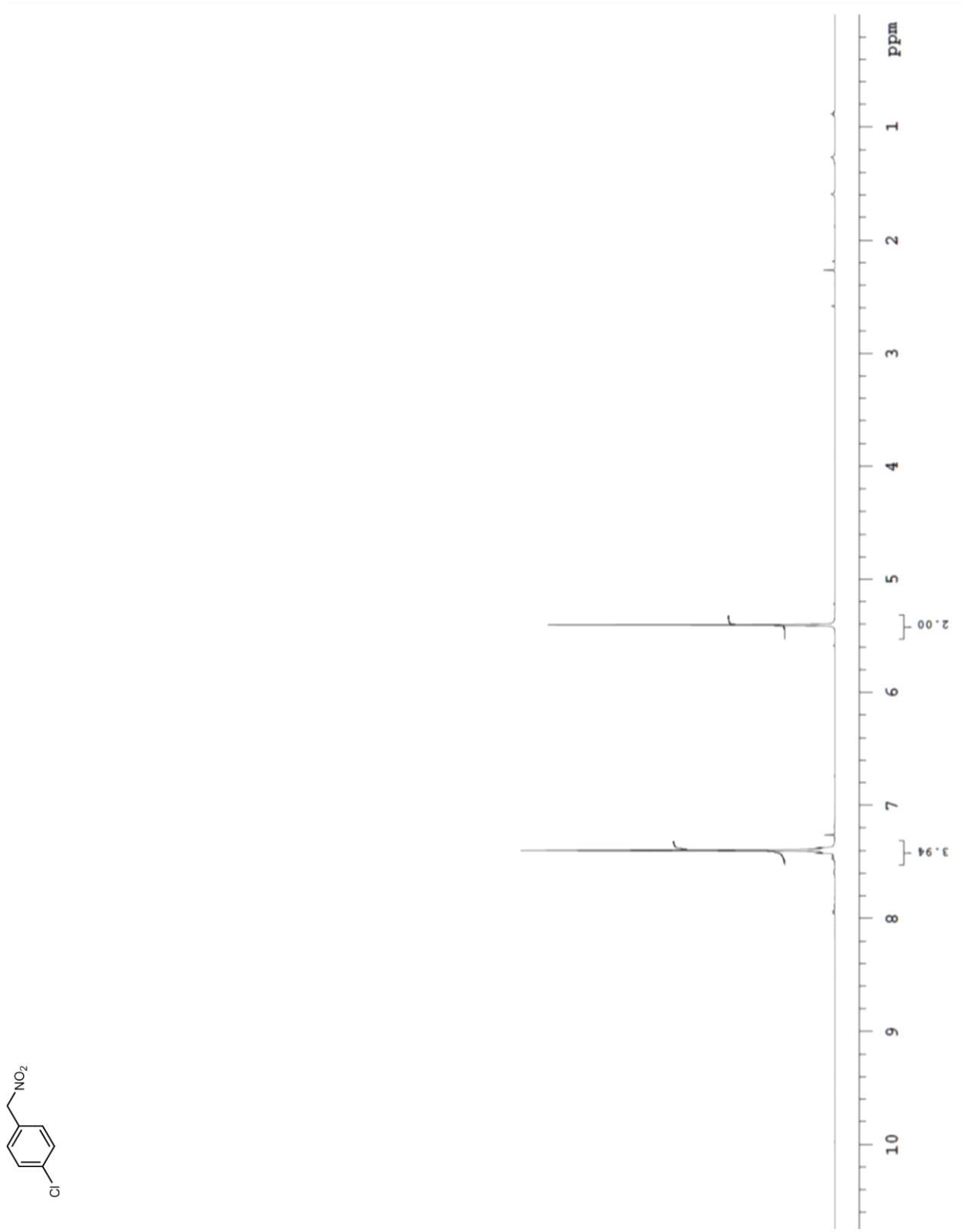


Figure S10. ^{13}C NMR data for 1-chloro-4-(nitromethyl)benzene (100 MHz, $CDCl_3$)

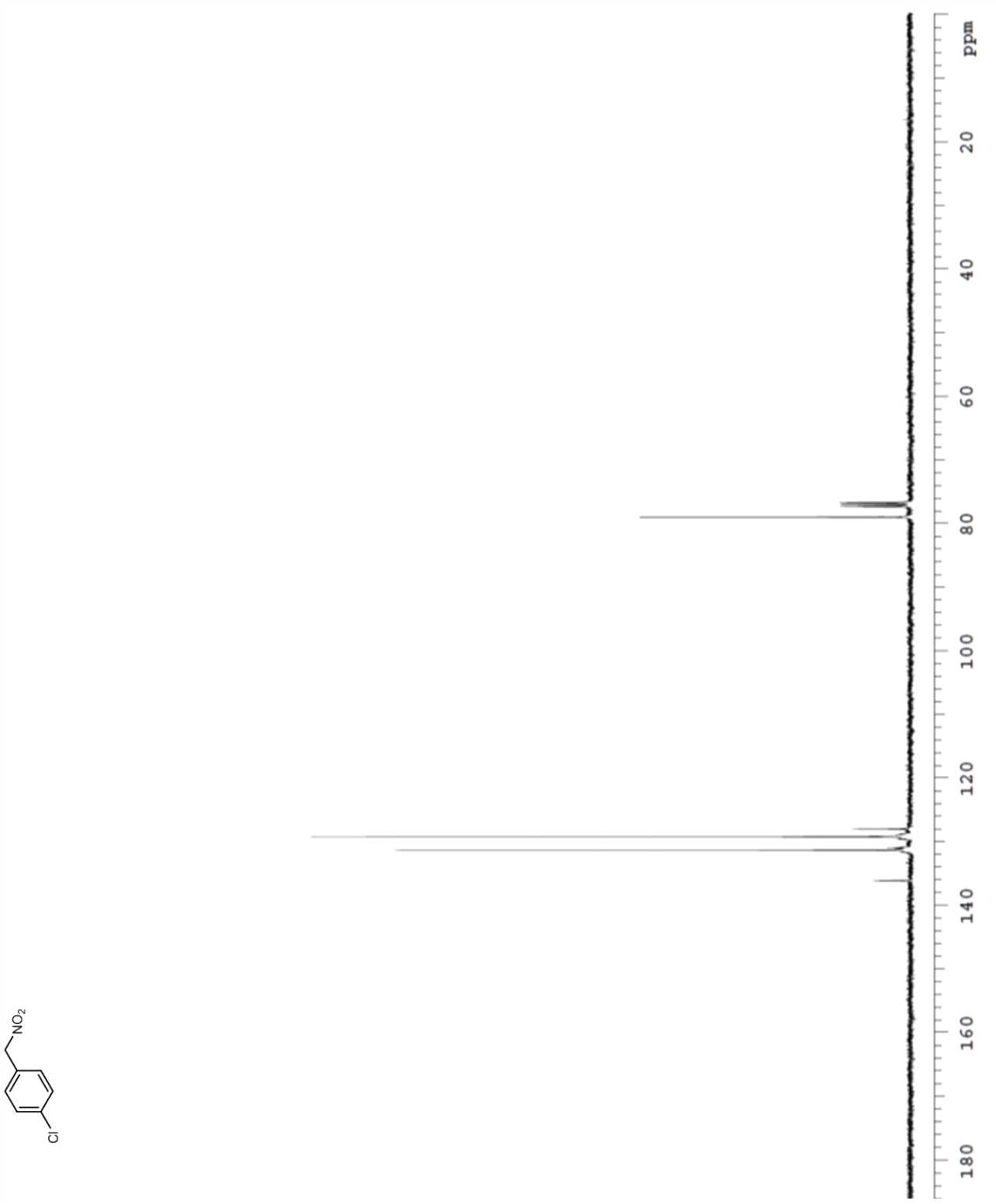


Figure S11. ^{1}H NMR data for 1-(tert-butyl)-4-(nitromethyl)benzene (400 MHz, $CDCl_3$)

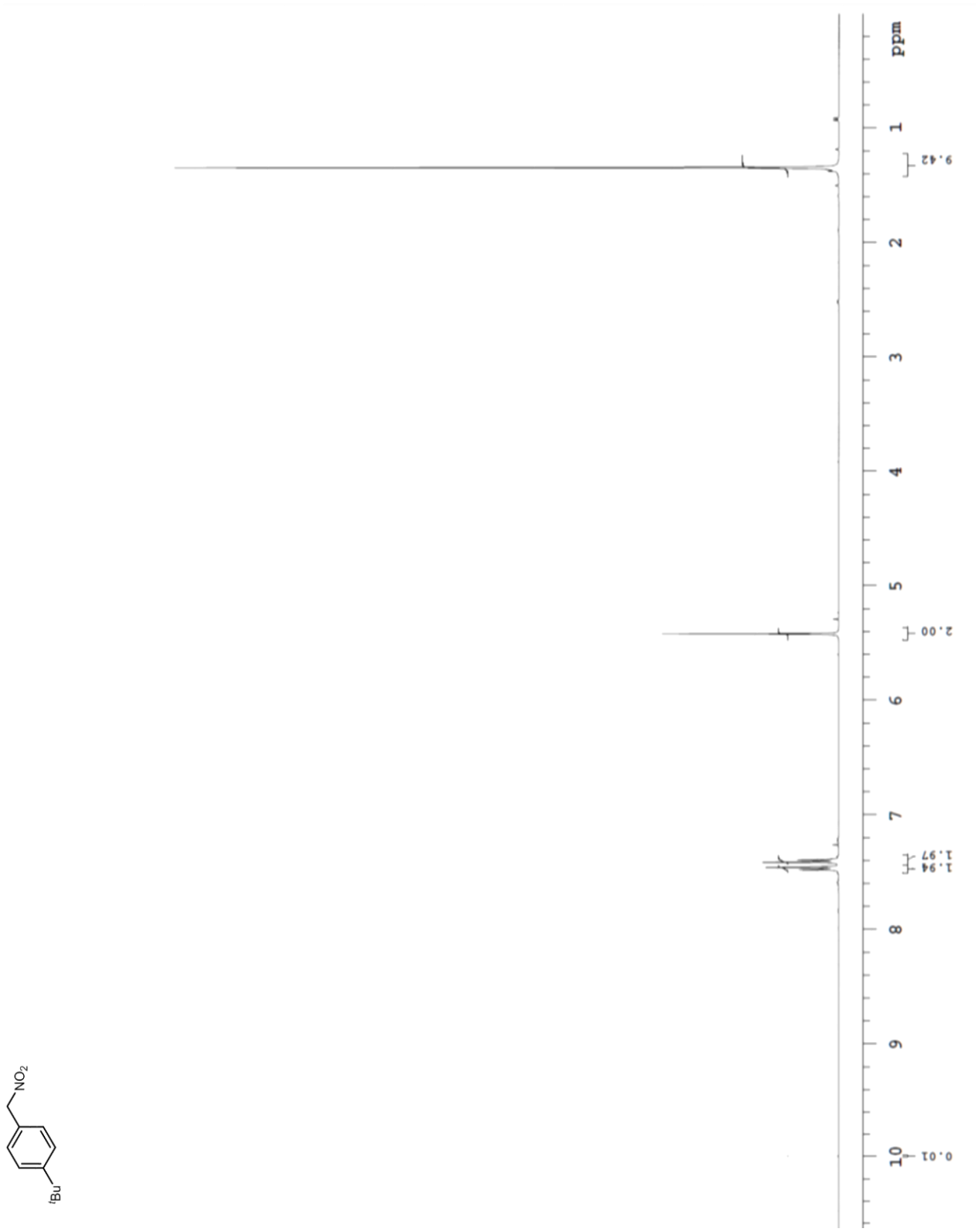


Figure S12. ^{13}C NMR data for 1-(tert-butyl)-4-(nitromethyl)benzene (100 MHz, $CDCl_3$)

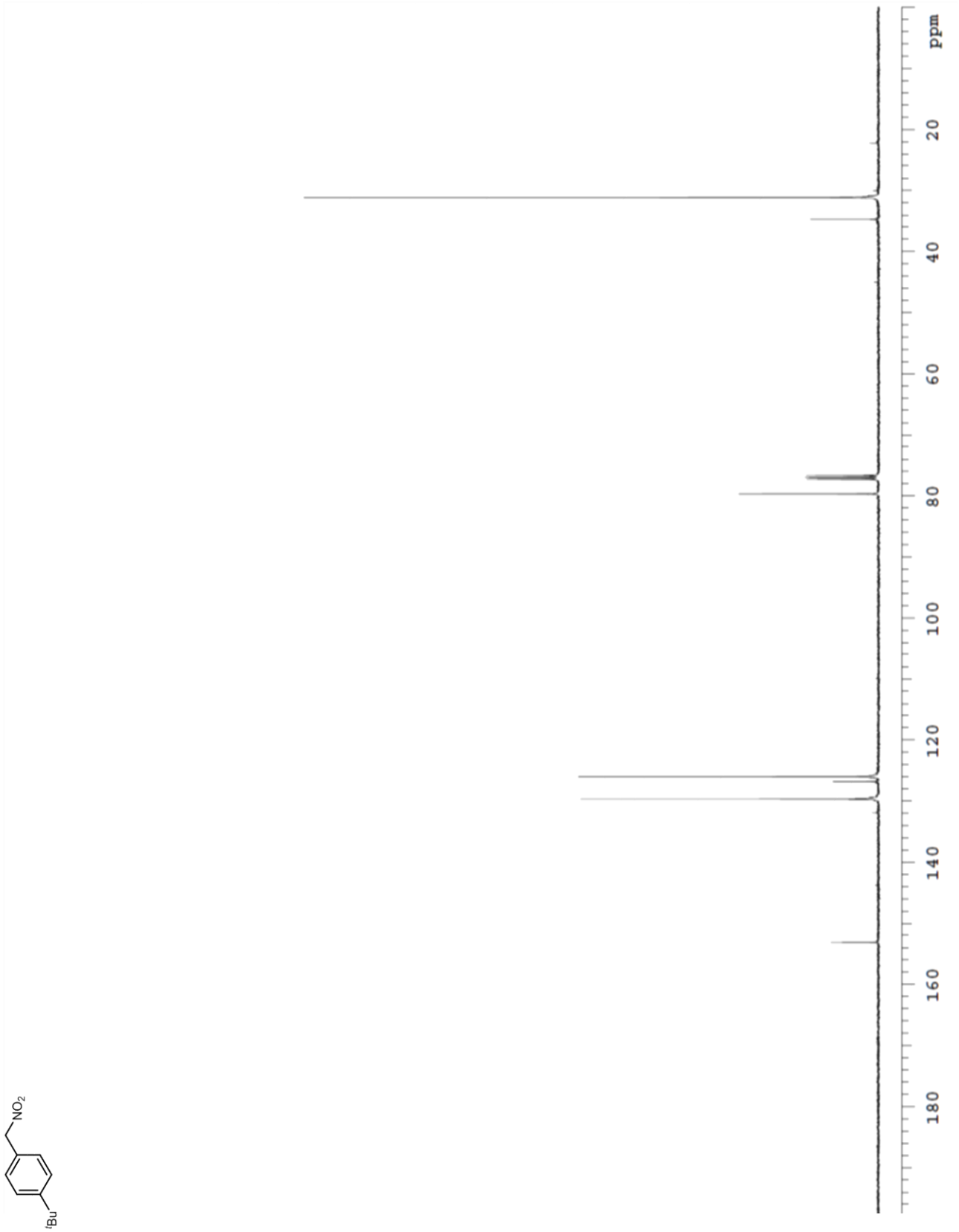


Figure S13. ^{1}H NMR data for 1-methoxy-3-(nitromethyl)benzene (400 MHz, $CDCl_3$)

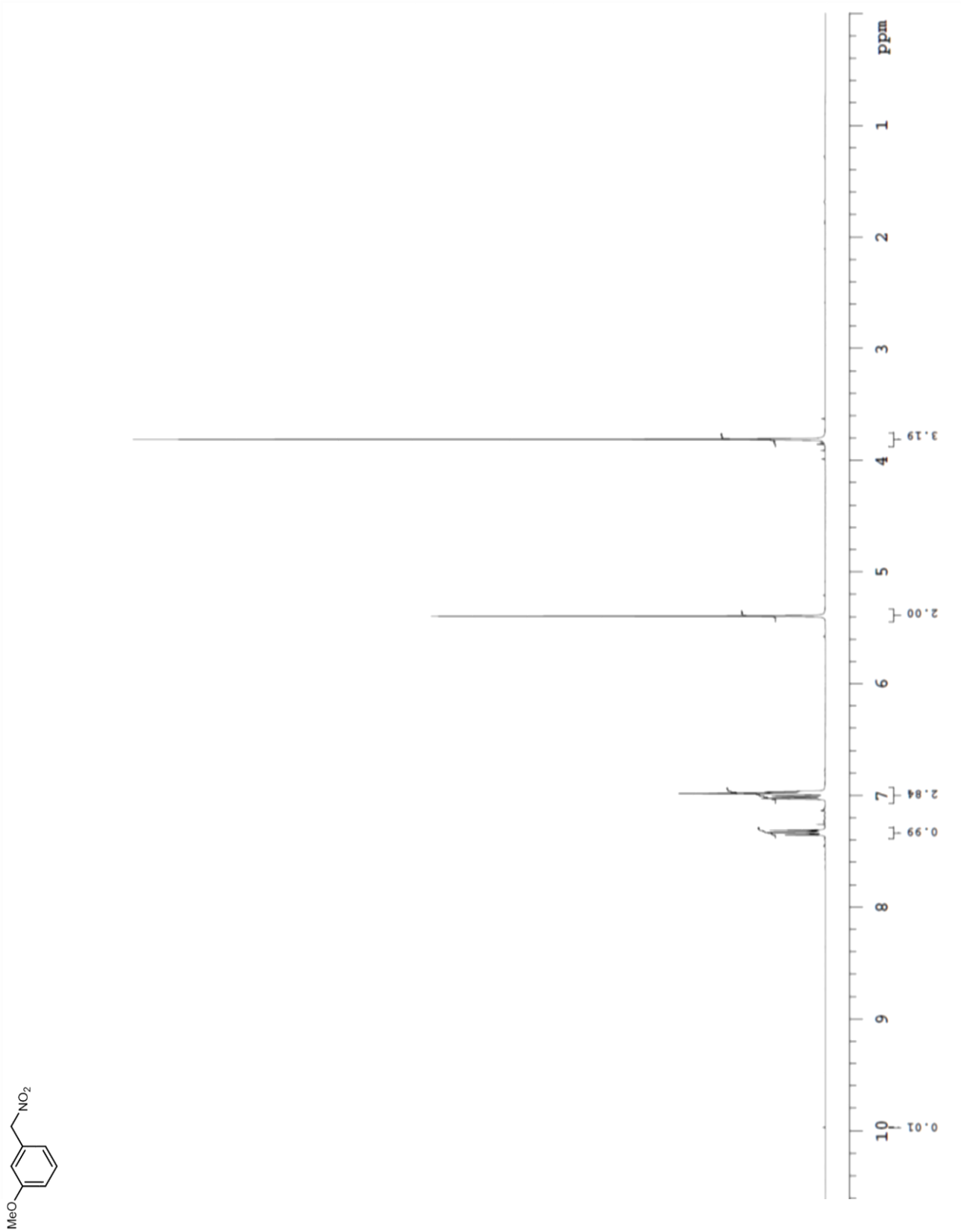


Figure S14. ^{13}C NMR data for 1-methoxy-3-(nitromethyl)benzene (100 MHz, $CDCl_3$)

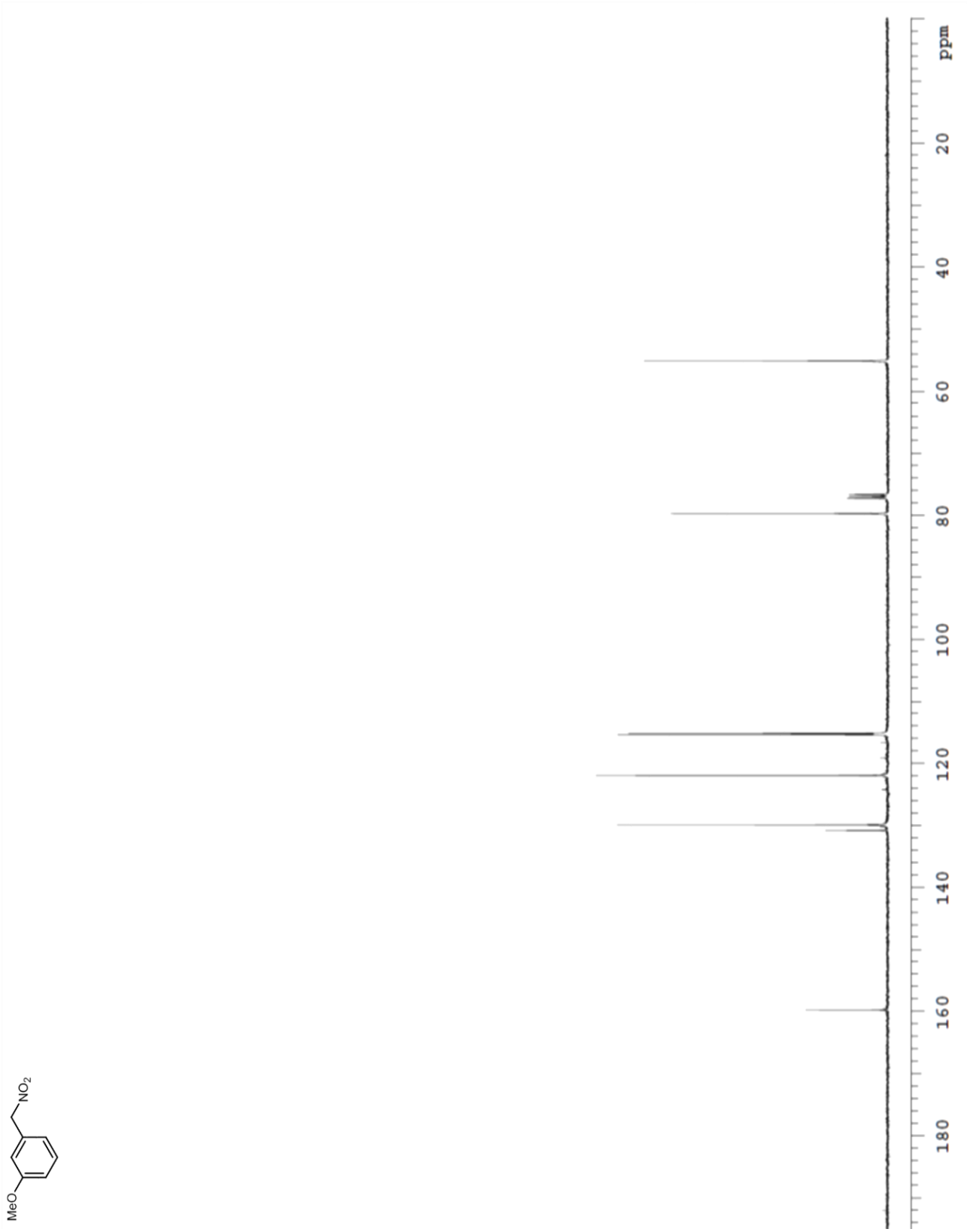


Figure S15. ^{1}H NMR data for 1-methyl-4-(nitromethyl)benzene (400 MHz, $CDCl_3$)

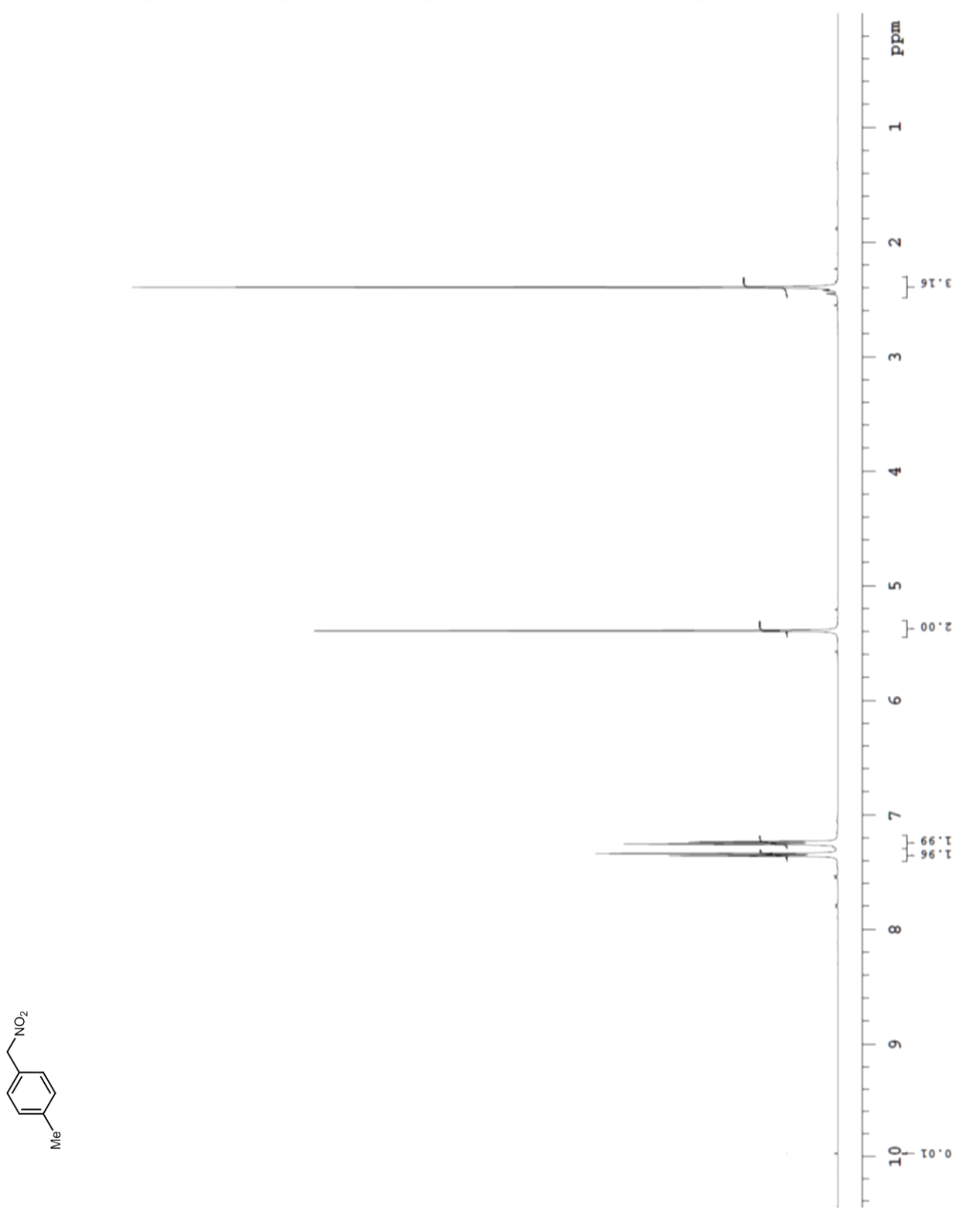


Figure S16. ^{13}C NMR data for 1-methyl-4-(nitromethyl)benzene (100 MHz, $CDCl_3$)

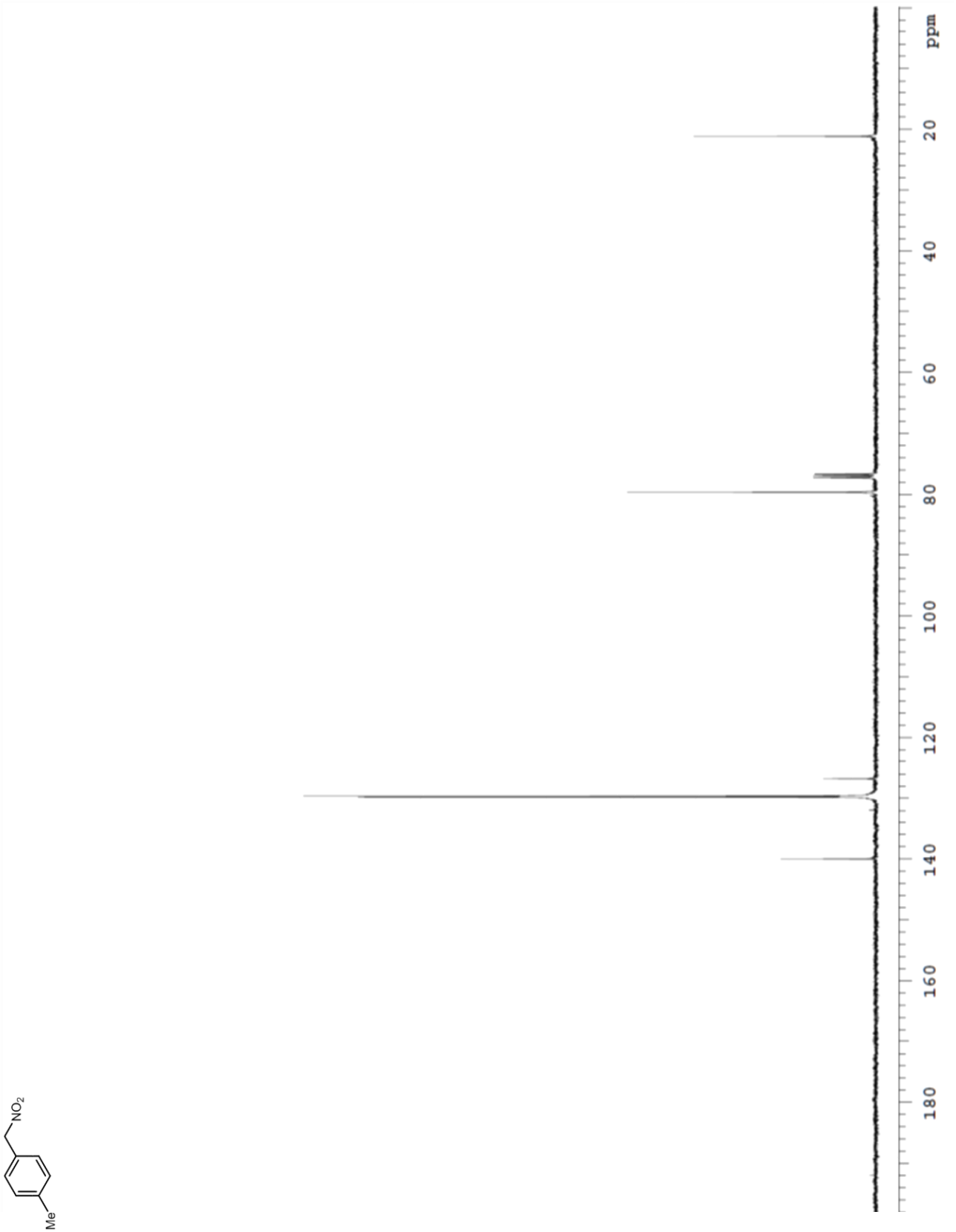


Figure S17. ^{1}H NMR data for 1,2,3-trimethoxy-5-(nitromethyl)benzene (400 MHz, $CDCl_3$)

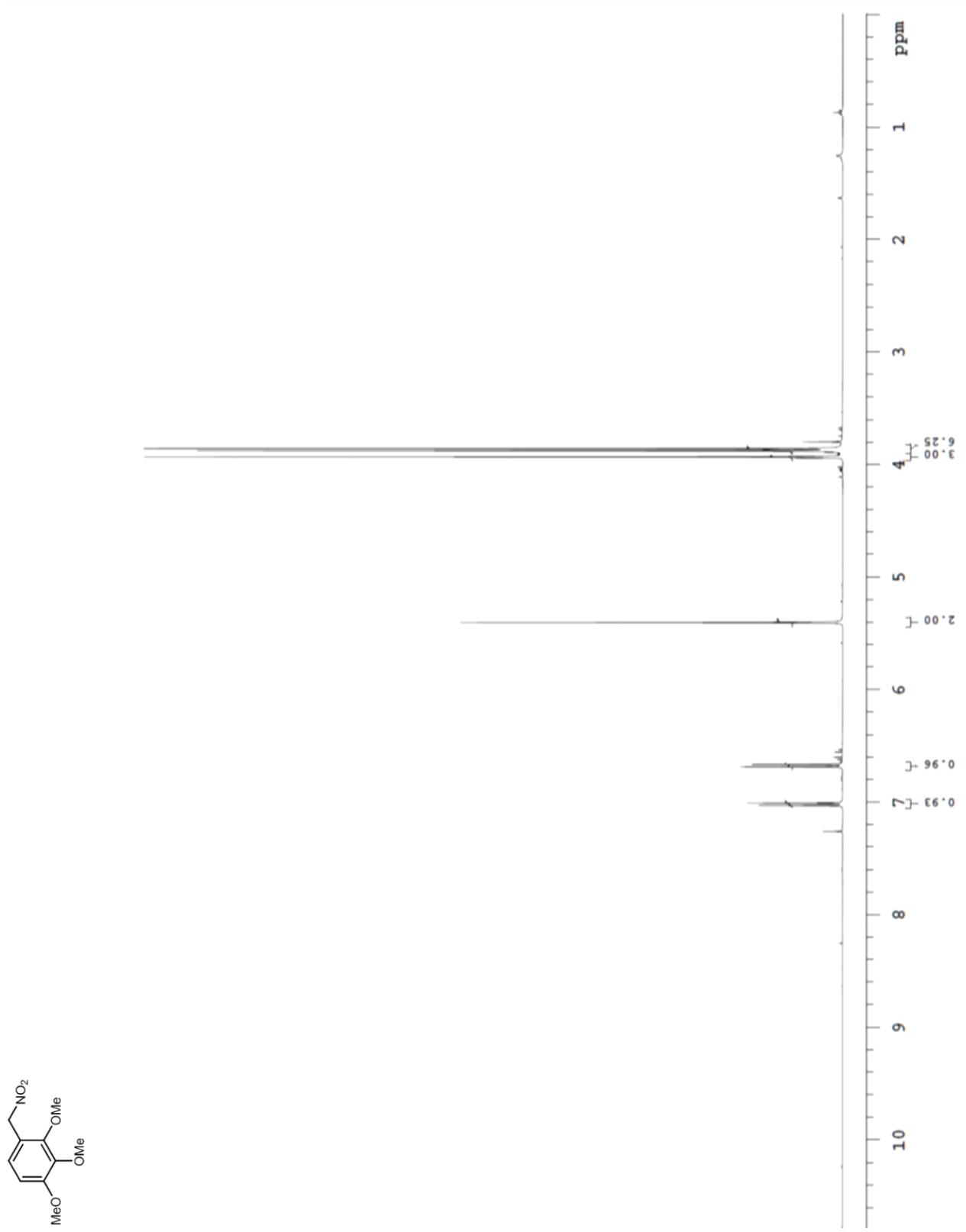


Figure S18. ^{13}C NMR data for 1,2,3-trimethoxy-5-(nitromethyl)benzene (100 MHz, $CDCl_3$)

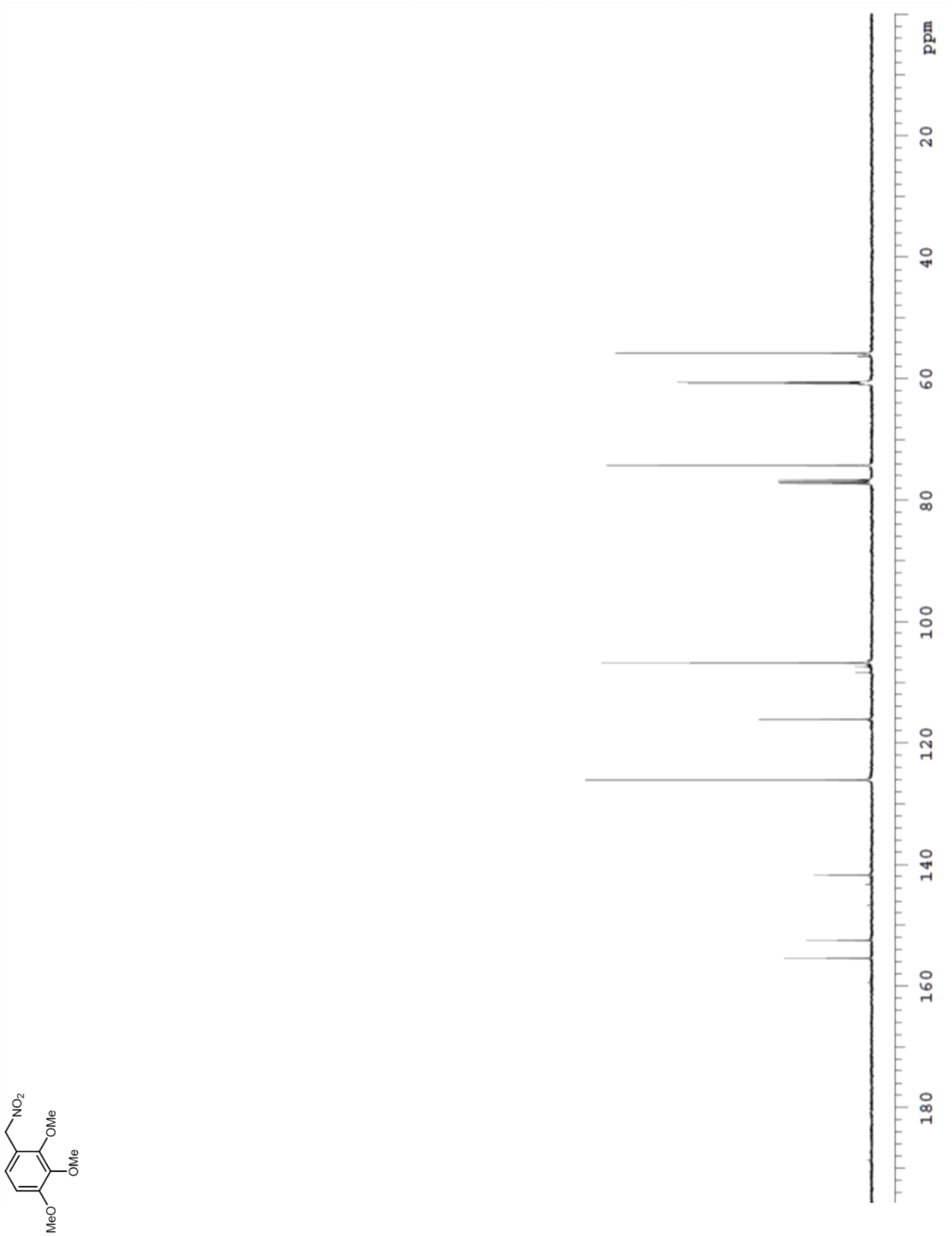


Figure S19. ^{1}H NMR data for 1-(nitromethyl)-2-(trifluoromethyl)benzene (400 MHz, $CDCl_3$)

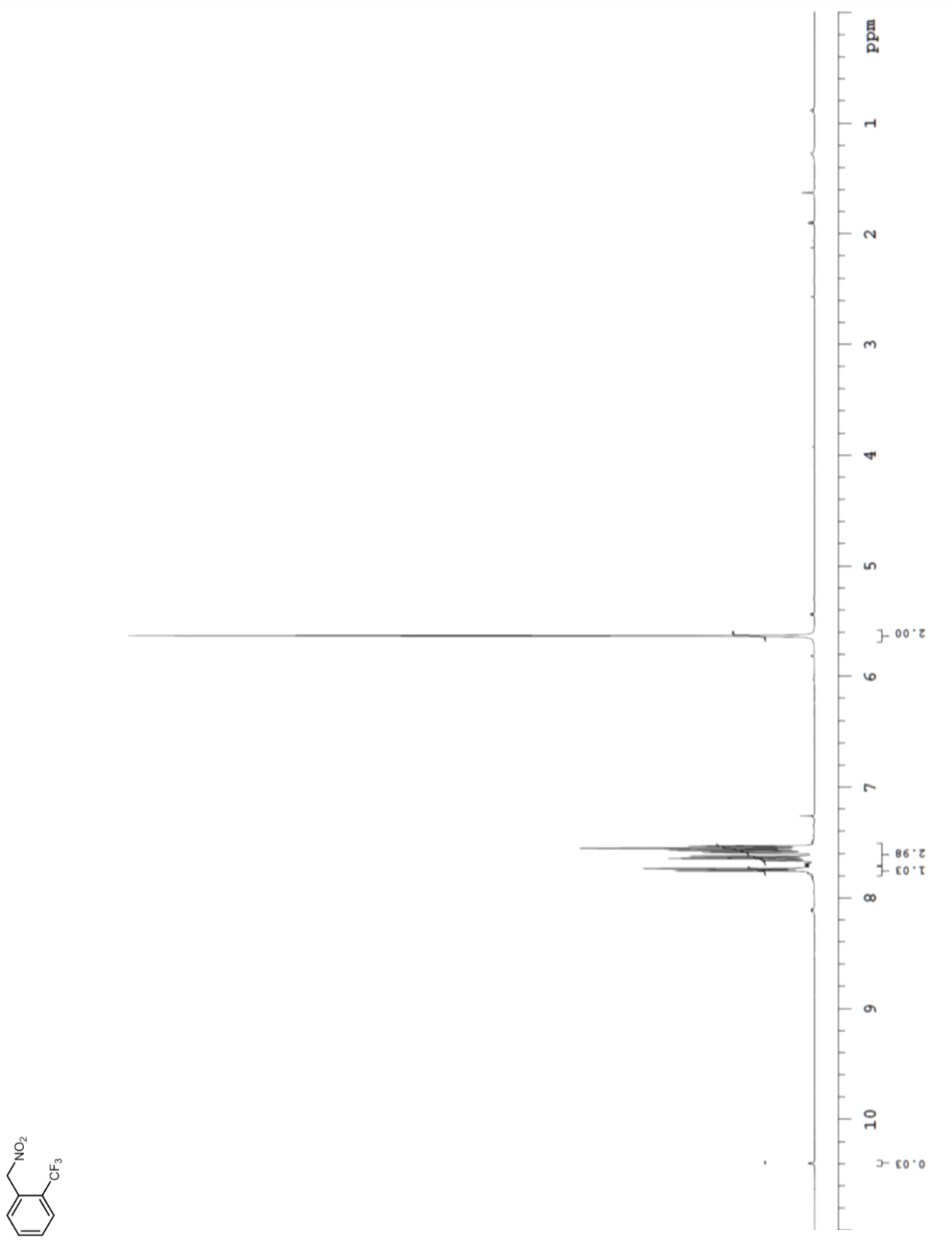


Figure S20. ^{13}C NMR data for 1-(nitromethyl)-2-(trifluoromethyl)benzene (100 MHz, $CDCl_3$)

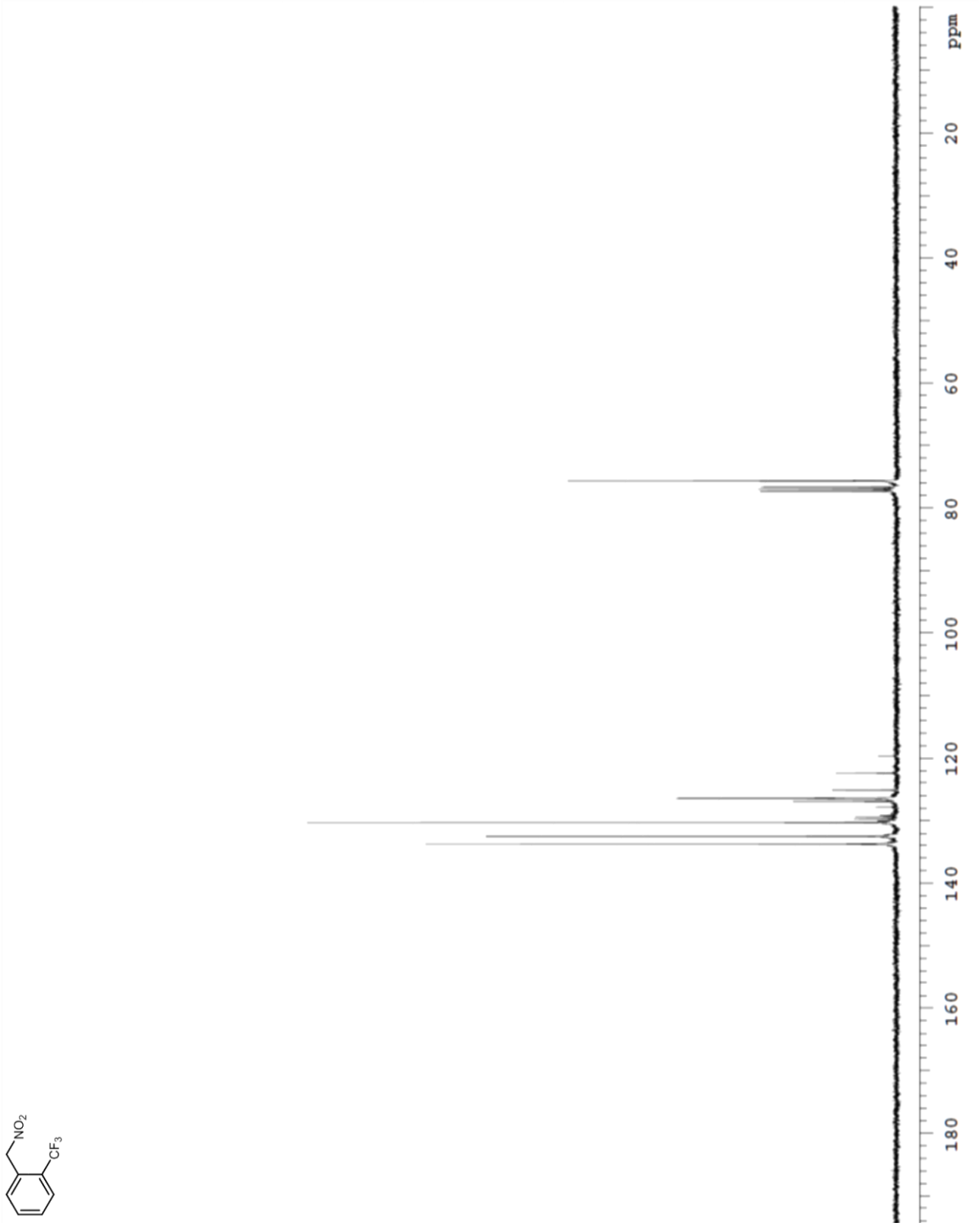


Figure S21. ^{1}H NMR data for 1,3-difluoro-5-(nitromethyl)benzene (400 MHz, $CDCl_3$)

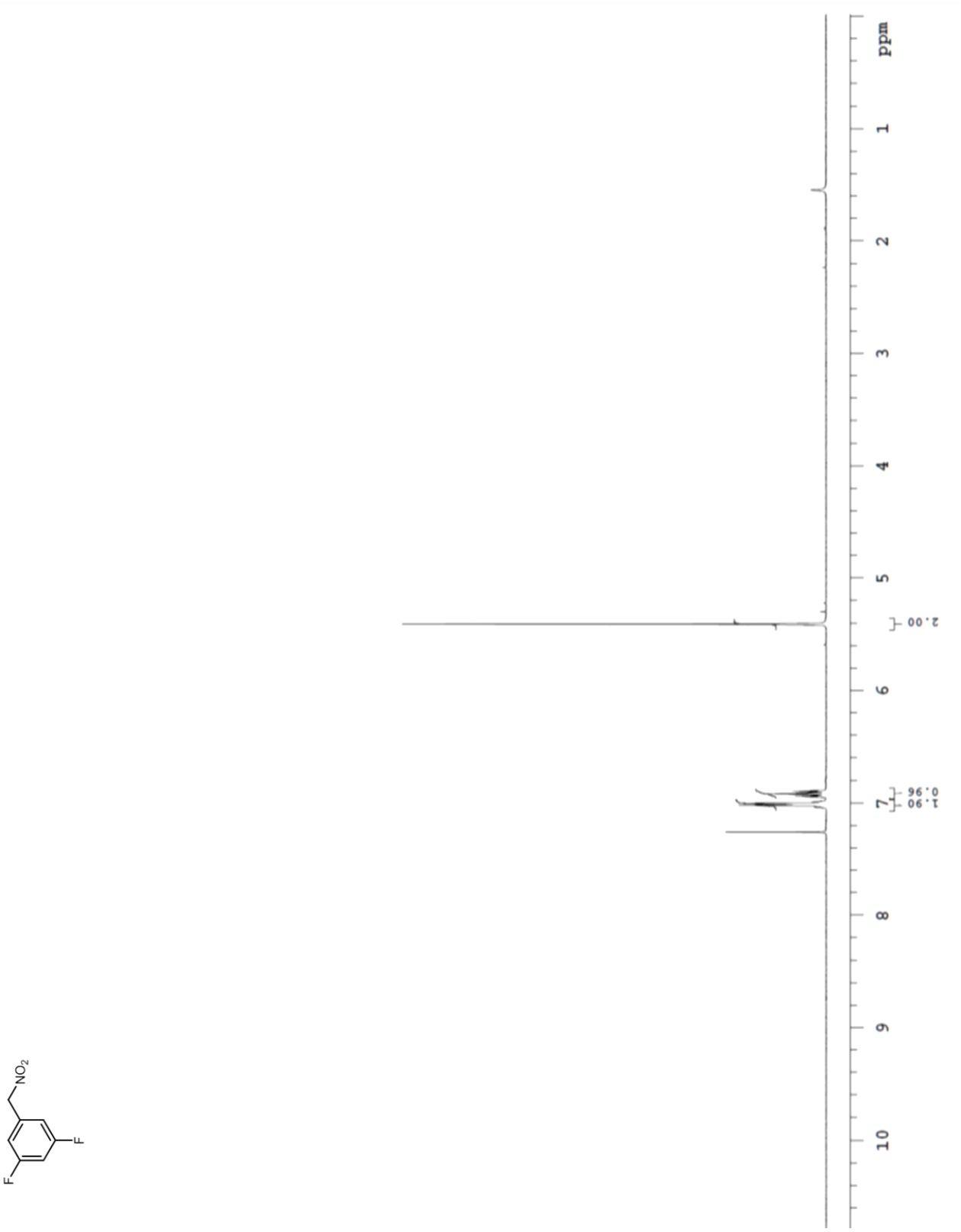


Figure S22. ^{13}C NMR data for 1,3-difluoro-5-(nitromethyl)benzene (100 MHz, $CDCl_3$)

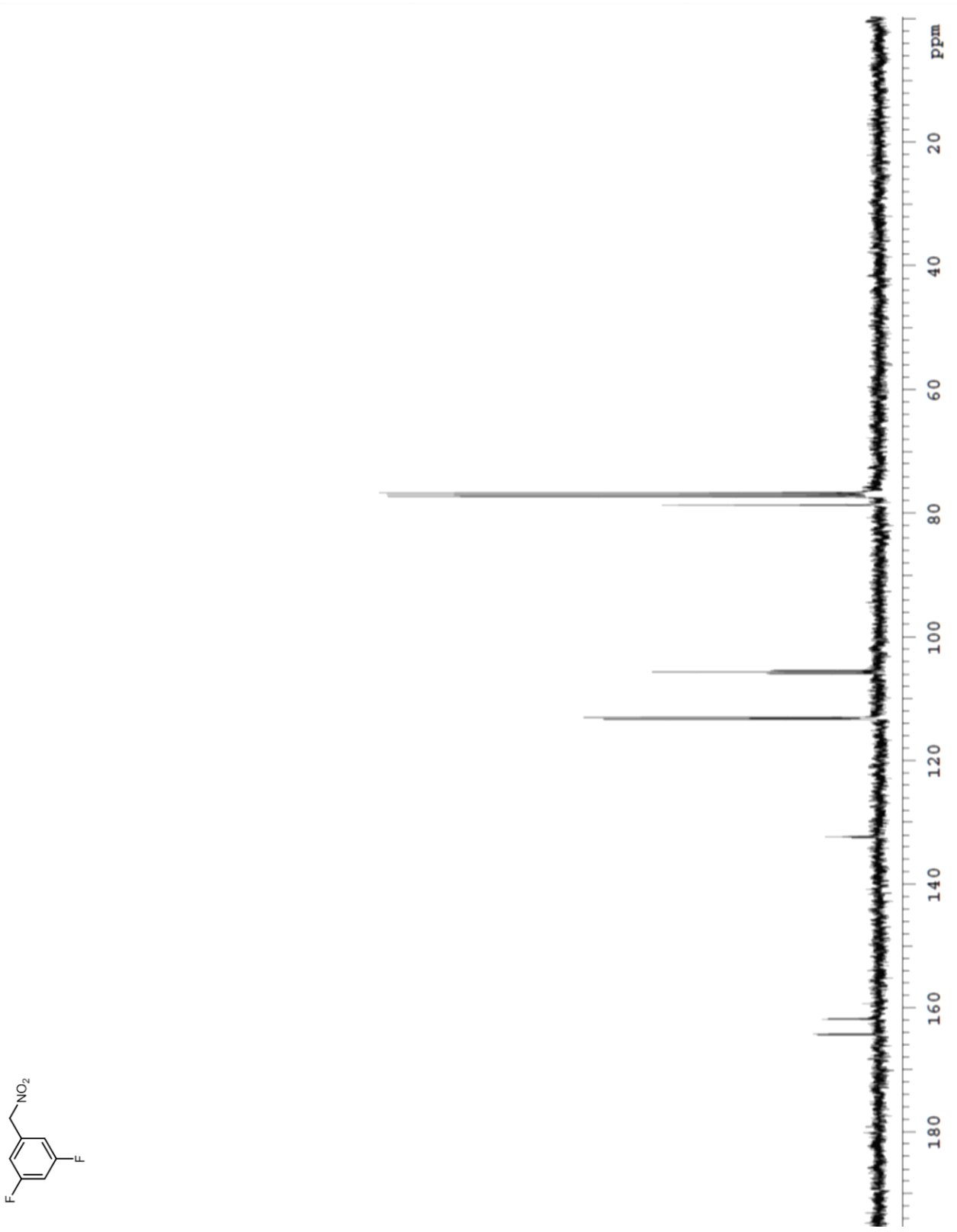


Figure S23. ^{1}H NMR data for 1-(nitromethyl)-4-(trifluoromethoxy)benzene (400 MHz, $CDCl_3$)

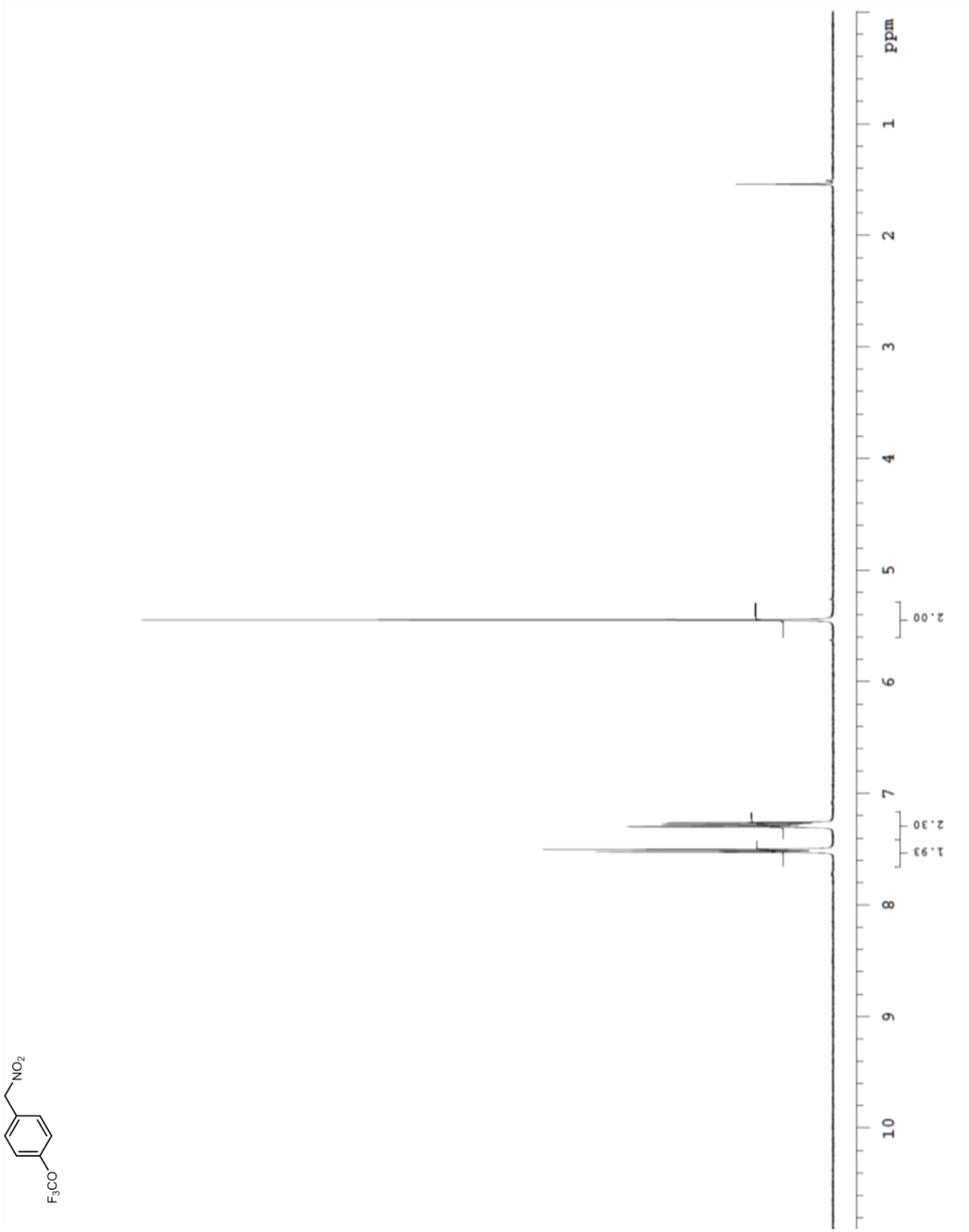


Figure S24. ^{13}C NMR data for 1-(nitromethyl)-4-(trifluoromethoxy)benzene (100 MHz, $CDCl_3$)

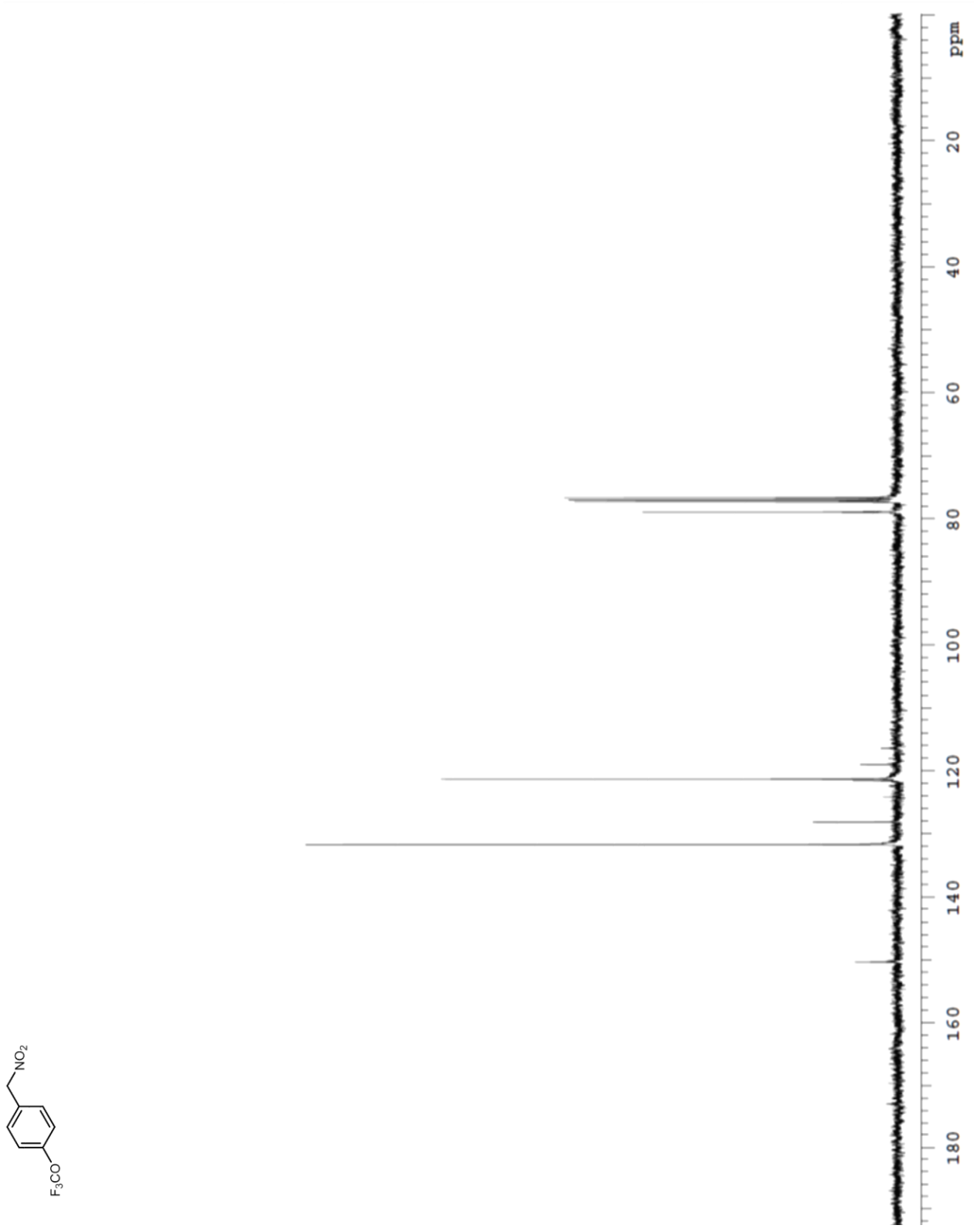


Figure S25. ^{1}H NMR data for 1-nitro-2-(nitromethyl)benzene (400 MHz, $CDCl_3$)

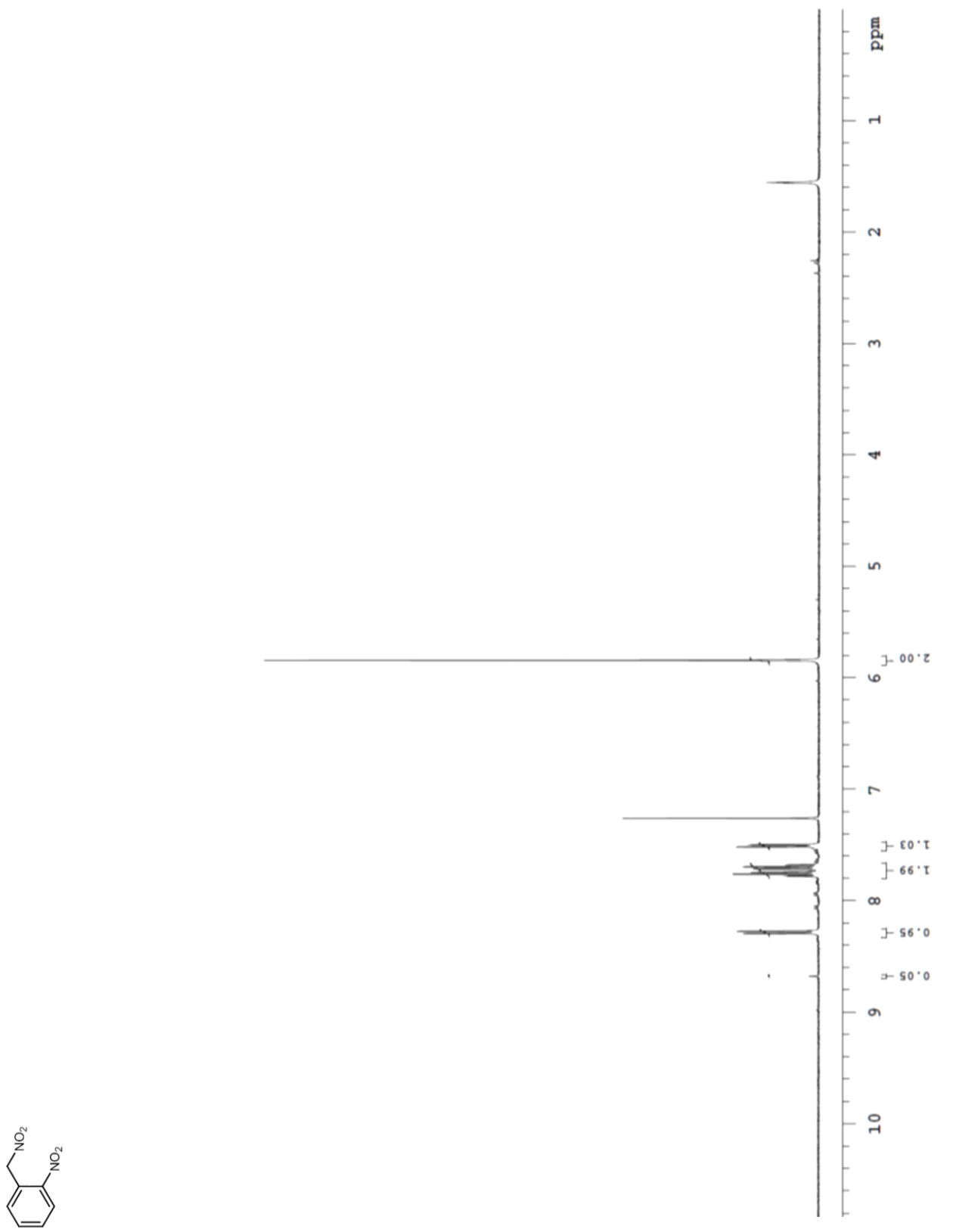


Figure S26. ^{13}C NMR data for 1-nitro-2-(nitromethyl)benzene (100 MHz, $CDCl_3$)

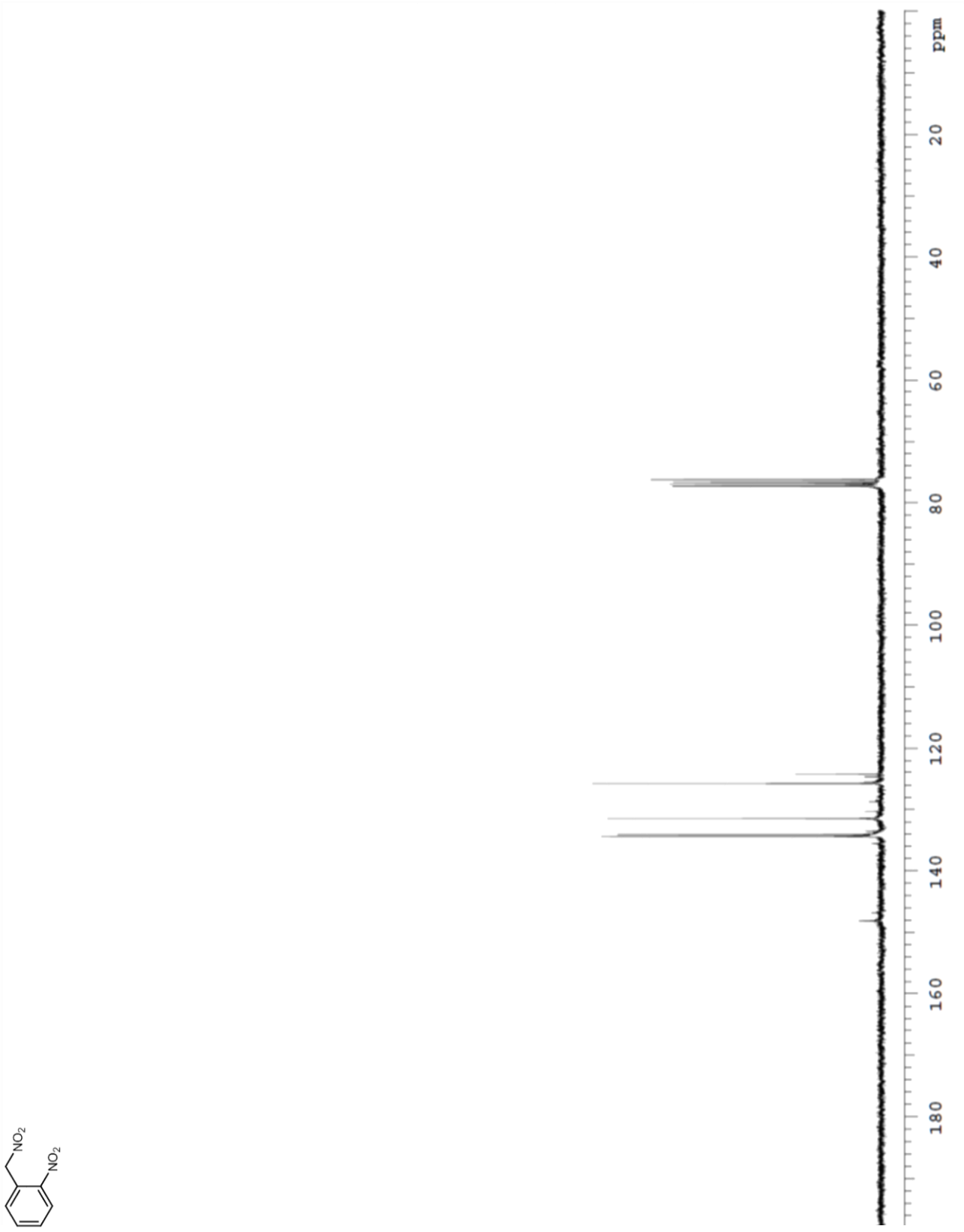


Figure S27. ^{1}H NMR data for (1-nitroethyl)benzene (400 MHz, $CDCl_3$)

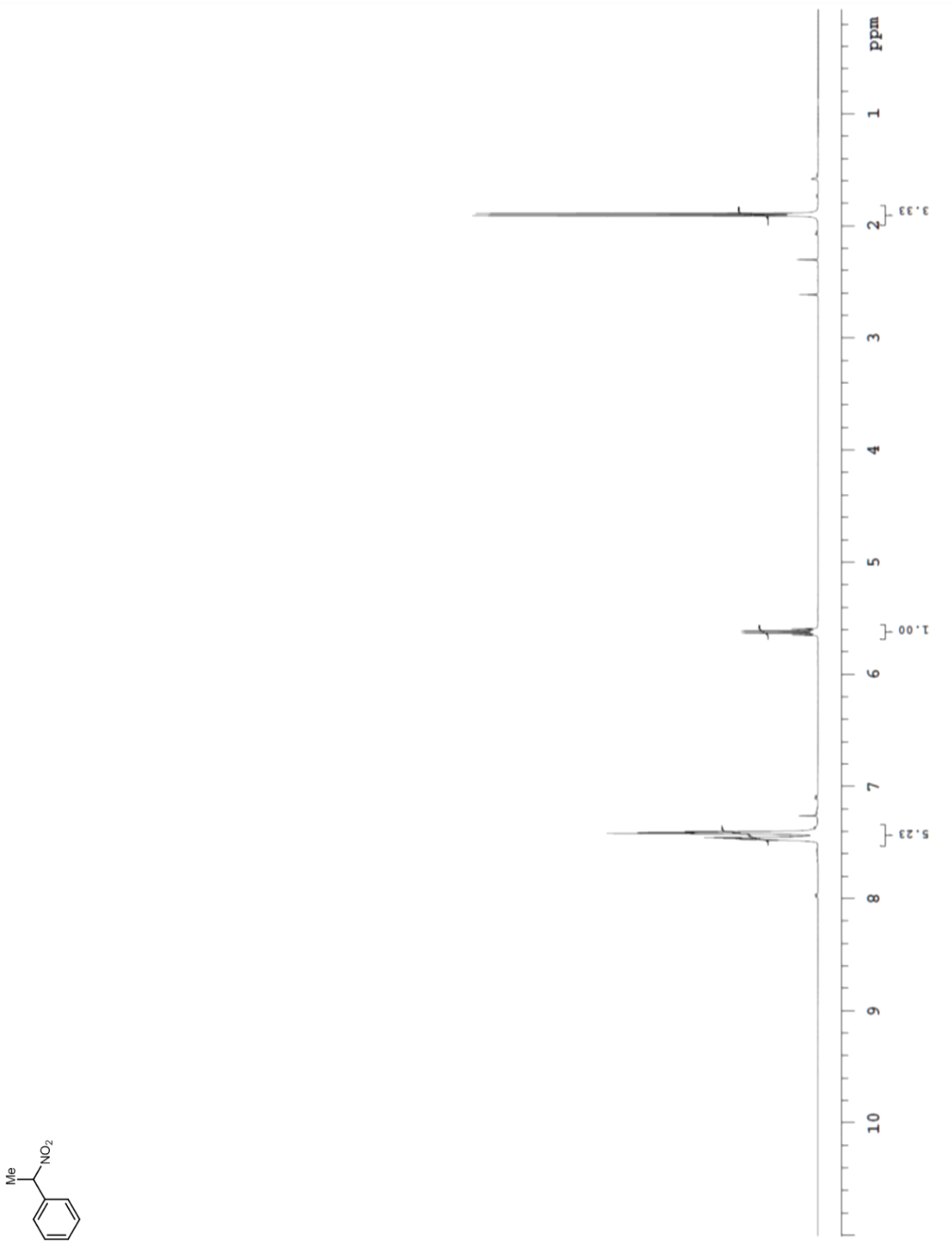


Figure S28. ^{13}C NMR data for (1-nitroethyl)benzene (100 MHz, $CDCl_3$)

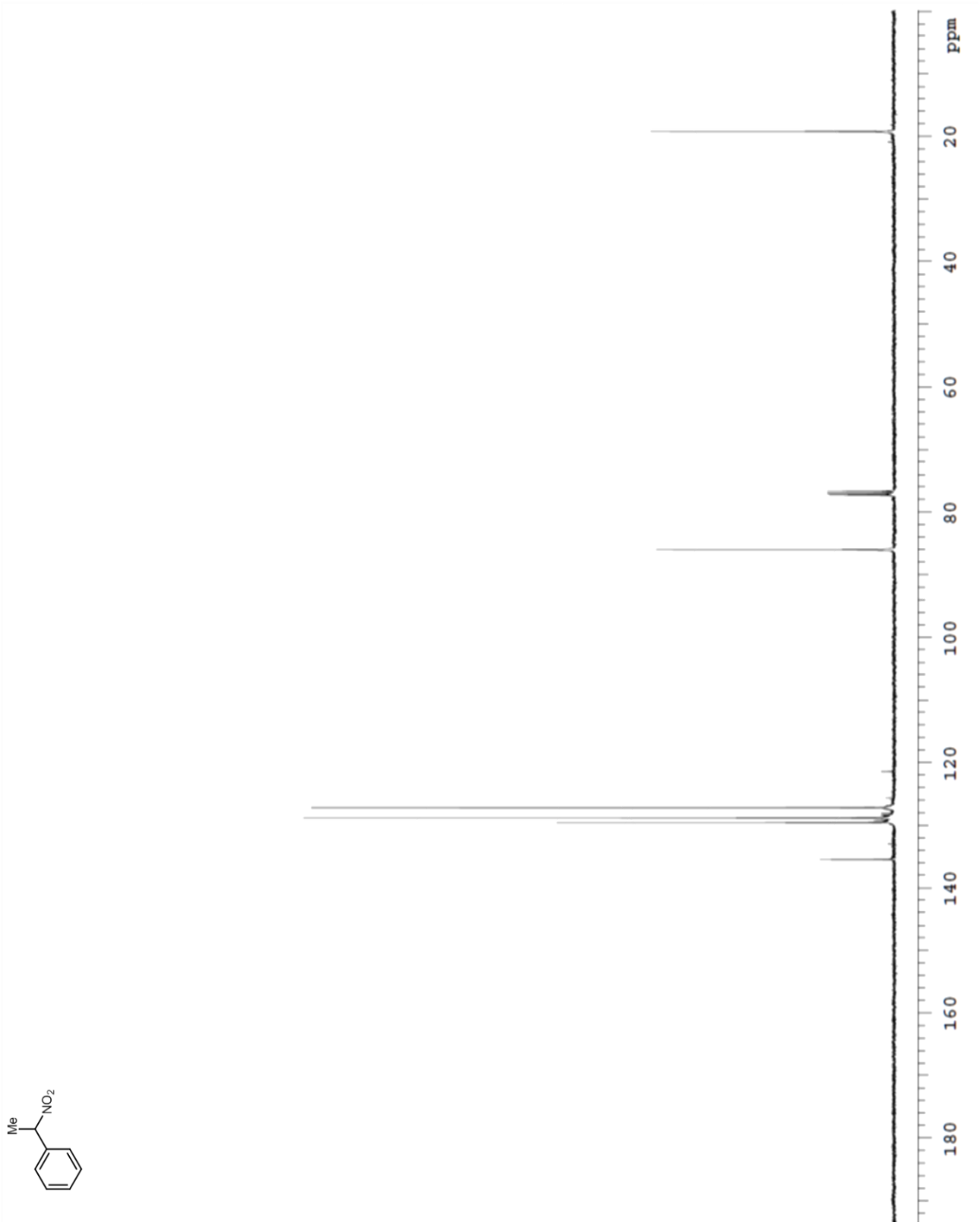


Figure S29. ^{1}H NMR data for (2,2,2-trifluoro-1-nitroethyl)benzene (400 MHz, $CDCl_3$)

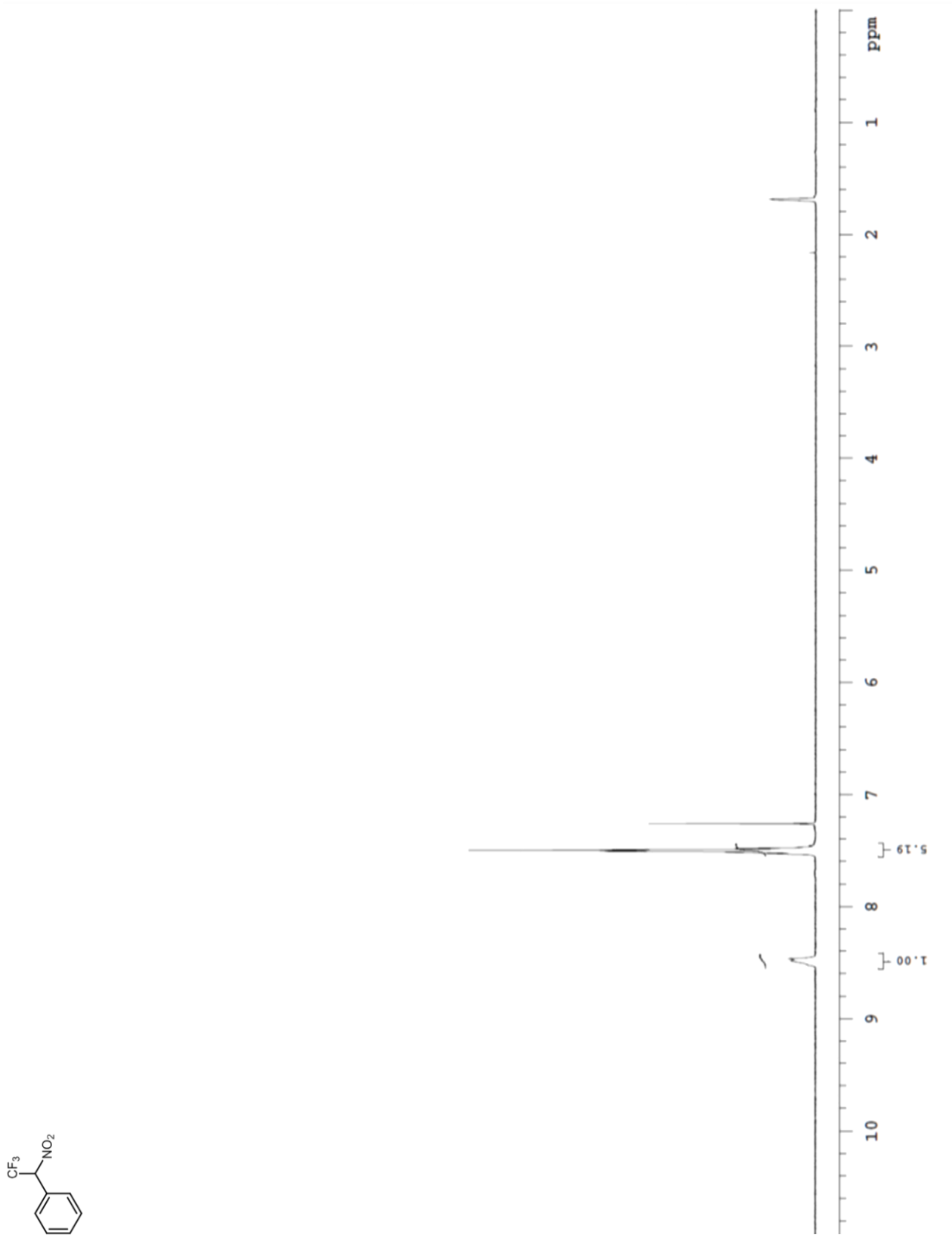


Figure S30. ^{13}C NMR data for (2,2,2-trifluoro-1-nitroethyl)benzene (100 MHz, $CDCl_3$)

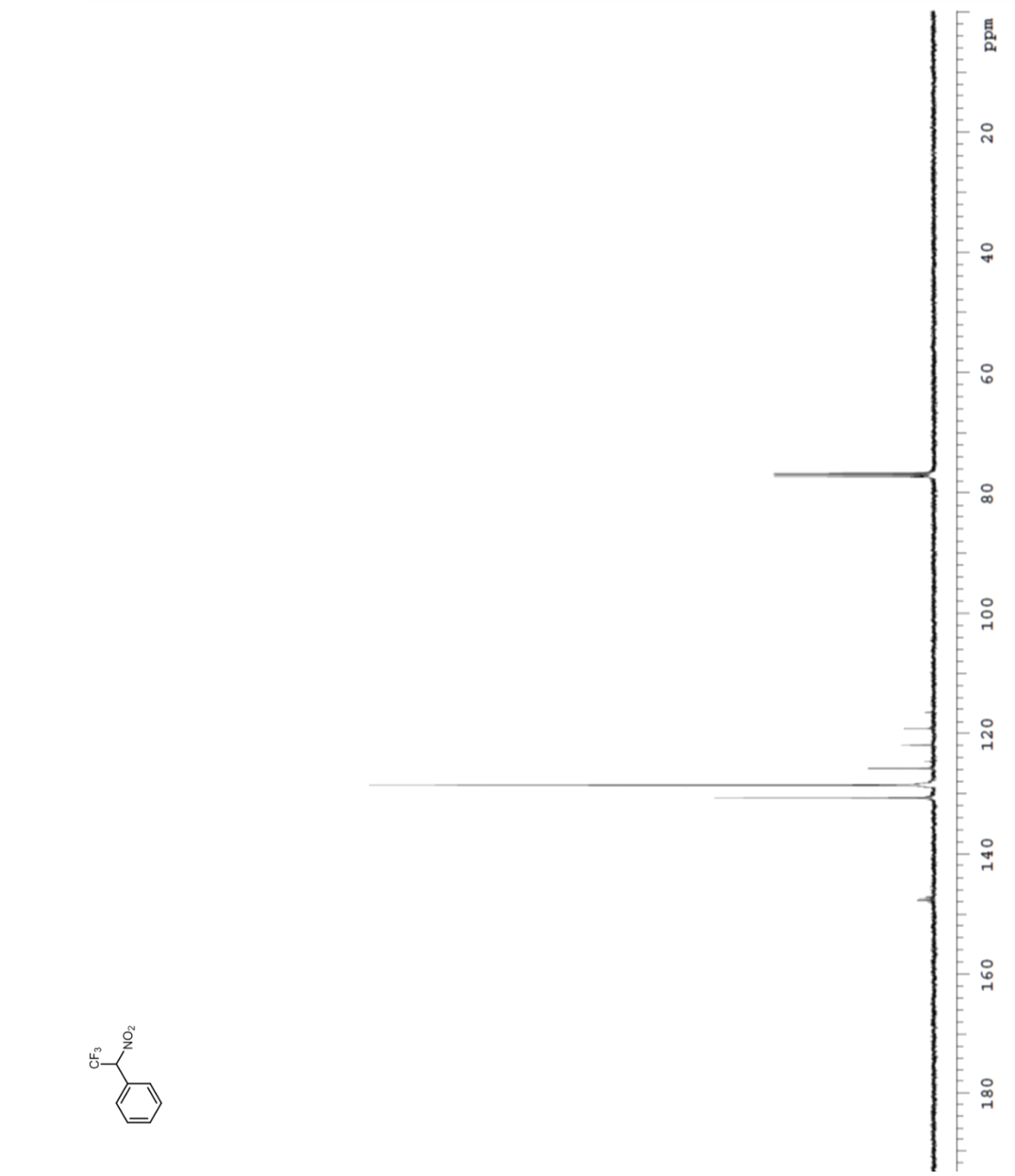


Figure S31. ^{1}H NMR data for (nitromethyl)cyclohexane (400 MHz, $CDCl_3$)

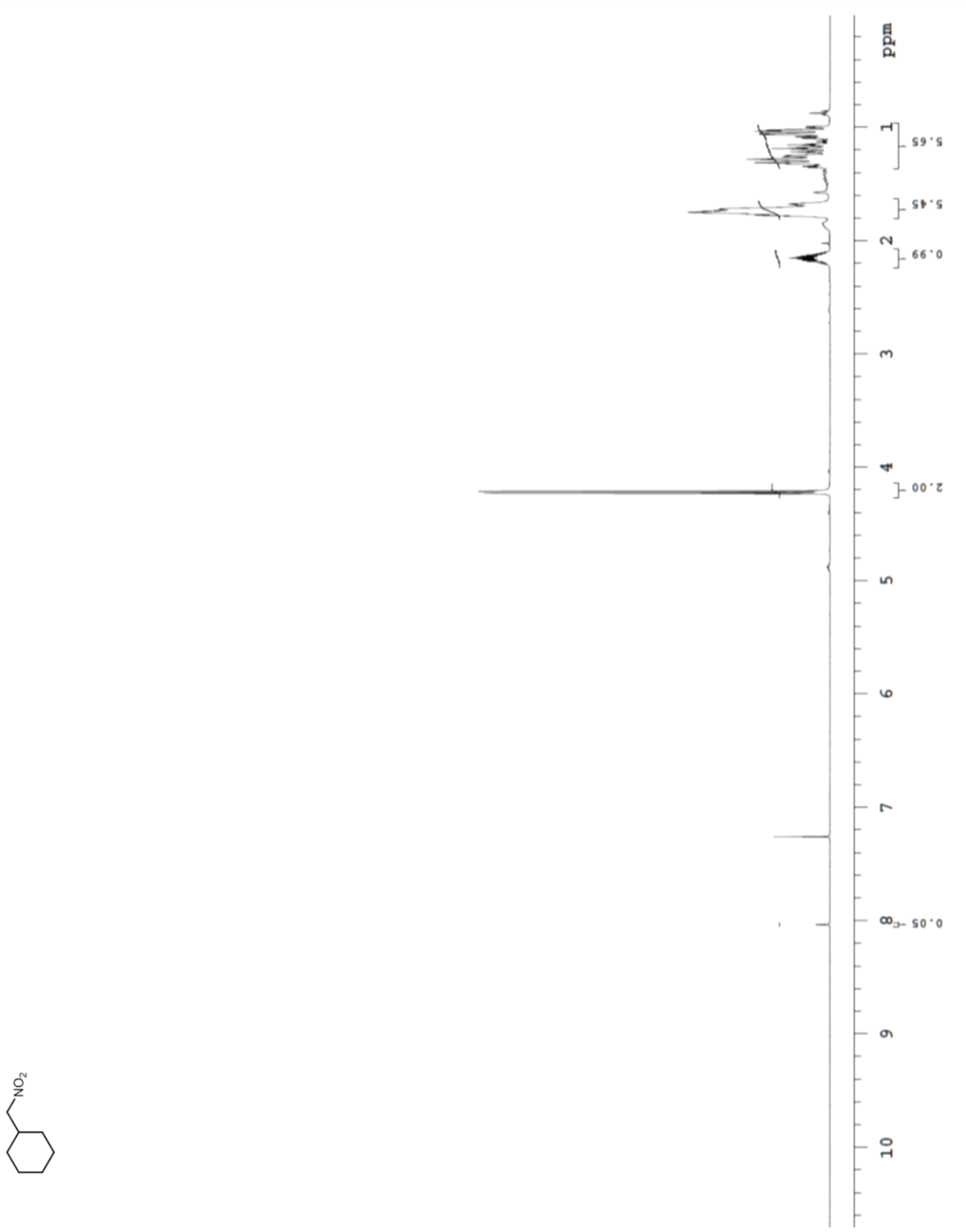


Figure S32. ^{13}C NMR data for (nitromethyl)cyclohexane (100 MHz, $CDCl_3$)

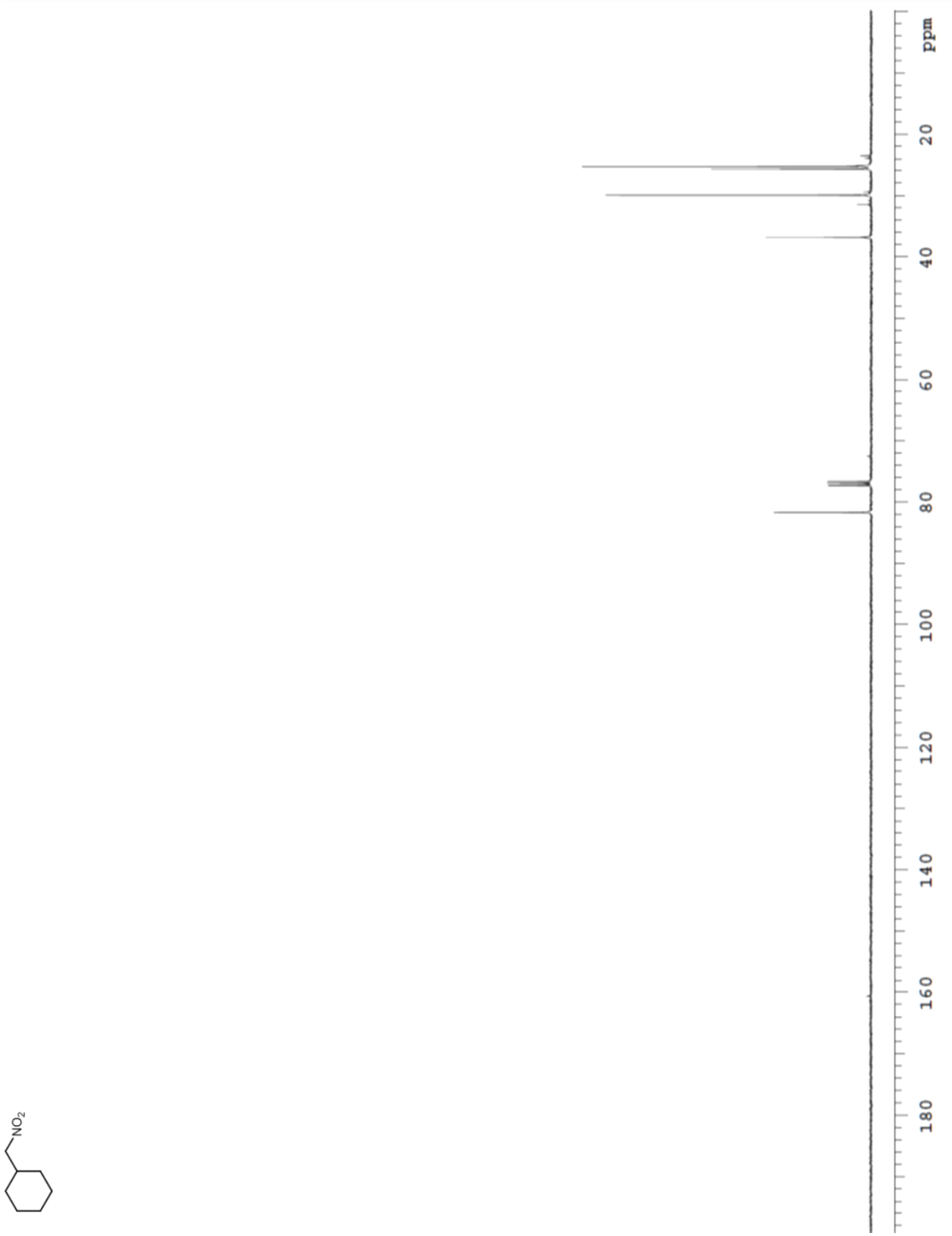


Figure S33. ^{1}H NMR data for 1-nitrohexane (400 MHz, $CDCl_3$)

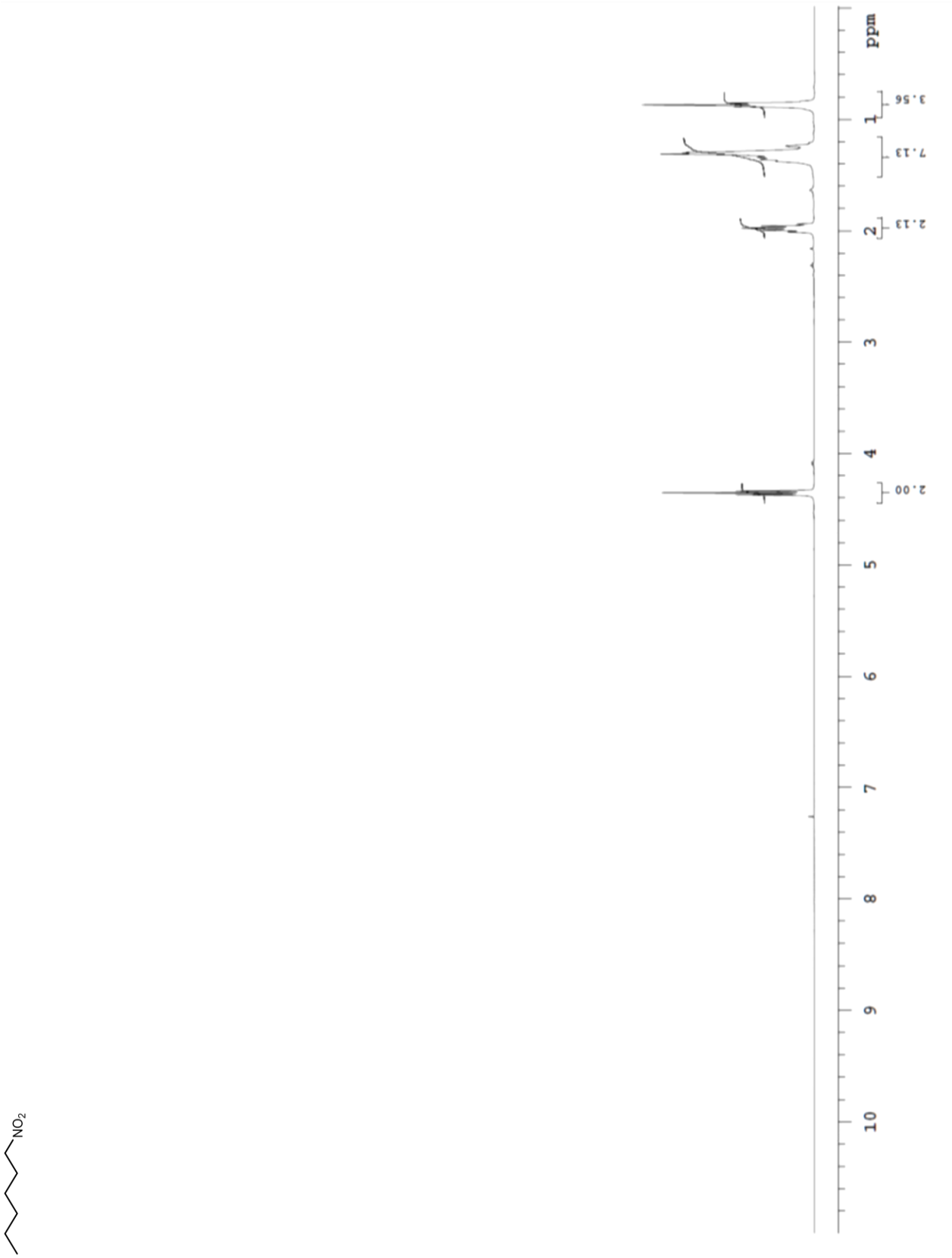


Figure S34. ^{13}C NMR data for 1-nitrohexane (100 MHz, $CDCl_3$)

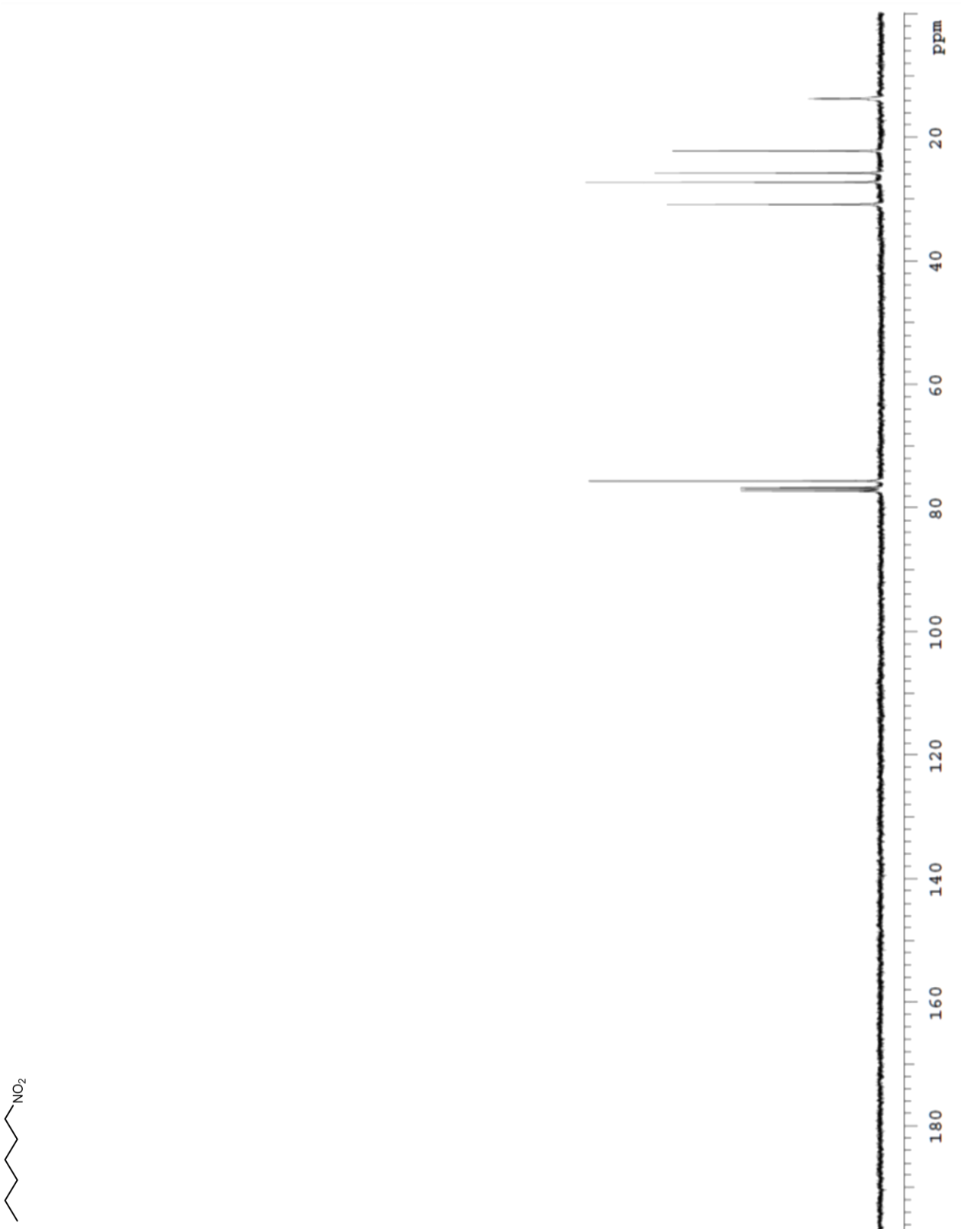


Figure S35. ^{1}H NMR data for 3-nitrohexane (400 MHz, $CDCl_3$)

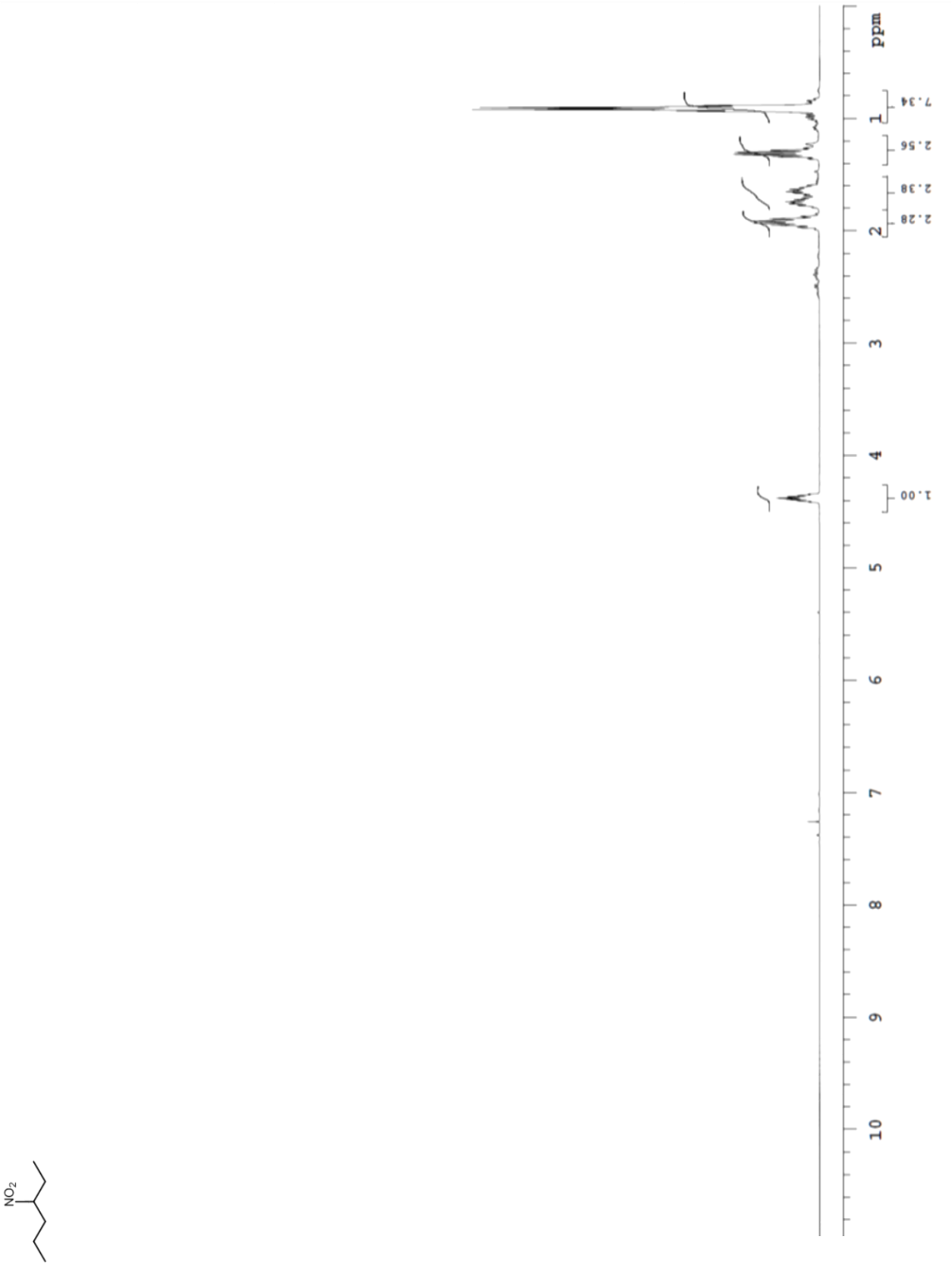


Figure S36. ^{13}C NMR data for 3-nitrohexane (100 MHz, $CDCl_3$)

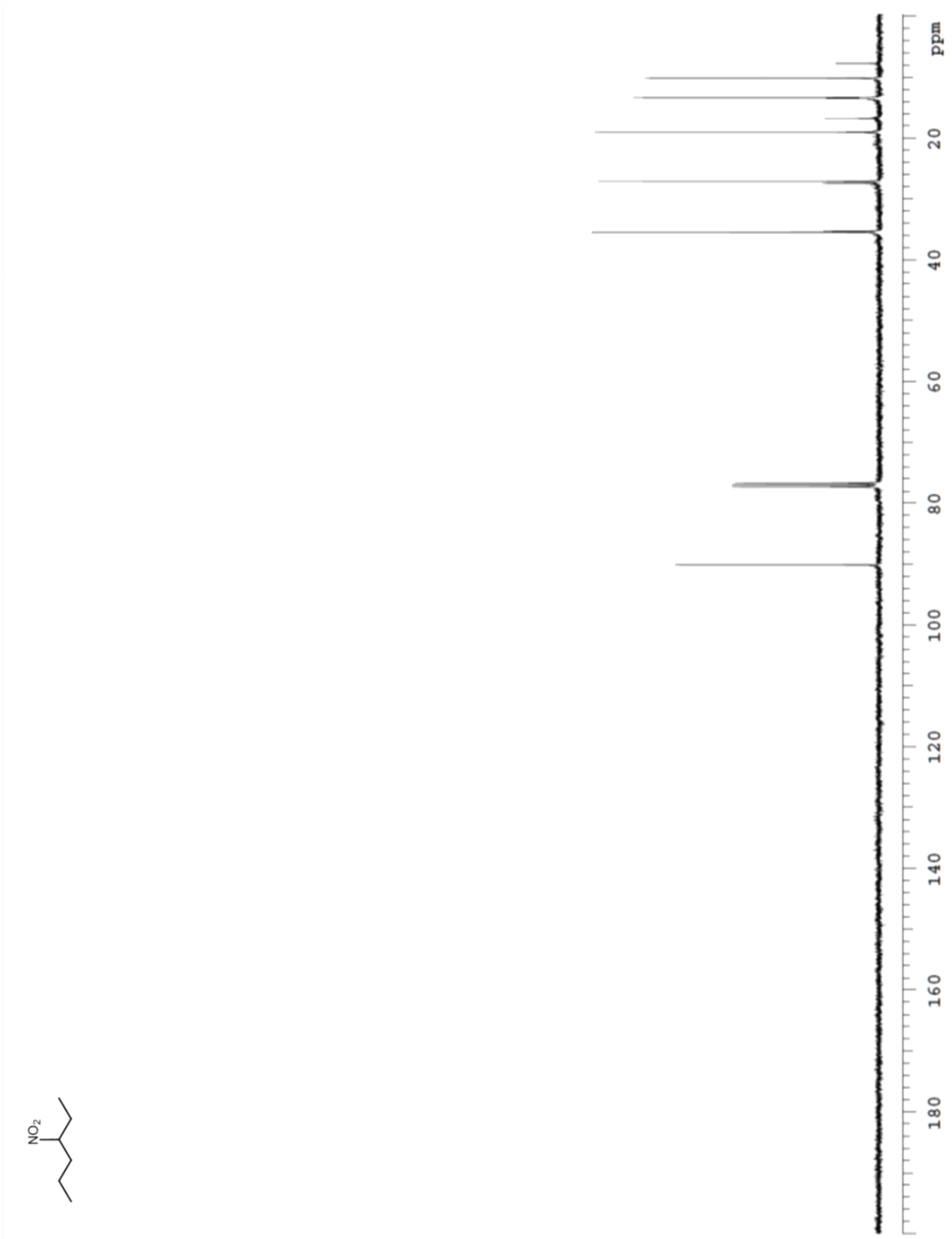


Figure S37. ^{1}H NMR data for tert-butyl ((1R,2S)-2-(4-(tert-butyl)phenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (400 MHz, $CDCl_3$)

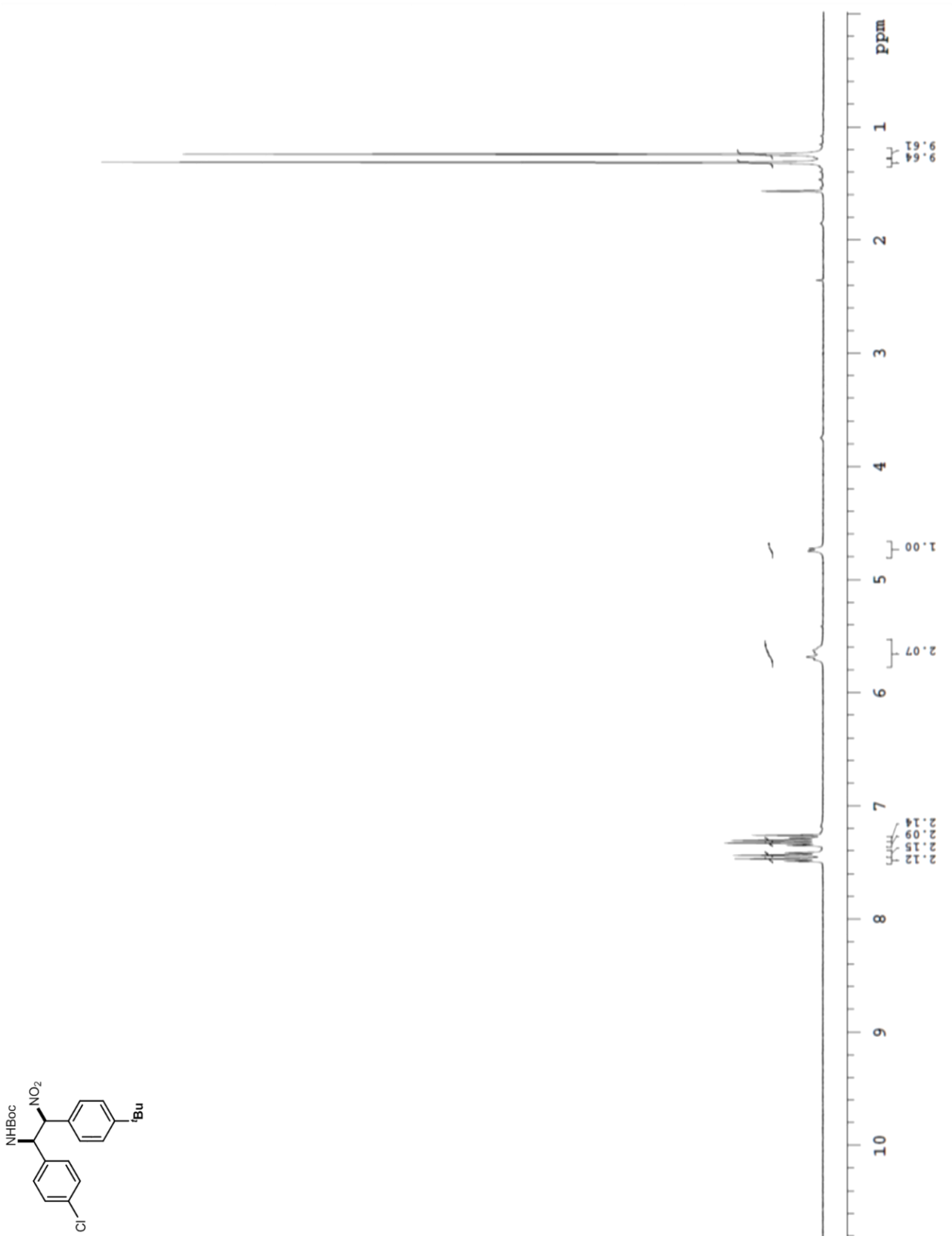


Figure S38. ^{13}C NMR data for tert-butyl ((1R,2S)-2-(4-(tert-butyl)phenyl)-1-(4-chlorophenyl)-2-nitroethyl)carbamate (100 MHz, $CDCl_3$)

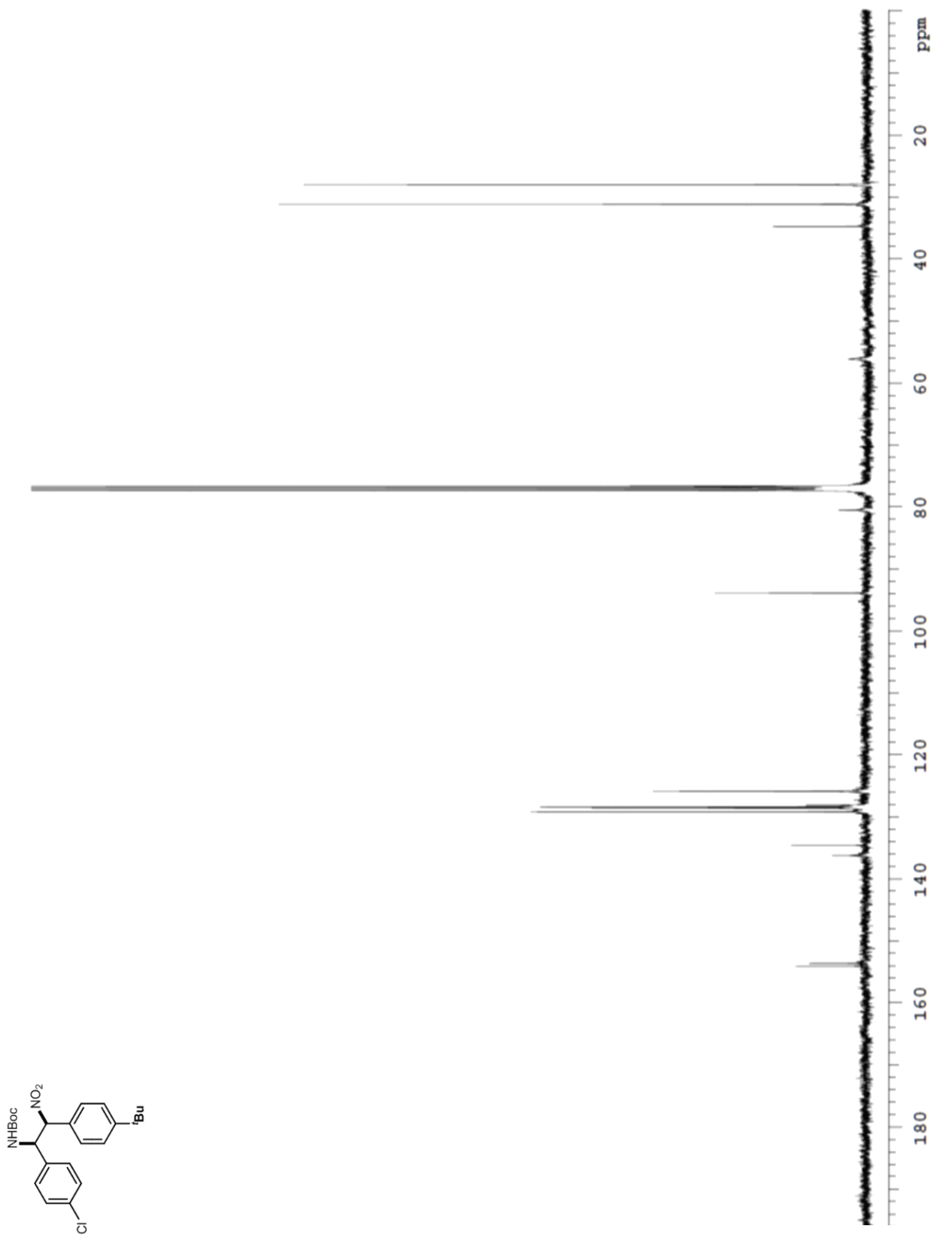


Figure S39. ^{1}H NMR data for 2-3 h toluene fraction after extraction (400 MHz, $CDCl_3$)

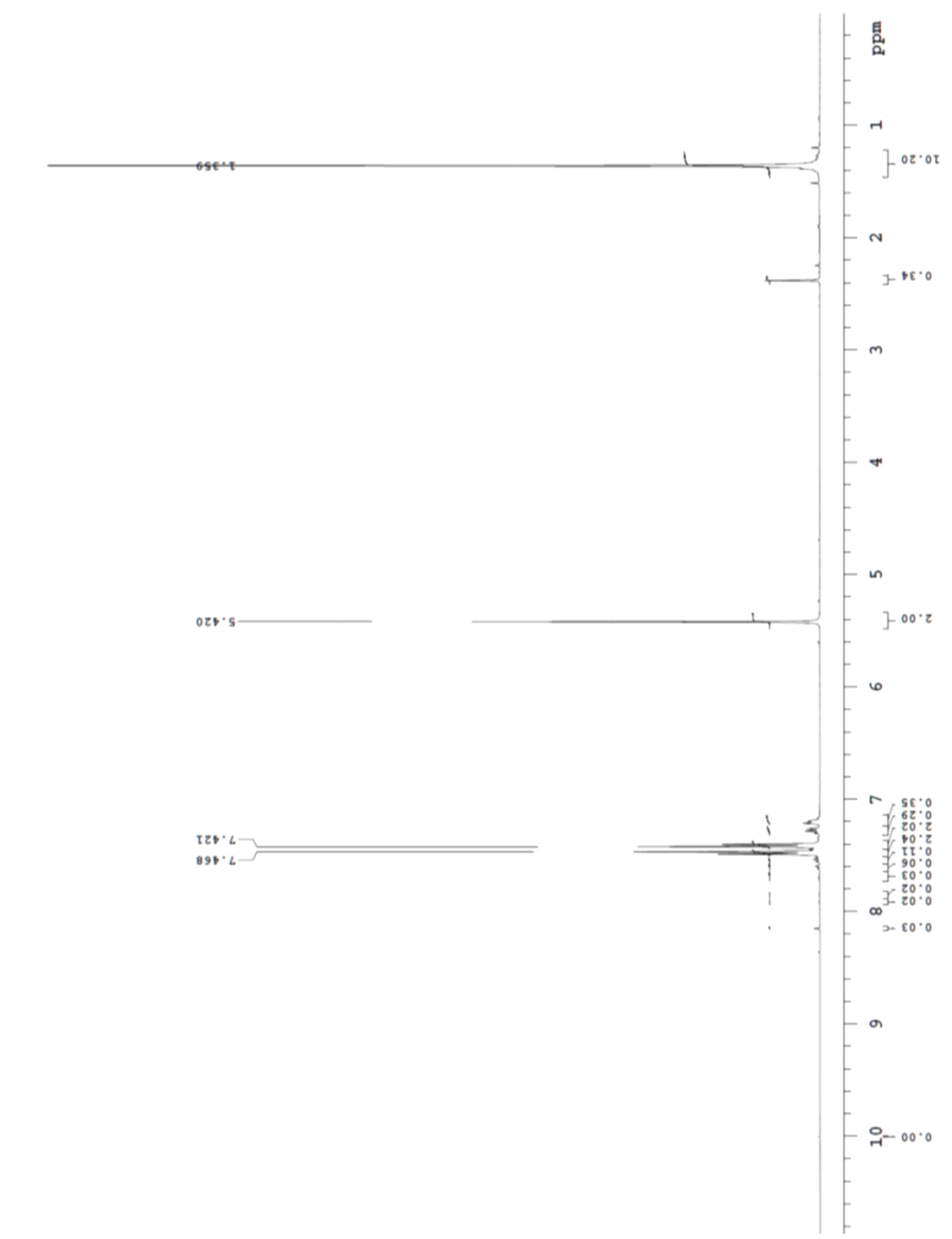


Figure S40. ^{1}H NMR data for 5-6 h toluene fraction after extraction (400 MHz, $CDCl_3$)

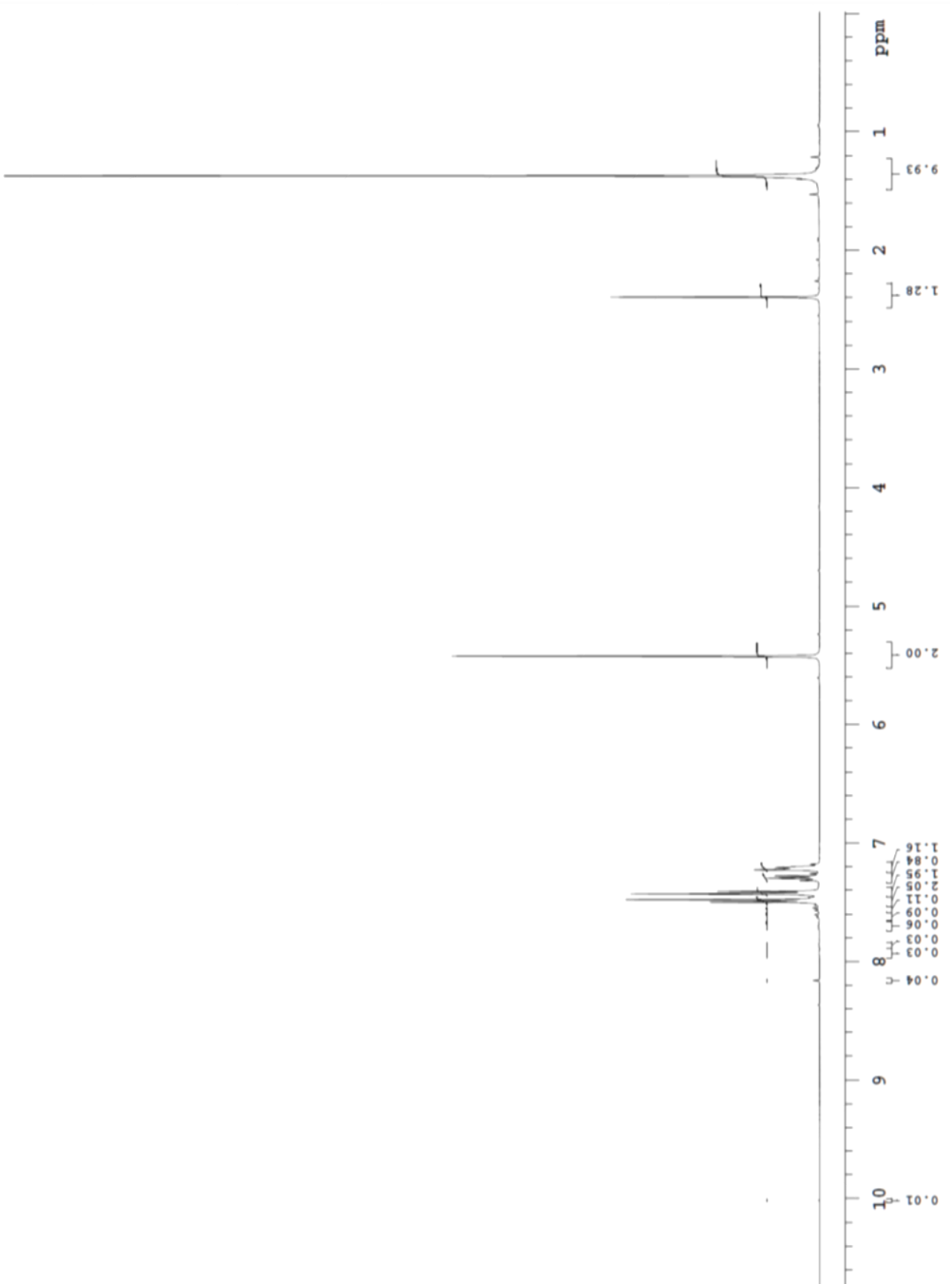


Figure S41. ^{1}H NMR data for 8-9 h toluene fraction after extraction (400 MHz, $CDCl_3$)

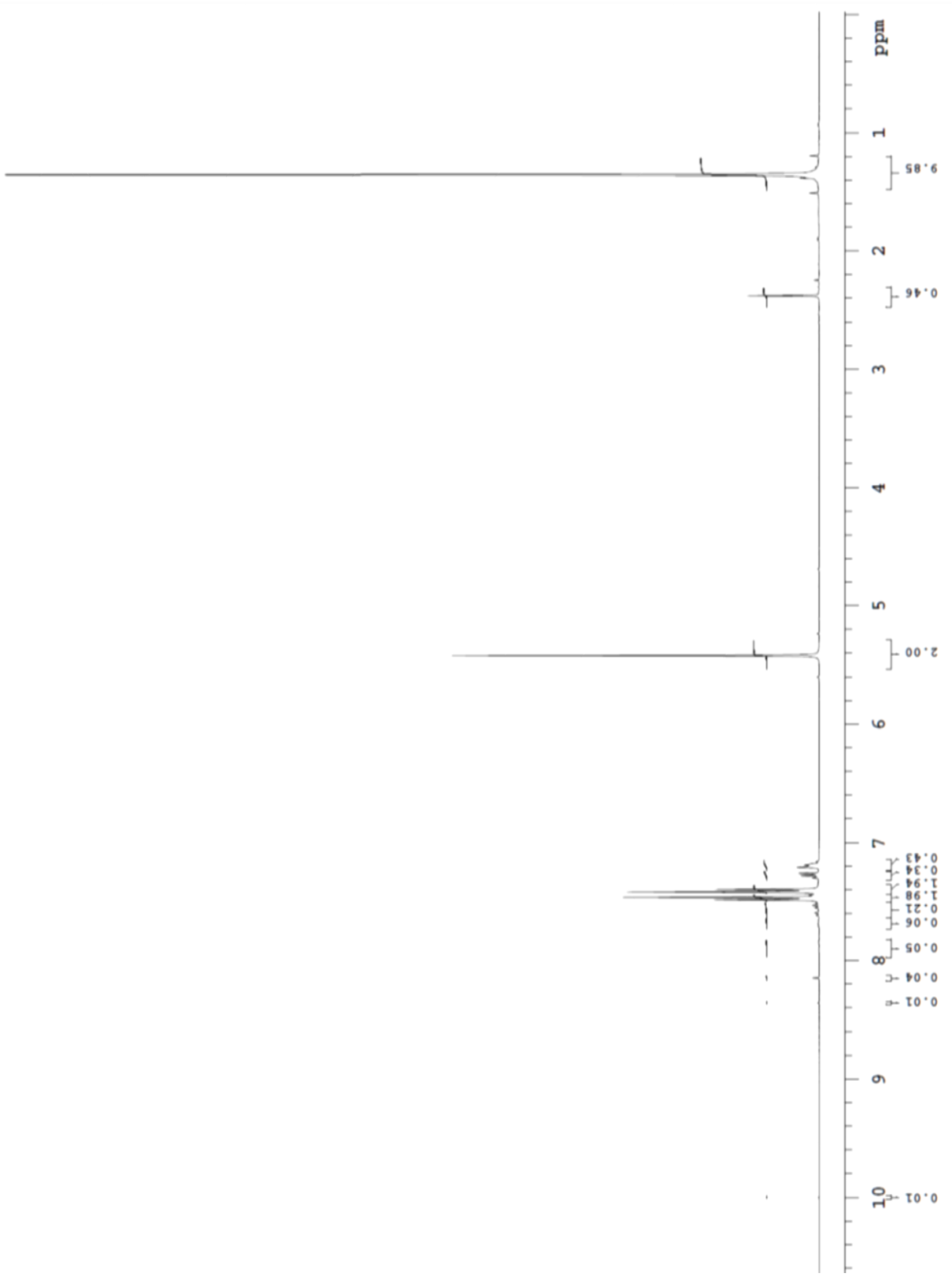


Figure S42. ^{1}H NMR data for 11-12 h toluene fraction after extraction (400 MHz, $CDCl_3$)

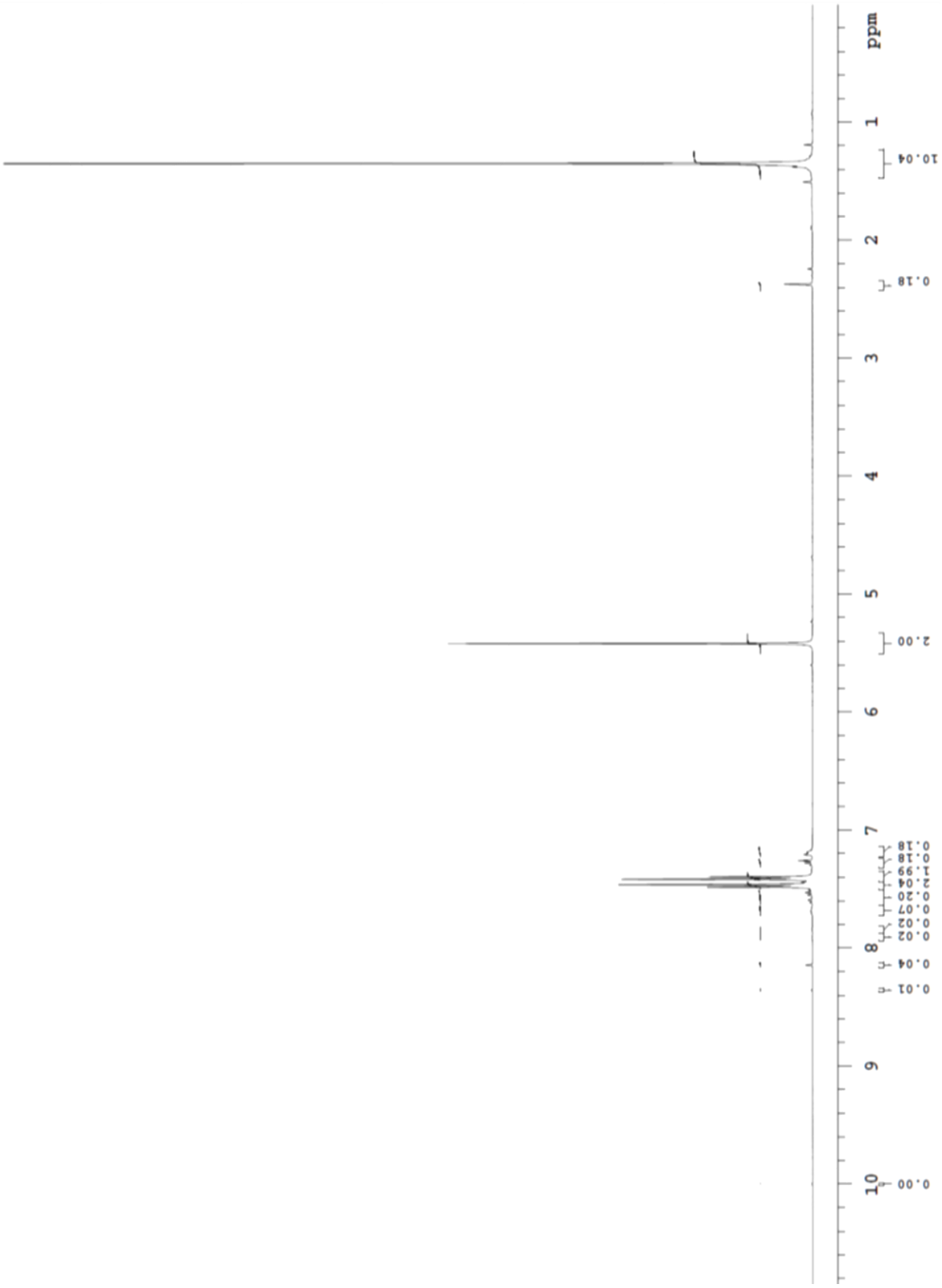


Figure S43. ^{1}H NMR data for 14-15 h toluene fraction after extraction (400 MHz, $CDCl_3$)

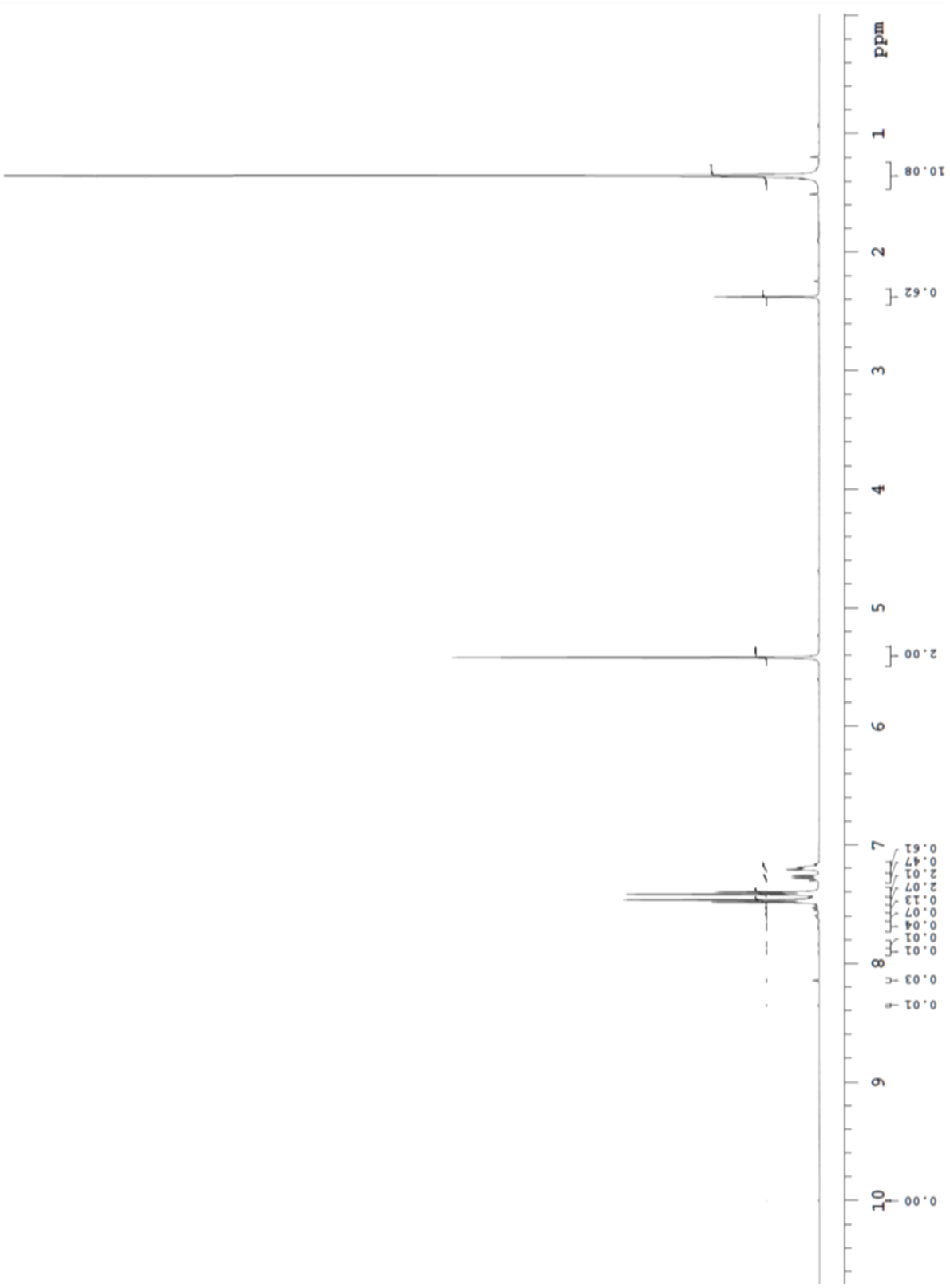


Figure S44. ^{13}C NMR data for 3 h AcOOH solution (100 MHz, $CDCl_3$)

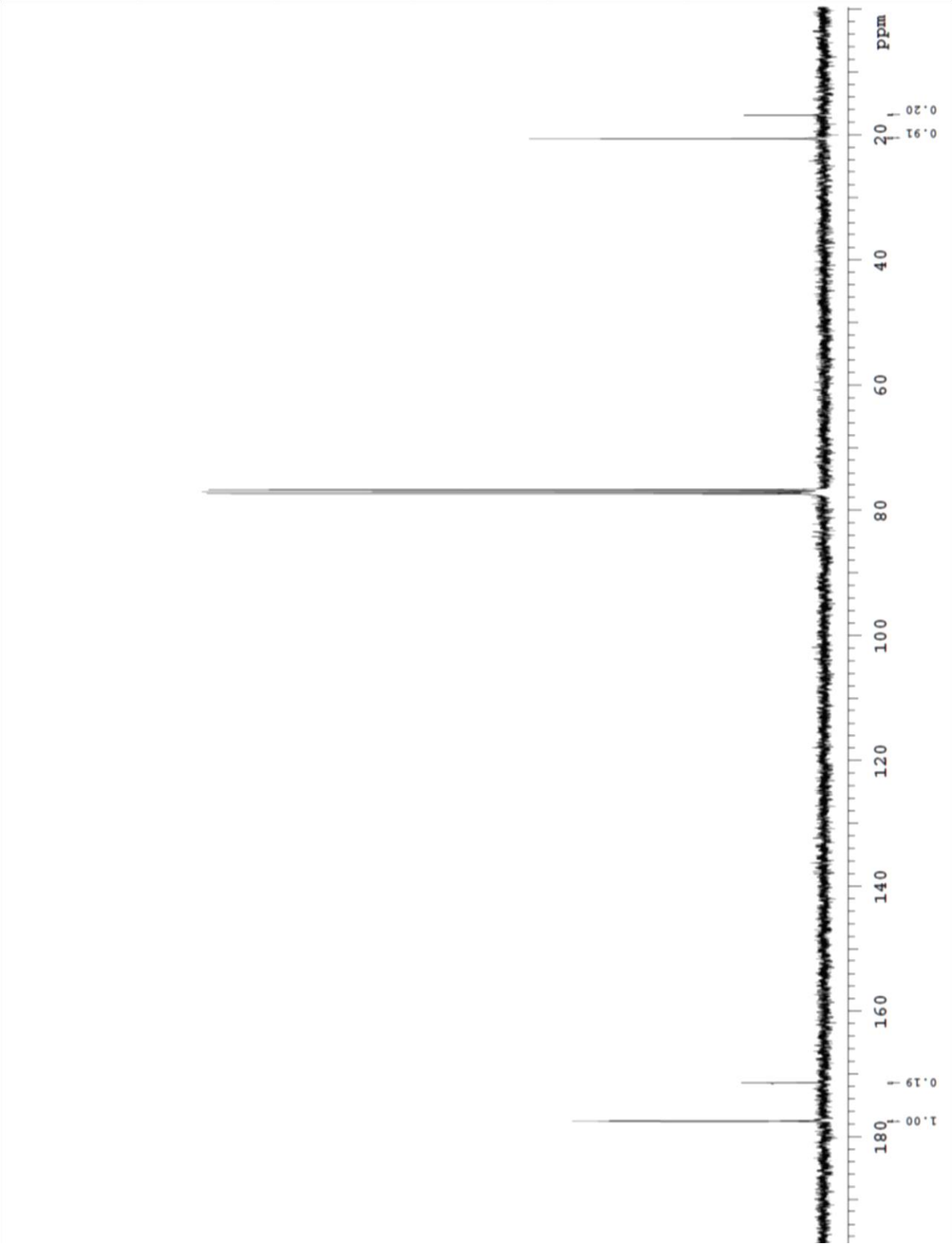


Figure S45. ^{13}C NMR data for 6 h AcOOH solution (100 MHz, $CDCl_3$)

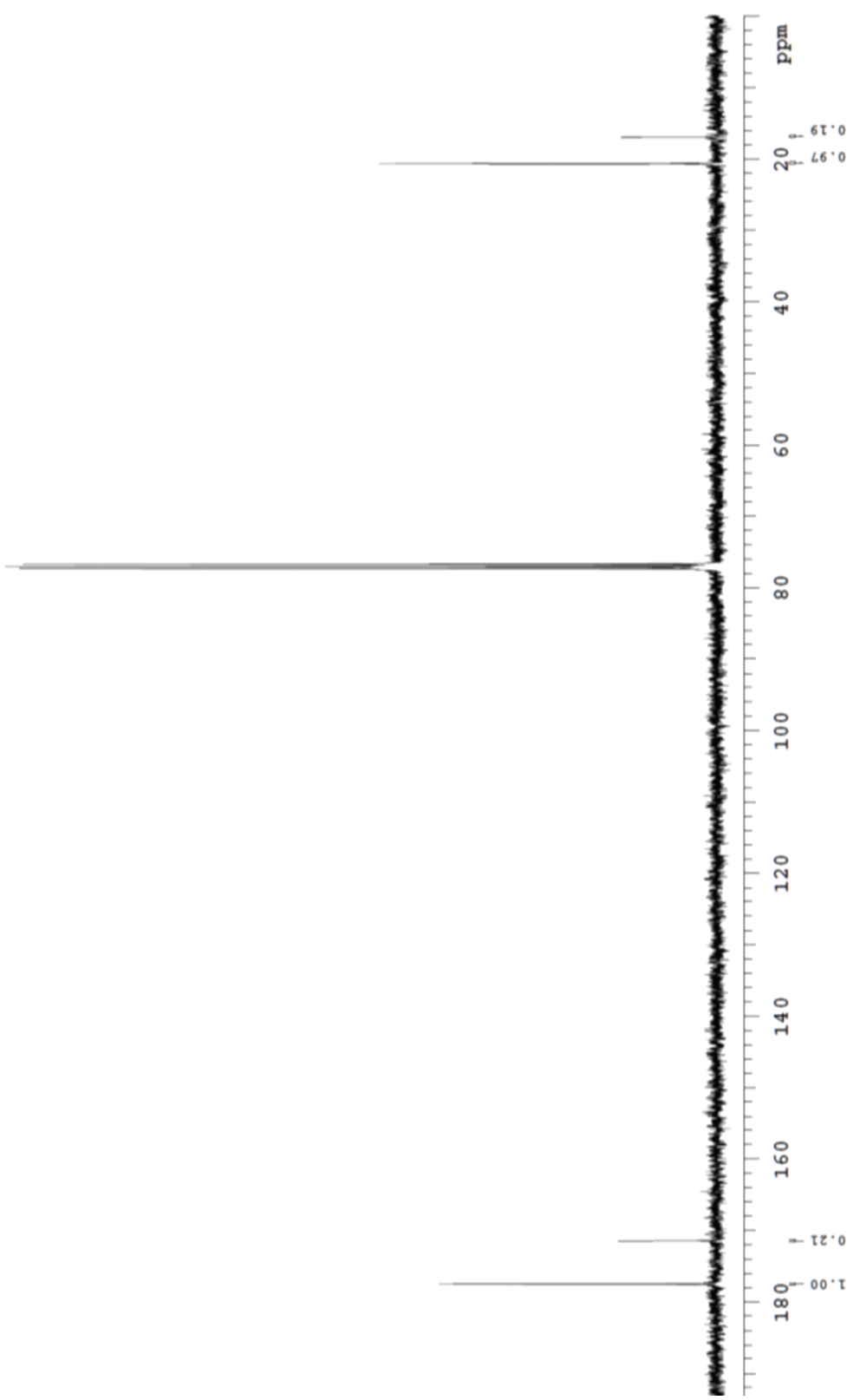


Figure S46. ^{13}C NMR data for 9 h AcOOH solution (100 MHz, $CDCl_3$)

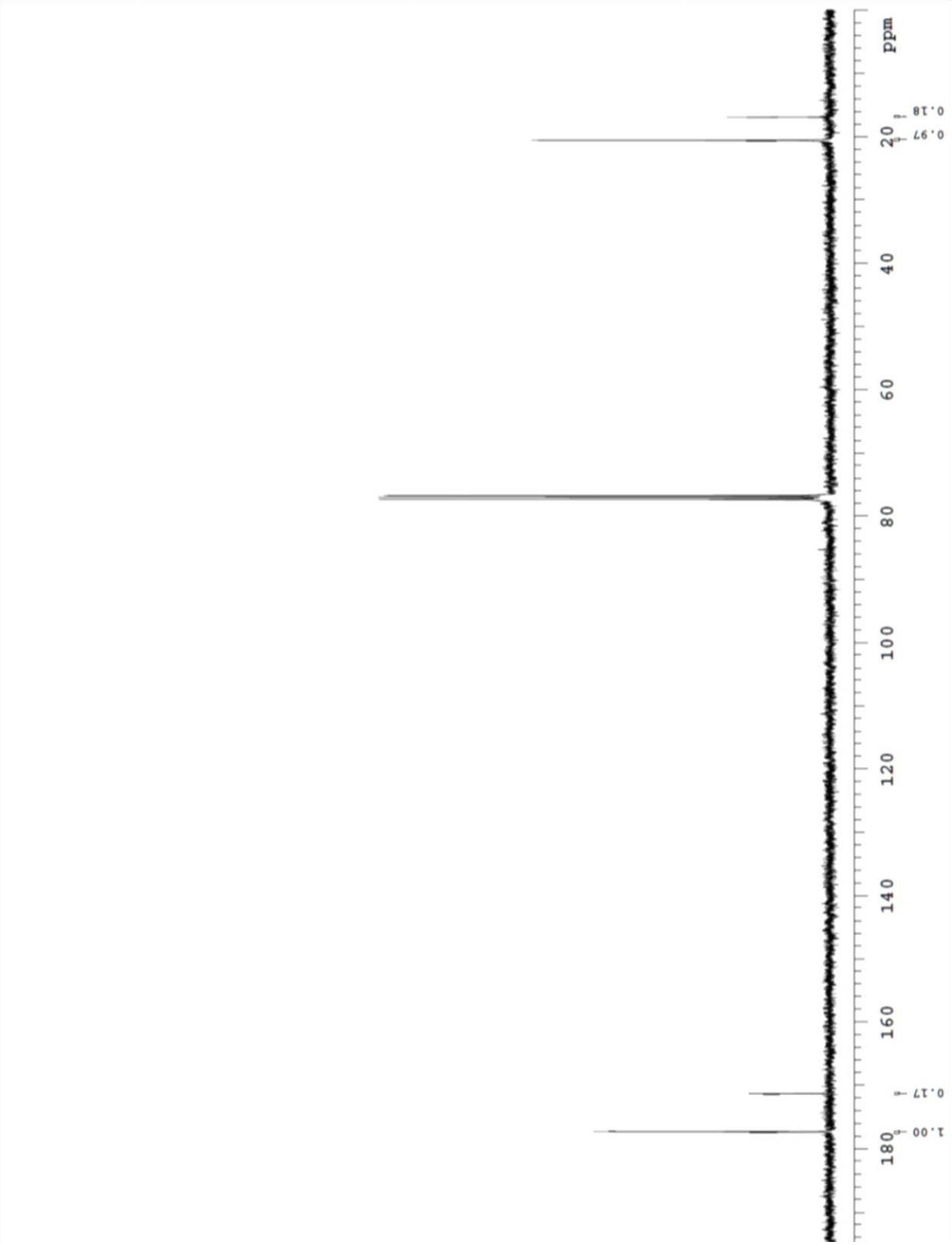


Figure S47. ^{13}C NMR data for 12 h AcOOH solution (100 MHz, $CDCl_3$)

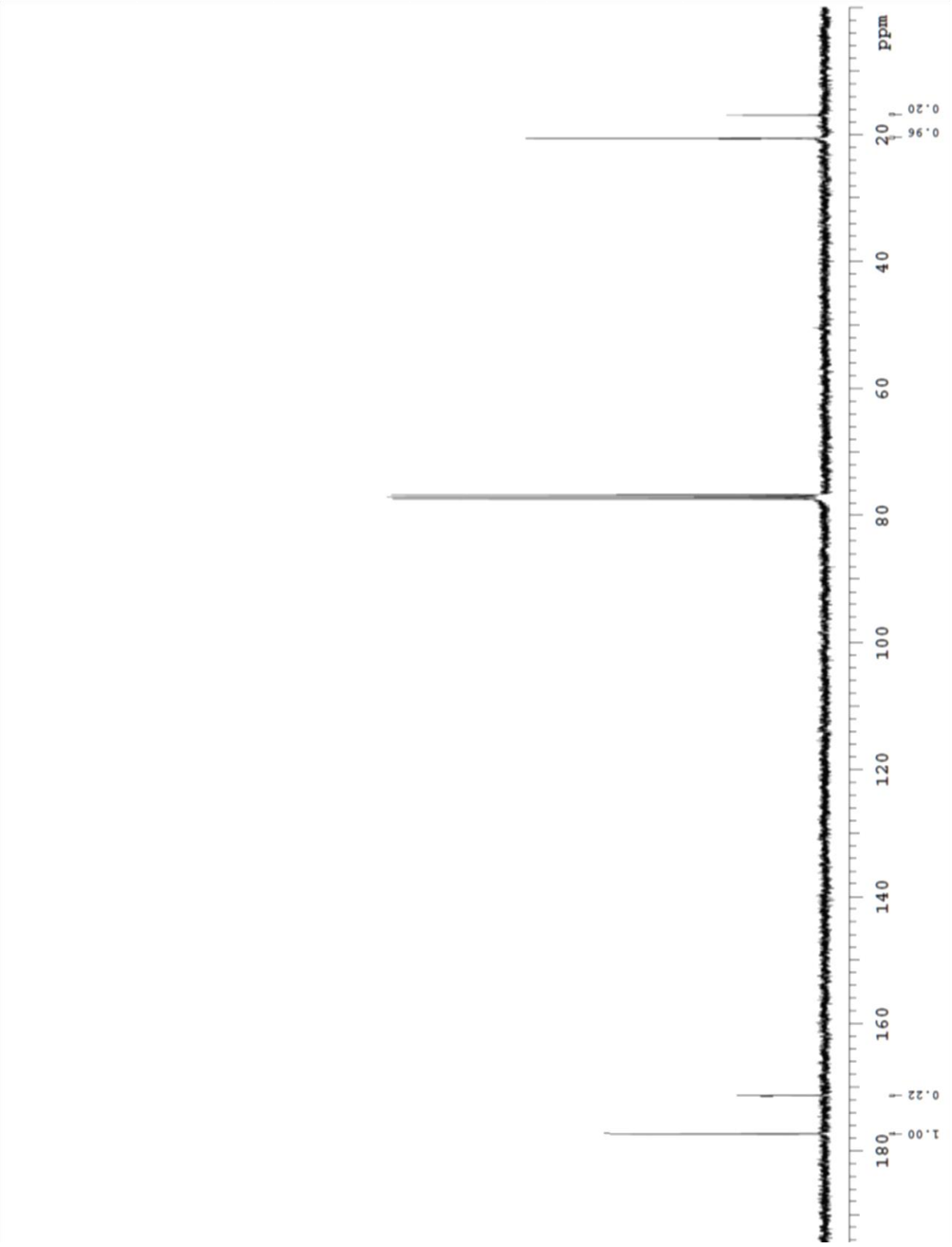


Figure S48. ^{13}C NMR data for 15 h AcOOH solution (100 MHz, $CDCl_3$)

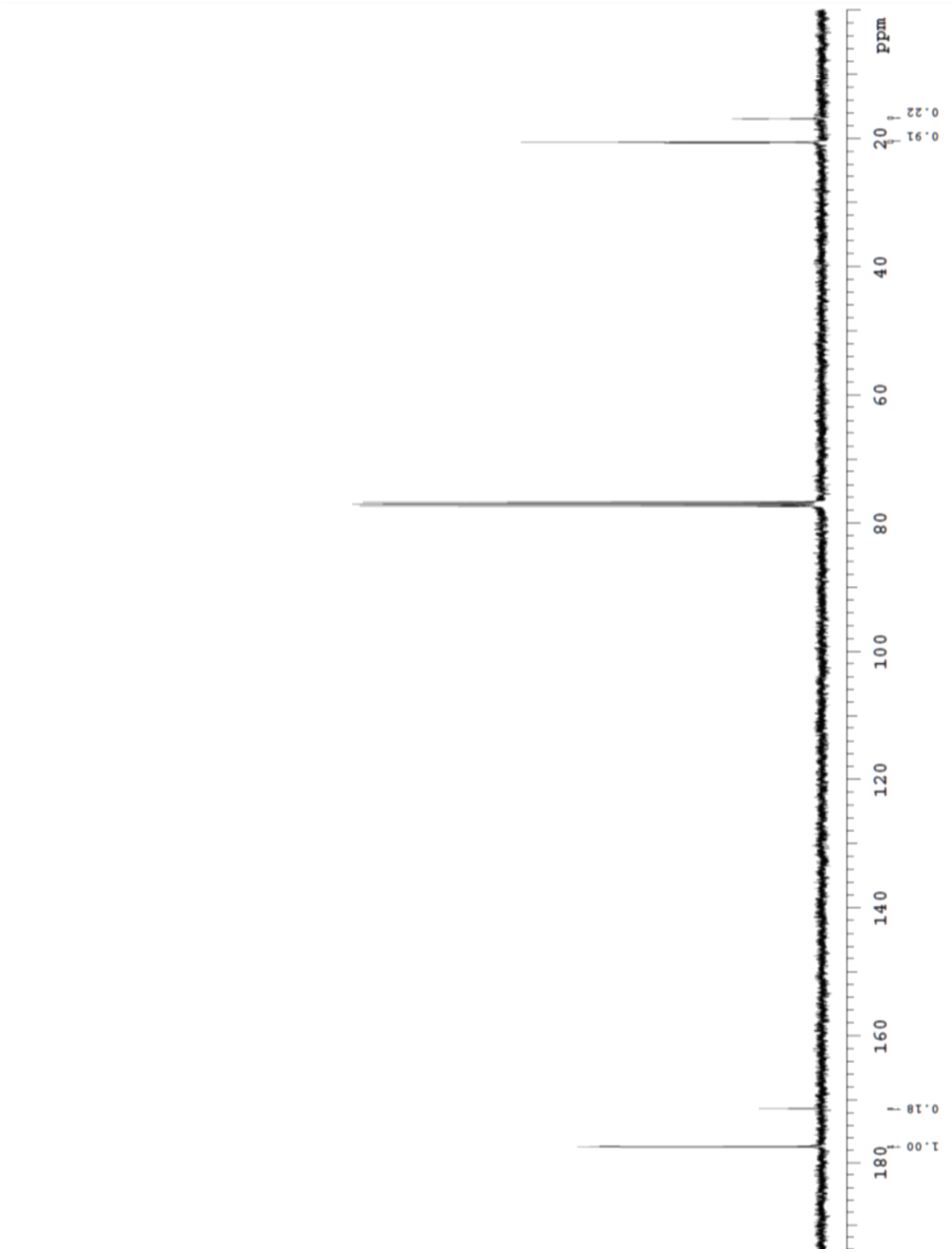


Figure S49. ^{1}H NMR data for 7 h crude reaction mixture (400 MHz, $CDCl_3$)

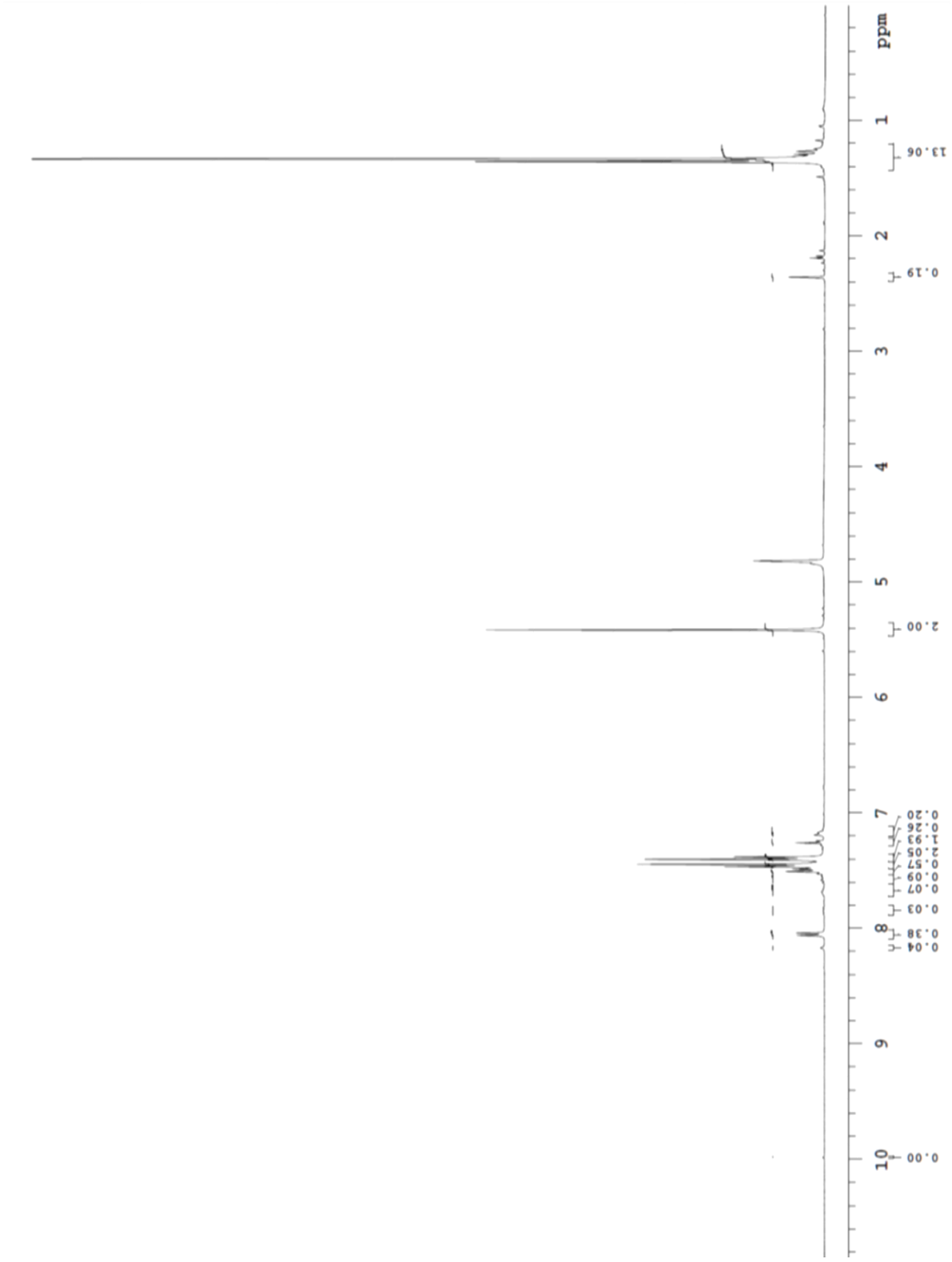


Figure S50. ^{1}H NMR data for 9.5 h crude reaction mixture (400 MHz, $CDCl_3$)

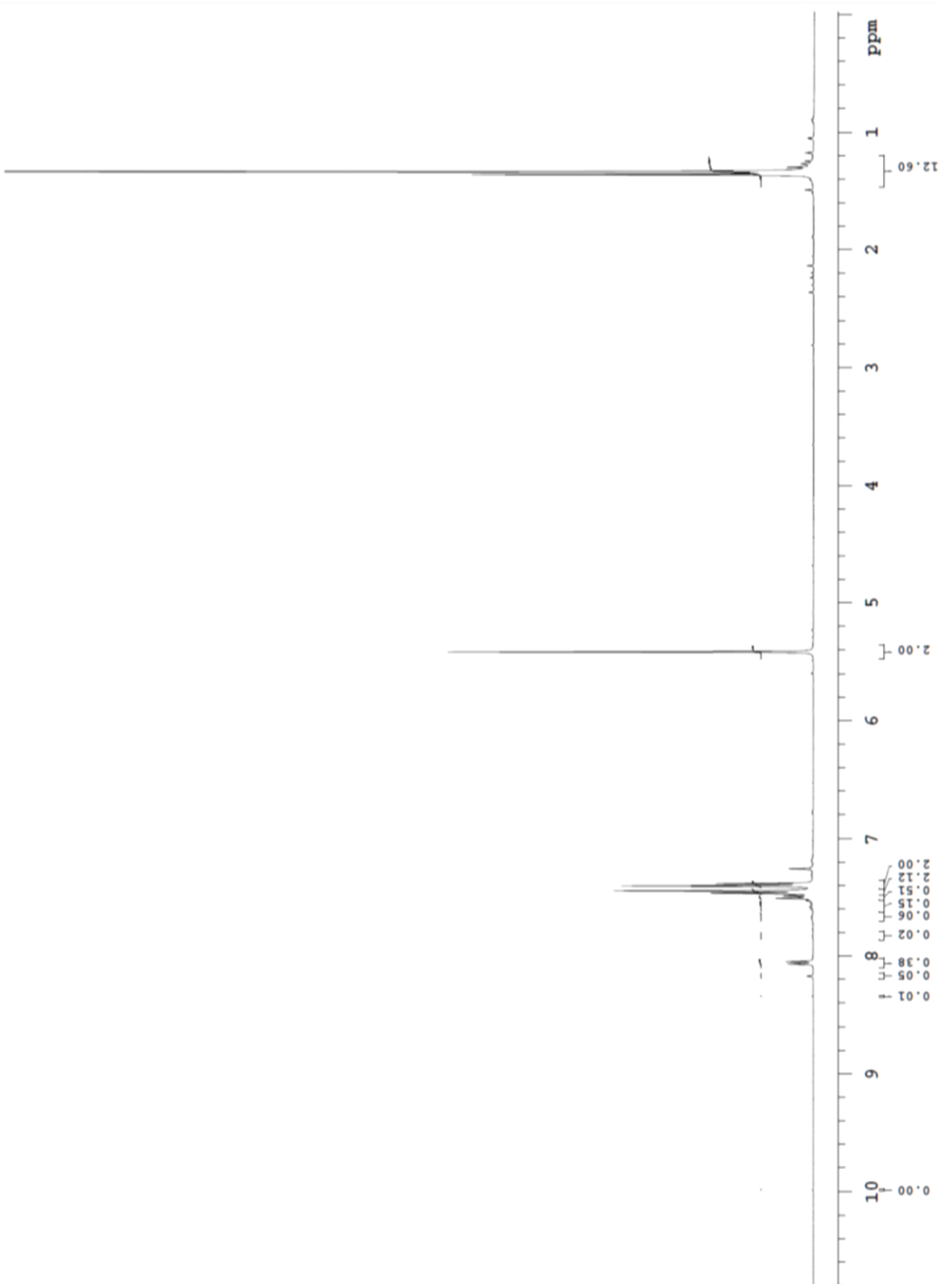


Figure S51. ^{1}H NMR data for 12 h crude reaction mixture (400 MHz, $CDCl_3$)

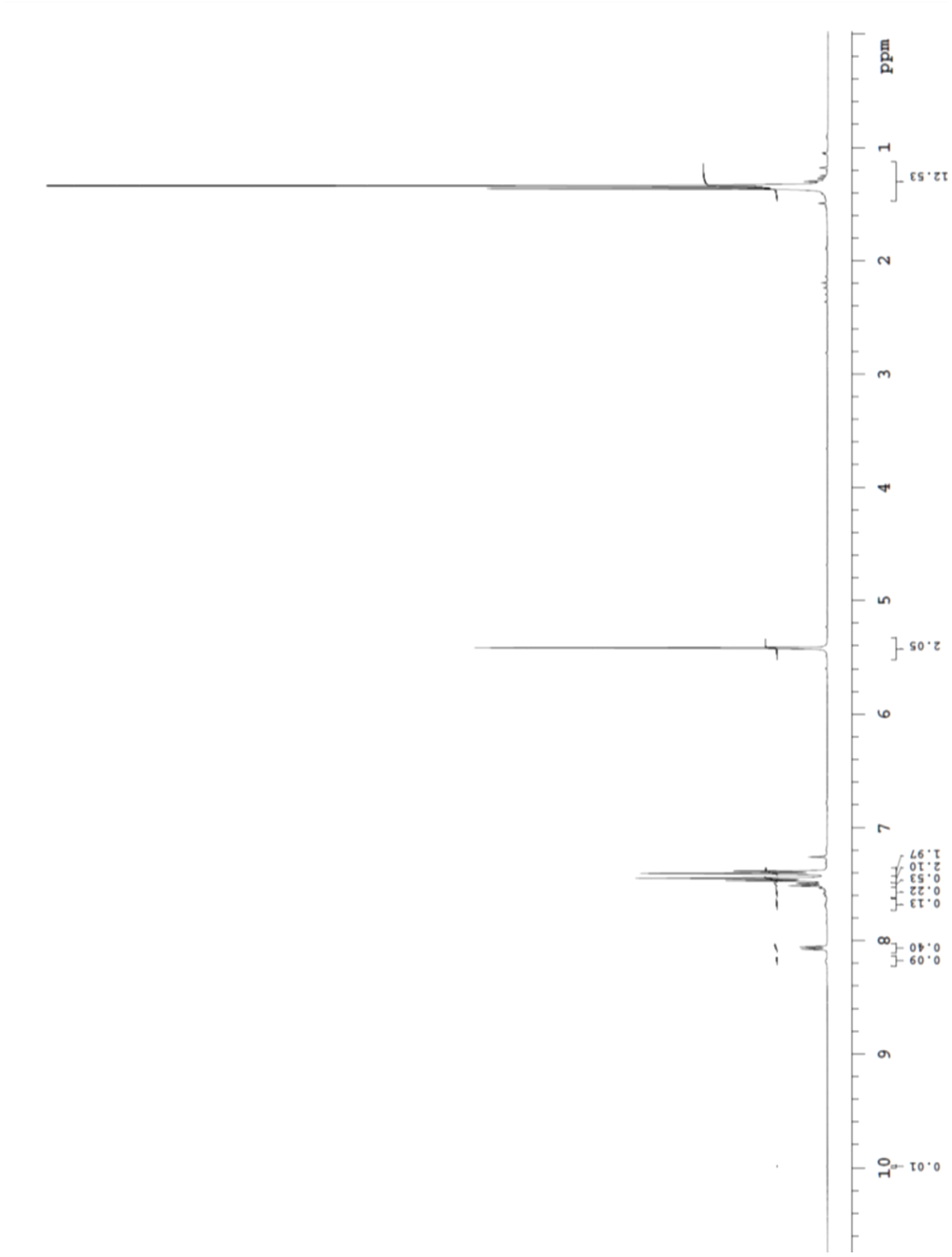
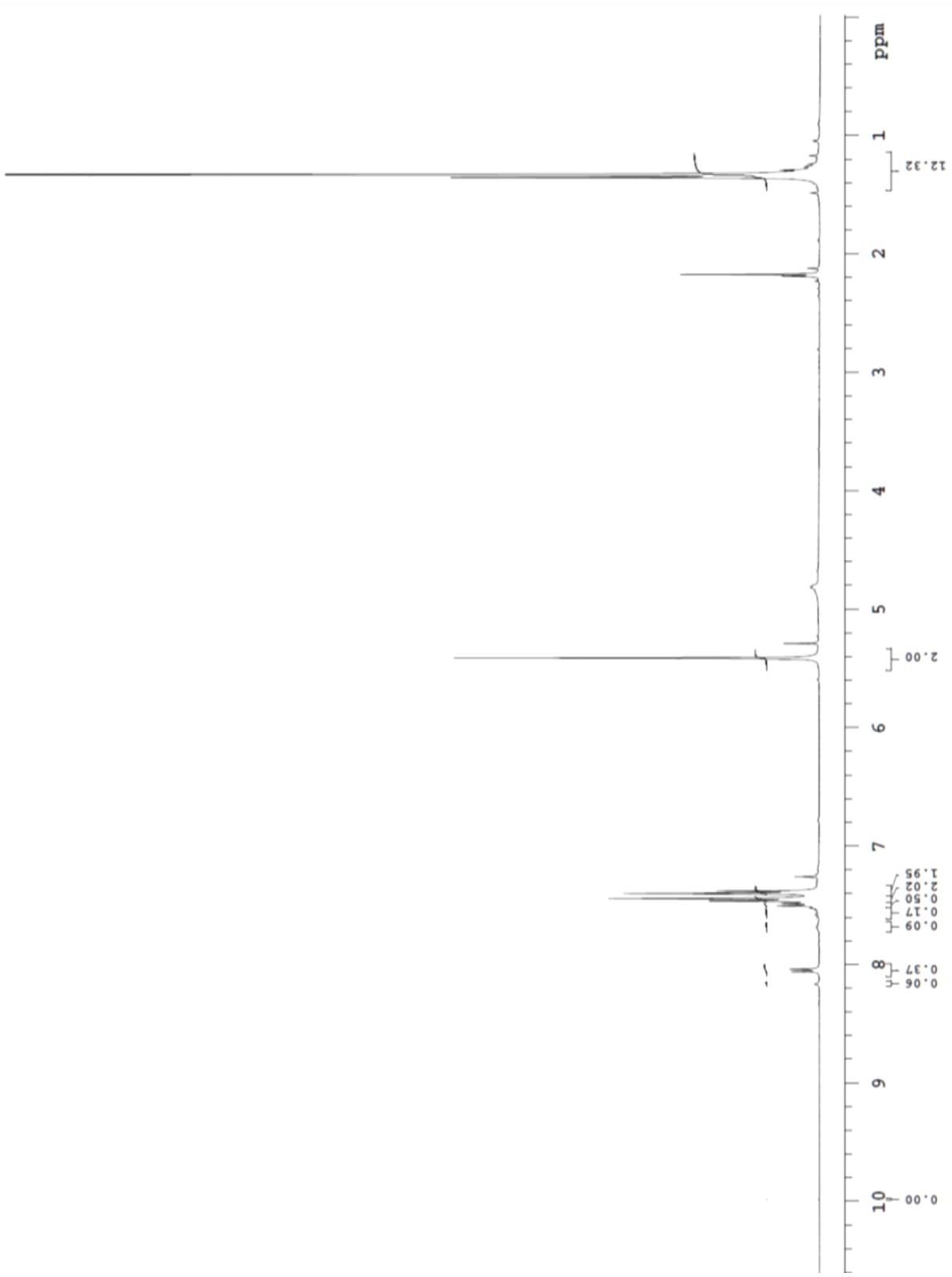


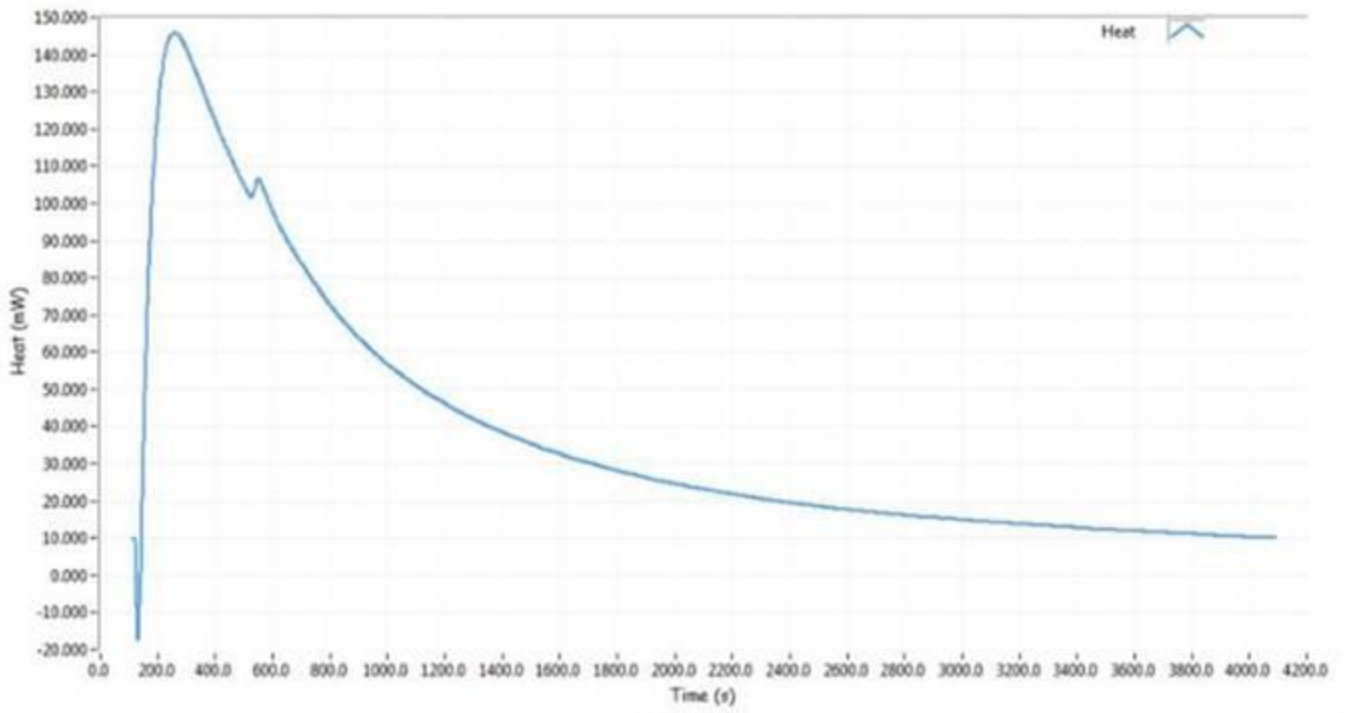
Figure S52. ^{1}H NMR data for 15 h crude reaction mixture (400 MHz, $CDCl_3$)



8. Microcalorimetry data for 1-(*tert*-butyl)-4-(nitromethyl)benzene

General procedure.

Power compensation reaction calorimetry data was collected using a Thermal Hazard Technology Micro Reaction Calorimeter operating in titration mode. A blank solution containing acetic acid was placed in the reference cell, and a solution of peracetic acid (380 µL of a 2.20 M solution in acetic acid, 0.836 mmol) was placed into a sample vial and was heated to 90 °C while stirring at 200 rpm. Oxime (150 µL of a 1.35 M solution in acetic acid, 0.203 mmol) was added at a rate of 20 µL/s, and the heat flow was measured.



Q_{rxn} = -112.804 J

Adiabatic Temperature Rise Calculation

For the purposes of preliminary screening, the effect of the heat of mixing was neglected for the adiabatic heat rise calculation. This likely leads to an artificially low heat of reaction determination. All heat generated is assumed to come from the primary reaction. Due to the large amount of solvent present, it is assumed that the heat capacity of the acetic acid solvent dominates and is representative of the heat capacity of the solution. Per standard practice, the heat capacity at 25 °C is used.

$$\Delta T_{ad} = \frac{(-\Delta H_{rxn}) \cdot [C_{LR}]}{\rho_{solvent} \cdot C'_{p(solvent)}} = \frac{-Q_{rxn}}{m_{solvent} \cdot C'_{p,solvent}}$$

Q_{rxn} = -112.80 J

$m_{solvent}$ = 0.5565 g

$$C'_p(solvent) = 123.1 \ \frac{J}{mol(solvent) \cdot K} \times \frac{1 \ mol \ (solvent)}{60.05 \ g \ (solvent)} = 2.05 \ \frac{J}{g(solvent) \cdot K}$$

$$\Delta T_{ad} = \frac{-Q_{rxn}}{m_{solvent} \cdot C'_{p,solvent}} = \frac{-(-112.80 \ J)}{0.5565 \ g \cdot 2.05 \ {}^{J}/_{g \cdot K}} \sim 99 \ K$$

9. ARC data

EXPERIMENTAL PROCEDURE

The Accelerating Rate Calorimeter (ARC) permits a small sample of a chemical to undergo thermal decomposition due to self-heating. The primary data given in this report are the temperature and pressure variations as a function of time during such a 'thermal runaway' reaction. Secondly, certain modelling functions based upon the experimental values are presented. The specified amount of sample is introduced into the sample container (or 'bomb') which is in turn mounted in the calorimeter and the temperature and pressure sensors are attached.

The calorimeter is then rapidly heated to the 'Start Temperature' after which either an Isothermal Age mode or a Heat-Wait-Search sequence is entered, to determine onset of sample self-heating. After each 'Heat' step there is a 'Wait' period intended to allow the sample-bomb system to reach thermal equilibrium. This in turn is followed by a self-heating 'Search' period. When less than the present self-heat rate threshold ('Slope Sensitivity') is observed during the Search mode, or at the end of the Isothermal Age time, a Heat step is applied to the sample and bomb. The Heat-Wait-Search sequence is repeated until the 'End Temperature' is reached or until self-heating is detected above the 'Slope Sensitivity' threshold. At this point the reaction is allowed to proceed under very closely controlled adiabatic conditions and time, temperature and pressure data are collected and stored.

Table S6. ARC data for 1-*tert*-butyl-4-nitromethylbenzene

	DataSet 1	DataSet 2
MB (Test Cell Mass (g))	12.94	12.94
Ms (Samplel Mass (g))	2.21	2.21
Cb (Test ell Specific Heat (j/gK))	0.42	0.42
Cs (Sample Specific Heat (j/gk))	2.10	2.10
Phi (Thermal Inertia)	0.0000	2.1715
EXPERIMENTAL PARAMETERS:		
	DataSet 1	DataSet 2
2 Sample Data		
2.1 Molecular Weight (g/mol):	193.24	193.24
3 Bomb Data		
3.1 Type:	1/8" neck Hastelloy C w/ bottom clip	1/8" neck Hastelloy C w/ bottom clip
3.2 Sample Volume (mL)	2.5	2.5
EXPERIMENTAL CONDITIONS:		
	DataSet 1	DataSet 2
1. Start Temperature (°C)	40.00	40.00
2. End Temperature (°C)	300.00	300.00
3. Slope Sensitivity (°C/min)	0.02	0.02
4. Heat Step Temperature (°C)	5.00	5.00
5. Wait Time (min)	10.00	10.00
6. Data Step Temperature (°C)	0.00	0.00
7. Data Step Time (min)	0.00	0.00
8. Calculation Step Temperature (°C)	0.20	0.20
9. Maximum Temperature Drop (°C)	25.00	25.00
10. Maximum Pressure Drop (bar)	20.00	20.00
11. Cool Temperature (°C)	30.00	30.00
12. Release Temperature (°C)	50.00	50.00
13. Safety Pressure (bar)	200.00	200.00
14. Driver Heater Power (%)	1.00	1.00
15. Radiant Heater Use	Yes	Yes
16. Isothermal Mode	No	No
17. Isothermal Age Time (min)	0.25	0.25
18. Isothermal Window (°C)	2.50	2.50
19. Ramp Mode	Yes	Yes
20. Ramp Rate (°C/min)	60.00	60.00
EXPERIMENTAL RESULTS		
	DataSet 2/Analysis1	

1. Observed Onset Temperature (°C)	142.3
2. Onset Temperature Rate (°C/min)	0.031
3. Temperature at Maximum Rate (°C)	244.3
4. Maximum Temperature Rate (°C/min)	702.044
5. Maximum Pressure (bar)	78
6. Maximum Pressure Rate (bar/min)	1182.42
7. Final Adiabatic Temperature (°C)	295.9
8. Adiabatic Temperature Rise (°C)	153.6

RESULTS CORRECTED FOR THERMAL INERTIA

	DataSet 2/Analysis1
1. Adiabatic Temp Rise (C)	153.6
2. Final Adiabatic Temp (C)	295.9
3. Heat of Reation (J/mol)	700.538
4. Total Enthalpy (J)	1547.01

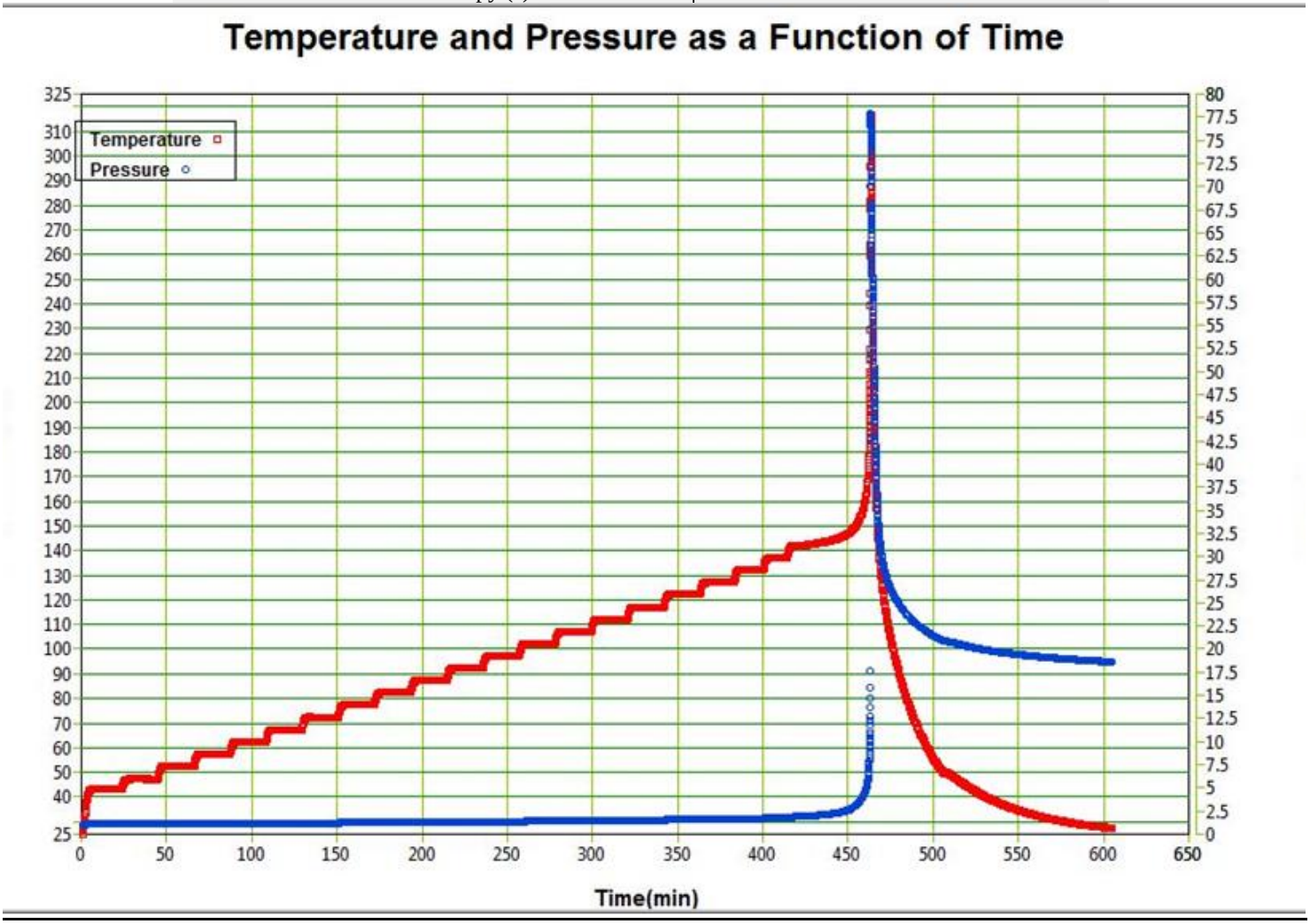


Figure S53. ARC data

Thermal stability of peracetic acid solutions is discussed in the following reference.[32]

10. References

[1] (a) Hou, Y.; Lu, S.; Liu, G. Iodine(III)-Mediated [3 + 2] Cyclization for One-Pot Synthesis of Benzo[d]isoxazole-4,7-diols in Aqueous Medium, *J. Org. Chem*. **2013**, *78*, 8386-8395. (b) Jain, N.; Kumar, A.; Chauhan, S. M. S. Metalloporphyrin and heteropoly acid catalyzed oxidation of CNOH bonds in an ionic liquid: biomimetic models of nitric oxide synthase, *Tetrahedron Lett.* **2005**, *46*, 2599–2602.

[2] (a) Wang, E.-C.; Huang, K.-S.; Chen, H.-M.; Wu, C.-C.; Lin, G.-J. An Efficient Method for the Preparation of Nitriles via the Dehydration of Aldoximes with Phthalic Anhydride, *J. Chin. Chem. Soc*. **2004**, *51*, 619–627. (b) Ramon, R. S.; Bosson, J.; Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. Au/Ag-Cocatalyzed Aldoximes to Amides Rearrangement under Solvent- and Acid-Free Conditions, *J. Org. Chem*. **2010**, *75*, 1197-1202.

[3] Di Nunno, L.; Vitale, P.; Scilimati, A. Effect of the aryl group substituent in the dimerization of 3-arylisoxazoles to syn 2,6-diaryl-3,7-diazatricyclo[4.2.0.02,5]octan-4,8-diones induced by LDA, *Tetrahedron*, **2008**, *64*, 11198-11204.

[4] Moriya, M.; Yasuhara, A.; Sakagami, K.; Ohta, H.; Abe, K.; Yamamoto, S.; Araki, Y.; Urabe, H.; Sun, X.-M. Glycine Transporter Inhibitor, Patent, WO 2012036278, March 22, 2012.

[5] (a) Jeong, H. J.; Park, Y.-D.; Park, H.-Y.; Jeong, I. Y.; Jeong, T.-S.; Lee, W. S. Potent inhibitors of lipoprotein-associated phospholipase A(2): benzaldehyde O-heterocycle-4-carbonyloxime, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5576-5579. (b) Xiea, F.; Ni, T.; Zhao, J.; Pang, L.; Lia, R.; Caia, Z.; Dinga, Z.; Wanga, T.; Yua, S.; Jina, Y.; Zhanga, D.; Jiang Y. Design, synthesis, and in vitro evaluation of novel antifungal triazoles, *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2171-2173. (c) Pang, G. X.; Niu, C.; Mamat, N.; Aisa, H. A. Synthesis and in vitro biological evaluation of novel coumarin derivatives containing isoxazole moieties on melanin synthesis in B16 cells and inhibition on bacteria, *Bioorg. Med. Chem. Lett.*, **2017**, *27*, 2674-2677.

[6] Yoshimura, A.; Middleton, K. R.; Todora, A. D.; Kastern, B. J.; Koski, S. R.; Maskaev, A. V.; Zhdankin, V. V. Hypervalent Iodine Catalyzed Generation of Nitrile Oxides from Oximes and their Cycloaddition with Alkenes or Alkynes, *Org. Lett*. **2013**, *15*, 4010-4013.

[7] Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. Generation of Nitrile Oxides from Oximes Using t-BuOI and Their Cycloaddition, *Org. Lett*. **2011**, *13*, 2966-2969.

[8] Ferrer-Casal, M.; Barboza, A. P.; Szajnman, S. H.; Rodriguez, J. B. 1,3-Dipolar Cycloadditions of the Versatile Intermediate Tetraethyl Vinylidenebisphosphonate, *Synthesis*, **2013**, *45*, 2397-2404.

[9] (a) Ke, J.; Tang, Y.; Yi, H.; Li, Y.; Cheng, Y.; Liu, C.; Lei, A. Copper-Catalyzed Radical/Radical C(sp 3)-H/P-H Cross-Coupling: α-Phosphorylation of Aryl Ketone O-Acetyloximes, *Angew. Chem. Int. Ed*. **2015**, *54*, 6604 - 6607. (b) Yu, J.; Lu, M. Copper(II)-promoted direct conversion of methylarenes into aromatic oximes, *Org. Biomol. Chem*., **2015**, *13*, 7397–7401.

[10] (a) Liu, K.-C.; Shelton, B. R. Howe, R. K. A particularly convenient preparation of benzohydroximinoyl chlorides (nitrile oxide precursors), *J. Org. Chem*. **1980**, *45*, 3916–3918. (b) McIntosh, M. L.; Naffziger, M. R.; Ashburn, B. O.; Zakharov, L. N.; Carter, R. G. Highly regioselective nitrile oxide dipolar cycloadditions with ortho-nitrophenyl alkynes, *Org. Biomol. Chem*. **2012**, *10*, 9204-9213.

[11] (a) Buckley, G. D. 289. Aliphatic nitro-compounds. Part X. Action of grignard reagents on the α-nitro-olefins, *J. Chem. Soc*. **1947**, 1494-1497. (b) Vogel, A. I.; Creswell, W. T.; Jeffery, G. H.; Leiceste, J. 98. Physical properties and chemical constitution. Part XXIV. Aliphatic aldoximes, ketoximes, and ketoxime O-alkyl ethers, NN-dialkylhydrazines, aliphatic ketazines, mono- and di-alkylaminopropionitriles, alkoxypropionitriles, dialkyl azodiformates, and dialkyl carbonates. Bond parachors, bond refractions, and bondrefraction coefficients, *J. Chem. Soc*. **1952**, 514. (c) Boss, C.; Corminboeuf, O.; Grisostomi, C.; Meyer, S.; Jones, A. F.; Prade, L.; Binkert, C.; Fischli, W.; Weller, T.; Bur, D. Achiral, cheap, and potent inhibitors of Plasmepsins I, II, and IV. C*hemMedChem.* **2006**, *1*, 1341 – 1345.

[12] (a) Wang, Y.; Mosher, H. S. 19F NMR non-equivalence of diastereomeric amides of 2,2,2-trifluoro-1-phenylethylamine, *Tetrahedron Lett*. **1991**, *32*, 987-990. (b) Shepard, R. A.; Wentworth, S. E. Polyfluorodiazo compounds. II. 1-Phenyl-2,2,2-trifluorodiazoethane, *J. Org. Chem*. **1967**, *32*, 3197.
[13] Tambara, K.; Pantos, G. D. Conversion of aldoximes into nitriles and amides under mild conditions, *Org. Biomol. Chem*. **2013**, *11*, 2466-2472.
[14] Johnston, J. N.; Davis, T. A. Catalytic, enantioselective synthesis of stilbene *cis*-diamines: A concise preparation of (−)-Nutlin-3, a potent p53/MDM2 inhibitor, *Chem. Sci*. **2011**, *2*, 1076-1077.
[15] Manna, M. S. and Mukherjee S. Organocatalytic Enantioselective Formal C(sp2)–H Alkylation, *J. Am. Chem. Soc*., **2015**, *137*, 130–133.
[16] Barr, L.; Easton, C. J.; Leea, K.; Lincoln S. F. Aminocyclodextrins to facilitate the deprotonation of 4-tert-butyl-alpha-nitrotoluene, *Org. Biomol. Chem*. **2005**, *3*. 2990-2993.
[17] (a) Hauser, M. F.; Baghdanov, V. M. Convenient preparation of ring-methoxylated phenylnitromethanes, *J. Org. Chem*. **1988**, *53*, 2872–2873. (b) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. Palladium-Catalyzed Nitromethylation of Aryl Halides: An Orthogonal Formylation Equivalent, *Org. Lett*. **2012**, *14*, 4086.
[18] Ando, K.; Shimazu, Y.; Seki N.; Yamataka, H. Kinetic Study of Proton-Transfer Reactions of Phenylnitromethanes. Implication for the Origin of Nitroalkane Anomaly, *J. Org. Chem*., **2011**, *76*, 3937.
[19] Kolczewski, S.; Pinard, E.; Henri, S. Aroylamin - and Heteoroaroylamino-Substituted Piperidines as GLYT-1 Inhibitors, WO2010086251, Aug. 5, 2010.
[20] Marce, P.; Lynch, J.; Blackerb A. J.; Williams J. M. J. Conversion of nitroalkanes into carboxylic acids via iodide catalysis in water, *Chem. Commun*., **2016**, *52*, 1013-1016.
[21] Suzuki, H.; Murashima, T.; Kozai, I.; Mori, T. Ozone-mediated nitration of alkylbenzenes and related compounds with nitrogen dioxide, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1591-1597.
[22] (a) Base, D. S.; Vanajatha, G. A Versatile Method for the Conversion of Oximes to Nitroalkanes, *Synth. Commun.* **1998**, *28*, 4531. (b) Baruah, A.; Kalita, B.; Barua, N. C. A Simple and Highly Efficient Procedure for the Preparation of Aliphatic Nitro Compounds Directly from Alcohols, *Synlett* **2000**, 1064.
[23] Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D.; Kalinowski, H.-O. Structure, Synthesis, and Properties of Some Persubstituted 1,2-Dintroethanes. In Quest of Nitrocyclopropyl-Anion Derivatives, *Helv. Chim. Acta*. **1982**, *65*, 137.
[24] (a) Maegawa, T.; Takahashi, T.; Yoshimura, M.; H. Suzuka, H.; Monguchi, Y.; Sajiki H. Development of Molecular Sieves-Supported Palladium Catalyst and Chemoselective Hydrogenation of Unsaturated Bonds in the Presence of Nitro Groups, *Adv. Synth. Catal*., **2009**, *351*, 2091–2095. (b) Takahashi, T.; Yoshimura, M.; Suzuka, H.; Maegawa, T.; Sawama, Y.; Monguchi, Y.; Sajiki, H. Chemoselective hydrogenation using molecular sieves-supported Pd catalysts: Pd/MS3A and Pd/MS5A, *Tetrahedron*, **2012**, *68*, 8293-8299.
[25] (a) Iffland, D. C.; Yen T.-F. Preparation of Nitro Compounds from Oximes. III. The Synthesis of Nitroalkanes, *J. Am. Chem. Soc*. **1954**, *76*, 4083–4085. (b) Sakaguchi, S.; Nishiwaki, Y.; Kitamura, T.; Ishii, Y. Efficient Catalytic Alkane Nitration with NO2 under Air Assisted by N-Hydroxyphthalimide, *Angew. Chem., Int. Ed*. **2001**, *40*, 222-224.
[26] Stiefel, F. J. Synthesis of 2-phenyl-1,3-propanediol. U.S. Patent 5,072,056 Dec. 10, 1991
[27] Emmons, W. D.; Pagano, A. S. Peroxytrifluoroacetic Acid. VI. The Oxidation of Oximes to Nitroparaffins, *J. Am. Chem. Soc.* **1957**, *77*, 4557.
[28] Ballini, R.; Marcantoni, E.; Petrini, M.; Synthesis of functionalized nitroalkanes by oxidation of oximes with urea-hydrogen peroxide complex and trifluoroacetic anhydride, *Tetrahedron Lett*. **1992**, *33*, 4835.
[29] Cardona, F.; Soldaini, G.; Goti, A. Methyltrioxorhenium-Catalyzed Oxidation of Aromatic Aldoximes, *Synlett*, **2004**, *9*, 1553.
[30] Ballistreri, F. P.; Barbuzzi, E.; Tomaselli, G. A.; Toscano, R. M. Useful Oxidation Procedure of Oximes to Nitro Compounds with Benz-Mo in Acetonitrile, *Synlett* **1996**, 1093.
[31] Walvoord, R. R.; Kozlowski, M. C. Cinchonidinium acetate as a convenient catalyst for the asymmetric synthesis of *cis*-stilbenediamines, *Tetrahedron Lett.* **2015**, *56*, 3070–3074.

[32] Chen, W.-C.; Lin, J.-R.; Liao, M.-S.; Wang, Y.-W.; Shu, C.-M. Green approach to evaluating the thermal hazard reaction of peracetic acid through various kinetic methods, *J. Thermal. Anal. Calorim*. **2017**, *127*, 1019-1026.