

Supplementary Material

Generation and Reactions of Pyridyllithium Compounds via Br/Li Exchange Reaction Using Flow Microreactor Systems

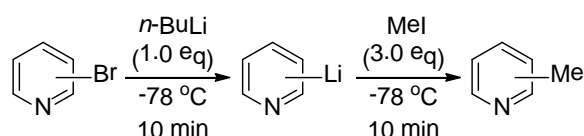
Aiichiro Nagaki, Daisuke Yamada, Shigeyuki Yamada, Masatomo Doi, Daisuke Ichinari, Yutaka Tomida, Naofumi Takabayashi, and Jun-ichi Yoshida

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

General

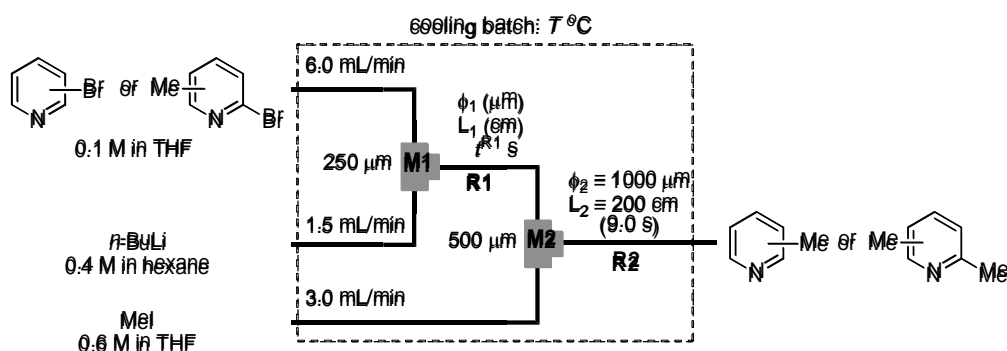
GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBPI; 0.25 mm x 25 m). ^1H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or CDCl_3 as a standard in CDCl_3 unless otherwise noted. EI mass spectra were recorded on a JEOL JMS-SX102A spectrometer. ESI and APCI mass spectra were recorded on a JEOL JMS-T100CS spectrometer. THF was purchased from Kanto Chemical Co., Inc. as a dry solvent and were used without further purification. Hexane was purchased from Wako, was distilled before use, and was stored over molecular sieves 4A. 2-Bromopyridine, 3-bromopyridine, 2-methylpyridine, 3-methylpyridine, 2-bromo-3-methylpyridine, 2-bromo-5-methylpyridine, 2-bromo-6-methylpyridine, 2,3-dibromopyridine, 2,5-dibromopyridine, 2,6-dibromopyridine, iodomethane, chlorotrimethylsilane, benzaldehyde, cyanobenzene and acetophenone were commercially available. Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 μm and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 250, 500 and 1000 μm were purchased from GL Sciences. The micromixers and the microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 O.U.W.). The flow microreactor system was dipped in a cooling bath to control the temperature. Solutions were introduced to the flow microreactor system using syringe pumps, Harvard Model 11, equipped with gastight syringes purchased from SGE.

The Br/Li Exchange Reaction of Bromopyridines Followed by Reaction with Iodomethane in a Macro Batch System



A solution of 2-bromopyridine or 3-bromopyridine (0.10 M, 3.0 mL) in THF was stirred at $-78\text{ }^\circ\text{C}$. A solution of $n\text{-BuLi}$ (0.40 M, 0.75 mL) in hexane was added dropwise to this solution at regular pace for 1.0 min. After stirring for 10 min, iodomethane (0.60 M, 1.5 mL) was added dropwise to this mixture at regular pace for 1.0 min. After stirring at $-78\text{ }^\circ\text{C}$ for 10 min, a cooling bath was removed. When the reaction mixture reached room temperature and was quenched with H_2O , the yields of 2-methylpyridine (42%) or 3-methylpyridine (13%), and the conversion of 2-bromopyridine (85%) or 3-bromopyridine (100%) were determined by GC.

Typical Procedure for The Br/Li Exchange Reaction of Bromopyridines Followed by Reaction with Iodomethane in a Flow Microreactor System



A flow microreactor system consisting of two T-shaped micromixers (**M1** ($\phi = 250 \mu\text{m}$) and **M2** ($\phi = 500 \mu\text{m}$)), two microtube reactors (**R1** and **R2** ($\phi_2 = 1000 \mu\text{m}$, $L_2 = 200 \text{ cm}$)), and three tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. A solution of bromopyridines (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 1.50 mL min^{-1}) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of iodomethane (0.40 M in THF) (flow rate: 3.00 mL min^{-1}) in **M2**. The resulting solution was passed through **R2**. After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O . The reaction mixture was analyzed by gas chromatography. The results obtained by changing the residence time in **R1** are summarized in Table S-1. In the case of 2-bromopyridine and 3-bromopyridine, $t^{\text{R1}} = 0.055 \text{ s}$ was used for reactions with chlorotrimethylsilane and benzaldehyde. In the case of 2-bromo-3-methylpyridine, 2-bromo-5-methylpyridine, and 2-bromo-6-methylpyridine, $t^{\text{R1}} = 0.78 \text{ s}$ was used for the reaction with benzaldehyde.

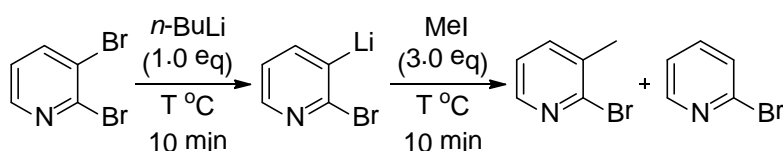
Table S-1. The Br/Li exchange reaction of bromopyridines with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

bromopyridines	L_1 (cm)	ϕ_1 (μm)	t^{R1} (s)	T ($^{\circ}\text{C}$)	conversion (%)	yield (%)
2-bromopyridine	3.50	500	0.055	-28	73	72
	3.50	1000	0.22	-28	67	67
	12.5		0.79	-28	93	71
	50.0		3.1	-28	92	80
	200		13	-28	96	72
2-bromopyridine	3.50	500	0.055	0	95	57
3-bromopyridine	3.50	500	0.055	-28	88	68
	3.50	1000	0.22	-28	93	59
	12.5		0.79	-28	94	49
	50.0		3.1	-28	100	42
	200		13	-28	100	36
3-bromopyridine	3.50	500	0.055	0	59	10
2-bromo-3-methylpyridine	3.50	500	0.055	-28	78	76
	12.5	1000	0.79	-28	78	76
2-bromo-5-methylpyridine	3.50	500	0.055	-28	52	47
	12.5	1000	0.79	-28	90	90
2-bromo-6-methylpyridine	3.50	500	0.055	-28	56	53
	12.5	1000	0.79	-28	94	92

2-Methylpyridine, 2-trimethylsilylpyridine, 3-Methylpyridine, 3-trimethylsilylpyridine, 2,3-lutidine, 2,5-lutidine, and 2,6-lutidine were in accordance with the spectral data of the commercially available compounds.

Phenyl-pyridin-2-yl-methanol and phenyl-pyridin-3-yl-methanol were identical to those reported in the literature.¹

The Br/Li Exchange Reaction of 2,3-Dibromopyridine Followed by Reaction with Iodomethane in a Macro Batch System

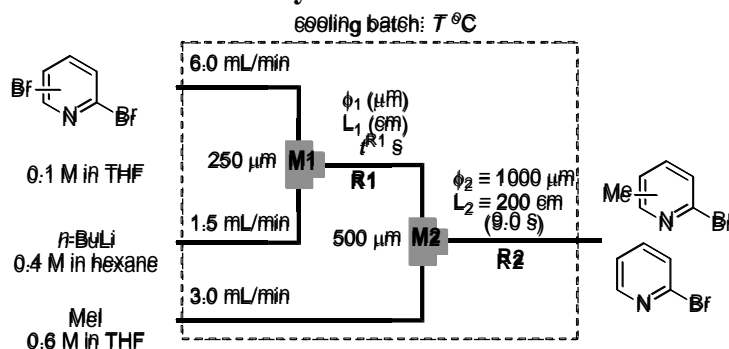


A solution of 2,3-dibromopyridine (0.10 M, 3.0 mL) in THF was stirred at T °C. A solution of *n*-BuLi (0.40 M, 0.75 mL) in hexane was added dropwise to this solution at regular pace for 1.0 min. After stirring for 10 min, iodomethane (0.60 M, 1.5 mL) was added dropwise to this mixture at regular pace for 1.0 min. After stirring at T °C for 10 min, a cooling bath was removed. When the reaction mixture reached room temperature and was quenched with H₂O, the yields of 2-bromo-3-methylpyridine and 2-bromopyridine, and the conversion of 2,3-dibromopyridine was analyzed by GC. The results are summarized in Table S-2.

Table S-2. The Br/Li exchange reaction of 2,3-dibromopyridine followed by reaction with iodomethane in a macro batch system.

T (°C)	2,3-dibromopyridine conversion (%)	2-bromo-3-methylpyridine yield (%)	2-bromopyridine yield (%)
-78	0	48	24
-48	0	19	26
-28	0	0	34
0	0	0	21

Typical Procedure for The Br/Li Exchange Reaction of Dibromopyridines Followed by Reaction with Iodomethane in a Flow Microreactor System



A flow microreactor system consisting of two T-shaped micromixers (**M1** ($\phi = 250 \mu\text{m}$) and **M2** ($\phi = 500 \mu\text{m}$)), two microtube reactors (**R1** and **R2** ($\phi_2 = 1000 \mu\text{m}$, $L_2 = 200 \text{ cm}$)), and three tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. A solution of dibromopyridines (0.100 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 1.50 mL min^{-1}) were introduced to **M1** by syringe pumps. The resulting solution was passed through **R1** and was mixed with a solution of iodomethane (0.40 M in THF) (flow rate: 3.00 mL min^{-1}) in **M2**. The resulting solution was passed through **R2**. After a steady state was reached, the product solution was collected for 30 s while being quenched with H₂O. The reaction mixture was analyzed by gas chromatography. The results are summarized in Table S-3, S-4 and S-5.

Table S-3. The Br/Li exchange reaction of 2,3-dibromopyridine with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

L_1 (cm)	ϕ_1 (μm)	t^{R1} (s)	T (°C)	conversion (%)		yield (%)	
				2,3-dibromopyridine	2-bromo-3-methylpyridine	2-bromopyridine	2-bromopyridine
3.50	250	0.014	25	94	64	3	
3.50	500	0.055		100	60	1	
3.50	1000	0.22		100	57	4	
12.5		0.79		100	31	7	
50.0		3.1		100	10	6	
200		13		100	0	6	
3.50	250	0.014	0	100	84	1	
3.50	500	0.055		100	87	1	

3.50	1000	0.22		100	83	4
12.5		0.79		100	74	5
50.0		3.1		100	70	5
200		13		100	49	7
3.50	250	0.014	-28	100	92	5
3.50	500	0.055		100	88	5
3.50	1000	0.22		100	86	4
12.5		0.79		100	86	5
50.0		3.1		100	84	4
200		13		100	69	3
3.50	250	0.014	-48	100	88	5
3.50	500	0.055		100	88	4
3.50	1000	0.22		100	90	4
12.5		0.79		100	85	4
50.0		3.1		100	91	3
200		13		100	80	4
3.50	250	0.014	-78	100	91	5
3.50	500	0.055		100	93	4
3.50	1000	0.22		100	93	4
12.5		0.79		100	93	5
50.0		3.1		97	86	5
200		13		100	89	3

Table S-4. The Br/Li exchange reaction of 2,5-dibromopyridine with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

L ₁ (cm)	φ ₁ (μm)	t ^{R1} (s)	T (°C)	conversion (%)		yield (%)
				2,5-dibromopyridine	2-bromo-5-methylpyridine	2-bromopyridine
3.50	250	0.014	25	100	70	8
3.50	500	0.055		100	75	6
3.50	1000	0.22		100	72	8
12.5		0.79		100	77	7
50.0		3.1		100	72	9
200		13		100	70	7
3.50	250	0.014	0	100	80	6
3.50	500	0.055		100	84	5
3.50	1000	0.22		100	73	8
12.5		0.79		100	78	8
50.0		3.1		100	78	8
200		13		100	78	5
3.50	250	0.014	-28	100	81	7
3.50	500	0.055		100	88	5
3.50	1000	0.22		100	87	4
12.5		0.79		100	79	8
50.0		3.1		100	69	13
200		13		100	74	13
3.50	250	0.014	-48	100	83	9
3.50	500	0.055		100	86	6
3.50	1000	0.22		100	90	6
12.5		0.79		100	90	5
50.0		3.1		100	87	5
200		13		100	83	5
3.50	250	0.014	-78	100	75	9
3.50	500	0.055		100	73	14
3.50	1000	0.22		100	73	13
12.5		0.79		100	66	15

50.0	3.1	100	77	9
200	13	100	79	7

Table S-5. The Br/Li exchange reaction of 2,6-dibromopyridine with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

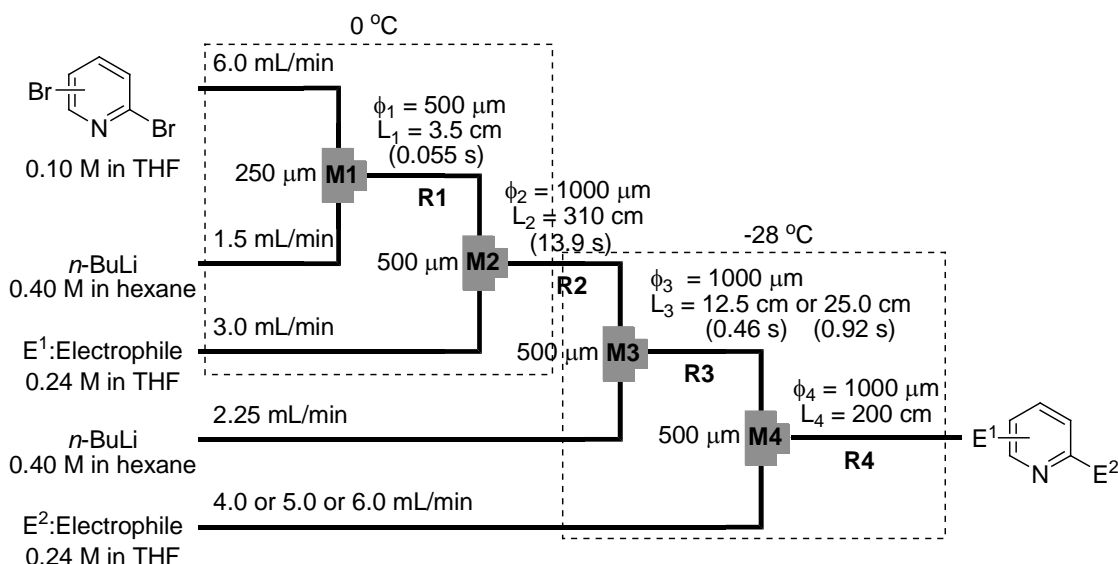
L ₁ (cm)	φ ₁ (μm)	t ^{R1} (s)	T (°C)	conversion (%)		yield (%)
				2,6-dibromopyridine	2-bromo-6-methylpyridine	2-bromopyridine
3.50	250	0.014	25	100	92	3
3.50	500	0.055		100	94	3
3.50	1000	0.22		100	89	4
12.5		0.79		100	88	3
50.0		3.1		94	69	6
200		13		100	69	3
3.50	250	0.014	0	100	82	6
3.50	500	0.055		100	90	4
3.50	1000	0.22		98	90	4
12.5		0.79		99	91	4
50.0		3.1		99	90	4
200		13		95	80	6
3.50	250	0.014	-28	100	85	2
3.50	500	0.055		100	93	2
3.50	1000	0.22		100	92	2
12.5		0.79		100	89	2
50.0		3.1		100	89	3
200		13		100	82	5
3.50	250	0.014	-48	89	81	3
3.50	500	0.055		95	85	3
3.50	1000	0.22		99	92	4
12.5		0.79		100	91	4
50.0		3.1		95	86	5
200		13		100	87	5
3.50	250	0.014	-78	85	78	4
3.50	500	0.055		93	89	3
3.50	1000	0.22		92	86	3
12.5		0.79		95	89	4
50.0		3.1		97	91	3
200		13		99	90	3

In all cases of 2,3-dibromopyridine, 2,5-dibromopyridine, and 2,6-dibromopyridine, $T = 0$ °C was selected as a bath temperature under the $t^{\text{R1}} = 0.055$ s.

The spectral data of 2-bromo-3-trimethylsilylpyridine, 2-bromo-3-(α -hydroxybenzyl)pyridine, 2-bromo-5-(α -hydroxybenzyl)pyridine, 2-bromo-6-trimethylsilylpyridine, 2-bromo-6-(α -hydroxybenzyl)pyridine were identical to those reported in the literature.¹

The analytical data for 2-bromo-5-trimethylsilylpyridine were identical to those reported in the literature.²

Typical Procedure for Sequential Introduction of Two Electrophiles into Dibromopyridines



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3** and **M4**), four microtube reactors (**R1**, **R2**, **R3** and **R4**) and six tube pre-cooling units (**P1** (inner diameter $\phi = 1000 \mu\text{m}$, length $L = 100 \text{ cm}$), **P2** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$) and **P3** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$), **P4** ($\phi = 1000 \mu\text{m}$, $L = 50 \text{ cm}$), **P5** ($\phi = 1000 \mu\text{m}$, $L = 100 \text{ cm}$)) was used. The flow microreactor system consisting of **M1**, **M2**, **R1**, **R2**, **P1**, **P2** and **P3** was dipped in a cooling bath at $0 \text{ }^\circ\text{C}$. The flow microreactor system consisting of **M3**, **M4**, **R2**, **R3**, **R4**, **P4** and **P5** was dipped in a bath cooled at $-28 \text{ }^\circ\text{C}$. A solution of dibromopyridines (0.10 M in THF) (flow rate: 6.00 mL min^{-1}) and a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 1.5 mL min^{-1}) were introduced to **M1** ($\phi = 250 \mu\text{m}$). The resulting solution was passed through **R1** ($\phi_1 = 500 \mu\text{m}$, $L_1 = 3.5 \text{ cm}$) and was mixed with a solution of a first electrophile (E^1 : Electrophile-1) (0.24 M in THF) (flow rate: 3.0 mL min^{-1}) in **M2** ($\phi = 500 \mu\text{m}$). The resulting solution was passed through **R2** ($\phi_2 = 1000 \mu\text{m}$, $L_2 = 310 \text{ cm}$ (200 cm at $0 \text{ }^\circ\text{C}$, 10 cm at ambient temperature, and 100 cm at $-28 \text{ }^\circ\text{C}$)), and was introduced to **M3** ($\phi = 500 \mu\text{m}$) where the solution was mixed with a solution of *n*-BuLi (0.40 M in *n*-hexane) (flow rate: 2.25 mL min^{-1}). The resulting solution was passed through **R3** ($\phi_3 = 1000 \mu\text{m}$, $L_3 = 12.5$ or 25 cm) and was introduced to **M4** ($\phi = 500 \mu\text{m}$) where the solution was mixed with a solution of a second electrophile (E^2 : Electrophile-2) (0.24 M in THF) (flow rate: 4.0 or 5.0 or 6.0 mL min^{-1}). The resulting solution was passed through **R4** ($\phi_4 = 1000 \mu\text{m}$, $L_4 = 200 \text{ cm}$). After a steady state was reached, the product solution was collected for 30 s while being quenched with H_2O . The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was concentrated, and the resulting crude product was purified by flash chromatography on silica gel.

2-(α -Hydroxybenzyl)-3-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi = 1000 \mu\text{m}$, $L = 12.5 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 2-(α -hydroxybenzyl)-3-methylpyridine (40.4 mg, 68% yield, 88% purity (determined by GC)). 3-(α -Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC). $^1\text{H NMR}$ for title compound (400 MHz, CDCl_3) δ 2.07 (s, 3H), 5.73 (s, 1H), 5.92-6.12 (s, 1H), 7.14-7.46 (m, 8H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 17.8, 72.5, 122.6, 127.7, 127.8, 128.4, 130.4, 138.5, 142.3, 144.9, 157.9 ppm; HRMS (CI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1073. When the reactions in **R3** and **R4** were carried out at $0 \text{ }^\circ\text{C}$, the yield was lower (23.0 mg, 38%).

2-Benzoyl-3-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzonitrile (Electrophile-2): 5.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 27.9 mg of 2-benzoyl-3-methylpyridine (47% yield, 97% purity (GC)). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 2.42 (s, 3H), 7.33 (dd, $J = 8.0, 4.8 \text{ Hz}$, 1H), 7.42-7.50 (m, 2H), 7.54-7.62 (m, 1H), 7.66 (dd, $J = 6.8, 0.8 \text{ Hz}$, 1H), 7.84-7.90 (m, 2H), 8.51 (dd, $J = 4.8, 1.2 \text{ Hz}$, 1H) ppm; $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 18.4, 124.6, 128.4, 130.5, 132.8, 133.4, 136.4, 139.0, 146.0, 155.0, 195.3 ppm; HRMS (EI) m/z calcd for (M^+) $\text{C}_{13}\text{H}_{11}\text{NO}$: 197.0841, found: 197.0840.

2-(α -Hydroxybenzyl)-5-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi = 1000 \mu\text{m}$, $L = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 1/2) to afford 2-(α -hydroxybenzyl)-5-methylpyridine (44.9 mg, 75% yield, 81% purity (GC)).

5-(α -Hydroxybenzyl)-2-methylpyridine was observed by GCMS as a major byproduct (9%, GC). 2- and 3-Hydroxybenzylpyridines as unpurified byproducts were also observed by GCMS (total 10%, GC). ^1H NMR for title compound (400 MHz, CDCl_3) δ 2.31 (s, 3H), 4.65-5.50 (m, 1H), 5.72 (s, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 7.21-7.45 (m, 6H), 8.35-8.40 (m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 18.0, 74.7, 120.74, 126.9, 127.7, 128.5, 131.9, 137.5, 143.4, 148.0, 158.1 ppm; HRMS (ESI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1073.

2-(α -Hydroxybenzyl)-5-trimethylsilylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 12.5 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 39.6 mg of 2-(α -hydroxybenzyl)-5-trimethylsilylpyridine (51% yield, 93% purity (GC)). 5-(α -Hydroxybenzyl)-2-trimethylsilylpyridine was observed by GCMS as a major byproduct (7%, GC). ^1H NMR (400 MHz, CDCl_3) δ 0.29 (s, 9H), 5.74 (s, 1H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.22-7.42 (m, 5H), 7.72 (dd, $J = 7.6, 7.6$ Hz, 1H), 8.60-8.64 (m, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 1.3, 74.8, 120.8, 127.0, 127.8, 128.5, 133.8, 124.0, 143.2, 151.8, 160.9 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{15}\text{H}_{20}\text{NOSi}$: 258.1315, found: 258.1238.

2-(α -Hydroxybenzyl)-6-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzaldehyde (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 40.0 mg of 2-(α -hydroxybenzyl)-6-methylpyridine (67% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 2.57 (s, 3H), 5.69 (s, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 7.6$ Hz, 1H), 7.22-7.42 (m, 5H), 7.47 (dd, $J = 7.6, 7.6$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 24.2, 74.5, 118.3, 121.8, 127.1, 127.6, 128.4, 137.0, 143.4, 156.6, 159.8 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1076, found: 200.1074.

2-Benzoyl-6-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzonitrile (Electrophile-2): 6.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 32.9 mg of 2-benzoyl-6-methylpyridine (56% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 2.63 (s, 3H), 7.31-7.36 (m, 1H), 7.44-7.52 (m, 2H), 7.54-7.62 (m, 1H), 7.72-7.80 (m, 2H), 8.06-8.12 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 24.5, 121.6, 125.7, 128.0, 131.2, 132.8, 136.2, 137.0, 154.7, 157.7, 193.9 ppm; HRMS (APCI) m/z calcd for (MH^+) $\text{C}_{13}\text{H}_{12}\text{NO}$: 198.0920, found: 198.0913.

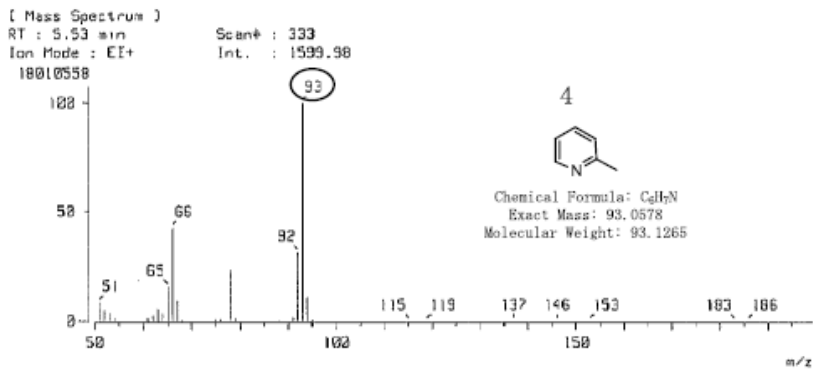
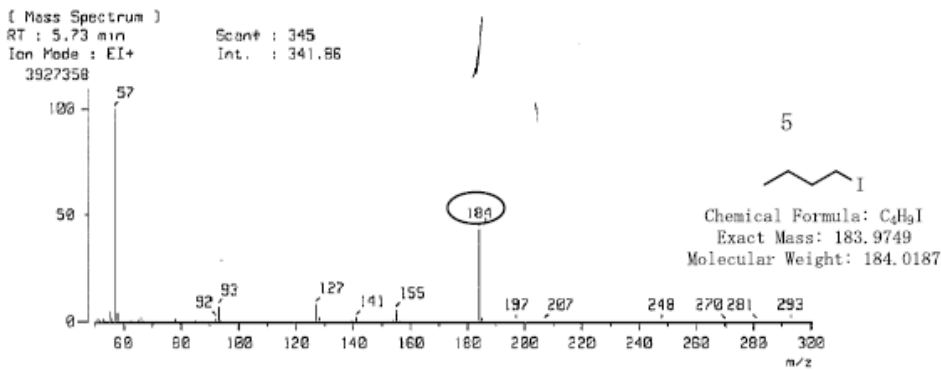
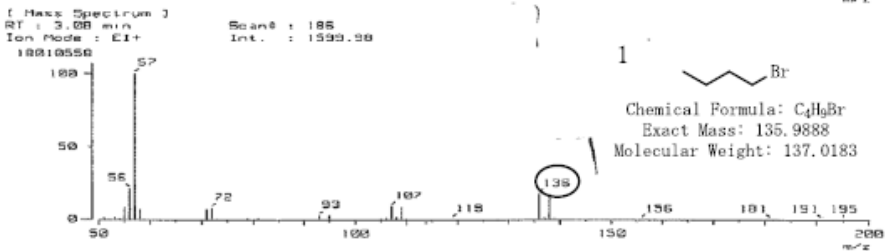
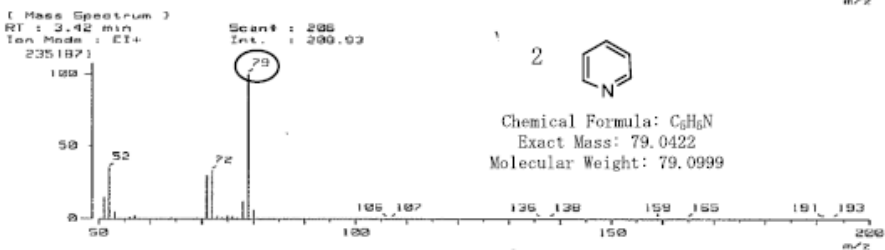
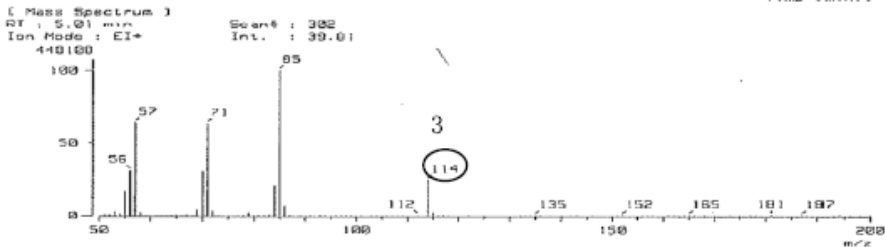
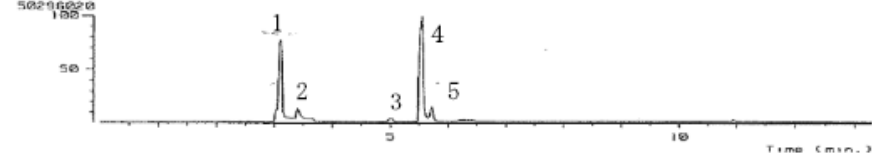
2-(1-Hydroxy-1-phenylethyl)-6-trimethylsilylpyridine. The reaction was performed under the following condition; flow rate of a solution of acetophenone (Electrophile-2): 4.0 mL min^{-1} , **R3**: $\phi_3 = 1000 \mu\text{m}$, $L_3 = 25 \text{ cm}$. After extraction with Et_2O , the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 45.7 mg of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine (56% yield, >99% purity (GC)). ^1H NMR (400 MHz, CDCl_3) δ 0.33 (s, 9H), 1.92 (s, 3H), 6.82 (s, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 7.17-7.24 (m, 1H), 7.28-7.34 (m, 2H), 7.39 (d, $J = 7.2$ Hz, 1H), 7.46-7.56 (m, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ -1.9, 29.1, 74.6, 119.5, 126.0, 126.8, 127.1, 128.1, 135.1, 147.3, 163.7, 165.3 ppm; HRMS (ESI) m/z calcd for (MH^+) $\text{C}_{16}\text{H}_{21}\text{NOSi}$: 272.1471, found: 272.1465.

References

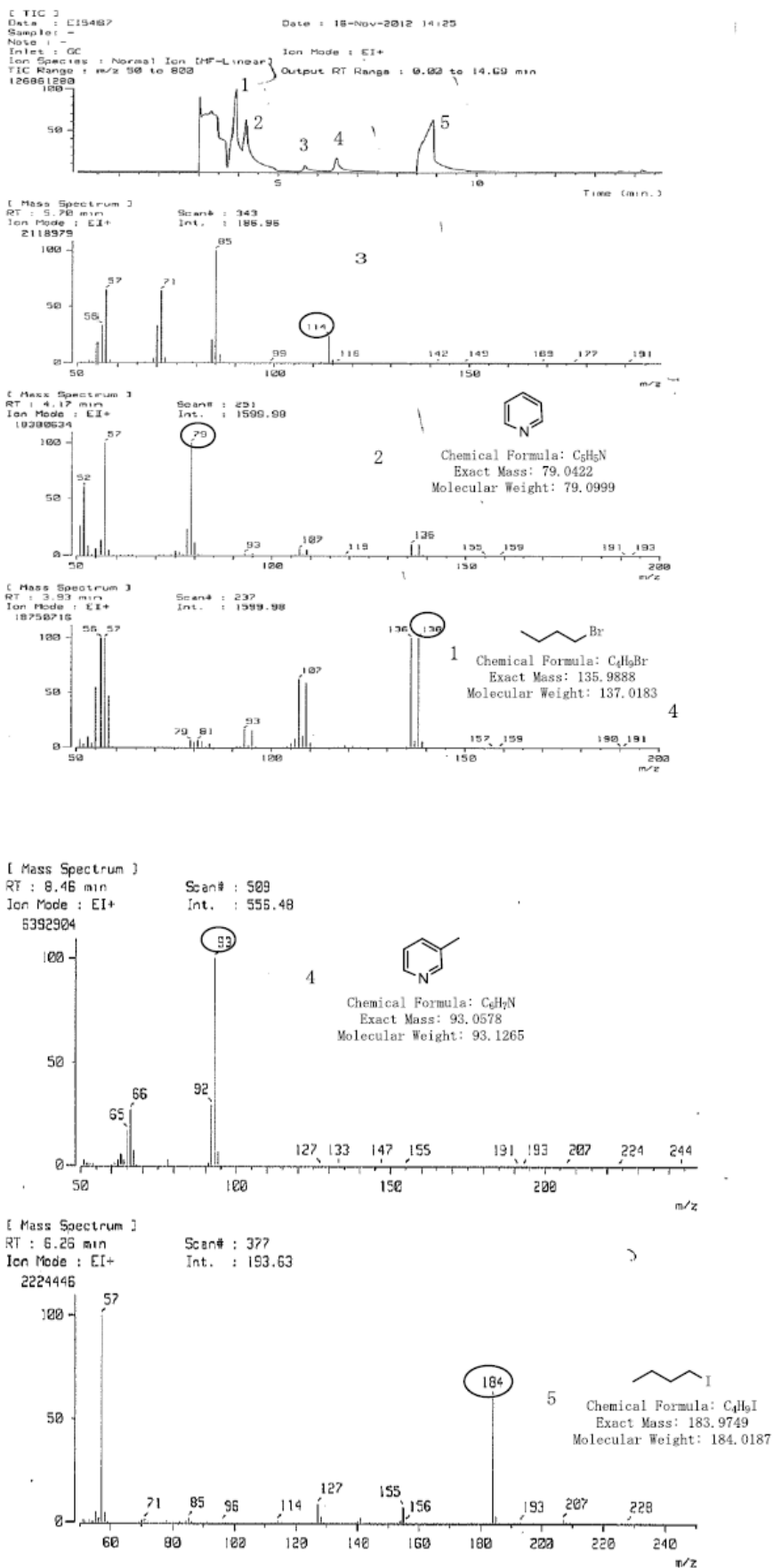
¹ Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron*, **2000**, *56*, 1349-1360.

² For the spectral data of 2-bromo-5-trimethylsilylpyridine; Stange, A. F.; Tokura, S.; Kira, M. *J. Organomet. Chem.* **2000**, *612*, 117-124.

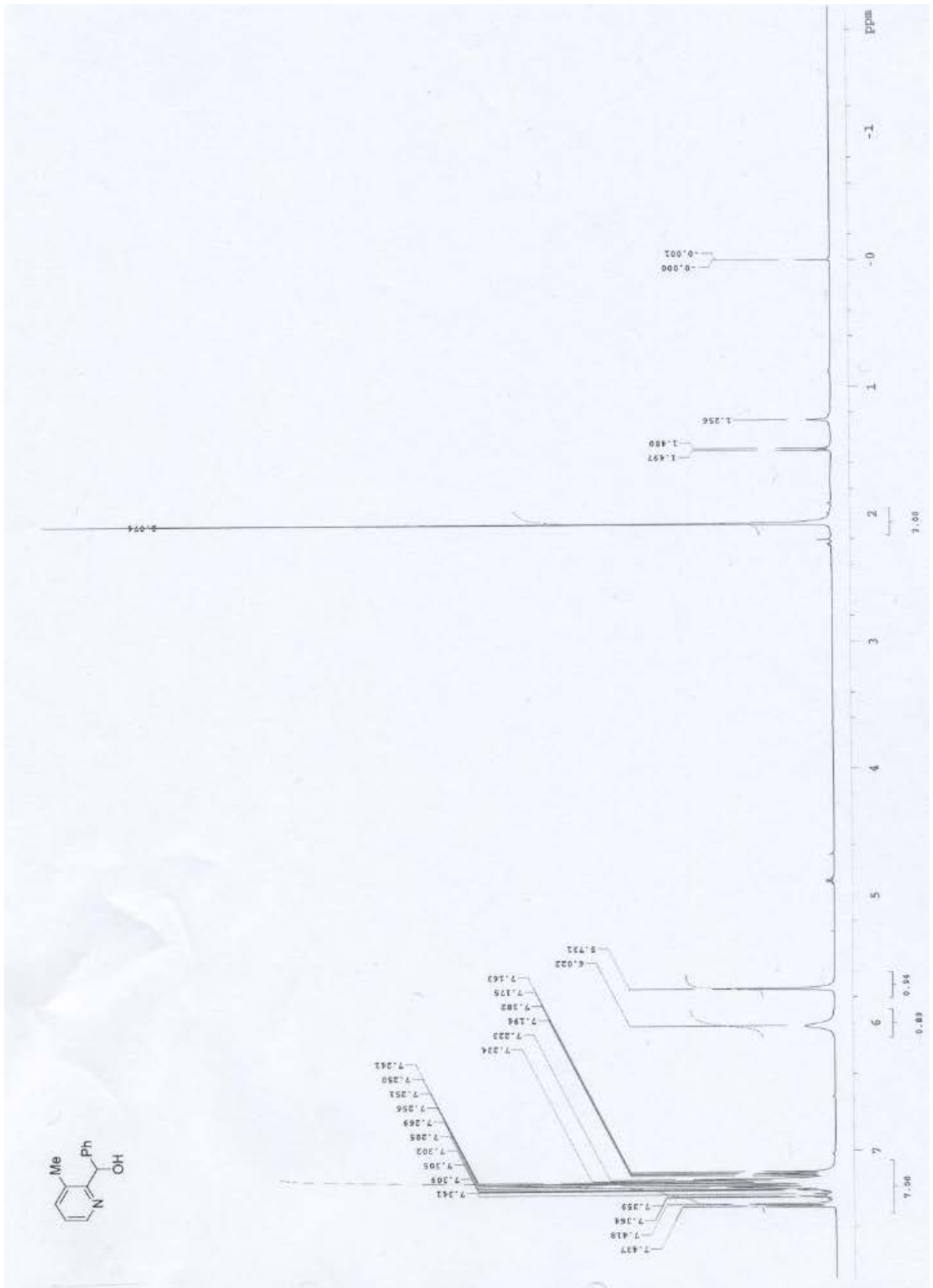
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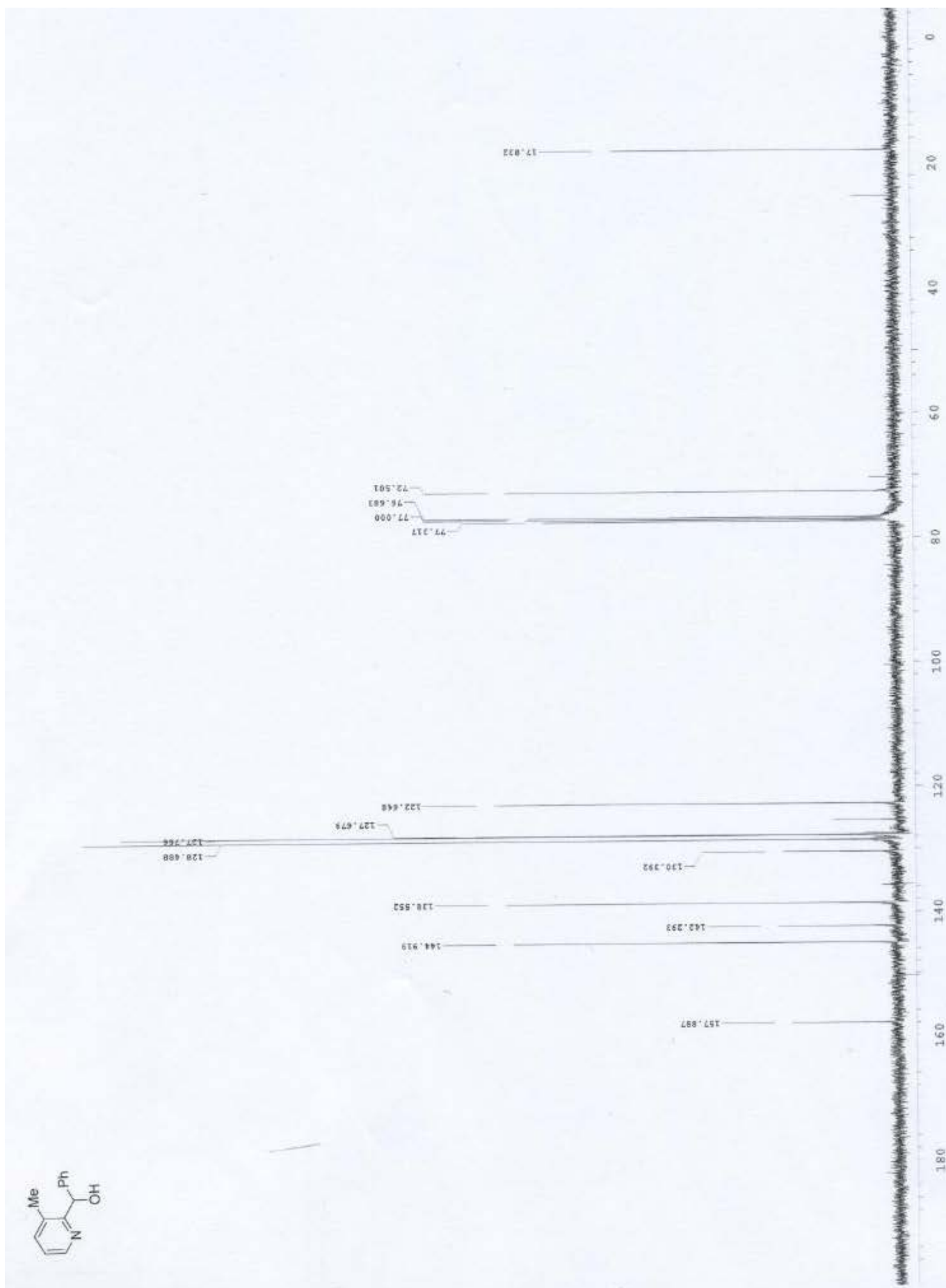
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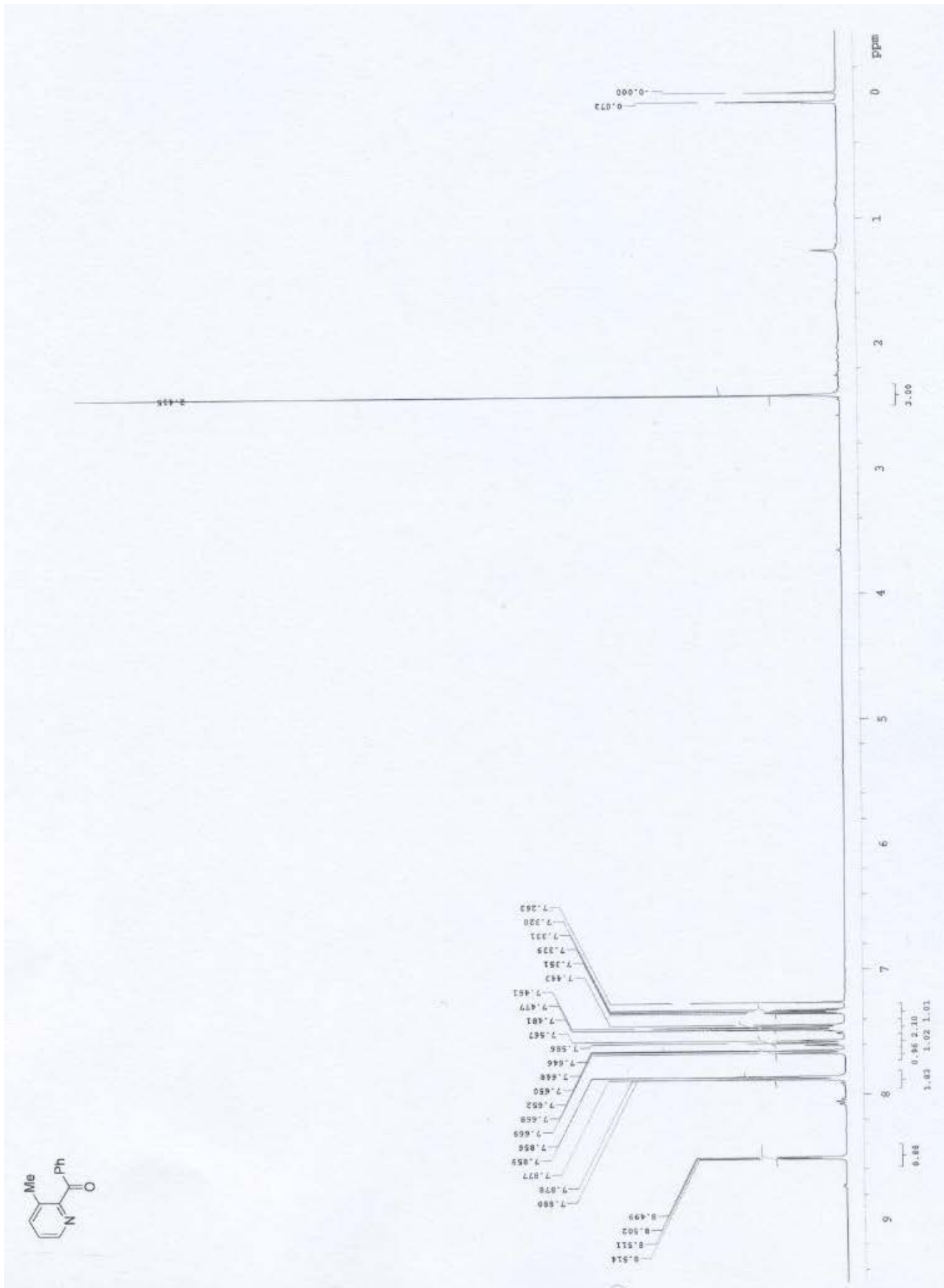
GCMS trace of the crude reaction product on the lithiation of 3-bromopyridine followed by the reaction with iodomethane in a conventional macro batch reactor



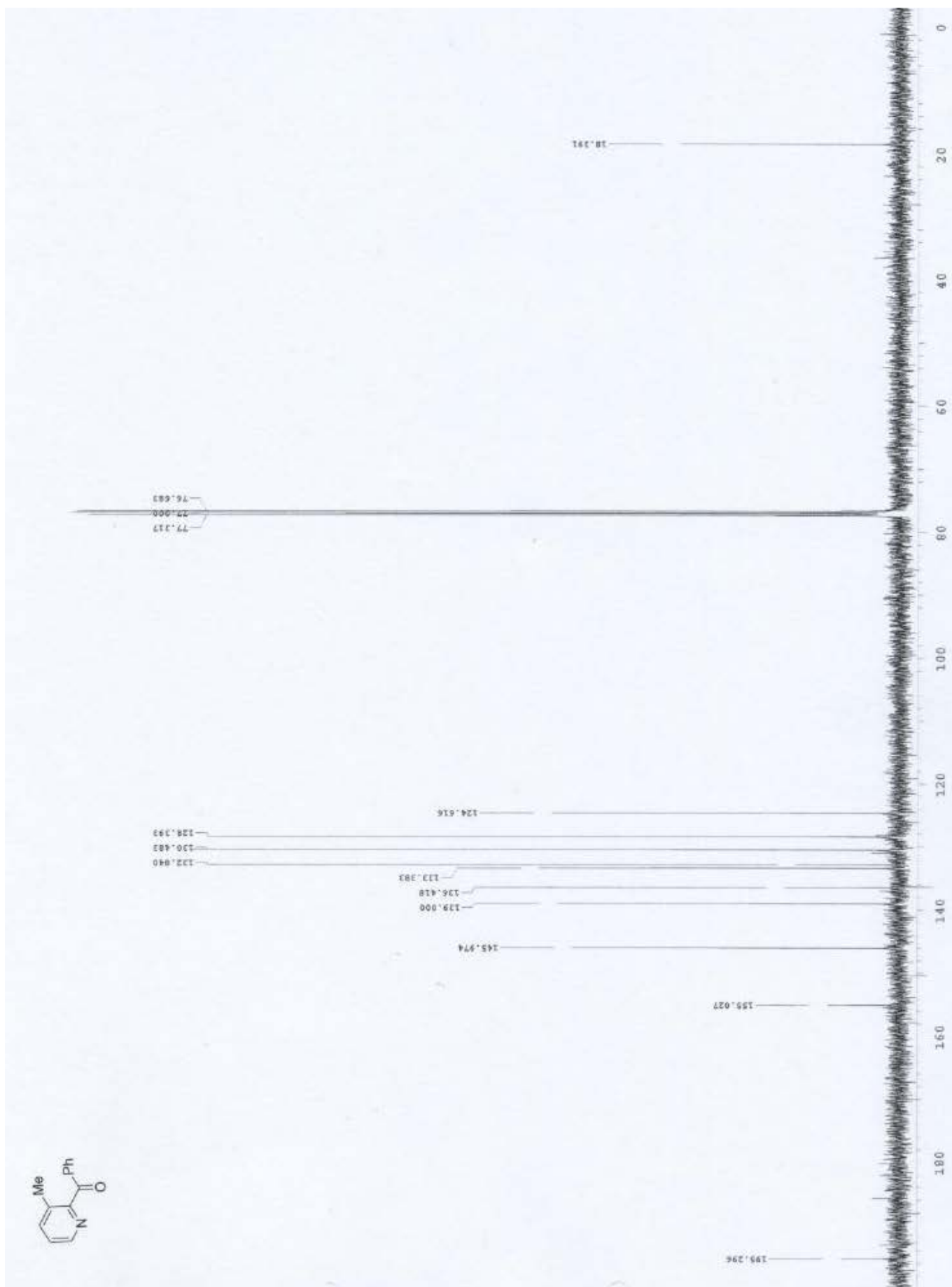
^1H NMR spectrum of 2-(α -hydroxybenzyl)-3-methylpyridine



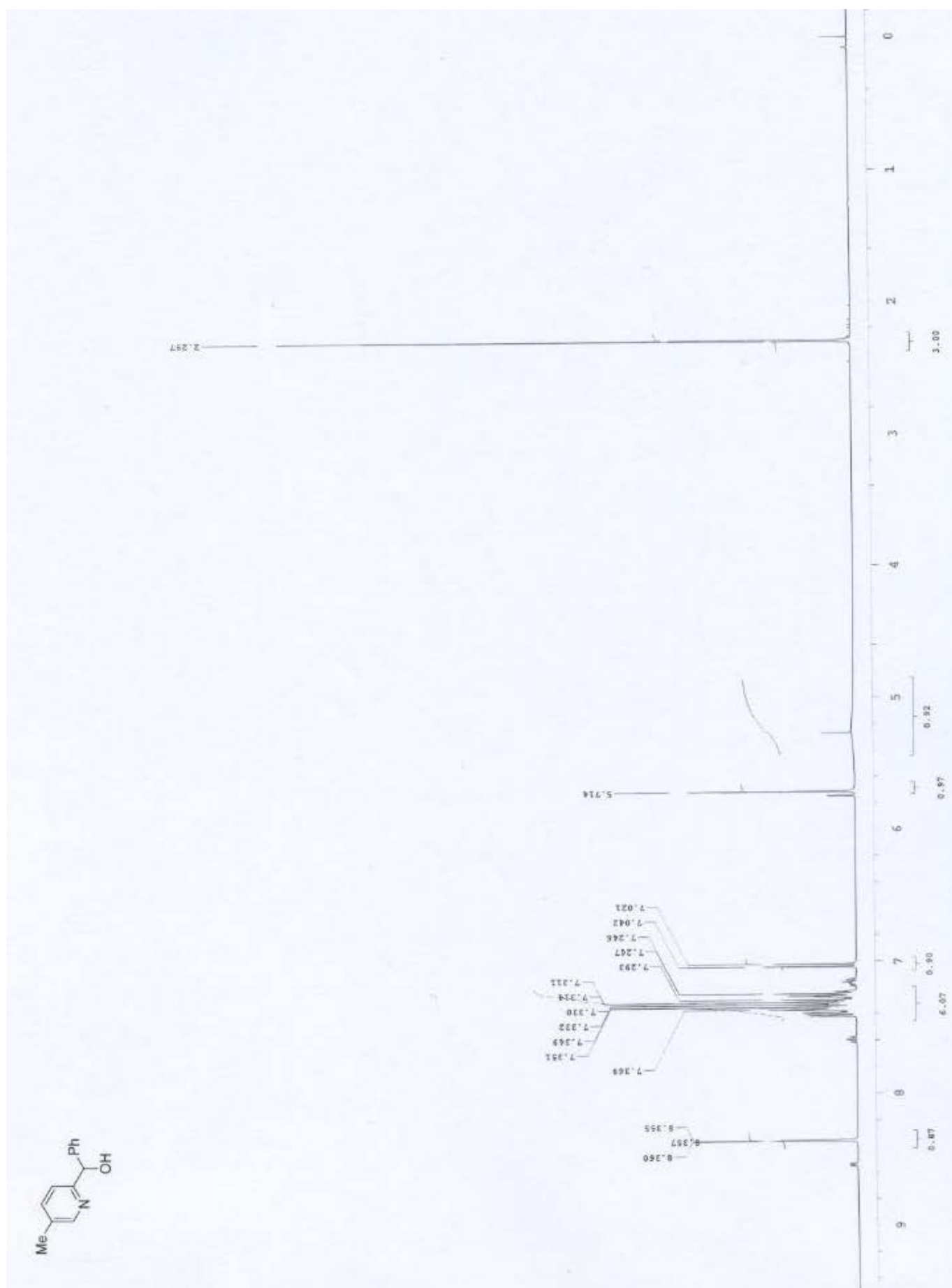
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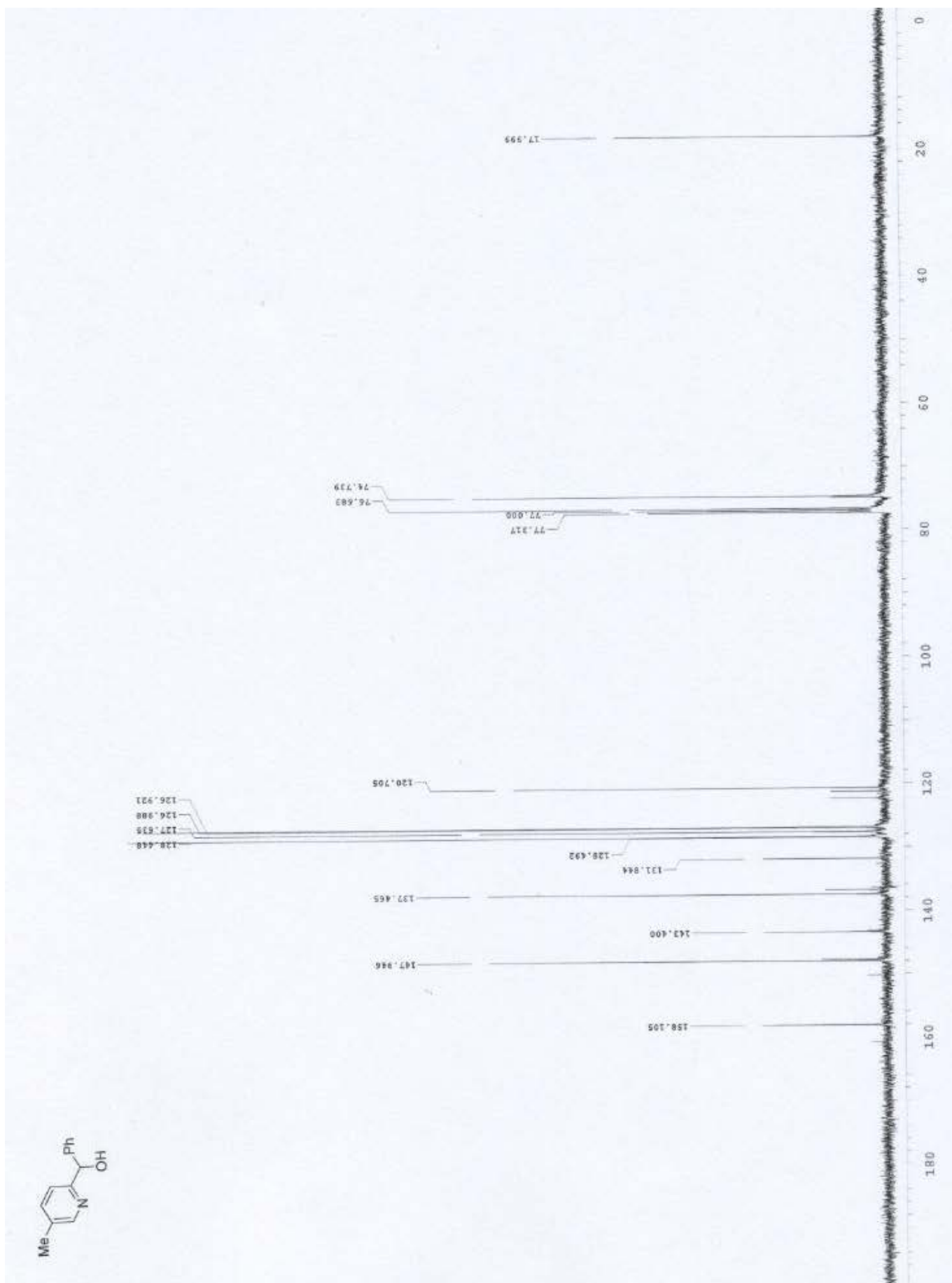
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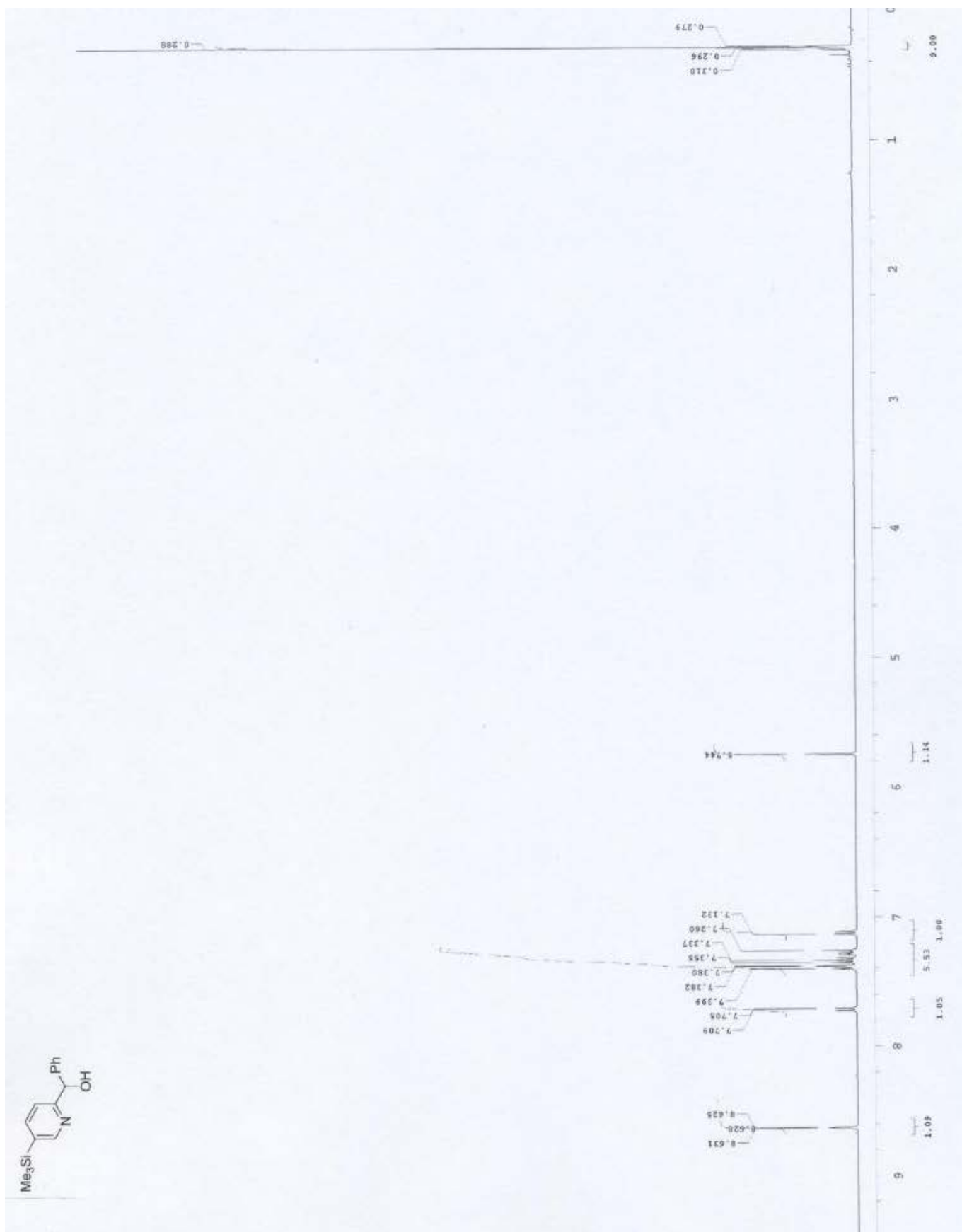
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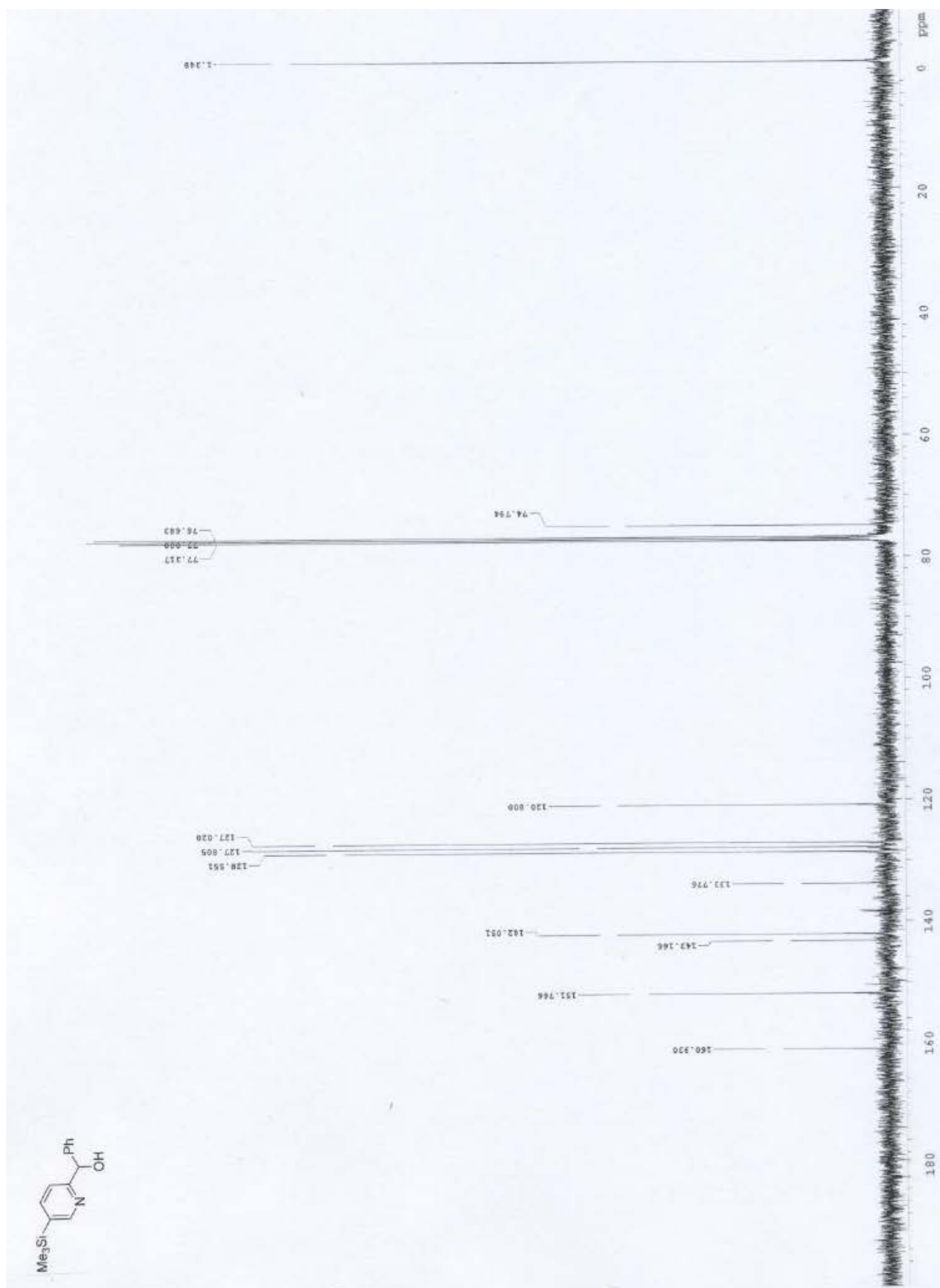
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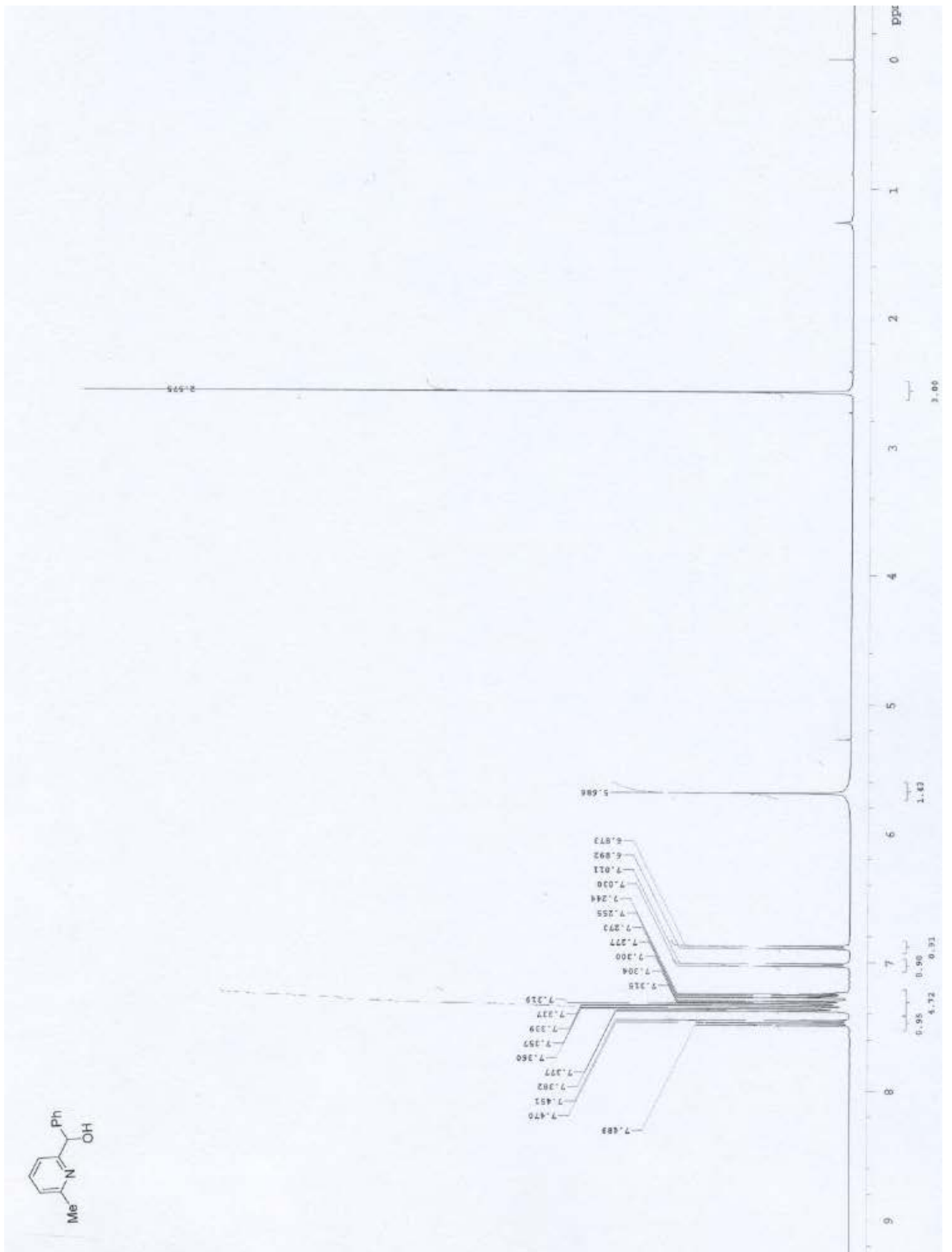
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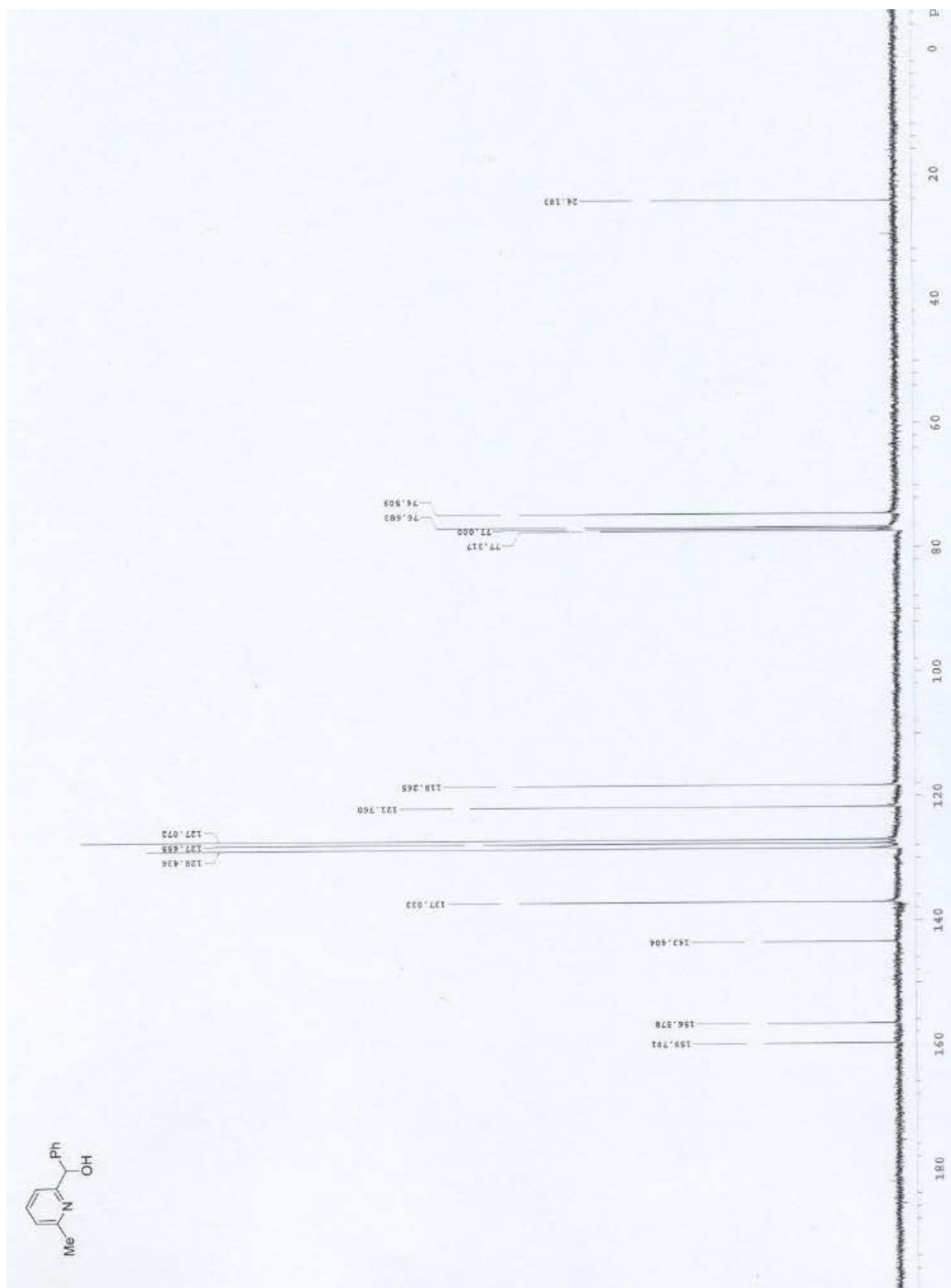
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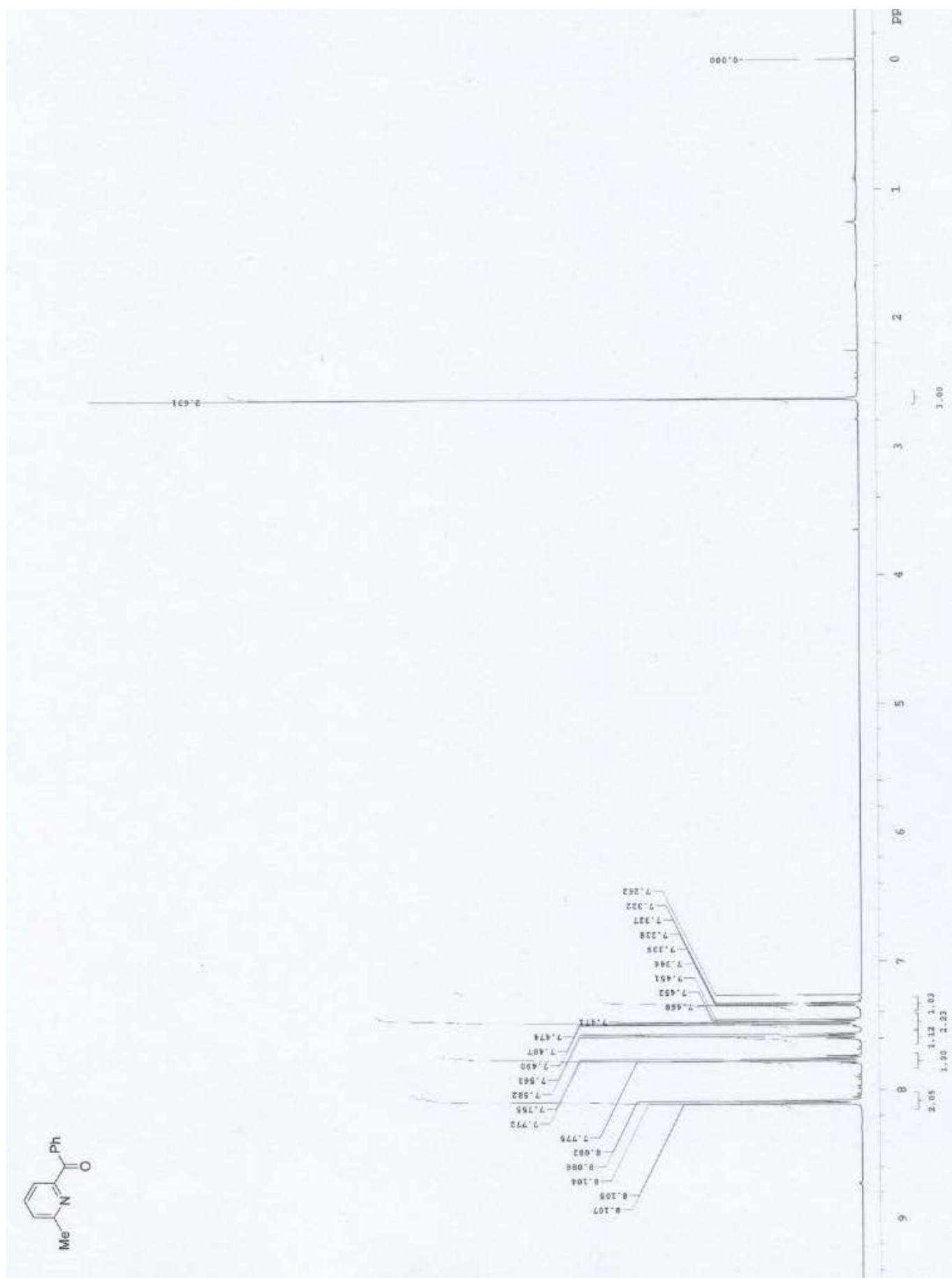
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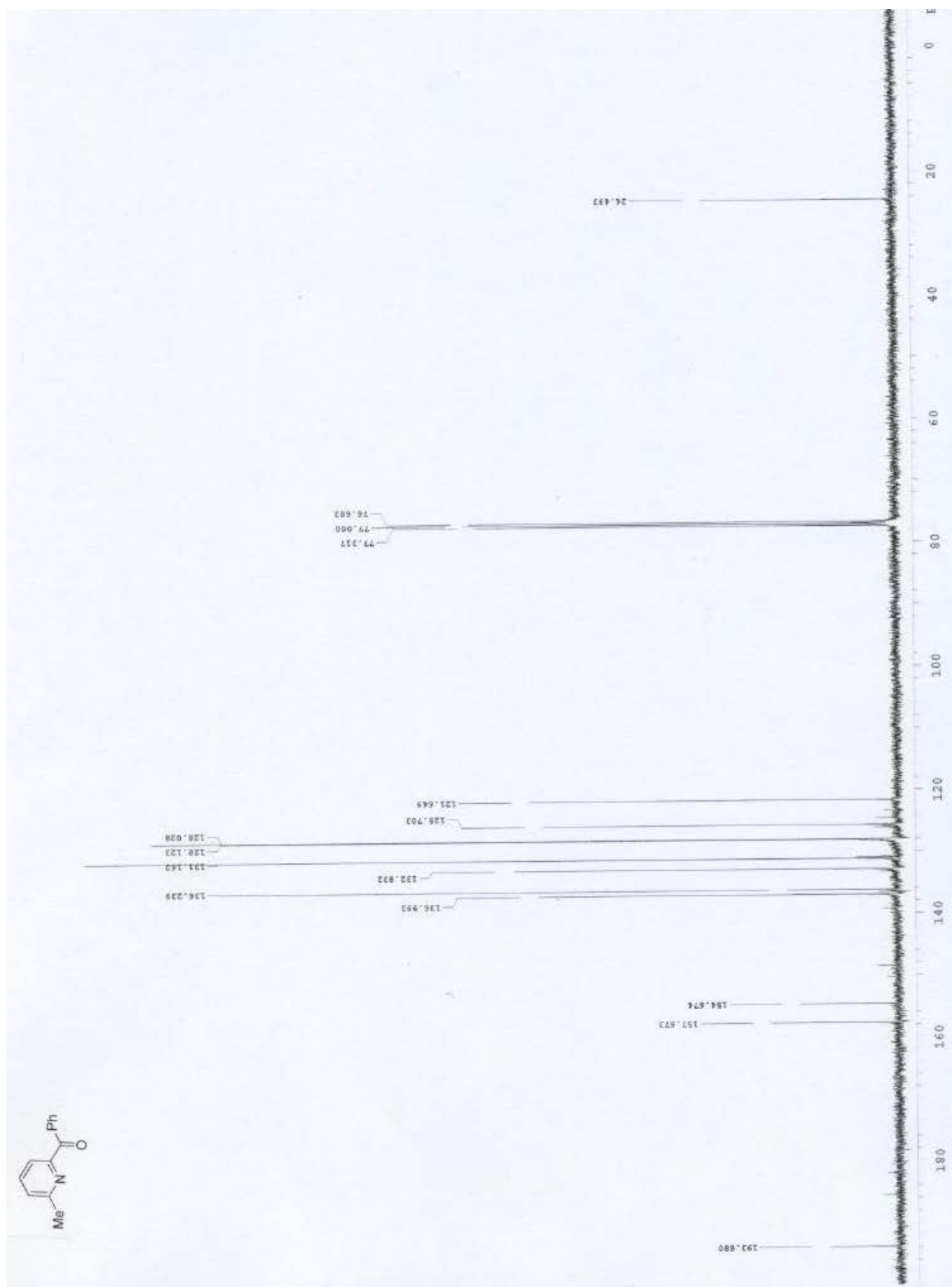
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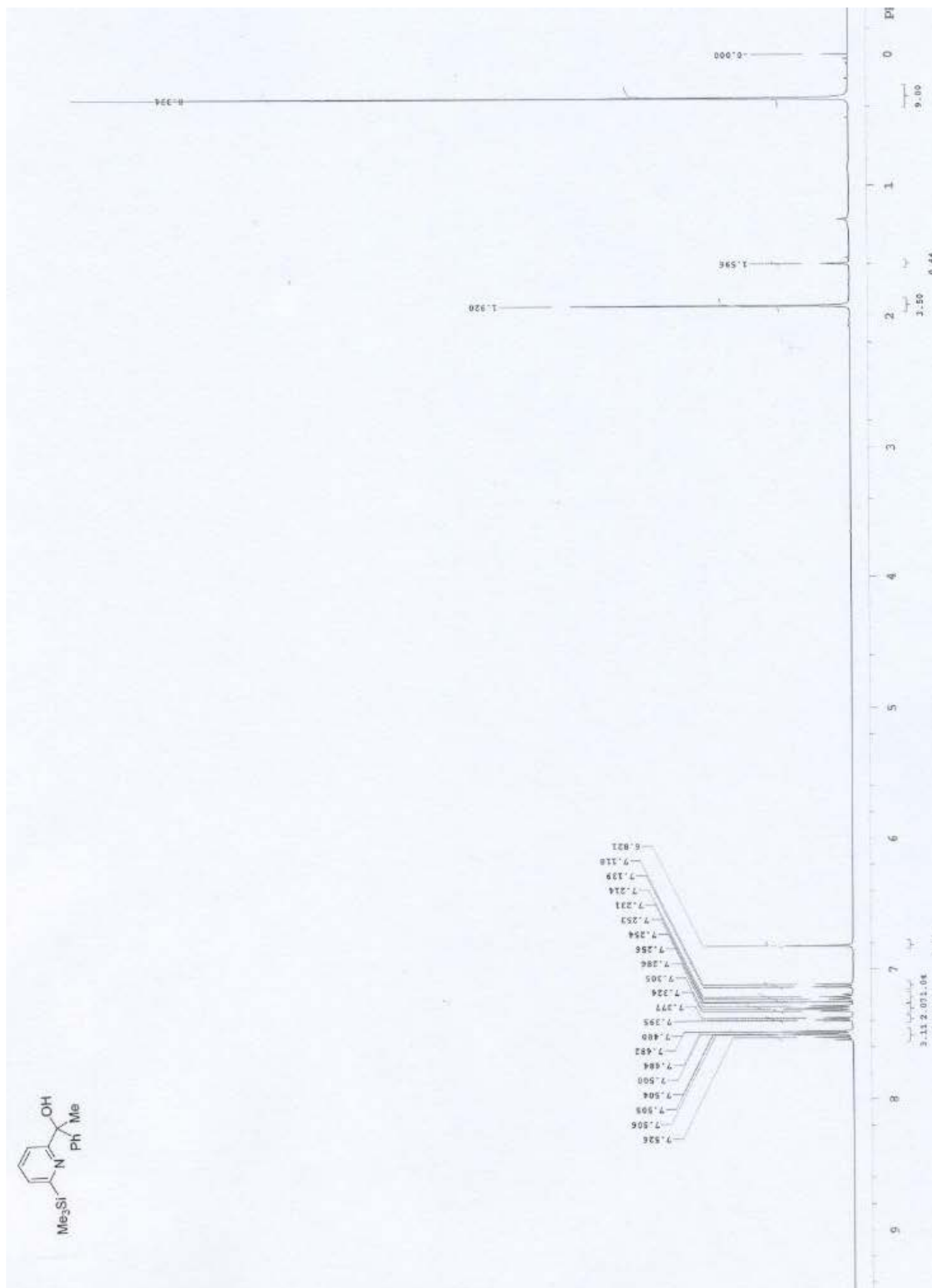
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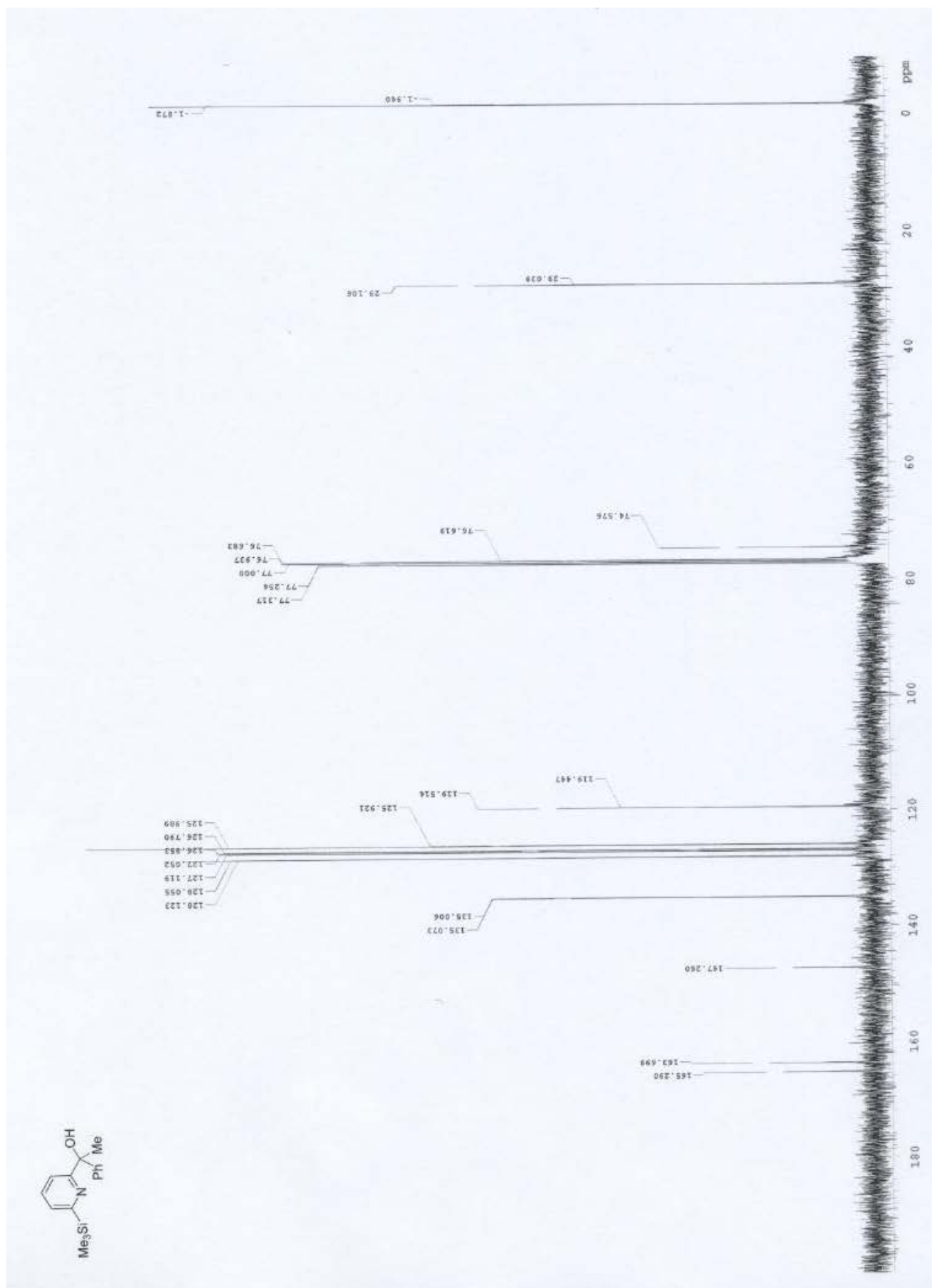
¹H NMR spectrum of 2-benzoyl-6-methylpyridine



^{13}C NMR spectrum of 2-benzoyl-6-methylpyridine



¹H NMR spectrum of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine



¹³C NMR spectrum of 2-(1-hydroxy-1-phenylethyl)-6-trimethylsilylpyridine