Supporting Information

Flow Microreactor Synthesis of Disubstituted Pyridines from Dibromopyridines via Br/Li Exchange without Using Cryogenic Conditions

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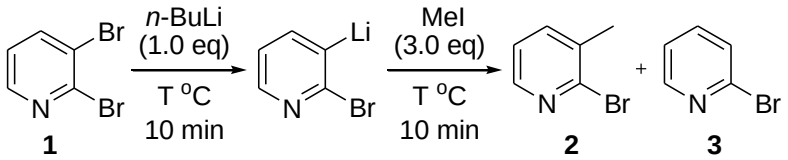
General

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). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^{1}H 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. 2,3-Dibromopyridine, 2-bromo-3-methylpyridine, 2,5-dibromopyridine, 2-bromo-5-methylpyridine, 2,6-dibromopyridine, 2-bromo-6-methylpyridine, 2-bromopyridine, 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 OUW). 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 2,3-Dibromopyridine (1) Followed by Reaction with Iodomethane in a Macro Batch System



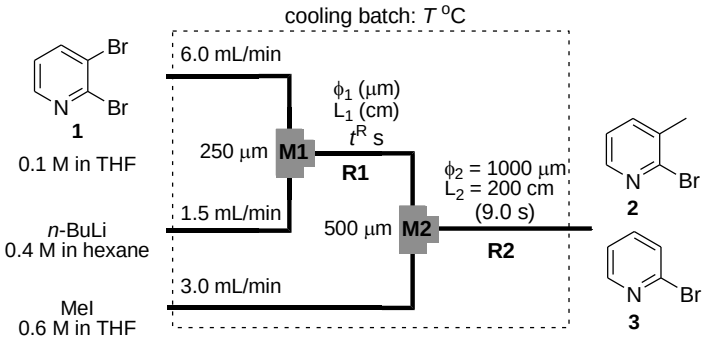
1 **2** **3**

A solution of 2,3-dibromopyridine (**1**) (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 H_2O, the yields of 2-bromo-3-methylpyridine (**2**) and 2-bromopyridine (**3**), and the conversion of 2,3-dibromopyridine (**1**) was analyzed by GC. The results are summarized in Table S-1.

Table S-1. The Br/Li exchange reaction of 2,3-dibromopyridine (**1**) followed by reaction with iodomethane in a macro batch system.

T (°C)	**1** conversion (%)	**2** yield (%)	**3** yield (%)
-78	0	48	24
-48	0	19	26
-28	0	0	34
0	0	0	21

The Br/Li Exchange Reaction of 2,3-Dibromopyridine (1) Followed by Reaction with Iodomethane in a Flow Microreactor System



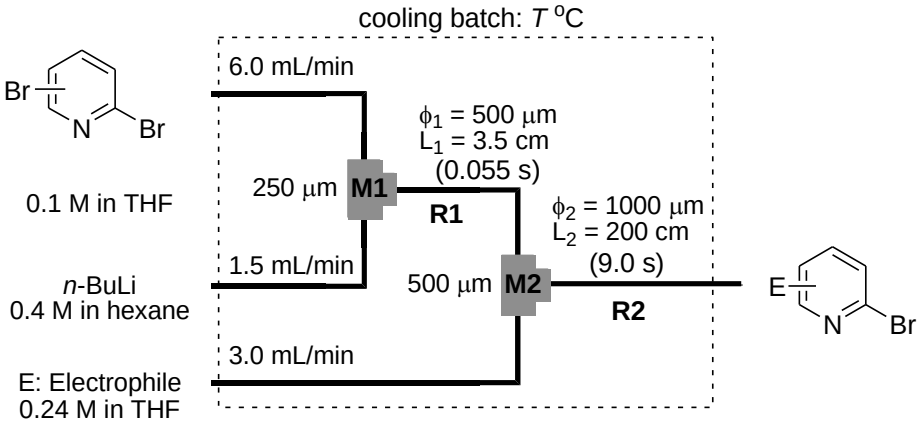
A flow microreactor system consisting of two T-shaped micromixers (**M1** (ϕ = 250 μm) and **M2** (ϕ = 500 μm)), two microtube reactors (**R1** and **R2** (ϕ_2 = 1000 μm, L_2 = 200 cm)), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of 2,3-dibromopyridine (**1**) (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 are summarized in Table S-2.

Table S-2. Deprotonation reaction of 2,3-dibromopyridine (**1**) with *n*-BuLi (1.0 eq) followed by reaction with iodomethane in flow microreactor systems.

L_1	ϕ_1	t^R	T	conversion (%)	yield (%)	
(cm)	(μm)	(s)	(°C)	**1**	**2**	**3**
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

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



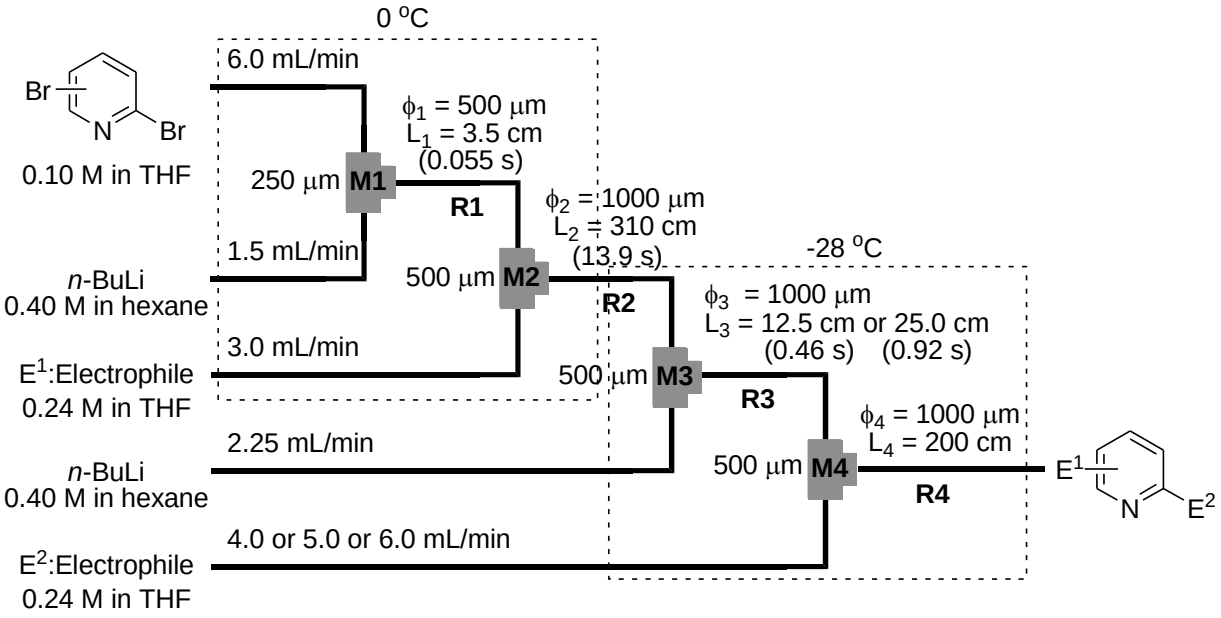
A flow microreactor system consisting of two T-shaped micromixers (**M1** (ϕ = 250 μm) and **M2** (ϕ = 500 μm)), two microtube reactors (**R1** (ϕ_1 = 500 μm, L_1 = 3.5 cm) and **R2** (ϕ = 1000 μm, L = 200 cm)), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm)) was used. A solution of bromopyridine (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 (0.24 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. Yields were determined by gas chromatography or isolation. In all cases of 2,3-dibromopyridine (**1**), 2,5-dibromopyridine, and 2,6-dibromopyridine, T = 0 °C was selected as a bath temperature.

2-Bromo-3-methylpyridine, 2-bromo-5-methylpyridine, and 2-bromo-6-methylpyridine were in accordance with the spectral data of the commercially available compounds.

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 ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm) and **P3** (ϕ = 1000 μm, L = 100 cm) , **P4** (ϕ = 1000 μm, L = 50 cm), **P5** (ϕ = 1000 μm, L = 100 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 °C. The flow microreactor system consisting of **M3**, **M4**, **R2**, **R3**, **R4**, **P4** and **P5** was dipped in a bath cooled at -28 °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** (ϕ = 250 μm). The resulting solution was passed through **R1** (ϕ_1 = 500 μm, L_1 = 3.5 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** (ϕ = 500 μm). The resulting solution was passed through **R2** (ϕ_2 = 1000 μm, L_2 = 310 cm (200 cm at 0 °C, 10 cm at ambient temperature, and 100 cm at -28 °C)), and was introduced to **M3** (ϕ = 500 μm) 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** (ϕ_3 = 1000 μm, L_3 = 12.5 or 25 cm) and was introduced to **M4** (ϕ = 500 μm) 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** (ϕ_4 = 1000 μm, L_4 = 200 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**: ϕ = 1000 μm, L = 12.5 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}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}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^+) $C_{13}H_{14}NO$: 200.1076, found: 200.1073. When the reactions in **R3** and **R4** were carried out at 0 °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**: ϕ_3 = 1000 μm, L_3 = 25 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}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.33 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.42-7.50 (m, 2H), 7.54-7.62 (m, 1H), 7.66 (dd, *J* = 6.8, 0.8 Hz, 1H), 7.84-7.90 (m, 2H), 8.51 (dd, *J* = 4.8, 1.2 Hz, 1H) ppm; ^{13}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^+) $C_{13}H_{11}NO$: 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**: ϕ = 1000 μm, L = 25 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-Hydroxybenzylpiridines as unpurified byproducts were also observed by GCMS (total 10%, GC). ^{1}H 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^+) $C_{13}H_{14}NO$: 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**: ϕ_3 = 1000 μm, L_3 = 12.5 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). ^{1}H 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^+) $C_{15}H_{20}NOSi$: 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**: ϕ_3 = 1000 μm, L_3 = 25 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)). ^{1}H 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^+) $C_{13}H_{14}NO$: 200.1076, found: 200.1074.

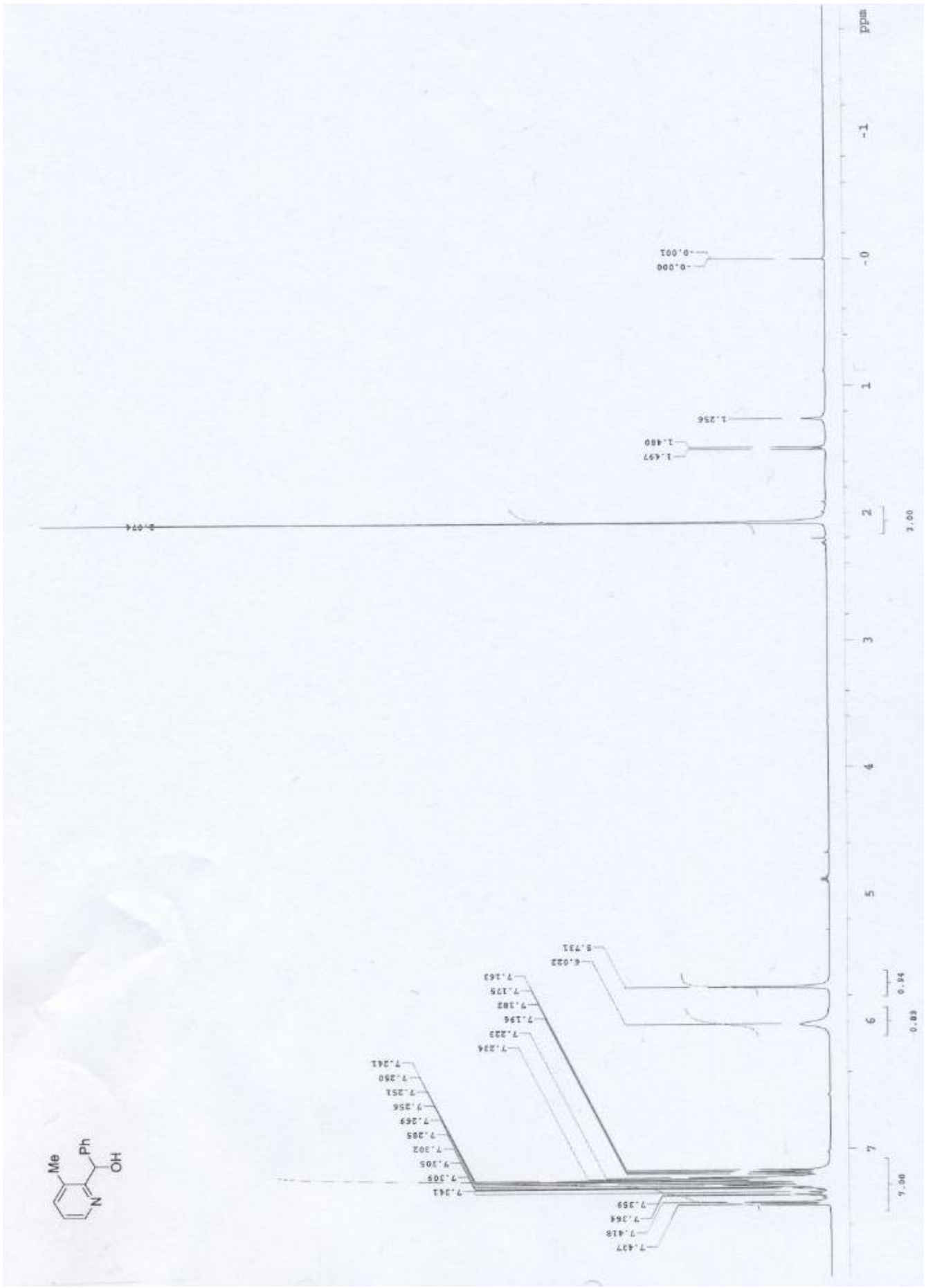
2-Benzoyl-6-methylpyridine. The reaction was performed under the following condition; flow rate of a solution of benzonitrile (Electrophile-2): 6.0 mL min^{-1}, **R3**: ϕ_3 = 1000 μm, L_3 = 25 cm. After extraction with Et_2O, the crude product was purified by silica gel chromatography (hexane/AcOEt = 2/1) to afford 32.9 mg of 2-benzoyl-6-methylpyridine (56% yield, >99% purity (GC)). ^{1}H 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^+) $C_{13}H_{12}NO$: 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**: ϕ_3 = 1000 μm, L_3 = 25 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)). ^{1}H 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^+) $C_{16}H_{21}NOSi$: 272.1471, found: 272.1465.

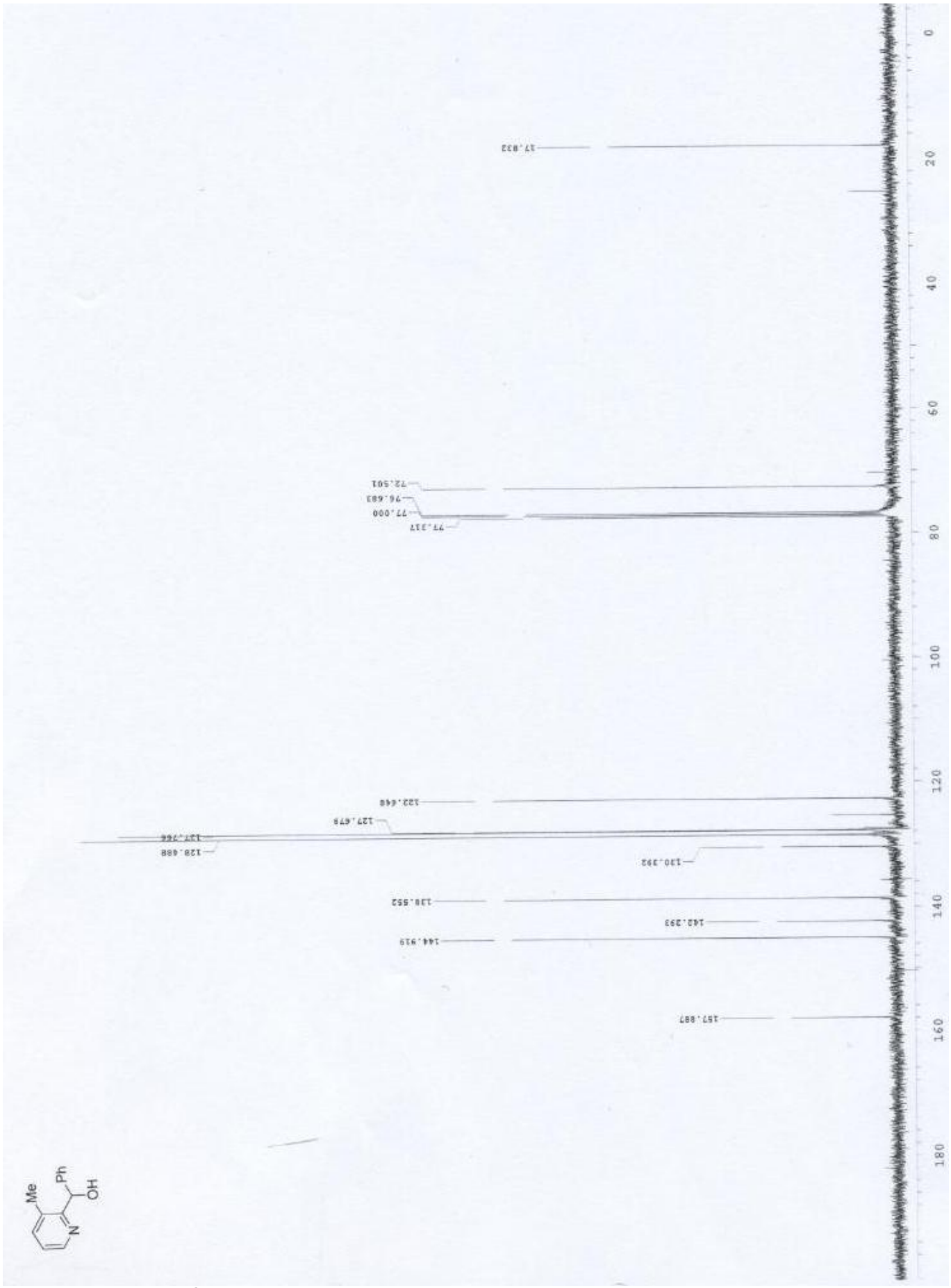
References

[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.



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



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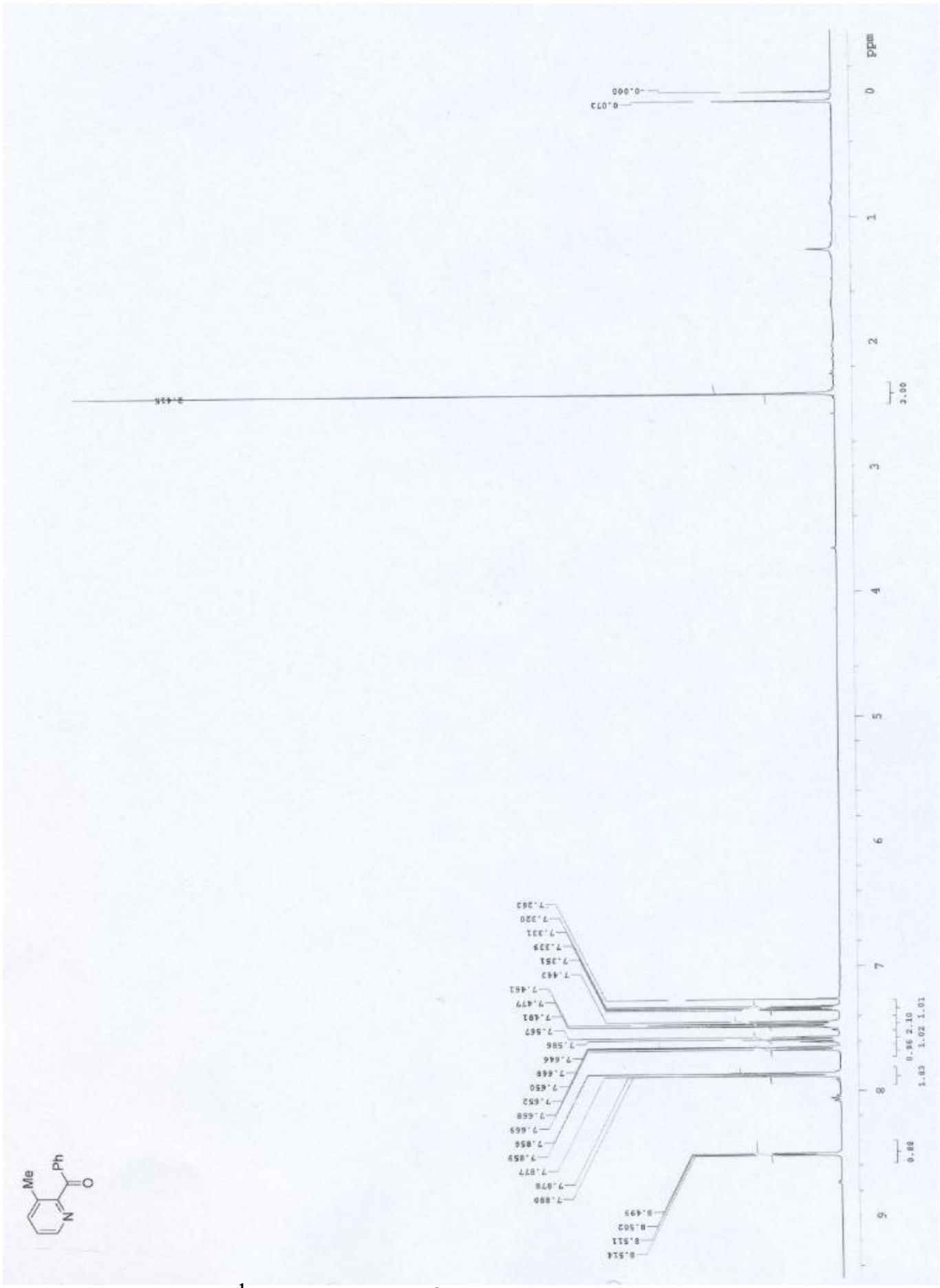
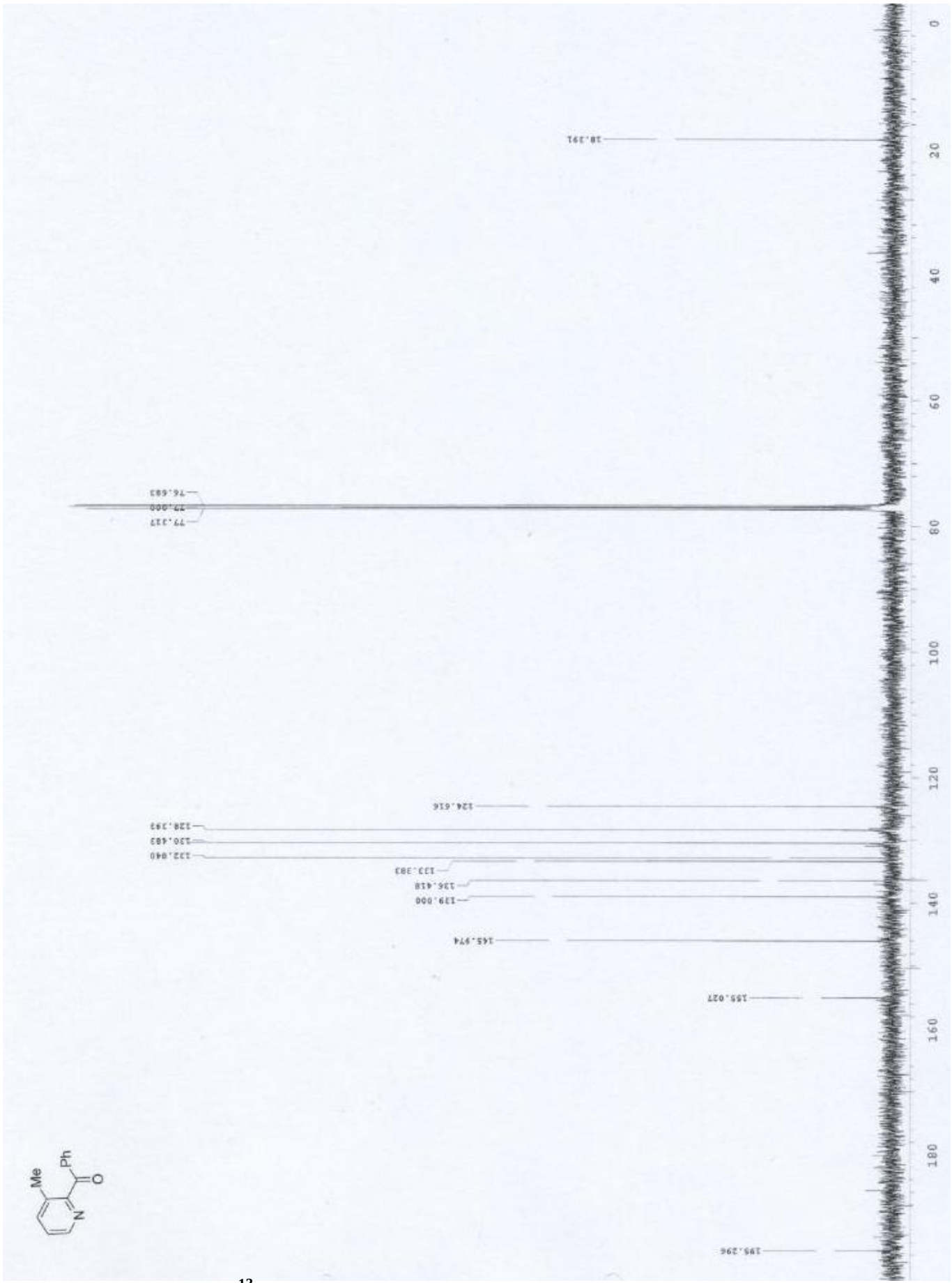


^{1}H NMR spectrum of 2-benzoyl-3-methylpyridine



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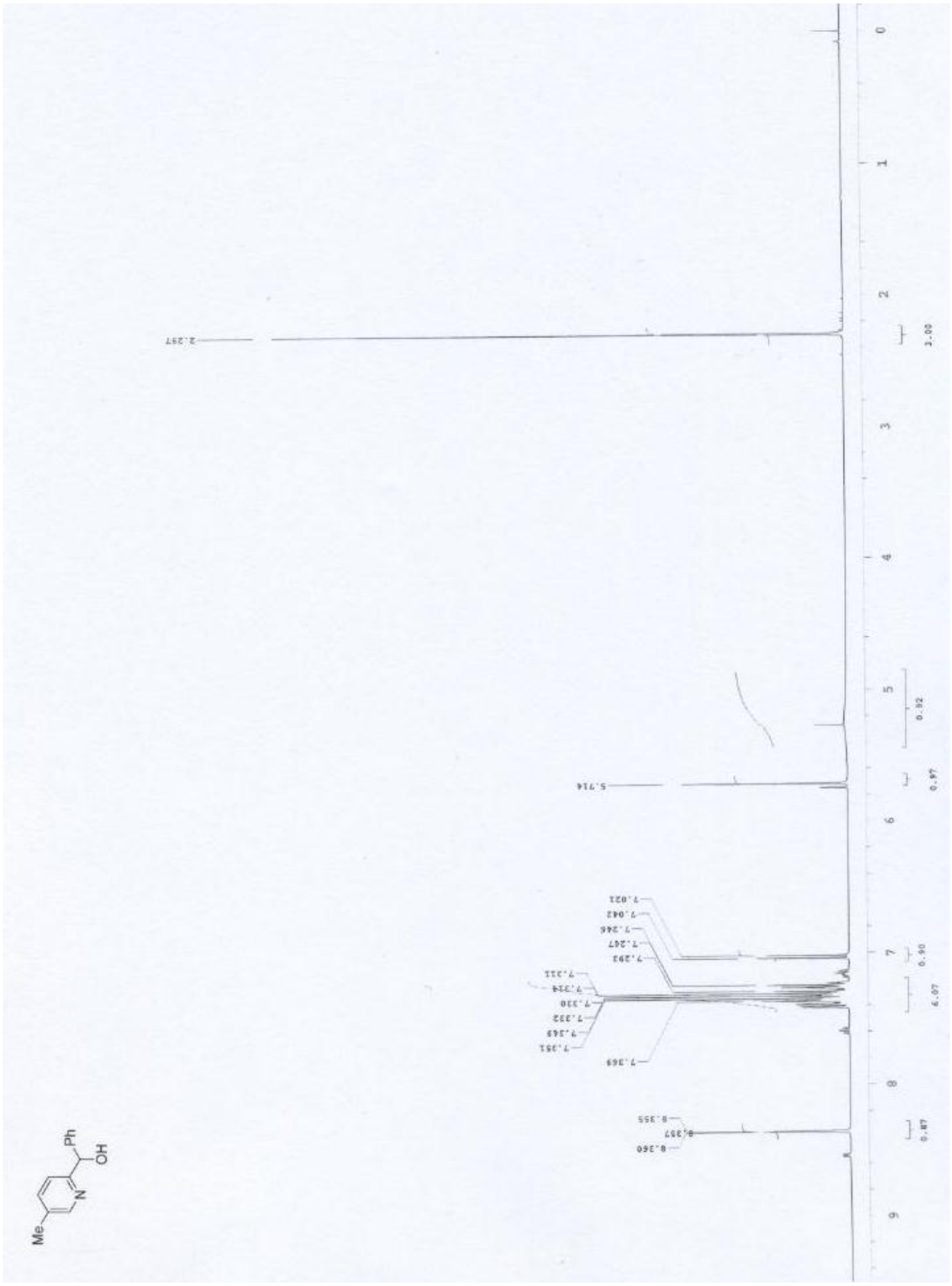

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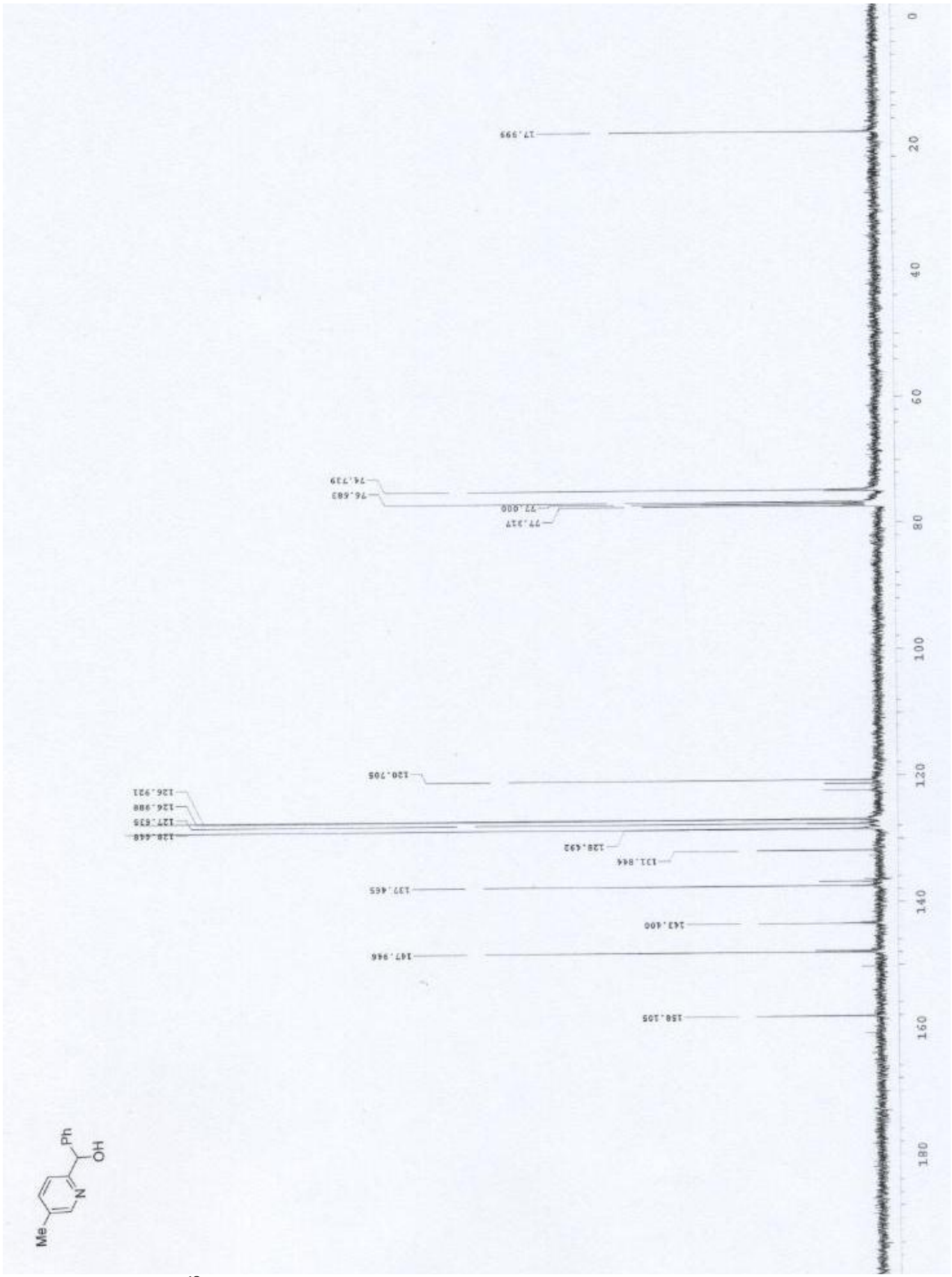

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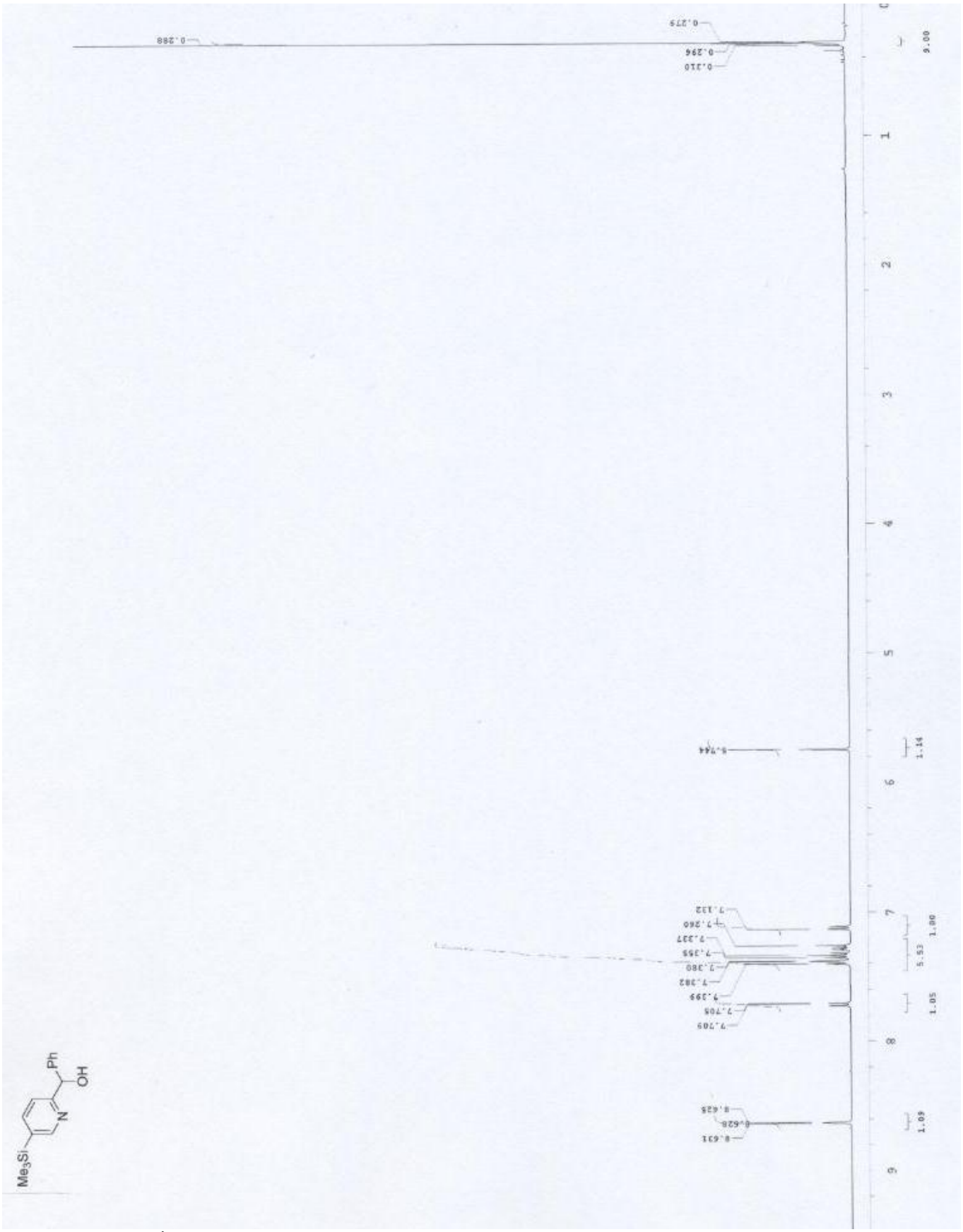
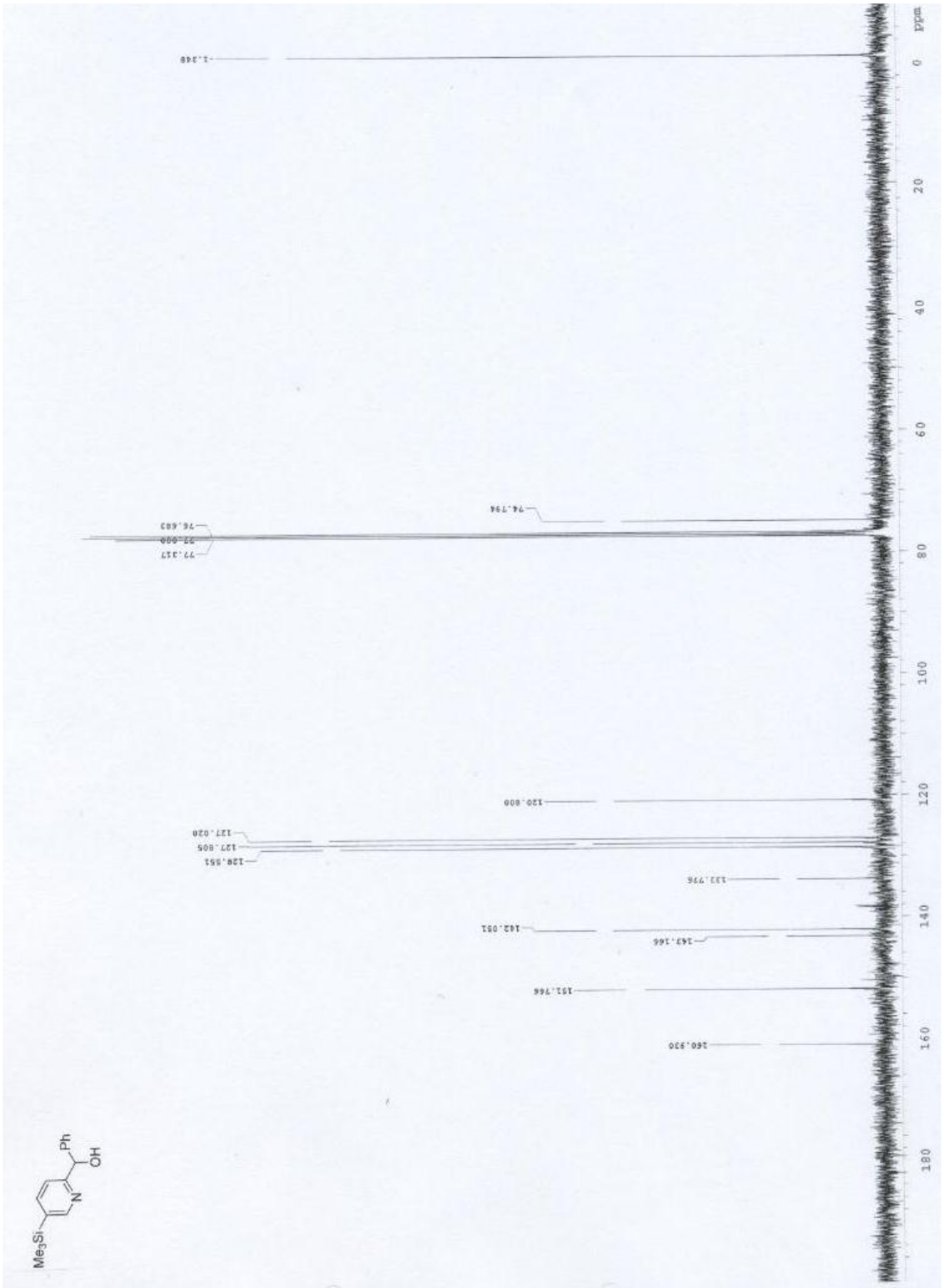
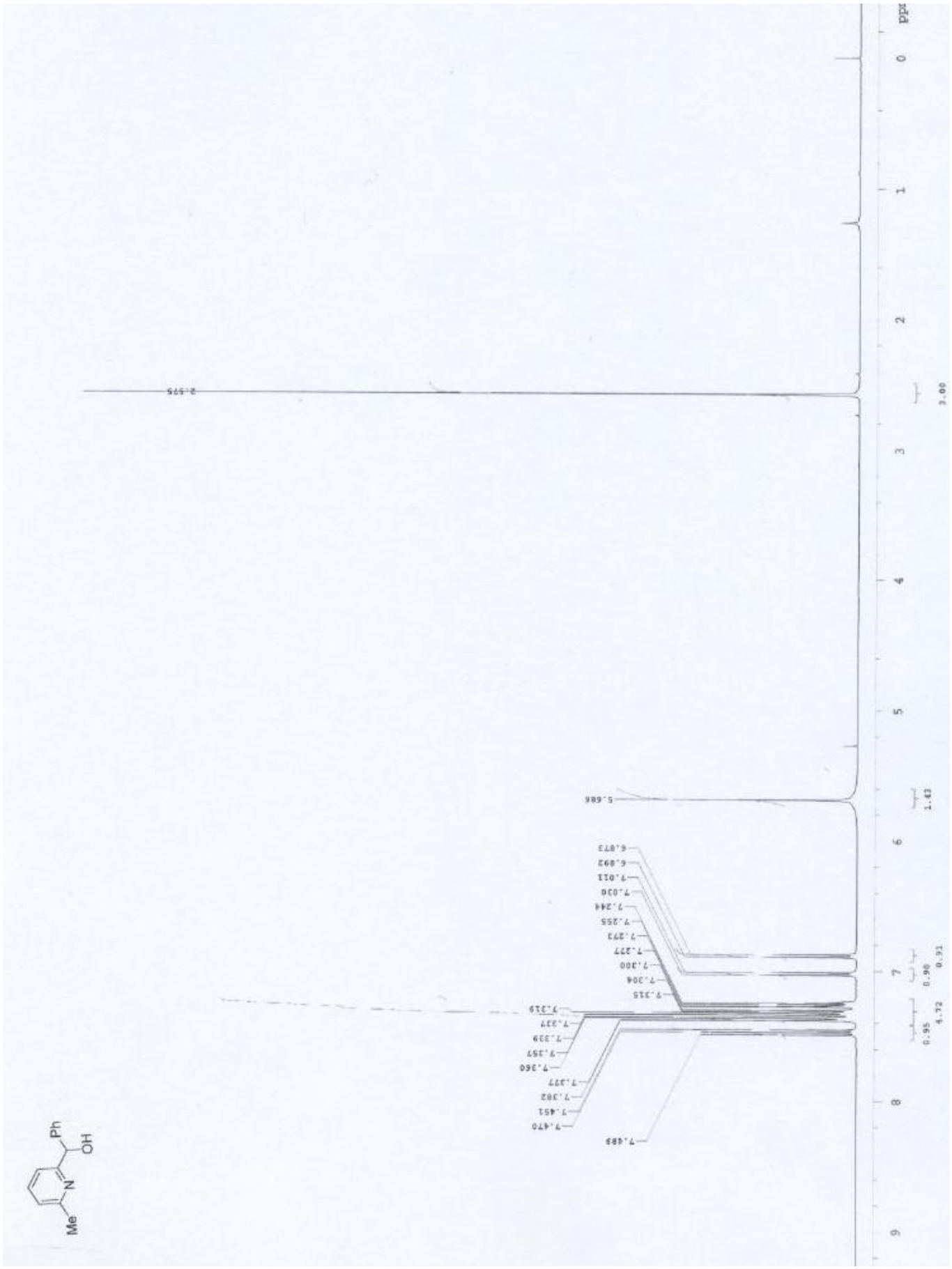


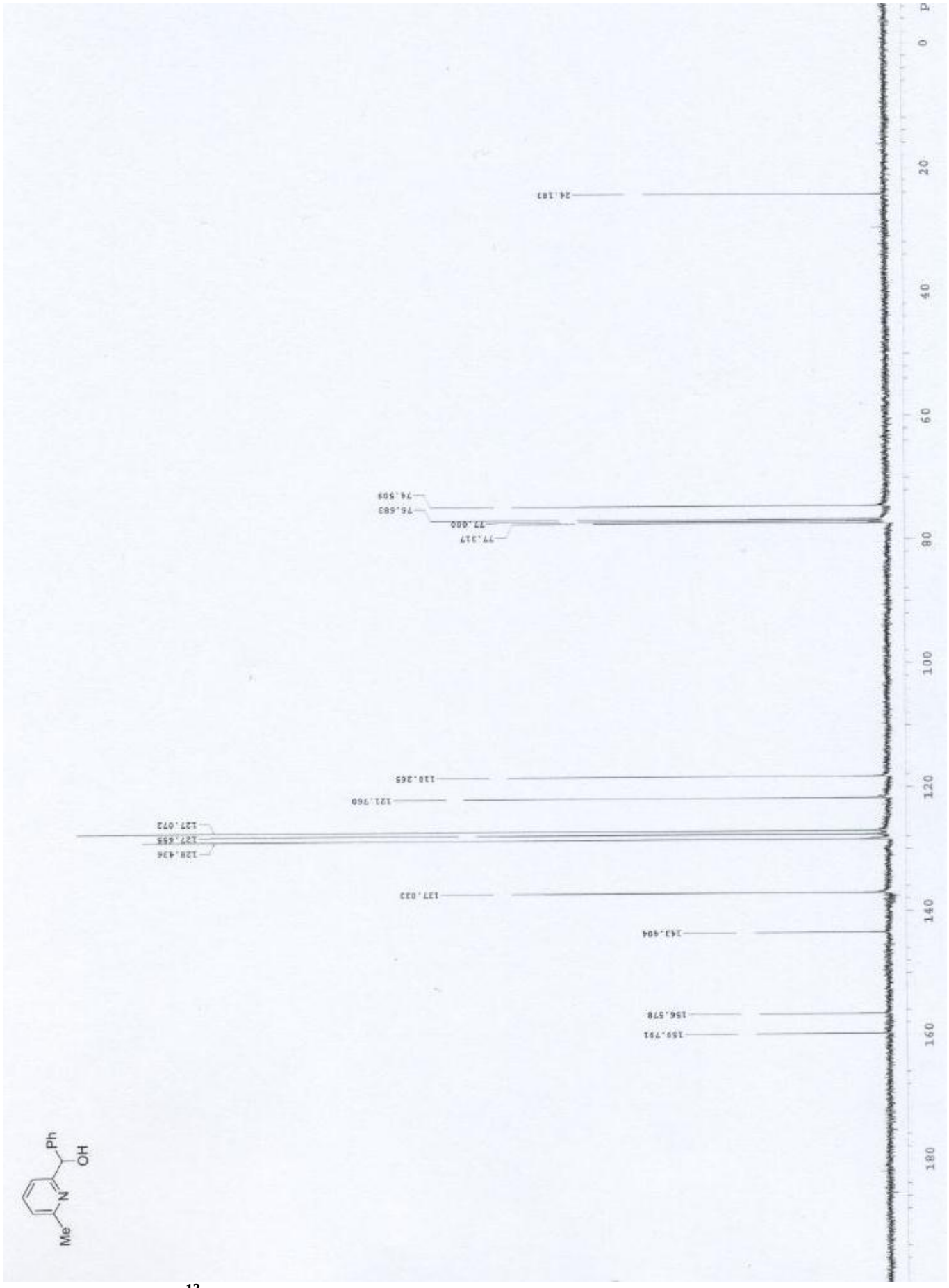
^{1}H NMR spectrum of 2-(α-hydroxybenzyl)-5-trimethylsilylpyridine



^{13}C NMR spectrum of 2-(α-hydroxybenzyl)-5-trimethylsilylpyridine



^{1}H NMR spectrum of 2-(α-hydroxybenzyl)-6-methylpyridine



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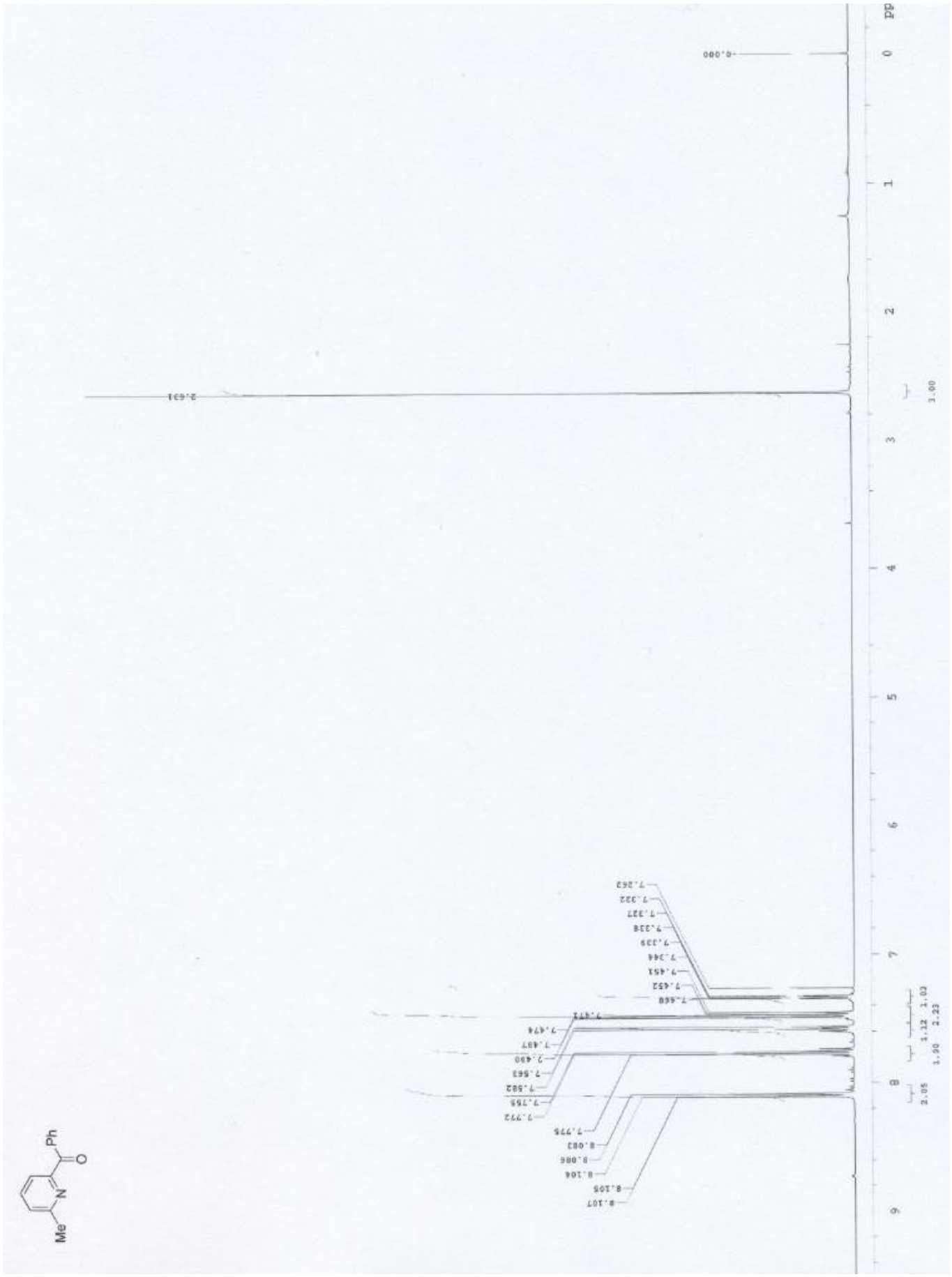

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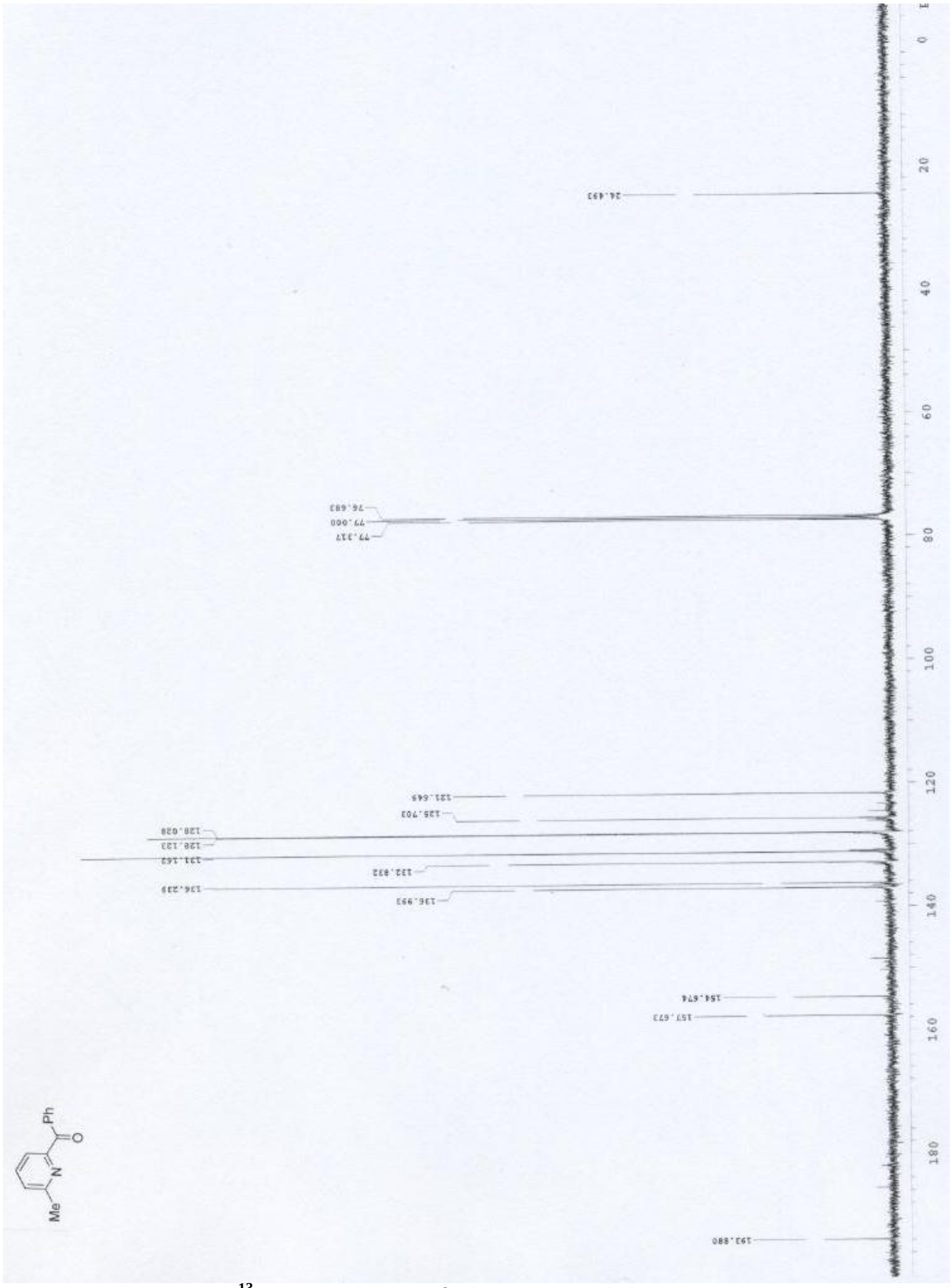
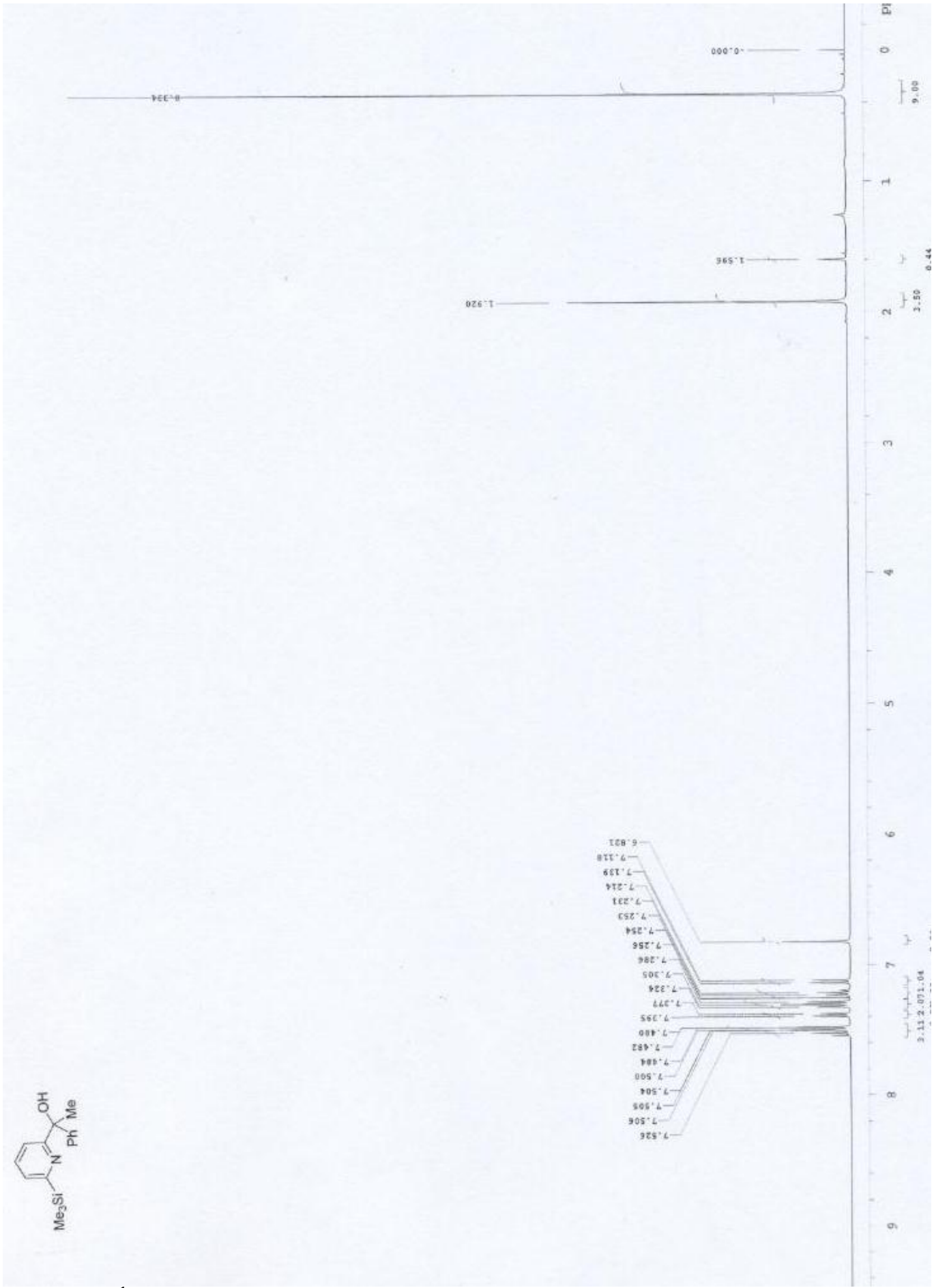
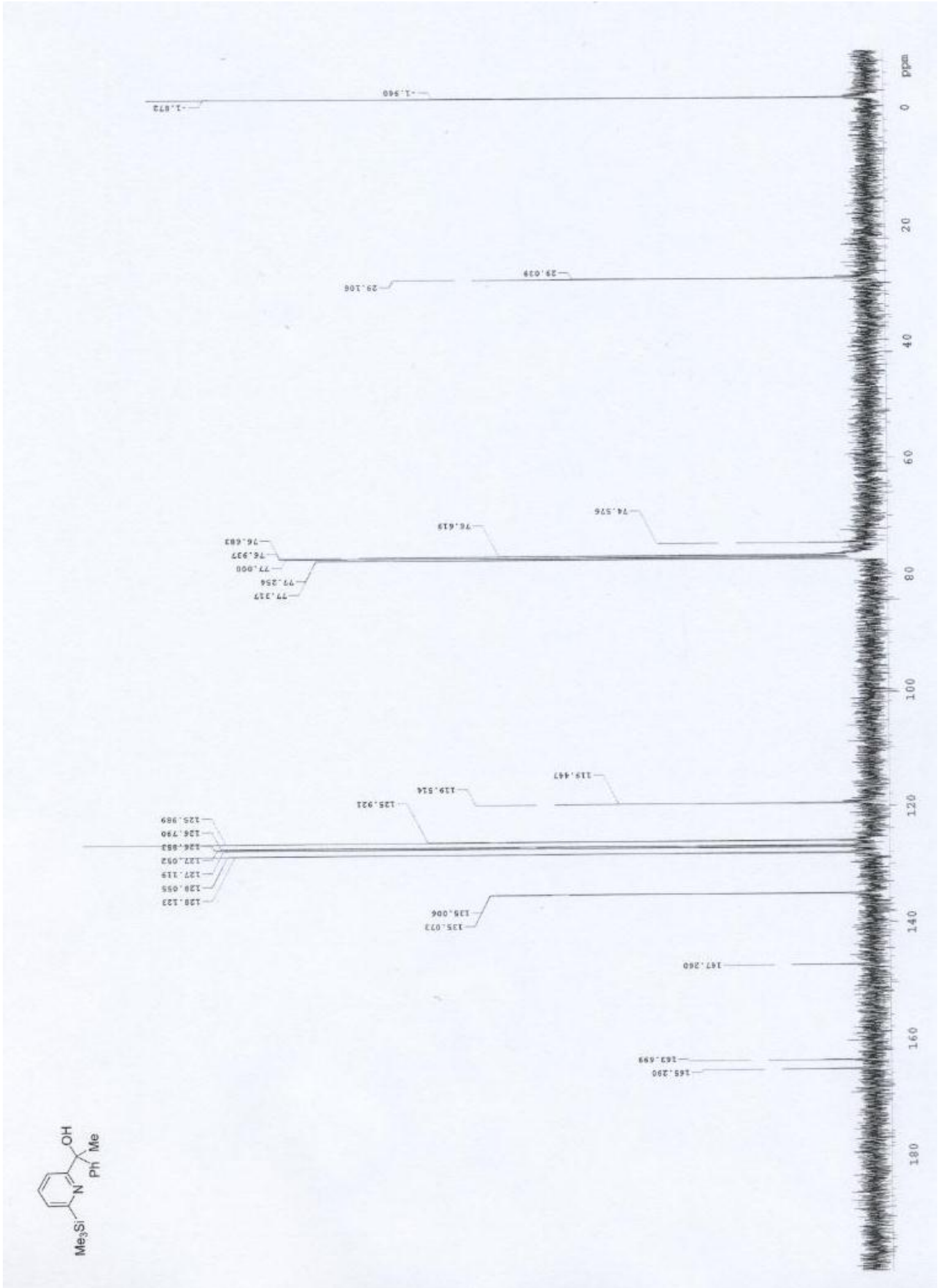


^{13}C NMR spectrum of 2-benzoyl-6-methylpyridine



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



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