

Supporting Information

Manganese-Catalyzed Directed Methylation of C(sp²)–H Bonds at 25 °C with High Catalytic Turnover

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1. Materials and Methods

General. All reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under an atmosphere of nitrogen. Gas-liquid chromatographic (GC) analysis was performed on a Shimadzu GC-2025 machine equipped with glass capillary column HR-1 (0.25-mm i.d. \times 25 m). Flash silica gel column chromatography was performed on silica gel 60N (Kanto, spherical and neutral, 140–325 mesh) as described by Still.¹ Gel permeation column chromatography was performed on a Japan Analytical Industry LC-92XX II (eluent: chloroform) with JAIGEL 1H and 2H polystyrene columns. Melting points were determined by MEL-TEMP II. IR spectra were recorded on JACSO FT/IR-6100 equipped with an attenuated total reflection (ATR) and are reported as wavenumber (ν) cm^{-1} . NMR spectra were measured on JEOL ECZ-500 spectrometer and reported in parts per million from tetramethylsilane or DMSO. ¹H NMR spectra in CDCl_3 or DMSO were referenced internally to tetramethylsilane (0.0 ppm) or DMSO (2.49 ppm) as a standard, respectively. ¹³C NMR spectra in CDCl_3 or DMSO were referenced to CDCl_3 (77.0 ppm) or DMSO (39.5 ppm) as a standard, respectively. ¹⁹F NMR spectra were referenced to C_6F_6 (−164.9 ppm) as a standard. Mass spectra (GC MS) are taken at SHIMADZU Parvum 2 gas chromatograph mass spectrometer. High resolution mass spectra were acquired by atmospheric pressure ionization (APCI) using a time-of-flight mass analyzer on Bruker micrOTF II with a calibration standard of polyethylene glycol (MW 600) or JEOL JMS-T100LC (AccuTOF) spectrometer with a calibration standard of Reserpine (MW 609).

Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and used without further purification. Anhydrous ethereal solvents (stabilizer-free) were purchased from WAKO Pure Chemical and purified by a solvent purification system (GlassContour)² equipped with columns of activated alumina and supported copper catalyst (Q-5) prior to use. The water content was determined with a Karl-Fischer moisture titrator (MKC-210, Kyoto Electronics Company) to be less than 30 ppm. Manganese(II) chloride (99.99%) was purchased from Alfa Aesar. Manganese ate complex ($\text{MnCl}_2 \bullet 2\text{LiCl}$) was prepared from

manganese(II) chloride and anhydrous lithium chloride in THF.³ Methylmagnesium bromide in THF was purchased from TCI and titrated prior to use.

2. Preparation of Substrates

The following compounds were prepared according to the literature procedures. The spectral data showed good agreement with the literature data.

N,3-dimethylbenzamide⁴

N-methyl-3-(trifluoromethyl)benzamide⁴

3-fluoro-*N*-methylbenzamide⁴

3-bromo-*N*-methylbenzamide⁵

3-methoxy-*N*-methylbenzamide⁶

N-methyl-1-naphthamide⁴

N-methyl-2-thiophenecarboxamide⁶

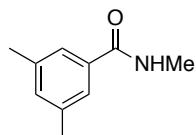
N,1-dimethyl-1*H*-indole-2-carboxamide⁶

N-(1-naphthyl)picolinamide⁷

N-methyl-1-cyclohexene-1-carboxamide⁸

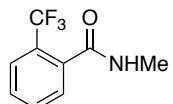
N-methyl-2,3,4,5,6-pentadeueriobenzamide⁴

N,3,5-Trimethylbenzamide:



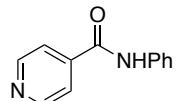
To a solution of 3,5-dimethylbenzoyl chloride (0.74 mL, 5.0 mmol) and MeNH₂•HCl (0.51 g, 7.5 mmol) in THF (10 mL) was added Et₃N (2.8 mL, 20 mmol). The mixture was stirred at 25 °C overnight, diluted with EtOAc (20 mL) and washed with H₂O (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by recrystallization from CH₂Cl₂/hexane to afford the desired product as white needles (0.50 g, 61%). Melting Point: 80-81 °C (CH₂Cl₂/hexane); IR (ATR): 3297, 3001, 2952, 2924, 2857, 1637, 1601, 1541, 1457, 1396, 1328 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.36 (s, 2H), 7.12 (s, 1H), 6.10 (br, 1H), 3.00 (d, *J* = 4.8 Hz, 3H), 2.35 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 168.6, 138.1, 134.6, 132.9, 124.6, 26.7, 21.2; HRMS (APCI) Calcd for C₁₀H₁₄NO⁺ [M + H]⁺ 164.1075, found, 164.1072.

***N*-Methyl-2-(trifluoromethyl)benzamide:**



To a solution of 2-(trifluoromethyl)benzoyl chloride (1.5 mL, 10 mmol) and MeNH₂•HCl (1.0 g, 15 mmol) in CH₂Cl₂ (15 mL) was added Et₃N (5.6 mL, 40 mmol). The mixture was stirred at 25 °C for 30 min, diluted with CH₂Cl₂ (30 mL) and washed with H₂O (3 × 15 mL). The organic layer was dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by recrystallization from CH₂Cl₂/hexane to afford the desired product as white needles (1.1 g, 53%). Melting Point: 114-115 °C (CH₂Cl₂/hexane); IR (ATR): 3284, 3083, 1636, 1558, 1315, 1138, 775 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.57–7.47 (m, 3H), 6.03 (s, 1H), 2.96–2.95 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 135.8 (q, *J*_{C-F} = 1.8 Hz), 131.9, 129.7, 128.5, 127.1 (q, *J*_{C-F} = 31.8 Hz), 126.2 (q, *J*_{C-F} = 5.4 Hz), 123.5 (q, *J*_{C-F} = 271.8 Hz), 26.8; ¹⁹F NMR (470 MHz, CDCl₃) δ -62.3; HRMS (APCI) Calcd for C₉H₉F₃NO⁺ [M + H]⁺ 204.0636, found, 204.0632.

***N*-Phenyl-4-pyridinecarboxamide:**



To a solution of isonicotinoyl chloride hydrochloride (1.8 g, 10 mmol) and aniline (1.0 mL, 11 mmol) in THF (30 mL) was added Et₃N (4.2 mL, 30 mmol). The mixture was stirred at 25 °C overnight, diluted with EtOAc (20 mL) and washed with H₂O (3 × 15 mL). The organic layer was dried over anhydrous Na₂SO₄. The solvent was evaporated and the crude product was purified by recrystallization from CH₂Cl₂/hexane to afford the desired product as a white granular solid (1.3 g, 60%). Melting Point: 169-170 °C (CH₂Cl₂/hexane); IR (ATR): 3337, 2989, 2955, 1653, 1600, 1542, 746, 687 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.77 (dd, *J* = 4.6, 1.4 Hz, 2H), 8.06 (br, 1H), 7.70 (d, *J* = 6.0 Hz, 2H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 163.8, 150.7, 142.1, 137.2, 129.2, 125.3, 120.9, 120.4; HRMS (APCI) Calcd for C₁₂H₁₁N₂O⁺ [M + H]⁺ 199.0871, found, 199.0876.

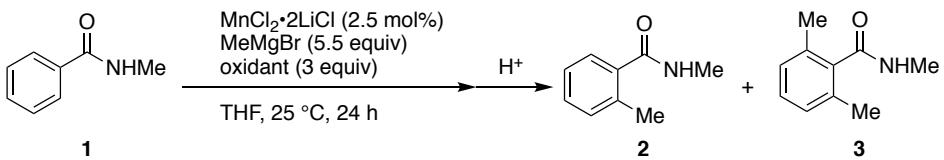
3. Investigation of the Key Reaction Parameters

3.1. Investigation of manganese catalyst

entry	[Mn]	GC yield (%)		
		2	3	1
1	$\text{MnCl}_2 \cdot 2\text{LiCl}$	<5	77	<5
2	MnCl_2	<5	74	<5
3	MnBr_2	<5	73	<5
4	$\text{Mn}(\text{acac})_2$	<5	70	<5
5	$\text{Mn}(\text{acac})_3$	<5	79	<5
6	$\text{Mn}(\text{OAc})_2$	<5	77	<5
7	$\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$	<5	78	<5
8	MnF_2	38	n.d.	60
9	MnF_3	32	n.d.	44
10	none	n.d.	n.d.	80

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and the manganese catalyst (0.010 mmol). MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol) and 1-bromo-2-chloroethane (50 μL , 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH₄Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

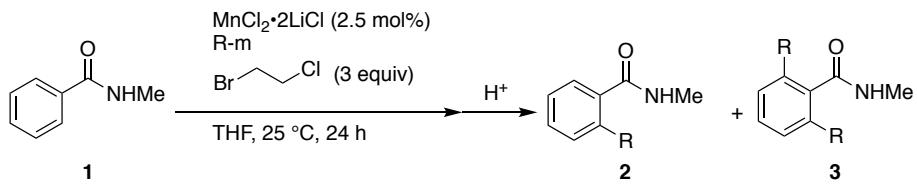
3.2. Investigation of oxidant



entry	oxidant	GC yield (%)		
		2	3	1
1		<5	86	<5
2		n.d.	n.d.	85
3		n.d.	n.d.	91
4		n.d.	n.d.	80
5		19	26	<5
6		15	25	<5
7		32	18	<5
8	none	n.d.	n.d.	82

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and a solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (50 μL , 0.10 M, 0.0050 mmol). MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol) and 1-bromo-2-chloroethane (50 μL , 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

3.3. Investigation of organometallic reagent



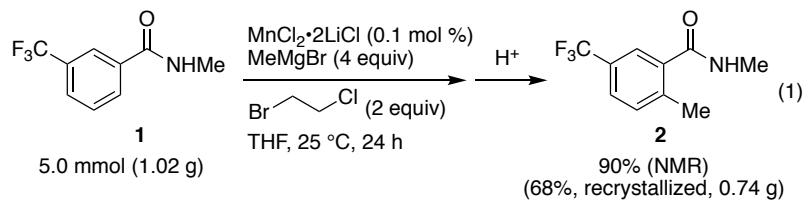
entry	R-m	GC yield (%)			others
		2	3	1	
1	MeMgBr (5.5 equiv)	<5	86	<5	
2	MeMgBr (5.5 equiv) + ZnCl ₂ •TMEDA (4.5 equiv) ^a	n.d.	n.d.	96	
3	MeMgBr (10 equiv) + ZnCl ₂ •TMEDA (4.5 equiv) ^a	n.d.	n.d.	91	
4	MeLi (5.5 equiv)	8	n.d.	58	
5	OctylMgBr (5.5 equiv)	n.d.	n.d.	64	octene (173%), octane (276%)
6	PhMgBr (5.5 equiv)	n.d.	n.d.	64	Ph-Ph (280%)

^aTMEDA = *N,N,N',N'*-tetramethylethylenediamine.

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and the organometallic reagent was added. The solvent was removed in *vacuo*, and then THF (1.1 mL) was added if necessary. A solution of **MnCl₂•2LiCl** in THF (50 μ L, 0.10 M, 0.0050 mmol) and 1-bromo-2-chloroethane (50 μ L, 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH₄Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

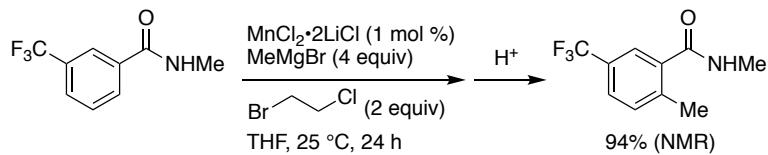
4. Manganese-Catalyzed Directed Methylation of *N*-Methyl-3-(trifluoromethyl)benzamide

Reaction on gram scale (eq 1):



In a 100 mL oven-dried two-necked round bottom flask were placed *N*-methyl-3-(trifluoromethyl)benzamide (1.02 g, 5.0 mmol) and MeMgBr in THF (20 mL, 1.00 M, 20 mmol) was added at 0 °C. A solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (10 μL , 0.50 M, 0.0050 mmol) and 1-bromo-2-chloroethane (0.83 mL, 10 mmol) were sequentially added at 25 °C. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL) and a small amount of water. After extraction with ethyl acetate (3×50 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 90%, recovery: 10%). The crude product was purified by recrystallization from CH_2Cl_2 /hexane to afford the desired product as a white solid (0.74 g, 68%).

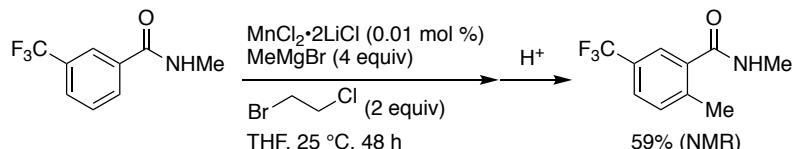
Reaction with 1 mol % of catalyst:



In an oven-dried Schlenk tube were placed *N*-methyl-3-(trifluoromethyl)benzamide (41 mg, 0.20 mmol) and a solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (20 μL , 0.10 M, 0.0020 mmol). MeMgBr in THF (0.80 mL, 1.00 M, 0.80 mmol) and 1-bromo-2-chloroethane (33 μL , 0.40 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. After extraction with ethyl acetate (3×3 mL), the

combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 94%, recovery: 6%).

Reaction with 0.01 mol % of catalyst:



In an oven-dried Schlenk tube were placed *N*-Methyl-3-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) and a solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (5.0 μL , 0.10 M, 0.00050 mmol). MeMgBr in THF (2.00 mL, 1.00 M, 2.00 mmol) and 1-bromo-2-chloroethane (83 μL , 1.0 mmol) were sequentially added. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 48 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with ethyl acetate (3×5 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 59%, recovery: 41%).

5. Stoichiometric Reaction (eq 2)

In an oven-dried Schlenk tube were placed *N*-methyl-3-(trifluoromethyl)benzamide (41 mg, 0.20 mmol) and a manganese salt (0.20 mmol). MeMgBr in THF (0.84 mL, 0.95 M, 0.80 mmol) was added. 1-Bromo-2-chloroethane (33 μL , 0.40 mmol) was added if necessary. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 30 min, and then it was quenched by the addition of D_2O (1 mL). After extraction with ethyl acetate (3×3 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. Deuterium was not incorporated in all cases.

6. General Procedure of Manganese-Catalyzed Directed Methylation

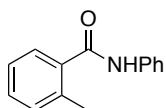
General Procedure A (Table 1):

In an oven-dried Schlenk tube were placed the substrate (0.50 mmol) and a solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (50 μL , 0.10 M, 0.0050 mmol). MeMgBr in THF (2.00 mL, 1.00 M, 2.00 mmol) and 1-bromo-2-chloroethane (83 μL , 1.0 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with ethyl acetate (3×5 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by gel permeation column chromatography (eluent: CHCl_3) to afford the desired product.

General Procedure B (Table 2):

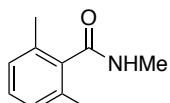
In an oven-dried Schlenk tube were placed the substrate (0.50 mmol) and a solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (50 μL , 0.50 M, 0.025 mmol). MeMgBr in THF (2.25 mL, 1.00 M, 2.25 mmol) and 1-bromo-2-chloroethane (124 μL , 1.50 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 48 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with ethyl acetate (3×5 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by gel permeation column chromatography (eluent: CHCl_3) to afford the desired product.

2-Methyl-*N*-phenylbenzamide (Table 1, entry 1):



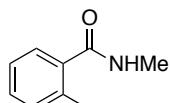
The general procedure A was applied to *N*-phenylbenzamide (99 mg, 0.50 mmol) for 48 h. The title compound was obtained (104 mg, 98%) (¹H NMR yield: 99%). The analytically pure product was obtained after a short pass over a silica gel column. The title compound was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 126-127 °C (CH₂Cl₂/hexane); ¹H NMR (500 MHz, CDCl₃): δ 7.78 (br, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.33-7.30 (m, 3H), 7.21-7.16 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.2, 138.0, 136.3, 136.2, 131.1, 130.1, 128.9, 126.6, 125.7, 124.4, 119.9, 19.7; HRMS (APCI) Calcd for C₁₄H₁₄NO⁺ [M + H]⁺ 212.1070, found, 212.1072. The compound data was in good agreement with the literature data.⁹

N,2,6-Trimethylbenzamide (Table 1, entry 2):



The general procedure A was applied to *N*-methylbenzamide (68 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL, 1.50 mmol) for 48 h. The title compound was obtained (62 mg, 83%) (¹H NMR yield: 89%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 146-147 °C (CH₂Cl₂/hexane); ¹H NMR (500 MHz, CDCl₃): δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 2H), 5.81 (br, 1H), 2.97 (d, *J* = 5.0 Hz, 3H), 2.28 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 171.1, 137.6, 134.1, 128.6, 127.3, 26.2, 19.1; HRMS (APCI) Calcd for C₁₀H₁₄NO⁺ [M + H]⁺ 164.1070, found, 164.1077. The compound data was in good agreement with the literature data.¹⁰

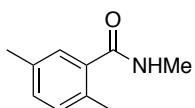
N,2-Dimethylbenzamide (Table 1, entry 3):



The general procedure A was applied to *N*-methylbenzamide (68 mg, 0.50 mmol) using MeMgBr in THF (1.55 mL, 1.00 M, 1.55 mmol). The title compound was obtained (45 mg, 60%) (¹H NMR yield: 69%). A dimethylated product was also obtained (11 mg, 13%) (¹H NMR yield: 16%). The title compound was further purified by

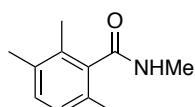
recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 63-64 °C (CH_2Cl_2 /hexane); ^1H NMR (500 MHz, CDCl_3): δ 7.28–7.25 (m, 2H), 7.18–7.12 (m, 2H), 6.14 (br, 1H), 2.91 (dd, J = 5.1, 1.4 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.8, 136.4, 135.8, 130.8, 129.6, 126.6, 125.5, 26.4, 19.6; HRMS (APCI) Calcd for $\text{C}_9\text{H}_{12}\text{NO}^+$ $[\text{M} + \text{H}]^+$ 150.0913, found, 150.0918. The compound data was in good agreement with the literature data.⁶

N,2,5-Trimethylbenzamide (Table 1, entry 4):



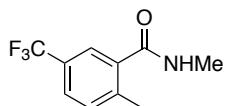
The general procedure A was applied to *N*,3-dimethylbenzamide (75 mg, 0.50 mmol). The title compound was obtained (56 mg, 69%) (^1H NMR yield: 81%). Dimethylated product was also obtained (5.3 mg, 6%) (^1H NMR yield: 9%). The title compound was further purified by recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 122-123 °C (CH_2Cl_2 /hexane); ^1H NMR (500 MHz, CDCl_3): δ 7.11 (s, 1H), 7.09–7.05 (m, 2H), 6.05 (s, 1H), 2.92 (dd, J = 4.8, 1.1 Hz, 3H), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 136.2, 135.0, 132.6, 130.7, 130.3, 127.4, 26.4, 20.7, 19.1; HRMS (APCI) Calcd for $\text{C}_{10}\text{H}_{14}\text{NO}^+$ $[\text{M} + \text{H}]^+$ 164.1070, found, 164.1077. The compound data was in good agreement with the literature data.¹⁰

N,2,3,6-Tetramethylbenzamide (Table 1, entry 4):



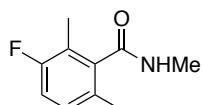
The title compound was further purified by recrystallization from CH_2Cl_2 /hexane as a white amorphous solid. Melting Point: 139-140 °C (CH_2Cl_2 /hexane); IR (ATR): 3254, 3086, 2924, 2852, 1634, 1568, 1559, 1508, 1457, 1316, 816 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.04 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 5.65 (br, 1H), 3.01 (d, J = 4.9 Hz, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.7, 137.9, 134.3, 132.5, 131.6, 130.0, 127.3, 26.4, 19.8, 19.0, 16.4; HRMS (APCI) Calcd for $\text{C}_{11}\text{H}_{16}\text{NO}^+$ $[\text{M} + \text{H}]^+$ 178.1232, found, 178.1225.

***N*,2-Dimethyl-5-(trifluoromethyl)benzamide (Table 1, entry 5):**



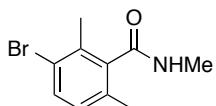
The general procedure A was applied to *N*-methyl-3-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) using $\text{MnCl}_2 \bullet 2\text{LiCl}$ in THF (5.0 μL , 0.10 M, 0.00050 mmol). The title compound was obtained (82 mg, 75%) (^1H NMR yield: 90%). The product was further purified by recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 122-123 °C (CH_2Cl_2 /hexane); IR (ATR): 3292, 3095, 2925, 2875, 1643, 1556, 1541, 1408, 1342, 1111, 712 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.52–7.50 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 6.46 (br, 1H), 2.91 (d, J = 4.9 Hz, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.4, 140.2, 136.9, 131.3, 128.0 (q, $J_{\text{C-F}} = 32.4$ Hz), 126.2 (q, $J_{\text{C-F}} = 4.2$ Hz), 123.8 (q, $J_{\text{C-F}} = 270.0$ Hz), 123.6 (q, $J_{\text{C-F}} = 3.6$ Hz), 26.5, 19.6; ^{19}F NMR (470 MHz, CDCl_3) δ -65.7; HRMS (APCI) Calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{NO}^+ [\text{M} + \text{H}]^+$ 218.0793, found, 218.0793.

3-Fluoro-*N*,2,6-trimethylbenzamide (Table 1, entry 6):



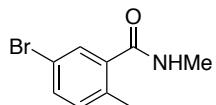
The general procedure A was applied to 3-fluoro-*N*-methylbenzamide (77 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL , 1.50 mmol) for 48 h. The title compound was obtained (66 mg, 73%) (^1H NMR yield: 79%). The product was further purified by recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 133-134 °C (CH_2Cl_2 /hexane); IR (ATR): 3280, 2989, 2957, 1652, 1636, 1558, 1542, 1409, 1320, 1242, 820 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 6.94–6.86 (m, 2H), 6.04 (br, 1H), 2.94 (d, J = 4.9 Hz, 3H), 2.20 (s, 3H), 2.14 (d, J = 2.3 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.8 (d, $J_{\text{C-F}} = 3.0$ Hz), 159.2 (d, $J_{\text{C-F}} = 241.8$ Hz), 139.2 (d, $J_{\text{C-F}} = 3.6$ Hz), 129.5 (d, $J_{\text{C-F}} = 4.2$ Hz), 128.5 (d, $J_{\text{C-F}} = 7.8$ Hz), 121.3 (d, $J_{\text{C-F}} = 18.0$ Hz), 115.1 (d, $J_{\text{C-F}} = 22.2$ Hz), 26.2, 18.5, 11.4; ^{19}F NMR (470 MHz, CDCl_3) δ -123.3; HRMS (APCI) Calcd for $\text{C}_{10}\text{H}_{13}\text{FNO}^+ [\text{M} + \text{H}]^+$ 182.0981, found, 182.0973.

3-Bromo-*N*,2,6-trimethylbenzamide (Table 1, entry 7):



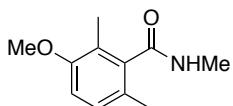
The general procedure A was applied to 3-bromo-*N*-methylbenzamide (107 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μ L, 1.50 mmol) for 48 h. The title compound was obtained (77 mg, 64%) (1 H NMR yield: 70%). Monomethylated product was also obtained (19 mg, 16%) (1 H NMR yield: 21%). The title compound was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 174-175 °C (CH₂Cl₂/hexane); IR (ATR): 3283, 2998, 2954, 2922, 1653, 1557, 1542, 1412, 1311, 822 cm⁻¹; 1 H NMR (500 MHz, CDCl₃): δ 7.39 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.05 (br, 1H), 2.94 (d, J = 5.1 Hz, 3H), 2.29 (s, 3H), 2.19 (s, 3H); 13 C NMR (125 MHz, CDCl₃) δ 170.1, 139.1, 133.7, 133.5, 132.5, 128.9, 122.6, 26.3, 19.9, 18.8; HRMS (APCI) Calcd for C₁₀H₁₃⁷⁹BrNO⁺ [M + H]⁺ 242.0175, found, 242.0170.

5-Bromo-*N*,2-dimethylbenzamide (Table 1, entry 7):



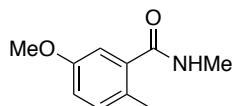
The title compound was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 139-140 °C (CH₂Cl₂/hexane); IR (ATR): 3284, 3001, 2953, 2924, 1645, 1550, 1542, 1404, 1319, 1038, 819 cm⁻¹; 1 H NMR (500 MHz, CDCl₃): δ 7.47 (d, J = 2.2 Hz, 1H), 7.41 (dd, J = 8.0, 2.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 5.81 (br, 1H), 2.98 (d, J = 4.1 Hz, 3H), 2.38 (s, 3H); 13 C NMR (125 MHz, CDCl₃) δ 169.1, 138.2, 135.1, 132.7, 132.6, 129.6, 119.1, 26.7, 19.3; HRMS (APCI) Calcd for C₉H₁₁⁷⁹BrNO⁺ [M + H]⁺ 228.0024, found, 228.0023.

3-Methoxy-*N*,2,6-trimethylbenzamide (Table 1, entry 8):



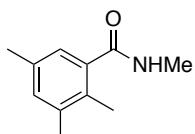
The general procedure A was applied to 3-methoxy-*N*-methylbenzamide (83 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μ L, 1.50 mmol) for 48 h. After purification, a mixture of di- and monomethylated product was obtained (78 mg; di-: 48%, mono-: 37%). The title compound was isolated after further purification by using gel permeation column chromatography (1 H NMR yield: 49%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 133-134 °C (CH₂Cl₂/hexane); IR (ATR): 3245, 2955, 2924, 2838, 1635, 1588, 1558, 1457, 1403, 1316, 1099, 811 cm⁻¹; 1 H NMR (500 MHz, CDCl₃): δ 6.98 (d, *J* = 8.3 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.63 (br, 1H), 3.80 (s, 3H), 3.01 (d, *J* = 4.8 Hz, 3H), 2.24 (s, 3H), 2.16 (s, 3H); 13 C NMR (125 MHz, CDCl₃) δ 170.9, 155.7, 138.8, 128.0, 125.8, 123.0, 110.5, 55.6, 26.4, 18.4, 12.8; HRMS (APCI) Calcd for C₁₁H₁₆NO₂⁺ [M + H]⁺ 194.1181, found, 194.1181.

5-Methoxy-*N*,2-dimethylbenzamide (Table 1, entry 8):



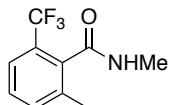
The title compound was isolated after further purification by using gel permeation column chromatography as a white amorphous solid (1 H NMR yield: 37%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 99-100 °C (CH₂Cl₂/hexane); IR (ATR): 3274, 2958, 2922, 2835, 1636, 1596, 1557, 1457, 1397, 1317, 1033, 824 cm⁻¹; 1 H NMR (500 MHz, CDCl₃): δ 7.08 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.05 (br, 1H), 3.76 (s, 3H), 2.93 (d, *J* = 4.8 Hz, 3H), 2.31 (s, 3H); 13 C NMR (125 MHz, CDCl₃) δ 170.5, 157.3, 137.2, 131.8, 127.4, 115.3, 112.1, 55.3, 26.5, 18.7; HRMS (APCI) Calcd for C₁₀H₁₄NO₂⁺ [M + H]⁺ 180.1025, found, 180.1018.

***N*,2,3,5-Tetramethylbenzamide (Table 1, entry 9):**



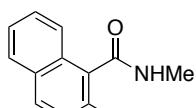
The general procedure A was applied to *N*,3,5-trimethylbenzamide (82 mg, 0.50 mmol). The title compound was obtained (74 mg, 84%) (¹H NMR yield: 90%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 142-143 °C (CH₂Cl₂/hexane); IR (ATR): 3307, 3010, 2950, 2924, 2857, 1635, 1604, 1541, 1457, 1324 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.98 (s, 1H), 6.93 (s, 1H), 5.97 (br, 1H), 2.92 (d, *J* = 4.8 Hz, 3H), 2.25-2.21 (m, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 171.7, 137.5, 137.2, 134.7, 131.7, 130.6, 124.7, 26.4, 20.6, 20.0, 15.7; HRMS (APCI) Calcd for C₁₁H₁₆NO⁺ [M + H]⁺ 178.1232, found, 178.1225.

***N*,6-Dimethyl-2-(trifluoromethyl)benzamide (Table 1, entry 10):**



The general procedure A was applied to *N*-methyl-2-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) for 48 h. The title compound was obtained in (87 mg, 81%) (¹H NMR yield: 92%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 148-149 °C (CH₂Cl₂/hexane); IR (ATR): 3272, 3090, 2918, 2858, 1646, 1557, 1542, 1318, 1116, 801 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.45-7.42 (m, 1H), 7.36-7.34 (m, 1H), 6.13 (s, 1H), 2.93 (d, *J* = 5.1 Hz, 3H), 2.30 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 168.1, 136.5, 135.2 (d, *J*_{C-F} = 2.4 Hz), 133.7, 128.8, 126.9 (q, *J*_{C-F} = 30.6 Hz), 123.7 (q, *J*_{C-F} = 272.4 Hz), 123.3 (q, *J*_{C-F} = 10.2 Hz), 26.4, 18.9; ¹⁹F NMR (470 MHz, CDCl₃) δ -62.4; HRMS (APCI) Calcd for C₁₀H₁₁F₃NO⁺ [M + H]⁺ 218.0793, found, 218.0797.

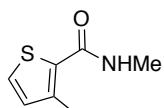
***N*,2-Dimethyl-1-naphthalenecarboxamide (Table 1, entry 11):**



The general procedure A was applied to *N*-methyl-1-naphthalenecarboxamide (93 mg, 0.50 mmol). The title compound was obtained (78 mg, 78%) (¹H NMR yield: 89%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 188-189 °C (CH₂Cl₂/hexane); ¹H NMR (500 MHz, CDCl₃):

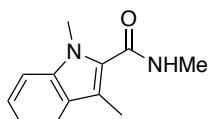
δ 7.75 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 9.1 Hz, 2H), 7.44–7.38 (m, 2H), 7.21 (d, J = 8.3 Hz, 1H), 6.07 (br, 1H), 2.95 (d, J = 4.8 Hz, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.5, 133.8, 131.9, 131.5, 130.0, 128.6, 128.2, 127.8, 126.6, 125.2, 124.4, 26.3, 19.4; HRMS (APCI) Calcd for $\text{C}_{13}\text{H}_{14}\text{NO}^+$ $[\text{M} + \text{H}]^+$ 200.1070, found, 200.1072. The compound data was in good agreement with the literature data.¹¹

N,3-Dimethyl-2-thiophenecarboxamide (Table 1, entry 12):



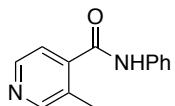
The general procedure A was applied to *N*-methyl-2-thiophenecarboxamide (71 mg, 0.50 mmol). The title compound was obtained (46 mg, 60%) as a yellow oil (^1H NMR yield: 68%). IR (ATR): 3307, 3102, 2935, 1626, 1543, 1518, 1408, 1287 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.24 (d, J = 5.1 Hz, 1H), 6.87 (d, J = 4.9 Hz, 1H), 6.02 (br, 1H), 2.95 (d, J = 4.8 Hz, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.8, 140.7, 131.8, 130.9, 126.1, 26.6, 15.5; HRMS (APCI) Calcd for $\text{C}_7\text{H}_{10}\text{NOS}^+$ $[\text{M} + \text{H}]^+$ 156.0478, found, 156.0484.

N,1,3-Trimethyl-1*H*-indole-2-carboxamide (Table 1, entry 13):



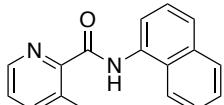
The general procedure A was applied to *N*,1-dimethyl-1*H*-indole-2-carboxamide (93 mg, 0.50 mmol). The title compound was obtained (61 mg, 61%) (^1H NMR yield: 70%). The product was further purified by recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 188–189 °C (CH_2Cl_2 /hexane); IR (ATR): 3306, 3003, 2924, 2853, 1608, 1541, 1457, 1360, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.55 (d, J = 8.0 Hz, 1H), 7.31–7.26 (m, 2H), 7.14–7.10 (m, 1H), 5.97 (br, 1H), 3.81 (s, 3H), 3.02 (d, J = 4.8 Hz, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.7, 137.7, 130.3, 127.1, 123.8, 119.8, 119.4, 111.6, 109.7, 31.1, 26.4, 10.0; HRMS (APCI) Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}^+$ $[\text{M}]^+$ 202.1101, found, 202.1110.

3-Methyl-*N*-phenyl-4-pyridinecarboxamide (Table 1, entry 14):



The general procedure A was applied to *N*-phenyl-4-pyridinecarboxamide (99 mg, 0.50 mmol). The title compound was obtained (84 mg, 79%) (¹H NMR yield: 89%). The product was further purified by recrystallization from CH₂Cl₂/hexane as yellow needles. Melting Point: 108-109 °C (CH₂Cl₂/hexane); IR (ATR): 3293, 2989, 2955, 1654, 1558, 1542, 1406, 1321, 747, 689 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ 10.5 (br, 1H), 8.56 (br, 2H), 7.71 (d, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 4.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.1 Hz, 1H), 2.35 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.7, 151.9, 147.4, 143.3, 137.5, 130.7, 129.2, 125.1, 120.4, 120.1, 16.5; HRMS (APCI) Calcd for C₁₃H₁₃N₂O⁺ [M + H]⁺ 213.1028, found, 213.1031.

3-Methyl-*N*-(naphthalen-1-yl)picolinamide (Table 1, entry 15):



In an oven-dried Schlenk tube were placed *N*-(1-naphthyl)picolinamide (50 mg, 0.20 mmol) and a solution of MnCl₂•2LiCl in THF (40 μL, 0.50 M, 0.020 mmol). MeMgBr in THF (0.77 mL, 1.04 M, 0.80 mmol) and 1-bromo-2-chloroethane (33 μL, 0.4 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH₄Cl (1 mL) and small amount of water. After extraction with ethyl acetate (3 × 3 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford the title compound (49 mg, 92%). The product was further purified by recrystallization from CH₂Cl₂/hexane as white needles. Melting Point: 143-144 °C (CH₂Cl₂/hexane); IR (ATR): 3328, 3011, 2924, 2853, 1688, 1525, 1497, 1340, 792, 772 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 11.0 (br, 1H), 8.56 (dd, *J* = 4.3, 0.8 Hz, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.70–7.69 (m, 2H), 7.60–7.51 (m,

3H), 7.42 (dd, J = 7.7, 4.6 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.8, 147.0, 145.5, 141.4, 136.3, 134.1, 132.7, 128.8, 126.6, 126.1 (2C), 126.0, 125.9, 124.8, 120.7, 118.6, 20.9; HRMS (APCI) Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}^+$ $[\text{M} + \text{H}]^+$ 263.1184, found, 263.1186.

• **X-ray crystallographic analysis**

The diffraction images for X-ray crystallographic analysis were collected on a Rigaku Rapid II diffractometer equipped with an imaging plate (IP) using $\text{Cu K}\alpha$ (λ = 1.5419 Å) radiation. The positional and thermal parameters were refined by the full-matrix least-squares method using SHELXL-2014/7 program.¹² The Yadokari-XG software was used for refinement of the structure.¹³

CCDC 1560075 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

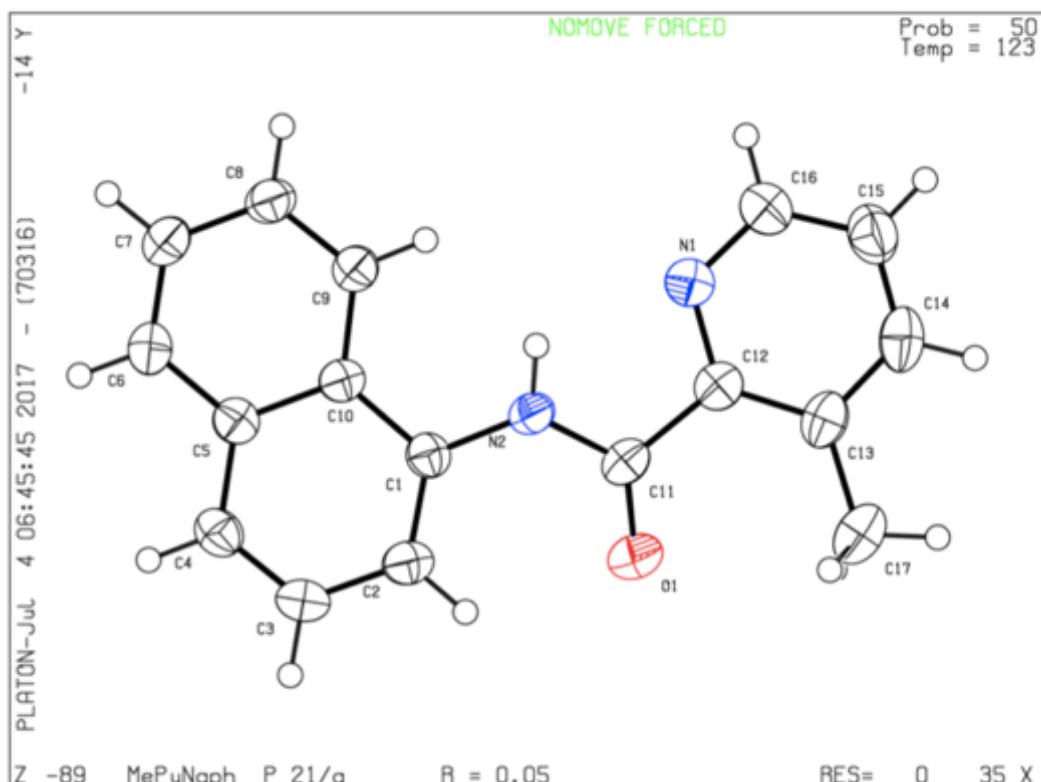
Crystal data for X (CCDC 1560075)

Formula	$\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$
Formula weight	262.30
Measurement temperature	123(2) K
Crystal system	monoclinic
Space group	P 21/a
Lattice parameters	a = 14.4154(6) Å b = 6.0240(2) Å c = 15.0935(6) Å α = 90° β = 94.616(7)° γ = 90°
Volume	1306.44(9) Å ³
Z value	4
Density (calculated)	1.334 g/cm ³
$F(000)$	552.0
Number of reflections measured	13222
Number of unique reflections	2385
R_{int}	0.0514
Number of observed reflections ($I > 2\sigma(I)$)	1615

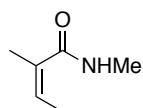
Goodness of fit indicator	1.040
Final R ₁ indices [$I > 2\sigma(I)$] (R_{obs} , wR_{obs})	0.0517, 0.1215
R indices [all data] (R_{all} , wR_{all})	0.0846, 0.1370
Largest diff peak and hole	0.171/-0.197 e·Å ⁻³

PLATON version of 27/03/2017; check.def file version of 24/03/2017

Datablock MePyNaph - ellipsoid plot

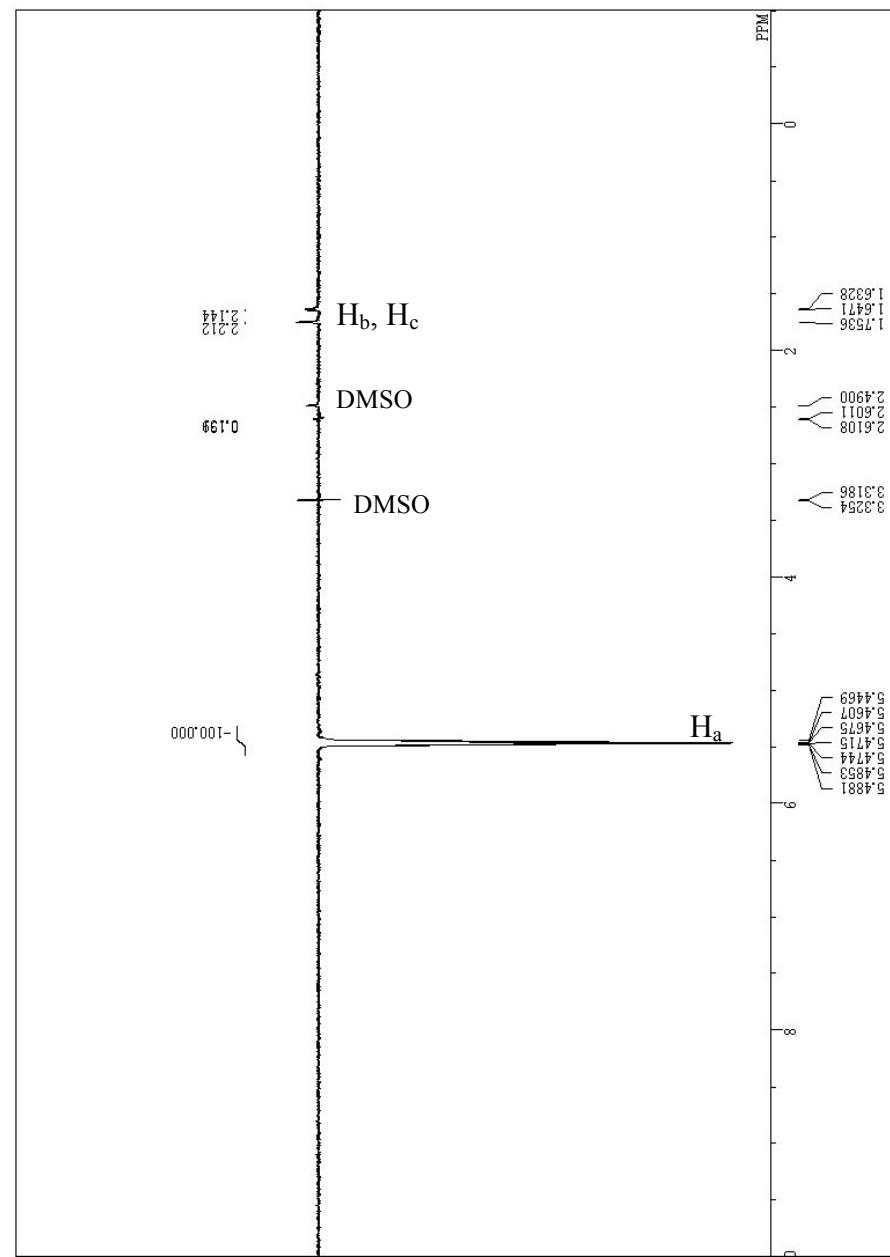
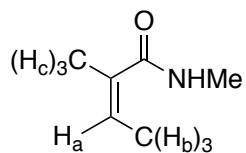


(Z)-N,2-Dimethyl-2-butenamide (Table 1, entry 16):

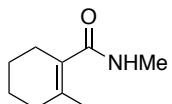


The general procedure A was applied to *N*-methylmethacrylamide (50 mg, 0.50 mmol). The title compound was obtained (37 mg, 65%) as a colorless oil (¹H NMR yield: 80%). IR (ATR): 3291, 3079, 2945, 1626, 1523, 1456, 1407, 829 cm⁻¹; ¹H NMR (500 MHz, DMSO): δ 7.65 (br, 1H), 5.47 (qd, J = 6.9, 1.4 Hz, 1H), 2.61 (dd, J = 4.5, 1.1 Hz, 3H), 1.76 (d, J = 1.4 Hz, 3H), 1.64 (d, J = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 132.7, 127.4, 25.9, 20.7, 15.0; HRMS (APCI) Calcd for C₆H₁₂NO⁺ [M + H]⁺ 114.0919,

found, 114.0915. The stereochemistry of the compound was determined by NOE experiments, using CDCl_3 as a solvent. When signal H_a at $\delta = 5.47$ (qd, $J = 6.9, 1.4$ Hz, 1H) was irradiated, the two methyl signals H_b and H_c at $\delta = 1.76$ (d, $J = 1.4$ Hz, 3H) and $\delta = 1.64$ (d, $J = 6.9$ Hz, 3H) exhibited an enhancement by 2.1% and 2.2%.

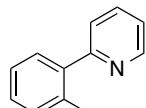


N,2-Dimethyl-1-cyclohexene-1-carboxamide (Table 1, entry 17):



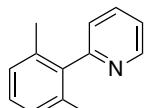
The general procedure A was applied to *N*-methyl-1-cyclohexene-1-carboxamide (70 mg, 0.50 mmol). The title compound was obtained (68 mg, 88%) (^1H NMR yield: 93%). The product was further purified by recrystallization from CH_2Cl_2 /hexane as white needles. Melting Point: 63–64 °C (CH_2Cl_2 /hexane); IR (ATR): 3299, 2929, 2856, 1616, 1522, 1473, 1457, 1397 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 5.82 (br, 1H), 2.85 (d, J = 4.8 Hz, 3H), 2.20–2.19 (m, 2H), 1.99–1.97 (br, 2H), 1.75 (s, 3H), 1.61–1.60 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.6, 134.0, 129.3, 31.1, 26.8, 25.9, 22.3, 22.1, 20.7; HRMS (APCI) Calcd for $\text{C}_9\text{H}_{16}\text{NO}^+$ [M + H] $^+$ 154.1226, found, 154.1232.

2-(2-Methylphenyl)pyridine (Table 2, entry 1):



The general procedure B was applied to 2-phenylpyridine (78 mg, 0.50 mmol). The title compound was obtained (54 mg, 64%) as a yellow oil (^1H NMR yield: 80%). A dimethylated product was also obtained (7.4 mg, 8%) as a yellow oil (^1H NMR yield: 10%). ^1H NMR (500 MHz, CDCl_3): δ 8.69 (d, J = 4.6 Hz, 1H), 7.73 (td, J = 7.2, 1.7 Hz, 1H), 7.39 (d, J = 6.8 Hz, 2H), 7.31–7.21 (m, 4H), 2.36(s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.9, 149.1, 140.3, 136.1, 135.6, 130.6, 129.5, 128.2, 125.8, 124.0, 121.5, 20.2; HRMS (APCI) Calcd for $\text{C}_{12}\text{H}_{12}\text{N}^+$ [M + H] $^+$ 170.0964, found, 170.0964. The compound data was in good agreement with the literature data.¹⁴

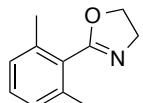
2-(2,6-Dimethylphenyl)pyridine (Table 2, entry 1):



^1H NMR (500 MHz, CDCl_3): δ 8.72 (d, J = 4.8 Hz, 1H), 7.76 (td, J = 7.7, 1.7 Hz, 1H), 7.27–7.09 (m, 3H), 7.10 (d, J = 7.7 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.9, 149.7, 140.5, 136.2, 135.7, 127.8, 127.5, 124.4, 121.6, 20.2; HRMS (APCI)

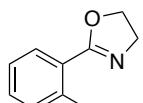
Calcd for $C_{13}H_{14}N^+ [M + H]^+$ 184.1126, found, 184.1134. The compound data was in good agreement with the literature data.¹⁴

2-(2,6-Dimethylphenyl)-4,5-dihydrooxazole (Table 2, entry 2):



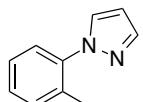
The general procedure B was applied to 2-phenyl-4,5-dihydrooxazole (74 mg, 0.50 mmol) at 40 °C. The title compound was obtained (23 mg, 26%) as a yellow oil (¹H NMR yield: 41%). A dimethylated product was also obtained (11 mg, 14%) as a yellow oil (¹H NMR yield: 19%). IR (ATR): 2965, 1660, 1465, 1349, 1239, 1047, 774 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.18 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 2H), 4.41 (t, *J* = 9.4 Hz, 2H), 4.09 (t, *J* = 9.7 Hz, 2H), 2.32 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 164.8, 136.9, 129.3, 128.9, 127.3, 67.1, 55.1, 19.7; HRMS (APCI) Calcd for C₁₁H₁₄NO⁺ [M + H]⁺ 176.1070, found, 176.1070.

2-(2-Methylphenyl)-4,5-dihydrooxazole (Table 2, entry 2):



¹H NMR (500 MHz, CDCl₃): δ 7.80 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.33 (td, *J* = 7.4, 1.1 Hz, 1H), 7.24–7.20 (m, 2H), 4.38 (t, *J* = 9.7 Hz, 2H), 4.10 (t, *J* = 9.7 Hz, 2H), 2.59 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.0, 138.7, 131.1, 130.5, 129.8, 127.1, 125.5, 66.8, 55.4, 21.7; HRMS (APCI) Calcd for C₁₀H₁₂NO⁺ [M + H]⁺ 162.0919, found, 162.0916. The compound data was in good agreement with the literature data.¹⁵

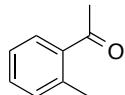
1-(2-Methylphenyl)pyrazole (Table 2, entry 3):



The general procedure B was applied to 1-phenylpyrazole (72 mg, 0.50 mmol) at 40 °C. The title compound was obtained (25 mg, 32%) as a yellow oil (¹H NMR yield: 47%). ¹H NMR (500 MHz, CDCl₃): δ 7.72 (d, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.33–

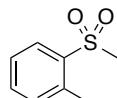
7.26 (m, 4H), 6.44 (t, J = 2.0 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.2, 134.0, 133.7, 131.2, 130.5, 128.3, 126.5, 126.1, 106.1, 18.0; HRMS (APCI) Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2^+$ $[\text{M} + \text{H}]^+$ 159.0917, found, 159.0918. The compound data was in good agreement with the literature data.¹⁶

1-(2-Methylphenyl)ethanone (Table 2, entry 4):



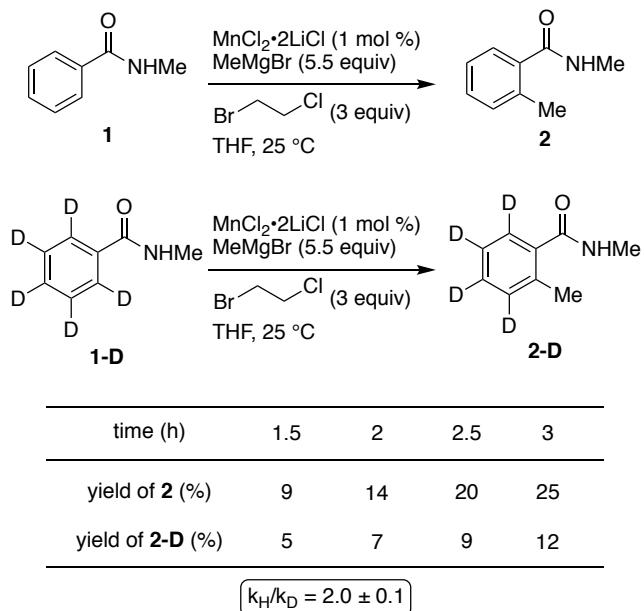
The general procedure B was applied to benzonitrile (52 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol). The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and a 3M aqueous solution of HCl (2 mL). The resulting mixture was stirred for 1 h. After extraction, the combined organic layers were passed over a Florisil pad. The title compound was obtained (33 mg, 50%) as a yellow oil (^1H NMR yield: 67%). ^1H NMR (500 MHz, CDCl_3): δ 7.69 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.28–7.24 (m, 2H), 2.58 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 201.4, 138.1, 137.3, 131.7, 131.2, 129.1, 125.4, 29.3, 21.3; HRMS (APCI) Calcd for $\text{C}_9\text{H}_{11}\text{O}^+$ $[\text{M} + \text{H}]^+$ 135.0804, found, 135.0798. The compound data was in good agreement with the literature data.¹⁷

1-Methyl-2-(methylsulfonyl)benzene (Table 2, entry 5):



The general procedure B was applied to methyl phenyl sulfone (78 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 2,3-dibromobutane (184 μL , 1.50 mmol) instead of 1-bromo-2-chloroethane. The title compound was obtained (19 mg, 22%) as a yellow oil (^1H NMR yield: 34%). ^1H NMR (500 MHz, CDCl_3): δ 8.04 (dd, J = 7.7, 0.9 Hz, 1H), 7.53 (td, J = 7.4, 1.1 Hz, 1H), 7.04–7.34 (m, 2H), 3.08 (s, 1H), 2.72 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 138.6, 137.5, 133.7, 132.7, 129.2, 126.7, 43.6, 20.3; HRMS (APCI) Calcd for $\text{C}_8\text{H}_{11}\text{O}_2\text{S}^+$ $[\text{M} + \text{H}]^+$ 171.0474, found, 171.0482. The compound data was in good agreement with the literature data.¹⁸

7. KIE Experiment



In two oven-dried Schlenk tubes were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and *N*-methyl-2,3,4,5,6-pentadeuteriobenzamide (28 mg, 0.20 mmol), respectively. A solution of $\text{MnCl}_2 \cdot 2\text{LiCl}$ in THF (20 μL , 0.10 M, 0.0020 mmol), tridecane (36 mg, 0.20 mmol), MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol), and 1-bromo-2-chloroethane (50 μL , 0.60 mmol) were sequentially added to each reaction tube. The two reaction mixtures were stirred at 25 °C and sampled after 1.5 h, 2 h, 2.5 h, and 3 h. The samples were analyzed by GC analysis in the presence of tridecane as an internal standard.

8. References

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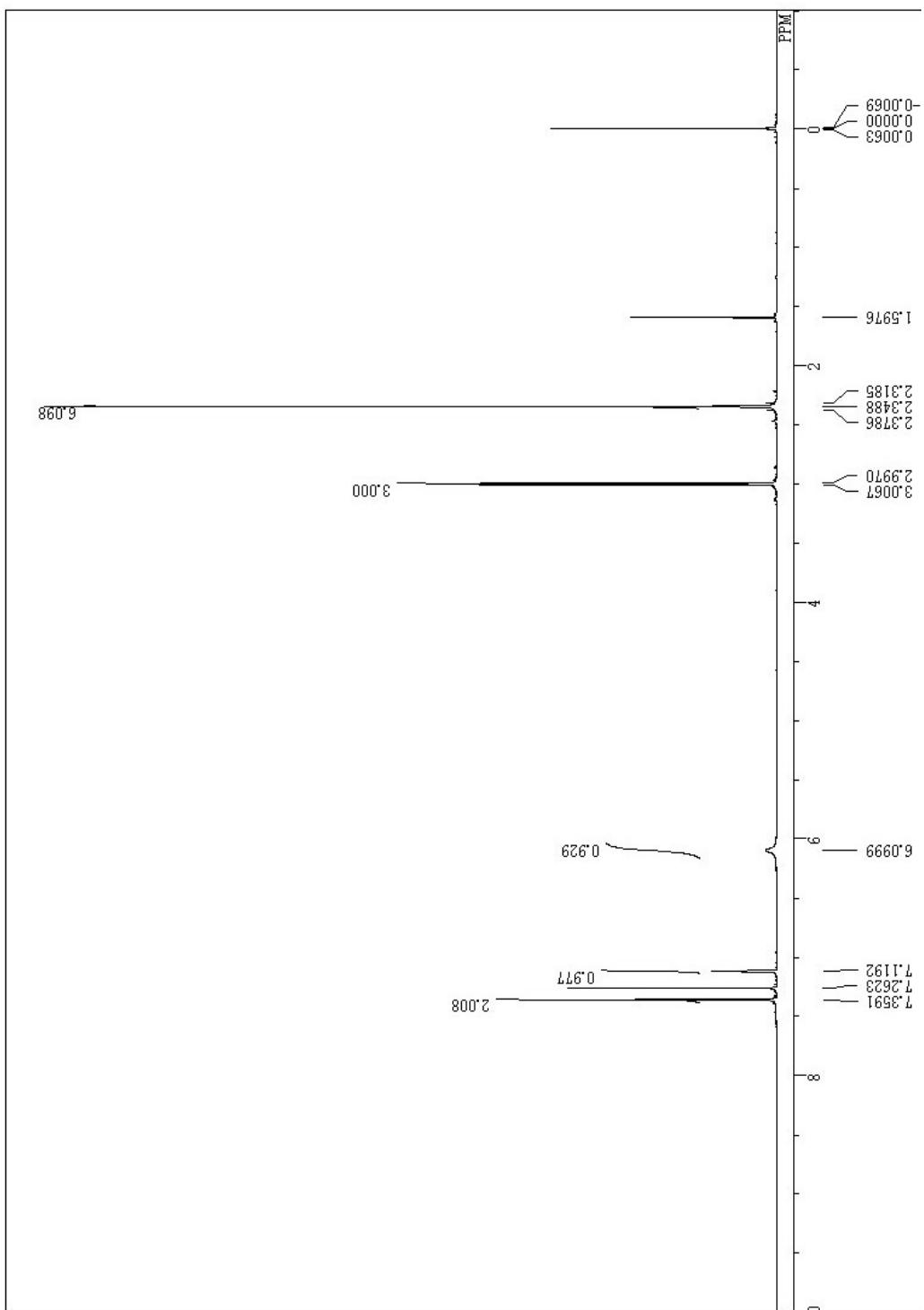
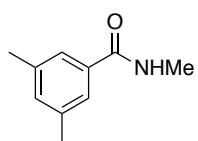
¹⁶ Asaumi, T.; Matsuo, T.; Fukuyama, T.; Ie, Y.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 4433–4440.

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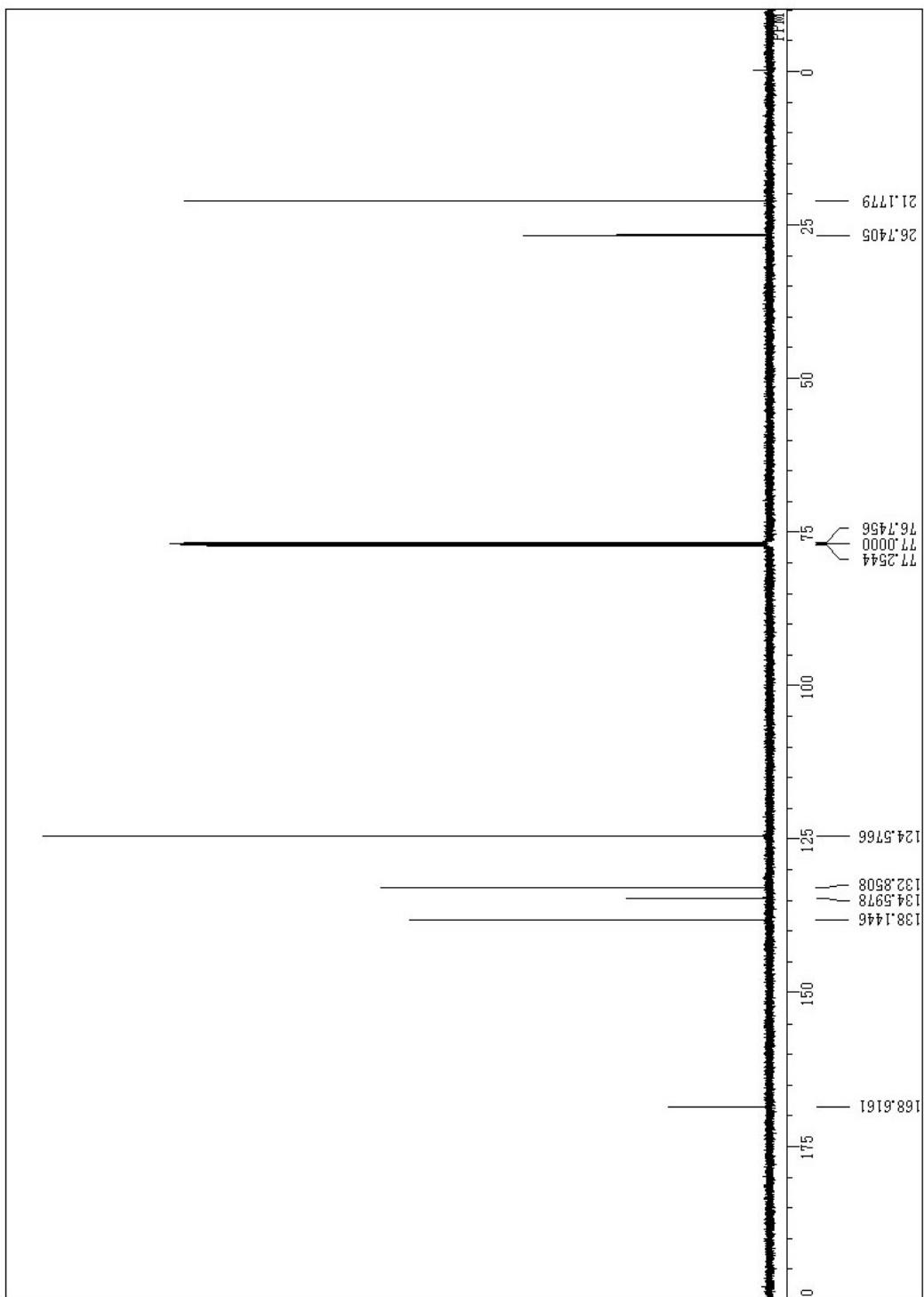
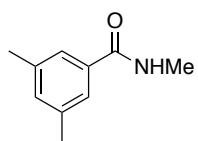
¹⁸ Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423–4425.

9. ^1H , ^{13}C and ^{19}F Spectra

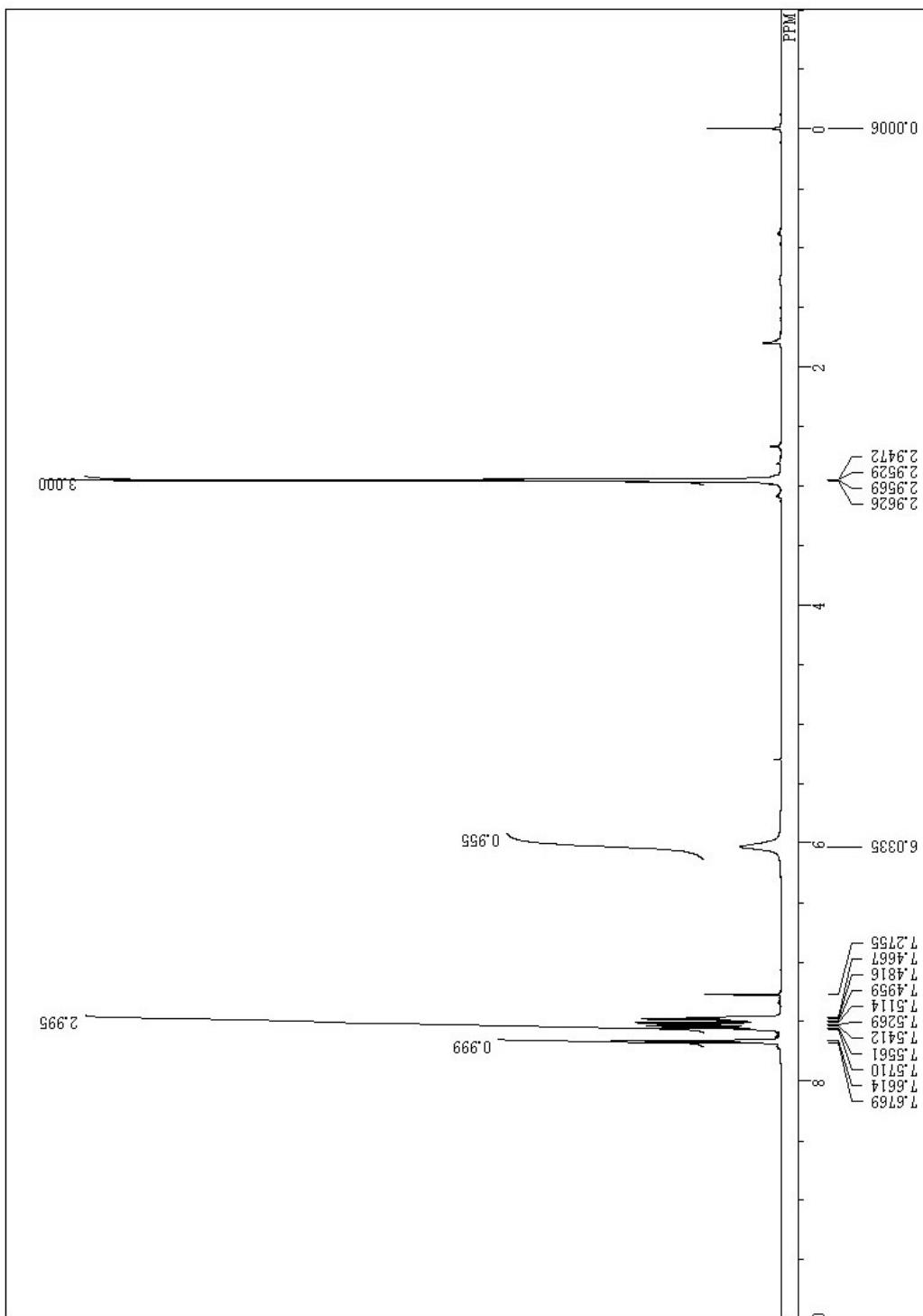
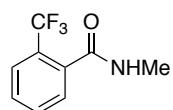
^1H NMR of *N*,3,5-Trimethylbenzamide



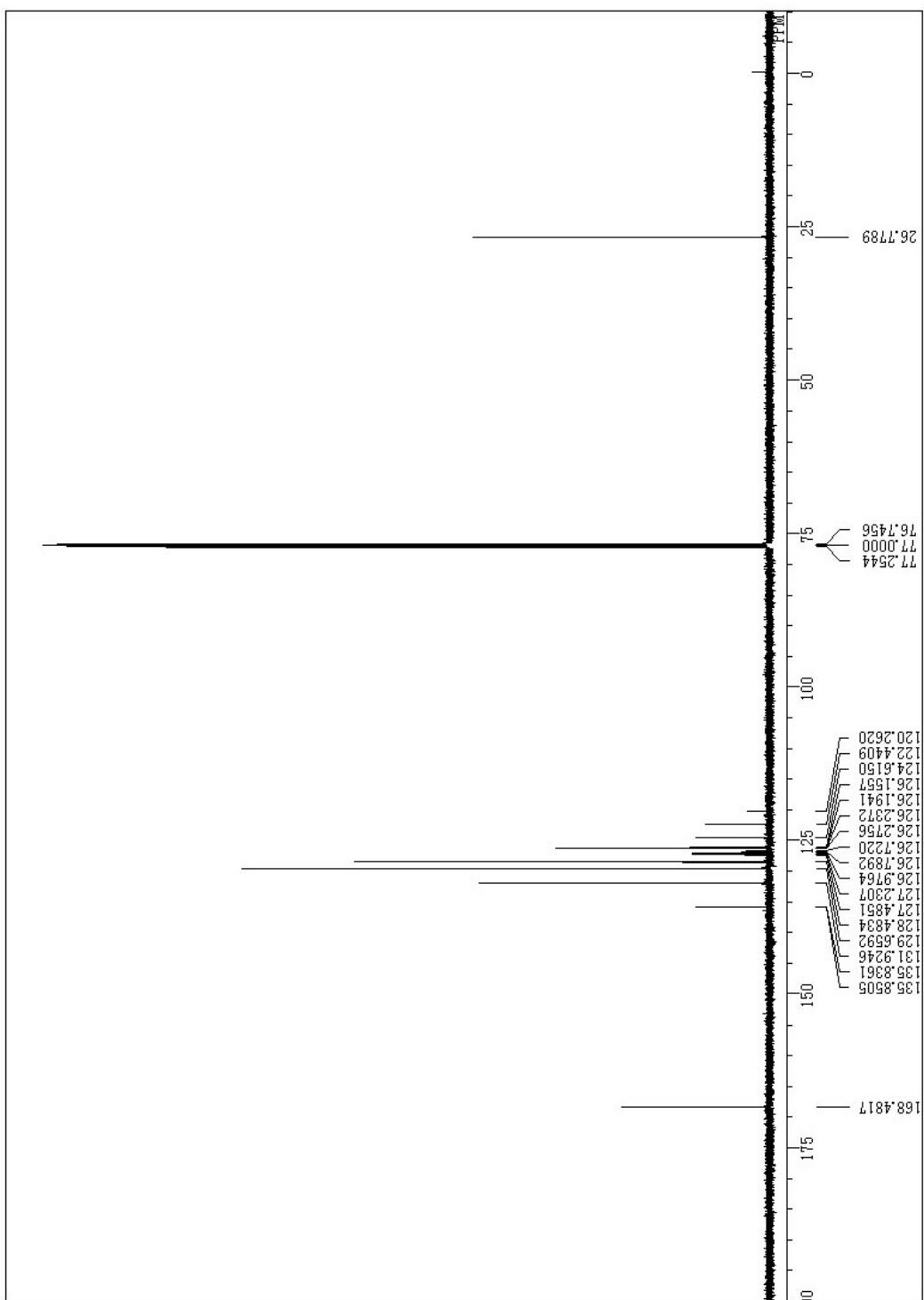
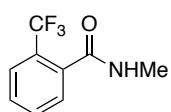
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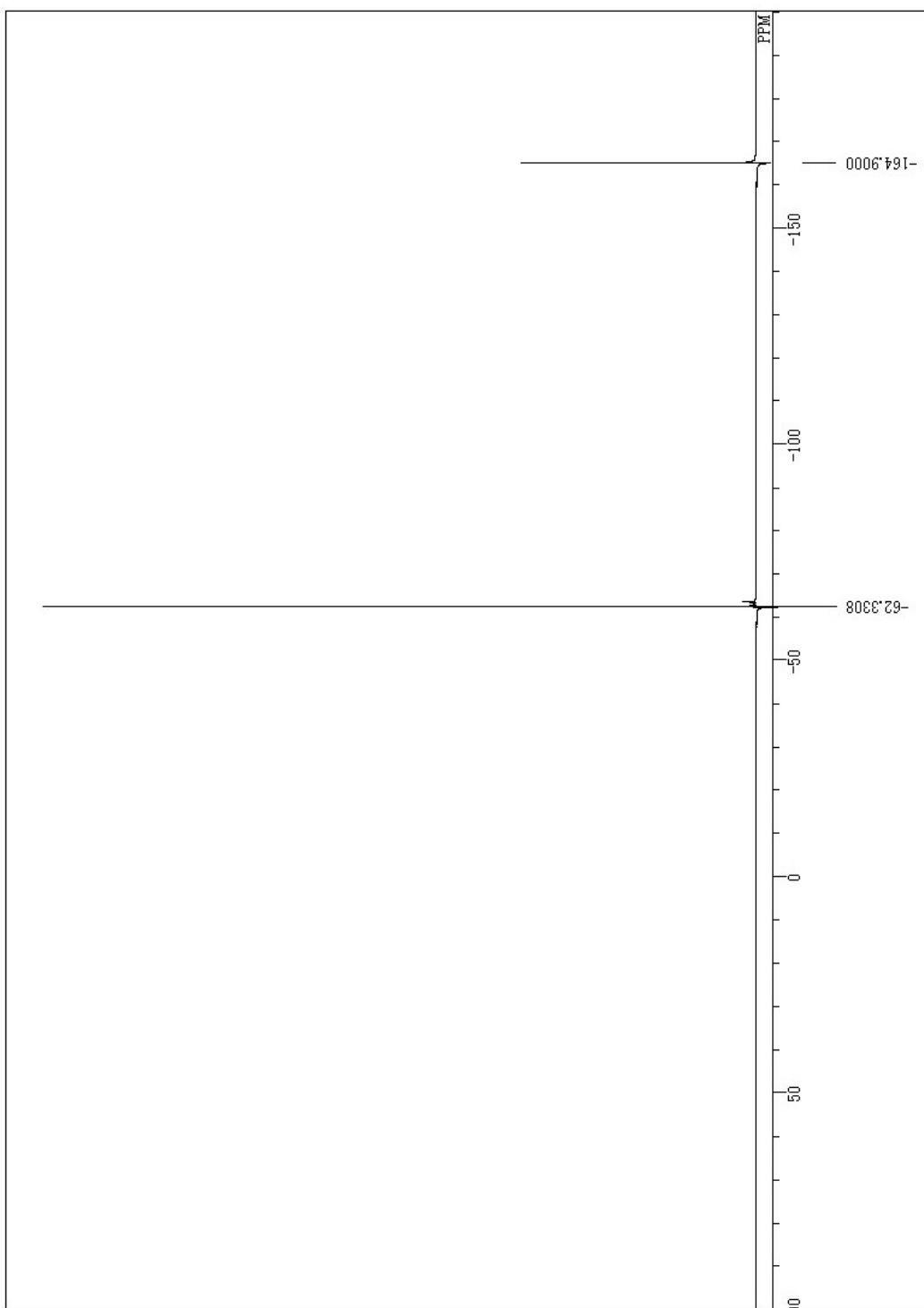
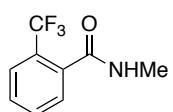
¹H NMR of *N*-Methyl-2-(trifluoromethyl)benzamide



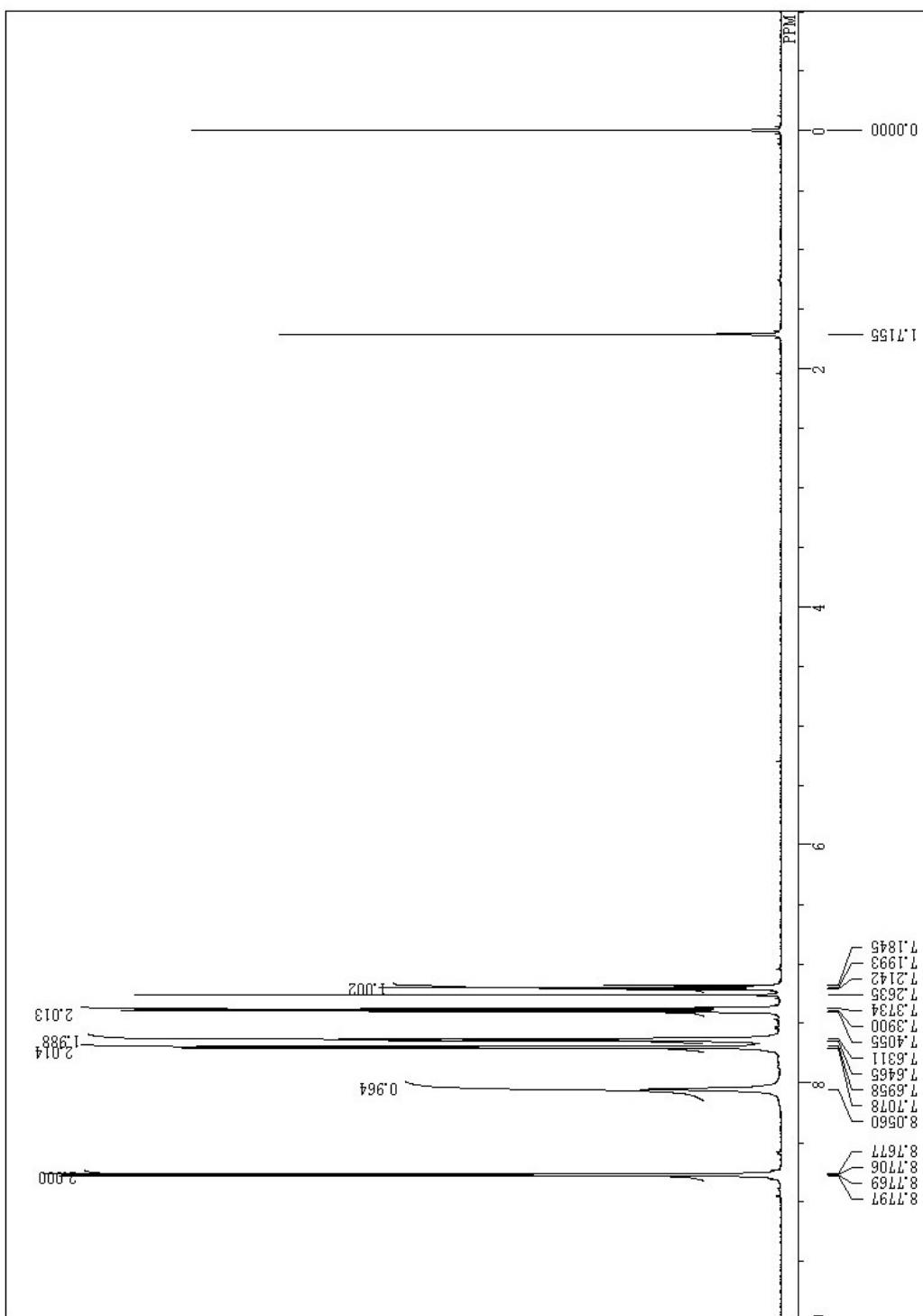
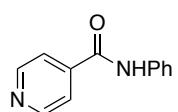
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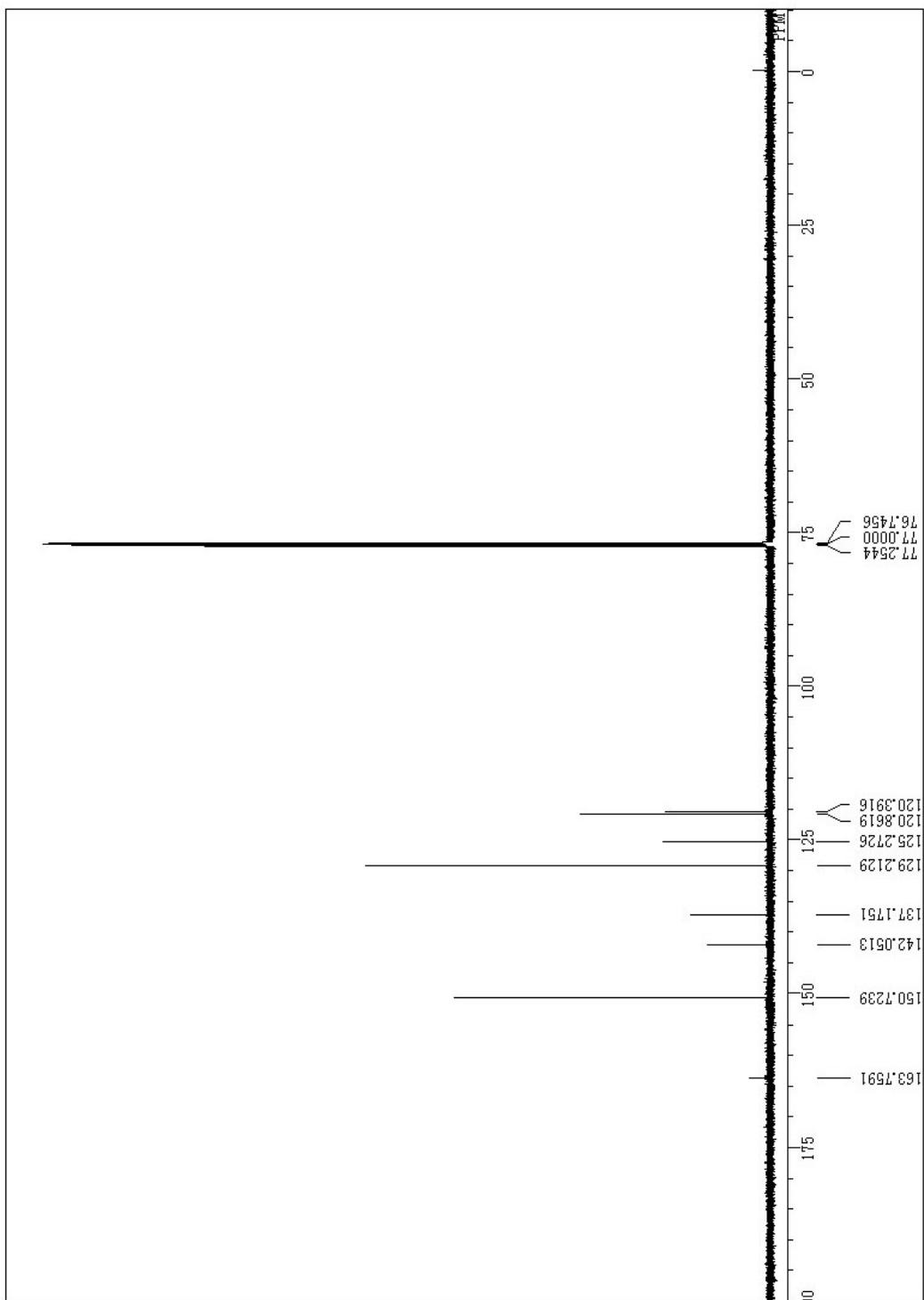
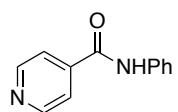
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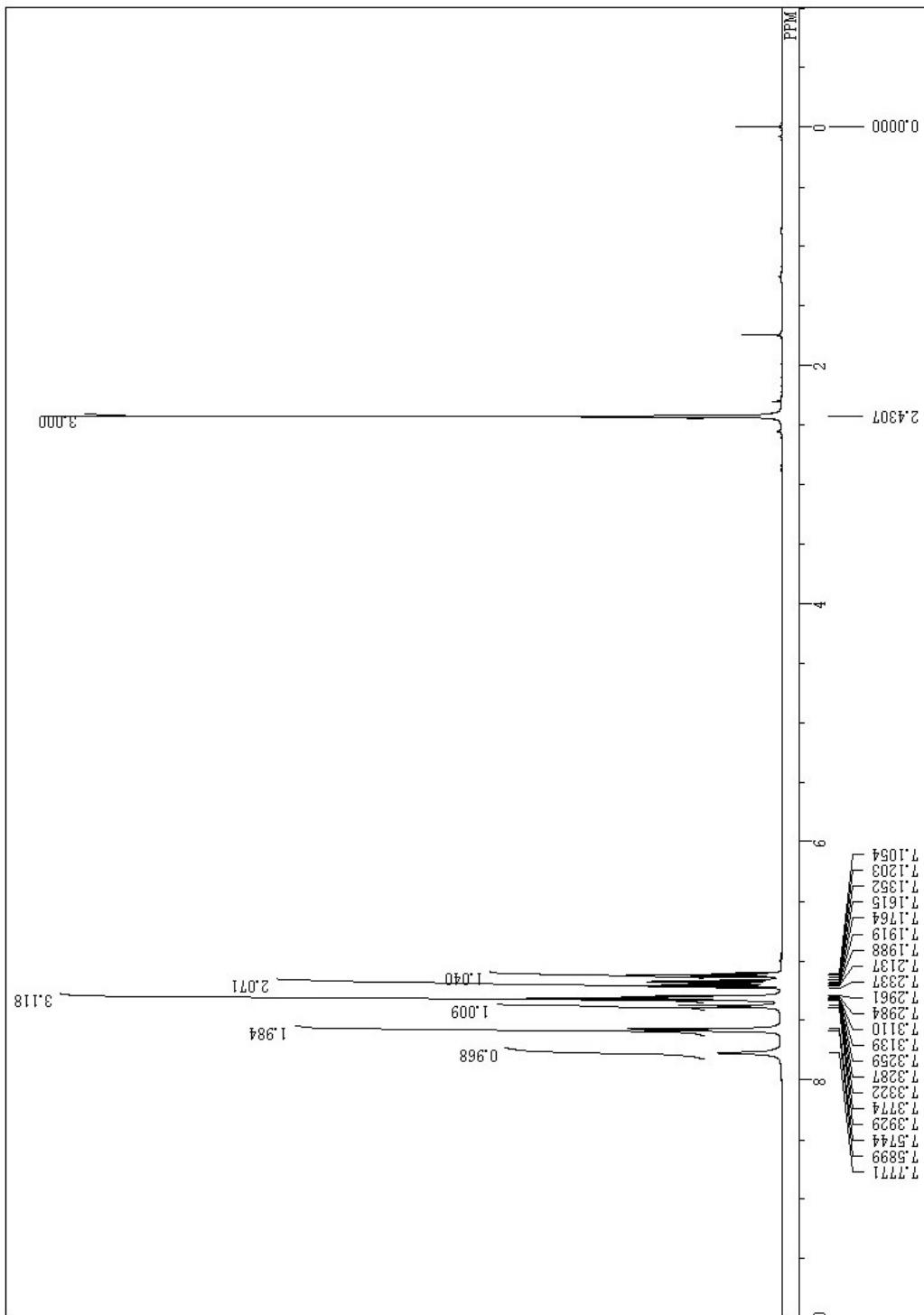
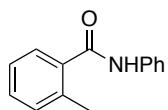
¹H NMR of *N*-Phenyl-4-pyridinecarboxamide



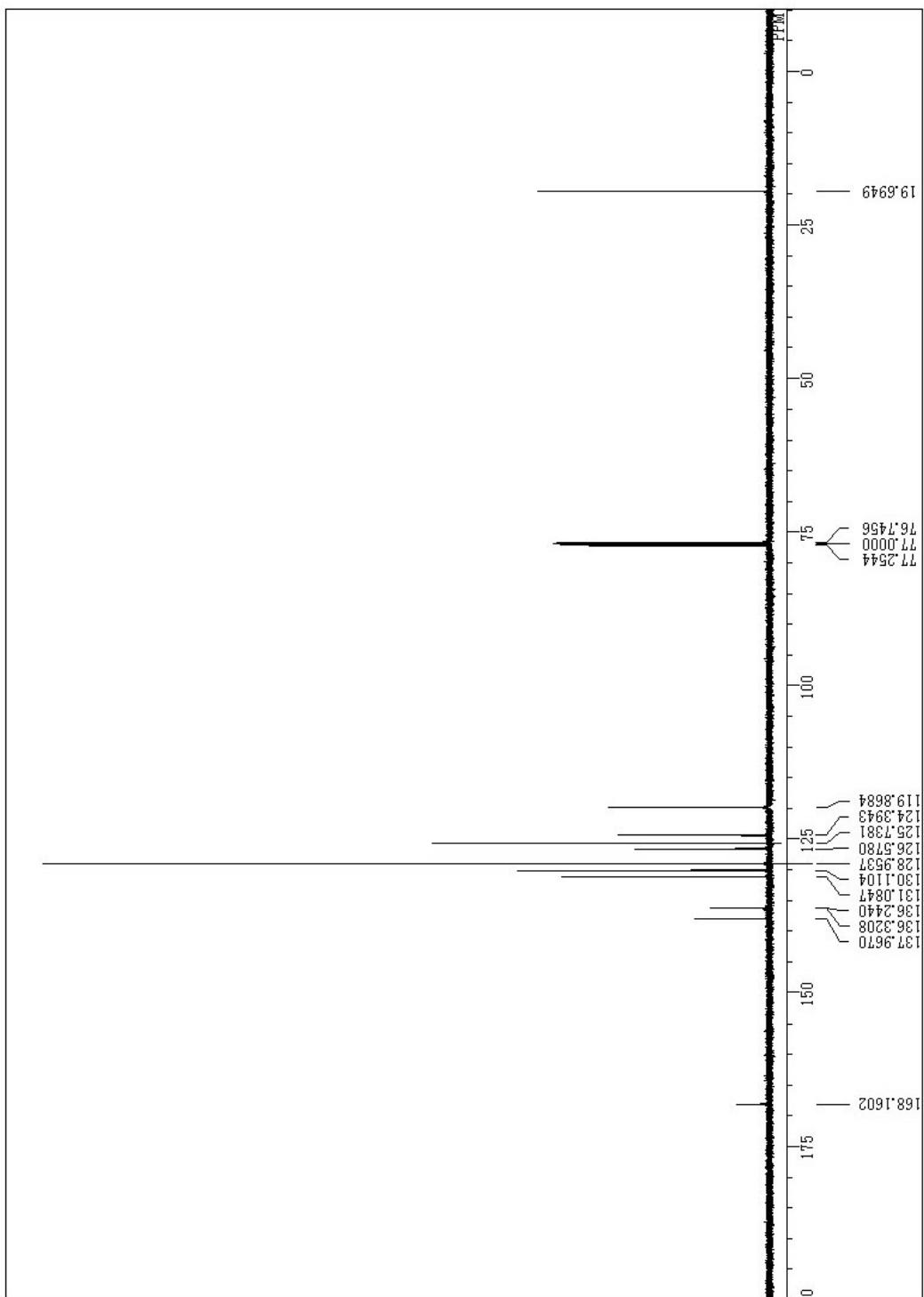
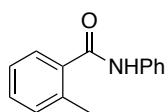
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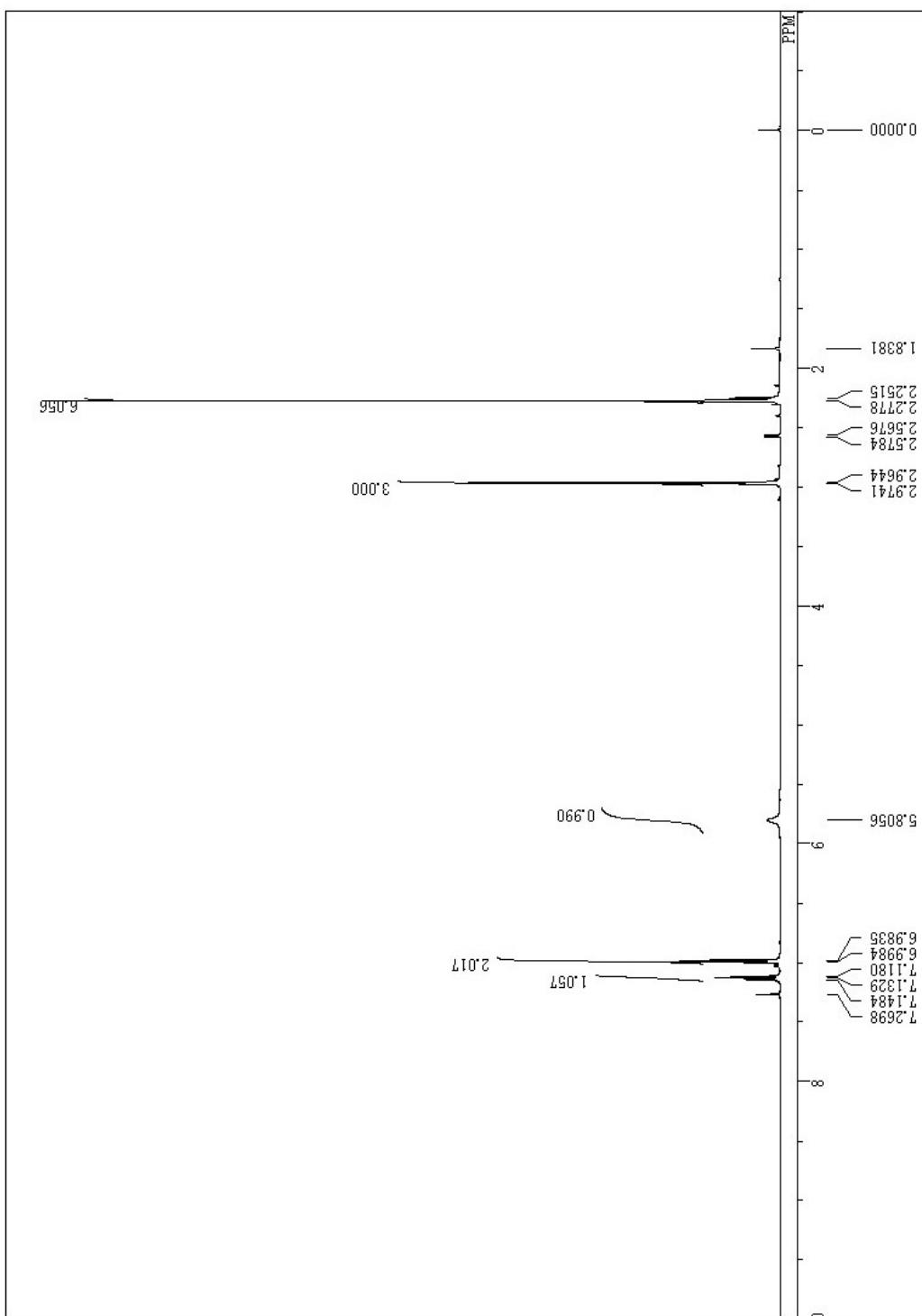
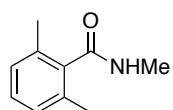
¹H NMR of 2-Methyl-*N*-phenylbenzamide (Table 1, entry 1)



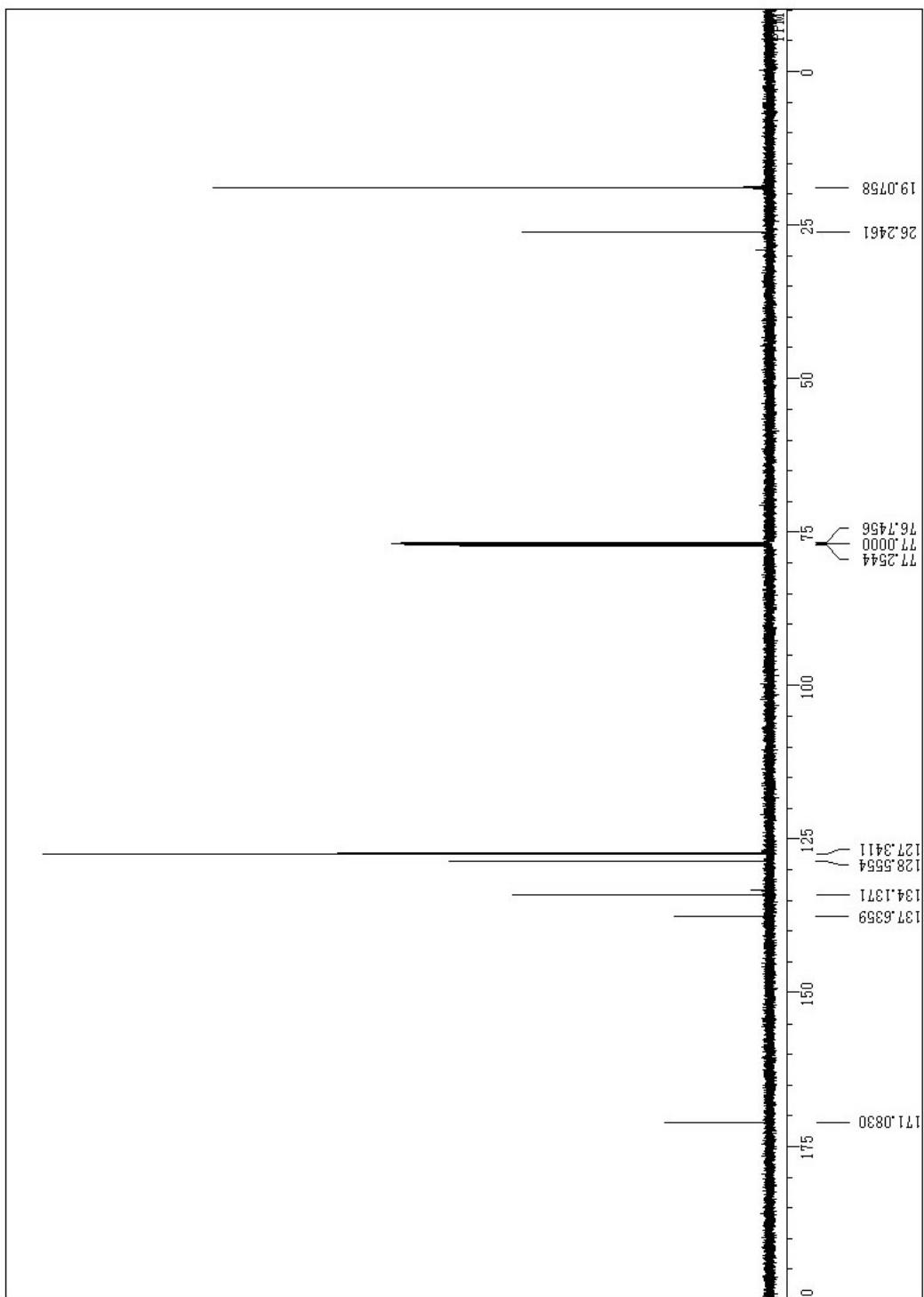
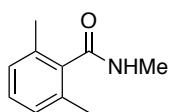
^{13}C NMR of 2-Methyl-*N*-phenylbenzamide (Table 1, entry 1)



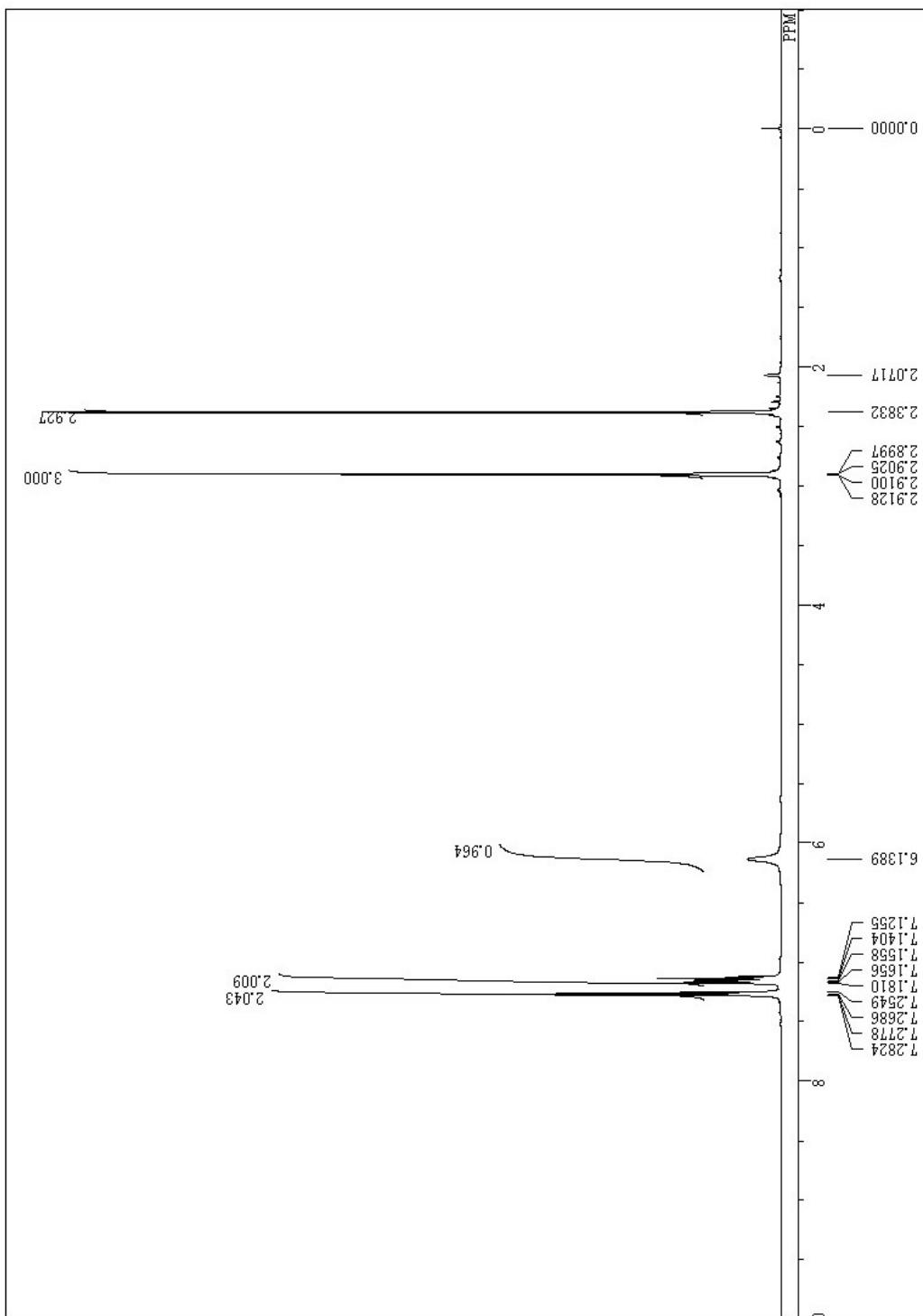
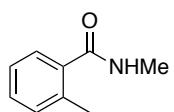
¹H NMR of *N*,2,6-Trimethylbenzamide (Table 1, entry 2)



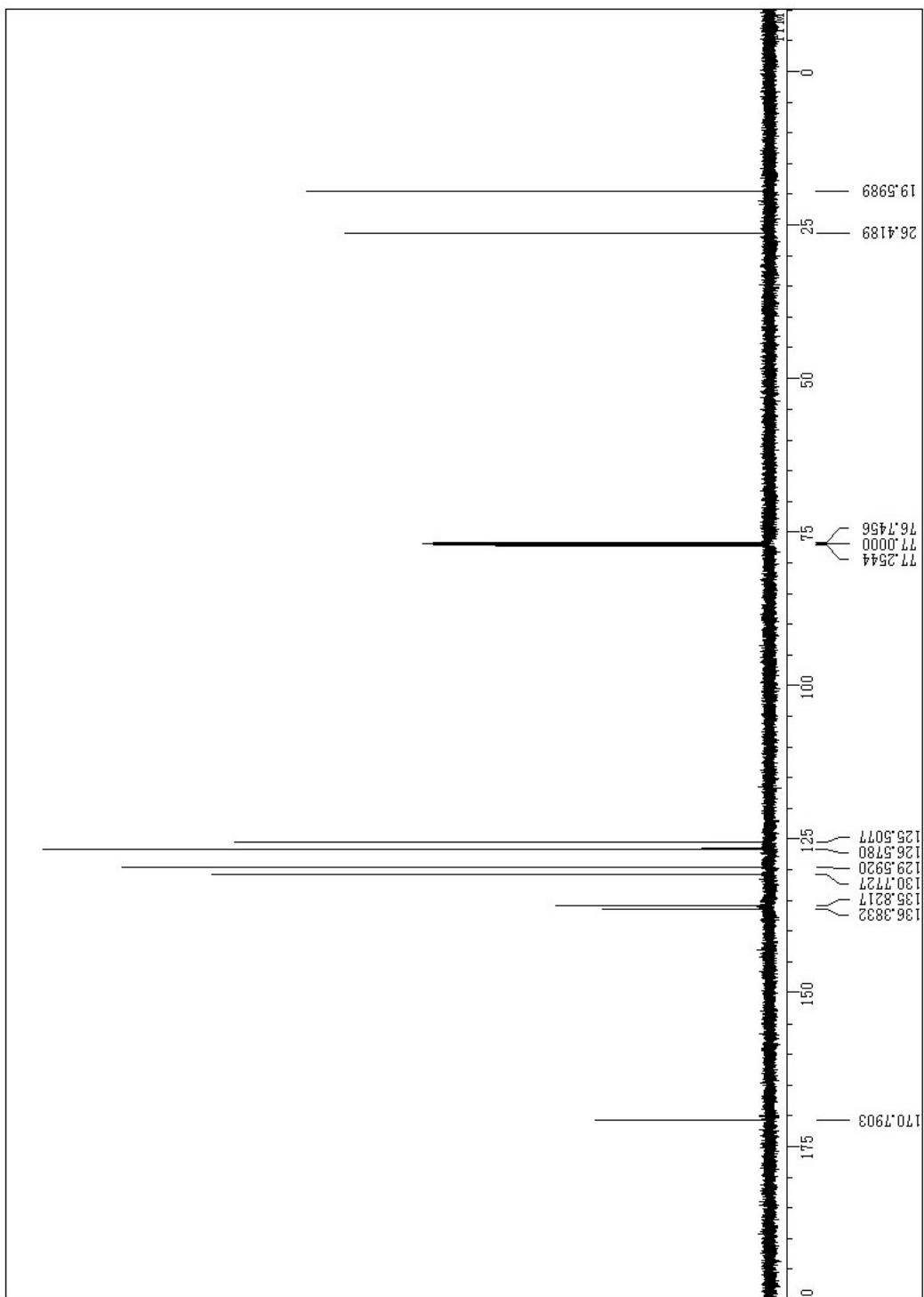
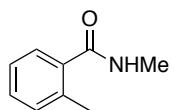
¹³C NMR of *N*,2,6-Trimethylbenzamide (Table 1, entry 2)



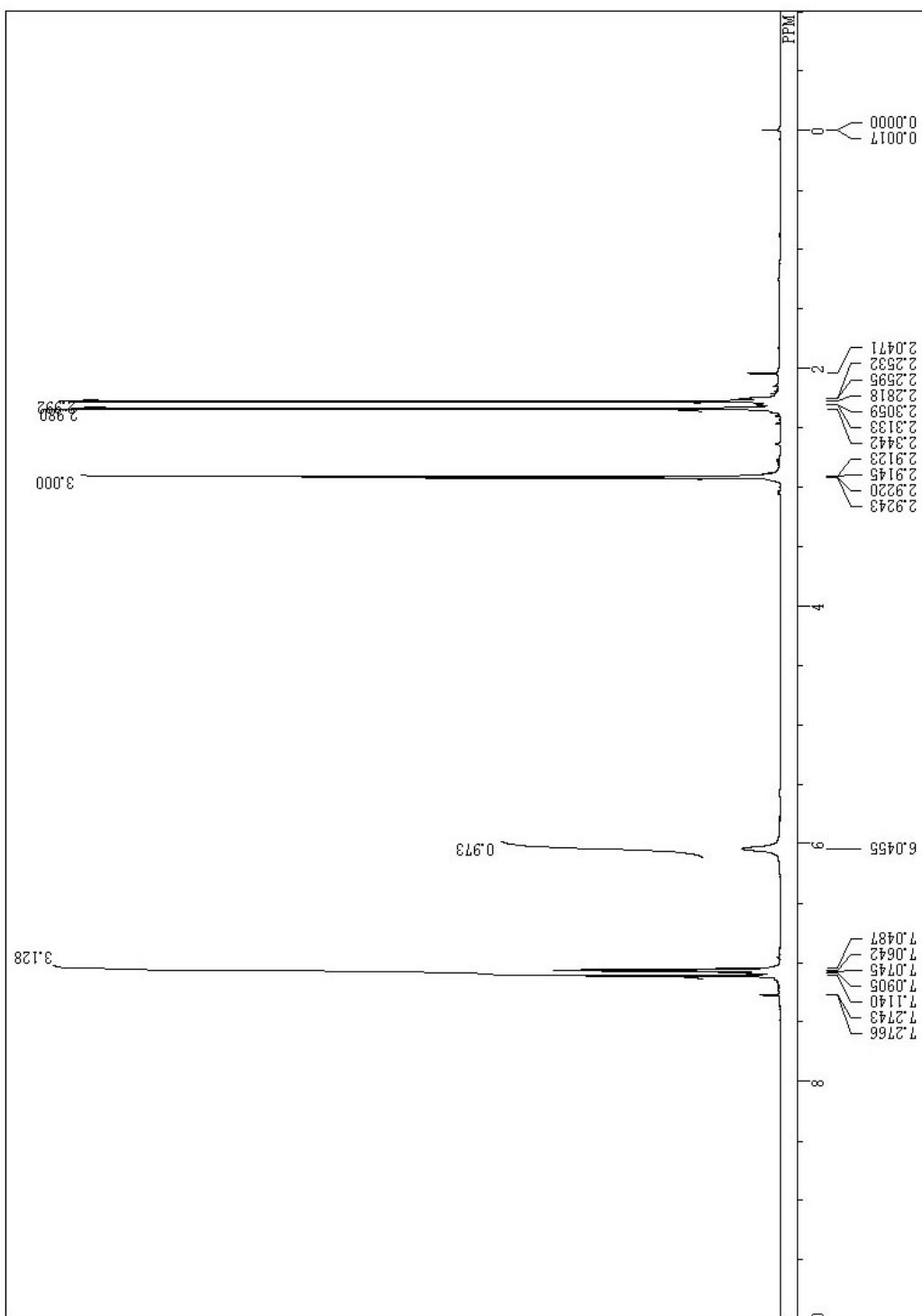
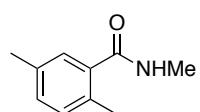
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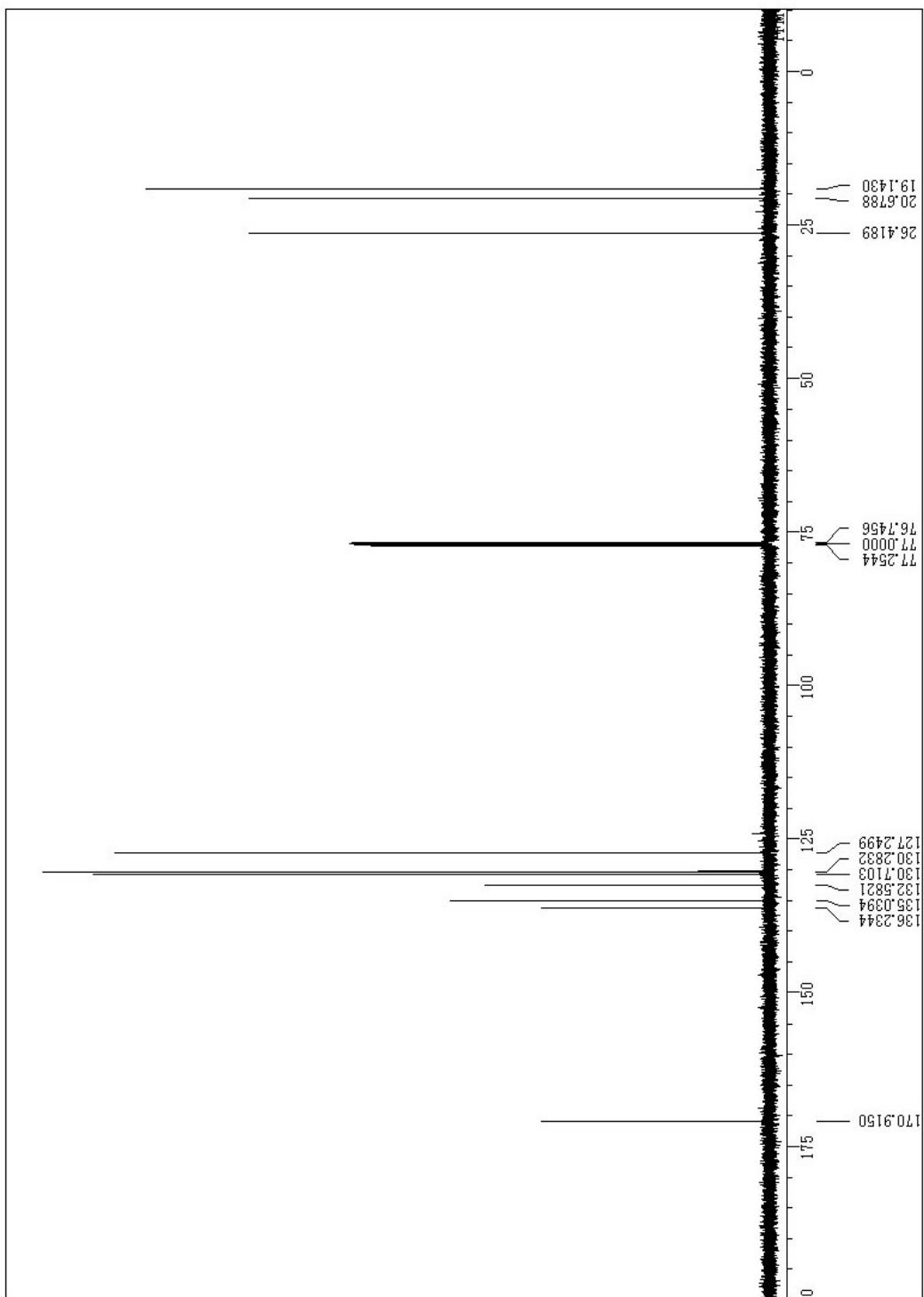
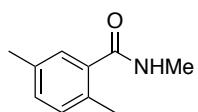
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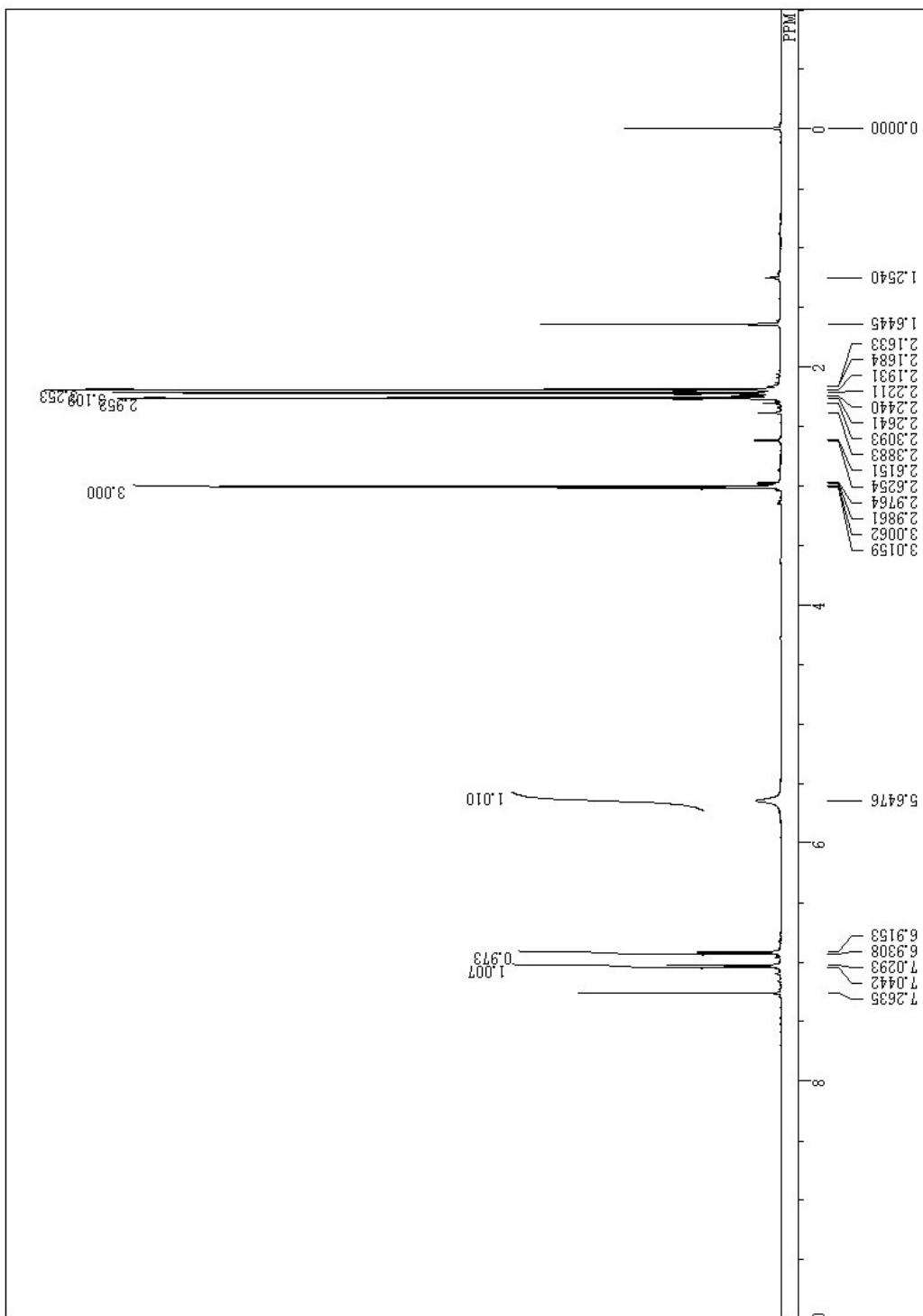
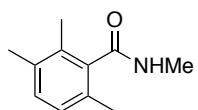
¹H NMR of *N*,2,5-Trimethylbenzamide (Table 1, entry 4)



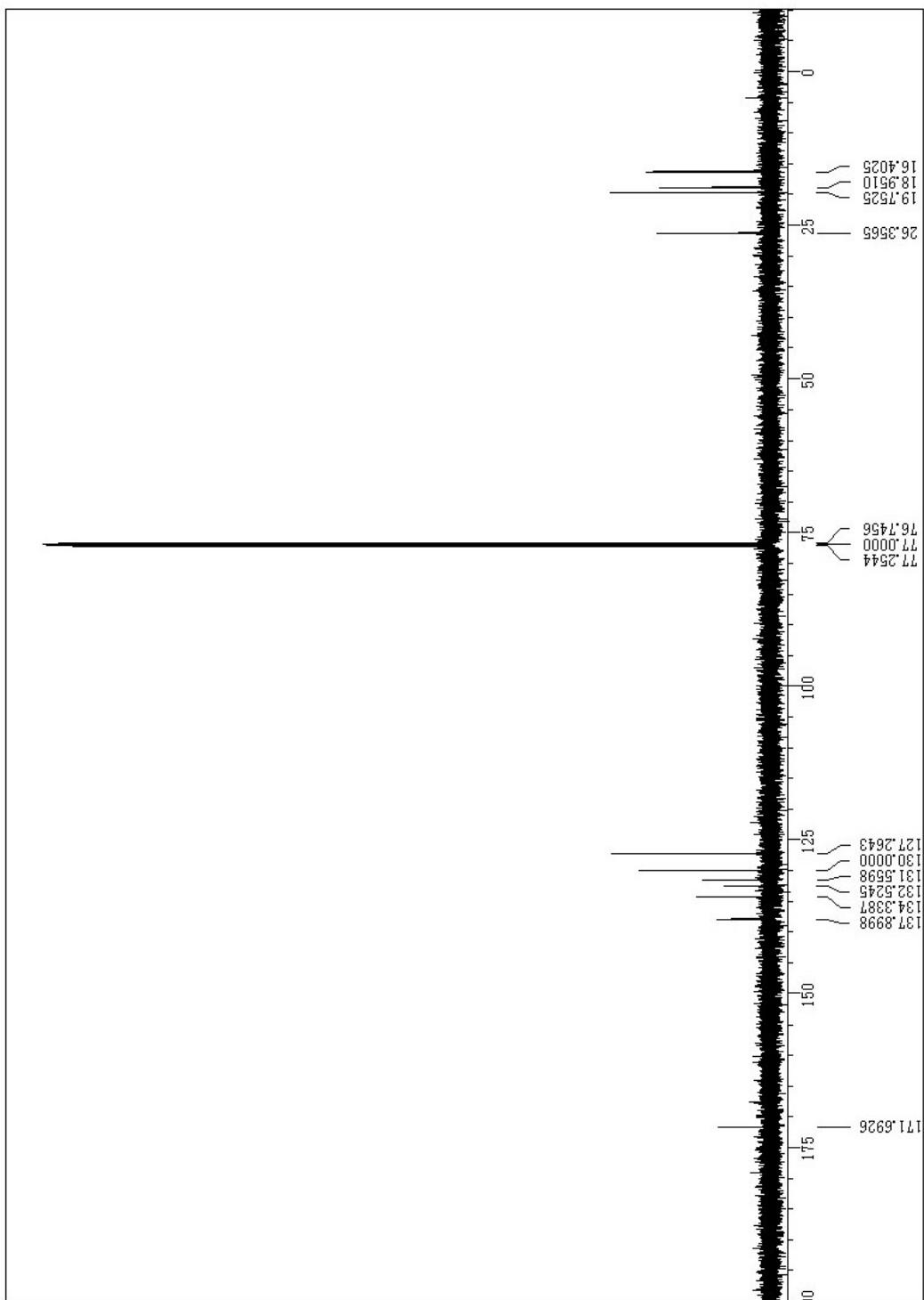
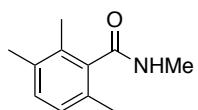
^{13}C NMR of *N*,2,5-Trimethylbenzamide (Table 1, entry 4)



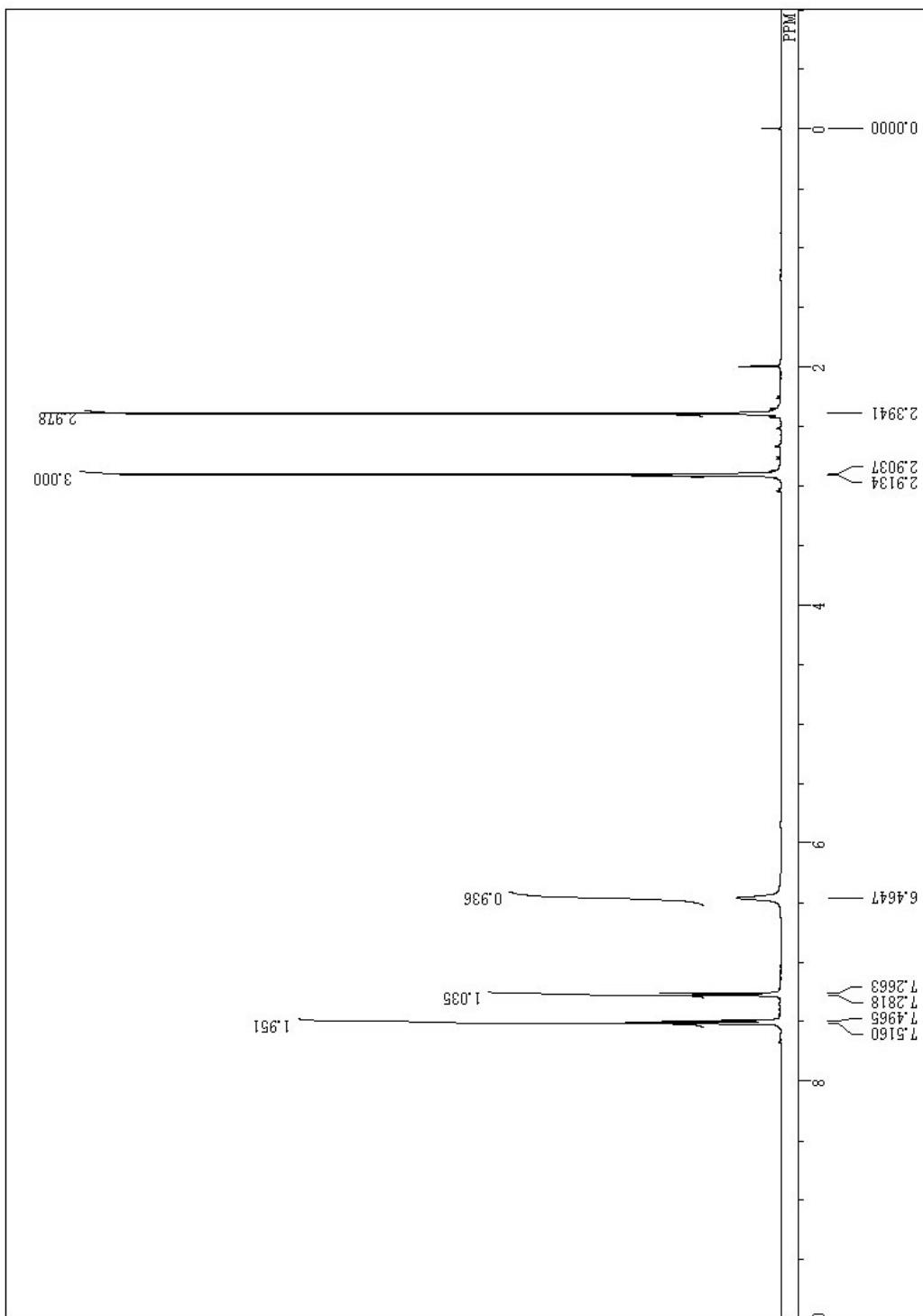
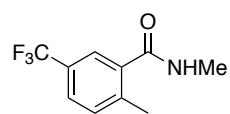
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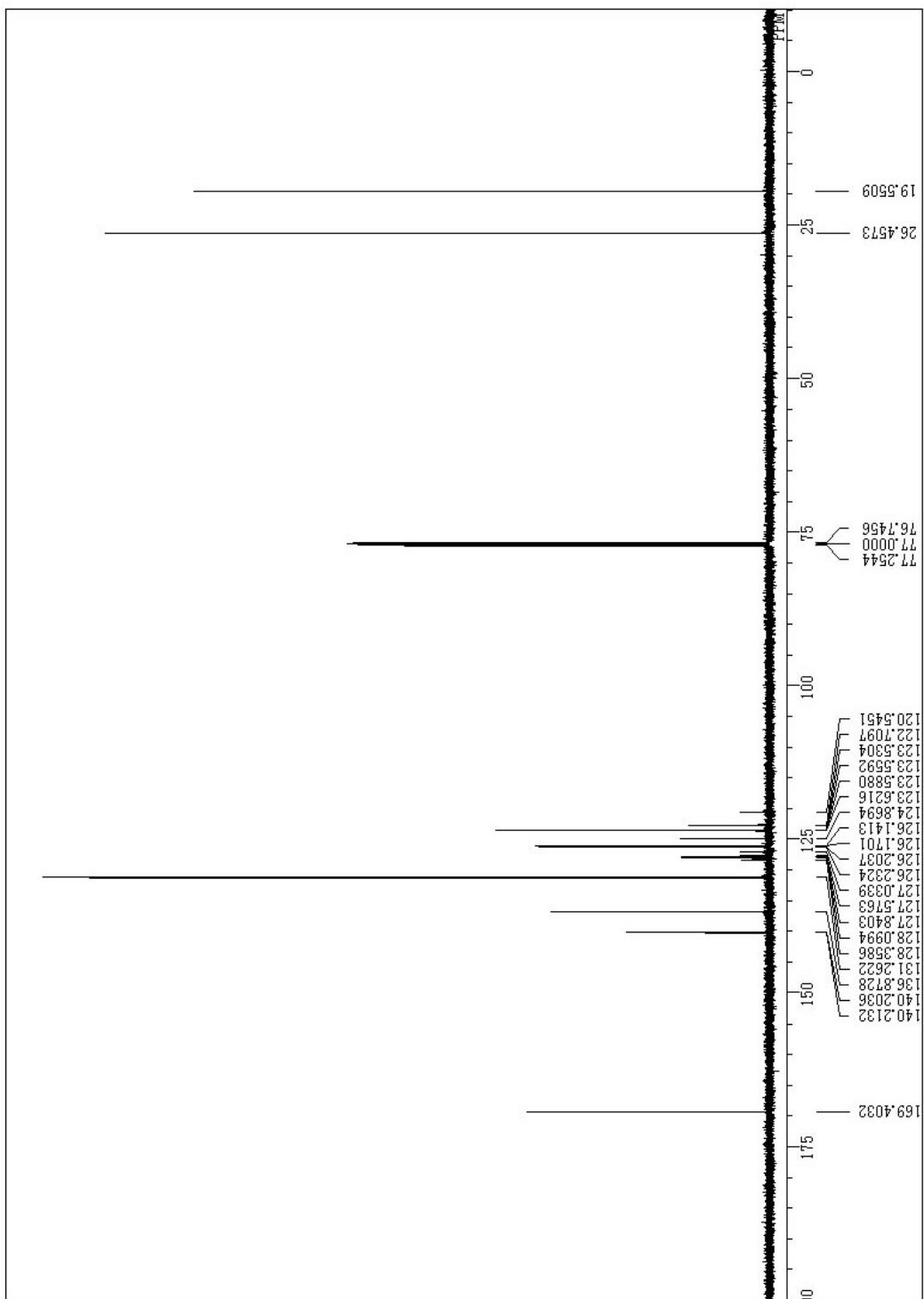
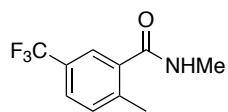
¹³C NMR of *N*,2,3,6-Tetramethylbenzamide (Table 1, entry 4)



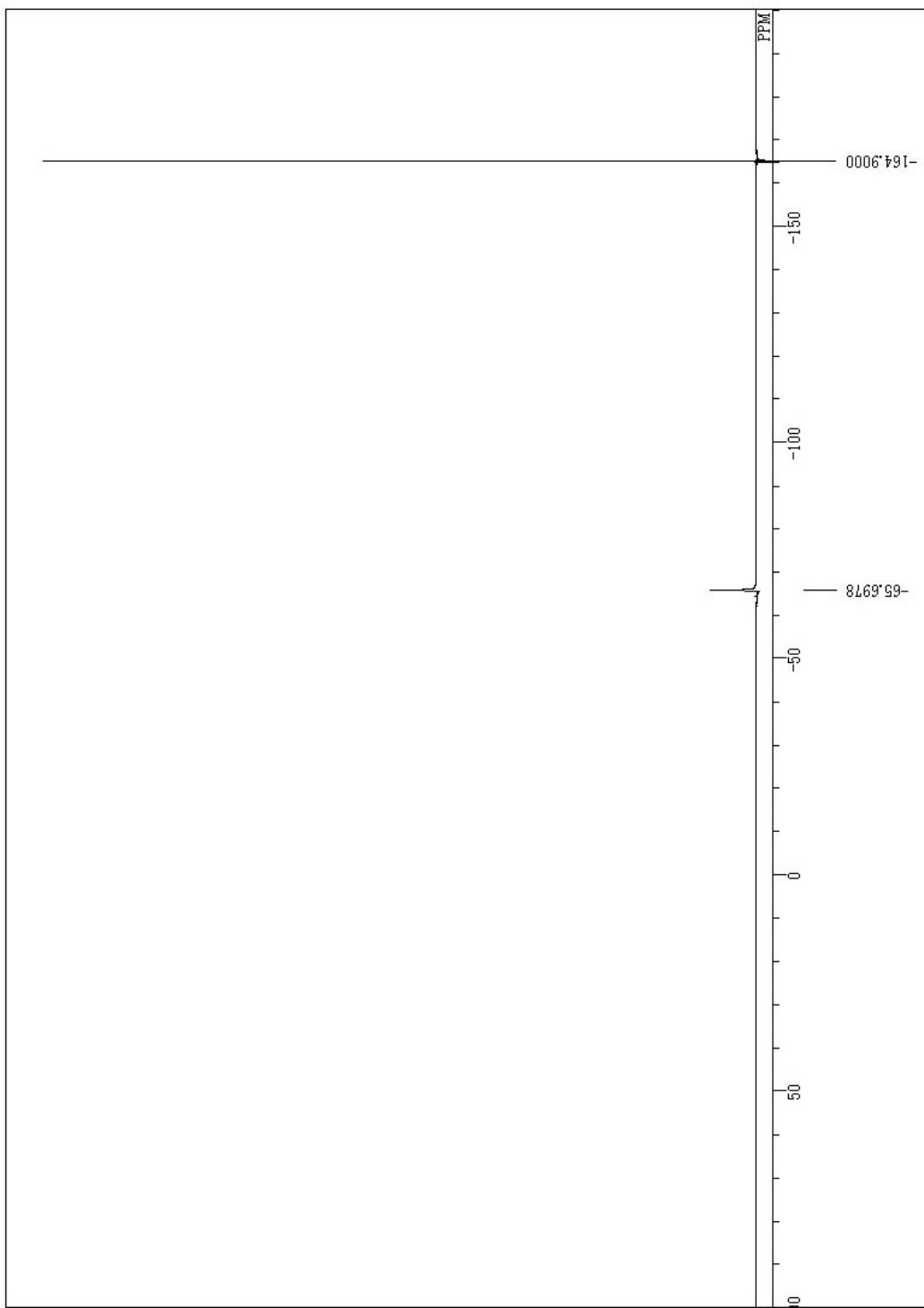
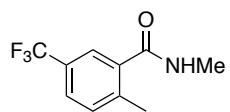
¹H NMR of *N*,2-Dimethyl-5-(trifluoromethyl)benzamide (Table 1, entry 5)



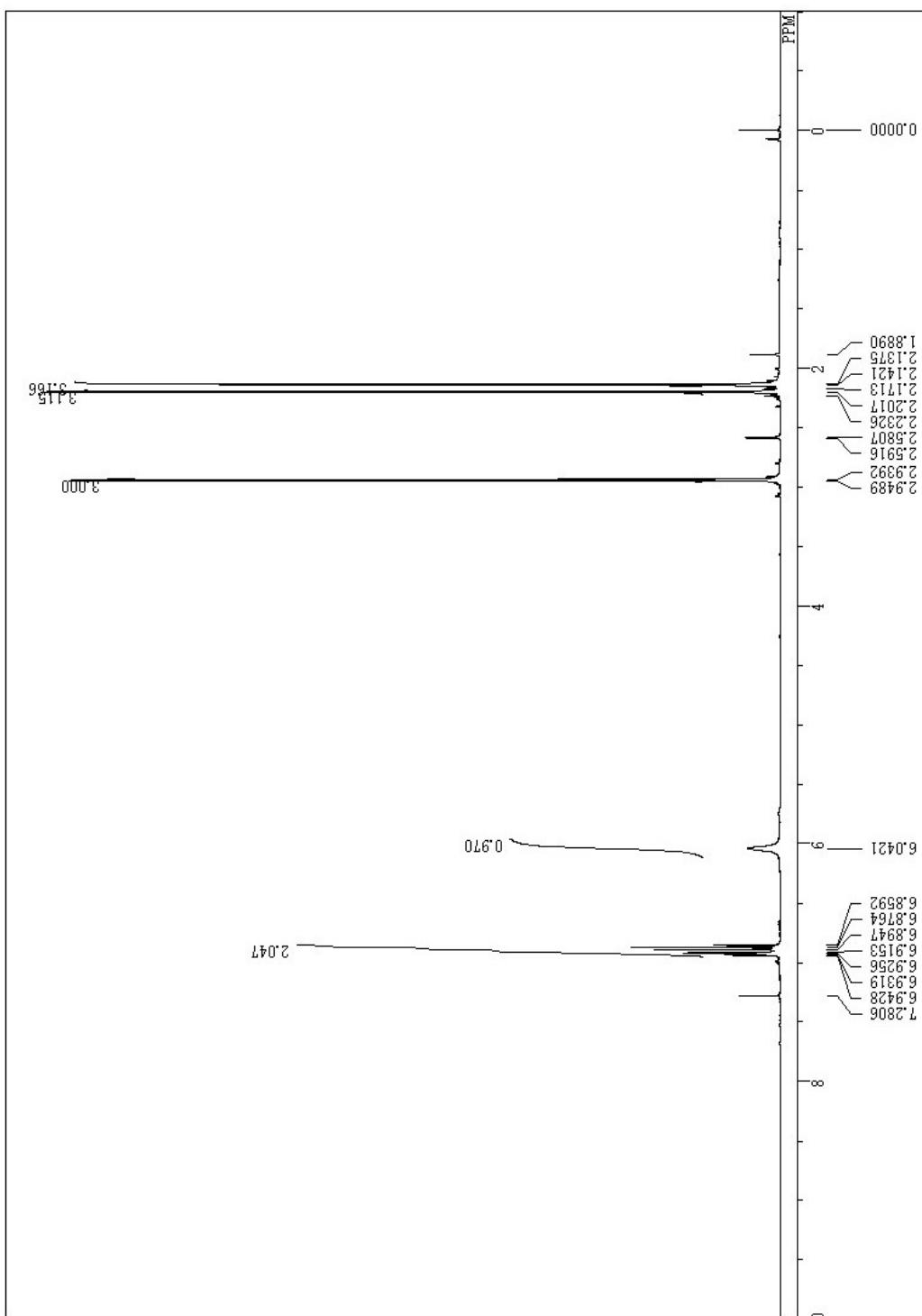
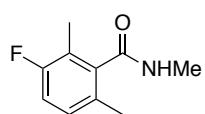
¹³C NMR of *N*,2-Dimethyl-5-(trifluoromethyl)benzamide (Table 1, entry 5)



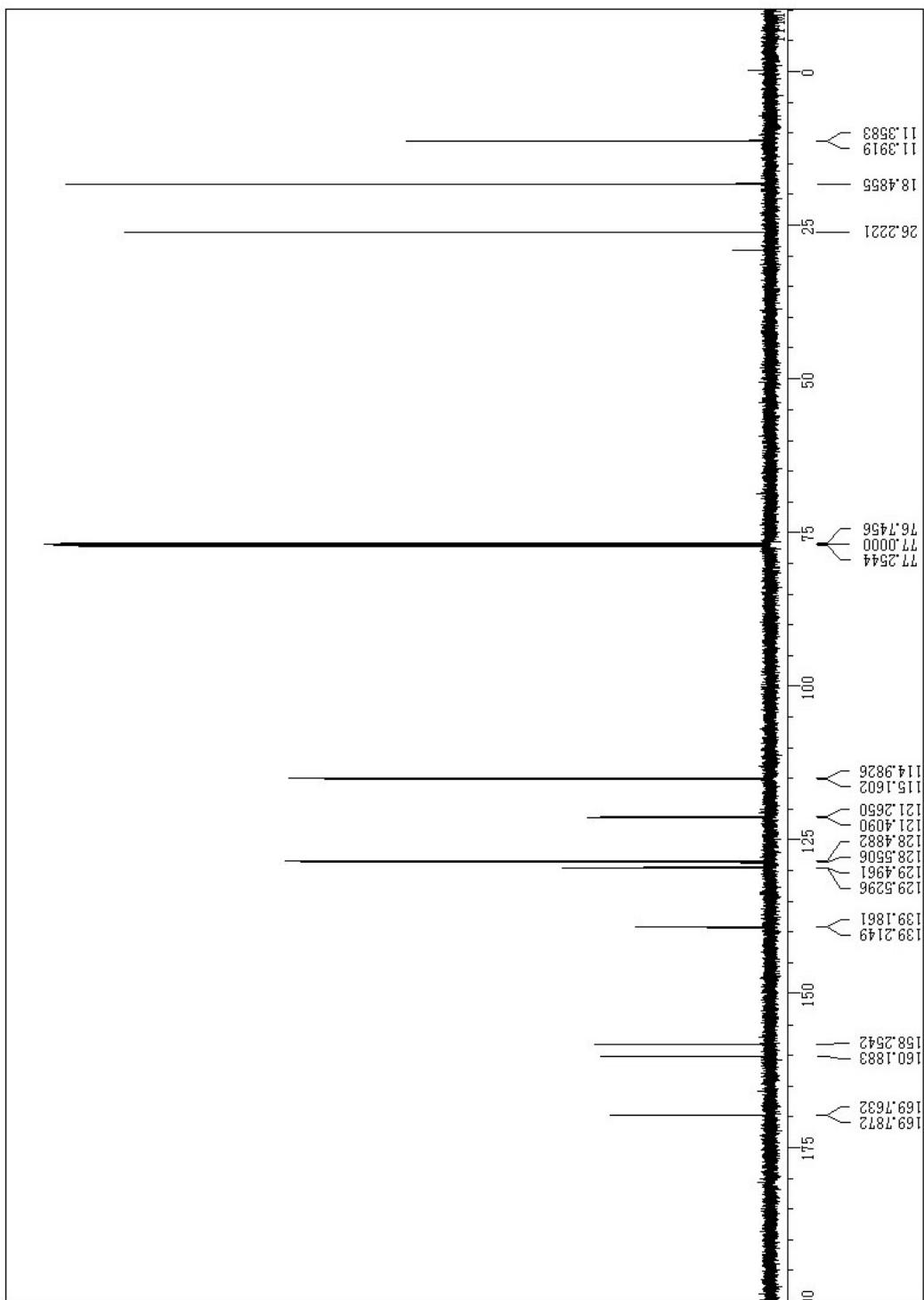
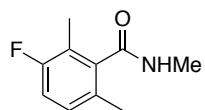
¹⁹F NMR of *N*,2-Dimethyl-5-(trifluoromethyl)benzamide (Table 1, entry 5)



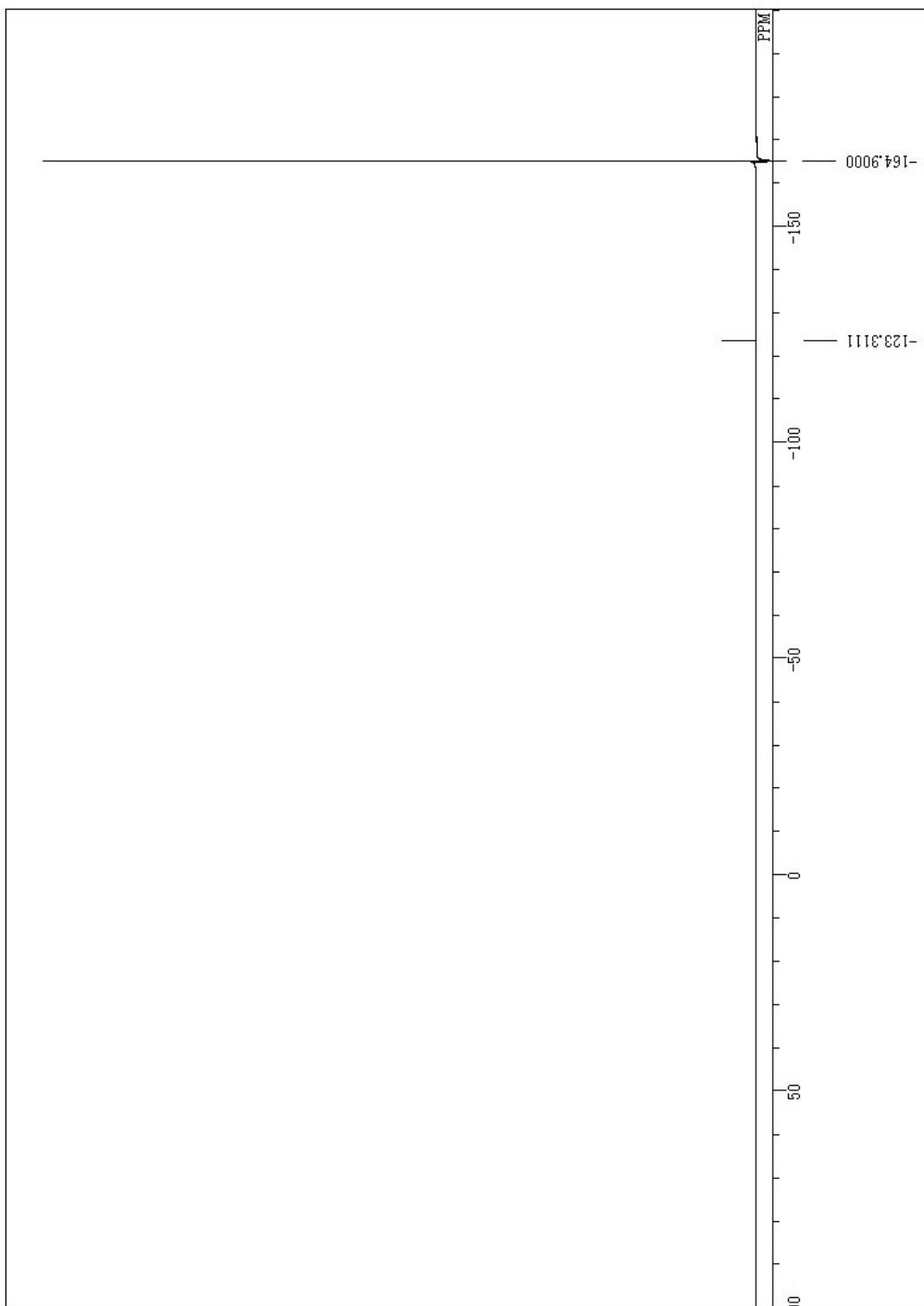
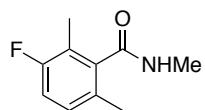
¹H NMR of 3-Fluoro-*N*,2,6-trimethylbenzamide (Table 1, entry 6)



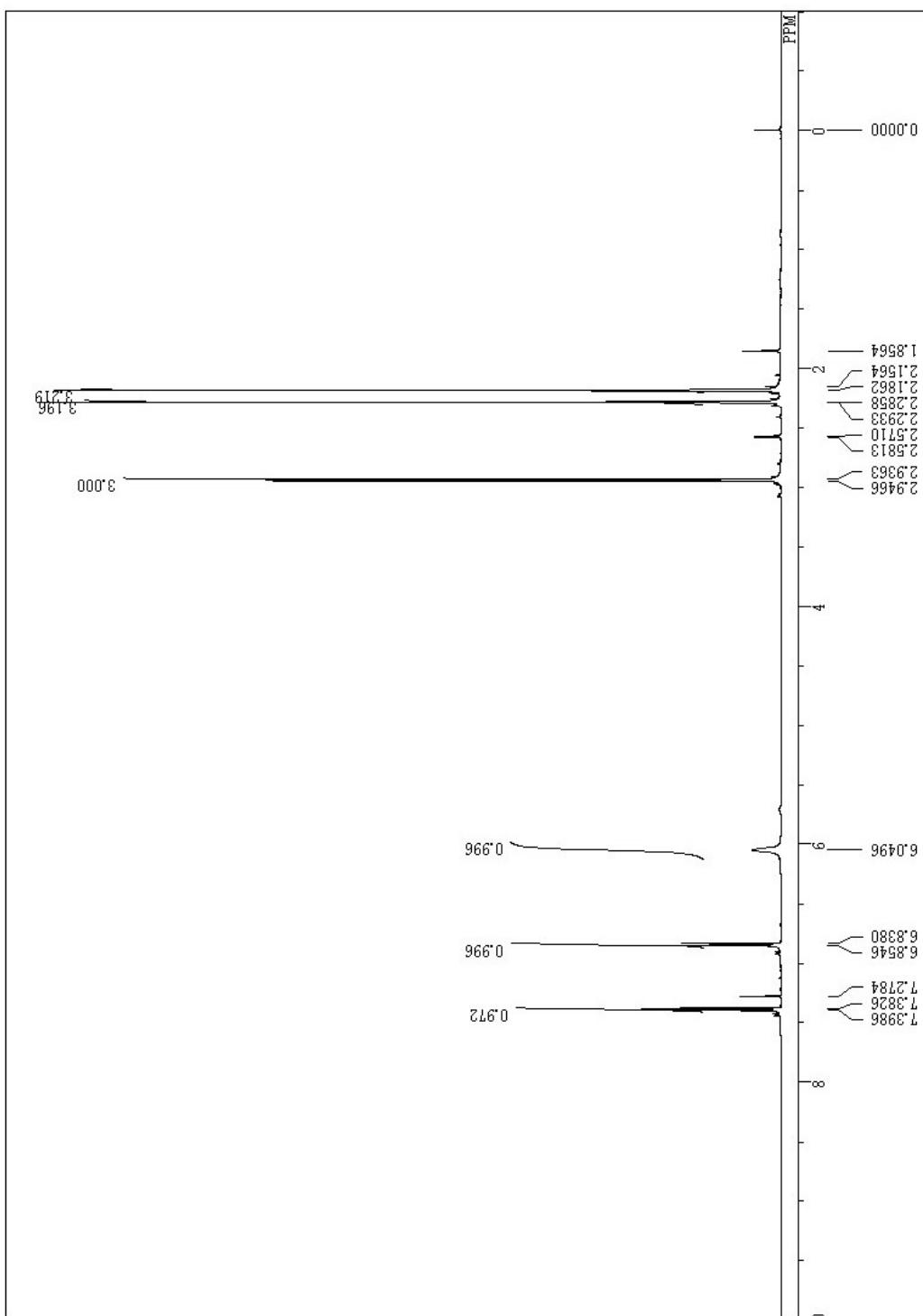
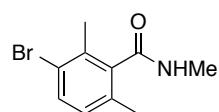
¹³C NMR of 3-Fluoro-*N*,2,6-trimethylbenzamide (Table 1, entry 6)



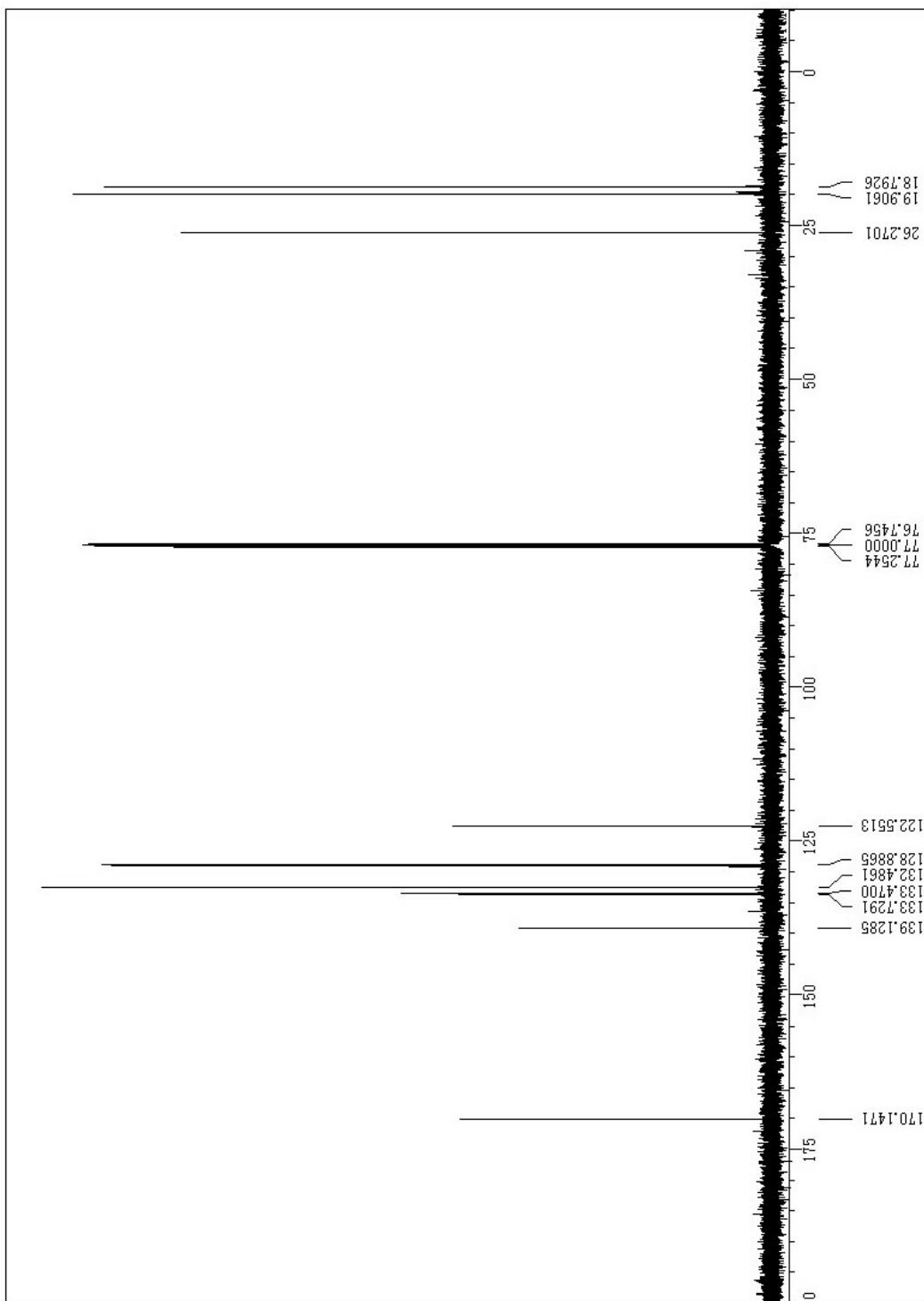
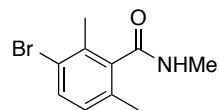
¹⁹F NMR of 3-Fluoro-*N*,2,6-trimethylbenzamide (Table 1, entry 6)



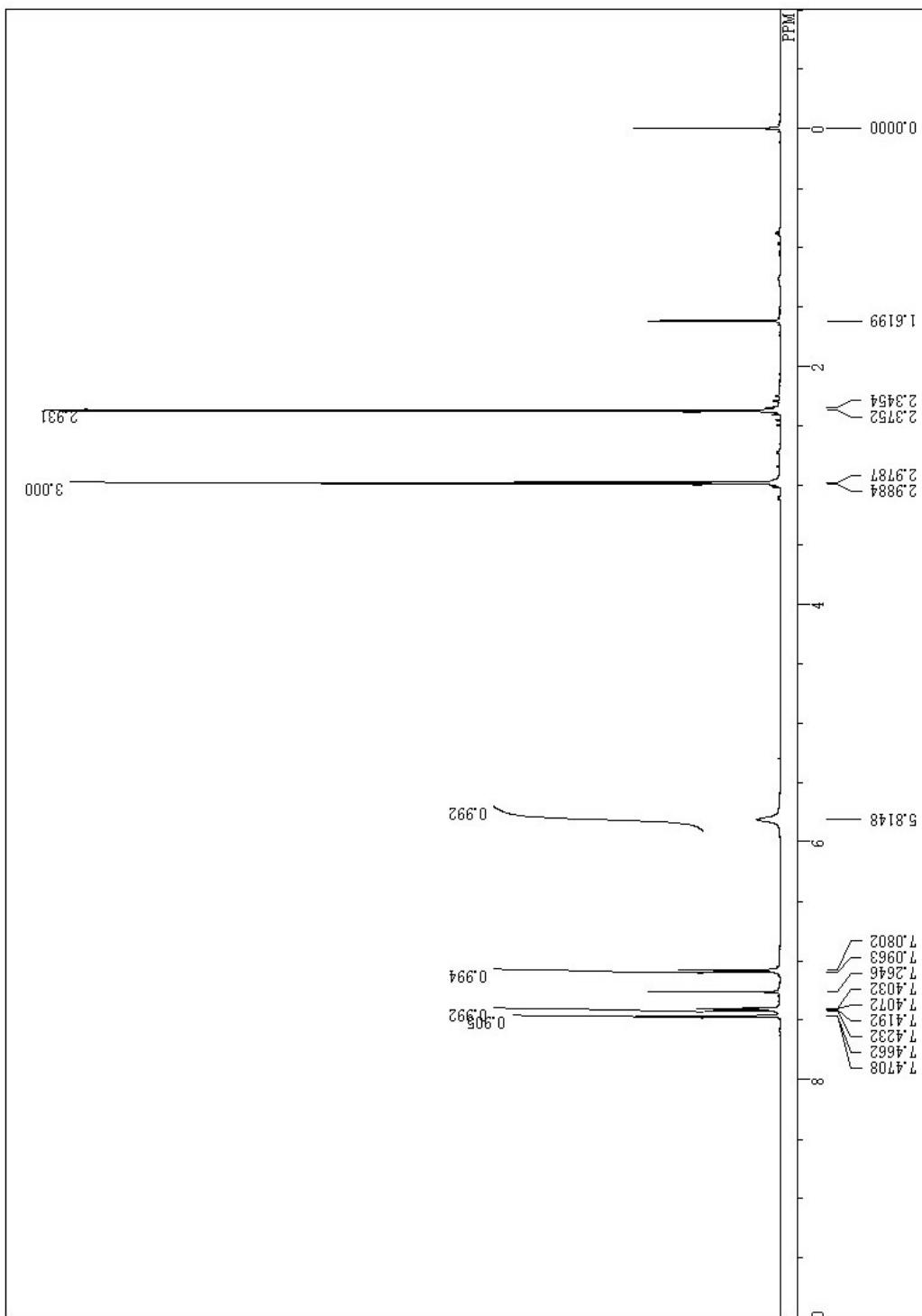
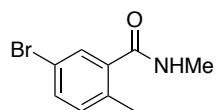
¹H NMR of 3-Bromo-N,2,6-trimethylbenzamide (Table 1, entry 7)



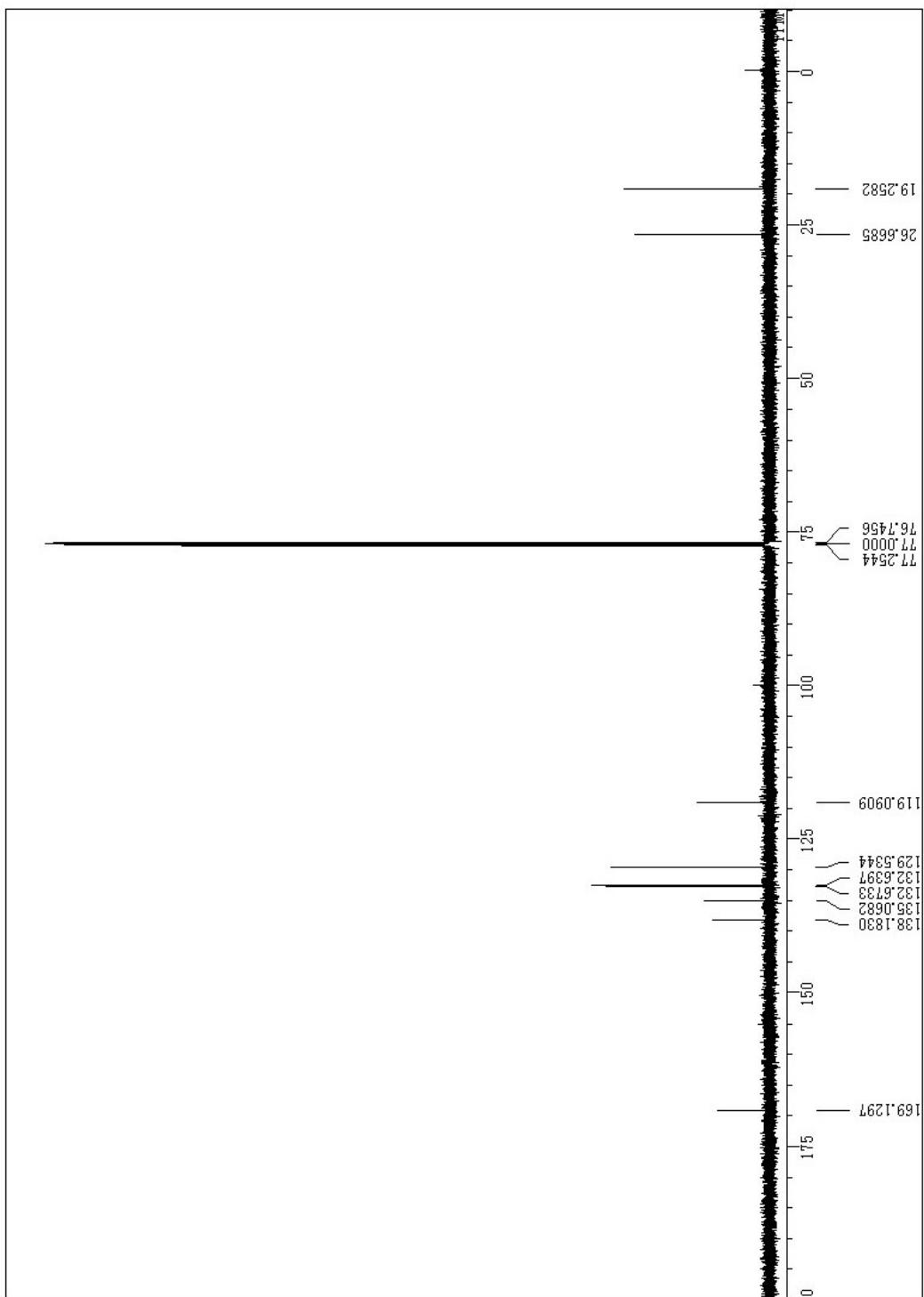
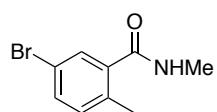
¹³C NMR of 3-Bromo-N,2,6-trimethylbenzamide (Table 1, entry 7)



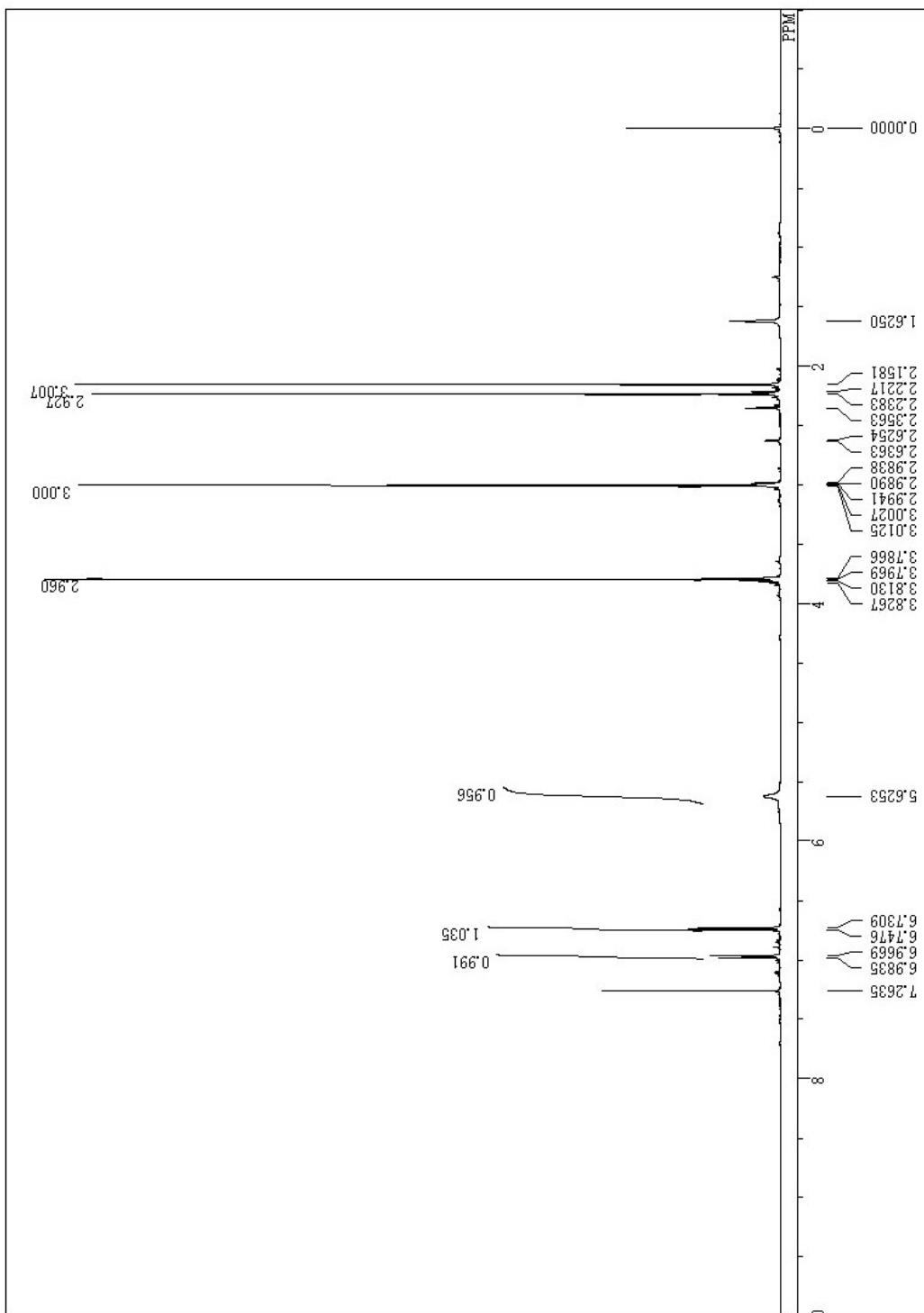
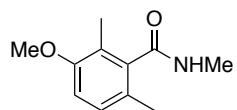
¹H NMR of 5-Bromo-N,2-dimethylbenzamide (Table 1, entry 7)



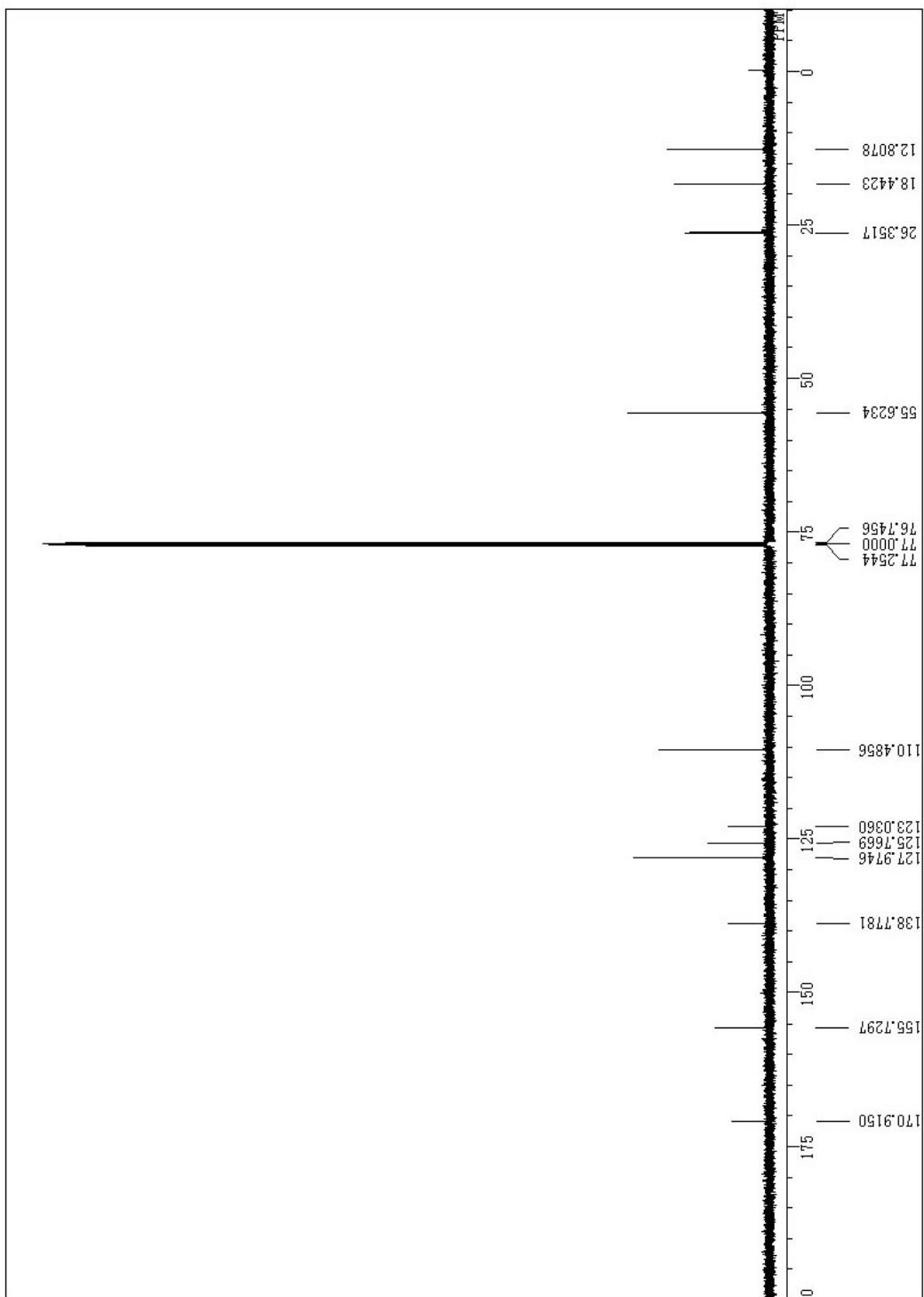
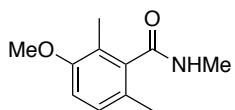
¹³C NMR of 5-Bromo-N,2-dimethylbenzamide (Table 1, entry 7)



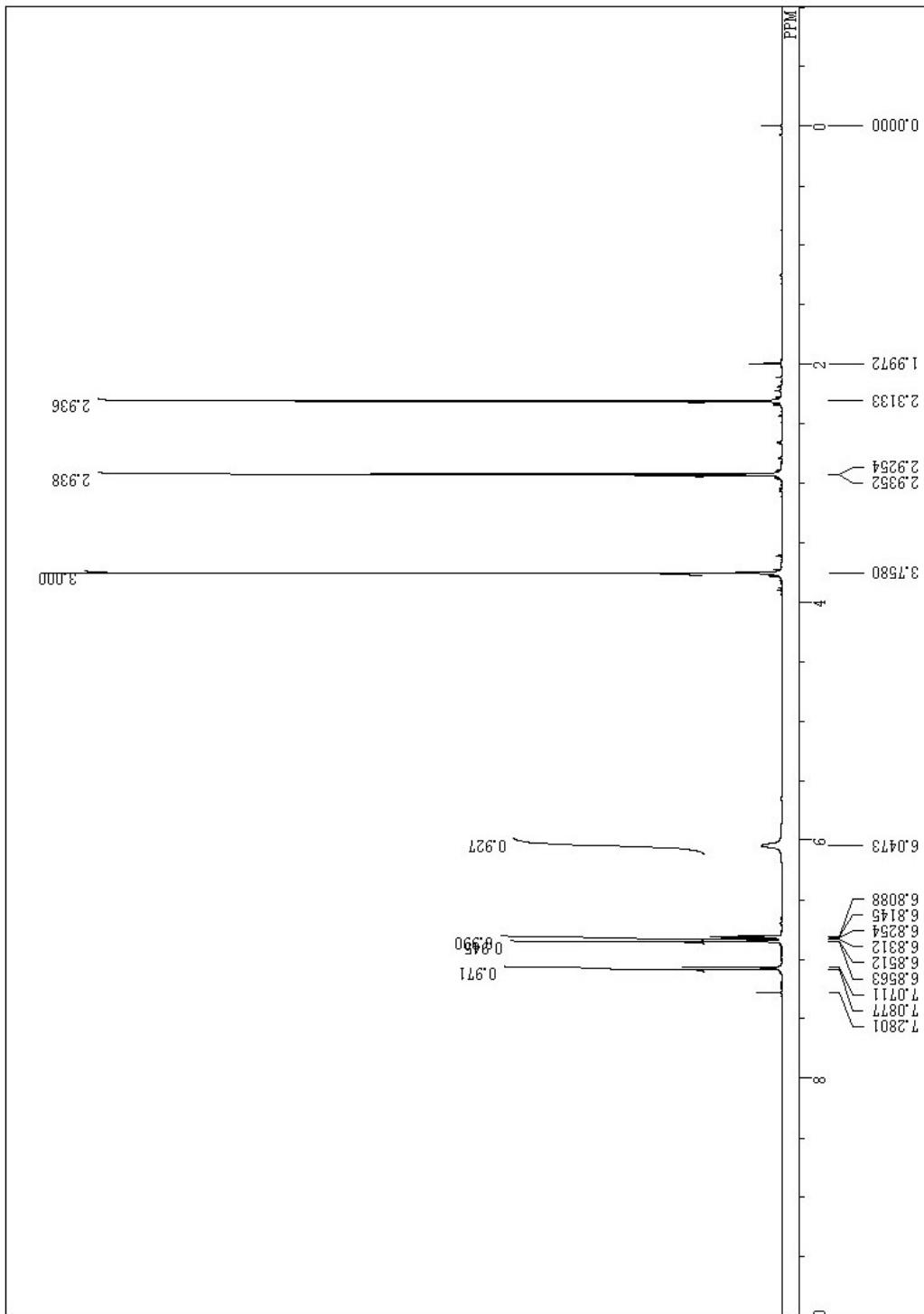
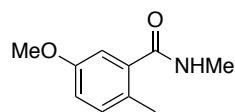
¹H NMR of 3-Methoxy-*N*,2,6-trimethylbenzamide (Table 1, entry 8)



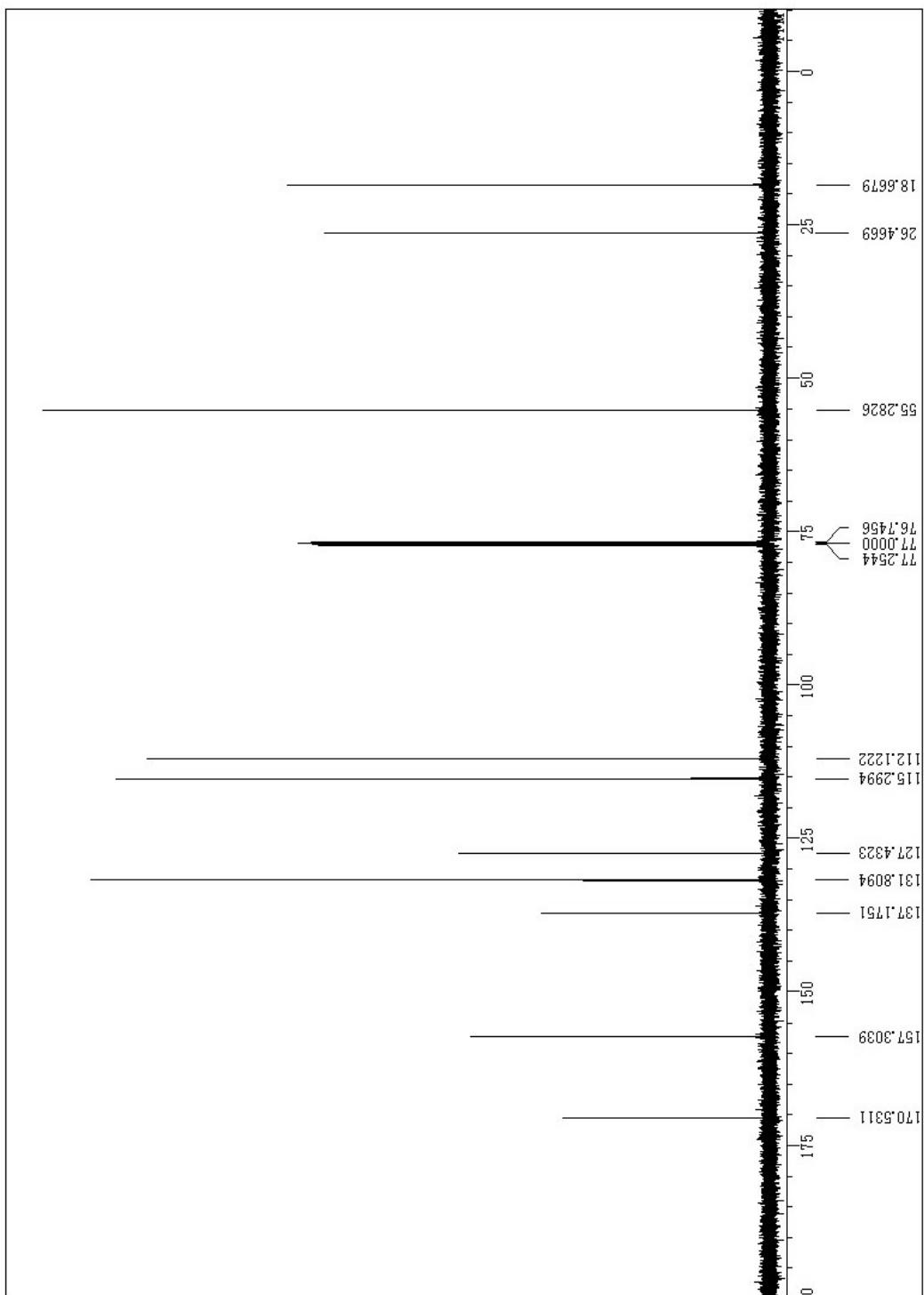
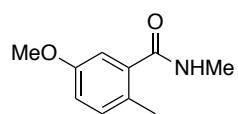
¹³C NMR of 3-Methoxy-*N*,2,6-trimethylbenzamide (Table 1, entry 8)



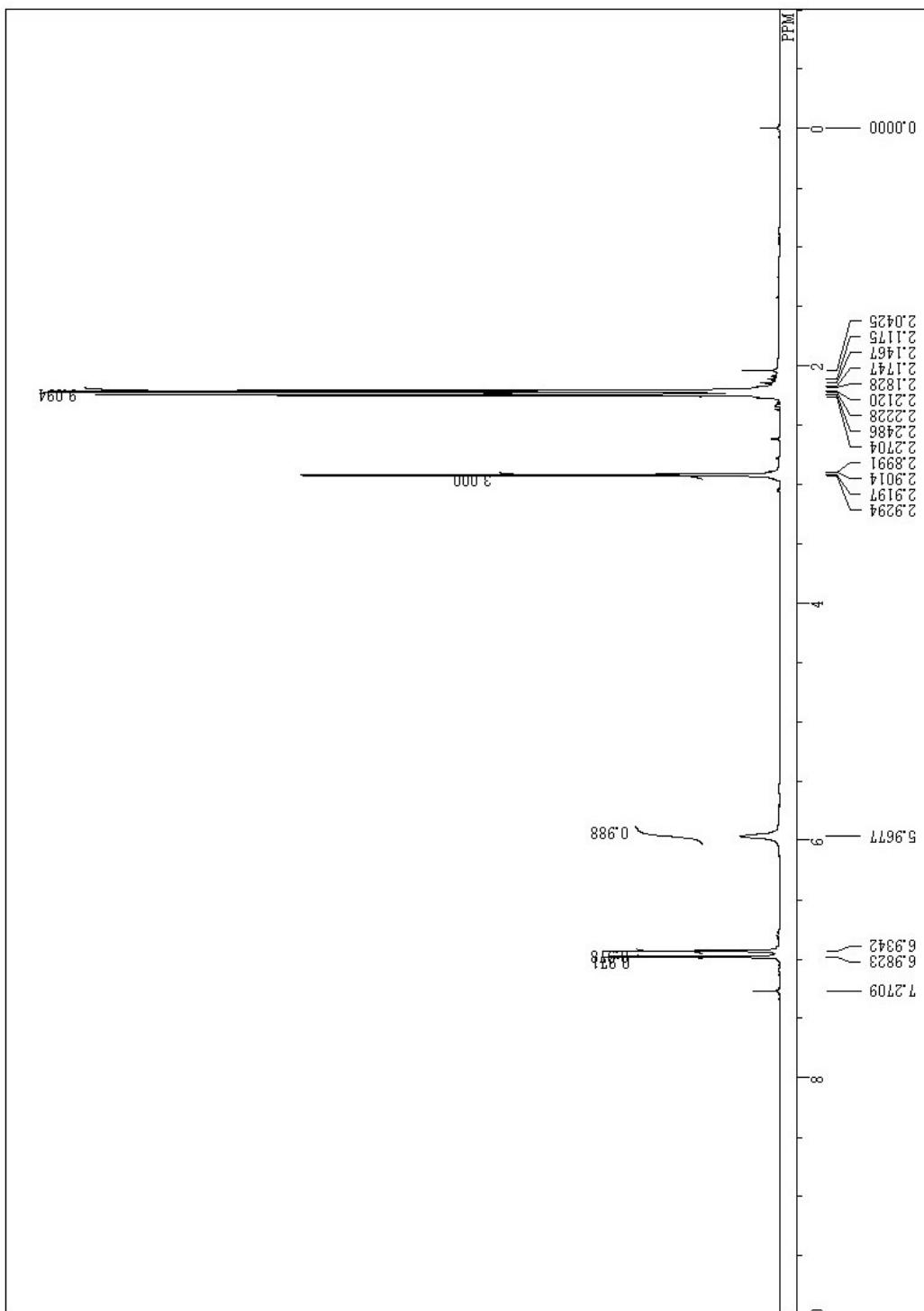
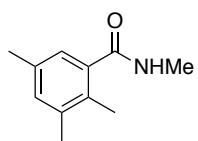
¹H NMR of 5-Methoxy-*N*,2-dimethylbenzamide (Table 1, entry 8)



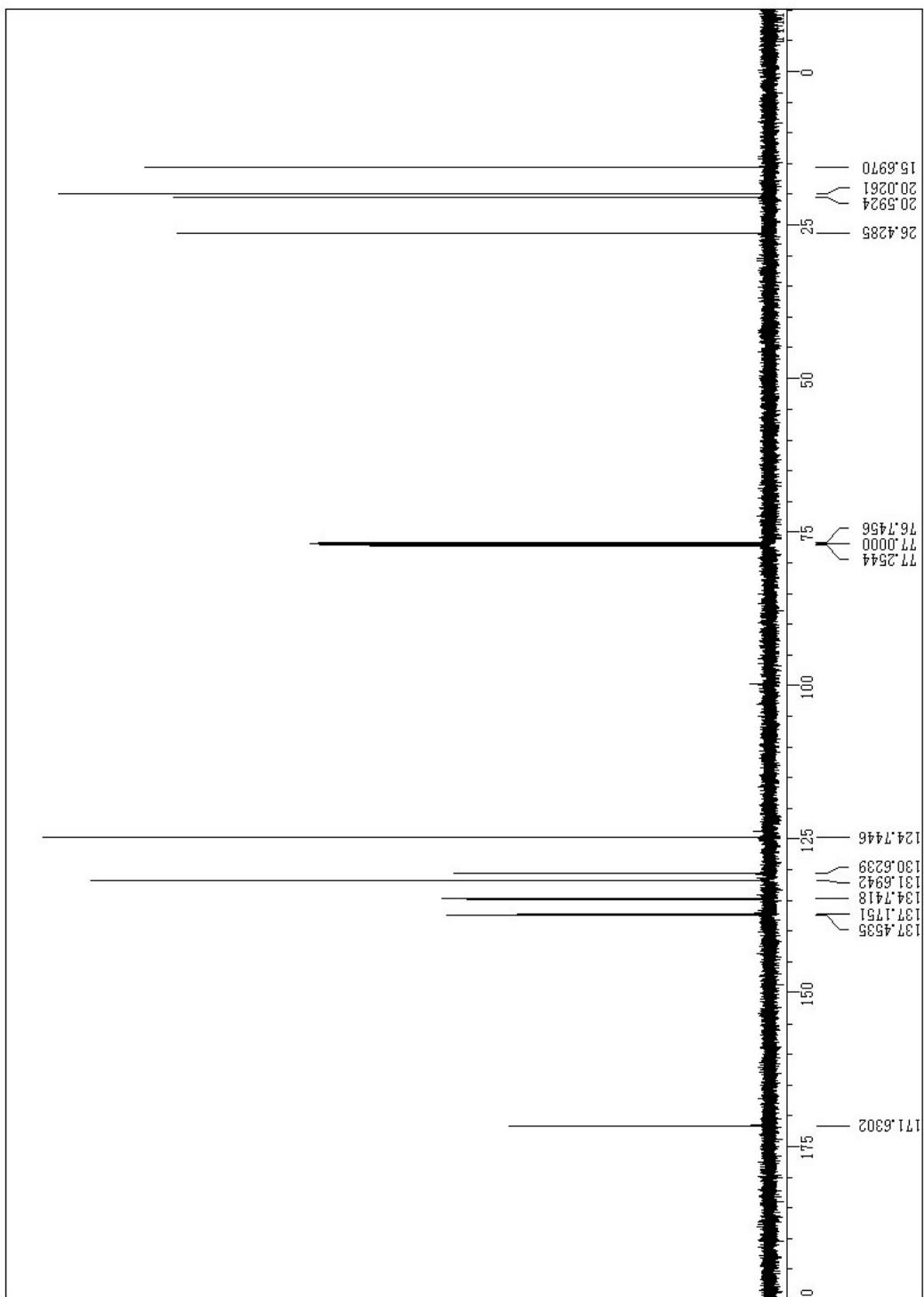
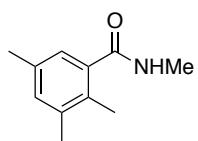
¹³C NMR of 5-Methoxy-*N*,2-dimethylbenzamide (Table 1, entry 8)



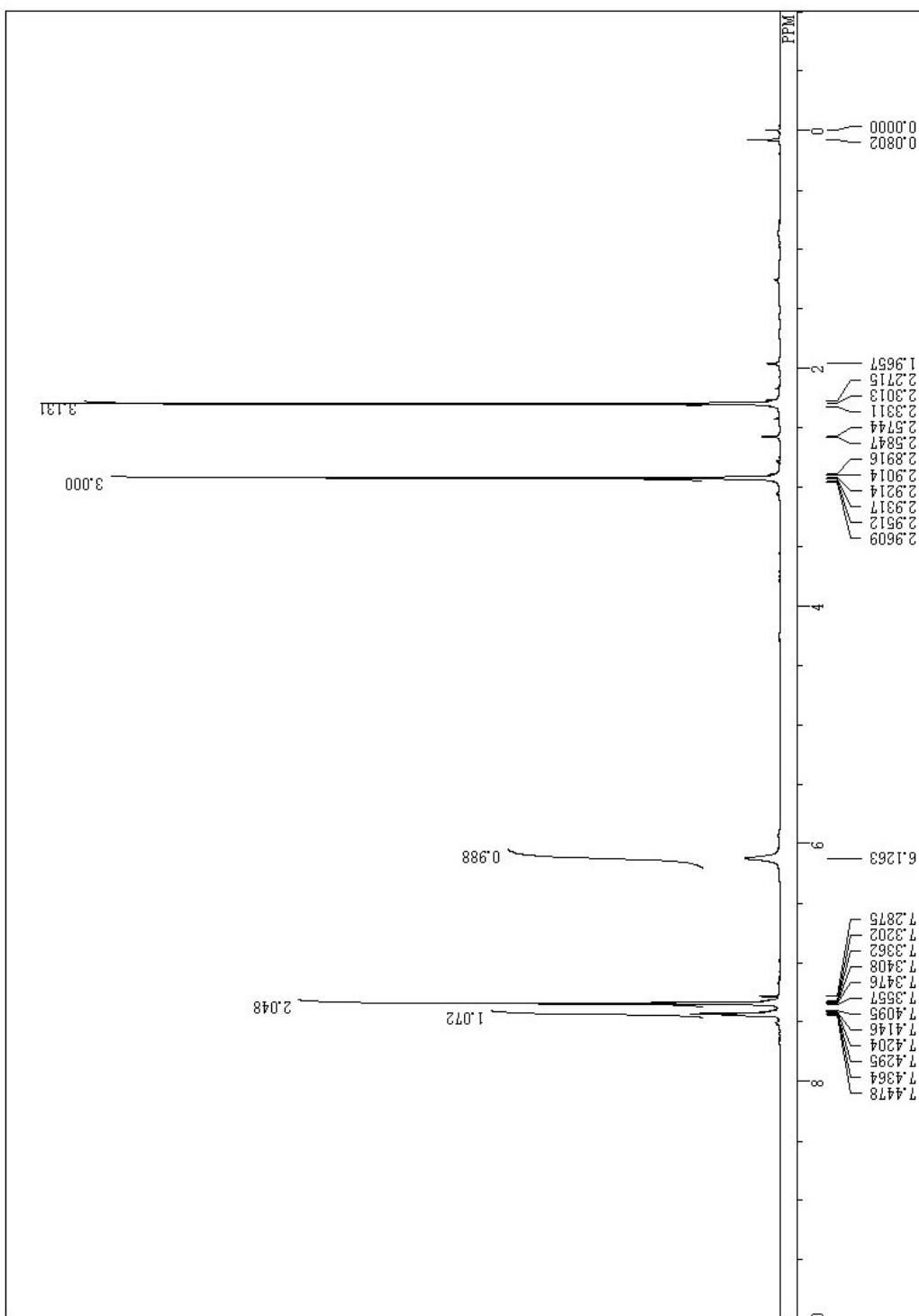
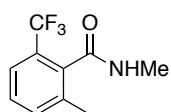
¹H NMR of *N*,2,3,5-Tetramethylbenzamide (Table 1, entry 9)



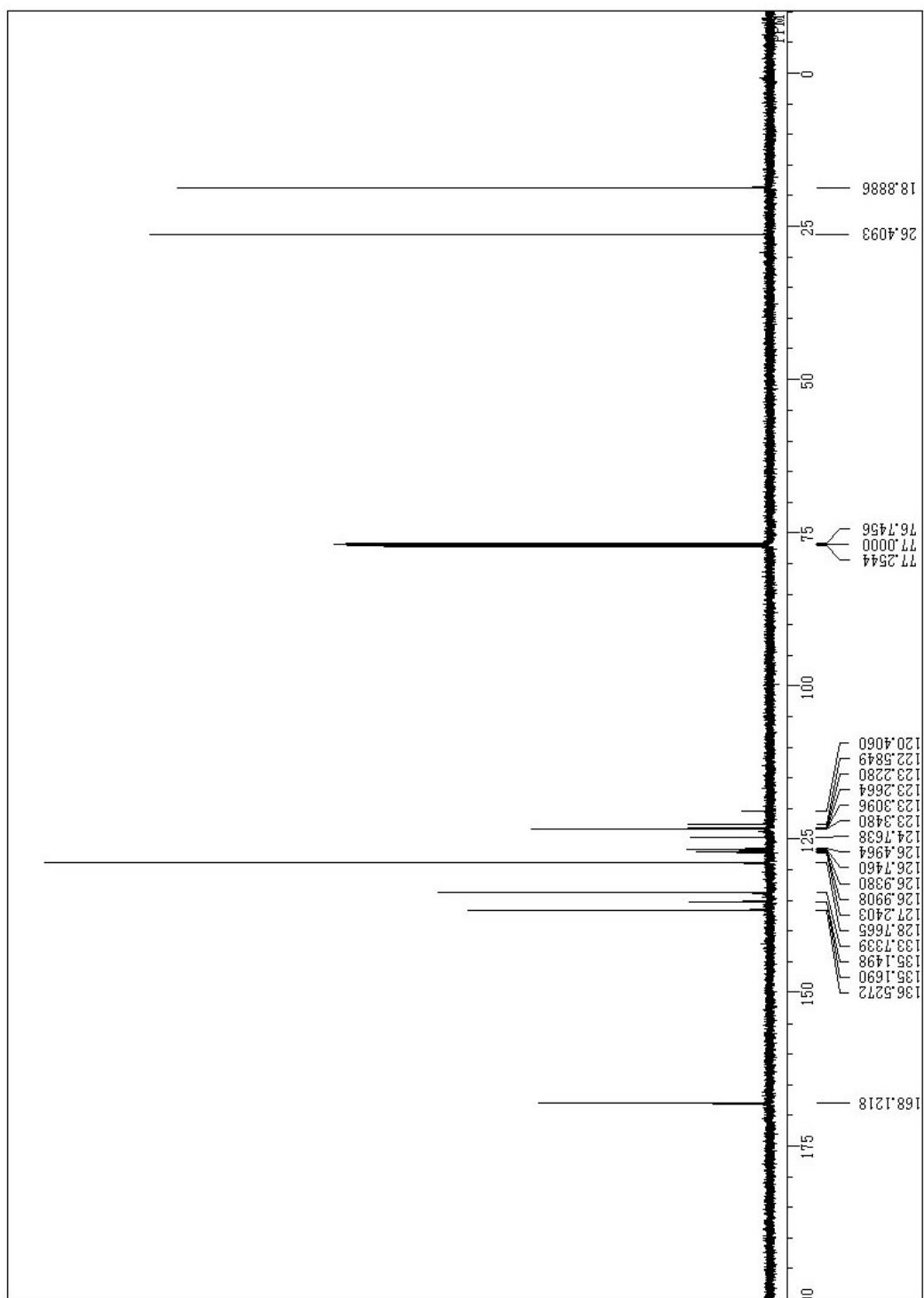
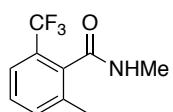
^{13}C NMR of *N*,2,3,5-Tetramethylbenzamide (Table 1, entry 9)



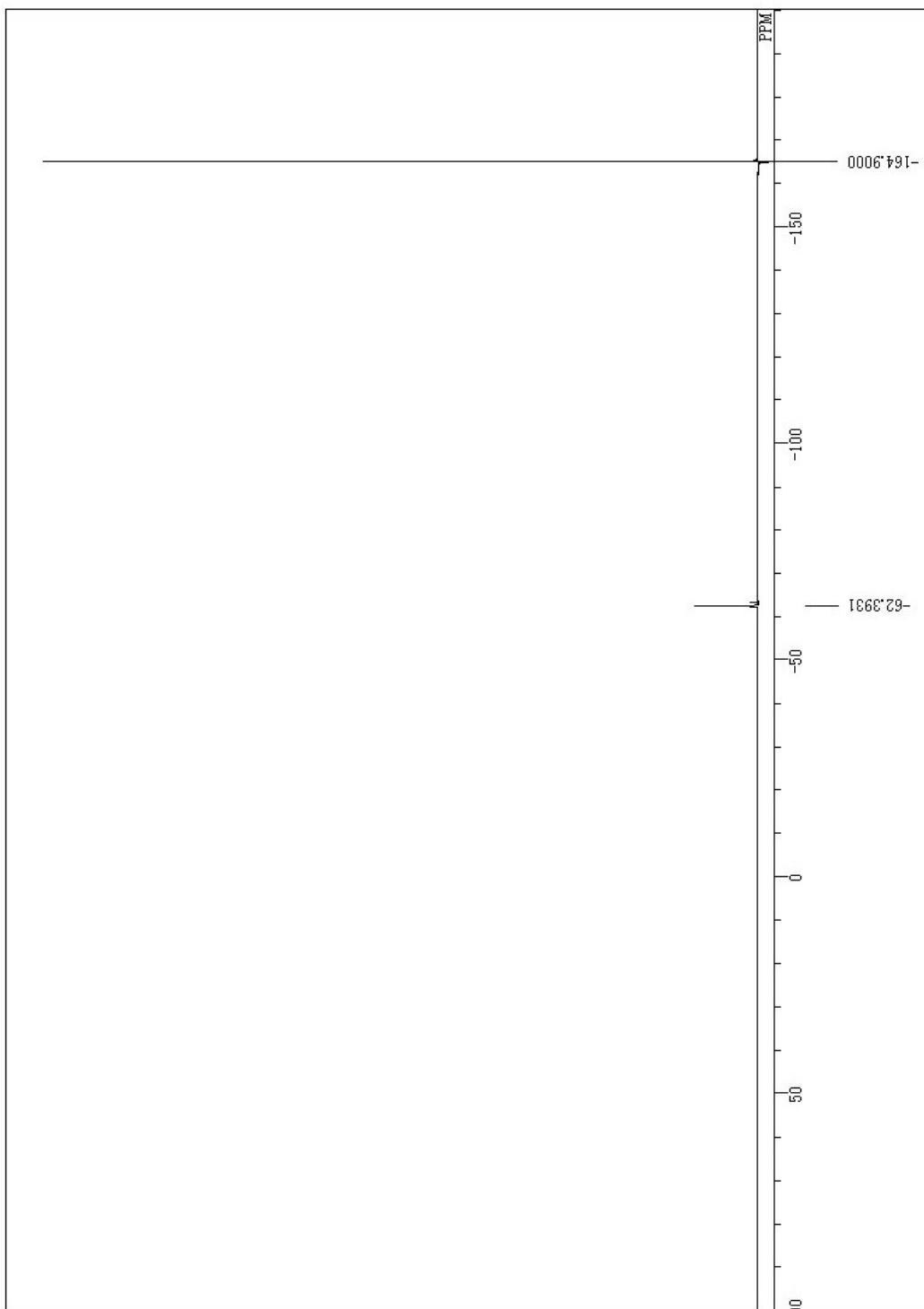
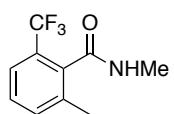
¹H NMR of *N*,6-Dimethyl-2-(trifluoromethyl)benzamide (Table 1, entry 10)



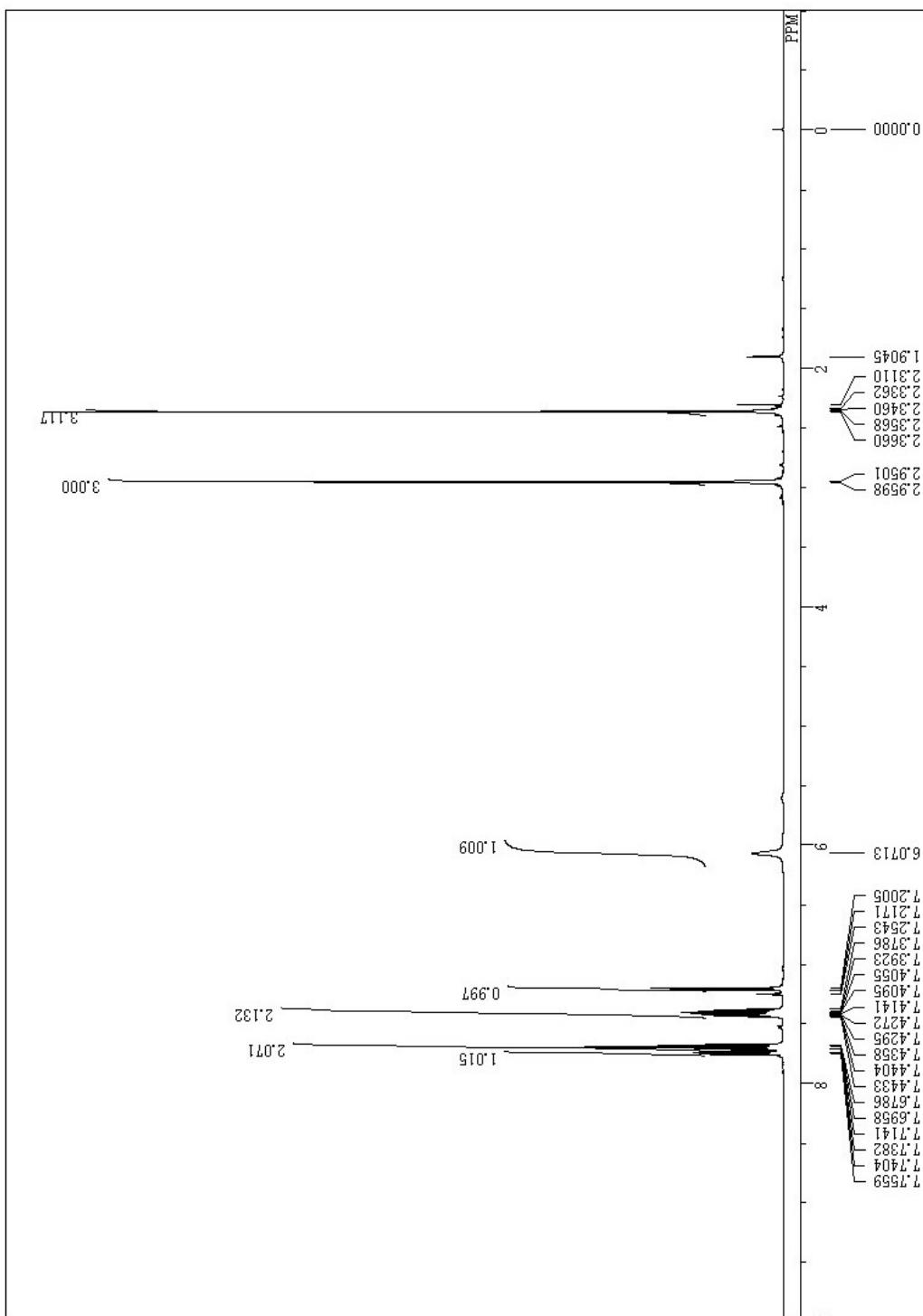
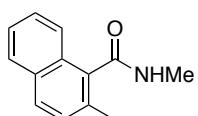
^{13}C NMR of *N*,6-Dimethyl-2-(trifluoromethyl)benzamide (Table 1, entry 10)



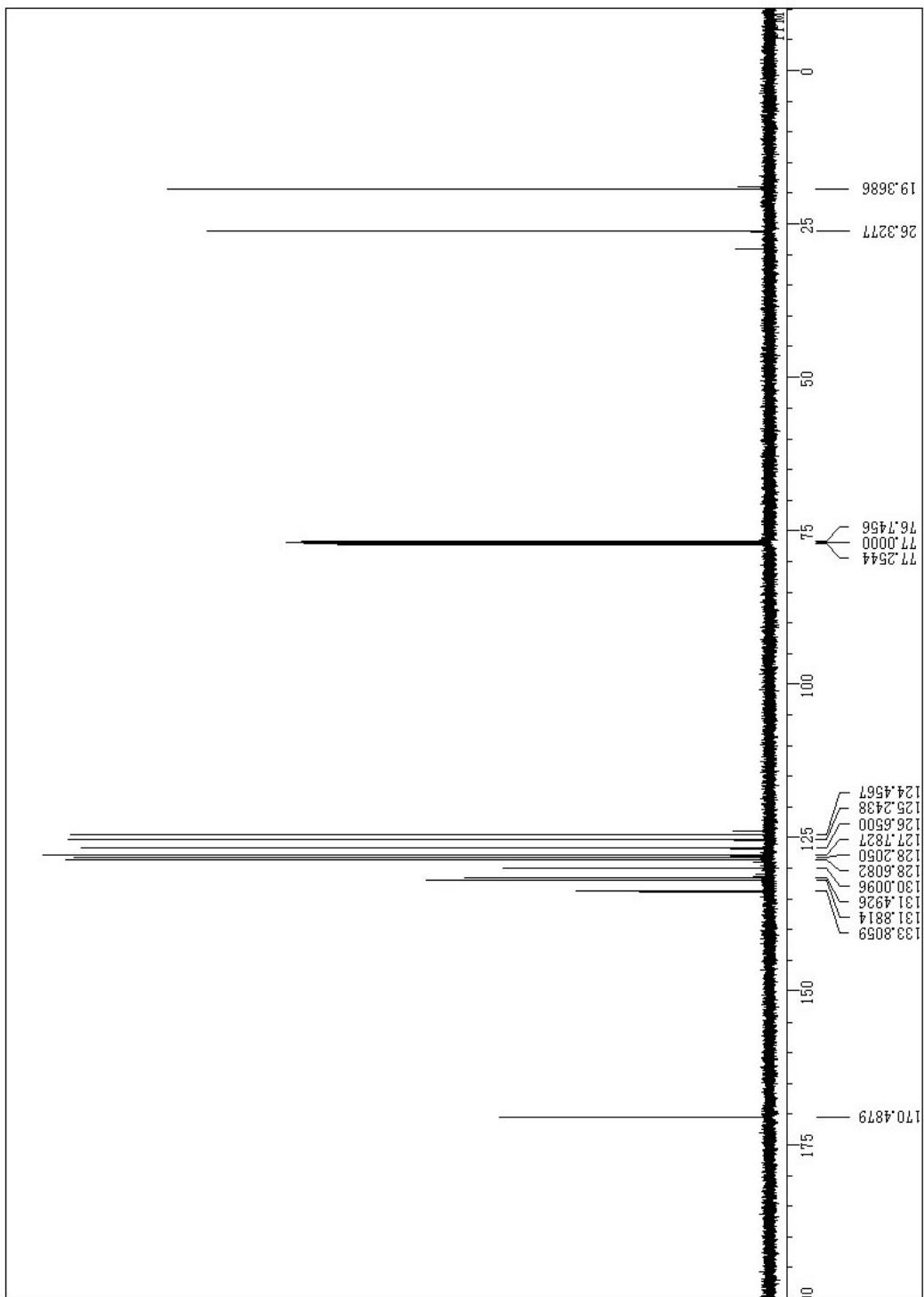
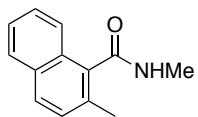
¹⁹F NMR of *N*,6-Dimethyl-2-(trifluoromethyl)benzamide (Table 1, entry 10)



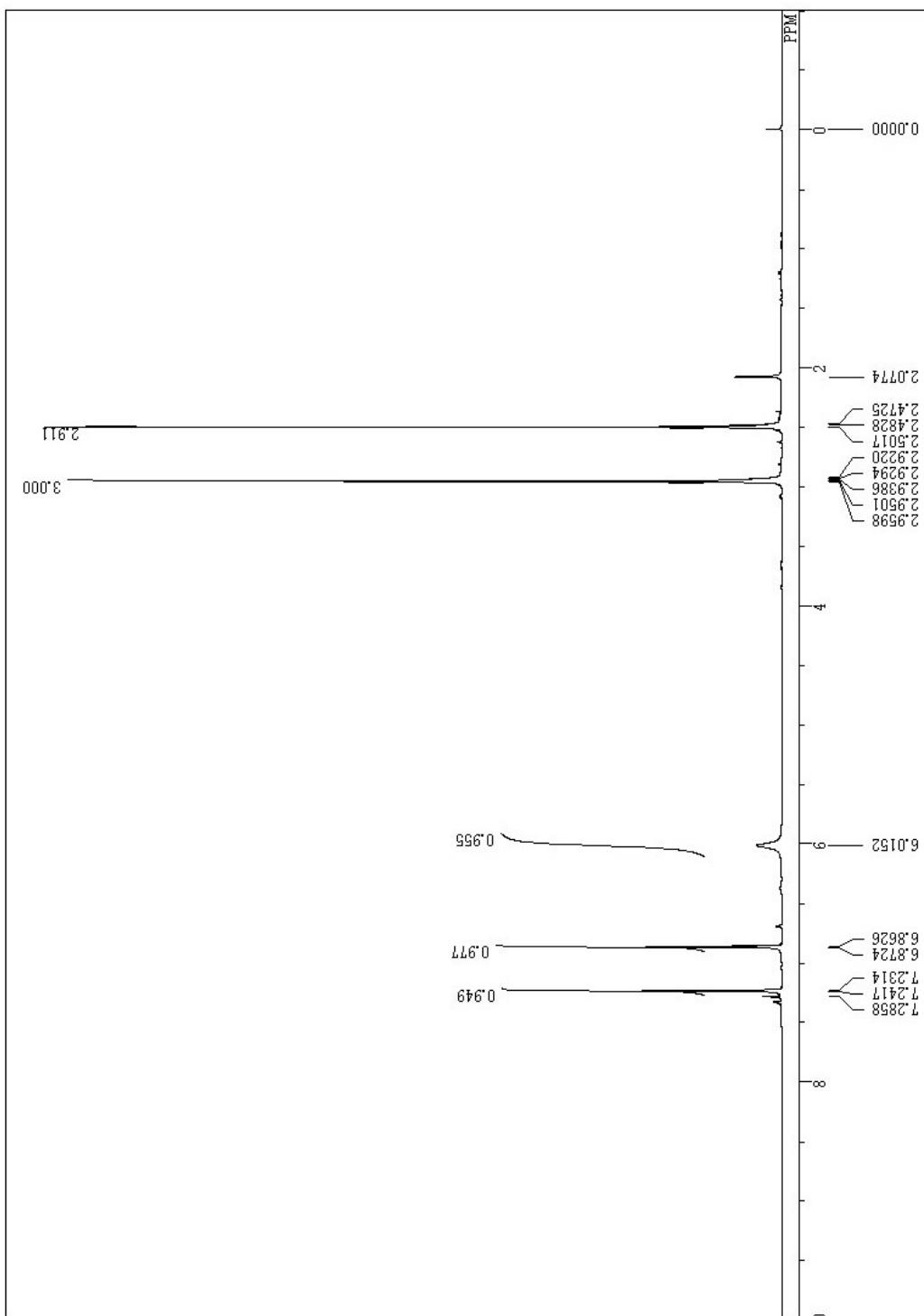
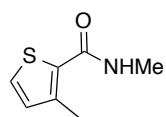
¹H NMR of *N*,2-Dimethyl-1-naphthalenecarboxamide (Table 1, entry 11)



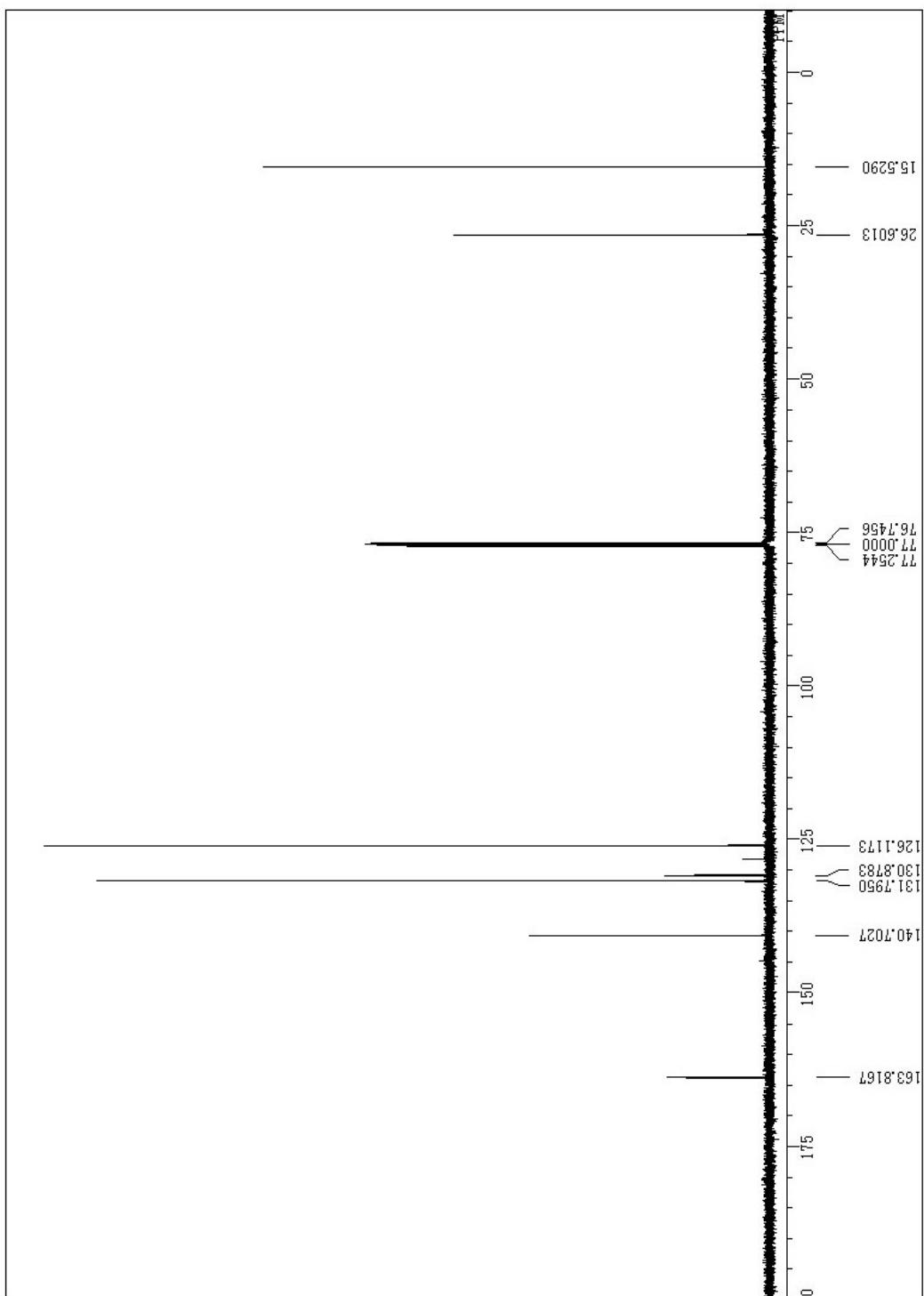
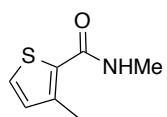
¹³C NMR of *N*,2-Dimethyl-1-naphthalenecarboxamide (Table 1, entry 11)



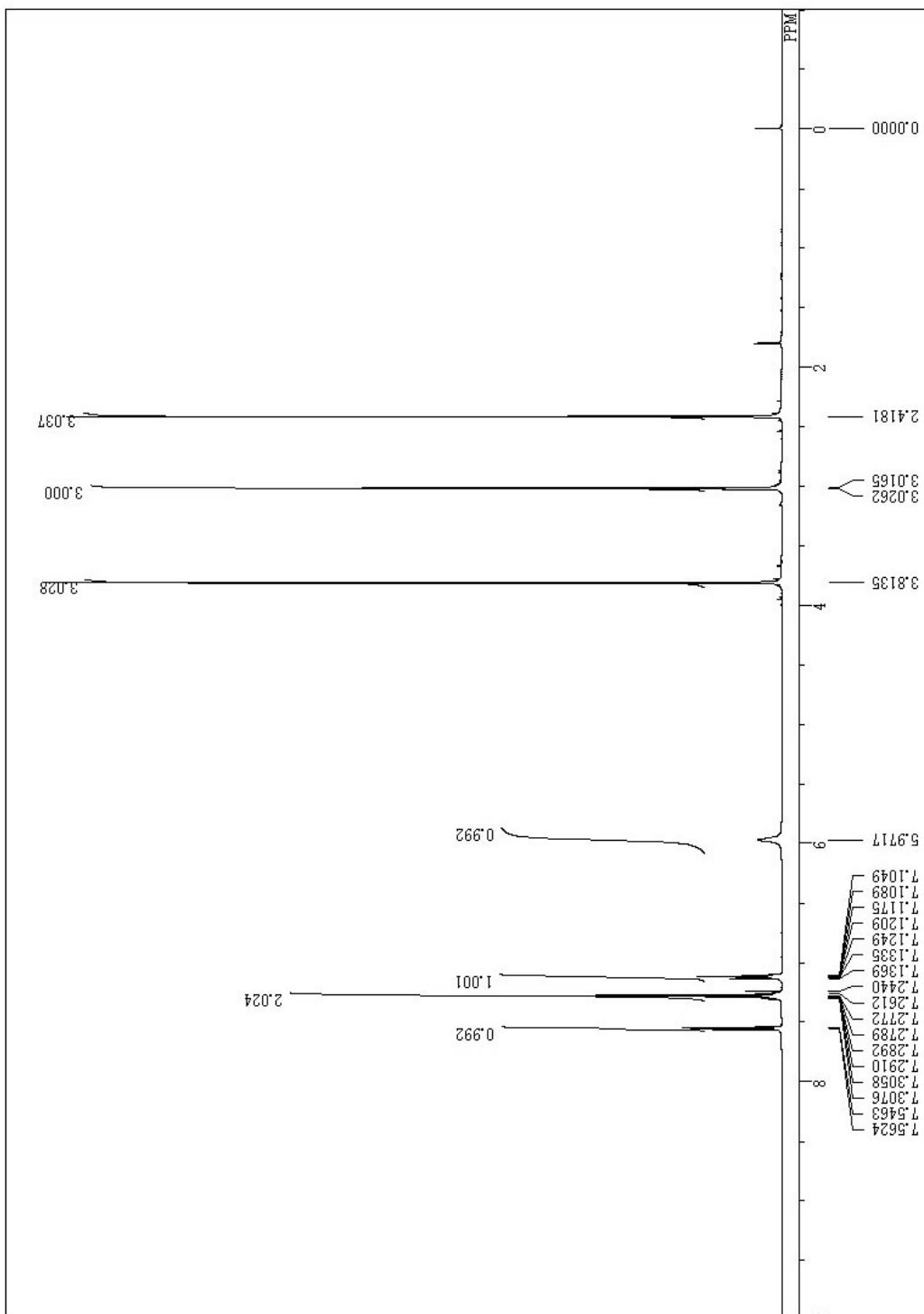
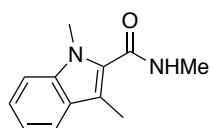
¹H NMR of *N*,3-Dimethyl-2-thiophenecarboxamide (Table 1, entry 12)



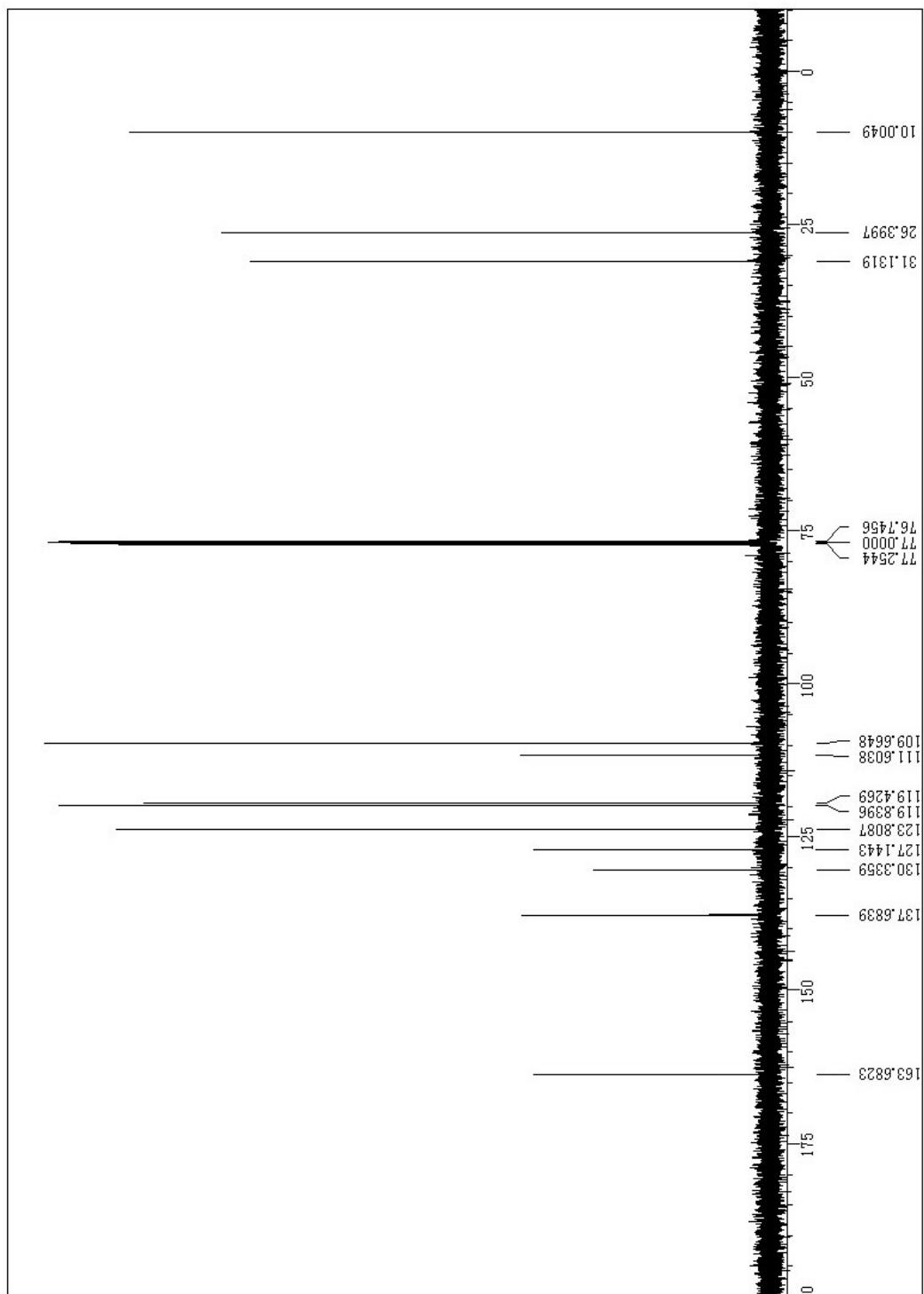
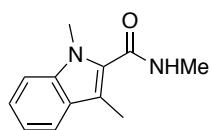
^{13}C NMR of *N*,3-Dimethyl-2-thiophenecarboxamide (Table 1, entry 12)



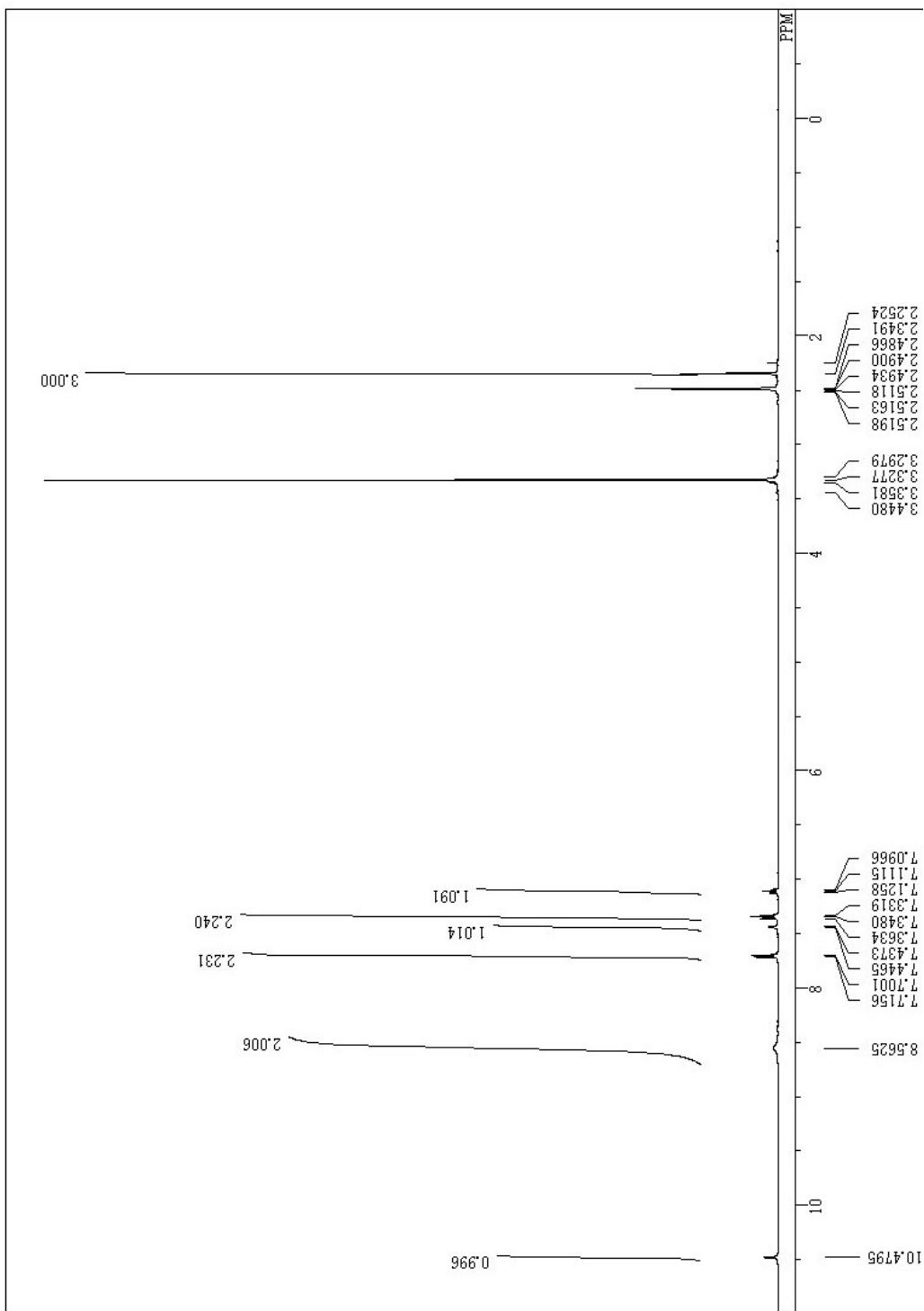
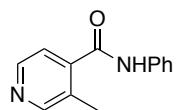
¹H NMR of *N*,1,3-Trimethyl-1*H*-indole-2-carboxamide (Table 1, entry 13)



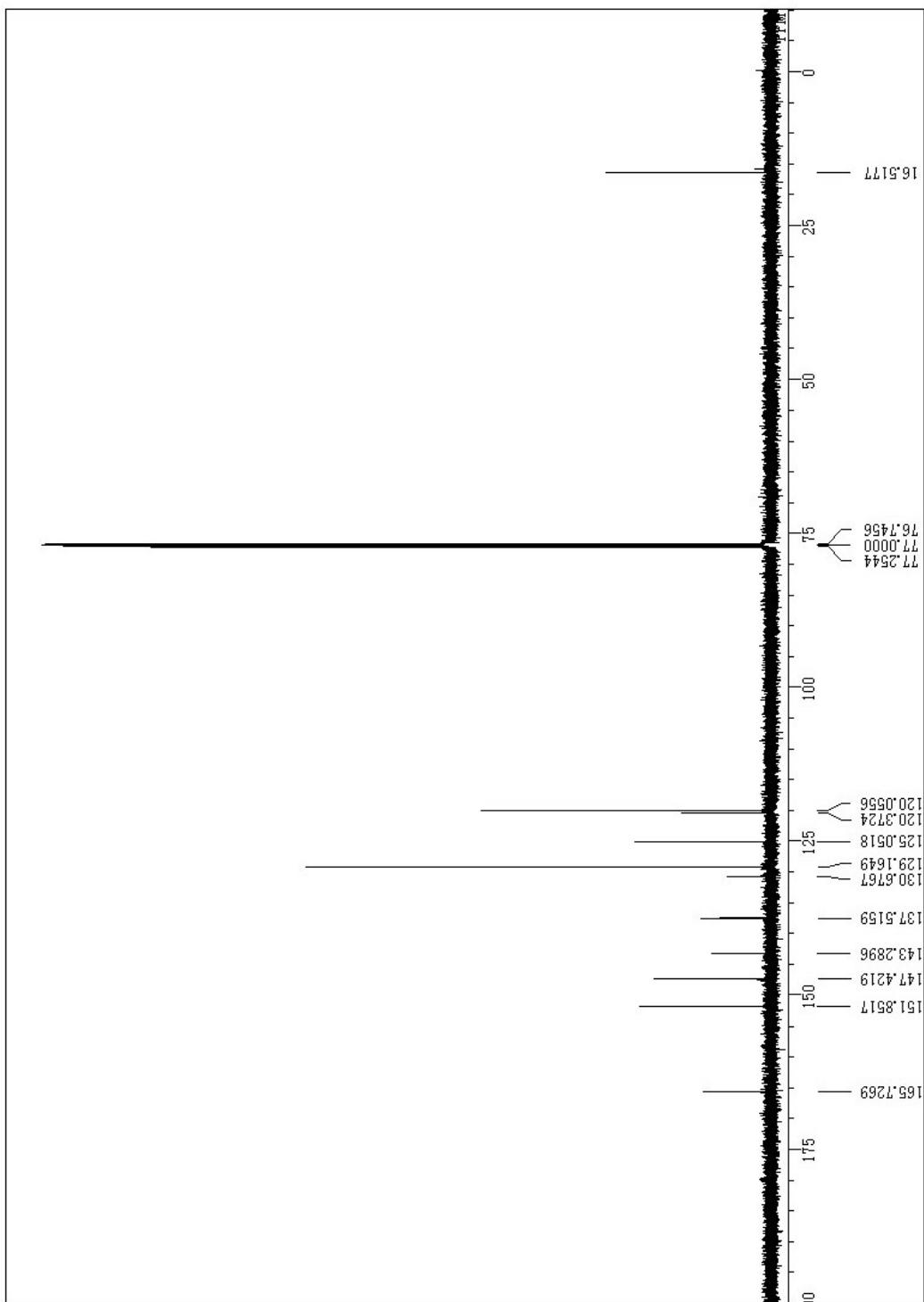
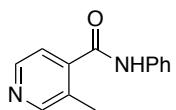
^{13}C NMR of *N*,1,3-Trimethyl-1*H*-indole-2-carboxamide (Table 1, entry 13)



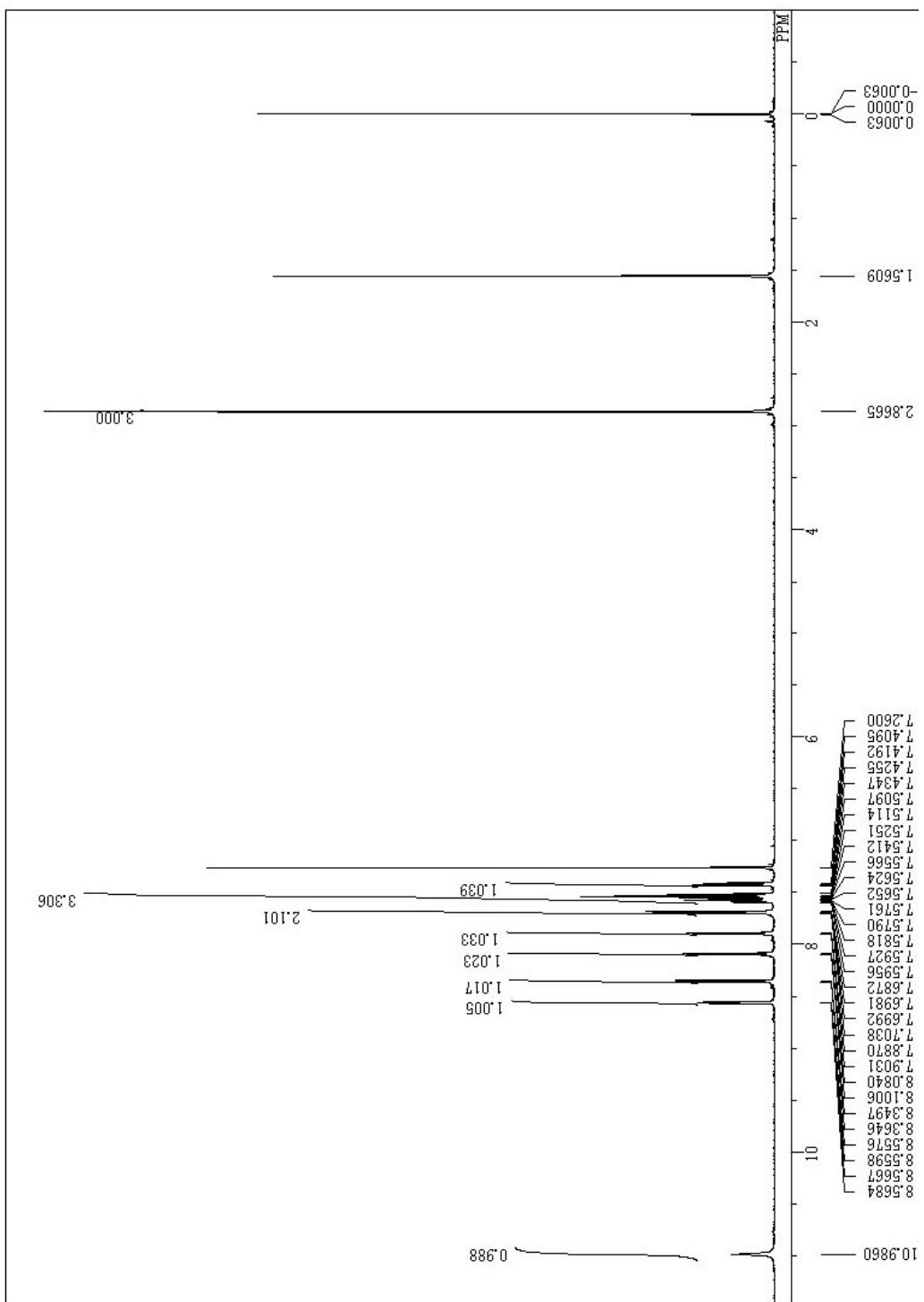
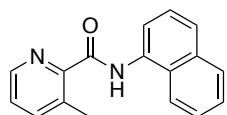
¹H NMR of 3-Methyl-N-phenyl-4-pyridinecarboxamide (Table 1, entry 14)



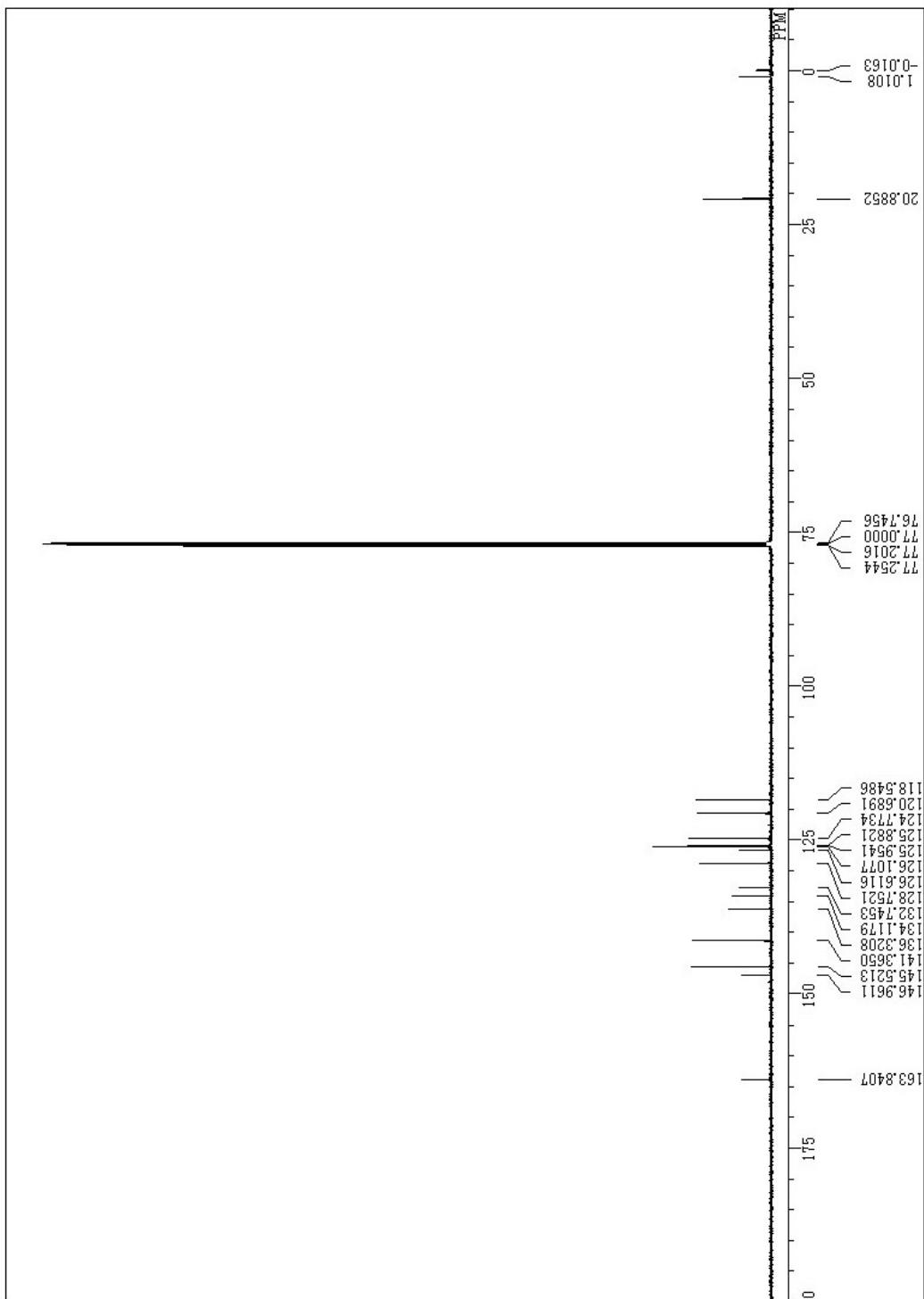
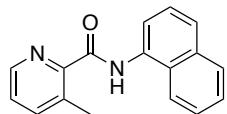
¹³C NMR of 3-Methyl-N-phenyl-4-pyridinecarboxamide (Table 1, entry 14)



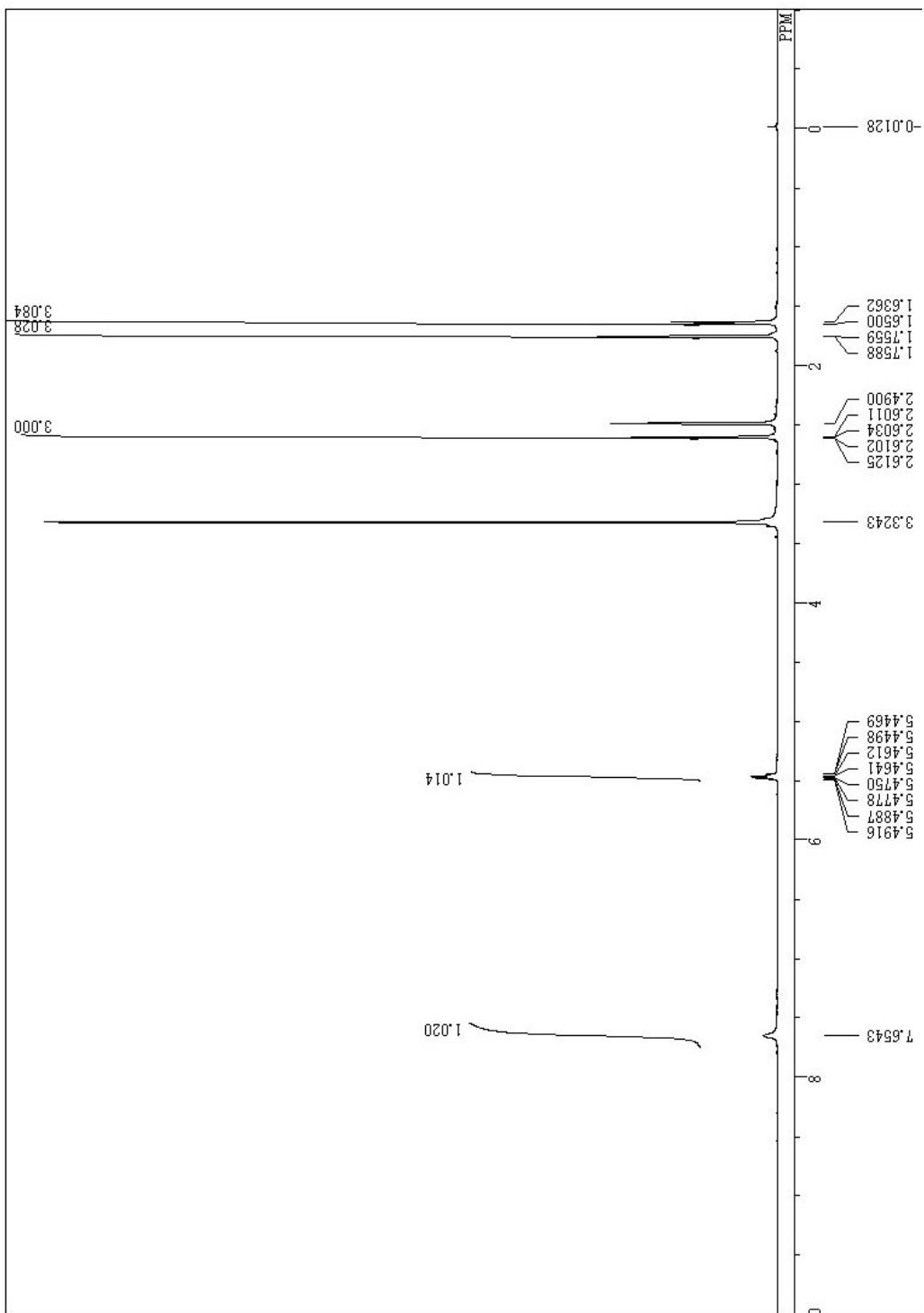
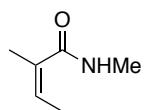
¹H NMR of 3-Methyl-*N*-(naphthalen-1-yl)picolinamide (Table 1, entry 15)



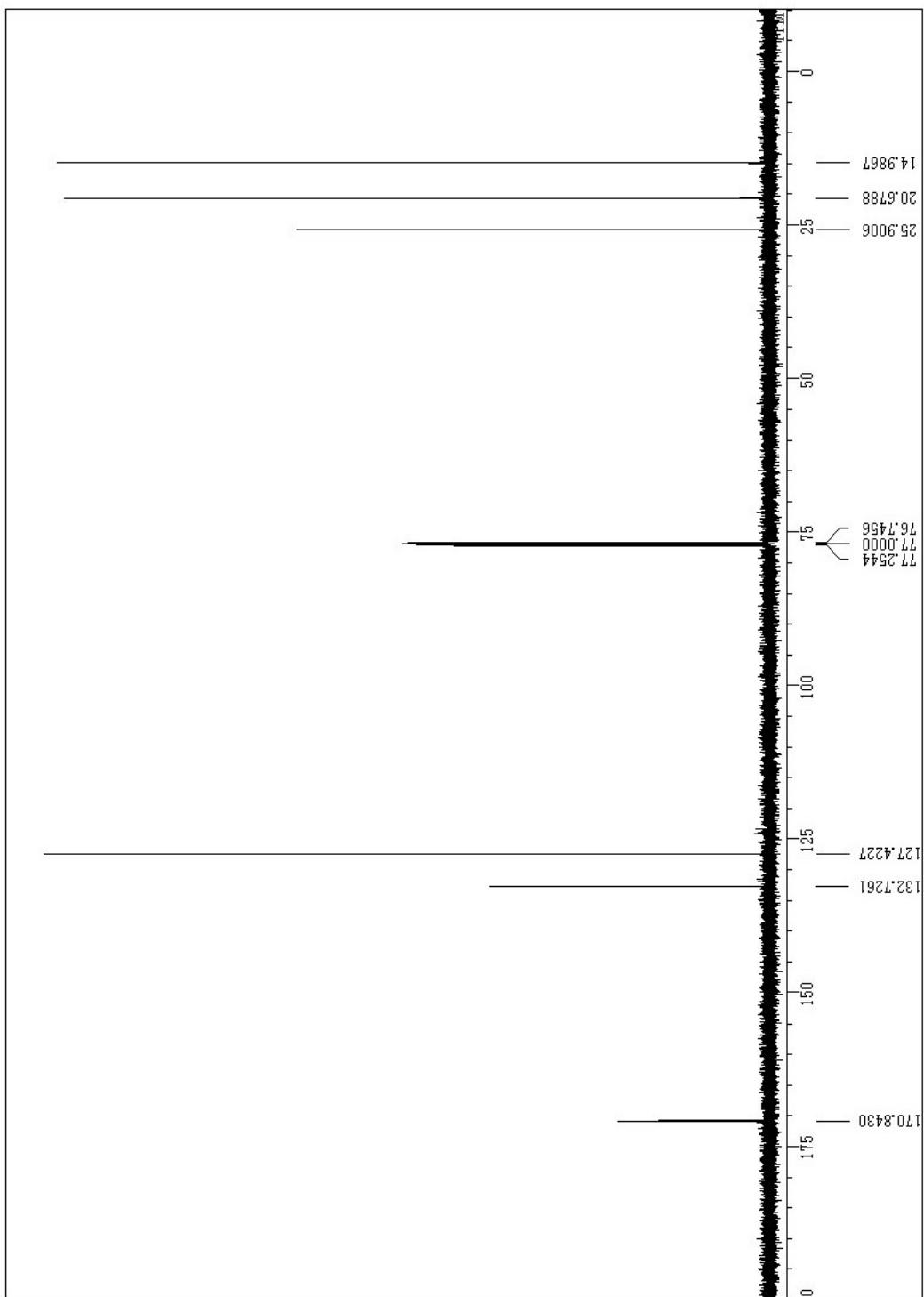
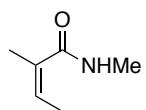
¹³C NMR of 3-Methyl-*N*-(naphthalen-1-yl)picolinamide (Table 1, entry 15)



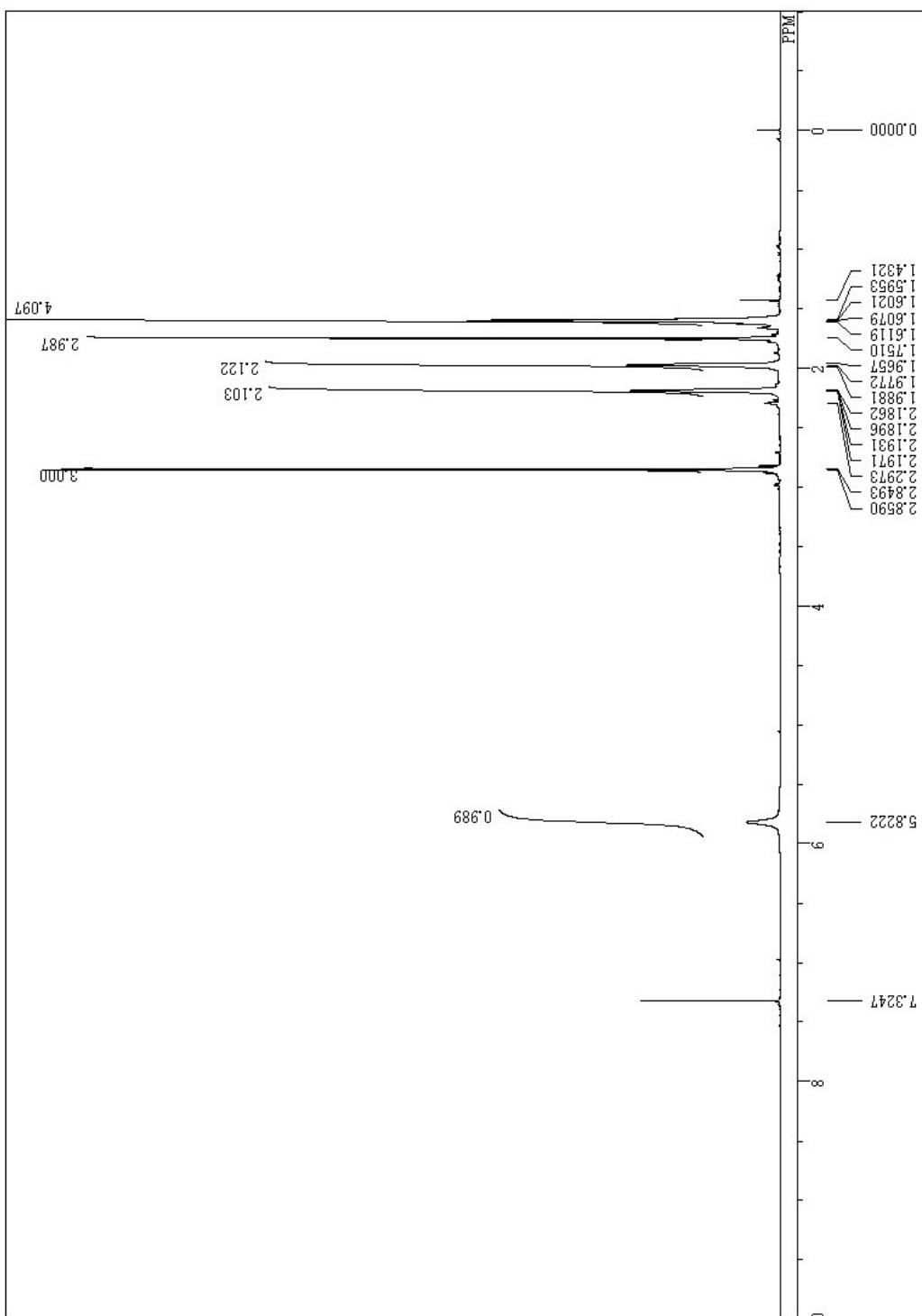
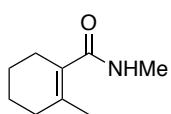
¹H NMR of (Z)-N,2-Dimethyl-2-butenamide (Table 1, entry 16)



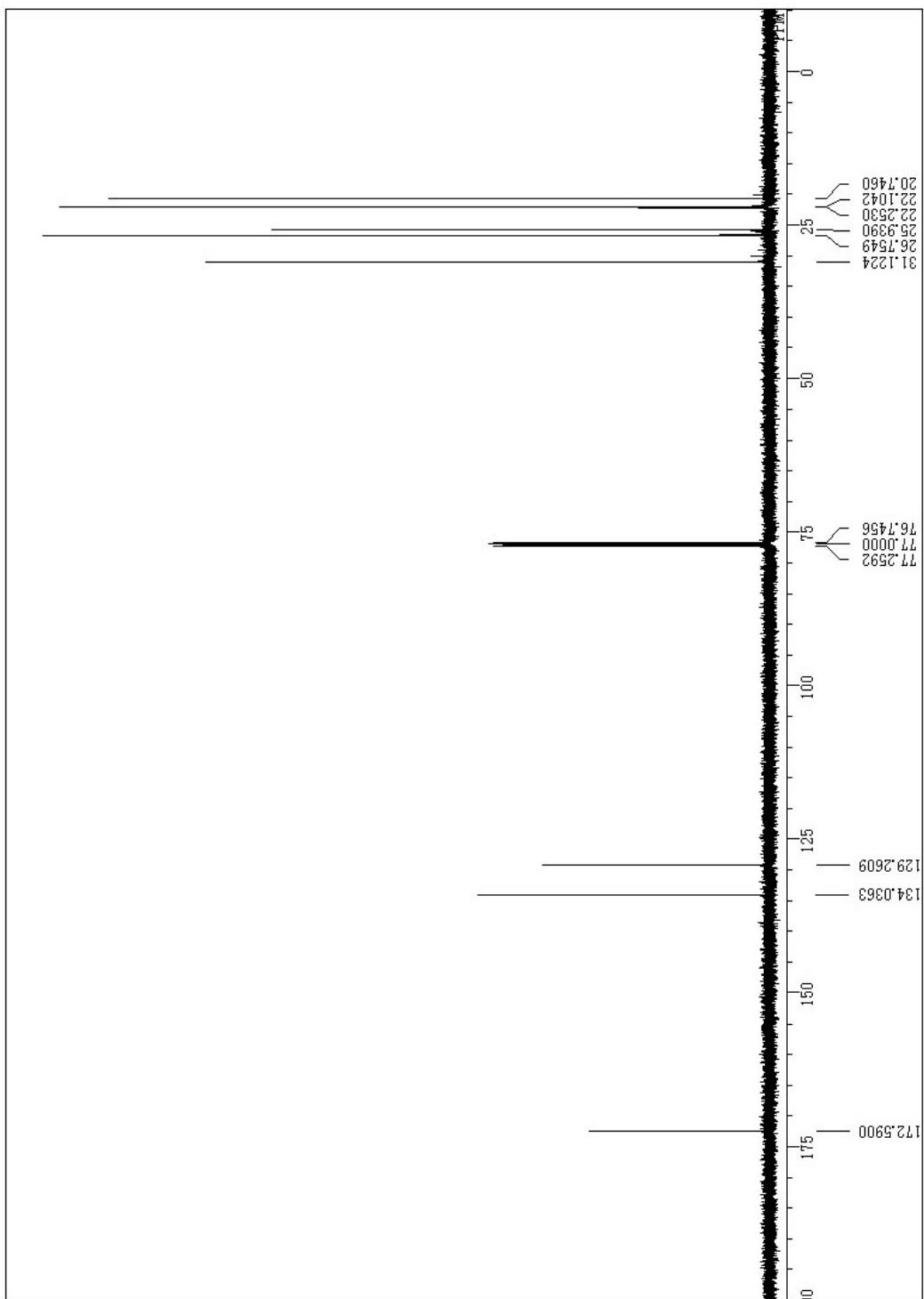
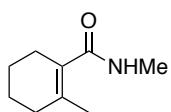
^{13}C NMR of (*Z*)-*N*,2-Dimethyl-2-butenamide (Table 1, entry 16)



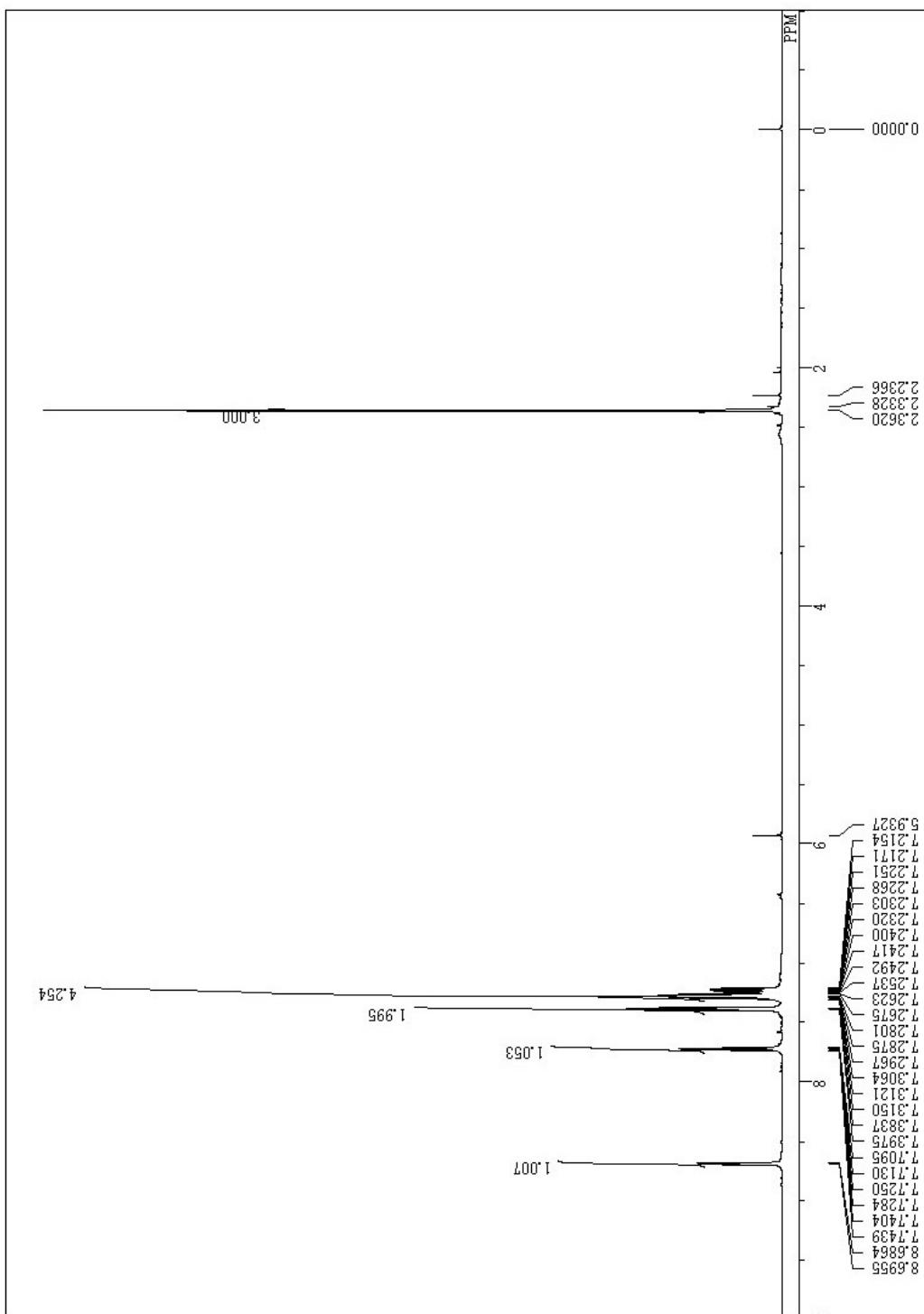
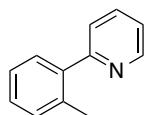
¹H NMR of *N*,2-Dimethyl-1-cyclohexene-1-carboxamide (Table 1, entry 17)



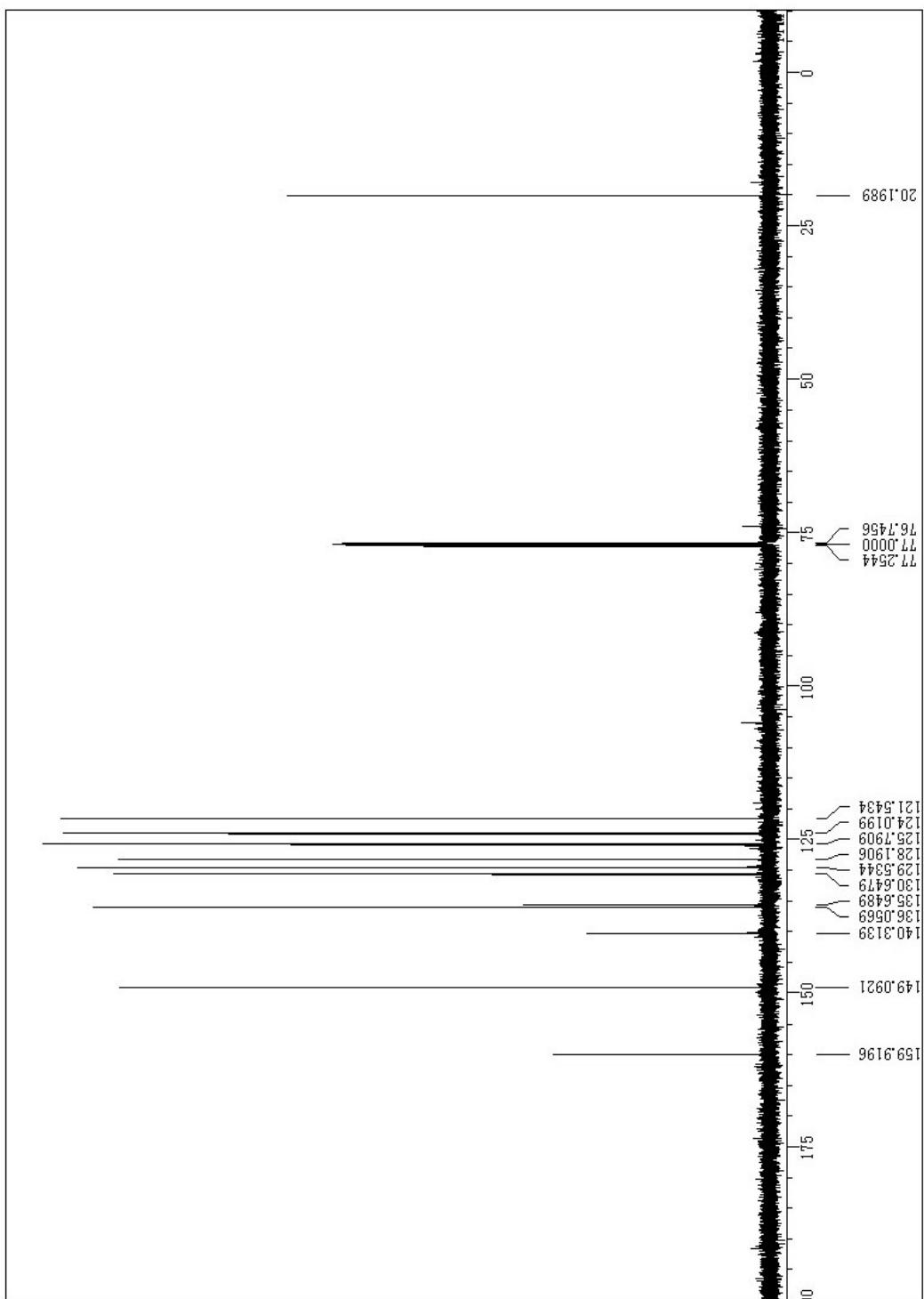
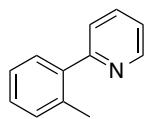
¹³C NMR of *N*,2-Dimethyl-1-cyclohexene-1-carboxamide (Table 1, entry 17)



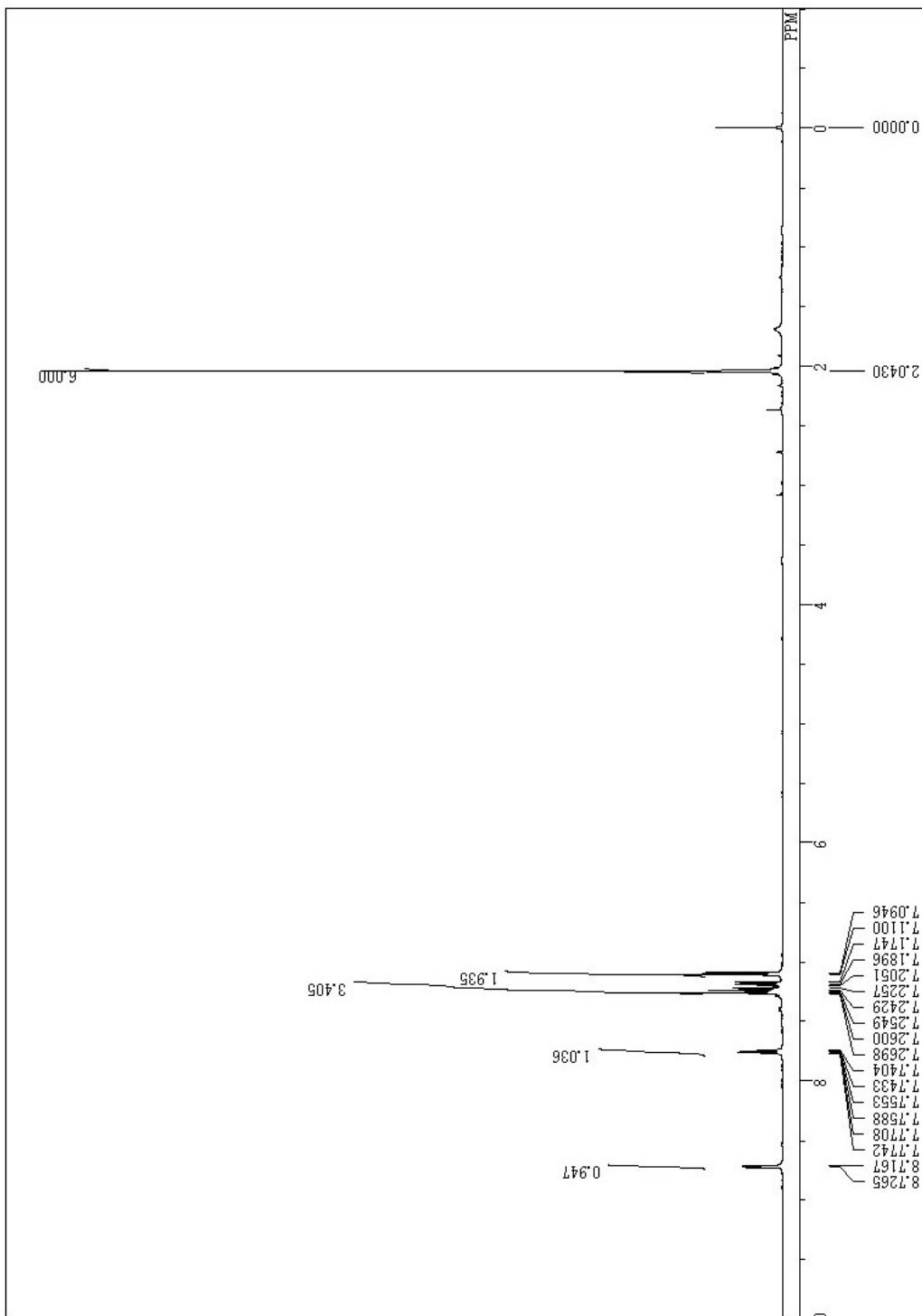
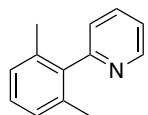
¹H NMR of 2-(2-Methylphenyl)pyridine (Table 2, entry 1)



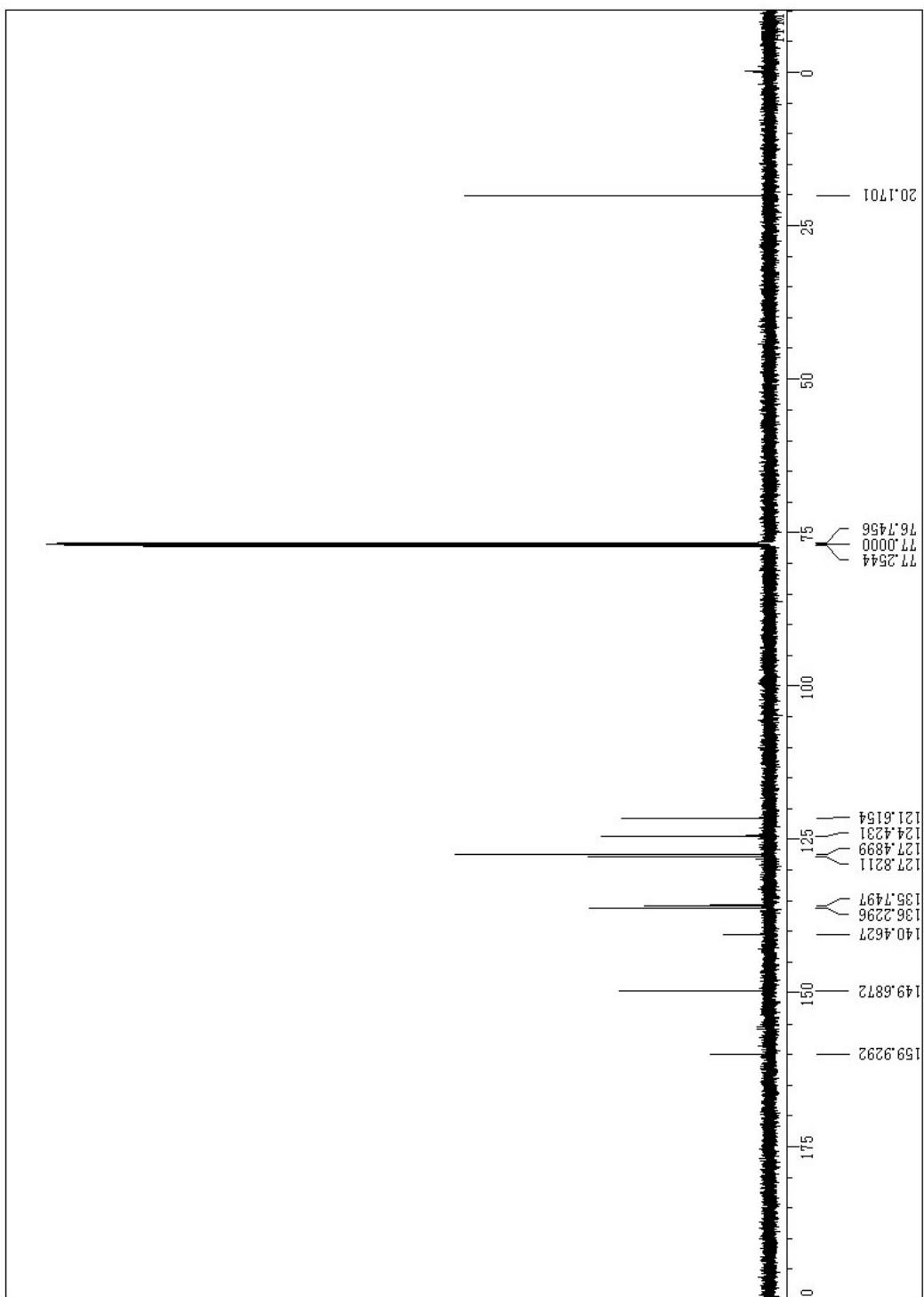
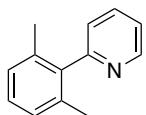
^{13}C NMR of 2-(2-Methylphenyl)pyridine (Table 2, entry 1)



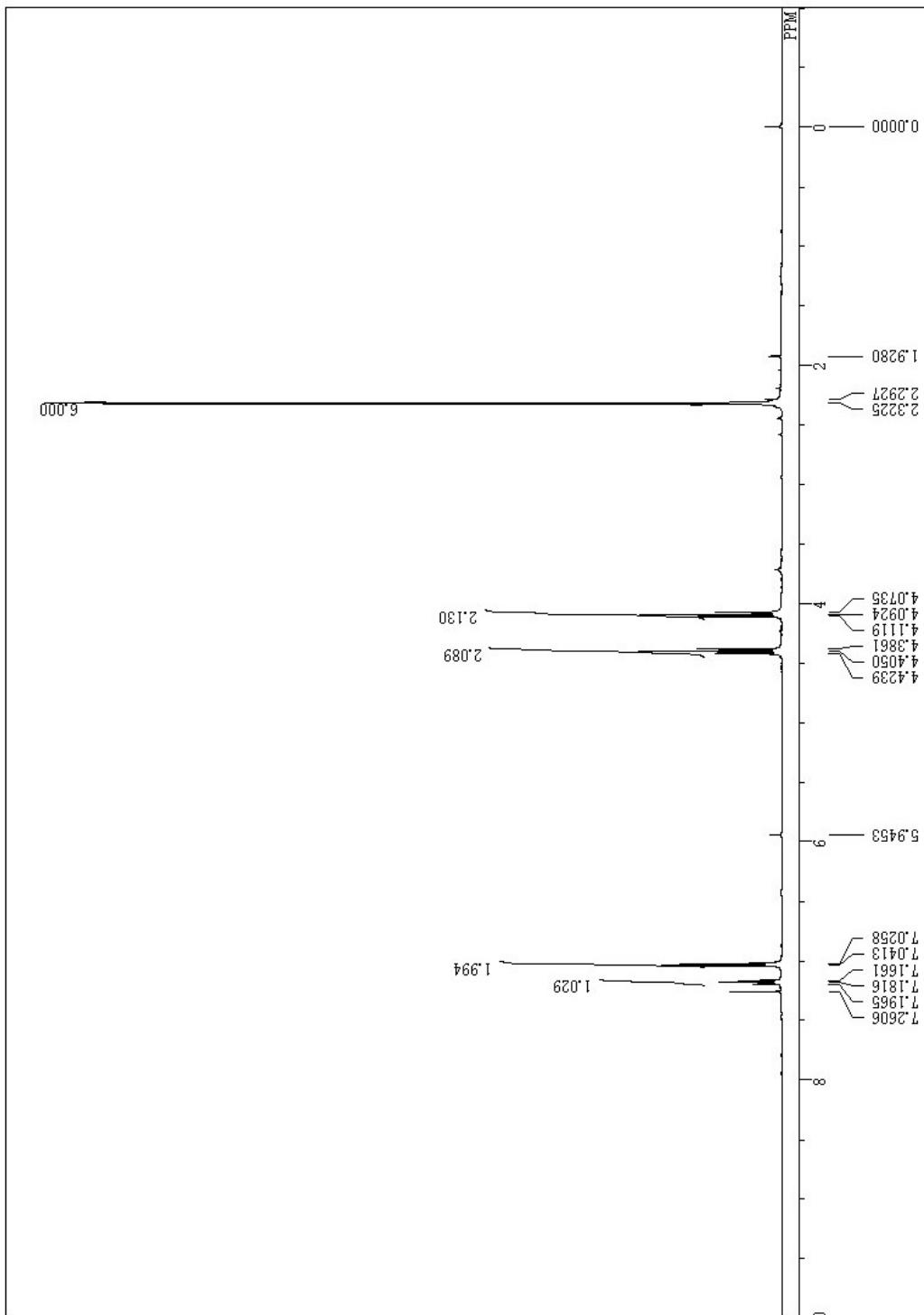
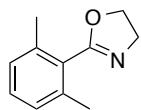
¹H NMR of 2-(2,6-Dimethylphenyl)pyridine (Table 2, entry 1)



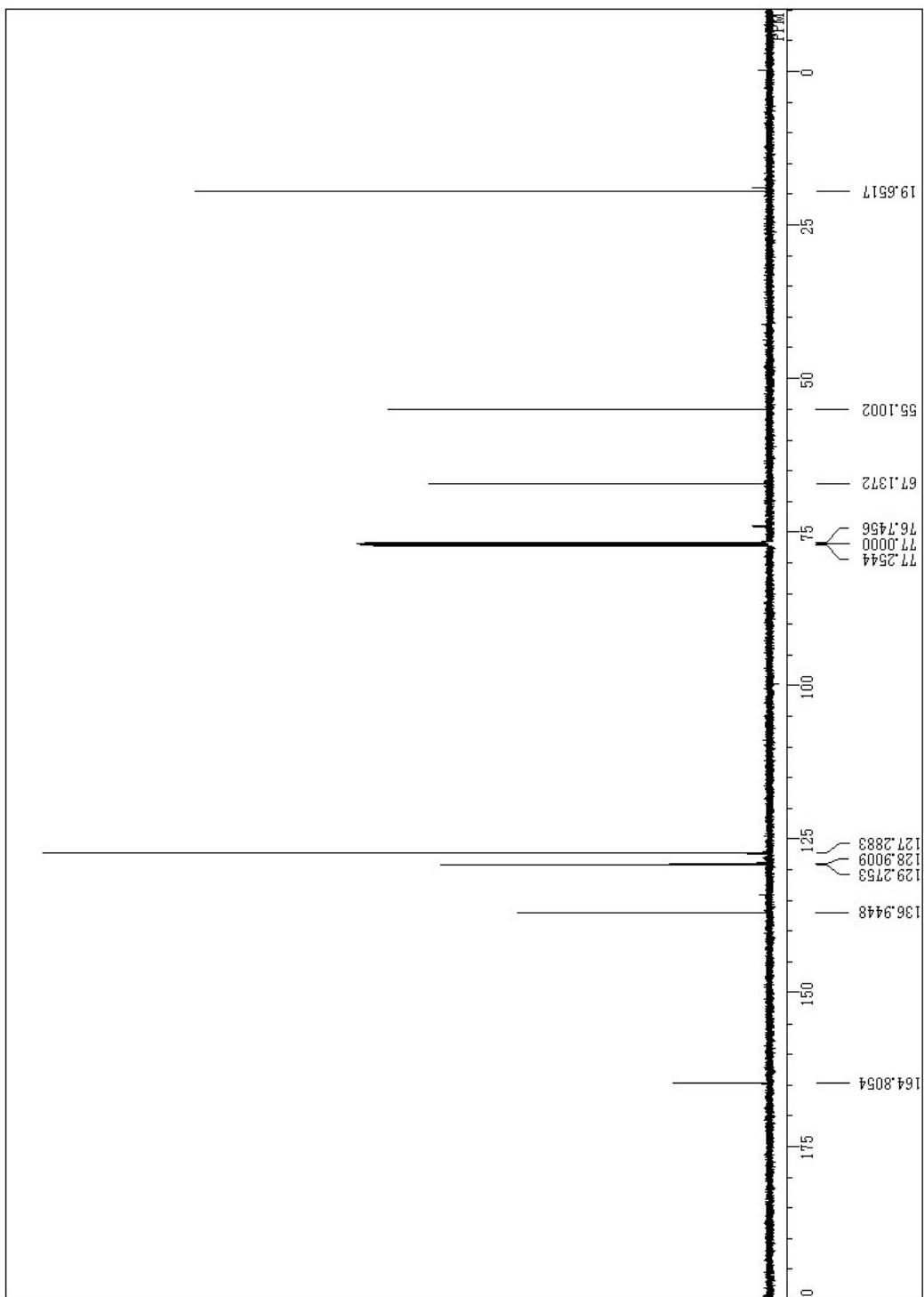
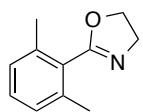
¹³C NMR of 2-(2,6-Dimethylphenyl)pyridine (Table 2, entry 1)



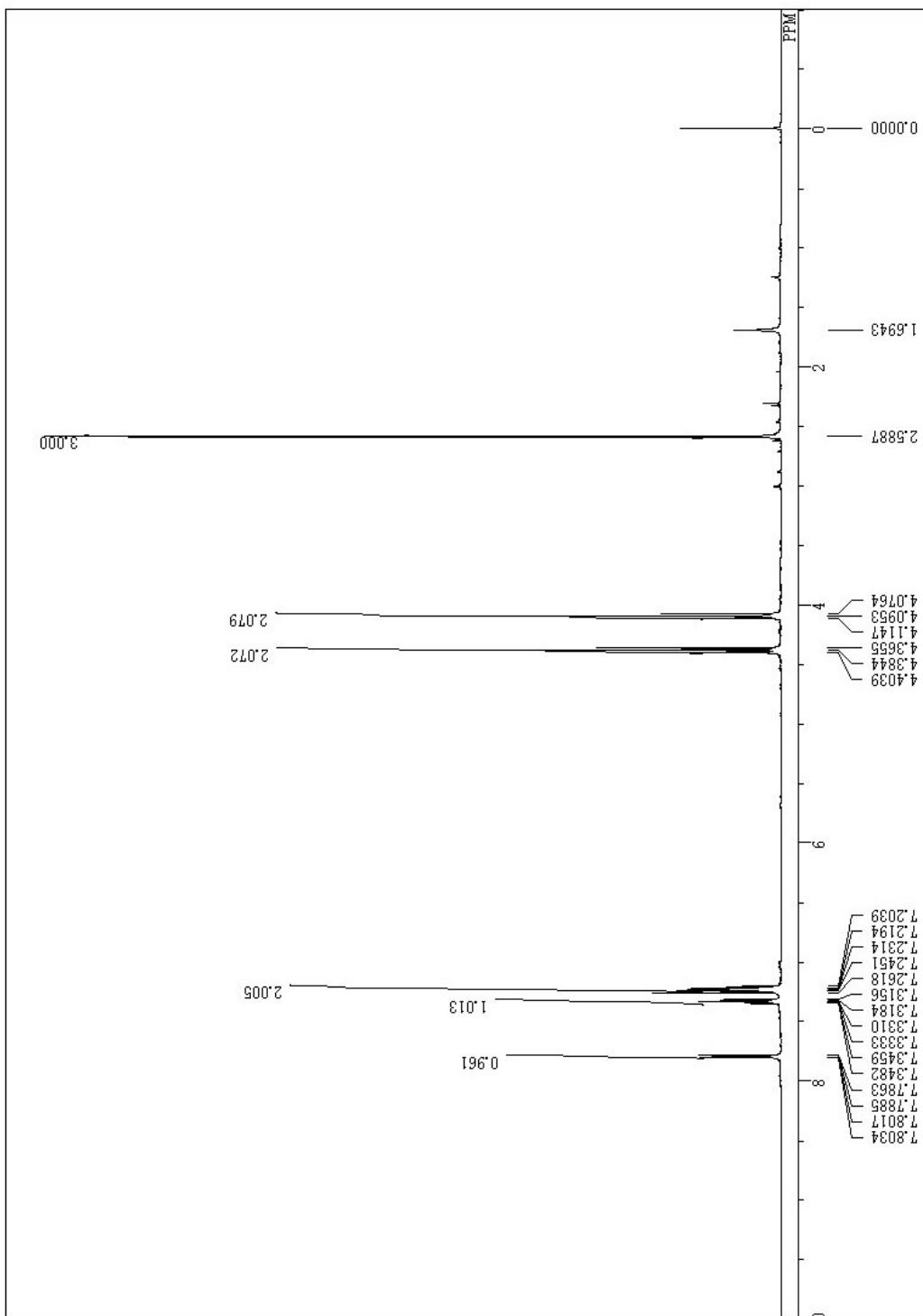
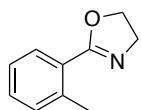
¹H NMR of 2-(2,6-Dimethylphenyl)-4,5-dihydrooxazole (Table 2, entry 2)



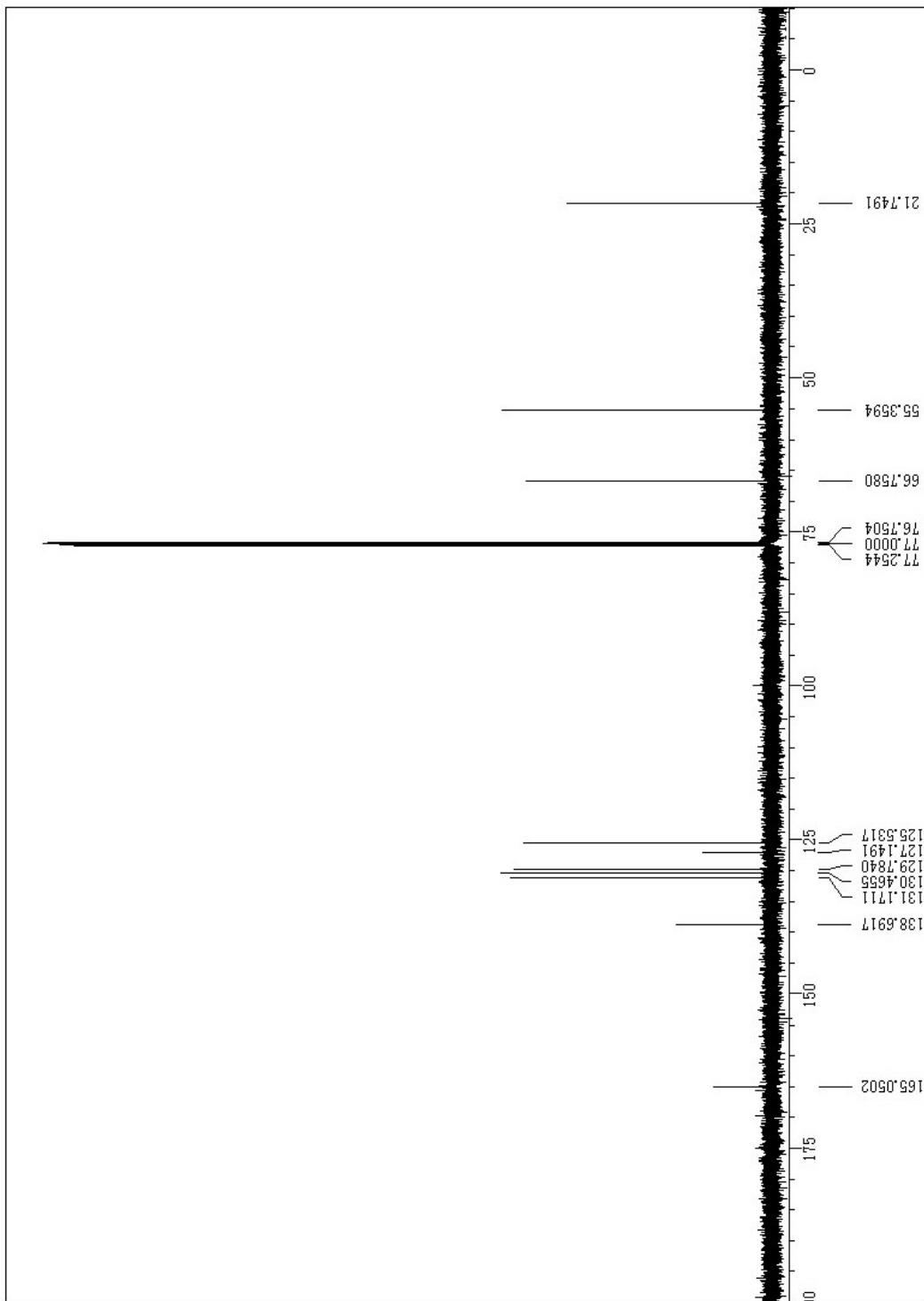
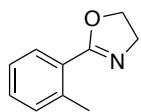
¹³C NMR of 2-(2,6-Dimethylphenyl)-4,5-dihydrooxazole (Table 2, entry 2)



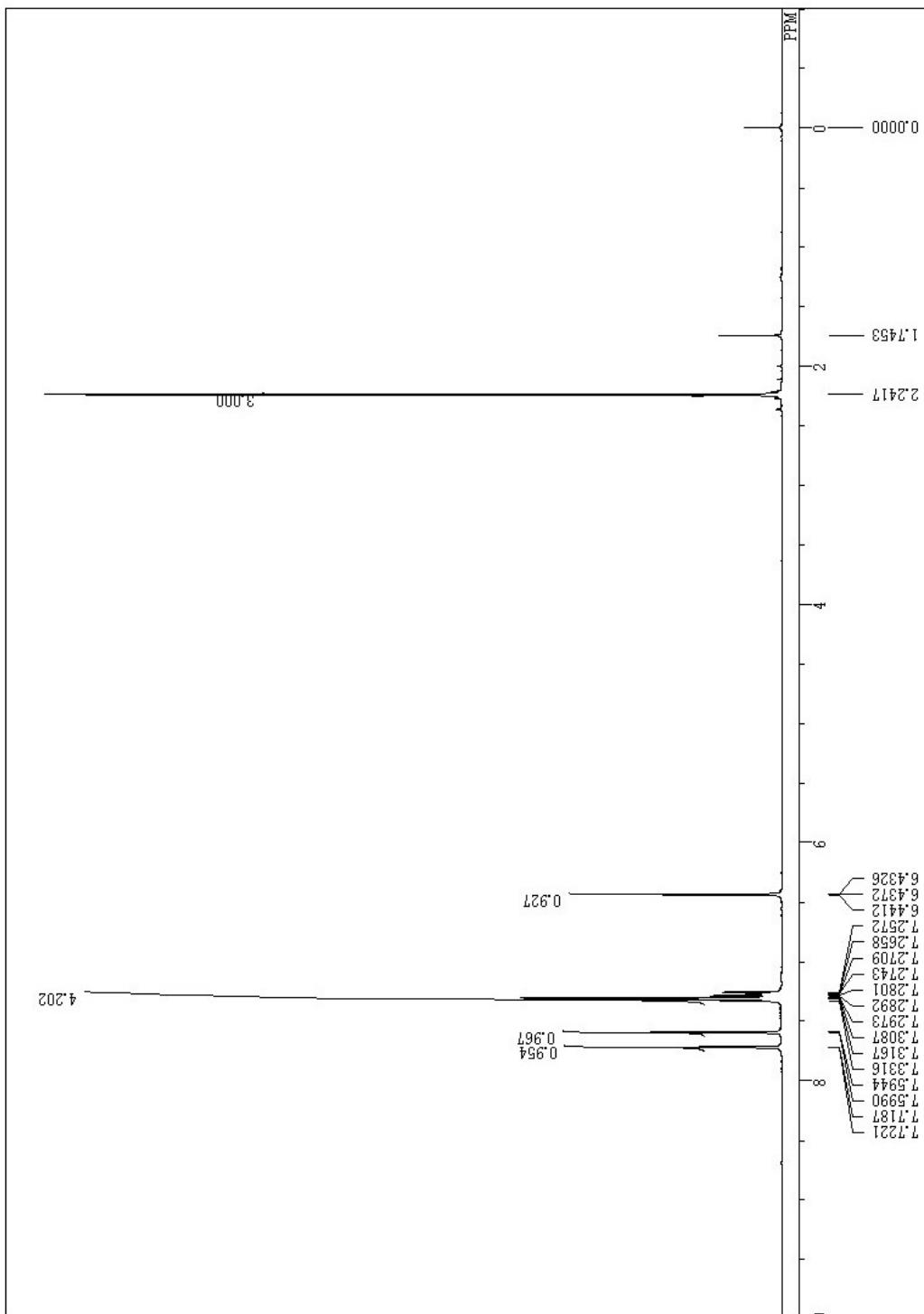
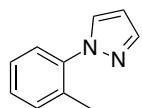
¹H NMR of 2-(2-Methylphenyl)-4,5-dihydrooxazole (Table 2, entry 2)



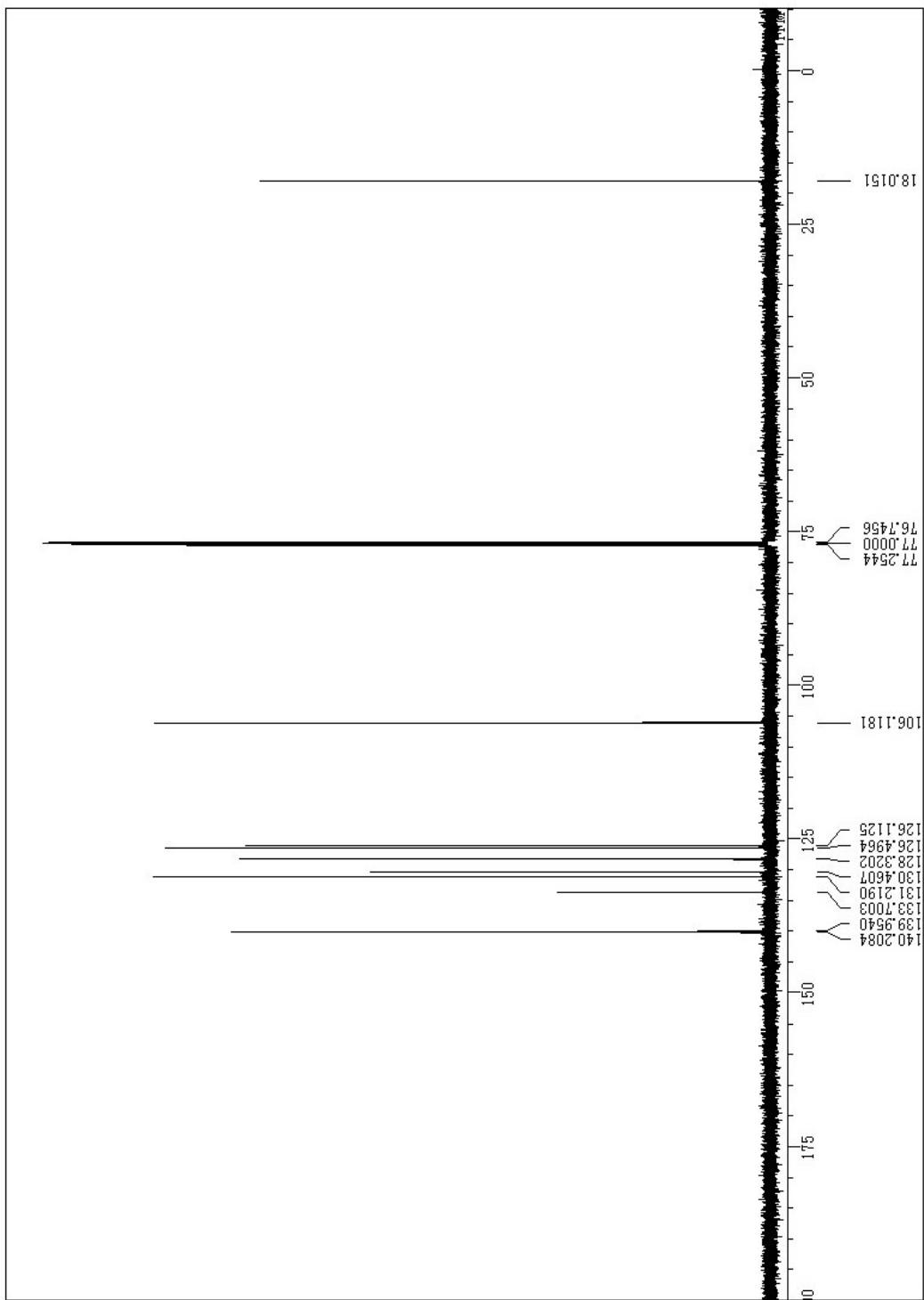
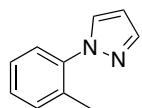
¹³C NMR of 2-(2-Methylphenyl)-4,5-dihydrooxazole (Table 2, entry 2)



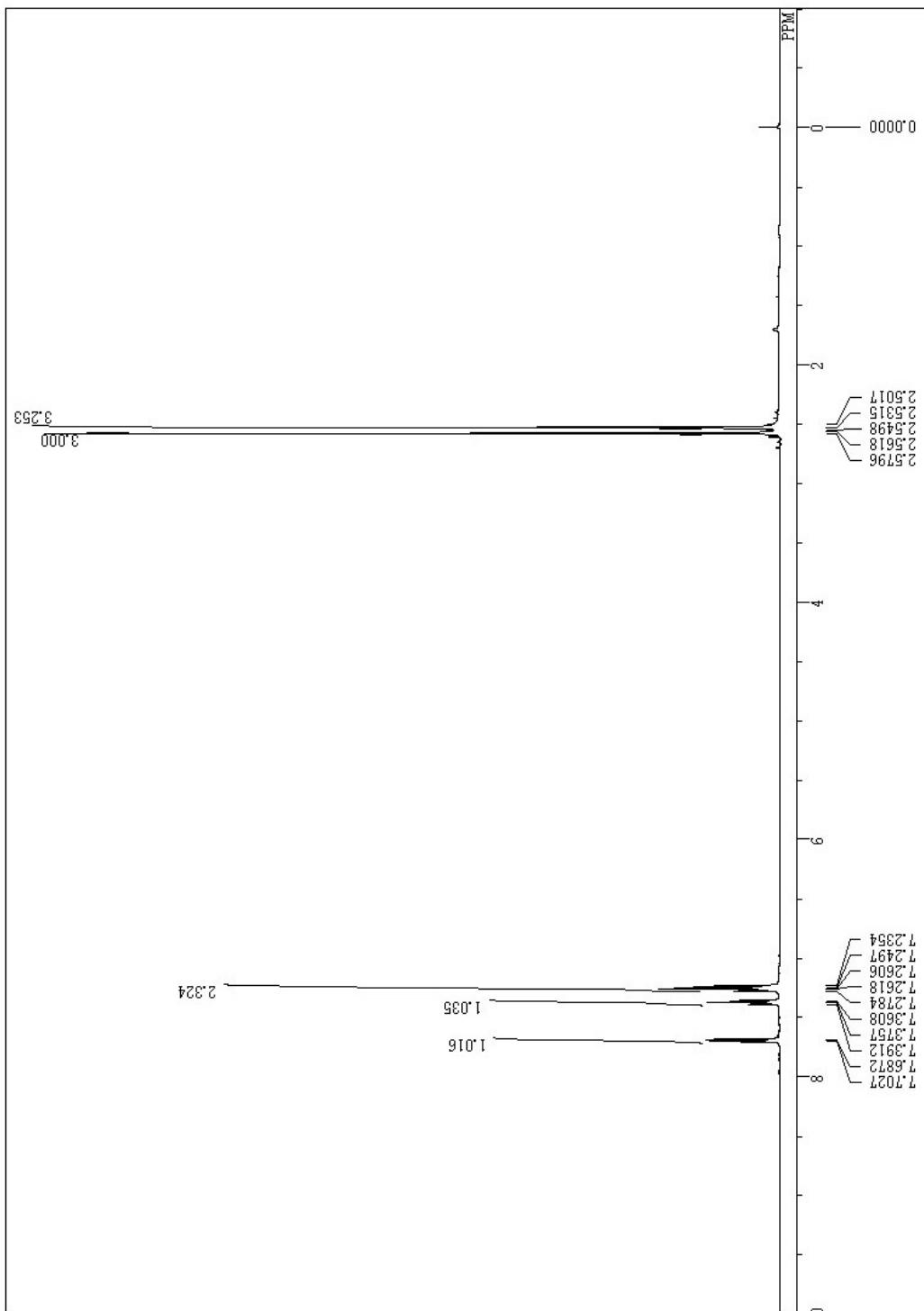
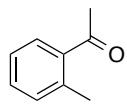
¹H NMR of 1-(2-Methylphenyl)pyrazole (Table 2, entry 3)



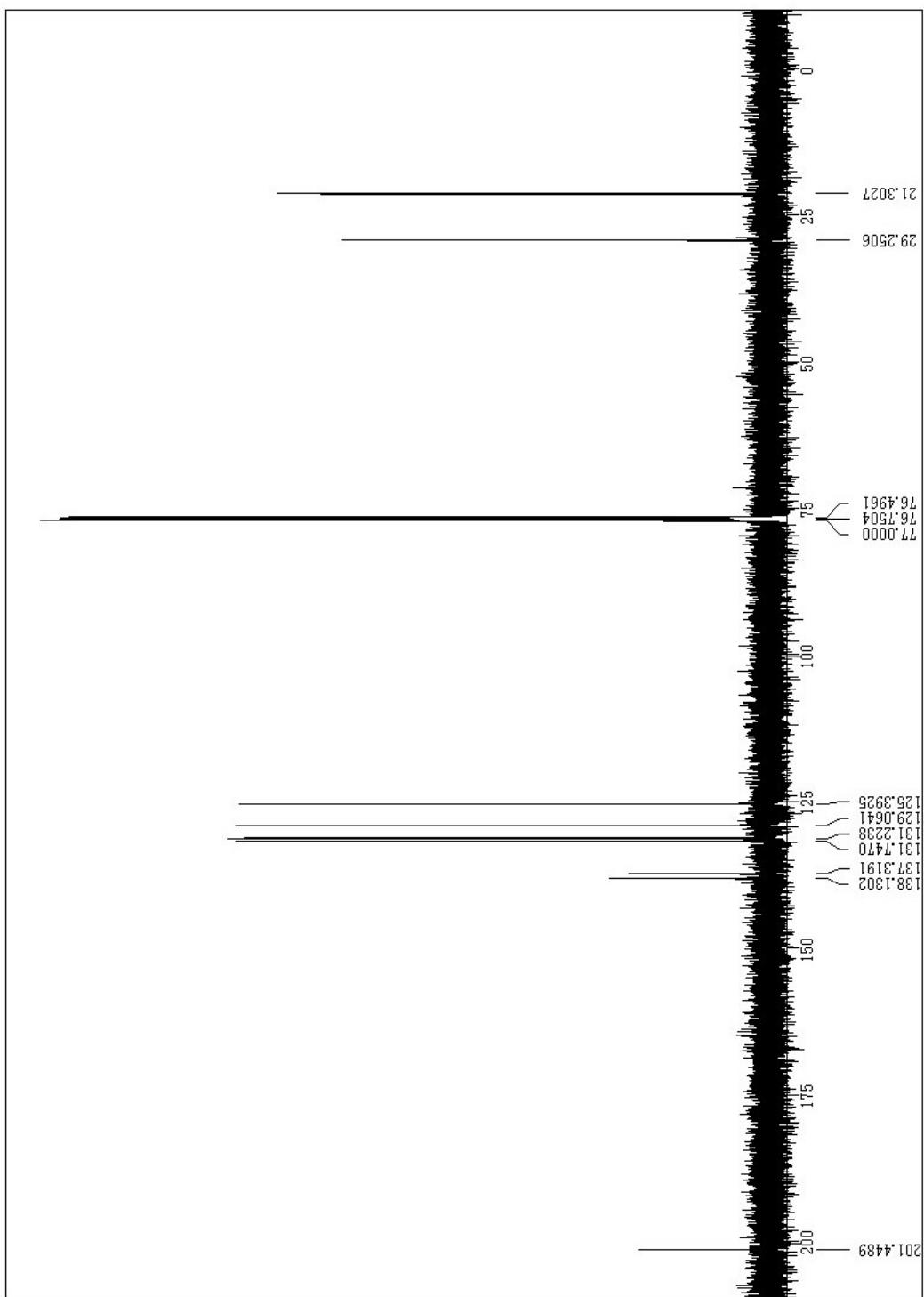
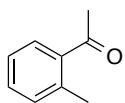
^{13}C NMR of 1-(2-Methylphenyl)pyrazole (Table 2, entry 3)



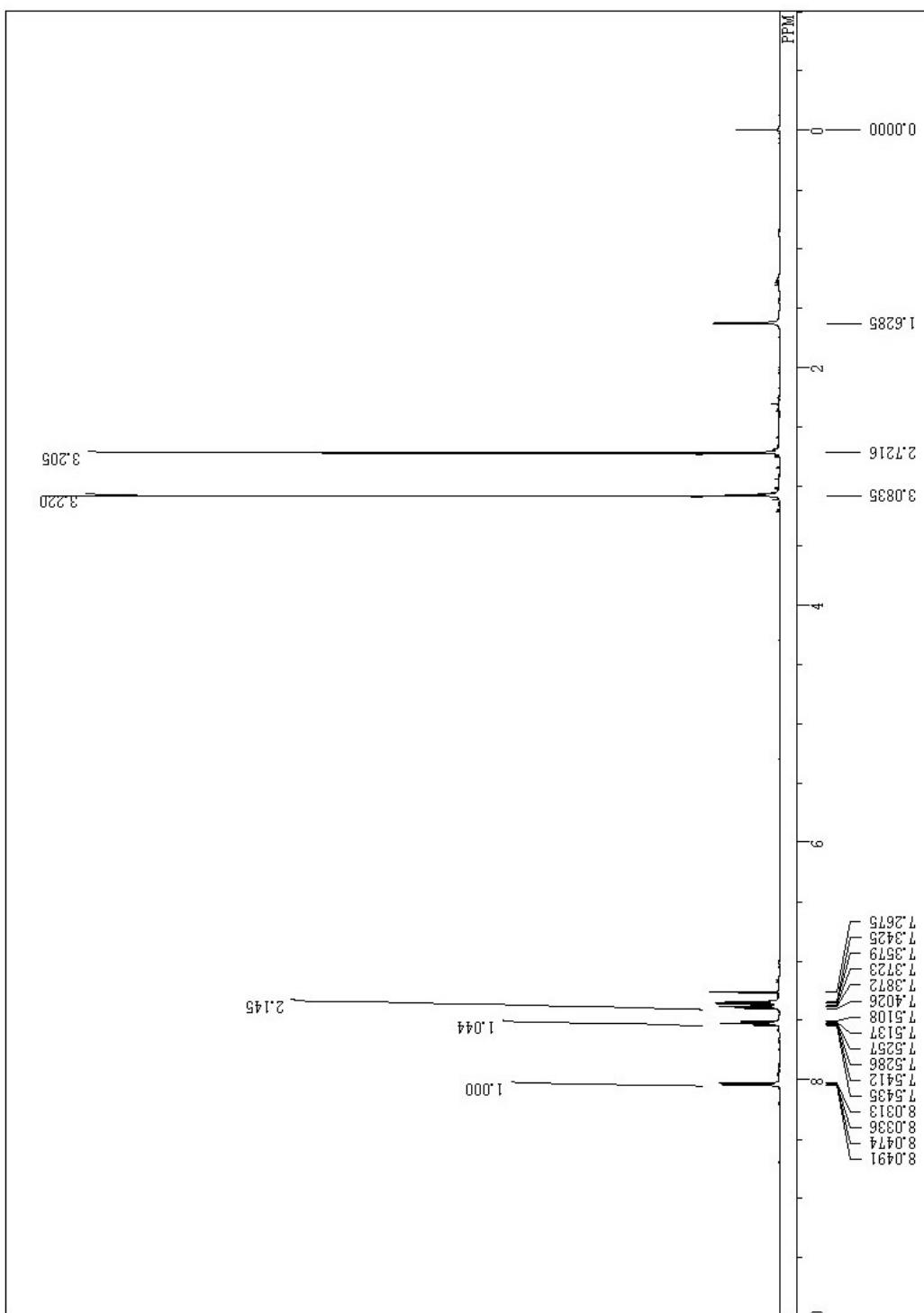
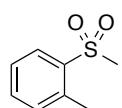
¹H NMR of 1-(2-Methylphenyl)ethanone (Table 2, entry 4)



^{13}C NMR of 1-(2-Methylphenyl)ethanone (Table 2, entry 4)



¹H NMR of 1-Methyl-2-(methylsulfonyl)benzene (Table 2, entry 5)



¹³C NMR of 1-Methyl-2-(methylsulfonyl)benzene (Table 2, entry 5)

