

Supporting Information for:
Synthesis of 1-Formyldipyrromethanes

Marcin Ptaszek, Brian E. McDowell, and Jonathan S. Lindsey

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General Methods. ^1H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were collected at room temperature in CDCl_3 unless noted otherwise. Melting points are uncorrected. Flash chromatography was performed with flash silica (80-200 mesh). THF was distilled over sodium metal and benzophenone as required. All other solvents were used as received.

Noncommercial Compounds. Compounds **1a–e**,¹⁰ **1f**,¹⁹ **1g**,¹⁸ **1h**,¹⁹ **1i**,¹ **1j**,²⁰ and **1k**²¹ were prepared as described in the literature. Compounds **2a**⁹ and **2b**^{6,13} have been prepared earlier by routes different from those described herein.

Characterization. Compounds **1b–E**, **1b–N**, **2e**, and **2k** were obtained as sticky semi-solids, for which melting points were not determined. The nature of the product obtained varied depending on the solvent employed from which the solid was obtained. For example, CH_2Cl_2 often gave a foam or film, whereas hexanes gave an amorphous powder.

Vilsmeier Formylation and Dibutyltin Complexation

1-Formyl-5-phenyldipyrromethane (2b). Following the procedure for the preparation of **2a**, a sample of **1b** (1.00 g, 4.50 mmol) was subjected to standard Vilsmeier conditions and tin complexation. The resulting black solid was chromatographed [deactivated silica (2.5% TEA), $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{ethyl acetate}$ (4:1)]. The resulting solid was recrystallized ($\text{MeOH}/\text{H}_2\text{O}$, 4:1) to afford brown crystals (307 mg, 27%): mp 141–142 °C (lit.⁶ 142–143.5 °C); ^1H NMR δ 5.51 (s, 1H), 5.94–5.96 (m, 1H), 6.08–6.11 (m, 1H), 6.14–6.17 (m, 1H), 6.70–6.72 (m, 1H), 6.88–6.90 (m, 1H), 7.15–7.35 (m, 5H), 8.05 (br s, 1H), 9.31–9.32 (m, 2H); ^{13}C NMR δ 44.4, 108.1, 108.9, 111.1, 118.2, 122.4, 127.8, 128.6, 129.2, 130.7, 132.5, 140.6, 142.7, 178.9; FAB-MS obsd 250.1099, calcd 250.1106 ($\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$).

1-Formyl-5-(2,4,6-trimethylphenyl)dipyrromethane (2c). Following the procedure for the preparation of **2a**, a sample of **1c** (0.615 g, 2.33 mmol) was subjected to standard Vilsmeier conditions and tin complexation. The resulting black solid was chromatographed [silica, CH_2Cl_2 (1% TEA) $\rightarrow \text{CH}_2\text{Cl}_2/\text{ethyl acetate}$ (9:1 containing 1% TEA)]. The resulting solid was dissolved in a minimum amount of ethyl acetate. The addition of hexanes caused a precipitate, which was collected to give a pale brown solid (159 mg, 23% overall): mp 195–197 °C; ^1H NMR ($\text{THF}-d_8$) δ 2.05 (s, 6H), 2.23 (s, 3H), 5.61 (s, 1H), 5.80–5.81 (m, 2H), 5.93–5.95 (m, 1H), 6.60–6.62 (m, 1H), 6.75–6.77 (m, 1H), 6.80 (s, 2H), 9.36 (s, 1H), 9.69 (br s, 1H), 11.02 (br s, 1H); ^{13}C NMR δ 20.3, 29.9, 39.5, 106.8, 107.4, 110.1, 116.8, 120.0, 130.0, 130.7, 133.3, 135.0, 135.9, 137.4, 142.3, 177.3; FAB-MS obsd 292.1594, calcd 292.1576 ($\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}$).

Attempted Scale-up Procedure for 1-Formyldipyrromethane (2a). The procedure for preparing **2a** was carried out at slightly larger scale. A sample of **1a** (5.00 g, 34.2 mmol) was subjected to standard Vilsmeier conditions, followed by tin complexation and chromatography

[silica, ethyl acetate/hexanes (1:9 → 1:3 → 1:1 then 3:1 containing 2.5% TEA)]. TLC analysis (silica, hexanes/ethyl acetate (1:1)) of the product obtained upon column chromatography exhibited a small amount of the uncomplexed, 1,9-diformyldipyrromethane species **3a** ($R_f = 0.38$) and a large quantity of the 1-formyldipyrromethane **2a** ($R_f = 0.58$). No dibutyltin complex **Bu₂Sn-3a** was detected, which is quite nonpolar and chromatographs at the solvent front under these conditions. The crude product was recrystallized (ethyl acetates/hexanes) to afford a brown solid (1.03 g, 17% overall, 93:7 ratio of the 1-formyldipyrromethane to the 1,9-diformyldipyrromethane as assessed by ¹H NMR spectroscopy).

Synthesis and Examination of Potential Formylating Agents

O-Ethyl S-2-pyridyl carbonothioate (4). A sample of ethyl chloroformate (0.969 mL, 10.2 mmol) in THF (10 mL) was treated with 2-mercaptopyridine (1.11 g, 10.0 mmol). The resulting mixture was stirred at room temperature. After 1 h, the reaction mixture was poured into saturated aqueous NaHCO₃ and stirred for 5 min. The mixture was extracted with CH₂Cl₂. The extract was washed (water and brine) and dried (Na₂SO₄). Removal of the solvent afforded the crude title compound as a light-brown oil (1.68 g, 92%), which was used in the next step without further purification. An analytical sample was obtained by chromatography [silica, ethyl acetate/CH₂Cl₂ (1:10)]: ¹H NMR δ 1.33 (t, $J = 7.2$ Hz, 3H), 4.33 (q, $J = 7.2$ Hz, 2H), 7.28–7.29 (m, 1H), 7.72–7.74 (m, 2H), 8.58–8.60 (m, 1H); ¹³C NMR δ 14.5, 64.5, 123.6, 129.6, 137.5, 150.4, 152.1, 168.6; Anal. calcd for C₈H₉NO₂S: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.50; H, 5.01; N, 7.61.

1-Ethoxycarbonyl-5-phenyldipyrromethane (1b-E). A sample of **1b** (0.220 g, 1.00 mmol) in THF (1 mL) was treated with EtMgBr (2.5 mL, 1 M in THF, ~2.5 mmol). The resulting mixture was stirred at room temperature for 10 min, then cooled to –78 °C and treated with a solution of **4** (0.183 g, 1.00 mmol) in THF (1 mL). The resulting mixture was stirred at –78 °C. After 30 min, the reaction mixture was allowed to warm to room temperature, whereupon the reaction was quenched by the addition of saturated aqueous NH₄Cl. The mixture was extracted with CH₂Cl₂. The organic phase was washed (water and brine), dried (Na₂SO₄), and concentrated to afford an orange-brown oil. Column chromatography (silica, CH₂Cl₂) afforded a light-yellow gummy solid (0.133 g, 45%): ¹H NMR δ 1.31 (t, $J = 7.2$ Hz, 3H), 4.24 (q, $J = 7.2$ Hz, 2H), 5.47 (s, 1H), 5.92–5.93 (m, 1H), 5.95–5.97 (m, 1H), 6.14–6.17 (m, 1H), 6.69–6.71 (m, 1H), 6.83–6.84 (m, 1H), 7.17–7.19 (m, 2H), 7.23–7.34 (m, 3H), 7.90–8.03 (br s, 1H), 8.93–9.02 (br s, 1H); ¹³C NMR δ 14.7, 44.3, 60.5, 107.9, 108.8, 110.0, 116.0, 117.9, 122.5, 127.6, 128.6, 129.1, 131.46, 138.5, 141.2, 161.5; FAB-MS obsd 294.1369, calcd 294.1368 (C₁₈H₁₈N₂O₂).

1-Cyano-5-phenyldipyrromethane (1b-N). Following a general procedure,¹⁶ a sample of **1b** (1.11 g, 5.00 mmol) in THF (5 mL) was treated with EtMgBr (10 mL, 1 M in THF, ~10 mmol). The resulting mixture was stirred at room temperature for 10 min, then cooled to –78 °C and treated with a solution of *p*-tosyl cyanide (1.00 g, 5.00 mmol) in THF (5 mL). The resulting mixture was stirred at –78 °C. After 2 h, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of saturated aqueous NH₄Cl. The mixture was extracted with CH₂Cl₂. The organic extract was washed (water and brine), dried (Na₂SO₄), and concentrated to afford an orange-brown oil. TLC showed the presence of starting material and three additional spots. Column chromatography [silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (3:1)] afforded the desired product as the main fraction contaminated with byproducts. A second column (silica, CH₂Cl₂) afforded a light-pink gummy solid (0.38 g, 31%): ¹H NMR δ 5.47 (s, 1H), 5.94–5.95 (m, 1H), 5.98–5.99 (m, 1H), 6.16–6.19 (m, 1H), 6.69–6.73 (m, 1H),

6.78–6.80 (m, 1H), 7.17–7.19 (m, 2H), 7.25–7.35 (m, 3H), 7.85–7.95 (br s, 1H), 8.52–8.58 (br s, 1H); ^{13}C NMR δ 44.2, 108.1, 109.0, 109.5, 114.7, 118.3, 121.06, 127.2, 128.6, 129.3, 139.3, 140.5; FAB-MS obsd 247.1113, calcd 247.1109 ($\text{C}_{16}\text{H}_{13}\text{N}_3$).

Grignard-Mediated Formylation

1-Formyldipyrromethane (2a). The reaction of **1a** (1.44 g, 10.0 mmol) as described for **1b** with chromatography [silica, CH_2Cl_2 /ethyl acetate (10:1 \rightarrow 5:1)] yielded the crude product. The crude product was dissolved in CH_2Cl_2 and treated with hexanes, affording a brownish powder (0.550 g, 32%). The characterization data (^1H NMR and FAB-MS spectra) were consistent with that described above.

1-Formyl-5-(2,4,6-trimethylphenyl)dipyrromethane (2c). The reaction of **1c** (2.64 g, 10.0 mmol) as described for **1b** afforded a brownish powder (0.935 g, 32%). The characterization data (^1H NMR and FAB-MS spectra) were consistent with that described above.

1-Formyl-5-(4-methoxyphenyl)dipyrromethane (2d). A sample of **1d** (2.52 g, 10.0 mmol) in THF (20 mL) was reacted as described for **1b**. The resulting crude mixture was stored overnight at $-15\text{ }^\circ\text{C}$. The resulting dark solid was treated with cold CH_2Cl_2 (15 mL) and filtered. The filtered material was collected, washed with CH_2Cl_2 , and dried to afford a light yellow powder (1.071 g, 38%): mp 154–156 $^\circ\text{C}$; ^1H NMR δ 3.79 (s, 3H), 5.46 (s, 1H), 5.94–5.95 (m, 1H), 6.09–6.10 (m, 1H), 6.15–6.17 (m, 1H), 6.70–6.72 (m, 1H), 8.47 (d, $J = 8.6$ Hz, 2H), 6.88–6.90 (m, 1H), 7.09 (d, $J = 8.6$ Hz, 2H), 7.96–8.00 (br s, 1H), 9.14–9.18 (br s, 1H), 9.36 (s, 1H); ^{13}C NMR δ 43.6, 55.5, 108.0, 108.9, 110.9, 114.5, 118.1, 122.3, 129.6, 131.0, 132.4, 132.6, 143.0, 159.1, 178.8; FAB-MS obsd 280.1208, calcd 280.1212 ($\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$).

1-Formyl-5-(pentafluorophenyl)dipyrromethane (2e). The reaction of **1e** (3.12 g, 10.0 mmol) as described for **1b** afforded a blackish sticky foam (0.953 g, 28%): ^1H NMR δ 5.91 (s, 1H), 6.09–6.10 (m, 1H), 6.13–6.14 (m, 1H), 6.16–6.18 (m, 1H), 6.76–6.77 (m, 1H), 6.90–6.92 (m, 1H), 8.36–8.40 (br s, 1H), 9.35 (s, 1H), 9.74–9.78 (br s, 1H); ^{13}C NMR δ 33.4, 109.0, 109.2, 110.7, 119.2, 122.4, 126.3, 132.9, 136.7 (m), 138.9, 139.3 (m), 142.2 (m), 143.9 (m), 146.4 (m), 179.1; Anal. calcd for $\text{C}_{16}\text{H}_9\text{F}_5\text{N}_2\text{O}$: C, 56.48; H, 2.67; N, 8.23. Found: C, 56.41; H, 3.06; N, 7.77.

1-Formyl-5-(4-iodophenyl)dipyrromethane (2h). The reaction of **1h** (3.06 g, 8.80 mmol) as described for **1b** afforded an off-white solid (1.12 g, 34%): mp 175–177 $^\circ\text{C}$; ^1H NMR δ 5.46 (s, 1H), 6.07–6.09 (m, 1H), 6.16–6.18 (m, 1H), 6.73–6.75 (m, 1H), 6.90–6.92 (m, 1H), 6.92 (d, $J = 8.6$ Hz, 2H), 6.93–6.95 (m, 1H), 7.65 (d, $J = 8.6$ Hz, 2H), 8.03–8.06 (br s, 1H), 9.28–9.31 (br s, 1H), 9.35 (s, 1H); ^{13}C NMR δ 43.9, 93.3, 108.4, 109.1, 111.1, 118.5, 122.3, 130.5, 132.7, 138.2, 140.4, 141.8, 179.0; Anal. calcd for $\text{C}_{16}\text{H}_{13}\text{N}_2\text{IO}$: C, 51.08; H, 3.48; N, 7.45. Found: C, 51.31; H, 3.63; N, 7.19.

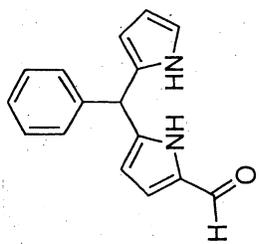
1-Formyl-5-[4-(2-(triisopropylsilyl)ethynyl)phenyl]dipyrromethane (2i). The reaction of **1i** (2.01 g, 5.00 mmol) as described for **1b** afforded a brown foam (0.815 g, 38%): mp 66–68 $^\circ\text{C}$; ^1H NMR 1.09–1.35 (m, 21 H), 5.50 (s, 1H), 5.94–5.96 (m, 1H), 6.07–6.09 (m, 1H), 6.15–6.17 (m, 1H), 6.72–6.73 (m, 1H), 6.89–6.90 (m, 1H), 7.09 (d, $J = 8.2$ Hz, 2H), 7.41 (d, $J = 8.2$ Hz, 2H), 8.12–8.16 (br s, 1H), 9.28 (s, 1H), 9.44–8.48 (br s, 1H); ^{13}C NMR 11.5, 18.9, 44.2, 91.4, 106.7, 108.3, 109.0, 111.1, 118.4, 122.5, 123.0, 128.4, 130.1, 132.6, 132.7, 140.9, 178.9; Anal. calcd for $\text{C}_{27}\text{H}_{34}\text{N}_2\text{OSi}$: C, 75.30; H, 7.96; N, 6.50. Found: C, 75.58; H, 7.90; N, 6.46.

5-[1,5-Bis(*tert*-butyldimethylsilyloxy)pent-3-yl]-1-formyldipyrromethane (2j) The reaction of **1j** (0.222 g, 0.466 mmol) in THF (1 mL) as described for **1b** (phenyl formate was added at 0 °C) afforded a dark-yellow oil which solidified to an off-white solid (0.135 g, 57%); mp 70–71 °C; ¹H NMR δ 0.07 (s, 3H), 0.08 (s, 3H), 0.087 (s, 3H), (0.094 (s, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 1.30–1.36 (m, 1H), 1.43–1.50 (m, 1H), 1.63–1.73 (m, 2H), 2.44–2.49 (m, 1H), 3.62–3.68 (m, 2H), 3.71–3.78 (m, 2H), 4.48 (d, *J* = 5.2 Hz, 1H), 5.96–6.00 (m, 1H), 6.15–6.17 (m, 1H), 6.18–6.20 (m, 1H), 6.68–6.70 (m, 1H), 6.89–6.90 (m, 1H), 8.99 (br s, 1H), 9.39 (s, 1H), 9.45–9.51 (br s, 1H); ¹³C NMR δ -5.15, -5.10, 18.6, 26.26, 26.28, 34.5, 34.8, 35.9, 40.9, 61.98, 62.03, 107.8, 108.7, 110.6, 117.0, 122.1, 130.2, 132.0, 178.4; Anal. calcd for C₂₇H₄₈N₂O₃Si₂: C, 64.23; H, 9.58; N, 5.55. Found: C, 64.43; H, 9.70; N, 5.50.

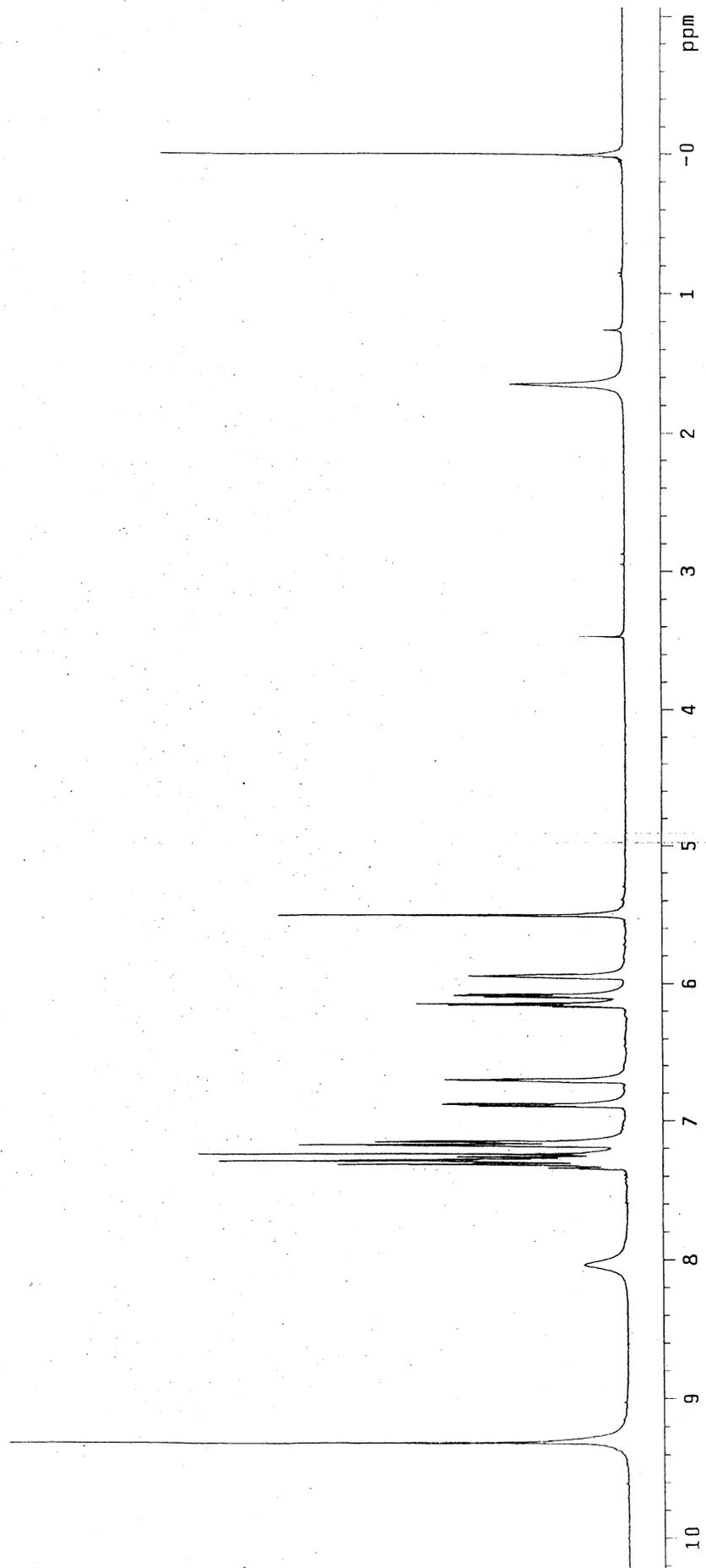
5-(5,5-Dimethyl-1,3-dioxan-2-yl)-1-formyldipyrromethane (2k). The reaction of **1k** (1.30 g, 5.00 mmol) as described for **1b** afforded a light-yellow foam which darkened upon storage (0.942 g, 65%); ¹H NMR δ 0.74 (s, 3H), 1.12 (s, 3H), 3.48–3.52 (m, 2H), 3.69–3.77 (m, 2H), 4.42 (d, *J* = 2.8 Hz, 1H), 4.86 (d, *J* = 2.8 Hz, 1H), 5.99–6.01 (m, 1H), 6.13–6.15 (m, 1H), 6.74–6.76 (m, 1H), 6.84–6.85 (m, 1H), 8.77–8.79 (br s, 1H), 9.42 (s, 1H), 9.76–9.77 (br s, 1H); ¹³C NMR δ 21.9, 23.2, 30.5, 42.3, 77.6, 77.7, 103.0, 108.2, 108.3, 111.4, 118.2, 121.3, 127.2, 132.6, 139.2, 178.8; Anal. calcd for C₁₆H₂₀N₂O₃: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.32; H, 6.90; N, 9.48.

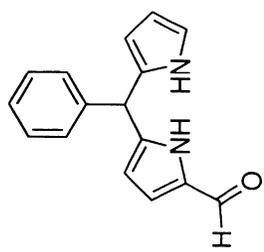
1,11-Diformyl-5-(2,4,6-trimethylphenyl)dipyrromethane (5c). The following procedure describes the isolation of the title compound as a byproduct of the 1-formylation process. A sample of **1c** (2.64 g, 10.0 mmol) in THF (20 mL) was treated with EtMgBr (20.0 mL, 1 M in THF, ~20 mmol). After 10 min, the mixture was cooled to -10 °C. Methyl formate (0.620 mL, 10.0 mmol) was added. The reaction mixture was stirred at -10 – 0 °C for 1 h. The cooling bath was removed and stirring was continued for 1 h. The reaction was quenched by adding saturated aqueous NH₄Cl. The resulting mixture was extracted with CH₂Cl₂. The organic extract was washed (water, brine), dried and concentrated. The resulting oil was chromatographed twice [first column: silica, CH₂Cl₂ → CH₂Cl₂/ethyl acetate (10:1), second column: silica, CH₂Cl₂/ethyl acetate (10:1)] to afford a pale brown solid (1.057 g, 33%, purity ~90%); ¹H NMR δ 2.04 (s, 6H), 2.27 (s, 3H), 5.89 (s, 1H), 5.98–6.01 (m, 1H), 6.12–6.21 (m, 1H), 6.22–6.24 (m, 1H), 6.85 (s, 2H), 6.88–6.89 (m, 1H), 7.28–7.32 (m, 1H), 8.79 (s, 1H), 9.02–9.15 (br s, 1H), 9.36 (s, 1H); ¹³C NMR δ 20.9, 21.0, 38.5, 111.3, 113.3, 116.0, 122.1, 130.8, 131.0, 132.4, 132.8, 137.2, 137.8, 158.5, 178.8; FAB-MS obsd 321.1589, calcd 321.1603 [(M + H)⁺, M = C₂₀H₂₁N₂O₂].

Hydrolysis of 5c. A sample of **5c** (0.060 g, 0.19 mmol) in CH₃CN (5 mL) was treated with 15% aqueous NaOH (5 mL). The resulting biphasic mixture was stirred vigorously at room temperature. After 1 h, water (20 mL) was added. The mixture was extracted with CH₂Cl₂. The organic extract was washed (saturated aqueous NH₄Cl, water, brine), dried (Na₂SO₄) and concentrated. The ¹H NMR spectrum of the crude mixture showed complete hydrolysis of **5c** and exclusive formation of **2c**.

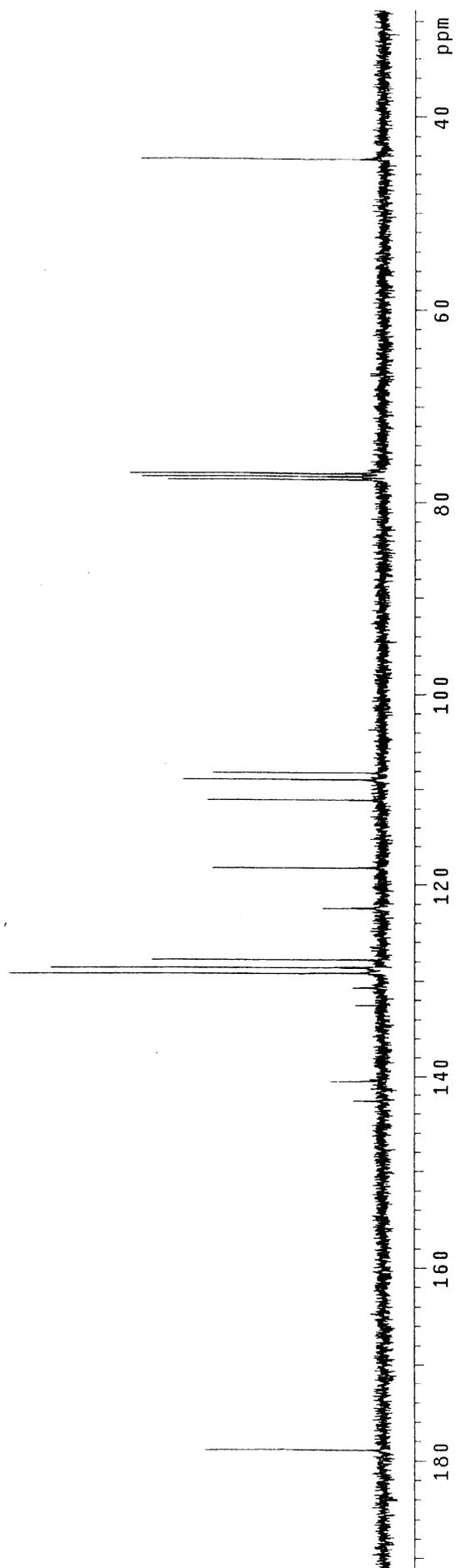


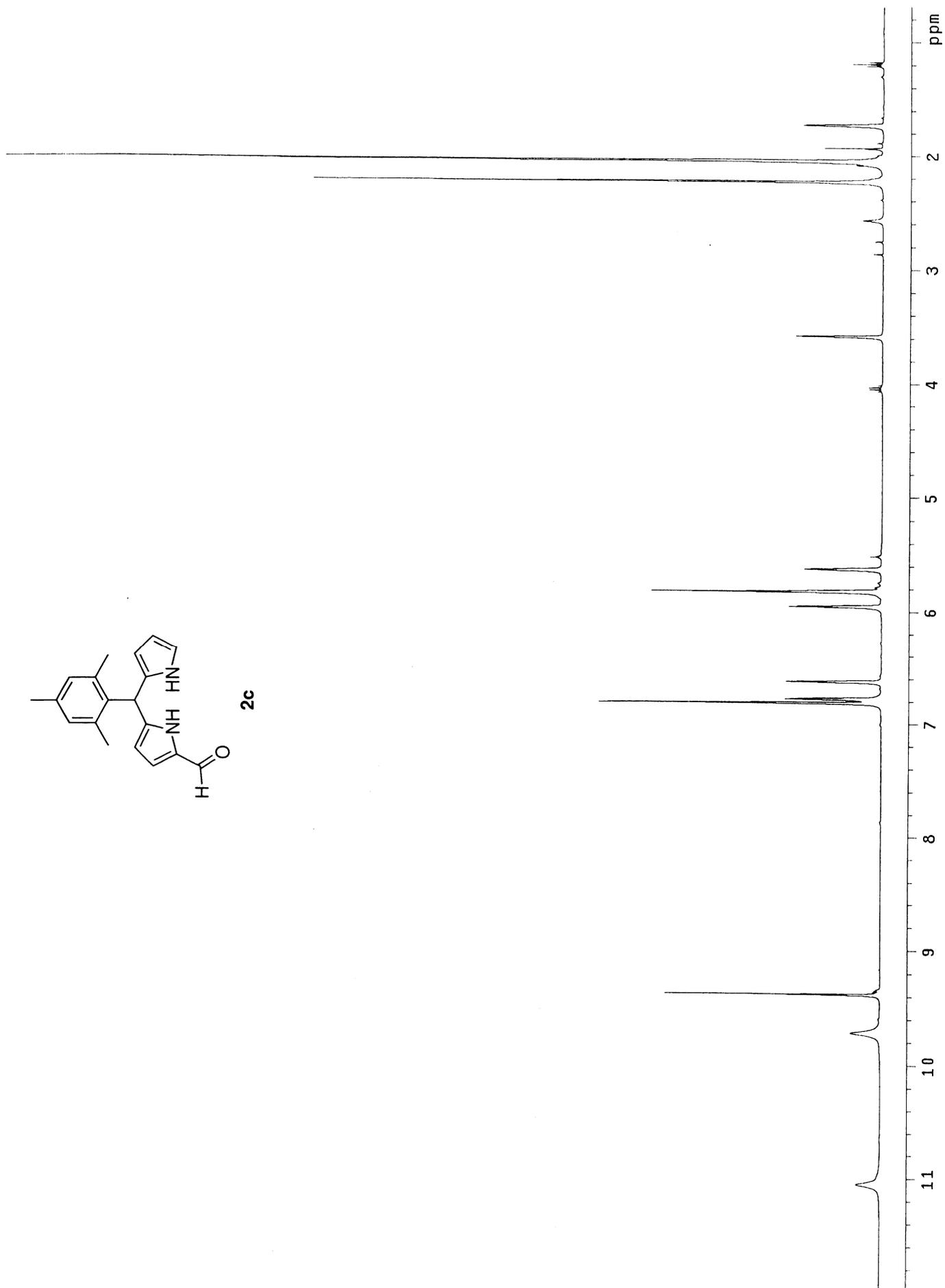
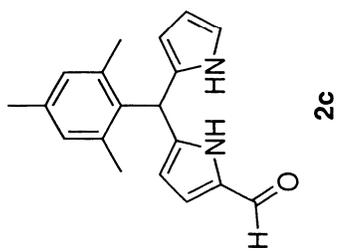
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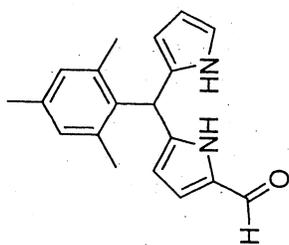




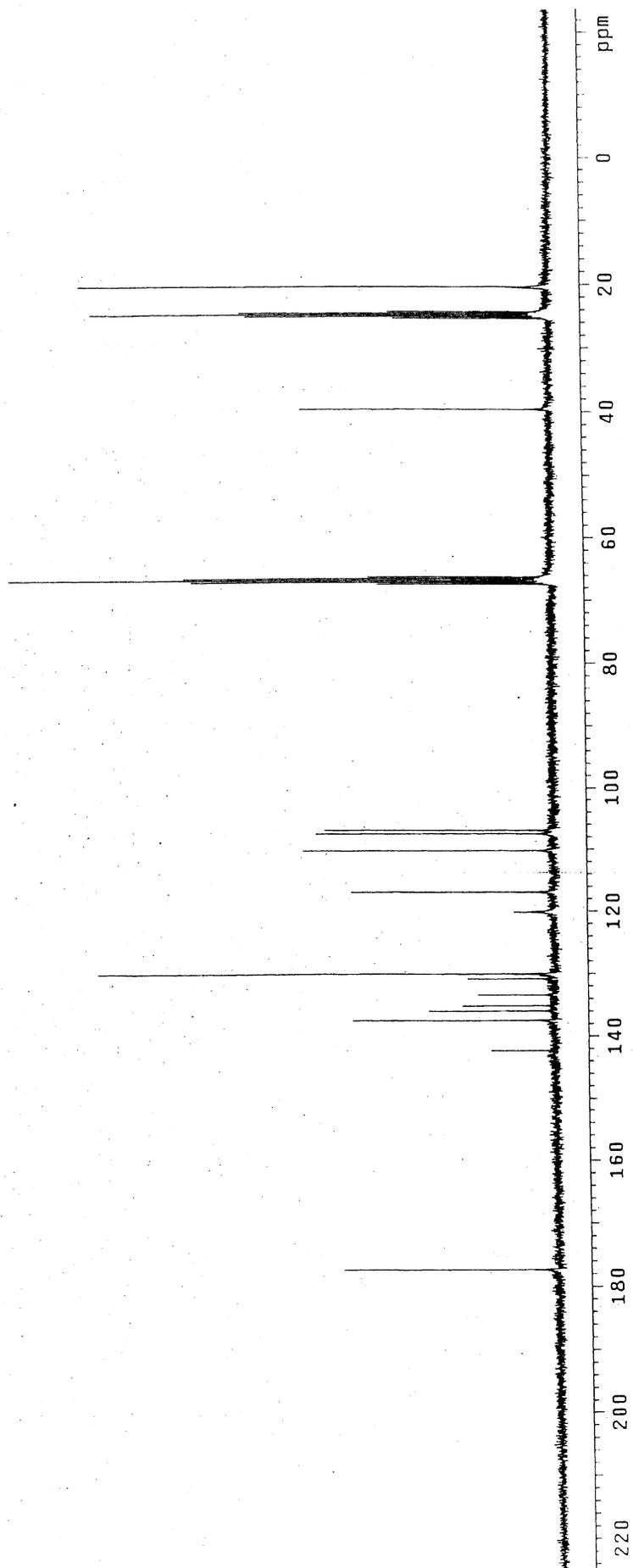
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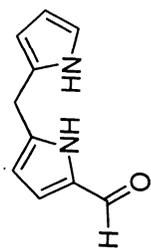




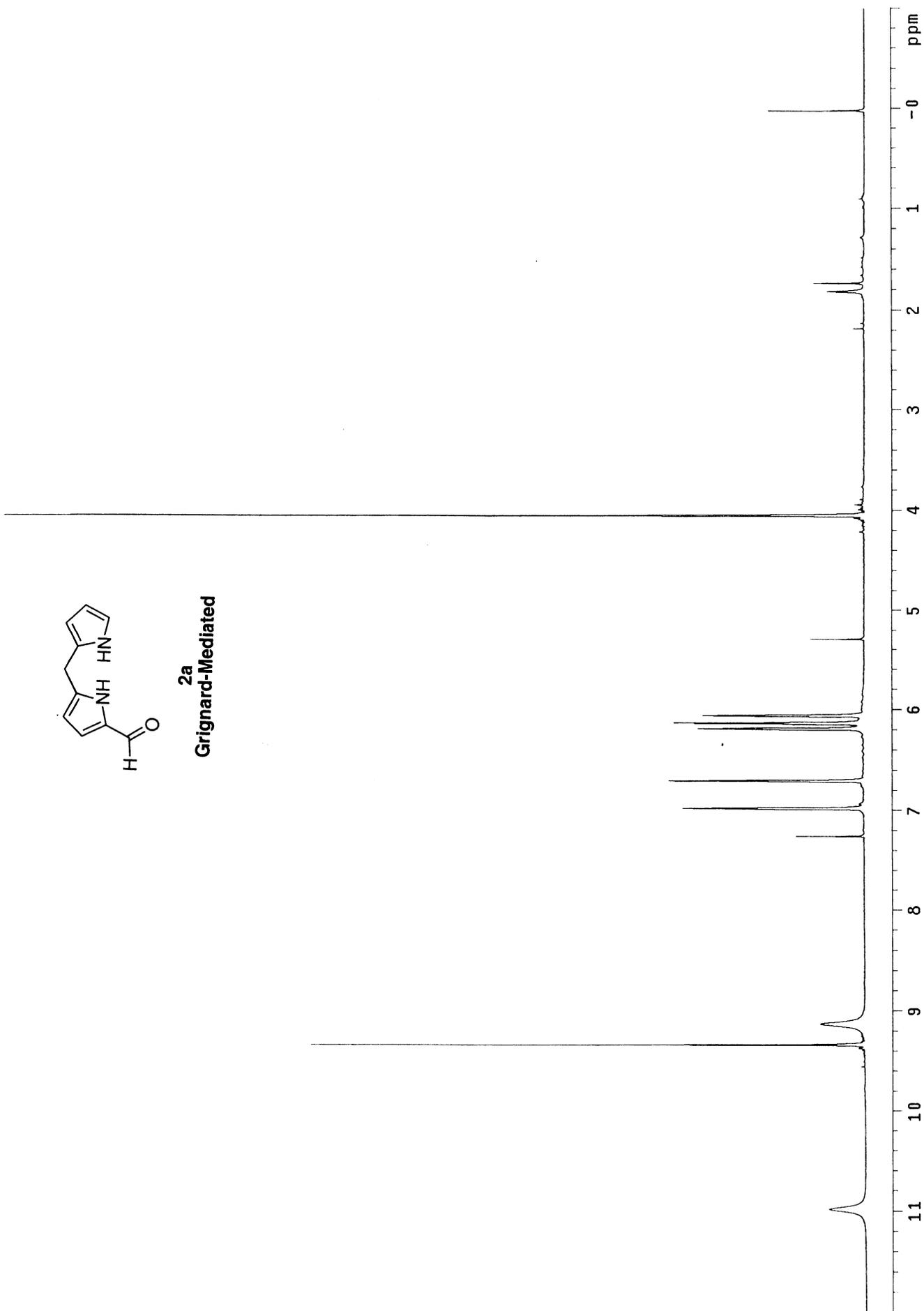


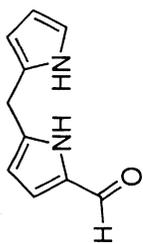
2c



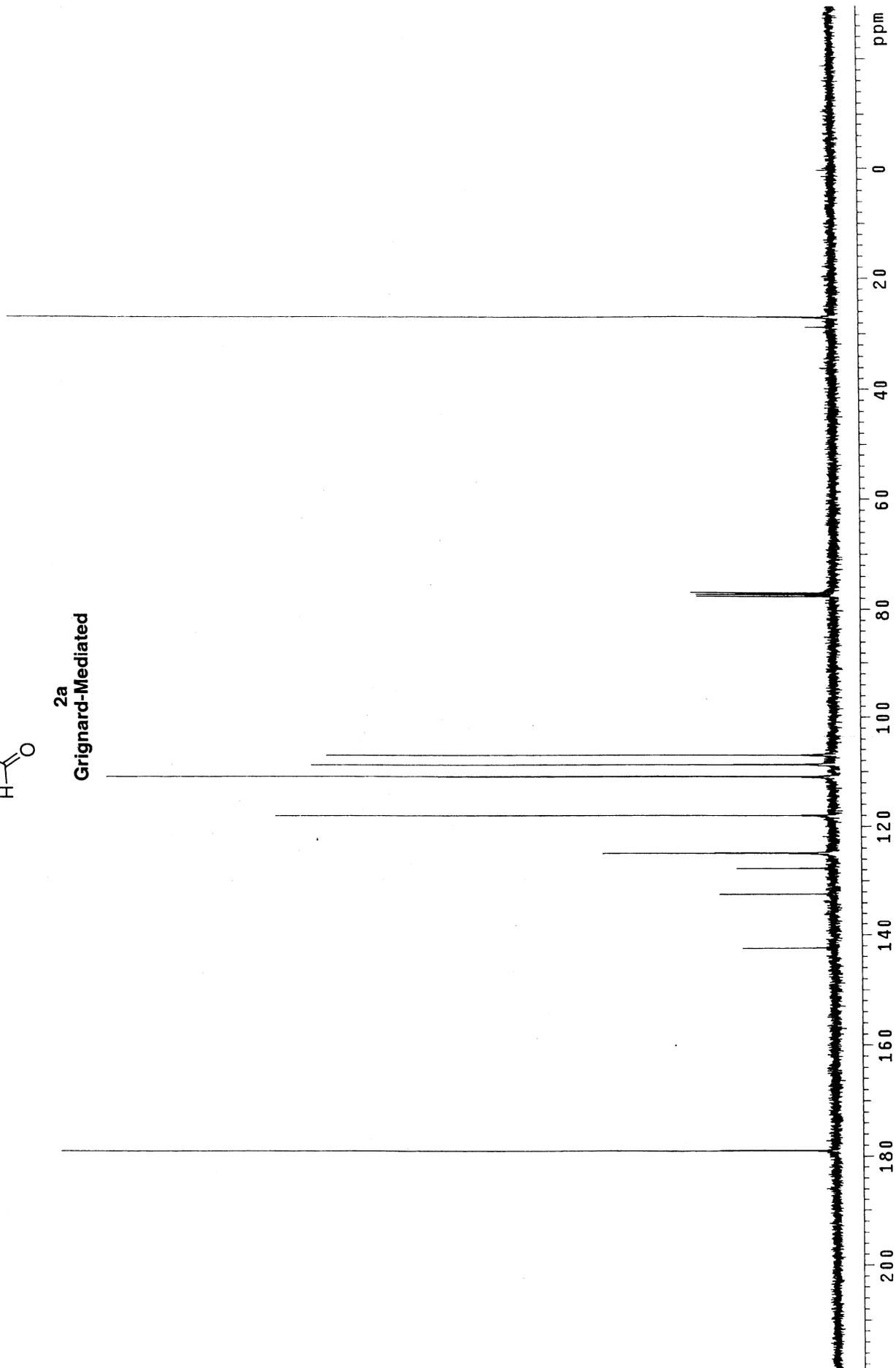


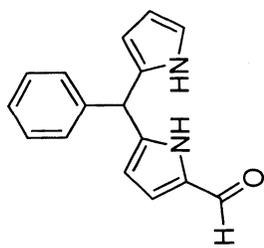
2a
Grignard-Mediated



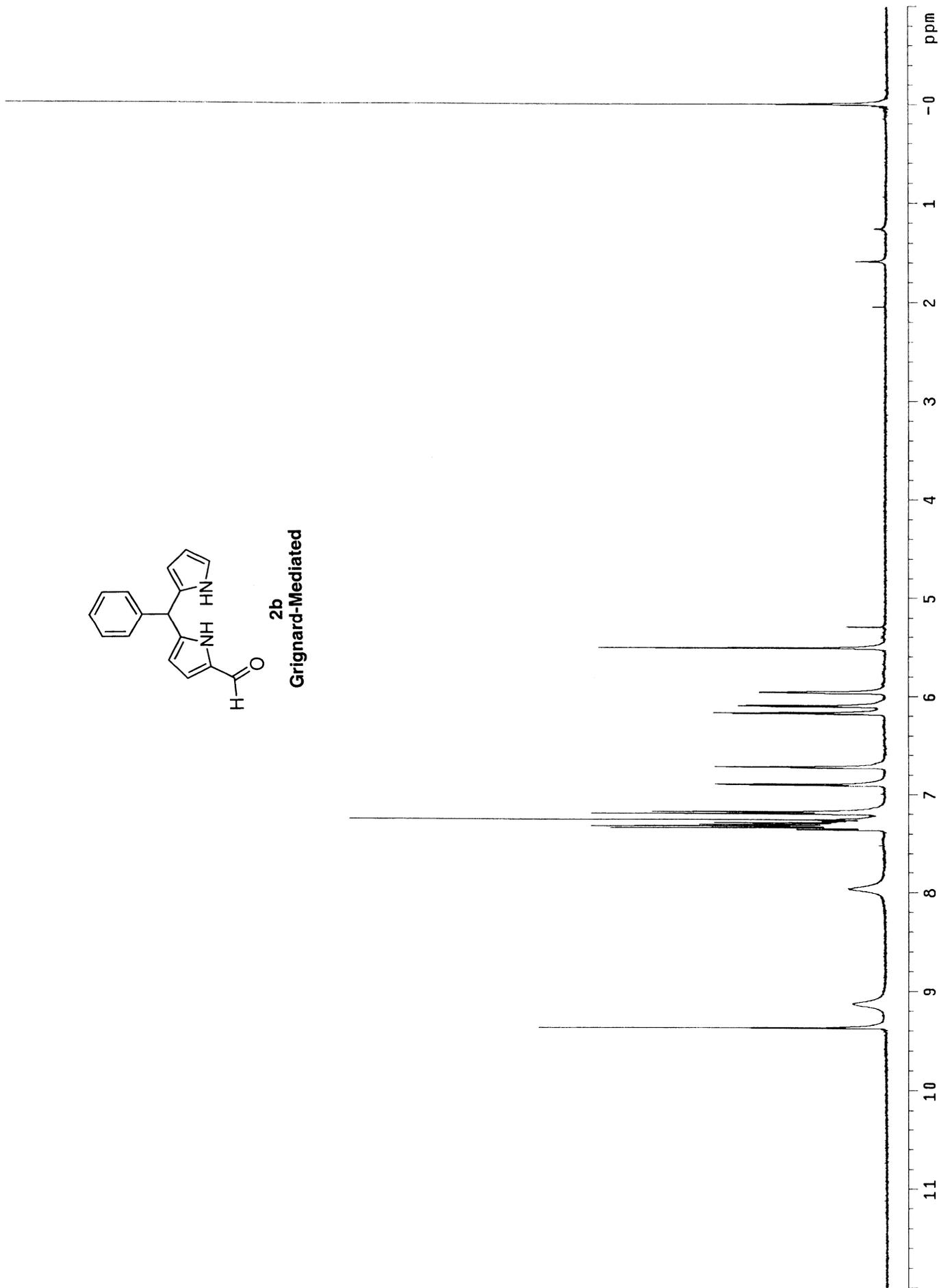


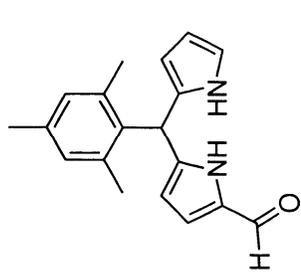
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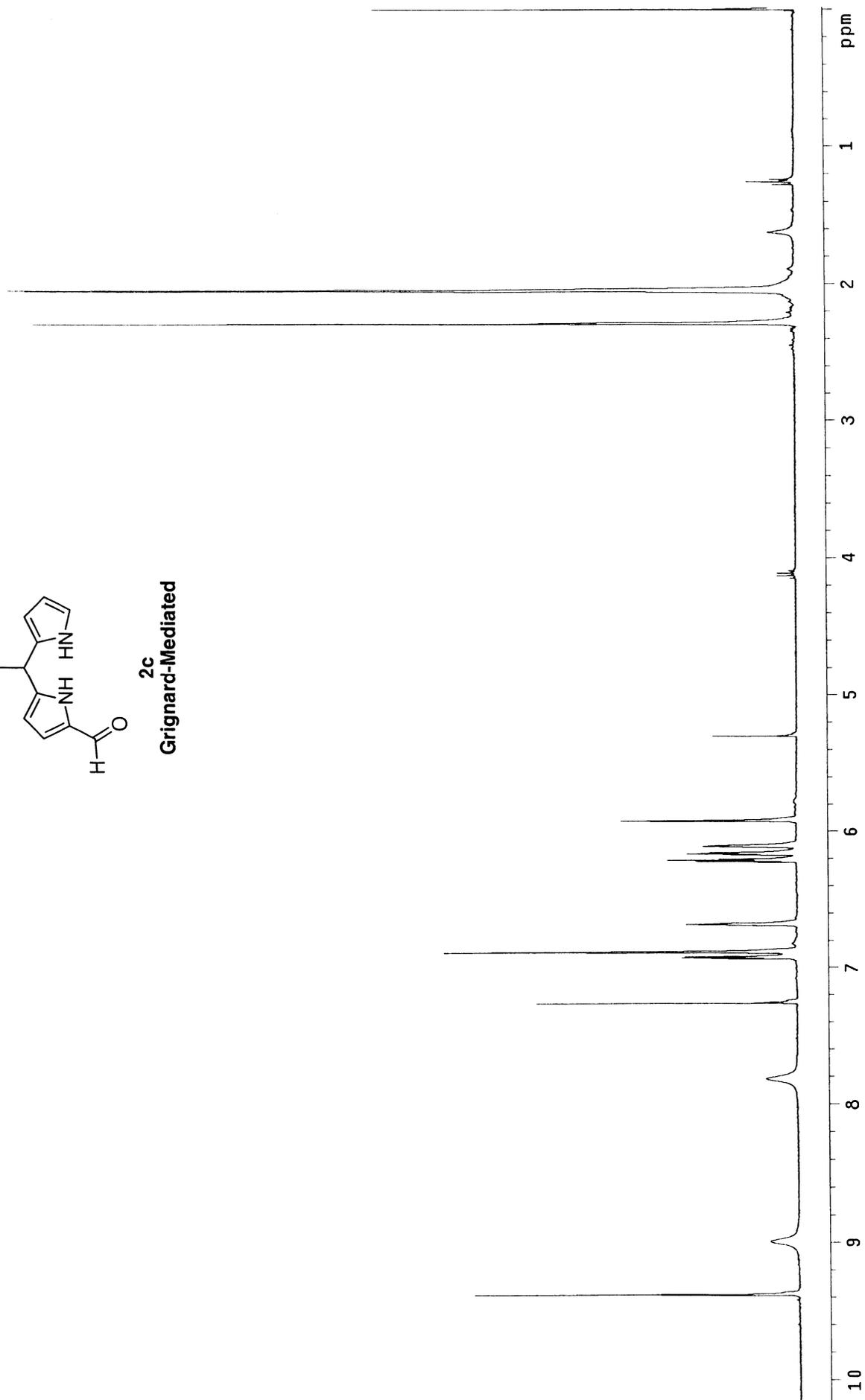


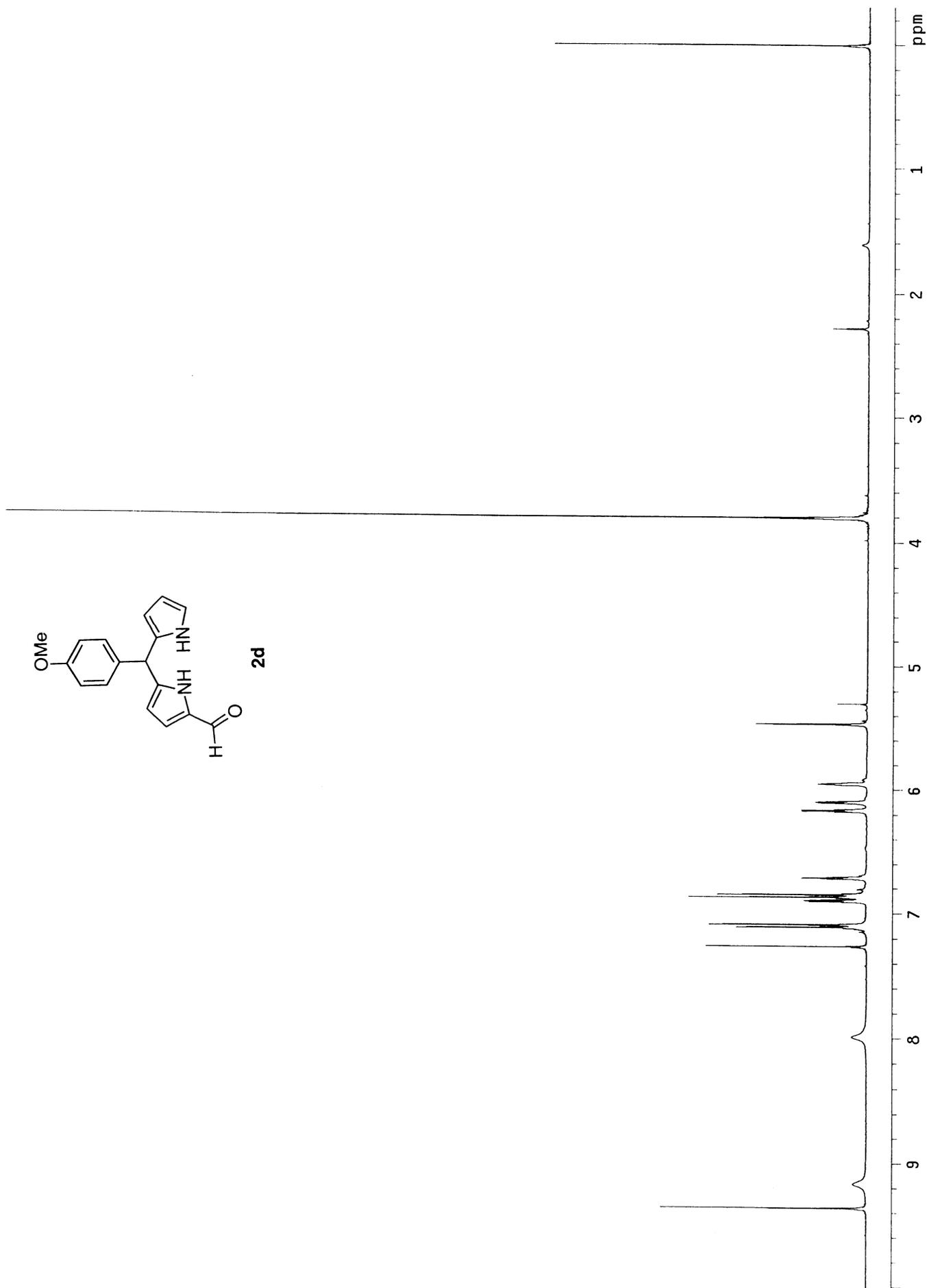
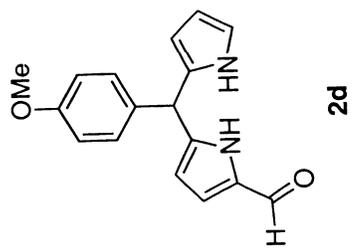
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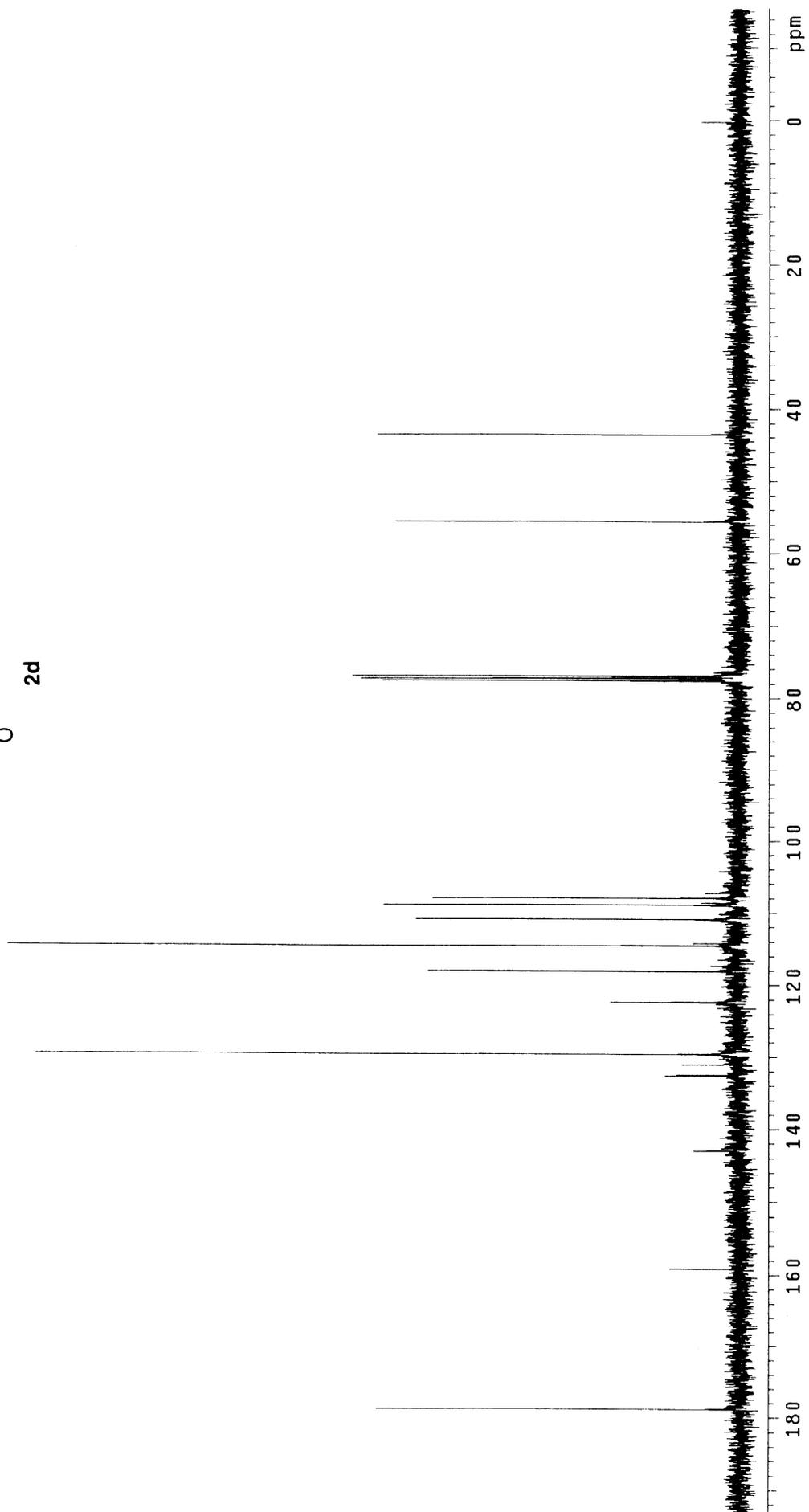
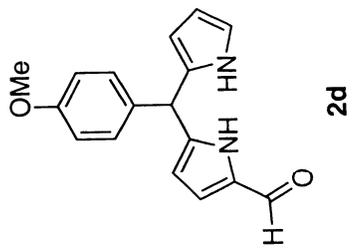


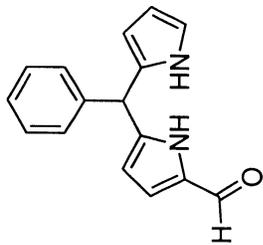


2c
Grignard-Mediated

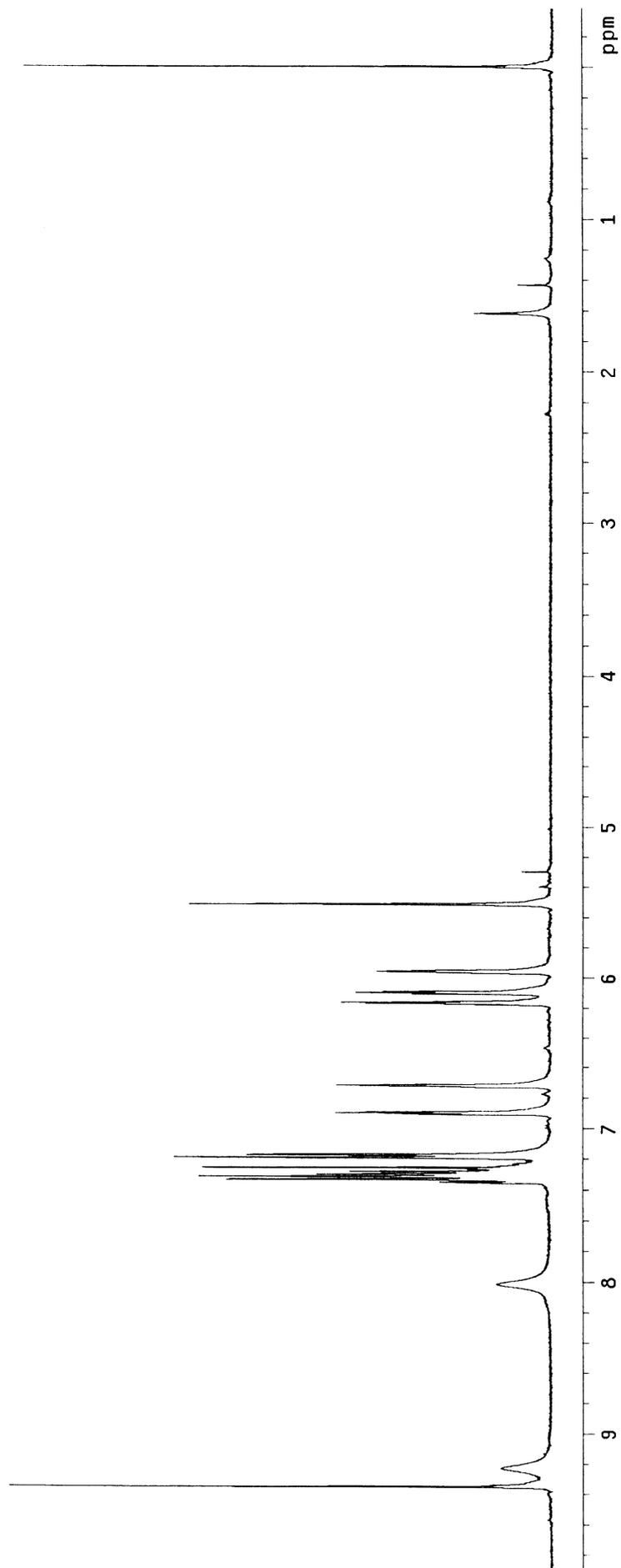


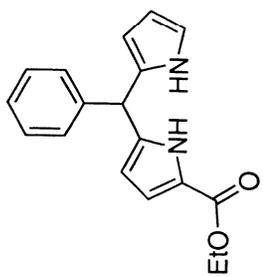




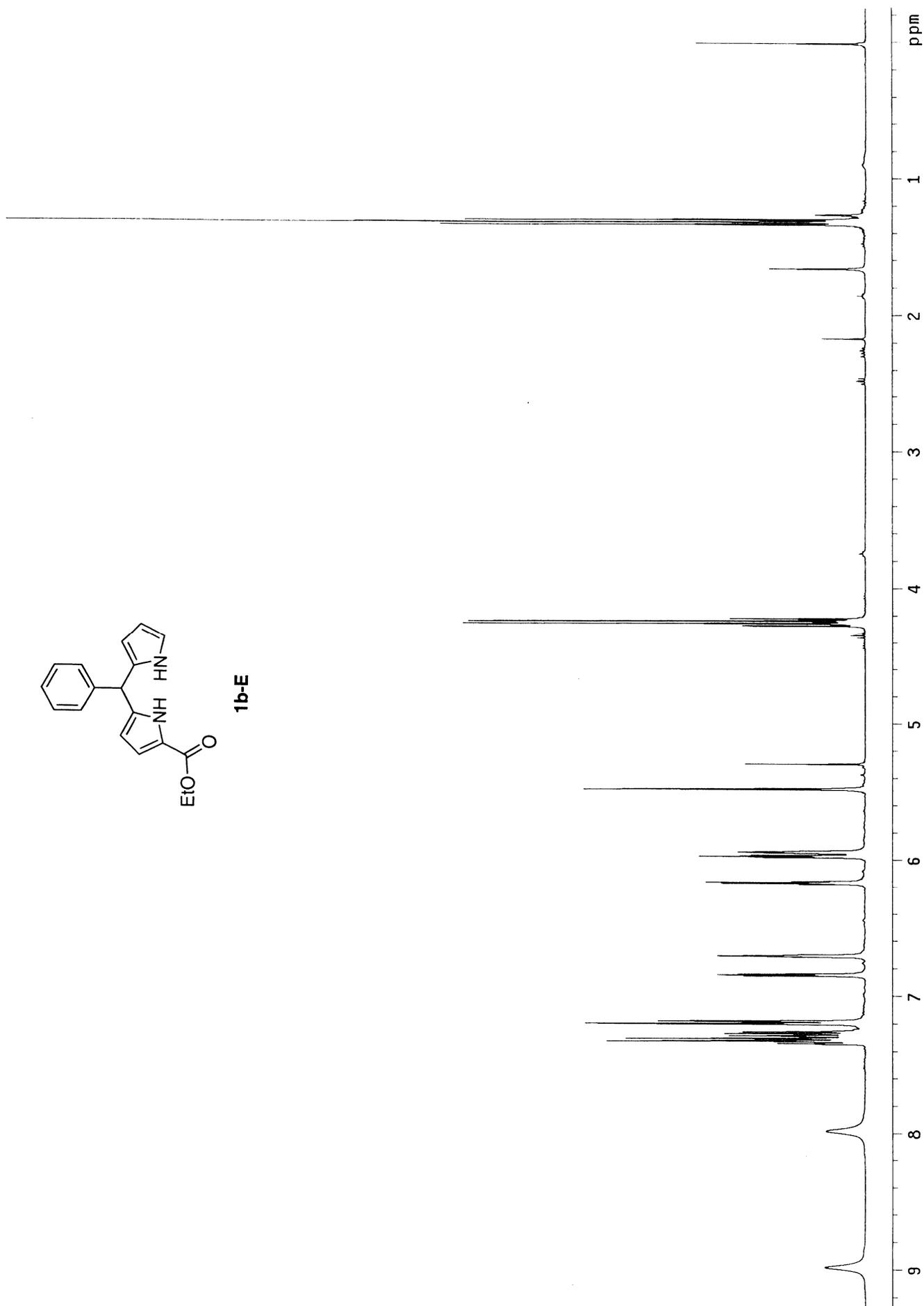


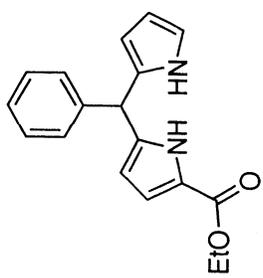
2b
50 mmol scale



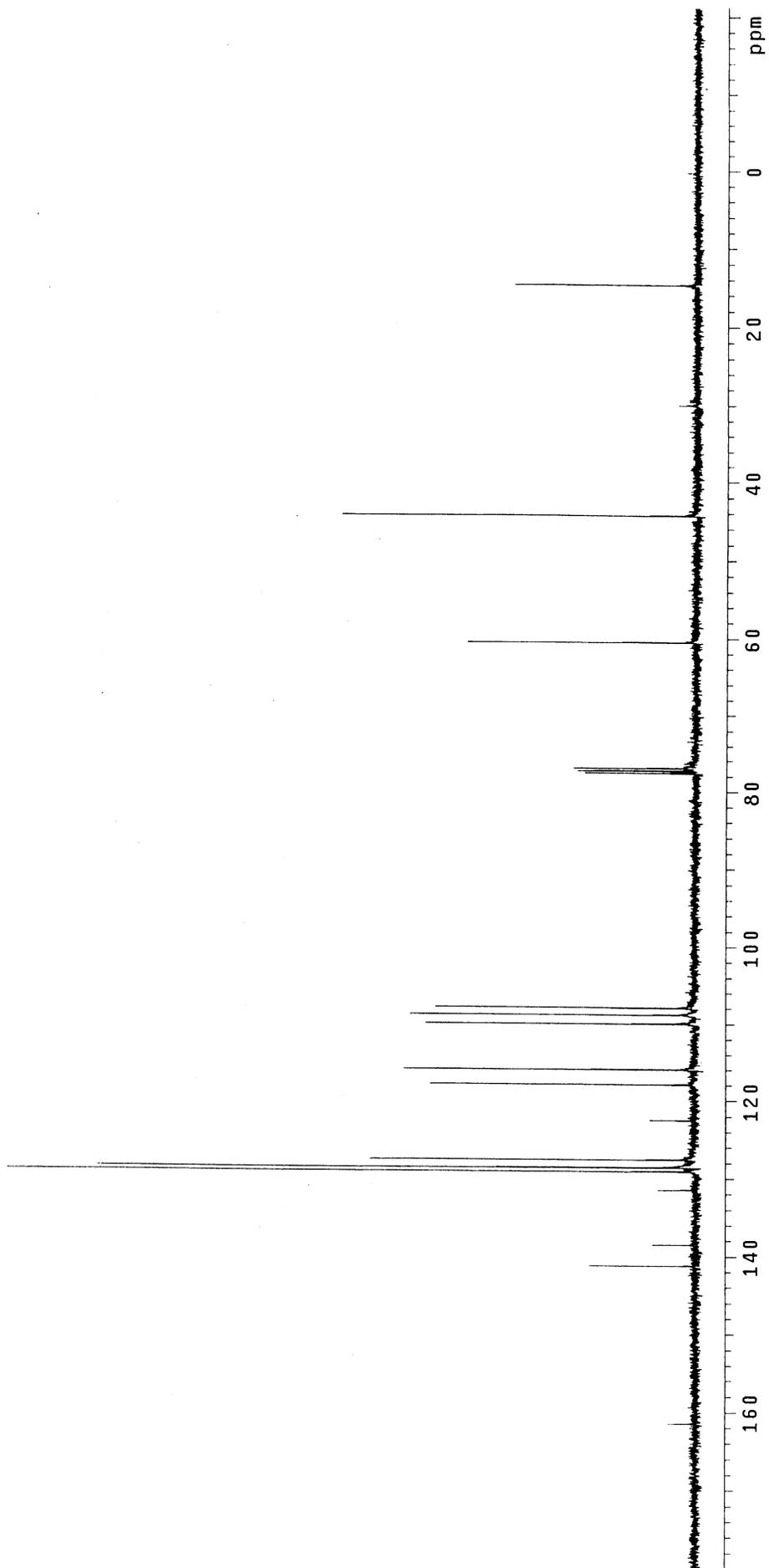


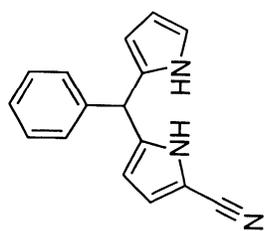
1b-E



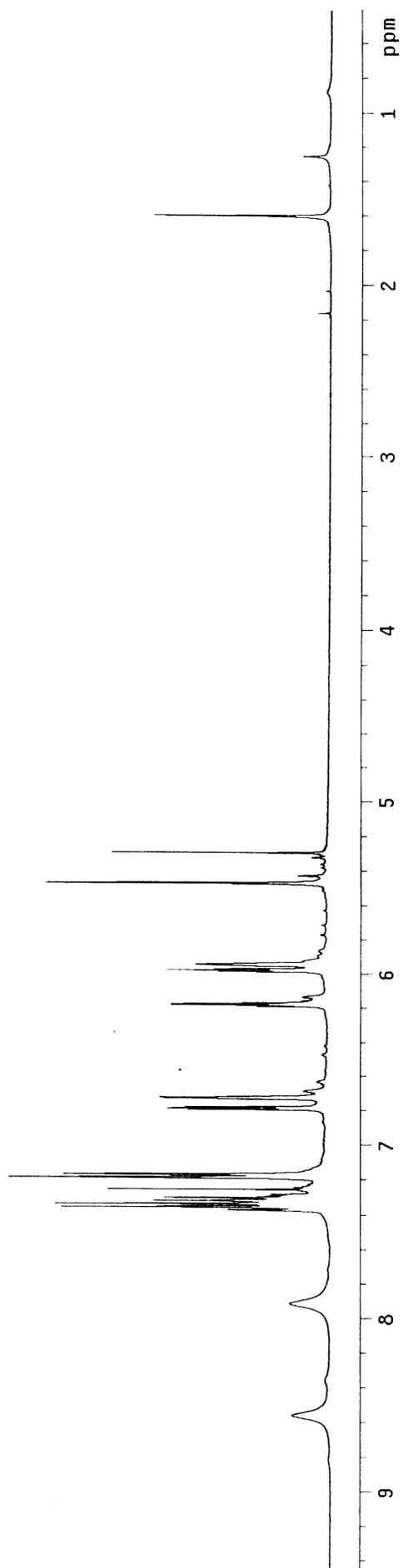


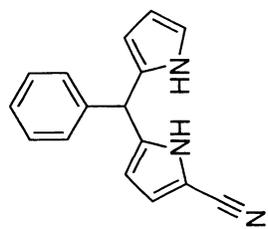
1b-E





1b-N





1b-N

