Supporting Information

One-Pot Construction of Pyrazoles and Isoxazoles with Palladium-Catalyzed Four-Component Coupling

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Experimental:

General. All reactions were performed under an atmosphere of carbon monoxide using the standard Schlenk technique. Melting points were recorded using an Electrothermal melting point apparatus. Infrared spectra were recorded on Shimadzu FT/IR-8100 spectrometer and presented in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR spectrometer in $CDCl_3$. The ^{1}H (300 MHz) and ^{13}C (75 MHz) chemical shifts were referenced to residual $CHCl_3$ (δ 7.26 ppm) for ^{1}H and (77.00 ppm) for ^{13}C. High resolution mass spectra (HRMS) were recorded using JEOL JMS-700 (70eV).

General procedure for the synthesis of 3,5-disubstituted pyrazoles: To a Schlenk tube equipped with a magnetic stirring bar under argon were added $PdCl_2(PPh_3)_2$ (1-5 mol%), CuI (0-2 mol%), and THF. Alkyne **1** (1.2 equiv) and aryl iodide **2** were added successively to the mixture to form a pale yellow solution. Then, an aqueous solution of hydrazine or methylhydrazine (0.5 M, 3 equiv) was added dropwise via syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature. After the period shown in Table 1, the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with chloroform and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash

chromatography using hexanes-ethyl acetate to afford the corresponding 3,5-disubstituted pyrazole (**3** and **4**). [**CAUTION:** The reaction using carbon monoxide should be carried out in a well ventilated hood.]

3,5-Diphenyl-1H-pyrazole (3aa):[1] According to the general procedure, $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) and THF (3 mL). Phenylethyne (**1a**) (0.066 mL, 0.6 mmol) and **2a** (0.117 g, 0.5 mmol) were added successively to the mixture to form a pale yellow solution. Then, aqueous hydrazine solution (0.5 M, 3 mL, 1.5 mmol) was added dropwise via syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature for 36 h, the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with chloroform (3 × 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (5:1 hexanes:ethyl acetate) to afford 65 mg of **3aa** (59%) as a colorless solid; mp 201-203 °C (lit. 201 °C). IR (KBr) 3098 brs, 3065, 3004, 2928 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.08 (brs, 1H), 6.87 (s, 1H), 7.33-7.43 (m, 6H), 7.73-7.76 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 99.99, 125.60, 128.11, 128.78, 131.21, 148.65.

1-Methyl-3,5-diphenylpyrazole (4aa): [2] Purified by flash chromatography (30:1 hexanes:ethyl acetate) to afford 107 mg of **4aa** (91%) as a colorless solid; mp 58-59 °C (lit. 59-60 °C). IR (KBr) 2928, 2855, 1558, 1368 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.95 (s, 3H), 6.62 (s, 1H), 7.26-7.48 (m, 8H), 7.83-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 37.48, 103.15, 125.45, 127.54, 128.47, 128.56, 128.64, 128.66, 130.57, 133.34, 145.00, 150.41.

3-(4-Methoxyphenyl)-5-phenyl-1H-pyrazole (3ab):[3] Purified by flash chromatography (5:1 hexanes:ethyl acetate) to afford 100 mg of **3ab** (80%) as a colorless solid; mp 169-

170 °C (lit. 166-168 °C). IR (KBr) 3129brs, 3004, 2957, 2934, 2836, 1615, 1509 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 5.02 (brs, 1H), 6.78 (s,1H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.34-7.44 (m, 3H), 7.65 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.6 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 55.14, 99.16, 114.04, 123.70, 125.54, 126.84, 127.80, 128.61, 131.50, 147.94, 148.97, 159.38.

1-Methyl-3-(4-Methoxyphenyl)-5-phenylpyrazole (**4ab**): [4] Purified by flash chromatography using hexanes-ethyl acetate to afford 110 mg of **4ab** (83%) as a pale yellow solid; mp 93-94 °C (lit. 92-93 °C). IR (KBr) 3004, 2965, 2836, 1613, 1362 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.93 (s, 3H), 6.54 (s, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 7.44-7.48 (m, 5H), 7.77 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 37.41, 55.20, 102.67, 113.95, 126.18, 126.69, 128.42, 128.62, 128.65, 130.67, 144.94, 150.27, 159.22.

1-Methyl-3-(4-Methylphenyl)-5-phenylpyrazole (4ac): [5] Purified by flash chromatography (20:1 hexanes:ethyl acetate) to afford 95 mg of **4ac** (88%) as a cream solid; mp 136-137 °C (lit. 135-137 °C). IR (KBr) 2923, 2857, 1558, 1350 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.95 (s, 3H), 6.59 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.44-7.47 (m, 5H), 7.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.19, 37.44, 102.96, 125.35, 128.41, 128.61, 128.64, 129.25, 130.51, 130.63, 137.24, 144.90, 150.46.

1-Methyl-3-phenyl-5-(4-Methylphenyl)pyrazole (4ca):[5] Purified by flash chromatography (30:1 hexanes:ethyl acetate) to afford 70 mg of **4ca** (65%) as a cream solid; mp 68-69 °C (lit. 70-72 °C). IR (KBr) 3303, 3112, 3060, 3001, 2961, 2938, 2840, 1611 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.93 (s, 3H), 6.58 (s, 1H), 7.27-7.40 (m, 7H), 7.82 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 21.24, 37.48, 102.99, 125.46, 127.50, 127.69, 128.56, 129.35, 133.44, 138.46, 145.06, 150.38.

1-Methyl-3-(2-thieno)-5-phenylpyrazole (4ad): Purified by flash chromatography (50:1 hexanes:ethyl acetate) to afford 102 mg of **4ad** (85%) as a pale yellow liquid. IR (neat) 3113, 3007, 2840, 1614, 1520 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.91 (s, 3H), 6.52 (s, 1H), 7.06 (dd, *J* = 3.6, 1.5 Hz, 1H), 7.24 (d, *J* = 0.9 Hz, 1H), 7.35 (dd, *J* = 1.2, 2.4 Hz, 1H), 7.43-7.49 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 37.39, 103.06, 123.35, 124.18, 127.34, 128.56, 128.62, 130.22, 136.56, 144.96, 145.68. HRMS (EI) m/z calcd for $C_{14}H_{12}N_2S$ 240.0721, found 240.0710.

1-Methyl-3-(4-Methoxyphenyl)-5-*n*-hexylpyrazole (4eb): Purified by flash chromatography (30:1 hexanes:ethyl acetate) to afford 133 mg of **4eb** (92.5%) as a colorless solid; mp 51-52 °C. IR (KBr) 2953, 2928, 2855, 1559, 1368, 1458, 1437 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.32-1.43 (m, 6H), 1.62-1.72 (m, 2H), 2.59 (t, *J* = 8.1 Hz, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 6.25 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.99, 22.48, 25.59, 28.34, 28.86, 31.49, 35.95, 55.12, 100.78, 113.80, 126.49, 129.81, 144.46, 149.68, 158.96. HRMS (EI) m/z calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1873.

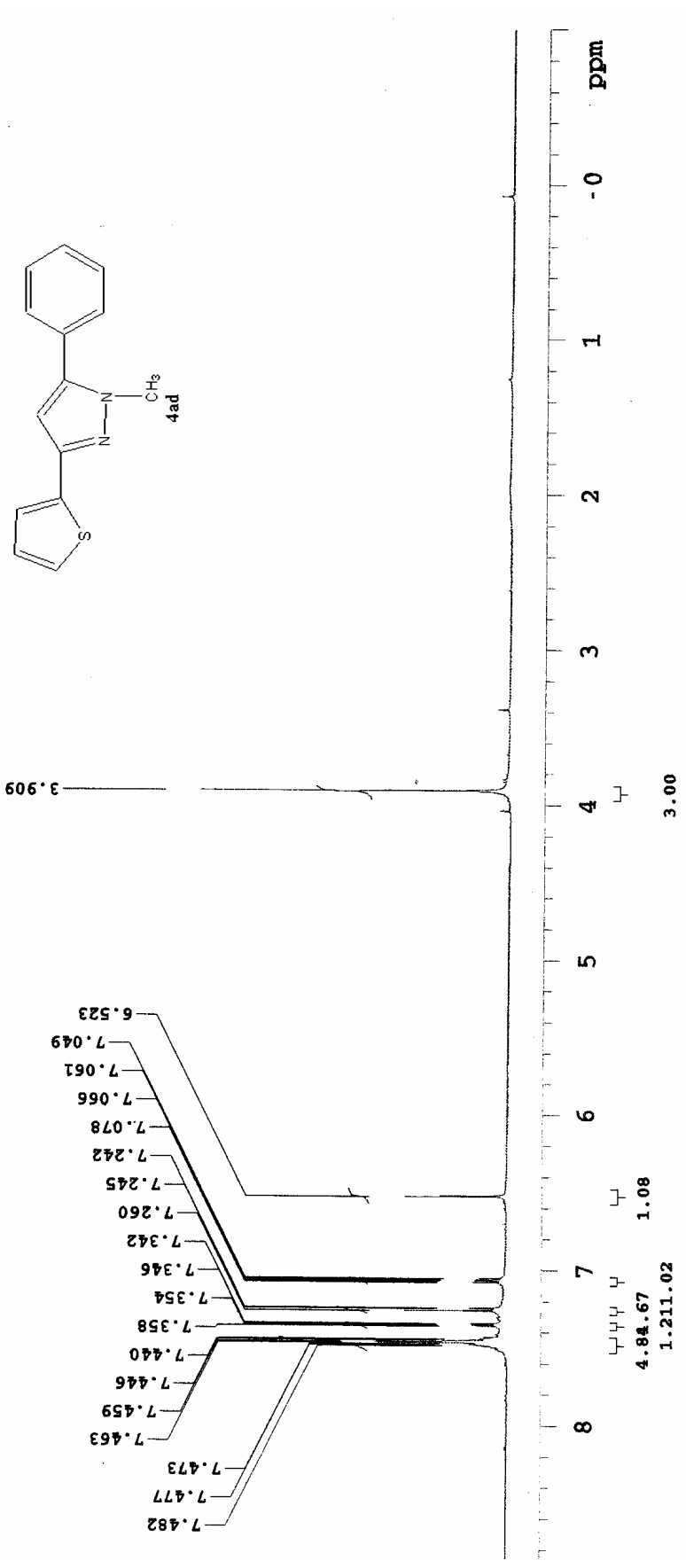
1-Methyl-3-(4-Methylphenyl)-5-*n*-hexylpyrazole (4ec): Purified by flash chromatography (30:1 hexanes:ethyl acetate) to afford 126 mg of **4ec** (93%) as a colorless solid; mp 67-68 °C. IR (KBr) 2996, 2951, 2930, 2849, 1458, 1435, 1368 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.32-1.41 (m, 6H), 1.62-1.75 (m, 2H), 2.35 (s, 3H), 2.59 (t, *J* = 8.1 Hz, 2H), 3.82 (s, 3H), 6.29 (s, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.99, 21.15, 22.50, 25.63, 28.35, 28.88, 31.50, 36.03, 101.11, 125.20, 129.13, 130.89, 136.88, 144.44, 149.94. HRMS (EI) m/z calcd for $C_{17}H_{24}N_2$ 256.1939, found 256.1935.

General procedure for the synthesis of 3,5-disubstituted isoxazole: To a Schlenk tube equipped with a magnetic stirring bar under argon were added $PdCl_2(PPh_3)_2$ (1 mol%) and DMF. Alkyne **1** (1.2 equiv) and **2** were added successively to the mixture to form a pale yellow solution. Then, a mixture of 0.5 M aqueous ammonia (3 equiv) and hydroxylamine hydrochloride (3 equiv) was added dropwise via syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature. After the period shown in Table 2, the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with chloroform and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using hexanes-ethyl acetate to afford the corresponding 3,5-disubstituted isoxazole (**5**). [**CAUTION:** The reaction using carbon monoxide should be carried out in a well ventilated hood.]

3-(4-Methoxyphenyl)-5-phenyl-isoxazole (**5ab**):[6] According to the general procedure, $PdCl_2(PPh_3)_2$ (3.5 mg, 0.005 mmol) and DMF (3 mL). Phenylethyne (**1a**) (0.066 mL, 0.6 mmol) and **2b** (0.117 g, 0.5 mmol) were added successively to the mixture to form a pale yellow solution. Then, a mixture of ammonia (0.5 M, 3 mL, 1.5 mmol) and hydroxylamine hydrochloride (104.4 mg, 1.5 mmol) was added dropwise via syringe. The atmosphere was replaced with carbon monoxide with a balloon and stirring was continued at room temperature for 37 h, the mixture was passed through a Celite pad and the filtrate was washed with brine. The aqueous layer was extracted with chloroform (3 × 15 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography using (10:1 hexanes-ethyl acetate) to afford 83 mg of **5ab** (66%) as a pale yellow solid; mp 125-126

°C (lit. 126-127 °C). IR (KBr) 3119, 3006, 2963, 2839, 1615, 1362 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 6.72 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.46-7.48 (m, 3H), 7.79 (d, *J* = 8.7 Hz, 2H), 7.85-7.87 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 55.37, 96.09, 113.96, 114.39, 120.29, 126.77, 127.41, 128.86, 129.26, 129.89, 161.11, 170.36.

3-phenyl-5-(4-Methoxyphenyl)-isoxazole (**5ba**):[6] Purified by flash chromatography (20:1 hexanes:ethyl acetate) to afford 68 mg of **5ba** (54%) as a colorless solid; IR (KBr) 3115, 3102, 3067, 2946, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.93 (s, 3H), 6.59 (s, 1H), 7.28-7.47 (m, 7H), 7.81-7.85 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 37.52, 103.02, 114.30, 125.50, 125.80, 127.54, 128.19, 128.61, 128.96, 129.38, 138.51, 150.42.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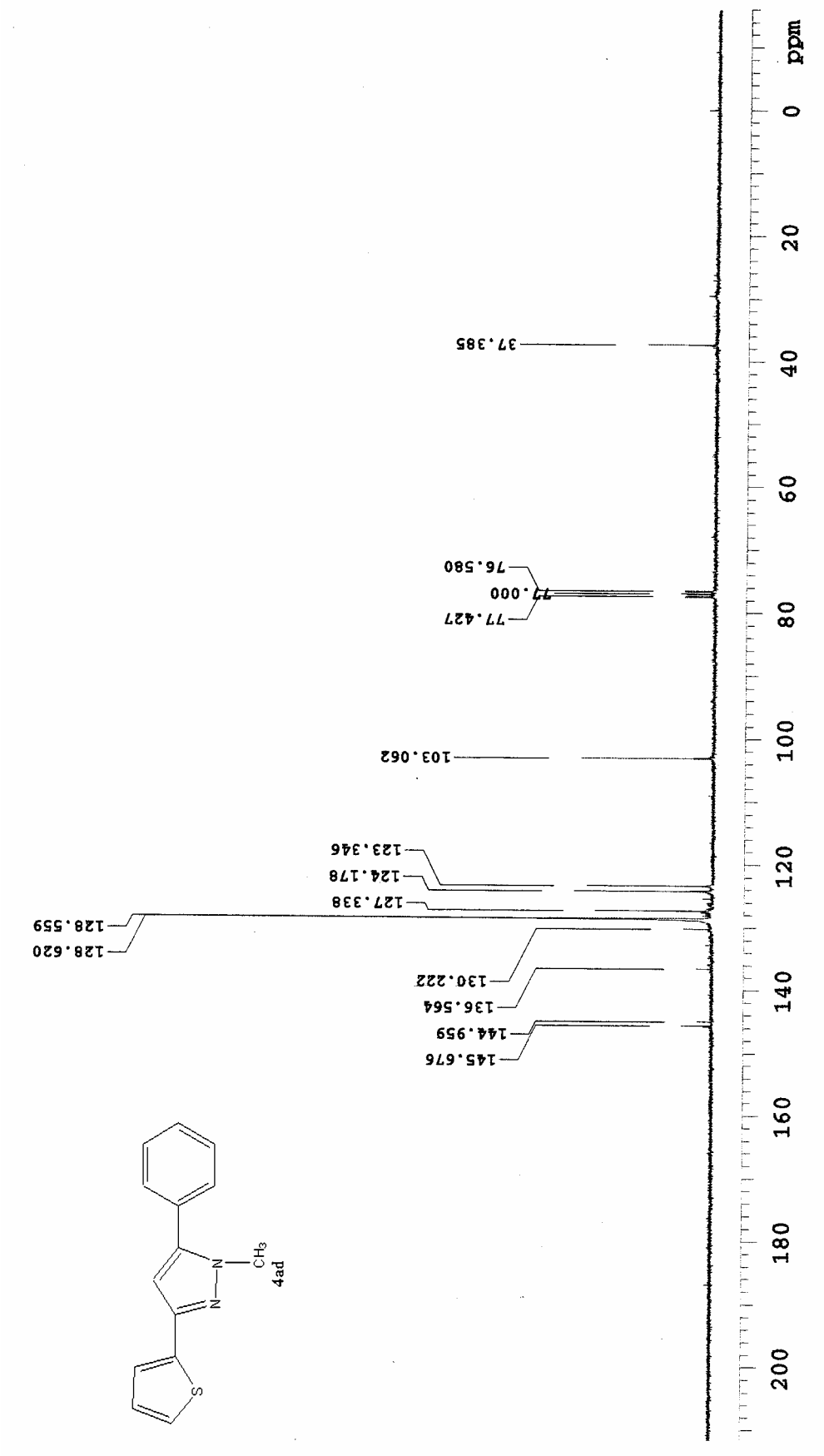
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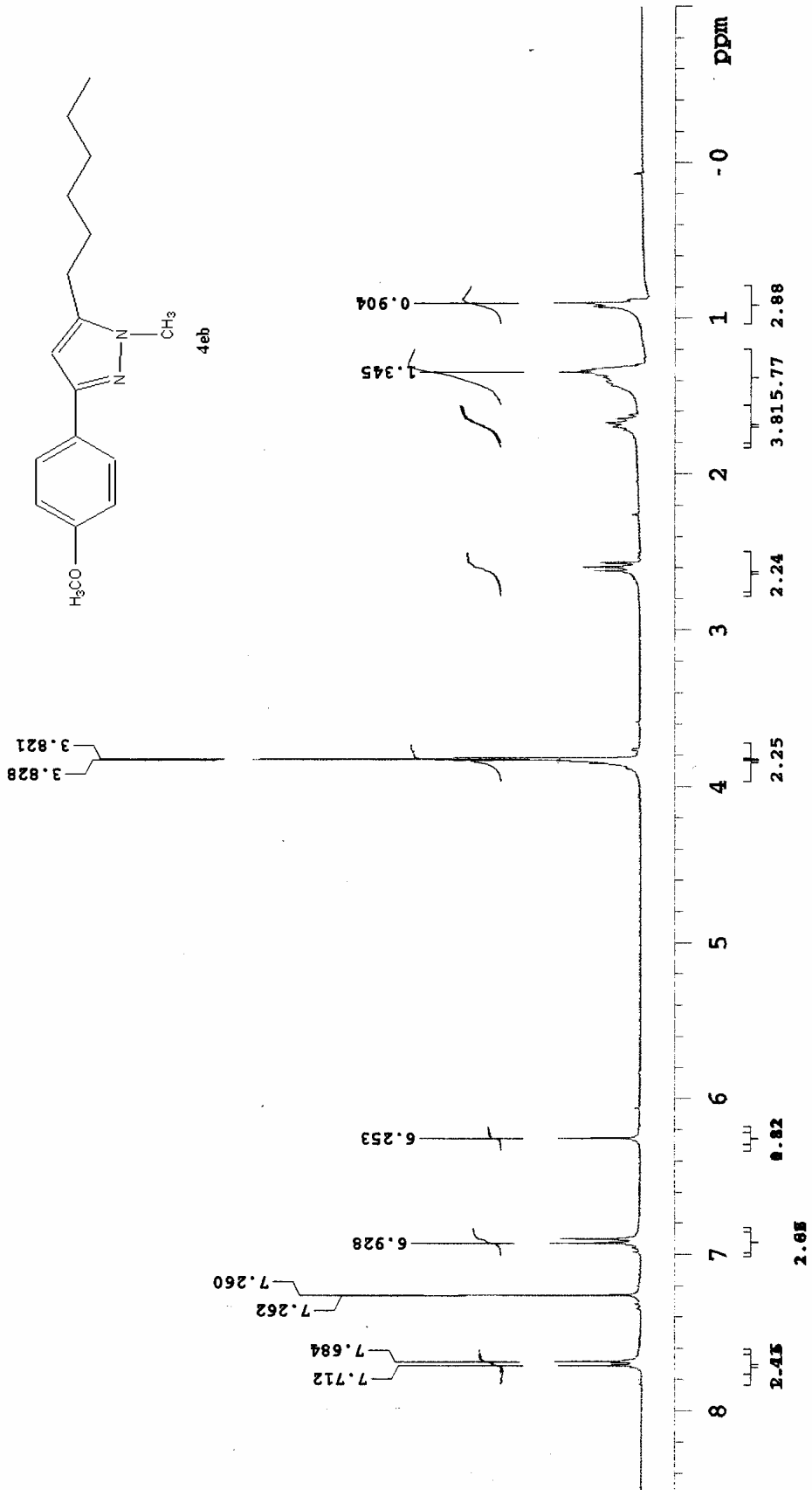
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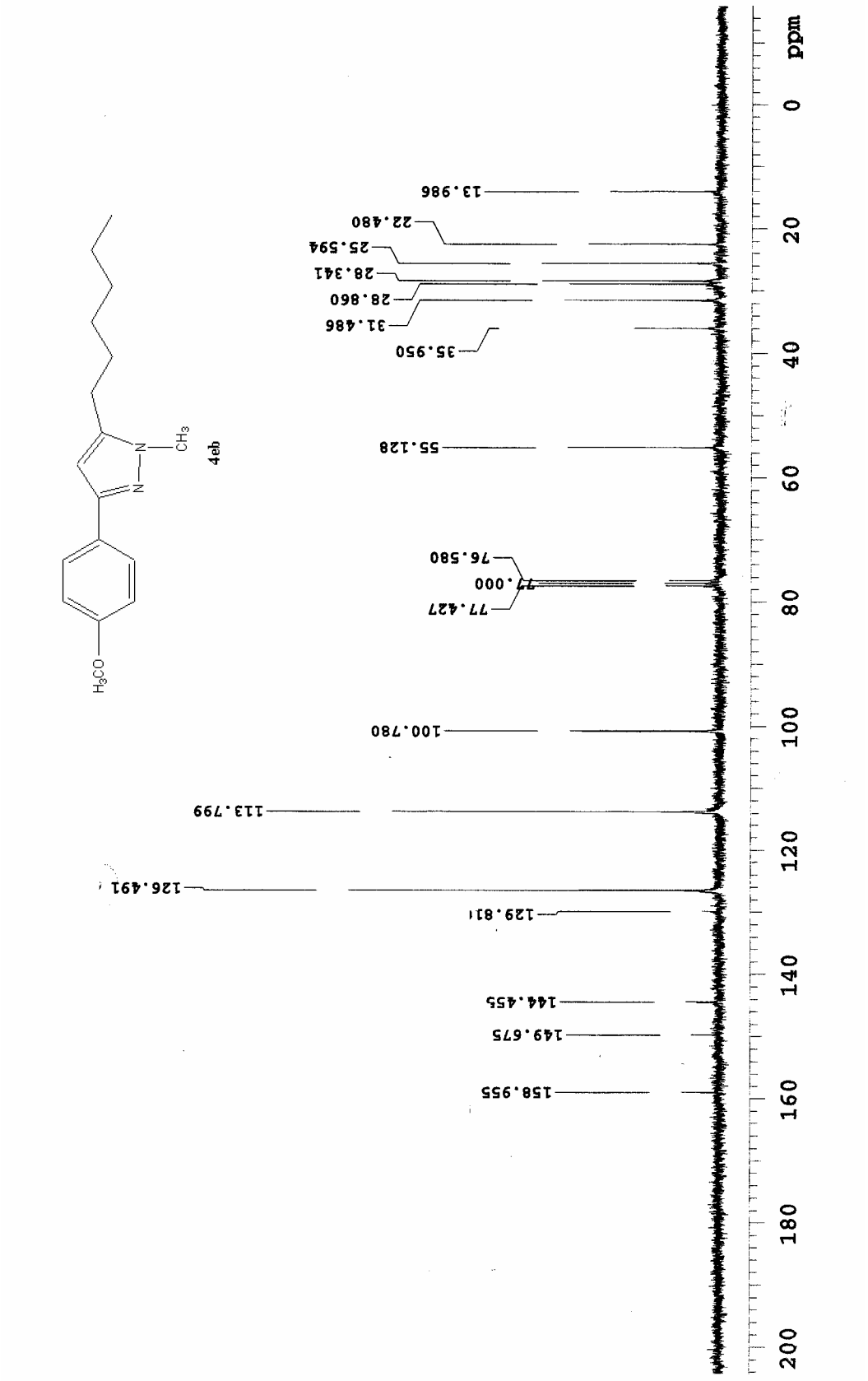
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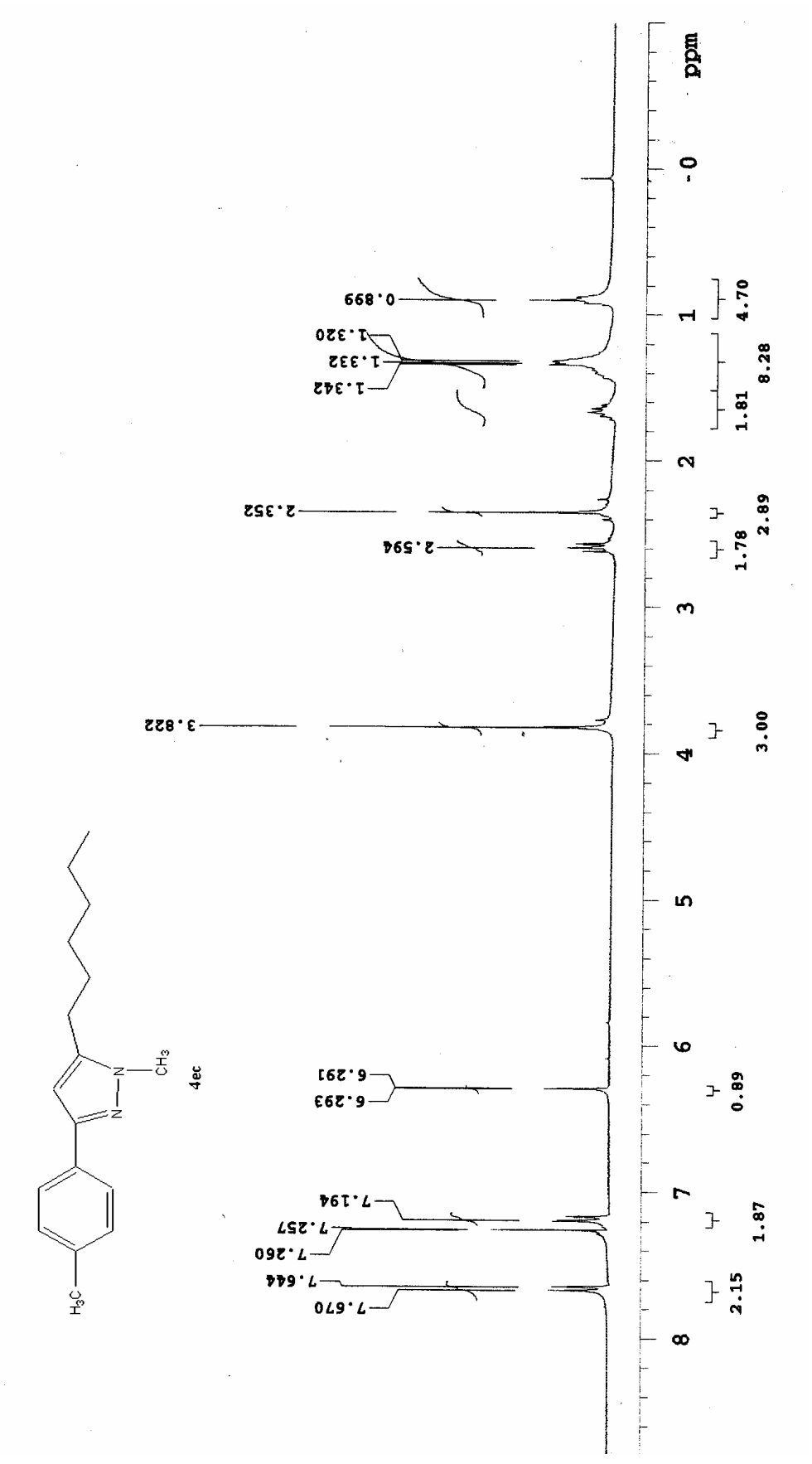
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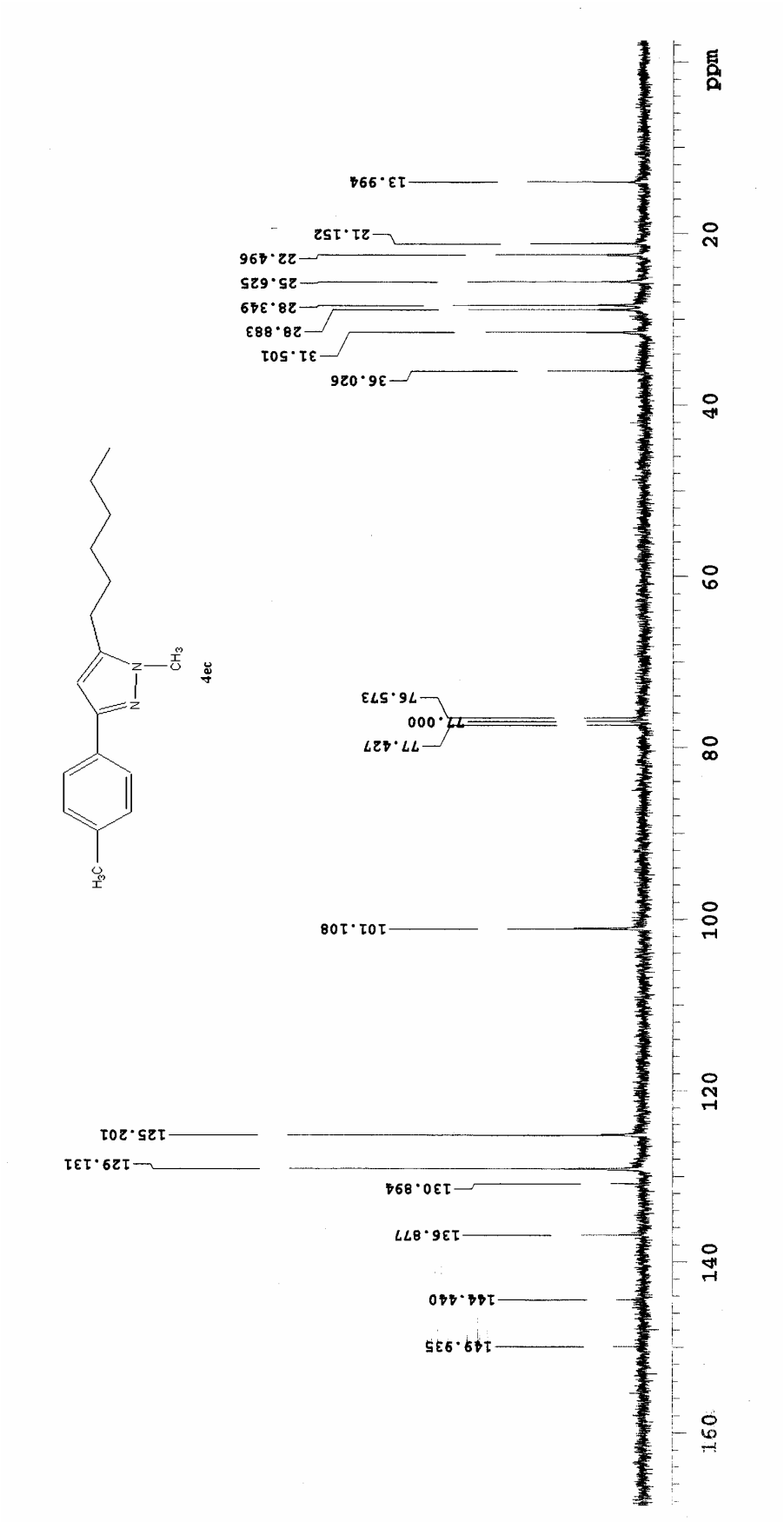
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References

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