

Pd-Catalyzed Cross-Coupling of Aromatic Compounds with Carboxylic Acids via C-H Bond Activation

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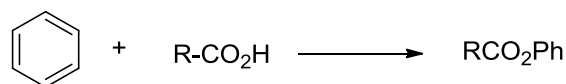
General considerations

Unless otherwise specified, all reactions were carried out under air atmosphere. The reagents and solvents were directly used from Sigma-Aldrich, Alfa Aesar and TCI without further purification unless noted. Reactions were monitored through thin layer chromatography [Merck 60 F254 precoated silica gel plate (0.2 mm thickness)]. Subsequent to elution, spots were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Flash chromatography was performed using silica gel 60 with distilled solvents. HRMS spectra were recorded on a Waters Q-Tofermier TM mass Spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker Avance 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 7.260, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); td (triplet of doublet); m (multiplets) and etc. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-d (δ 77.00, triplet). Compound numbers used in the experimental section correspond to those employed in the main paper.

Experimental Procedure

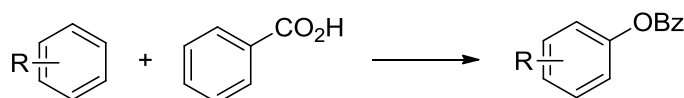
General coupling procedure (Table 2)

Condition A



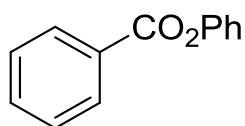
0.5 mmol carboxylic acid, 1 mmol iodosobenzene and 5mol% Pd(OAc)₂ and 2 mL benzene were added into the Schlenk tube. The mixture was stirred at 120 °C for 40 h and cooled down to room temperature, quenched with saturated sodium bicarbonate solution (50 mL) and extracted thrice with ethyl acetate (30 mL) and the combined organic phase was dried over Na₂SO₄. After evaporation of the solvents the residue was purified by silica gel chromatography or thin layer chromatography (TLC).

Condition B



0.5 mmol benzoic acid, 1 mmol aromatic compound, 1mmol iodosobenzene, 0.75 mmol CSA and 2 mL DCE were added into the Schlenk tube. The mixture was heated at 120 °C for 40 h and cooled down to room temperature, quenched with saturated sodium bicarbonate solution (50 mL) and extracted thrice with ethyl acetate (30 mL) and the combined organic phase was dried over Na₂SO₄. After evaporation of the solvents the residue was purified by silica gel chromatography or thin layer chromatography (TLC).

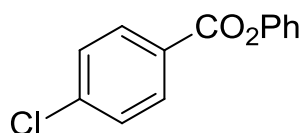
Phenyl benzoate 3a¹



White solid: ¹H NMR (400 MHz, CDCl₃) ppm: 8.21 (d, *J* = 7.20 Hz, 2H), 7.64 (t, *J* = 7.60 Hz, 1H), 7.51 (t, *J* = 7.60 Hz, 2H), 7.43 (t, *J* = 7.60 Hz, 2H), 7.27 (t, *J* = 7.60 Hz,

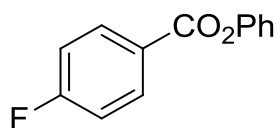
1H), 7.23 (d, $J = 7.60$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): 165.17, 150.98, 133.55, 130.16, 129.61, 129.48, 128.56, 125.87, 121.71. HRMS (ESI) Calcd. for $\text{C}_{13}\text{H}_{10}\text{O}_2$: $[\text{M}+\text{H}]^+$, 199.0759. Found: m/z 199.0760.

Phenyl 4-chlorobenzoate **3b**²



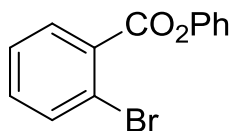
White solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.14 (d, $J = 8.80$ Hz, 2H), 7.49 (d, $J = 8.80$ Hz, 2H), 7.44 (t, $J = 7.60$ Hz, 2H), 7.29 (t, $J = 7.60$ Hz, 1H), 7.21 (d, $J = 8.40$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): 164.31, 150.77, 140.11, 131.52, 129.52, 128.93, 128.03, 126.02, 121.59. HRMS (ESI) Calcd. for $\text{C}_{13}\text{H}_9\text{ClO}_2$: $[\text{M}+\text{H}]^+$, 233.0369. Found: m/z 233.0372.

Phenyl 4-fluorobenzoate **3c**²



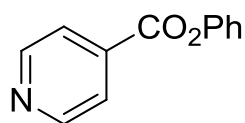
Pale yellow solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.25-8.22 (m, 2H), 7.44 (t, $J = 7.60$ Hz, 2H), 7.29 (t, $J = 7.20$ Hz, 1H), 7.23-7.17 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): 167.41, 164.88, 164.19, 150.83, 132.82, 129.51, 125.84, 121.64, 115.88. ^{19}F NMR (100 MHz, CDCl_3): -104.45. HRMS (ESI) Calcd. for $\text{C}_{13}\text{H}_9\text{FO}_2$: $[\text{M}+\text{H}]^+$, 217.0665. Found: m/z 217.0666.

Phenyl 2-bromobenzoate **3d**



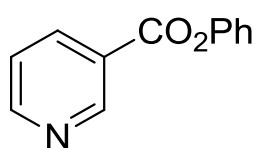
Yellow oil: ^1H NMR (400 MHz, CDCl_3) ppm: 8.00 (dd, $J = 7.60$ Hz, 2.00 Hz, 1H), 7.74 (dd, $J = 7.60$ Hz, 1.20 Hz, 1H), 7.47-7.38 (m, 4H), 7.31-7.26 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): 164.56, 150.67, 134.59, 133.10, 131.76, 131.44, 129.52, 127.30, 126.11, 122.23, 121.55. HRMS (ESI) Calcd. for $\text{C}_{13}\text{H}_9\text{BrO}_2$: $[\text{M}+\text{H}]^+$, 276.9864. Found: m/z 276.9857.

Phenyl isonicotinate **3e**³



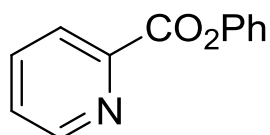
White solid: ¹H NMR (400 MHz, CDCl₃) ppm: 8.67 (s, 2H), 7.64 (d, *J* = 6.80 Hz, 2H), 7.52-7.44 (m, 5H). ¹³C NMR (100 MHz, CDCl₃): 150.23, 148.41, 138.16, 129.12, 129.06, 127.00, 121.68. HRMS (ESI) Calcd. for C₁₂H₉NO₂: [M+H]⁺, 200.0712. Found: m/z 200.0709.

Phenyl nicotinate **3f**³



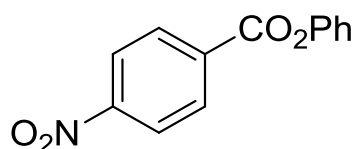
Pale yellow oil: ¹H NMR (400 MHz, CDCl₃) ppm: 9.37 (s, 1H), 8.85-8.83 (m, 1H), 8.46-8.41 (m, 1H), 7.47-7.41 (m, 3H), 7.30-7.21 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): 163.81, 153.95, 151.32, 150.48, 137.50, 129.55, 126.18, 125.55, 123.41, 121.50. HRMS (ESI) Calcd. for C₁₂H₉NO₂: [M+H]⁺, 200.0712. Found: m/z 200.0709.

Phenyl picolinate **3g**³



Yellow solid: ¹H NMR (400 MHz, CDCl₃) ppm: 8.70 (d, *J* = 4.80 Hz, 1H), 8.00 (d, *J* = 6.80 Hz, 2H), 7.76-7.72 (m, 2H), 7.50-7.40 (m, 3H), 7.25-7.22 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): 157.48, 149.66, 139.39, 136.74, 128.94, 128.73, 126.90, 122.08, 120.56. HRMS (ESI) Calcd. for C₁₂H₉NO₂: [M+H]⁺, 200.0712. Found: m/z 200.0709.

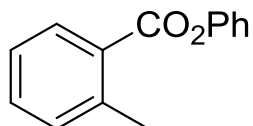
Phenyl 4-nitrobenzoate **3h**⁴



Pale yellow solid: ¹H NMR (400 MHz, CDCl₃) ppm: 8.43-8.38 (m, 4H), 7.50 (t, *J* = 7.60 Hz, 2H), 7.35 (t, *J* = 7.20 Hz, 1H), 7.28 (d, *J* = 8.80 Hz, 2H). ¹³C NMR (100

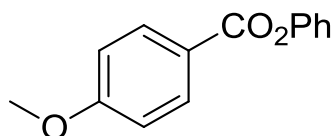
MHz, CDCl₃): 163.29, 150.88, 150.49, 134.96, 131.26, 129.65, 126.38, 123.69, 121.38. HRMS (ESI) Calcd. for C₁₃H₉NO₄: [M+H]⁺, 244.0610. Found: m/z 244.0609.

Phenyl 2-methylbenzoate **3i**⁵



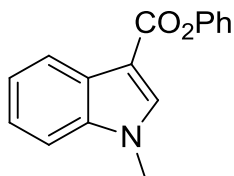
Pale yellow oil: ¹H NMR (400 MHz, CDCl₃) ppm: 8.17 (d, *J* = 7.60 Hz, 1H), 7.51-7.43 (m, 3H), 7.35-7.28 (m, 3H), 7.23-7.21 (m, 2H), 2.69 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 165.83, 150.92, 141.30, 132.69, 131.95, 131.15, 129.47, 128.57, 125.90, 125.80, 121.82, 21.93. HRMS (ESI) Calcd. for C₁₄H₁₂O₂: [M+H]⁺, 213.0916. Found: m/z 213.0920.

Phenyl 4-methoxybenzoate **3j**⁶



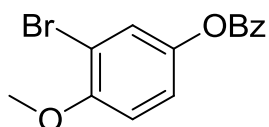
Pale yellow solid: ¹H NMR (400 MHz, CDCl₃) ppm: 8.17 (d, *J* = 9.20 Hz, 2H), 7.43 (t, *J* = 7.20 Hz, 2H), 7.27 (t, *J* = 7.20 Hz, 1H), 7.21 (d, *J* = 8.40 Hz, 2H), 6.99 (d, *J* = 9.20 Hz, 2H), 3.90 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 164.87, 163.86, 151.05, 132.25, 129.39, 125.67, 121.86, 121.77, 113.80, 55.47. HRMS (ESI) Calcd. for C₁₄H₁₂O₃: [M+H]⁺, 229.0865. Found: m/z 229.0869.

Phenyl 1-methyl indole-3-carboxylate **3l**⁷



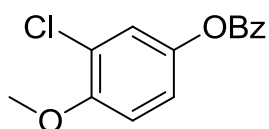
Colorless oil: ¹H NMR (400 MHz, CDCl₃) ppm: 8.29-8.27 (m, 1H), 8.27 (s, 1H), 7.48-7.26 (m, 8H), 3.85 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 163.07, 150.92, 137.26, 136.07, 129.31, 126.73, 125.37, 123.01, 122.19, 122.02, 121.62, 109.89, 105.99, 33.45. HRMS (ESI) Calcd. for C₁₆H₁₃NO₂: [M+H]⁺, 252.1024. Found: m/z 252.1020.

3-Bromo-4-methoxyphenyl benzoate **3m**



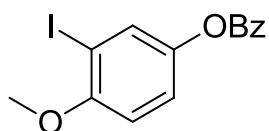
Pale yellow solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.18 (d, $J = 8.00$ Hz, 2H), 7.64 (t, $J = 7.20$ Hz, 1H), 7.51 (t, $J = 7.60$ Hz, 2H), 7.45 (d, $J = 2.40$ Hz, 1H), 7.16 (dd, $J = 8.80$ Hz, 2.40 Hz, 1H), 6.94 (d, $J = 8.80$ Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 165.17, 153.95, 144.40, 133.70, 130.16, 129.23, 128.60, 126.71, 121.45, 111.95, 111.59, 56.61. HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{11}\text{BrO}_3$: $[\text{M}+\text{H}]^+$, 306.9970. Found: m/z 306.9972.

3-chloro-4-methoxyphenyl benzoate 3n



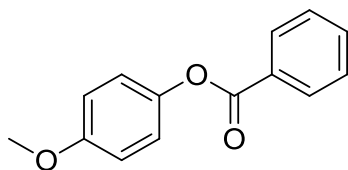
White solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.18 (d, $J = 7.20$ Hz, 2H), 7.64 (t, $J = 7.60$ Hz, 1H), 7.51 (t, $J = 8.00$ Hz, 2H), 7.29 (d, $J = 2.80$ Hz, 1H), 7.12 (dd, $J = 8.80$ Hz, 2.80 Hz, 1H), 6.96 (d, $J = 8.80$ Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 165.18, 153.06, 144.14, 133.72, 130.16, 129.22, 128.60, 123.81, 122.78, 120.74, 112.18, 56.50. HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{11}\text{ClO}_3$: $[\text{M}+\text{H}]^+$, 263.0475. Found: m/z 263.0471.

3-Iodo-4-methoxyphenyl benzoate 3o



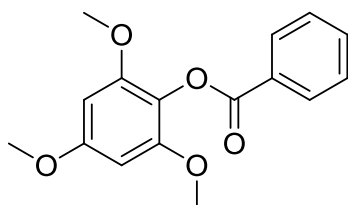
Pale yellow solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.18 (dd, $J = 8.40$ Hz, 1.2 Hz, 2H), 7.66-7.62 (m, 2H), 7.51 (t, $J = 8.00$ Hz, 2H), 7.20 (dd, $J = 8.80$ Hz, 2.80 Hz, 1H), 6.85 (d, $J = 8.80$ Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 165.20, 156.16, 144.63, 133.68, 132.44, 130.13, 129.21, 128.58, 122.42, 110.67, 85.31, 56.75. HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{11}\text{IO}_3$: $[\text{M}+\text{H}]^+$, 354.9831. Found: m/z 354.9831.

4-Methoxyphenyl benzoate 3p²



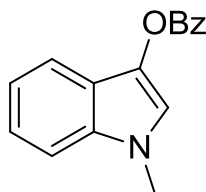
White solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.22 (dd, $J = 8.00$ Hz, 1.6 Hz, 2H), 7.64 (t, $J = 7.60$ Hz, 1H), 7.51 (t, $J = 8.00$ Hz, 2H), 7.14 (d, $J = 8.80$ Hz, 2H), 6.95 (d, $J = 9.20$ Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 165.49, 157.30, 144.42, 133.45, 130.10, 129.65, 128.50, 122.41, 114.50, 55.58. HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_3$: $[\text{M}+\text{H}]^+$, 229.0865. Found: m/z 229.0869.

2, 4, 6-Trimethoxyphenyl benzoate **3q**⁸



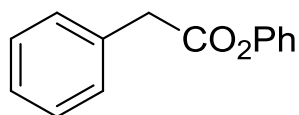
Yellow solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.24 (d, $J = 7.20$ Hz, 2H), 7.61 (t, $J = 7.20$ Hz, 1H), 7.50 (t, $J = 8.00$ Hz, 2H), 6.23 (s, 2H), 3.82 (2, 3H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): 164.79, 158.27, 152.74, 133.20, 130.28, 129.46, 128.35, 122.80, 91.45, 56.06, 55.49. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_5$: $[\text{M}+\text{H}]^+$, 289.1076. Found: m/z 289.1067.

1-Methyl-1H-indol-3-yl benzoate **3s**



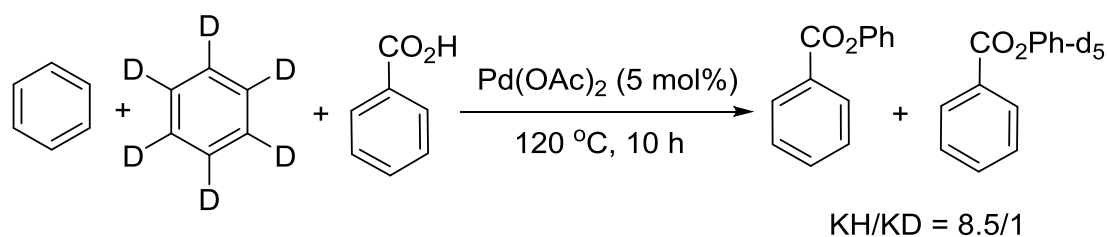
White solid: ^1H NMR (400 MHz, CDCl_3) ppm: 8.30-8.28 (m, 2H), 7.69-7.63(m, 2H), 7.55 (t, $J = 8.00$ Hz, 2H), 7.45 (s, 1H), 7.34 (d, $J = 8.00$ Hz, 1H), 7.30-7.26 (m, 1H), 7.19-7.15 (m, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): 164.22, 133.73, 133.33, 130.04, 129.71, 129.25, 128.55, 122.36, 120.26, 119.33, 118.02, 117.61, 109.28, 32.86. HRMS (ESI) Calcd. for $\text{C}_{16}\text{H}_{13}\text{NO}_2$: $[\text{M}+\text{H}]^+$, 252.1025. Found: m/z 252.1023.

Phenyl phenylacetate **3t**⁹



White solid: ^1H NMR (400 MHz, CDCl_3) ppm: 7.42-7.32 (m, 7H), 7.24 (m, 1H), 7.06 (d, $J = 8.40$ Hz, 2H), 3.87 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): 169.96, 150.72, 133.45, 129.35, 129.28, 127.32, 125.82, 121.41, 41.42. HRMS (ESI) Calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2$: $[\text{M}+\text{H}]^+$, 213.0916. Found: m/z 213.0920.

KIE experiment

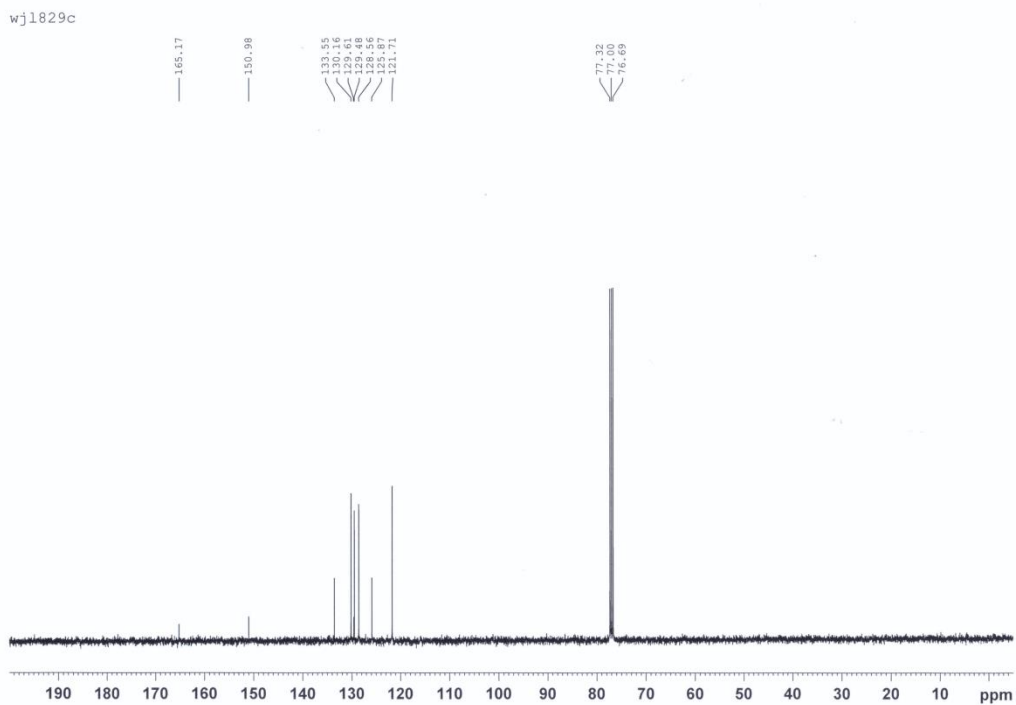
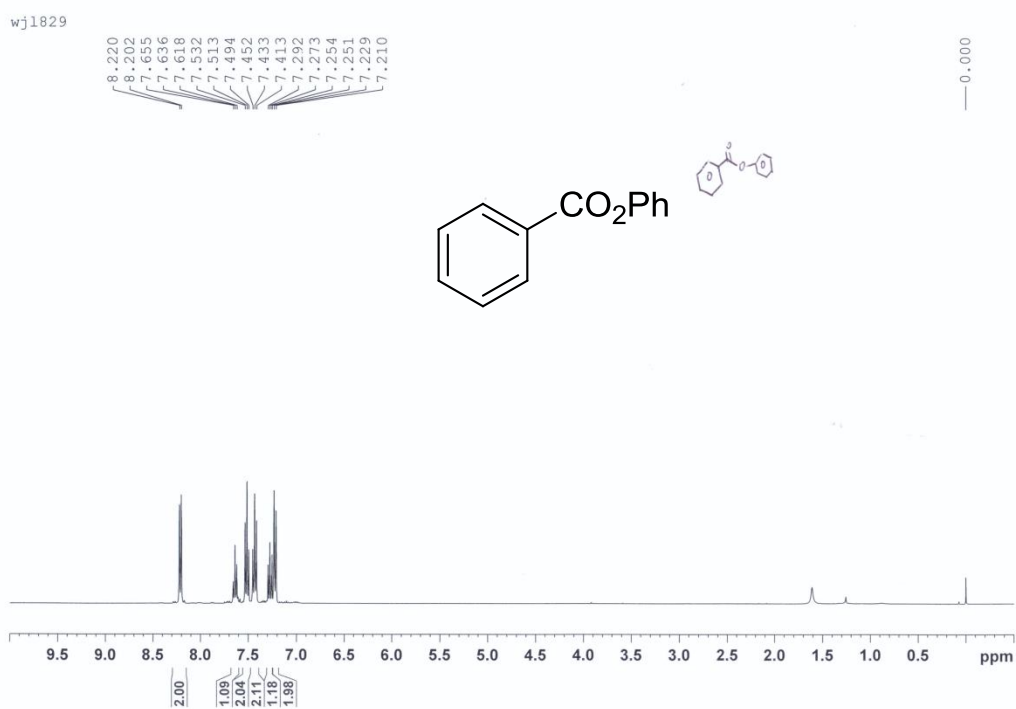


0.5 mmol carboxylic acid, 1 mmol iodobenzene and 5mol% $\text{Pd}(\text{OAc})_2$, 0.5 mL benzene and 0.5 mL benzene- d_6 were added into the Schlenk tube. The mixture was stirred at 120 °C for 10 h and cooled down to room temperature, quenched with saturated sodium bicarbonate solution (50 mL) and extracted thrice with ethyl acetate (30 mL) and the combined organic phase was dried over Na_2SO_4 . After evaporation of the solvents the residue was purified by silica gel chromatography.

References

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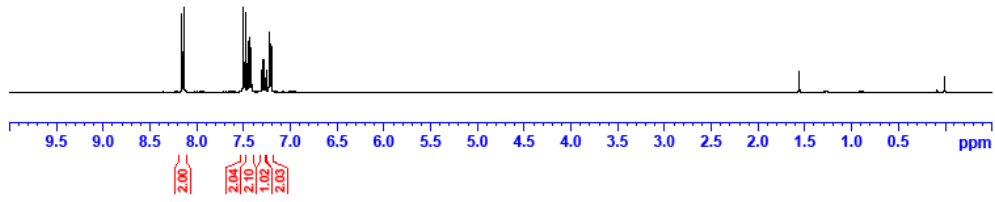
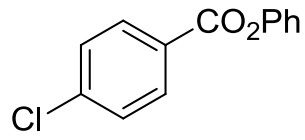
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wj1-3b

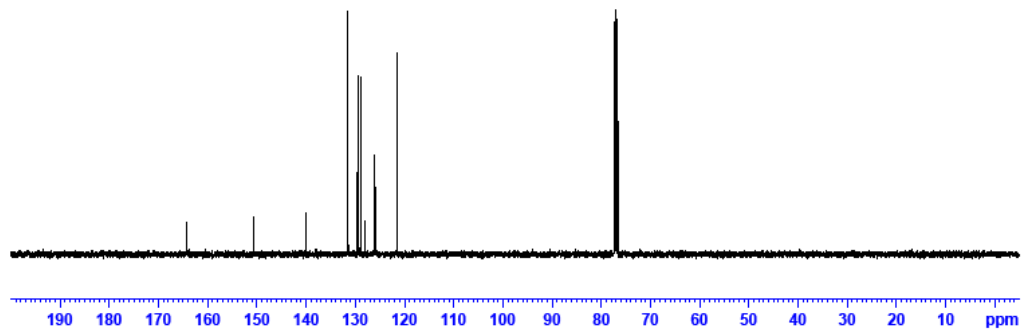
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7.228
7.225
7.206
7.204

0.011



wj1-3bc

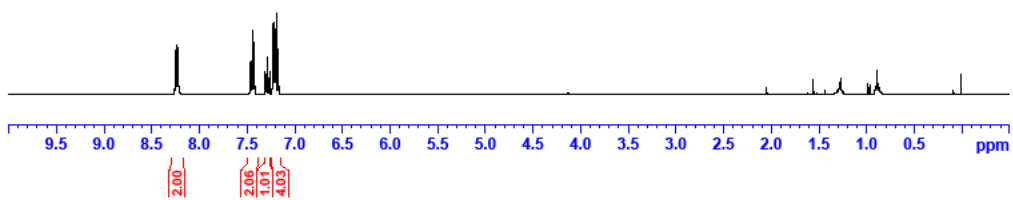
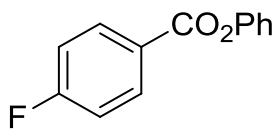
164.31
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77.33
77.00
76.68



wj1-3c

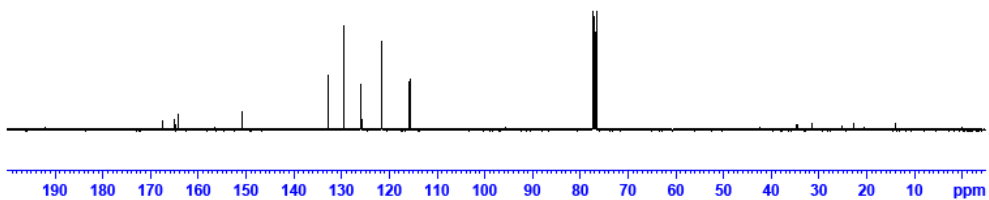
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7.208
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7.169

0.012



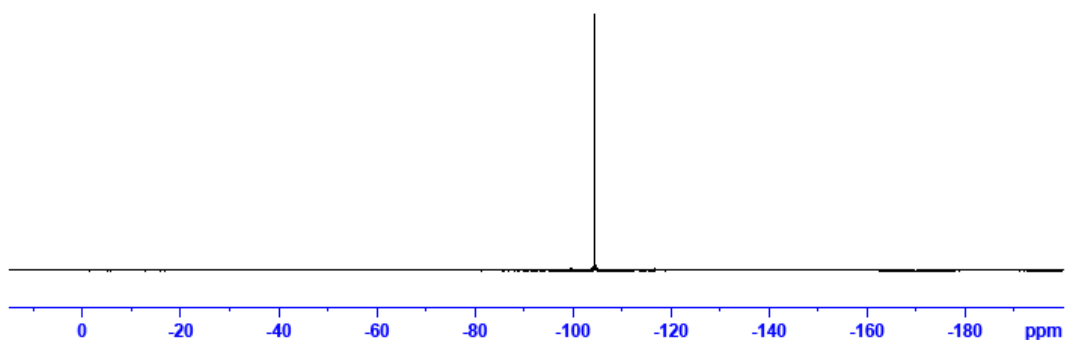
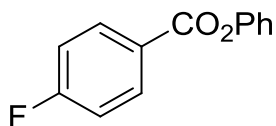
wj1-3cc

167.43
164.19
150.83
132.92
129.52
129.51
128.96
125.81
121.64
115.88
115.66
77.32
77.00
76.88



wjl-3cf

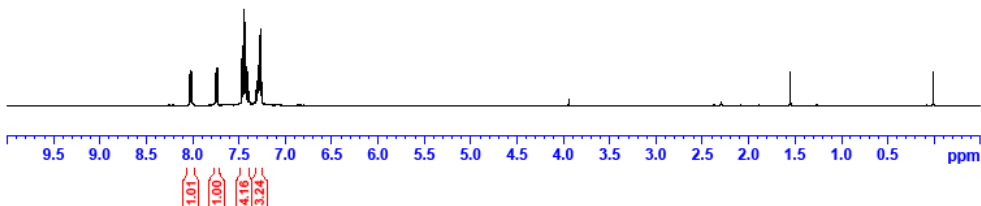
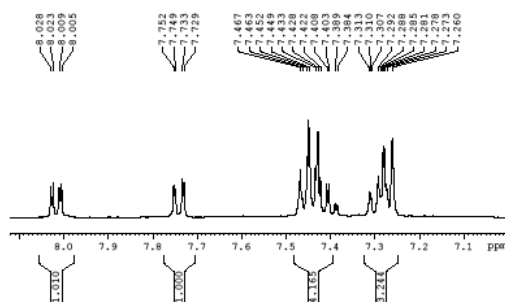
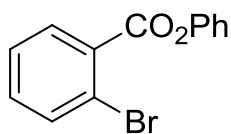
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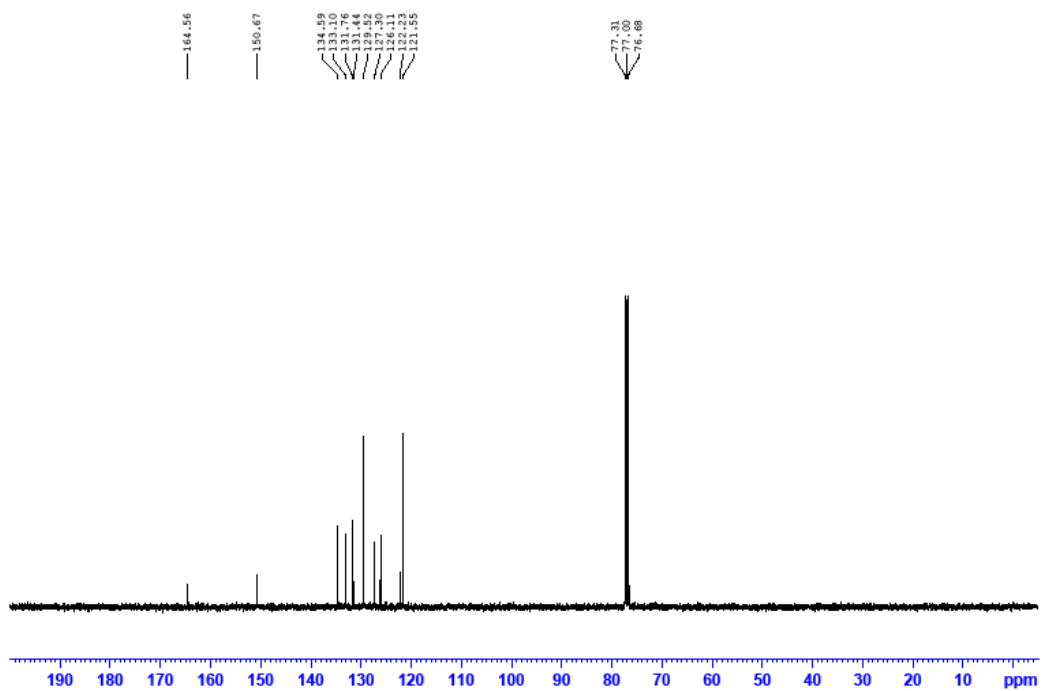
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8.023
8.009
8.005
7.752
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7.733
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7.463
7.452
7.449
7.433
7.428
7.422
7.408
7.403
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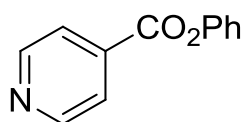
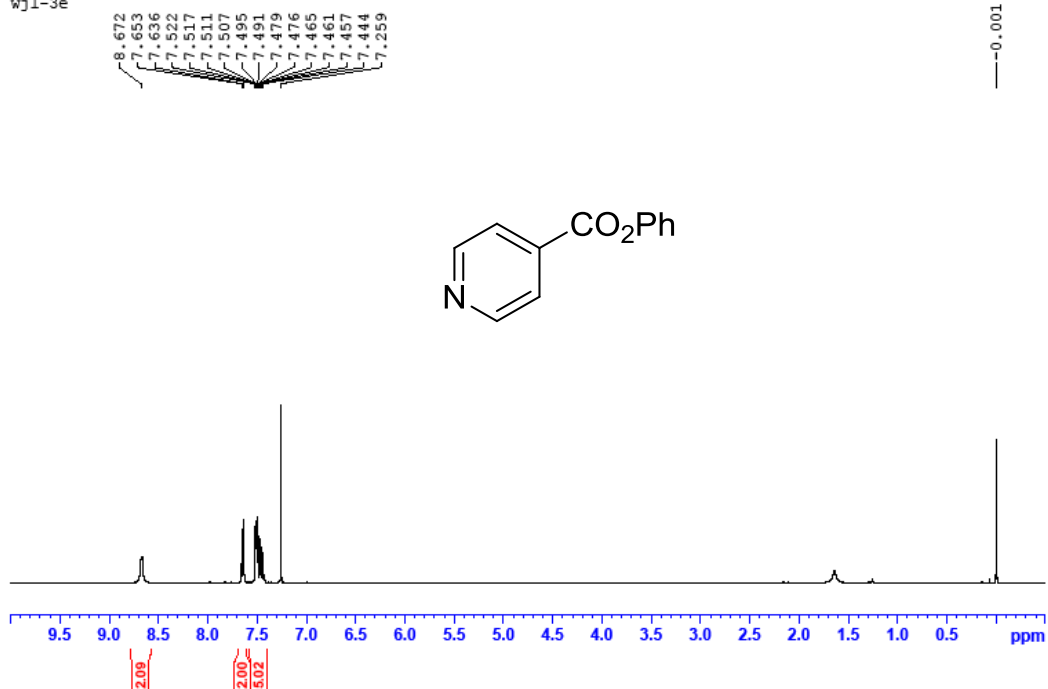
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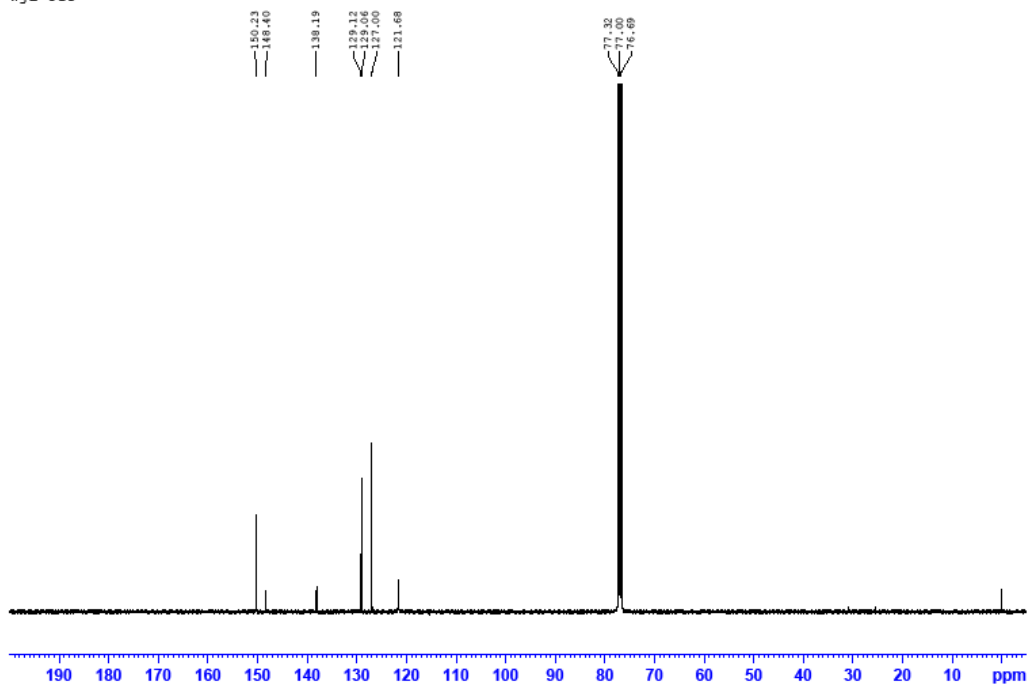
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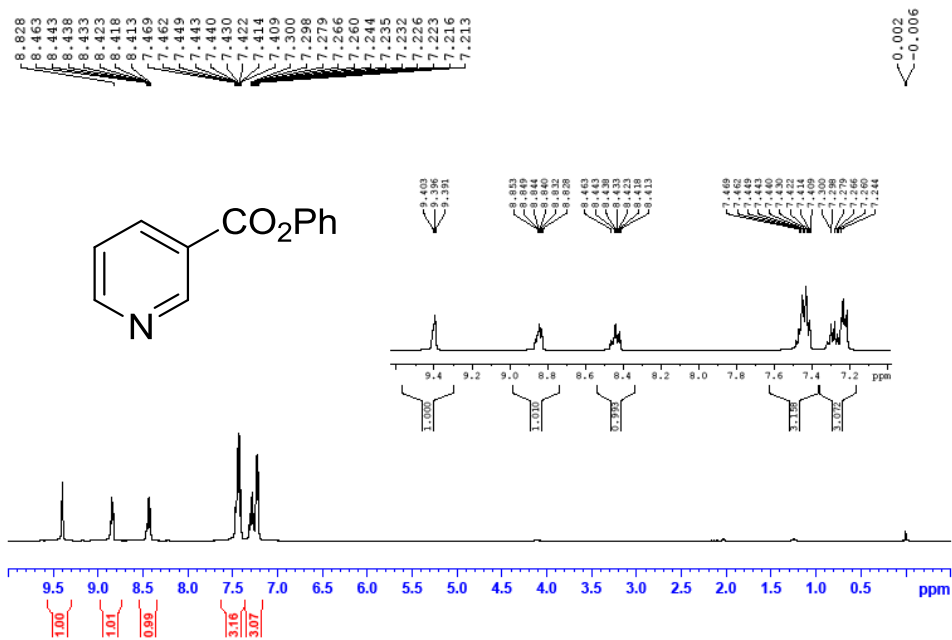
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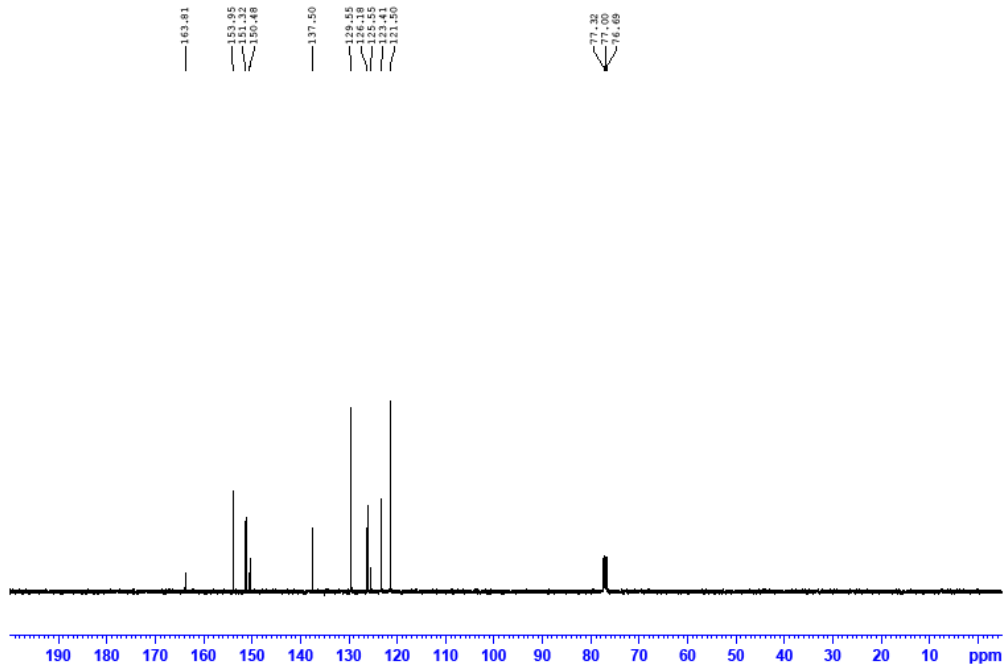
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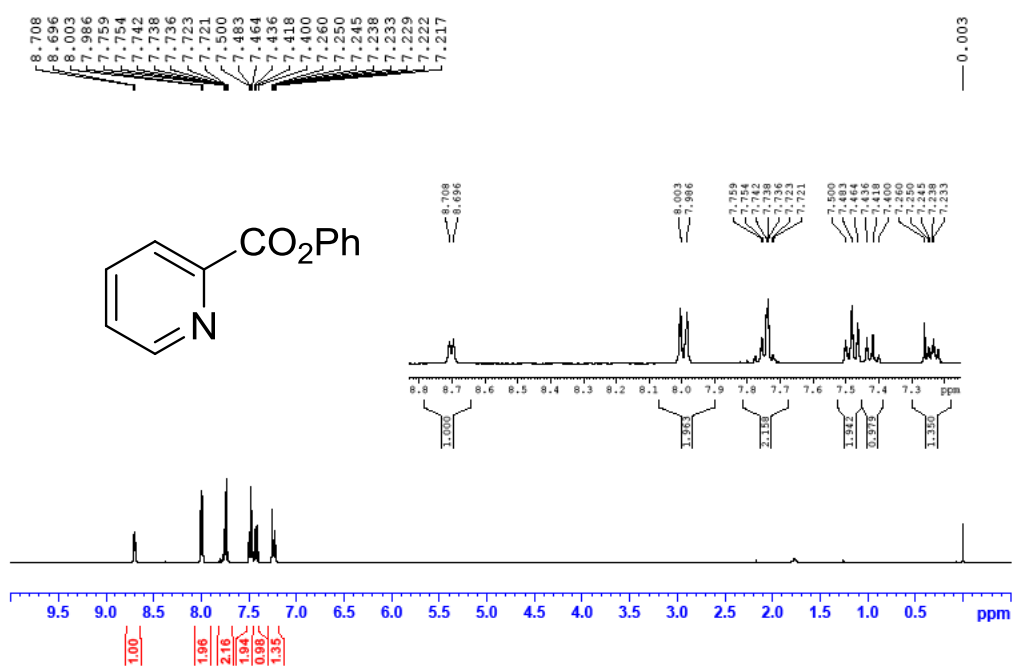
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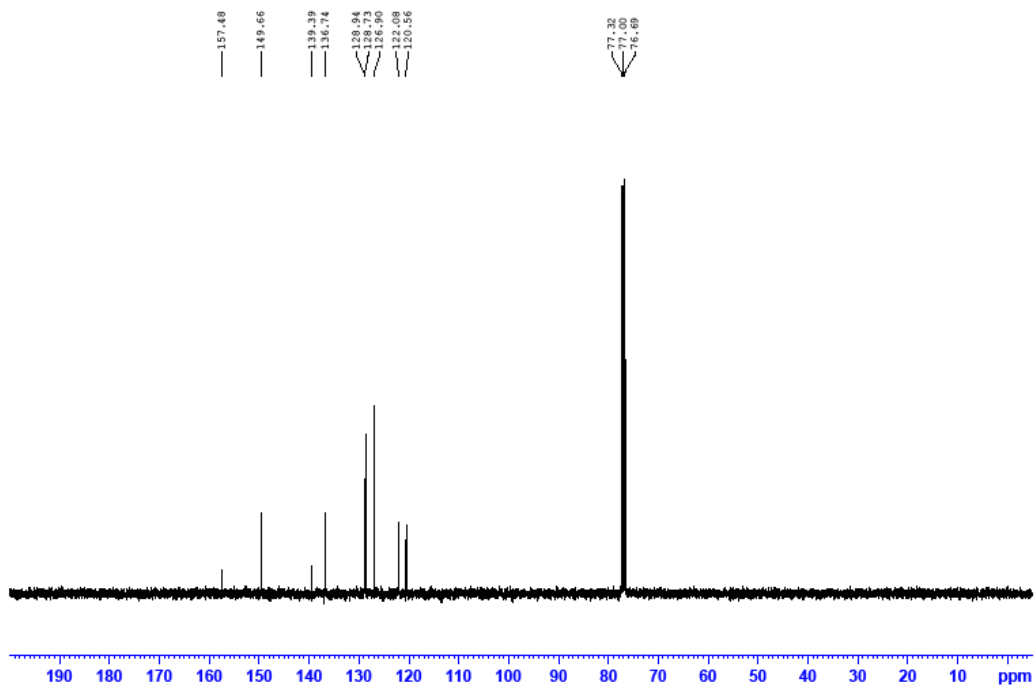
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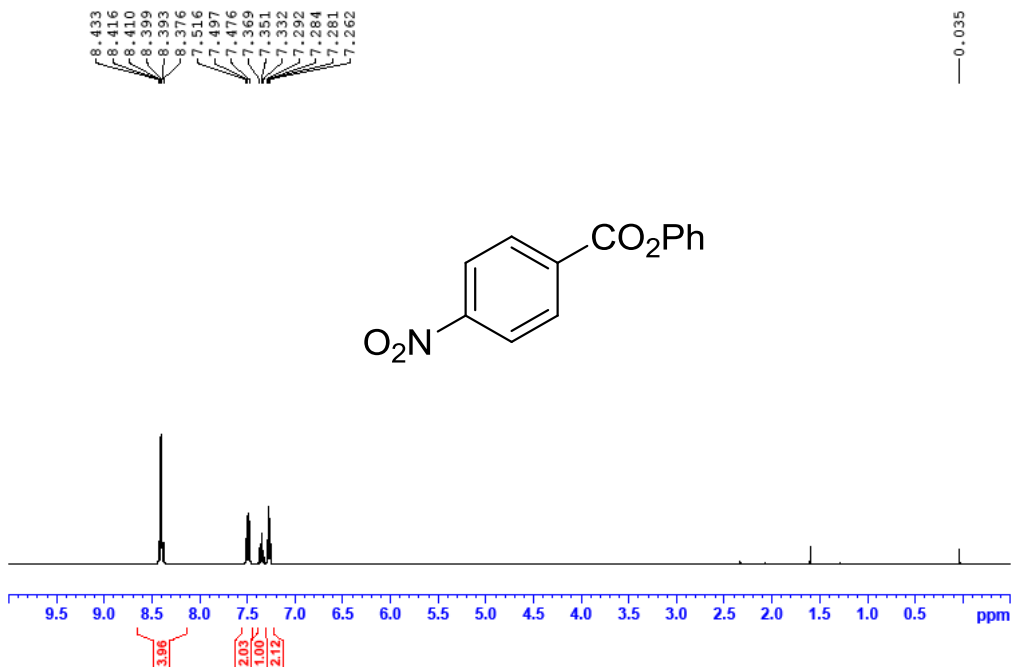
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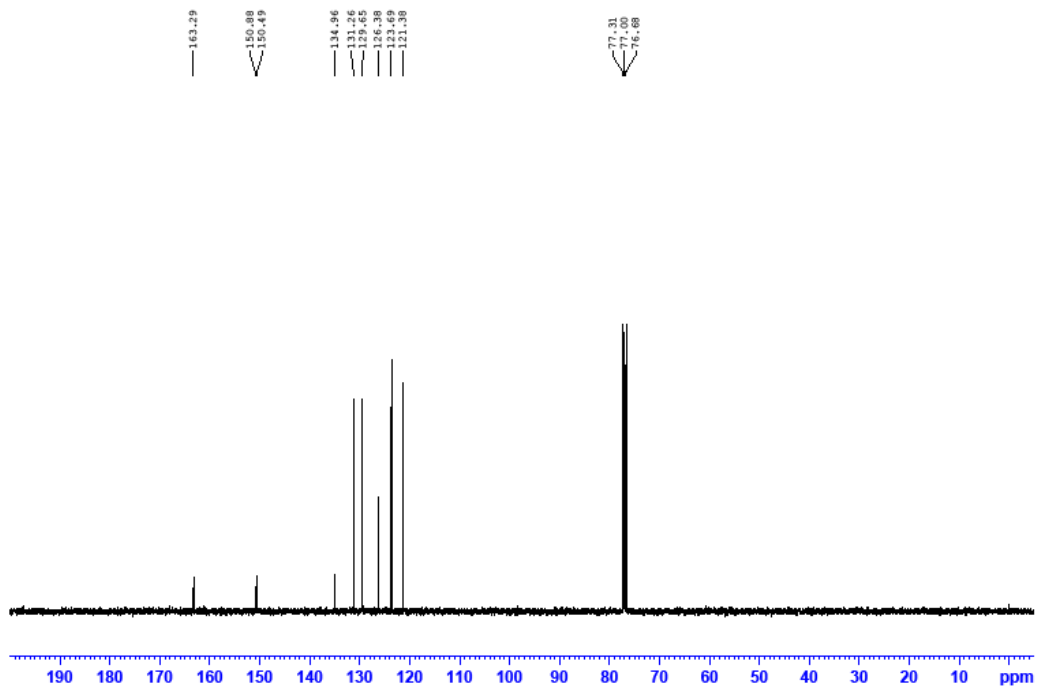
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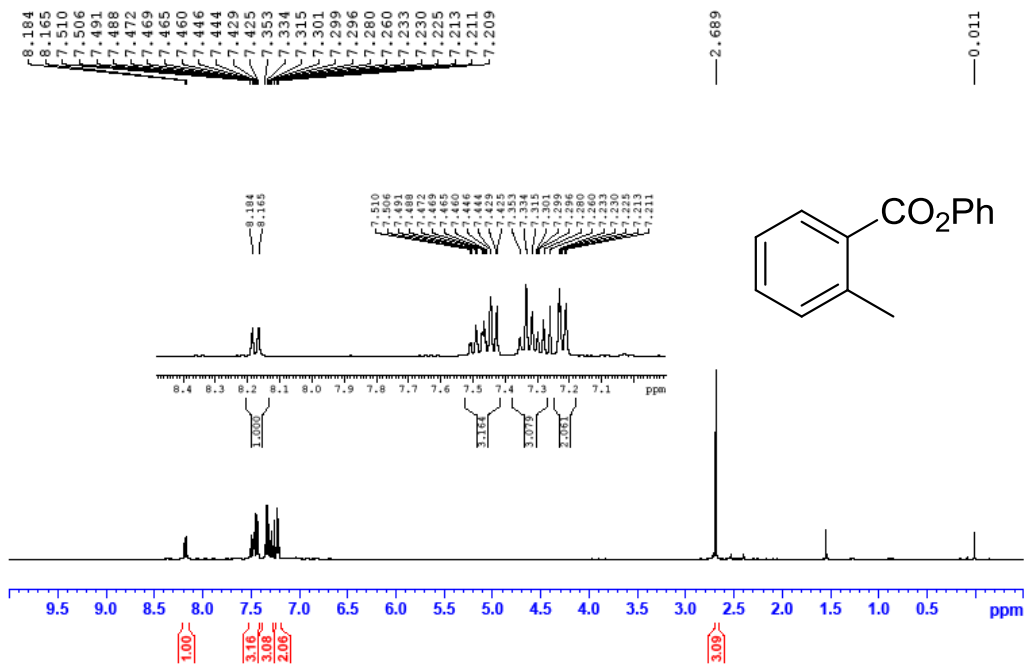
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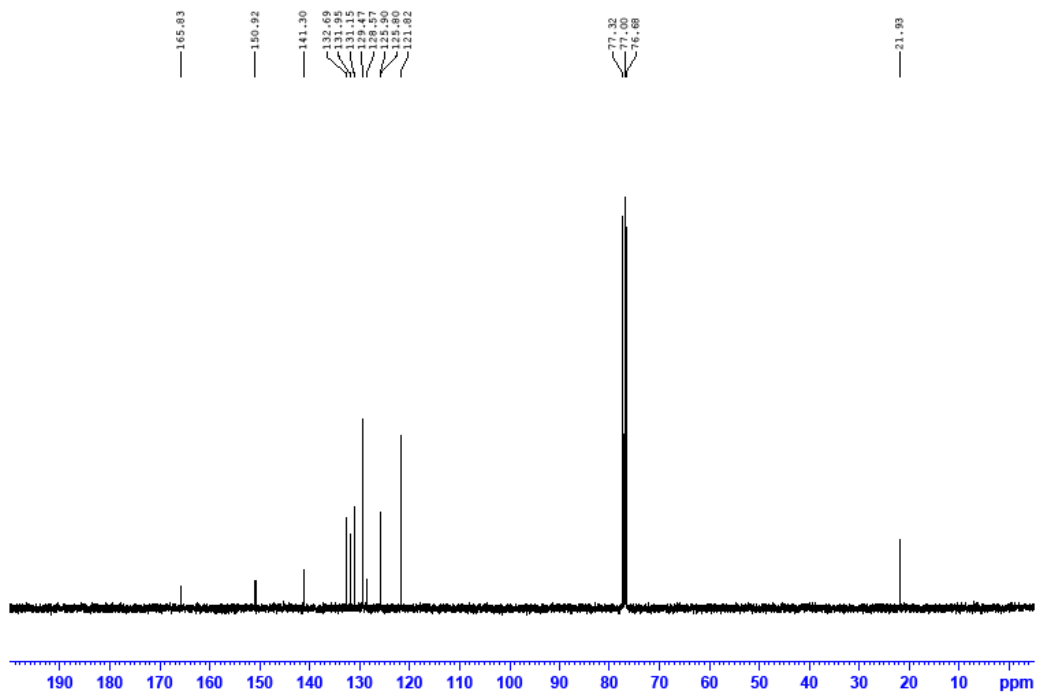
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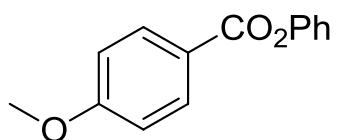
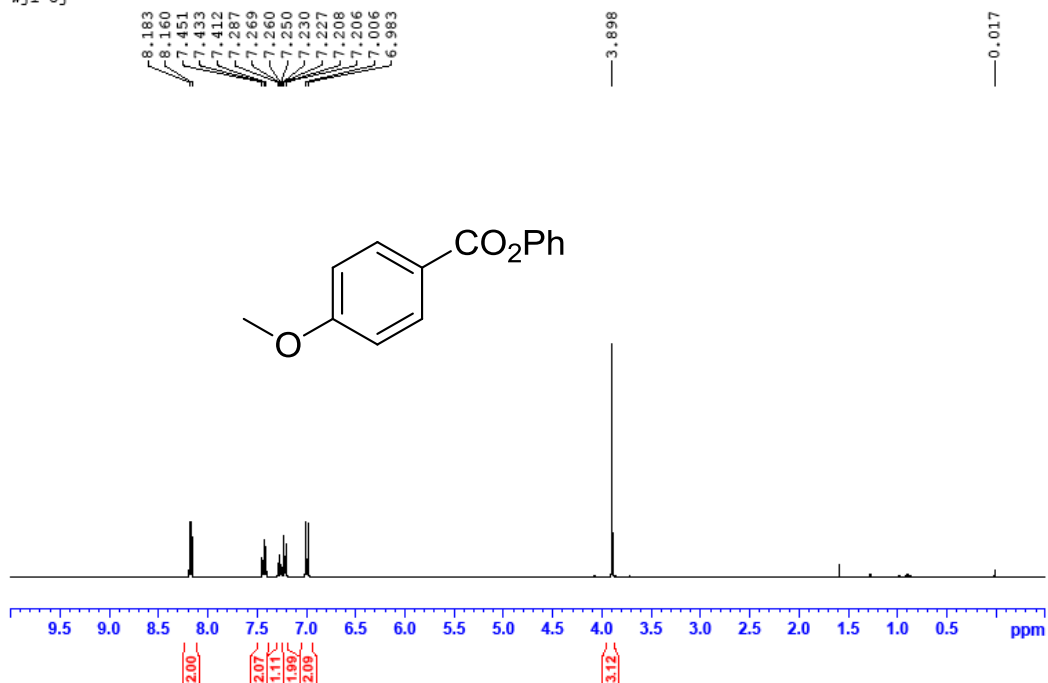
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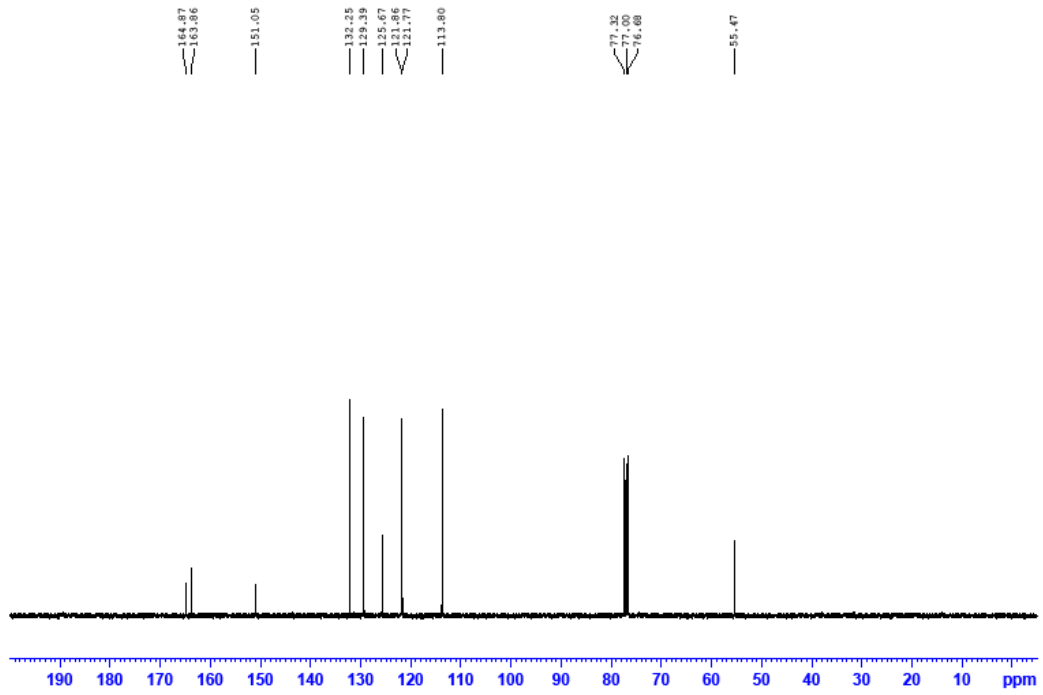
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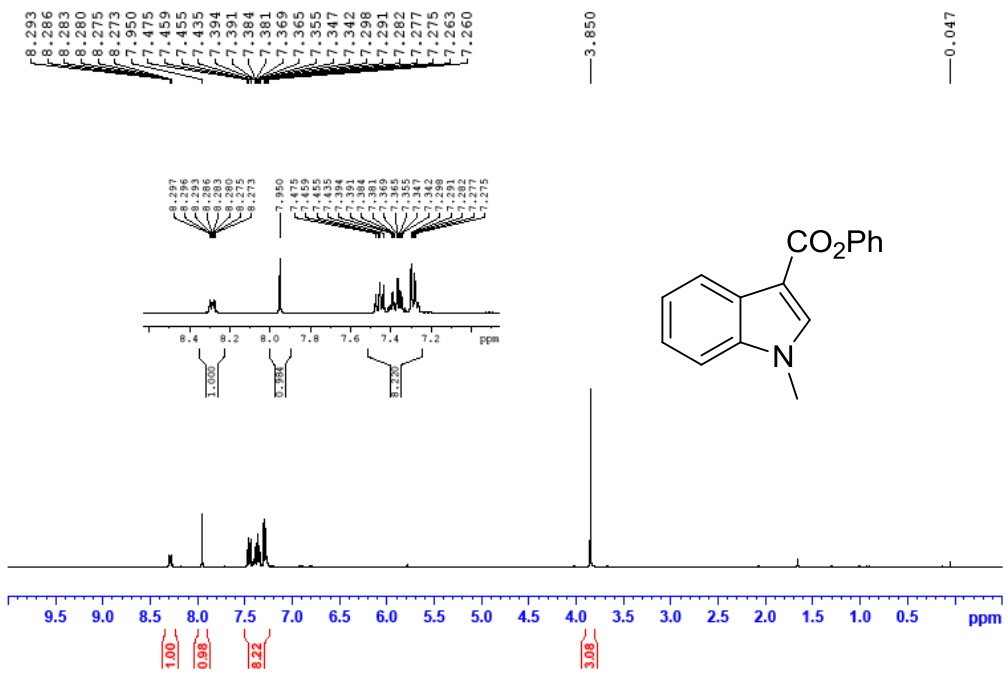
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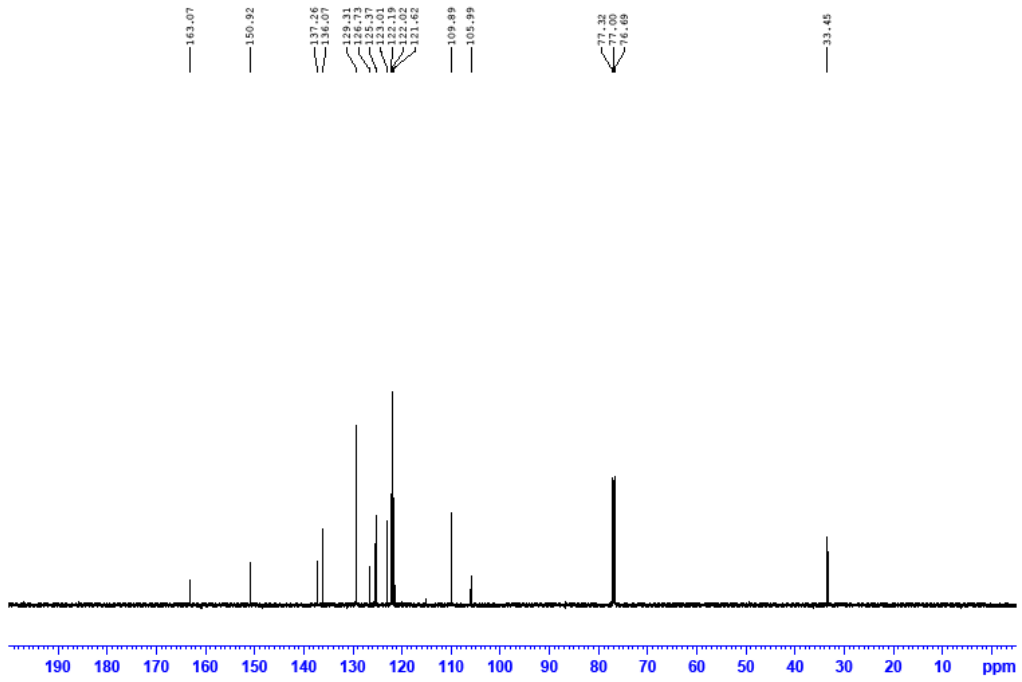
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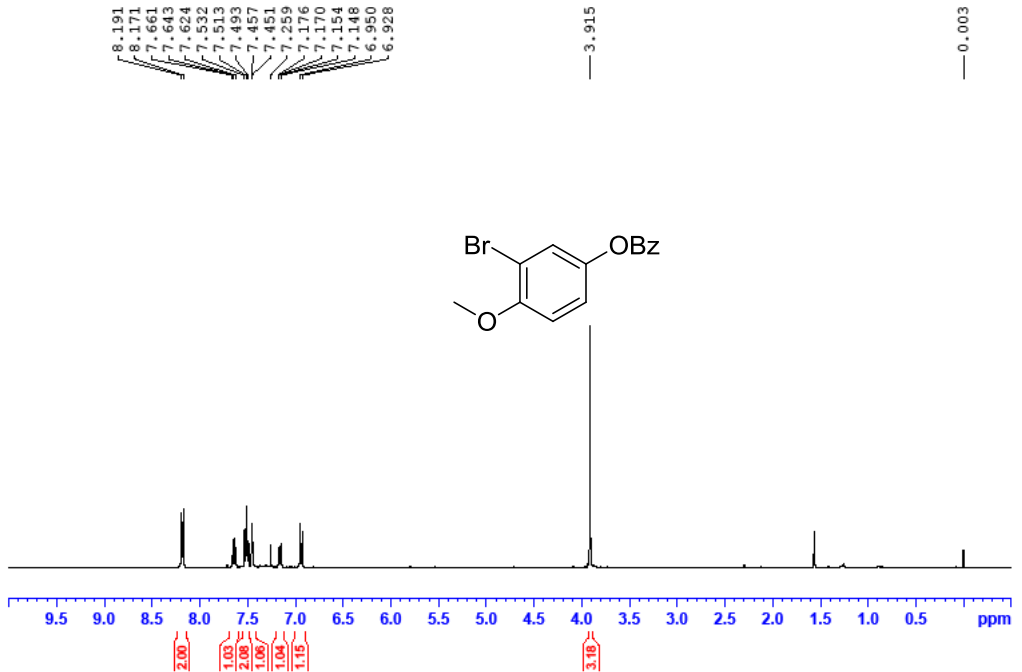
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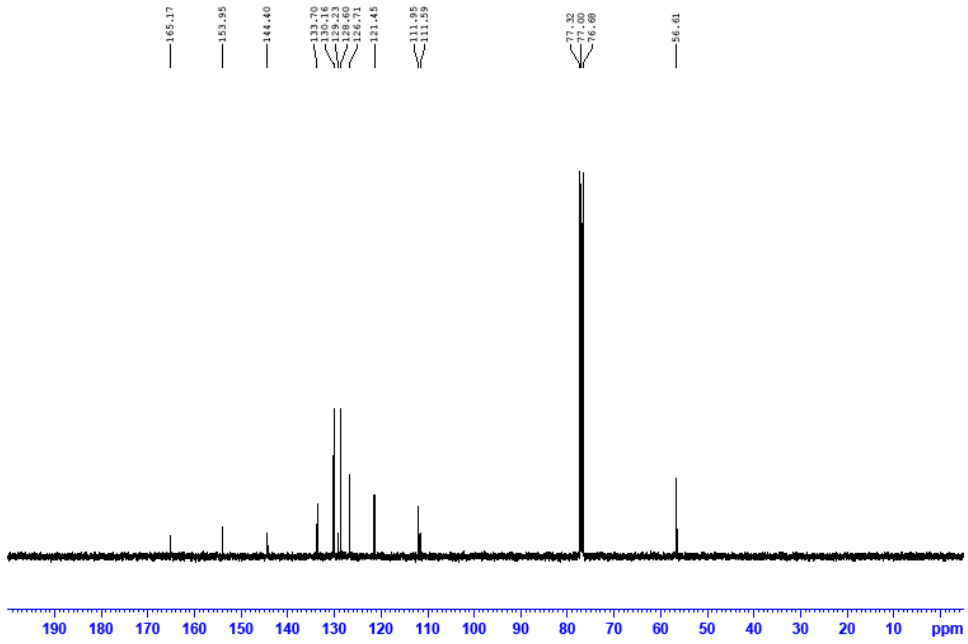
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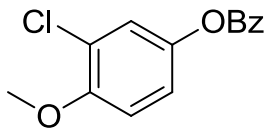
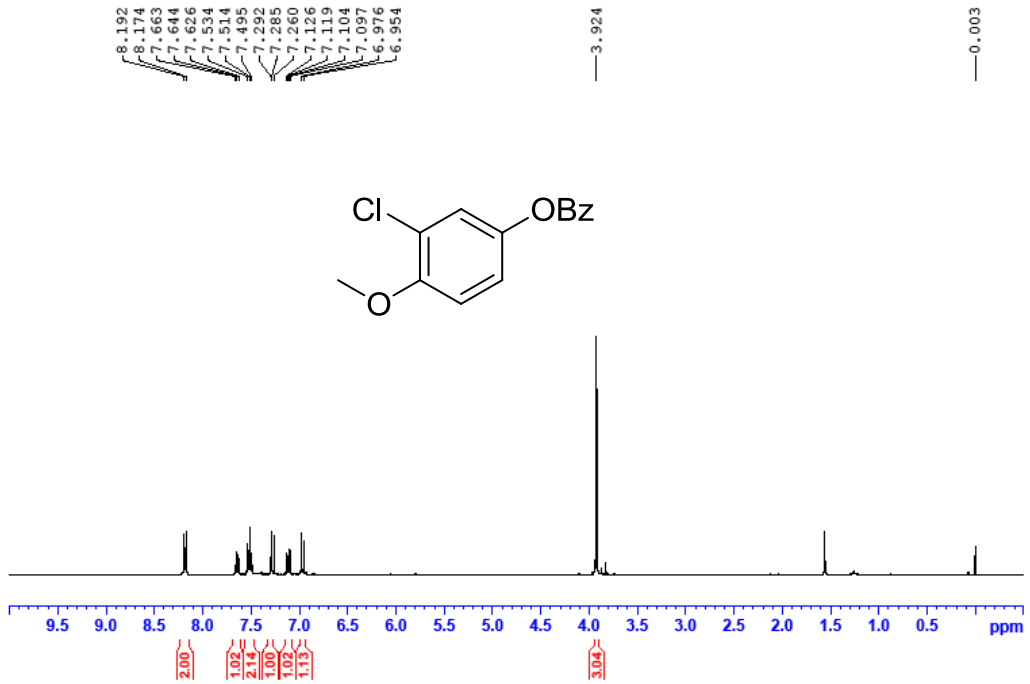
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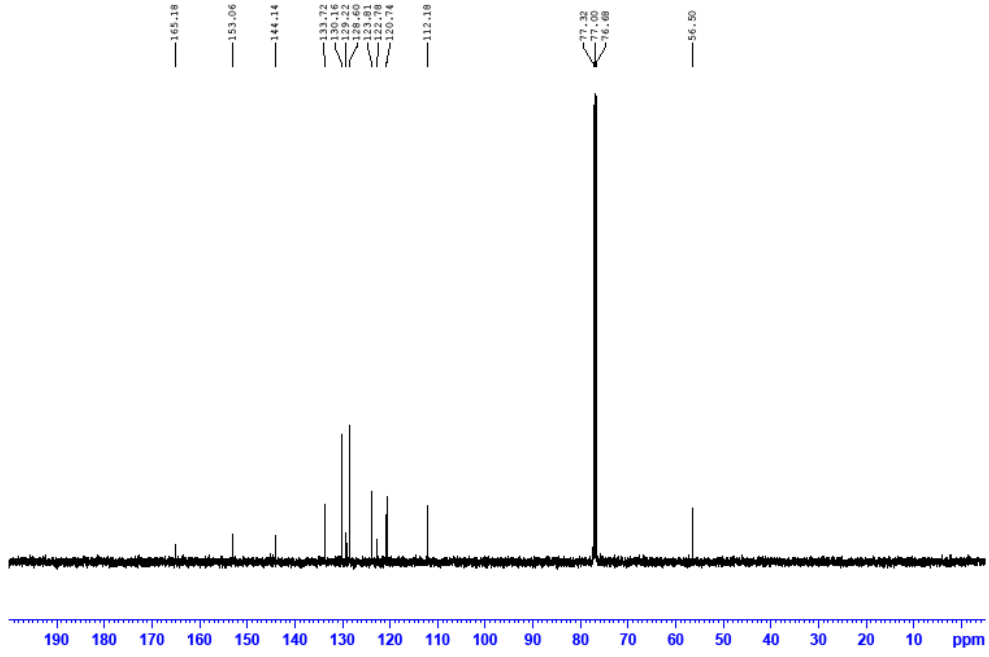
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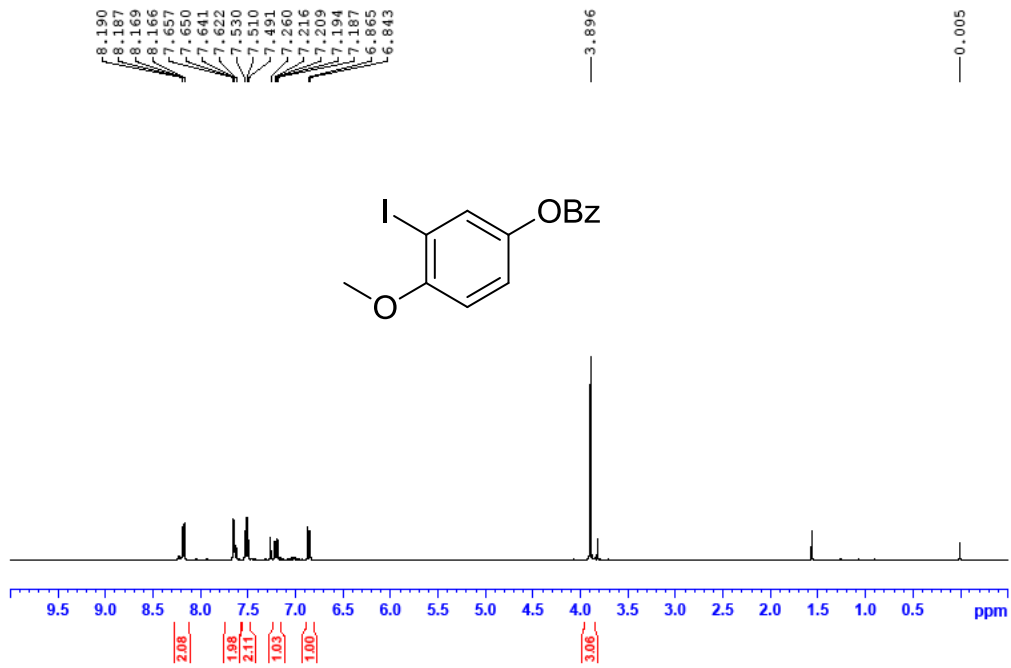
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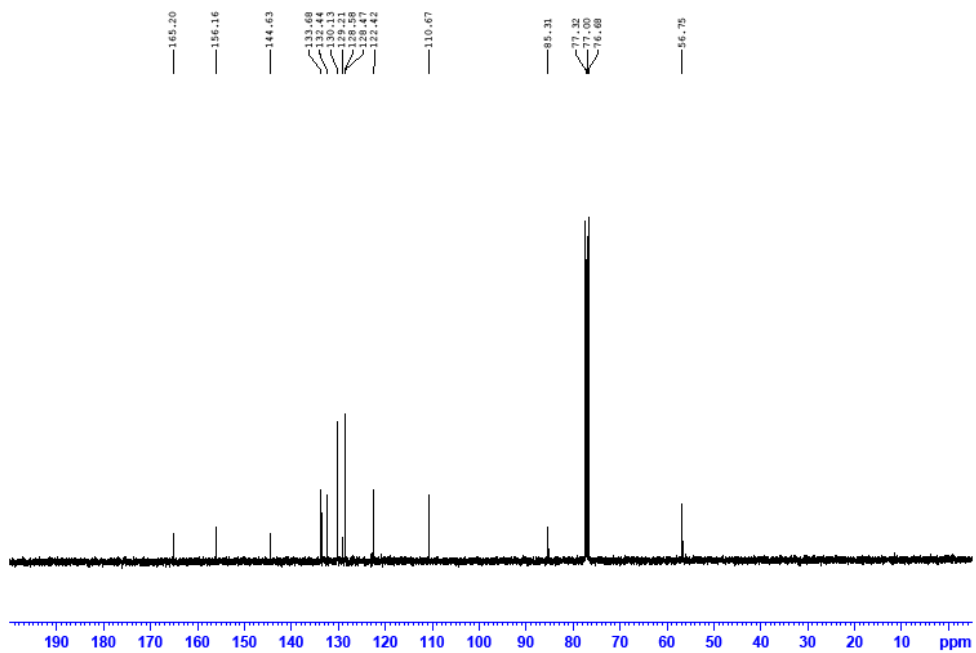
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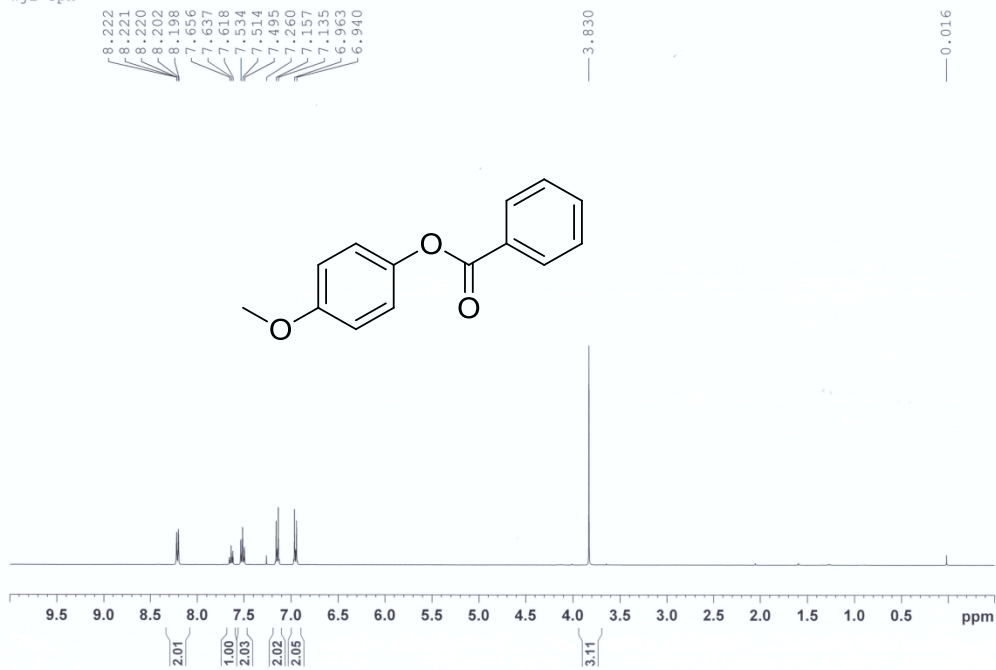
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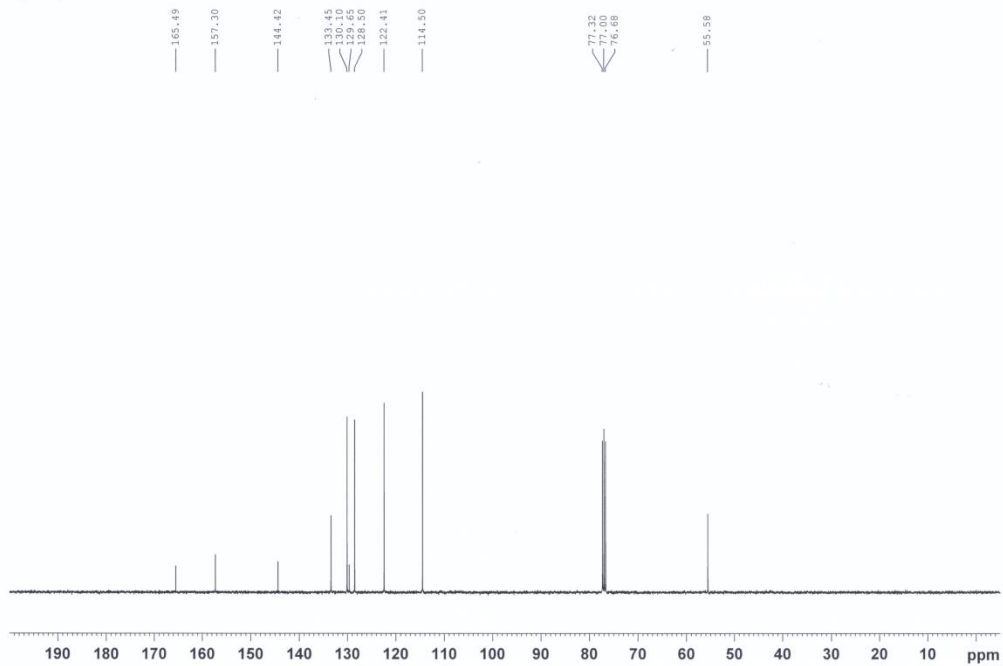
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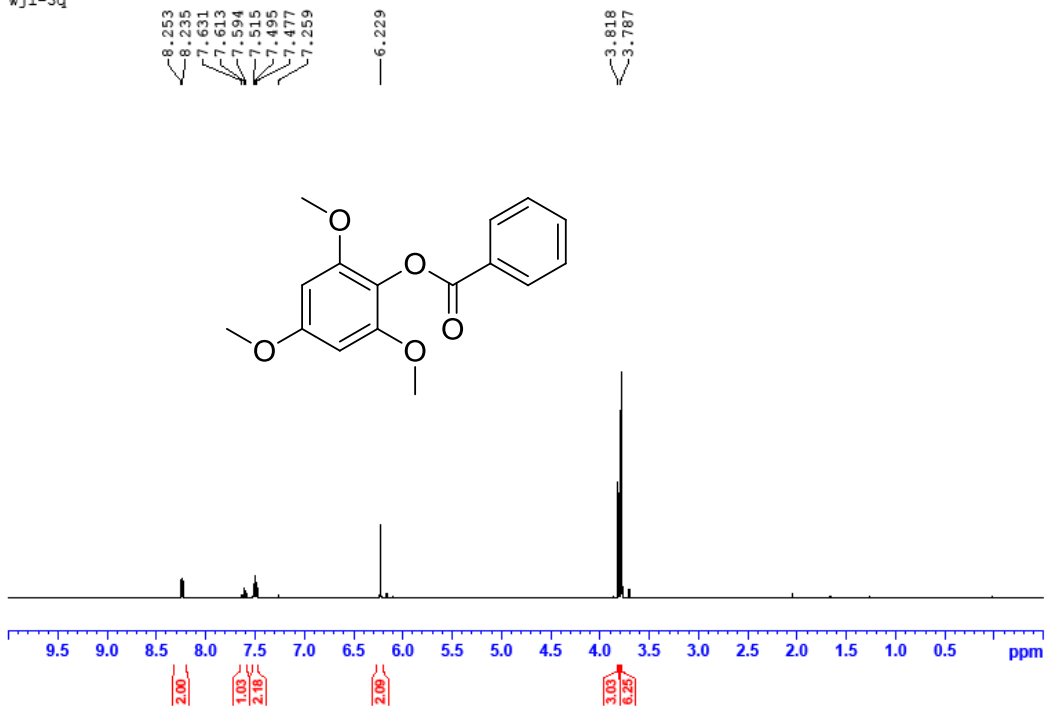
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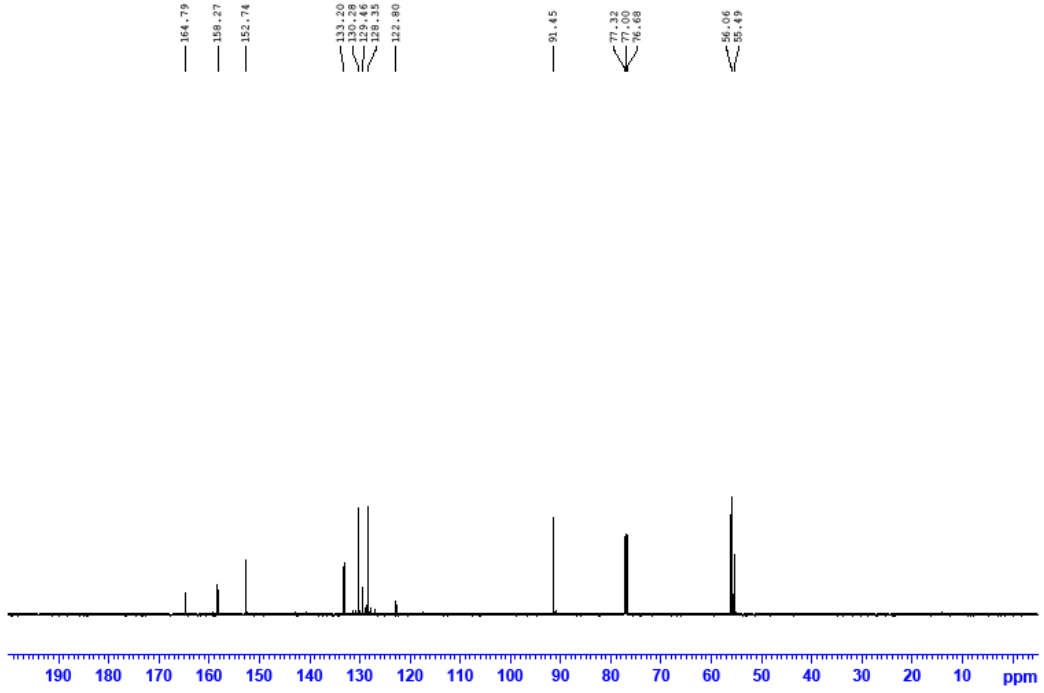
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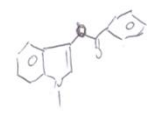
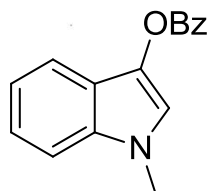
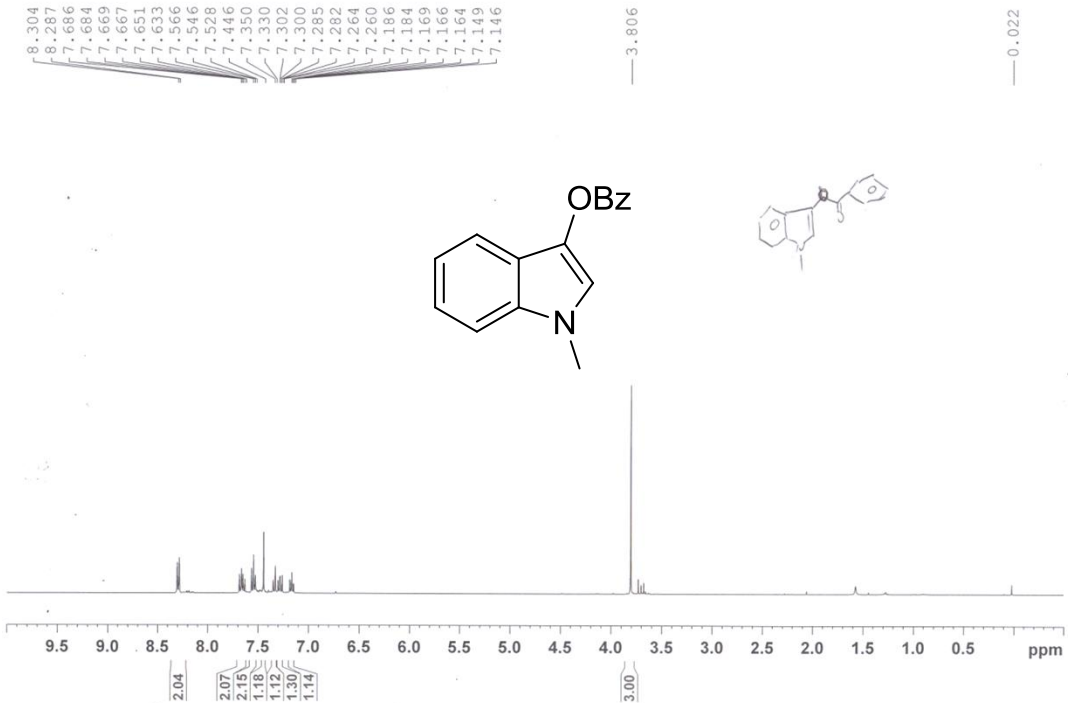
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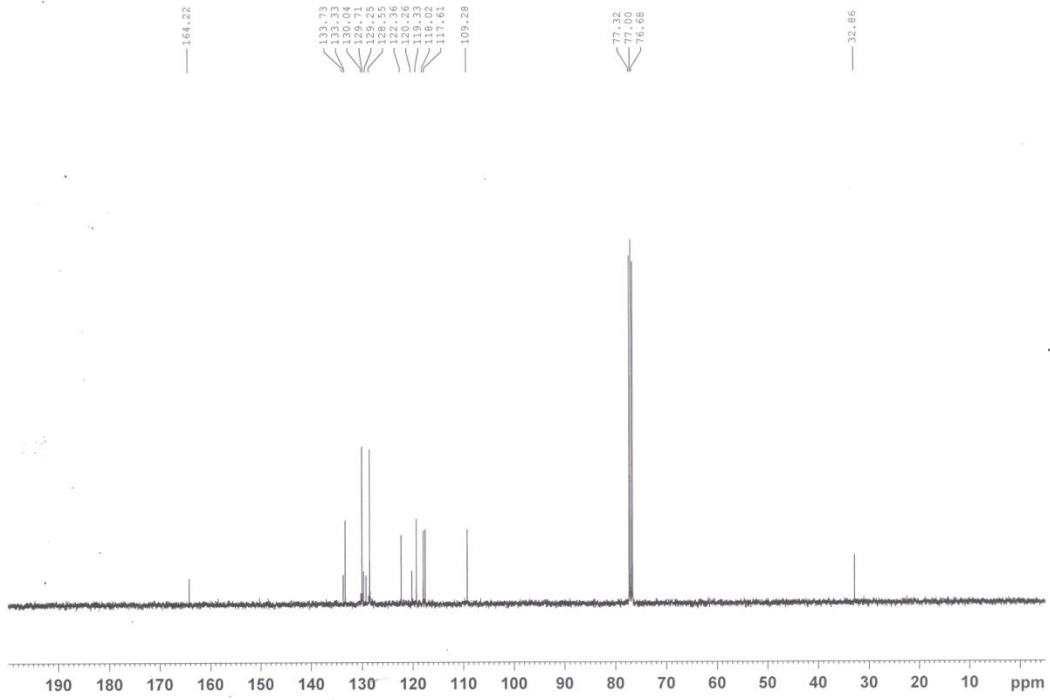
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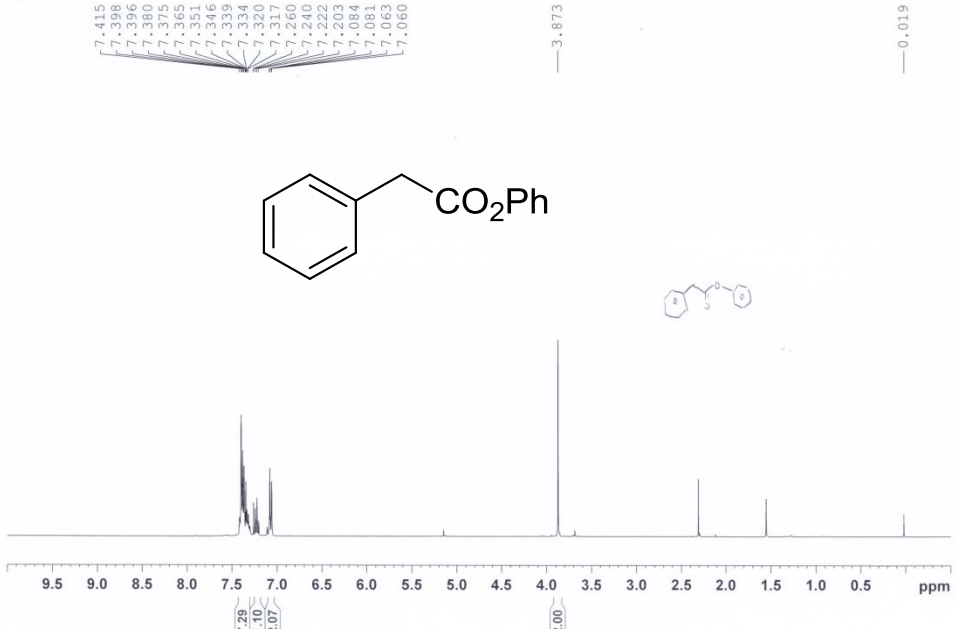
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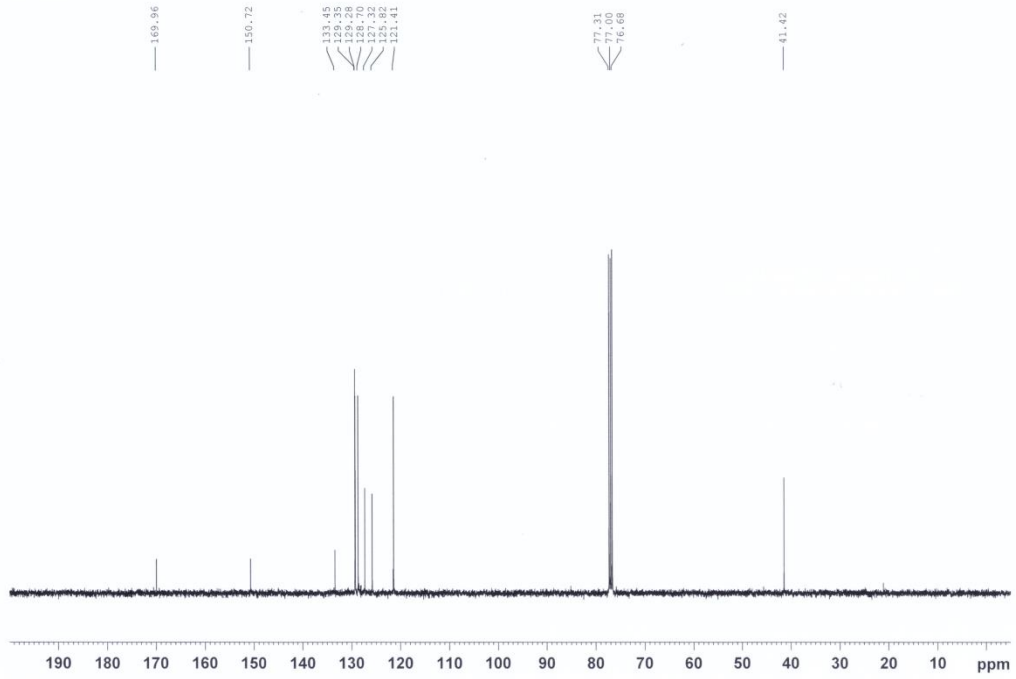
wj1842c



wj1901



wj1901c



WJ1-KIE

