Supporting Information

Aqueous *N*-heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-assisted Syntheses of *N*-azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine and Phthalazine Derivatives

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Contents

Experimental procedures:

General

All starting amines, hydrazines, and alkylhalides were used as obtained. 1,3-Propane-diol-ditosylate, and 1,4-butane-diol-ditosylate were prepared according to literature.[1] 1,3-dichloro-1,3-diphenylpropane was synthesized by the reaction of benzaldehyde and styrene using boron trichloride.[2] The crude products were identified by GC/MS qualitative analysis using a GC system with a Mass selective detector. The identities were further confirmed by ^{1}H and ^{13}C NMR spectra that were recorded for the pure products in chloroform-*d* ($CDCl_3$) with TMS as internal reference using a 300 MHz NMR spectrometer; the exact masses of unknown compounds were obtained using electronspray ionization from a Quadruple Time-of-flight (Micro) high resolution mass spectrometer.

Typical procedure

Synthesis of azacycloalkanes: 1.0 mmol aniline (0.093 g), 1.1 mmol 1,4-dibromobutane (0.237 g) and 1.1 mmol potassium carbonate (0.162 g) in 2 mL distilled water were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a Focused Microwave Synthesis System, operated at 120 $\pm$ 5 ^{o}C (measured by an Infrared temperature sensor) for 20 mins with a 3 mins ramp time, power 80 - 100 Watt and pressure 40 – 80 psi for 20 minutes. After completion of the reaction, the organic portion was extracted into ethyl acetate. Removal of the solvent under reduced pressure and flash column chromatography using hexane/ethyl acetate (90/10) as eluent to afford the crude product 1-phenylpyrrolidine in 89% yield. Satisfactory ^{1}H and ^{13}C NMR data was consistent with those found in literature.

Synthesis of 2,3-dihydro-1H-isoindoles: 1.0 mmol aniline (0.093 g), 1.1 mmol 1,2-bisbromomethyl-benzene (0.270 g) and 1.1 mmol potassium carbonate (0.162 g) in 2 mL distilled water were placed in 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a Focused Microwave Synthesis System, operated at 120 $\pm$ 5 ^{o}C (measured by an Infrared temperature sensor) for 20 mins with a 3 mins ramp time, power 70 - 100 Watt and pressure 40 – 80 psi for 20 minutes. After completion of the reaction, the solid product was separated from the aqueous phase and filtered, washed with cold hexanes for three times afforded the off-white solid 2-phenyl-2,3-dihydro-1*H*-isoindole in 92% yield. Satisfactory ^{1}H and ^{13}C NMR data was obtained and consistent with those found in literature.

Synthesis of 4,5-dihydro-pyrazole, pyrazolidine and 1,2-dihydro-phthalazine derivatives: 1,2-diethylhydrazine dihydrochloride (1 mmol, 0.161 g), 1,2-bis-chloromethyl-benzene (1 mmol, 0.175 g), 2 M sodium hydroxide (1 mL) and potassium carbonate (1 mmol, 0.138g) in water (2 mL) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a Focused Microwave Synthesis System, operated at 120 $\pm$ 5 ^{o}C (temperature monitored by a built-in infrared sensor), power 70 - 100 Watt and pressure 40 – 80 psi for 20 minutes. After completion of the reaction, the biphasic system was allowed to stir in the air for 6 h and the product was extracted into ethyl acetate. The removal of the solvent under reduced pressure (rotary evaporator) and flash column chromatography using hexane/ethyl acetate (9/1) as eluent afforded the product, 2,3-diethyl-1,2,3,4-tetrahydro- phthalazine 0.114 g (60% yield).

The typical microwave-assisted reaction conditions in terms of temperature, pressure, microwave power and reaction time are shown in **Figure 1**.

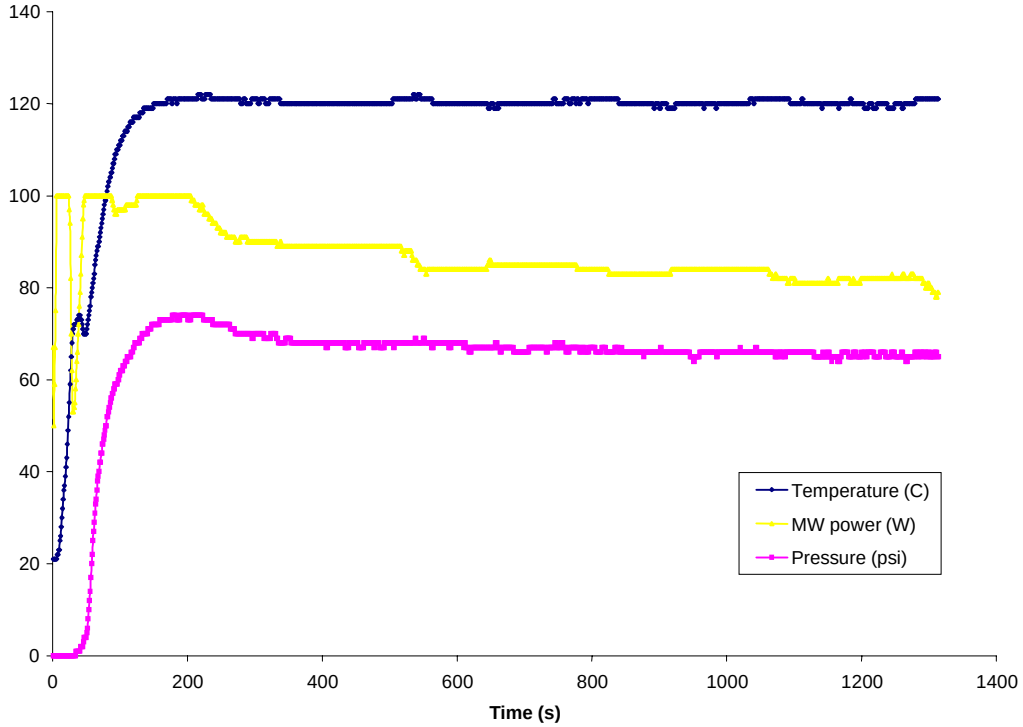
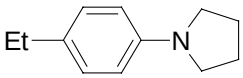


Figure 1. Typical MW reaction condition profile

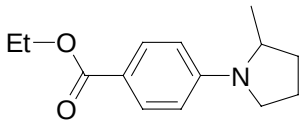
The spectroscopic data of synthesized compounds (**3a-g**, **3i-k** and **3m-r**), (**3aa-ac**, **3af-ai**), (**3'a-o**) are in accord with the literature. **3a**,[3] **3b**,[4] **3c**,[5] **3d**,[6] **3e**,[7] **3f**,[8] **3g**,[9] **3i**,[10] **3j**,[7] **3k**,[11] **3m**,[12] **3n**,[13] **3o**,[8a,14] **3p**,[7] **3q**,[7] **3r**,[4b,15] **3aa**,[16] **3ab**,[17] **3ac**,[18] **3af**,[19] **3ag**,[20] **3ah**,[21] **3ai**,[22] **3'a**,[23] **3'b**,[24] **3'c**,[25] **3'd**,[26] **3'e**,[27] **3'f**,[27] **3'g**,[28] **3'h**,[29] **3'i**,[30] **3'j**,[31] **3k**,[32] **3'l**,[33] **3'm**,[34] **3'n**,[35] **3'o**.[36]

Characterization of unknown compounds:

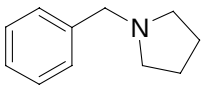


1-(4-Ethylphenyl)-pyrrolidine (**3h**). The reaction of 4-ethylaniline (1.0 mmol, 0.121 g), 1,4-butanediol-ditosylate (1.1 mmol, 0.418 g) was carried out as described earlier and produced

0.154 g (88%) of 1-(4-Ethylphenyl)-pyrrolidine as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.04 (dd, 2H, *J* = 8.4, 4.1 Hz), 6.51 (d, 2H, *J* = 8.5, 4.2 Hz), 3.23 (t, 4H, *J* = 6.6 Hz), 2.50 (q, 2H, *J* = 7.5 Hz), 1.94 (t, 4H, , *J* = 6.6 Hz), 1.18 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 146.4, 131.3, 128.6, 111.9, 47.9, 28.0, 25.5, 16.2; MS (EI) *m/z* (relative intensity, %) 175 (*M*, 53), 174 (M^+, 30), 160 (100), 119 (11), 118 (9), 91 (6), 77 (5). calcd $(M+H)^+$ for $C_{12}H_{17}N$: 176.1439 ($C_{12}H_{18}N^+$), found $(M+H)^+$ 176.1433.

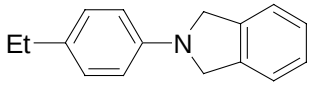


4-(2-Methylpyrrolidinyl)-benzoic acid ethyl ester (**3l**). The reaction of 4-amino benzoic acid ethyl ester (1.0 mmol, 0.165 g), 1,4-dibromopentane (1.1 mmol, 0.253 g) was carried out as described earlier and produced 0.207 g (89%) of 4-(2-methylpyrrolidinyl)-benzoic acid ethyl ester as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.91 (d, 2H, *J* = 8.5 Hz), 6.52 (d, 2H, *J* = 8.4 Hz), 4.32 (q, 2H, *J* = 7.2 Hz), 3.96 (q, 1H, *J* = 6.4 Hz), 3.46 (m, 1H), 3.24 ((m, 1H), 2.05 (m, 3H), 1.80 (m, 1H), 1.36 (q, 3H, *J* = 7.0 Hz), 1.18 (d, 3H, *J* = 6.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 167.2, 150.2, 131.0, 116.5, 110.8, 60.0, 53.7, 47.9, 32.9, 23.1, 18.9, 14.5. MS (EI) *m/z* (relative intensity, %) 233 (*M*, 29), 219 (16), 218 (100), 190 (36), 188 (19), 145 (7). HR-MS (ESI): calcd $(M+H)^+$ for $C_{14}H_{19}NO_2$: 234.1494 ($C_{14}H_{20}NO_2^+$), found $(M+H)^+$ 234.1508.

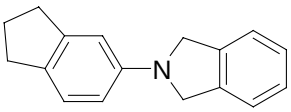


1-Benzyl-pyrrolidine (**3s**). The reaction of benzylamine (1.0 mmol, 0.106 g), 1,4-dibromobutane (1.1 mmol, 0.231g) was carried out as described earlier and produced 0.143 g (89%) of 1-benzyl-pyrrolidine as a yellow oil. . ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.24 (m, 5H), 3.53 (s, 2H), 2.42 (m, 4H), 1.70 (m, 4H, *J* = 4.6 Hz). ^{13}C NMR (75.5 MHz,

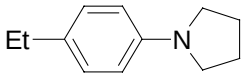
$CDCl_3$/TMS) δ ppm 139.4, 128.9, 128.2, 126.9, 60.8, 54.2, 23.5. MS (EI) *m/z* (relative intensity, %) 161 (*M*, 69), 160 (M^+, 96), 91 (100), 84 (56), 70 (34), 42 (19). HR-MS (ESI): calcd $(M+H)^+$ for $C_{11}H_{15}N$: 162.1283 ($C_{11}H_{16}N^+$), found $(M+H)^+$ 162.1286.



2-(4-Ethylphenyl)-2,3-dihydro-1*H*-isoindole (**3ad**). The reaction of 4-ethylaniline (1.0 mmol, 0.121 g), 1,2-bischloromethyl-benzene (1.1 mmol, 0.195 g) was carried out as described earlier and produced 0.196 g (88%) of 2-(4-ethylphenyl)-2,3-dihydro-1*H*-isoindole as a yellow solid. ^{1}H NMR (300 MHz $CDCl_3$/TMS) δ ppm 7.29 (m, 4H), 7.14 (d, 2H, *J* = 8.4 Hz), 6.62 (d, 2H, *J* = 8.5 Hz), 4.61 (s, 4H), 2.57 (q, 2H, *J* = 7.8 Hz), 1.22 (t, 3H, *J* = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 145.4, 138.2, 132.0, 128.8, 127.1, 122.6 , 111.7, 54.0, 28.0, 16.1; MS (EI) *m/z* (relative intensity, %) 223 (*M*, 71), 222 (M^+, 100), 208 (33), 206 (11), 193 (4), 165 (4), 104 (6), 90 (5), 77 (4).); HR-MS (ESI): calcd $(M+H)^+$ for $C_{16}H_{17}N$: 224.1439 ($C_{16}H_{18}N^+$), found $(M+H)^+$ 224.1440.



2-Indan-5-yl-2,3-dihydro-1*H*-isoindole (**3ae**). The reaction of indanyl-5-amine (1.0 mmol, 0.133 g), 2-bischloromethyl-benzene (1.1 mmol, 0.195 g) was carried out as described earlier and produced 0.197 g (84%) of 2-indan-5-yl-2,3-dihydro-1*H*-isoindole as a light yellow solid. ^{1}H NMR (300 MHz $CDCl_3$/TMS) δ ppm 7.29 (m, 4H), 7.14 (m, 1H), 6.54 (s, 2H), 6.49 (t, *J* = 8.2), 4.63 (s, 4H), 2.86 (t, 4H, , *J* = 9.8 Hz), 2.04 (m, 2H); ^{13}C NMR (75.5 MHz $CDCl_3$/TMS) δ ppm 146.2, 145.6, 138.1, 132.2, 127.1, 124.9, 122.5, 110.1, 108.0, 54.3, 33.4, 31.9, 25.8; MS (EI) *m/z* (relative intensity, %) 235 (*M*, 61), 234 (M^+, 100), 233 (14), 115 (9), 104 (4), 91 (4); HR-MS (ESI): calcd $(M+H)^+$ for $C_{17}H_{17}N$: 236.1439 ($C_{17}H_{18}N^+$), found $(M+H)^+$ 236.1436.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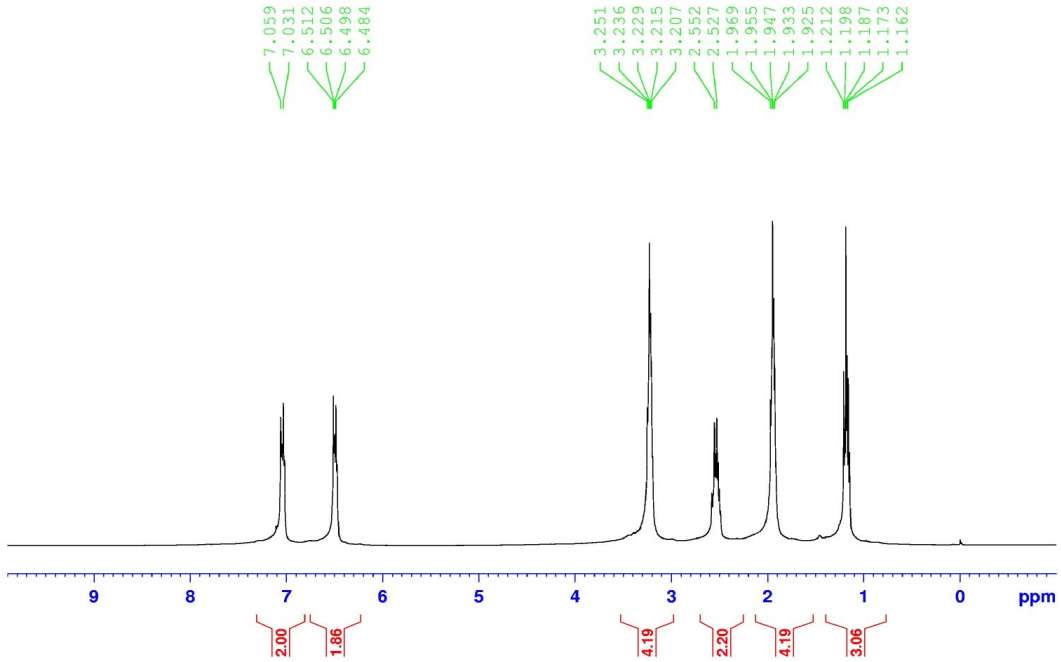
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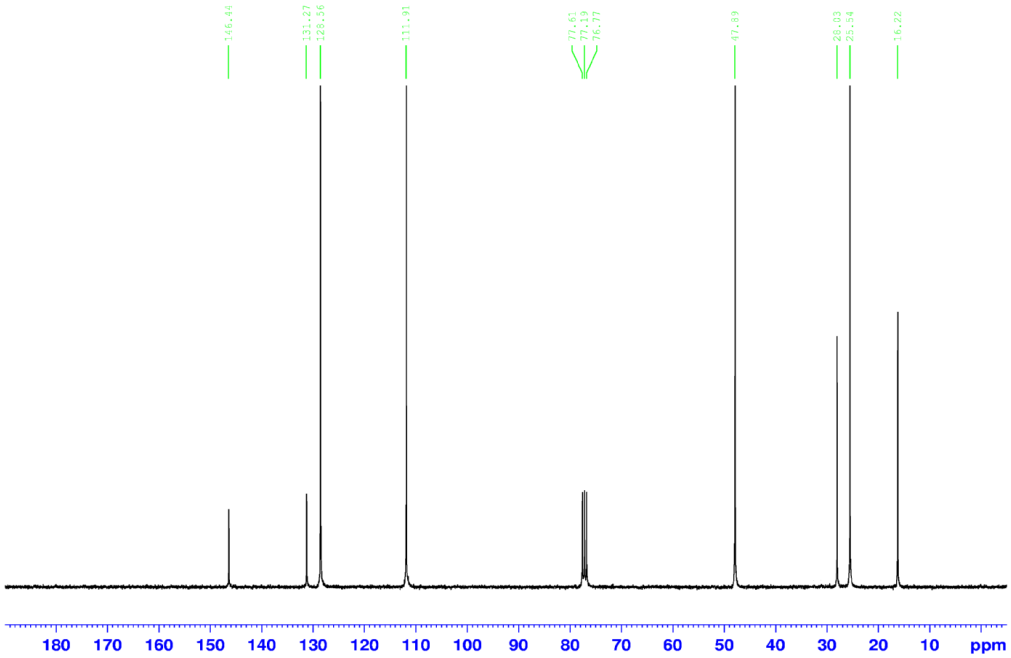
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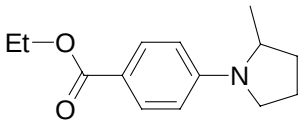
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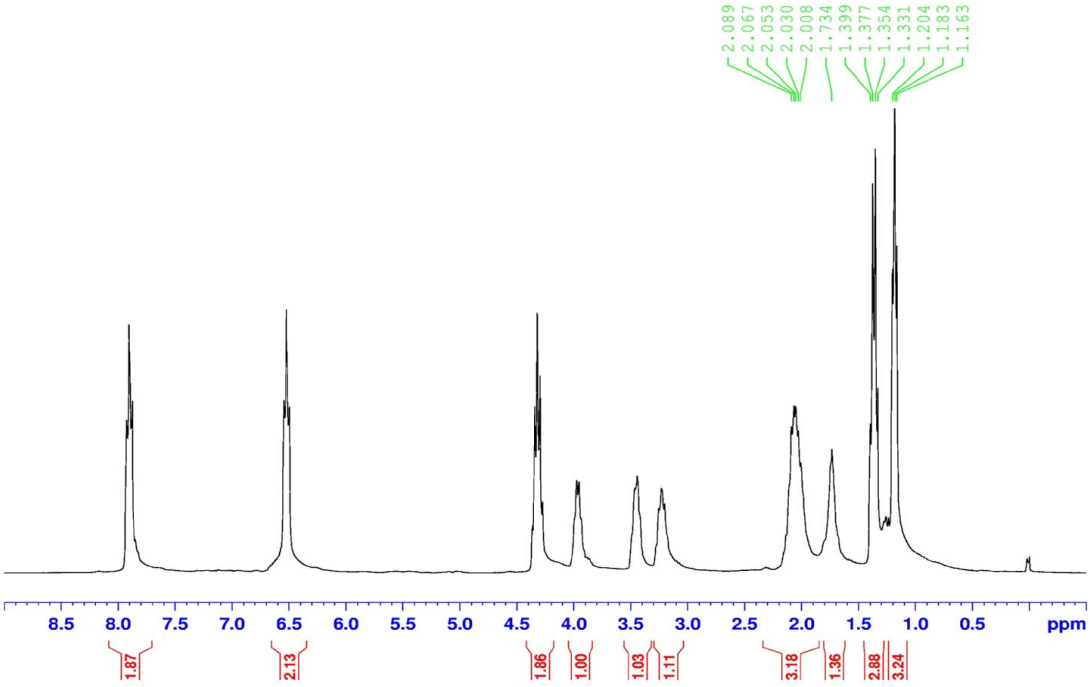
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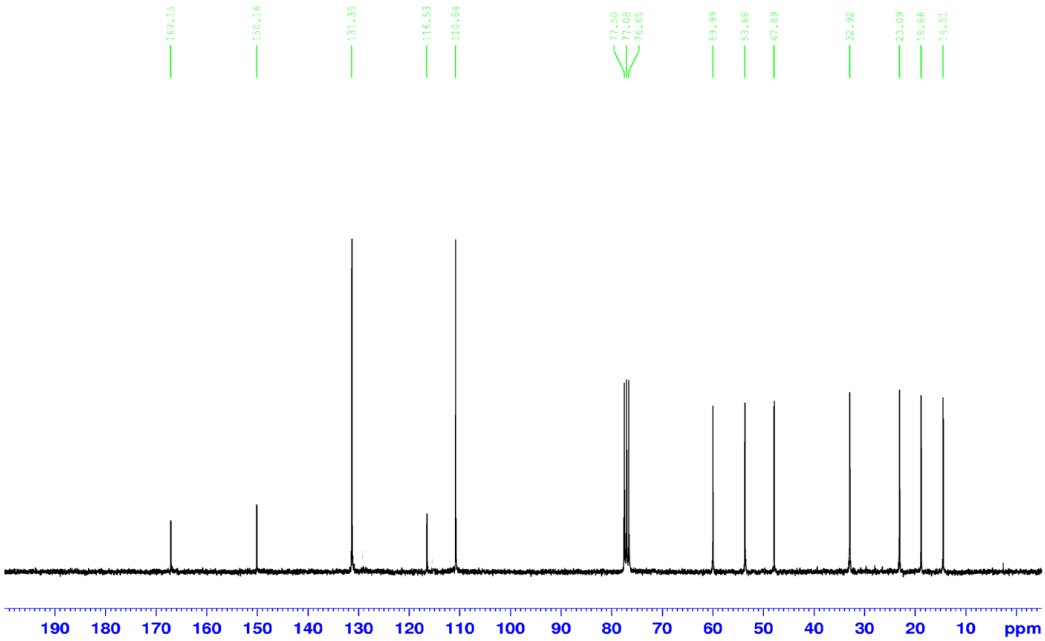
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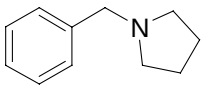
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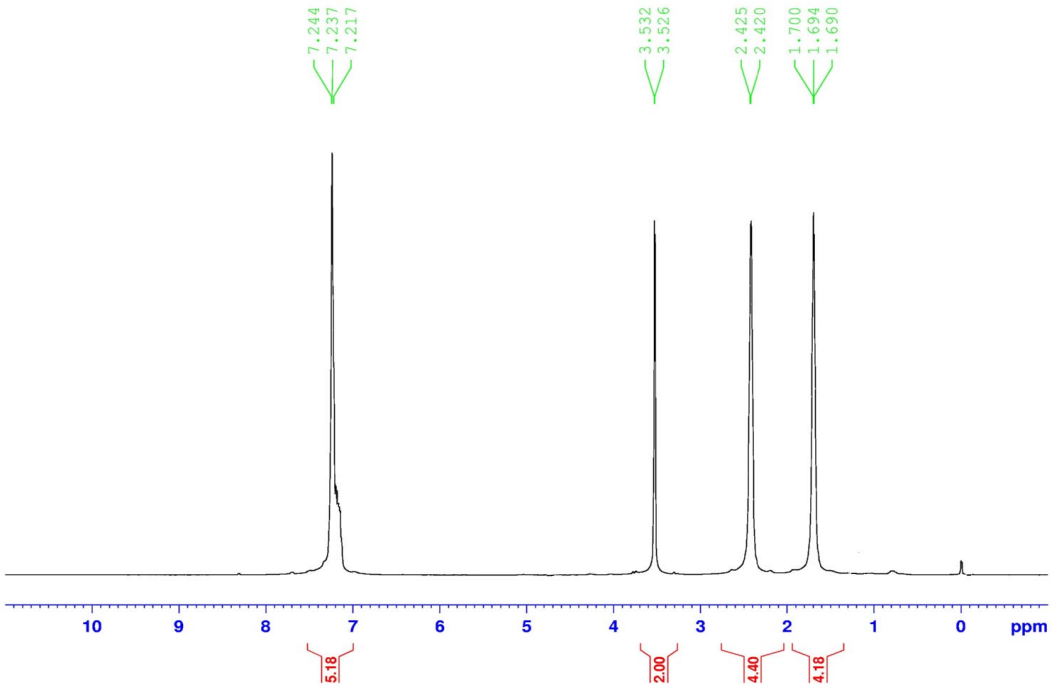
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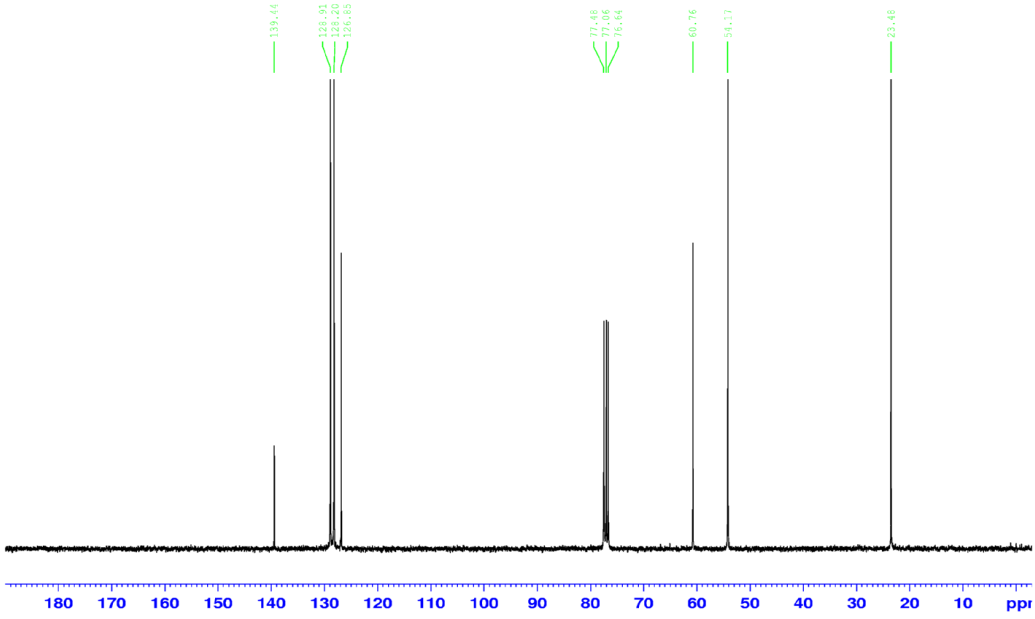
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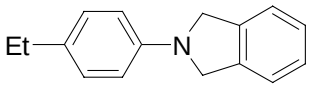
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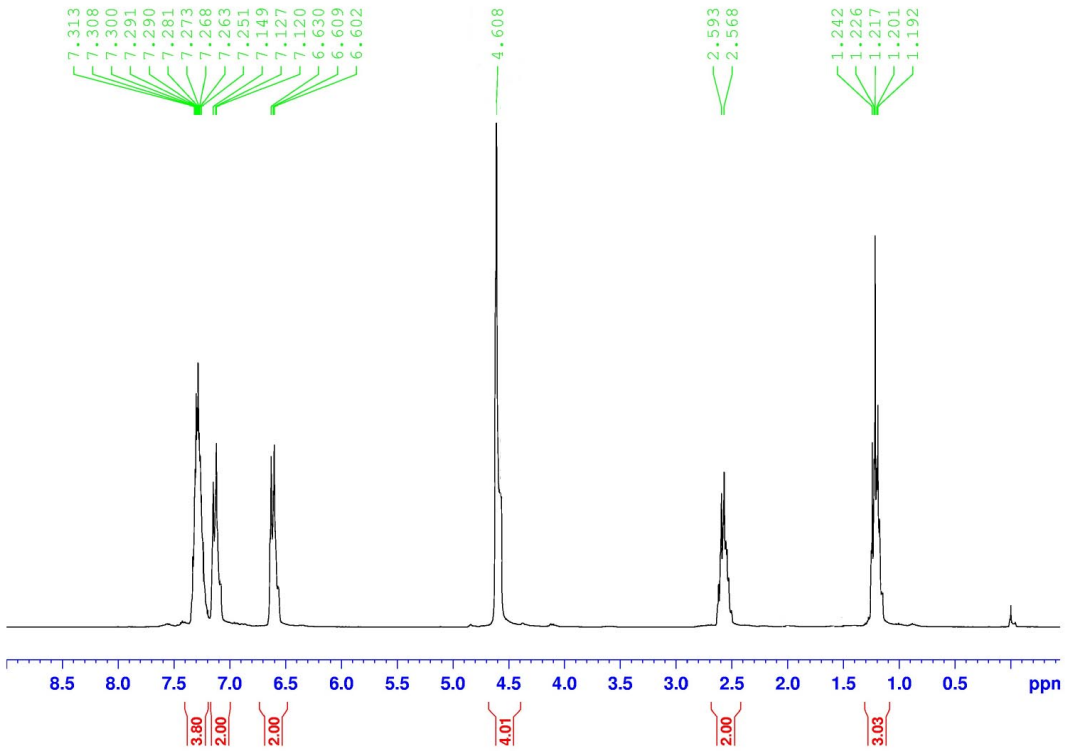
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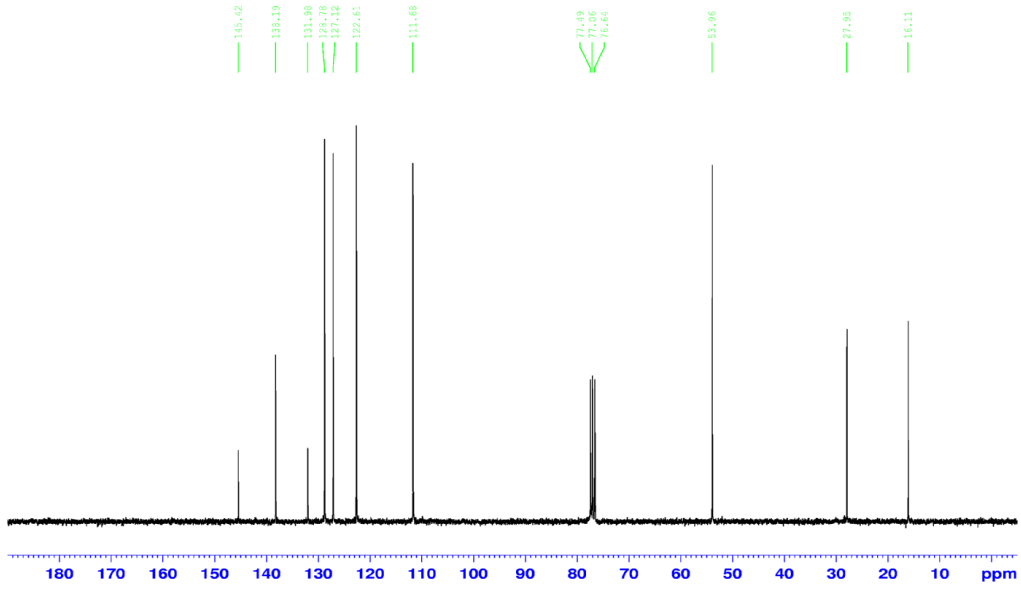
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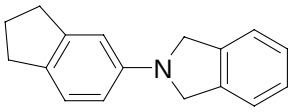
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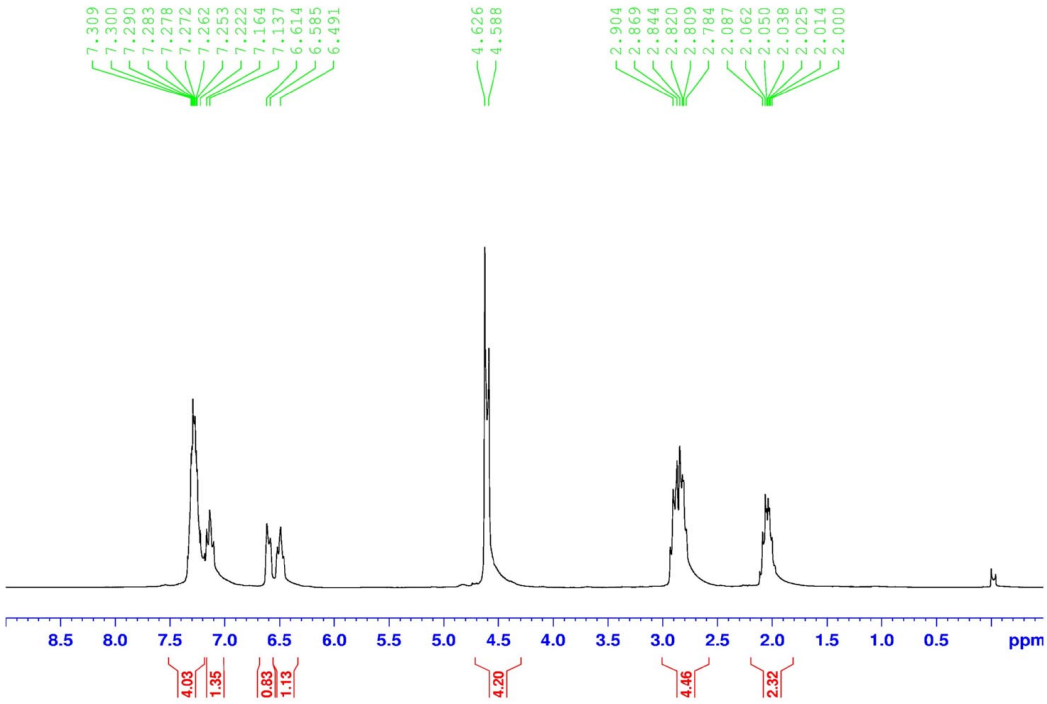
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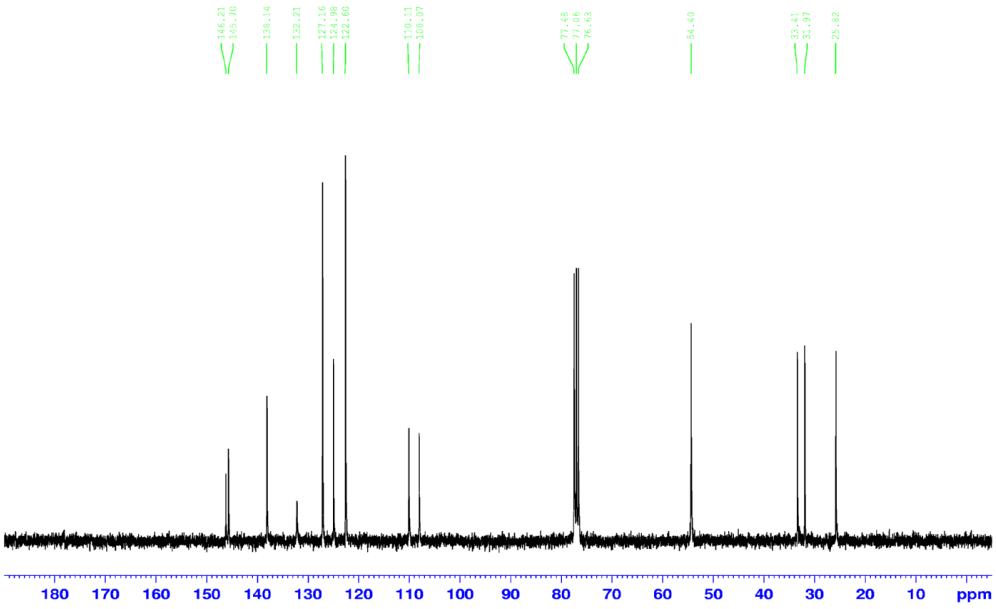
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References:

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