Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION

A Novel Zn-catalyzed Hydroamination of Propargylamides: A General Synthesis of Di- and Tri-substituted Imidazoles

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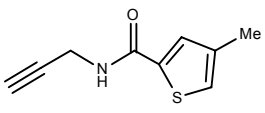
General Information

All reactions were carried out under argon atmosphere. Reactions were monitored by TLC analysis (pre-coated silica gel plates with fluorescent indicator UV_{254}, 0.2 mm) and visualized with 254 nm UV light or iodine. Chemicals were purchased from Aldrich, Fluka, Acros, AlfaAsar, Strem and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC-MS, HRMS and IR spectroscopy. ^{1}H spectra were recorded on Bruker AV 300 and AV 400 spectrometers. ^{13}C NMR and ^{19}F NMR spectra were recorded at 75.5 MHz and 282 MHz respectively. Chemical shifts are reported in ppm relative to the center of solvent resonance. Melting points were determined on a digital SMP3 (Stuart). IR spectra were recorded on FT-IR ALPHA (Bruker) with Platinum-ATR (Bruker). EI (70 eV) mass spectra were recorded on MAT 95XP (Thermo ELECTRON CORPORATION). GC was performed on Agilent 6890 chromatograph with a 30 m HP5 column. HRMS was performed on MAT 95XP (EI) and Agilent 6210 Time-of-Flight LC/MS (ESI). GC-MS was performed on Agilent 5973 chromatograph Mass Selective Detector. All yields reported refer to isolated yields.

General procedure for imidazole synthesis: A mixture of amine **4** (1.5 mmol), propargylamide **5** (1.0 mmol) and zinc triflate (18 mg, 5 mol%) in dry toluene (1 – 2 mL) was heated in reaction vial in CEM Discover microwave reactor cavity for 1 h at 140 °C. After removal of the solvent, the corresponding crude imidazole product **6 – 18** was purified by column chromatography using heptane/ethyl acetate.

General procedure for propargylamide synthesis: To the solution of propargylamine (1.2 mL, 17.5 mmol), DMAP (43 mg, 2 mol%) and triethylamine (2.4 ml) in CH_2Cl_2 (6 ml) was added corresponding acyl chloride (17.5 mmol) in CH_2Cl_2 (6 ml) at 0°C under an argon atmosphere. After 30 min the reaction mixture was allowed to warm to room temperature and stirring was continued until the reaction was complete (TLC control). After extraction with ethyl acetate (or CH_2Cl_2) and concentration in vacuum, the solid rest was recrystallized from hot heptane or heptane / ethyl acetate to give desired propargylamides in good to excellent yields.

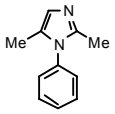
4-Methyl-thiophene-2-carboxylic acid prop-2-ynylamide (5e)



Yield: 2.91 g (93 %); white crystals; **Mp** 132-133 °C (from ethyl acetate / heptane); $\mathbf{R_f}$ = 0.46 (heptane / ethyl acetate 1:1); **^{1}H NMR** (300 MHz, Aceton-d_6): δ = 2.22 (s, 3H), 2.67 (t, 1H, *J* = 2.54 Hz), 4.14 (dd, 2H, *J* = 2.51, 5.64 Hz), 7.26 (dd, 1H), 7.54 (d, 1H), 8.01 (bs, 1H); **^{13}C NMR** (Aceton-d_6): δ = 15.26, 28.92, 71.66, 80.92, 126.53, 130.52, 138.68, 139.57, 161.61; **GC-MS** (EI): *m/z* (%) 179 (13) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_9H_{10}NOS$: 180.0478; found: 180.0478; **HRMS pos.** (ESI): Calc for [M+Na], C_9H_9NNaOS:

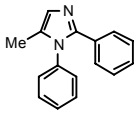
202.0297; found: 202.0297; **FTIR** (ATR, cm^{-1}): 3310, 3277, 3080, 3044, 2955, 2928, 2860, 1622, 1555, 1524, 1418, 1301, 1254, 1231, 866, 766, 671, 632, 574, 456.

2,5-Dimethyl-1-phenyl-1*H*-imidazole (6)



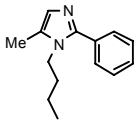
Yield: 126 mg (73 %); colorless crystals; **Mp** 69-72 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.3 (ethyl acetate / ethanol 10:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.95 (d, 3H, *J* = 0.76 Hz), 2.16 (s, 3H), 6.70 (d, 1H, *J* = 1.0 Hz), 7.15 (m, 2H), 7.44 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ = 10.03, 13.79, 124.45, 127.31 (2C), 128.11, 128.53, 129.41 (2C), 136.59, 144.44; **GC-MS** (EI): *m/z* (%) 172 (100) [M^+]; **HRMS** (EI): Calc for [M+H], $C_{11}H_{13}N_2$: 173.1073; found: 173.1074; **FTIR** (ATR, cm^{-1}): 3063, 2923, 1598, 1498, 1402, 1271, 1146, 987, 806, 777, 736, 696, 676, 639, 548, 376.

5-Methyl-1,2-diphenyl-1*H*-imidazole (7)



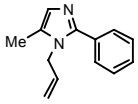
Yield: 190 mg (87 %); white crystals; **Mp** 123-124 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.32 (heptane / ethyl acetate 1:1); **^{1}H NMR** (300 MHz, Aceton-d_6): δ = 2.05 (d, 3H, *J* = 0.97 Hz), 6.90 (d, 1H, *J* = 0.92 Hz), 7.19 (m, 3H), 7.29 (m, 2H), 7.34 (m, 2H), 7.52 (m, 3H); **^{13}C NMR** (Aceton-d_6): δ = 10.07, 127.09, 128.15, 128.42 (2C), 128.51 (2C), 128.64 (2C), 129.32, 130.29 (2C), 130.82, 132.15, 138.48, 146.88; **GC-MS** (EI): *m/z* (%) 234 (100) [M^+]; **HRMS** (EI): Calc for [M+H], $C_{16}H_{15}N_2$: 235.123; found: 235.123; **FTIR** (ATR, cm^{-1}): 3092, 3061, 2943, 2907, 2860, 2743, 1495, 1466, 1454, 1397, 954, 833, 770, 711, 689, 645, 570, 413.

1-Butyl-5-methyl-2-phenyl-1*H*-imidazole (8)



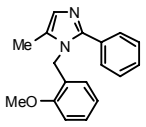
Yield: 204 mg (95 %); colorless syrup; $\mathbf{R_f}$ = 0.6 (ethyl acetate / ethanol 9:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 0.84 (t, 3H, *J* = 7.34 Hz), 1.23 (m, 2H), 1.61 (m, 2H), 2.27 (d, 3H, *J* = 0.94 Hz), 3.89 (m, 2H), 6.85 (d, 1H, *J* = 0.96 Hz), 7.41 (m, 3H), 7.54 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ = 10.00, 13.49, 19.74, 32.76, 44.02, 126.36, 128.31, 128.34, 128.42 (2C), 128.70 (2C), 131.79, 147.49; **GC-MS** (EI): *m/z* (%) 214 (100) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{14}H_{19}N_2$: 215.1543; found: 215.1543; **FTIR** (ATR, cm^{-1}): 3063, 2958, 2931, 2872, 1566, 1449, 1403, 1366, 1270, 1074, 964, 810, 771, 698, 650.

1-Allyl-5-methyl-2-phenyl-1*H*-imidazole (9)



Yield: 190 mg (96 %); white crystals; **Mp** 84-86 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.4 (ethyl acetate); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.21 (d, 3H, *J* = 1.02 Hz), 4.50 (m, 2H), 4.93 (m, 1H), 5.27 (m, 1H), 5.96 (m, 1H), 6.89 (d, 1H, *J* = 0.96 Hz), 7.39 (m, 3H), 7.58 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ = 9.57, 46.40, 116.62, 126.34, 128.37 (2C), 128.38 (2C), 128.43, 128.87, 131.09, 133.29, 147.73; **GC-MS** (EI): *m/z* (%) 198 (100) [M^+]; **HRMS** (EI): Calc for $C_{13}H_{14}N_2$: 198.11515; found: 198.115048; **FTIR** (ATR, cm^{-1}): 3089, 3058, 2980, 2924, 1439, 920, 805, 772, 701, 658, 637, 566, 546, 517.

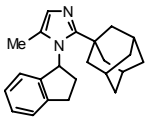
1-(2-Methoxy-phenyl)-5-methyl-2-phenyl-1*H*-imidazole (10)



Yield: 268 mg (96 %); white crystals; **Mp** 112-113 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.5 (ethyl acetate); **^{1}H NMR** (300 MHz, CD_3OD): δ = 2.21 (d, 3H, *J* = 1.02 Hz), 3.82 (s, 3H), 5.15 (s, 2H), 6.51 (m, 1H), 6.88 (ddd, 1H), 6.92 (dd, 1H), 7.00 (dd, 1H), 7.28 (m, 1H), 7.39 (m, 5H); **^{13}C NMR** (CD_3OD): δ = 9.58, 44.38,

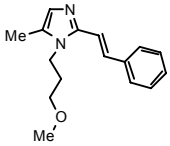
55.86, 111.48, 121.79, 126.25, 126.39, 126.83, 129.64 (4C), 129.99, 130.09, 130.99, 131.89, 149.48, 157.61; **GC-MS** (EI): *m/z* (%) 278 (48) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{18}H_{19}N_2O$: 279.1492; found: 279.1487; **FTIR** (ATR, cm^{-1}): 3056, 2941, 2839, 1441, 1242, 1025, 771, 755, 722, 693.

1-Indan-1-yl-5-methyl-2-(1-adamantyl)-1*H*-imidazole (11)



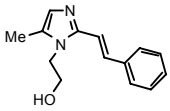
Yield: 259 mg (78 %); white crystals; **Mp** 213-215 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.4 (ethyl acetate / ethanol 9:1); **^{1}H NMR** (300 MHz, CD_3OD): δ = 1.60 (d, 3H, *J* = 1.05 Hz), 1.84 (m, 6H), 2.10 (m, 3H), 2.23 (m, 6H), 2.32 (m, 1H), 2.79 (m, 1H), 3.15 (m, 2H), 6.51 (t, 1H, *J* = 8.94 Hz), 6.55 (d, 1H, *J* = 0.78 Hz), 6.89 (dd, 1H, *J* = 0.54, 7.52 Hz), 7.21 (m, 1H), 7.30 (m, 2H); **^{13}C NMR** (CD_3OD): δ = 11.56, 30.02 (3C), 30.96, 32.86, 37.40, 37.69 (3C), 42.50 (3C), 62.64, 124.54, 126.19, 126.40, 128.15, 129.45, 130.00, 142.46, 144.05 155.96; **GC-MS** (EI): *m/z* (%) 332 (11) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{23}H_{29}N_2$: 333.2325; found: 333.2327; **FTIR** (ATR, cm^{-1}): 3077, 2901, 2883, 2850, 1474, 1457, 1388, 1372, 1267, 805, 757, 724, 650, 468, 422.

1-(3-Methoxy-propyl)-5-methyl-2-((E)-styryl)-1*H*-imidazole (12)



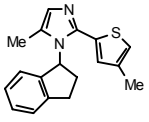
Yield: 208 mg (81 %); white crystals; **Mp** 60-62 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.35 (ethyl acetate); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.93 (m, 2H), 2.23 (d, 3H, *J* = 0.93 Hz), 3.29 (t, 2H), 3.30 (s, 3H), 4.06 (t, 2H, *J* = 6.72 Hz), 6.84 (d, 1H), 6.97 (d, 1H, *J* = 15.85 Hz), 7.25 (m, 1H), 7.34 (m, 2H), 7.52 (m, 2H), 7.57 (d, 1H); **^{13}C NMR** ($CDCl_3$): δ = 9.61, 30.79, 39.50, 58.57, 68.04, 113.83, 126.53 (2C), 126.93, 127.79, 128.11, 128.58 (2C), 131.04, 136.92, 145.21; **GC-MS** (EI): *m/z* (%) 255 (100) [M^+], 256 (28); **HRMS pos.** (ESI): Calc for [M+H], $C_{16}H_{21}N_2O$: 257.1648; found: 257.1646; **FTIR** (ATR, cm^{-1}): 3080, 3057, 3026, 2929, 2872, 2830, 1464, 1414, 1114, 1080, 1025, 962, 901, 823, 751, 709, 687, 630, 565, 527, 499.

2-[5-Methyl-2-((E)-styryl)-imidazol-1-yl]-ethanol (13)



Yield: 125 mg (55 %); colorless needles; **Mp** 163-165 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.45 (ethyl acetate / ethanol 9:1); **^{1}H NMR** (300 MHz, CD_3OD): δ = 2.27 (d, 3H, *J* = 0.87 Hz), 3.78 (t, 2H, *J* = 5.59 Hz), 4.15 (t, 2H), 6.76 (d, 1H), 7.12 (d, 1H, *J* = 16.05 Hz), 7.27 (ddd, 1H), 7.35 (m, 3H), 7.40 (d, 1H), 7.58 (m, 2H); **^{13}C NMR** (CD_3OD): δ = 9.85, 46.49, 62.36, 115.27, 126.50, 127.79 (2C), 129.22, 129.77 (2C), 130.58, 132.87, 138.15, 146.74; **GC-MS** (EI): *m/z* (%) 227 (100) [M^+], 228 (28); **HRMS pos.** (ESI): Calc for [M+H], $C_{14}H_{17}N_2O$: 229.1335; found: 229.1335; **FTIR** (ATR, cm^{-1}): 3136, 2982, 2906, 2849, 1473, 1421, 1067, 956, 757, 726, 703, 687, 566, 511.

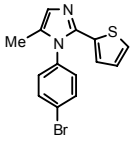
1-Indan-1-yl-5-methyl-2-(4-methyl-thiophen-2-yl)-1*H*-imidazole (14)



Yield: 230 mg (78 %); colorless crystals; **Mp** 103-104 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.6 (ethyl acetate / heptane 4:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.76 (s, 3H), 2.26 (s, 3H), 2.34 (m, 1H), 2.70 (m, 1H), 3.04 (m, 1H), 3.13 (m, 1H), 6.24 (s, 1H), 6.83 (s, 1H), 6.95 (s, 1H), 6.99 (dd, 1H), 7.20 (m, 1H), 7.27 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ = 11.23, 15.67, 30.22, 32.10, 61.07, 122.16, 123.88, 124.95, 127.05, 128.25 (2C), 128.77, 129.16, 132.80, 137.69, 140.95, 142.39 (2C); **GC-MS** (EI): *m/z* (%) 294 (23) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{18}H_{19}N_2S$: 295.1263; found:

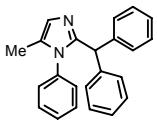
295.1266; **FTIR** (ATR, cm^{-1}): 3059, 3039, 2963, 2950, 2924, 2898, 2867, 2850, 1454, 1406, 1377, 1267, 867, 827, 761, 736, 697, 603, 524, 433, 415.

1-(4-Bromo-phenyl)-5-methyl-2-thiophen-2-yl-1*H*-imidazole (15)



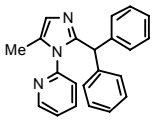
Yield: 121 mg (38 %); white crystals; **Mp** 146-148 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.33 (ethyl acetate / heptane 1:1); **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 2.02 (d, 3H, *J* = 1.1 Hz), 6.54 (dd, 1H, *J* = 1.13, 3.58 Hz), 6.82 (dd, 1H, *J* = 3.78, 5.1 Hz), 6.92 (q, 1H, *J* = 1.03, 2.04 Hz), 7.17 (m, 3H), 7.66 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ = 10.05, 123.55, 124.81, 125.72, 126.66, 127.15, 129.91 (2C), 130.02, 133.12 (2C), 133.42, 135.85, 142.04; **GC-MS** (EI): *m/z* (%) 318 (98) [M^+], 320 (100) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{14}H_{12}BrN_2S$: 318.9899 and 320.9879; found: 318.99 and 320.988; **FTIR** (ATR, cm^{-1}): 3093, 2918, 1485, 1414, 1395, 1228, 1070, 1009, 916, 847, 829, 817, 712, 645, 551, 468, 409.

2-Benzhydryl-5-methyl-1-phenyl-1*H*-imidazole (16)



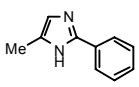
Yield: 198 mg (61 %); white crystals; **Mp** 142-144 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.45 (heptan / ethyl acetate 1:1); **^{1}H NMR** (300 MHz, Aceton-d_6): δ = 1.95 (d, 3H, *J* = 1.05 Hz), 5.14 (s, 1H), 6.77 (d, 1H), 7.18 (m, 12H), 7.51 (m, 3H); **^{13}C NMR** (Aceton-d_6): δ = 9.75, 49.53, 125.89, 126.80 (2C), 128.38, 128.53 (4C), 128.59 (2C), 129.39 (4C), 129.44, 130.06 (2C), 137.00, 143.01 (2C), 148.61; **GC-MS** (EI): *m/z* (%) 324 (51) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{23}H_{21}N_2$: 325.1699; found: 325.17; **FTIR** (ATR, cm^{-1}): 3026, 2916, 1493, 1447, 1408, 1069, 804, 773, 716, 695, 645, 631, 616, 590, 548, 494, 471.

2-(2-Benzhydryl-5-methyl-imidazol-1-yl)-pyridine (17)



Yield: 140 mg (43 %); white crystals; **Mp** 123-125 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.24 (heptan / ethyl acetate 1:1); **^{1}H NMR** (300 MHz, Aceton-d_6): δ = 2.04 (d, 3H), 5.47 (s, 1H), 6.76 (d, 1H, *J* = 0.99 Hz), 7.20 (m, 11H), 7.46 (ddd, 1H, *J* = 0.93, 4.90, 7.50 Hz), 7.89 (dt, 1H, *J* = 1.94, 7.66, 9.6 Hz), 8.63 (ddd, 1H, *J* = 0.79, 1.89, 4.84 Hz); **^{13}C NMR** (Aceton-d_6): δ = 9.81, 49.57, 122.79, 124.27, 126.02, 126.75 (2C), 128.10, 128.46 (4C), 129.44 (4C), 139.28, 142.76 (2C), 148.73, 150.23, 150.37; **GC-MS** (EI): *m/z* (%) 325 (100) [M^+]; **HRMS pos.** (ESI): Calc for [M+H], $C_{22}H_{20}N_3$: 326.1652; found: 326.1652; **FTIR** (ATR, cm^{-1}): 3325, 3055, 2917, 1586, 1494, 1466, 1437, 1407, 1141, 1034, 993, 799, 747, 730, 718, 697, 635, 614, 588, 553, 496, 465, 416.

5-Methyl-2-phenyl-1*H*-imidazole (18)



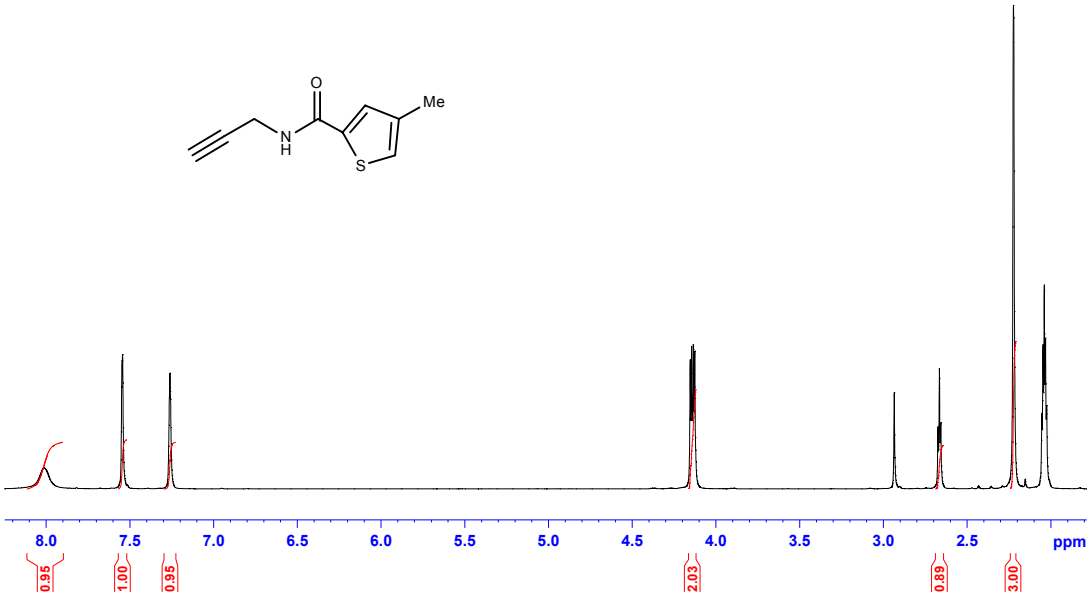
A mixture of propargylamide 2b (79.6 mg, 0.5 mmol) and $Zn(OTf)_2$ (9.1 mg, 5 mol%) in 1 ml dry toluene, was heated in autoclave under NH_3 pressure (~1.5 g ammonia) at 150 °C for 24 h. After removal of the solvent, the crude product was purified by column chromatography using heptane / ethyl acetate. **Yield**: 72 mg (91 %); white crystals; **Mp** 182-184 °C (from acetone / heptane); $\mathbf{R_f}$ = 0.5 (ethyl acetate); **^{1}H NMR** (400 MHz, Aceton-d_6): δ = 2.22 (d, 3H, *J* = 1.00 Hz), ~3.41 (bs, 0.64H), 6.82 (d, 1H, *J* = 0.92 Hz), 7.29 (tdd, 1H, *J* = 1.30, 2.07, 7.34 Hz), 7.39 (m, 2H), 7.94 (m, 2H); **^{13}C NMR** (Aceton-d_6): δ = 11.71, 120.24, 125.23 (2C), 128.17, 129.09 (2C), 131.82, 133.57, 145.89; **GC-MS** (EI): *m/z* (%) 158 (100) [M^+]; **HRMS** (EI): Calc for [M+H], $C_{10}H_{11}N_2$: 159.0917; found:

159.0919; **FTIR** (ATR, cm^{-1}): 3057, 3011, 2952, 2915, 2894, 2742, 2655, 2609, 2549, 2408, 1595, 1453, 1411, 1094, 969, 916, 811, 768, 705, 691, 639, 519, 460.

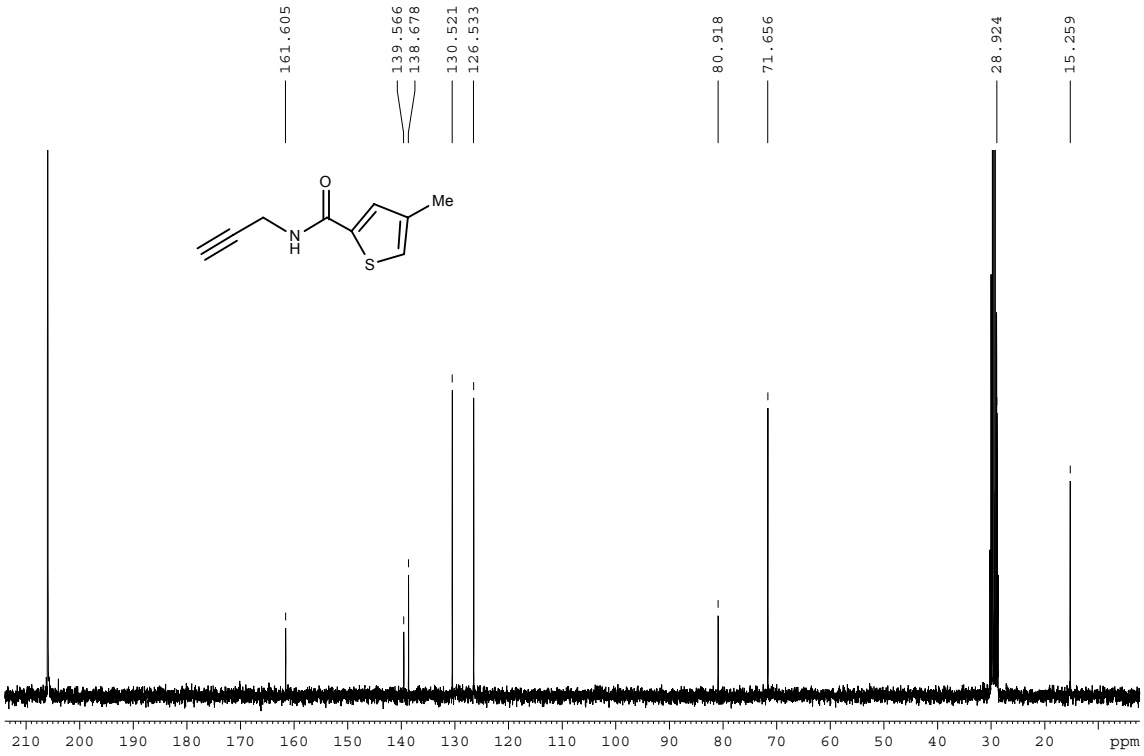
^{1}H and ^{13}C NMR spectra

4-Methyl-N-(prop-2-ynyl)thiophene-2-carboxamide (5e)

^{1}H NMR



^{13}C NMR



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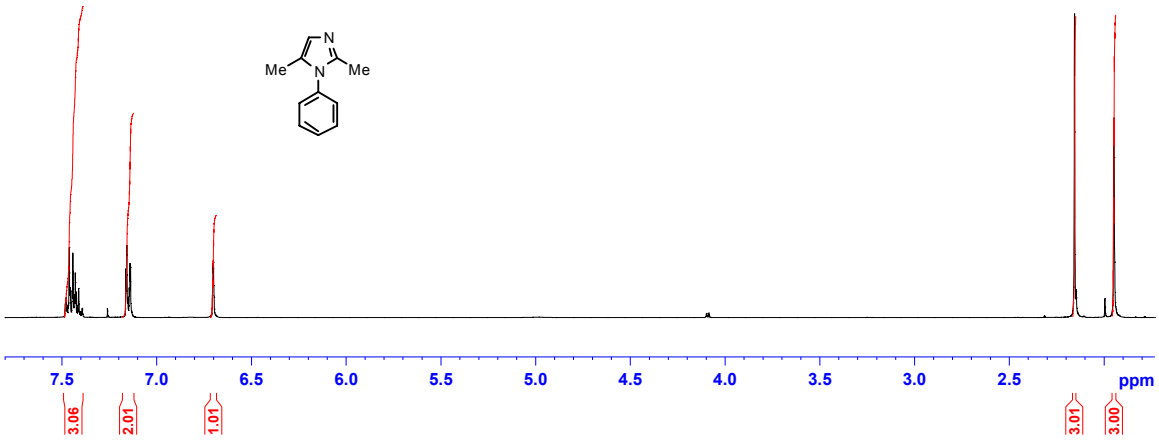
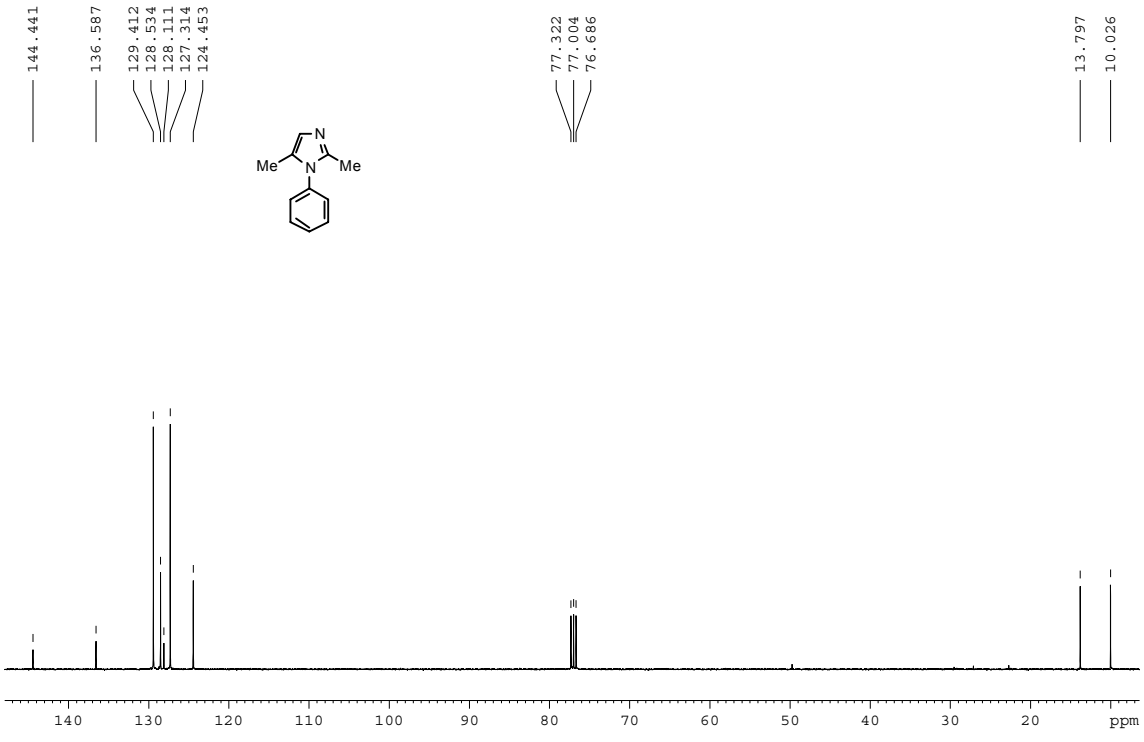
2,5-Dimethyl-1-phenyl-1*H*-imidazole (6)

^{1}H NMR



^{13}C NMR



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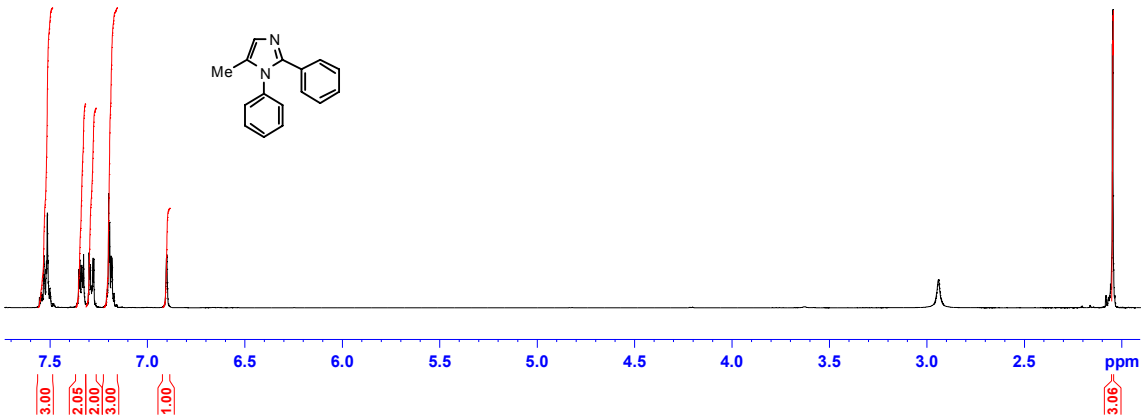
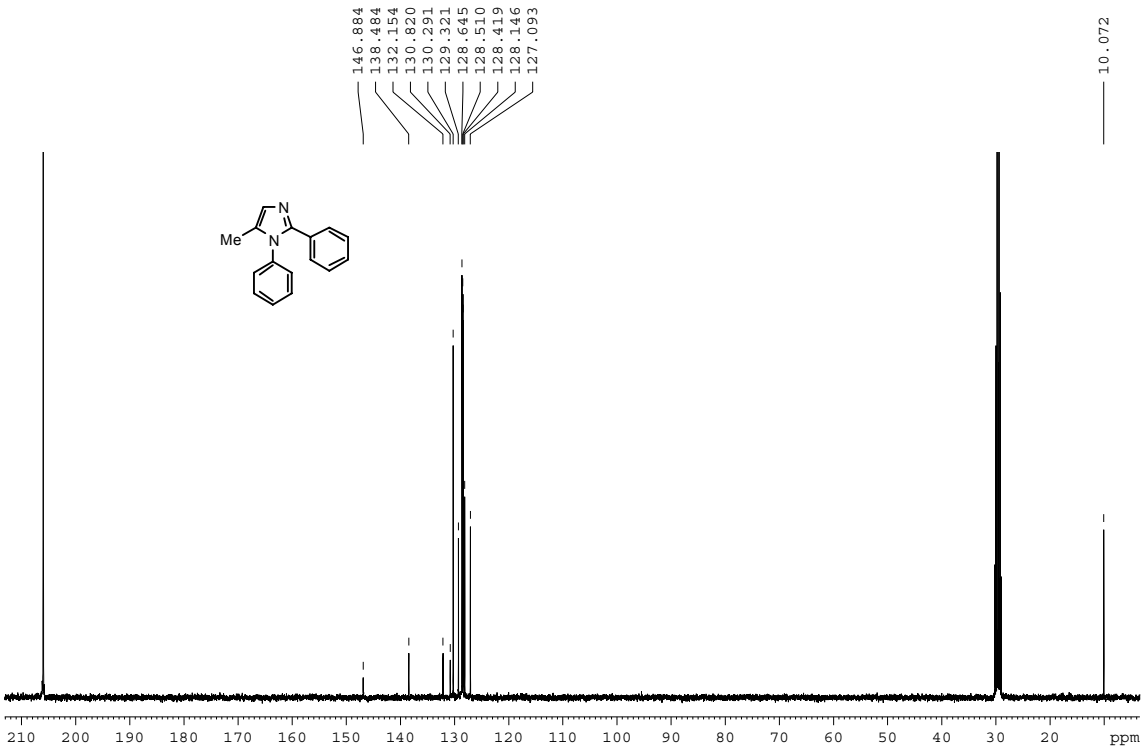
5-Methyl-1,2-diphenyl-1*H*-imidazole (7)

^{1}H NMR



^{13}C NMR



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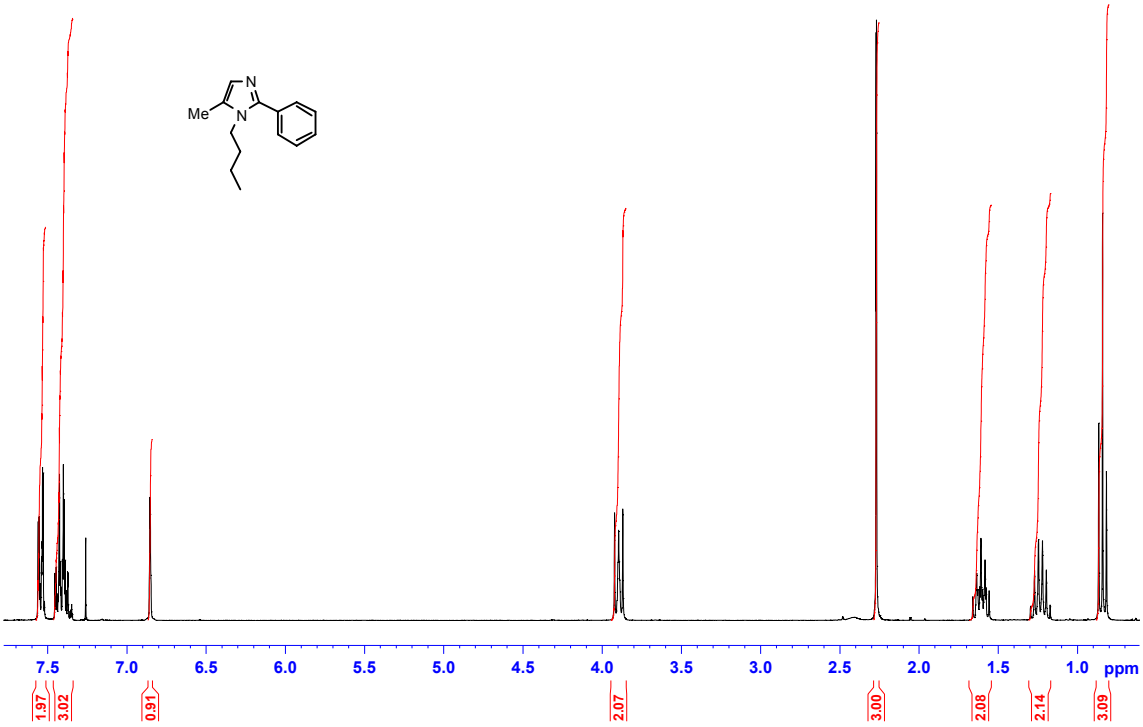
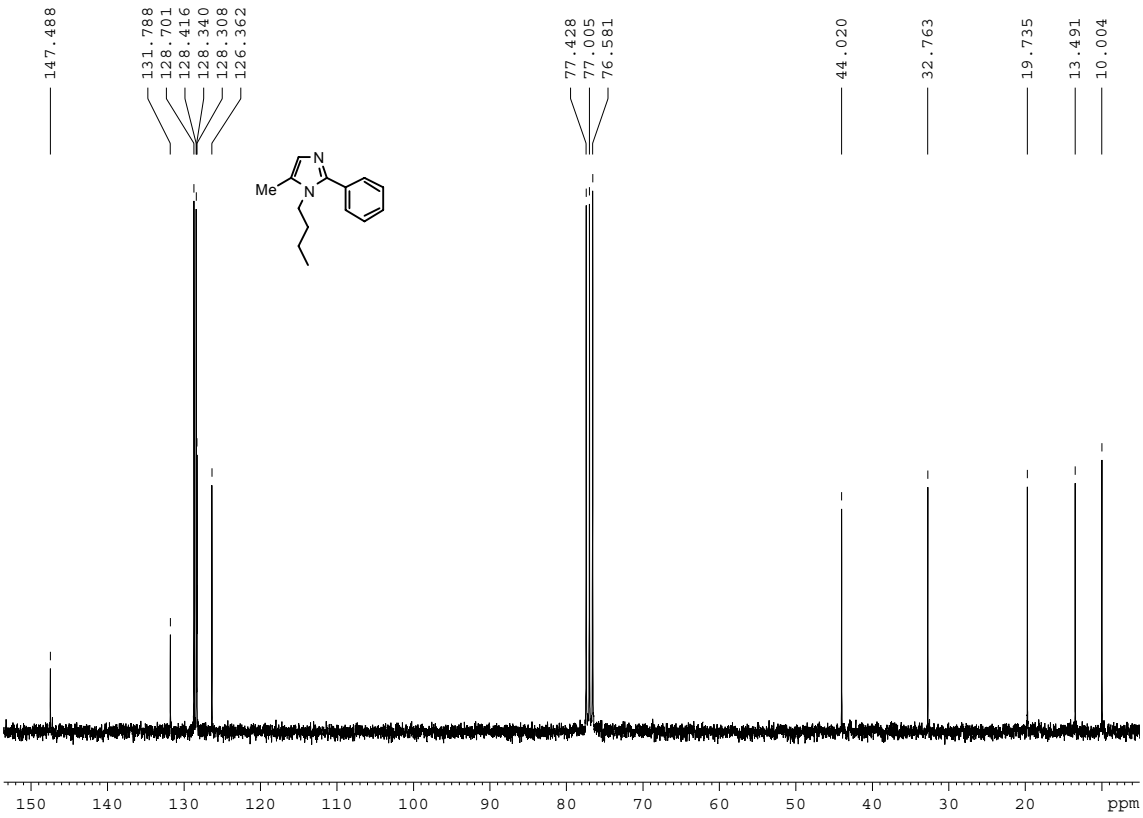
1-Butyl-5-methyl-2-phenyl-1*H*-imidazole (8)

^{1}H NMR



^{13}C NMR



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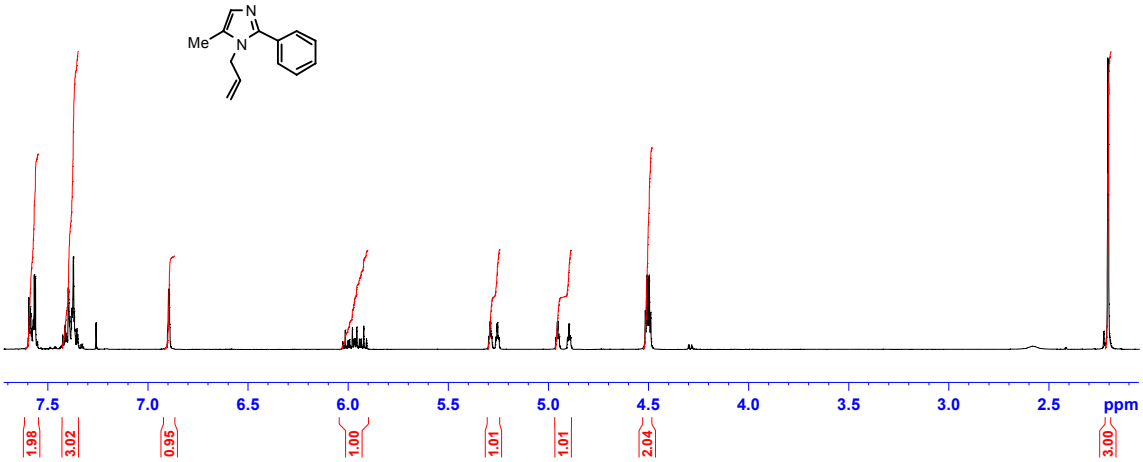
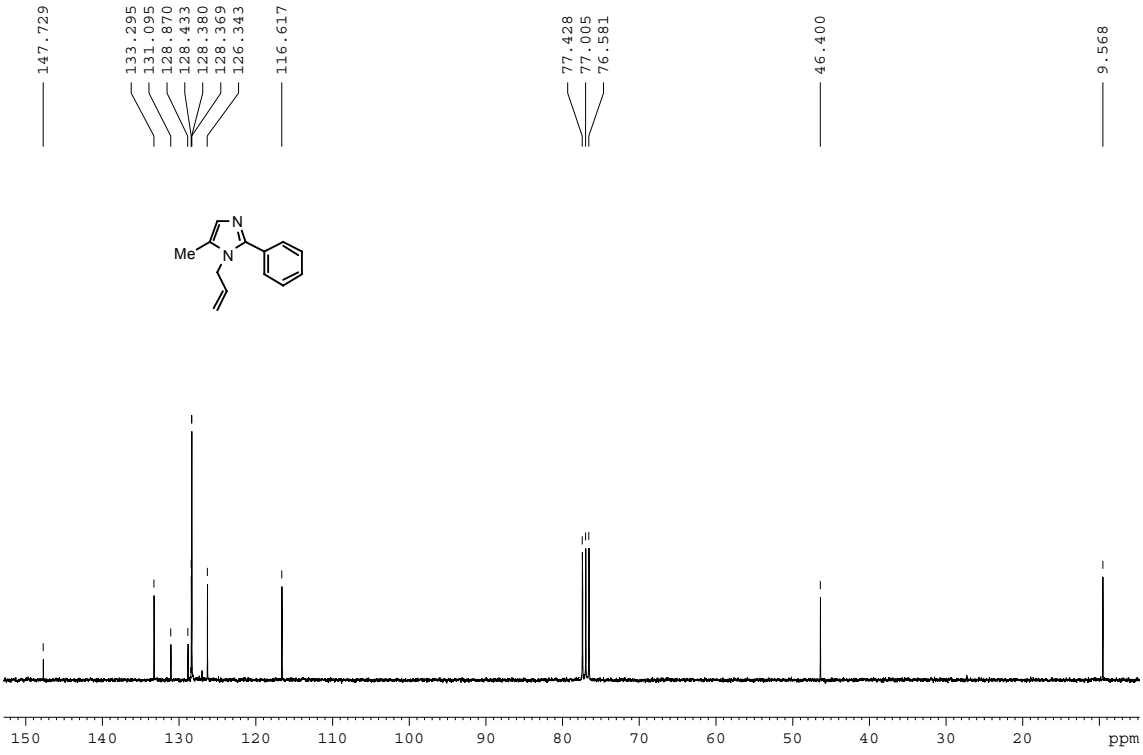
1-Allyl-5-methyl-2-phenyl-1*H*-imidazole (9)

^{1}H NMR

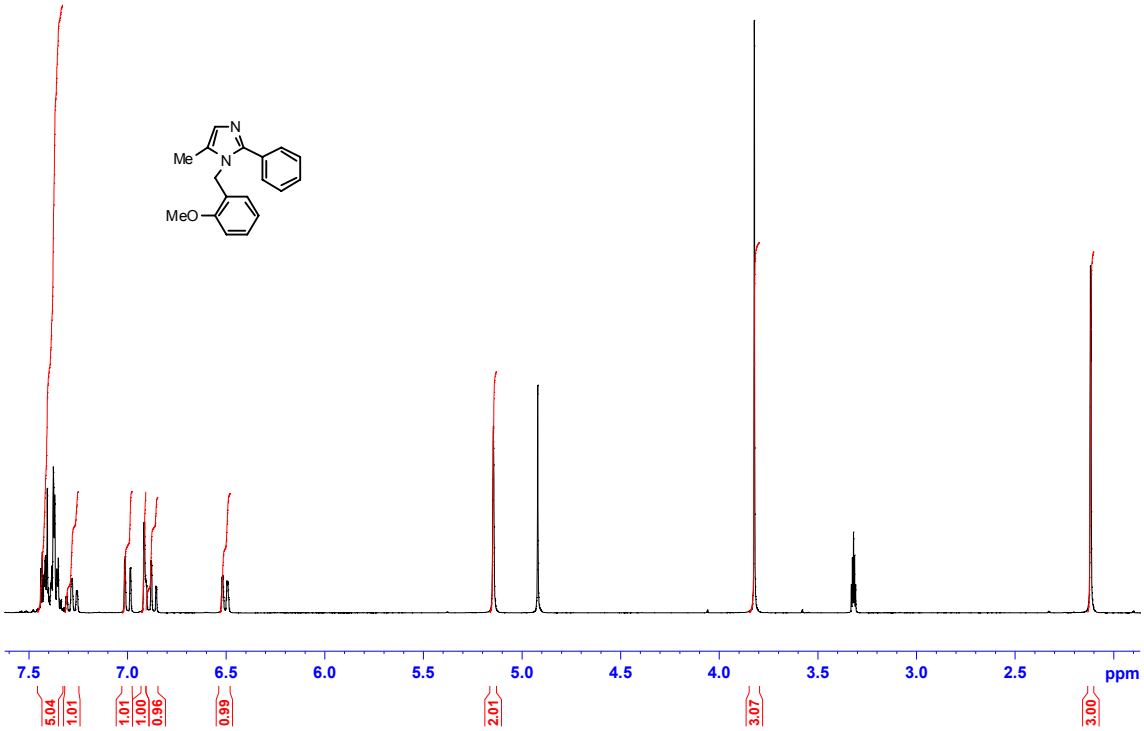


^{13}C NMR

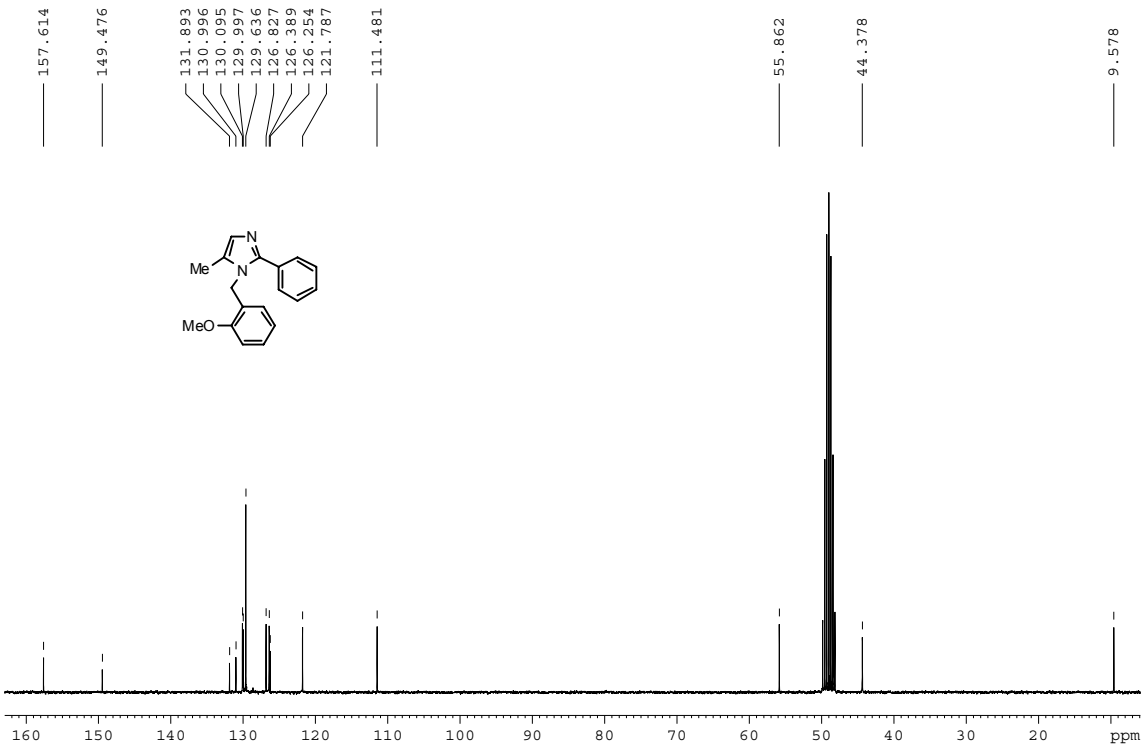


1-(2-Methoxy-phenyl)-5-methyl-2-phenyl-1*H*-imidazole (10)

^{1}H NMR



^{13}C NMR



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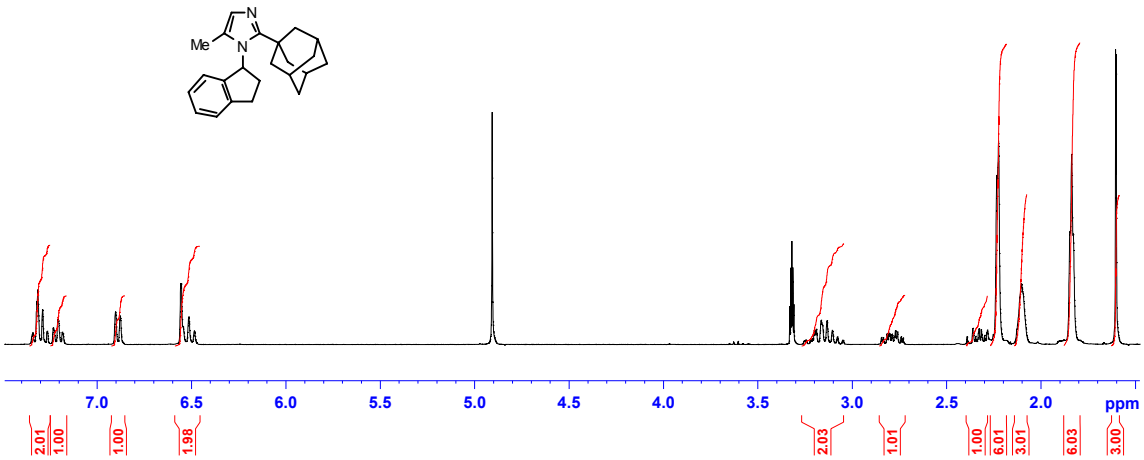
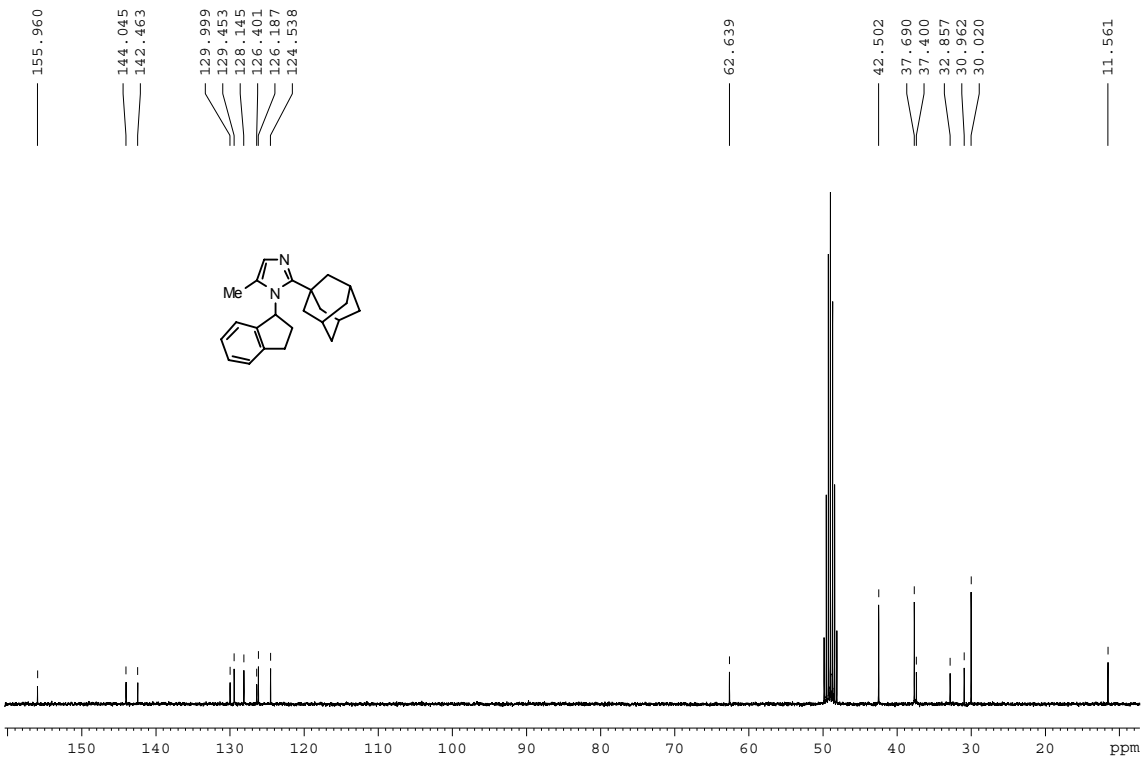
1-Indan-1-yl-5-methyl-2-(1-adamantyl)-1*H*-imidazole (11)

^{1}H NMR



^{13}C NMR



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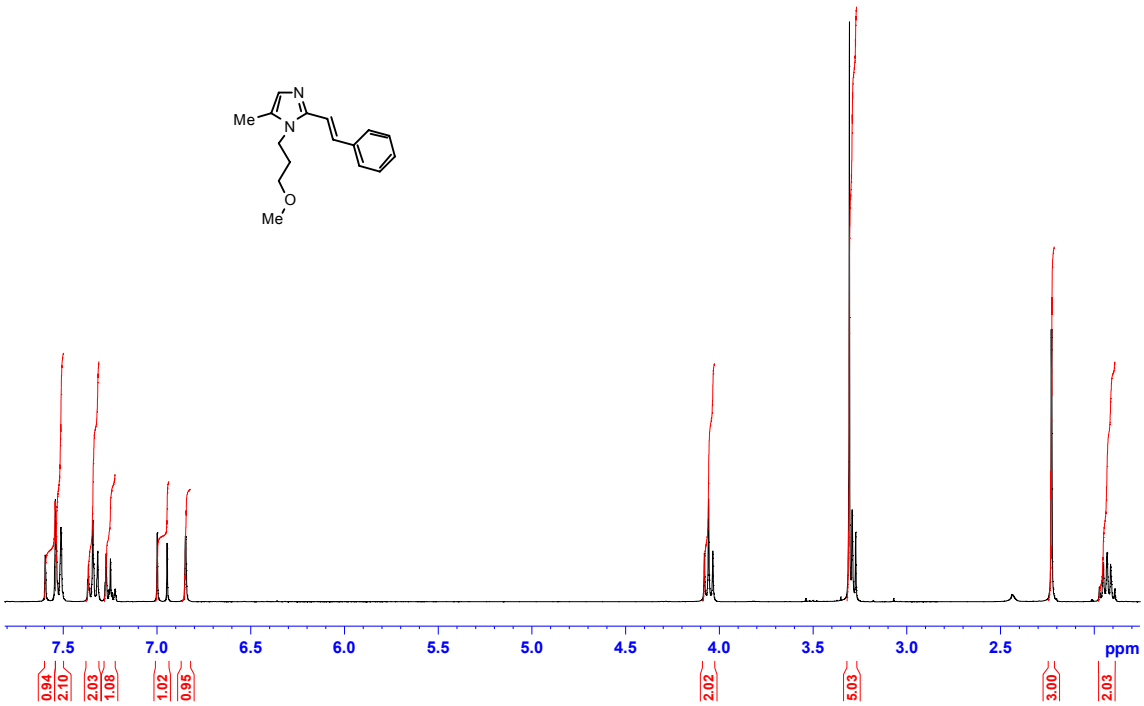
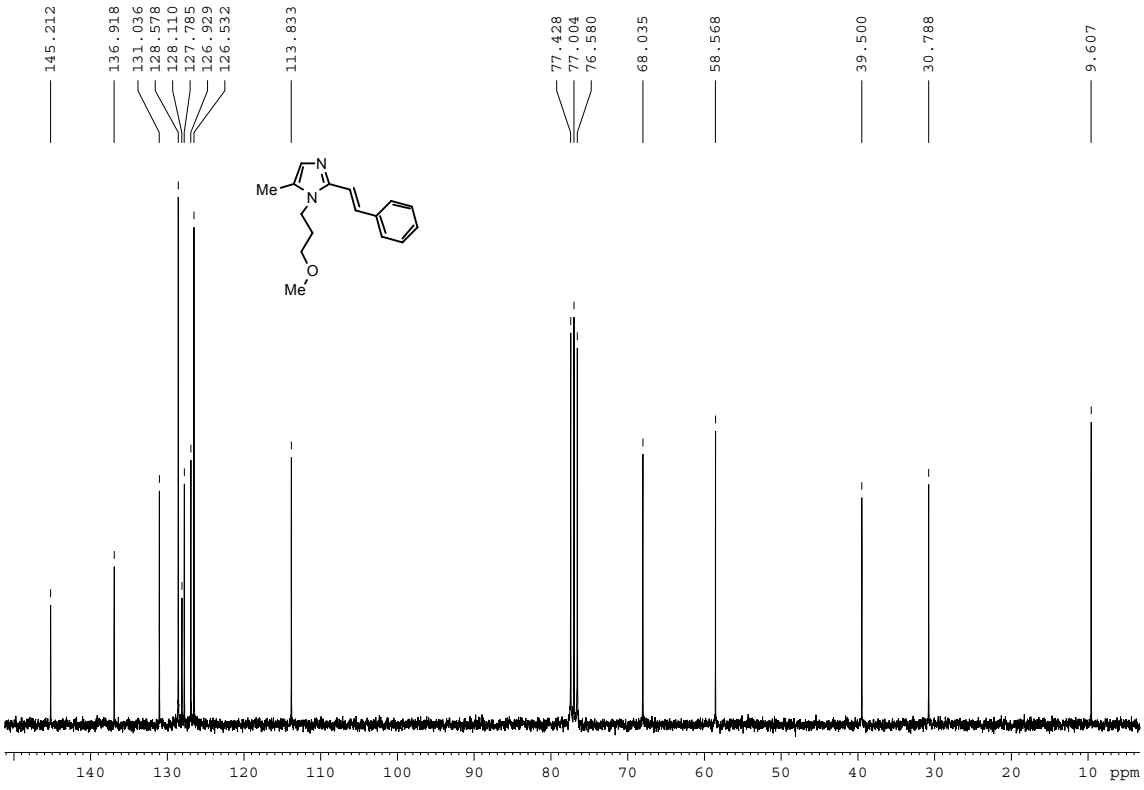
1-(3-Methoxy-propyl)-5-methyl-2-((E)-styryl)-1*H*-imidazole (12)

^{1}H NMR



^{13}C NMR



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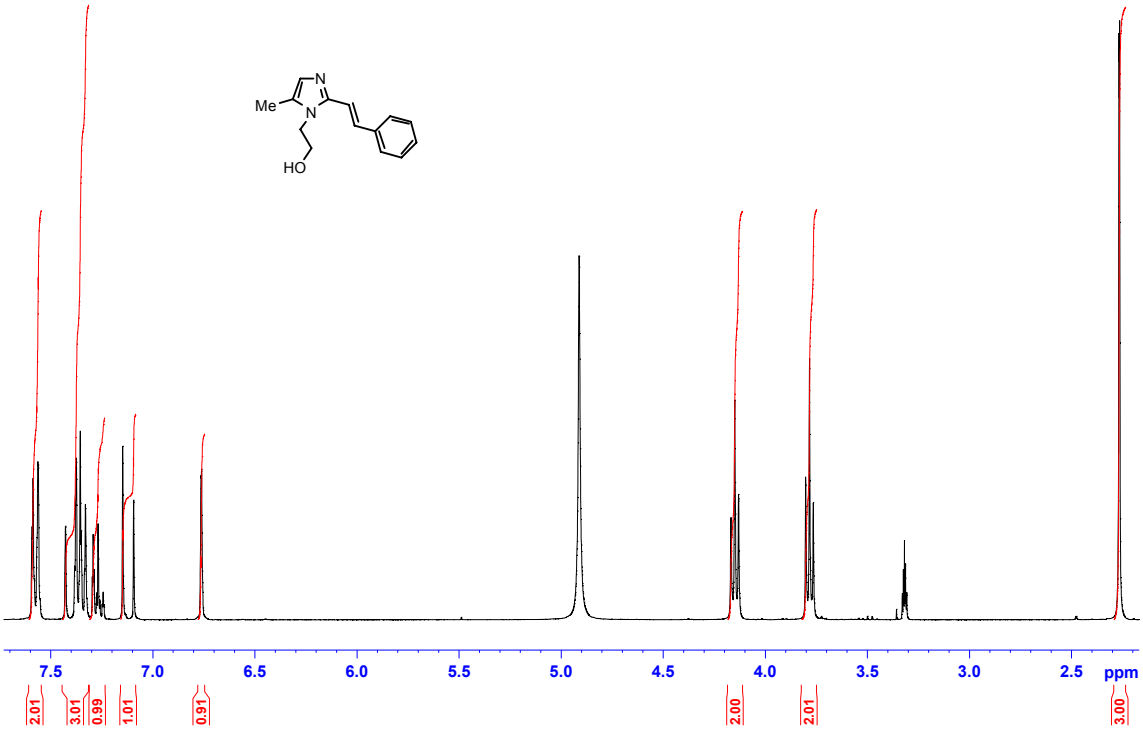
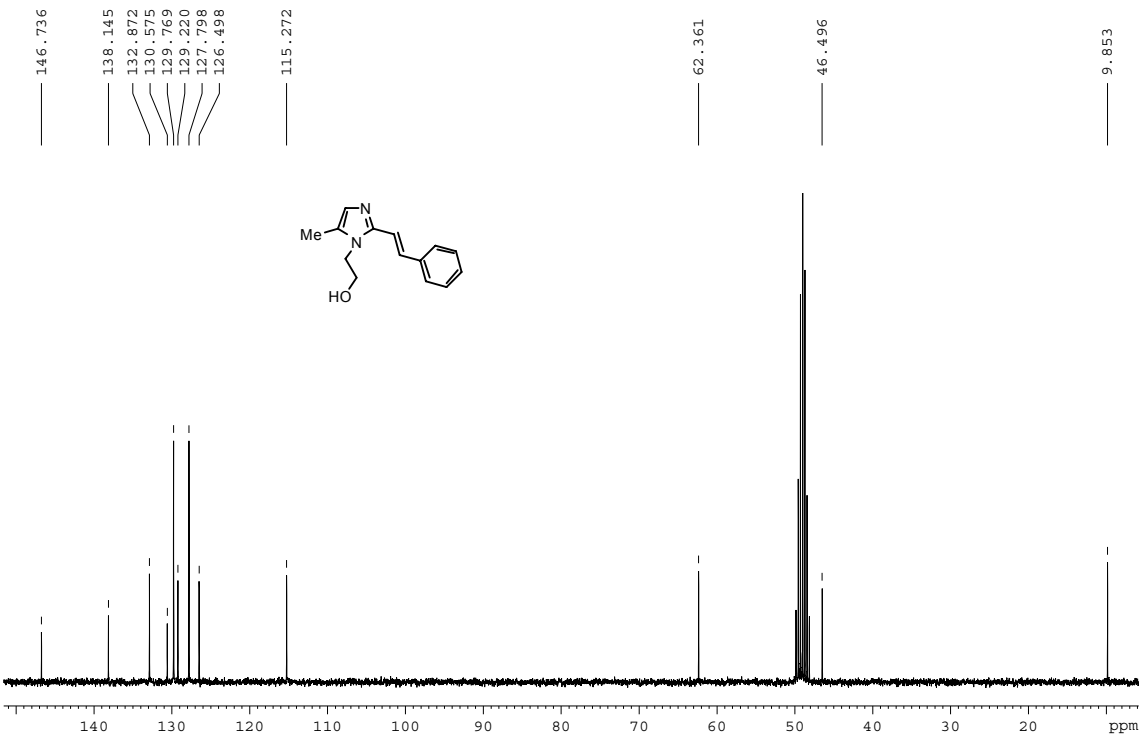
2-[5-Methyl-2-((E)-styryl)-imidazol-1-yl]-ethanol (13)

^{1}H NMR



^{13}C NMR



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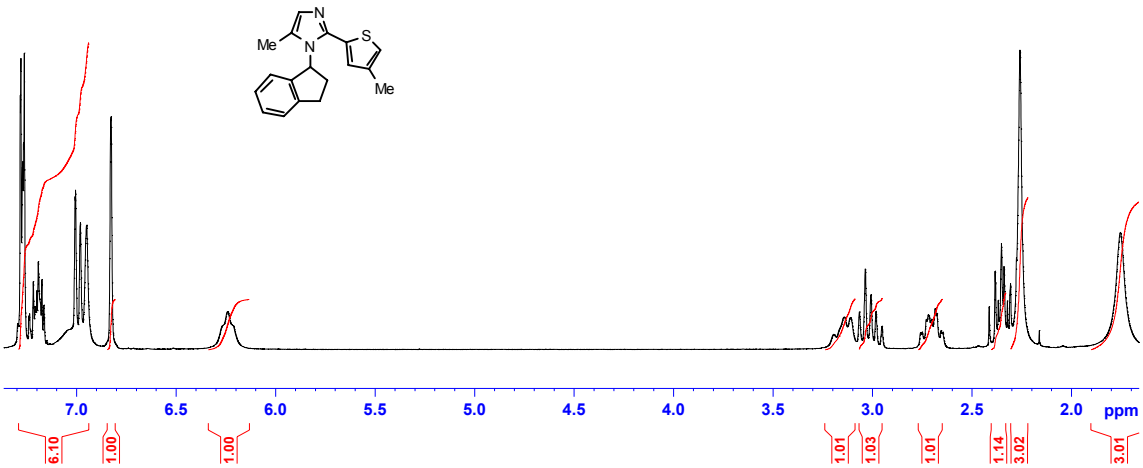
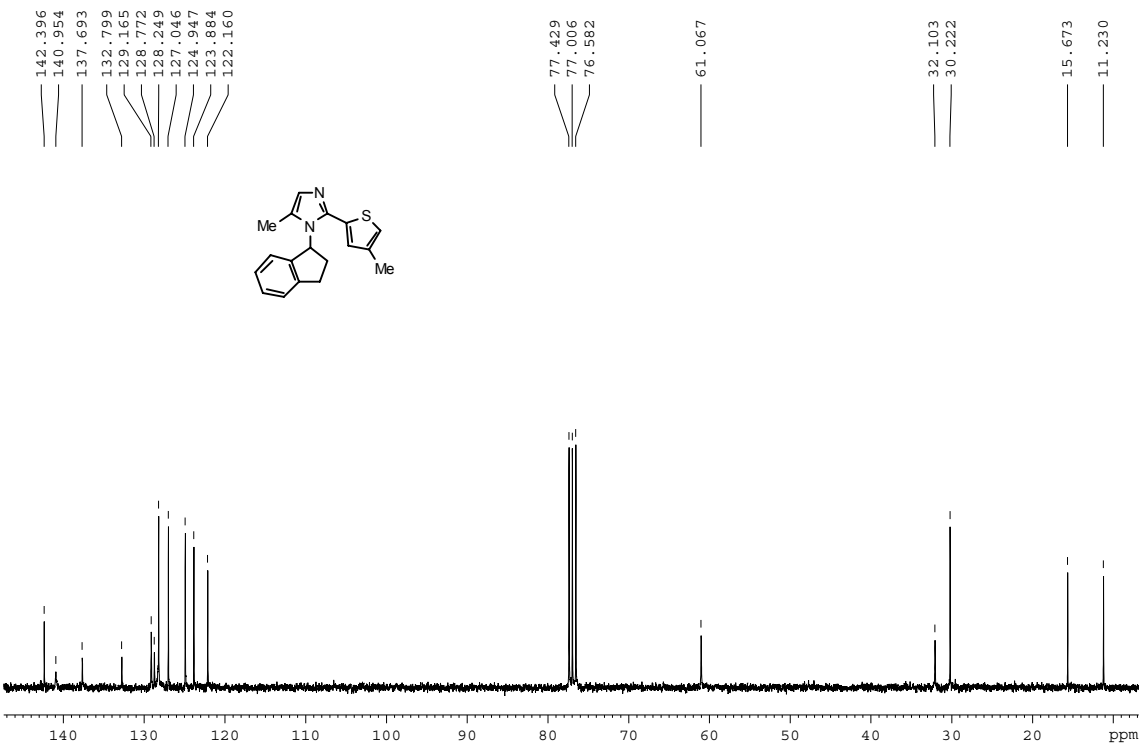
1-Indan-1-yl-5-methyl-2-(4-methyl-thiophen-2-yl)-1*H*-imidazole (14)

^{1}H NMR



^{13}C NMR



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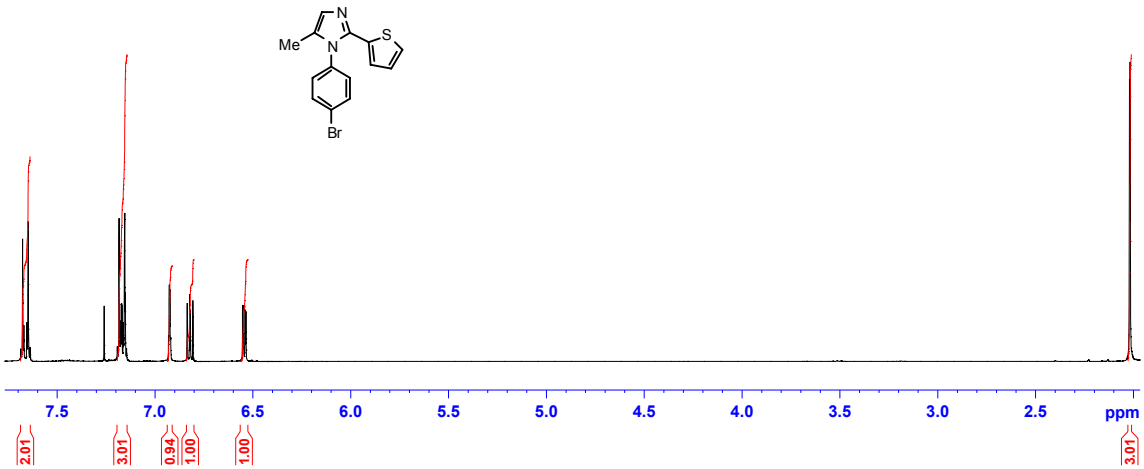
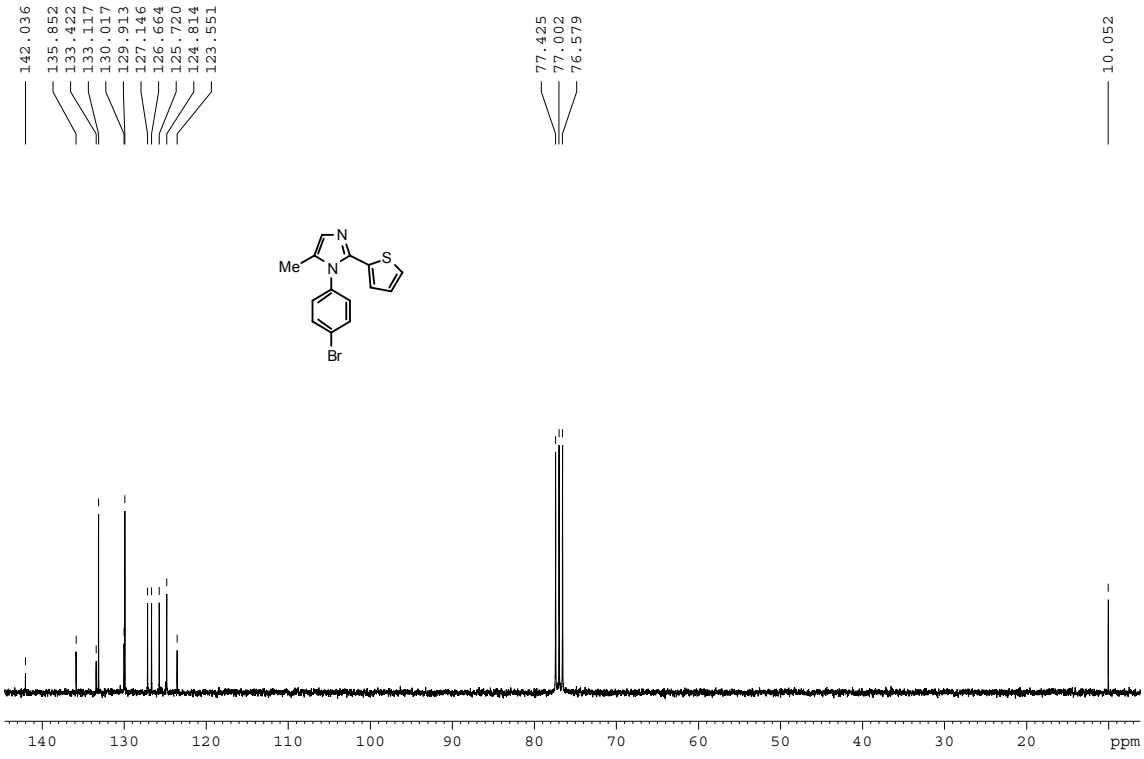
1-(4-Bromo-phenyl)-5-methyl-2-thiophen-2-yl-1*H*-imidazole (15)

^{1}H NMR

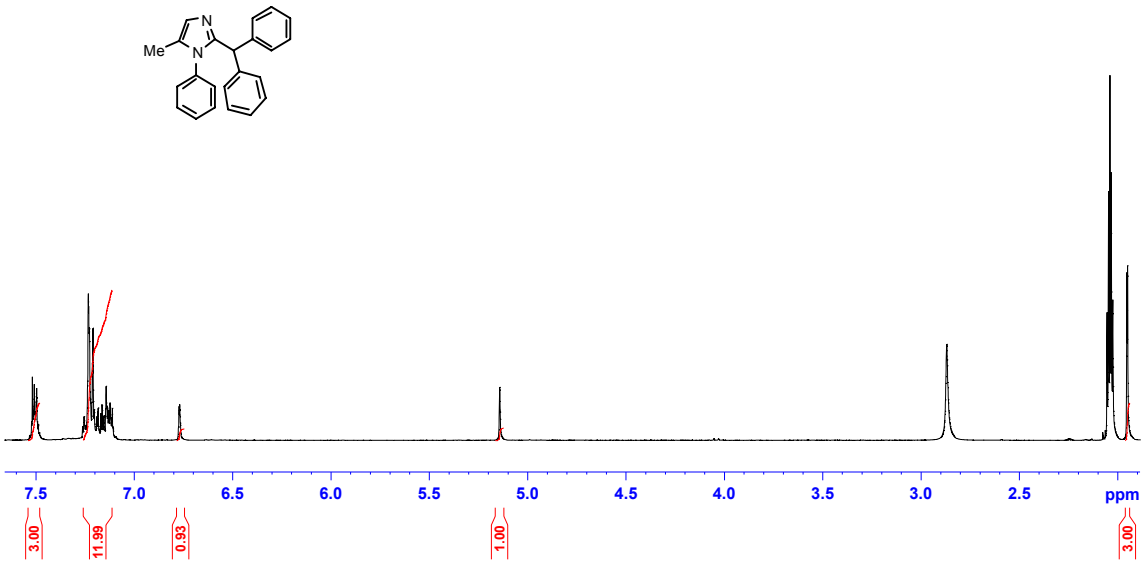


^{13}C NMR

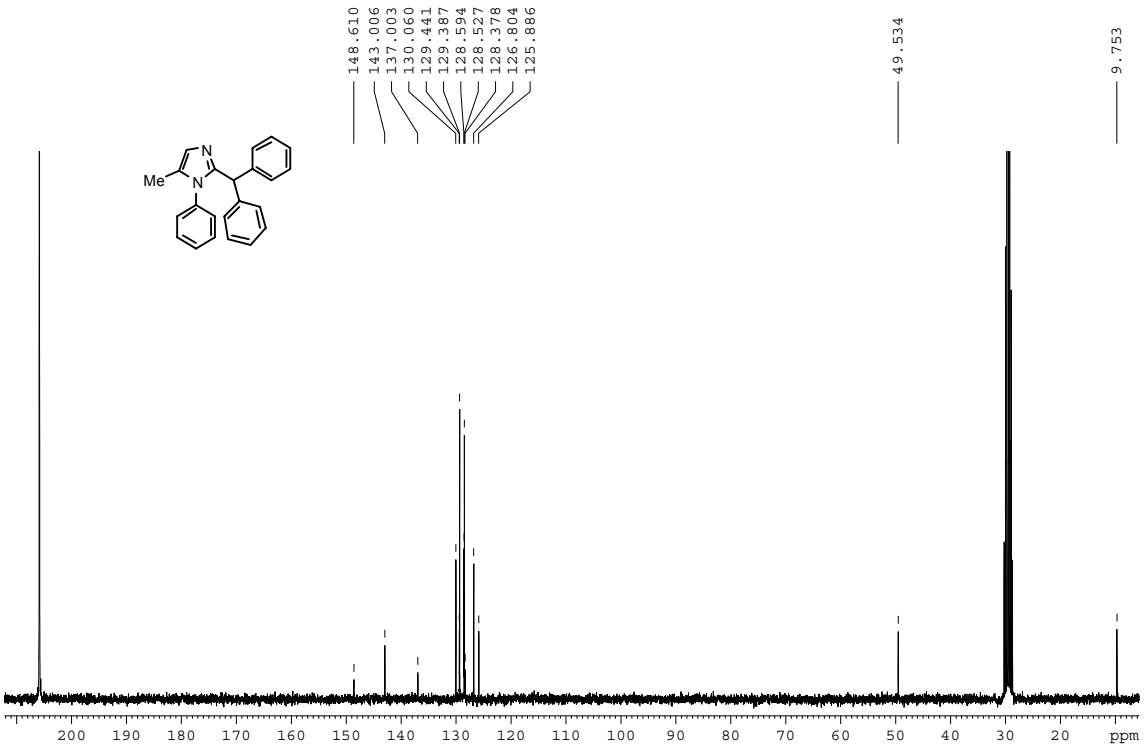


2-Benzhydryl-5-methyl-1-phenyl-1*H*-imidazole (16)

^{1}H NMR



^{13}C NMR



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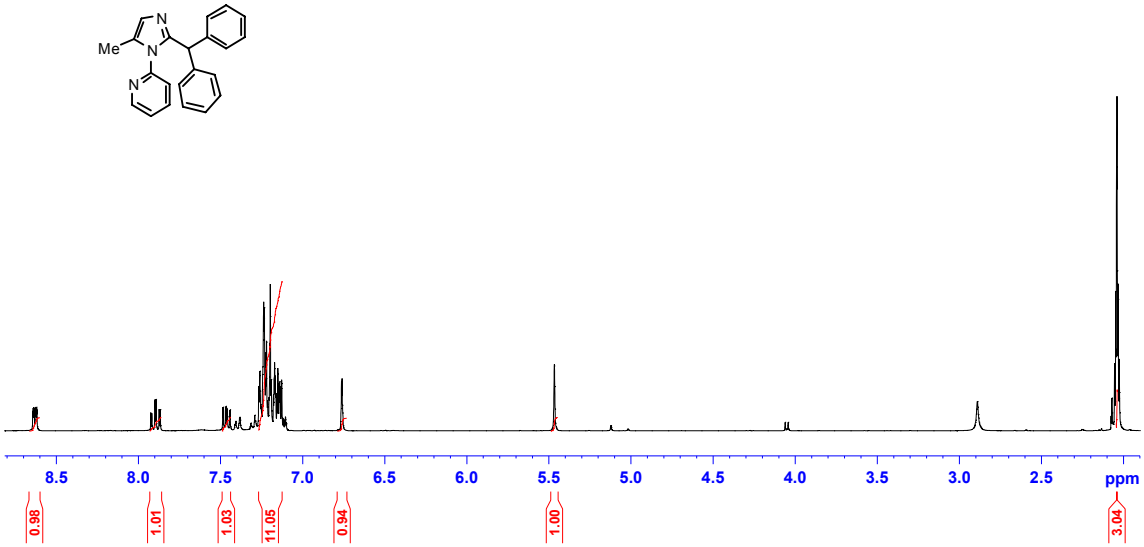
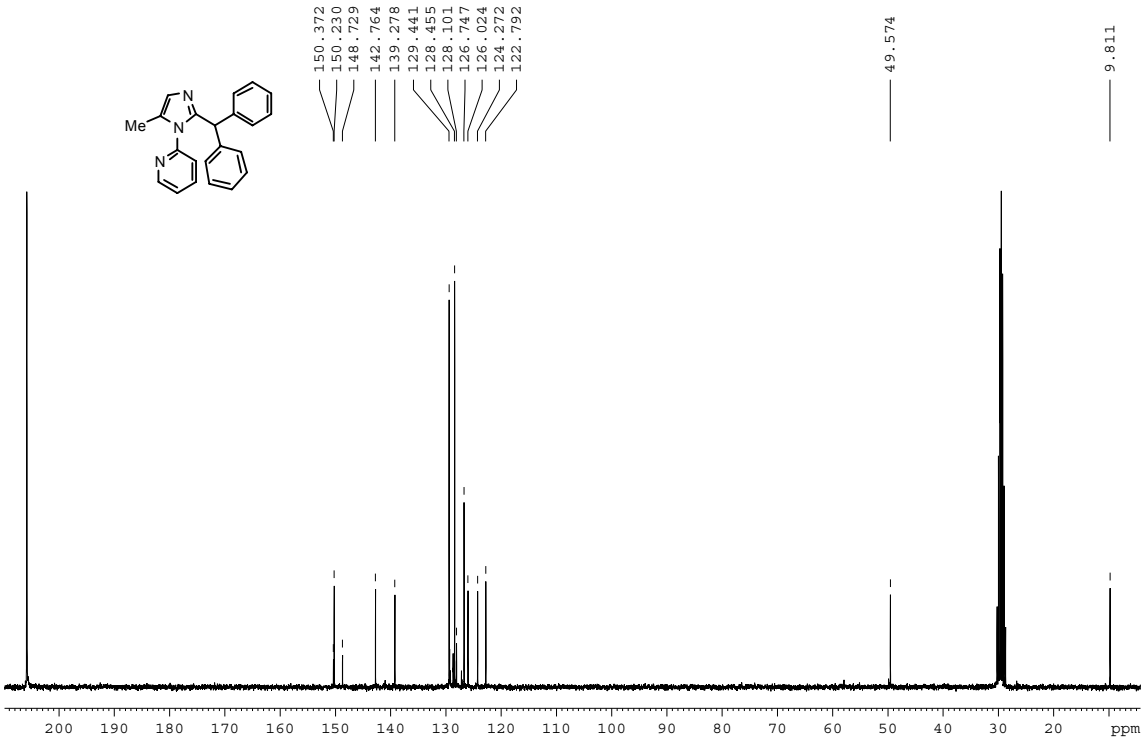
2-(2-Benzhydryl-5-methyl-imidazol-1-yl)-pyridine (17)

^{1}H NMR



^{13}C NMR



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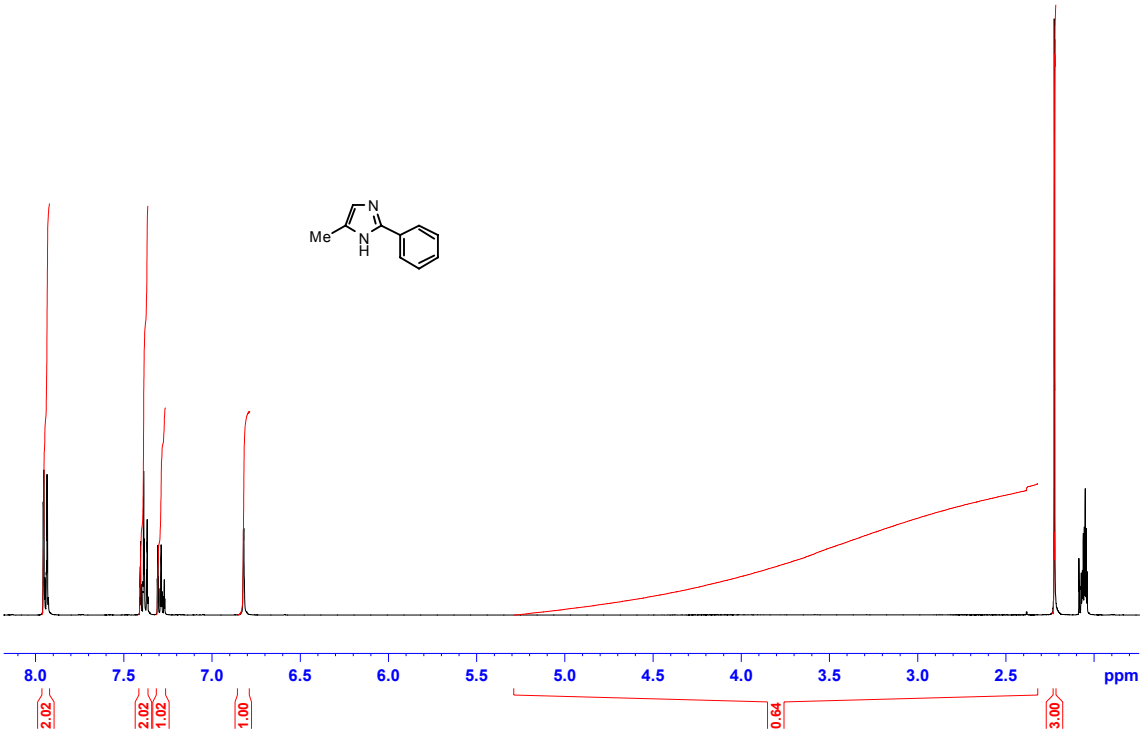
5(4)-Methyl-2-phenyl-1*H*-imidazole (18)

^{1}H NMR



^{13}C NMR