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# An easy one-step synthesis of imidazolin-2-ones from phthalic anhydrides and their antioxidant evaluation

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## 1 EXPERIMENTAL

### Chemistry

All reagents were purchased in the highest quality available and were used without further purification. The solvents used in column chromatography were obtained from commercial suppliers and used without distillation. Nuclear Magnetic Resonance of $^{1}$H (200 MHz) and $^{13}$C (50 MHz) spectra were recorded on a Varian Mercury 200 MHz Spectrometer in DMSO-$d_6$ with TMS as internal standard. Chemical Ionization Mass spectra were obtained at a GC-MS Varian Titan 4000 with ion trap, and the intensities were reported as a percentage relative to the base peak after the corresponding *m/z* value. Melting points were obtained on a Stuart apparatus model SMP30, the value is reported as an average of three separated experiments.

### General procedure for the synthesis of imidazolin-2-ones

To a solution of phthalic anhydride **1** in THF (1.0 mM) TMSA (4.0 equiv.) was added and the mixture was stirred at reflux temperature for 30 h. The resulting solution was concentrated *in vacuo* until a solid formed. The solid was washed with diethyl ether (5 x 4 ml) to obtain the imidazolin-2-ones in high purity.

**1*H*-Benz[*d*]imidazol-2(3*H*)-one (3a).** For full characterization see lit.[1]; yield 51%; mp 364-365 ºC; pale brown solid; $R_f$ 0.58 (acetonitrile); $^{1}$H-NMR (200 MHz, DMSO-$d_6$): δ

10.62 (s, 2 H), 6.93 (s, 4H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 155.1, 129.5, 120.3, 108.3; FT-IR (ATR): 3017, 2898, 2807, 1710, 1629, 1481, 1405, 1361, 1195, 1025 cm$^{-1}$; CG-MS *m/z*: 135 $[M+H]^+$

**5-(*tert*-Butyl)-1*H*-benz[*d*]imidazol-2(3*H*)-one (3b).** For full characterization see lit.[2]; yield 52%; mp 312-313 ºC; pale brown solid; $R_f$ 0.25 (acetonitrile); $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 10.47 (br s, 2H), 6.98-6.80 (m, 3H), 1.25 (s, 9H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 155.5, 143.1, 129.5, 127.4, 117.2, 107.9, 105.4, 34.2, 31.6; FT-IR (ATR): 2956, 1695, 1614, 1475, 1359, 1274, 1027 cm$^{-1}$; CG-MS *m/z*: 191 $[M+H]^+$

**5-Methyl-1*H*-benz[*d*]imidazol-2(3*H*)-one (3c).** For full characterization see lit.[2,3]; yield 77%; mp 301-302 ºC; pale brown solid; $R_f$ 0.50 (acetonitrile); $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 10.47 (d, *J*=6.6 Hz, 2H), 6.81-6.70 (m, 3H), 2.27 (s, 3H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 155.4, 129.8, 129.3, 127.4, 120.9, 109.0, 108.2, 21.0; FT-IR (ATR): 3100, 2998, 2917, 1677, 1637, 1612, 1506, 1477, 1373, 1209, 1027 cm$^{-1}$; CG-MS *m/z*: 149 $[M+H]^+$

**5-Fluoro-1*H*-benz[*d*]imidazol-2(3*H*)-one (3d).** For full characterization see lit.[2,3]; yield 50%; mp 299-300 ºC; white solid; $R_f$ 0.32 (acetonitrile); $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 10.77 (br. s, 1H), 10.66 (br. s, 1H), 6.91-6.68 (m, 3H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 158.0, 155.7, 155.1, 130.2, 126.0, 108.6, 106.3, 96.25; CG-MS *m/z*: 153 $[M+H]^+$

**1*H*-Imidazo[4,5-*b*]pyridin-2(3*H*)-one (3e).** For full characterization see lit.[1a,4]; yield 93%; mp 260-261 ºC; pale yellow solid; $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 11.31 (br s, 1H), 10.83 (br s, 1H), 7.84 (d, *J*=5.13 Hz, 1H), 7.21 (d, *J*=7.7 Hz, 1H), 6.92 (dd, $J_1$=7.7, $J_2$=5.13 Hz, 1H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 154.5, 144.8, 139.6, 123.7, 116.6, 114.4; FT-IR (ATR): 3002, 2898, 2790, 1681, 1631, 1612, 1581, 1430, 1363, 1226, 1184, 1045 cm$^{-1}$; CG-MS *m/z*: 136 $[M+H]^+$

**1*H*-Imidazo[4,5-*b*]pyrazin-2(3*H*)-one (3f).** For full characterization see lit.[1a,5]; yield 45%; mp >400 ºC; brown pale solid solid; $R_f$  (acetonitrilo); $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 11.73 (s, 2H), 7.83 (s, 2H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 153.9, 140.1, 134.4; CG-MS *m/z*: $[M+H]^+$

**4-Phenylimidazolidin-2-one (3g).** For full characterization see lit.[6]; yield 49%; mp 245-246 ºC; pale brown solid; $R_f$ 0.13 (acetonitrile); $^1$H-NMR (200 MHz, DMSO-$d_6$): δ 7.42-7.25 (m, 5H), 6.83 (s, 1H), 6.30 (s, 1H), 4.73 (dd, *J*=16.13, 1.1 Hz, 1H), 3.70 (t, *J*=8.8 Hz, 1H), 3.02 (td, $J$=8.07, 1.47 Hz, 1H); $^{13}$C-NMR (50 MHz, DMSO-$d_6$): δ 163.3, 142.8, 128.3, 127.2, 125.8, 55.2, 48.6; FT-IR (ATR): 3307, 2989, 1627, 1614, 1517, 1488, 1463, 1392, 1280, 1176, 1027 cm$^{-1}$; CG-MS $m/z$: 163 [M+H]$^+$, 325 [2M+H]$^+$

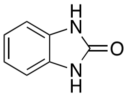
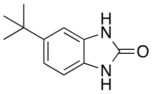
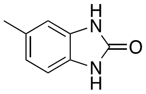
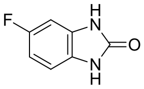
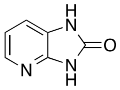
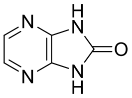
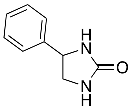
## DPPH-scavenging Activity

The DPPH• scavenging activities of the imidazolin-2-ones **3** were assessed as described by Sivakumar[7] with slight modifications. This method is based on the reduction of DPPH in the presence of antioxidants. Antioxidant activity is detected as a change from purple to yellow color in the solution. Briefly, a solution of DPPH (0.10 mM) in methanol (grade HPLC) was prepared. Then, 50 µl of the synthetic compounds (1, 5, 10, 15, 20, 25 and 100 µg ml$^{-1}$ in methanol) was mixed with 1.950 ml of the DPPH solution and the mixture is incubated for 20 min at room temperature in darkness conditions, and the absorbance was measured at 517 nm (Spectronic Genesys 5). The DPPH•-scavenging activity was calculated as follows:

$$DPPH\cdot\ scavenging\ effect\ (\%) = \left[\frac{A_0 - A_1}{A_0}\right] x100$$

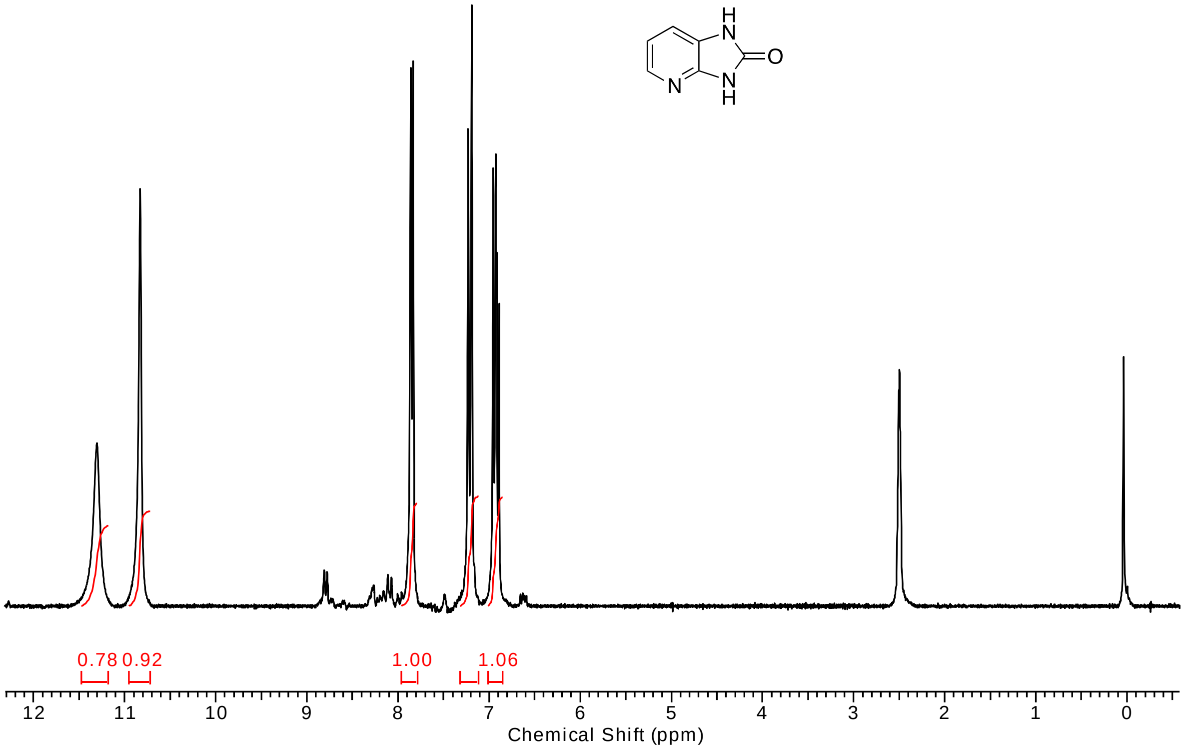
Where: $A_0$ was the absorbance of control; and $A_1$ was the absorbance in the presence of the synthetic compounds. The same methodology was using for assay the references standard Vitamin C and Gallic acid (0.1 – 25 µg ml$^{-1}$ in methanol). The assay compounds and reference standard are expressed as inhibitory concentration mean ($IC_{50}$) and was calculated from graph of X (concentration of compounds tested) vs Y (%DPPH-scavenging effect) using GraphPad Prism Software V6 (linear regression analysis; for $IC_{50}$ unknowns values were interpolate from standard curve with 95% confidence interval of X when Y is 50% of DPPH-scavenging effect).

**Table S1** Antioxidant activity of synthesized imidazolin-2-ones.

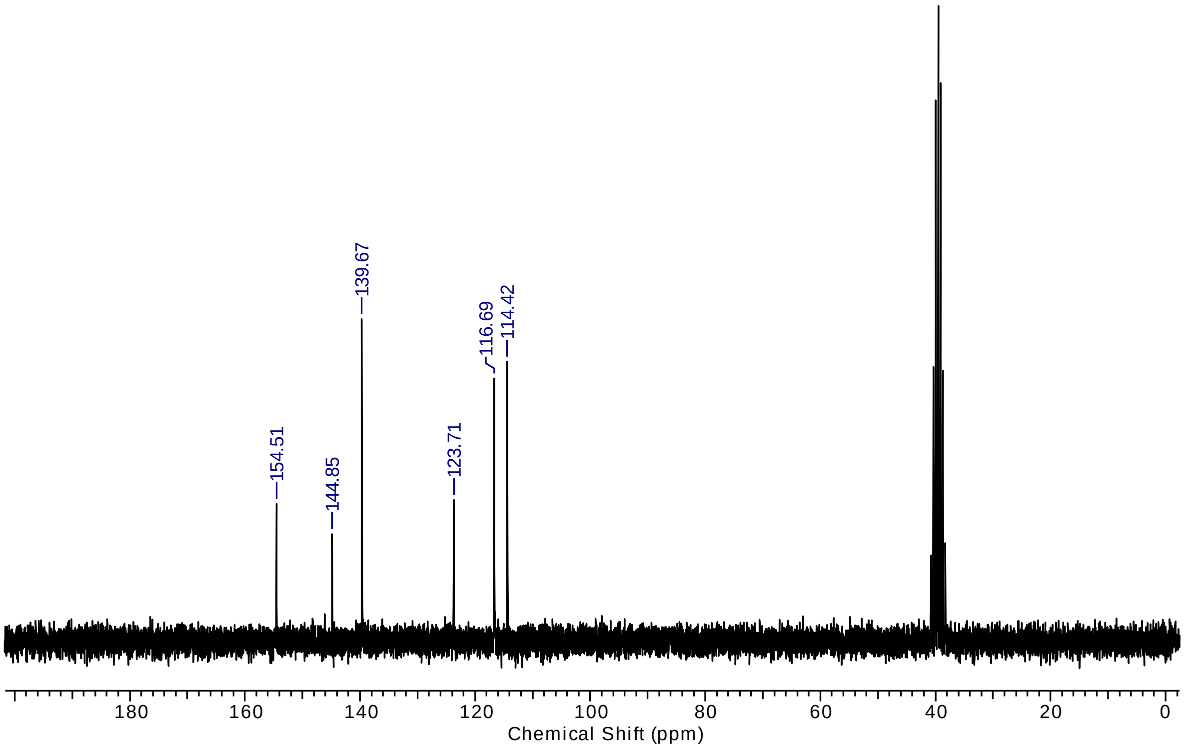
| Entry | Compound | IC$_{50}$ (µg mL$^{-1}$) | DPPH scavenging effect at 25 µg mL$^{-1}$ | Statistical parameters |
|---|---|---|---|---|
| **3a** |  | 2898 | 0.733 ± 0.431 | r$^2$ = 0.9798<br>Y = 0.01713X + 0.3515 |
| **3b** |  | 497 | 2.51 ± 0.134 | r$^2$ = 0.7946<br>Y = 0.1013X – 0.3265 |
| **3c** |  | 660 | 2.32 ± 1.335 | r$^2$ = 0.9309<br>Y = 0.0.7509X + 0.4165 |
| **3d** |  | 595 | 1.04 ± 0.241 | r$^2$ = 0.9694<br>Y = 0.08305X + 0.5484 |
| **3e** |  | 315 | 3.54 ± 0.266 | r$^2$ = 0.9781<br>Y = 0.1597X – 0.2906 |
| **3f** |  | 384 | 2.88 ± 0.347 | r$^2$ = 0.9405<br>Y = 0.1319X – 0.6621 |
| **3g** |  | 918 | 2.60 ± 1.102 | r$^2$ = 0.9887<br>Y = 0.05303X + 1.303 |
|  | Vitamin C | 10.21 | 96.37 ± 0.560 | r$^2$ = 0.9997<br>Y = 4.736X + 1.658 |
|  | Gallic acid | 10.40 | 94.30 ± 0.444 | r$^2$ = 0.9999<br>Y = 4.614X + 2.020 |

## 1*H*-imidazo[4,5-*b*]pyridin-2(3*H*)-one (3e).

### $^1$H-NMR

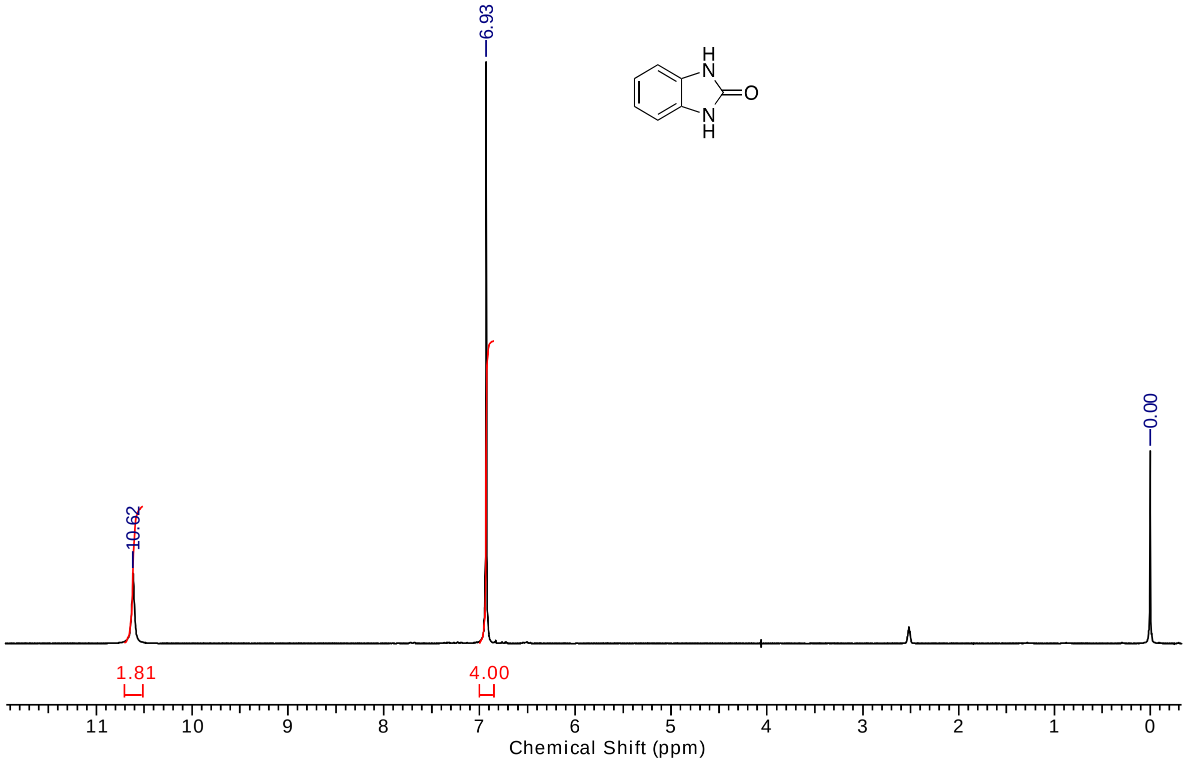


### $^{13}$C-NMR

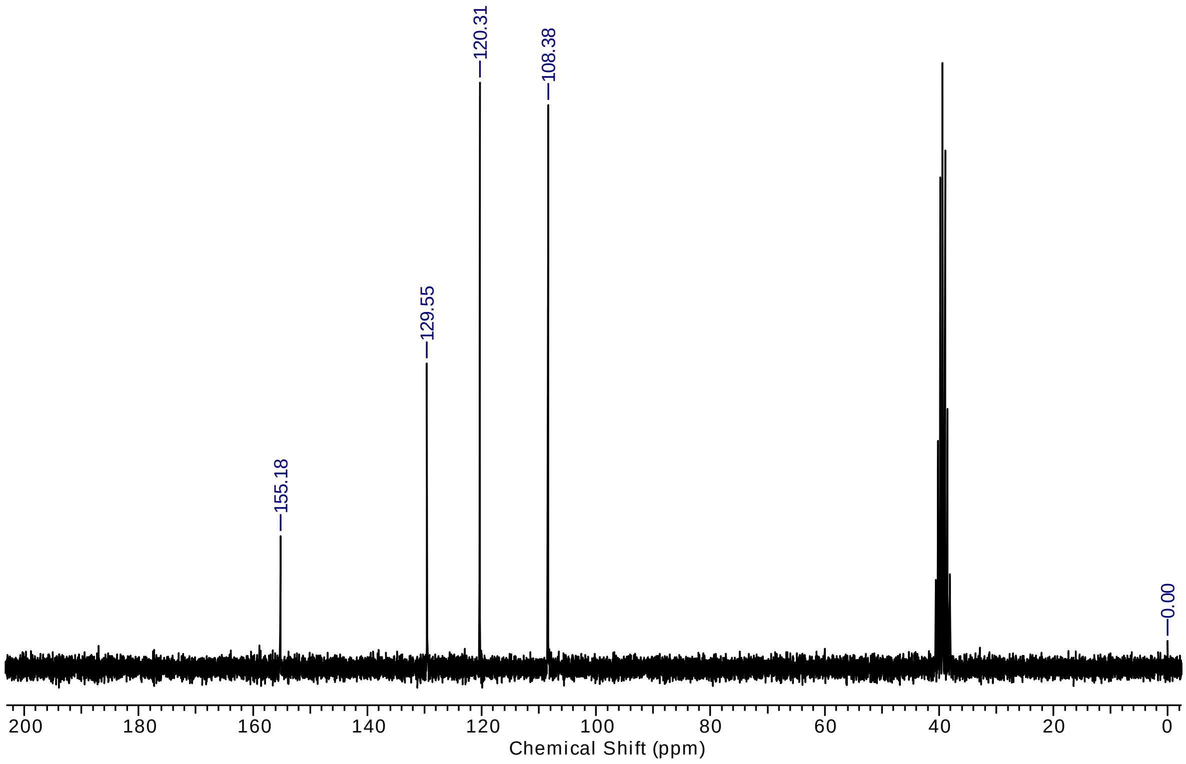


## 1*H*-benzo[*d*]imidazol-2(3*H*)-one (3a)

### $^{1}$H-NMR

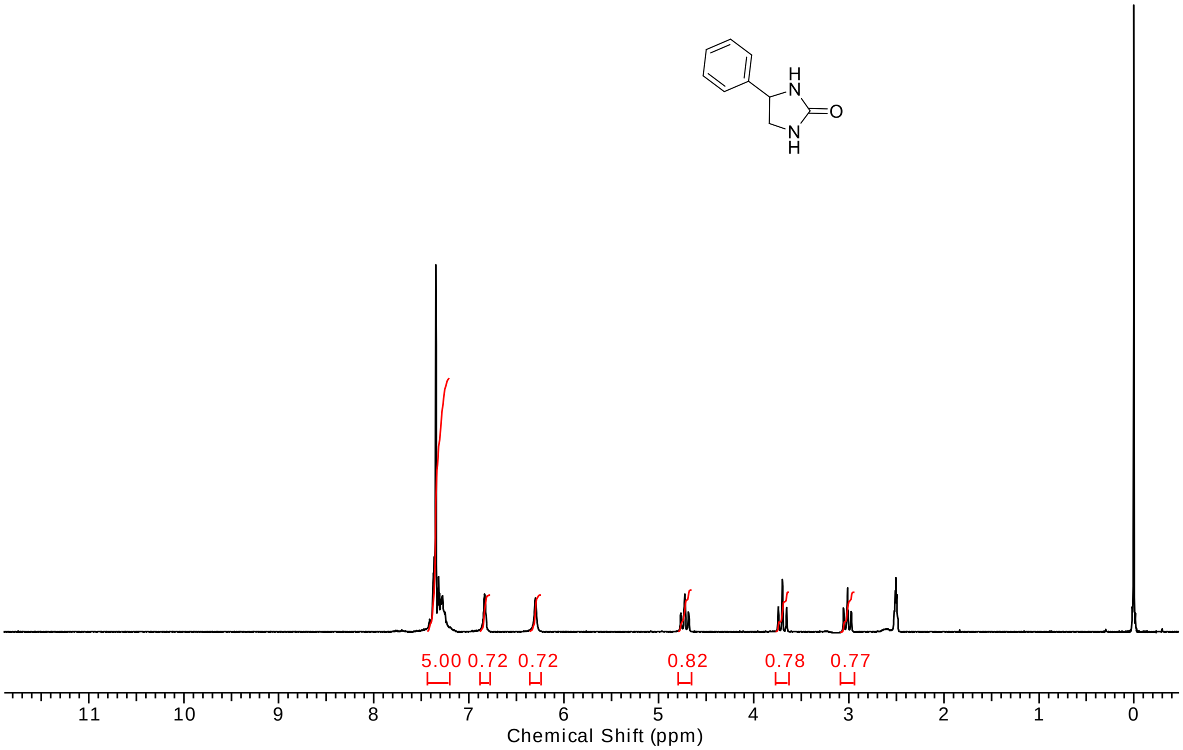


### $^{13}$C-NMR

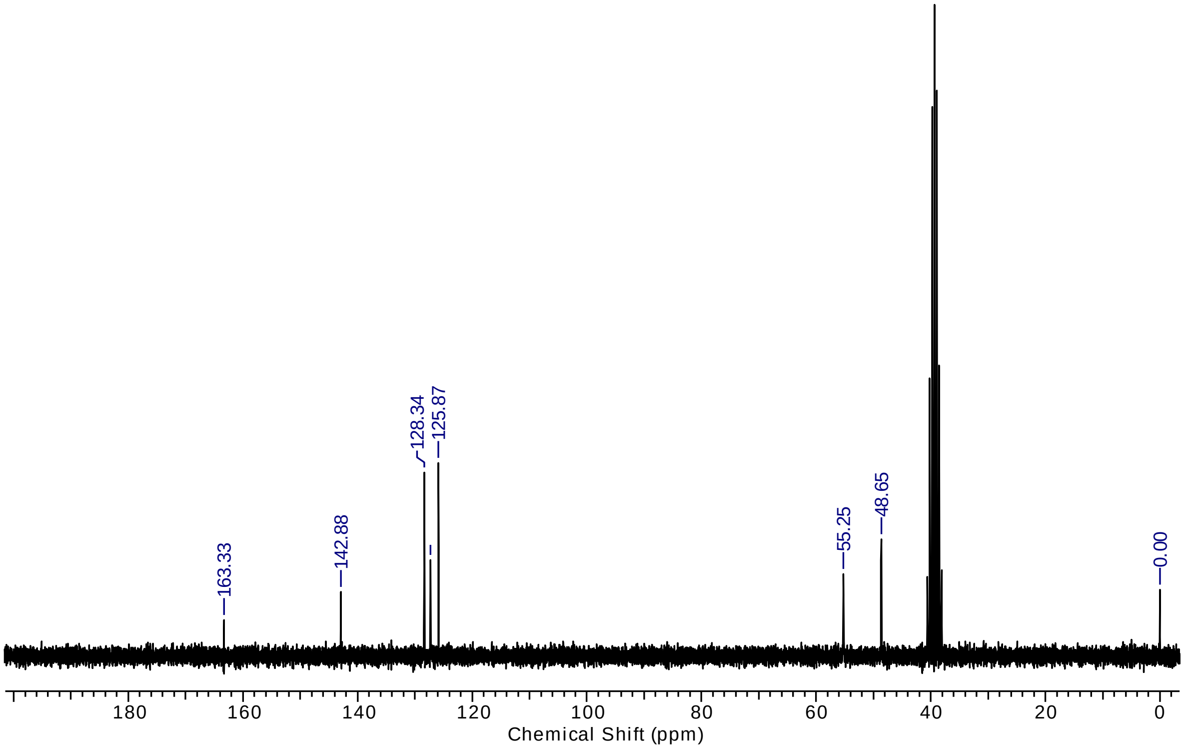


# 4-phenylimidazolidin-2-one (3g)

## $^1$H-NMR

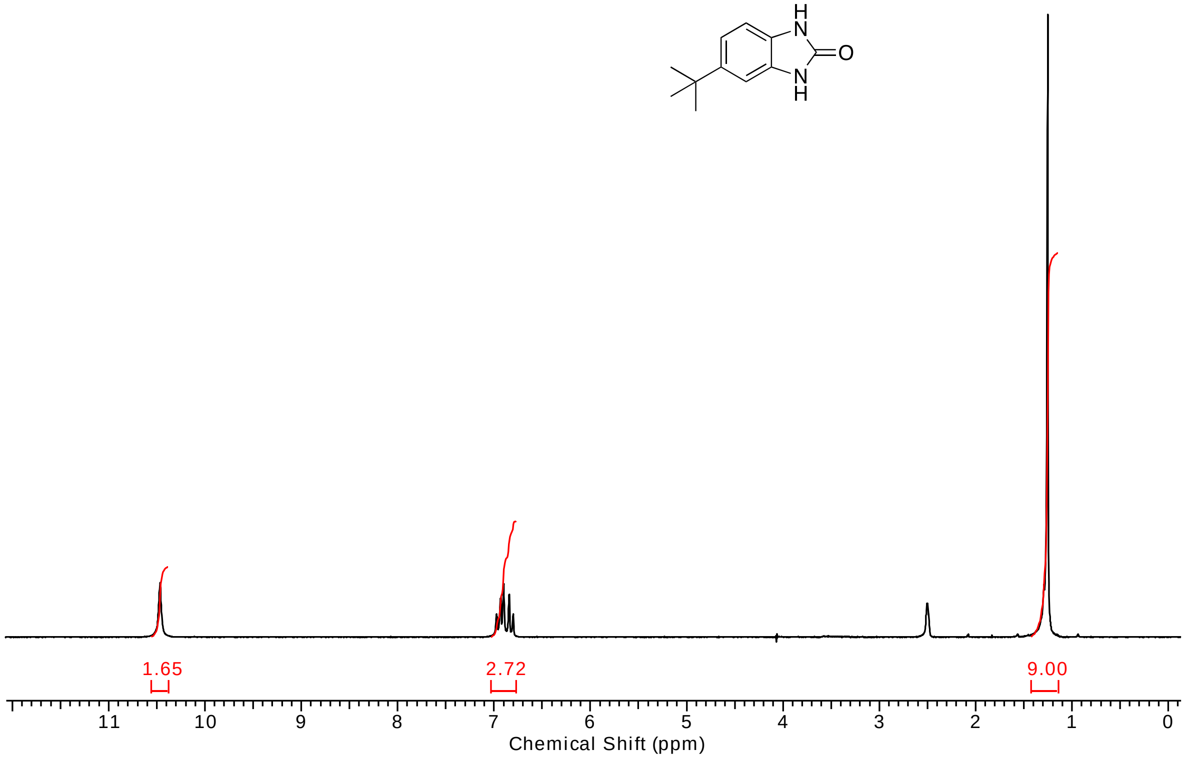


## $^{13}$C-NMR

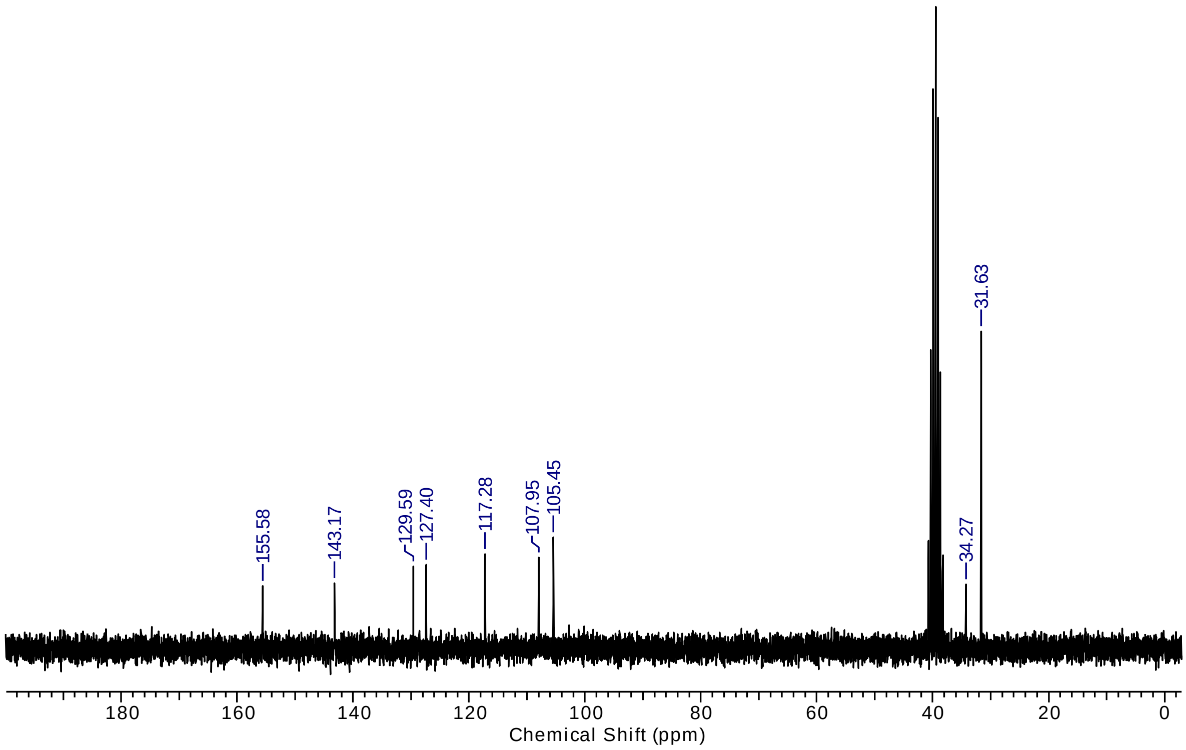


## 5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (3b)

### $^1$H-NMR

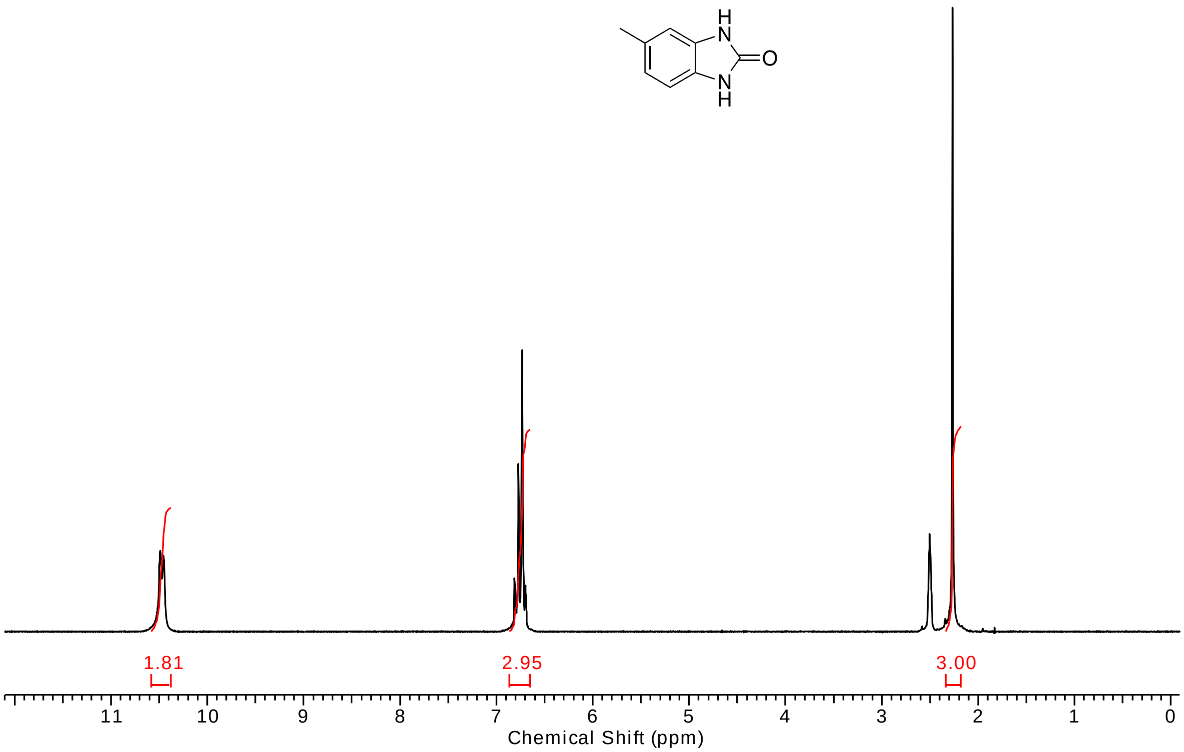


### $^{13}$C-NMR

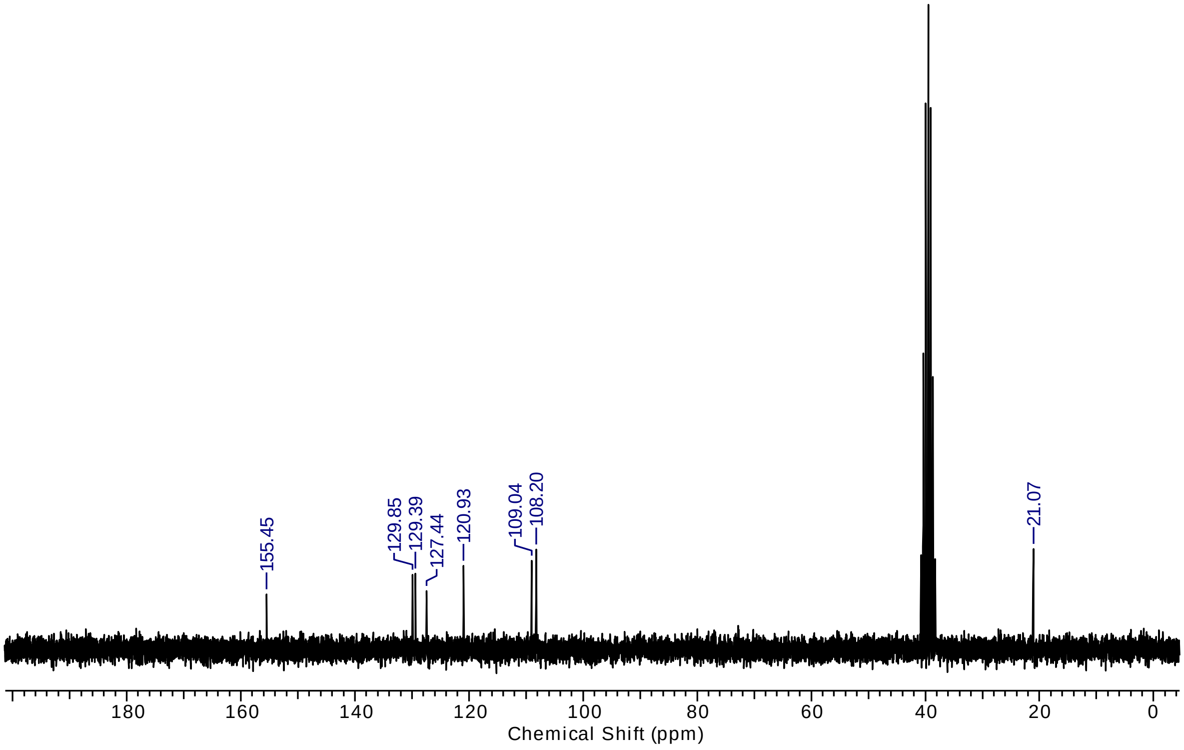


## 5-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one (3c)

### $^{1}$H-NMR

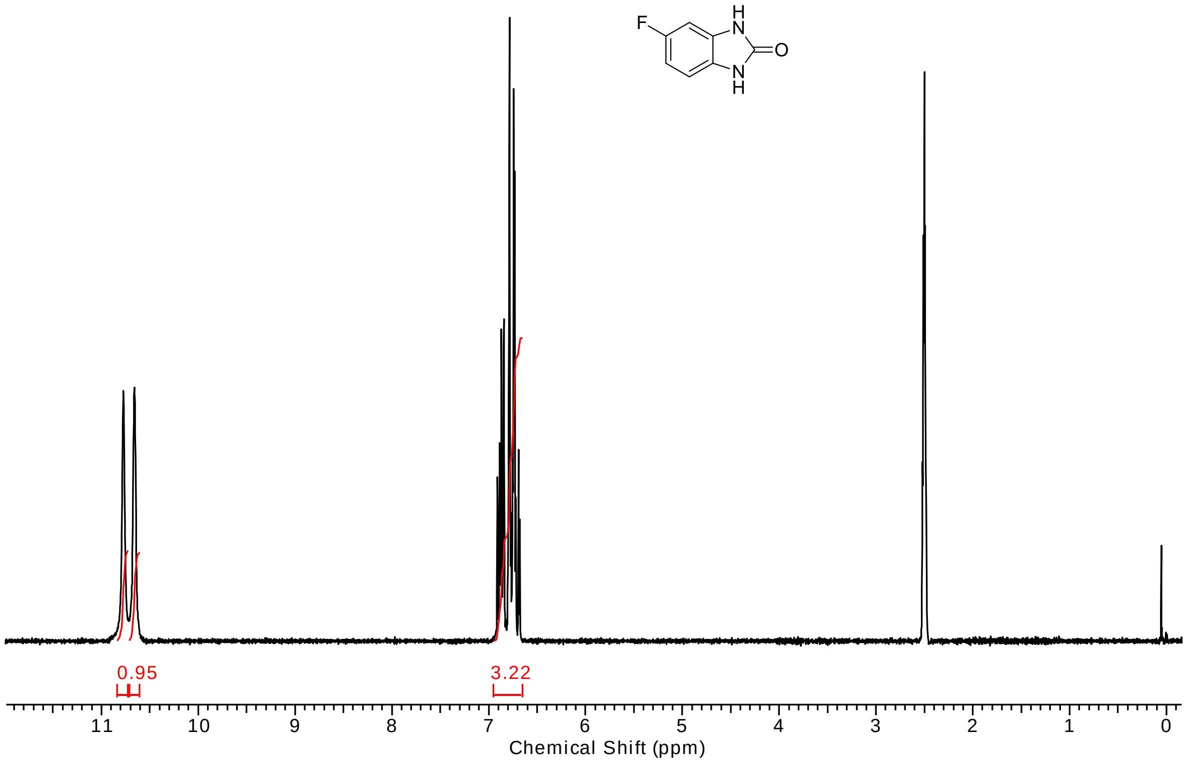


### $^{13}$C-NMR

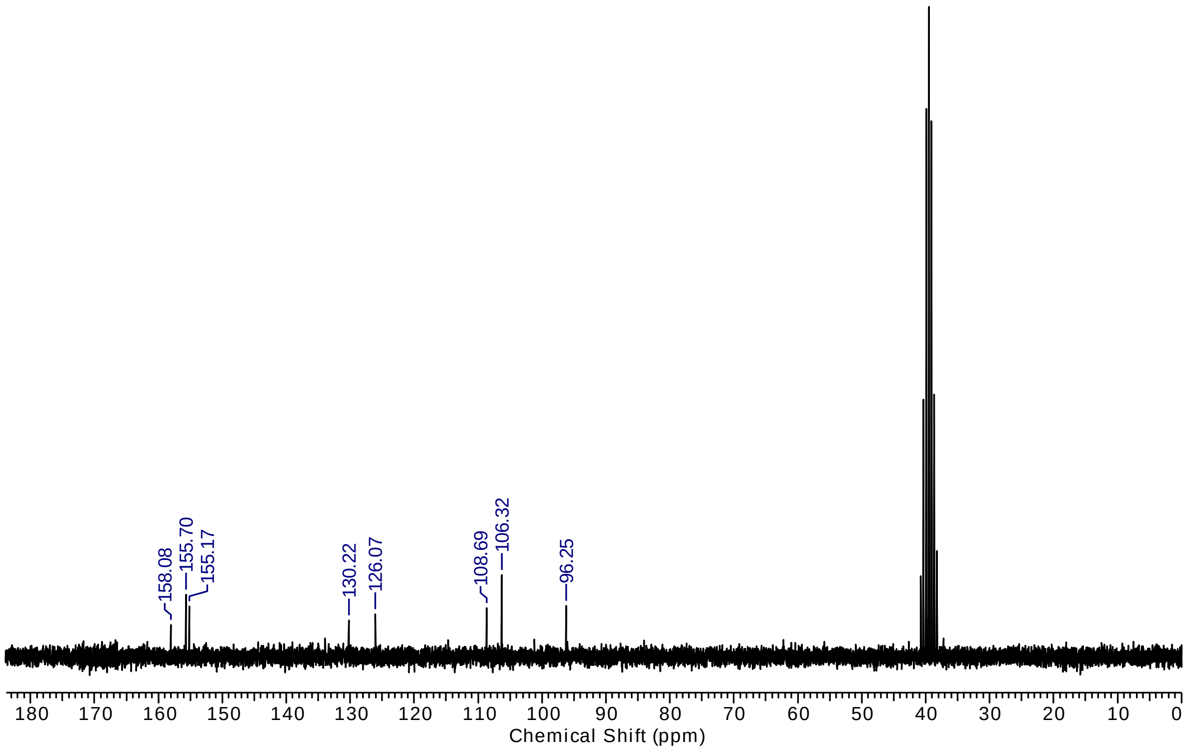


## 5-fluoro-1*H*-benzo[*d*]imidazol-2(3*H*)-one (3d)

### $^{1}$H-NMR

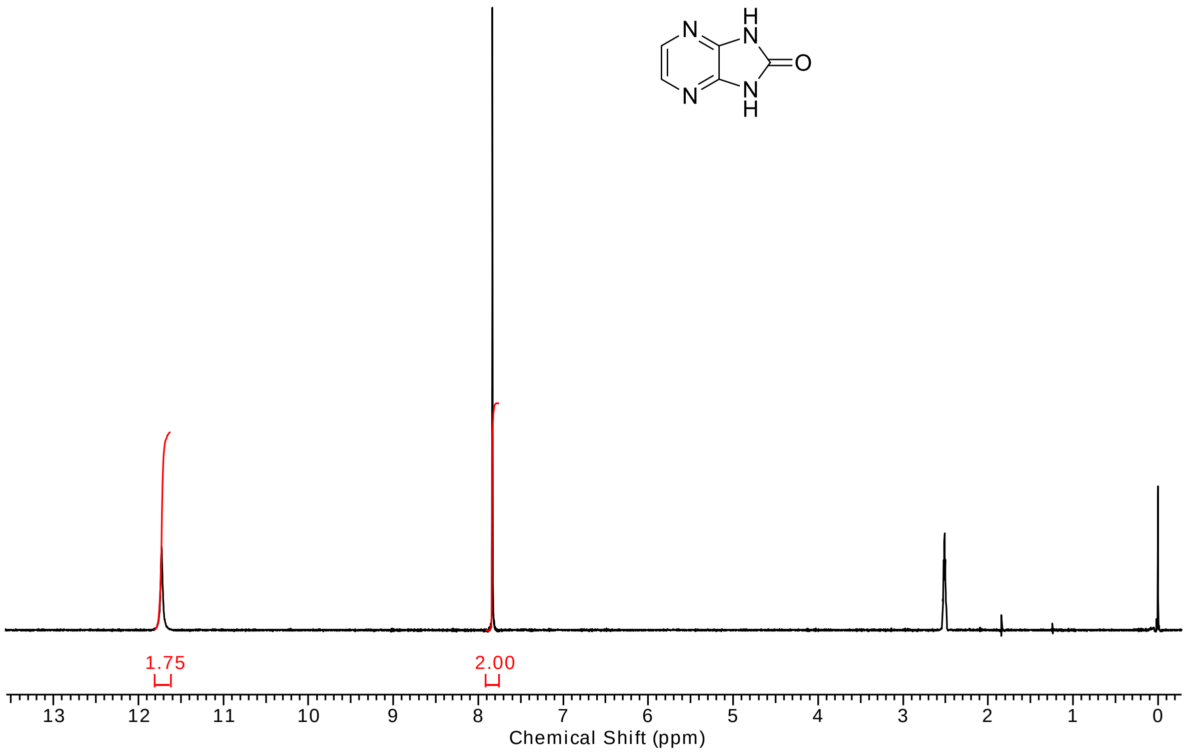


### $^{13}$C-NMR

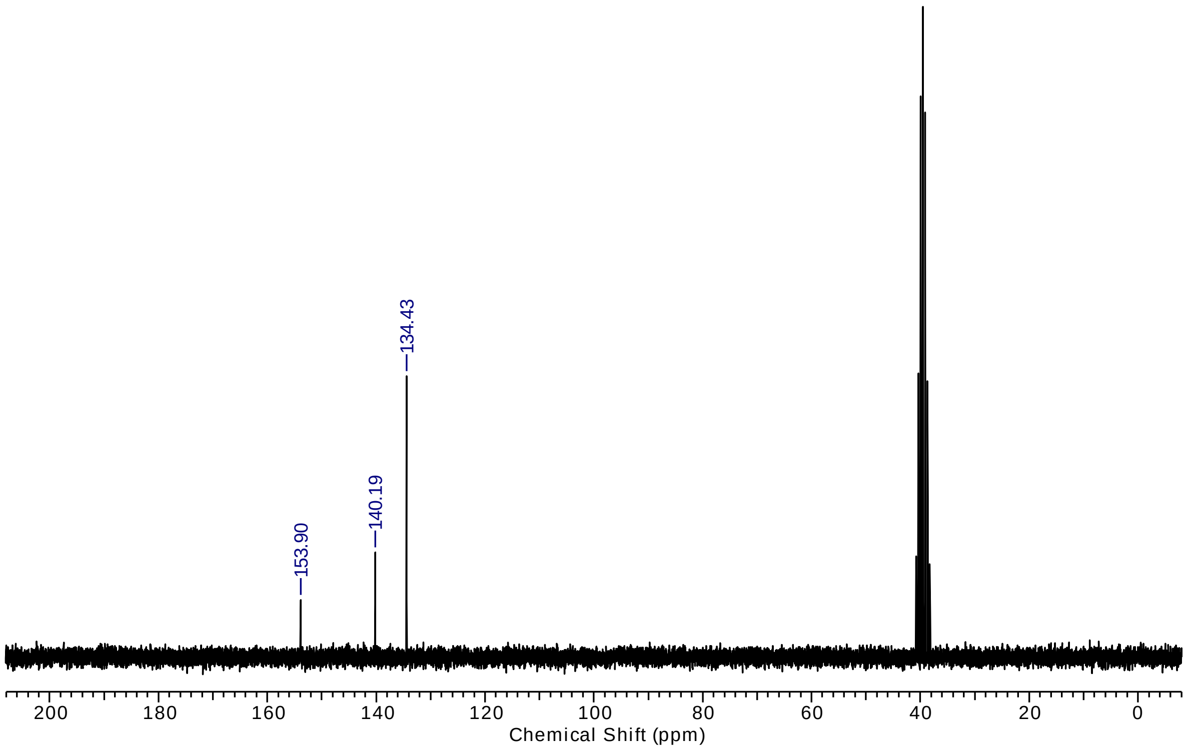


## 1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one (3f)

### $^{1}$H-NMR



### $^{13}$C-NMR



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