**A Two-Stage Iterative Process for the Synthesis of Polyoxazoles**

**Jeffery M. Atkins and Edwin Vedejs**

*Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109*

**Supporting Information**

## General Experimental

Unless otherwise specified, solvents were dried over activated alumina. Tosylmethyl isocyanide (TosMIC), glyoxylic acid monohydrate, and hexachloroethane were purchased from Aldrich and used with no further purification. Dimethylformamide (DMF) was dried over 3Å molecular sieves for 3 days and then distilled from $P_2O_5$. Organolithium reagents were titrated prior to use with diphenylacetic acid. Analytical thin-layer chromatography (tlc) was run on Whatman Partisil 250 μm K6F silica gel 60 Å plates visualized with the aid of UV light, iodine vapor, or $KMnO_4$ stain. Preparatory plate chromatography was run using Whatman 1000 μm Partisil PK6F silica gel 60 Å plates (20 cm x 20 cm). Flash chromatography was run using Whatman Silica Gel; Purasil 60A (230-400 mesh). Unless otherwise specified, all reactions were performed with either flame or oven dried glassware under an $N_2$ atmosphere.

4-Phenyl oxazole was made using the one-step procedure of Whitney, et. al.[1] 5-Phenyl oxazole was made using the procedure of Van Leusen, et. al.[2] 5-Phenethyl oxazole and 5-ethoxycarbonyl oxazole were made using the procedure of Schöllkopf et. al., with modifications.[3] 5-(2-Thiophenyl)oxazole was made using the procedure of Van Leusen, et. al.[4]

**2-Chloro-4-phenyloxazole (5a).**[5] To a solution of 4-phenyl oxazole[1] (0.114 g, 0.768 mmol) in anhydrous THF (4.0 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (0.44 mL of a 1.98 M in hexanes, 0.864 mmol) via syringe. Solid hexachloroethane (0.279 g, 1.179 mmol) was added to the resulting red solution after it had stirred at –78 °C for 20 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with $Et_2O$ and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by preparatory plate chromatography on silica gel (20 cm x 20 cm, 1000μm), eluent 1:5 EA/ hexanes to give 0.103 g (73%) of **(5a)** as a yellow-white solid; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.64. Recrystallized from hexanes, mp = 67-68 °C. IR (neat, $cm^{-1}$) 3114 (CH), 1764 (C=N), 1524 (C=C). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 7.87 (1H, s), 7.68 (2H, d, J = 7.3 Hz), 7.40 (2H, t, J = 7.2 Hz), 7.34 (1H, t, J = 7.2 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 147.2, 142.7, 135.4, 129.7, 128.8, 128.6, 125.3.

**2-Chloro-5-phenyloxazole (5b).** To a solution of 5-phenyl oxazole[2] (2.0 g, 13.8 mmol) in anhydrous THF (70 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (7.24 mL of a 2.1 M in hexanes, 15.2 mmol) via syringe. Solid hexachloroethane (4.9 g, 20.7 mmol) was added to the resulting red solution after it had stirred at –78 °C for 30 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with $Et_2O$ and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $MgSO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by flash chromatography on silica gel (20 x 3.5 cm), 100 mL hexanes, then 5%

EA/hexanes eluent to give 2.42 g (98%) of **(5b)** as a yellow-white solid; analytical TLC on silica gel 1:5 EA/Hex, Rf = 0.54. The product was identified by comparison to published spectra.[6]

**2-Chloro-5-phenethyloxazole (5c).** To a solution of 5-phenethyloxazole[3] (0.123 g, 0.710 mmol) in anhydrous THF (3.5 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (0.49 mL of a 1.59 M in hexanes, 0.781 mmol) via syringe. Solid hexachloroethane (0.252 g, 1.07 mmol) was added to the resulting deep yellow solution after it had stirred at –78 °C for 20 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with $Et_2O$ and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $MgSO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by preparatory plate chromatography on silica gel (20 cm x 20 cm, 1000μm), eluent 1:5 EA/hexanes to give 0.137 g (93%) of **(5c)** as a clear oil; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.46. HRMS calcd for $C_{11}H_{10}ClNO$: 207.0451: found m/z = 207.0444, error = 3 ppm; IR (neat, $cm^{-1}$) 3027 (CH), 2929 (CH), 1605 (C=N); $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 7.29 (2H, t, J = 7.3 Hz), 7.21 (1H, t, J = 7.6 Hz), 7.16 (2H, d, J = 7.1 Hz), 6.66 (1H, s), 2.93 (4H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 154.6, 145.2, 139.8, 128.5, 128.2, 126.4, 124.6, 33.5, 27.5.

**2-Chloro-5-(thiophen-2-yl)oxazole (5d).** To a solution of 5-(thiophen-2-yl)oxazole[4] (0.103 g, 0.681 mmol) in anhydrous THF (3.4 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (0.38 mL of a 1.98 M in hexanes, 0.749 mmol) via syringe. Solid hexachloroethane (0.241 g, 1.02 mmol) was added to the resulting red solution after it had stirred at –78 °C for 20 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with $Et_2O$ and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by preparatory plate chromatography on silica gel (20cm x 20 cm, 1000μm), 1:5 EA/hexanes eluent to give 0.101 g (80%) of **(5d)** as a yellow oil; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.54. HRMS calcd for $C_7H_4ClNOS$: 184.9702: found m/z = 184.9702, error = 1 ppm; IR (neat, $cm^{-1}$) 3110 (CH), 1615 (C=N), 1517 (C=C); $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 7.34 (1H, d, J = 5.1 Hz), 7.28 (1H, d, J = 3.5 Hz), 7.13 (1H, s), 7.07 (1H, t, J = 4.9 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 149.1, 145.5, 128.3, 127.8, 126.2, 124.9, 122.9.

**2-Chloro-5-(ethoxycarbonyl)oxazole (5e).** To a solution of 5-(ethoxycarbonyl)oxazole[4] (0.300 g, 2.13 mmol) in anhydrous THF (10.6 mL) at –42 °C under a $N_2$ atmosphere was slowly added a solution of LiHMDS (0.427 g, 2.55 mmol in 3.6 mL THF) via cannula. Solid hexachloroethane (0.773 g, 3.27 mmol) was added to the resulting yellow solution after it had stirred at –42 °C for 30 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with $Et_2O$ and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by flash chromatography on silica gel (12 x 2 cm), 75 mL hexanes, then 5% EA/hexanes eluent. Fractions 16-27 were collected to give 0.251 g (67%) of **(5e)** as a clear oil; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.52. HRMS calcd for $C_6H_6ClNO_3$: 175.0036: found m/z = 175.0036, error = 1 ppm; IR (neat, $cm^{-1}$) 2985 (CH), 1727 (C=O), 1588 (C=N), $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 7.71 (1H, s), 4.41 (2H, q, J = 7.1 Hz), 1.40 (3H, t, J = 7.3 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 156.4, 150.0, 144.5, 135.0, 61.8, 14.1.

**4-Phenyl-[2,4']bisoxazole (8a).** TosMIC (0.075 g, 0.385 mmol) was added to a suspension of NaH (0.036 g, 0.899 mmol, 60% dispersion in mineral oil) in DMF (1.5 mL) at 0 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2-chloro-4-phenyloxazole **(5a)** (0.046 g, 0.254 mmol) in DMF (0.8 mL) at 0 °C was slowly added via cannula to the mixture. After 1.5 h, solid glyoxylic acid monohydrate (0.051 g, 0.558 mmol) and $K_2CO_3$ (0.134 g, 0.977 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (7 x 1 cm), 1:5 EA/hexanes eluent to give 0.039 g (72%) of **(8a)** as a white solid; analytical TLC on silica gel 1:5 EA/Hex, Rf = 0.25. Recrystallized from toluene/hexanes, mp = 106-107 °C. HRMS calcd for $C_{12}H_8N_2O_2Na$: 235.0483: found m/z = 235.0487 [ESI, $M+Na^+$], error = 2 ppm; IR (neat, $cm^{-1}$) 3142 (CH), 1633 (C=N), 1539 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.32 (1H, s), 8.01 (1H, s), 7.98 (1H, s), 7.82 (2H, d, J = 7.3 Hz), 7.42 (2H, t, J = 7.4 Hz), 7.33 (1H, t, J = 7.3 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 155.0, 151.7, 142.0, 138.6, 133.5, 130.5, 130.3, 128.7, 128.3, 125.6.

**5-Phenyl-[2,4']bisoxazole (8b).** TosMIC (0.082 g, 0.418 mmol) was added to a suspension of NaH (0.039 g, 0.977 mmol, 60% dispersion in mineral oil) in DMF (1.5 mL) at 0 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2-chloro-5-phenyloxazole **(5b)** (0.050 g, 0.279 mmol) in DMF (1.0 mL) at 0 °C was slowly added via cannula to the mixture. After 1.5 h, solid glyoxylic acid monohydrate (0.051 g, 0.558 mmol) and $K_2CO_3$ (0.135 g, 0.977 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with $Et_2O$ and satd $NaHCO_3$. The aqueous layer was washed with $Et_2O$, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by prep plate chromatography on silica gel (20 x 20 cm), 1:1 EA/hexanes eluent to give 0.048 g (81%) of **(8b)** as a yellow solid; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.11. mp = 97-98 °C. HRMS calcd for $C_{12}H_8N_2O_2Na$: 235.0483: found m/z = 235.0481 [ESI, $M+Na^+$], error = 1 ppm; IR (neat, $cm^{-1}$) 3099 (CH), 1630 (C=O), 1528 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.32 (1H, s), 8.02 (1H, s), 7.73 (2H, d, J = 7.2 Hz), 7.45 (1H, s), 7.44 (2H, t, J = 7.5 Hz), 7.35 (1H, t, J = 7.3 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 154.2, 151.8, 151.5, 138.4, 130.4, 128.9, 128.7, 127.5, 124.3, 123.1.

**5-Phenethyl-[2,4']bisoxazole (8c).** TosMIC (0.064 g, 0.325 mmol) was added to a suspension of NaH (0.030 g, 0.760 mmol, 60% dispersion in mineral oil) in DMF (1.1 mL) at 25 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2-chloro-5-phenethyloxazole **(5c)** (0.045 g, 0.217 mmol) in DMF (0.9 mL) at 25 °C was slowly added via cannula to the mixture. After 300 min, solid glyoxylic acid monohydrate (0.040 g, 0.434 mmol) and $K_2CO_3$ (0.105 g, 0.760 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (8 x 1 cm), 1:5 EA/hexanes eluent to give 0.033 g (64%) of **(8c)** as a yellow gum; analytical TLC on silica gel 1:3 EA/hexanes, Rf =

0.18. mp = 66-69 °C. HRMS calcd for $C_{14}H_{12}N_2O_2Na$: 263.0796: found m/z = 263.0798 [ESI, $M+Na^+$], error = 1 ppm; IR (neat, $cm^{-1}$) 3132 (CH), 1733 (C=N), 1594 (C=C); $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.22 (1H, s), 7.98 (1H, s), 7.30 (2H, t, J = 7.3 Hz), 7.21 (3H, m), 6.82 (1H, s), 3.03 (1H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ153.8, 152.4, 151.6, 140.3, 137.9, 130.6, 128.5, 128.3, 126.3, 124.0, 33.8, 27.4.

**5-Thiophen-2-yl-[2,4']bisoxazole (8d).** TosMIC (0.119 g, 0.608 mmol) was added to a suspension of NaH (0.057 g, 1.42 mmol, 60% dispersion in mineral oil) in DMF (2.7 mL) at 0 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2-chloro-5-(thiophen-2-yl)oxazole **(5d)** (0.075 g, 0.405 mmol) in DMF (1.0 mL) at 0 °C was slowly added via cannula to the mixture. After 1 h, solid glyoxylic acid monohydrate (0.075 g, 0.810 mmol) and $K_2CO_3$ (0.197 g, 1.42 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (7 x 1 cm), 1:5 EA/hexanes eluent to give 0.065 g (74%) of **(8d)** as a yellow-white solid; analytical TLC on silica gel 1:3 EA/hexanes, Rf = 0.29. Recrystallized from toluene/hex, mp = 84-85 °C. HRMS calcd for $C_{10}H_6N_2O_2SNa$: 241.0048: found m/z = 241.0048 [ESI, $M+Na^+$], error = 0 ppm; IR (neat, $cm^{-1}$) 3112 (CH), 1629 (C=N), 1594 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (1H, s), 8.02 (1H, s), 7.40 (1H, d, J = 3.2 Hz), 7.35 (1H, d, J = 5.1 Hz), 7.31 (1H, s), 7.10 (1H, t, J = 3.6 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 153.7, 151.8, 147.0, 138.5, 130.2, 129.2, 127.8, 126.0, 124.8, 122.9.

**5-Ethoxycarbonyl-[2,4']bisoxazole (8e).** TosMIC (0.135 g, 0.692 mmol) was added to a suspension of NaH (0.065 g, 1.62 mmol, 60% dispersion in mineral oil) in DMF (3.4 mL) at 0 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2-chloro-5-ethoxycarbonyloxazole **(5e)** (0.081 g, 0.462 mmol) in DMF (0.6 mL) at 0 °C was slowly added via cannula to the mixture. After 45 min, solid glyoxylic acid monohydrate (0.085 g, 0.924 mmol) and $K_2CO_3$ (0.224 g, 1.617 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (17 x 1.5 cm), 1:5 EA/hexanes eluent to give 0.065 g (68%) of **(8e)** as a yellow-white solid; analytical TLC on silica gel 1:5 EA/Hex, Rf = 0.24. Recrystallized from EA/hexanes, mp = 95-96 °C.HRMS calcd for $C_9H_8N_2O_4Na$: 231.0382: found m/z = 231.0382 [ESI, $M+Na^+$], error = 0 ppm; IR (neat, $cm^{-1}$) 3081 (CH), 1723 (C=O), 1632 (C=N). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.41 (1H, s), 8.05 (1H, s), 7.87 (1H, s), 4.42 (2H, q, J = 7.1, 7.1 Hz), 1.41 (3H, t, J = 7.1 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 157.5, 157.2, 152.0, 142.4, 140.2, 135.0, 129.7, 61.6, 14.2.

**2-Oxazol-4-yl-benzoxazole (8f).** TosMIC (0.571 g, 2.95 mmol) was added to a suspension of NaH (0.273 g, 6.83 mmol, 60% dispersion in mineral oil) in DMF (14 mL) at 0 °C under an atmosphere of $N_2$, and the mixture stirred for 20 min. A solution of 2-chlorobenzoxazole (0.310 g, 1.95 mmol) in DMF (4 mL) at 0 °C was slowly added via cannula to the mixture. After 60 min, solid glyoxylic acid monohydrate (0.420 g, 3.90 mmol) and $K_2CO_3$ (0.947 g, 6.83 mmol)

were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (11 x 1.5 cm), 15% EA/hexanes eluent to give 0.262 g (73%) of **(8f)** as a off-white solid; analytical TLC on silica gel 1:5 EA/hexanes, Rf = 0.13. Recrystallized from toluene/hexanes, mp = 134-5 °C. HRMS calcd for $C_{10}H_6N_2O_2Na$: 209.0327: found m/z = 2090325 [ESI, $M+Na^+$], error = 1 ppm; IR (neat, $cm^{-1}$) 3105 (CH), 1644 (C=N), 1594 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.46 (1H, d, J = 1.0 Hz), 8.07 (1H, d, J = 0.7 Hz), 7.79-7.77 (1H, m), 7.61-7.59 (1H, m), 7.40-7.37 (2H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 156.0, 152.0, 150.3, 141.4, 140.3, 130.4, 125.6, 124.8, 120.2, 110.8.

**2'-Chloro-5-phenyl-[2,4']bisoxazole (9).** To a solution of 5-phenyl-[2,4']bisoxazole **(8b)** (0.050 g, 0.236 mmol) in anhydrous THF (1.2 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (0.15 mL of a 1.71 M in hexanes, 0.259 mmol) via syringe. Solid hexachloroethane (0.112 g, 0.472 mmol) was added to the resulting red solution after it had stirred at –78 °C for 30 min. The solution was allowed to slowly warm to room temperature and stir for 42 h. The reaction was diluted with ethyl acetate and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by preparatory plate chromatography on silica gel (20 x 20 cm, 1000 μm), 1:3 EA/hexanes eluent to give 0.045 g (76%) of **(9)** as a white solid; analytical TLC on silica gel 1:3 EA/hexanes, Rf = 0.60. Recrystallized from $CHCl_3$/hexanes, mp = 135-136 °C. HRMS calcd for $C_{12}H_7ClN_2O_2$: 246.0196: found m/z = 246.0199 [EI, $M^+$], error = 1 ppm; IR (neat, $cm^{-1}$) 3132 (CH), 1700 (C=N), 1596 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.24 (1H, s), 7.71 (2H, d, J = 7.6 Hz), 7.45 (1H, s), 7.44 (2H, t, J = 7.8 Hz), 7.36 (1H, t, J = 7.4 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 153.2, 151.8, 148.5, 139.7, 132.4, 128.9, 128.9, 127.3, 124.4, 123.2.

**5-phenyl-[2,4'; 2',4'']trisoxazole (10).** TosMIC (0.071 g, 0.365 mmol) was added to a suspension of NaH (0.034 g, 0.851 mmol, 60% dispersion in mineral oil) in DMF (1.1 mL) at -42 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution 2'-chloro-5-phenyl-[2,4']bisoxazole **(9)** (0.060 g, 0.243 mmol) in DMF (1.1 mL) at -42 °C was slowly added via cannula to the mixture. After 2.5 h, solid glyoxylic acid monohydrate (0.045 g, 0.486 mmol) and $K_2CO_3$ (0.118 g, 0.851 mmol) were added and the solution was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with $CH_2Cl_2$ and satd $NaHCO_3$. The aqueous layer was washed with $CH_2Cl_2$, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by flash chromatography on silica gel (7 x 1 cm), $CHCl_3$ eluent to give 0.044 g (64%) of **(10)** as a white solid; analytical TLC on silica gel 1:3 EA/Hex, Rf = 0.24. Recrystallized from $CHCl_3$/hexanes, mp = 178-180 °C. HRMS calcd for $C_{15}H_9N_3O_3Na$: 302.0542: found m/z = 302.0537 [ESI, $M+Na^+$], error = 2 ppm; IR (neat, $cm^{-1}$) 3107 (CH), 1638 (C=N), 1627 (C=C). $^1H$ NMR (500 MHz, $CDCl_3$, ppm) δ 8.44 (1H, s), 8.34 (1H, s), 8.04 (1H, s), 7.73 (2H, d, J = 7.3 Hz), 7.47 (1H, s), 7.43 (2H, t, J = 7.6 Hz), 7.34 (1H, t, J = 7.6 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$, ppm) δ 155.7, 154.1, 151.8, 151.6, 139.6, 138.0, 131.7, 129.7, 128.8, 128.6, 127.4, 124.3, 123.2.

**2''-Chloro-5-phenyl-[2,4'; 2',4'']trisoxazole (11).** To a solution of 5-phenyl-[2,4'; 2',4'']trisoxazole **(10)** (0.083 g, 0.297 mmol) in anhydrous THF (3.5 mL) at –78 °C under a $N_2$ atmosphere was slowly added a solution of *n*BuLi (0.46 mL of a 0.71 M in hexanes, 0.326 mmol) via syringe. Solid hexachloroethane (0.141 g, 0.594 mmol) was added to the resulting dark yellow solution after it had stirred at –78 °C for 30 min. The solution was allowed to slowly warm to room temperature and stir for 18 h. The reaction was diluted with ethyl acetate and the mixture was extracted two times with $H_2O$ and once with brine. The organic layer was dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator) the residue was purified by flash chromatography on silica gel (7 x 1 cm), 100 mL of 5% EA/hexanes, followed by 35% EA/hexanes eluent to give 0.066 g (72%) of **(11)** as a white solid; analytical TLC on silica gel 1:1 EA/Hex, Rf = 0.49. Recrystallized from EA/hexanes, mp = 186-7 °C. HRMS calcd for $C_{15}H_8ClN_3O_3$: 313.0254: found m/z = 313.0250 [$EI^+$], error = 1 ppm; IR (neat, $cm^{-1}$) 3116 (CH), 1737 (C=N), 1642 (C=C). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.36 (1H, s), 8.34 (1H, s), 7.72 (2H, d, J = 7.4 Hz), 7.46 (1H, s), 7.43 (2H, t, J = 7.6 Hz), 7.35 (1H, t, J = 7.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 154.7, 153.9, 151.6, 148.6, 140.9, 138.2, 131.8, 131.5, 128.8, 128.7, 127.3, 124.3, 123.2.

**5-phenyl-[2,4'; 2',4''; 2'',4''']tetraoxazole (12).** TosMIC (0.047 g, 0.240 mmol) was added to a suspension of NaH (0.023 g, 0.557 mmol, 60% dispersion in mineral oil) in DMF (0.7 mL) at -42 °C under an atmosphere of $N_2$, and the mixture stirred for 30 min. A solution of 2''-chloro-5-phenyl-[2,4'; 2',4'']trisoxazole **(11)** (0.050 g, 0.159 mmol) in DMF (1.2 mL) at -42 °C was slowly added via cannula to the mixture. After 3.75 h, solid glyoxylic acid monohydrate (0.022 g, 0.240 mmol) and $K_2CO_3$ (0.078 g, 0.557 mmol) were added to the dark yellow solution and the mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and satd $NaHCO_3$. The aqueous layer was washed with ethyl acetate, and the combined organic layers were washed with brine three times, dried with $Na_2SO_4$ and filtered. After removal of solvent (aspirator, then hi-vac) the residue was purified by preparatory plate chromatography on silica gel treated with $NEt_3$ (20 x 20 cm, 1000 μm), 1:1 EA/$CH_2Cl_2$ eluent to give 0.025 g (46%) of **(12)** as a white powder; analytical TLC on silica gel treated with $NEt_3$, 1:1 EA/$CH_2Cl_2$, Rf = 0.78. mp = 242-243 °C (dec). HRMS calcd for $C_{18}H_{10}N_4O_4Na$: 369.0600: found m/z = 369.0591 [ESI, $M+Na^+$], error = 2 ppm; IR (neat, $cm^{-1}$) 3124 (CH), 1641 (C=N), 1508 (C=C). $^1$H NMR (500 MHz, $CDCl_3$, ppm) δ 8.48 (1H, s), 8.45 (1H, s), 8.36 (1H, s), 8.05 (1H, s), 7.75 (2H, d, J = 7.6 Hz), 7.48 (1H, s), 7.45 (2H, t, J = 7.3 Hz), 7.36 (1H, t, J = 7.4 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$, ppm) δ 155.9, 155.6 154.1, 151.9, 151.7, 139.7, 139.4, 138.2, 131.9, 131.0, 129.6, 128.9, 128.7, 127.5, 124.4, 123.4.

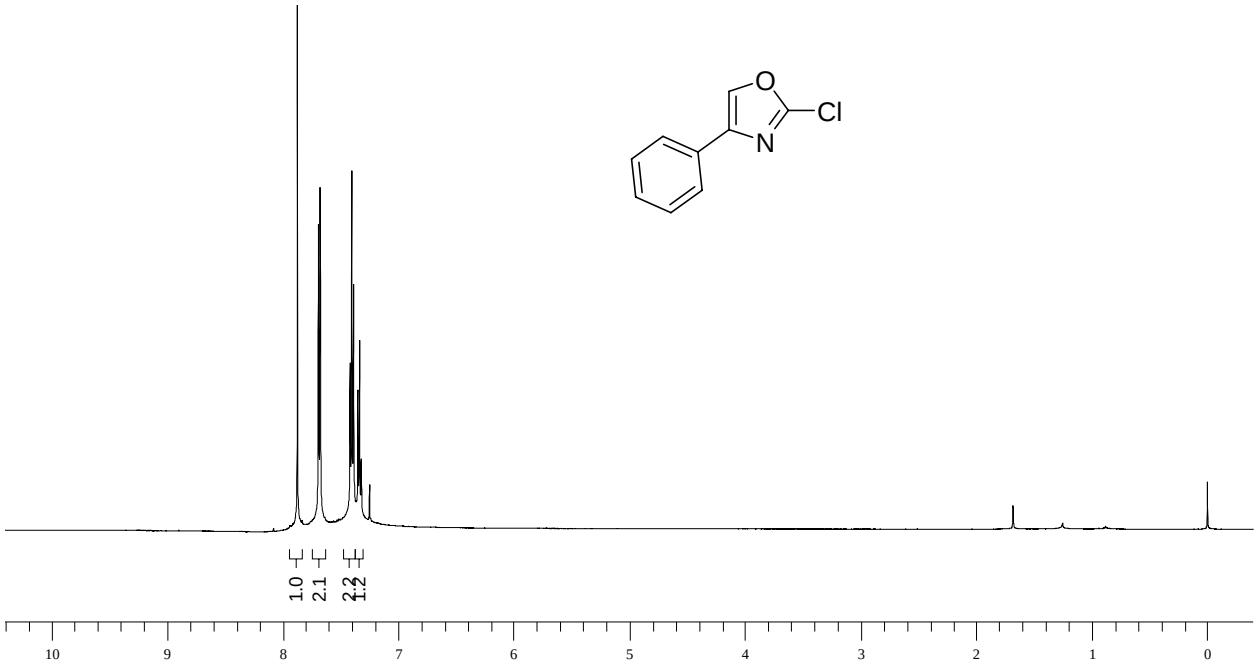
**References**

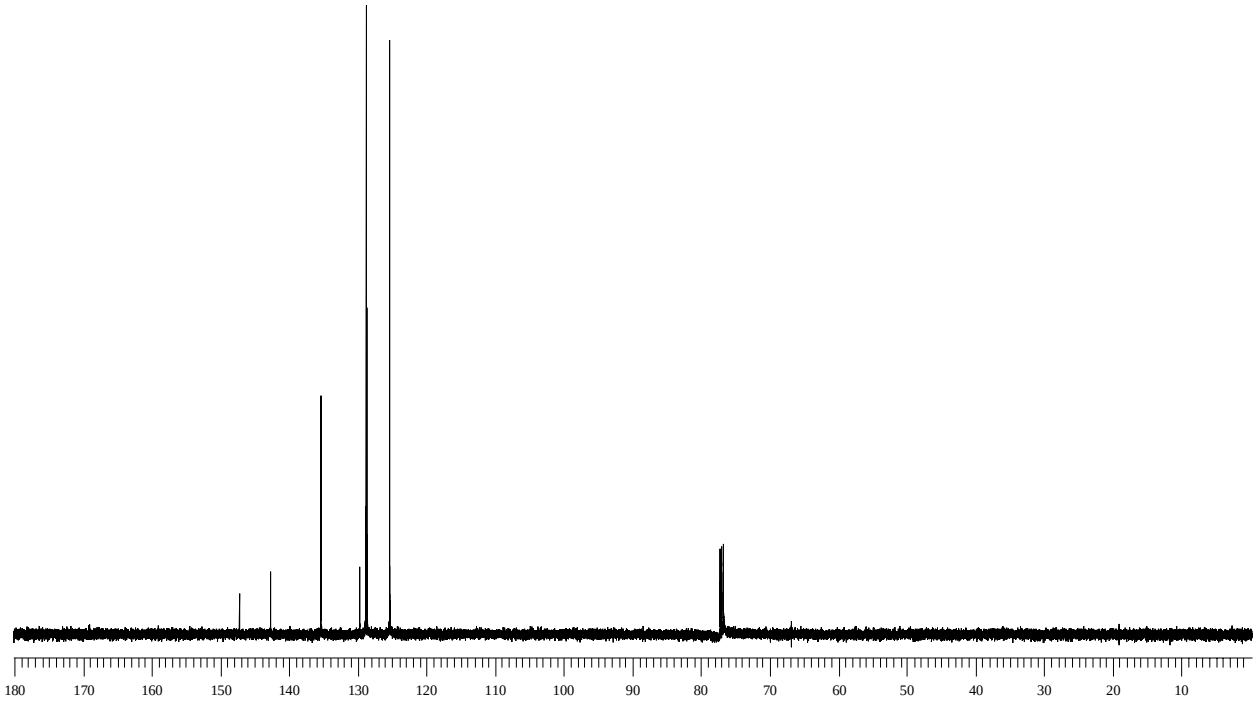

1) Whitney, S. E.; Winters, M.; Rickborn, B. *J. Org. Chem.* **1990**, *55*, 929.
2) Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* 1972, *23*, 2369.
3) (a) Schöllkopf, U.; Schröder, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 333. (b) Vedejs, E.; Luchetta, L. M.; *J. Org. Chem.* **1999,** *64*, 1011.
4) Saikachi, H.; Kitagawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *27*, 793.

5) Kikuchi, T., Mizukoshi, T., Niki, T. Jpn. Kokai Tokkyo Koho; *Chem. Abstr.* **2002**, *137*, 154930.

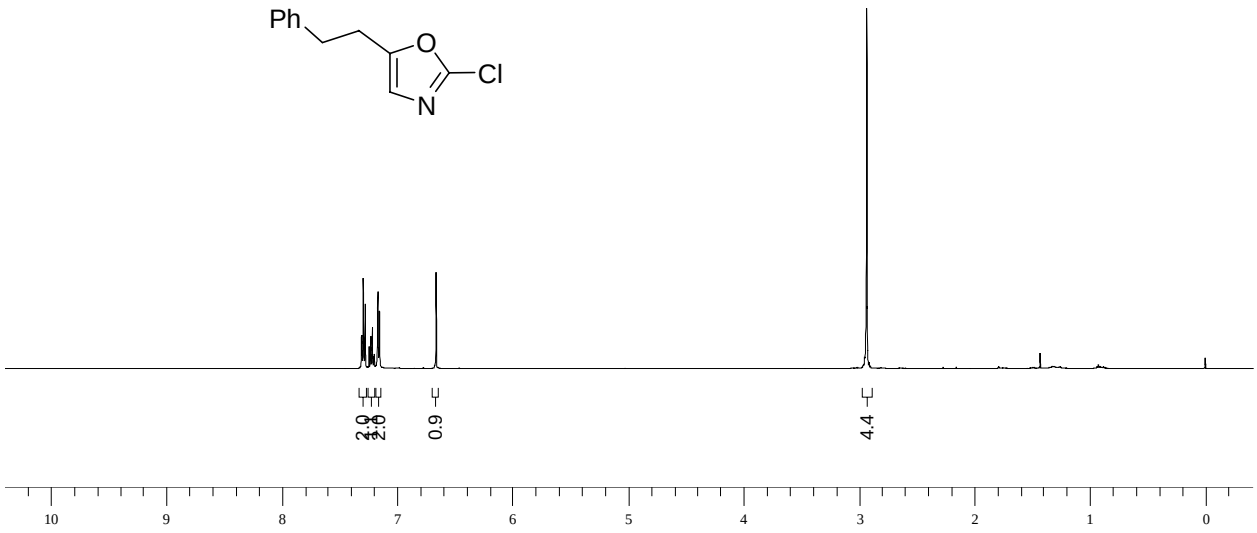
6) (a) Harrison, R. G.; Jamieson, W. B.; Ross, W. J.; Saunders, J. C. Ger. Offen. *Chem. Abstr*. **1977**, *86*, 155658. (b) Harrison, R. G. Ger. Offen. 2,459,380; *Chem. Abstr*. **1977**, *86*, 121320. (c) Maquestiau, A.; Ben A., Fouad B.; Flammang, R. *Bull. Soc. Chim. Belg*. **1990**, *99*, 89-101. (d) Vedejs, E. Monahan, S. D. *J. Org. Chem*. **1996**, *61*, 5192.

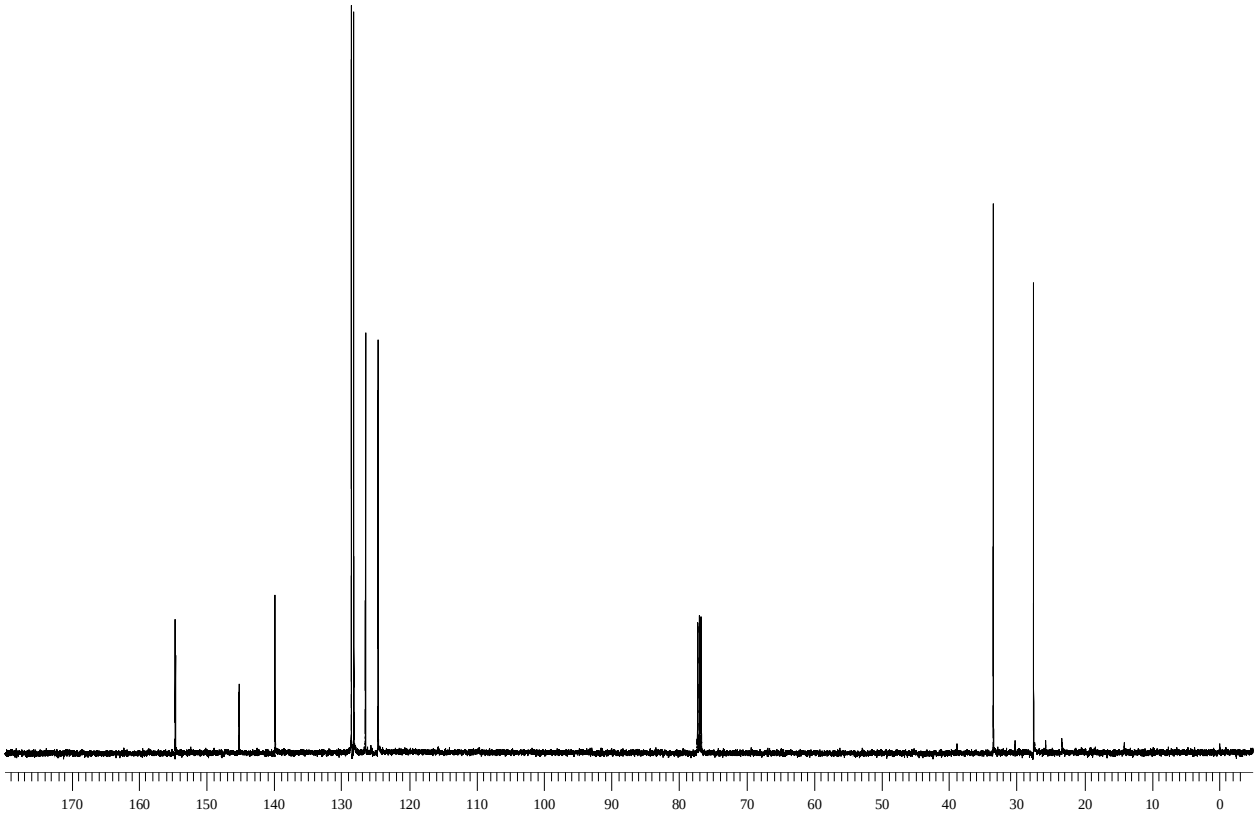
$^{1}H$ and $^{13}C$ NMR spectra of 2-chloro-4-phenyloxazole **(5a)**.



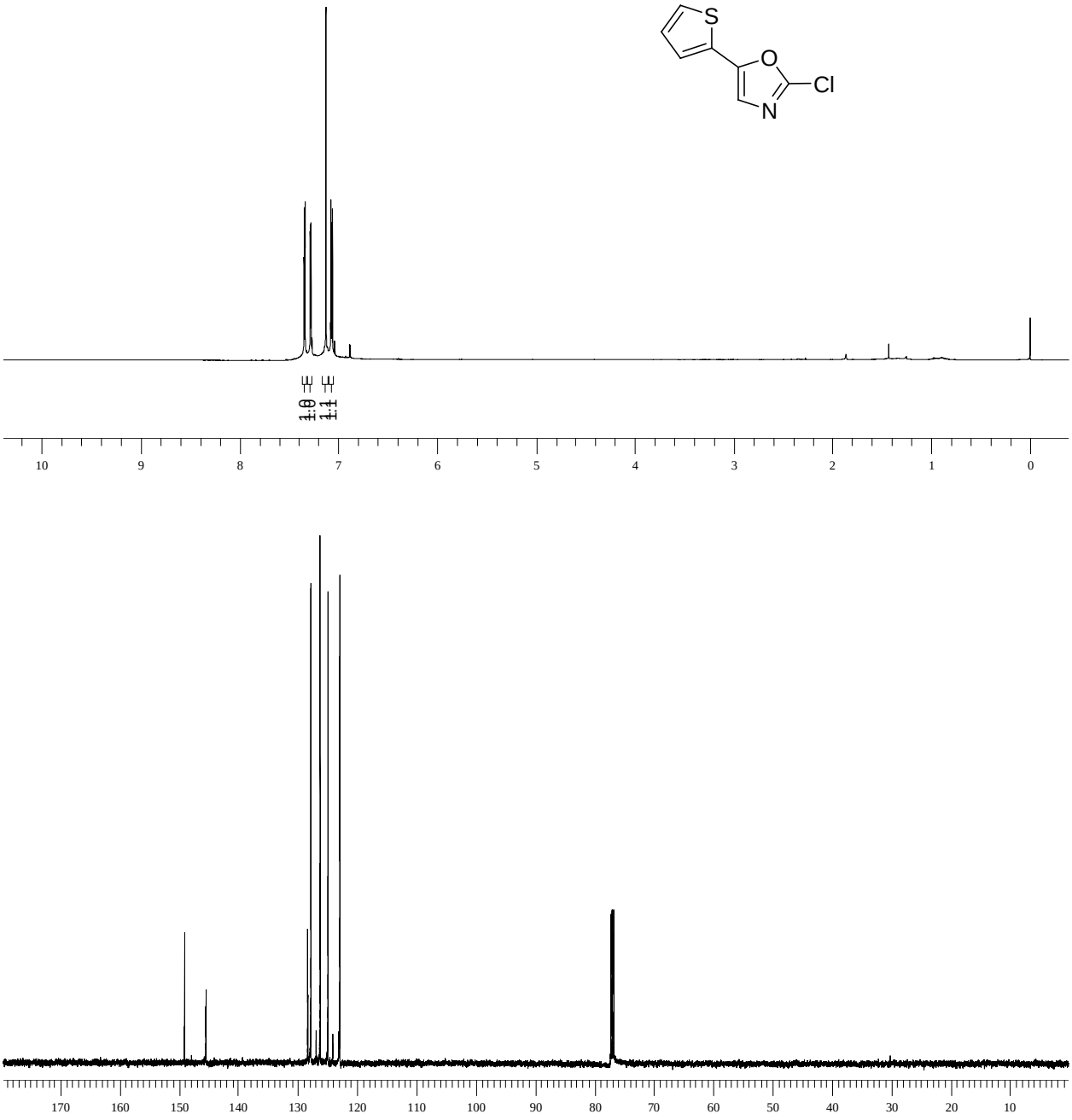



$^{1}H$ and $^{13}C$ NMR spectra of 2-chloro-5-phenethyl-oxazole **(5c)**.

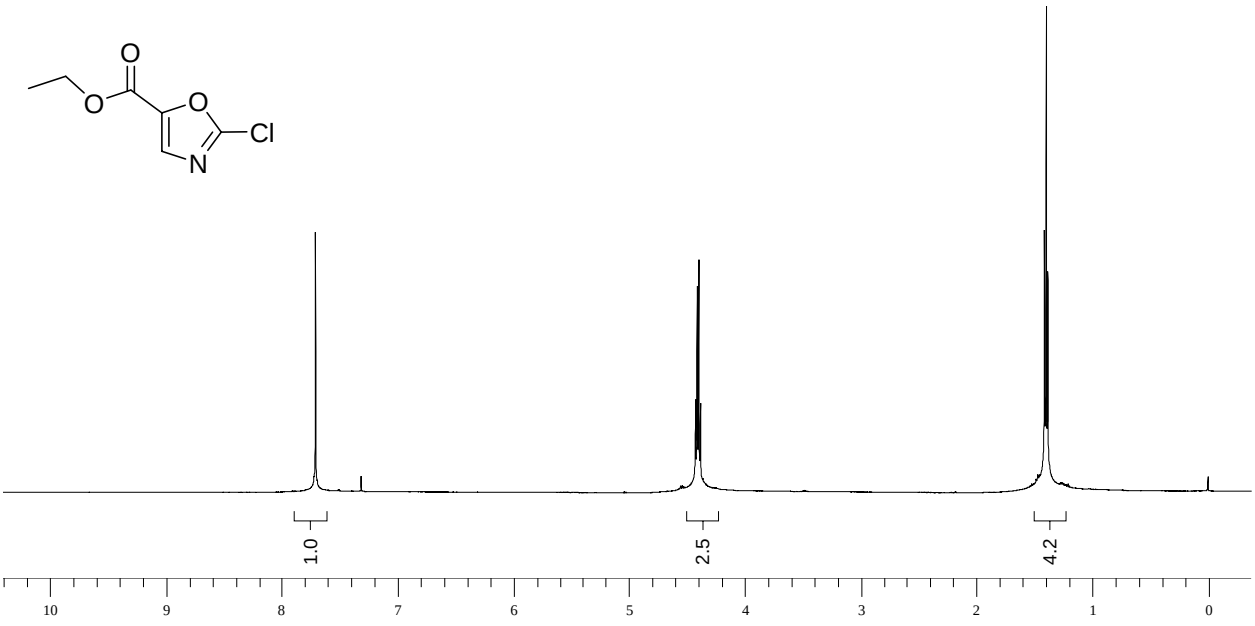


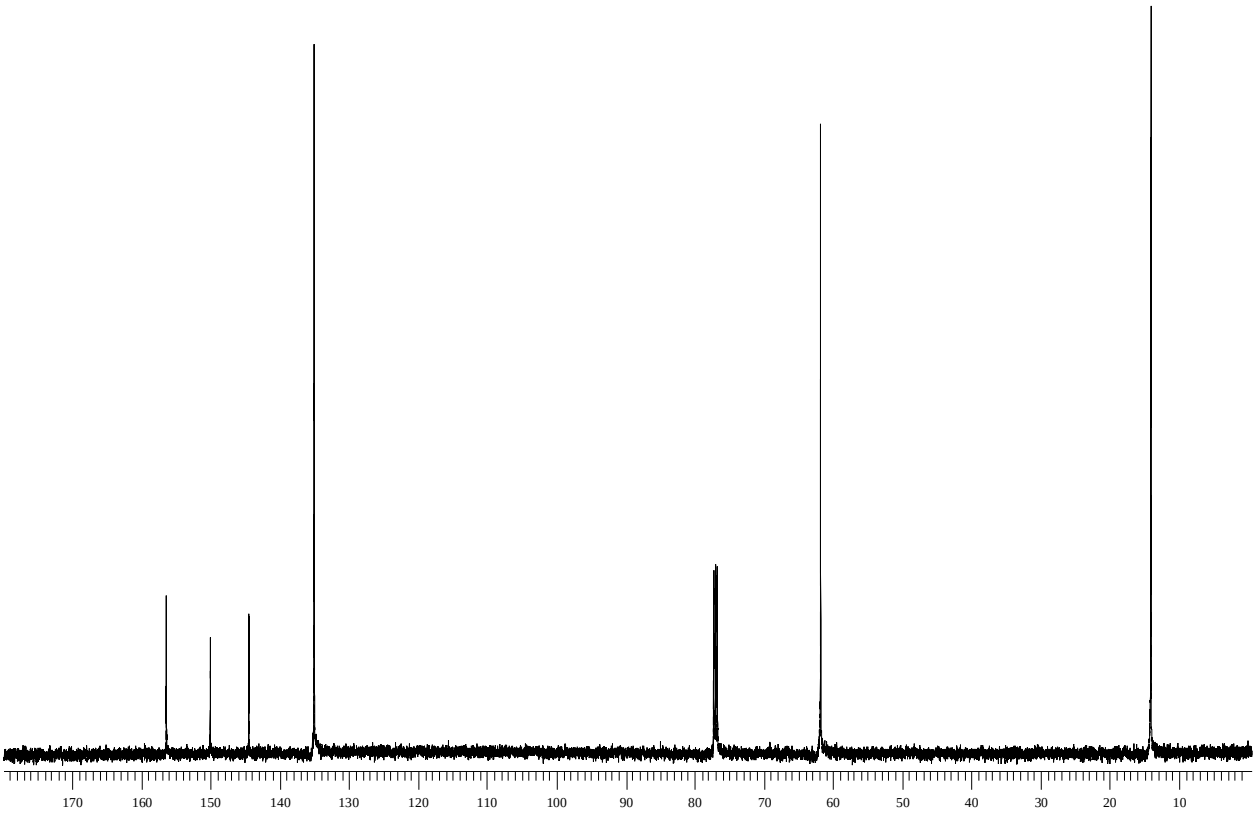



$^{1}H$ and $^{13}C$ NMR spectra of 2-chloro-5-thiophen-2-yl-oxazole **(5d)**.

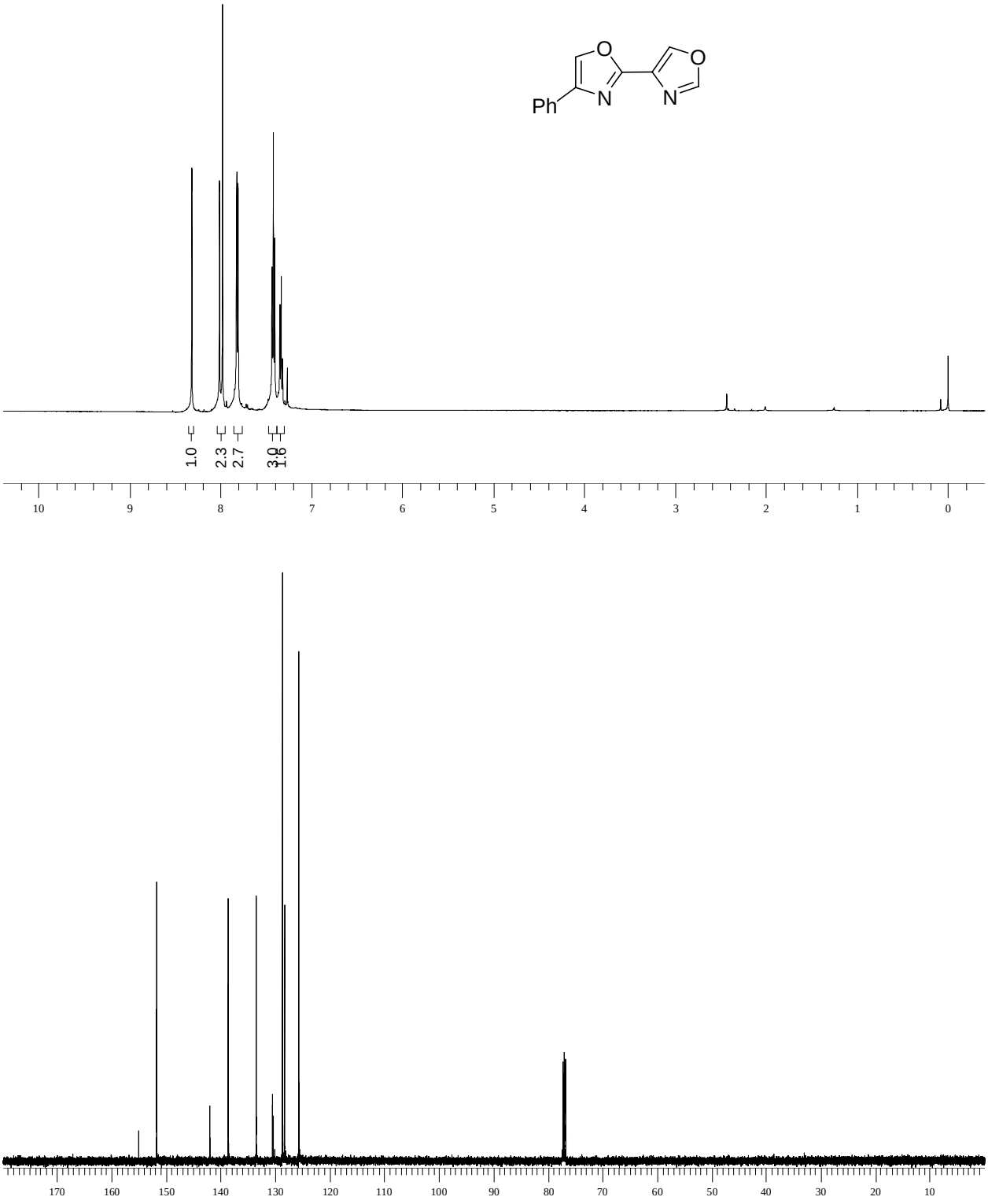


$^{1}H$ and $^{13}C$ NMR spectra of 2-chloro-5-(carboxyethyl) oxazole **(5e)**.

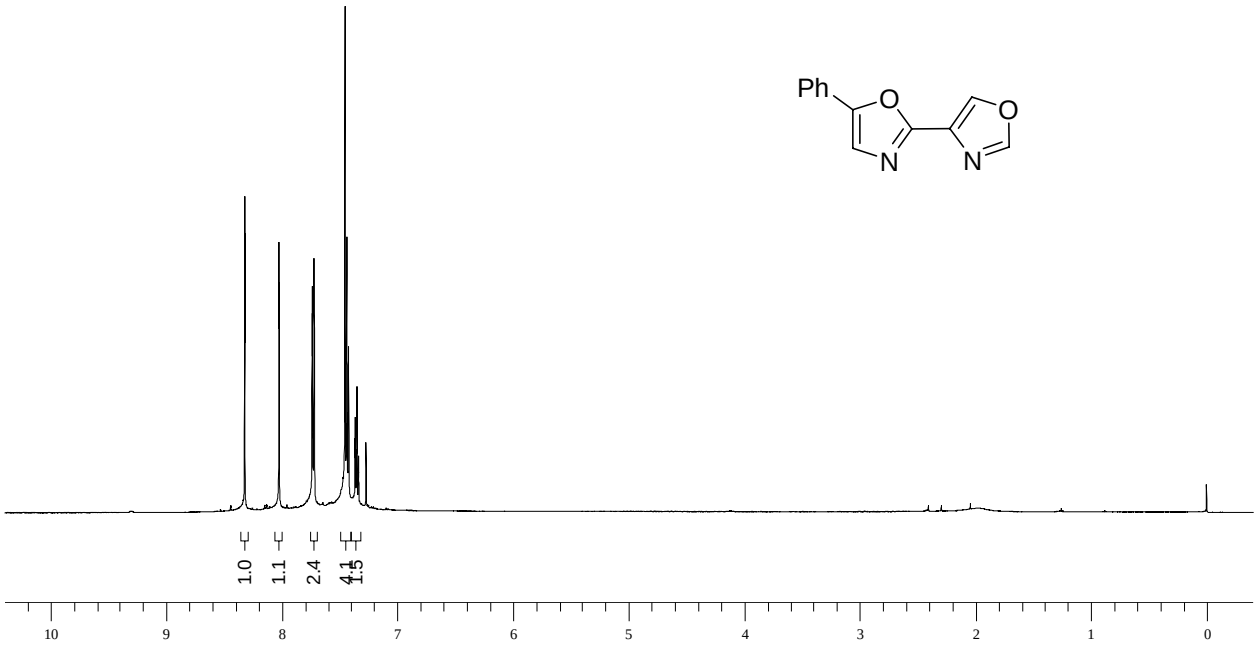


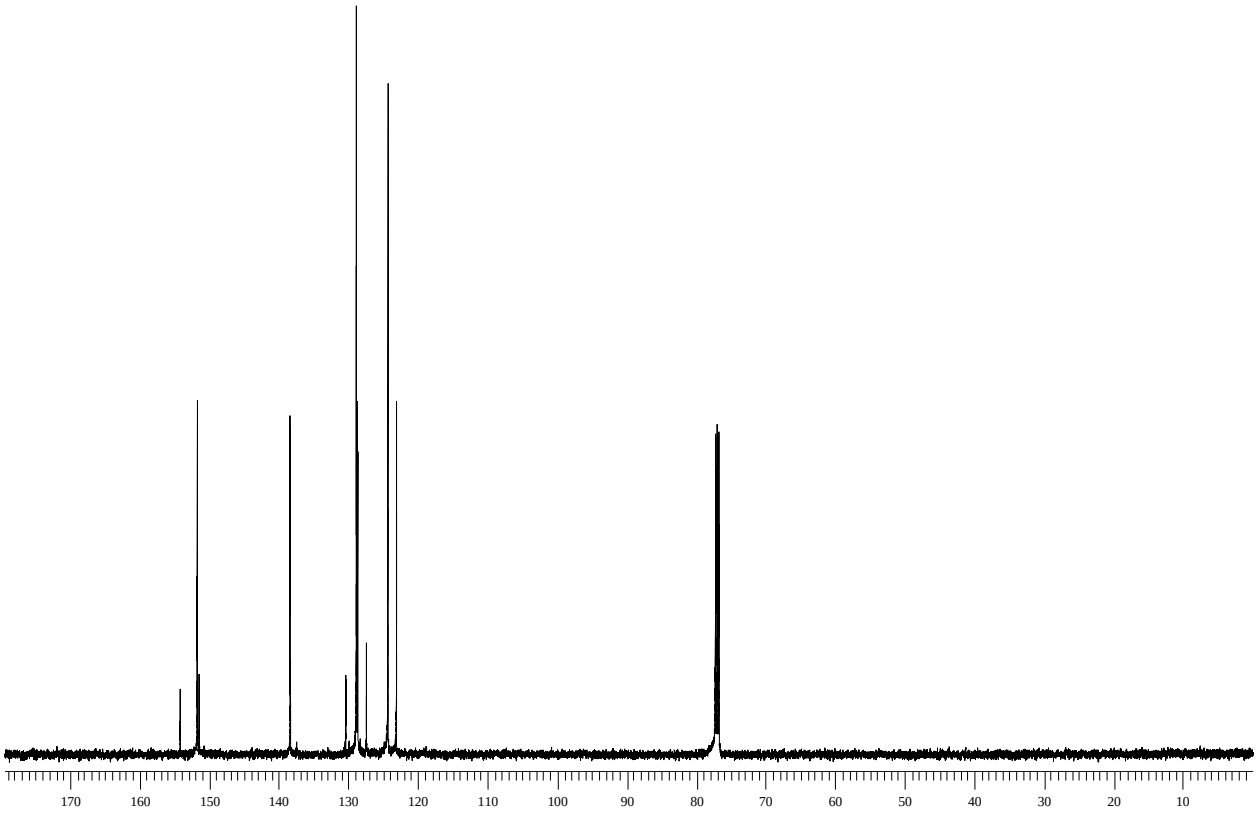



$^{1}H$ and $^{13}C$ NMR spectra of 4-phenyl-[2,4']bisoxazole **(8a)**.

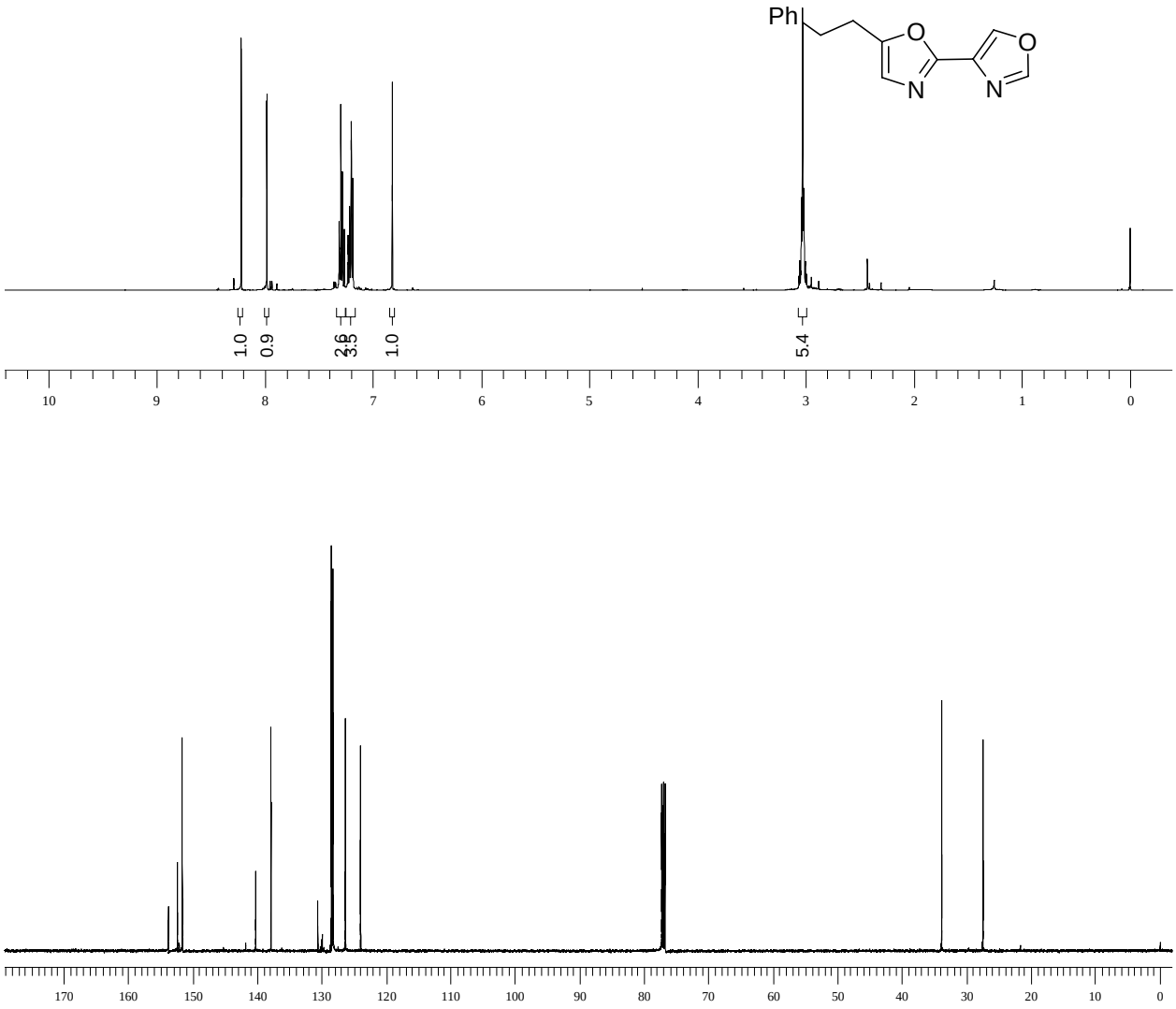


$^{1}H$ and $^{13}C$ NMR spectra of 5-phenyl-[2,4']bisoxazole **(8b)**.

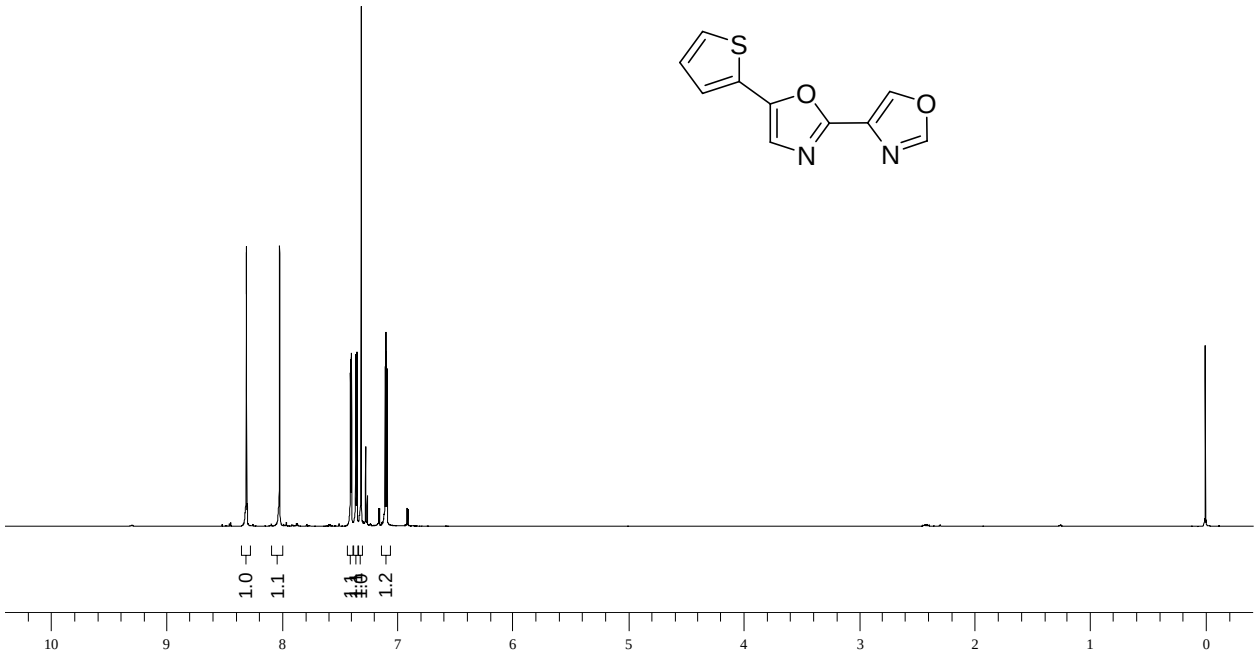


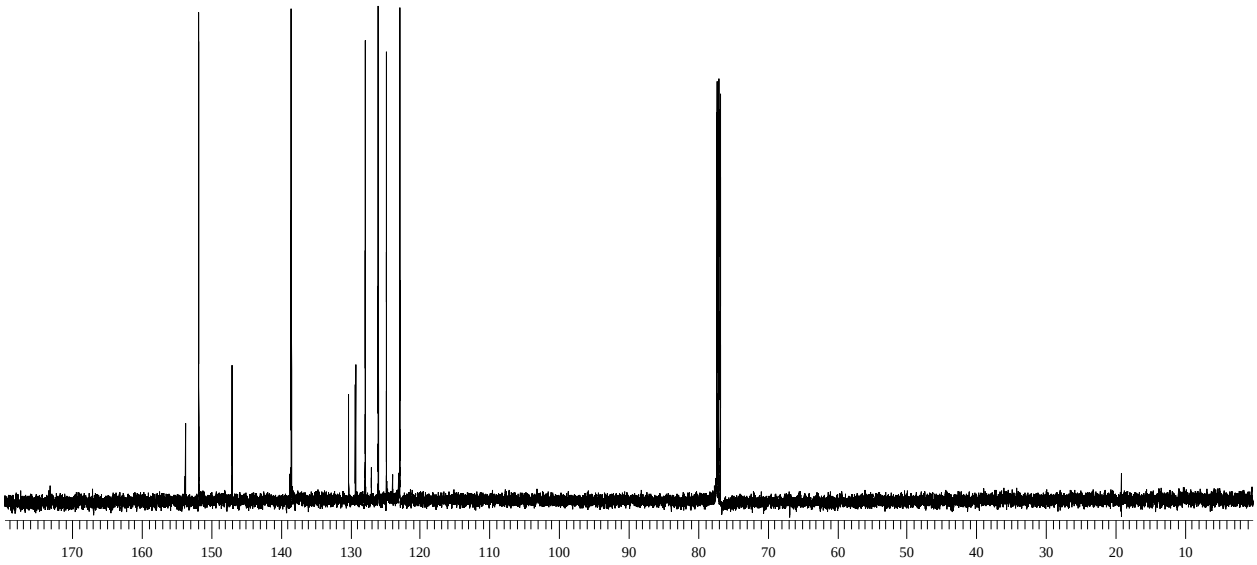



$^{1}H$ and $^{13}C$ NMR spectra of 5-phenethyl-[2,4']bisoxazole **(8c)**.

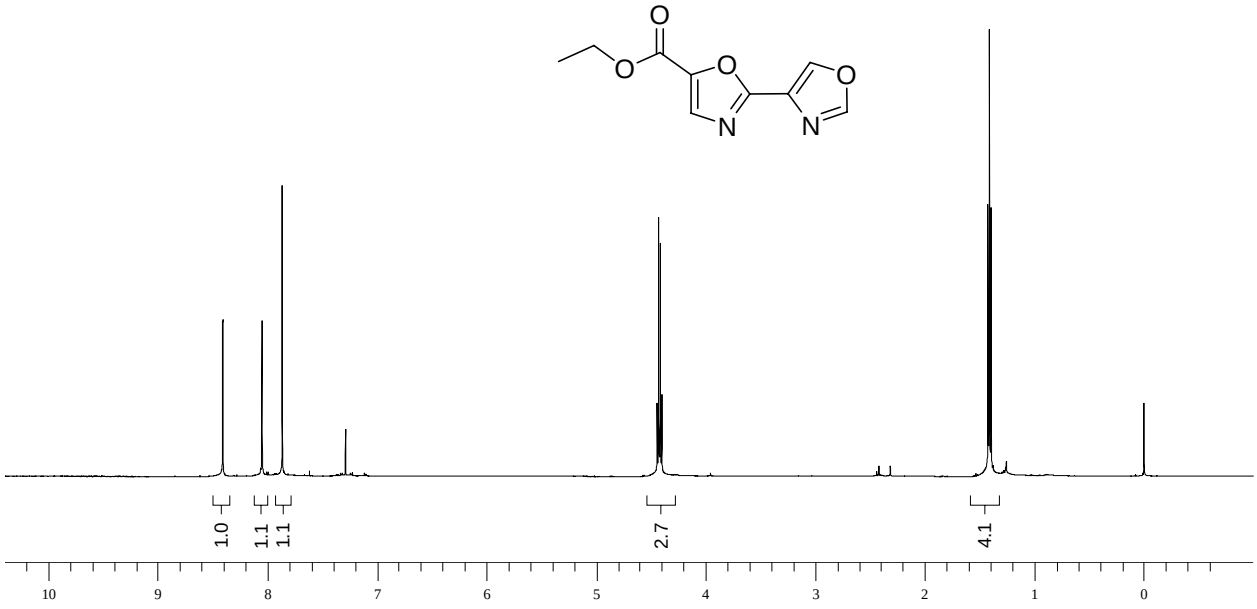


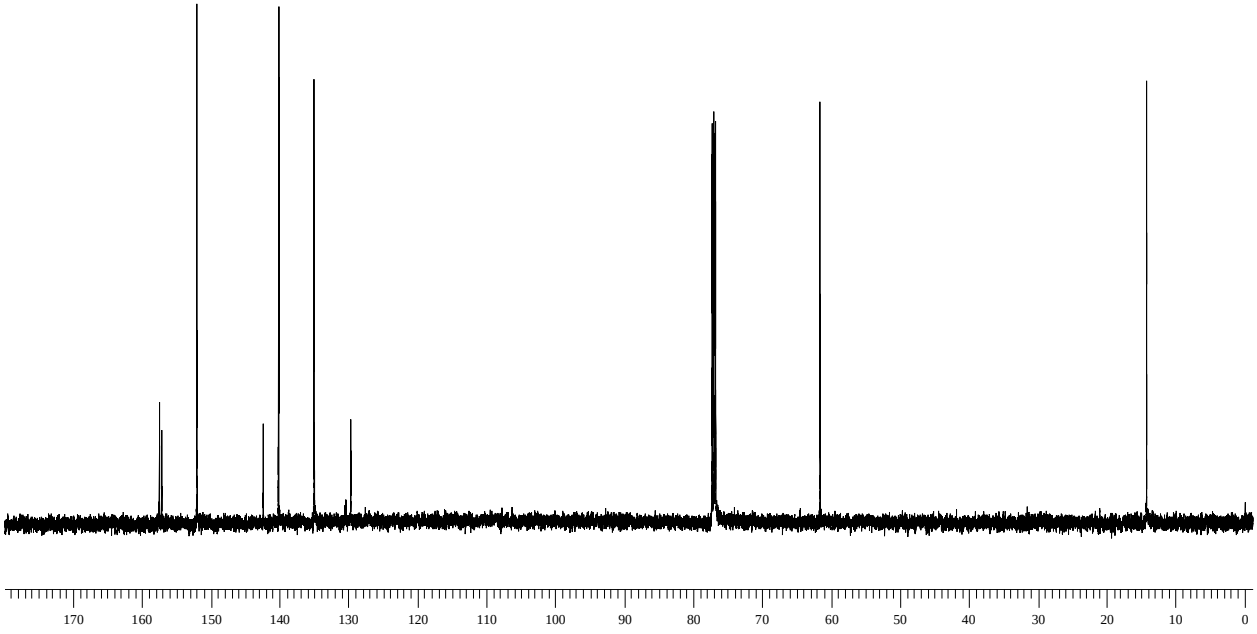
$^{1}H$ and $^{13}C$ NMR spectra of 5-thiophen-2-yl-[2,4']bisoxazole **(8d)**.



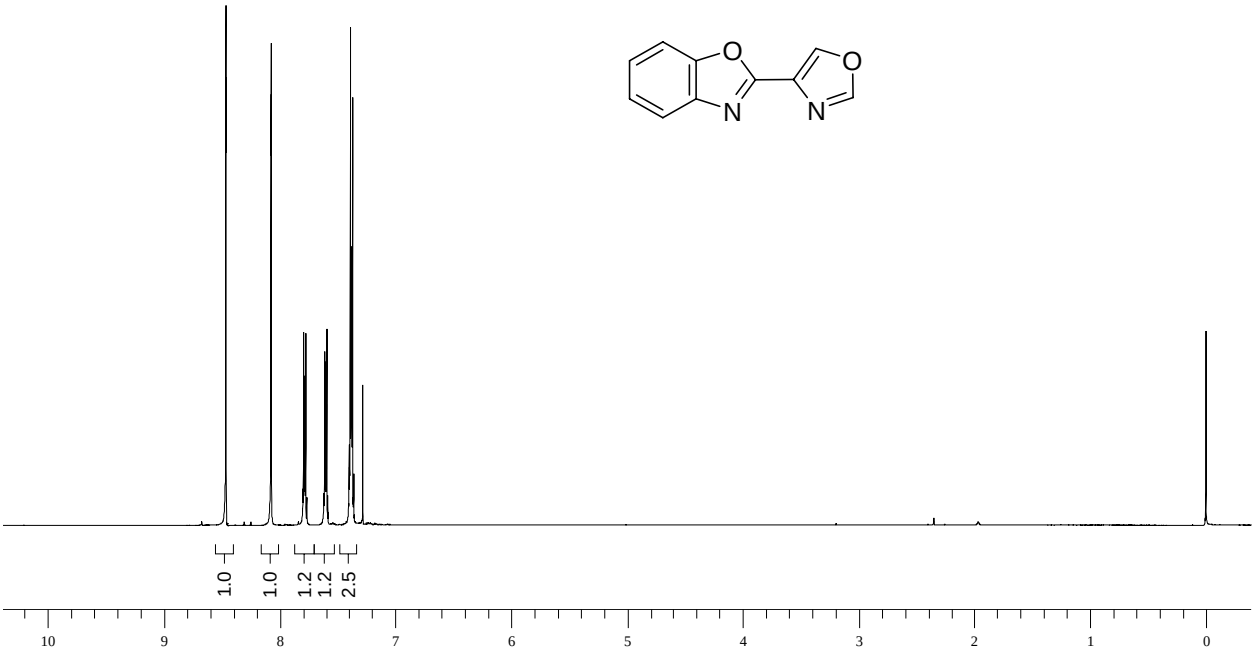



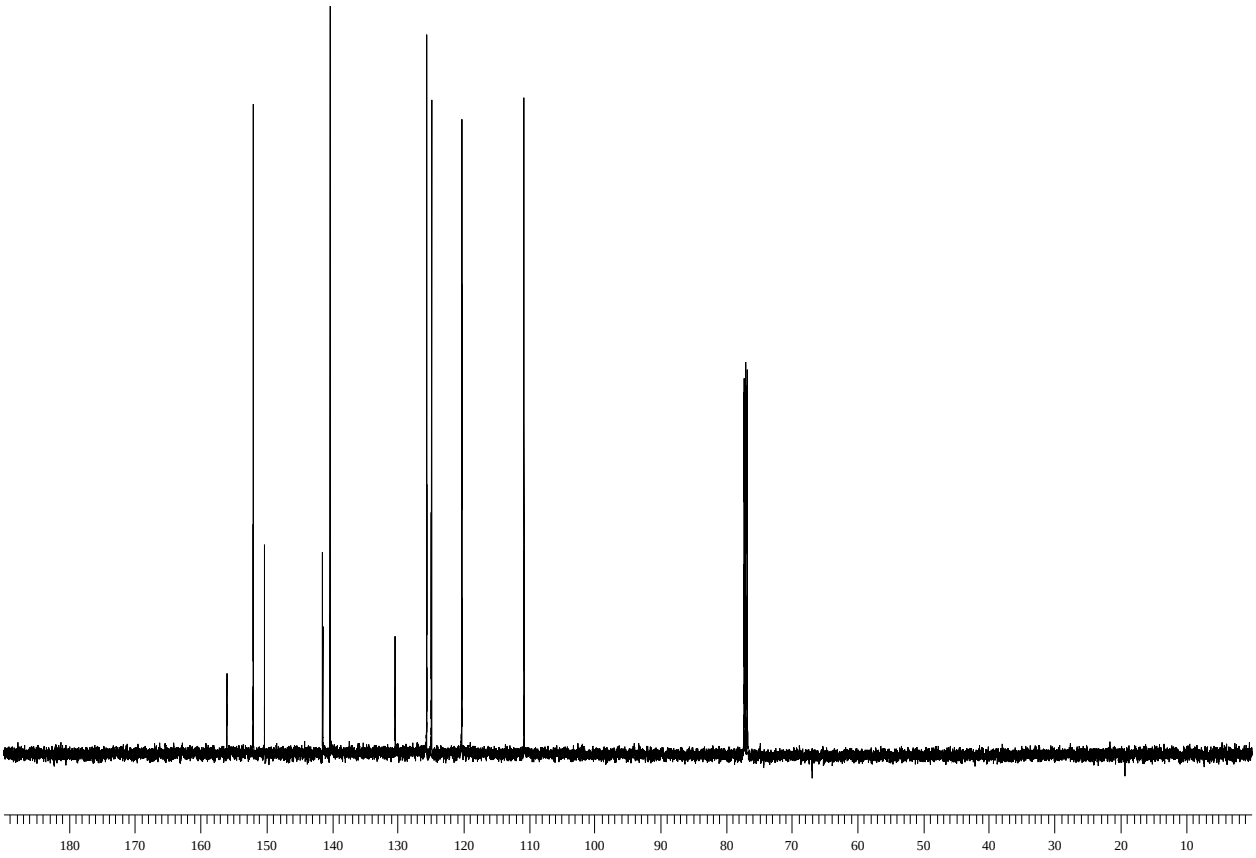
$^{1}H$ and $^{13}C$ NMR spectra of 5-(carboxy ethyl) [2,4']bisoxazole **(8e)**.



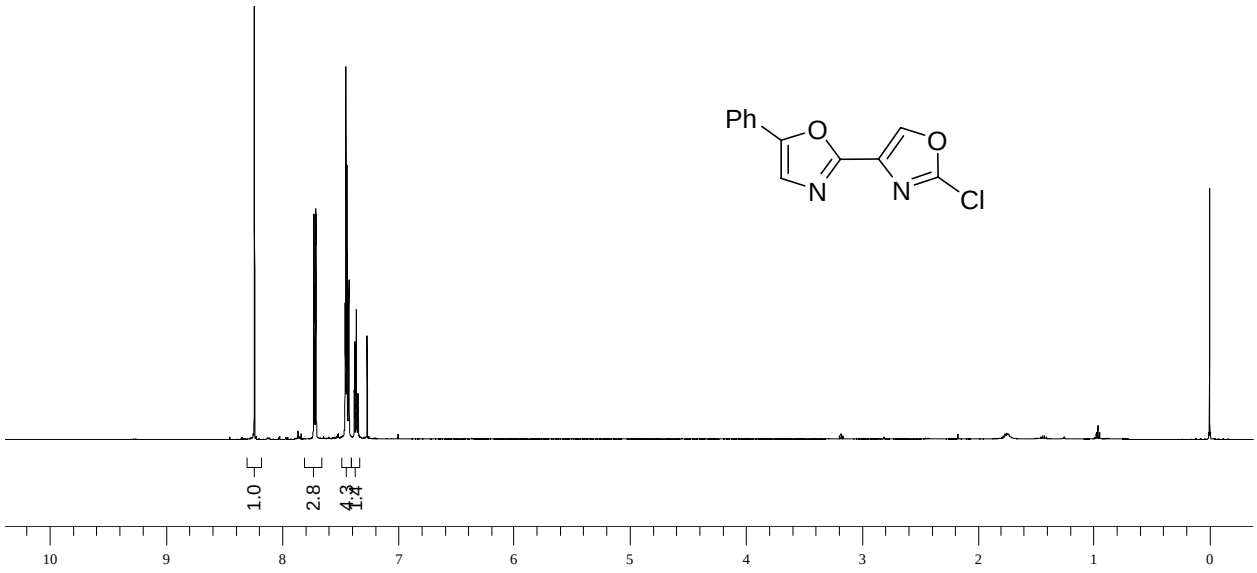



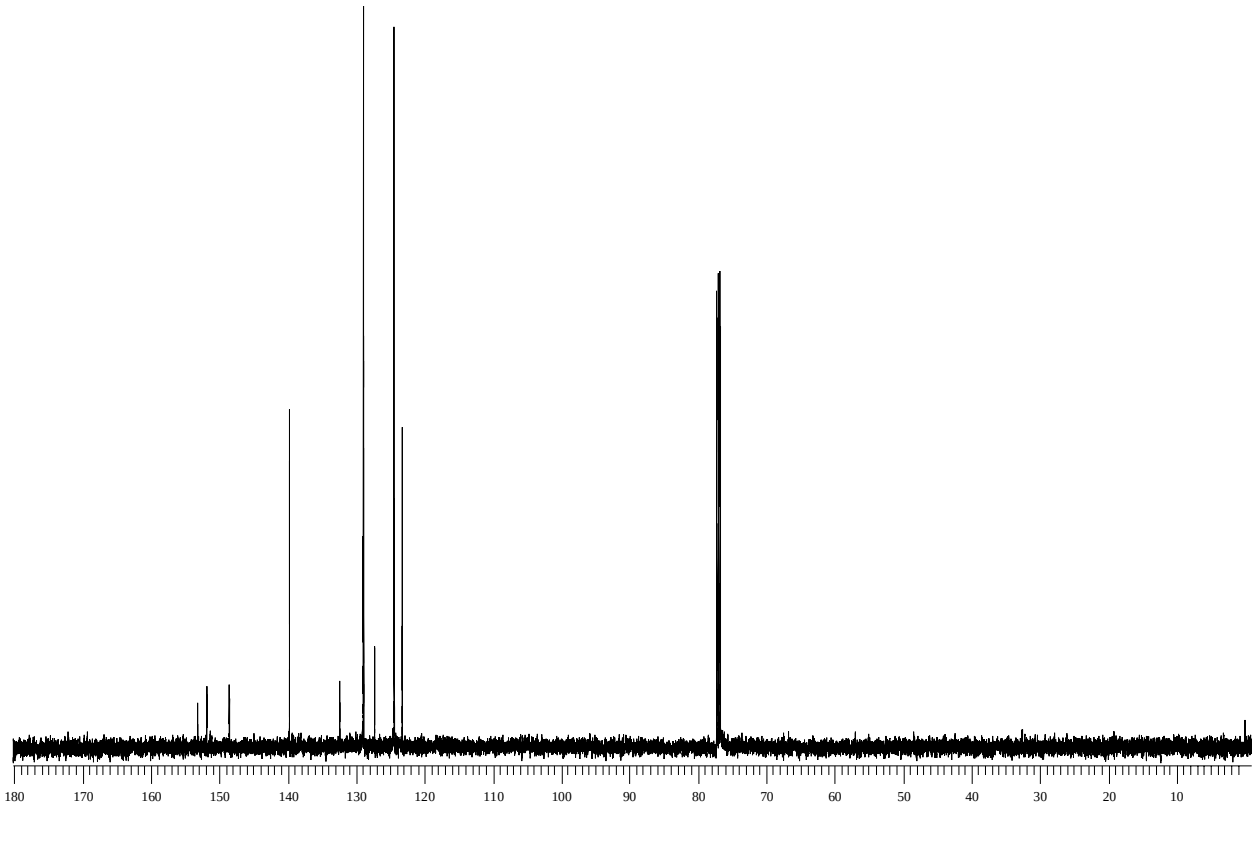
$^{1}H$ and $^{13}C$ NMR spectra of 2-oxazol-4-yl-benzooxazole **(8f)**.



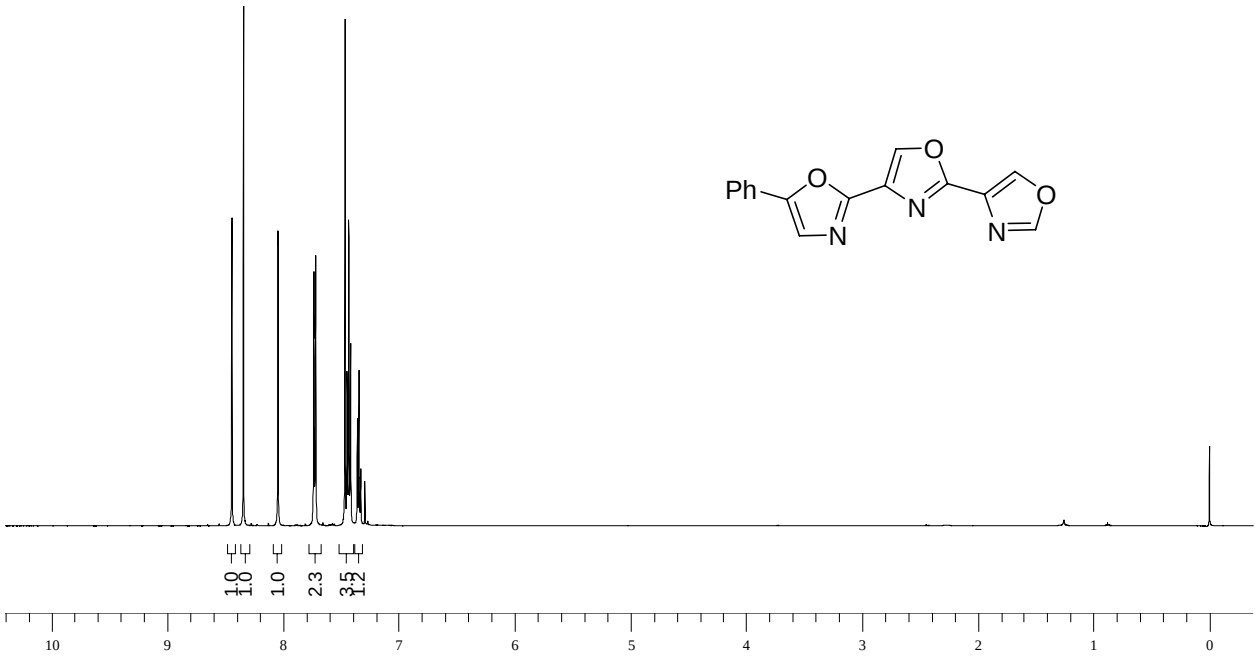



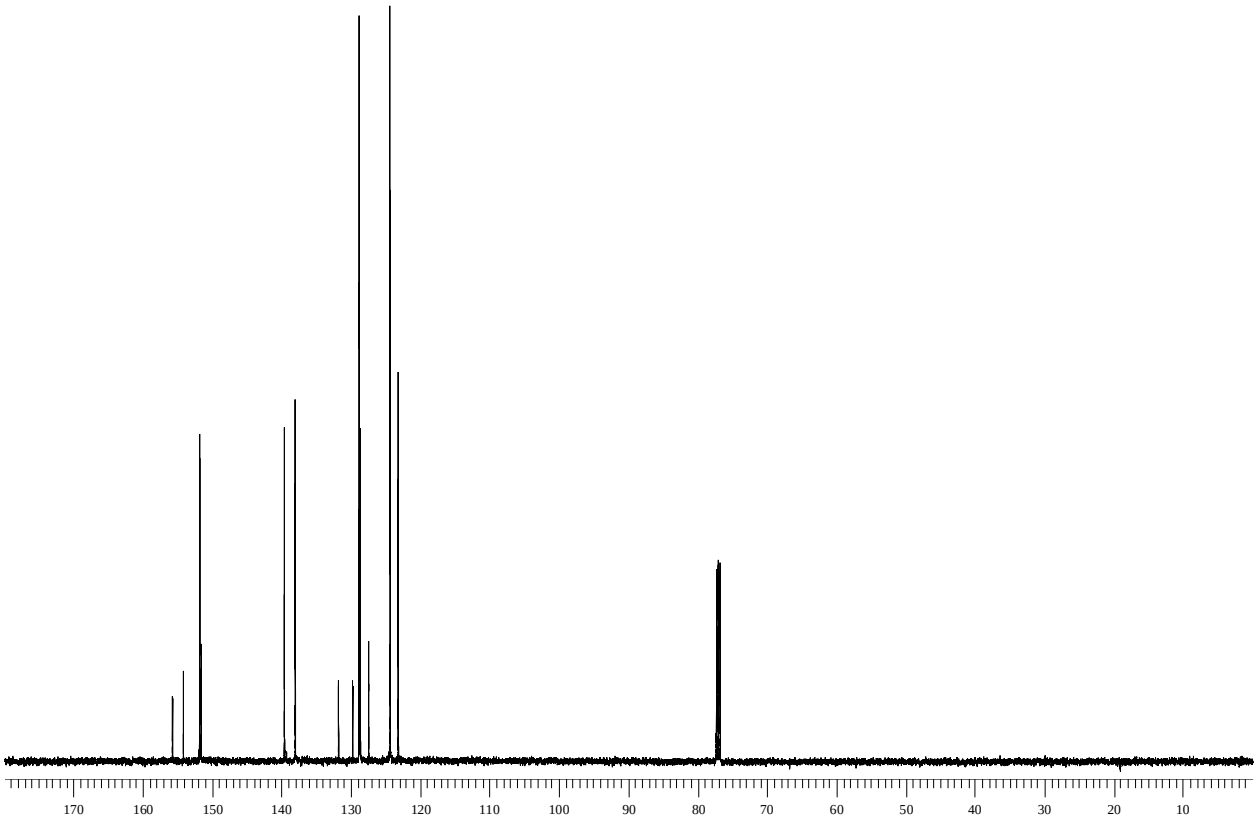
$^{1}H$ and $^{13}C$ NMR spectra of 2'-chloro 5-phenyl-[2,4']bisoxazole **(9)**.



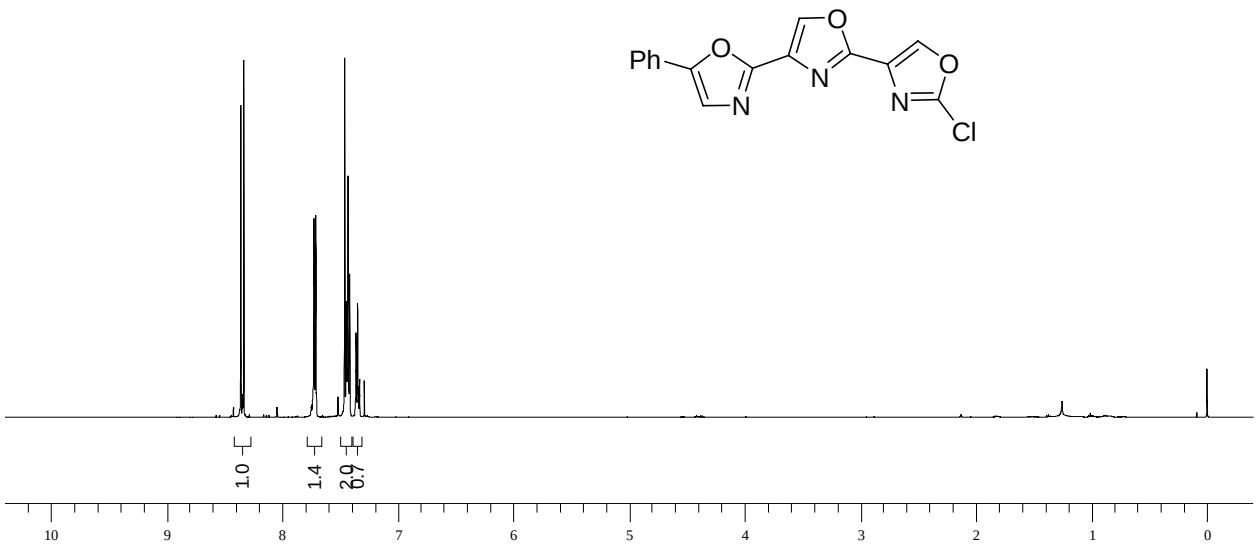



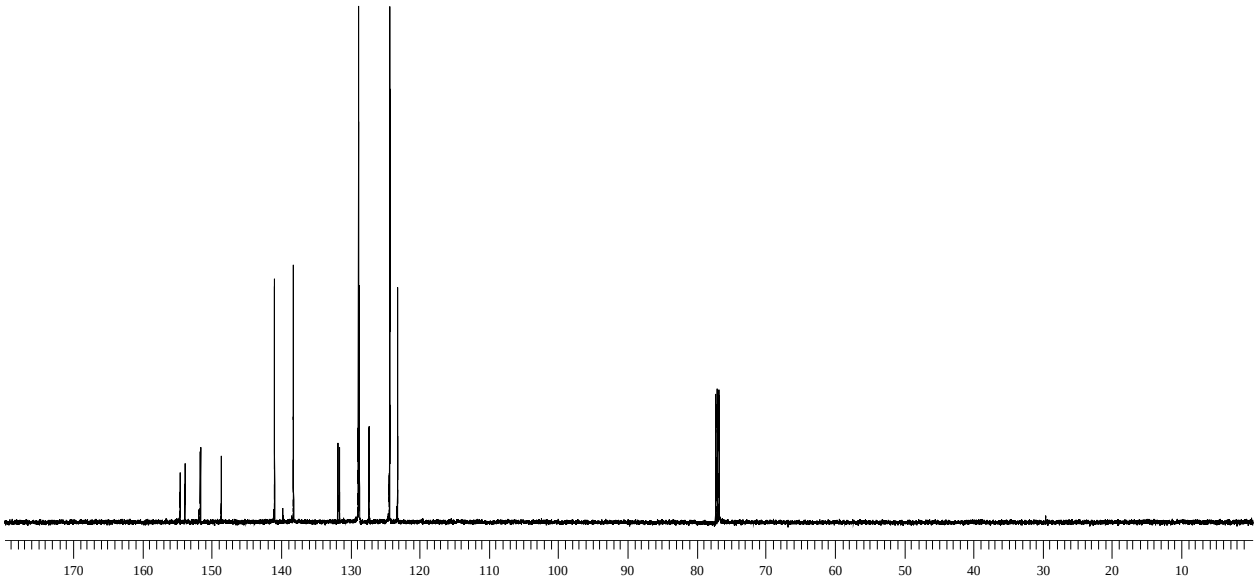
$^{1}H$ and $^{13}C$ NMR spectra of 5-phenyl-[2,4';2',4"]trisoxazole **(10)**.



$^{1}H$ and $^{13}C$ NMR spectra of 2"-chloro-5-phenyl-[2,4';2',4"]trisoxazole **(11)**.



$^{1}$H and $^{13}$C NMR spectra of 5-phenyl-[2,4';2',4";2",4"']tetraoxazole **(12)**.