Supporting information

Efficient and Regioselective Halogenations of 1,3-Thiazoles with Copper Salts

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Contents

1- General Information

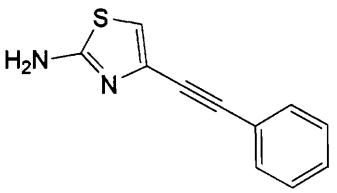
Materials and general methods. All commercial reagents and solvents were of the highest purity available (≥98%) and were used as purchased.

Thin layer chromatography (TLC) was performed with silica gel layers (type 60 F254; 400 – 630 Mesh) and compounds visualized under UV light at 254 nm. Column chromatography (CC) was carried out on silica gel with hexane and ethyl acetate (EtOAc) as eluents. Constituent proportions in chromatographic mobile phases are expressed by volume. Reverse phase HPLC was performed on a Prodigy column (10 μm, 250 × 10 mm) using a gradient of water and acetonitrile as solvents. Eluates were monitored for absorbance at 254 nm. Yields were recorded for chromatographically pure materials (≥98%) and purity of all new compounds was determined by analytical HPLC (Luna column, 10 μm, 250 × 4.6 mm) using an isocratic mixture of water and acetonitrile as solvents; absorbance was monitored at 254 nm.

The ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra of all compounds were acquired using the chemical shifts of residual deuterated solvents as internal standard; chemical shifts (δ) for the proton and carbon resonance are reported in parts per million (ppm) downfield from TMS (δ = 0). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double of doublet. Coupling constants, J were reported in hertz unit (Hz). Mass spectra were acquired with a LC-MS instrument equipped with a capillary RTX-5ms column (30 m × 0.25 mm; flow rate, 1 mL/min; carrier gas, He). High-resolution mass spectra were performed at the Mass Spectrometry Laboratory School of Chemical Sciences, University of Illinois. Mass spectra were acquired using the ESI method.

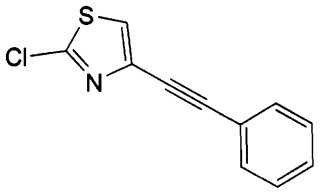
2 – Characterization of new compounds

4-(Phenylethynyl)thiazol-2-amine (4). 4-(Trimethylsilylethynyl)-2-thiazolylamine (750 mg, 3.82 mmol), iodobenzene (1.17 g, 5.73 mmol), CuI (49 mg, 0.25 mmol), $Pd(PPh_3)_4$ (147 mg, 0.13 mmol), and triethylamine (2.4 mL) were added to dimethylethylene glycol (DME; 24 mL) under an inert atmosphere. Argon was bubbled into the resulting dark solution while it was heated to 80°C. TBAF (5 mmol; 1.0 M solution in THF, 5 mL) was added via syringe over 45 min. The reaction mixture was heated at 80°C for 15 min, until TLC showed no starting material present. The reaction mixture was then cooled to room temperature and evaporated to dryness. The residue obtained was dissolved in ethyl acetate (25 mL), washed with water (2 × 40 mL) then brine (1 × 40 mL). The combined organic fractions were dried over $MgSO_4$, evaporated to dryness in vacuo and the product was purified by chromatography on silica gel (hexane-EtOAc, 70: 30, v/v) to yield 413 mg (54%) of **4**: m.p. 103 – 106 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.33 (m, 3H), 6.78 (s, 1H), 5.23 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (1C), 133.1(1C), 131.7(2C), 128.5(1C), 128.3(2C), 122.6(1C), 113.15(1C), 88.1(1C), 83.9(1C); HRMS (ESI+) calcd for $C_{11}H_9N_2S$ 201.0486, found 201.0485.

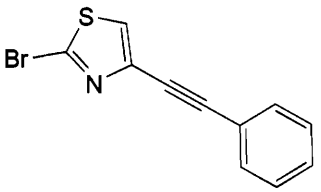


2-Chloro-4-(phenylethynyl)thiazole (5a). 5a was prepared following Method I, using **4** (115 mg, 0.57 mmol), butyl nitrite (100 μL, 0.86 mmol), and CuCl (85 mg, 0.86 mmol) in acetonitrile (5 mL). CC (EtOAc (3%) in hexane) yielded 41 mg (33%) of **5a**: m.p. 106 – 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.39 (s, 1H), 7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

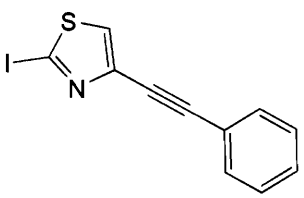
151.6 (1C), 136.5 (1C), 131.8 (2C), 129.0 (1C), 128.4 (2C), 124.0 (1C), 121.9 (1C), 89.7 (1C), 82.3 (1C); HRMS (ESI+) calc'd for $C_{11}H_7ClNS$ 219.9988, found 219.9990.



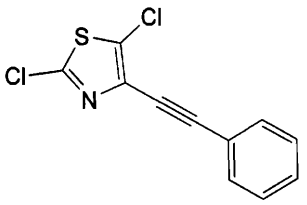
2-Bromo-4-(phenylethynyl)thiazole (5b). 5b was prepared following Method 1, using **4** (182 mg, 0.91 mmol), butyl nitrite (162 μL 1.39 mmol), and CuBr (200 mg, 1.39 mmol) in acetonitrile (8 mL). CC (EtOAc (3%) in hexane) yielded 111 mg (46%) of **5a**: m.p. 130–132°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.44 (s, 1H), 7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (1C), 135.7 (1C), 131.8 (2C), 129.0 (1C), 128.4 (2C), 125.7 (1C), 122.0 (1C), 90.1 (1C), 82.0 (1C); HRMS (ESI+) calcd for $C_{11}H_7{}^{79}BrNS$ 263.9483, found 263.9478.



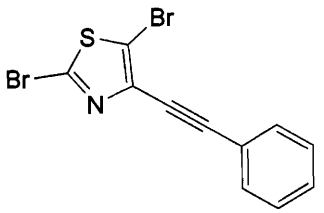
2-Iodo-4-(phenylethynyl)thiazole (5c). 5c was prepared following Method I, using **4** (150 mg, 0.75 mmol), butyl nitrite (131 μL, 1.13 mmol), and CuI (214 mg, 1.13 mmol) in acetonitrile (8 mL). CC (EtOAc (3%) in hexane) yielded 116 mg (50%) of **5c**: m.p. 136–138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.46 (s, 1H), 7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (1C), 131.8 (2C), 129.0 (1C), 128.4 (2C), 128.1 (1C), 122.0 (1C), 99.9 (1C), 90.4 (1C), 81.6 (1C); HRMS (ESI+) calc,d for $C_{11}H_7INS$ 311.9344, found 311.9339.



2,5-Dichloro-4-(phenylethynyl)thiazole (6a). 6a was prepared following Method II, using **4** (40 mg, 0.20 mmol), *n*-butyl nitrite (35 μL, 0.30 mmol) and anhydrous $CuCl_2$ (40 mg, 0.30 mmol) in acetonitrile (2 mL). CC (EtOAc (3%) in hexane) yielded 18 mg (35%) of **6a**: clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (1C), 134.5 (1C), 131.9 (2C), 129.3 (1C), 128.5 (2C), 121.7 (1C), 94.8 (1C), 79.6 (1C), (one carbon resonates within solvent peak); HRMS (ESI+) calc'd for $C_{11}H_6Cl_2NS$ 253.9598, found 253.9609.

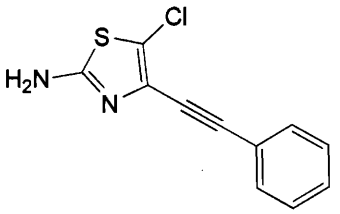


2,5-Dibromo-4-(phenylethynyl)thiazole (6b). 6b was prepared following Method II, using **4** (40 mg, 0.20 mmol), *n*-butyl nitrite (35 μL, 0.30 mmol) and $CuBr_2$ (67 mg, 0.30 mmol) in acetonitrile (2 mL). CC (EtOAc (3%) in hexane) yielded 54 mg (79%) of **6b**: clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9 (1C), 135.0 (1C), 131.9 (2C), 129.3 (1C), 128.4 (2C), 121.7 (1C), 114.4 (1C), 94.3 (1C), 80.5 (1C); HRMS (ESI+) calc'd for $C_{11}H_6{}^{79}Br_2NS$ 341.8588, found 341.8582.

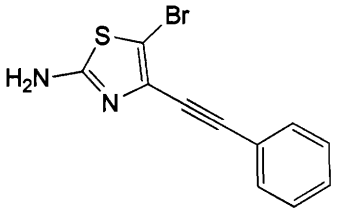


5-Chloro-4-(phenylethynyl)thiazol-2-amine (7a). 7a was prepared following Method III, using **4** (35 mg, 0.18 mmol) and anhydrous $CuCl_2$ (35 mg, 0.26 mmol) in acetonitrile (2 mL). CC (EtOAc (30%) in hexane) yielded 21 mg (51%) of **7a**: m.p. 126 – 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.35 (m, 3H), 5.13 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2

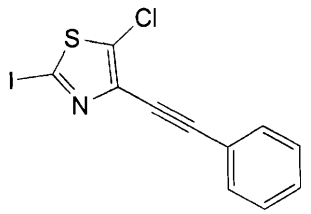
(1C), 131.8 (2C), 130.6 (1C), 128.9 (1C), 128.4 (2C), 122.2 (1C), 118.3 (1C), 93.4 (1C), 81.0 (1C); HRMS (ESI+) calc'd for $C_{11}H_8ClN_2S$ 235.0097, found 235.0104.



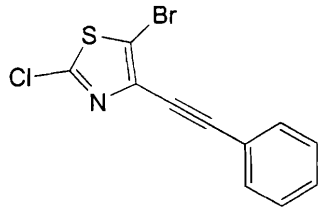
5-Bromo-4-(phenylethynyl)thiazol-2-amine (7b). 7b was prepared following Method III, using **4** (52 mg, 0.26 mmol) and $CuBr_2$ (58 mg, 0.26 mmol) in acetonitrile (2.5 mL). CC (EtOAc (30%) in hexane) yielded 68 mg (94%) of **7b**: m.p. 147 – 150°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.35 (m, 3H), 5.00 (br s, 2H); ^{1}H NMR (400 MHz, CD_3CN) δ 7.47 (m, 2H), 7.33 (m, 3H), 5.83 (br s, 2H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.0 (1C), 134.2 (1C), 132.5 (2C), 130.2 (1C), 129.8 (2C), 123.0 (1C), 92.8 (1C), 83.5 (1C), (one carbon resonates within solvent peak); HRMS (ESI+) calc'd for $C_{11}H_8{}^{79}BrN_2S$ 278.9592, found 278.9584.



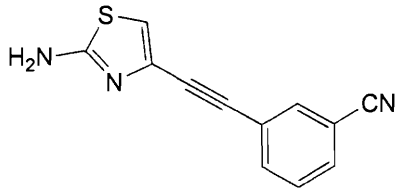
5-Chloro-2-iodo-4-(phenylethynyl)thiazole (8). 8 was prepared following Method I, using the aminothiazole derivative **7a** (13 mg, 0.06 mmol), butyl nitrite (10 µL, 0.09 mmol), and CuI (15 mg, 0.08 mmol) in acetonitrile (1 mL). CC (EtOAc (3%) in hexane) yielded 8 mg (42%) of **8**: m.p. 130 – 132° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (1C), 133.0 (1C), 131.9 (2C), 129.3 (1C), 128.4 (2C), 121.7 (1C), 96.4 (1C), 95.2 (1C), 79.1 (1C); HRMS (ESI+) calc'd for $C_{11}H_6ICINS$ 345.8954, found 345.8947.



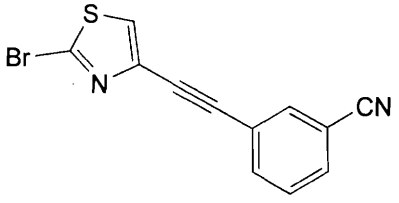
5-bromo-2-chloro-4-(phenylethynyl)thiazole (9). 9 was prepared following general procedure I, using the aminothiazole derivative **7b** (35 mg, 0.13 mmol), butyl nitrite (22 μL, 0.19 mmol), and CuCl (19 mg, 0.19 mmol) in acetonitrile (1.5 mL). CC (EtOAc (3%) in hexane) yielded 5 mg (13%) of **9**: clear oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8 (1C), 137.5 (1C), 132.0 (2C), 129.3 (1C), 128.5 (2C), 121.7 (1C), 112.9 (1C), 94.1 (1C), 80.7 (1C); HRMS (ESI+) calcd for $C_{11}H_6{}^{79}BrClNS$ 297.9080, found 297.9083.



3-((2-Aminothiazol-4-yl)ethynyl)benzonitrile (10). 10 was prepared following the procedure used to prepare **4**, with 3-iodobenzonitrile (1.312 g, 5.73 mmol) instead of iodobenzene. CC (EtOAc (30%) in hexane) yielded 377 mg (44%) of **10**: m.p. 186 – 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (td, J_1 = 1.65 Hz, J_2 = 0.60, 1H), 7.73 (ddd, J_1 = 7.86 Hz, J_2 = 1.65 Hz, J_3 = 1.24 Hz, 1H), 7.61 (ddd, J_1 = 7.81 Hz, J_2 = 1.61 Hz, J_3 = 1.25 Hz, 1H), 7.45 (td, J_1 = 7.84 Hz, J_2 = 0.64 Hz, 1H), 6.86 (s, 1H), 5.01 (br s, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.8 (1C), 136.7 (1C), 135.8 (1C), 133.1 (1C), 132.9 (1C), 130.8 (1C), 125.0 (1C), 119.0 (1C), 115.6 (1C), 113.8 (1C), 87.5 (1C), 85.9 (1C); HRMS (ESI+) calc'd for $C_{12}H_8N_3S$ 226.0439, found 226.0439.

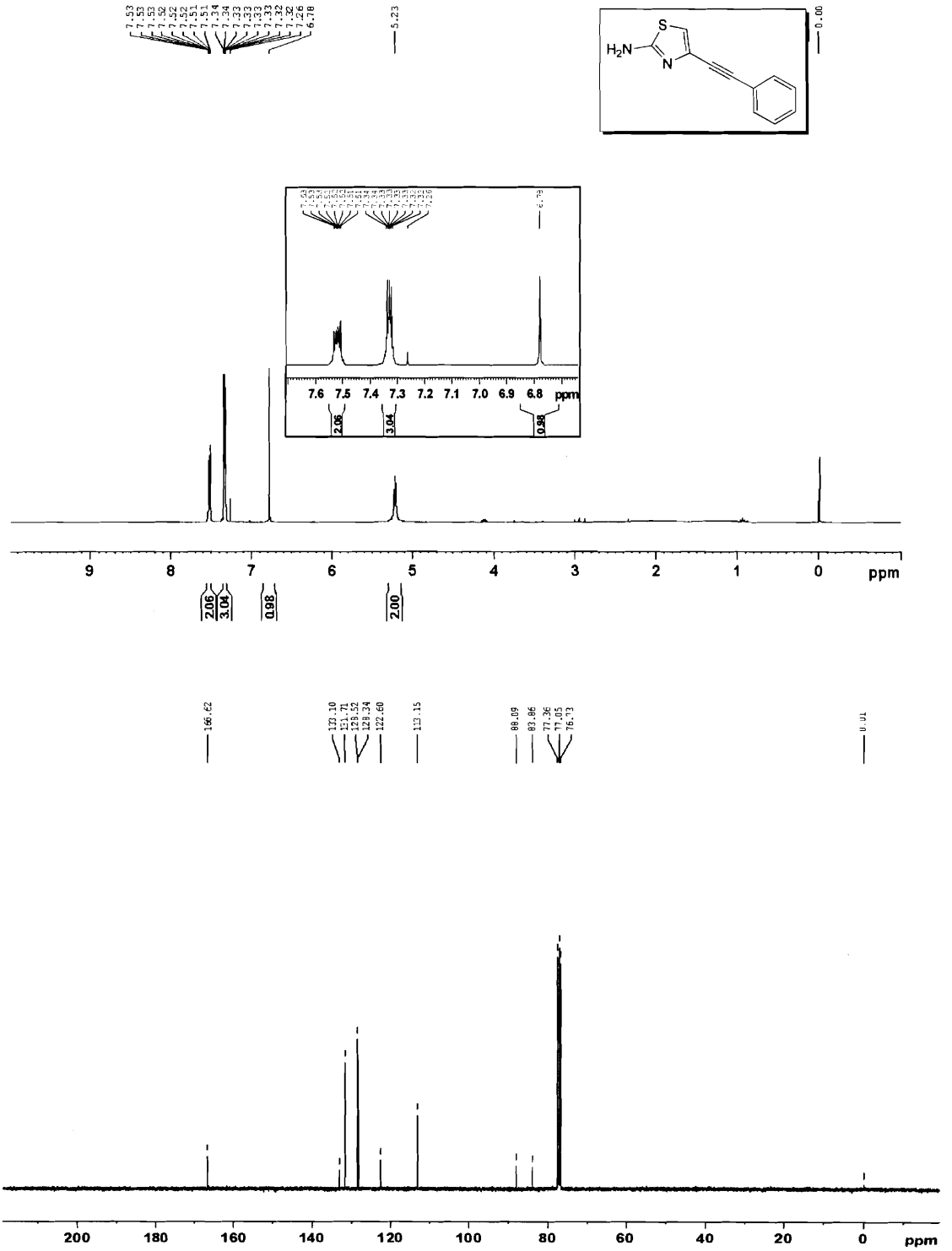


3-((2-Bromothiazol-4-yl)ethynyl)benzonitrile (11). 11 was prepared following Method I, using **9** (85 mg, 0.38 mmol), butyl nitrite (66 μL, 0.57 mmol), and CuBr (81 mg, 0.57 mmol) in acetonitrile (5 mL). CC (EtOAc (3%) in hexane) yielded 35 mg (32%) of **11**: m.p. 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (t, 1H, J = 1.4 Hz), 7.75 (dt, J_1 = 7.88 Hz, J_2 = 1.34 Hz, 1H), 7.65 (dt, J_1 = 7.84 Hz, J_2 = 1.33 Hz, 1H), 7.52 (s, 1H), 7.49 (t, J = 7.86 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1 (1C), 136.2 (1C), 135.8 (1C), 135.0 (1C), 132.2 (1C), 129.5 (1C), 127.0 (1C), 123.7 (1C), 117.9 (1C), 113.1 (1C), 87.4 (1C), 84.3 (1C); HRMS (ESI+) calc'd for $C_{12}H_6{}^{79}BrN_2S$ 288.9435, found 288.9448.

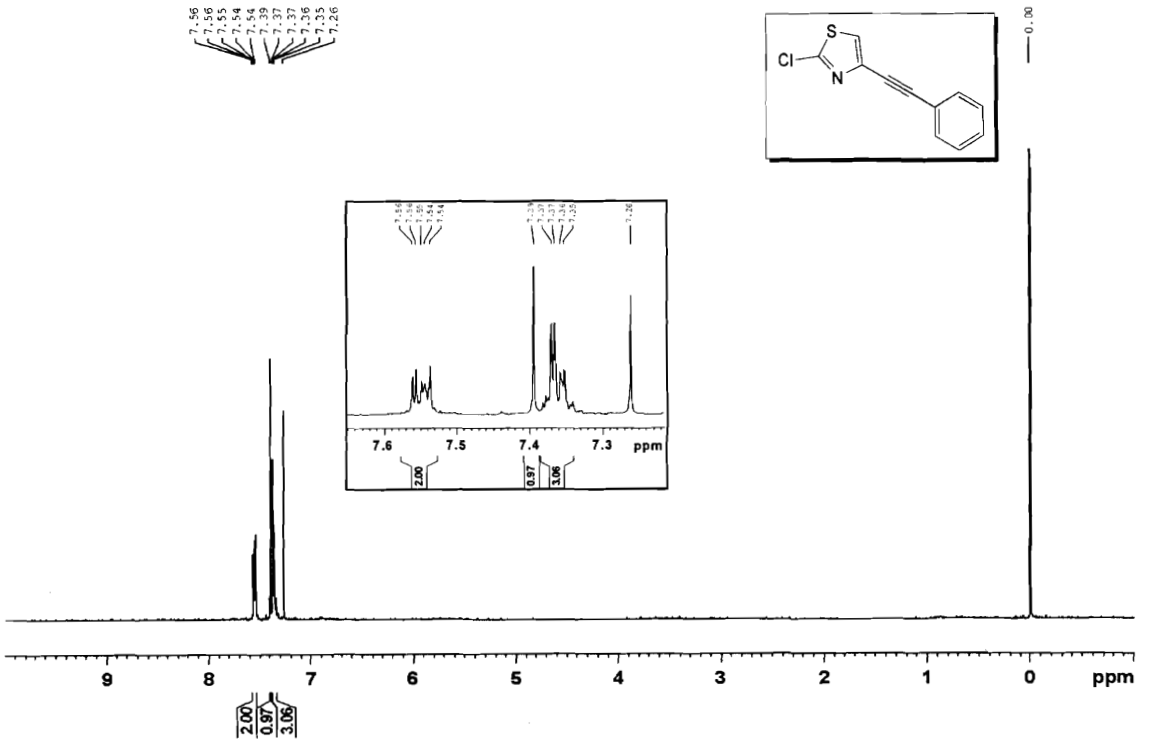


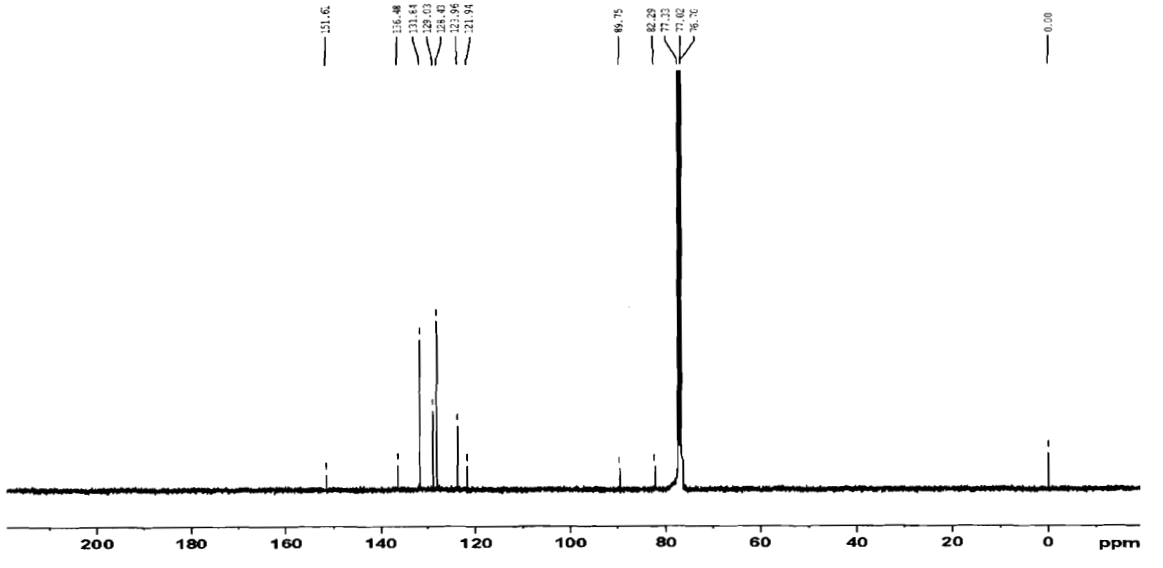
Spectral Copies of ^{1}H and ^{13}C NMR of Products Obtained in this Study.

4-(Phenylethynyl)thiazol-2-amine (Entry 4)

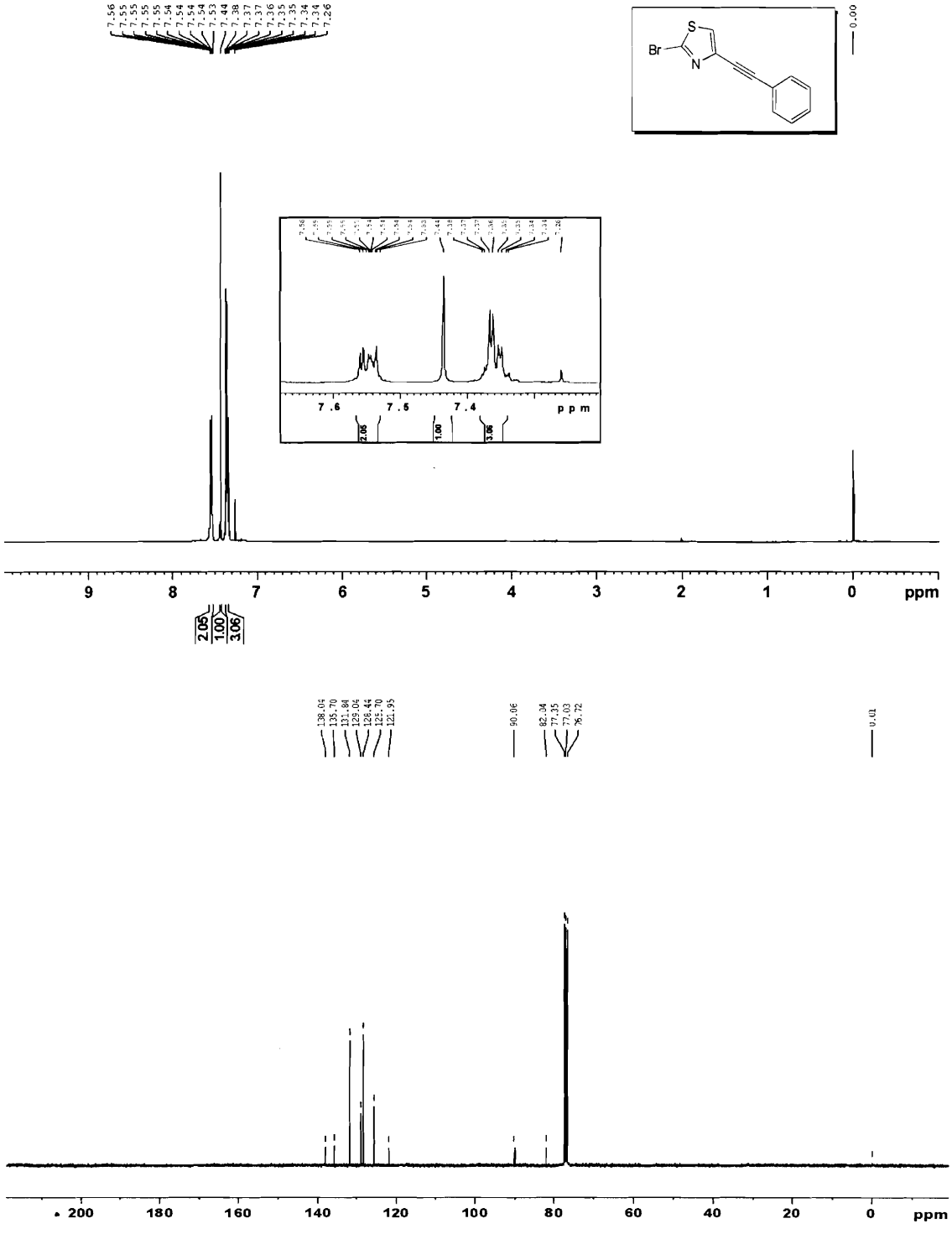


2-Chloro-4-(phenylethynyl)thiazole (Entry 5a)

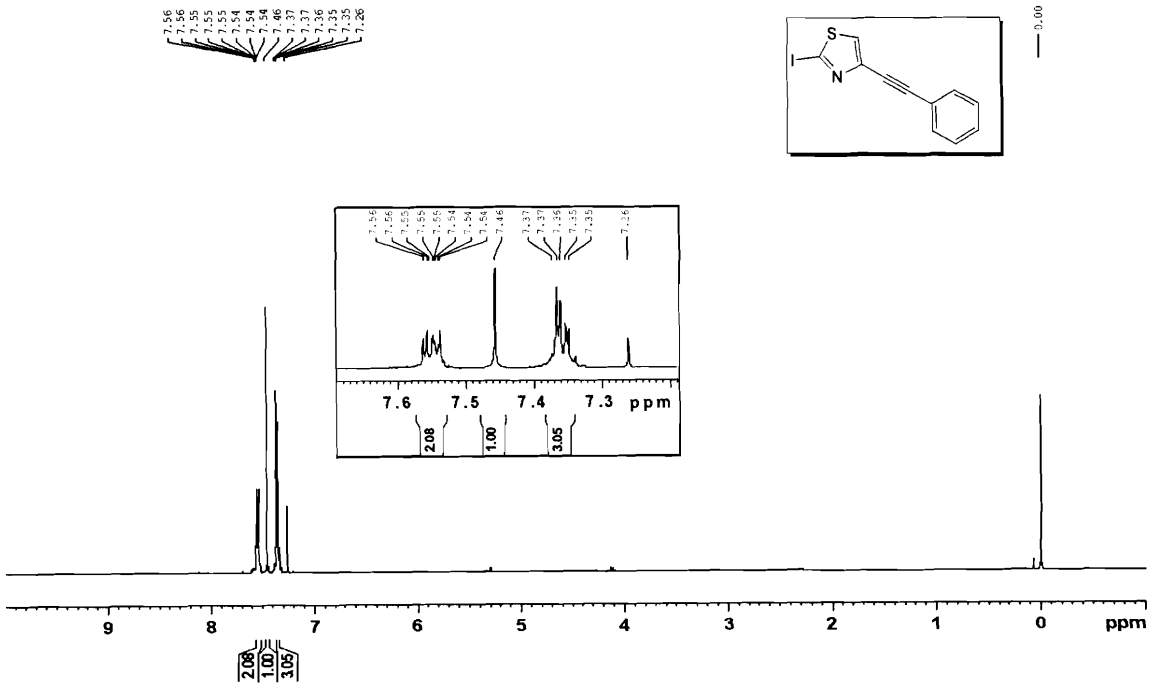


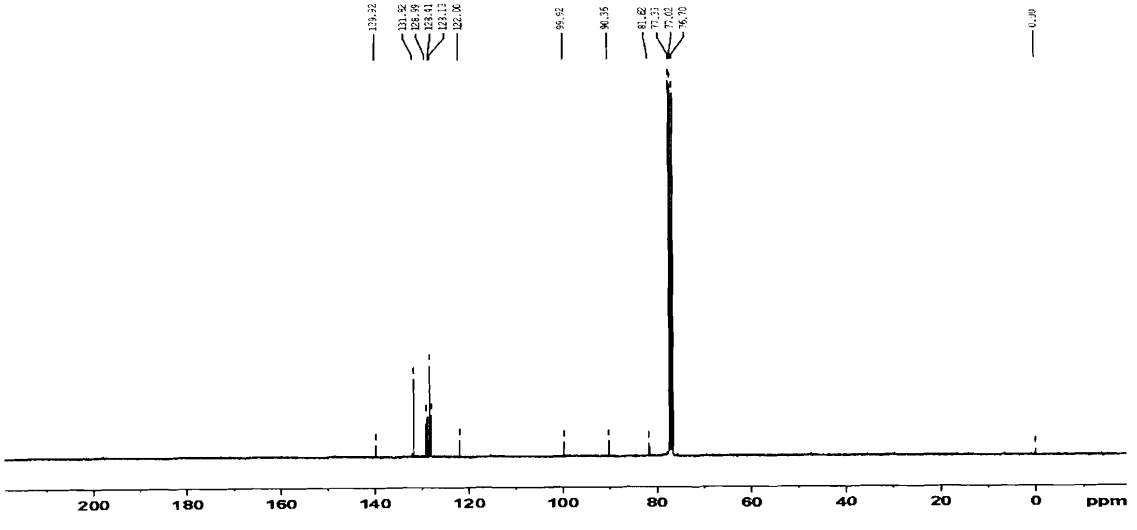


2-Bromo-4-(phenylethynyl)thiazole (Entry 5b)

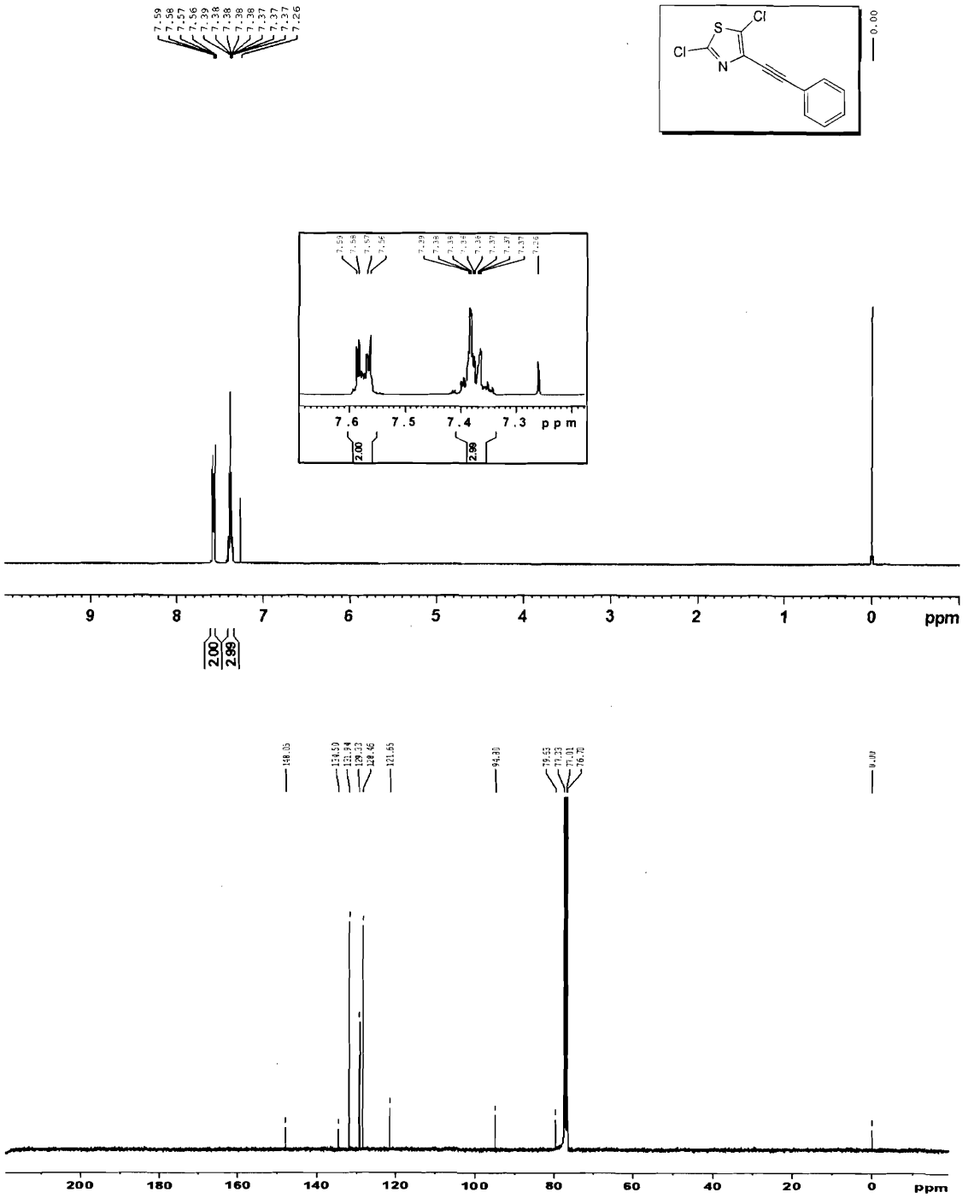


2-Iodo-4-(phenylethynyl)thiazole (Entry 5c)

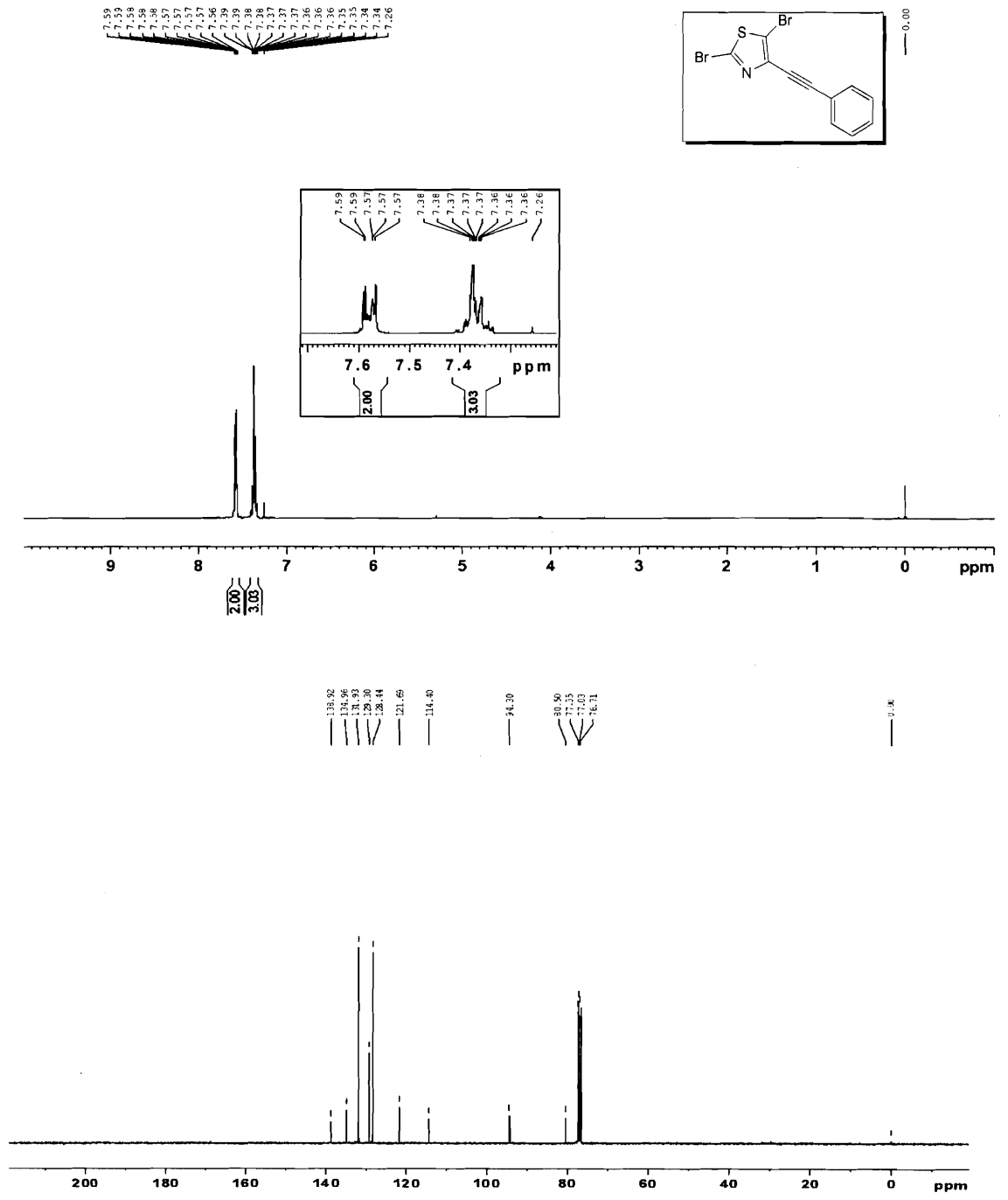




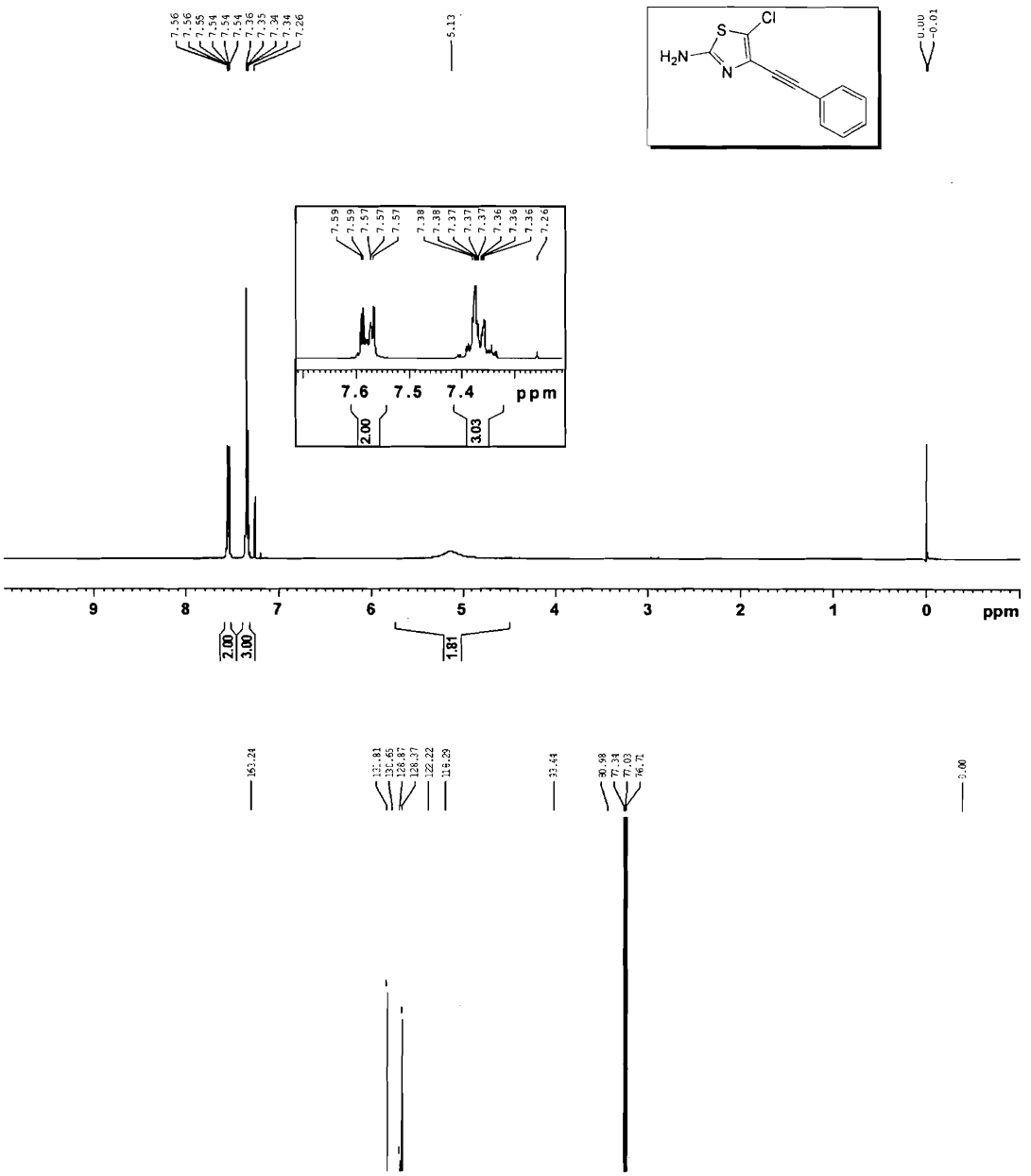
2,5-Dichloro-4-(phenylethynyl)thiazole (Entry 6a)



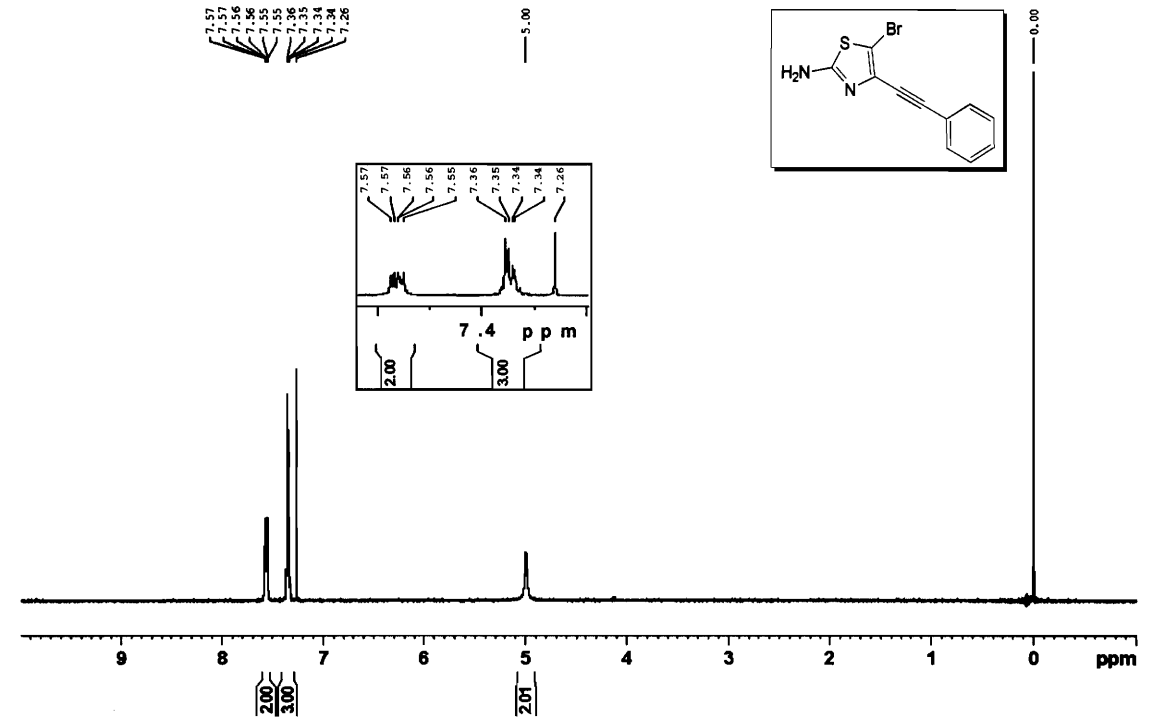
2,5-Dichloro-4-(phenylethynyl)thiazole (Entry 6b)

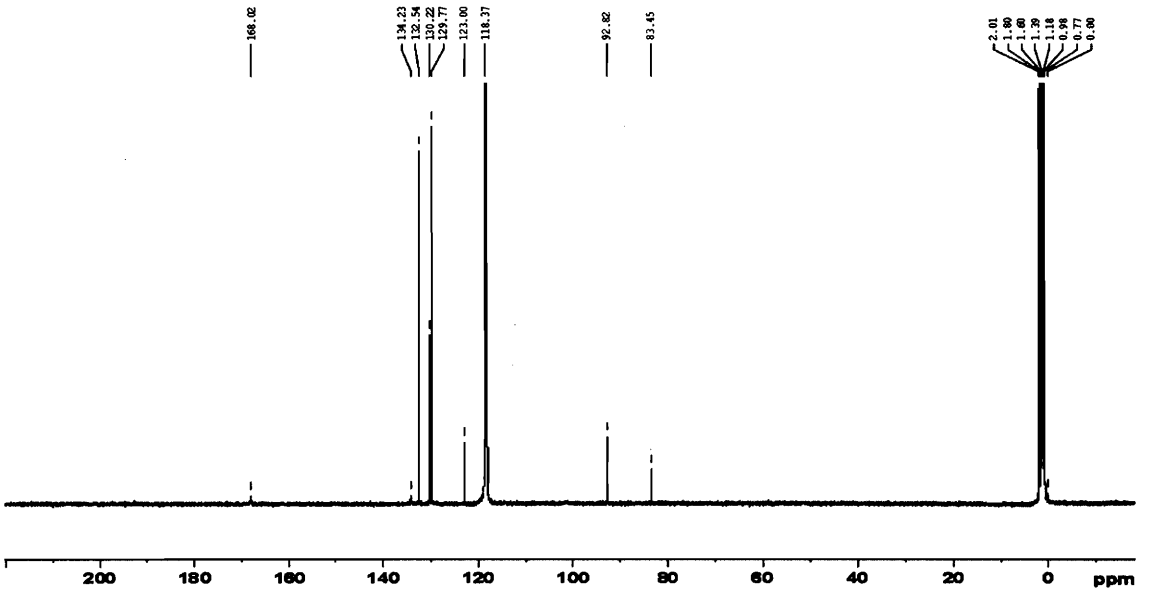


5-Chloro-4-(phenylethynyl)thiazol-2-amine (Entry 7a)

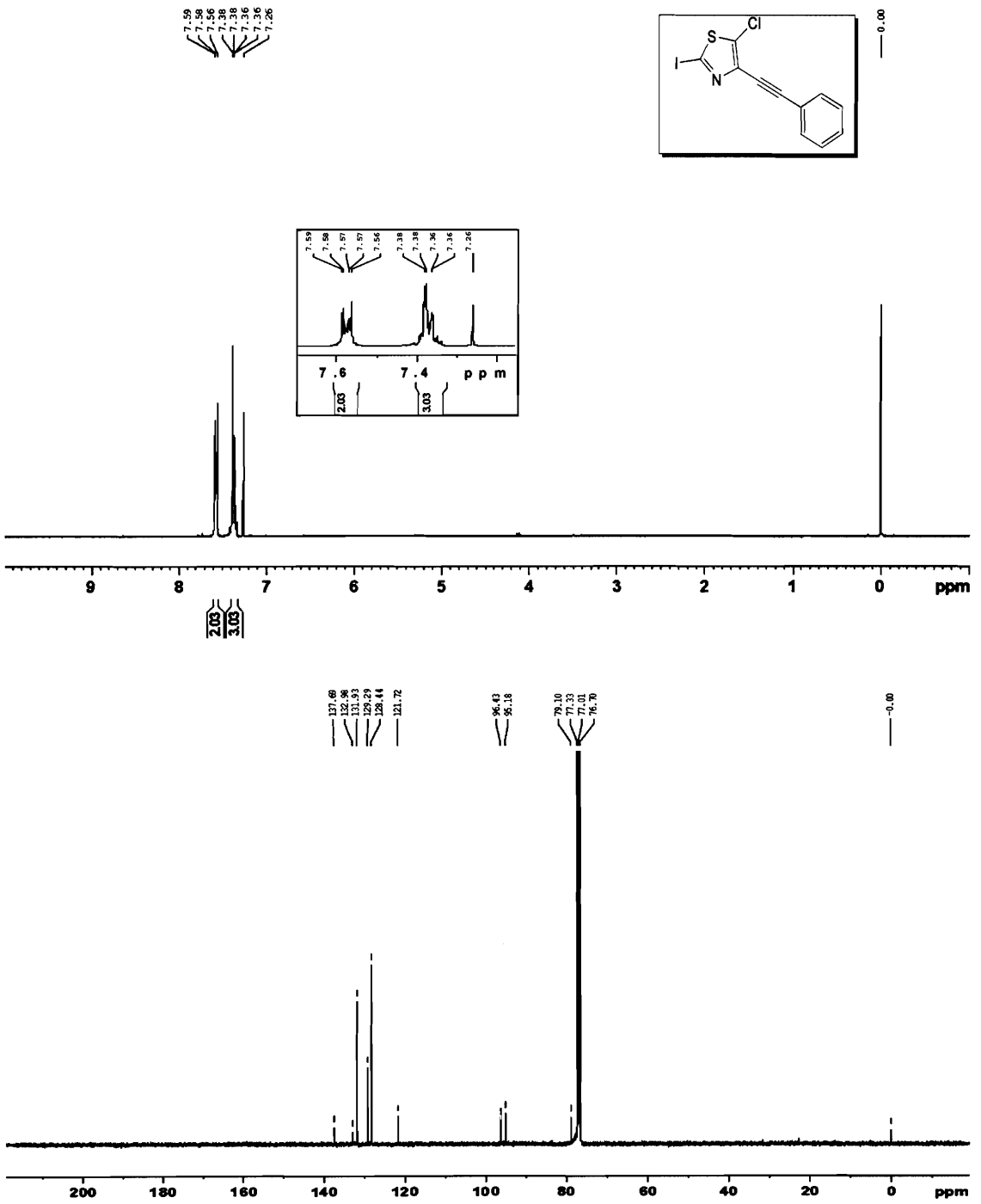


5-Chloro-4-(phenylethynyl)thiazol-2-amine (Entry 7b)

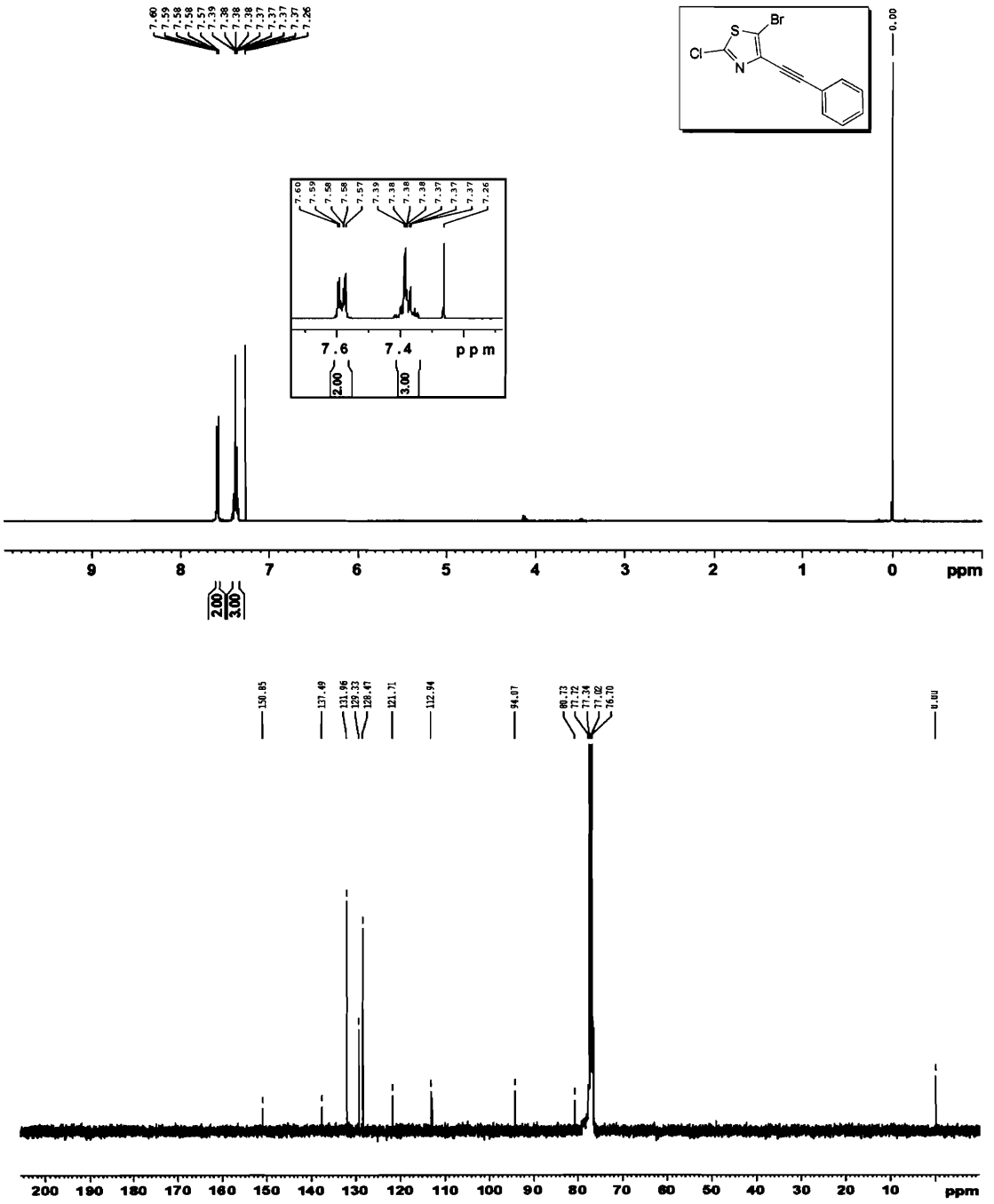




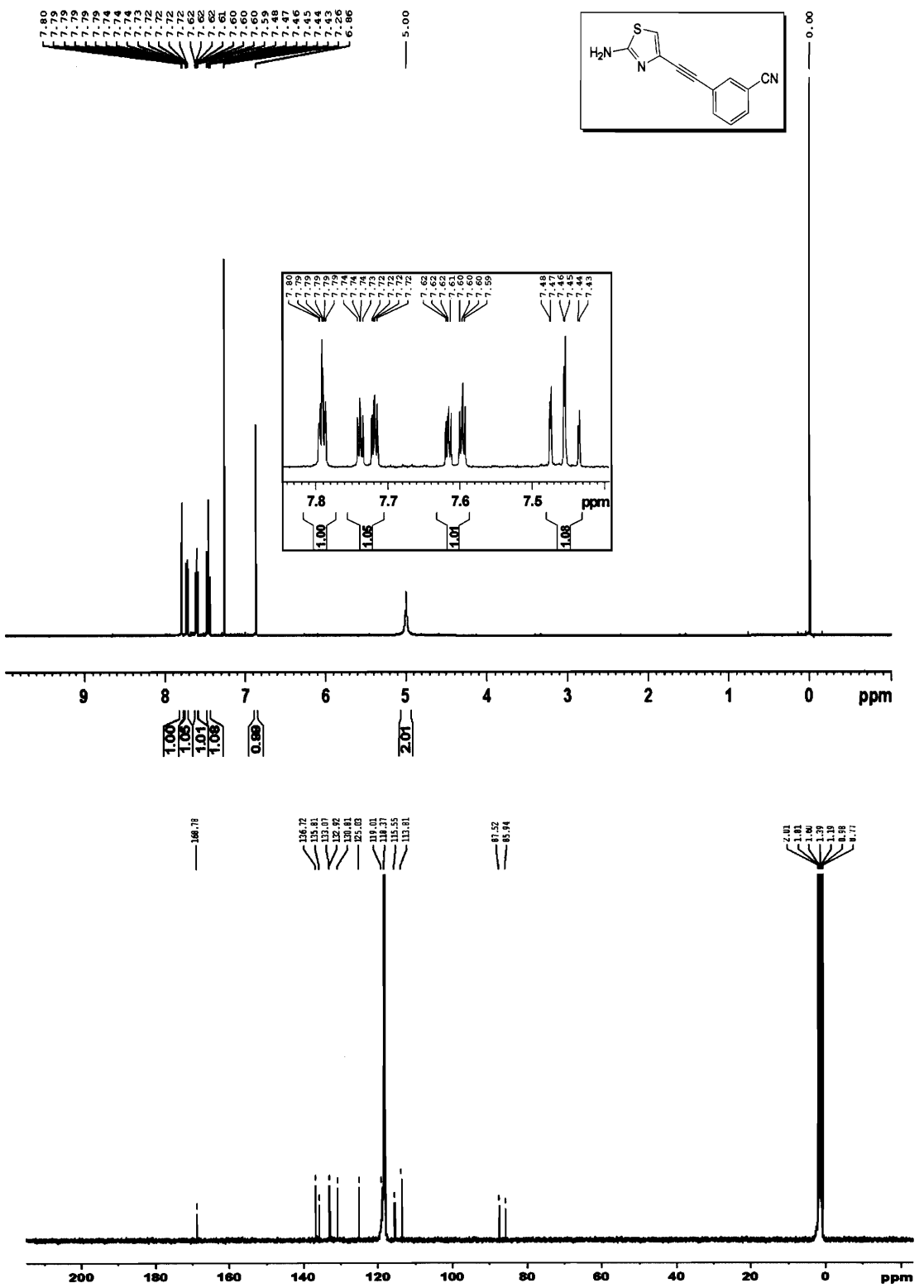
5-Chloro-2-iodo-4-(phenylethynyl)thiazole (Entry 8).



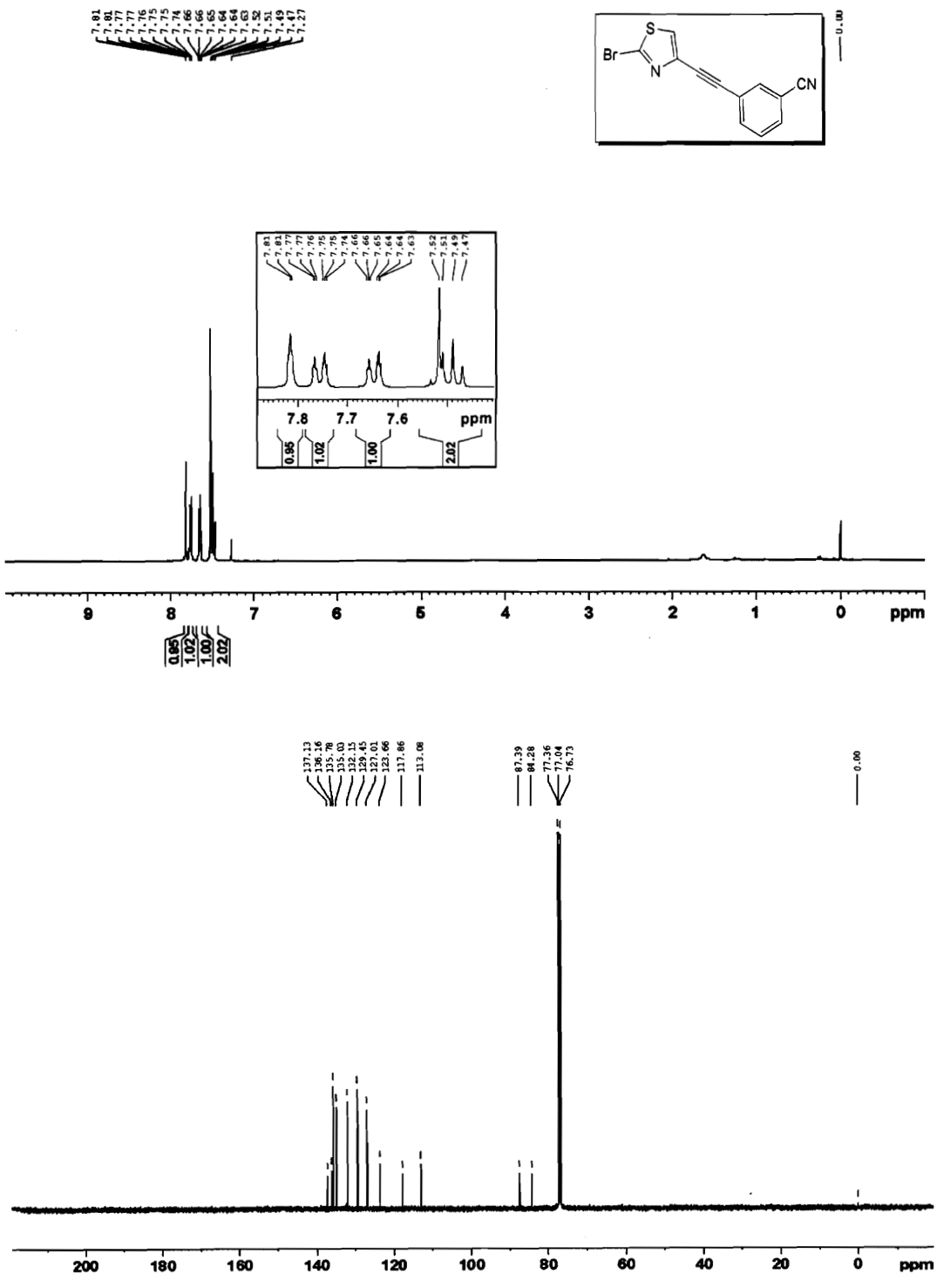
5-bromo-2-chloro-4-(phenylethynyl)thiazole (Entry 9).



3-((2-Aminothiazol-4-yl)ethynyl)benzonitrile (Entry 10).



3-((2-Bromothiazol-4-yl)ethynyl)benzonitrile (Entry 11)



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December 23, 2008

Dear Editor,

We am pleased to submit this manuscript entitled "Efficient and Regioselective Halogenations of 1,3-Thiazoles with Copper Salts" for publication as a Note in the *Journal of Organic Chemistry*.

In the course of our studies, and while developing a new class of ligands with high affinity for the metabotropic glutamate receptors, subtype 5, we found that copper(I) and copper(II) salts react with aminothiazole compounds to give either mono or dihalogeno thiazole derivatives with high selectivity (see Table 1). We also found that monohalogenation was also possible in very smooth conditions using a copper-based supported material. These observations are remarkable and could potentially deserve description in a full article. There is no doubt that, by their simplicity and their selectivity, these methods could be of broad application for the rapid functionalization of more complex molecules.

The quality of our research at the National Institute of Mental Health in Bethesda is well appreciated and often cited (see for example *Curr. Top. Med. Chem.* 2007, *7*, 15, 1541) and we have no doubt that after publication in the Journal of Organic Chemistry, this piece of work will be extensively used as a reference in further works.

We thank you for your interest and kind consideration and I personally present you with you my best wishes at the beginning of this Holiday season.

Very best regards

Fabrice Simeon

Please find attached the names and coordinates of five scientists who are highly qualified to serve as reviewers for this manuscript.

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