Supporting information

Flexible on-site halogenation paired with hydrogenation using halide electrolysis

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I. Experimental Details

Materials

Sodium bromide and sodium nitrate were purchased from Bio BASIC Inc. Sulfuric acid and aniline were purchased from Fisher Scientific Co. Ammonia solution was purchased from Acros Inc. Sodium chloride, tetrabutylammonium tetrafluoroborate and anhydrous sodium sulfate, sodium carbonate were purchased from Chem-Impex Int'l Inc. Tetra-n-butylammonium bromide, hydrogen bromide, styrene, 4-chloroaniline, acetophenone, dimethylaniline, cyclohexane, 1,3,5-trimethoxy-benzene, triethylamine, sodium phosphate, lithium bromide and Pt/C (10%) were purchased from Sigma-Aldrich. Anisole was purchased from Honeywell Fluka. Potassium bromide was purchased from LabChem Inc. 4-acetylbenzonitrile, benzo[*b*]thiophene, 2-vinylnaphthalene, 1-phenyl-1-propyne, 5-chloro-2-pyridinamine were purchased from Ambeed Inc.

On-site bromination methods

The bromide electrolysis was conducted in a three-bottleneck flask. The electrolyte was 0.5 M H_2SO_4 with saturated NaBr. The electrolysis was performed on Gamry Interface 1000 electrochemical workstation using two-electrode system. The platinum plates (1.0 cm × 1.0 cm) were employed as both working electrode and counter electrode. The electrolysis was conducted through constant current of 1 A. The generated Br_2 gas continuously transported to another flask containing substrates dissolved in solvents for bromination. The reaction process was monitored by thin layer chromatography (TLC).

For the syntheses of **2a-c**, 0.5 mmol substrate was dissolved in 10 mL of $CHCl_3$ solution. Afterwards, the solution was washed by saturated Na_2CO_3 solution for several times. The organic layer was evaporated to obtain the crude product. The purification was performed through silica chromatography.

For the syntheses of **2d-f**, it was similar with **2a-c**. The solution was kept at 0 ℃ and protected by N_2 gas during the entire process.

For the syntheses of **4**(**a-c**), 0.5 mmol substrate was dissolved in 10 mL of Et_2O solution containing AcOH (30 eqv.) and Et_3N (3 eqv.), which was kept at 0 ℃ and protected by N_2 gas. After the reaction, the precipitate was filtrated and the organic solution was removed by evaporation. It was dissolved in CH_2Cl_2 and added with ammonia solution until the pH was increased to 10. Then it

was washed by pure water and saturated brine. The organic layer was dried over anhydrous sodium sulfate and was evaporated. The crude product was further purified by silica chromatography.

For the synthesis of **4d**, 0.5 mmol substrate was dissolved in 10 mL of $CHCl_3$ containing AcOH (30 eqv.) protected by N_2 gas. The following workup after the reaction was similar with **4**(**a-c**).

For the synthesis of **6**, 8 mmol substrate was dissolved in 20 mL of $(CH_2)_2Cl_2$ containing anhydrous $AlCl_3$ (1.75 eqv.). The bromide electrolysis was conducted with Br_2 gas continuously transported to the above solution for 8 h. Then it was subjected to oil bath and under flex condition at 40 ℃ overnight. Afterwards, it was washed by pure water for several times. The organic layer was removed by vacuum evaporation. The crude product was further purified by silica chromatography.

For the synthesis of **8**, 0.5 mmol substrate was dissolved in 10 mL of Et_2O. The solution was kept at 0 ℃ and protected by N_2. Afterwards, the organic layer was evaporated to obtain the crude product. The purification was performed through silica chromatography.

On-site chlorination methods

The chloride electrolysis was conducted in a three-bottleneck flask. The electrolyte was 0.5 M H_2SO_4 with saturated NaCl. The electrolysis was performed on Gamry Interface 1000 electrochemical workstation using two-electrode system. The platinum plates (1.0 cm × 1.0 cm) were employed as both working electrode and counter electrode. The electrolysis was conducted at the constant current of 1 A.

For the on-site chlorination for **9**, 0.5 mmol substrate was dissolved in 10 mL of Et_2O. The solution was kept at 0 ℃ and protected by N_2. The electrolysis was conducted and Cl_2 gas continuously transported to the above solution. The reaction process was monitored by TLC. Afterwards, the organic layer was evaporated to obtain the crude product. The purification was performed through silica chromatography.

On-site hydrogenation methods

The electrolysis was conducted in a H-type cell separated by an ion exchange membrane (Nafion 117, Fuel Cell Store) with the electrolyte of 0.5 M H_2SO_4 at a constant current of 1 A. It was performed on Gamry Interface 1000 electrochemical workstation using two-electrode system. The platinum plates (1.0 cm × 1.0 cm) were employed as both working electrode and counter electrode.

For the on-site hydrogenation for **10**, 0.5 mmol substrate was mixed with 20% wt of commercial Pt/C (10% wt) in 15 mL of isopropanol, followed by transferring into a glass vial sealed with balloon. During the electrolysis, the generated H_2 gas from the cathode in H-type cell was continuously bubbled into the glass vial above for 6 h. Then the hydrogenation was performed

overnight and the catalyst was separated through filtration. Then the organic solution was removed by vacuum evaporation. The purification was performed through silica chromatography.

On-site bromination paired with hydrogenation methods

The electrolysis was conducted in a H-type cell separated by an ion exchange membrane (Nafion 117, Fuel Cell Store) at the constant current of 1 A. The catholyte was 0.5 M H_2SO_4, and the anolyte was 0.5 M H_2SO_4 containing saturated NaBr It was performed on Gamry Interface 1000 electrochemical workstation using two-electrode system. The platinum plates (1.0 cm × 1.0 cm) were employed as both working electrode and counter electrode.

For the syntheses of **2d** and **10**, 6 mmol of **1d** was dissolved in 50 mL of $CHCl_3$ solution and transferred to a glass vial (A). 1 mmol of **5** was dissolved in 20 mL of isopropanol solution containing 20% wt of Pt/C (10% wt) and transferred to another glass vial sealed with balloon (B). Then the electrolysis was conducted for 6 h, with Br_2 gas continuously transported to the A, while the H_2 gas continuously transported to the B. The following workup to obtain pure **2d** and **10** were similar with mentioned above.

Product quantification

NMR spectra were recorded on a Bruker Avance 400inv or 400sp Spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). The product yield was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. Gas chromatography-mass spectrometry (GC-MS) was measured with an Agilent 19091S-433 column (30 m × 0.25 mm × 0.25 mm).

Electrochemical measurements

Cyclic voltammetry (CV) of performed on Gamry Interface 1000 electrochemical workstation using three-electrode system. The glassy carbon electrode was used as working electrode, with Pt wire and Ag/AgCl as the counter and the reference electrode, respectively. The electrochemical behaviors of aniline compounds (**3a-d**, 10 mM) and tetrabutylammonium bromide (nBu_4NBr, 10 mM) were performed in CH_2Cl_2 containing 0.1 M nBu_4NBF_4 with scan rate of 50 mV s^{-1}. The potential was calibrated by ferrocene ($Fc^{+/0}$).

Faradaic efficiency measurement

Faradaic efficiency of electrochemically produced Br_2 was measured using UV-visible absorption. Specifically, the bromide electrolysis was conducted in a vial with a volume of 20 mL. The 10 mL electrolyte was composed of H_2SO_4 and saturated NaBr. The electrolysis was performed at a constant current of 1 A using a Gamry Interface 1000 electrochemical workstation in a two-electrode configuration. Pt foils were used as both anode and cathode. The generated Br_2 gas was continuously transported to another vial containing 4 mL CH_3CN. In order to avoid the evaporation of accumulated Br_2 in CH_3CN within a long-term electrolysis, the produced Br_2 was collected at the specific time of electrolysis (30, 50, 70, 90, 110 min) for only 10~12 min with fresh CH_3CN each time. Then 10 μL of the above Br_2 solution was transported to a cuvette (optical path length

of 1 cm) containing 2990 μL CH_3CN to collect the UV-vis absorption data.

The calibration curve for Br_2 quantification and the Faradaic efficiency measured at different electrolysis time are shown in Figures S1 and S2, respectively. Based on the calibration curve, our measured absorption coefficient of Br_2 at 400 nm is 160.3 M^{-1} cm^{-1}, which is very close to the reported value of 167 M^{-1} cm^{-1} in water (*Russ. J. Electrochem.*, 2018, 54, 1233-1242). From Figure S2, it is apparent that the Faradaic efficiency of Br_2 production in the collected vial is relatively low during the first hour of electrolysis, most likely due to the high solubility of Br_2 in the electrolyte solution. However, along the proceeding of electrolysis, more Br_2 will be transported to the reaction vial and its corresponding Faradaic efficiency is approaching 100% eventually. It should be noted that optimization of the electrolysis setup, including electrolyzer size, electrolyte volume, and electrolysis temperature will greatly influence the Faradaic efficiency of Br_2 collection in the bromination vial.

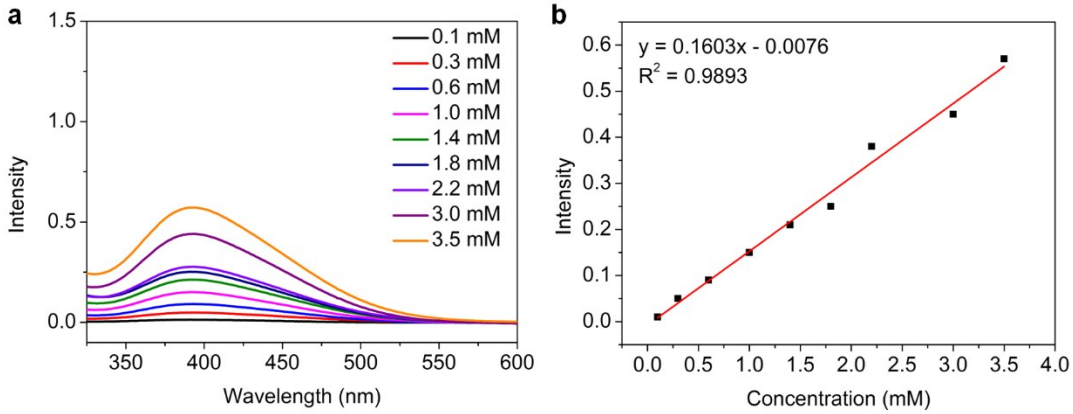


Figure S1. (a) UV-visible absorption spectra of B_2 in CH_3CN with different concentration and (b) its corresponding calibration plot regarding absorbance at 400 nm versus concentration.

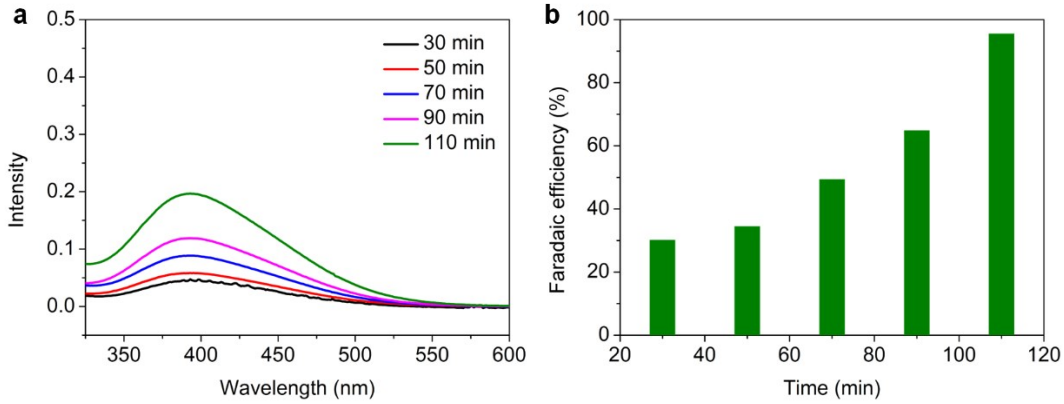


Figure S2. (a) UV-vis spectra of electrochemically produced Br_2 in CH_3CN collected at different electrolysis time. (b) Faradaic efficiency for the production of Br_2 measured at different electrolysis time.

Discussion of on-site bromination of acetophenone (5) without $AlCl_3$

On-site bromination of acetophenone in the absence of $AlCl_3$ was also performed. As shown in Figure S3, only bromination at the methyl group took place with the $AlCl_3$ catalyst. Both 2-bromoacetophenone and 2,2-dibromo-1-phenylethanone were detected.

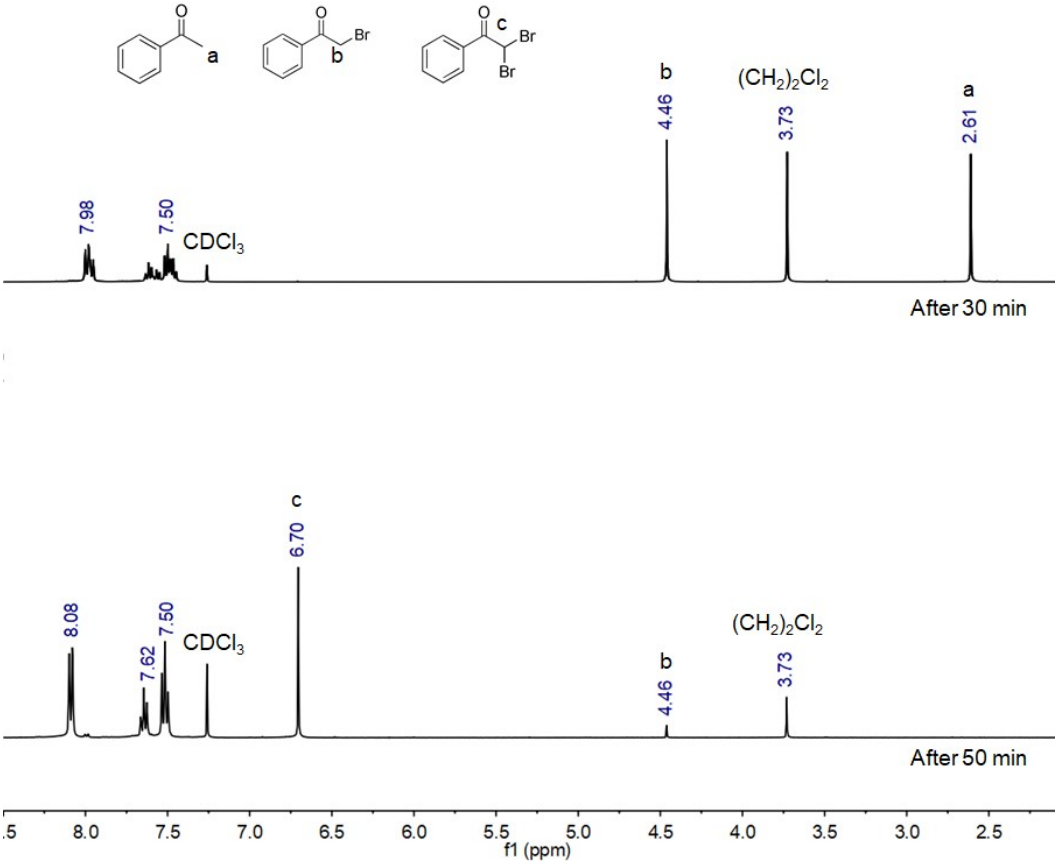


Figure S3. ^{1}H-NMR spectra of products obtained from on-site bromination of acetophenone with the addition of $AlCl_3$ (NMR solvent: $CDCl_3$).

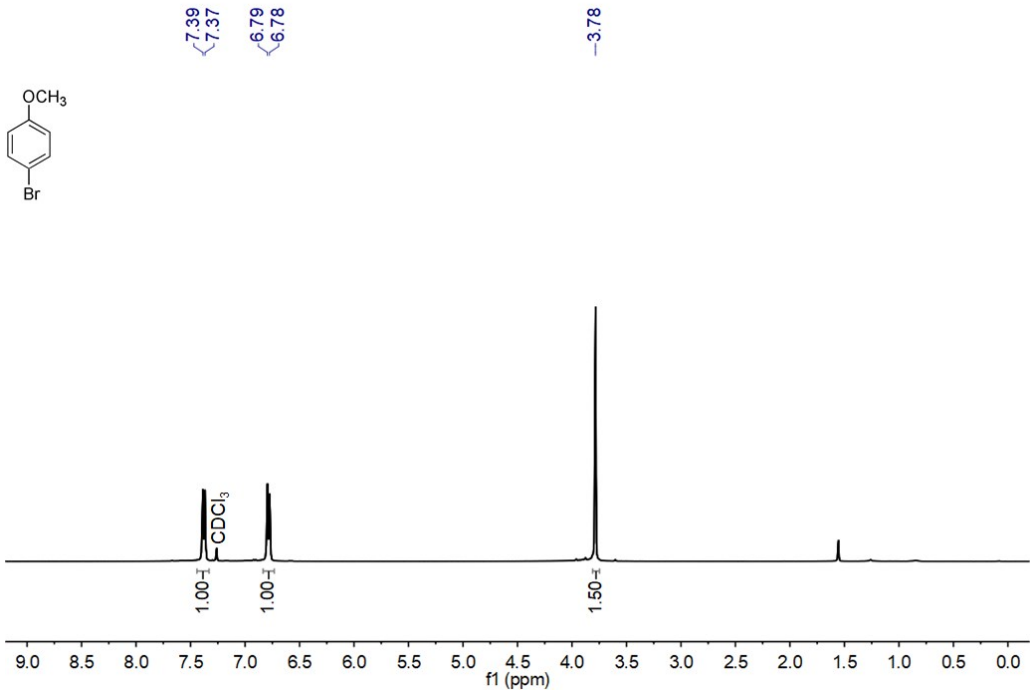
Reference

1 M. M. Petrov, P. A.Loktionov, D. V. Konev, A. E. Antipov, E. A. Astafiev and M. A. Vorotyntsev, *Russ. J. Electrochem.*, 2018, **54**, 1233-1242.

II. Product Characterization

1-bromo-4-methoxy-benzene (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 2 H), 6.78 (d, 2 H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.67, 132.22, 115.70, 112.79, 55.42. GC-MS *m*/*z*: 186 $[M]^+$, 188 $[M+2]^+$.



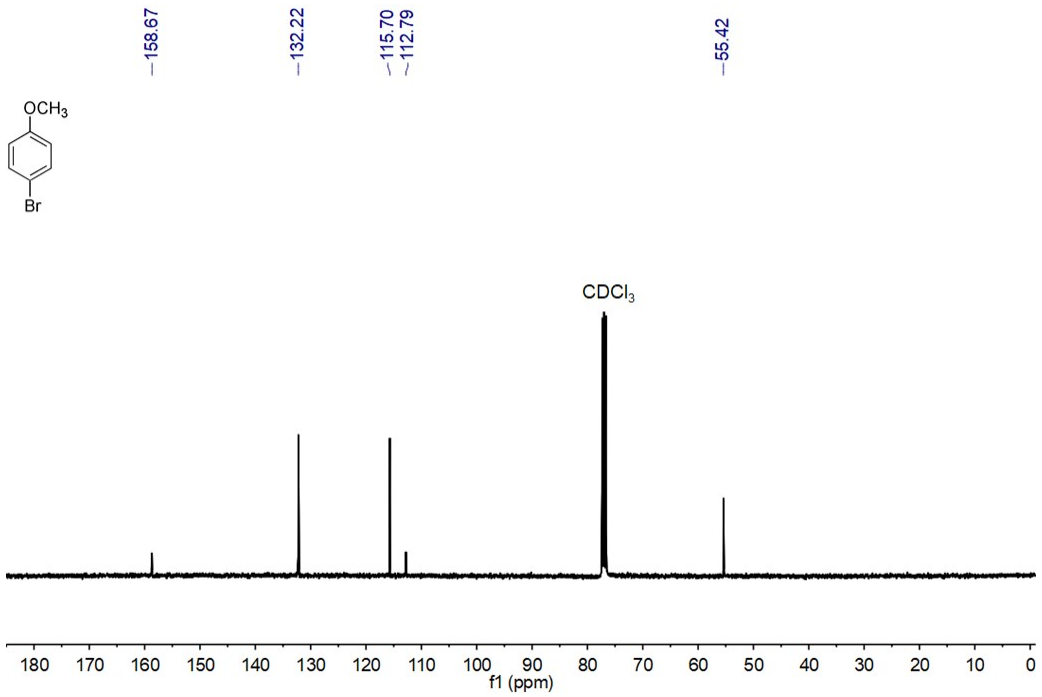
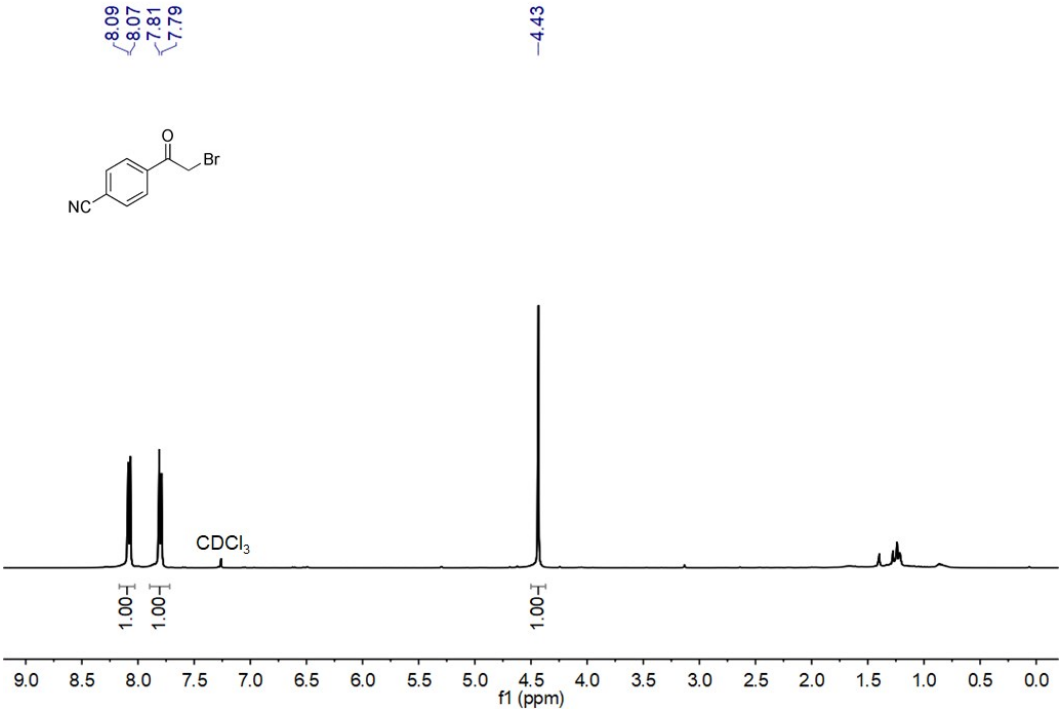


Figure S4. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 1-bromo-4-methoxy-benzene (**2a**).

4-(2-bromoacetyl)benzonitrile (2b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 2 H), 7.81 (d, 2 H), 4.43 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.06, 136.87, 132.66, 129.36, 117.16, 29.96. GC-MS *m*/*z*: 222.9 $[M]^{+}$.



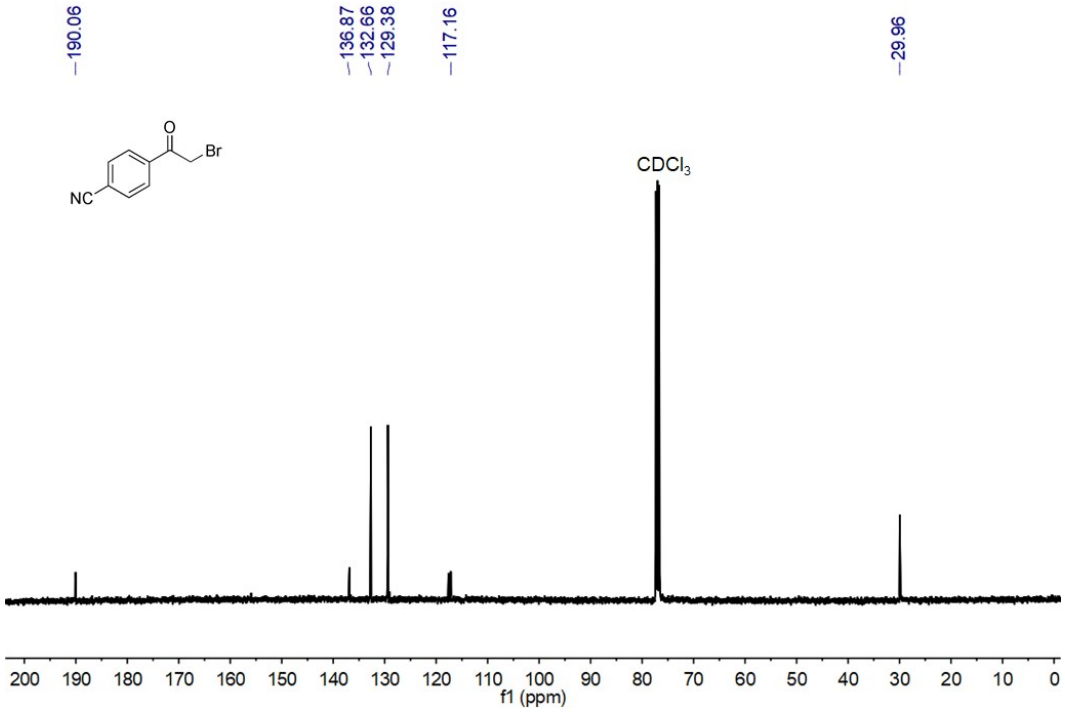


Figure S5. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 4-(2-bromoacetyl)benzonitrile (**2b**).

3-bromo-benzo[*b*]thiophene (2c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.87 (m, 2H), 7.53-7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.53, 137.47, 125.26, 124.99, 123.43, 123.01, 122.69, 107.64. GC-MS *m*/*z*: 212 $[M]^+$, 214 $[M+1]^+$.

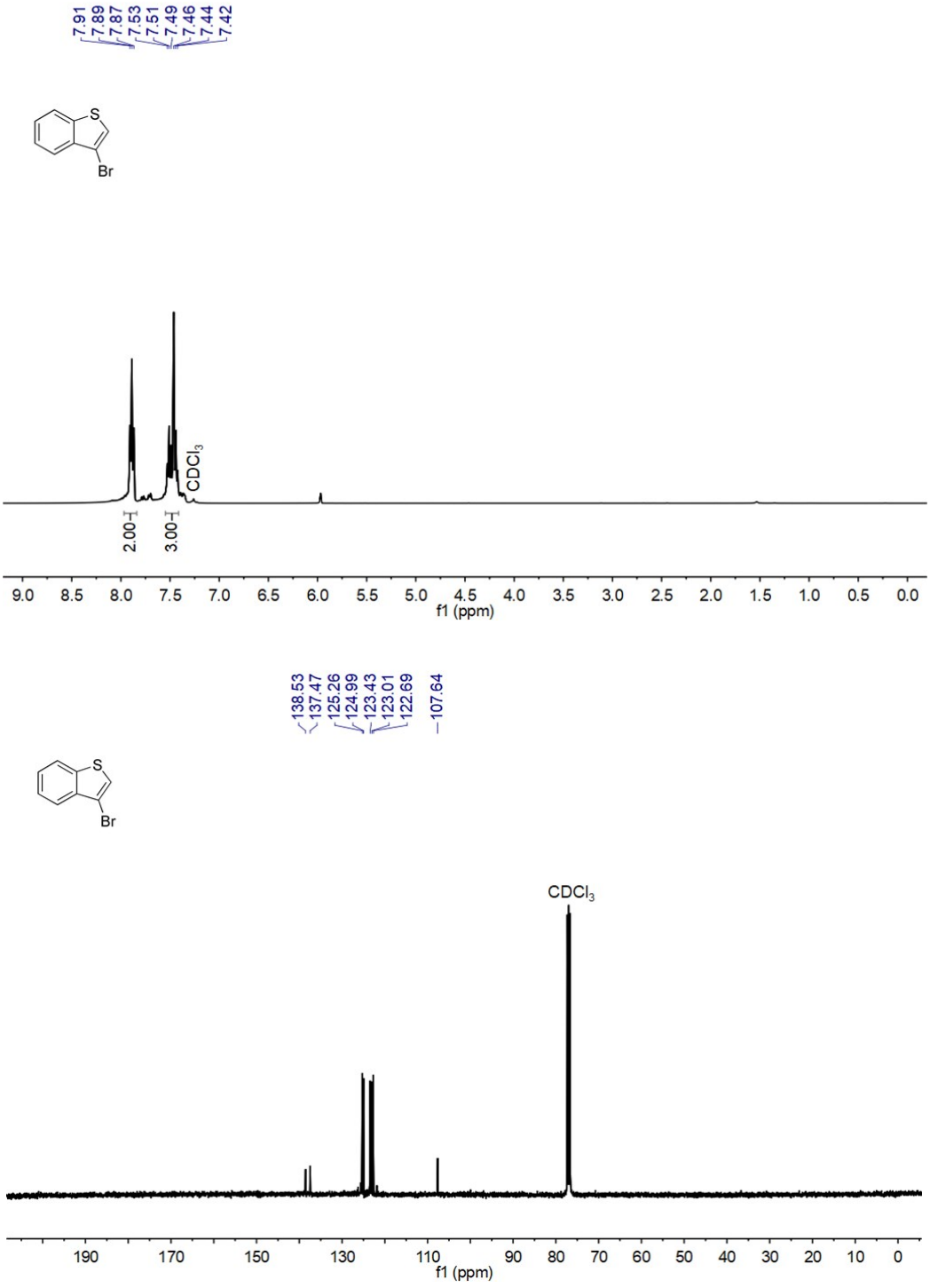


Figure S6. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 3-bromo-benzo[*b*]thiophene (**2c**).

(1,2-dibromoethyl)-benzene (2d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.37 (m, 5H), 5.17-5.13 (m, 1H), 4.08-4.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.59, 129.16, 128.84, 127.63, 50.85, 34.99. GC-MS *m*/*z*: 263.8 $[M]^+$, 265 $[M+1]^+$.

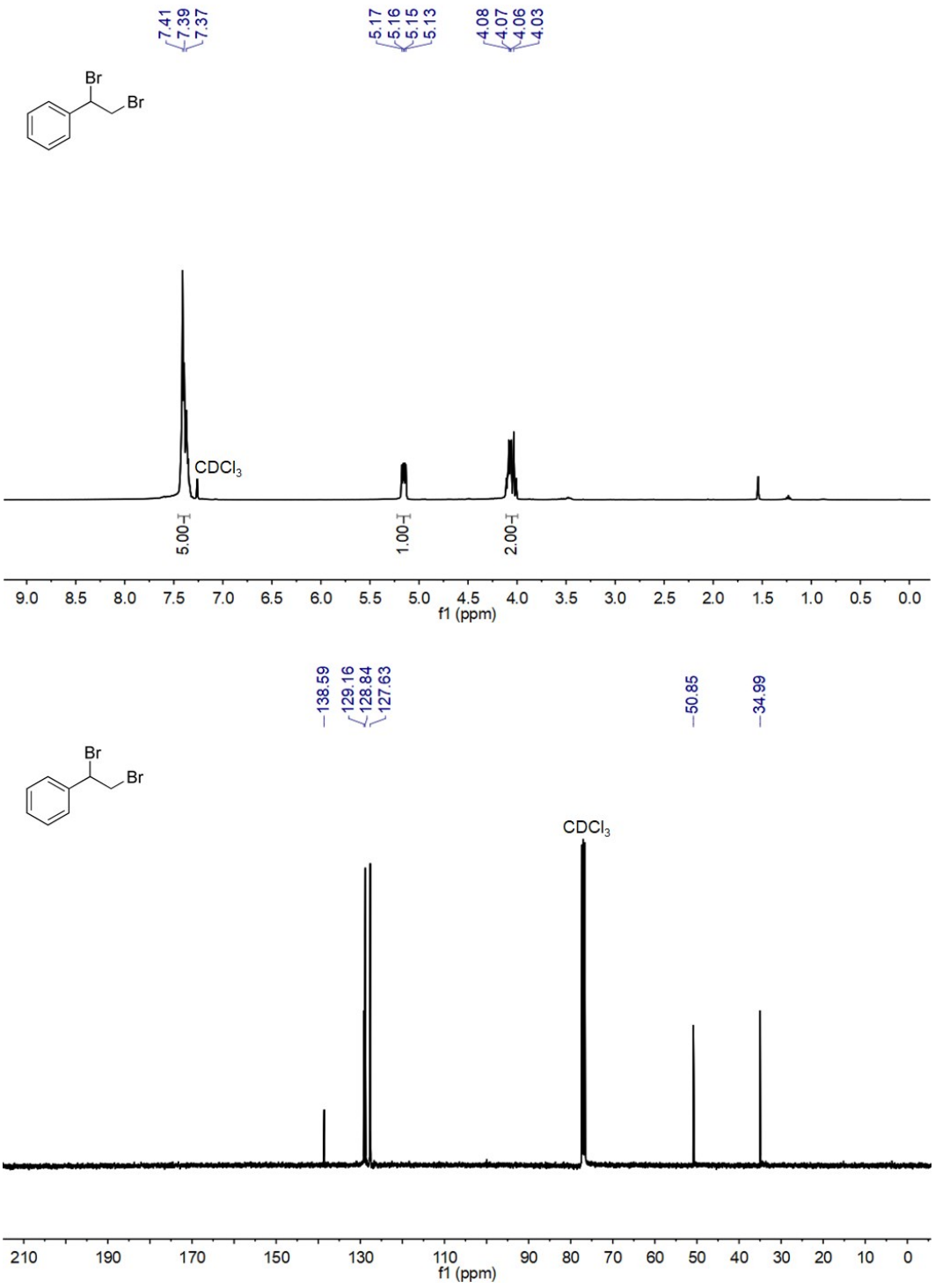


Figure S7. ^{1}H (top) and ^{13}C (bottom) NMR spectra of (1,2-dibromoethyl)-benzene (**2d**).

2-(1,2-dibromoethyl)-naphthalene (2e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.84 (m, 4H), 7.53-7.52 (m, 3H), 5.36-5.32 (m, 1H), 4.17-4.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.69, 133.50, 132.90, 129.10, 128.19, 127.78, 126.91, 126.69, 126.65, 124.34, 51.32, 34.77. GC-MS *m*/*z*: 315.9 $[M+1]^{+}$.

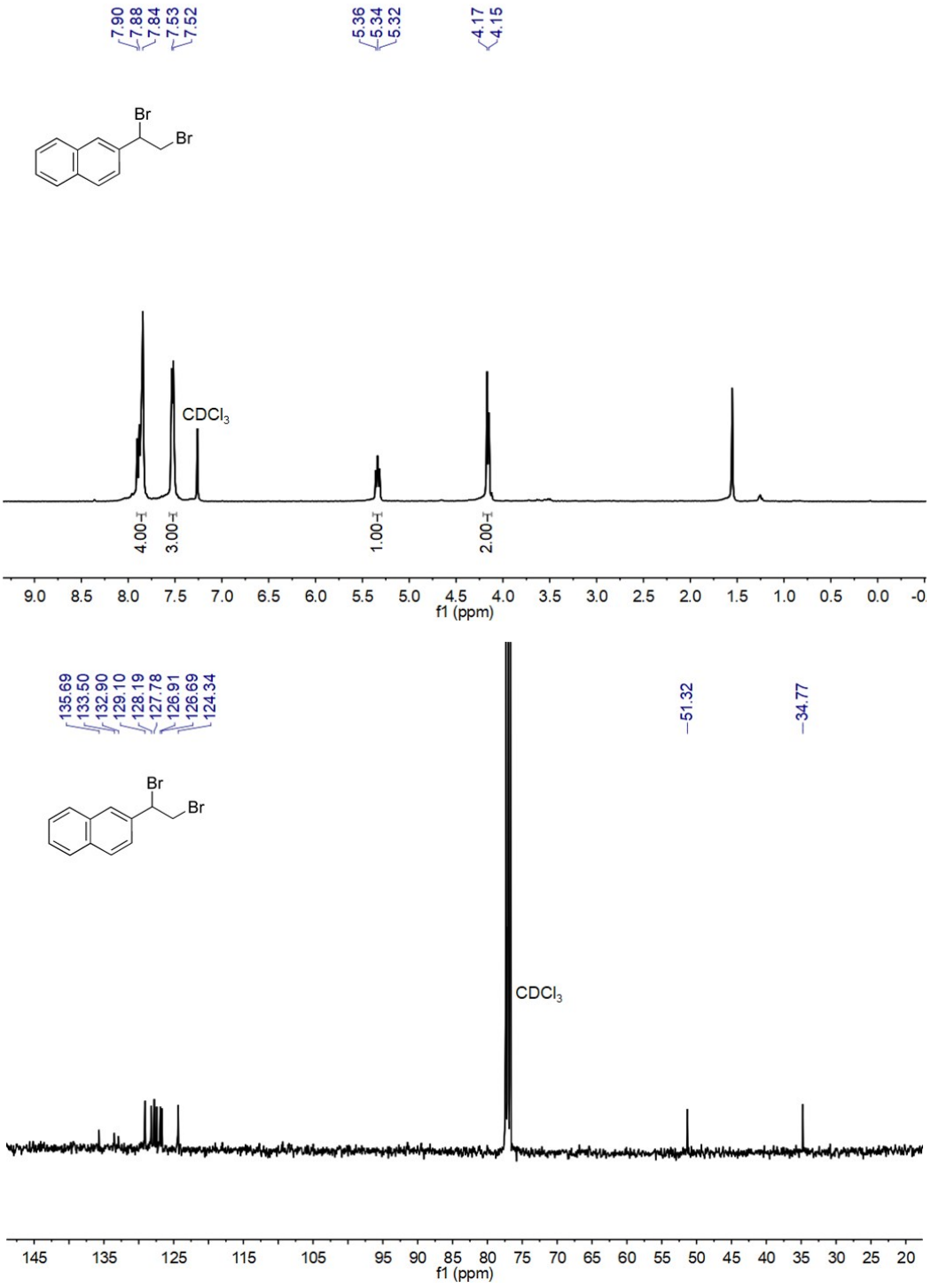


Figure S8. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-(1,2-dibromoethyl)-naphthalene (**2e**).

(1,2-dibromo-1-propen-1-yl)-benzene (2f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.37 (m, 5H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.71, 129.05, 128.55, 128.18, 117.19, 116.78, 29.30. GC-MS *m/z*: 275.9 $[M]^+$, 277.9 $[M+2]^+$.

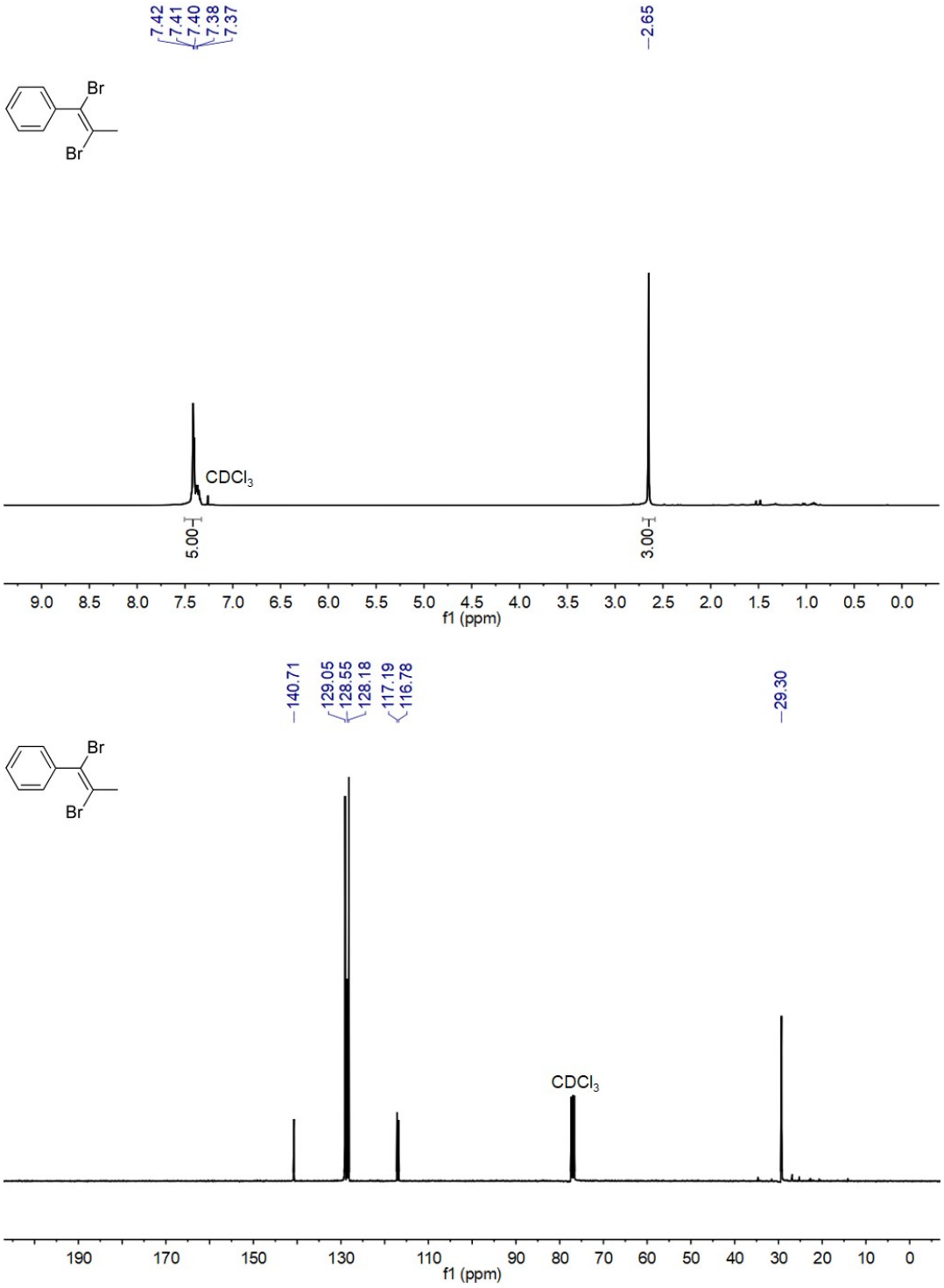


Figure S9. ^{1}H (top) and ^{13}C (bottom) NMR spectra of (1,2-dibromo-1-propen-1-yl)-benzene (**2f**).

4-bromo-benzenamine (4a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, 2H), 6.57 (d, 2H), 3.66 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.36, 131.97, 116.67, 110.16. GC-MS *m*/*z*: 171 $[M]^+$, 173 $[M+1]^+$.

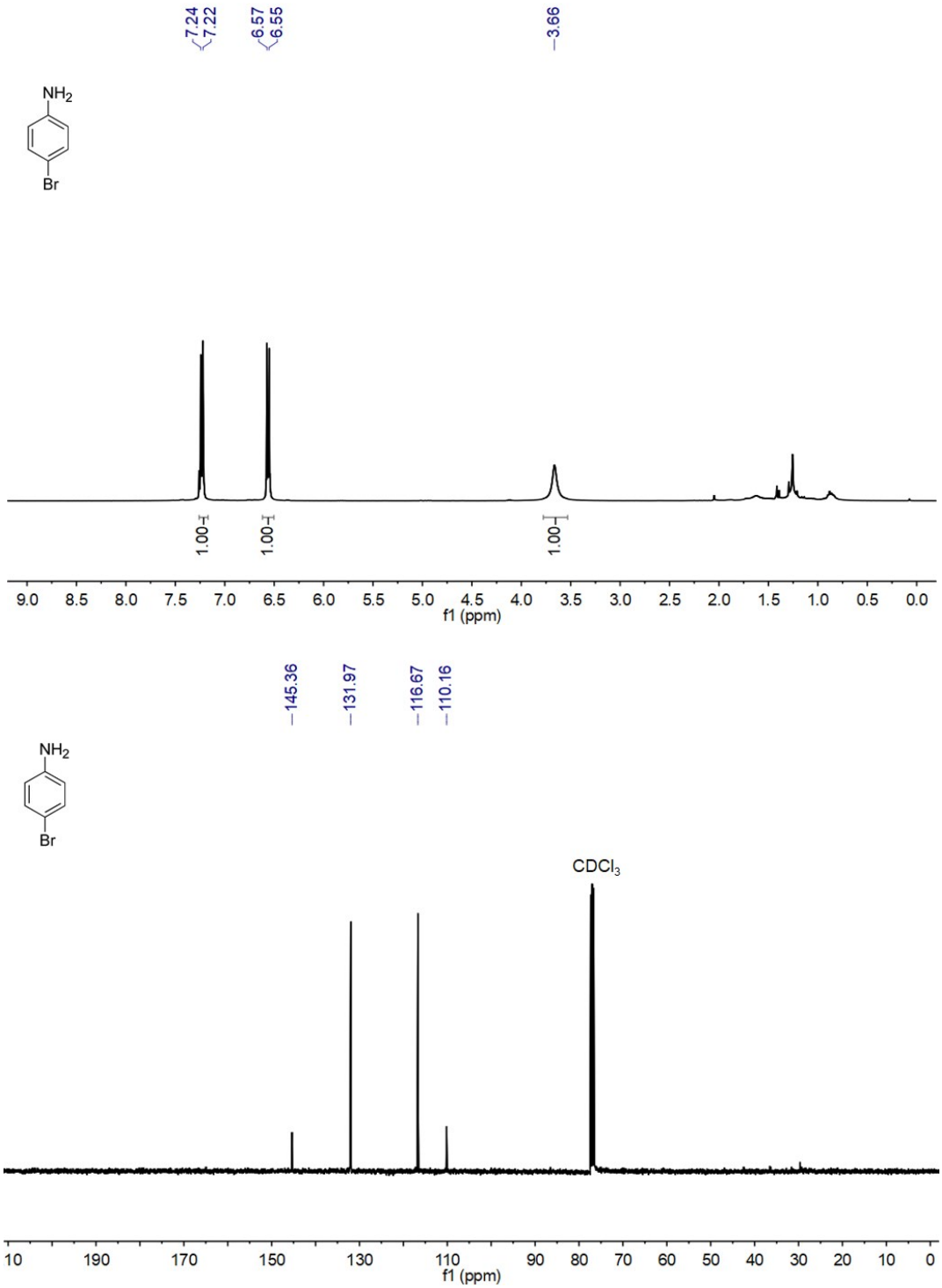


Figure S10. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 4-bromo-benzenamine (**4a**).

2-bromo-4-chloro-benzenamine (4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.06 (d, 2H), 6.68 (d, 2H), 4.08 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.76, 131.73, 128.26, 122.88, 116.14, 109.06. GC-MS *m*/*z*: 206.9 $[M]^{+}$,

208.9 $[M+2]^+$.

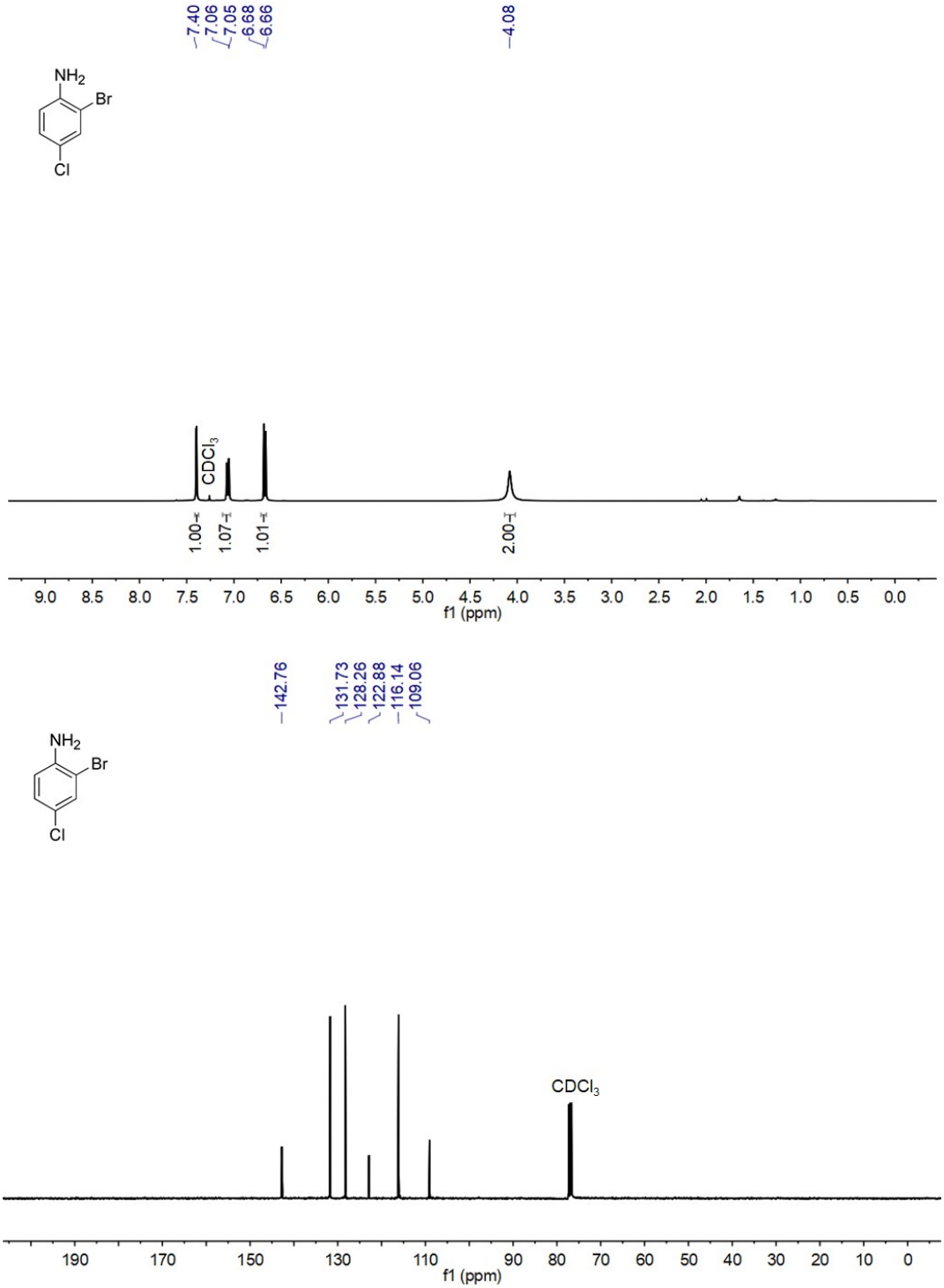


Figure S11. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-bromo-4-chloro-benzenamine (**4b**).

3-bromo-5-chloro-2-pyridinamine (4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 2H), 7.66 (d, 2H), 4.94 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.11, 145.23, 139.50, 120.16, 103.99. GC-MS *m*/*z*: 207.9 $[M]^+$, 209.9 $[M+2]^+$.

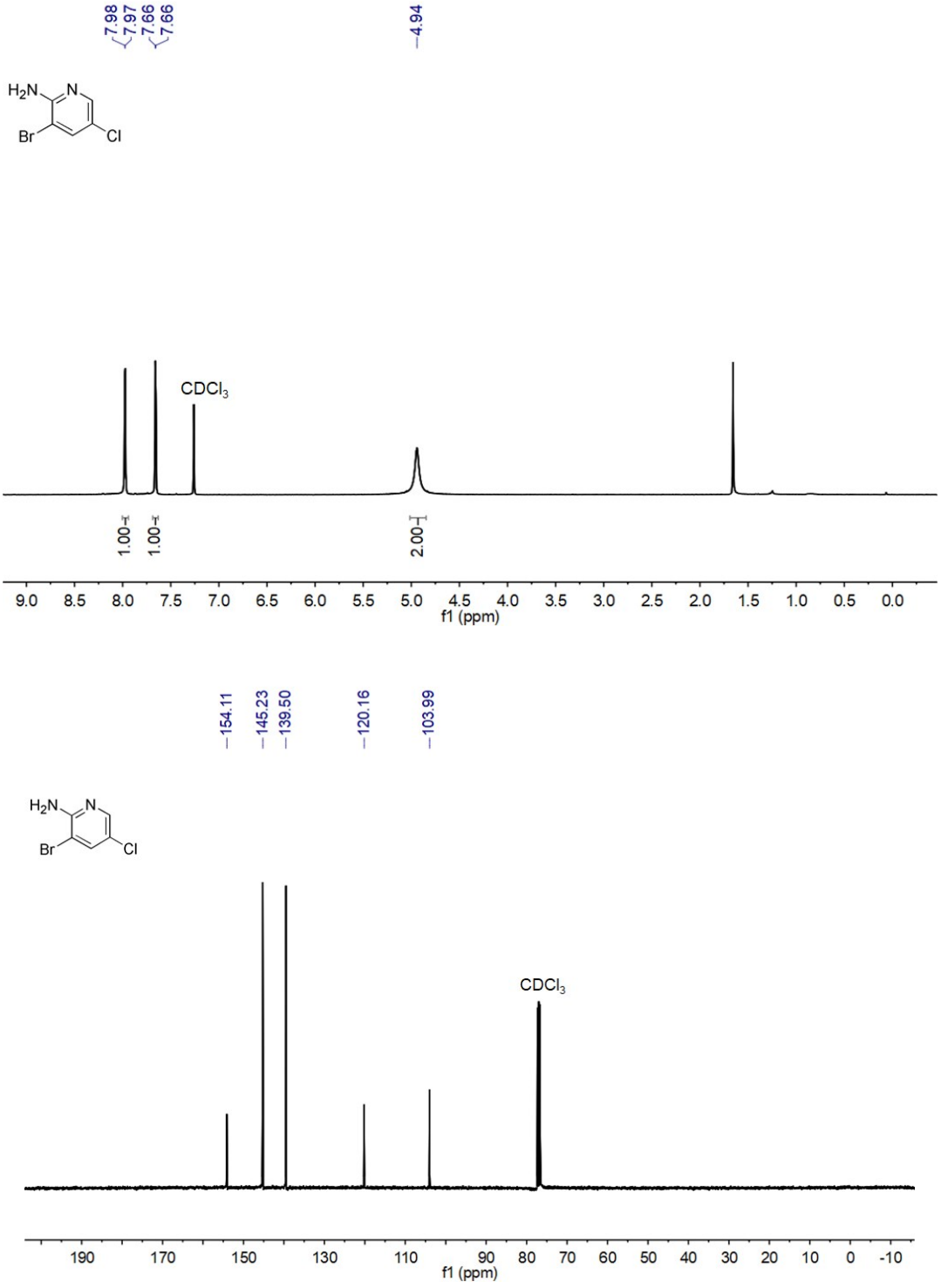


Figure S12. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 3-bromo-5-chloro-2-pyridinamine (**4c**).

4-bromo-*N*,*N*-dimethyl-benzenamine (4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 2H), 6.60 (d, 2H), 2.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.47, 131.63, 114.05, 108.44, 40.51. GC-MS *m*/*z*: 200 $[M]^+$, 201 $[M+1]^+$.

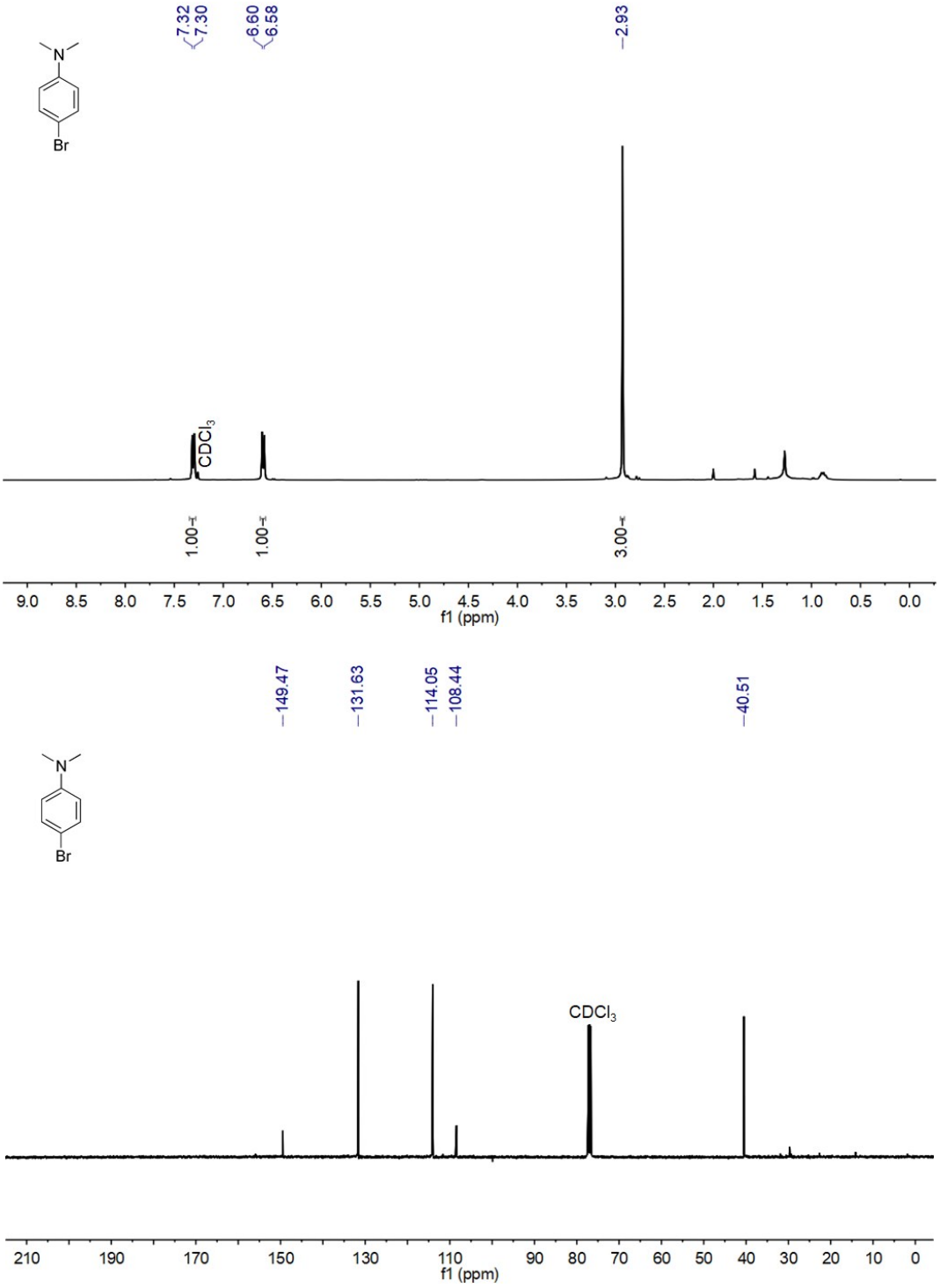


Figure S13. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 4-bromo-*N*,*N*-dimethyl-benzenamine (**4d**).

1-(3-bromophenyl)-ethanone (6)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.86 (d, 2H), 7.67 (d, 2H), 7.35 (dt, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 138.8, 135.95, 131.35, 130.23, 126.89, 122.96, 26.64. GC-

MS *m*/*z*: 200 $[M]^+$.

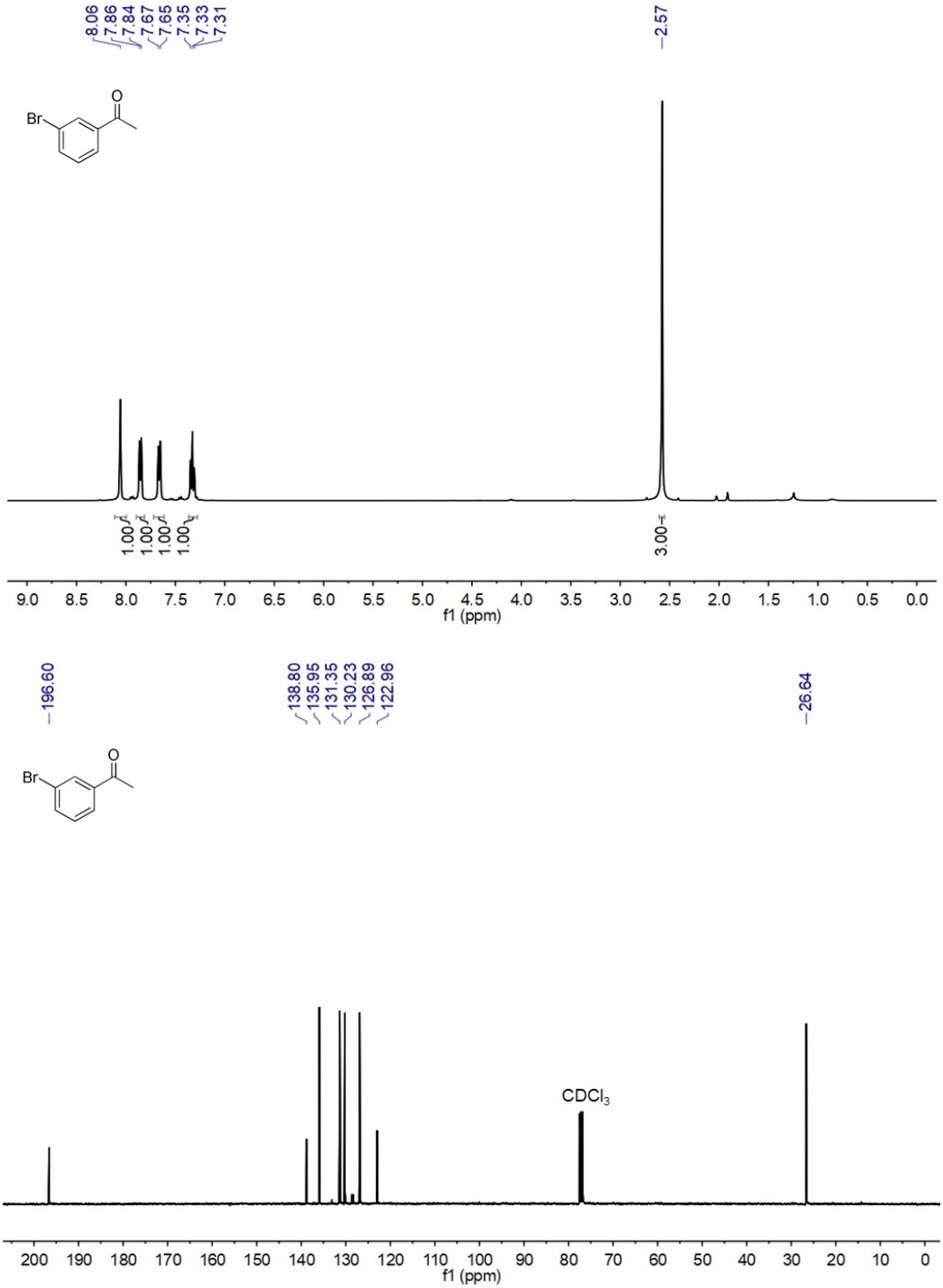


Figure S14. ^1H (top) and ^{13}C (bottom) NMR spectra of 1-(3-bromophenyl)-ethanone (**6**).

2-bromo-cyclohexanone (8)

^1H NMR (400 MHz, $CDCl_3$): δ 4.41 (m, 1H), 2.92 (m, 1H), 2.32 (m, 2H), 2.27 (m, 1H), 1.99 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.34, 53.44,

37.85, 36.69, 26.64, 22.05. GC-MS *m*/*z*: 178 $[M]^+$.

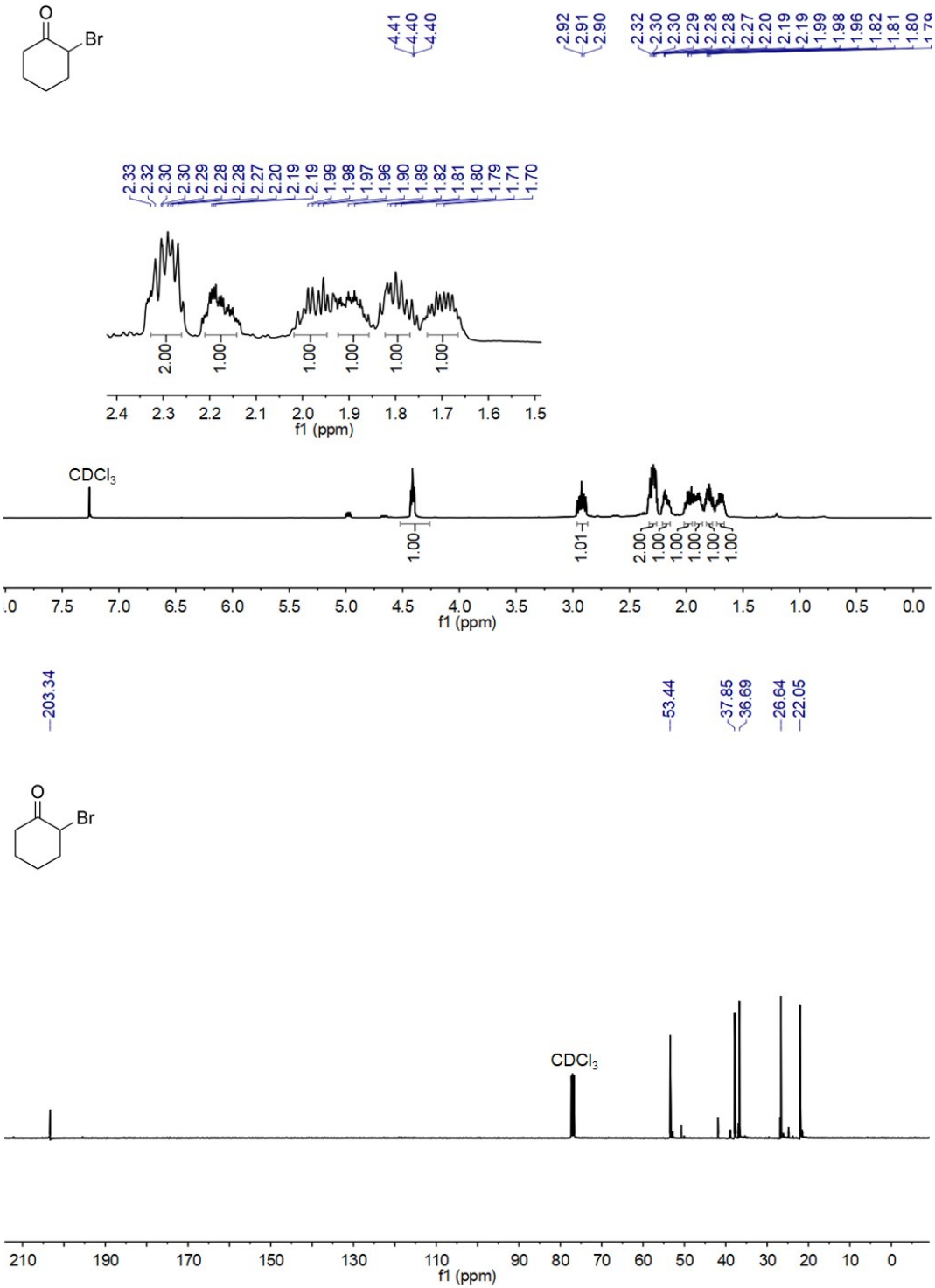


Figure S15. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 2-bromo-cyclohexanone (**8**).

(1,2-dichloroethyl)benzene (9)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.37 (m, 5H), 5.04 (dd, 1H), 4.04 (dd, 1H), 3.97 (dd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.92, 129.10, 128.76, 127.34, 61.70, 48.30. GC-MS *m*/*z*: 174 $[M]^+$.

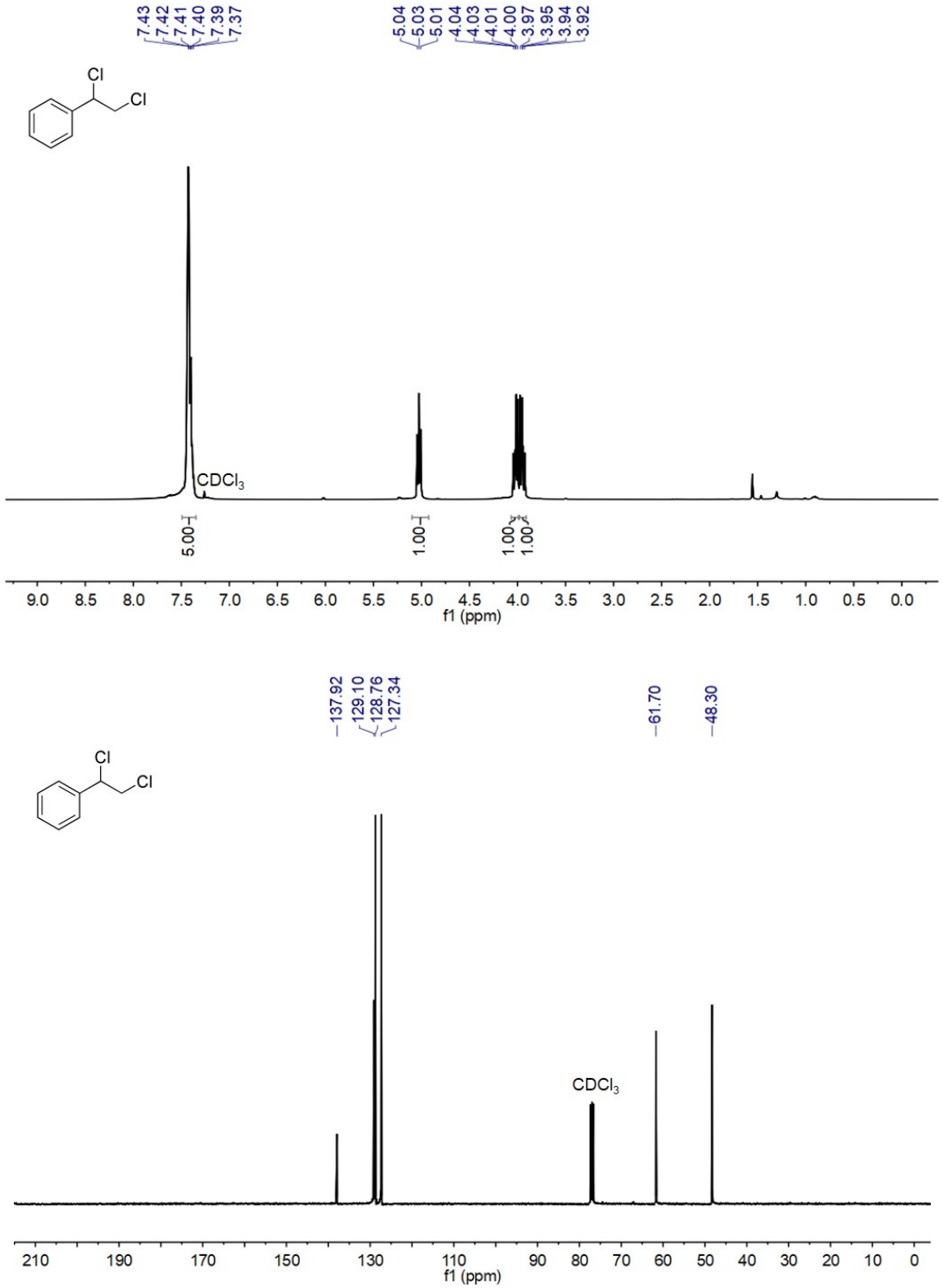


Figure S16. ^{1}H (top) and ^{13}C (bottom) NMR spectra of (1,2-dichloroethyl)benzene (**9**).

α-methyl-benzenemethanol (10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.28 (m, 5H), 4.89 (q, 1H), 1.96 (bs, 1H), 1.51(d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.90, 128.47, 127.41, 125.45, 70.27, 25.26. GC-MS *m*/*z*: 122.1

$[M]^+$.

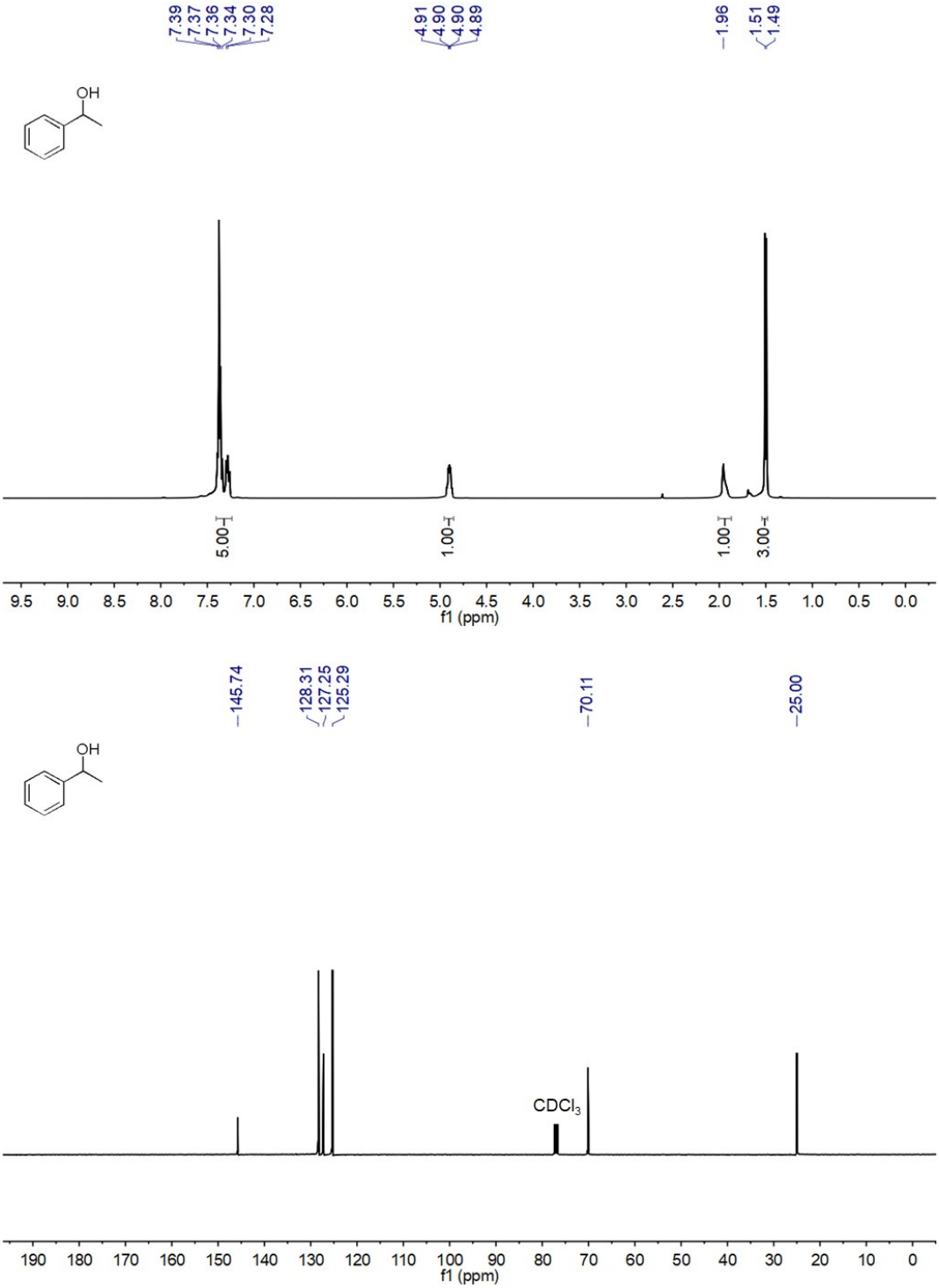


Figure S17. ^{1}H (top) and ^{13}C (bottom) NMR spectra of 1-phenylethanol (**10**).