SUPPORTING INFORMATION

Efficient synthesis of β-aminonitriles from arynes, and imines in acetonitrile

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CONTENTS

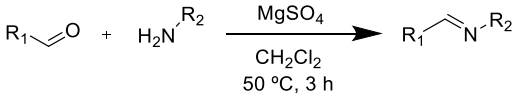
1. GENERAL METHODS

All reactions were carried out under argon atmosphere using oven-dried glassware. Solvents were dried and purified by a MBraun SPS-800 Solvent Purification System. Finely powdered CsF was dried under vacuum at 100 ºC, cooled under argon and stored in a glove-box. *n*-BuLi was used from a solution in hexane (2.40 M). The commercial reagents used in this work were purchased from commercial suppliers and used as received without any further purification. TLC was performed on Merck silica gel 60 F254; chromatograms were visualized with UV light (254 and 360 nm). Flash column chromatography was performed on Merck silica gel 60 (ASTM 230-400 mesh). ^{1}H and ^{13}C-NMR spectra were recorded at 300 MHz (Varian Mercury instrument). Low-resolution mass spectra (EI) were obtained at 70 eV on a HP-5988A instrument.

2. EXPERIMENTAL PROCEDURES AND SPECTROSCOPIC DATA

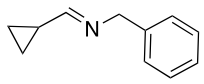
2.1 Synthesis of imines

Imines **1a-f** were prepared following previously reported procedures.[2]

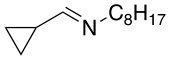


Scheme S1. General route for the synthesis of the imines **1a-f**.

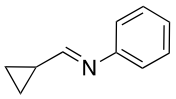
A mixture of the corresponding amine (1.1 equiv.), aldehyde (1 equiv.) and $MgSO_4$ (1.9 equiv.) in CH_2Cl_2 (0.6 M) was stirred at 50 °C for 3h in a flask under Ar atmosphere. After that time, the mixture was filtered, and concentrated under reduced pressure, affording the corresponding imine in a quantitative amount.



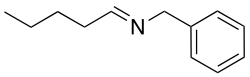
1a



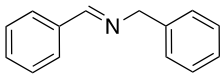
1b



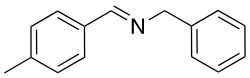
1c



1d



1e

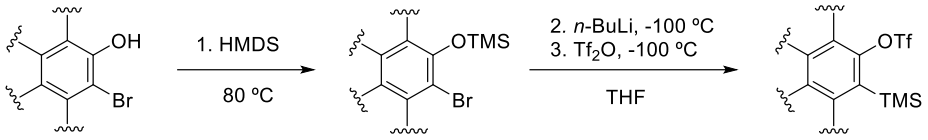


1f

Scheme S2. Imines **1a–f** prepared to test the multicomponent reaction.

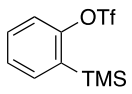
2.2 Synthesis of aryne precursors

Aryne precursors **2a-d** were prepared following previously reported procedures.[1]

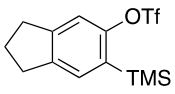


Scheme S3. General reaction for the synthesis of the aryne precursors **2a-d**.

A mixture of *o*-bromohydroxyarene and HMDS (1.0 equiv.) was stirred at 80 °C for 1 h in a flask under Ar atmosphere. The excess NH_3 and unreacted HMDS were then removed under vacuum, and after ^1H NMR confirmation of the quantitative formation of the corresponding silyl ether, the crude product was dissolved in THF (0.15 M), the solution was cooled to -100 °C (external temperature, liquid N_2/Et_2O bath) and *n*-BuLi (1.1 equiv.) was added dropwise. The mixture was stirred for 30 min while the temperature reached -80 °C. Then the mixture was again cooled to -100 °C, Tf_2O (1.2 equiv.) was added dropwise, and stirring was continued for 30 min while the temperature reached to -80 °C. A cold saturated solution of $NaHCO_3$ was added, the phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2) to afford the corresponding triflate.



2a



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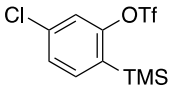
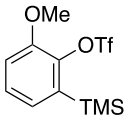


2c

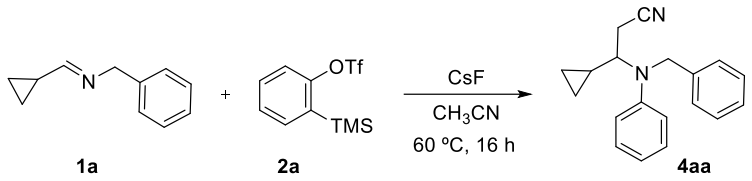


2d

Scheme S4. Aryne precursors **2a–d** prepared for the multicomponent reactions.

2.3 Multicomponent reaction of cyclopropil imines, arynes and nitriles

2.3.1 Synthesis of *β*-aminonitrile 4aa

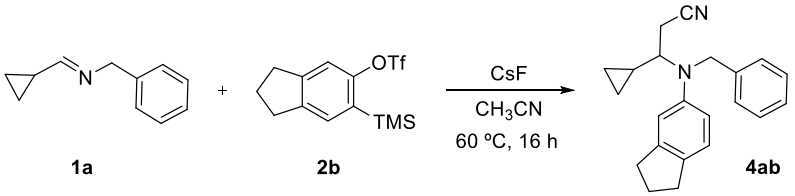


Scheme S5. Synthesis of *β*-aminonitrile **4aa**.

A mixture of compound **1a** (30 mg, 0.19 mmol), triflate **2a** (30 μL, 0.12 mmol) and CsF (57 mg, 0.37 mmol) in CH_3CN (2.5 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/Et_2O 8:2), affording **4aa** (29.1 mg, 88%) as a yellow oil.

Data for compound **4aa**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.33 (m, 4H), 7.18 (m, 3H), 6.76 (m, 3H) 4.77 (d, *J* = 17.1 Hz, 1H), 4.55 (d, *J* = 17.1 Hz, 1H), 3.33 (m, 1H), 2.71 (m, 2H), 1.14 (m, 1H), 0.79 (m, 1H), 0.46 (m, 3H) ppm.^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 148.1 (C), 139.3 (C), 129.4 (2CH), 128.5 (2CH), 126.9 (CH), 126.8 (2CH), 118.8 (CH), 118.4 (C), 115.1 (2CH), 61.8 (CH), 49.8 (CH_2), 21.3 (CH_2), 14.3 (CH), 6.0 (CH_2), 4.8 (CH_2) ppm. MS (IE+), m/z (%): 276 (M+, 100).

2.3.2 Synthesis of *β*-aminonitrile 4ab



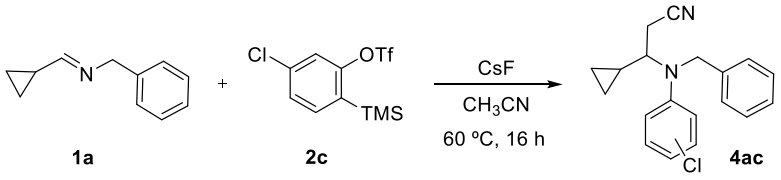
Scheme S6. Synthesis of *β*-aminonitrile **4ab**.

A mixture of compound **1a** (30 mg, 0.19 mmol), triflate **2b** (33 μL, 0.12 mmol) and CsF (57 mg, 0.37 mmol) in CH_3CN (2.5 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording **4ab** (20 mg, 50%) as a brownish oil.

Data for compound **4ab**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.32 (m, 4H), 7.20 (t, *J* = 6.9 Hz, 1H), 7.03 (d, *J* = 8.2 Hz,1H), 6.71 (s, 1H), 6.60 (dd, *J* = 8.2, 2.4 Hz, 1H), 4.69 (d, *J* = 16.6 Hz, 1H), 4.49 (d, *J* = 16.7 Hz, 1H), 3.24 (m, 1H), 2.80 (dd, *J* = 14.2, 7.1 Hz, 4H), 2.66 (m, 2H), 2.02 (m, 2H), 1.09 (m, 1H), 0.75 (m, 1H), 0.45 (m, 3H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 147.2 (C), 145.6 (C), 139.7 (C), 135.2 (C), 128.5 (2CH), 127.0 (2CH), 126.8 (CH), 124.9 (CH), 118.7 (C), 114.6 (CH), 112.5 (CH), 62.5 (CH),

50.7 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 25.7 (CH_2), 21.2 (CH_2), 14.4 (CH), 5.9 (CH_2), 4.9 (CH_2) ppm. MS (IE+), m/z (%): 316 (M+, 100).

2.3.3 Synthesis of *β*-aminonitriles 4ac

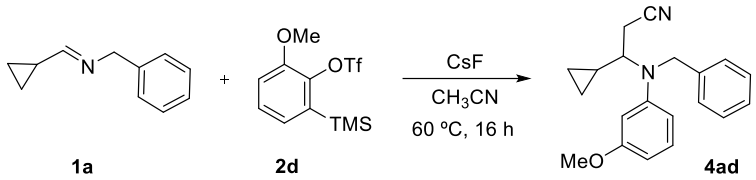


Scheme S7. Synthesis of *β*-aminonitrile **4ac**.

A mixture of compound **1a** (30 mg, 0.19 mmol), triflate **2c** (32 μL, 0.12 mmol) and CsF (57 mg, 0.37 mmol) in CH_3CN (2.50 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording a mixture of regioisomers **4ac** (22.50 mg, 58%) as a yellow oil.

Data for compound **4ac**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.33 (m, 7H), 7.13 (m, 5H), 6.65 (m, 6H), 4.74 (dd, *J* = 17.0, 13.3 Hz, 2H), 4.52 (dd, *J* = 17.1, 10.4 Hz, 2H), 3.25 (m, 2H), 2.72 (m, 4H), 1.13 (m, 2H), 0.84 (m, 2H), 0.45 (m, 6H) ppm. MS (IE+), *m/z* (%): 310 (M+, 100).

2.3.4 Synthesis of *β*-aminonitrile 4ad

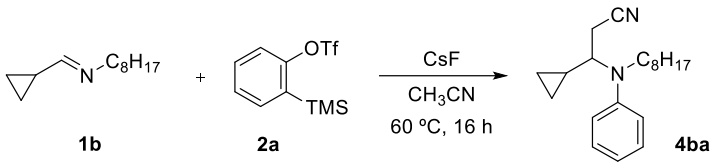


Scheme S8. Synthesis of *β*-aminonitrile **4ad**.

A mixture of compound **1a** (30 mg, 0.19 mmol), triflate **2d** (33 μL, 0.12 mmol) and CsF (57 mg, 0.37 mmol) in CH_3CN (2.50 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/Et_2O 8:2), affording **4ad** (17.60 mg, 48%) as a brownish solid.

Data for compound **4ad**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.28 (m, 4H), 7.21 (t, *J* = 6.9 Hz, 1H), 7.10 (m, 1H), 6.38 (m, 2H), 6.29 (s, 1H), 4.76 (d, *J* = 17.1 Hz, 1H), 4.53 (d, *J* = 17.1 Hz, 1H), 3.71 (s, 3H), 3.31 (m, 1H), 2.71 (m, 2H), 1.11 (m, 1H), 0.86 (m, 1H), 0.76 (m, 1H), 0.49 (m, 1H), 0.39 (m, 1H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 160.8 (C), 149.5 (C), 139.2 (C), 130.1 (CH), 128.6 (2CH), 126.9 (CH), 126.7 (2CH), 118.3 (C), 107.6 (CH), 103.1 (CH), 101.6 (CH), 61.7 (CH), 55.2 (CH_3), 49.8 (CH_2), 21.3 (CH_2), 14.3 (CH), 6.0 (CH_2), 4.8 (CH_2) ppm. MS (IE+), m/z (%): 306 (M+, 100).

2.3.5 Synthesis of *β*-aminonitrile 4ba

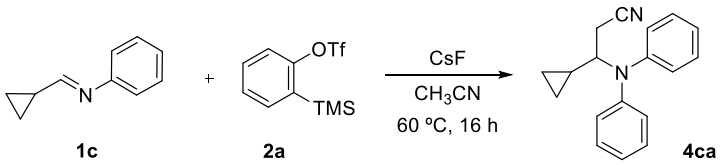


Scheme S9. Synthesis of *β*-aminonitrile **4ba**.

A mixture of compound **1b** (30 mg, 0.16 mmol), triflate **2a** (27 μL, 0.11 mmol) and CsF (50 mg, 0.33 mmol) in CH_3CN (2.24 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording **4ba** (21 mg, 64%) as a yellow oil.

Data for compound **4ba**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.25 (m, 2H), 6.77 (dd, *J* = 12.8, 7.6, 3H), 3.32 (m, 2H), 3.12 (dd, *J* = 15.5, 6.6 Hz, 1H), 2.64 (m, 2H) 1.58 (d, *J* = 11.5 Hz, 2H), 1.29 (d, *J* = 8.1 Hz, 10H), 1.13 (m, 1H), 0.85 (m, 3H), 0.81 (m, 1H), 0.63 (m, 1H), 0.45 (m, 1H), 0.34 (m, 1H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 147.7 (C), 129.3 (2CH), 118.4 (C), 118.3 (CH), 115.14 (2CH), 62.2 (CH), 45.5 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 21.3 (CH_2), 14.9 (CH_3), 14.1 (CH), 6.1 (CH_2), 4.3 (CH_2) ppm. MS (IE+), m/z (%): 298 (M+, 100).

2.3.6 Synthesis of *β*-aminonitrile 4ca

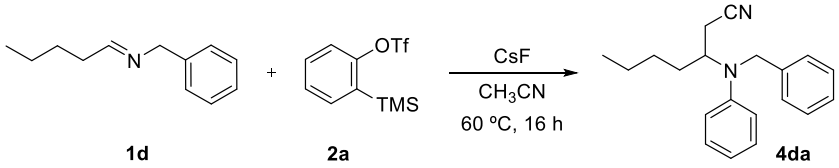


Scheme S10. Synthesis of *β*-aminonitrile **4ca**.

A mixture of compound **1c** (30 mg, 0.21 mmol), triflate **2a** (33 μL, 0.14 mmol) and CsF (63 mg, 0.41 mmol) in CH_3CN (2.70 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/Et_2O 5:5), affording **4ca** (17 mg, 47%) as a yellow oil.

Data for compound **4ca**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.30 (m, 4H), 7.04 (m, 2H), 6.90 (m, 4H), 3.48 (m, 2H), 2.78 (ddd, *J* = 24.3, 16.6, 6.5 Hz, 1H), 1.21 (m, 2H), 0.75 (m, 1H), 0.52 (m, 2H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 145.5 (2C), 129.6 (4CH), 122.8 (4CH), 122.7 (2CH), 118.6 (C), 60.2 (CH), 21.9 (CH_2), 15.8 (CH), 6.6 (CH_2), 4.6 (CH_2) ppm. MS (IE+), m/z (%): 262 (M+, 100).

2.3.7 Synthesis of *β*-aminonitrile 4da

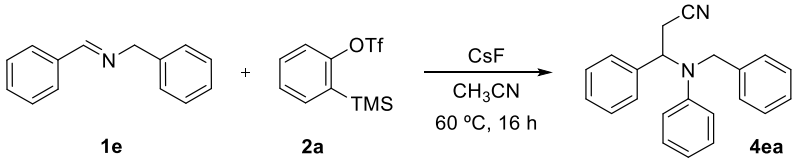


Scheme S11. Synthesis of *β*-aminonitrile **4da**.

A mixture of compound **1d** (30 mg, 0.17 mmol), triflate **2a** (28 μL, 0.11 mmol) and CsF (52 mg, 0.34 mmol) in CH_3CN (2.28 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording **4da** (6.80 mg, 20%) as a yellow solid.

Data for compound **4da**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.35 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.22 (m, 4H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 5.34 (t, *J* = 7.1 Hz, 1H), 4.22 (s, 2H), 2.95 (m, 2H), 1.53 (s, 3H), 1.27 (d, *J* = 8.9 Hz, 4H), 0.83 (m, 2H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 148.2 (C), 138.4 (C), 137.5 (C), 129.3 (CH), 128.9 (CH), 128.5 (CH), 128.3 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 120.4 (CH), 118.1 (CH), 117.9 (CH), 60.9 (CH), 51.3 ($2CH_2$), 29.7 (CH_2), 21.25 ($2CH_2$), 1.9 (CH_3) ppm. MS (IE+), *m/z* (%): 292 (M+, 100).

2.3.8 Synthesis of *β*-aminonitrile 4ea

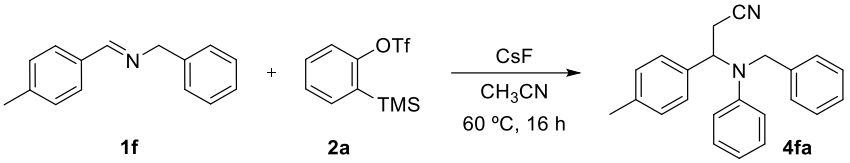


Scheme S12. Synthesis of *β*-aminonitrile **4ea**.

A mixture of compound **1e** (30 mg, 0.15 mmol), triflate **2a** (25 μL, 0.10 mmol) and CsF (47 mg, 0.31 mmol) in CH_3CN (2.06 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording **4ea** (13 mg, 40%) as a yellow oil.

Data for compound **4ea**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.38 (dt, *J* = 10.5, 6.9, Hz, 3H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.27 (m, 2H), 7.21 (m, 5H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.90 (m, 1H), 5.3 (t, *J* = 7.2 Hz, 1H), 4.3 (s, 2H), 3.0 (m, 2H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 148.2 (C), 138.4 (C), 137.5 (C), 129.3 (2CH), 128.9 (2CH), 128.5 (2CH), 128.4 (2CH), 127.3 (CH), 127.1 (2CH), 127.0 (2CH), 120.4 (CH), 118.2 (C), 117.9 (CH), 60.7 (CH), 51.1 (CH_2), 31.1 (CH_2) ppm. MS (IE+), *m/z* (%): 312 (M+, 100).

2.3.9 Synthesis of *β*-aminonitrile 4fa

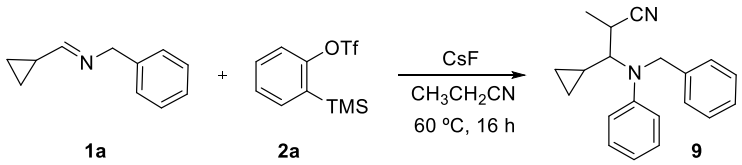


Scheme S13. Synthesis of *β*-aminonitrile **4fa**.

A mixture of compound **1f** (30 mg, 0.14 mmol), triflate **2a** (34.6 μL, 0.14 mmol) and CsF (65.2 mg, 0.43 mmol) in CH_3CN (2.86 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/CH_2Cl_2 8:2), affording **4fa** (32 mg, 68%) as a yellow solid.

Data for compound **4fa**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ: 7.20 (m, 10H), 6.95 (m, 4H), 5.31 (t, *J* = 7.3 Hz, 1H), 4.25 (s, 2H), 3.67 (m, 2H), 2.30 (s, 3H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ: 148.3 (C), 138.6 (C), 138.2 (C), 134.5 (C), 129.6 (2CH), 129.3 (2CH), 128.5 (2CH), 127.3 (2CH), 127.2 (2CH), 127.0 (CH), 120.3 (CH), 118.3 (C), 117.9 (2CH), 60.6 (CH), 51.0 ($2CH_2$), 21.2 (CH_3) ppm. MS (IE+), *m/z* (%): 326 (M+, 100).

2.3.10 Synthesis of *β*-aminonitrile 9



Scheme S14. Synthesis of *β*-aminonitrile **9**.

A mixture of compound **1a** (30 mg, 0.19 mmol), triflate **2a** (30 μL, 0.12 mmol) and CsF (57 mg, 0.37 mmol) in CH_3CH_2CN (2.50 mL, 0.05 M) was placed in an oven-dried Schlenck under Ar atmosphere. Then, the reaction mixture was stirred at 60 ºC for 16h. After that time, the solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (SiO_2; hexane/Et_2O 9:1), affording **9** (12.69 mg, 35%) as a yellow solid.

Data for compound **9**: ^{1}H NMR (298 K, 300 MHz, $CDCl_3$), δ 7.38 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.29 (m, 3H), 7.19 (m, 3H), 6.83 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.75 (tdt, *J* = 7.4, 3.1, 0.9 Hz, 1H), 6.68 (m, 1H), 4.83 (dd, *J* = 28.9, 17.0 Hz, 1H), 4.62 (dd, *J* = 28.9, 17.0 Hz, 1H), 3.19 (m, 2H), 1.47 (m, 3H), 1.16 (m, 1H), 0.83 (m, 1H), 0.45 (m, 3H) ppm. ^{13}C NMR (298 K, 75 MHz, $CDCl_3$), δ:148.1 (C), 138.5 (C), 129.5 (CH), 129.0 (CH), 128.4 (CH), 126.9 (CH) 126.7 (CH), 126.6 (CH), 124.3 (C) 118.6 (CH), 118.0 (CH), 115.9 (CH), 114.3 (CH), 68.2 (CH), 49.8 (CH_2), 28.3 (CH_3), 17.3 (CH), 15.7 (CH), 7.9 (CH_2), 6.0 (CH_2) ppm. MS (IE+), m/z (%): 290 (M+, 100).

The diastereomeric ratio (dr) of the mixture was determined by NMR spectroscopy (^{1}H NMR, 298 K, 300 MHz, $CDCl_3$). The relevant proton signals corresponding to the diastereomers used to measure the dr were identified at chemical shifts of 4.83 (dd, *J* = 28.9, 17.0 Hz, 1H) and 4.62 (dd, *J* = 28.9, 17.0 Hz, 1H) ppm. The resulting diastereomeric ratio was found to be 0.48.

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3. REFERENCES

1 D. Peña, A. Cobas, D. Pérez and E. Guitián, *Synthesis*, 2002, **10**, 1454–1458.

2 R. W. Layer, *Chem. Rev.*, 1963, **63**, 489–510.

4. NMR SPECTRA

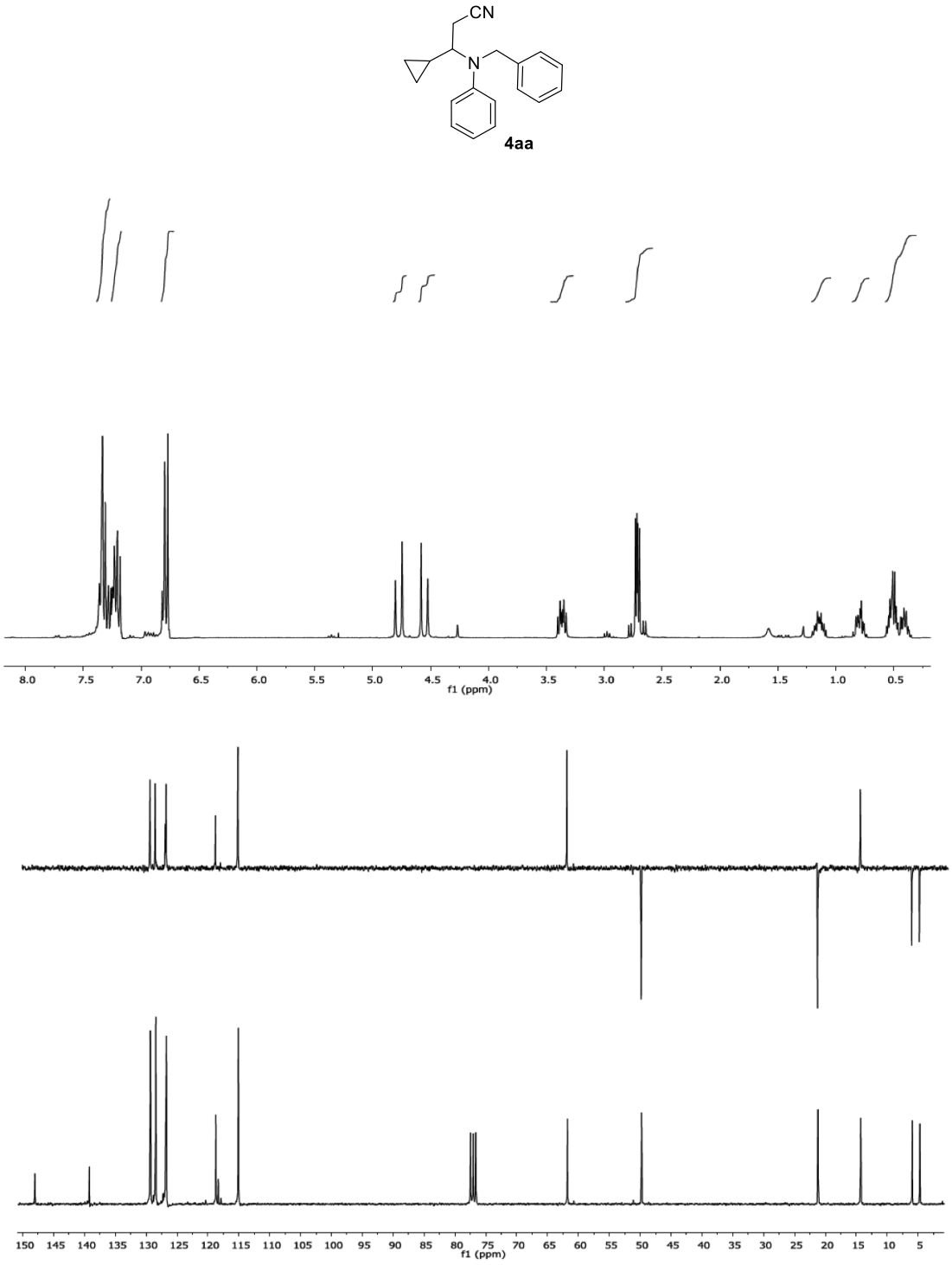

Figure S1. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4aa** in $CDCl_3$.

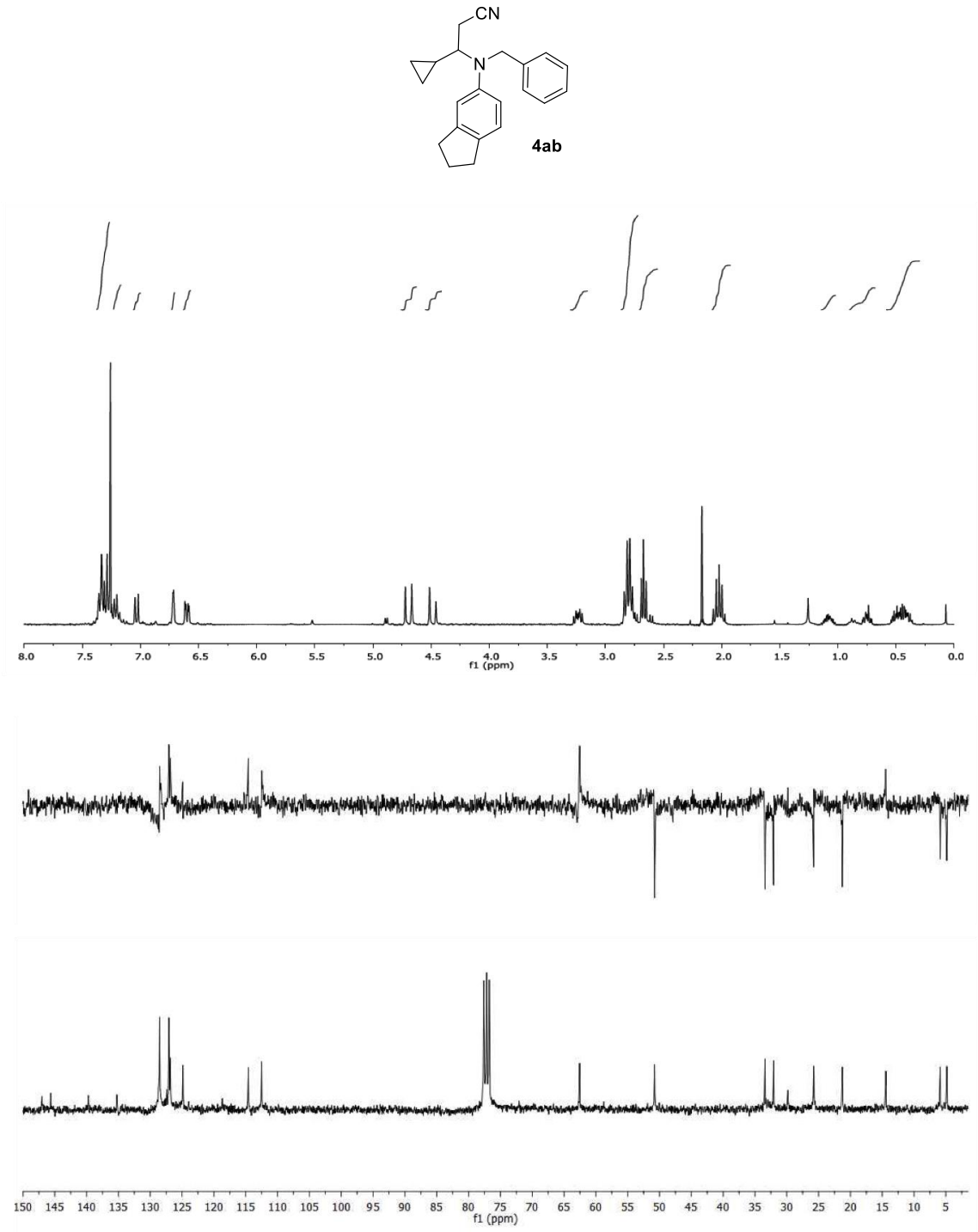

Figure S2. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4ab** in $CDCl_3$.

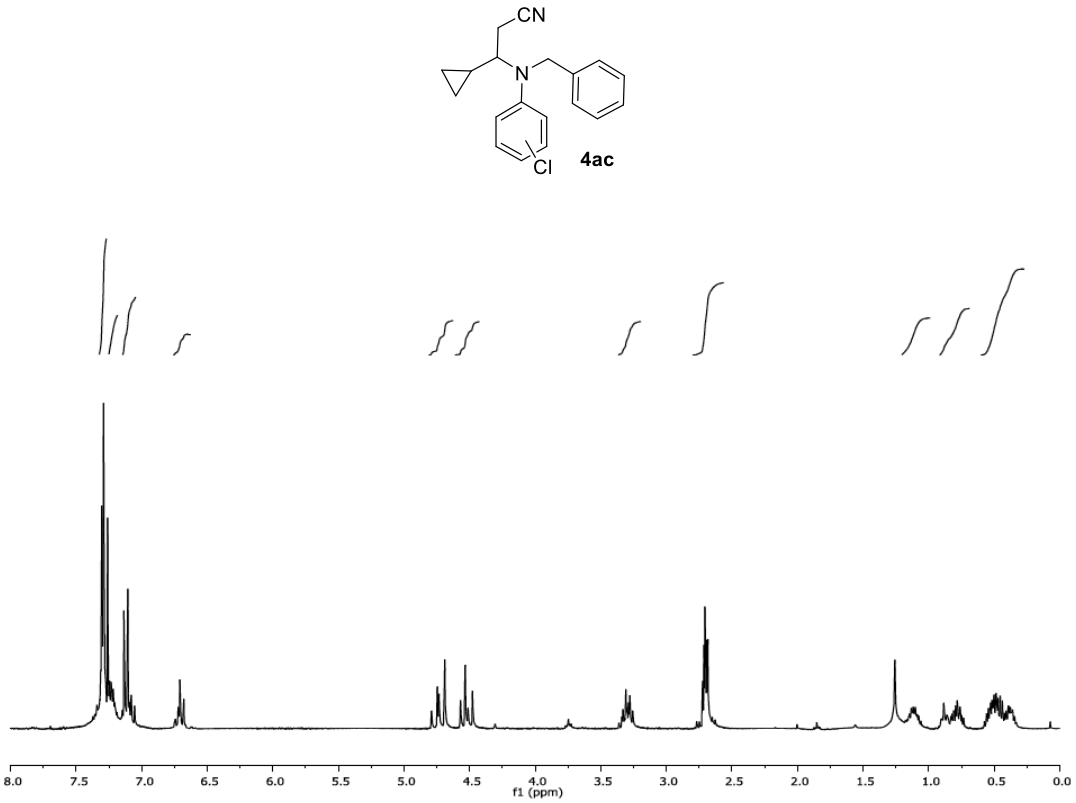

Figure S3. ^{1}H NMR spectrum of β-aminonitrile **4ac** in $CDCl_3$.

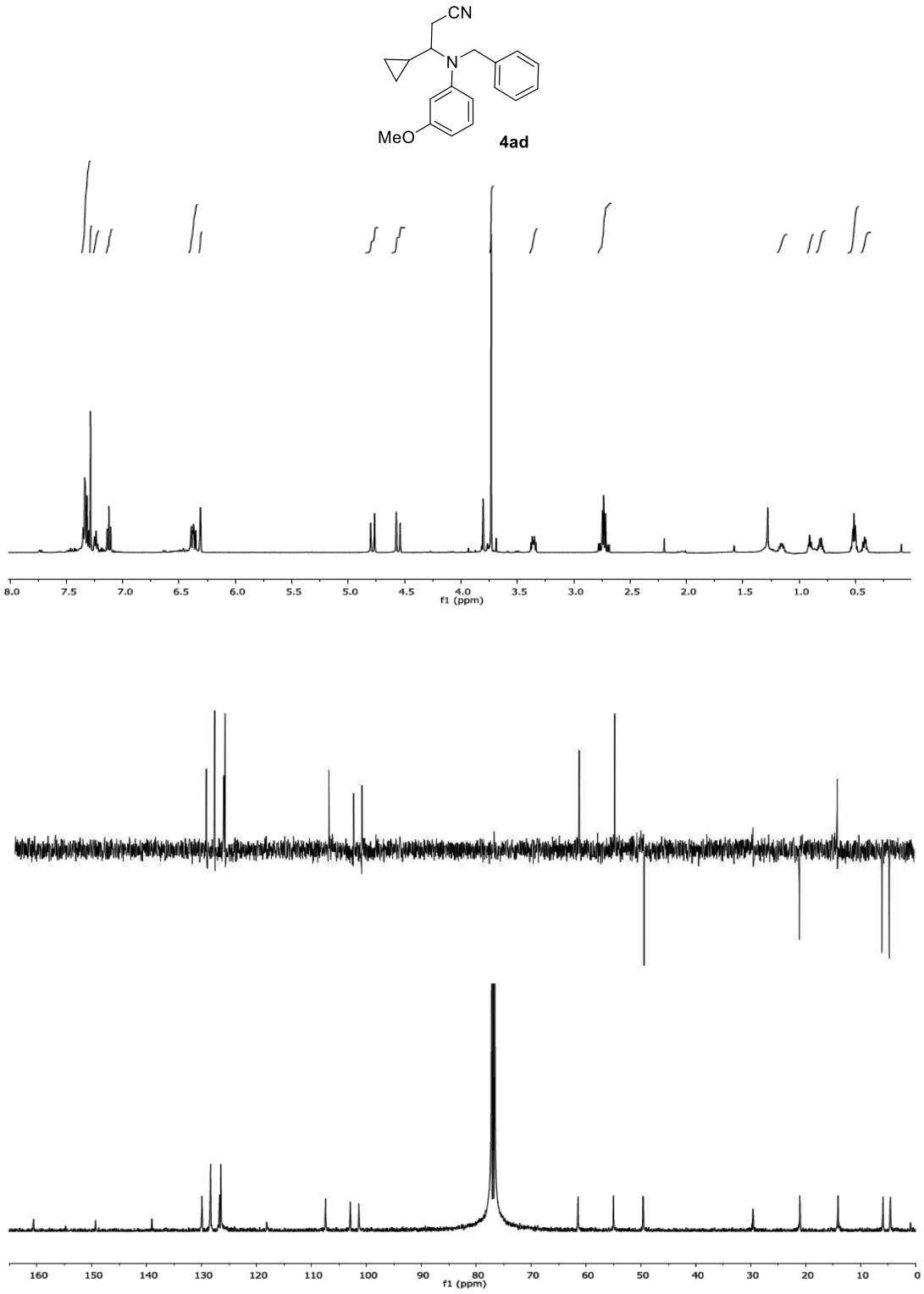

Figure S4. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4ad** in $CDCl_3$.

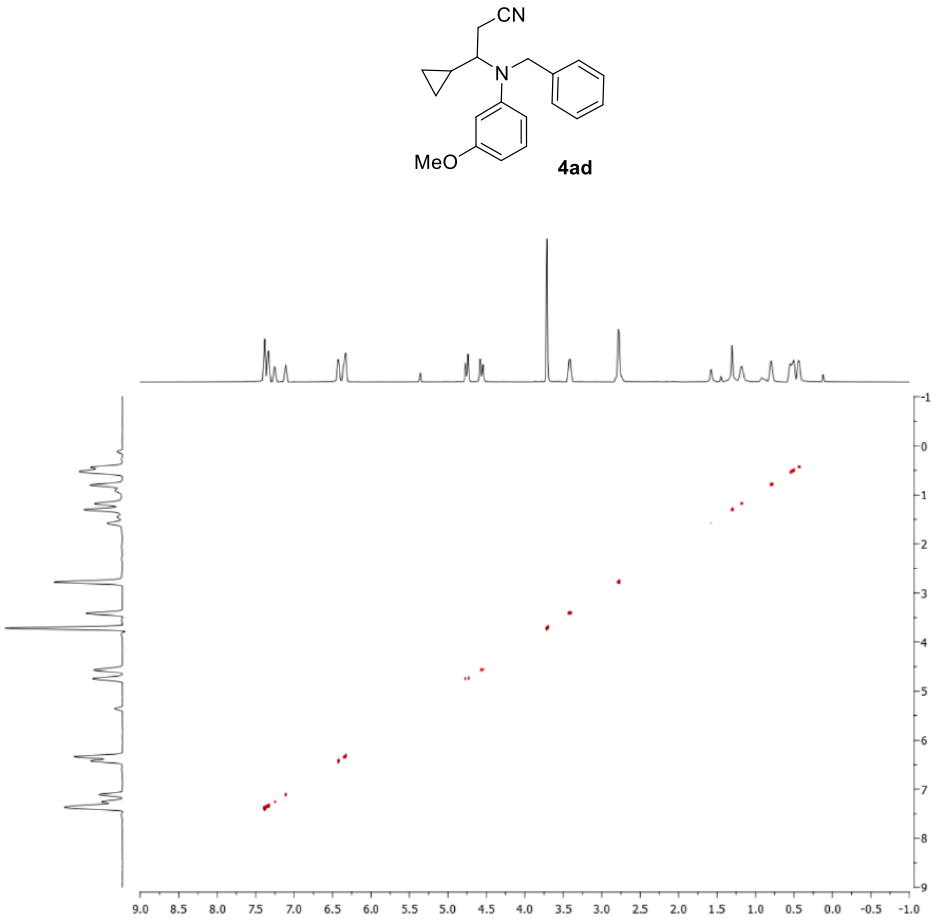

Figure S5. COSY NMR spectra of β-aminonitrile **4ad** recorded in $CDCl_3$.

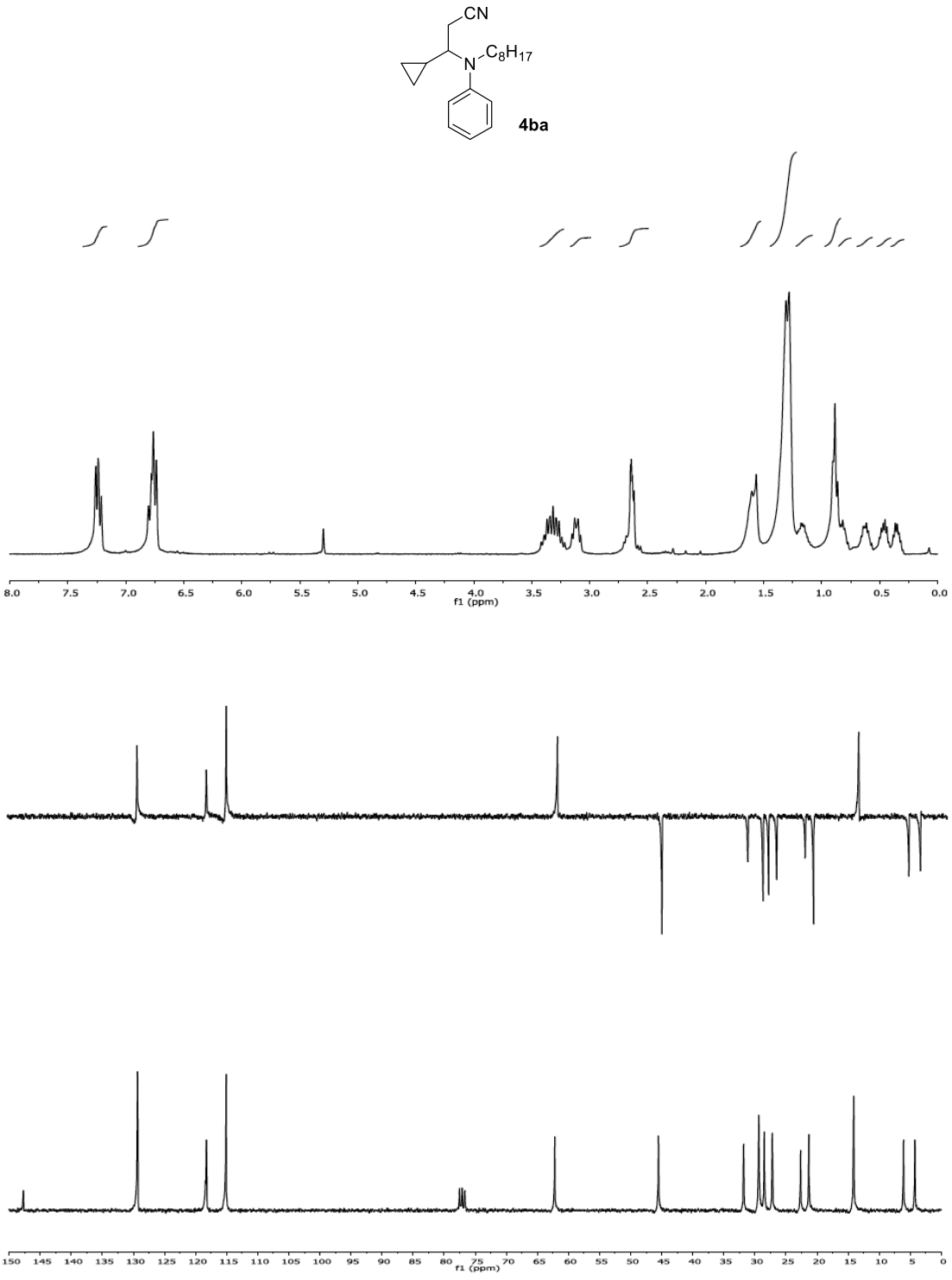

Figure S6. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of *β*-aminonitrile **4ba** in $CDCl_3$.

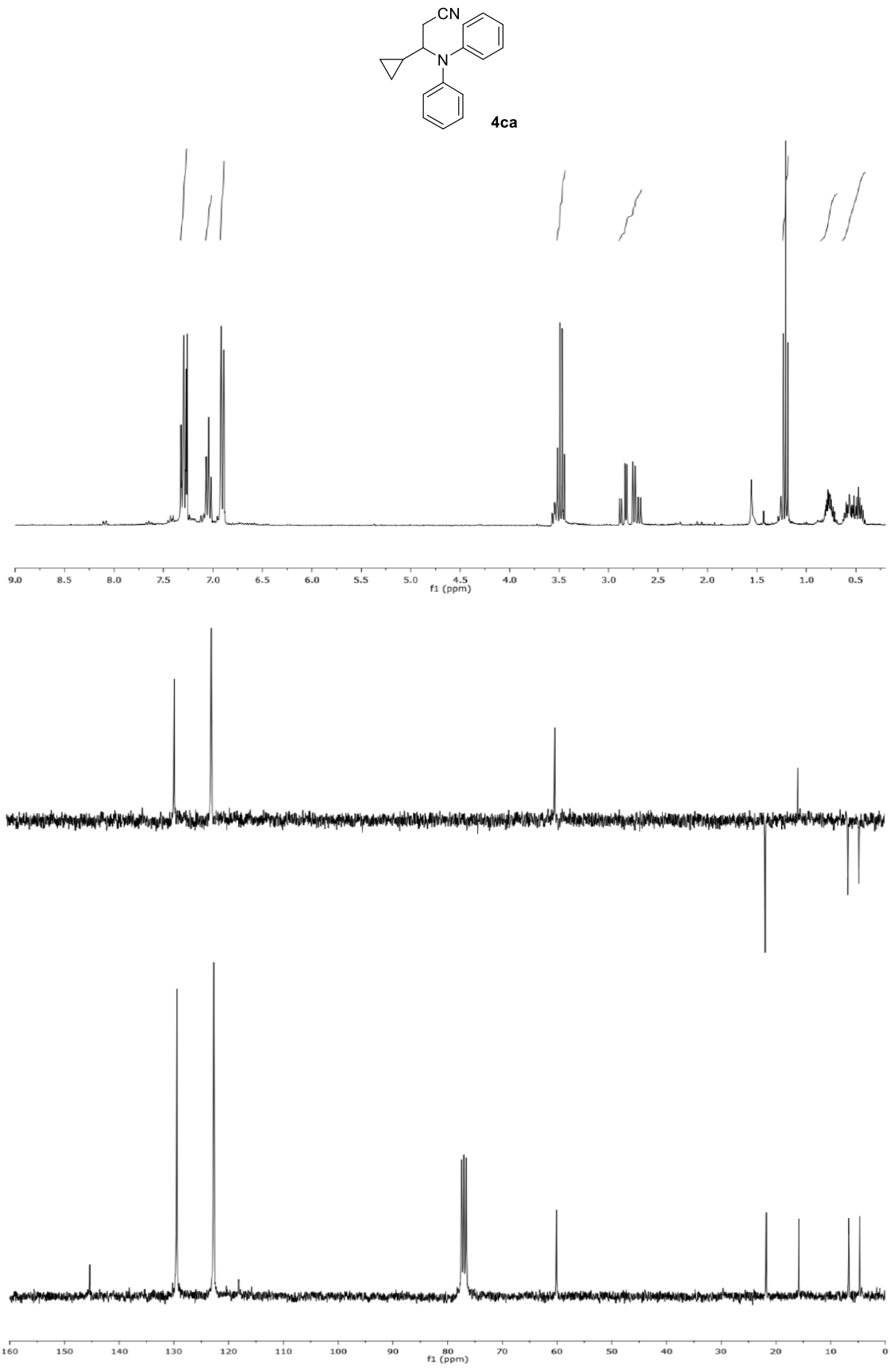

Figure S7. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4ca** in $CDCl_3$.

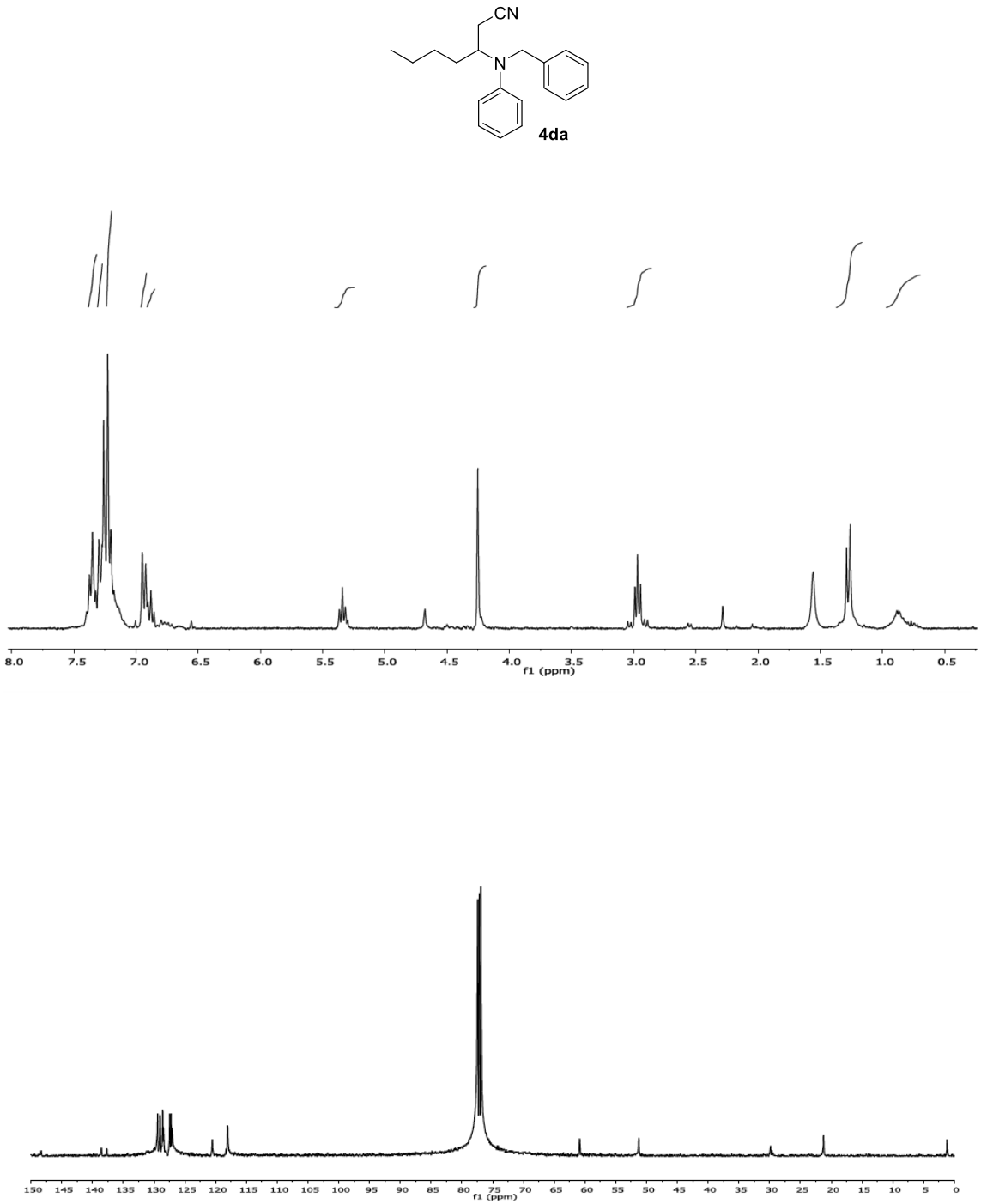

Figure S8. ^{1}H and ^{13}C NMR spectra of β-aminonitrile **4da** in $CDCl_3$.

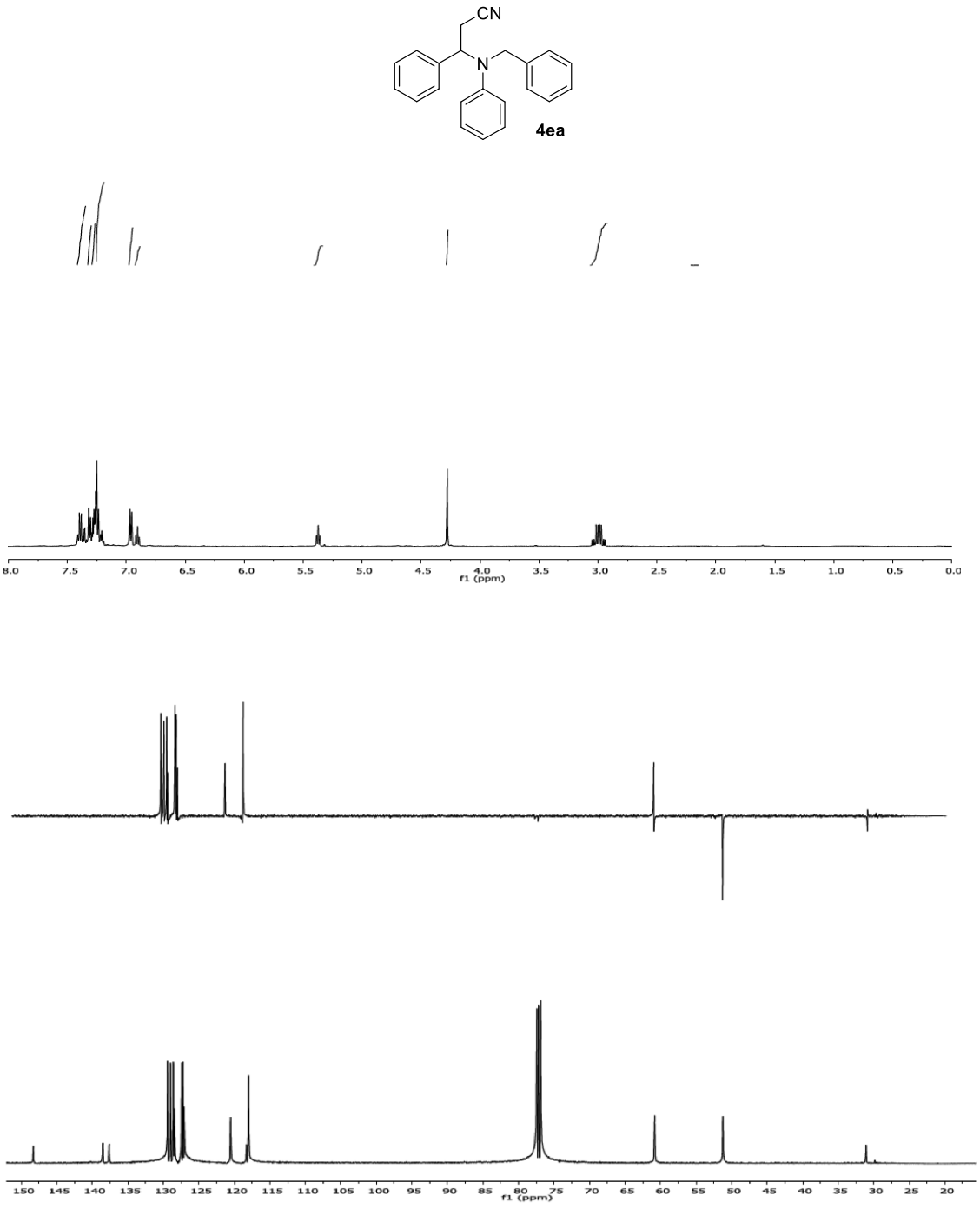

Figure S9. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4ea** in $CDCl_3$.

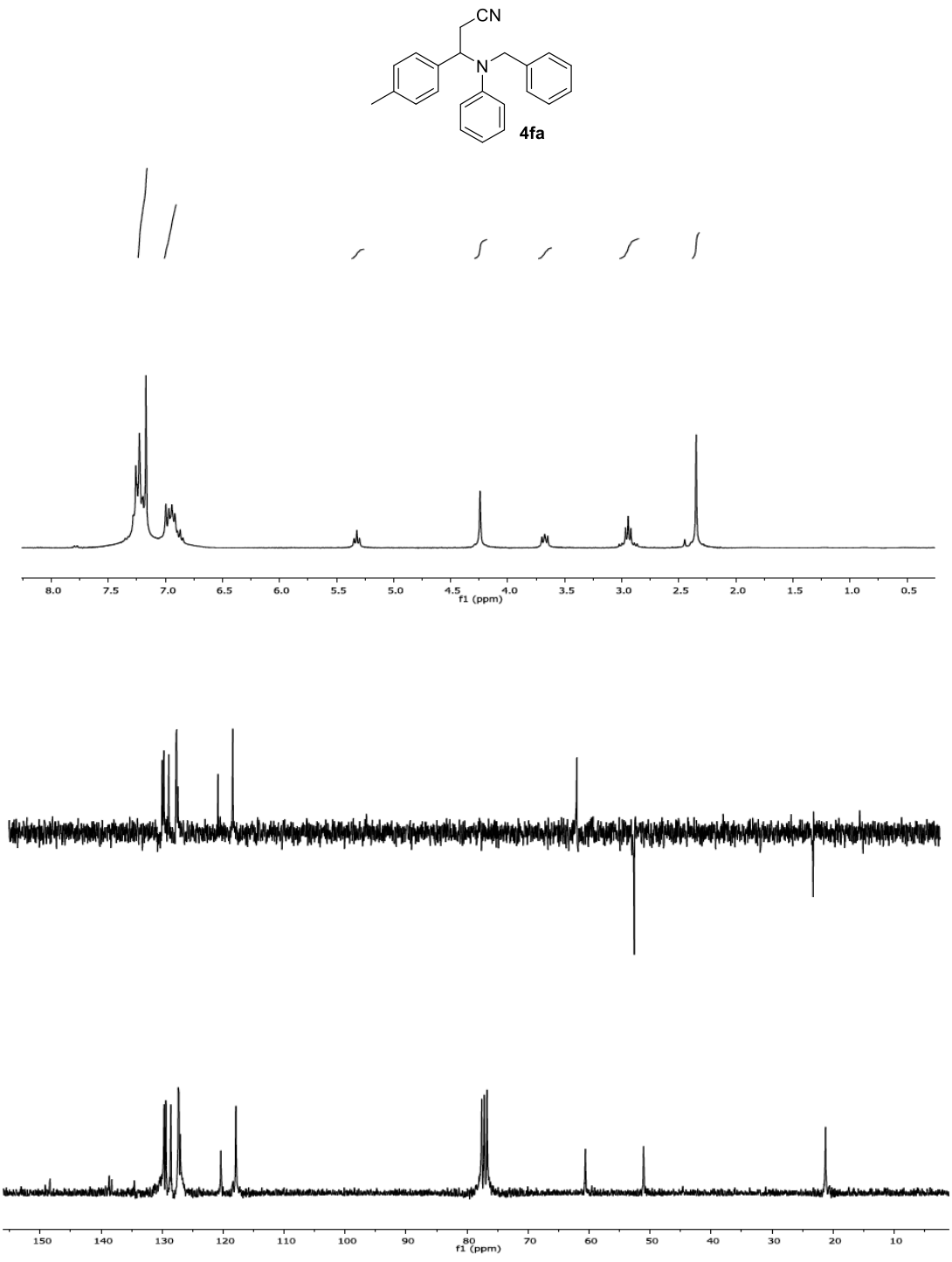

Figure S10. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **4fa** in $CDCl_3$.

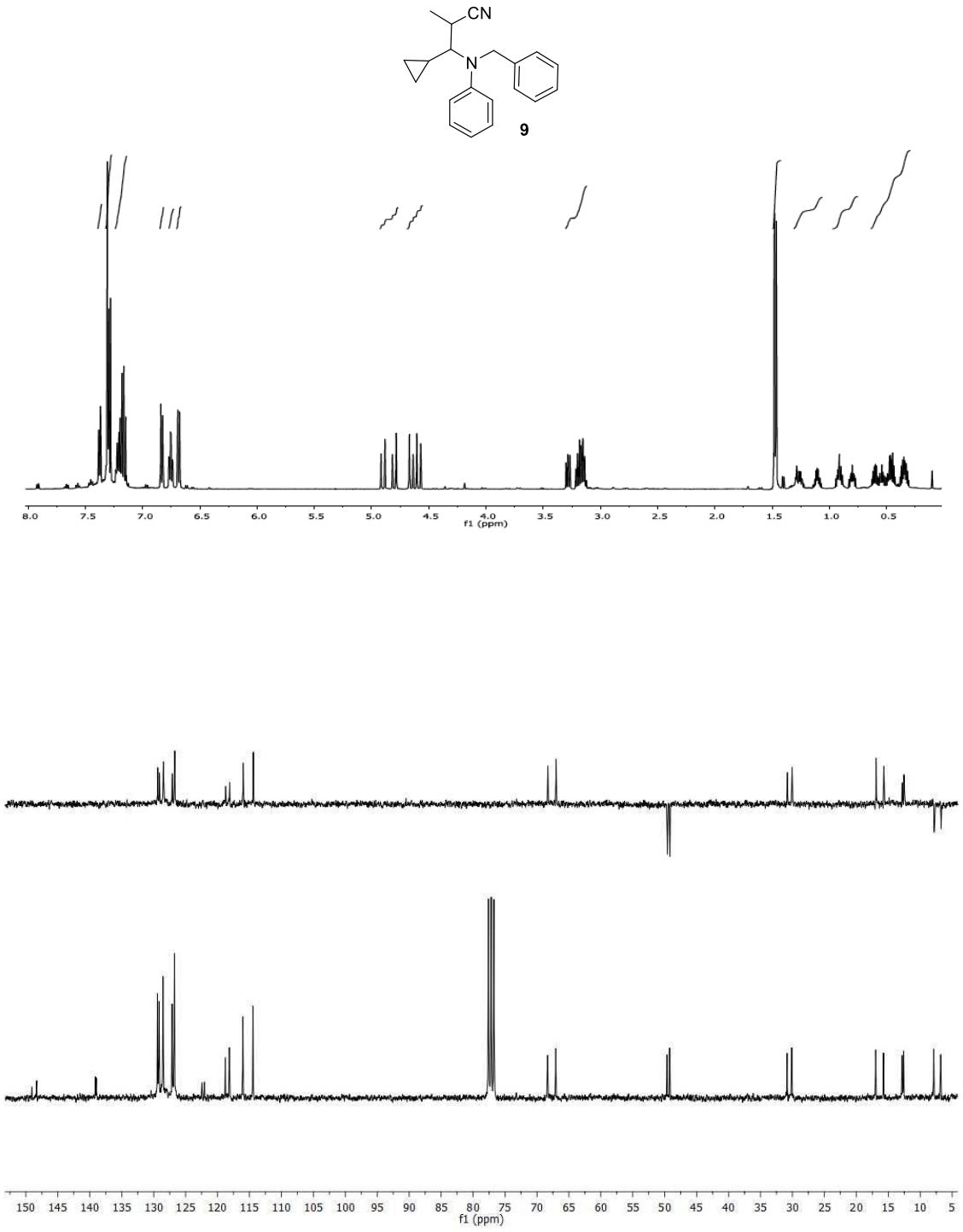

Figure S11. ^{1}H, ^{13}C DEPT 135 and ^{13}C NMR spectra of β-aminonitrile **9** in $CDCl_3$.