Supporting Information for

Chemoselective access to γ-ketoesters with stereogenic quaternary α-center or γ-keto nitriles by aerobic reaction of α-cyanoesters and styrenes

Song-Lin Zhang*, Xian-Jin Wang and Ze-Long Yu

Key Laboratory of Synthetic and Biological Colloids, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, Jiangsu Province, China

E-mail: slzhang@jiangnan.edu.cn

Contents

1. General experimental considerations

All the reactants and reagents were used as received commercially without further purification. All the reactions were performed under O_2 atmosphere using an oxygen balloon which was realized through evacuation/backfill techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD spectrometer (400 MHz for ^1H NMR and 101 MHz for ^{13}C NMR). Chemical shifts are reported in ppm relative to TMS or residual solvent peaks of $CHCl_3$. Coupling constants are reported in Hertz. FT-IR spectra were recorded on a IRTracer-100 spectrometer. Molecular mass were determined by LCZ/2690 XE/996. Elemental analyses were performed using Elementar VARIOEL III.

2. Procedure for copper-catalyzed aerobic reaction of styrenes with α-cyanoacetates to produce γ-ketoesters 3 and 4

General procedure: Into a Schlenk tube charged with a magnetic stir bar were added CuI (0.1 mmol), PPh_3 (0.1 mmol) and AgF (0.2 mmol). The tube was then sealed and evacuated and backfilled with dry O_2 using an O_2 balloon. A DCE solution (2 mL) of styrene (**1**, 0.5 mmol) and ethyl cyanoacetate (**2**, 2.0 mmol) was then added into the tube by syringe. The reaction mixture was stirred under O_2 at 80 ^oC (oil bath) for 20 hours. The reaction mixture was cooled to room temperature and diluted by CH_2Cl_2 (2 mL). After filtration, the combined filtrate and the washings were then evaporated to extrude the solvent to get solid residue. The residue was further purified by column chromatography on silica gel eluented with petroleum ether/EtOAC = 10:1~5:1 (v/v) to provide purified products **3** or **4**.

Example: The following details a synthetic example at a 1.0 mmol level for the synthesis of **4h**: Into a Schlenk tube charged with a magnetic stir bar were added CuI (0.2 mmol), PPh_3 (0.2 mmol) and AgF (0.4 mmol). The tube was then sealed and evacuated and backfilled with dry O_2 using an O_2 balloon. A DCE solution (4 mL) of *ortho*-chlorostyrene (**1h**, 1.0 mmol) and ethyl 2-cyano-2-phenylacetate (**2b**, 4.0 mmol) was then added into the tube by syringe. The reaction mixture was stirred under O_2 at 80 ^oC (oil bath) for 20 hours. The reaction mixture was cooled to room temperature

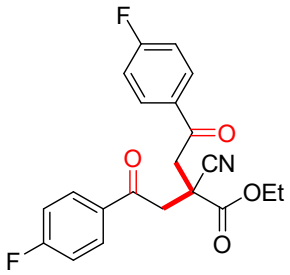
and diluted by CH_2Cl_2 (4 mL). After filtration, the combined filtrate and the washings were then evaporated to extrude the solvent to get solid residue. The residue was further purified by column chromatography on silica gel eluented with petroleum ether/EtOAC = 10:1~5:1 (v/v) to provide purified product **4h** in 0.183 g, 54% yield.

Ethyl 4-(2-chlorophenyl)-2-cyano-4-oxo-2-phenylbutanoate (**4h**). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.48–7.42 (m, 4H), 7.41–7.32 (m, 2H), 7.14– 7.10 (m, 1H), 4.40 (m, 2H), 4.25 (d, *J* = 18.2 Hz, 1H), 3.81 (d, *J* = 18.3 Hz, 1H), 1.35 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 167.1, 166.0, 133.5, 132.9, 131.7, 130.9, 130.2, 130.0, 129.4, 129.2, 129.0, 128.7, 128.5, 127.2, 126.1, 118.2, 115.5, 64.5, 63.6, 51.8, 50.2, 13.8, 13.7. IR (KBr, cm^{-1}): 2937, 2248, 1747, 1700, 1591, 1446, 1343, 1235, 759, 726, 697. Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.89; H, 4.60; N, 3.98.

3. Procedure for aerobic reaction of styrenes with α-cyanoacetates to produce γ-keto nitriles 5

Into a Schlenk tube charged with a magnetic stir bar were added CuI (0.1 mmol), PPh_3 (0.1 mmol) and AgF (0.2 mmol). The tube was then sealed and evacuated and backfilled with dry O_2 using an O_2 balloon. A DMSO solution (2 mL) of styrene (**1**, 0.5 mmol) and ethyl cyanoacetate (**2**, 2.0 mmol) was then added into the tube by syringe. The reaction mixture was stirred under O_2 at 120 °C (oil bath) for 3 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). After filtration and washing, the combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated in vacuum to give solid residue. The residue was further purified by column chromatography on silica gel eluented with petroleum ether/EtOAC = 10:1~5:1 (v/v) to provide purified products **5**.

4. Spectroscopic characterization data for all the products



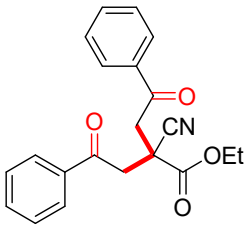
Ethyl 2-cyano-4-(4-fluorophenyl)-2-(2-(4-fluorophenyl)-2-oxoethyl)-4-oxobutanoate (**3a**; 64 mg, 66%).[1] Yellow solid;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.8, 5.3 Hz, 4H), 7.18 (t, *J* = 8.6 Hz, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.97– 3.86 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0 (s), 167.6 (s), 166.4 (d, *J* = 284.7 Hz), 132.1 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.6 Hz), 118.1 (s), 116.1 (d, *J* = 22.0 Hz), 63.6 (s), 42.8 (s), 41.6 (s), 13.9 (s).

IR (KBr, cm^{-1}): υ_{max} 2925, 2248, 1744, 1685, 1599, 1509, 1411, 1223, 840.

MS-EI: m/z (M+H) Calcd: 386.1; Found: 386.2.

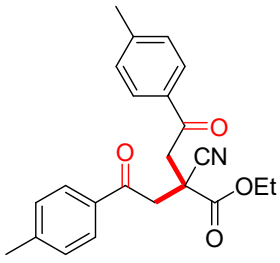


Ethyl 2-cyano-4-oxo-2-(2-oxo-2-phenylethyl)-4-phenylbutanoate (**3b**; 38 mg, 43%).[1,2] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.3 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.01–3.90 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 168.0, 135.7, 134.0, 128.8, 128.1, 118.2, 63.4, 43.0, 41.7, 13.9.

IR (KBr, cm^{-1}): 2929, 2248, 1742, 1688, 1599, 1449, 1261, 1221, 753, 689.

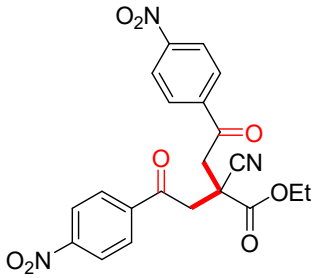
HRMS-EI: m/z (M+H) Calcd: 350.1314; Found: 350.1352.



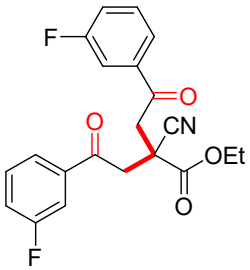
Ethyl 2-cyano-4-oxo-2-(2-oxo-2-(p-tolyl)ethyl)-4-(p-tolyl)butanoate (**3c**; 30 mg, 32%).[1] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 4H), 7.29 (d, *J* = 8.2 Hz, 4H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.96–3.86 (m, 4H), 2.44 (s, 6H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 168.1, 145.0, 133.3, 129.5, 128.3, 118.4, 63.4, 42.9, 41.7, 21.7, 13.9.

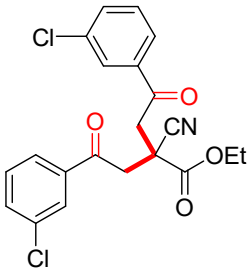
IR (KBr, cm^{-1}): 2921, 2248, 1743, 1681, 1602, 1453, 1226, 816.



Ethyl 2-cyano-4-(4-nitrophenyl)-2-(2-(4-nitrophenyl)-2-oxoethyl)-4-oxobutanoate (**3d**; 58mg, 53%).[1] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.9 Hz, 4H), 8.16 (d, *J* = 8.9 Hz, 4H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.05–3.95 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 167.3, 150.9, 139.7, 129.3, 124.1, 117.4, 64.0, 43.2, 41.5, 13.9.
IR (KBr, cm^{-1}): 2921, 2248, 1740, 1697, 1599, 1528, 1344, 1215, 855.



Ethyl 2-cyano-4-(3-fluorophenyl)-2-(2-(3-fluorophenyl)-2-oxoethyl)-4-oxobutanoate (**3e**; 29 mg, 30%). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.68–7.64 (m, 2H), 7.53–7.48 (m, 2H), 7.34 (td, *J* = 7.9, 2.2 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.92 (m, 4H), 1.37 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4 (d, *J* = 2.2 Hz), 167.6 (s), 162.9 (d, *J* = 249.1 Hz), 137.6 (d, *J* = 6.3 Hz), 130.6 (d, *J* = 7.7 Hz), 123.9 (d, *J* = 3.0 Hz), 121.2 (d, *J* = 21.5 Hz), 117.9 (s), 114.9 (d, *J* = 22.6 Hz), 63.6 (s), 43.0 (s), 41.5 (s), 13.9 (s).
IR (KBr, cm^{-1}): 2965, 2921, 2248, 1744, 1693, 1590, 1225, 870, 794.
Anal. Calcd for $C_{21}H_{17}F_2NO_4$: C, 65.45; H, 4.45; N, 3.63. Found: C, 65.36; H, 4.52; N, 3.70.

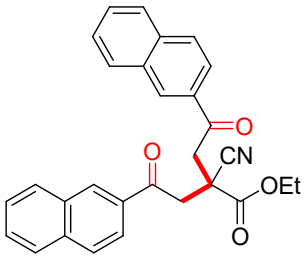


Ethyl 4-(3-chlorophenyl)-2-(2-(3-chlorophenyl)-2-oxoethyl)-2-cyano-4-oxobutanoate (**3f**; 39 mg, 37%). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (t, *J* = 1.8 Hz, 2H), 7.87 – 7.84 (m, 2H), 7.61 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.98 – 3.84 (m, 4H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4, 167.6, 137.1, 135.3, 134.0, 130.2, 128.3, 126.2, 117.8, 63.7, 43.0, 41.5, 13.8.

IR (KBr, cm^{-1}): 2961, 2925, 2248, 1740, 1693, 1571, 1261, 1216, 866, 793.

Anal. Calcd for $C_{21}H_{17}Cl_2NO_4$: C, 60.30; H, 4.10; N, 3.35. Found: C, 60.39; H, 4.02; N, 3.42.

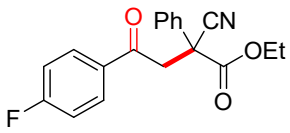


Ethyl 2-cyano-4-(naphthalen-2-yl)-2-(2-(naphthalen-2-yl)-2-oxoethyl)-4-oxobutanoate (**3g**; 73 mg, 65%). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 2H), 8.04 (dd, *J* = 8.6, 1.7 Hz, 2H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.89-7.94 (m, 4H), 7.66 (td, *J* = 7.4, 1.4 Hz, 2H), 7.60 (td, *J* = 7.2, 1.2 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.22–4.08 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 168.1, 136.0, 133.1, 132.4, 130.2, 129.7, 129.0, 128.8, 127.9, 127.1, 123.4, 118.4, 63.5, 43.1, 41.9, 13.9.

IR (KBr, cm^{-1}): 2965, 2925, 2248, 2209, 1744, 1685, 1591, 1262, 1183, 746.

Anal. Calcd for $C_{29}H_{23}NO_4$: C, 77.49; H, 5.16; N, 3.12. Found: C, 77.78; H, 5.35; N, 3.02.



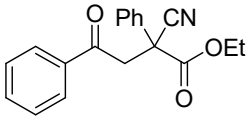
Ethyl 2-cyano-4-(4-fluorophenyl)-4-oxo-2-phenylbutanoate (**4a**; 88 mg, 54%). Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.67 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.51 – 7.42 (m, 3H), 7.17 (t, *J* = 8.6 Hz, 2H), 4.42–4.37 (m, 1H), 4.31–4.25 (m, 1H), 4.17 (d, *J* = 17.9 Hz, 1H), 3.74 (d, *J* = 17.9 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.66 (s), 167.25 (s), 166.25 (d, *J* = 256.3 Hz), 133.54 (s), 131.88 (d, *J* = 2.9 Hz), 130.90 (d, *J* = 9.5 Hz), 129.45 (s), 129.25 (s), 126.11 (s), 118.38 (s), 116.02 (d, *J* = 22.0 Hz), 63.54 (s), 49.94 (s), 48.29 (s), 13.81 (s).

IR (KBr, cm^{-1}): 2921, 2248, 1744, 1689, 1595, 1449, 1348, 1219, 800, 754, 695.

MS-EI: m/z (M+1) Calcd: 326.1; Found: 326.2.

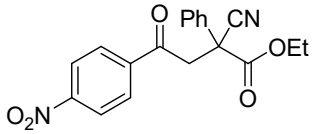
Anal. Calcd for $C_{19}H_{16}FNO_3$: C, 70.14; H, 4.96; N, 4.31. Found: C, 70.38; H, 5.10; N, 4.22.



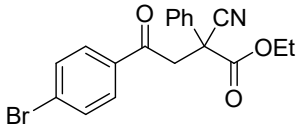
Ethyl 2-cyano-4-oxo-2,4-diphenylbutanoate (**4b**; 72 mg, 47%).[3] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.70–7.60 (m, 3H), 7.51–7.44 (m, 5H), 4.42–4.36 (m, 1H), 4.34–4.26 (m, 1H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.78 (d, *J* = 18.0 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 167.3, 135.4, 134.0, 133.7, 129.4, 129.2, 128.8, 128.2,

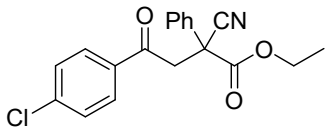
127.8, 126.8, 126.2, 118.5, 63.5, 50.0, 48.4, 13.8.
IR (KBr, cm^{-1}): 2933, 2248, 1744, 1687, 1599, 1449, 1348, 1261, 1220, 754, 693.



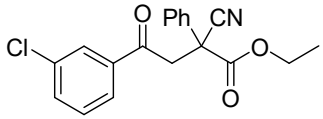
Ethyl 2-cyano-4-(4-nitrophenyl)-4-oxo-2-phenylbutanoate (**4c**; 80 mg, 45%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 7.67 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.47 (m, 3H), 4.43–4.37 (m, 1H), 4.32–4.27 (m, 1H), 4.22 (d, *J* = 18.1 Hz, 1H), 3.78 (d, *J* = 18.1 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 167.0, 150.9, 139.7, 133.2, 129.6, 129.4, 129.3, 126.0, 124.1, 118.0, 63.8, 49.8, 48.7, 13.8.
IR (KBr, cm^{-1}): 2941, 2248, 1744, 1688, 1599, 1525, 1499, 1343, 1214, 854, 755, 695.
Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.85; H, 4.49; N, 8.04.



Ethyl 4-(4-bromophenyl)-2-cyano-4-oxo-2-phenylbutanoate (**4d**; 117 mg, 61%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.66 (dd, *J* = 13.1, 5.1 Hz, 4H), 7.49–7.44 (m, 3H), 4.42–4.35 (m, 1H), 4.32–4.26 (m, 1H), 4.15 (d, *J* = 18.0 Hz, 1H), 3.72 (d, *J* = 18.0 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 167.2, 134.1, 133.5, 132.2, 129.6, 129.5, 129.3, 129.3, 128.8, 127.3, 126.9, 126.1, 118.3, 63.6, 49.9, 48.3, 13.8.
IR (KBr, cm^{-1}): 2929, 2248, 1743, 1685, 1586, 1449, 1348, 1218, 812, 757, 695.
Anal. Calcd for $C_{19}H_{16}BrNO_3$: C, 59.08; H, 4.18; N, 3.63. Found: C, 59.36; H, 4.29; N, 3.50.



Ethyl 4-(4-chlorophenyl)-2-cyano-4-oxo-2-phenylbutanoate (**4e**; 90 mg, 53%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.69–7.65 (m, 2H), 7.47 (m, 4H), 7.34 (d, *J* = 7.5 Hz, 1H), 4.43–4.36 (m, 1H), 4.31–4.26 (m, 1H), 4.16 (d, *J* = 18.0 Hz, 1H), 3.73 (d, *J* = 18.0 Hz, 1H), 1.33 (d, *J* = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 167.2, 166.0, 140.5, 133.7, 133.5, 130.2, 129.6, 129.5, 129.3, 129.2, 128.7, 128.5, 126.1, 118.3, 115.5, 64.4, 63.5, 49.9, 48.3, 13.8, 13.7.
IR (KBr, cm^{-1}): 2929, 2248, 1743, 1689, 1591, 1446, 1344, 1215, 816, 757, 694.
Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.85; H, 4.63; N, 4.18.

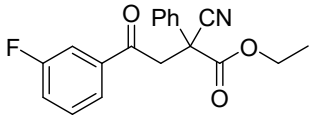


Ethyl 4-(3-chlorophenyl)-2-cyano-4-oxo-2-phenylbutanoate (**4f**; 104 mg, 61%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.85 (m, 2H), 7.69–7.65 (m, 2H), 7.62–7.59 (m, 1H), 7.50– 7.43 (m, 4H), 4.44–4.38 (m, 1H), 4.32–4.25 (m, 1H), 4.16 (d, *J* = 18.0 Hz, 1H), 3.73 (d, *J* = 18.0 Hz, 1H), 1.34 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 167.1, 166.0, 136.9, 135.2, 133.9, 133.4, 130.2, 129.5, 129.3, 128.7, 128.5, 128.3, 126.2, 126.1, 118.2, 115.4, 64.4, 63.6, 49.9, 48.4, 13.8 13.7.

IR (KBr, cm^{-1}): 2925, 2248, 1743, 1692, 1571, 1446, 1344, 1215, 860, 789, 726, 694.

Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.83; H, 4.65; N, 4.18.

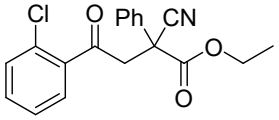


Ethyl 2-cyano-4-(3-fluorophenyl)-4-oxo-2-phenylbutanoate (**4g**; 88 mg, 55%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 3H), 7.50–7.43 (m, 4H), 7.35–7.31 (m, 1H), 4.43–4.35 (m, 1H), 4.33–4.24 (m, 1H), 4.17 (d, *J* = 18.1 Hz, 1H), 3.74 (d, *J* = 18.0 Hz, 1H), 1.34 (td, *J* = 7.1, 1.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.16 (s), 167.16 (s), 166.03 (s), 162.87 (d, *J* = 248.1 Hz), 137.37 (d, *J* = 7.4 Hz), 130.59 (d, *J* = 7.6 Hz), 130.19 (s), 129.48 (s), 129.30 (s), 128.7, 128.5, 123.95 (d, *J* = 2.8 Hz), 121.06 (d, *J* = 21.4 Hz), 118.32 (s), 114.95 (d, *J* = 22.6 Hz), 64.46 (s), 63.58 (s), 49.89 (s), 48.40 (s), 13.8, 13.7.

IR (KBr, cm^{-1}): 2933, 2248, 1744, 1693, 1589, 1447, 1347, 1237, 871, 757, 726, 695.

Anal. Calcd for $C_{19}H_{16}FNO_3$: C, 70.14; H, 4.96; N, 4.31. Found: C, 70.20; H, 4.88; N, 4.40.

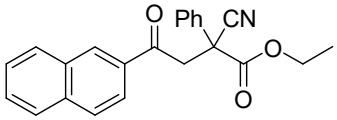


Ethyl 4-(2-chlorophenyl)-2-cyano-4-oxo-2-phenylbutanoate (**4h**; 117 mg, 69%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.48–7.42 (m, 4H), 7.41–7.32 (m, 2H), 7.14–7.10 (m, 1H), 4.40 (m, 2H), 4.25 (d, *J* = 18.2 Hz, 1H), 3.81 (d, *J* = 18.3 Hz, 1H), 1.35 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 167.1, 166.0, 133.5, 132.9, 131.7, 130.9, 130.2, 130.0, 129.4, 129.2, 129.0, 128.7, 128.5, 127.2, 126.1, 118.2, 115.5, 64.5, 63.6, 51.8, 50.2, 13.8, 13.7.

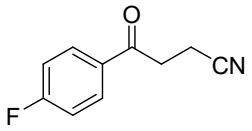
IR (KBr, cm^{-1}): 2937, 2248, 1747, 1700, 1591, 1446, 1343, 1235, 759, 726, 697.

Anal. Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.89; H, 4.60; N, 3.98.

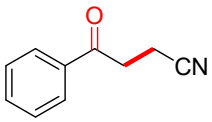


Ethyl 2-cyano-4-(naphthalen-2-yl)-4-oxo-2-phenylbutanoate (**4i**; 112 mg, 63%). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.98–7.85 (m, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.67–7.55 (m, 2H), 7.52–7.42 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 4.44 (m, 2H), 4.33 (d, *J* = 17.9 Hz, 1H), 3.93 (d, *J* = 17.9 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H).

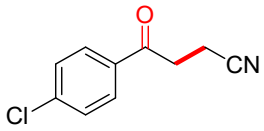
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.2, 167.4, 166.1, 136.0, 133.7, 132.7, 132.4, 130.2, 130.1, 129.6, 129.5, 129.2, 128.8, 128.7, 128.5, 127.9, 127.1, 126.2, 123.5, 118.6, 115.5, 64.5, 63.5, 50.1, 48.5, 13.9, 13.7.
IR (KBr, cm^{-1}): 2937, 2248, 1744, 1681, 1599, 1449, 1365, 1236, 820, 753, 726, 695.
Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.58; H, 5.62; N, 3.68.



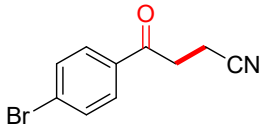
4-(4-Fluorophenyl)-4-oxobutanenitrile (**5a**; 44 mg, 50%).[4] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.19 (t, *J* = 8.6 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7 (s), 166.2 (d, *J* = 256.3 Hz), 132.1 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 9.5 Hz), 119.1 (s), 116.1 (d, *J* = 22.0 Hz), 34.2 (s), 11.8 (s).
IR (KBr, cm^{-1}): 2925, 2248, 1685, 1595, 1207, 847.



4-Oxo-4-phenylbutanenitrile (**5b**; 34 mg, 43%).[4] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 3.40 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 135.7, 133.9, 128.9, 128.0, 119.2, 34.3, 11.8.
IR (KBr, cm^{-1}): 2918, 2248, 1681, 1595, 1211, 741, 691.

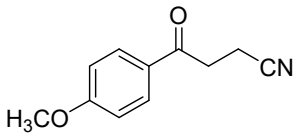


4-(4-Chlorophenyl)-4-oxobutanenitrile (**5c**; 34 mg, 19%).[4] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 140.5, 134.0, 129.4, 129.3, 119.0, 34.3, 11.9.
IR (KBr, cm^{-1}): 2918, 2248, 1673, 1591, 1211, 835.

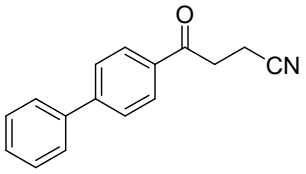


4-(4-Bromophenyl)-4-oxobutanenitrile (**5d**; 42 mg, 35%).[4] Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 3.37 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 134.3, 132.3, 129.5, 129.3, 118.9, 34.3, 11.8.

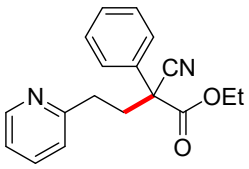
IR (KBr, cm^{-1}): 2918, 2248, 1677, 1587, 1211, 828.



4-(4-methoxyphenyl)-4-oxobutanenitrile (**5e**; 30 mg, 32%).[4] Yellow solid;
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H), 3.35 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 164.1, 130.4, 128.8, 119.4, 114.0, 55.6, 33.9, 11.9.
IR (KBr, cm^{-1}): 2925, 2248, 1670, 1595, 1258, 800.



4-(Biphenyl-4-yl)-4-oxobutanenitrile (**5f**; 52 mg, 44%).[5] White solid;
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 3.44 (t, *J* = 7.2 Hz, 1H), 2.83 (t, *J* = 7.2 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 146.6, 139.6, 134.3, 129.0, 128.6, 128.5, 127.5, 127.3, 119.2, 34.3, 11.9.
IR (KBr, cm^{-1}): 2914, 2248, 1681, 1599, 1258, 843.
MS-EI: m/z (M+1) Calcd 236.1; Found: 236.1.



Ethyl 2-cyano-2-phenyl-4-(pyridin-2-yl)butanoate (7; 116 mg, 79%**)**. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.2 Hz, 1H), 7.66 – 7.55 (m, 3H), 7.46 – 7.35 (m, 3H), 7.18 – 7.10 (m, 2H), 4.31 – 4.14 (m, 2H), 3.00 – 2.76 (m, 3H), 2.69 – 2.58 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.39, 159.52, 149.37, 136.50, 134.30, 129.18, 128.90, 126.16, 123.03, 121.54, 118.26, 63.25, 53.98, 37.45, 33.96, 13.83.
IR (KBr, cm^{-1}): 2937, 2244, 1743, 1684, 1590, 1449, 1234, 855, 749, 695.
MS-EI: m/z (M+1) Calcd: 295.1; Found: 295.2.
Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.67; H, 6.23; N, 9.40.

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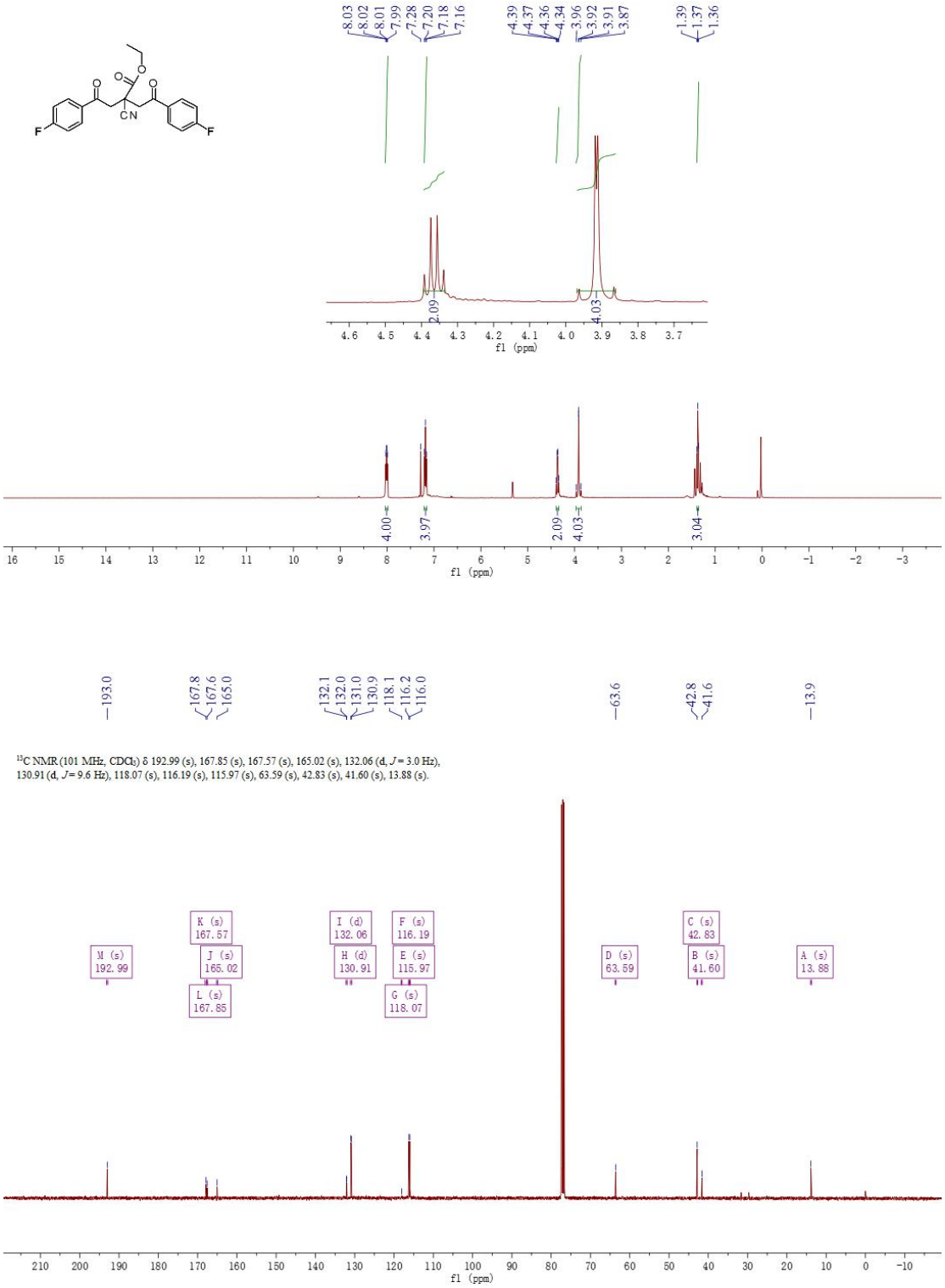
2. Riyadh, S. M.; Al-Matar, H. M.; Elnagdi, M. H. *Molecules* **2008**, *13*, 3140.
3. Qian, X.; Han, J.; Wang, L. *Adv. Synth. Catal.* **2016**, *358*, 940.
4. Lan, X.-W.; Wang, N.-X.; Bai, C.-B.; Zhang, T.; Lan, C.-L.; Chen, S.-L.; Xing, Y. *Org. Lett.* **2016**, *18*, 5986.
5. Burckhalter, J. H.; Short, J. H. *J. Org. Chem.* **1958**, *23*, 1281.

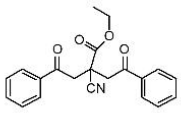
5. NMR spectra for all the products

3a (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

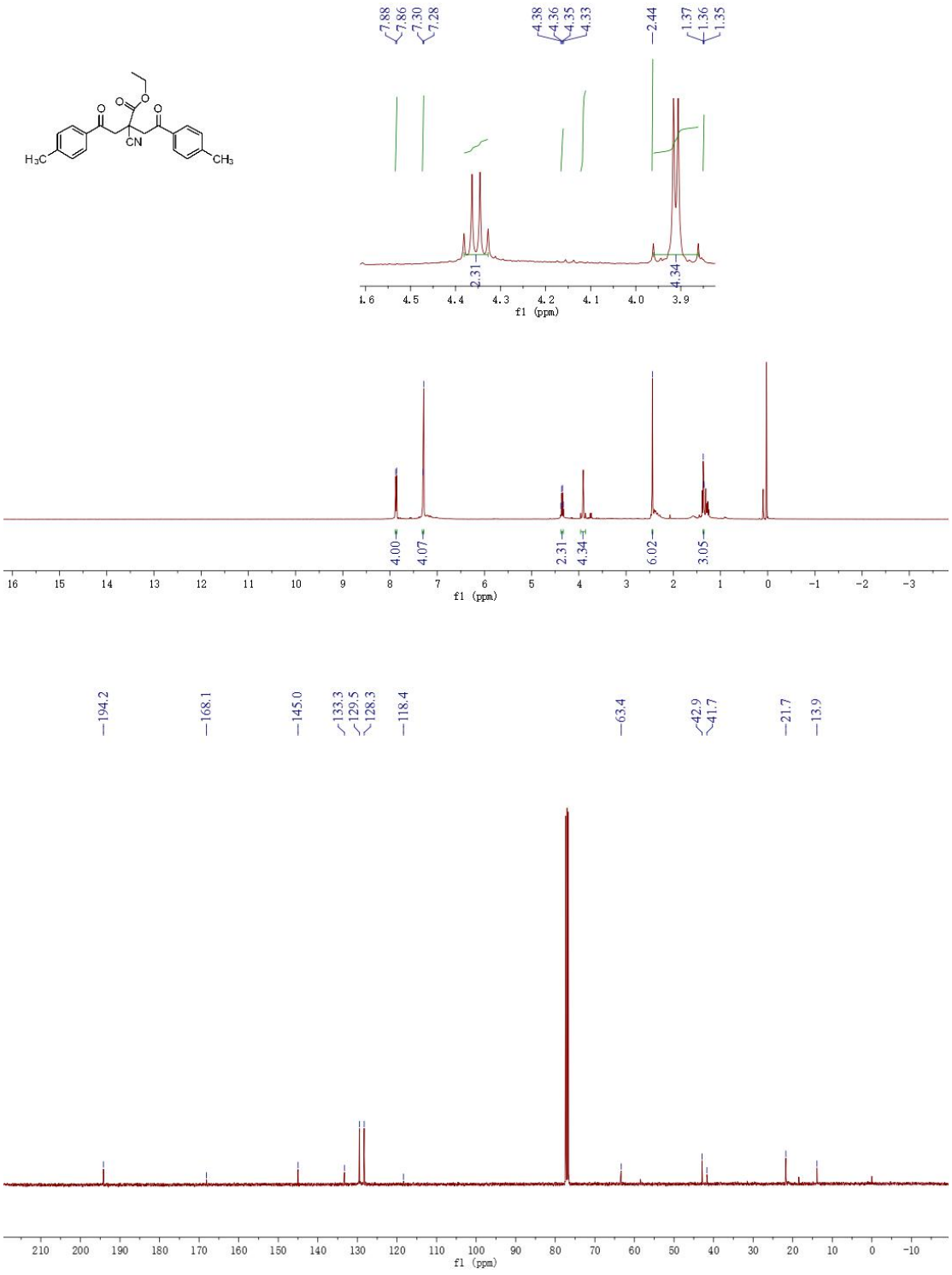


^{13}C NMR (101 MHz, $CDCl_3$) δ 192.99 (s), 167.85 (s), 167.57 (s), 165.02 (s), 132.06 (d, J = 3.0 Hz), 130.91 (d, J = 9.6 Hz), 118.07 (s), 116.19 (s), 115.97 (s), 63.59 (s), 42.83 (s), 41.60 (s), 13.88 (s).

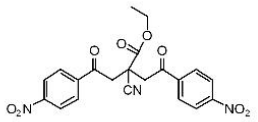
3b (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

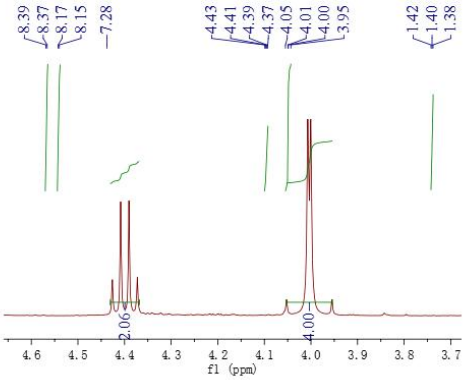


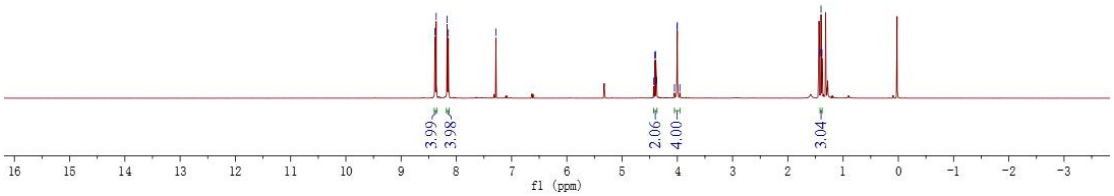
3c (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

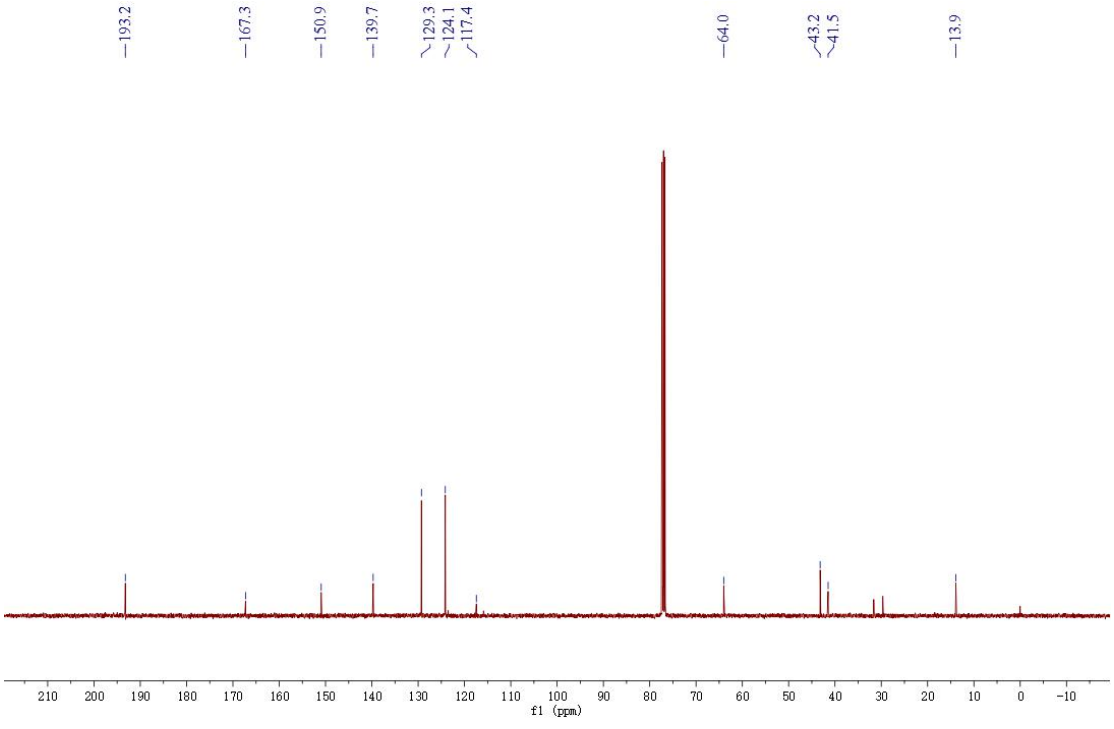


3d (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

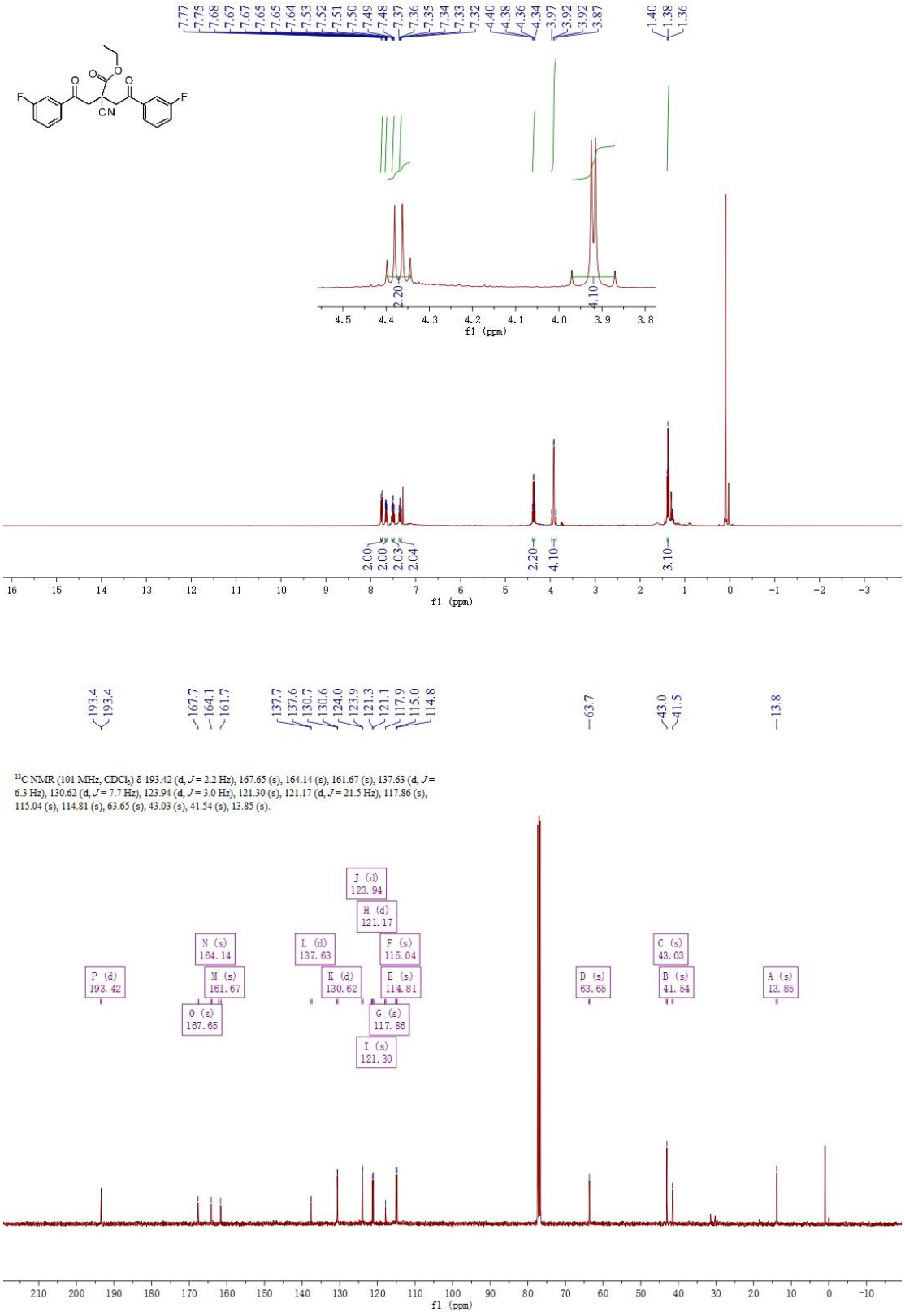






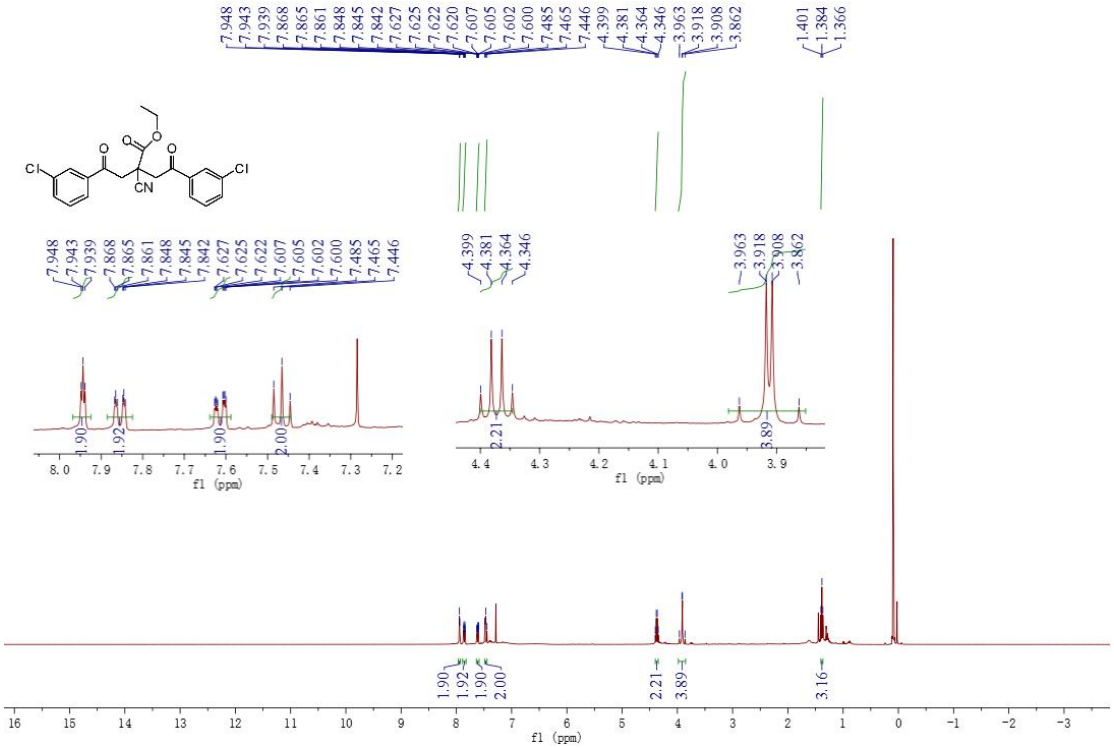


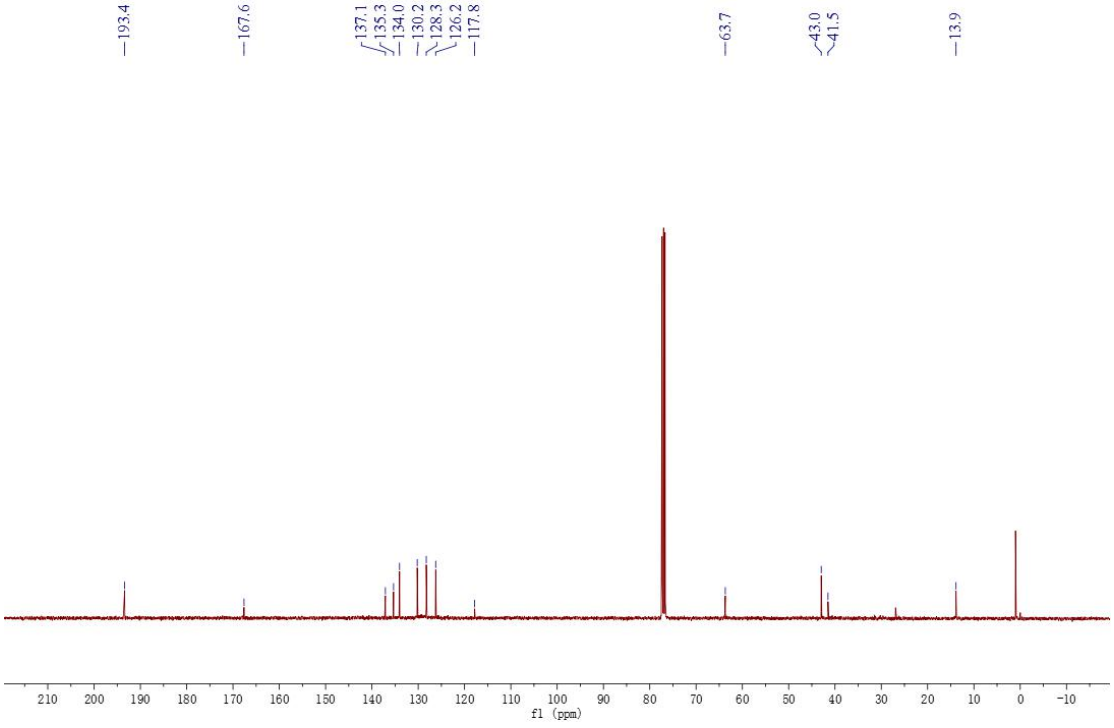
3e (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



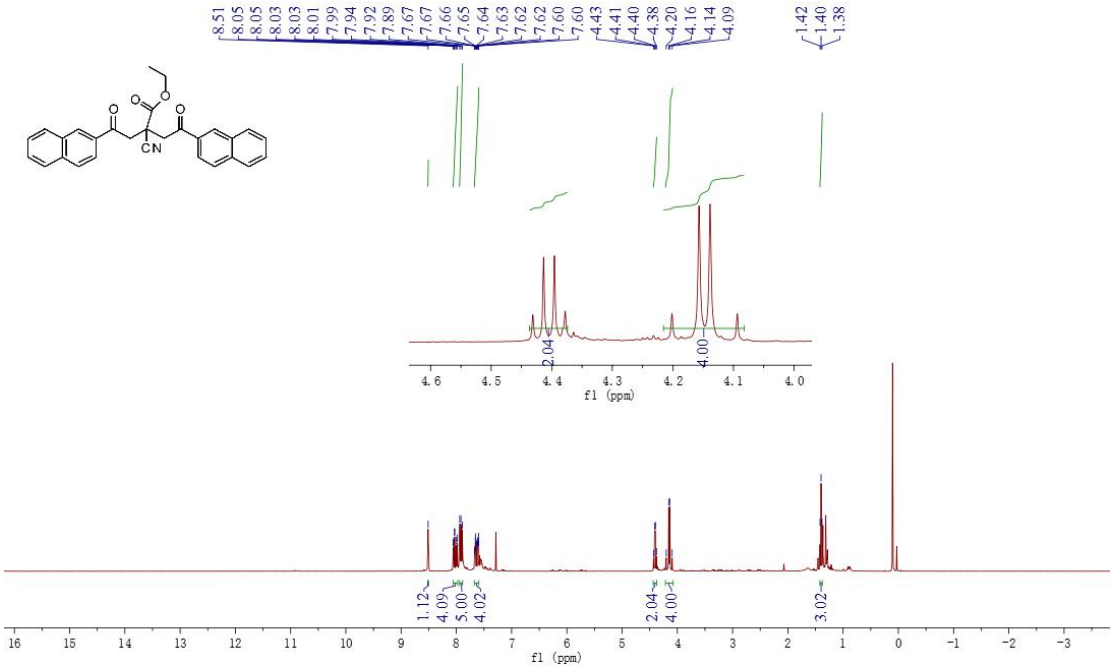
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.42 (d, J = 2.2 Hz), 167.65 (s), 164.14 (s), 161.67 (s), 137.63 (d, J = 6.3 Hz), 130.62 (d, J = 7.7 Hz), 123.94 (d, J = 3.0 Hz), 121.30 (s), 121.17 (d, J = 21.5 Hz), 117.86 (s), 115.04 (s), 114.81 (s), 63.65 (s), 43.03 (s), 41.54 (s), 13.85 (s).

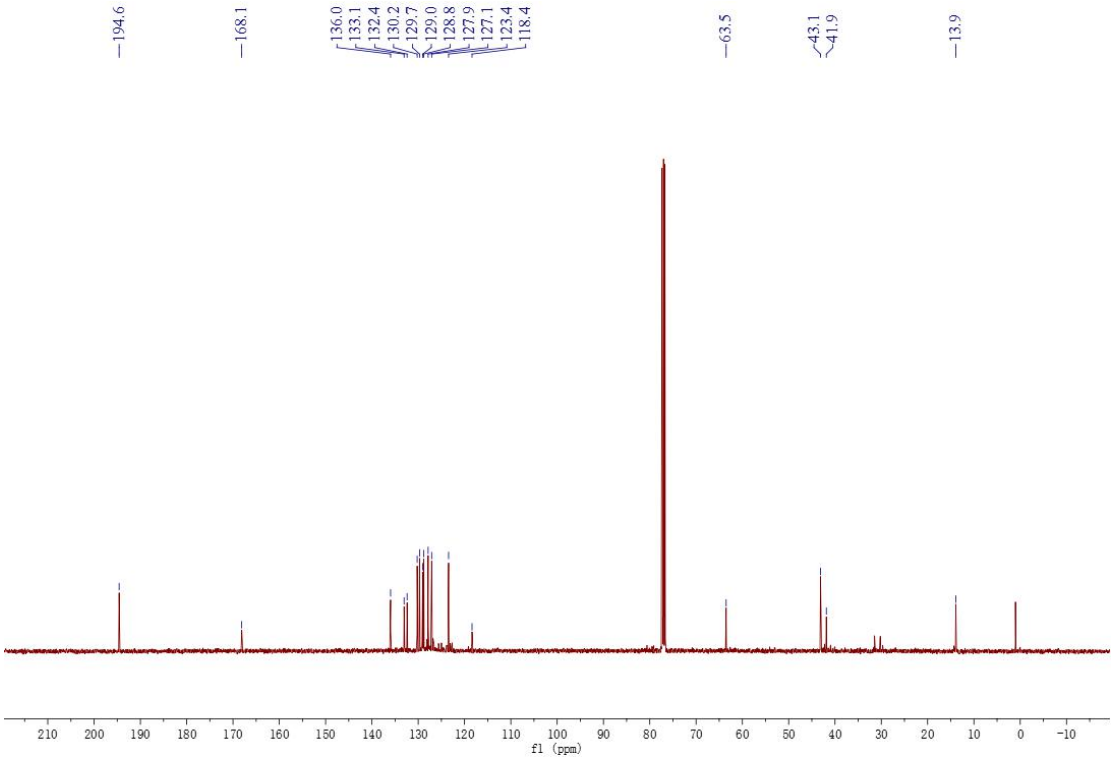
3f (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



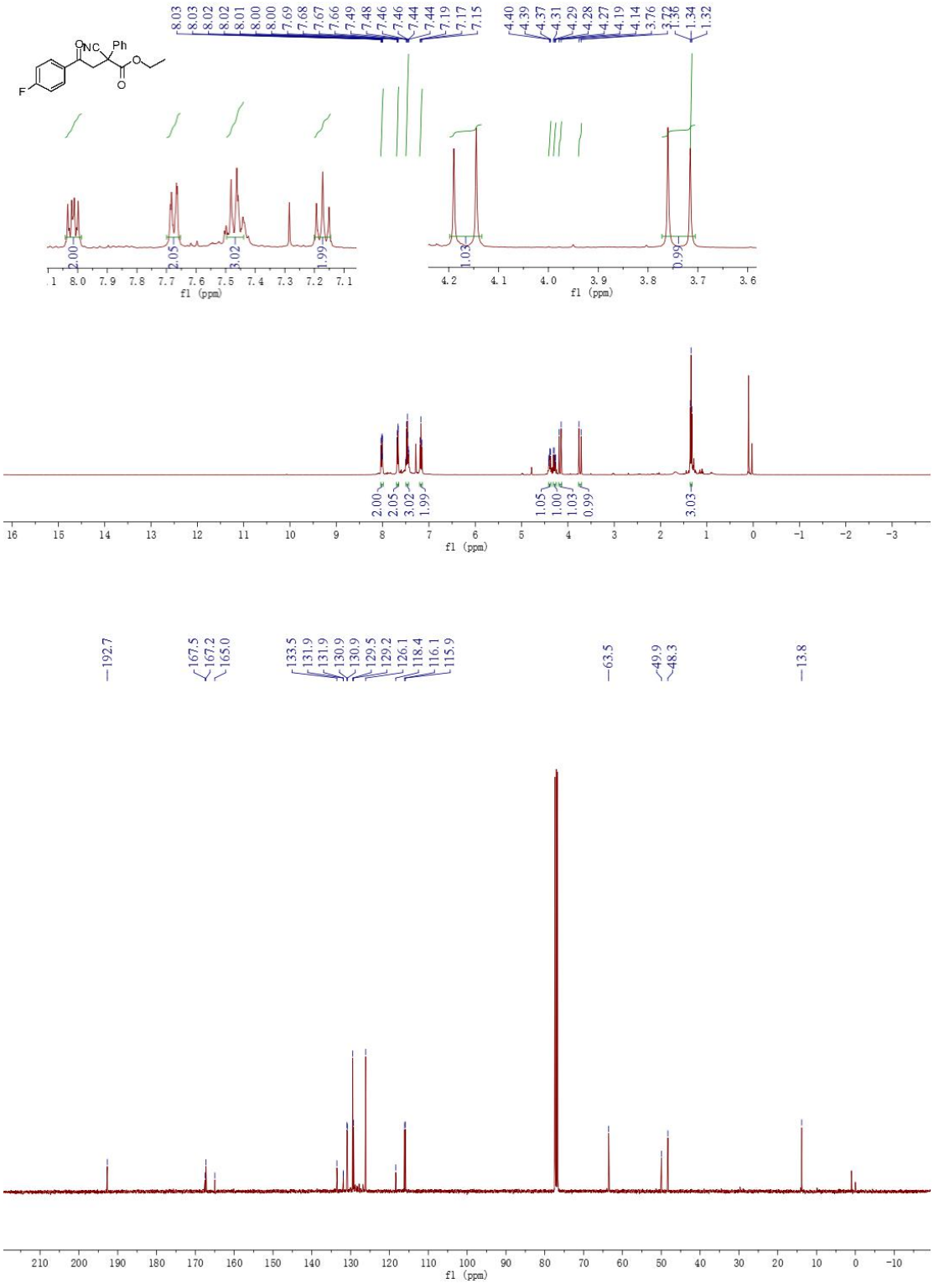


3g (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

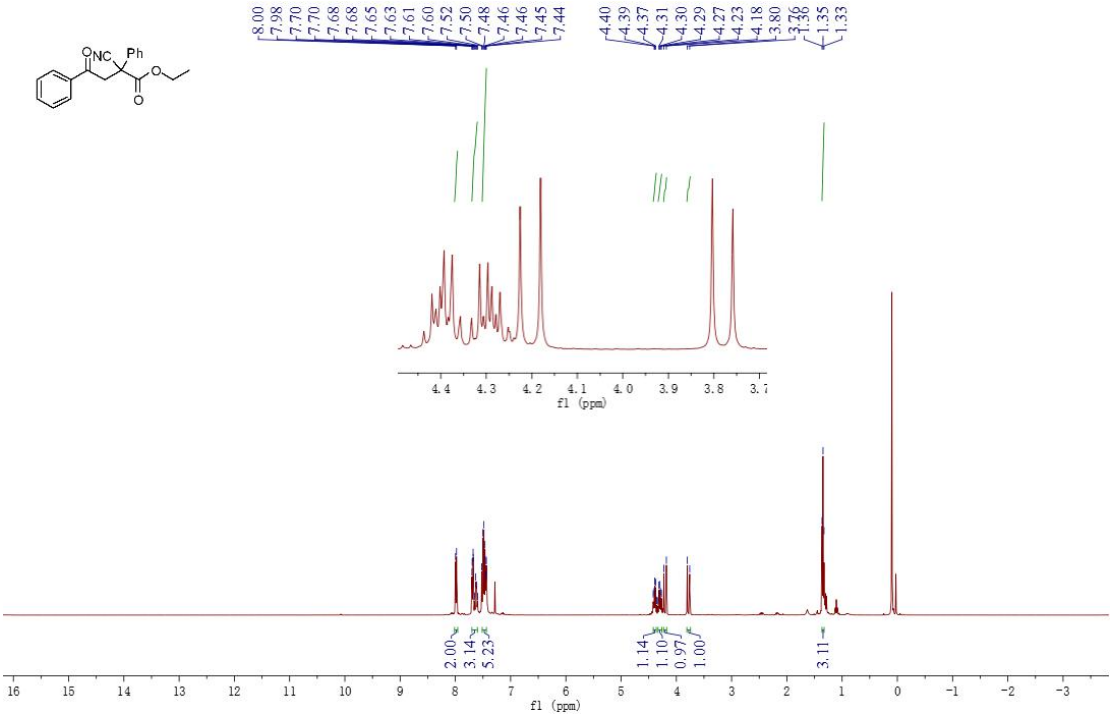


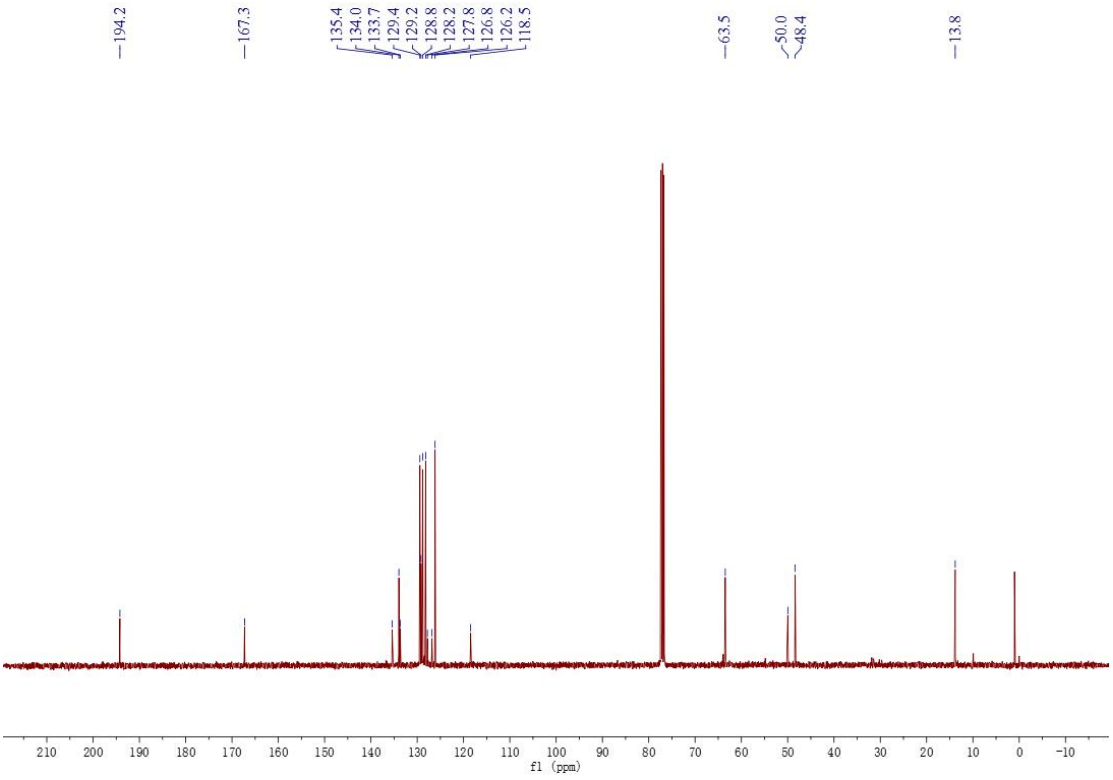


4a (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

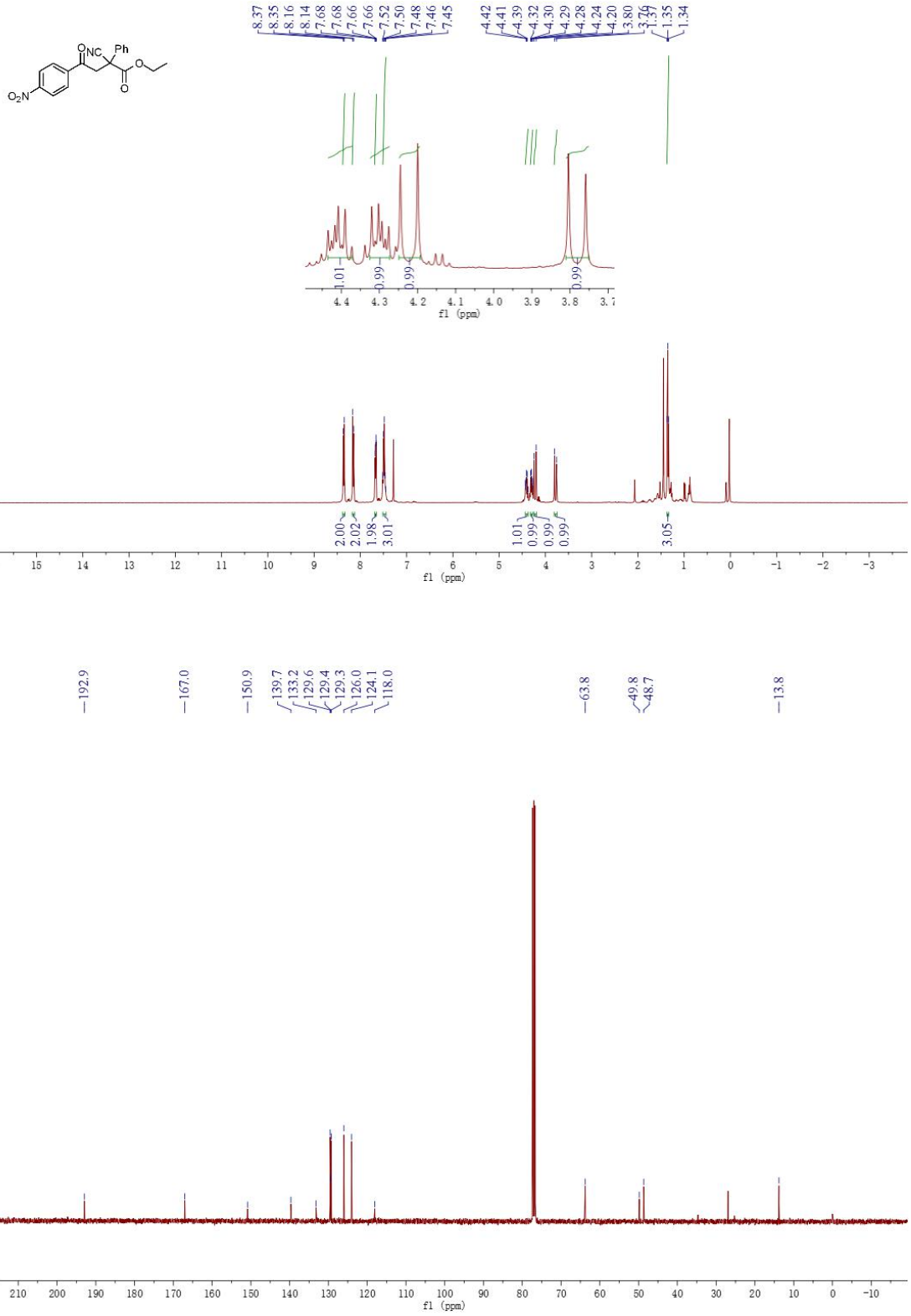


4b (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

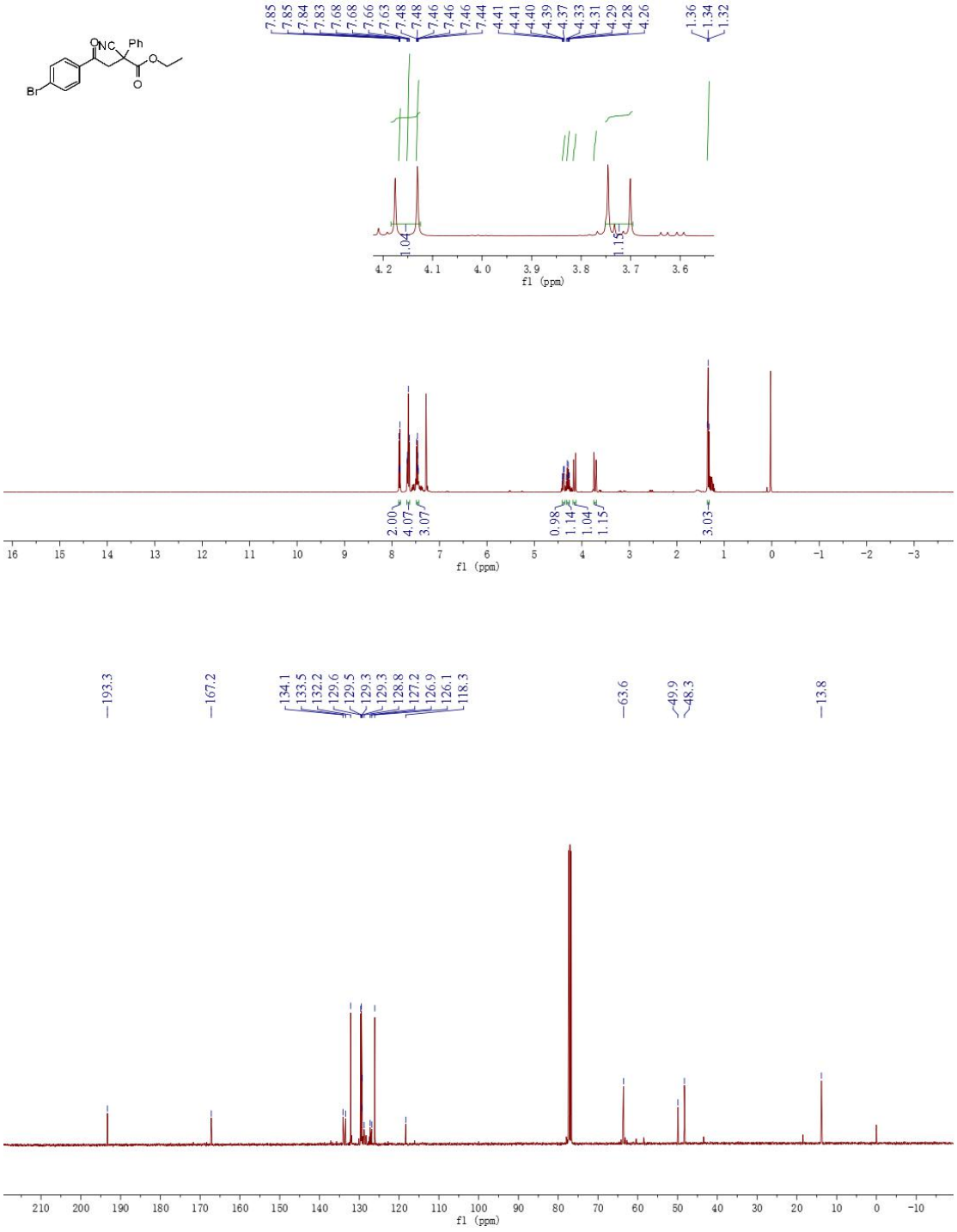




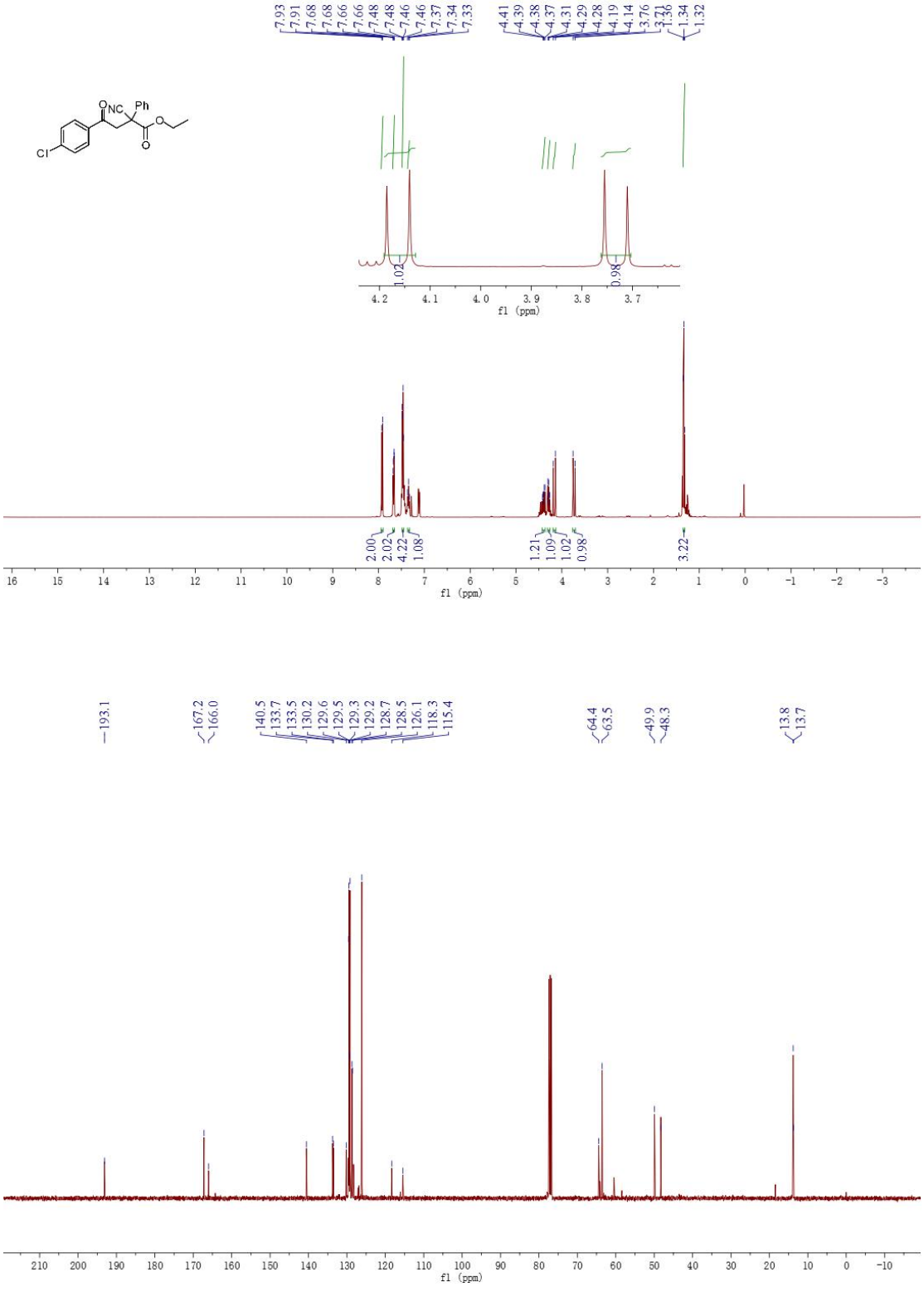
4c (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



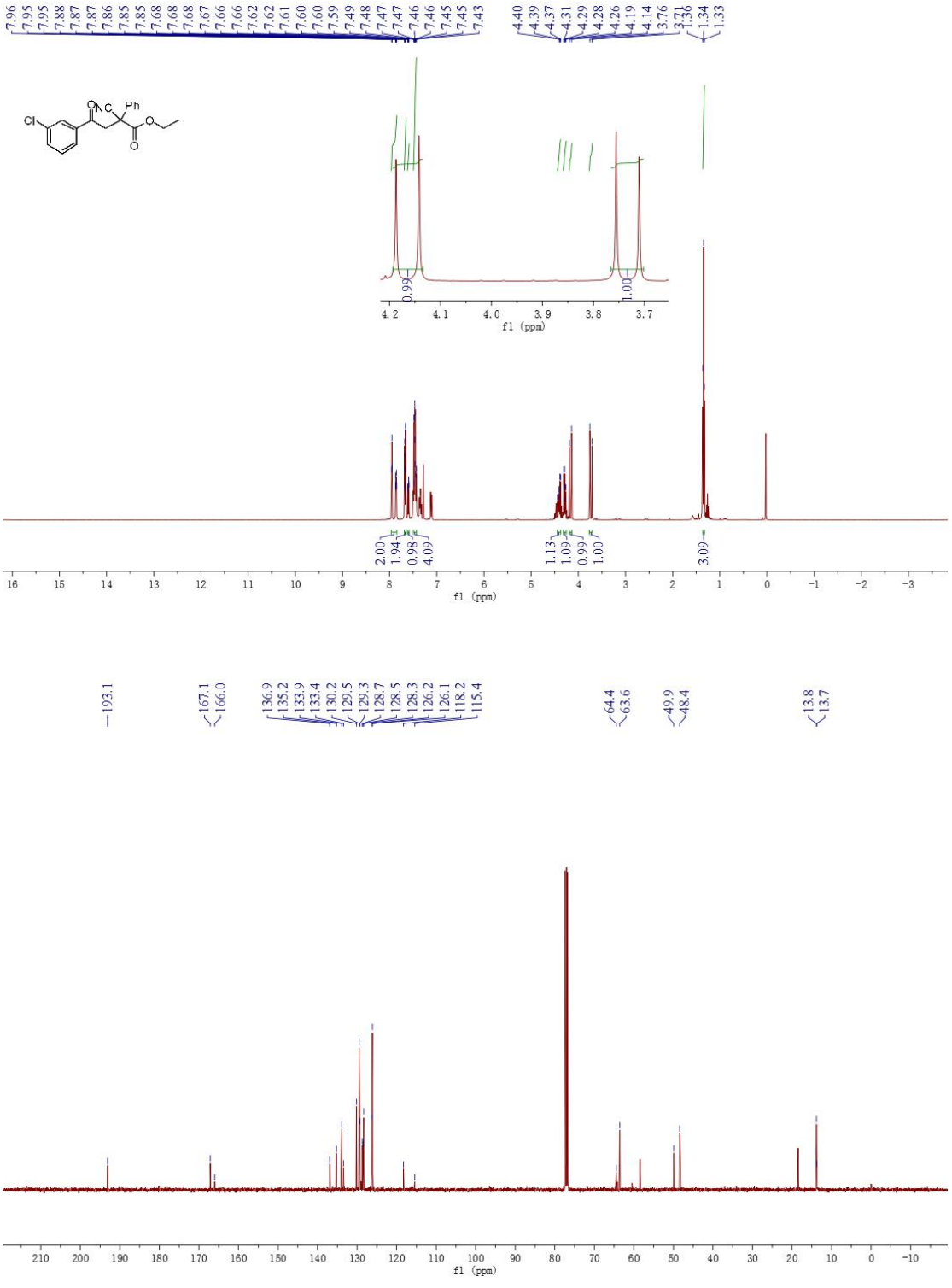
4d (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



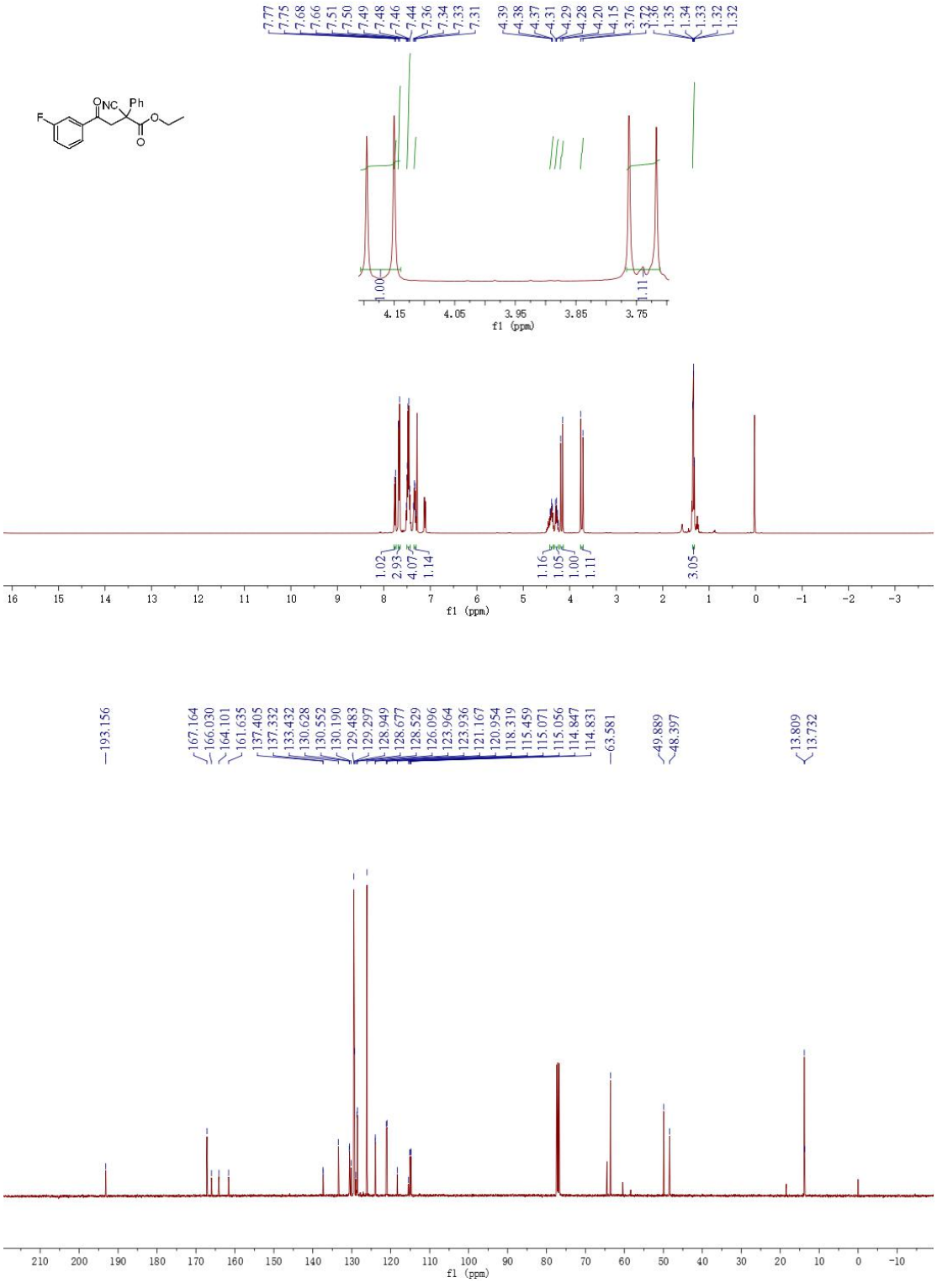
4e (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



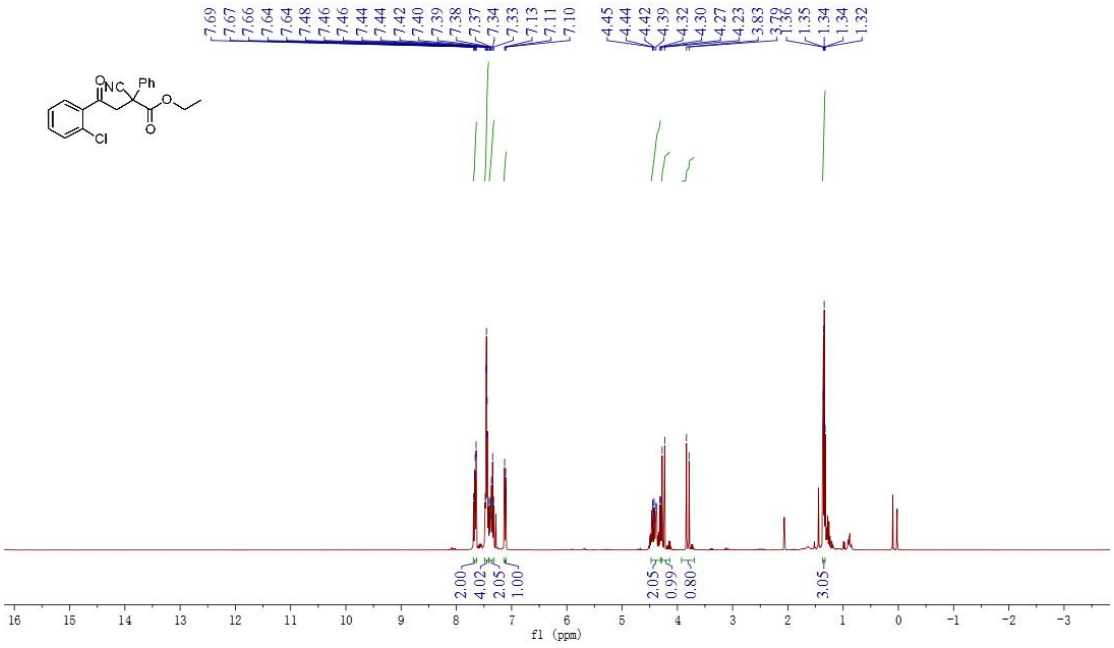
4f (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

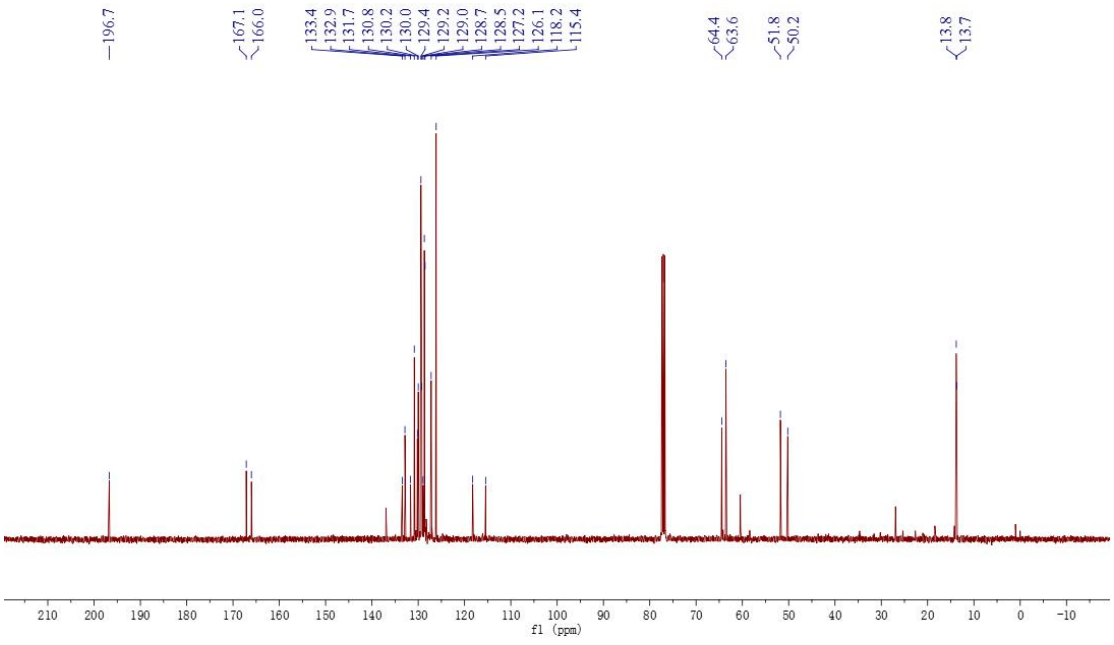


4g (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

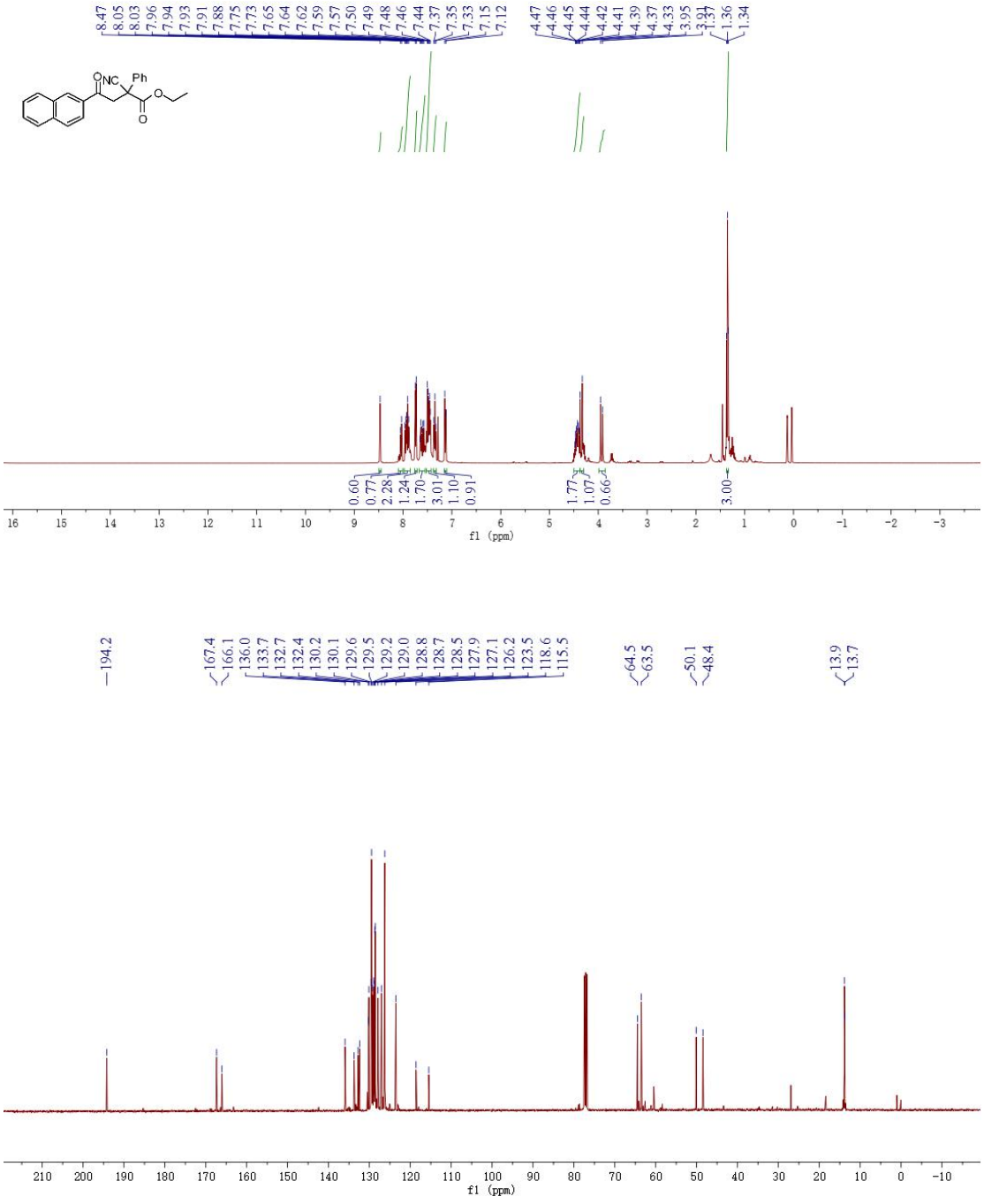


4h (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

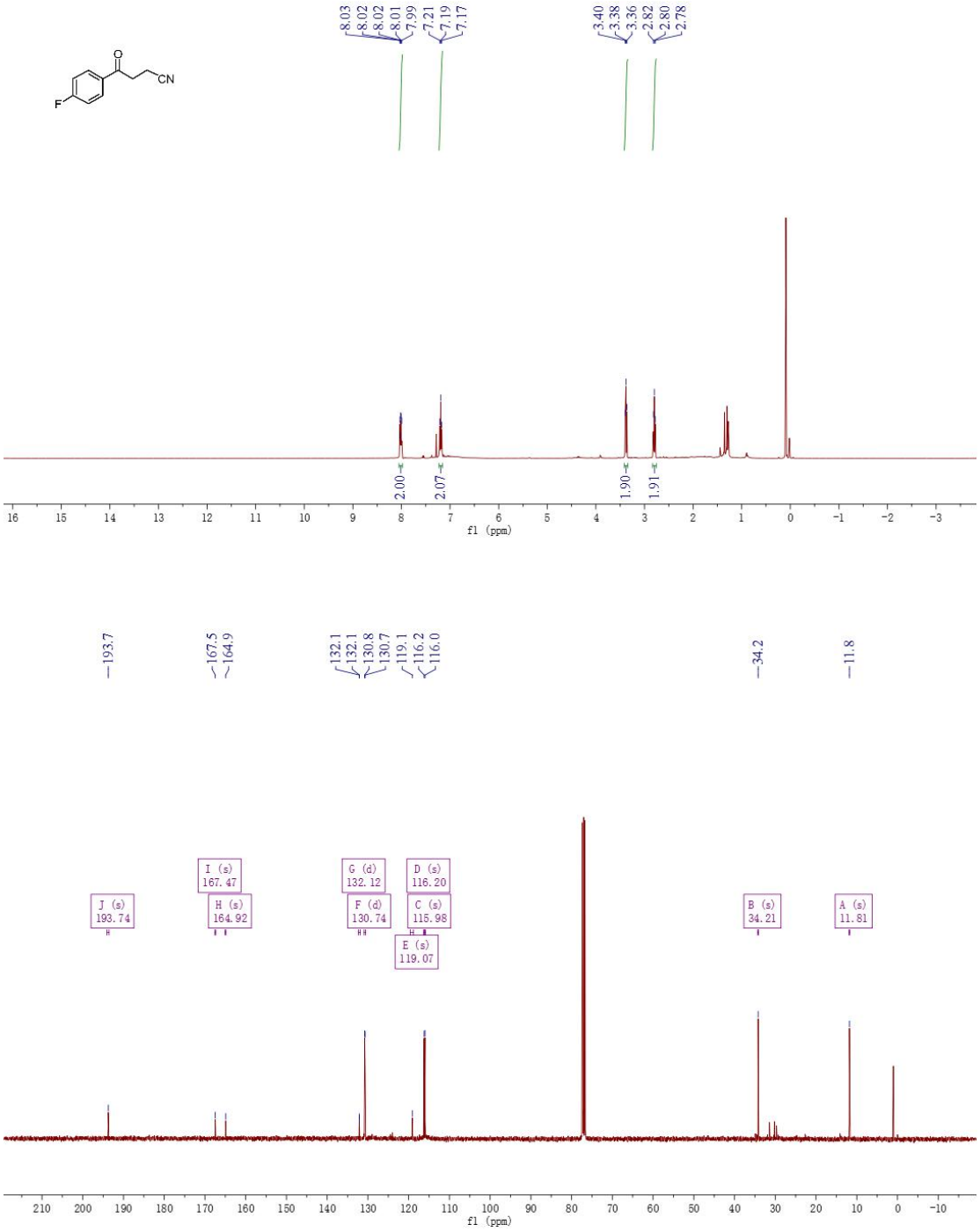




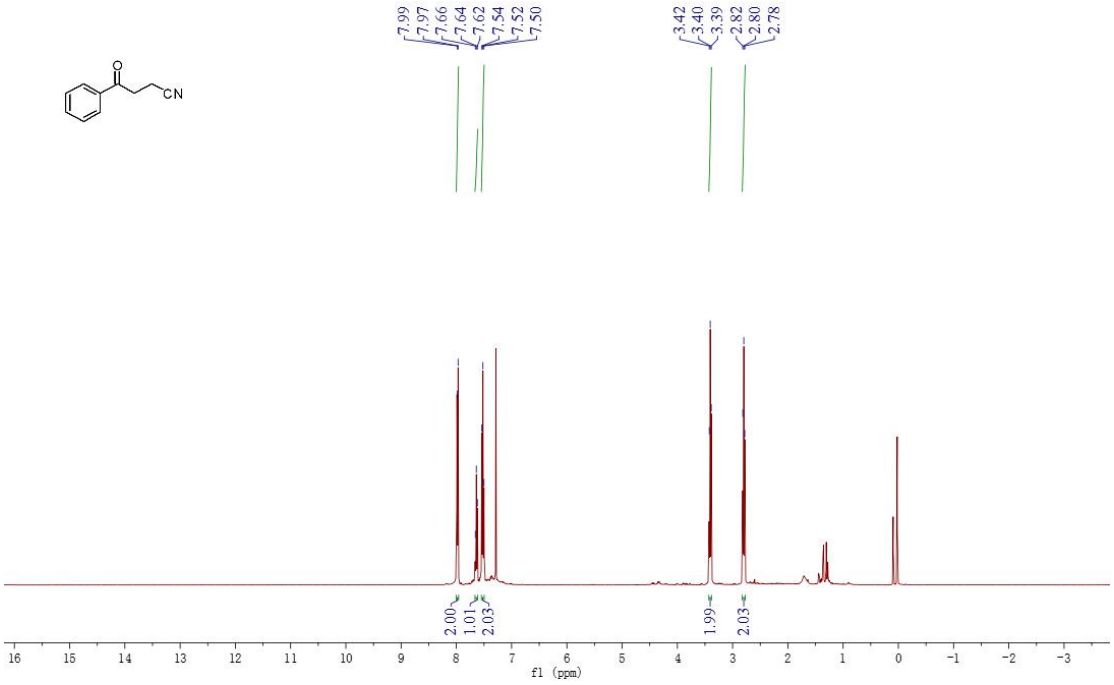
4i (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

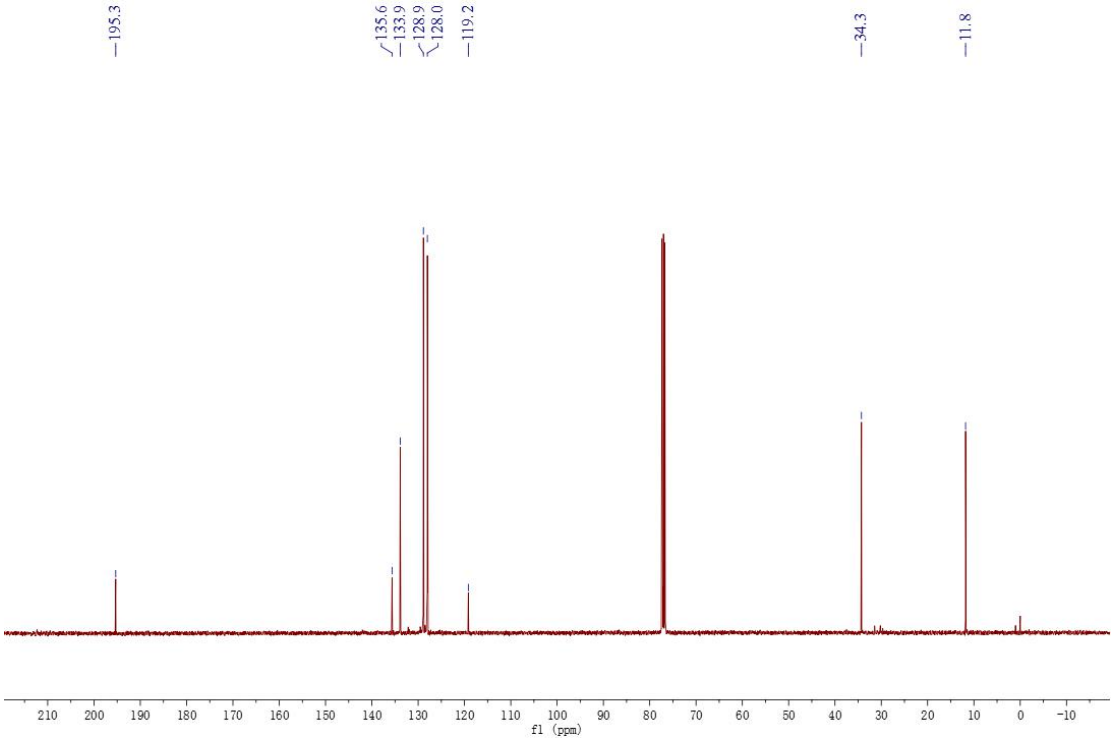


5a (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

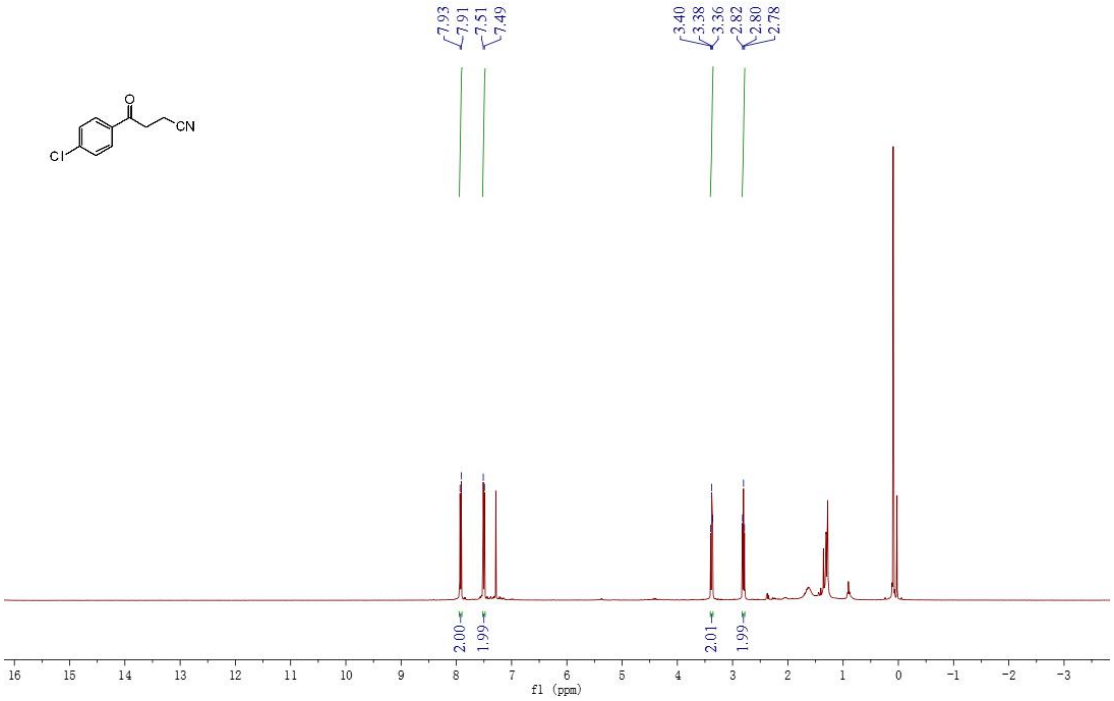


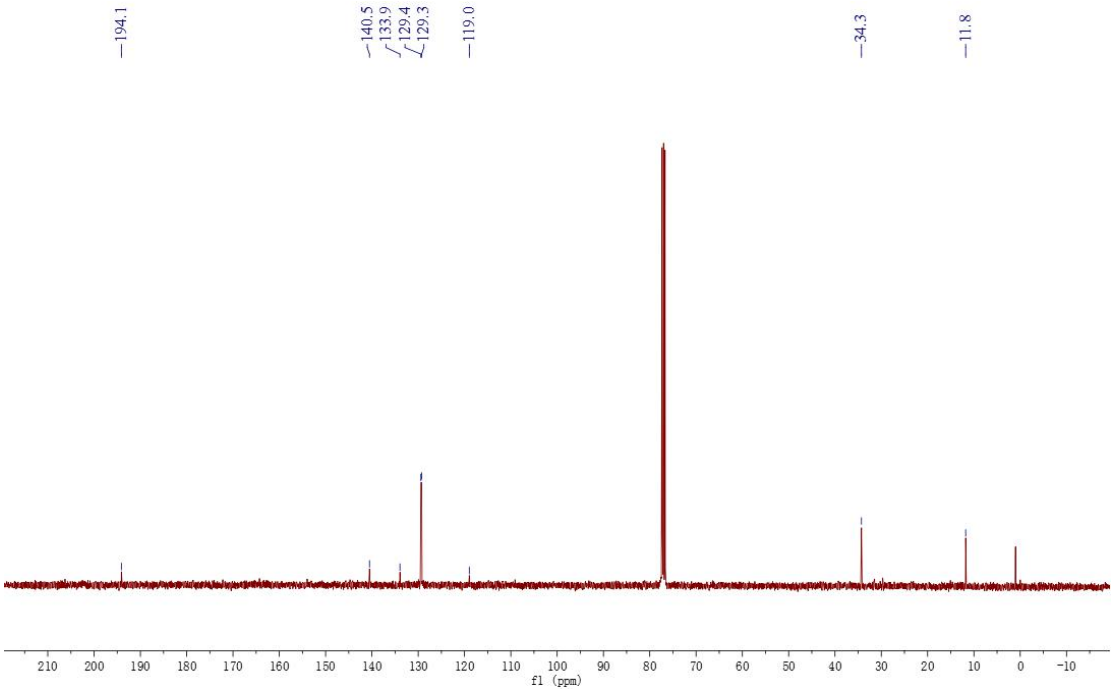
5b (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



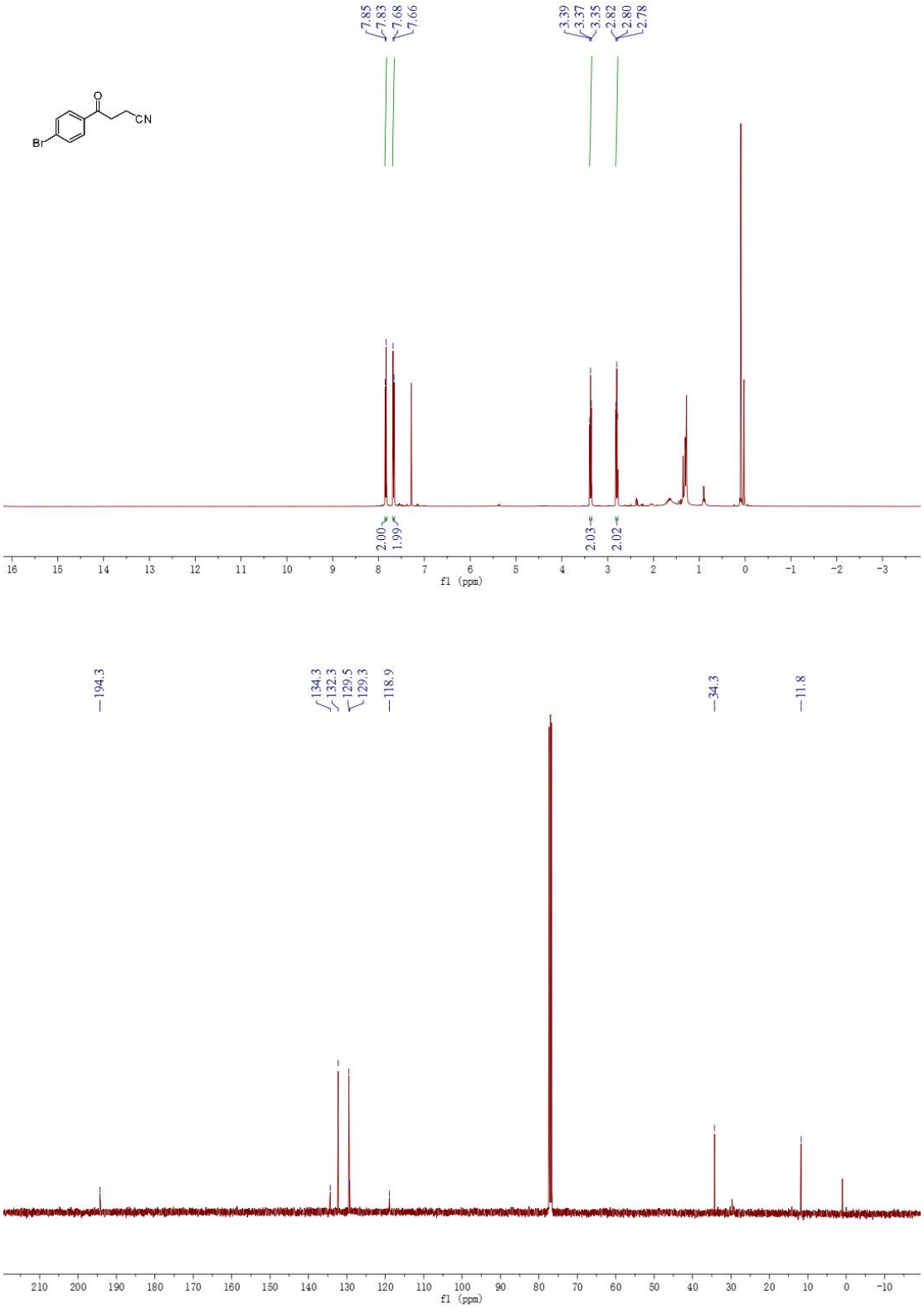


5c (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

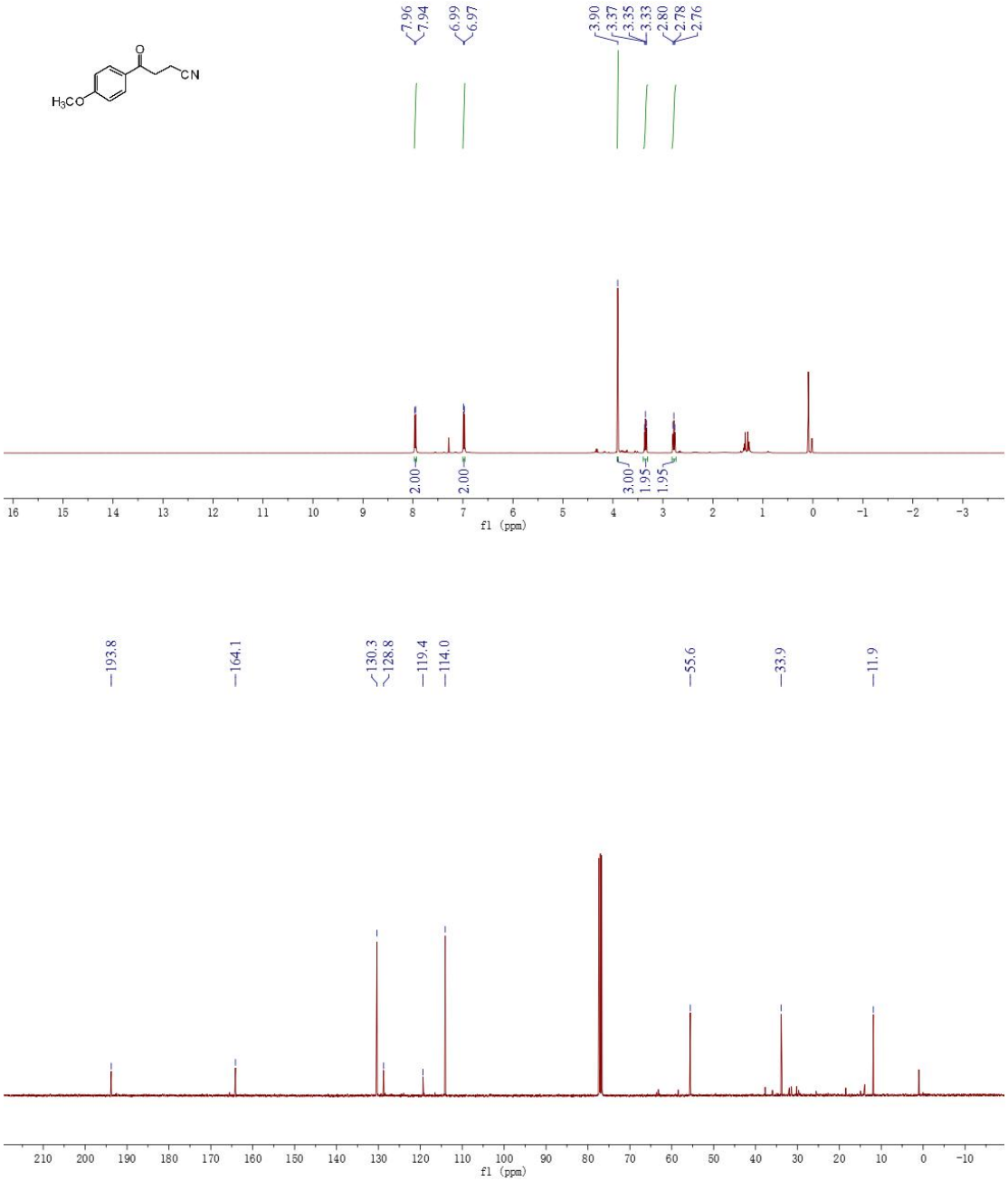




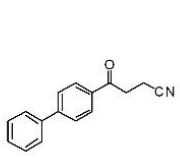
5d (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

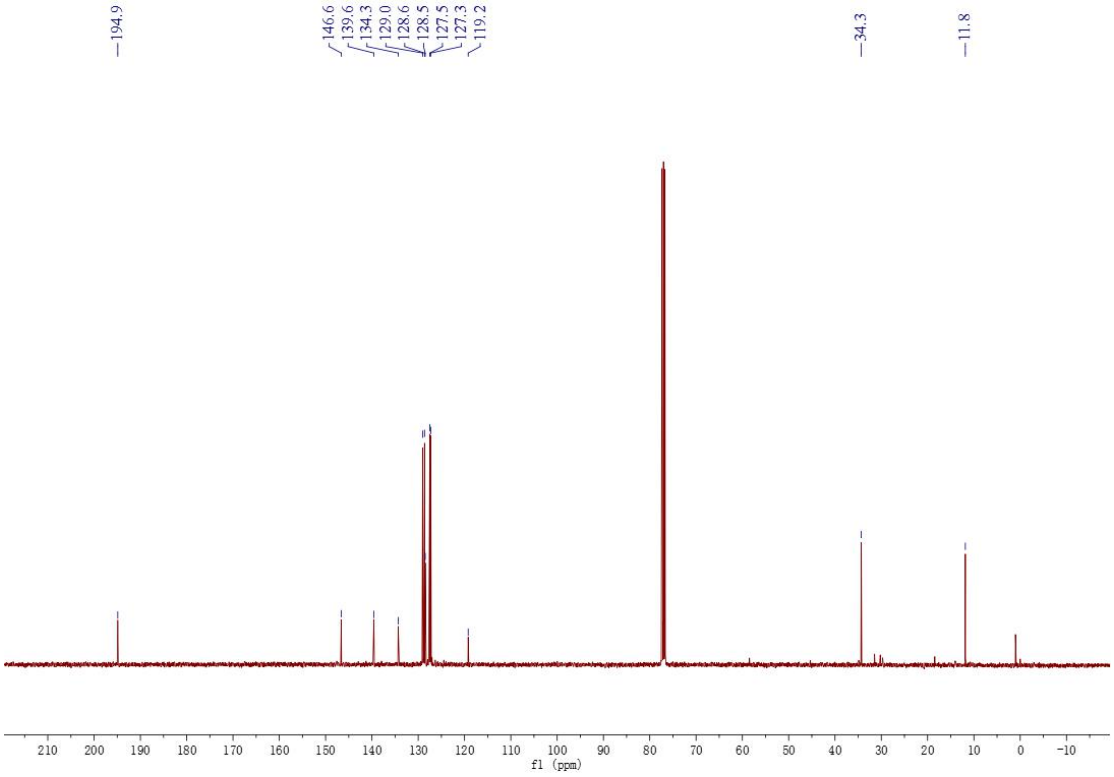


5e (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)

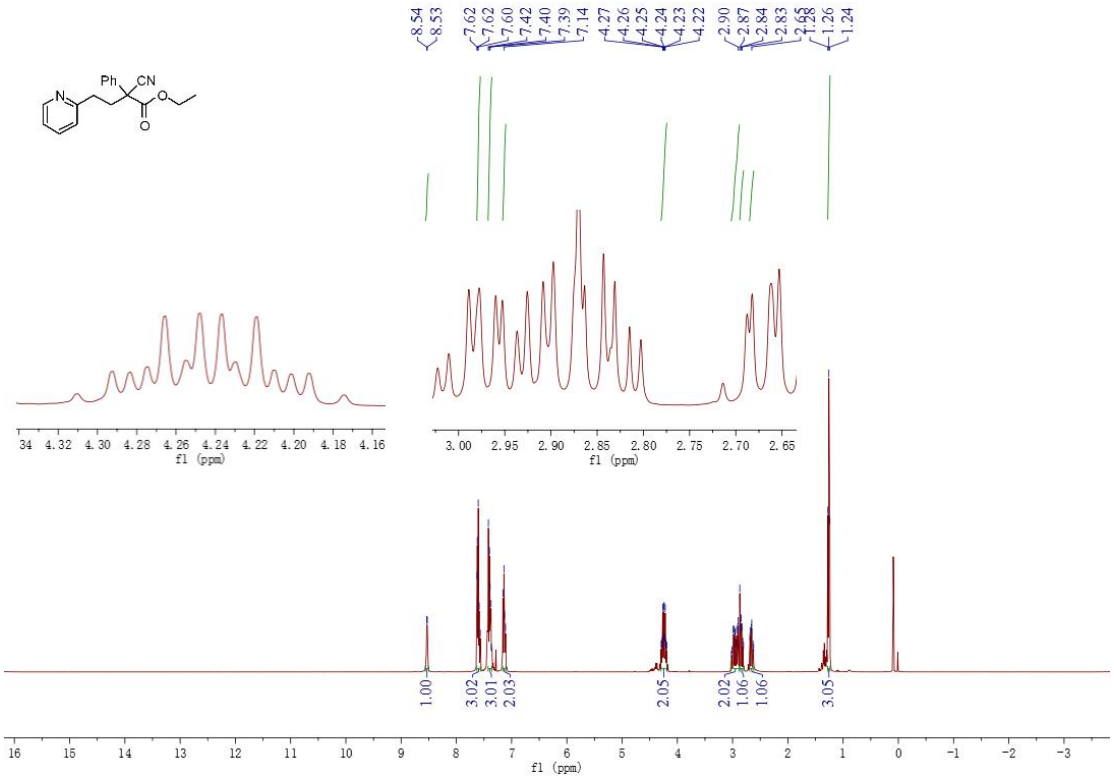


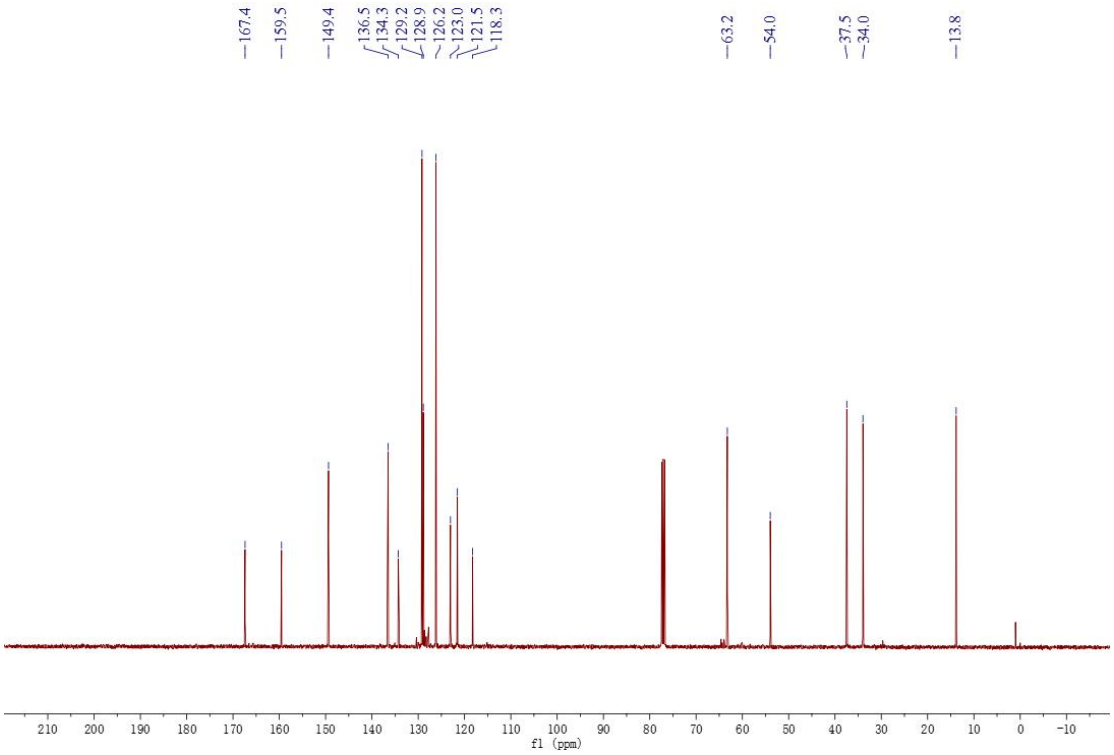
5f (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)



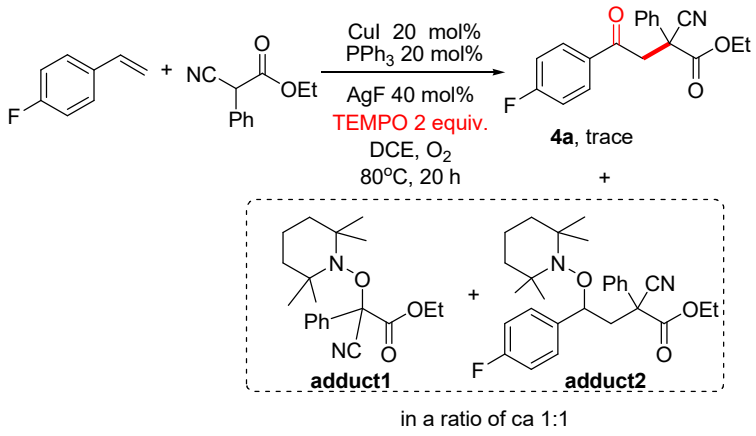


7 (^{1}H NMR 400 MHz, $CDCl_3$; ^{13}C NMR 101 MHz, $CDCl_3$)





6. Radical trapping experiment



Scheme S1. Radical trapping experiment.

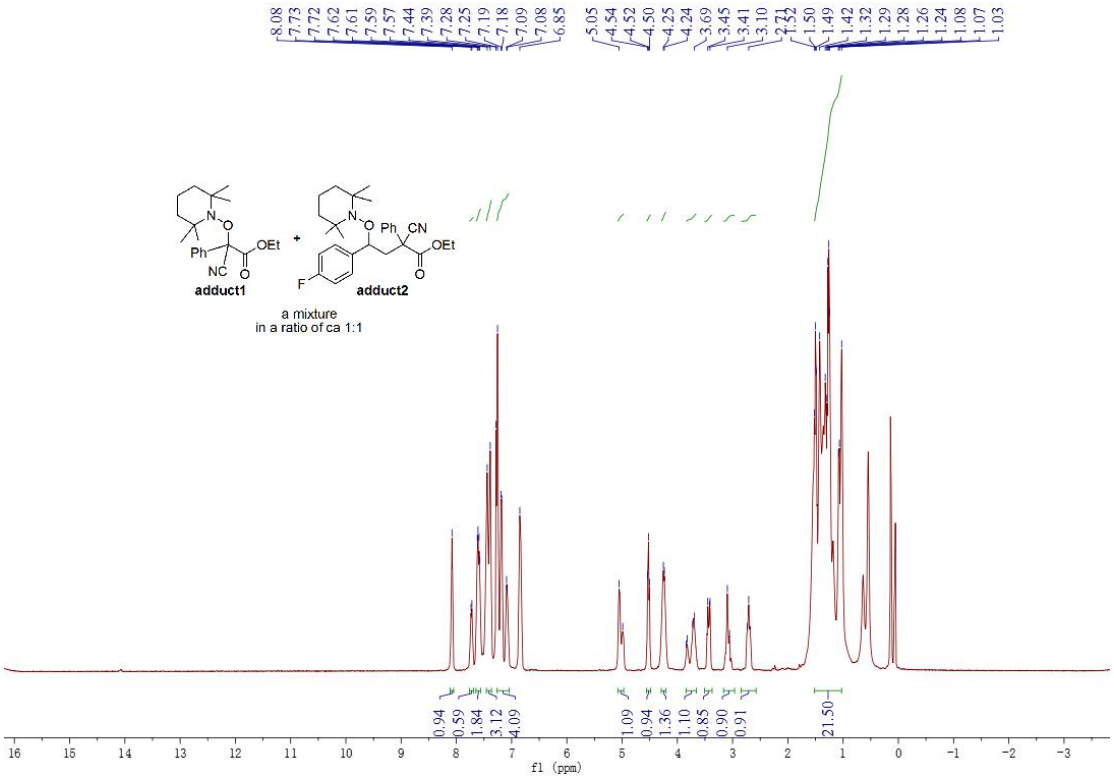


Figure S1. Isolation and determination of TEMPO adducts in radical trapping experiment.

Radical trapping experiment was done following the general reaction procedure in Section 2, albeit with additional 2 equivalents of TEMPO to investigate the radical scavenger effect. For the reaction shown in Scheme S1, in the presence of TEMPO, the desired product **4a** was observed in trace amount, but significant amounts of two new products were obtained as monitored by TLC analysis of the crude product

mixture. These two products are with very similar polarity as indicated by partially overlapped points in TLC plate. As a result, the new products were able to be isolated as a mixture by column chromatography on silica gel using petroleum ether/EtOAC = 20:1 (v/v) as the eluent. Figure S1 shows the ^{1}H NMR spectrum for the new products which are assigned to be a 1:1 mixture of **adduct1** and **adduct2**. These results confirm that radical species are involved during the reaction course for the synthesis of the desired γ-keto esters. Furthermore, it provides strong support that radical species **A** and **B** (in Figure 1 in the main text) are generated during the reaction course.