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One-pot synthesis of functionalized dihydroindolizinones from pyrrolylpropynoates and diethyl aminomalonate

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General information

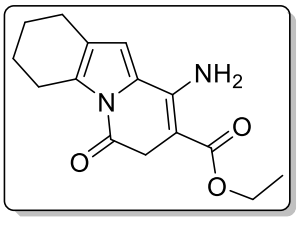
NMR spectra were recorded on a Bruker DPX-400 spectrometer (400.13 MHz for ^{1}H, 100.6 MHz for ^{13}C) in $CDCl_3$ and DMSO-d_6. The internal standards were HMDS (for ^{1}H) and the residual solvent signals (for ^{13}C). Resonance signals of carbon atoms were assigned based on $^{1}H–^{13}C$ HSQC and $^{1}H–^{13}C$ HMBC experiments. Coupling constants (*J*) were measured from one-dimensional spectra, and multiplicities were abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), q (quartet), t (triplet), m (multiplet). IR spectra were recorded on a two-beam Bruker Vertex 70 spectrometer, in a microlayer from chloroform. The C, H, N microanalyses were performed on a Flash EA 1112 CHNS-O/MAS analyzer.

Commercial samples of diethyl aminomalonate hydrochloride **2**, DMSO, MeCN, KOH, Cs_2CO_3, were used. Pyrrolylpropynoates **1a-c, 1′a** were obtained according to the literature procedures.[S1]

The reaction of ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynoate (1a) with diethylaminomalonate (2) in the KOH/DMSO system.

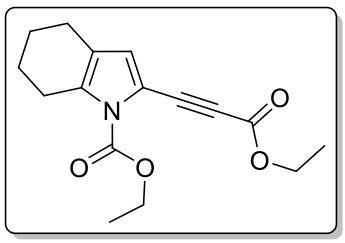
A suspension of diethyl aminomalonate hydrochloride **2** (211 mg, 1 mmol) and KOH (112 mg, 2 mmol) in DMSO (50 ml) was stirred at 20-25ºC for 30 min. Then a solution of pyrrolylpropynoate **1a** (217 mg, 1 mmol) in DMSO (50 ml) was added dropwise within 10 min. The reaction mixture was stirred at 100 ºC for 6 h. The reaction was monitored using ^{1}H NMR monitoring (until the signals of the starting propynoate **1a** completely disappeared). After the reaction completion, the mixture was diluted with water (150 ml) and extracted with diethyl ether (4 x 30 ml). The extracts were washed with water (3 x 20 ml) and dried over $CaCl_2$. The residue, after removing the solvent, was fractionated by column chromatography (SiO_2, *n*-hexane: diethyl ether, 1 : 1) to afford of the 49 mg (18%) of indolizinone **3a** and 35 mg (12%) of ethyl 2-(3-ethoxy-3-oxoprop-1-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate **4**.

***Ethyl 9-amino-6-oxo-1,2,3,4,6,7-hexahydropyrido[1,2-a]indole-8-carboxylate* (3a).**



Yield 49 mg (18%); brown oil. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21%. Found: C, 65.39; H, 6.41; N, 10.26%. ν_{max} (film), cm^{-1}: 3341, 2924, 2851, 1724, 1696, 1634, 1590, 1511, 1384, 1343, 1221, 1132, 1032, 932, 801, 733, 638. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.02 (s, 1H, H-3, pyrrole), 4.31 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.91 (s, 2H, NH_2), 3.85 (s, 2H, CH_2), 2.90 (m, 2H, CH_2-7), 2.52 (m, 2H, CH_2-4), 1.84-1.74 (m, 4H, CH_2-5,6), 1.36 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.4, 164.7, 137.8, 130.0, 126.9, 124.5, 108.1, 107.2, 61.7, 41.6, 23.4, 22.9, 22.6, 22.2, 14.5.

***Ethyl 2-(3-ethoxy-3-oxoprop-1-yn-1-yl)-4,5,6,7-tetrahydro-1H-indole-1-carboxylate* (4).**



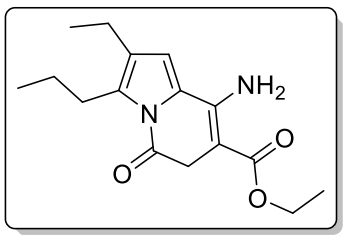
Yield 35 mg (12%); brown oil. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84%. Found: C, 66.26; H, 6.37; N, 5.00%. ν_{max} (film), cm^{-1}: 2929, 2855, 1750, 1702, 1653, 1508, 1457, 1374, 1319, 1297, 1272, 1224, 1151, 1099, 1026, 920, 745. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.65 (s, 1H, H-3 pyrrole), 4.43 (q, *J* = 7.1 Hz, 2H, NC(O)OC<u>H</u>$_2$), 4.27 (q, *J* = 7.0 Hz, 2H, OC<u>H</u>$_2$), 2.87 (m, 2H, C<u>H</u>$_2$-7), 2.43 (m, 2H, C<u>H</u>$_2$-4), 1.83-1.77 (m, 2H, C<u>H</u>$_2$-6), 1.74-1.67 (m, 2H, C<u>H</u>$_2$-5), 1.46 (t, *J* = 7.1 Hz, 3H, NC(O)OCH$_2$<u>CH$_3$</u>), 1.33 (t, *J* = 7.0 Hz, 3H, OCH$_2$<u>CH$_3$</u>). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 154.7, 150.4, 136.5, 125.7, 122.8, 111.2, 85.5, 80.8, 64.0, 61.8, 25.5, 23.1, 23.0, 22.6, 14.3, 14.1.

The reaction of pyrrolylpropynoates (1a-c) with diethylaminomalonate (2) in the Cs_2CO_3/MeCN system.

A suspension of diethyl aminomalonate hydrochloride **2** (211 mg, 1 mmol) and Cs_2CO_3 (650 mg, 2 mmol) in acetonitrile (50 mL) was stirred at 20-25ºC for 30 min. Then solution of pyrrolylpropynoate **1a-c** (1 mmol) in acetonitrile (50 mL) was added dropwise to the reaction mixture within 10 min. The mixture was stirred at 80 ºC for 6 h. The reaction was monitored using ^{1}H NMR monitoring (until the signals of the starting propynoate **1a-c** completely disappeared). After the reaction completion, the mixture was diluted with water (150 mL) and extracted with diethyl ether (4 x 30 mL). The ether extracts were washed with water (3 x 20 mL) and dried over $CaCl_2$. The residue, after removing the solvent, was fractionated by column chromatography (SiO_2, *n*-hexane: diethyl ether, 1 : 1) to afford of the indolizinones **3a-c**.

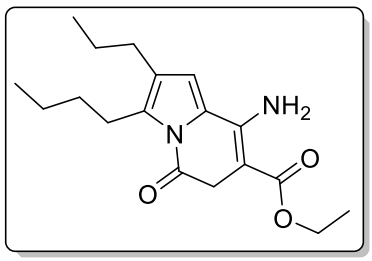
***Ethyl 9-amino-6-oxo-1,2,3,4,6,7-hexahydropyrido[1,2-a]indole-8-carboxylate* (3a)** *was obtained using this procedure in 72% yield (197 mg).*

***Ethyl 8-amino-2-ethyl-5-oxo-3-propyl-5,6-dihydroindolizine-7-carboxylate* (3b).**



Yield 226 mg (78%); brown oil. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65%. Found: C, 65.97; H, 7.46; N, 9.42%. ν_{max} (film), cm^{-1}: 3371, 2962, 2930, 2871, 1742, 1702, 1637, 1587, 1509, 1457, 1377, 1336, 1302, 1212, 1167, 1031, 783. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.11 (s, 1H, H-3, pyrrole), 4.31 (q, *J* = 7.1 Hz, 2H, OC<u>H</u>$_2$), 3.93 (br. s, 2H, NH_2), 3.86 (s, 2H, C<u>H</u>$_2$), 2.85-2.76 (m, 2H, C<u>H</u>$_2$), 2.44 (q, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.62 (m, 2H, C<u>H</u>$_2$), 1.36 (t, *J* = 7.1 Hz, 3H, C<u>H$_3$</u>), 1.18 (t, *J* = 7.6 Hz, 3H, CH_3), 0.92 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 164.8, 137.8, 134.4, 128.3, 124.3, 107.9, 107.7, 61.6, 41.8, 26.0, 23.3, 19.1, 15.2, 14.5, 13.8.

***Ethyl 8-amino-3-butyl-5-oxo-2-propyl-5,6-dihydroindolizine-7-carboxylate* (3c).**

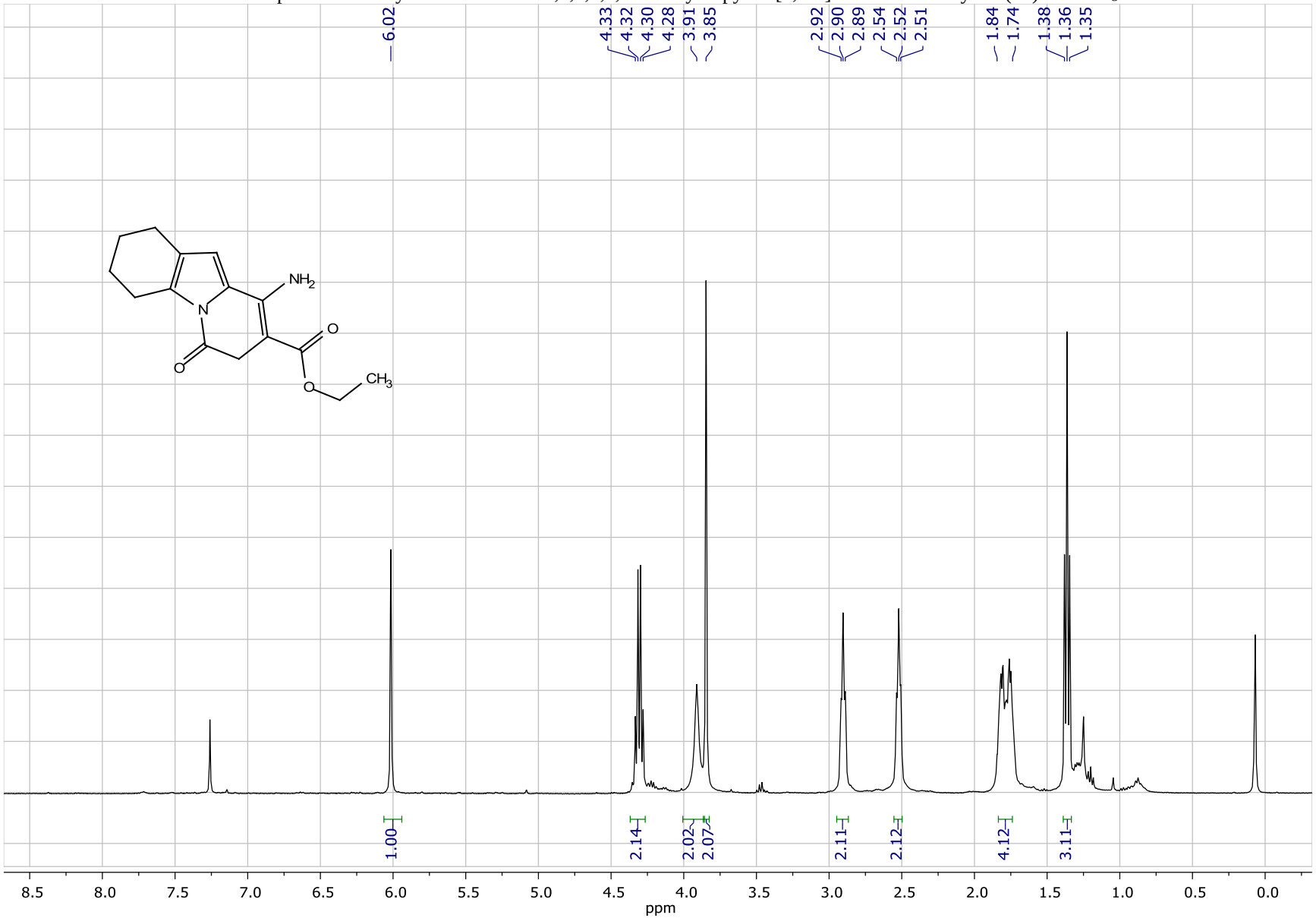


Yield 271 mg (85%); brown oil. Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80%. Found: C, 67.59; H, 8.02; N, 8.52%. ν_{max} (film), cm^{-1}: 3369, 2957, 2928, 2867, 1745, 1703, 1638, 1591, 1508, 1461, 1378, 1338, 1213, 1171, 1033, 785. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 6.08 (s, 1H, H-3, pyrrole), 4.30 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.91 (s, 2H, NH_2), 3.85 (s, 2H, CH_2), 2.81 (m, 2H, OCH_2), 2.40-2.36 (m, 2H, CH_2), 1.61-1.52 (m, 6H, CH_2), 1.36 (t, *J* = 7.2 Hz, 3H, CH_3), 0.95 (t, *J* = 7.1 Hz, 3H, CH_3), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 164.7, 137.6, 132.5, 129.1, 124.3, 108.2, 108.0, 61.6, 41.8, 32.3, 27.9, 23.8, 23.9, 22.5, 14.5, 14.1, 14.0.

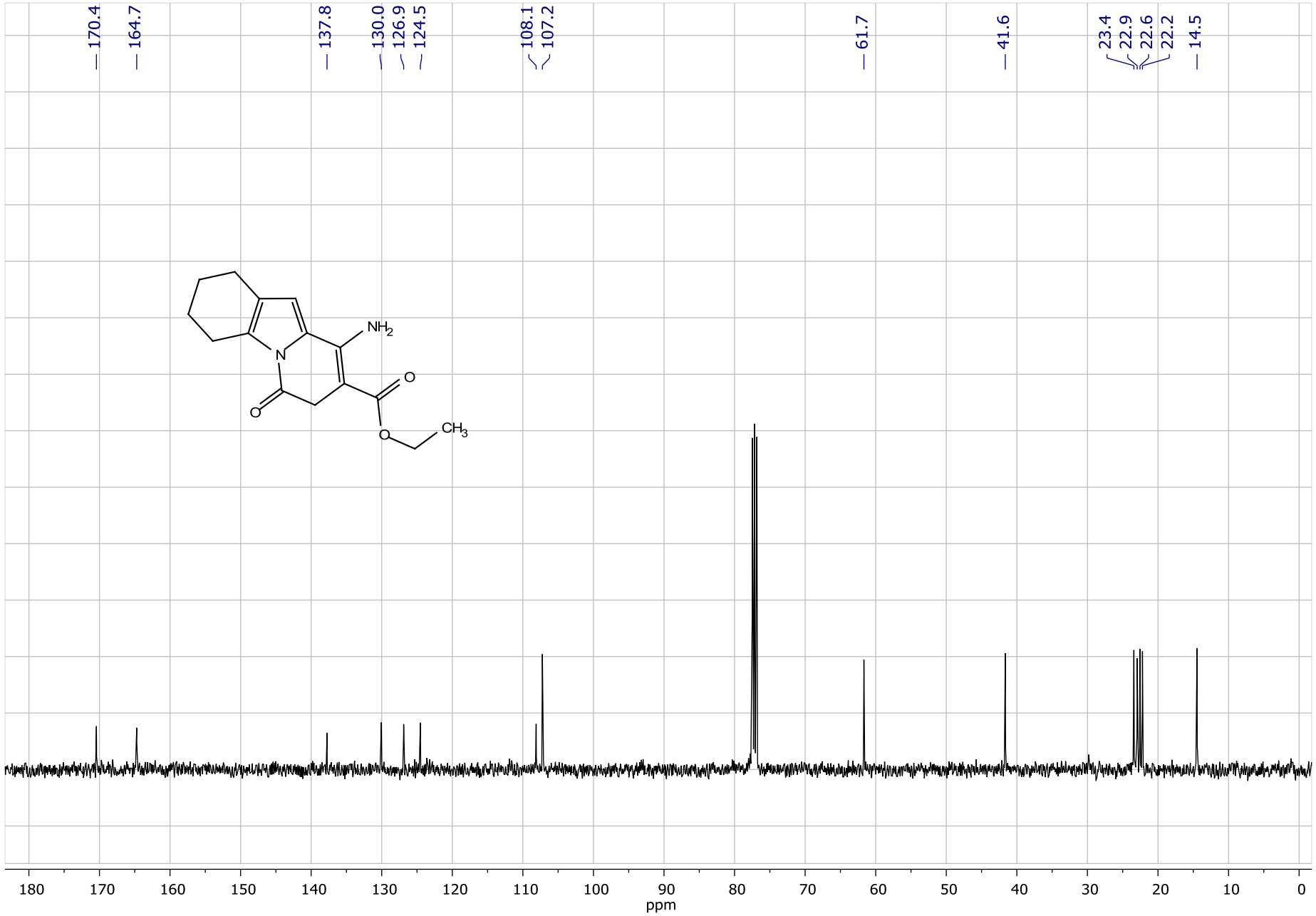
S1. B. A. Trofimov, L. N. Sobenina, Z. V. Stepanova, O. V. Petrova, I. A. Ushakov and A. I. Mikhaleva, *Tetrahedron Lett*., 2008, **49**, 3946; https://doi.org/10.1016/j.tetlet.2008.04.046.

The NMR spectra:

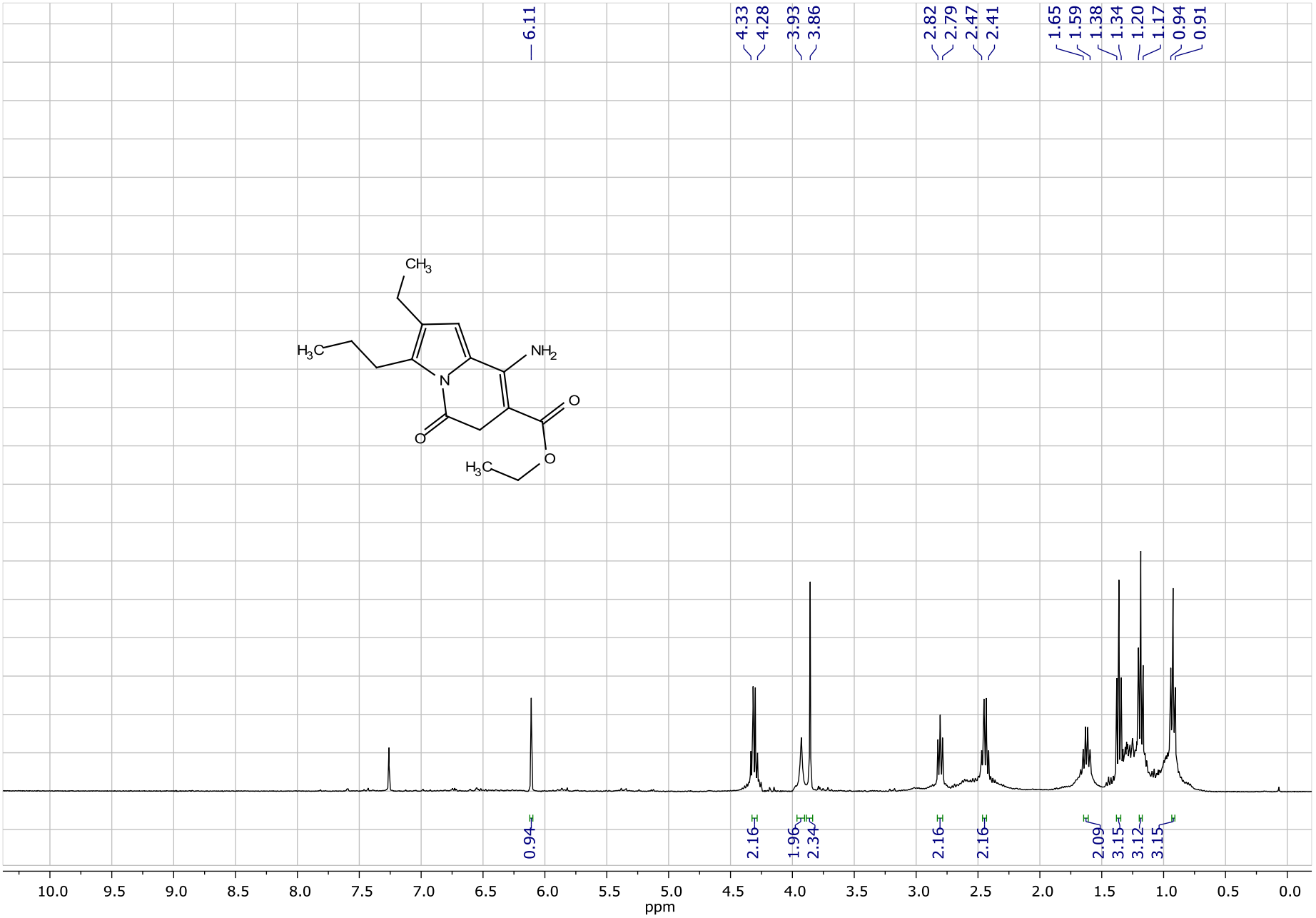
^{1}H NMR spectrum of ethyl 9-amino-6-oxo-1,2,3,4,6,7-hexahydropyrido[1,2-*a*]indole-8-carboxylate (**3a**) in $CDCl_3$.



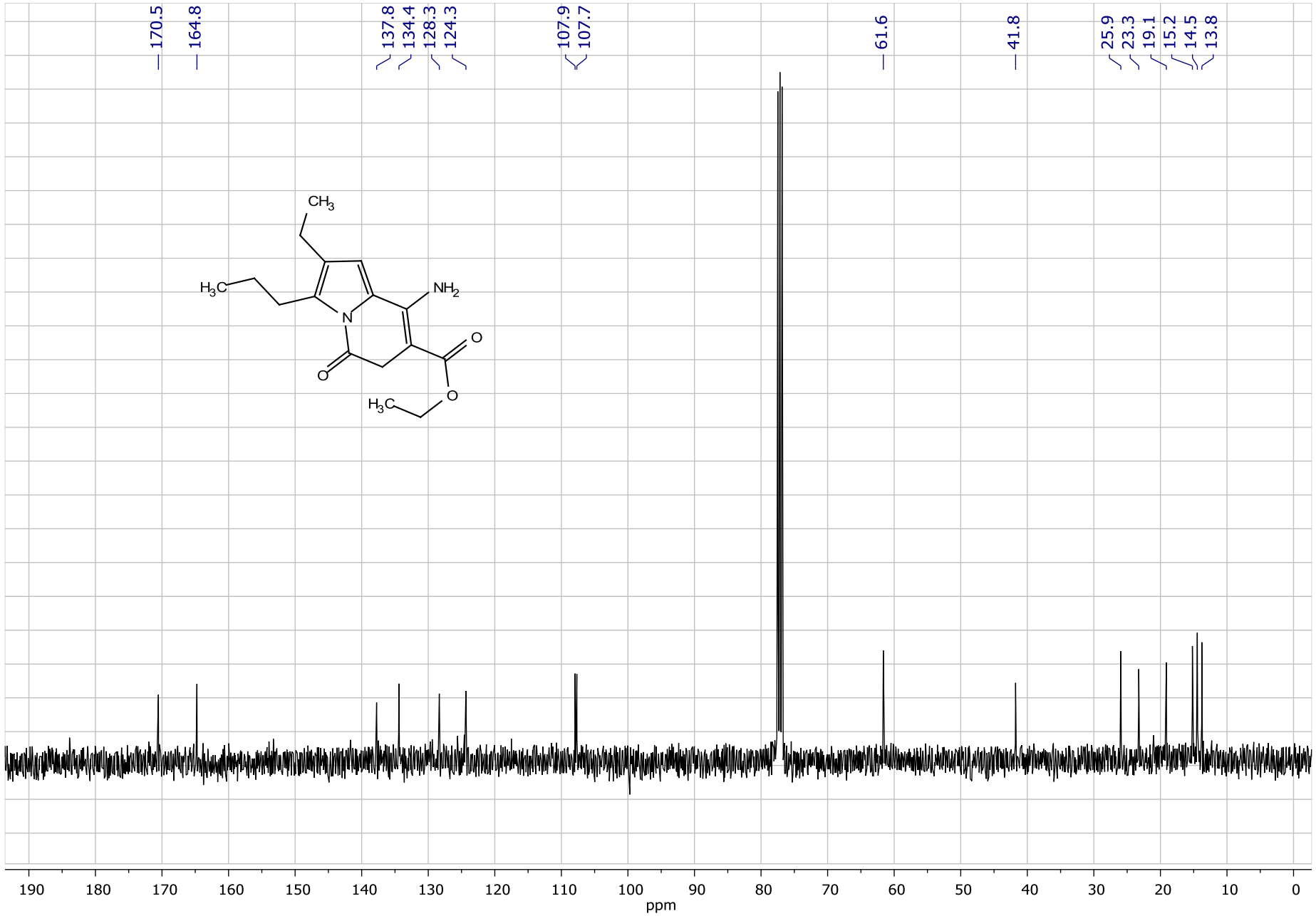
^{13}C NMR spectrum of ethyl 9-amino-6-oxo-1,2,3,4,6,7-hexahydropyrido[1,2-*a*]indole-8-carboxylate (**3a**) in $CDCl_3$.



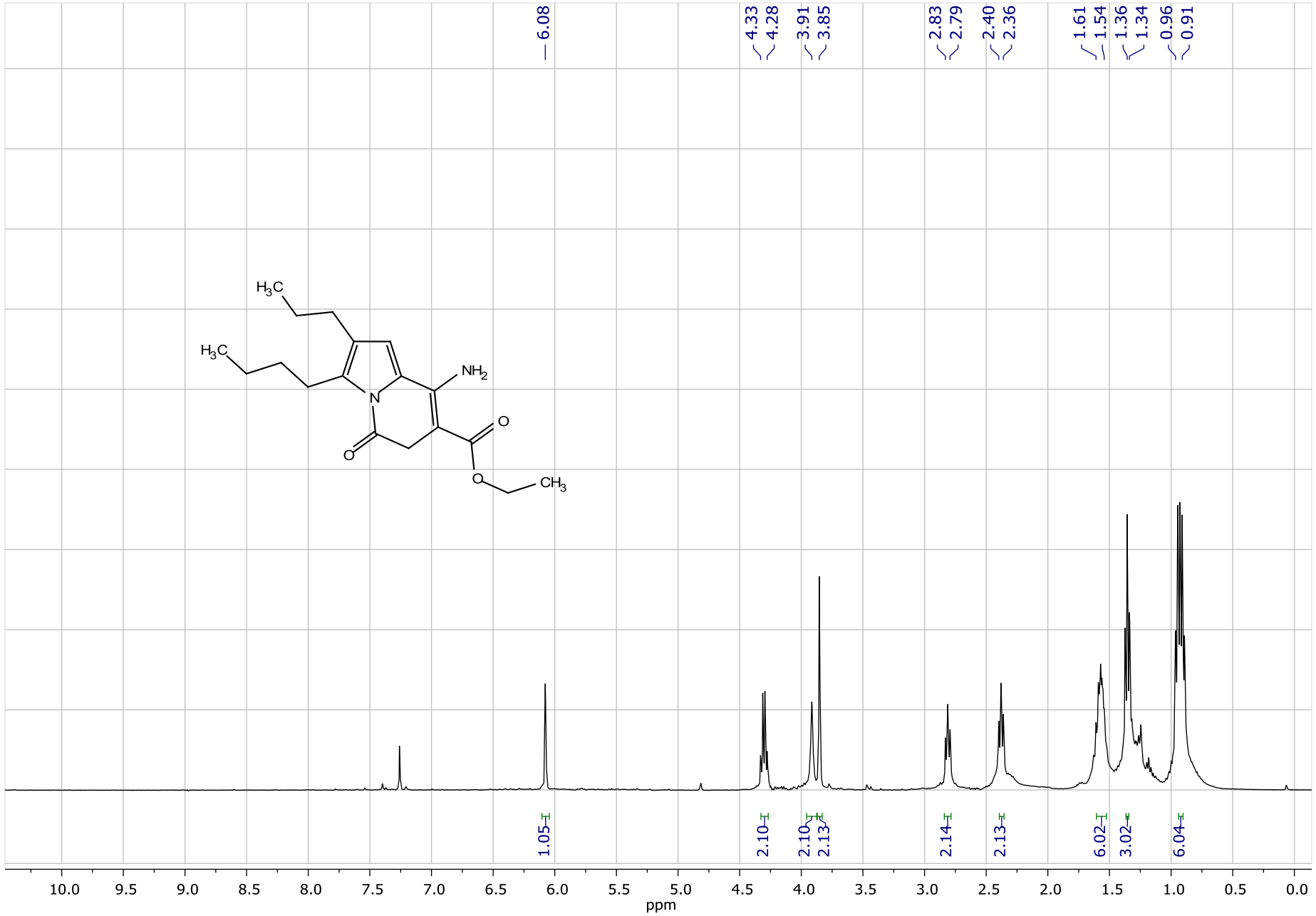
^{1}H NMR spectrum of ethyl 8-amino-2-ethyl-5-oxo-3-propyl-5,6-dihydroindolizine-7-carboxylate (**3b**) in $CDCl_3$.



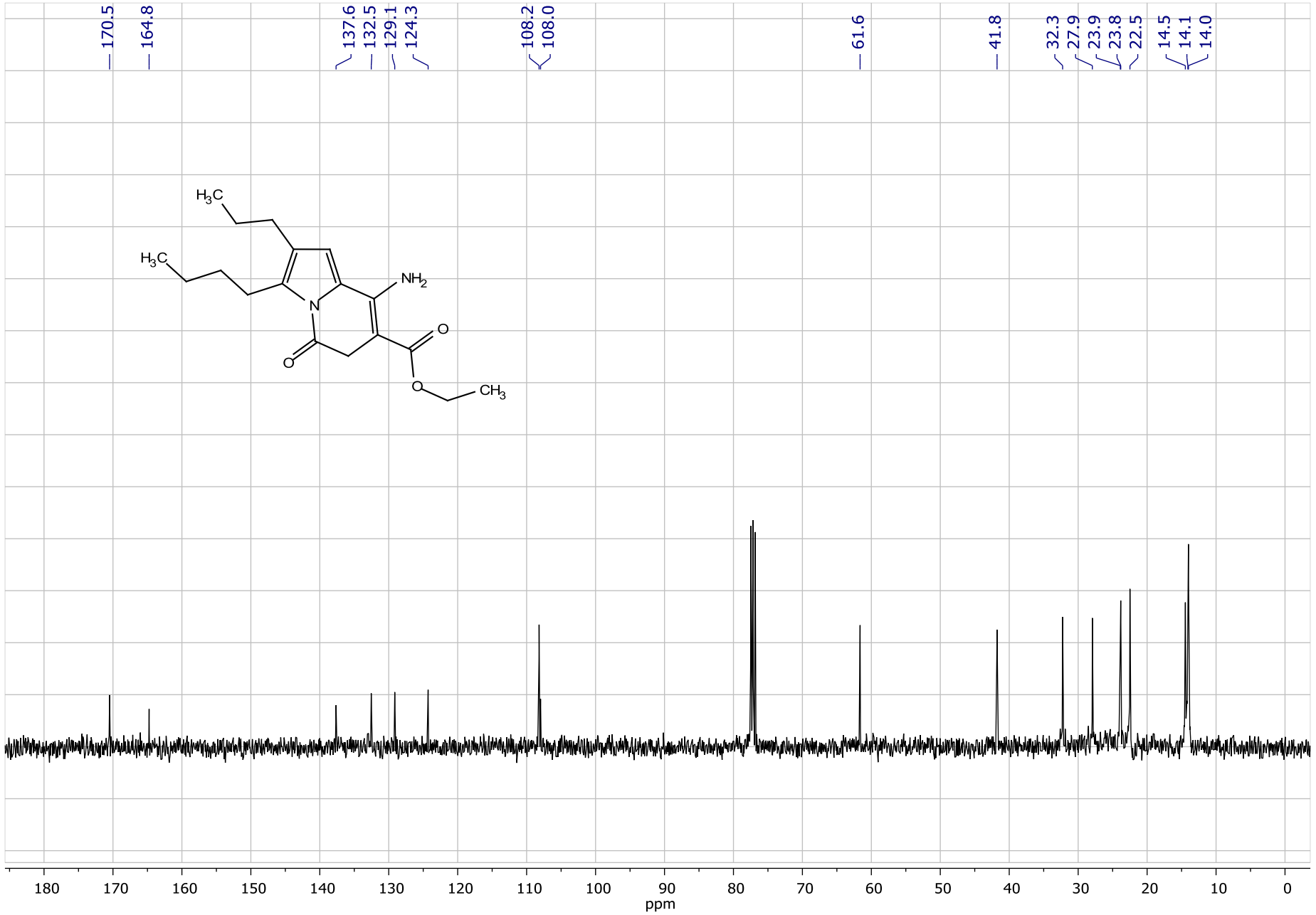
^{13}C NMR spectrum of ethyl 8-amino-2-ethyl-5-oxo-3-propyl-5,6-dihydroindolizine-7-carboxylate (**3b**) in $CDCl_3$.



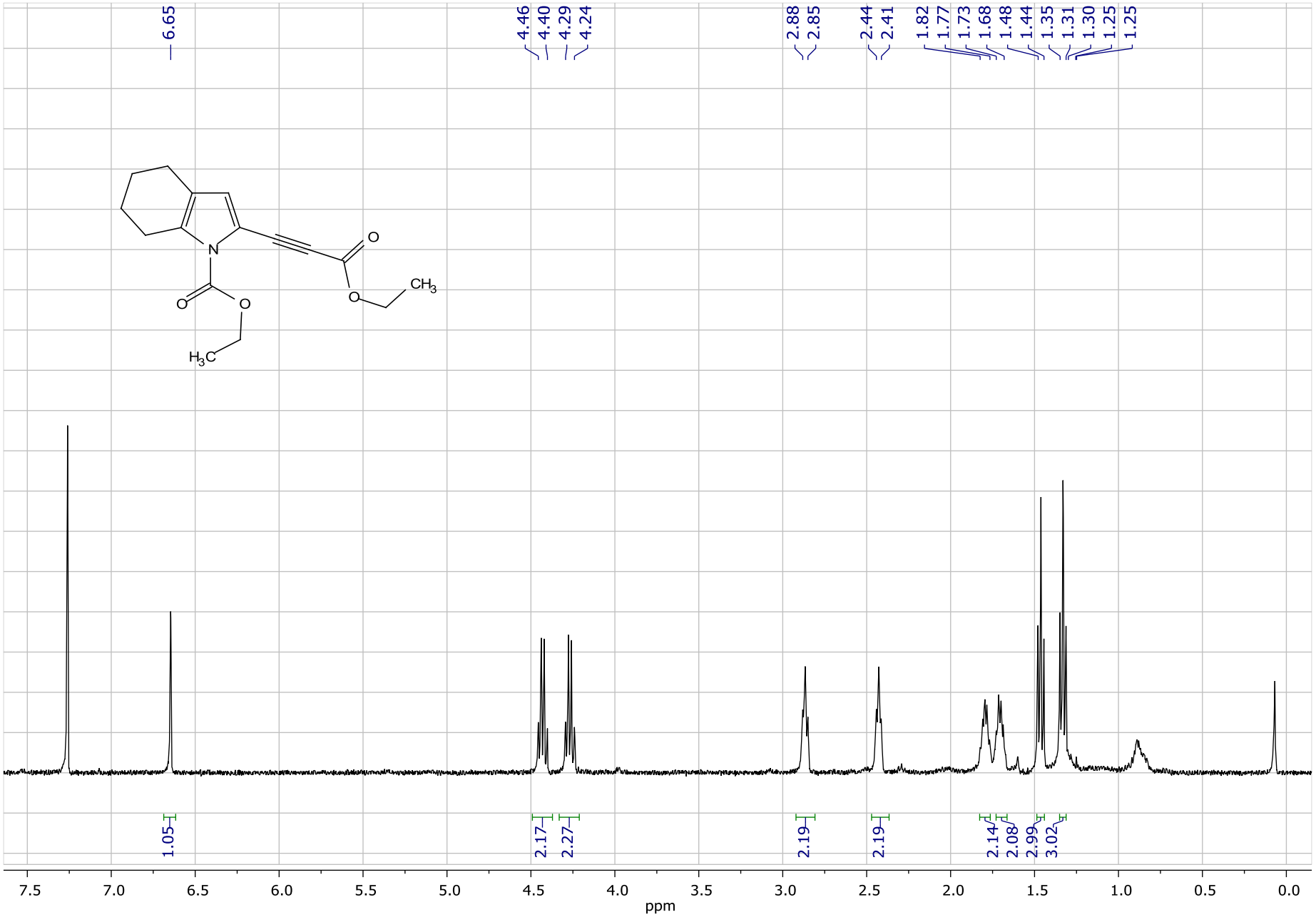
^{1}H NMR spectrum of ethyl 8-amino-3-butyl-5-oxo-2-propyl-5,6-dihydroindolizine-7-carboxylate (**3c**) in $CDCl_3$.



^{13}C NMR spectrum of ethyl 8-amino-3-butyl-5-oxo-2-propyl-5,6-dihydroindolizine-7-carboxylate (**3c**) in $CDCl_3$.



^{1}H NMR spectrum of ethyl 2-(3-ethoxy-3-oxoprop-1-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (**4**) in $CDCl_3$.



^{13}C NMR spectrum of ethyl 2-(3-ethoxy-3-oxoprop-1-yn-1-yl)-4,5,6,7-tetrahydro-1*H*-indole-1-carboxylate (**4**) in $CDCl_3$.