Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Formal reductive addition of acetonitrile to aldehydes and ketones

Supporting information

Karim Muratov,[a] § Ekaterina Kuchuk,[a] § Sreekumar Vellalath,[b] Oleg I. Afanasyev,[a] Alexei P. Moskovets,[a] Gleb Denisov[a] and Denis Chusov*,[a]

[a]*Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 119991, Russia*

[b]*Department of Chemistry and Biochemistry, Baylor University, Waco, TX 76798, USA*

§ These authors are contributed equally.

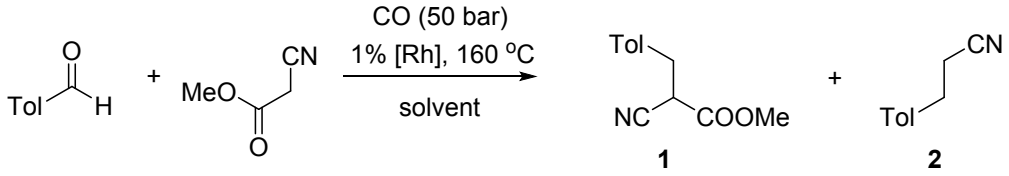
E-mail: chusov@ineos.ac.ru or denis.chusov@gmail.com

Table of contents

1. General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Rhodium complexes $[(C_4Et_4)Rh(p\text{-xylene})]PF_6$[1], $IndRhCpPF_6$[2] were synthesized according to published procedures. For all reactions, distilled water was used. Carbon monoxide of >98% purity was obtained from NII KM (Moscow, Russia). Isolation of products was performed by column chromatography (Acros Organics, silica gel 0.06-0.200 mm). The ^1H and ^{13}C NMR spectroscopic data were recorded with Bruker AV-300, AV400, and AV-600 and Varian Inova400 spectrometers at ambient temperature. Chemical shifts are reported in parts per million relative to $CHCl_3$ (7.26 and 77.16 ppm for ^1H and ^{13}C respectively). Chemical shifts δ are reported in ppm relative to the solvent resonance signal as an internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad; coupling constants are given in Hertz (Hz). GC detection was performed on GC Chromatec Crystall 5000.2. The IR spectra were obtained using a Shimadzu model IRPrestige21 spectrophotometer in CaF_2 cell with d=0.517mm or in KBr pellet.

Optimization of reaction conditions



#	Catalyst	Solvent	Time, h	Water equivalents	1, %	2, %	Aldehyde, %
1	$RhCl_3 \cdot 3H_2O$	MeOH	4	2	43	43	traces
2	$RhCl_3 \cdot 3H_2O$	THF	4	2	24	41	2
3	$RhCl_3 \cdot 3H_2O$	H_2O	4	50	0	47	11
4	$RhCl_3 \cdot 3H_2O$	EtOH	4	2	15 (+48)[a]	22	1 (2)
5	$RhCl_3 \cdot 3H_2O$	iPrOH	4	2	30 (+38)[a]	16	4 (3)
6	$RhCl_3 \cdot 3H_2O$	MeOH	4	5	24	68	2 (3)
7	$RhCl_3 \cdot 3H_2O$	MeOH	4	10	12	71	1 (16)
8	$[(C_4Et_4)Rh(p\text{-xylene})]PF_6$	MeOH	4	5	63	16	2
9	$[(Cod)RhCl]_2$	MeOH	4	5	9	87	2 (2)
10	$IndRhCpPF_6$	MeOH	4	5	43	17	8 (1)
11	$Rh_2(TFA)_4$	MeOH	4	5	4	78	1 (5)
12	$[Cp^*RhCl_2]_2$	MeOH	4	5	6	66	8 (1)
13[b]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	5	51	7 (2)
14[c]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	11	33	11 (<1)
15[d]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	traces	12	19 (0)
16[e]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	1	82	<1 (4)
17[f]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	1	85	0 (1)
18[g]	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	4	37	11 (4)
19[h]	$RhCl_3 \cdot 3H_2O$	MeOH	21.5	5	42	28	0 (1)
20	$RhCl_3 \cdot 3H_2O$	MeOH	6	5	4	77	<1 (4)

[a] -Transesterification product with solvent is observed, [b]-20 bar, [c]-10 bar, [d]-5 bar, [e]- 0.5 mol %, [f]- 0.2 mol % [g]- 0.1 mol%, [h]-2 mol %, 140 °C.

2. Spectroscopic and analytical data

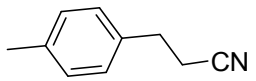
Reaction of 4-chlorobenzaldehyde with $NaBH_4$

To a stirred solution of $RhCl_3 \cdot 3H_2O$ (2.16 mg; 8.2 µmol; 0.2 mol%), 4-chlorobenzaldehyde (576 mg; 4.10 mmol; 100 mol%), methyl cyanoacetate (362.9 µl; 407.5 mg; 4.11 mmol; 100 mol%), methanol (2 ml) and water (367.2 µl; 367.2 mg; 20.40 mmol; 497 mol%) in 25 ml flask with reflux condenser was added $NaBH_4$ (647.4 mg; 17.11 mmol; 417 mol%) and stirred for 24h at 65°C. The reaction mixture was filtered, the flask was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR (no product was observed).

Reaction of 4-chlorobenzaldehyde with H_2

A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.2 mg; 0.76 µmol; 0.2 mol%), 4-chlorobenzaldehyde (50 mg; 0.36 mmol; 100 mol%), methanol (356 µl), methyl cyanoacetate (31 µl; 0.35 mmol; 97 mol%) and water (32 µl; 1.78 mmol; 494 mol%). The autoclave was sealed, flushed 3 times with 10 atm of H_2, and then charged with 50 atm H_2. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR (20% of the product).

3-(p-tolyl)propanenitrile (4)



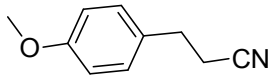
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.56 mg; 2.1 µmol; 0.2 mol%), 4-methylbenzaldehyde (125 µl; 127.4 mg; 1.06 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (94.1 µl; 105.7 mg; 1.07 mmol; 101 mol%) and water (95.2 µl; 95.2 mg; 5.28 mmol; 498 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 86% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 30/1 (R_f = 0.18). Isolated as a colorless oil - 68% (105 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.10 (m, 4H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.35 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 135.1, 129.6, 128.2, 119.3, 31.2, 21.1, 19.5

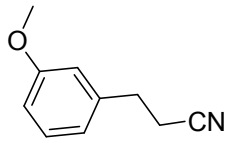
The obtained NMR data are in agreement with the literature report[3]

3-(4-methoxyphenyl)propanenitrile (5)



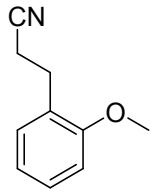
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.56 mg; 2.1 µmol; 0.19 mol%), 4-methoxybenzaldehyde (136 µl; 152.2 mg; 1.12 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (94.1 µl; 105.6 mg; 1.07 mmol; 96 mol%) and water (95.2 µl; 95.2 mg; 5.28 mmol; 472 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 86% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 10/1 (R_f = 0.18). Isolated as a pale-yellow oil - 74% (127 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 2.89 (t, *J* = 7.3 Hz, 2H), 2.57 (t, *J* = 7.3 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 130.2, 129.4, 119.4, 114.2, 55.3, 30.7, 19.7
The obtained NMR data are in agreement with the literature report[4]

3-(3-methoxyphenyl)propanenitrile (6)



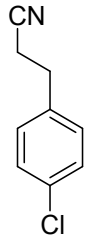
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.25 mg 0.95 µmol; 0.2 mol%), 3-methoxybenzaldehyde (58 µl; 64.8 mg; 0.48 mmol; 100 mol%), methanol (238 µl), methyl cyanoacetate (42 µl; 47.1 mg; 0.48 mmol; 100 mol%) and water (42.5 µl; 42.5 mg; 2.36 mmol; 491 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 83% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 10/1 (R_f = 0.17). Isolated as a pale-yellow oil - 68% (53 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd appears as t, *J* = 7.8 Hz, 1H), 6.93 – 6.81 (m, 3H), 3.87 (s, 3H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 139.7, 130.0, 120.6, 119.3, 114.1, 112.5, 55.3, 31.6, 19.3
The obtained NMR data are in agreement with the literature report[5]

3-(2-methoxyphenyl)propanenitrile (7)



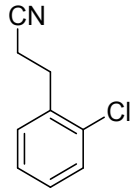
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.56 mg 2.1 µmol; 0.2 mol%), 3-methoxybenzaldehyde (144.5 mg; 1.06 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (92.4 µl; 103.8 mg; 1.05 mmol; 99 mol%) and water (93.5 µl; 93.5 mg; 5.19 mmol; 490 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 88% NMR yield. Purification: gradient column chromatography, eluent hexane/ethyl acetate from 30/1 (R_f = 0.14) to 15/1 (R_f = 0.21). Isolated as a pale-yellow oil - 74% (124.7 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (dd appears as t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.06 – 6.89 (m, 2H), 3.90 (s, 3H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.69 (t, *J* = 7.4 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 130.3, 128.7, 126.4, 120.7, 119.8, 110.4, 55.2, 27.1, 17.5
The obtained NMR data are in agreement with the literature report[6]

3-(4-chlorophenyl)propanenitrile (8)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.2 mg 0.76 µmol; 0.2 mol%), 4-chlorobenzaldehyde (50 mg; 0.36 mmol; 100 mol%), methanol (260 µl), methyl cyanoacetate (31 µl; 34.8 mg; 0.35 mmol; 97 mol%) and water (32 µl; 32 mg; 1.80 mmol; 500 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 86% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 20/1 (R_f = 0.13). Isolated as a colorless oil - 81% (47.1 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz; 2H), 7.17 (d, *J* = 8.3 Hz; 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 133.2, 129.8, 129.1, 119.0, 30.9, 19.4
The obtained NMR data are in agreement with the literature report[6]

3-(2-chlorophenyl)propanenitrile (9)

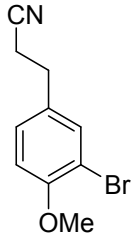


A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.22 mg 0.83 µmol; 0.23 mol%), 2-chlorobenzaldehyde (40 µl, 50 mg; 0.36 mmol; 100 mol%), methanol (250 µl), methyl cyanoacetate (31 µl; 34.8 mg; 0.35 mmol; 97 mol%) and water (32 µl; 32 mg; 1.80

mmol; 500 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 83% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 20/1 (R_f = 0.21). Isolated as a colorless oil - 68% (39.3 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 1H), 7.30 – 7.15 (m, 3H), 3.05 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 133.8, 130.9, 129.9, 129.0, 127.4, 119.0, 29.7, 17.5

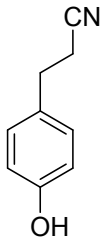
The obtained NMR data are in agreement with the literature report[7]

3-(3-bromo-4-methoxyphenyl)propanenitrile (10)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.17 mg 0.65 µmol; 0.2 mol%), 3-bromo-4-methoxybenzaldehyde (70 mg; 0.326 mmol; 100 mol%), methanol (250 µl), methyl cyanoacetate (28.7 µl; 32.2 mg; 0.33 mmol; 100 mol%) and water (29 µl; 29 mg; 1.61 mmol; 494 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 75% NMR yield. Purification: gradient column chromatography, eluent hexane/ethyl acetate from 25/1 to 10/1 (R_f = 0.05). Isolated as a pale-yellow oil - 67% (52.2 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H)
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 133.1, 131.6, 128.5, 119.0, 112.2, 111.8, 56.3, 30.3, 19.6
The obtained NMR data are in agreement with the literature report[7]

3-(4-hydroxyphenyl)propanenitrile (11)

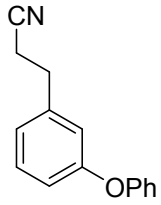


A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.28 mg 1.06 µmol; 0.2 mol%), 4-hydroxybenzaldehyde (65 mg; 0.53 mmol; 100 mol%), methanol (280 µl), methyl cyanoacetate (47 µl; 52.8 mg; 0.53 µmol; 100 mol%) and water (48 µl; 48 mg; 2.66 mmol; 501 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then

charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 76% NMR yield. Purification: gradient column chromatography, eluent hexane/ethyl acetate from 10/1 to 5/1 (R_f = 0.09). Isolated as a pale-yellow oil - 66% (51.4 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.4 – 6.05 (br s, 1H), 2.86 (t, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 129.8, 129.5, 119.5, 115.8, 30.6, 19.7

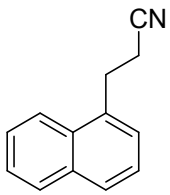
The obtained NMR data are in agreement with the literature report[8]

3-(3-phenoxyphenyl)propanenitrile (12)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.58 mg 2.2 µmol; 0.2 mol%), 3-phenoxybenzaldehyde (190 µl; 217.9 mg; 1.10 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (97.5 µl; 109.5 mg; 1.10 mmol; 100 mol%) and water (98.6 µl; 98.6 mg; 5.48 mmol; 498 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 77% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 10/1 (R_f = 0.22). Isolated as a colorless oil - 70% (171.8 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 3H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.06 – 6.88 (m, 5H), 2.93 (t, *J* = 7.4 Hz, 2H), 2.61 (t, *J* = 7.4 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 156.9, 140.0, 130.3, 129.9, 123.6, 123.1, 119.1, 119.0, 118.6, 117.5, 31.4, 19.2.
The obtained NMR data are in agreement with the literature report[9]

3-(naphthalen-1-yl)propanenitrile (13)



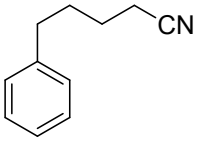
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.52 mg; 2 µmol; 0.2 mol%), 1-naphthaldehyde (134 µl; 154.1 mg; 0.99 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (87.4 µl; 98.1 mg; 0.99 mmol; 100 mol%) and water (88.5 µl; 88.5 mg; 4.91 mmol; 497 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h,

the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 83% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 12/1 (R_f = 0.26). Isolated as pale – yellow oil - 76% (137 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 – 7.88 (m, 2H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.50 (m, 2H), 7.49 – 7.38 (m, 2H), 3.43 (t, *J* = 7.6 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 133.9, 131.1, 129.2, 128.2, 126.6, 126.0, 125.7, 122.7, 119.3, 28.8, 18.5

The obtained NMR data are in agreement with the literature report[7]

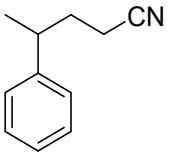
5-phenylpentanenitrile (14)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.6 mg; 2.3 µmol; 0.2 mol%), 3-phenylpropionaldehyde (142 µl; 143.4 mg; 1.07 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (100.8 µl; 113.2 mg; 1.14 mmol; 106 mol%) and water (102 µl; 102 mg; 5.67 mmol; 530 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. >96% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 10/1 (R_f = 0.28). Isolated as a colorless oil - 65% (110 mg).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (dd appears as t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 1.86 – 1.79 (m, 2H), 1.75 – 1.68 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 128.3, 128.2, 125.9, 119.6, 34.8, 30.1, 24.7, 16.9

The obtained NMR data are in agreement with the literature report[10]

4-phenylpentanenitrile (15)



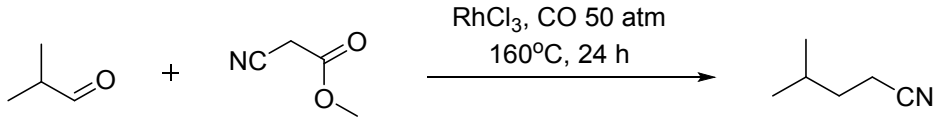
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.55 mg 2.1 µmol; 0.2 mol%), 2-phenylpropionaldehyde (132 µl; 132.2 mg; 0.99 mmol; 100 mol%), methanol (475 µl), methyl cyanoacetate (92.4 µl; 103.7 mg; 1.05 mmol; 106 mol%) and water (93.5 µl; 93.5 mg; 5.19 mmol; 524 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction

mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then concentrated on a rotary evaporator, extracted with dichloromethane from water, solvent was removed under reduced pressure and the residue was analyzed by NMR. 73% NMR yield. Purification: column chromatography, eluent hexane/ethyl acetate 10/1 (R_f = 0.31). Isolated as a colorless oil - 63% (99 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd appears as t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 2.97 – 2.86 (m, 1H), 2.36 – 1.86 (m, 4H), 1.35 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 128.8, 126.9, 126.8, 119.7, 38.9, 33.5, 21.9, 15.4

The obtained NMR data are in agreement with the literature report[11]

Experiment with several consecutive reaction cycles



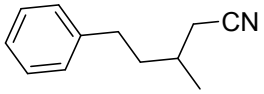
16

A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.22 mg; 8.3 μmol; 0.02 mol%), isobutyraldehyde (378.4 μl; 298.9 mg; 4.15 mmol; 100 mol%), methanol (2080 μl), methyl cyanoacetate (368.4 μl; 413.7 mg; 4.18 mmol; 101 mol%) and water (372.8 μl; 372.8 mg; 20.70 mmol; 499 mol%). The autoclave was sealed and charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to liquid nitrogen temperature and depressurized. Then 90 μl of mesitylene was added in to the reaction mixture and 30 μl of solution was taken from reactor and analyzed by NMR. 82% NMR yield. Then autoclave was charged with isobutyraldehyde (378.4 μl; 298.9 mg; 4.15 mmol; 100 mol%), methyl cyanoacetate (368.4 μl; 413.7 mg; 4.18 mmol; 101 mol%) and water (74.5 μl; 74.5 mg; 4.14 mmol; 100 mol%), sealed and charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to liquid nitrogen temperature and depressurized. Then 41.5 mg of 1,4-dinitrobenzene was added into the reaction mixture and 30 μl of solution was taken from reactor and analyzed by NMR. 32% NMR yield in the second step. The total TON = 5700.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (t, *J* = 7.4 Hz, 2H), 1.77 – 1.61 (m, 1H), 1.51 (q, *J* = 7.4 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 120.0, 33.9, 27.2, 21.7, 15.1

The obtained NMR data are in agreement with the literature report[12]

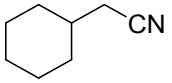
3-methyl-5-phenylpentanenitrile (17)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (2 mg; 7.6 μmol; 2 mol%), 4-phenylbutan-2-one (56.9 μl; 56.3 mg; 0.38 mmol; 100 mol%), methanol (200 μl), methyl cyanoacetate (50.3 μl; 56.4 mg; 0.57 mmol; 150 mol%) and water (6.8 μl; 6.8 mg; 0.38 mmol; 100 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then solvent was

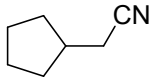
removed under reduced pressure on a rotary evaporator and the residue was analyzed by NMR. 76% NMR yield. Purification: column chromatography, eluent hexane/DCM 2/1 (R_f = 0.4). Isolated as a colorless oil - 68% (45 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 2.80 – 2.55 (m, 2H), 2.41 – 2.21 (m, 2H), 1.96 – 1.85 (m, 1H), 1.84 – 1.72 (m, 1H), 1.70 – 1.62 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 128.6, 128.4, 126.2, 118.8, 37.6, 33.2, 30.0, 24.6, 19.5
The obtained NMR data are in agreement with the literature report[3]

2-cyclohexylacetonitrile (18)



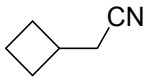
A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (2 mg; 7.6 µmol; 2 mol%), cyclohexanone (39.3 µl; 37.3 mg; 0.38 mmol; 100 mol%), methanol (200 µl), methyl cyanoacetate (50.3 µl; 56.4 mg; 0.57 mmol; 150 mol%) and water (6.8 µl; 6.8 mg; 0.38 mmol; 100 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then solvent was removed under reduced pressure on a rotary evaporator and the residue was analyzed by NMR. 68% NMR yield. Purification: column chromatography, eluent hexane/DCM 1/1. Detection with GC. Isolated as a colorless oil - 60% (28 mg).
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (d, *J* = 5.3 Hz, 2H), 1.94 – 1.56 (m, 6H), 1.38 – 0.94 (m, 5H)
^{13}C NMR (101 MHz, $CDCl_3$) δ 119.1, 34.9, 32.5, 25.8, 25.8, 24.9
The obtained NMR data are in agreement with the literature report[13]

2-cyclopentylacetonitrile (19)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (7.9 mg; 30 µmol; 2 mol%), cyclopentanone (132.5 µl; 126.0 mg; 1.5 mmol; 100 mol%), methanol (800 µl), methyl cyanoacetate (198.7 µl; 222.8 mg; 2.25 mmol; 150 mol%) and water (27 µl; 27 mg; 1.5 mmol; 100 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then solvent was removed under reduced pressure and the residue was analyzed by GC. 53% GC yield. Purification: column chromatography, eluent pentane/DCM 2/1. Detection with GC. Isolated as a colorless oil - 40% (65.4 mg).
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (d, *J* = 6.8 Hz, 2H), 2.22 – 2.13 (m, 1H), 1.94 – 1.83 (m, 2H), 1.73 – 1.64 (m, 2H), 1.64 – 1.55 (m, 2H), 1.35 – 1.25 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 119.6, 36.4, 32.2, 25.1, 22.9
The obtained NMR data are in agreement with the literature report[13]

2-cyclobutylacetonitrile (20)



A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (8.0 mg; 30.4 μmol; 2 mol%), cyclobutanone (113.5 μl; 106.5 mg; 1.5 mmol; 100 mol%), methanol (800 μl), methyl cyanoacetate (201.1 μl; 225.8 mg; 2.28 mmol; 150 mol%) and water (54 μl; 54 mg; 3 mmol; 200 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. The reaction mixture was transferred to a flask, and the autoclave was washed with dichloromethane (2 × 1 mL). The reaction mixture and the dichloromethane from rinsing were combined and then solvent was removed under reduced pressure and the residue was analyzed by GC. 84% GC yield. Purification: column chromatography, eluent pentane/DCM 2/1. Detection with GC. Isolated as a colorless oil - 56% (81 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 – 2.56 (m, 1H), 2.40 (d, J = 6.7 Hz, 2H), 2.23 – 2.10 (m, 2H), 1.96 – 1.77 (m, 4H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 118.9, 31.6, 27.4, 23.7, 17.9.

The obtained NMR data are in agreement with the literature report[14]

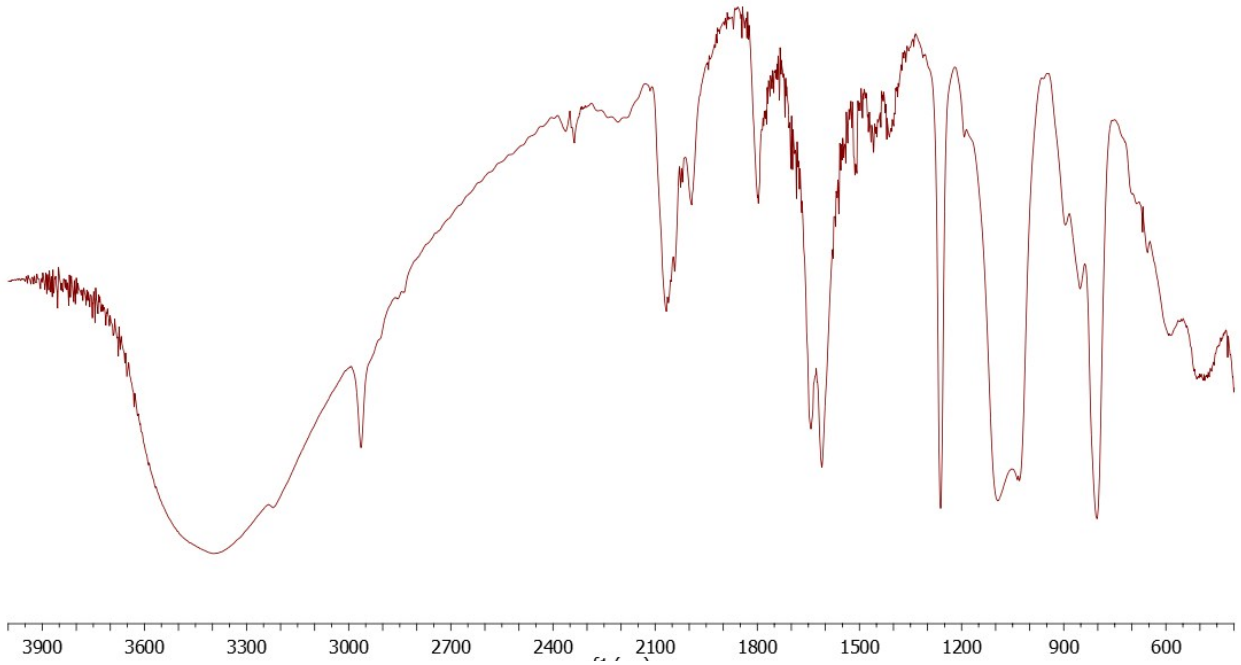
IR spectroscopic analysis

To confirm the presence of intermediate carbonyl rhodium complex some FT-IR experiments were done.

First pure rhodium chloride trihydrate was dissolved in water-methanol mixture in the stainless steel autoclave, autoclave was flushed with 10 bar of CO and charged with 50 bar of CO. After heating for 20 hours resulting mixture was transferred to a round-bottom flask, volatile compounds were evaporated in vacuum, and FT-IR spectrum was measured in KBr pellet.

This spectrum had a series of absorption bands at 2100 – 1950 cm^{-1} corresponding to terminal CO molecules, coordinated to rhodium, and a band at 1800 cm^{-1}, corresponding to bridged CO molecules.[15]

Fig. 1. IR spectrum of $RhCl_3$, incubated in carbon monoxide atmosphere for 20 hours



With this result in hands reaction of nitrile synthesis from 4-tolylaldehyde and methyl cyanoacetate with 50 mol% loading of rhodium chloride was done:

A glass vial in a 10 mL stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (20.0 mg; 71 µmol; 50 mol%), 4-methylbenzaldehyde (17 µl; 17 mg; 0.14 mmol; 100 mol%), methanol (500 µl), methyl cyanoacetate (13 µl; 14.1 mg; 0.14 mmol; 100 mol%) and water (13 µl; 13 mg; 0.71 mmol; 500 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 24 h, the reactor was cooled to room temperature and depressurized. FT-IR spectrum of this reaction mixture (as is) revealed two absorption bands at 2075 and 2001 cm^{-1} and no bands at 1800 cm^{-1} (fig. 2). The same absorption bands were found in FT-IR spectrum of reaction mixture in a thin film.

This means, that no bridged CO molecules present in reaction.

To confirm that no absorption bands interfere with these signals FT-IR spectra of reaction products were registered.

Fig. 2. FT-IR spectrum of reaction mixture in methanol (solvent spectrum withdrawn)

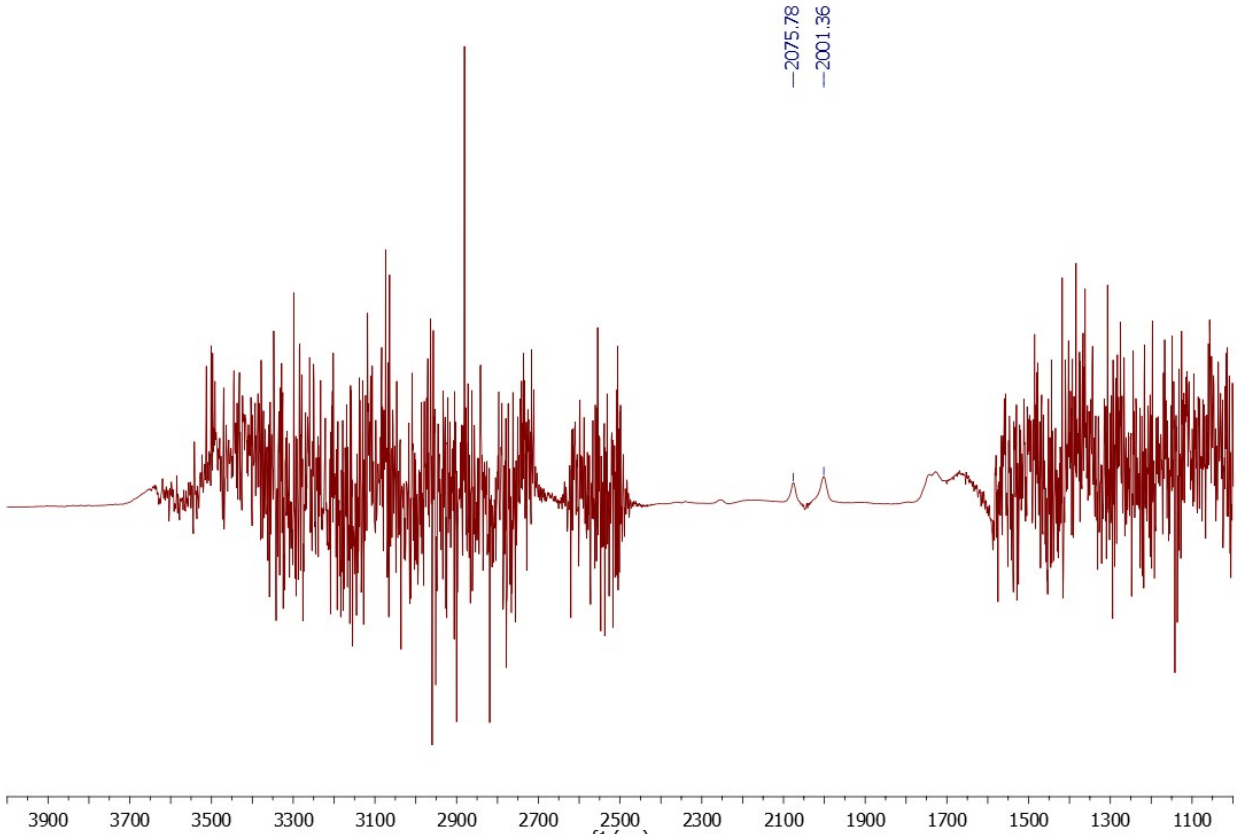


Fig. 3. FT-IR spectrum of reaction mixture in a thin film

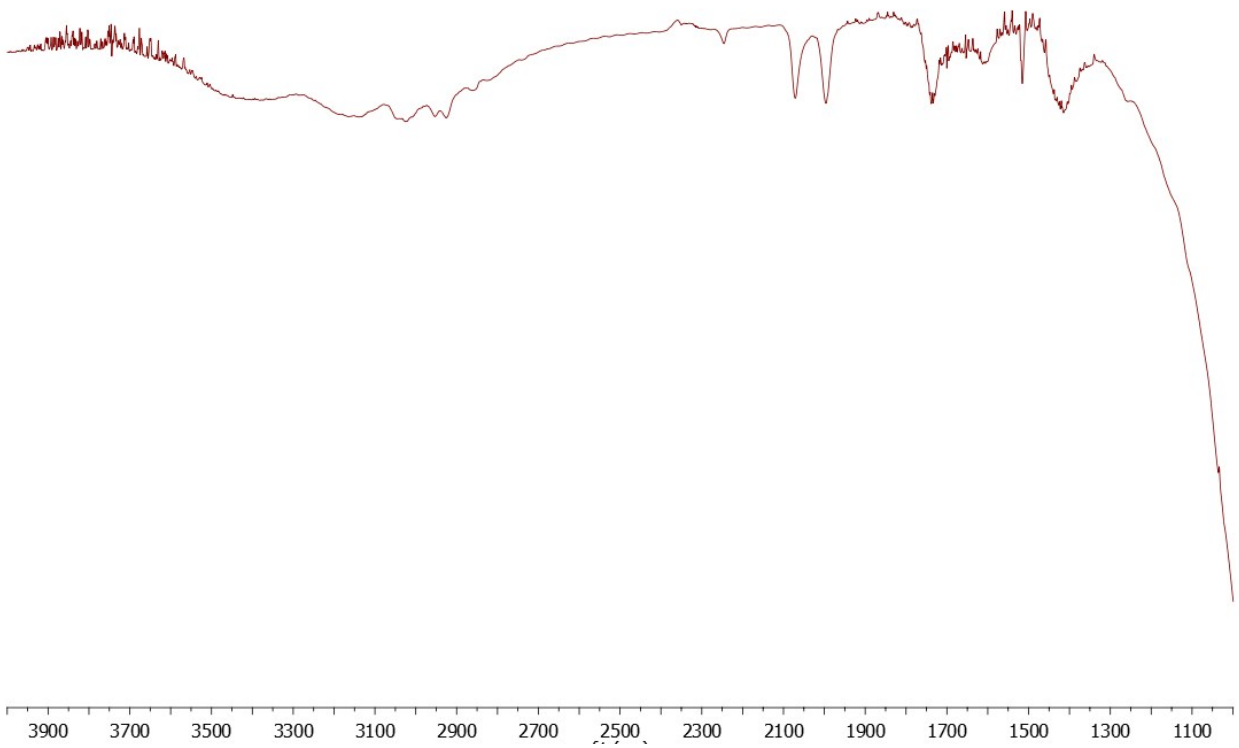
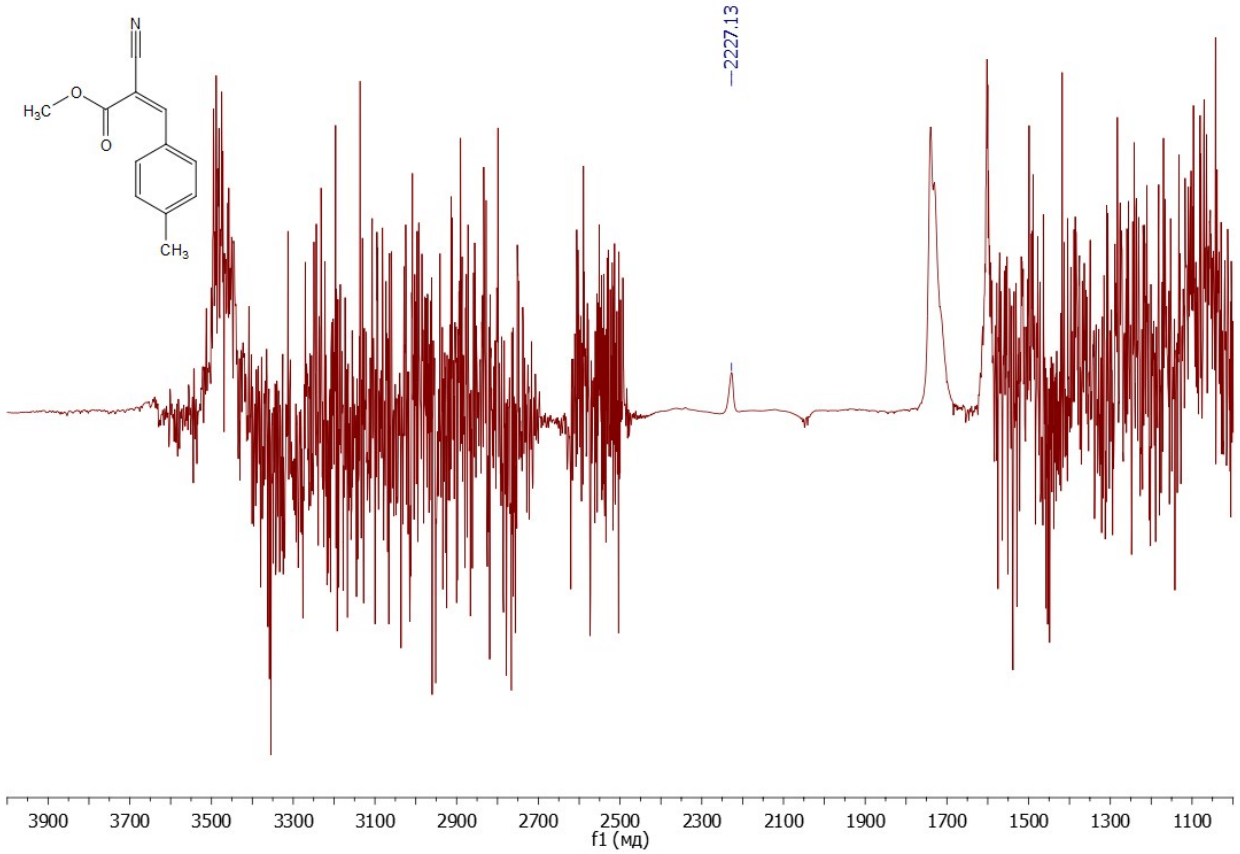


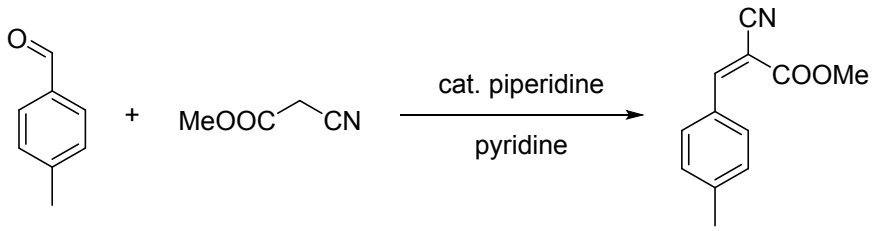
Fig. 4. FT-IR spectrum of methyl (Z)-2-cyano-3-(p-tolyl)acrylate in methanol (solvent spectrum withdrawn)



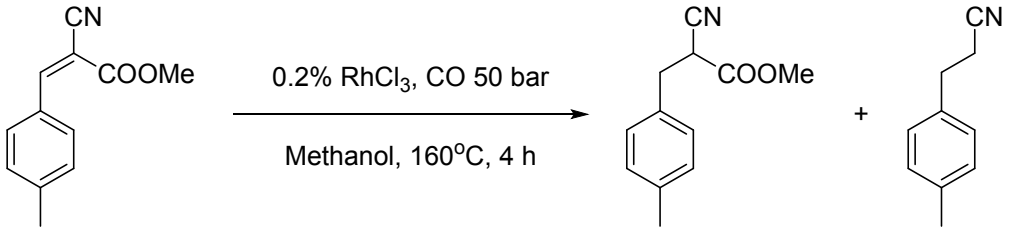
Another substance, that can affect FT-IR spectrum, is Knoevenagel adduct methyl (Z)-2-cyano-3-(p-tolyl)acrylate. Fig. 4 shows, that this compound has only one peak in the region of interest at 2227 cm^{-1}, and it does not interfere with signals of rhodium carbonyl compounds.
So we conclude, that reaction intermediates include different rhodium carbonyl complexes with only terminal CO molecules. No bridged CO molecules were detected.

Control experiments

For further understanding of the reaction pathways we carried out some control experiments.
First Knoevenagel adduct was prepared:



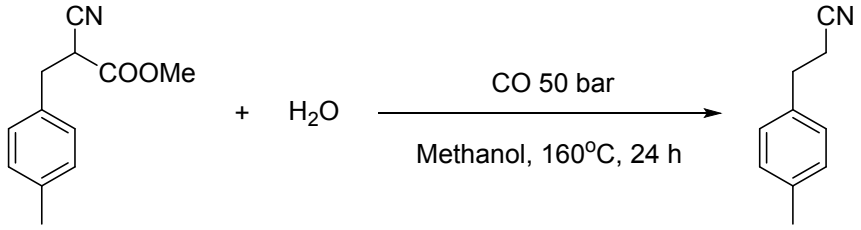
Round-bottom flask, equipped with magnetic stirrer and reflux condenser was charged with 20 ml of pyridine, 1 g (0.98 ml, 8.32 mmol) of 4-methylbenzaldehyde, 0.82 g (0.74 ml, 8.32 mmol) of methyl cyanoacetate and 0.076 ml of piperidine. Reaction mixture was refluxed for two hours, cooled to room temperature. 10 ml of water was added, and reaction mixture was acidified with diluted hydrochloric acid to pH 3. Mixture was cooled, and precipitated product was filtered off. Recrystallization of crude product from ethanol gave 0.73 g (42%) of desired product.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 3.93 (s, 3H), 2.44 (s, 3H).



A 10 ml stainless steel autoclave was charged with $RhCl_3 \cdot 3H_2O$ (0.2 mg; 0.71 μmol; 0,2 mol%), methyl (Z)-2-cyano-3-(p-tolyl)acrylate (71.5 mg; 0.36 mmol; 100 mol%), methanol (500 μl), and water (32 μl; 32 mg; 1.78 mmol; 500 mol%). The autoclave was sealed, flushed 3 times with 10 atm of CO, and then charged with 50 atm CO. The reactor was placed into a preheated to 160 °C oil bath. After 4 h, the reactor was cooled to room temperature and depressurized. NMR analysis of reaction mixture revealed 44% of target product and 51% of the ester.

Control experiment was accomplished according to the general procedure using $RhCl_3 \cdot 3H_2O$ (0.56 mg; 2.1 μmol; 0.2 mol%), 4-methylbenzaldehyde (125 μl; 127.4 mg; 1.06 mmol; 100 mol%), methanol (475 μl), methyl cyanoacetate (94.1 μl; 105.7 mg; 1.07 mmol; 101 mol%) and water (95.2 μl; 95.2 mg; 5.28 mmol; 498 mol%). Reaction time was 4 hours. 78% NMR yield.

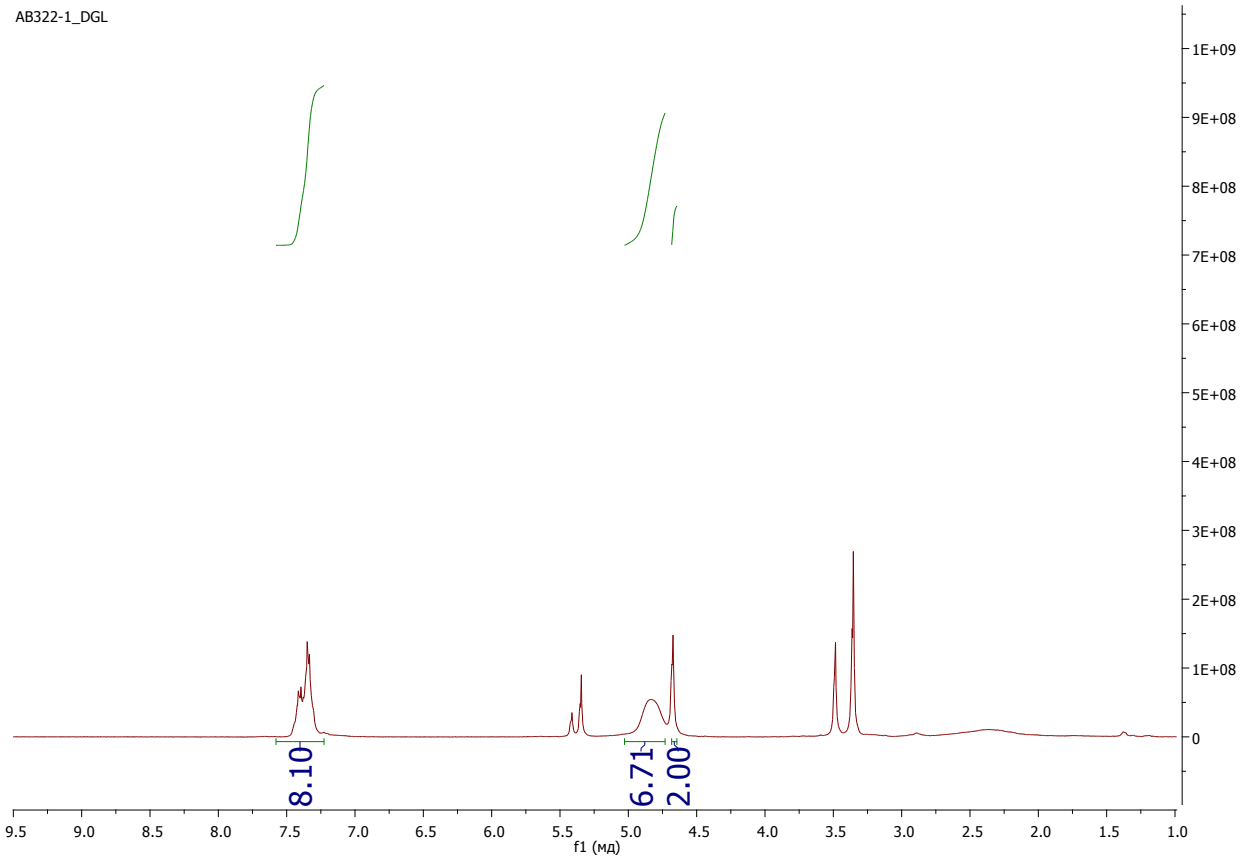
To check, is rhodium necessary for hydrolysis and decarboxylation step, we accomplished two control experiments:



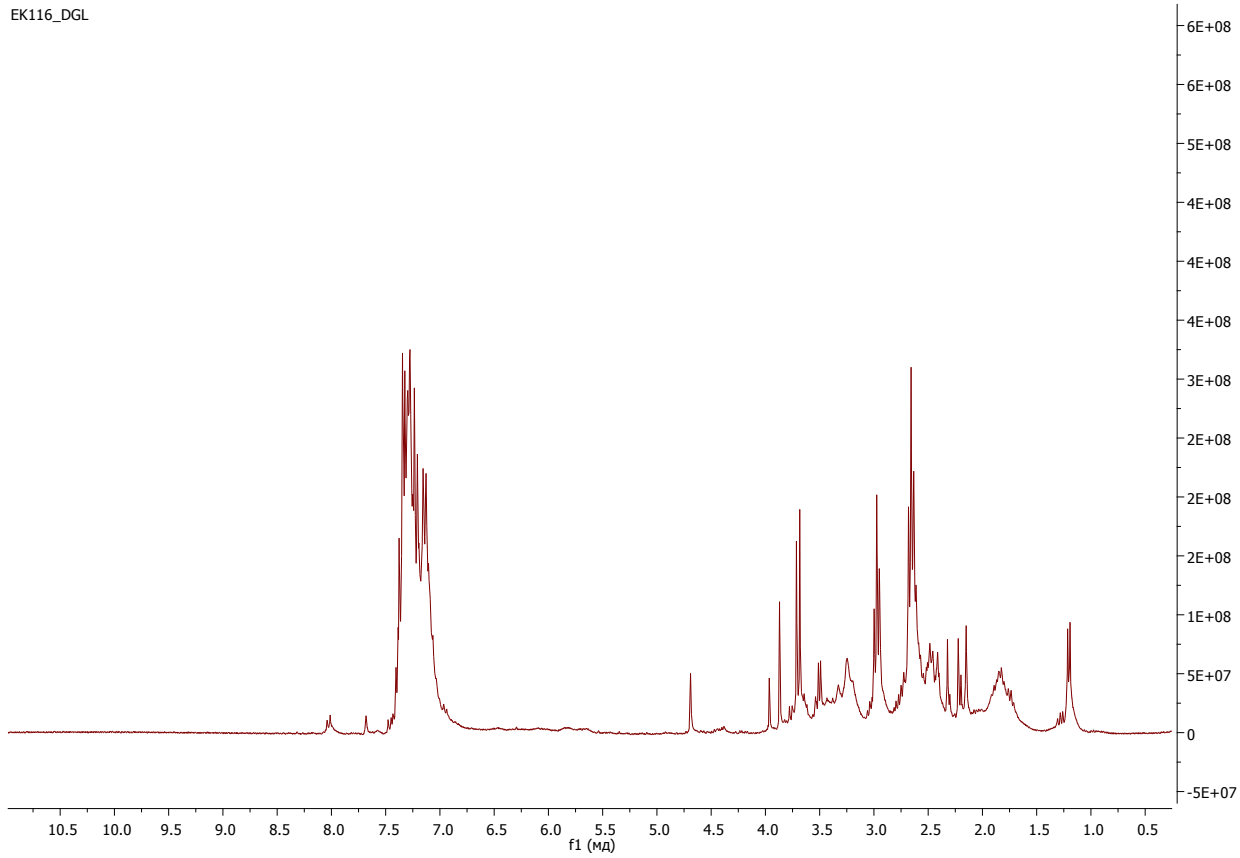
Two 10 ml stainless steel autoclaves were charged with 36 mg (100 mol %, 0.17 mmol) of methyl 2-cyano-3-(p-tolyl)propanoate (prepared according to previously described procedure[16]), 16 mg (500 mol %, 0.89 mmol) of water and 500 μL of methanol. $RhCl_3 \cdot 3H_2O$ (0.1 mg; 0.2 mol%) was charged into first autoclave, and no catalyst was added to second autoclave. Autoclaves were sealed, flushed 3 times with 10 bar of CO, and then charged with 50 bar CO. Reactors were placed into a preheated to 160 °C oil bath. After 24 h, reactors were cooled to room temperature and depressurized. NMR analysis of reaction mixtures revealed 99% yield in case of reaction with catalyst and 96% yield without catalyst.

3. 1H and 13C NMR spectra of obtained compounds

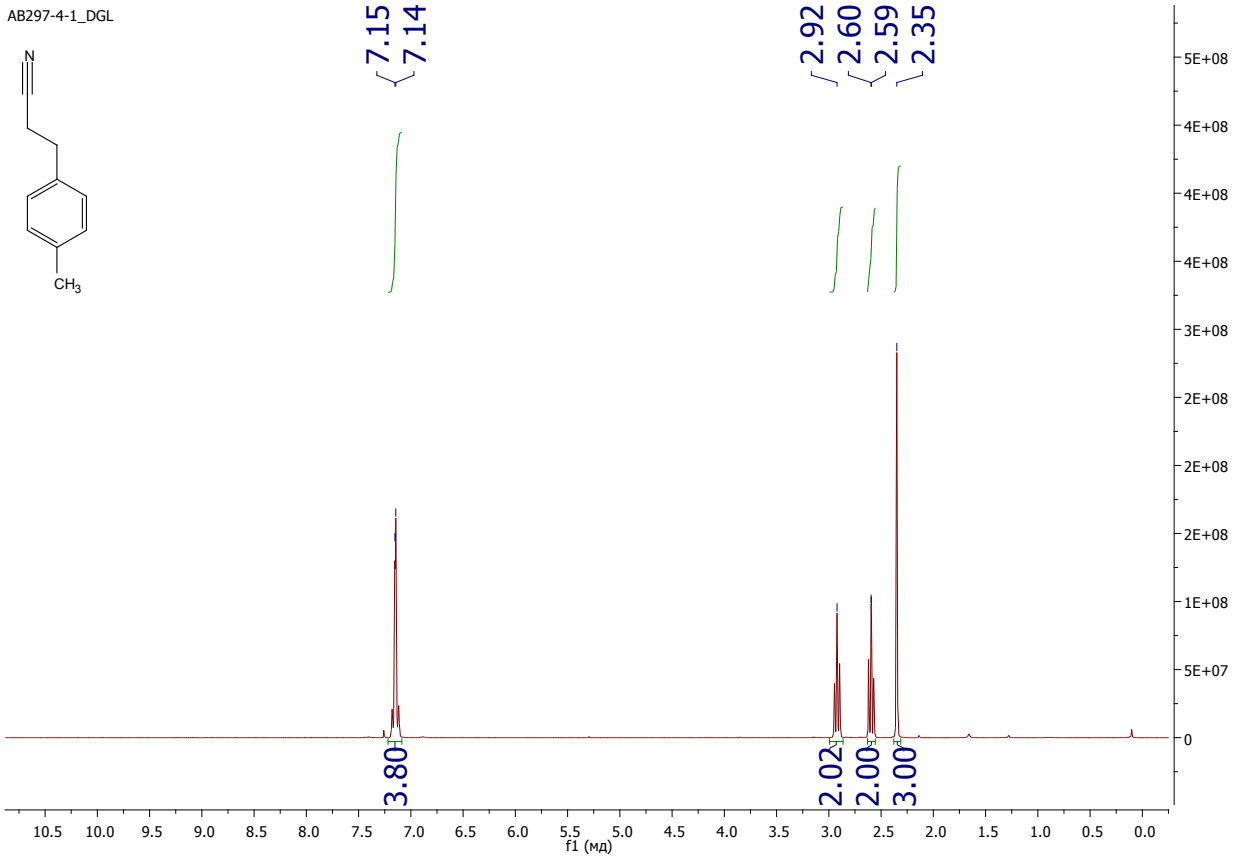
Spectrum of reaction mixture of 4-chlorobenzaldehyde with $NaBH_4$

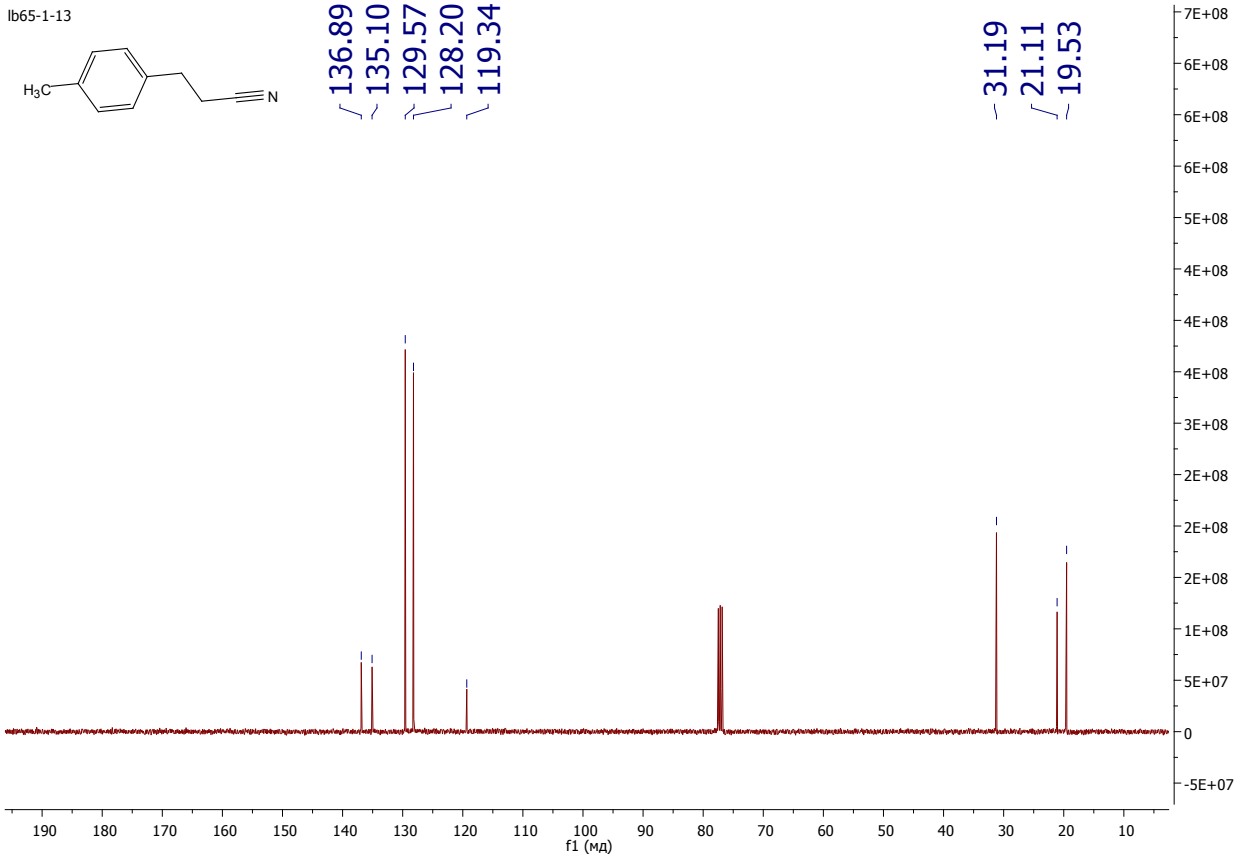


Spectrum of reaction mixture of 4-chlorobenzaldehyde with H_2

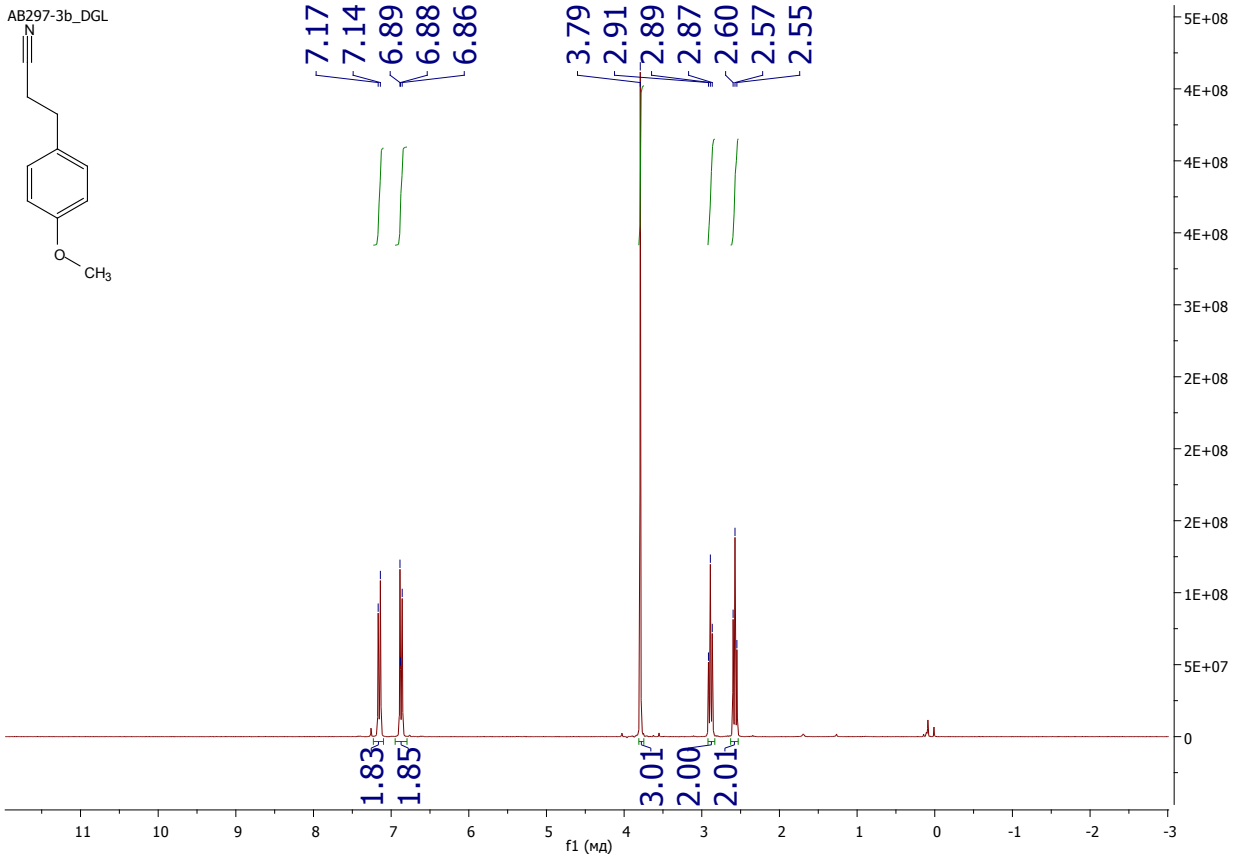


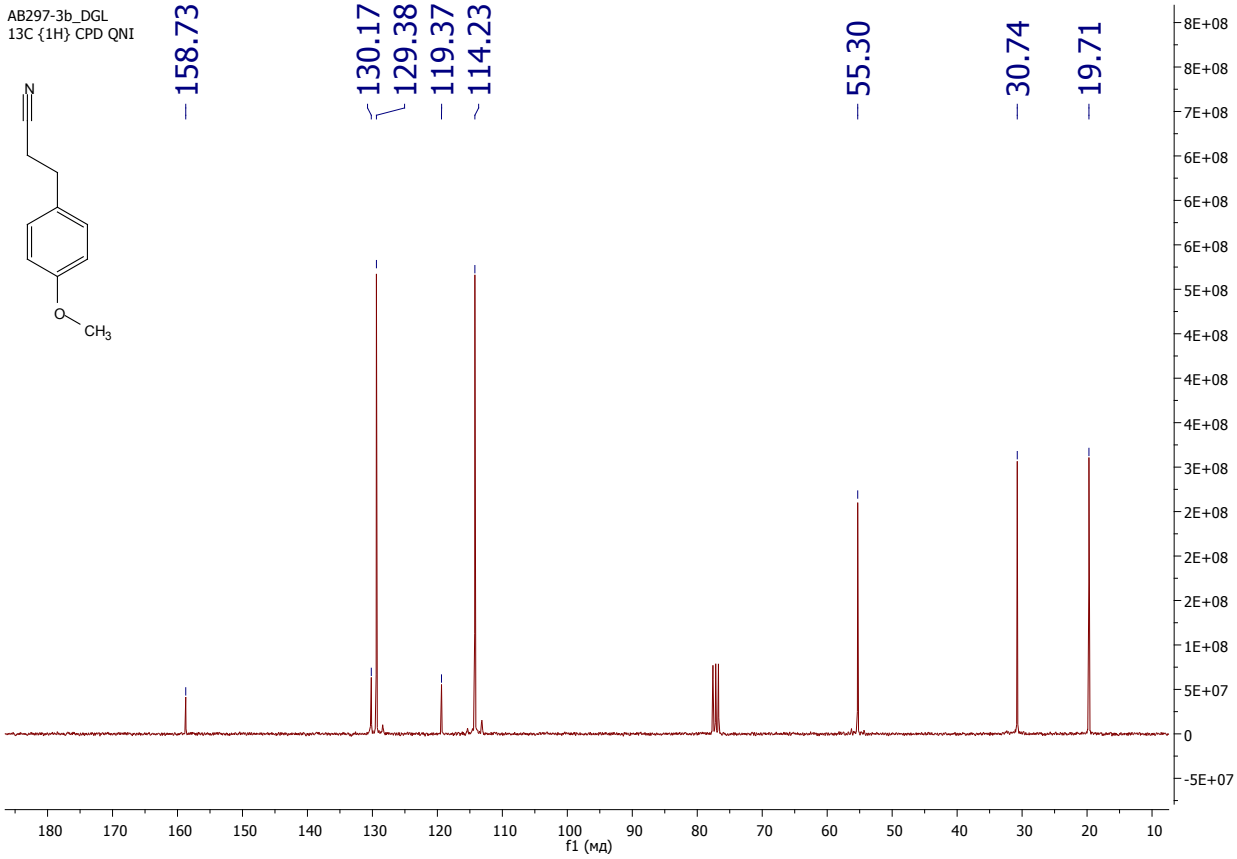
3-(p-tolyl)propanenitrile (4)



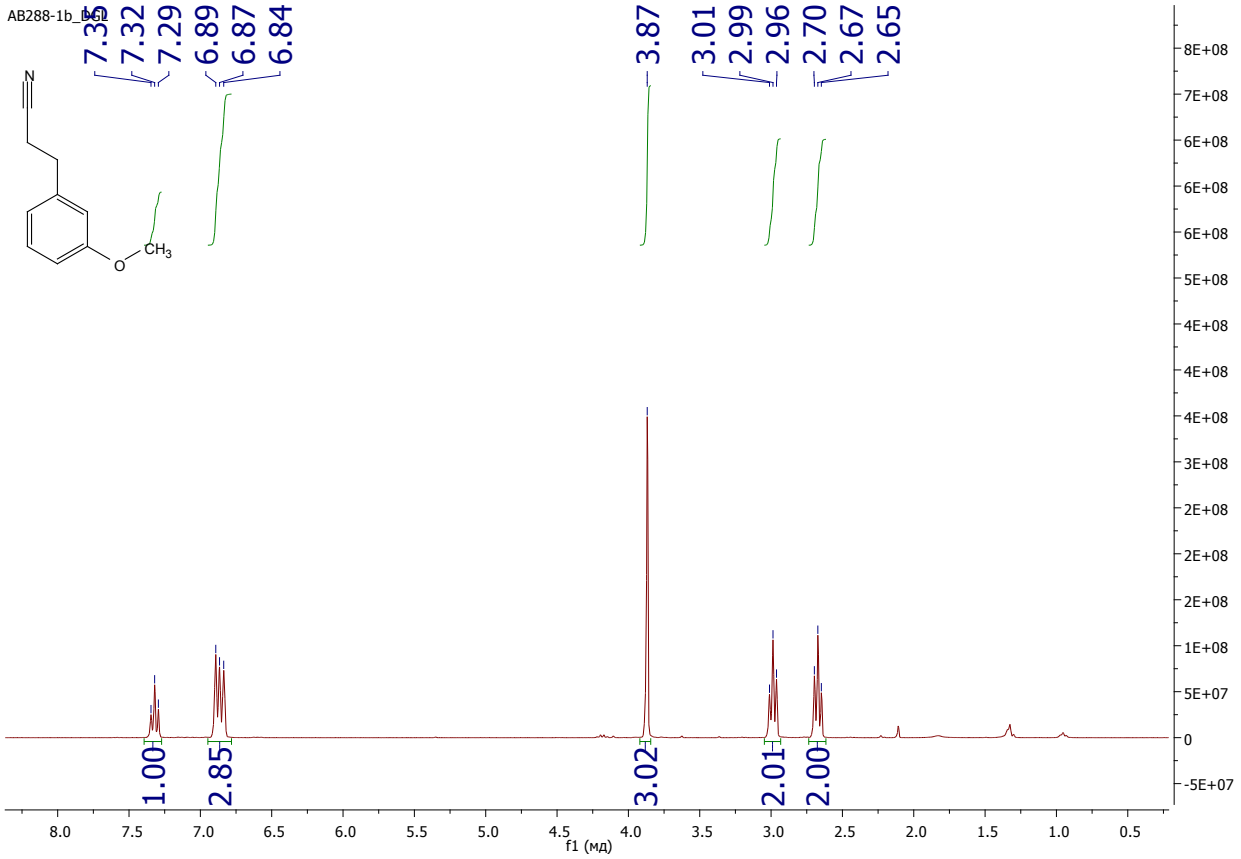


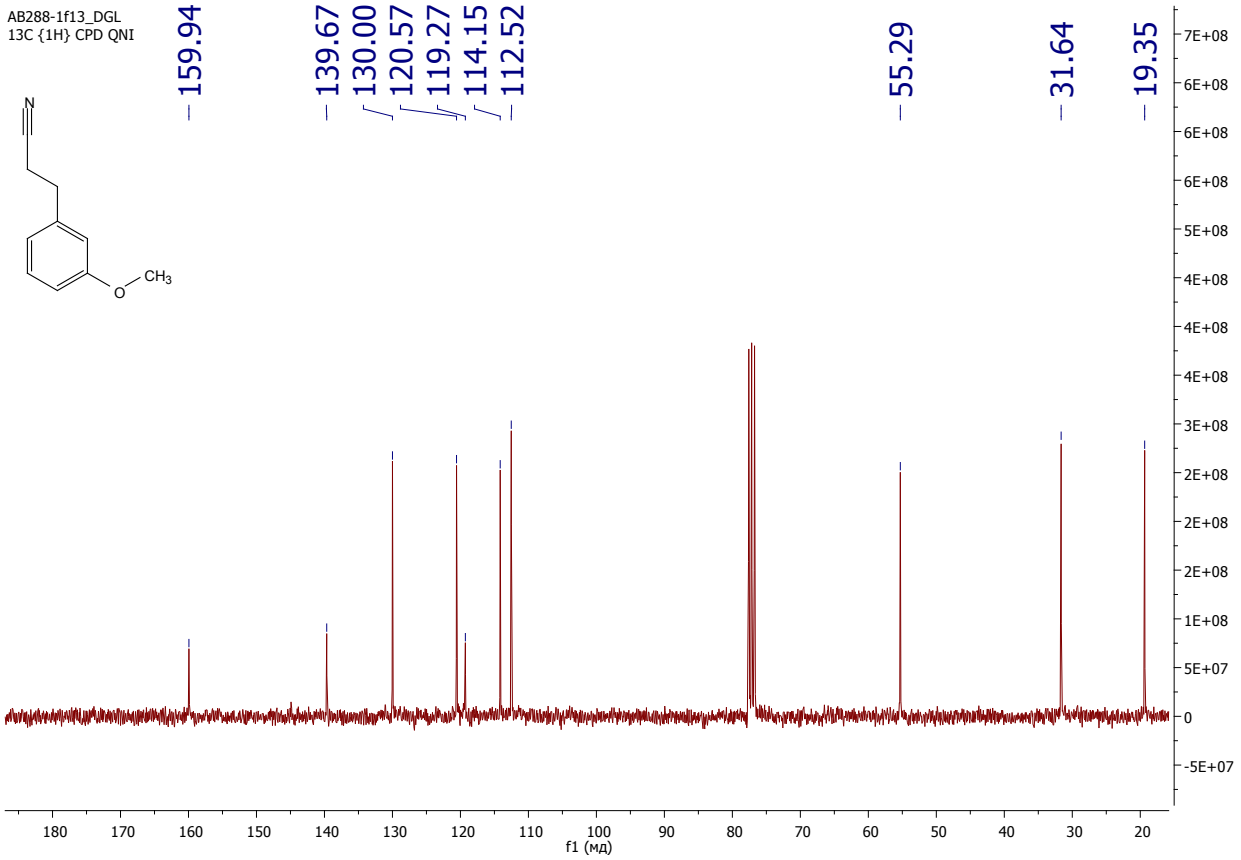
3-(4-methoxyphenyl)propanenitrile (5)



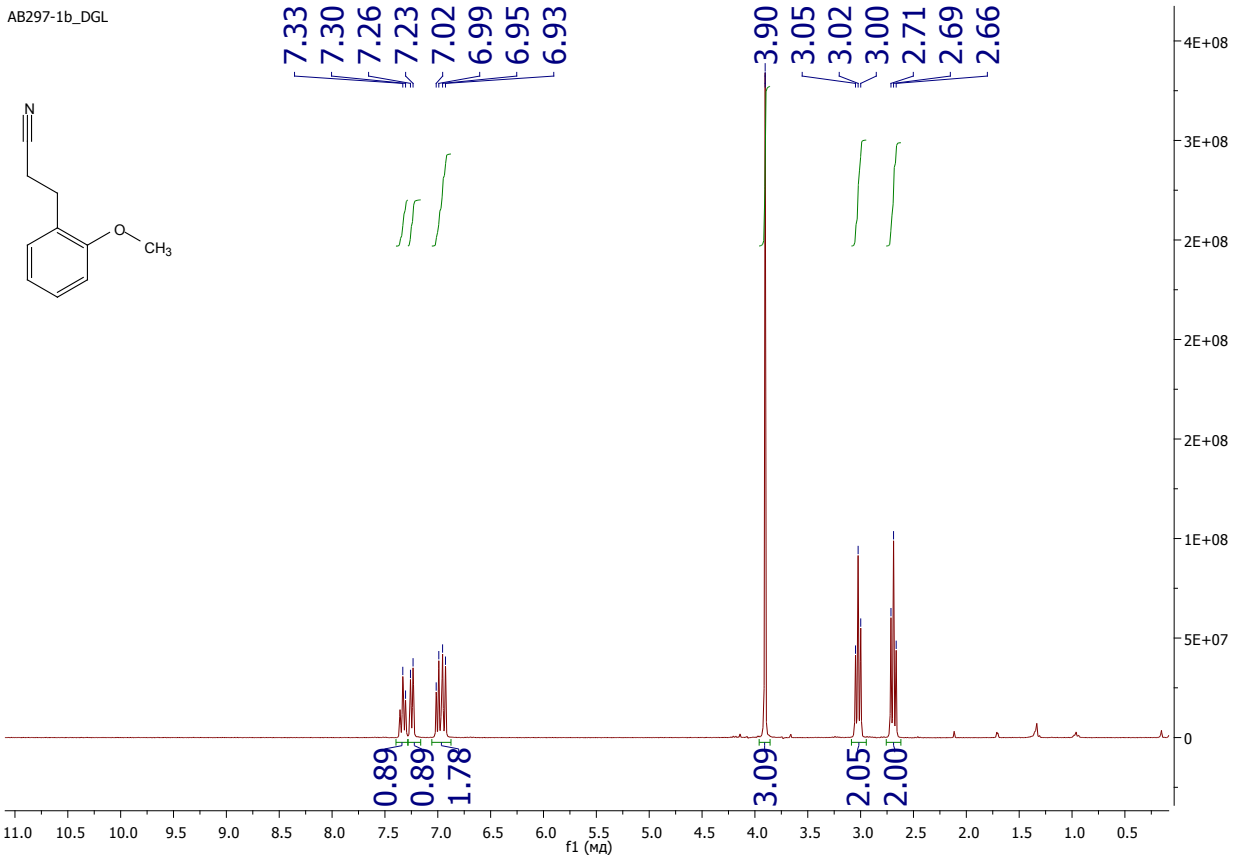


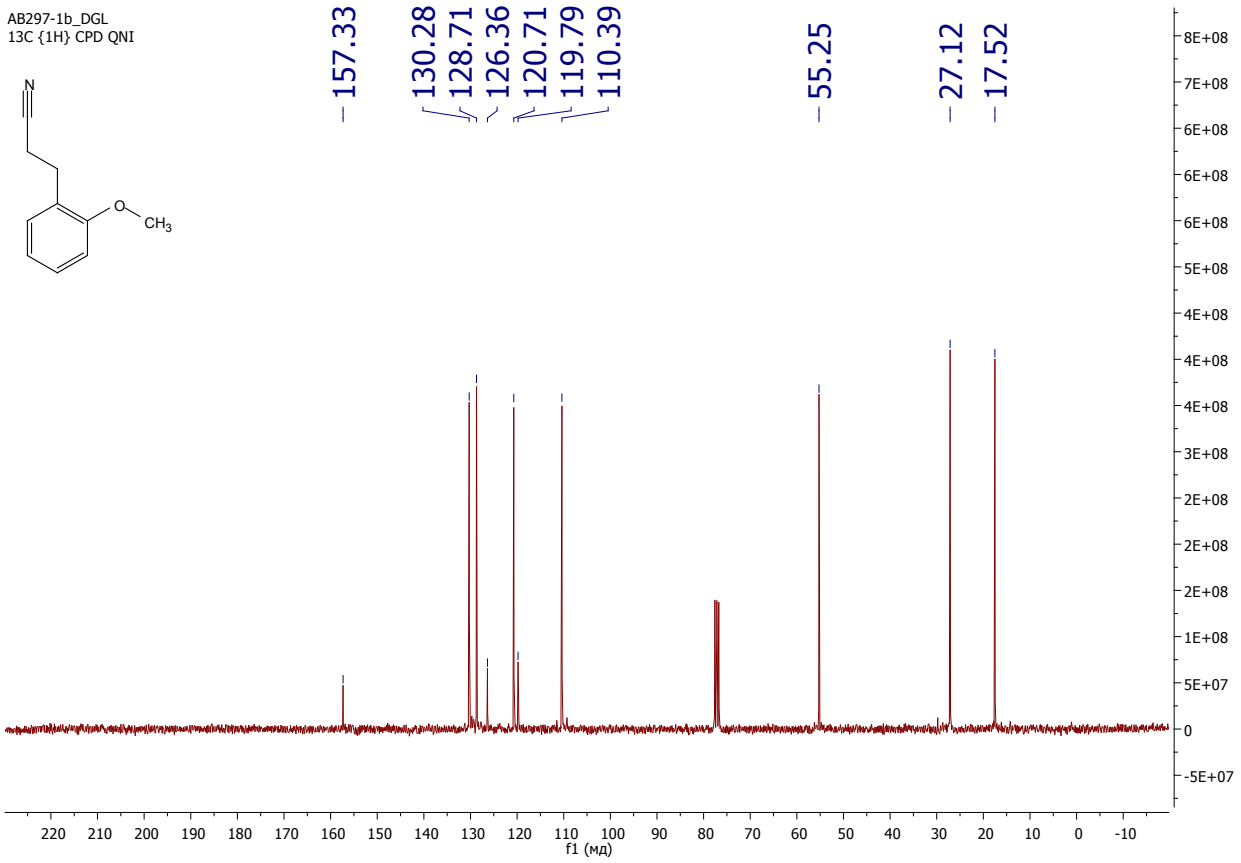
3-(3-methoxyphenyl)propanenitrile (6)



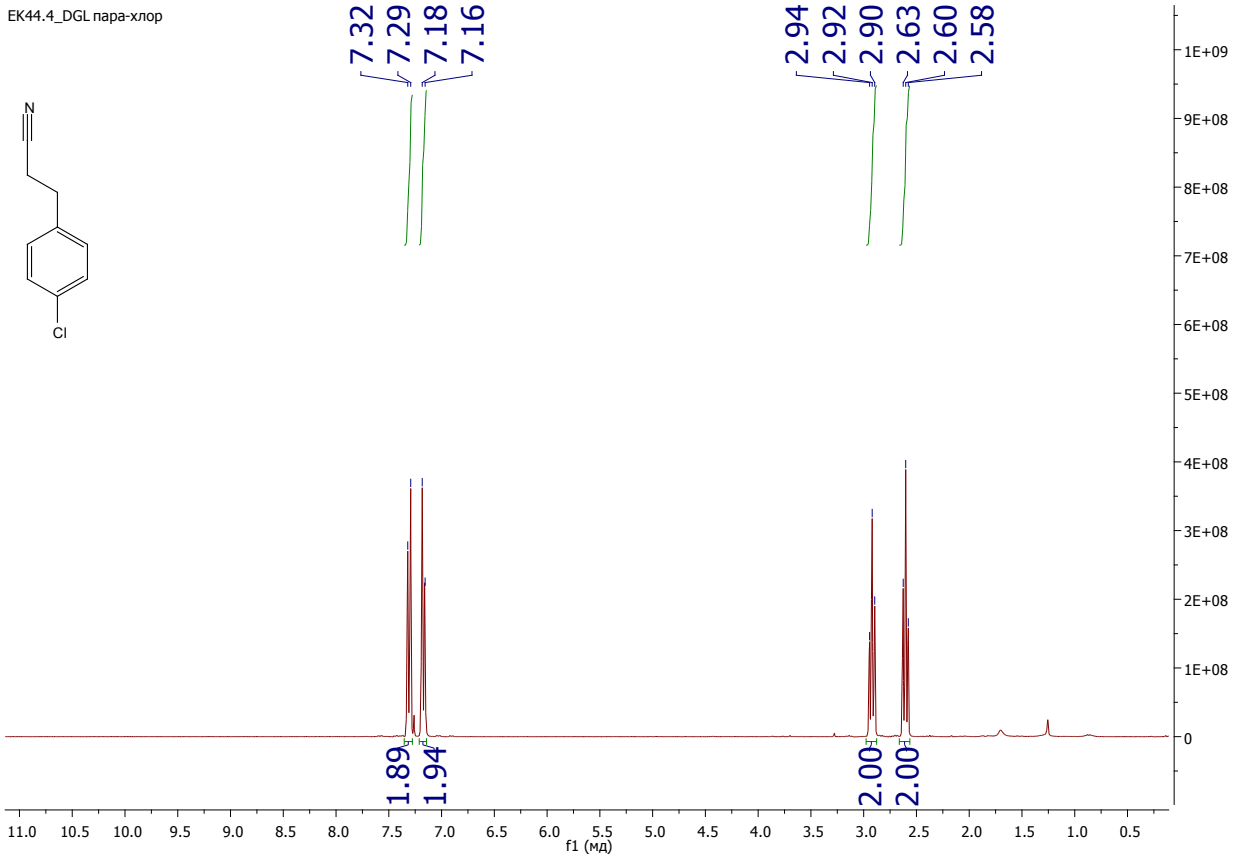


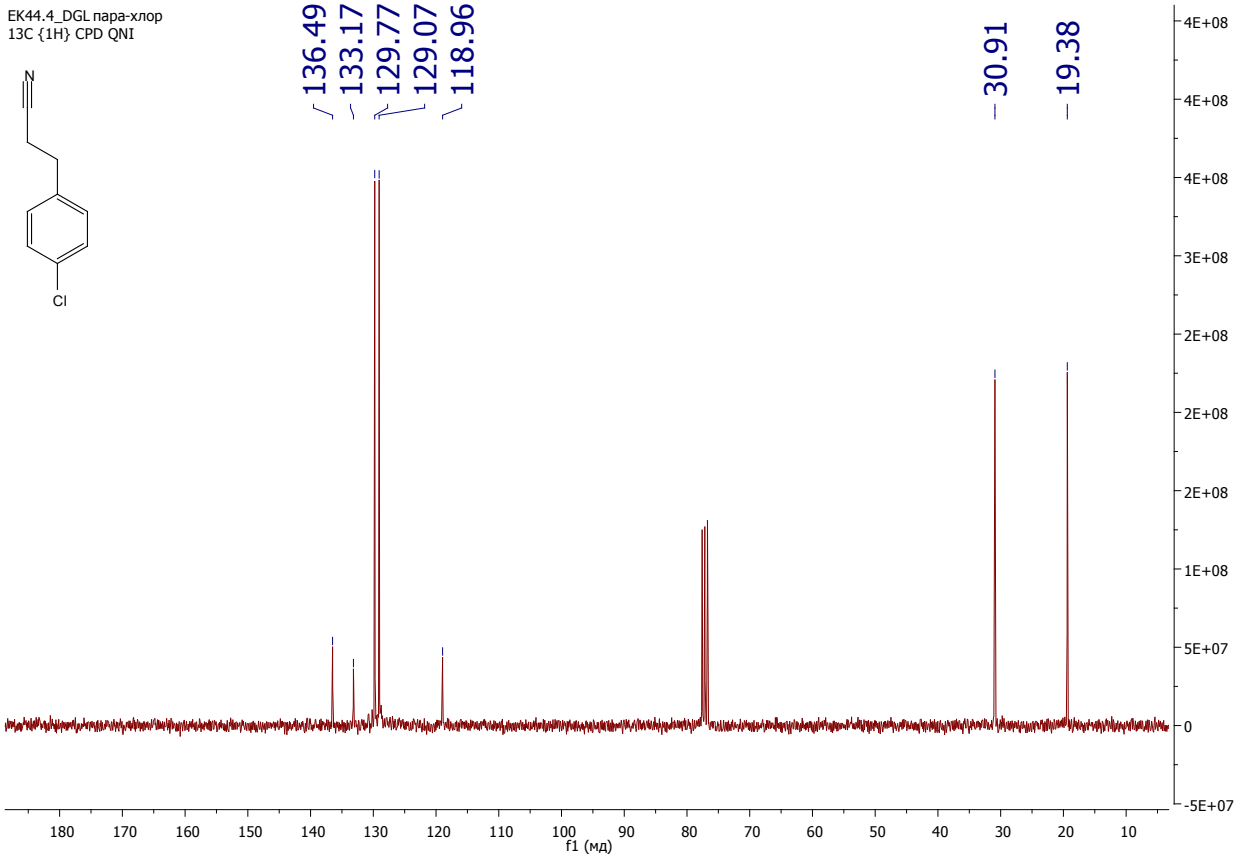
3-(2-methoxyphenyl)propanenitrile (7)



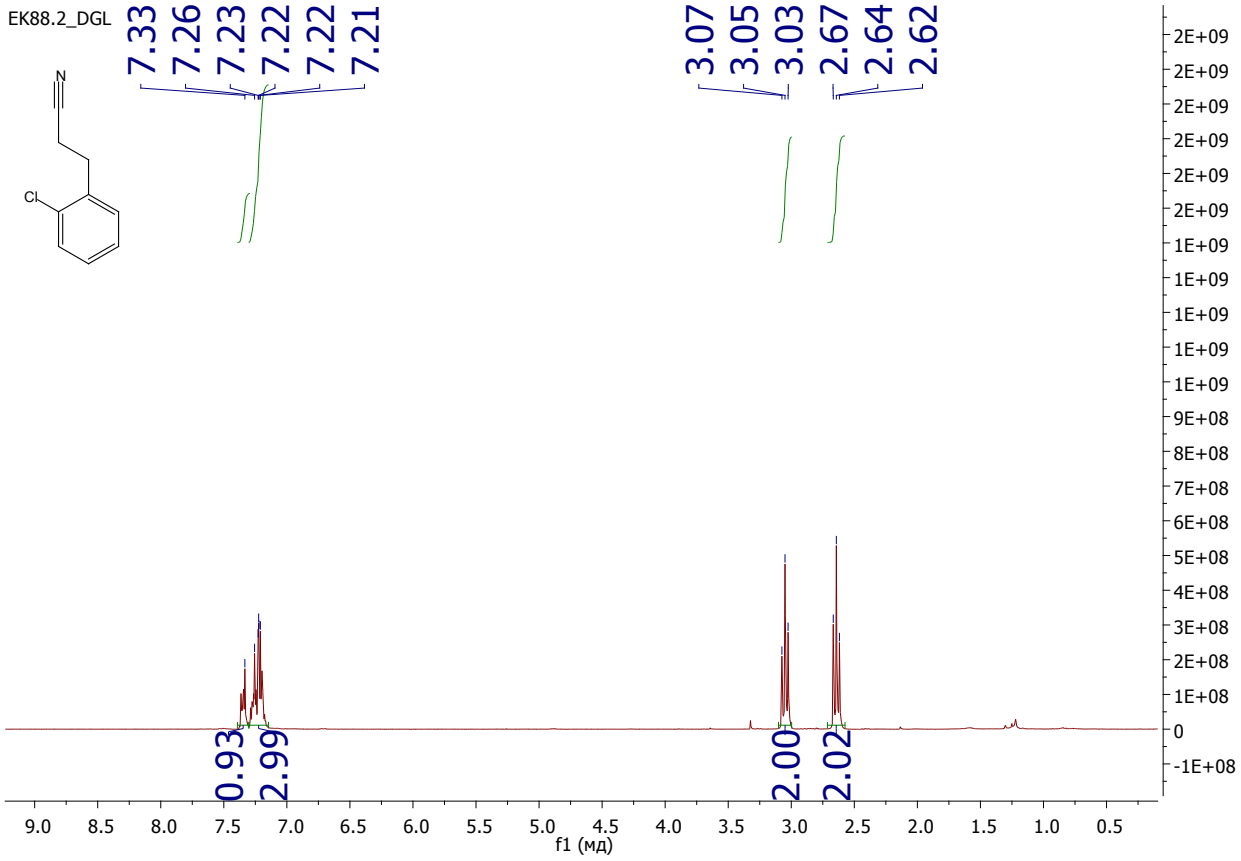


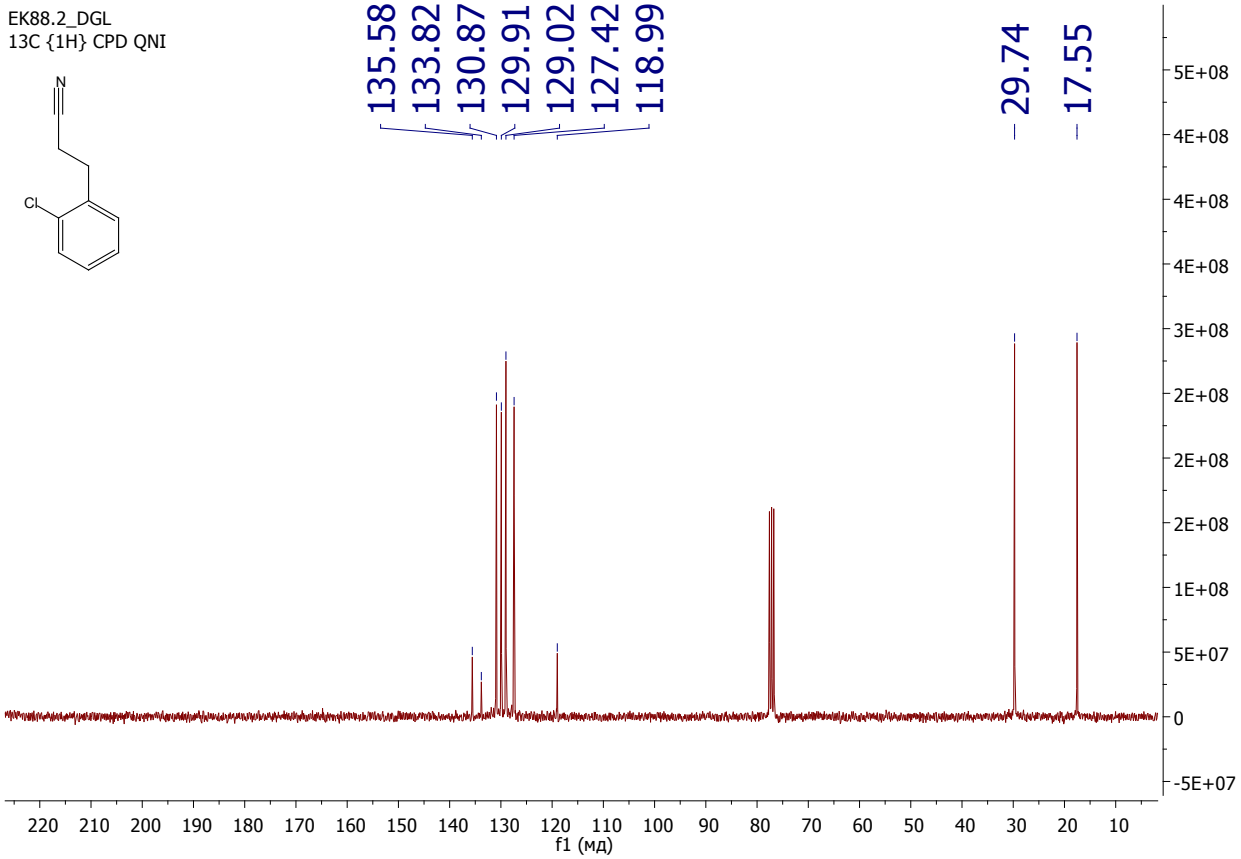
3-(4-chlorophenyl)propanenitrile (8)



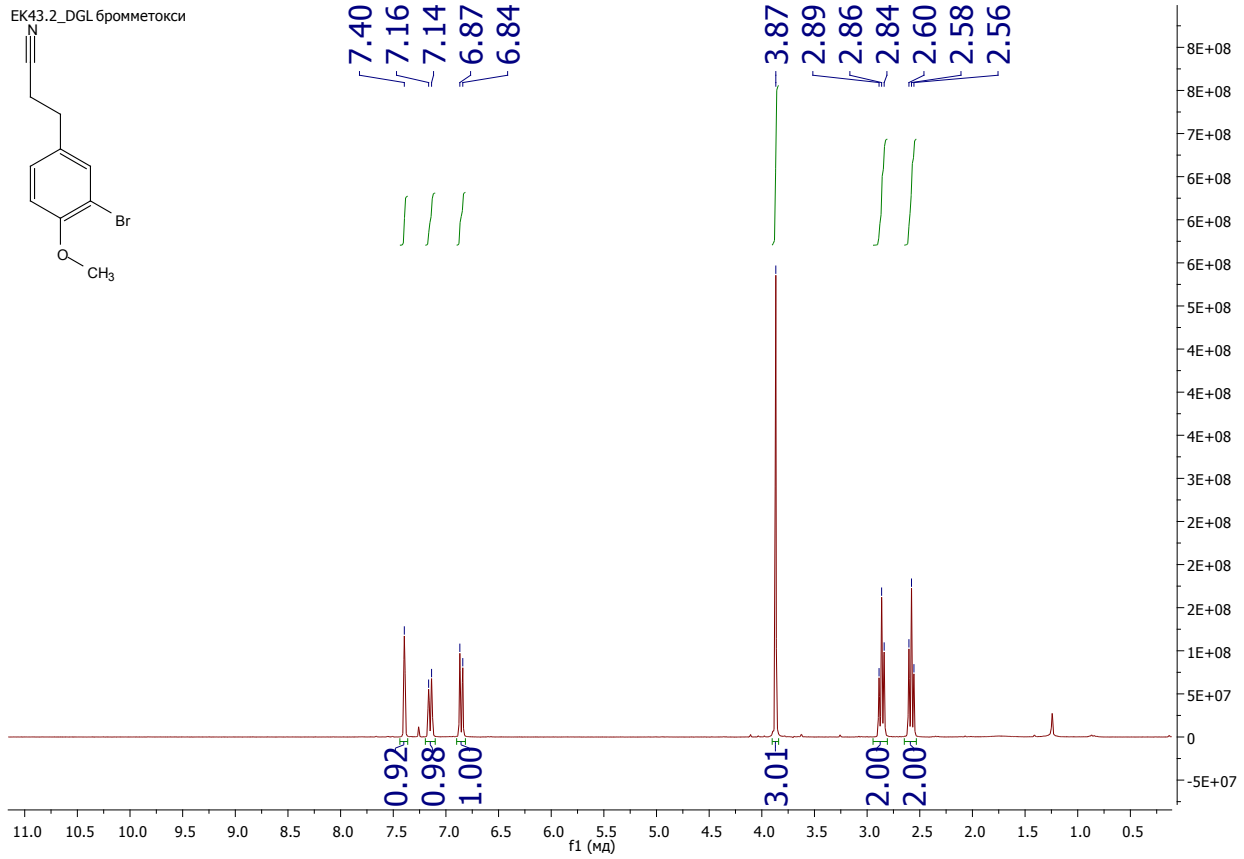


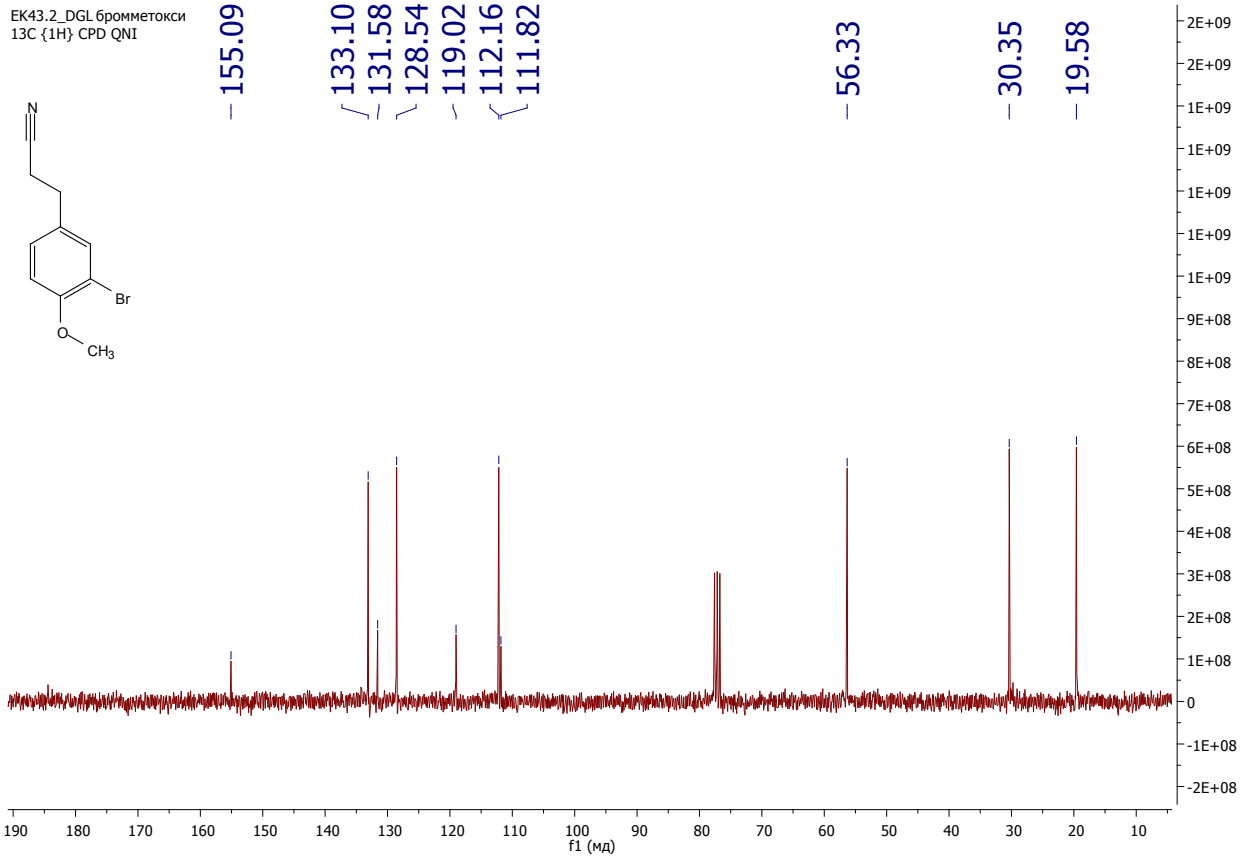
3-(2-chlorophenyl)propanenitrile (9)



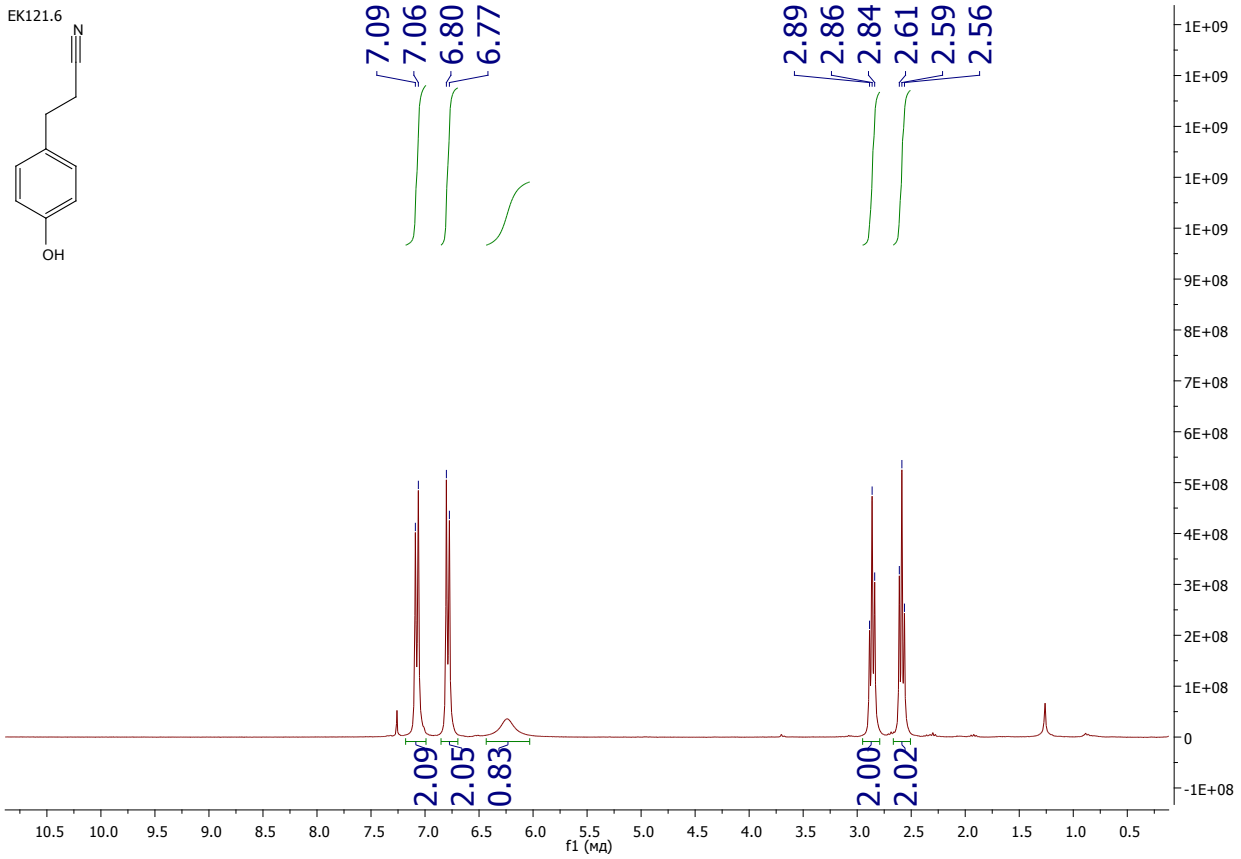


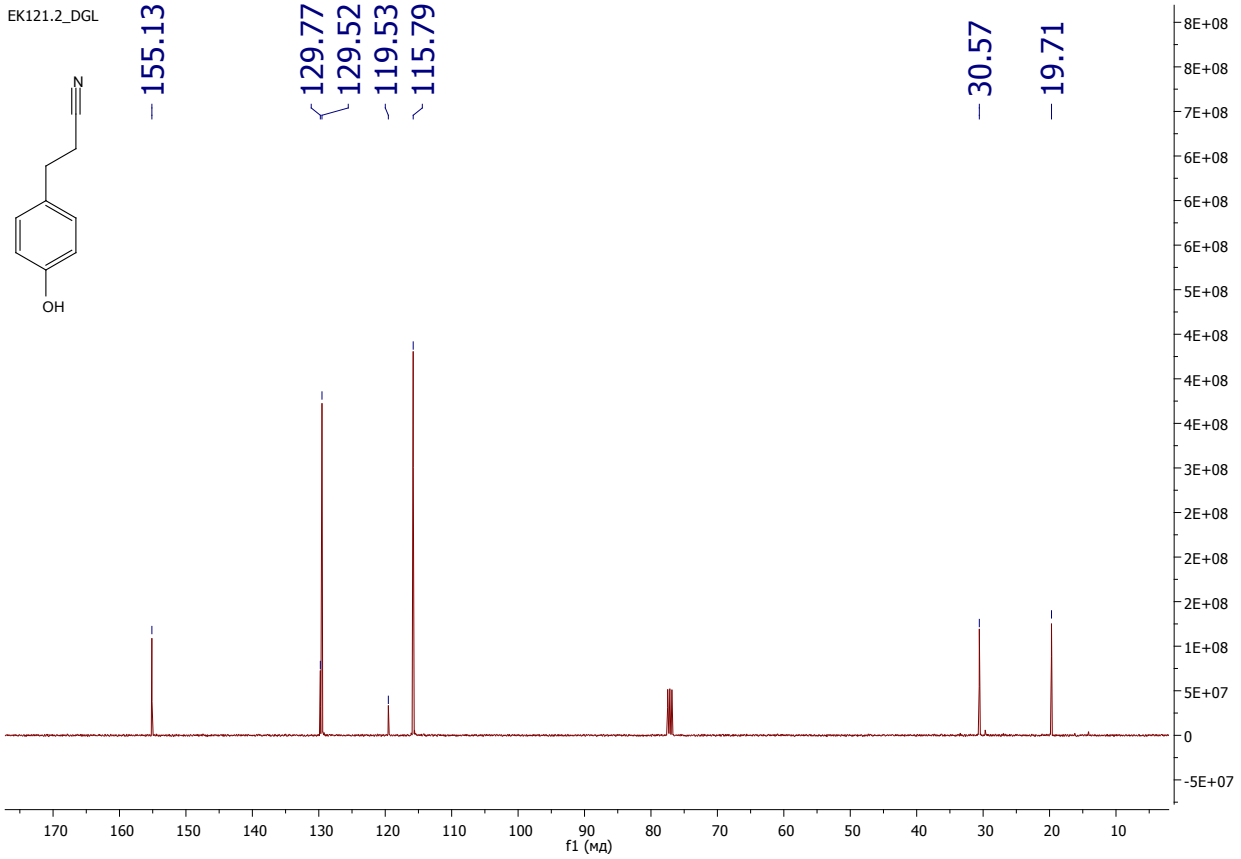
3-(3-bromo-4-methoxyphenyl)propanenitrile (10)



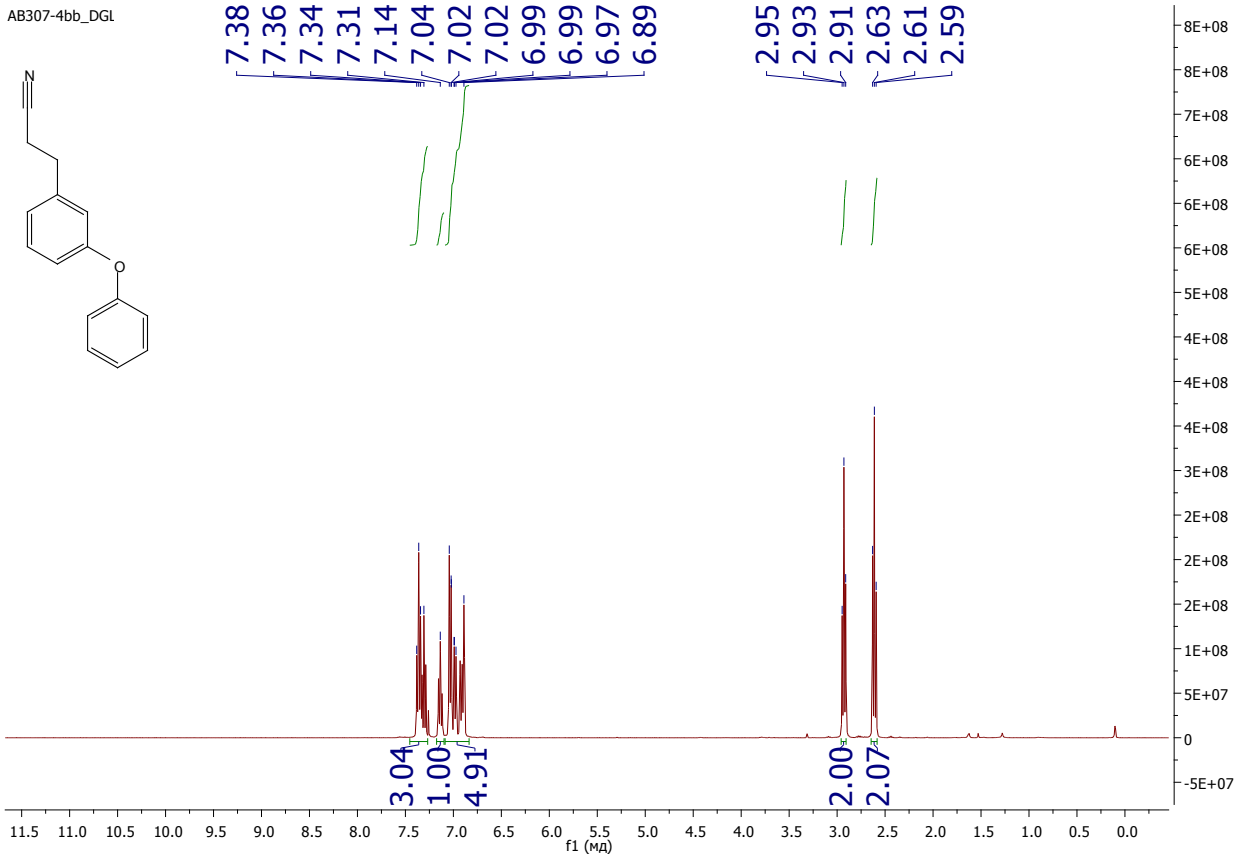


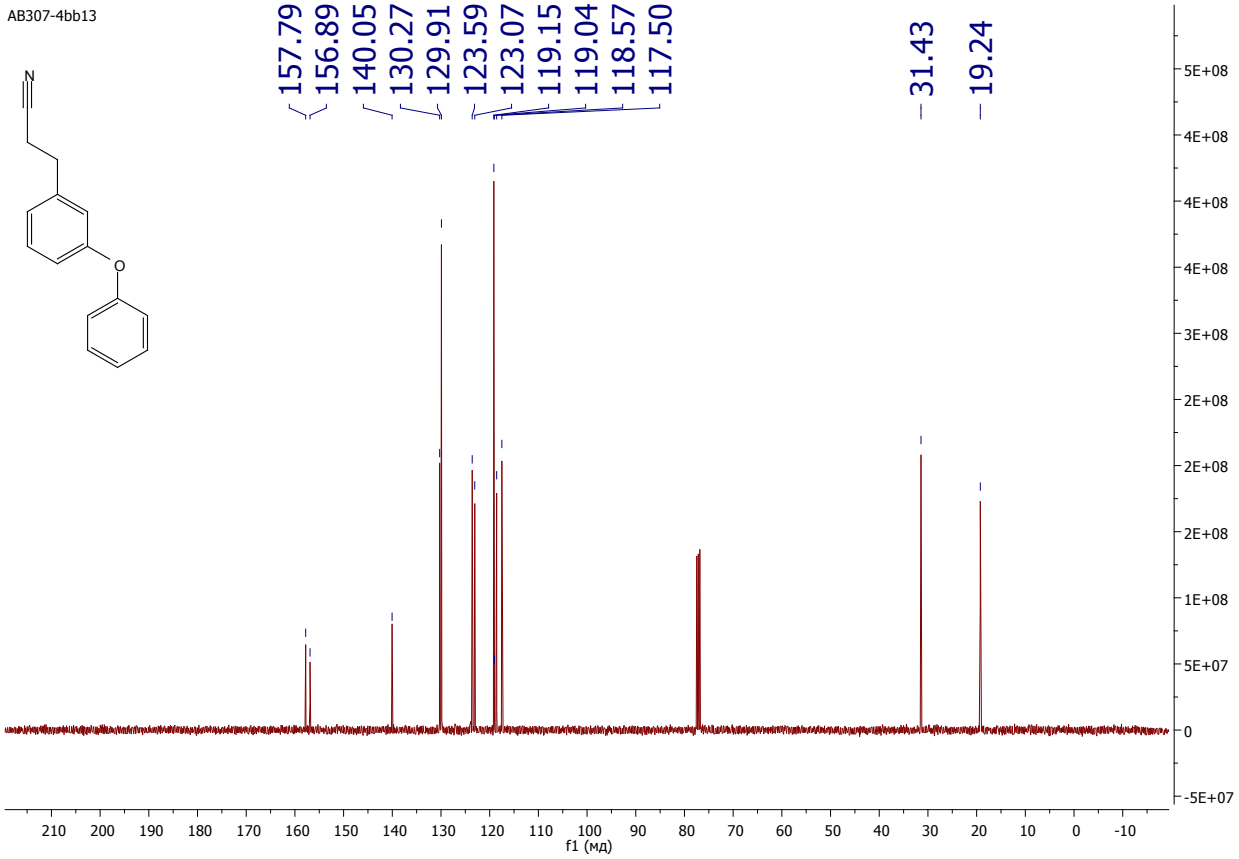
3-(4-hydroxyphenyl)propanenitrile (11)



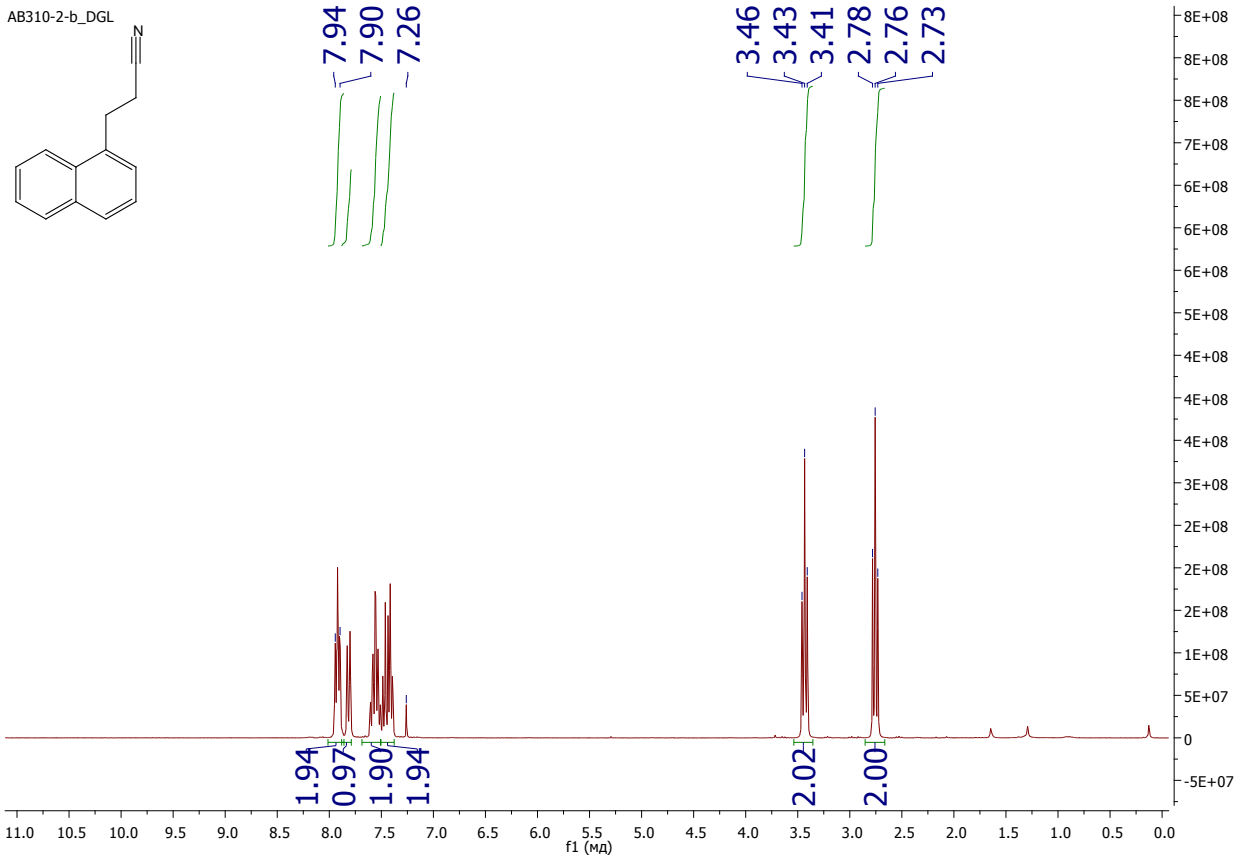


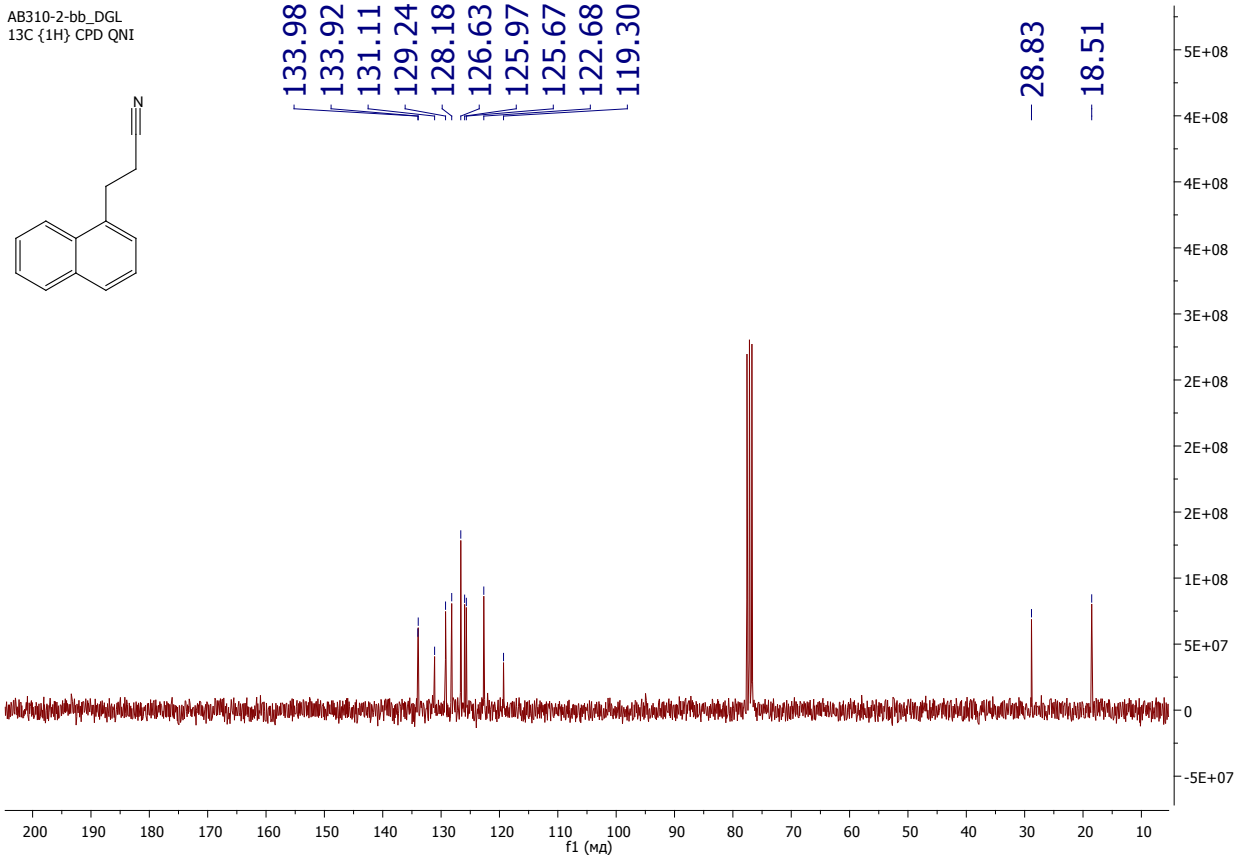
3-(3-phenoxyphenyl)propanenitrile (12)



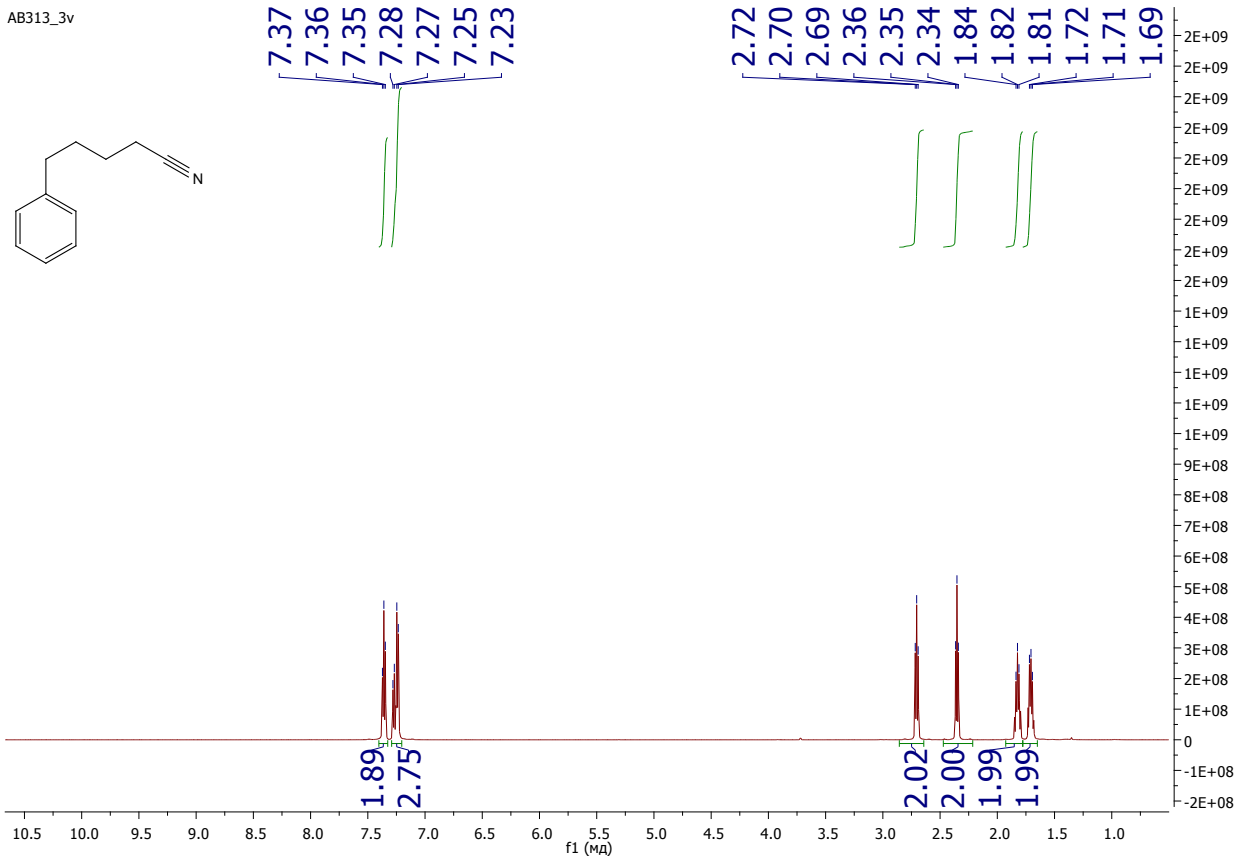


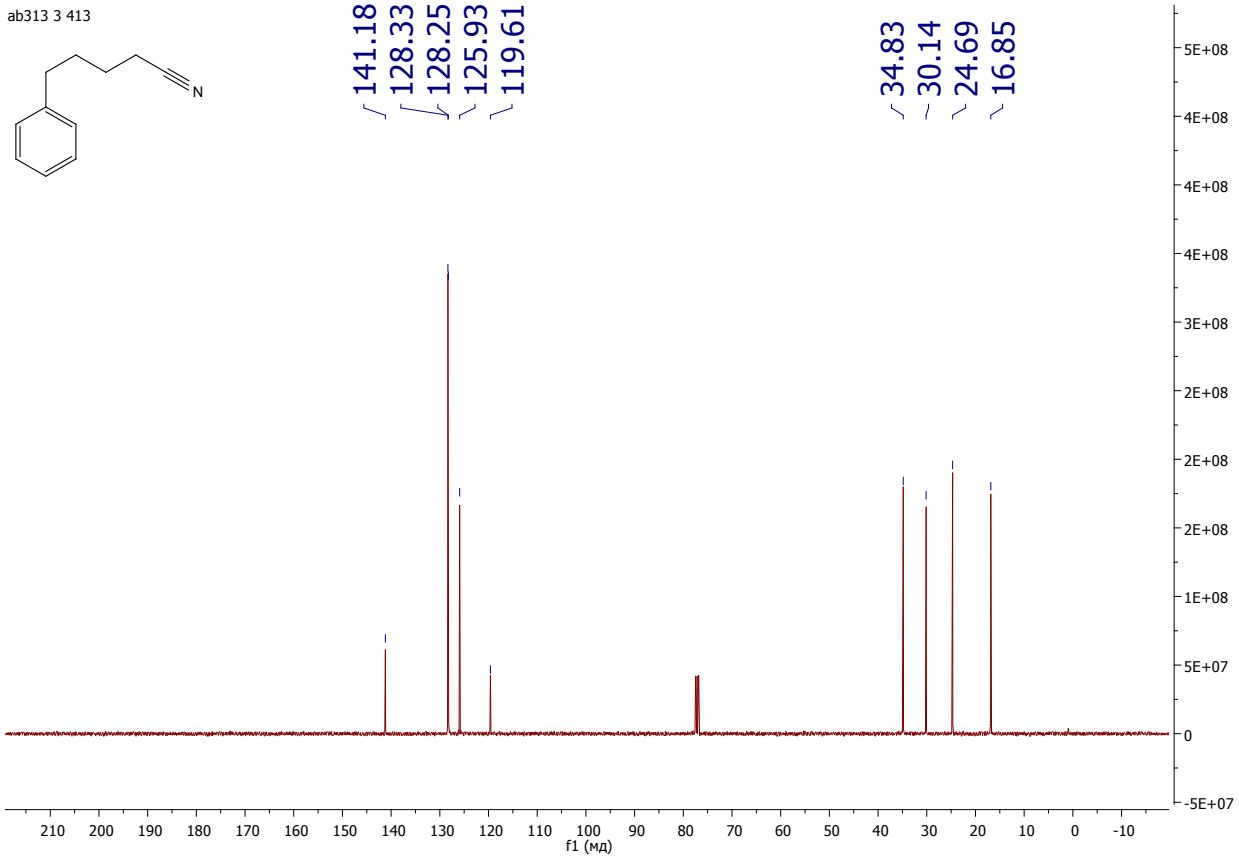
3-(naphthalen-1-yl)propanenitrile (13)



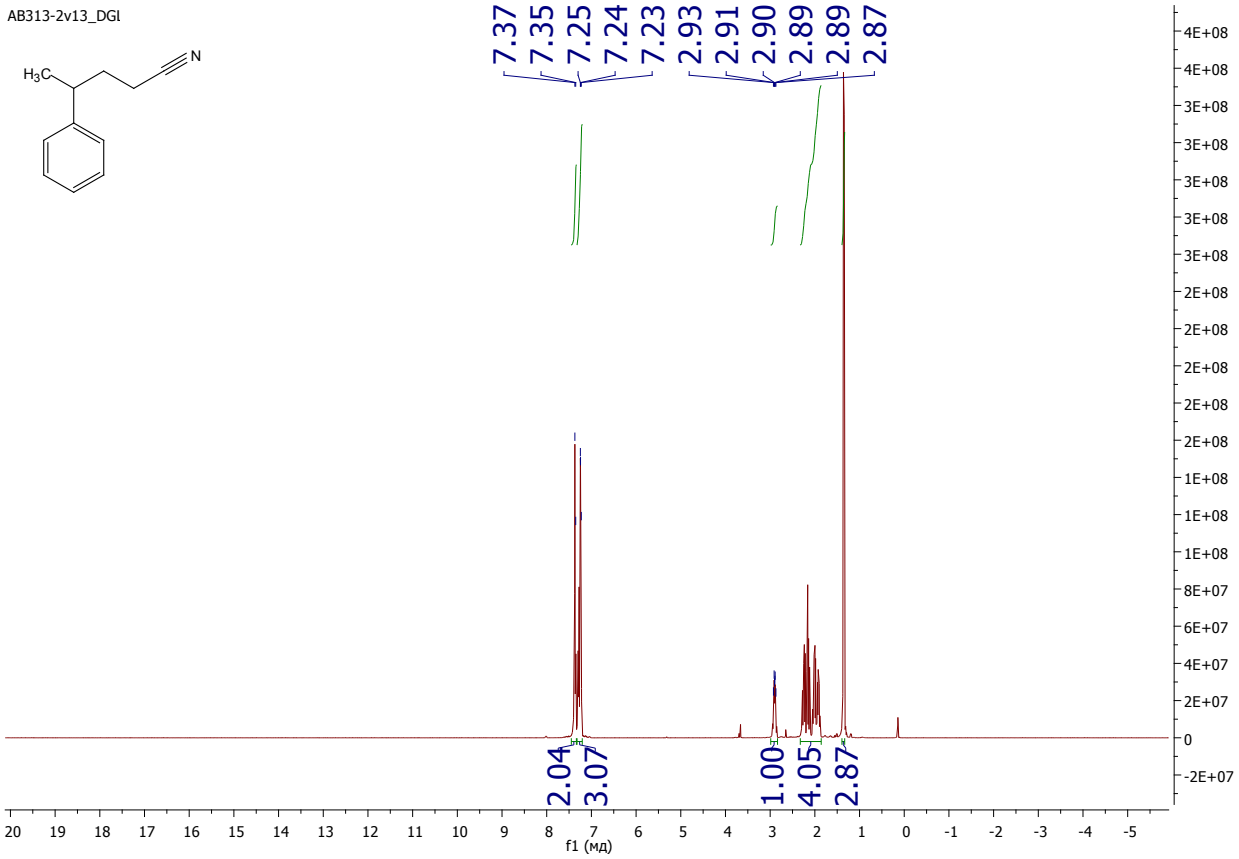


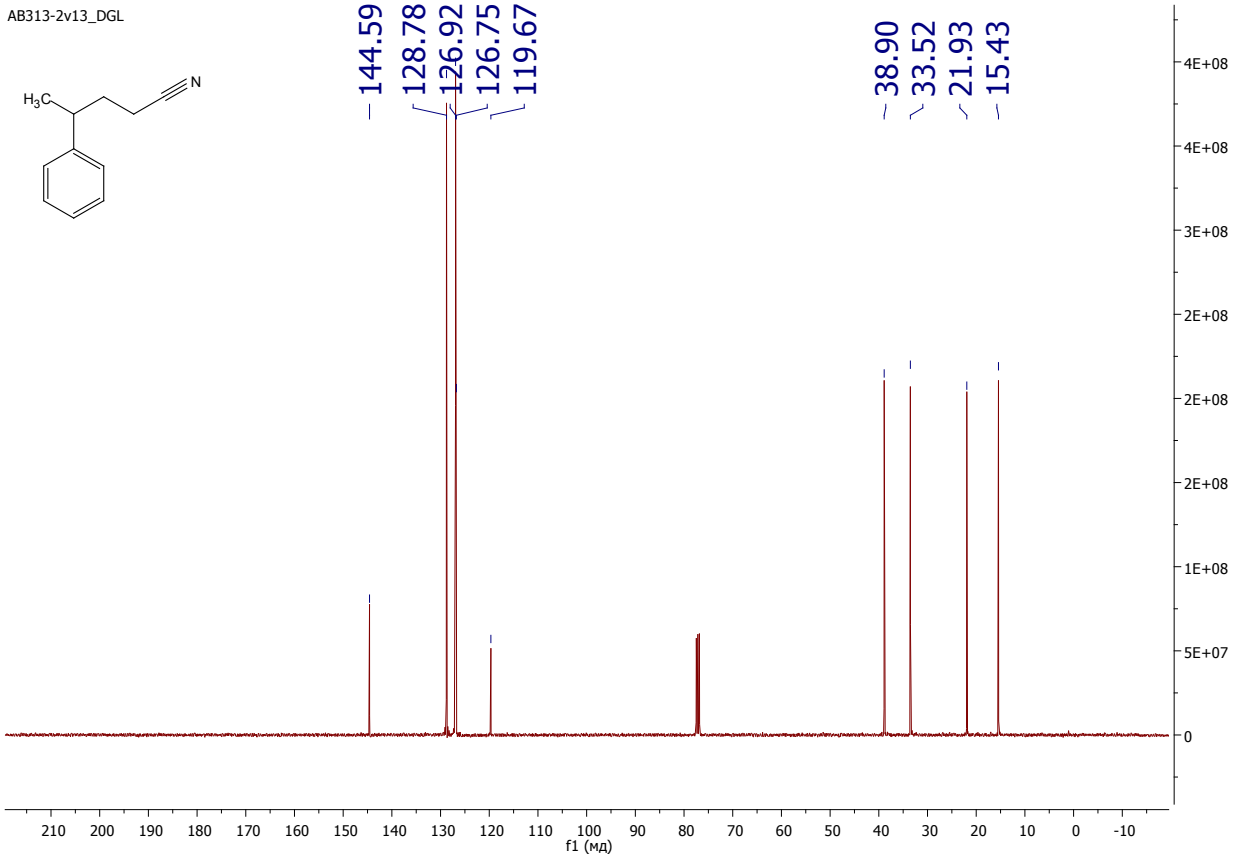
5-phenylpentanenitrile (14)



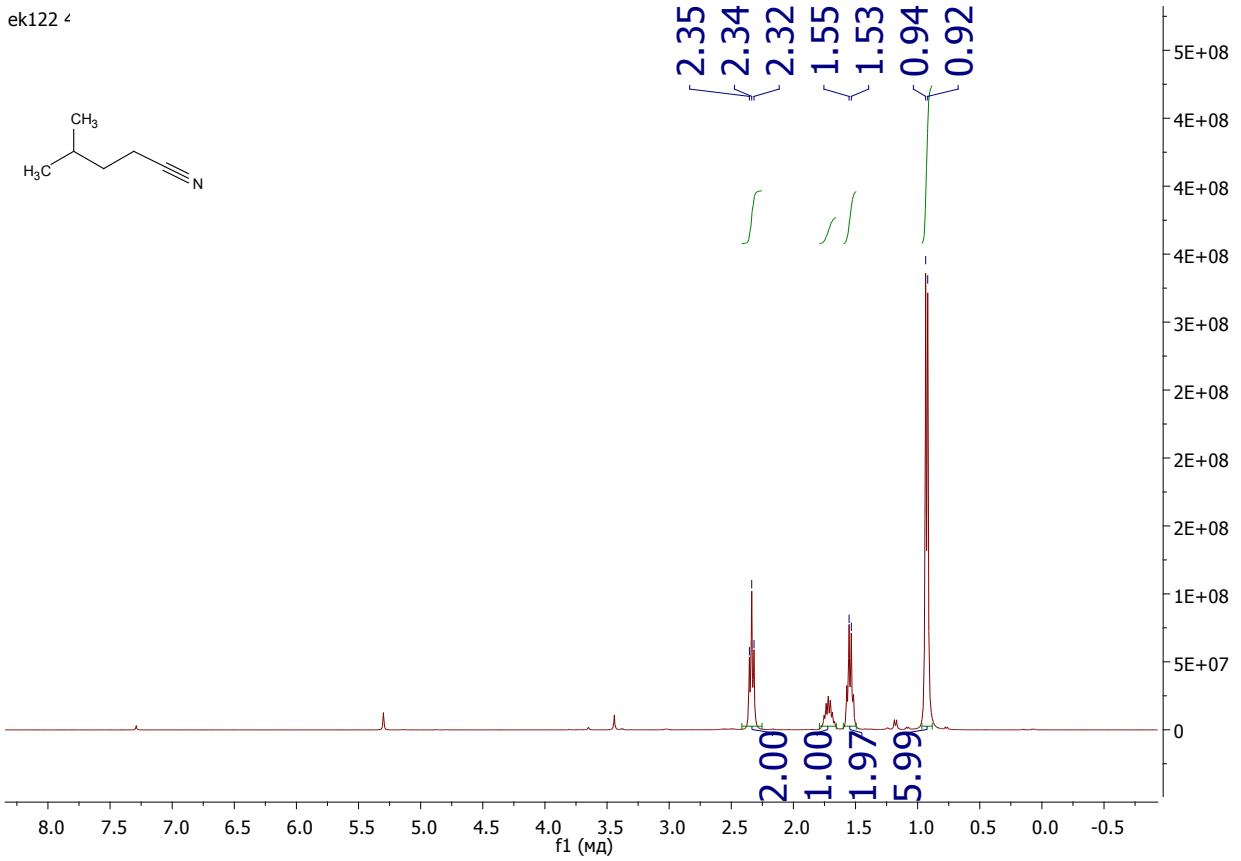


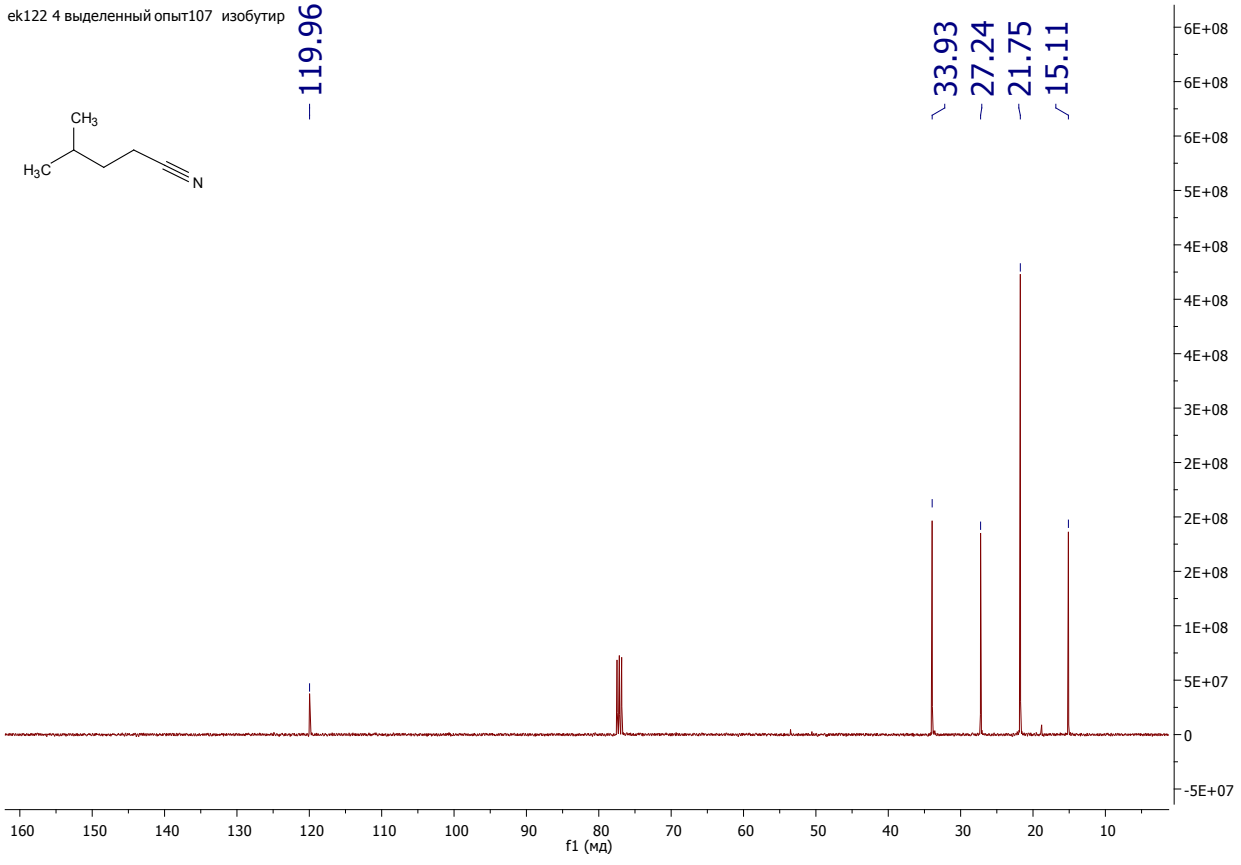
4-phenylpentanenitrile (15)



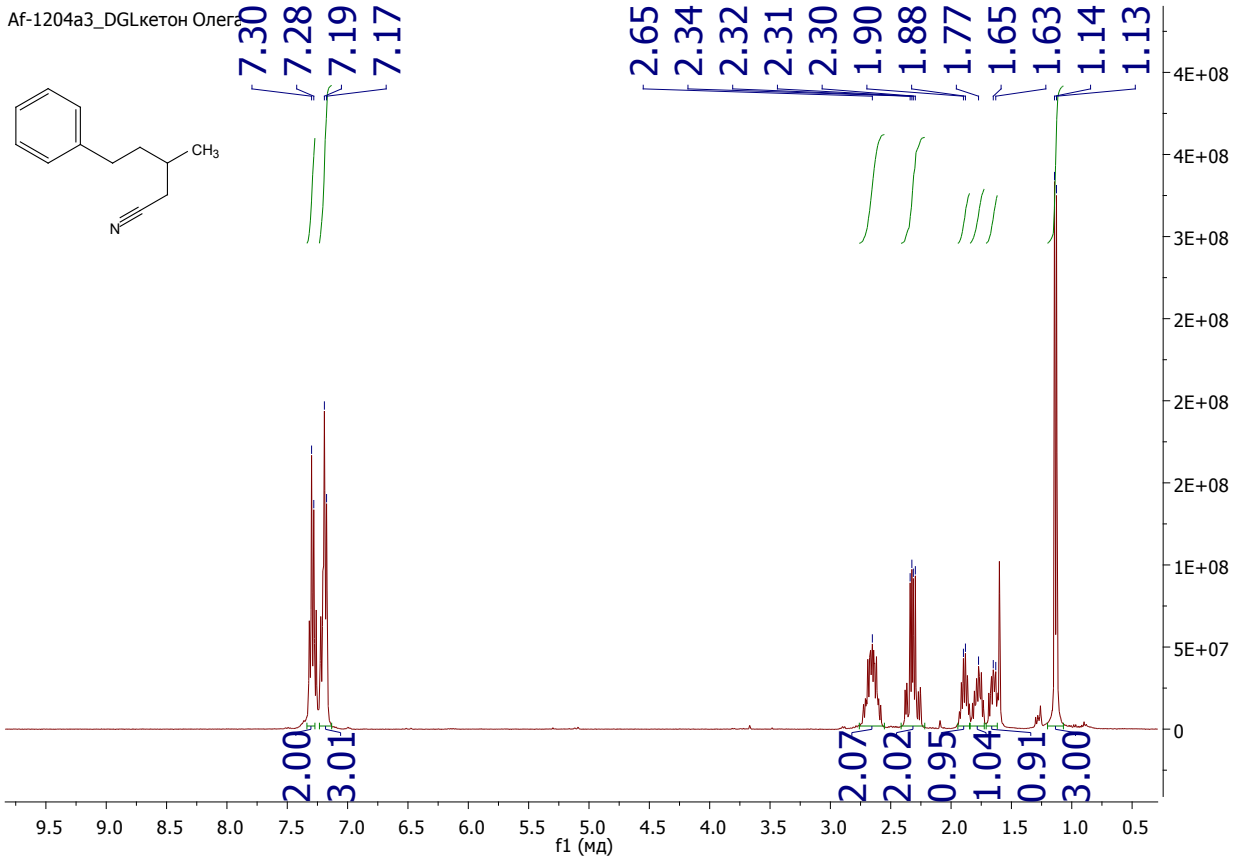


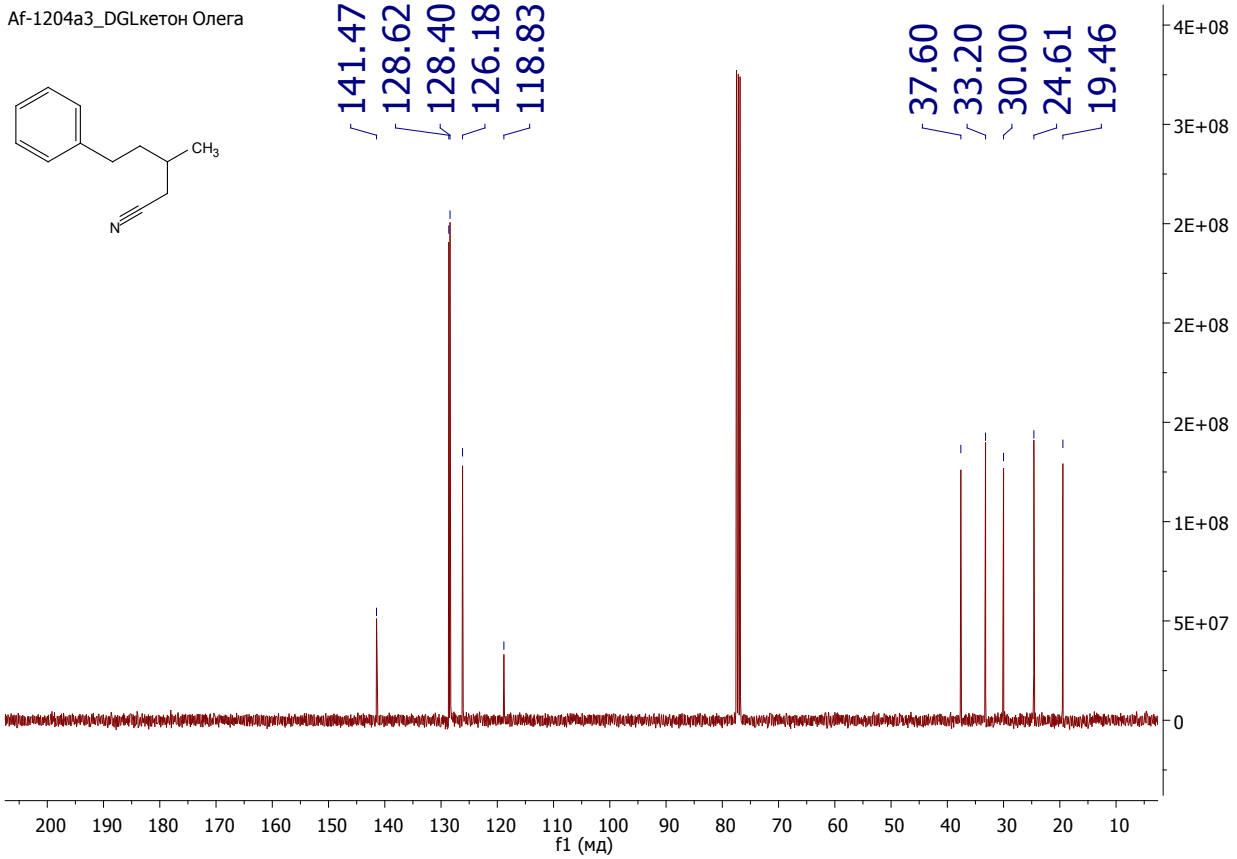
4-methylpentanenitrile (16)



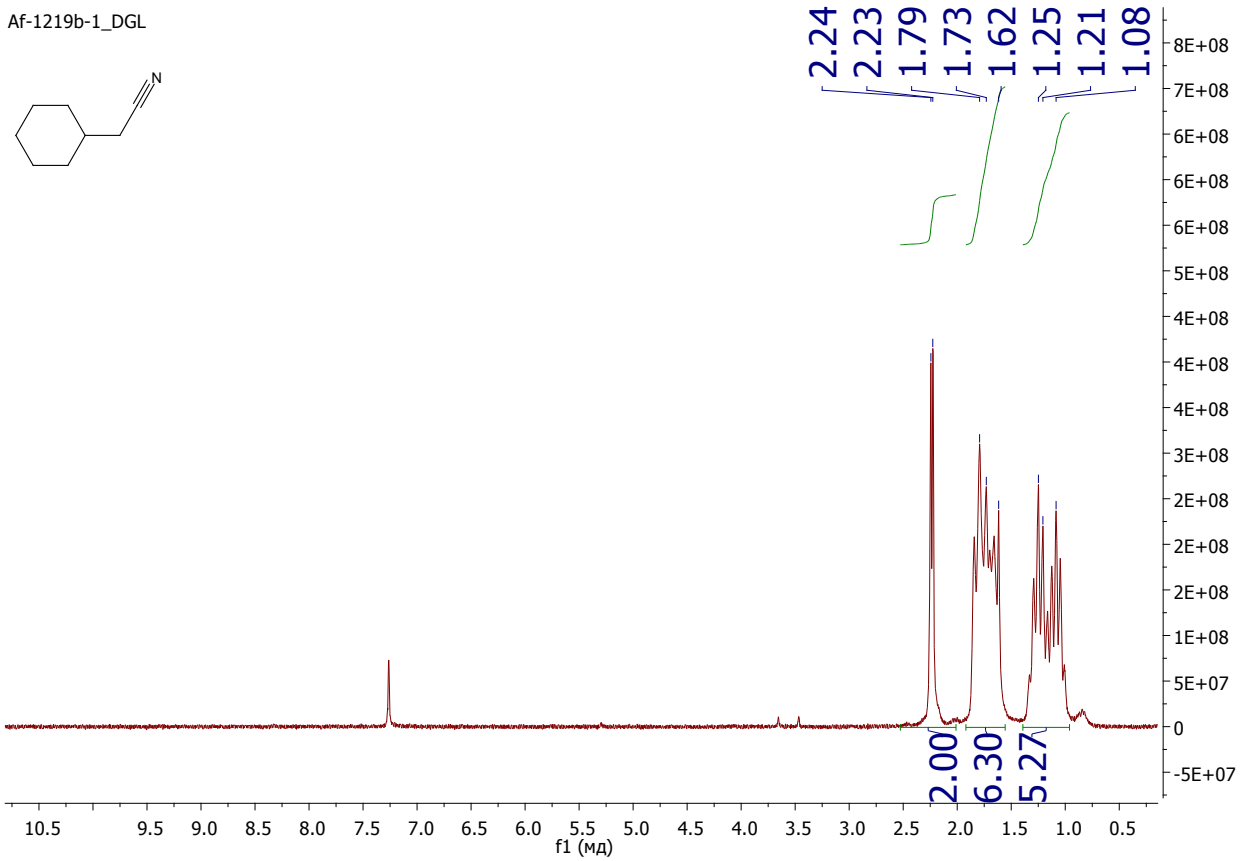


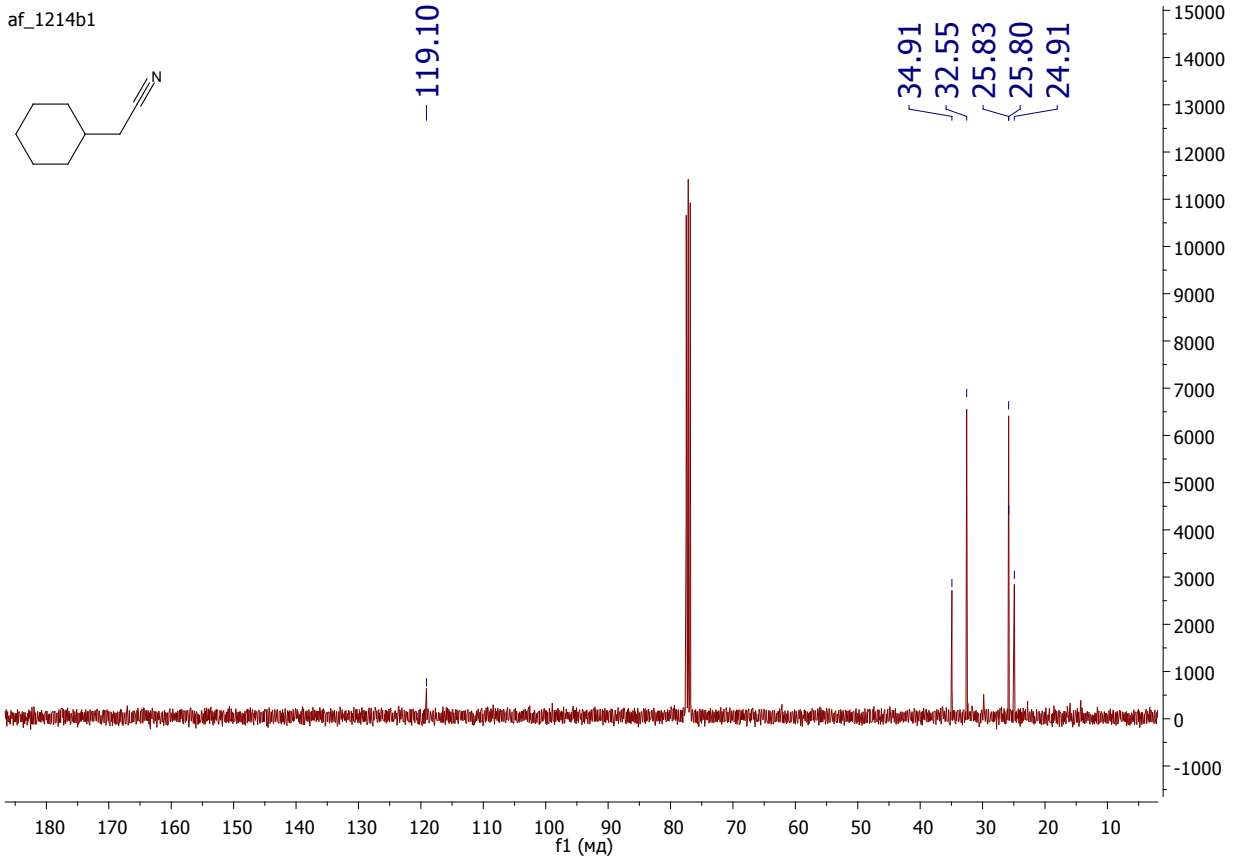
3-methyl-5-phenylpentanenitrile (17)



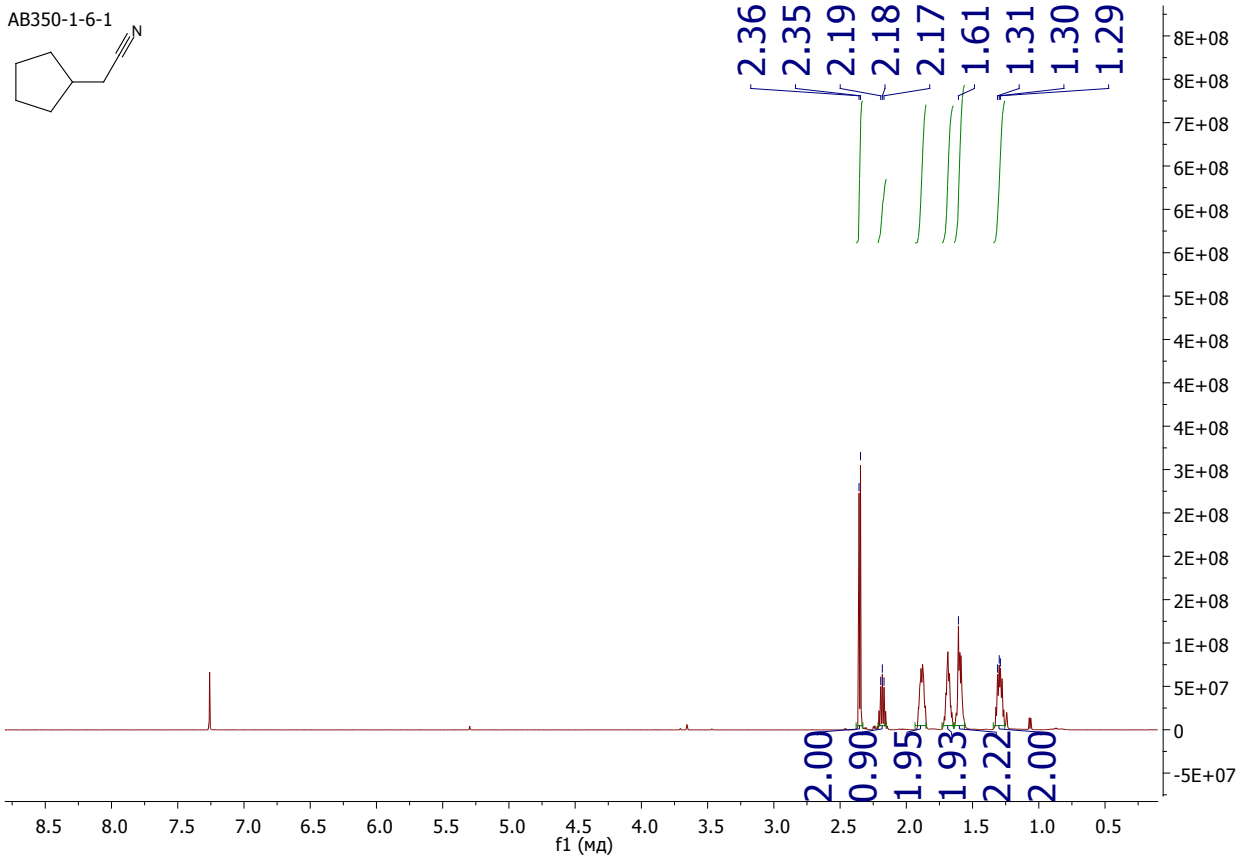


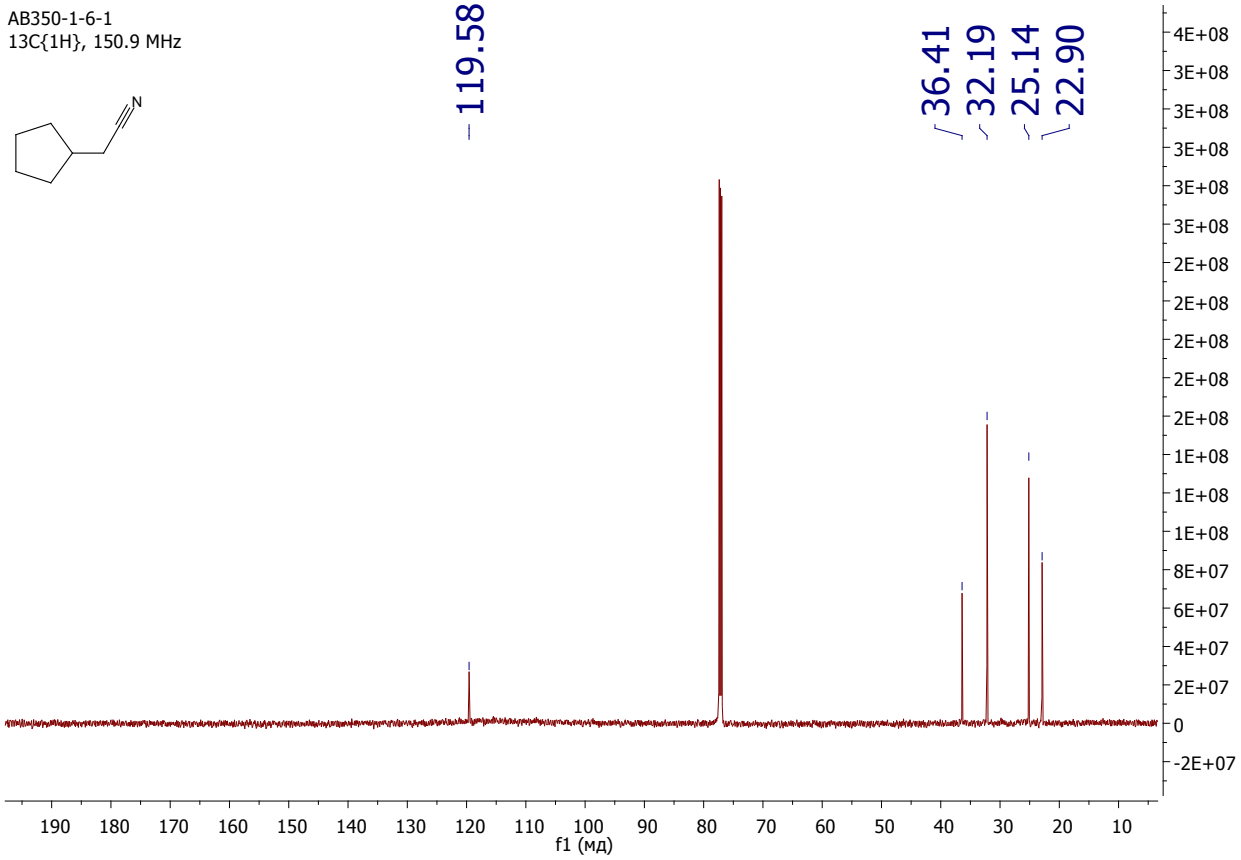
2-cyclohexylacetonitrile (18)



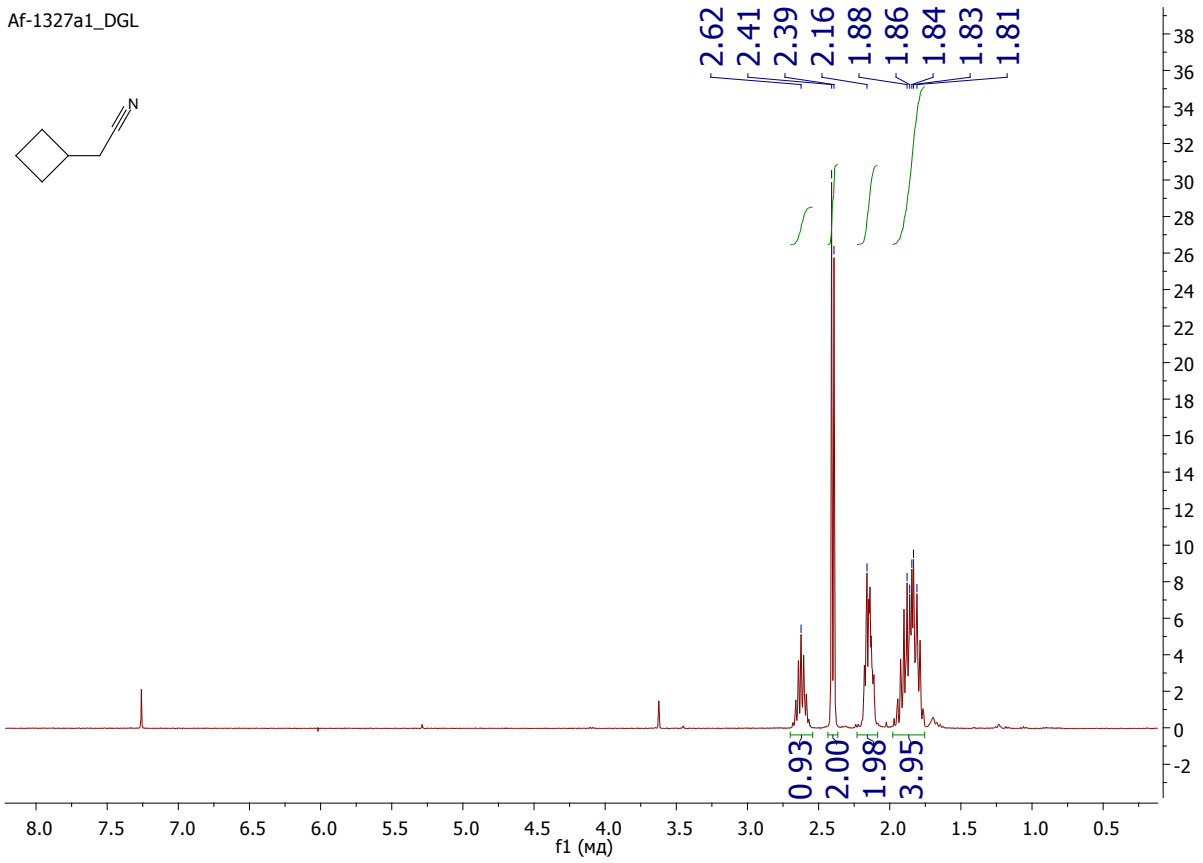


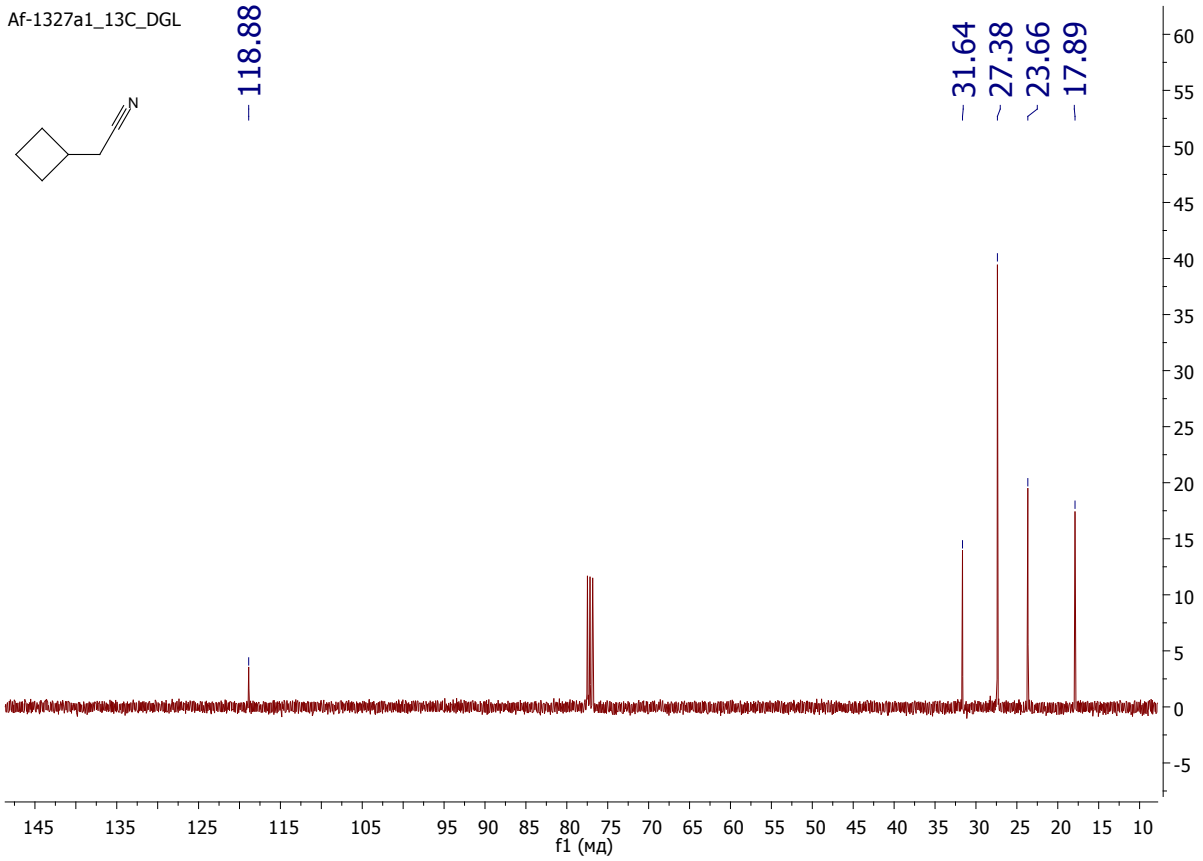
2-cyclopentylacetonitrile (19)





2-cyclobutylacetonitrile (20)





References

1 O. I. Afanasyev, A. A. Tsygankov, D. L. Usanov, D. S. Perekalin, N. V. Shvydkiy, V. I. Maleev, A. R. Kudinov, and D. Chusov, *ACS Catal.*, 2016, **6** (3), 2043–2046.

2 S. A. Runikhina, M. A. Arsenov, V. B. Kharitonov et al., *J. Organomet. Chem*., 2018, **867**, 106–112.

3 T. Sawaguchi, Y. Obora, *Chem. Lett.*, 2011, **40**, 1055–1057

4 P. N. Kolesnikov, D. L. Usanov, E. A. Barablina, V. I. Maleev, D. Chusov, *Org. Lett.,* 2014, **16**, 5068–5071

5 T. Kuwahara, T. Fukuyama, I. Ryu, *Chem. Lett*., 2013, **42**, 1163–1165

6 B. Anxionnat, D. G. Pardo, G. Ricci, J. Cossy, *Org. Lett*., 2011, **13** (15), 4084–4087

7 N. Z. Yagafarov, D. L. Usanov, A. P. Moskovets, N. D. Kagramanov, V. I. Maleev, D. Chusov, *ChemCatChem*, 2015, **7** (17), 2590–2593

8 C.-Z. Dong, A. Ahamada-Himidi, S. Plocki, D. Aoun, M. Touaibia, N. Meddad-Bel Habich, J. Huet, C. Redeuilh, J.-E. Ombetta, J.-J. Godfroid, F. Massico, F. Heymans, *Bioorganic & Medicinal Chemistry*, 2005, **13** (6), 1989-2007

9 Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y. and Liu L. *Adv.Synth.Catal*., 2012, **354** (13), 2465–2472

10 O. Vechorkin, V. Proust, X. Hu, *J. Am. Chem. Soc.*, 2009, **131** (28), 9756–9766

11 F. F. Fleming, W. Liu, *European Journal of Organic Chemistry*, 2009, **5**, 699–708

12 S. Alaux, M. Kusk, E. Sagot, J. Bolte, A. A. Jensen, H. Bräuner-Osborne, T. Gefflaut, and L. Bunch, *J. Med. Chem.*, 2005, **48** (25), 7980–7992

13 J. W. Bruno, T. J. Marks, F. D. Lewis, *J. Am. Chem. Soc.*, 1982, **104** (21), 5580–5585

14 J. Jin and M. Newcomb, *J. Org. Chem.*, 2008, **73** (12), 4740–4742

15 J. L. Vidal and W. E. Walker, *Inorg. Chem.*, 1980, **19**, 896–903.

16 P. N. Kolesnikov, D. L. Usanov, E. A. Barablina, V. I. Maleev and D. Chusov, *Org. Lett.*, 2014, **16**, 5068–5071.