Deciphering the Knoevenagel Condensation: Towards a Catalyst-Free and Water-Mediated Process

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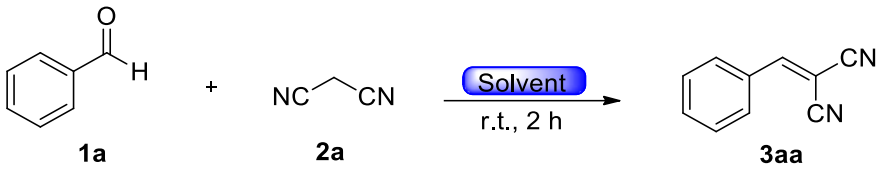
SUPPORTING INFORMATION

General Remarks

Chromatographic purification of products was accomplished using forced-flow chromatography on Merck® Kieselgel 60 230-400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid or potassium permanganate stains. Melting points were determined on a Buchi® 530 hot stage apparatus and are uncorrected. Mass spectra (ESI) were recorded on a Finningan® Surveyor MSQ LC-MS spectrometer. HRMS spectra were recorded on Bruker® Maxis Impact QTOF spectrometer. ^{1}H-NMR, ^{19}F-NMR and ^{13}C-NMR spectra were recorded on Varian® Mercury (200 MHz, 188 MHz and 50 MHz, respectively) and on an Avance III HD Brucker (400 MHz, 376 MHz, and 100 MHz, respectively) and are internally referenced to residual solvent signals. Data for ^{1}H-NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal), coupling constant and assignment. Data for ^{13}C-NMR are reported in terms of chemical shift (δ ppm). Mass spectra and conversions of the reactions were also recorded on a Shimadzu® GCMS-QP2010. The reactions were performed on a BUCHI Syncore Polyvap R96 apparatus.

Optimization of the Knoevenagel Condensation between Benzaldehyde (1a) and Malononitrile (2a)

Solvent Study



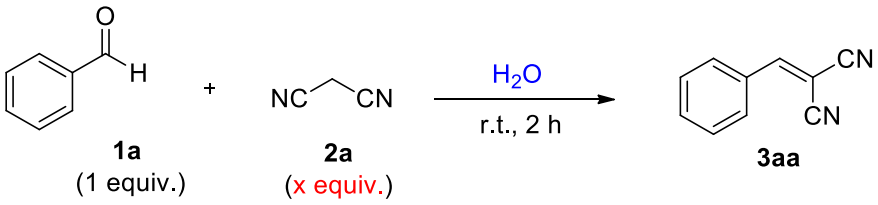
1a **2a** **3aa**

Entry	Solvent	Yield (%)[a]
1	H_2O	100 (85)
2	H_2O (HPLC)	95
3	H_2O (plastic bottle)	99 (78)
4	H_2O (deionized)	93 (76)
5	*t*-BuOH	13
6	MeOH (anhydrous)	85 (67)
7	EtOH	55 (43)
8	*i*-PrOH	30
9	$CHCl_3$	0
10	DMSO (dry)	64 (44)
11	DMF (anhydrous)	26 (10)
12	Pet. Eth.	0
13	CH_2Cl_2	0
14	EtOAc	0
15	MeCN	0
16	Toluene	0
17	No Solvent	0

[a]Yield determined by ^{1}H-NMR using internal standard, yield of product after isolation by column chromatography in parenthesis. The reaction was performed with benzaldehyde (**1a**) (53 mg, 0.50 mmol), malononitrile (**2a**) (66 mg, 1.00 mmol) in solvent (1 mL) for 2 h.

Optimization of the Knoevenagel Condensation between Benzaldehyde (1a) and Malononitrile (2a)

Malononitrile Equivalent study

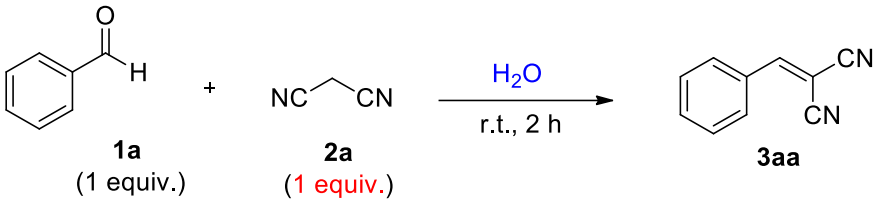


Entry	2a (equiv.)	Yield (%)[a]
1	2	100 (83)
2	1.5	100 (81)
3	1.0	100 (80)

[a]Yield determined by ^{1}H-NMR using internal standard, yield of product after isolation by column chromatography in parenthesis. The reaction was performed with benzaldehyde (**1a**) (53 mg, 0.50 mmol), malononitrile (**2a**) in H_2O (1 mL) for 2 h.

Optimization of the Knoevenagel Condensation between Benzaldehyde (1a) and Malononitrile (2a)

Solvent Amount Study



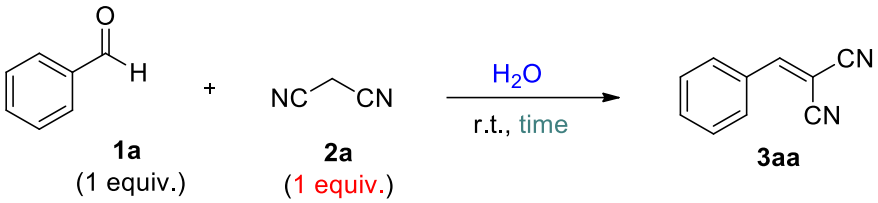
1a (1 equiv.) **2a** (1 equiv.) **3aa**

Entry	Solvent (mL)	Yield (%)[a]
1	0.5	83 (60)
2	1	100 (80)
3	2	97 (72)

[a]Yield determined by ^{1}H-NMR using internal standard, yield of product after isolation by column chromatography in parenthesis. The reaction was performed with benzaldehyde (**1a**) (53 mg, 0.50 mmol), malononitrile (**2a**) (33 mg, 0.50 mmol) in H_2O for 2 h.

Optimization of the Knoevenagel Condensation between Benzaldehyde (1a) and Malononitrile (2a)

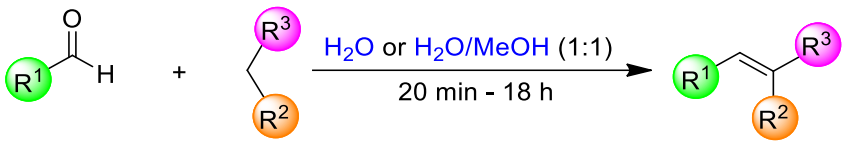
Reaction Time Study



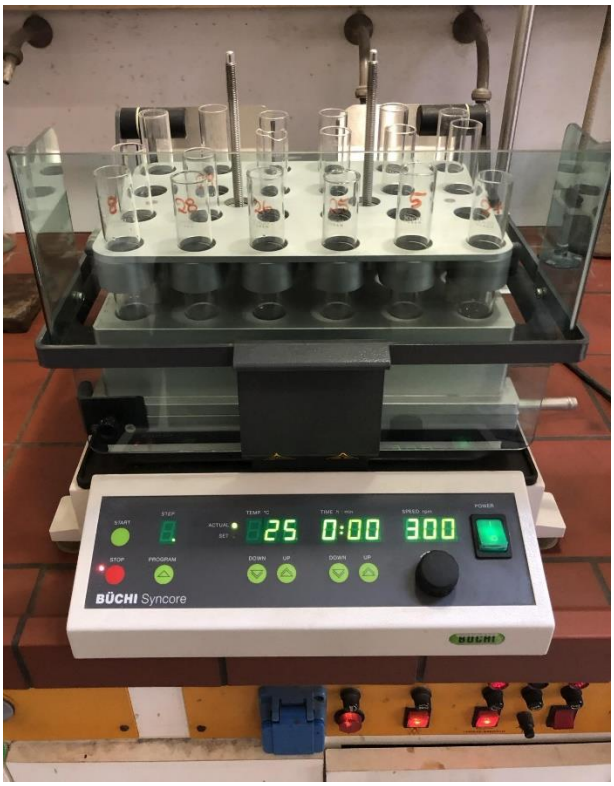
Entry	Time (h)	Yield (%)[a]
1	0.5	(52)
2	1	(60)
3	1.5	(66)
4	2	100 (83)
5	4	100 (90)
6	18	100 (95)
7[b]	2	(45)
8[b]	18	(60)

[a]Yield determined by ^{1}H-NMR using internal standard, yield of product after isolation by column chromatography in parenthesis. The reaction was performed with benzaldehyde (**1a**) (53 mg, 0.50 mmol), malononitrile (**2a**) (33 mg, 0.50 mmol) in solvent (1 mL), [b]Heptanal (**1b**) (57 mg, 0.50 mmol) was used instead of benzaldehyde (**1a**).

General Procedure for the Water-mediated Knoevenagel Condensation

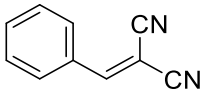


A glass vial containing aldehyde **1** (1.00 mmol, 1.00 equiv.) and the active methylene compound **2** (1.00 mmol, 1.00 equiv.) in H_2O (2 mL), or a mixture of H_2O/MeOH: 1/1 (2 mL) if mentioned, was left stirring until reaction completion (monitored by TLC, 20 min – 18 h) in a BUCHI Syncore apparatus, where a maximum amount of 24 reactions were performed simultaneously. The reaction mixture was evaporated *in vacuo* and the pure product was obtained without further purification. In the few cases where starting material was observed in the crude ^{1}H-NMR, the product was isolated via column chromatography.



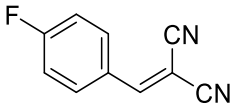
Scheme 1: BUCHI Syncore apparatus utilised for the parallel Knoevenagel reactions.

2-Benzylidenemalononitrile (3aa)[1]



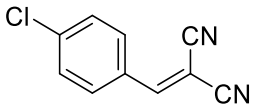
White solid; Yield 90%; Reaction time: 4 h; mp 80-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.91 (2H, d, J = 7.5 Hz, ArH), 7.78 (1H, s, =CH), 7.64 (1H, t, J = 7.5 Hz, ArH), 7.55 (2H, t, J = 7.5 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.9, 134.6, 130.9, 130.7, 129.6, 113.7, 112.5, 82.9; MS (ESI) m/z 177 $[M+Na]^+$.

2-(4-Fluorobenzylidene)malononitrile (3ab)[1]



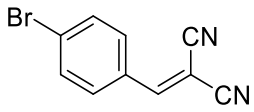
White solid; Yield 88%; Reaction time: 4 h; mp 122-124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02-7.92 (2H, m, ArH), 7.74 (1H, s, =CH), 7.29-7.20 (2H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 166.1 (d, J = 260.2 Hz), 158.3, 133.4 (d, J = 9.8 Hz), 127.3 (d, J = 3.6 Hz), 117.2 (d, J = 22.1 Hz), 113.5, 112.5, 82.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ: -100.00; MS (ESI) m/z 195 $[M+Na]^+$.

2-(4-Chlorobenzylidene)malononitrile (3ac)[2]



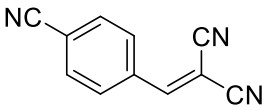
White solid; Yield 97%; Reaction time: 5 h; mp 144-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.86 (2H, d, J = 8.0 Hz, ArH), 7.73 (1H, s, =CH), 7.52 (2H, d, J = 8.0 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.3, 141.2, 131.8, 130.1, 129.2, 113.4, 112.3, 83.3; MS (ESI) m/z 211 $[M+Na]^+$.

2-(4-Bromobenzylidene)malononitrile (3ad)[3]



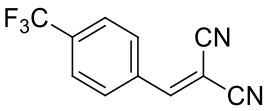
White solid; Yield 90%; Reaction time: 18 h; mp 159-161 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.77 (2H, d, J = 8.3 Hz, ArH), 7.72 (1H, s, =CH), 7.68 (2H, d, J = 8.3 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.4, 133.0, 131.8, 129.9, 129.6, 113.4, 112.3, 83.4; MS (ESI) m/z 255 $[M+Na]^+$.

2-(4-Cyanobenzylidene)malononitrile (3ae)[4]



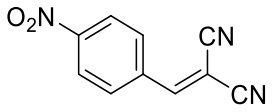
White solid; Yield 93%; Reaction time: 4 h; mp 144-146 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.03-7.97 (2H, m, ArH), 7.87-7.80 (3H, m, ArH and =CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.3, 134.2, 133.1, 130.7, 117.3, 117.2, 112.7, 111.7, 86.9; MS (ESI) m/z 202 $[M+Na]^+$.

2-(4-(Trifluoromethyl)benzylidene)malononitrile (3ef)[3]



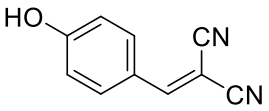
White solid; Yield 99%; Reaction time: 4 h; mp 106-108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.02 (2H, d, J = 8.2 Hz, ArH), 7.86 (1H, s, =CH), 7.80 (2H, d, J = 8.2 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.1, 135.2 (q, J = 33.5 Hz), 133.7, 130.7, 126.5 (q, J = 3.7 Hz), 123.9 (q, J = 273.9 Hz), 112.9, 111.9, 85.9; MS (ESI) m/z 245 $[M+Na]^+$.

2-(4-Nitrobenzylidene)malononitrile (3ag)[1]



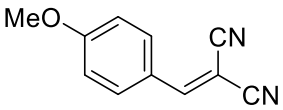
Yellow solid; Yield 98%; Reaction time: 5 h; mp 160-162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.39 (2H, d, J = 8.4 Hz, ArH), 8.08 (2H, d, J = 8.4 Hz, ArH), 7.89 (1H, s, =CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.8, 150.4, 135.8, 131.1, 124.6, 112.6, 111.6, 87.5; MS (ESI) m/z 222 $[M+Na]^+$.

2-(4-Hydroxybenzylidene)malononitrile (3ah)[5]



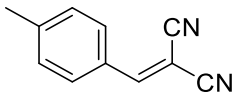
Yellow solid; Yield 90%; Reaction time: 30 min; mp 180-182 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ: 7.90-7.84 (3H, m, ArH and =CH), 6.90 (2H, d, J = 8.2 Hz, ArH), 4.99 (1H, br s, OH); **^{13}C NMR** (100 MHz, CD_3OD) δ: 165.4, 161.0, 135.0, 124.5, 117.5, 115.9, 115.0, 77.2; MS (ESI) m/z 193 $[M+Na]^+$.

2-(4-Methoxybenzylidene)malononitrile (3ai)[1]



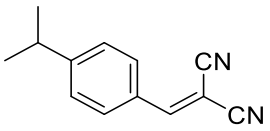
Yellow solid; Yield 94%; Reaction time: 4 h; mp 108-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.91 (2H, d, J = 8.0 Hz, ArH), 7.65 (1H, s, =CH), 7.01 (2H, d, J = 8.0 Hz, ArH), 3.91 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 164.8, 158.9, 133.4, 124.0, 115.1, 114.4, 113.3, 78.5, 55.8; MS (ESI) m/z 207 $[M+Na]^+$.

2-(4-Methylbenzylidene)malononitrile (3aj)[1]



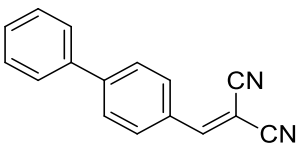
White solid; Yield 99%; Reaction time: 18 h; mp 132-134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.82 (2H, d, J = 7.9 Hz, ArH), 7.22 (1H, s, =CH), 7.34 (2H, d, J = 7.9 Hz, ArH), 2.46 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.7, 146.4, 130.9, 130.4, 128.5, 114.0, 112.8, 81.2, 22.0; MS (ESI) m/z 191 $[M+Na]^+$.

2-(4-Isopropylbenzylidene)malononitrile (3ak)



Yellow oil; Yield 93%; Reaction time: 8 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.85 (2H, d, J = 8.0 Hz, ArH), 7.73 (1H, s, =CH), 7.39 (2H. d, J = 8.0 Hz, ArH), 3.00 (1H, hept, J = 6.9 Hz, CH), 1.28 (6H, d, J = 6.9 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.7, 156.8, 131.0, 128.6, 127.7, 113.9, 112.8, 80.9, 34.3, 23.3; HRMS exact mass calculated for $[M+Na]^+$ ($C_{13}H_{12}N_2Na^+$) requires m/z 219.0893, found m/z 219.0891.

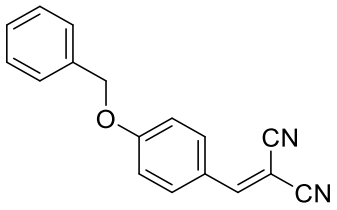
2-([1,1'-Biphenyl]-4-ylmethylene)malononitrile (3al)



Yellow solid; Yield 87%; Reaction time: 7 h; mp 142-144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.99 (2H, d, J = 8.0 Hz, ArH), 7.82-7.74 (3H, m, ArH and =CH), 7.65 (2H, d, J = 7.5 Hz, ArH), 7.54-7.42 (3H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 159.2, 147.3, 138.9, 131.4, 129.8, 129.2, 129.0, 128.0, 127.2, 113.9, 112.8, 81.9; HRMS

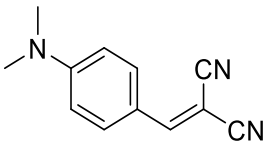
exact mass calculated for $[M+H]^+$ ($C_{16}H_{11}N_2$) requires m/z 231.0917, found m/z 231.0916.

2-(4-(Benzyloxy)benzylidene)malononitrile (3am)[6]



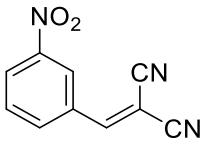
Yellow solid; Yield 78%; Reaction time: 4 h; mp 152-154 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.91 (2H, d, J = 8.5 Hz, ArH), 7.64 (1H, s, =CH), 7.45-7.34 (5H, m, ArH), 7.08 (2H, d, J = 8.5 Hz, ArH), 5.17 (2H, s, OCH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 163.9, 158.8, 135.4, 133.4, 128.8, 128.5, 127.5, 124.2, 115.9, 114.4, 113.3, 78.7, 70.5; MS (ESI) m/z 283 $[M+Na]^+$.

2-(4-(Dimethylamino)benzylidene)malononitrile (3an)[7]



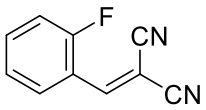
Orange solid; Yield 66%; Reaction time: 8 h; mp 174-176 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (2H, d, J = 8.9 Hz, ArH), 7.44 (1H, s, =CH), 6.70 (2H, d, J = 8.9 Hz, ArH), 3.14 (6H, s, 2 x NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.0, 154.1, 133.7, 119.4, 115.9, 114.9, 111.7, 71.9, 40.1; MS (ESI) m/z 220 $[M+Na]^+$.

2-(3-Nitrobenzylidene)malononitrile (3ao)[2]



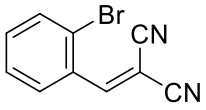
Yellow solid; Yield 99%; Reaction time: 3 h; mp 102-104 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.68 (1H, s, ArH), 8.40 (1H, d, J = 8.2 Hz, ArH), 8.31 (1H, d, J = 8.2 Hz, ArH), 7.94 (1H, s, =CH), 7.80 (1H, t, J = 8.2 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.2, 148.5, 134.9, 131.9, 130.9, 128.1, 125.4, 112.6. 111.6, 86.5; MS (ESI) m/z 222 $[M+Na]^+$.

2-(2-Fluorobenzylidene)malononitrile (3ap)[8]



White solid; Yield 87%; Reaction time: 5 h; mp 108-110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.28 (1H, t, J = 7.5 Hz, ArH), 8.10 (1H, s, =CH), 7.64 (1H, dd, J = 9.5 and 7.5 Hz, ArH), 7.34 (1H, t, J = 7.5 Hz, ArH), 7.23 (1H, t, J = 9.5 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 161.3 (d, J = 259.4 Hz), 151.3 (d, J = 8.1 Hz), 136.7 (d, J = 9.5 Hz), 128.5, 125.3 (d, J = 3.7 Hz), 119.5, 116.5 (d, J = 21.5 Hz), 113.4, 112.2, 84.5; **^{19}F NMR** (375 MHz, $CDCl_3$) δ: -110.94; MS (ESI) m/z 195 $[M+Na]^+$.

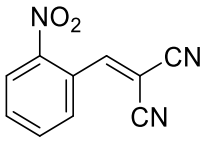
2-(2-Bromobenzylidene)malononitrile (3aq)[9]



White solid; Yield 85%; Reaction time: 18 h; mp 88-90 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.22 (1H, s, =CH), 8.12 (1H, d, J = 7.8 Hz, ArH), 7.75 (1H, d, J = 7.8 Hz,

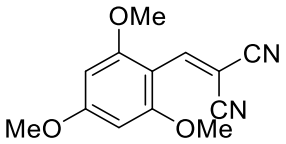
ArH), 7.53-7.43 (2H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.2, 134.9, 134.0, 130.7, 129.8, 128.3, 126.4, 113.1, 111.8, 86.0; MS (ESI) m/z 255 $[M+Na]^+$.

2-(2-Nitrobenzylidene)malononitrile (3ar)[10]



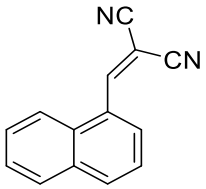
Light brown solid; Yield 96%; Reaction time: 4 h; mp 133-135 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.45 (1H, s, =CH), 8.35 (1H, d, J = 8.2 Hz, ArH), 7.91-7.78 (3H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 158.8, 146.7, 134.9, 133.4, 130.4, 126.7, 125.8, 112.2, 110.9, 88.5; MS (ESI) m/z 222 $[M+Na]^+$.

2-(2,4,6-Trimethoxybenzylidene)malononitrile (3as)



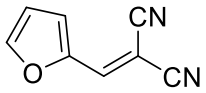
Yellow solid; Yield 81%; Reaction time: 1 h; mp 166-168 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.89 (1H, s, =CH), 6.07 (2H, s, ArH), 3.89 (9H, s, 3 x OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 167.1, 161.7, 150.4, 116.5, 113.8, 104.6, 90.3, 80.3, 55.7, 55.3; HRMS exact mass calculated for $[M+Na]^+$ ($C_{13}H_{12}N_2O_3Na^+$) requires m/z 267.0740, found m/z 267.0740.

2-(Naphthalen-2-ylmethylene)malononitrile (3at)[4]



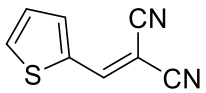
Yellow solid; Yield 99%; Reaction time: 7 h; mp 160-162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.60 (1H, s, =CH), 8.28 (1H, d, J = 7.5 Hz, ArH), 8.11 (1H, d, J = 8.0 Hz, ArH), 7.96 (2H, d, J = 8.0 Hz, ArH) 7.72-7.59 (3H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.7, 134.9, 133.5, 131.0, 129.4, 128.6, 128.5, 127.5, 127.3, 125.4, 122.3, 113.7, 112.5, 86.2; MS (ESI) m/z 227 $[M+Na]^+$.

2-(Furan-2-ylmethylene)malononitrile (3au)[4]



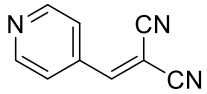
Pale yellow solid; Yield 99%; Reaction time: 4 h; mp 72-74 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.80 (1H, s, =CH), 7.56-7.49 (1H, m, ArH), 7.34 (1H, d, J = 3.0 Hz, ArH), 6.73-6.69 (1H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 149.5, 147.9, 143.0, 123.6, 114.4, 113.7, 112.5, 77.2; MS (ESI) m/z 167 $[M+Na]^+$.

2-(Thiophen-2-ylmethylene)malononitrile (3av)[3]



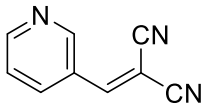
Light brown solid; Yield 96%; Reaction time: 90 min; mp 92-94 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.94-7.89 (2H, m, ArH and =CH), 7.83 (1H, d, J = 3.6 Hz, ArH), 7.32-7.27 (1H, m, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 151.2, 138.3, 136.9, 135.3, 128.9, 113.7, 112.9, 78.0; MS (ESI) m/z 183 $[M+Na]^+$.

2-(Pyridin-4-ylmethylene)malononitrile (3aw)[11]



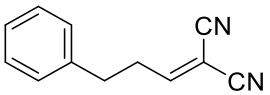
Red solid; Yield 81%; Reaction time: 20 min; mp 98-100 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.87 (2H, d, J = 4.7 Hz, ArH), 7.79 (1H, s, =CH), 7.67 (2H, d, J = 4.7 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 157.4, 151.5, 137.0, 122.5, 112.4, 111.3, 88.6; MS (ESI) m/z 178 $[M+Na]^+$.

2-(Pyridin-3-ylmethylene)malononitrile (3ax)[4]



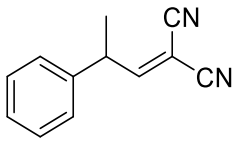
Brown solid; Yield 94%; Reaction time: 30 min; mp 80-82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.88 (1H, s, ArH), 8.81 (1H, d, J = 4.7 Hz, ArH), 8.46 (1H, d, J = 8.0 Hz, ArH), 7.83 (1H, s, =CH), 7.51 (1H, dd, J = 8.0 and 4.7 Hz, ArH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 156.5, 154.6, 152.3, 135.6, 127.0, 124.3, 112.9, 111.9, 85.6; MS (ESI) m/z 178 $[M+Na]^+$.

2-(3-Phenylpropylidene)malononitrile (3ay)[12]



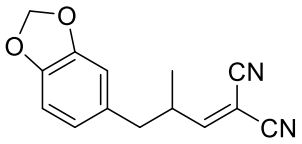
Yellow oil; Yield 95%; Reaction time: 1 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 (2H, t, J = 7.5 Hz, ArH), 7.31-7.25 (2H, m, ArH and =CH), 7.18 (2H, d, J = 7.5 Hz, ArH), 2.96-2.85 (4H, m, 2 x CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 168.3, 138.1, 128.9, 128.2, 127.0, 111.9, 110.3, 90.4, 34.2, 33.3; MS (ESI) m/z 205 $[M+Na]^+$.

2-(2-Phenylpropylidene)malononitrile (3az)[13]



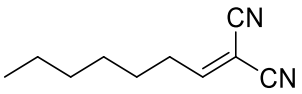
Yellow oil; Yield 96%; Reaction time: 18 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.43-7.39 (2H, m, ArH), 7.36-7.33 (2H, m, ArH and =CH), 7.27 (2H, d, J = 7.5 Hz, ArH), 4.15 (1H, dq, J = 11.0 and 6.9 Hz, CH), 1.57 (3H, d, J = 6.9 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 171.5, 139.2, 129.4, 128.1, 126.9, 111.9, 110.5, 87.7, 42.8, 19.5; MS (ESI) m/z 205 $[M+Na]^+$.

2-(3-(Benzo[d][1,3]dioxol-5-yl)-2-methylpropylidene)malononitrile (3ba)



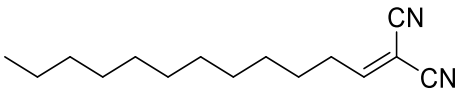
Pale yellow oil; Yield 91%; Reaction time: 18 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.11 (1H, d, J = 10.7 Hz, =CH), 6.75 (1H, d, J = 7.8 Hz, ArH), 6.61 (1H, s, ArH), 6.56 (1H, d, J = 7.8 Hz, ArH), 5.95 (2H, s, OCH_2), 3.18-3.07 (1H, m, CH), 2.75 (1H, dd, J = 13.8 and 6.4 Hz, CH*H*), 2.63 (1H, dd, J = 13.8 and 6.4 Hz, C*H*H), 1.19 (3H, d, J = 6.4 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 173.2, 147.9, 146.6, 130.6, 121.9, 111.9, 110.3, 109.1, 108.4, 101.0, 88.9, 41.5, 40.1, 18.7; HRMS exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}N_2O_2Na^+$) requires m/z 263.0791, found m/z 263.0791.

2-Heptylidenemalononitrile (3bb)[14]



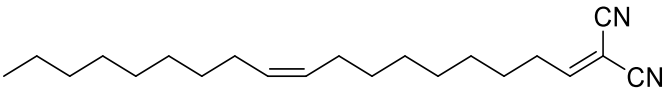
Yellow oil; Yield 60%; Reaction time: 18 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 (1H, t, J = 8.0 Hz, =CH), 2.58 (2H, q, J = 8.0 Hz, CH_2), 1.64-1.50 (2H, m, CH_2), 1.42-1.25 (6H, m, 3 x CH_2), 0.89 (3H, t, J = 6.0 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.9, 112.1, 110.5, 89.7, 32.8, 31.2, 28.7, 27.4, 22.3, 13.9; MS (ESI) m/z 185 $[M+Na]^+$.

2-Dodecylidenemalononitrile (3bc)[15]



A mixture of methanol and water (1:1) was used as the solvent. Yellow oil; Yield 60%; Reaction time: 18 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 (1H, t, J = 8.0 Hz, =CH), 2.59 (2H, q, J = 8.0 Hz, CH_2), 1.60-1.51 (2H, m, CH_2), 1.38-1.19 (16H, m, 8 x CH_2), 0.88 (3H, t, J = 6.4 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.8, 112.1, 110.5, 89.9, 32.9, 31.9, 29.5, 29.5, 29.3, 29.3, 29.1, 29.1, 27.6, 22.7, 14.1; MS (ESI) m/z 255 $[M+Na]^+$.

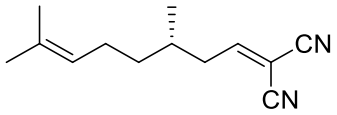
(*Z*)-2-(Octadec-9-en-1-ylidene)malononitrile (3bd)



A mixture of methanol and water (1:1) was used as the solvent. Yellow Oil; Yield 97%; Reaction time: 18 h; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.33 (1H, t, J = 8.0 Hz, =CH), 5.38-5.28 (2H, m, 2 x =CH), 2.60-2.54 (2H, q, J = 7.6 Hz, CH_2), 2.06-1.92 (4H, m, 2 x CH_2), 1.59-1.51 (2H, m, CH_2) 1.35-1.20 (20H, m, 10 x CH_2), 0.87 (3H, t, J = 6.4 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.8, 130.0, 129.4, 112.0, 110.4,

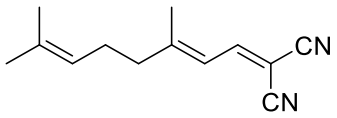
89.6, 32.7, 31.8, 29.6, 29.5, 29.5, 29.4, 29.2, 29.0, 28.9, 28.8, 27.4, 27.1, 27.0, 22.5, 14.0; HRMS exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}N_2O_2Na^+$) requires m/z 337.2614, found m/z 337.2617.

(*S*)-2-(3,7-Dimethyloct-6-en-1-ylidene)malononitrile (3be)[16]



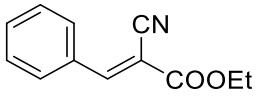
A mixture of methanol and water (1:1) was used as the solvent. Yellow Oil; Yield 99%; Reaction time: 6 h; $[\alpha]^{20}_D$ = +20.0 (c = 1.00 in MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.35 (1H, t, J = 8.0 Hz, =CH), 5.03 (1H, t, J = 6.6 Hz, =CH), 2.59-2.38 (2H, m, CH_2), 2.06-1.90 (2H, m, CH_2), 1.81-1.72 (1H, m, CH), 1.66 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.38-1.21 (2H, m, CH_2), 0.94 (3H, d, J = 6.8 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 169.2, 131.8, 123.3, 112.0, 110.5, 90.0, 39.7, 36.3, 32.1, 25.4, 25.0, 19.1, 17.4; MS (ESI) m/z 225 $[M+Na]^+$.

(*E*)-2-(3,7-Dimethylocta-2,6-dien-1-ylidene)malononitrile (3bf)



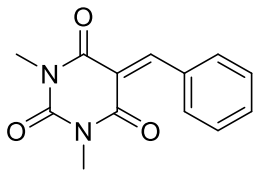
A mixture of methanol and water (1:1) was used as the solvent. Yellow Oil; Yield 93%; Reaction time: 3 h;′**^{1}H NMR** (400 MHz, $CDCl_3$) (E/Z 70:30) δ:7.76 (0.7H, d, J = 12.2 Hz, =CH), 7.67 (0.3H, d, J = 12.2 Hz, =CH), 6.43 (1H, d, J = 12.2 Hz, =CH), 5.04-4.97 (1H, m, =CH), 2.38-2.27 (2H, m, CH_2), 2.22-2.11 (2H, m, CH_2), 2.04 (0.9H, s, CH_3), 1,99 (2.1H, s, CH_3), 1.64 (3H, s, CH_3), 1.57 (2.1H, s, CH_3), 1.54 (0.9H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 165.1, 164.9, 156.0, 155.9, 133.9, 132.9, 122.1, 122.0, 121.8, 121.2, 113.8, 113.7, 111.5, 80.6, 80.1, 40.7, 33.8, 26.5, 25.8, 25.3, 25.3, 18.6, 17.4; HRMS exact mass calculated for $[M+Na]^+$ ($C_{14}H_{12}N_2O_2Na^+$) requires m/z 200.1313, found m/z 200/.1313.

Ethyl-2-cyano-3-phenylacrylate (3bg)[2]



White solid; Yield 67%; Reaction time: 18 h; mp 48-50 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.24 (1H, s, =CH), 7.98 (2H, d, J = 7.5 Hz, ArH), 7.53-7.47 (3H, m, ArH), 4.38 (2H, q, J = 7.0 Hz, CH_2), 1.39 (3H, t, J = 7.0 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.4, 155.0, 133.2, 131.4, 131.0, 129.2, 115.4, 103.0, 62.7, 14.1; MS (ESI) m/z 224 $[M+Na]^+$.

5-Benzylidene-1,3-dimethylpyrimidine-2,4,6(*1H,3H,5H*)-trione (3bh)[17]



White solid; Yield 94%; Reaction time: 1 h; mp 152-154 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.57 (1H, s, =CH), 8.05 (2H, d, J = 7.8 Hz, ArH), 7.55-7.43 (3H, m, ArH), 3.42 (3H, s, NCH_3), 3.37 (3H, s, NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 162.5, 160.3, 159.3, 151.2, 133.4, 132.9, 132.6, 128.2, 117.5, 29.1, 28.4; MS (ESI) m/z 267 $[M+Na]^+$.

Calculation of Green Metrics

Malononitrile **2a** (66 mg, 1.00 mmol) was added in a glass vial, containing benzaldehyde **1a** (106 mg, 1.00 mmol) in H_2O (2 mL). The reaction mixture was left stirring for 18 hours in a BUCHI Syncore apparatus. After reaction completion, the reaction mixture was evaporated *in vacuo* and the pure product was obtained without further purification.

E-factor calculation

For the calculation of the E-factor for our methodology, all quantities mentioned in the general procedure are taken into consideration. Concerning the other literature protocols, we used the quantities mentioned in the general procedures without taking into account the reagents used for purification.

After obtaining 146 mg of the desired product, the E-factor was calculated:

E-factor = mg (waste) / mg (product) = [66 (malononitrile) + 106 (benzaldehyde) + 2000 (H_2O) – 146 (product)] mg / 146 mg = **13.9**

Das' Photocatalytic Protocol[9]

E-factor = [124 (malononitrile) + 100 (benzaldehyde) + 17.5 (rose bengal) + 1580 (EtOH) + 22000 (H_2O) - 130 (product)] mg / 130 mg = **185**

Shirinis' Organocatalytic Protocol[18]

E-factor = [72 (malononitrile) + 106 (benzaldehyde) + 25 (taurine) + 22000 (H_2O) - 132 (product)] mg / 132 mg = **167**

Atom economy calculation

% Atom economy = (Molar Mass of the product / Molar Mass of the reagents) * 100% = (154 / 172) * 100% = 89.5%

Atom efficiency

For the formation of one molecule of product, one molecule of water is lost.

Carbon efficiency

No carbon atoms are lost.

Process Mass Intensity (PMI)

PMI = (Mass of Materials/Mass of Isolated Product) = [66 (malononitrile) + 106 (benzaldehyde) + 2000 (H_2O)] mg / 146 (product) mg = 14.9

Reaction Mass Efficiency (RME)

RME = (Mass of Product/Mass of Materials Used) = 1/PMI = 0.068

Procedure for the Gram Scale Reaction

In a large glass vial, benzaldehyde **1a** (1.06 g, 10.00 mmol) and malononitrile **2a** (660 mg, 10.00 mmol) were added consecutively in H_2O (20 mL) and allowed to stir for 18 h. The reaction mixture was extracted with $CHCl_3$ (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Product was obtained with no further purification, 1.43 g, 93% yield.

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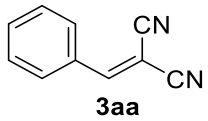
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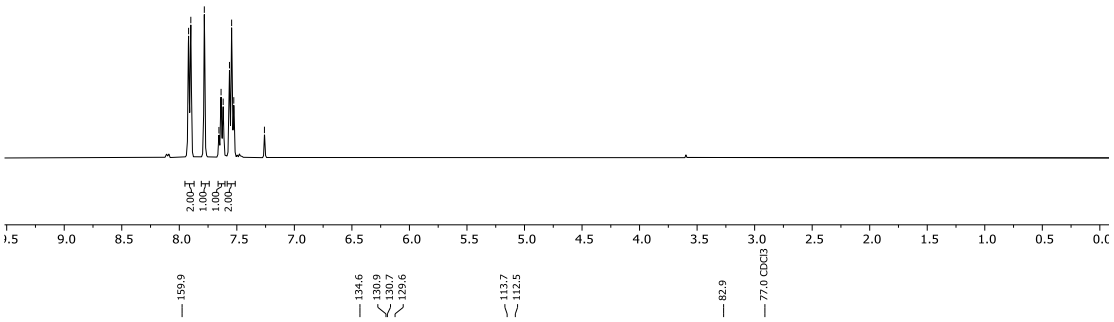
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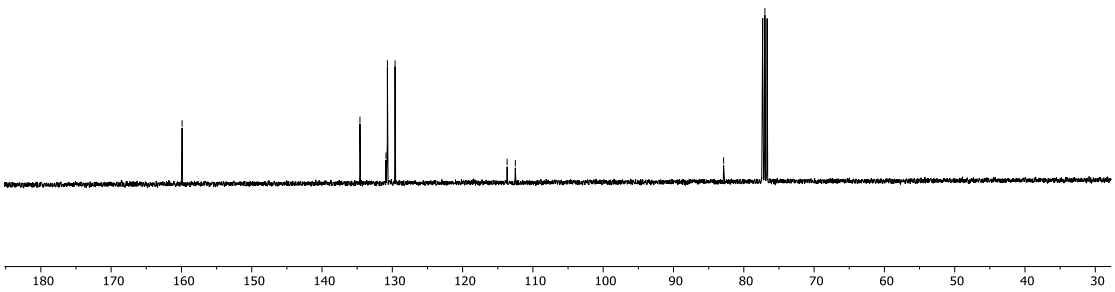

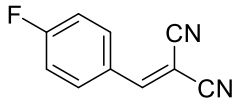
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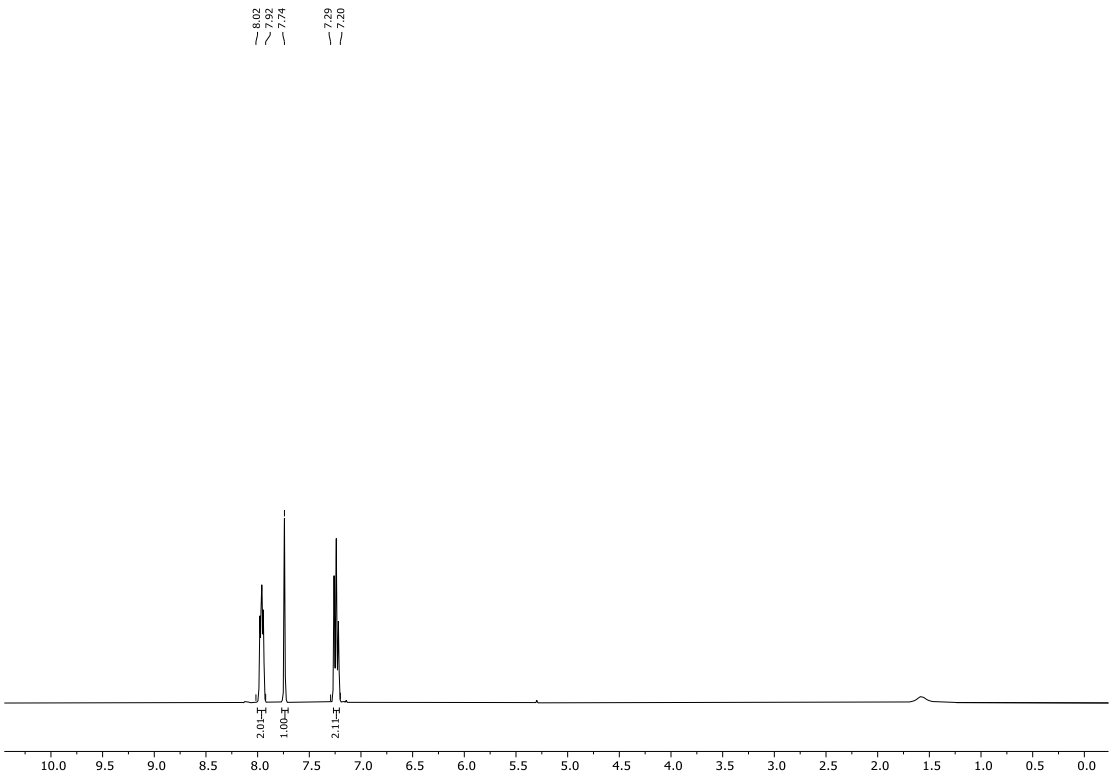
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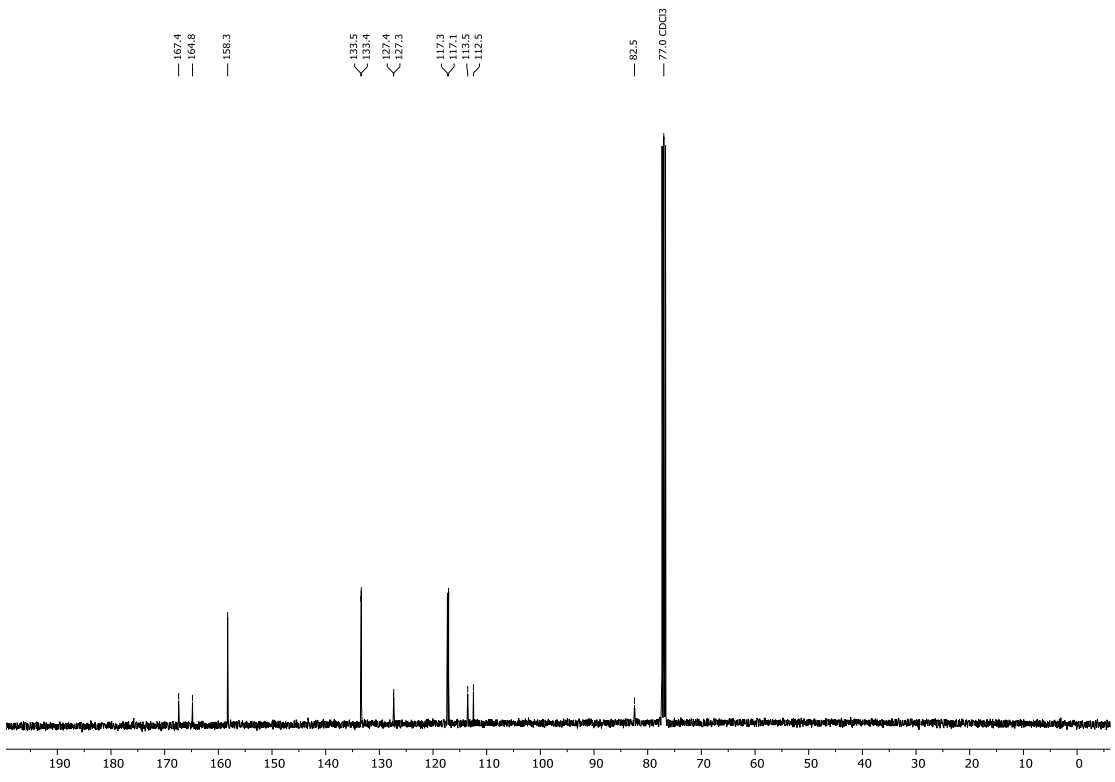
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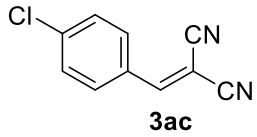
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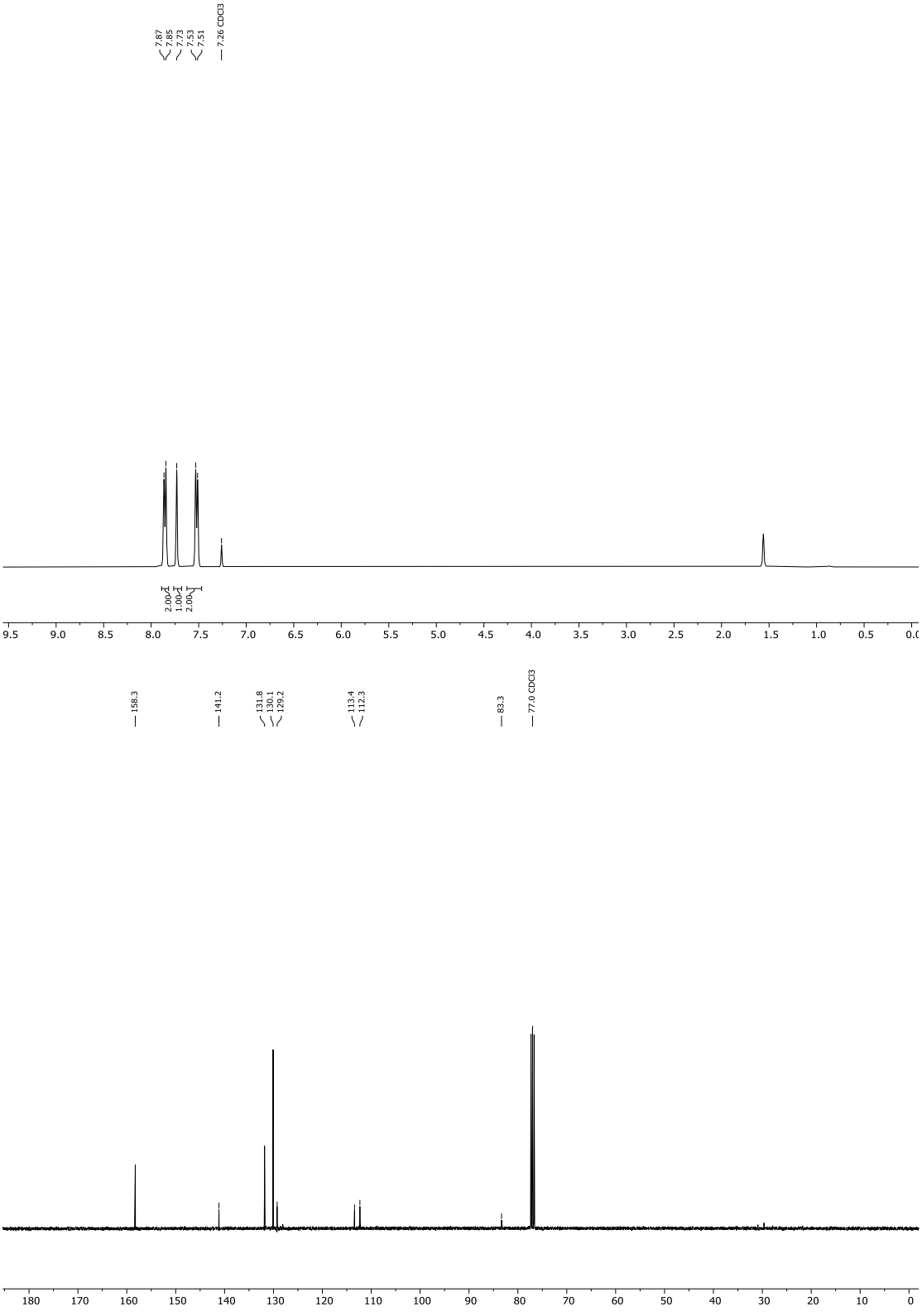
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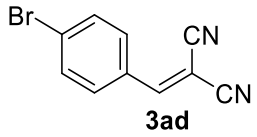
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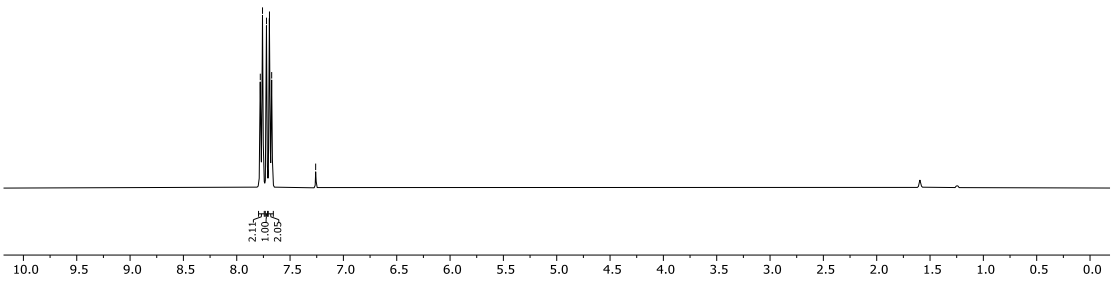
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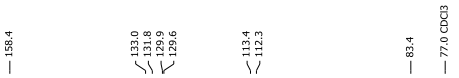
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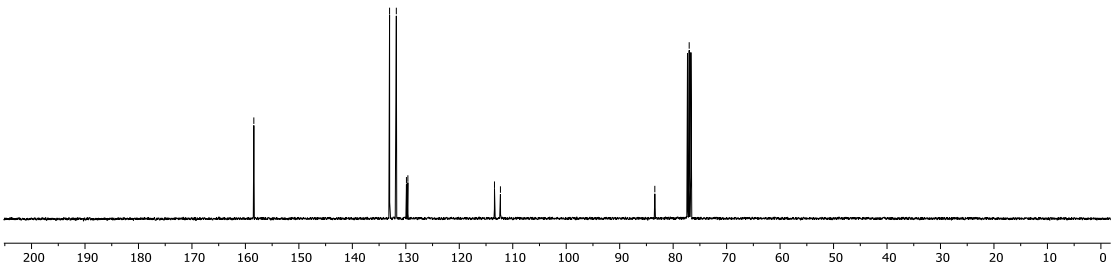
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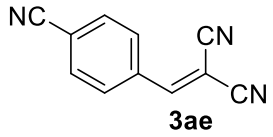
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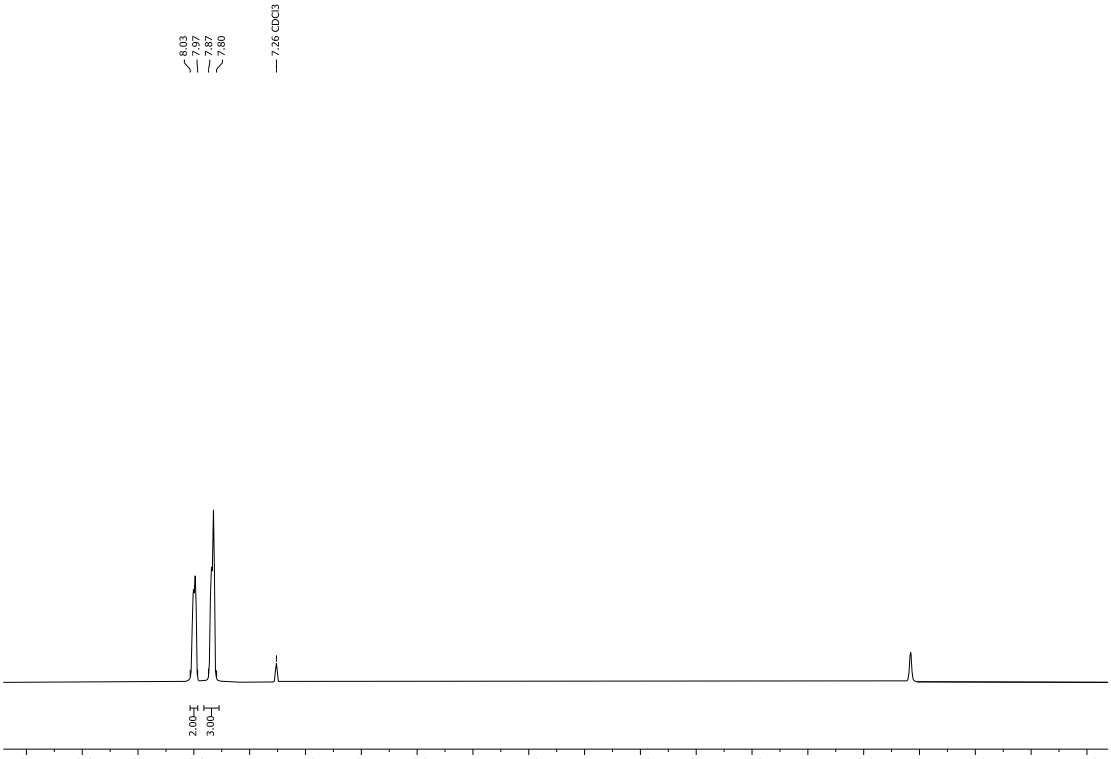
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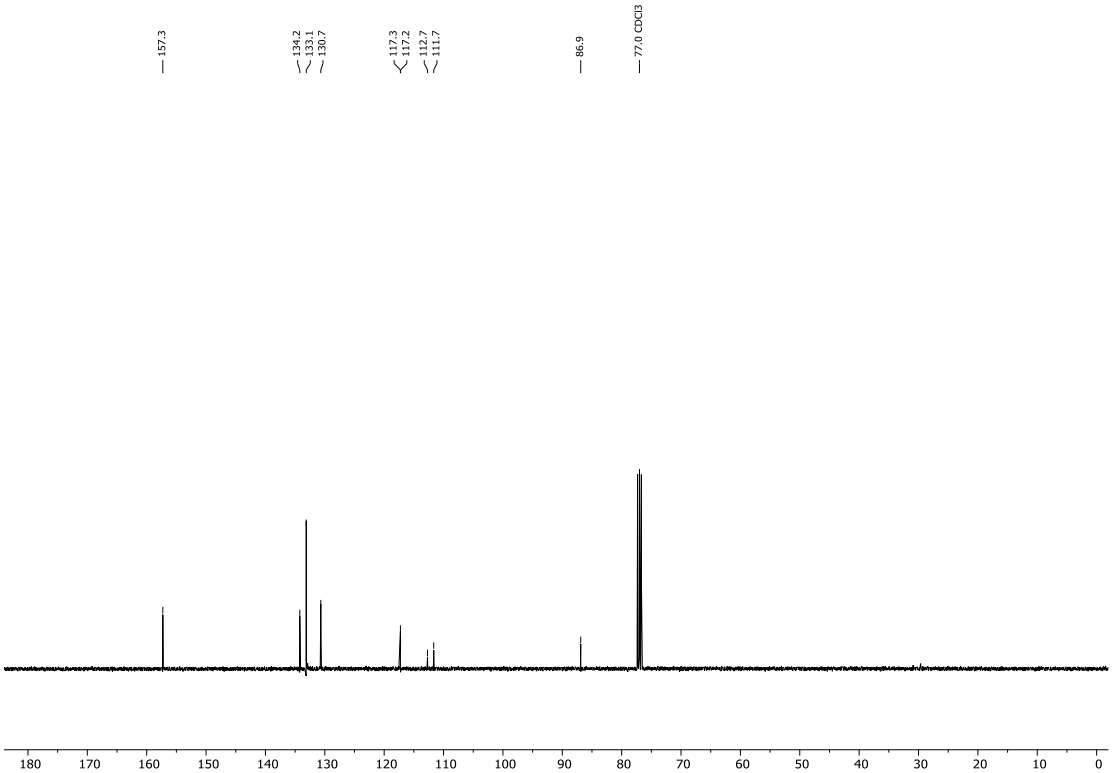
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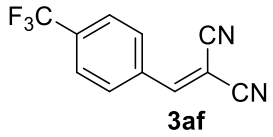
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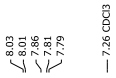
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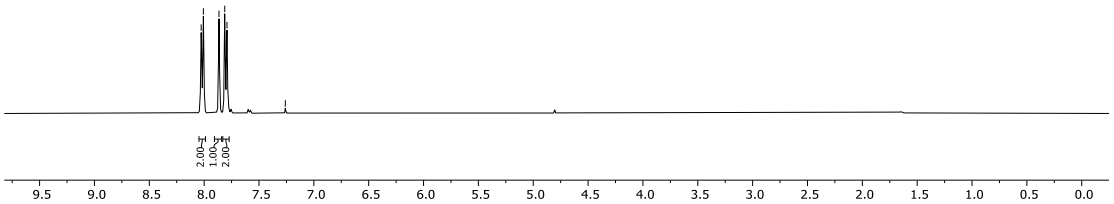
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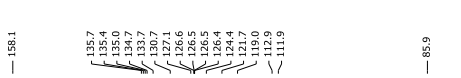
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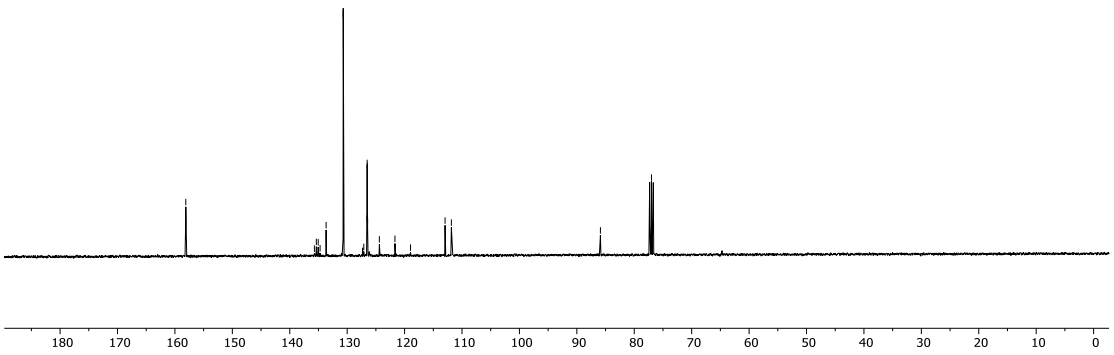
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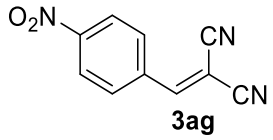
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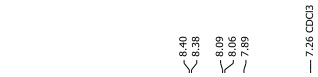
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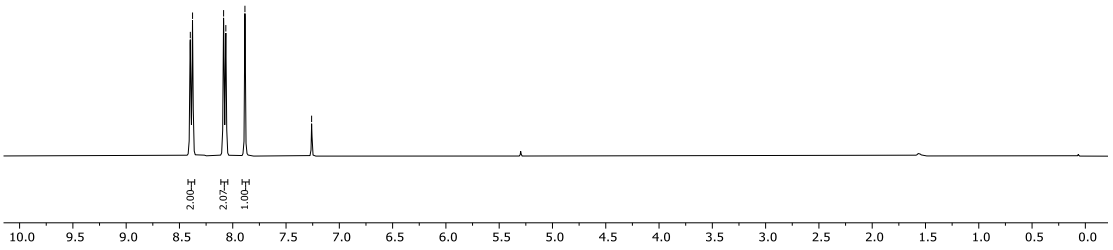
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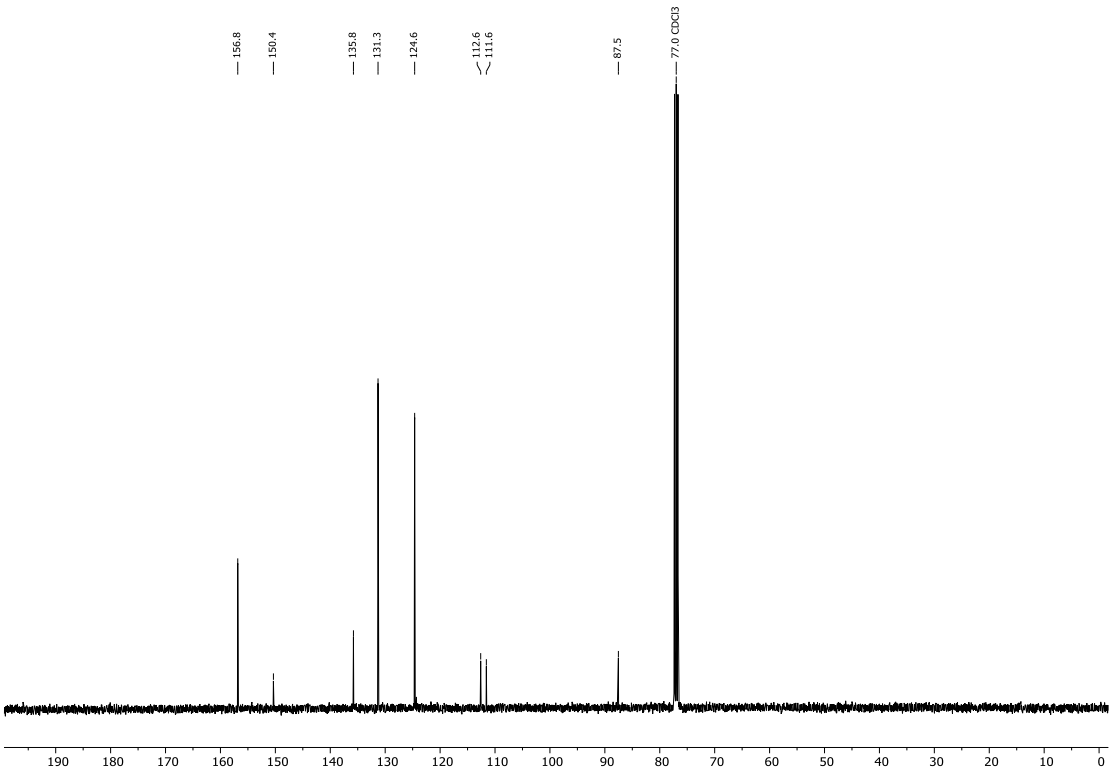
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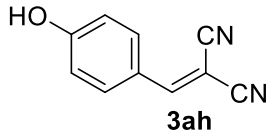
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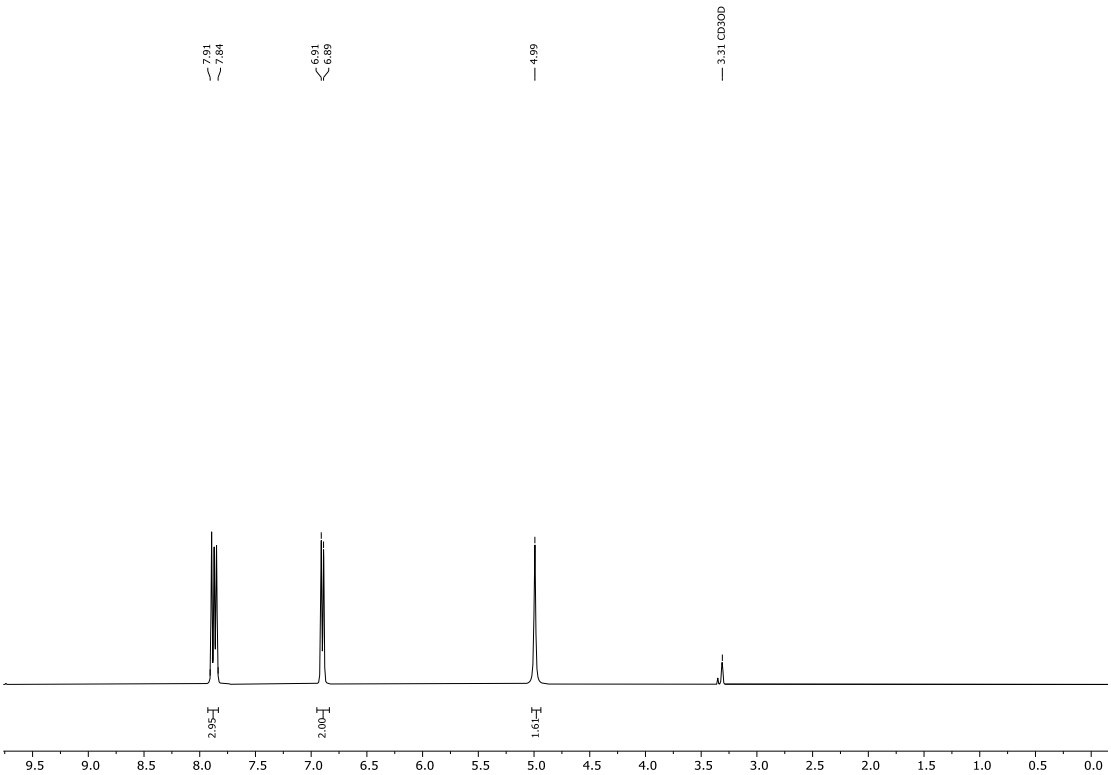
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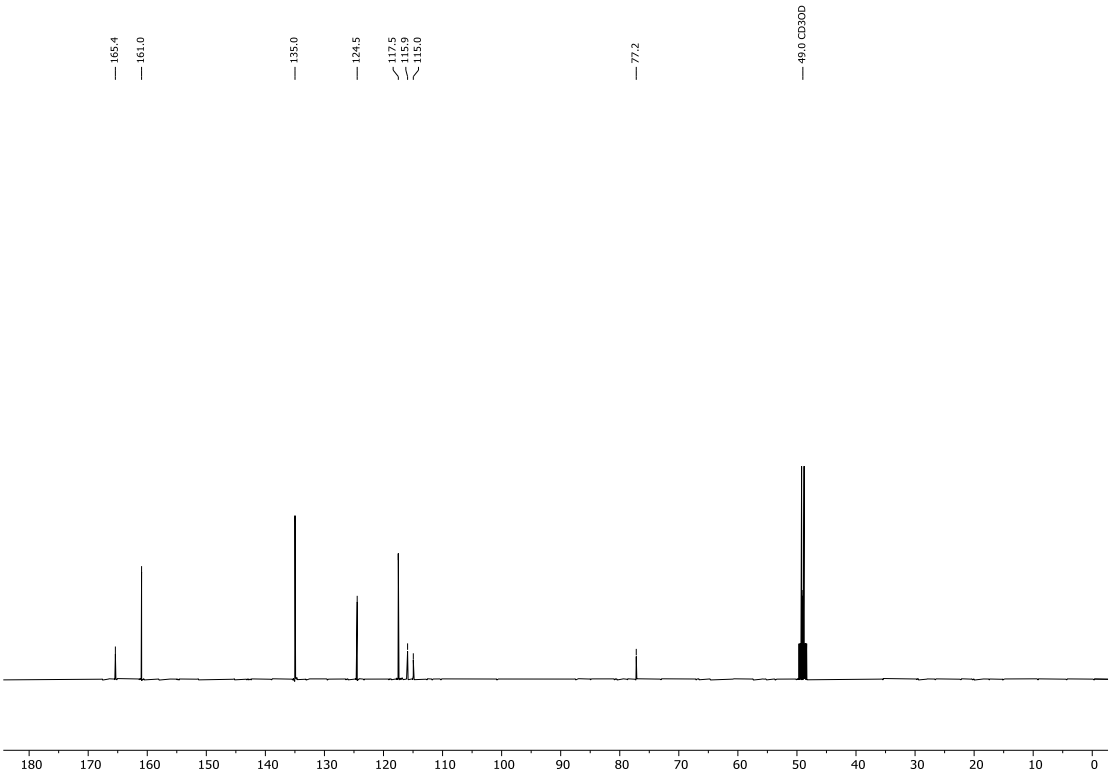
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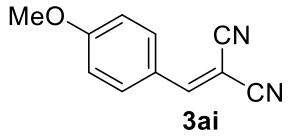
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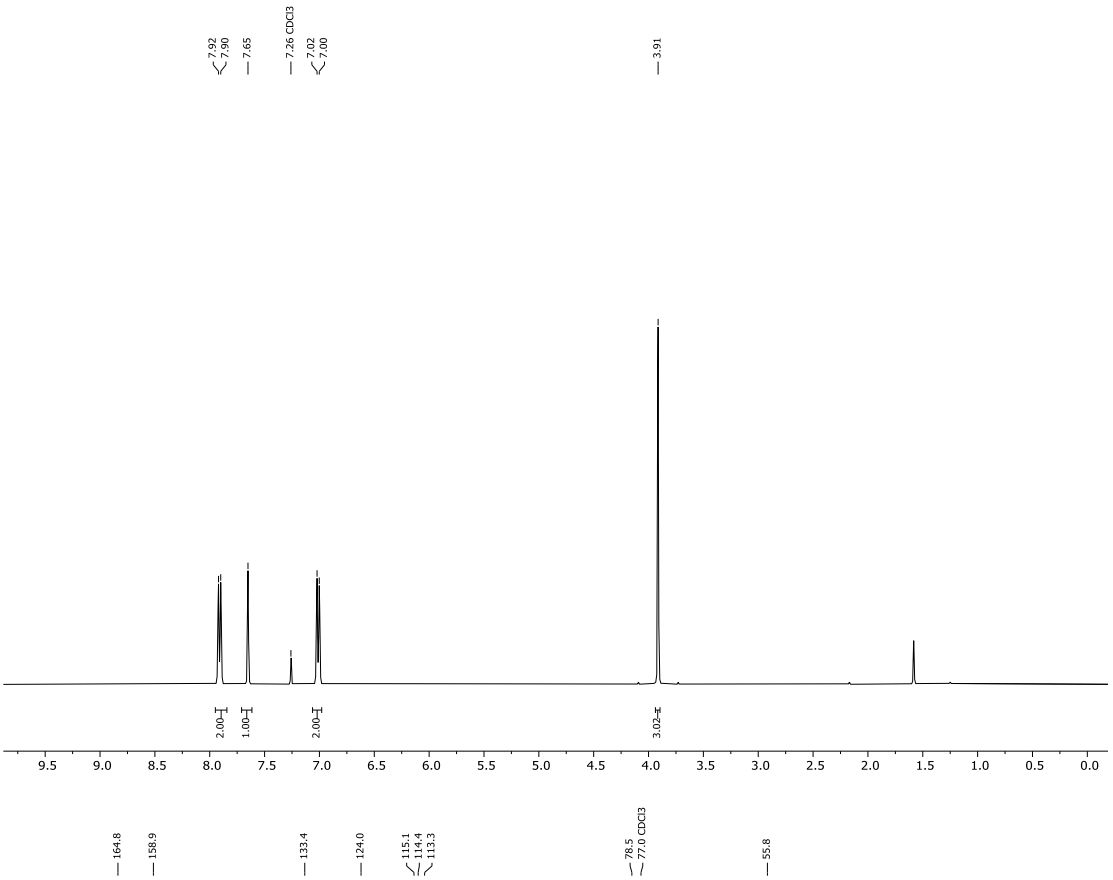
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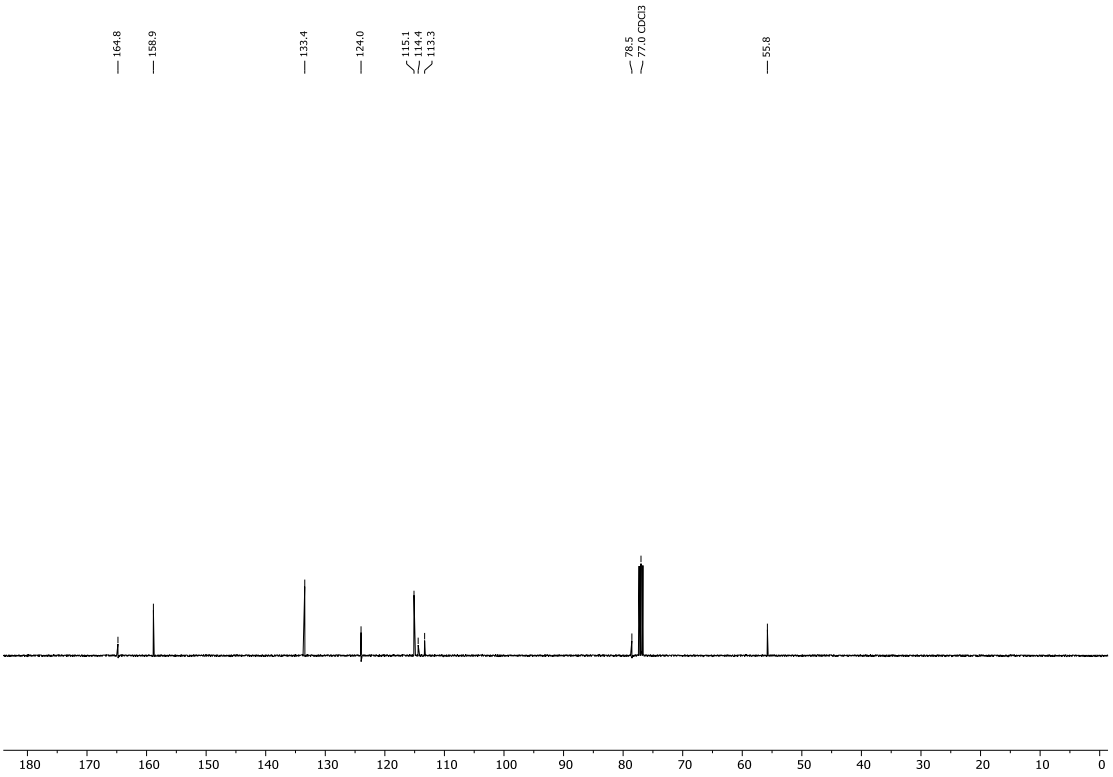
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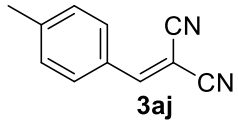
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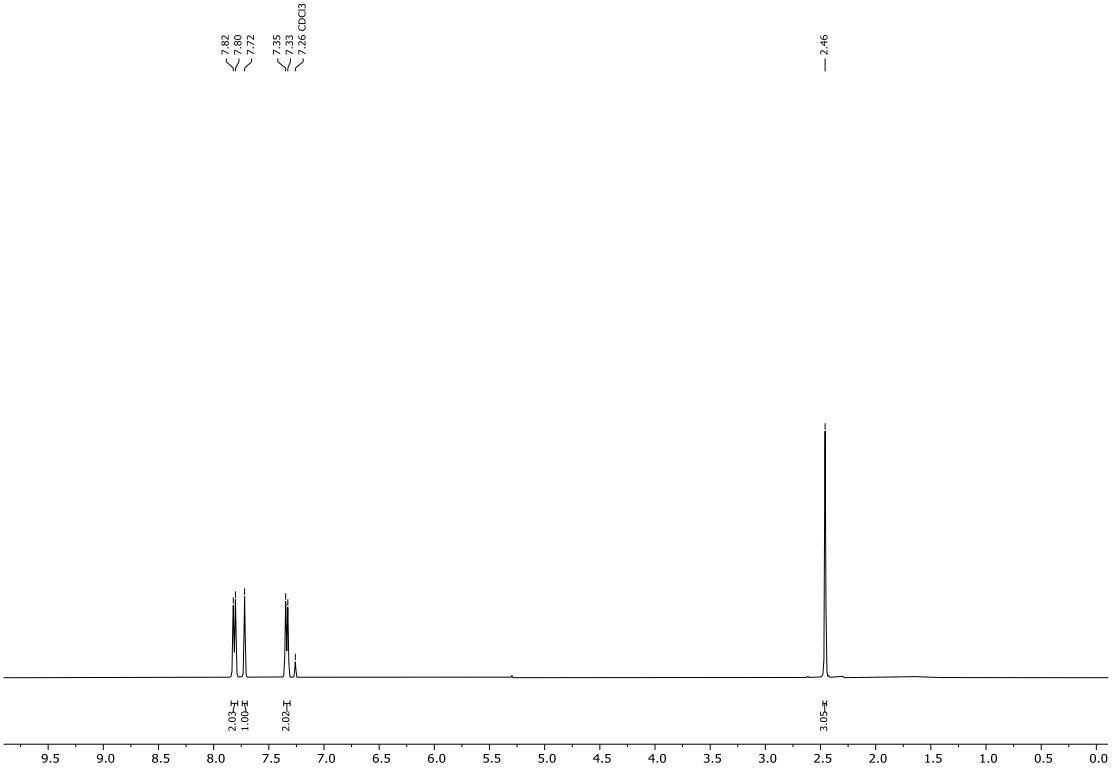
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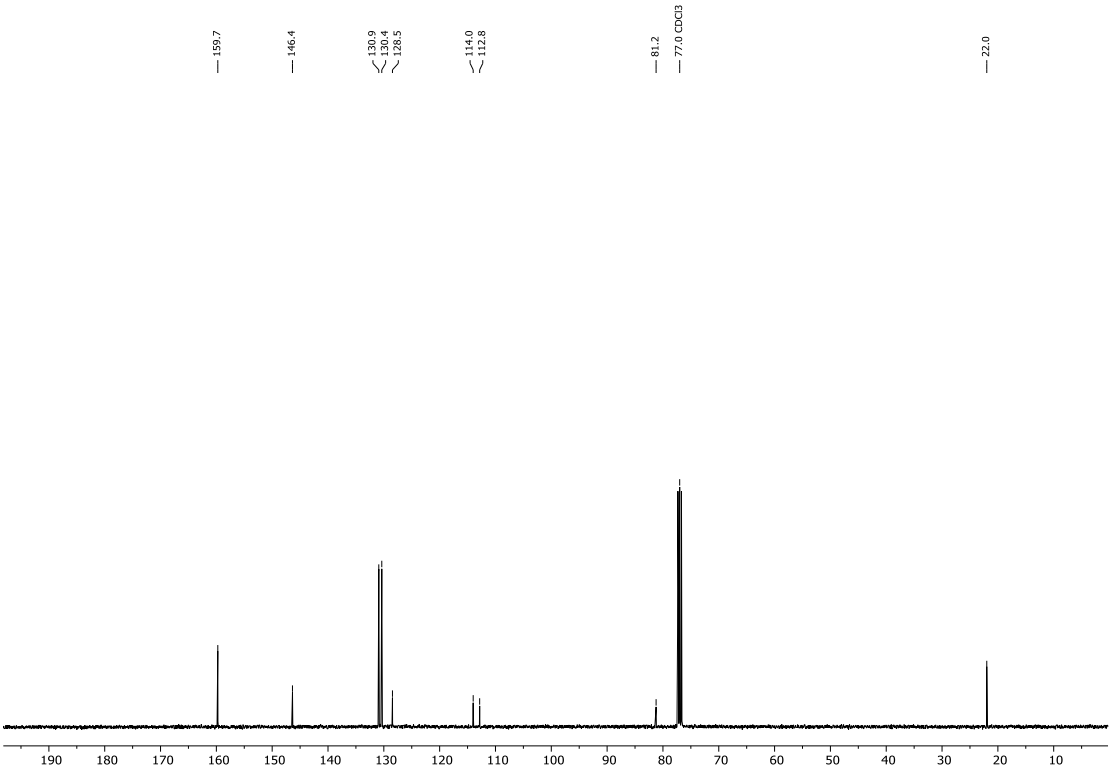
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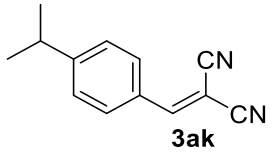
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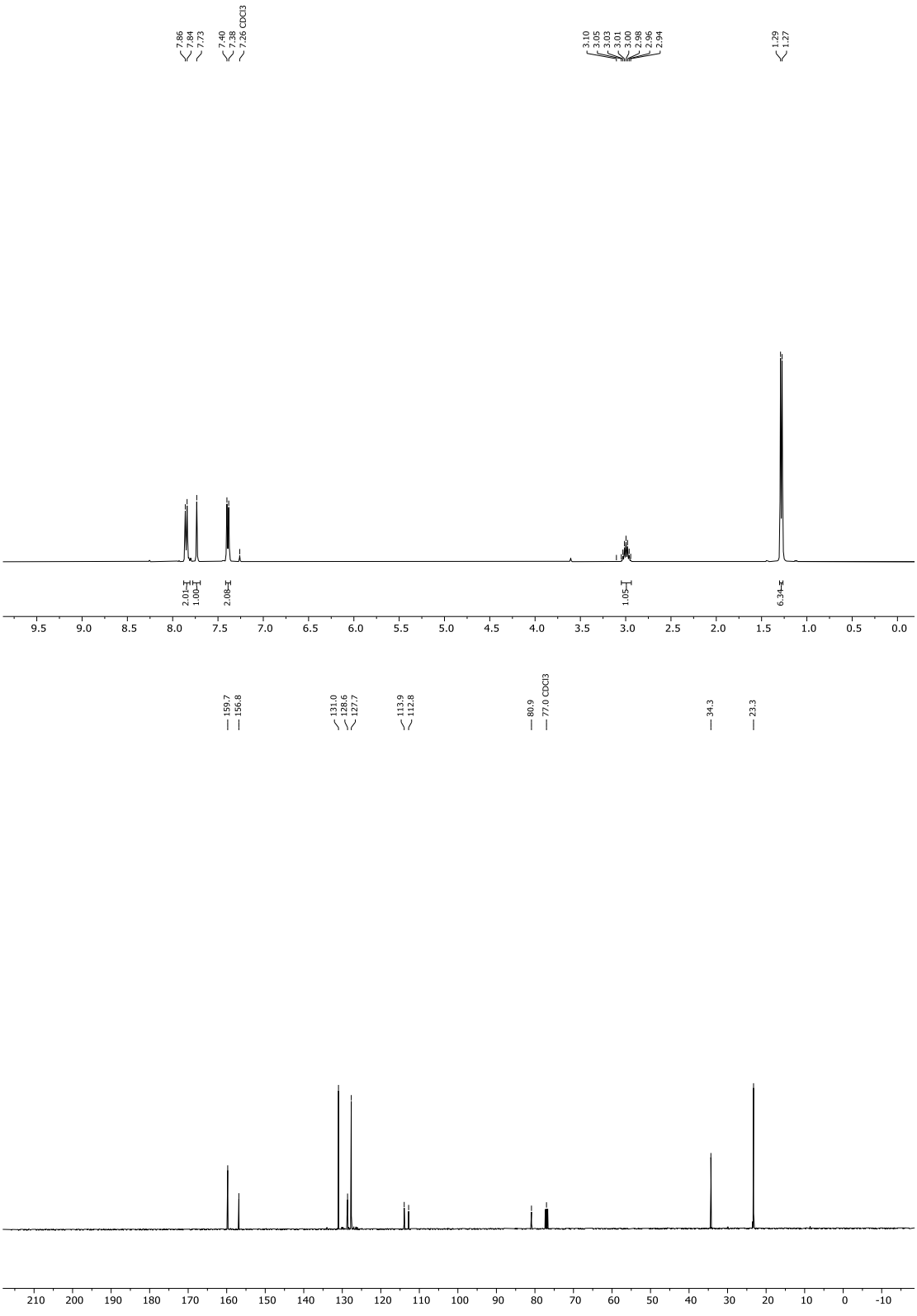
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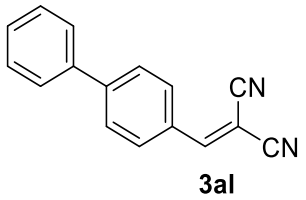
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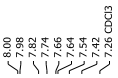
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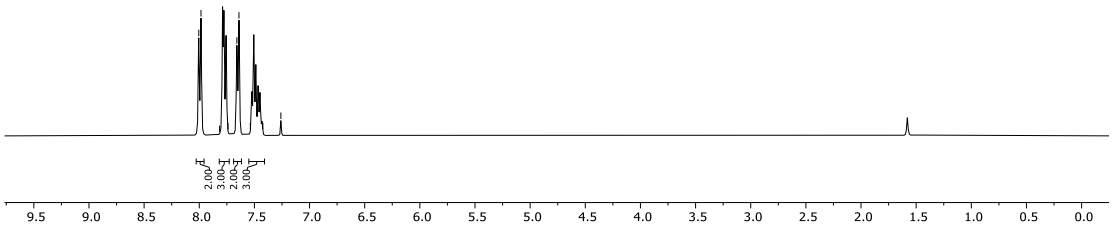
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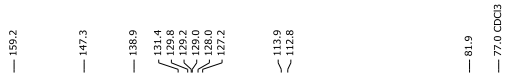
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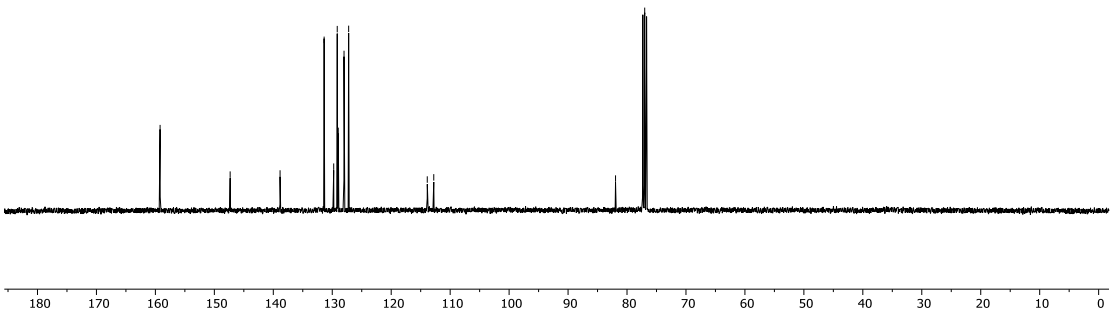
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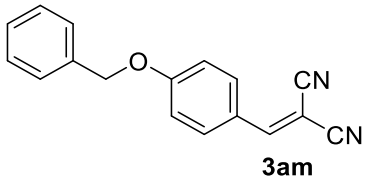
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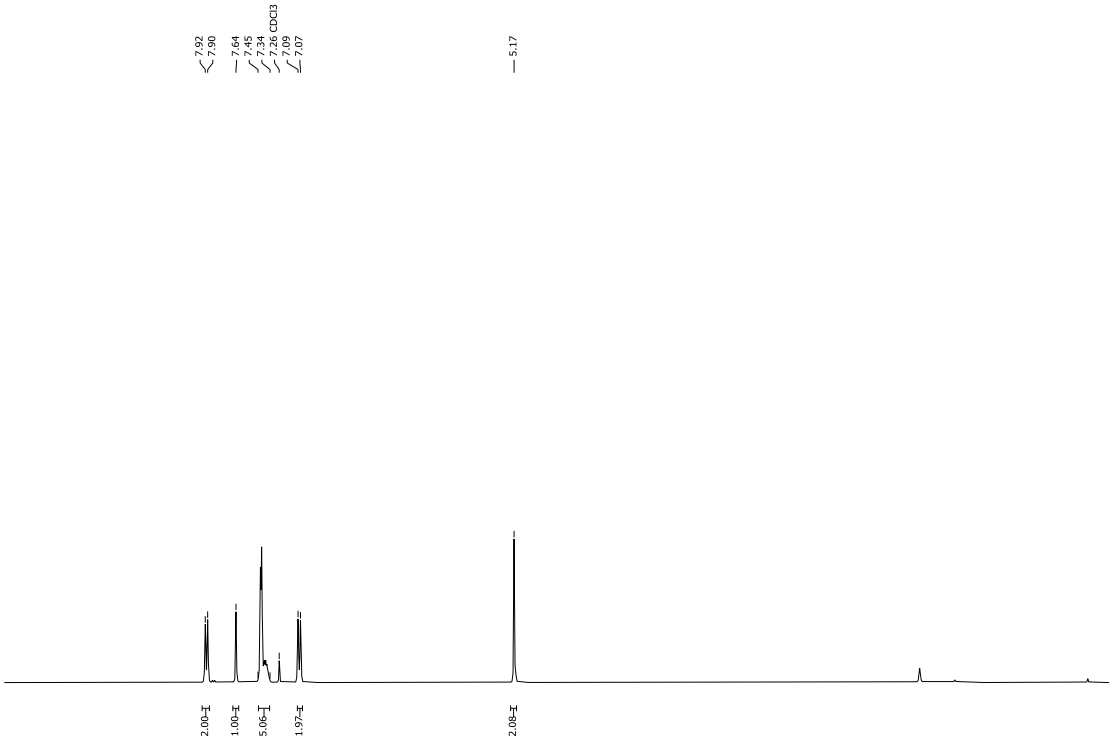
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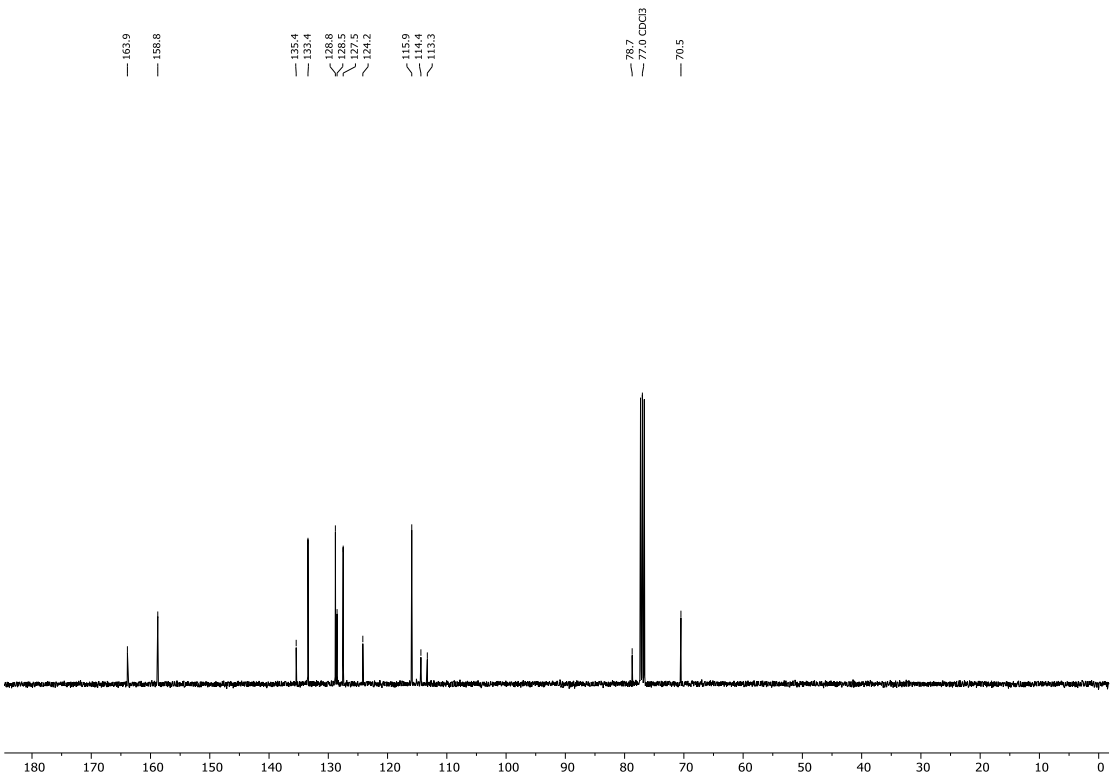
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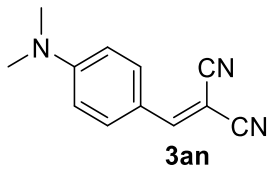
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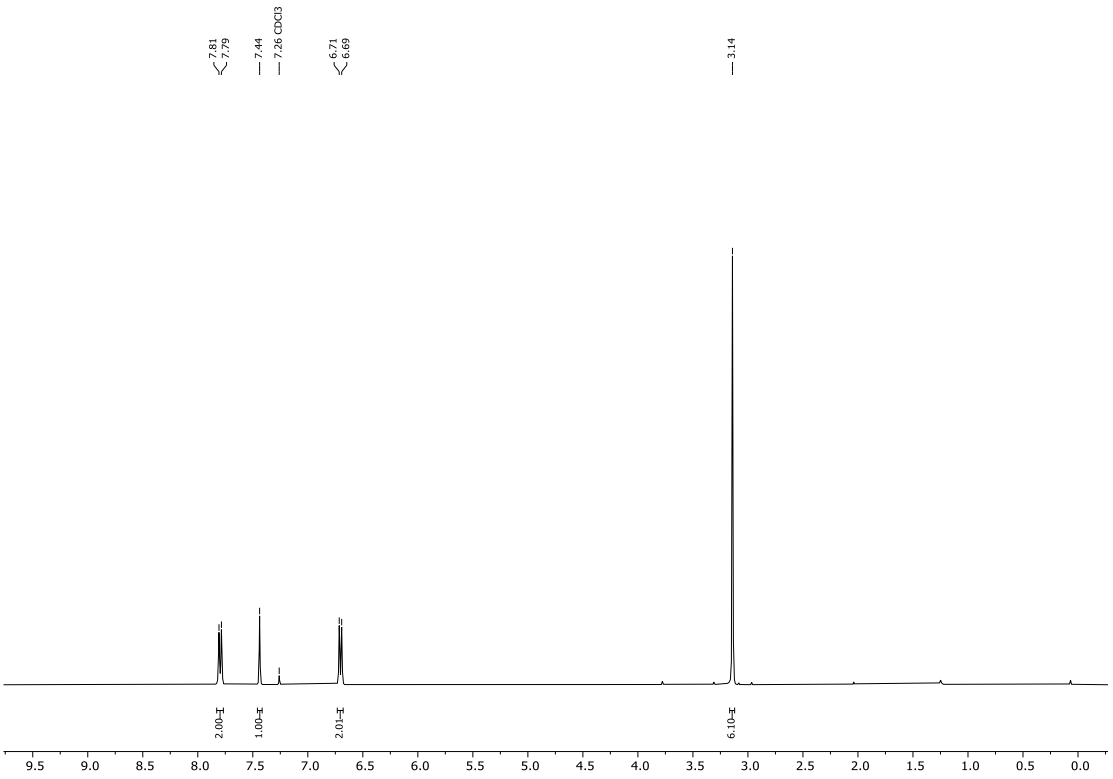
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1.00
2.01
6.10
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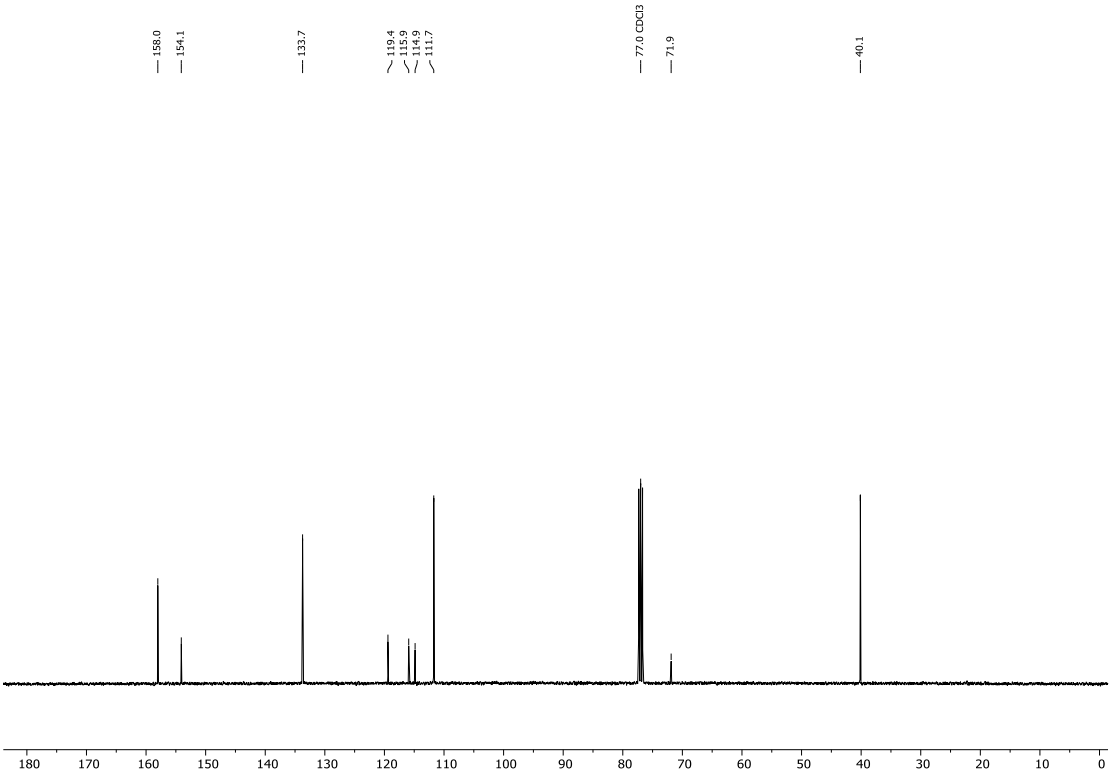
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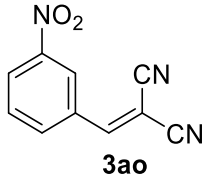
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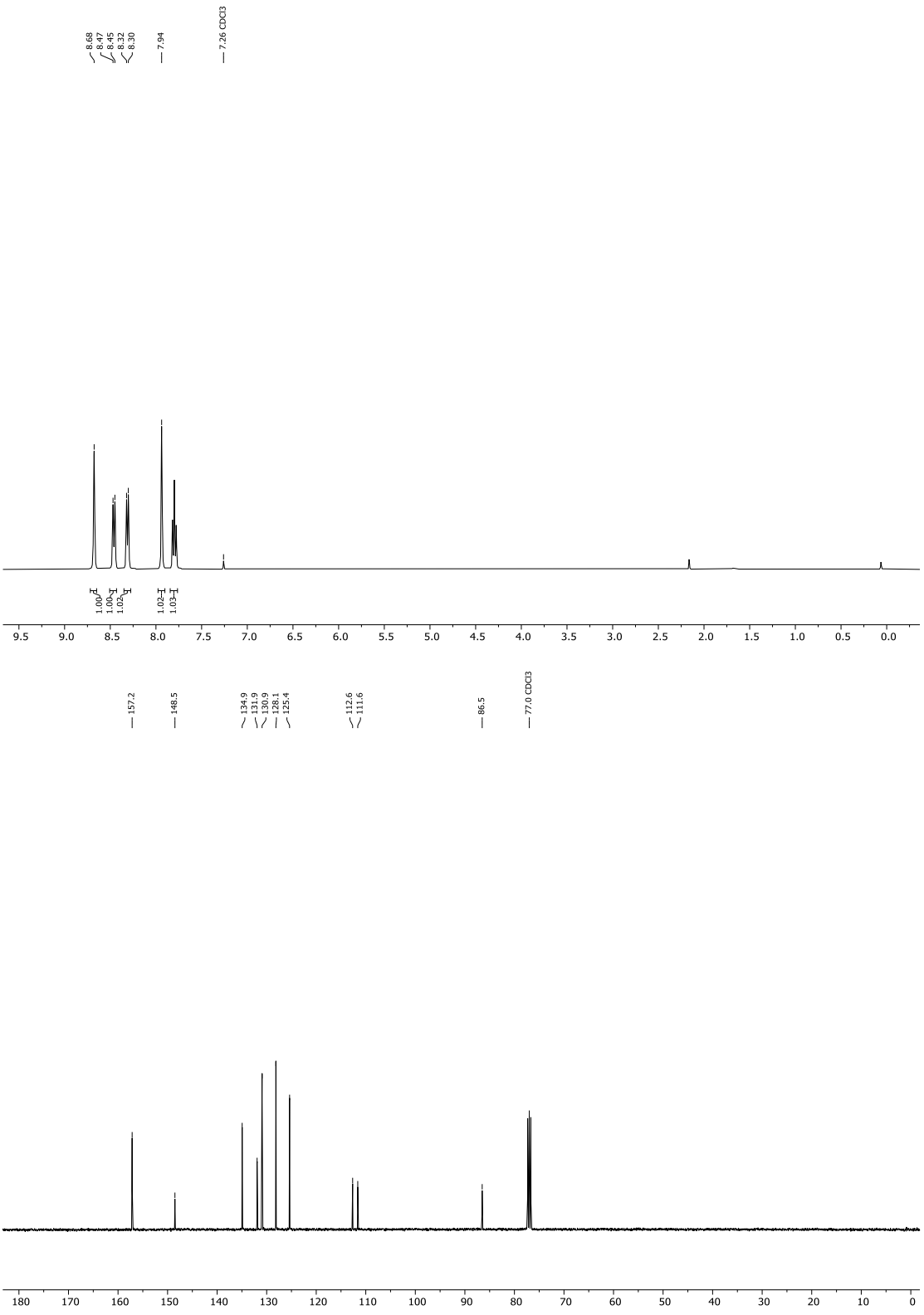
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157.2
148.5
134.9
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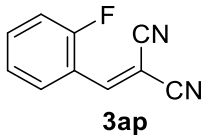
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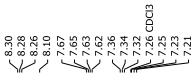
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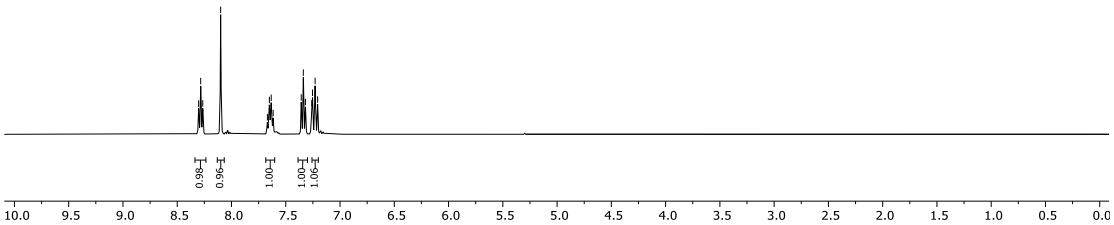
7.25
7.23
7.21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1.00
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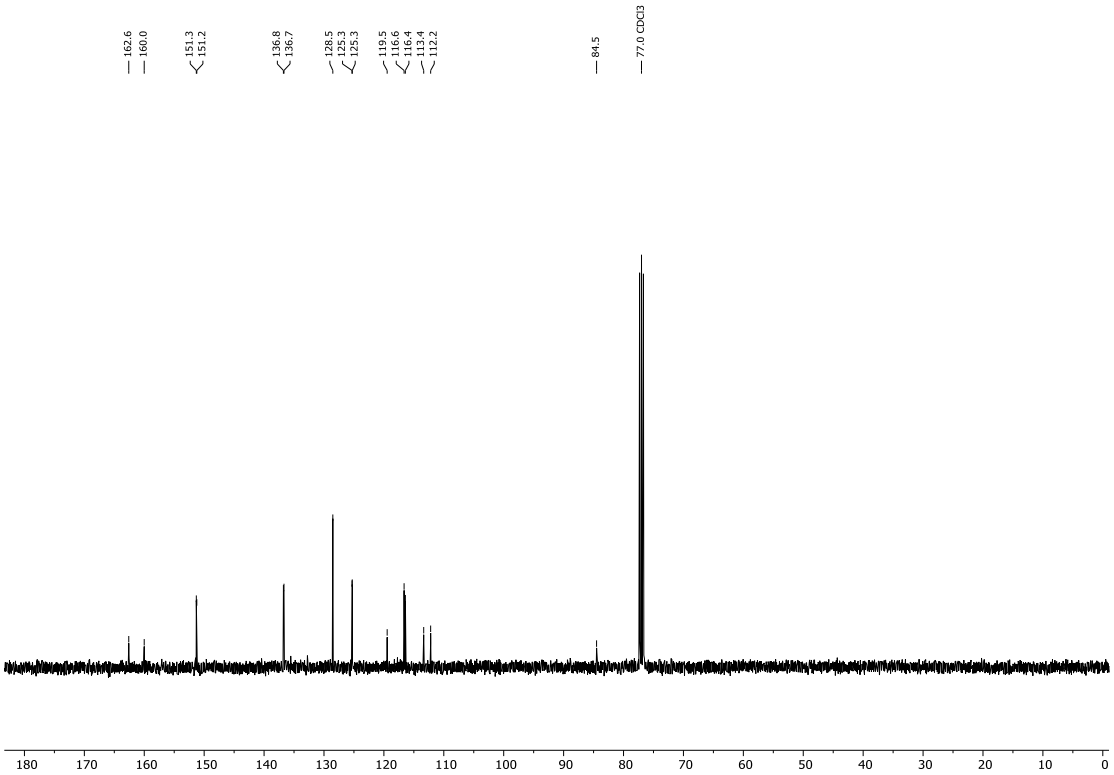
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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125.3
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77.0 CDCl3
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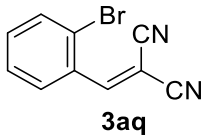
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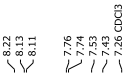
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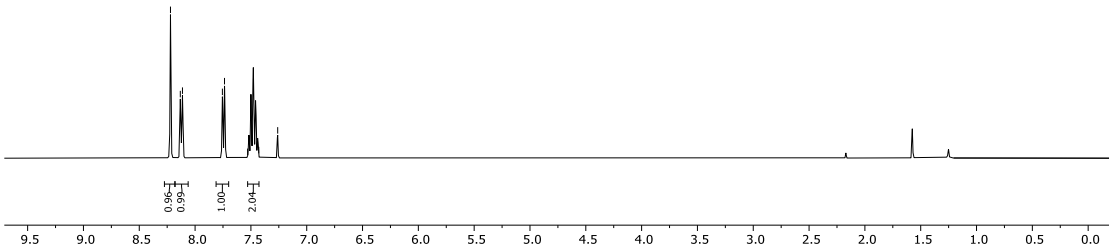
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0.99
1.00
2.04
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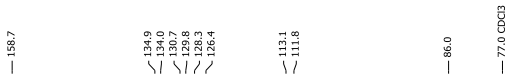
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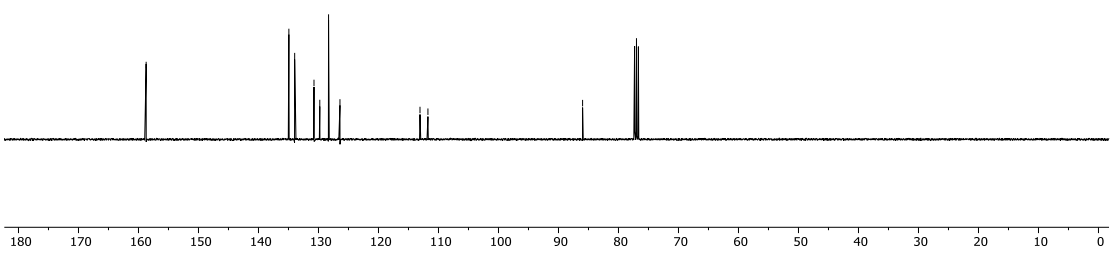
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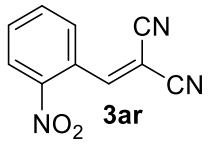
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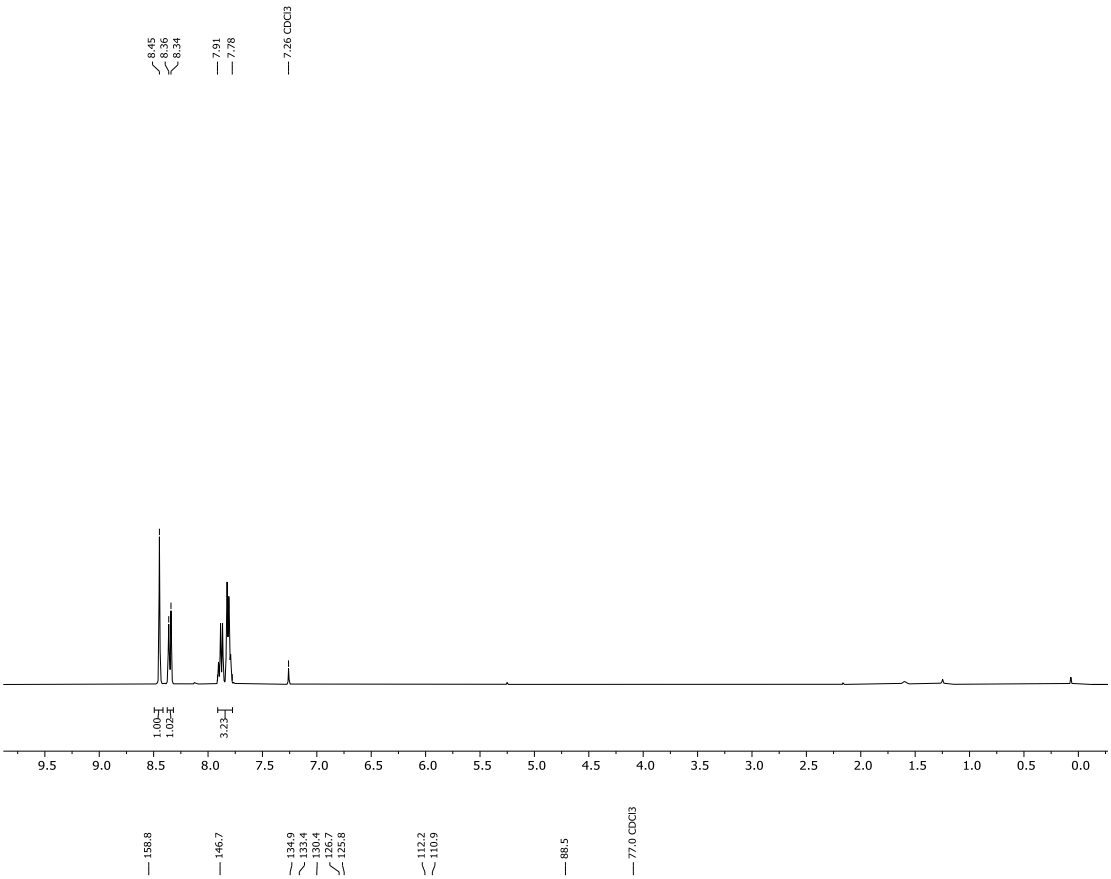
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1.02
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8.0
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7.0
6.5
6.0
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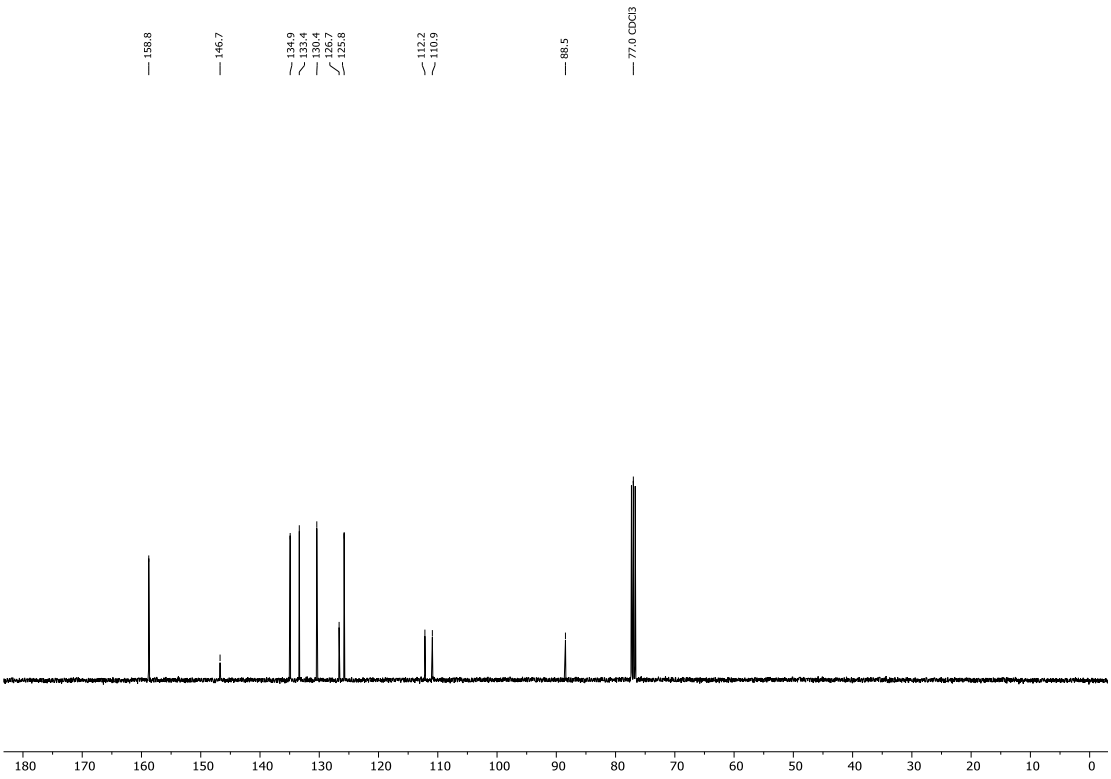
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88.5
77.0 CDCl3
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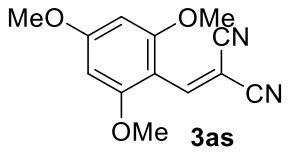
0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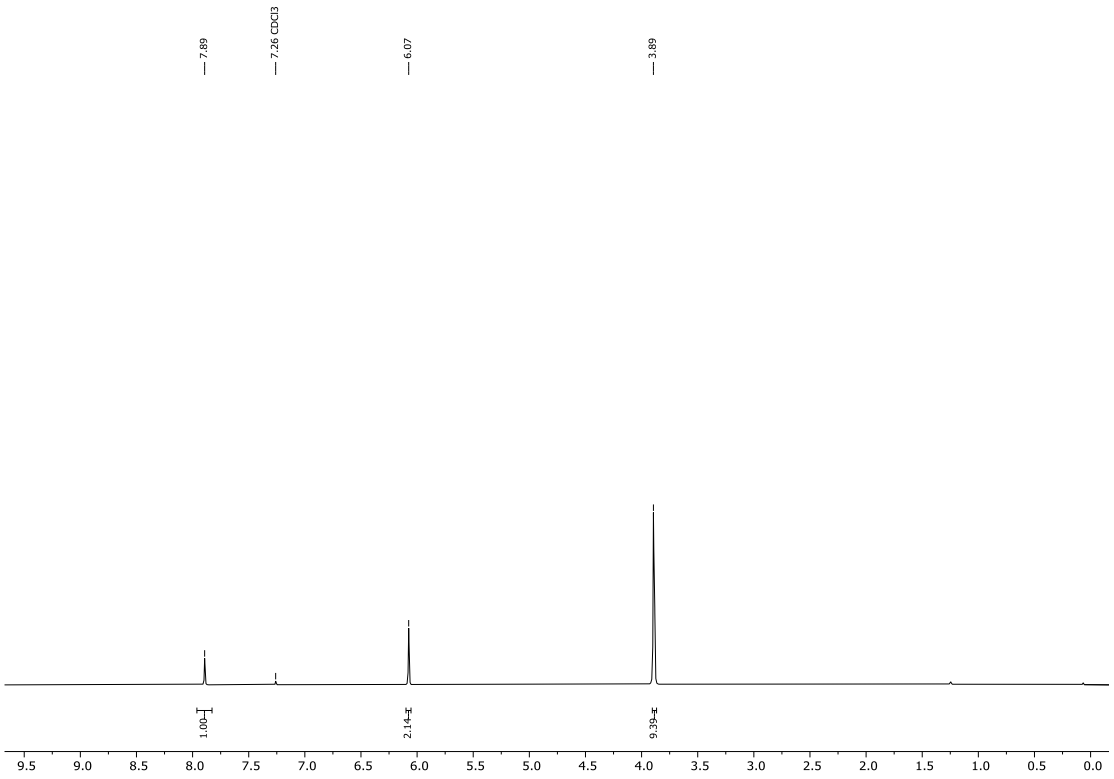
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1.00
2.14
9.39
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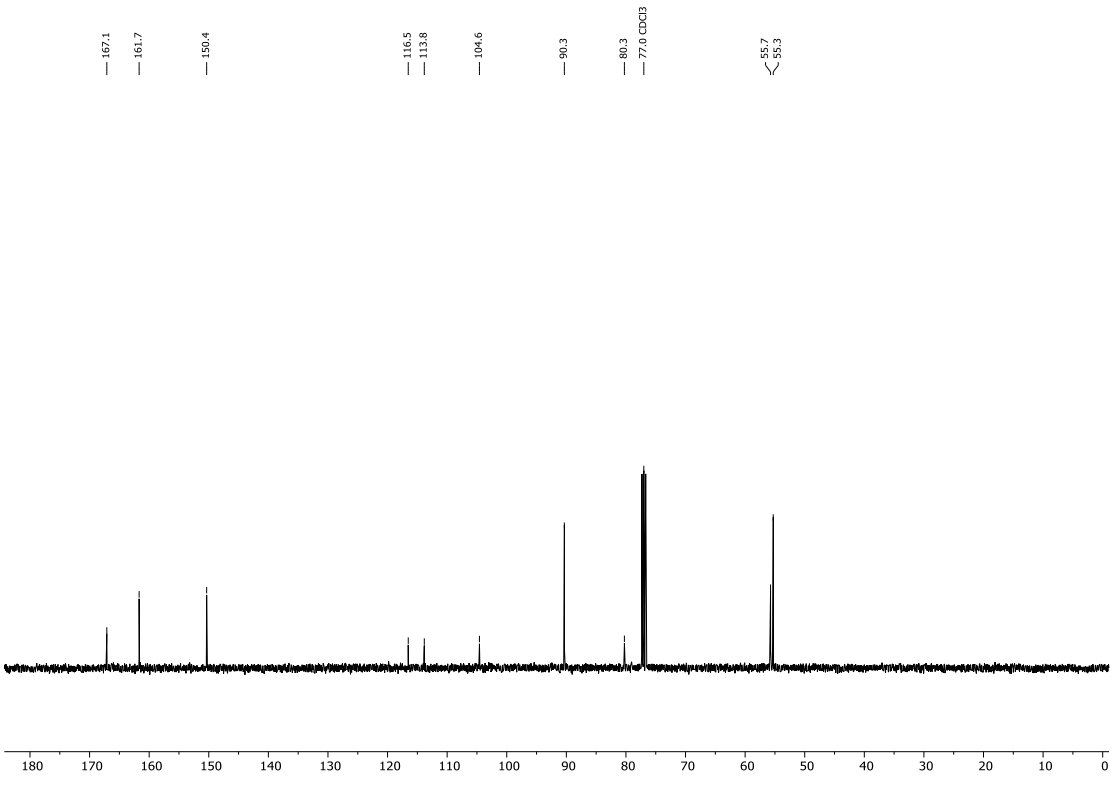
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150.4
116.5
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90.3
80.3
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55.7
55.3
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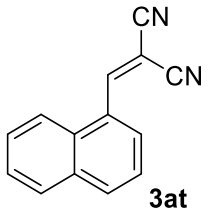
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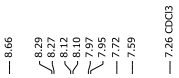
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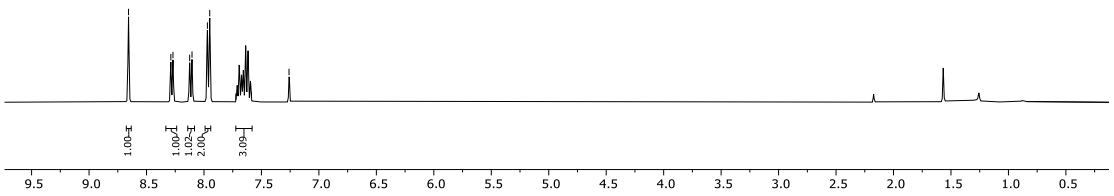
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6.5
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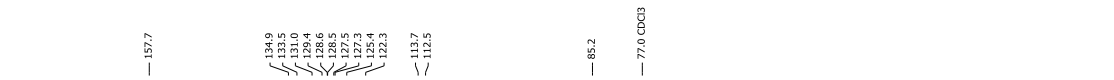
0.5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113.7
112.5
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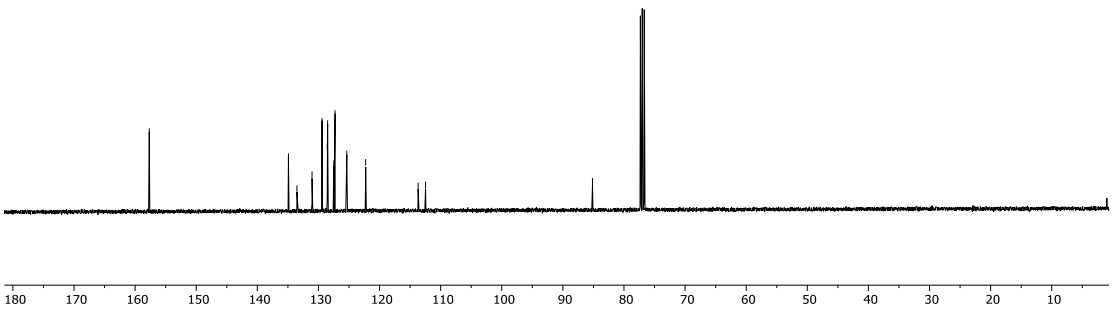
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20
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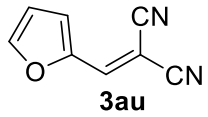
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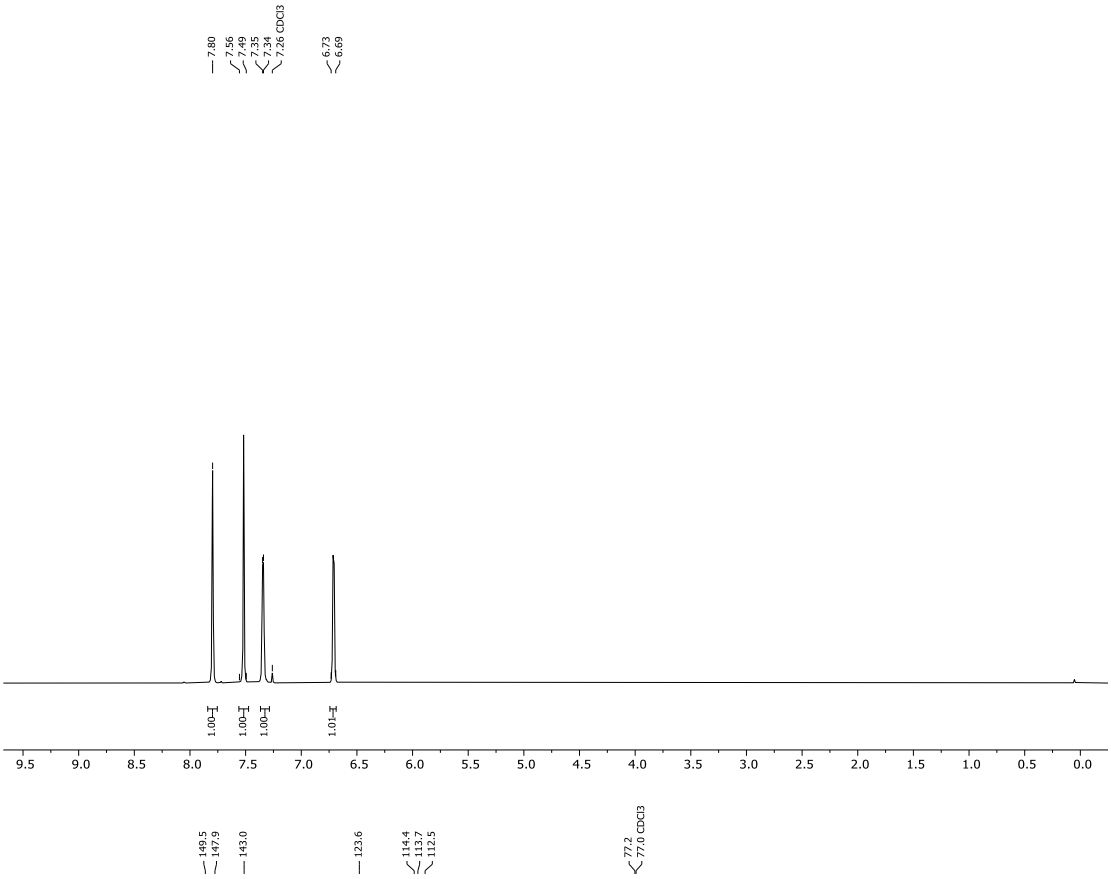
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6.69
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1.00
1.00
1.01
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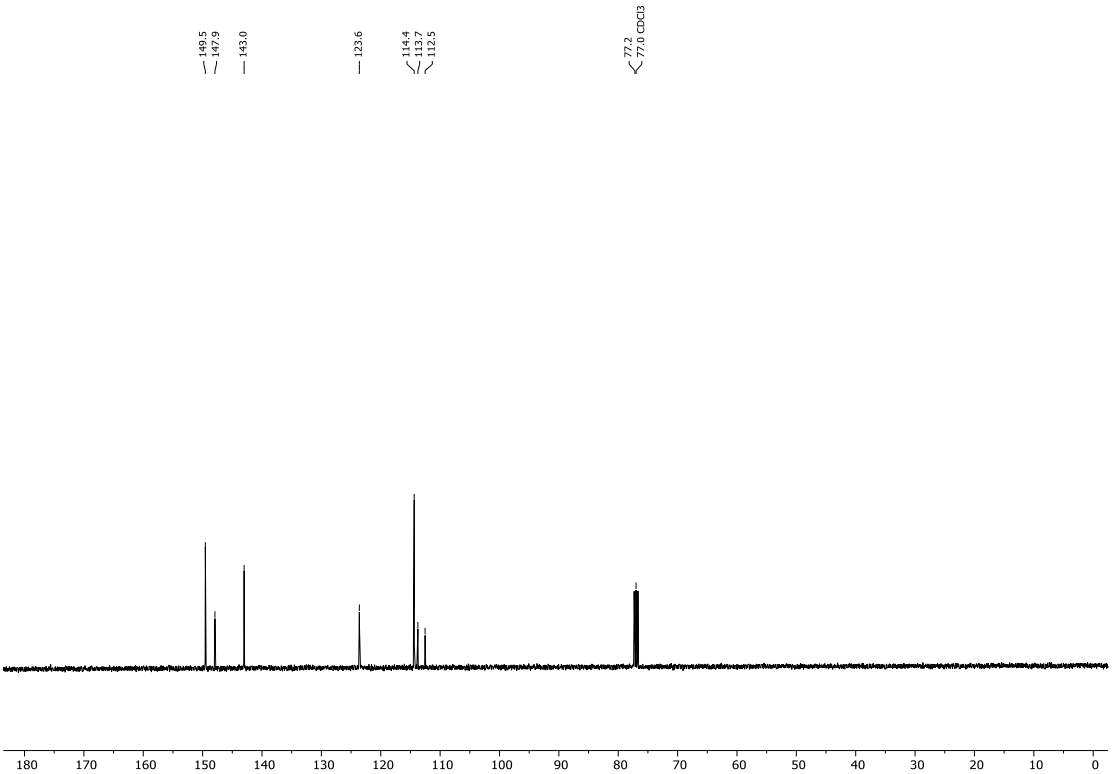
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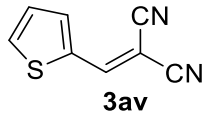
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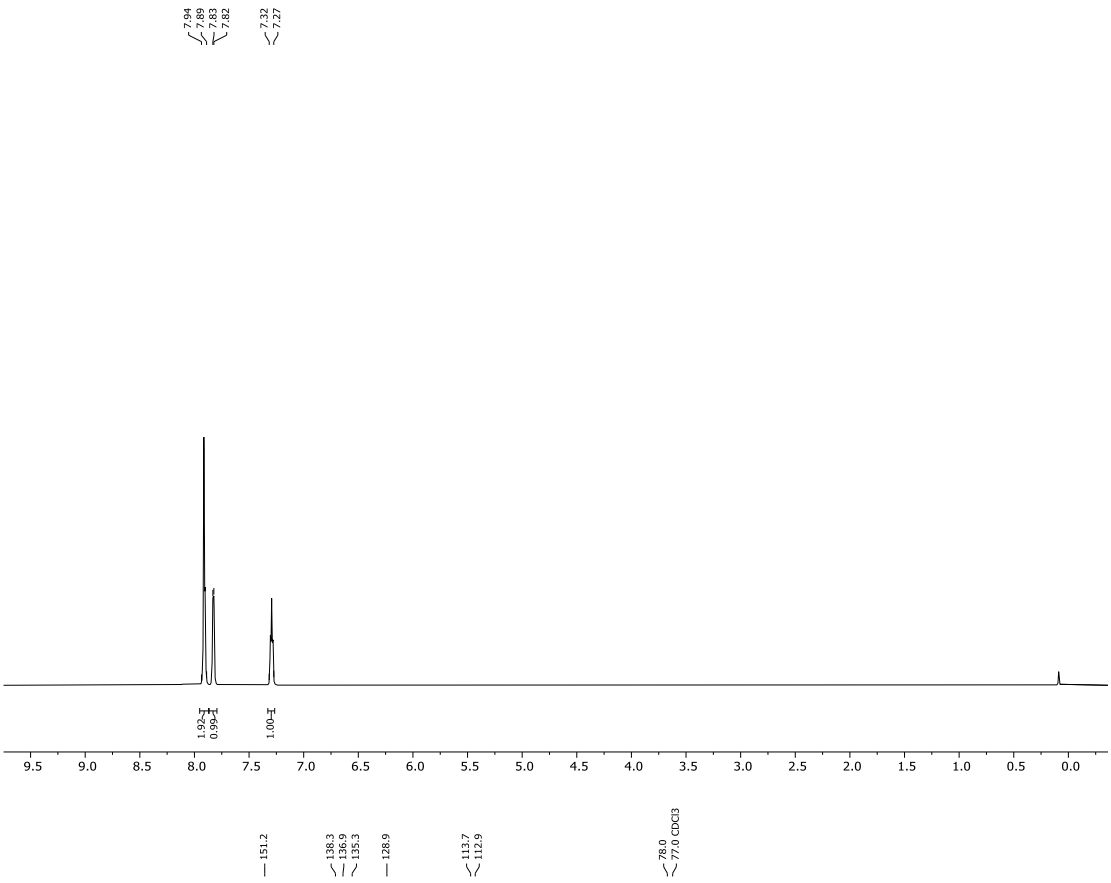
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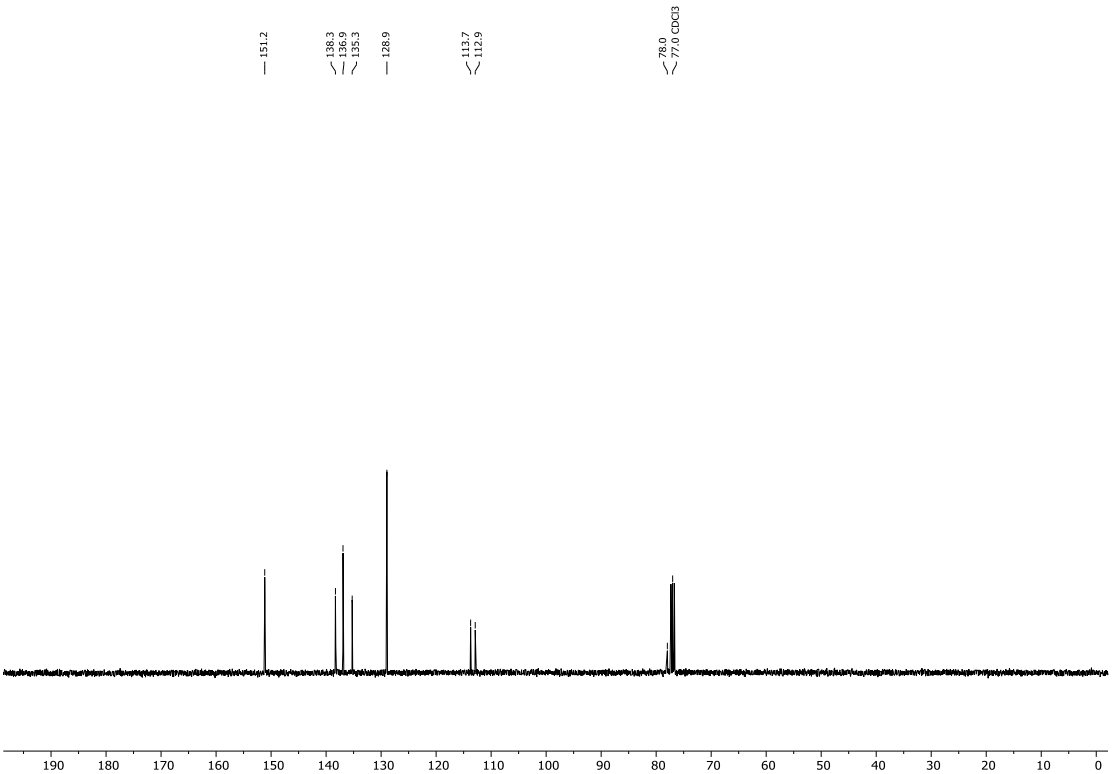
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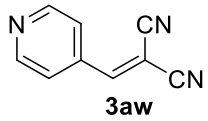
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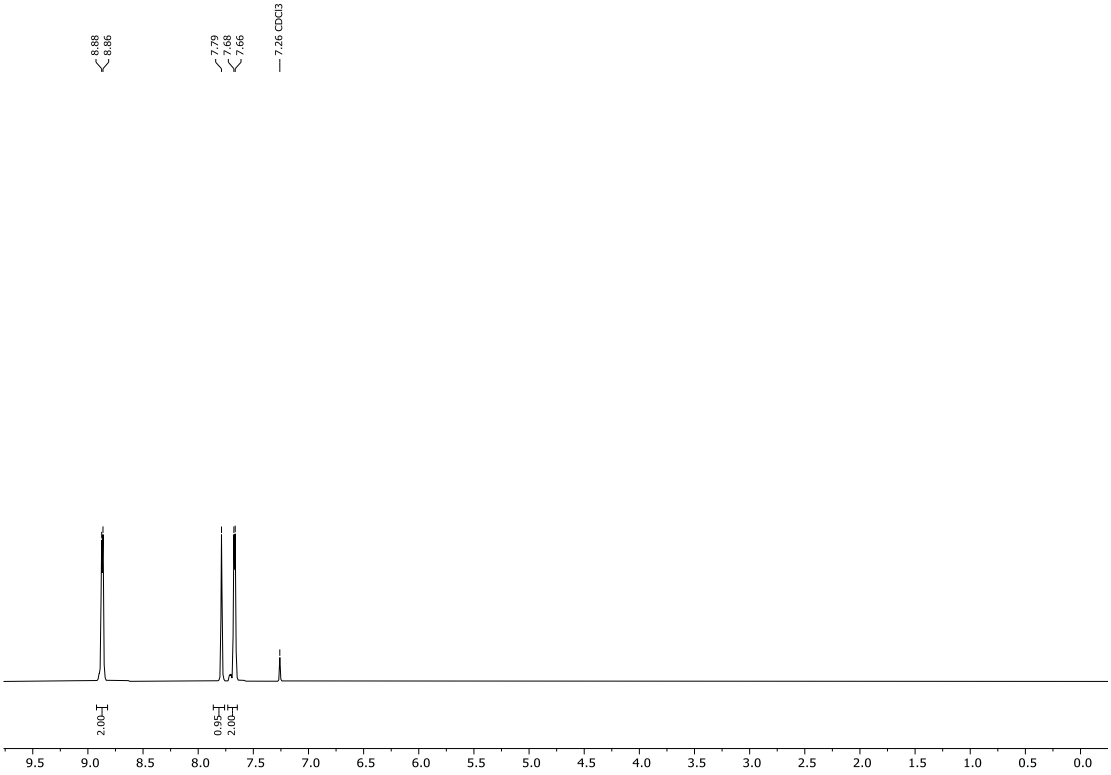
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0.95
2.00
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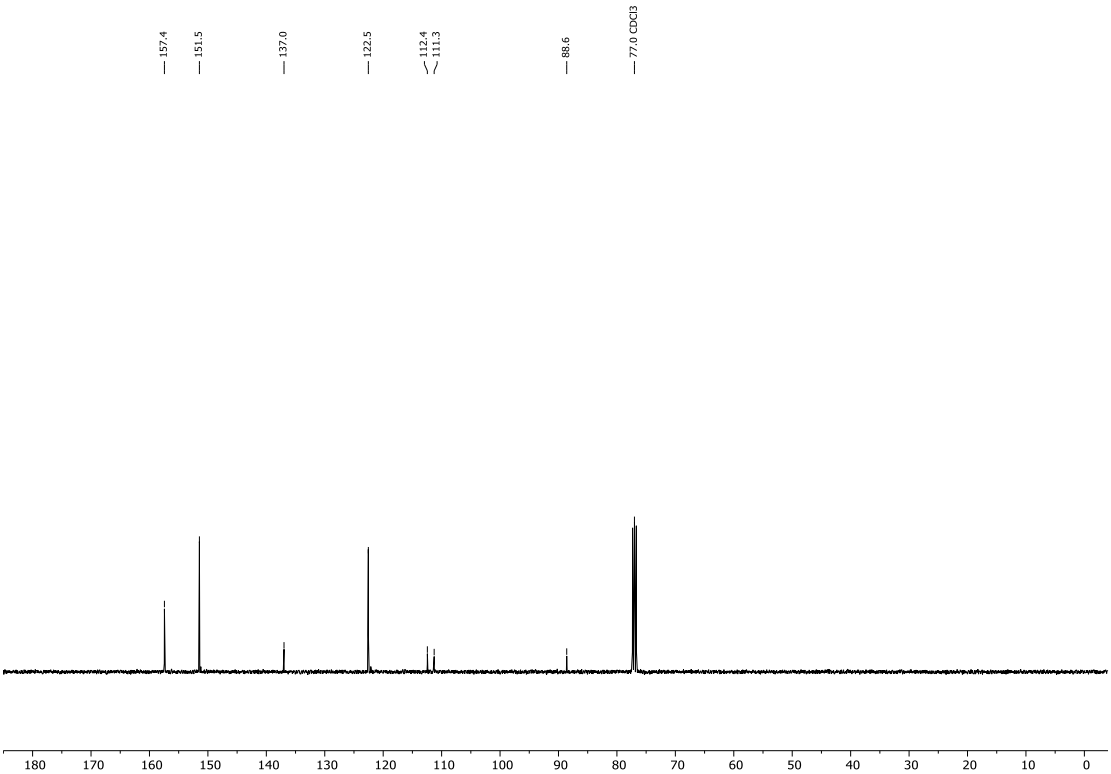
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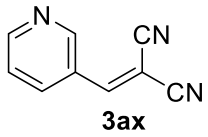
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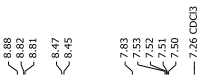
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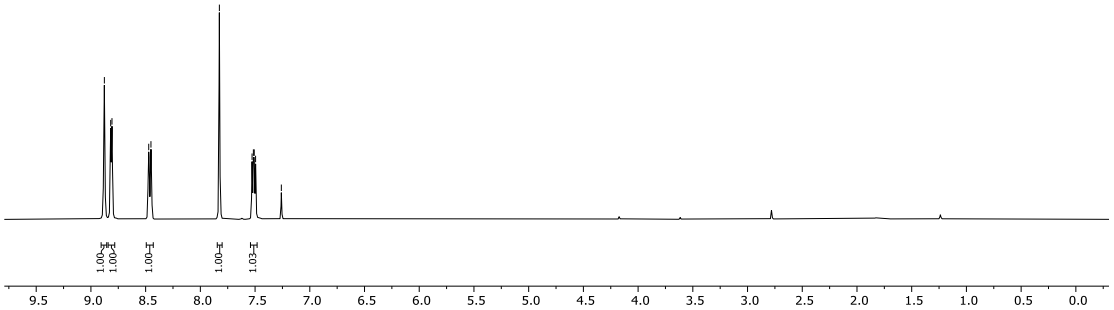
7.50
7.26 CDCl3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1.00
1.00
1.00
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


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154.6
152.3
135.6
127.0
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112.9
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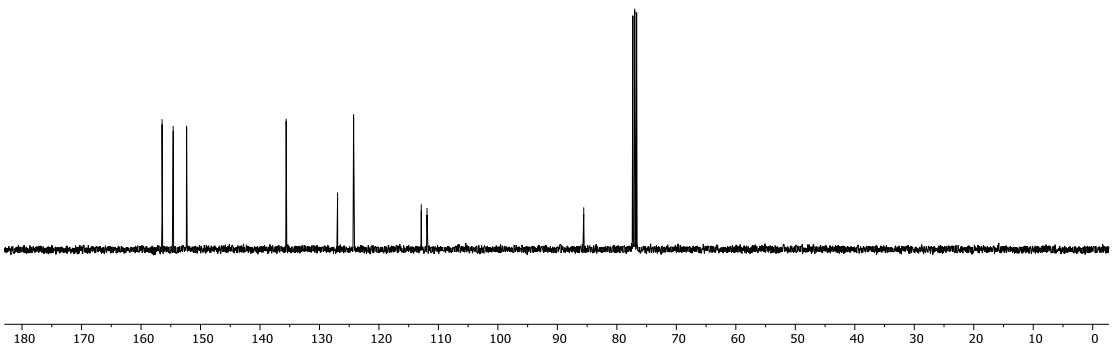
85.6
77.0 CDCl3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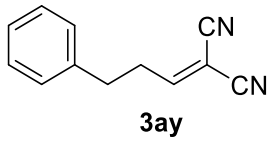
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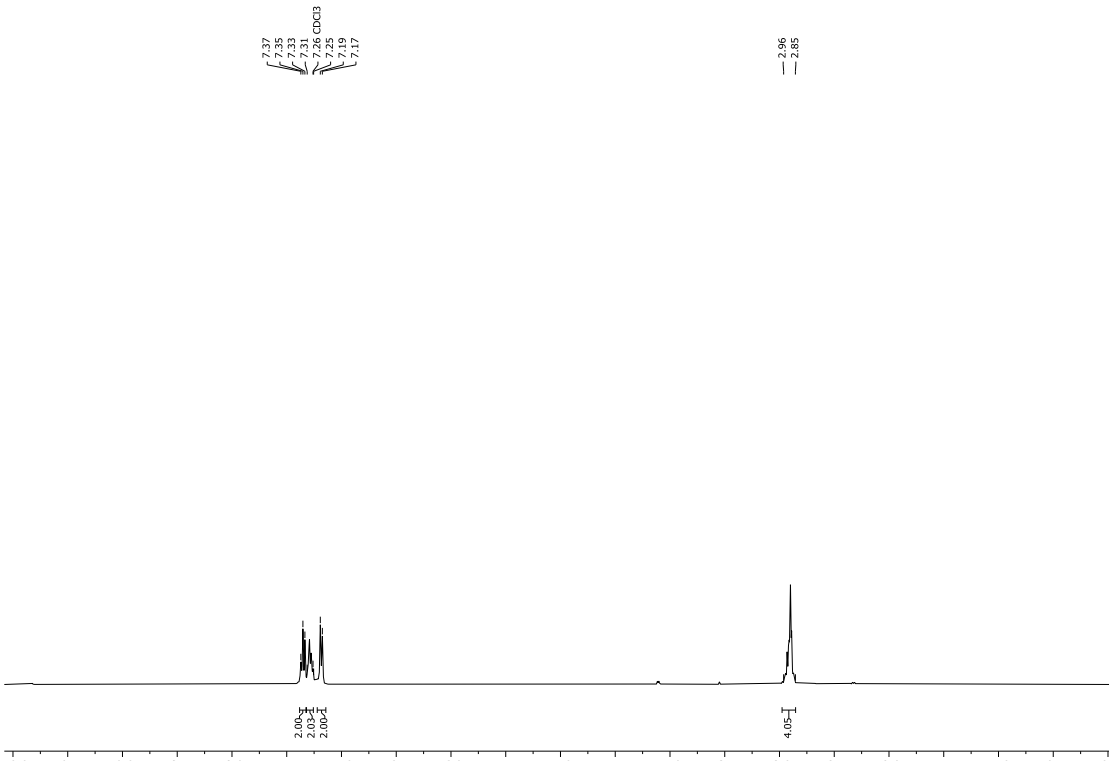
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2.85
2.00
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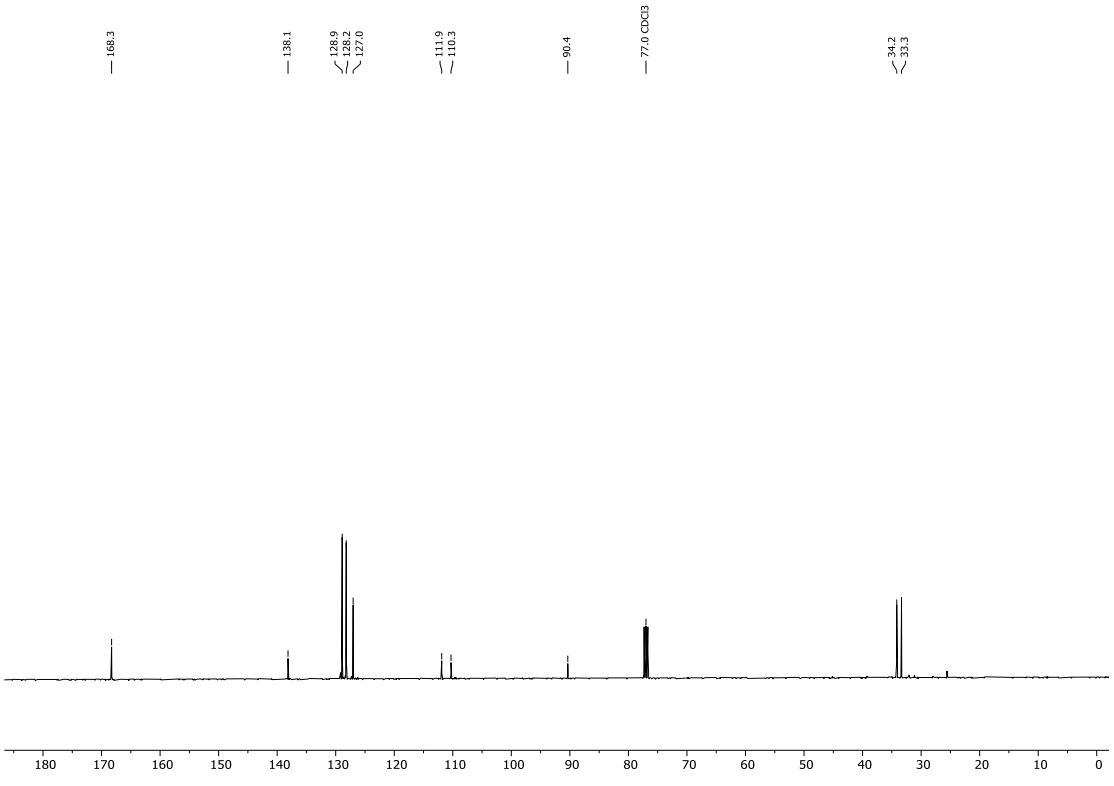
2.00
4.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5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90.4
77.0 CDCl3
34.2
33.3
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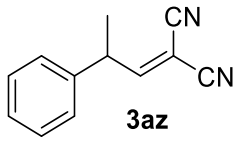
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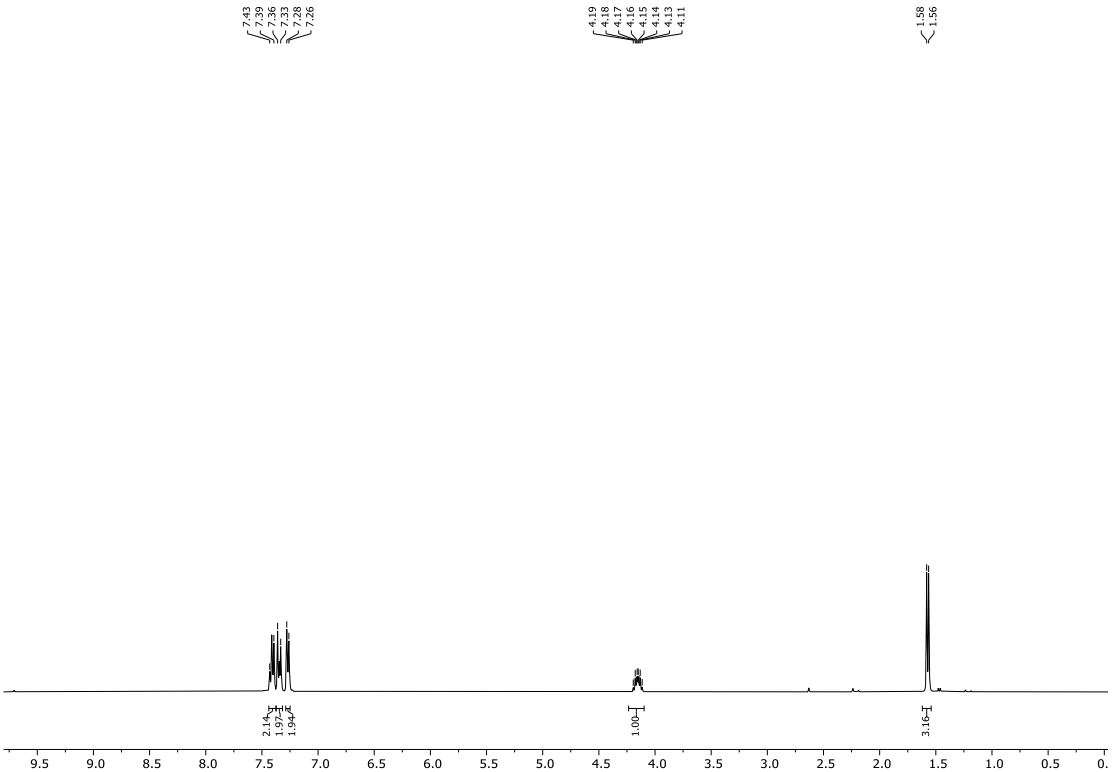
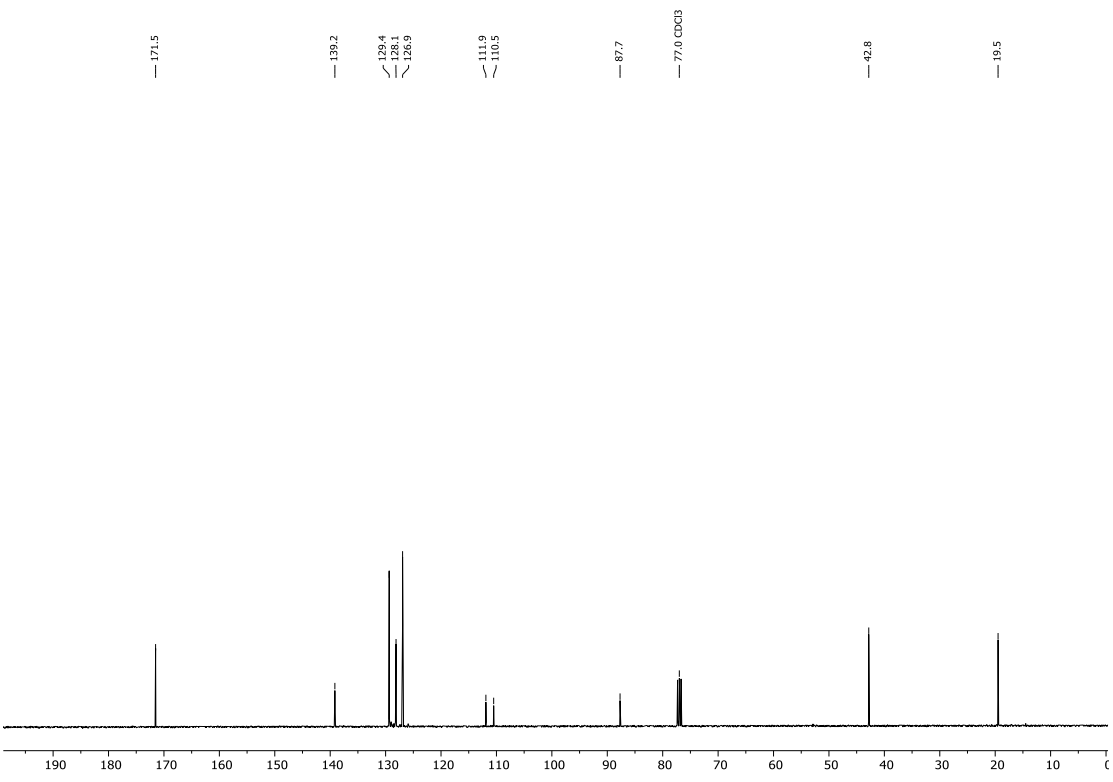
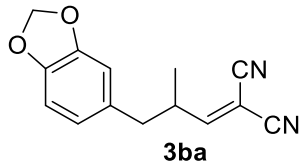

7.43
7.39
7.36
7.33
7.28
7.26
4.19
4.18
4.17
4.16
4.15
4.14
4.13
4.11
1.58
1.56
2.14
1.97
1.94
1.00
3.16


171.5
139.2
129.4
128.1
126.9
111.9
110.5
87.7
77.0 CDCl3
42.8
19.5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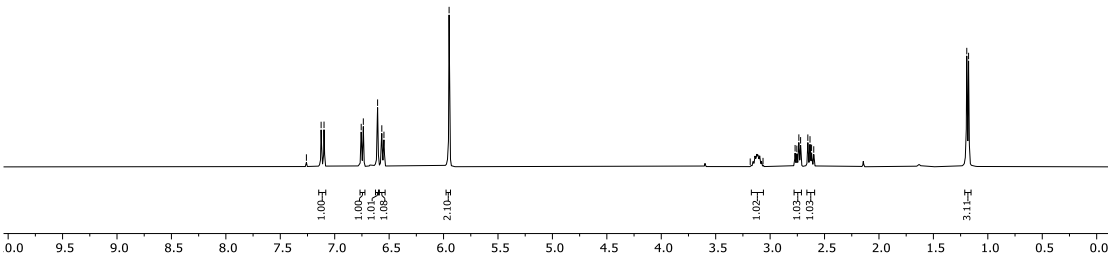
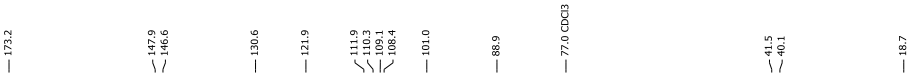
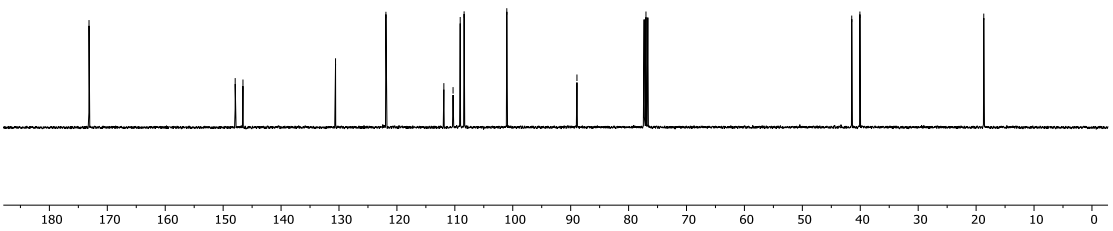
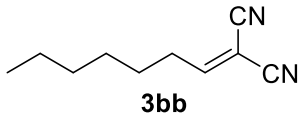
3ba


7.26 CDCl3
7.12
7.10
6.76
6.74
6.61
6.57
6.55
5.95
3.18
3.07
2.77
2.75
2.74
2.72
2.65
2.63
2.62
2.60
1.19
1.18


1.00
1.00
1.01
1.08
2.10
1.02
1.03
1.03
3.11
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


173.2
147.9
146.6
130.6
121.9
111.9
110.3
109.1
108.4
101.0
88.9
77.0 CDCl3
41.5
40.1
18.7


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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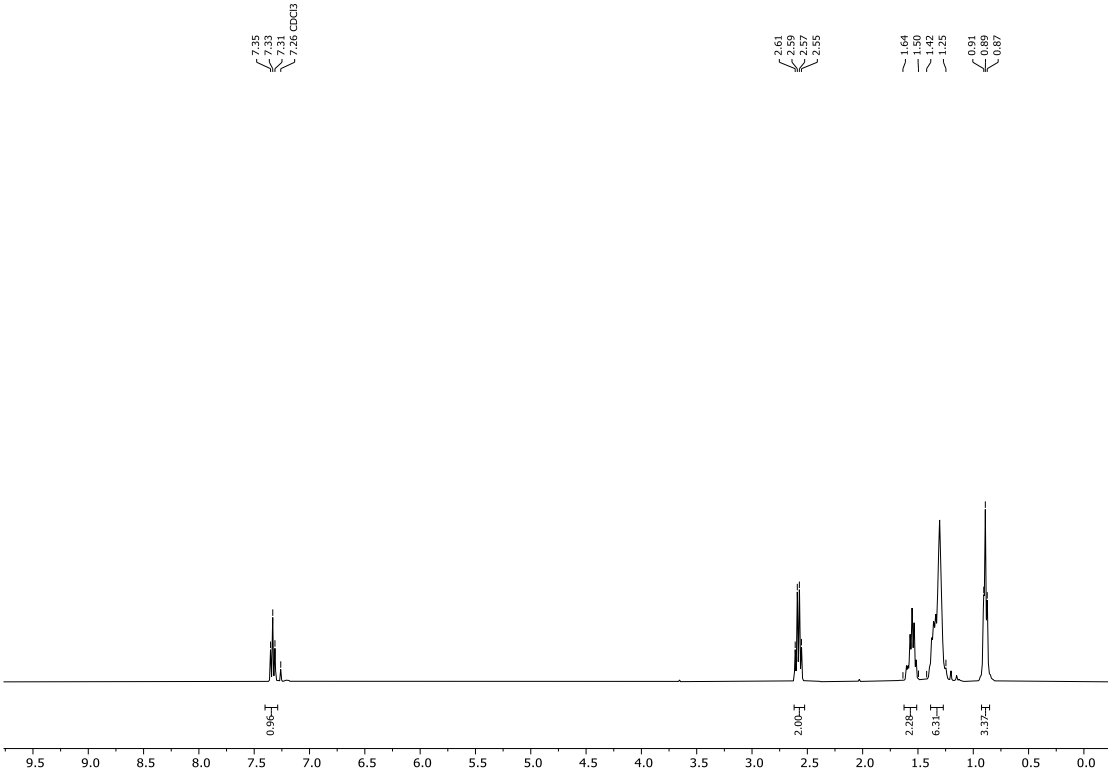
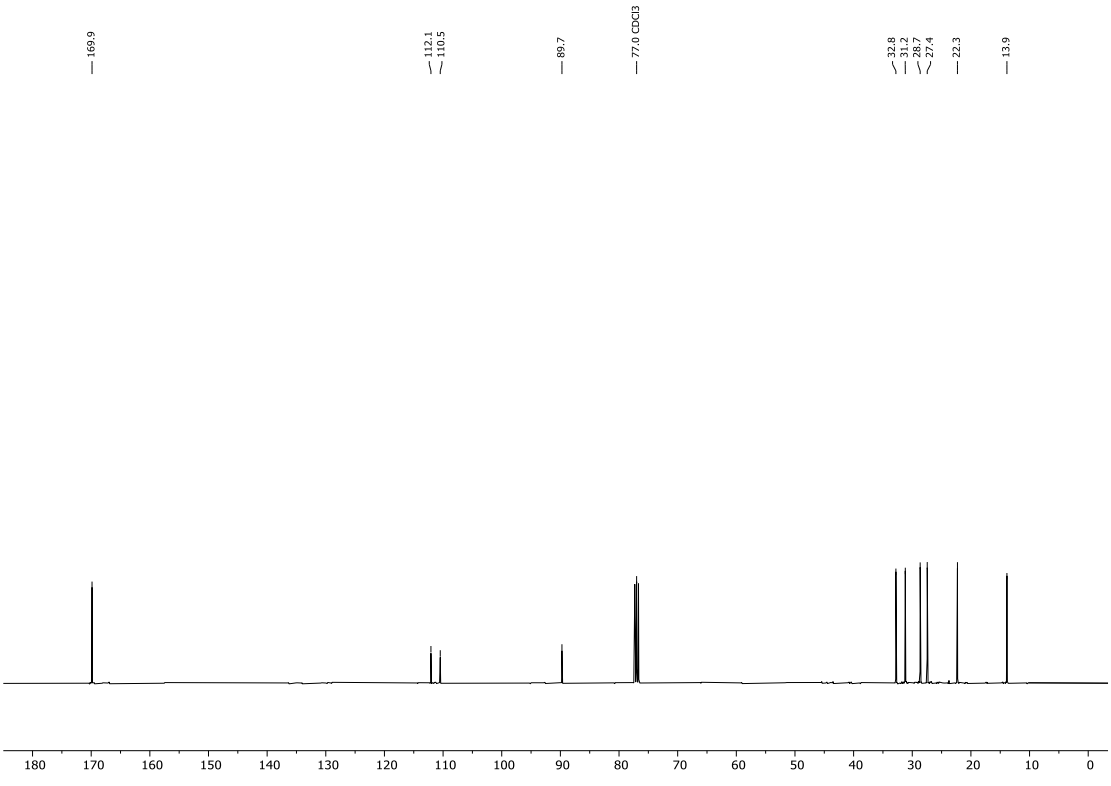
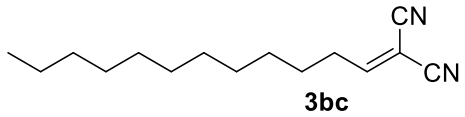

7.35
7.33
7.31
7.26 CDCl3
2.61
2.59
2.57
2.55
1.64
1.50
1.42
1.25
0.91
0.89
0.87
0.96
2.00
2.28
6.31
3.37
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


169.9
112.1
110.5
89.7
77.0 CDCl3
32.8
31.2
28.7
27.4
22.3
13.9
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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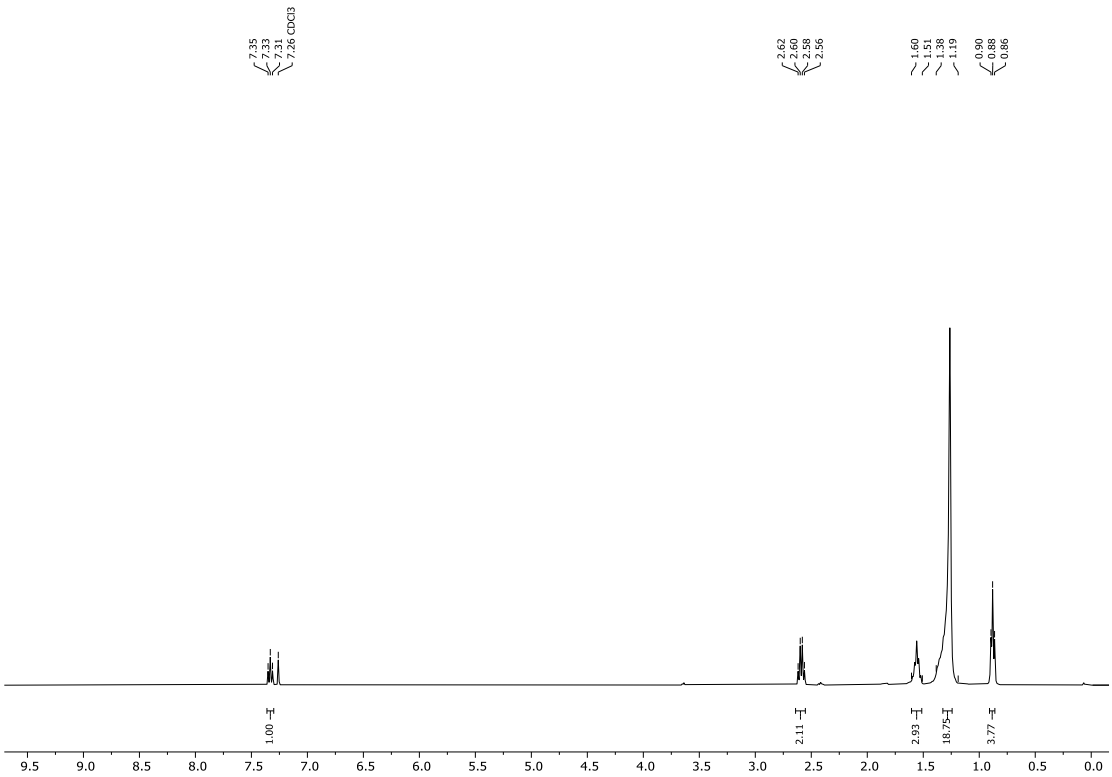
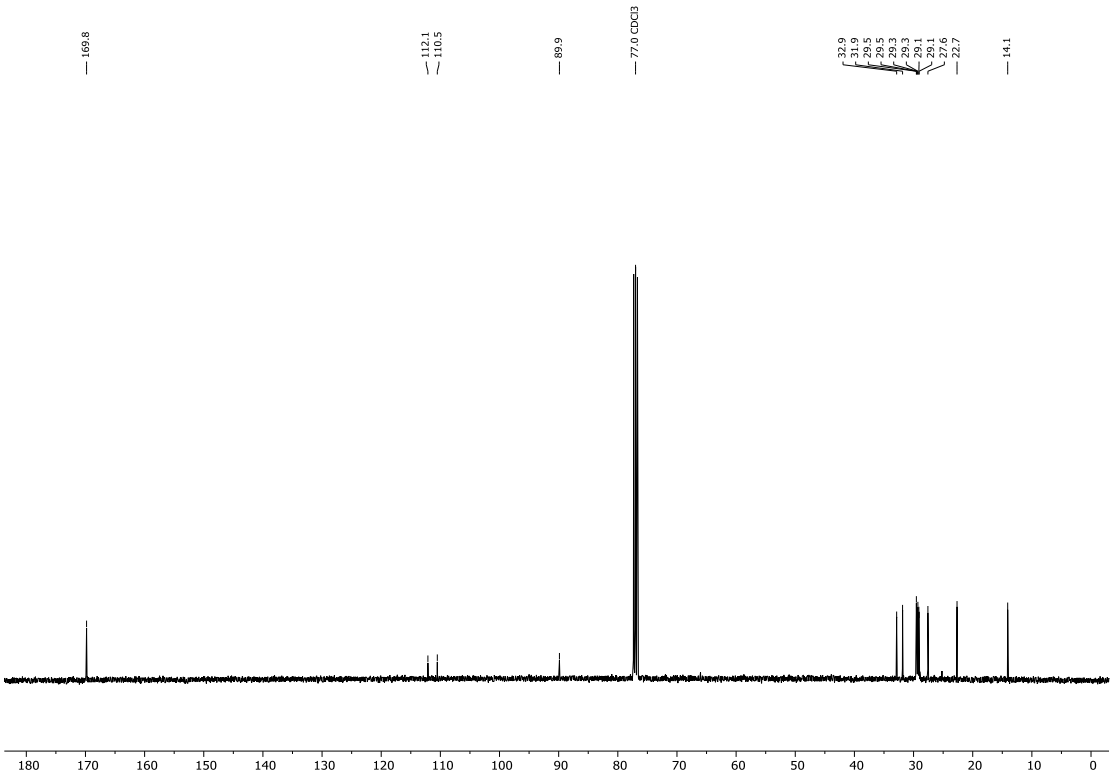
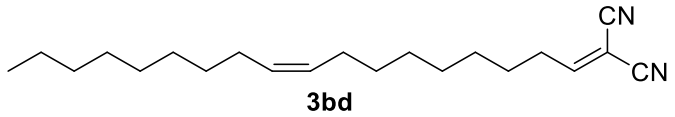

7.35
7.33
7.31
7.26 CDCl3
2.62
2.60
2.58
2.56
1.60
1.51
1.38
1.19
0.90
0.88
0.86
1.00
2.11
2.93
18.75
3.77


169.8
112.1
110.5
89.9
77.0 CDCl3
32.9
31.9
29.5
29.5
29.3
29.3
29.1
29.1
27.6
22.7
14.1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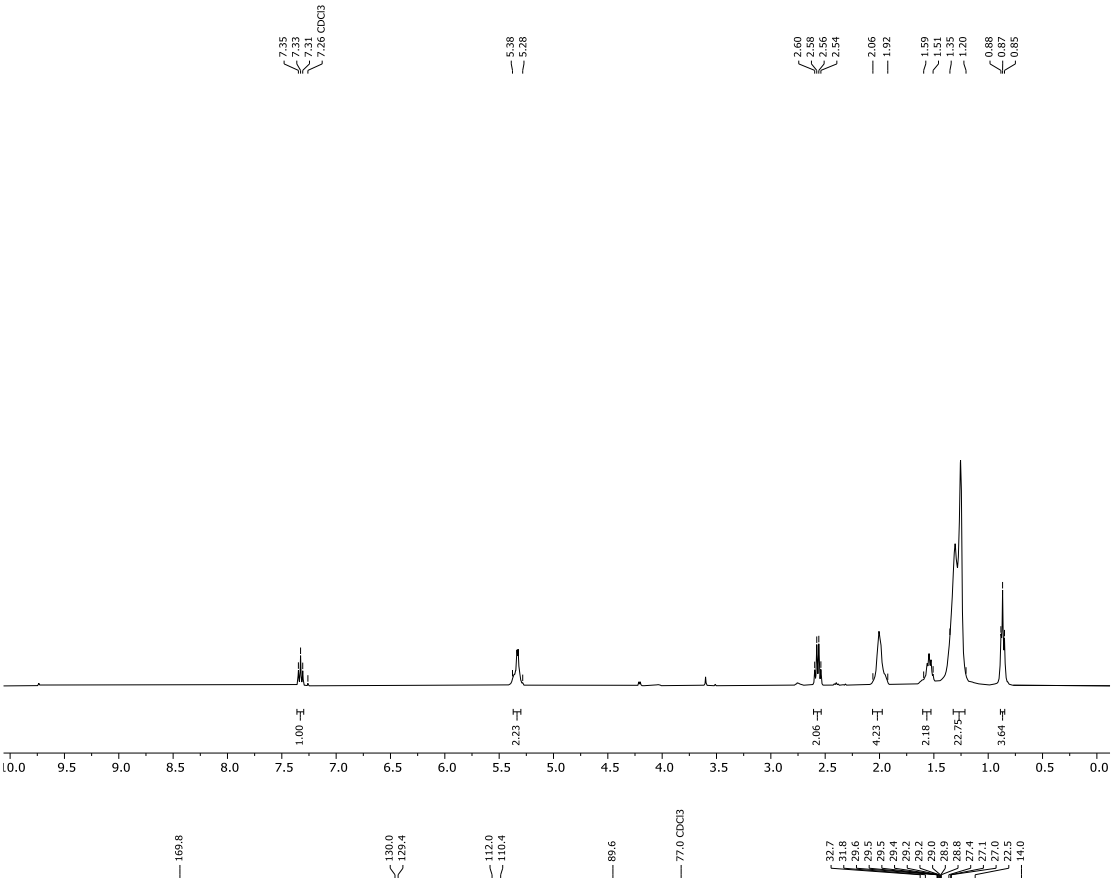
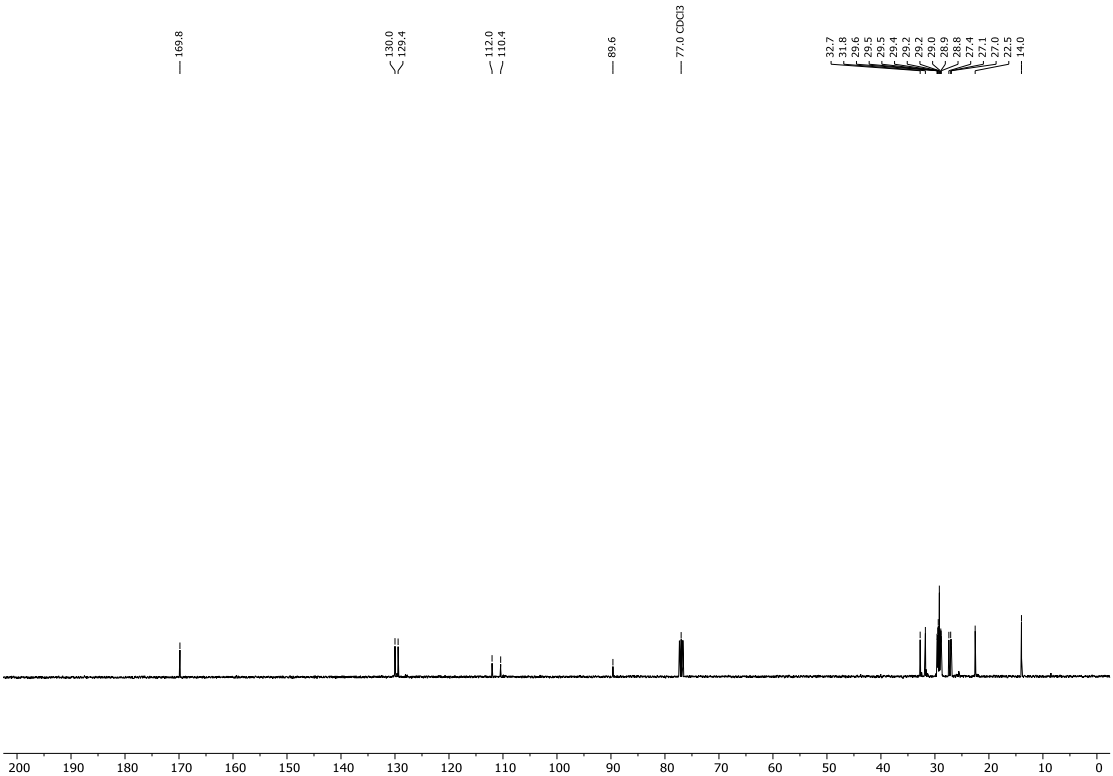
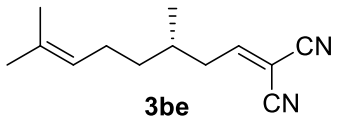

7.35
7.33
7.31
7.26 CDCl3
5.38
5.28
2.60
2.58
2.56
2.54
2.06
1.92
1.59
1.51
1.35
1.20
0.88
0.87
0.85
1.00
2.23
2.06
4.23
2.18
22.75
3.64


169.8
130.0
129.4
112.0
110.4
89.6
77.0 CDCl3
32.7
31.8
29.6
29.5
29.4
29.2
29.2
29.0
28.9
28.8
27.4
27.1
27.0
22.6
14.0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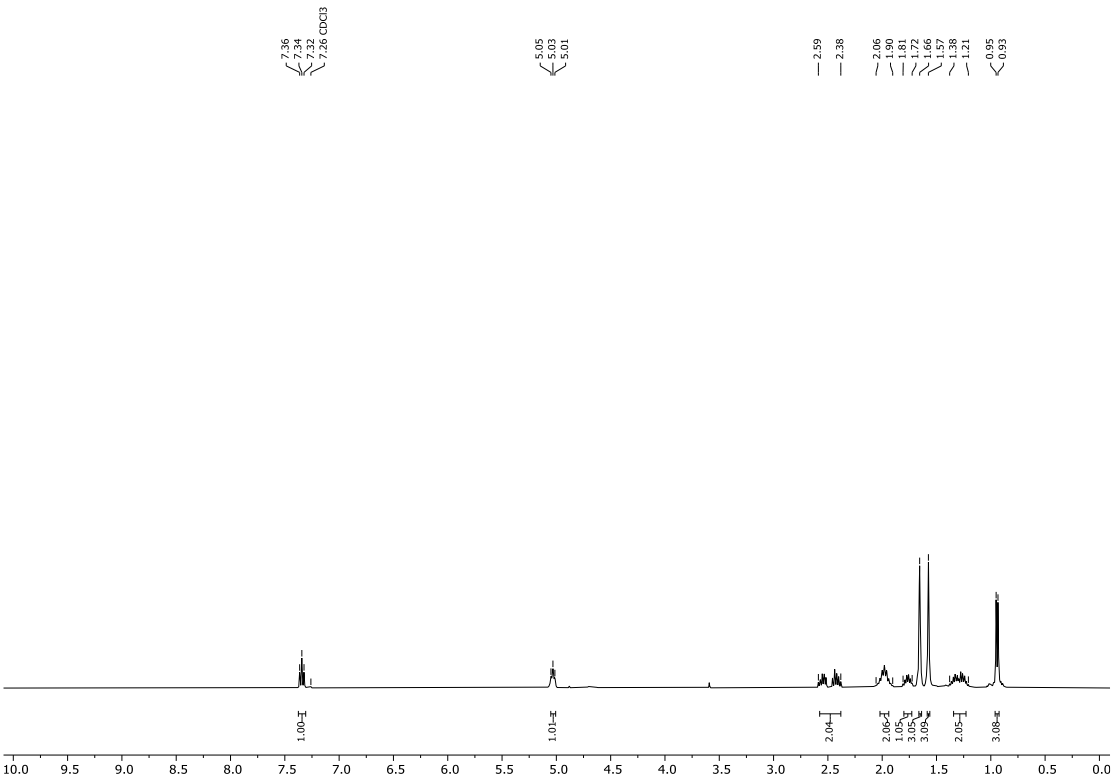
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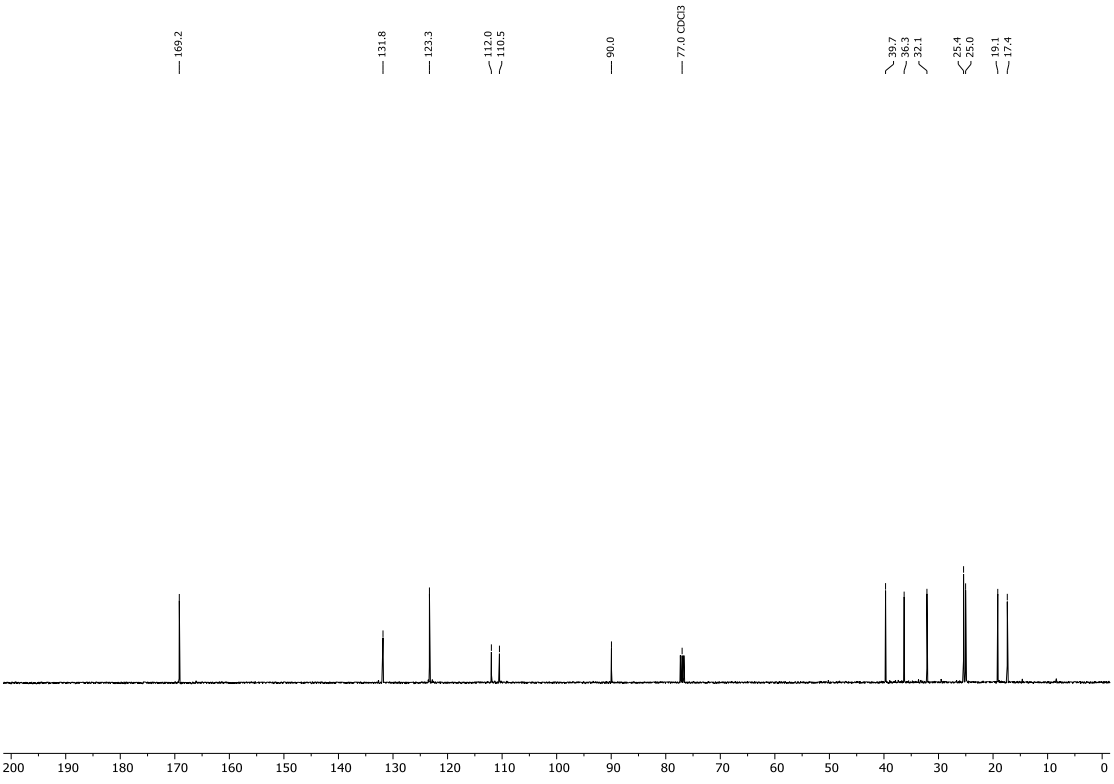
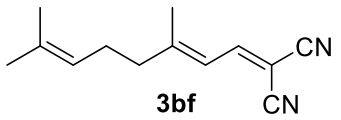
7.34
7.32
7.26 CDCl3
5.05
5.03
5.01
2.59
2.38
2.06
1.90
1.81
1.72
1.66
1.57
1.38
1.21
0.95
0.93
1.00
1.01
2.04
2.06
1.05
3.05
3.09
2.05
3.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


169.2
131.8
123.3
112.0
110.5
90.0
77.0 CDCl3
39.7
36.3
32.1
25.4
25.0
19.1
17.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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CN

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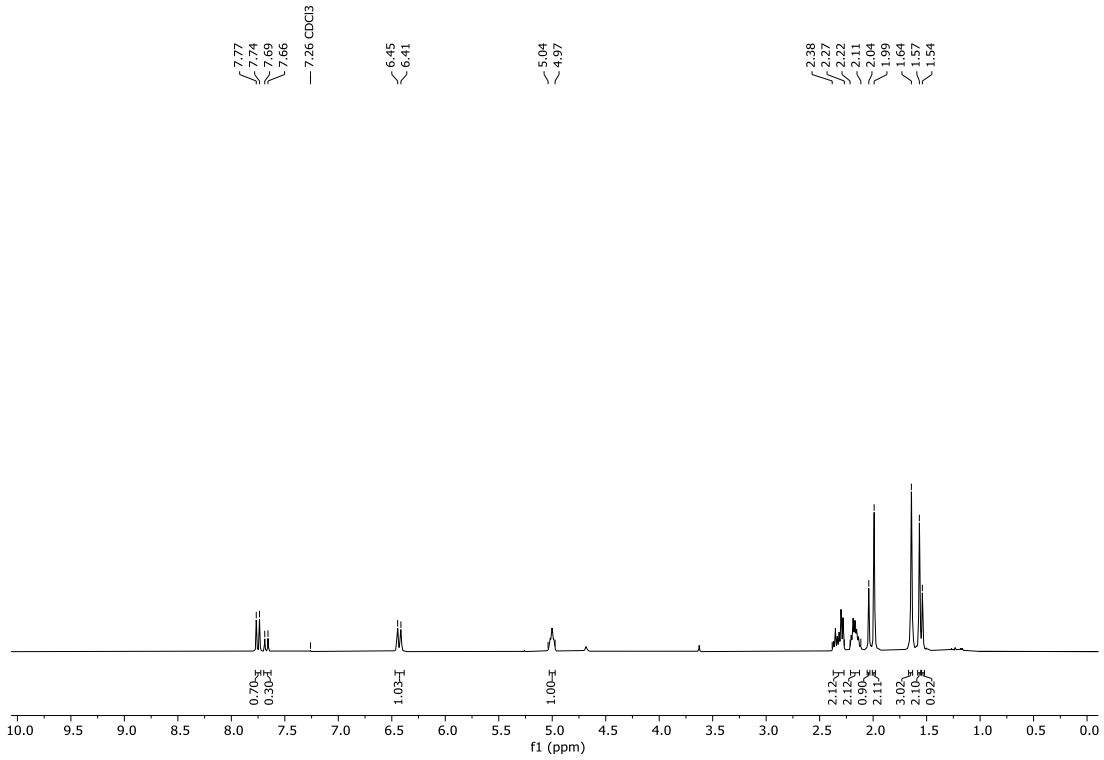
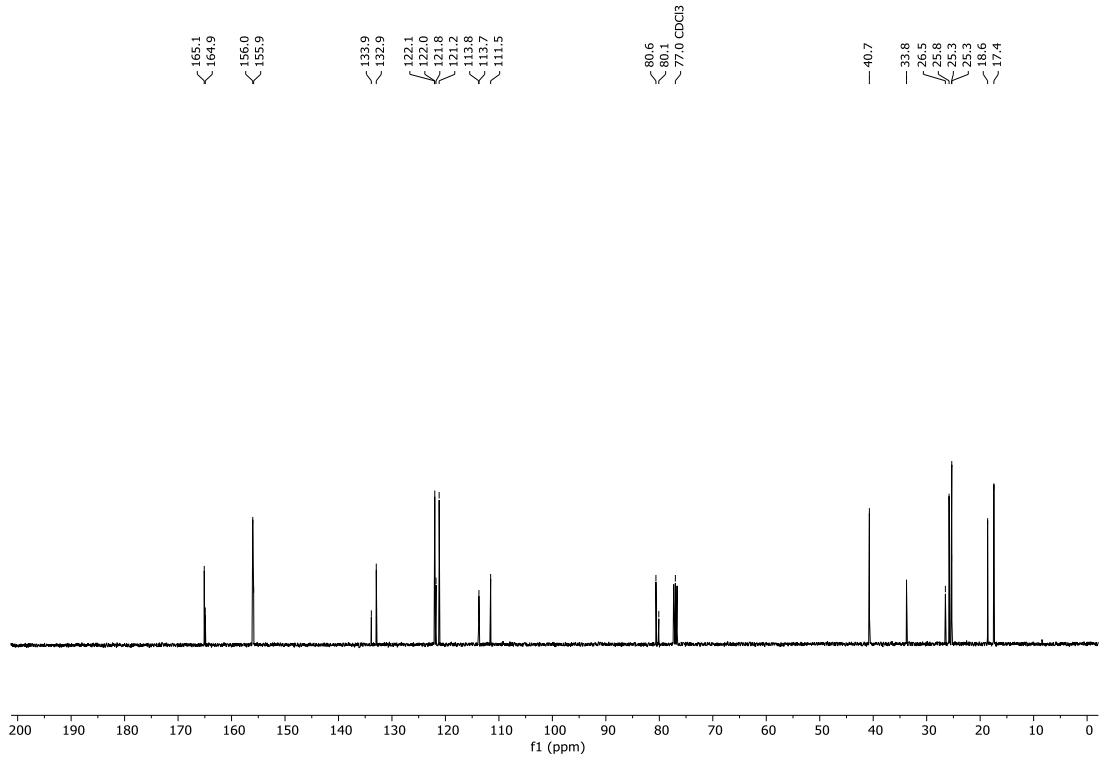
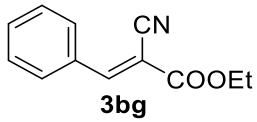
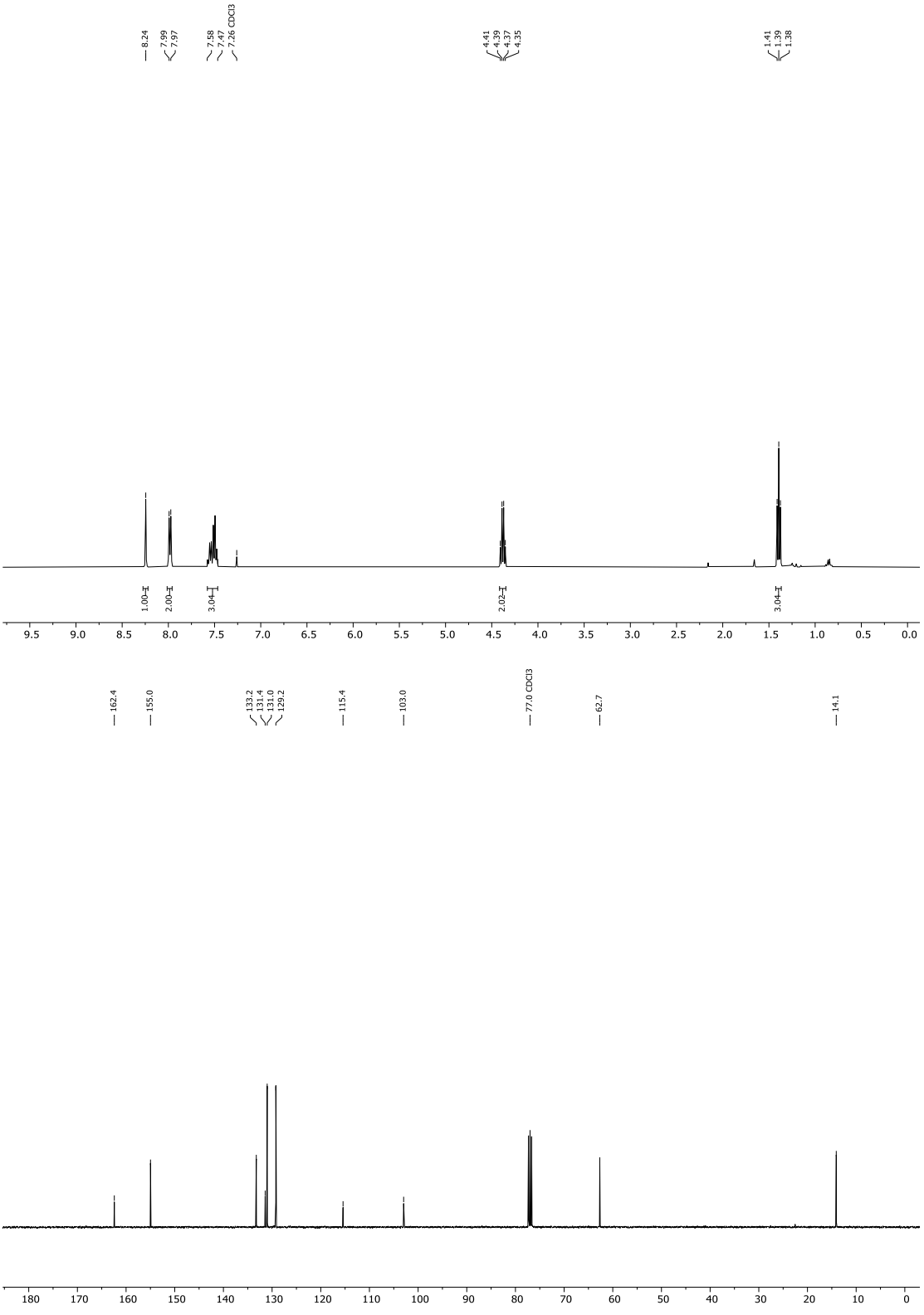

7.77
7.74
7.69
7.66
7.26 CDCl3
6.45
6.41
5.04
4.97
2.38
2.27
2.22
2.11
2.04
1.99
1.64
1.57
1.54
0.70
0.30
1.03
1.00
2.12
2.12
0.90
2.11
3.02
2.10
0.92
f1 (ppm)


165.1
164.9
156.0
155.9
133.9
132.9
122.1
122.0
121.8
121.2
113.8
113.7
111.5
80.6
80.1
77.0 CDCl3
40.7
33.8
26.5
25.8
25.3
25.3
18.6
17.4
f1 (ppm)


CN
COOEt

3bg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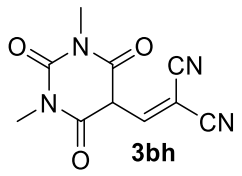
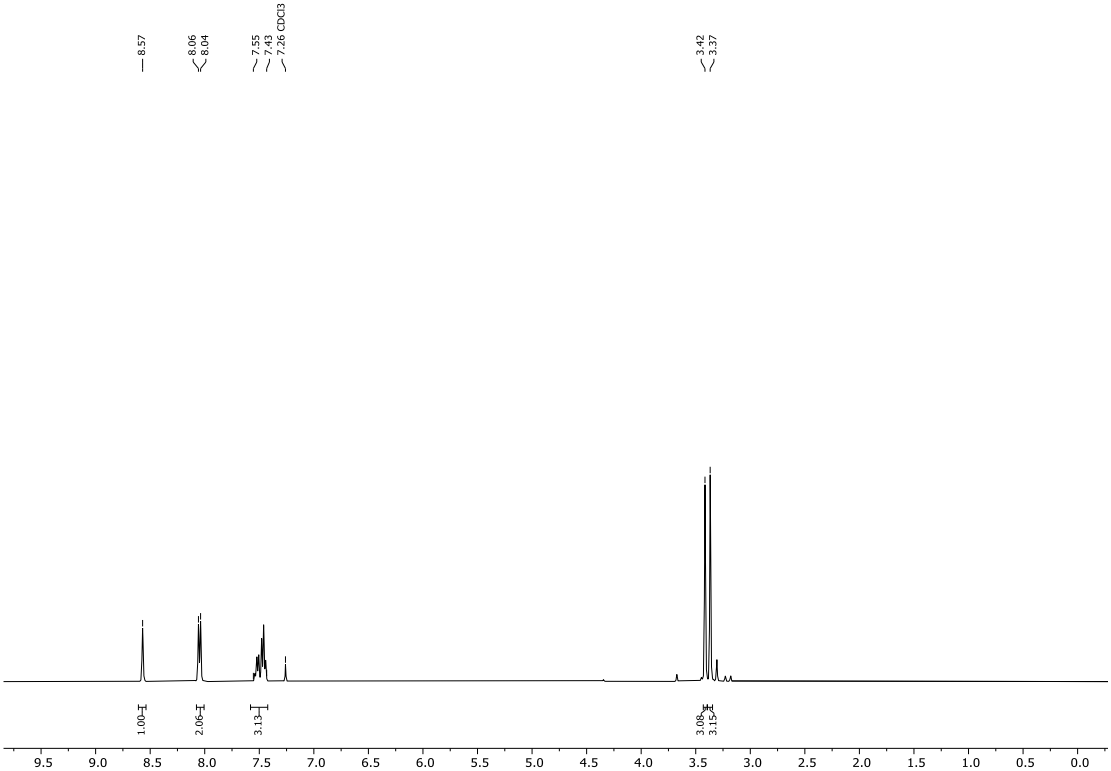
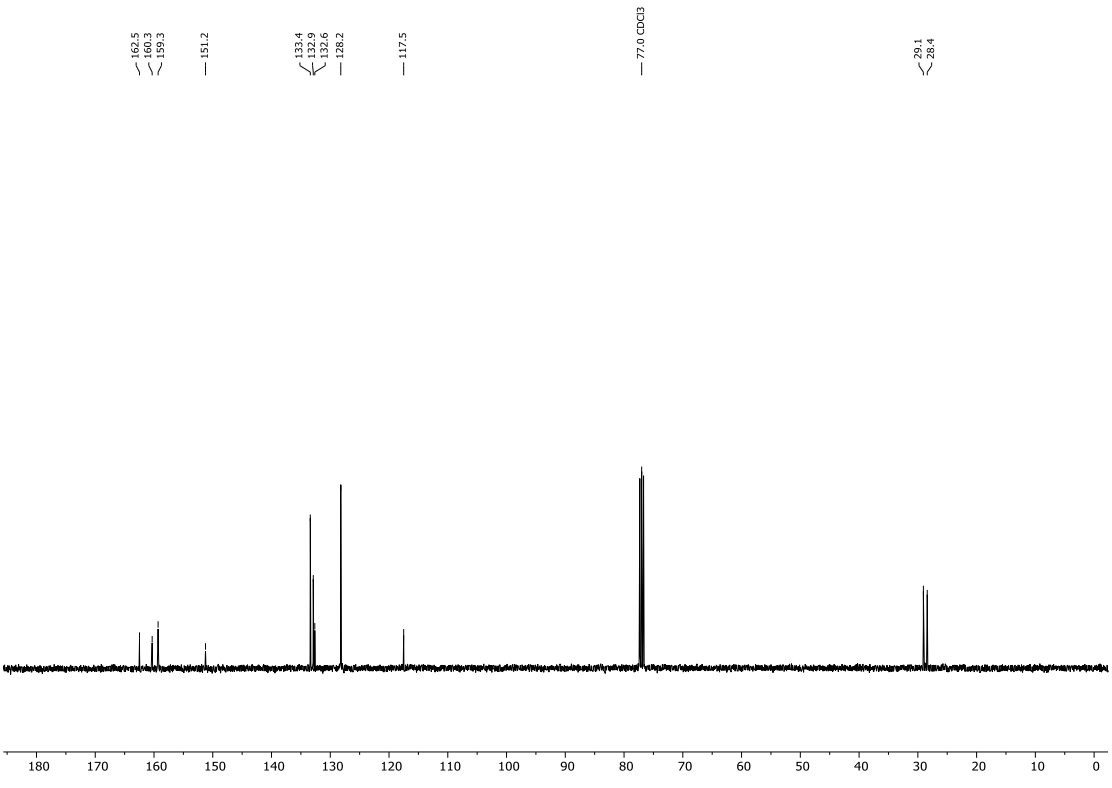
7.99
7.97
7.58
7.47
7.26 CDCl3
4.41
4.39
4.37
4.35
1.41
1.39
1.38
1.00
2.00
3.04
2.02
3.04
162.4
155.0
133.2
131.4
131.0
129.2
115.4
103.0
77.0 CDCl3
62.7
14.1


O
N
O
CN
N
CN
O

3bh


8.57
8.06
8.04
7.55
7.43
7.26 CDCl3
3.42
3.37
1.00
2.06
3.13
3.08
3.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0


162.5
160.3
159.3
151.2
133.4
132.9
132.6
128.2
117.5
77.0 CDCl3
29.1
28.4
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0