Functionalisation of aldehydes via aerobic hydroacylation of azodicarboxylates 'on' water

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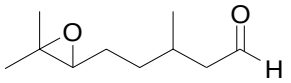
General Experimental

All reagents were purchased from Aldrich or AlfaAesar and were used as received without further purification. Aldehydes **1g**, **1l** and **1m** were synthesised using the methods of Vanderhaeghe, Terashima and Quici respectively.[1-3] All reactions were carried out with HPLC gradient grade water (demineralised) purchased from Fisher Scientific. All reactions were carried out in carousel tubes (15 cm × 2 cm) equipped with an octagon-shaped magnetic stirrer bar (12.7 mm × 3 mm). Where described below petrol refers to petroleum ether (40-60). All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254μm). Flash column chromatography was carried out with Kiesegel 60M 0.04/0.063mm (200-400 mesh) silica gel. ^{1}H NMR spectra were recorded at 500 MHz and 600 MHz and ^{13}C NMR at 125 MHz and 150 MHz on Bruker AMX500 and AMX600 spectrometers at ambient temperature in $CDCl_3$ as indicated below The chemical shifts (δ) for ^{1}H and ^{13}C are quoted relative to residual signals of the solvent on the ppm scale. Coupling constants (*J* values) are reported in Hertz (Hz) and are H-H coupling constants unless otherwise stated. Signal multiplicities in ^{13}C NMR were determined using the distortionless enhancement by phase transfer (DEPT) spectral editing technique. For hydrazides **2a-d** and hydrazides **3a-m** only the peaks for the major rotamer are assigned. Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer 343 polarimeter. Chiral High Performance Liquid Chromatography (HPLC) was performed on a Varian HPLC instrument equipped with a manual injector, binary pump, and a UV detector (214 nm) using CHIRALCEL® OD column (4.6mm x 250mm, 10μm) from Chiral Technologies (West Chester, PA) eluting with hexane:*i*-PrOH (99:1) with a flow rate of 0.6 mL/min.

5-(3,3-dimethyloxiran-2-yl)-3-methylpentanal 1h

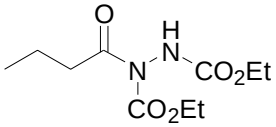


To a stirring solution of (±)-citronellal (771 mg, 902 μL, 5 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of *m*-CPBA (1.04 g, 6 mmol) in CH_2Cl_2 (10 mL) at 0 °C under argon. The reaction mixture was allowed to warm to 21 °C and stirred for a further 90 min. The reaction mixture was filtered and the filtrate washed with sat. K_2CO_3 (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to afford 5-(3,3-dimethyloxiran-2-yl)-3-methylpentanal as a colourless oil (809 mg, 4.75 mmol, 95%) as a 1:1 mixture of diastereoisomers A and B: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1H), 2.70-2.68 (m, 1H), 2.42 (ddd, *J* = 2.0, 3.5 and 11.0 Hz, 1H), 2.30-2.25 (m, 1H), 2.14-2.09 (m, 1H), 1.60-1.42 (m, 4H), 1.30 (s, 3H), 1.26 (s, 3H of diastereoisomer A, 1.5H), 1.26 (s, 3H of diastereoisomer B, 1.5H), 0.98 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.7 (CH), 202.6 (CH), 64.3 (CH_2), 64.2 (CH_2), 58.4 (C), 58.3 (C), 51.0 (CH_2), 50.9 (CH_2), 33.5 (CH_2), 27.9 (CH), 26.4 (CH_2), 26.4 (CH_2), 25.0 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 18.7 (CH_3), 18.7 (CH_3); IR (thin film) 2960, 2927, 1722 cm^{-1}; LRMS (FAB) 193 (60, $[M+Na]^+$), 169 (100); HRMS (FAB) calcd for $C_{10}H_{18}O_2Na$ $[M+Na]^+$ 193.1205, observed 193.1208.

General Procedure for the functionalisation of aldehyde with DEAD and DIAD

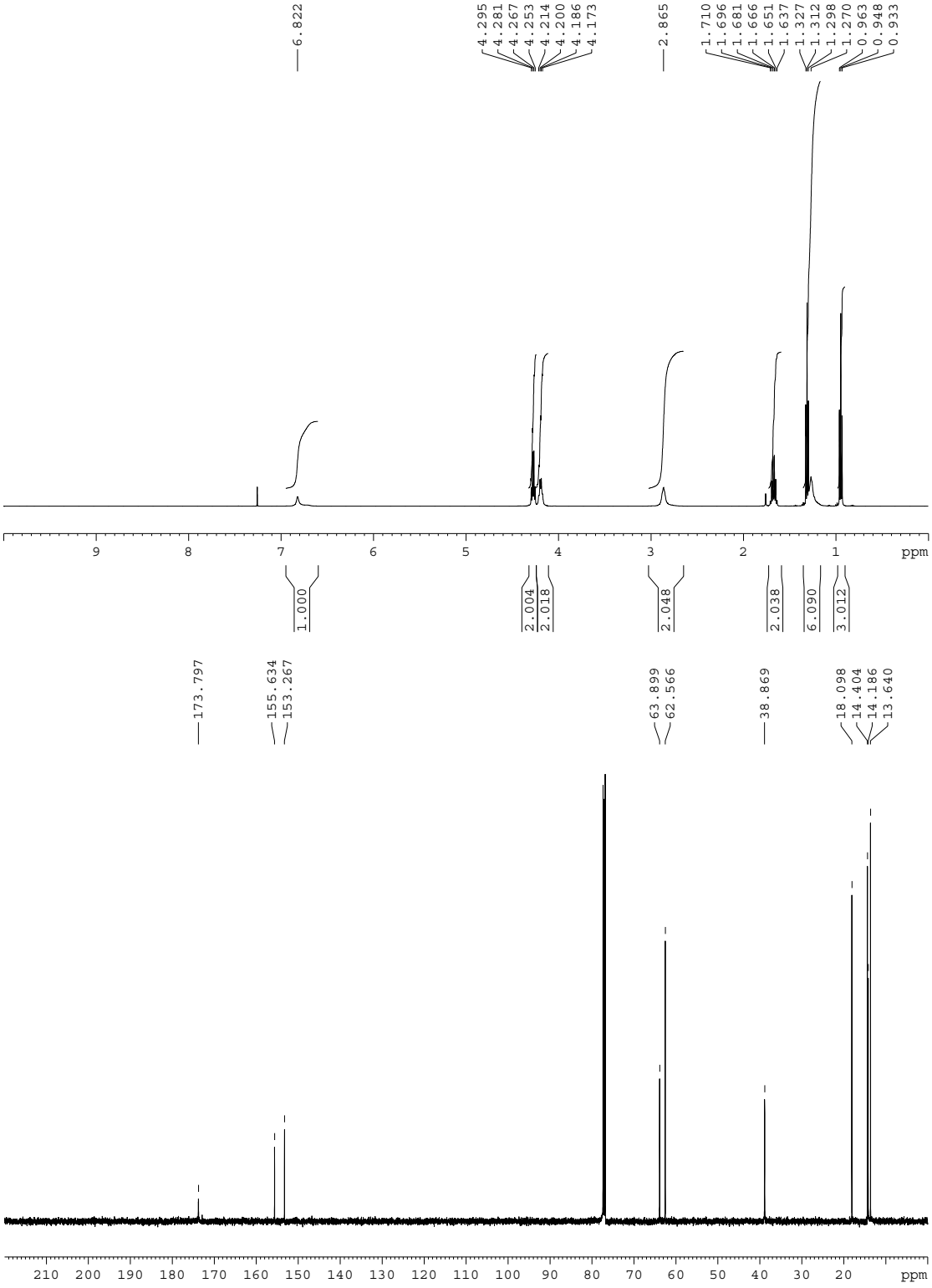
Aldehyde (1.0 mmol) was added to a mixture of azodicarboxylate (1.2 mmol) and H_2O (500 μL) and the reaction mixture stirred at 300 rpm at 21 °C in a stoppered carousel tube for the time specified below. The solvent was removed *in vacuo* and the product purified as specified below.

Diethyl 1-butanoylhydrazine-1,2-dicarboxylate 2a

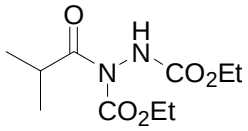


Reaction was stirred for 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-butanoylhydrazine-1,2-dicarboxylate as a colourless oil (221 mg, 0.90 mmol, 90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (br s, NH, 1H), 4.28 (q, *J* = 7.0 Hz, 2H), 4.19 (q, *J* = 7.0 Hz, 2H), 2.90-2.80 (m, 2H), 1.68 (sextet, *J* = 7.5 Hz, 2H), 1.35-1.17 (m, 6H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C), 155.6 (C), 153.3 (C), 63.9 (CH_2), 62.6 (CH_2), 38.9 (CH_2), 18.1 (CH_2), 14.4 (CH_3), 14.2 (CH_3), 13.6 (CH_3); IR

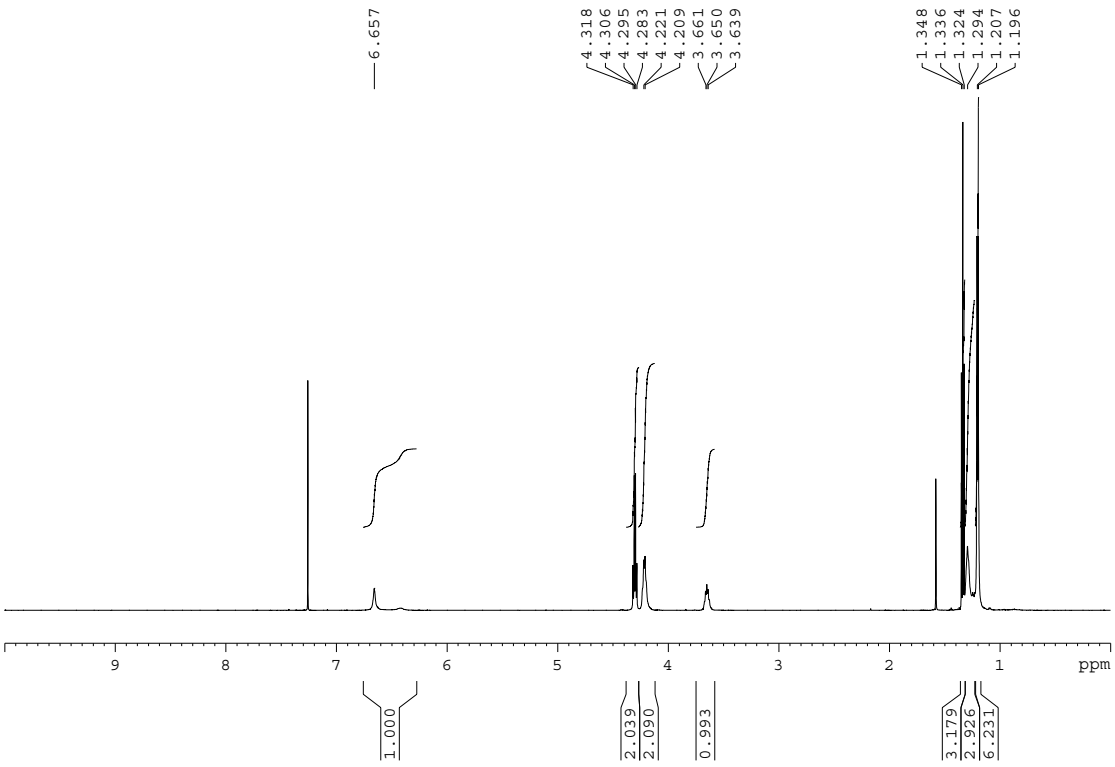
(thin film) 3309, 2968, 2877, 1738, 1717 cm^{-1}; LRMS (FAB) 269 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{10}H_{18}N_2O_5Na$ $[M+Na]^+$ 269.1113, observed 269.1118.

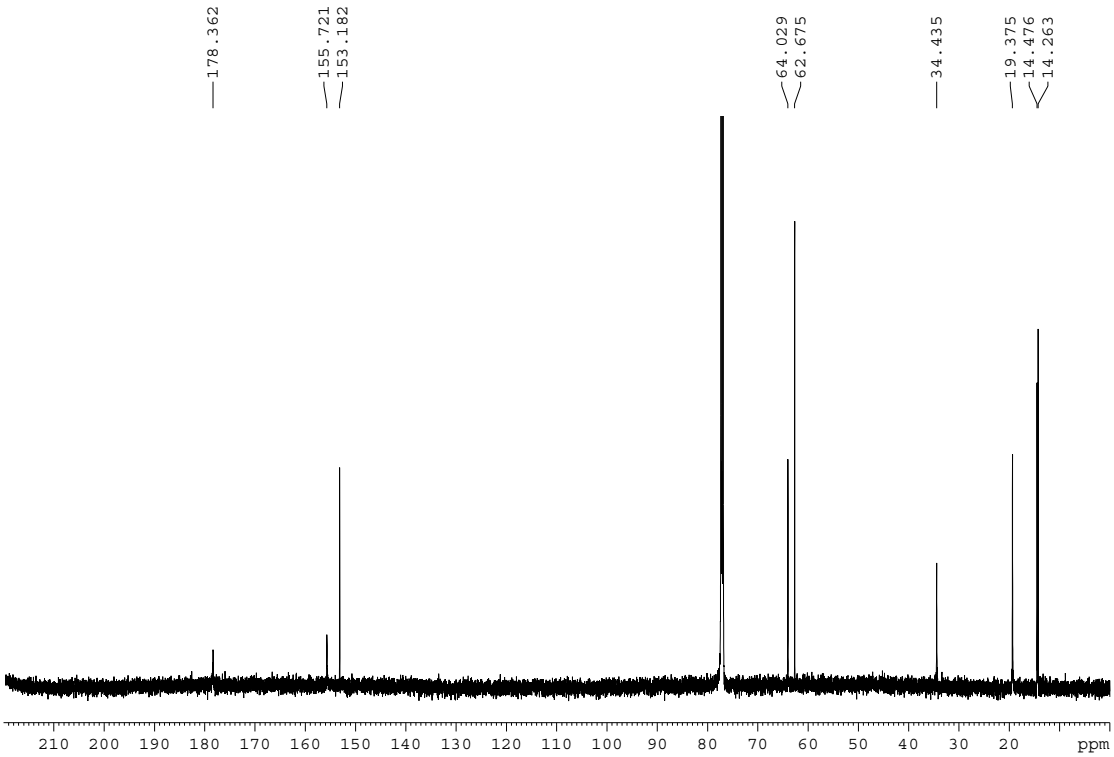


Diethyl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate 2b

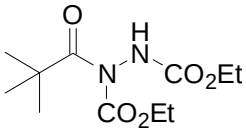


Reaction was stirred for 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (177 mg, 0.72 mmol, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.65 (br s, NH, 1H), 4.29 (q, *J* = 7.0 Hz, 2H), 4.21 (q, *J* = 7.0 Hz, 2H), 3.65 (br septet, *J* = 6.5 Hz, 1H), 1.35-1.24 (m, 6H), 1.20 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.4 (C), 155.7 (C), 153.2 (C), 64.0 (CH_2), 62.7 (CH_2), 34.4 (CH), 19.4 (CH_3), 14.5 (CH_3), 14.3 (CH_3); IR (thin film) 3312, 2984, 2938, 1742, 1725 cm^{-1}; LRMS (FAB) 247 (100, $[M+H]^+$); HRMS (FAB) calcd for $C_{10}H_{19}N_2O_5$ $[M+H]^+$ 247.1294, observed 247.1284.

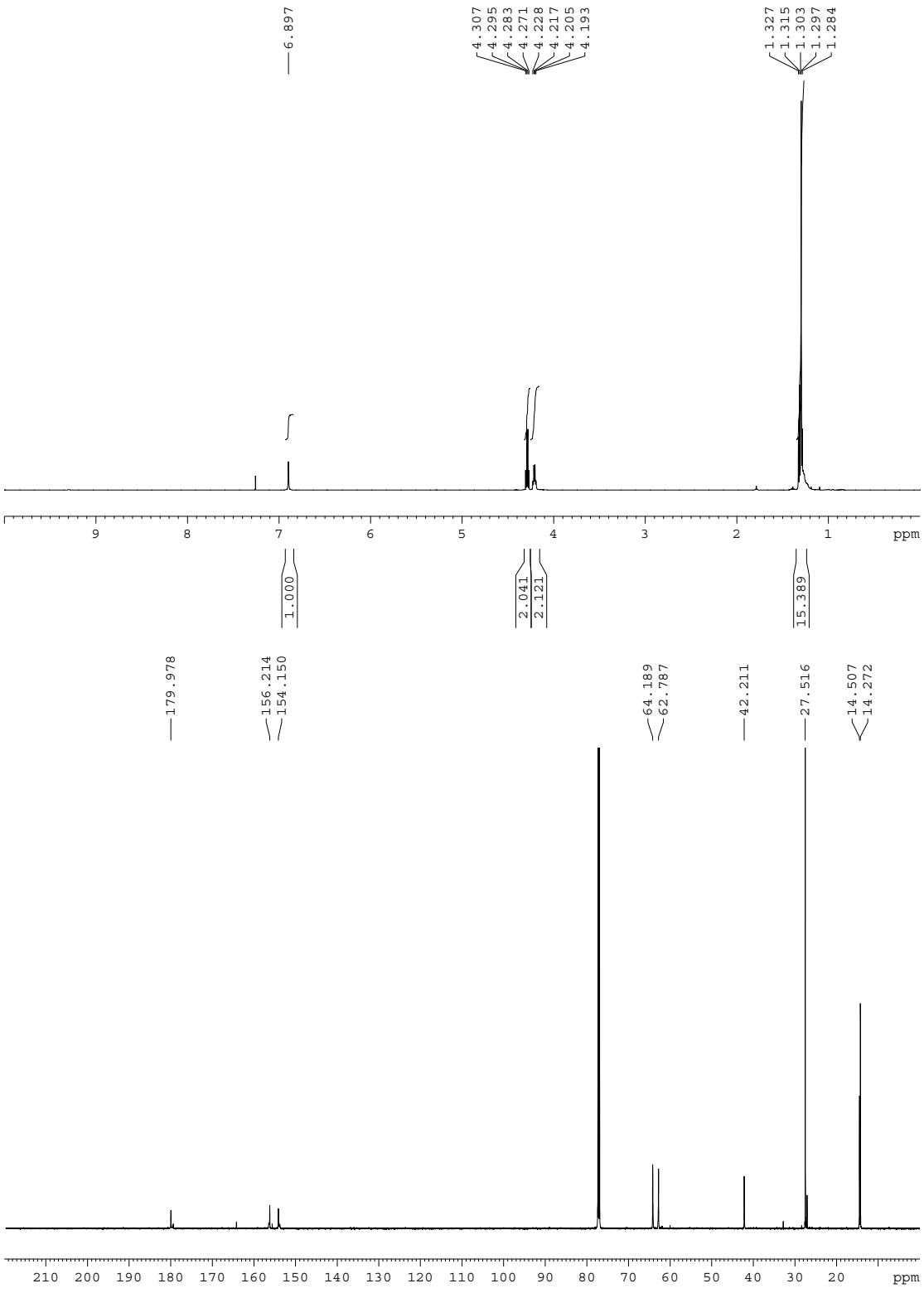




Diethyl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate 2c



Reaction was stirred for 24 h. Purification by column chromatography (20%-50% EtOAc/petrol) gave diethyl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (166 mg, 0.64 mmol, 64%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 (br s, NH, 1H), 4.29 (q, J = 7.0 Hz, 2H), 4.21 (q, J = 7.0 Hz, 2H), 1.34-1.20 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0 (C), 156.2 (C), 154.2 (C), 64.2 (CH_2), 62.8 (CH_2), 42.2 (C), 27.5 (CH_3), 14.5 (CH_3), 14.3 (CH_3); IR (thin film) 3295, 2982, 2938, 1782, 1734, 1715 cm^{-1}; LRMS (FAB) 283 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{11}H_{20}N_2O_5Na$ $[M+Na]^+$ 283.1270, observed 283.1270.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1.284
9
8
7
6
5
4
3
2
1
ppm
1.000
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179.978
156.214
154.150
64.189
62.787
42.211
27.516
14.507
14.272
210
200
190
180
170
160
150
140
130
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110
100
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80
70
60
50
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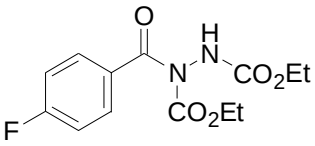
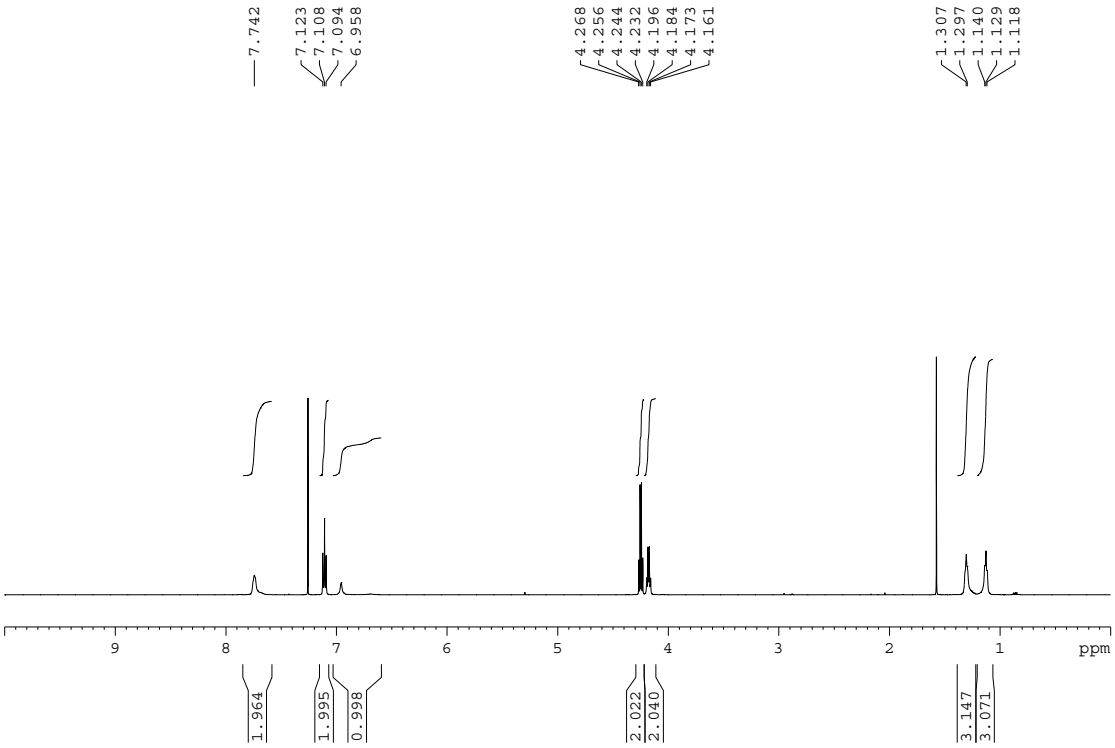
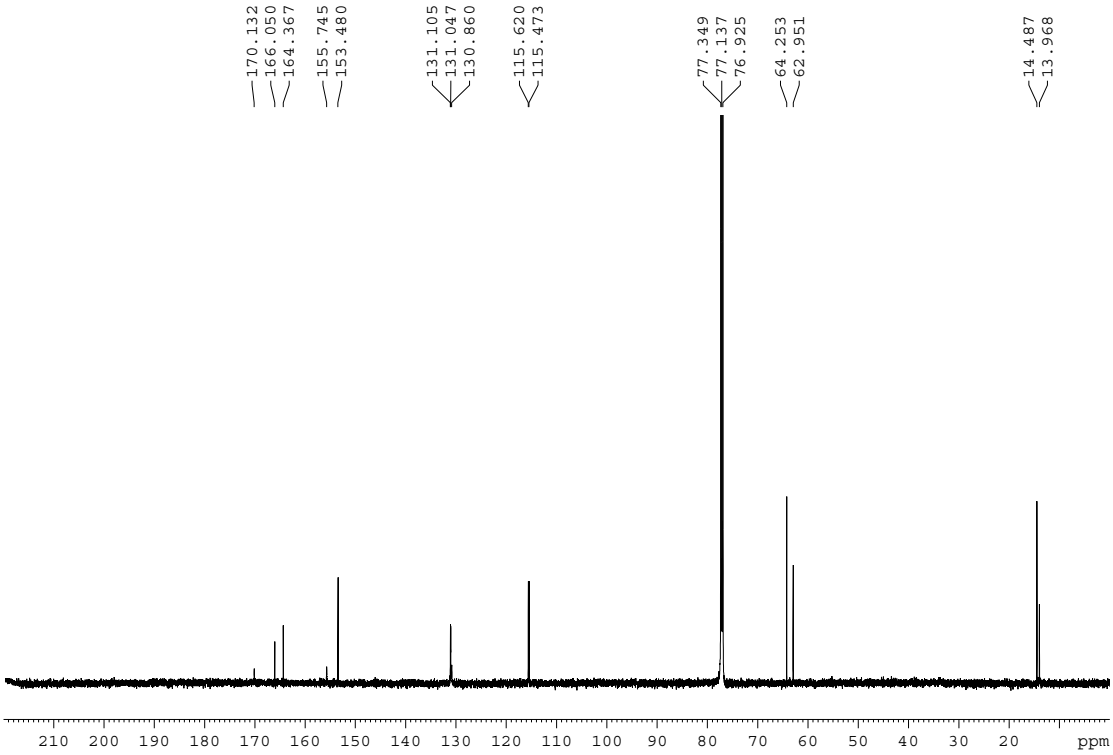
ppm

Diethyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate 2d

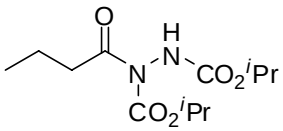


Reaction was stirred for 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave diethyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate as a colourless oil (185 mg, 0.62 mmol, 62%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.69 (m, 2H), 7.12-7.08 (m, 2H), 6.96 (br s, NH, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 1.31-1.23 (m, 3H), 1.17-1.11 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1 (C), 165.2 (d, $J_{C\text{-}F}$ = 252 Hz, C), 155.8 (C), 153.5 (C), 131.1 (C), 130.9 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 115.5 (d, $J_{C\text{-}F}$ = 21.0 Hz, CH), 64.2 (CH_2), 63.0 (CH_2), 14.5 (CH_3), 14.0 (CH_3); IR (thin film) 3309, 2986, 2938, 1740, 1706, 1603, 1507 cm^{-1}; LRMS (FAB) 321 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{13}H_{15}N_2O_5FNa$ $[M+Na]^+$ 321.0863, observed 321.0856.

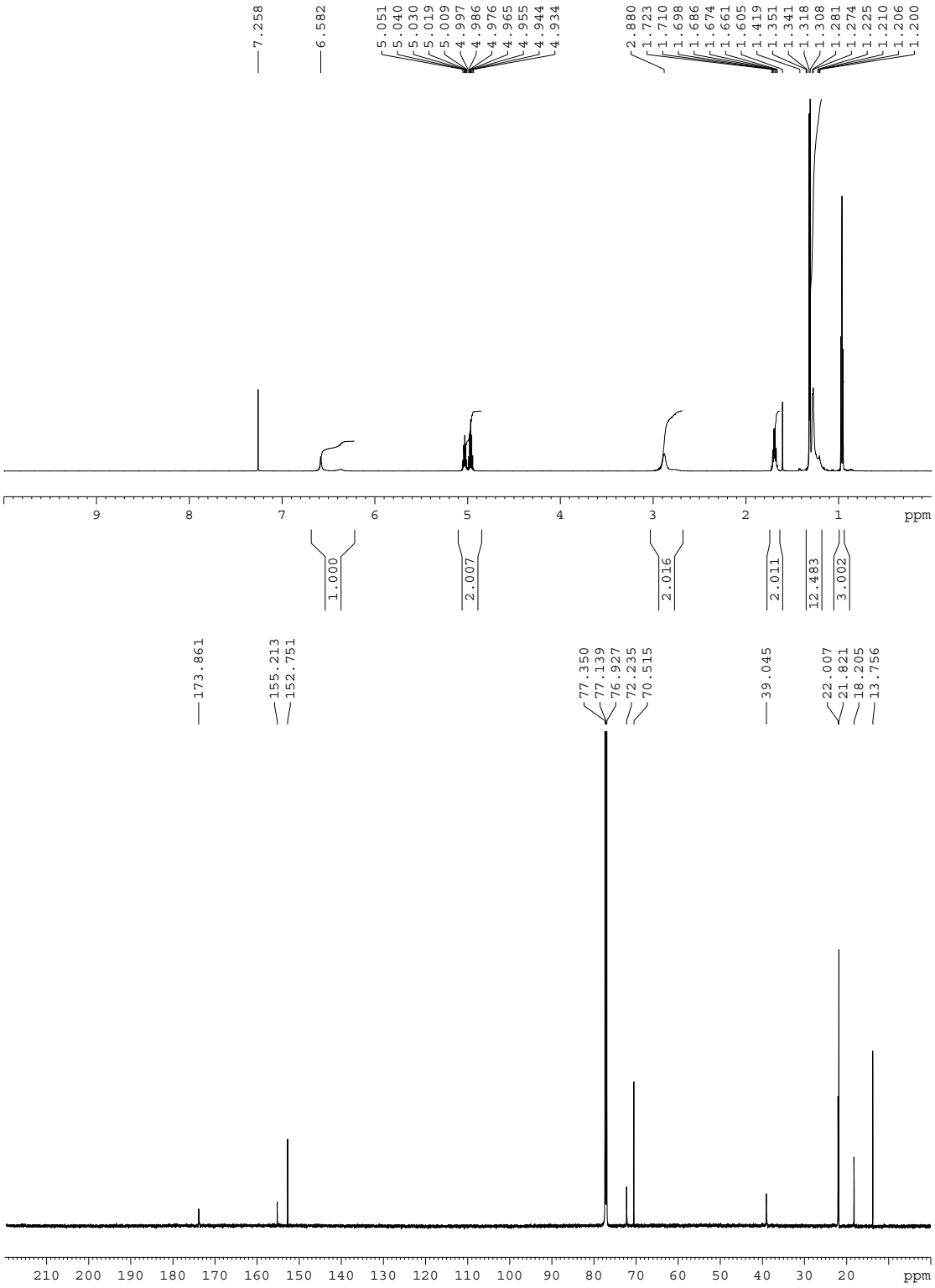




Dipropan-2-yl 1-butanoylhydrazine-1,2-dicarboxylate 3a



Reaction was stirred for 24 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave dipropan-2-yl 1-butanoylhydrazine-1,2-dicarboxylate as a colourless oil (249 mg, 0.91 mmol, 91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (br s, NH, 1H), 5.03 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 2.94-2.74 (m, 2H), 1.69 (sextet, *J* = 7.5 Hz, 2H), 1.34-1.17 (m, 12H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 39.1 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 18.2 (CH_2), 13.8 (CH_3); IR (thin film) 3317, 2982, 2938, 1736, 1717 cm^{-1}; LRMS (CI) 275 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{23}N_2O_5$ $[M+H]^+$ 275.1607, observed 275.1609.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1.605
1.419
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1.308
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1.225
1.210
1.206
1.200
ppm
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2.011
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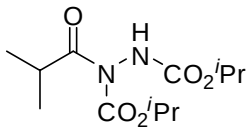
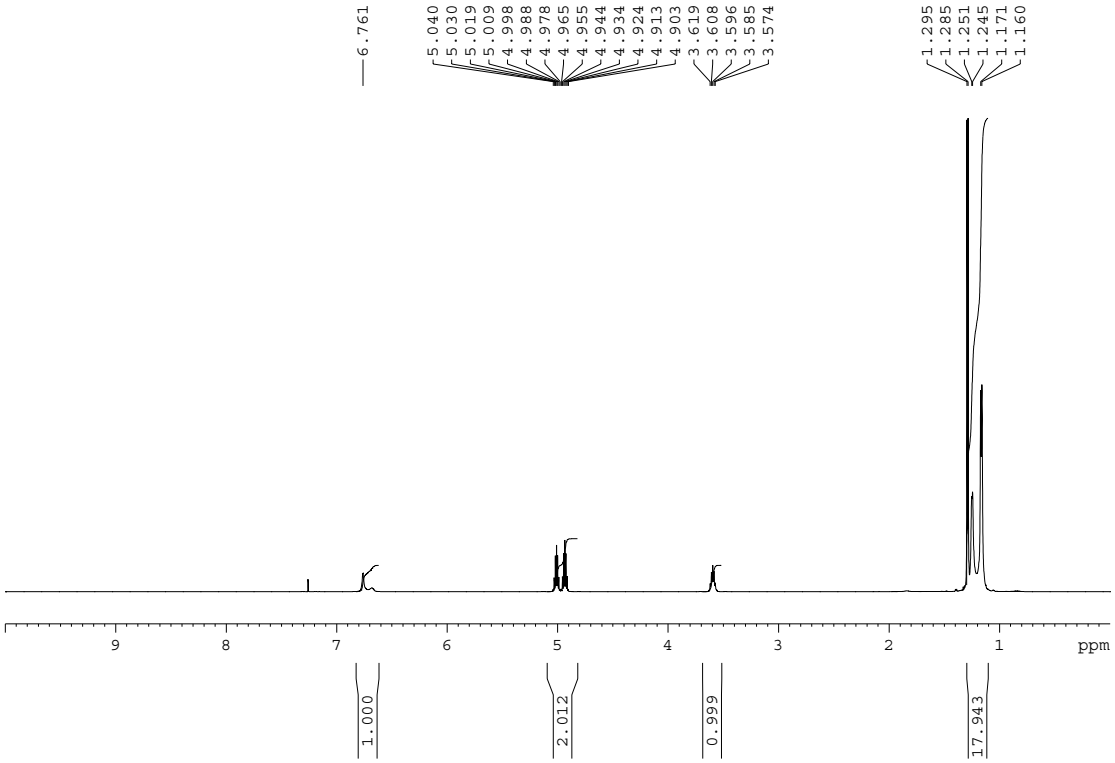
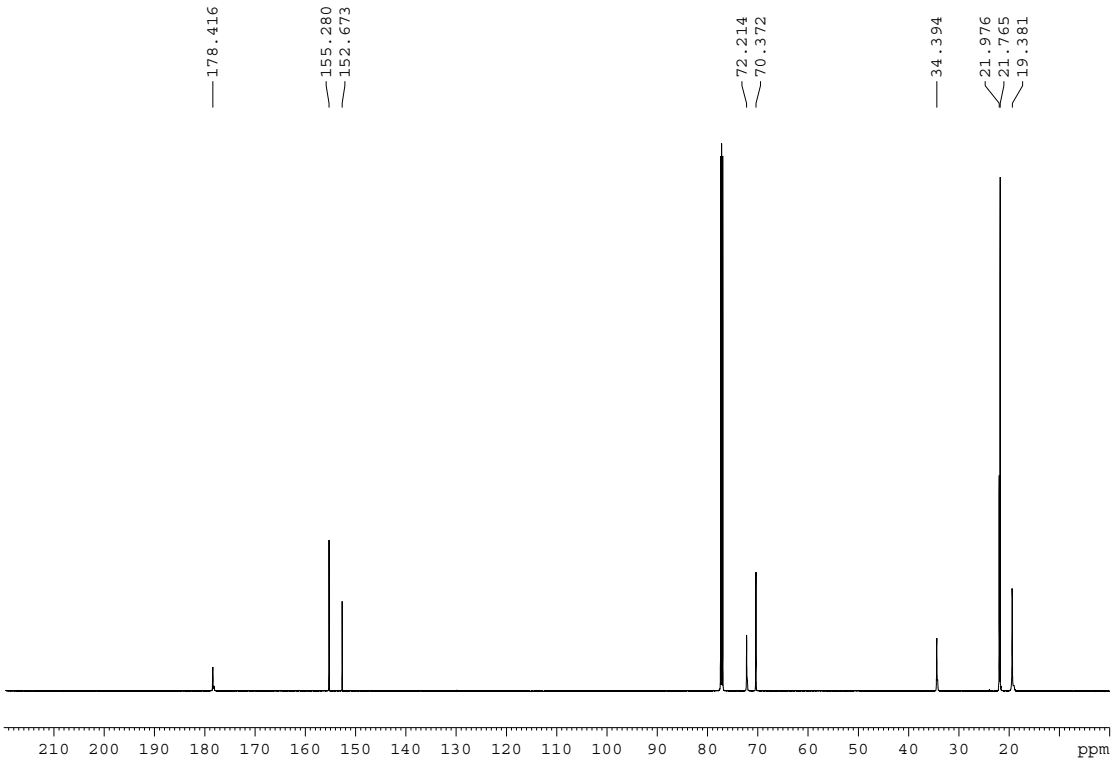
Dipropan-2-yl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate 3b

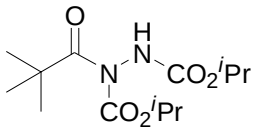


Reaction was stirred for 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave dipropan-2-yl 1-(2-methylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (217 mg, 0.79 mmol, 79%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.76 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.93 (septet, J = 6.5 Hz, 1H), 3.60 (septet, J = 7.0 Hz, 1H), 1.33-1.12 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 34.4 (CH), 22.0 (CH_3), 21.8 (CH_3), 19.4 (CH_3); IR (thin film) 3322, 2982, 2938, 1736, 1718 cm^{-1}; LRMS (CI) 275 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{12}H_{23}N_2O_5$ $[M+H]^+$ 275.1607, observed 275.1598.

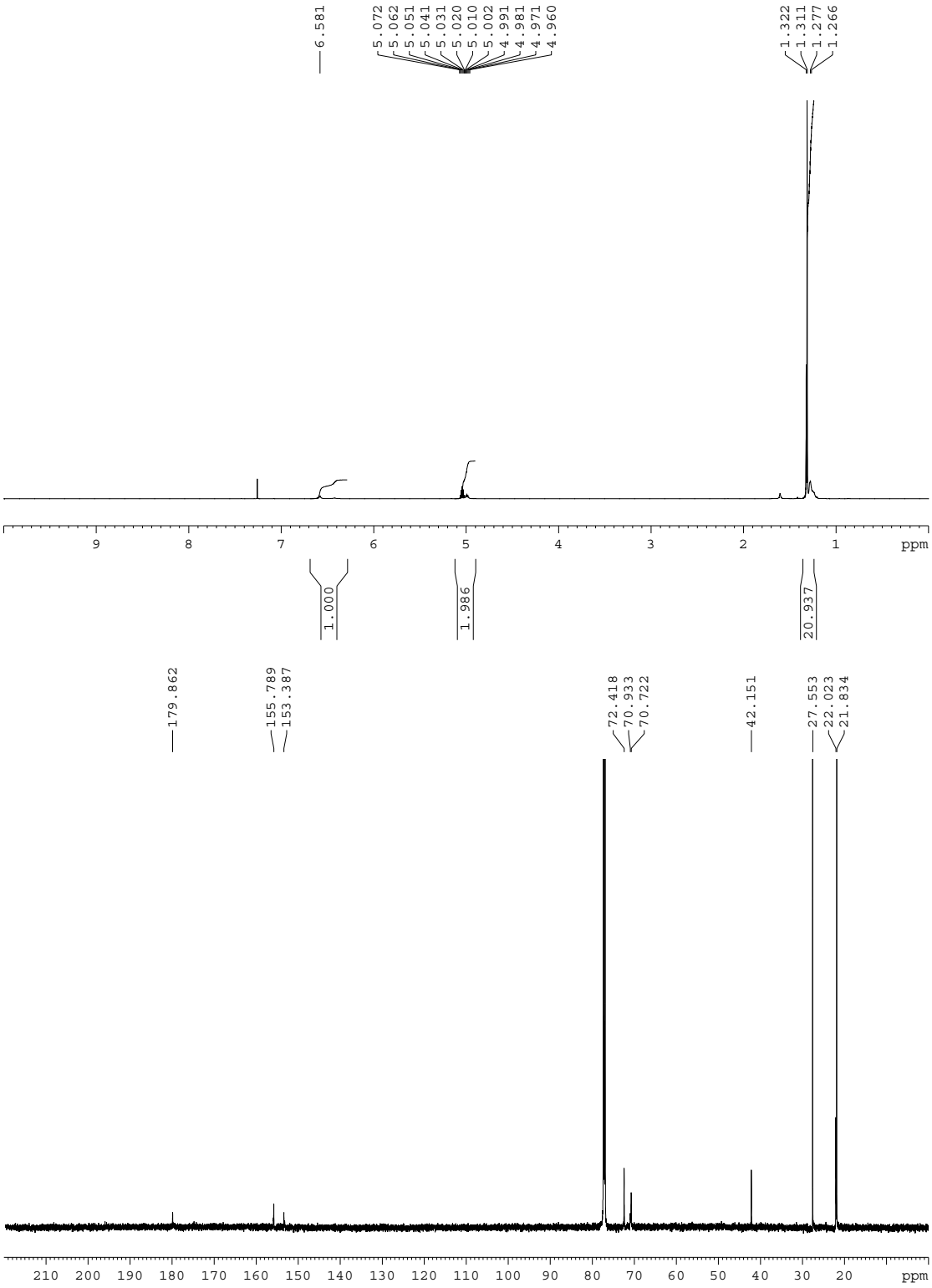




Dipropan-2-yl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate 3c



Reaction was stirred for 48 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave dipropan-2-yl 1-(2,2-dimethylpropanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (199 mg, 0.69 mmol, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (br s, NH, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.99 (septet, J = 6.5 Hz, 1H), 1.33-1.18 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 179.9 (C), 155.8 (C), 153.4 (C), 72.4 (CH), 70.7 (CH), 42.2 (C), 27.6 (CH_3), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3293, 2982, 2937, 1777, 1734, 1721 cm^{-1}; LRMS (FAB) 311 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{13}H_{24}N_2O_5Na$ $[M+Na]^+$ 311.1583, observed 311.1588.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1.322
1.311
1.277
1.266
9
8
7
6
5
4
3
2
1
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70.722
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200
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170
160
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130
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110
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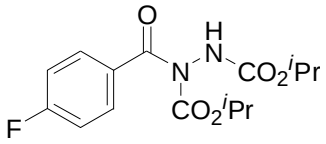
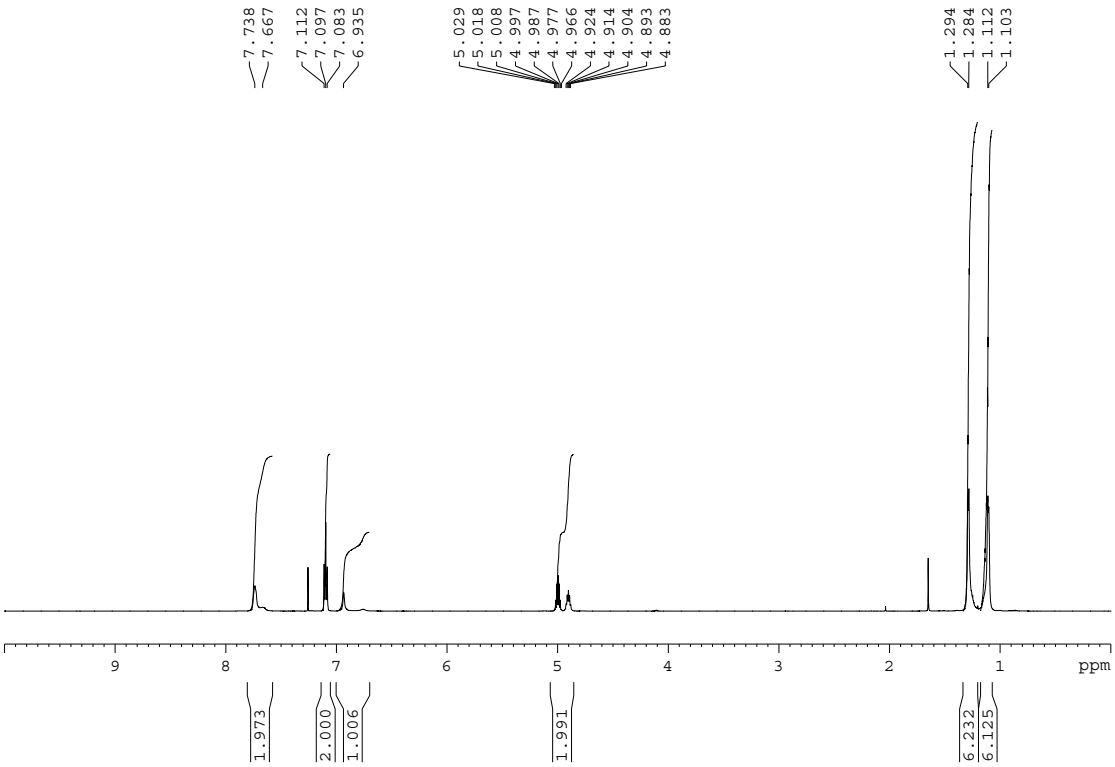
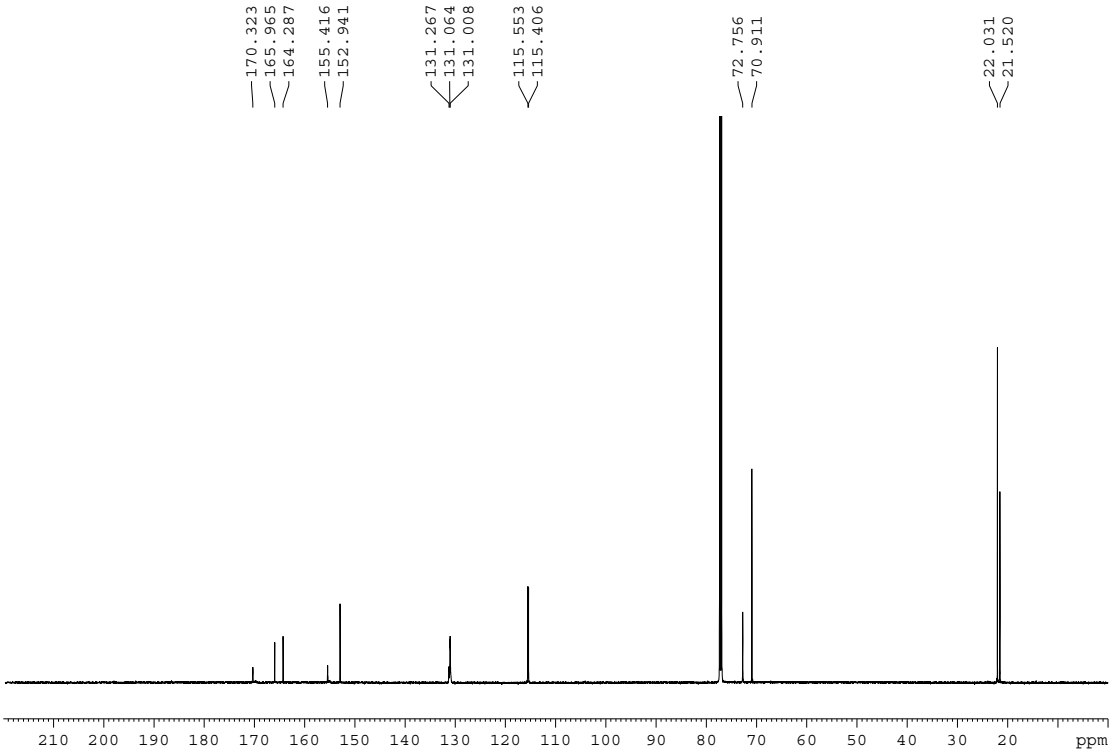
ppm

Dipropan-2-yl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate 3d

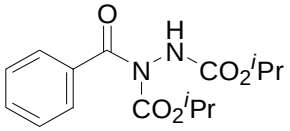


Reaction was stirred for 96 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate as a colourless oil (245 mg, 0.75 mmol, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.69 (m, 2H), 7.12-7.08 (m, 2H), 6.93 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.90 (septet, J = 6.5 Hz, 1H), 1.30-1.22 (m, 6H), 1.20-1.05 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3 (C), 165.1 (d, $J_{C\text{-}F}$ = 252 Hz, C), 155.4 (C), 153.0 (C), 131.3 (C), 131.0 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 115.5 (d, $J_{C\text{-}F}$ = 21.0 Hz, CH), 72.8 (CH), 70.9 (CH), 22.0 (CH_3), 21.5 (CH_3); IR (thin film) 3313, 2984, 2938, 1734, 1705, 1603, 1507 cm^{-1}; LRMS (FAB) 349 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{15}H_{19}N_2O_5FNa$ $[M+Na]^+$ 349.1176, observed 349.1171.

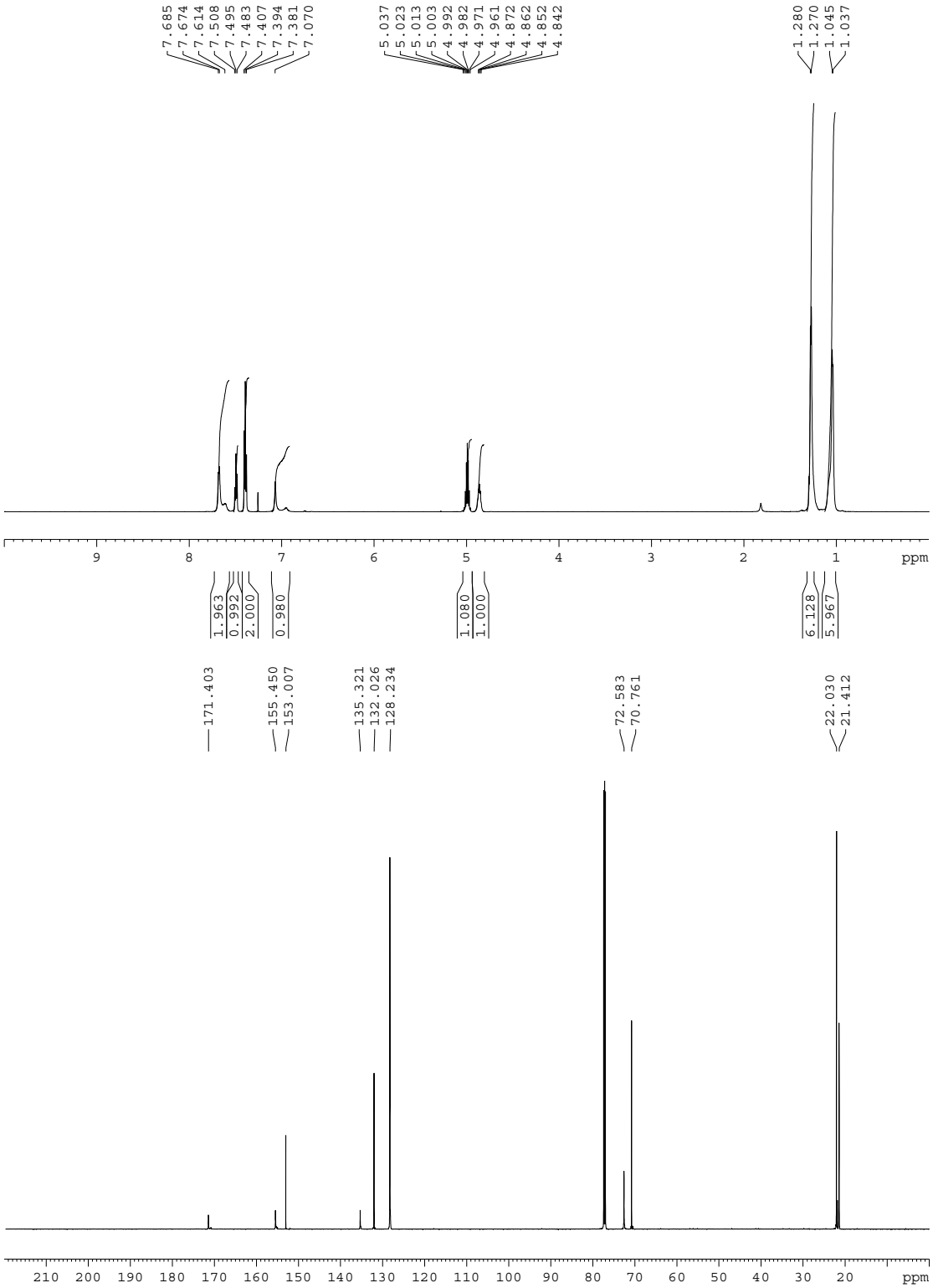




Dipropan-2-yl 1-benzoylhydrazine-1,2-dicarboxylate 3e



Reaction was stirred for 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-benzoylhydrazine-1,2-dicarboxylate as a white solid (243 mg, 0.79 mmol, 79%): m.p. 98-101 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72-7.59 (m, 2H), 7.52-7.48 (m 1H), 7.43-7.37 (m, 2H), 7.07 (br s, NH, 1H), 5.00 (septet, J = 6.5 Hz, 1H), 4.92-4.84 (m, 1H), 1.31-1.23 (m, 6H), 1.10-1.02 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3 (C), 155.4 (C), 152.9 (C), 135.2 (C), 131.9 (CH), 128.2 (CH), 128.1 (CH), 72.5 (CH), 70.6 (CH), 21.9 (CH_3), 21.3 (CH_3); IR (thin film) 3265, 2988, 1755, 1738, 1682, 1601, 1519 cm^{-1}; LRMS (ES^-) 307 (100, $[M-H]^-$); HRMS (ES^-) calcd for $C_{15}H_{19}N_2O_5$ $[M-H]^-$ 307.1294, observed 307.1289. Data agrees with that reported by Ni and Headley.[4]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7.381
7.070
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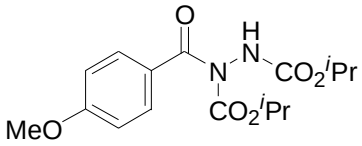
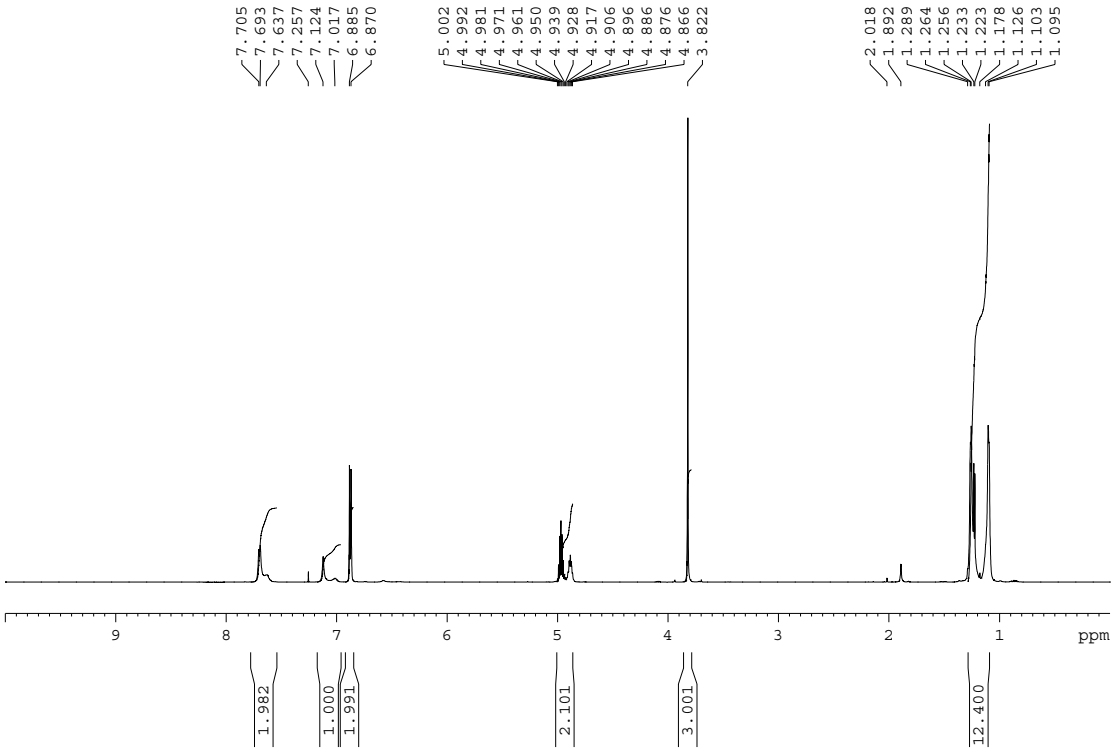
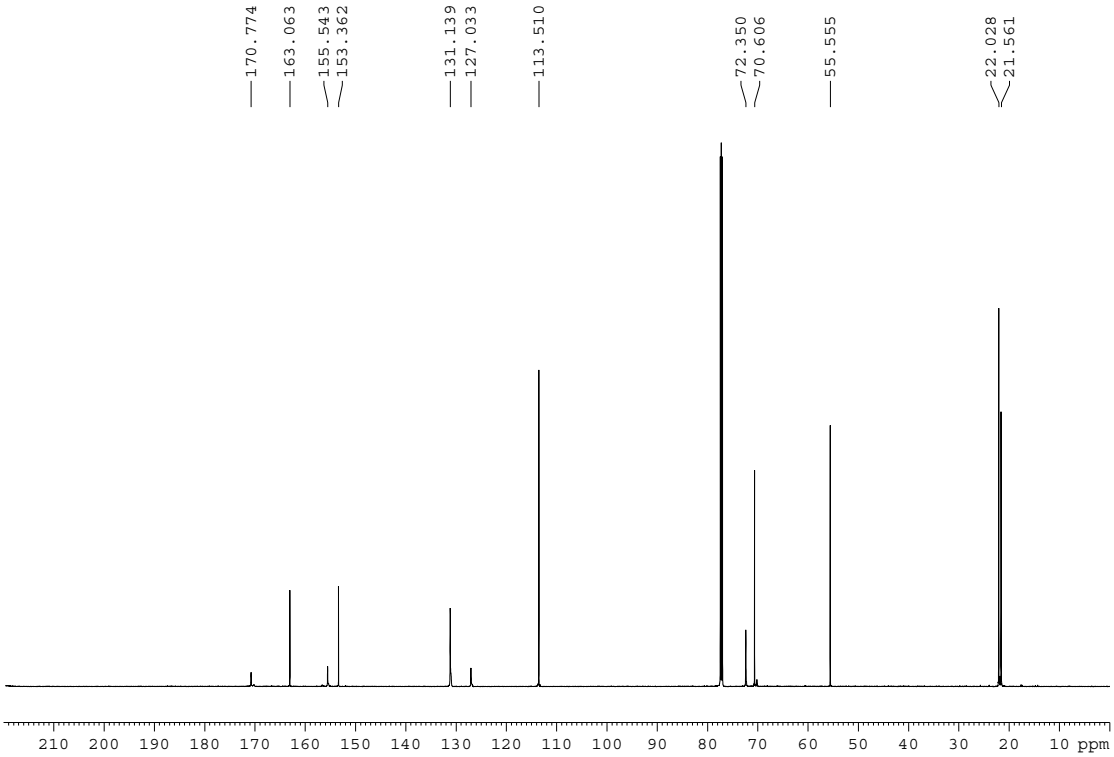
5.023
5.013
5.003
4.992
4.982
4.971
4.961
4.872
4.862
4.852
4.842
1.280
1.270
1.045
1.037
ppm
1.963
0.992
2.000
0.980
1.080
1.000
6.128
5.967
171.403
155.450
153.007
135.321
132.026
128.234
72.583
70.761
22.030
21.412
ppm

Dipropan-2-yl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate 3f

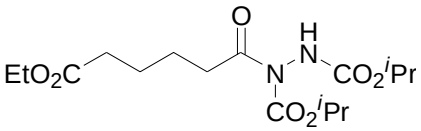


Reaction was stirred for 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate as a white solid (149 mg, 0.44 mmol, 44%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73-7.60 (m, 2H), 7.12 (br s, NH, 1H) 6.87 (d, J = 8.5 Hz, 2H), 4.97 (septet, J = 6.5 Hz, 1H), 4.89 (septet, J = 6.5 Hz, 1H) 3.82 (s, 3H), 1.29-1.07 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8 (C), 163.1 (C), 155.5 (C), 153.4 (C), 131.1 (CH), 127.0 (C), 113.5 (CH), 72.4 (CH), 70.6 (CH), 55.6 (CH_3), 22.0 (CH_3), 21.6 (CH_3); IR (thin film) 3309, 2982, 2938, 1733, 1701, 1604, 1579 cm^{-1}; LRMS (ES$^-$) 337 (100, [M-H]$^-$); HRMS (ES$^-$) calcd for $C_{16}H_{21}N_2O_6$ [M-H]$^-$ 337.1400, observed 337.1406. Data agrees with that reported by Lee.[5]

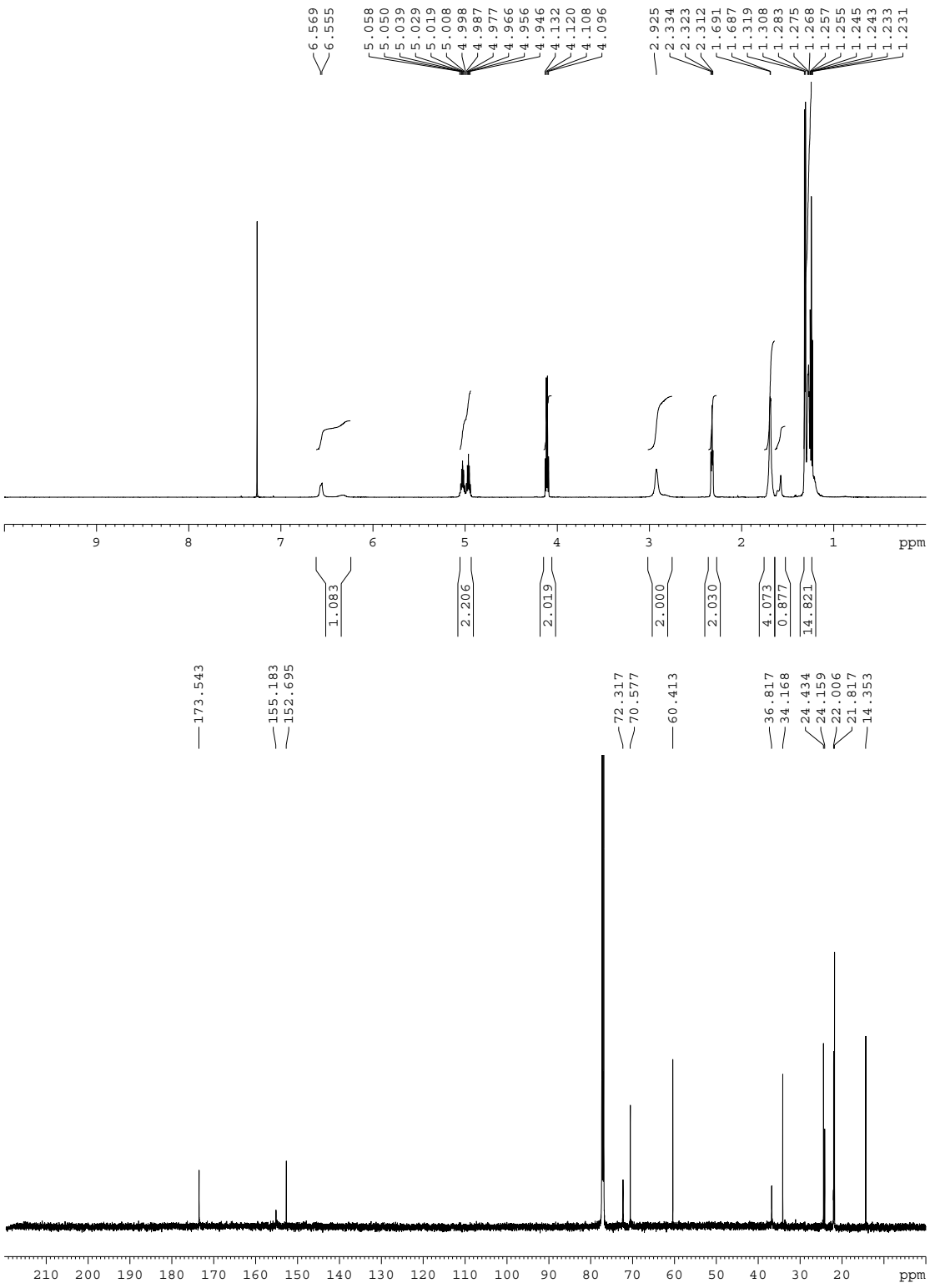




Dipropan-2-yl 1-(6-ethoxy-6-oxohexanoyl)hydrazine-1,2-dicarboxylate 3g



Reaction was stirred for 96 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-(6-ethoxy-6-oxohexanoyl)hydrazine-1,2-dicarboxylate as a colourless oil (288 mg, 0.80 mmol, 80%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (br s, NH, 1H), 5.03 (septet, J = 6.0 Hz, 1H), 4.97 (septet, J = 6.0 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.97-2.82 (m, 2H), 2.32 (t, J = 7.0 Hz, 2H), 1.73-1.65 (m, 4H), 1.32-1.23 (m, 15H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.5 (C), 173.4 (C), 155.2 (C), 152.7 (C), 72.3 (CH), 70.6 (CH), 60.4 (CH_2), 36.8 (CH_2), 34.2 (CH_2), 24.4 (CH_2), 24.2 (CH_2) 22.0 (CH_3), 21.8 (CH_3), 14.4 (CH_3); IR (thin film) 3321, 2982, 1788, 1727, 1725 cm^{-1}; LRMS (ES$^-$) 359 (100, [M-H]$^-$); HRMS (ES$^-$) calcd for $C_{16}H_{27}N_2O_7$ [M-H]$^-$ 359.1818, observed 359.1826.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5.008
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4.946
4.132
4.120
4.108
4.096
2.925
2.334
2.323
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1.255
1.245
1.243
1.233
1.231
ppm
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2.206
2.019
2.000
2.030
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0.877
14.821
173.543
155.183
152.695
72.317
70.577
60.413
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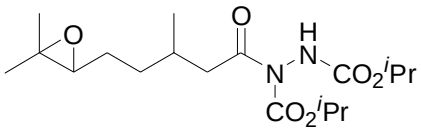
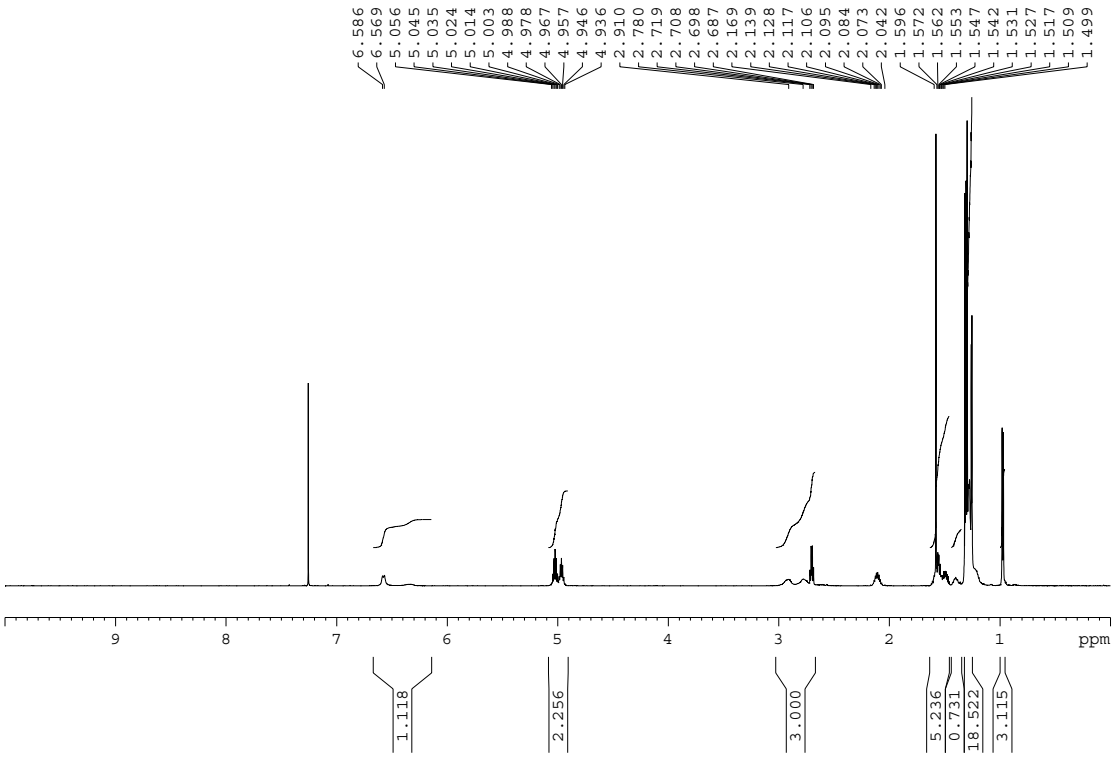
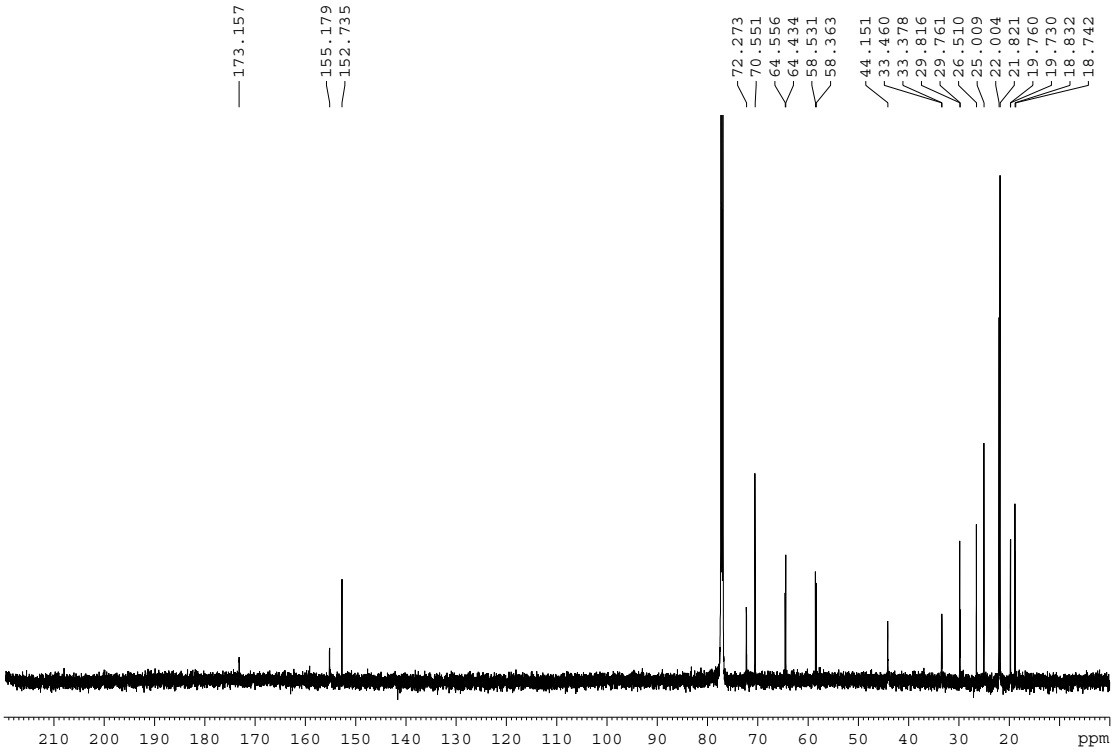
34.168
24.434
24.159
22.006
21.817
14.353
ppm

Dipropan-2-yl 1-[5-(3,3-dimethyloxiran-2-yl)-3-methylpentanoyl]hydrazine-1,2-dicarboxylate 3h

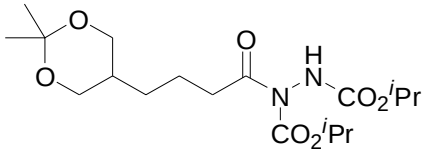


Reaction was stirred for 48 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-[5-(3,3-dimethyloxiran-2-yl)-3-methylpentanoyl]hydrazine-1,2-dicarboxylate as a colourless oil (249 mg, 0.67 mmol, 67%) as a 1:1 mixture of diastereoisomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (br s, NH, 1H), 5.02 (septet, J = 6.0 Hz, 1H) 4.97 (septet, J = 6.5 Hz, 1H), 2.97-2.73 (m, 2H), 2.72-2.68 (m, 1H), 2.11 (m, 1H) 1.62-1.35 (m, 4H), 1.33-1.23 (m, 18H), 0.96 (d, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2 (C), 155.2 (C), 152.7 (C), 72.3 (CH), 70.6 (CH), 64.6 (CH), 64.4 (CH), 58.5 (C), 58.4 (C), 44.2 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 29.8 (CH), 29.8 (CH), 26.53 (CH_2), 26.51 (CH_2), 25.0, 22.0, 21.8, 19.8, 19.7, 18.8, 18.7; IR (thin film) 3298, 2932, 1788, 1736, 1722, 1104 cm^{-1}; LRMS (ES$^+$) 395 (100, [M+Na]$^+$); HRMS (ES$^+$) calcd for $C_{18}H_{32}N_2O_6Na$ [M+Na]$^+$ 395.2158, observed 395.2150.

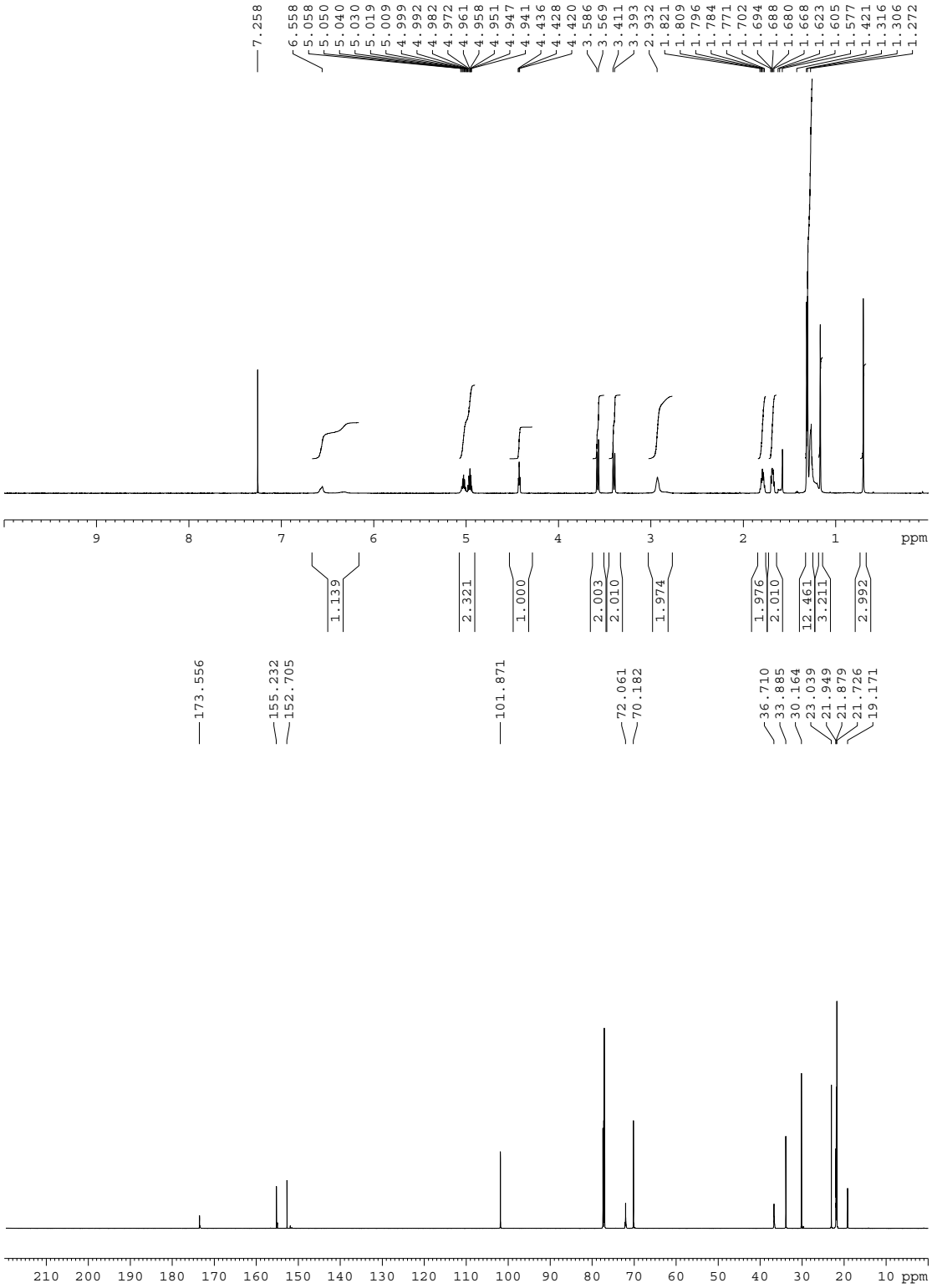




Dipropan-2-yl 1-[4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoyl]hydrazine-1,2-dicarboxylate 3i



Reaction was stirred for 24 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-[4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoyl]hydrazine-1,2-dicarboxylate as a colourless oil (268 mg, 0.69 mmol, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (br s, NH, 1H), 5.03 (septet, J = 6.0 Hz, 1H), 4.96 (septet, J = 6.0 Hz, 1H), 4.43 (t, J = 5.0 Hz, 1H), 3.57 (d, J = 10.5 Hz, 2H), 3.40 (d, J = 11.0 Hz, 2H), 2.97-2.87 (m, 2H), 1.82-1.77 (m 2H), 1.70-1.67 (m, 2H), 1.32-1.20 (m, 12H), 1.17 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6 (C), 155.2 (C), 152.7 (C), 101.9 (CH), 77.5 (CH_2), 72.1 (CH), 70.2 (CH), 36.7 (CH_2), 33.9 (CH_2), 30.2 (C), 23.0 (CH_3), 21.9 (CH_3), 21.8 (CH_3), 21.7 (CH_3), 19.2 (CH_2); IR (thin film) 3299, 2955, 2848, 1780, 1738, 1734 cm^{-1}; LRMS (ES^+) 411 (100, $[M+Na]^+$); HRMS (ES^+) calcd for $C_{18}H_{32}N_2O_7Na$ $[M+Na]^+$ 411.2107, observed 411.2116.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2.932
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1.809
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1.784
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1.976
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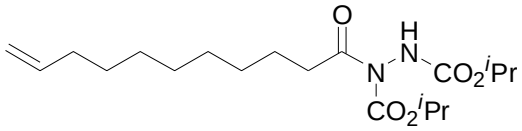
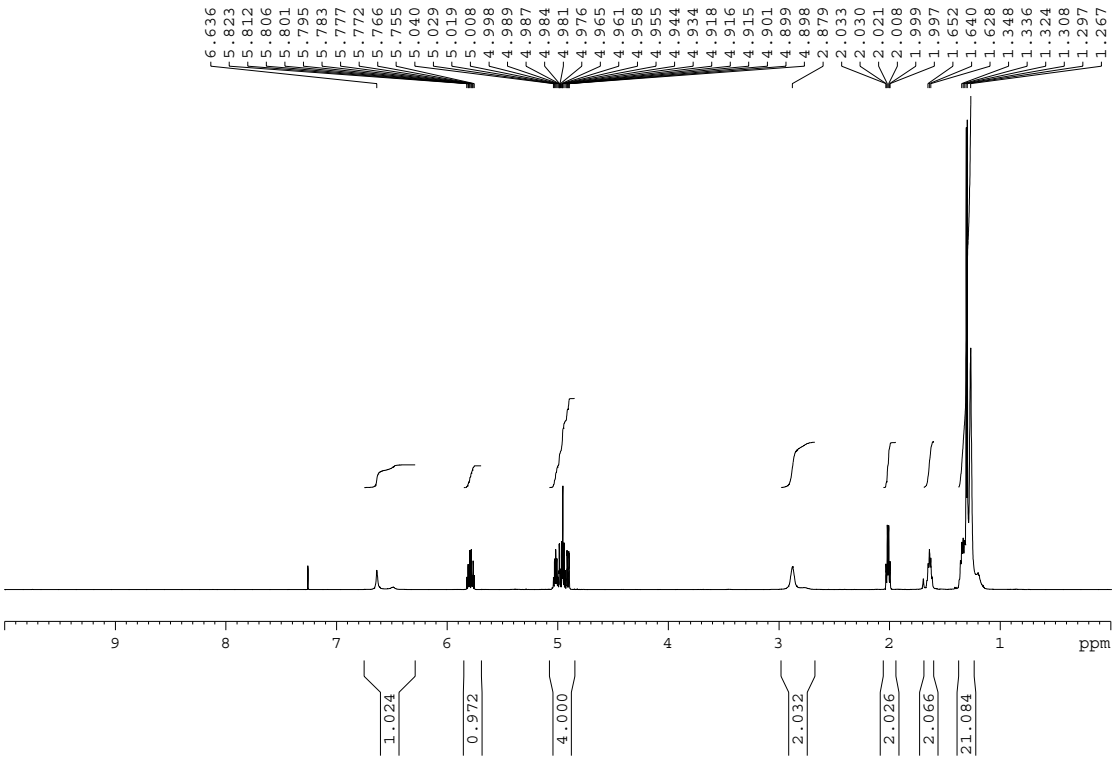
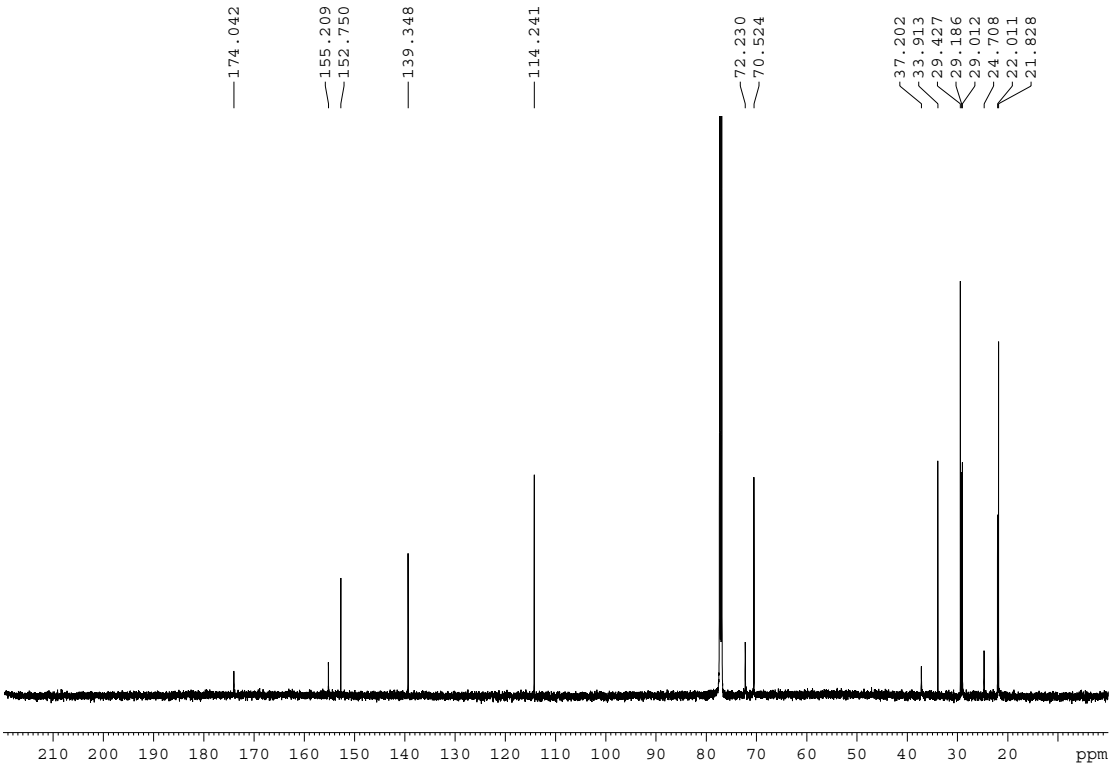
2.992
173.556
155.232
152.705
101.871
72.061
70.182
36.710
33.885
30.164
23.039
21.949
21.879
21.726
19.171
ppm

Dipropan-2-yl 1-(undec-10-enoyl)hydrazine-1,2-dicarboxylate 3j

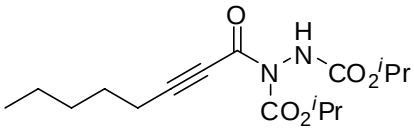


Reaction was stirred for 72 h. Purification by column chromatography (10-20% EtOAc/Petrol) gave dipropan-2-yl 1-(undec-10-enoyl)hydrazine-1,2-dicarboxylate as a colourless oil (285 mg, 0.77 mmol, 77%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (br s, NH, 1H), 5.80 (ddt, *J* = 17.0, 10.0 and 6.5 Hz 1H), 5.03 (septet, *J* = 6.0 Hz, 1H), 5.01-4.90 (m, 3H), 2.94-2.89 (m, 2H), 2.03 (q, *J* = 7.0 Hz, 2H), 1.65 (quin, *J* = 6.9 Hz, 2H), 1.38-1.22 (m, 22H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0 (C), 155.2 (C), 152.8 (C), 139.4 (CH), 114.2 (CH_2), 72.2 (CH), 70.5 (CH), 37.2 (CH_2), 33.9 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 24.7 (CH_2), 22.0 (CH_3), 21.8 (CH_3); IR (thin film) 3313, 2981, 2855, 1788, 1736, 1722 cm^{-1}; LRMS (CI) 371 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{19}H_{35}N_2O_5$ $[M+H]^+$ 371.2546, observed 371.2548.

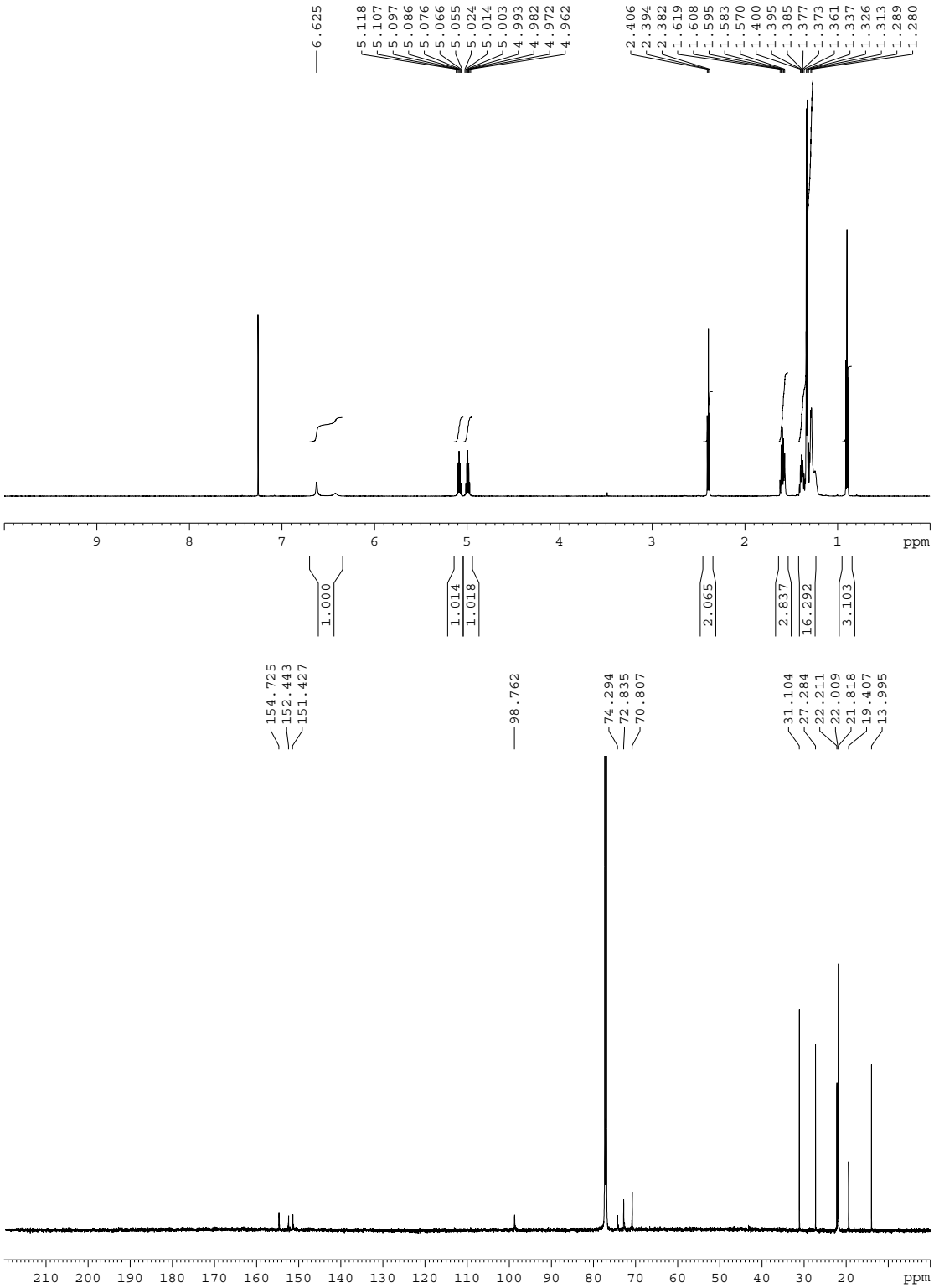




Dipropan-2-yl 1-(oct-2-ynoyl)hydrazine-1,2-dicarboxylate 3k



Reaction was stirred for 72 h. Purification by column chromatography (10-40% EtOAc/Petrol) gave dipropan-2-yl 1-(oct-2-ynoyl)hydrazine-1,2-dicarboxylate as a colourless oil (179 mg, 0.55 mmol, 55%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (br s, NH, 1H), 5.08 (septet, J = 6.5 Hz, 1H), 4.99 (septet, J = 6.5 Hz, 1H), 2.39 (t, J = 7.0 Hz, 2H), 1.62-1.55 (m, 2H), 1.42-1.22 (m, 16H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7 (C), 152.4 (C), 151.4 (C), 98.8 (C), 74.3 (C), 72.8 (CH), 70.8 (CH), 31.1 (CH_2), 27.3 (CH_2), 22.2 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 19.4 (CH_2), 14.0 (CH_3); IR (thin film) 3314, 2983, 2936, 2873, 2229, 1741, 1724, 1687 cm^{-1}; LRMS (FAB) 349 (100, $[M+Na]^+$); HRMS (FAB) calcd for $C_{16}H_{26}N_2O_5Na$ $[M+Na]^+$ 349.1739, observed 349.1733.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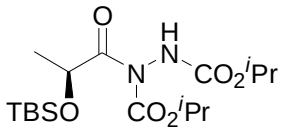
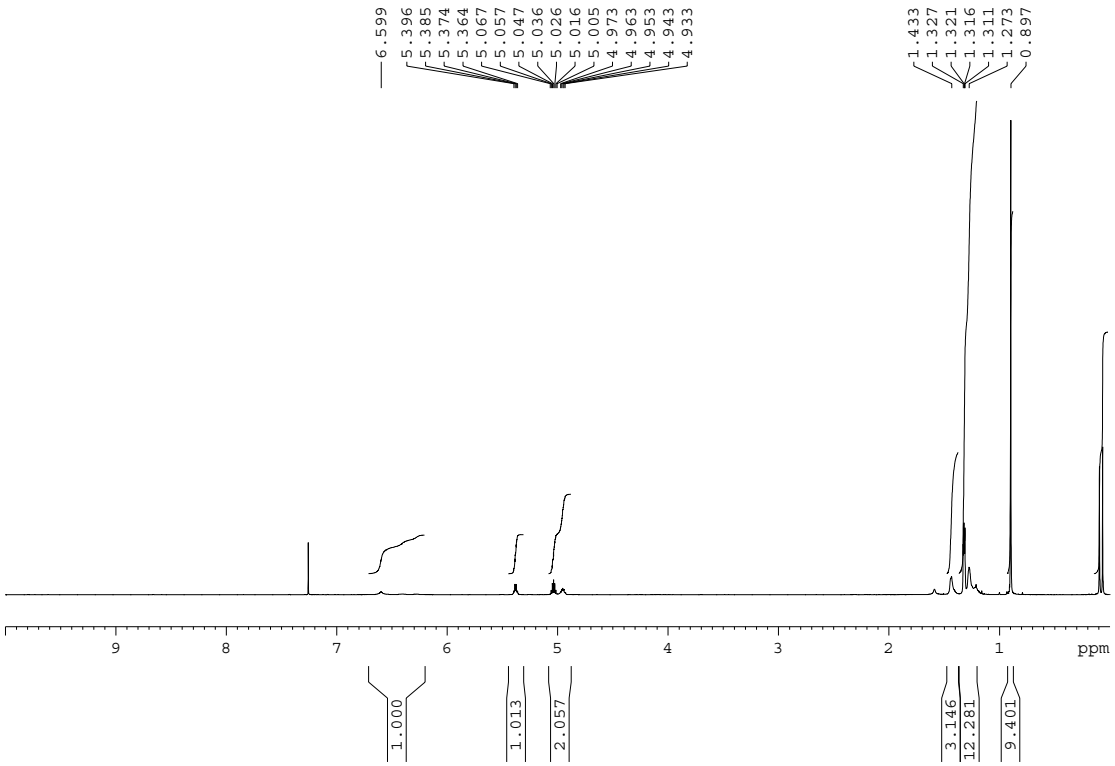
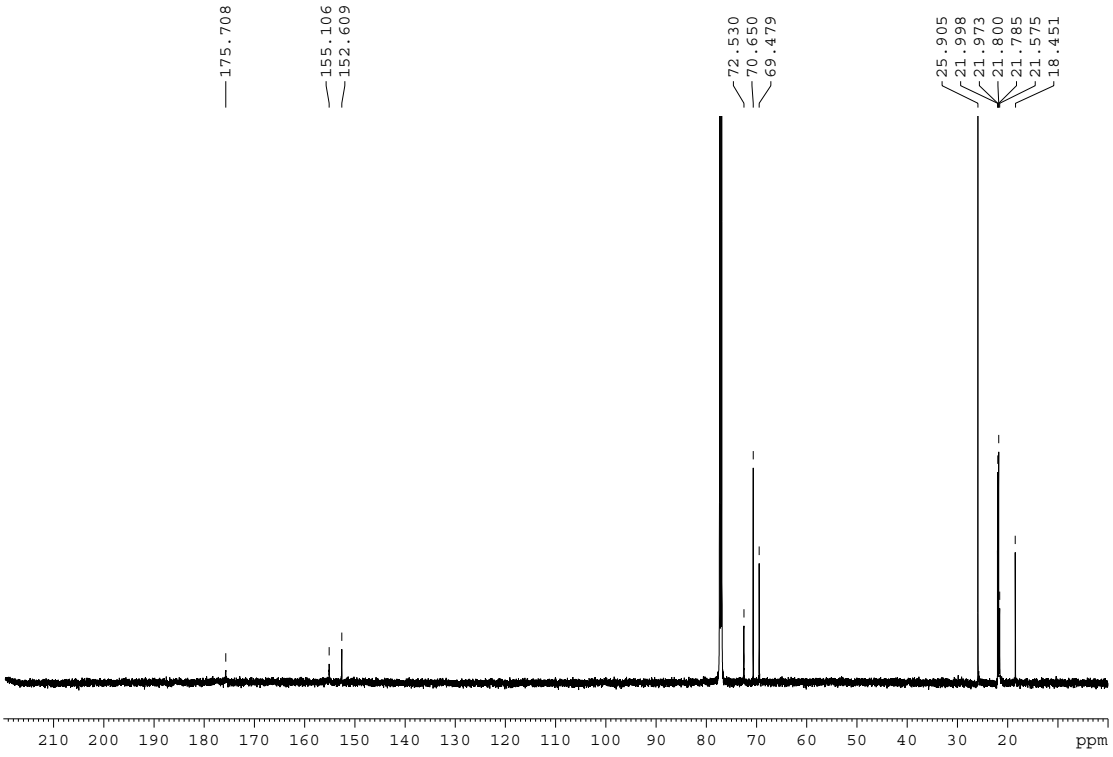
151.427
98.762
74.294
72.835
70.807
31.104
27.284
22.211
22.009
21.818
19.407
13.995
ppm

Dipropan-2-yl 1-[(2S)-2-(*tert*-butyldimethysilyloxy)propanoyl]hydrazine-1,2-dicarboxylate

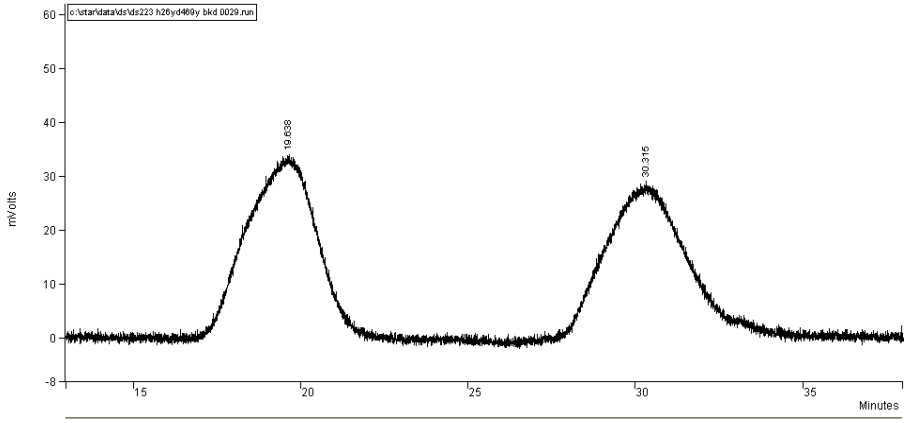


Reaction was stirred for 96 h. Purification by column chromatography (5-10% EtOAc/Petrol) gave dipropan-2-yl 1-[(2S)-2-(tert-butyldimethysilyloxy)propanoyl]hydrazine-1,2-dicarboxylate as a colourless oil (238 mg, 0.61 mmol, 61%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60 (br s, NH, 1H), 5.38 (q, J = 6.5 Hz, 1H), 5.04 (septet, J = 6.5 Hz, 1H), 4.98-4.92 (m, 1H), 1.47-1.40 (m, 3H), 1.34-1.17 (m, 12H), 0.91 (s, 9H), 0.09 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7 (C), 155.1 (C), 152.6 (C), 72.5 (CH), 70.7 (CH), 69.5 (CH), 25.9 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 21.8 (CH_3), 21.8 (CH_3), 21.6 (CH_3), 18.5 (C), –4.7 (CH_3), –5.1 (CH_3); IR (thin film) 3309, 2931, 2858, 1788, 1741, 1727 cm^{-1}; LRMS (ES$^+$) 413 (100, $[M+Na]^+$); HRMS (ES$^+$) calcd for $C_{17}H_{34}N_2O_6NaSi$ $[M+Na]^+$ 413.2084, observed 413.2069. $[\alpha]_D^{20}$ = +22.7 (*c* 0.55, $CHCl_3$); HPLC analysis indicates 99% ee, t_R (major) = 19.8 min, t_R (minor) = 30.1 min

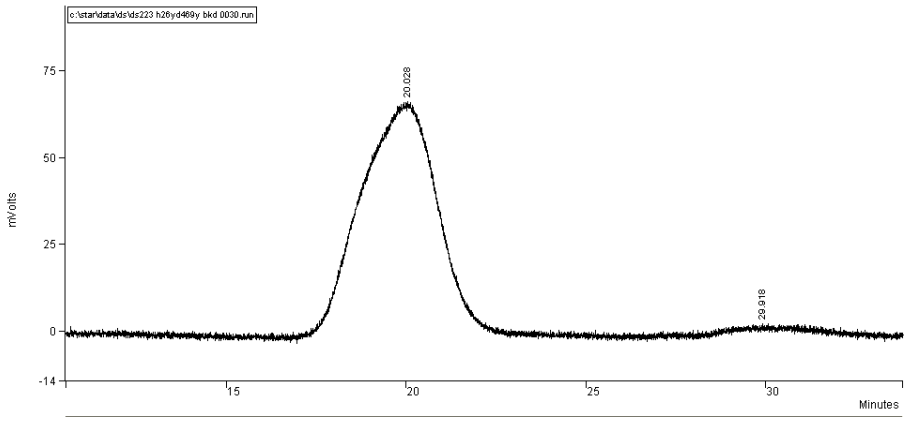




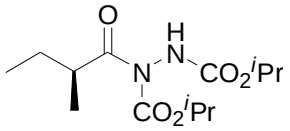
HPLC trace for *rac*-dipropan-2-yl 1-[-2-(*tert*-butyldimethysilyloxy)propanoyl]hydrazine-1,2-dicarboxylate



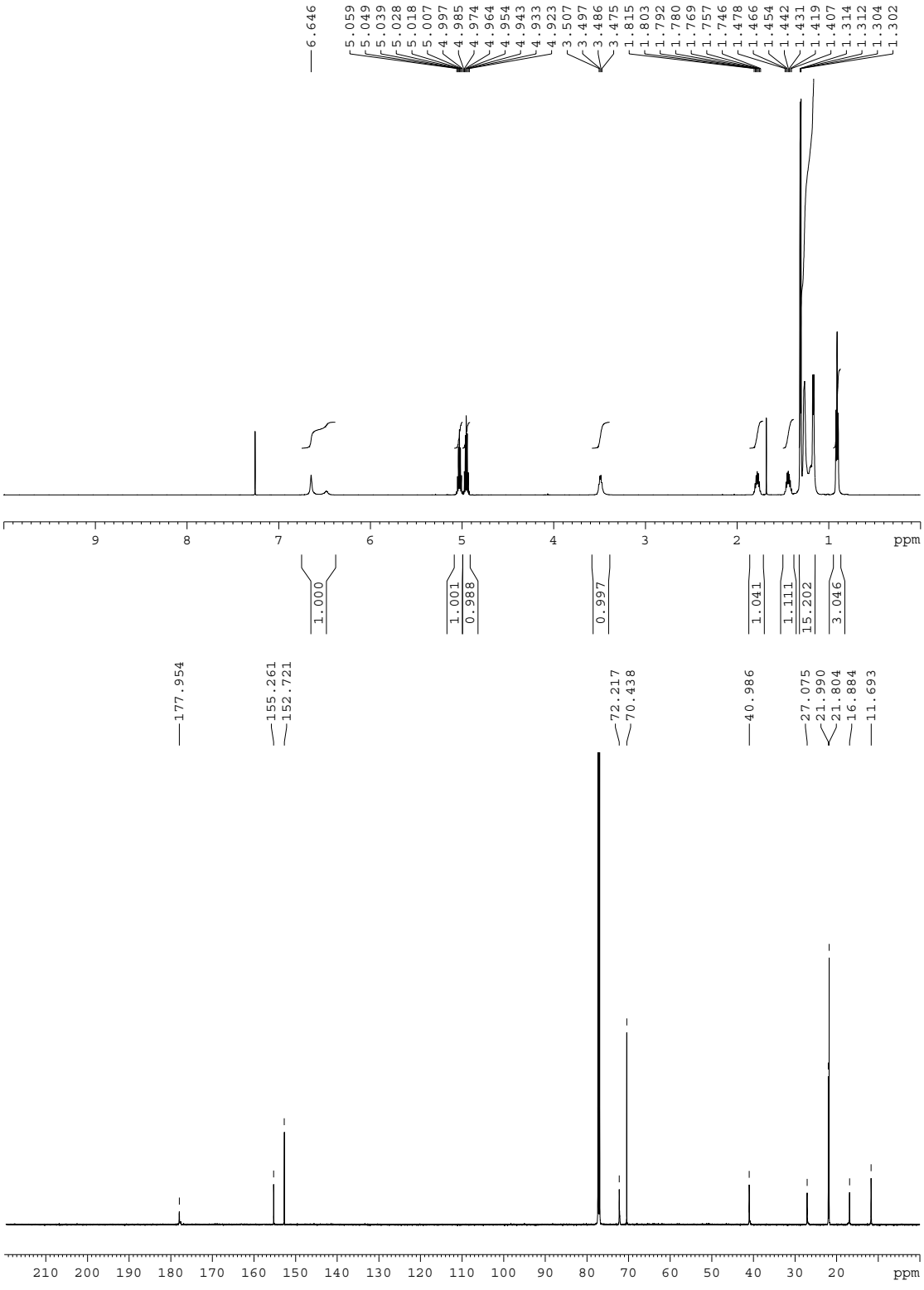
HPLC trace for dipropan-2-yl 1-[(2S)-2-(*tert*-butyldimethysilyloxy)propanoyl]hydrazine-1,2-dicarboxylate **3l**



Dipropan-2-yl 1-[(2*S*)-2-methylbutanoyl]hydrazine-1,2-dicarboxylate 3m



Reaction was stirred for 24 h. Purification by column chromatography (10%-40% EtOAc/Petrol) gave dipropan-2-yl 1-[(2*S*)-2-methylbutanoyl]hydrazine-1,2-dicarboxylate as a colourless oil (254 mg, 0.88 mmol, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (br s, NH, 1H), 5.05 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 3.55-3.47 (m, 1H), 1.80 (doublet of quintets, *J* = 14.5, 7.5 Hz, 1H), 1.46 (doublet of quintets, *J* = 14.5, 7.0 Hz, 1H), 1.34-1.17 (m, 15H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 41.0 (CH), 27.1 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 16.9 (CH_3), 11.7 (CH_3); IR (thin film) 3313, 2981, 2938, 1736, 1718 cm^{-1}; LRMS (CI) 289 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{13}H_{25}N_2O_5$ $[M+H]^+$ 289.1764, observed 289.1757; $[\alpha]_D^{20}$ = +20.0 (*c* 0.48, $CHCl_3$); HPLC analysis indicates 98% ee, t_R (major) = 36.8 min, t_R (minor) = 42.9 min.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4.954
4.943
4.933
4.923
3.507
3.497
3.486
3.475
1.815
1.803
1.792
1.780
1.769
1.757
1.746
1.478
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1.442
1.431
1.419
1.407
1.314
1.312
1.304
1.302
ppm
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1.001
0.988
0.997
1.041
1.111
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3.046
177.954
155.261
152.721
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70.438
40.986
27.075
21.990
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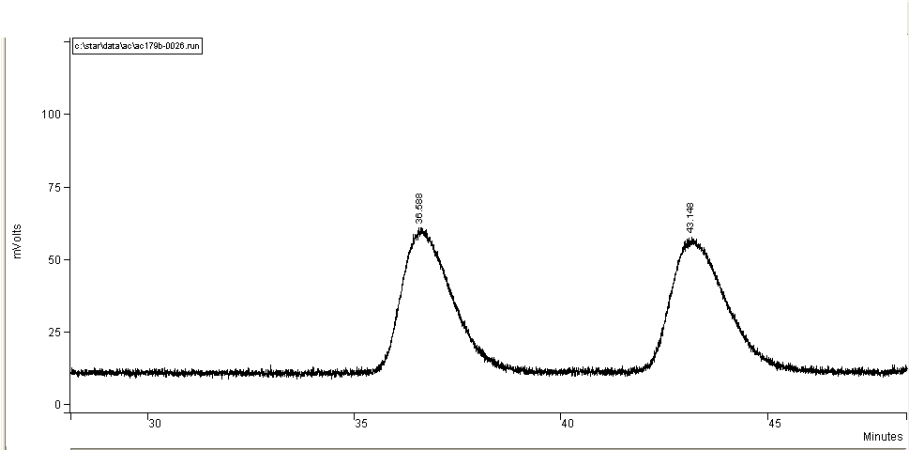
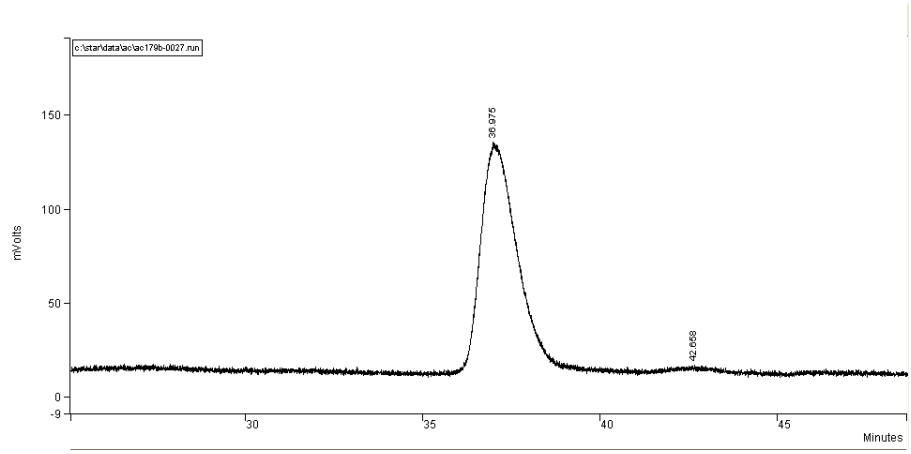
11.693
ppm

HPLC trace for *rac*-dipropan-2-yl 1-[2-methylbutanoyl]hydrazine-1,2-dicarboxylate



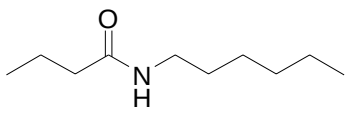
HPLC trace for dipropan-2-yl 1-[(2*S*)-2-methylbutanoyl]hydrazine-1,2-dicarboxylate **3m**



General procedure for the synthesis of amides

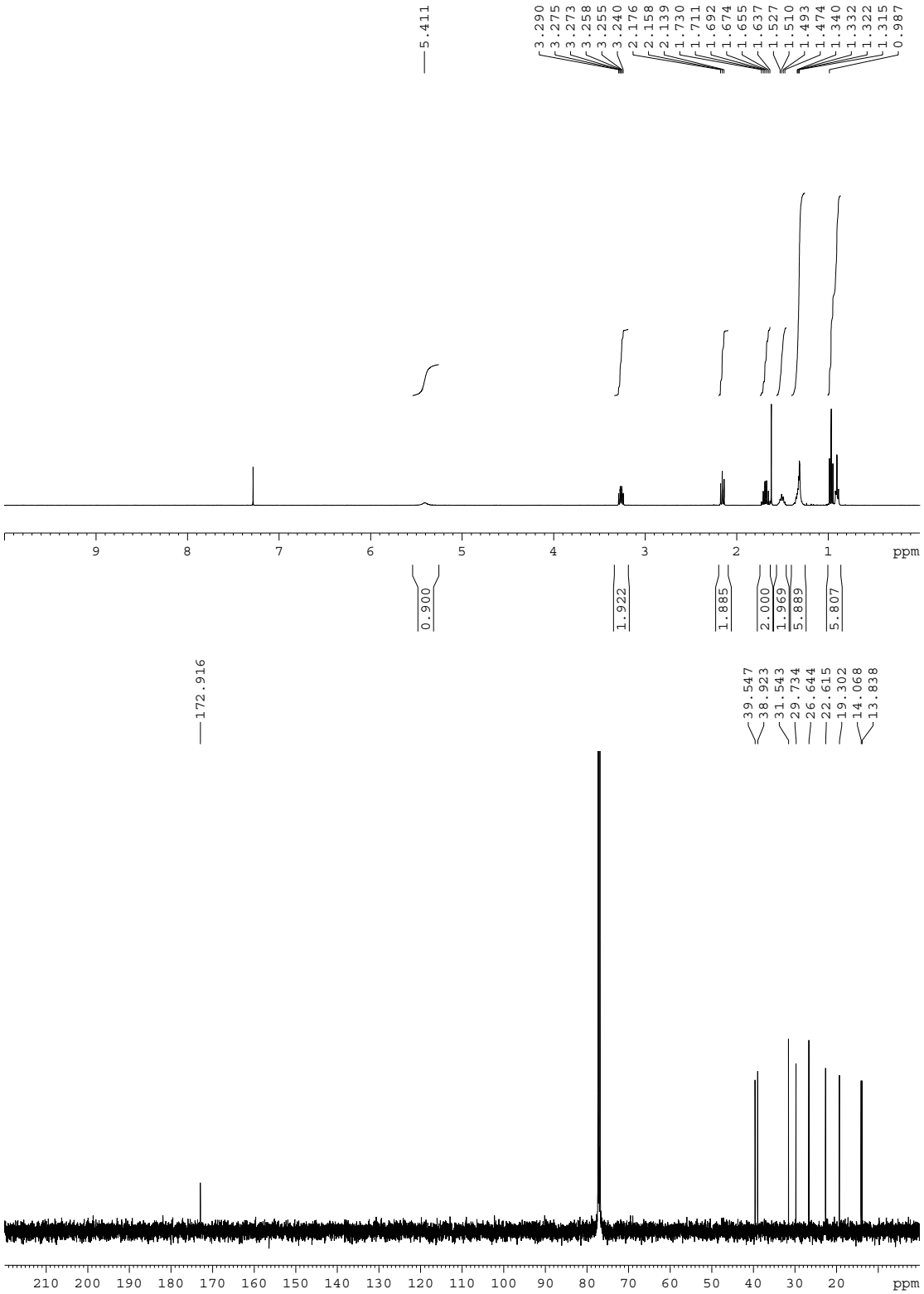
Amine (2.5 mmol) was added to a solution of *N*,*N'*-bis[(propan-2-yloxy)carbonyl]butanehydrazide (1 mmol) in CH_2Cl_2 (2.0 mL) and the reaction mixture stirred at 300 rpm at 21 °C in a stoppered carousel tube for 16 h. The solvent was removed *in vacuo* and the product purified as described below.

***N*-Hexylbutanamide 6**

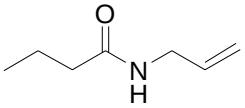


Purification by column chromatography (20%-60% EtOAc/petrol) gave *N*-hexylbutanamide as a colourless oil (164 mg, 0.96 mmol, 96%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.45-5.35 (m, NH, 1H), 3.26 (q, *J* = 7.0 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.68 (sextet, *J* = 7.5 Hz, 2H), 1.51 (quintet, *J* = 7.0 Hz, 2H), 1.36-1.24 (m, 6H), 1.00 (t, *J* = 7.5 Hz, 3H). 0.95 (t, *J* = 7.5 Hz, 3H);

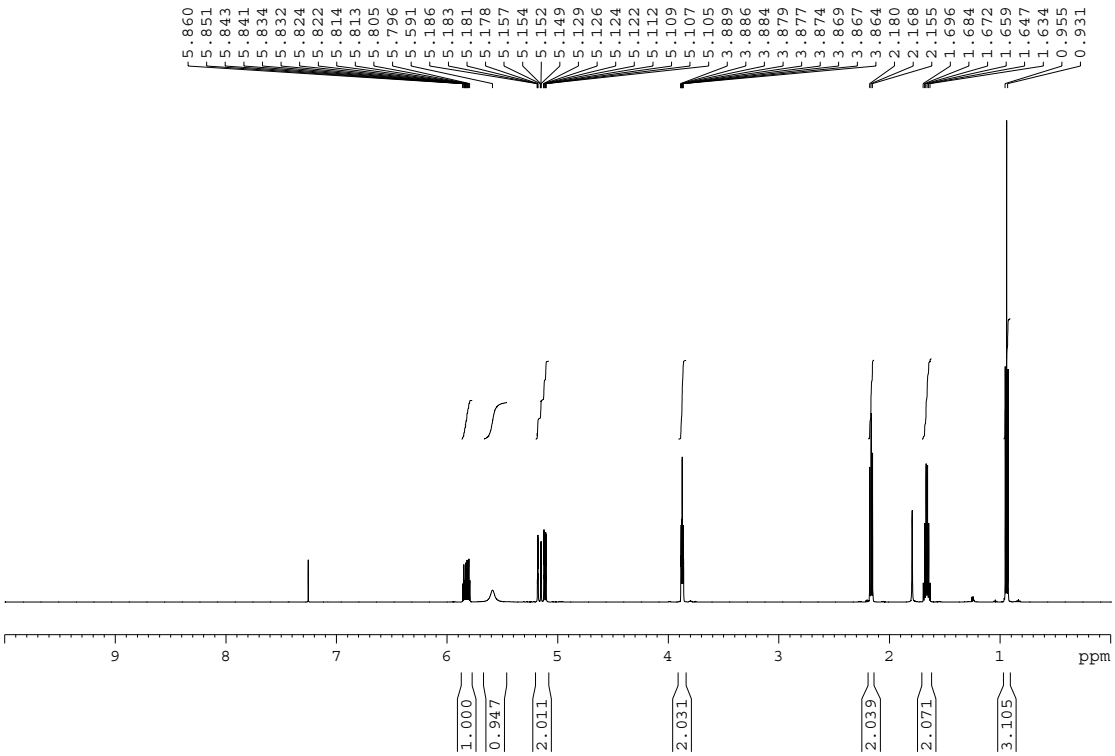
^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9 (C), 39.6 (CH_2), 38.9 (CH_2), 31.5 (CH_2), 29.7 (CH_2), 26.6 (CH_2), 22.6 (CH_2), 19.3 (CH_2), 14.1 (CH_3), 13.8 (CH_3); IR (thin film) 3290, 3083, 2959, 2929, 2872, 1643, 1550 cm^{-1}; LRMS (CI) 172 (100, $[M+H]^+$); HRMS (CI) calcd for $C_{10}H_{22}NO$ $[M+H]^+$ 172.1701, observed 172.1698.

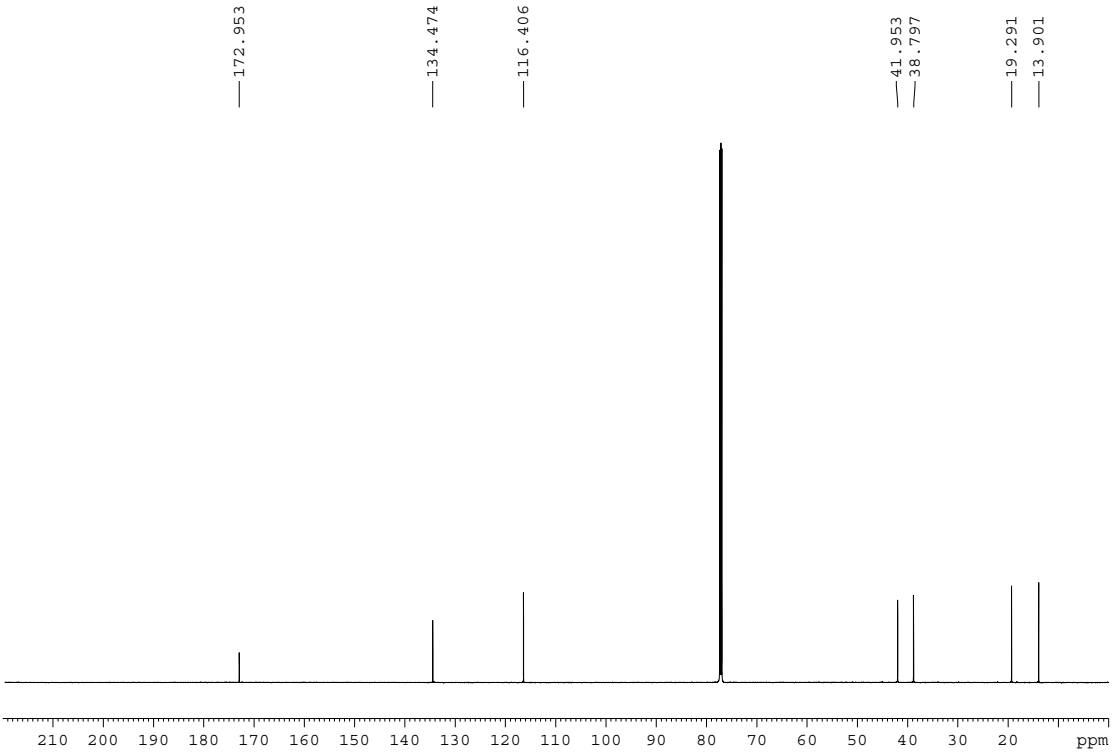


_N_-(Prop-2-en-1-yl)butanamide

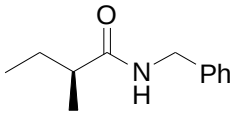


Purification by column chromatography (20%-60% EtOAc/petrol) gave *N*-(prop-2-en-1-yl)butanamide as a colourless oil (121 mg, 0.95 mmol, 95%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.0, 11.5, 6.0 Hz, 1H), 5.64-5.56 (m, NH, 1H), 5.08 (dq, *J* = 17.0, 1.5 Hz, 1H), 4.99 (dq, *J* = 11.5, 1.5 Hz, 1H), 3.88 (tt, *J* = 6.0, 1.5 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 1.67 (sextet, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0 (C), 134.5 (CH), 116.4 (CH_2), 42.0 (CH_2), 38.8 (CH_2), 19.3 (CH_2), 13.9 (CH_3); IR (thin film) 3290, 3083, 2964, 2930, 2874, 1643, 1548 cm^{-1}; LRMS (EI) 127 (100, $[M]^{+\cdot}$); HRMS (EI) calcd for $C_7H_{13}NO$ $[M]^{+\cdot}$ 127.0992, observed 127.0995.

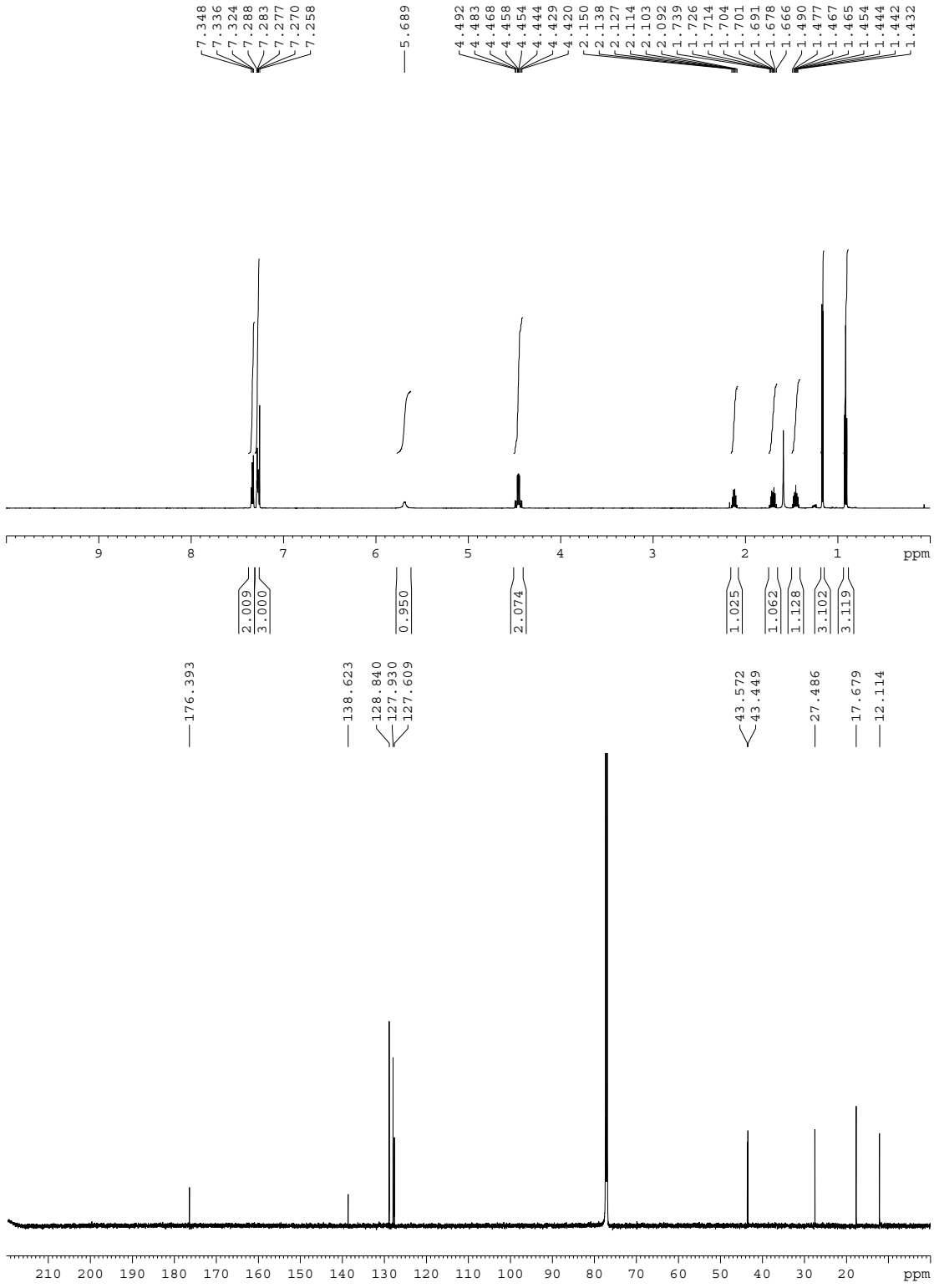




(2*S*)-*N*-Benzyl-2-methylbutanamide



Purification by column chromatography (50% Et_2O/petrol) gave (2*S*)-*N*-benzyl-2-methylbutanamide (86% yield, determined by integration of crude ^{1}H NMR relative to pentachlrorbenzene as internal standard) as a colourless oil: $[\alpha]_D^{20}$ = +16.0 (*c* 1.08, Acetone); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.29-7.25 (m, 3H), 5.70-5.62 (m, NH, 1H), 4.49-4.42 (m, 2H), 2.12 (sextet, *J* = 7.0 Hz, 2H), 1.74-1.66 (m, 1H), 1.45 (ddq, *J* = 14.5, 13.5, 7.5 Hz, 1H), 1.16 (d, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4 (C), 138.6 (C), 128.8 (CH), 127.9 (CH), 127.6 (CH), 43.6 (CH_2), 43.4 (CH), 27.5 (CH_2), 17.7 (CH_3), 12.1 (CH_3); IR (thin film) 3282, 2965, 2929, 2876, 1646, 1548 cm^{-1}; LRMS (CI) 192 (100, $[M+H]^+$); HRMS (EI) calcd for $C_{12}H_{18}NO$ $[M+H]^+$ 192.1388, observed 192.1392 ; Data agrees with that reported by Yamakawa[6] and Gago.[7]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4.444
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2.127
2.114
2.103
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3.119
176.393
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ppm

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