Electronic Supplementary Material (ESI) for Chemical Communications

Organocatalysed decarboxylative protonation process from Meldrum's acid: enantioselective synthesis of isoxazolidones

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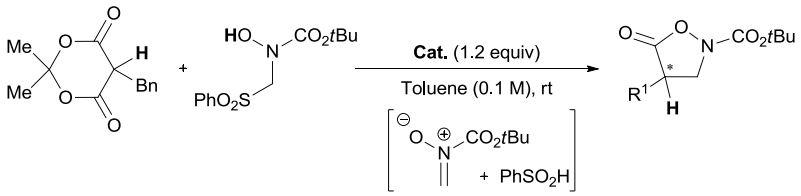
I General information

Solvents were purchased as dehydrated ones, and toluene or CH_2Cl_2 was distilled on CaH_2. All reagents were used as received unless otherwise indicated. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1] Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or $KMnO_4$ oxidation. ^1H NMR spectra were recorded on a Bruker AVANCE 300 at 300 MHz. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^1H decoupling. The hydrogen multiplicity was obtained by DEPT135 or Attached Proton Test (APT) using JMOD pulse program. IR spectra were recorded on a Perkin Elmer IRTF 100 spectrometer using an ATR (Attenuated Total Reflectance) sampling with solid dispersed or neat or on a Perkin Elmer IRFT 1650 with solid dispersed on KBr pastille. Mp's stand uncorrected. HRMS analyses were measured on a Q-TOF Micro WATERS spectrometer. HPLC analyses were performed with Daicel Chiralpack® columns (4.6 mm × 25 cm). A spectrosystem UV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used. GC analyses were performed on a Varian 3900 using ChiralsilDex-CB® (25m x 0.25mm, 0.25μm), carrier gas: He, carrier gas flow at constant pressure: 20 psi, Injector: split, 250°C, Detector range 11: FID, 250°C. The 5-substituted Meldrum's acids were synthesis following the Ramachary's procedure.[2] The nitrone precursors **5** were prepared according to Denis' protocol.[3]

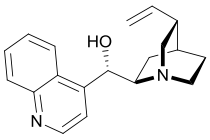
[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
[2] (a) D. B. Ramachary and G. B. Reddy, *Org. Biomol. Chem.*, 2006, **4**, 4463; (b) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651.
[3] X. Guinchard, Y. Vallée and J.-N. Denis, *Org. Lett.*, 2005, **7**, 5147.

II Optimization

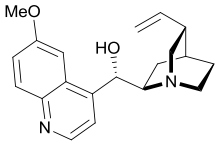
II-1 Screening of organocatalysts of catalysts



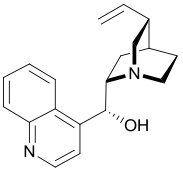
In order to evaluate the capability of a given catalyst to promote this enantioselective reprotonation reaction, without facing any background reaction promoted by a co-base, 1.2 equivalent of catalyst was used. One equivalent is involved into generation of the nitrone intermediate by trapping the liberated sulfinic acid and 0.2 equivalent to promote the catalytic reaction (see next page).



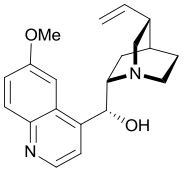
25% ee, 40%



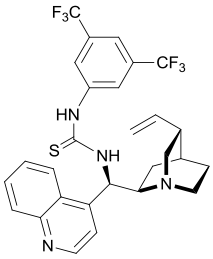
66% ee, 99%



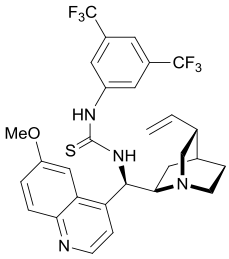
19% ee, 93%



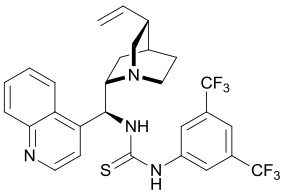
47% ee, 46%



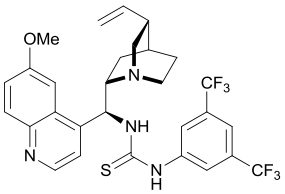
80% ee, 90%



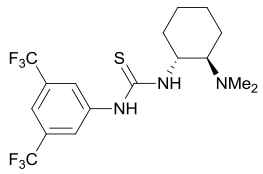
80% ee, 97%



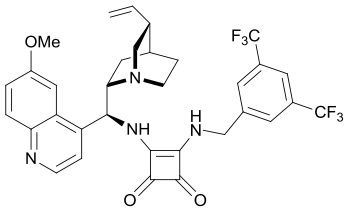
81% ee, 75%



79% ee, 100%
80% ee, 86% (0°C)



62% ee, 100%



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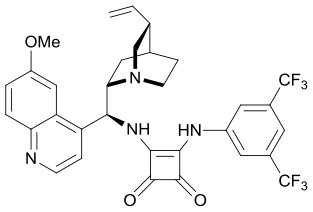
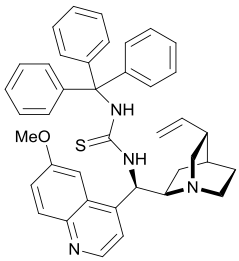


52% ee, 86%



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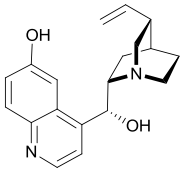

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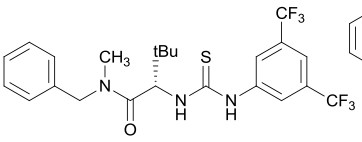

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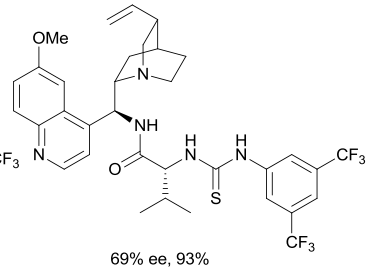
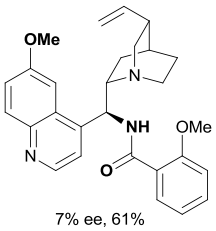
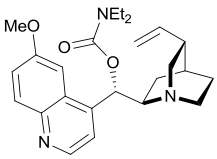


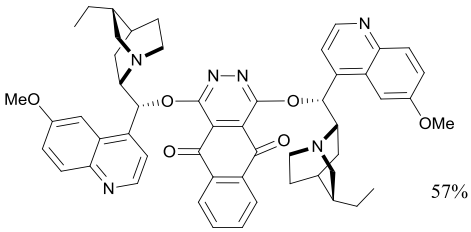
69% ee, 93%



7% ee, 61%

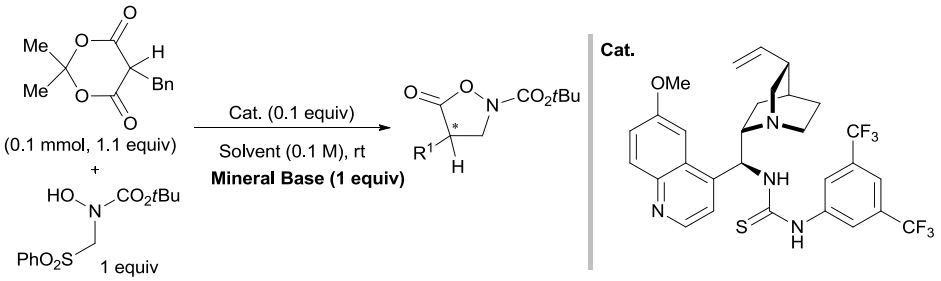


17% ee, 21%



57% ee, 68%

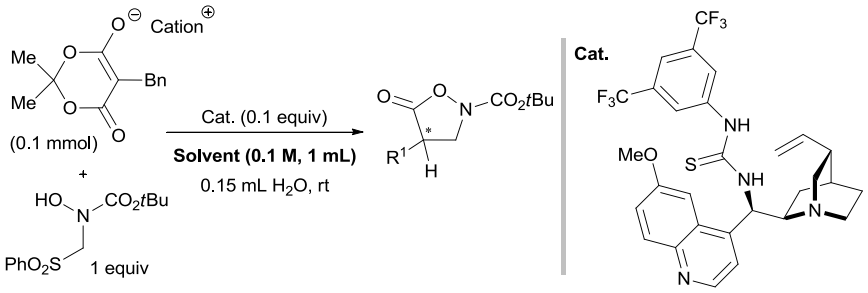
II-2 Representative optimizations : co-base, solvent and water



entry	base (equiv)	solvent (1 mL)	temp (°C)	time (h)	yield[a] (%)	ee (%)
1	-[b]	Toluene	24	17	0	-
2	-[c]	Toluene	20	6.5	99	-79
3	Cs_2CO_3 (1.0)	Toluene	20	18	86	-23
4	Cs_2CO_3 (1.0)	THF	20	18	54	0
5	K_2CO_3 (1.0)[b]	Toluene	20	20	50	0
6	K_2CO_3 (1.0)[b]	Toluene	0	24	0	-
7	K_2CO_3 (1.0)	Toluene	20	24	79	-56
8	***Na_2CO_3 (1.0)[d]***	***Toluene***	***20***	***24***	***56***	***+68***
9	***Na_2CO_3 (1.0)[d]***	***Toluene (0.15 mL H_2O)***	***20***	***24***	***64***	***+74***
10	AcONa (1.0)	Toluene	20	20	23	-47
11	*t*BuOK (1.0)	Toluene	20	20	61	-41

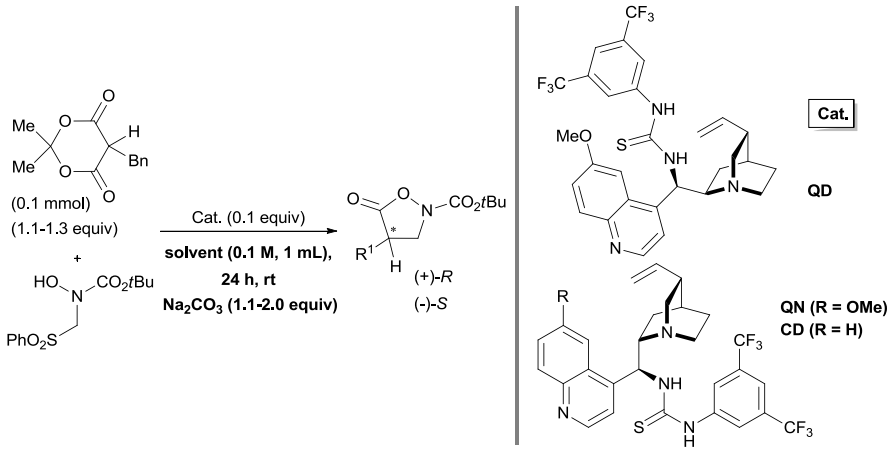
[a] Isolated yield after column chromatography. [b] Without catalyst. [c] With 1.2 equivalents of catalyst. [d] With 9-epi-amino-quinidine thiourea derived catalyst.

The investigation of solvents was directly carried out with the Meldrum's acid conjugated base to prevent any background reaction interference from the Meldrum's acid acidity.



entry	Cation^{+}	solvent (1 mL)	temp (°C)	time (h)	yield[a] (%)	ee (%)
1	Na	Toluene	20	24	79	+74
2	K	Toluene	20	24	79	+73
3	Me_4N^+	Toluene	20	24	76	+74
4	Na	THF	20	24	86	+36
5	Na	MeCN	20	24	93	+41
6	Na	CH_2Cl_2	20	24	72	+57
7	Na	DMF	20	24	68	+14
8	Na	acetone	20	24	76	+34
9	Na	$PhCF_3$	20	24	83	+72
10	Na	MeCy	20	24	65	+75
11	**Na**	***m*-xylene**	**20**	**24**	**68**	**+79**
12	Na[b]	*m*-xylene[c]	20	5	66[e]	-
13	Na[b]	*m*-xylene[d]	20	5	90[e]	-

[a] Isolated yield after column chromatography. [b] Without catalyst. [c] With 1 equivalent of water. [d] Without water. [e] Yield estimated on the crude product by ^{1}H NMR with an internal standard.

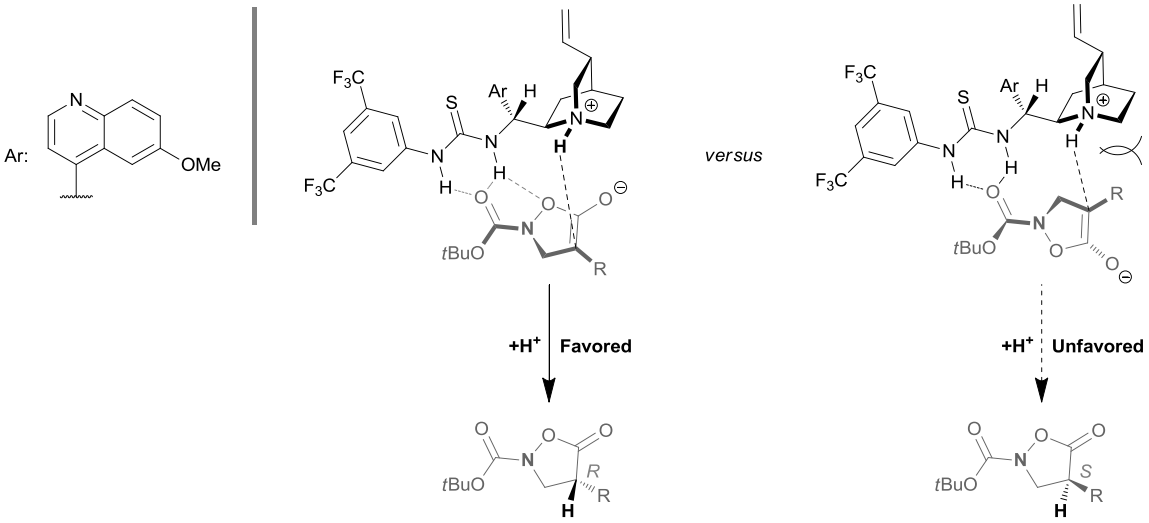


entry	Cat. (equiv)	solvent (M)	H_2O (mL)	time (h)	temp (°C)	yield[a] (%)	ee (%)
1	0.1 QD[b]	Toluene (0.1)	0.15	24	20	76	+77
2	0.2 QD[b]	Toluene (0.1)	0.15	24	20	72	+78
3	0.1 QD[b]	*m*-Xylene (0.1)	0.15	24	20	68	+79
4	0.1 QD[b]	*m*-Xylene (0.05)	0.15	24	20	73	+79
5	0.1 QD[b]	*m*-Xylene (0.025)	0.15	24	20	68	+79
6	0.1 QD[b]	*m*-Xylene (0.1)	0.15	24	*0*	51	+64
7	0.1 QD[b]	*m*-Xylene (0.1)	0.5	24	20	65	+79
8	0.1 QD[b]	*m*-Xylene (0.1)	1.0	24	20	72	+81
9	0.1 QD[b]	*m*-Xylene (0.1)	2.0	24	20	65	+81
10	**0.1 QD[c]**	***m*-Xylene (0.1)**	**1.0**	24	**20**	**75**	**+84**
11	0.1 QD[d]	*m*-Xylene (0.1)	1.0	24	20	68	+84
12	0.05 QD[c]	*m*-Xylene (0.1)	1.0	24	20	76	+73
13	0.1 QD[c]	*m*-Xylene (0.1)	1.0	1.5	20	98[e]	+81
14	0[c]	*m*-Xylene (0.1)	1.0	1.5	20	22[e]	-
15	0[c]	*m*-Xylene (0.1)	1.0	5	20	65[e]	-
16	0.1 QN[c]	*m*-Xylene (0.1)	1.0	24	20	76	-73
17	**0.1 CD[c]**	***m*-Xylene (0.1)**	**1.0**	**24**	**20**	**74**	**-84**

[a] Isolated yield after column chromatography. [b] 1.1 equivalent of Meldrum's acid. [c] 1.3 equivalent of Meldrum's acid and Na_2CO_3. [d] 2.0 equivalent of Meldrum's acid and Na_2CO_3. [e] Yield estimated on the crude product by ^1H NMR with an internal standard.

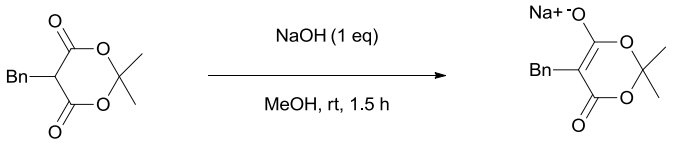
II-3 Proposed transition state

For a discussion over the mechanism of decarboxylative protonation reaction promoted by thiourea cinchona alkaloid catalysts see the work of Sunoj.[4]



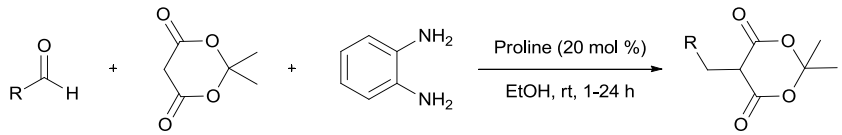
[4] A. Sengupta and R. B. Sunoj, *J. Org. Chem.*, 2012, **77**, 10525.

III Experimental procedures



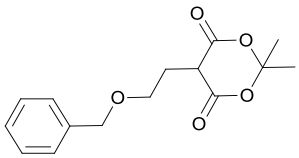
4a **7b**

Sodium 5-benzyl-2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-olate (7b). To a solution of 5-benzyl Meldrum's acid **4a** (1 mmol, 234 mg) in methanol (5 mL) was added sodium hydroxide at room temperature (44.7 mg, 1 mmol). The solution was stirred for 1.5 hours and evaporated at dryness. The crude product was crystallized in acetonitrile. The resulting solid was washed with cold methanol to remove traces of acetonitrile and dried under vacuum with P_2O_5 to give a white solid (259 mg, 91 %). m.p. = 153-155 °C (decomposition yellow solid). IR (neat): ν_{max} : 1553, 1401, 1370, 1260, 1204, 1107, 979, 716 cm^{-1}. ^1H NMR (300 MHz, MeOD): δ 1.60 (s, 6H), 3.51 (s, 2H), 6.99-7.09 (m, 1H), 7.11-7.20 (m, 2H), 7.21-7.30 (m, 2H). ^{13}C NMR (75 MHz, MeOD): δ 26.0 (2 CH_3), 30.4 (CH_2), 76.9 (C), 102.5 (C), 125.9 (CH), 128.6 (CH), 129.2 (CH), 145.2 (C), 170.2 (C).

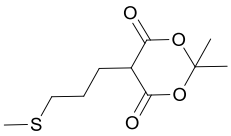


2 equiv 1 equiv 1 equiv

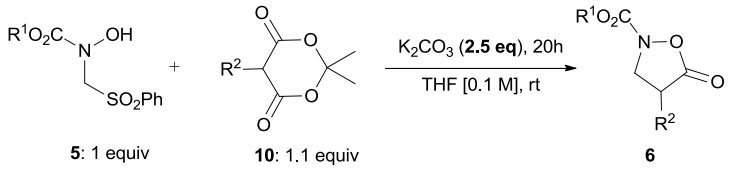
Typical procedure for the preparation for 5-substituted-2,2-dimethyl-1,3-dioxane-4,6-dione (4).[2] To a solution of *o*-phenylene diamine (1 equiv) in absolute ethanol (0.05 M) at room temperature was added proline (0.2 equiv), Meldrum's acid (1 equiv) and aldehyde (2 equiv). The solution was vigorously stirred for 24 hours and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with an aqueous solution and an HCl solution (1M). The acidic aqueous solution was extracted 3 times with CH_2Cl_2. The combined CH_2Cl_2 layers was washed with water, filtered and concentrated at dryness. The desired product was obtained after purification by column chromatography on silica gel using dichloromethane as eluent.



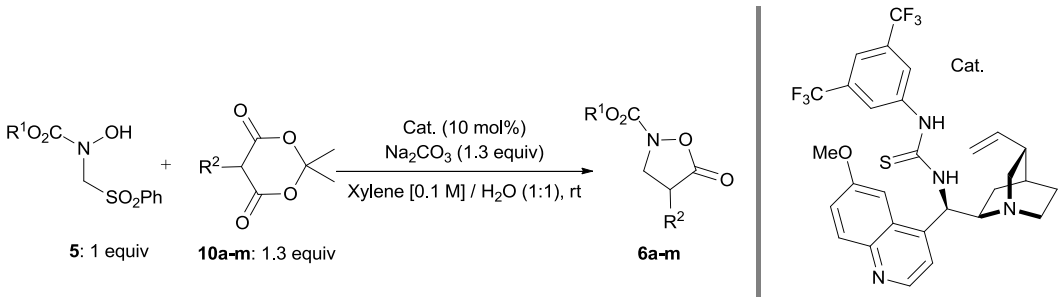
5-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4i). Following the general procedure from 2-benzyloxyacetaldehyde 95 % (3.33 mmol, 0.5 g), the title compound was obtained as a yellow oil (145 mg, 31 %); R_f = 0.6 (CH_2Cl_2); IR (neat) ν_{max} 2873, 1738, 1454, 1383, 1288, 1203, 1069, 983, 739 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.14-7.33 (5H, m), 4.41 (2H, s), 3.61-3.71 (3H, m), 2.37 (2H, dd, J = 5.9 Hz, J = 11.50 Hz), 1.69 (3H, s), 1.61 (3H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 165.8 (2C), 138.0 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 104.9 (C), 73.0 (CH_2), 66.1 (CH_2), 42.4 (CH), 28.3 (CH_2), 26.7 (CH_3), 26.3 (CH_3); HRMS (ESI+): calcd for $C_{15}H_{18}O_5Na$ $[M+Na]^+$: 301.1046; Found: 301.1051.



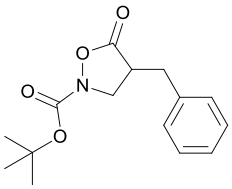
2,2-dimethyl-5-(3-(methylthio)propyl)-1,3-dioxane-4,6-dione (4j). Following the general procedure from 3-(methylthio)propanal (578 mg, 5.55 mmol), the title compound was obtained as a yellow oil (140 mg, 22 %); R_f = 0.5 (CH_2Cl_2); IR (KBr) ν_{max} 2997, 2969, 2946, 1798, 1748, 1460, 1381, 1306, 1244, 1054, 990, 878, 643 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 3.63 (1H, t, J = 5.2 Hz), 2.53 (2H, t, J = 7.1 Hz), 2.19 (2H, dd, J = 5.2, 2.1 Hz), 2.07 (3H, s), 1.85–1.64 (8H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 165.4 (2C), 105.0 (C), 45.9 (CH), 33.8 (CH_2), 28.5 (CH_2), 26.8 (CH_2), 25.5 (CH_3), 25.4 (CH_3), 15.3 (CH_3). HRMS (ESI-): calcd for $C_{10}H_{15}SO_4$ $[M-H]^+$: 231.0697; Found: 231.0687.



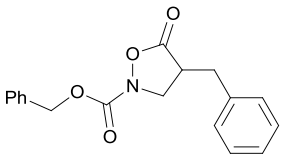
Typical procedure for the preparation of racemic isoxazolidinones 6. To a mixture of sulfone-amide **5** (1 equiv), Meldrum's acid **4** (1.1 equiv) and potassium carbonate (2.5 equiv) was added THF (0.1 M) at room temperature. The mixture was stirred for 24h and filtrated. The solid was washed by diethyl ether and the filtrates were evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using Et_2O/PE as eluent to give the desired isoxazolidinone **6**.



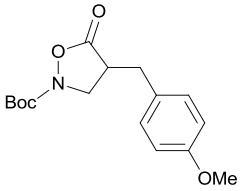
Typical procedure for the preparation of enantioenriched isoxazolidinone 6. To a mixture of sulfone-amide **5** (1 equiv), Meldrum's acid **4** (1.3 equiv.), sodium carbonate (1.3 equiv) and catalyst (0.1 equiv) was added *m*-xylene (0.1 M) and subsequently deionized water (*m*-xylene:H_2O 1:1). The resulting solution was vigorously stirred at room temperature for 24h (an emulsion is rapidly formed). The two phases were separated and the aqueous phase was extracted by ethyl acetate. The combined organic phases was dried with magnesium sulfate, filtrated and evaporated under reduced pressure (water bath at a maximum of 45°C). The crude product was purified by silica gel column chromatography as described below to give the desired isoxazolidinone **6**.



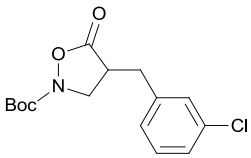
***Tert*-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate** (**6a**). Following the general procedure from 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (152 mg, 0.65 mmol), the title compound was obtained as white solid (102 mg, 74 %); m.p. = 65-67°C, R_f = 0.4 (Petroleum ether/ Ether: 4/1); IR (neat) ν_{max} 2982, 2932, 1789, 1708, 1454, 1357, 1142, 994, 705 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.39–7.15 (5H, m), 4.15 (1H, dd, J = 11.1, 8.4 Hz), 3.71 (1H, dd, J = 11.1, 9.1 Hz), 3.33–3.11 (2H, m), 2.80 (1H, J = 13.8, 9.7 Hz), 1.51 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.2 (C), 155.9 (C), 136.9 (C), 128.9 (2CH), 128.7 (2CH), 127.2 (CH), 84.1 (C), 52.9 (CH_2), 42.1 (CH_2), 34.3 (CH), 28.0 ($3CH_3$); HRMS (ESI+): calcd for $C_{15}H_{19}NO_4K$ $[M+K]^+$: 316.0946; Found: 316.0949; HPLC analysis: 91:09 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 12 min for major *R* enantiomer; t_2 = 15 min for minor *S* enantiomer). The product was recrystallized twice from ether/pentane (1/9) to give 99 % ee (48 mg, 36 %); $[\alpha]_D^{20}$ +7.3 ± 1 (*c* 1.0, $CHCl_3$).



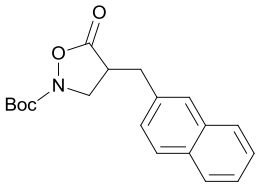
Benzyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate (**6b**). Following the general procedure from 5-benzyl-2,2-dimethyl-1,3-dioxane-4,6-dione (76 mg, 0.325 mmol) and Cbz-protected sulfone-amide **5b** (80 mg, 0.25 mmol), the title compound was obtained as a yellow oil (68 mg, 87 %); R_f = 0.2 (Petroleum ether/Ether: 4/1); IR (neat) ν_{max} 1799, 1751, 1723, 1455, 1392, 1317, 1212, 1143, 978 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.35–6.97 (10H, m), 5.11 (2H, s), 4.10 (1H, dd, J = 11.1, 8.5 Hz), 3.68 (1H, dd, J = 11.1, 8.9 Hz), 3.09 (2H, m), 2.68 (1H, dd, J = 15.3, 10.9 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.0 (C), 156.8 (C), 136.7 (C), 134.9 (C), 129.1 (2CH), 128.8 (CH), 128.8 (2CH), 128.8 (2CH), 128.5 (2CH), 127.4 (CH), 69.9 (CH_2), 52.9 (CH_2), 42.0 (CH_2), 34.5 (CH); HRMS (ESI+): calcd for $C_{18}H_{17}NO_4K$ $[M+K]^+$: 350.0789; Found: 350.0792; HPLC analysis: 79.5:20.5 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 15 min for major *R* enantiomer; t_2 = 17 min for minor *S* enantiomer).



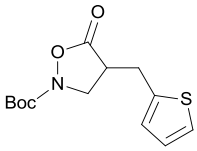
***tert*-butyl 4-(4-methoxybenzyl)-5-oxoisoxazolidine-2-carboxylate (6c).** Following the general procedure from 5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (34 mg, 0.13 mmol), the title compound was obtained as colorless oil (24 mg, 78 %); R_f = 0.31 (Petroleum ether/ Ether: 4/1); IR (neat) ν_{max} 2980, 1795, 1714, 1513, 1369, 1246, 1135, 1031, 844, 811, 768 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.10 (2H, d, J = 8.7 Hz), 6.85 (2H, d, J = 8.7 Hz), 4.12 (1H, dd, J = 11.1, 8.4 Hz), 3.79 (3H, s), 3.70 (1H, dd, J = 11.1, 9.0 Hz), 3.23 – 3.07 (2H, m), 2.86 – 2.66 (1H, m), 1.50 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.4 (C), 158.9 (C), 156.0 (C), 129.9 (2CH), 128.9 (C), 114.4 (2CH), 84.2 (C), 55.4 (CH_3), 52.9 (CH_2), 42.5 (CH_2), 33.7 (CH), 28.1 ($3CH_3$); HRMS (ESI+): calcd for $C_{16}H_{21}NO_5K$ [M+K+]: 346.1051; Found: 346.1059; HPLC analysis: 91:9 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 14 min for major *R* enantiomer; t_2 = 17 min for minor *S* enantiomer).



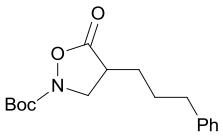
***tert*-butyl 4-(3-chlorobenzyl)-5-oxoisoxazolidine-2-carboxylate (6d).** Following the general procedure from 5-(3-chlorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (87 mg, 0.325 mmol), the title compound was obtained as an colorless oil (66 mg, 85 %); R_f = 0.3 (Petroleum ether/ Ether: 7/3); IR (neat) ν_{max} 2981, 2932, 1795, 1772, 1714, 1476, 1369, 1136, 845, 778 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.36 – 6.94 (4H, m), 4.13 (1H, dd, J = 11.1, 8.4 Hz), 3.64 (1H, dd, J = 11.1, 9.3 Hz), 3.29 – 3.02 (2H, m), 2.74 (1H, dd, J = 13.0, 8.6 Hz), 1.47 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 173.8 (C), 155.8 (C), 138.9 (C), 134.7 (C), 130.3 (CH), 128.8 (CH), 127.5 (CH), 126.9 (CH), 84.3 (C), 52.8 (CH_2), 41.9 (CH_2), 34.0 (CH), 28.0 ($3CH_3$); HRMS (ESI+): calcd for $C_{15}H_{18}NO_4ClK$ $[M+K]^+$: 350.0556; Found: 350.0564; HPLC analysis: 78 % ee (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 13 min for major *R* enantiomer; t_2 = 15 min for minor *S* enantiomer).



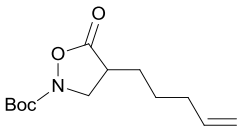
***tert*-butyl 4-(naphthalen-2-ylmethyl)-5-oxoisoxazolidine-2-carboxylate (6e).** Following the general procedure from 2,2-dimethyl-5-(naphthalen-2-ylmethyl)-1,3-dioxane-4,6-dione (92 mg, 0.325 mmol), the title compound was obtained as white solid (62 mg, 76 %); m.p. = 94-96 °C, R_f = 0.25 (Petroleum ether/ Ether: 4/1); IR (neat) ν_{max} 2981, 1807, 1742, 1478, 1332, 1152, 818, 742 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.81 – 7.64 (3H, m), 7.55 (1H, s), 7.45 – 7.35 (2H, m), 7.22 (1H, dd, J = 8.4, 1.8 Hz), 4.06 (1H, dd, J = 11.1, 8.5 Hz), 3.66 (1H, dd, J = 11.1, 9.3 Hz), 3.33 (1H, dd, J = 14.0, 4.4 Hz), 3.20-3.11 (1H, m), 2.87 (1H, dd, J = 14.0, 9.8 Hz), 1.41 (9H, s);^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.3 (C), 156 (C), 134.5 (C), 133.6 (C), 132.6 (C), 128.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 126.7 (CH), 126.6 (CH), 126.1 (CH), 84.3 (C), 53.0 (CH_2), 42.3 (CH_2), 34.7 (CH), 28.1 ($3CH_3$); HRMS (ESI+): calcd for $C_{19}H_{21}NO_4Na$ $[M+Na]^+$: 350.1363; Found: 350.1354; HPLC analysis: 86.5:13.5 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 13 min for major *R* enantiomer; t_2 = 17 min for minor *S* enantiomer). The product was recrystallized from ether/pentane (1/1) giving 93.5-6.5 er (48 mg, 59 %); a second recrystallization gave 99:1 er (30 mg, 37 %).



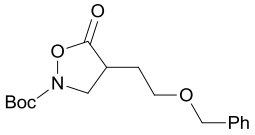
***tert*-butyl 5-oxo-4-(thiophen-2-ylmethyl)isoxazolidine-2-carboxylate (6f).** Following the general procedure from 2,2-dimethyl-5-(thiophen-2-ylmethyl)-1,3-dioxane-4,6-dione (93 mg, 0.325 mmol), the title compound was obtained as white solid (53 mg, 75 %); m.p. = 72-74°C, R_f = 0.25 (Petroleum ether/ Ether: 7/3); IR (neat) ν_{max} 2983, 1800, 1731, 1460, 1368, 1327 1141, 966, 713 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.20 (1H, dd, J = 5.2, 1.2 Hz), 6.95 (1H, dd, J = 5.2, 3.5 Hz), 6.91 – 6.83 (1H, m), 4.26 (1H, dd, J = 11.1, 8.4 Hz), 3.74 (1H, dd, J = 11.1, 9.3 Hz), 3.51 – 3.35 (1H, m), 3.32 – 2.98 (2H, m), 1.51 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 173.8 (C), 155.9 (C), 138.7 (C), 127.4 (CH), 126.5 (CH), 125 (CH), 84.4 (C), 53.0 (CH_2), 42.5 (CH_2), 28.7 (CH) , 28.1 ($3CH_3$); HRMS (ESI+): calcd for $C_{13}H_{17}NO_4SK$ $[M+K]^+$: 322.0510; Found: 322.0515; HPLC analysis: 90:10 er (Chiral column IC, hexane/iPrOH = 90:10, flow rate 1 mL/min, 242 nm, t_1 = 17 min for major *R* enantiomer; t_2 = 19 min for minor *S* enantiomer).



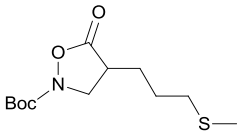
***tert*-butyl 5-oxo-4-(3-phenylpropyl)isoxazolidine-2-carboxylate (6g).** Following the general procedure from 2,2-dimethyl-5-(3-phenylpropyl)-1,3-dioxane-4,6-dione (85 mg, 0.325 mmol), the title compound was obtained as white solid (58 mg, 79 %); m.p. = 57-59°C, R_f = 0.36 (Petroleum ether/ Ether: 4/1); IR (neat) ν_{max} 2974, 2866, 1795, 1733, 1454, 1369, 1141, 960, 753 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.36 – 7.13 (5H, m), 4.27 (1H, dd, J = 11.0, 8.6 Hz), 3.63 (1H, dd, J = 11.0, 9.3 Hz), 2.86 (1H, dd, J = 9.0, 5.3 Hz), 2.66 (2H, t, J = 7.4 Hz), 1.96 – 1.52 (4H, m), 1.51 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.8 (C), 156.0 (C), 141.2 (C), 128.5 (2CH), 128.4 (2CH), 126.1 (CH), 84.1 (C), 53.6 (CH_2), 40.2 (CH_2), 35.5 (CH), 28.8 (CH_2), 28.3 (CH_2), 28.1 ($3CH_3$); HRMS (ESI+): calcd for $C_{17}H_{23}NO_4K$ [M+K+]: 344.1259; Found: 344.1269; HPLC analysis: 86.5:13.5 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 12 min for major *R* enantiomer; t_2 = 14 min for minor *S* enantiomer).



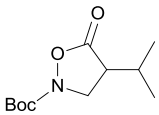
***tert*-butyl 5-oxo-4-(pent-4-en-1-yl)isoxazolidine-2-carboxylate (6h).** Following the general procedure from 2,2-dimethyl-5-(pent-4-en-1-yl)-1,3-dioxane-4,6-dione (69 mg, 0.325 mmol), the title compound was obtained as a colorless oil (51 mg, 80 %); R_f = 0.6 (Petroleum ether/ Ether: 7/3); IR (neat) ν_{max} 2979, 2934, 1797, 1715, 1369, 1138, 912, 847, 768 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 5.76 (1H, ddt, *J* = 16.9, 10.2, 6.7 Hz), 5.18 – 4.89 (2H, m), 4.28 (1H, dd, *J* = 11.0, 8.6 Hz), 3.65 (1H, dd, *J* = 11.0, 9.2 Hz), 2.99 – 2.76 (1H, m), 2.16 – 2.01 (2H, m), 1.97 – 1.79 (1H, m), 1.63 – 1.40 (12H, m); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 175.0 (C), 156.2 (C), 137.6 (CH), 115.6 (CH), 84.2 (C), 53.6 (CH_2), 40.3 (CH_2), 33.3 (CH), 28.3 (CH_2), 28.1 ($3CH_3$), 26.3 (CH_2); HRMS (ESI+): calcd for $C_{13}H_{25}N_2O_4$ $[M+NH_4]^+$: 273.1809; Found: 273.1816; HPLC analysis: 89:11 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 23 min for major *R* enantiomer; t_2 = 25 min for minor *S* enantiomer).



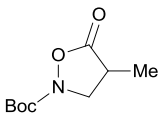
tert-butyl 4-(2-(benzyloxy)ethyl)-5-oxoisoxazolidine-2-carboxylate (6i). Following the general procedure from 5-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (45 mg, 0.162 mmol), the title compound was obtained as a yellow oil (29 mg, 72 %); R_f = 0.19 (Petroleum ether/ Ether: 7/3); IR (neat) ν_{max} 2979, 2867, 1797, 1715, 1455, 1368, 1140, 1095, 846, 736 cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.44 – 7.22 (5H, m), 4.57 – 4.44 (2H, m), 4.36 (1H, dd, *J* = 11.1, 8.8 Hz), 3.75 – 3.50 (3H, m), 3.05 (1H, dtd, *J* = 10.1, 9.0, 4.8 Hz,), 2.19 (1H, ddt, *J* = 15.4, 6.0, 4.8 Hz), 1.84 (1H, m), 1.52 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 175.2 (C), 156.1 (C), 138 (C), 128.6 (2CH), 128 (CH), 127.8 (2CH), 84.1 (C), 73.3 (CH_2), 67.3 (CH_2), 54.1 (CH_2), 38.4 (CH_2), 29.0 (CH), 28.17 ($3CH_3$); HRMS (ESI+): calcd for $C_{17}H_{27}N_2O_5$ $[M+NH_4+]$: 339.1914; Found: 339.1918; HPLC analysis: 87.5:12.5 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 16 min for major *R* enantiomer; t_2 = 17 min for minor *S* enantiomer).



***tert*-butyl 4-(3-(methylthio)propyl)-5-oxoisoxazolidine-2-carboxylate (6j).** Following the general procedure from 2,2-dimethyl-5-(3-(methylthio)propyl)-1,3-dioxane-4,6-dione (75 mg, 0.325 mmol), the title compound was obtained as a oil (57 mg, 83 %); R_f = 0.25 (Petroleum ether/ Ether: 7/3); IR (KBr) ν_{max} 2979, 2918, 1798, 1720, 1370, 1144, 967, 848, 776; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.30 (1H, dd, J = 11.0, 8.6 Hz), 3.66 (1H, dd, J = 11.0, 9.3 Hz), 3.07 – 2.75 (1H, m), 2.52 (2H, t, J = 6.9 Hz), 2.09 (3H, s), 1.95 (1H, ddd, J = 10.0, 6.6, 1.9 Hz), 1.85 – 1.60 (3H, m), 1.51 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.8 (C), 156.1 (C), 84.3 (C), 53.7 (CH_2), 40.1 (CH_2), 33.7 (CH), 28.2 ($3CH_3$), 27.8 (CH_2), 26.4 (CH_2), 15.6 (CH_3); HRMS (ESI+): calcd for $C_{12}H_{22}NO_4S$ $[M+H]^+$: 276.1264; Found: 276.1264; HPLC analysis: 89:11 er (Chiral column IC, hexane/iPrOH = 80:20, flow rate 1 mL/min, 242 nm, t_1 = 15 min for major *R* enantiomer; t_2 = 17 min for minor *S* enantiomer).

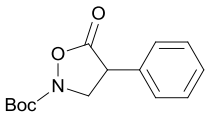


***tert*-butyl 4-isopropyl-5-oxoisoxazolidine-2-carboxylate (6k).** Following the general procedure from 5-isopropyl-2,2-dimethyl-1,3-dioxane-4,6-dione (60 mg, 0.325 mmol), the title compound was obtained as a colorless oil (49 mg, 86 %); R_f = 0.3 (Petroleum ether/ Ether: 8/2); IR (KBr) ν_{max} 2970, 2935, 1795, 1715, 1371, 1149, 969, 768 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.15 (1H, dd, J = 11.1, 9.1 Hz), 3.79 (1H, dd, J = 11.1, 8.6 Hz,), 2.76 (1H, m), 2.14 (1H, dd, J = 12.8, 6.8 Hz), 1.50 (9H, s), 1.07 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.8 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 174.2 (C), 156.1 (C), 84.0 (C), 50.5 (CH_2), 46.3 (CH_2), 28.1 (CH), 28.0 (CH), 20.2 (CH_3), 18.8 (CH_3); HRMS (ESI+): calcd for $C_{11}H_{23}N_2O_4$ $[M+NH4]^+$: 247.1652; Found: 247.1661; GC analysis: 82:12 er (isotherm 115°C, split ratio 50, t_1 = 29 min for minor *S* enantiomer; t_2 = 22 min for major *R* enantiomer).

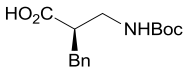


***tert*-butyl 4-methyl-5-oxoisoxazolidine-2-carboxylate (6l).** Following the general procedure from 2,2,5-trimethyl-1,3-dioxane-4,6-dione (51 mg, 0.325 mmol), the title compound was obtained as a colorless oil (42 mg, 83 %); R_f = 0.3 (Petroleum ether/ Ether: 7/3); IR (neat) ν_{max} 2981, 1798, 1714, 1457, 1369, 1136, 1032, 846 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.34 (1H, dd, J = 10.9, 8.6 Hz), 3.57 (1H, dd, J = 10.9, 10.0 Hz), 2.94 (1H, ddq, J = 10.0, 8.6, 7.1 Hz,), 1.51 (9H, s), 1.31 (4H, d, J = 7.1 Hz); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 175.7 (C), 156.1

(C), 84.2 (C), 55.3 (CH_2), 35.4 (CH), 28.12 ($3CH_3$), 13.24 (CH_3); HRMS (ESI+): calcd for $C_9H_{19}N_2O_4$ $[M+NH4]^+$: 219.1339; Found: 219.1344; GC analysis: 94:6 er (isotherm 110°C, split ratio 20, t_1 = 70 min for minor *S* enantiomer; t_2 = 72 min for major *R* enantiomer).



***tert*-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate (6m).** Following the general procedure from 2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione (71 mg, 0.325 mmol), the title compound was obtained as a colorless oil (25 mg, 38 %); R_f = 0.5 (Petroleum ether/ Ether: 4/1); IR (neat) ν_{max} 2972, 2912, 1786, 1705, 1452, 1359, 1142, 993, cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.53 – 7.07 (5H, m), 4.57 (1H, dd, J = 15.0, 12.4 Hz), 4.25 – 3.97 (m, 2H), 1.52 (9H, s); ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 173.5 (C), 156.0 (C), 133.4 (C), 129.4 (2CH), 128.6 (CH), 128.0 (2CH), 84.5 (C), 55.8 (CH_2), 46.4 (CH), 28.13 (CH_3); HRMS (ESI+): calcd for C14H17NO4K $[M+K]^+$: 302.0789; Found: 302.0791

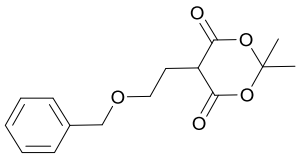


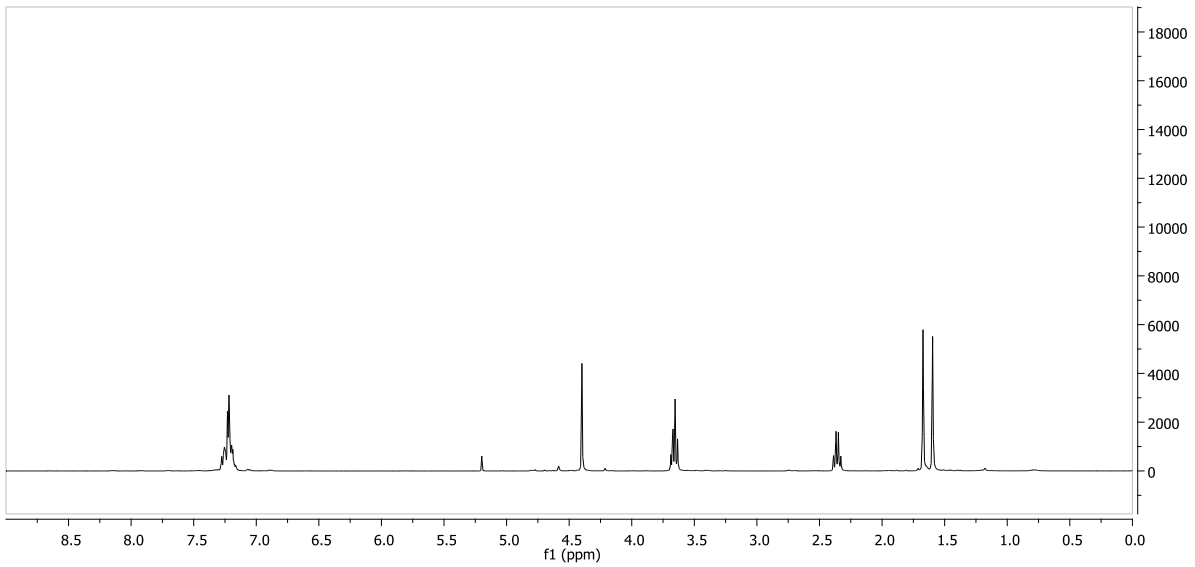
***(R)*-*N*-Boc-β^2-homophenylalanine (12a).**[5] Isoxazolidinone **6a** (25 mg, 0.09 mmol) was dissolved in *t*BuOH (1 mL) at room temperature. Ammonium formate (75 mg, 1.2 mmol) and 10% Pd/C (8 mg) were then added to the solution. The mixture was stirred at 60 °C for 2 h (the disappearance of starting material was monitored by TLC). The resulting mixture was cooled to room temperature, filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography using CH_2Cl_2/MeOH (95:5, R_f = 0.5) as eluent to give the desired compound as a white solid (19 mg, 76 %). The observed optical rotation $[\alpha]_D^{27}$ +11.8 (*c* 0.5, $CHCl_3$); Litt.[6] $[\alpha]_D^{27}$ +12.0 (*c* 0.5, $CHCl_3$). The analytical data match the previously reported NMR spectra.[6]

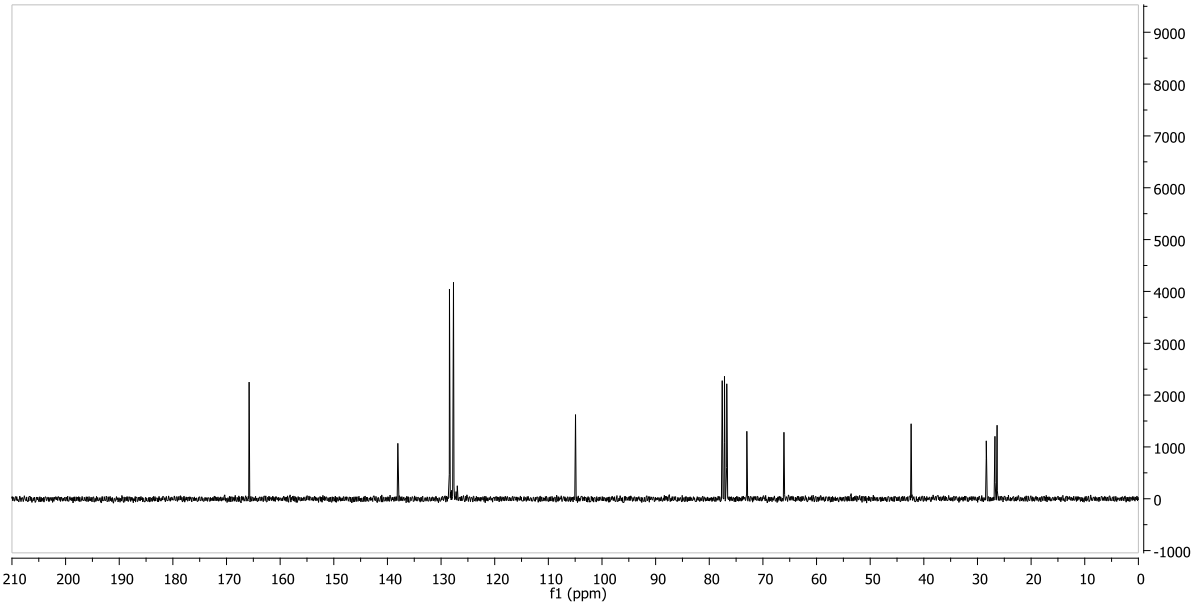
[5] H.-S. Lee, J.-S. Park, B. M. Kim and S. H. Gellman, *J. Org. Chem.*, 2003, **68**, 1575.
[6] A. Tessier, N. Lahmar, J. Pytkowicz and T. Brigaud, *J. Org. Chem.*, 2008, **73**, 3970.

IV NMR spectra

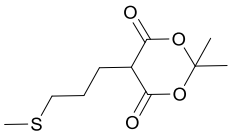
IV-1 5-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (10i)

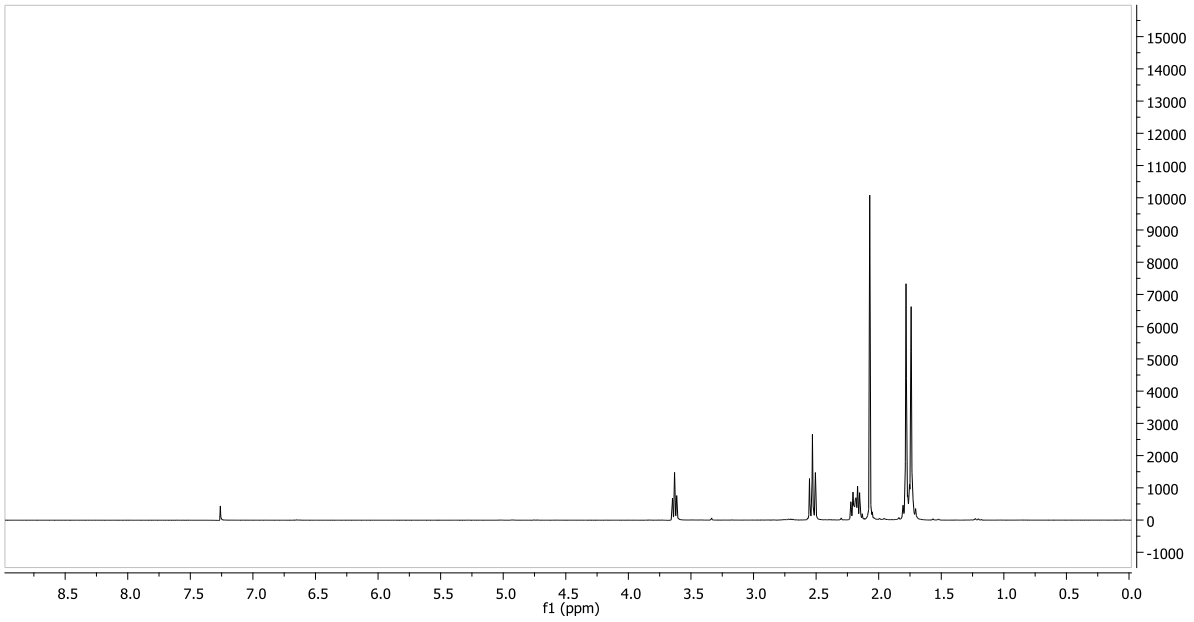


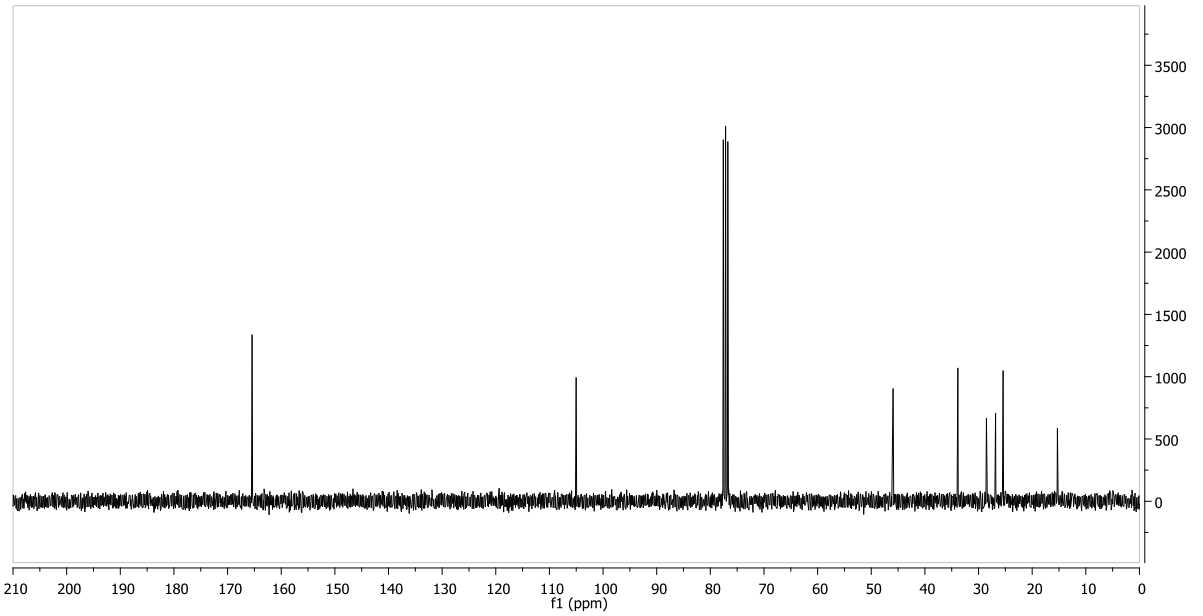




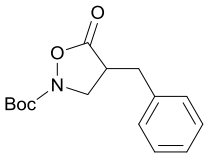
IV-2 2,2-dimethyl-5-(3-(methylthio)propyl)-1,3-dioxane-4,6-dione (10j)

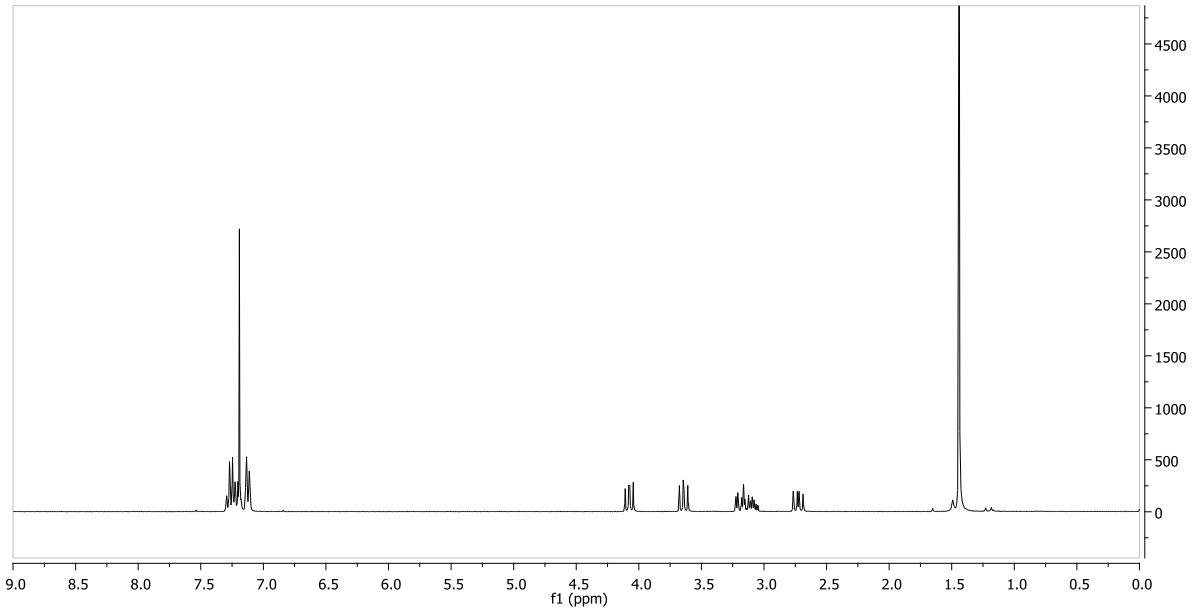


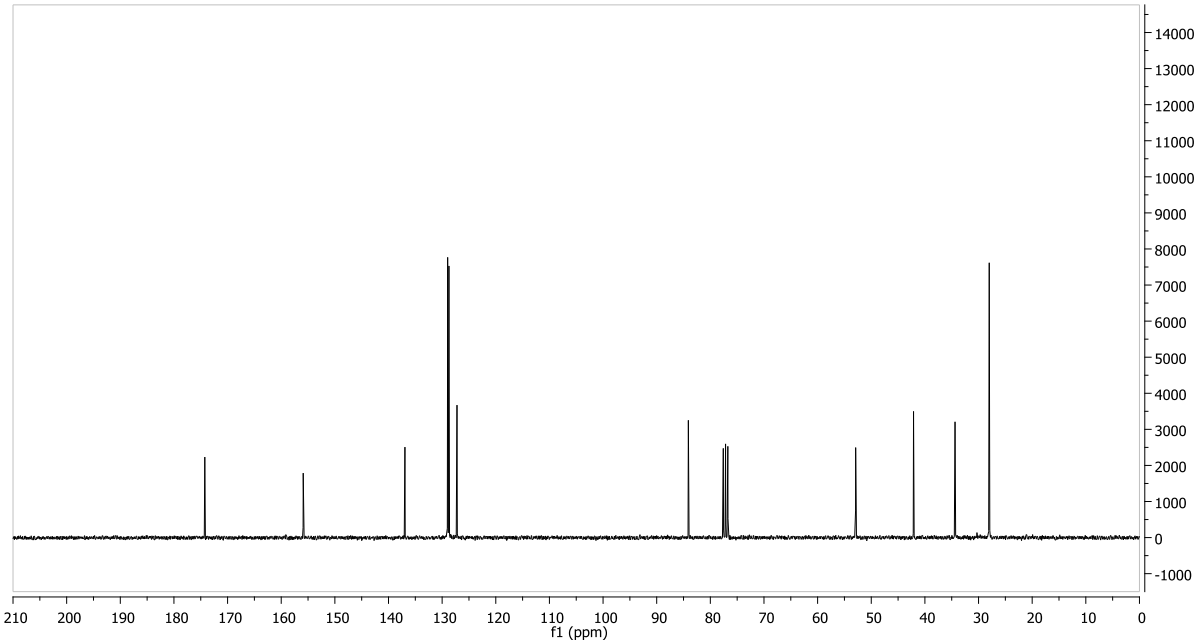




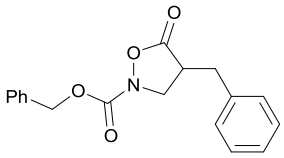
IV-3 Tert-butyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate (6a)

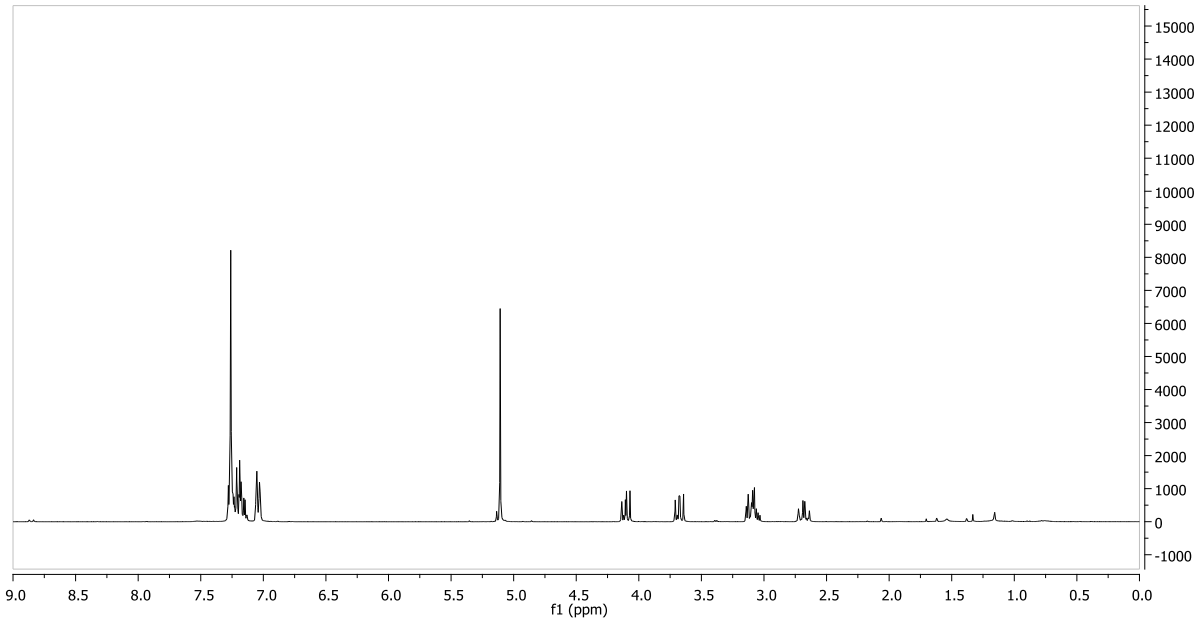


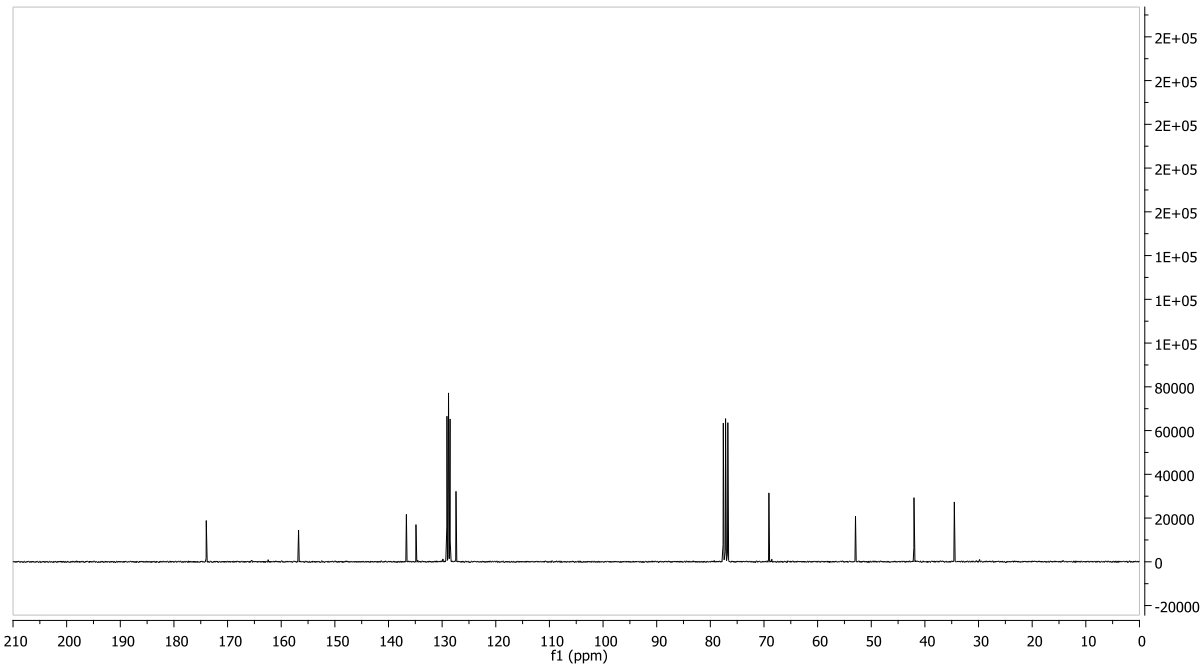




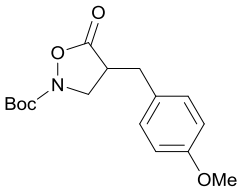
IV-4 Benzyl 4-benzyl-5-oxoisoxazolidine-2-carboxylate (6b)

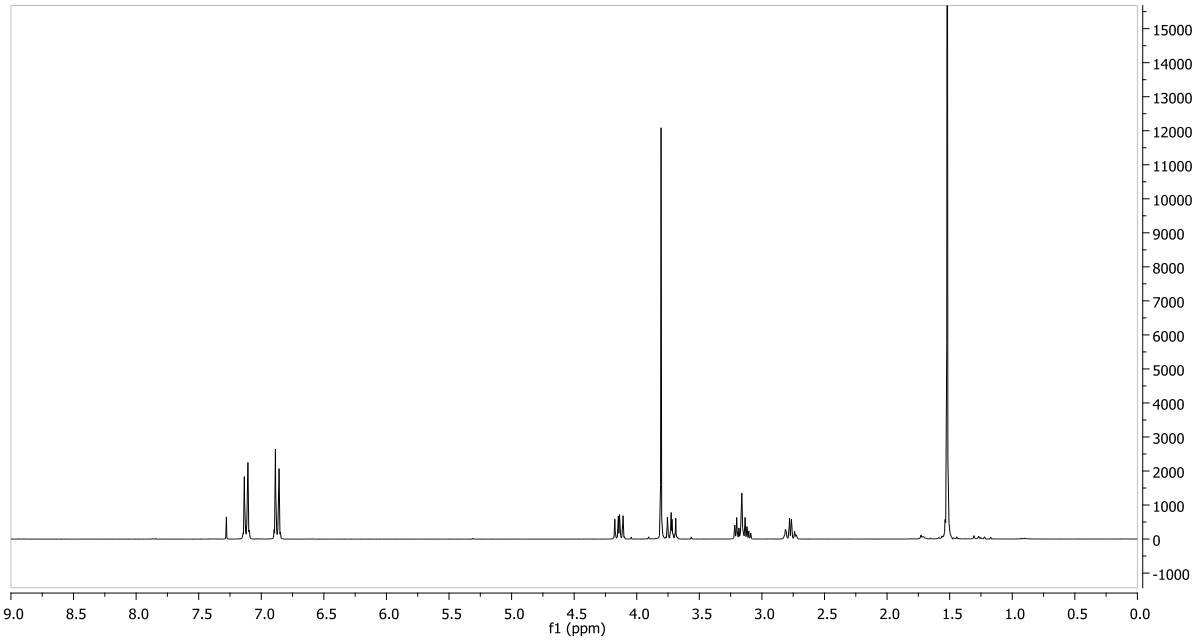


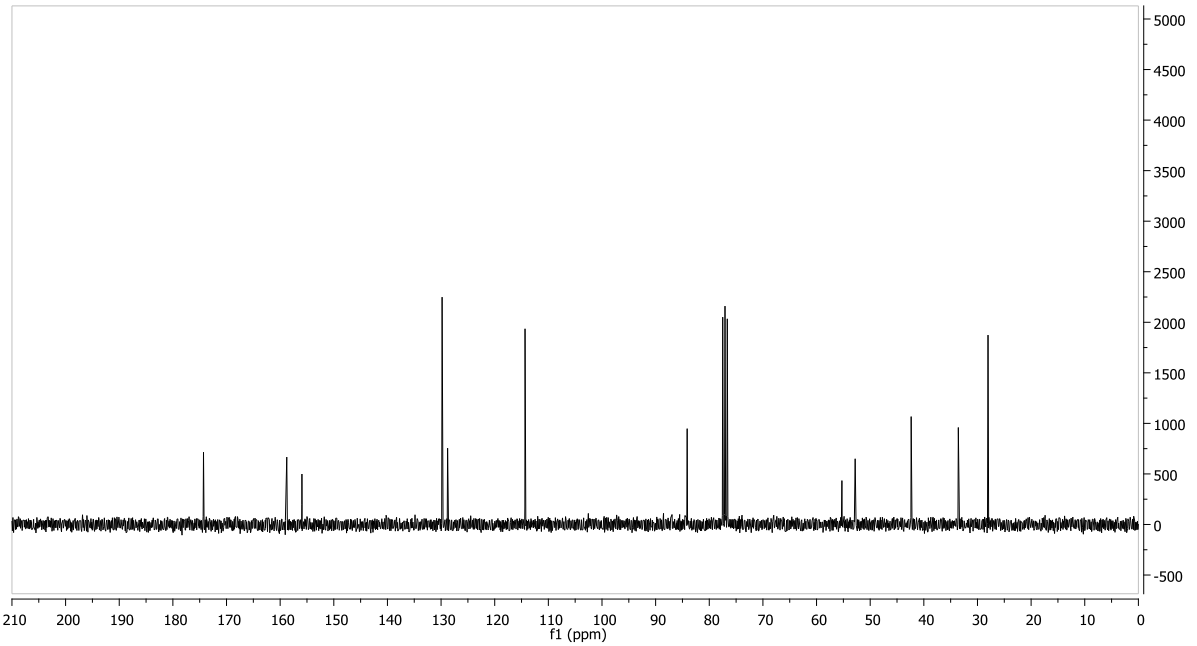




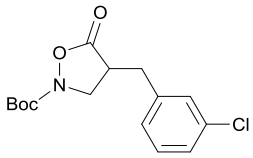
IV-5 tert-butyl 4-(4-methoxybenzyl)-5-oxoisoxazolidine-2-carboxylate (6c)

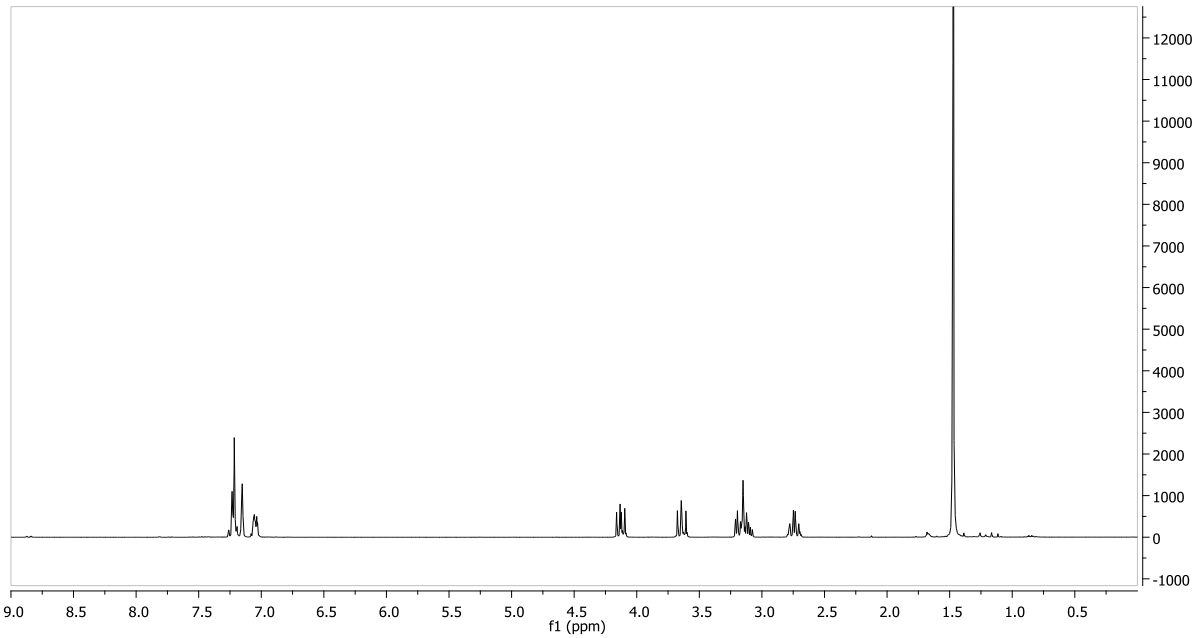


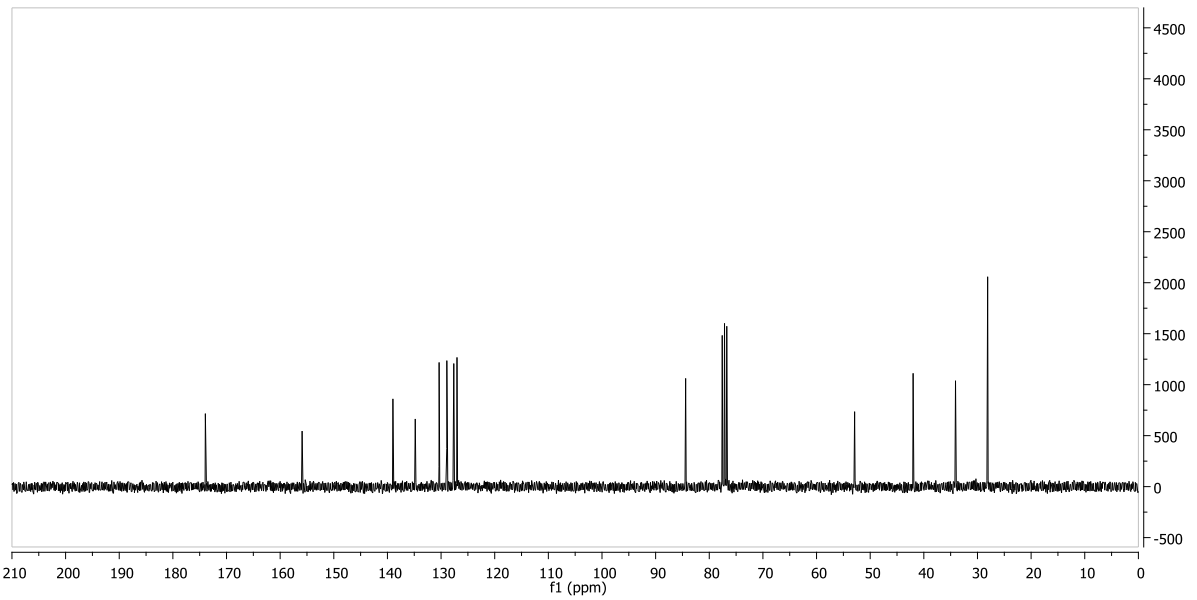




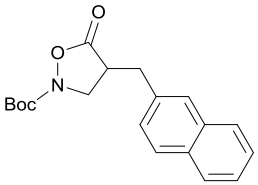
IV-6 tert-butyl 4-(3-chlorobenzyl)-5-oxoisoxazolidine-2-carboxylate (6d)

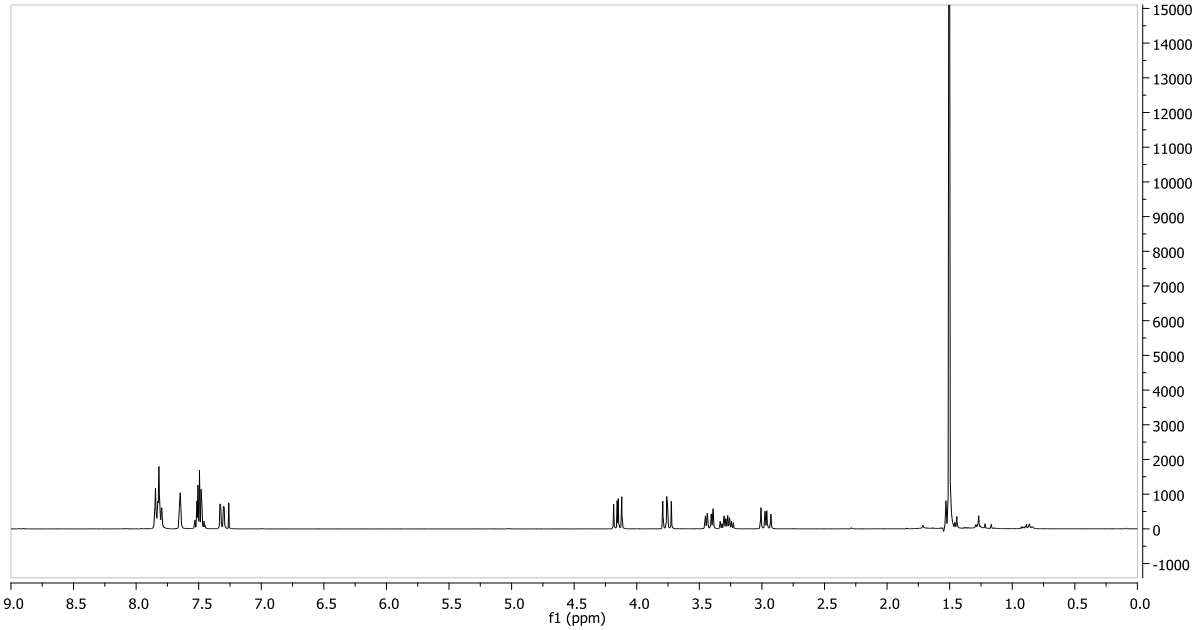


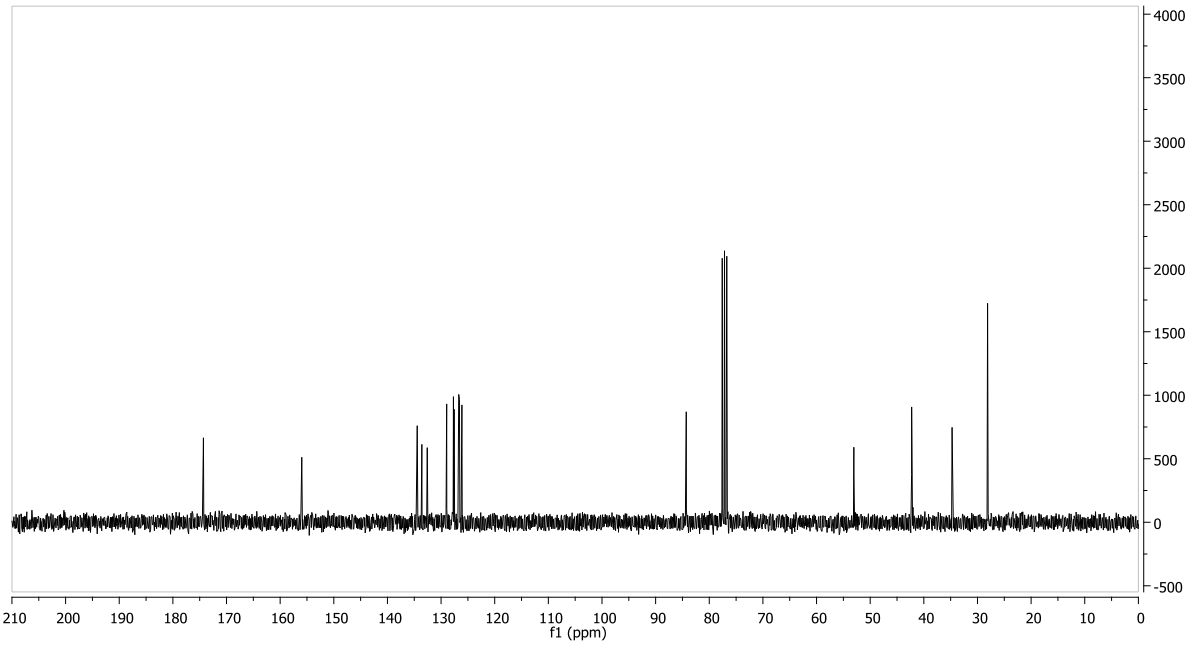




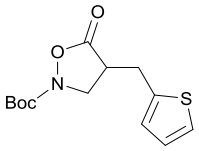
IV-7 tert-butyl 4-(naphthalen-2-ylmethyl)-5-oxoisoxazolidine-2-carboxylate (6e)

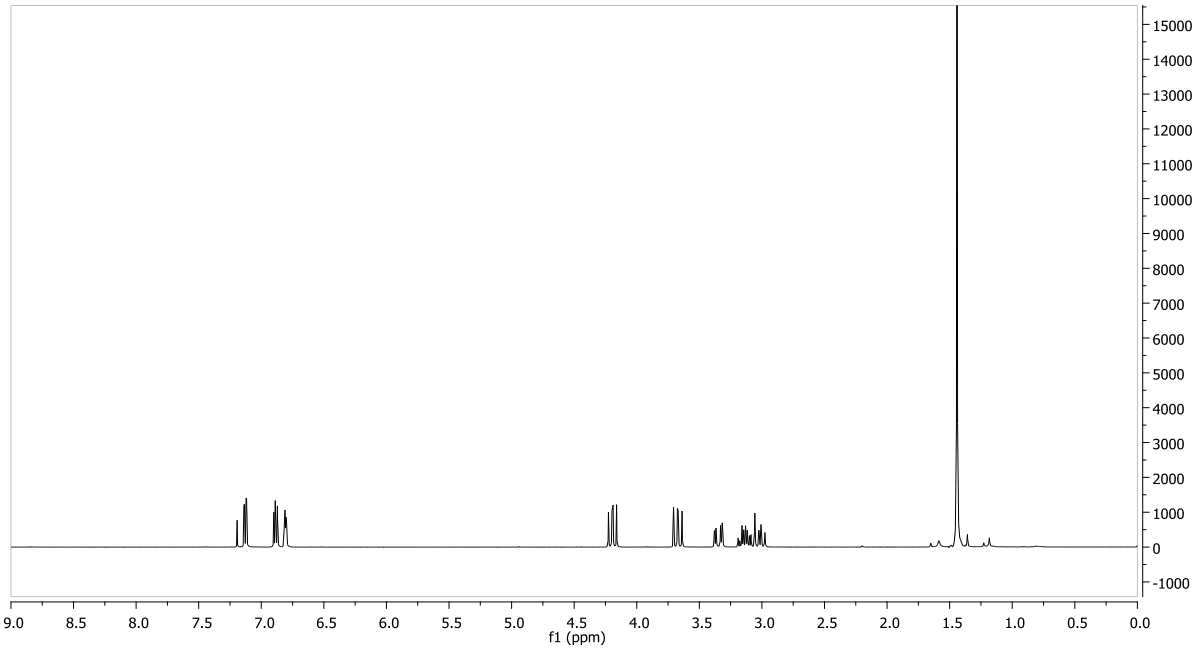


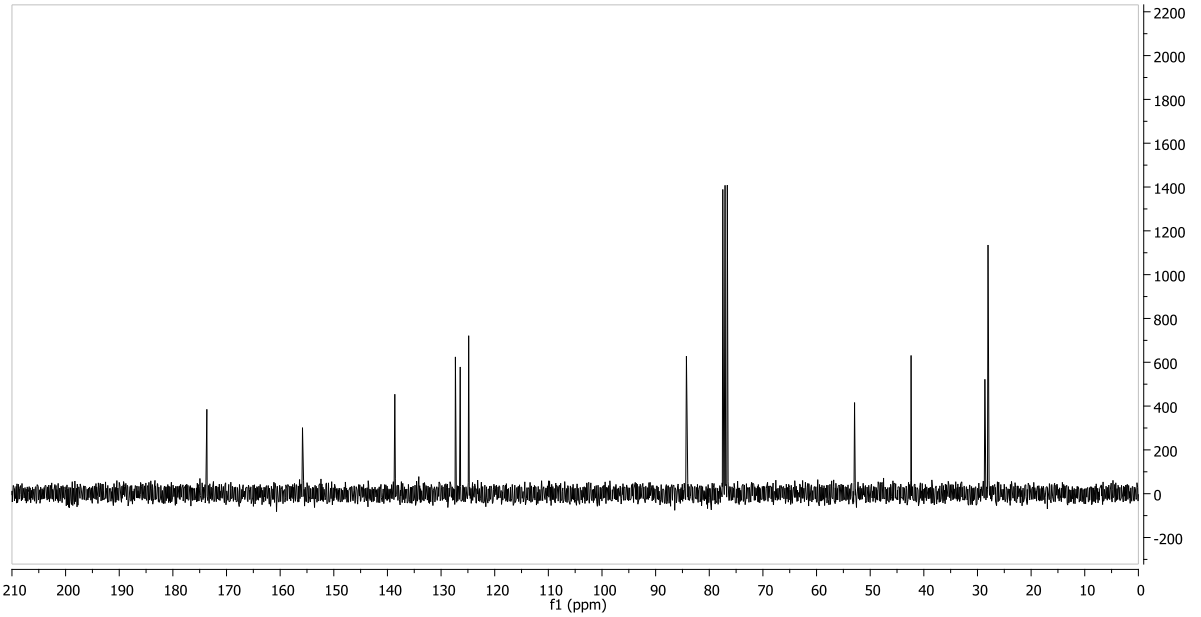




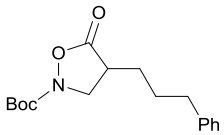
IV-8 tert-butyl 5-oxo-4-(thiophen-2-ylmethyl)isoxazolidine-2-carboxylate (6f)

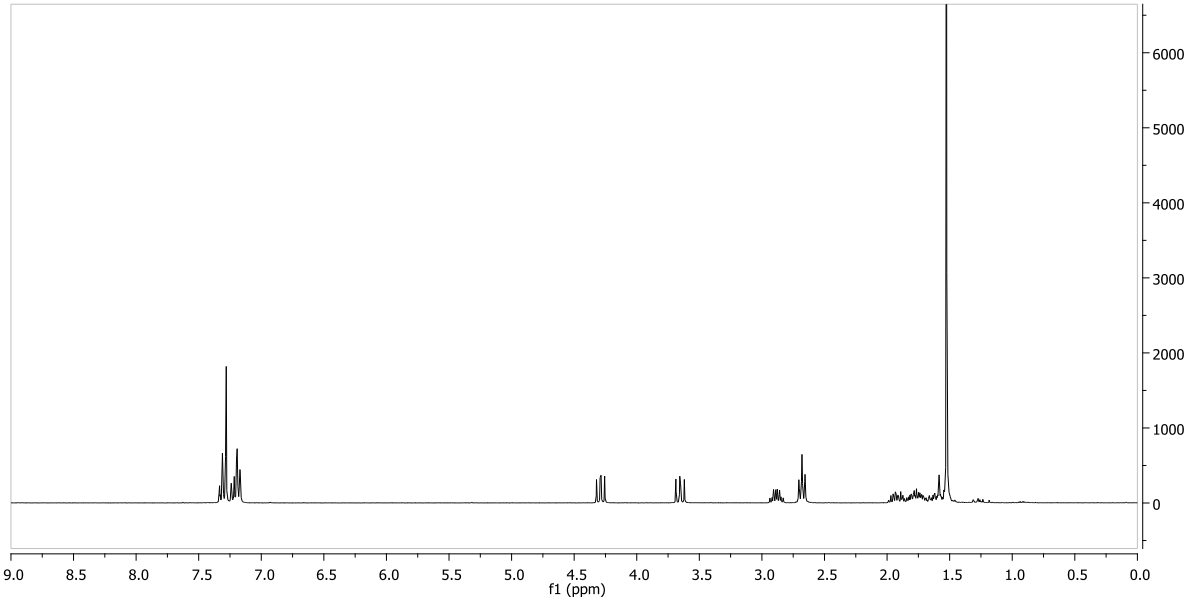


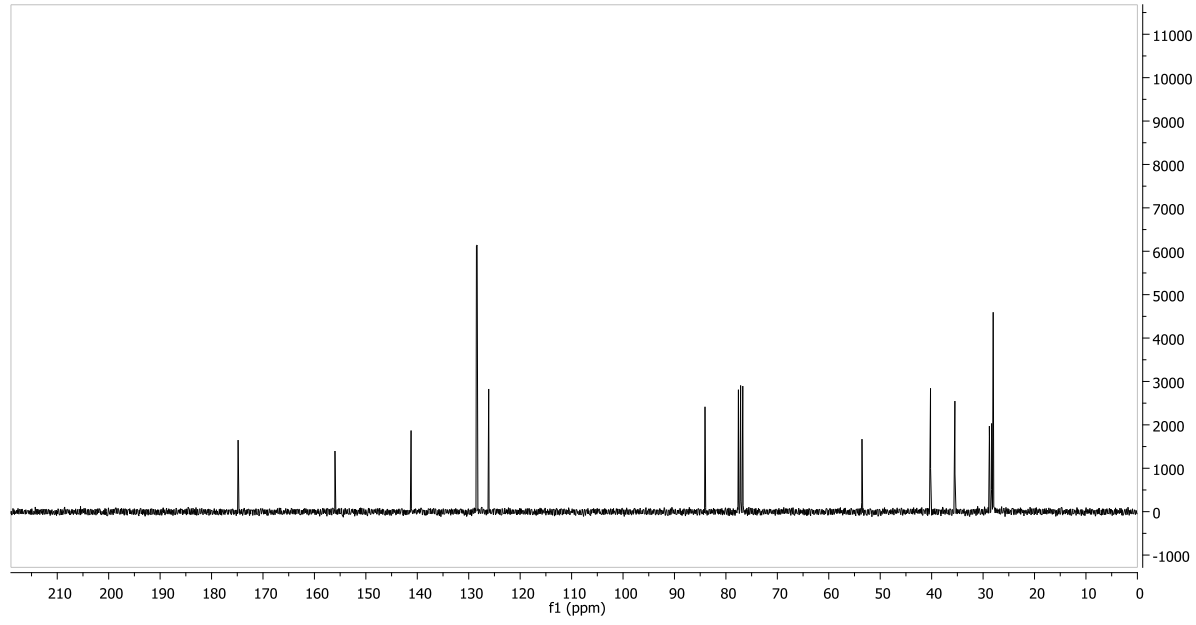




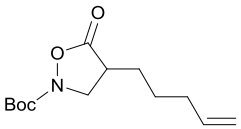
IV-9 tert-butyl 5-oxo-4-(3-phenylpropyl)isoxazolidine-2-carboxylate (6g)

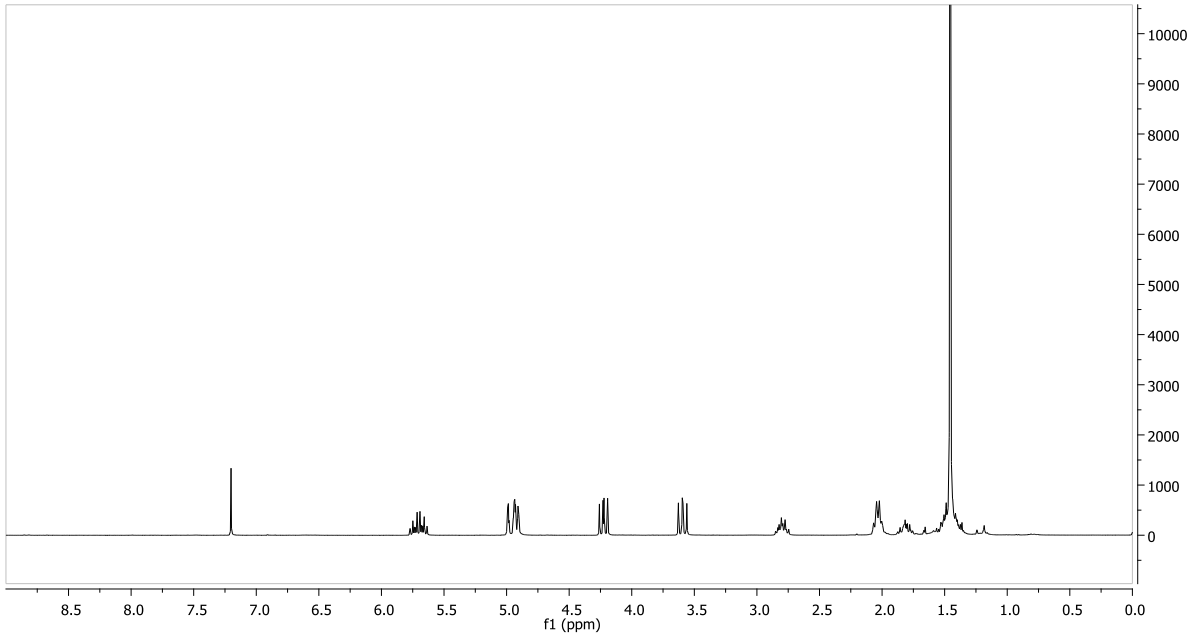


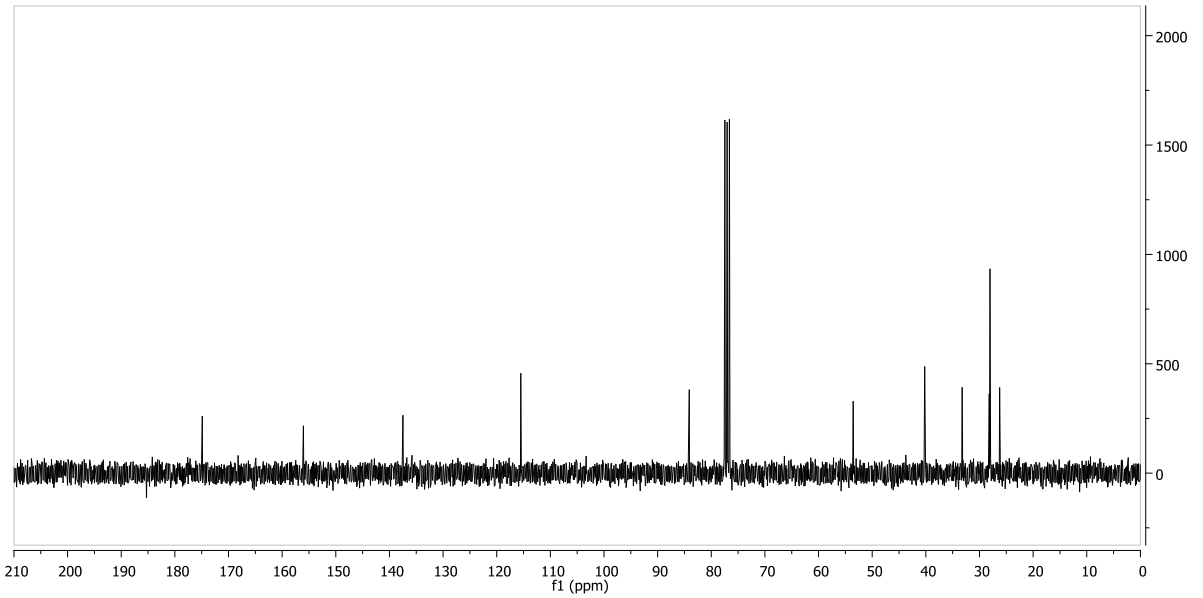




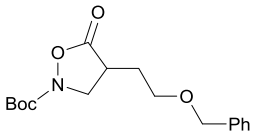
IV-10 tert-butyl 5-oxo-4-(pent-4-en-1-yl)isoxazolidine-2-carboxylate (6h)

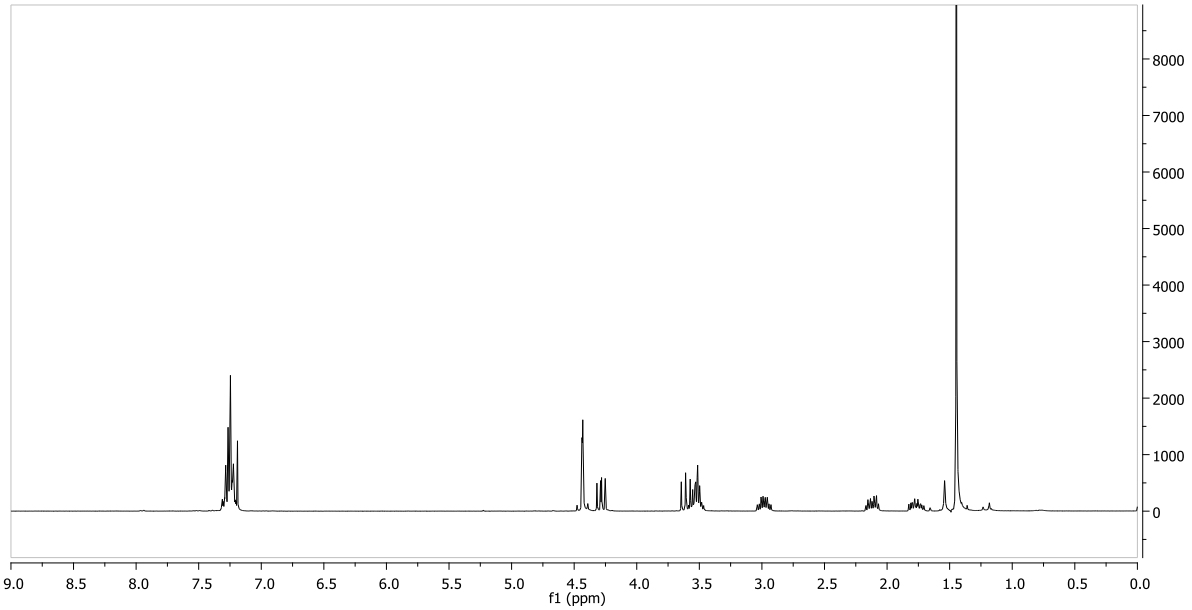


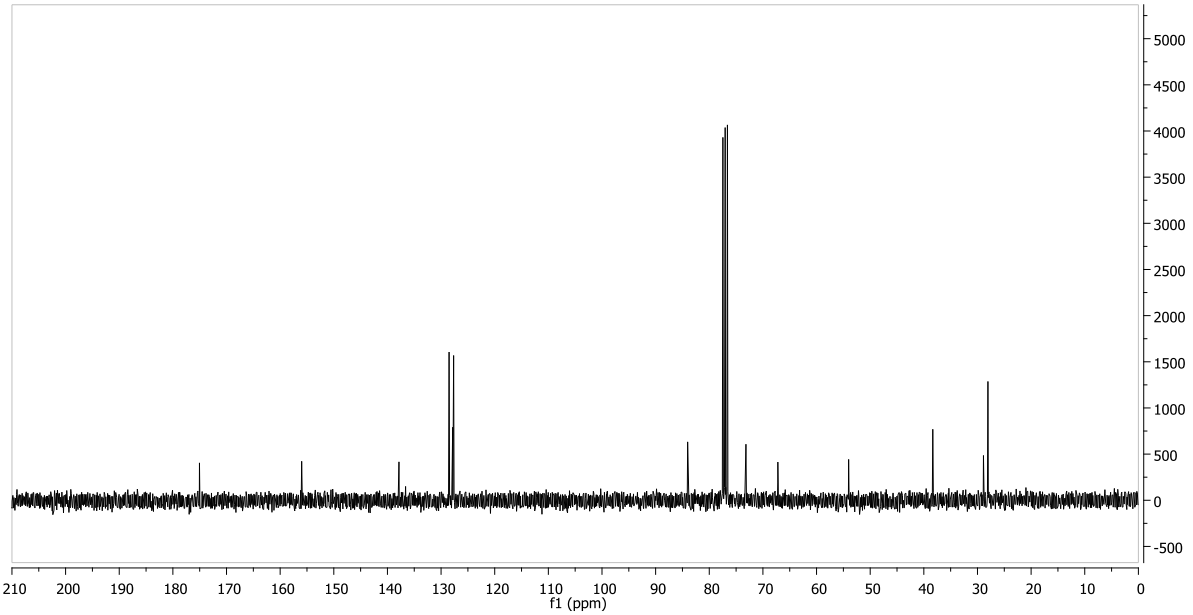




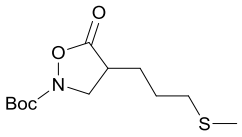
IV-11 tert-butyl 4-(2-(benzyloxy)ethyl)-5-oxoisoxazolidine-2-carboxylate (6i)

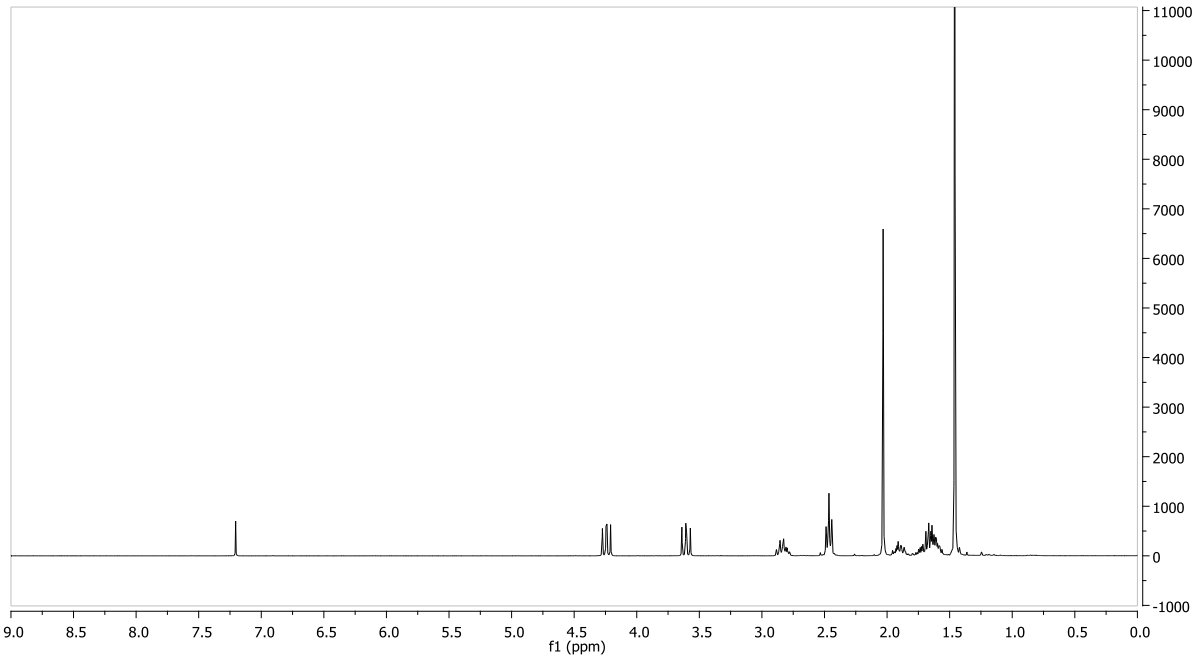


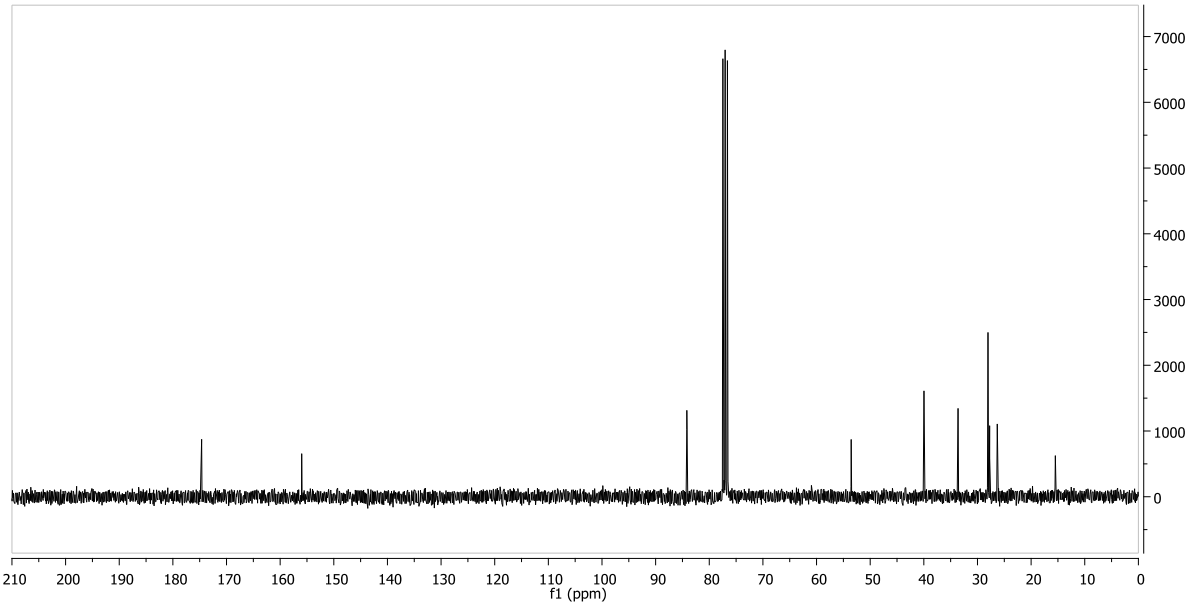




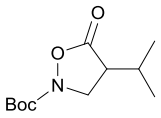
IV-12 tert-butyl 4-(3-(methylthio)propyl)-5-oxoisoxazolidine-2-carboxylate (6j)

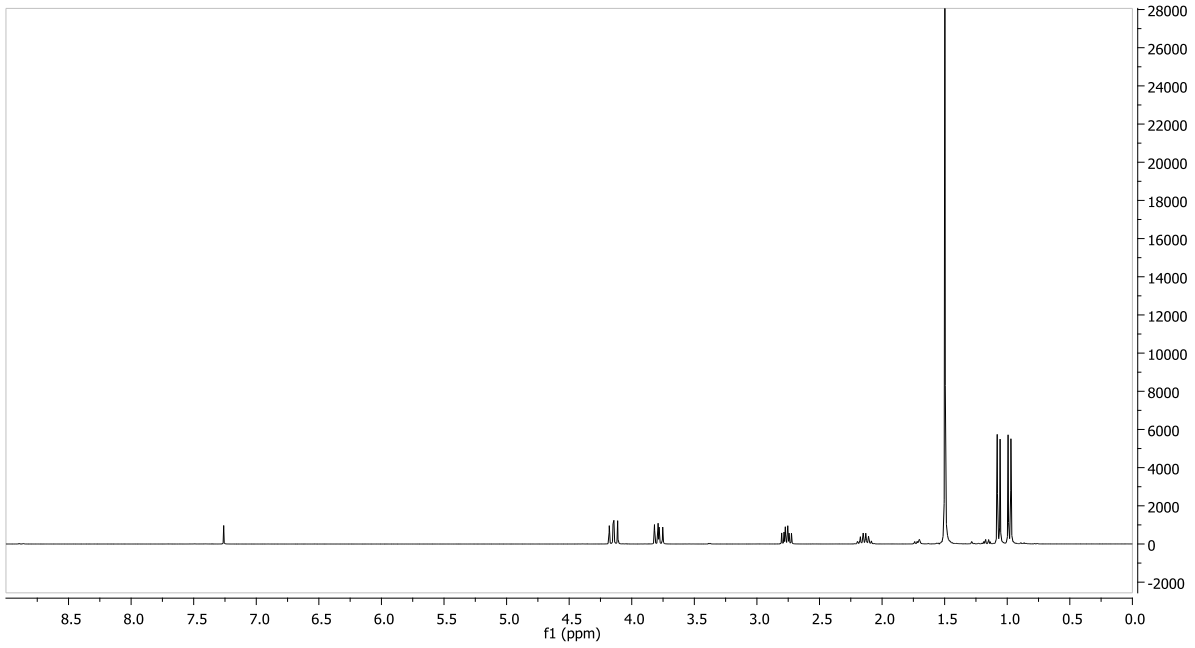


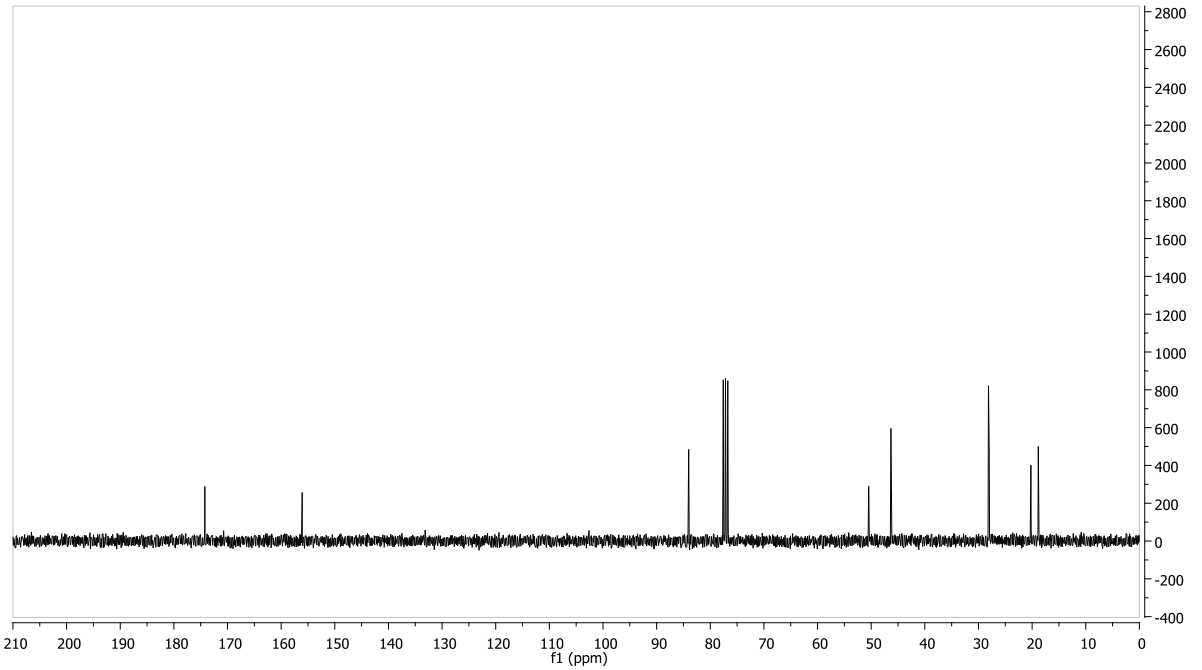




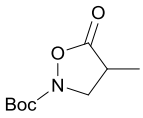
IV-13 tert-butyl 4-isopropyl-5-oxoisoxazolidine-2-carboxylate (6k)

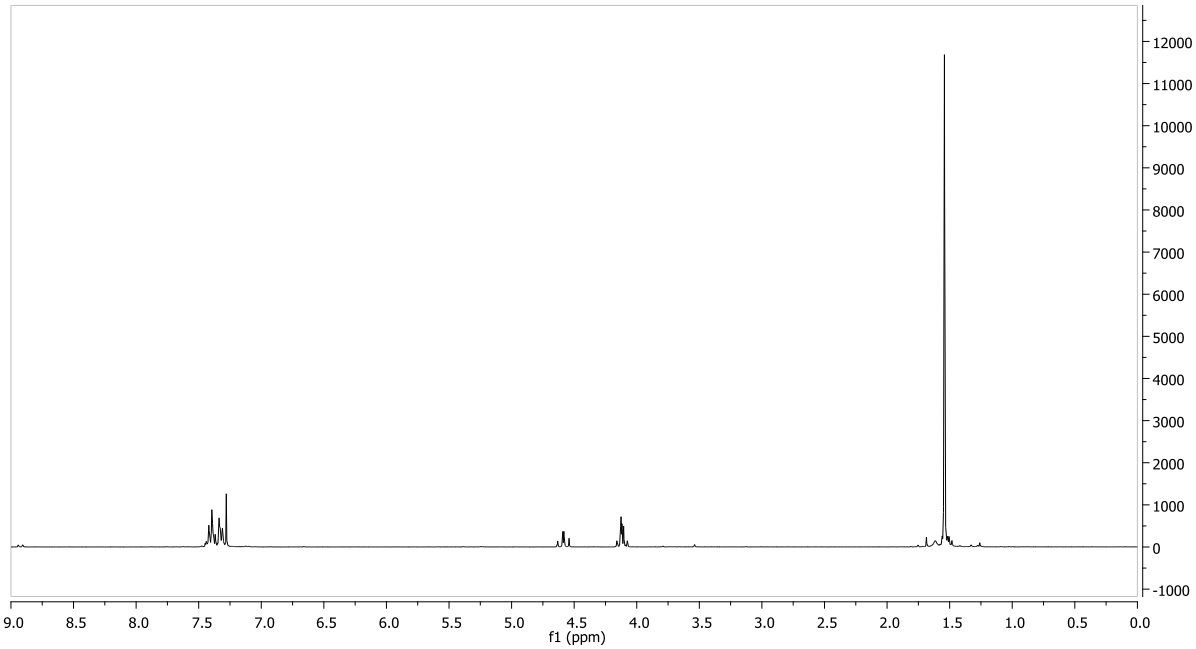


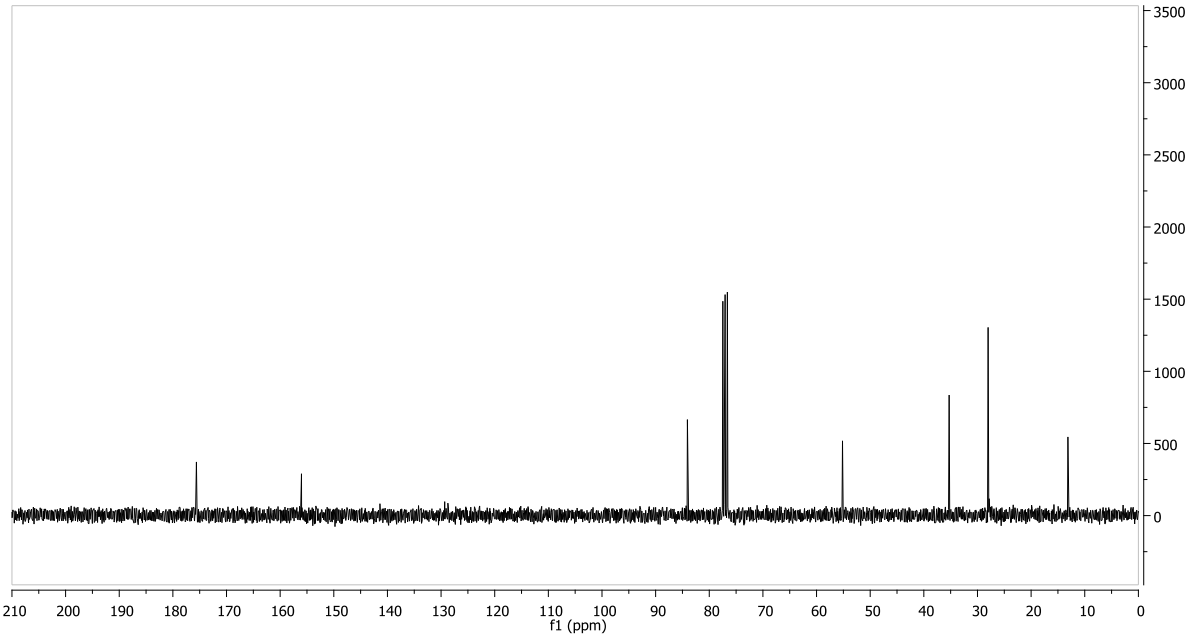




IV-14 tert-butyl 4-methyl-5-oxoisoxazolidine-2-carboxylate (6l)







IV-15 tert-butyl 5-oxo-4-phenylisoxazolidine-2-carboxylate (6m)