

Continuous preparation and use of dibromoformaldoxime as a reactive intermediate for the synthesis of 3-bromoisoxazolines

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Contents

1. General information.....	2
2. Synthetic procedures for DFBO and 3-bromoisoxazolines	3
<i>Step 1: synthesis of hydroximinoacetic acid 6</i>	3
<i>Step 2: synthesis of DBFO 2</i>	3
<i>Step 3: synthesis of 3-bromoisoxazolines</i>	4
Large scale, telescoped synthesis of <i>N</i> -(3-Bromo-4,5-dihydroisoxazol-5-yl)benzamide (7a) ...	5
3. Mixing elements and liquid-liquid separator	6
4. Safety data	8
Hydroxyiminoacetic acid 6	8
Dibromoformaldoxime 2	11
5. Characterization of compounds 7a-n	17
6. Copies of ¹ H- and ¹³ C-NMR spectra.....	22
References	35

1. General information

All batch reactions were performed using oven-dried glassware (200 °C) under an atmosphere of argon unless otherwise stated. All flow reactions were performed using a Vapourtec R2+R4 system,¹ a Vapourtec E-Series system,² HiTech Zang SyrDos syringe pumps³ and Knauer pumps K120.⁴

Unless stated otherwise, reagents were obtained from commercial sources and used without further purification.

Flash column chromatography was performed using high-purity grade silica gel (Merck grade 9385) with a pore size 60 Å and 230–400 mesh particle size under air pressure. Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated glass backed plates and visualized by ultraviolet radiation (254 nm) and/or potassium permanganate solution as appropriate.

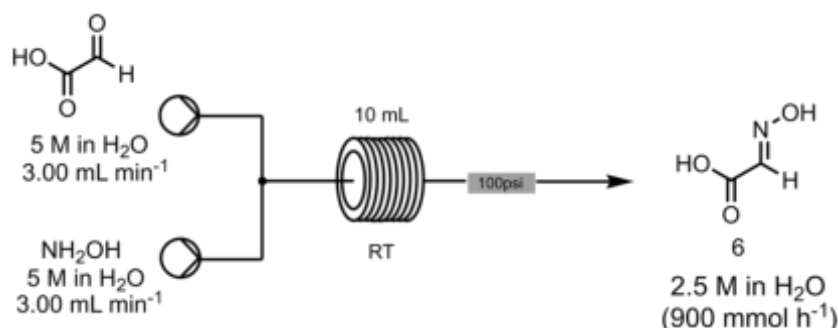
¹H NMR spectra were recorded on Bruker Avance DPX-600 (600 MHz), with the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm). ¹H resonances are reported to the nearest 0.01 ppm. ¹³C-NMR spectra were recorded on the same spectrometer with proton decoupling, with the solvent peak as the internal reference (CDCl₃ = 77.00 ppm). All ¹³C resonances are reported to the nearest 0.01 ppm. The multiplicity of ¹H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quadruplet, sext = sextet, m = multiplet, br = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, measures of the same coupling constant are averaged. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

High resolution mass spectrometry (HRMS) was performed using positive electrospray ionisation (ESI+), on either a Waters Micromass LCT Premier spectrometer or performed by the Mass Spectrometry Service for the Chemistry Department at the University of Cambridge. All *m/z* values are reported to 4 decimal places and are within ± 5 ppm of theoretical values.

Infrared spectra were recorded on a Perkin-Elmer Spectrum RX One FT-IR ATR (Attenuated Total Reflectance) spectrometer. The samples were prepared as thin films deposited on the ATR, unless otherwise specified. Only structurally important absorptions are quoted. Absorption maxima (*ν*_{max}) are reported in wavenumbers (cm⁻¹).

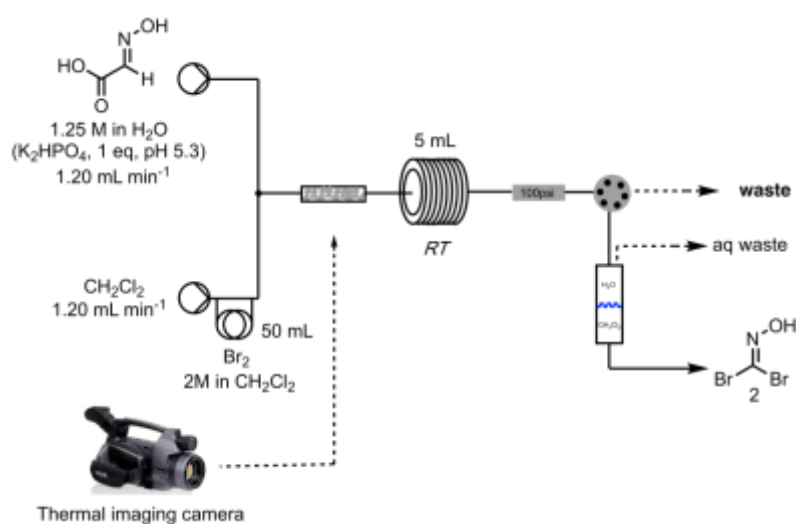
2. Synthetic procedures for DFBO and 3-bromoisoxazolines

Step 1: synthesis of hydroximinoacetic acid **6**



An aqueous stream of glyoxylic acid (5 M in H₂O, 3 mL min⁻¹) was combined at a T-piece with a stream of hydroxylamine aqueous solution (5 M in H₂O, 3 mL min⁻¹). The resulting reaction stream was then directed towards a 10 mL polytetrafluoroethylene (PTFE) coil reactor (o.d. 1/16", $\tau = 130$ s), operating at room temperature, to ensure full conversion to hydroximinoacetic acid **6**. The reaction solution was directed through a 75 psi back-pressure regulator (BPR) and the reactor output was collected in a reservoir.

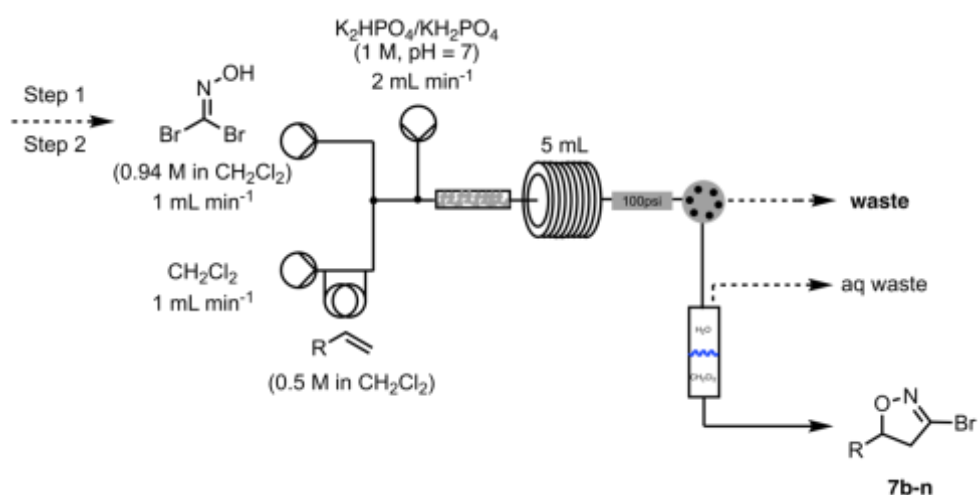
Step 2: synthesis of DBFO **2**



A solution of bromine (2.0 M, in CH₂Cl₂) was loaded in a 50 mL perfluoroalkoxy alkane (PFA) pre-loading coil (o.d. 1/8") before being mixed at a T-piece with a solution of **6** (1.25 M, in H₂O). The resulting mixture was pumped (flow rate 1.20 mL min⁻¹ each channel) through the

packed bed column mixing element and then directed into 5 mL PFA coil reactor (o.d. 1/16", $\tau = 126$ s). The output stream of DBFO **2** was directed through a 100 psi BPR and then towards a multi-port valve. After reaching steady-state, the valve was switched to collection and the reaction mixture directed to a liquid-liquid separator, equipped with a turbulence settler. An IR thermal imaging camera⁵ was used to monitor the reaction exotherm.

Step 3: synthesis of 3-bromoisoxazolines



The solution of DBFO **2** was pumped (1 mL min⁻¹) to meet a stream of the appropriate alkene (0.5 M, in CH₂Cl₂, flow rate of 1 mL min⁻¹), at a T-piece, combined with a KH₂PO₄/K₂HPO₄ buffer (1.0 M, in H₂O, pH = 6.8) delivered at a flow rate of 2 mL min⁻¹, allowed to mix through the packed bed column mixing element, and then reacted in a 5 mL PFA coil reactor (o.d. 1/16"). The reactor output was directed towards a multi-port valve. After reaching steady-state, the valve was switched to collection and the reaction mixture directed to a liquid-liquid separator, where the organic layer was recovered and the solvent evaporated *in vacuo*.

The crude mixture was purified by flash chromatography (eluent: Hexane/EtOAc 100:0 to 0:100) to afford the desired products **7b-n**.

Large scale, telescoped synthesis of *N*-(3-Bromo-4,5-dihydroisoxazol-5-yl)benzamide (7a)

An aqueous stream of glyoxylic acid (5 M in H₂O, 3 mL min⁻¹) was combined at a T-piece with a stream of hydroxylamine aqueous solution (5 M in H₂O, 3 mL min⁻¹). The resulting reaction stream was then directed towards a 10mL PTFE coil reactor (o.d. 1/16", $\tau = 130$ s), operating at room temperature, to ensure full conversion to hydroxyiminoacetic acid **6**. The reaction solution was directed through a 75 psi back-pressure regulator (BPR) and the reactor output was combined with a solution of potassium monohydrogen phosphate (2.5 M, 6 mL min⁻¹) and then passed through a mixing element prior to going being directed though a 100 psi bpr and hydroxyiminoacetic acid **6** is collected in a reservoir. The freshly made solution of **6** was then combined with a solution of bromine (2.0 M, in CH₂Cl₂) at a T-piece (flow rate 11 mL min⁻¹ each channel) into a 20 mL Vapourtec "static mixer" coil reactor⁶ (o.d. 1/8"). An IR thermal imaging camera⁵ was used to monitor the reaction exotherm (tested over a period of 4 h, Figure S1).

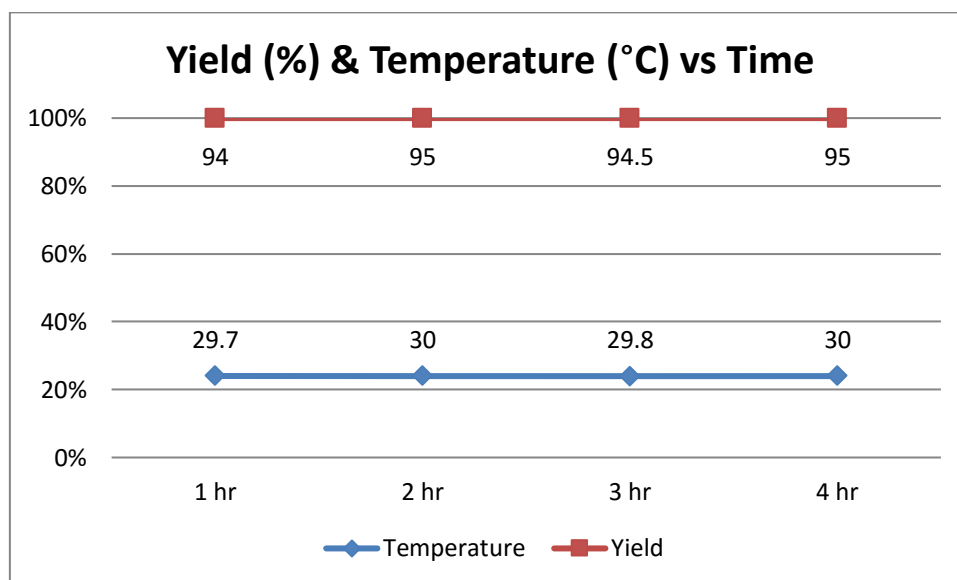


Figure S1. Yield of DBFO **2** and temperature detection at the mixing element during a reaction period of 4 h.

The output stream of DBFO **2** was directed through a 100 psi BPR and then directed towards a multiport valve. After reaching steady-state, the valve was switched and the reaction

mixture directed to a liquid-liquid separator, equipped with a turbulence settler (see Figure S5). The solution of DBFO **2** was then pumped (10 mL min^{-1}) to meet a stream of N-vinylbenzamide **8a** (0.75 M , in CH_2Cl_2 , flow rate of 10 mL min^{-1}), at a T-piece, combined with a $\text{KH}_2\text{PO}_4/\text{K}_2\text{HPO}_4$ buffer (1.0 M , in H_2O , $\text{pH} = 6.8$) delivered at a flow rate of 20 mL min^{-1} , and then reacted through a 20 mL Vapourtec “static mixer” coil reactor⁶ (o.d. $1/8''$). The resulting biphasic mixture was collected, the organic layer recovered and the solvent evaporated *in vacuo* to give **7a** (97% yield) (Figure S2).



Figure S2. Reaction set up for the telescoped synthesis of **7a**.

3. Mixing elements and liquid-liquid separator

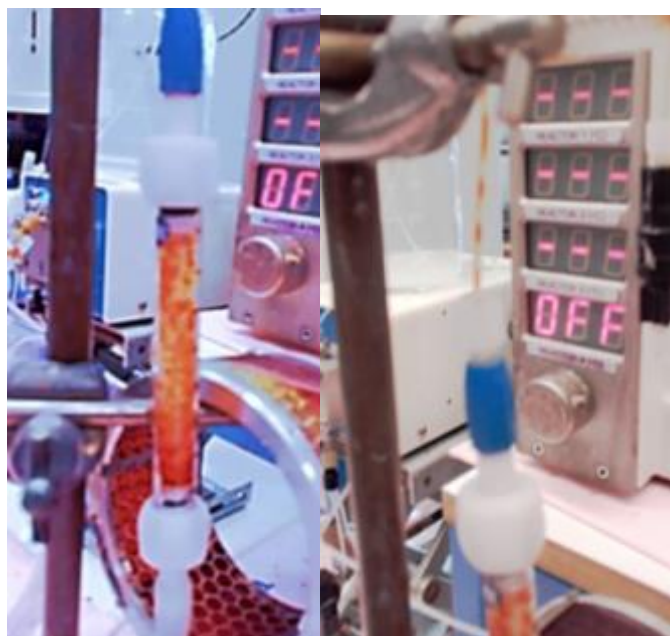


Figure S3. Packed bed column mixing element, Step 2.

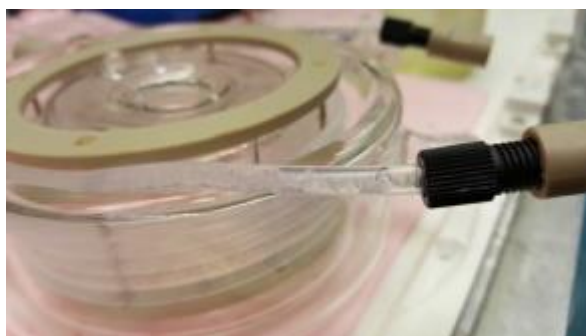


Figure S4. Static mixer coil (20 mL).

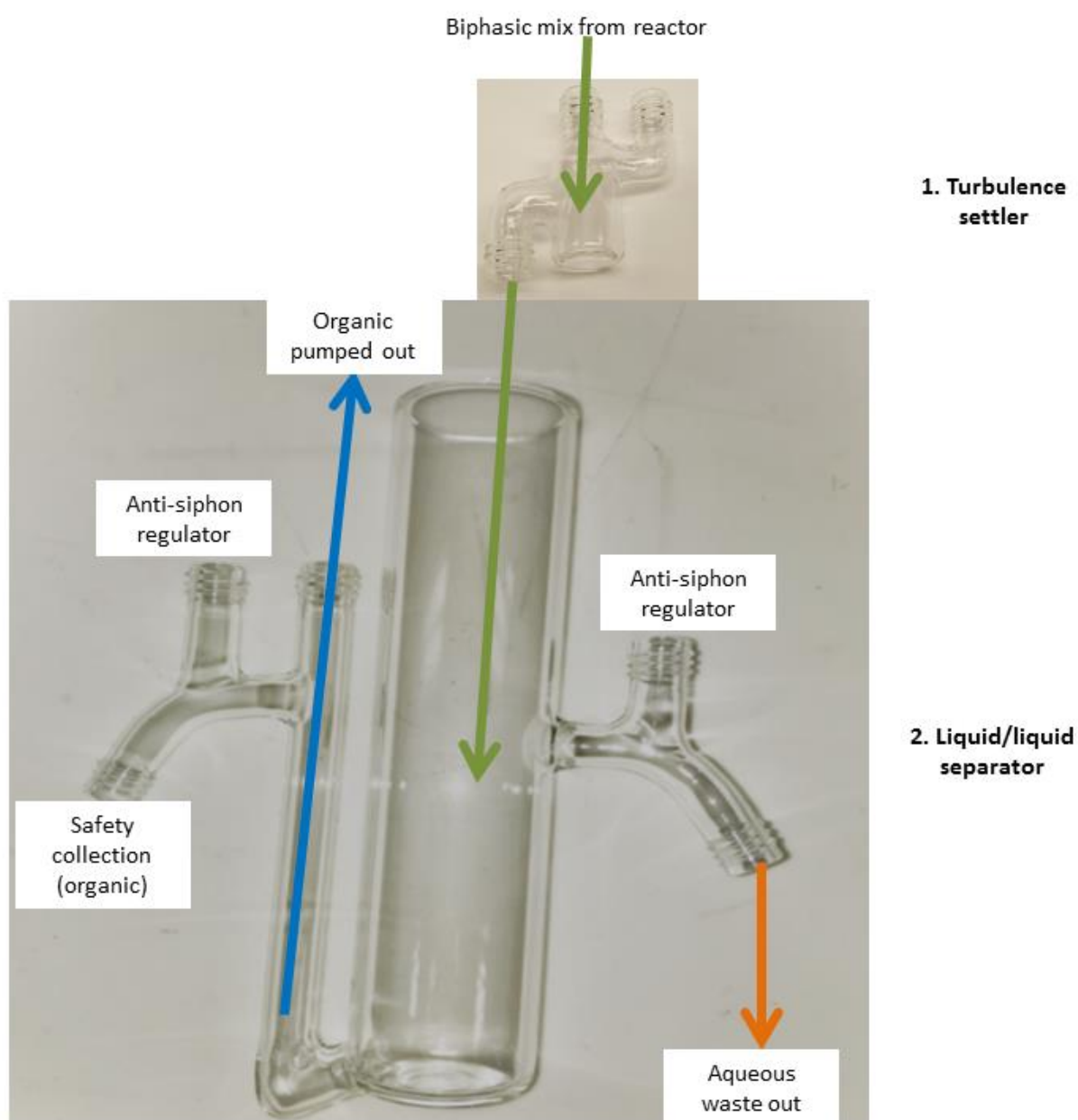


Figure S5. Turbulence settler and liquid-liquid separator.

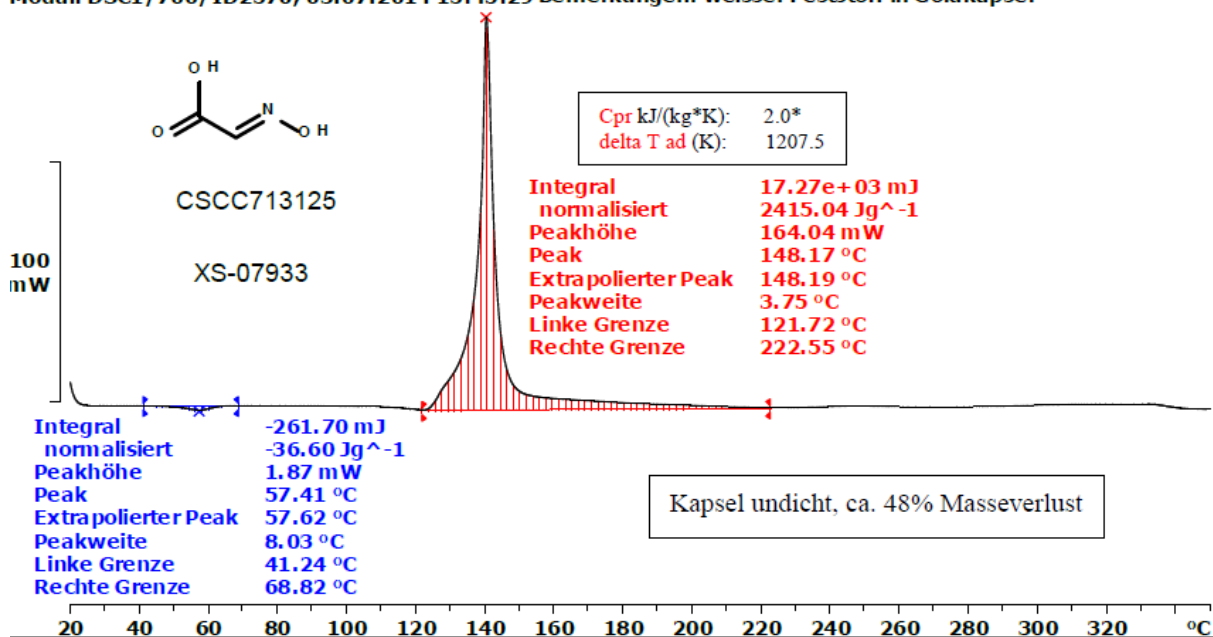
4. Safety data

Hydroxyiminoacetic acid 6

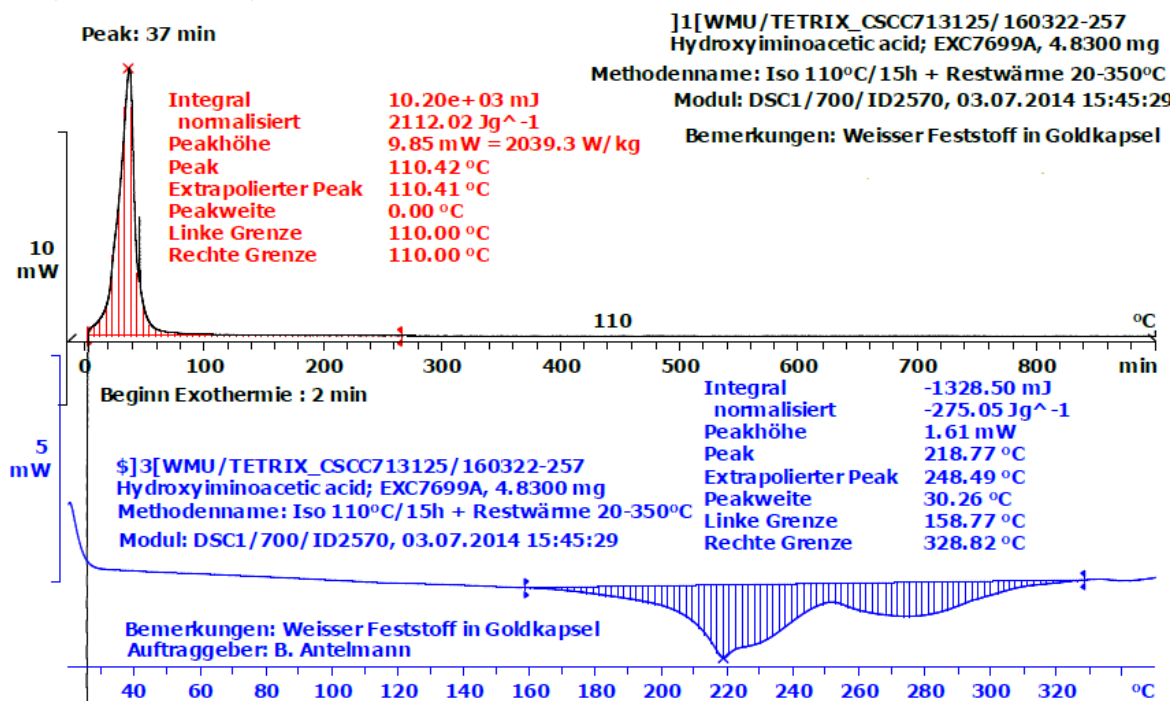
Differential Scanning Calorimetry (DSC)

Methodenname: 20-350°C 4°Min.

Modul: DSC1/700/ID2570, 03.07.2014 15:45:29 Bemerkungen: weisser Feststoff in Goldkapsel



DSC, isotherm 110°C, 15h



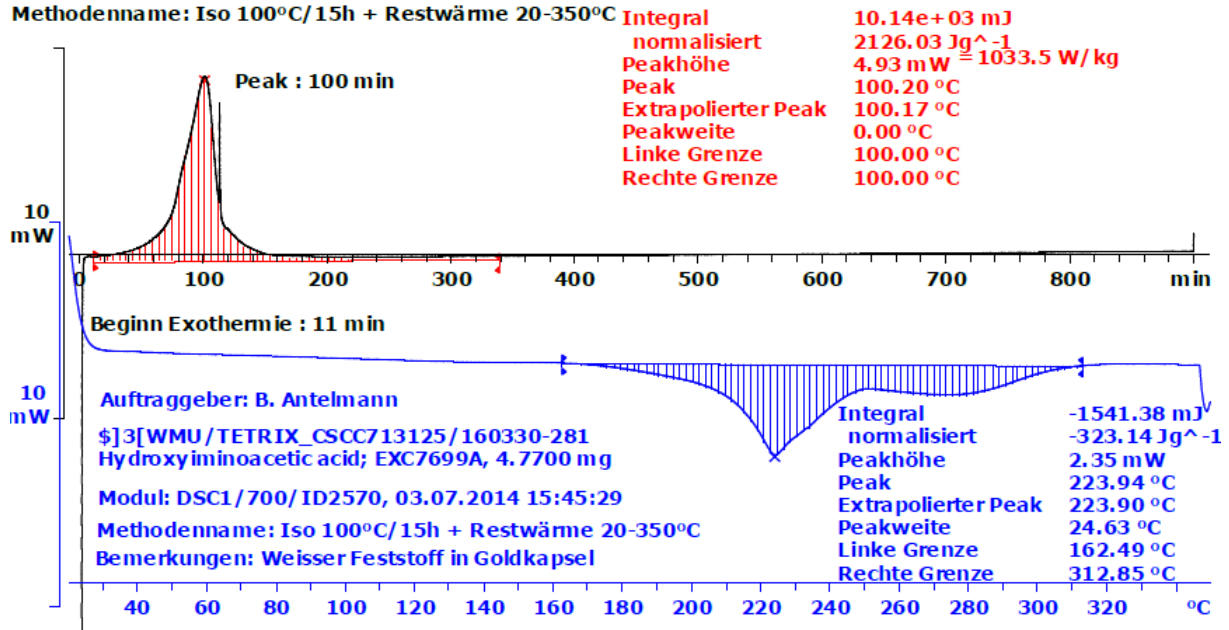
DSC, isotherm 100°C, 15h

Hydroxyiminoacetic acid; EXC7699A, 4.7700 mg

Modul: DSC1/700/ID2570, 03.07.2014 15:45:29

Methodenname: Iso 100°C/15h + Restwärme 20-350°C

Bemerkungen: Weisser Feststoff in Goldkapsel



DSC, isotherm 90°C, 15h

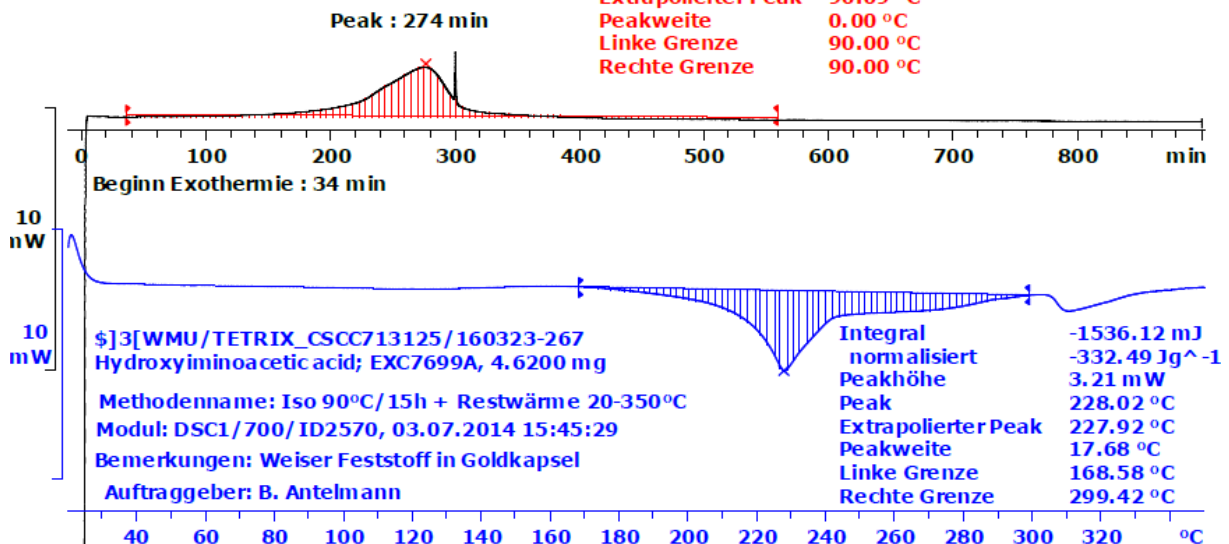
Hydroxyiminoacetic acid; EXC7699A, 4.6200 mg

Methodenname: Iso 90°C/15h + Restwärme 20-350°C

Modul: DSC1/700/ID2570, 03.07.2014 15:45:29

Bemerkungen: Weiser Feststoff in Goldkapsel

Integral	9457.04 mJ
normalisiert	2046.98 Jg ⁻¹
Peakhöhe	1.96 mW = 424.2 W/kg
Peak	90.08 °C
Extrapolierter Peak	90.09 °C
Peakweite	0.00 °C
Linke Grenze	90.00 °C
Rechte Grenze	90.00 °C



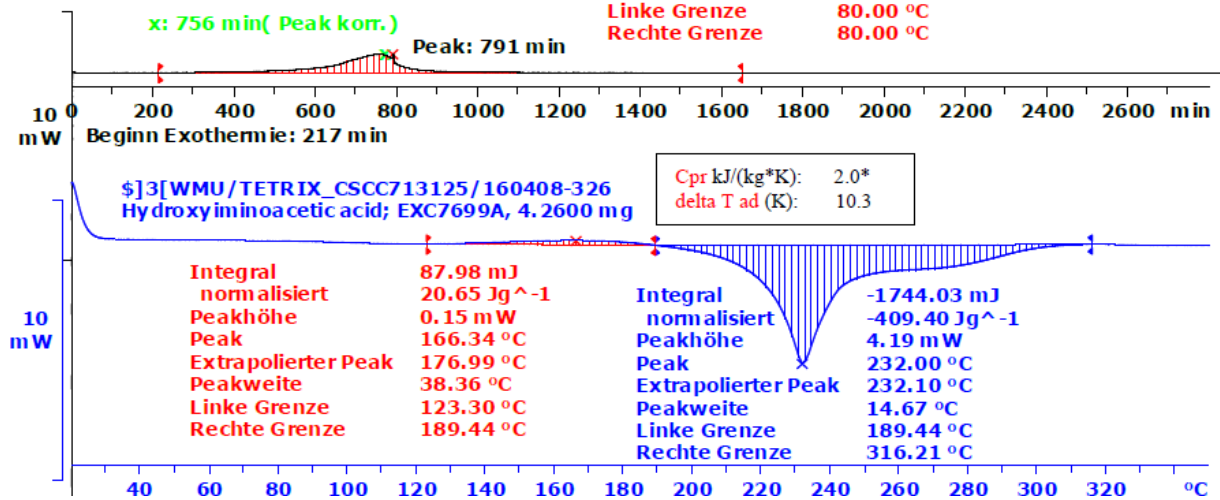
DSC, isotherm 80°C, 48h

Hydroxyiminoacetic acid; EXC7699A, 4.2600 mg

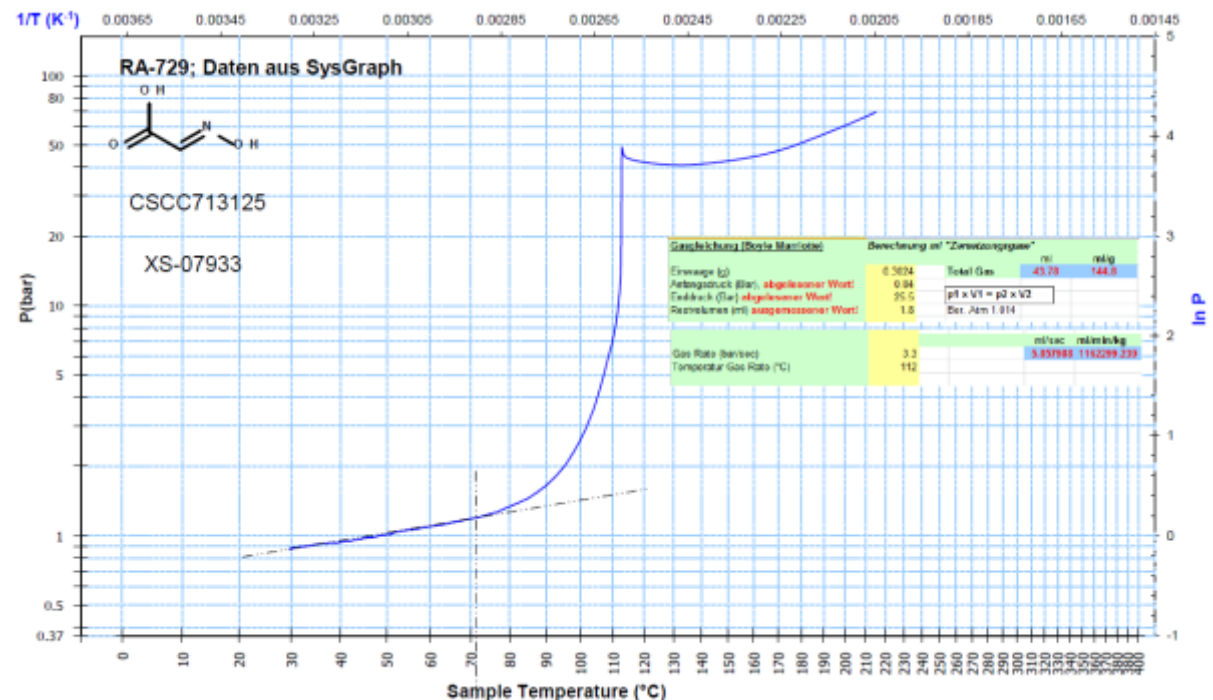
Methodenname: Iso 80°C/48h + Restwärme 20-350°C
 Modul: DSC1/700/ID2570, 03.07.2014 15:45:29

Bemerkungen: weisser Feststoff in Goldkapsel

Integral 8825.36 mJ
 normalisiert 2071.68 Jg⁻¹
 Peakhöhe 0.78 mW= 183.1 W/kg
 Peak 80.03 °C
 Extrapolierter Peak 80.03 °C
 Peakweite 0.00 °C
 Linke Grenze 80.00 °C
 Rechte Grenze 80.00 °C



RADEX



decompose. The total volume of gas generated is equivalent to *ca.* 57.5 L/kg at ambient temperature.

The thermal stability experiments confirmed the initial analysis which indicated that the material could undergo a violent exothermic decomposition. The results of the initial screening tests pointed out that the necessary analyses are to be carried out on this material, in accordance with the UN Transport Regulations (Orange book), to determine whether the compound is to be classified as an explosive, should it need to be prepared on a large scale.

Based upon this data, it is not possible to define a safe temperature threshold which can guarantee that no violent decomposition would occur; however, additional experimental work allowed defining parameters to safely store this material, for a limited period.

Storage stability

The exothermic event shown in the DSC analysis and the pressure curve in the RADEX test are of concern, as they exhibit the classic profile of an autocatalytic decomposition process. This means that safe storage of the material cannot be simply based upon temperature considerations, as the storage period might have a significant impact upon the stability.

To investigate the autocatalytic nature of decomposition, a series of isothermal DSC experiments were carried out with particular focus on the storage period (induction time) which would induce decomposition.

The isothermal DSC experiments carried out at 80, 90 and 100°C showed excellent agreement with both the 'induction time' (*i.e.*, time before heat output was detected) and the "time to peak" rate of decomposition; this was used to calculate the data given in the table below:

Table S1.

Temperature (°C)	Time to start of decomposition (hours)	Time to peak rate of decomposition (hours)	Time from "start of decomposition to peak" rate (hours)
-40	6000	60330	54330
-35	3390	30100	26710
-30	1960	15450	13490
-25	1160	8145	6985
-23	945	6350	5405
-20	700	4405	3705
-15	432	2440	2008
-10	271	1382	1111
-5	173	800	627
0	112	472	360
5	74	284	210
10	49.5	174	124.5
15	33.5	108	74.5
20	23	68.6	45.6
25	16	44.1	28.1

30	11.3	28.8	17.5
35	8	19	11
40	5.8	12.75	6.95
45	4.2	8.7	4.5
50	3.1	5.95	2.85
55	2.3	4.13	1.83
60	1.7	2.9	1.2
65	1.3	2.06	0.76
70	1	1.48	0.48
75	0.76	1.07	0.31
80	0.59	0.78	0.19
85	0.46	0.575	0.115
90	0.35	0.43	0.08
95	0.28	0.32	0.04
100	0.22	0.24	0.02

The sample tested had been obtained from a third party and it is not known how old the material were, and how it had been stored. However, given the decomposition potential of this material the values shown in the second column should be used as the basis for determining appropriate safe storage period for this material.

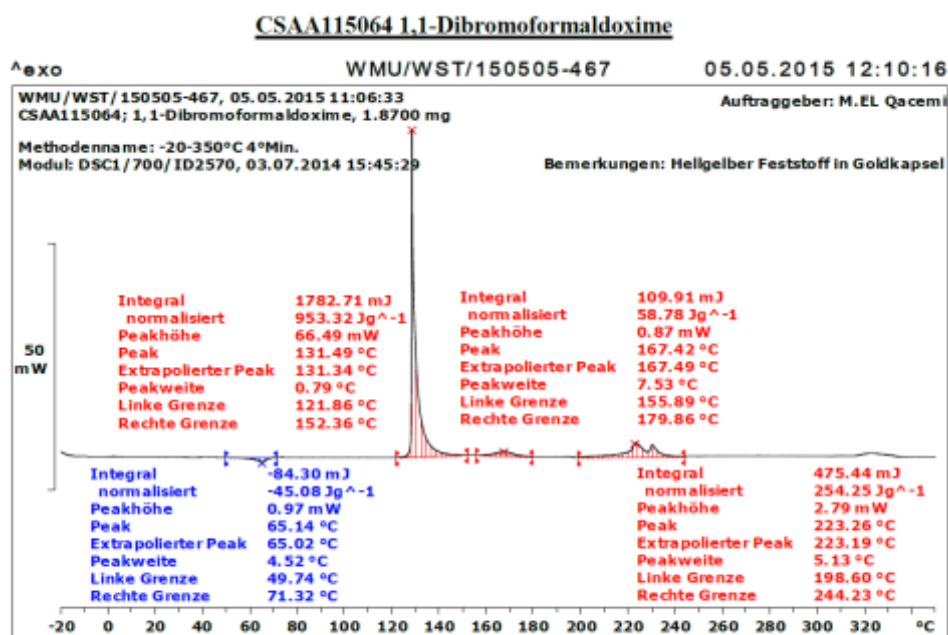
Due to the thermal instability of the material, its use as a synthetic reagent would need to be carefully considered, especially on scale.

Generation of the reagent in-situ may be a more likely prospect for larger scale operation or indeed safer laboratory scale work.

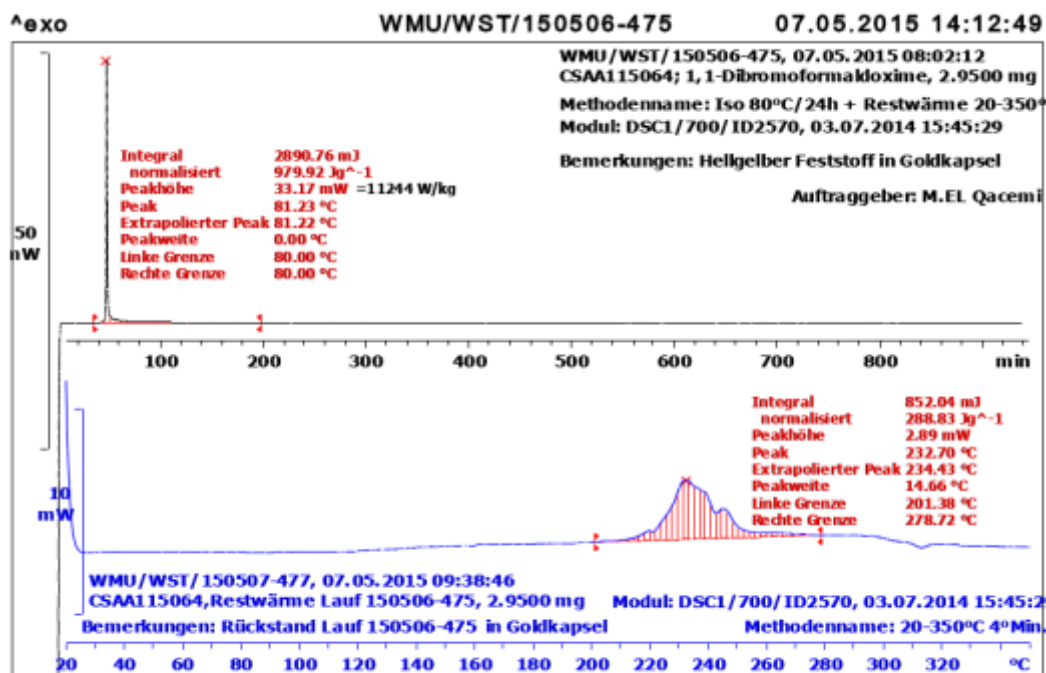
Differential Scanning Calorimetry (DSC)

Experimental investigations were carried out in the PHS laboratory at Muenchewilen (Switzerland). Gold plated stainless steel high pressure crucibles were used with a heating rate of 4 K/min over the range -20 to 350°C for the initial dynamic test and 20 – 350°C for the tests carried out after isothermal experiments.

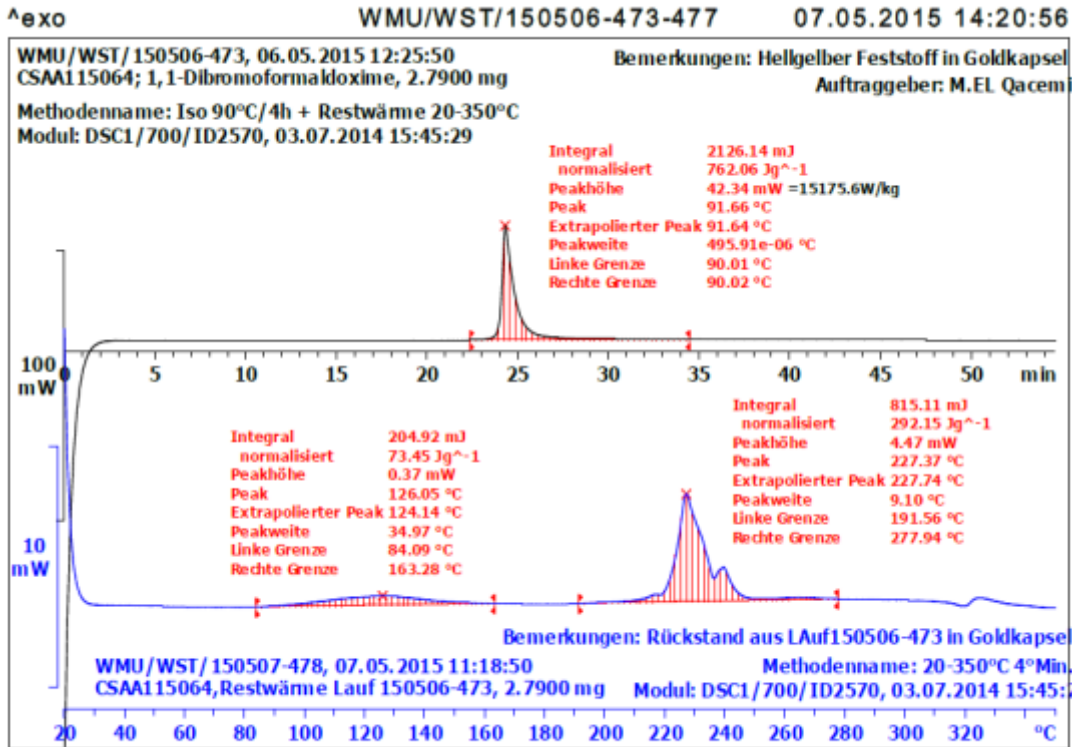
Initial dynamic test



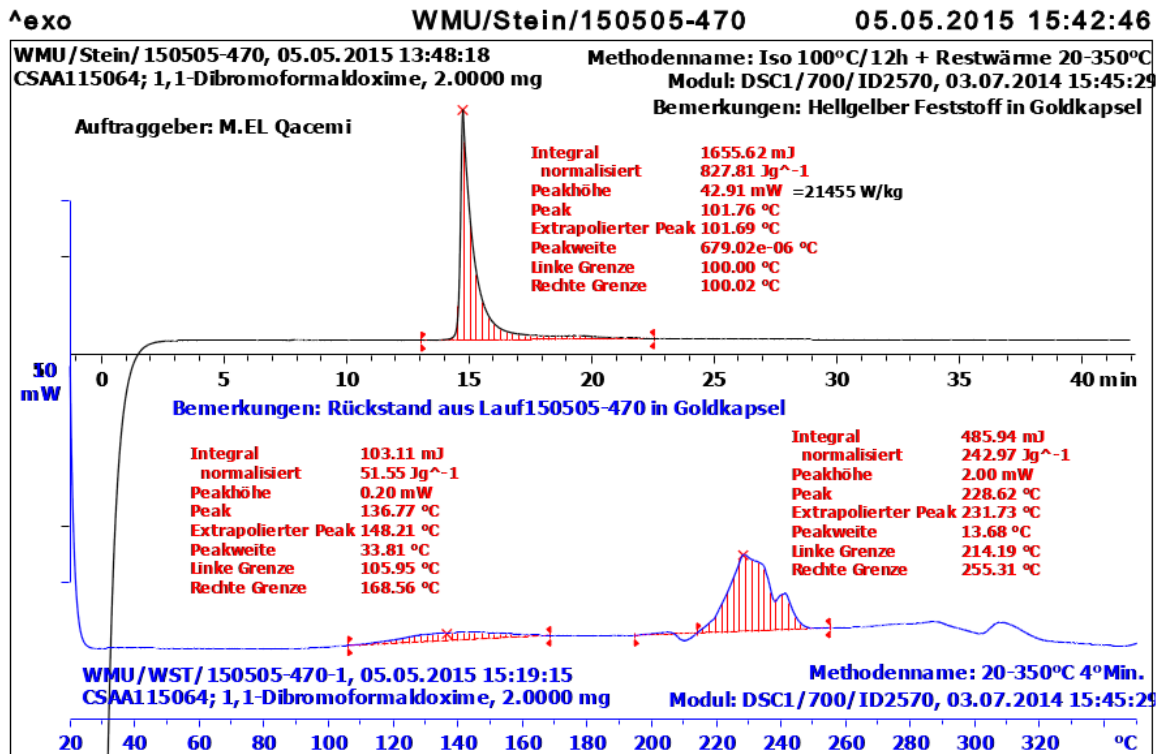
Isothermal at 80°C



Isothermal at 90°C

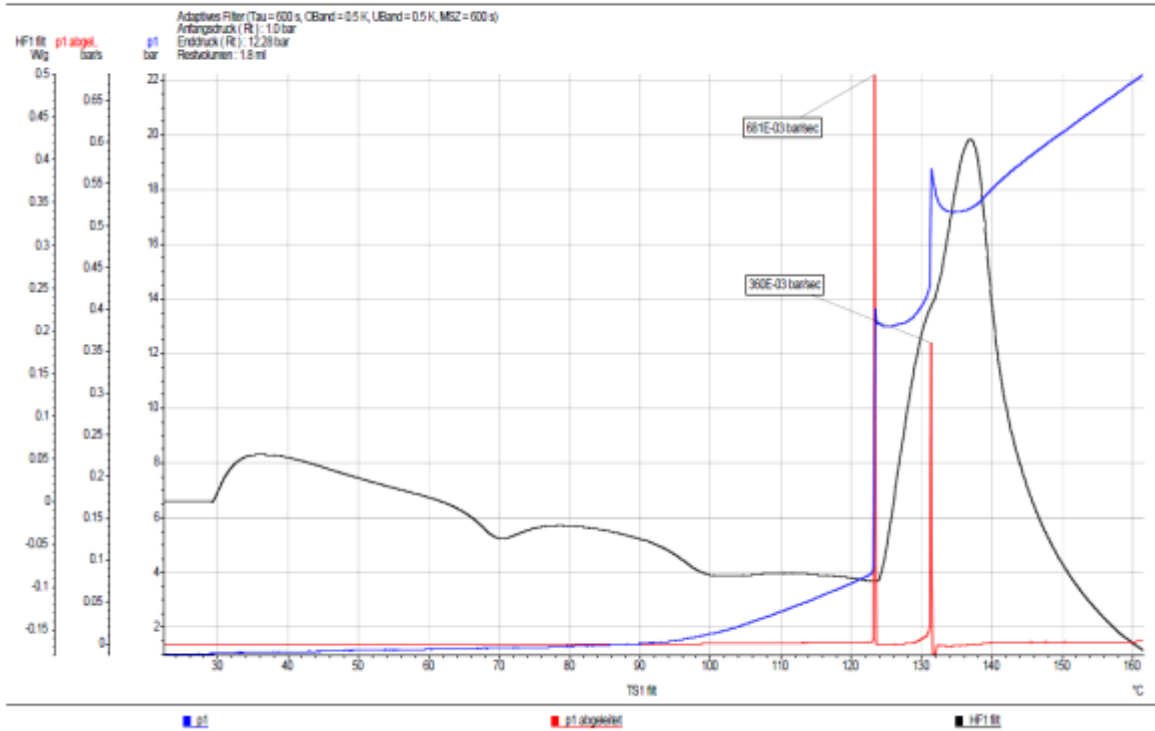


Isothermal at 100°C

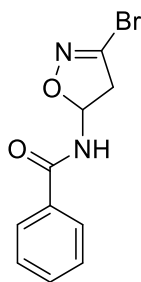


Radex; pressure/power output relation

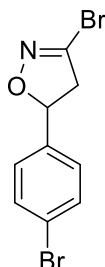
Ableitung Druck: C:\FeySys\REPORTS\Analyse\ScanRadexPa-607_1.1-Dibromoformaldeide CSAA115064_scan_lined_gasoset bis 130°C_mehr_Einwaage\Scanning_mit_120Timer_20150507_110322_P1\Scanning_mit_120Timer_20150507_110322_86D_P1 -



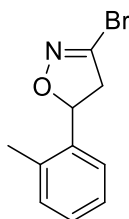
5. Characterization of compounds 7a-n



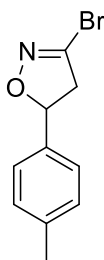
N-(3-Bromo-4,5-dihydroisoxazol-5-yl)benzamide (7a): yellowish solid (97%). $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.40 (s, 1H), 7.58 (d, $J = 7.5$ Hz, 2H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.17 (t, $J = 7.6$ Hz, 2H), 5.17 (dd, $J = 7.6, 9.8$ Hz, 1H), 3.68 (dd, $J = 9.8, 18$ Hz, 1H), 3.61 (dd, $J = 7.6, 18$ Hz, 1H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3): δ 167.7, 139.3, 136.4, 129.1, 125.1, 119.9, 79.1, 45.9 ppm.⁷



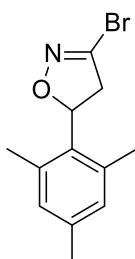
3-Bromo-5-(4-bromophenyl)isoxazoline (7b): yellow solid (98%). **FTIR** (ν_{max} , cm^{-1}) 1593. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.61 – 7.44 (m, 2H), 7.25 – 7.21 (m, 2H), 5.64 (dd, $J = 10.9, 8.8$ Hz, 1H), 3.64 (dd, $J = 17.3, 11.0$ Hz, 1H), 3.17 (ddd, $J = 17.3, 8.7, 3.9$ Hz, 1H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 138.4, 136.8, 132.1, 127.7, 122.8, 82.5, 49.2 ppm. **HRMS** (ESI) calculated for $\text{C}_9\text{H}_7\text{Br}_2\text{NO}$ $[\text{M}+\text{H}]^+$ 303.8967, found 303.8960.



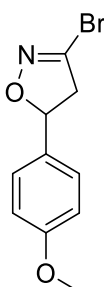
3-Bromo-5-(o-tolyl)isoxazoline (7c): yellowish oil (98%). **FTIR** (ν_{max} , cm^{-1}) 1607. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.35 – 7.29 (m, 1H), 7.18 – 7.12 (m, 2H), 7.11 – 7.06 (m, 1H), 5.74 (dd, $J = 11.0, 9.0$ Hz, 1H), 3.54 (dd, $J = 17.2, 11.1$ Hz, 1H), 2.98 (dd, $J = 17.2, 9.0$ Hz, 1H), 2.21 (s, 3H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 137.5, 136.7, 134.4, 130.7, 128.4, 126.6, 125.2, 80.8, 48.3, 19.3 ppm. **HRMS** (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{BrNO}$ $[\text{M}+\text{H}]^+$ 240.0019, found 240.0015.



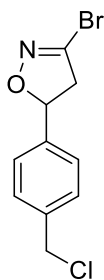
3-Bromo-5-(p-tolyl)-isoxazoline (7d): colourless oil (98%). IR (ν_{\max} , cm^{-1}) 1607, 2925. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.13 (d, $J = 8.1$ Hz, 2H), 7.10 (d, $J = 8.2$ Hz, 2H) 5.52 (dt, $J = 20.2, 10.1$ Hz, 1H), 3.48 (dd, $J = 17.3, 10.9$ Hz, 1H), 3.09 (dd, $J = 17.3, 9.2$ Hz, 1H), 2.27 (s, 3H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 138.7, 136.8, 136.2, 129.6, 126.1, 83.3, 49.1, 21.2 ppm. **HRMS** (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{BrNO}$ $[\text{M}+\text{H}]^+$ 240.0019, found 240.0008.



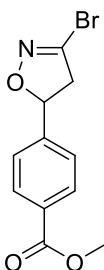
3-Bromo-5-mesityl-isoxazoline (7e): yellowish solid (20%). IR (ν_{\max} cm^{-1}) 1608, 2967. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.88 (s, 2H), 6.07 (t, $J = 12.2$ Hz, 1H), 3.44 (dd, $J = 17.5, 11.9$ Hz, 1H), 3.25 (dd, $J = 17.5, 12.5$ Hz, 1H), 2.33 (s, 6H), 2.28 (s, 3H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 138.3, 137.0, 136.5, 130.3, 130.3, 80.7, 46.7, 20.8, 20.1 ppm. **HRMS** (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{BrNO}$ $[\text{M}+\text{H}]^+$ 268.0332, found 268.0326.



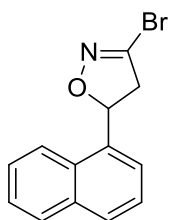
3-Bromo-5-(4-methoxyphenyl)-isoxazoline (7f): amber solid (98%). IR (ν_{\max} , cm^{-1}) 1609, 2960. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.27 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 5.62 (dd, $J = 10.5, 9.7$ Hz, 1H), 3.81 (s, 3H), 3.56 (dd, $J = 17.3, 10.8$ Hz, 1H), 3.20 (dd, $J = 17.3, 9.4$ Hz, 1H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 160.1, 136.8, 131.1, 127.7, 114.4, 83.4, 55.5, 49.1 ppm. **HRMS** (ESI) calculated for $\text{C}_{10}\text{H}_{10}\text{BrNO}_2$ $[\text{M}+\text{H}]^+$ 255.9968, found 255.9964.



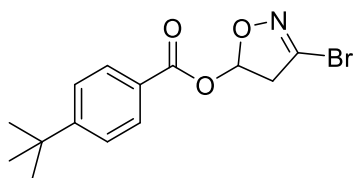
3-Bromo-5-(4-(chloromethyl)phenyl)-isoxazoline (7g): brown solid (98%). **FTIR** (ν_{\max} , cm^{-1}) 1609, 2965. **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ 7.40 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.2$ Hz, 2H, H1-H5), 5.66 (dd, $J = 10.9, 8.9$ Hz, 1H), 4.58 (s, 2H), 3.62 (dd, $J = 17.3, 11.0$ Hz, 1H), 3.17 (dd, $J = 17.3, 8.8$ Hz, 1H) ppm. **$^{13}\text{C NMR}$** (151 MHz, CDCl_3) δ 139.5, 138.0, 136.9, 129.1, 126.3, 82.7, 49.1, 45.7 ppm. **HRMS** (ESI) calculated for $\text{C}_{10}\text{H}_9\text{BrClNO}$ $[\text{M}+\text{H}]^+$ 273.9629, found 273.9624.



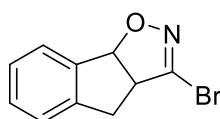
3-Bromo-5-(4-methyl benzoyl)-isoxazoline (7h): white powder (96%). **IR** (ν_{\max} , cm^{-1}) 1612, 1709. **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ 8.13 – 8.01 (m, 2H), 7.41 (d, $J = 8.3$ Hz, 2H), 5.73 (dd, $J = 11.0, 8.7$ Hz, 1H), 3.92 (s, 3H), 3.67 (dd, $J = 17.3, 11.1$ Hz, 1H), 3.18 (dd, $J = 17.3, 8.6$ Hz, 1H) ppm. **$^{13}\text{C NMR}$** (151 MHz, CDCl_3) δ 166.5, 144.2, 136.6, 130.5, 130.2, 125.8, 82.5, 52.3, 49.3 ppm. **HRMS** (ESI) calculated for $\text{C}_{11}\text{H}_{10}\text{BrNO}_3$ $[\text{M}+\text{H}]^+$ 283.9917, found 283.9912.



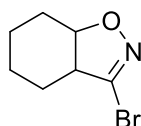
3-bromo-5-(naphthalen-1-yl)-isoxazoline (7i): orange oil (98%). **IR** (ν_{\max} , cm^{-1}) 1600, 3056. **$^1\text{H NMR}$** (600 MHz, CDCl_3) δ 7.92 (d, $J = 7.5$ Hz, 1H), 7.85 (d, $J = 8.2$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 7.1$ Hz, 1H), 7.58 – 7.47 (m, 3H), 6.36 (dd, $J = 11.1, 8.5$ Hz, 1H), 3.84 (dd, $J = 17.2, 11.2$ Hz, 1H), 3.25 (dd, $J = 17.2, 8.5$ Hz, 1H) ppm. **$^{13}\text{C NMR}$** (151 MHz, CDCl_3) δ 137.3, 134.7, 134.1, 129.7, 129.4, 129.2, 126.8, 126.1, 125.6, 123.2, 122.6, 81.1, 49.2 ppm. **HRMS** (ESI) calculated for $\text{C}_{13}\text{H}_{10}\text{BrNO}$ $[\text{M}+\text{H}]^+$ 276.0019, found 276.0015.



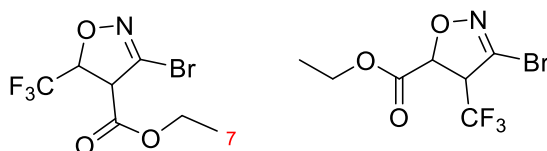
3-bromo-isoxazolin-5-yl 4-(tert-butyl)benzoate (7j): white solid (50%). IR (ν_{\max} , cm^{-1}) 1640, 1728, 2915. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.95 (d, $J = 8.6$ Hz, 2H), 7.46 (d, $J = 8.6$ Hz, 2H), 6.92 (dd, $J = 7.0, 1.6$ Hz, 1H), 3.64 (dd, $J = 18.4, 7.0$ Hz, 1H), 3.29 (dd, $J = 18.4, 1.6$ Hz, 1H), 1.33 (s, 9H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 165.0, 157.8, 138.3, 130.0, 126.0, 125.6, 96.7, 47.8, 35.3, 31.2 ppm. HRMS (ESI) calculated for $\text{C}_{14}\text{H}_{16}\text{BrNO}_3$ $[\text{M}+\text{Na}]^+$ 348.0206, found 348.0199.



3-Bromo-3a,8b-dihydro-4H-indeno[2,1-d]isoxazole (7k): white solid (38%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.49 (d, $J = 7.5$ Hz, 1H), 7.36-7.29 (m, 3H), 6.10 (d, $J = 8.9$ Hz, 1H), 4.14 (dt, $J = 8.9, 5.3$ Hz, 1H), 3.32 (d, $J = 5.3$ Hz, 2H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 141.9, 139.8, 139.6, 130.1, 128.1, 125.9, 124.9, 89.0, 55.7, 35.2 ppm. HRMS (ESI) calculated for $\text{C}_{10}\text{H}_8\text{BrNO}$ $[\text{M}+\text{H}]^+$ 237.9862, found 237.9858.

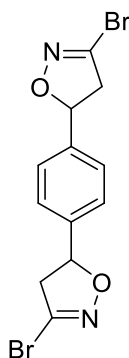


3-Bromo-3a,4,5,6,7,7a-hexahydrobenzo[d]isoxazole (7l): colourless oil (48%). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.60 (dt, $J = 8.4, 5.0$ Hz, 1H), 3.13-3.09 (m, 1H), 1.95 – 1.71 (m, 3H), 1.60 - 1.29 (m, 5H) ppm. $^{13}\text{C NMR}$ (151 MHz, CDCl_3) δ 145.7, 80.4, 50.0, 25.8, 24.4, 21.2, 20.0 ppm. HRMS (ESI) calculated for $\text{C}_7\text{H}_{10}\text{BrNO}$ $[\text{M}+\text{H}]^+$ 204.0019, found 204.0010.⁸



Ethyl 3-bromo-5-(trifluoromethyl)-dihydroisoxazoline-4-carboxylate, ethyl 3-bromo-4-(trifluoromethyl)-dihydroisoxazoline-5-carboxylate (7m): white solid (90%). IR (ν_{\max} , cm^{-1}) 1605, 1742. $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.29 (m, $J = 6.5$ Hz, 1H), 5.16 (d, $J = 5.8$ Hz, 1H), 4.42

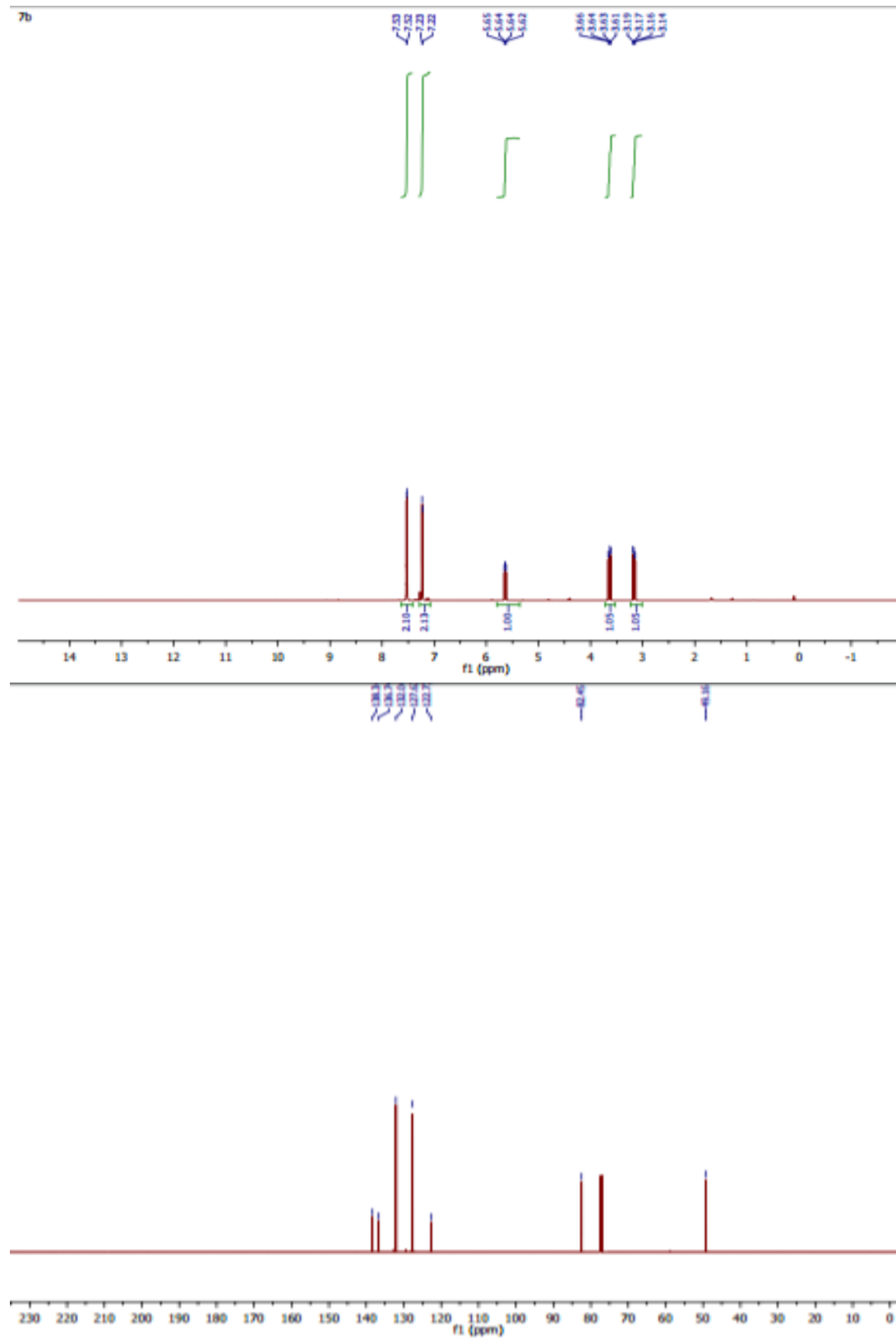
(dd, $J = 8.0, 5.8$ Hz, 1H), 4.37 – 4.22 (m, 5H), 1.34 (dd, $J = 14.0, 7.0$ Hz, 6H) ppm. ^{13}C NMR (151 MHz, CDCl_3) δ 166.65, 164.60, 136.94, 134.13, 125.81, 125.31, 123.96, 123.45, 122.10, 121.59, 120.24, 119.73, 81.04, 80.81, 80.58, 80.36, 79.60, 79.58, 63.70, 63.40, 59.85, 59.65, 59.44, 59.23, 59.01, 59.00, 29.76, 14.13, 14.04, 14.02 ppm. HRMS (ESI) calculated for $\text{C}_7\text{H}_7\text{BrF}_3\text{NO}_3$ $[\text{M}+\text{H}]^+$ 289.9634, found 289.9622.



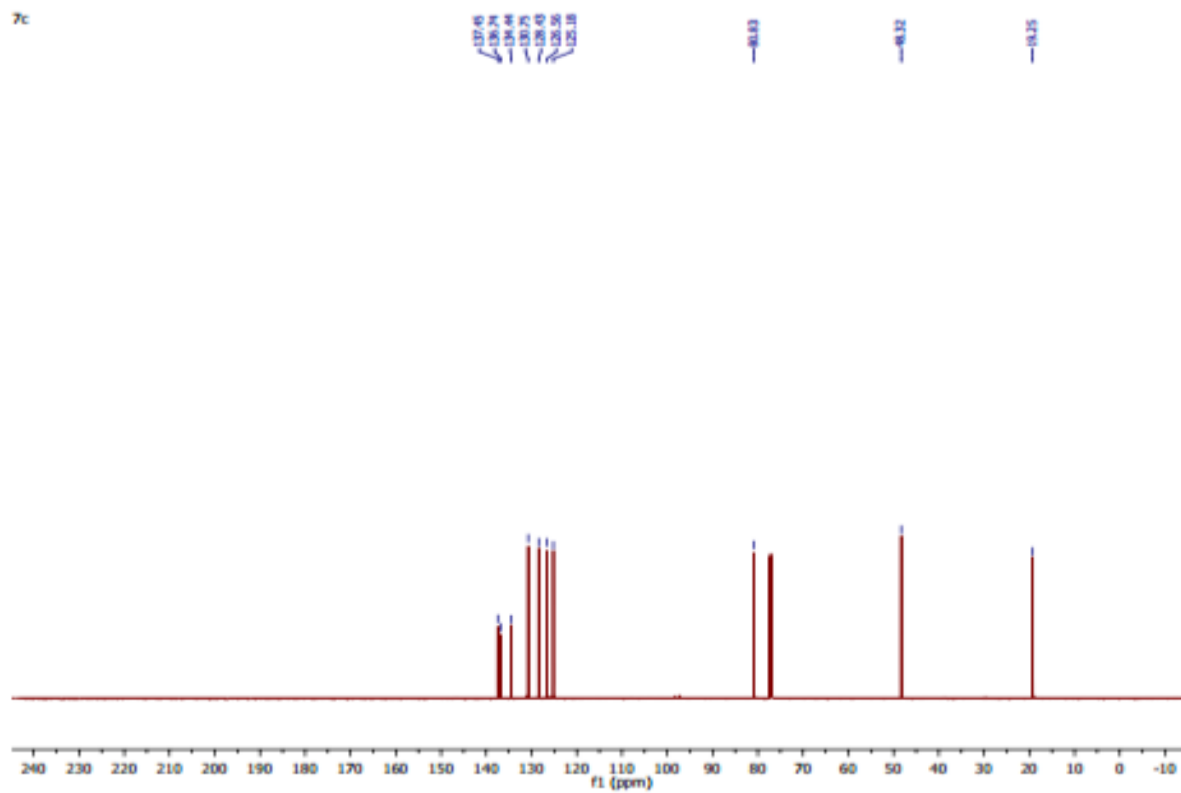
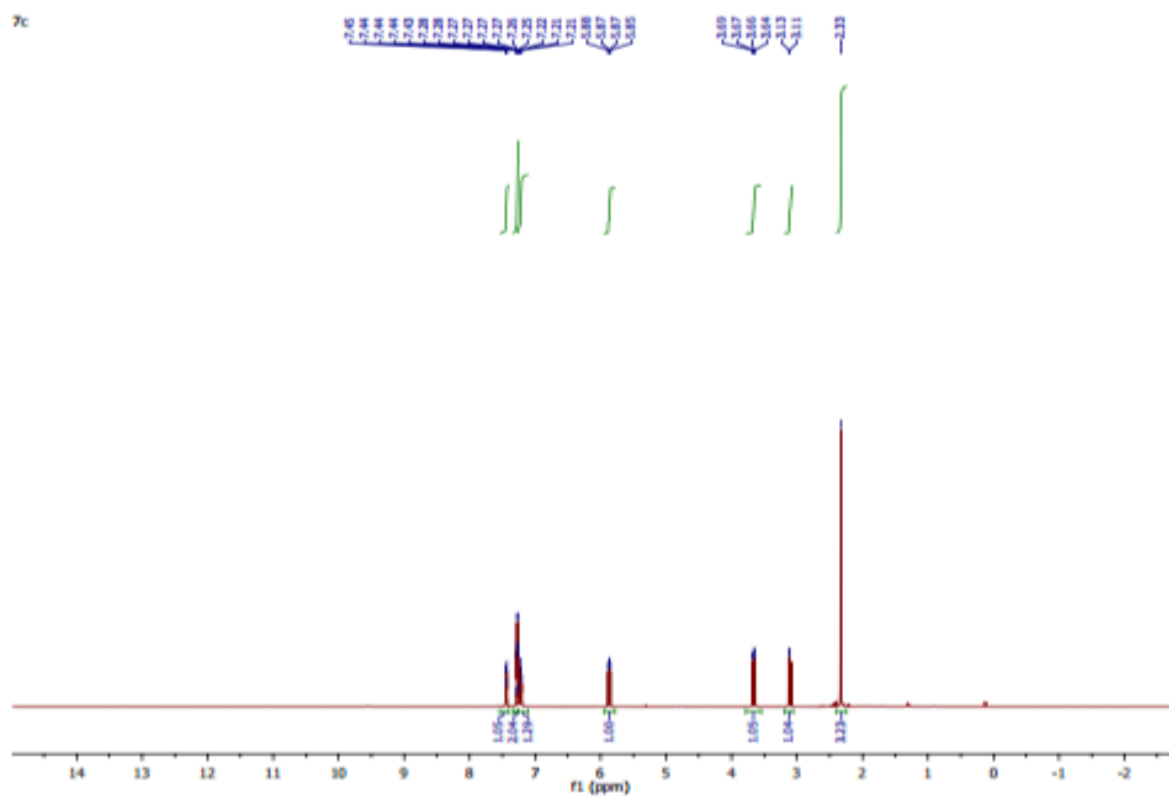
1,4-bis-(3-bromo-isoxazolin-5-yl)benzene (7n): yellowish solid (98%). FTIR (ν_{max} , cm^{-1}) 1600, 2992, 3215. ^1H NMR (600 MHz, CDCl_3) δ 7.37 (d, $J = 4.3$ Hz, 4H), 5.68 (dd, $J = 10.9, 8.8$ Hz, 2H), 3.64 (dd, $J = 17.3, 11.0$ Hz, 2H), 3.18 (ddd, $J = 17.3, 8.8, 1.0$ Hz, 2H) ppm. ^{13}C NMR (151 MHz, CDCl_3) δ 140.0, 136.9, 126.6, 82.8, 49.3 ppm. HRMS (ESI) calculated for $\text{C}_{12}\text{H}_{10}\text{Br}_2\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 372.9182, found 372.9178.

6. Copies of ^1H - and ^{13}C -NMR spectra

3-Bromo-5-(4-bromophenyl)-isoxazoline (7b)

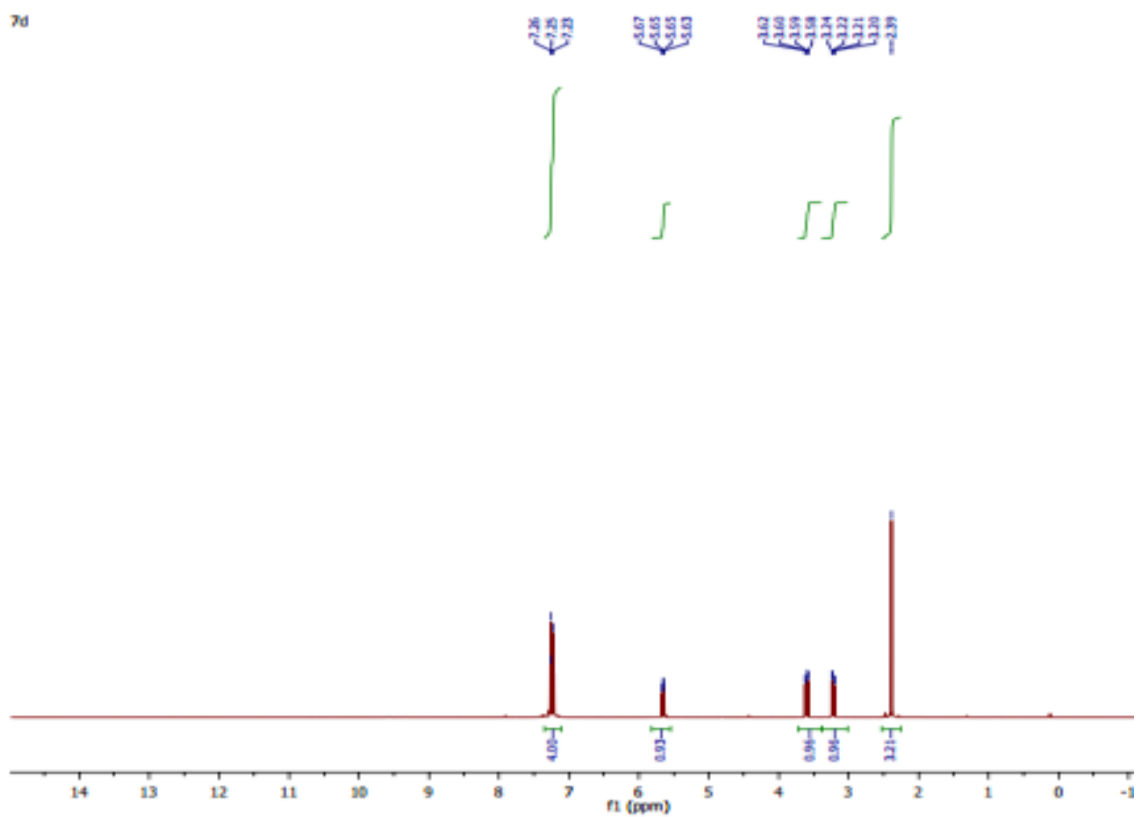


3-Bromo-5-(o-tolyl)-isoxazoline (7c)

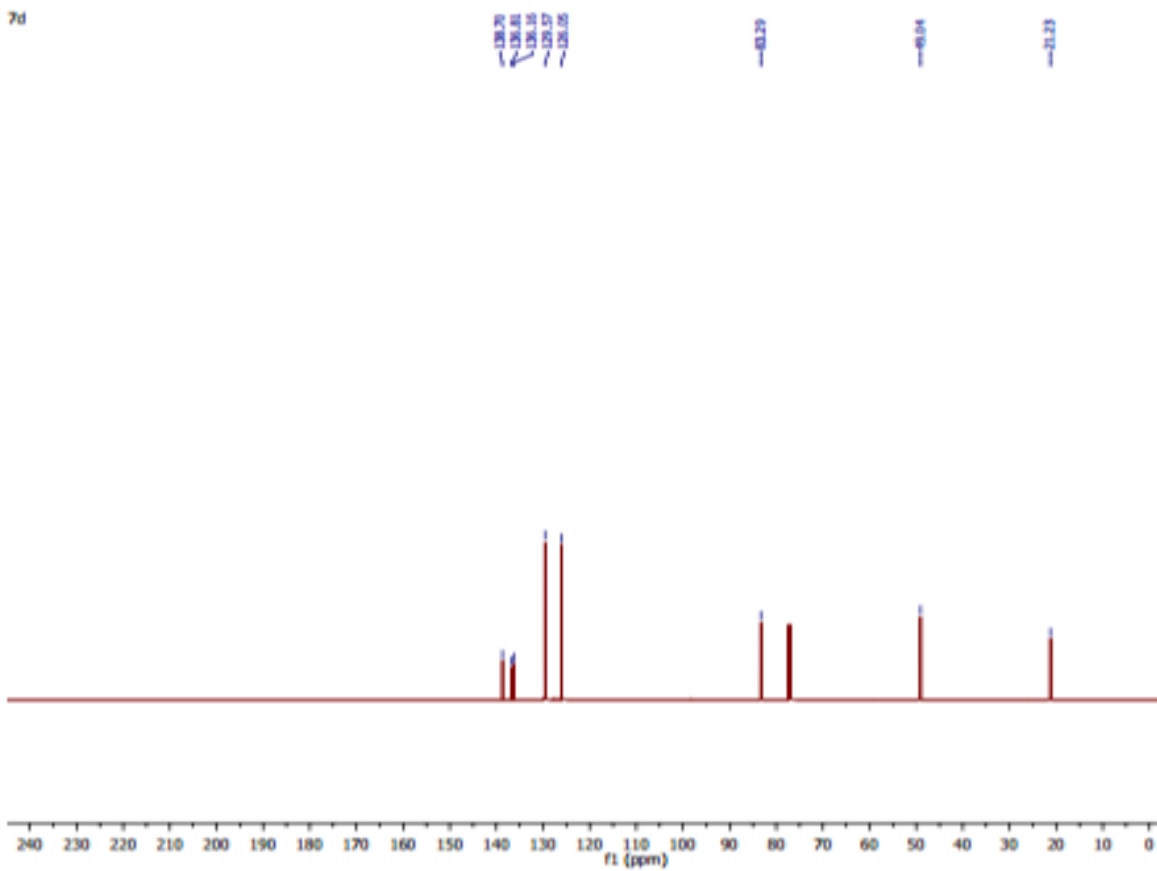


3-Bromo-5-(p-tolyl)-isoxazoline (7d)

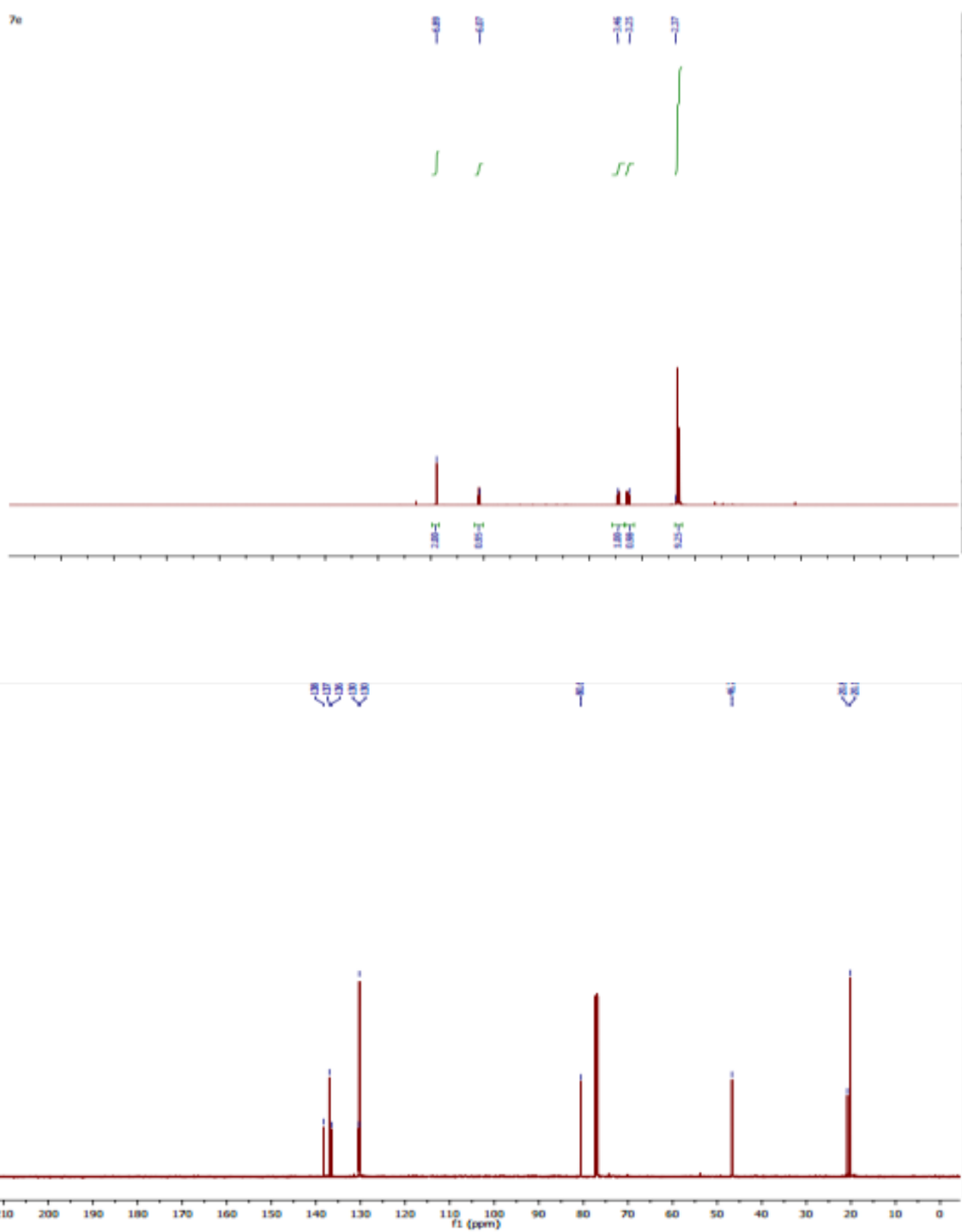
7d



7d

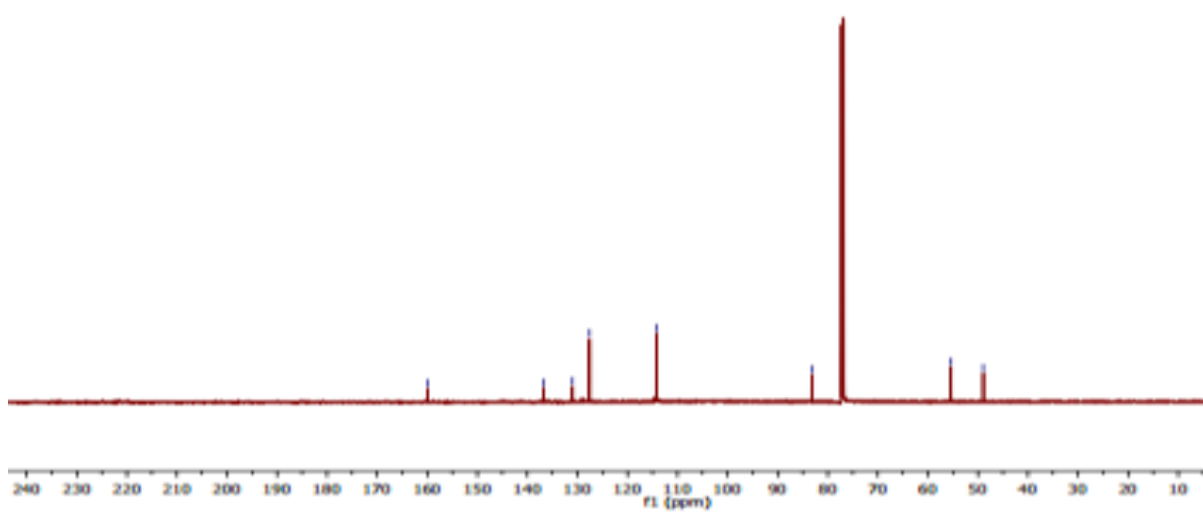
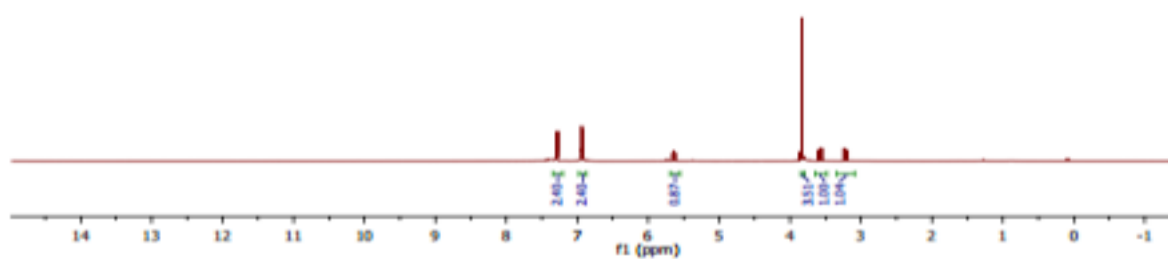


3-Bromo-5-mesityl-isoxazoline (7e)

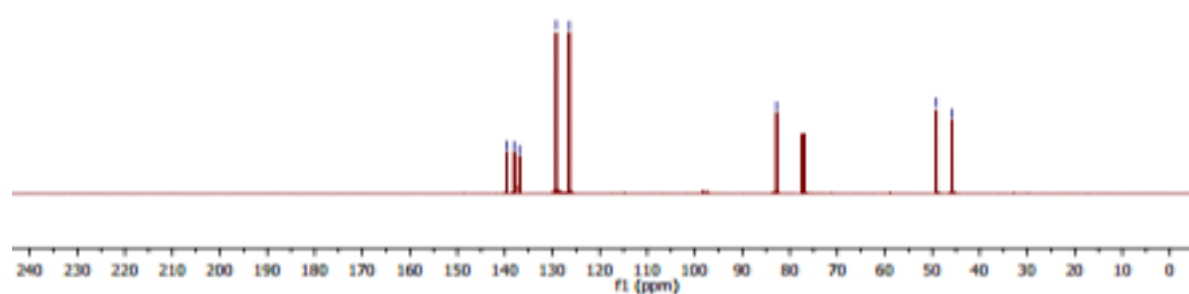
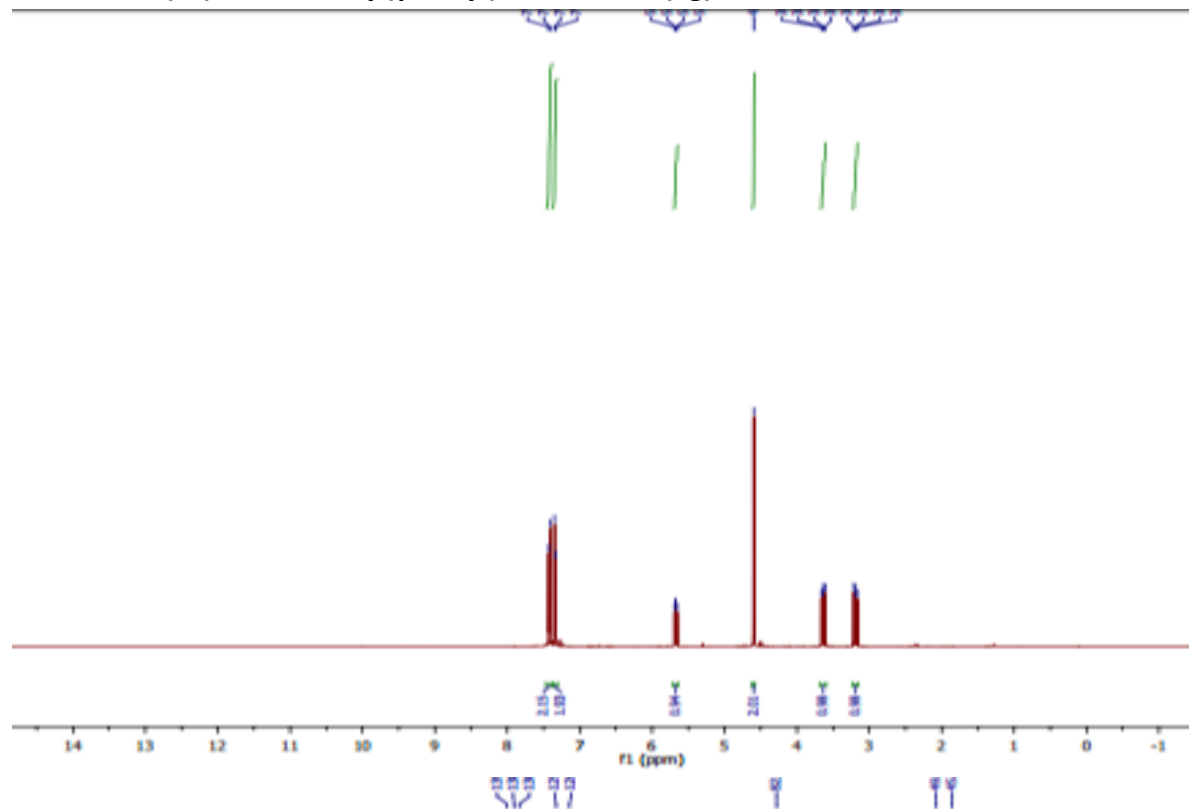


3-Bromo-5-(4-methoxyphenyl)-isoxazoline (7f)

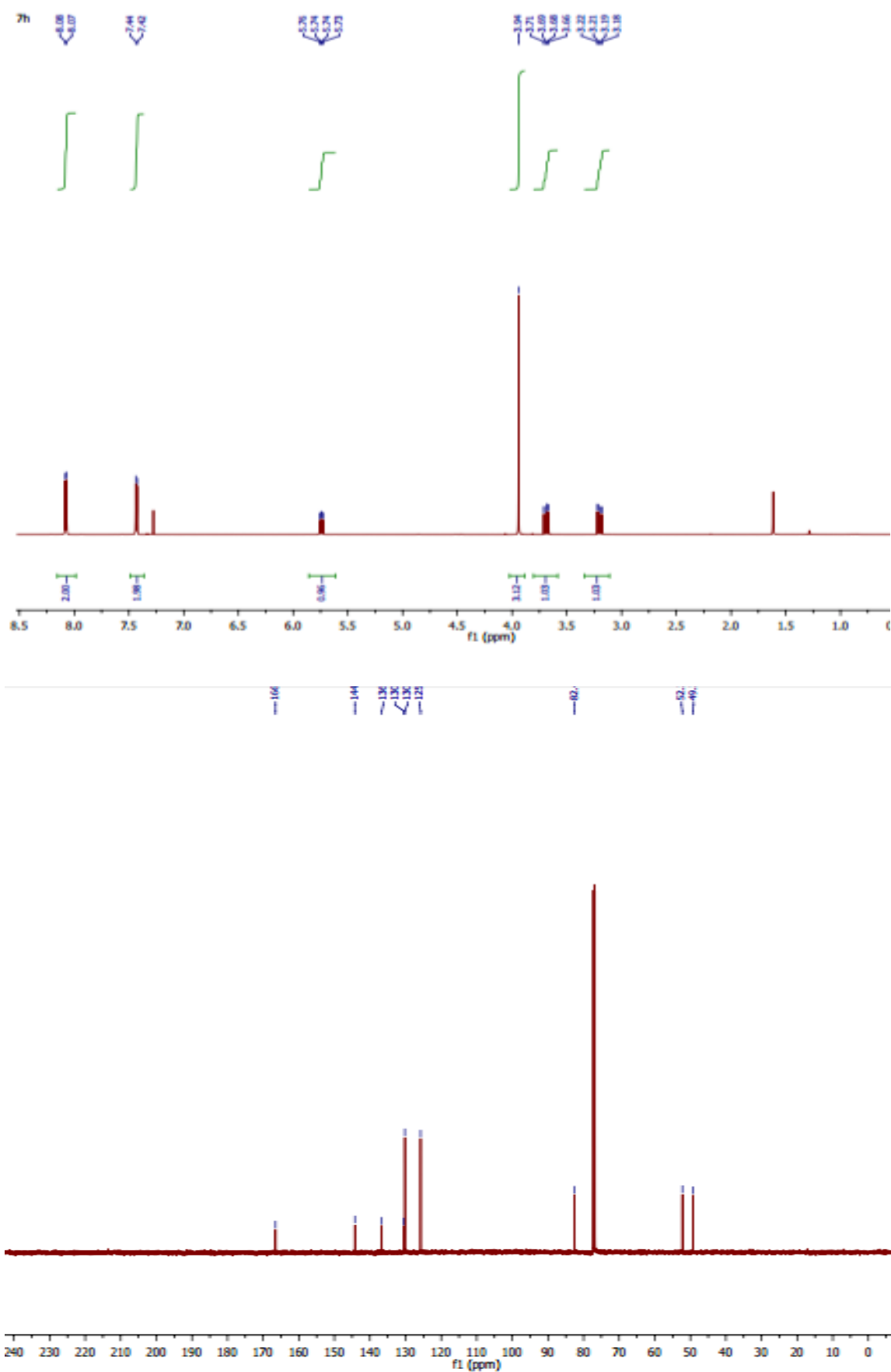
7f



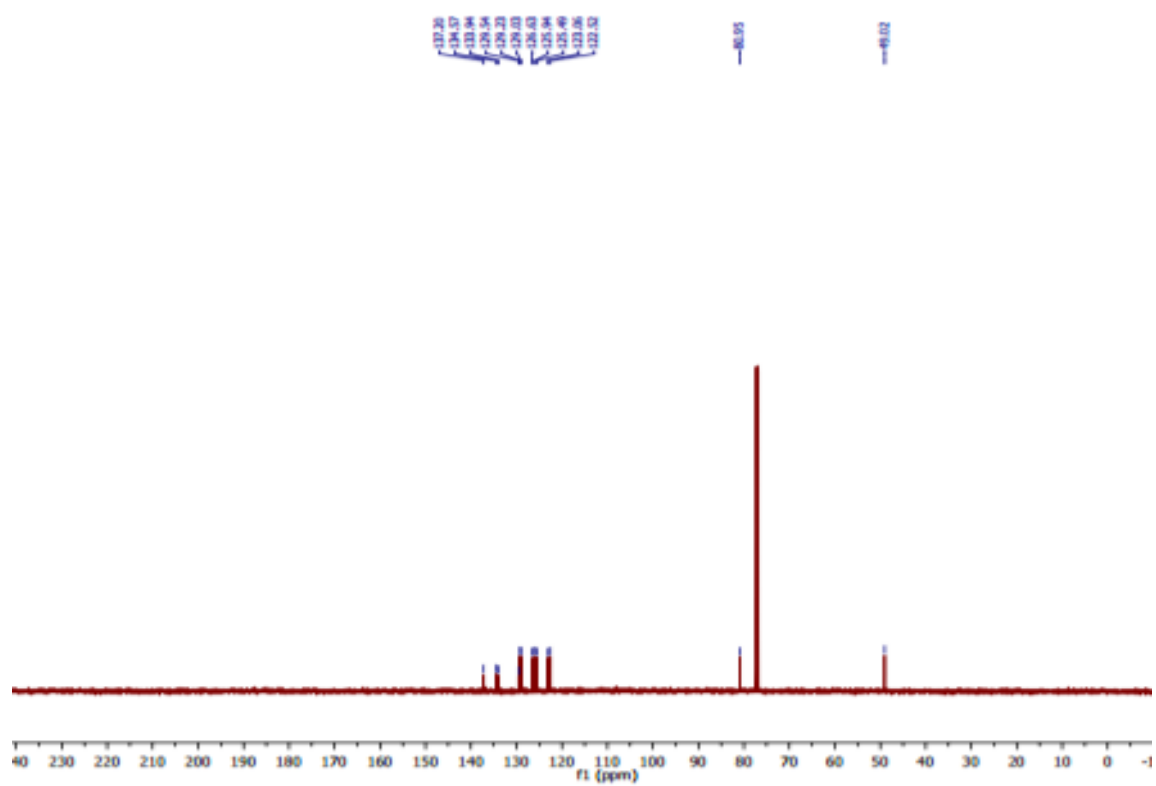
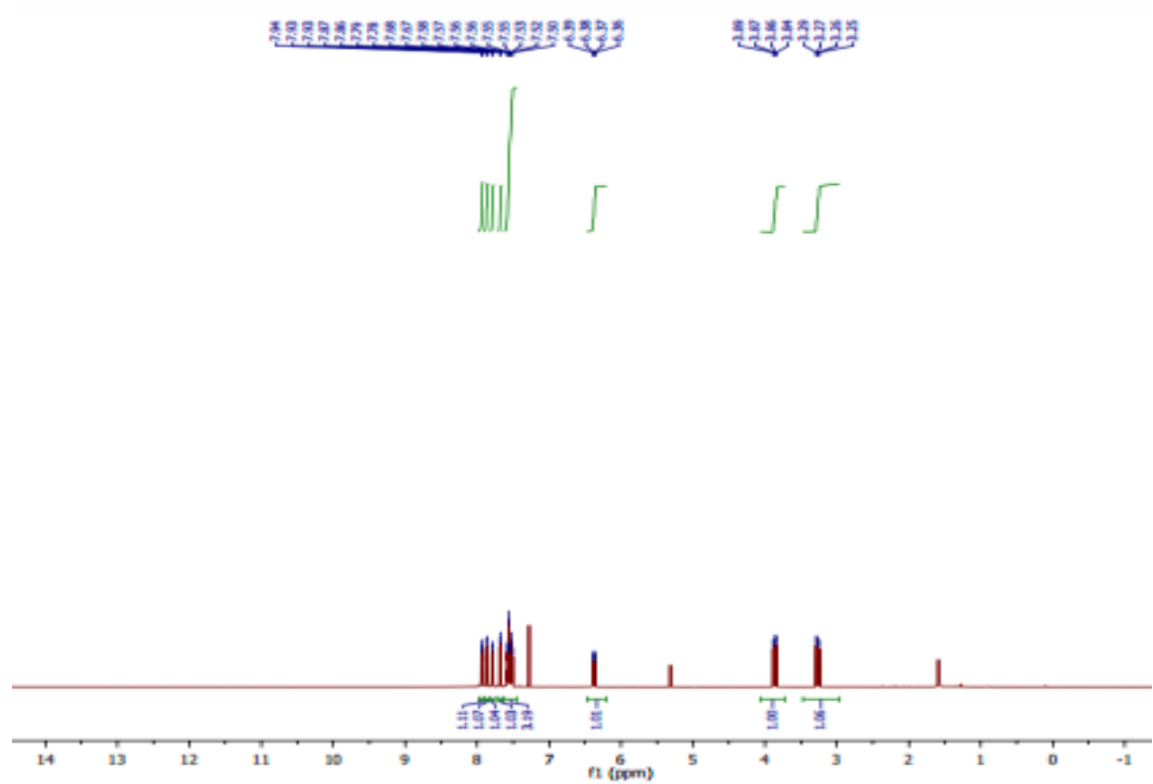
3-Bromo-5-(4-(chloromethyl)phenyl)-isoxazoline (7g)



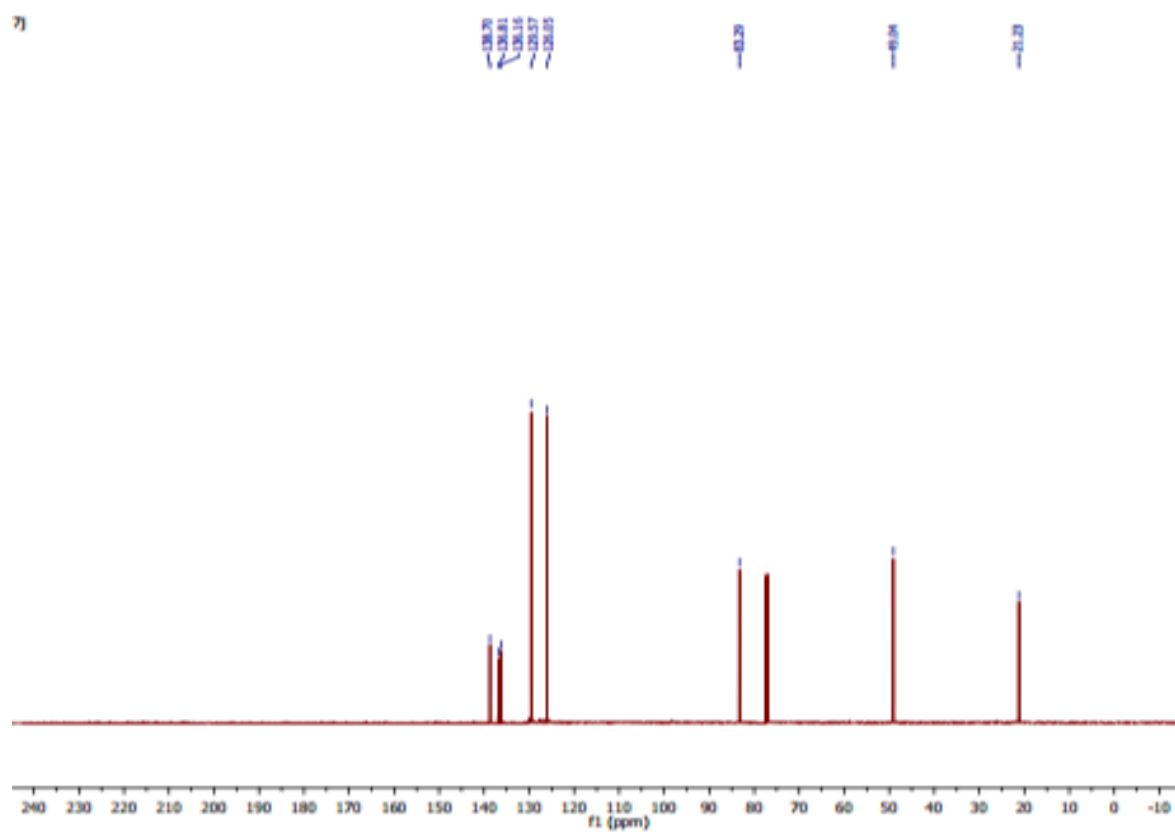
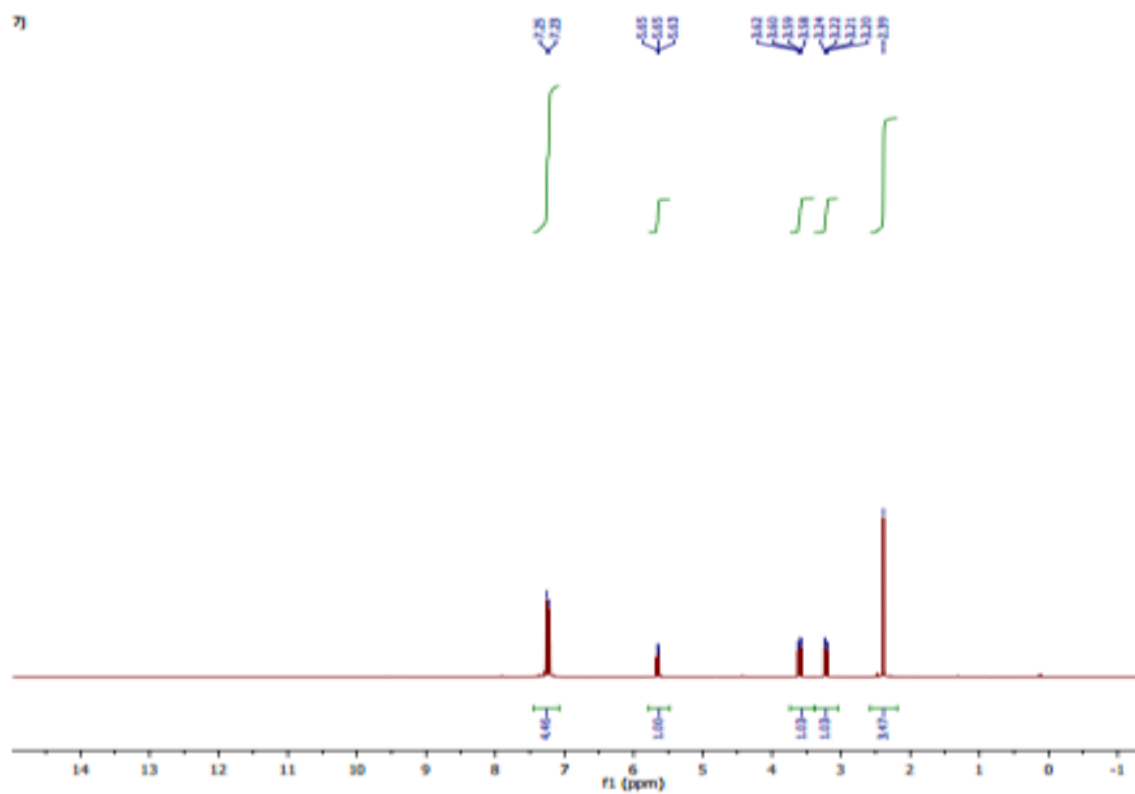
3-Bromo-5-(4-methyl benzoyl)-isoxazoline (7h)



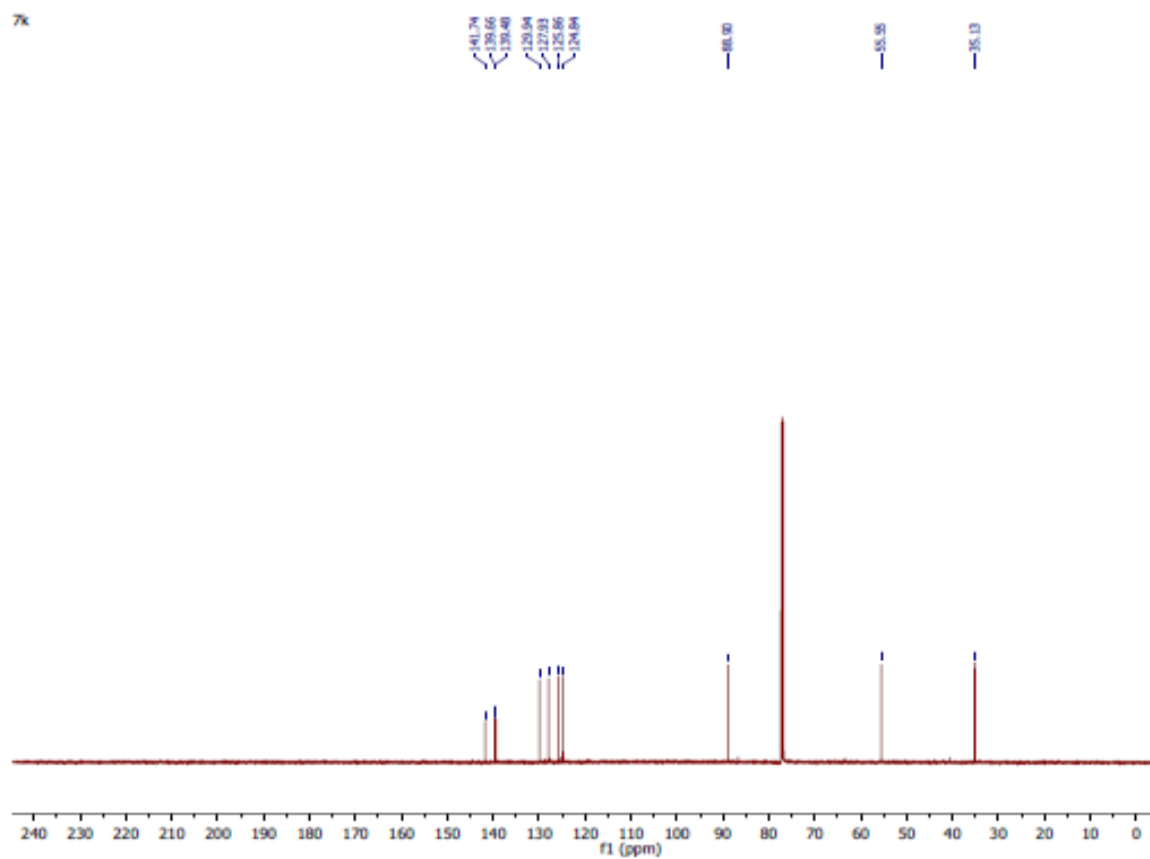
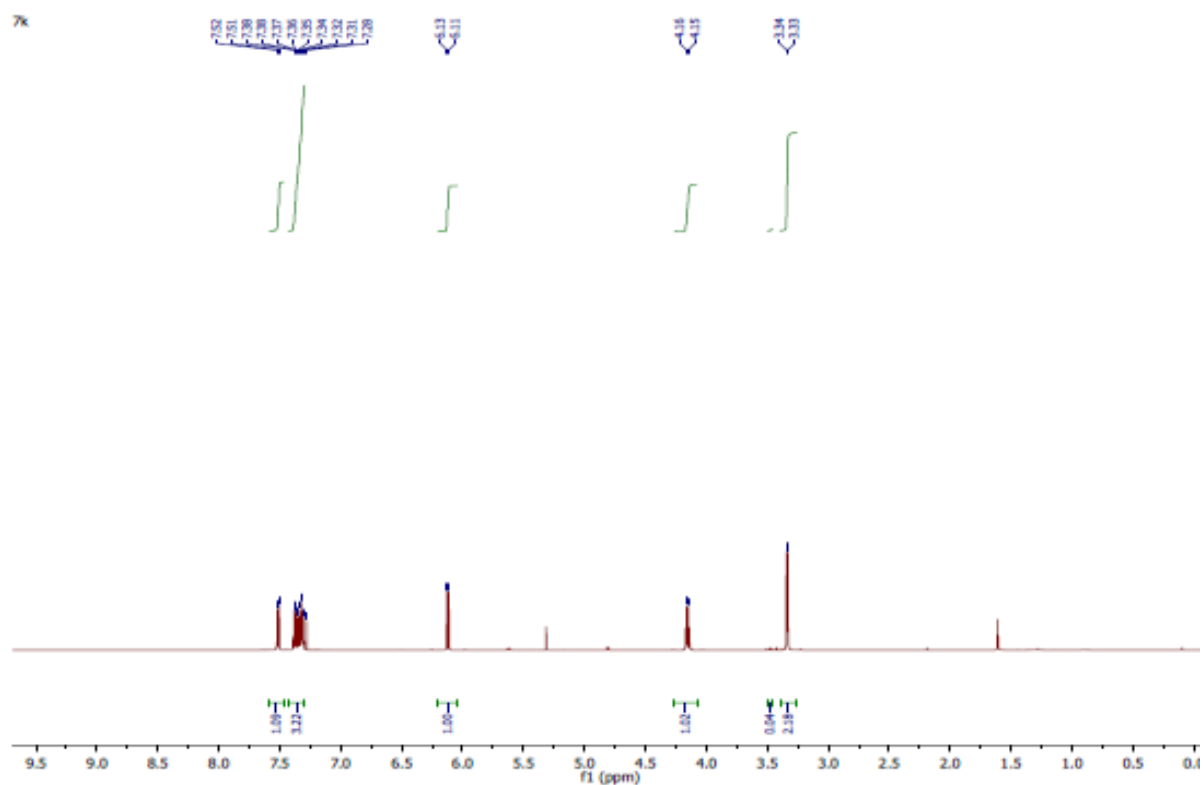
3-Bromo-5-(naphthalen-1-yl)-isoxazoline (7i)



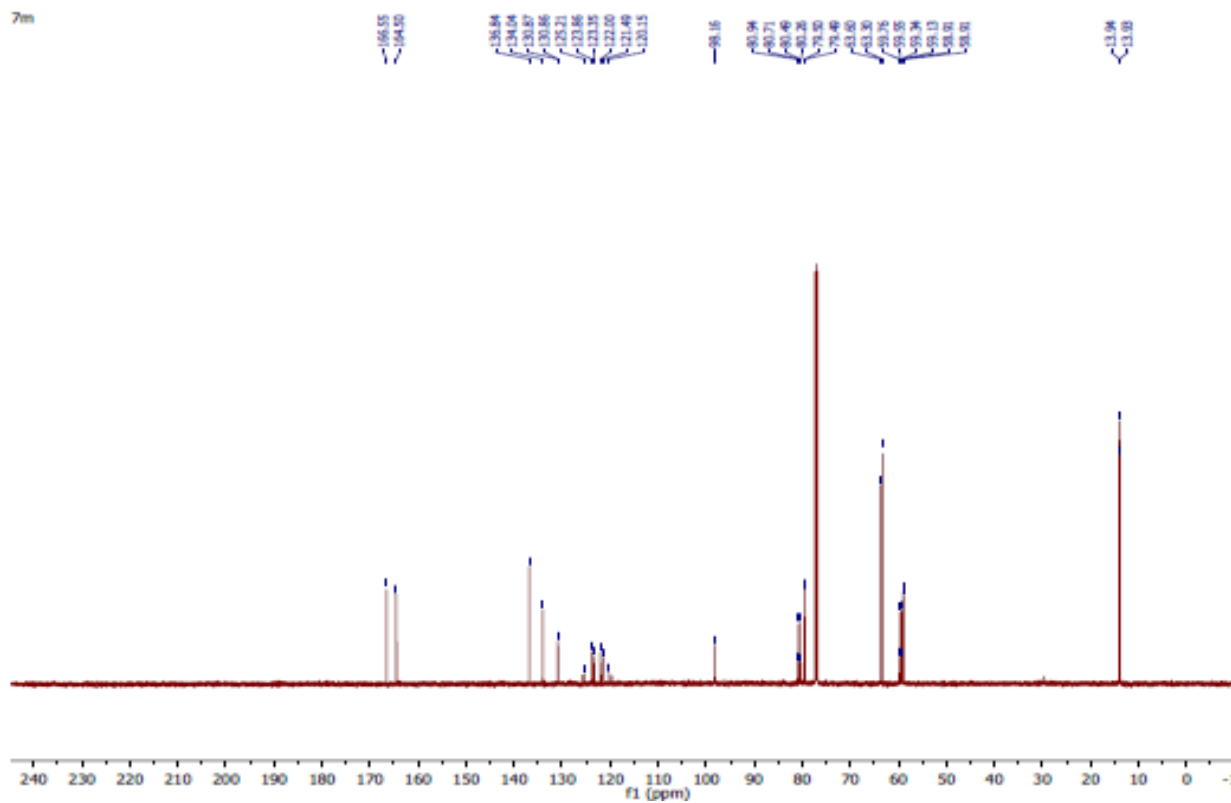
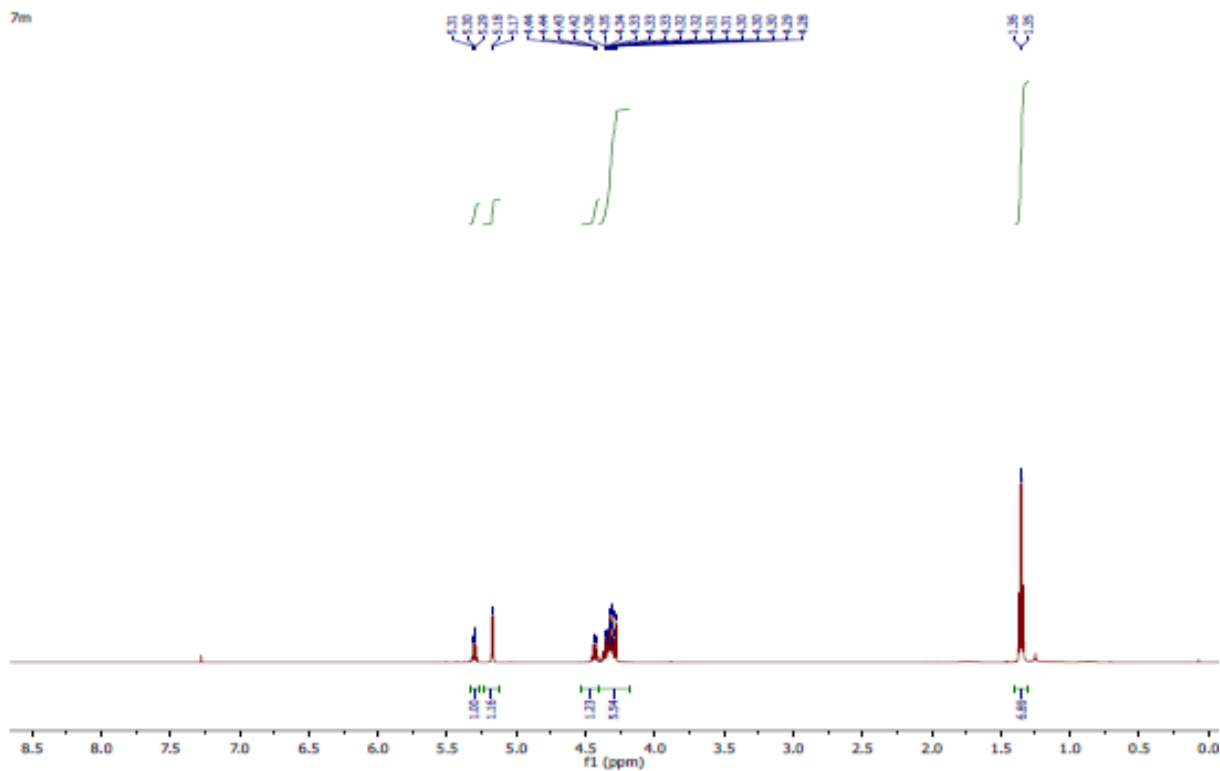
3-Bromo-isoxazolin-5-yl 4-(tert-butyl)benzoate (7j)



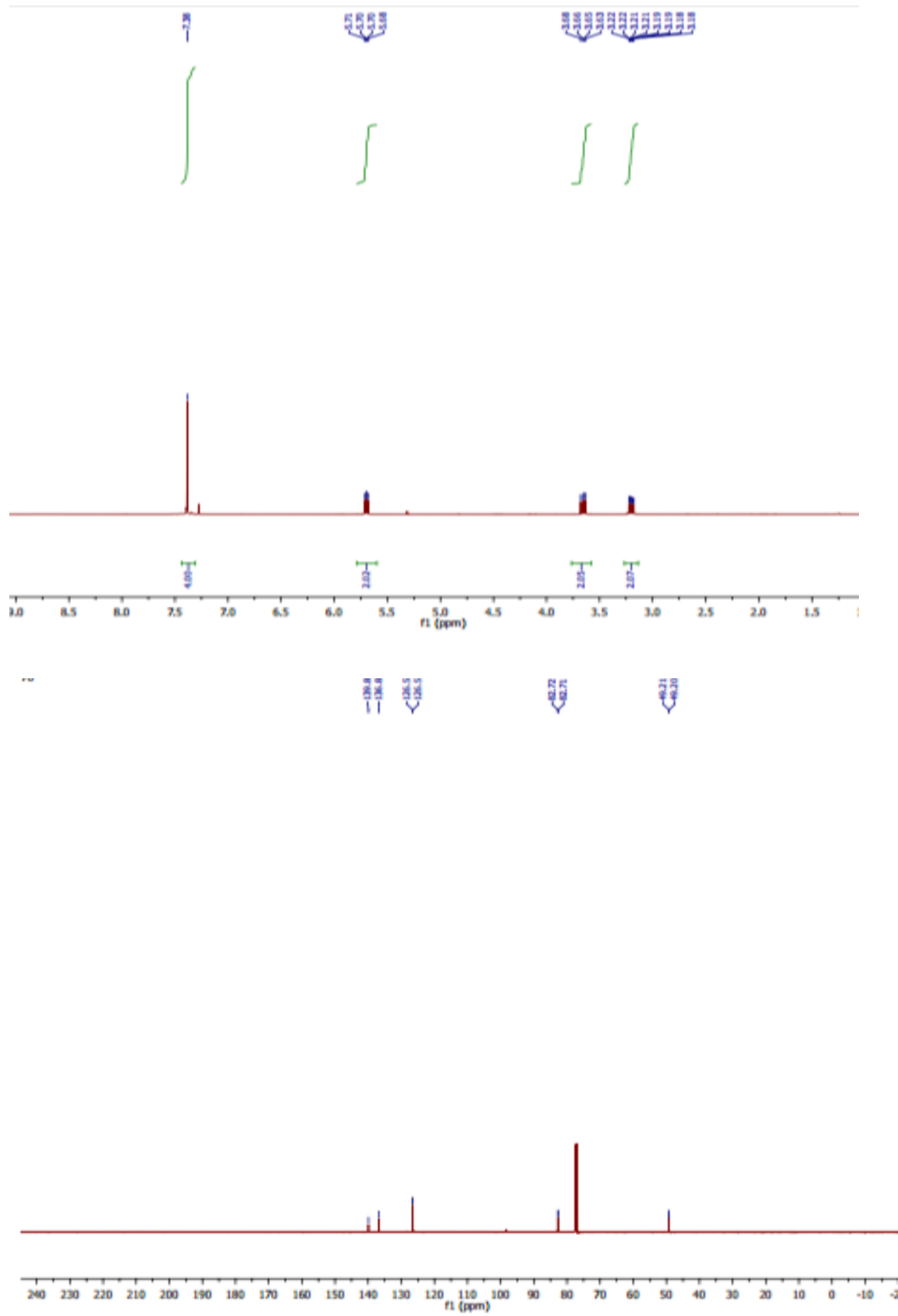
3-Bromo-3a,8b-dihydro-4H-indeno[2,1-d]isoxazole (7k)



Ethyl 3-bromo-5-(trifluoromethyl)-dihydroisoxazoline-4-carboxylate, ethyl 3-bromo-4-(trifluoromethyl)-dihydroisoxazoline-5-carboxylate (7m)



1,4-bis-(3-bromo-isoxazolin-5-yl)benzene (7n)



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