

Supporting Information

A Convergent Continuous Multistep Process for the Preparation of C₄-Oxime-Substituted Thiazoles

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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 Vapourtec R2+R4 system,¹ Vapourtec SF-10 peristaltic pump,¹ Knauer pumps,² and SyrDos syringe pumps.³

Unless stated otherwise, reagents were obtained from commercial sources and used without further purification. New compounds have been fully characterized.

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.

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}).

Batch reactions

Preparation of 9. KOH (4.9 kg, 89 mol, 1.16 eq.) was charged in water (50.0 kg) and stirred for 10-15 min at room temperature and then cooled to 0 °C. Ethyl acetoacetate (10.0 kg, 76.9 mol) was added dropwise over 2h. The resulting mixture was allowed to reach 25-30 °C and stirred for 12 h. It was then cooled to 10 °C, and the sodium nitrite (6.2 kg, 89.2 mol, 1.16 eq.) was added portionwise, over a period of 2h. An aqueous solution of sulfuric acid (2.6 L, 4.78 kg, 48.8 mol, 0.6 eq. in 10.0 kg water) was added over 2-3 h while maintaining the temperature at 0-5 °C. Upon completion of the addition, the resulting mixture was stirred for 1h at room temperature. The mixture was next extracted with ethyl acetate (4 x 18 kg). The combined organic layer was dried over sodium sulfate, filtered and the solvent was evaporated under reduced pressure to obtain the desired product **9** (6.69 kg, 99% yield *tel quel*).

Preparation of 10. Crude compound **9** (6.6kg, 76.8 mol) and water (12 L) were charged in to a clean and dry 250 L SSR and stirred for 10-15 min at RT, then cooled to 5-10 °C. To the batch, sodium hydroxide solution (3.3 kg, 84.5 mol) in water (12 L) was added drop wise for 1-2 h at 0-5 °C, followed by dimethylsulfate (12.59 kg, 99.99 mol) was added drop wise for 2h. After the addition was complete, the reaction mass was stirred for 20 h at 25-30 °C, reaction was monitored by GC. Reaction mass was extracted with dichloromethane (4x15 L), combined organic layer was dried over sodium sulphate, filtered and distilled to half of

original volume and taken as such to next stage (7.8 kg theoretical, 90% chemical yield; 90% pure by GC AUC).

Preparation of 7. In a 1L 3-necked flask with thermometer (equipped with a scrubber filled with aqueous $\text{NaHCO}_3/\text{NaS}_2\text{O}_3$) were charged compound **10** (396 mmol, 40g, 40.2 mL, 1 eq.), CH_3CN (360 mL) and MeOH (15.8 g, 20 mL, 1.25 eq.). The mixture was cooled to 0°C , and a solution of bromine (63.9 g, 20.0 mL, 1 eq.) in CH_3CN (80 mL) was added dropwise over 1h. A light exotherm was observed on mixing at $0-5^\circ\text{C}$. The solution evolved from red to brown) and was stirred further at $0-5^\circ\text{C}$ for 30 min (LC/MS controlled after 20min indicated a visible fallout). Aqueous saturated NaHCO_3 (350 mL) was added at $5-10^\circ\text{C}$. The mixture was extracted with EtOAc (1x300 mL and 2x200mL), washed saturated NaHCO_3 (1x100mL and 1x50mL), dried over Na_2SO_4 , filter and concentrated under moderate vacuum (no heating of rotavap bath). A redish oil (71.7g) was obtained.

The crude compound 3-bromo-2-oxopropanal *O*-methyl oxime **7** was distilled over a 2cm Vigreux column (oil bath temperature 85°C). Several fractions were collected:

Fraction 1: until $67^\circ\text{C}/5\text{mbar}$: 1.899g of a colorless oil 3-bromo-2-oxopropanal *O*-methyl oxime **7** in ca ~60% purity (3% recovered yield)

Oilbath temperature next set to 90°C

Fraction 2: $73^\circ\text{C}/5\text{mbar}$: 41.303g of a colorless oil: 3-bromo-2-oxopropanal *O*-methyl oxime **7** (52% yield, 89%purity containing 5% dibrominated compound E2)

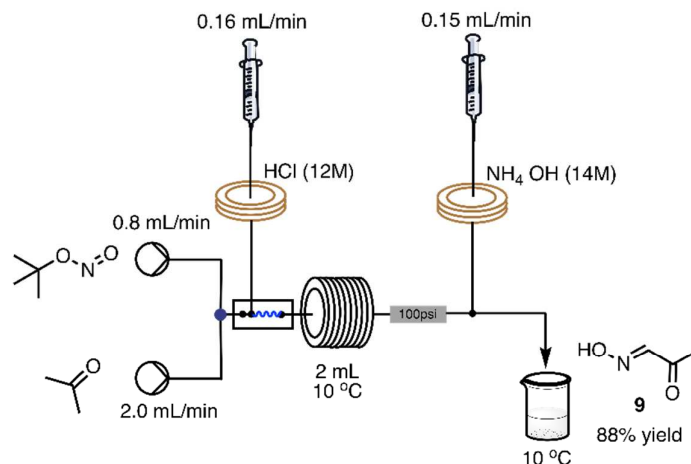
Oilbath temperature next set 100°C

Fraction 3: $73^\circ\text{C}/5\text{mbar}$: 4.129g of a colourless oil: 3-bromo-2-oxopropanal *O*-methyl oxime **7** (5% yield, ca 80% purity)

In the CO₂(s) cooled-condenser was collected 10.44g of a colourless liquid which turned out to mostly be EtOAc

Continuous flow reactions

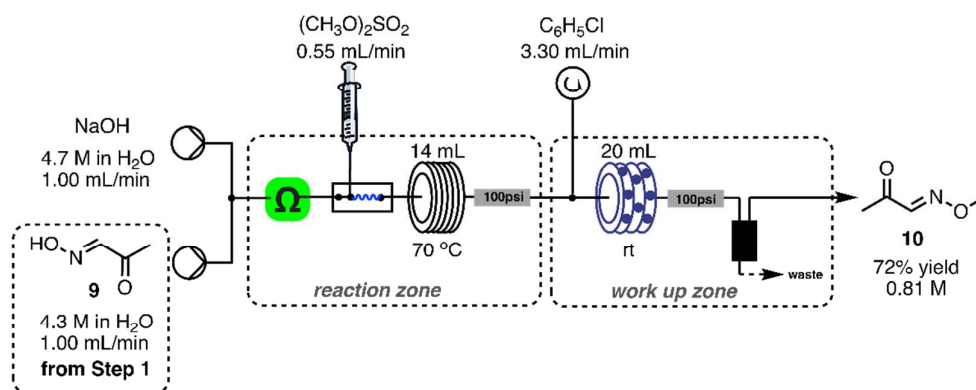
Step 1: synthesis of 2-oxapropanal oxime (9)



Scheme S1. Flow synthesis of **9**

Acetone (reagent grade) is pumped at 2.00 mL/min and combined⁴ with *tert*-butyl nitrite (neat),⁵ pumped at 0.8 mL/min, and the mixture mixed with HCl (12M aqueous solution, preloaded in a PFA loop, pumped at 0.16 mL/min) using an interdigital mixing unit.⁶ The reagents mixture was directed to a reactor coil (PFA, 1/16", 2 mL volume) kept at 10 °C and the output was then combined at a Y-piece with concentrated aqueous ammonia solution (14M aqueous solution, preloaded in a PFA loop and pumped at 0.15 mL/min). The solution was collected in a flask cooled at 10 °C, to obtain **9** in 88% yield (94% purity).

Step 2: synthesis of 3-methoxyimino propan-2-one (10)



Scheme S2. Flow synthesis of **10**

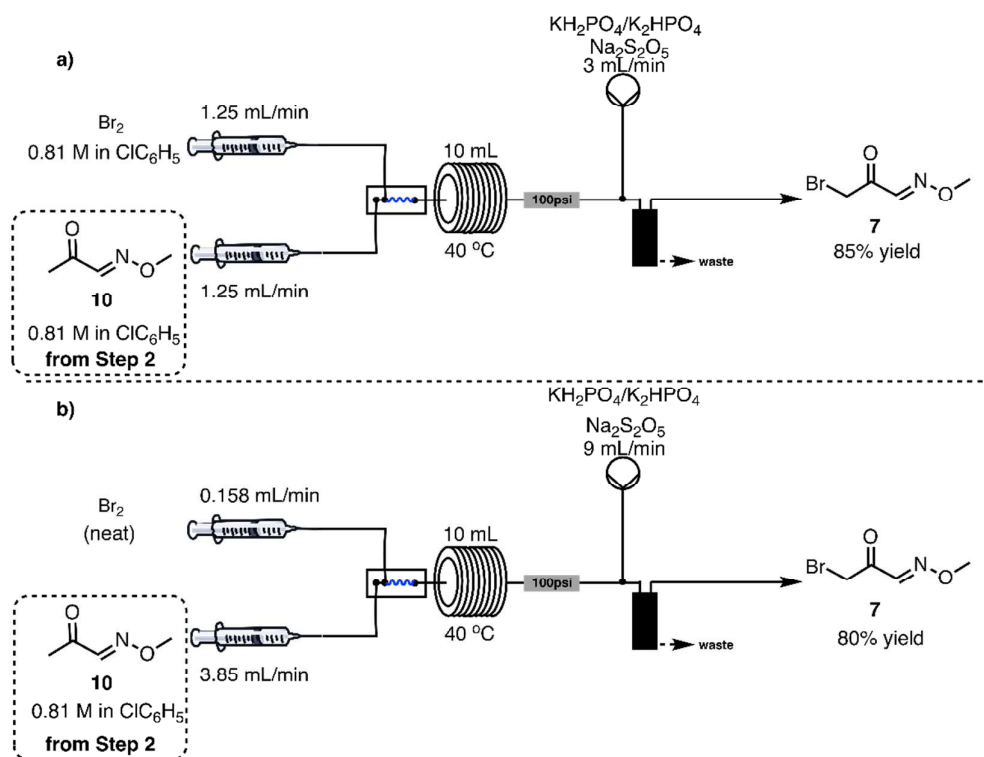
An aqueous solution of intermediate **9** (4.3 M) and an aqueous solution of NaOH (4.7 M) were pumped at 1.00 mL/min, each channel, and combined within a mixing element.⁴ The stream was passed through a conductivity cell,⁷ so as to monitor steady state, and merged within an interdigital mixer,⁶ with neat dimethyl sulfate pumped at a flow rate of 0.55 mL/min. The mixture was reacted further in a 14-mL reactor coil (PFA, 1/16" o.d.) at 70 °C, before reaching a mixing T-piece, where chlorobenzene was combined with the reaction stream to perform an extraction step. This operation was aided by the use of a “static mixer coil”.⁸ The reactor output was directed towards a liquid/liquid separator (Figure S1). The organic phase was analyzed *via* ¹H-NMR (against an internal standard, see SI) and indicated a 72.5% yield of intermediate **10** (0.81 M solution in PhCl).



Figure S1. Liquid/liquid separator

Step 3: synthesis of 1-bromo-3-methoxyimino propan-2-one (7)

Use of bromine solution: A 0.81 M solution of **10** in chlorobenzene (directly from step 2) was pumped at a flow rate of 1.25 mL/min and combined⁶ with a 0.81 M solution of Br₂ pumped at 1.25 mL/min, before reacting in a PFA coil reactor, heated at 40 °C. The reaction output was merged with an aqueous feed containing a phosphate buffer (2 M) and sodium bisulfite (0.5 M). A standard work-up of the reaction flow stream afforded **7** in 85% yield.

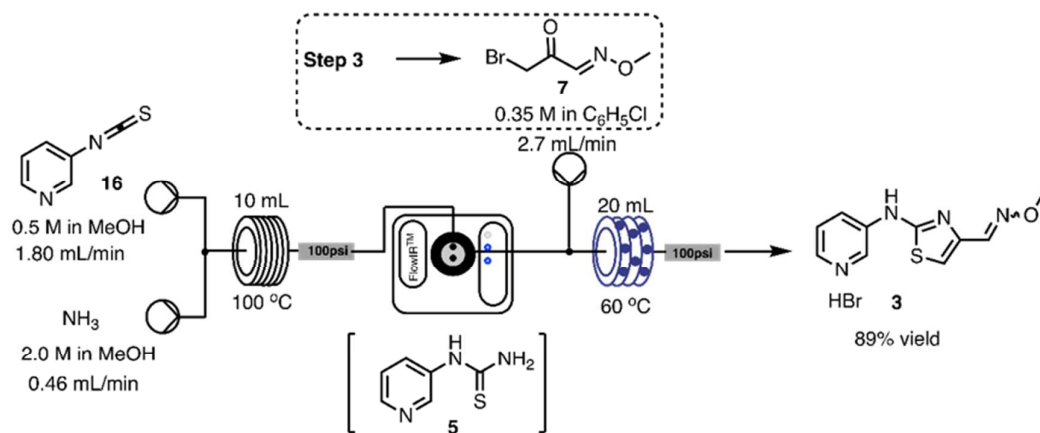


Scheme S3. Flow synthesis of **7**

Use of neat bromine: the solution of **10** (0.81 M) was delivered at 3.85 mL/min and combined⁴ using an interdigital mixer⁶ with neat Br₂, delivered at 0.158 mL/min. The resulting stream was next sent into a 10 mL reactor coil (PFA, 1/16' o.d.) heated at 40 °C (2.5 min residence time). The output was quenched in-line using the same technique described above and then analyzed. This afforded **7** in 80% yield, with a high degree selectivity (20:1).

Pleasingly, this intensified process produced an output of 149 mmol/h (26.9 g/h), equating to 3.59 mol/day (646 g/day).

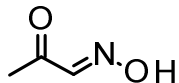
Step 4: synthesis of 2-(pyridin-3-ylamino)thiazole-4-carbaldehyde *O*-methyl oxime (3)



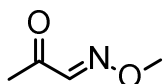
Scheme S4. Flow synthesis of **3**

A solution of isothiocyanate (0.5 M in MeOH) was combined with a concentrated solution of ammonia (2 M in MeOH) and reacted in a 10 mL reactor coil (PFA, 1/16" o.d., residence time 4 min 40 sec), heated at 100 °C, and then analyzed in-line with the use of an in-line IR system;⁹ the reactor output was then directed to a T-piece where the thiourea intermediate was combined with a stream of **7** (0.35 M in chlorobenzene, flow rate 2.7 mL/min) and further reacted in a 20 mL reactor⁸ (4 min residence time), heated at 60 °C, and the output collected to produce **3** (HBr salt) in 89% yield, as a mixture of isomers E/Z.

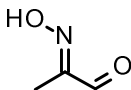
Characterization data



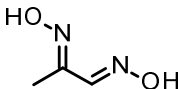
2-Oxapropanal oxime (9) Off-white solid (84%). Data match the one reported in the literature.⁹



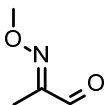
3-Methoxyimino propan-2-one (10) The material was characterized in solution. ¹H NMR (600 MHz, CDCl₃): δ 7.60 (s, 1H), 4.10 (s, 3H), 2.36 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃): δ 195.5, 147.9, 63.2, 25.3 ppm.



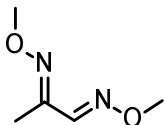
2-Hydroxyiminopropanal (11). We have never isolated this material in pure form. Matches data reported in the literature.¹⁰ ¹H NMR (400 MHz, CDCl₃): δ = 9.49 (s, 1 H), 7.57 (s, 1 H), 1.96 (s, 3 H) ppm



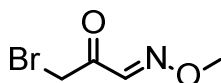
2-Hydroxyiminopropanal oxime (12). We have never isolated this material in pure form. ¹H NMR (400 MHz, DMSO-d₆): δ = 11.53 (s, 1 H), 11.42 (s, 1H), 7.63 (s, 1 H), 1.91 (s, 3 H) ppm.



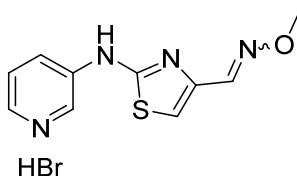
2-Methoxyiminopropanal (13). This compound was never isolated in pure form. ¹H NMR (400 MHz, CDCl₃): δ = 9.45 (s, 1 H), 4.14 (s, 3H), 1.89 (s, 3 H) ppm



Dimethoxypropane-1,2-diimine (14). ^1H NMR (400 MHz, CDCl_3); δ = 7.65 (s, 1 H), 3.93 (s, 3H), 3.95 (s, 3H), 1.97 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3); δ = 152.7, 147.2, 62.0, 61.0, 9.72 ppm.



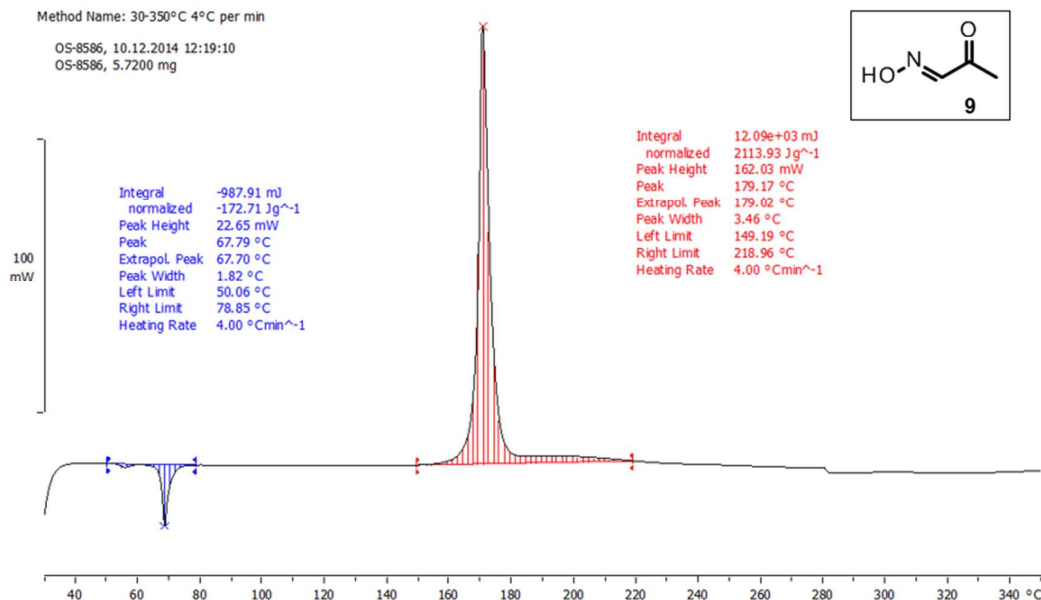
1-Bromo-3-methoxyimino propan-2-one (7) ^1H NMR (600 MHz, CDCl_3): δ 7.65 (s, 1H), 4.44 (s, 2H), 4.17 (s, 3H) ppm. ^{13}C NMR (151 MHz, CDCl_3): δ 188.4, 145.6, 63.8, 30.6 ppm. LC-MS: retention time 3.60 min, m/z $[\text{M}-\text{H}] = 178.8$.



2-(pyridin-3-ylamino)thiazole-4-carbaldehyde *O*-methyl oxime hydrobromic acid salt (3) ^1H NMR (600 MHz, CDCl_3): δ 11.49 (s broad, 1H), 9.32 (s, 1H), 8.45 (m, 2H), 7.77 (m, 2H), 7.58 (s, 1H), 3.38 (s, 3 H) ppm. HRMS for $\text{C}_{10}\text{H}_{11}\text{ON}_4\text{S}$ calculated 235.0640, found 235.0648; FT-IR, ν cm^{-1} : 2870, 1613, 1587, 1505, 1394, 1137, 1059, 784.

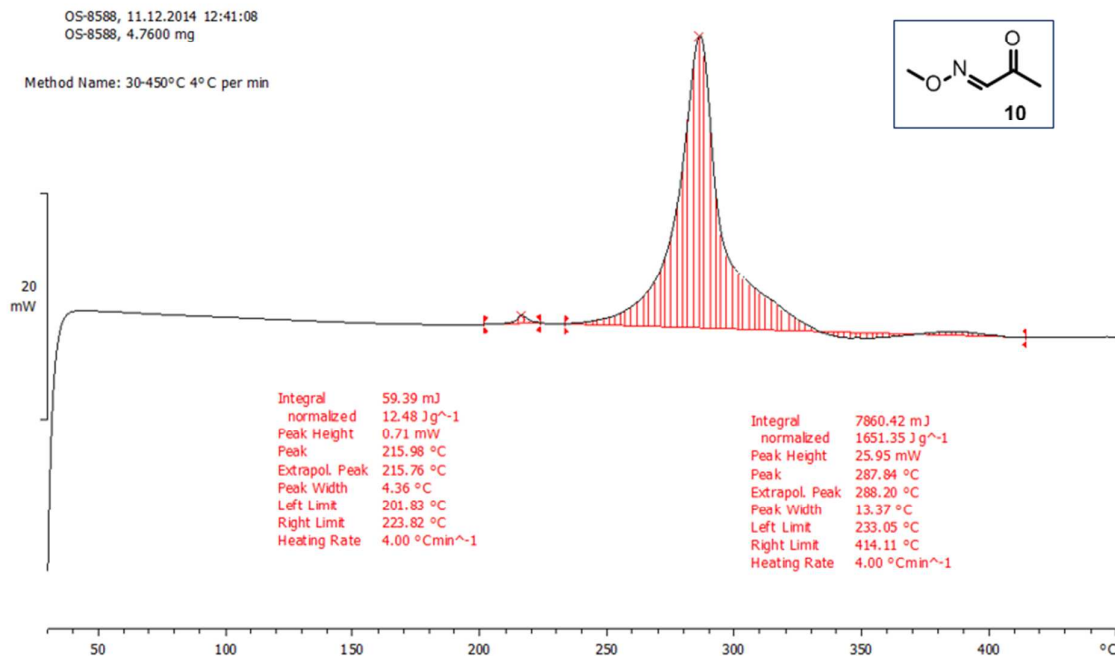
Differential Scanning Calorimetry

Intermediate 9



- An endotherm is present between 52°C and 80°C with heat of 173 J/g. The shape suggests that this is not a simple melt.
- Exothermic activity is apparent between 140°C and ca. 275°C with a heat output of ca. 2450 J/g which, under adiabatic conditions, has the potential to result in a temperature rise of > 1400 K. The shape of the exotherm is indicative of autocatalytic decomposition.
- The crucible became unsealed during the test which is a qualitative indicator of gas evolution.

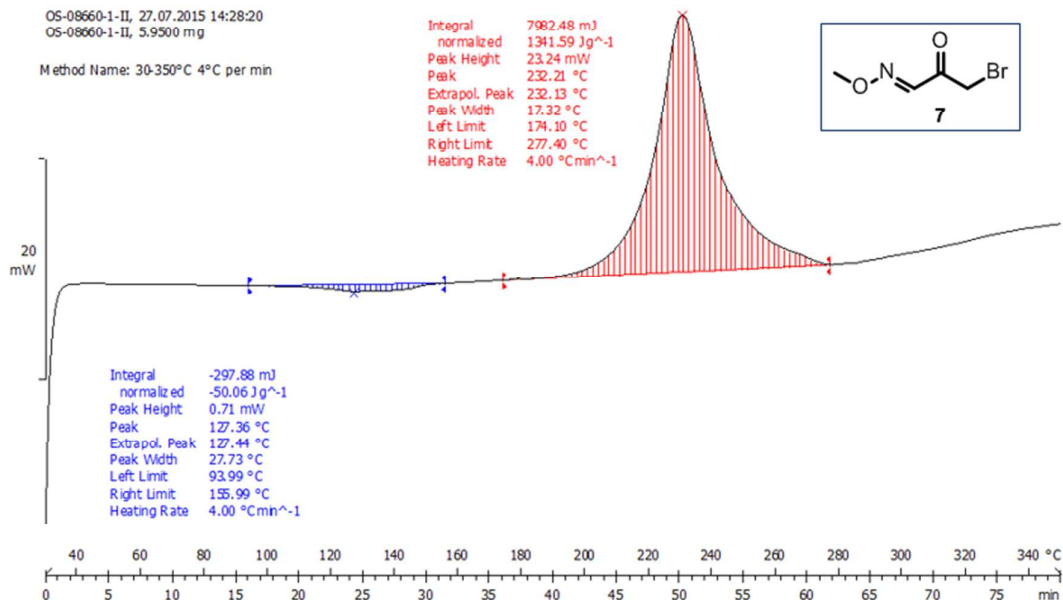
Intermediate 10



- Complex exothermic activity is apparent between 184°C and ca. 345°C with a heat output of ca. 1870 J/g which under adiabatic conditions has the potential to result in a temperature rise of > 1100 K. The exotherm is made up of a number of events the first of which peaks at 216°C and as this recovers it runs into a significant decomposition exotherm with a peak at 288°C as this subsides there is evidence of a third event around 316°C. There is further exothermicity apparent between 353°C and 409°C.
- The crucible became unsealed during the test which is a qualitative indicator of gas evolution.

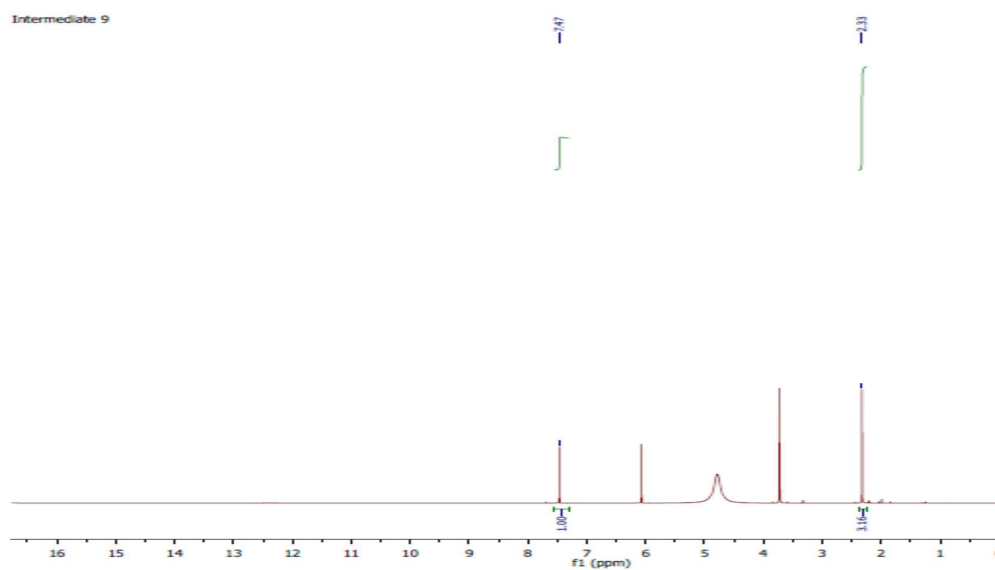
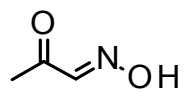
IMPORTANT NOTE ON SAFETY: upon attempting to distil **10** on a 70g scale, we observed a deflagration incident. The distillation was carried out at 200mbar and ~70°C bath temperature. As *ca.* 70% of the material had been successfully distilled out of the reaction flask, before the incident had occurred it seems unlikely that the thermal stability of **10** is the cause of the incident. Most likely cause of the incident is the unstable residues (possibly the accumulation and concentration of bis-oxime **14** within the residual pot) being subjected to prolonged heating at a temperature from which decomposition (both heat and gas evolving) was occurring. We strongly advise not to attempt batch distillation of crude **10**. Although our reported process has been demonstrated not to require any isolation of **10**, if such purification were required, we advise to perform a thin-film continuous distillation. We have proven this technique to be successful and incident-free. By reducing the length of time over which the material is exposed to elevated temperatures the potential for decomposition is dramatically reduced, typically of the order of <1 minute. Unstable residues (or products) quickly flow away from the heated surfaces and cool rapidly thus preventing decomposition. It should be noted that the risk of decomposition cannot be totally eliminated.

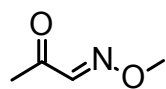
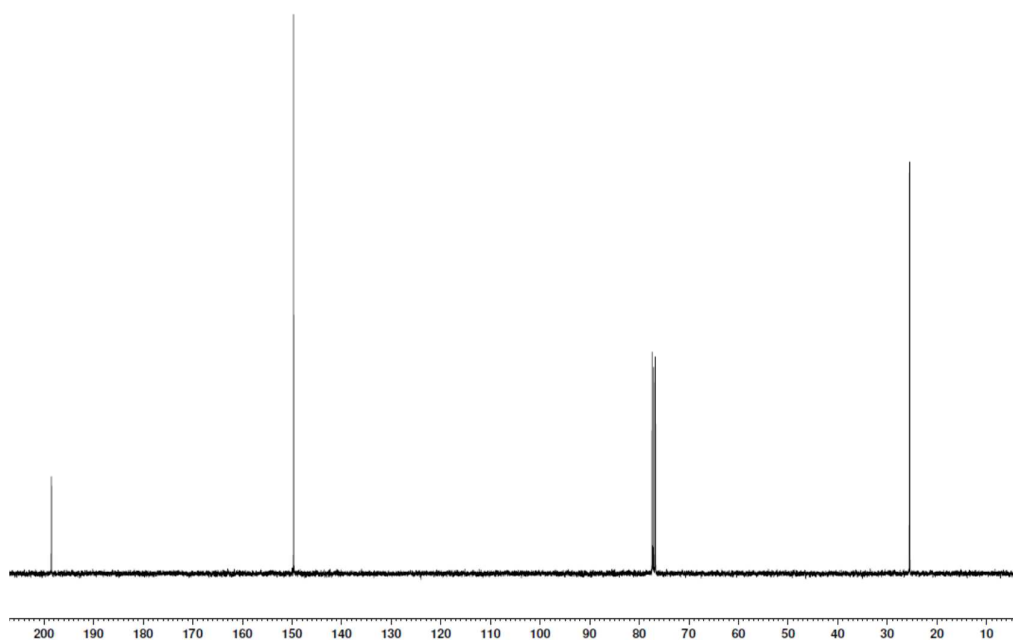
Intermediate 7



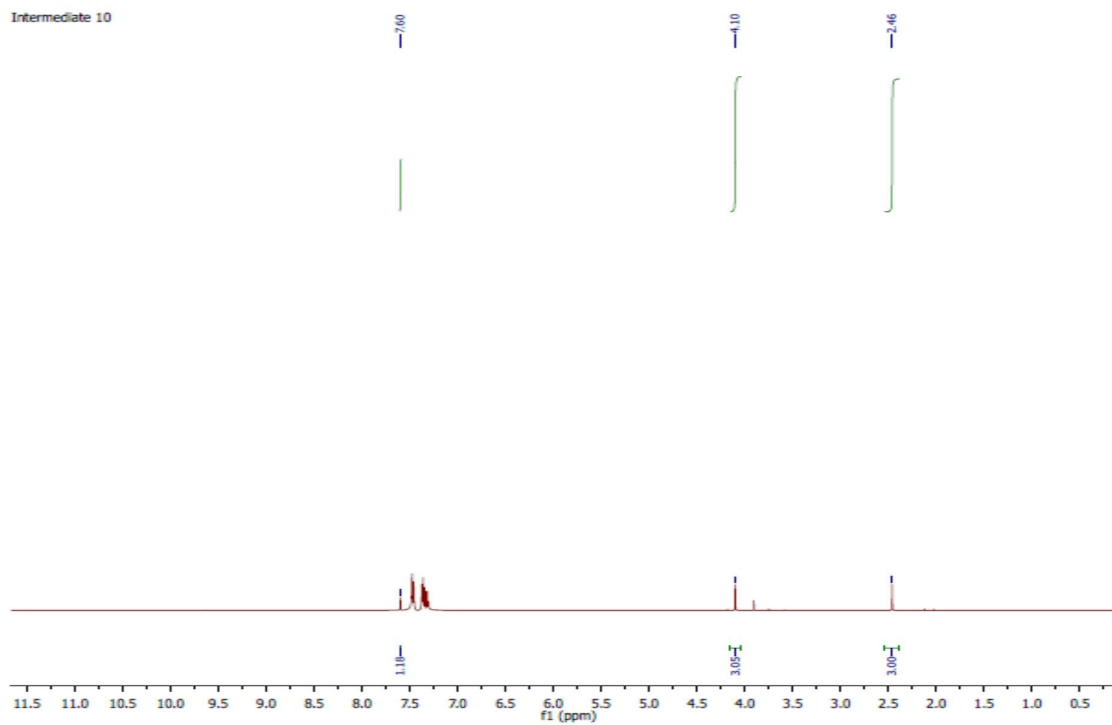
- A broad endotherm is apparent between 86°C and 158°C with heat of 56 J/g. The shape and magnitude suggests that this is not due to a simple melting process.
- Exothermic activity is apparent between 170°C and ca. 278°C with a heat output of ca. 1350 J/g which under adiabatic conditions has the potential to result in a temperature rise of > 800 K. The shape of the exotherm indicates that there are a number of thermal events occurring but the overall profile is indicative of an nth order process.
- The crucible became unsealed during the test (possibly around 180°C) which is a qualitative indicator of gas evolution.

^1H - and ^{13}C -NMR spectra

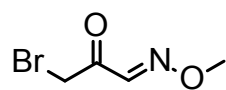
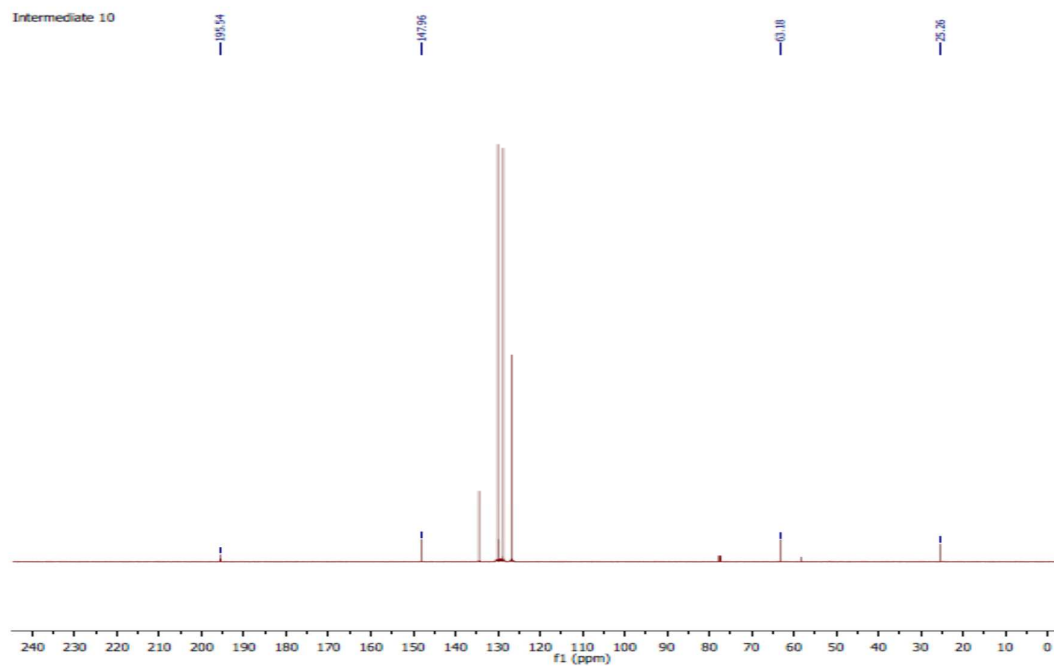




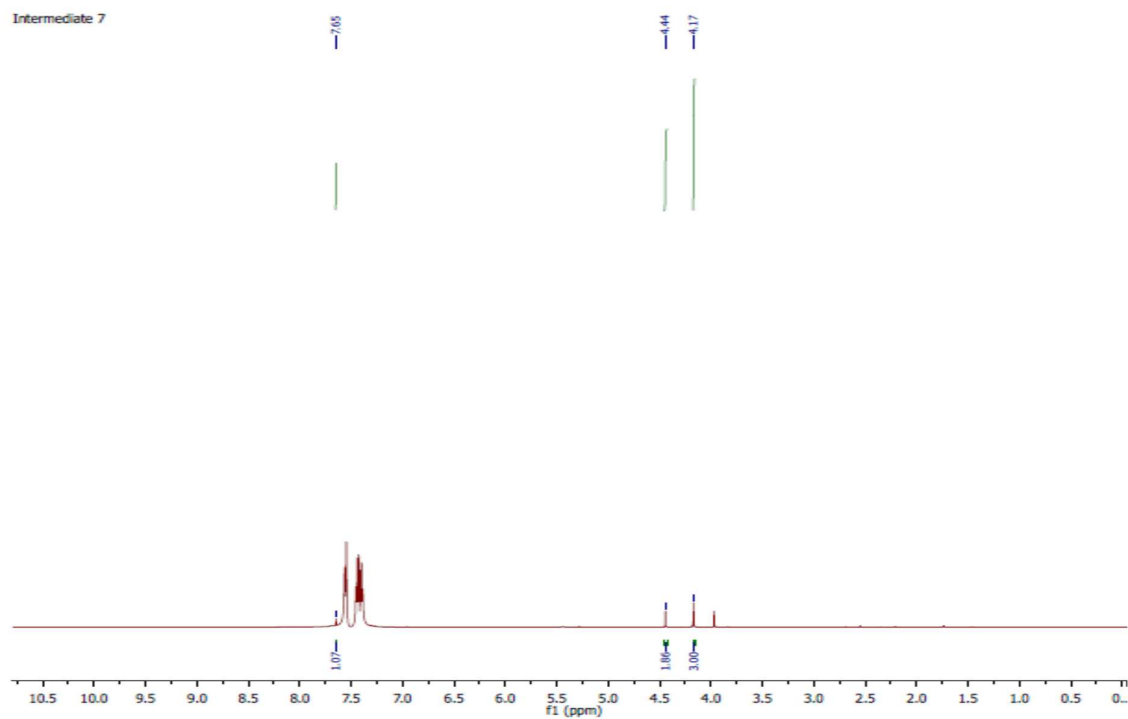
Intermediate 10

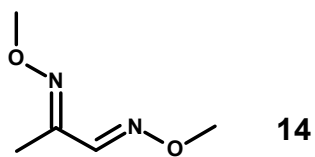
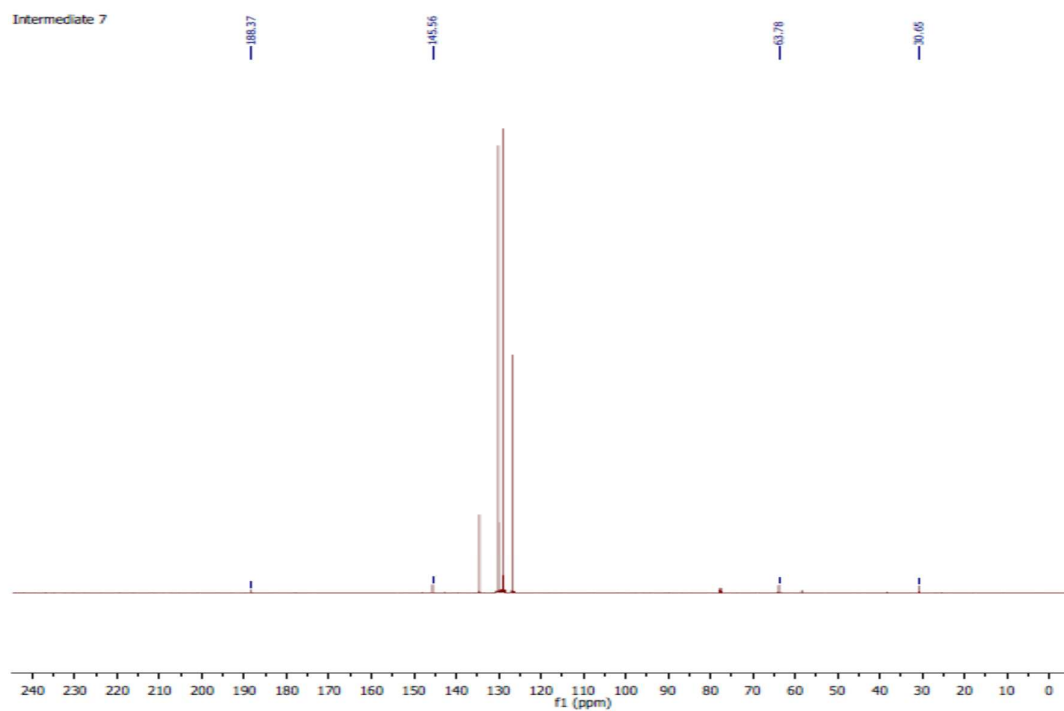


Intermediate 10

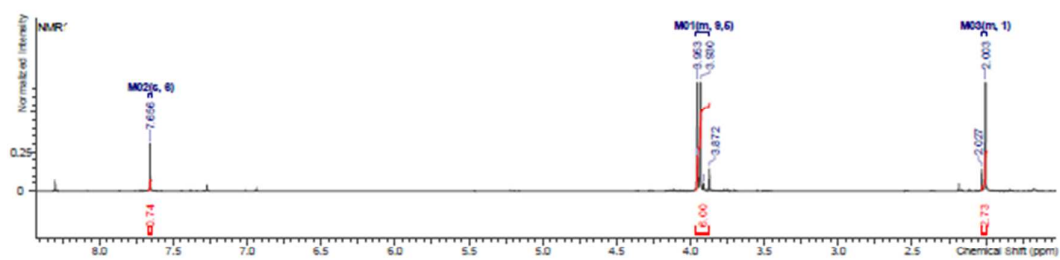


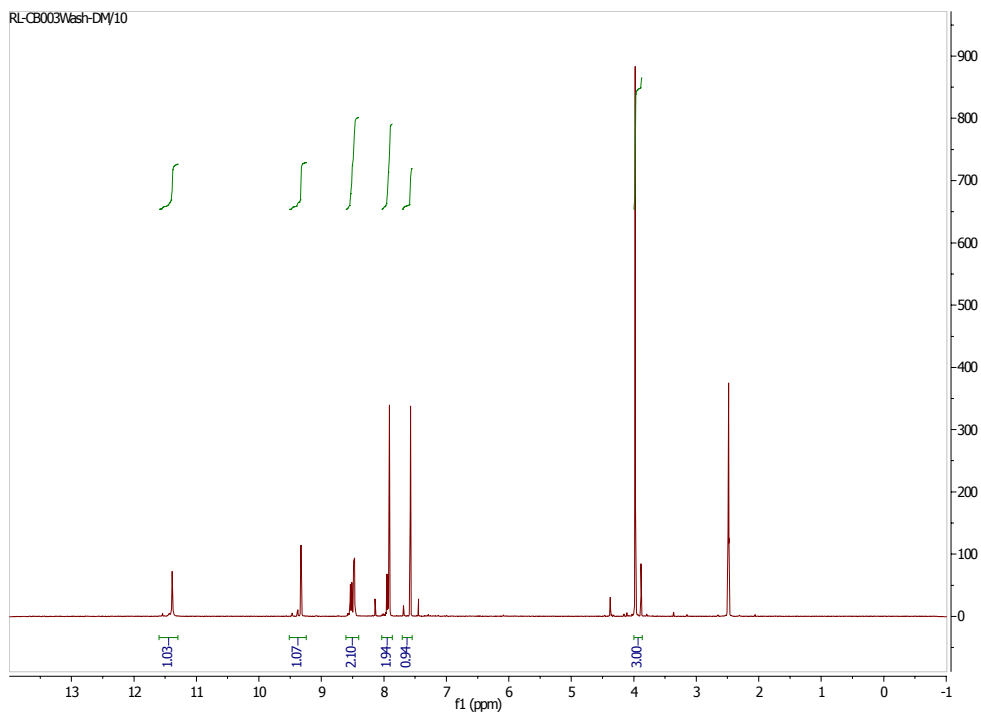
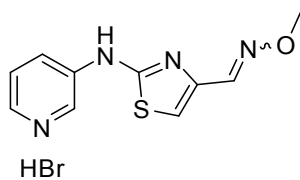
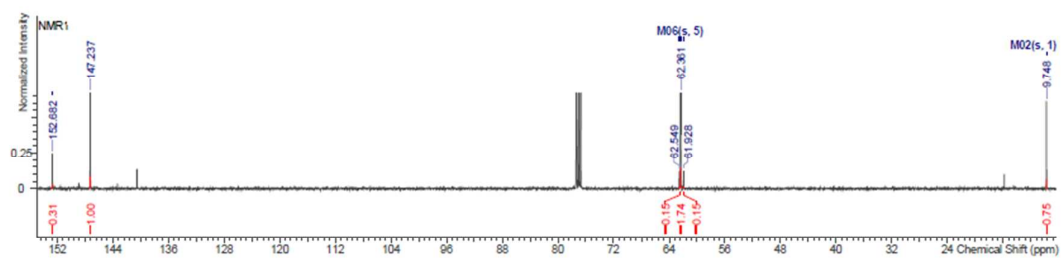
Intermediate 7



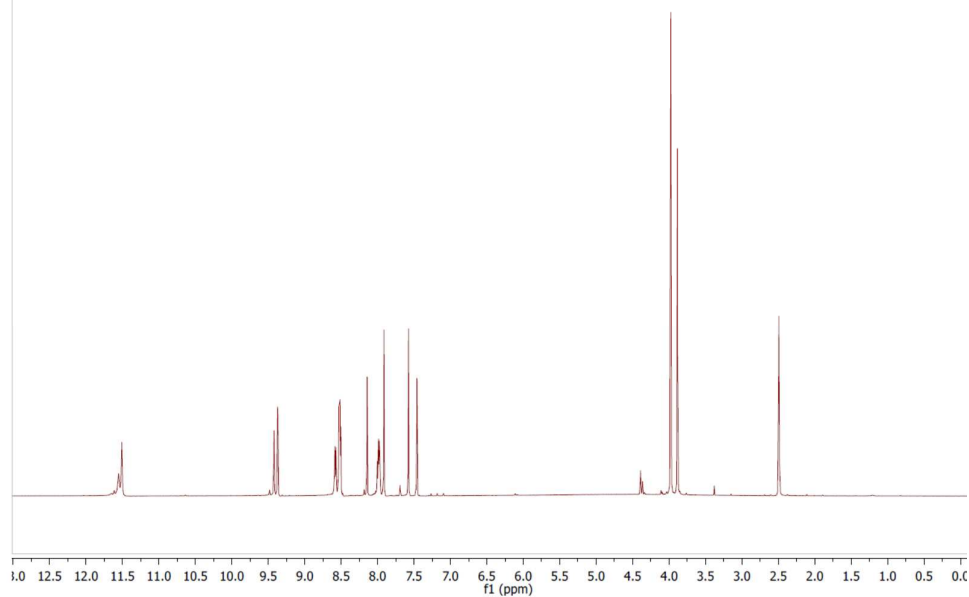


Byproduct 14

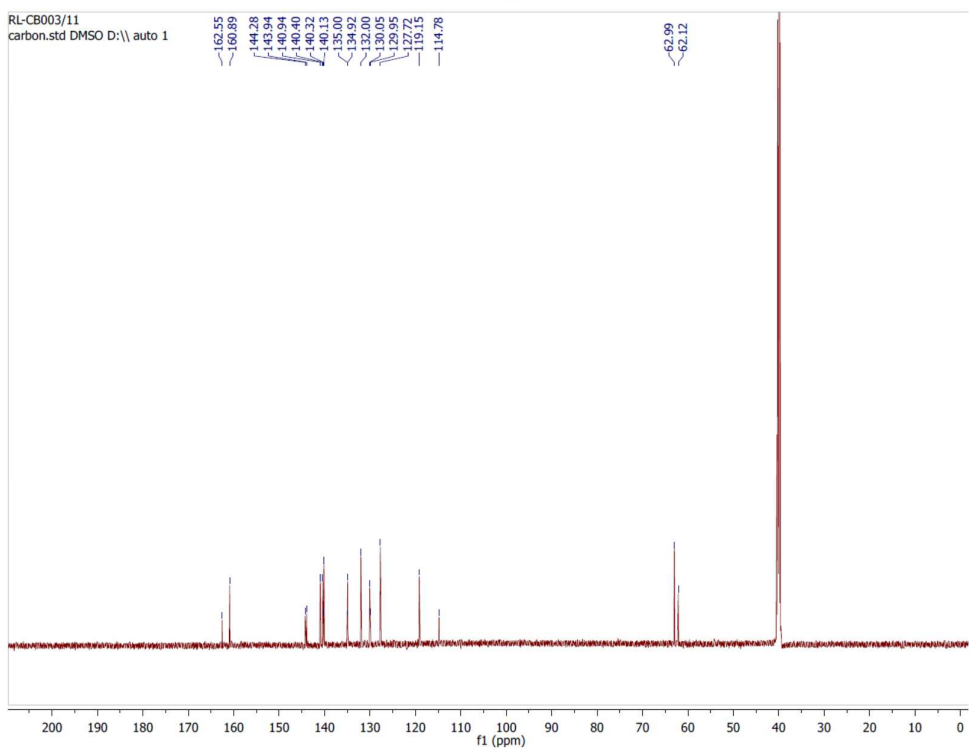


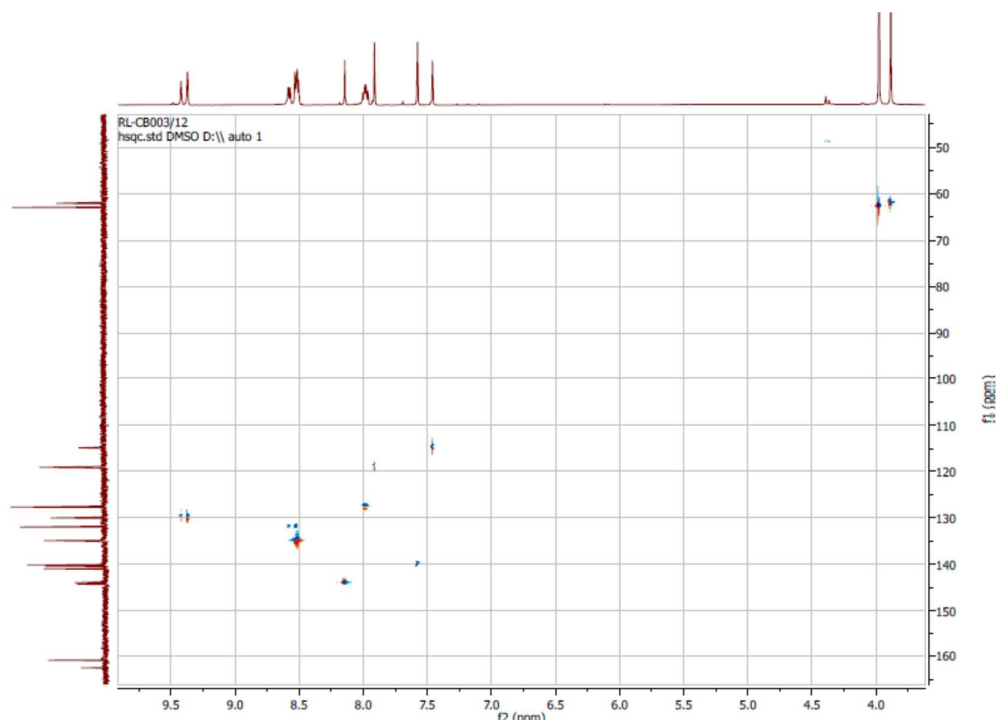


RI-CB003/10
proton2 DMSO D:\ auto 1



RI-CB003/11
carbon.std DMSO D:\ auto 1





References

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- ² <https://www.knauer.net/en/Systems-Solutions/Pumps>
- ³ <http://www.hitec-zang.de/>
- ⁴ We used a IMM mixer unit
- ⁵ Leis, J. R.; Pena, M. E.; Williams, D. L. H. *J. Chem. Soc., Chem. Comm.* **1987**, 2, 45-47; George R. Coraor, Woodbury, N. J. Process For Preparing Oximinoacetone. U.S. Patent 2,731,499, Jan 17, 1956
- ⁶ MMH-040T interdigital mixer purchased from Invenios Europe GmbH, now Corning
- ⁷ Mettler Toledohehe:
<https://www.mt.com/au/en/home/products/Process-Analytics/conductivity-sensor/conductivity-resistivity-cell-water.html>
- ⁸ Static mixer coil: <https://www.vapourtec.com/products/r-series-flow-chemistry-system-overview/>
- ⁹ Mettler Toldedo Flow IR
- ¹⁰ Baidya, M.; Yamamoto, H., *J.Am.Chem.Soc.* **2011**, 133, 13880-13882