Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

The electrochemical oxidation of a thioether to form an API intermediate and the effects of substrate electronics on impurity formation

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Supplementary information

Contents

1. General considerations

All starting materials were purchased from commercial sources and used without further purification, with the exception of **1a** which was produced during a manufacturing campaign to supply material for clinical trials.

NMR spectra were measured on either a Bruker Ultrashield AVIII spectrometer fitted with a QCI cryoprobe, operating with Topspin3.5pl5 software, with an operating frequency of 499.9 MHz for proton NMR and 125.7 MHz for 13C NMR or on a Bruker Ultrashield AVIII spectrometer fitted with a BBFO probe, operating with Topspin3.5pl5 software, with an operating frequency of 400.1 MHz for proton NMR and 100.6 MHz for 13C NMR. Chemical shifts (δ) are expressed in ppm downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively.

UPLC-MS analyses were carried out on a Waters UPLC-MS machine using a C18 column. A mobile phase of decreasingly polar mixtures of acetonitrile in water, where either ammonium acetate or trifluoroacetic acid were employed as modifiers.

Silica chromatography was conducted using pre-packed silica columns (12 g) and materials were purified using a Teledyne-Isco® Combiflash RF+. Fractions in silica chromatography were collected based on UV absorbance.

2. Batch studies

2.1. General considerations for batch electrochemistry

The IKA electrasyn was used for all batch electrochemistry. All electrodes were purchased from IKA, apart from the RuO_2 on titanium electrodes (6-12 µm thick coating), which were purchased from Shaanxi Yunzhong Metal Technology Company (Shaanxi, China). All the electrodes used in batch had dimensions of 52x8x2 mm. Electrodes were cleaned by wiping with acetone, followed by dilute HCl, water and then acetone before being left to air dry. Reactions were analysed by removing 50 µL samples, diluting with diluent (1 mL, 1:1 mixture of acetonitrile and water) and analysing *via* UPLC-MS with 2.0 µL injections to obtain the area% of reaction components.

2.2. Reaction monitoring

A 10 mL electrasyn vial was charged with Bu_4NPF_6 (0.201 g, 0.508 mmol) and **1a** (0.142 g, 0.504 mmol). Acetonitrile (7.20 mL) and aqueous HCl (0.1 M, 1.2 mL) were added to the vial and stirred until all of the solid had dissolved. RuO_2 electrodes were used to apply 4.0 V. Samples (50 µL) were removed every 10 minutes and analysed *via* UPLC. The current was noted throughout the reaction and used to calculate the electron equivalents applied at each time point.

Entry	Component	Retention time (min)
1	**1a**	3.088
2	**1b**	2.262
3	**1c**	2.628
4	**1d**	2.453

Table 2.1: Retention times for reaction components.

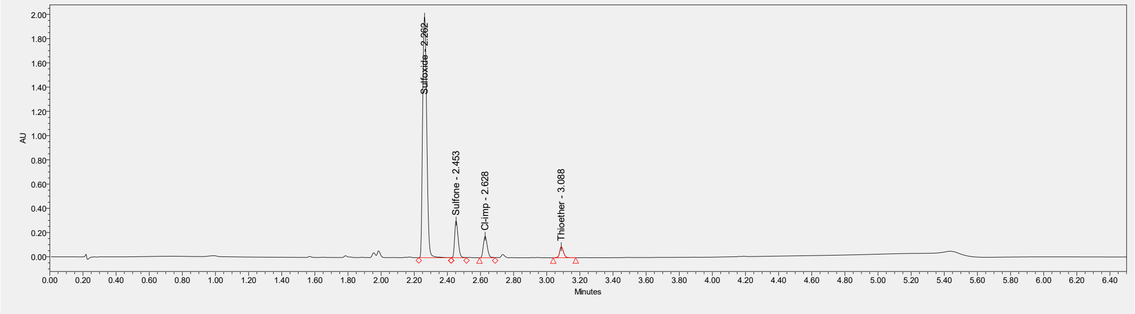


Figure 2.1: Typical chromatogram obtained using UPLC (specifically entry 4 from Table 2.2).

Entry	Time (min)	Potential (V)	Current (mA)	F mol-1	Area%			
					1a	**1b**	**1c**	**1d**
1	0	4.0	0	0	91.33	4.08	0.20	0.08
2	10	4.0	65	0.89	62.19	31.39	1.57	1.03
3	20	4.0	64	1.60	32.76	57.19	3.50	2.6
4	30	4.0	59	2.34	3.22	74.79	9.65	6.45
5	40	4.0	52	2.98	0.86	54.04	21.54	13.12
6	50	4.0	46	3.56	1.82	34.91	31.57	18.44
7	60	4.0	38	4.03	2.50	24.3	37.70	21.38
8	70	4.0	35	4.50	3.31	14.98	42.31	23.8

Table 2.2: Samples taken over the course of a batch experiment.

2.3. Substrate scope

10 mL electrasyn vials were charged with a thioether (0.50 mmol) and Bu_4NPF_6 (196 mg, 0.50 mmol). Aqueous HCl (0.1 M, 1.2 mL) and acetonitrile (7.2 mL) were added. RuO_2 electrodes were used to apply 4.0 V for 4.0 F mol^{-1}. Samples (50 µL) were removed at the end of the reactions and analysed *via* UPLC-MS. Different analytical methods were required in some instances, as summarised in Table 2.3. Different columns were used with a mobile phase of decreasingly polar mixtures of acetonitrile or methanol in water, different modifiers were employed.

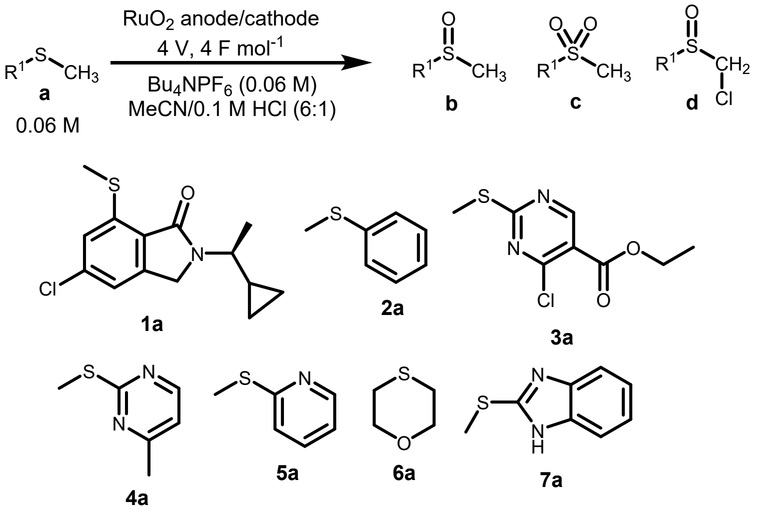


Figure 2.2: Conditions substrates for the substrate scope.

Entry	Substrate	Area% a	b	c	d	Column and method
1	**1a**	1.97	36.6	35.59	16.57	BEHC18_ACN_TFA_C8
2	**2a**	0.56	10.89	76.6	6.61	BEHC18_ACN_TFA_C8
3	**3a**	0.69	18.66	59.68	0	BEHC18_ACN_TFA_C8
4	**4a**	4.82	8.04	83.08	0	BEHC18_ACN_AmAC_C8
5	**5a**	1.28	6.39	90.1	1.43	BEHRP18_ACN_Am_C8
6	**6a**	0	65.74	0	10.27	BEHC18_MeOH_Am_C5
7	**7a**	5.91	69.94	16.62	2.49	ACEESC18_ACN_Am_C8

Table 2.3: Area% of reaction components after 4.0 F mol^{-1} for different substrates.

3. Mechanistic studies

3.1. Predicted chemical shifts

Chemical shifts of the methyl groups were predicted using ACD CNMR predictor for the proposed sulfoxide intermediates.

Entry	**Sulfoxide**	δ C13 CH3 (ppm)
1	**1b**	44.1
2	**2b**	43.9
3	**3b**	40.1
4	**4b**	39.0
5	**5b**	39.7
6	**6b**	46.2
7	**7b**	42.6

Table 3.1: Chemical shifts for the methyl groups of sulfoxides.

3.2. Calculating bond dissociation energies

The bond dissosiation energies for C-H bonds were calculated using AutoOX, an automated tool at AstraZeneca. This tool uses the B3LYP method to obtian the hydrogen abstraction energies. Details can found in the original publication (*Journal of Pharmaceutical Sciences*, 2014, **103**, 1949-1955).[1]

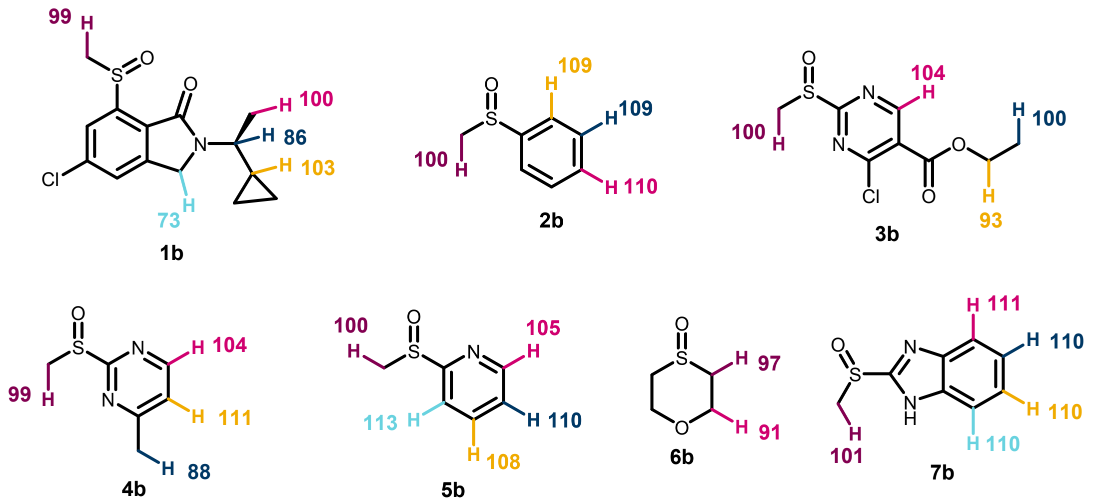


Figure 3.1: Bond dissociation energies of proposed sulfoxide intermediates. Values are given in kcal mol^{-1} and the five lowest energies are shown.

3.3. Different chlorinating species

Three electrasyn vials were charged with **1a** (0.50 mmol) and Bu_4NPF_6 (0.50 mmol). HCl (0.1 M, 1.2 mL) and MeCN (7.2 mL) were added. RuO_2 electrodes were used to apply a constant potential of 4.0 V to each of the vials for 2.0 F mol^{-1}. After 2 F mol^{-1} had elapsed samples were taken from each vial for analysis *via* UPLC (t = 0 hours).

One of three chlorine containing species (2.0 equivalents) was added to each vial. The three vials were stirred for 1 hour before being resampled.

Entry	Additive	Time (h)	Area%			
			1d	1a	1b	1c
1	HCl	0	3.84	20.86	63.23	6.17
2	HCl	1	3.77	20.54	62.75	6.21
3	OCl	0	3.75	21.07	63.24	5.97
4	OCl	1	10.6	1.52	29.14	40.78
5	NCS	0	4.01	20.53	62.49	6.8
6	NCS	1	5.92	0.45	70.27	12.59

Table 3.2: Area% obtained *via* UPLC after electrolysing the reaction of 2.0 F mol^{-1} (t = 0) and adding a chlorine source and stirring (t = 1)

4. Continuous studies

4.1. General considerations for continuous electrochemical reactions

Reactions were conducted in flow using the VapourTec Ion Electrochemical reactor with RuO_2 on titanium electrodes (6-12 µm thick coating), which were purchased from Shaanxi Yunzhong Metal Technology Company (Shaanxi, China) and a flow channel (called a membrane by VapourTec) 0.5 mm thick from VapourTec (Figure 4.1). The Ion Electrochemical reaction controller, from VapourTec, was used as a power supply and the VapourTec E-series, with the VapourTec V-3 pumps, was used to pump reaction solutions through the electrochemical reactor. 1/16” tubing was used to join the pumps to the electrochemical reactor. Electrodes were cleaned by wiping with acetone, followed by dilute HCl, water and then acetone before being left to air dry.

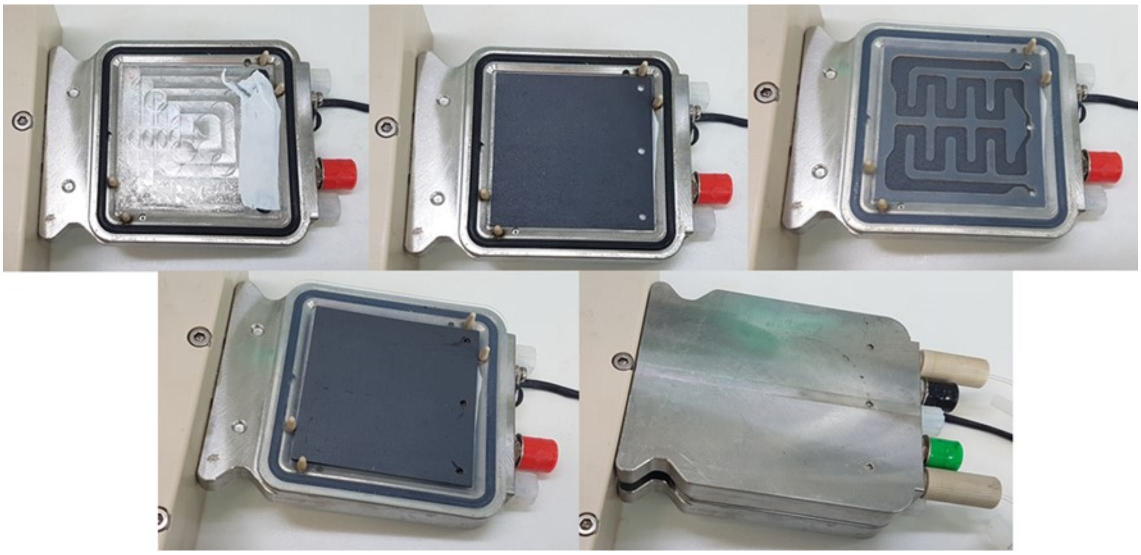
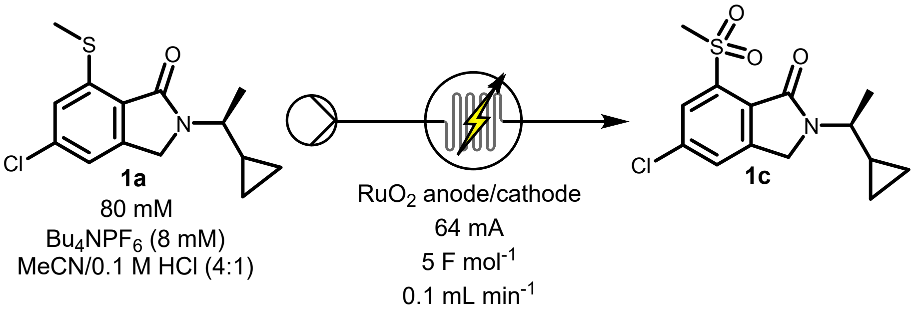


Figure 4.1: Assembling the VapourTec Ion electrochemical reactor (left to right). PTFE applied to the bottom plate to ensure that the steel housing doesn't come into contact with the reaction solution. Electrode is placed onto the bottom steel plate, the flow channel is placed on top of this, followed by the second electrode and finally the top steel plate.

All of the flow reactions were conducted in a recirculating set-up. A three necked round bottom flask was charged with the reaction solution and agitated with a magentic stir bar. The headspace was continually flushed with nitrogen gas to dilute any hydrogen produced during the reaction. An outlet drew solution from the round bottom flask and through the VapourTec pump, before passing it through the Ion electrochemical reactor, where it was electrolysed with two RuO_2 on titanium electrodes. The solution was then returned to the round bottom flask through another piece of tubing. No back presure was applied to the reactor. The reaction was run for enough time to deliver the desired electron equivalents at the applied current. Reactions were analysed by removing 50 µL samples, diluting with diluent (1 mL, 1:1 mixture of acetonitrile and water) and analysing *via* UPLC-MS with 1.2 µL injections to obtain areas of the reaction components. From this the yield of **1c** was calculated against the area of a sample with a known concentration that was run at the same time.

4.2. Single pass electrolysis

The first flow experiments were conducted in a single pass. As the inter-electrode distance was much smaller in the Vapourtec Ion, when compared to the IKA electrasyn, the amount of electrolyte was reduced to 0.1 equivalents. The reaction solution was pumped through the reactor at 0.1 mL min^{-1}, while a current of 64 mA was applied using RuO_2 electrodes (Figure 4.2). 2 residence times were allowed to elapse before a sample was collected for 1 residence time and analysed *via* UPLC (Table 4.1). The reaction did not proceed as far as in batch, with large amounts of starting material left. A lower flow rate or higher current would be required progress the reaction further. Large amounts of gas were also observed, making it challenging to know how many electron equivalents had been applied and the precise residence time. This may have contributed to the lack of progression observed. With these considerations in mind it was decided to swap to a recirculating flow set up.



1a

80 mM

Bu_4NPF_6 (8 mM)

MeCN/0.1 M HCl (4:1)

RuO_2 anode/cathode

64 mA

5 F mol^{-1}

0.1 mL min^{-1}

1c

Figure 4.2: Reaction conditions for electrolysis in a single pass.

Component	Area%
1a	24.2
1b	14.0
1c	14.7
1d	6.4

Table 4.1: Area% *via* UPLC for the single pass reaction.

4.3. Calculating electron equivalents and time

Time, electron equivalents and current can be related to each other using Equation 4.1.[2] This was used to calculate the time required to process different amounts of material when using different current densities.

$$t = \frac{n\,F\,N}{I}$$

Equation 4.1: Equation relating time, current and electron equivalents. Where *t* is time (s), *n* is the number of electrons transferred per molecule of starting material, *F* is Faraday's constant (C mol^{-1}), *N* is the amount of starting material (mol) and *I* is the current (A).

Entry	Units	Value
Amount of **1a**	mol	0.040
Mass of **1a**	g	11.3
Number of electrons transferred		6
Faraday's constant	C mol^{-1}	96485
Current	mA	64
Time	s	361818
	days	4.19
Throughput (assuming 50% yield)	mg h^{-1}	59.7

Table 4.2: Calculated time and throughput for an 11 g reaction conducted at 64 mA.

4.4. Screening conditions

Prior to a DoE a screen of conditions was conducted (Figure 4.3). The results are sumarised in Table 4.3.

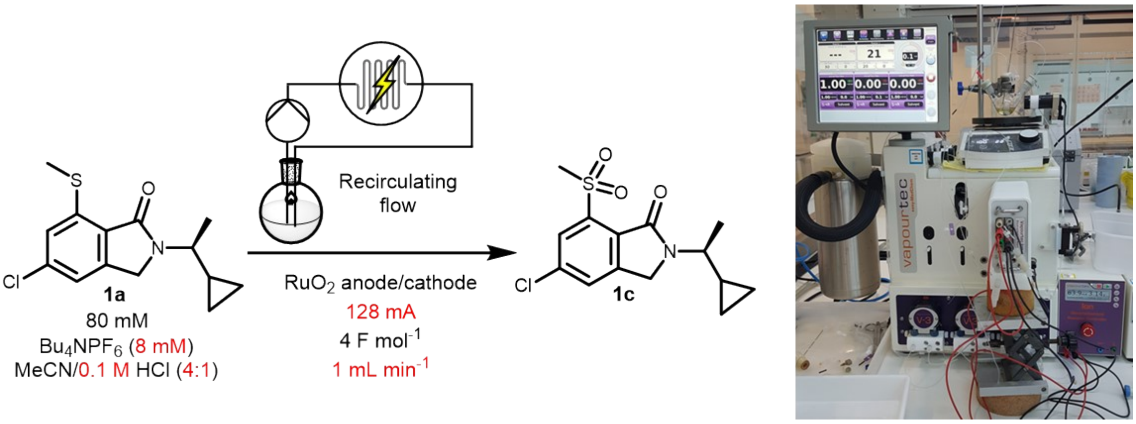


Figure 4.3: Left - the standard reaction conditions for the screening reactions with the variables that were changed highlighted in red. Right - picture of the reaction set up.

Entry	Reaction	1a conc. (mM)	Bu_4NPF_6 (mM)	MeCN/ water	Acid (equiv.)	Current (mA)	Flow rate (mL min-1)	Electrodes	F mol-1	Time (min)	UPLC Areas			
											1a	1b	1c	1d
1	Standard conditions	80	8	4	0.25	128	1	Ru/Ru	4	40	414352	1462578	2321459	1138814
2	Low current	80	8	4	0.25	64	1	Ru/Ru	4	80	147075	1438434	1854235	773218
3	High current	80	8	4	0.25	256	1	Ru/Ru	4	20	1269977	1717432	1605327	842877
4	High flow rate	80	8	4	0.25	128	4	Ru/Ru	4	40	69525	1413153	2170988	1116415
5	Low flow rate	80	8	4	0.25	128	0.25	Ru/Ru	4	40	2481131	821755	1539939	780935
6	High [acid]	80	8	4	0.5	128	1	Ru/Ru	4	40	226431	1074466	2057935	1335792
7	High [electrolyte]	80	80	4	0.25	128	1	Ru/Ru	4	40	613965	1870451	1707223	932227

Table 4.3: Summary of reaction conditions screened in flow. Deviations from the standard conditions are highlighted in yellow.

4.5. Design of experiments

A 3-factor full factoral DoE was performed using MODDE. The factors chosen were flow rate, current and electron equivalents. The yield and throughput were used as the responses (Table 4.4). Reactions were analysed by removing 50 µL samples, diluting with diluent (1 mL, 1:1 mixture of acetonitrile and water) and analysed *via* UPLC-MS with 1.2 µL injections to obtain areas of the reaction components. From this the yield of **1c** were calculated against the area of a sample with a known concentration run at the same time.

Entry	Parameter	Units	Low	High
1	Current	mA	64	264
2	Flow rate	mL min^{-1}	0.5	8
3	Electron equivalents	F mol^{-1}	4	6

Table 4.4: Parameters varied during the DoE.

A 100 mL volumetric flask was charged with **1a** (2.24 g, 7.96 mmol) and Bu_4NPF_6 (314 mg, 0.79 mmol). Aqueous HCl (20 mL, 0.1 M) and acetonitrile (80 mL) was added and the solution stirred. The experiments were conducted on a 0.2 g scale, charging the stock solution (10 mL) to a three necked round bottom flask, in a recirculating fashion with the flow rate and current varried, while sampling at different electron equivalents (Figure 4.4). The results are summarised in Table 4.5.

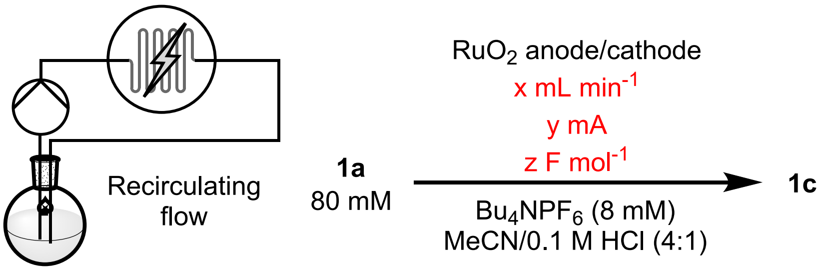


Figure 4.4: Reaction set up for the DoE, varying the flow rate, current and electron equivalents.

The optimiser tool in MODDE was used to find the predicted optimum conditions for maximising the yield and throughput, with a minimum 50% yield and 150 mg h^{-1}. The yield was given a weighting of 1 and the throughput a weighting of 0.2. These gave predicted conditions of 8.0 mL min^{-1}, 204 mA and 6.0 F mol^{-1} and predicted responses of 56.3% yield and 238 mg h^{-1}. These conditions were tested in entry 19 (Table 4.5), sampling at multiple points throughout the reaction (Table 4.6).

Entry	**Flow rate (mL min-1)**	**Current (mA)**	**F mol-1**	**UPLC yield (%)**	**Time (min)**	**Throughput (mg h-1)**	**1c area**	**1d area**	**1c:1d**
1	0.5	64	4	40.6	80.0	76.5	1123627	442431	2.54
2	0.5	64	5	50.7	100.0	76.4	1401751	497446	2.82
3	0.5	64	6	54.0	120.0	67.9	1494781	490889	3.05
4	0.5	264	4	22.1	20.0	166.5	611165	317358	1.93
5	0.5	264	5	25.3	25.0	152.6	700308	345308	2.03
6	0.5	264	6	26.2	30.0	131.6	724376	342339	2.12
7	8	64	4	40.2	80.0	75.8	1063614	382545	2.78
8	8	64	5	50.8	100.0	76.5	1343179	471294	2.85
9	8	64	6	58.1	120.0	73.0	1536252	531105	2.89
10	8	264	4	43.2	20.0	325.7	1143077	591512	1.93
11	8	264	5	49.6	25.0	299.1	1312076	591002	2.22
12	8	264	6	54.4	30.0	273.2	1438167	585629	2.46
13	4	128	4	45.7	40.0	172.4	1209912	632540	1.91
14	4	128	5	52.8	50.0	159.1	1396101	618960	2.26
15	4	128	6	56.8	60.0	142.7	1502538	603102	2.49
16	4	128	4	41.1	40.0	155.0	1087679	598664	1.82
17	4	128	5	47.0	50.0	141.6	1242216	627499	1.98
18	4	128	6	52.7	60.0	132.3	1393303	673170	2.07
19	8	204	6	54.2	38.0	215.0	1414163	567933	2.49

Table 4.5: Summary of experimental data for the DoE (entries 1 to 18) and the optimum conditions (entry 19).

Entry	F mol-1	Area				UPLC yield (%)
		1a	1b	1c	1d	
1	0.0	4555448	4270	9876	39478	1.5
2	1.0	2619530	1372100	48322	97112	3.7
3	2.1	798561	2137322	212065	322063	12.3
4	3.0	197534	1624769	466199	741835	28.4
5	4.0	71109	978005	584506	1074141	41.2
6	5.1	58406	478976	587394	1298767	49.8
7	6.0	65738	270558	567933	1414163	54.2
8	7.0	71795	150342	527310	1424560	54.6
9	8.1	77885	75455	494462	1495315	57.3

Table 4.6: Experimental results for the optimal conditions (204 mA, 8 mL min^{-1}) with sampling at multiple points.

4.5.1. Statistical anaysis

Below are several plots describing the validity of the model, along with a table summarising the statistical descriptors. All were generated using MODDE.

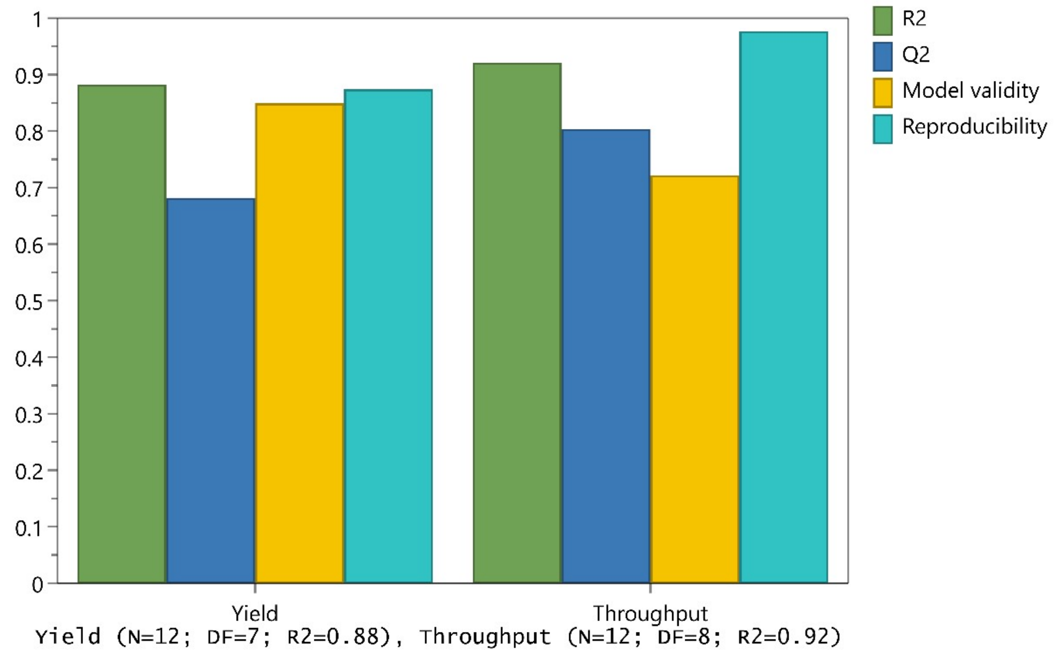


Figure 4.5: Summary of fit plot.

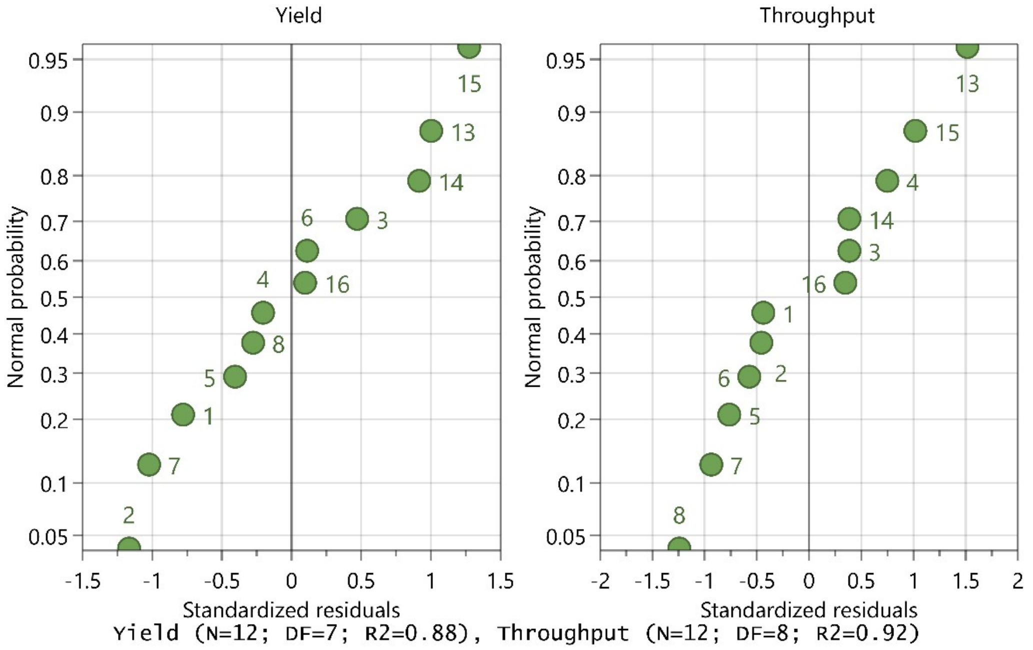


Figure 4.6: Residuals plot.

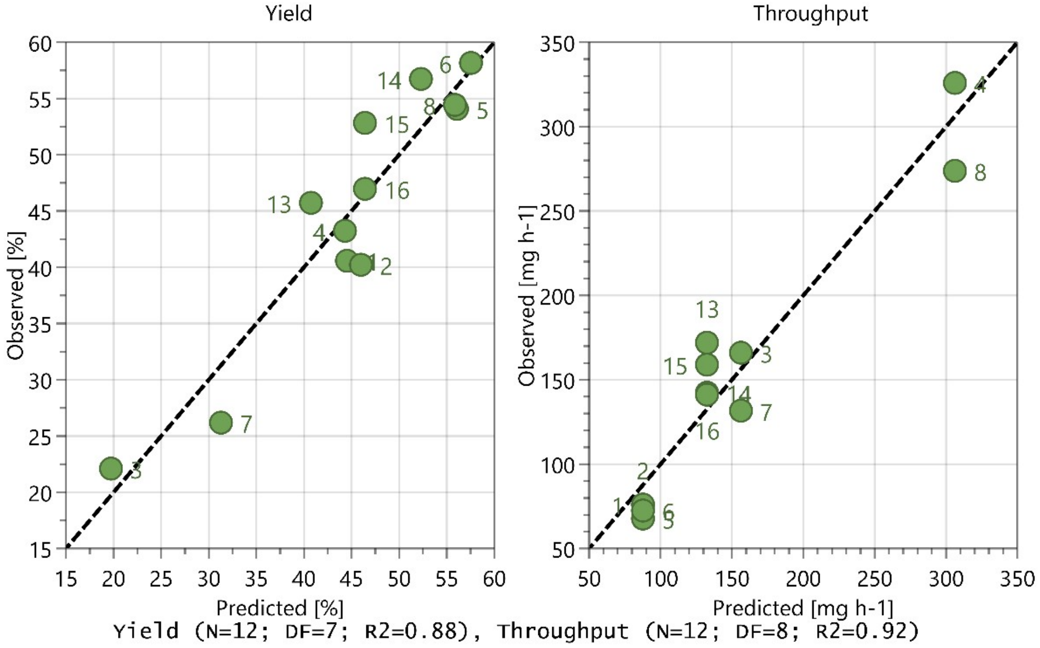


Figure 4.7: Predicted *vs* observed plot

	Yield	**Throughput**
Worksheet statistics		
Worksheet runs	12	12
N	12	12
Min	22.1	67.9
Max	58.1	325.7
Mean	45.0917	150.5

Q(25%)	40.4	76.15
Q(75%)	54.2	169.45
Median	46.35	142.15
Std. dev.	11.5559	80.3075
Min/Max	0.380379	0.208474
Std. dev./Mean	0.256276	0.533605
Skewness	-0.942029	1.13345
Skewness test	-1.47815	1.77852
Kurtosis	0.142531	0.94107
Model statistics		
Model type	Evaluation of PLS model	Evaluation of PLS model
Scaling type	All factors are scaled to unit variance	All factors are scaled to unit variance
DF	7	8
R2	0.881919	0.920719
R2 adj	0.814445	0.890989
Q2	0.681804	0.80321
Condition number	1.20757	1.20757
Model terms	5	4
DF residual	7	8
RSD	4.97784	26.515
p model	0.00231206	9.40877e-05
DF lack of fit	6	7
p lack of fit	0.547233	0.328604
DF pure error (repl. runs)	1	1
SD pure error	4.10122	12.3744
Residual skewness	0.146352	0.277013
Residual skewness test	0.229642	0.434666

Table 4.7: Summary of descriptive statistics.

4.5.2. Factor effects and interaction plots

Below are several plots showing the effects of different factors and interactions between them. All were generated using MODDE.

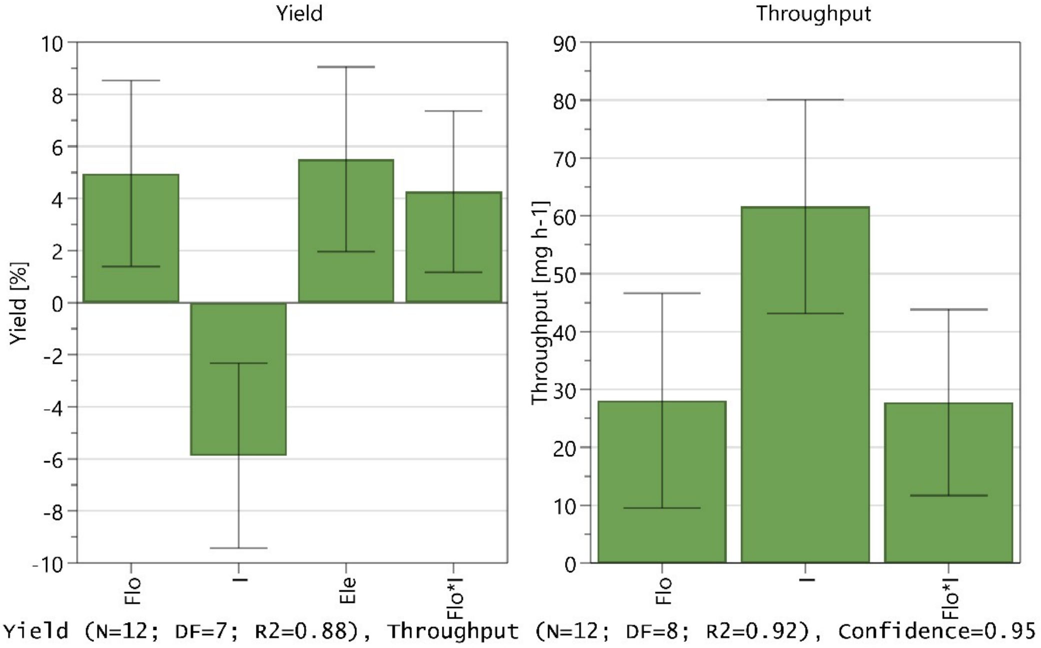


Figure 4.8: Plots showing the effects of the different factors on the yield and throughput.

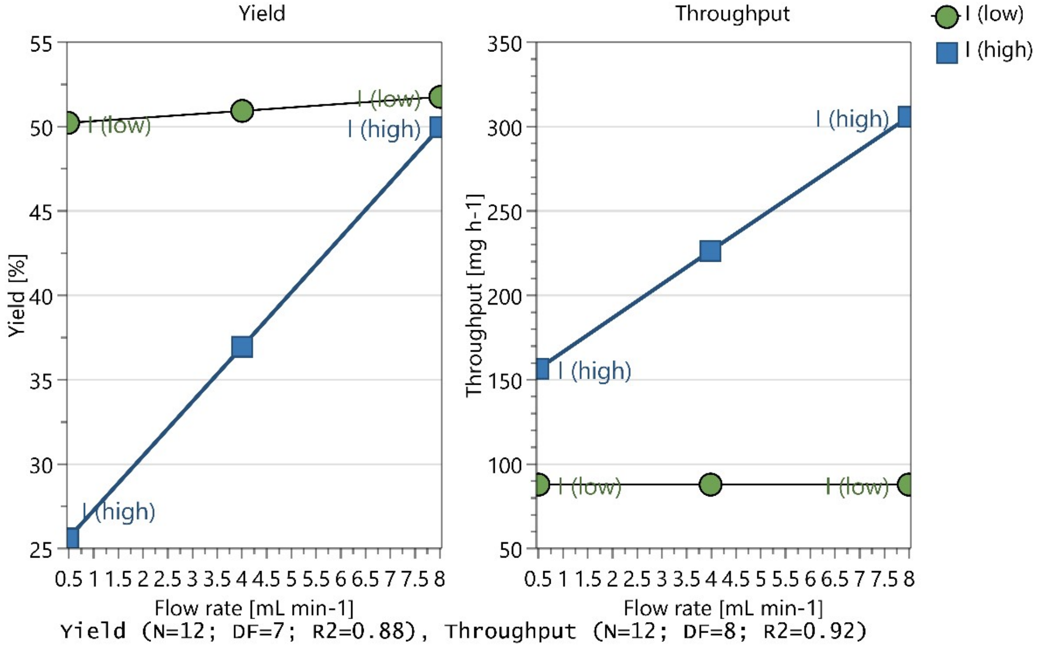


Figure 4.9: Plots showing the interaction between the current and flow rate and how that impacts the yield and throughput.

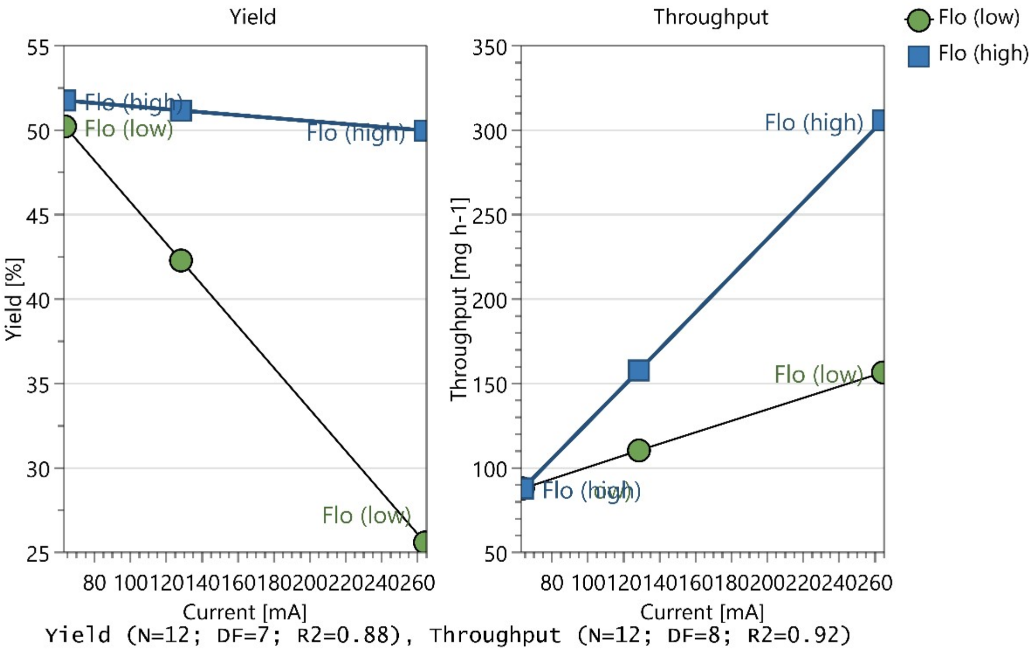


Figure 4.10: Plots showing the interaction between the current and flow rate and how that impacts the yield and throughput.

4.5.3. Predicting the optimum

Below are several plots showing the predicted effect of different factors contour plots of the predicted responses and the region where the target responses can be obtained. All were generated using MODDE.

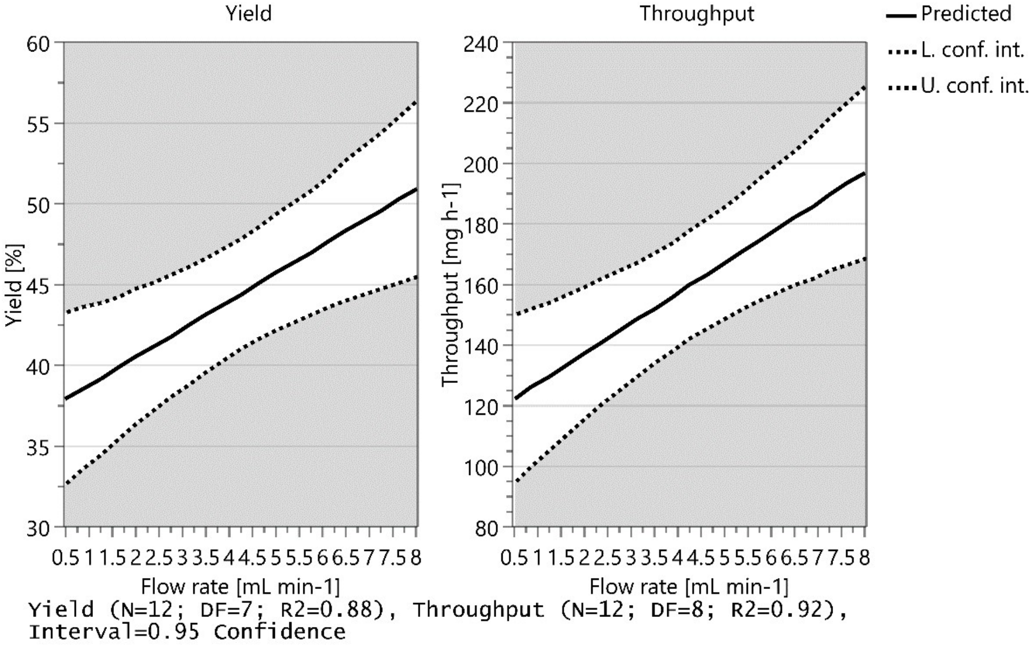


Figure 4.11: Predicted effect of flow rate on yield and throughput.

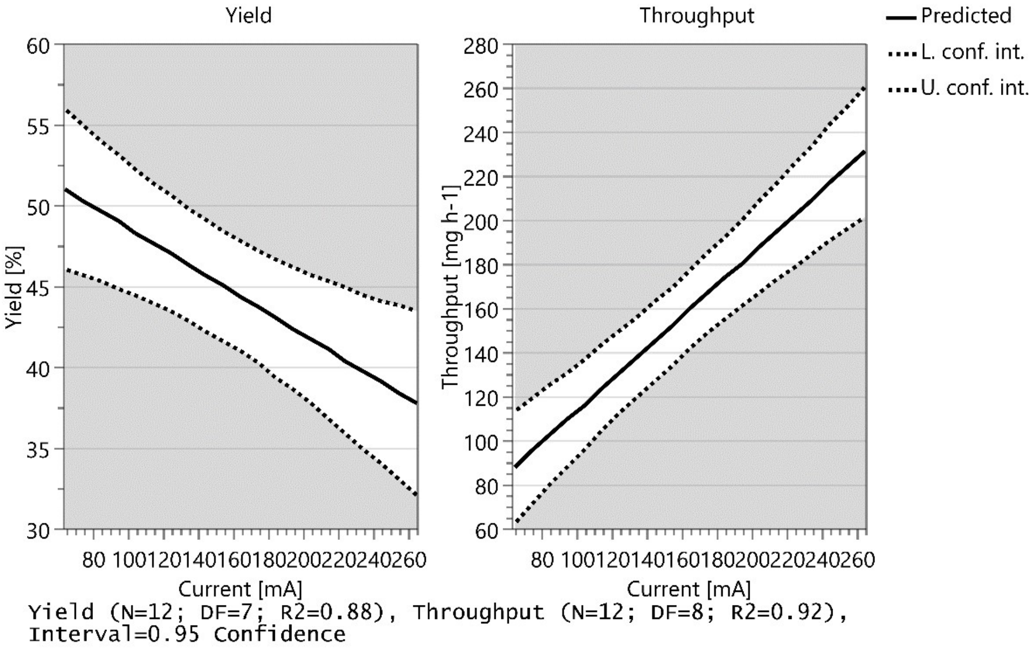


Figure 4.12: Predicted effect of current on yield and throughput.

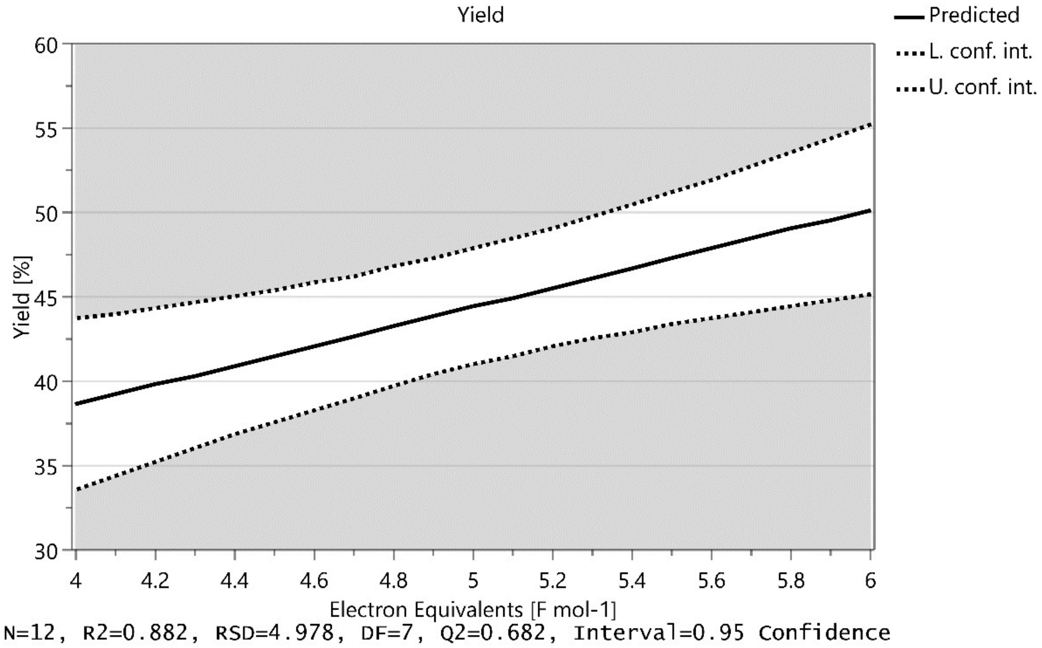


Figure 4.13: Predicted effect of electron equivalents on yield and throughput.

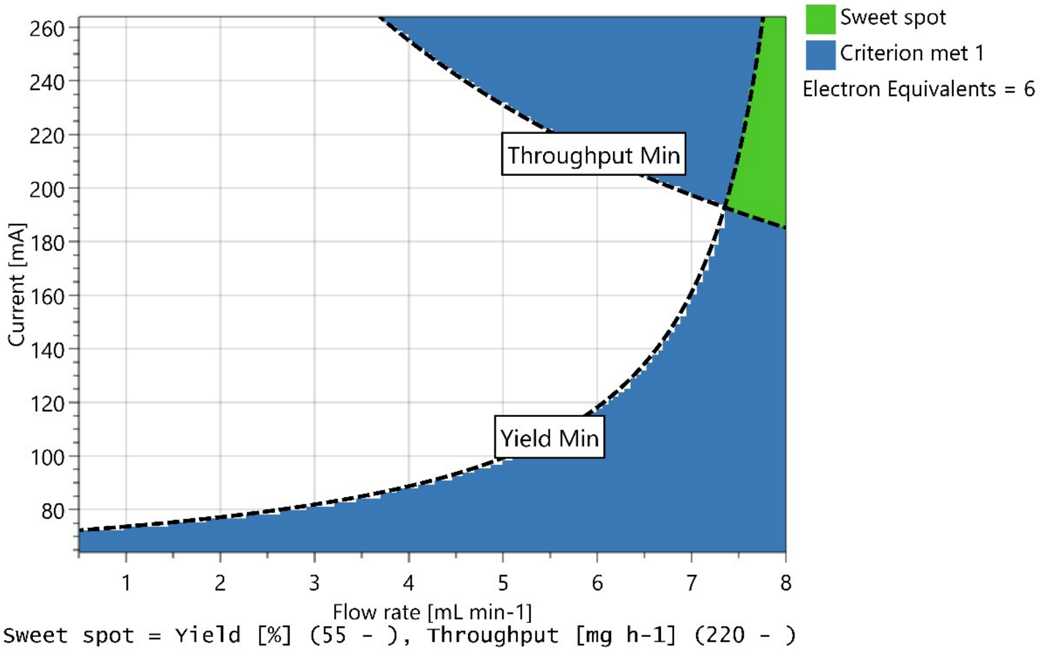


Figure 4.14: Plot showing the area of reaction space that offers a good compromise between yield and throughput at 6.0 F mol^{-1}.

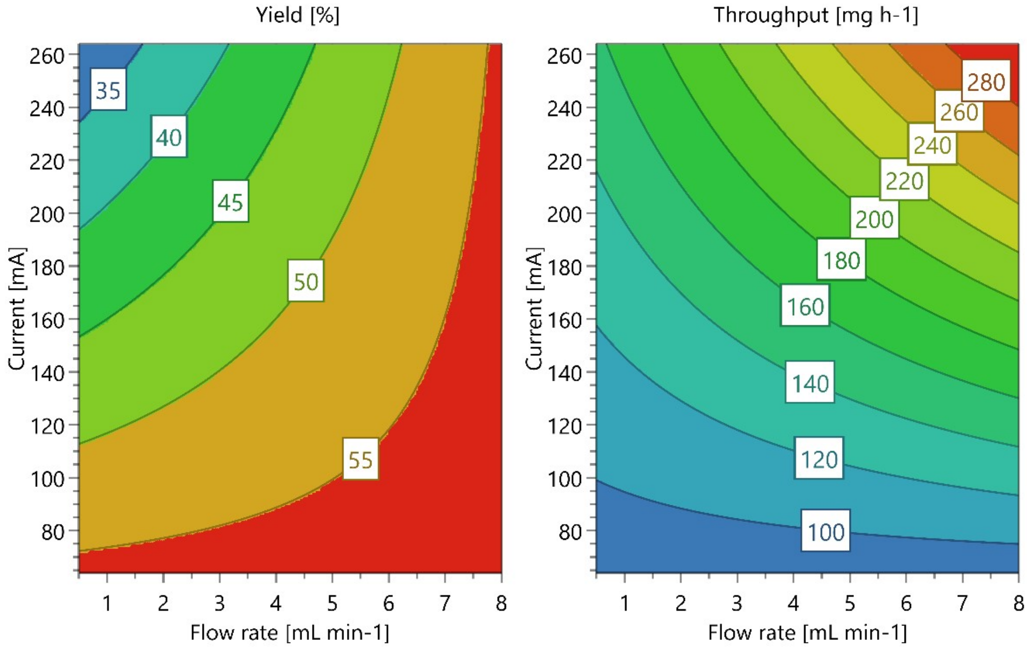


Figure 4.15: Contour plots for yield and throughput at 6.0 F mol^{-1}.

4.6. Scale up reactions

4.6.1. Gram scale

A 50 mL volumetric flask was charged with **1a** (1.13 g, 3.99 mmol) and Bu_4NPF_6 (163 mg, 0.41 mmol). A solution of acetonitrile and aqueous HCl (4:1 ratio of MeCN to 0.1 M HCl) was added and the mixture diluted up to the 50 mL mark. The mixture was stirred until all of the solids had dissolved. The reaction solution was transferred to a four necked round bottom flask and agitated with a magnetic stirrer. A needle and nitrogen supply was used to flush the headspace with nitrogen and to dilute any hydrogen produced during the reaction. The solution was pumped through the rea (204 mA). No back pressure was applied to t analysed *via* UPLC.

Figure 4.16: Image of the gram scale reaction set-up.

Entry	Time (min)	F mol-1	Area				1c yield (%)
			1a	**1b**	**1c**	**1d**	
1	0	0.0	4287529	0	5397	90898	0.2
2	30	1.0	2580998	1410168	54546	22427	2.1
3	60	1.9	760444	2123978	201199	114693	7.8
4	90	2.9	192367	1953233	564257	353152	22.0
5	120	3.8	17248	1248820	939538	505379	36.6
6	150	4.8	67160	792963	1140209	542048	44.4
7	180	5.7	68559	576192	1197719	529782	46.7
8	190	6.0	69753	534814	1228505	529777	47.9
9	260	8.2	58038	146673	1480796	599283	57.7

Table 4.8: Samples taken during the gram scale reaction.

4.6.2. 11.3 g scale

A 1 L round bottom flask was charged with **1a** (11.28 g, 40.0 mmol) and Bu_4NPF_6 (1.57 g, 3.97 mmol). A solution of acetonitrile and aqueous HCl (4:1 ratio of MeCN to 0.1 M HCl, 500 mL) was added and the mixture stirred until all of the solids had dissolved. A needle and nitrogen supply was used to flush the headspace with nitrogen and to dilute any hydrogen produced during the reaction. The solution was pumped through the reactor at 8.0 mL min^{-1}, whilst being electrolysed (204 mA). No back pressure was applied to the system. Samples were taken periodically and analysed *via* UPLC. Following the reaction a sample of the reaction solution was analysed using ICP-MS. No ruthenium or titanium was observed to be in the sample.

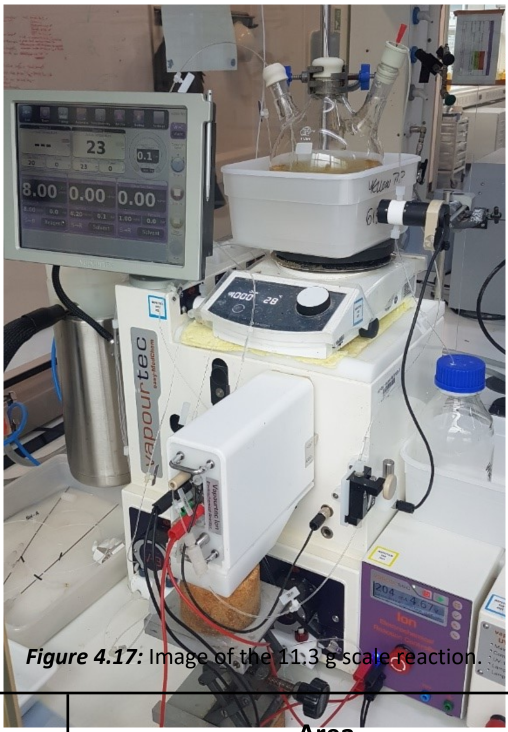


Figure 4.17: Image of the 11.3 g scale reaction.

Entry	**Time (min)**	**F mol-1**	**Area**				**1c yield (%)**
			1a	**1b**	**1c**	**1d**	
1	0	0.0	4554263	0	0	0	0.0
2	178	0.6	3467724	838284	26930	29757	1.1
3	355	1.1	2254347	1478505	55340	56826	2.2
4	1345	4.3	81927	1125659	1013837	523780	40.6
5	1535	4.9	89979	833383	1150148	568455	46.1
6	1665	5.3	12951	622965	1216589	585767	48.7
7	2040	6.4	14516	349929	1244213	578815	49.8
8	2220	7.0	14465	252139	1280549	594526	51.3

Table 4.9: Samples taken during the 11.3 g scale reaction.

5. PMI calculations

The PMI was calculated for three different ways of oxidising **1a** to **1c**. As a suitable workup for the electrochemical method had not been developed the work up was excluded from the calculations.

$$PMI = (Mass\ of\ reaction\ components)/(Mass\ of\ product)$$

5.1. Oxone method

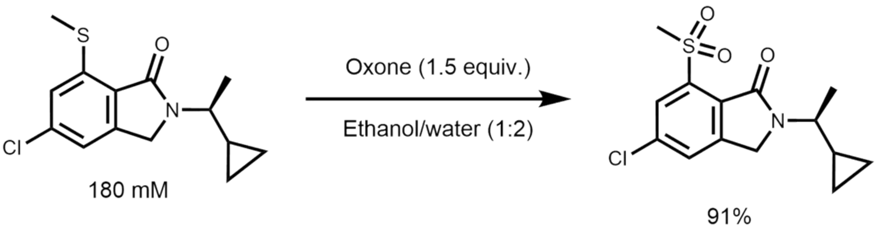


Figure 5.1: Oxidation of **1a** using oxone.

1a (10.00 g, 35.49 mmol) was charged to a jacketed vessel heated to 25 °C. Ethanol (79.1 g, 100.0 mL) and water (10.0 g, 10.0 mL) were charged to the vessel. An overhead stirrer was used to agitate the slurry with a speed of 600 rpm and the temperature ramped to 50 °C. A solution of oxone (1.50 equiv., 53.23 mmol, 32.72 g, 28.2 mL) in water (150.0 g, 150.0 mL) was added to the reaction vessel over 3 hours. The slurry was stirred for 1 hour before being cooled to 20 °C. A solution of sodium metabisulfite (1.25 equiv., 44.36 mmol, 8.433 g,) in water (100.0 g, 100.0 mL) was prepared and charged to the jacketed vessel over 30 minutes while the slurry was stirred.

The reaction mixture was filtered to give the crude solid. The jacketed vessel was charged with the isolated solid and water (150.0 g, 150.0 mL) was charged to the vessel. The slurry was stirred for 1 hour at 20 °C. The slurry was filtered again and washed twice with water (100 mL). The filter cake was dried overnight in a vacuum oven at 45 °C to give **1c** (91%, 10.12 g)

Material	Role	Mass (g)
Thioether	Reactant	10.00
Ethanol	Solvent	79.10
Water	Solvent	160.00
Oxone	Reagent	32.72
Sulfone	Product	10.13
	PMI	27.81

Table 5.1: Contribution of materials towards the PMI when using oxone.

5.2. H_2O_2 method

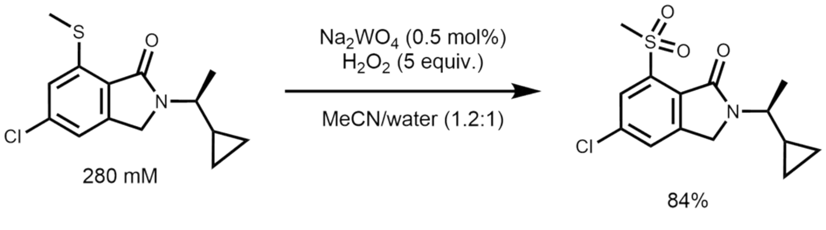


Figure 5.2: Oxidation of **1a** using H_2O_2.

A 100 mL RB flask was charged with **1a** (3.000 g, 10.65 mmol) and sodium tungstate dihydrate (0.0500 equiv., 0.5323 mmol, 0.1756 g,). Acetonitrile (14.1 g, 18.00 mL) was charged and the slurry was magnetically stirred under nitrogen. Water (15.0 g, 15.00 mL) was added. Hydrogen peroxide (30% solution in water) (5.00 equiv., 53.23 mmol, 6.035 g, 5.44 mL) was charged and the slurry was stirred at room temperature for 24 hours. The reaction mixture was filtered and the cake washed twice with MeCN/water to give **1c** (86%, 2.81 g).

Material	Role	Mass (g)
Thioether	Reactant	3.00

Sodium Tungstate	Catalyst	0.18
MeCN	Solvent	14.10
H_2O_2	Reagent	6.04
Water	Solvent	15.00
Sulfone	Product	2.81
	PMI	13.65

Table 5.2: Contribution of materials towards the PMI when using H_2O_2.

5.3. Electrolysis method

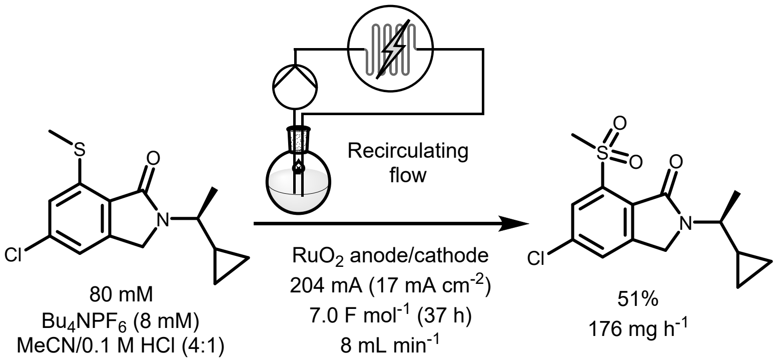


Figure 5.3: Oxidation of **1a** using electrolysis.

The reaction was performed as described in section 4.6.2.

Material	**Role**	**Mass (g)**
Thioether	Reactant	11.28
Bu_4PF_6	Electrolyte	1.57
0.1 M HCl	Catalyst	100.00
MeCN	Solvent	313.20
Sulfone	Product	6.53
	PMI	65.23

Table 5.3: Contribution of materials towards the PMI when using electrolysis.

5.4. Comparison

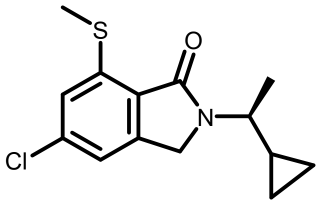
Entry	**Reaction**	**Solvent**	**Conc. (mM)**	**Yield (%)**	**PMI**
1	Oxone	EtOH/Water (1:1.6)	180	91	27.8
2	H_2O_2	MeCN/Water (1:1)	280	84	13.6
3	Electrochemistry	MeCN/Water (4:1)	80	51	65.2

Table 5.4: Comparison of the PMI of different oxidation strategies.

6. Reaction components

The reaction components were isolated *via* silica gel column chromatography (0-10% ethyl acetate in heptane).

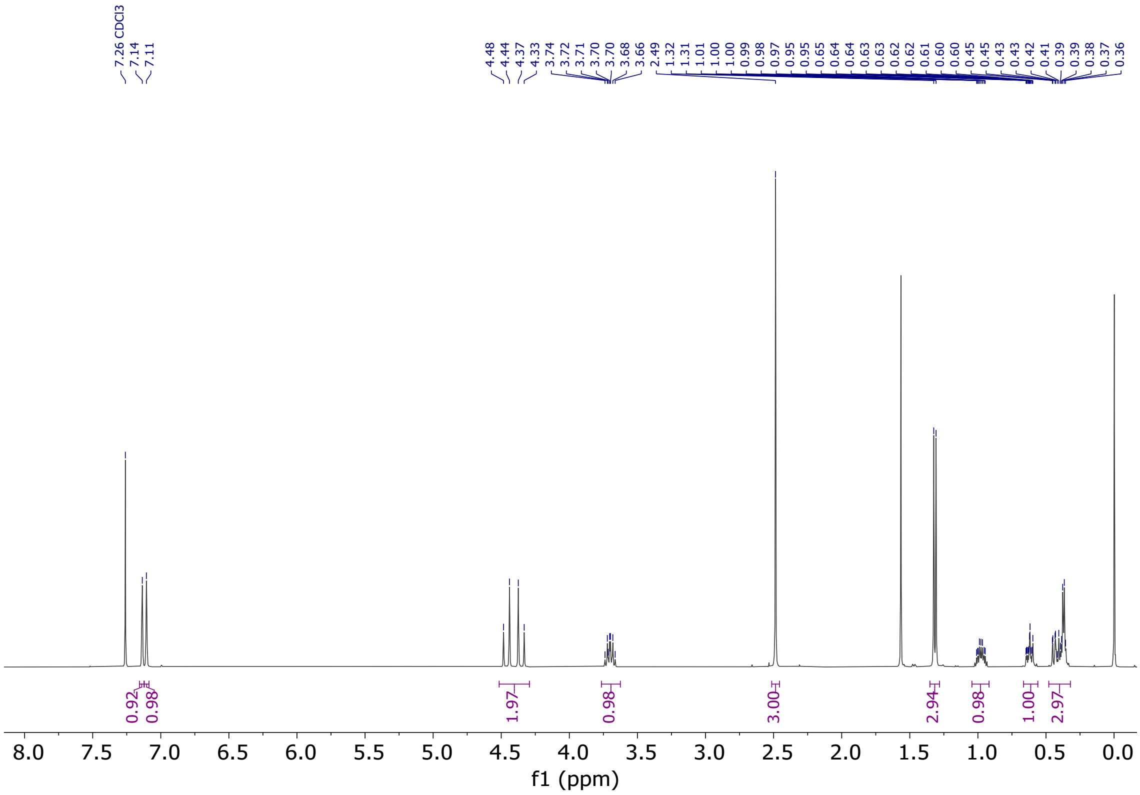
6.1. 1a

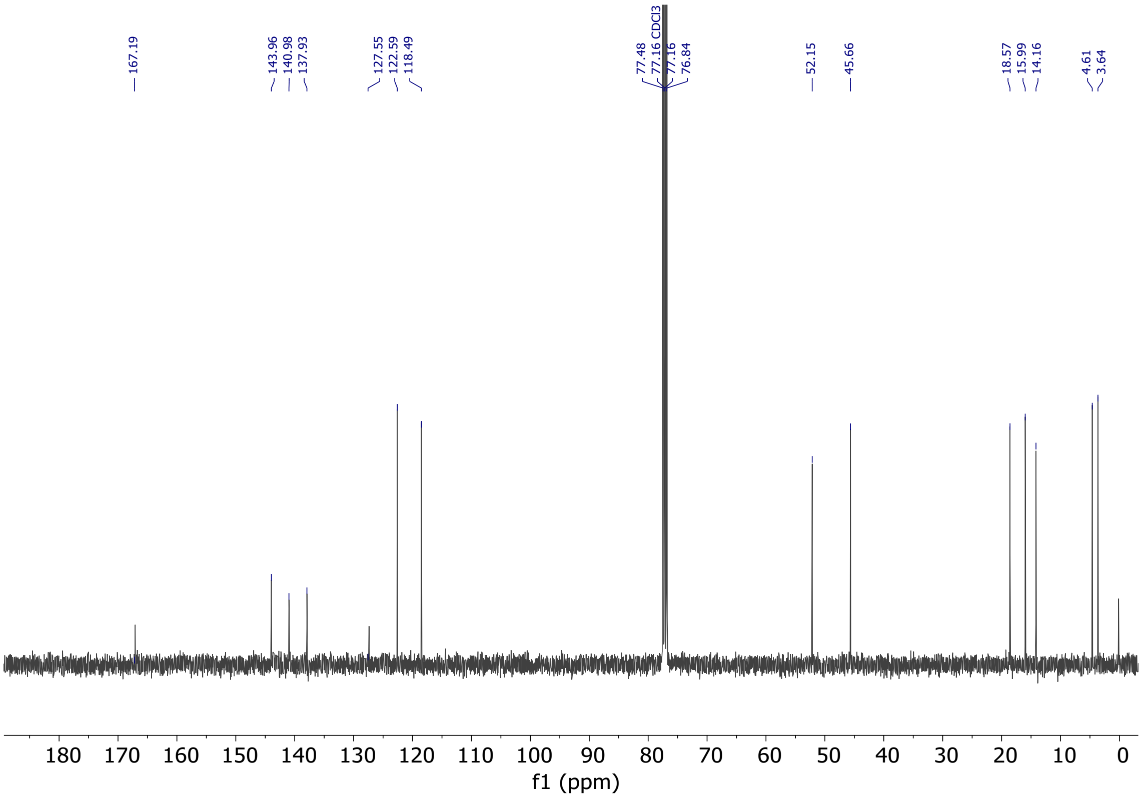


1H NMR (400 MHz, CDCl$_3$, 27°C) 0.32 – 0.48 (m, 3H, CH$_{2\ \mathrm{cyclopropyl}}$), 0.56 – 0.66 (m, 1H, CH$_{2\ \mathrm{cyclopropyl}}$), 0.92 – 1.04 (m, 1H, CH$_{\mathrm{cyclopropyl}}$), 1.32 (d, *J* = 6.8 Hz, 3H, CH$_3$), 2.49 (s, 3H, S-CH$_3$), 3.63 – 3.76 (m, 1H, N-CH), 4.29 – 4.52 (m, 2H, CH$_{2\ \mathrm{lactam}}$), 7.11 (s, 1H, ArH), 7.14 (s, 1H, ArH).

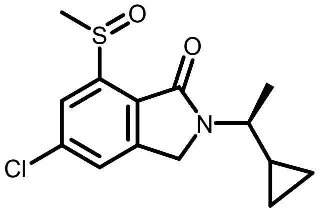
13C NMR (101 MHz, CDCl$_3$, 27°C) 167.19 (CO), 143.96 (Ar), 140.98 (Ar), 137.93 (Ar), 127.55 (Ar), 122.59 (Ar), 118.49 (Ar), 52.15 (CH), 45.66 (CH$_2$), 18.57 (CH$_3$), 15.99 (CH$_3$), 14.16 (CH), 4.61 (CH$_2$), 3.64 (CH$_2$).

HRMS (ESI=) m/z 282.0729 [M+H]$^+$, calcd. 282.0719





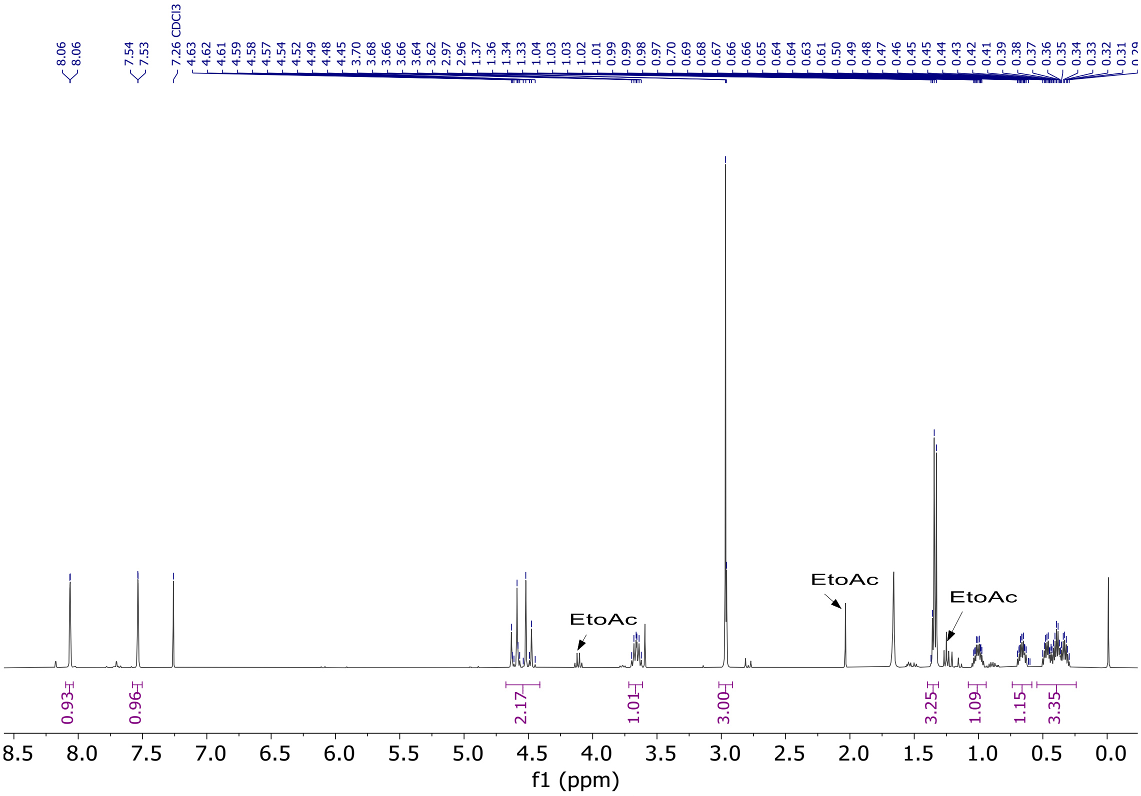
6.2. 1b



1H NMR (400 MHz, $CDCl_3$, 27°C) 0.24 – 0.55 (m, 3H, $CH_{2\ cyclopropyl}$), 0.59 – 0.74 (m, 1H, $CH_{2\ cyclopropyl}$), 0.94 – 1.08 (m, 1H, $CH_{cyclopropyl}$), 1.34 (d, *J* = 6.8 Hz, 3H, CH_3), 2.97 (s, 3H, S-CH_3), 3.61 – 3.72 (m, 1H, N-CH), 4.41 – 4.67 (m, 2H, $CH_{2\ lactam}$), 7.54 (d, *J* = 0.9 Hz, 1H, ArH), 8.06 (d, *J* = 1.3 Hz, 1H, ArH).

13C NMR (101 MHz, $CDCl_3$, 27°C) 165.49 (CO), 146.04 (Ar), 143.64 (Ar), 138.99 (Ar), 127.41 (Ar), 124.78 (Ar), 123.40 (Ar), 52.42 (CH), 46.34 (CH_2), 43.10 (CH_3) 18.23 (CH_3), 15.66 (CH), 4.37 (CH_2), 3.33 (CH_2).

HRMS (ESI=) m/z 298.0683 $[M+H]^+$, calcd. 298.0638.


8.06
8.06
7.54
7.53
7.26 CDCl3
4.63
4.62
4.61
4.59
4.58
4.57
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4.52
4.49
4.48
4.45
3.70
3.68
3.66
3.66
3.64
3.62
2.97
2.96
1.37
1.36
1.34
1.33
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1.03
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0.31
EtoAc
EtoAc
EtoAc
0.93
0.96
2.17
1.01
3.00
3.25
1.09
1.15
3.35
8.5
8.0
7.5
7.0
6.5
6.0
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4.5
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2.0
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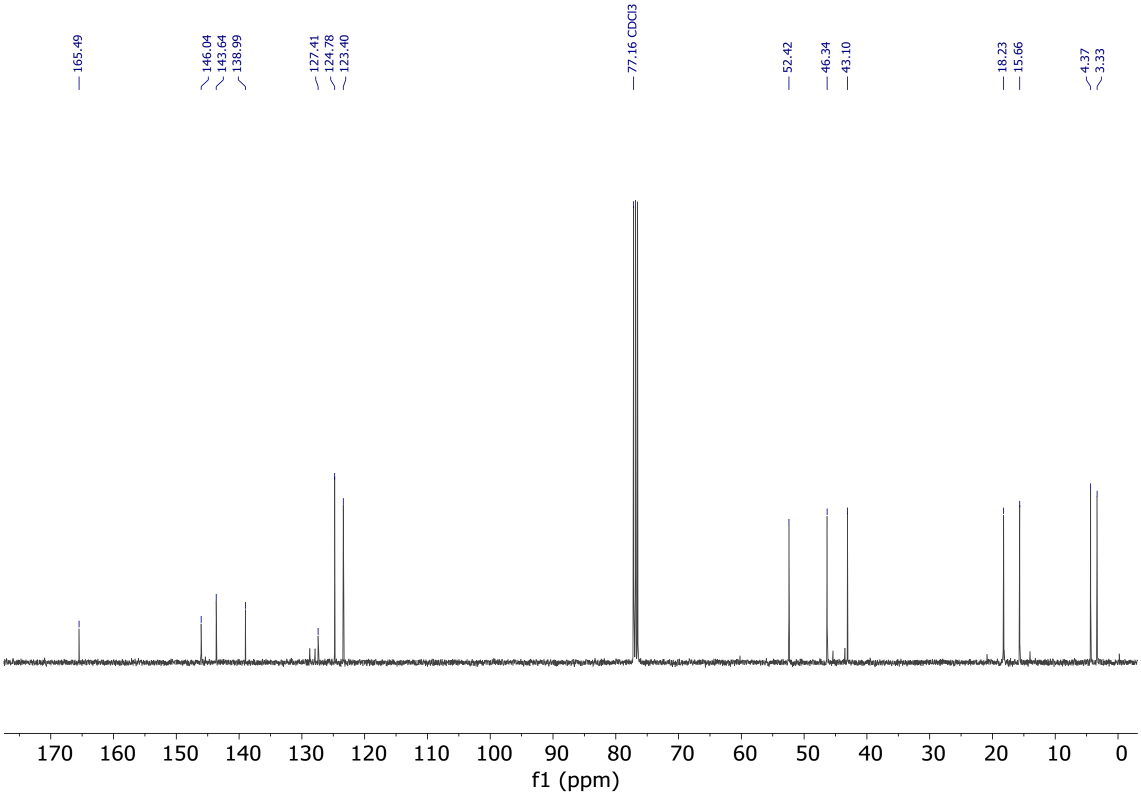
1.0
0.5
0.0
f1 (ppm)


165.49
146.04
143.64
138.99
127.41
124.78
123.40
77.16 CDCl3
52.42
46.34
43.10
18.23
15.66
4.37
3.33
170
160
150
140
130
120
110
100
90
80
70
60
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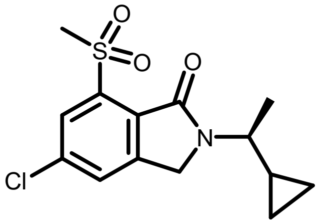
40
30
20
10
0
f1 (ppm)

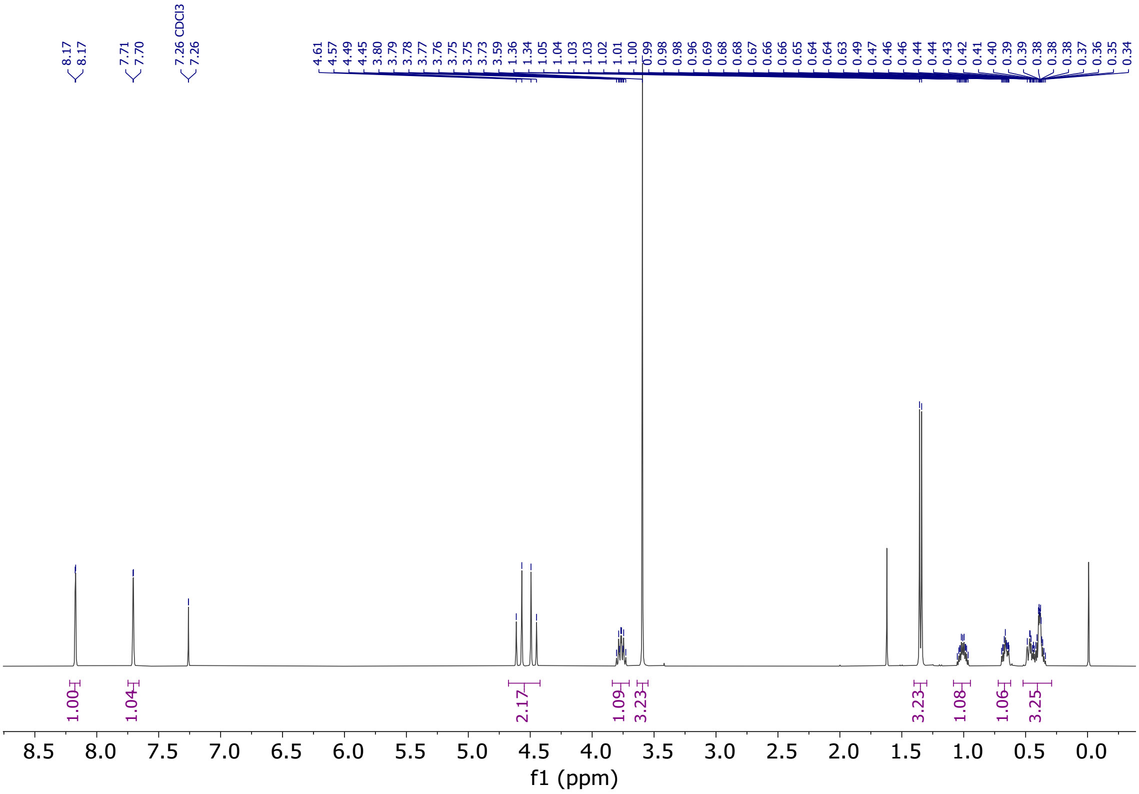
6.3. 1c

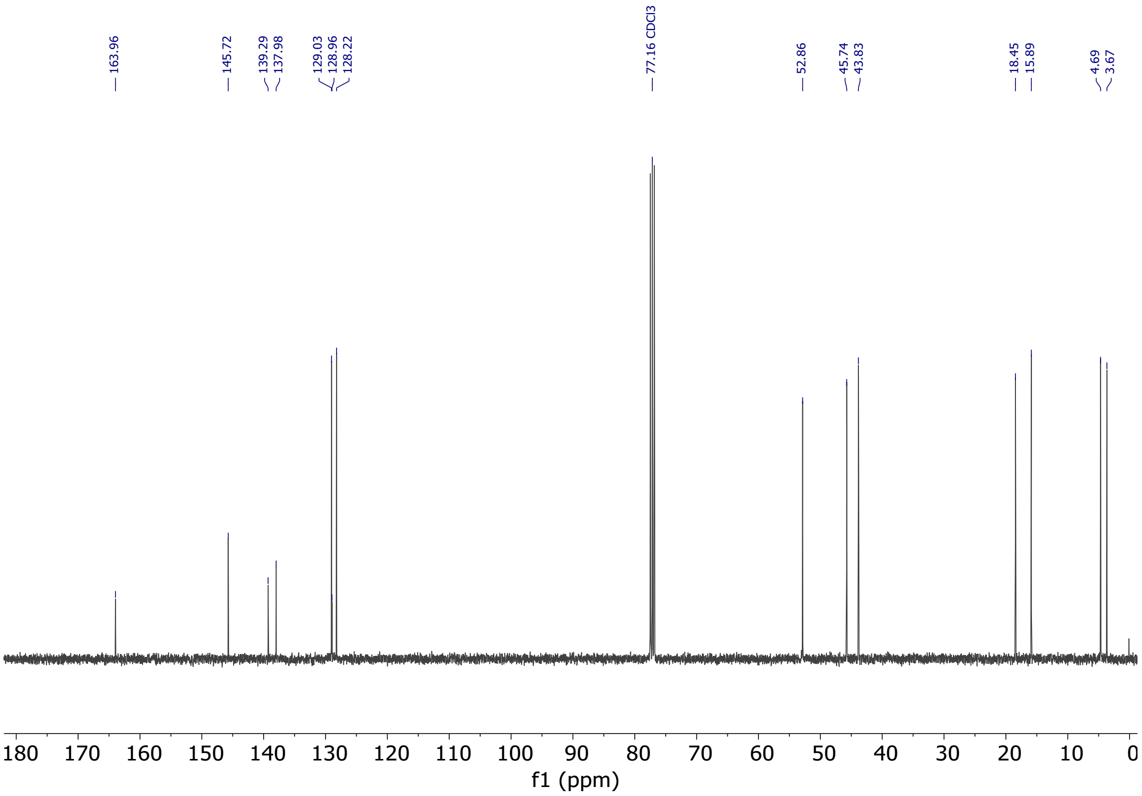


1H NMR (400 MHz, $CDCl_3$, 27°C) 0.29 – 0.52 (m, 3H, $CH_{2\ cyclopropyl}$), 0.62 – 0.72 (m, 1H, $CH_{2\ cyclopropyl}$), 0.95 – 1.08 (m, 1H, $CH_{cyclopropyl}$), 1.35 (d, *J* = 6.8 Hz, 3H, CH_3), 3.59 (s, 3H, S-CH_3), 3.70-3.84 (m, 1H, N-CH), 4.42 – 4.68 (m, 2H, $CH_{2\ lactam}$), 7.71 (d, *J* = 1.3 Hz, 1H, ArH), 8.17 (d, *J* = 1.6 Hz, 1H, ArH).

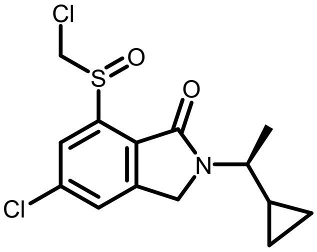
13C NMR (101 MHz, $CDCl_3$, 27°C) 163.96 (CO), 145.72 (Ar), 139.29 (Ar), 137.98 (Ar), 129.03 (Ar), 128.96 (Ar), 128.22 (Ar), 52.86 (CH), 45.74 (CH_2), 43.83 (CH_3), 18.45 (CH_3), 15.89 (CH), 4.69 (CH_2), 3.67 (CH_2).

HRMS (ESI=) m/z 314.0628 $[M+H]^+$, calcd. 314.0618





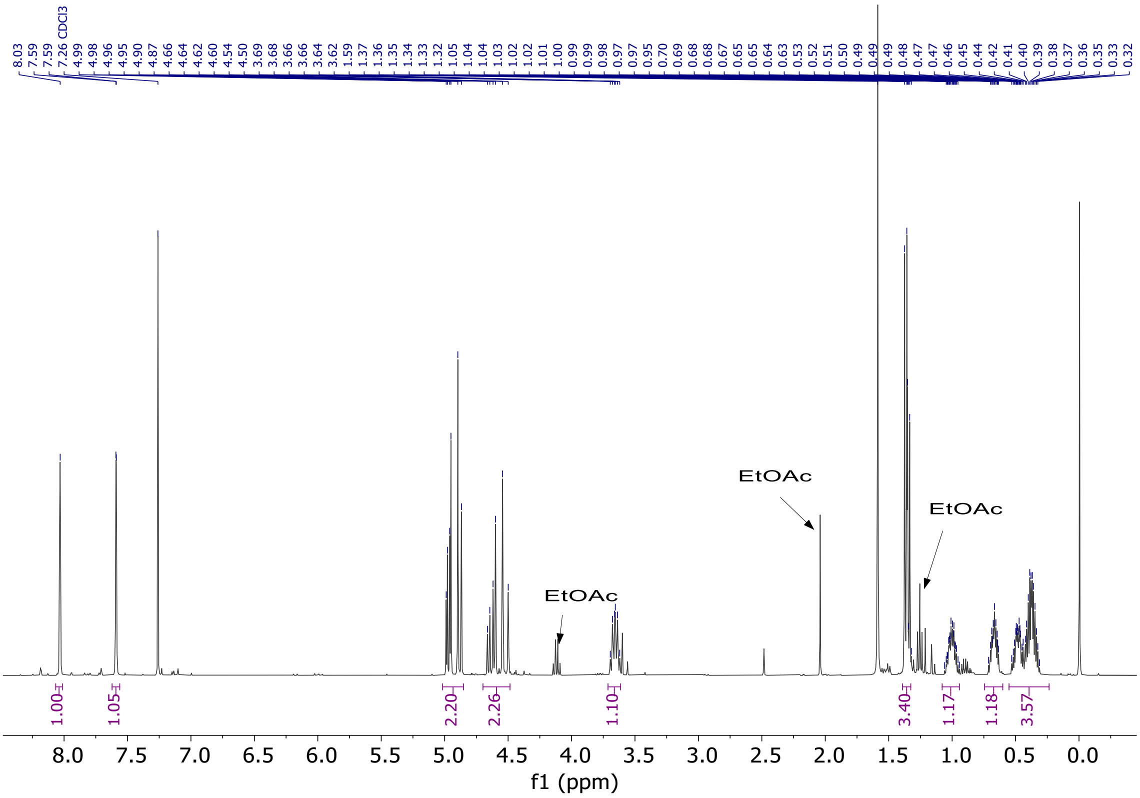
6.4. 1d

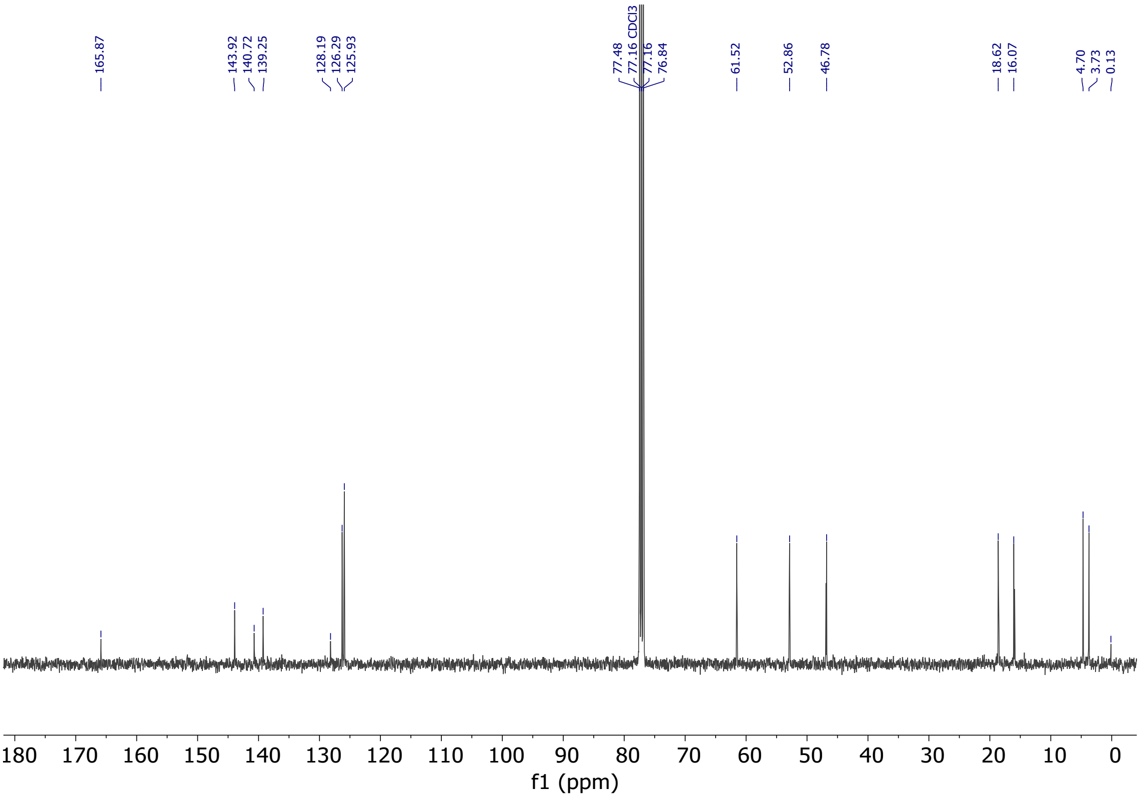


1H NMR (400 MHz, $CDCl_3$, 27°C) 0.3 – 0.55 (m, 3H, $CH_{2\ cyclopropyl}$), 0.6 – 0.74 (m, 1H, $CH_{2\ cyclopropyl}$), 0.94 – 1.08 (m, 1H, $CH_{cyclopropyl}$), 1.35 (dd, *J* = 9.1, 6.9 Hz, 3H, CH_3), 3.61 – 3.71 (m, 1H, m, 1H, N-CH), 4.48 – 4.7 (m, 2H, $CH_{2\ lactam}$), 4.85 – 5.02 (m, 2H, S-CH_2Cl), 7.59 (d, *J* = 1.3 Hz, 1H, ArH), 8.03 (d, *J* = 1.2 Hz, 1H, ArH).

13C NMR (101 MHz, $CDCl_3$, 27°C) 165.87 (CO), 143.92 (Ar), 140.72 (Ar), 139.25 (Ar), 128.19 (Ar), 126.29 (Ar), 125.93 (Ar), 61.52(CH_2), 52.86 (CH), 46.78 (CH_2), 18.62 (CH_3), 16.07 (CH), 4.70 (CH_2), 3.73 (CH_2).

HRMS (ESI=) m/z 332.0289 $[M+H]^+$, calcd. 332.0279





7. References

1. T. Andersson, A. Broo and E. Evertsson, *Journal of Pharmaceutical Sciences*, 2014, **103**, 1949-1955.
2. C. Schotten, T. P. Nicholls, R. A. Bourne, N. Kapur, B. N. Nguyen and C. E. Willans, *Green Chemistry*, 2020, **22**, 3358-3375.