Engineering Chemistry: Integrating batch and flow reactions on a single, automated reactor platform.

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Supporting Information

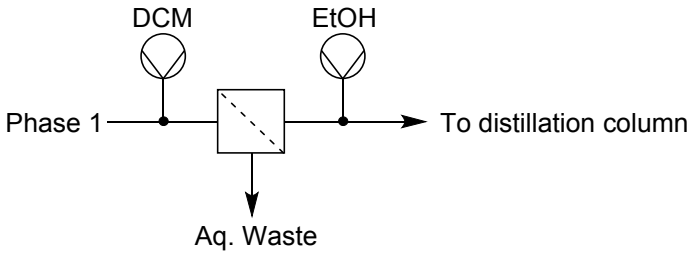
1.0 Process Design Revisions

In this section we describe some of the revisions that were applied to the equipment layout during the development of the process. Each change arose when a specific problem was encountered. We have also included schematics for the original process designs.

Phase 1

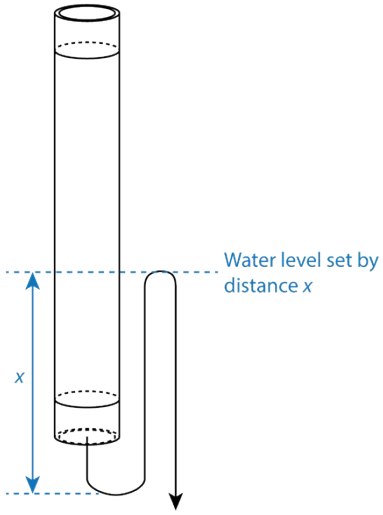
We did not encounter any problems with our initial design for Phase 1 (shown in Figure 3 of the main text). As such no revisions were made to this process layout.

Phase 2



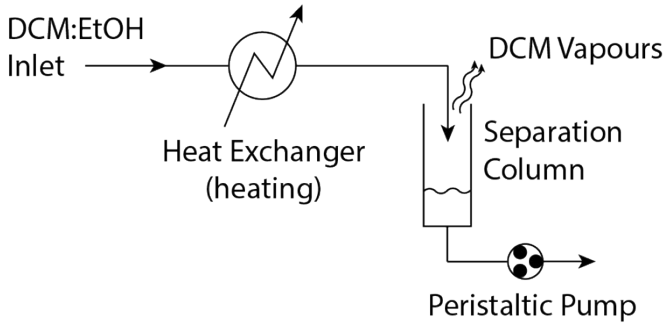
Initially our study did not incorporate a machine-vision liquid-liquid separator. Instead, we attempted to use a hydrophobic membrane to effect separation. However, downstream pressure fluctuations on the organic side caused by piston movements in the ethanol pump led to unstable operation. Back pressure regulators were added to the separator's aqueous and organic outlets in an attempt to combat this, however this resulted in breakthrough of water into the exiting organic stream.

Accordingly we switched to the machine-vision separation column, as described in the text of the main article.



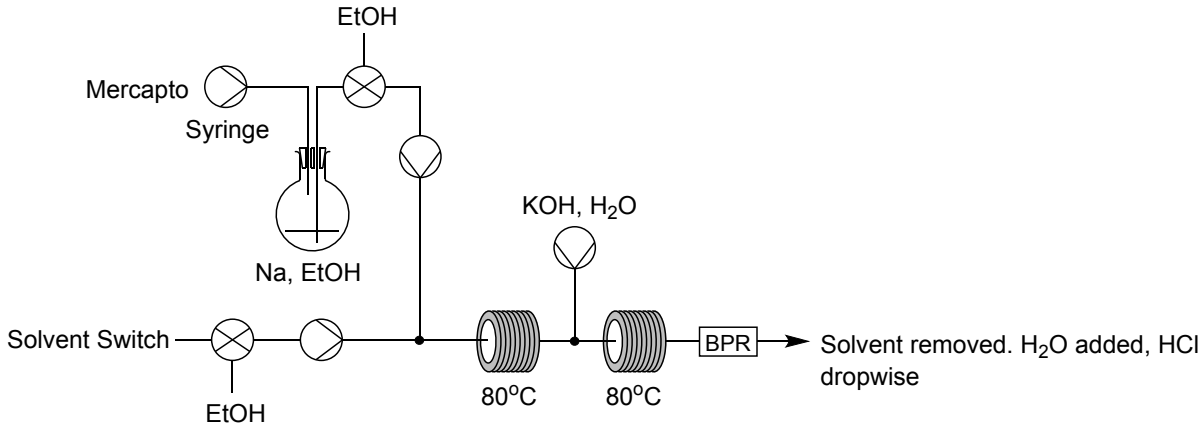
A modification was also made to the distillation column. Initially, we attempted to use gravity to drain liquid from the column, in a syphon arrangement. The rate of bubble formation within the column prevented this from operating effectively, however, and liquid accumulated in the column at a rate faster than it drained. As such we added a small peristaltic pump to the bottom of the column to drive drainage. A peristaltic pump was chosen to enable multiphasic pumping that standard piston pumps cannot handle.

Initially we sought to switch from DCM to THF, as Phase 3 was originally carried out using this solvent. However, the difference in boiling points between these two solvents was insufficient to drive effective distillation and so we decided to change to EtOH instead. More information about our distillation trials is given below.

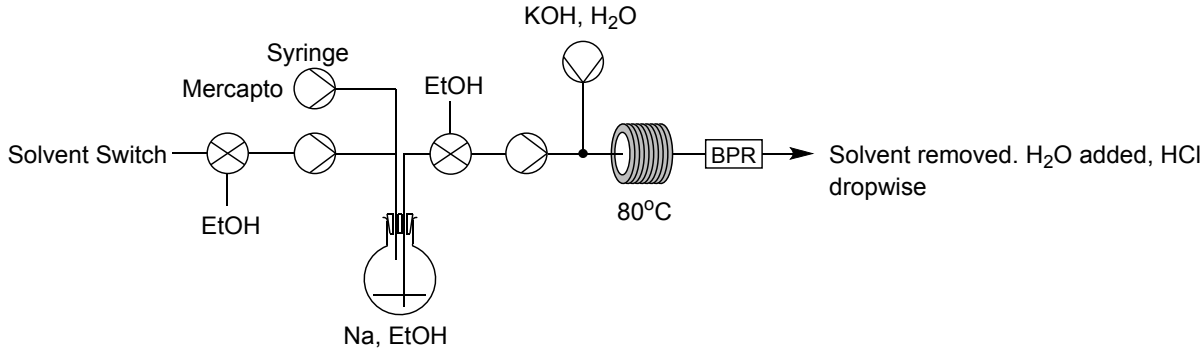


An additional schematic, put together to be viewed with the main article text (Figure 7), has been included above. It shows a conceptual representation of how the distillation unit works.

Phase 3



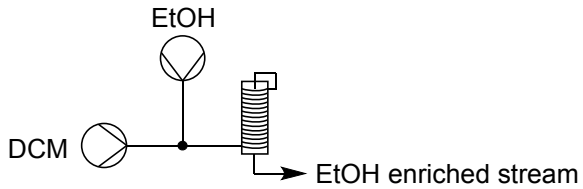
During initial experimentation in this phase (schematic shown above), we experienced significant issues with solid formation leading to tube blockages.



We modified the design in an attempt to prevent this issue, by conducting the first three steps in the batch vessel (formation of sodium ethoxide, addition of ethyl 2-mercaptoacetate then addition of stream from phase 2), as shown in the schematic above. To prevent solids affecting pump operation, an inline filter was placed before the switching valve directly after the flask (before the pump). Very quickly, however, this filter became blocked and thus prevented the pump from drawing solution out of the batch vessel.

We finally settled on conducting all operations associated with Phase 3 in batch-mode, negating the need for the pumps and flow coil. This schematic is shown in the main article text, in Figure 3.

2.0 Distillation



In order to find optimal set point conditions to operate the distillation column, we set up a simple system as shown in the schematic above. We tried various temperature set points, pump flow rates and pump ratios and checked output stream composition using NMR. Our results are summarised in the table below.

	Temp	F (DCM)	F (EtOH)	Integral DCM (5.3)	Integral EtOH (1.24)	Molar F DCM	Molar F EtOH	Inlet Molar % DCM	Exit Molar % DCM	% Removal DCM
Prelim	80	1	1	0.19	3	0.015659955	0.017126112	0.477640545	0.059561129	87.5
1	80	2	1	0.47	3	0.031319911	0.017126112	0.646490849	0.135446686	79
2	80	1	2	0.12	3	0.015659955	0.034252225	0.313750175	0.038461538	87.7
3	80	2	2	0.39	3	0.031319911	0.034252225	0.477640545	0.115044248	75.9
4	90	1	1	0.08	3	0.015659955	0.017126112	0.477640545	0.025974026	94.6
5	90	2	1	0.16	3	0.031319911	0.017126112	0.646490849	0.050632911	92.2
6	90	1	2	0.13	3	0.015659955	0.034252225	0.313750175	0.041533546	86.8
7	90	2	2	0.15	3	0.031319911	0.034252225	0.477640545	0.047619048	90
8	100	1	1	0.08	3	0.015659955	0.017126112	0.477640545	0.025974026	94.6
9	100	2	1	0.23	3	0.031319911	0.017126112	0.646490849	0.07120743	89
10	100	1	2	0.06	3	0.015659955	0.034252225	0.313750175	0.019607843	93.8
11	100	2	2	0.1	3	0.031319911	0.034252225	0.477640545	0.032258065	93.2

The two results highlighted in green represent the best results, and were obtained when the system reached the azeotrope for the binary mixture of EtOH and DCM.

3.0 Process Automation

The automation code for the experiment has been included below.

Phase 1:

```
<?php
        function experiment_start(){
                //Syringe pump initialisation
                executeequipmentfunction('Aladdin1', 'init', [9.6]);

          //Vapourtec 1 initialisation
          executeequipmentfunction('Vapourtec1','keypress',['loop1','load']);
                executeequipmentfunction('Vapourtec1','keypress',['loop2','load']);
                executeequipmentfunction('Vapourtec1','keypress',['pumpA','solvent']);
                executeequipmentfunction('Vapourtec1','keypress',['pumpB','solvent']);
                executeequipmentfunction('Vapourtec1','keypress',['output','waste']);
          executeequipmentfunction('Vapourtec1','setFlowRate',['pumpA',0]);
                executeequipmentfunction('Vapourtec1','setFlowRate',['pumpB',0]);
          executeequipmentfunction('Vapourtec1','setTemperature',[1,-1000]);
          executeequipmentfunction('Vapourtec1','setTemperature',[2,-1000]);
          executeequipmentfunction('Vapourtec1','setTemperature',[3,-1000]);
          executeequipmentfunction('Vapourtec1','setTemperature',[4,-1000]);
          executeequipmentfunction('Vapourtec1','start',[]);

          //Knauer initialisation
          executeequipmentfunction('Knauer1', 'Stop', []);
          executeequipmentfunction('Knauer2', 'Stop', []);

          //Start experiment
          phase1_1();
        }

    //--------------------== Phase 1.1 ==--------------------------------
    function phase1_1(){
        //Phase1 cools flask1 to 0 degrees, then adds POCl3 dropwise, then stirs
for 30 mins at room temp
        executeequipmentfunction('Vapourtec1','setTemperature',[1,0]);


        addlistener("round((float)getequipmentdata('Vapourtec1')['temperatures']['sl
        ot1']['temperature'],0)","equals","1", "phase1_2()");
```

```
    }

    function phase1_2(){
        //Start POCl3 dropwise (2mL over four mins)
        executeequipmentfunction('Aladdin1', 'setPumpDirection', ["INF"]);
        executeequipmentfunction('Aladdin1', 'setPumpRate', [0.500]);
        executeequipmentfunction('Aladdin1', 'setVolume', [2.240]);
        executeequipmentfunction('Aladdin1', 'start', []);


       addlistener("(float)getequipmentdata('Aladdin1')['dispensed']['inject']","gr
       eaterthanequalto","2", "phase1_3()");
    }

    function phase1_3(){
        //Warm to room temp
        executeequipmentfunction('Vapourtec1','setTemperature',[1,-1000]);


       addlistener("round((float)getequipmentdata('Vapourtec1')['temperatures']['sl
       ot1']['temperature'],0)","greaterthanequalto","15", "phase1_4()");
    }

    function phase1_4(){
        //Stir for 35 mins with coil preheating starting during stirring
        $time = time() + 1800;
        addlistener("time()","greaterthanequalto",$time, "phase1_5()");
    }

    function phase1_5(){
        //Start preheating and flushing
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpA',0.25]);
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpB',0.25]);
        executeequipmentfunction('Vapourtec1','setTemperature',[2, 90]);

        $time = time() + 300;
        addlistener("time()","greaterthanequalto",$time, "phase2_1()");
    }

    //--------------------== Phase 1.2 ==----------------------
    function phase2_1(){
        //Set pump flowrates and switch valves
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpA',0.5]);
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpB',0.5]);
        executeequipmentfunction('Vapourtec1','keypress',['output','collect']);
             executeequipmentfunction('Vapourtec1','keypress',['pumpB','reagent']);

        //Switch valves back to solvent after 28 mins (14mL at 0.5 mL/min, from
each pump) - 97 seconds for coil difference
        $time = time() + 1680 - 97;
        addlistener("time()","greaterthanequalto",$time, "phase2_2()");

        //Sodium acetate pump after 10 mins (one residence time) + 4 mins for
travel time - 67 seconds for differences in reactor coils
        $time = time() + 840 - 67;
        addlistener("time()","greaterthanequalto",$time, "phase2_3()");
    }

    function phase2_2(){
        //Switch valves back to solvent
        executeequipmentfunction('Vapourtec1','keypress',['output','waste']);
             executeequipmentfunction('Vapourtec1','keypress',['pumpB','solvent']);
    }

    function phase2_3(){
        //Start sodium acetate pump
        executeequipmentfunction('Knauer1', 'setFlowRate', [1.0]);
        executeequipmentfunction('Knauer1', 'Start', []);
```

```
        //Start DCM pump
        executeequipmentfunction('Knauer2', 'setFlowRate', [1.0]);
        executeequipmentfunction('Knauer2', 'Start', []);

        //Start collecting product
        executeequipmentfunction('Vapourtec1','keypress',['loop2','inject']);

        //Start cooling and stop collecting after 28 mins (material processing
time), +4 mins for travel time +1 min 10 s for dispersion - 322 seconds for coil
change
        $time = time() + 2020 - 322;
        addlistener("time()","greaterthanequalto",$time, "shutdown1()");
    }


    //--------------------------== Shutdown sequence ==-------------------------
    function shutdown1(){
        //Switch back to waste
        executeequipmentfunction('Vapourtec1','keypress',['loop2','load']);

        //Turn off heater
        executeequipmentfunction('Vapourtec1','setTemperature',[2,-1000]);

        //Sodium acetate pump off
        executeequipmentfunction('Knauer1', 'Stop', []);

        //When coil back at room temp, switch off

addlistener("round((float)getequipmentdata('Vapourtec1')['temperatures']['slot2']['
temperature'],0)","lessthanequalto","30", "shutdown2()");
    }

    function shutdown2(){
        //Turn off pumps
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpA',0]);
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpB',0]);

        //Vapourtec off
        executeequipmentfunction('Vapourtec1','stop',[]);

        //Run DCM pump for extra minute
        $time = time() + 60;
        addlistener("time()", "greaterthanequalto", $time,
"experiment_shutdown()");
    }

       function experiment_shutdown(){
              //This code executes when the experiment ends
              executeequipmentfunction('Knauer2', 'Stop', []);
              stopexperiment();
       }
?>
```

Phase 2:

```
<?php
       function experiment_start(){
        //Knauer initialisation
        executeequipmentfunction('Knauer3', 'Stop', []);
        executeequipmentfunction('Knauer4', 'Stop', []);

        //Vapourtec 1 initialisation
       executeequipmentfunction('Vapourtec1','keypress',['loop1','load']);
        executeequipmentfunction('Vapourtec1','keypress',['loop2','load']);
        executeequipmentfunction('Vapourtec1','keypress',['pumpA','solvent']);
```

```
        executeequipmentfunction('Vapourtec1','keypress',['pumpB','solvent']);
        executeequipmentfunction('Vapourtec1','keypress',['output','waste']);
       executeequipmentfunction('Vapourtec1','setFlowRate',['pumpA',0]);
        executeequipmentfunction('Vapourtec1','setFlowRate',['pumpB',0]);
       executeequipmentfunction('Vapourtec1','setTemperature',[1,-1000]);
       executeequipmentfunction('Vapourtec1','setTemperature',[2,-1000]);
       executeequipmentfunction('Vapourtec1','setTemperature',[3,-1000]);
       executeequipmentfunction('Vapourtec1','setTemperature',[4,-1000]);
       executeequipmentfunction('Vapourtec1','start',[]);

         //Start heating column
         executeequipmentfunction('Vapourtec1','setTemperature',[4, 90]);

         //Listener

addlistener("round((float)getequipmentdata('Vapourtec1')['temperatures']['slot4']['
temperature'],0)","equals","90", "phase1_1()");
       }

    //-----------------------== Phase 2.1 ==----------------------
    function phase1_1(){
        //Start pumps at 1mL/min each
        executeequipmentfunction('Knauer3', 'setFlowRate', [1.0]);
        executeequipmentfunction('Knauer3', 'Start', []);

        executeequipmentfunction('Knauer4', 'setFlowRate', [1.0]);
        executeequipmentfunction('Knauer4', 'Start', []);
    }

       function experiment_shutdown(){
              //Manual experiment end
              executeequipmentfunction('Knauer3', 'Stop', []);
         executeequipmentfunction('Knauer4', 'Stop', []);

              stopexperiment();
       }
?>
```

The python code powering the liquid-liquid machine vision system can be found in references 22, 23 and 24.

Phase 3:

```
<?php
       function experiment_start(){
              //Syringe pump initialisation
              executeequipmentfunction('Aladdin2', 'init', [9.6]);

         //Vapourtec initialisation
         executeequipmentfunction('Vapourtec2','keypress',['loop1','load']);
              executeequipmentfunction('Vapourtec2','keypress',['loop2','load']);
              executeequipmentfunction('Vapourtec2','keypress',['pumpA','reagent']);
//Lines switched owing to space considerations (i.e. reagent connects to reservoir)
              executeequipmentfunction('Vapourtec2','keypress',['pumpB','solvent']);
              executeequipmentfunction('Vapourtec2','keypress',['output','waste']);
         executeequipmentfunction('Vapourtec2','setFlowRate',['pumpA',0]);
              executeequipmentfunction('Vapourtec2','setFlowRate',['pumpB',0]);
         executeequipmentfunction('Vapourtec2','setTemperature',[1,-1000]);
         executeequipmentfunction('Vapourtec2','setTemperature',[2,-1000]);
         executeequipmentfunction('Vapourtec2','setTemperature',[3,-1000]);
         executeequipmentfunction('Vapourtec2','setTemperature',[4,-1000]);
         executeequipmentfunction('Vapourtec2','start',[]);

         //Start experiment
         phase1_1();
       }
```

```
    //--------------------------== Phase 3.1 ============================
    function phase1_1(){
        //Phase1 cools flask1 to 0 degrees, then adds Mercapto dropwise, then stirs
for 65 mins at room temp
        executeequipmentfunction('Vapourtec2','setTemperature',[1,0]);


addlistener("round((float)getequipmentdata('Vapourtec2')['temperatures']['slot1']['
temperature'],0)","equals","2", "phase1_2()");
    }

    function phase1_2(){
        //Start Mercapto dropwise (2.85mL over six mins)
        executeequipmentfunction('Aladdin2', 'setPumpDirection', ["INF"]);
        executeequipmentfunction('Aladdin2', 'setPumpRate', [0.500]);
        executeequipmentfunction('Aladdin2', 'setVolume', [2.850]);
        executeequipmentfunction('Aladdin2', 'start', []);


addlistener("(float)getequipmentdata('Aladdin2')['dispensed']['inject']","greaterth
anequalto","2", "phase1_3()");
    }

    function phase1_3(){
        //Warm to room temp
        executeequipmentfunction('Vapourtec2','setTemperature',[1,-1000]);


addlistener("round((float)getequipmentdata('Vapourtec2')['temperatures']['slot1']['
temperature'],0)","greaterthanequalto","15", "phase1_4()");
    }

    function phase1_4(){
        //Stir for 60 mins
        $time = time() + 3600;
        addlistener("time()","greaterthanequalto",$time, "phase1_5()");
    }

    function phase1_5(){
        //Add phase 2 material dropwise and heat
        executeequipmentfunction('Vapourtec2','keypress',['output','collect']);
        executeequipmentfunction('Vapourtec2','setTemperature',[1,90]);
//BP ethanol is 78.4 C

        //Stir for 2 hours
        $time = time() + 7200;
        addlistener("time()","greaterthanequalto",$time, "phase1_6()");
    }

    function phase1_6(){
        //Close dropwise valve, ADD KOH SOLUTION TO VERTICAL COLUMN
        executeequipmentfunction('Vapourtec2','keypress',['output','waste']);

        $time = time() + 300;
        addlistener("time()","greaterthanequalto",$time, "phase2_1()");
    }

    //-----------------------== Phase 3.2 ============================
    function phase2_1(){
        //Add KOH dropwise
        executeequipmentfunction('Vapourtec2','keypress',['output','collect']);

        // Turn off heater after 4 hours
        $time = time() + 14400;
        addlistener("time()","greaterthanequalto",$time, "phase2_2()");
    }

    function phase2_2(){
```

```
        executeequipmentfunction('Vapourtec2','keypress',['output','waste']);
        executeequipmentfunction('Vapourtec2','setTemperature',[1,-1000]);

        //Wait for vessel to cool

addlistener("round((float)getequipmentdata('Vapourtec2')['temperatures']['slot3']['
temperature'],0)","lessthanequalto","30", "experiment_shutdown()");
    }

      function experiment_shutdown(){
            //This code executes when the experiment ends
            executeequipmentfunction('Vapourtec2','stop',[]);
            stopexperiment();
      }
?>
```

4.0 General Experimental

^{1}H-NMR spectra were recorded on a Bruker Avance DPX-600 spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm, d_6-DMSO = 2.50 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm, d_6- DMSO = 39.52 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of 1H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, 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, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant.

Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbency of the peak: w = weak, less than 30% of the most intense peak; m = medium, ca. 31-69% of the most intense peak; s = strong, greater than 70% of the most intense peak.

Melting points were performed on a Stanford Research Systems MPA100 (OptiMelt) automated melting point system, and are uncorrected.

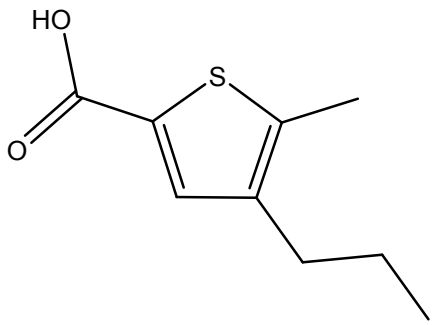
High resolution mass spectrometry (HRMS) within ± 5 ppm was carried out on a Waters Micromass LCT Premier spectrometer using time of flight with positive ESI.

Flash column chromatography was performed on a Biotage SP1 using Biotage or Silicycle columns packed with high-purity grade silica gel (Sigma-Aldrich, pore size 60 Å, 230-400 mesh particle size).

Elemental composition microanalysis was performed by the Microanalytical Laboratories at the Department of Chemistry, University of Cambridge and results are reported to two decimal places.

Unless stated otherwise, reagents were obtained from commercial sources and used without purification. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

Synthesis of ***5-methyl-4-propylthiophene-2-carboxylic acid.***



---- Phase 1

2.24 mL of phosphorous oxychloride was added dropwise to a mixture of 2 mL dichloromethane (DCM) in 10 mL dimethylformamide at 0 ^{o}C, and stirred vigorously in a 50 mL integrated batch flask. The mixture was allowed to warm to room temperature, then left to stir for 35 minutes.

The product mixture was pumped at 0.5 mL.min^{-1} through a T-piece where it met a solution of hexanone in DCM (17.3 mmol in 12 mL DCM) before passing through a 10 mL PTFE coil held at 90 ^{o}C. On exiting the coil, the product mixture met a sodium acetate stream (7.0 g in 20 mL H_2O) pumped at 1.0 mL.min^{-1}, and a dilution stream of DCM at 1.0 mL.min^{-1}.

---- Phase 2

The biphasic mixture passed through a length of tubing to promote interphasic mixing between the aqueous and organic layers, before entering a separation column. As described in the main article and in text above, an automated system was used to control the phase boundary level in this column. The organic layer was collected and stored in a reservoir, while the aqueous layer was discarded as waste.

Organic solution stored in this column was mixed at 1 mL.min^{-1} with an ethanol stream (also at 1 mL.min^{-1}) and pumped into our single stage distillation column, held at 90 ^{o}C. Ethanol-enriched product mixture was pumped from this column into a reservoir held above the 100 mL integrated batch vessel used for Phase 3.

---- Phase 3

700 mg of sodium was added to 30 mL ethanol at 0 ^{o}C, and left to stir until completely reacted (approx. 1 hour). 2.85 mL of ethyl 2-mercaptoacetate was added dropwise, then the solution was allowed to warm to room temperature and stirred for 60 minutes. The organic mixture from Phase 2 was added dropwise before the reaction flask was heated to 90 ^{o}C, and stirred vigorously while under reflux for 2 hours. A solution of potassium hydroxide in water (2.5 g in 75 mL H_2O) was added dropwise and the resulting mixture left to stir for 4 hours.

967 mg of the product (5.2 mmol, **30% yield**), 5-methyl-4-propylthiophene-2-carboxylic acid, was isolated as a white solid after the product mixture was purified using flask chromatography over silica (DCM and methanol, gradient of 0% to 7% methanol over 25 column volumes) and excess solvent removed under vacuum.

Although this compound is commercially available, full characterisation data have not been reported previously and so are included here.

^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ = 12.77 (s, 1H), 7.48 (s, 1H), 2.47 (t, J = 7.5 Hz, 2H), 2.37 (s, 3H), 1.57 – 1.51 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

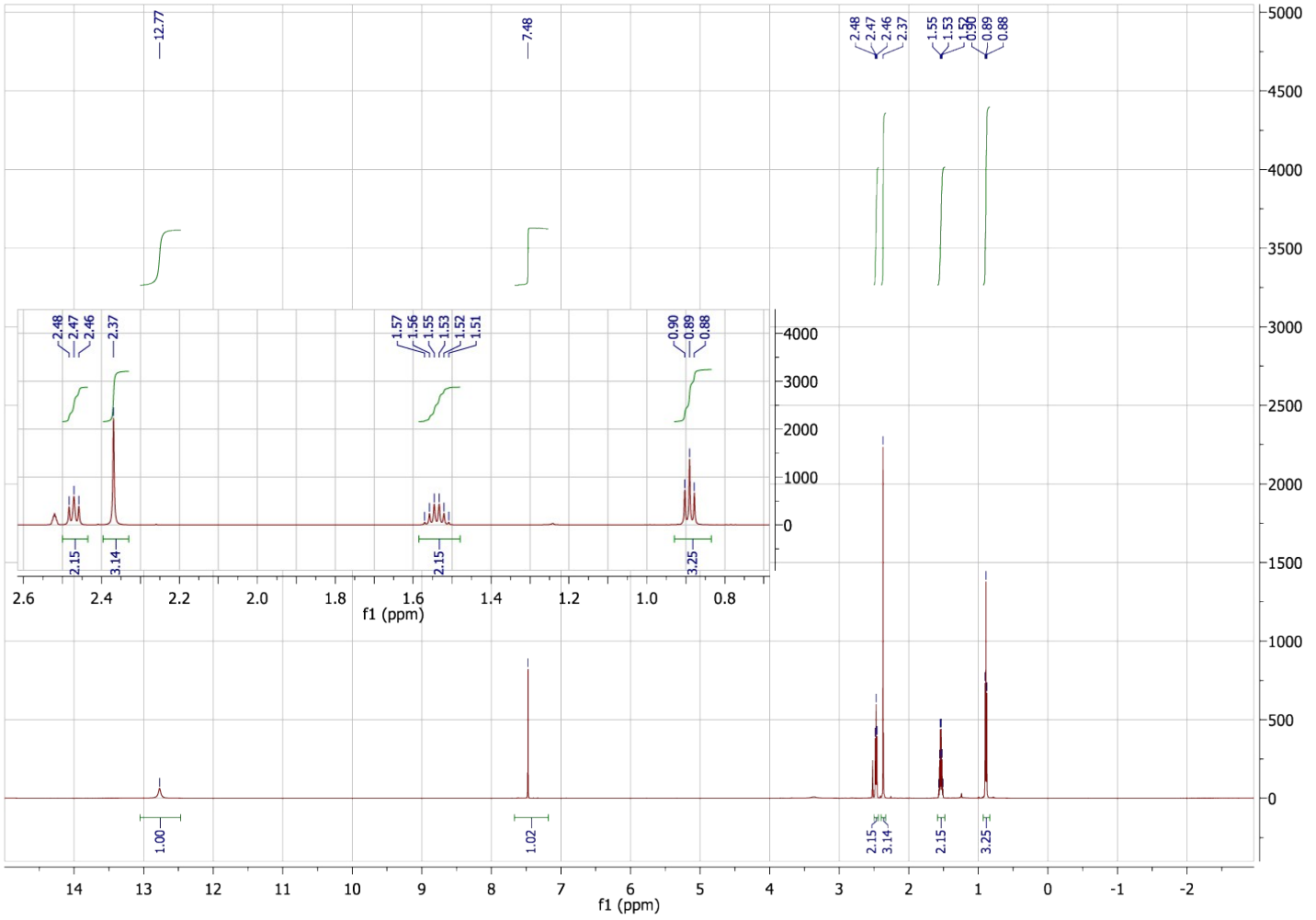
^{13}C NMR (151 MHz, $(CD_3)_2SO$): δ = 163.3, 141.3, 139.8, 135.3, 129.8, 29.8, 23.4, 14.0, 13.6.

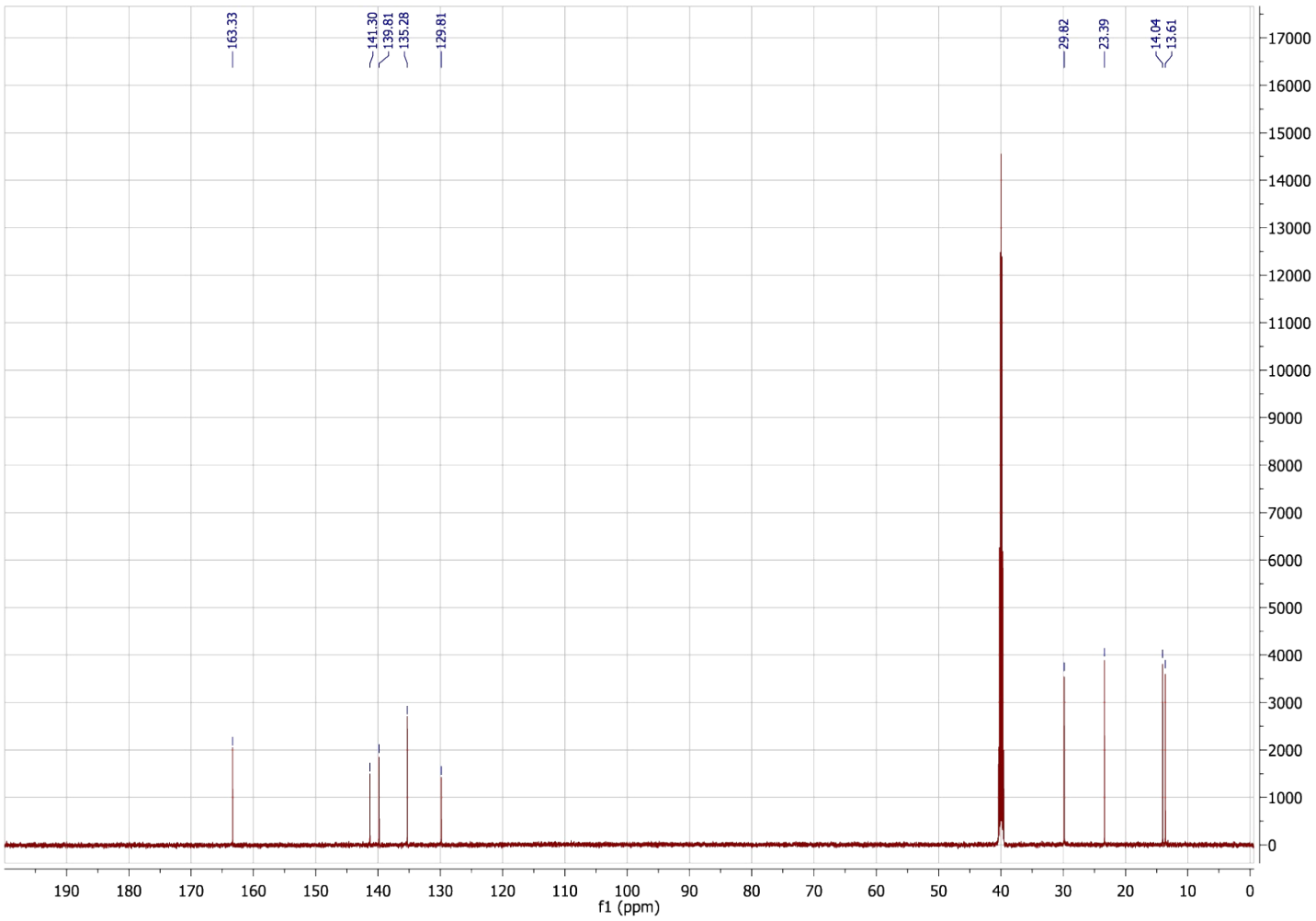
IR (neat): ν /cm^{-1} = 2961 (m), 2928 (m), 2857 (w), 2524 (w), 1645 (s), 1522 (m), 1444 (s), 1374 (w), 1307 (s), 1273 (s), 1231 (m), 1199 (m), 1160 (m), 1121 (m), 1064 (m), 1049 (m), 944 (m), 894 (m), 866 (w), 843 (w), 785 (w), 760 (s), 716 (m), 645 (m).

HRMS: *m*/*z* calc. for $[C_9H_{13}O_2S]^+$ ($[M + H]^+$) 185.0636, found 185.0639, Δ = 1.9 ppm.

Elemental Analysis: Found: C, 58.8%; H, 6.6%. $C_9H_{12}O_2S$ requires C, 58.6%; H, 6.6%.

Melting Point: 89 – 90 °C (dichloromethane).


12.77
7.48
2.48
2.47
2.46
2.37
1.55
1.53
1.52
0.90
0.89
0.88
1.57
1.56
1.55
1.53
1.52
1.51
2.15
3.14
2.15
3.25
1.00
1.02
2.15
3.14
2.15
3.25
f1 (ppm)
f1 (ppm)


163.33
141.30
139.81
135.28
129.81
29.82
23.39
14.04
13.61
f1 (ppm)