

A prototype device for evaporation in flow and batch chemical processes

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1 General chemistry

¹H-NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, *d*₆-DMSO = 2.50 ppm). ¹H resonances are reported to the nearest 0.01 ppm. ¹³C-NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference (CDCl₃ = 77.16 ppm, *d*₆-DMSO = 39.52 ppm). All ¹³C 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, t = triplet, 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. Unless stated otherwise, reagents were obtained from commercial sources and used without purification.

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

High resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight with positive ESI, or conducted by Mr Paul Skelton on a Bruker BioApex 47e FTICR spectrometer using positive ESI or EI at 70 eV to within a tolerance of 5 ppm of the theoretically calculated value.

LC-MS analysis was performed on an Agilent HP 1100 series chromatography (Mercury Luna 3u C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionization source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. Retention time (*R*_t) is given in minutes (min) to the nearest 0.1 min and the *m/z* value is reported to the nearest mass unit (m.u.).

X-ray crystal structures were determined by Dr John Davies at the Department of Chemistry, University of Cambridge. CIF numbers are reported as part of compound characterization.

Elemental analyses within a tolerance of ±0.3% of the theoretical values were determined by Mr Alan Dickerson and Mrs Patricia Irele in the microanalytical laboratories at the Department of Chemistry, University of Cambridge.

Dichloromethane (DCM), Ethyl acetate (EtOAc), *n*-hexane, acetone and methanol (MeOH) were obtained as laboratory reagent grade solvents from Fischer Scientific and distilled before use. All other solvents were obtained as reagent grade and used without further purification.

2 Construction of the prototype

The prototype was constructed in-house from commercially available components which are commonly found in laboratories performing flow chemistry. The only exception to this was the top end piece insert (Part 2) for the column which was bored out with a 1/4 inch hole to accommodate insertion of the 1/4"

PTFE tube (Part 6) (**Figure S-1**, **Table S-1**). Components were sourced from Upchurch Scientific,¹ Vapourtec,² Omnifit,³ Cole Parmer⁴ and Swagelok.⁵

Table S-1 Component part list for the prototype.

1	Omnifit® column 100 x 15 mm o.d.
2	Modified top end piece assembly
3	Bottom end piece assembly
4	PTFE end fitting
5	Connection cap
6	PTFE tubing 1/4" (6.35 mm) o.d. x 3/16" (4.8 mm) i.d.
7	Swagelok® stainless steel union tee, 1/4" (6.35 mm) tube o.d.
8	Swagelok® stainless steel bored-through reducer, 1/8" (3.17mm) x 1/4" (6.35 mm) tube o.d.
9	Stainless steel tubing, 1/8" (3.17mm) o.d. x 0.080" (2.03mm) i.d.
10	Swagelok® stainless steel union tee, 1/8" (3.17mm) tube o.d.
11	Swagelok® stainless steel bored-through reducer, 1/16" (1.587mm) x 1/8" (3.17mm) tube o.d.
12	Stainless steel tubing, 1/16" (1.587mm) o.d. x 1/200" (0.127mm) i.d.

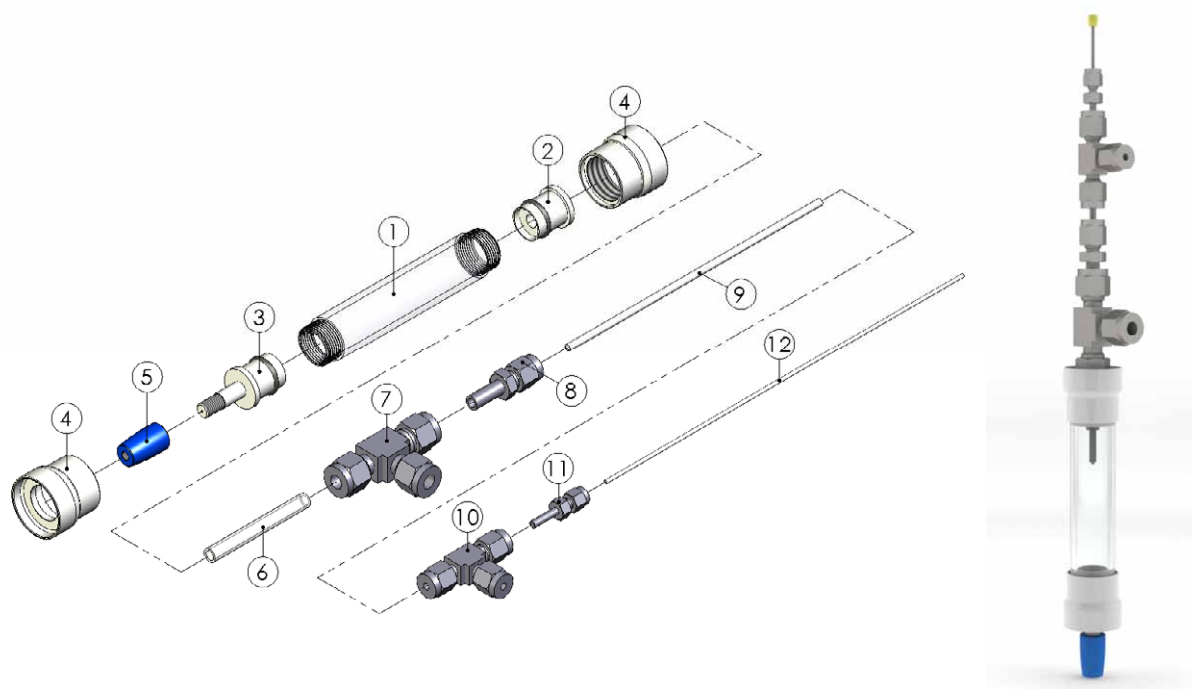


Figure S-1 Expanded (left) and assembled (right) diagrams of the prototype.

The spray tip of the prototype was setup as shown in **Figure S-2**. The central 1/16" diameter tube protruded 1 mm from the 1/8" gas supply tube which protruded 15 mm from the 1/4" PTFE gas outlet. The 1/4" PTFE gas outlet protruded 4 mm from the inside of the column end piece (**Figure S-2**).

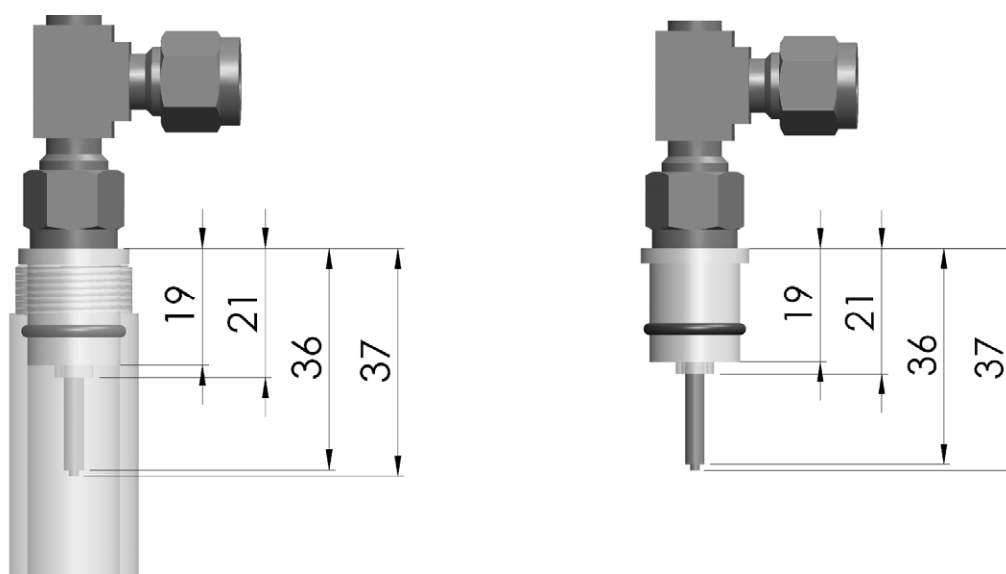


Figure S-2 Dimensions of the prototype spray tip (values are reported in mm).

3 General operation of the prototype

The liquid and gas inlets, and the gas/vapour outlet are shown in **Figure S-3**. The liquid feed to the prototype was pumped by one of the HPLC pumps on a Vapourtec R2/R4 flow reactor while heating of the prototype was achieved by placing the Omnifit column inside a glass Vapourtec column heater attached to the Vapourtec R2/R4 flow reactor.² The desolvation gas inlet was connected to a 1 bar in-house nitrogen gas supply, via an analogue adjustable gas flow meter. The gas outflow of the prototype was connected to a cold trap kept at $-78\text{ }^{\circ}\text{C}$ by dry ice and acetone, or any other efficient condensing apparatus. The solvent output from the prototype was controlled by a WPI Peristar-Pro peristaltic pump.⁶

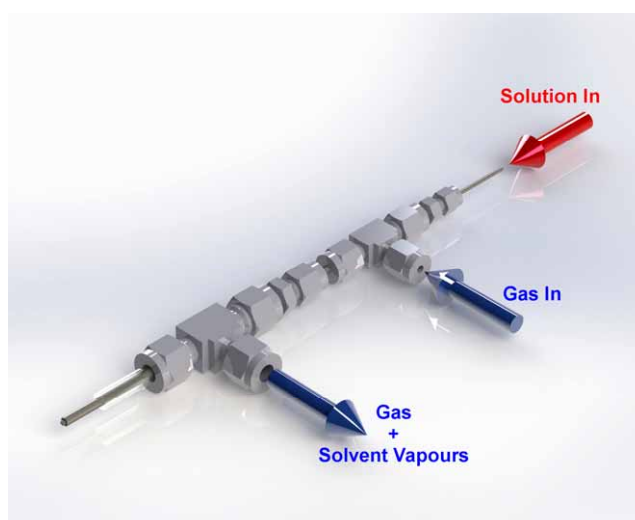


Figure S-3 Operation of the prototype evaporator.

4 Solvent removal using the prototype

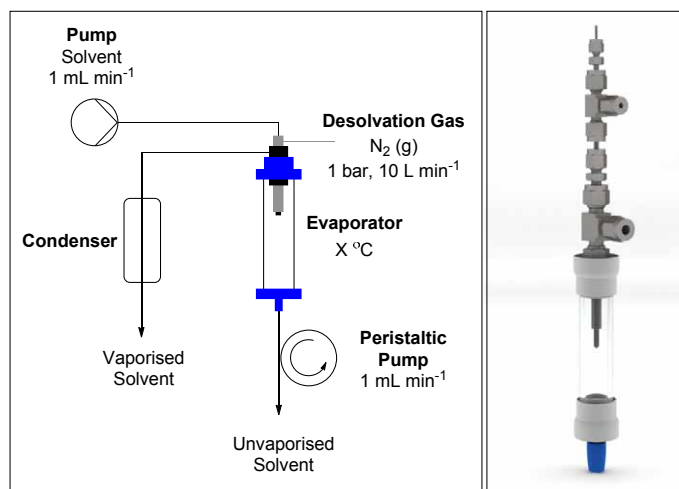


Figure S-4 Graphical representation of the prototype setup for investigating solvent removal.

The prototype was setup as shown in **Figure S-4**. The solvent to be tested was pumped (1 mL min^{-1}) into the device by a Vapourtec R2/R4 pump and the flow rate of the nitrogen desolvation gas was maintained at 10 L min^{-1} . The evaporation chamber (an Omnifit column) was heated to temperatures of 25, 40, 60 or $80 \text{ }^\circ\text{C}$ using a Vapourtec R2/R4 column heater. The output of unvaporised solvent was controlled by a WPI Peristar-Pro peristaltic pump (1 mL min^{-1}).

The prototype was run in this way for a period of 5 min during which time the output of unvaporised solvent was measured by a standard laboratory measuring cylinder.

5 Solvent switch: telescoped flow synthesis of 2',6'-dimethoxyacetophenone (2)

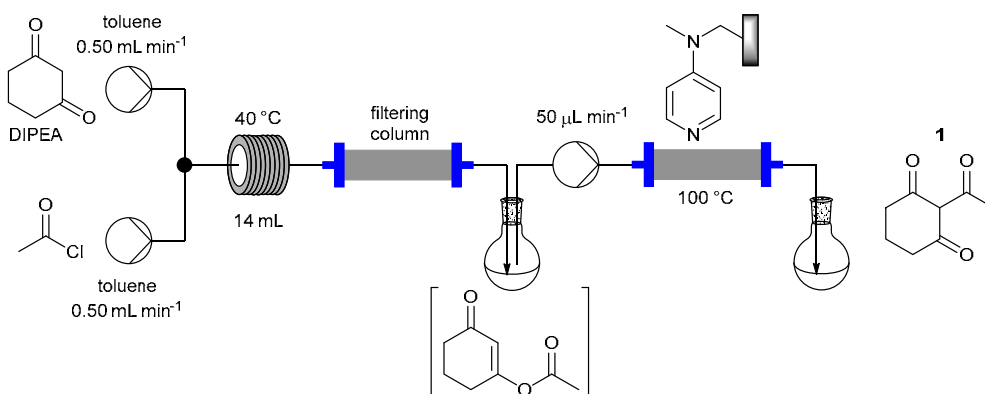


Figure S-5 Flow synthesis of **1**.

5.1 Flow synthesis of 2-acetyl 1,3-cyclohexandione (**1**)

The flow synthesis of **1** was performed according to the procedure previously described by Battilocchio *et al* (Figure S-5).⁷

Red oil; δ_H (400 MHz, CDCl₃, 25 °C) 15.75 (1H, s), 2.65 (2H, t, $J = 6.9$ Hz), 2.61 (3H, s), 2.48 (2H, t, $J = 6.9$ Hz) and 1.97 (2H, m, $J = 6.9$ Hz); δ_C (100 MHz, CDCl₃, 25 °C) 203.1 (C), 198.7 (C), 195.4 (C), 113.2 (C), 38.6 (CH₂), 33.2 (CH₂), 28.7 (CH₂) and 19.0 (CH₃); ν_{max}/cm^{-1} 2953, 1660, 1550, 1410, 1351, 1188, 1007, 919 and 841; LC-MS $R_t = 2.62$ min, m/z $[M+H]^+ = 155.35$; HRMS (ESI) m/z calcd for C₈H₁₁O₃⁺ 155.0708; found 155.0705.

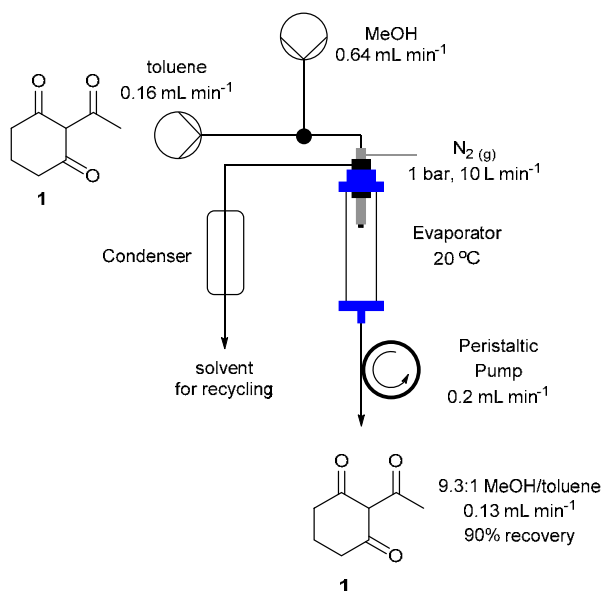


Figure S-6 Solvent switch of **1** from toluene to MeOH.

5.2 Solvent switch of **1** from toluene to MeOH

The toluene solution of **1** (10 mL, 1.5 M) was pumped (0.16 mL min^{-1}) to a T-piece where it combined with a flow of MeOH (0.64 mL min^{-1}) before going into the central tube of the prototype evaporator (**Figure S-6**). Nitrogen gas was flowed (10 L min^{-1} , 1 bar) into the desolvation gas line and the evaporation chamber was maintained at $20 \text{ }^\circ\text{C}$. A solution of **1** in MeOH/toluene (9.3:1 MeOH/toluene, 0.13 mL min^{-1}) was removed from the evaporator by the peristaltic pump (0.2 mL min^{-1}) over a period of 1 h and used in the next step of the flow synthesis (**Figure S-6**). A portion of the output solution (1 mL) was further concentrated by rotary evaporation and dried in *vacuo* to return **1** (0.2496 g, 90%).

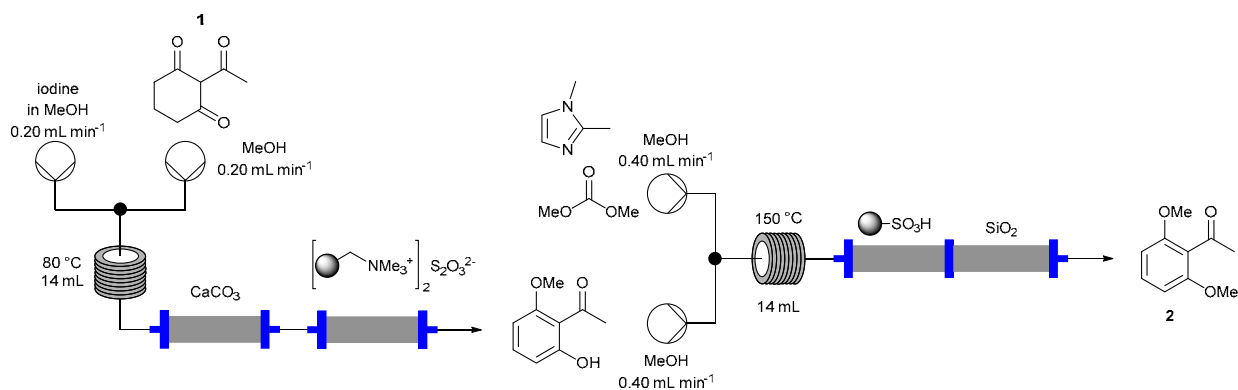


Figure S-7 Flow synthesis of **2**.

5.3 Flow synthesis of 2',6'-dimethoxyacetophenone (**2**)

The MeOH enriched solution of **1** could be processed according to the flow procedure previously described by Battilocchio *et al* (**Figure S-7**).⁷

Yellow solid; Mp $67\text{--}71 \text{ }^\circ\text{C}$; δ_{H} (400 MHz, CDCl_3 , $25 \text{ }^\circ\text{C}$) 7.26 (1H, t, $J = 8.7 \text{ Hz}$), 6.55 (2H, d, $J = 8.7 \text{ Hz}$), 3.80 (6H, s), 2.47 (3H, s); δ_{C} (100 MHz, CDCl_3 , $25 \text{ }^\circ\text{C}$) 202.8 (C), 156.8 (C), 130.6 (CH), 104.0 (CH), 55.9 (CH_3), 32.3 (CH_3); $\nu_{\text{max}}/\text{cm}^{-1}$ 3000, 2943, 1696, 1590, 1471, 1434, 1358, 1282, 1249, 1107, 781, 759, 735; LC-MS $R_t = 4.20 \text{ min}$, m/z $[\text{M}+\text{H}]^+ = 181.37$; HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_{13}\text{O}_3^+$ 181.0865; found 181.0857.

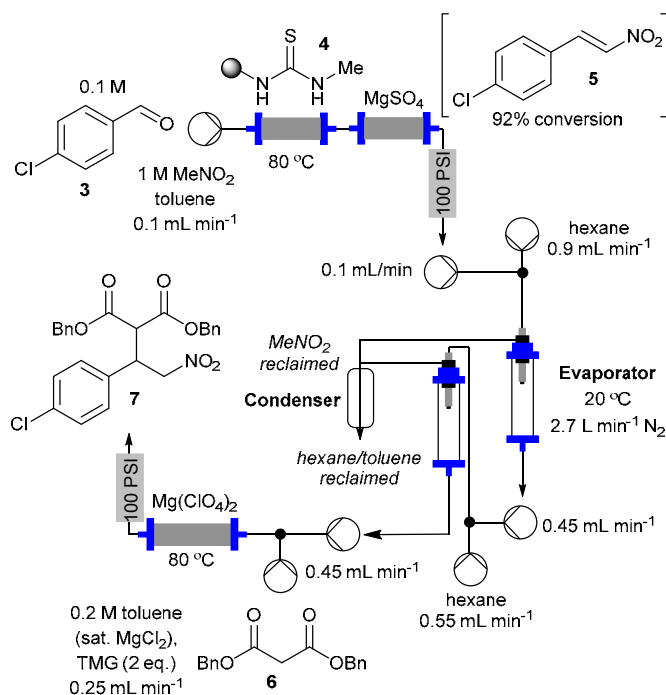


Figure S-8 In-line removal of nitromethane.

6 In-line removal of excess nitromethane and flow synthesis of dibenzyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (7)

6.1 Synthesis of (*E*)-1-chloro-4-(2-nitrovinyl)benzene (5)

A solution of 4'-chlorobenzaldehyde (**3**) (0.1 M, 5.6 g, 39 mmol) and nitromethane (1 M, 24.4 g, 0.38 mol) in toluene (400 mL) was pumped (0.1 mL min⁻¹) through an Omnifit column containing silica supported methyl thiourea (Si-MTU) (1.4 g, 0.8-1.4 mmol/g) (**4**) heated to 80 °C on a Uniqsis FlowSyn reactor. The solution of nitro alkene **5** obtained was then dried by passing through a column of anhydrous MgSO₄. The solution of **5** exited the flow reactor via a 100 psi back pressure regulator (bpr) and was collected in a flask. Analysis of the obtained solution by ¹H NMR indicated that 92% of **3** was converted to **5** (Figure S-8).

A sample was concentrated and dried *in vacuo* for characterisation. Yellow solid; Mp 112-114 °C; δ_H (400 MHz, CDCl₃, 25 °C) 7.94 (1H, d, *J* = 13.7 Hz), 7.56 (1H, d, *J* = 13.7 Hz), 7.48 (2H, d, *J* = 8.6 Hz), 7.41 (2H, d, *J* = 8.6 Hz); δ_C (100 MHz, CDCl₃, 25 °C) 138.3 (C), 137.7 (CH), 137.5 (CH), 130.4 (CH), 129.8 (CH), 128.6 (C); ν_{max}/cm^{-1} 3105, 1633, 1592, 1568, 1516, 1490, 1406, 1335, 1260, 1203, 1180, 1112, 1086, 1013, 969, 941, 854, 816, 745, 728, 669; LCMS *R*_t = 4.79 min, [M+H]⁺ = 184.17; microanalysis found: C, 52.3; H, 3.3; N, 7.6%. C₈H₆NO₂Cl requires C, 52.3; H, 3.3; N, 7.5%; the structure was unambiguously confirmed by single X-ray crystallography and deposited at Cambridge University with the unique reference CCDC940593, space group P2₁/n, *a* = 7.307 Å, *b* = 7.137 Å, *c* = 15.626 Å, α = 90.0°, β = 91.5°, γ = 90.0°.

6.2 Removal of excess nitromethane reagent

On a Vapourtec R2/R4 flow reactor the solution of nitro alkene **5** (0.092 M) in nitromethane (ca 0.9 M) and toluene (20 mL) was pumped (0.1 mL min⁻¹) to a T-piece where it combined with a flow stream of hexane (0.9 mL min⁻¹). The toluene/hexane solution was introduced to the prototype evaporator along with a 2.7 L min⁻¹ flow of nitrogen desolvation gas. The evaporation chamber was maintained at 20 °C and the outlet peristaltic pump was operated at 0.5 mL min⁻¹. Over 90 min the 0.45 mL min⁻¹ flow of **5** was collected and subjected to ¹H-NMR analysis to determine its composition (5.6:1 mole ratio of hexane to toluene, 1.4:1 mole ratio of nitromethane to **5**). The new solution of **5** was pumped (0.45 mL min⁻¹) back into the evaporator (20 °C, 2.7 L min⁻¹ N₂) along with an additional flow of hexane (0.55 mL min⁻¹). A 0.5 mL min⁻¹ flow of unvaporised solution was collected from the outlet and subjected to ¹H-NMR analysis to determine its composition (10:1 mole ratio of hexane to toluene, 0.04:1 mole ratio of nitromethane to **5**) (**Figure S-8**).

¹H-NMR analysis of the condensed solvent revealed it to be 8.3:1 hexane to toluene with only trace levels of nitromethane. This solvent could be recycled into either of the hexane flow streams. The nitromethane was found to form a solid on the condenser walls and was thus easily isolated in good purity (trace levels of hexane and toluene evident in the ¹H-NMR spectrum).

6.3 Synthesis of dibenzyl 2-(1-(4-chlorophenyl)-2-nitroethyl)malonate (7)

The solution of **5**, now free from nitromethane, was pumped (0.45 mL min⁻¹) on a Uniqsis FlowSyn flow reactor where it was combined with a solution (2 mL) of dibenzyl malonate (**6**) (0.2 M, 113.6 mg, 0.4 mmol) and 1,1,3,3-tetramethyl guanidine (TMG) (0.8 M, 0.1 mL, 0.8 mmol) in toluene which had been pre-saturated with MgCl₂ overnight and filtered before pumping (0.25 mL min⁻¹). The combined solutions reacted inside an Omnifit column packed with Mg(ClO₄)₂ (1 g, 4 mmol) heated to 80 °C before exiting the flow reactor via a 100 psi back pressure regulator (bpr). The solution was collected and concentrated *in vacuo* to provide the crude product (**7**). Crystallisation by slow evaporation from a DCM/hexane solution provided **7** in analytical purity as an off-white solid (0.11 g, 0.24 mmol, 60%) (**Figure S-8**).

Off-white solid; Mp 77-80 °C; δ_H (400 MHz, CDCl₃, 25 °C) 7.42-7.25 (10H, m), 7.19 (2H, d, $J = 8.4$ Hz), 7.09 (2H, d, $J = 8.6$ Hz), 5.18 (2H, s), 4.98 (2H, s), 4.90-4.73 (2H, m), 4.24 (1H, td, $J = 9.4, 4.9$ Hz), 3.91 (1H, d, $J = 9.3$ Hz); δ_C (100 MHz, CDCl₃, 25 °C) 167.0 (C), 166.4 (C), 134.7 (C), 134.6 (C), 134.5 (C), 134.4 (C), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 77.3 (CH₂), 68.0 (CH₂), 67.8 (CH₂), 54.8 (CH), 42.4 (CH); ν_{max}/cm^{-1} 3033, 1731, 1553, 1493, 1456, 1376, 1255, 1214, 1149, 1095, 1015, 972, 906, 828, 738, 696; LC-MS $R_t = 5.40$ min, m/z [M+Na]⁺ = 489.93; HRMS (ESI): m/z calcd for C₂₅H₂₂NO₆ClNa⁺ 490.1033, found 490.1024.

7 References

[1] <http://webstore.idex-hs.com/>

[2] <http://www.vapourtec.co.uk>

[3] <http://www.omnifit.com/>

[4] <http://www.coleparmer.co.uk/>

[5] <http://www.swagelok.co.uk/landingpages/index-uk.htm>

[6] http://store.wpiinc.com/Peri-Star-Pro-Peristaltic-Pump-_p_1676.html

[7] C. Battilocchio, B. J. Deadman, N. Nikbin, M. O. Kitching, I. R. Baxendale, and S. V. Ley, *Chem. Eur. J.*, 2013, DOI: 10.1002/chem.201300696.