

Supporting Information

Continuous multi-step synthesis by extrusion - telescoping solvent-free reactions for greater efficiency

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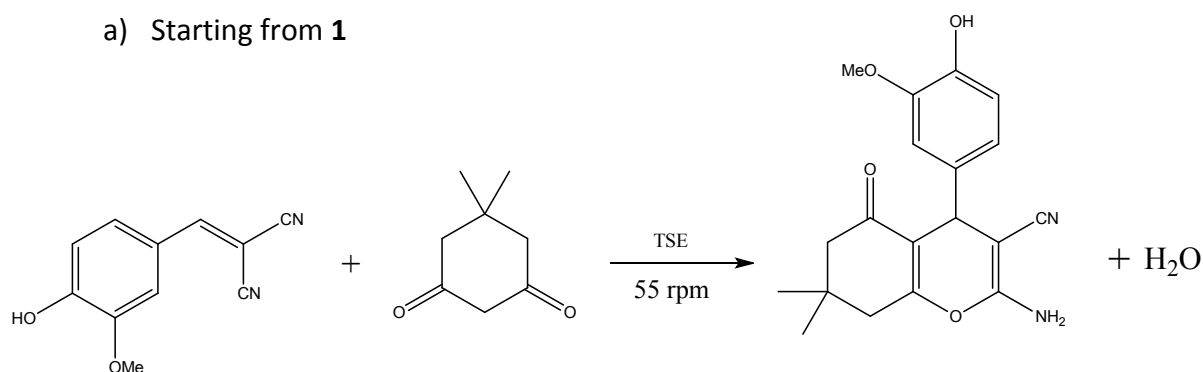
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1. Experimental Details

All materials were purchased from Sigma Aldrich UK with >98% purity and were used as received, unless indicated. Extrusion was carried out using a Three-Tec 12 mm, 40:1 L:D co-rotating twin screw extruder with six heating zones. NMR spectroscopy was carried out with a Bruker Advance DPX 300 with d^6 -DMSO as solvent. Elemental analysis was carried out on a Perkin Elmer PE2400CHNS instrument in CHN mode.

2. Synthesis of 2

a) Starting from 1



Each of the twin screw extruders six heating zones were heated to 160 °C. A volumetric feeder was used to feed **1** (20.0 g, 99.9 mmol) and dimedone (14.0 g, 99.9 mmol) into the barrel at a feed rate of 4 %, with a screw speed of 55 rpm. Under these conditions, 100 % conversion to product was achieved as determined by ¹H NMR spectroscopy in d^6 -DMSO. The product obtained was observed as a fine orange powder.

¹H NMR (300 MHz, d^6 -DMSO) δ 8.86 (s, 1H, OH), 6.93 (s, 2H, NH₂), 6.66 (d, J = 11.6 Hz, 2H, Ar), 6.51 (d, J = 7.9 Hz, 1H, Ar), 4.07 (s, 1H, CH), 3.71 (s, 3H, CH₃), 2.26 (d, J = 15.9 Hz, 1H, CH), 2.10 (d, J = 13.1 Hz, H, CH), 1.04 (s, 3H, CH₃), 0.97 (s, 3H, CH₃).

CHNS Theoretical: C 67.05 %, H 5.92 %, N 8.23 % Actual: C 67.24 %, H 5.72 %, N 7.61 %.

b) Telescoping of the Knoevenagel and Michael addition to form 2

Section 1 of the twin screw extruder was set to a temperature of 25 °C, sections 2 and 3 were set to 120 °C, with section 4 heated to 135 °C and the final two sections (5 and 6) were heated to 160 °C. A screw speed of 55 rpm was employed. To Feeder A, vanillin (20 g, 0.131 mol), malononitrile (8.68 g, 0.131 mol) and sodium carbonate (1.3 g, 0.01 mol) were added and fed into the extruder at a rate of 192.4 ghr⁻¹ whilst Feeder B was charged with dimedone,

which was fed into the extruder at a rate of 158.8 ghr⁻¹. An orange solid was produced at a throughput rate of 154 ghr⁻¹.

¹H NMR (300 MHz, *d*⁶-DMSO) δ 8.85 (s, 1H, OH), 6.94 (s, 2H, NH₂), 6.65 (d, *J* = 11.6 Hz, 2H, Ar), 6.53 (d, *J* = 8.0 Hz, 1H, Ar), 4.07 (s, 1H, CH), 3.71 (s, 3H, CH₃), 2.28 (d, *J* = 15.8 Hz, 1H, CH), 2.07 (d, *J* = 13.0 Hz, H, CH), 1.04 (s, 3H, CH₃), 0.97 (s, 3H, CH₃).

CHNS Theoretical: C 67.05 %, H 5.92 %, N 8.23 % Actual: C 67.12 %, H 5.91 %, N 8.13 %.

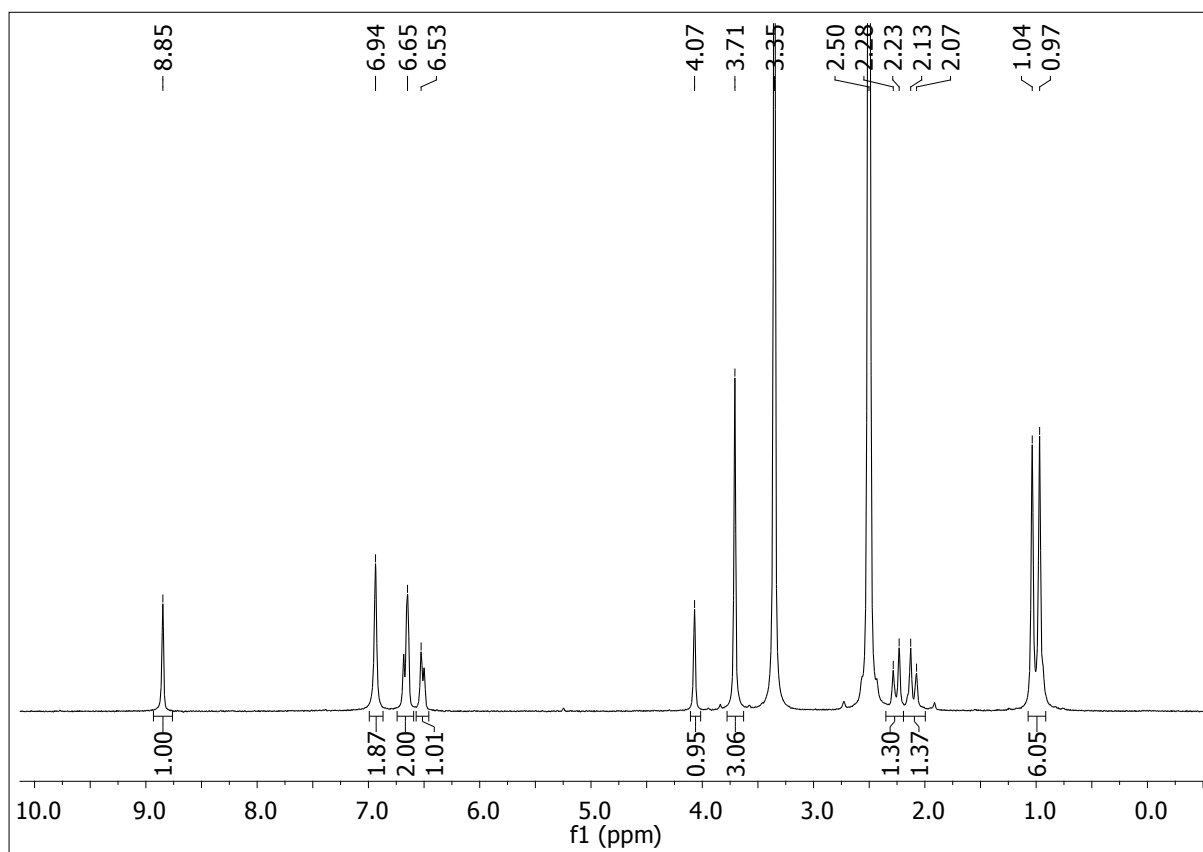
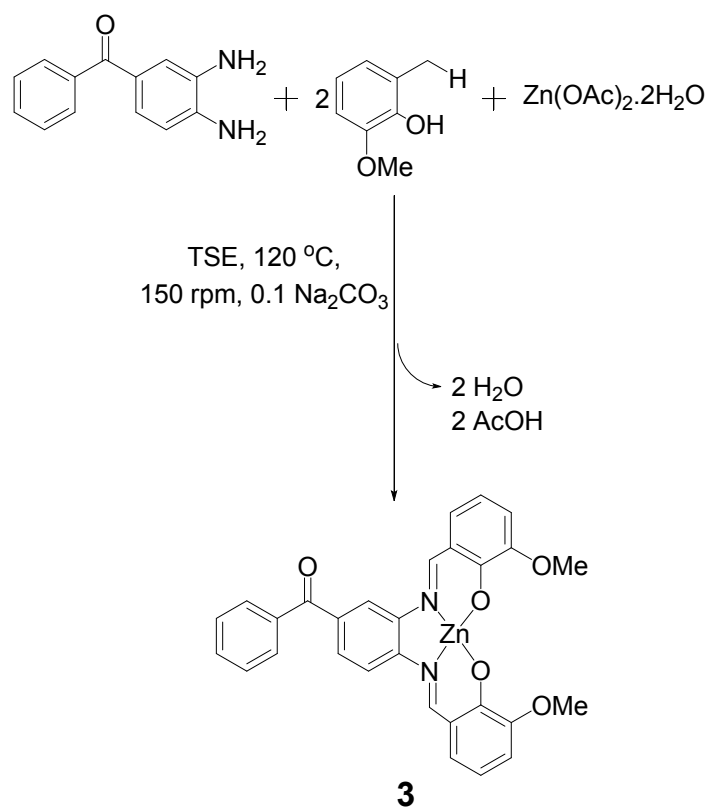


Figure S1: ¹H NMR spectrum (in *d*⁶-DMSO) of the Knoevenagel condensation – Michael Addition telescoped reaction.

3. Synthesis of 3



Each of the extruders six heating zones were set to 120 °C, with a screw speed of 150 rpm. A volumetric feeder was charged with *o*-vanillin (10 g, 66 mmol), 3,4-diaminobenzophenone (6.97 g, 33 mmol) and zinc acetate dihydrate (7.24 g, 33 mmol), which was fed into the extruder at a rate of 345.0 ghr⁻¹. Under these conditions, 100 % conversion to product was achieved as determined by ¹H NMR spectroscopy in *d*⁶-DMSO with a throughput of 128 ghr⁻¹.

¹H NMR (300 MHz, *d*⁶-DMSO) δ 9.08 (d, J = 9.8, 2H, CH), 8.25 (s, 1H, Ar), 8.03 (d, J = 8.6 Hz, 1H, Ar), 7.83 (d, J = 7.2 Hz, 2H, Ar), 7.71 (d, J = 7.4 Hz, 1H, Ar), 7.62 (dd, J = 15.0, 7.3 Hz, 3H, Ar), 7.06 (s, 2H, Ar), 6.88 (t, J = 6.1 Hz, 2H, Ar), 6.45 (dd, J = 17.5 Hz, 7.8, 2H, Ar), 3.77 (d, J = 1.9, 6H, OCH₃).

CHNS Theoretical: C 64.04 % H 4.08 % N 5.15 % Zn 12.02 % Actual: C 64.00 % H 3.92 % N 5.13 % Zn 12.39 %

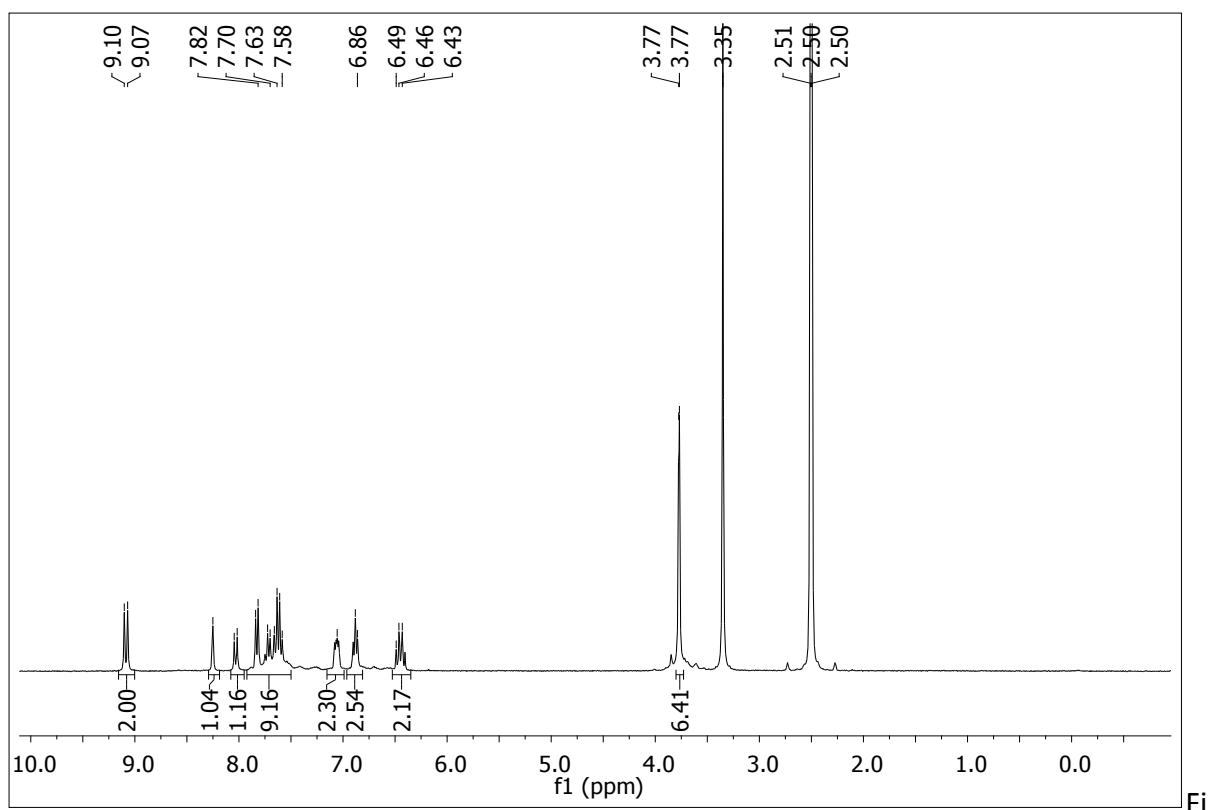
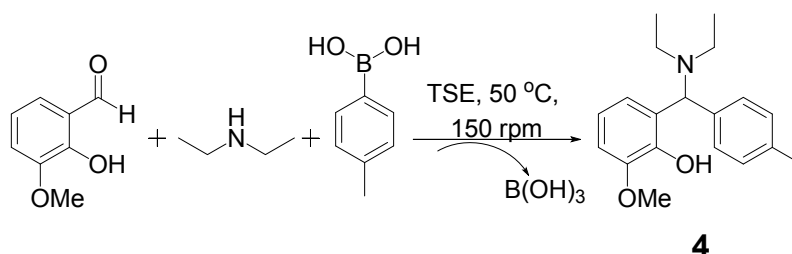


Figure S2: ^1H NMR spectrum (in d^6 -DMSO) of the zinc complexed Schiff base, **3**.

4. Synthesis of 4



Each of the extruder heating zones were set to 50 °C, with a screw speed of 150 rpm, employing the screw configuration consisting of reverse screw segments. A volumetric feeder was charged with 4-methylphenylboronic acid (17.86 g, 131.36 mmol) and *o*-vanillin (20.0 g, 131.36 mmol), which was fed into the extruder at a rate of 181.7 g hr⁻¹. A syringe pump was attached charged with diethylamine (13.4 mL, 131.36 mmol), and this was fed into the extruder at a rate of 65.1 ml hr⁻¹. Under these conditions, 100 % conversion to product was achieved as determined by ^1H NMR spectroscopy in d^6 -DMSO with a throughput of 184.6 g hr⁻¹. A sample was purified by dissolving in ethyl acetate (20 mL) and washing with distilled water (20 mL) three times to remove the presence of boric acid. The organic layer was isolated and the solvent removed under pressure to yield an orange solid that was dried in a desiccator overnight.

^1H NMR (300 MHz, d^6 -DMSO) δ 7.59-7.46 (dd, $J = 9.0, 6.0$ Hz, 3H, Ar), 7.08-6.95 (dd, $J = 9.0, 6.0$ Hz, 3H, Ar), 6.69 (m, 1H, Ar), 6.49 (t, $J = 9.1$ Hz, 1H, OH), 5.92 (s, 1H, NCH), 3.66 (s, 3H, OCH₃), 2.88 (s (br), 4H, CH₂), 2.26 (s, 3H, CH₃), 1.13 (t, $J = 9.0$ Hz, 6H, CH₃).

CHNS Theoretical: C 76.22 % H 8.42 % N 4.68 % Actual: C 76.10 % H 8.41 % N 4.49 %

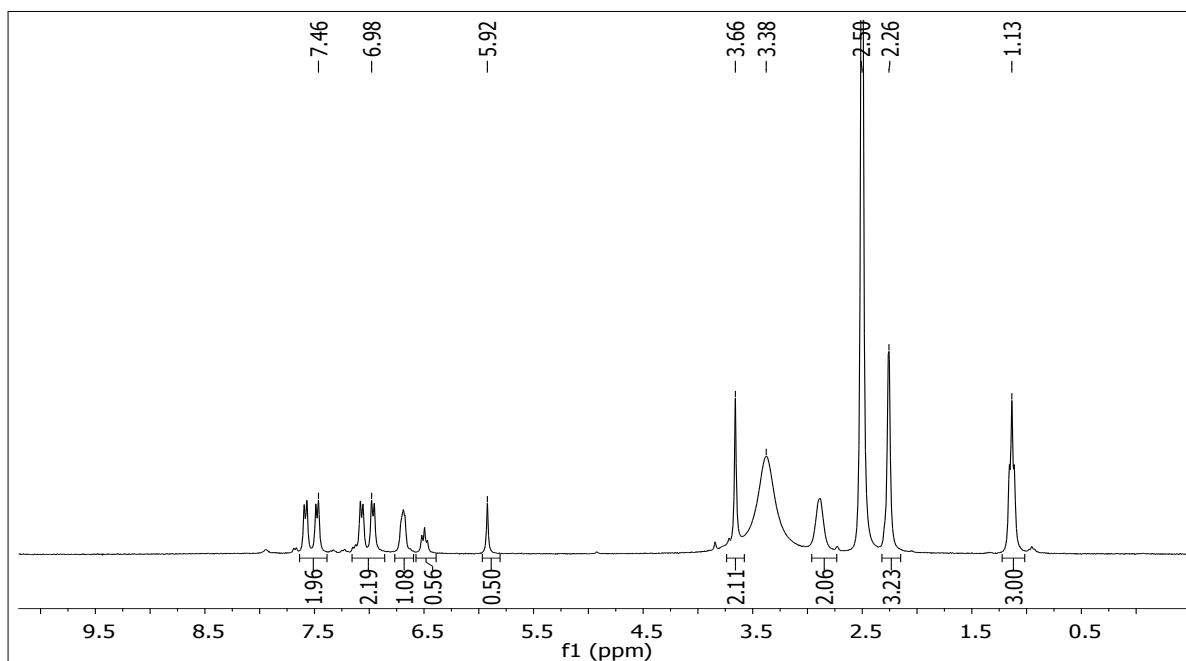


Figure S3: ^1H NMR spectrum (in d^6 -DMSO) of **4** after post process purification.

5. Screw configurations employed

Standard screw profile

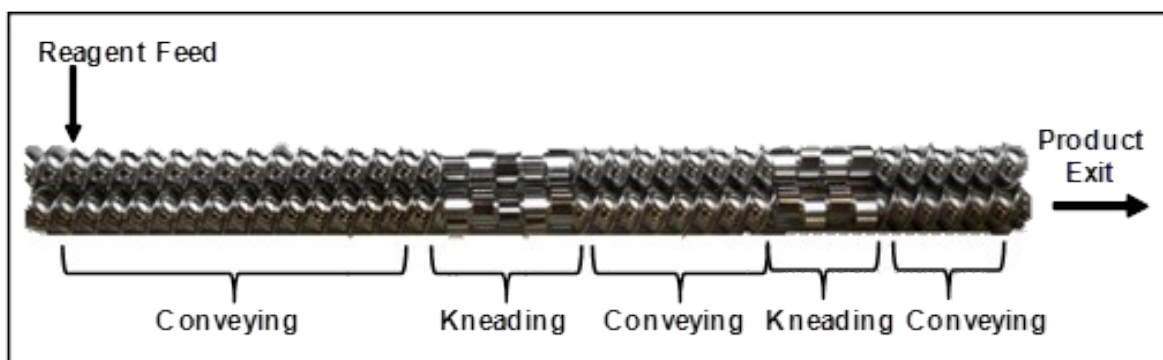


Figure S4: Standard screw configuration made up of conveying and kneading segments.

Screw profile consisting of the reverse screw segments

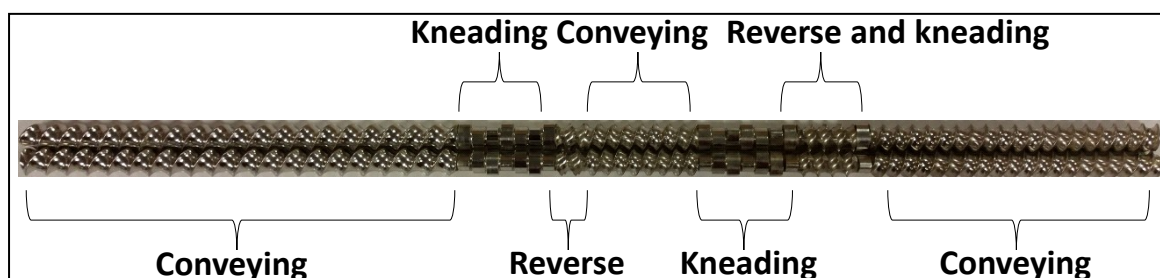


Figure S5: Alternative screw configuration employed, containing reverse conveying segments, employed for the Petasis reaction.