Electronic Supplementary Information for

**Thermolysis of azidoacrylates in continuous flow. Application to the synthesis of heterocycles and related pharmaceutical intermediates.**

Alexander G. O’Brien, François Lévesque, and Peter H. Seeberger*

**General experimental**

Commercial grade reagents and solvents were used without further purification except as indicated below. All batch reactions were conducted under an Ar atmosphere, while reactions performed in flow were conducted without an inert atmosphere. Azide thermolyses were performed using a Vapourtec R series system consisting of an R2+ pump and R4 heater. The injection loop used was a standard Rheodyne 6-position valve that allowed switching between load (for filling the loop) and inject (for delivering the substrate to the reactor) positions. $^1$H-NMR and $^{13}$C-NMR spectra were measured with a Varian 400-MR spectrometer. The proton signal of residual, non-deuterated solvent (δ 7.26 ppm for CHCl₃) was used as an internal reference for $^1$H spectra. For $^{13}$C spectra, the chemical shifts are reported relative to the δ 77.36 ppm resonance of CDCl₃. Coupling constants are reported in Hertz (Hz). The following abbreviations are used to indicate the multiplicities: s, singlet, d, doublet; t, triplet; m multiplet. Infrared (IR) spectra were recorded as thin films on a Perkin Elmer Spectrum 100 FTIR spectrophotometer. Melting points were recorded using an Electrothermal IA 9300 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and by staining with potassium permanganate solution (potassium permanganate in basic aqueous solution). Column chromatography was performed using Kieselgel 60 (230–400 mesh). PFA refers to perfluoroalkoxy polymer tubing.

**Safety note**

This communication describes the preparation of numerous potentially explosive, low molecular weight organic azides. Although we did not experience any explosive
behaviour during these studies, all reactions were carried out behind a blast shield. Sodium azide was handled using non-metallic utensils.

**System diagram for the continuous flow preparation of 11a–d, 16 and 18–21.**

![Diagram 1](image1)

**Figure 1**

**System diagram for the large-scale continuous flow preparation of 21.**

![Diagram 2](image2)

**Figure 2**
**General procedure A: for the preparation of azidoacrylates 8a–d, 15 and 17 a–d.**

To a solution of aldehyde 7 (20.9 mmol, 1.0 equiv) and methyl 2-azidoacetate (6.0 g, 52.1 mmol, 2.5 equiv) in methanol (29.6 mL) was added a solution of sodium metal (1.2 g, 52.1 mmol, 2.5 equiv) in methanol (29.6 mL) at –15 ºC via cannula. After stirring at –15 ºC for 1.5 h, the reaction flask was moved to a cold room and stirred at 4 ºC overnight, covered with foil to protect from light. The cold reaction mixture was poured onto ice cold saturated NH₄Claq (40 mL). A precipitate formed, which was collected by filtration using a Buchner funnel. The precipitate was washed with cold water and air dried for 30 min before being taken up in dichloromethane. The solution was dried (MgSO₄) and concentrated under reduced pressure to give the corresponding azidoacrylate.

**General procedure B: for the preparation of azidoacrylates 8a–d, 15 and 17 a–d.**

To a solution of aldehyde 7 (20.9 mmol, 1.0 equiv) and methyl 2-azidoacetate (6.0 g, 52.1 mmol, 2.5 equiv) in methanol (29.6 mL) was added a solution of sodium metal (1.2 g, 52.1 mmol, 2.5 equiv) in methanol (29.6 mL) at –15 ºC via cannula. After stirring at –15 ºC for 1.5 h, the reaction flask was moved to a cold room and stirred at 4 ºC overnight, covered with foil to protect from light. The cold reaction mixture poured onto ice cold saturated NH₄Claq (40 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure to give the corresponding azidoacrylate.

**General procedure C: for the continuous flow thermolysis of azidoacrylates.**

A Vapourtec R series flow reactor system was set up as described in Figure 1. With both pumps set to flow at equal rates, a solution of the azidoacrylate 8a–d, 15 or 17 a–d (0.40 mmol) in toluene (1.0 or 0.5 M as described below) was loaded into the reactor via an injection loop. The system was configured to collect the product in a single vessel. The product solution was concentrated under reduced pressure to afford the corresponding heterocyclic product. If required, the products were purified by recrystallisation or chromatography over silica gel as appropriate.

**Methyl 2-azidoacetate**

To a solution of methyl 2-bromoacetate (5.00 ml, 54.3 mmol, 1.0 equiv) in methanol (4 mL) was added a slurry of sodium azide (4.34 g, 66.8 mmol, 1.2 equiv) in water (3
mL) at rt, with the reaction vessel submerged in a water bath. The resulting suspension was stirred at rt for 20 min then heated to 80 °C for 2 h. After cooling to rt, the heterogeneous reaction mixture was concentrated under reduced pressure to remove methanol. The residue was poured onto water (50 mL) and extracted with ether (3 x 80 mL). The combined organic extracts were dried (MgSO₄) and carefully concentrated under reduced pressure behind a Perspex blast shield to give methyl 2-azidoacetate (6.03 g, 96%) as a colourless oil: δH (400 MHz, CDCl₃) 3.89 (2H, s), 3.80 (3H, s); in agreement with published data.¹

(Z)-methyl 2-azido-3-phenylacrylate (8a)

Benzaldehyde (2.03 g, 1.93 mL, 19.1 mmol) was reacted according to procedure B to afford (Z)-methyl 2-azido-3-phenylacrylate 8a (3.40 g, 88%) as a light yellow solid: mp 37–39 °C; νmax (film) 2115, 1715, 1614, 1378, 1255, 1085 cm⁻¹; δH (400 MHz, CDCl₃) 7.81 (2H, d, J 7.5), 7.41–7.34 (3H, m), 6.92 (1H, s), 3.92 (3H, s); δC (100 MHz, CDCl₃) 164.1, 133.3, 130.7, 129.6, 128.6, 125.7, 125.5, 53.0; in agreement with published data.²

(Z)-methyl 2-azido-3-(2-chlorophenyl)acrylate (8b)

2-chlorobenzaldehyde (2.42 g, 1.94 mL, 17.2 mmol) was reacted according to procedure A to afford (Z)-methyl 2-azido-3-(2-chlorophenyl)acrylate 8b (2.43 g, 60%) as a white solid: νmax (film) 2114, 1707, 1716, 1608, 1435, 1243, 1080 cm⁻¹; δH (400 MHz, CDCl₃) 8.17 (1H, dd, J 7.5, 2.0), 7.42 (1H, dd, J 7.5, 1.5), 7.32–7.24 (3H, m), 3.94 (3H, s); δC (100 MHz, CDCl₃) 163.9, 134.8, 131.3, 131.2, 130.3, 129.8, 127.3, 126.7, 120.9, 53.3; in agreement with published data.²

(Z)-methyl 2-azido-3-(3-methoxyphenyl)acrylate (8c)

3-Methoxybenzaldehyde (2.86 g, 21.0 mmol) was reacted according to procedure A to afford (Z)-methyl 2-azido-3-(3-methoxyphenyl)acrylate 8c (3.14 g, 64%) as a yellow solid: νmax (film) 2122, 1715, 1620, 1574, 1434, 1232 cm⁻¹; δH (400 MHz, CDCl₃)

7.13–7.12 (1H, m), 7.04–6.95 (2H, m), 6.60–6.70 (2H, m), 3.60 (3H, s), 3.53 (3H, s); δC (100 MHz, CDCl3) 163.9, 159.4, 134.3, 129.4, 125.5, 125.4, 123.4, 115.5, 115.3, 55.3, 52.9; in agreement with published data.3

(Z)-methyl 2-azido-3-(3-(benzyloxy)phenyl)acrylate (8d)
3-(Benzyloxy)benzaldehyde (4.47 g, 21.0 mmol) was reacted according to procedure to afford (Z)-methyl 2-azido-3-(3-(benzyloxy)phenyl)acrylate 8d (4.98 g, 77%) as a yellow solid: mp 89–90 ºC, νmax (film) 2118, 1707, 1624, 1581, 1235, 1018 cm⁻¹; δH (400 MHz, CDCl3) 7.51–7.20 (8H, m), 6.94–6.91 (1H, m), 6.83 (1H, s), 5.05 (2H, s), 3.86 (3H, s); δC (100 MHz, CDCl3) 163.9, 158.8, 136.8, 134.3, 129.4, 128.6, 128.0, 127.4, 125.5, 125.3, 123.7, 116.4, 116.3, 70.1, 52.9.

(E)-(2-azidovinyl)benzene (10)
To a suspension of (E)-styrylboronic acid 9 (2.96 g, 20.0 mmol, 1.0 equiv) and copper (II) sulfate (0.319 g, 0.20 mmol, 0.1 equiv) in methanol (60.6 mL) was added sodium azide (1.56 g, 24.0 mmol, 1.2 equiv) at rt to give a brown mixture. After stirring for 24 h, the mixture was concentrated under reduced pressure to remove methanol, taken up in ether/hexane (30:70 v/v, 100 mL) and passed over a plug of silica gel. The filtrate was concentrated under reduced pressure to give (E)-(2-azidovinyl)benzene 10 (2.90 g, 69%) as a yellow oil: νmax (film) 2100, 1637, 1258, 930, 748 cm⁻¹; δH (400 MHz, CDCl3) 7.33–7.22 (5H, m), 6.61 (1H, d, J 14.0), 6.28 (1H, d, J 14.0); δC (100 MHz, CDCl3) 135.2, 128.9, 127.5, 126.8, 126.0, 119.9; in agreement with published data.4

(2Z,4E)-methyl 2-azido-5-phenylpenta-2,4-dienoate (15)
Cinnamaldehyde (4.93 g, 4.69 mL, 37.3 mmol) was reacted according to procedure B to afford (2Z,4E)-methyl 2-azido-5-phenylpenta-2,4-dienoate 15 (3.80 g, 44%) as a yellow solid following purification over silica gel (2–20% EtOAc/hexane): mp 56–59 ºC; νmax (film) 2108, 1711, 1613, 1597, 1438, 1370, 1232, 1072 cm⁻¹; δH (400 MHz, CDCl3) 7.33–7.22 (5H, m), 6.61 (1H, d, J 14.0), 6.28 (1H, d, J 14.0); δC (100 MHz, CDCl3) 135.2, 128.9, 127.5, 126.8, 126.0, 119.9; in agreement with published data.4

CDCl₃) 7.49 (2H, d, J 8.0), 7.38–7.28 (3H, m), 7.17 (1H, dd, J 16.0, 11.0), 6.81 (1H, d, J 16.0), 6.76 (1H, d, J 11.0), 3.88 (3H, s); δC (100 MHz, CDCl₃) 163.7, 139.2, 136.4, 129.1, 128.9, 127.4, 127.2, 125.6, 122.3, 52.8; in agreement with published data.⁵

(Z)-methyl 2-azido-3-(pyridin-2-yl)acrylate (17a)

Pyridine-2-carboxaldehyde (2.23 g, 1.98 mmol) was reacted according to procedure A to afford (Z)-methyl 2-azido-3-(pyridin-2-yl)acrylate 17a (3.40 g, 80%) as a white solid: νmax (film) 2116, 1716, 1612, 1380, 1250 cm⁻¹; δH (400 MHz, CDCl₃) 8.65 (1H, d, J 5.0), 8.19 (1H, d, J 8.0), 7.73 (1H, ddd, J 10.0, 8.0, 2.0), 7.20 (1H, ddd, J 8.0, 5.0, 2.0), 7.09 (1H, s), 3.92 (3H, s); δC (100 MHz, CDCl₃) 163.9, 152.5, 149.9, 136.4, 128.2, 125.6, 125.4, 123.2, 53.3; in agreement with published data.⁶

(Z)-methyl 2-azido-3-(pyridin-3-yl)acrylate (17b)

Pyridine-3-carboxaldehyde (4.00 g, 3.51 mL, 37.30 mmol) was reacted according to procedure A to afford a 7:1 mixture of (Z)-methyl 2-azido-3-(pyridin-4-yl)acrylate (Z)-17b and (E)-methyl 2-azido-3-(pyridin-4-yl)acrylate (E)-17b respectively (3.81 g, 50%) as a yellow low-melting solid. Further purification over silica gel (10% EtOAc, 5% TEA/hexanes) afforded a pure sample of (Z)-methyl 2-azido-3-(pyridin-4-yl)acrylate (Z)-17b (1.55 g, 20%) as a yellow low-melting solid: νmax (film) 2120, 1715, 1618, 1583, 1563, 1376, 1248 cm⁻¹; δH (400 MHz, CDCl₃) 8.82 (1H, d, J 2.0), 8.53 (1H, dd, J 5.0, 1.5), 8.32 (1H, ddd, J 8.0, 4.0, 2.0), 7.33 (1H, ddd, J 8.0, 5.0), 6.85 (1H, s), 3.93 (3H, s); δC (100 MHz, CDCl₃) 163.3, 151.5, 149.7, 136.5, 129.2, 127.4, 123.2, 121.4, 53.0; in agreement with published data.⁶

(Z)-methyl 2-azido-3-(pyridin-4-yl)acrylate (17c)

Pyridine 4-carboxaldehyde (2.25 g, 21.0 mmol) was reacted according to procedure A to afford (Z)-methyl 2-azido-3-(pyridin-4-yl)acrylate 17c (0.80 g, 19%) as a yellow solid: νmax (film) 2122, 1717, 1515, 1595, 1435, 1254 cm⁻¹; δH (400 MHz, CDCl₃) 8.63 (2H, d, J 5.0), 7.61 (2H, d, J 5.0), 6.76 (1H, s), 3.93 (3H, s); δC (100 MHz, CDCl₃) 163.0, 150.5, 150.0, 149.7, 136.5, 130.4, 127.4, 123.2, 121.4, 53.0; in agreement with published data.⁶

CDCl₃) 163.3, 150.2, 140.1, 129.7, 124.0, 121.7, 53.3; in agreement with published data.⁶

(Z)-methyl 2-azido-3-(furan-2-yl)acrylate (17d)
Furan-2-carboxaldehyde (2.92 g, 30.4 mmol) was reacted according to procedure A to afford (Z)-methyl 2-azido-3-(furan-2-yl)acrylate 17d (3.36 g, 57%) as a yellow solid: mp 29–31 ºC; ν max (film) 2108, 1704, 1615, 1439, 1277, 1180 cm⁻¹; δH (400 MHz, CDCl₃) 7.49 (1H, d, J 1.5), 7.10 (1H, d, J 3.5), 6.86 (1H, s), 6.52 (1H, dd, J 3.5, 1.5), 3.88 (3H, s); δC (100 MHz, CDCl₃) 163.6, 149.6, 144.1, 122.8, 115.5, 113.8, 112.7, 53.0; in agreement with published data.²

Methyl 1H-indole-2-carboxylate (11a)
A solution of (Z)-methyl 2-azido-3-phenylacrylate 8a (81 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to procedure C at a flow rate of 4.0 mL/min (residence time 30 s) and a temperature of 220 ºC to afford methyl 1H-indole-2-carboxylate 11a (56 mg, 80%) as a white solid following purification over silica gel (10% EtOAc/hexane): mp 144–146 ºC; ν max (film) 3314, 1698, 1687, 1527, 1439, 1253, 1209 cm⁻¹; δH (400 MHz, CDCl₃) 8.97 (1H, s), 7.70 (1H, dd, J 8.0, 1.0), 7.43 (1H, dd, J 8.0, 1.0), 7.33 (1H, ddd, J 8.0, 7.0, 1.0), 7.23 (1H, dd, J 2.0, 1.0), 7.16 (1H, ddd, J 8.0, 7.0, 1.0), 3.96 (3H, s); δC (100 MHz, CDCl₃) 162.6, 137.0, 127.6, 127.3, 125.6, 122.8, 121.0, 112.0, 109.0, 52.2; in agreement with published data.²

Methyl 4-chloro-1H-indole-2-carboxylate (11b)
A solution of (Z)-methyl 2-azido-3-(2-chlorophenyl) 8b (93 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to procedure C at a flow rate of 4.0 mL/min (residence time 30 s) and a temperature of 220 ºC to afford methyl 4-chloro-1H-indole-2-carboxylate 11b (77 mg, 80%, 94% purity) as a white solid. Further purification by recrystallisation from methanol afforded an analytically pure sample of 11b: ν max (film) 3327, 1751, 1694, 1523, 1441, 1254, 1209, 1183 cm⁻¹; δH (400 MHz, CDCl₃) 9.03 (1H, s), 7.34–7.32 (2H, m), 7.22 (1H, d, J 8.5), 7.16 (1H, dd, J 7.5, 1.0), 3.97 (3H, s); δC (100 MHz, CDCl₃) 162.0, 137.0, 127.9, 127.5, 126.6, 125.9, 120.5, 110.5, 107.2, 52.2; in agreement with published data.²
Methyl 5-methoxy-1H-indole-2-carboxylate (5-11c) and methyl 7-methoxy-1H-indole-2-carboxylate (7-11c)

A solution of (Z)-methyl 2-azido-3-(3-methoxyphenyl)acrylate 8c (93 mg, 0.4 mmol) was reacted according to procedure C at a flow rate of 4.0 mL/min (residence time 30 s) and a temperature of 220 °C to afford a 1:1 (by 1H-NMR analysis) mixture of methyl 5-methoxy-1H-indole-2-carboxylate 5-11c and methyl 7-methoxy-1H-indole-2-carboxylate 7-11c. Further purification over silica gel (10% EtOAc/hexane) afforded less polar methyl 5-methoxy-1H-indole-2-carboxylate 5-11c (22 mg, 27%): ν_max (film) 3315, 1686, 1621, 1526, 1344, 1032, 1015 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.83 (1H, s), 7.31 (1H, d, J 9.0), 7.14 (1H, d, J 2.0), 7.08 (1H, d, J 2.0), 7.01 (1H, dd, J 9.0, 2.0); 3.94 (3H, s), 3.85 (3H, s); δ_C (100 MHz, CDCl₃) 162.5, 154.9, 132.3, 128.0, 127.7, 117.3, 112.9, 108.5, 102.7, 55.8, 52.1; more polar methyl 7-methoxy-1H-indole-2-carboxylate 7-11c (10 mg, 12%): ν_max (film) 3327, 1701, 1581, 1438, 1257, 1032, 1011 cm⁻¹; δ_H (400 MHz, CDCl₃) 9.06 (1H, s), 7.28 (1H, d, J 8.0), 7.19 (1H, d, J 2.5), 7.06 (1H, dd, J 8.0, 8.0), 6.73 (1H, d, J 8.0), 3.97 (3H, s), 3.94 (3H, s); δ_C (100 MHz, CDCl₃) 162.4, 146.6, 128.8, 128.3, 127.0, 121.4, 114.9, 109.1, 104.3, 55.6, 52.1; and a fraction containing a mixture of both isomers (38 mg, 46%); in agreement with published data.³

Methyl 5-(benzyloxy)-1H-indole-2-carboxylate (5-11d) and methyl 7-(benzyloxy)-1H-indole-2-carboxylate (7-11d)

A solution of (Z)-methyl 2-azido-3-(3-(benzyloxy)phenyl)acrylate 8d (124 mg, 0.4 mmol) was reacted according to procedure C at a flow rate of 4.0 mL/min (residence time 30 s) and a temperature of 220 °C to afford a 1:1 (by 1H-NMR analysis) mixture of methyl 5-(benzyloxy)-1H-indole-2-carboxylate 5-11d and methyl 7-(benzyloxy)-1H-indole-2-carboxylate 7-11d. Purification of the mixture over silica gel (5% EtOAc/hexane) afforded less polar methyl 7-(benzyloxy)-1H-indole-2-carboxylate 7-11d (52 mg, 46%) as a white solid: ν_max (film) 3326, 1693, 1622, 1525, 1436, 1235, 1019 cm⁻¹; δ_H (400 MHz, CDCl₃) 9.07 (1H, s), 7.51–7.38 (5H, m), 7.30 (1H, d, J 9.0), 7.21 (1H, d, J 2.0), 7.06 (1H, dd, J 8.0, 8.0), 6.81 (1H, d, J 9.0), 5.22 (2H, s), 3.93 (3H, s); δ_C (100 MHz, CDCl₃) 162.2, 145.6, 136.6, 128.73, 128.67, 128.3, 127.8,
126.9, 121.2, 115.0, 109.0, 105.4, 70.3, 51.9; in agreement with published data\(^7\) and, with further purification by recrystallisation from methanol, more polar methyl 5-(benzyloxy)-1\(H\)-indole-2-carboxylate \textbf{5-11d} (33 mg, 29\%) as a white solid: \(\nu_{\text{max}}\) (film) 3320, 1699, 1579, 1438, 1239, 1076 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 8.94 (1H, s), 7.48 (2H, d, \(J\) 7.5), 7.40 (2H, dd, \(J\) 7.5, 7.5), 7.35–7.31 (2H, m), 7.17 (1H, d, \(J\) 2.0), 7.14 (1H, d, \(J\) 2.0), 7.09 (1H, dd, \(J\) 9.0, 2.0), 5.10 (2H, s), 3.94 (3H, s); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 162.5, 154.0, 137.4, 132.5, 128.7, 128.0, 127.9, 127.7, 117.8, 112.9, 108.5, 104.3, 70.8, 52.1; in agreement with published data.\(^8\)

**Methyl 5-phenyl-1\(H\)-pyrrole-2-carboxylate (16)**

A solution of (2\(Z\),4\(E\))-methyl 2-azido-5-phenylpenta-2,4-dienoate \textbf{15} (92 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to procedure \(\text{C}\) at a flow rate of 10.0 mL/min (residence time 12 s) and a temperature of 180 \(^\circ\)C to afford methyl 5-phenyl-1\(H\)-pyrrole-2-carboxylate \textbf{16} (78 mg, 97\%) as a white solid: mp 142–144 \(^\circ\)C; \(\nu_{\text{max}}\) (film) 3290, 1675, 1606, 1465, 1268, 1152 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 9.45 (1H, s), 7.58 (2H, dd, \(J\) 8.0, 1.0), 7.43–7.39 (2H, m), 7.33–7.29 (1H, m), 6.97 (1H, dd, \(J\) 4.0, 2.5), 6.55 (1H, dd, \(J\) 4.0, 2.5), 3.88 (3H, s); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 161.8, 137.0, 131.5, 129.2, 127.9, 124.9, 123.2, 117.0, 108.4, 51.7; in agreement with published data.\(^5\)

**Methyl pyrazolo[1,5-\(a\)]pyridine-2-carboxylate (18)**

A solution of (Z)-methyl 2-azido-3-(pyridin-2-yl)acrylate \textbf{17a} (82 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to general procedure \(\text{C}\) at a flow rate of 4.5 mL/min (residence time 26.5 s) and a temperature of 220 \(^\circ\)C to afford methyl pyrazolo[1,5-\(a\)]pyridine-2-carboxylate \textbf{18} (70 mg, >99\%) as a yellow solid: \(\nu_{\text{max}}\) (film) 1732, 1635 cm\(^{-1}\); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 8.49 (1H, d, \(J\) 7.0), 7.57 (1H, d, \(J\) 9.0), 7.14 (1H, dd, \(J\) 9.0, 7.0), 7.05 (1H, s), 6.87 (1H, dd, \(J\) 8.0, 7.0), 3.97 (3H, s); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 163.3, 144.7, 140.9, 129.0, 124.0, 119.3, 114.2, 100.2, 52.4; in agreement with published data.\(^9\)


**Methyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate (19)**

A solution of (Z)-methyl 2-azido-3-(pyridin-3-yl)acrylate 17b (82 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to general procedure C at a flow rate of 4.0 mL/min (residence time 30 s) and a temperature of 220 °C. Concentration of the reactor output and recrystallisation of the residue from mesitylene afforded methyl 1H-pyrrolo[2,3-b]pyridine-2-carboxylate 19 (40 mg, 57 %) as a white solid: $\nu_{\text{max}}$ (film) 3342, 1719, 1615, 1436, 1206 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 13.02 (1H, s), 8.69 (1H, dd, $J$ 5.0, 1.5), 8.08 (1H, dd, $J$ 8.0, 1.5), 7.19 (1H, s), 7.18 (1H, dd, $J$ 8.0, 5.0), 4.02 (3H, s); $\delta_C$ (100 MHz, CDCl$_3$) 162.4, 148.9, 146.5, 131.7, 128.3, 120.4, 117.0, 106.8, 52.3; in agreement with published data.$^6$

**Methyl 4H-furo[3,2-b]pyrrole-5-carboxylate (21)**

A solution of (Z)-methyl 2-azido-3-(furan-2-yl)acrylate 17d (77 mg, 0.4 mmol) was reacted according to procedure C at a flow rate of 10.0 mL/min (residence time 12 s) and a temperature of 180 °C to afford methyl 4H-furo[3,2-b]pyrrole-5-carboxylate 21 (66 mg, >99%) as a light brown solid: mp 128–130 °C; $\nu_{\text{max}}$ (film) 3271, 1661, 1550, 1447, 1315, 1274; $\delta_H$ (400 MHz, CDCl$_3$) 8.90 (1H, s), 7.52 (1H, d, $J$ 2.0), 6.76 (1H, s), 6.45 (1H, d, $J$ 2.0), 3.88 (3H, s); $\delta_C$ (100 MHz, CDCl$_3$) 162.7, 148.8, 148.1, 129.0, 123.4, 99.0, 97.1, 51.7; in agreement with published data.$^2$

**Large scale preparation of methyl 4H-furo[3,2-b]pyrrole-5-carboxylate 21 in continuous flow.**

A Vapourtec R series flow reactor system was set up as described in Figure 2. Prior to reaction, toluene was passed through the reactor at 0.25 mL/min until the coil reached a temperature of 180 °C. With both pumps set to flow at equal rates (5.0 mL/min), a solution of (Z)-methyl 2-azido-3-(furan-2-yl)acrylate (10.0 g, 51.8 mmol) in toluene (104 mL) was pumped into a 2 mL stainless steel reactor heated to 180 °C at a flow rate of 10.0 mL/min (12 s residence time). Following reaction, toluene (15 mL) was pumped through the system at the same flow rate. The resulting solution was concentrated under reduced pressure to afford methyl 4H-furo[3,2-b]pyrrole-5-carboxylate 21 (8.50 g, 99%) as a light brown solid.

(a) Br. Pat., 051 235, 2010; (b) US Pat., 053 094, 2010; (c) US Pat., 071 642, 2009;