Electronic Supplementary Information for

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

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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 $CHCl_3$) 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 $CDCl_3$. 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.

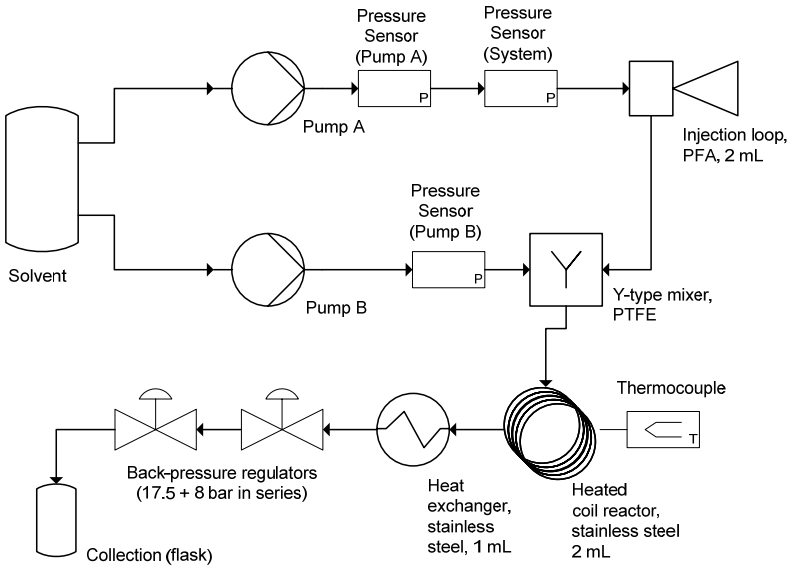

Figure 1

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

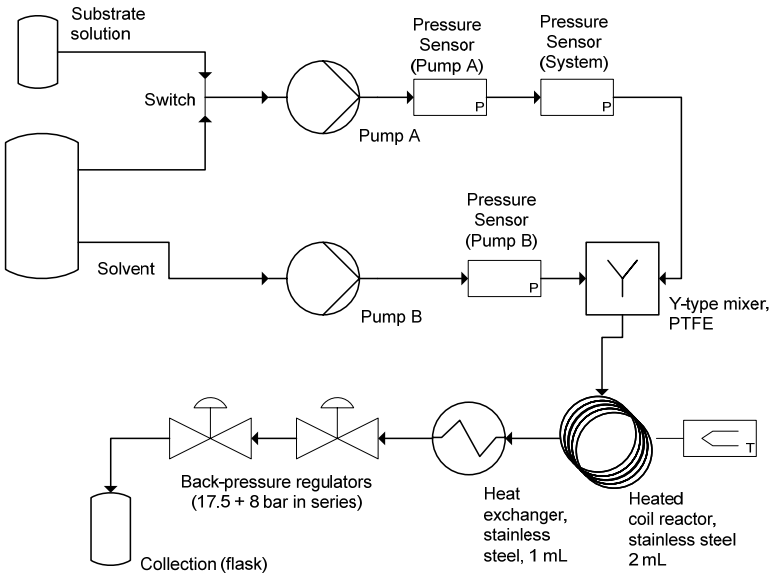

Figure 2

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 NH_4Cl_{aq} (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 ($MgSO_4$) 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 NH_4Cl_{aq} (40 mL) and extracted with ethyl acetate (3 x 75 mL). The combined organic extracts were dried ($MgSO_4$) 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 ºC 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 ($MgSO_4$) and carefully concentrated under reduced pressure behind a Perspex blast shield to give methyl 2-azidoacetate (6.03 g, 96%) as a colourless oil: δ_H (400 MHz, $CDCl_3$) 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 ºC; ν_{max} (film) 2115, 1715, 1614, 1378, 1255, 1085 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 7.5), 7.41–7.34 (3H, m), 6.92 (1H, s), 3.92 (3H, s); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2114, 1707, 1716, 1608, 1435, 1243, 1080 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2122, 1715, 1620, 1574, 1434, 1232 cm^{-1}; δ_H (400 MHz, $CDCl_3$)

[1] (a) P. J. Roy, C. Dufresne, N. Lachance, J.-P. Leclerc, M. Boisvert, Z. Wang, and Y. Leblanc, *Synthesis*, 2005, 2751; (b) P. J. Roy, M. Boisvert and Y. Leblanc, *Org. Syn.* 2007, **84**, 262.
[2] B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.* 2007, **129**, 7500.

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); δ_C (100 MHz, $CDCl_3$) 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, ν_{max} (film) 2118, 1707, 1624, 1581, 1235, 1018 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.51–7.20 (8H, m), 6.94–6.91 (1H, m), 6.83 (1H, s), 5.05 (2H, s), 3.86 (3H, s); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2100, 1637, 1258, 930, 748 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.22 (5H, m), 6.61 (1H, d, *J* 14.0), 6.28 (1H, d, *J* 14.0); δ_C (100 MHz, $CDCl_3$) 135.2, 128.9, 127.5, 126.8, 126.0, 119.9; in agreement with published data.[4]

(2*Z*,4*E*)-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 (2*Z*,4*E*)-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; ν_{max} (film) 2108, 1711, 1613, 1597, 1438, 1370, 1232, 1072 cm^{-1}; δ_H (400 MHz,

[3] D. Coowar, J. Bouissac, M. Hanbali, M. Paschaki, E. Mohier and B. Luu, *J. Med. Chem.* 2004, **47**, 6270.
[4] C.-Z. Tao, X. Cui, J. Li, A.-X. Liu, L. Liu and Q.-X. Guo, *Tetrahedron Lett.* 2007, **48**, 3525.

$CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2116, 1716, 1612, 1380, 1250 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2120, 1715, 1618, 1583, 1563, 1376, 1248 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, dd, *J* 8.0, 5.0), 6.85 (1H, s), 3.93 (3H, s); δ_C (100 MHz, $CDCl_3$) 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: ν_{max} (film) 2122, 1717, 1515, 1595, 1435, 1254 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.63 (2H, d, *J* 5.0), 7.61 (2H, d, *J* 5.0), 6.76 (1H, s), 3.93 (3H, s); δ_C (100 MHz,

[5] H. Dong, M. Shen, J. E. Redford, B. J. Stokes, A. L. Pumphrey and T. G. Driver, *Org. Lett.*, 2007, **9**, 5191.
[6] P. J. Roy, C. Dufresne, N. Lachance, J.-P. Leclerc, M. Boisvert, Z. Wang, and Y. Leblanc, *Synthesis*, 2005, 2751.

$CDCl_3$) 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}; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 163.6, 149.6, 144.1, 122.8, 115.5, 113.8, 112.7, 53.0; in agreement with published data.[2]

Methyl 1*H*-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 1*H*-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}; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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-1*H*-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-1*H*-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}; δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 162.0, 137.2, 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-1*H*-indole-2-carboxylate (5-11c) and methyl 7-methoxy-1*H*-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 ºC to to afford a 1:1 (by ^{1}H-NMR analysis) mixture of methyl 5-methoxy-1*H*-indole-2-carboxylate **5-11c** and methyl 7-methoxy-1*H*-indole-2-carboxylate **7-11c**. Further purification over silica gel (10% EtOAc/hexane) afforded less polar methyl 5-methoxy-1*H*-indole-2-carboxylate **5-11c** (22 mg, 27%): ν_{max} (film) 3315, 1686, 1621, 1526, 1344, 1032, 1015 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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-1*H*-indole-2-carboxylate **7-11c** (10 mg, 12%): ν_{max} (film) 3327, 1701, 1581, 1438, 1257, 1032, 1011 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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)-1*H*-indole-2-carboxylate (5-11d) and methyl 7-(benzyloxy)-1*H*-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 ºC to afford a 1:1 (by ^{1}H-NMR analysis) mixture of methyl 5-(benzyloxy)-1*H*-indole-2-carboxylate **5-11d** and methyl 7-(benzyloxy)-1*H*-indole-2-carboxylate **7-11d**. Purification of the mixture over silica gel (5% EtOAc/hexane) afforded less polar methyl 7-(benzyloxy)-1*H*-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, $CDCl_3$) 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, $CDCl_3$) 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 **5-11d** (33 mg, 29%) as a white solid: ν_{max} (film) 3320, 1699, 1579, 1438, 1239, 1076 cm^{-1}; δ_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); δ_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 **15** (92 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to procedure **C** at a flow rate of 10.0 mL/min (residence time 12 s) and a temperature of 180 ºC to afford methyl 5-phenyl-1*H*-pyrrole-2-carboxylate **16** (78 mg, 97%) as a white solid: mp 142–144 ºC; ν_{max} (film) 3290, 1675, 1606, 1465, 1268, 1152 cm^{-1}; δ_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); δ_C (100 MHz, $CDCl_3$) 161.8, 137.0, 131.5, 129.2, 127.9, 124.9, 123.2, 117.0, 108.2, 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 **17a** (82 mg, 0.40 mmol) in toluene (0.4 mL) was reacted according to general procedure **C** at a flow rate of 4.5 mL/min (residence time 26.5 s) and a temperature of 220 ºC to afford methyl pyrazolo[1,5-*a*]pyridine-2-carboxylate **18** (70 mg, >99%) as a yellow solid: ν_{max} (film) 1732, 1635 cm^{-1}; δ_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); δ_C (100 MHz, $CDCl_3$) 163.3, 144.7, 140.9, 129.0, 124.1, 119.3, 114.2, 100.2, 52.4; in agreement with published data.[9]

[7] R. Albrecht, J. Heindl, O. Loge, *Eur. J. Med. Chem.* 1985, **20**, 57.
[8] T. O. Vieira, L. A. Meaney, Y.-L. Shi and Howard Alper, *Org. Lett.*, 2008, **10**, 4899.
[9] G.-H. Tian, G.-X. Xia, W.-X. Jin, X.-J. Chen, S.-A. Lai, Y.-B. Wei, R.-Y. Ji and J.-S. Shen, *Chin. J. Chem.*, 2007, **25**, 241.

Methyl 1*H*-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 ºC. Concentration of the reactor output and recrystallisation of the residue from mesitylene afforded methyl 1*H*-pyrrolo[2,3-b]pyridine-2-carboxylate **19** (40 mg, 57 %) as a white solid: ν_{max} (film) 3342, 1719, 1615, 1577, 1436, 1206 cm^{-1}; δ_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); δ_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 4*H*-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 ºC to afford methyl 4*H*-furo[3,2-b]pyrrole-5-carboxylate **21** (66 mg, >99%) as a light brown solid: mp 128–130 ºC; ν_{max} (film) 3271, 1661, 1550, 1447, 1315, 1274; δ_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); δ_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 4*H*-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 ºC. 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 ºC 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 4*H*-furo[3,2-b]pyrrole-5-carboxylate **21** (8.50 g, 99%) as a light brown solid.

Reference 28c: Patents describing compound 24.

(a) *Br. Pat.*, 051 235, 2010; (b) *US Pat*., 053 094, 2010; (c) *US Pat*., 071 642, 2009; (d) *US Pat*., 20080058395, 2008; (e) *US Pat*., 20080004328, 2008; (f) *Ru. Pat.*, 000 163, 2007.