Cu-Catalysed Pyrazole Synthesis in Continuous Flow

Júlia Comas-Barceló, Daniel Blanco-Ania, Sebastian A. M. W. van den Broek, Pieter J. Nieuwland, Joseph P. A. Harrity* and Floris P. J. T. Rutjes*

Supporting Information

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GENERAL INFORMATION

All reactions were conducted in dried glassware under inert atmosphere unless otherwise stated. Thin layer chromatography was performed on glass-backed plates pre-coated with silica, which were developed using standard visualising agents: ultraviolet light or potassium permanganate. Flash chromatography was performed on silica gel mesh 35-70. The solvent system used was graduated from 100% heptane, increasing polarity towards the solvent mixture stated in the procedure. Melting points were performed on recrystallised solids and are uncorrected.

$^1$H and $^{13}$C NMR spectra were recorded on 500 and 400 MHz spectrometers. Proton magnetic resonance chemical shifts are reported in ppm from tetramethylsilane with the residual protic solvent resonance as the internal standard (CHCl$_3$: $\delta = 7.26$ ppm), unless otherwise stated. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, m = multiplet), coupling constant (Hz), integration and assignation. Carbon magnetic resonance chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CHCl$_3$: $\delta = 77.16$ ppm), unless otherwise stated. Infrared (IR) spectra were recorded on chloroform or CH$_2$Cl$_2$ solutions of the samples, $\nu_{\text{max}}$ in cm$^{-1}$. Bands are characterised as broad (br), strong (s), medium (m) or weak (w).

High-resolution mass spectra (HRMS) were recorded using a magnetic sector mass analyser, operating in Electrospray, FAB, EI or CI modes. Ratios of pyrazole products were determined on crude reaction mixtures by 400 MHz $^1$H-NMR analysis. All solvents and reagents were purified using standard laboratory techniques according to methods published in Purification of Laboratory Chemicals, by Perrin, Amarego and Chai (Pergamon Press, 1966).

Sydnones 1-3 were prepared according to literature procedures.$^1$
EXPERIMENTAL PROCEDURES

Preparation of the supported catalysts

a) Amberlyst® A-21 supported copper2:

Wet Amberlyst® A-21 beads directly purchased from Sigma-Aldrich were subjected to a pre-drying treatment before supporting the copper catalysts (CuI and Cu(OAc)2 in this case). To do so, the resin was left to soak in methanol for 30 minutes, filtered and washed with methanol (x 3 times). The same procedure was sub-sequentially repeated using dichloromethane and after, the resin was dried under vacuum for 16 h.

Next, the corresponding copper salt (2.0 mmol / g of A-21) was dissolved in acetonitrile and the dry A-21 added to the solution. The mixture was left under orbital stirring for 16 h and after, filtered, washed with acetonitrile (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.

Quantification of the copper loading was determined by ICP-MS analysis: 9.42 ± 0.18% (wt) (A-21·CuI) and 6.62% (wt) (A-21·Cu(OAc)2).

b) Silica-supported copper3:

Synthesis of precursor 1:

To a stirring solution of silica gel (30-70 μm, 60A, 1.1 eq.) in dry toluene was added (3-aminopropyl)triethoxysilane (APTES) (1 eq.) and the mixture was heated at reflux under inert atmosphere over 24 h. Upon cooling, the silica was filtered, washed with acetone (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.

Synthesis of precursor 2:

To a stirring solution of silica gel (30-70 μm, 60A, 1.1 eq.) in dry toluene was added [3-(2-aminoethylamino)propyl]trimethoxysilane (AAPTS) (1 eq.) and the mixture was heated at reflux under inert atmosphere over 24 h. Upon cooling, the silica was filtered, washed with acetone (x 2 times), dichloromethane (x 2 times) and dried under vacuum for 16 h.

For the copper incorporation, to a stirred solution of the corresponding modified silica (1 or 2) in ethanol, Cu(OAc)2 was added (0.5 mmol / g of silica) and the mixture was left stirring under inert atmosphere for 4 h. After, silica was filtered, washed with acetone (x 2 times), methanol (x 2 times) and dried under vacuum for 8 hours.

Quantification of the copper loading was determined by ICP-MS analysis: 3.22% (wt) (Silica-1) and 4.01 ± 0.20% (wt) (Silica-2).
Batch synthesis of 1,4-disubstituted-1H-pyrazoles

To a stirring solution of sydnone (1 eq.) and supported catalyst Silica-2 (0.3 eq., 4.02% Cu) in o-dichlorobenzene (0.20 - 0.25 M) under N₂ at room temperature, was added the alkyne (1 eq.). The mixture was left stirring at room temperature for 5 minutes and afterwards, heated at 140 °C for the designated length of time. After cooling, the reaction mixture was filtered and the crude product was purified by flash chromatography on silica gel (eluting solvent: 5 % ethyl acetate in heptane, unless otherwise stated). Further purification of the pyrazole products could be obtained by recrystallisation from CH₂Cl₂ – heptane if required.

1,4-Diphenyl-1H-pyrazole (4)

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and phenylacetylene (70 μL, 0.62 mmol) for 2 h, 1,4-diphenyl-1H-pyrazole was isolated as a yellow solid (135 mg, 100% yield, regioselectivity: >95:5).

Melting point: 92-94 °C (lit. 95-96 °C). ¹H NMR (CDCl₃, 500 MHz): δ 8.17 (d, J = 0.5 Hz, 1H, PyzH), 8.01 (d, J = 0.5 Hz, 1H, PyzH), 7.77 – 7.72 (m, 2H, PhH), 7.59 – 7.55 (m, 2H, PhH), 7.51 – 7.46 (m, 2H, PhH), 7.45 – 7.38 (m, 2H, PhH), 7.34 – 7.27 (m, 2H, PhH). ¹³C NMR (CDCl₃, 126 MHz): δ 140.2, 138.9, 132.2, 129.6, 129.1, 127.0, 126.7, 125.9, 125.1, 123.5, 119.2.

1-(p-Methoxyphenyl)-4-phenyl-1H-pyrazole (9)

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and phenylacetylene (57 μL, 0.52 mmol) for 5 h, 1-(p-methoxyphenyl)-4-phenyl-1H-pyrazole was isolated as a pale orange solid (110 mg, 85% yield, regioselectivity: >95:5).

Melting point: 126-128 °C (lit. 124-125 °C). ¹H NMR (CDCl₃, 500 MHz): δ 8.07 (d, J = 0.5 Hz, 1H, PyzH), 7.97 (d, J = 0.5 Hz, 1H, PyzH), 7.66 – 7.60 (m, 2H, PhH), 7.59 – 7.55 (m, 2H, PhH), 7.51 – 7.46 (m, 2H, PhH), 7.45 – 7.38 (m, 2H, PhH), 7.34 – 7.27 (m, 2H, PhH). ¹³C NMR (CDCl₃, 126 MHz): δ 140.2, 138.9, 132.2, 129.6, 129.1, 127.0, 126.7, 125.9, 125.1, 123.5, 119.2.
**NMR (CDCl₃, 126 MHz):** δ 158.5, 138.4, 134.0, 132.3, 129.1, 126.9, 125.8, 124.7, 123.6, 120.9, 114.7, 55.7.

1-Benzyl-4-phenyl-1H-pyrazole (14)

Following the general procedure using N-benzylsydnone (100 mg, 0.57 mmol) and phenylacetylene (62 μL, 0.57 mmol) for 16 h, 1-benzyl-4-phenyl-1H-pyrazole was isolated as a pale yellow solid (63 mg, 47% yield, regioselectivity: >95:5).

Melting point: 92-94 °C (lit. 92-94 °C).

**1H NMR (CDCl₃, 500 MHz):** δ 7.84 (s, 1H, PyzlH), 7.62 (s, 1H, PyzlH), 7.49 – 7.44 (m, 2H, PhH), 7.39 – 7.31 (m, 5H, PhH), 7.29 – 7.25 (m, 2H, PhH), 7.25 – 7.19 (m, 1H, PhH), 5.35 (s, 2H, Ph-CH₂-).

**13C NMR (CDCl₃, 126 MHz):** δ 137.1, 136.5, 132.6, 129.0 (x2), 128.3, 127.9, 126.5, 126.3, 125.6, 123.6, 56.4.

Ethyl 1-phenyl-1H-pyrazole-4-carboxylate (5)

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and ethyl propiolate (63 μL, 0.62 mmol) for 6 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (94 mg, 71% yield, regioselectivity: >95:5).

Melting point: 90-92 °C (lit. 90-93 °C).

**1H NMR (CDCl₃, 500 MHz):** δ 8.41 (s, 1H, PyzlH), 8.10 (s, 1H, PyzlH), 7.73 – 7.66 (m, 2H, PhH), 7.50 – 7.44 (m, 2H, PhH), 7.38 – 7.31 (m, 1H, PhH), 4.34 (q, J = 7.0 Hz, 2H, -OC₂H₅), 1.37 (t, J = 7.0 Hz, 3H, -OCH₂C₂H₅).

**13C NMR (CDCl₃, 126 MHz):** δ 163.0, 142.3, 139.5, 130.1, 129.7, 127.7, 119.7, 117.1, 60.6, 14.5.

Ethyl 1-((p-methoxyphenyl)-1H-pyrazole-4-carboxylate (10)

Following the general procedure using N-(p-methoxyphehnyl)sydnone (100 mg, 0.52 mmol) and ethyl propiolate (53 μL, 0.52 mmol) for 6 h, ethyl 1-benzyl-1H-pyrazole-4-carboxylate was isolated as an amorphous pale yellow solid (60 mg, 47% yield, regioselectivity: >95:5).

Melting point: 74-76 °C (lit. 77-79 °C).

**1H NMR (CDCl₃, 400 MHz):** δ 8.29 (d, J = 0.5 Hz, 1H, PyzlH), 8.06 (d, J = 0.5 Hz, 1H, PyzlH), 7.61 – 7.56 (m, 2H, PhH), 6.99 – 6.94 (m, 2H, PhH), 4.32 (q, J = 7.0 Hz, 2H, -OCH₂CH₃), 3.83 (s, 3H, -OCH₃), 1.36 (t, J = 7.0 Hz, 3H, -OCH₂CH₃).

**13C NMR (CDCl₃, 100.6 MHz):** δ 163.0, 159.1, 141.9, 133.2, 130.0, 121.3, 116.6, 114.7, 60.5, 55.7, 14.5.

Ethyl 1-benzyl-1H-pyrazole-4-carboxylate (15)

Following the general procedure using N-benzylsydnone (100 mg, 0.57 mmol) and ethyl propiolate (58 μL, 0.57 mmol) for 16 h, ethyl 1-benzyl-1H-pyrazole-4-carboxylate was isolated as an amorphous pale yellow solid (28 mg, 21% yield, regioselectivity: >95:5).

**1H NMR (CDCl₃, 400 MHz):** δ 7.94 (s, 1H, PyzlH), 7.85 (s, 1H, PyzlH), 7.41 – 7.31 (m, 3H, PhH), 7.29 – 7.20 (m, 2H, PhH), 5.30 (s, 2H, Ph-CH₂-), 4.27 (q, J = 7.0 Hz, 2H, -OCH₂CH₃), 1.32 (t, J = 7.0 Hz, 3H, -OCH₂CH₃).

**13C NMR (CDCl₃, 100.6 MHz):** δ 163.1, 141.4, 135.4, 132.7, 129.1, 128.6, 128.1, 115.7, 60.3, 56.6, 14.5.

1-Phenyl-4-(2-pyridinyl)-1H-pyrazole (8)
Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and 2-ethynylpyridine (62 μL, 0.62 mmol) for 7 h, 1-phenyl-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale brown solid (95 mg, 70% yield, regioselectivity: >95:5).

**Melting point:** 94-96 °C (lit. 86-88 °C). ¹H NMR (CDCl₃, 500 MHz): δ 8.60 (ddd, J = 5.0, 2.0, 1.0 Hz, 1H, PyH), 8.50 (d, J = 0.5 Hz, 1H, PyzlH), 8.18 (s, 1H, PyzlH), 7.79 – 7.73 (m, 2H, PhH), 7.69 (td, J = 7.5, 2.0 Hz, 1H, PyH), 7.54 (dt, J = 7.5, 1.0 Hz, 1H, PyH), 7.51 – 7.44 (m, 2H, PhH), 7.35 – 7.28 (m, 1H, PhH), 7.14 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H, PyH). ¹³C NMR (CDCl₃, 126 MHz): 151.6, 149.9, 140.0, 139.3, 136.8, 129.6, 126.9, 125.4, 125.3, 121.6, 119.9, 119.2.

**1-(p-Methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole (13)**

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and 2-ethynylpyridine (53 μL, 0.52 mmol) for 7.5 h, 1-(p-methoxyphenyl)-4-(2-pyridinyl)-1H-pyrazole was isolated as a pale brown solid (89 mg, 68% yield, regioselectivity: >95:5).

**Melting point:** 98-100 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.58 (ddd, J = 5.0, 1.5, 1.0 Hz, 1H, PyH), 8.39 (s, 1H, PyzlH), 8.14 (s, 1H, PyzlH), 7.71 – 7.60 (m, 3H, PhH), 7.52 (dt, J = 7.5, 1.0 Hz, 1H, PyH), 7.12 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H, PyH), 7.06 – 6.93 (m, 2H, PhH), 3.83 (s, 3H, -OC₃H₃). ¹³C NMR (CDCl₃, 126 MHz): δ 158.6, 151.7, 149.8, 138.8, 136.8, 133.8, 125.4, 125.0, 121.5, 120.9, 119.8, 114.7, 55.7. FTIR: νmax 3434 (br, s), 1643 (m), 1598 (m), 1519 (s), 1304 (w), 1250 (m), 1173 (w), 1036 (w), 962 (w), 834 (w), 781 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₅H₁₃N₃O: 252.1131, found: 252.1129.

**1-(Phenyl-1H-pyrazol-4-yl)methanol (7)**

Following the general procedure using N-phenylsydnone (100 mg, 0.62 mmol) and propargyl alcohol (36 μL, 0.62 mmol) for 20 h, (1-phenyl-1H-pyrazol-4-yl)methanol was isolated as a white solid (51 mg, 47% yield, regioselectivity: >95:5).

**Melting point:** 62-64 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.91 (s, 1H, PyzlH), 7.70 (s, 1H, PyzlH), 7.67 – 7.62 (m, 2H, PhH), 7.47 – 7.40 (m, 2H, PhH), 7.31 – 7.26 (m, 1H, PhH), 4.66 (s, 2H, -CH₂OH), 1.95 (s, 1H, -CH₂OH). ¹³C NMR (CDCl₃, 126 MHz): δ 140.5, 140.1, 129.6, 126.7, 123.6, 119.2, 56.2. FTIR: νmax 3354 (br), 2922 (w), 1599 (m), 1571 (m), 1503 (s), 1209 (w), 1046 (m), 996 (m), 954 (m), 757 (m) cm⁻¹. HRMS: m/z [MH⁺] calc. for C₁₀H₁₀N₂O: 175.0866, found: 175.0864.

**1-(p-Methoxyphenyl)-1H-pyrazol-4-yl)methanol (12)**

Following the general procedure using N-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and propargyl alcohol (31 μL, 0.52 mmol) for 20 h, (1-(p-methoxyphenyl)-1H-pyrazol-4-yl)methanol was isolated as a white solid (58 mg, 55% yield, regioselectivity: >95:5).

**Melting point:** 82-84 °C. ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (s, 1H, PyzlH), 7.65 (s, 1H, PyzlH), 7.55 – 7.51 (m, 2H, PhH), 6.96 – 6.92 (m, 2H, PhH), 4.63 (s, 2H, -CH₂OH), 3.82 (s, 3H, -OCH₃), 2.12 (s, 1H, -CH₂OH). ¹³C NMR (CDCl₃, 126 MHz): δ 158.4, 140.0, 133.9, 126.0, 123.2,
120.9, 114.6, 56.2, 55.7. FTIR: \( \nu_{\text{max}} \) 3434 (s, br), 1642 (m), 1523 (w), 1248 (w), 1031 (w), 827 (m) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{13}\)H\(_{12}\)N\(_2\)O\(_2\): 205.0972, found: 205.0970.

4-Cyclopentyl-1-phenyl-1H-pyrazole (6)

Following the general procedure using \( N \)-phenylsydnone (100 mg, 0.62 mmol) and cyclopentylacetylene (72 \( \mu \)L, 0.62 mmol) for 6 h, 4-cyclopentyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (44 mg, 33% yield, regioselectivity: >95:5).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.73 (t, \( J = 0.5 \) Hz, 1H, Pyzl\( H \)), 7.71 – 7.67 (m, 2H, Ph\( H \)), 7.60 (s, 1H, Pyzl\( H \)), 7.48 – 7.41 (m, 2H, Ph\( H \)), 7.31 – 7.24 (m, 1H, Ph\( H \)), 3.05 – 2.94 (m, 1H, \(-CH(=)\)), 2.17 – 2.02 (m, 2H, \(-CH(=)\)), 1.86 – 1.76 (m, 2H, \(-CH(=)\)), 1.76 – 1.65 (m, 2H, \(-CH(=)\)), 1.64 – 1.51 (m, 2H, \(-CH(=)\)). \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 140.4, 140.1, 129.4, 128.8, 126.0, 123.9, 118.9, 35.9, 34.4, 25.1.

FTIR: \( \nu_{\text{max}} \) 3435 (br), 2954 (s), 2868 (m), 1643 (m), 1602 (s), 1505 (s), 1463 (w), 1403 (m), 1332 (w), 1016 (w), 954 (m), 755 (m) cm\(^{-1}\).

HRMS: m/z [MH\(^+\)] calc. for C\(_{14}\)H\(_{16}\)N\(_2\): 213.1386, found: 213.1385.

4-Cyclopentyl-1-(p-methoxyphenyl)-1H-pyrazole (11)

Following the general procedure using \( N \)-(p-methoxyphenyl)sydnone (100 mg, 0.52 mmol) and cyclopentylacetylene (60 \( \mu \)L, 0.52 mmol) for 6 h, 4-cyclopentyl-1-(p-methoxyphenyl)-1H-pyrazole was isolated as an orange oil (36 mg, 28% yield, regioselectivity: >95:5).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.61 (s, 1H, Pyzl\( H \)), 7.57 – 7.54 (m, 2H, Ph\( H \)), 7.53 (s, 1H, Pyzl\( H \)), 6.98 – 6.91 (m, 2H, Ph\( H \)), 3.83 (s, 3H, \(-OCH\(_3\)\)), 3.03 – 2.88 (m, 1H, \(-CH(=)\)), 2.11 – 2.00 (m, 2H, \(-CH(=)\)), 1.71 – 1.45 (m, 2H, \(-CH(=)\)). \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 158.0, 139.6, 134.3, 128.4, 124.1, 120.6, 114.6, 55.7, 35.9, 34.5, 25.1. FTIR: \( \nu_{\text{max}} \) 2954 (m), 2868 (w), 1518 (s), 1464 (w), 1400 (w), 1246 (m), 1181 (w), 1170 (w), 1054 (m), 1038 (m), 956 (m), 830 (m) cm\(^{-1}\). HRMS: m/z [MH\(^+\)] calc. for C\(_{15}\)H\(_{18}\)N\(_2\)O: 243.1000, found: 243.1000.

Synthesis of 1,4-disubstituted-1H-pyrazoles in flow

Cartridge assembly:
Both ends of a U-shaped 10-cm Stainless steel tubing (1/8” OD, 1.75 mm ID, a) were blocked with cotton wool, fitted with assembled flat bottom super flangeless fittings + metal ferrules (1/8” OD, P-359, IDEX, b) and male nut parts (LT-215, IDEX, c). These connections were mounted onto flat unions (P-703-01, IDEX, d). For the filling of the cartridges, only one end was blocked at first, the cartridge was filled with the catalyst employing vacuum suction and after, the other end was blocked to seal the cartridge.

Microreactor setup:
All gas-tight syringes (5 mL, B-247, FutureChemistry Holding BV) were mounted on syringe pumps (B-230, FutureChemistry Holding BV, max flow rate: 35 mL/h, min flow rate: 0.73 \( \mu \)L/h) and connected to Tefzel* tubing (1/16” OD, 1529, IDEX) via female Luer adapters (P-628, IDEX).
Throughout the flow system, all the tubing (Tefzel® 1/16” OD, 1529, IDEX) was assembled with super flangeless nut connections (P-287, IDEX) and assembled ferrules (P-259, IDEX) in order to achieve leak-free fluid connections. Also, a 5 bar back pressure regulator (B-444, FutureChemistry Holding BV, 25-75 psi pressure range) guaranteed pressurisation inside the system before eluting into a collection flask (see Figure 1).

![Figure 1. Flow set-up including back pressure regulator (detail, right).](image)

**Experimental procedure:**
Two feed solutions were employed: stream A containing the sydnone of choice in toluene (0.025 M), and stream B containing the alkyne in toluene (0.050 M), both driven by syringe pumps ($\phi_A = 2 \cdot \phi_B$). These were mixed in a PEEK T-mixer connection (P-713, IDEX) before entering the microreactor (consisting of a 10 cm stainless steel cartridge packed with the supported copper catalyst) at 140 °C for 5 to 15 minutes. By removing the solvent in vacuo, the desired pyrazole products were obtained. In some cases, further purification was achieved by flash chromatography on silica gel (5-10% ethyl acetate in heptane) and/or by recrystallisation from dichloromethane/heptane.

Full characterisation of the pyrazole products can be found within the general procedure for the preparation of the title compounds in batch.

**Yield calculation for reactions performed under flow conditions:**
For the reactions performed in flow, yields were calculated taking into account the total moles of product obtained ($n(\text{Collected Product})$), the flow rate ($\phi_{SM}$) and the concentration ($[\text{SM}]$) of the starting material and the overall collection time ($t(\text{Collection})$), as shown in the equation below.

\[
\eta_{\text{FLOW}}(\%) = \frac{n(\text{Collected Product})}{[\text{SM}] \cdot \phi_{\text{SM}} \cdot t(\text{Collection})} \times 100
\]

**1,4-Diphenyl-1H-pyrazole (4)**

Following the general procedure using $N$-phenylsydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 31.00 μL·min⁻¹ and collecting for 2 h, 1,4-diphenyl-1H-pyrazole was isolated as a yellow solid (24 mg, 100% yield, regioselectivity: >95:5).
1-\(p\)-Methoxyphenyl)-4-phenyl-1\(H\)-pyrazole (9)

Following the general procedure using \(N\)-(p-methoxyphenyl)sydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 31.90 µL-min\(^{-1}\) and collecting for 2 h, 1-(p-methoxyphenyl)-4-phenyl-1\(H\)-pyrazole was isolated as a pale yellow solid (12 mg, 75% yield, regioselectivity: >95:5).

1-Benzyl-4-phenyl-1\(H\)-pyrazole (14)

Following the general procedure using \(N\)-benzylsydnone (0.025 M) and phenylacetylene (0.050 M) with retention time = 5 min, total flow = 20.60 µL-min\(^{-1}\) and collecting for 2 h, 1-benzyl-4-phenyl-1\(H\)-pyrazole was isolated as a pale yellow solid (11 mg, 77% yield, regioselectivity: >95:5).

Ethyl 1-phenyl-1\(H\)-pyrazole-4-carboxylate (5)

Following the general procedure using \(N\)-phenylsydnone (0.025 M) and ethyl propiolate (0.050 M) with retention time = 5 min, total flow = 31.41 µL-min\(^{-1}\) and collecting for 2 h, ethyl 1-phenyl-1\(H\)-pyrazole-4-carboxylate was isolated as a yellow solid (13 mg, 95% yield, regioselectivity: >95:5).

Ethyl 1-(p-methoxyphenyl)-1\(H\)-pyrazole-4-carboxylate (10)

Following the general procedure using \(N\)-(p-methoxyphenyl)sydnone (0.025 M) and ethyl propiolate (0.050 M) with retention time = 5 min, total flow = 30.00 µL-min\(^{-1}\) and collecting for 2.5 h, ethyl 1-(p-methoxyphenyl)-1\(H\)-pyrazole-4-carboxylate was isolated as a pale yellow solid (10 mg, 56% yield, regioselectivity: >95:5).

1-Phenyl-4-(2-pyridinyl)-1\(H\)-pyrazole (8)

Following the general procedure using \(N\)-phenylsydnone (0.025 M) and 2-ethynylpyridine (0.050 M) with retention time = 5 min, total flow = 30.00 µL-min\(^{-1}\) and collecting for 3 h, 1-phenyl-4-(2-pyridinyl)-1\(H\)-pyrazole was isolated as a pale yellow solid (5 mg, 24% yield, regioselectivity: >95:5).

1-(p-Methoxyphenyl)-4-(2-pyridinyl)-1\(H\)-pyrazole (13)

Following the general procedure using \(N\)-(p-methoxyphenyl)sydnone (0.025 M) and 2-ethynylpyridine (0.050 M) with retention time = 10 min, total flow = 15.00 µL-min\(^{-1}\) and collecting for 5 h, 1-(p-methoxyphenyl)-4-(2-pyridinyl)-1\(H\)-pyrazole was isolated as a pale yellow solid (5 mg, 26% yield, regioselectivity: >95:5).

(1-Phenyl-1\(H\)-pyrazol-4-yl)methanol (7)
Following the general procedure using N-phenylsydnone (0.025 M) and propargyl alcohol (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 6 h 15 min, (1-phenyl-1H-pyrazol-4-yl)methanol was isolated as a pale yellow solid (2 mg, 18% yield, regioselectivity: >95:5).

(1-(p-Methoxyphenyl)-1H-pyrazol-4-yl)methanol (12)
Following the general procedure using N-(p-methoxyphenyl)sydnone (0.025 M) and propargyl alcohol (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 6 h, (1-(p-methoxyphenyl)-1H-pyrazol-4-yl)methanol was isolated as a white solid (4 mg, 33% yield, regioselectivity: >95:5).

4-Cyclopentyl-1-phenyl-1H-pyrazole (6)
Following the general procedure using N-phenylsydnone (0.025 M) and cyclopentylacetylene (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 5 h, 4-cyclopentyl-1-phenyl-1H-pyrazole was isolated as a yellow oil (8 mg, 73% yield, regioselectivity: >95:5).

4-Cyclopentyl-1-(p-methoxyphenyl)-1H-pyrazole (11)
Following the general procedure using N-(p-methoxyphenyl)sydnone (0.025 M) and cyclopentylacetylene (0.050 M) with retention time = 15 min, total flow = 10.00 μL·min⁻¹ and collecting for 5.5 h, 4-cyclopentyl-1-(p-methoxyphenyl)-1H-pyrazole was isolated as an orange oil (3 mg, 24% yield – 38% conversion, regioselectivity: >95:5).

**Scaling up of the synthesis of 1,4-disubstituted-1H-pyrazoles in flow**

**Cartridge assembly:**
An empty stainless steel HPLC Column (12.5 x 0.46 cm, A2103-1, KNAUER) was filled with the catalyst and sealed using 7 μm pore-size frits.

**Microreactor setup:**
The feed stock from a glass container was injected into the flow system with a piston pump (Smartline Pump 100, KNAUER) and connected to Tefzel® tubing (1/16" OD, 1529, IDEX) with super flangeless nut connections (P-287, IDEX) and assembled ferrules (P-259, IDEX) in order to achieve leak-free fluid connections. Also, a 5 bar back pressure regulator (B-444, FutureChemistry Holding BV) guaranteed pressurisation inside the system before eluting into a collection flask (see Figure 2).

*Note that best results were obtained when a glass container for the oil bath was employed instead of a stainless steel container as shown in the figure below.*
**Experimental procedure:**
One feed solution was employed containing the sydnone of choice (0.0125 M) and the alkyne (0.0125 M) in toluene, driven by a piston pump, which entered the microreactor (an empty 12.5 x 0.46 cm stainless steel HPLC column packed with the supported copper catalyst) at 140 °C for 5 minutes. By removing the solvent *in vacuo*, the desired pyrazole products were obtained. Further purification was achieved by flash chromatography on silica gel (5-10% ethyl acetate in heptane).

Full characterisation of the pyrazole products can be found within the general procedure for the preparation of the title compounds in batch.

**Ethyl 1-phenyl-1H-pyrazole-4-carboxylate (5)**

Following the general procedure using *N*-phenylsydnone and ethyl propiolate with retention time = 5 min, total flow = 0.44 mL·min⁻¹ and collecting for 2 h, ethyl 1-phenyl-1H-pyrazole-4-carboxylate was isolated as a yellow solid (36 mg, 44% yield, regioselectivity: >95:5).

**Ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate (10)**

Following the general procedure using *N*-(p-methoxyphenyl)sydnone and ethyl propiolate with retention time = 5 min, total flow = 0.26 mL·min⁻¹ and collecting for 5 h, ethyl 1-(p-methoxyphenyl)-1H-pyrazole-4-carboxylate was isolated as a pale yellow solid (72 mg, 30% yield, regioselectivity: >95:5).
$^{1}\text{H}, ^{13}\text{C- NMR SPECTRA}$
REFERENCES