

The continuous-flow synthesis of carbazate hydrazones using a simplified computer-vision controlled liquid-liquid extraction system. [Supporting Information]

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General Experimental Information:

Unless specified otherwise, all reagents were purchased from commercial suppliers (Sigma-Aldrich, Fisher, Alfa-Aesar, Acros, TCI) and were used as received without further purification. Dichloromethane was purchased from Fisher Scientific (D/1850/17 2.5L). Completion of reactions was initially determined using thin layer chromatography (TLC). TLC plates used were Merck Silica-Gel 60 F₂₅₄, aluminium backed, 1.005554.0001). TLC plates were visualized using vanillin, potassium permanganate, iodine vapor or shortwave ultraviolet light (254 nm).

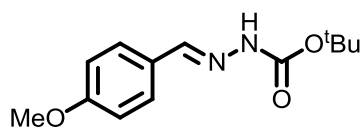
NMR spectroscopy was carried out on Bruker Sytems (300 MHz: Magnet - Bruker Spectrospin 300 MHz/52 mm, Spectrometer – Avance 300), (400 MHz: Magnet - Bruker Ascend 400, Spectrometer: Avance III 400). CDCl₃ was purchased from Cambridge Isotopes, Andover Massachusetts, USA (99.8% D, DLM-7TB-100) and was stored over granular anhydrous potassium carbonate (approx. 5 g added to bottle). NMR data are quoted in parts-per-million (ppm) relative to tetramethylsilane (TMS) at 0 ppm. Proton NMR spectra were calibrated in relation to the residual H solvent peak (CDCl₃ = 7.26 ppm) ¹³C NMR spectra were calibrated in relation to the solvent peak (CDCl₃ – central peak of triplet = 77.0 ppm). Multiplicity is indicated by: d-doublet, t-triplet, q-quartet, dd-doublet of doublets etc). Coupling constants (*J*) are given in Hertz (Hz).

HPLC pumps were used to pump liquids. Substrate/PPTS: Jasco PU-980. *tert*-Butyl-carbazate: Waters 510. Aqueous-in: Milton-Roy Constrametric.

General procedure for the continuous-flow hydrazone synthesis (products 3a-j)

Following initiation of the control script, using the apparatus shown in Figure 3, the system was primed with dichloromethane and the aqueous extraction solvent for several minutes until there were no air gaps in the flow path. The aldehyde (0.20 M) and pyridinium paratoluenesulfonate (PPTS) (0.10 M) in dichloromethane (7.5 mL) were loaded in to the corresponding 7.5 mL injection loop. *tert*-Butyl carbazate (0.4 M) in dichloromethane (10.0 mL) was loaded into the 10.0 mL injection loop. The *tert*-butyl carbazate loop was injected into the system 30 seconds prior to the substrate loop. Organic solution exiting the system was collected for 40 minutes. The solvent was then removed under reduced pressure to afford a solid.

3a



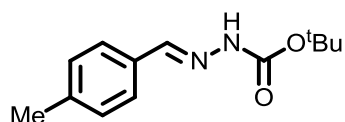
2a: 204 mg. Yield: 357 mg (95%).

¹H NMR (300 MHz, CDCl₃) δ ppm 7.87 (s, 1H), 7.77 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 1.53 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) 160.49, 152.90, 143.77, 128.41, 126.67, 113.66, 80.63, 54.97, 28.07

B. Wagner, W. Hiller, H. Ohno and N. Krause, *Org. Biomol. Chem.*, 2016, **14**, 1579-1583.

3b

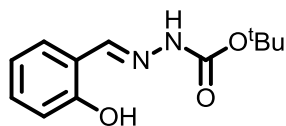


2b: 180 mg. Yield: 320 mg (91%).

¹H NMR (300 MHz, CDCl₃) δ ppm 8.15 (s, 1H), 7.80 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 2.34 (s, 3H), 1.53 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) 152.50, 143.79, 139.96, 131.10, 129.22, 127.10, 81.26, 28.23, 21.40

3c



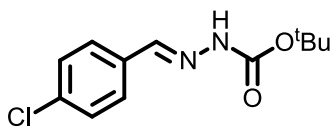
2c: 183 mg. Yield: 291 mg (82%).

¹H NMR (300 MHz, CDCl₃) δ ppm 11.14 (s (br), 1H), 9.90-8.11 (m (br), 1H), 7.92 (s, 1H), 7.30-7.21 (m, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 7.40 Hz, 1H), 1.57 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) 157.91, 153.56, 144.82, 131.02, 130.28, 119.16, 117.75, 116.93, 82.18, 28.18

H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G. W. A. Milne, Y. Pommier and T. R. Burke, *J. Med. Chem.*, 1997, **40**, 937-941.

3d



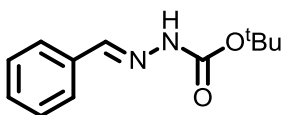
2d: 211 mg. Yield: 344 mg (90%).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.62 (s, 1H), 7.88 (s, 1H), 7.56 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 1.53 (s, 9H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 152.64, 142.41, 135.39, 132.44, 128.68, 128.16, 81.42, 28.17

J. Lee, M.-h. Kim, S.-s. Jew, H.-g. Park and B.-S. Jeong, *Chem. Commun.*, 2008, 1932-1934.

3e



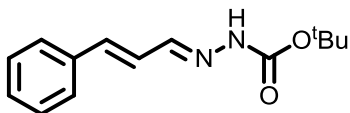
2e: 159 mg. Yield: 314 mg (95%).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.08 (s, 1H), 7.84 (s, 1H), 7.71-7.64 (m, 2H), 7.39-7.32 (m, 3H), 1.54 (s, 9H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 152.43, 143.57, 133.82, 129.79, 128.52, 127.14, 81.45, 28.24

N. C. Giampietro and J. P. Wolfe, *J. Am. Chem. Soc.*, 2008, **130**, 12907-12911.

3f

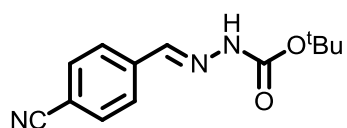


2f: 198 mg. Yield: 347 mg (94%).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.22 (s, 1H), 7.66 (d, $J = 8.20$ Hz, 1H), 7.44-7.36 (m, 2H), 7.36-7.22 (m, 3H), 6.99 (dd, $J = 16.1, 9.10$ Hz, 1H), 6.77 (d, $J = 16.1$ Hz, 1H), 1.53 (s, 9H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 152.39, 145.38, 137.96, 135.87, 128.72, 128.67, 126.81, 125.26, 81.40, 28.21

3g



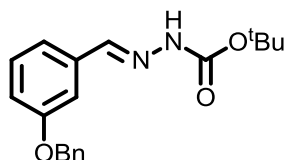
2g: 197 mg. Yield: 320 mg (87%).

¹H NMR (300 MHz, *CDCl*₃) δ ppm 8.96 (s, 1H), 7.94 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 1.48 (s, 9H)

¹³C NMR (75 MHz, *CDCl*₃) δ ppm 152.49, 141.15, 138.37, 132.13, 127.19, 118.45, 112.31, 81.70, 28.05

A. Zega, G. Mlinšek, P. Šepic, S. Golič Grdadolnik, T. Šolmajer, T. B. Tschopp, B. Steiner, D. Kikelj and U. Urleb, *Bioorganic & Medicinal Chemistry*, 2001, **9**, 2745-2756.

3h

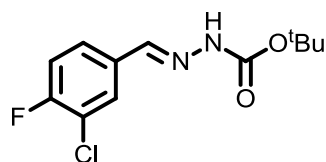


2h: 318 mg. Yield: 441 mg (91%).

¹H NMR (300 MHz, *CDCl*₃) δ ppm 8.46 (s, 1H), 7.85 (s, 1H), 7.45-7.28 (m, 6H), 7.26-7.14 (m, 2H), 6.95 (ddd, *J* = 8.0, 2.5, 1.2 Hz, 1H), 5.01 (s, 2H), 1.54 (s, 9H)

¹³C NMR (75 MHz, *CDCl*₃) δ ppm 158.88, 152.57, 143.60, 136.64, 135.31, 129.45, 128.44, 127.87, 127.49, 120.64, 117.28, 111.37, 81.27, 69.83, 28.19

3i

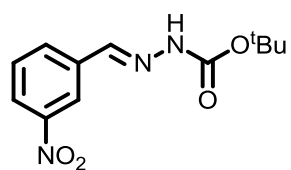


2i: 238 mg. Yield: 364 mg (89%).

¹H NMR (300 MHz, *CDCl*₃) δ ppm 8.76 (s, 1H), 7.86 (s, 1H), 7.66 (dd, *J* = 7.1, 2.1 Hz, 1H), 7.45 (ddd, *J* = 8.5, 4.6, 2.1 Hz, 1H), 7.04 (t, *J* = 8.5, 8.6 Hz, 1H), 1.50 (s, 9H)

¹³C NMR (75 MHz, *CDCl*₃) δ ppm 158.59 (d, *J* = 252.42 Hz), 152.72, 141.17, 131.32 (d, *J* = 3.84 Hz), 128.85, 126.77 (d, *J* = 7.50 Hz), 121.44 (d, *J* = 18.30 Hz), 116.63 (d, *J* = 21.74 Hz), 81.59, 28.15.

3j



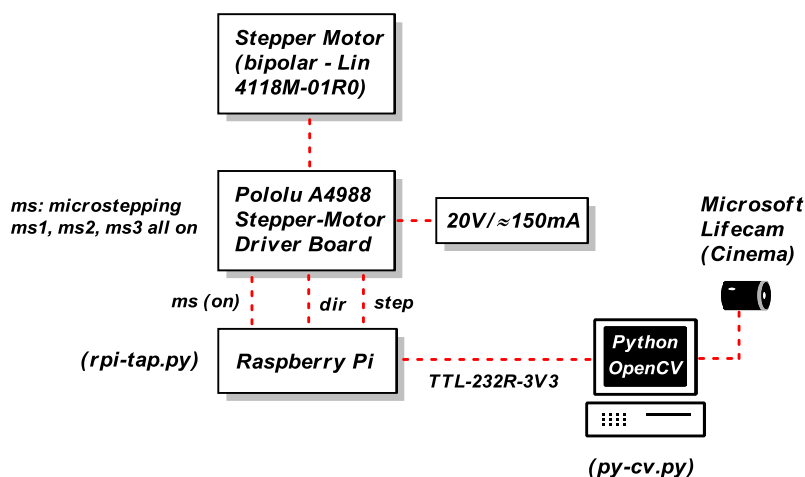
2j: 227 mg. Yield: 370 mg (93%).

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.41 (s, 1H), 8.32 (s (br), 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 8.07 (d, $J = 8.0$ Hz, 1H), 7.98 (s, 1H), 7.53 (t, $J = 8.0$ Hz, 1H), 1.54 (s, 9H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 152.20, 148.42, 140.68, 135.85, 132.22, 129.57, 124.09, 121.97, 82.02, 28.19

Details of the Control System

General Schematic:



The control computer was running the `py-cv.py` script. A Raspberry Pi (Model 3-b, Raspbian Jessie) computer (connected via a serial TTL-232R-3V3 cable), running the `rpi-tap.py` script, was used to control the stepper motor (Lin Engineering 4118M-01R0) via an Allegro A4988 driver board (Pololu). This could also be achieved with any number of microcontrollers (PIC, AVR etc) rather than using a Raspberry Pi. A separate power supply (Tenma) was used to provide the main power to the driver board (20 V, with a continuous fairly constant draw of about 150 mA). The `py-cv.py` and `rpi-tap.py` scripts are provided in individual files. Images of the separator are shown below. The body of the separator is the barrel of a 5 mL disposable syringe. The luer tap at the bottom was used only during the initial development and testing stages. It is not required for normal operation and was kept closed during the work described in the manuscript. The inlet and two outlets are via holes bored through a rubber bung. The holes were made with a bench drill press and were made to be tightly fitting. As can be seen from the image, the end of the biphasic inlet tube was located approximately midway down the vessel, the end of the organic outlet tube was at the bottom of the vessel, and the end of the aqueous outlet tube was just below the rubber bung.

Further below are shown some images of the stepper-motor and tap assembly. The assembly, motor-driver and Raspberry Pi were placed inside a plastic box to protect the components from any spillages etc.

