

Continuous flow iodination using an automated computer-vision controlled liquid-liquid extraction system [Supporting Information]

Matthew O'Brien*, Dennis A. Cooper and Jonathan Dolan.

Lennard-Jones Building, Keele University, Keele, Borough of Newcastle-under-Lyme, Staffordshire, ST5 5BG. UK.

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).

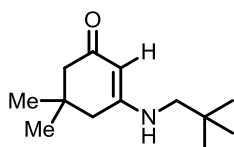
NMR spectroscopy was carried out on Bruker Systems (300 MHz: Magnet - Bruker Spectrospin 300 MHz/52 mm, Spectrometer – Avance 300), (400 MHz: Magnet - Bruker Ascend 400, Spectrometer: Avance III 400). CDCl₃ was purchased from Cambridge Isotopes, Andover Massachusetts, USA (99.8% D, DLM-7TB-100) and was 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). Protons coupling to two other non-identical protons but with identical coupling constants are generally referred to as doublets of doublets, rather than triplets (or apparent triplets). Assignment of peaks in the proton NMR spectra was carried out using chemical-shift values, coupling constants, COSY, TOCSY, HMBC and HSQC.

HPLC pumps were used to pump liquids. Substrate: LKB Bromma 2150. N-iodosuccinimide: Walters 510. Aqueous-in: Milton-Roy Constrametric. Aqueous-out: Merck-Hitachi L6000 (see the supporting information of M. O'Brien, D. A. Cooper, *Synlett*, **2016**, 27(1), p.164-168 for details of the electronic interface between the control computer and the pump).

General Procedure for the Formation of Enaminones 3a-c:

Diketone (14.2 mmol, 1 equiv.) and amine (16.2 mmol, 1.14 equiv) were added to a flask under nitrogen. To this was added toluene (40 mL) and ethanol (2.0 mL) and the mixture was stirred at reflux for one hour. After cooling to room temperature a pale yellow precipitate was observed in each case. The solvent was removed under reduced pressure. The solid remaining was recrystallised from toluene.

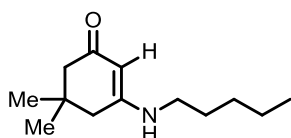
3a



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 5.14 (s, 1H), 4.56 (s, 1H), 2.87 (d, $J = 5.8$, 2H), 2.20 (s, 2H), 2.16 (s, 2H), 1.05 (s, 6H), 0.94 (s, 9H)

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ ppm 196.73, 163.10, 95.56, 54.15, 50.26, 44.07, 44.04, 32.71, 31.83, 28.24, 27.37

3b

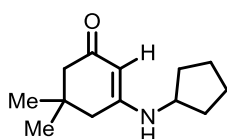


$^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 5.08 (s, 1H), 4.83 (s, 1H), 3.05 (q, $J = 6.5$, 2H), 2.16 (s, 2H), 2.15 (s, 2H), 1.62-1.51 (m, 2H), 1.33-1.27 (m, 4H), 1.04 (s, 6H), 0.88 (t, $J = 6.0$, 3H)

$^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ ppm 196.60, 162.78, 95.27, 50.25, 43.60, 42.92, 32.73, 29.07, 28.24, 28.16, 22.27, 13.89

Nemeryuk, M. P.; Tolokontseva, L. A.; Yadrovskaya, V. A.; Polezhaeva, A. I.; Petrova, G. A.; Safonova, T. S.; Mashkovskii, M. D., *Pharm Chem J* **1985**, 19, (7), 459-462.

3c



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 5.12 (s, 1H), 4.43 (s, 1H), 3.74 (m, 1H), 2.17 (s, 2H), 2.13 (s, 2H), 2.06-1.92 (m, 2H), 1.74-1.54 (m, 4H), 1.52-1.39 (m, 2H), 1.05 (s, 6H)

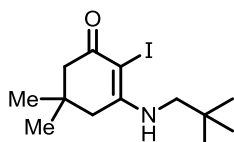
$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 196.63, 161.75, 96.42, 54.02, 50.15, 43.75, 33.11, 32.82, 28.27, 24.03

Takahashi, T.; Nagase, T.; Sasaki, T.; Nagumo, A.; Shimamura, K.; Miyamoto, Y.; Kitazawa, H.; Kanesaka, M.; Yoshimoto, R.; Aragane, K.; Tokita, S.; Sato, N. *J. Med. Chem.* **2009**, 52, 3142.

General procedure for the continuous-flow iodination (product 5a-5m)

Using the apparatus shown in figure 2, 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 enaminone **3a-m** (0.051 M in CH₂Cl₂-MeCN 7:3) was loaded in to the 11.6 mL injection loop. *N*-Iodosuccinimide (0.077 M in CH₂Cl₂-MeCN 7:3) was loaded into the 13.0 mL injection loop. The NIS loop was injected into the system 20 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.

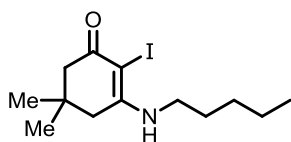
5a



¹H NMR (300 MHz, CDCl₃) δ ppm 5.82 (s, 1H), 3.07 (d, *J* = 6.2, 2H), 2.44 (s, 2H), 2.39 (s, 2H), 1.08 (s, 6H), 1.00 (s, 9H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 188.31, 162.72, 74.25, 54.87, 49.44, 40.20, 32.17, 31.93, 27.89, 26.80

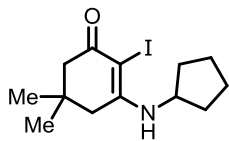
5b



¹H NMR (300 MHz, CDCl₃) δ ppm 5.64 (s, 1H), 3.28 (td, *J* = 5.9, 7.1, 2H), 2.40 (s, 4H), 1.70-1.50 (m, 2H), 1.41-1.31 (m, 4H), 1.06 (s, 6H), 0.91 (m, 3H)

¹³C NMR (75 MHz, CDCl₃) δ ppm 188.64, 162.83, 74.19, 49.57, 43.79, 40.32, 32.32, 29.88, 28.72, 28.09, 22.20, 13.86

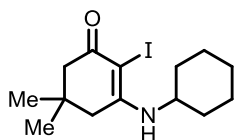
5c



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 5.68 (d, $J = 6.8$, 1H), 4.00-3.85 (m, 1H), 2.45 (s, 2H), 2.40 (s, 2H), 2.10-1.96 (m, 2H), 1.83-1.70 (m, 2H), 1.70-1.57 (m, 2H), 1.58-1.44 (m, 2H), 1.06 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 188.56, 162.47, 74.46, 55.09, 49.59, 40.75, 34.41, 32.40, 28.03, 23.63

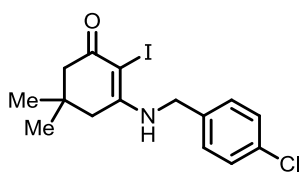
5d



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 5.64 (d, $J = 8.0$, 1H), 3.47-3.30 (m, 1H), 2.42 (s, 2H), 2.41 (s, 2H), 1.96-1.83 (m, 2H), 1.82-1.72 (m, 2H), 1.68-1.56 (m, 1H), 1.45-1.17 (m, 5H), 1.07 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 188.58, 161.90, 74.54, 52.21, 49.65, 40.26, 34.15, 32.43, 28.01, 25.01, 24.42

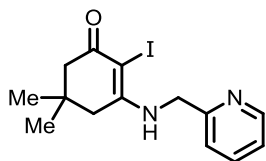
5e



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.35 (d, $J = 8.2$, 2H), 7.18 (d, $J = 8.2$, 2H), 6.04 (s, 1H), 4.51 (d, $J = 6.1$, 2H), 2.40 (s, 2H), 2.36 (s, 2H), 1.01 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.08, 162.74, 135.72, 133.72, 129.18, 127.80, 75.59, 49.53, 46.73, 40.21, 32.42, 27.96

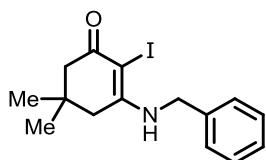
5f



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 8.60 (ddd, $J = 4.9, 1.5, 0.9$, 1H), 7.71 (dt, $J = 7.7, 1.8$, 1H), 7.28-7.20 (m, 2H), 6.93 (s, 1H), 4.63 (d, $J = 5.5$, 2H), 2.46 (s, 2H), 2.42 (s, 2H), 1.04 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.02, 162.70, 155.30, 149.42, 137.02, 122.78, 121.06, 74.80, 49.53, 48.18, 40.88, 32.44, 28.07

5g

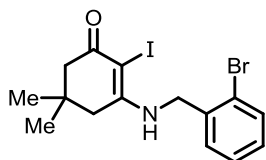


$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.45-7.29 (m, 3H), 7.29-7.21 (m, 2H), 6.08 (s, 1H), 4.55 (d, $J = 6.2$, 2H), 2.43 (s, 2H), 2.42 (s, 2H), 1.03 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.05, 162.99, 137.11, 129.03, 127.92, 126.47, 75.22, 49.57, 47.40, 40.23, 32.40, 27.98

Jirkovsky. I. *Can. J. Chem.* **1974**, 52, 55.

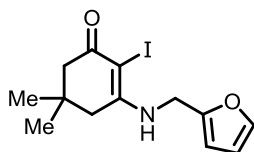
5h



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.59 (dd, $J = 8.3, 1.2$, 1H), 7.34 (dt, $J = 1.2, 7.8$, 1H), 7.24-7.17 (m, 2H), 6.13 (t, $J = 6.3$, 1H), 4.56 (d, $J = 6.3$, 2H), 2.41 (s, 2H), 2.37 (s, 2H), 1.02 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.10, 162.69, 136.32, 133.14, 129.55, 128.11, 127.96, 122.66, 75.64, 49.55, 47.67, 40.00, 32.43, 27.96

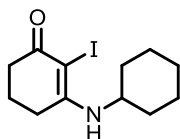
5i



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.40 (dd, $J = 1.8, 0.8$, 1H), 6.36 (dd, $J = 3.2, 1.8$, 1H), 6.24 (dd, $J = 3.2, 0.8$, 1H), 5.96 (s, 1H), 4.48 (d, $J = 6.2$, 1H), 2.51 (s, 2H), 2.43 (s, 2H), 1.08 (s, 6H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.22, 162.53, 150.21, 142.83, 110.53, 107.72, 75.63, 49.58, 40.76, 40.06, 32.47, 28.06

5j

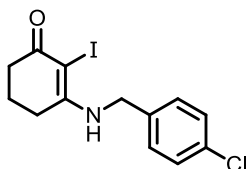


$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 5.66 (d, $J = 7.8$, 1H), 3.50-3.33 (m, 1H), 2.60 (t, $J = 6.2$, 2H), 2.54 (t, $J = 6.2$, 2H), 1.99-1.85 (m, 4H), 1.84-1.69 (m, 2H), 1.68-1.56 (m, 1H), 1.46-1.16 (m, 5H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.08, 163.57, 76.44, 52.33, 36.12, 34.00, 26.78, 25.00, 24.40, 21.39

Kim, J. M.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6317.

5k

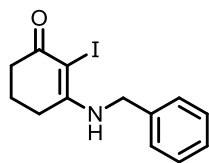


$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.35 (d, $J = 8.5$, 2H), 7.19 (d, $J = 8.5$, 2H), 6.06 (m, 1H), 4.51 (d, $J = 6.18$, 2H), 2.56-2.49 (m, 4H), 1.96-1.86 (m, 2H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.45, 164.44, 135.54, 133.75, 129.21, 127.95, 46.87, 35.96, 26.82, 21.19

(peak obscured by CDCl_3 solvent peaks, c.f. 76.44 ppm in 5j)

5l

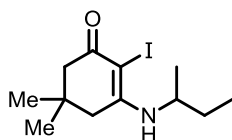


$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 7.43-7.28 (m, 3H), 7.28-7.22 (m, 2H), 6.09 (s, 1H), 4.54 (d, $J = 6.1$, 2H), 2.60-2.49 (m, 4H), 1.92 (m, 2H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 189.42, 164.67, 136.93, 129.05, 127.94, 126.58, 77.05, 47.52, 35.98, 26.85, 21.21

Kim, J. M.; Na, J. E.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6317.

5m



$^1\text{H NMR}$ (300 MHz, CDCl_3) δ ppm 5.51 (d, $J = 8.4$, 1H), 3.55 (m, 1H), 2.40 (s, 4H), 1.67-1.46 (m, 2H), 1.22 (d, $J = 6.5$, 3H), 1.06 (s, 6H), 0.93 (t, $J = 7.4$, 3H)

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ ppm 188.56, 162.17, 74.55, 50.92, 49.60, 40.45, 32.44, 30.61, 28.04, 27.93, 21.75, 10.19