Tetrahedron Letters 57 (2016) 5188–5191

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The continuous-flow synthesis of carbazate hydrazones using a simplified computer-vision controlled liquid–liquid extraction system

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ARTICLE INFO

Article history:
Received 9 September 2016
Revised 2 October 2016
Accepted 7 October 2016
Available online 10 October 2016

Keywords:
Continuous-flow
Computer-vision
Open-source
Liquid–liquid extraction
Hydrazone

ABSTRACT

A computer-vision controlled liquid–liquid extraction system was used in the continuous-flow synthesis of a series of carbazate hydrazones. The system uses open-source software components (Python, OpenCV) and is simpler and potentially more economical, in terms of hardware, than one we have described previously.

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In recent years, the emergence of continuous flow methodology has created new opportunities for chemical synthesis.[1] Compared with traditional batch processes, flow methods can often offer significant safety benefits, particularly for transformations involving hazardous conditions or reagents.[2] Additionally, the small dimensional scales involved lead to the efficient and scale-invariant interfacial transfer of energy and matter.[3] A particularly attractive aspect of flow chemistry is the ability to incorporate inline purification stages. Solid-supported scavengers[4] and phase-switching protocols have been extremely successful in this regard.[5] However, solid-supported chemicals can often be much more expensive than their solution phase counterparts.[6] In addition, they often give rise to significant and scale-dependent dispersion effects[7] and become depleted over time, thus requiring replacement or regeneration. This can be a time consuming operation which usually necessitates halting of the flow process. As liquids can be continuously pumped through the system, inline liquid–liquid phase separation does not suffer from this problem and, whilst dispersion cannot be eliminated, it can be controlled and rendered scale invariant.

One general method of inline liquid–liquid separation used in continuous flow makes use of the selective wetting of certain materials, particularly expanded porous PTFE membranes, to separate aqueous and organic solutions.[8] We have been interested, however, in gravity-based separations of immiscible liquids based on their densities.[9] This is essentially a continuous flow adaptation of the classical separating funnel. The basic concept is shown in Figure 1.

A biphasic stream of immiscible liquids with differing densities will, when passed into a suitable vessel, separate vertically. The dense phase will exit the vessel through a lower exit and the light phase will exit the vessel through an upper exit. In Figure 1 the organic phase is the dense phase and the aqueous extractant is the light phase, although these roles could be switched if less dense organic solvents, e.g. diethyl ether, were required. Obviously, it is important to maintain the interface within the separation vessel, otherwise liquids may leave through the wrong outlets. This

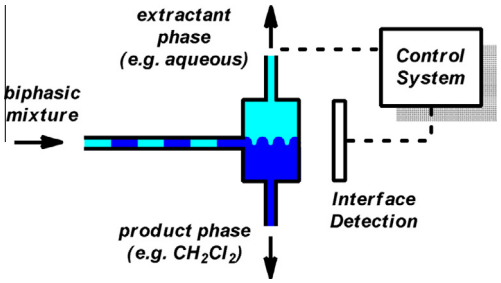

Figure 1. General schematic for inline separation.

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http://dx.doi.org/10.1016/j.tetlet.2016.10.018
0040-4039/© 2016 Published by Elsevier Ltd.

requires some kind of positional feedback system. Although several methods for determining the position of the interface could be used (including refractive index[10] and electrical impedance),[11] in the growing context of camera-enabled synthesis technologies[12] we have focused on the use of computer-vision systems, in conjunction with inexpensive and readily available web-cams, to locate a coloured interfacial float. In our previously described system, the control computer used the determined interfacial position to dynamically adjust the flow rate of the extractant-out pump (Fig. 2A). Although we have used this successfully in a number of continuous flow reactions, we sought to develop a streamlined and more cost-efficient system by reducing the overall number of pumps involved.

In situations where a smoothly varying response to interface level perturbations is not necessary, the extractant-out pump could be replaced by a simple motor actuated valve providing a binary on/off response. If the open valve provides the path of least resistance to the liquid (which it will if there is any back-pressure downstream of other outlets) the extractant phase will leave through the valve. This is shown schematically in Figure 2B. Thus, if the extractant (i.e. aqueous phase) has a higher volumetric flow rate than the organic phase, the position of the interface will fall. If it falls below a lower bound, the valve can be opened, allowing liquid to leave through the upper (extractant) outlet. When the interface level reaches an upper bound, the valve can be closed again which will force liquid to exit via the lower (product) outlet. Thus, a hysteresis pattern will result, with the interface position oscillating between the two boundary points. The check-valve prevents any of the product stream siphoning back in when the aqueous-out valve is open. As this system uses one less pump than that shown in Figure 2A, it represents a significant economic benefit. HPLC pumps typically cost upwards of £1000, whereas a stepper motor and required ancillary components can be obtained for under £50.

For this work we used a simple luer PTFE stopcock which was actuated using a stepper motor (for technical details and images, see the ESI).

We were interested in applying this system to the formation of carbazate hydrazones[13] **3a–j** using a condensation reaction, catalysed by pyridinium toluenesulfonate (PPTS), between *tert*-butyl carbazate **1** and a range of aromatic aldehydes **2a–j** (Scheme 1). In this case, excess carbazate was used to ensure reactions went to completion in a timely manner. Unreacted carbazate material, due to its basicity, could be extracted from the product stream, along with the PPTS catalyst, using an inline liquid–liquid extraction with aqueous phosphoric acid.

The flow setup is shown in Figure 3. Solutions of carbazate and aldehyde/PPTS (cat.) are introduced into the solvent flow streams (CH_2Cl_2) via separate injection loops. The carbazate solution was injected into the flow stream 30 s prior to the aldehyde/PPTS solution to ensure that the aldehyde was always accompanied by the carbazate. This corresponds to an overlap of 30 s at the injection front and 2 min at the tail. These meet at a T-piece and pass into a residence-loop where they react at room temperature. The reaction flow stream is then met by a flow stream of aqueous phosphoric acid. The phases are efficiently mixed together by passing through a magnetically stirred mixer (several tiny magnetic stirrer bars inside an omnifit column on the plate of a stirrer/hotplate).[14] On exiting the mixer the phases rapidly revert to plug-flow. The

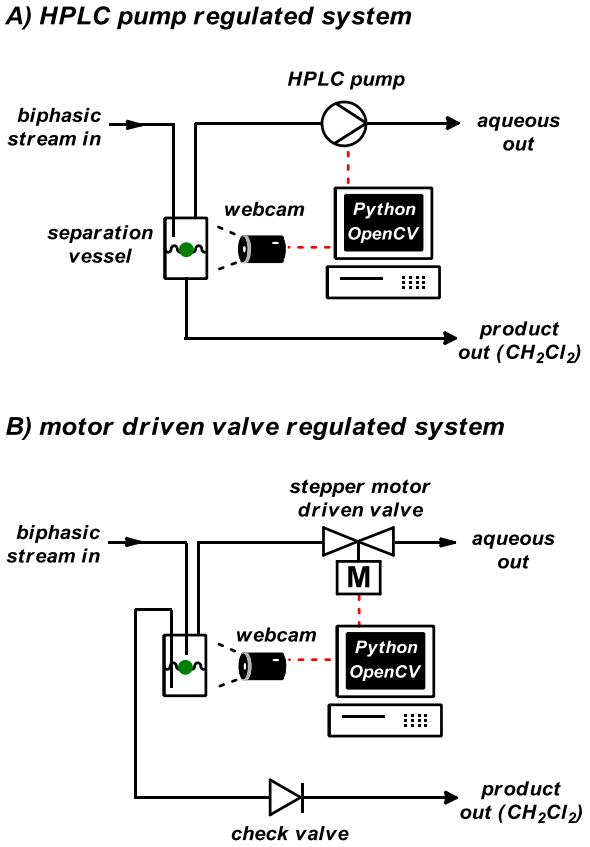
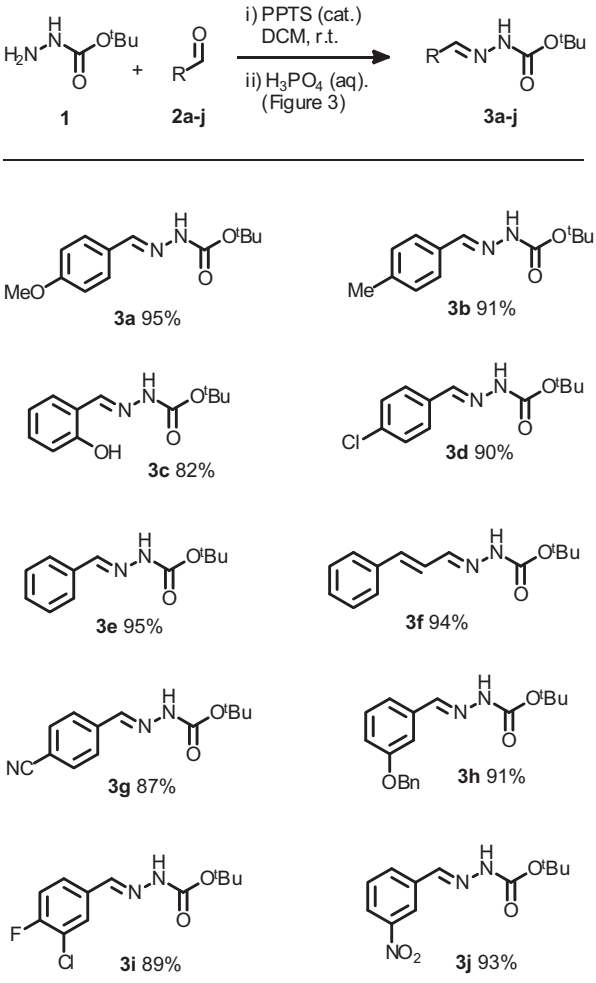


Figure 2. (A) HPLC pump regulated extraction system. (B) Motor driven valve regulated extraction system.



Scheme 1. Results for the synthesis of carbazate hydrazones **3a–j**.

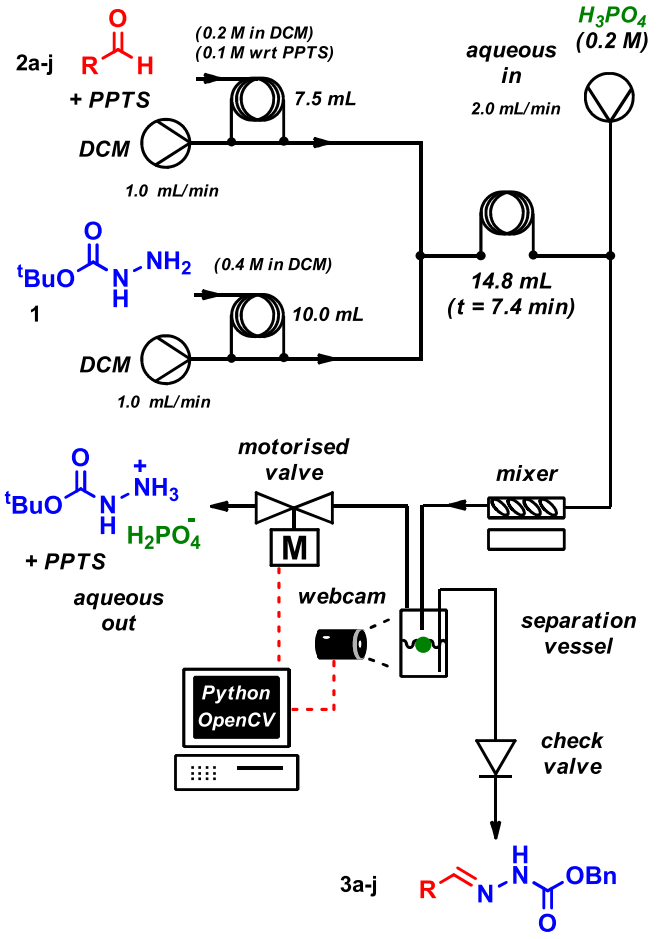


Figure 3. Flow apparatus for the hydrazone formation.

biphasic flow stream then enters the separating vessel where the two phases settle under gravity according to density. A plastic float, whose density is between that of the two liquid phases,[9a] is placed in the vessel to locate the vertical position of the liquid–liquid interface using the webcam.[15]

The webcam stream is fed to the control computer running a Python script incorporating several open-source software components. In addition to the critical OpenCV computer vision library,[16] other key components included NumPy[17] and PySerial[18] (for details of the scripts see the ESI).

We began our investigation with *p*-anisaldehyde (**2a**). A brief survey of reaction times revealed that a residence loop of 14.8 mL (corresponding to 7.4 min reaction time) was sufficient to ensure complete conversion to the hydrazone **3a**. The outlet stream was collected for 40 min and the product isolated in very high yield simply by removing the solvent under reduced pressure. Pleasingly, NMR spectroscopy revealed that the PPTS and excess carbazate reagent had been completely extracted, affording a pure product. Figure 4 shows a portion of the spectrum of the product isolated with (A) and without (B) the liquid–liquid purification stage.

As can be seen in Figure 4B, if the extraction step is bypassed, in addition to the excess carbazate, the product is also contaminated with significant residual aromatic material from the PPTS.

Having established appropriate conditions for the hydrazone formation and extraction, the flow reaction was carried out on a range of aldehydes **2a–j**, in each case affording products **3a–j** in excellent yield and high purity (^{1}H and ^{13}C NMR spectra of all the products are provided in the ESI). It should be pointed out that

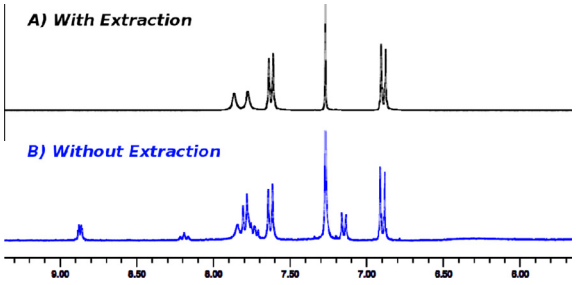


Figure 4. Portion of the ^{1}H NMR spectra of (A) product following extraction. (B) Product bypassing extraction.

the same flow setup was used for all these reactions with no dismantling or cleaning and no cross-contamination of the products was observed.

In conclusion, a simplified computer-vision controlled inline liquid–liquid extraction system has been developed for use in continuous flow synthesis. Requiring fewer pump units than our previously reported system, this new configuration may provide significant cost benefits in cases where uniform flow of the outlet stream is not required. The system was used in the synthesis of a series of carbazate hydrazones.

The excess carbazate and PPTS catalyst were efficiently extracted by an aqueous phosphoric acid stream affording the products in excellent yield and high purity. We are currently working on the application of this system to a range of other reactions. We are also investigating the process properties of the system, including quantification of dispersion effects, and will report our findings in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.018.

References and notes

1. For reviews see: (a) Hessel, V.; Kralisch, D.; Kockmann, N.; Noel, T.; Wang, Q. *ChemSusChem* **2013**, *6*, 746–789; (b) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688–6728; (c) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384–6389; (d) Wiles, C.; Watts, P. *Chem. Commun.* **2011**, *47*, 6512–6535; (e) Yoshida, J. I. *Chem. Rec.* **2010**, *10*, 332–341; (f) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378–390; (g) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17–57; (h) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680; (i) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869; (j) Anderson, N. G. *Org. Proc. Res. Dev.* **2012**, *16*, 852–869; (k) Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456–1472; (l)*Microreactors in Organic Chemistry and Catalysis*; Wirth, T., Ed., 2nd ed.; Wiley: Hoboken, 2013.
2. (a) Razzaq, T.; Kappe, C. O. *Chem.-Asian J.* **2010**, *5*, 1274–1289; (b) Gross, U.; Koos, P.; O'Brien, M.; Polyzos, A.; Ley, S. V. *Eur. J. Org. Chem.* **2014**, 6418–6430; (c) Mueller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245–250; (d) Maurya, R. A.; Park, C. P.; Lee, J. H.; Kim, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5952–5955; (e) Delville, M. M. E.; van Hest, J. C. M.; Rutjes, F. P. J. T. *Beilstein J. Org. Chem.* **2013**, *9*, 1813–1818; (f) Dallinger, D.; Pinho, V. D.; Gutmann, B.; Kappe, C. O. *J. Org. Chem.* **2016**, *81*, 5814–5823.
3. (a) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596–1598; (b) Park, C. P.; Kim, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 10102–10106; (c) Fukuyama, T.; Totoki, T.; Ryu, I. *Green Chem.* **2014**, *16*, 2042–2050; (d) Jensen, K. F. *Chem. Eng. Sci.* **2001**, *56*, 293–303; (e) Ahmed-Omer, B.; Brandt, J. C.; Wirth, T. *Org. Biomol. Chem.* **2007**, *5*, 733–740; (f) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250–1257; (g) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305–1308; (h) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052; (i) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349–362.
4. Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195.
5. O'Brien, M.; Denton, R.; Ley, S. V. *Synthesis* **2011**, 1157–1192.
6. At time of writing: Sigma-Aldrich: Amberlyst 15 Hydrogen form (06423-1 KG) costs £ 23.50/mol (GB). Sulfuric acid (320501-1L-D) costs £ 1.10/mol.

7. Lange, H.; Carter, C. F.; Hopkin, M. D.; Burke, A.; Goode, J. G.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 765–769.
8. (a) Kralj, J. G.; Sahoo, H. R.; Jensen, K. F. *Lab Chip* **2007**, *7*, 256–263; (b) Castell, O. K.; Allender, C. J.; Barrow, D. A. *Lab Chip* **2009**, *9*, 388–396; (c) Atallah, R. H.; Ruzicka, J.; Christian, G. D. *Anal. Chem.* **1987**, *59*, 2909–2914; (d) Kolehmainen, E.; Turunen, I. *Chem. Eng. Process.* **2007**, *46*, 834–839.
9. (a) O'Brien, M.; Koos, P.; Browne, D. L.; Ley, S. V. *Org. Biomol. Chem.* **2012**, *10*, 7031–7036; (b) Hu, D. X.; O'Brien, M.; Ley, S. V. *Org. Lett.* **2012**, *14*, 4246–4249; (c) O'Brien, M.; Cooper, D. *Synlett* **2016**, 164–168; (d) Bourne, S. L.; O'Brien, M.; Kasinathan, S.; Koos, P.; Tolstoy, P.; Hu, D. X.; Bates, R. W.; Martin, B.; Schenkel, B.; Ley, S. V. *ChemCatChem* **2013**, *5*, 159–172.
10. Maslana, E.; Schmitt, R.; Pan, J. *J. Autom. Methods Manage. Chem.* **2000**, *22*, 187–194.
11. Sprecher, H.; Payán, M.; Weber, M.; Yilmaz, G.; Wille, G. *J. Flow Chem.* **2012**, *2*, 20–23.
12. (a) Ley, S. V.; Ingham, R. J.; O'Brien, M.; Browne, D. L. *Beilstein J. Org. Chem.* **2013**, *9*, 1051–1072; (b) Ingham, R. J.; Battilocchio, C.; Fitzpatrick, D. E.; Sliwinski, E.; Hawkins, J. M.; Ley, S. V. *Angew. Chem., Int. Ed.* **2015**, *54*, 144–148.
13. (a) Einhorn, A. *Justus Liebigs Annalen der Chemie* **1898**, *300*, 135–155; (b) Backer, H. J. *Recueil des Travaux Chimiques des Pays-Bas et de la Belgique* **1912**, *31*, 1–29.
14. R. E. Gugger,; S. M. Mozersky, US 4054270 1977.
15. In this system, the vertical position of the float is directly related to its vertical position in the image. For an approach that relates the size of an object's image to its distance from the camera see: Wang, T.-H.; Lu, M.-C.; Hsu, C.-C.; Chen, C.-C.; Tan, J.-D. *Measurement* **2009**, *42*, 604–610.
16. (a) Bradski, G. *Dr. Dobbs J.* **2000**, *25*, 120–125; (b) http://opencv.org, (last accessed 6/9/2016).
17. http://www.numpy.org, (last accessed 6/9/2016).
18. https://github.com/pyserial/pyserial, (last accessed 6/9/2016).