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PII: S0040-4039(17)30051-5
DOI: <http://dx.doi.org/10.1016/j.tetlet.2017.01.029>
Reference: TETL 48532

To appear in: *Tetrahedron Letters*

Received Date: 28 November 2016
Revised Date: 5 January 2017
Accepted Date: 10 January 2017

Please cite this article as: O'Brien, M., Cooper, D.A., Dolan, J., Continuous flow iodination using an automated computer-vision controlled liquid-liquid extraction system., *Tetrahedron Letters* (2017), doi: <http://dx.doi.org/10.1016/j.tetlet.2017.01.029>

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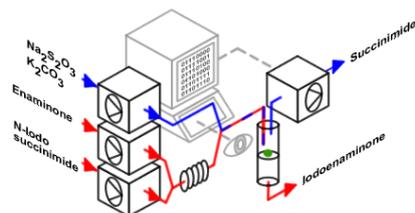
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Continuous flow iodination using an automated computer-vision controlled liquid-liquid extraction system

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ARTICLE INFO

Article history:

Received
Received in revised form
Accepted
Available online

Keywords:

Open-Source
Automation
Computer-Vision
Continuous-Flow
Iodination

ABSTRACT

A dynamic computer-vision control system incorporating open-source software technologies (Python, OpenCV) was used to automate a gravity based in-line liquid-liquid extraction during the iodination of enamines in continuous flow. The system was able to cope with significant colouration of the organic reaction stream and with significant volume/flow changes in the aqueous and organic phase streams due to extraction of the water soluble acetonitrile co-solvent.

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Over the last decade or so, flow chemistry has emerged as an alternative model to more traditional batch approaches to synthesis.¹ In addition to offering significant safety benefits when using hazardous reagents, intermediates or conditions,² flow chemistry often enables superior control over interfacial exchange parameters³ leading to highly efficient and scale-invariant chemical processes. A particularly attractive feature of flow chemistry is the ability to incorporate in-line purification techniques. The use of solid-supported scavengers⁴ and phase-switching reagents have enabled many noteworthy flow syntheses.⁵ In-line liquid-liquid extraction is also emerging as an alternative approach. Whilst it has limitations (obviously relying on efficient extraction from one phase to another) it can also offer advantages. Firstly, solid-supported reagents are often much more expensive than the equivalent soluble form.⁶ Secondly, unless some regeneration protocol is incorporated into the system, solid-supported reagents become depleted over time and at some point will need replacing, possibly requiring the system to be temporarily shut down. Liquid extractants, which can be pumped continuously into the system, do not suffer from this issue. The use of solid supports also causes significant scale-dependent dispersive effects.⁷ Whilst there will also be unavoidable dispersive effects associated with liquid-liquid extraction processes these can, in principle, be rendered scale-invariant. Semi-permeable hydrophobic membranes, particularly those based on expanded PTFE,⁸ have been used to effect continuous flow separation of aqueous and organic flow streams.⁹ An alternative approach, essentially a flow adaptation of the traditional separating funnel, relies on the vertical separation of immiscible liquids under gravity. If a flow stream containing a mixture of two immiscible liquids is fed into a separating vessel with upper and lower exits, the dense phase will leave through

the lower exit and the light phase will leave through the upper exit (Fig. 1).

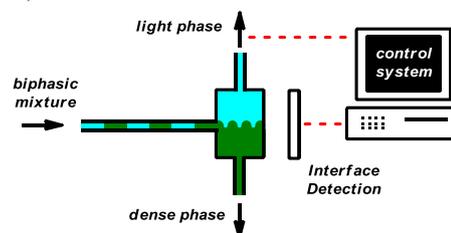


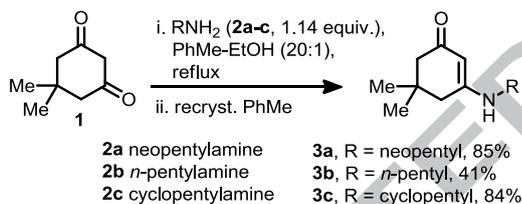
Figure 1. Gravity based liquid-liquid extraction in continuous flow.

It is important that the position of the liquid-liquid interface be kept within the vessel, otherwise the liquids may exit the vessel through the wrong channels. Due to material extraction between phases, the flow rates of each phase (and therefore the position of the interface) may vary. It is therefore desirable to acquire a means of dynamic positional control. This requires a method of determining the interface position. Sprecher and co-workers have shown that differences in the electrical impedance of the aqueous and organic phases can be used to achieve this in a continuous flow system.¹⁰ Refractive index differences have also been used in automated batch systems.¹¹ In the growing context of camera-enabled synthesis,¹² we have been interested in the use of computer-vision systems, together with inexpensive digital 'webcams', to facilitate interface location. Rather than using the system to directly 'see' the liquid-liquid interface, we instead use a coloured plastic float which, having a density between that of the two phases, sits at the interface. With hue filtering, it is straightforward to determine the position of the float in a digital image stream. This system has been successfully employed for a range of continuous flow transformations including hydrazone formation, dithiane synthesis, alkene epoxidations,¹³ amino acid

diazotisations,¹⁴ ethylene-Heck reactions,¹⁵ and enamine brominations.¹⁶ Recently, the Ley group reported the use of this system in a multi-step flow synthesis of 2-aminoadamantane-2-carboxylic acid, where computer-vision was also used to dynamically measure liquid volumes in solution reservoirs.¹⁷ The use of a gravity based separator in continuous flow was also described by the Wirth group, although it was not reported whether any positional control system was used.¹⁸ Herein, we report our findings on the use of a computer-vision controlled liquid-liquid extraction system in the continuous flow iodination of a series of enamines with *N*-iodosuccinimide,¹⁹ wherein the succinimide by-product is efficiently removed using a solution of aqueous alkali. We present data that suggest the use of a water soluble component in the injected reaction solvent (7:3 CH₂Cl₂-MeCN) leads to a significant perturbation of the interfacial position during the liquid-liquid extraction process. This perturbation was mitigated by the dynamic control system. Additionally, we describe how the computer-vision system tolerates significant colouration of the organic phase during the extraction process.

Results and Discussion

The substrate enamines **3a-c** were synthesised by condensing dimedone **1** with primary amines **2a-c** at reflux in a 20:1 mixture of toluene and ethanol (Scheme 1).²⁰ Enamines **3d-m** were synthesised in a similar manner.¹³ Our iodination studies began with enamine **3a** using the flow apparatus setup shown in Figure 2. The starting material and *N*-iodosuccinimide are introduced into separate flow streams (which have the same flow rate) *via* injection loops.



Scheme 1. Enaminone formation

The reagent loop is longer than the starting material loop, to ensure that starting material always passes through the system in the presence of reagent. The starting material and reagent streams are mixed at a T-piece and pass into a residence-time loop where they react at room temperature. The reaction mixture is then met by a stream of aqueous extractant. Sodium thiosulfate ensures that excess *N*-iodosuccinimide is reduced to succinimide and potassium carbonate helps to extract the mildly acidic succinimide into the aqueous phase. Efficient mixing of the aqueous and organic phases is facilitated by passing the biphasic stream through a small glass column containing several tiny magnetic stirrer beads, sitting on the plate of a magnetic stirrer.²¹ Upon exiting the mixer, the phases rapidly settle back into plug-flow and pass into the separating chamber where they separate into bulk phases according to gravity. The computer-vision system, incorporating an inexpensive webcam, monitors the position of the interfacial float. Filtration of the digital images in the webcam stream according to hue values allows the position of the float, and therefore the liquid-liquid interface, to be ascertained in a straightforward manner. In simple terms, a fall in the level of the interface below the desired set point causes the aqueous-out pump to increase its flow rate, thereby lifting the interface level. If the interface level goes above the desired point, the flow rate of the aqueous-out pump decreases, causing the interface level to drop. The software system used was based on

the freely available OpenCV²² libraries incorporated into a Python²³ script.

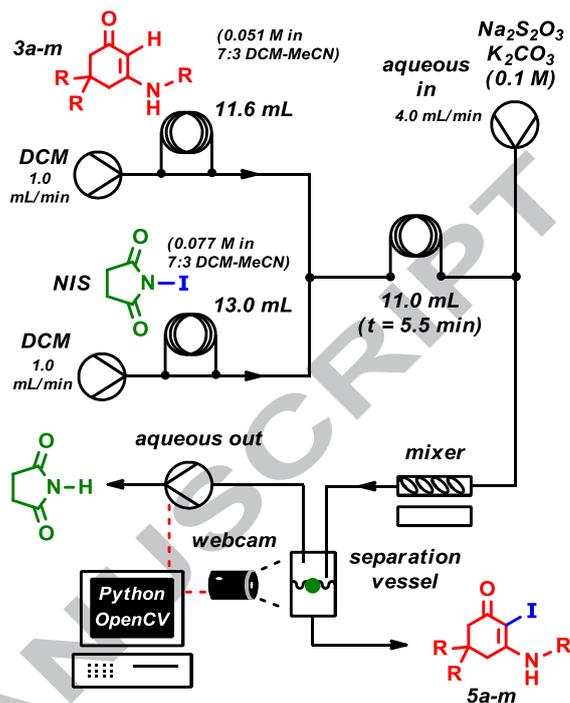


Figure 2. Flow system for enamine iodination

Whilst our previously reported script used the original OpenCV API and required the VideoCapture library²⁴ to access frames which were then converted between PIL (Python Image Library)²⁵ and OpenCV formats, the script used in this work (see ESI) uses the newer CV2 OpenCV API and does not require these additional file conversions. Based on our previous bromination studies using *N*-bromosuccinimide,¹³ we began with neat dichloromethane as the reaction solvent. However, *N*-iodosuccinimide proved to be significantly less soluble than *N*-bromosuccinimide in this solvent and only concentrations of 0.025 M could be obtained. We quickly abandoned our investigations with this solvent due to the low reaction rates and the low material throughput. Changing to a binary solvent (7:3 CH₂Cl₂-MeCN) enabled much higher concentrations of *N*-iodosuccinimide (0.077 M) to be used whilst still providing complete phase separation, and efficient removal of succinimide, following aqueous extraction. An immediate consequence of the change of solvent, however, was that the float we were using for neat dichloromethane, made by melting together 186 mg of polyacetal (from a green Keck clip) and 29 mg of low density polyethylene (from the plunger of a 1 mL disposable syringe), was no longer suitable. When 3 mL of CH₂Cl₂-MeCN (7:3) was extracted with 6 mL of water in a glass vial, this 'float' sank to the bottom of the vessel, clearly indicating that some MeCN remained in the organic phase, lowering its density. This was rectified by using a different mixture of plastics. Experiments determined that a float made by melting together 138 mg of polyacetal (green Keck clip) with 64 mg of the low density polyethylene (syringe plunger) was of a suitable density to remain at the interface, both before and after extraction. The quantities of each plastic contained in the floats are only approximate as the method used to combine them (holding the pieces together with tweezers and heating with a heat gun) led to some mechanical loss of material. With a more accurate melting technique, it should be possible to create floats of any required density. Having obtained a suitable float, we continued with the

iodination reactions. Both the *N*-iodosuccinimide and the starting material were dissolved in the 7:3 CH₂Cl₂-MeCN mixture, although these solutions were injected, *via* the loops, into flow streams of neat dichloromethane (both at 1 mL min⁻¹). With the *N*-iodosuccinimide at 0.077 M, a concentration of 0.051 M was used for the starting material **3a**. An excess of *N*-iodosuccinimide was used to facilitate complete and rapid reactions. An aqueous extraction stream of Na₂S₂O₃/K₂CO₃ (0.1 M) was fed into the system at a rate of 4 mL min⁻¹. A small number of experiments revealed that an 11 mL reaction loop (5.5 min reaction time) was sufficient to ensure complete conversion of **3a** to iodoenaminone **5a** at room temperature. The *N*-iodosuccinimide flow stream was injected 20 seconds prior to the starting material. This corresponds to an overlap of 20 seconds at the injection front and 64 seconds at the tail. The product stream was collected for 40 minutes. A very high yield of **5a** (99%), which was analytically pure by ¹H and ¹³C NMR analysis, was obtained simply by removing the solvent under reduced pressure. No drying step was used. Liquid-liquid separation in batch, e.g. using a separating funnel, typically leads to an organic phase visibly contaminated with small droplets of aqueous liquid (held in place due to surface forces) and generally necessitates the use of a desiccant. As the mechanical agitation and settling processes are confined to separate vessels, the flow extraction system does not suffer from this problem. Although trace quantities of dissolved water were presumably present before solvent removal on the rotary evaporator, no visible water droplets were ever observed in the product streams. Importantly, all of the succinimide, and excess *N*-iodosuccinimide, had been efficiently removed by the in-line liquid-liquid extraction system (Fig. 3). Using the same setup and conditions, the iodination of a series of enaminones **3a-m** led to the efficient synthesis of the corresponding iodoenaminones **5a-m** in very high yield (Scheme 2).

Effect of colouration on hue filtering

Although the majority of iodination reactions in Scheme 2 led to colourless or pale yellow product streams, in the case of the pyridyl compound **3f** the reaction was accompanied by significant yellow/brown colouration. Despite this, the tolerances in the computer-vision algorithm were such that the position of the green float could be discerned by the system throughout the entire reaction.

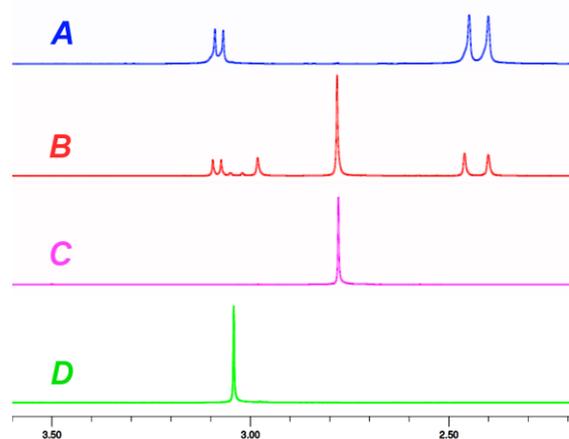
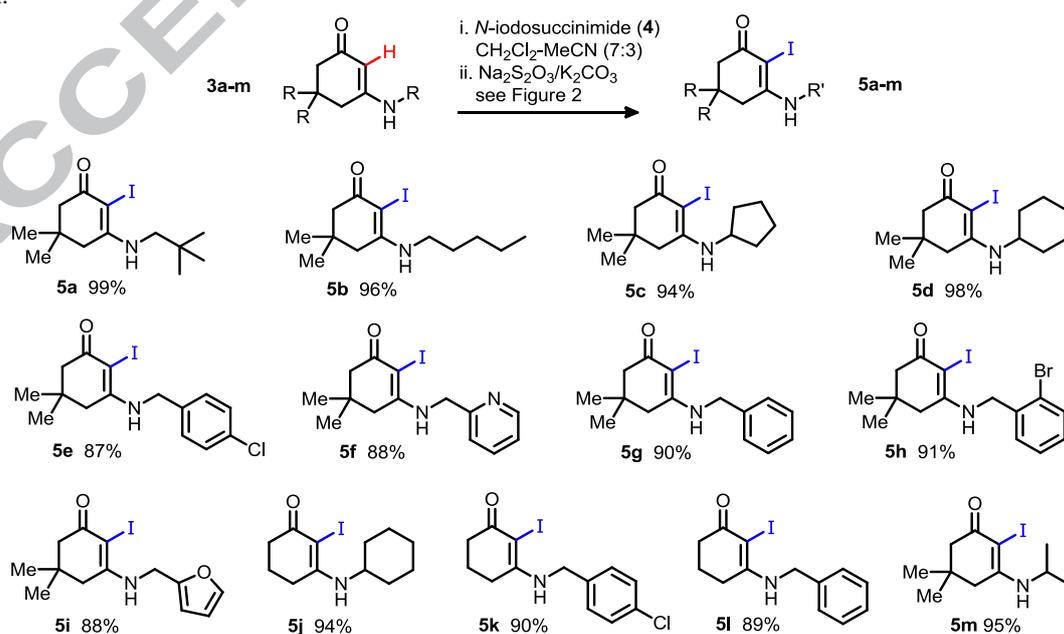


Figure 3. A: ¹H NMR spectrum of product **5a** isolated after continuous flow synthesis incorporating liquid-liquid extraction. B: ¹H NMR spectrum of product **5a** isolated when the extraction unit is bypassed. C: ¹H NMR spectrum of succinimide alone. D: ¹H NMR spectrum of *N*-iodosuccinimide alone. All spectra obtained in CDCl₃.

We were interested in quantifying how the colouration affected the hue recognition during this reaction. For this purpose, the iodination of **3f** was repeated but all flow streams were halted part way through (after 10 min.) whilst observations were made. Figure 4 shows the feed from the digital webcam at this point. Although the lower organic layer is very dark, the green float, which happened to be situated towards the front of the separation vessel, is still easily seen but it is clear that the brown colouration has perturbed its appearance. Hue histograms of three regions of the image stream (A, B and C) were obtained and are shown on the right of the figure. Region A has a hue histogram practically identical to that obtained for the float in clean solvent. Almost all of the pixels are in the green region of the HSV colourspace with a narrow distribution around a maximum of 75 (the hue values in the OpenCV HSV images used have a range of 0-180 from red through to red, see colourbar at the bottom of Figure 4). The hue histogram for region B (the organic solution) is quite clearly in the red/yellow hue region.



Scheme 2. Continuous flow iodinations.

In region C, the colour of the solution has clearly affected the observed hue of the float. A significant portion of the histogram is now in the yellow region, with the most populated histogram bin having a hue value of 58, a shift of 16 units compared with region A. When a flow chemistry run is initiated, the user of the system selects a portion of the image (i.e. the green float) from which the system obtains a hue histogram and identifies the most common hue. Subsequently, all images are filtered based on whether pixels have matching hue values, within a specified tolerance. Clearly, very narrow tolerance limits might affect the ability of the system to recognise the green float in the event of such colouration. Shown in Figure 5 are several images (A1, B1, C1, D1) taken from the webcam feed during the paused iodination of **3f**, and the corresponding images (A2, B2, C2, D2) following hue filtering with various hue tolerances.

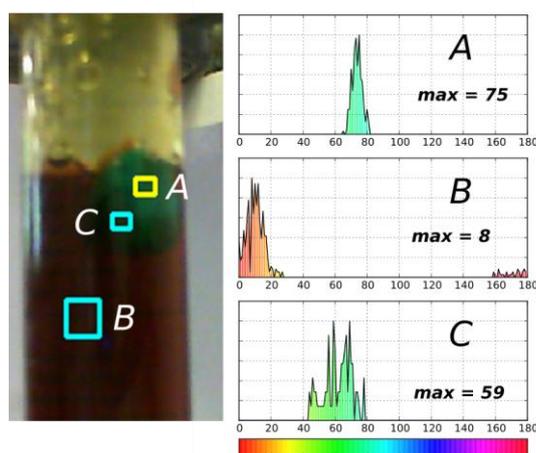


Fig 4. Hue histograms (right) for selected regions of the web-cam feed (left), during the halted iodination of **3f**.

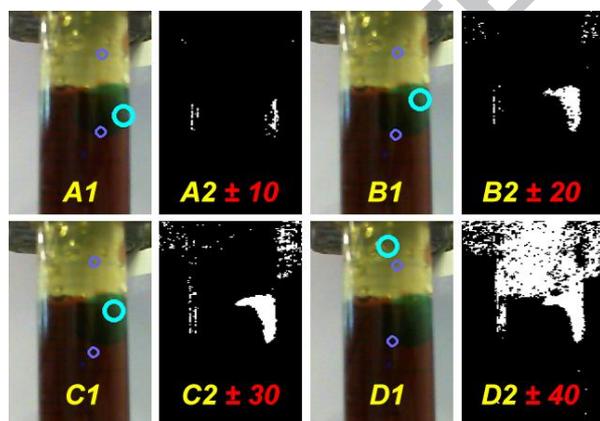


Fig 5. Web-cam feed images during interrupted iodination of **3f** (A1, B1, C1, D1) and corresponding filtered images (A2, B2, C2, D2) using different hue-tolerance values (± 10 means that pixels would be selected if they had hue values within ± 10 units of the most populated hue value from the histogram of the originally selected coloured object, in this case the green float). The position of the centroid of the largest filtered 'object' is indicated by a turquoise circle.

In A2, very few pixels in the image are between ± 10 hue units of the originally selected green colour. The centroid of the largest group of 'correct' pixels (after additional noise removal steps) is indicated with a turquoise circle in A1 while the smaller blue circles indicate the positions of the upper and lower bounds

selected when starting each run. In B2, many more pixels fall within the wider tolerance limits of ± 20 hue units. In C2, the tolerance limits of ± 30 lead to a similar situation, with the green float being correctly identified and located. With tolerance limits of ± 40 , however, there is insufficient filtration of pixels (D2) and the system fails to correctly locate the float, as can be seen from the position of the turquoise circle in D1. With suitable tolerance limits (± 20) the system was able to cope with the significant colouration seen in the iodination of **3f**.

Positional Control

The presence of MeCN in the reaction solvent raised the possibility of significant mass transfer from the organic phase to the aqueous phase during extraction. This would cause a substantial increase in the volumetric flow rate of the aqueous outlet stream following injection of the reactant solutions into the flow streams of neat CH_2Cl_2 . We were interested in the system's response to this perturbation and in order to gauge the potential for interfacial transfer of MeCN during the extraction step, we carried out a simple batch liquid-liquid partitioning experiment (Fig. 6).

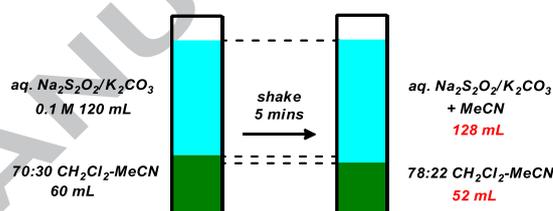


Figure 6. Illustration of the batch liquid-liquid extraction experiment using an aqueous $\text{Na}_2\text{S}_2\text{O}_3/\text{K}_2\text{CO}_3$ solution and CH_2Cl_2 -MeCN solvent mixture.

To 60 mL of CH_2Cl_2 -MeCN (7:3, vol:vol) in a graduated cylinder, 120 mL of the aqueous extraction solution (0.1 M $\text{Na}_2\text{S}_2\text{O}_3/\text{K}_2\text{CO}_3$) was carefully added without mixing. The interface level remained at the 60 mL mark. The cylinder was stoppered and the contents shaken vigorously for 5 minutes. After settling, the volume of the lower organic phase was now 52 mL and that of the upper aqueous phase was 128 mL (the total volume was unchanged at 180 mL). Unsurprisingly, a significant amount of material had clearly passed from the organic phase to the aqueous phase. ^1H NMR analysis of the two organic solvent mixtures before and after extraction indicated that the vol.-vol. ratio of CH_2Cl_2 -MeCN had changed from 70:30 to approximately 78:22. To measure the response of our in-line liquid-liquid extraction system to such mass transfer, we carried out a run using the same setup shown in Figure 2, where we recorded both the position of the green float as well as the flow rate for the aqueous-out pump. For simplicity, this was done without any starting materials or *N*-iodosuccinimide, although the $\text{Na}_2\text{S}_2\text{O}_3/\text{K}_2\text{CO}_3$ (0.1 M) solution was still used as the aqueous phase. The two injection loops were filled with the CH_2Cl_2 -MeCN (7:3) solvent mixture and injected into the flow stream of neat CH_2Cl_2 . The results are shown in Figure 7. Both the interfacial position and the aqueous-out flow rate share the same horizontal time axis but have separate vertical axes as indicated. The interfacial position is displayed in terms of the fraction of the vertical distance between the lower and upper bounds selected during initialisation (corresponding to the 1 mL and 3 mL marks on the syringe barrel that formed the separation vessel). The time shown is relative to the injection of the CH_2Cl_2 -MeCN mixtures into the flow streams of neat CH_2Cl_2 . To remove the high-frequency oscillatory component from the raw data (shown in

light colours), a Butterworth low-pass filter²⁶ was applied to the two sets of data. The resulting lines (bold, Fig. 7) allow the general trend to be more easily discerned. As can be seen, following an initial delay as the CH₂Cl₂-MeCN mixture works its way through the reaction loop and in-line mixer, there is a noticeable lowering of the interface level at around 500 sec.

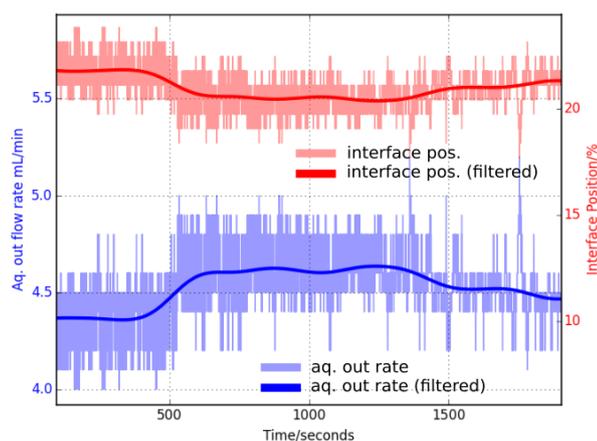


Figure 7. Data for the position of the interfacial float (red) and the flow rate of the aqueous-out pump (blue). Raw data is shown in light colours while the smoothed data (Butterworth low pass filter) is shown as a dark line.

This is consistent with an increase in the aqueous phase volumetric flow rate and a corresponding decrease in the organic phase volumetric flow rate, brought about by extraction of MeCN between the two phases. This was confirmed by ¹H NMR analysis of the organic outlet stream, which had the same CH₂Cl₂-MeCN ratio as in the batch extraction experiment shown in Figure 6. The perturbation in the interface level is accompanied by a corresponding increase in the aqueous-out flow rate as the system tries to compensate. This continues for some time until the position of the interface and the aqueous-out flow rate begin to return to their original values. Clearly, the results shown in Figure 7 reinforce the need for dynamic positional control in order to keep the liquid-liquid interface within the desired bounds. The ability of the system to respond to perturbations becomes more critical when low organic phase volumes are used in the separator as there is less ‘buffer’ volume between the interface and the organic outlet. This is an important consideration from a process standpoint as the use of a low organic phase volume is desirable to minimise unwanted dispersion effects.²⁷ In addition, the ability to keep the organic phase volume within desired bounds provides control over such dispersion, leading to time and/or scale invariance.

Conclusions

The computer-vision controlled liquid-liquid extraction system used in this work enabled the automated continuous-flow iodination of a series of enamines using *N*-iodosuccinimide as the halogen source. The system efficiently extracted all of the succinimide by-products from the product stream, affording analytically pure compounds in high yield. The system was able to cope well with significant colouration of the product stream. It also responded well to the perturbation in the relative flow rates of the two phases brought about by the interfacial transfer of MeCN. We are currently investigating the application of this system to a wide range of other reaction types. We are also continuing our investigations into the perturbation of interface position due to the extraction of miscible solvents into the aqueous phase and will report our findings in due course.

Supporting Information

NMR spectral data and spectra of compounds **3a-c**, **5a-m**, and the Python control script are included in the ESI.

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Highlights

Open-source technologies were harnessed to provide low-cost automation.

Computer-vision was used in a continuous-flow liquid-liquid extraction process.

Iodo-enaminones were synthesised in high yield and purity.

ACCEPTED MANUSCRIPT