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Scale-up and Optimization of a Continuous Flow Synthesis of an α-Thio-β-chloroacrylamide

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KEYWORDS: Continuous processing, flow chemistry, process impurities, α-thio-β-chloroacrylamides

ABSTRACT:

Use of continuous flow processing to undertake a multistep chlorination cascade has been achieved with effective inline work-up and end-of-line crystallization in batch leading to isolation of α-thio-β-chloroacrylamide ***Z*-3** in pure form from a complex reaction mixture, exploiting the advantage of efficient heat transfer in flow. During the development of a continuous flow strategy

for the production of appreciable quantities of the *α*-thio-*β*-chloroacrylamides, difficulties surrounding a labour and resource intensive work-up followed by final product isolation were addressed. A greener solvent choice was applied to the chemical synthesis which enabled inline purification and separation, resulting in the crystallization of pure product directly from the reaction mixture. This process was readily scalable and demonstrated control over impurity formation and removal, which is key in an industrial setting.

INTRODUCTION

α-Thio-*β*-chloroacrylamides are valuable compounds for organic synthesis due to their diverse functionality which enables a wide array of useful transformations,[1-2] including nucleophilic substitution,[3-4] 1,3-dipolar cycloadditions,[5-6] oxidation of the sulfide group[7-8] and Diels–Alder reactions[9] (Figure 1). Preparation of the prototypical *α*-thio-*β*-chloroacrylamide ***Z*-3** consists of a three step synthesis (Scheme 1), including a cascade reaction as the final step (Scheme 2). Control over the cascade temperature and efficient heat transfer are crucial parameters in directing the reaction to the desired *α*-thio-*β*-chloroacrylamide product. Therefore, when conducted in batch, a previously optimised 'hot plunge' method is necessary to achieve this, whereby a solution of *α*-thioamide **2** and *N*-chlorosuccinimide (NCS) in toluene is immersed into a preheated oil bath at 90 °C; slower heating was found to noticeably compromise product yield and purity.[3]

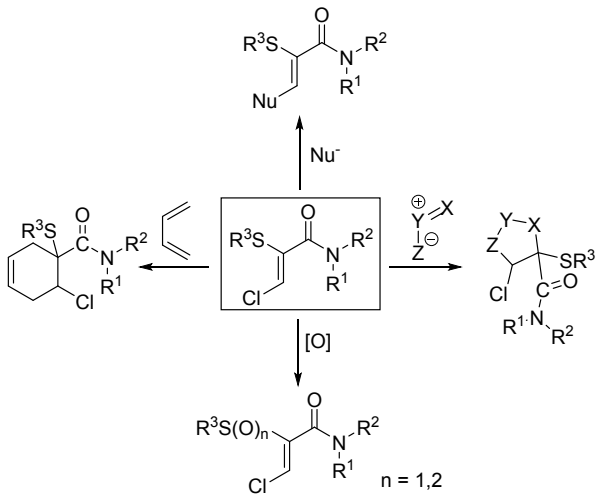
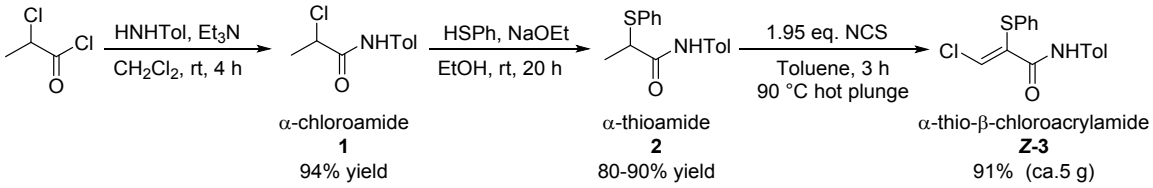


Figure 1. Synthetic transformations of α-thio-β-chloroacrylamides.[1-9]

Scheme 1. Three-step small scale batch preparation of α-thio-β-chloroacrylamides[1]



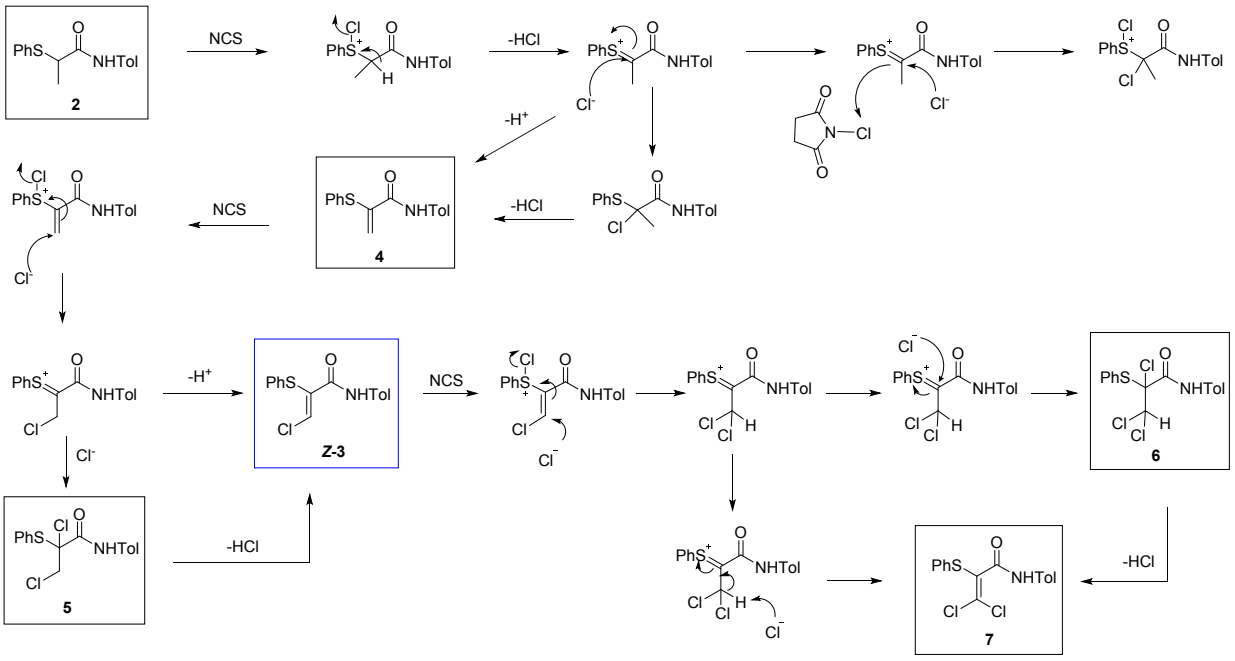
Recent work has assessed the challenges associated with scaling-up this three-step process, successfully enabling samples of up to 25 g of the α-thioamide **2** to be prepared (Scheme 3).[10, 11] However, scale-up of the final cascade step has posed more serious practical considerations with regard to achieving the 'hot-plunge' effect in batch. Heat transfer through larger volumes results in a delay reaching the desired temperature in the bulk of the reaction medium.

Over the past two decades, continuous processing has been employed with increasing frequency within the pharmaceutical and fine chemical industries for synthesis of active pharmaceutical ingredients (APIs) and natural products.[12–14] The process advantages inherent to flow chemistry include improved mass transfer and efficient heat transfer, facilitated by use of high surface-area-

to-volume ratios of tubular reactors, safer access to extreme temperature and pressure conditions, enhanced reproducibility, inline workups and automated operation.[15–20] Use of flow chemistry has been shown to enable additional possibilities for introducing process control via feedback loops, where suitable inline or online spectroscopic analysis allows the product profile of the reactor output to be managed in real-time.[21] Ease of scale-up is a further positive attribute of continuous processing; while traditional scale-up, with its associated challenges, is required for batch processes, additional, alternative, options to achieve increased production are available through flow chemistry, whereby the process can either be run for longer (scale-out) or whereby multi-reactors can be run in parallel (numbering up).[12,22,23]

Continuous flow processing has been successfully applied to this step as a scalable 'hot plunge' equivalent and to overcome these heat transfer issues. This enabled the production of more material than would be possible in batch through scaling-out the process, therefore removing the any potential problems associated with heat and mass transfer in scale-up. Significant difficulties still remained in achieving a complete process operable on the desired scale, including management of the various impurities generated in the cascade process, removal of the poorly soluble succinimide by-product and isolation of batches of solid ***Z*-3** in acceptable yield and purity.[10,11]

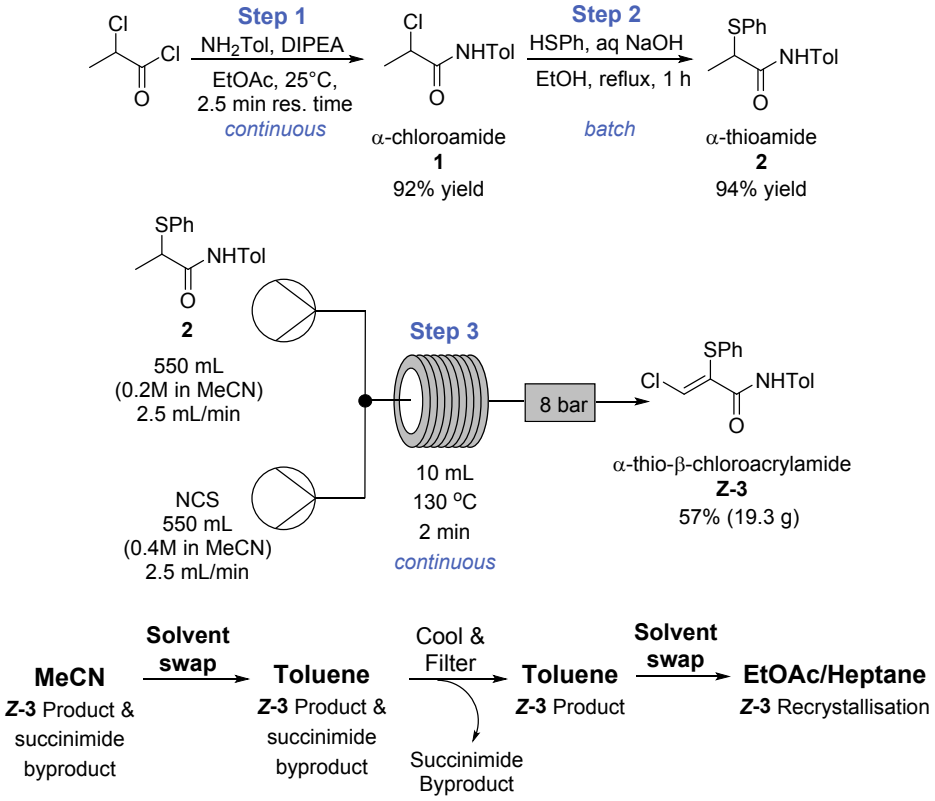
Scheme 2. *α*-Thio-*β*-chloroacrylamide cascade mechanism.[24]



In the batch process, toluene was used as the reaction solvent for the final step (Scheme 1). The succinimide by-product is only soluble in toluene at higher temperatures, allowing it to be effectively removed by precipitation and filtration on cooling the reaction mixture.[3] However, in a continuous flow process precipitation of succinimide causes blockages in the system. This difficulty had been addressed by replacing toluene with acetonitrile as the reaction solvent, as succinimide is highly soluble in acetonitrile, enabling the reaction implementation in a continuous flow process (Scheme 3).[10] Removal of the succinimide by-product subsequently required employment of a static batch-type work-up, in which acetonitrile was evaporated under vacuum, the residue was then dissolved in toluene and cooled on ice, enabling separation of the precipitated succinimide by filtration. Toluene was then removed from the filtrate and the product mixture was purified by recrystallization from an ethyl acetate/heptane mixture (Scheme 3).[10] A fully operational flow process would require that the succinimide by-product removal also be carried out in flow. Herein, we describe the development of a fully operational flow

process for this step, including reaction and inline work-up before product isolation as a batch crystallization process.

Scheme 3. Overview of previously reported modified continuous and batch process approach for the 3 step synthesis and isolation of *Z*-3 (including implentation of the cascade reaction as continuous using acetonitrile as the solvent)[10]



RESULTS AND DISCUSSION

The requirement for multiple solvent swaps for effective implementation of the *α*-thio-*β*-chloroacrylamide cascade step in a continuous system was identified as a key process challenge. Ethyl acetate was proposed as a potentially suitable alternative solvent for the reaction due to its success as a crystallization solvent.[10] Successful implementation and optimization of ethyl acetate as solvent for the process could make an inline aqueous work-up feasible, which is not possible in acetonitrile, due to its miscibility. Ethyl acetate was tested as the reaction solvent on a small scale using the batch 'hot plunge' method, which established that the cascade reaction would proceed successfully in that solvent, and displayed a similar performance to using acetonitrile or toluene in batch. Full consumption of *α*-thioamide **2** was observed, with a crude product consisting of 87.7% for the desired ***Z*-3**, 8.8% of the isomer ***E*-3** and 3.5% of the acrylamide **4** (by ^{1}H NMR analysis). Once the reaction was complete, a water wash was effective at removing the succinimide by-product. In advance of transferring this process to a continuous flow system (Scheme 4), the practical solubility limitation of NCS in ethyl acetate at room temperature was examined and a 0.25M solution established as the maximum working process concentration (a 0.3M solution was found to be saturated at room temperature and contained precipitated material). Our previously reported flow method (using acetonitrile),[10] was initially attempted with 0.1M solution of *α*-thioamide **2** and 0.2M solution of NCS, but using ethyl acetate as an alternative solvent. The parameters chosen for investigation on a 10 mL scale were a 2 min residence time, 2.5 mL/min flow rate at each pump, and reaction temperatures of both 130 °C and 120 °C. Analysis of these experiments indicated that they had not gone to completion, with large quantities of dichloride **5** and acrylamide **4** remaining in the crude reaction mixture. Further conditions were therefore investigated to optimize the reaction in ethyl acetate on a continuous flow platform (Tables 1–4),

with the work-up consisting of taking the reaction solution into an offline separating funnel and washing with water and brine to remove the succinimide by-product. As evident from Table 1, longer residence times were needed to produce ***Z*-3** as the major product compared to the conditions optimized for acetonitrile.

Scheme 4. Proposed continuous synthesis of *Z*-3 in ethyl acetate

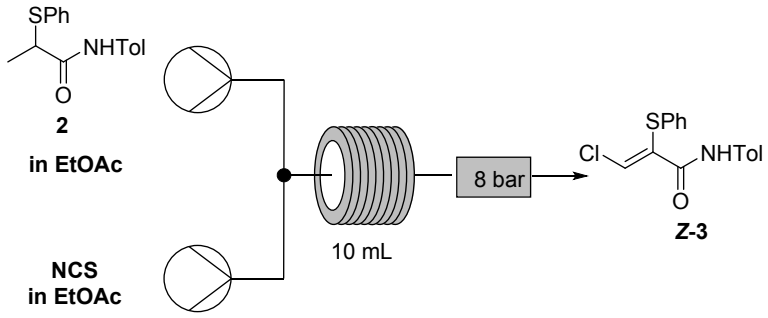
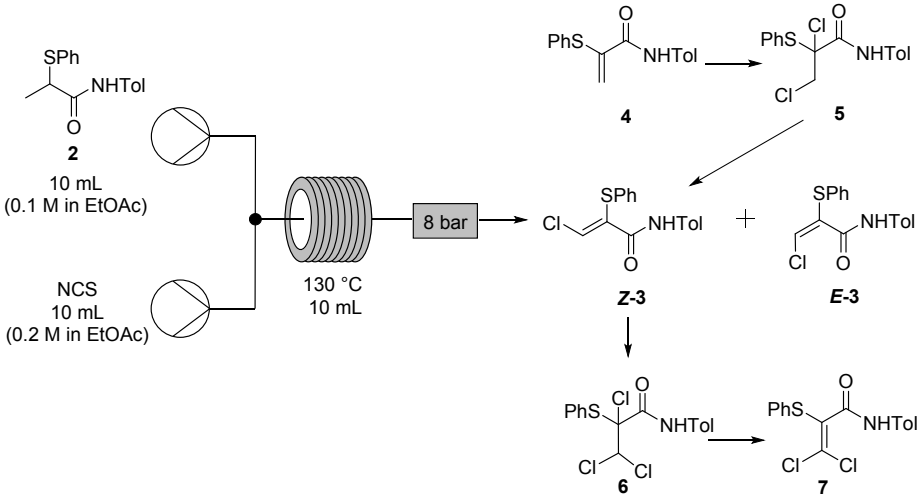


Table 1. Optimization of residence time for synthesis of *α*-thio-*β*-chloroacrylamide *Z*-3 in a continuous process using EtOAc as solvent[a]



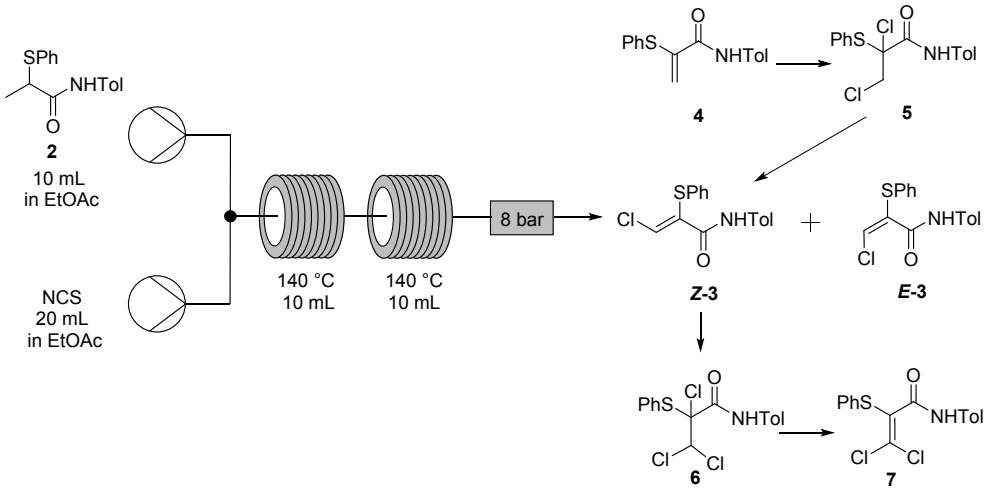
entry	residence time (min)	flow rate (mL/min)	product ratio					
			***Z*-3** (%[b])	***E*-3** (%[b])	**4** (%[b])	**5** (%[b])	**7** (%[b])	**6** (%[b])
1	2	2.5	50.3	11.0	6.0	32.4	0.0	0.3
2	3	1.667	76.3	10.4	4.8	8.0	0.0	0.5
3	4	1.25	77.9	11.4	3.6	3.1	3.2	0.8
4	5	1	83.3	11.5	3.2	0.4	0.5	1.1
5	6	0.833	85.8	10.6	2.0	0.1	0.3	1.2

[a]1 equivalent of **2** (10 mL of 0.1 M solution in EtOAc) was reacted with 2 equivalents of NCS (10 mL of 0.2 M in EtOAc). [b]Molar ratio (%) determined by HPLC analysis using relative response factors to compare the peak area of each component (see Supporting Information); samples were prepared following aqueous work-up and concentration of EtOAc solution, for dissolution in MeCN for HPLC analysis.

To improve the overall process intensity, the system volume was increased by adding another reactor coil (see SI, Table S3); this change resulted in a higher throughput while maintaining the residence time and therefore increased the reaction output per unit of time. The reaction temperature was further increased to 140 °C, with a view to increasing the rate of reaction and to confirm that an 8 bar back-pressure regulator was sufficient to keep ethyl acetate as a liquid.[25] To

enhance the process output further, the flow rates (rather than the solution concentration) were used to control the reaction stoichiometry. This enabled an increased concentration of α-thioamide **2** to be used as a feedstock while working within the solubility limitations of NCS in ethyl acetate. Therefore, a 1:1 ratio of reagent concentration was used, with a 1:2 ratio of flow rates. These concentrations were then increased from 0.1M to 0.15M and then to 0.2M solutions with residence times being optimized once again (Table 2 and SI, Table S4). Excellent conversion to ***Z*-3** was observed at 0.15M concentration using a 7 min residence time (Table 2, entry 2), with this possibly attributable to the increased concentration of HCl in solution. When assessed beside a higher concentration of 0.2M for a 5 min residence time (Table 2, entry 3), there was a slight decrease in the relative quantity of product obtained. However, considering the increase in reaction output per unit of time (due to the higher concentration and shorter residence time), this still represented an improvement in process intensity for scale-up.

Table 2. Optimization of residence times for synthesis of *α*-thio-*β*-chloroacrylamide *Z*-3 in a continuous process using 1:1 reagent concentrations and 1:2 flow rates[a]



entry	conc. (M)	flow rate **2** (mL/min)	flow rate NCS (mL/min)	residence time (min)	product ratio					
					***Z*-3** (%[b])	***E*-3** (%[b])	**4** (%[b])	**5** (%[b])	**7** (%[b])	**6** (%[b])
1	0.15	1.333	2.667	5	85.6	10.7	1.7	0.4	0.4	1.2
2	0.15	0.952	1.905	7	91.8	5.9	1.2	0.0	0.5	0.6
3	0.2	1.333	2.667	5	86.5	9.1	3.2	0.0	0.5	0.7
4	0.2	1.111	2.222	6	87.6	8.1	3.1	0.0	0.5	0.7
5	0.2	0.741	1.48	9	89.9	6.2	3.0	0.0	0.6	0.3

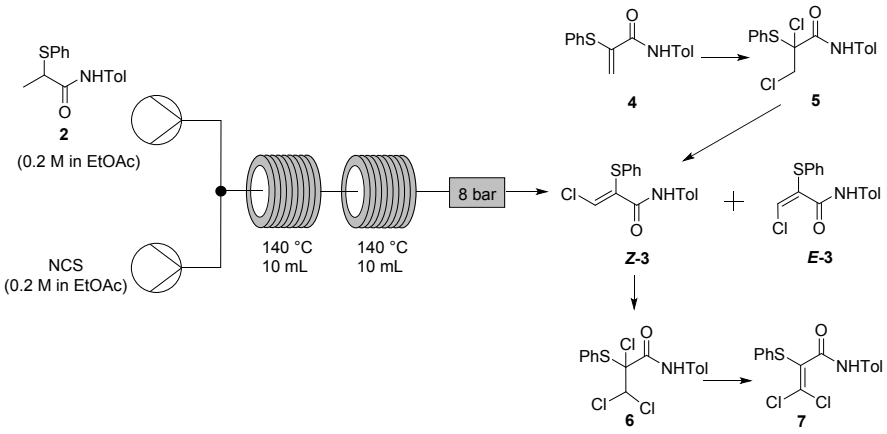
[a]1 equivalent of **2** (in EtOAc) was reacted with 2 equivalents of NCS (in EtOAc) by using a 1:2 ratio of flow rates (rather than solution concentration) at 140 °C. [b]Molar ratio (%) determined by HPLC analysis using relative response factors to compare the peak area of each component (see Supporting Information); samples were prepared following aqueous work-up and concentration of EtOAc solution, for dissolution in MeCN for HPLC analysis. Additional entries to this table are available in Table S4, SI

As success for this transformation is dependent on reaction stoichiometry, data on the impact of adjusting the equivalents of NCS using various flow rates was also gathered. The results obtained (Table 3) were comparable to Table 2, entry 3 at a 5 min residence time and using 0.2 M reagent

solutions. The reaction was run with a 1:2 ratio of *α*-thioamide **2** to NCS and the corresponding reaction mixture contained 87% of the desired *Z*-*α*-thio-*β*-chloroacrylamide ***Z*-3**. 1.95 equivalents of NCS are typically employed in the batch process, this ratio of NCS to starting material being found to optimize the yield of the required product ***Z*-3** *versus* impurities. The experiments in Table 3 highlight the sensitivity of the reaction to stoichiometry as this is a critical parameter of the process. The results obtained demonstrate the enhanced control over the cascade reaction by exploiting a key advantage of a continuous approach in that the flow rate of a reagent stream can be adjusted to predictably alter the product profile.

In this case, by adjusting the flow rate of NCS to a 1:1 ratio of *α*-thioamide **2** to the NCS (Table 3, entry 1), the major product of the reaction was observed to be acrylamide **4,** at approximately 79% of the crude reaction mixture. It was also seen that 2.1 equivalents (Table 3, entry 5) gave the highest percentage of the *Z*-*α*-thio-*β*-chloroacrylamide ***Z*-3**, although there was also an increase seen for the *E*-isomer ***E*-3** and over-chlorination products, which can be more difficult to remove in higher quantities.

Table 3. Optimization of equivalents of NCS for synthesis of *α*-thio-*β*-chloroacrylamide *Z*-3 in a continuous process using 5 min residence time[a]



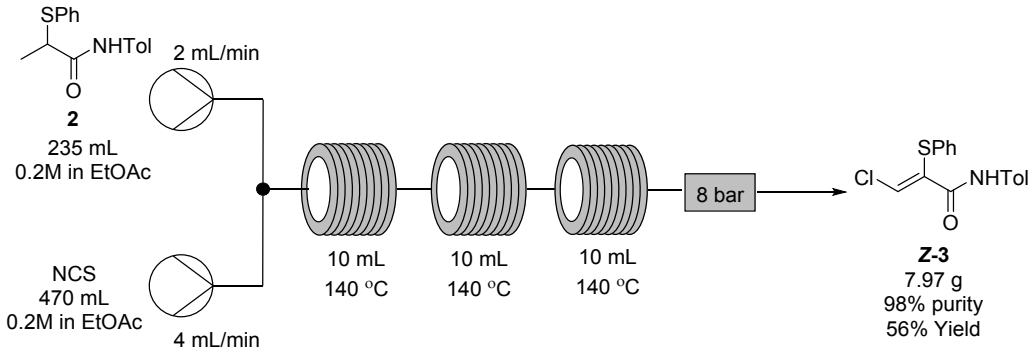
entry	equiv of NCS	flow rate **2** (mL/min)	flow rate NCS (mL/min)	product ratio						
				***Z*-3** (%[b])	***E*-3** (%[b])	**2** (%[b])	**4** (%[b])	**5** (%[b])	**7** (%[b])	**6** (%[b])
1	1	2	2	9.1	1.2	10.7	79.0	0.0	0.0	0.0
2	1.8	1.429	2.571	71.7	8.0	0.0	19.7	0.0	0.1	0.5
3	1.9	1.379	2.621	80.2	8.0	0.1	11.1	0.0	0.2	0.4
4	1.95	1.356	2.644	84.5	7.7	0.0	7.2	0.0	0.2	0.4
5	2.1	1.290	2.710	88.5	8.9	0.0	0.4	0.0	0.7	1.5
6	2.2	1.25	2.75	83.4	7.1	0.0	0.9	0.0	3.2	5.4

[a]1 equivalent of **2** (10 mL of 0.2M solution in EtOAc) was reacted with various equivalents of NCS (0.2M in EtOAc) at 140 °C for a 5 min residence time. [b]Molar ratio % determined by HPLC analysis using relative response factors to compare the peak area of each component (see Supporting Information); samples were prepared following aqueous work-up and concentration of EtOAc solution, for dissolution in MeCN for HPLC analysis.

Measures to reduce the overall reaction times were also examined by expanding the system volume through addition of a third reaction coil. The maximum combined flow rate in the PFA coils when working above 100 °C is 6 mL/min, therefore 5 min was the lowest residence time possible (comparable to Table 2, entry 3). Shorter times were checked using two coils but no improvement in efficiency was evident (Table S5). Following this series of optimization experiments, a trial

scale-up experiment was carried out using approximately 13 g of the α-thioamide **2**, which took ca. 2 h 15 min to complete (Scheme 5). The work-up was completed offline (washing with water, brine and drying over $MgSO_4$). The crude product ratio for this experiment, analysed by HPLC, showed 80% of ***Z*-3** relative to the other reaction impurities. The isolated product required two recrystallizations (ethyl acetate/heptane) to obtain 7.97 g (56% yield) of 98% pure material by HPLC.

Scheme 5. Scaled-up preparation of *Z*-3 at 140 °C, with a residence time of 5 min and using 2.0 equiv NCS



To improve on this result, the reaction temperature was increased to 145 °C while keeping ethyl acetate from vaporizing, allowing a number of different sets of conditions to be run using 3 coil reactors. The optimum conditions were found to be 2.05 equivalents of NCS at 145 °C (Table 4, entry 2) and these conditions were brought forward to optimize an inline work-up.

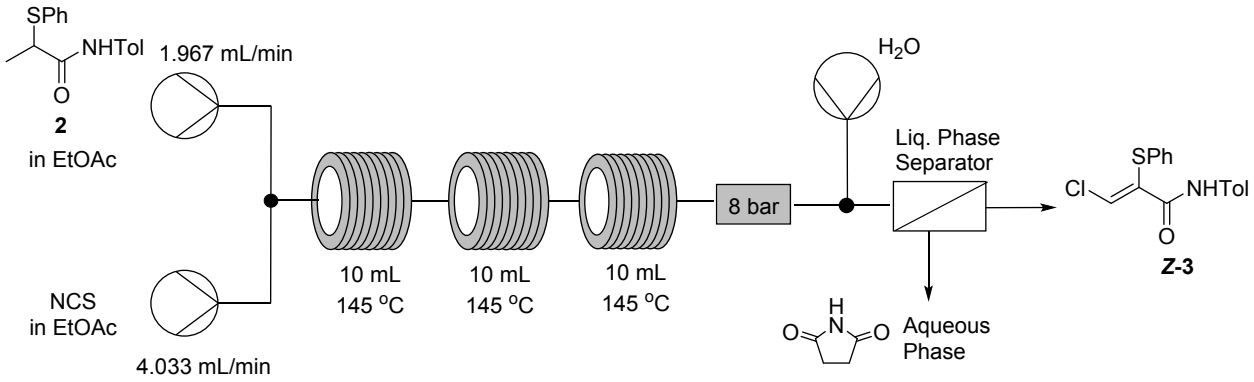
Table 4. Optimization of residence time and stoichiometry at 145 °C for synthesis of *α*-thio-*β*-chloroacrylamide *Z*-3 in a continuous process[a]

entry	residence time (min)	temp (°C)	equiv of NCS	product ratio					
				***Z*-3** (%[b])	***E*-3** (%[b])	**4** (%[b])	**5** (%[b])	**7** (%[b])	**6** (%[b])
1	5	145	2	79.8	8.6	10.8	0.0	0.3	0.5
2	5	145	2.05	82.2	8.2	8.8	0.0	0.3	0.5
3	5.5	145	2	79.0	8.1	12.1	0.0	0.3	0.5
4	5.5	140	2	79.6	8.0	11.7	0.0	0.2	0.5

[a]1 equivalent of **2** (0.2M solution in EtOAc) was reacted with a solution of NCS (0.2M in EtOAc). [b]Molar ratio % determined by HPLC analysis using relative response factors to compare the peak area of each component (see Supporting Information); samples were prepared following aqueous work-up and concentration of EtOAc solution, for dissolution in MeCN for HPLC analysis.

Inline work-up development. After the synthetic parameters for the final step were optimized, the next goal was to develop a product isolation protocol that could be carried out in a continuous manner. This work involved using a membrane separator to remove the succinimide by-product via extraction into an aqueous wash, while keeping the product in an organic phase. Initial development involved pumping water to join the product stream via a T-piece (Scheme 6), as extraction into water had been found to work well for a conventional batch work-up and product isolation.

Scheme 6. Continuous synthesis of *Z*-3 in ethyl acetate with inline separation of succinimide using an aqueous wash



The reaction employs 2.05 equivalents of NCS and, as such, the aim of the work-up would be to entirely remove the succinimide by-product that is generated. In this case, ^{1}H NMR spectroscopic analysis was used to monitor succinimide removal, as its characteristic resonance can be clearly seen as a 4H signal at 2.76 ppm in $CDCl_3$, and could be compared to the β-hydrogen singlet of ***Z*-3** at 8.05 ppm to afford a product ratio. HPLC was not a suitable analytical technique for this work as small quantities of the succinimide were not readily detected by this method. When the aqueous stream was added at a 2 mL/min flow rate (relative to a combined organic stream at 6 mL/min), the ratio of product to succinimide in the crude material recovered was observed to be 1:1.06 (Table 5, entry 1) and when increased to a 5 mL/min stream of water, a product to succinimide ratio of 1:0.63 was determined by ^{1}H NMR integration (Table 4, entry 4). The minor difference in efficiency of removal of succinimide between entries 5 and 6 is not believed to be experimentally significant.

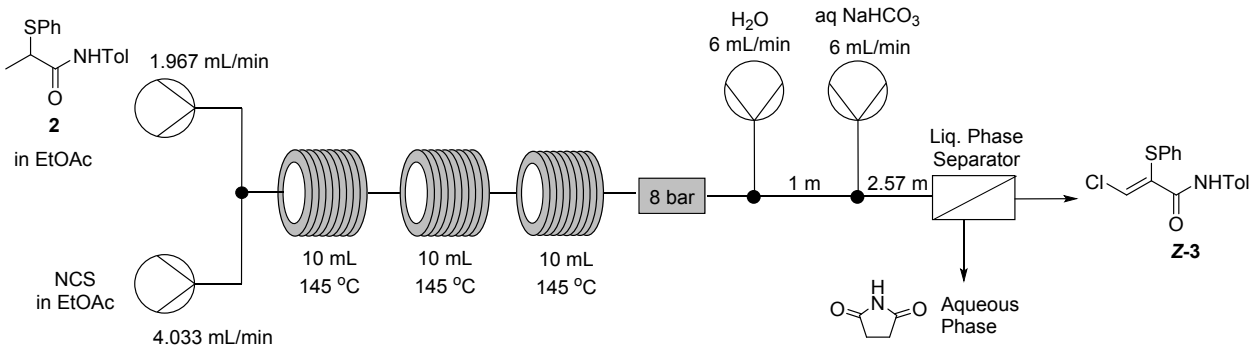
Table 5. Impact of flow rate of water on the level of succinimide by-product present in the crude product mixture from continuous synthesis of Z-3 in ethyl acetate (Scheme 6)[a]

entry	flow rate of H_2O (mL/min)	ratio of ***Z*-3** vs. succinimide[b]
1	2	1 : 1.06
2	3	1 : 0.94
3	4	1 : 0.82
4	5	1: 0.63
5	6	1: 0.75

[a]Combined organic product stream at a flow rate of 6 mL/min, as in Scheme 6, for all entries. [b]Ratio determined by ^{1}H NMR using the 4H succinimide signal at 2.76 ppm, which was compared to the β-hydrogen singlet of ***Z*-3** at 8.05 ppm.

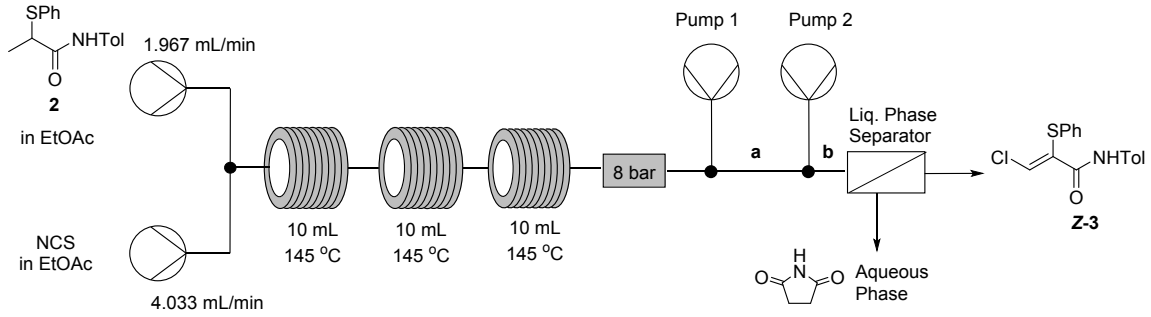
Aqueous saturated sodium bicarbonate solutions were investigated as an alternative to water but very similar results were observed. A second aqueous addition was also examined; this was connected and the tubing used was extended, where various combinations of two water additions, two aqueous saturated sodium bicarbonate additions and a combination of water and aqueous saturated sodium bicarbonate additions were assessed, with improved performance noted when adding water first, followed by $NaHCO_3$ solution. The best result for the process was where combined organic streams at a flow rate of 6 mL/min met successive aqueous streams, both work-up streams, each also at a flow rate of 6 mL/min, which afforded a product to succinimide ratio of 1:0.19, as observed by ^{1}H NMR analysis (Table S6, entry 16 in SI).

Scheme 7. Reaction setup using an aqueous $NaHCO_3$ work-up stream (see, Table S7 entry 16 in SI)



In using a combination of water and sodium bicarbonate mixtures with various lengths of tubing and a chip mixer to maximise contact and mixing between the immiscible phases, it proved difficult to reduce the succinimide level below 1:0.19. Consequently, sodium hydroxide solutions were examined as an alternative to sodium bicarbonate, to investigate if any improved performance could be seen without degrading the product (Table 5). Substantial improvement was observed when 1M NaOH was used, especially when this was employed as the first aqueous addition, followed by water as the second aqueous addition (Table 5, entry 6).

Table 6. Optimization of continuous work-up using aqueous NaOH and water for removal of succinimide by-product[a]

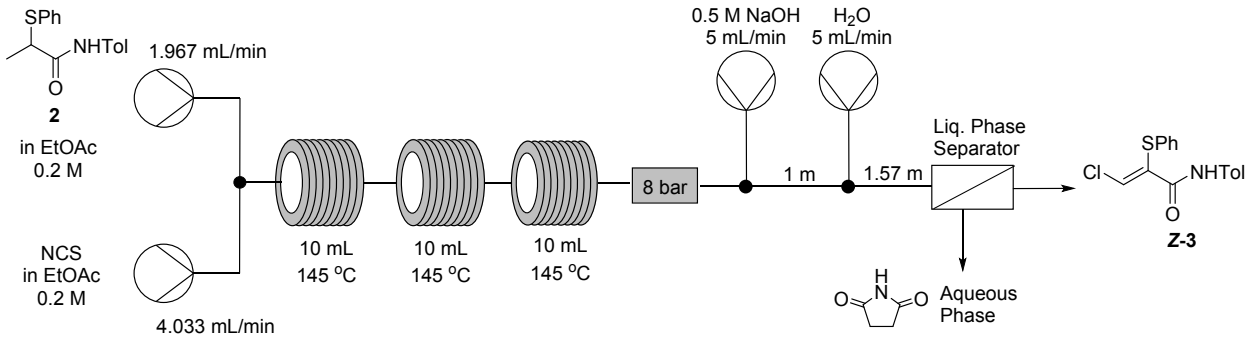


entry	work-up pump 1 reagent [flow rate (mL/min)]	work-up pump 2 reagent [flow rate (mL/min)]	tube length a + b (m)	ratio of ***Z*-3** vs. succimimide[b]
1	H_2O [5]	0.5 M NaOH [3]	1 + 1.57	1 : 0.42
2	H_2O [5]	0.5 M NaOH [5]	1 + 1.57	1 : 0.39
3	H_2O [5]	1 M NaOH [5]	1 + 1.57	1 : 0.03
4	H_2O [6]	1 M NaOH [6]	1 + 1.57	1 : 0.03
5	H_2O [6]	1 M NaOH [6]	1 + 2.57	1 : 0.01
6	1M NaOH [6]	H_2O [6]	1 + 2.57	1 : 0.002
7	0.5M NaOH [5]	H_2O [5]	1 + 1.57	1 : 0.024
8	0.5M NaOH [6]	H_2O [6]	1 + 1.57	1 : 0.017
9	1M NaOH [5]	H_2O [5]	1 + 1.57	1 : 0.011
10	1 M NaOH [4]	H_2O [4]	1 + 1.57	1 : 0.014
11	1 M NaOH [3]	H_2O [3]	1 + 1.57	1 : 0.016
12	1 M NaOH [3]	H_2O [5]	1 + 1.57	1 : 0.017

[a]Combined organic stream at a flow rate of 6 mL/min for all entries. [b]Ratio determined by ^{1}H NMR using the 4H succinimide signal at 2.76 ppm, which was compared to the β-hydrogen singlet of ***Z*-3** at 8.05 ppm.

Following this work-up optimization, where each of these reactions were carried out on an 8 mL scale, a mid-scale trial was performed including an inline work-up (Scheme 8), flowing 118 mL (containing 6.4 g) of *α*-thioamide **2** solution through the system and using a 5 mL/min flow rate of 0.5M aqueous NaOH followed by 5 mL/min of water. This experiment was also carried out to look out for possible degradation of the desired product on contact with aqueous NaOH, potentially with a resulting decrease in yield. The yield obtained after recrystallization from an ethyl acetate, heptane mixture was 70%, producing 5 g of *α*-thio-*β*-chloroacrylamide ***Z*-3**, with a ***Z*-3** to succinimide ratio of 1:0.021.

Scheme 8. Continuous *α*-thio-*β*-chloroacrylamide synthesis performed at a mid-scale including an inline work-up

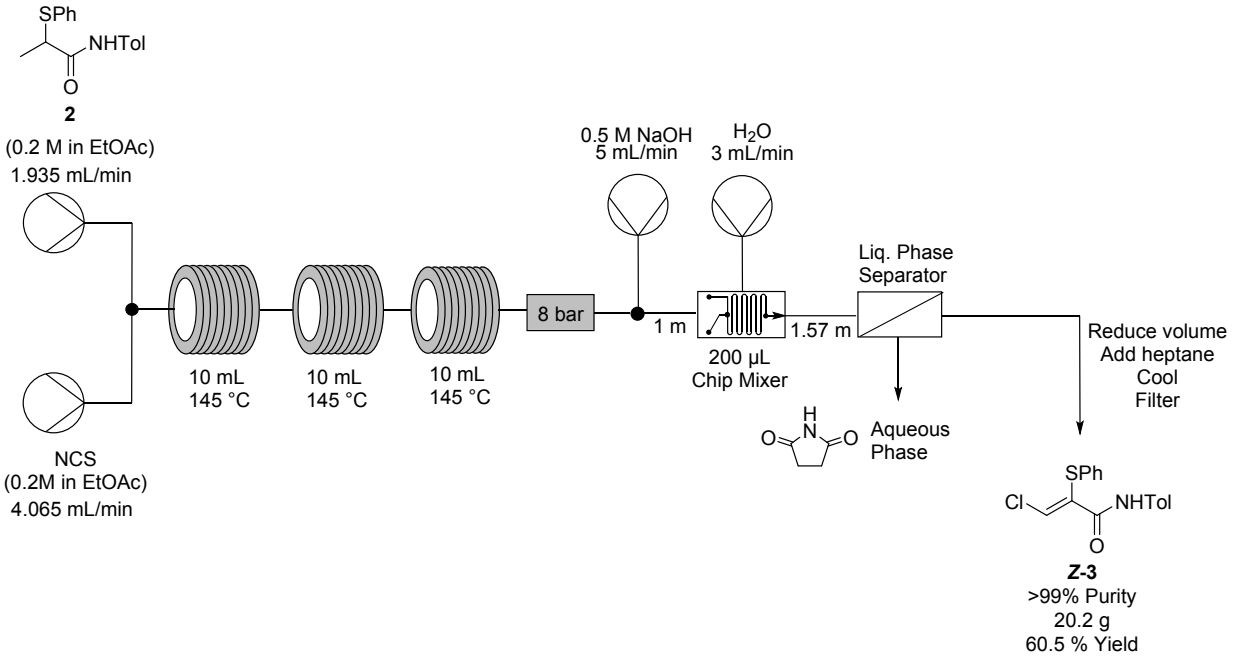


However, when using a NaOH work-up on a larger scale, it was noticed that liquid–liquid membrane separation did not perform as well as at test scale, requiring some manual separation of the organic layer from the aqueous layer. There was further investigation into reducing the volumes of the aqueous additions (Table S7 in SI); however, no improvement in separation was observed. Going forward, a gravity-based continuous separator was used for the final optimized work-up (Table S8 in SI). In the scale-up development, impurities **4** and ***E*-3** remained in the crystallized

***Z*-3** product; to overcome this the number of equivalents of NCS used was increased to 2.1 (Table S8 in SI).

The corresponding experiment was performed with the first aqueous addition of 0.5 M NaOH pumping at 5 mL/min, followed by the second addition of water at 3 mL/min through a 200 μL chip mixer (in place of the T-piece) to improve the mixing at the final aqueous addition (Scheme 9). No succinimide was observed in the ***Z*-3** product by ^{1}H NMR spectroscopy when run at a 5 g scale. These final conditions were subsequently scaled-up (scaled-out) to a process using 30 g of α-thioamide **2** over approximately 5 hours, with the ***Z*-3** product being crystallized from the reaction solution by reducing the volume of ethyl acetate in vacuo and carrying out a solvent/anti-solvent batch crystallization with heptane, and cooling on ice. 20.2 g (60.5 % yield) of the product ***Z*-3** was obtained which was >99 % pure by HPLC analysis and did not contain any evidence for the presence of succinimide by ^{1}H NMR spectroscopic analysis. The recovery of over 60% yield of ***Z*-3** (>3 times the scale possible in batch) in analytically pure form from this streamlined continuous process without chromatography is particularly notable as the composition of the crude reaction mixture prior to the inline washings and crystallization (based on the optimization work) contains a complex mixture including 2.1 equivalents of succinimide, approx. 85-88% of ***Z*-3**, 8-9% of ***E*-3**, with minor amounts of the other by-products **4**, **6** and **7**.

Scheme 9. Optimized scale-up of continuous *α*-thio-*β*-chloroacrylamide synthesis using 2.1 equiv. of NCS and an inline work-up



CONCLUSION

A continuous flow process has been optimized for a cascade chlorination process to include an inline work-up and an end-of-line batch crystallization, and has been successfully scaled-up to processing 30 g in approximately 5 hours. This process optimization achieved the complete removal of 2.1 equivalents of the succinimide by-product, as well as isolation by crystallization to effectively remove all cascade impurities. This strategy demonstrates a broader approach to reaction process optimization, proactively addressing issues commonly posed in industrial process development—including impurity management, heat transfer, inline work-up and removal of stoichiometric by-products—through use of continuous processing technology to facilitate

streamlining of the required unit operations into sequential directly telescoped steps. Scalability issues are overcome by means of 'scale-out', while incorporating a greener approach by using reduced solvent volume and a greener solvent. It demonstrates an improved safety profile by reducing product handling due to end-of-line isolation only. There is an increase in time economy and simplicity by conveniently streamlining the process in continuous flow and removing tedious work-up and purification steps. Effective management of impurity formation is achieved by enhanced control of the reaction, and this could potentially be developed further through the inclusion of inline spectroscopic analysis to provide live feedback of the reaction progress for immediate parameter adjustment. Achieving this level of control in a complex multistep reaction cascade (Scheme 2) which proceeds through a series of intermediates is particularly notable. The continuous flow process enables the chlorination cascade to be undertaken at scale; under batch conditions the scale is limited (typically 1−10 g) by the efficiency of heat transfer in a 'hot plunge'.[3]

EXPERIMENTAL

General Experimental

Solvents were distilled prior to use as follows: ethyl acetate was distilled from potassium carbonate. All commercial reagents were used without further purification unless otherwise stated.

^{1}H (300 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). Low resolution mass spectra (LRMS) were recorded on a Waters

Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were prepared employing acetonitrile as solvent.

HPLC was performed on an Agilent Technologies 1290 Infinity II LC system (Agilent Technologies, Santa Clara, CA, USA) on Agilent Chemstation (Rev. C.01.07 SR2 [255]) software for data acquisition. Chromatography was carried out using an Agilent Eclipse XDB-C18 reverse phase column (150 mm x 4.6 mm, 5 μm) with a flow rate of 0.7 mL/min. Samples were injected (2 μL) by the autosampler and were detected by the Diode Array Detector at 250 nm.

All continuous processes were carried out using a Vapourtec R-series flow reactor. This consists of four piston pumps and has the potential to connect four temperature controlled tubular reactors. Before using the system, the pumps and all reaction tubing, coils and connections are purged with the solvent to be used in the reaction in preparation. The tubular reactor coils contained PFA tubing of 1 mm internal diameter and had an internal volume of 10 mL. The reactor coils used for this work had a temperature range of −70 °C to 150 °C and, when used above 100 °C, the maximum flow rate was 6 mL/min, to accommodate an operating pressure limit of 15 bar for the process. The temperature control was via a contact thermometer, measuring the external temperature of the reactor coil. The gravity liquid–liquid separator involved the aqueous–organic stream flowing into approximately 100 mL of water and the organic layer was continuously removed once it reached in excess of approximately 20 mL.

Optimized Flow Process with Inline Workup

A solution of α-thioamide (30.0 g, 0.11 mol) in EtOAc (553 mL) and a solution of *N*-chlorosuccinimide (31.0 g, 0.23 mol) in EtOAc (1,161 mL) were prepared. The α-thioamide

solution was pumped (1.935 mL/min) into a T-piece where it met the solution of NCS (4.065 mL/min). The combined stream passed through three 10 mL reactor coils at 145 °C (5.0 min residence time). To the reaction stream, 0.5 M aqueous NaOH was pumped (5 mL/min) through 1 m of tubing before water was pumped (3 mL/min) to join the stream in a 200 µL chip mixer and was pumped through 1.57 m of tubing before entering the continuous liquid phase separator. The reactor output was collected and most of the solvent was removed under reduced pressure, with heptane added as an antisolvent to crystallize the product from solution. The desired ***Z*-3** product was isolated as an off-white solid (20.2 g, 60.5 %); δ_H (300 MHz, $CDCl_3$) 2.29 (3H, s, ArC*H*$_3$), 7.09 (2H, d, *J* 8.4, Ar*H*), 7.20-7.31 (7H, m, Ar*H*), 8.04 (1H, s, C*H*Cl), 8.61 (1H, br s, N*H*); MS (ESI+): m/z 304 ($[M+H]^+$).

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, optimization tables for additional work supporting development of the continuous process in ethyl acetate (PDF)

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Notes

The authors declare no competing financial interest.

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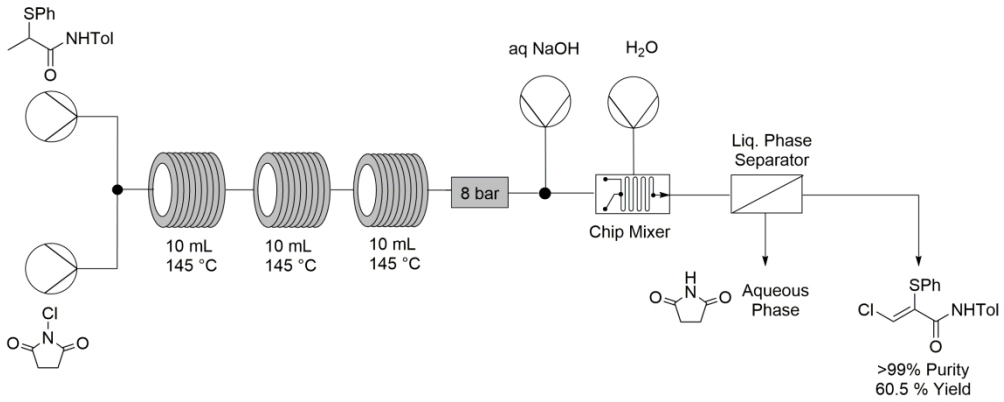
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(25) 8 bar was sufficient back pressure to avoid vaporizing ethyl acetate at 140 °C as no air bubbles were observed – system pressure limitation was 15 bar when using PFA tubing and working at

temperatures above 100 °C, therefore it was not possible to add additional back-pressure and increase the system pressure.



graphical abstract

207x83mm (300 x 300 DPI)