

Full Paper

Continuous preparation and use of dibromoformaldoxime as a reactive intermediate for the synthesis of 3-bromoisoxazolines

Claudio Battilocchio, Francesco Bosica, Sam M. Rowe, Bruna Lacerda Abreu, Edouard Godineau, Matthias Lehmann, and Steven V Ley

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00229 • Publication Date (Web): 03 Aug 2017

Downloaded from <http://pubs.acs.org> on August 3, 2017

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



ACS Publications

Continuous preparation and use of dibromoformaldoxime as a reactive intermediate for the synthesis of 3-bromoisoxazolines

Claudio Battilocchio,^{1} Francesco Bosica,¹ Sam M. Rowe,¹ Bruna L. Abreu,¹ Edouard Godineau,^{2*} Matthias Lehmann,² Steven V. Ley¹*

¹Innovative Technology Centre, Department of Chemistry, University of Cambridge, Lensfield Road, CB2 1EW, UK; ²Syngenta Crop Protection AG, Crop Protection Research, Schaffhauser strasse 101, CH-4332, Switzerland

KEYWORDS. Continuous Processing, Dibromoformaldoxime, Flow Chemistry, Hazardous Chemistry, Isoxazolines, Multistep synthesis.

ABSTRACT. We report the multistep continuous process for the preparation of dibromoformaldoxime (DBFO) as a precursor to generate bromoisoxazolines. We also report process improvements that afford a productivity of over 620 mmol h⁻¹ of DBFO.

Dihaloformaldoximes **1** and **2** are highly versatile and reactive intermediates that can be used to prepare interesting building blocks (Figure 1).¹ Both dichloro (**1**) and dibromoformaldoximes (**2**) are known to afford, respectively, nitrile oxides (**3**) and (**4**) in good yields, *via* HCl and HBr elimination. These reactive nitrile oxide species (**3** and **4**) have been successfully employed in [3+2] cycloadditions, with a variety of olefins, to yield 3-Cl/3-Br substituted isoxazoline building blocks (Figure 1).² Notably, both **1** and **2** have been commonly used for the preparation of microbicides, pesticides or pharmaceutical agents³, as well as bioactive natural products such as Acivicin (**5a**) and its unnatural analogue, bromo-Acivicin (**5b**).⁴

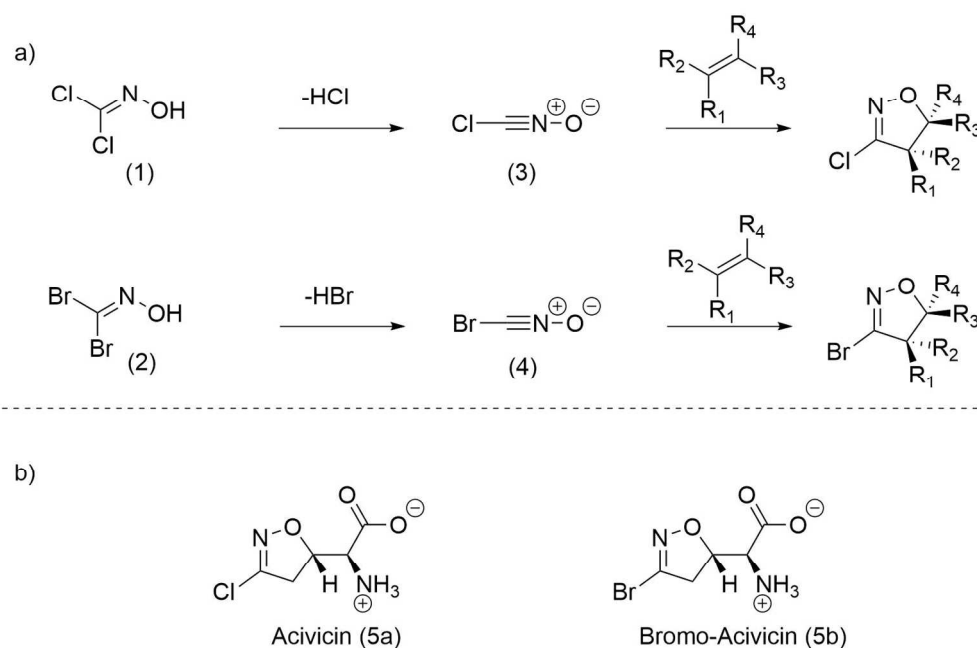


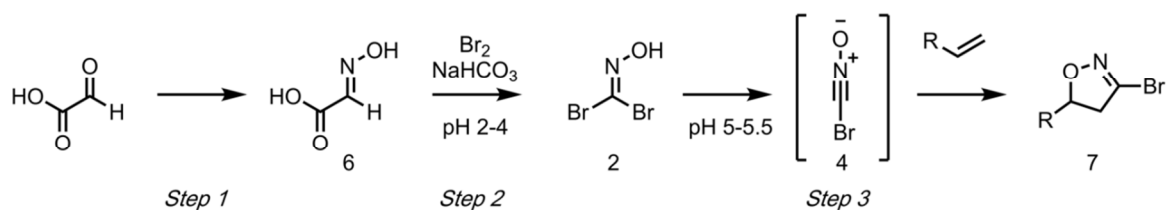
Figure 1. a) Synthesis of ClCNO (**3**) and BrCNO (**4**), and b) structure of Acivicin and Bromo-Acivicin.

Dichloroformaldoxime **1** was originally classified as a warfare agent,⁵ as evidenced by its historical name of phosgene oxime, underlying the toxicity and its self-evident safety issues. Although less information is known regarding DBFO **2**, a similar unfavorable toxicological

1
2
3 profile can be expected. Moreover, DBFO **2** displays safety properties which make its production
4 and use on a large scale quite challenging (*vide infra*).
5
6

7
8 As part of a synthetic exploratory program to obtain these useful building blocks, we became
9 interested in the preparation and use of larger amounts of DBFO **2**. We argued that the
10 preparation of **2** using continuous flow chemistry-based technologies⁶ would mitigate the safety
11 concerns that arise during the handling of this reactive intermediate, especially on scale. A fully
12 integrated multistep generation and use of DBFO **2** was therefore designed, which addresses the
13 challenges associated with molecules of this general type.⁷ Here, we disclose our effort towards
14 the development of a scalable, robust, and controllable generation of **2**. In this work, we
15 demonstrate the clear advantages that accrue from the use of continuous flow chemistry,
16 enabling the use of this hazardous reagent.
17
18
19
20
21
22
23
24
25
26
27
28

29 The synthesis of DBFO **2** is known and is outlined in Scheme 1. Previous work reports the use of
30 glyoxylic acid that is initially condensed with hydroxylamine to afford the intermediate
31 hydroxyimino acetic acid **6**. DBFO **2** is then generated by electrophilic dibromination using
32 NBS⁸ or bromine^{1,4,9} (Scheme 1). Based on handling issues associated with both **6** and **2**, we
33 have selected a continuous flow approach as an attractive alternative to these batch methods.⁶
34 While the literature adequately describes the potential hazards associated with DBFO (**2**, *vide*
35 *supra*), we wished to further use this material as a precursor to 3-bromoisoxazoline building
36 blocks on a larger scale. Our route, therefore, focused firstly on a stepwise approach which could
37 subsequently be developed as an integrated, fully telescoped sequence, to obviate the isolation of
38 highly energetic intermediates **6** and **2** (*vide supra*).
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



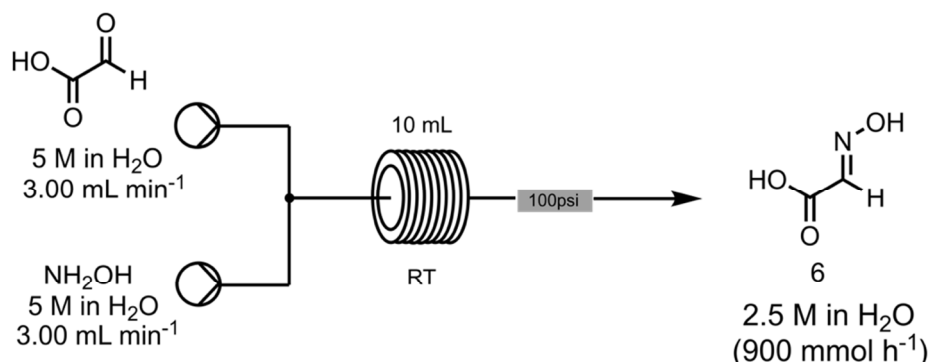
Scheme 1. Synthesis of DBFO and cycloaddition to 3-bromoisoxazolines.

Step 1: Preparation of hydroxyiminoacetic acid **6**

The differential scanning calorimetry (DSC) analysis of hydroxyiminoacetic acid **6** (see ESI) indicates an exothermic event with an onset temperature at *ca.* 124 °C, suggesting that an autocatalytic decomposition pathway might occur. The associated heat flow to this event is *ca.* 2220 J·g⁻¹, which is problematic. From these data, it appears clearly that only a highly rigorous control of the temperature could enable safe handling of **6** in batch mode operations.

Although the preparation of **6** under standard batch mode conditions has been performed previously without incidents, the safety concerns prompted us to explore a continuous process to this intermediate. We designed a simple flow set-up whereby an aqueous stream of glyoxylic acid (5 M in H₂O, 3 mL min⁻¹) was combined through a T-piece with a stream of hydroxylamine aqueous solution (5 M in H₂O, 3 mL min⁻¹). The resulting reaction stream was then directed towards a 10mL PTFE coiled reactor, operating at room temperature to ensure full conversion to hydroxyiminoacetic acid **6**.¹⁰ A rapid temperature rise at the T-piece was immediately observed, confirming the highly exothermic nature of the process. By using an IR thermal-imaging camera,¹¹ we could accurately monitor and interpret these temperature effects.¹² Analysis of the reaction showed a noticeable rise in temperature to 30 °C at the mixing point. This information would suggest a batch process producing **6** on scale would require careful mitigation of this potential hazard by using internal heat exchangers, for example. Under the optimized flow

conditions, we could safely generate intermediate **6** with a productivity approaching 900 mmol h^{-1} ($21.6 \text{ mol day}^{-1}$), equating to 80.1 g h^{-1} (Scheme 2) (see ESI).



Scheme 2. Reaction flow setup to produce glyoxylic acid oxime **6**.

Step 2: synthesis of DBFO **2** from hydroxyiminoacetic acid **6**

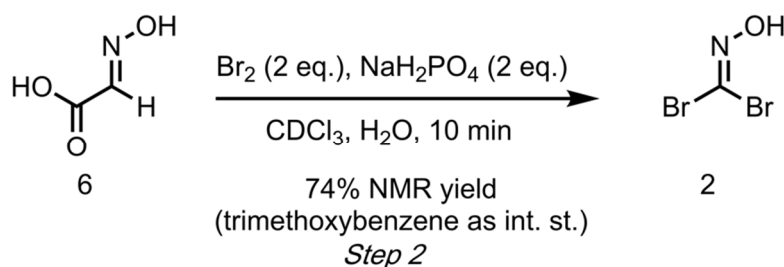
To understand the safety window associated with the generation/handling of DBFO **2**, we commenced a more detailed study of this intermediate. DSC data (see ESI) indicates a relevant exothermic event corresponding to an extremely sharp peak, with an onset temperature of $122 \text{ }^{\circ}\text{C}$ and a maximum peak at $131 \text{ }^{\circ}\text{C}$ (peak height 66.5 mW). The associated heat output (*ca.* $950 \text{ J}\cdot\text{g}^{-1}$) and further exothermic activity observed above $156 \text{ }^{\circ}\text{C}$ are cause for concern. The magnitude of the sharp exotherm is sufficient to result in a temperature rise under low heat loss conditions of more than 550K . Due to the structure of **2**, it is to be expected the decomposition to also be accompanied by the generation of significant quantities of gas. RADEX¹³ studies confirmed this hypothesis, and a pressure rise, attributed to a gas efflux event, was observed from $78 \text{ }^{\circ}\text{C}$ up to *ca.* $123\text{--}131 \text{ }^{\circ}\text{C}$. The two pressure spikes observed were extremely rapid, indicating the decomposition of **2** is very likely to be autocatalytic. The potential volume of gas generated was

1
2
3 estimated to be approximately 57.5 L Kg⁻¹ of **2** (at room temperature). Finally, further thermal
4
5 stability tests have confirmed that **2** can undergo violent exothermic decomposition (see ESI).
6

7
8 Although it could be extrapolated from the data that storage of **2** is safe at -23 °C (at this
9
10 temperature, decomposition time is *ca.* 943h, see ESI), it was decided to dispose of all our stock
11
12 of DBFO **2**, previously purchased from commercial vendors.
13

14
15 The major safety concerns discussed above focused our efforts on the development of a
16
17 continuous protocol to generate DBFO **2**. Prior to this study, the literature suggested the
18
19 conversion of hydroxyiminoacetic acid **6** to **2** was highly pH-dependent¹ and that below pH 1.5,
20
21 the reaction is very slow. In addition to this, at pH values between 2-4, the reaction occurs
22
23 rapidly, and is dose rate controlled; at pH above 5, the DBFO **2** is generated very rapidly,
24
25 however the latter undergoes further HBr elimination to generate nitrile oxide **4**, which, in the
26
27 absence of an alkene partner, leads to by-product formation.
28
29

30
31 The DBFO **2** formation (Step 2) using neat bromine is also described in the literature without the
32
33 need for a base to be present^{1,9d} (76% yield based on Br₂). In this case, since 2 eq. of HBr are
34
35 generated during the conversion of **6** to **2**, the reaction mixture becomes progressively acidic,
36
37 resulting in a decrease of reaction rate. Using a standard batch arrangement, we could identify a
38
39 suitable buffer system to maintain the pH in the target window.¹ Among the many buffer systems
40
41 evaluated, NaH₂PO₄ was optimal (Scheme 3). NaHCO₃ was less effective particularly owing to
42
43 the production of CO₂ gas. Additionally, with the batch process we could not obtain high yields
44
45 of **2** using NaOH as a base.
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



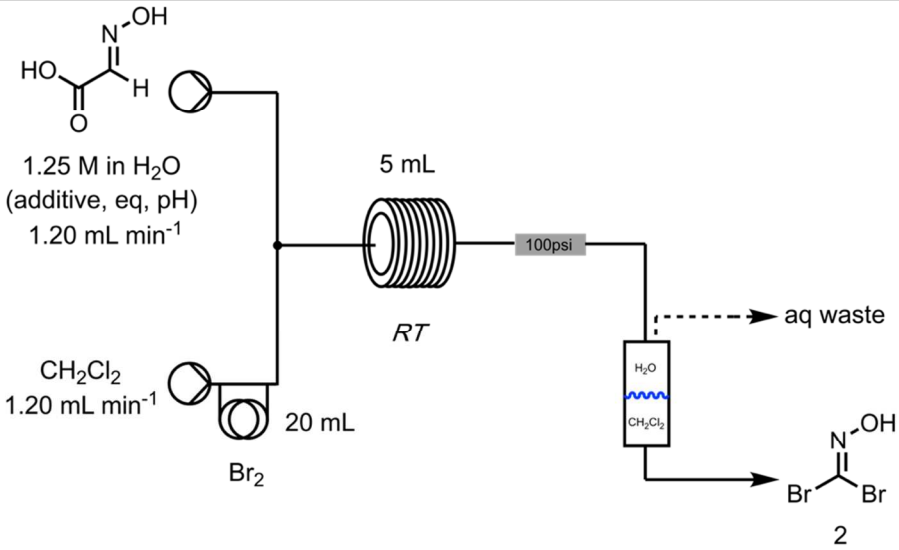
Scheme 3. Controlled conversion of **6** to **2** under buffered conditions.

The conversion of **6** to **2** constitutes a particularly exothermic step. During our safety studies (*vide infra*), we determined that the decomposition of **2** is indeed highly sensitive to temperature (see ESI). In batch mode, yields of dibromofolmadoxime **2** were scale-dependant, and careful dosage of the bromine was required. We had anticipated therefore that a careful control of the temperature would improve the reaction reproducibility. Consequently, the use of continuous flow technology to convert **6** into **2** seemed to be a sensible strategy to achieve accurate control of both pH and temperature, throughout the reaction profile.

The schematic for the flow system is shown in Table 1 and was based on two pumps, a mixing element, a pH meter, and a liquid-liquid separator.

A piston pump was used to deliver the solution of hydroxyiminoacetic acid **6** (1.7 M solution in H₂O), while the solution of Br₂ (2 M in CH₂Cl₂) was introduced via a loaded 50 mL coil (made of perfluoroalkoxy alkane, PFA), to avoid a potential corrosion of the pumping units.

We began the optimization program by evaluating a variety of buffers added to the hydroxyiminoacetic acid **6** flow stream (*i.e.* solutions of **6** at different pH levels). Different additives (bases or buffers) were also investigated. Use of NaOH as a base, gave yields of 45% - 75% (Table 1), which was notably better than the batch process.

Table 1. Optimization of pH values for the preparation of **2**.


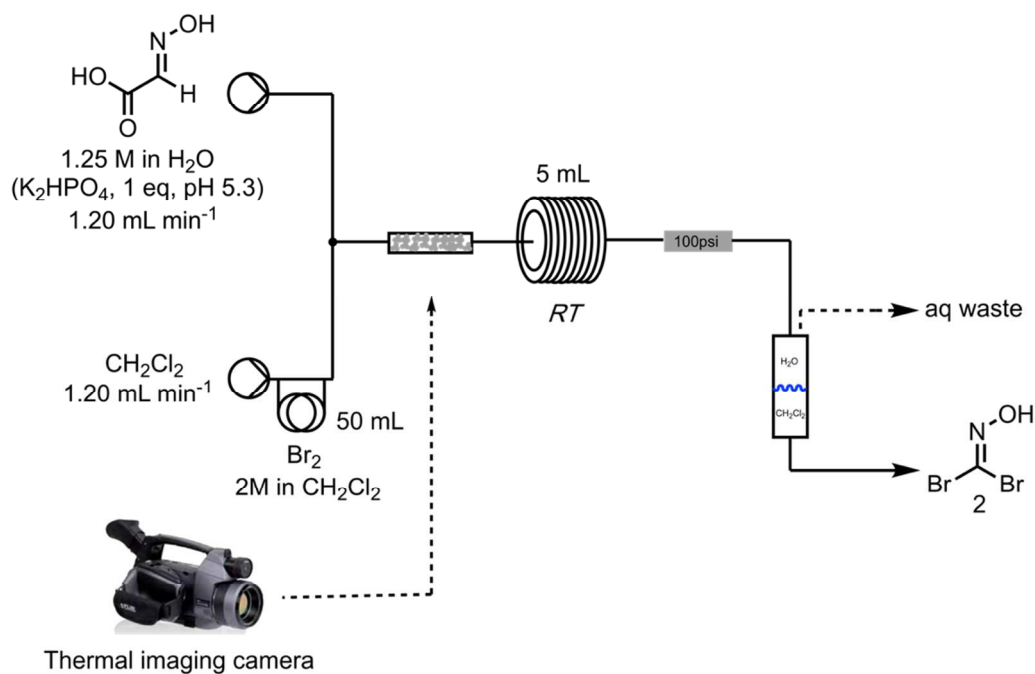
entry	additive	equiv.	pH ^b	yield ^a
1	NaOH	0.6	3.4	50%
2	NaOH	1.0	6.3	75%
3	NaOH	1.2	9.3	69%
4	NaOH	2.0	13	45%
5	NaOAc	1.0	3.7	70%
6	K ₂ HPO ₄	0.5	3.2	72%
7	K ₂ HPO ₄	0.75	4.1	87%
8	K₂HPO₄	1.0	5.3	94%

^a determined by ¹H-NMR of crude solution of **2** using 1,3,5-tribromobenzene as internal standard
^b pH of the aqueous stream feed of **6**, see scheme above

Following screening of different buffers, we found that K_2HPO_4 (1 equiv.) was the optimal candidate (pH 5.3), affording 94% yield of DBFO (**2**), as measured by ^1H -NMR (i.e. 1,3,5-tribromobenzene as internal standard) (entry 8, Table 1). Mixing, mass (as the reaction is biphasic) and heat transfer were key aspects for the initial design of our mesofluidic system.

Mixing. The process involves the mixing of a deep red Br_2 feed in CH_2Cl_2 solution with a colorless aqueous stream of **6** buffered to pH 5.3; simple visual inspection provides qualitative information regarding the reaction progress (see ESI). Progressive discoloration of the organic phase along the transparent PFA tube reactor also serves an efficient qualitative way to estimate conversion of Br_2 . During our early investigations, we noticed that mixing between the two phases was inconsistent over an extended period, leading to small variations in yield of DBFO **2**. This lack of robustness was suboptimal and unsuitable for larger scale applications. We therefore looked at alternative options to upgrade the mixing reproducibility. Our first solution consisted of a glass column (10 mm i.d. x 100 mm length) packed with glass beads (0.2-0.5 mm diameter).^{14,15} Here we observed an improvement in mixing and mass transfer between the two immiscible phases and, using this set-up, it was possible to run a series of reproducible experiments with negligible divergence in yield.

Heat transfer. We again used a thermal-imaging camera to generate information regarding the exothermic behaviour of the reaction (Scheme 4).



26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Scheme 4. Optimized synthesis of **2** with the use of thermal-imaging camera

We observed that the yield of **2** roughly correlated with the temperature measured at the mixing point of the organic feed of Br₂ and aqueous feed of **6**. For instance, when the pH of the aqueous feed of **6** was around 13 (entry 4, Table 1), the camera indicated a rapid rise in temperature at the mixing point to 59.4 °C. Under these conditions, **2** was produced in only 45% yield. The reduced yield clearly confirmed that poor temperature control due to the highly exothermic reaction rapidly led to decomposition of **2**. This trend was indeed confirmed using feeds of **6** set at pH 9.3 and 5.3 (entries 3 and 8, Table 1), where temperatures of 50 °C and 30 °C were detected, and the yields of DBFO **2**, 70 and 94% respectively (Figure 2).

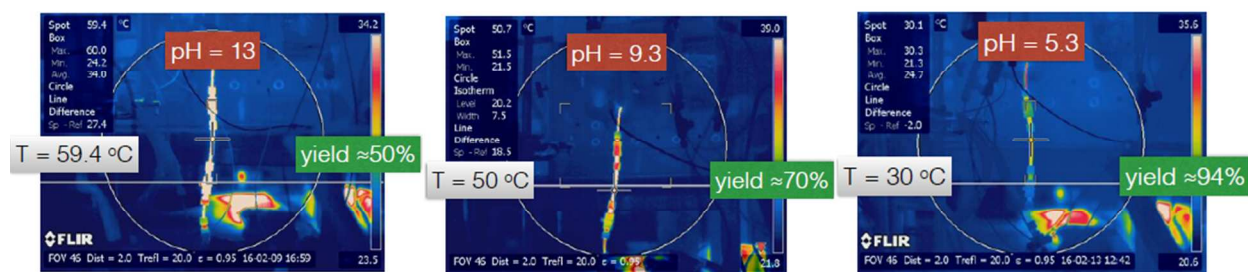


Figure 2. Thermal images of mixing elements using solutions of **6** in H₂O at pH 13 (left), pH 9.3 (middle) and pH 5.3 (right).

This imaging system allowed us to monitor and predict the performance of the reaction based on temperature during each reaction run. To probe the robustness of the continuous generation of DBFO **2** as well as confirming the thermal-imaging camera as a reliable analytical tool, we conducted a 4 hrs continuous production run of **2**. The reactor set-up was fully reproducible over the time-span and further confirmed the usefulness of the camera as a potential PAT device. Finally, although DBFO **2** is known to be soluble in H₂O, we observed negligible losses of DBFO **2** during the extraction process. We attribute this to the low pH value (~ 1.3) of the aqueous stream, and a more favorable partition coefficient for the organic layer.

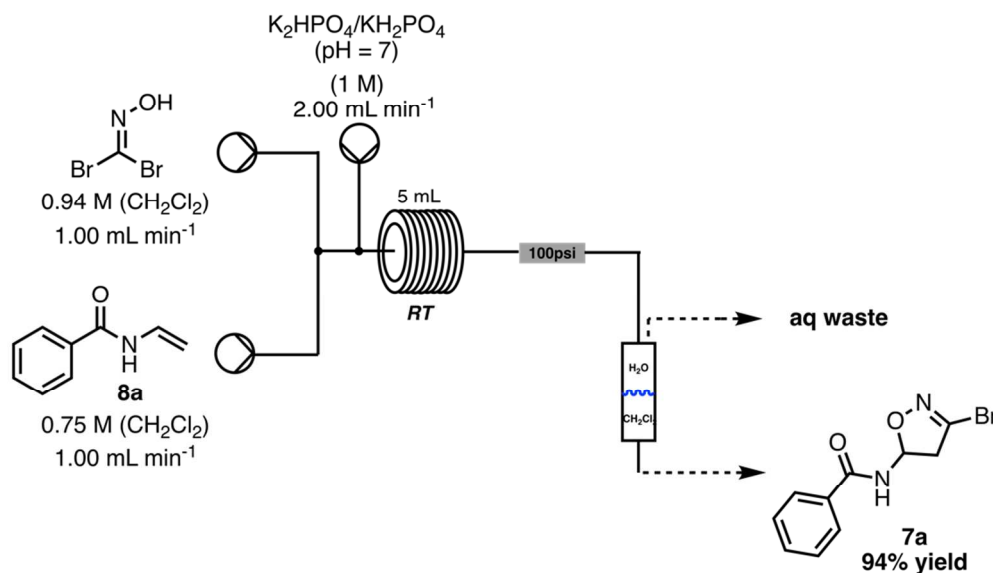
Step 3: [3+2] cycloaddition with N-vinyl benzamide

The typical batch procedure^{1,3,4} for the [3+2] cycloaddition of **4** with an olefin involves its in-situ generation from DBFO **2** using a weak base. Nevertheless, the controlled generation of bromonitrile oxide **4** from **2** can be a challenging process, especially on scale. This observation is corroborated by many procedures which use mixing conditions which are heterogeneous, where for example an insoluble base (i.e. sodium hydrogen carbonate) is stirred with a solution of DBFO **2**.² In addition, studies highlight that the use of organic bases (to adjust the pH values) is detrimental to the reaction, and therefore this tends to limit the screening to inorganic bases only.¹

To study the various parameters affecting the controlled cycloaddition process, a vinyl amide coupling partner (i.e. N-vinyl benzamide, ^{16,17} **8a**) was selected as suitable trap for the nitrile oxide **4**. This system also employed a similar approach to the previous step, where biphasic mixing is a crucial element to the successful outcome of the reaction.

While the use of carbonates, as base, caused issues due to the production of CO₂ gas, it was found that using a phosphate buffer to adjust the pH was an excellent solution. After a thorough screening of pH conditions, we established that the use of a phosphate buffer at pH 7 represented the optimized value for the reaction.

The stream of DBFO **2** from the previous step (0.94 M, analyzed by ¹H-NMR) was mixed with a solution of **8a** (0.75 M in CH₂Cl₂), with each channel flowing at a rate of 1 mL min⁻¹, and then combined with the buffer at a T-piece. The solution was then reacted in a 5mL reactor coil (residence time 75 seconds), after which the two phases separated with the aid of a liquid/liquid separator. These conditions afforded **7a** in 94% yield (Scheme 5).



Scheme 5. Controlled generation of bromo-nitrile oxide and its in-situ trapping with N-vinyl benzamide.

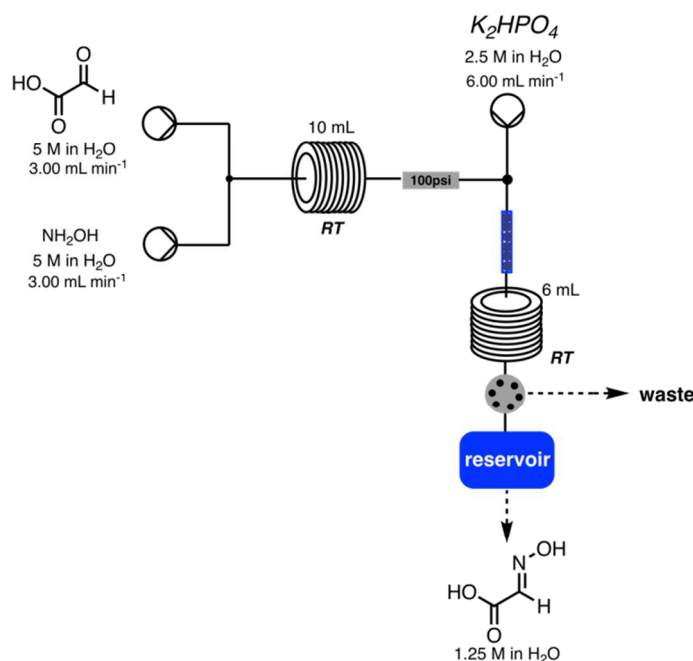
Analogously to the previous step, to ensure mixing between the two phases a glass column (10 mm id x 100 mm length) packed with glass beads (0.2-0.5 mm diameter) was employed as static in-line mixer, which resulted in a consistent mass transfer. The use of the thermal-imaging camera confirmed that at the set pH value no major rise in temperature was observed (26 °C detected at the mixing point).

Telescoped protocol and scale up

With a stepwise route to the final 3-bromoisoxazoline **7a** in hand, we next focused on the practicality of using a fully telescoped continuous process. Indeed, such approach would obviate the isolation and storage of any large amounts of both intermediates **6** and **2**.

An analysis of the essential reaction conditions for each step indicated the need to adjust the parameters between the steps, most notably pH control and overall throughput.

To connect the first two steps, the pH of the solution of oxime **6** had to be set to a pH value of 5.3. To achieve this, a further integrated step was devised where the solution output from step 1 was combined with a stream of K_2HPO_4 (2.5 M solution) at a flow rate of 6.00 mL min^{-1} (Scheme 6). These two solutions were then mixed through a static mixer and directed to a 6 mL coil, to ensure effective mixing, prior to reaching a multiport valve. After reaching steady-state, the solution was directed towards a reservoir for collection. This yielded a solution of oxime **6** at pH 5.3.



Scheme 6. Modification of step 1, pH adjustment for suitable interface with step 2.

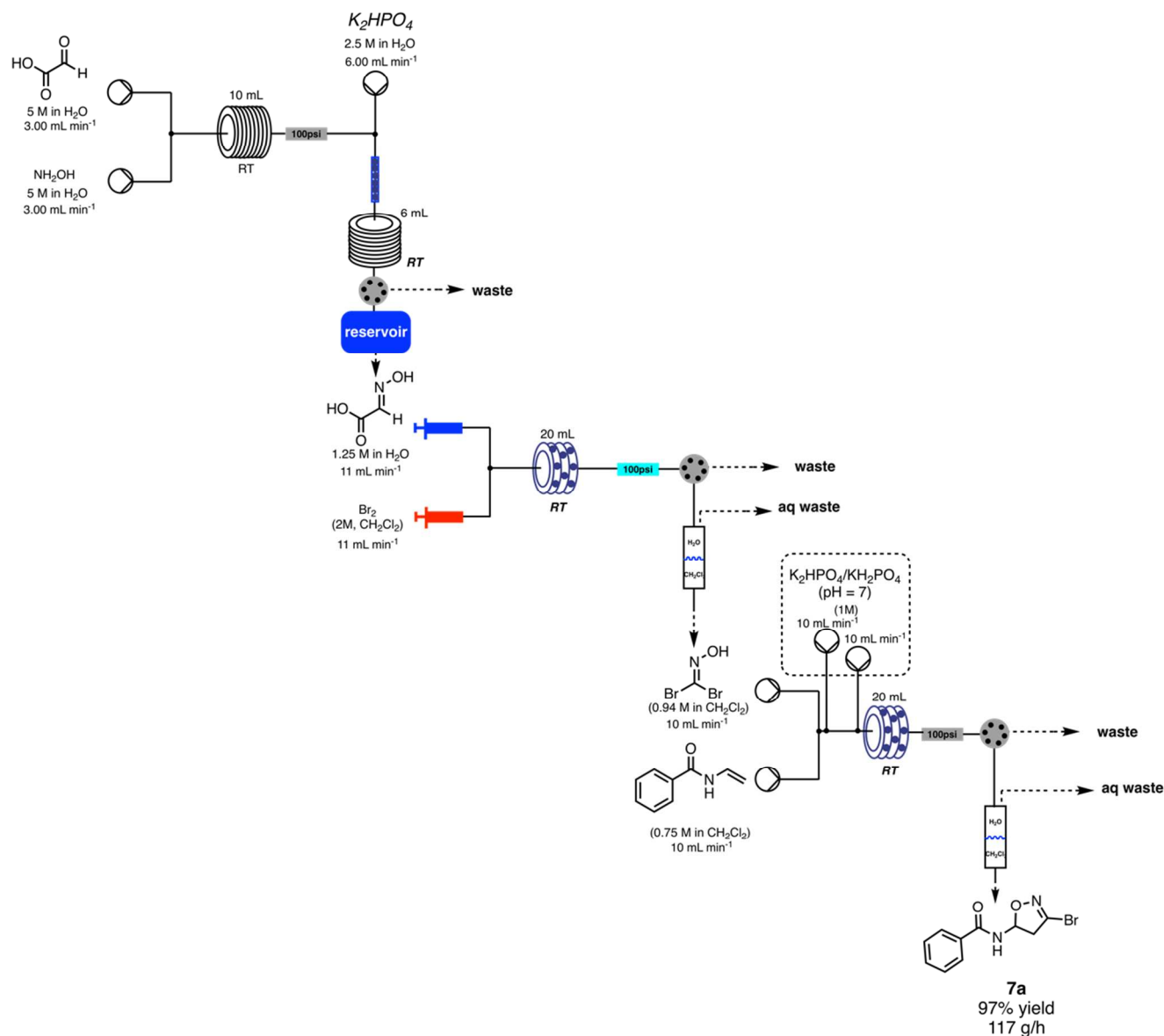
Moreover, as the throughput of material from step 1 was greater than that one for step 2, further reaction improvements were necessary.

Given that mass transfer between two immiscible solvents is a crucial parameter,^{6g} it was envisaged that the use of a new “static-mixer coil”¹⁸ would achieve improved and consistent mixing at high flow rates, hence ensuring a good level of scalability for the synthesis of **2**. The goal was achieved by using a coil pre-packed with helical static mixers (20 mL, see ESI).

This arrangement afforded extremely efficient mixing throughout the reactor coil. Using this device, it was possible to drive the system to achieve a combined flow rate of 22 mL min⁻¹. Both yield and exothermic behaviour were characterized, with consistent outcomes comparable to the small-scale procedure. Under the new conditions, a productivity of 10.34 mmol min⁻¹ of dibromofolmaldoxime **2** (equating to 620.4 mmol h⁻¹) was achieved.¹⁹

To streamline the sequence, we adopted the use of a gravity-based liquid/liquid separator (equipped with a small turbulence settler)²⁰ which allowed the solution of **2** to be stored temporarily before directing it towards the following stage of the synthesis (see ESI).

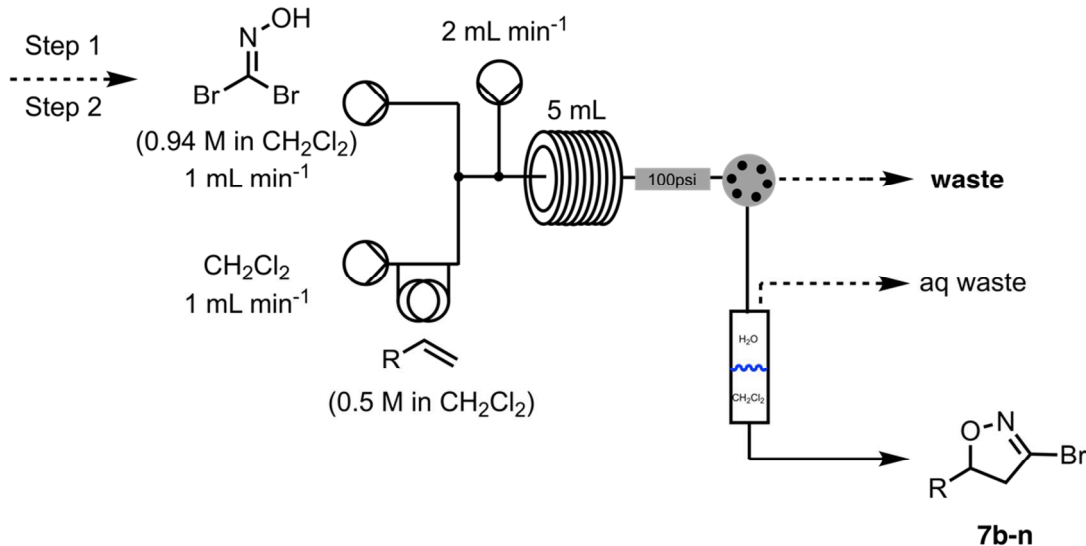
Similarly, we could easily modify step 3 to accommodate a much larger throughput. Both the dibromofolmaldoxime **2** solution and the vinyl amide partner **8a** were pumped at a flow rate of 10 mL min⁻¹ and then reacted with a solution of phosphate buffer (rate of 20 mL min⁻¹) again through the static mixer coil, with an overall flow rate of 40 mL min⁻¹ and a residence time of around 30 s (which represents an improvement compared to the smaller scale reaction). Under these fully telescoped and optimized conditions, the full system could operate for 2h producing **7a** with an output of 117 g h⁻¹ (2.8 kg day⁻¹), without issues (Scheme 7).



Scheme 7. Telescoped system for the synthesis of **7a**.

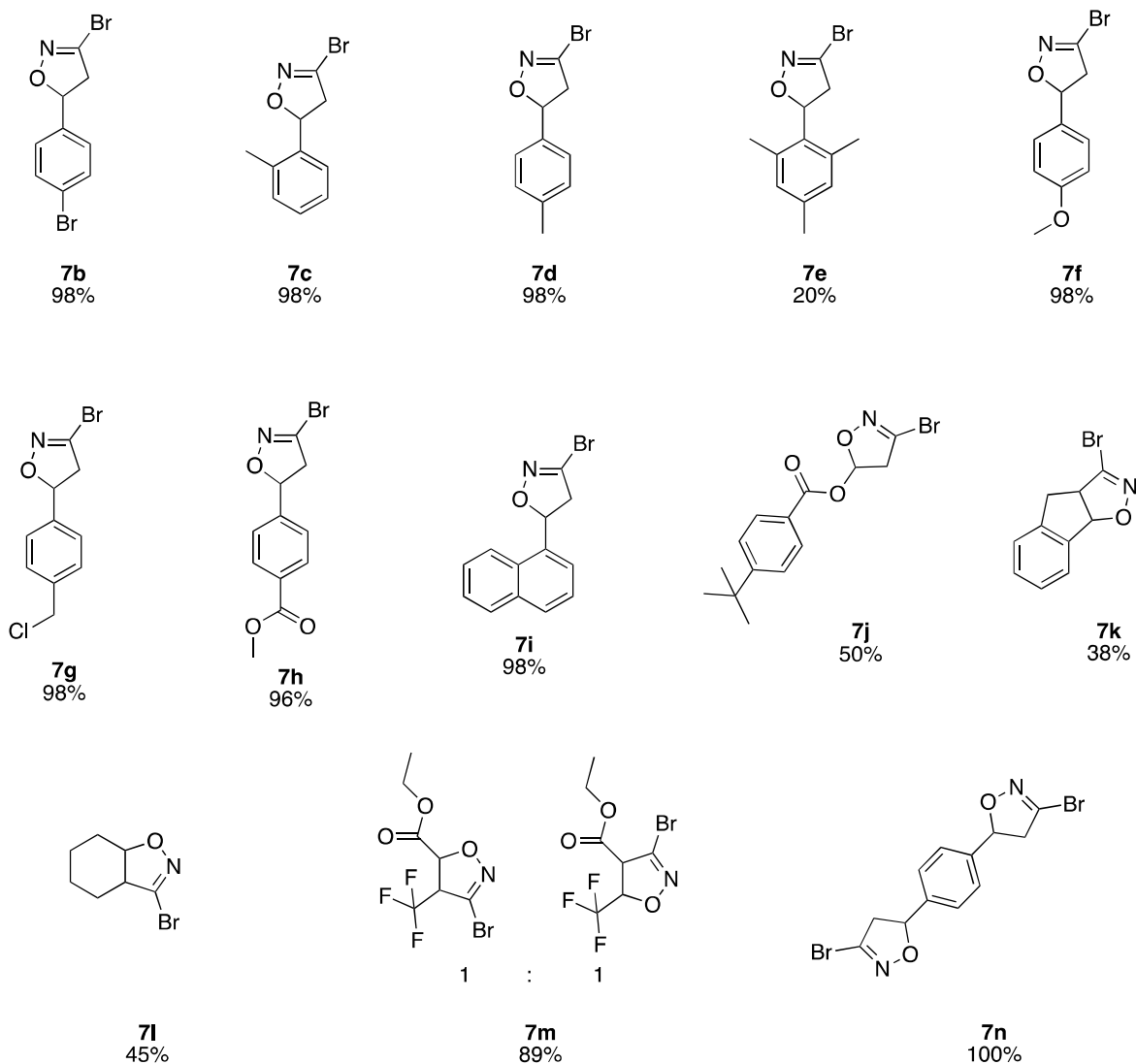
Library of 3-bromoisoxazolines

With this fully telescoped and high throughput method in place, the sequence could be applied to the preparation of a small library of 3-bromo-isoxazolines. We found that the use of a slightly larger excess of **2** was needed for most of the styrene derivatives. In these cases, the system was adjusted to deliver a 0.5 M solution of the styrene coupling partner (Scheme 8).



Scheme 8. Preparation of a library of 3-bromoisoxazolines **7b-n**.

The alkene coupling material (0.5 M in CH₂Cl₂) was loaded onto a loop (5 mL) and combined with the DBFO **2** feed (0.94 M in CH₂Cl₂) generated continuously by the telescoped steps 1 and 2. Both electron-rich and electron-poor styrenes performed well and afforded good to excellent yields of products (*e.g.* **7f** and **7h**). Aliphatic alkenes also delivered the expected 3-bromoisoxazoline cycloadducts (*i.e.* **7l**), albeit in moderate yield. Ethyl 4,4,4-trifluoro-2-butenate reacted with in-situ generated nitrile oxide **4** to provide 1:1 mixture of regioisomers (**7m**), in good yield. Finally, another particularly interesting example resulted from the use 1,4-divinyl benzene which gave bis-cycloadduct **7n** in quantitative yield.

Table 2. Library of 3-bromoisoxazolines synthesized using the telescoped protocol.

Conclusions

We have designed and developed a continuous multistep process for the synthesis of DBFO **2** and its continuous use in [3+2] cycloaddition reactions. Dihaloformaldoximes are well-known

intermediates, however their synthetic access on scale in batch has proven to be challenging due to technical and safety issues. We have therefore assembled a fully integrated continuous process, generating DBFO **2** “on demand”. We believe this process offers several advantages such as: i) use of bench-stable starting material feeds; ii) generation and direct use of highly energetic intermediates (*i.e.* hydroxyiminoacetic acid **6** and DBFO **2**); iii) improved process robustness and reliability over the batch mode, on large scale (*ca.* 100-500g); iv) high productivity, using a small footprint system, equating to kg amounts of 3-bromo-isoxazoline products per day. In addition, the scope of the newly formulated process could be expanded to rapidly prepare a library of 3-bromoisoxazolines intermediates (**7b-o**).

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge: Compounds characterization data (PDF) and reaction setup (PDF); additional data is available from the University of Cambridge Data Repository website: <https://doi.org/10.17863/CAM.12125>.

AUTHOR INFORMATION

Corresponding Author

Dr Claudio Battilocchio, email: cb700@cam.ac.uk

Dr. Edouard Godineau, email: edouard.godineau@syngenta.com

ACKNOWLEDGMENTS

We would like to thank Syngenta Crop Protection AG (CB) and the EPSRC (SVL, grant # EP/K009494/1, EP/M004120/1 and EP/K039520/1) for financial support. We thank Ian Priestley and Markus Luginbuehl for the safety discussions on the intermediates mentioned herein. We thank Myriem El Qacemi and Tomas Smejkal for their fruitful discussions and their support. We thank Prashantha Kamath for the synthesis of N-vinylbenzamide. We would also like to thank Duncan Guthrie (Vapourtec Ltd) for his support.

REFERENCES

¹ Berrier, J.V.; Umarvadia, A.S. EP0979814

² a) Pasinszki, T.; Westwood, N.P.C. *J. Chem. Soc., Faraday Trans.*, **1997**, 93, 43-51; b) I. De Paolini, *Gazz. Chim. Ital.*, **1930**, 60, 700; c) L. Birkenbach and K. Sennewald, *Liebigs Ann. Chem.*, **1931**, 489, 7; d) L. Birkenbach and K. Sennewald, *Chem. Ber.*, **1932**, 65, 546; e) G. Endres, *Chem. Ber.*, 1932, 65, 65

³ a) Frederich, J.H.; Matsui, J.K.; Chang, R.O.; Harran, P.G. *Tetrahedron Letters*, **2013**, 54, 2645–2647; b) Coutouli-Argyropoulou, E.; Kyritsis, C.; Ruszkowski, M. *ARKIVOC* **2009**, 181-192; c) Pinto, A.; Conti, P.; Tamborini, L.; De Micheli, C. *Tetrahedron: Asymmetry*, **2009**, 20, 508–511; d) Hsu, A. Ch. T. (Rohm and Haas Co.) *Eur. Pat. Appl.*, **1987**, EP 232,012; e) Munro, D.; Patel, B. (Shell Int. Res. Maatschappij B. V.) *Eur. Pat. Appl.*, **1993**, EP 555,931; f) Mizukai, M.; Tsukaguchi, N.; Yoneda, T.; Kondo, Y.; Oota, H.; Kato, S.; Tanaka, J. (Sankyo Co.) *Jpn. Kokai Tokkyo Koho*, **1993**, JP 05,105,672 [93,105,672]; g) Hagedorn III, A. A.; Miller, B. J.; Nagy, J. O. *Tetrahedron Lett.*, **1988**, 21, 229; h) Wade, P. A.; Pillay, M. K.; Singh, S. M. *Tetrahedron Lett.*, **1982**, 23, 4563; h) De Amici, M.; De Micheli, C.; Misani, V. *Tetrahedron*, **1990**, 46, 1975; i) Diana, G.D.; Cutcliffe, D.; Volkots, D.L.; Mallamo, J.P.; Bailey, T.R.; Vescio, N.; Oglesby, R.C.; Nitz, T.J.; Wetzell, J.; Giranda, V.; Pevear, D.C.; Dutko, F.J. *J. Med. Chem.*, **1993**, 36, 3240.

⁴ Vyas, D.M.; Chiang, Y.; Doyle, T.W. *Tetrahedron Letters*, **1984**, 25, 487-490.

⁵ Sartori, M. The war gases, chemistry and analysis, London: J. & A. Churchill, Ltd., **1939**.

⁶ For selected review regarding flow chemistry technologies, see: a) Movsisyan, M.; Delbeke, E.I.P.; Berton, J.K.E.T.; Battilocchio, C.; Ley, S.V.; Stevens, C.V. *Chem. Soc. Rev.*, **2016**, 45, 4892-4928; b) Baumann, M.; Baxendale, I.R.; *Beilstein J. Org. Chem.* **2015**, 11, 1194-1219; c) Ley, S.V.; Fitzpatrick, D.E.; Myers, R.M.; Battilocchio, C.; Ingham, R.J. *Angew. Chem. Int. Ed.* **2015**, 54, 10122-10136; d) Brzozowski, M.; O'Brien, M.; Ley, S.V.; Polyzos, A. *Acc. Chem. Res.*, **2015**, 349-362; e) Hessel, V.; Kralisch, D.; Kockmann, N.; Noël T.; Wang, Q. *ChemSusChem* **2013**, 6, 746-789; f) Pastre, J.C.; Browne, D.L.; Ley, S.V. *Chem. Soc. Rev.* **2013**, 42, 8801-8869; g) Webb, D.; Jamison, T.F. *Chem. Sci.* **2010**, 1, 675-680; h) Hartman, R.L.; McMullen J.P.; Jensen, K.F. *Angew. Chem. Int. Ed.* **2011**, 50, 7502-7519

⁷ For selected examples from our groups, see: a) Battilocchio, C.; Iannucci, G.; Wang, S.; Godineau, E.; Kolleth, A.; De Mesmaeker, A.; Ley, S.V. *React. Chem. Eng.*, **2017**, 2, 295-298; b) Battilocchio, C.; Feist, F.; Hafner, A.; Simon, M.; Tran, D.N.; Allwood, D.M.; Blakemore, D.C.; Ley, S.V. *Nature Chem.*, **2016**, 8, 360-367; c) Lau, S.-H.; Galván, A.; Merchant, R.R.; Battilocchio, C.; Souto, J.A.; Berry, M.B.; Ley, S.V. *Org. Lett.* **2015**, 17, 3218-3221; d) Battilocchio, C.; Deadman, B.J.; Baxendale, I.R.; Kitching, M.O.; Ley, S.V. *Chem. Eur. J.* **2013**, 19, 7917-7930; e) Battilocchio, C.; Baxendale, I.R.; Biava, M.; Kitching, M.O.; Ley, S.V. *Org. Process Res. Dev.* **2012**, 16, 798-810; f) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, 2, 1250-1257; g) Polyzos, A.; O'Brien, M.; Petersen, T.P.; Baxendale, I.R.; Ley, S.V. *Angew. Chem. Int. Ed.*, **2011**, 1190-1193; h) O'Brien, M.; Baxendale, I.R.; Ley, S.V. *Org. Lett.* **2010**, 1596-1598;

⁸ a) Halling, K.; Thomsen, I.; Torsell, K. B. G. *Liebigs Annalen der Chemie* **1989**, 1989, 985-990 ; b) Han, Y.; Yang, S.-M.; Wang, X.-Y.; Li, F.-N. *Archives of Pharmacal Research* **2014**, 37, 440-451

⁹ a) Soleimani, E.; Yazdani, H.; Saei P. *Tet. Lett.* **2015**, 56, 1635-1637; b) Rohloff, J. C.; Robinson III, J.; Gardner J. O. *Tet. Lett.* **1992**, 33, 3113-3116; d) Orth, R.; Bottcher, T.; Sieber, S. A. *Chem. Comm.* **2010**, 46, 8475-8477; e) M. Savion, M. G. Memeo, B. Bovio, G. Grazioso, L. Legnani, P. Quadrelli, *Tetrahedron* **2012**, 68, 1845-1852

¹⁰ a) Schwolow, S.; Hollmann, J.; Schenkel, B.; Röder, T. *Org. Proc. Res. & Dev.* **2012**, *16*, 1513-1522; b) Reckamp, J. M.; Bindels, A.; Duffield, S.; Liu, Y. C.; Bradford, E.; Ricci, E.; Susanne, F.; Rutter, A. *Org. Proc. Res. & Dev.* **2017**, ASAP.

¹¹ Please visit the FLIR website: <http://www.flir.com.hk/cs/display/?id=41965>

¹² Ley, S.V.; Ingham, R.J.; O'Brien, M.; Browne, D.L. *Beilstein J. Org. Chem.* **2013**, *9*, 1051-1072

¹³ RADEX is commercialized by SYSTAG and is a versatile tool which can be operated in several modes such as dynamic, isoperibolic and adiabatic. It is used as a dynamic screening tool, providing data on heat- and pressure-generating events. For more information, please visit: <https://www.systag.ch/applications/thermal-analysis.html>

¹⁴ a) Naber, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9469-9474; b) Bogdan, A.; McQuade, D. T. *Beilstein J. Org. Chem.* **2009**, *5*, No. 17.

¹⁵ Similar set up using Rashig rings as static mixers: Kilcher, E.; Freymond, S.; Vanoli, E.; Marti, R.; Schmidt, G.; Abele, S. *Org. Proc. Res. & Dev.* **2016**, *20*, 432-439

¹⁶ N-vinylbenzamide **8a** was prepared according to: Tu, S.; Zhang, C. *Org. Process Res. Dev.* **2015**, *19*, 2045-2049; see also: O'Sullivan, A. C.; El Qacemi, M.; Cassayre, J. Y.; Pitterna, T.; Stoller, A. **2017**, WO2017050921; Cassayre, J. Y., Stoller, A.; Pitterna, T.; El Qacemi, M. **2017**, WO2017050922

¹⁷ Cycloaddition of dibromoformaldoxime **2** with N-vinylbenzamide **8a** is described in: Joest, C.; Nitsche, C.; Scholz, T.; Roux, L.; Klein, C. D. *J. Med. Chem.* **2014**, *57*, 7590-7599.

¹⁸ Please visit the Vapourtec website: <https://www.vapourtec.com/products/flow-reactors/large-diameter-tubular-reactor-for-rapid-mixing-features>

¹⁹ Please visit the HiTec Zang website: <http://www.hitec-zang.de/en/laboratory-devices/syringe-doser.html>

¹⁹ Please visit the HiTec Zang website: <http://www.hitec-zang.de/en/laboratory-devices/syringe-doser.html>

²⁰ Recent examples of liquid/liquid separations under continuous flow: a) O'Brien, M.; Koos, P.; Browne, D.L.; Ley, S.V. *Org. Biomol. Chem.* **2012**, 7031-7036; b) Hu, D.X.; O'Brien, M.; Ley, S.V. *Org. Lett.* **2012**, 4246-4249; c) O'Brien, M.; Konings, L.; Martin, M.; Heap, J. *Tetrahedron. Lett.* **2017**, *58*, 2409-2413.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



