
Peer reviewed version

Link to published version (if available):
10.1021/acs.oprd.1c00187

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via American Chemical Society at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00187. Please refer to any applicable terms of use of the publisher.

**University of Bristol - Explore Bristol Research**

**General rights**

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

Luke D. Elliott,* Kevin I. Booker-Milburn,* Alastair J. J. Lennox*

School of Chemistry, University of Bristol, Cantock’s Close, Bristol, BS8 1TS

*Email: luke.elliott@bristol.ac.uk, k.booker-milburn@bristol.ac.uk, a.lennox@bristol.ac.uk

KEYWORDS Cascade, Photochemistry, Visible light, Flow, Diels-Alder, Rearrangement

ABSTRACT: A highly efficient visible light mediated photochemical [2+2] cycloaddition is coupled with an atom economic thermal cascade reaction in a continuous flow process. By moving the photochemistry from UV to visible it is made more energy efficient and can be conducted with readily available equipment. The application of high-temperature flow chemistry to the thermal cascade step allows for safe and reliable scale-up with short reaction times. Thus, we demonstrate a rare example of a photo/thermal daisy-chained process and, specifically, the first visible light mediated excited state to thermal cascade reaction as a fully continuous process (20 g/h). The synthetic utility of flow chemistry is further showcased by the isolation of a reactive intermediate at quantities not possible under batch conditions.

Introduction

Multi-step continuous flow synthesis is increasingly being utilized into the synthesis of APIs.1–3 Established techniques include continuous extractions, hydrogenation, solid support catalysts, reagent capture and other advanced methods.4–8 Despite this growing list of techniques, it is rare to incorporate a photochemical step into a multi-step continuous process.9–11 Successful photochemistry frequently requires highly pure solutions to avoid low yields. Indeed, some of the most synthetically interesting photochemical reactions often suffer low yield or productivity,12 which makes multistep processes impractical, which is due to either additional purification steps or a mismatch between practical flow rates. Hence, daisy-chaining photochemistry with other techniques in a continuous process can be highly challenging.

Photochemically generated products can be interesting scaffolds with potential applications in drug discovery programs.13–15 The sp3-rich compounds have attracted significant recent attention, due to the novel area of molecular space they occupy and their potentially favorable physiochemical properties.16–18 We have recently investigated the use of these products as energetic stepping-stones by exploiting their inherent reactivities to generate further complexity, Figure 1A. The triplet sensitized cross [2+2] of allylic enamides is a high yielding reaction driven by UV irradiation up to kg scale.19 In the presence of maleic anhydride, the 2,4-methano pyrrolidinone products were shown to undergo a thermal electrocyclic cascade process to give complex multi-functional bicyclic lactams.20

Figure 1. Photocycloaddition and Thermal Cascade Sequence from Aryl Enamides

There are several drawbacks to performing the photochemical [2+2] / thermal electrocyclic cascade in batch mode. Despite demonstrating the process on a multi-gram scale (20 mmol),20 further scale-up was limited for safety reasons as heating xylene beyond its boiling point was required in a sealed tube. In addition, purification of the product was
Results and Discussion

Batch/Batch (Photo/Thermal): The batch conditions reported for the photochemical cyclisation to form 2,4-methanopyrrolidines (2) employed acetonitrile as solvent, a medium pressure Hg UV lamp, and a UV absorbing triplet sensitizer, isopropylthioxanthone (ITX). Although the reaction is high yielding and productive, the MeCN solvent was deemed unsuitable for telescoping into the thermal process due to its impractically low boiling point. In addition, the use of specialist UV equipment makes it inaccessible to many and requires additional safety precautions. Hence our initial investigations were centered on improving these two aspects.

Thioxanthone derivatives have proved to be versatile triplet sensitizers, and we have recently developed a series that cover a broad range of UV-vis absorptions and triplet energies. The lowest energy derivative, 2,2'-MeOTX was particularly effective at sensitizing this class of reaction when irradiated with blue COB (chip on board) LEDs (36 W blue, 455 nm). Using an improved, water-cooled reactor, we began by further investigating the use of lower energy sensitizers in different solvents, in order to establish a combination that would be suitable for daisy-chaining to the thermal process. Reaction screening was carried out at a concentration of 0.5 M and a scale 15 or 30 mmol with 1% sensitizer. In addition to the previously optimized thioxanthone 2,2'-MeOTX, several other visible light absorbing organic triplet sensitizers were investigated as a point of comparison. As an accurate way of quantifying the results, the initial productivities, at incomplete conversion (≤ 50%), for the various conditions screened are shown in Table 1. In all cases the yield was >90% at full conversion (see SI).

Table 1. Batch Photochemistry Optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (mmol)</th>
<th>Sensitizer</th>
<th>Solvent</th>
<th>Productivity (mmol/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 a</td>
<td>15</td>
<td>2,2'-MeOTX</td>
<td>MeCN</td>
<td>10</td>
</tr>
<tr>
<td>2 b</td>
<td>15</td>
<td>2,2'-MeOTX</td>
<td>MeCN</td>
<td>16</td>
</tr>
</tbody>
</table>

The results first demonstrate an increase in productivity when using the water-cooled COB set-up (entry 1 vs 2), from 10 to 16 mmol/h in acetonitrile, making it as productive as a 400 W Hg lamp with ITX. 2CZPN has recently been used as an inexpensive alternative to iridium based visible light absorbing triplet sensitizers; however, when tested in our reaction, the productivity was lower than 2,2'-MeOTX (entry 2 vs 3). This may be due to a weaker overlap of the sensitizer absorption with the emission band of the blue COB LED (Figure 2). Brominated thioxanthone derivative, 2,2'-BrTX, proved to be insoluble in acetonitrile and so toluene was employed. Unfortunately, the productivity was very low, likely due to a poor absorption overlap with the blue emission band.

Figure 2. Visible absorptions of organic sensitizers (5x10⁻³ M)

The use of xylene, which is a more thermally suitable solvent for telescoping into the thermal process, was tested with 2,2'-MeOTX. Reassuringly, the yield remained high despite the productivity decreasing only by ca. 25% compared to acetonitrile. This result is significant because it facilities a one-pot process to be developed in xylene without having the heat MeCN to 140 - 180°C in sealed tubes.

Using the xylene photosylate solutions, we tested the thermal cascade step to demonstrate a one-pot, batch photo/thermal process. Hence, following irradiation, maleic anhydride was added and the vessel was heated at 180°C for 40 mins in a sealed tube. The product remained in solution during thermolysis but could be precipitated out by the addition of methanol to the cooled mixture, Figure 3. The overall isolated yield was 63%, which represents a reasonable improvement over the two-step procedure that gave 57% overall. This one-pot process in xylene provided good evidence that a fully continuous photo/thermal sequence should be possible through daisy-chaining a photochemical and a high-temperature / high-pressure thermal flow reactor.
Despite the elevated temperature and flow rate, product 3a began to precipitate out in the collection line and the reactor became fully blocked after about 30 mL was collected. Precipitation was not observed in batch mode, even when cooled and at full conversion, until the addition of methanol. The high surface area of the narrow bore flow channel offers more opportunities for nucleation and the sticky gel-like precipitated product makes it likely to block the tubing.

Despite the encouraging results using xylene in the one-pot process, Figure 3, precipitation of 3a forced us to reconsider the use of acetonitrile. Although, MeCN works well in the photochemistry step, we initially discarded its use in the thermal step due to safety implications of heating it to such a high temperature. Nevertheless, the use of a flow set-up greatly enhances the ability to heat solution under high temperature / pressure conditions. Large volumes can be safely processed since a relatively small volume is heated at a given time. This allowed us to return to the use of MeCN, hoping it would prevent blockages. To initially explore the viability of MeCN in the thermal cascade reaction, stock solutions of the isolated pyrrolidine 2a were made. Two concentrations of 2a were tested (0.25 M and 0.5 M) and mixed with maleic anhydride in MeCN in a ratio that gave 1:1 equivalents (See SI). A screen of temperatures and residence times was then conducted using the FlowSyn reactor, Table 2. At either concentration, full conversion to lactam 3a was observed at 200 °C and with a residence time of 5 minutes (entries 5 and 12). The yield was again limited to 70% at full conversion, the remaining material being lost to polymerization and degradation. Decreasing the residence time to 4 or 3 mins gave only a minor drop in conversion and yield (entries 8, 9, 13 and 14). Temperatures of 190 °C or below gave incomplete conversion for a 5 min residence time. However, the conversion was still higher in MeCN than when xylene was used: a 5 min residence time at 180 °C in xylene gave 24% 3a, whereas in MeCN gave 49% 3a, which indicates the reaction is faster in the more polar solvent. Increasing the equivalents of maleic anhydride from 1.1 to 1.5 eq had no impact on the yield of the reaction (Entries 6 and 11). Consistent with the xylene experiments on small scales (10 mL), there was no evidence of any blockages in the tubing. However, upon cooling in MeCN, 3a crystallized out, which contrasts to that in xylene that gave a thick, gel-like mass upon addition of MeOH (See SI for more details).

![Flowchart](image)

**Figure 3.** One-Pot Photo/Thermal Batch Reaction

**Batch/Flow (Photo/Thermal):** The next step to achieving a fully continuous process was to optimize the high temperature thermal flow step. Thus, using a Uniqsis FlowSyn steel coil reactor (30 mL), we began by screening a range of temperatures using the un-purified photolysis solution from the previous step (2a 0.5 M in xylene with 1% 2,2'-MeOTX). Maleic anhydride (1.1 M) was introduced in a flow ratio of 1:0.5 to give 1.1 eq of the dienophile to a reaction concentration of 0.33 M. Using the automation mode on the FlowSyn, 10 mL samples were flowed through the reactor at various temperatures with a fixed residence time of 5 minutes each. The reaction was monitored by quantitative 1H-NMR using 1,3,5-trimethoxybenzene as an internal standard and the results are shown in Table 2, Entries 1-4. The reaction proceeded to full conversion in the 5 min residence time at temperatures of 200 °C and above (entries 1 and 2), but was reduced at temperatures lower than this (entries 3 and 4). The optimal yield achieved at 210 °C was consistent with the batch conditions in a sealed tube (180 °C for 40 min). The optimal conditions were then scaled up to 30 mmol, which involved flowing a full 60 mL of photosylate through the reactor. The residence time was reduced to 3 mins (10 mL/min flow rate) which still gave full conversion at 210 °C. However, despite the elevated temperature and flow rate, product 3a began to precipitate out in the collection line and the reactor became fully blocked after about 30 mL was collected. Precipitation was not observed in batch mode, even when cooled and at full conversion, until the addition of methanol. The high surface area of the narrow bore flow channel offers more opportunities for nucleation and the sticky gel-like precipitated product makes it likely to block the tubing.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>1a Conc /M</th>
<th>Temperature (°C)</th>
<th>Residence (min)</th>
<th>Time</th>
<th>Lactam (%)</th>
<th>3a</th>
<th>Cyclobutene (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Xylene</td>
<td>0.5</td>
<td>210</td>
<td>5</td>
<td>66</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Xylene</td>
<td>0.5</td>
<td>200</td>
<td>5</td>
<td>64</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Xylene</td>
<td>0.5</td>
<td>190</td>
<td>5</td>
<td>54</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Xylene</td>
<td>0.5</td>
<td>180</td>
<td>5</td>
<td>24</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>0.25</td>
<td>200</td>
<td>5</td>
<td>70</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>0.25</td>
<td>200⁺</td>
<td>5</td>
<td>70</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>0.25</td>
<td>200</td>
<td>4</td>
<td>68</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>0.25</td>
<td>200</td>
<td>3</td>
<td>65</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>MeCN</td>
<td>0.25</td>
<td>190</td>
<td>5</td>
<td>66</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The parent phenyl derivative 3a, along with the 3-substituted F, Br and OMe derivatives (3b, 3c and 3d respectively), gave good yields (Figure 4), which were comparable to running the thermal step in xylene in sealed tubes. Moreover, the product material that precipitated out of the cooled acetonitrile was of a higher purity and more readily filtered, as when precipitated from xylene with methanol, the product formed a thick gel-like mass that was difficult to filter and dry. Although the 4-CF$_3$ derivative gave the most productive photochemical reaction (40 mmol/h), intermediate 2e proved resistant to the fragmentation, presumably due to the electron withdrawing effect of the CF$_3$ group.

Isolation of intermediate diene (6): In addition to being able to safely process large volumes of solvent under high temperature / pressure conditions, continuous flow chemistry allows for rapid and precise heating and cooling. We exploited this feature to isolate the diene intermediate (6), which was too reactive to isolate under batch conditions. The uncyclized anhydride Diels-Alder adduct 7a, was observed during the optimization of the continuous-flow thermal cascade reaction. This observation prompted a re-investigation of the thermolysis in the absence of the MA dienophile to enable formation of 6. A screen of reaction conditions using the FlowSyn reactor rapidly identified optimal conditions for the formation of diene 6a. With a residence time of just 2 minutes at 210°C in MeCN, the diene was isolated in over 60% yield (Figure 5). The rapid heating and then subsequent cooling of the solution enabled the thermolysis to proceed, but not the subsequent dimerization reaction, which is unavoidable using batch conditions in the absence of MA.

**Figure 4.** Batch/Flow process and substrate scope tested. Yields in parentheses are NMR yields.

**Figure 5.** Continuous-flow synthesis of diene 6a
Flow/Flow (Photo/Thermal Daisy-Chain): The final step was to translate the photochemical batch conditions to continuous flow with the Uniqsis PhotoSyn reactor. Based on the different powers of the light sources (36 W blue COB vs 560 W Uniqsis PhotoSyn (700 W run at 80%)), we estimated that an optimal flow rate of ca. 8 mL/min should give complete conversion with the PhotoSyn reactor when processing a 0.5 M solution. However, this estimate assumes both a comparable LED efficiency and light capture. Thus, a lower flow rate of 4 mL/min was initially tested, which unfortunately gave a low yield and productivity (7%, 8.4 mmol/h). (Table 3, entry 1). This poor performance was rationalized by the difference in light absorption. Whereas the path length in the batch process (100 mL round bottomed flask) is several centimeters thick, the coiled tube (1/16" o.d.) PhotoSyn flow reactor has a path length of one millimeter or less. This issue was exacerbated by the tubing not being tightly wrapped, with significant spacing between the coil. This difference is significant since the extinction coefficient of the thioxanthone is relatively weak at the region of overlap with the blue COB emission (Figure 2), and so more light is expected to be lost by direct transmission. To improve the light absorption of the system, we replaced the PFA 1/16" (o.d.) coil with 2 layers of tightly wrapped 1/8" FEP tubing, which raised the volume to 160 mL and increased the path length. Using this configuration, the productivity increased almost 10-fold to 80 mmol/h at around 50% conversion (Table 3, entry 2).

Further optimizations were conducted in acetonitrile to match the recently developed high temperature thermal cascade flow step. At a reduced concentration (0.25 M) the reaction was close to full conversion at 88% yield (66 mmol/h) when run at 5 mL/min (entry 3). Retaining the concentration of 0.5 M and flowing at 3 mL/min led to full conversion and almost quantitative yield (88 mmol/h) (entry 4).

### Table 3. Photochemical Flow Reactor Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Configuration</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>Flow Rate (ml/min)</th>
<th>Product (%)</th>
<th>Productivity (mmol/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14 mL PFA</td>
<td>xylene</td>
<td>0.5</td>
<td>4</td>
<td>7</td>
<td>8.4</td>
</tr>
<tr>
<td>2</td>
<td>160 mL FEP</td>
<td>xylene</td>
<td>0.5</td>
<td>5</td>
<td>53</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>160 mL FEP</td>
<td>MeCN</td>
<td>0.25</td>
<td>5</td>
<td>88</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>160 mL FEP</td>
<td>MeCN</td>
<td>0.5</td>
<td>3</td>
<td>98</td>
<td>88</td>
</tr>
</tbody>
</table>

All PhotoSyn results run at 560 W, yield determined by 1H-NMR using an internal standard.

Following these optimization studies, a fully daisy-chained photo/thermal flow process was performed. Hence, the photochemical step was conducted with 0.5 M 1a, 1% 2,2'-MeOTX (5 mM) sensitizer and run at 3 mL/min (entry 4), and allowed to collect in a beaker until the volume reached about 40 mL. The thermal flow process was initiated at this point and the photosylate stream was mixed with maleic anhydride (MeCN, 0.55 M) before flowing through the 30 mL coil at 200°C with a 5 min residence time, Figure 6. The process was run for exactly 1 hour, after which the solution was concentrated to approximately 250 mL. The material, which crystallized out of the acetonitrile solution, was filtered and washed with Et3O, giving 20.4 g of lactam product 3a (63%) in excellent purity, Figure 7. The ease at which this could be purified by filtration represents one of the main benefits of acetonitrile over xylene and would not be possible without the use of continuous flow technology. This result represents a 24 h productivity of 490 g.

In conclusion, we have demonstrated a rare example of an excited state photochemical reaction successfully daisy-chained with a thermal reaction as a continuous flow sequence. The photochemical step highlights the synthetic utility of modern, organic, visible-light absorbing triplet sensitizers to give exceptional yields and productivity with simple equipment. The application of continuous flow techniques to the thermal cascade reaction demonstrates how conditions of high temperature and pressure can be rapidly screened and safely scaled-up. The ability to rapidly heat and cool solutions with fine control over reaction times, allowed the isolation of a reactive, diene intermediate on a scale and yield unachievable with traditional batch apparatus. The combination of excited state photochemistry with high temperature thermal flow reactions thus offers rapid access to novel molecular architecture under reagentless conditions.

![Figure 6](image_url) Daisy-chained PhotoSyn / FlowSyn and pure product collected by filtration.
ASSOCIATED CONTENT
Experimental procedures for reaction optimization, compound characterizations, NMR spectra, and details on the reactors are all given in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION
Corresponding Authors
* Luke Elliott (luke.elliott@bristol.ac.uk)
* Kevin Booker-Milburn (k.booker-milburn@bristol.ac.uk)
* Alastair J. J. Lennox (a.lennox@bristol.ac.uk)
University of Bristol, School of Chemistry, Cantock’s Close, Bristol, BS8 1TS.

Funding Sources
Any funds used to support the research of the manuscript should be placed here (per journal style).

Notes
Any additional relevant notes should be placed here.

ACKNOWLEDGMENT
We thank the EPSRC (EP/P013341/1 and EP/S018050/1) and the Royal Society (University Research Fellowship to AJL) for funding, Steve Evans and Mark Ladlow (Uniqsis) for the loan of the FlowSyn and PhotoSyn reactors, and Paul Dinham and Paul Chappell (University of Bristol) for reactor construction.

REFERENCES
+ 2,2′-MeOTX (1%)