Towards a Scalable Synthesis of 2-Oxabicyclo[2.2.0]hex-5-en-3-one Using Flow Photochemistry
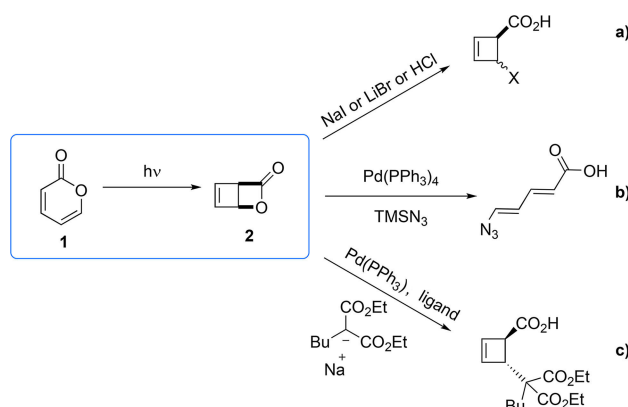
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Cyclobutene lactones hold great potential as synthetic building blocks, yet their preparation by photochemical rearrangement in batch can often be a bottleneck in synthetic studies. We report the use of flow photochemistry as a tool to enable a higher-throughput approach to the synthesis of 2-oxabicyclo[2.2.0]hex-5-en-3-one, which reduces reaction times from 24 h to 10 min. Accordingly, a significantly improved throughput of 144 mg/h (vs 14–21 mg/h in batch) was achieved. Scale-out experiments showed problematic reactor fouling and steps were taken to explore and minimize this effect.

Scheme 1. The photochemical synthesis of cyclobutene lactone 2 from 2-pyrone 1, and a selection of its synthetic transformations, illustrating the importance of this photochemical step.

In synthetic chemistry, cyclobutane derivatives represent a versatile class of carbocyclic small molecule fragments, which are used in the synthesis of a wide range of complex synthetic targets.[1] Within this family of compounds bicyclic cyclobutene lactones, such as 2-oxabicyclo[2.2.0]hex-5-en-3-one 2, are of particular synthetic use, since they also allow functionalization by initial nucleophilic attack from a diverse range of nucleophiles, opening the lactone ring. This reactivity has been demonstrated with halides (Scheme 1a),[2] as well as various soft and hard nucleophiles.[3] Heteroatomic (O— and N— based) nucleophiles, on the other hand, have been demonstrated to induce a spontaneous ring opening in a highly stereocontrolled

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manner, to furnish the diene product (Scheme 1b).[4] This was rationalized by push-pull stabilization in a recent computational study.[5]

Palladium-catalyzed allylic alkylations of 2 using soft nucleophiles have been achieved with a high degree of diastereo- and enantioselectivity. Indeed, it has been demonstrated that all four enantiomers of the resulting monocyclic cyclobutene can be accessed by diastereodivergent deracemization with exceptional enantiocontrol (Scheme 1c).[6] Furthermore, the cyclobutene portion of the molecule can be invoked in other complexity-generating synthetic steps, such as carbene insertion[7] or cross-coupling reactions of the linear diene product.[2] Consequently, these and related cyclobutenes and cyclobutane derivatives have been utilized as key intermediates in numerous natural product syntheses[2,7,8] and, therefore, robust and scalable methods for their preparation are of great interest to many members of the synthetic organic chemistry community.

Synthesis of these cyclobutene lactones by the disrotatory 4-pi photoelectrocyclization of 2-pyrone derivatives has become well established, since its first report by Corey in 1964.[9] As a piece of classical photochemistry, this has been examined with a variety of coumalic esters,[10] and other substituted 2-pyrones,[3a] resulting in valuable starting materials for the aforementioned chemistries (Scheme 1). However, as with many classical photochemical methodologies, the equipment and methods used to carry out these reactions have not changed since their first discovery and still generally consist of

immersion well glassware, with a pressurized mercury lamp, whereby the only control over emission wavelength is achieved by application of various band-pass or exclusion filters.

Several of the issues observed in batch operation of this chemistry are reminiscent of other UV-mediated photochemical transformations. For instance, low reagent concentrations are required in order to allow efficient light penetration and to prevent undesired intermolecular reaction. Long reaction times are required, increasing the likelihood of onward reaction from the desired product. Finally, downstream synthetic efforts have been hampered by the inherent lack of scalability in these procedures, acting as bottlenecks in methodology development, or natural product synthesis. Many repetitions of small scale reactions are required to fulfill this demand, resulting in ineffective use of a chemist's time.

The renaissance in modern photochemical methods for organic synthesis has begun to challenge these procedures and in many cases offer improvements based on new light source and reactor technologies.[11] In particular, flow photochemistry offers lower reaction times, achieved by implementing a short irradiation path length. Precise control over irradiation times can limit the extent of decomposition and onward reaction of the desired product and, finally, larger quantities of material can be prepared by simply "scaling out" the same process over an extended reaction period.[12] By applying these principles, we aim to develop a continuous flow procedure, for the preparation of synthetically useful quantities of cyclobutene lactone **2**.

With this goal in mind, an initial analysis of the reaction substrate was undertaken, considering its absorption, but also a computational estimation of its triplet energy (Figure 1). With this information, it was anticipated that a suitable light source could be selected, perhaps replacing the classically-used medium pressure Hg lamp. Use of longer wavelengths (in combination with a photosensitizer) may serve to lessen the extent of polymerization by avoiding direct substrate irradiation. The reaction substrate was found to absorb at wavelengths between 240 and 330 nm, with a λ_{max} of 288 nm. A relatively low triplet energy of 58.9 kcal/mol was calculated using DFT (M062X/TZVP level of theory) which implies that the substrate should be susceptible to triplet transfer from a wide range of sensitizers.[13]
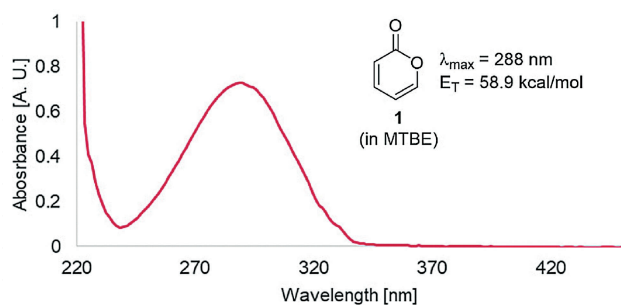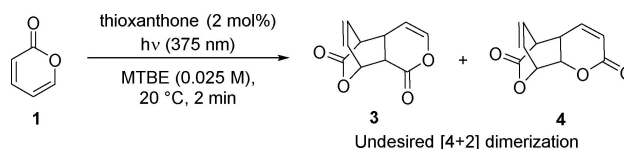
Figure 1. UV/Vis absorption spectrum and calculated triplet energy of the 2-pyrone starting material. Triplet energy calculated by DFT using M062X/TZVP.

Scheme 2. Triplet sensitized reaction of 2-pyrone **1**, showing selectivity for a dimerization pathway, rather than the desired internal [2+2] rearrangement.

Initial reactions using 375 nm irradiation with a suitable triplet sensitizer were selective for an alternative reaction pathway, furnishing the undesired [4+2] dimeric products **3** and **4** (Scheme 2). Accordingly, the desired product **2** must be obtained via a singlet reaction pathway, by direct irradiation. Although this result did not come as a surprise, since this triplet pathway has been previously reported,[14] we can corroborate the previous structural assignment using NMR techniques which were unavailable at the time of initial report (see Supporting Information). We also confirm that this reaction pathway operates effectively under more "modernized" reaction conditions: using longer wavelength pseudomonochromatic LED irradiation (375 nm) and a more efficient photosensitizer (thioxanthone).

Since a triplet reaction pathway (by the use of a sensitizer) has been ruled out, optimization efforts in flow began by examining a range of different light sources. It was anticipated that a 254 nm UV lamp or 365 nm blacklight CFL would exhibit sufficient spectral overlap for reaction to take place, yet no conversion of starting material was observed (see Supporting Information Table S2). However, when an 8 W 303 nm UV lamp was employed, conversion to the desired product was observed (Table 1, entry 1). Increasing the concentration of **1** resulted in a lesser extent of reaction (entry 2), which did not see significant improvement with an extended residence time of 50 minutes (entry 3). Although the desired product was formed using this lamp, the observed productivity was too low for preparative use. Accordingly, our attention turned towards implementing a higher energy light source, in the form of a (150 W) medium pressure mercury vapor lamp, in a Vapourtec UV-150 system.

At a low concentration (25 mM), complete conversion of the starting 2-pyrone **1** was achieved in a shorter residence time of 10 minutes (entry 4). Also due to the larger reactor volume (10 mL vs 2 mL), faster flowrates were employed which resulted in greatly improved productivity of 144 mg/h. These conditions were then examined at a lower temperature of 10 °C, where it was found that the reaction rate was not negatively affected (entry 5). In a bid to increase productivity further, the concentration of pyrone **1** was raised to 50 mM. Unsurprisingly, the rate of reaction was slower, likely due to poorer light penetration, resulting in only 58% conversion (entry 6). Extending the residence time to 20 minutes allowed complete consumption of pyrone **1**. With increasing reaction concentration, an increased residence time was required (in a roughly linear fashion), implying that productivity cannot be increased by this approach (entry 4 vs entry 7).

Still, in order to decrease solvent consumption, the reaction concentration was further increased to 100 mM (entry 8). Again,

incomplete reaction was observed, but elongating the residence time in this case resulted in the production of a substantial quantity of an insoluble white solid. This solid was anticipated to be the result of polymerization, which has been previously observed when operating this reaction at higher concentrations in batch. In order to combat this unwanted side reaction, the temperature was again lowered to 10 °C, but the solid by-product was still produced (entry 10). The intermediate concentration (50 mM) was selected to minimize solvent wastage, with a temperature of 50 °C (entry 7), since this allows the reactor to be operated without cooling by dry ice.

To demonstrate the procedure's synthetic utility, the optimized conditions were applied to a "scale-out" experiment, in which the reactor was operated continuously for 8 hours, with monitoring by low-field ^{1}H NMR throughout. Unfortunately, the reaction performance decreased significantly throughout the course of the synthetic run (Figure 2a, orange line). Almost complete conversion was observed after 1 hour, yet the next recorded time point revealed a dramatic change, where 20% of the starting material 1 still remained. This downward trend continued in a roughly linear fashion, until the level of conversion dropped to 53% after 8 hours of processing, corresponding to a 6.6%/h decrease in conversion. Following this reaction, the reactor coil had undergone fouling by the accumulation of a brown coating on the inside of the PFA tubing (Figure 2b), which could only be removed using sodium hydroxide. This type of fouling is fairly common in photochemical reactions which use high power light sources, and is thought to arise from unspecific reactions or polymerization of the starting materials/products, when under irradiation by short wavelengths.[15]
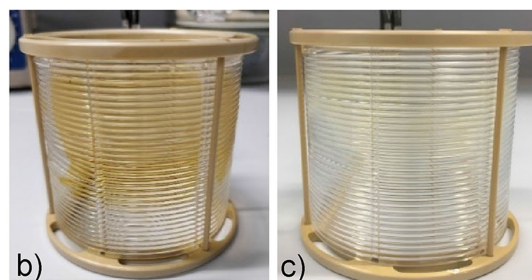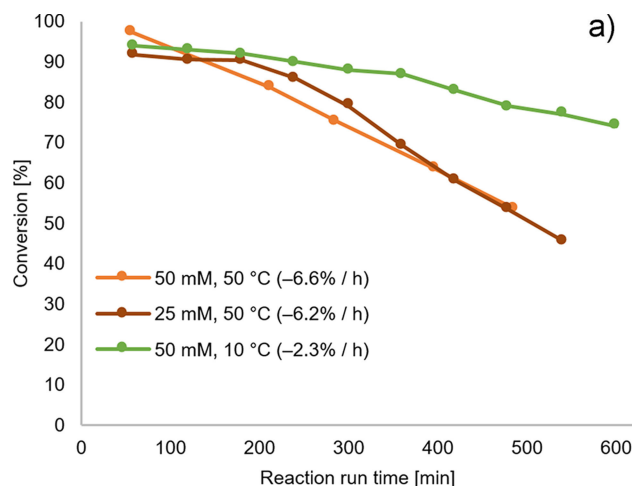

Figure 2. a) Reaction performance over time during extended reaction periods (8–10 h), using different temperature and concentration combinations; b) fouled reactor coil, following an 8 h reaction using 50 mM concentration and 50 °C temperature; c) minor fouling on the reactor coil, following a 10 h reaction using 50 mM concentration and 10 °C temperature.

We endeavoured to explore this reactor fouling in more detail, with a view to developing conditions which minimize its effect. It was anticipated that reducing the reaction temperature and concentration could prevent the occurrence of fouling, and accordingly, additional scale-out experiments were carried out to examine these parameters (Figure 2a). The conditions employed in each case were altered to maintain the same level of productivity (i.e. lower concentration reactions were conducted with a shorter residence time).

Upon decreasing the reaction concentration to 25 mM (Figure 2a, brown line), good conversion was maintained for the first three hours of reaction, but then decreased rapidly, resulting in a similar value to the previous reaction (53%), after 8 hours. Overall, this corresponds to a slightly reduced rate of fouling: an average loss of 6.2%/h conversion. To examine the effect of temperature, a reaction was carried out at 50 mM concentration, but a lower temperature of 10 °C (Figure 2a, green line). The resulting productivity decrease was far more gradual, still providing 79% conversion after 8 hours, and 74% after 10 hours. This equates to a significantly reduced linear conversion decrease of 2.3%/h. The resulting reactor fouling appeared comparatively minor (Figure 2c), which highlights the importance of regularly cleaning or replacing such PFA tubing reactors, even if fouling is not obvious. Furthermore, this comparison (50 mM at 50 °C versus 10 °C) provides evidence

Table 1. Optimization studies of 2-pyrone **1** photoisomerization to cyclobutene lactone **2** in flow.

Entry	Conc. [mM]	Residence time [min]	Temp. [°C]	Conversion [%][a]	Productivity [mg/h]
1[c]	25	20	40	68	9.8[b]
2[c]	50	20	40	43	12.4[b]
3[c]	50	50	40	55	3.2[b]
4[d]	25	10	50	>95	144
5[d]	25	10	10	>95	144
6[d]	50	10	50	58	167[b]
7[d]	50	20	50	>95	144
8[d]	100	20	50	62	179[b]
9[d]	100	40	50	>95[e]	144[b]
10[d]	100	40	10	>95[e]	144[b]

[a] Reaction conversion determined by the ratio of starting material to product peaks by NMR spectroscopy. [b] Experiments which result in incomplete conversion or polymerization; these productivities are not a useful comparison. [c] Reaction performed under irradiation by an 8 W 303 nm UV lamp with a 2 mL reactor volume. [d] Reaction performed under irradiation by a medium pressure Hg lamp (Vapourtec UV-150 with "gold" filter #2) with a 10 mL reactor volume. [e] An insoluble product was formed, assumed to be a product of polymerization.

that such fouling events are, at least in this case, more temperature- than concentration-dependent.

In conclusion, the first continuous flow synthesis of cyclobutene lactone **2** has been demonstrated, achieving a productivity increase roughly ten-fold versus the batch comparison (144 mg/h versus 14–21 mg/h).[3c] A screen of different light sources revealed that a high photon flux at around 300 nm is necessary for useful levels of conversion. Attempting to utilize a triplet-sensitized methodology provided the alternative [4+2] products **3** and **4**, reinforcing the fact that direct irradiation of the starting material cannot be avoided. When scaling out the optimized reaction conditions, it soon became apparent that productivity would be severely hindered over time by fouling of the reactor. Nevertheless, further studies into this fouling revealed that it could be significantly reduced by decreasing reaction temperature and, therefore, implementation of this process is expected to significantly benefit downstream synthetic studies.

Experimental Section

Example procedure for scale-out experiment (50 mM, 50 °C, figure 2a): A 350 mL solution of pyrone **1** (1.68 g, 17.5 mmol) was made up to 50 mM in degassed MTBE (sparged with argon for 15 min prior to use). The Vapourtec medium pressure Hg lamp was ignited, reactor temperature set to 40 °C and the solution was pumped through the 10 mL photoreactor using a V-3 peristaltic pump at 0.5 mL/min, providing a 20 min residence time. Prior to beginning collection, the reactor output was diverted to waste for 1.5 reactor volumes. The reactor output was then collected in a flask cooled to 0 °C in an ice bath for the reaction duration of 8 h. The output stream was collected at intervals and analyzed directly by low-field ^{1}H NMR. Conversion was calculated by comparing the integration of product cyclobutene **2**[2] with unconsumed 2-pyrone **1**.

Note: when the reactor was set to 40 °C, dry ice was not used to provide additional cooling. As a result, the reactor temperature equilibrated around 50 °C.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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