Application Note 48:

Photochemical synthesis of Cubanes

Produced by Vapourtec

Abstract

This application note demonstrates the preparation of cage compound 2 from an advanced diene precursor 1, which can be prepared from cyclopentanone. After optimization, this key photochemical [2+2] photocycloaddition was successfully scaled up to multigram scale, and the cycloadduct was transformed to 1,4-cubane dicarboxylate 3.

Scheme 1

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Background

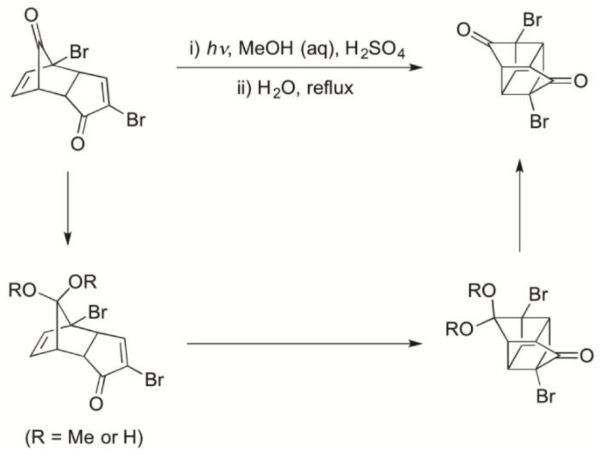
Utilizing photochemistry with flow chemistry offers many advantages and potential uses from chemical manufacture to pharmaceuticals. The key factors for this combination include:

- Uniform and constant light exposure throughout the entire reactor.
- Highly controllable parameters, such as exposure intensity, reaction time and temperature, which can all be controlled simultaneously.
- Continual removal of products from the reactor, preventing any unwanted side or over reactions, as well as limiting any potential competing absorbtions, which may potential slow the reaction or prevent full conversion.

Batch is limited in these regards, as exposure is not be uniform and products remain in the reaction vessel. While photochemistry is still an underused synthetic technique, applying continuous flow photochemistry offers accuracy and reproducibility in every reaction.

Cubanes are fascinating molecules that are of interest in the pharmaceutical industry, but rarely studied due to not being readily available to researchers. Nevertheless, an efficient process route to 1,4-cubane dicarboxylate has been developed by Tsanaktsidis and co-workers,1 which delivers over half a kilo of the product per batch. Tsanaktisidis's synthetic route comprises a key photochemical step: the intramolecular [2+2] photocycloaddition of diene 1 to give cage structure 2 (Scheme 1). The reaction was carried out in a large 6.4-litre photolysis flow cell, employing a 2 kilowatt mercury lamp. The reaction mixture (approximately 55 liters) was continually circulated through the photoreactor for 173 hours in order to achieve full conversion of the diene starting material, and the resulting photoadduct was then converted to cubane-1,4-dicarboxylate 3. The photoreaction does not appear to suffer from over-irradiation problems, as no degradation is observed upon long reaction times. This application note presents a study of this photoreaction using Vapourtec's easy-Photochem system, with optimization for convenient application on multigram scales without the need for a specially designed photoreactor.

The key photocycloaddition is carried out in acidic aqueous methanol, which ensures the conversion of the dione starting material 1 to the corresponding acetal or hemiacetal (Scheme 2). This is vital to the success of the reaction, since irradiation in other solvents (e.g. acetonitrile, toluene) does not yield the desired product. As a result, after completion of the photocycloaddition, it is necessary to heat the photoadduct 2 in water in order to convert any remaining acetals/hemiacetals to the ketone. This procedure ensures efficient conversion in the subsequent synthetic steps en route to cubane-1,4-dicarboxylate 3.



Scheme 2

Optimization

As stated above, the aim of this work was to optimize an intramolecular [2+2] photocycloaddition using the UV-150 mercury lamp.

Setup

The flow reactor was set up using the Vapourtec E-Series as shown in Fig.1.

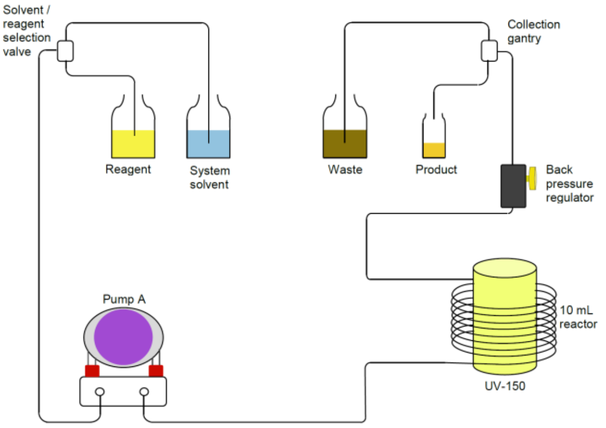


Figure 1

The UV-150 was fitted with a 10 mL reactor, a connecting tube in series and a manually adjustable back pressure regulator. The elution outflow was collected via the waste/collection switching valve.

Pump Tubing

The E-Series is fitted with two or three high performance V-3 peristaltic pumps and features a fluoropolymer tube as its core. The pumps feature more than one different tube type to ensure the largest range in compatibility of solvents. Therefore, the correct selection of tubing is crucial for any given reaction. A table showing recommended tube type compatibility with a wide selection of solvents, acids and bases is available within the E-Series manual and also built into the user interface software. The solvent used was methanol-water-sulfuric acid, therefore the V-3 pumps were used with the red tubing in this study.

Reagents

Reagent A- endo-2,4-Dibromodicyclopentadiene-1,8-dione (1; synthesized as described in reference 1), dissolved in a mixture of methanol mixture (85 mL), water (15 mL) and sulfuric acid (120 μL); various substrate concentrations were prepared. The resulting substrate solutions were deoxygenated by bubbling through with argon gas for 10 minutes directly before use.

System Parameters

System solvent:	Mixture of methanol (85 mL), water (15 mL) and sulfuric acid (120 μL)
Solution A:	Substrate A dissolved in the system solvent (0.05/0.10/0.15/0.2 M)
UV Light Sources:	Medium pressure Hg lamp set to full power (red filter no.3 used)
Flow rate A:	0.5 – 5 mL/min
Reactor volume:	10 mL reactor
Reactor temperature:	0 – 30 °C
Back pressure regulator:	3 bar set with the variable BPR

The optimization process followed the sequence of steps listed below:

1. *Priming the pumps with system solvent:*
   The selection valve was set to 'Solvent' and the pump was primed with system solvent. This is done by selecting the prime function from the touchpad control. The priming process is fully automated.
2. *Prepping the system*
   The reaction system was prepped with the easy-MedChem™ software using the flow-wizard option, where reaction conditions, flow rate and parameters were set and left for the lamp to turn on and the reactor to (usually) 20 °C.
3. *Reaction optimization:*
   The effect of temperature, flow rate and substrate concentration were evaluated using the flow-wizard. For each reaction, 10 mL of reagent A solution was input and collected in a 50 mL round-bottomed flask via the waste/collection switching valve, then evaporated under reduced pressure.
4. *Work-up and analysis:*
   The residue was suspended in water (10 mL), heated at 100 °C for 3 hours then evaporated under reduced pressure. A small sample was removed and analyzed by ^{1}H NMR spectroscopy, in order to determine the ratio of starting material and product. From this data, the percentage conversion of the starting material into the product was calculated.

Results and discussion

Effect of temperature

Firstly, the effect of the reactor temperature was studied, keeping the substrate concentration (0.05 M), lamp power (100%) and the flow rate (2.0 mL/min) constant. The temperature was varied between 0 °C and 30 °C, and the results are summarized in Table 1. The extent of conversion of substrate to product was not affected by changing the temperature within the range studied, thus a standard temperature of 20 °C was selected for subsequent optimization experiments. It was noted that incomplete conversion was obtained at a flow rate of 2.0 mL/min, and the effect of flow rate is discussed in the next section.

Table 1

Entry	Temp (°C)	Flow rate (mL/min)	Substrate Conc (M)	Conversion (%)
1	30	2.0	0.05	83
2	20	2.0	0.05	88
3	10	2.0	0.05	86
4	0	2.0	0.05	87

Effect of flow rate and substrate concentration

Given the heavy dependence of the rate of a photochemical reaction on the substrate concentration, the effect of the flow rate at several different substrate concentrations was next studied, keeping lamp power (100%) and the temperature (20 °C) constant. Thus, the flow rate was varied between 0.5 mL/min and 5 mL/min, at substrate concentrations of 0.05 M (entries 1-3), 0.10 M (entries 4-6) and 0.20 M (entries 7-9), and the results are summarized in Table 2. At 0.05 M substrate concentration, a 1 mL/min flow rate was required for complete conversion of the substrate, whilst at 0.10 M, it was necessary to halve the flow rate to achieve full conversion. Similarly, upon doubling the substrate concentration from 0.10 M to 0.20 M, a small amount of starting material remained after the reaction even at 0.5 mL/min.

Table 2

Entry	Temp (°C)	Flow rate (mL/min)	Substrate Conc (M)	Conversion (%)
1	20	5.0	0.05	42
2	20	2.0	0.05	88
3	20	1.0	0.05	100
4	20	2.0	0.10	60
5	20	1.0	0.10	94
6	20	0.5	0.10	100
7	20	2.0	0.20	38
8	20	1.0	0.20	59
9	20	0.5	0.20	95

Scale-up run using optimized conditions

Given the incomplete conversion observed at 0.20 M substrate concentration even at very low flow rates (Table 2, entry 9), it was decided that the substrate concentration should be lowered to 0.15 M for the scale-up run, keeping the flow rate (0.5 mL/min), lamp power (100%) and the temperature (20 °C) constant. 100 mL of solution A was prepared by dissolving reagent A (4.77 g, 15.0 mmol) in 85 mL methanol, 15 mL water and 120 μL of concentrated sulfuric acid. 90 mL of this solution was processed in three hours under the conditions summarized in Scheme 2, with full conversion of reagent A to the product. The elution outflow was collected and evaporated under reduced pressure in a 100 mL round-bottomed flask to leave an orange viscous oil (6.28 g), which was suspended in water (30 mL), and the resulting mixture was heated at 100 °C for three hours, then allowed to cool to room temperature. Sodium hydroxide (10.5 g, 0.26 mol) was added portionwise at room temperature and the resulting mixture was heated at reflux for 3 hours. The mixture was allowed to cool to room temperature then cooled to 0 °C, and concentrated hydrochloric acid (approximately 23 mL) was added dropwise until pH 1 was reached. The resulting suspension was stirred at room temperature for 12 hours, then filtered under vacuum. The filter cake was washed with ice-cold water (2 x 8 mL) and dried on the filter then further dried under high vacuum to give cubane 1,4-dicarboxylate (1.46 g, 6.20 mmol, 46% yield) as a medium-brown solid.

Conclusion

The work described in this application note demonstrates that the Vapourtec easy-Photochem is well-suited for processing the intramolecular [2+2] photocycloaddition of diene 1 to cage compound 2 in a straightforward and controlled manner. Further transformation of the cycloadduct was shown to allow access to cubane-1,4-dicarboxylate on a scale suitable for application in medicinal chemistry programs.

References

1. Falkiner, M. J.; Littler, S. W.; McRae, K. J.; Savage, G. P.; Tsanaktsidis, J. *Org. Proc. Res. Dev.* **2013**, 17, 1503-1509

Acknowledgements

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