

A new home-made UV reactor for scale-up production of α -hydroxycyclopenteno-aziridines

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Introduction

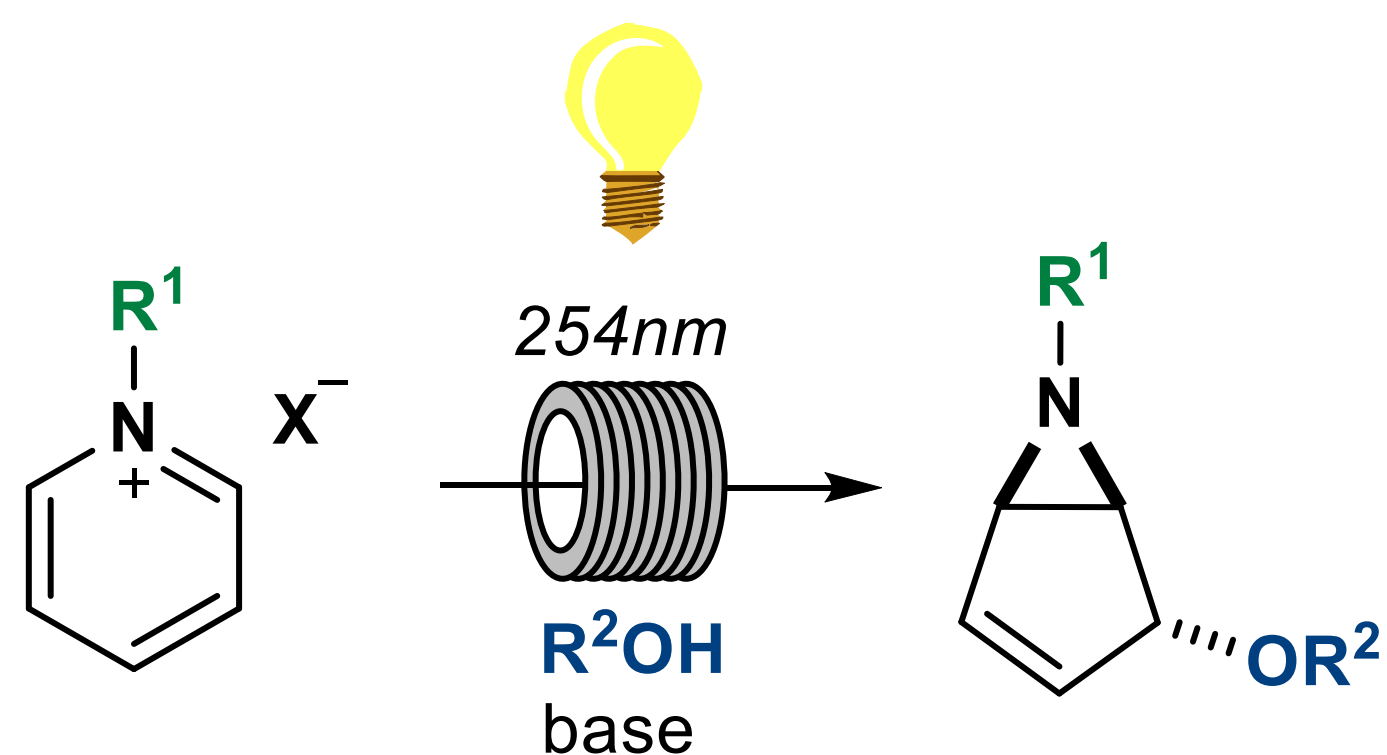
α -hydroxycyclopenteno-aziridines are valuable intermediates to achieve molecules with biological activity.¹ They can be obtained through photochemical transformation of pyridinium salts.^{1,2} However, reaction in batch has low productivities.³ Scale-up options are limited due to low penetration of photons in the solution with the increase of reactor dimensions.⁴ By using flow reactors, we can overcome this problem, as we demonstrated in a previous work.⁵ We hereby present the development of a new home-made UV reactor and a flow parallel quartz tube reactor to production intensification of 6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol and 6-butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol.⁶

Results: Development of the photochemical reactor with 12 parallel quartz tubes and best continuous-flow conditions

First, the best reaction conditions under batch were established of the **allyl pyridinium salt**, by evaluating diverse parameters such as reaction concentration (20, 40, 60, and 80 mM), residence time (up to 10 h), and the internal diameter of the quartz tubes (QTs) (0.2, 0.4 and 0.6 cm).

Flow experiments were initiated by mimicking the best batch results (concentration 20 mM, 1h of residence time, QTs with 0.6 cm of diameter) and progressed with adjusted residence times to yield the best conversions and productivities, resulting in a productivity of 129 mg.h⁻¹ of 6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol.

The same conditions were applied to the transformation of the **butyl pyridinium salt** (conc. 20 mM, QTs 0.6 cm) adjusting the residence time (2.3 hours) to give a productivity of 398 mg.h⁻¹.



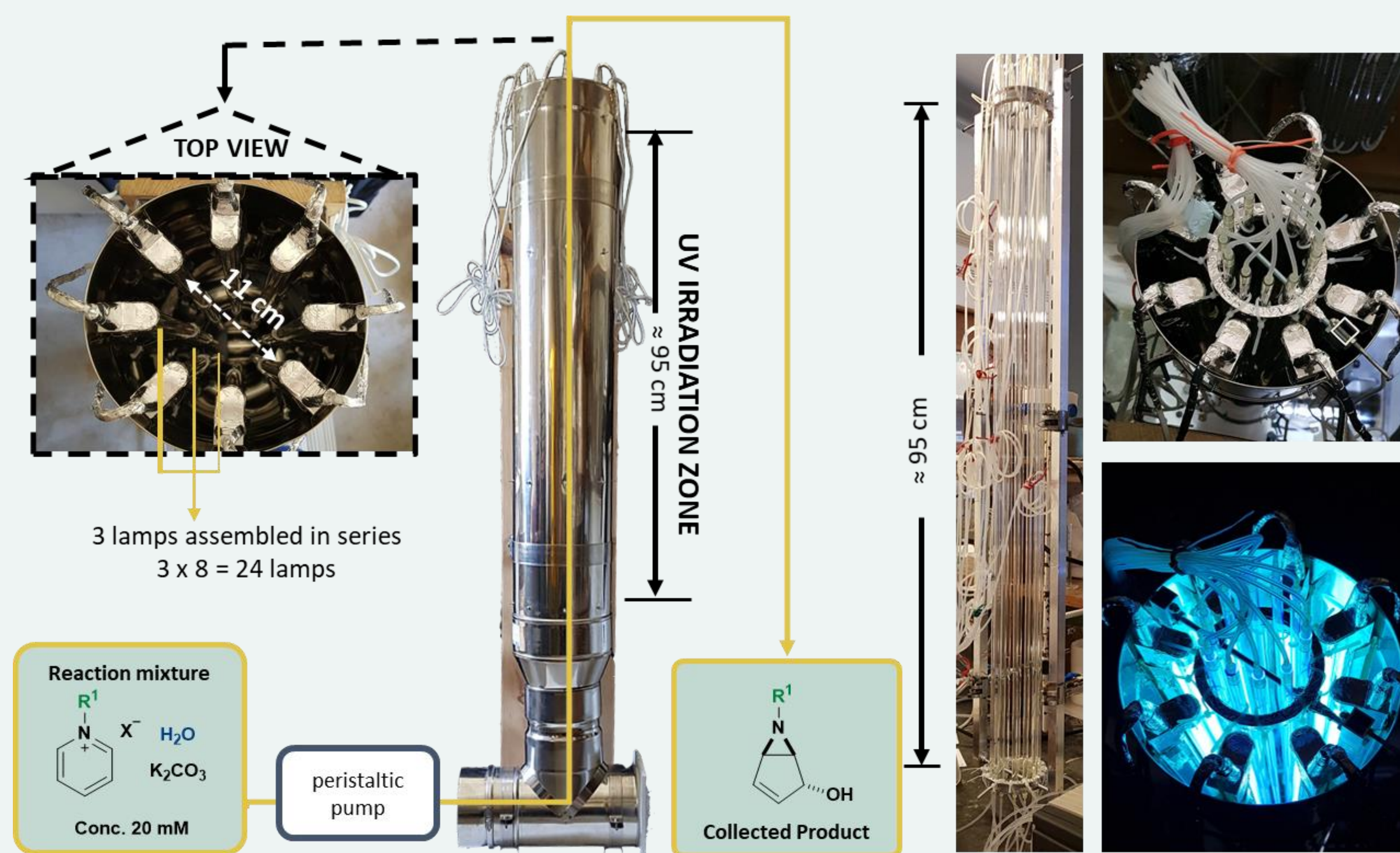
| | Previous work (Siopa and Afonso 2018) | This work | Improvement to the previous work |
|----------------------------------|--|------------------------|-------------------------------------|
| R ¹ = allyl | 41 mg.h ⁻¹ | 129 mg.h ⁻¹ | 1:3 |
| R ¹ = <i>n</i> -butyl | 87 mg.h ⁻¹ | 398 mg.h ⁻¹ | 1:5 |

Table 1. Process intensification under continuous-flow of 6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol

| Reaction time (h) | Cycle | Conv. (%) ¹ | Volume out of the reactor (mL) |
|-------------------|-------|------------------------|--------------------------------|
| 4 | 1 | 49 | 350 |
| 8 | 2 | 92 | 360 |
| 13 | 3 | 82 | 450 |
| 19 | 4 | 66 | 550 |
| 27 | 5 | 41 | 710 |

Flow rate 0.12 ml/min (3 rpm), residence time 4 hours. ¹ Determined by ¹H NMR analysis.

New home-made UV reactor and continuous-flow parallel quartz tube reactor



(A) Overview of the new home-made UV reactor; (B) Synthetic methodology for α -hydroxycyclopenteno-aziridines synthesis; (C) Top-view UV reactor; (D) 12 assembled parallel quartz tube reactor; (E) Top-view reactors; (F) Top-view reactors under photochemical irradiation.

The reactor was designed to have 12 parallel quartz tubes, each tube with internal diameter of 0.6 cm and 95 cm of irradiation length, allowing for a total irradiated volume of 0.323 L.

The inflow of the reaction solution to the reactor is allowed by a 12 channel cassette pumps Watson Marlow 205S, through silicon tubes connected to the QTs.

Table 2. Process intensification under continuous-flow of 6-butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol

| Reaction time (h) | Cycle | Conv. (%) ¹ | Volume out of the reactor (mL) |
|-------------------|-------|------------------------|--------------------------------|
| 2.30 | 1 | 100 | 380 |
| 5 | 2 | 92 | 370 |
| 7.30 | 3 | 90.5 | 355 |
| 11.30 | 4 | 89 | 670 |
| 19.16 | 5 | 94 | 1070 |
| 23.16 | 6 | 86 | 800 |
| 32.41 | 7 | - | 1000 |
| 36.21 | 8 | - | 910 |
| 42.42 | 9 | 55 | 960 |

Flow rate 0.21 ml/min (5 rpm), residence time 2.3 hours. ¹ Determined by ¹H NMR analysis.

Conclusions

With this technology we were able to improve our previous results and produce and isolate **1.94 g** of 6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol after 15 h of irradiation, and **16.99 g** of 6-butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol after 42.7 h of irradiation.

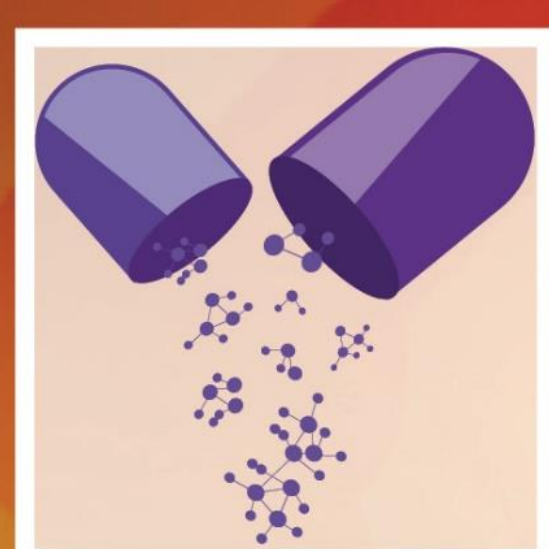
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