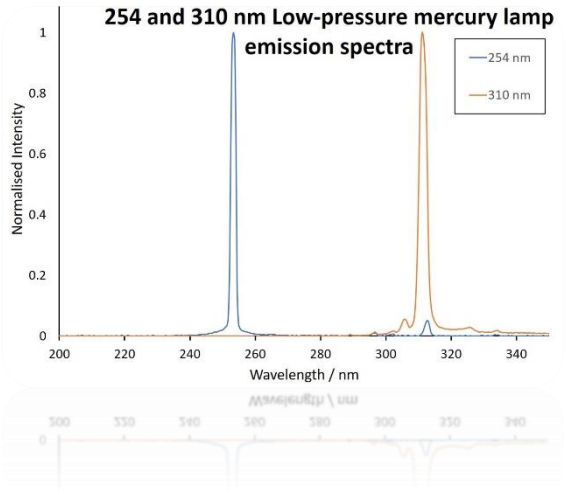

Application Note 62: Synthesis of pharmaceutical intermediate by cross-coupling with non-stabilised diazo compounds

Abstract

After the Ley group, of the University of Cambridge, published a fascinating method of generating non-stabilised diazo compounds using a photochemical method,[1,2] the team at New Path Molecular Research have applied the method to increase the product throughput of the synthesis of a pharmaceutical intermediate, using a newly developed high-power low-pressure mercury lamp.

This application note describes:

- The use of a **28 W** low-pressure mercury lamp at 310 nm
- The effective, **3-fold** increase in product throughput of a pharmaceutical intermediate

For more details, please contact:
application.support@vapourtec.com or call:
+44 (0) 1284 728659

Background

Aryl-alkyl cross coupling reactions represent one of the most important emerging topics in synthesis[3], which linked with hitherto difficult to access highly reactive chemical intermediates[4] represent an exciting area for exploitation by flow chemical methods.

In this application note we illustrate the synthesis of a 4-aryl piperidine, an important pharmaceutical intermediate, based around the seminal contribution of Ley et al[1,2] using a photochemical reaction of the bench stable oxadiazoline to produce the unstable diazonium intermediate. The reaction proceeded simply and safely, producing the desired intermediate in high quantities.

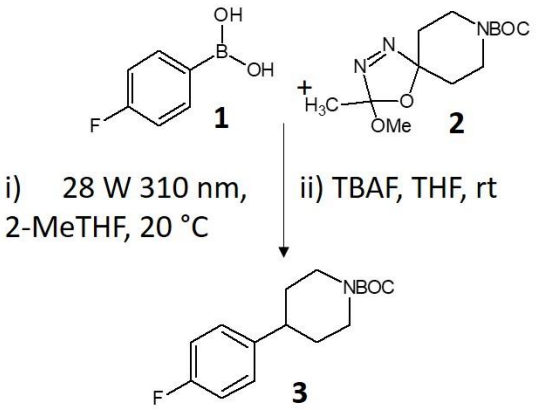

Figure 1: sp^2-sp^3 cross-coupling achieved using a non-stabilised diazo species photochemically generated in-situ from N-Boc piperidine derived oxadiazoline **2**

Setup

All experiments were performed using a Vapourtec R-Series equipped with an R2C+ pump module and UV-150 photochemical reactor with a 310 nm low-pressure mercury lamp. The reactor temperature was maintained at 20 °C using a cooled-gas generator filled with dry ice and supplied with dry air. The reaction is maintained at 100 psi using a 100 psi back-pressure regulator after the reactor. Oxadiazoline (4.0 mmol, 1 equiv.) and boronic acid (4.0 mmol, 1.0 equiv.) were dissolved in 40.0 ml of 2-Methyl THF.

All materials except the oxadiazoline were obtained from commercial suppliers: Fluorochem (boronic acids, tert-butyl 4-oxopiperidine-1-carboxylate, acylhydrazine, (Diacetoxyiodo)benzene and tetrabutylammonium fluoride (TBAF, 1 M in THF)), Acros Organics (toluene, THF and 2-Me-THF) and VWR (MeOH). Oxadiazoline tert-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate was prepared according to the literature.

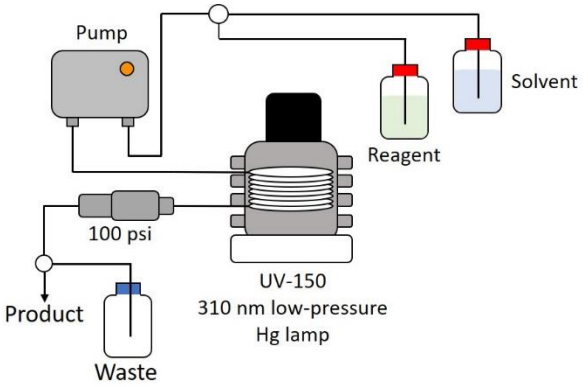

Figure 2: Schematic of the equipment used in this application note. The reagent solution is pumped into a UV-150 photochemical reactor equipped with a 310 nm low-pressure mercury lamp maintained at 20 °C.

Results

In 2017, Prof. Steven Ley and his group at the University of Cambridge collaborated with UCB Biopharma and Pfizer to publish a novel approach to the synthesis of non-stabilised diazo compounds from bench-stable oxadiazoline precursors.[1] A photochemical protocol was used to convert the oxadiazoline to the active diazo species in-situ, and mixed with aryl boronic acids to produce the sp^2-sp^3 cross-coupled product. Taking inspiration from this work, this application note describes the increase in product throughput of the synthesis of an analogous arylated heterocycle, used in the synthesis of the antiviral agent Pibrentasvir, using a continuous flow photochemical reactor equipped with a 28 W 310 nm low-pressure mercury lamp.

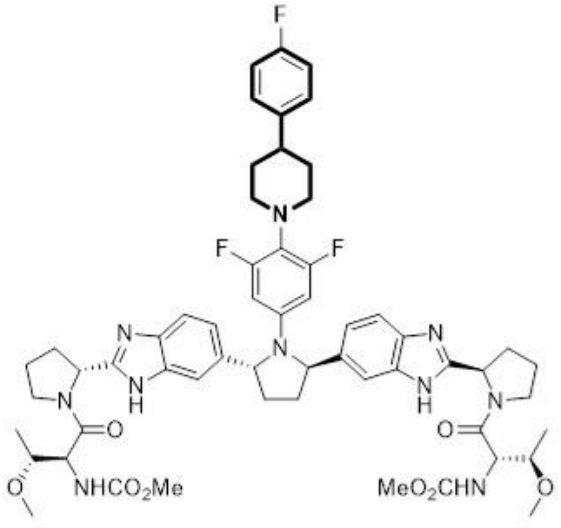

Figure 3: Pibrentasvir with the aryl-heterocycle motif highlighted

For this throughput investigation, the solvent was changed from dichloromethane to the more environmentally benign 2-methyl THF. To increase the throughput of this synthesis, the concentration of the boronic acid was increased from 0.05 M as in the original paper, to 0.1 M. As a result, the reagents were used in a 1:1 ratio, a change which improved the throughput of the reaction and ensured that any diazo compound generated from the oxadiazoline was destroyed before collection; an important consideration for safety when collecting a larger quantity of the reaction output.

The N-Boc piperidine derived oxadiazoline **2** was combined with p-fluorophenyl boronic acid **1** in 2-methyl THF and passed into a UV-150 photochemical reactor equipped with a 10 ml coil and a newly developed Vapourtec 28 W 310 nm low-pressure mercury lamp. This 28 W lamp was used to enable higher throughput than the source used in the original publication (9 W).

By exploiting the higher power output of the low-pressure mercury lamp, it was possible to both increase the concentration of reagent solution, and to also increase the flow rate of the reagents. A flow rate of 0.25 ml/min represents a reduction by half of the residence time within the reactor, greatly increasing the throughput of the synthesis.

The reactor output was collected into a 1.0 M solution of tetrabutylammonium fluoride and stirred to yield the desired phenyl N-Boc piperidine **3**. The solvent was removed under reduced pressure and the residue purified by column chromatography to yield 690 mg (2.5 mmol, 67 %) of the desired product at a rate of 0.95 mmol per hour. This represents a 3-fold increase in product throughput when compared to the literature (0.32 mmol per hour).

Conclusion

The team at New Path Molecular Research have investigated, and successfully increased the product throughput of the synthesis of an intermediate of the antiviral agent Pibrentasvir. Using a newly developed high-power low-pressure mercury lamp with an output wavelength of 310 nm, the team were able to maximise throughput by increasing reagent concentration and reducing the residence time resulting in a significant increase in rate of production of the intermediate. The team at New Path Molecular believe that this approach will prove a highly useful method for producing analogous intermediates, commonly used in a range of different pharmaceutical applications.

Acknowledgements

Vapourtec wish to thank New Path Molecular Research for conducting the experimentation and analysis in this application note.

Analysis

Following isolation, the product was analysed using HPLC and ^{1}H NMR

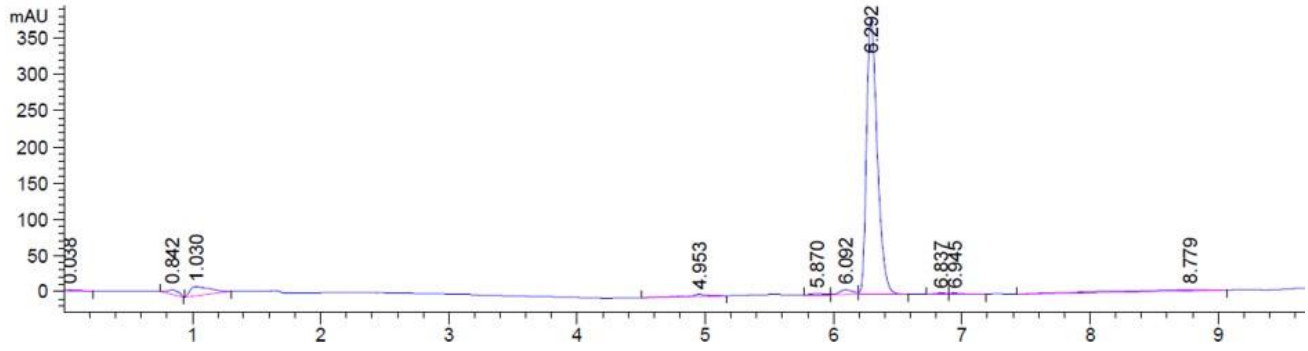

Figure 4: Chromatogram showing the high purity of the isolated pharmaceutical intermediate

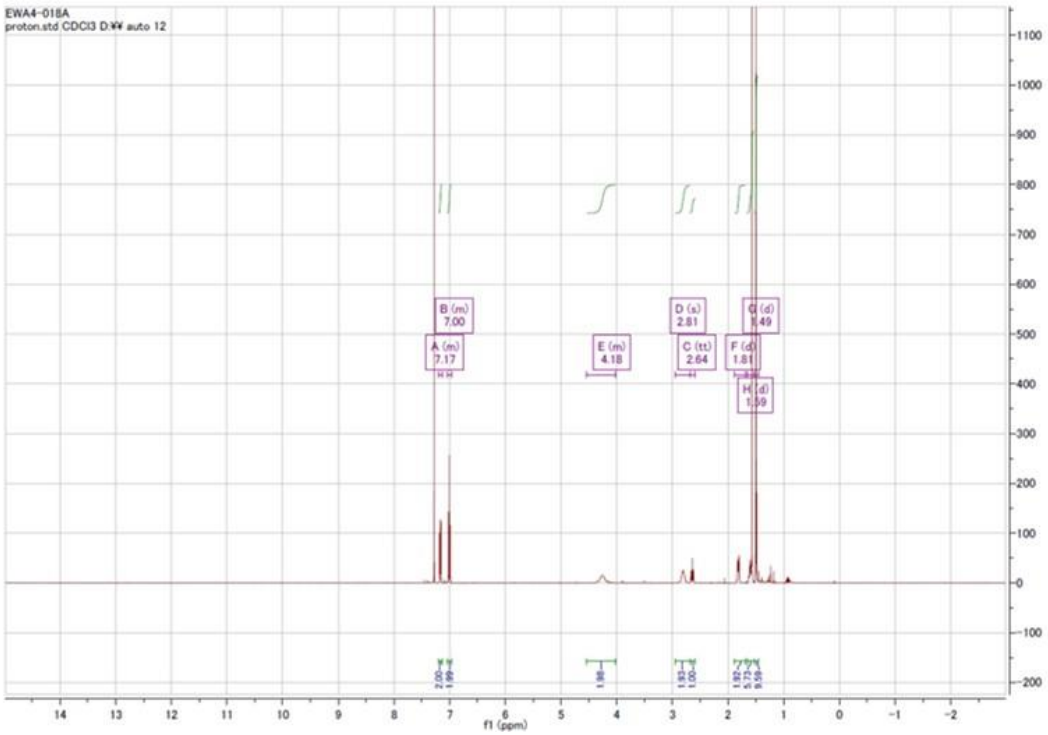

Figure 5: ^{1}H NMR of the isolated pharmaceutical intermediate

References

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4. 2) See, for example, Diazo Compounds Properties and Synthesis, M. Regitz, G. Maas Academic Press, Orlando, **1986**