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Flow Chemistry Highlights

Flow Chemistry Network

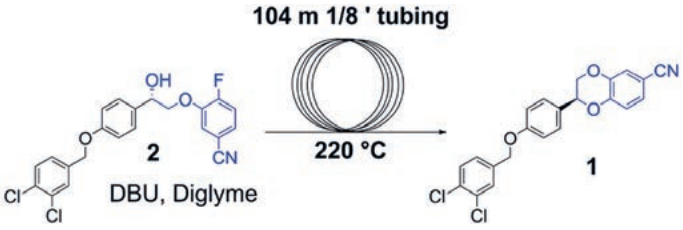
Review of recent literature on flow chemistry. Selected topic: Intensification

Continuous Flow Conditions for High Temperature Formation of a Benzodioxan Pharmaceutical Intermediate: Rapid Scaleup for Early Phase Material Delivery

P. Li, S. Yang, R. Zhu, B. Sun, Z. Li, P. Huang, J. Y. Buser, J. M. Minguez, S. J. Ryan, *Org. Process Res. Dev.* **2020**, *24*, 1938–1947, https://doi.org/10.1021/acs.oprd.9b00499

Enantiopure benzodioxane **1** is a pharmaceutical intermediate, and initial synthesis by high-temperature S_NAr reaction with sodium hydride as reagent highlighted the thermal instability of the product above 140 °C. Flow reactors are convenient tools to access temperatures above the boiling point of the solvents by virtue of installing a back-pressure regulator to pressurize tubular reactors and retain solvents in the liquid-phase. Additionally, the heating and cooling equilibration periods are rapid, and so highly defined time-control at the elevated temperature can be obtained. Processes are thus safely intensified in the sense that material of high quality can be obtained at shortened time-frames.

Small scale flow screening identified DBU as base in diglyme, with temperatures of 220 °C providing the product in highest yield within 30 minutes. For scale-up a hastelloy metal tubular reactor could provide heating and cooling, each within 1 minute, and this was used to process 850 g of compound **2** over an uninterrupted 24 hr process. Product decomposition could be avoided, and 540 g of benzodioxane **1** was obtained in high quality, ready for further processing for preclinical supply.



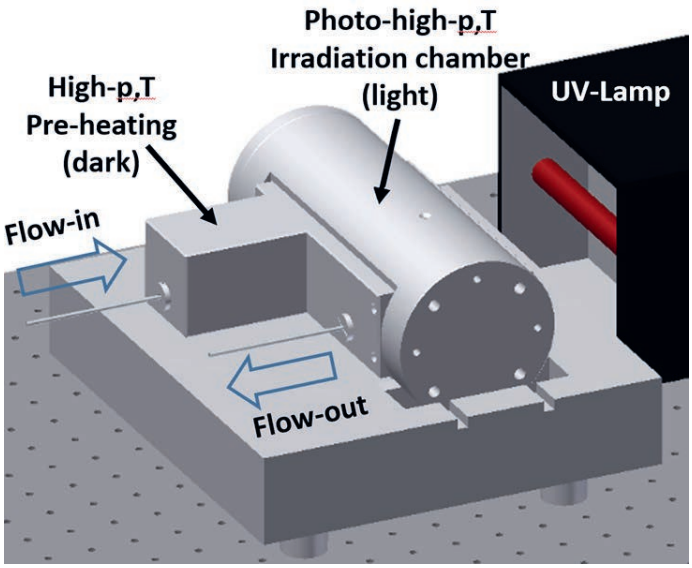
Microflow High-p,T Intensification of Vitamin D3 Synthesis Using an Ultraviolet Lamp

M. Escribà-Gelonch, T. Noël, V. Hessel*, *Org. Process Res. Dev.* **2018**, *22*, 147–155, https://doi.org/10.1021/acs.oprd.7b00318

Flow chemistry offers high potential for process intensification, as good heat- and mass-transfer and small reacting volumes facilitate conditions unachievable in batch, enabling synthesis in so-called 'novel process windows'. In this contribution, the authors benefit from elevated temperature and pressure to perform a one-step UV-assisted synthesis of vitamin D3. As the flow setup is pressurized, the reaction can be performed above the boiling point of the solvent, which significantly reduces the necessary residence time. Furthermore, photochemical transformations benefit from high surface-to-volume ratio of the microreactor setup, which allows efficient irradiation of the reactor volume, in turn facilitating high concentration of the starting material. The synthesis is usually performed in two steps, but with a specially constructed setup it was reduced to one step with simultaneous irradiation and high temperature, simplifying screening for optimal process conditions. As a result, the reaction is performed in just 43 seconds, resulting in 17% yield and 42% conversion. Most importantly, this translates to increased productivity of the vitamin D3 synthesis.

Author's comments*:

"Counter-intuitive thinking is much relevant to explore novel process windows in flow chemistry, which is a field we have started about 15 years ago. Pumping more radiation and heat energy into a flow process might pay off in the total balance of sustainability; even energy-wise."



Would you like to propose a Flow Chemistry Highlight topic here?
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