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Evaluation of a flow-photochemistry platform for the synthesis of compact modules

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ABSTRACT

A custom-made meso-scale continuous flow-photochemistry platform was evaluated with the aim to enable the synthesis of synthetically relevant amounts (>5 g, with the option of 10–100 g) of novel compact modules, whose synthesis is based upon a photochemical transformation. The flow-photochemistry concept relies on the irradiation of thin-layers (20–90 μm) of reactant dissolved in a suitable solvent that is pumped through the single-pass photoreactor. The commercially available Ehrfeld Photoreactor XL system was equipped with standard UV lamps (emission maximum at 254 nm) which are cheap, durable and low in power consumption (8 W). The flow photochemistry system was evaluated using a known intramolecular [2+2] cycloaddition reaction investigating influence of flow rate (irradiation time), layer-thickness and reactant concentration. After a short initial optimisation phase, the system delivered in a first run 6 g of tricycle **4** which was further successfully up-scaled to 48 g, demonstrating the robustness and reliability of this flow photoreactor-platform.

Compact modules have recently received much attention within the pharmaceutical community as they can serve as surrogates for well-established medicinal chemistry scaffolds or building blocks.[1] They usually are low-molecular-weight mono-, bi-, or fused heterocyclic scaffolds which are intended to render the properties of the new molecules in a beneficial way with respect to physico-chemical, metabolic and safety related properties.[2] In addition, they impart versatility in view of shape diversity as well as, due to their novelty, establishing an exclusive IP position.[3]

In the ongoing search for such novel topologies both modern and traditional techniques have been used to provide a quick access to such building blocks. Photochemically induced organic reactions provide a powerful methodology to access complex products often from simple starting materials which are otherwise difficult to obtain.[4] This methodology appears to be somewhat underutilized due to some disadvantages of the traditionally used equipment. Powerful light sources such as high-pressure mercury lamps (or high performance LEDs) are routinely employed to irradiate the reaction mixtures. However, due to the rapid absorption of light in liquids which affect photochemical reactions (irradiation typically at: 200–400 nm) the dimension of the reaction vessels is rather limited. This directly affects the quantity of material which can be efficiently produced in one batch. Using strong light sources not only exposes the substrate to the reaction conditions required for the photochemical reaction, but also the product which itself can undergo undesired side reactions, thereby reducing the yield of the desired product. Further, such high-power light sources produce considerable heat, making it necessary to efficiently cool the reaction vessel. With the advent of flow chemistry[5] the combination of this technology with photochemistry promised to solve some of those issues due to continuous removal of the product from the irradiation zone. By accurate control of the flow rate, the starting material solution is only irradiated as long as necessary to effect the photochemical reaction, a fundamental concept of any flow microreactor system.[6]

An attractive synthesis of a desired new compact module based on a photochemical transformation[7] needs to be reproducible on a multi-gram scale (10–100 g) in order to ensure access to sufficient quantities of the building block for further modification. In the search for a practical and simple protocol to operate a flow-photochemistry platform for large scale laboratory synthesis, a recent report[8] caught our attention. It comments on a single-pass large scale synthesis (∼500 g) of a heterocycle with a traditional water cooled reactor having wrapped around UV transparent tubing through which the reaction solution is pumped at a certain flow rate. The light emitted from a high power UV lamp is used to penetrate the tubing and affect the reaction.[9]

To avoid the use of high-power UV lamps and still embrace the principle of a single pass reactor, the Ehrfeld Photoreactor XL[10] (Fig. 1) was considered as a viable alternative. This reactor is designed as a single pass photoreactor where starting material dissolved in any suitable solvent is pumped through a chamber as a thin film (20–90 μM) at varying flow rates. The chamber is

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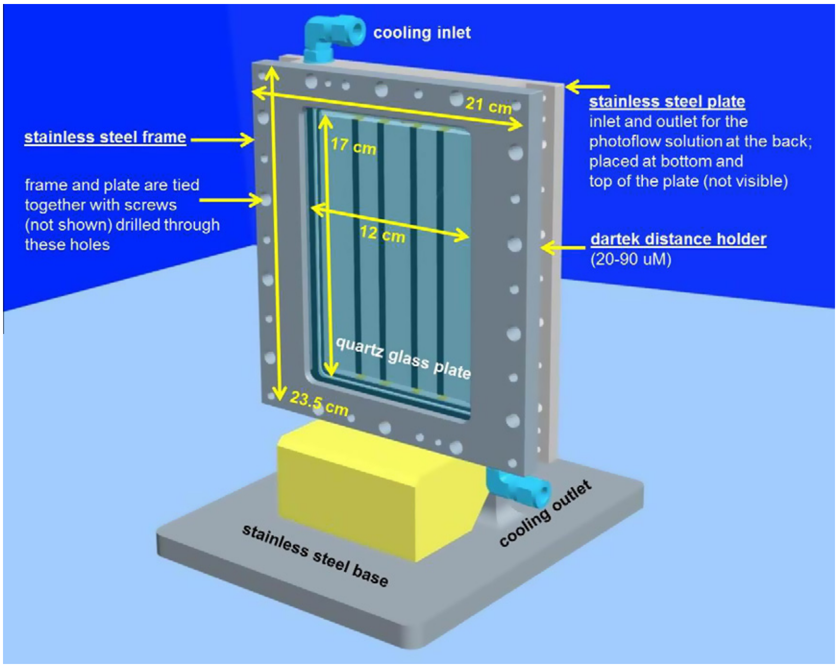

Figure 1. Schematic representation of the Ehrfeld Photoreactor XL using thin-layer technology.

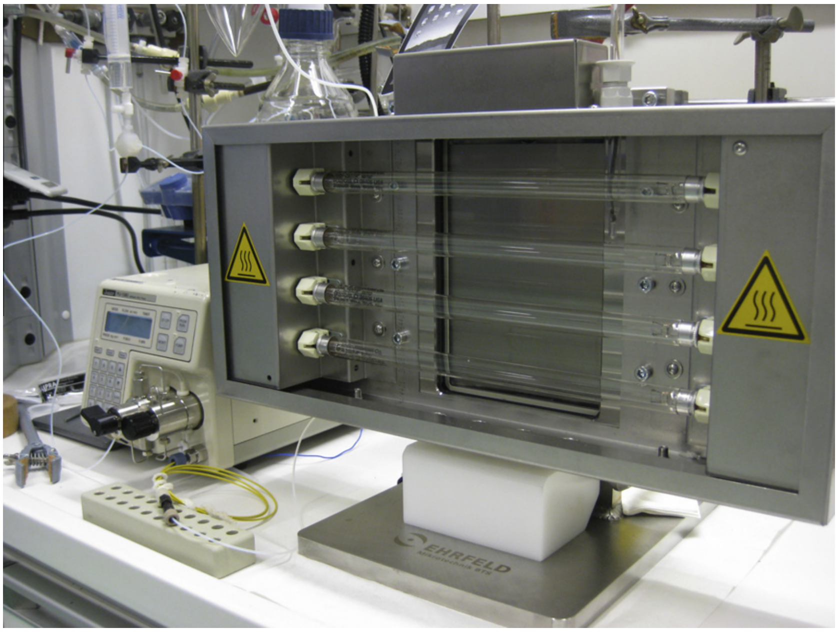

Figure 2. In-house modified Ehrfeld Photoreactor XL equipped with 4 × 254 nm 8 W 30 cm low-pressure mercury arcs.

built from a stainless steel plate and a quartz-glass which are separated from each other by a thin distance holder (20–90 μM; volume of the chamber: 0.41–1.94 mL). According to Lambert–Beer law the intensity of the UV-light to penetrate these thin films should be considerably reduced.

Therefore, the Ehrfeld Photoreactor XL was adapted in-house with 4 conventional 254 nm 8 W 30 cm low-pressure mercury arcs, commonly used as TLC light bulbs[11] (flexibly exchangeable with 302 or 356 nm) placing them at a distance of 4 cm in front of the quartz glass plate (Fig. 2), optionally covered with an aluminium lid. These light bulbs are in-expensive, work reliably with the same intensity of light for multiple 1000 h time periods and are easy to exchange for any reason (damage, use of different wavelengths or combination of different wave-lengths to affect orthogonal organic photochemistry in the same reactor).

To establish the versatility and reliability of this photo-flow platform for the synthesis of new chemical modules a prototypical intramolecular [2+2] cycloaddtion[12] to form a cyclobutane derivative was chosen. The formation of bicyclo[3.2.0]heptane **4** from cyclopentenone **3** in its' achiral version was studied. The chiral version of this particular reaction is described in a batch mode process at 254 nm with 97 mg (60%) isolated yield. Our process started with the isomerisation of furfuryl alcohol **1** to the respective cyclopentenone derivative **2** under basic conditions in varying yields.[13]