Making APIs and fine chemicals with light

BIOMATERIALS & NANOMATERIALS

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KEYWORDS: API, fine chemicals, photochemistry.

"The main barrier to using photochemistry is the fear of photochemistry itself", (1) commented Booker-Milburn five years after introducing the FEP photoreactor that opened the route to the practically feasible photocatalytic synthesis of fine chemicals (2).

Very few industrial synthetic processes are based on visible light photochemical processes including the low-cost synthesis of rose oxide, (3) and the production of the anthelmintic drug ascaridole via solar irradiation of alpha-terpinene carried out since 1943 (4). Even more, the high cost of light due to the poor efficiency of most electric light sources (until the advent of LEDs in the early 2000s) discouraged chemical companies from introducing light photons as chemical reagents, no matter how clean they could be (5).

The fundamental limitation to synthetic organic photochemistry, indeed, resides in the logarithmic law governing light penetration in solution, thanks to which very little light is available beyond a very short path length off the lamp irradiating the solution. For example, in a 0.05 M solution of a compound with modest extinction coefficient, 90% of the incident light is absorbed from the first 1 mm solution layer around the lamp.

The practical consequence for photochemical reaction in batch reactors typically driven by an immersed lamp was the need for over-irradiation and prolonged reaction times that, coupled to poor heat/mass transfer rates in large volume reactors, usually led to poor yields and selectivities. This obsolescence, we have recently argued along with Xu, (6) will shortly be ended by the new advantages offered by continuous flow photochemistry.
The first breakthrough occurred in 2005 when academic and industrial researchers devised a simple new photoreactor to carry out photochemistry under flow consisting of a flow reactor comprised of an UV-transparent and solvent resistant fluoropolymer (FEP, fluorinated ethylene propylene copolymer) tubing wrapped around a UV lamp.

The new continuous flow photochemical reactor solved the two main problems of old photocatalysis in batch, ensuring an high photon flux within the reaction volume and little or no flux in nonirradiated volumes, overcoming the light penetration issue mentioned above as the thickness of the irradiated fluid is often <1.5 mm. Furthermore, continuous product removal due to the continuous nature of the reactor

SCALABLE AND CLEAN SYNTHESIS OF METHIONINE SULFOXIDE

One eminent recent example of waste-free, chemoselective and safe synthesis of high relevance for fine chemical manufacturers, is the singlet oxygen ($^1O_2$) oxidation of methionine to methionine sulfoxide in water developed by academic and industrial researchers (12).

Using the Corning flow G1 photoreactor, the team out-scaled the best conditions for the catalytic photooxidation of methionine to methionine sulfoxide (Figure 1) with singlet oxygen formed *in situ* thanks to the photochemical reaction between Rose Bengal (0.1 mol %) and a slight excess of oxygen (1.1 equiv of O_2) at room temperature and with a residence time of 1.4 min only, under white light irradiation (4000K). These conditions allowed to process more than 70 mL min^{-1} (31.1 mol or 5.1 kg day^{-1} productivity). Using the G3 version of the same reactor with similar process conditions would increase the productivity up to 6 tonnes y^{-1}.

The use of static mixers along the reactor path ensured fast oxidation rates regardless of the modest oxygen solubility in water, avoiding the need of a large excess of oxygen typical of previously reported photooxidations in water. The same conditions indeed were found amenable to the conversion of other substrates affording valued fine chemicals.

prevents secondary reactions which are a known issue with most photochemical conversions.

Likewise to continuous flow reactors, being scale-independent, the need for expensive (and hazardous) bigger lamps when scaling up the photochemical reaction is prevented.

In the course of the subsequent decade, quick and concomitant technological progress in LED lighting and microfluidic reactors led to widespread adoption of the new coninuous approach introduced in 2005, making the synthesis of active pharmaceutical ingredients (APIs) and fine chemicals using continuous flow photochemistry a fully viable option also for industry.

A first progress was the introduction of a commercial version of the FEP reactor (7). Almost concomitantly, Booker-Milburn and co-workers introduced a new flow reactor (Firefly) consisting of a succession of quartz tubes in parallel connected together, which turns out to be 30% more power efficient than the FEP reactor and, above all, affords a 10-fold reduction in reaction times, with productivities of 1, 4 and 8 kg of product in 24 h, though using UV light (8)

An eminent application of photochemistry to APIs synthesis was reported in 2012 by Seeberger and Lévesque who developed a continuous-flow photochemical route to the anti-malaria drug artemisinin based on singlet oxygen ($^1O_2$) formed *in situ* with light in the presence of a sensitizer that converts dihydroartemisinic acid into artemisinin (9).

Three years later chemists at a large pharmaceutical company along with academic scholars in the UK and in Germany, applied the green chemistry principles to the same synthesis using and immobilized photosensitizer and a mixture of solvents, further reducing the cost of the process (10). Numerous other pharmaceutical and fine chemical companies today use photoredox syntheses for making APIs and other valued functional molecules. Suppliers of chemical reactors are starting to offer the first photoreaction systems, and most flow chemistry companies offer photochemical microreactors suitable for a wide variety of photoredox reactions.

Merging knowledge and skills in nanochemistry, photochemistry, flow chemistry, chemical engineering, and even LED lighting, interdisciplinary teams now regularly report new commercial photochemical syntheses in all main organic chemistry and chemical engineering journals. As recently put it by König "we should have followed up much earlier on the initial ideas of Giacomo Ciamician for innovative and sustainable organic synthesis using visible light" (11).

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