Organic Process Research & Development **2002**, *6,* 187–189

A Microfabricated Nanoreactor for Safe, Continuous Generation and Use of Singlet Oxygen

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Abstract:

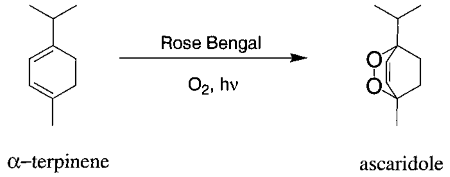
Singlet oxygen was effectively and safely generated in a nanoscale reactor and used for the synthesis of ascaridole. The technique allows for the generation of singlet oxygen without the inherent dangers of large quantities of oxygenated solvents. The methodology allows for facile scale-out of the process.

Introduction

The use of photosensitisers to effect the singlet oxygen oxidation of terpenes and conjugated dienes has a long history, particularly in the perfume industry.[1] Despite the utility of the functionality introduced by this transformation there are inherent difficulties in adapting the process for large-scale production. These include the difficulty of introducing adequate intensities of the required wavelength of light into the reactor and achieving sufficient oxygen saturation. The challenge for the process chemist in achieving adequate illumination is made more difficult by the strong absorption of sensitiser dyes. This leads to a shortened effective path length even under quite powerful irradiation and also the formation of dimers and higher aggregates, many of which are insoluble.[2] Furthermore, the use of tungsten lamps or sunlight in this regard brings with it difficulties for scale-up and unwanted sample heating, necessitating the use of collimators or refrigeration. The explosive nature of oxygenated organic liquids[3] is well-known and can lead to significant health and safety issues.[4] Even aerated organic solvents can be extraordinarily hazardous on a laboratory scale and more so on an industrial scale. Recent developments in this area have addressed the problem of adequate illumination but still leave the safety issues associated with large quantities of oxygenated organic solvents unsolved. For example, most "small tube" flow devices involve recirculating feedstock from a large reservoir through an illuminated tube, leaving large quantities of aerated solvents in reservoir.[5] Yields for this type of synthesis are as high as 90% for terpene oxidation, but the problems posed by accidental pipe rupture are still of concern.

The application of nanoreactor technology to address difficulties in synthetic chemistry is an area of increasing interest to the chemical community.[6] The term "nanoreactor" denotes reactors with an instantaneous reaction volume most conveniently measured in nanolitres. Because of increased efficiencies of mixing and separation combined with high rates of thermal and mass transfer, nanoreactors are ideal for processing valuable or hazardous reaction components and in many instances for improving reaction selectivities.[7] Moreover, the low-Reynolds-number environments encountered within most nanofluidic devices afford a high degree of control over processes performed in continuous-flow formats.[7] Importantly, continuous-flow alternatives to traditional batch processes can be scaled with facility by the use of a multiparallel (or scale-out) approach.[6]

Scheme 1. **Singlet oxygen addition to α-terpinene**



Motivated by these advantages, we describe herein the application of nanoreactor technology to the safe, efficient, continuous-flow synthesis of ascaridole from α-terpinene, as shown in Scheme 1. Miniaturising the reactor footprint takes advantage of the small length scales and high surface-to-volume ratios of microfabricated devices, and since the microfluidic channels fabricated are approximately 50 μm deep, radiation can easily penetrate through the entirety of the reaction environment. Importantly, the technique allows for the generation of singlet oxygen without the inherent dangers of large quantities of oxygenated solvents.

Nanoreactor Fabrication

The glass microchip (footprint 5 cm × 2 cm) was made in-house using direct-write laser lithography, wet chemical etching and bonding techniques as previously described.[8] Briefly, a positive photoresist (S 1818, Shipley Corporation, Whitehall, PA) was spun onto the surface of a glass substrate, and the channel design transferred to the substrate into the photoresist using a DWL system (DWL2.0, Heidelberg Instruments, Heidelberg, Germany). After the photoresist was developed (Microposit 351, Shipley Europe Ltd, Coventry, UK), the channels were etched into the glass substrate using a buffered oxide etching solution (HF/NH_4F). A glass cover

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10.1021/op0155155 CCC: $22.00

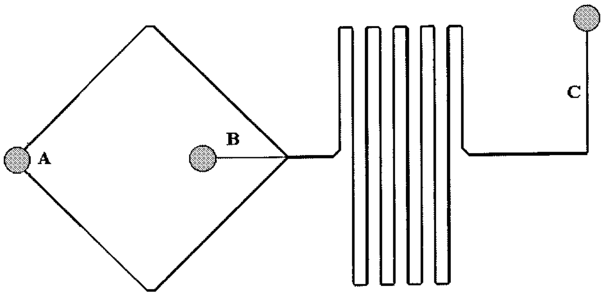

Figure 1. **Schematic of reactor chip for singlet oxygen reactions.**

plate, with holes drilled for external access, was cleaned in H_2SO_4/H_2O_2 and aligned before contact with the etched glass substrate. To form enclosed channels, the plates were thermally bonded in an oven.

The reactor channel pattern is schematically described in Figure 1. The chip consists of a divergent inlet channel (A), a secondary inlet channel (B), a serpentine irradiation sector, and an outlet channel (C). The etched channels have an average depth of 50 μm and an average width of 150 μm. The serpentine section has a total length of 50 mm.

Results and Discussion

Under the reaction conditions optimised for the reactor chip no presaturation of the α-terpinene solution with oxygen was necessary, meaning that at any given instant the total volume of oxygenated solvent could be measured in picolitres. This small volume of oxygenated solvent present at any one time minimises the risks involved in the synthesis. Furthermore, nitrogen degassing of chip effluent can be undertaken as soon as the effluent is collected, to avoid accumulation of oxygenated solvents or the elevation of oxygen saturation in the reactor surroundings.

To effect the synthesis of ascaridole from α-terpinene the delay section was irradiated using an unfiltered, 20-W, 6-V overhead tungsten lamp on an inverted microscope stage (Leica DMIL, Milton Keynes, UK). A solution of sensitiser dye and terpinene in methanol was introduced through A, and a stream of oxygen was introduced through B. The effluent was collected at C and worked up by diluting 10:1 with diethyl ether, passing through a silica plug, and evaporating off the excess solvent with a stream of nitrogen. Transformation was monitored using capillary gas chromatography (GC), utilising a HP Innowax stationary phase. GC samples were introduced using an autosampler and a HP 68190 autoinjector array to avoid operator errors. Samples were compared to a sample of ascaridole prepared by standard methods that had been characterised by spectral comparison to literature data.[9] Samples thus prepared coran in GC analysis with chip-produced products. Crude material from the microchip effluent was submitted to NMR analysis and demonstrated ascaridole present as the majority product.

In common with laboratory-scale procedures pure oxygen and a relatively concentrated sensitiser solution were chosen for use. It should be noted that oxygen and air are considered interchangeable for many (although not all) singlet oxygen preparations, although an adjustment in flow rate would have to be made to compensate for the lower partial pressure of oxygen in air. Rose Bengal is readily recyclable, so that relatively high concentrations of sensitiser are not necessarily a cost issue. Furthermore, since the effective optical path length is 50 μm, a high sensitiser concentration does not pose any experimental problems. The molar extinction coefficient of Rose Bengal in methanol is 99 800 cm^{-1} M^{-1} at 550 nm. Despite this high value a concentration of 5×10^{-3} M Rose Bengal yields a total absorbance of 0.025 (equating to a transmittance of approximately 95%). This means that molecules at any position within the irradiation zone will experience a broadly similar photon flux. Consequently, the use of a microfabricated reactor actually facilitates the use of high sensitiser concentrations, which is desirable in most circumstances.

In addition, it should be noted that the small cross section of the reactor channels results in effective irradiation even from relatively low-intensity light sources. This leads to reduced sample heating and therefore reduced radical recombination. Efficient transformation ($>$80% conversion of feedstock by GC area analysis as described) can be achieved with an irradiation (reaction) time of less than 5 s. Figure 2 shows typical GC traces of the chip feedstock solution and the chip product after work-up. Although the method of analysis is crude, the identification of the product peak by separately synthesised authentic ascaridole renders it less ambiguous.

It is likely than the majority of microfluidic devices will eventually be structured from polymeric materials (rather than silicon or glass) due to the wide availability of base materials, commercial chip manufacturers, and highly cost-effective fabrication methods (such as injection molding and hot-embossing). This means that the reactor chips described herein may be "printed" and bonded *en masse* at low unit cost.[10] Furthermore, since light can penetrate the substrate material from any direction and the chips function perfectly in any orientation, large arrays of chips can be linked together to form three-dimensional structures surrounding light sources. Altering the size of the serpentine section will also allow for faster flow rates with similar irradiation times.

In conclusion the use of a microfabricated nanoreactor to effect the safe, continuous generation and reaction of singlet oxygen has been demonstrated. The technique avoids the major dangers inherent in the method and allows for reliable reaction even with relatively low-intensity light sources.

Experimental Section

Reagents and solvents were obtained from commercial sources and used as received.

Continuous Flow Synthesis of Ascaridole. A solution of α-terpinene (85%, 0.6 mL) and Rose Bengal (certified, 0.1 g) in methanol (20 mL) was prepared. This solution was introduced into inlet A of the reactor chip at a flow rate of

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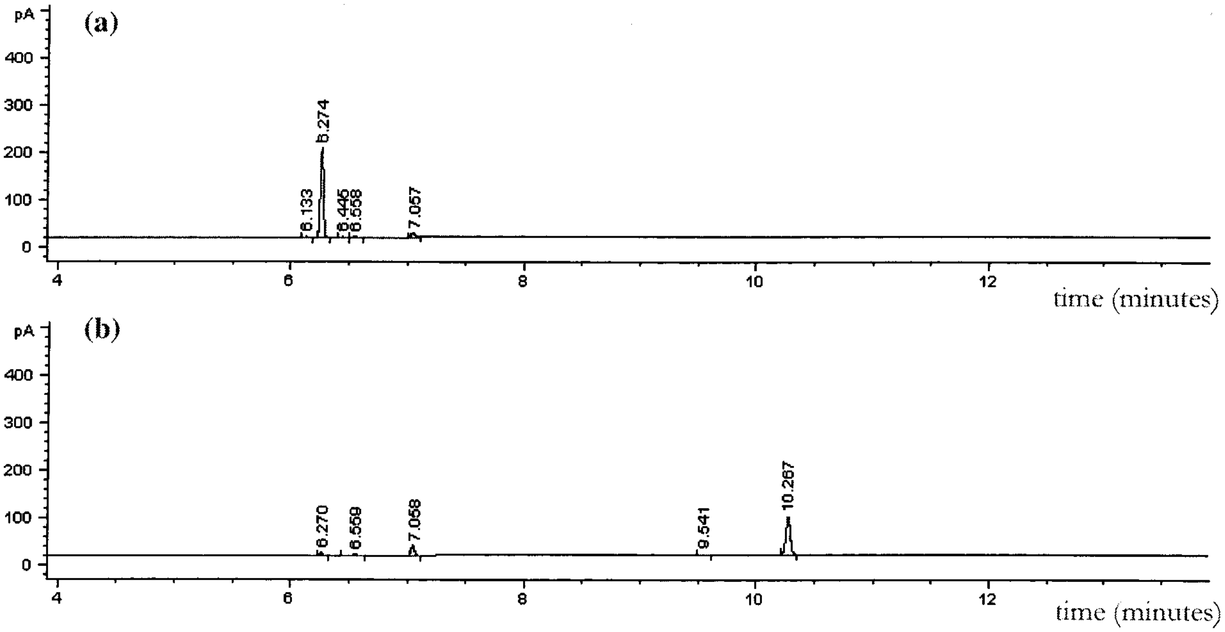

Figure 2. **GC traces of (a) chip feedstock solution, (b) chip effluent.**

1 μL/min. Pure oxygen was introduced into inlet B of the reactor chip at a flow rate of 15 μL/min. Both were introduced using a Hamilton PHD 2000 syringe pump. The serpentine section of the chip was irradiated at full power using the microscope overhead lamp as described at a distance of 10 cm from the reactor surface and the product collected in a brown glass vial. The product was diluted 10:1 with diethyl ether and passed through a short silica plug, and the solvent was evaporated using a nitrogen stream. The product was analysed by GC giving a conversion by area analysis of 85%, and a crude NMR spectrum was obtained.

Laboratory Synthesis of Ascaridole. α-Terpinene (1 mL), Rose Bengal (0.2 g), and methanol (40 mL) were combined in a 100-mL round-bottomed flask fitted for reflux. Oxygen was bubbled through the mixture for 5 min and then the flask was illuminated with a 500-W tungsten lamp at a distance of 20 cm from the flask. Illumination and oxygenation were continued for 4 h. The mixture was evaporated, and then the residue was dissolved in diethyl ether (20 mL) and filtered through a short silica plug. The resulting solution was concentrated and purified by flash chromatography on silica (hexane eluent, $R_f = 0.65$) giving ascaridole (0.7 g, 67%).

NMR	(Bruker 250 MHz) δ 0.99 (6H, d, $J = 6$ Hz), 1.37 (3H, s), 1.49−1.56 (2H, m), 2.01 (1H, hept, $J = 6$ Hz), 2.02−2.05 (2H, m), 6.41 (1H, d, $J = 8$ Hz), 6.49 (1H, d, $J = 8$ Hz) ppm.
MS	(C. I. Ammonia) *m/z* 186 (MNH_4^+), 169 (MH^+) 152, 135, 121, 109, 93
GC	HP Innowax capillary GC column, 30 m in length. Helium carrier gas operating at a flow rate of 1.3 mL/min *inlet temperature*: 300 °C *column temperature*: 60 °C, maintained for 3 min, then ramped at 40 °C/min to a maximum of 230 °C, maintained for 10 min *retention times*: α-terpinene 6.30 min, ascaridole 10.26 min

Acknowledgment

We thank EPSRC UK, the Department of Trade and Industry (DTI), Lab-on-a-Chip Consortium for financial support. R.F. is grateful to SmithKlineBeecham Pharmaceuticals for an EPSRC CASE studentship.

Supporting Information Available

NMR and MS spectra for ascaridole (bulk method), crude NMR for ascaridole (continuous synthesis). This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review November 1, 2001.

OP0155155