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Scalable Photocatalytic Oxidation of Methionine under Continuous-Flow Conditions

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ABSTRACT

Highly efficient and chemoselective singlet oxygen oxidation of unprotected methionine was performed in water using a continuous mesofluidic reactor. Sustainable process engineering and conditions were combined to maximize process efficiency and atom-economy, with virtually no waste generation and safe operating conditions. Three water soluble metal-free photosensitizers (Rose Bengal, Methylene Blue, and tetrakis(4-carboxyphenyl)porphyrin) were assessed. The best results were obtained with Rose Bengal (0.1 mol%) at room temperature under white light irradiation and a slight excess of oxygen. Process and reaction parameters were monitored in real-time with in-line NMR. Other classical organic substrates (α -terpinene and citronellol) were oxidized under similar conditions with excellent performances.

KEYWORDS

Singlet oxygen, Continuous-flow process, Photooxidation, Metal-free photosensitizer, Sustainable conditions

INTRODUCTION

Oxidation reactions are one of the most ubiquitous chemical transformations in living matter and chemical labs, and a huge palette of oxidizers, *i.e.* chemicals prone to extract electrons from other substrates, are available to the chemist.¹ In the context of developing more sustainable chemical processes, molecular oxygen is most likely the cheapest, the most widely available and greenest oxidant. Oxidation reactions using ground state triplet oxygen $[X^{3}\Sigma_{g}]$ often require high pressure and/or coordination complexes, increasing safety and environmental concerns at larger scale.² Compared to triplet oxygen, singlet oxygen $[a^{1}\Delta_{g}]$ shows a much higher reactivity that usually alleviates the use of drastic process conditions, but, on the downside, that could also

trigger a variety of side reactions if not tamed appropriately. Singlet oxygen is conveniently generated via an energy transfer to triplet oxygen from catalytic metal-free or metal-based photosensitizers (PS) upon exposure to UV or visible light. The association of light (in particular visible light), a widely accessible and environmentally benign gas, a catalyst and mild process conditions is setting essential foundations whereupon sustainable and green oxidation processes can be designed.^{3,4} However, the inherent limitations of catalytic photosensitized oxidations, *i.e.* light penetration in macroscopic reaction media, gas-liquid mass transfer, solubility of oxygen in solution and the transient nature of singlet oxygen, impose long irradiation/reaction times, consequent energy input for active mixing, large excess of oxygen, and the use of noxious solvents or additives, hence challenging process sustainability and efficiency.^{3,5} Photochemistry in continuous-flow microreactors is now widely recognized as an enabling combination,⁶⁻⁹ providing major process assets arising from a much improved light penetration and accurate control of irradiation time, high mass and heat transfer, safe and efficient handling of transient species, and seamless scalability. Many organic substrates have been successfully oxidized with singlet oxygen in microfluidic devices.^{6,10–14} For instance, Alemán *et al.* reported a microfluidic procedure utilizing Pt(II) coordination complexes for the visible light photooxidation of various sulfides.¹⁰

Sulfoxides are found in many natural products¹⁵ and are important organic building blocks with tremendous applications in organic synthesis, pharmaceutical sciences, biochemistry and material sciences.^{16,17} Sulfoxides are traditionally obtained from the oxidation of sulfides with peroxides,¹⁸ peracids¹⁹ or periodates,²⁰ with optionally metal catalysts,²¹ but these methods suffer from a high risk of overoxidation to sulfones.²² The recent developments in catalytic photosensitized oxidations have led to robust and chemoselective oxidation procedures, either in

batch,^{3,10} or in microfluidic devices.^{10,23} Methionine sulfoxide **2a** (Figure 1), *i.e.* the sulfoxide of essential amino acid methionine (**1a**) has attracted considerable attention over the last few years.^{17,24–26} It has numerous applications in studying the pathogenesis of neurodegenerative diseases,^{27,28} cell aging and oxidative stress,²⁹ peptide sciences,^{30–32} material sciences,^{33,34} and in organic synthesis.^{35,36} To date, only one report described the catalytic photooxidation of **1a** methyl ester in D₂O using a microfluidic setup in the presence of supported [60]fullerene PS.²³ This process took advantage of ¹O₂ longer lifetime and faster oxidation kinetics in deuterated solvents,²⁶ with a quantitative conversion in 33 s residence time. The output remained, however, at a slender 0.5 mmol d⁻¹ scale.

In this communication, we report for the first time the development of a scalable continuousflow strategy for the photocatalytic oxidation of methionine **1a** towards methionine sulfoxide **2a** under mild, chemoselective, atom-economic, safe and sustainable process conditions (Figure 1). The best results (1 mol day⁻¹) were obtained with an extremely low loading of Rose Bengal (0.1 mol%) as photocatalyst, at room temperature under white light irradiation (4000K) and a slight excess of oxygen (1.1 equiv.). This was enabled by innovative reactor design combining high mixing and irradiation efficiencies. Other classical organic substrates such as α -terpinene **1b** and citronellol **1c** were oxidized under similar conditions with excellent performances (Figure 1).



Figure 1. (L)-methionine (1a), α -terpinene (1b) and citronellol (1c) and the corresponding catalytic photooxidation products (2a-c') (see Supporting Information for details).

EXPERIMENTAL SECTION

Continuous-flow setup

The continuous-flow setup (Figure 2) involved a compact commercial glass mesofluidic module (Corning[®] Lab ReactorTM, 155 x 125 mm size, 400 μ m I.D. reaction path, 2.6 mL internal volume) integrated with static mixers and sandwiched in a high capacity heat-exchanger (2 layers, 22 mL, 1 W mL⁻¹K⁻¹). The integrated static mixers were designed to optimize multiphase mass transfer.^{37,38} LED panels were mounted on both sides of the fluidic module (40 mm from the center of the reaction path). Each LED panel was equipped with multiple wavelengths (20 LEDs for each wavelength) and a heat exchanger (T = 10 °C). The continuous-flow reactor was alimented in aqueous **1a** through a FLOM[®] HPLC pump (0.01 – 100 mL min⁻¹) and with industrial grade oxygen (99.99%, ALPHAGAZ 1, Air Liquide) through a Bronkhorst[®] mass flow controller (MFC). A Zaiput Flow Technologies[®] dome-type back-pressure regulator (BPR) was inserted downstream (set point: 8 barg). Analysis of the reactor effluent was carried out by in-and off-line NMR (Supporting Information).

Feed preparation

The feed solutions of **1a-c** were prepared in D.I. water or in methanol containing 0.1 mol% of PS, and stored in brown bottles.

Typical Run

The HPLC pump used to deliver the aqueous solution of **1a** (0.3 M) and **RB** (0.1 mol%) was set to 1 mL min⁻¹ and the oxygen flow was set to 7.5 mL_N min⁻¹ with the MFC, and both fluids were

conveyed to the continuous-flow photoreactor through perfluoroalkoxyalkane (PFA) tubing (1/8" O.D.). Mixing and irradiation (white LED, 100% intensity) occurred along the entire reaction channel (2.6 mL internal volume, 1.4 min residence time) under 8 barg of pressure. Conversion: >99%; selectivity: >99%; Output: 132 g day⁻¹.



Figure 2. Continuous-flow setup for the catalyzed photooxidation of **1a**. The fluidic module and the LED panels are integrated with heat exchangers (omitted for clarity).

RESULTS AND DISCUSSION

Water-soluble metal-free Rose Bengal (**RB**), Methylene Blue (**MB**), and tetrakis(4carboxyphenyl)porphyrin (**TCPP**) sensitizing dyes were selected for dye-sensitized generation of singlet oxygen.³⁸ These PS are harmless, widely available and can be photodegraded as an additional post-reaction treatment.^{39,40} Two competitive mechanisms are generally accepted for photocatalytic oxidations of organic substrates: (a) an oxidative process involving the unique reactivity of singlet oxygen via an energy transfer and (b) an oxidative process involving radical intermediates such as the superoxide radical anion.^{10,26} The prevalence of the singlet oxygen or the radical mechanism essentially depends on the PS and on the reaction medium.^{10,26,41} In the case of sulfides, both mechanisms result in the formation of sulfoxides.⁴¹ Preliminary experiments were designed to set the boundary conditions for the PS effective concentration (0.1 mol%) and oxygen excess to ensure total conversion within short reaction times (Supporting Information). Controlled experiments were run in the absence of light, PS or oxygen, and **2a** was not detected in the reactor effluent. The reaction temperature had no notable effect on the conversion, and the temperature was set at 20 °C for all experiments. The concentration in **1a** of the feed solution had a significant impact on the reaction: at saturation (0.3 M), completion was obtained within a residence time of 1.4 min, while at lower concentrations, the residence time to reach completion dropped to 0.6 min (0.1 M), with 0.1 mol% PS and a 1.1:1 O₂/**1a** ratio (Table 1). Upon optimization, the O₂/**1a** ratio was decreased from 12.9 to 1.1, still affording complete conversion in 1.4 min residence time. The oxygen excess (equiv.) was thus successfully reduced from 3.8 to 0.1. The best set of conditions involved a liquid flow of 1 mL min⁻¹ and a gas flow of 7.5 mL_N min⁻¹ of oxygen, corresponding to an estimated residence time of 1.4 min. The consumption of oxygen could be visually monitored through the glass continuous-flow reactor.

The light intensity had a profound impact on the conversion (Table 1). With white light LEDs (4000K) and in the presence of **RB** ($\lambda_{max} = 550$ nm), the conversion was still complete with 80% intensity, and then dropped to 54% with 20% intensity. The lower conversion observed at lower irradiation intensity reflects the lower amount of singlet oxygen available in the system. Changing white LEDs to monochromatic LEDs affected more severely the conversion with 4% at 622 nm, and 63% at 385 nm, although complete conversion was obtained with blue (405 nm) LEDs under the same conditions (Table 1).

Table 1. Optimization of the photocatalytic oxidation of **1a** under continuous-flow conditions in

 the presence of Rose Bengal

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Entry	[1a] (M)	Feed 1 (mL min ⁻¹)	Feed 2 (mL _N min ⁻¹)	T (°C)	Res. time (min)	LEDs (intensity)	Conv. (%)
1	0.1	2.5	15	rt	0.6	White (100%)	quant.
2	0.2	1.5	7.5	rt	1	White (100%)	quant.
3	0.3	1	7.5	rt	1.4	White (100%)	quant.
4	0.1	2.5	15	10	0.6	White (100%)	quant.
5	0.1	2.5	15	50	0.6	White (100%)	quant.
6	0.2	1.5	7.5	rt	1	White (50%)	89
7	0.2	1.5	7.5	rt	1	White (20%)	54
8	0.3	1	7.5	rt	1.4	622 nm (100%)	4
9	0.3	1	7.5	rt	1.4	385 nm (100%)	63
10	0.3	1	7.5	rt	1.4	405 nm (100%)	quant.

The nature of the photosensitizer had also a profound impact on the oxidation efficiency. Stock solutions were prepared with **MB** and **TCPP** (0.1 mol% each), and handled as described above. The optimal conditions for the photooxidation of **1a** with **RB** (1.4 min residence time, 1.1 equiv. O_2 , room temperature, white LEDs) only led to partial conversion when the photooxidation was carried out with **MB** ($\lambda_{max} = 610 \text{ nm}$)⁴² as photocatalyst. Shifting to orange LEDs (622 nm) increased the conversion, but the optimum required a larger excess of oxygen (1.5 equiv.). The light intensity also impacted the conversion (Supporting Information). At 80 and 50% intensity, the conversion dropped to 91 and 65%, respectively. Changing the LEDs to 385 nm expectantly reduced the conversion (13%). **TCPP** ($\lambda_{max} = 405 \text{ nm}$)⁴³ performed even less under white light irradiation, with a mere 25% conversion under the optimized conditions with white LEDs. Adjusting the wavelength to 405 nm together with an increase of the residence time to 1.4 min and 1.5 equivalent of oxygen led to full conversion. Decreasing light intensity also led to lower conversions (88% conversion at 50% intensity), similarly to **RB**.

These results emphasized **RB** as a superior sensitizer for the photooxidation of **1a** under sustainable process conditions.³ Various production campaigns (8 h runs) emphasized stable reactor operation and provided consistent results. Decompression after the BPR released the

excess oxygen. Downstream treatment of reactor effluents included the filtration of the solution on activated charcoal to remove the PS, concentration of the solution and antisolvent recrystallization (slow addition of *i*-PrOH), giving **2a** in 79% isolated yield (99% purity).

Similar conditions were amenable to other organic substrates (Figure 1 and Supporting information). In particular, α -terpinene (**1b**) and citronellol (**1c**) are very common model organic substrates for assessing photocatalytic singlet oxygen process efficiency.^{27,44} For solubility reasons, methanol was utilized for these trials. Feed solutions of **1b** with concentrations of up to 1 M were submitted to photocatalytic oxidation using white light and a slightly larger excess of oxygen (1.4 equiv.). Total conversion was observed with 2.2 min of residence time, with no detectable traces of *p*-cymene, giving a productivity of up to 273 g d⁻¹ (1.6 mol d⁻¹). Quantitative photocatalytic oxidation of **1c** (0.1 M) was obtained within 1 min residence time with 3 equiv. of oxygen, yielding a 3:2 ratio of peroxides **2c,c'** (Supporting Information).

Out-scaling the best conditions for the catalytic photooxidation of **1a** with **RB** (0.3 M, 1.1 equiv. O₂, room temperature and residence time of 1.4 min) with a similar light input and surface to volume ratio in a Corning[®] Advanced-flow G1TM photoreactor would allow to process *ca*. 72 mL min⁻¹ (daily productivity of 31.1 mol day⁻¹ or 5.1 kg day⁻¹). A Corning[®] Advanced-flow G3 reactorTM with similar process conditions would increase the productivity up to 6 T y⁻¹.

In conclusion, we have developed a scalable catalytic photooxidation process for the production of methionine sulfoxide under sustainable process conditions. By contrast to previously reported catalytic photooxidation processes where a large excess of oxygen is required, the integration of static mixers along the reactor path ensured an excellent mass transfer and, hence, fast oxidation rates despite the moderate solubility of oxygen in the reaction medium.

The conditions are amenable to other organic substrates, and provided high productivities within short residence time for ascaridole **1b** and Rose oxide synthetic intermediates **1c,c**'.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd. Details of the continuous-flow setup, typical runs and optimizations, and analytical data (¹H NMR).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest. Marc Winter, Clemens R. Horn and Alessandra Vizza are employees of Corning SAS.

ABBREVIATIONS

BPR, Back pressure regulator; LED, light-emitting diode; MB, Methylene Blue; NMR, nuclear magnetic resonance; PS, photosensitizer; RB, Rose Bengal; TCPP, tetrakis(4-carboxyphenyl)porphyrin)

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