

A Novel Nebulizer-Based Continuous Flow Reactor: Introducing the Use of Pneumatically Generated Aerosols for Highly Productive Photooxidations

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Abstract: A very effective and highly innovative continuous flow reactor (CFR) for undertaking important large scale photooxidations is presented. Until now, two major issues have obstructed the widespread use of photooxidation CFRs; both problems are nullified by this novel and yet extremely simple reactor design. The first issue related to the detrimental effect of poor oxygen solubility on the rate of the biphasic gas-liquid reactions and the second was the rapid attenuation of light by solutions which severely limited dimension enlarging opportunities. The new and easy to operate reactor works by nebulizing a photooxidation solution inside a cylindrical chamber surrounded by a low energy LED strip; thus, the interfacial area between the two phases is maximized, leading to greatly improved reaction rates and excellent light penetration. This pneumatic nebulizer-based photooxygenation system (NebPhotOX) can use air (as the oxygen source) and very concentrated photooxidation solutions. NebPhotOX has very high productivity and could potentially be scaled up easily to work in an industrial setting.

One of the overarching goals of modern synthetic chemistry is the development of sustainable ways to access the important motifs needed by the various chemical industries. Whatever terminology is preferred -sustainable chemistry, green chemistry or ideal synthesis- many of the same ideas are being targeted and plenty of energy is being expended to meet the stringent criteria that have emerged from this paradigm shift. On a research laboratory scale, singlet oxygen methodologies have proved to be of ever-growing value to the crusade because they have been shown to excel in so many of the different facets of sustainability.¹ For example, singlet oxygen ($^1\text{O}_2$) is a traceless reagent that can be generated from air using visible spectrum light (sunlight or low energy LED technologies) and natural photosensitisers - it is clean and atom economic. Furthermore, the reactions of singlet oxygen can be undertaken at very high concentrations and in "preferred green" solvents (MeOH, or water). Singlet oxygen chemistry is also perfectly poised to make productive use of the bulk furans coming from biomass sources. However, the benefits do not end here; $^1\text{O}_2$ is also a very selective oxidant. The rates of the reactions of $^1\text{O}_2$ with a broad range of functional groups (or even the same functional group substituted to a different degree; e.g. a di- versus a

monosubstituted furan both found within the same molecule) are such that differentiation is very easily achieved. In addition, $^1\text{O}_2$ does not react with alcohols and can be used in the presence of unprotected amines;^{2,3} thus, rendering protecting groups essentially redundant, quite unlike a large number of other oxidants. Finally, the number of methodologies using singlet oxygen is currently multiplying very rapidly because $^1\text{O}_2$ can be used to initiate high yielding cascade reaction sequences which involve rapid and dramatic increases in molecular complexity – this characteristic represents both step economy and facilitated access to new chemical space.¹ Indeed, it might be said that the biggest remaining obstacle standing in the way of singlet oxygen chemistry being adopted and applied even more widely - including in industrial settings- is its scalability.

With the recent and rapid rise to prominence of Continuous Flow Reactors (CFRs), the hope was that the scalability problem with singlet oxygen chemistry might be permanently solved. However, it was quickly identified that simple dimension enlarging was doomed to failure; mostly; due to rapid light attenuation (Bouger-Lambert-Beer Law) and the low solubility of oxygen in the reaction solutions (main issues). Thus, the initial focus was on microreactors which used a large surface area to volume ratio to get uniform light distribution across the reaction solution.⁴⁻¹⁶ Applying a similar logic macro-reactors were also designed wherein a thin annular vessel, or coiled tubing, were used to meet the demand for a large surface area for the reaction solution.^{17,18} The low solubility of oxygen in these reaction solutions continued to throw up problems; particularly, in regard to conversion and productivity. One solution was the design of CFRs using supercritical CO_2 (sc CO_2) which also supports longer $^1\text{O}_2$ lifetimes^{19,20} Higher product yields were achieved, but the drawback of this technology comes from the specialized equipment needed to perform high pressure reactions in sc CO_2 .

A very productive continuous flow macro-reactor for singlet oxygen reactions was developed in 2011 by Lévesque and Seeberger¹⁸ based on the design of Booker-Milburn.²¹ Fluorinated ethylene propylene (FEP) tubing was wrapped around a 450 W mercury lamp while the substrate and oxygen were mixed using a polytetrafluoroethylene (PTFE) T-mixer. The high productivity of this photoreactor was attributed to the increase in specific surface area (up to 25,300 m^2/m^3 vs 2,000 m^2/m^3 for equivalent batch reactors) when biphasic gas-liquid reactions were conducted at high flow rates.^{18,22,23} Similar set-ups were applied to the synthesis of the antimalaria drug artemisinin,²⁴⁻²⁶ α -aminonitriles,²⁷ α -cyanoepoxides²⁸ and the photooxygenation of the bio-derived 5-hydroxymethylfurfural.²⁹ Despite the excellent productivity of these CFRs, it is obvious that further increases in the reactor's size would require added

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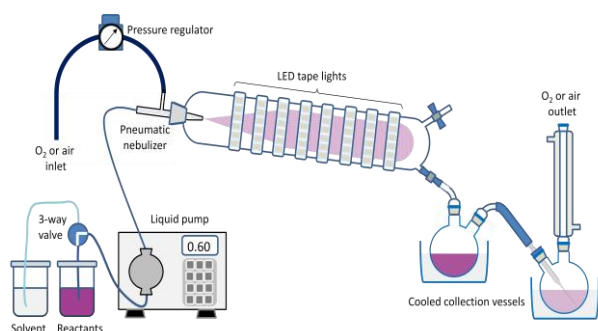


Figure 1. Schematic representation of NebPhotOX.

layers of complexity and additional problem solving to refine the equipment; and, furthermore, maintaining the high productivity might become ever-more challenging.

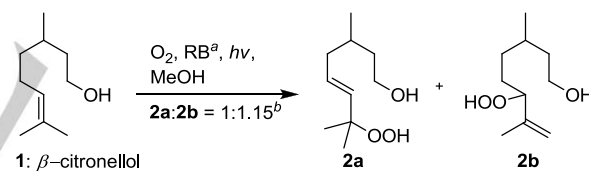
While acknowledging the importance of surface area to light penetration and oxygen solubility, we hoped to be able to rip up the plans and begin afresh with much simpler apparatus; and, therefore apparatus that was much easier to amplify in size and scale up. Nature carries out a great deal of oxygen chemistry within the earth's atmosphere -high up in the clouds- and these processes now became our inspiration. In other words, the key idea was that such biphasic reactions as the ones we wanted to carry out are ideally suited to nebulization because this would increase the interfacial area between the two phases by many orders of magnitude. More specifically, the photooxygenation solution (containing the substrate and the photosensitizer) could be nebulized into a chamber surrounded by LED light strips using either oxygen, or, better still, air. The desired reactions would occur in this cloud and the product solution could be collected in cooled vessels downstream; thus, inspired by Nature, the concept of how to do "cloud chemistry" began to take form for us.

In the set-up for our pneumatic nebulizer-based photooxygenation system (NebPhotOX), an LED light strip-jacket covers a Pyrex glass cylinder (length = 37 cm, diameter = 6.5 cm, Figure 1) while the photooxygenation solution was sprayed by oxygen or air, with a nebulizer, into the cylinder's central cavity.

The "heart" of the NebPhotOX system is a robust pneumatic nebulizer suitable for nebulizing solutions containing high amounts of dissolved solids (originally developed to spray seawater, *vide infra*). Either oxygen or air can be used in excess for efficient nebulization of the reactant solutions, with flow backpressures of between 40 – 60 psi (0.7 – 1.1 L/min) for the optimized conditions. Reactant solutions are provided via a single-piston liquid pump, for solvent flows from 0.5 – 1.0 mL/min. The uptake line is fitted with a particle filter. A three-way valve on the uptake line allows for convenient switching between the reactant solution and a solvent used for flushing out the apparatus between reactions. The pneumatic nebulizer has been fitted to one end of the cylindrical glass chamber. LED light tapes (neutral white light 3800 – 4200 K, 10 W/m, 1050 Lm/m) have been mounted onto a piece of plastic sheeting that was then joined along its long edges to make a cylinder. This cylinder acts as a removable jacket that can be used to cover the glass

cylinder. The distance between the mounted LED strips is 2 – 3 mm while distance from the glass cylinder, in order to avoid heat transfer, is around 1 cm. The cylindrical chamber is placed with a slight downward angle in order to drain any remaining reaction solution into the 1st spherical product collection vessel. A 2nd spherical product collection vessel equipped with a water cooled condenser is placed in the series in order to prevent any product loss. Both vessels are placed in ice baths.

The pneumatic nebulizer used in the present study was a SeaSpray U-Series Nebulizer (Glass Expansion) designed to deliver solutions containing elevated levels of dissolved solids (tolerance up to 20%). One of the most important characteristics of the pneumatic nebulizer is its ability to produce aerosols consisting of fine droplets. This particular nebulizer when operated with argon gas and water-based solutions has been reported to provide droplets with an average diameter of approximately 6 μm , referred to as the Sauter mean diameter ($D_{3,2}$) which is defined as the diameter of a sphere that has the same volume/surface area ratio as the particle/droplet of interest.³⁰ However, due to differences in the solvent used (methanol is mainly used in the present study), the nebulizing gas (herein, oxygen or air) and the different solution uptake and gas flow rates, the produced droplet size is expected to vary to some extent from the aforementioned value. Despite being difficult to predict the exact effect on average droplet diameter, we have adopted three droplet size scenarios and calculated the droplet surface area for each one of these options for comparison purposes. The scenarios used are as follows; firstly, the previously reported value 6 μm droplet size for this nebulizer

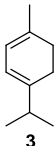

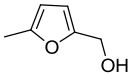
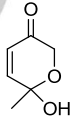


entry	concn of 1 (M)	flow rate (mL/min)	pressure of O ₂ (psi)	conversion (%) ^c	productivity (mmol/min)
1	0.25	0.67	20	93	0.16
2	0.25	0.84	30	91	0.19
3	0.25	0.89	40	93	0.21
4	0.25	0.85	50	95	0.20
5	0.25	0.79	60	95	0.19
6	0.50	0.66	20	90	0.30
7	0.50	0.83	30	87	0.36
8	0.50	0.86	40	89	0.38
9	0.50	0.86	50	93	0.40
10	0.50	0.77	60	93	0.36
11	1.00	0.71	30	84	0.60
12	1.00	0.80	40	89	0.71
13	1.00	0.82	50	86	0.71
14	1.00	0.76	60	92	0.69
15	1.25	0.68	40	82	0.70
16	1.25	0.80	50	79	0.79

^a 0.8 mol% of rose Bengal were used.

^{b,c} Relative ratios and conversions were determined by ¹H NMR of the crude mixtures.

Figure 2. Continuous flow photooxidation of β -citronellol using NebPhotOX.

substrate	entry	concn (M)	rose Bengal (mol%)	flow rate (mL/min)	pressure of O ₂ (psi)	conversion (%) ^a	productivity (mmol/min)	product
	1	1.00	0.8	0.79	40	>99	0.79	
	2	1.00	0.8	0.78	50	>99	0.78	
	3	1.00	0.8	0.80	60	>99	0.80	
	4	2.00	0.2	0.79	60	80	1.26	
	5	2.00	0.3	0.79	50	84	1.33	
	6	2.00	0.4	0.76	50	86	1.30	
	7	2.00	0.4	0.75	60	90	1.35	
	8	2.00	0.6	0.73	40	86	1.26	
	9	2.00	0.6	0.76	50	87	1.32	
	10	2.00	0.6	0.75	60	91	1.37	
	11	2.00	0.8	0.72	40	85	1.22	
	12	2.00	0.8	0.76	50	80	1.22	
	13	2.00	0.8	0.75	60	94	1.41	
	14	2.00	1.0	0.70	60	95	1.33	
	15	2.00	1.5	0.65	60	95	1.24	
	16	1.00	0.8	0.83	40	93	0.77	
	17	1.00	0.8	0.87	50	92	0.80	
	18	1.00	0.8	0.85	60	92	0.78	
	19	1.25	0.8	0.81	40	94	0.94	
	20	1.25	0.8	0.83	50	91	0.94	
	21	1.25	0.8	0.83	60	90	0.93	
	22	1.50	0.8	0.81	50	78	0.95	
	23	1.50	0.8	0.82	60	84	1.03	

^a Conversions were determined by ¹H NMR of the crude mixtures.

^b Final product after addition of Me₂S.

Figure 3. Continuous flow photooxidation of α -terpinene and (5-methylfuran-2-yl)methanol using NebPhotOX.

and then both 5 \times and 10 \times this value, representing droplet sizes of 30 and 60 μ m, respectively. These three size scenarios correspond to droplet specific surface areas of 1,000,000 m²/m³, 200,000 m²/m³ and 100,000 m²/m³, respectively. This clearly shows the dramatic improvement in specific surface area, even using the most conservative estimate of droplet size (60 μ m), over the best previously achieved using continuous gas-liquid flow photooxygenators.¹⁸ It was our hypothesis that the huge increase in specific surface area would lead to more efficient continuous flow reactions.

The first test reaction chosen for NebPhotOX was the ene reaction of β -citronellol (**1**). Different concentrations of citronellol solutions in MeOH (0.25 – 1.25 M) and different flow backpressures of the nebulizing gas O₂ (20 – 60 psi, 0.4 – 1.1 L/min) were employed (Figure 2). The flow rates reported in Figure 2 are the exact flow rates, as measured based on the time needed for the nebulization of 5 mL of photooxidation solution containing 0.8 mol% of rose Bengal (RB) as photosensitizer. To our delight, the system works extremely efficiently with excellent conversions (> 90%) even at

substrate	entry	concn (M)	rose Bengal (mol%)	flow rate (mL/min)	pressure of air (psi)	conversion (%) ^a	productivity (mmol/min)	product
1	1	0.25	0.8	0.84	50	91	0.19	2a:2b (1.06:1 ^b)
	2	0.25	0.8	0.82	60	96	0.20	
	3	0.50	0.8	0.82	50	97	0.40	
	4	0.50	0.8	0.80	60	93	0.37	
	5	1.00	0.8	0.80	50	79	0.63	
	6	1.00	0.8	0.79	60	69	0.55	
3	7	1.00	0.8	0.77	50	>99	0.77	4
	8	1.00	0.8	0.75	60	>99	0.75	
	9	1.50	0.8	0.77	50	93	1.07	
	10	1.50	0.8	0.76	60	89	1.01	
	11	2.00	0.8	0.76	50	71	1.08	
	12	2.00	0.8	0.75	60	79	1.19	
5	13	0.50	0.8	0.82	50	98	0.40	6^c
	14	0.50	0.8	0.85	60	96	0.40	
	15	0.75	0.8	0.86	50	84	0.54	
	16	0.75	0.8	0.86	60	82	0.53	
	17	1.00	0.8	0.92	50	75	0.69	
	18	1.00	0.8	0.88	60	71	0.62	

^{a,b} Conversions and relative ratios were determined by ¹H NMR of the crude mixtures.

^c Final product after addition of Me₂S.

Figure 4. Continuous flow photooxidation of β -citronellol, α -terpinene and (5-methylfuran-2-yl)methanol using NebPhotOX and air as nebulizing gas.

high concentrations of **1** (1.0 M). Since the flow rate varies slightly from experiment to experiment, the best way to measure the efficiency of the reactions is through the productivity (productivity = concentration \times flow rate \times conversion). Based on the results reported in Figure 2, the productivity of this reaction reaches a maximum at 50 psi of oxygen pressure. The isolated yield was measured for Entry 14 (Figure 2) after reduction of the hydroperoxides **2a** and **2b** with Me₂S and subsequent column chromatography; it was found to be 87%.

Based on the results reported for the photooxidation of β -citronellol (**1**) O₂, pressures of 40, 50 and 60 psi were chosen for the next experiments which included investigation of the Diels-Alder reactions of singlet oxygen with α -terpinene (**3**) and (5-methylfuran-2-yl)methanol (**5**, Figure 3). These [4+2]-cycloadditions successfully formed the anthelmintic drug ascaridol (**4**) starting from **3**, or pyranone **6** when starting from **5**. In the latter case, addition of Me₂S was needed to accomplish the fast and complete transformation of the intermediate methoxy hydroperoxide (intermediate wherein the [4+2]-adduct has been trapped by MeOH, see SI)³¹ into the final pyranone **6**. In the case of **3**, the conversions are very high (> 90%) even at very high concentrations of α -terpinene (2 M), leading to very high productivities (up to 1.41 mmol/min); while, in case of **5**, the conversion was up to 94% with a 1.25 M concentration of the starting furan. The isolated yield for Entry 3 (Figure 3) following column chromatography was 93%; while; for Entry 19 after reduction with Me₂S and subsequent column chromatography, it was 85%.

The influence on the process of the concentration of the photosensitizer was investigated next. A range of photosensitizer (rose Bengal) amounts (0.2 – 1.5 mol%, Figure 3) were used in the photooxidation of a 2 M solution of α -terpinene. These changes had a negligible influence on the productivity of the reaction when compared against one another for reactions with the same flow backpressure of oxygen (60 psi, Entries 4, 7, 10, 13, 14 and 15, Figure 3); leading us to choose the 0.8 mol% of RB as the standardized option.

The last study, and the culmination of the NebPhotOX investigation overall, involved looking at the replacement of O₂ as the nebulizing gas with air. As evidenced by the results for the photooxidations of **1**, **3** and **5** (Figure 4), the productivity of the reactions using air remains almost unchanged when compared with those reported for oxygen (Figures 2 & 3) for the lower concentrations of substrates (0.25 M and 0.5 M of **1** and 1 M of **3**), while a small drop in the productivity was observed when more demanding concentrations were used (1 M of **1**, 2 M of **3** and 1 M of **5**). In other words, a small reduction in the concentration of what are, in reality, very concentrated solutions is enough to guarantee high conversions when air is used as the nebulizing gas.

An extremely efficient and innovative continuous flow reactor for undertaking bi-phasic photooxygenations has been presented. The reactor uses pneumatically generated aerosols to maximize the surface area to volume ratio for the reaction solution; thus, effectively eliminating the traditional problems associated with light penetration and oxygen solubility. For these reasons, the productivities of reactions undertaken using this continuous flow reactor are exceptionally high. This new reactor can facilitate the scaling-up of singlet oxygen reactions assisting

in the development of truly sustainable methods for use in synthetic organic chemistry. Whilst the new reactor design, as a starting point was tested for reactions using singlet oxygen, the same principles should apply to other bi-phasic reaction systems. Furthermore, the simplicity of the reactor design means that it should be amenable to significant problem-free dimension enlarging allowing it to be used to address industrial needs.

Experimental Section

General procedure for photooxidations: The substrates, either β -citronellol (**1**), α -terpinene (**3**) or (5-methylfuran-2-yl)methanol (**5**) and rose Bengal (usually 0.8 mol%) were dissolved in MeOH (total volume of 5 mL). The resulting solutions were provided to the nebulizer via a single piston liquid pump (flow rate set at 0.6 mL/min). Concomitantly, the solution was sprayed with the pneumatic nebulizer into the reaction cylinder using oxygen or air as the nebulizing gas. Different flow backpressures for the nebulizing gases (20 – 60 psi, 0.4 – 1.1 L/min) were used. The flow rates reported in Figures 2-4 are the exact flow rates, as measured based on the time needed for the nebulization of 5 mL of photooxidation solution. The crude photooxidized solutions were collected in the two cooled spherical vessels placed in series. The solutions were concentrated under reduced pressure and the conversion was determined by ¹H NMR. In the case of β -citronellol (**1**) and (5-methylfuran-2-yl)methanol (**5**), Me₂S (4.0 eq) was added after the photooxygenation for the reduction of the initially formed hydroperoxides (see SI) to afford the final products **2a'** and **2b'**, and **6**, respectively. Despite the fact that the crude mixtures obtained are quite clean, the final products were purified by flash column chromatography (silica gel, petroleum ether:EtOAc = 3:1 for **2a'** and **2b'**, 6:1 for **4** and 2:1 for **6**). In case of **1** and **3**, 50 mL of 1 M solutions containing 0.8 mol% of rose Bengal were photooxidized with NebPhotOX, leading to results very similar with those obtained when 5 mL solutions were used.

SAFETY CAUTION: Measures were taken to eliminate all possible ignition sources from the fumehood area (sparks or flames, e.g. the electricity transformer for the LEDs was kept outside of the fumehood) in which the NebPhotOX system was operated. This included operating the reactor at room temperature and pressure conditions without any significant heat input from the low power LEDs used. In addition, the fumehood was always adequately ventilated with a high air flow. System operating conditions prevented oxygen stagnation in the system. Additional cautions included that the operator wears safety glasses with side shields and flame resistant safety clothing.

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Keywords: continuous flow reactor • aerosol • singlet oxygen • photooxidation • nebulizer

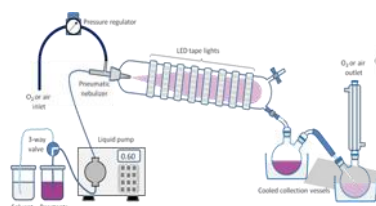
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Layout 1:

COMMUNICATION

A very effective and highly innovative continuous flow reactor for undertaking important, large scale, bi-phasic photooxidations is presented. The reactor uses pneumatically generated aerosols to maximize the interfacial area between the two phases; thus, effectively eliminating the traditional problems associated with oxygen solubility and light penetration. For these reasons, the productivities of reactions undertaken using this set-up are very high.



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A Novel Nebulizer-Based Continuous Flow Reactor: Introducing the Use of Pneumatically Generated Aerosols for Highly Productive Photooxidations