ORGANIC
LETTERS

2011
Vol. 13, No. 19
5008–5011

Highly Efficient Continuous Flow Reactions Using Singlet Oxygen as a "Green" Reagent

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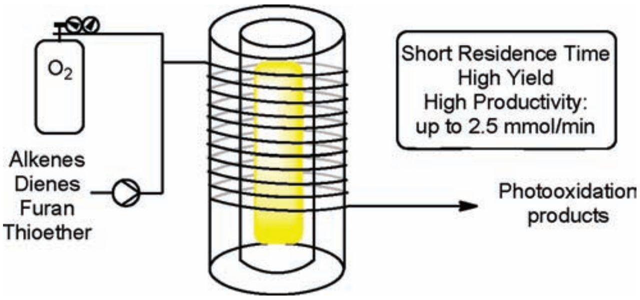
Received July 1, 2011

ABSTRACT



Described is a new method for the efficient *in situ* production of singlet oxygen in a simple continuous flow photochemical reactor. The extremely large interfacial area generated by running the biphasic mixture in a narrow channel at a high flow rate ensures high throughput as well as fast and efficient oxidation of various alkenes, 1,3-dienes, and thioethers on a preparative scale.

Molecular oxygen is an attractive reagent due to its availability, low cost, and negligible environmental impact. Singlet oxygen[1] ($^1O_2$) is formed *via* dye-sensitized photoexcitation of triplet oxygen ($^3O_2$) and facilitates heteroatom oxidations, ene reactions, and [4 + 2] and [2 + 2] cycloadditions.[2] Consequently, $^1O_2$ has been used for the synthesis of natural products[3] and fragrances.[4] Widespread use of $^1O_2$ in conventional batch systems has been prevented by the need for specialized equipment to produce the reagent, technical challenges associated with scaling-up photochemical reactions,[5] and the low rate of mass transfer of oxygen gas into the solution.

Continuous flow reactors allow for easy scale-up as no change in reactor size is required,[6] provide a large surface-to-volume ratio that ensures efficient irradiation,[7] and enable precise control over the reaction time to minimize unwanted side reactions due to secondary photochemical reactions.[8] In addition, continuous flow reactors improve safety as reactive intermediates[9] are quenched[10] or further transformed[11] immediately after production. Photochemical flow reactors have been explored[12] for the generation and use of $^1O_2$. Although complete conversion was achieved in a short residence time, the process suffered from very low productivity,[12a] only 0.18 μmol/min,[13] rendering the system inapplicable to use on a preparative

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(10) For an example of endoperoxide quenching in a continuous flow system, see: Jähnisch, K.; Dingerdissen, U. *Chem. Eng. Technol.* **2005**, *28*, 426.

(11) For examples of uses of peroxides, see: (a) Adam, W.; Braun, M. A.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* **1989**, *111*, 203. (b) Staben, S. T.; Linghu, X.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12658.

10.1021/ol2017643

scale. Other groups have tackled the problem of low $O_{2(g)}$ mass transfer using supercritical carbon dioxide as a solvent, though this mandates a highly specialized reaction setup.[14]

Here, we report a simple continuous flow system that renders reactions involving $^1O_2$ practical for synthetic chemists. Efficient mass transfer and sufficient irradiation enable the straightforward production and use of $^1O_2$ as a reagent in several transformations such as oxidations and cycloadditions.

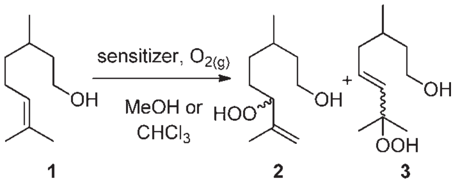
Efficient oxidations are dependent on the solution concentration of $^1O_2$, which in turn is proportional to the solution concentration of $^3O_2$. Therefore, the productivity of the oxidation depends on the rate of mass transfer ($d[^3O_{2(sol)}]/dt$) of $^3O_{2(g)}$ into the solution. Based on Fick's law (eq 1) the rate of mass transfer is determined by the liquid film transfer coefficient (K_L), the specific surface area of the solution (a), and the oxygen deficit within the solution ($[^3O_{2(sol)}]_{sat} - [^3O_{2(sol)}]$).

$$d[^3O_{2(sol)}]/dt = K_L a([^3O_{2(sol)}]_{sat} - [^3O_{2(sol)}]) \qquad (1)$$

When biphasic gas–liquid reactions are conducted at high flow rates, the specific surface areas in continuous flow reactors (up to 25 300 m^2/m^3) can greatly exceed those attained in conventional batch reactors (up to 2000 m^2/m^{-3})[15] due to flow pattern effects.[16] To date, synthetic organic chemists have not taken full advantage of variations in the flow patterns of biphasic reactions.[17]

Initial reactions were conducted in a 78 μL silicon-glass microreactor[18] irradiated with an LED lamp[19] to form $^1O_2$ for the well-documented photo-oxidation of citronellol (**1**), a key intermediate en route to the valuable rose oxide fragrance[3] (Table 1). Quantitative conversion was achieved within a 2 min residence time using the photosensitizer rose bengal (Table 1). The productivity of this system (0.65 μmol/min) was limited by the small reactor volume and the low lamp power that limited flow rates.

Table 1. Influence of the Flow Rate on the $^1O_2$ Oxidation of Citronellol[a]



		flow rates (μL/min)			
entry	concn of **1** (M)	solution of **1**	O_2	conversion (%)[b]	productivity (μmol/min)
1	0.10	26	130	31%	0.81
2	0.10	13	65	55%	0.72
3	0.10	6.5	33	≥95%	0.65

[a] Reactions were performed in MeOH under the irradiation of a green LED lamp (1 W), with rose bengal (5.1 mM) as the sensitizer. [b] Determined by ^1H NMR

To increase material throughput, a system based on the design of Booker-Milburn[20] was constructed. Fluorinated ethylene propylene (FEP) tubing was wrapped around a Schenk photochemical reactor containing a 450 W medium pressure mercury lamp that was cooled to 25 °C. Substrate and oxygen were added *via* gastight syringes and mixed using a polytetrafluoroethylene (PTFE) T-mixer.[19] To overcome the photobleaching of rose bengal with this more powerful lamp, tetraphenylporphyrin (TPP) was instead used as a sensitizer.

First, the influence of oxygen stoichiometry on conversion and productivity was investigated using a 10:1 v/v ratio of oxygen gas to citronellol solution.[21] Quantitative conversion was achieved with as little as 1.6 equiv of oxygen (Table 2, entry 3). A flow rate increase from 1.0 to 2.5 mL/min led to a 23% average rise of conversion (Table 2, entries 2–5) as expected from Fick's law.

Table 2. Influence of Oxygen Stoichiometry and Flow Rate on the $^1O_2$ Oxidation of Citronellol[a]

		flow rates (mL/min)				
entry	concn of **1** (M)	solution of **1**	O_2	equiv of O_2	conversion (%)[b]	productivity (μmol/min)
1	0.10	0.23	2.27	4.0	≥95%	23.0
2	0.25	0.09	0.91	1.6	78%	17.6
3	0.25	0.23	2.27	1.6	≥95%	57.5
4	0.50	0.09	0.91	0.8	57%	25.7
5	0.50	0.23	2.27	0.8	80%	92.0
6[c]	0.10	0.23	2.27	0.8	66%	15.2

[a] Reactions were performed in a 5 mL reactor in CHCl$_3$ with TPP (0.25 mM) as sensitizer. [b] Determined by ^1H NMR. [c] Air was used instead of pure oxygen.

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(13) Productivity is defined as the amount of material, in mmol, generated per minute. It is calculated by multiplying the flow rate by the concentration of the substrate and the conversion.

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(19) See Supporting Information for description of the system.

The greater mass transfer allowed for a reduction in the total amount of oxygen needed without affecting conversion. The precise control of oxygen reduces the risk of flammability associated with unreacted oxygen[22] and constitutes a major advantage compared to traditional batch Schenck photoreactors where oxygen is constantly bubbled through the solution. Good conversion was even possible when air was used in place of pure oxygen (Table 2, entry 6).

To further increase the productivity,[13] much higher flow rates were required. Use of an HPLC pump for substrate delivery and connection of a mass flow controller at the gas cylinder ensured accurate and consistent oxygen delivery and enabled even greater mass transfer.[19] In addition, the total reactor volume was increased from 5 to 14 mL to allow for faster flow rates while maintaining sufficient irradiation. Conducting the reaction at a solution flow rate of 5 mL/min and an O_2 flow rate of 10 mL/min resulted in up to 85% conversion (Table 3). Based on Karayiannis' flow pattern map,[23] these conditions generate a slug flow pattern characterized by the formation of large bubbles surrounded by a thin liquid film,[24] thereby increasing both the specific surface area and mass transfer.

Table 3. Oxidation of Citronellol by $^1O_2$ under Pressure[a]

		flow rates (mL/min)				
entry	concn of **1** (M)	solution of **1**	O_2	back pressure (bar)	conversion (%)[b]	productivity (mmol/min)
1	0.25	5	10	–	85%	1.06
2	0.25	5	11	6.9	≥95%	1.25
3	0.25	3	12	6.9	81%	0.61

[a] Reactions were performed in a 14 mL reactor in $CHCl_3$ with TPP (0.25 mM) as sensitizer. [b] Determined by ^1H NMR.

Considering Henry's law, pressurizing a reactor should increase the concentration of oxygen at saturation ($[^3O_{2(sol)}]_{sat}$, eq 1) and consequently improve mass transfer. Indeed, pressurizing the system by connecting a 6.9 bar back-pressure regulator[25] resulted in quantitative conversion (Table 3, entry 2). Attempts to increase the flow rate beyond 5 mL/min yielded lower conversion, due to insufficient irradiation times.

The oxidation of citronellol (**1**) was shown to be dependent on the sensitizer concentration. Increasing the TPP concentration in general led to improved conversion. However, at concentrations above 2.0 mM conversion decreased due to quenching of $^1O_2$ by excess TPP (Figure 1).[26]

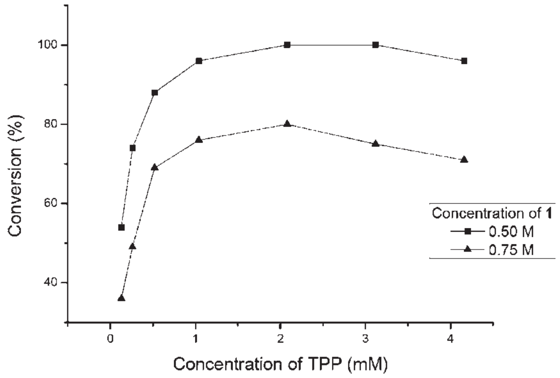
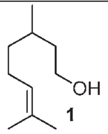
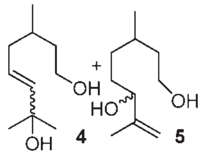
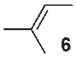
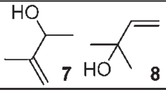
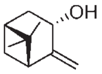
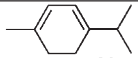
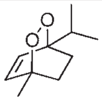
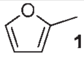
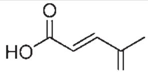
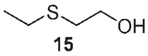
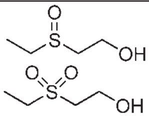


Figure 1. Influence of TPP concentrations on conversion.

Table 4. Oxidation of Various Substrates by $^1O_2$[a]

entry	substrate concentration (M)	product	conversion[b]	yield (%) ratio[b]
1[c]	 **1** 0.50 M	 **4** + **5**	≥ 95%	88% **4:5** 1.1:1.0
2[c]	 **6** 0.50 M	 **7** **8**	≥ 95%	75% **7:8** 1.3:1.0
3[d,e]	 **9** 0.50 M	 **10**	70%	63%
4	 **11** 0.50 M	 **12**	≥ 95%	85%
5[f]	 **13** 0.50 M	 **14**	88%	68%
6	 **15** 0.25 M	 **16** **17**	≥ 95%	95% **16:17** 3.0:1.0

[a] Reactions were performed in a 14 mL reactor in $CHCl_3$ with TPP (2.0 mM) as sensitizer. Solution and oxygen were delivered at a flow rate of 5 and 12 mL/min, respectively. Residence time: 0.8 min. [b] Determined by ^1H NMR. [c] The hydroperoxides formed were reduced with sodium sulfite to the corresponding alcohols. [d] Solution and oxygen were delivered at a flow rate of 1 and 10 mL/min, respectively. Residence time: 1.3 min. [e] The hydroperoxide formed was reduced with triphenylphosphine to the corresponding alcohol. [f] The product of photooxydation was treated with pyridine in a mixture of THF, acetone, and H_2O to give ketoacid **14**.

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(24) For a schematic representation of the flow pattern, see Supporting Information.

(25) Use of a back-pressure regulator was incompatible with the system using a syringe pump, because we needed to refill the syringes in the middle of the run, leading to depressurization.

Under optimal continuous flow conditions (Table 4, entry 1), 27 mL of citronellol were oxidized in 1 h, demonstrating the stability and scalabiltiy of the process. Optimization of the reaction conditions allowed an unprecendented productivity of 2.5 mmol/min, an improvement by a factor of 3800 compared to the productivity obtained with the silicon-glass microreactor (Table 1, entry 3).

The optimized reaction setup was readily applied to other reactions using $^1O_2$ (Table 4).[27] Oxidation of α-pinene (**9**) generated **10**, a useful precursor to a diphosphine chiral ligand.[28] [4 + 2] Cycloaddition to form endoperoxide **12** (Table 4, entry 4) was successful. Endoperoxides are key functional groups in antimalarial compounds[29] and a precursor to 1,2,3,4-tetraols,[30] a motif present in several natural products.

The oxidation of furan **13** provided access to **14**, a key substrate to produce drug substances[31] and Diels–Alder reactions.[32] The photo-oxygenation of furans to generate butenolides is a key step in numerous natural product syntheses.[2] Finally, the setup was used to oxidize sulfide **15** to a mixture of the corresponding sulfoxide **16** and sulfone **17**.

In conclusion, we have developed a simple and inexpensive continuous flow reactor system that enables synthetic organic chemists to generate and use singlet oxygen for a variety of transformations with minimal environmental impact. The reactions produce up to 2.5 mmol of product per min and benefitted from an increase in specific surface area that allowed for faster flow rates. Continuous flow processes hold great potential for the acceleration of biphasic reactions involving oxygen and other gases.

Acknowledgment. The authors gratefully thank the Max Planck Society for generous funding. F.L. is the recipient of a postdoctoral fellowship from Fonds Québécois de la recherche sur la nature et les technologies (FQRNT).

Supporting Information Available. Schematic diagrams of reactor setup and flow patterns, experimental procedures, spectroscopic data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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