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High throughput photo-oxidations in a packed bed reactor system

Caleb J. Kong [a], Daniel Fisher [a], Bimbisar K. Desai, Yuan Yang, Saeed Ahmad *, Katherine Belecki *, B. Frank Gupton *

Department of Chemistry, Virginia Commonwealth University, 601W. Main St, Richmond, VA 23220, USA
Department of Chemical and Life Science Engineering, Virginia Commonwealth University, 601W. Main St, Richmond, VA 23220, USA

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ABSTRACT

The efficiency gains produced by continuous-flow systems in conducting photochemical transformations have been extensively demonstrated. Recently, these systems have been used in developing safe and efficient methods for photo-oxidations using singlet oxygen generated by photosensitizers. Much of the previous work has focused on the use of homogeneous photocatalysts. The development of a unique, packed-bed photoreactor system using immobilized rose bengal expands these capabilities as this robust photocatalyst allows access to and elaboration from these highly useful building blocks without the need for further purification. With this platform we were able to demonstrate a wide scope of singlet oxygen ene, [4+2] cycloadditions and heteroatom oxidations. Furthermore, we applied this method as a strategic element in the synthesis of the high-volume antimalarial artemisinin.

1. Introduction

Singlet oxygen[1] has received significant attention for its use in constructing complex organic molecules *via* ene reactions,[2] heteroatom oxidations and cycloadditions.[3,4] The appeal of this highly reactive oxygen species stems from its inexpensive, abundant source, molecular oxygen and the environmentally friendly photocatalytic processes that generate it.[5] From the medicinal chemist's standpoint, singlet oxygen chemistry is attractive as the peroxides formed can be further elaborated into a variety of other products.[6]

Despite the many advantages, application of this technology has been restricted to small-scale use. Challenges inherent to conducting photochemistry in large volume batch reactors, such as limited penetration depth of the irradiated light, inadequate oxygen saturation, formation of byproducts, as well as other safety concerns, have inhibited its use in most industrial settings.[7]

Recent efforts to circumvent these issues have focused on adapting photochemical processes to continuous flow operations.[8–12] While the benefits of continuous flow chemistry have been well documented,[13–17] the operational advantages to conducting photo-oxidation reactions continuously are especially remarkable. Photochemical flow reactors enable greater exposure to the radiation and improve the mass transport of oxygen by providing much larger surface–to–volume ratios.[18–20] These systems also reduce the safety risks associated with oxygenating large amounts of flammable organic solvents.

To further improve the efficiency of this technology, some groups have substituted organic solvents with supercritical CO_2 and homogeneous photocatalysts with heterogenized ones.[21–23] Heterogeneous photocatalysts offer the functional advantages of easy separation from products combined with the atom economic benefits of reuse.[24–26] While these systems have proved effective, the use of supercritical CO_2 necessitates specialized equipment with high energy demands to engender its formation.[27]

Our work exploits the benefits of employing a heterogeneous photocatalyst, rose bengal immobilized onto polystyrene,[24–29] in continuous operations while using solvents common to photochemistry. Rose bengal is an effective and popular singlet oxygen sensitizer.[28] Yet, the polymer-supported variation of this dye expands its capabilities. It is functional in solvents in which the free dye is insoluble, and is recyclable with minimal reduction in efficiency. Compared to its homogeneous counterpart, the bound sensitizer is more resistant to photobleaching as well as the formation of aggregates.[30,31] From an operational perspective, use of heterogeneous rose bengal in continuous flow reactors obviates the need for product purification from the sensitizer, which enables multiple synthetic steps to be telescoped.[28–30] The immobilized photocatalyst's reusability improves process efficiency as it circumvents the laborious steps associated with column repacking after each experiment. As a result, medicinal chemists are afforded rapid, easy access to a wide variety of oxidation products. The

* Corresponding authors at: Department of Chemistry, Virginia Commonwealth University, 601W. Main St, Richmond, VA 23220, USA.
E-mail address: bfgupton@vcu.edu (B.F. Gupton).
[a] These authors contributed equally to this article.

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value of this reactor set up, however, transcends the simplicity of executing the chemistry. Ultimately, it establishes a direct line of sight from discovery to development with the potential to streamline the technology transfer process from benchtop to industrial scale.

2. Results and discussion

2.1. Description of packed bed photoreactor prototype

To conduct continuous photochemically induced singlet oxygen reactions, we utilized a custom built, packed bed photoreactor (Fig. 1).[32] The reactor functioned as a standalone prototype unit, assembled with the dimensions to accommodate a transparent column containing our photocatalyst. In the form of a tripod, the metal reactor frame contains a mixture of 580 and 530 nm light emitting diodes (LEDs) that extended vertically along the interior of each side to irradiate polymer-supported rose bengal near 558 nm, the wavelength reported for optimum photoexcitation.[28] (Spectral data for rose bengal irradiated by the photoreactor is included in the Supplementary Data). The LEDs illuminate a central manifold containing a packed, transparent column of photocatalyst (90 W). Connected to the backside of the LEDs are baffles that protrude outward from the reactor. In addition to the baffles, we mitigated excessive heat by directing a stream of forced air around the column. Since its early assembly, improvements have been engineered into the unit to better dissipate heat; these changes have resulted in a more self-sustaining photoreactor.

2.2. Photooxidation of α-terpinene

Initially, we subjected α-terpinene, **1**, to a continuous photochemical [4+2] cycloaddition. The reaction parameters were varied in an effort to ascertain the optimum continuous flow conditions (Table 1). It was found that by reducing the flow rate of the substrate, **1**, to 1.0 mL min^{-1} while feeding the system with 5.0 mL min^{-1} of O_2, formation of the endoperoxide in **2** was maximized (Table 1, entry 3). The 94% yield is very competitive with previously reported work, which exposed **1** to comparable conditions except for the use of a homogeneous sensitizer.[11] Furthermore, under these conditions, conversion was maintained for over 10 h with the same packed bed of polymer-supported rose bengal.

2.3. Substrate scope

With optimal flow conditions established, we applied the reactor set up to a diverse set of substrates to explore the versatility of the system (Table 2). Ene reactions were investigated on several different cyclic and acyclic olefin-containing molecules. 2,3 dimethyl-2-butene, **3**, was converted to **4** in 88% yield (Table 2, entry 1). Likewise, a tertiary olefin, **5**, was successfully oxygenated, producing two isomers in a 4:3 ratio of **6** and **7** (Table 2, entry 2). Further examples of oxidation of unsaturated molecules *via* ene reactions were demonstrated. α-pinene, **8**, was transformed to **9** in 60% yield (Table 2, entry 4). Although the conversion of this polycyclic compound was lower than the other alkenes we evaluated, the yield exhibited in our continuous process was superior to that in batch using immobilized rose bengal.[25] Heteroatom oxidation was also proven successful with this system. Use of the exact same procedures oxidized the sulfide, **10**, to a mixture of **11** and **12** in a 1–10 ratio in an overall 98% yield (Table 2, entry 4). Another example of heteroatom oxidation was illustrated as triphenylphosphine **13** was converted to the phosphine oxide **14** in 92% yield (Table 2, entry 5). Finally, we subjected 1,3 cyclohexadiene, **15**, to identical photo-oxidation conditions to deliver the endoperoxide, **16**, demonstrating another example of a [4+2] cycloaddition (Table 2, entry 6). In generating this scope we gauged the throughput of this system with the industrially relevant metric, volume-time output (VTO), which is the productivity of a chemical step relative to its reactor space, to enjoy an average VTO of 0.622337 m^3 - h kg^{-1}. As a reference, in industrial manufacturing whereby

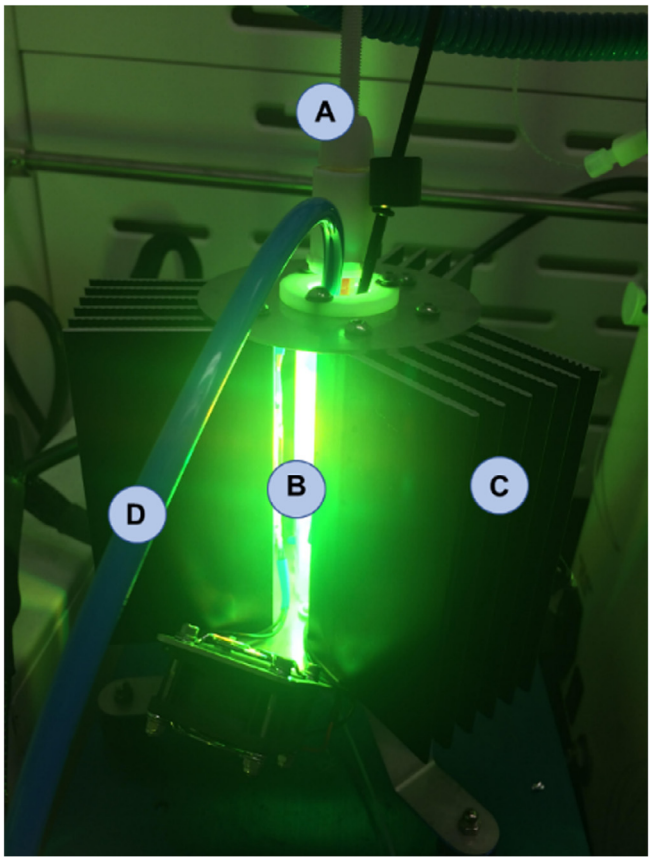
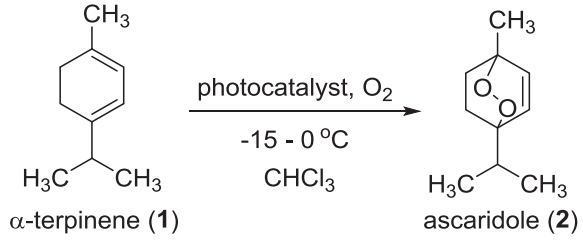


Fig. 1. Diagram of photoreactor prototype. (A) 6.6 × 150 mm Omnifit column filled with polymer-supported rose bengal. (B) Light source and manifold. (C) Heat-exchange baffles. (D) Cooled airline. BPR = back pressure regulator (100 PSI).

Table 1
Optimization of photo-oxidation of α-terpinene.



α-terpinene (**1**) ascaridole (**2**)

Entry	**1** Flow Rate (mL min^{-1})[a]	O_2 Flow Rate (mL min^{-1})	%Yield[b]
1	0.1	1.0	57
2	1.0	5.0	46
3	0.1	5.0	94

[a] All reactions conducted using 15 mM solution of **1**.
[b] Yield determined by ^{1}H NMR relative to an internal standard.