



# Combining engineering and chemistry for the selective continuous production of four different oxygenated compounds by photo-oxidation of cyclopentadiene using liquid and supercritical CO<sub>2</sub> as solvents

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## ABSTRACT

A range of products is reported from the photo-oxidation of cyclopentadiene from photochemically generated singlet oxygen (<sup>1</sup>O<sub>2</sub>) using carbon dioxide (CO<sub>2</sub>) as a solvent and 5,10,15,20-tetrakis-(pentafluorophenyl)porphyrin (TPFPP) as a CO<sub>2</sub>-soluble photosensitizer. The endo-peroxide intermediate, generated from the reaction with singlet oxygen, is transformed into one of several different products in good yield depending on the conditions applied and by adding different reactors and reagents downstream of the photo-reactor, allowing the reaction products to be switched in one streamlined process. The addition of a thermal reactor facilitated the rearrangement of the endoperoxide to form Z-4,5-epoxy-2-pentanal. Quenching with thiourea yielded the *syn*-diol, (1R,3S)-cyclopent-4-ene-1,3-diol. Treatment with acid or base afforded furfuryl alcohol and 4-hydroxy-2-cyclopentenone respectively. High productivities for all products were obtained when compared to traditional batch reactions.

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## 1. Introduction

Molecular oxygen is a widely available, inexpensive and environmentally acceptable reagent and is often considered as a highly attractive oxidant. The photochemical generation of singlet oxygen (<sup>1</sup>O<sub>2</sub>), a relatively reactive species, from molecular oxygen, has gained interest in contemporary organic synthesis over the past decade, <sup>1</sup>O<sub>2</sub> provides a green and sustainable route to access higher oxidation state chemicals with high atom efficiency.<sup>1–4</sup> From a green chemistry aspect, the generation of <sup>1</sup>O<sub>2</sub> using low energy visible light *via* photosensitisation with an appropriate catalytic photosensitizer (e.g. anthracene, xanthenes, or porphyrins) is both simple and efficient. <sup>1</sup>O<sub>2</sub> reacts with 1,3-dienes through a [4 + 2] cycloaddition process to form endoperoxides, which are reactive

species that can easily be converted into a variety of compounds.<sup>1,5–11</sup>

Larger scale processes involving <sup>1</sup>O<sub>2</sub> often require the use of non-flammable halogenated solvents.<sup>12</sup> Supercritical CO<sub>2</sub> (scCO<sub>2</sub>) or liquid CO<sub>2</sub> (liqCO<sub>2</sub>) are non-flammable alternatives to more traditional organic solvents, and have many attractive properties, especially for oxidation reactions as CO<sub>2</sub> is fully-oxidized, non-flammable and non-toxic.<sup>13,14</sup> Furthermore, O<sub>2</sub> is completely miscible with the CO<sub>2</sub> solvent and photo generated <sup>1</sup>O<sub>2</sub> has been shown to have a longer lifetimes in scCO<sub>2</sub>.<sup>15–18</sup> However, the use of CO<sub>2</sub> as a solvent for reactions requires specialized engineering compared to more conventional batch and flow synthetic approaches and requires high pressure. Nevertheless CO<sub>2</sub> is an attractive solvent for continuous flow reactions, especially as liquid and supercritical CO<sub>2</sub> have a low viscosities and higher diffusivities than more conventional solvents and products may easily be recovered at the end of the experiments by simply reducing the pressure.<sup>19</sup> Continuous flow reactors are highly suited for scaling up processes as they can be operated almost indefinitely and have added safety benefits as they minimize the volume of reactants

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inside the reactor at any given instant.

We have reported the development of a number of flow techniques for reactions in CO<sub>2</sub>.<sup>20–24</sup> Reactions include acid-catalyzed alkylation<sup>25</sup> and etherification,<sup>26</sup> as well as hydrogenation,<sup>27</sup> a process, which was successfully scaled up to 1000 tons/yr.<sup>28</sup> We also pioneered the use of self-optimizing flow reactors in CO<sub>2</sub>.<sup>29–33</sup> We have also demonstrated that appropriate reactor design can permit switching between the selective production of five different products from a single feedstock, namely furfural.<sup>34</sup> Most relevant to this paper, we have reported the use of scCO<sub>2</sub>, as an alternative solvent, enabling both thermal oxidation<sup>35</sup> and photo-oxidation<sup>36–38</sup> to be carried out safely in non-flammable and non-toxic solvent. Early work involved the photo-oxidation of  $\alpha$ -terpinene with <sup>1</sup>O<sub>2</sub> in scCO<sub>2</sub> which was transferred from a small volume batch reactor to a larger flow reactor, with excellent space-time yields. More recently, we reported the photochemical synthesis of artemisinin from dihydroartemisinic acid in a reactor which combined liquid CO<sub>2</sub> with a dual-function solid acid/photosensitizer.<sup>39</sup>

In this paper we show that multiple products can be produced by switching reactors and reagents applied to the photo-oxidation of cyclopentadiene (**1**) in liqCO<sub>2</sub> and scCO<sub>2</sub> to selectively make one of four products in a continuous flow system (Scheme 1).

The photochemical oxidation of **1** is a relatively well-known reaction, proceeding via a [4 + 2] cycloaddition reaction with <sup>1</sup>O<sub>2</sub> generating endoperoxide **2**.<sup>40</sup> This reaction has been widely reported with generation of the endoperoxide **2** after irradiation at low temperatures *i.e.* –20 to –130 °C.<sup>41</sup> However, the isolation of **2** has been reported under conditions where the irradiation and work-up was carried out at *ca.* minus 100 °C due to instability of the endoperoxide **2**, which decomposes in to **3** at *ca.* > minus 30 °C).<sup>42</sup> A one pot synthesis of **4** from the photo-oxidation of **1** was demonstrated using dichloromethane or carbon tetrachloride as solvents in a biphasic mixture, however the yield was low.<sup>43</sup> The use of a falling-film microreactor for the photo-oxidation of low concentrations of **1** has been reported; however reduction of the endoperoxide **2** with thiourea only yielded 20% of **4**.<sup>44</sup> Here we report the use of a continuous flow reactor for the photo-oxidation of cyclopentadiene in CO<sub>2</sub> and show how the downstream reactions

of the endoperoxide can be switched to produce four different compounds **3–6**.

## 2. Results and discussion

### 2.1. High pressure continuous flow apparatus

Initially, we carried out very small-scale batch reactions in a previously reported high pressure spectroscopic cell<sup>45</sup> which permitted FTIR monitoring and kinetic measurements for the various reaction. These results indicated that it should be possible to synthesize **3–6** following the photo-oxidation of **1** in scCO<sub>2</sub> using a scaled-up continuous flow setup, since the key endoperoxide intermediate **2** was found to have a lifetime of the order of several minutes, in scCO<sub>2</sub> under a range of conditions at temperatures as high as 40 °C. A schematic diagram of the reactor system for continuous photoreactions is shown in Fig. 1.

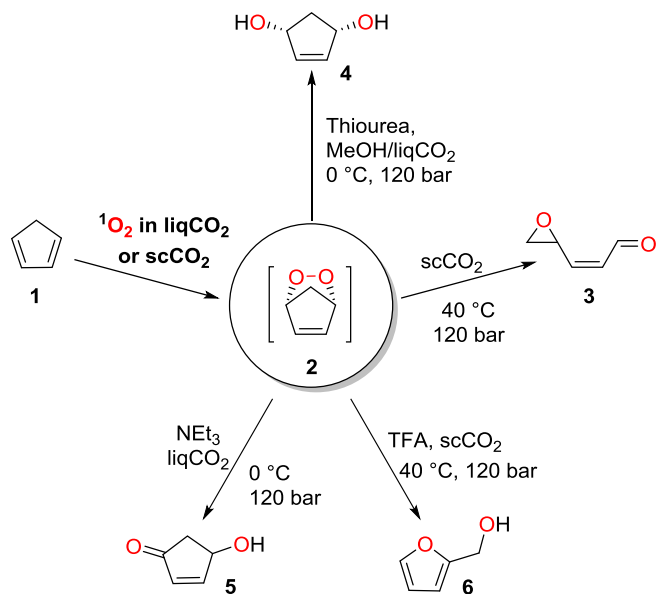
A key engineering challenge for safe operation is to ensure efficient mixing because the organic substrate is flammable, even if the CO<sub>2</sub> solvent is not itself flammable. It can be seen from Fig. 1 that we premix the O<sub>2</sub> and CO<sub>2</sub> and pass them through a static mixer (a stainless steel tube, filled with sand) before they contact the organic stream containing **1**. The combined streams are then passed through a second static mixer before entering the reactor. This strategy has previously been successfully used for catalytic thermal oxidation.<sup>35</sup> After the photo-reactor, different arrangements of additional reactors and mixers as well as a quenching reagent feed can be employed depending on the desired product (different configurations are shown in Fig. 1 with dashed lines).

### 2.2. Synthesis and reactions of the cyclopentadiene endoperoxide (**2**) in CO<sub>2</sub>

Initially the photo-oxidation of **1** was carried out in the continuous flow photo-reactor where complete consumption of the starting material was obtained over a range of conditions (Table 1). Under both liquid CO<sub>2</sub> and supercritical conditions (Table 1, entry 4–6), the complete conversion of **1** was observed. The products were a mixture of **2** and **3**, but were often obtained in different ratios due to the unstable nature of **2** above –30 °C, but the reaction appeared quantitative, with few side products detected.

In order to ensure that all of the endoperoxide **2** was converted to the *Z*-aldehyde **3**, a simple thermal reactor was added downstream after the photo-reactor. This reactor consisted of 4 × tubular reactors in series which were filled with glass beads and heated to 40 °C to promote the thermal isomerization of **2** to **3**. The optimal conditions from the photo-oxidation (Table 1, entry 5) were run with this additional reactor, which gave quantitative conversion to the aldehyde **3**.

Cleavage of the O–O bond of an endo-peroxide to yield a syn-diol, which is an attractive motif present in a range of prostaglandins<sup>48</sup> is often facilitated using thiourea as a quencher.<sup>43,49</sup> In order to synthesize **4** following the photo-oxidation of **1** in the continuous CO<sub>2</sub> photo-reactor, an additional reagent stream was added downstream of the photo-reactor (See Fig. 1, with organic pump **2** in configuration A, shown in blue). Initially, supercritical conditions were used (Table 2, entry 1) but the elevated temperature required for the supercritical conditions resulted in inconsistent yields throughout the experiments as the endo-peroxide **2** can decompose to **3** at the elevated temperatures before it could react with thiourea. Lowering the temperature to 0 °C to increase the lifetime of the endoperoxide **2** (Table 2, entries 2–3) meant operating in liqCO<sub>2</sub>, but, under these conditions, a slight increase in the yield of the diol **4** was observed. Diluting **1** by the addition of a co-solvent proved to be successful in increasing the yield of **4**, in both scCO<sub>2</sub>



**Scheme 1.** Compounds of interest from the different treatments after the photo-oxidation of Cyclopentadiene (**1**); **2**, 3-dioxabicyclo[2.2.1]hept-5-ene (**2**), 4,5-epoxycis-2-pental (**3**), (1*R*,3*S*)-cyclopent-4-ene-1,3-diol (**4**), 4-hydroxy-2-cyclopentenone (**5**), and furfuryl alcohol (**6**).

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