

# SYNLETT Spotlight 275

## Singlet Oxygen

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

### Introduction

Like molecular oxygen ( $^3\text{O}_2$ ), singlet oxygen ( $^1\text{O}_2$ ) plays an important role in atmospheric and biological processes. It is also a powerful and inexpensive organic reagent whose chemistry has been initiated by Foote and co-workers in the 1960's (Figure 1).<sup>1</sup>

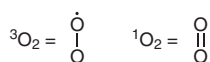
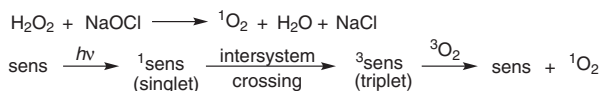


Figure 1 Triplet ( $^3\text{O}_2$ ) and singlet ( $^1\text{O}_2$ ) oxygen

Singlet oxygen can be synthesized by several ways. The oldest and simplest method consists in a mixture of hydrogen peroxide and sodium hypochlorite to form singlet oxygen, water and sodium chloride (Scheme 1).<sup>2</sup>

The currently most widely used method is the use of triplet oxygen in the presence of light and a sensitizer (e.g., rose bengal, methylene blue, tetraphenylporphyrin, vide infra).



Scheme 1 Synthetic ways for the formation of  $^1\text{O}_2$

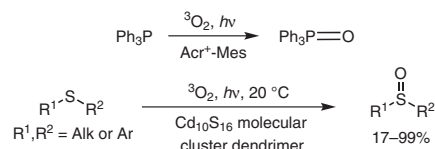
Storable singlet oxygen sources can also be used. For example,  $^1\text{O}_2$  can be obtained thanks to a mixture of triphenyl phosphite and ozone ( $\text{O}_3$ ) (via the formation of an ozonide intermediate),<sup>3</sup> the use of calcium peroxide diperhydroxide ( $\text{CaO}_2 \cdot 2\text{H}_2\text{O}$ ),<sup>4</sup> or the use of 9,10-diphenylanthracene peroxide<sup>5</sup> and its water soluble analogue 1,4-endoperoxide of 3-(4-methyl-1-naphthyl)propionic acid.<sup>6</sup>

The reactions involving singlet oxygen are usually oxidations or addition reactions that afford clean reactions which are consistent with the concept of atom economy.<sup>7</sup> In this spotlight a special emphasis has been made for illustrating different types of organic reactions in the context of the total synthesis of natural products.

### Abstracts

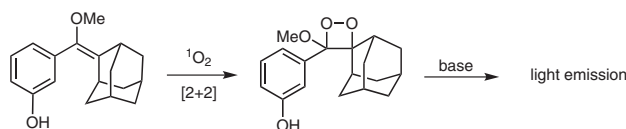
#### (A) Oxidation of Heteroatom Compounds:

Singlet oxygen can be used as a smooth oxidation reagent in the photooxidation of heteroatom compounds. For example, the oxidation of triphenylphosphine was performed in the presence of light, molecular oxygen and the sensitizer 9-mesityl-10-methylacridinium ion ( $\text{Acr}^+\text{-Mes}$ ).<sup>8</sup> The oxidation of sulfurous compound was also reported. The synthesis of sulfoxides from various thioethers was recently performed with a  $\text{Cd}_{10}\text{S}_6$  molecular cluster dendrimer as a sensitizer.<sup>9</sup>



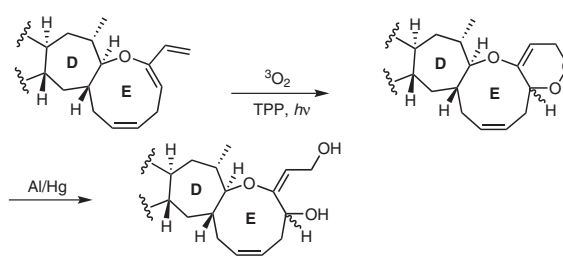
#### (B) [2+2] Cycloaddition:

The reaction of an electron-rich olefin with singlet oxygen might result in a [2+2] cycloaddition to form a 1,2-dioxetane. Matsumoto and co-workers have developed efficient methods to synthesize such compounds.<sup>10</sup> In particular, when a phenol moiety is introduced in the *meta* position of the 1,2-dioxetane, the resulting compound is particularly appealing since it can emit light in the presence of a base. Thus, these 1,2-dioxetanes have found useful applications in the development of probes for the detection of enzyme activities.<sup>11</sup>



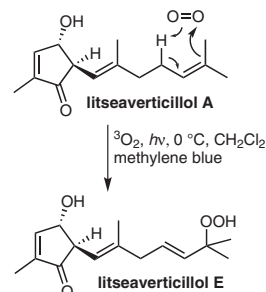
## (C) Hetero Diels–Alder [4+2] Cycloaddition:

Singlet oxygen, generated with tetraphenylporphyrin (TPP) as a sensitizer, was used during the investigations of the Nicolaou's group in their synthesis of brevetoxin A.<sup>12</sup> A hetero Diels–Alder [4+2] cycloaddition<sup>13</sup> between  $^1\text{O}_2$  and a complex diene afforded the corresponding cycloadduct. Thus, the molecule was functionalized quickly since a diol was easily obtained after the cleavage of the O–O bond by aluminum amalgam.



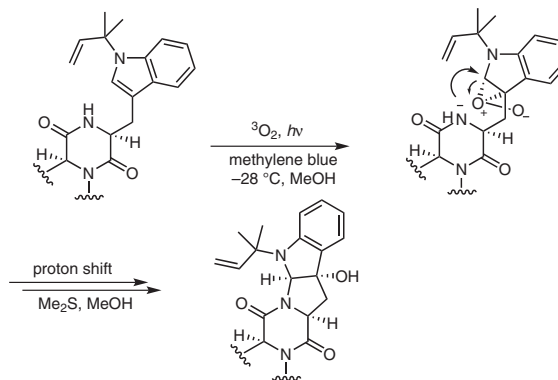
## (D) Ene Reaction:

Singlet oxygen appeared to be a key reagent in the biomimetic synthesis of the litseaverticillols family of natural products by G. Vassilikogiannakis et al.<sup>14</sup> Indeed, a hetero Diels–Alder was first performed between  $^1\text{O}_2$  and a furan to afford litseaverticillol A. This reaction was followed by an ene reaction<sup>15</sup> with  $^1\text{O}_2$ , generated with methylene blue as a sensitizer, and allowed the synthesis and the re-assignment of litseaverticillol E.



## (E) Peperoxide Synthesis:

Singlet oxygen was smartly used by E. J. Corey and co-workers in their total synthesis of okaramine N.  $^1\text{O}_2$  was added to the indole double bond with facial selectivity to form a transient intermediate peperoxide. The latter was opened by the diketopiperazine ring to form the last five-membered ring of okaramine N. The subsequent cleavage of the hydroperoxide by  $\text{Me}_2\text{S}$  allowed the formation of the tertiary alcohol and the completion of the synthesis.<sup>16</sup>



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