

SYNLETT Spotlight 275

Singlet Oxygen

Compiled by Jean-Alexandre Richard

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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).¹

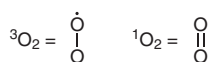
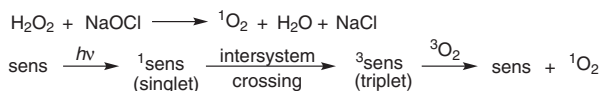


Figure 1 Triplet ($^3\text{O}_2$) and singlet ($^1\text{O}_2$) oxygen

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).²

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 $^1\text{O}_2$

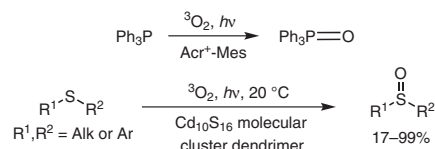
Storable singlet oxygen sources can also be used. For example, $^1\text{O}_2$ can be obtained thanks to a mixture of triphenyl phosphite and ozone (O_3) (via the formation of an ozonide intermediate),³ the use of calcium peroxide diperhydroxide ($\text{CaO}_2 \cdot 2\text{H}_2\text{O}$),⁴ or the use of 9,10-diphenylanthracene peroxide⁵ and its water soluble analogue 1,4-endoperoxide of 3-(4-methyl-1-naphthyl)propionic acid.⁶

The reactions involving singlet oxygen are usually oxidations or addition reactions that afford clean reactions which are consistent with the concept of atom economy.⁷ 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

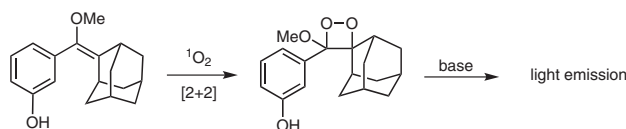
(A) Oxidation of Heteroatom Compounds:

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 ($\text{Acr}^+\text{-Mes}$).⁸ The oxidation of sulfurous compound was also reported. The synthesis of sulfoxides from various thioethers was recently performed with a Cd_{10}S_6 molecular cluster dendrimer as a sensitizer.⁹



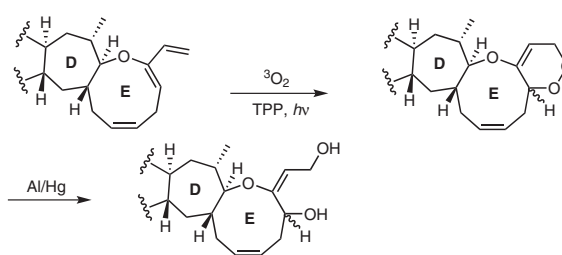
(B) [2+2] Cycloaddition:

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.¹⁰ 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.¹¹



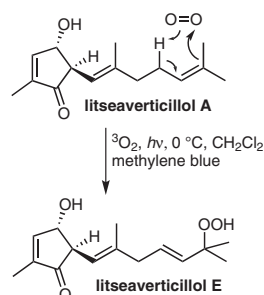
(C) Hetero Diels–Alder [4+2] Cycloaddition:

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.¹² A hetero Diels–Alder [4+2] cycloaddition¹³ 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.



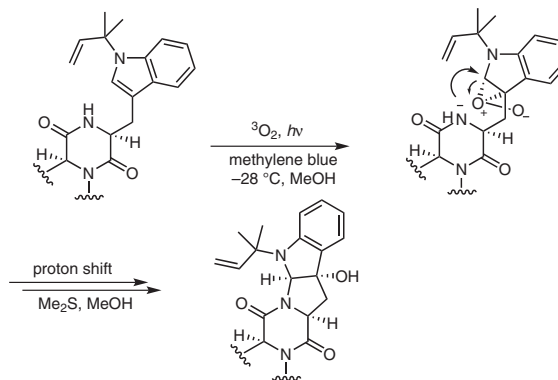
(D) Ene Reaction:

Singlet oxygen appeared to be a key reagent in the biomimetic synthesis of the litseaverticillols family of natural products by G. Vassilikogiannakis et al.¹⁴ 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 reaction¹⁵ 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 Me_2S allowed the formation of the tertiary alcohol and the completion of the synthesis.¹⁶



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