SYNLETT Spotlight 275

Singlet Oxygen

Compiled by Jean-Alexandre Richard

Jean-Alexandre Richard was born in Tours, France, in 1982. He received his Master degree in 2005 under the guidance of Prof. Ivan Jabin at the University of Le Havre. He is currently pursuing his Ph.D. studies in Rouen under the supervision of Prof. P.-Y. Renard and Dr. A. Romieu. His research interests involve the development of luminescent probes for the detection of enzyme activities.

Laboratoire de Chimie Bioorganique - Université et INSA de Rouen, UMR CNRS 6014 and FR CNRS 3038, COBRA - IRCOF, Rue Lucien Tesnière, 76130 Mont-Saint-Aignan, France.
E-mail: jarichard2000@yahoo.fr

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 diperoxhydrate ($\text{CaO}_2 \cdot 2\text{H}_2\text{O}$),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 $\text{Cd}_{10}\text{S}_{16}$ 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

References

- (1) (a) Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104.
(b) Wasserman, H. H.; DeSimone, R. W. *Singlet Oxygen In Encyclopedia of Reagents for Organic Synthesis*; Parquette, L. A., Ed.; John Wiley & Sons Ltd.: New York, **2005**, 4478–4484. (c) For recent advances in singlet oxygen chemistry, see: Clennan, E. L.; Pace, A. *Tetrahedron* **2005**, *61*, 6665.
- (2) Greer, A. *Acc. Chem. Res.* **2006**, *39*, 797.
- (3) Schaap, A. P.; Bartlett, P. D. *J. Am. Chem. Soc.* **1970**, *92*, 6055.
- (4) Pierlot, C.; Nardello, V.; Schrive, J.; Mabile, C.; Sombret, B.; Aubry, J.-M. *J. Org. Chem.* **2002**, *67*, 2418.
- (5) Wasserman, H. H.; Scheffer, J. R.; Cooper, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 4991.
- (6) Saito, I.; Matsuura, T.; Inoue, K. *J. Am. Chem. Soc.* **1981**, *103*, 188.
- (7) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) ; Trost, B. M. *Angew. Chem. Int. Ed.* **1995**, *34*, 259.
- (8) Ohkubo, K.; Nanjo, T.; Fukuzumi, S. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1489.
- (9) (a) Clennan, E. L. *Acc. Chem. Res.* **2001**, *34*, 875.
(b) Tsuboi, T.; Takaguchi, Y.; Tsuboi, S. *Chem. Commun.* **2008**, 76.
- (10) For a recent review, see: Matsumoto, M. *J. Photochem. Photobiol., C* **2004**, *5*, 27; and references therein.
- (11) For representative examples, see: (a) Bronstein, I.; Voyta, J. C.; Thorpe, G. H. G.; Kricka, L. J.; Armstrong, G. *Clin. Chem.* **1989**, 1441. (b) Sabelle, S.; P, Y.; Pecorella, K.; de Suzzoni-Dezard, S.; Creminon, C.; Grassi, J.; Mioskowski, C. *J. Am. Chem. Soc.* **2002**, *124*, 4874. (c) Richard, J.-A.; Jean, L.; Romieu, A.; Massonneau, M.; Noack-Fraissignes, P.; Renard, P. Y. *Org. Lett.* **2007**, *9*, 4853.
- (12) Nicolaou, K. C.; Gunzner, J. L.; Shi, G. Q.; Agrios, K. A.; Gartner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 646.
- (13) For a review, see: Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243.
- (14) (a) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5465. (b) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T. *Org. Lett.* **2004**, *6*, 2039.
(c) Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem. Eur. J.* **2005**, *11*, 5899. (d) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001.
- (15) For a review, see: Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595.
- (16) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.