Synthesis of natural molecules with isotopically labelled oxygen

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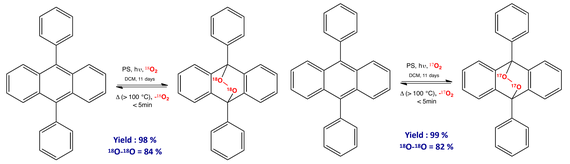
Introduction

Radioisotope labeling is a method of choice for elucidating molecular mechanisms, especially in biological research [1] . Oxygen plays a key role in several functional groups, and its isotopic labeling is often decisive for the understanding of the mechanisms. Among the different sources of isotopic oxygen atoms, oxygen has been successfully used for the production of a wide variety of natural products and drugs, and would allow the advantageous introduction of two labeled oxygen atoms at the same time. Among the different possibilities offered by O_2, its photosensitized singlet state has very interesting properties [2]. The objective of our study is to implement a new method for generating labeled O_2 and to use stoichiometric amounts of it to *O-labelled bioactives molecules via singlet oxygen.

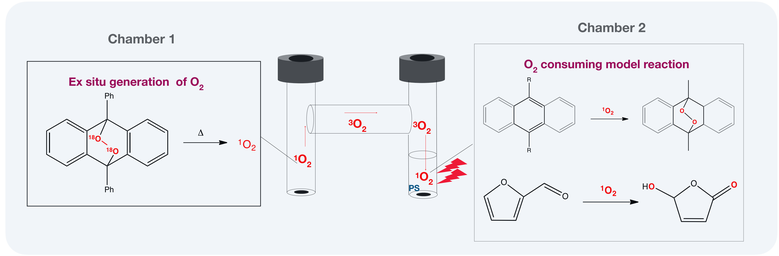
Material and methods

Synthesis of 9,10-diphenylanthracene endoperoxide and use as surrogate of O_2 [3]



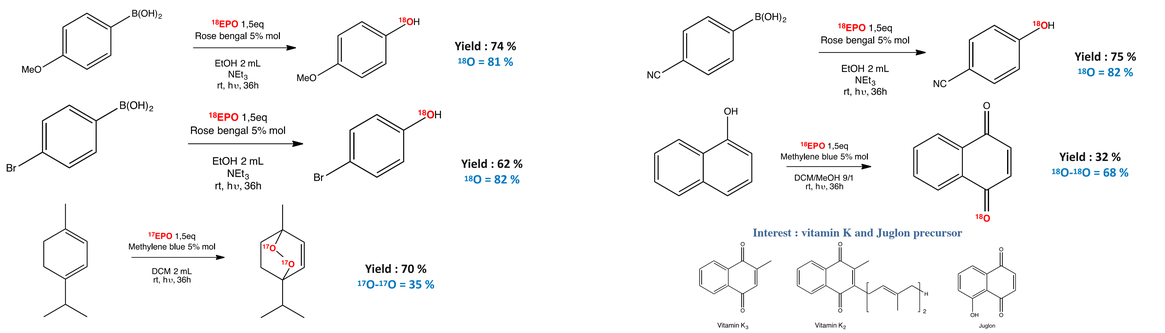
✓Easy to synthesize
✓Good yield
✓Stable at room temperature
✓Break down on heating with release of O_2 in the singlet state

Two-chamber system

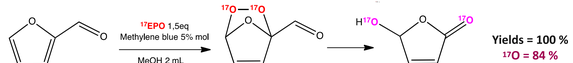


Goals : confirm the efficiency of two-chamber system using reactions with highly $^1O_2$ sensitive species

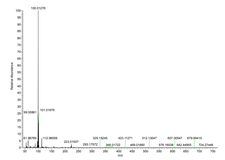
Synthesis of natural and bioactive molecules [4]



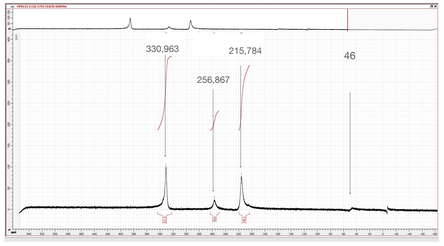
Mechanism elucidation [5]



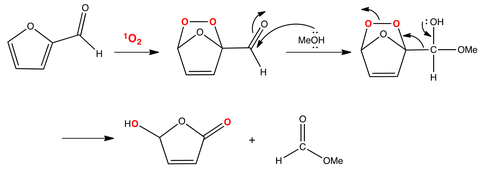
Mass spectrometry spectrum



NMR ^{17}O spectrum

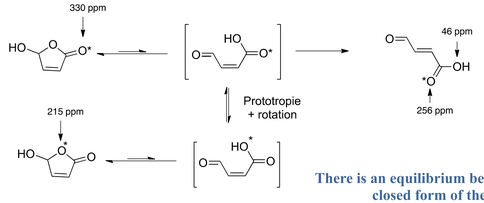


Mechanism describe in the literature



Normally, 2 O-labelled atoms : doesn't correspond to our observations

Interpretation of our spectra



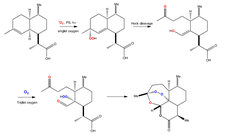
There is an equilibrium between the open and closed form of the molecule.

Conclusion

✓ Double-chamber system is efficient
✓ Ex-situ generation of $^1O_2$ from endoperoxide
✓ Synthesis of O-labeled molecules

Perspective

➢ Use double-chamber and triple-chamber system to synthetise drugs and understand mechanism
➢ Synthesize artemisinin with labelled oxygen and understand metabolism of this bioactive molecule
➢ Good results already obtained : to be optimized



[1] *Radioisotopes in Biology : A Practical Approach*, Second edition; Slater, R. J., Ed; Oxford University Press: Oxford, **2002**, 130–263.
[2] Theodorou et al., *J. Label Compd. Radiopharm* **2014**, 57 481–508
[3] Wasserman H. H. Murray R. W. (1979). Singlet oxygen. New York : Academic Press
[4] Carney et al., *Synthesis*, **2012**, 44, 2560–2566
[5] Castiglione et al., *Annu. Rep. NMR Spectrosc.* **2015**, 45, 143–195