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$NDPO_2$ AS A SELECTIVE GENERATOR OF $^1O_2$ USED IN THE SCAVENGING ACTIVITY ASSAY OF 2,3-DIARYLXANTHONES

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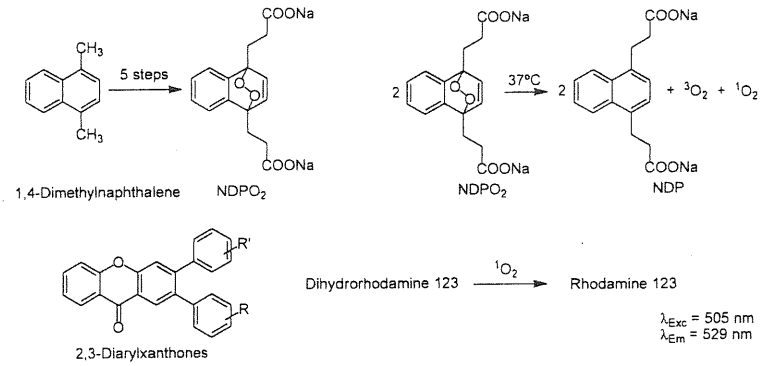
Singlet oxygen ($^1O_2$) is a highly reactive form of molecular oxygen towards biological targets such as DNA, RNA, proteins and unsaturated fatty acids. This reactive oxygen species is related to many oxidative stress pathophysiologies, and thus its specific scavenging is considered of high therapeutic importance.

Several efforts have been made to develop suitable $^1O_2$ generators based on the thermal decomposition of endoperoxides obtained by synthesis.[1] We will describe the synthesis of the thermodissociable endoperoxide disodium 3,3'-(1,4-naphthalene)bispropionate ($NDPO_2$) used for the chemical generation of $^1O_2$.[2] We will also present the $^1O_2$ scavenging activity of various 2,3-diarylxanthones derivatives, measured by monitoring the oxidation of non fluorescent dihydrorhodamine 123 to fluorescent rhodamine 123, as previously described,[3] in order to better understand their antioxidant potentialities.



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(1) Nagano T. *J. Clin. Biochem. Nutr.* **2009**, *45*, 111-124.
(2) Costa D, Fernandes E, Santos JLM, Pinto DCGA, Silva AMS, Lima JLFC. *Anal. Bioanal. Chem.* **2007**, *387*, 2071-2081.
(3) Gomes A, Fernandes E, Silva AMS, Santos CMM, Pinto DCGA, Cavaleiro JAS, Lima JLFC. *Bioorg. Med. Chem.* **2007**, *15*, 6027-6036.

NDPO$_2$ AS A SELECTIVE GENERATOR OF $^1O_2$ USED IN THE SCAVENGING ACTIVITY ASSAY OF 2,3-DIARYLXANTHONES

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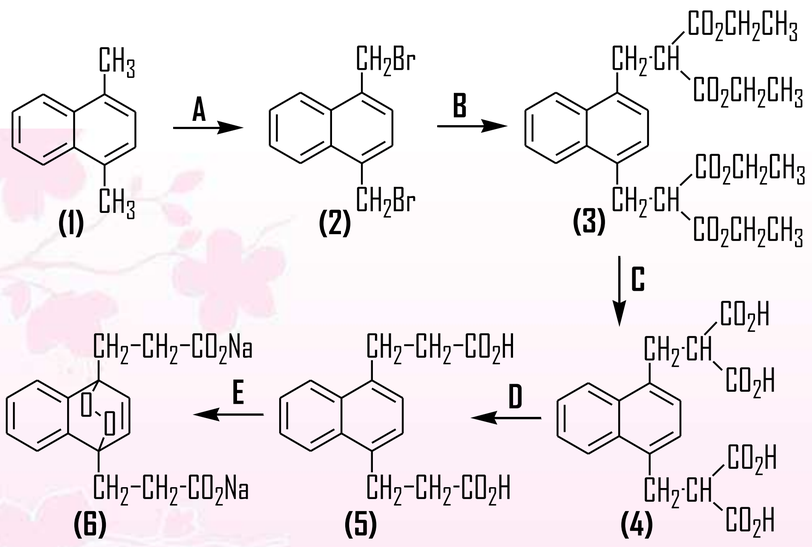
INTRODUCTION

- Singlet oxygen ($^1O_2$) is a highly reactive form of molecular oxygen towards biological targets such as DNA, RNA, proteins and unsaturated fatty acids. This reactive oxygen species is related to many oxidative stress pathophysiologies, and thus its specific scavenging activity is considered of high therapeutic importance.
- Several efforts have been made to develop suitable $^1O_2$ generators based on the thermal decomposition of endoperoxides obtained by synthesis.[1] We will describe the synthesis of the thermodissociable endoperoxide disodium 3,3'-(1,4-naphthalene)bispropionate (NDPO$_2$) **6** used for the chemical generation of $^1O_2$ (Scheme 1).[2]
- We will also present the $^1O_2$ scavenging activity of various 2,3-diarylxanthones derivatives **14a-i** (Scheme 2), measured by monitoring the oxidation of non fluorescent dihydrorhodamine 123 to fluorescent rhodamine 123, as previously discribed[3], in order to better understand their antioxidant potentialities.

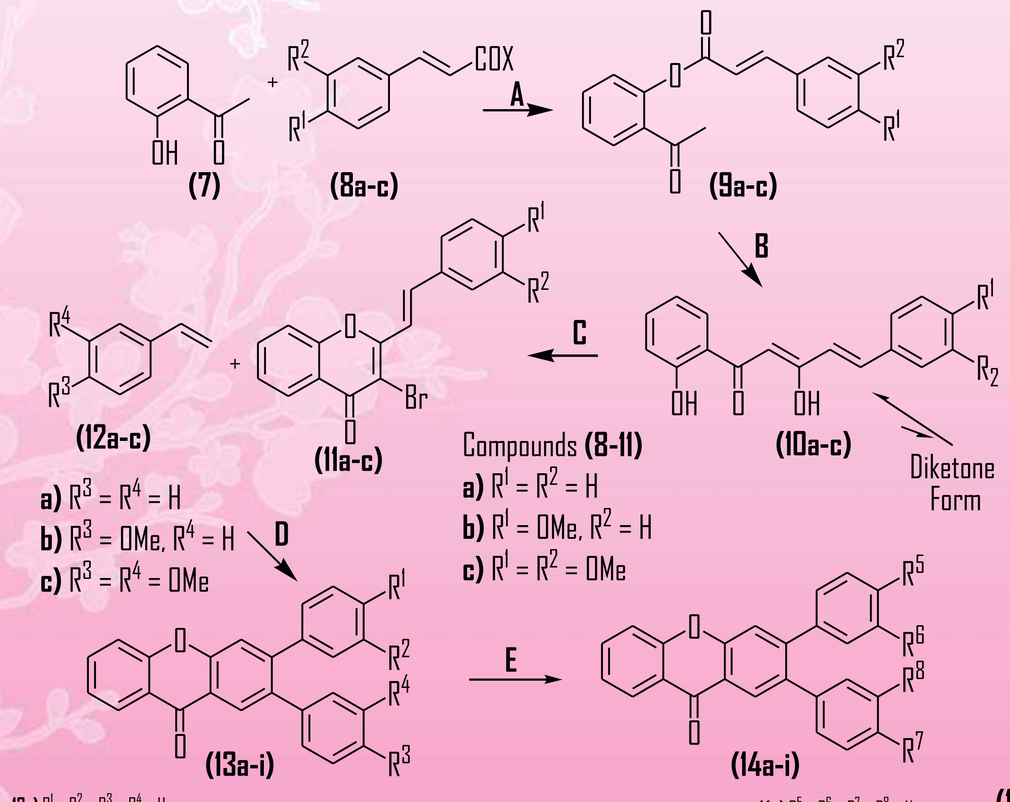
SYNTHESIS

Scheme 1: Synthesis of disodium 3,3'-(1,4-naphthalene)bispropionate **6** (NDPO$_2$)



A: CCl_4, NBS, AIBN, reflux, 3h
B: THF, NAH, $CH_2(CO_2Et)_2$, reflux, 2h
C: MeOH, NaOH, H_2O, 90°C, 1h
D: 200°C
E: **i)** H_2O, NaOH, $NaHCO_3$, Na_2CO_3, Na_2MoO_4, H_2O_2, 0°C, 72 min
ii) MeONa, MeOH

Scheme 2: Synthesis of 2,3-diarylxanthones **14a-i**



Compounds **(8-11)**
a) $R^1 = R^2 = H$
b) $R^1 = OMe$, $R^2 = H$
c) $R^1 = R^2 = OMe$

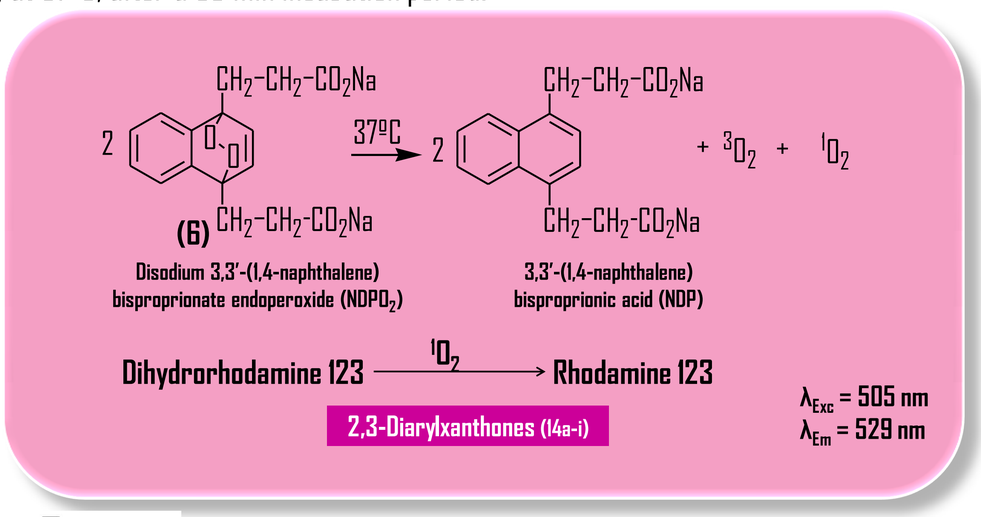
13a) $R^1 = R^2 = R^3 = R^4 = H$
13b) $R^1 = R^2 = R^4 = H$; $R^3 = OMe$
13c) $R^1 = R^2 = H$; $R^3 = R^4 = OMe$
13d) $R^1 = OMe$; $R^2 = R^3 = R^4 = H$
13e) $R^1 = R^3 = OMe$; $R^2 = R^4 = H$
13f) $R^1 = R^3 = R^4 = OMe$; $R^2 = H$
13g) $R^1 = R^2 = OMe$; $R^3 = R^4 = H$
13h) $R^1 = R^2 = R^3 = OMe$; $R^4 = H$
13i) $R^1 = R^2 = R^3 = R^4 = OMe$

A: X = Cl, Dry Py, room temp., 2h or X = OH, Dry Py, $POCl_3$, 60°C, 2h
B: DMSO, KOH, room temp., 2 h
C: THF, PTT, room temp., 12 h
D: NMP, $Pd(PPh_3)_4$, PPh_3, Et_3N, 160°C to reflux
E: CH_2Cl_2, BBr_3, -78 °C to room temp., N_2, 1-4h

14a) $R^5 = R^6 = R^7 = R^8 = H$
14b) $R^5 = R^6 = R^8 = H$; $R^7 = OH$
14c) $R^5 = R^6 = H$; $R^7 = R^8 = OH$
14d) $R^5 = OH$; $R^6 = R^7 = R^8 = H$
14e) $R^5 = R^7 = OH$; $R^6 = R^8 = H$
14f) $R^5 = R^7 = R^8 = OH$; $R^6 = H$
14g) $R^5 = R^6 = OH$; $R^7 = R^8 = H$
14h) $R^5 = R^6 = R^7 = OH$; $R^8 = H$
14i) $R^5 = R^6 = R^7 = R^8 = OH$

SCAVENGING ACTIVITY OF SINGLET OXYGEN ($^1O_2$)

The $^1O_2$ was generated by the thermal decomposition of a previously synthesized water-soluble endoperoxide **6** [disodium 3,3'-(1,4-naphthalene)bispropionate (NDPO$_2$)]. The $^1O_2$ scavenging activity was measured by monitoring the oxidation of non-fluorescent DHR to fluorescent rhodamine 123, at 37ºC, after a 30 min incubation period.



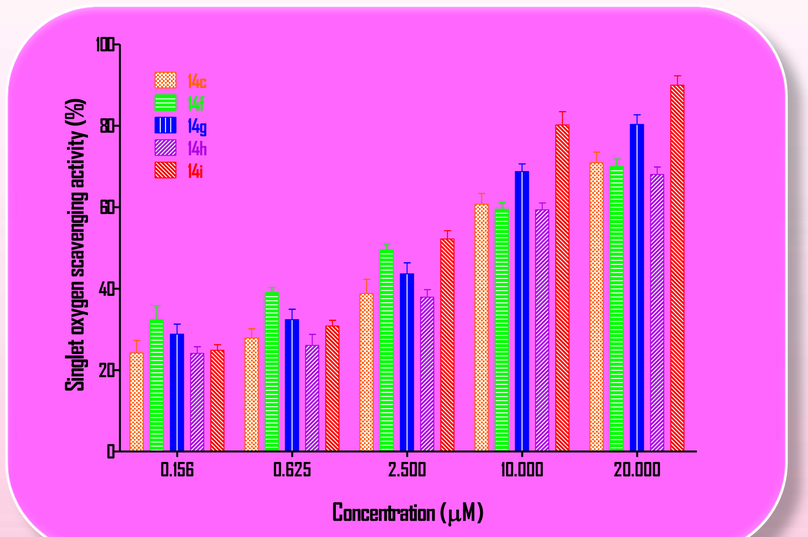
Synergy HT Multi-Mode Microplate Reader

- Tested compounds dissolved in DMSO.
- Ascorbic acid was used as positive control.
- Each assay corresponds to five experiments, conducted in triplicate.
- The results were expressed as the percentage inhibition of $^1O_2$-induced oxidation of DHR.

$$\text{Scavenging effect} = \frac{A_{antioxidant} - A_{blank}}{A_{control} - A_{blank}} \times 100\ \%$$

Compound	$^1O_2$ IC_{50} (μM)
14a	27%*100μM
14b	80 ± 11
14c	6.0 ± 1.0
14d	68.8 ± 6.2
14e	58.4 ± 4.9
14f	3.3 ± 0.7
14g	4.5 ± 0.6
14h	6.8 ± 0.5
14i	2.5 ± 0.2
Ascorbic acid	1.8 ± 0.1

*Scavenging effect (mean %) at the highest tested concentration



CONCLUSIONS

- ☑ The synthesis of the thermodissociable endoperoxide disodium 3,3'-(1,4-naphthalene)bispropionate (NDPO$_2$) **6** was achieved after 5 steps, starting from the 1,4-dimethylnaphthalene.
- ☑ The xanthones **14a-i** were synthesized by cinnamoylation of 2'-hydroxyacetophenone **7** with cinnamoyl chlorides **8a-c**, followed by Baker-Venkataraman rearrangement. The bromination and cyclisation processes leads to the 3-bromo-2-styrylchromones **11a-c**, which after Heck reaction with styrenes **12a-c** afforded the methoxy-2,3-diarylxanthones **13a-i**. The last step was the cleavage of the hydroxy protecting groups with boron tribromide.
- ☑ The results in the scavenging activity of singlet oxygen seem to be largely affected by the number and position of hydroxyl groups of the 2,3-diarylxanthones derivatives.
- ☑ The xanthone **14i** (with two catechol rings) was the most potent scavenger of singlet oxygen scavenging assay.

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(1) Nagano T. *J. Clin. Biochem. Nutr.* **2009**, *45*, 111-124.
(2) Costa D, Fernandes E, Santos J L M, Pinto D C G A, Silva, A M S, Lima J L F C. *Anal. Bioanal. Chem.* **2007**, *387*, 2071-2081.
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