



A singlet oxygen approach to oxaspirocycles

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ABSTRACT

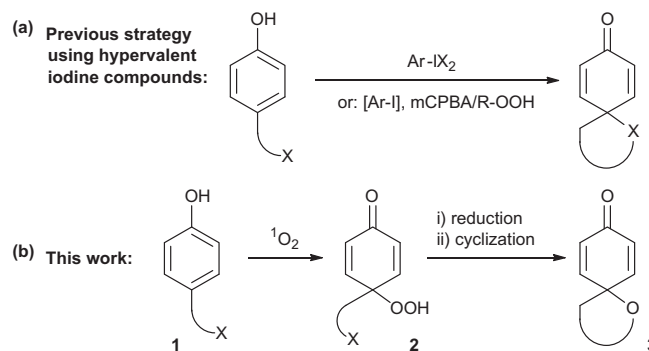
A method for the preparation of oxygen containing spirocycles using singlet oxygen is reported. A series of phenols were converted into the corresponding peroxy-cyclohexadienone derivatives by irradiation with visible light in the presence of a sensitizer and oxygen. The resulting peroxides could be converted into ether and lactone spirocycles in one or two steps. The synthesis of the oxaspirocycles from the phenols can also be performed in a one-pot fashion, avoiding the isolation of the peroxide intermediates.

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The oxidative dearomatization of phenols provides an expedient route to oxaspirocycles, which serve as useful building blocks in organic chemistry and represent important intermediates in natural product synthesis.¹ As a result, several reagent combinations have been developed to promote this reaction. Most prominent among those methods is the use of hypervalent iodine reagents,² which have been shown to efficiently promote the direct conversion of phenol derivatives to the oxaspirocycles.³ These reactions are usually performed with stoichiometric amounts of hypervalent iodine(III) reagents, but the catalytic use of iodine compounds together with a simpler terminal oxidant is also possible (Scheme 1a).⁴ Alternative methods using other oxidants have also been reported.⁵

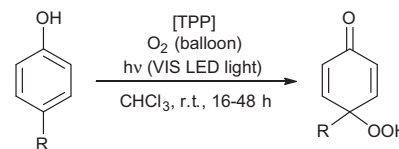
In recent years, we have become interested in developing synthetic methodologies which harness the reactivity of molecular oxygen or proceed via intermediate peroxides.⁶ In line with this research theme, we were intrigued by the reaction of singlet oxygen with substituted phenols⁷ and wondered if we could incorporate this into a new approach to oxaspirocycles. We reasoned that a substituted phenol bearing an appropriate electrophile **1** could be reacted with singlet oxygen to give the corresponding peroxy quinol **2**. Reduction of the hydro peroxide to the alcohol and subsequent cyclization would then provide the desired spirocyclic product **3** (Scheme 1b). A related reaction was studied by Matsuura, Saito et al., who observed the formation of two spiro-lactones in low yield as byproducts of the photooxidation of phenols, without optimizing their synthesis.⁸

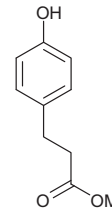
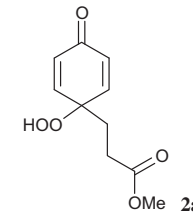
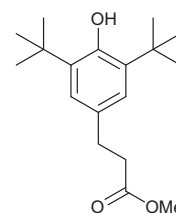
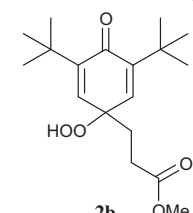
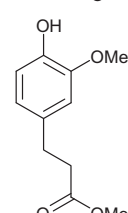
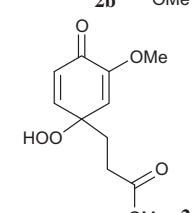
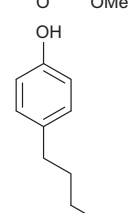
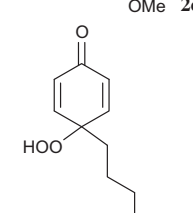
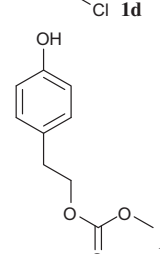
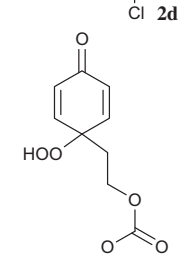
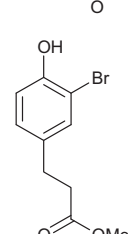
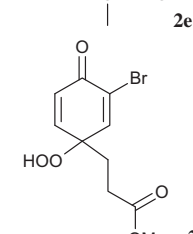
We began our study by examining the photochemical conversion of methyl 3-(4-hydroxyphenyl)propionate (**1a**) to the corresponding peroxy-quinol. A brief survey of reaction conditions revealed that irradiation of a methanol solution of **1a** containing 5 mol % tetraphenylporphyrin (TPP) with white visible light using LEDs provided **2a** in 90% yield after 16 h. Pleasingly, this method was found to be reasonably general and could be extended to a variety of phenol derivatives (Table 1). The starting materials were synthesized from commercially available phenol derivatives by known procedures: esterification in methanol in case of **1a–c** and **1f**,⁹ chlorination of the alcohol in case of **1d**,¹⁰ reaction with dimethylcarbonate in case of **1e**¹¹ and bromination with NBS in case of **1f**¹² (see the Supplementary data for details). The reaction was tolerant of sterically demanding substrates such as *tert*-butyl substituted phenol **1b** and provided peroxy quinol **2b** in near



Scheme 1. Singlet oxygen approach to oxaspirocycles vs use of hypervalent iodine compounds.

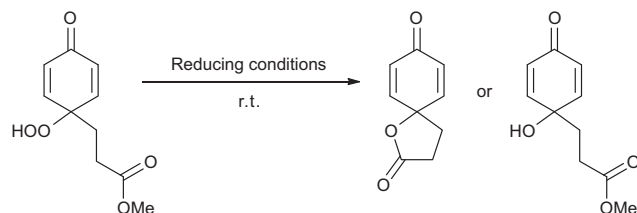
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Table 1
Singlet oxygen promoted de-aromatization


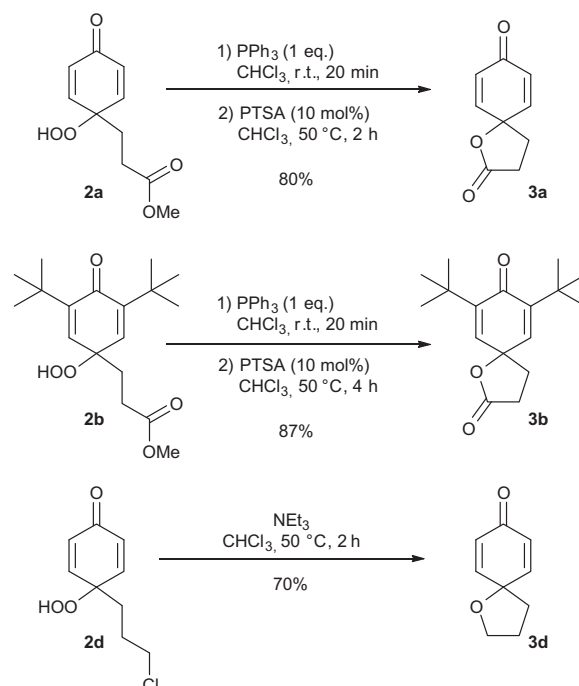
Entry	Starting material	Product	Yield (%)
1			90
2			98
3			50
4			50
5			52
6			0

Conditions: phenol (0.1 g), tetraphenylporphyrin (TPP, 5 mg, 0.01 mmol), CHCl₃ (5 ml), O₂-balloon, 16–48 h, white LED light.

quantitative yield (entry 2). The reaction was also tolerant of electron rich phenols, delivering the desired product **2c** albeit in somewhat reduced yields (50%, entry 3). Incorporation of a tethered

Table 2
Examining the reduction–cyclization cascade


Entry	Reducing conditions	Product	Yield (%)
1	1M Na ₂ SO ₃	3a	10
2	1M Sodium dithionite	—	0
3	H ₂ /Pd-C	—	0
4	1M Na ₂ S ₂ O ₃	3a	50
5	Triethylamine	4a	78
6	Triphenylphosphine	4a	90

**Scheme 2.** Formation of oxygen containing spirocycles.

chloride or carbonate protected alcohol was also tolerated, providing **2d** and **2e** in 50% and 52% yield, respectively (entries 4 and 5).

It should be noted that the lower yields of **2c–e** can be attributed to degradation of TPP before the reaction reached completion, which is observable by a colour change. The use of larger amounts of TPP or addition of a second batch did not improve the yields. However, the reaction mixtures contained only desired product and unreacted starting material, suggesting optimization for each substrate may be possible. The brominated phenol **1e** failed to react under these conditions and only unreacted starting material could be detected (entry 6).

With a practical method for the formation of peroxy quinols **2a–e** in hand, we turned our attention to the proposed reduction/cyclization cascade. We began by examining the reduction of **2a** with a variety of common reducing agents (Table 2). Initial tests with hydrogen and palladium on charcoal, sodium sulfite and sodium dithionite were disappointing and resulted in either

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