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# 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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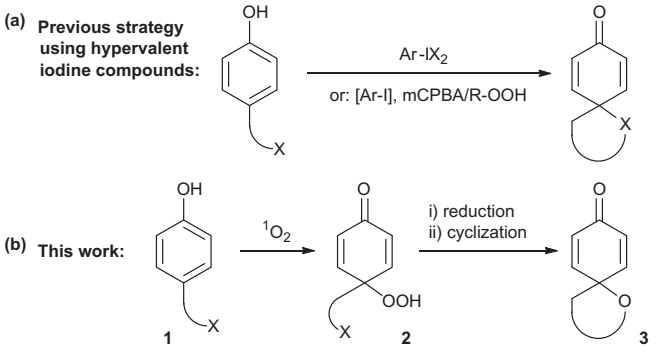
The oxidative dearomatization of phenols provides an expedient route to oxaspirocycles, which serve as useful building blocks in organic chemistry and represent important intermediates in natural product synthesis.[1] As a result, several reagent combinations have been developed to promote this reaction. 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 phenols[7] 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 spirolactones 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-hydroxyphenol)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 % tetraphenylporphin (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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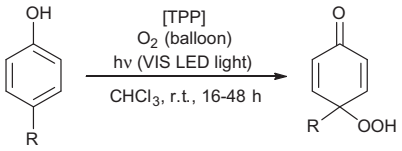
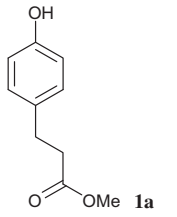
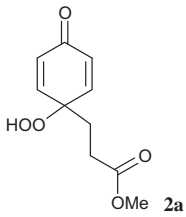
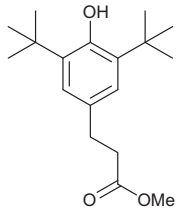
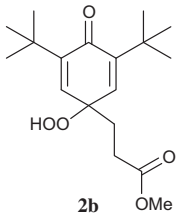
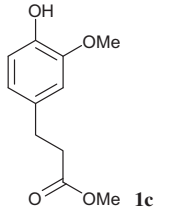
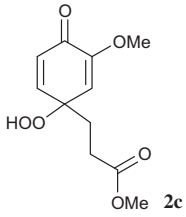
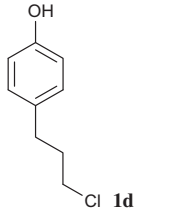
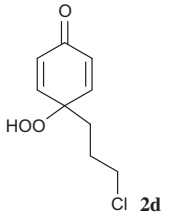
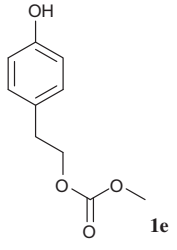
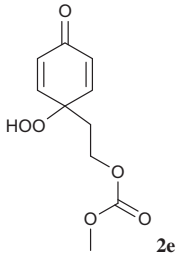
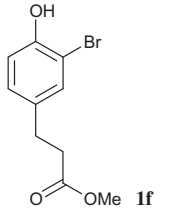
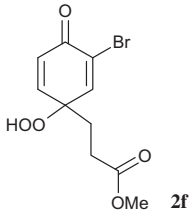
**Table 1**
Singlet oxygen promoted de-aromatization




| Entry | Starting material | Product | Yield (%) |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 90 |
| 2 |  **1b** |  **2b** | 98 |
| 3 |  **1c** |  **2c** | 50 |
| 4 |  **1d** |  **2d** | 50 |
| 5 |  **1e** |  **2e** | 52 |
| 6 |  **1f** |  **2f** | 0 |

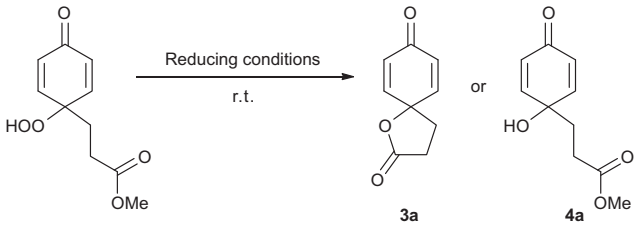
Conditions: phenol (0.1 g), tetraphenylporphin (TPP, 5 mg, 0.01 mmol), $CHCl_3$ (5 ml), $O_2$-balloon, 16–48 h, white LED light.

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

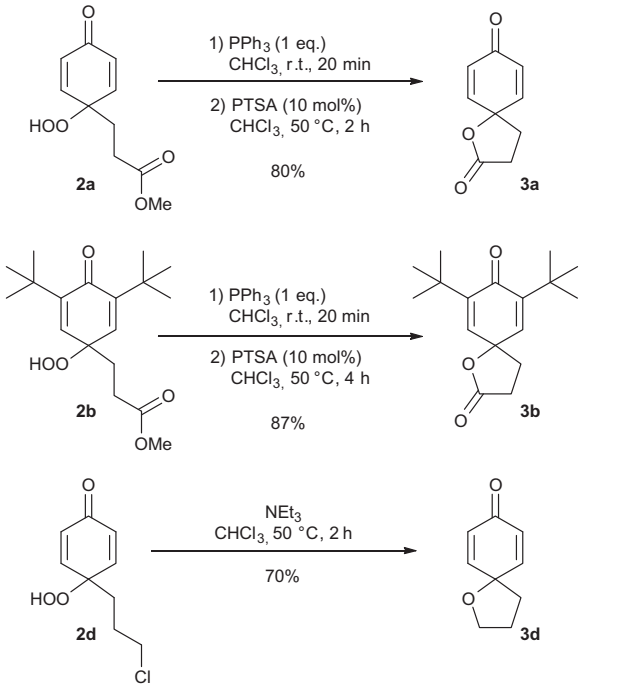
It should be noted that the lower yields of **2c–e** can be attributed to degradation of TPP before the reaction reached completion, which is observable by a colour change. The use of larger amounts of TPP or addition of a second batch did not improve the yields. However, the reaction mixtures contained 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

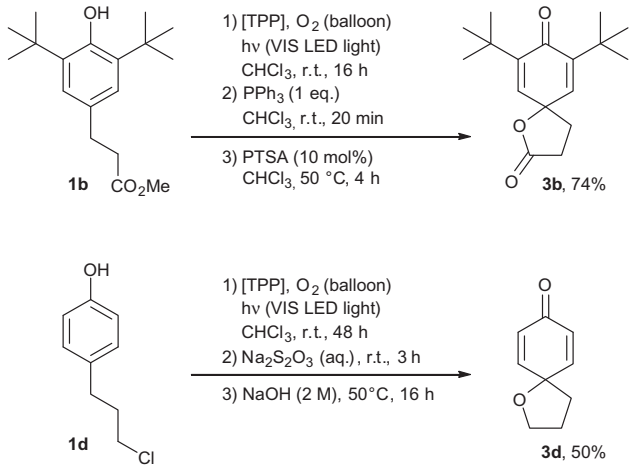
**Table 2**
Examining the reduction–cyclization cascade



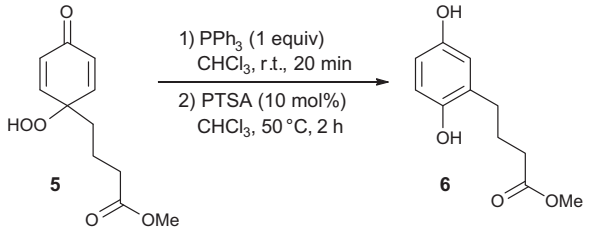

| Entry | Reducing conditions | Product | Yield (%) |
|---|---|---|---|
| 1 | 1M $Na_2S0_3$ | **3a** | 10 |
| 2 | 1M Sodium dithionite | — | 0 |
| 3 | $H_2$/Pd–C | — | 0 |
| 4 | 1M $Na_2S_2O_3$ | **3a** | 50 |
| 5 | Triethylamine | **4a** | 78 |
| 6 | Triphenylphosphine | **4a** | 90 |




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




**Scheme 3.** Formation of oxaspirocycles in a one-pot fashion.




**Scheme 4.** Rearrangement in the attempted formation of a six-membered lactone.

poor mass recovery or complex reaction mixtures (entries 1–3). A more positive result was achieved when sodium thiosulfate was adopted, providing the desired lactone **3a** in 50% isolated yield, although mass recovery remained a significant problem and attempts to optimize the isolated yield failed. Finally, the use of either triethylamine or triphenylphosphine was effective at promoting the reduction of the peroxy quinol to the corresponding alcohol **4a** in good yield (entries 5 and 6).

Although triphenylphosphine or triethylamine delivered the open chain alcohol **4a** and not the desired lactone **3a**, we reasoned that the alcohol could easily be converted into the lactone by simply adding an acid catalyst to promote cyclization, analogous to related reactions forming spirocycles.[13] On this basis we developed a one pot, two step procedure as shown in Scheme 2. The peroxide is reduced with triphenylphosphine in chloroform, followed by addition of catalytic amounts of *para*-toluene sulfonic acid and heating the solution to 50 °C. Isolation by column chromatography gave the lactone **3a** in a combined yield of 80%. This procedure could also be applied to peroxy quinol **2b**, giving the spirocycle **3b** in 87% yield.

Attempts to form the lactone with **2c** only gave a complex reaction mixture, presumably due to unwanted reactions of the electron rich enol ether moiety. Also, attempts to form the cyclic carbonate from **2e** were unsuccessful, under both acidic and basic conditions over a range of temperatures. In contrast, formation of the spiro-ether **3d** from the peroxy quinol **2d** could be achieved in a single step by using triethylamine as both reductant and base to promote cyclization (Scheme 2).

The sequence of peroxide formation, reduction and cyclization can also be performed in a one-pot fashion, avoiding the isolation of the hydroperoxides. For example, phenol–ester **1b** could be transformed into spirolactone **3b** with an overall yield of 74% (Scheme 3). Similarly, the spiroether **3d** could be formed in a slightly modified one-pot procedure comprising oxidation with singlet oxygen, reduction with sodium thiosulfate in a biphasic system and cyclization with sodium hydroxide, with an overall isolated yield of 50% based on phenol **1d**.

Unfortunately, the attempt to extend this strategy to the formation of 6,6-spirocyclic compounds failed. When the peroxyquinol **5** was subjected to the reduction–cyclization cascade, the rearranged hydroquinone **6** was isolated instead of the desired spirocycle (Scheme 4). A rearrangement of this kind had been observed before with similar compounds under acidic or basic conditions.[8b,14]

In conclusion, we have developed a singlet oxygen promoted method for the formation of oxaspirocycles, including five-membered lactone and ether units. The method involves an aerobic photosensitized dearomatization of phenols, a reduction of the resulting hydroperoxides to the alcohols and an acid- or base-catalysed cyclization step. The reaction sequence can be performed in a one pot fashion, avoiding the isolation of the peroxide intermediates. Although the substrate scope is limited, this method provides an alternative to the use of hypervalent iodine reagents.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.064.

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