Oxidation of Furans

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One-Pot Transformation of Simple Furans into 4-Hydroxy-2-cyclopentenones in Water**

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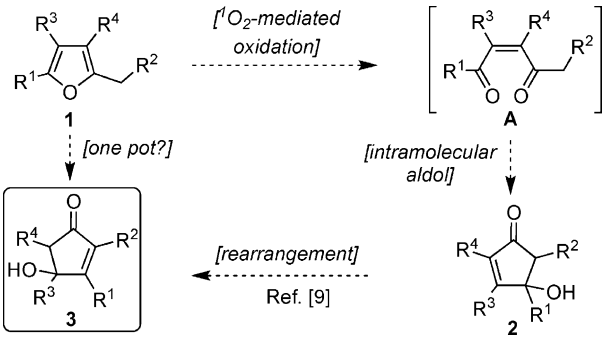
In memory of Yiannis Elemes

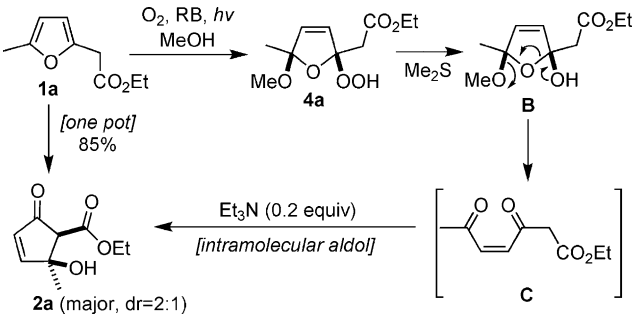
Abstract: *A highly efficient one-pot transformation of readily accessible furans into 4-hydroxy-2-cyclopentenones in H_2O, using singlet oxygen as oxidant, has been developed.*

The 4-hydroxy-2-cyclopentenones **2** and **3** (Scheme 1) are a ubiquitous class of molecules; for, not only do they represent a structural motif that is present in many bioactive compounds, but, they are common building blocks en route to numerous other targets.[1,2a] It comes, therefore, as no surprise that many synthetic groups have worked on ways to construct this privileged scaffold.[2–5] Some decades ago, Piancatelli et al.[3g] established that furans could offer a useful starting point when they showed that 2-(α-hydroxyalkyl) furans could be transformed into 4-hydroxy-2-cyclopentenones by the action of strong acids. Since then a number of milder variants of this reaction have been developed.[3] Very recently, Dy(OTf)$_3$ has been shown to catalytically mediate a Piancatelli-type reaction.[3a] Microwave-assisted conversion of 2-(α-hydroxyalkyl) furans to 4-hydroxy-2-cyclopentenones without use of a catalyst has also been reported.[3d] In a different strategy, which includes the direct oxidation of the furan nucleus (**1**→**A**, Scheme 1), more general furan substrates have sometimes been used;[4] however, this approach was accompanied by the separation of the transformation into several independent steps (up to three). The oxidative first step has been mediated by *meta*-chloroperoxybenzoic acid (*m*-CPBA), *N*-bromosuccinimide (NBS), Br_2, H_2O_2, as well as, by electrolysis.[4] Whilst most of the recent methods[3,4] use conditions that are milder than Piancatelli's original, broad functional group tolerance combined with applicability across a wide variety of furan substrates cannot yet be said to have been achieved.



Scheme 1. Proposed one-pot synthesis of 4-hydroxy-2-cyclopentenones (types **2** and **3**).

Herein, we present a new one-pot methodology which is extremely mild, starts from readily accessible furans (not limited to 2-(α-hydroxyalkyl) furans, or furans substituted with an activating group) and has very broad functional group compatibility. It uses the highly selective and environmentally benign oxidant, singlet oxygen ($^1O_2$).[5] In addition, we have shown that, by making small changes to the reaction conditions, the outcome can be tailored to access just one of a number of different possible structures. Finally, in the latter stages of the investigation described herein, a green and



Scheme 2. Singlet oxygen initiated one-pot synthesis of cyclopentenone **2a**.

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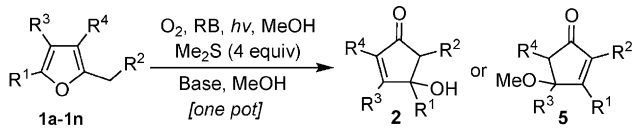
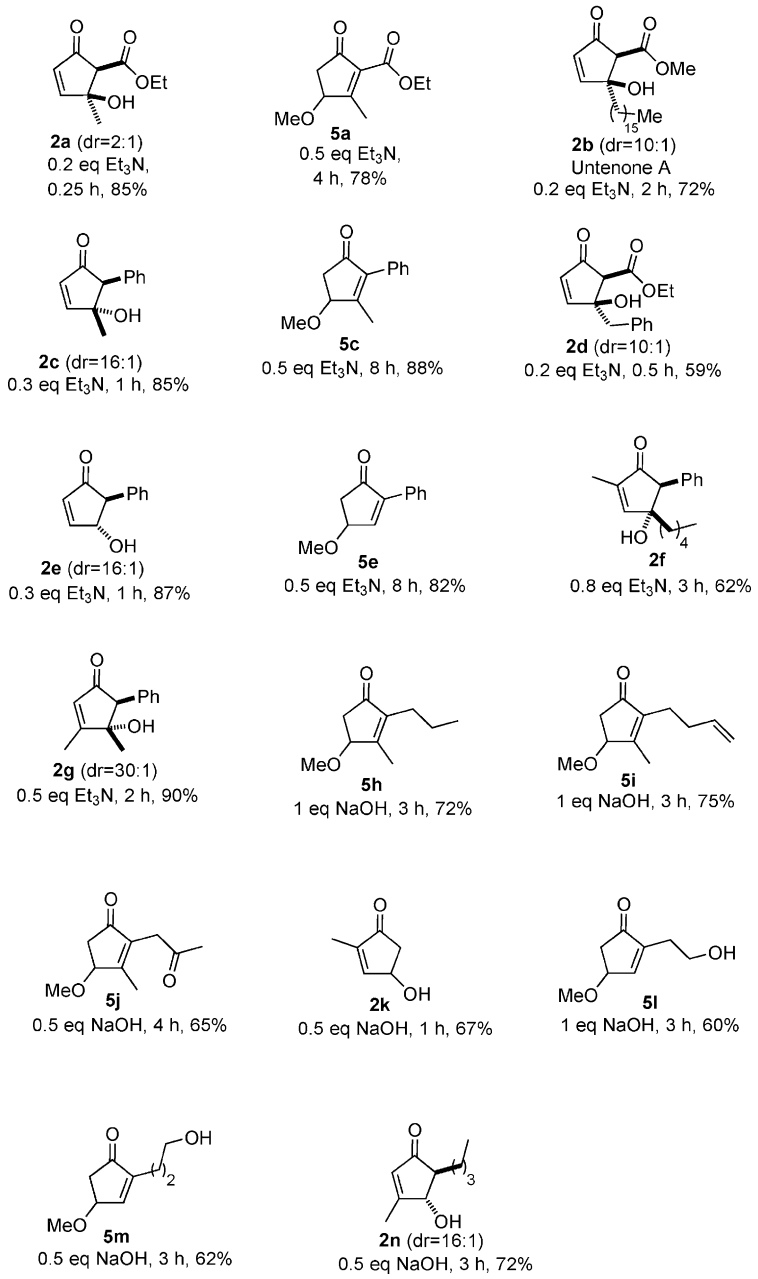


1a: R^1=-Me, R^2=-CO_2Et, R^3=-H, R^4=-H
1b: R^1=-$(CH_2)_{15}CH_3$, R^2=-CO_2Me, R^3=-H, R^4=-H
1c: R^1=-Me, R^2=-Ph, R^3=-H, R^4=-H
1d: R^1=-Bn, R^2=-CO_2Et, R^3=-H, R^4=-H
1e: R^1=-H, R^2=-Ph, R^3=-H, R^4=-H
1f: R^1=-$(CH_2)_4CH_3$, R^2=-Ph, R^3=-H, R^4=-Me
1g: R^1=-Me, R^2=-Ph, R^3=-Me, R^4=-H
1h: R^1=-Me, R^2=-$(CH_2)_2CH_3$, R^3=-H, R^4=-H
1i: R^1=-Me, R^2=-$(CH_2)_2CH{=}CH_2$, R^3=-H, R^4=-H
1j: R^1=-Me, R^2=-CH_2COCH_3, R^3=-H, R^4=-H
1k: R^1=-H, R^2=-H, R^3=-H, R^4=-Me
1l: R^1=-H, R^2=-CH_2CH_2OH, R^3=-H, R^4=-H
1m: R^1=-H, R^2=-$(CH_2)_2CH_2OH$, R^3=-H, R^4=-H
1n: R^1=-H, R^2=-$(CH_2)_3CH_3$, R^3=-Me, R^4=-H



Scheme 3. Synthesis of 4-hydroxy- and 4-methoxy-2-cyclopentenones in MeOH. Here and throughout this investigation both eq and [conc.] of the base are important, see the Supporting Information for full details. Furan **1l** was used in its Ac-protected form, see the Supporting Information for details.

sustainable protocol has been developed wherein it was possible to achieve the desired transformation in water with minimal additives.

$^1O_2$ has been applied to the synthesis of cyclopentenone scaffolds in protocols that start from either dienes[6a–c] or masked *o*-benzoquinones.[6d] However, neither of these starting points offers the flexibility for elaboration that is innately provided by the furan nucleus. Also, we have previously reported a lone example starting from a furan, but merely as a part of the total synthesis of the litseaverticillols,[7] a family of natural products containing a 4-hydroxy-2-cyclopentenone scaffold of type **2** (Scheme 1).

When the project was initiated, we sought to take advantage of the ability of singlet oxygen to initiate complex cascade reaction sequences,[8] so we planned to focus on the possibility of developing a one-pot transformation of simple furans into 4-hydroxy-2-cyclopentenones (**2**, Scheme 1), and, if possible, to further manipulate the same sequence so that we could also obtain the rearranged analogues **3**[9] if so-desired (**1**→**3** in one synthetic operation has never been reported before). This latter motif is important as it constitutes, for example, the skeleton of prostaglandins E and D.[10]

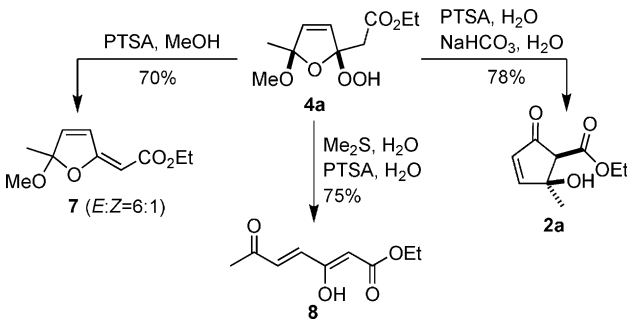
Our investigation commenced with substrate **1a** which was subjected to our standard photooxygenation conditions (irradiation with visible light whilst bubbling O_2 through the MeOH solution containing 10^{-4} M rose Bengal as sensitizer) followed by in situ reduction (Me_2S, Scheme 2). Treatment of the resulting enedione (**C**, not isolated) with catalytic amounts of Et_3N initiated an intramolecular aldol condensation affording exclusively the desired cyclopentenone **2a** (85% yield). The success of this proof-of-principle reaction encouraged us to submit a range of other furans (**1b**–**1n**), including non-activated exemplars (intermediate **C** arising from **1a** has very acidic hydrogens), to these conditions using either Et_3N, or, when required for cyclization, NaOH (Scheme 3).

All the reactions proceeded with good yields (59–90%, Scheme 3), especially if one takes into account the complexity of the transformation achieved in one pot. In particular, when R_2 = an activating group (CO_2R, Ph) mildly basic conditions (Et_3N, **2a**–**g**, Scheme 3) could be applied to promote the intramolecular aldol reaction. It was observed, however, that the rearranged 4-methoxy analogues (**5a**, **5c**, and **5e**)[11] were formed in increasing amounts with both longer reaction times and when larger equivalents of Et_3N were used. Analogous products (**5**) were also isolated in the case of alkyl substituted furans (**1h**–**j** and **1l**, **m**) where stronger basic conditions were applied to accomplish the cyclization. These 4-methoxy analogues (**5**) are also common building blocks for bioactive targets.[12] Furans **1k** and **1n** exhibit different behavior; here

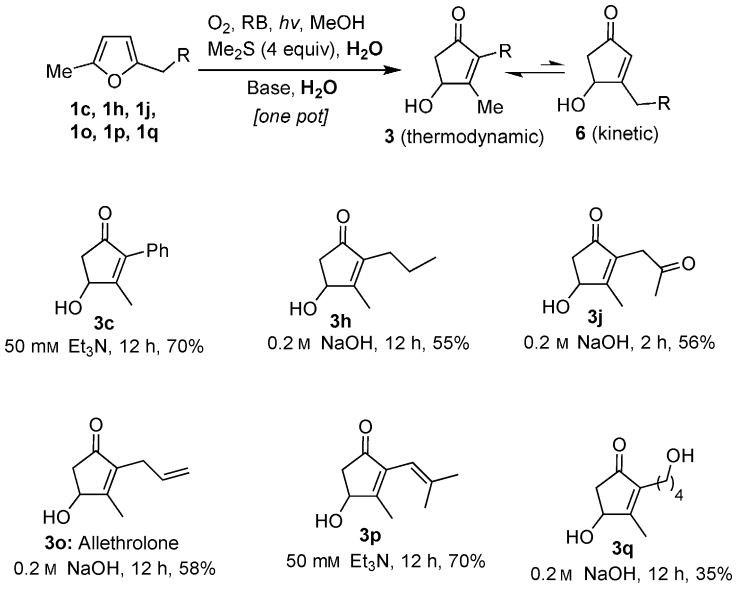
the initially formed cyclopentenones **2k** and **2n** are the most thermodynamically stable products (trisubstituted double bond), and, are therefore, those that were always isolated (no rearrangement **2**→**3** occurs). Another interesting observation is that the major diastereoisomer for products **2a**, **2b**, and **2d** was the *cis*-isomer, whereas in all the other cases (**2c**, **2e**–**g,** and **2n**) the *trans*-isomer was favored. Probably, the *trans*-isomer is the preferred product of the intramolecular aldol reaction; but, in the case where the products are easily enolizable ($R^2 = CO_2R$), it rapidly epimerizes to afford the more stable *cis*-analogue. As proof of the efficiency of the new method, it was applied to the high yielding (72%) one-step synthesis of the natural product, untenone A (**2b**),[13] from furan-containing natural product, plakorsin A (**1b**, itself made in just four steps).

Singlet oxygen is an ideal reagent for many reasons; one of the most important is because it fits very well into the modern paradigm which targets greater sustainability in chemistry.[8a,c] Not only is this profile due to its intrinsic characteristics (atom economy, selectivity etc.), but it arises from the conditions under which it can be employed (for example, green solvents, natural sensitizers). We, therefore, next sought to improve the environmental credentials of the method by testing whether parts of this transformation could be undertaken in water. Initially, the same protocol was applied, except the reductant (Me_2S) and the appropriate base (Et_3N or NaOH) were added in water instead of MeOH affording the desired 4-hydroxy-2-cyclopentenones (**3c**, **3h**, **3j**, and **3o**–**q**, Scheme 4).[9] Using mild basic conditions (Et_3N), cyclopentenones **3c** and **3p** were afforded as the sole products of the reaction because activation (benzyl or dimethylallyl group at the 2-position of the starting furan) promoted the intramolecular aldol reaction. The desired product **3j** was also isolated without the formation of any other product. This behavior is similar to that observed in the case of **5j** and is attributable to activation by the enol form of the pendant methyl ketone. In the cases of substrates **1h** and **1o**, using lower NaOH concentrations (0.1M), led to a mixture of thermodynamic (**3**) and kinetic products arising from the regioisomeric aldol condensation of the intermediate enedione followed by rearrangement (**6**, never produced as the sole product, Scheme 4), as determined by ^{1}H NMR spectroscopy. An increase in the final concentration of NaOH to 0.2 M results to the exclusive formation of **3h** and **3o**. In terms of applications for this method, it should be noted that allethrolone (**3o**),[4g,14] a useful pyrethrin insecticide,[15] has now been synthesized in one step starting from the very simple furan **1o**.

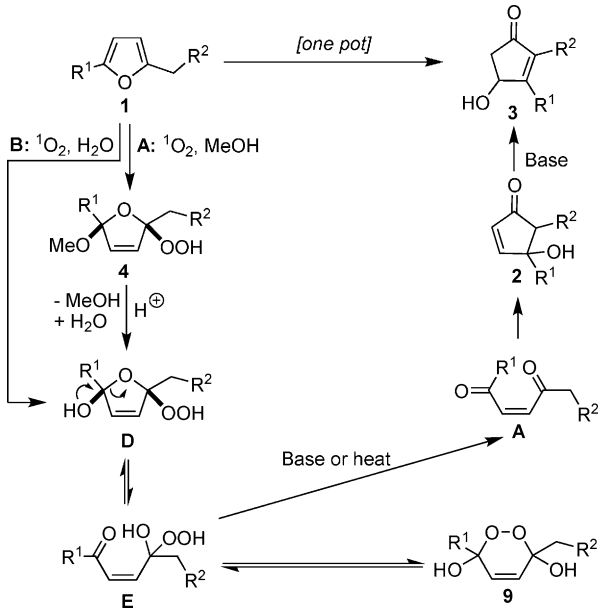
Looking to further simplify the protocol, we next sought to study the consequences of removing the reducing agent. Scheme 5, with its summary of the conversions of substrate **4a** (produced by photooxidation of **1a**) under different conditions, reinforces the flexibility of the method and its potentially diverse applications. Although scaffold **7** is common in natural products,[16] the result that attracted our attention was the formation of cyclopentenone **2a** in water and in the absence of a reducing agent. Intriguingly, the same reaction done in water, but with Me_2S, had furnished the isomerized analogue of *cis*-enedione **C** (Scheme 2), *trans*-enedione **8**. To understand the transformation of **4a** into **2a** mechanistically, the reaction was monitored by ^{1}H NMR spectroscopy. This experiment revealed the unexpected formation of a never previously observed intermediate, endoperoxy-*bis*-hemiketal[17] **9** (Scheme 6), which, although not very stable, could, with care, be isolated. This led us to propose the mechanism shown in Scheme 6 wherein the hydroperoxy intermediate **4** is hydrolyzed by *p*-toluenesulfonic acid (PTSA), in water, to hemiketal **D**, which then ring expands to afford endoperoxy-*bis*-hemiketal **9** via the intermediacy of **E**. Intermediate **9** could then collapse (induced by heat, or base) to furnish enedione **A** (via **E**), which, in turn, would yield the desired cyclopentenone **2** or **3** after cyclization. On the basis of this result, a variety of substituted furans were successfully subjected to this simplified protocol and the results are shown in Scheme 7 (conditions A). Thus, cyclopentenones **2a** and **2d** were produced by treating their respective intermediates of type **4** with catalytic PTSA in H_2O followed by addition of small



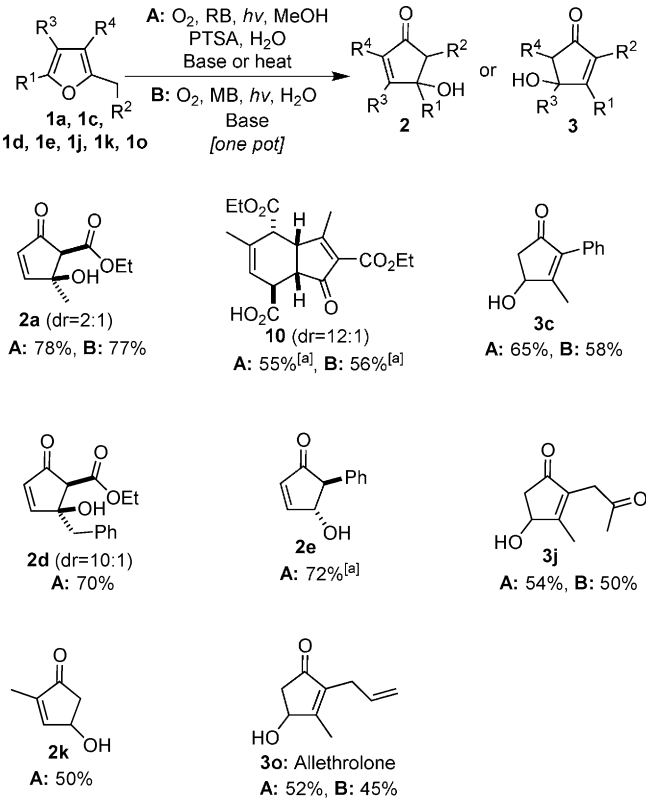
Scheme 5. Conversions of intermediate **4a**.



Scheme 4. Synthesis of 4-hydroxy-2-cyclopentenones in water. The final concentration of the base is reported. Lower yield for **3q** due to its high solubility in water.



Scheme 6. Mechanistic proposal for the transformation of photooxidized furans to 4-hydroxy-2-cyclopentenones without the use of a reducing agent.



Scheme 7. Synthesis of 4-hydroxy-2-cyclopentenones in water without reducing agent. [a] No addition of base. 0.1–0.2 equiv of PTSA, 45 °C, 12 h.

amounts of $NaHCO_3$ (to increase the pH).[18] Modifications to these conditions (heat instead of base) allowed direct access to manzamenone analogue **10**[19] to be achieved, in 55% isolated yield, via the dimerization of **2a** followed by a retro-Dieckmann ring-opening reaction.[20] In case of 2-benzyl furan (**1e**), the same conditions (heat instead of base) afforded a single diastereomer of **2e**, while for the 2-benzyl-5-methyl furan (**1c**) a final addition of Et_3N, after the formation of intermediate of type **9**, led to the rearranged product **3c**.[18] Similarly, the rearranged cyclopentenones **3j** and **3o** were obtained by applying a stronger base (NaOH) at the end of the sequence.[18]

To complete the investigation, we asked ourselves whether it was necessary to go through intermediate **4** each time. In other words, we wondered whether the entire sequence could be conducted in water without a reductant (Scheme 6, **1**→**2** or **3** via **D**, **E** and **9**); in which case, the protocol would have become extremely simple and much greener than all the alternative approaches. Scheme 7 (conditions B)[18] shows that this was indeed possible. Direct formation of **9** was observed after photooxygenation without use of any additive; thus, a step was taken towards the sustainable ideal.[21]

In summary, we have introduced a general method for the one-pot synthesis of 4-oxo-substituted-2-cyclopentenones starting from readily accessible and simple furan substrates using the green oxidant singlet oxygen. It was found that the protocol could be simplified from its more traditional starting point, such that no reductant was necessary, and, furthermore, the reaction sequence could be undertaken from start to finish in water.

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[17] For the preparation of similar endoperoxy-*mono*-hemiketals, or endoperoxy-*bis*-ketals, via photooxidation of α,β-unsaturated ketones, or dienes, see; references [6b] and [6c].

[18] For more details see the Supporting Information.

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