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Using Water, Light, Air and Spirulina To Access a Wide Variety of Polyoxygenated Compounds

Dimitris Noutsias, Ioanna Alexopoulou, Tamsyn Montagnon and Georgios Vassilikogiannakis*

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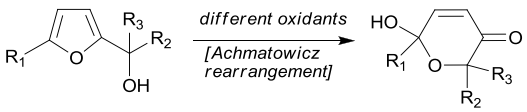
A new set of completely green methods utilising air, light, water and spirulina to transform readily accessible furan substrates into a diverse range of synthetically useful polyoxygenated motifs commonly found in natural products, is presented herein.

The ideal green methodology encompasses a host of very different concepts, and, as such, is a far from simple goal to achieve. The practitioner is not just looking for non-polluting, non-toxic reagents to be used in reactions devoid of the traditionally-employed organic solvents, but must also consider ideas such as atom-[1] and step-economy,[2] elimination of protecting group usage[3] (and other non-constructive refunctionalisation steps),[4] and overall efficiency for the operation (e.g. the degree to which structural complexity is increased). Indeed, in these latter themes the goals of green chemistry coalesce with those of organic synthesis as a whole where the application of ideal synthetic principles is seen as the only way to overcome factors that have been limiting further progress in the field.[4] Many claim green credentials for their new methods by honing one out of the many criteria identified above, but few actually endow chemistry with technologies that embrace the whole package. Herein is presented a powerful set of new methods, targeting a range of complex polyoxygenated motifs (to be found in an array of different bioactive natural products or other important synthetic targets), that meet the green ideal completely. The methods use oxygen from the air as the reagent, water as solvent, visible spectrum light as the energy source, spirulina (a commercial cyanobacteria product) as a source of photosensitizers, atom economy is maximized (both oxygen atoms are added into the substrates) and each of the methods involves a complex cascade of reactions that induces a dramatic increase in molecular complexity in a single operation. Furthermore, the individual oxidation reactions employed are so specific (or can be tailored and controlled by engaging with their kinetics) that protecting groups are rendered essentially redundant; a feature that is extremely rare in any strategy targeting such polyoxygenated structures which are traditionally rife with oxygen functionality protections and deprotections and/or oxidation level adjustments.

The orchestrating reagent at the heart of this new set of methods is singlet oxygen ($^1O_2$). Singlet oxygen has been shown to be an excellent initiator for complexity-enhancing cascade sequences,[5] and, unlike so many of the oxidants currently employed in synthetic chemistry that are either based on heavy metal compounds or hypervalent iodine compounds, singlet oxygen ($^1O_2$) is both non-toxic and completely atom economic.

All the methods presented herein, begin from simple furan substrates that are easy to access. The oxidation of furans has long been recognized as a productive and important transformation in organic synthesis; for example, literature protocols for the direct oxidation of furans to 1,4-enediones are known, but frequently involve treatment with hazardous and/or dangerous chemicals, including; Br_2, NBS, peracids, dioxiranes, Cr^{vi}-based oxidants.

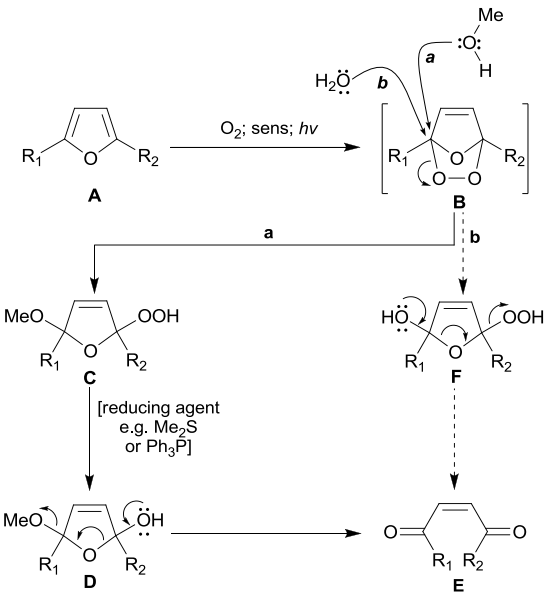


Scheme 1 The synthetically-useful Achmatowicz rearrangement

In a specific example, 2-(α-hydroxyalkyl) furans can be oxidised to afford the corresponding and synthetically highly valuable, 6-hydroxy-3(*2H*)-pyranones (Scheme 1), under a variety of conditions including; Br_2/MeOH,[6] peracids (e.g. *m*-CPBA,[7] magnesium monoperoxypthalate[8]), NBS,[9] dioxiranes (DMDO[10]), metal-based oxidations (PCC,[11] VO(acac)$_2$/*t*-BuOOH[12]). The proliferation of methods available to undertake this particular transformation attests to the synthetic versatility of the 6-hydroxy-3(*2H*)-pyranone unit; and, yet, major problems remain to anyone wishing to apply these protocols within a synthetic context, mostly arising from the harshness/lack of selectivity associated with the existing methods. Within the set of new methods highlighted herein, a solution is offered to this problem in the form of a new mild green alternative for this (and other) key transformations.

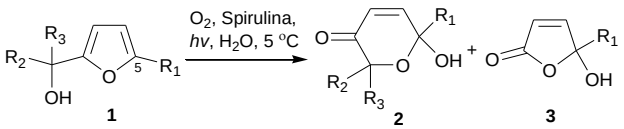
In the last years the primary focus of our research has been the development of new methodologies based on singlet oxygen-mediated furan oxidation[13, 14] cascades which lead to

the formation of a diverse array important polyoxygenated motifs, including; γ-spiroketal-γ-lactones,[15] [6,6]-spiroketals,[16] [5,5,5],[17] [6,5,6][17] and [6,6,5]-bis-spiroketals,[16] 4-hydroxy-cyclopentenones,[18] 3-keto-tetrahydrofurans,[19] [5,6]-spiroperoxylactones[20] as well as 6,8-dioxabicyclo[3.2.1]oct-3-en-2-ones.[21] Some of the developed methodologies have been successfully applied to the total synthesis of natural products. In all cases, intra- or inter-molecular opening of the intermediate ozonide **B** (Scheme 2) by either a hydroxyl of the 2-alkyl furan substituent (not shown), or by MeOH, led to the formation of hydroperoxide **C** (path a). Reduction of **C** (with Me_2S or Ph_3P) followed by slow elimination of MeOH from the intermediate hemiketal **D** resulted in the formation of 1,4-enedione **E**, which is a highly flexible intermediate capable of participating in a slew of different reaction sequences[15-21] depending on the nature of R_1 and R_2. Despite the green nature of singlet oxygen itself, and, the achievement of step- and atom-economies, the developed methodologies were still off-target in terms of the green ideal, because: a) the oxidations were all performed in organic solvents; b) organic photosensitizers were used; and, c) additional reducing agents were required. All of these hindrances have now been addressed.



Scheme 2 The singlet oxygen mediated oxidation of furans to the corresponding 1,4-enedione; the traditional (path **a**) versus the proposed (path **b**).

The first major discrepancy from the green ideal in these methodologies is the reaction solvent. It was felt that because all the substrates contained one or more hydroxyl functionalities they should be water soluble enough for unhindered reaction. Furthermore, it was hoped that with this change to a green solvent, the need for an "ungreen" reducing agent (**C** → **D**, Scheme 2) to be included in the reaction protocol would be concomitantly eliminated because a subtle alteration in reaction mechanism would be engendered. The mechanistic deviation was expected to occur because water would now open the fleeting ozonide **B** yielding intermediate hydroperoxide **F** (Scheme 2, path b), which might then eliminate a molecule of H_2O_2 without recourse to the use of any reducing agents; thus, affording the requisite 1,4-enedione **E**, directly. In order to achieve a clean sweep, it was also considered necessary to look for a water-soluble, natural, photosensitizer to replace the previously used rose bengal or methylene blue systems. A human/animal nutritional supplement, widely available in powdered water- soluble form, named Spirulina, was found to work very well. Spirulina is made primarily from two easily cultivated species of cyanobacteria - *Arthrospira platensis* and *Arthrospira maxima*.[22,23] With this last innovation, every single aspect of the new protocols (detailed herein) should be more than acceptable to any researcher undertaking a green audit of this synthetically very useful chemistry.



furan	R_1	R_2	R_3	**2** (yield %)[a]	**3** (yield %)[a]
1a	H	H	H	48	39
1b	H	H	EtO_2C	28	53
1c	H	H	*n*-Bu	25	57
1d	Me	H	H	80	-
1e	Me	Me	Me	71	-
1f	Me	H	*n*-Bu	74	-

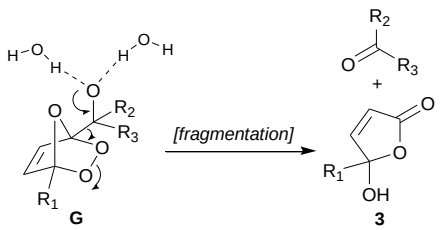
[a] isolated yields

Scheme 3 Results obtained for the photooxidation of furans **1a** – **1f** under the newly developed green conditions.

Turning to the details of each of these new methods, the first involves the oxidation of 2-(α-hydroxyalkyl) furans to 6-hydroxy-3(*2H*)-pyranones, also known as Achmatowicz-type rearrangement (Scheme 1), which is a widely-used, key transformation in synthetic chemistry, and, as such, provided the ideal testing ground for the proposed new water-mediated green photooxidations. In previous studies[21] into the photooxygenation of 2-(α-hydroxyalkyl) furans in MeOH with subsequent *in situ* reduction of the intermediate hydroperoxides (type **C**, Scheme 2), the formation of mixtures of 6-hydroxy-3(*2H*)-pyranones and 5-hydroxy-2(5*H*)-furanones had been seen. Indeed, the relative ratio of the final products had been shown to be highly dependent on the 5-substitution of the starting furan substrate.[21] In search of improved product distribution, as well as, a greener reaction protocol, 2-(α-hydroxyalkyl) furans **1a – 1f** (Scheme 3) were dissolved in H_2O and powdered spirulina was added, at which point the solution took on a green colour (green by appearance, as well as, by credentials!). Singlet oxygen ($^1O_2$) photooxygenation conditions (oxygen, or air, bubbling through the reaction mixture with irradiation from a visible spectrum light source) were applied for 30 – 60 mins resulting in the direct (no reducing agent is now required) formation of 6-hydroxy-3(*2H*)-pyranones **2** accompanied, in some cases, by the fragmentation product 5-hydroxy-2(5*H*)-furanones **3**

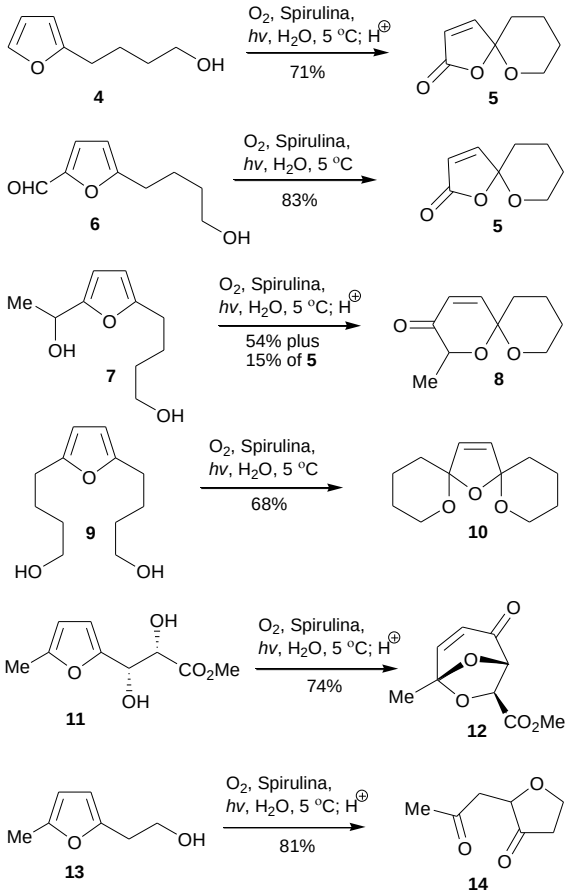
(Scheme 3). In **ALL** cases, the **2**:**3** relative ratios were much improved relative to those previously reported[21] for reactions run in MeOH with a reducing agent. Even the substrates previously found to deliver exclusively the fragmentation product **3**, namely **1b** and **1c**, now afforded substantial amounts of the 6-hydroxy-3(*2H*)-pyranones **2** under the newly developed reaction conditions (Scheme 3). In all cases where the substrate bears a substituent at the position-5 of the furan (**1d**, **1e** and **1f**), the reaction affords exclusively the corresponding 6-hydroxy-3(2H)-pyranones.

The improved **2**:**3** relative ratio may be attributed to a more effective hydrogen bonding environment for the –OH group in the intermediate ozonide, which is now surrounded by molecules of water instead of methanol, (**G**, Scheme 4); thus, making the unpaired electrons on the oxygen less available for initiation of the unwanted fragmentation pathway. The reduced steric demand of water, in comparison to methanol, may also enhance the rate of the productive pathway b (**B** → **F**, Scheme 2).



Scheme 4 Fragmentation of ozonide intermediate **G** to yield 5-hydroxy-2(5*H*)-furanones.

With the goal of extending these principles to a diverse array of other targets of synthesis, so that a whole new set of improved green methodologies could be delineated, a variety of furanols (**4**, **6**[25] and **13**, Scheme 5) and furan-diols (**7**, **9** and **11**, Scheme 4) were photooxidized. All these substrates showed good solubility in H_2O. Photooxygenations of substrates (**4**, **7**, **9**, **11**, and **13**) in organic solvents required the addition of an ungreen reducing agent (Me_2S or Ph_3P) for the reduction of the intermediate hydroperoxides of type **C** (Scheme 2) and the subsequent formation of the polyoxygenated skeletons **5**, **8**, **10**, **12** and **14** (it should be noted that these products are very important because they are all key motifs from bioactive natural products frequently targeted in synthetic organic chemistry). In the new highly efficient water-mediated photooxidations using spirulina as photosensitiser, addition of an ungreen reducing agent is NOT required. Specifically, water-mediated photooxidation 2-(δ-hydroxyalkyl) furan **4** followed by treatment of the intermediate spiro-hydroperoxide (not shown) with either silica gel, or *p*-TsOH, or Ac_2O/Py, resulted in its clean conversion to δ-spiroketal γ-lactone **5**. The final product, a [6,5]-spiroketal, is reminiscent of the AB-spiroketal motif from pectenotoxins 1-7 (PTXs 1-7).[26] Furthermore, photooxygenation in water of the furfural derivative **6** afforded, directly, the same δ-spiroketal γ-lactone **5**, via decarboxylation of a 4-membered dioxetane intermediate,[25] without the use of any additives. Moving on to the synthesis of yet another important motif present in many biologically active natural products, such as, the terrestrially derived



Scheme 5 Examples proving that a diverse array of target motifs may be made using these new green methods.

ionophore antibiotics salinomycin[27] and narasin,[28] as well as, the marine derived cytotoxic compounds PTX2c, PTX8-10, and PTX11c;[26] photooxidation of the readily accessible 2-(α-hydroxyalkyl)-5-(δ-hydroxyalkyl) furan **7**, followed by treatment with a catalytic amount of *p*-TsOH, afforded the [6,6]-spiroketal **8** (5:1 mixture of anomers) accompanied by only small amounts of the fragmentation product **5**. Even more impressively, the one-pot formation [6,5,6]-*bis*-spiroketal **10** (1:1 mixture of anomers, Scheme 5) was observed upon exposure of the very simple and readily accessible 2-(δ-hydroxyalkyl)-5-(δ-hydroxyalkyl) furan **9** to singlet oxygen in aqueous media. Several different classes of frequently targeted marine toxin including, the pinnatoxins,[29] pteriatoxins,[30] and the azaspiracids,[31] contain such a motif. Spiroketals are very common within a range of different synthetic targets; however, they are most frequently made using one method, namely, stepwise acid-mediated spiroketalizations; a strategy that innately carries a need for protecting groups and the shuttling back and forth between oxidation levels of the various oxygen functionalities. In other words, the method reported herein, not only uses green reaction conditions, but offers very significant improvements in overall efficiency and step- and atom-economies.

In the next example (Scheme 5), a dramatic increase in molecular complexity is once again achieved in a simple to execute green operation. Thus, photooxygenation of 2-(α, β-dihydroxyalkyl) furan **11** in H_2O, followed by *in situ*

ketalization of the intermediate 6-hydroxy-3(*2H*)-pyranone of type **2** (not shown) using acid catalysis, cleanly provides the 6,8-dioxabicyclo[3.2.1]oct-3-en-2-one framework **12**. This particular motif can be found in several different classes of natural products including the pinnatoxins,[29] pteriatoxins,[30] didemniserinolipids,[32] as well as, in 2-hydroxy-*exo*-brevicomin.[33] Finally, water mediated photooxygenation of 2-(β-hydroxyalkyl) furan **13**, followed by *in situ* treatment with trace acid, affords, in one synthetic operation, 3-keto-tetrahydrofuran motif **14**. This reaction proceeds via an intramolecular *oxa*-Michael addition to the intermediate 1,4-enedione (type **E**, Scheme 2). Similar 3-ketotetrahydrofuran motifs can be found in a variety of natural products, including; phyllanthocin,[34] and pectenotoxins.[26]

With regard to the photosensitizer, similar results (product distribution and isolated yields) were observed when either macerated leaves of spinach (a source of chlorophyll), or rose bengal were used as photosensitizer instead of spirulina. It was true that in the case of chopped leaves of spinach as the source of the photosensitizer, the irradiation times were 2-3 times longer than those needed when using spirulina. When rose bengal was used as photosensitizer the irradiation time was reduced to one fourth of that required by the spirulina system.

In summary, a diverse array of polyoxygenated motifs, found in many different bioactive natural products, has been synthesized with ease. Each of the new methods employed begins from simple and readily accessible furan precursors and uses completely green protocols. The protocols; employ green, non-toxic reagents and conditions (water, light, air and spirulina); are highly step-economic (simple precursor → complex motif in one operation) in a field (namely, the construction of polyoxygenated molecules) that has traditionally employed many non-constructive steps (protections/deprotections and redox shuttling); and, are highly efficient from the perspective of atom economy.

General procedure for photooxidations. A solution of furanols **1a-f**, **4**, **6**, **13**, or furan-diols **7**, **9** and **11**, (0.5 mmol) in water (10 mL), containing spirulina (20 mg) as photosensitizer, was placed in a test tube and cooled with an ice bath (5 ºC). Oxygen was bubbled through the solution immediately before, and, during, its irradiation by a xenon Variac Eimac Cermax 300 W visible spectrum lamp. More spirulina (20 mg) was added for every 15 min of irradiation. Complete consumption of the starting material was observed by TLC after 20 – 110 mins of irradiation. In the case of **1a-f**, **6** and **9** the reaction mixture was extracted with EtOAc (3×), the combined organics were dried (Na_2SO_4), concentrated *in vacuo* and purified (when necessary) by flash column chromatography to afford pure **2a-f**, **5** and **10**, respectively. In the case of furans **4**, **7**, **11** and **13** the EtOAc extracts were treated with catalytic amounts of *p*-TsOH (see supporting information).

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Notes and references

University of Crete, Department of Chemistry, Vasilika Vouton, 71003 Iraklion, Crete, Greece. Fax: +30 2810 545001; Tel: +30 2810 545074; E-mail: vasil@chemistry.uoc.gr

† Electronic Supplementary Information (ESI) available: Full experimental procedures, analytical data and copies of all relevant ^{1}H and ^{13}C NMR spectra are presented. See DOI: 10.1039/b000000x/

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