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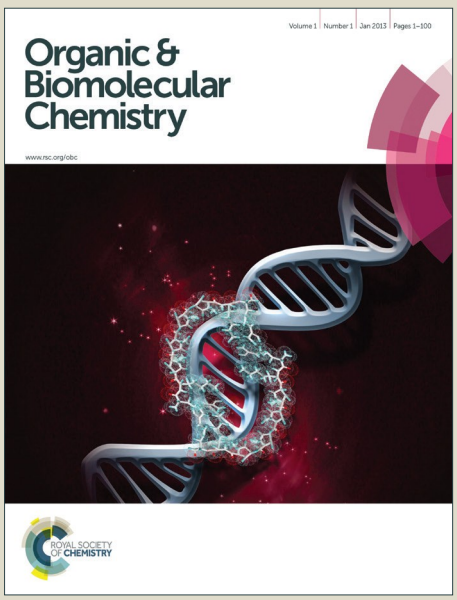

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ARTICLE

Chemoselective photooxygenation of furans bearing unprotected amines: Use in alkaloid synthesis.

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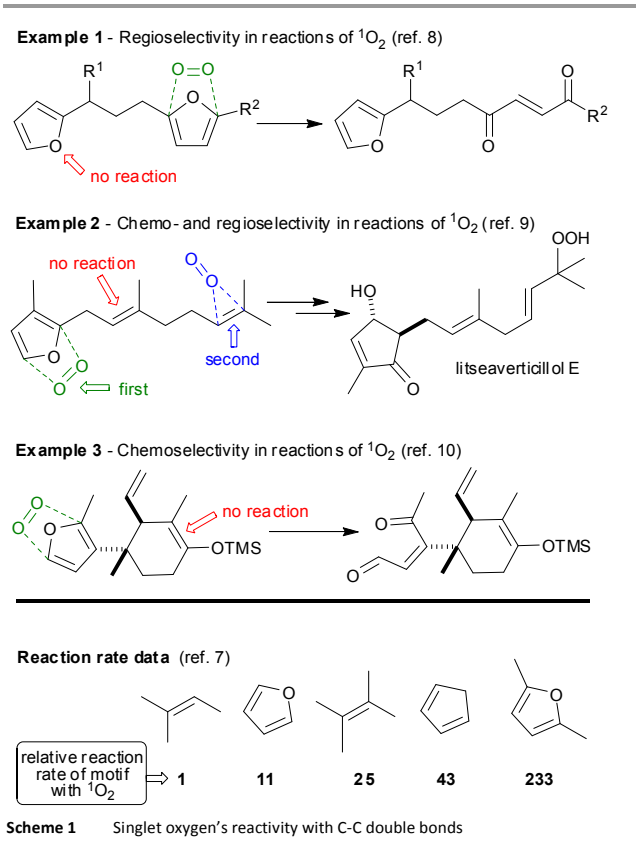
Abstract: Very recent investigations are described which have shown how basic and unprotected nitrogen functionalities can be included, problem-free, in the furan photooxidation step of singlet oxygen-initiated cascade reaction sequences. The amine groups do not react with singlet oxygen, but, instead, participate later on in the sequences that ultimately yield a diverse range of important alkaloid motifs. To illustrate the versatility of this chemistry, six natural products were made very rapidly and efficiently. Furthermore, the new technologies all operate under green conditions and without the use of a single protecting group.

Why use singlet oxygen in the first place?

Singlet oxygen ($^1O_2$) should be used more widely. It is a reagent that goes a very long way towards meeting all of the strict operational criteria being demanded of synthetic chemistry today. Indeed, it might be said to be an ideal reagent for doing ideal chemistry.[1] Why? It can be generated from the oxygen present in air, simply by bubbling the latter through the reaction solution. Its generation occurs upon irradiation of this solution with visible spectrum light (a process greatly facilitated by recent improvements in low energy LED technologies) in the presence of very small quantities of a photosensitiser (PS, which may be a natural one[2]). It can be used in water,[2,3] or MeOH, both preferred solvents for green chemistry.[4] It leaves no waste or residues; it is therefore clean and atom-economic. In addition, it is highly selective, rendering protecting groups essentially redundant. Crucially, and, somewhat uniquely for an oxidant, this feature is nowhere more evident than within the normally intransigent class of molecules bearing a high density of oxygen-based functionalities.[5] Furthermore, it can also initiate a wide range of diverse cascade reaction sequences[5] that lead to very rapid and dramatic increases in molecular complexity (step-economy). Finally, if we think about preferred substrate sourcing, singlet oxygen is perfectly positioned to make productive use of the bulk furans readily obtained from biomass (e.g. sugars converted to furans).[6] Thus it is that singlet oxygen is a powerful and versatile reagent whose efficiency in orchestrating cascade reaction sequences is unparalleled[5] and which has very low environmental impact across a broad range of criteria.[2,5]



Scheme 1 Singlet oxygen's reactivity with C-C double bonds

Perceptions about selectivity, or the lack thereof: Are they limiting singlet oxygen use?

Why then is $^1O_2$ not more frequently employed? One answer to this question might be due to concern over its selectivity within complex molecular environments. Singlet oxygen is

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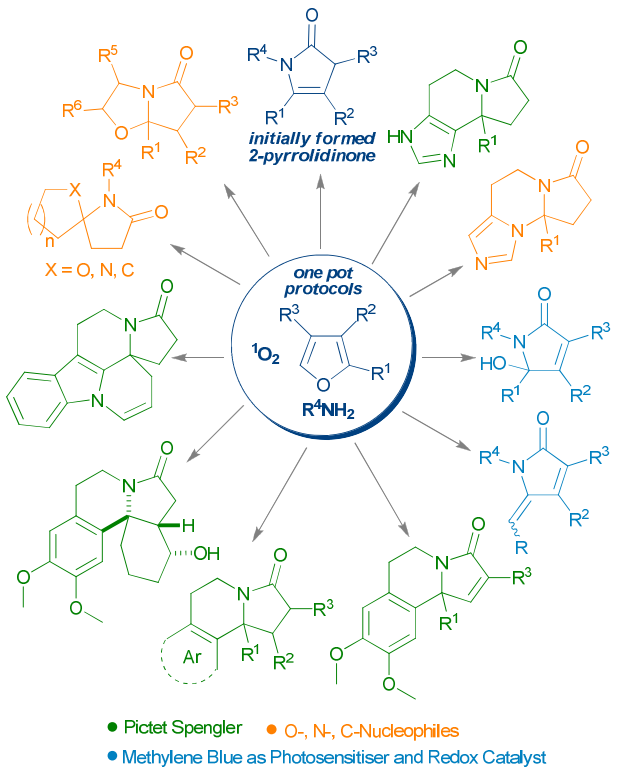

Scheme 2 Cascade reaction sequence products; amines were added after photooxidation.

generally known as a highly reactive electrophilic species which can react with a wide variety of different functional groups.[7] Furthermore, it is not a reagent where one equivalent can be carefully measured out and added to a reaction to circumvent reaction at more than one site within the substrate molecule. In combination, these features have given rise to a natural aversion to using singlet oxygen. However, it has long been known that a very high degree of selectivity can be achieved in singlet oxygen's reactions with C-C double bonds (Scheme 1).[7] For instance, Feringa et al. showed in a substrate bearing two very similar furan motifs, that one (the one substituted to a marginally higher degree) could be selectively oxidised with singlet oxygen (Example 1, Scheme 1).[8] Our group has also shown, during the synthesis of natural products, the litseaverticillols,[9] that a high degree of chemo- and regioselectivity could be obtained from the reaction of singlet oxygen with furan substrates bearing two C-C double bonds where only quite subtle differences existed between each of them (Example 2, Scheme 1). A similar striking differentiation between furan and an electron-rich tetrasubstituted double bond of a silyl enol ether was achieved in the gram scale photooxidation undertaken during the total synthesis of pallambins C and D published just as we were writing this perspective (Example 3, Scheme 1).[10] Indeed, it has been a major theme in our work over recent years to further explore and exemplify just how versatile singlet oxygen can be in synthesis by seeking to broaden the range and complexity of molecules and motifs targeted.[5] Despite generally making good progress, one bastion that remained unchallenged until very recently was the widely held belief that it was necessary to exclude basic –unprotected– nitrogen from the photooxidation substrates (unless one was targeting the oxidation of this functionality[11a-d]). This omission is, of course, so important because of the high prevalence of basic nitrogen in synthetic targets; especially when one is interested in bioactive molecules, or biological systems.

The status quo and the first steps towards changing it.

The field of amine-singlet oxygen chemistry is not easy to delineate because multiple mechanistic pathways are available and not very much investigation into rate differentiation has been done. Existing literature precedent would suggest one needs to consider concomitantly the potential chemical reaction of amines (examples exist for 1°, 2° and 3° amines) with singlet oxygen,[11a-d] the reaction temperature[11e] as well as, the physical quenching of the excited states by amines[12] (either those of the photosensitisers, or that of singlet oxygen itself – with rates following the progression 3°>2°>1° amine[12]). Initially, and, in order to simplify the task, we investigated only adding amines into the reaction cascades after the furan photooxidation. With this approach we were successful in achieving rapid access to a diverse range of privileged nitrogen polycycles (Scheme 2). The common intermediate in all these tandem transformations was a 2-pyrrolidinone.[13-19] In addition, alternative strategies were pursued by other groups; such as, the incorporation into the furan photooxygenation substrates of nitrogen motifs such as azide groups,[20] or Boc-protected amine groups.[20,21] The inclusion of free and nucleophilic nitrogen functionalities within furan photooxygenation substrates, however, remained notably absent and could have been described as seriously curtailing the synthetic utility of such chemistry.

The door opens: Unprotected amines are included in furan photooxygenation substrates without disrupting the desired reactions.

During the development of a methylene blue double oxidation methodology,[18] we were scouring the literature for possible synthetic applications for this new technology when we came across the natural product pandamarine which had been isolated from *Pandanus amaryllifolius* leaf extracts[22] (**4**, Scheme 3). It was tantalisingly obvious (especially in light of the proposed biosynthesis[22]) that retrosynthetic analysis of pandamarine could take it back to a readily accessible and symmetrical difuran **1**. In the forward sense, and for the cascade reaction sequence to work as the elegant single operation that we hoped for, everything hinged around whether an unprotected secondary alkyl amine could be included within the photooxidation substrate and be expected to remain inert until required later on in the series of reactions. To our delight when this matter was investigated,

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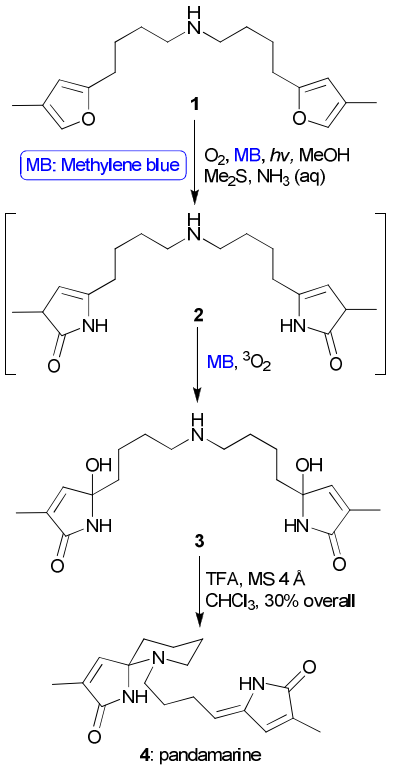
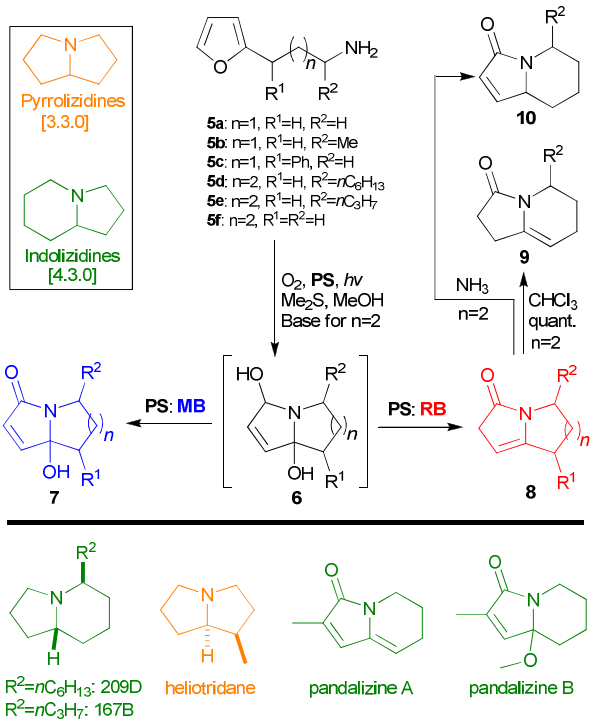


Scheme 3 Double oxidation cascade reaction sequence beginning from symmetrical difuran **1** and yielding pandamarine **4**.

the unprotected basic nitrogen functionality did not hinder the desired double photooxidation reaction in the least, but was able to participate later on in the sequence delivering pandamarine **4** just as had been originally envisaged (Scheme 3).[23]

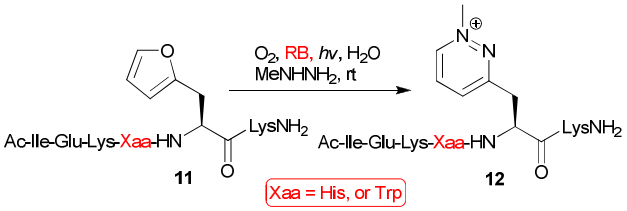
Following the success of the pandamarine synthesis, we were driven to further explore the inclusion of unprotected amines in photooxygenation substrates. Our target molecules this time were the ubiquitous pyrrolizidine and indolizidine alkaloids.[24] The -izidine alkaloids represent 30% of all known alkaloids and exhibit a diverse range of interesting biological activities. Commercially available and readily accessible furylalkylamines were subjected to one of a number of standard photooxidation conditions we had developed. The desired bicyclic products (**7**-**10**, Scheme 4) were obtained in excellent yields especially when one considers the complexity of the cascades involved.[24] Of particular note here is not just the presence of the free primary amine in the photooxidation step, but also the cacade's tunability (**5a**-**c** → **7**, or **8** and **5d**-**f** → **7**, or **8**, or **9**, or **10**) which is dependent on the choice of photosensitiser (methylene blue – MB, or rose Bengal – RB) and the additive. This tunability (formation of either **7** or **8**) arises from the ability of methylene blue to further oxidise the initially formed 2-pyrrolidinone **8** to the corresponding 5-hydroxy analogue **7**, through a proton coupled electron transfer (PCET) procedure which uses molecular oxygen as the terminal oxidant.[24] As proof of the versatility of this newly developed method, it was used to synthesise five natural products (and unnatural δ-coniceine) starting from simple



Scheme 4 Synthesis of pyrrolizidine and indolizidine motifs by photooxygenation of furans bearing unprotected primary amines.

furylalkylamines using extremely short sequences and no protecting groups (Scheme 4). These last syntheses serve to illustrate the numerous advantages of singlet oxygen-furan reaction cascades which encompass unprotected amines and provide the first indicators as to how they might be further exploited.

As a final and interesting postscript, it is worth noting that singlet oxygen's reactions with furan-containing peptides which bear sensitive amino acid residues (e.g. histidine, or tryptophan, Scheme 5) are beginning to be used for site-specific and chemoselective peptide ligation.[25] These molecules have their own special sensitivities alongside a high prevalence of various different nitrogen functionalities, so success here further underlines the controllability and exciting potential of these reactions.



Scheme 5 Site specific and chemoselective peptide ligation sequence induced by singlet oxygen reaction with furan-containing peptides.

The new methodologies that have been highlighted in this article show how the door has been opened for the synthesis of many nitrogen bearing molecules using singlet oxygen-furan cascade chemistry.

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Conclusions

The rate differentiation in its reactions with different functional groups is such that it has repeatedly been found that singlet oxygen reacts with a very high degree of selectivity. We have now added something crucial to the known data; namely, the fact that unprotected amines can be included in furan-containing photooxygenation substrates without disrupting the reactions of singlet oxygen with the furan nuclei. This added capability is crucial to the future applications of this field of chemistry which already possesses so many innate advantages -from its green credentials to its highly effective molecular building- because it allows singlet oxygen to be used in the protecting group-free synthesis of alkaloids and other nitrogen bearing molecules, or within biological systems. One of the most important challenges for the future is the use of unprotected amines in photooxygenation substrates containing other functional groups which can react with singlet oxygen.

Acknowledgements

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