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Rapid Access to 3-Acyl-5-alkoxy-butyrolactams Using Triplet and Singlet Oxygen

Manolis Sofiadis, John Sarris, Tamsyn Montagnon, Dimitris Kalaitzakis* and Georgios Vassilikogiannakis*

Dedication ((optional))

Abstract: A straightforward singlet oxygen-initiated cascade reaction sequence for the synthesis of a variety of key 3-acyl-5-alkoxy-butyrolactams from furans has been developed.

Introduction

Natural products containing tetramic and non-tetramic butyrolactam motifs are both ubiquitous and are of considerable importance owing to their potent and diverse biological properties.[1,2] While the 5-hydroxy-butyrolactam unit dominates in the family of natural tetramic and non-tetramic γ-lactams, its less fragile 3-acyl-5-alkoxy counterpart of type **A** (Figure 1) can be found in many natural and unnatural products which have interesting biological activities.[3] Furthermore, these easy-to-handle compounds are useful precursors for the synthesis of a wide variety of other naturally occurring counterparts.[4]

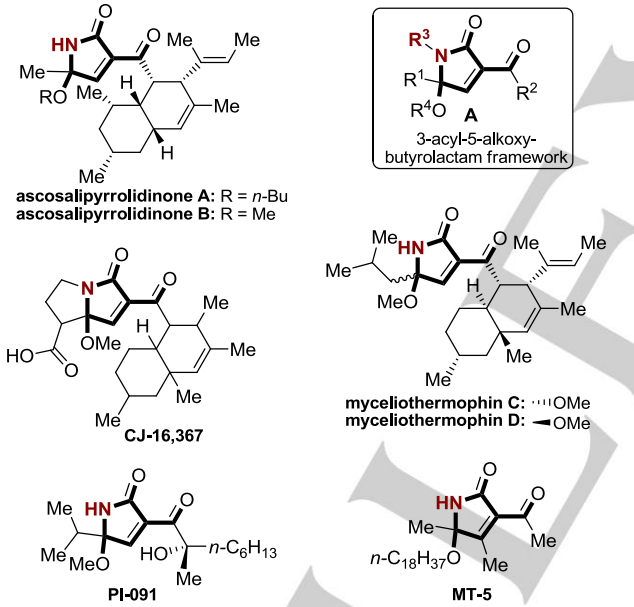
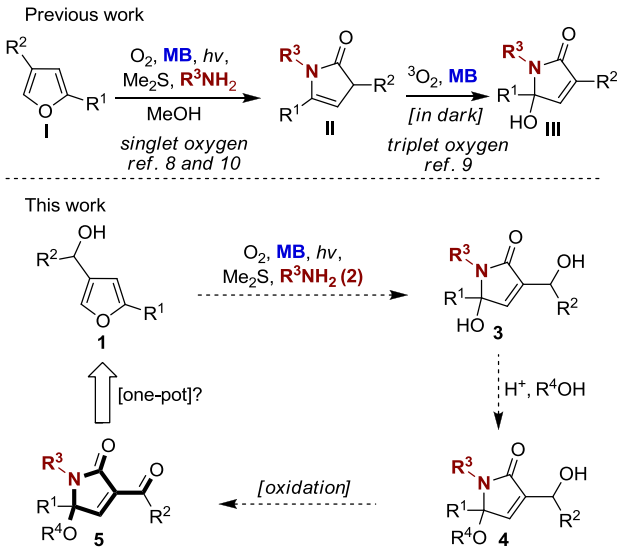


Figure 1. Biologically active compounds containing the 3-acyl-5-alkoxy-butyrolactam framework.

Although considerable efforts have been expended towards achieving the synthesis of 5-hydroxy-butyrolactam frameworks,[5] only a few of the resulting methodologies have also tackled construction of the versatile 5-alkoxy congeners of type **A** (Figure 1).[3e,6,7] In the few examples dealing with the construction of the corresponding 5-methoxy analogues,[6,7] many synthetic hurdles have been faced, mostly derived from their susceptibility to hydrolysis and/or ring opening.[6a,7b] Moreover, a common strategy is to use saturated lactams as precursors; however, this approach imposes the need for additional derivatization steps in order to introduce the α,β-unsaturated moiety in a procedure that necessitates protection of the lactam's nitrogen.[6] Thus, there is a pressing need to develop a simple and general method for the synthesis of compounds of type **A** (Figure 1) starting from simple precursors.

Results and Discussion

Herein, we demonstrate a straightforward and general protocol for the synthesis of α-acyl-γ-alkoxy-butyrolactams starting from readily accessible furans and molecular oxygen.[8] Recently, we developed a sustainable singlet oxygen-mediated methodology



Scheme 1. Envisioned scenario for the synthesis of 3-acyl-5-alkoxy-butyrolactams **5**.

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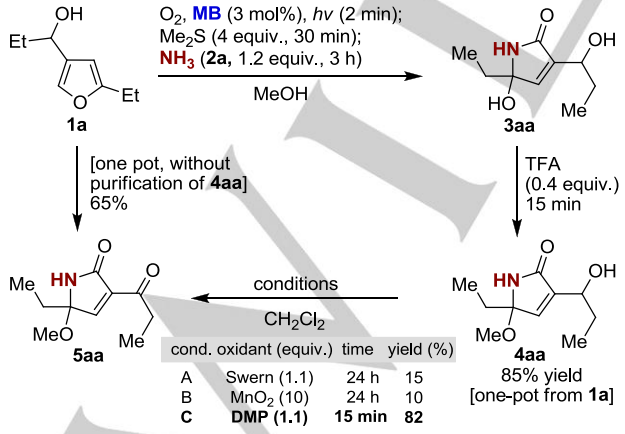
for the construction of γ-hydroxy-γ-lactams of type **III** starting from substituted furans **I** (Scheme 1).[9] More specifically, the photooxygenation (singlet oxygen) of simple furans followed by addition of primary amines or ammonia, leads to the formation of 2-pyrrolidinones of type **II** (**I** → **II**, Scheme 1).[8,10] The subsequent oxidation of **II**, by a process where MB acts as a radical initiator in the dark and triplet oxygen as the terminal oxidant, yields the corresponding lactam **III** (**II** → **III**, Scheme 1).[9] We envisioned that these dual photosensitizing and redox activities of MB might be exploited in the synthesis of the privileged 3-acyl-5-alkoxy-buryrolactam scaffolds **5** as is illustrated in Scheme 1. This would require the inclusion of more, and, potentially disrupting, functionality in the starting furans. Thus, furans of type **1**, bearing an unprotected pendent hydroxyl group (present on the 4-substituent of the furan), would need to be transformed to the corresponding γ-hydroxy-γ-lactams **3**. The acid induced alcoholysis of **3** to the corresponding compound **4**, followed by its oxidation, would then be required to reach the desired polysubstituted α-acyl-γ-alkoxy-α,β-unsaturated-γ-lactams **5.** For excellence, the entire protocol going from furan to lactam product (**1** → **5**) should be amenable to operation as a one-pot process.

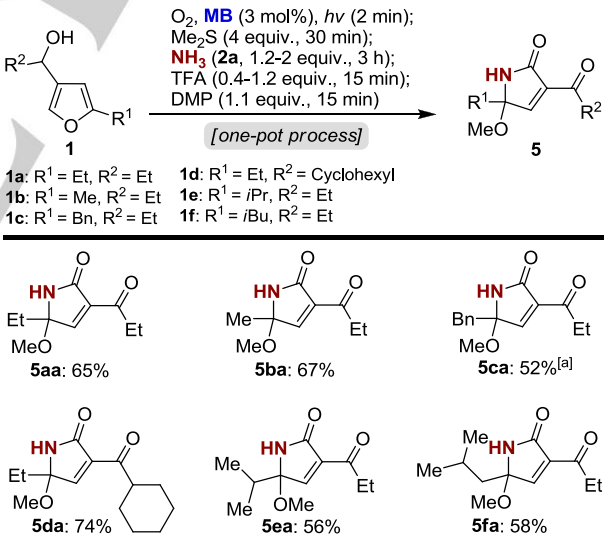
The investigation began with the easily accessible furan **1a** (see Supporting Information for the facile preparation of the furan precursors) which was subjected to established photooxygenation conditions (Scheme 2). More specifically, the substrate in methanol and in the presence of oxygen (bubbled through the solution) and catalytic amounts of MB (3 mol%) was subjected to visible irradiation (2 min). This photooxygenation step was followed by treatment of the resultant adduct with, first Me_2S (4 equiv., 30 min) and then ammonia (1.2 equiv., 3 h). This tandem reaction sequence delivered the corresponding hydroxy lactam **3aa** which was immediately treated *in-situ* with trifluoroacetic acid (0.4 equiv.) for just 15 min. Gratifyingly, the reaction gave the desired methoxylated product **4aa** with an exceptional isolated yield of 85%. With **4aa** in hand, various oxidation conditions for the preparation of the targeted compound **5aa** were investigated. Amongst the oxidants tested, Dess-Martin periodinane (DMP, 1.1 equiv.) proved to be the



Scheme 2. Optimization of the conditions for the synthesis of **5aa**.

most efficient, since the desired 3-acyl-5-methoxy-butyrolactam **5aa** was produced in 82% isolated yield after just 15 min reaction time (conditions C, Scheme 2). Most importantly, these optimal oxidation conditions could be applied smoothly without purification of compound **4aa**. In this instance, the solvent methanol was simply replaced with CH_2Cl_2 prior to the DMP addition, with the result that the full one-pot oxidation reaction sequence gave the final product **5aa** directly, in 65% overall yield, starting from the corresponding furan **1a** (Scheme 2).

After the optimal conditions had been found and validated, various substituted furans, which would yield the motifs seen in the molecules of biological interest, were tested in order to explore the scope and limitations of the newly developed synthetic protocol. Starting from substrates **1a**-**1d**, the reactions efficiently afforded the desired products **5aa**-**5da** regardless of the R^1 and R^2 substituents (52-74% yield, Scheme 3). In the case of furans **1e** and **1f**, bearing bulkier R^1 substituents, an increase in the amount of ammonia (2 equiv., 3 h), and, consequently, also of TFA (1.2 equiv., 15 min) proved essential for the formation of the intermediate lactams of type **4** (Scheme 1). The subsequent oxidation was, once again, accomplished using DMP (15 min) to furnish the corresponding compounds **5ea** and **5fa** in 56% and 58% yield respectively. The isolated yields may be considered highly satisfactory since six discrete transformations are contiguously incorporated in this tandem reaction sequence.



Scheme 3. Synthesis of 3-acyl-5-methoxy-butyrolactams **5** from furans and ammonia. [a] Starting from the benzyl-substituted furan **1c**, the optimal total yield of **5ca** (52%) was obtained when the photoxidation was undertaken using rose Bengal instead of MB. In this case, MB was then added after the addition of NH_3 (see SI).

In an effort to expand the synthetic utility of the new methodology, the investigation was continued using various primary amines, instead of ammonia. Retaining methanol as the solvent, the incorporation of primary amines **2b-2d** (1 equiv.) was not found to impede the reaction sequence from forming the desired 5-methoxy-butyrolactams of type **5** (Scheme 4).

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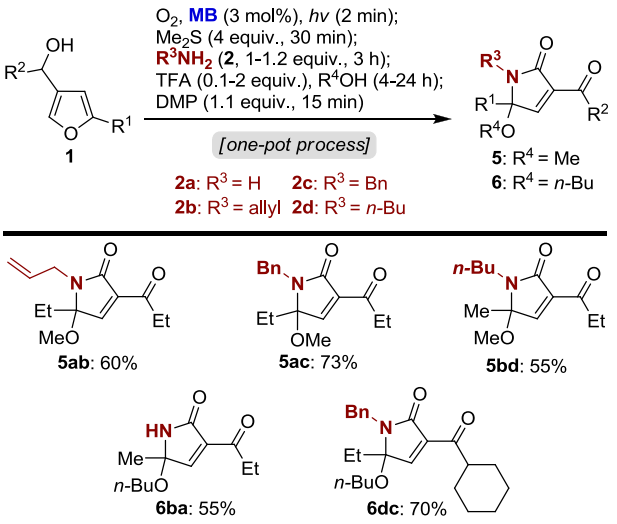
Crucially, however, a simple alteration to the amount of TFA (1 equiv.) was essential for the implementation of the methanolysis step, which was then completed within 4 h. The DMP oxidation part of the tandem sequence led to the final 3-acyl-5-methoxy-butyrolactams **5ab**, **5ac** and **5bd** in 55-73% total isolated yield (Scheme 4).



Scheme 4. Synthesis of various 3-acyl-5-alkoxy-butyrolactams of type **5** or **6** from furans and primary amines or ammonia.

The ability to adapt the cascade reaction sequence in order to install different alkoxy groups at the 5-position of the lactam moiety was also highly pertinent due to the presence of such variation in the biologically active molecules of interest (Figure 1). To this end, we studied the alcoholysis procedure using 1-butanol as the alkoxy source. Specifically, starting the process using furan **1b**, and, ammonia (1.2 equiv.), consistently gave the corresponding lactam of type **3** (Scheme 1). Then, by simply replacing the solvent (MeOH) with 20 equiv. of 1-butanol, TFA (0.1 equiv.) could be used to catalyse the alcoholysis step which was completed within 24 h. The lower amount of TFA required here in comparison to the previous methanolysis procedure (Scheme 3, 0.4 equiv. of TFA) can be attributed to the removal of excess ammonia during the solvent exchange. The DMP oxidation in CH_2Cl_2 was also efficiently accomplished, affording lactam **6ba** in 55% isolated yield. Using benzyl amine (**2c**) and starting the reaction sequence with substrate **1d** the synthetic protocol also proceeded as expected. In agreement with the previous examples where primary amines had been used (compounds **5ab**, **5ac** and **5bd**, Scheme 4), the amount of TFA had to be increased (2 equiv.) in order to achieve the completion of the alcoholysis step (24 h). Finally, compound **6dc** was produced in 70% overall yield after the DMP oxidation. Consequently, it has been shown that by auspicious choice of the nitrogen, as well as, of the alkoxy source, access to the entitled privileged scaffolds can readily be achieved. Most importantly, many of the synthesized frameworks displayed in Schemes 3 and 4 have all the correct structural features of the heavily adorned lactam cores from many biologically active alkaloids (Figure 1).

Conclusions

Naturally occurring α,β-unsaturated-α-acyl-γ-alkoxy-γ-lactams alongside their synthetic congeners make up an important class of alkaloids of biological interest. However, they are also relatively fragile compounds richly adorned with functionality whose synthesis can, therefore, be quite complex. We have developed a new and highly effective methodology for the synthesis of these lactams, which starts from readily accessible furans. The operationally simple one-pot method is initially choreographed by singlet oxygen, but also later uses ground state oxygen (triplet oxygen) and is reliant throughout upon methylene blue which acts in dual catalytic roles; first as a sensitizer and then as a redox agent and radical initiator in the dark.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental procedures, and compound characterization data (^{1}H NMR, ^{13}C NMR). This material is available free of charge in the Supporting Information.

Acknowledgements

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Keywords: methylene blue • triplet oxygen • singlet oxygen • butyrolactams • furans

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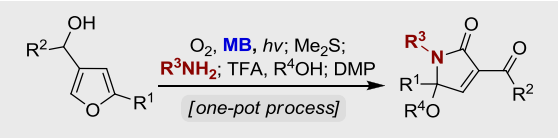

Synthetic methodology*

Manolis Sofiadis, John Sarris, Tamsyn Montagnon, Dimitris Kalaitzakis and Georgios Vassilikogiannakis**

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A new and highly effective methodology for the synthesis of 3-acyl-5-alkoxy-butyrolactam units from readily accessible furans, has been developed. The operationally simple one-pot method is initiated by singlet oxygen, but also later uses ground state oxygen (triplet oxygen) and is dependent by methylene blue which acts in dual roles; first as a sensitizer and then as a radical initiator in the dark.

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