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Catch Phrase

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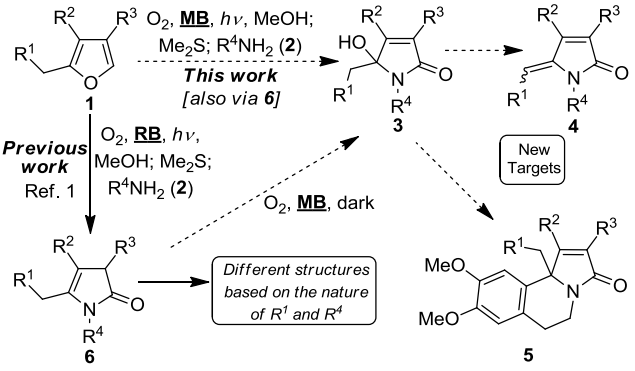
Methylene Blue as Photosensitizer and Redox Agent: Synthesis of 5-Hydroxy-1*H*-pyrrol-2(5*H*)-ones from Furans**

*Dimitris Kalaitzakis, Antonia Kouridaki, Dimitris Noutsias, Tamsyn Montagnon, and Georgios Vassilikogiannakis**

Dedicated to the memory of Christopher S. Foote on the occasion of the 50th anniversary of the Foote/Wexler discovery

Abstract: *A highly efficient and general singlet oxygen-initiated one pot transformation of readily accessible furans into 5-hydroxy-1H-pyrrol-2(5H)-ones has been developed. The methodology was extended to include the synthesis of high value α,β-unsaturated-γ-lactams. This useful set of transformations relies on exploiting not just the photosensitizing ability of methylene blue, but also its redox properties; properties that have until now been virtually ignored in a synthetic context.*

We recently developed a synthetic methodology for the construction of γ-lactam motifs starting from furans.[1] In this case, singlet oxygen, generated in the presence of rose Bengal (RB) and visible light, initiated a complex reaction sequence which finally afforded important nitrogen-containing polycycles[1] through the intermediacy of 2-pyrrolidinones type **6** (Scheme 1). Herein, we are proposing to alter the outcome of the sequence simply by changing the photosensitizer used from rose Bengal (RB) to methylene blue (MB). Thus, we intend to exploit for the first time, both the inherent photosensitizing ability and the catalytic redox capability of methylene blue within the same synthetic procedure.



Scheme 1. Proposed synthesis of α,β-unsaturated γ-lactams derivatives **3**, **4**, and **5** from furans.

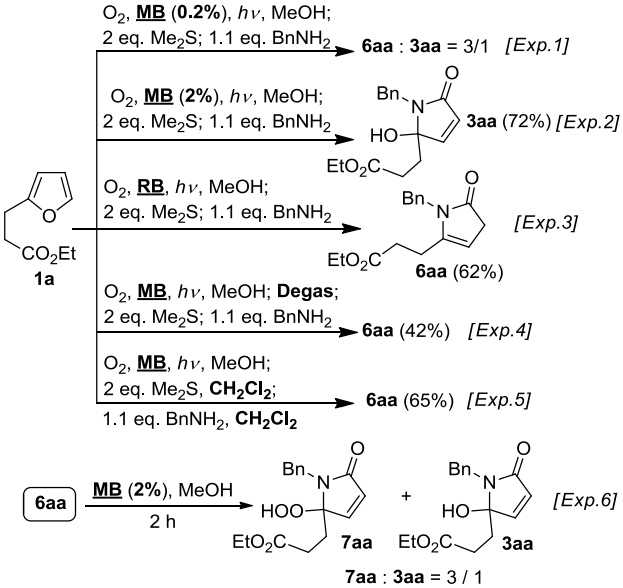
In organic synthesis, MB has been quite sparsely employed as an oxidant and when it has been used it has mostly been in photocatalysis where the oxidation is performed in the presence of light and a tertiary amine (a sacrificial electron donor).[2] However, the ground state of methylene blue also has a redox potential[3] that does not preclude it facilitating the oxidation of suitable substrates;[4] including, carbohydrates,[5] or ascorbic acid,[6] but, thus far, only under difficult conditions that have limited wider applications.

We propose that 2-pyrrolidinone **6** (which is the keto-tautomer of a pyrrol-2-ol) might be oxidized by MB in the presence of molecular oxygen to afford the desired 5-hydroxy-1*H*-pyrrol-2(5*H*)-one **3** and from here give access to 5-ylidenepyrrol-2(5*H*)-ones **4** and α,β-unsaturated-γ-lactams of type **5** (Scheme 1).

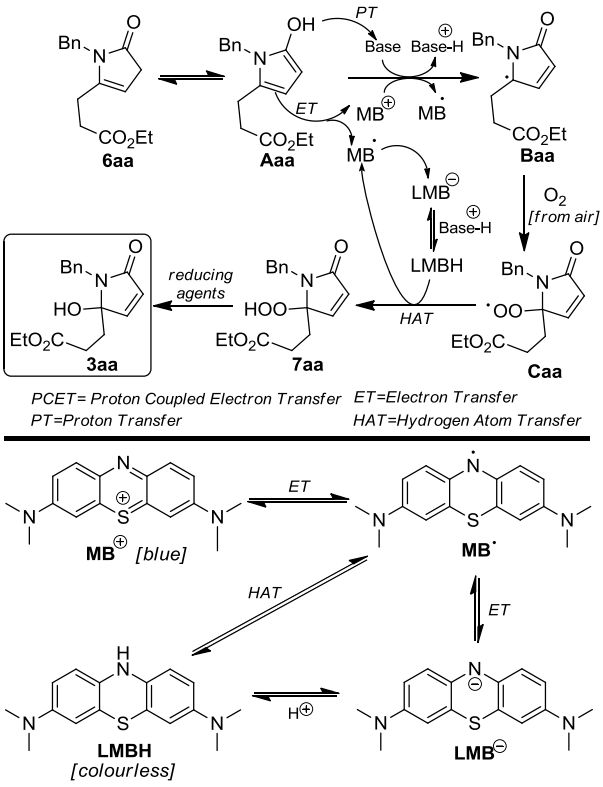
The targets of this methodology have been carefully chosen since 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3** are highly important heterocyclic motifs. Not only do they exist in a slew of natural products,[7] but they also exhibit significant biological activities.[8] There are a number of methodologies focusing on the synthesis of these important scaffolds.[7,9-13] Many of these strategies, however, require preparation of a complex substrate and/or suffer from substrate limitations and/or apply harsh reaction conditions. In a small number of cases, specifically substituted furans have been utilized as starting materials.[11-13]

The dehydrated counterparts, 5-ylidenepyrrol-2(5*H*)-ones (**4**, Scheme 1) are also highly important compounds as they constitute motifs seen in many natural products and pharmaceuticals.[7,14] They have also attracted attention as products of human metabolic degradation of hemoglobin[15] and as fragmentation products from abasic lesions of DNA.[16] Many of the methodologies developed for their synthesis[7,10] are based on the dehydration of the 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3**.[10]

Our study began with the photooxidation of the commercially available furan **1a** (0.5 mmol, final concentration 83 mM, Scheme 2, Exp. 1) using a catalytic amount of MB (0.2 mol%, 0.17 mM) as photosensitizer and was followed by the reduction of the photooxidation product (excess Me_2S).[1] Intriguingly, upon addition of benzylamine (1.1 eq., 91 mM), instant decolorization of the solution was observed suggesting that MB^+ had been reduced to



Scheme 2. Control experiments.



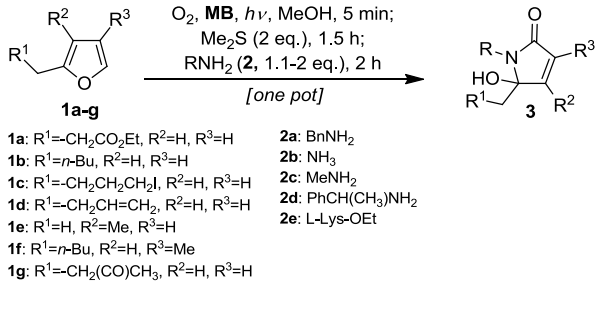
Scheme 3. Possible PCET mechanistic explanation for the oxidation of 2-pyrrolidinone **6aa**.

leuco methylene blue (LMB). After 6 hours of stirring, analysis of the crude reaction mixture revealed the formation of 2-pyrrolidinone **6aa**[1] and its oxidized analogue **3aa** in a 3/1 ratio. Increasing the amount of MB (2 mol%, final concentration 1.7 mM) led to the exclusive formation of **3aa** in 2 h and in 72% isolated yield (Scheme 2, Exp. 2). This oxidation process (**6aa** → **3aa**) was smoothly performed in complete darkness suggesting that this is not a light-induced oxidation.[2] The same reaction was also performed on a larger scale (4 mmol of **1a**, with final concentrations of 160 and 3.2 mM for the furan and MB, respectively) where lactam **3aa** was produced in 70% yield (see SI). In contrast, the exact same procedure, undertaken using RB (0.2 and 2 mol%) instead of MB, afforded exclusively 2-pyrrolidinone **6aa** (Scheme 2, Exp. 3),[1] while addition of catalytic amount of MB (2 mol%) to the same reaction mixture, after the formation of compound **6aa**, led to the formation of product **3aa**. Ultraviolet-visible spectrum absorption measurements revealed that, after the addition of the $BnNH_2$, the characteristic absorption of MB^+ at 660 nm decreased to near zero and a characteristic band for LMB appeared at 250 nm (see SI). Neither the reaction's initial blue colour, nor the characteristic 660 nm absorption band for MB^+, were seen to be regenerated over the course of the reaction. The participation of O_2 in the catalytic cycle was proven by degassing the reaction solution using argon after the photooxidation (Scheme 2, Exp. 4); in this case, no formation of the oxidized product **3aa** was observed. Finally, the solvent (MeOH) could not be replaced by CH_2Cl_2 (Scheme 2, Exp. 5). In order to further study the oxidation mechanism, 2-pyrrolidinone **6aa** was isolated (Scheme 2, Exp. 3) and added to a solution of MB (2 mol% in MeOH). Full consumption of compound **6aa** was observed after 2 h of stirring and analysis of the crude reaction mixture revealed the formation of a mixture of **7aa**:**3aa** in a 3:1 ratio (Scheme 2, Exp. 6). This reaction could be accelerated such that complete consumption of **6aa** was achieved in 30 min upon addition of benzylamine (0.3 eq.).

The information from these experiments (for example: acceleration by base, solvent dependency) was incorporated into a proton coupled electron transfer (PCET)[17] mechanistic proposal (Scheme 3). It is suggested that **Aaa** (a tautomer of **6aa**) might undergo both proton (to the base) and electron (to MB^+) transfer; thus, producing the captodative radical **Baa** which might, in turn, be trapped by molecular oxygen to afford hydroperoxy radical **Caa**. Thus, molecular oxygen from air is acting as the terminal oxidant in this process. Hydrogen atom transfer from LMBH would convert **Caa** to **7aa** with the MB radical ($MB^{\cdot}$) so-produced propagating the cycle by generating **Baa** upon further electron transfer (**Aaa** to $MB^{\cdot}$). Alternatively, **Caa** might abstract a hydrogen atom directly from **6aa**, thus regenerating **Baa** and propagating the cycle. The hydroperoxy intermediate **7aa** may be reduced to the product **3aa** in the presence of Me_2S, or LMB,[18] or another of the reducing agents present in the mixture.

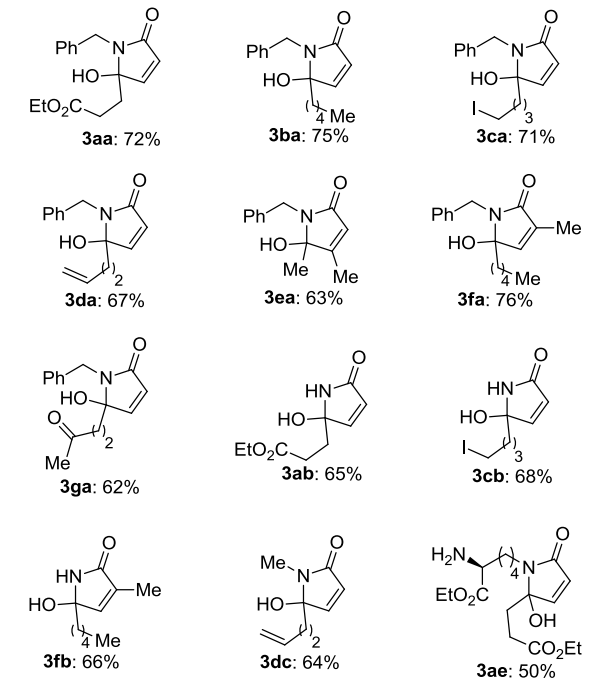
Having optimized the reaction conditions, we explored the behavior of other substrates (both furans and amines) chosen to probe the scope of the reaction. Table 1 clearly demonstrates the preparation of the desired 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones with good isolated yields (50-76%) and in short reaction times (2 h) when stoichiometric amounts of amines (1.1 eq. for primary amines and 2 eq. for ammonia) were employed. In particular, the reaction with benzylamine (**2a**) resulted in every case in the formation of the desired γ-hydroxy γ-lactams (**3aa-3ga**). The presence of water did not affect the reaction outcome as the use of aqueous ammonia (**2b**),

Table 1. One pot synthesis of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3**.



1a: R^1=-CH_2CO_2Et, R^2=H, R^3=H
1b: R^1=*n*-Bu, R^2=H, R^3=H
1c: R^1=-$CH_2CH_2CH_2I$, R^2=H, R^3=H
1d: R^1=-CH_2CH=CH_2, R^2=H, R^3=H
1e: R^1=H, R^2=Me, R^3=H
1f: R^1=*n*-Bu, R^2=H, R^3=Me
1g: R^1=-$CH_2(CO)CH_3$, R^2=H, R^3=H

2a: $BnNH_2$
2b: NH_3
2c: $MeNH_2$
2d: $PhCH(CH_3)NH_2$
2e: L-Lys-OEt

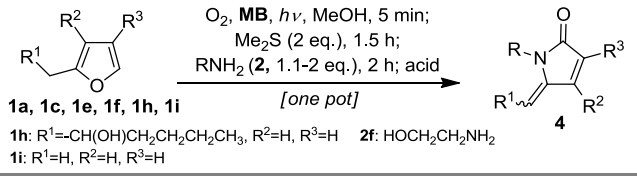


or aqueous methylamine (**2c**), both led to the corresponding lactams (**3ab**, **3cb**, **3fb** and **3dc**) in good isolated yields. It is also important to note that sensitive moieties such as an iodide (furan **1c**), an olefin (furan **1d**) or even a keto-group (furan **1g**) remained untouched during the cascade reaction sequence. In addition, different furan substitution patterns (see **1e** and **1f**) are readily tolerated increasing the synthetic scope of the current methodology. Branched amines (such as **2d**) are not suitable candidates for this reaction; product **3ad** (not shown) was only produced in very small yields. We could take advantage of this feature to distinguish between different amine groups in the same substrate; for example, when using the ester of the naturally occurring aminoacid L-lysine (L-Lys-OEt, **2e**), **3ae** was formed exclusively.

Having synthesized a variety of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones we now focused on the one-pot formation of their dehydrated counterparts, 5-ylidenepyrrol-2(5*H*)-ones **4**. The same protocol was applied, and, as shown in Table 2, all that was required to efficiently obtain the desired products was the addition of an acid at the final stage of the sequence. When ammonia was used, the intermediate 5-hydroxy-1*H*-pyrrol-2(5*H*)-one was stirred in HCOOH leading predominantly to the Z-isomer of the final product (compounds **4cb** and **4fb**, *Z*:*E*=4:1), while with benzylamine the *E*-isomers (compounds **4aa**, **4ca** and **4ha**) were produced exclusively. In the case of furan **1h**, the use of HCOOH for the final dehydration step gave the formate ester **4ha**, while the use of PTSA (0.5 eq. in refluxing $CHCl_3$) afforded the fully dehydrated lactam **4ha′**. The use of a more challenging *bis*-nucleophilic amine (ethanolamine, **2f**) did not affect the course of the reaction with *E*-lactam **4ff** being accessed in this case when HCOOH was employed for the dehydration step of the sequence. Strikingly, when L-Lys-OEt was used, dehydration with TFA (2eq. in CH_2Cl_2) selectively afforded **4ie**. This product constitutes a close analogue of DNA fragmentation products seen when DNA lesions, formed by oxidative damage, interact with various L-lysine-rich proteins.[16]

Compounds of type **3** and **4** are important intermediates whose manipulation via the *N*-acyliminium ion (NAI)[19] can furnish us with complex nitrogen-containing polycycles.

Table 2. One pot synthesis of 5-ylidenepyrrol-2(5*H*)-ones **4**.



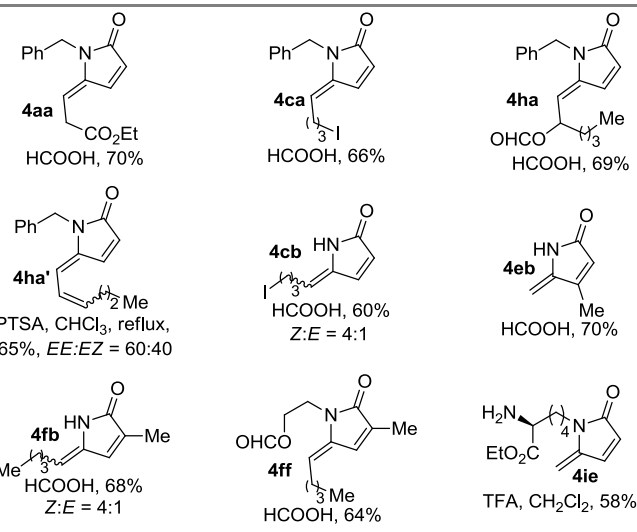
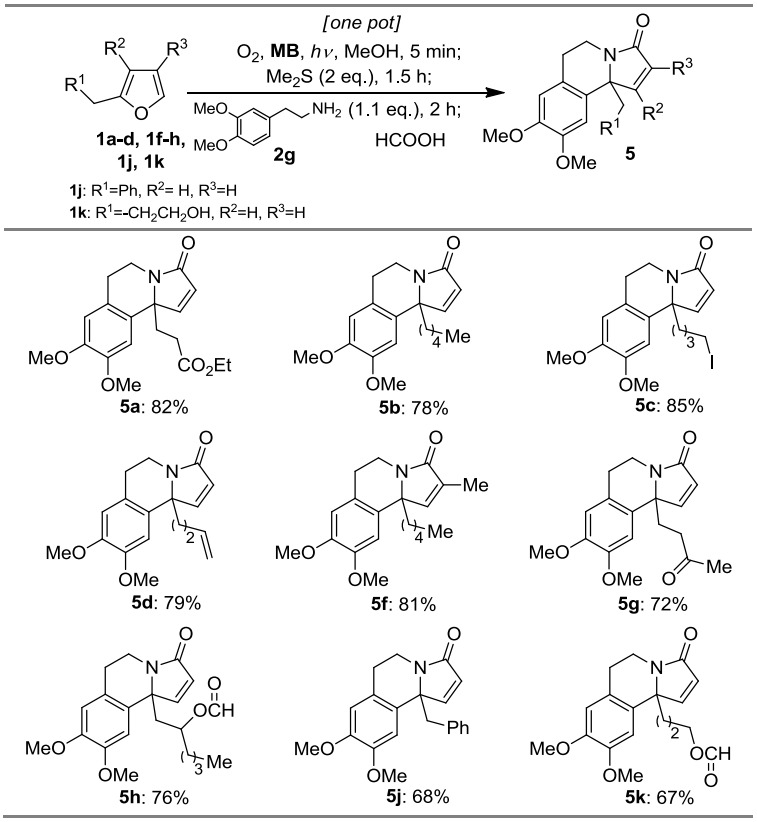


Table 3. One pot reaction synthesis of lactams **5**.



Thus, if an intramolecular nucleophilic addition of an aromatic nucleus to the NAI (a Pictet-Spengler cyclisation)[20] is incorporated into the one pot sequence it concludes with the formation of the tricycle **5** (Table 3)[9a,b,10b,21] which is of high value due to its appearance in many synthetic targets such as the *erythrina* alkaloids.[22] More specifically, the use of commercially available 2-(3,4-dimethoxyphenyl) ethanamine (**2g**) gave the desired products of type **5** (Table 3), via the corresponding γ-hydroxy γ-lactams of type **3**. HCOOH was found to be the acid of choice for the formation of the intermediate *N*-acyliminium ion which spontaneously cyclised forming the tricycles of type **5**. The reactions proceeded as single synthetic operations with remarkably good yields (67–85%); especially, when consideration is given to the degree by which molecular complexity is increased.

In conclusion, a set of methodologies have been developed in which methylene blue fulfils two roles within the same one pot sequence that ultimately furnishes either 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones or 5-ylidenepyrrol-2(5*H*)-ones. The sequences rapidly and efficiently deliver complex and high value synthetic targets in one operation starting from simple furans.

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Layout 2:

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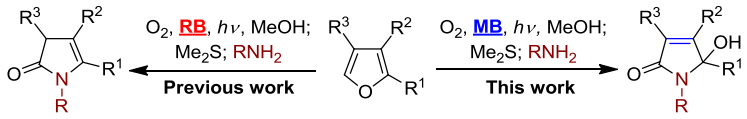

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