Synthetic Methods

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

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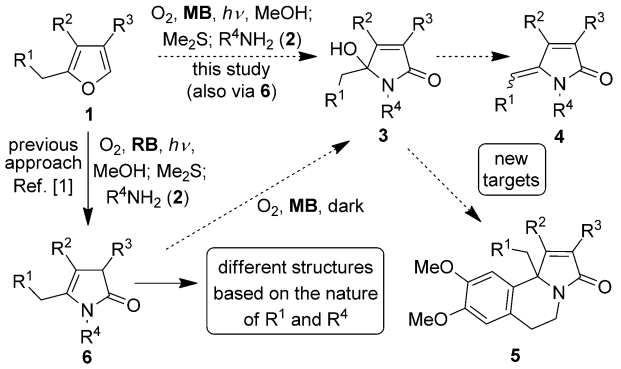
In memory of Christopher S. Foote

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 the synthesis of other high-value α,β-unsaturated γ-lactams. This useful set of transformations relies not only on the photosensitizing ability of methylene blue, but also on its redox properties: properties that have until now been virtually ignored in a synthetic context.*

We recently developed synthetic methodology for the construction of γ-lactam motifs from furans.[1] In this approach, 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 **6** (Scheme 1). Herein, we are proposing to alter the outcome of the sequence simply by changing the photosensitizer used from rose Bengal to methylene blue (MB). Thus, we will 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-lactam 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, whereby 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] which has been reported to facilitate the oxidation of suitable substrates,[4] including carbohydrates[5] and ascorbic acid,[6] but until now only under difficult conditions that have limited wider application.

We propose that 2-pyrrolidinones **6** (the keto tautomers of pyrrol-2-ols) might be oxidized by MB in the presence of molecular oxygen to afford the corresponding 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3** and thus provide access to 5-ylidenepyrrol-2(5*H*)-ones **4** and α,β-unsaturated γ-lactams **5** (Scheme 1). The targets of this methodology were 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 large number of natural products,[7] but they also exhibit significant biological activity.[8] There are a number of methods for the synthesis of these important scaffolds.[7,9–13] Many of these strategies, however, require the preparation of a complex substrate, and/or suffer from substrate limitations, and/or require 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 this motif occurs in many natural products and pharmaceuticals.[7,14] They have also attracted attention as products of the human metabolic degradation of hemoglobin[15] and as fragmentation products from abasic lesions of DNA.[16] Many of the methods developed for their synthesis[7,10] are based on the dehydration of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3**.[10]

Our study began with photooxidation of the commercially available furan **1a** [0.5 mmol, final concentration 83 mM; Scheme 2, Eq. (1)] with a catalytic amount of MB (0.2 mol%, 0.17 mM) as the photosensitizer and subsequent reduction of the photooxidation product (excess Me_2S).[1] Intriguingly, upon the addition of benzylamine (1.1 equiv, 91 mM), instant decolorization of the solution was observed, which suggested

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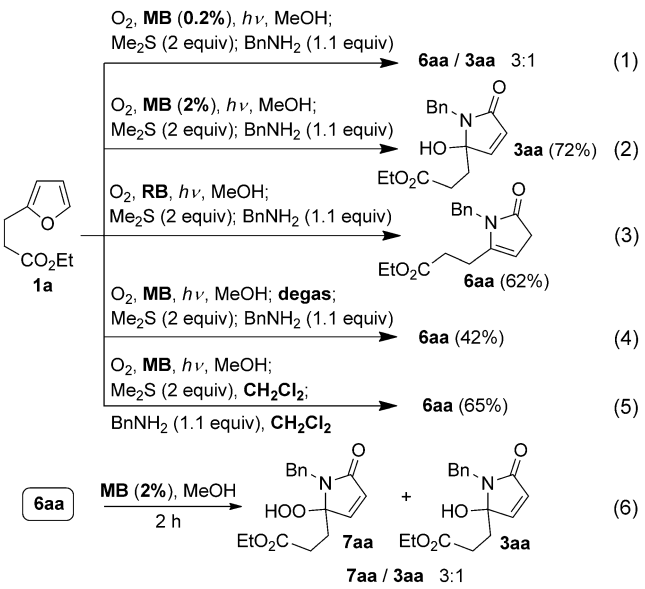
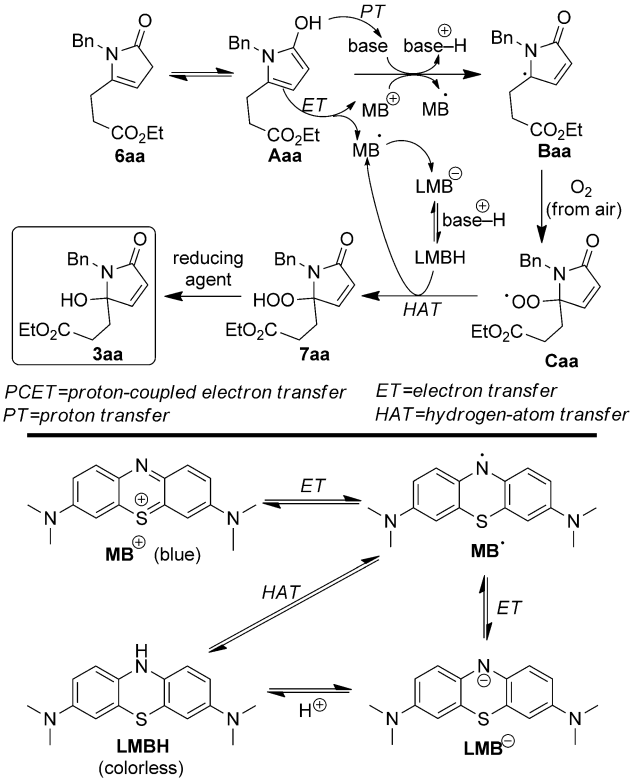


Scheme 2. Control experiments. Bn = benzyl.

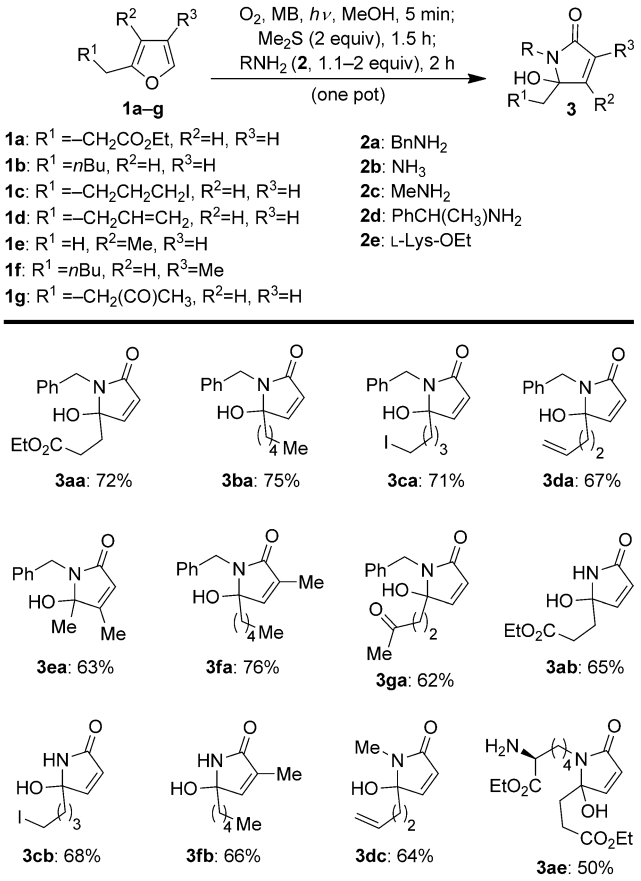
that MB^+ had been reduced to leucomethylene blue (LMB). After stirring for 6 h, analysis of the crude reaction mixture revealed the formation of 2-pyrrolidinone **6aa**[1] and its oxidized analogue **3aa** in a 3:1 ratio. An increase in the amount of MB used to 2 mol% (final concentration 1.7 mM) led to the exclusive formation of **3aa** in 2 h and 72% yield [Scheme 2, Eq. (2)]. This oxidation process (**6aa**→**3aa**) occurred smoothly in complete darkness, thus indicating that the oxidation is not a light-induced process.[2] When the same reaction was performed on a larger scale (4 mmol of **1a**, with final concentrations of 160 and 3.2 mM for the furan and MB, respectively), lactam **3aa** was produced in 70% yield (see the Supporting Information). In contrast, the use of RB (0.2 and 2 mol%) instead of MB under otherwise identical conditions afforded exclusively 2-pyrrolidinone **6aa** [Scheme 2, Eq. (3)],[1] whereas the addition of a catalytic amount of MB (2 mol%) to the reaction mixture after the formation of compound **6aa** led to the formation of product **3aa**. After the addition of $BnNH_2$, the characteristic absorption of MB^+ at 660 nm in the UV/Vis absorption spectrum decreased to nearly zero, and a characteristic band for LMB appeared at 250 nm (see the Supporting Information). Neither the initial blue color of the reaction mixture 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 with argon after the photooxidation [Scheme 2, Eq. (4)]; in this case, no formation of the oxidized product **3aa** was observed. Finally, the solvent MeOH could not be replaced with CH_2Cl_2 [Scheme 2, Eq. (5)]. To further study the oxidation mechanism, we isolated 2-pyrrolidinone **6aa** from the reaction described in Scheme 2, Equation (3) and added it to a solution of MB (2 mol% in MeOH). Full consumption of compound **6aa** was observed after stirring for 2 h, and analysis of the crude reaction mixture revealed the formation of a mixture of **7aa** and **3aa** in a 3:1 ratio [Scheme 2, Eq. (6)]. This reaction could be accelerated by the addition of benzylamine (0.3 equiv) to enable the complete consumption of **6aa** within 30 min.

The information from these experiments (for example, acceleration by a base, solvent dependency) was incorporated into a proton-coupled electron-transfer (PCET)[17] mechanistic proposal (Scheme 3). We suggest that **Aaa** (a tautomer of **6aa**) might undergo both proton (to the base) and electron transfer (to MB^+), thus producing the captodative radical **Baa**, which might, in turn, be trapped by molecular oxygen to afford the 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** into **7aa**, and the MB radical ($MB^{\bullet}$) produced in this way would propagate the cycle by generating **Baa** upon further electron transfer (**Aaa** to $MB^{\bullet}$). 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** by Me_2S, LMB,[18] or another of the reducing agents present in the mixture.

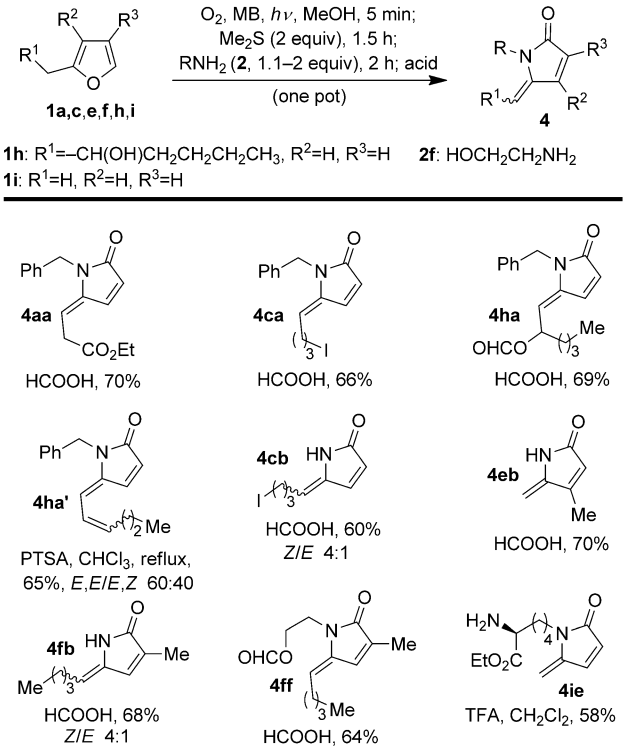


Scheme 3. Possible PCET mechanistic explanation for the oxidation of 2-pyrrolidinone **6aa**.

Having optimized the reaction conditions, we explored the behavior of other substrates (both furans and amines) to probe the scope of the reaction. The desired 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones were prepared in good yields (50–76% yield of the isolated product) and in short reaction times (2 h) when a stoichiometric amount of the amine (1.1 equiv for primary amines and 2 equiv for ammonia) was used



Scheme 4. One-pot synthesis of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **3**.

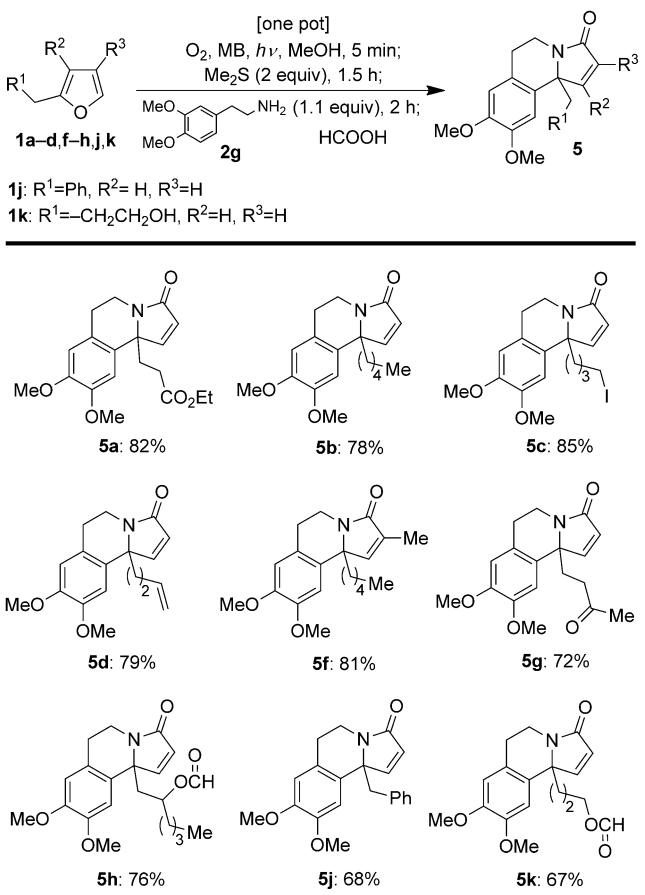


Scheme 5. One-pot synthesis of 5-ylidenepyrrol-2(5*H*)-ones **4**. PTSA = *p*-toluenesulfonic acid, TFA = trifluoroacetic acid.

(Scheme 4). In particular, the reaction with benzylamine (**2a**) resulted in every case in the formation of the desired γ-hydroxy γ-lactam (products **3aa**–**ga**). The presence of water did not affect the reaction outcome, as the use of aqueous ammonia (**2b**) or aqueous methylamine (**2c**) led to the corresponding lactams **3ab**, **3cb**, **3fb**, and **3dc** in good yields. Importantly, sensitive moieties, such as an iodide (in furan **1c**), an olefin (in furan **1d**), or even a keto group (in furan **1g**), remained untouched during the cascade reaction sequence. Furthermore, different furan substitution patterns (see **1e** and **1f**) are tolerated, thus increasing the synthetic scope of the current methodology. Branched amines (such as **2d**) are not suitable substrates for this reaction; product **3ad** (not shown) was only produced in very low yield. We could take advantage of this feature to distinguish between different amine groups in the same substrate; for example, when we used an ester of the naturally occurring amino acid 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 all that was required to efficiently obtain the desired products was the addition of an acid in the final stage of the sequence (Scheme 5). When ammonia was used and the intermediate 5-hydroxy-1*H*-pyrrol-2(5*H*)-one was stirred in HCOOH, the reaction led predominantly to the *Z* isomer of the final product (compounds **4cb** and **4fb**, *Z*/*E* 4:1), whereas 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**, whereas the use of PTSA (0.5 equiv in $CHCl_3$ at reflux) afforded the fully dehydrated lactam **4ha′**. The use of a more challenging amine with two nucleophilic functionalities (ethanolamine, **2f**) did not affect the course of the reaction; in this case the *E* lactam **4ff** was obtained when HCOOH was employed for the dehydration step of the sequence. Strikingly, when L-Lys-OEt was used, dehydration with TFA (2 equiv 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 an *N*-acyliminium ion (NAI)[19] can furnish complex nitrogen-containing polycycles. Thus, if an intramolecular nucleophilic addition of an aromatic nucleus to the NAI (a Pictet–Spengler cyclization)[20] is incorporated into the one-pot sequence, the sequence concludes with the formation of a tricycle **5** (Scheme 6).[9a,b,10b,21] This structural motif is of high value owing 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** (Scheme 6) 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



Scheme 6. One-pot synthesis of lactams **5**.

spontaneously cyclized to form the tricycles of type **5**. The reactions proceeded as single synthetic operations in remarkably good yields (67–85%), especially when consideration is given to the degree by which molecular complexity is increased.

In conclusion, a set of transformations 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 transformations rapidly and efficiently deliver complex high-value synthetic targets in one operation starting from simple furans.

Keywords: furan oxidation · methylene blue · singlet oxygen · sustainable chemistry · α,β-unsaturated γ-lactams

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