Synthetic Methods

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# A Versatile Synthesis of Meyers' Bicyclic Lactams from Furans: Singlet-Oxygen-Initiated Reaction Cascade**

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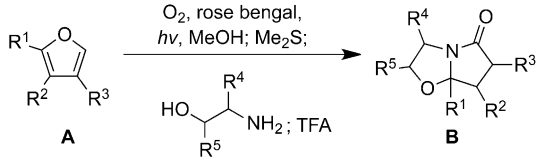
*Dedicated to Professor K. C. Nicolaou*

Ever since they were pioneered by Meyers the homochiral bicyclic lactams[1,2] bearing his name (**B**, Scheme 1) have been exceedingly popular and versatile scaffolds for the enantioselective construction of new stereogenic centers, including the most challenging type, quaternary carbon centers. These




***Scheme 1.*** Generalized representation of the transformation achieved with this new method. TFA = trifluoroacetic acid.

bicyclic lactams have been utilized in a myriad of different ways in the synthesis of a wide variety of natural products[2,3] and nonnatural molecules possessing interesting biological activity,[2,4] and, also in a diverse array of other synthetic endeavors.[2,5] The most general method for their synthesis, introduced in the seminal work by Meyers et al.,[1,2] wherein a γ-ketoacid is condensed with an amino alcohol under dehydrating conditions in toluene, heated to reflux, is still, by far, the most commonly employed means of accessing the bicyclic scaffold **B**. Modifications have been made to the Meyers' lactamization with the aim of introducing milder conditions;[6] these modifications range from using microwave energy[6a] or employing Lewis acid catalysis,[6b] to activating the acid.[6c] A second commonly employed,[7] but stepwise, route to these bicyclic lactams, also originating from the Meyers' group,[2a] relies heavily on *N*-acyliminium chemistry, which has been extensively elucidated by Speckamp and Hiemstra.[8] In this case, a succinimide intermediate is substituted at the C5-position (usually by addition of a Grignard reagent) and then undergoes intramolecular cyclization under acidic conditions. Several domino reactions affording specific bicyclic lactams have also been reported recently,[9] as well as, other stepwise approaches to the scaffold.[10] This unceasing interest in finding new syntheses for the Meyers' bicyclic lactams in itself provides testament to the usefulness of the scaffold and the diversity of potential applications there are for it.

Herein, we introduce a new and mild method for the synthesis of a wide variety of Meyers' bicyclic lactams. This novel approach, which uses a singlet-oxygen-mediated reaction cascade, is particularly powerful because the one-pot reaction begins from furan substrates which can be variously functionalized (**A**, Scheme 1) with ease, thus allowing direct access to highly substituted scaffolds of type **B** (frequently with excellent stereoselectivity). In this way, the new method also exhibits a very high degree of step[11] and atom economy[12] and utilizes the selective "green" reagent, singlet oxygen, to achieve these rapid increases in molecular complexity with precision and minimum production of waste products, thereby attaining many of the recently established criteria for an "ideal synthesis".[13]

The idea for this new method was born from our experience in the field of furan photooxygenations,[14] which has taught us to regard the furan motif as a readily accessible and easy-to-manipulate 1,4-enedione equivalent (or precursor).[15] This fact led us to ask whether the intermediate **C** (Scheme 2) could be intercepted by an 1,2-aminoalcohol, and, subsequently rearrange and cyclize (under acid catalysis) to afford the Meyers' bicyclic lactams, without the need for dehydrating conditions, or high temperatures, which have traditionally been employed. This ambitious concept is summarized, in mechanistic terms, in Scheme 2 (note: only selected steps and intermediates are shown). Thus, when a furan is oxidized upon exposure to singlet oxygen in MeOH, intermediates of type **C** are known to form easily from the in situ reduction (with $Me_2S$) of a hydroperoxy functionality, which is formed after the solvent-induced collapse of the initially formed endoperoxide adduct has occurred.[14,15] We hypothesized that addition of a 1,2-aminoalcohol at this stage should regioselectively afford the aminal **D** (via the more-stable, more-substituted oxonium cation). Aminal **D** would ring open to imino enal **E**, as shown in Scheme 2, and then ring close again to afford 2-pyrrolidinone **G**, via 2*H*-pyrrol-2-

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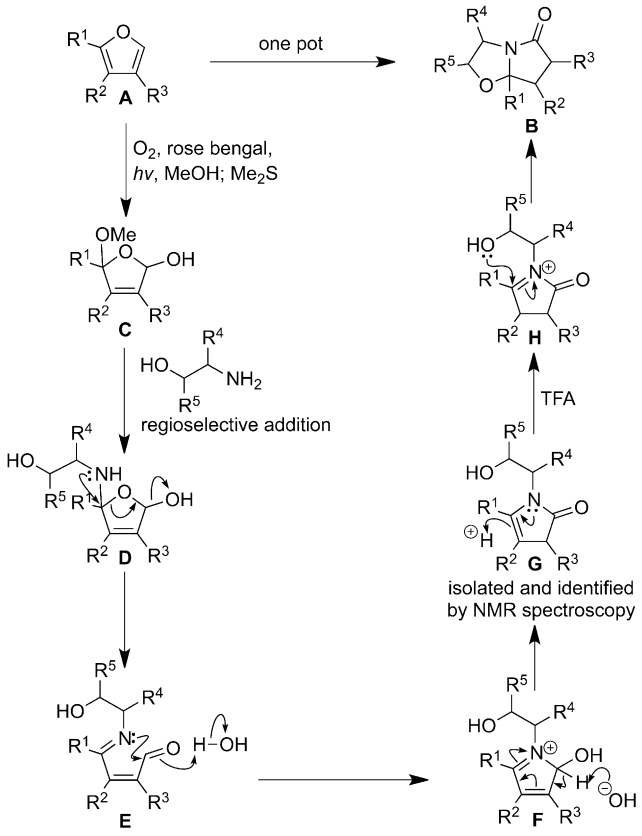


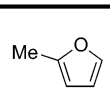
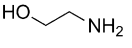
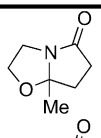
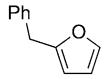
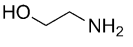
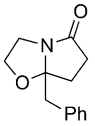
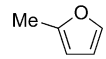
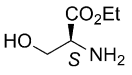
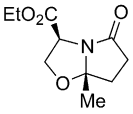
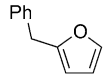
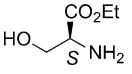
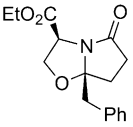
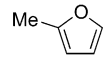
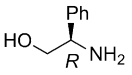
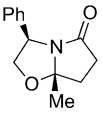
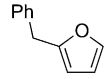
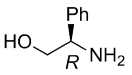
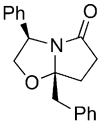
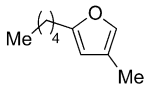
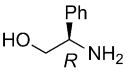
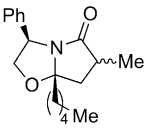
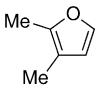
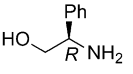
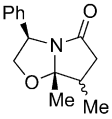
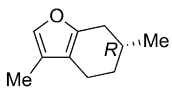
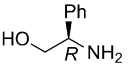
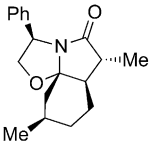
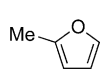
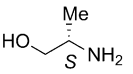
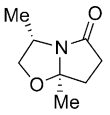
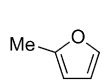
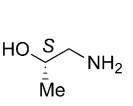
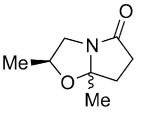

***Scheme 2.*** Mechanistic summary for the one-pot cascade reaction sequence that transforms furans **A** into bicyclic lactams **B**.

ol **F**. It was hoped that addition of an acid at this point, would affect the desired hydroxy acyl iminium cyclization to give the corresponding bicyclic lactam (**H**→**B**) as the final product of a one-pot reaction cascade.

Gratifyingly, despite the extraordinary complexity of the designed reaction cascade, we were able to successfully transfer this hypothesis into a working laboratory protocol (Table 1). Thus, in the simplest case where 2-methylfuran was oxidized with singlet oxygen,[16] in MeOH followed by in situ reduction ($Me_2S$) of the resultant hydroperoxide, and then by the addition of 2-aminoethanol, and later catalytic TFA (20 mol%), the desired corresponding Meyers' bicyclic lactam was obtained (entry 1).

With this proof of principle in hand, we set out to systematically investigate the effect of varying both the furan and 1,2-aminoalcohol substituents, and, concomitantly, delineate the precise stereochemical outcomes of the reaction cascade (Table 1). Commercially available furan starting materials were used throughout except in the cases of 2-benzylfuran (entries 2, 4, and 6) and the furan shown in entry 7, where the requisite substrates were synthesized using known procedures.[17] In general, the yields are good when the large increase in molecular complexity that has been achieved in this one-pot procedure is taken into consideration, and given the intricate nature of the reaction cascade. With regards to the stereochemical outcomes (confirmed by NOE studies),[18] the presence of a defined stereogenic center adjacent to the amino group ($R^4$ attachment position) on the 1,2-aminoalcohol induces highly stereoselective formation of the ring junction of the product ($R^1$ attachment position in the product **B**, Scheme 1), as can be seen in entries 3–10. In contrast, when there is a defined stereogenic center adjacent to the alcohol ($R^5$ attachment position) on the 1,2-aminoalcohol no significant stereoselectivity is achieved for the

***Table 1:*** One-pot synthesis of various bicyclic lactams starting from furan substrates.

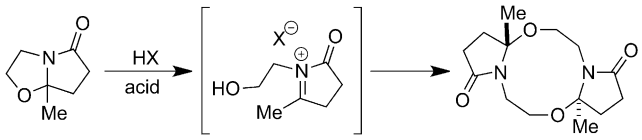
| Entry | Substrate | Trapping agent | Product | Yield [%][a] |
|---|---|---|---|---|
| 1 |  |  |  | 55 |
| 2 |  |  |  | 30 |
| 3 |  |  |  | 68 |
| 4 |  |  |  | 59 |
| 5 |  |  |  | 65 |
| 6 |  |  |  | 58 |
| 7[b] |  |  |  | 75 |
| 8[b] |  |  |  | 60 |
| 9 |  |  |  | 80 |
| 10 |  |  |  | 65 |
| 11[c] |  |  |  | 68 |

[a] Yields are of the isolated products. [b] Separable diastereoisomers. [c] Inseparable diastereoisomers.

overall reaction, as both ring-junction isomers are formed (d.r. = 55:45, $R^1/R^5$ *anti*: $R^1/R^5$ *syn*, entry 11). Similarly, substituents at the $R^2$ and $R^3$ positions of the furan substrate are incorporated in the final bicyclic lactam products with no significant stereoselectivity (d.r. = 55:45, $R^1/R^3$ *anti*: $R^1/R^3$ *syn*, entry 7; d.r. = 55:45, $R^1/R^2$ *syn*: $R^1/R^2$ *anti*, entry 8), except in the case of menthofuran (entry 9), which differs as it is bicyclic.

The following observations are also worthy of note. It has been reported in the literature[19] that the product of the reaction shown in entry 1, readily opens and reacts intermolecularly to form the centrosymmetric dimer under aqueous acidic conditions (Scheme 3). We found this to be true




***Scheme 3.*** Acid-catalyzed dimerization of bicyclic lactams.

(indeed, it also applied to other more heavily substituted products, although to a lesser extent), but we also found that this undesired dimerization could be avoided by moderating the amount of TFA employed in the cyclization step, and, in the most vulnerable cases, by neutralizing this TFA with $Et_3N$ prior to concentration of the sample. In general, 20 mol% of TFA was initially added and further additions (up to a maximum of 60 mol%) were only made when deemed necessary according to TLC analysis of the reaction mixture. The TFA-catalyzed cyclization took between 1 to 9 hours to reach completion. This tendency to dimerize may be the reason that, somewhat counterintuitively, it would appear that the bulkier the ring-junction $R^1$ substituent is, the higher the yields obtained are (entries 7 and 9). For other methods[10a] that proceed through intermediates of type **G** (Scheme 2) it has been reported that these intermediates were fleeting and could not be isolated and characterized; however, though they cannot be described as stable, we have been able to isolate and obtain $^1H$ and $^{13}C$ NMR spectra of some representative intermediates (see the Supporting Information).

In the case of entry 8, the two stereoisomeric final products could be separated by column chromatography, but subsequently proved to be highly susceptible to racemization (even on brief standing in $CDCl_3$ solution) by the opening up of the bicyclic lactam to the 2-pyrrolidinone (analogous to intermediate **G**, Scheme 2) and subsequent reclosure. Finally, and again related to intermediate **G**, when 2-benzylfuran was photooxidized and reacted with 2-aminoethanol, the yield was a mere 30% (entry 2) and the product isolated was in equilibrium with an open form;[20] however, when 2-aminoethanol is replaced with either (*S*)-serine ethyl ester (entry 4), or (*R*)-phenylglycinol (entry 6), the product yield improves dramatically to 59 and 58%, respectively, presumably owing to the Thorpe–Ingold angle compression effect favoring ring closure.

In summary, we have introduced a new and versatile method for the synthesis of Meyers' bicyclic lactams using a "green", step- and atom-economic singlet-oxygen-initiated reaction cascade. This method has broad synthetic potential as it begins from simple furan substrates, which can be readily synthesized and functionalized with various substituents, as desired; a feature that contrasts with the limitations (both in terms of their synthesis and subsequent handling and purification) imposed by the γ-ketoacid precursors used in the traditional synthesis of Meyers et al.[1,2] Furthermore, the cascade initiator, singlet oxygen, is an extremely selective reagent conferring on its reactions very broad functional group tolerance and a lack of need for protecting groups.[14] For all these reasons, it is believed that this method will prove to be a powerful addition to the synthetic chemist's armory.

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**Keywords:** nitrogen heterocycles · domino reactions · furan oxidation · Meyers' bicyclic lactams · singlet oxygen

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