Synthetic Methods

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Photooxygenation of Furylalkylamines: Easy Access to Pyrrolizidine and Indolizidine Scaffolds

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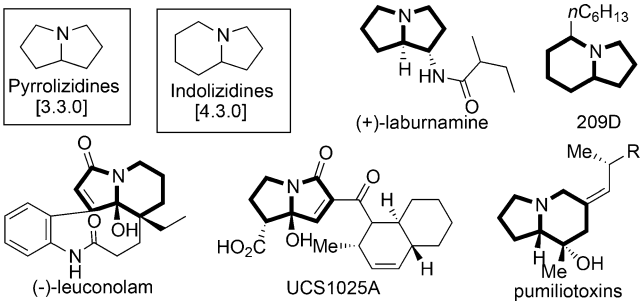
In memory of Maria Hatzimarinaki

Abstract: *A highly adaptable method targeting the ubiquitous and very important pyrrolizidine and indolizidine scaffolds is presented. The general synthetic utility of the method is underscored by its application to the rapid and easy synthesis of five natural products starting from readily accessible alkylfuran precursors. These unprotected primary furylalkylamines are subjected to photooxygenation conditions, which initiate a complex cascade reaction sequence concluding with the production of high value motifs. This sequence can be tailored to need by varying the choice of both photosensitizer and base additive.*

Nitrogen-containing polycycles make up a vast class of natural products. The izidine alkaloids, which have fused azabicyclic frameworks, are perhaps the most important subclass because its members are said to constitute nearly 30% of all known natural alkaloids. Exemplars of particular interest are the pyrrolizidines and indolizidines (Scheme 1).[1–6] Besides being abundant throughout nature, izidine alkaloids are also of considerable importance owing to their potent and diverse biological activities.[7] Characteristic examples include UCS1025A,[8] laburnamine,[9] leuconolam,[10] indolizidine 209D,[7a] and the pumiliotoxins[1] (Scheme 1). Many of these compounds have been shown to exhibit potent antitumor properties and/or antimicrobial activities.[11] Furthermore, the high and subtype-selective affinity for the nicotinic acetylcholine receptor,[7a,9,12] as well as the positive modulation of voltage-dependent sodium channels,[13] renders them potential candidates for the treatment of various important CNS disorders,[14] or as cardiotonic drugs,[13] respectively.



Scheme 1. Biologically active natural products containing the pyrrolizidine or indolizidine scaffold.

The aforementioned fundamental biological activities have contributed to countless sustained efforts over many years directed towards their construction.[15,16] However, their synthesis usually requires many steps or reagents, the preparation of complex substrates, suffers from severe substrate limitations and/or requires harsh reaction conditions. Furthermore, only a few limited examples have been designed to construct both the pyrrolizidine and indolizidine cores.[16a–c,g–h] Consequently, the development of an efficient, sustainable, and general synthetic approach to both classes of these pivotal nitrogen-containing bicycles remains a significant and unmet challenge.

Recently, we demonstrated that amines could be added intermolecularly to photooxygenated furan nuclei, thus permitting the construction of a variety of different γ-lactams[17] depending on the photosensitizer employed (rose Bengal, RB; or methylene blue–MB).[17e] Now, we questioned whether a pendant amine group on the 2-alkyl chain of the furan (furylalkylamine) might engage in an intramolecular reaction to afford the desired izidine skeletons (Scheme 2) in a one-pot process initiated by the non-toxic (as used), green, and completely atom-economic singlet oxygen.[18] The selective oxidation of a furan nucleus in the presence of an unprotected primary amine, that can itself be readily oxidized by singlet oxygen,[19] has not yet been achieved.[20]

We anticipated that the photooxygenation of the furylalkylamine in MeOH might chemoselectively afford hydroperoxide **A** (Scheme 2). After reduction (Me_2S), an enedione moiety **B** might be formed with which the amine could react intramolecularly. The resulting diaminal **C** might follow either one of two different elimination paths. Path **a** would afford the desired compounds **2** and **3** through iminium **D**, but path **b** could produce the undesired bicyclic pyrrole **4** via iminium **E**. To investigate the proposed scenario, furylalkylamine **1a** was subjected to photooxygenation conditions (visible irradiation of a 40 mM methanolic solution of **1a** containing 10^{-4} M rose Bengal with O_2 bubbling through the solution) followed by in situ reduction (Me_2S; Scheme 3). The crude ^{1}H NMR spectrum revealed the exclusive formation of the desired

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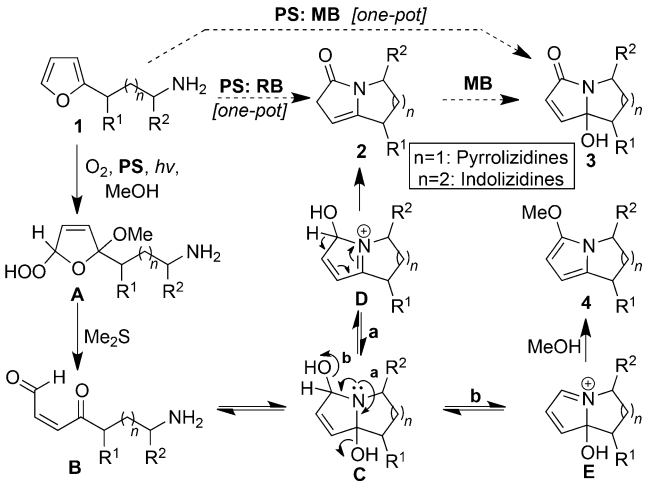
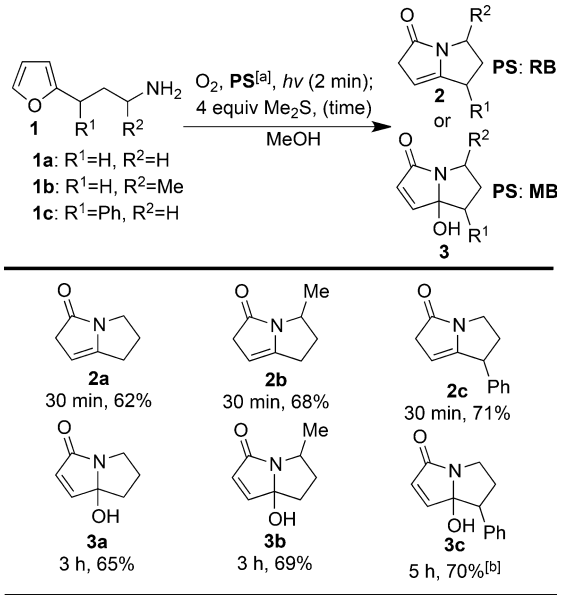


Scheme 2. Proposed mechanistic scenario for the one pot transformation of furylalkylamines to pyrrolizidinones and indolizidinones of type **2** and **3**.

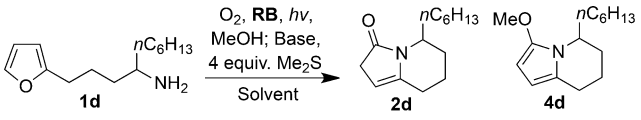


Scheme 3. Results obtained from the photooxidation of furans **1a**–**1c**. [a] For the synthesis of **2**, a 10^{-4} M of RB was used. For the synthesis of **3**, a catalytic amount of 3 mol% of MB was used. [b] 0.3 equiv. of Et_3N was used as an additive.

product **2a**, indicating that: 1) the singlet oxygen selectively reacted with the furan nucleus; and, 2) the reaction exclusively proceeded through path **a** (Scheme 2). Notably, the transformation was completed in 30 min and compound **2a** was isolated in 62% yield. Encouraged by this result, we subjected the commercially available furans **1b** and **1c** to the same conditions and, in every case, the desired products **2b** and **2c** were isolated (68% and 71% yield, respectively; Scheme 3).

Next, we tried to further expand this methodology to the synthesis of pyrrolizidinones of type **3** via an in situ oxidation of **2** by methylene blue (**2**→**3**; Scheme 2), with molecular oxygen acting as the terminal oxidant through a proton-coupled electron transfer (PCET) procedure.[17e] Therefore we applied similar reaction conditions to substrates **1a–c** using MB instead of RB (see SI). As shown in Scheme 3, substrate **1a** was exclusively transformed into the corresponding pyrrolizidinone **3a** (65% isolated yield) in a one-pot process. Similar results were recorded for furylalkylamines **1b** and **1c** where the corresponding compounds **3b** and **3c** were formed with yields of 69% and 70%, respectively. These yields are very good, given the complexity of the transformation. In the case of substrate **1c**, catalytic triethylamine was added to accelerate the final oxidation step (**2c**→**3c**).[17e] Without the base, the reaction proceeded with only 75% conversion in 24 hours. Therefore, it is feasible to selectively synthesize pyrrolizidinone motifs of type **2** or type **3** in a one-pot operation, just by tailoring the choice of the photosensitizer. It is important to note here that, with the synthesis of **3a**, a large fragment of the antimitotic agent UCS1025A[8] (Scheme 1) has been constructed. Likewise, compound **2c** represents a one-step synthesis of a large proportion of a highly potent second-generation phosphodiesterase (PDE) IV inhibitor candidate.[21]

The focus now shifted to the construction of indolizidine scaffolds. However, this reaction proved to be more complicated than the previous ones (**1a–c**; Scheme 3). When furylalkylamine **1d** was subjected to the exact same conditions, a mixture of bicyclic products **2d** and **4d** in a 1.6:1 ratio was obtained (Scheme 4, Entry 1). This result indicates



Entry	Solvent	Base (equiv.)	**2d** (%)[a]	**4d** (%)[a]	yield of **2d** (%)
1	MeOH	-	62	38	31
2	CH_2Cl_2	-	100	-	18
3	DMSO	-	100	-	22
4	CH_3CN	-	100	-	25
5	THF	-	100	-	24
6	Et_2O	-	100	-	24
7	MeOH	Et_3N (1 equiv.)	63	37	32
8	CH_2Cl_2	Et_3N (1 equiv.)	100	-	39
9	MeOH	NH_3 (1 equiv.)	84	16	50
10	CH_2Cl_2	NH_3 (1 equiv.)	100	-	41
11	Et_2O	NH_3 (1 equiv.)	100	-	35
12	THF	NH_3 (1 equiv.)	100	-	30
13	EtOH	NH_3 (1.2 equiv.)	95	5[b]	52
14	*i*PrOH	NH_3 (1.2 equiv.)	100	-	54
15	MeOH/*i*PrOH (1:1)	NH_3 (1 equiv.)	92	8	52
16	$CHCl_3$	NH_3 (1.2 equiv.)	100	-	44
17	**$CHCl_3$**	**NH_3 (2 equiv.)**	**100**	-	**62**
18	MeOH	Allylamine (1 equiv.)	92	8	58
19	**MeOH**	**Allylamine (1.4 equiv.)**	**94**	**6**	**62**
20	$CHCl_3$	Allylamine (1.4 equiv.)	100	-	50

Scheme 4. Optimization of the reaction conditions. [a] Relative ratios were determined by ^1H NMR of the crude mixtures. [b] The corresponding ethoxy pyrrole was formed.

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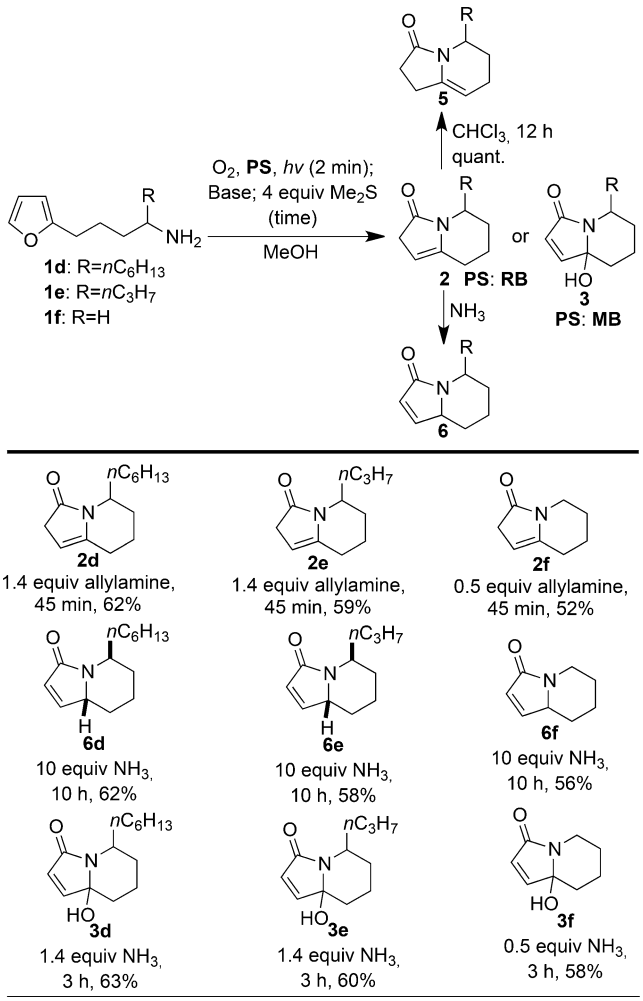
that the reaction here is following both paths **a** and **b** (Scheme 2). In an attempt to suppress path **b**, we examined a number of the reaction parameters starting with the replacement of solvent (methanol) after the photooxygenation reaction (Entries 2–6). The reaction led to a mixture of byproducts, and the final isolated yield of **2d** was disappointingly low (18–25%).

Based on the proposed mechanism of the reaction (Scheme 2), it was suggested that the addition of a base might accelerate the abstraction of the aminal hydrogen (**D** → **2**) and shift the reaction towards the desired products. The lack of significant improvement seen when Et_3N was used (Entries 7, 8) was attributed to its being a hindered tertiary base. Following this assessment, addition of ammonia was found to favor the formation of compound **2d** (**2d**:**4d** = 5.2:1, Entry 9) and to increase the isolated yield to 50%. Generally, it was found that protic solvents outperformed non-protic ones (Entries 10–15). Increases in the amount of ammonia added in protic solvents led to an isomerization trend furnishing ever-greater quantities of the corresponding α,β-unsaturated analogue of **2d**. This double bond shift was not observed with $CHCl_3$ as solvent, even when the amount of ammonia was increased to 2 equivalents; only the desired yield increase was seen (Entry 17, 62% yield). Interestingly, when allylamine was used as the base in methanol, a similar yield increase was observed (Entry 19, 62% yield). Consequently, it was decided to apply these conditions to other substrates because not only was a change of solvent avoided, but methanol is a much more acceptable solvent than $CHCl_3$ when green criteria are considered. Thus, with substrate **1e** the reaction afforded the desired product **2e** (59% isolated yield; Scheme 5). In the case of furylalkylamine **1f** without any additive, the reaction afforded a 6:1 mixture of indolizidinone **2f**:pyrrole byproduct **4f**. Addition of only 0.5 equiv of allylamine was enough to promote the exclusive formation of final indolizidinone **2f** (52% yield, **2f** is relatively volatile).

All of the final products exhibited a tendency to isomerize quantitatively to the enamides of type **5** (Scheme 5) after stirring in the slightly acidic solvent $CHCl_3$ for 12 hours at room temperature. Thus, indolizidinones **5d**, **5e**, and **5f** could be prepared starting from the corresponding furylalkylamines. The product **5f** has been used for the synthesis of hydroxylated indolizidines.[22] Once again, addition of larger amounts of base accelerated the isomerization of the initial products (type **2**) to the α,β-unsaturated analogues **6** (Scheme 5). Thus, using 10 equiv of ammonia allowed one-pot access to the corresponding indolizidinones **6d**, **6e**, and **6f** in isolated yields of 62%, 58%, and 56%, respectively (product **6f** has been used for the synthesis of hydroxylated indolizidines[23]). Both **6d** and **6e** were formed as single diastereomers.

With replacement of the photosensitizer from RB to MB, one-pot formation of the indolizidinone analogues of type **3** (**3d**–**f**, 58–63%; Scheme 5) was achieved. In this case, ammonia was used as an additive (0.5–1.4 equiv) to avoid the formation of pyrrole of type **4** and to accelerate the methylene-blue-catalyzed oxidation.[17e] It is notable that compound **3f** appears in its entirety in the natural product (−)-leuconolam[10] (Scheme 1).



Scheme 5. Results obtained from the photooxidation of furans **1d**–**1f** under the newly developed conditions.

To further underscore the synthetic utility of the present methodology, the rapid and easy synthesis of indolizidine alkaloids[5] δ-coniceine (**7f**), 209D (**7d**), and 167B (**7e**; Scheme 6) was accomplished.[7a,24] The first step towards 209D and 167B was the photooxygenation of the requisite furylalkylamines (**1d** and **1e**; Scheme 5). The resultant compounds **2d** and **2e** were reduced using first Et_3SiH and then LAH to afford the alkaloids 209D (**7d**) and 167B (**7e**) as single diastereomers (total yield over 3 steps: 45% for 209D and 42% for 167B; Scheme 6). This route required an additional purification step, so an alternative route was also elaborated using the α,β-unsaturated analogues **6d** and **6e** (Scheme 5). In this case, hydrogenation followed by LAH reduction afforded 209D (**7d**) and 167B (**7e**), again as single diastereomers (total yield over 3 steps 48% for 209D and 45% for 167B). The synthesis of δ-coniceine (**7f**) began from furan **1f**, which was subjected to the MB procedure to afford indolizidine **3f** (Scheme 5). This compound was readily hydrogenated and reduced by LAH to afford δ-coniceine in 44% yield over 3 steps. The key necine base, heliotridane (**7g**; Scheme 6),[25] was also readily accessible using these innovations. The methylene blue procedure was applied to furylal-

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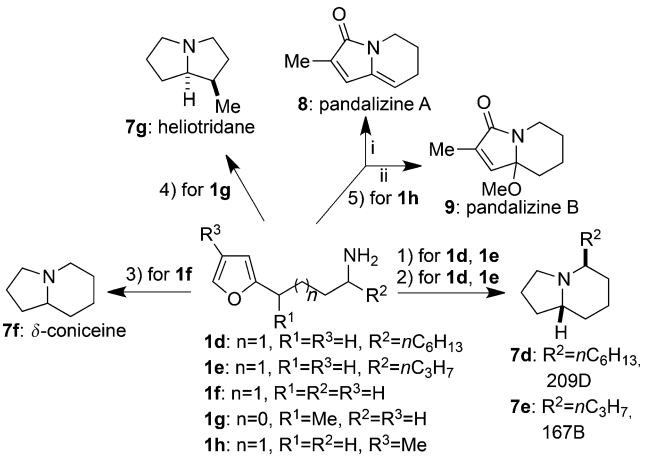

1) i) O_2, *hv*, **RB**, MeOH; 1.4 equiv allylamine, Me_2S, MeOH; ii) Et_3SiH, TFA, CH_2Cl_2; iii) $LiAlH_4$, Et_2O (45% for 209D and 42% for 167B over three steps). **2)** i) O_2, *hv*, **RB**, MeOH; 10 equiv NH_3, Me_2S, MeOH; ii) H_2, Pd/C, MeOH; iii) $LiAlH_4$, Et_2O (48% for 209D and 45% for 167B over three steps). **3)** i) O_2, *hv*, **MB**, MeOH; NH_3, Me_2S, MeOH; ii) H_2, Pd/C, MeOH; iii) $LiAlH_4$, Et_2O (44% over three steps). **4)** i) O_2, *hv*, **MB**, MeOH; Et_3N, Me_2S, MeOH; ii) H_2, PtO_2, EtOAc; iii) $LiAlH_4$, Et_2O (42% over three steps). **5)** O_2, *hv*, **MB**, MeOH; NH_3, Me_2S, MeOH, then i) TFA, $CHCl_3$, (68%), or ii) TFA, MeOH (61%).

Scheme 6. Synthesis of natural alkaloids 209D, 167B, heliotridane, pandalizines A and B and the unnatural δ-coniceine starting from simple furylalkylamines.

kylamine **1g**, using Et_3N (0.3 equiv) to accelerate the oxidation step. The reaction gave the corresponding pyrrolizidinone of type **3** (**3g**, not shown, 59% yield) that was sequentially reduced first by H_2 and then by LAH to afford heliotridane (42% overall yield for all three steps). Finally, the synthesis of both pandalizine A and B (**8** and **9**; Scheme 6) was accomplished. These natural alkaloids have only just very recently been isolated from the medicinal plant *Pandanus amaryllifolius* Roxb.[26] Here, the substrate for the photooxygenation was the *meta*-methyl substituted furylalkylamine **1h** which was directly converted to the indolizidine **3h** (not shown). The isolation report suggests that **3h** is the biogenetic precursor to pandalizines A and B,[26] and indeed, the natural products could be obtained upon addition of TFA in $CHCl_3$ or MeOH, respectively, as the culmination of the one-pot process (68% overall isolated yield for pandalizine A and 61% for pandalizine B).

In summary, a diverse array of important pyrrolizidine and indolizidine motifs, including five natural products, have been synthesized from readily accessible furan precursors. The procedures employ green reagents and conditions (oxygen and visible spectrum light) and, despite the context wherein it is normal to use many non-constructive steps enroute to these targets, the current procedures are highly atom- and step-economic; a very simple precursor leads each time to a complex motif in one operation. Finally, no protecting groups are used; the avoidance of which, for the primary amines present in the molecules during the singlet oxygen photooxygenation, is unprecedented.

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Keywords: alkaloids · indolizidines · pandalizines · pyrrolizidines · singlet oxygen

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