

Photooxygenation of Furylalkylamines: An Easy Access to Pyrrolizidine and Indolizidine Scaffolds

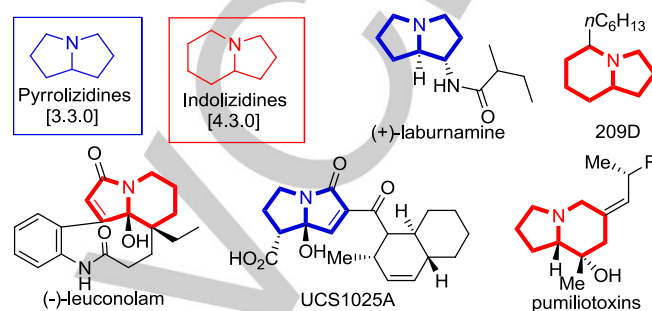
Dimitris Kalaitzakis, Myron Triantafyllakis, Manolis Sofiadis, Dimitris Noutsias and Georgios Vassilikogiannakis*

In memory of Maria Hatzimarini

Abstract: A new highly adaptable method targeting the ubiquitous and very important pyrrolizidine and indolizidine scaffolds is presented. The method's general synthetic utility is underscored by its application to the rapid and easy synthesis of five natural products starting from readily accessible furylalkylamine 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. If we home in on the “-izidine” alkaloids, which have fused azabicyclic frameworks, we have found perhaps the most important sub-class because its members are said to constitute almost 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 due to their potent and diverse biological activities.⁷ Characteristic examples include; UCS1025A,⁸ laburnamine,⁹ leuconolam,¹⁰ indolizidine 209D^{7a} and the pumiliotoxins¹ (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 cardiotoxic drugs,¹³ respectively.

The aforementioned fundamental biological activities have contributed to countless sustained efforts over many years being made 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, as and when required.^{16a-c,16g-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.



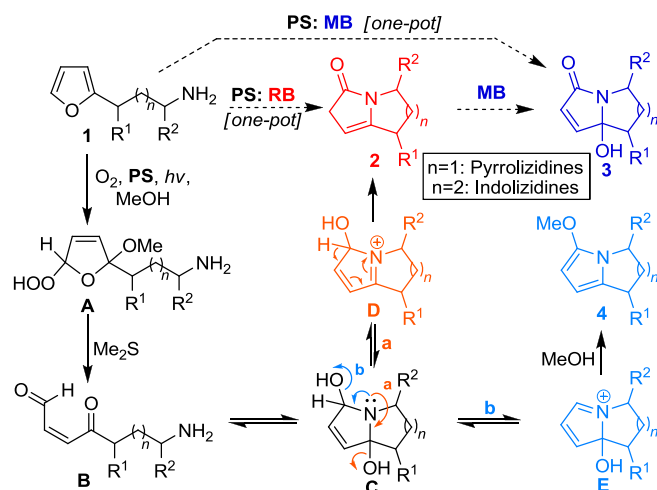
Scheme 1. Biologically active natural products containing the pyrrolizidine or indolizidine scaffold.

Recently, we demonstrated that amines could be added intermolecularly to photooxygenated furan nuclei; thus, permitting the construction of a variety of different γ -lactams¹⁷ depending on the photosensitizer employed (rose Bengal - RB, or methylene blue - MB).^{17e} Now, we questioned whether a pendent amine group on the 2-alkyl chain of the furan (furylalkylamine) might be encouraged to 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 afford hydroperoxide **A**, chemoselectively (Scheme 2). After reduction (Me₂S), 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**. In order 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 O₂ bubbling through the solution) followed by *in situ* reduction (Me₂S, Scheme 3). Crude ¹H NMR spectrum revealed the exclusive formation of the desired 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 minutes 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).

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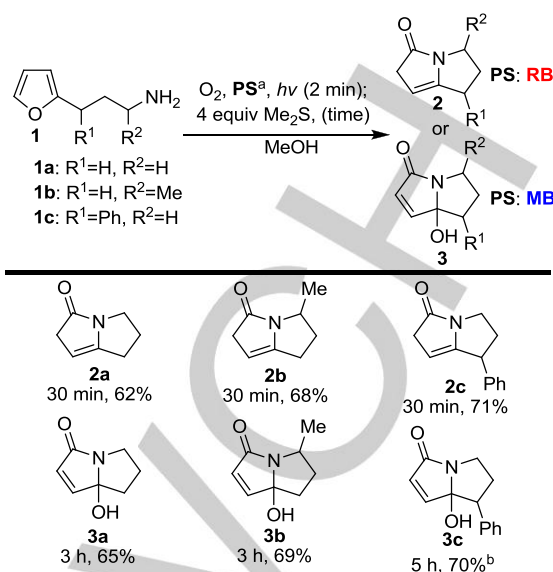
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Scheme 2. Proposed mechanistic scenario for the one pot transformation of furylalkylamines to pyrrolizidinones and indolizidinones of type **2** and **3**.

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 **2b** and **2c** 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 what had been achieved. In the case of substrate **1c**, catalytic triethylamine was added in order 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 big fragment of the antimetabolic agent UCS1025A⁸ (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 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 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%).



^aFor the synthesis of **2**, a 10⁻⁴ M solution of RB was used. For the synthesis of **3**, a catalytic amount of 3 mol% of MB was used.
^b0.3 equiv. of Et₃N was used as an additive.

Scheme 3. Results obtained from the photooxidation of furans **1a-1c**.

Entry	Solvent	Base (equiv.)	2d (%) ^a	4d (%) ^a	yield of 2d (%)
1	MeOH	-	62	38	31
2	CH ₂ Cl ₂	-	100	-	18
3	DMSO	-	100	-	22
4	CH ₃ CN	-	100	-	25
5	THF	-	100	-	24
6	Et ₂ O	-	100	-	24
7	MeOH	Et ₃ N (1 equiv.)	63	37	32
8	CH ₂ Cl ₂	Et ₃ N (1 equiv.)	100	-	39
9	MeOH	NH ₃ (1 equiv.)	84	16	50
10	CH ₂ Cl ₂	NH ₃ (1 equiv.)	100	-	41
11	Et ₂ O	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>i</i> PrOH	NH ₃ (1.2 equiv.)	100	-	54
15	MeOH/ <i>i</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

^aRelative ratios were determined by ¹H NMR of the crude mixtures.

^bThe corresponding ethoxy pyrrole was formed

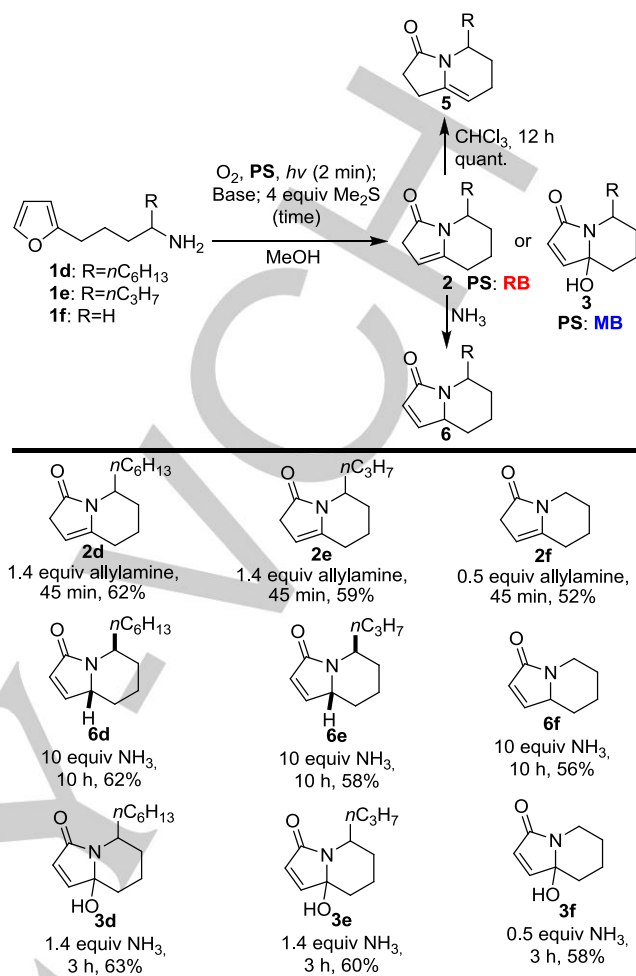
Scheme 4. Optimization of the reaction conditions.

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 Et₃N 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 to the amount of ammonia added in protic solvents led to an isomerization trend furnishing ever-greater quantities the corresponding α,β -unsaturated analogue of **2d**. This double bond shift was not observed with CHCl₃ as solvent even when the amount of ammonia was increased to 2 equivalents; here, 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 when green criteria are considered than CHCl₃. Thus, with substrate **1e** the reaction afforded the desired product **2e** (59% isolated yield, Scheme 5). In 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 the final products exhibited a tendency to isomerize quantitatively to the enamides of type **5** (Scheme 5) after stirring in the slightly acidic solvent CHCl₃ 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 indolizidines²³). Both **6d** and **6e** were formed as single diastereomers.

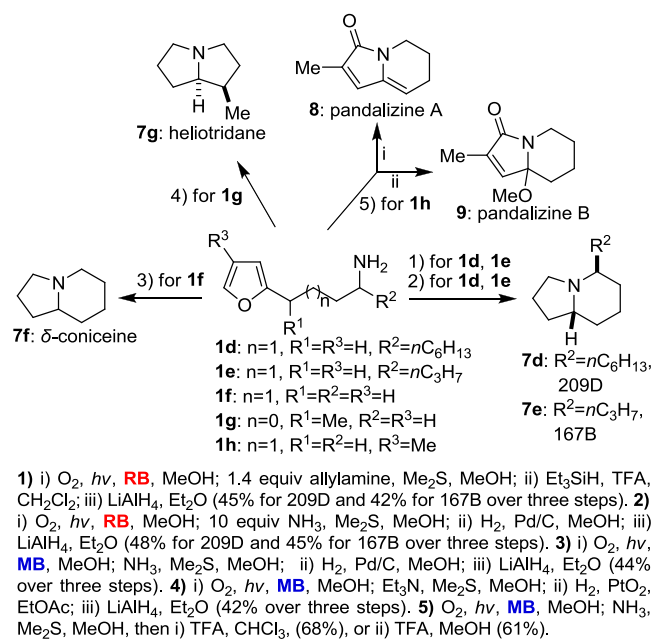
With replacement of the photosensitizer from RB to MB one-pot formation of the indolizidinone analogues of type **3** (**3d-f**, 58–63%, Scheme 5) was achieved. In this case, ammonia was used as an additive (0.5–1.4 equiv.) in order to avoid the formation of pyrrole of type **4** and to accelerate the methylene blue catalyzed oxidation.^{17e} It is notable that compound **3f** appears in its entirety in the natural product (–)-leuconolam¹⁰ (Scheme 1).

To further underscore the synthetic utility of the present methodology, the rapid and easy synthesis of indolizidine alkaloids⁵ 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 Et₃SiH and then LAH to afford the alkaloids 209D (**7d**) and 167B (**7e**) as single diastereomers (total yield



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

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 via 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-protocol 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 protocol was applied to furylalkylamine **1g** with Et₃N (0.3 equiv.) used to accelerate the oxidation step. The reaction gave the corresponding pyrrolizidine of type **3** (**3g**, not shown, 59% yield) that was sequentially reduced first by H₂ 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



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

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 pandalazines 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 pandalazine A and 61% for pandalazine 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 protocols employ green reagents and conditions (oxygen and visible spectrum light) and, despite the context wherein it is normal to use many non-constructive steps en-route 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.

Acknowledgements

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Keywords: pyrrolizidines • indolizidines • singlet oxygen • pandalazines • alkaloids

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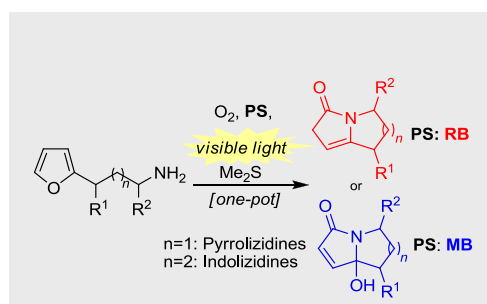
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Entry for the Table of Contents

Layout 1:

COMMUNICATION

Singlet oxygen is able to transform unprotected primary furylalkylamines into the important pyrrolizidine and indolizidine scaffolds. The outcome of the one-pot sequences can be readily tailored to need by varying the choice of sensitizer. The general synthetic utility of this novel methodology is underscored by its application to the rapid and easy synthesis of five natural products.



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