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# From simple furans to complex *N*-bearing aromatic polycycles via a flexible and general reaction sequence initiated by singlet oxygen

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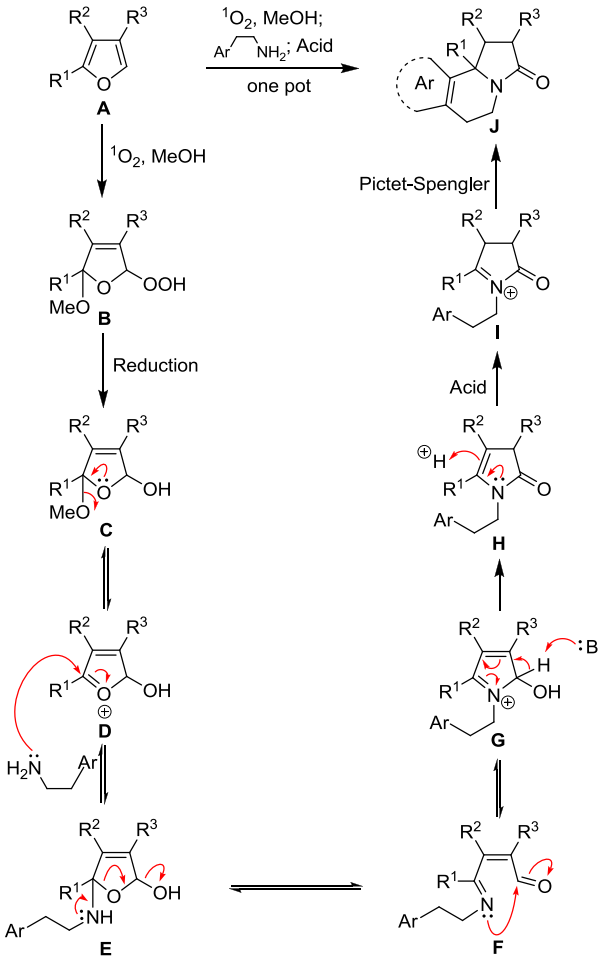
*Dedicated to Professor Michael Orfanopoulos on the occasion of his 65th birthday*

Employing one-pot reaction sequences in synthesis has proven to be a powerful way to improve efficiency and achieve rapid and impressive increases in molecular complexity.[1] Herein, we report a new and general reaction sequence initiated by singlet oxygen that transforms simple furan substrates into complex *N*-bearing aromatic polycycles having all the structural features of a number of important natural products (for example; the erythrina alkaloids,[2] Structure **J**, Scheme 1). The procedure itself uses mild conditions and has wide functional group tolerance.

At the heart of this new method is the generation of an *N*-acyliminium ion (NAI, see **I**, Scheme 1) in a novel way (**A** → **I**, Scheme 1), and, afterwards, in the same pot, its reaction with a pendent aromatic nucleus (**I** → **J**) introduced earlier in the reaction sequence. Investigating the diverse reactions of NAIs has long been an extremely productive field of research,[3] and, in particular their reaction with aromatic nucleophiles (a sub-group of reactions falling under the broader Pictet-Spengler[4] banner, **I** → **J**) has afforded a variety of new ways to access complex target skeletons. Many methods have been reported for the stepwise assembly of a NAI-precursor and its subsequent reactions with a pendant aromatic nucleus;[3] recent noteworthy examples employing a diverse range of strategies to accomplish this overall goal attest to the continuing attraction of the chemistry.[5-11]

Clearly, however, such an approach becomes all the more powerful when the whole process is included in a one-pot reaction sequence. This difficult-to-attain goal has only been achieved relatively rarely because it requires that the conditions for assembly of the NAI precursor must be the same as, or, at least,




Scheme 1. Summary of mechanistic rationale for proposed one-pot reaction sequence.

compatible with, those for NAI generation and its subsequent reaction. The most common approach successful in attaining an "all-in-one" reaction sequence is inspired by the pioneering work of Meyers,[12] wherein the acid catalysed condensation of a 4-keto-

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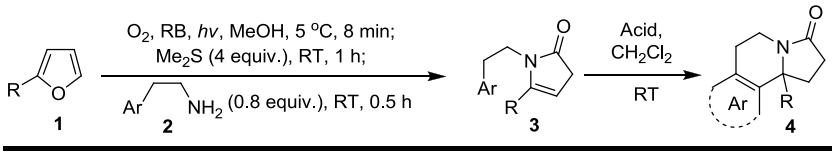
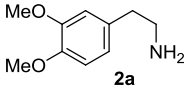
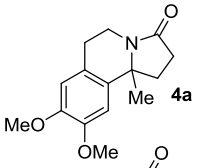
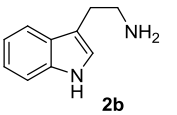
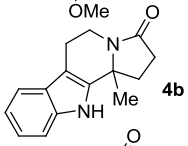
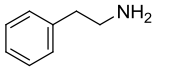
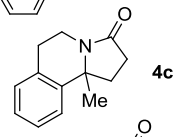
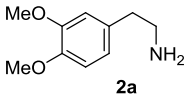
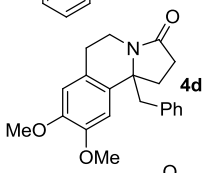
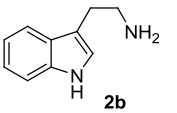
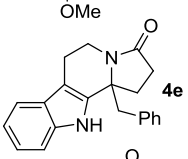
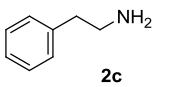
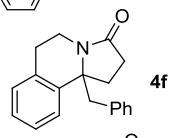
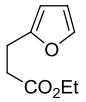
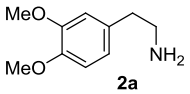
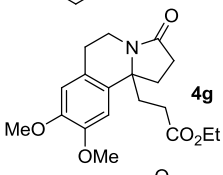
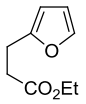
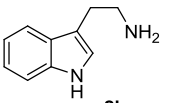
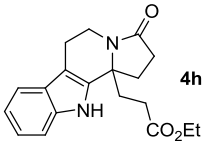
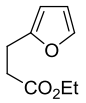
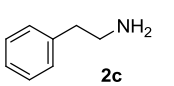
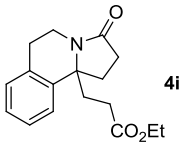
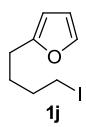
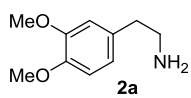
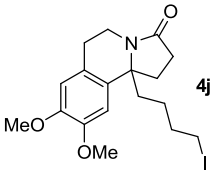
Table 1. One-pot reaction sequence results for monosubstituted furans.




| Entry | Furan **1** | Amine **2** | Acid (equiv., time) | Product **4** | Isolated Yield (%) |
|---|---|---|---|---|---|
| a |  **1a** |  **2a** | TFA (0.8 equiv., 6 h) |  **4a** | 60 |
| b |  **1a** |  **2b** | TFA (0.4 equiv., 3 h) |  **4b** | 62 |
| c |  **1a** |  **2c** | $AlCl_3$ (2.4 equiv., 12 h) |  **4c** | 65 |
| d |  **1d** |  **2a** | HCOOH (as solv., 4 h) |  **4d** | 58 |
| e |  **1d** |  **2b** | TFA (0.8 equiv., 2 h) |  **4e** | 63 |
| f |  **1d** |  **2c** | $AlCl_3$ (2.4 equiv., 12 h) |  **4f** | 60 |
| g |  **1g** |  **2a** | HCOOH (as solv., 2 h) |  **4g** | 67 |
| h |  **1g** |  **2b** | TFA (0.8 equiv., 3 h) |  **4h** | 67 |
| i |  **1g** |  **2c** | $AlCl_3$ (3 equiv., 12 h) |  **4i** | 63 |
| j |  **1j** |  **2a** | HCOOH (as solv., 2 h) |  **4j** | 70 |

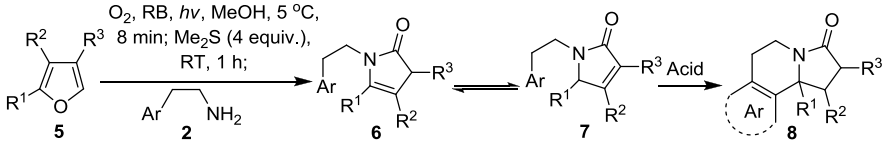
acid (or 4-keto-ester) with an appropriately substituted amine forms, and, then reacts, an NAI *in situ*; recent examples have originated from the laboratories of Dixon (using chiral polyphosphoric acids),[13] Dominguez,[14] Fokas,[15] Jida (using microwave assistance),[16] Padwa[17] and Tietze.[18] Modifications to the dielectrophile substrate (the keto-acid) such as its replacement with a δ-chloro-α,β-diketoester,[19] or a 2,3-dioxopent-4-enoate,[20] have also yielded some nice sequences. In a contrasting approach, transition metal catalysis has also been successfully employed; for example, Liu's gold catalysed indole annulation,[21] or the impressive rhodium catalysed hydrofomylation sequences used by Mann[22] and Chiou.[23]

We begun our own investigation from the premise that the 4-keto-acid component used might be replaced by an alternative 1,4-dielectrophile (**C**,[24] Scheme 1) arising readily from the photooxygenation in methanol of a simple and readily accessible furan using singlet oxygen[25] (Scheme 1). Intermediate **C** might be intercepted by an amine bearing a pendant aromatic nucleus (**C** → **H**).[26] It is important to note that the nature and reactivity of the dielectrophile **C** may allow us to conduct this condensation to pyrrolidinone **H** under mild reaction conditions. Following addition of an appropriate acid (Brønsted, or Lewis), the *N*-acyliminium ion **I** might be formed and encouraged to react with the proximal aromatic nucleus (6-*endo* cyclisation) to yield the final desired aromatic *N*-bearing polycycle (**H** → **J**). At this stage, it is important to note that the entire process described in this scheme was envisaged as a one-pot cascade reaction sequence to be achieved by the serial addition of the desired reagents as required when indicated by tlc analysis of the reaction mixture.

After validation of the general idea, our initial foray would focus on deconvoluting optimal conditions for the reaction of monosubstituted furan substrates (**1a**, **1d**, **1g** and **1j**, Table 1) in combination with one of three commercially available amines $ArCH_2CH_2NH_2$ bearing aromatic units of differential nucleophilicity (a simple phenyl ring in **2c**, a phenyl ring activated by two methoxy substituents in **2a** and an indole in**2b**). Gratifyingly, the cascade reaction sequence proceeded as envisaged, and, despite the formation of a tertiary carbon centre in the final step, the desired products were obtained, in each of the three series, in remarkably good yields especially when considering the degree by which molecular complexity had been increased (58 – 70%, Table 1). An indicator that the proposed mechanistic sequence was indeed in play came from the isolation of several intermediates of type **3** (Table 1).[27]

While the method by which the NAI precursor had been obtained (**1** → **3**, Table 1) was new and exceptionally mild, there

Table 2. One-pot reaction sequence results for di- and trisubstituted furans.

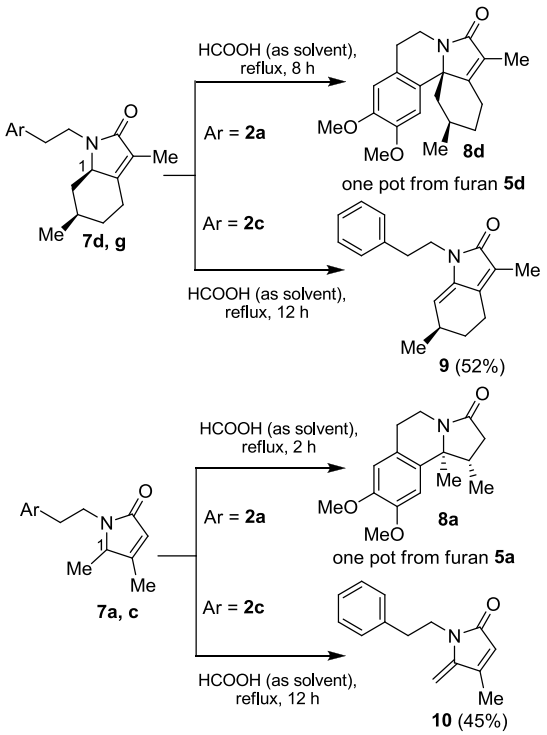



| Entry | Furan **5** | Amine **2** equiv., solv., temp., time | Acid (equiv.) solv., temp., time | Product (**7** or **8**) | Isolated Yield (%) |
|---|---|---|---|---|---|
| a | **5a** | **2a** 0.8 equiv., MeOH, RT, 1 h | HCOOH (as solv.), reflux, 2 h | **8a** | 65 |
| b | **5a** | **2b** 0.8 equiv., MeOH, RT, 1 h | TFA (0.8 equiv.), $CH_2Cl_2$, RT, 6 h | **8b** | 67 |
| c | **5a** | **2c** 0.8 equiv., $CH_2Cl_2$, RT, 1 h | $AlCl_3$ (2.4 equiv.), $CH_2Cl_2$, RT, 2 h | **7c** | 58 |
| d | **5d** | **2a** 1.2 equiv., MeOH, reflux, 4 h | HCOOH (as solv.), reflux, 8 h | **8d** | 70 |
| e | **5d** | **2a** 1.2 equiv., $CHCl_3$, reflux, 4 h | HCOOH (as solv.), RT, 2 h | **8e** | 78 |
| f | **5d** | **2b** 1.2 equiv., $CHCl_3$, reflux, 4 h | TFA (1 equiv.), $CHCl_3$, RT, 8 h | **8f** | 75 |
| g | **5d** | **2c** 1.2 equiv., $CHCl_3$, reflux, 4 h | $AlCl_3$ (2.4 equiv.), $CHCl_3$, RT, 12 h | **7g** | 65 |

exists substantial precedent for the last acid catalysed Pictet-Spengler-type cyclisation step of the one-pot reaction sequence in which a diverse array of different acid catalysts and conditions have been described, some of which are considerably milder than others (*vide supra*). After surveying a number of Brønsted and Lewis acids, we were satisfied that TFA (in $CH_2Cl_2$ at RT) or formic acid (as solvent, at RT) were the mildest and most effective conditions for the 6-*endo* cyclisation step that terminates the sequence, at least, when the aromatic nucleus was activated (i.e. in the dimethoxyphenyl, or indole series; entries a, b, d, e, g, h and j - Table 1). Entry j, wherein the starting furan substrate **1j** has an alkyl iodide side chain appended to it, serves to show just how mild and tolerant this one-pot reaction sequence is, as this delicate functionality remains untouched throughout the complex reaction sequence.

Achieving this type of cyclisation when the aromatic nucleus is not activated (i.e. Ar = phenyl) is more difficult, requires harsher conditions and has been reported much more rarely.[5, 28] Furthermore, within this relatively sparse precedent there is little agreement on conditions that might be applied generally. For example some substrates react smoothly with $BF_3.OEt_2$[28a] whilst others show poor,[28b] or no reaction,[5c] under the same conditions. We found that $AlCl_3$[28c] was the reagent of choice (in $CH_2Cl_2$ at 0 ºC → RT) for all the substrates that we tested, furnishing the desired products in highly respectable yield (60-65%, entries c, f and i – Table 1). Interestingly, for entry i, if the number equivalents of $AlCl_3$ used was reduced slightly from 3.0 to 2.4, the product **4i** was found to be contaminated with significant amounts of the uncyclised regiosomer of **3i** (not shown) wherein the double bond is exocyclic, not endocyclic. This result mirrors the one seen in entry g wherein use of TFA (0.8 equiv.) instead of HCOOH led to the rapid formation of the uncyclised intermediate with an exocyclic double bond (the regiosomer to **3g**, see Supporting Information) and that for entry j where similar observations were also made.

To expand the scope of this productive sequence, we next sought to explore the reactions of more highly substituted furans; the results of this survey are shown in Table 2. For both 2,3-dimethylfuran (**5a**) and menthofuran (**5d**) it was once again possible, when the conditions were appropriately tailored, to achieve the proposed complex one-pot reaction sequence for the two aromatic partners (the dimethoxyphenyl **2a** and indole nucleophiles **2b**, entries a, b, e and f, yields 65-78%). In contrast, however, the now greater degree of substitution in the starting furan substrates did preclude the cyclisation in the case of the unactivated exemplars (where Ar = a simple phenyl ring); the intermediates could not be coaxed into reacting even using the stronger conditions ($AlCl_3$, entries c and g) that had worked for the earlier examples. We believe that this is due to the rapid isomerisation of the initially formed 2-pyrrolidinone **6** to product **7** which now affords a slightly more stable (compared to Table 1 substrates) tri/tetrasubstituted and conjugated double bond; indeed it was compounds of type **7** that were isolated in both cases (entries c and g). For cyclisation, the 2-pyrrolidinone **6** is required (not isomer **7**), and, here the added stability of isomer 7 shuts down the cyclisation pathway in the case where the aromatic partner is reluctant also. As an aside, it is worthy of note that products **8d** and **8e** contain the entire intact




Scheme 2. Observed further oxidations under controlled conditions.

skeleton of the erythrina alkaloids[2] synthesised in one single step; albeit, not yet correctly substituted for completion of a synthesis.

From a stereochemical perspective some very interesting results were obtained in this second series of examples (Table 2). Starting with 2,3-dimethylfuran; the NAI cyclisation reaction with the dimethoxyphenyl residue was highly selective and the formation of only one diastereoisomer **8a** was observed; the one in which the aromatic nucleophile has approached the face of the NAI that is opposite to the methyl group appended to the adjacent carbon (Table 2, entry a). In contrast, with the more facile indole-NAI reaction, which presumably has an earlier transition state less influenced by the substitution adjacent to the NAI, no such selectivity was observed (diastereomeric ratio = 60:40, entry b). Likewise with menthofuran, the slower NAI cyclisation is more selective yielding just two seperable diastereoisomers in a ratio of 7:3 (entry e); while the faster NAI-indole cyclisation yields four diastereoisomers (entry f).[27]

With this second series of examples, we began to see another set of synthetically useful and highly tuneable observations. In the case of menthofuran with the dimethoxyphenyl aromatic partner, when the process was carried out according to the developed protocol (without purification of intermediates), and, when given a slightly longer reaction time with HCOOH, another oxidation was seen to take place giving the unsaturated product **8d** (as a single isomer, Table 2, entry d). Presumably, this occurs via hydrogen abstraction from intermediate **7d** (and likewise **7c** and **7g)** to afford the highly stabilised tertiary radical (at C1, Scheme 2) which is subsequently oxidised to the corresponding cation[29] from which the double bond is generated following elimination of a proton. Support for this scenario comes in the form of diene **9** isolated as the only product of the one-pot reaction sequence involving menthofuran and a simple unactivated aromatic partner (**5d** → **9**, Scheme 2). In a similar manner, diene **10** was isolated from the reaction of 2,3-dimethylfuran with phenylethylamine **2c**. However, in contrast to the menthofuran results, when 2,3-dimethylfuran was reacted with the dimethoxyphenyl aromatic partner the cyclised product formed (**8a**) without the extra double bond. We believe that this is due to the rapid interconversion between **6a** and **7a** which promotes cyclisation and prevents **7a** having the lifetime required to undergo the oxidation sequence (unlike **7d**, which is stabilised by the additional double bond substitution and may undergo oxidation followed by cyclisation). It is very important that these pathways do not lead to mixtures and that the outcome is completely controllable through alterations to the reaction conditions, especially since introduction of the second bond in **8d** affords a handle from which further synthetically useful manipulations could be accomplished.

In summary, we have introduced a remarkably mild and highly controllable one-pot reaction sequence, beginning from extremely simple furan substrates, which can be applied generally and successfully to the construction of advanced *N*-bearing polycycles. The one-pot reaction sequence is initiated by the highly selective and green oxidant, singlet oxygen. Given the number of transformations included in this reaction sequence and the impressive increases in molecular complexity achieved, the yields attained are high and should make this method a genuinely useful synthetic strategy.

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**Keywords:** singlet oxygen • *N*-acyliminium • Pictet-Spengler • one-pot reaction sequence • erythrina alkaloids

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**Furans Transformed**

*Dimitris Kalaitzakis, Tamsyn Montagnon, Eirini Antonatou, Nuria Bardají and Georgios Vassilikogiannakis** ……..…

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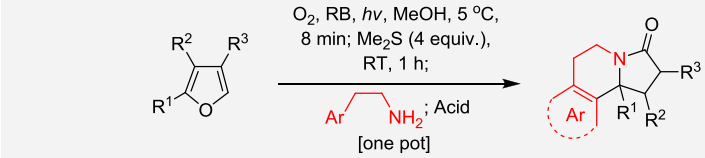
**From simple furans to complex *N*-bearing aromatic polycycles via a flexible and general reaction sequence initiated by singlet oxygen**




A new and general cascade reaction sequence initiated by singlet oxygen that transforms simple furan substrates into complex *N*-bearing aromatic polycycles having all the structural features of a number of important natural products (for example; the erythrina alkaloids) is reported. The cascade itself uses mild conditions and has wide functional group tolerance.