A New Method for the Formation of Octahydroindole Alkaloids via the Intramolecular Diels−Alder Reaction of 2-Amidofurans

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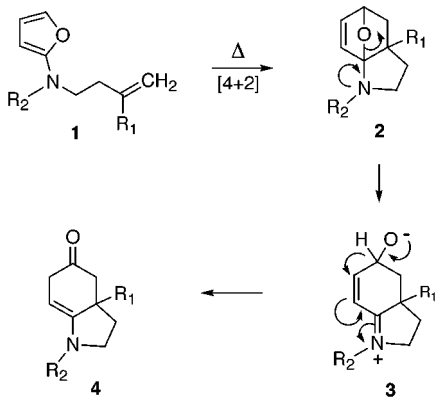
Octahydroindole-based alkaloids possess diverse physiological properties, as well as structural complexity, and have attracted the interest of synthetic chemists.[1] A plethora of strategies based on both convergent and divergent methods have been developed for the synthesis of these azabicyclic compounds.[2] Despite the availability of many synthetic methods, there still exists a need to develop more efficient procedures than those currently in existence. Herein, we report our preliminary results regarding the intramolecular [4 + 2] cycloaddition of 2-amidofurans, which represents a new and general method for the synthesis of the hexahydroindolinone ring system.

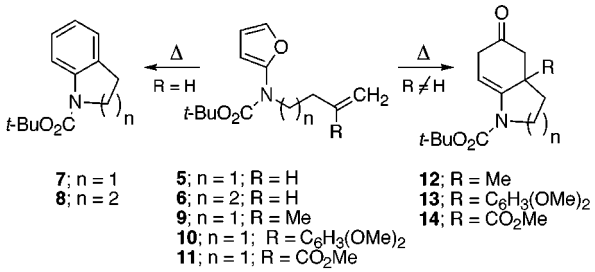
Our initial interest in this area was stimulated by the prospect of designing a stereoselective entry to a variety of Amaryllidaceae alkaloids according to the strategy outlined in Scheme 1. The key feature of our approach is based upon an intramolecular Diels−Alder reaction[3] (IMDAF) of 2-aminofurans such as **1**. The initially formed cycloadduct **2** was expected to undergo ready ring opening to be followed by a subsequent hydrogen shift of the resulting zwitterion **3**. In this paper, we report the first examples of this protocol and provide applications of the method toward the core skeleton of the dendrobium,[4] lycorane,[5] and strychnos[6] alkaloid ring systems.

In previous work, we demonstrated that 2-aminofurans react with various dienophiles in an intermolecular fashion with high regioselectivity.[7] The resultant ring-opened cycloadducts were readily dehydrated to give polysubstituted anilines. To establish the viability of the IMDAF sequence outlined in Scheme 1, several 2-amidofurans containing olefinic tethers were prepared from the reaction of *N-tert*-butylfuranyl carbamate with various alkenyl halides in the presence of base. We first examined the Diels−Alder cycloaddition (165 °C) of the acyclic monosubstituted alkenyl furans **5** and **6** (R = H), which furnished the cyclized aromatic carbamates **7** and **8** as the only isolable products (Scheme 2). In both cases, the initial oxa-bridged cycloadducts were not isolated, as they readily underwent ring opening followed by subsequent dehydration.[8]

Scheme 1



Scheme 2



7; n = 1
8; n = 2

5; n = 1; R = H
6; n = 2; R = H
9; n = 1; R = Me
10; n = 1; R = $C_6H_3(OMe)_2$
11; n = 1; R = CO_2Me

12; R = Me
13; R = $C_6H_3(OMe)_2$
14; R = CO_2Me

To avoid the dehydration step, we prepared the disubstituted olefinic amidofurans **9**−**11** (R ≠ H). In these cases, subjection of all three furans to the thermal conditions (165 °C) afforded the rearranged ketones **12**−**14** in 71%, 77%, and 87% yield, respectively. The isolation of these hexahydroindolinones is in full agreement with the proposed *cycloaddition/ring opening/rearrangement* sequence outlined in Scheme 1.

It was envisioned that the enamide functionality present in the rearranged keto system could be used to facilitate bond construction at several locations in the molecule. Access to the lycorane ring skeleton was achieved by utilization of ketone **12**, as shown in Scheme 3. Acid hydrolysis of **12** gave imine **15** as a labile oil that was immediately converted to enamide **16** in 72% overall yield. Intramolecular Heck cyclizations generally show a preference for the exo mode of cyclization.[9] By following a protocol reported by the Rigby group,[10] we found that treatment of **16** using the Jeffrey palladium catalyst system[11] ($Pd(OAc)_2$ (10 mol %), *n*-Bu_4NCl (2 equiv), KOAc (5 equiv), DMF (0.2 M, 100 °C)) provided only pentacycle **17** derived from the endo cyclization pathway in 50% unoptimized yield.[12]

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(8) For an earlier example of an IMDAF reaction of a nitrogen-substituted furan, see: Himbert, G.; Schlindwein, H. J. *Liebigs Ann. Recl.* **1997**, 435.

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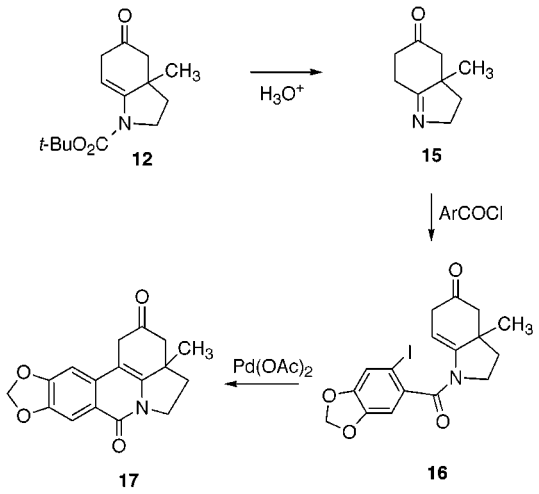
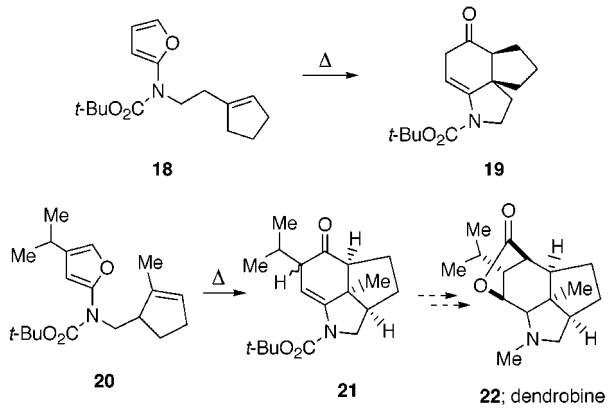
Scheme 3



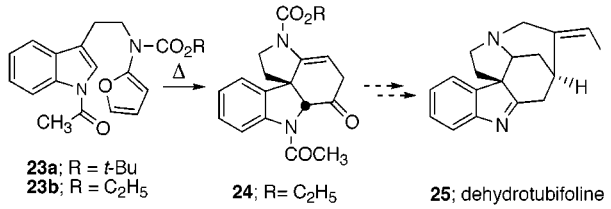
So that a cross section of additional information could be obtained with regard to the scope and generality of the sequence outlined in Scheme 1, it was necessary to evaluate a series of 2-amidofurans containing a variety of π-bonds. In this regard, we first investigated the IMDAF chemistry of **18**, which possesses a tethered cyclopentenyl group. Heating a sample of furan **18** afforded azapolycycle **19** as a single diastereomer in 78% yield (Scheme 4). To further illustrate the viability of this sequence as a practical strategy for the synthesis of complex alkaloids, we have explored the utility of this reaction in the context of a total synthesis of (±)-dendrobine (**22**).[13] This alkaloid is the principle component of the Chinese Folk medicine "Chin-Shih-Hu" and has been shown to exhibit antipyretic and hypotensive activity.[14] The key step in our plan for the synthesis of (±)-dendrobine involves the intramolecular Diels−Alder reaction of 2-amidofuran **20** to give hexahydroindolinone **21** with three of the asymmetric centers established. We were gratified to find that the thermolysis of **20** proceeded in 74% yield to produce **21** as a 2:1 mixture of diastereomers. Further transformations of **21** to **22** using the existing functional groups to establish the remaining asymmetric centers are currently underway.

Given the success in forming the azatricyclic ring system from the IMDAF reaction of 2-amidofurans **18** and **20**, it seemed to us that a related process could be used to synthesize the strychnos or aspidosperma alkaloid skeletons.

Scheme 4



Scheme 5



To test this proposition, the thermal behavior of indolyl-substituted 2-amidofuran **23** was investigated. It was found, however, that thermolysis of the *tert*-butyl carbamate **23a** did not lead to the desired cycloaddition but instead gave products derived from loss of the thermally labile *t*-Boc group. Heating a sample of the corresponding *N*-ethylcarbamate **23b**, on the other hand, resulted in the formation of **24** in 62% yield (Scheme 5). This is presumably a reflection of the greater thermal stability of the *N*-ethylcarbamate, which allows the intramolecular [4 + 2] cycloaddition reaction to take place across the indole π-bond at 240 °C. Further efforts to streamline this protocol and to utilize it to complete total syntheses of the strychnos alkaloids are in progress and will be reported in due course.

In summary, a highly convergent synthesis of octahydroindole derivatives has been devised. Application of this methodology toward the construction of more complex alkaloids containing the octahydroindole skeleton is currently in progress in our laboratory and will be reported at a later date.

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Supporting Information Available: Experimental procedures, compound characterization data and copies of spectra (20 pages).

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(12) We wish to thank Professor Jim Rigby for providing experimental conditions for the endo cyclization of enamide **16**.

(13) For several pertinent references dealing with some successful total and formal syntheses of (±)-dendrobine, see: Sha, C. K.; Chiu, R. T.; Yang, C. F.; Yao, N. T.; Tseng, W. H.; Liao, F. L.; Wang, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4130.

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