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A New and Convenient Synthesis of 2-Amidofurans Using the Jacobi *Bis*-Heteroannulation Method

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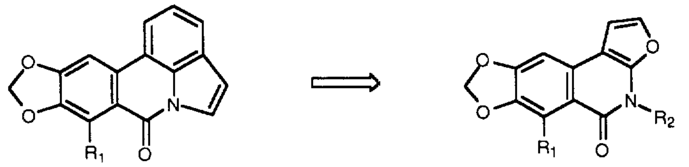
Abstract: Cyclic 2-amidofurans were obtained using an intramolecular Diels-Alder reaction of 2-amido substituted oxazoles containing a tethered alkyne. This transformation represents a new route to this rare heterocyclic ring system.

The pyrrolophenanthridone alkaloids[1] are a group of compounds isolated from Amaryllidaceae plants.[2] These alkaloids have attracted the attention of chemists and pharmacologists due to the interesting properties of some of its members.[3] One of the more prevalent members of this family is hippadine (**1**), which is known to inhibit fertility in male rats.[4] While several procedures for the synthesis of individual pyrrolophenanthridones have been developed,[5-7] a short and efficient general method is not yet available. In connection with our work on the Diels-Alder reaction of furans,[8] we became interested in the intramolecular [4+2]-cycloaddition reactions of a number of cyclic 2-amidofurans such as **2** as an approach toward hippadine and related structures. In this communication, we address the issue of preparing the novel molecular framework represented by the fused amidofuran system. Details concerning the cycloaddition chemistry of these compounds will be described in a forthcoming publication.



1; R_1 = H (Hippadine) **2**; R_1 = H; R_2 = $CH_2CH_2CH{=}CH$

An obvious approach toward the synthesis of amidofuran **2** involves the formation of a C-C bond between the aryl and furanyl rings by a Heck reaction.[9] It is well known that the palladium catalyzed coupling of an aryl halide with an olefin is an excellent way to form a five, six or seven-membered ring fused to an aromatic ring.[10] The intramolecular Heck reaction has been utilized by many workers to form complex heterocyclic ring systems.[11] The requisite aryl iodide **5** was synthesized in high yield by treating carbamate **3** with the iodo substituted benzyl bromide **4** in the presence of base. Unfortunately, under a wide variety of traditional Heck conditions, only a low yield (<15%) of the desired aminofuran **6** could be isolated. Exposure of the carbamate to the Jeffrey palladium catalyst system[12] provided **6**, but only in 38% yield.[13]

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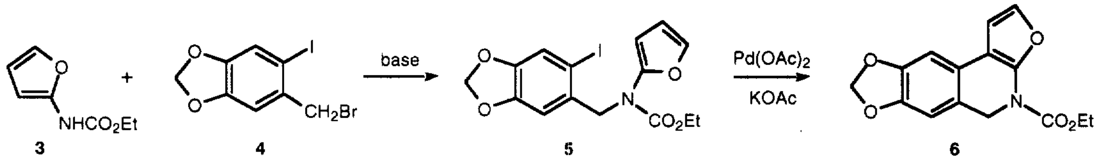
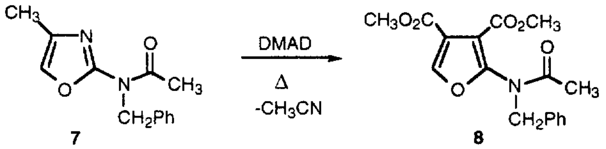
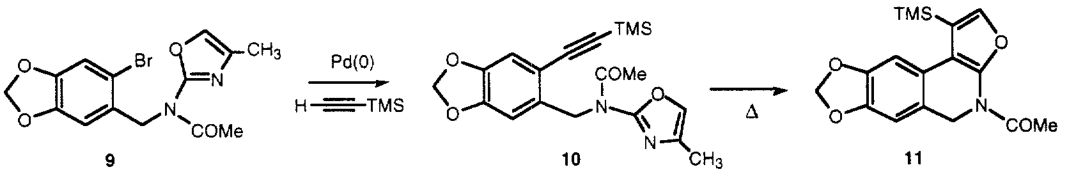


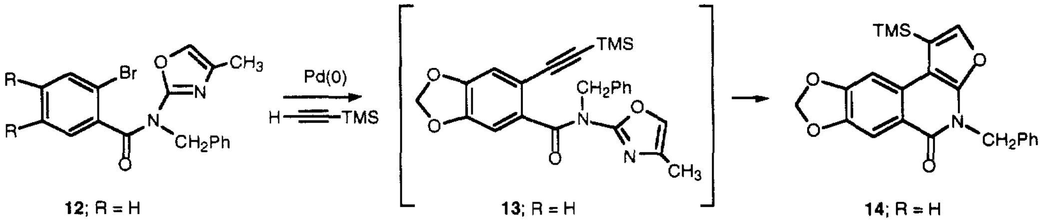
Our failure to efficiently effect the intramolecular Heck reaction of amide **5** forced reconsideration of our strategy based on this coupling approach. An alternative sequence in which the amidofuran would be elaborated from a 2-amido substituted oxazole seemed attractive. Oxazoles have been extensively used as azadienes in cycloadditions,[14] particularly for the synthesis of furans by the *Jacobi bis-heteroannulation* procedure.[15] The feasibility of this approach clearly hinged upon 2-amidooxazoles[16] undergoing [4+2]-cycloaddition chemistry with acetylenic dipolarophiles. Since this tactic was the focal point of our plan, we opted to first verify the viability of this reaction. We were gratified to find that the reaction of 2-acetamidooxazole **7** with dimethyl acetylenedicarboxylate proceeded smoothly to give 2-acetamidofuran **8** in 92% yield. The conversion of **7** into **8** represents a rare example of the Jacobi annulation applied to the synthesis of 2-amidofurans.[17]



We next focused our attention on the structurally related acetylenic 2-amidooxazole **10** which presented the opportunity to test the intramolecular *cycloaddition/cycloreversion bis-heteroannulation* approach. Preparation of this compound involved a palladium catalyzed cross coupling reaction of acetamidooxazole **9** with trimethylsilylacetylene using the Sonogashira catalyst system[18] which furnished **10** in 60% yield. Thermolysis of **10** proceeded smoothly at 200 °C to give the desired amidofuran **11** in 93% yield.



For comparison purposes, we also investigated the chemistry of the related 2-amidooxazole **13** where the carbonyl group of the amide has been switched from *"outside"* the tether to the *"inside"* position. When the precursor bromoaryl amide **12** was cross-coupled with TMS-acetylene, the initially formed alkyne **13** underwent ready intramolecular cycloaddition under the reaction conditions used (80 °C) to form the cyclic amidofuran **14**. Similar results were obtained with the corresponding methylenedioxy-substituted aromatic amide (*i.e.*, **15** →**16** →**17**). The accelerating effect encountered by having the carbonyl group *internal* to the tether is probably related to a shortening of the path between the ground state and the corresponding transition state thereby reducing the activation barrier. This rate enhancement is clearly of synthetic advantage as it offers the opportunity to facilitate the intramolecular [4+2]-cycloaddition reaction of these systems.

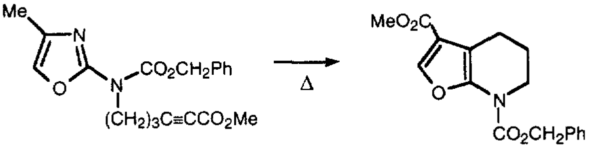


12; R = H
15; R = -OCH$_2$O-

13; R = H
16; R = -OCH$_2$O-

14; R = H
17; R = -OCH$_2$O-

To further illustrate the scope and utility of the amidooxazole cycloaddition sequence, we examined the thermal chemistry of oxazole **18** where the acetylenic π-bond has been tethered to the amido nitrogen atom. We were pleased to find that heating a sample of **18** at 160 °C provided the expected amidofuran **19** in 85% yield.[19]



18 **19**

In conclusion, this study has demonstrated that the intramolecular Diels-Alder cycloaddition reaction of 2-amidooxazoles represents a highly efficient method for the synthesis of a variety of 2-amido substituted furans. As a consequence of its practical simplicity and high efficiency, this method is expected to have wide synthetic utility for heterocyclic synthesis. Further efforts to streamline this protocol and to utilize these furans for the synthesis of several pyrrolophenanthridone alkaloids are in progress and will be reported in due course.

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