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Intramolecular [4+2]-cycloaddition reactions of cyclic 2-thiomethyl-5-amidofurans†

John D. Ginn, Stephen M. Lynch and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, GA 30322, USA

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Abstract

Cyclic 2-thiomethyl-5-amidofurans possessing tethered π-bonds were prepared by a dimethyl(methylthio) sulfonium tetrafluoroborate (DMTSF) induced cyclization of various amido dithioacetals. Upon heating, these systems undergo an intramolecular 4+2-cycloaddition reaction. The initially formed Diels–Alder cycloadduct further rearranges by ring opening of the oxygen bridge followed by a subsequent 1,2-thiomethyl shift.

Keywords: amidofuran; Diels–Alder; intramolecular; DMTSF; Pummerer; cyclization.

The intramolecular Diels–Alder cycloaddition of 2-amido substituted furans[1] represents a versatile tool for the synthesis of fused, nitrogen-containing heterocycles.[2] As part of a program designed to explore this reaction for alkaloid synthesis, we have employed the *IMDAF* cycloaddition for the construction of a variety of hexahydroindolinone ring systems.[3] As detailed in an earlier account,[2] the tethered indolyl substituted 2-amidofuran **1** was used to set the ABCE cyclic core of the aspidosperma alkaloid skeleton (i.e. **1**→**2**).[4] Further exploitation of the above strategy toward aspidospermidine **5**, while appealing, appeared difficult due to the necessity of introducing the final D-ring from the initially formed cycloadduct **2**. We therefore decided to explore an alternate tactic, which involves using a cyclic amidofuran such as **3**. In this case, the furan and piperidine rings are already annealed and thus, the expected cycloadduct **4** would possess the complete [6.5.6.6.5] ABCDE skeleton of the aspidosperma family.[4] Before attempting the more challenging [4+2]-cycloaddition across the indolyl π-bond,[5] we first opted to investigate the scope of the reaction using cyclic amidofurans, which contain a more reactive set of tethered dienophiles. In this letter we describe a highly efficient synthesis of these furans using a thionium ion induced cyclization reaction and their subsequent cycloaddition behavior.

* Corresponding author. Fax: 360-838-9418; e-mail: chemap@emory.edu

† Dedicated to Harry H. Wasserman on the occasion of his 80th birthday and for his many important contributions to the field of organic chemistry.

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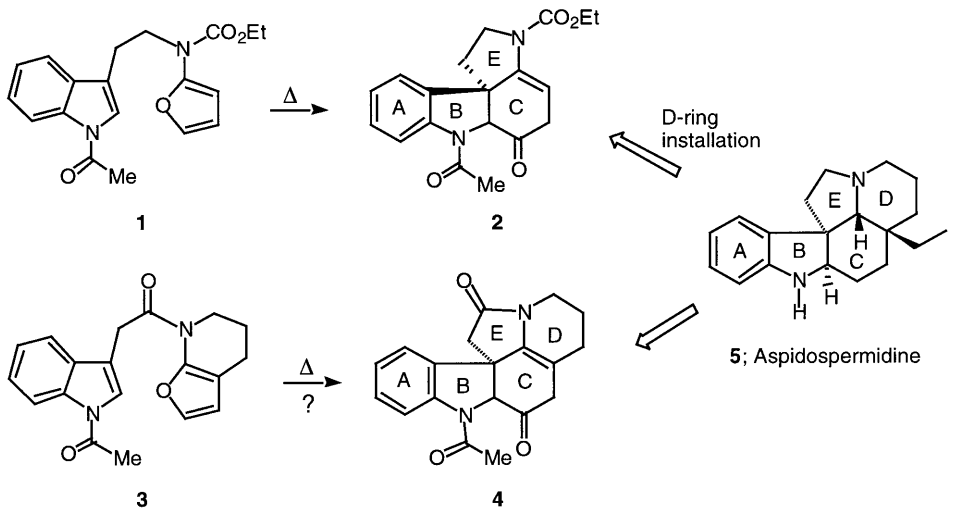
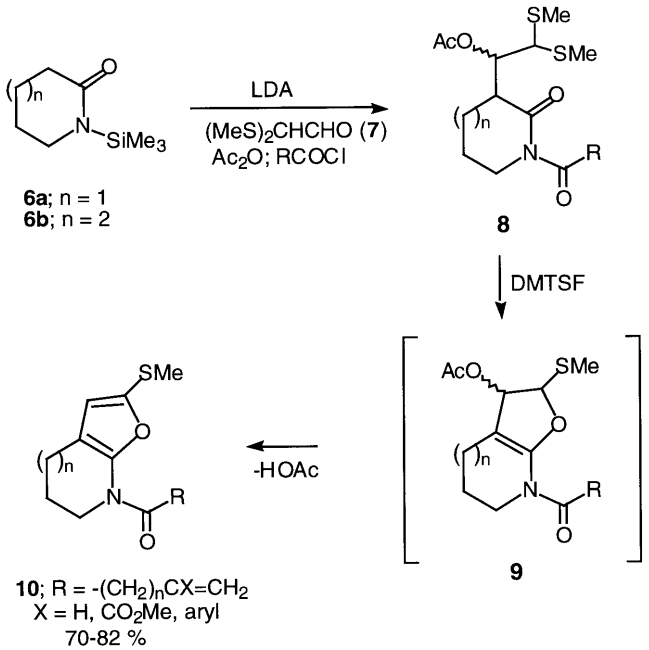


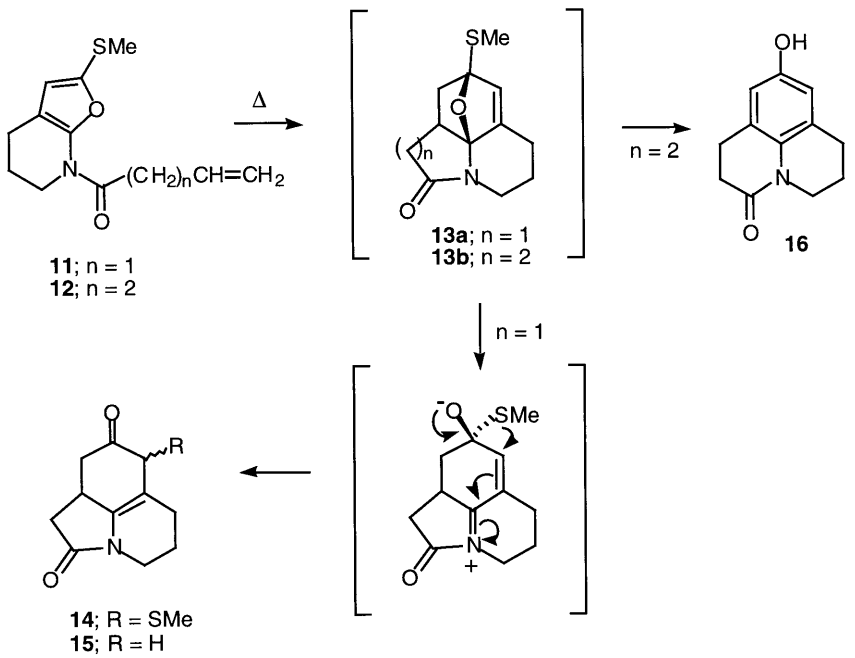
We first sought to develop a general method for preparing cyclic 2-amidofurans since properly functionalized intermediates of this sort would allow for the ready access of a variety of novel azapolycyclic ring systems. In our earlier studies, several cyclic amidofurans were prepared using the Jacobi bis-heteroannulation method.[6,7] In the current investigation, we found that this procedure was not always reliable and that a more effective way to synthesize these amidofurans involved a Pummerer induced cyclization of imido dithioacetals of type **8**.[8] The starting substrates were prepared by the mixed aldol reaction of the *N*-trimethylsilyl protected δ-valerolactam **6a** (or ε-caprolactam **6b**) with bis-(methylsulfanyl)acetaldehyde **7**. Quenching the reaction with acetic anhydride followed by aqueous workup provided the expected aldol product in high yield as a 4:1-mixture of diastereomers. The cyclic lactams were acylated with various acid chlorides using powdered 4 Å molecular sieves as a neutral acid scavenger[9] to provide the corresponding imides **8** in 60–98% yield. It was known from earlier work in the literature that treatment of thioketals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) causes the carbon–sulfur bond

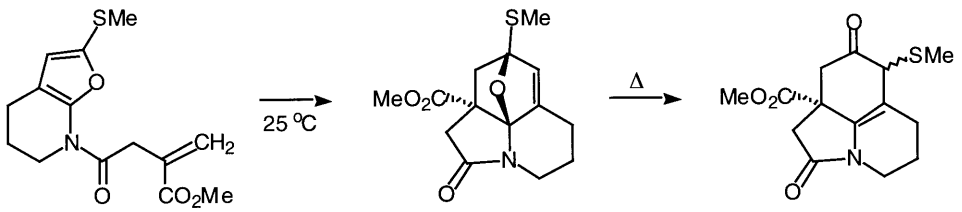


to become labile upon methylthiolation.[10] The initially formed alkylthiosulfonium ion easily dissociates to produce a thionium ion and methyl sulfide.[11] Cyclization of the Pummerer intermediate onto the amide carbonyl group first affords dihydrofuran **9** which undergoes a subsequent elimination of acetic acid to give the cyclic 2-thio-amidofuran system **10** in a high overall yield.

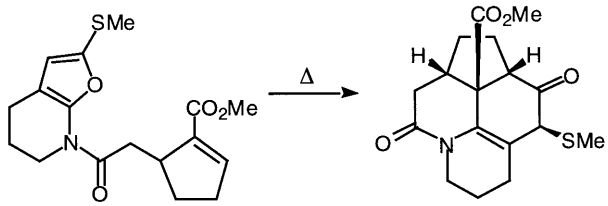
With a satisfactory method for the synthesis of the cycloaddition precursors in place, we began our cycloaddition investigations by first examining the Diels–Alder reaction of the *N*-yl-but-3-en-1-one substituted amidofuran **11** ($n=1$). Thermolysis of **11** at 110°C furnished the rearranged hexahydro-pyrroloquinolin-2-one **14** as the only isolable product in 92% yield as a 3:2 mixture of diastereomers after silica gel chromatography.[12] Dethiomethylation occurred smoothly when a sample of **14** was subjected to Raney-nickel reduction in 95% ethanol, producing **15** in 85% yield. In contrast to the above result, thermolysis of the homologous *N*-yl-pent-4-en-1-one amidofuran **12** gave phenol **16** in 82% yield. In both cases, the initially formed oxo-bridged cycloadducts (i.e. **13**) could not be isolated, as they readily underwent ring opening to produce the observed products. Furan **12**, with the longer five-carbon tether, required more forcing conditions (200°C) for the Diels–Alder cycloaddition and this resulted in the formation of phenol **16**. Presumably, the initially formed cycloadduct **13b** underwent ring opening/thiomethyl migration, but this was followed by elimination of methanethiol at the higher temperatures employed.

Because electron-withdrawing substituents on the π-bond exhibit a powerful influence on the rate of HOMO-dienyl [4+2]-cycloadditions,[13] a study of the thermal behavior of the 2-carbomethoxy substituted alkenyl amidofuran **17** appeared to us to be a worthwhile goal. Indeed, incorporation of this activating substituent on the alkenyl π-bond greatly facilitated the cycloaddition and it was possible to isolate the Diels–Alder adduct **18** as a single diastereomer in 45% yield simply by stirring a sample of **17** in benzene at 25°C. The structure of **18** was firmly established by X-ray crystallography which revealed an *anti*-stereochemical relationship between the carbomethoxy group and oxygen bridge. The formation of this *endo*-cycloadduct is in full accord with molecular mechanics calculations, which show a large ground state energy difference between the two diastereomers. Heating a sample of **18** at 90°C gave the rearranged hexahydro-pyrroloquinolinone **19** in 78% yield as a 1:1-mixture of diastereomers.[14]





To further illustrate the viability of this sequence as a practical strategy for the synthesis of complex polyazacyclic systems, we studied the cycloaddition behavior of the related amidofuran **20**. We were gratified to find that heating **20** at 110°C for 2 h gave the rearranged amide **21** as a single diastereomer in 80% yield. The 1,2-thiomethyl shift that occurs from the transient Diels–Alder cycloadduct probably proceeds via an episulfonium ion and consequently only one diastereomer would be expected.[15,16] Further transformations of **19** and **21** using the existing functional groups to establish additional stereogenic centers are currently underway.



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

Acknowledgements

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