ORGANIC LETTERS

2002
Vol. 4, No. 26
4643−4645

Intramolecular Amidofuran Cycloadditions across an Indole π-Bond: An Efficient Approach to the *Aspidosperma* and *Strychnos ABCE* Core

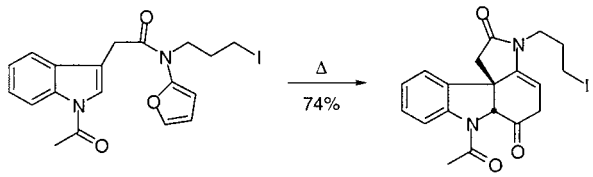
Stephen M. Lynch, Scott K. Bur,[†] and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

chemap@emory.edu

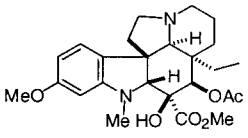
Received October 3, 2002

ABSTRACT

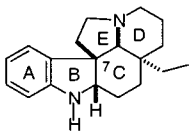


The intramolecular Diels–Alder reaction between an amidofuran moiety tethered onto an indole component was examined as a strategy for the synthesis of *Aspidosperma* and *Strychnos* alkaloids. Furanyl carbamate 13 was acylated using the mixed anhydride 16 to provide amidofuran 12 in 68% yield. Further N-acylation of this indole furnished 17 in 88% yield. Cyclization precursors were prepared by removing the carbamate moiety followed by N-alkylation with the appropriate alkyl halides. Thermolysis of 25 provided the novel tetracyclic ketone 26 in 74% yield.

Indole alkaloids,[1] which include the *Strychnos* and *Aspidosperma* families, are widely encountered natural products that continue to challenge synthetic chemists. The medicinal importance and interesting architecture of alkaloids such as vindoline (**1**)[2] have spurred many researchers to meet this synthetic challenge through a variety of creative approaches.[3]



1



2

One of the specific problems posed by the *Aspidosperma* skeleton, typified by aspidospermidine (**2**), involves the construction of the quaternary C(7) center. Because this center is contained within the six-membered *C* ring, a reaction that fashions both the *C* ring and the spirocyclic *BE* junction represents a very efficient strategy for the construction of this polycyclic array that is also present in many of the *Strychnos* alkaloids.[4] Kuehne's[5] use of a tandem ammonium ion rearrangement/intramolecular Diels−Alder cycloaddition and the more recent amido-diene cycloaddition sequence reported by Rawal[6] are the only approaches that construct both the *C* ring and the *BE* junction in one synthetic step.[7]

In recent years, we have been investigating the intramolecular [4 + 2]-cycloaddition/rearrangment cascade of 2-

[†] NIH Postdoctoral Fellow; Grant GM20666.

(1) Saxton, J. E. *Nat. Prod. Rep.* **1993**, *10*, 349−395.

(2) *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37, pp 145−204.

(3) Overman, L. E.; Sworin, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1985; Vol. 3, pp 275−307.

(4) Aimi, N.; Sakai, S.-I. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 1−68.

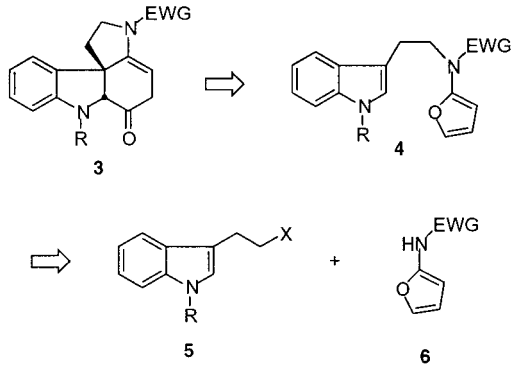
(5) (a) Kuehne, M. E.; Roland, D. M.; Hafter, R. *J. Org. Chem.* **1978**, *43*, 3705−3710. (b) Kuehne, M. E.; Bornmann, W. G.; Earley, W. G.; Marko, I. *J. Org. Chem.* **1986**, *51*, 2913−2927.

(6) (a) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. (b) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686.

10.1021/ol027024q CCC: $22.00
Published on Web 12/05/2002

amidofurans as a strategy for the synthesis of hexahydroindolinone alkaloids.[8] Our experience with this domino sequence prompted us to examine a Diels−Alder approach to the *ABCE* tetracyclic core **3**, wherein an indole moiety participates as the dienophilic partner (Scheme 1). An

Scheme 1. Intramolecular [4 + 2] Approach to the *ABCE* Core

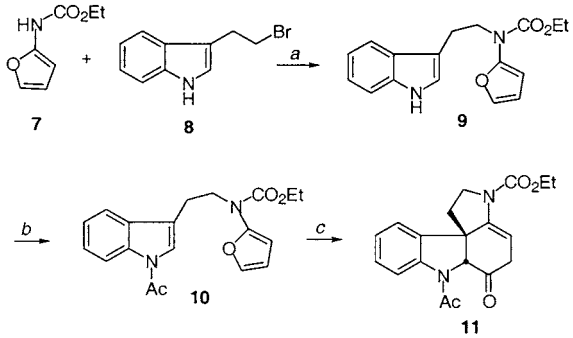


appropriate cyclization substrate such as **4** would come from the alkylation of indole derivative **5** with a 2-amidofuran **6** that possesses an electron-withdrawing group on the nitrogen atom.

The seminal work of Wenkert[9a] and Kraus[9b] established that the C(2)−C(3) double bond of indole can act as a 2π-partner in [4 + 2]-cycloaddition chemistry.[9c] This strategy, however, has not been extensively utilized for the synthesis of complex azapolycyclic ring systems.[9d] Some years ago, we reported the efficient participation of the indole C(2)−C(3) double bond as the 2π component in 1,3-dipolar cycloadditions with push−pull carbonyl ylides,[10] and Boger's recent report outlines a similar dipolar cycloaddition approach toward vindoline.[11] We now report the findings of our cycloaddition studies using 2-amidofurans as the 4π component.

Our initial attempts to build tetracycle **3** started by N-alkylating furan **7** with 3-(2-bromoethyl)indole (**8**) to provide indole **9** in 80% yield (Scheme 2).[8b] Not unexpectedly, thermolysis of **9**, which lacks an electron-withdrawing group on the indole, failed to induce cyclization even at temperatures above 200 °C. N-Acylation of **9** under phase

Scheme 2 [a]



[a] Reagents: (a) Cs_2CO_3, 4:1 DMF/THF, 80 °C, 80%; (b) Bu_4NHSO_4, NaOH, AcCl, CH_2Cl_2, rt, 90%; (c) benzene (sealed tube), 240 °C, 18 h, 30%.

transfer conditions provided **10** in 90% yield. Cyclization to **11** did occur, but only in 30% isolated yield (62% based on recovered starting material), after heating at 240 °C for 18 h.

Encouraged by this result, we searched for a way to increase the efficiency of the reaction. In previous studies, structural features that facilitate the intramolecular Diels−Alder reactions of amidofurans were discovered.[12,13] Specifically, the incorporation of a carbonyl group such that an amide linkage joined the dienophile and the furan moieties resulted in a conformation of the tether that brings the dienophile into closer proximity with the furan.[13]

Exploiting this effect in the indole system required an amidofuran such as **12** (Scheme 3). Initially, we had envisioned **12** arising from the simple acylation of **13** with the acid chloride derived from indole acetic acid (**14**). However, under a variety of conditions (DMAP, 4 Å molecular sieves,[14] etc.), furanyl carbamate **13** proved to be remarkably resistant toward acylation. After some experimentation, we found that the addition of **15**, formed by the action of *n*-BuLi on **13**, to a solution of the mixed anhydride **16** provided **12** in 68% yield. Subsequent N-acylation under phase transfer conditions smoothly produced **17** in 88% yield.

Unfortunately, our attempts to effect the cycloaddition of **17** resulted only in the removal of the thermally labile *tert*-butyloxy carbonyl group to give **18**. While **18** should still be a viable cyclization precursor, the use of temperatures exceeding 300 °C failed to promote the desired cycloaddition; only starting **18** was recovered.

Upon further consideration, this result is not so surprising: conformational preferences about an amide bond have been implicated in the efficiency of other cyclization reactions.[15] The strong preference of secondary amides to

(7) For a very recent paper using a related approach, see: Bodwell, G. J.; Li, J. *Angew Chem., Int. Ed.* **2002**, *41*, 3261−3263.

(8) (a) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1997**, *62*, 4088−4096. (b) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.* **1998**, *63*, 5304−5305. (c) Padwa, A.; Brodney, M. A.; Satake, K.; Straub, C. S. *J. Org. Chem.* **1999**, *64*, 4617−4626.

(9) (a) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188−7194. (b) Kraus, G. A.; Raggon, P. J.; Thomas, P. J.; Bougie, D. *Tetrahedron Lett.* **1988**, *29*, 5605−5608. (c) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. M. E. *J. Org. Chem.* **2001**, *66*, 3906−3912. (d) For a representative example within the context of indole alkaloids, see: Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35−41.

(10) (a)Padwa, A.; Price, A. T. *J. Org. Chem.* **1995**, *60*, 6258−6259. (b) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556−565.

(11) Wilkie, G. D.; Elliot, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292−11294.

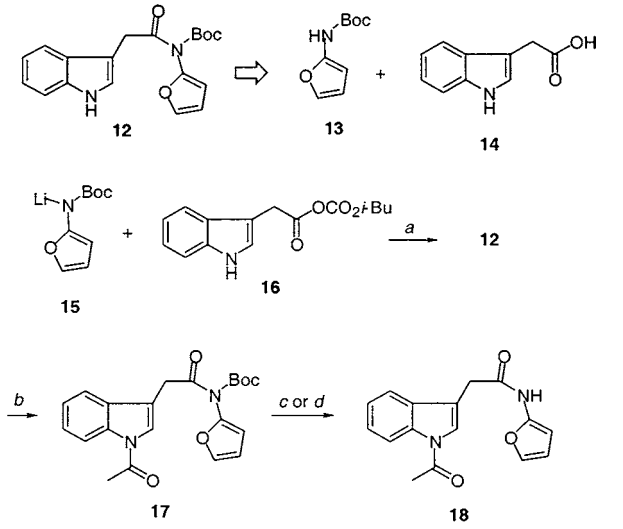
(12) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *64*, 3412−3424.

(13) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473−476.

(14) Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, *16*, 3979.

(15) For recent examples, see: (a) Jones, K.; Wilkinson, J.; Ewin, R. *Tetrahedron Lett.* **1994**, *35*, 7673−7676. (b) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537−5545.

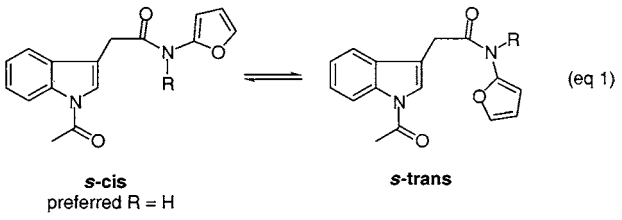
Scheme 3 [a]



[a] Reagents: (a) **14**, *i*-BuO_2CCl, *N*-methylmorpholine, filter, then **15**, 0 °C, 68%; (b) Bu_4NHSO_4, NaOH, AcCl, CH_2Cl_2, rt, 88%; (c) benzene, sealed tube, 200 °C; (d) $MgClO_4$, Ch_3CN, 50 °C, 77%.

adopt an *s*-cis conformation is well established.[16] More than likely, **18** resides predominantly in the *s*-cis conformation where the furan ring is far removed from the indole π-bond (eq 1). We reasoned that replacing the hydrogen with a larger group would cause the reactive *s*-trans conformation to be be more highly populated, and therefore the cycloaddition will be more prone to occur.

To test this hypothesis, several tertiary amides derived from **18** were prepared. This necessitated a more experimentally benign protocol for removing the carbamate moiety from **17**, and we found that $MgClO_4$ in CH_3CN efficiently provided **18**.[17] Alkylating the sodium salt of **18** with benzyl bromide or allyl iodide provided **19** or **20** in 82 and 50% yields, respectively (Scheme 4).

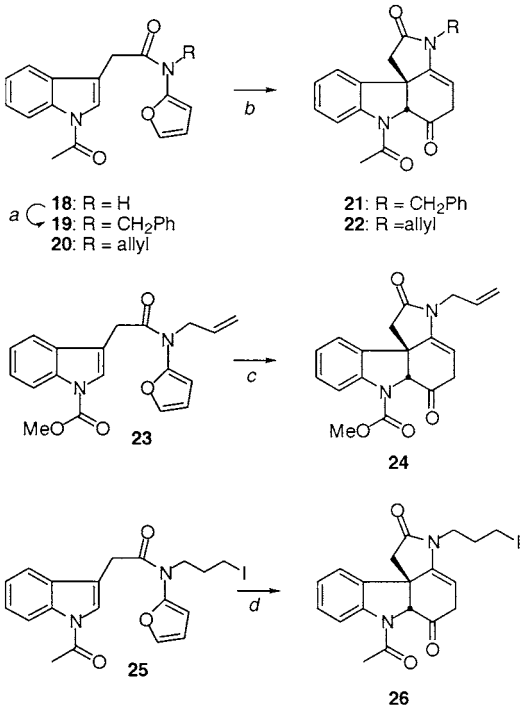


Heating a sample of indole **19** at 200 °C for 12 h gave the novel azatricycle **21** in 56% yield. Similarly, the thermolysis of **20** cleanly afforded **22** in 77% yield after only 2 h. Furan **23**, which contains a methoxycarbonyl group on

(16) (a) Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517−551. (b) See also: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley & Sons: New York, 1994; p 620.

(17) Stafford, J. A.; Brackeen, M. F.; Karanewsky, D. S.; Valvano, N. L. *Tetrahedron Lett.* **1993**, *34*, 7873−7876.

Scheme 4 [a]



[a] Reagents: (a) NaH, alkyl halide, DMF, rt; 82% (CH_2Ph), 50% (allyl). (b) Toluene (sealed tube), 200 °C, 12 h (CH_2Ph), 56% or 2 h (allyl), 77%. (c) Toluene (sealed tube), 200 °C, 2 h, 91%. (d) Toluene (sealed tube), 200 °C, 1.5 h, 74%.

the indole nitrogen, readily produced **24** in 91% yield after heating for 2 h at 200 °C. We also examined the cyclization of **25**, which bears functionality on the side chain that may allow for eventual functionalization of the D-ring. We were pleased to note that heating **25** at 200 °C for 1.5 h furnished the rearranged cycloadduct **26** in 74% yield.

In conclusion, our studies have shown that these [4 + 2]-cycloaddition reactions are remarkably efficient given that two aromatic systems are compromised in the reaction. These examples also demonstrate the utility of such an approach in the rapid construction of the *ABCE* tetracyclic core found in both the *Aspidosperma* and *Strychnos* families of indole alkaloids. The application of this approach to natural product targets is currently under investigation, the results of which will be disclosed in due course.

Acknowledgment. We thank the National Institutes of Health (GM59384 and GM60003) for generous support of this work. We acknowledge the use of shared instrumentation provided by grants from the NIH and NSF.

Supporting Information Available: Complete description of the synthesis and characterization of all new compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027024Q