Pergamon

Tetrahedron Letters 40 (1999) 4003–4006

TETRAHEDRON LETTERS

A Push-Pull Carbonyl Ylide Cycloaddition Approach Directed Toward Lycorine

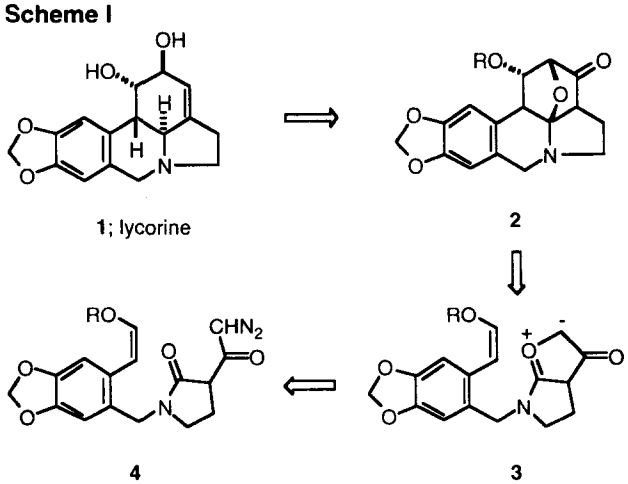
*William S. Kissel and Albert Padwa**
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received 26 January 1999; accepted 29 March 1999

Abstract: Cyclic 2-amidofurans were obtained using a Rh(II)-catalyzed reaction of α-diazoketo substituted pyrrolidinone derivatives. Acylation followed by a Diels-Alder reaction of the resulting amidofuran furnished both inter and intramolecular cycloadducts.

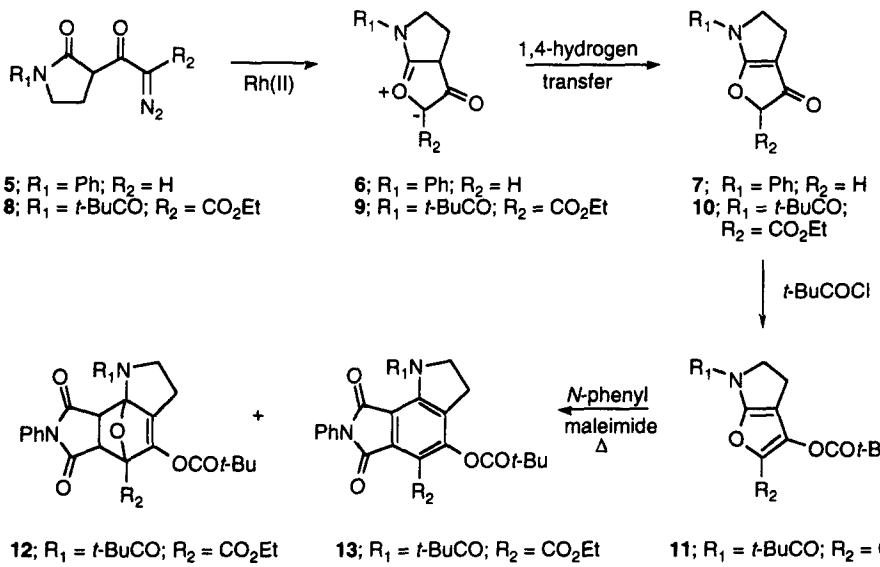
The lycorine alkaloids, a group of compounds isolated from *Amarylidaceae* plants, have attracted the attention of chemists and pharmacologists due to the interesting properties of some of its members.[1,2] Consequently, considerable effort has been directed toward the synthesis of the oxygenated octahydroindole skeleton found in this class of alkaloids.[3-7] Among the many approaches to the lycorine family,[8] intermolecular and intramolecular Diels-Alder reactions have played a key role in the synthesis of these natural products.[9] Our synthetic plan toward lycorine (**1**) is part of a general approach to the total synthesis of azapolycyclic natural products based upon the Rh(II)-catalyzed cyclization of diazoimides.[10] Prompted by our earlier work dealing with the internal dipolar-cycloaddition reaction of *push-pull* carbonyl ylides for synthesis of the *aspidosperma* skeleton,[11] we became interested in determining whether a related process could be used to assemble the carbon framework of lycorine (**1**). We envisioned diazoamide **4** functioning as a possible precursor for the generation of dipole **3**. Intramolecular cycloaddition across the neighboring enol ether π-bond followed by reductive ring opening of the transient azabicyclic adduct **2** would provide the lycorine skeleton with the correct relative stereochemistry (Scheme I). In this communication, we report that the Rh(II)-catalyzed reaction of *N*-substituted diazo pyrrolidinones furnishes fused cyclic amidofuranones which can be further utilized for [4+2]-cycloaddition chemistry.

Scheme I



0040-4039/99/$ - see front matter
PII: S0040-4039(99)00670-X

As a model system for exploring the cyclization-cycloaddition sequence, diazoamide **5** was first examined. Reaction of **5** with $Rh_2(OAc)_4$ led to the expected *push-pull* dipole **6**. However, even in the presence of an excess of trapping agent such as DMAD, a rapid [1,4]-hydrogen shift[12] to form furanone **7** occurred before bimolecular cycloaddition. With this transformation in mind, we decided to use the furanone ring to our advantage for an anticipated Diels-Alder cycloaddition. It was envisioned that acylation of the furanone would provide a fused amidofuran (*i.e.*, **11**) that could be subsequently utilized in a bimolecular cycloaddition reaction.[13]



5; R_1 = Ph; R_2 = H
8; R_1 = *t*-BuCO; R_2 = CO_2Et

6; R_1 = Ph; R_2 = H
9; R_1 = *t*-BuCO; R_2 = CO_2Et

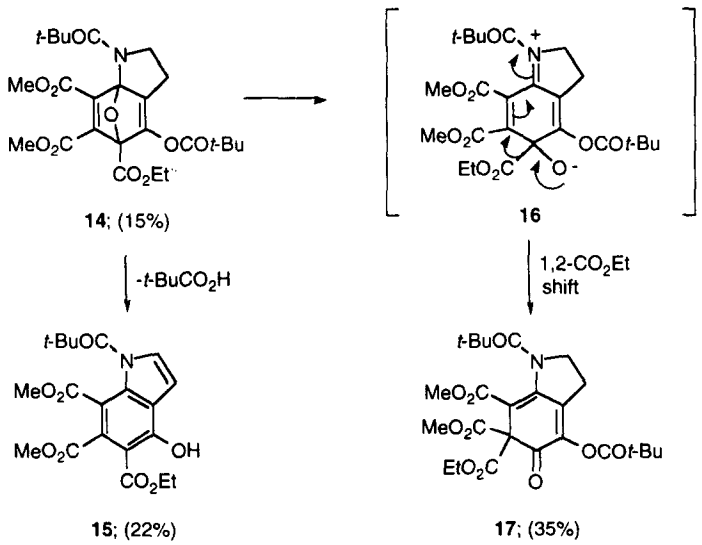
7; R_1 = Ph; R_2 = H
10; R_1 = *t*-BuCO; R_2 = CO_2Et

12; R_1 = *t*-BuCO; R_2 = CO_2Et

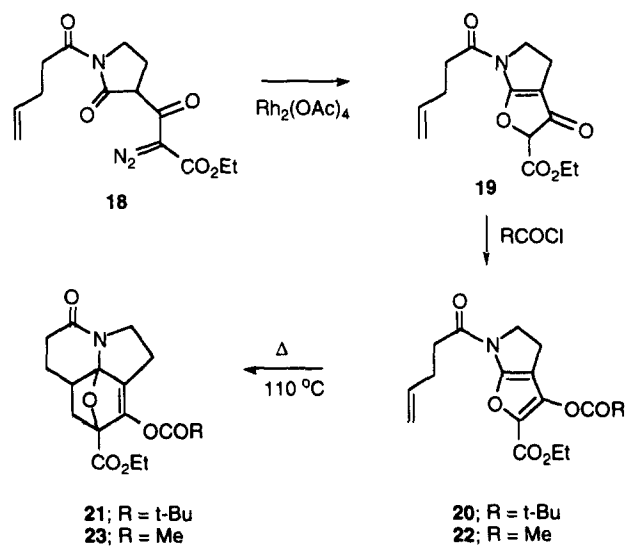
13; R_1 = *t*-BuCO; R_2 = CO_2Et

11; R_1 = *t*-BuCO; R_2 = CO_2Et

Exploring this approach required that three key steps be tested. First, the diazoimide must be able to efficiently cyclize to form the furanone ring. Secondly, the furanone would need to readily react with an acylating agent to furnish the fused amidofuran **11**. Finally, the tetrasubstituted furan would need to undergo a facile Diels-Alder reaction with an electron rich π-bond.[14] Diazoimide **8** was synthesized from *N*-pivalyl pyrrolidinone by deprotonation with $NaN(TMS)_2$ followed by treatment with benzyl chloroformate. Hydrogenolysis of the benzyl ester to the carboxylic acid was followed by conversion to the acid chloride and reaction with ethyl diazoacetate. Decomposition of **8** using $Rh_2(OAc)_4$ gave furanone **10** which was transformed into amidofuran **11** by treatment with pivalyl chloride and NEt_3. Heating a sample of **11** with *N*-phenyl maleimide afforded a 1:3-mixture of cycloadduct **12** together with indoline **13**, derived by oxa-bicyclic ring opening followed by elimination of water, in 95% overall yield.[15] Indeed, treatment of **12** in the presence of acid afforded **13** in high yield. Interestingly, the reaction of **11** with DMAD afforded a mixture of cycloadduct **14** (15%), indole **15** (22%) and the rearranged cyclohexadienone **17** (35%). The structure of **17** was unequivocally established by a single crystal X-ray analysis, and its formation can be rationalized by a ring opening-rearrangement reaction analogous to that reported in the furo[3,4-*d*]oxazole series.[16]



Having established the feasibility of the bimolecular cycloaddition sequence using activated π-bonds, we initiated a study of the intramolecular reaction related to that outlined in Scheme I. Specifically, we were interested in examining a case where an alkenyl group would be tethered to the imido nitrogen atom. Diazoimide **18** was synthesized in a manner similar to that used to prepare pyrrolidinone **8**. As before, decomposition of the diazoimide using $Rh_2(OAc)_4$ provided the intermediate furanone **19** which was reacted with pivalyl chloride to furnish amidofuran **20**. Heating a toluene solution of **20** at reflux provided cycloadduct **21** as the only detectable product in high overall yield for the three-step process (70%). A similar [4+2]-cycloaddition reaction occurred with the corresponding acetate **22**, but with lower overall yield (25%), perhaps as a consequence of a competitive thermal deacetylation reaction.



In conclusion, we have shown that α-diazo keto pyrrolidinones undergo a ready Rh(II)-catalyzed cyclization reaction to furnish amidofuranones. These compounds are derived by a [1,4]-hydrogen transfer from an initially formed carbonyl ylide dipole. Acylation of the resulting furanone system gives fused cyclic amidofurans which are reactive partners for both inter and intramolecular Diels-Alder reactions. Extension of the methodology toward the synthesis of lycorine and some related galanthan alkaloids is currently in progress.

Acknowledgment: We gratefully acknowledge support of this work by the National Science Foundation (CHE-9806331) and the National Institute of Health. Use of the high-field NMR spectrometer used in these studies was made possible through equipment grants from the NIH and NSF.

References

1. Martin, S. F. in *The Alkaloids;* Brossi, A., Ed.; Academic Press Inc.: New York, 1987. Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329.
2. Pettit, G. R.; Gaddamidi, V.; Goswami, A.; Gragg, G. M. *J. Nat. Prod.* **1994**, *47*, 796. Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochem.* **1985**, *24*, 2141.
3. Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904.
4. Meyers, A. I.; Hutchings, R. H. *Tetrahedron Lett.* **1993**, *34*, 6185.
5. Grotjahn, D. B.; Vollhardt, K. P. *Synthesis* **1993**, 579.
6. Pérez, D.; Burés, G.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650.
7. Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. I* **1995**, 2671.
8. For some leading references, see: González, C.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1995**, *60*, 6318.
9. Hill, R. K.; Joule, J. A.; Loeffler, L. *J. Am. Chem. Soc.* **1962**, *84*, 4951. Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Irie, H.; Tanaka, H.; Takagi, S.; Yamaki, S.; Murata, M. *J. Chem. Soc., Chem. Commun.* **1975**, 933. Stork, G.; Morgans, D. J. Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7110. Martin, S. F.; Tu, C. Y.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634. Hwang, G.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1983**, 693. Boeckman, R. K. Jr.; Sabatucci, J. P.; Goldstein, S. W.; Springer, D. M.; Jackson, P. F. *J. Org. Chem.* **1986**, *51*, 3740.
10. Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001.
11. Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556.
12. Kharasch, M. S.; Ruby, T.; Nudenberg, W.; Buchi, G. *J. Org. Chem.* **1953**, *18*, 1030. Lottes, A.; Landgreb, J. A.; Larsen, K. *Tetrahedron Lett.* **1989**, *30*, 4089. Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhang, Z. *J. Org. Chem.* **1991**, *56*, 3271.
13. Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. *J. Org. Chem.* **1998**, *63*, 3986. Schlessinger, R. H.; Bergstrom, C. P. *J. Org. Chem.* **1995**, *60*, 16.
14. Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.
15. All new compounds in this study were fully characterized (IR, NMR, elemental analysis and/or HRMS).
16. Reck, S.; Friedrichson, W. *J. Org. Chem.* **1998**, *63*, 7680. For a related process involving a [1,2]-phenyl shift, see Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 3495.