ORGANIC LETTERS

1999
Vol. 1, No. 2
349−351

Nonstabilized *N*-Unsubstituted Azomethine Ylides: A Synthesis of Indolizidine 239CD

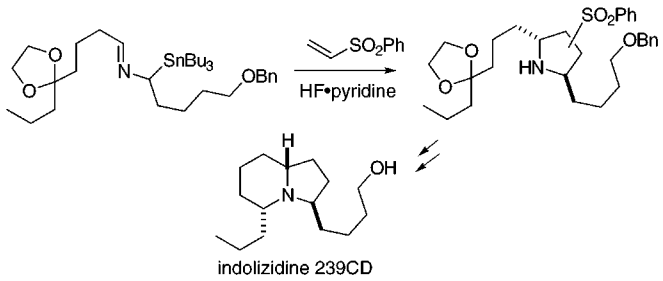
Roger B. Clark and William H. Pearson*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1055

wpearson@umich.edu

Received May 19, 1999

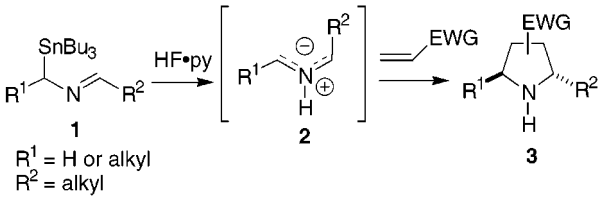
ABSTRACT



Treatment of a (2-azaallyl)stannane with HF·pyridine generated a nonstabilized *N*-unsubstituted azomethine ylide, which was found to undergo an efficient and stereoselective dipolar cycloaddition with phenyl vinyl sulfone to produce a *trans*-2,5-dialkylpyrrolidine that was further transformed into the dendrobatid alkaloid indolizidine 239CD.

We recently reported a convenient method for the generation and cycloaddition of nonstabilized *N*-unsubstituted azomethine ylides **2** (Scheme 1), a rare subclass of these ylides.[1]

Scheme 1



Treatment of (2-azaallyl)stannanes **1** with HF·pyridine produced the ylides **2** by *N*-protonation and destannylation.[2] Compared to other methods for azomethine ylide formation,[1−3] notable features of this route include the tolerance for aliphatic groups, good *trans*-2,5 diastereoselectivity in the pyrrolidine product, mild reaction conditions, and of course the lack of a substituent at nitrogen. We now wish to report the application of this method for the synthesis of (±)-

(1) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1999**, in press.

(2) For a related approach using other electrophiles to initiate the formation of azomethine ylides from (2-azaallyl)stannanes, see: Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441−5444.

(3) (a) Lown, W. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1; pp 663−732. (b) Pearson, W. H. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1988; Vol. 1; pp 323−358. (c) Vedejs, E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1; pp 33−51. (d) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231−349. (e) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4; pp 1069−1109. (f) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4; pp 1111−1168.

(4) Azomethine ylides have been used to make indolizidines and pyrrolizidines. See: refs 2 and 3c−e above and (a) Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* **1988**, *27*, 981−1008. (b) Pandey, G.; Lakshmaiah, G.; Ghatak, A. *Tetrahedron Lett.* **1993**, *34*, 7301−4. During the course of this work, a related approach to indolizidines and pyrrolizidines involving the dipolar cycloaddition of *stabilized* azomethine ylides with alkenes followed by intramolecular reductive amination was published. See: (c) Grigg, R.; Hargreves, S.; Redpath, J.; Turchi, S.; Yoganathan, G. *Synthesis* **1999**, 441−446.

(5) For a review on the synthesis of 2,5-disubstituted pyrrolidines that includes azomethine ylide cycloadditions, see: M. Pichon, B. Figadère, *Tetrahedron: Asymmetry* **1996**, *7*, 927−964.

10.1021/ol990677v CCC: $18.00
Published on Web 06/15/1999

indolizidine 239CD (**4**), one of several naturally occurring indolizidines that include a *trans*-2,5-disubstituted pyrrolidine in their structures.[4,5]

Poison frogs of the species *Dendrobates histrionicus* yield four 3,5-disubstituted indolizidines, namely, 223AB, 239AB, 239CD, and 195B (Figure 1).[6−9] A retrosynthetic analysis

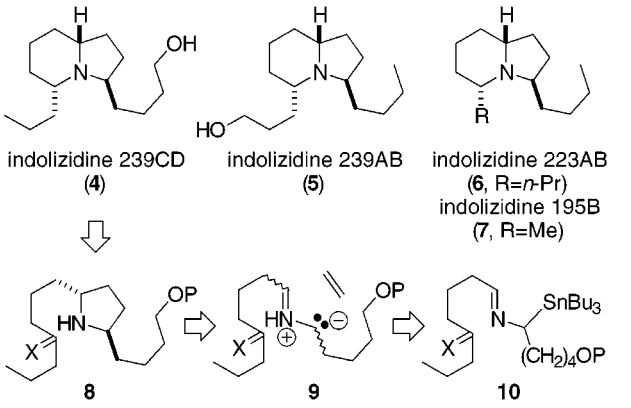
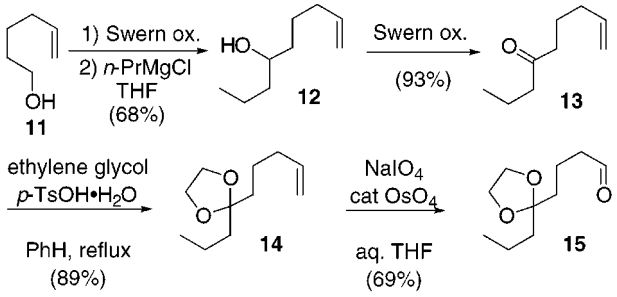


Figure 1. Structures of indolizidines 239CD, 239AB, 223AB, and 195B and retrosynthetic analysis of indolizidine 239CD.

is shown. Formation of the piperidine ring at a late stage would rely on an intramolecular reductive amination involving **8**, a well-known strategy for indolizidine synthesis.[9] The pyrrolidine **8** would require the cycloaddition of the azomethine ylide **9**, available from the (2-azaallyl)stannane **10**, with ethylene or its equivalent. The stannane **10** should be available from an aldehyde and an α-stannylamine.[10,11]

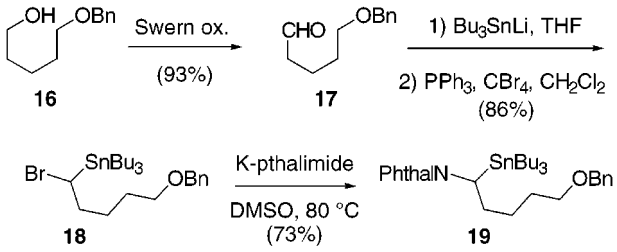
The requisite aldehyde **15** was prepared by the route shown in Scheme 2, beginning with the commercially available alcohol **11**. Oxidation, chain extension, reoxidation, protection, and unmasking of the aldehyde by oxidative cleavage of the alkene proceeded smoothly.

Scheme 2



The synthesis of the phthalimide **19**, the precursor of the desired α-stannylamine, is shown in Scheme 3. Oxidation of the commercially available alcohol **16** gave the aldehyde **17**, which was treated with tri-*n*-butylstannyllithium to provide an α-hydroxy stannane. Without purification, this

Scheme 3



alcohol was transformed into the bromide **18** in good yield, which was subjected to displacement chemistry to provide the pthlalimide **19**.

Completion of the synthesis of indolizidine 239CD is shown in Scheme 4. Hydrazinolysis of the pthalimide **19**

(6) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453−3460.

(7) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265−280.

(8) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4; pp 1−274. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43; pp 185−288. (c) Daly, J. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1997; Vol. 50. (d) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; John Wiley & Sons: New York, 1999; Vol. 13; p 1.

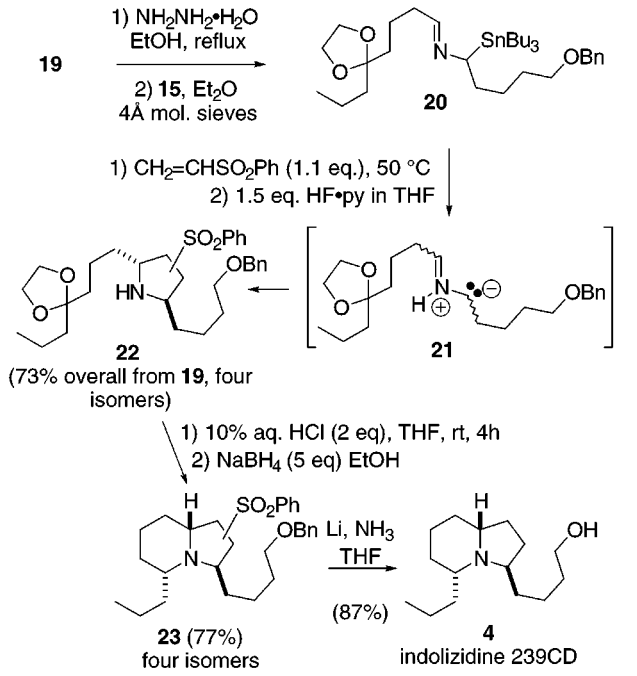
(9) Many syntheses of these and related indolizidines have been published. For the latest in a series of reviews covering the synthesis of indolizidines and pyrrolizidines, see: (a) Michael, J. P. *Nat. Prod. Rep.* **1998**, *15*, 571−594. For syntheses of indolizidines 195B, 223AB, 239AB, and 239CD by an approach involving *trans*-2,5-disubstituted pyrrolidines, see: (b) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178−5189. (c) Machingaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405−407. For other approaches to indolizidines 195B, 223AB, and 239AB involving *trans*-2,5-disubstituted pyrrolidines, see: (d) Thanh, G. V.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2211−2212. (e) Célimène, C.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457−10468. (f) Dhimane, H.; Vanucci-Bacqué, C.; Hamon, L.; Lhommet, G. *Eur. J. Org. Chem.* **1998**, 1955−1963. For selected additional syntheses of indolizidine 195B, see: (g) Bloch, R.; Brillet-Fernandez, C.; Kühn, P.; Mandville, G. *Heterocycles* **1994**, *38*, 1589−1594. (h) Solladie, G.; Chu, G.-H. *Tetrahedron Lett.* **1996**, *37*, 111−14. (i) Lee, E.; Kang, T. S.; Chung, C. K. *Bull. Korean Chem. Soc.* **1996**, *17*, 212−14. (j) Somfai, P.; Jarevang, T.; Lindstrom, U. M.; Svensson, A. *Acta Chem. Scand.* **1997**, *51*, 1024−1029. For selected additional syntheses of indolizidine 223AB, see: (k) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 4088−97. (l) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990−5994. (m) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717−722. (n) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* **1995**, *41*, 1797−1804. (o) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1315−1321.

(10) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354−6357.

(11) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220−2222.

(12) See ref 1 for a comparison with existing methods for the generation of nonstabilized *N*-substituted and *N*-unsubstituted azomethine ylides. Regarding nonstabilized *N*-unsubstituted azomethine ylides, two other methods for their generation are known, the decarboxylation of imines derived from the condensation of α-amino acids with aldehydes [leading references: (a) Tsuge, O.; Kanemasa, S.; Ohe, M.; Takenaka, S. *Bull. Soc. Chem. Jpn.* **1987**, *60*, 4079−4089. (b) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1988**, *44*, 4953−4966] and the water-induced generation of such ylides from *N*-(silylmethyl)imines [Tsuge, O.; Kanemasa, S.; Hatada, A.; Matsuda, K. *Bull. Soc. Chem. Jpn.* **1986**, *59*, 2537−2545]. The first method suffers from low yields and poor *trans:cis* stereoselectivity, while the second is limited to nonenolizable imines with no branching next to silicon (i.e., monosubstituted azomethine ylides).

Scheme 4



gave an amine, which was not purified but directly condensed with the aldehyde **15** under typical imine formation conditions to produce the (2-azaallyl)stannane **20**. The unpurified imine was mixed with phenyl vinyl sulfone, and the mixture was warmed to 50 °C and treated with HF·pyridine for 10 min. Workup provided the pyrrolidine **22** as a nearly equal mixture of four isomers in 73% overall yield from the pthalimide **19**. Removal of the ketal and intramolecular reductive amination proceeded in good yield to produce **23**, again as a mixture of four isomers. We were not able to determine the stereo- and regiochemistry of either **22** or **23**. Reductive cleavage of the benzyl ether and the sulfone was initially a troublesome transformation but was found to be efficient with lithium and ammonia. The four isomers of **23** converged to a single compound, indolizidine 239CD (**4**), thus providing evidence that **22** and **23** were a mixture of regio- and stereoisomers at the sulfone position and that the cycloaddition had proceeded with high *trans*-2,5 stereoselectivity.

In conclusion, our recent method for the synthesis of *trans*-2,5-dialkyl-*N*-unsubstituted-pyrrolidines has proven to be effective for use in more complex situations, resulting in a convergent, efficient, and relatively short synthesis of indolizidine 239CD (**4**). Significant features of the synthesis are the efficiency, stereoselectivity, and mildness of the azomethine ylide cycloaddition. Prior to our work, access to nonstabilized *N*-unsubstituted azomethine ylides such as those described herein had been very limited.[12]

Acknowledgment. Support for this research was provided by the National Institutes of Health.

OL990677V