Communications to the Editor

Intramolecular Bicyclizations of Tosylamide-Containing Alkynyliodonium Salts as an Efficient Entry into Polycyclic Alkaloid Skeleta

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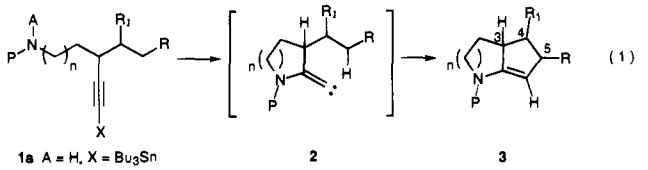
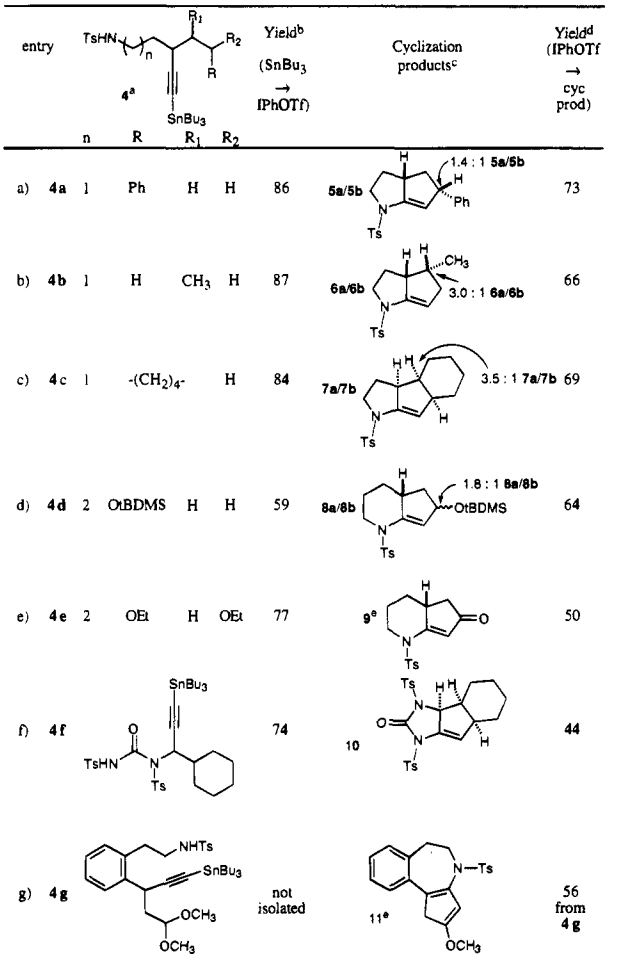
Development of efficient strategies for the assembly of nitrogen-containing polycyclic molecular frameworks remains an enduring challenge in alkaloid total synthesis. One structurally (but not biogenically) related subclass, which features a cyclopentylamine core embedded in a polycyclic array, includes many "classical" (ajmaline[1] and cephalotaxine[2]) as well as contemporary (agelastatin A[3] and huperserratinine[4]) targets. Approaches to the synthesis of these disparate cyclopentylamine-containing species have relied on various incarnations of Mannich, Michael, or Diels−Alder reactions, inter alia, for preparation of this key region of the alkaloid. However, an alternative and unexplored approach which might serve to integrate these targets into a unified synthesis strategy can be envisioned, eq 1. This chemistry, which relies on an intramolecular combination of alkynyliodonium salts with *p*-toluenesulfonamide anions, takes advantage of the iodonium species' unique ability to form two bonds in tandem, first by nucleophile capture and then by proximal insertion into an (unactivated) C−H bond, to furnish five membered rings in a single operation.[5,6]



Seminal studies from the laboratories of Stang[5] and Ochiai[6] have documented the scope of *inter*molecular addition/cyclizations of carbon (and to a lesser extent oxygen and sulfur) nucleophiles to alkynyliodonium salts. However, the use of nitrogen nucleophiles is limited at present to azide[5c] and Ph_2NLi;[5d] only the former species affords cyclic product. Furthermore, no examples of *intra*molecular nucleophile/alkynyliodonium combination have been reported. The former limitation perhaps results from the relatively narrow "bandwidth" of nucleophilicity tolerated by these sensitive electrophiles, while the latter omission may reflect the perceived difficulties associated with introduction of the fragile alkynyliodonium unit in the presence of a nucleophilic entity. Thus, successful execution of the chemistry outlined in eq 1 will require resolution of two primary issues: (1) identification of an activating/protecting group "P" (cf **1**) which brings the nitrogen's nucleophilicity into an acceptable range for reaction with the alkynyliodonium electrophile and (2) determination of permissible tether lengths (*n*) separating nucleophilic and electrophilic atoms. In addition, secondary issues of chemical selectivity are raised in eq 1 which require (1) examination of the influence that the group "R" has upon efficiency of C−H insertion and (2) elucidation of diastereoselectivity along the C(3)−C(5) periphery upon cyclization.

The tosylamide-bearing stannylalkyne **4a** (Table 1, entry *a*)

Table 1. Synthesis and Bicyclization of Alkynyliodonium Tosylamides To Furnish Polycyclic Tosylenamides



[a] Substrate syntheses with full spectral characterization can be found in the supplementary material. [b] Determined by integration of the ^{1}H NMR spectrum. [c] Major stereoisomer shown. Stereochemistry was assigned through analysis of decoupling and NOE data (supplementary material). [d] Chromatographically pure material. [e] The ketal was transformed to the indicated functionality upon workup/chromatography.

(1) (a) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506. (b) van Tamelen, E. E.; Oliver, L. K. *J. Am. Chem. Soc.* **1970**, *92*, 2136.

(2) For leading references to cephalotaxine syntheses, see: (a) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. (b) Lin, X.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 9791. (c) For a review of cephalotaxine chemistry through 1986, see: Hudlicky, T.; Kwart, L. D.; Reed, J. W. in *Alkaloids, Chemical and Biological Perspectives*; Pelletier, S. W., Ed., Springer, Verlag: New York; 1987; Vol. 5, chapter 5.

(3) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895.

(4) Zhu, D.-Y.; Jiang, S.-H.; Huang, M.-F.; Lin, L.-Z.; Cordell, G. A. *Phytochemistry* **1994**, *36*, 1069.

(5) (a) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (c) Kitamura, T.; Stang, P. J. *Tetrahedron Lett.* **1988**, *29*, 1887. (d) Murch, P.; Williamson, B. L.; Stang, P. J. *Synthesis* **1994**, 1255. (e) Zhdankin, V. V.; Crittell, C. M.; Stang, P. J.; Zefirov, N. S. *Tetrahedron Lett.* **1990**, *31*, 4821.

(6) (a) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281. (b) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135.

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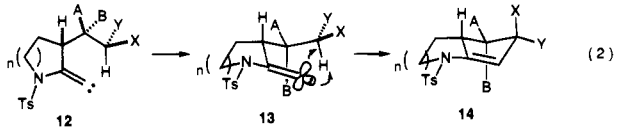
featured the first pairing of "P" and "*n*" which led cleanly and in good yield to bicyclic enamide products, **5a/b**. Treatment of substrate **4a** with PhICNOTf[5e] furnished an intermediate alkynyliodonium salt as a white foam (purity assayed by ^{1}H NMR). In practice this sensitive material[7] was best treated immediately with base (*t*-BuOK or TMS_2NLi in THF) to deliver directly the cyclized product **5a/b** following chromatography with a trace of triethylamine in the eluent to suppress decomposition of the acid-labile products. An examination of the remaining entries in Table 1 reveals that five-, six-, and seven-membered rings are equally accessible via initial cyclization of a tosylamide anion with the alkynyliodonium electrophile. In contrast, attempted cyclization of a substrate related to **4a** with $n = 4$ did not afford any cyclooctanoid products. Alkylidene carbene insertion occurs with similar facility into C−H bonds positioned on primary (entry *b*), secondary (entries *a*, *c*, *d*, and *f*), and tertiary (entries *e* and *g*) carbons bearing H, Ph, alkyl, and ethereal substituents, in accord with expectations for this very reactive and not particularly discriminating intermediate.[8-10]

The stereochemical outcome of these cyclizations can be interpreted in terms of a transition state model proposed by Gilbert for vinylidene carbene insertion/cyclization, eq 2.[8a] Thus, cyclization of **4a** through a construct **13** where steric interactions between the non-hydrogen group on C(5) and the remainder of the molecular assembly are minimized (i.e., A = B = X = H, Y = Ph) leads to the major product **5a**. Cyclizations of the similar species **4b**, **4c**, and **4f** to afford the major isomers shown plausibly proceed through related conformations **13** where A = X = Y = H, B = CH_3 (**4b**) or A = X = H, B = Y = $(CH_2)_4$ (**4c** and **4f**). The salient steric/stereoelectronic interactions which contribute to these preferences have yet to be elucidated.



(2)

The last two entries (*f* and *g*) address the feasibility of applying this reaction sequence to complex natural product synthesis. Bicyclization of the imide anion/iodonium salt derived from readily available tosylurea **4f** leads to a tricyclic product **10** structurally related to the novel marine alkaloid agelastatin A. In addition, the acetal **4g** can be processed similarly to the diene **11** which embodies three out of the four central rings of the cephalotaxine family of anticancer alkaloids. In summary, the tandem nucleophile addition/carbene insertion sequence characteristic of alkynyliodonium salts can be extended to intramolecularly disposed nitrogen containing nucleophiles. Base induced bicyclization of the alkynyliodonium/tosylamide substrates leads to a rapid increase in molecular complexity and provides efficient access to a variety of cyclopentylamine-containing alkaloid skeleta.

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Supporting Information Available: Experimental procedures and full spectral characterization for **4a−f**, **5−11** (22 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(7) None of the alkynyliodonium salts reported in this study could be obtained in crystalline form. These species, isolated as oils/foams, decomposed rapidly (<5 min at 25 °C → 0 °C) in a variety of solvents ($CDCl_3$, C_6D_6, CD_3CN, CD_3COCD_3) and could only be characterized by ^{1}H NMR (see supplementary material).

(8) (a) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557. (b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656. (c) Gilbert, J. C.; Giamalva, D. H. *J. Org. Chem.* **1985**, *50*, 2586. (d) Gilbert, J. C.; Blackburn, B. K. *Tetrahedron Lett.* **1984**, *25*, 4067. (e) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251.

(9) (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Davis, J. H.; Goddard, W. A., III; Harding, L. B. *J. Am. Chem. Soc.* **1977**, *99*, 2919. (c) Gallo, M. M.; Hamilton, T. P.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1990**, *112*, 8714. (d) DeLeeuw, B. J.; Fermann, J. T.; Xie, Y.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1993**, *115*, 1039.

(10) Other approaches to the formation of vinylidene carbenes can be found in the following: (a) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721. (b) Taber, D. F.; Walter, R.; Meagley, R. P. *J. Org. Chem.* **1994**, *59*, 6014. (c) Taber, D. F.; Meagley, R. P. *Tetrahedron Lett.* **1994**, *35*, 7909. (d) von Karph, M.; Dreiding, A. S. *Helv. Chim. Acta* **1979**, *62*, 852. (e) Padwa, A.; Austin, D. J.; Gareau, Y.; Kassir, J. M.; Xu, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 2637. (f) Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35*, 7253. (g) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1994**, *35*, 8405. (h) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142. (i) Likhotvorik, I. R.; Brown, D. W.; Jones, M., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 6175. (j) Baird, M. S.; Baxter, A. G. W.; Hoorfar, A.; Jeffries, I. *J. Chem. Soc., Perkin Trans 1* **1991**, 2575.