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Novel Iminium Ion Equivalents Prepared through C−H Oxidation for the Stereocontrolled Synthesis of Functionalized Propargylic Amine Derivatives

James J. Fleming, Kristin Williams Fiori, and J. Du Bois*

Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received October 11, 2002; E-mail: jdubois@stanford.edu

The rich variety of nitrogen-containing structures that occur as natural and synthetic products inspires the continued development of new strategies for the stereocontrolled synthesis of polyfunctionalized amines.[1] One general approach to such compounds capitalizes on the reactivity of *N*-acyl- or *N*-sulfonyliminium ions with substituted carbon nucleophiles.[2] The value of these intermediates in synthesis has been fully appreciated only through the advent of novel iminium ion equivalents, stable precursors which can be activated as electrophiles in the presence of external reagents.[2b,3] Herein, we describe a unique and diverse class of oxathiazinane *N*,*O*-acetals that function with exceptional performance as latent iminium ions (Figure 1). Access to such compounds is made possible through sulfamate ester C−H insertion, methodology recently advanced by our lab.[4] The following work details the preparation of these heterocyclic acetals and their subsequent coupling reactions with alkynylzinc nucleophiles. Acetylide addition to the intermediate iminium species occurs with predictable and high levels of stereocontrol. The products obtained are versatile synthetic building blocks having both the alkyne moiety and the electrophilic oxathiazinane core. Collectively, these new findings further validate the potential power of C−H amination methods in synthesis.

Efforts to formulate broadly applicable methods for saturated C−H bond amination have manifest in a novel Rh-catalyzed sulfamate insertion reaction.[4] Through our continuing investigations, we have noted the remarkable activity of ethereal α-C−H bonds as substrates for this process.[5] The ability to oxidize selectively the α-position of an ether unit can be exploited for the purpose of generating unique *N*,*O*-acetal structures that serve as surrogate iminium ions. As demonstrated in Figure 2, *N*,*O*-acetals with varying substitution patterns may be prepared following our standard protocol in high yield (72−92%) and with insertion occurring exclusively at the γ-C−H bond. In one example, for which amination can result at either of two γ-positions (compound **2**, Figure 2), insertion into the unactivated $-CH_2$ center is not observed.[6] With the exception of **1** and **2**, the product acetals are generally afforded as stereoisomeric mixtures, a problem of no consequence given subsequent iminium ion generation. These compounds show moderate to good stability over prolonged storage and may be purified by chromatography on silica gel.[7] To our knowledge, the synthesis, characterization, and reactions with oxathiazinanes of this type are unprecedented.

Studies designed to explore the electrophilic reactivity of *N*,*O*-acetals **1**−**5** were performed in combination with alkynylzinc reagents. The addition of metal acetylides to such starting materials affords oxathiazinane products that are uniquely configured for any number of subsequent chemical manipulations.[8] Through a series of screens that included Ti, Al, and lanthanide Lewis acids, $BF_3{\cdot}OEt_2$ was identified as the optimal promoter for this coupling process. When $BF_3{\cdot}OEt_2$ was added to a THF solution of **1** and hexynylzinc chloride (prepared by transmetalation of the Li-

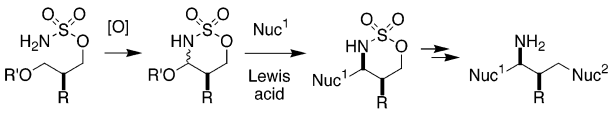


Figure 1. Novel *N*,*O*-acetal oxathiazinane heterocycles as reactive iminium ion equivalents.

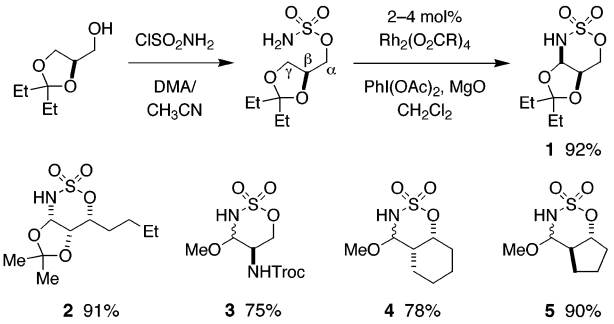
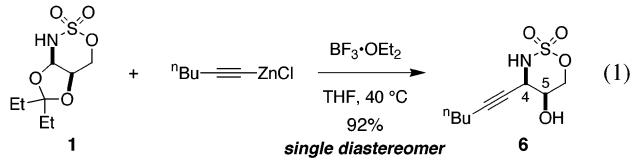


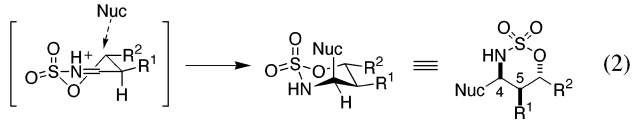
Figure 2. Rh-catalyzed C−H insertion furnishes *N*,*O*-acetal substrates.

acetylide with $ZnCl_2$), the starting acetal was consumed in 15 min (40 °C) to furnish the desired product **6** as a single diastereomer in 92% yield (eq 1). The efficiency and selectivity recorded for this transformation are noteworthy and compare favorably against reported reactions of *N*-acyl- and *N*-sulfonyliminium ions.[2]



(1)

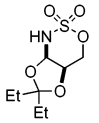
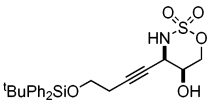
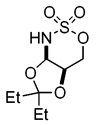
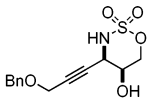
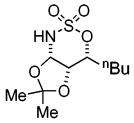
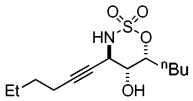
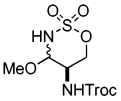
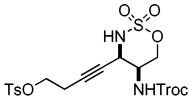
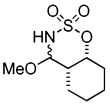
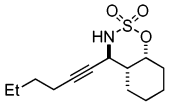
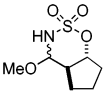
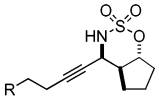
Conditions formulated for the reaction of **1** and hexynylzinc may be employed with different combinations of *N*,*O*-acetals **2**−**5** and Zn-acetylide reagents (Table 1). As suggested by these data, our method profits from the compatibility of organozinc reagents with a broad range of disparate structural groups.[9] Product yields are typically >70%, and the cis-C4,C5 stereoisomer is generally obtained.[10] The sense of induction in these reactions can be rationalized by invoking a TS‡ model analogous to that proposed by Stevens for nucleophilic additions to tetrahydropyridinium ions.[11] Axial attack by the alkynyl anion on the twist-chair form of the iminium intermediate would thus give the cis-C4,C5 stereochemistry (eq 2). Although speculative, this analysis offers a useful predictive tool for which an exception has not yet been found.[12]



(2)

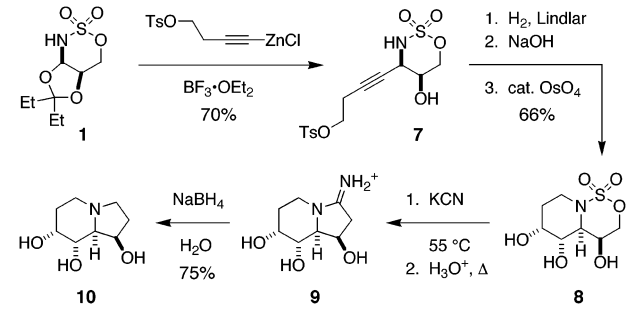
10.1021/ja028916o CCC: $25.00

Table 1. Alkynylzinc Addition Reactions with *N*,*O*-Acetals

Entry	Substrate	Major isomer[a]	Selectivity[b]	Yield[c]
1			20:1	85
2			20:1	82
3			12:1	71
4			8:1	70
5			20:1	76
6			R = Et 6:1 = OP 6:1	80 63[d]

[a] All reactions with the exception of entry 4 were performed at 40 °C with 2 equiv of alkyne, 2 equiv of ^{n}BuLi, 2.1 equiv of $ZnCl_2$, and 1−3 equiv of $BF_3{\cdot}OEt_2$ (see the Supporting Information for details). [b] Product ratios determined by ^{1}H NMR integration. [c] Combined yield of both diastereomers. [d] P = Si^{t}BuPh$_2$.

Scheme 1



The oxathiazinane products isolated from *N*,*O*-acetals **1**−**5** are moderate electrophiles that undergo ring opening with agents such as CN^-, N_3^-, RS^-, and R_2NH.[4,13] We have made use of this property to illustrate the potential of the alkynylated compounds as building blocks for synthesis. Accordingly, the polyhydroxylated indolizidine **10** was assembled in 34% overall yield through a six-step reaction sequence commencing from **1** (Scheme 1).[14] X-ray analysis of the first intermediate, a crystalline tosylate **7**, confirmed the cis product stereochemistry (Figure 3).[15] In addition to the selective formation of **7**, other salient features marking the synthesis of **10** include (1) stereoselective OsO_4-catalyzed olefin dihydroxylation (>20:1 ds); (2) facile and quantitative oxathiazinane ring opening using KCN; (3) efficient amidinium ion reduction with $NaBH_4$ in H_2O; and (4) the absence of any protecting groups.[16] In all, the pathway outlined from acetal **1** to indolizidine **10** offers a potentially general strategy for preparing other members of this large family of important alkaloid structures.[1a]

We have defined a new class of heterocyclic reagents for the synthesis of stereochemically complex, propargylic amine derivatives. Reactions of these compounds with alkynylzincs increase greatly the collection of structures that can be assembled through Rh-catalyzed sulfamate ester C−H insertion. The application of other nucleophiles for coupling to oxathiazinane *N*,*O*-acetals presents additional opportunities for invention and will be reported in due course.

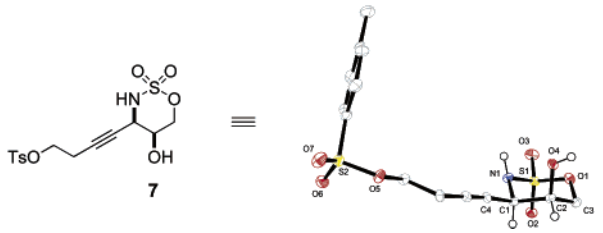


Figure 3. X-ray structure of **7** confirms cis-stereochemistry.

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Supporting Information Available: Experimental details and analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Diazoalkane C−H insertion reactions also occur preferentially at heteroatom-substituted C−H centers, see: (a) Sulikowski, G. A.; Lee, S. *Tetrahedron Lett.* **1999**, *40*, 8035−8038. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296−3305 and references thererin.

(6) Substrates that afford compounds **4** and **5** have three unique γ-CH_2 centers. We have never observed transannular C−H insertion, however, with any cycloalkanol-derived sulfamate.

(7) In select cases, purification of the insertion product is best performed using Davisil SiO_2, grade 643 (see the Supporting Information for details).

(8) Metal-acetylides have been employed in novel, highly selective addition reactions, see: (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535−2538. (b) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381 and references therein.

(9) For a comprehensive review of organozinc chemistry, see: Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417−731.

(10) Stereochemistry was determined by a combination of ^{1}H NMR coupling constant, NOE, and/or X-ray analysis.

(11) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.

(12) In entries 3 and 5 (Table 1), the product stereochemistry is in accord with the proposed model having the C5 substituent (R^1) positioned pseudoaxially and the C6 group (R^2) pseudoequatorially.

(13) Atfani, M.; Wei, L.; Lubell, W. D. *Org. Lett.* **2001**, *3*, 2965−2968.

(14) Carretero has reported the synthesis of **10**, see: Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993−3005 and references therein.

(15) Details for the X-ray structure of **7** are in the Supporting Information.

(16) The conversion of amidines to amines using $NaBH_4$ has been described previously, see: Okamoto, Y.; Kinoshita, T. *Chem. Pharm. Bull.* **1981**, *29*, 1165−1169. In our hands, these conditions proved uniquely effective for this rather unusual transformation.

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