



0040-4039(94)E0388-E

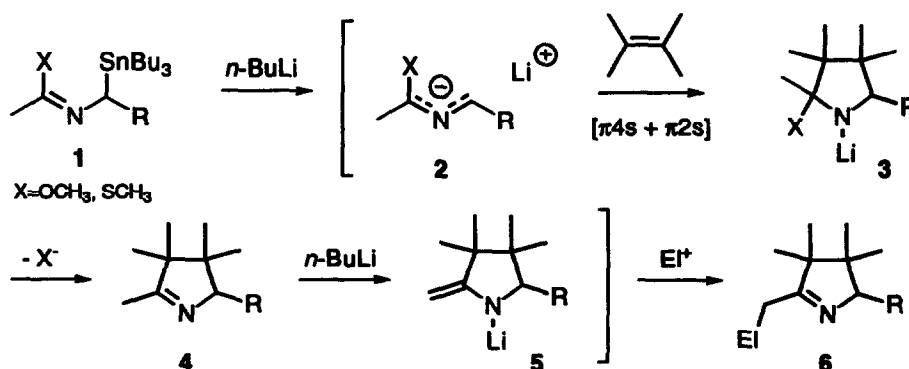
Generation and Cycloaddition of Heteroatom-Substituted 2-Azaallyl Anions with Alkenes and Alkynes. Synthesis of 1-Pyrrolines and Pyrroles

William H. Pearson* and Erland P. Stevens

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

Abstract: Imidates and thioimidates **1** bearing an N-(1-tri-*n*-butylstannyl)alkyl group (e.g., **7-9**) were transmetalated with *n*-BuLi to generate heteroatom-substituted 2-azaallyl anions **2**. These anions underwent [$2\pi+4\pi$] cycloadditions with alkenes to produce 1-pyrrolines **4** after loss of alkoxide or thiolate. The pyrrolines were further deprotonated *in situ* with *n*-BuLi to generate 1-metalloenamines **5**, which could be quenched with water or CH₃I to produce 1-pyrrolines **4** or **6**. The use of diphenylacetylene in the cycloaddition resulted in the formation of a pyrrole.

We have previously described the synthesis of pyrrolidines by the [$\pi 4s+\pi 2s$] cycloaddition of non-stabilized 2-azaallyl anions with electron-rich alkenes.^{1,2} The anions were generated by tin-lithium exchange of 2-azaallyl stannanes. The 2-azaallyl anion method is complementary to azomethine ylide cycloaddition chemistry, since the latter species generally require electron-poor dipolarophiles.³ We now wish to describe the generation and cycloaddition chemistry of heteroatom-substituted 2-azaallyl anions **2**, which allow access to 1-pyrrolines **4** and **6** (Scheme 1).



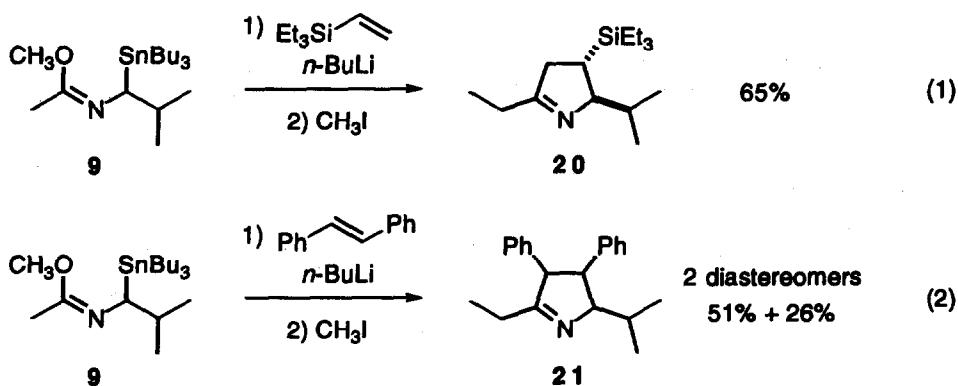
Scheme 1. Generation and Cycloaddition of Heteroatom-Substituted 2-Azaallyl Anions **2**.

The archetype for the conversion of an alkene to a 1-pyrroline involves the cycloaddition of a nitrile ylide.⁴ The cycloaddition of aryl-substituted nitrile ylides $\text{ArC}=\text{N}(+)\text{C}(-)\text{HR}$ with electron-poor dipolarophiles has been widely studied. Nitrile ylides without aromatic substitution are rare.^{5,6} Heteroatom-substituted azomethine ylides have been used frequently as synthetic equivalents of a nitrile ylides in cycloadditions with electron poor dipolarophiles.⁷⁻¹² The reactions of certain stabilized heteroatom-substituted 2-azaallyl

anions^{13,10c} or N-metalloazomethine ylides⁵ with carbonyl compounds or electron-poor alkenes have also been studied. In order to complement the approach to 1-pyrrolines based on heteroatom-substituted 1,3-dipoles, we felt that the higher reactivity of 2-azaallyl anions would allow cycloaddition with less reactive alkenes. We wish to report that non-stabilized heteroatom-substituted 2-azaallyl anions **2** may be generated by tin-lithium exchange on stannyl imidates and thioimidates **1**. These anions undergo cycloadditions with relatively electron-rich alkenes, producing intermediate N-lithiopyrrolidines **3**, which undergo loss of alkoxide or thiolate to give 1-pyrrolines **4**. Under the basic reaction conditions, **4** is deprotonated to give the metalloenamine **5**. This may be quenched with water to regenerate **4**, or may be alkylated to give a different 1-pyrroline **6**.

The tin-substituted imidates and thioimidates **7-9**¹⁴ were mixed with various anionophiles (1 equiv.) and added to *n*-BuLi (ca. 5 equiv.) in THF at -78 °C. After about 30 minutes, workup with aqueous NH₄Cl and column chromatography (SiO₂) afforded good to excellent isolated yields of the pyrrolines **10-18** (Table 1).¹⁵ The use of an acetylenic anionophile provided the pyrrole **19** in modest yield. Particularly noteworthy is the opposite regioselectivity observed in entries 1 and 2, where the only difference is the heteroatom substituent (oxygen versus sulfur) on the 2-azaallyl anion. The generality of this regioselectivity is currently under investigation. The shift in regioselectivity observed in entries 1 and 3 is also notable. In both cases, the most crowded regioisomer is formed selectively. Complete regiocontrol was observed in the cycloaddition with a vinyl silane (entry 4). Entries 5 and 6 produce the same products **15-18**, even though the geometry of the anionophile is different. Normally, we observe stereospecificity with respect to the alkene geometry.¹ However, imines with adjacent aromatic substituents are capable of undergoing imine-enamine tautomerization,^{16,17} which allows scrambling of the stereochemistry of these cycloadducts. The formation of oxidized products, tentatively assigned as **17** and **18**, presumably occurs by air oxidation upon purification. Norbornene and ethyl acrylate were unsuccessful in attempted cycloadditions using **9**.

The use of at least 2 equivalents of *n*-BuLi was found to be necessary because of *in situ* deprotonation of the initial pyrroline products **4** to form metalloenamines **5**. The presence of **5** was shown by workup of the cycloadditions with methyl iodide, which led to the formation of the 2-ethyl pyrrolines **20** and **21** in good yield (eq. 1,2).



In conclusion, the cycloaddition of oxygen- and sulfur-substituted 2-azaallyl anions with alkenes is complementary to 1,3-dipolar methods for making 1-pyrrolines. These anions are far more reactive (i.e., cycloaddition occurs at -78 °C), allowing the use of relatively electron-rich alkenes. Metalloenamines are formed, which are known to be useful synthetic intermediates for further functionalization. Finally, a striking difference in the regioselectivity of oxygen- versus sulfur-substituted 2-azaallyl anions was observed. We are currently exploring this interesting selectivity, as well as nitrogen-substituted 2-azaallyl anions and particularly anions bearing a chiral heteroatom-linked auxiliary for asymmetric cycloadditions.

Table I. Generation and Cycloaddition of Heteroatom-Substituted 2-Azaallyl Anions

Entry	Stannane	Anionophile	Product(s)	Yield, Ratio ^a
1				88% (10:1) ^b
2				65% (1:4.5) ^b
3				80% + 13%
4				97%
5				85% (6.8:1.2:5.2:1) ^c
6				93% (1:3.0:3.6:2.8) ^d
7				33%

(a) Isolated, chromatographed yields. (b) Isomers not separated. (c) Isolated yield of three chromatographic fractions: 41% of 15, 22% of a 1:2 mixture of 16 and 17, and 22% of a 3:1 mixture of 17 and 18. (d) Isolated yield of three chromatographic fractions: 9% of 15, 59% of a 1:1.2 mixture of 16 and 17, and 25% of 18.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

NOTES AND REFERENCES

- (1) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett* **1988**, *29*, 761-764. (b) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354-6357. (c) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329-1345.
- (2) For a review of 2-azaallyl anion chemistry, see: Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627-639.
- (3) (a) Lown, W. J. In *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; Wiley: New York, 1984; Vol. 1; pp 663-732. (b) Pearson, W. H. In *Studies in Natural Products Chemistry*; A. Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1; pp 323-358. (c) Vedejs, E. In *Advances in Cycloaddition*; D. P. Curran, Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1; pp 33-51. (d) Tsuge, O.; Kanemasa, S. *Adv. Het. Chem.* **1989**, *45*, 231-349.
- (4) Hansen, H.-J.; Heimgartner, H. In *1,3-Dipolar Cycloaddition Chemistry*; A. Padwa, Ed.; Wiley: New York, 1984; Vol. 1; pp 177-290.
- (5) (a) Turro, N. J.; Cha, Y.; Gould, I. R.; Padwa, A.; Gasdaska, J. R.; Tomas, M. *J. Org. Chem.* **1985**, *50*, 4415-4417. (b) Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y.; Gould, I. R. *J. Am. Chem. Soc.* **1986**, *108*, 6739-6746. (c) Padwa, A.; Gasdaska, J. R.; Haffmanns, G.; Rebello, H. *J. Org. Chem.* **1987**, *52*, 1027-1035.
- (6) Berrée, F.; Marchand, E.; Morel, G. *Tetrahedron Lett.* **1992**, *33*, 6155-6158.
- (7) (a) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1980**, *102*, 7993-7994. (b) Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773-4774. (c) Vedejs, E.; Larsen, S.; West, F. G. *J. Org. Chem.* **1985**, *50*, 2170-2174. (d) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941-955.
- (8) (a) Padwa, A.; Haffmanns, G.; Tomas, M. *Tetrahedron Lett.* **1983**, *24*, 4303-4306. (b) Padwa, A.; Chen, Y.-Y.; Koehler, K. F.; Tomas, M. *Bull. Soc. Chem. Belg.* **1983**, *92*, 811-817. (c) Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314-3322.
- (9) (a) Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 210-211. (b) Smith, R.; Livinghouse, T. *J. Org. Chem.* **1983**, *48*, 1554-1555. (c) Smith, R.; Livinghouse, T. *Tetrahedron* **1985**, *41*, 3559-3568.
- (10) (a) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1985**, 1411. (b) Tsuge, O.; Kanemasa, S.; Matsuda, K. *J. Org. Chem.* **1986**, *51*, 1997-2004. (c) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523-30.
- (11) (a) Alanine, A. I. D.; Fishwick, C. W. G. *Tetrahedron Lett.* **1989**, *30*, 4443-4446. (b) Alanine, A. I. D.; Fishwick, C. W. G.; Szantay, C., Jr. *Tetrahedron Lett.* **1989**, *30*, 6573-6576.
- (12) (a) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537-3545. (b) Jones, R. C. F.; Nichols, J. R.; Cox, M. T. *Tetrahedron Lett.* **1990**, *31*, 2333-2336. (c) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813-5816. (d) Lerestif, J. M.; Bazureau, J. P.; Hamelin, J. *Tetrahedron Lett.* **1993**, *34*, 4639-4642.
- (13) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett* **1984**, 1827.
- (14) *Imidate 7*: Treatment of Bu₃SnCH₂I with acetamide (5 equiv.) and NaH (1 equiv.) in THF/DMF at 0 °C gave AcNHCH₂SnBu₃ (65%). Heating this material with neat Me₂SO₄ (1 equiv.) at 60 °C gave **7** (61%, Kugelrohr distillation). *Thioimidate 8*: Treatment of AcNHCH₂SnBu₃ with Lawesson's reagent in THF using ultrasound gave CH₃C(S)NHCH₂SnBu₃ (49%), which was alkylated with Me₂SO₄ (1 equiv., neat, 23 °C) to produce **8** (85%, Kugelrohr distillation). *Imidate 9*: Prepared from AcNHCH(Bt)CHMe₂ (Katritzky, A. R.; Drewniak, M.; Lue, P. *J. Org. Chem.* **1988**, *53*, 5854-5856, Bt = benzotriazolyl) by the following sequence: (1) 2 eq. Bu₃SnLi, THF, 0 °C (86%); (2) Me₂SO₄ (1 equiv.), neat, 60 °C (74%, Kugelrohr distillation). See: Pearson, W. H.; Stevens, E. P. *Synthesis* **1994**, 0000.
- (15) The stereochemical assignments of the cycloadducts **12-14** were based on NOE studies.
- (16) Burchalter, J. H.; Short, J. H. *J. Org. Chem.* **1958**, *23*, 1278-1281.
- (17) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783-6789.

(Received in USA 14 December 1993; revised 8 February 1994; accepted 17 February 1994)