

Communications

A Stereoselective Approach to the Synthesis of Allylic and Homoallylic Amines



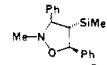

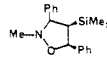

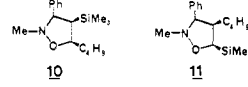

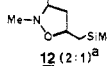

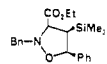
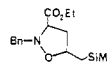

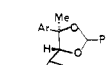
Summary: Nitrones undergo [3 + 2] dipolar cycloaddition with vinyl- and allylsilane derivatives to produce substituted isoxazolidines which are versatile intermediates for the preparation of allylic and homoallylic amines. During olefination, the alkene geometry can be controlled by the appropriate selection of reaction conditions.

Sir: Dipolar cycloaddition of nitrones with alkenes is an efficient method for the simultaneous introduction of a nitrogen substituent and creation of a carbon-carbon bond,²⁻⁴ and this strategy has been extensively exploited in the synthesis of alkaloidal natural products.^{5,6} We have recently demonstrated that nitrono cycloadditions with vinyltrimethylsilane⁷ occurs with complete regioselectivity and high stereoselectivity. The resulting 5-silyl-isoxazolidines can be transformed into β -amino aldehydes and α,β -unsaturated aldehydes, respectively.

In this communication we report that *substituted* vinylsilanes and allyltrimethylsilane undergo facile nitrono addition to produce isoxazolidines. The regioselectivity and stereoselectivity of the cycloaddition depends upon the silane employed. These silyl isoxazolidines are versatile intermediates for organic synthesis and can be transformed into allylic or homoallylic amines.

Nitrones 1-3⁸ underwent dipolar cycloaddition with vinylsilanes 4-6⁹ and allyltrimethylsilane (7), in good yield as indicated by the results in Table I. Nitrones incorporating either an aryl or carboethoxy group appear to function equally well in the cycloaddition, and even the sensitive benzylidene acetal moiety of nitrono 3 was tolerated.

The regioselectivity of cycloaddition depended upon the particular silane employed as the dipolarophile. With (arylvinyl)silanes 4 and 5, 4-(trimethylsilyl)isoxazolidines 8 and 9, respectively, were the only regioisomers produced in the cycloaddition. The aryl group on the alkene controlled the regioselectivity of the cycloaddition.¹⁰ Alkyl vinylsilane 6, however, displayed diminished regioselectivity and gave a 7:3 mixture of isoxazolidines in which the 4-silyl regioisomer predominated. These results were surprising since we had previously demonstrated that vinyltrimethylsilane underwent cycloaddition with nitrones to produce the 5-silyl isoxazolidines with complete regioselectivity. This alteration in regioselectivity of the cycloaddition is presumably a manifestation of subtle changes in the HOMO/LUMO coefficients of the silanes induced by the addition of substituents.¹²

entry	nitrono	silane	products	yield, % ^b
1				60
2	1			60
3	1			70
			10 : 11 = 7 : 3 ^c	
4	1			95
5		5		65
6	2	7		91
7		7		87

^a Numbers in parentheses represent the ratio of stereoisomers. Ratios were determined by isolation or ¹H NMR analysis (360 MHz). ^b Yield of product mixture after purification by chromatography. Purity is $\geq 95\%$. ^c A mixture of regioisomers 10 and 11 in a ratio of 7:3. Each regioisomer is a single stereoisomer of undefined stereochemistry.

Allyltrimethylsilane (7) displayed total regioselectivity in the nitrono cycloaddition to produce 5-(trimethylsilyl)methylisoxazolidines 12, 14, and 15 (entries 4, 6, 7; Table I). The regiochemistry of the cycloadducts was established by decoupling experiments.¹³

The nitrono cycloaddition also displayed modest stereoselectivity with silane dipolarophiles as indicated in Table I. Because the stereocenters at C-4 and C-5 in the corresponding isoxazolidines are lost in subsequent

- (1) Air Force Institute of Technology Graduate Fellow.
 (2) Huisgen, R.; Grashy, R.; Seidl, H.; Hauck, H. *Chem. Ber.* 1968, 101, 2559.
 (3) LeBel, N. A.; Post, M. E.; Hwang, D. *J. Org. Chem.* 1979, 44, 1819 and references cited therein.
 (4) For reviews of nitrono chemistry, see: (a) Hamer, J.; Macaluso, A. *Chem. Rev.* 1964, 64, 473. (b) Black, D. S. C.; Crozier, R. F.; Davis, V. C. *Synthesis* 1975, 205. (c) Padwa, A. *Angew. Chem., Int. Ed. Engl.* 1976, 15, 123. (d) Oppolzer, W. *Ibid.* 1977, 16, 10.
 (5) Tufariello, J. J. *Acc. Chem. Res.* 1979, 12, 396 and references cited therein.
 (6) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* 1984, 106, 5598. DeShong, P.; Leginus, J. M. *Tetrahedron Lett.* 1984, 25, 5355.
 (7) DeShong, P.; Leginus, J. M. *J. Org. Chem.* 1984, 49, 3421.
 (8) The nitrones are routinely prepared in excellent yield by the reaction of an aldehyde and the appropriate N-substituted hydroxylamine.^{6,7}
 (9) Miller, R. B.; McGarvey, G. *J. Org. Chem.* 1978, 43, 4424. Eisch, J. J.; Foxton, N. W. *J. Org. Chem.* 1971, 36, 3520.
 (10) Huisgen demonstrated that styrene adds to nitrones to produce exclusively the 5-phenylisoxazolidine. See: Huisgen, R.; Echsell, A. *Tetrahedron Lett.* 1960, 12, 9.
 (11) Assignment of regiochemistry was made by analysis of the ¹H NMR spectra of the cycloadducts. For the 5-(trimethylsilyl)isoxazolidines the chemical shift of the proton at C-5 was approximately δ 3.9, whereas, the C-5 proton of the 4-(trimethylsilyl)isoxazolidines was observed at δ 4.3. (Compare 10, and 12 with 11.) Decoupling experiments also supported this assignment.

(12) We are currently performing molecular orbital calculations to verify this point. DeShong, P.; Lowe, J. P.; LaFemina, J., unpublished results.

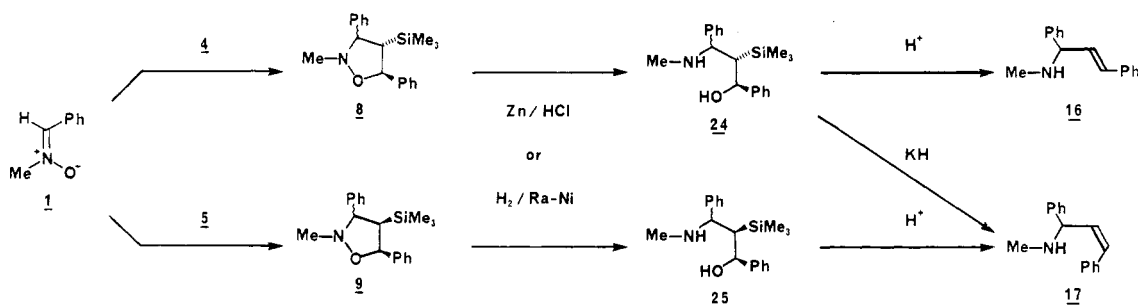
(13) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. J. *J. Org. Chem.* 1982, 47, 4397.

Table II

entry	isoxazolidine	conditions ^a	product	yield, %	entry	isoxazolidine	conditions ^a	product	yield, %
1		A		87	7		B		78
2		C,E		75	8		C,E		71
3		C,F		84	9		D		78
4		A		75	10		G		48
5		A		89					
6		C,F		64					

^a Single alkene geometry by gas chromatography (>99% purity). ^b Single alkene by ¹H NMR (>95% purity). ^c (A) Zn/10% HCl (aqueous), THF (1:1 v/v), 50 °C, 1 h; (B) Zn/HCl, EtOH (1 M), 50 °C, 1 h; (C) H₂, Raney Ni (W-2)/20% NaOH (aqueous), MeOH (1:10 v/v), 12 h room temperature; (D) (i) H₂, Raney Ni (W-2)/EtOH, 12 h, room temperature, (ii) HCl, EtOH (1 M), 50 °C, 4 h; (E) H₂SO₄ (catalytic)/THF, 16 h, room temperature; (F) KH/THF, 1 h, room temperature; (G) (i) Zn, HOAc-H₂O (2:1 v/v), 18 h, 80 °C, (ii) Ac₂O, pyridine, 6 h, room temperature, (iii) Bu₄N⁺F⁻, 70 °C, 1 h.

Scheme I



transformations, the relative configuration of the stereoisomers was not determined.

As shown in Table II, reductive cleavage of the N,O bond of isoxazolidines derived from substituted vinylsilanes followed by Peterson olefination¹⁴ resulted in the formation of allylic amines with a single alkene geometry (entries 1–7, Table II).¹⁵ This approach to the preparation of allylic amines is especially useful because the geometry of the alkene can be controlled by choice of elimination conditions. For instance, nitrone 1 reacted with *E* silane 4 and *Z* silane 5 to give isoxazolidines 8 and 9, respectively. Treatment of 8 with Zn/HCl resulted in cleavage of the N,O bond and concomitant stereospecific anti elimination of trimethylsilanol¹⁴ to give (*E*)-alkene 16 (entry 1, Table II). Analogous treatment of isoxazolidine 9 gave (*Z*)-alkene 17 (entry 4; Table II). Alternatively, alkenes 16 and 17 could be prepared stereospecifically from isox-

azolidine 8 by a two-step process in which Raney nickel reduction of 8 allowed isolation of the corresponding amino alcohol 24. Stereospecific anti elimination¹⁴ from 24 produced 16, while KH-promoted syn elimination¹⁴ gave 17 (see Scheme I).

Homoallylic amines¹⁵ 21–23 were prepared from the allyltrimethylsilane derived adducts 12, 14, and 15, respectively, by reduction of the N,O bond followed by elimination of trimethylsilanol.¹⁶

The results summarized in this communication indicate that the isoxazolidines derived from cycloadditions of nitrones with vinylsilanes and allyltrimethylsilane are versatile synthetic intermediates which can be elaborated into allylic and homoallylic amines, respectively. The application of this methodology to the total synthesis of natural products is in progress and will be reported in due course.

Acknowledgment. We acknowledge the National Institutes of Health for generous financial support (GM

(14) Peterson, D.; Hudrlík, P. F. *J. Am. Chem. Soc.* **1975**, *97*, 1464 and references cited therein.

(15) Alternative methods for the preparation of allylic amines: Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218 and references cited therein. For alternative methods for the preparation of homoallylic amines, see: Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146 and references cited therein.

(16) For another recent synthesis of 21 via 12, see: Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049.

(17) LeBel, N., Wayne State University, personal communication.

30743). We thank Dr. Robert Minard and Greg Hancock for help in obtaining mass spectra and Alan Freyer and Dr. V. Elango for FT NMR spectra. We thank Dr. Normal LeBel for informing us prior to publication of similar results obtained in his laboratory concerning nitrene-vinylsilane cycloadditions.¹⁷

Registry No. 1, 3376-23-6; 2, 99948-25-1; 3, 91328-47-1; 4, 19372-00-0; 5, 19319-11-0; 6, 52835-06-0; 7, 762-72-1; 8 (isomer 1), 99948-26-2; 8 (isomer 2), 99948-41-1; 9 (isomer 1), 99948-27-3; 9 (isomer 2), 99948-42-2; 10, 99948-28-4; 11, 99948-29-5; *cis*-12, 99948-30-8; *trans*-12, 99948-43-3; 13, 99948-31-9; *cis*-14, 99948-32-0; *trans*-14, 99948-44-4; 15, 99948-33-1; 16, 99948-34-2; 17, 99948-35-3; 18, 99948-36-4; 19, 99948-37-5; 20, 99948-38-6; 21, 49603-23-8; 22, 99948-39-7; 23, 99948-40-0; 24, 99948-45-5.

Supplementary Material Available: Preparation, reduction, and elimination procedures for applicable compounds and spectral data for isoxazolidines 8–15 (3 pages). Ordering information is given on any current masthead page.

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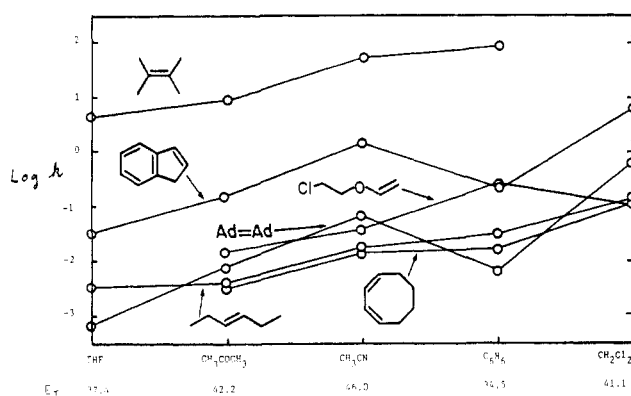
Additions and Corrections

Vol. 49, 1984

Chen-Chih Cheng, Catherine A. Seymour, Michael A. Petti, Frederick D. Greene,* and John F. Blount. Reaction of Electrophiles with Unsaturated Systems: Triazolinedione-Olefin Reactions.

Page 2912, column 2, Figure 3. Identification and values of the abscissa and the ordinate are missing. A complete version of Figure 3 is shown below.

Effect of solvent on rates of reaction of olefins with RTAD: tetramethylethylene,¹² indene,¹² adamantylideneadamantane,¹² 2-chloroethyl vinyl ether,^{3a} and *trans*-3-hexene^{2b,12} with PhTAD at 25 °C; 1,3-cyclooctadiene¹¹ with MeTAD at 20 °C.



Vol. 50, 1985

Herbert C. Brown,* David L. Vander Jagt, Irvin Rothberg, W. James Hammar, and James H. Kawakami. Structural Effects in Solvolytic Reactions. 50. Steric Retardation in the Solvolysis of Tertiary Endo Bicyclic Derivatives. Evidence That the Exo:Endo Rate/Product Ratios for Typical Reactions in Rigid U-Shaped Bicyclics is a General Steric Phenomenon.

Page 2185. The relative rate for 13 is incorrect. It should be 1/23.

Stanley J. Cristol* and M. Zaki Ali. Photochemical Transformations. 38. Novel Transformations of Diarobicyclo[3.2.1]-octadienes to Phenanthrenes and Dihydrophenanthrenes.

Page 2502. The scheme which should have been designated as III is described as II, and vice versa.

Cornelis J. Elsevier and Peter Vermeer*. Stereochemistry of the Palladium(0)-Catalyzed Phenylation of 1-Halogenoallenes.

Page 3044. In Scheme IV the complexes 8 and 9 should be numbered 7 and 8, respectively. The radical pair in Scheme VI should not be numbered.

Add ref 3c: Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* 1980, 21, 5019.

William G. Dauben,* Vincent P. Rocco, and Gideon Shapiro. Intramolecular [2 + 2] Photocycloaddition of 4-Substituted Cyclopent-2-en-1-ones.

Page 3157, column 2. In General Procedure for Analytical Irradiations, 3rd line, correct 1 mg/L to read 1 mg/mL.

David J. Hart* and Won-Pyo Hong. Lythraceae Alkaloids: Total Synthesis of (±)-Lythrancepine II.

Page 3671, line 5: (12) should be (11).

Theodore Cohen,* Lin-Chen Yu, and Wlodzimierz Daniewski. Sulfur-Assisted Ring Expansion of the Potassium Salts of 1-Vinylcyclobutanols. A Versatile Synthesis of Cyclohexanones.

Page 4598. A vinyl group was omitted from compound 16. The correct structure is

