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Intramolecular Cycloaddition Reactions of Silyl Nitronate Tethered to Vinylsilyl Group: 2-Nitroalkanols as Precursors for Amino Polyols

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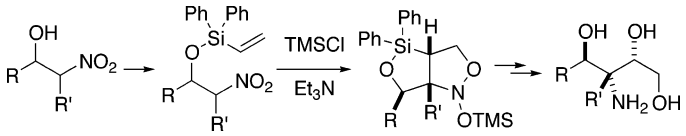
ABSTRACT



A method for converting 2-nitroalkanols to precursors for stereodefined amino polyols is described. Diphenylvinylsilylation of the 2-nitroalkanols' hydroxy groups and subsequent silyl nitronate generation by using TMS-Cl and Et_3N in CH_3CN at 0 °C to room temperature led to fused-bicyclic heterocycles through stereoselective intramolecular nitronate-olefin [3 + 2] cycloaddition reaction. Some examples for transforming the cycloadducts to amino polyols are also presented.

Silicon-tethered strategies for controlling regio- and stereoselectivity of 1,3-dipolar cycloaddition reactions have received much attention and been accepted as a powerful tool for the construction of complex molecules.[1] In our own efforts pertinent to this field, we have disclosed the potential of silicon-tethered intramolecular nitrone cycloaddition as an efficient method for the synthesis of stereodefined amino polyols as shown in Scheme 1 (*route A*).[2] In this transformation, a chiral α- or *β*-hydroxy ester can lead to a nitrone (**B**) through a series of reactions involving DIBALH reduction, introduction of a vinylsilyl group to a hydroxy group (**A**), and condensation with an *N*-benzylhydroxylamine. Thus-obtained silicon-tethered system **B**, on being heated at elevated temperature, afforded a cycloadduct (**C**) with a high level of diastereoselectivity as a precursor for an amino polyol (**D**).

Relying again on the silicon-tethered strategy of this class, we have undertaken further development of a method for synthesizing amino polyols of type **H** concerned with *route B*. We thought that if 2-nitroalkanols (**E**) are treated with a chlorovinylsilane reagent in the presence of base, double silylation of **E** at both the hydroxy and nitro groups might proceed. In addition, the silylation of nitro group would result in the formation of a silyl nitronate under the conditions. Thus, **E** could lead to desired system **F** in one pot under the reaction conditions as indicated above. Probably, **F** would immediately undergo cycloaddition reaction in the same pot, giving rise to isoxazolidines (**G**), which could be a precursor for intended amino polyols **H**.

To the best of our knowledge, there has been no previous report concerned with *route B*.[3] Due to the apparent advantages such as ready availability of 2-nitroalkanols **E** via the Henry reaction[4] and the operational simplicity of a process, *route B* deserves consideration in terms of practicality. Furthermore, recent advances in catalytic asymmetric Henry reactions[5] will make *route B* highly attractive. Also, stereo-

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(1) (a) Rong, J.; Roselt, P.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 4921−4936. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc*. **1996**, *118*, 9446−9447. (c) Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J*. **1998**, *4*, 2501−2512. (d) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem*. **1997**, *621*, 1668−1674. (e) Garner, P.; Cox, P. B.; Anderson, J. A.; Protasiewicz, J.; Zaniewski, R. *J. Org. Chem*. **1997**, *62*, 493−498. (f) Young, D. G. J.; G.-Bengoa, E.; Hoveyda, A. H. *J. Org. Chem*. **1999**, *64*, 692−693. (g) Marrugo, H.; Dogbéavou, R.; Breau, L. *Tetrahedron Lett*. **1999**, *40*, 8979−8983.

(2) Ishikawa, T.; Kudo, T.; Shigemori, K.; Saito, S. *J. Am. Chem. Soc*. **2000**, *122*, 7633−7637.

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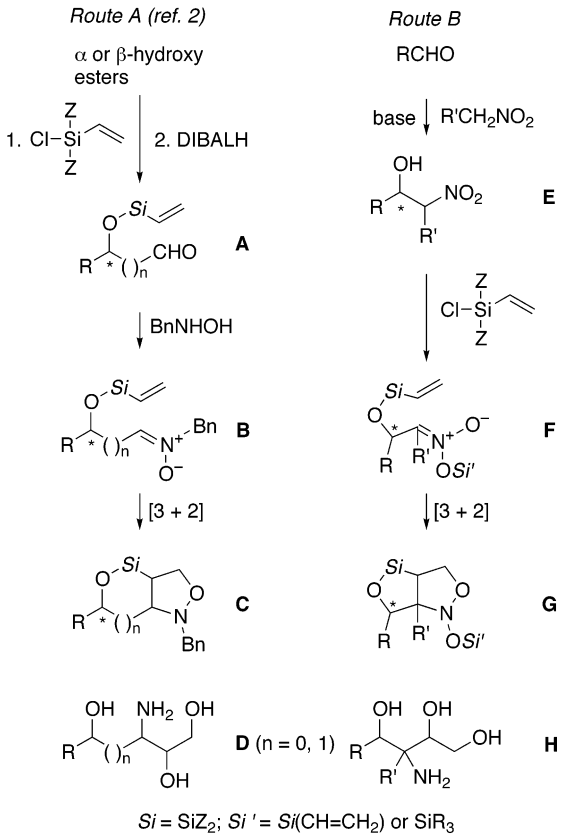
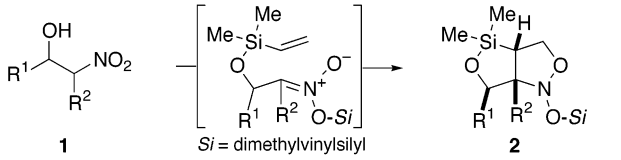
Scheme 1. Silicon-Tethered Intramolecular [3 + 2] Cycloaddition Reactions



chemical outcomes of the cycloaddition may be predictable on the basis of a possible bicyclo[3.3.0]-type transition state and, hence, might result in a very high level of stereoselectivity because of the rather rigid transition state structure of this class.[2] In this communication are described the successful results of not only the cycloaddition reaction (**F** to **G**) but also some examples for the conversion of the cycloadducts to amino polyol derivatives including a ribose backbone.

Table 1 summarizes the results of one-pot conversions of 2-nitroalkanols (**1**) to isoxazolidines (**2**) by treatment with chlorodimethylvinylsilane (220 mol %) in acetonitrile in the presence of triethylamine (400 mol %) and a catalytic amount of DMAP. The desired cycloaddition reactions proceeded at 0 °C to room temperature after mixing **1** with the silylation agent at 0 °C, although prolonged reaction time was sometimes required. Then, after a usual aqueous workup, all the volatile components were removed under reduced pressure and finally under high vacuum to afford **2a**−**i**. Thus-obtained adducts were so pure that we could not only determine % yields on the basis of recovered weight but also subject the adducts to NMR experiments for structure elucidation or diasteremeric ratio analysis. NOE data gave the unequivocal structures of these adducts. A very high diastereomeric ratio (>99:1) generally resulted except for the cases of **1a**,**b** (dr = 5:1, entries 1 and 2 in Table 1).[6]

Table 1. One-Pot Conversion of 2-Nitroalkanols **1** to Isoxazolidines **2**[a]



1 **2**

entry	**1**	R^1	R^2	time, h	**2**	yield, % (dr)[b]
1	**1a**	isopropyl	H	24	**2a**	75 (5:1)
2	**1b**	*n*-pentyl	H	24	**2b**	78 (5:1)
3	**1c**	cyclohexyl	H	10	**2c**	90 (>99:1)
4	**1d**	phenyl	H	8	**2d**	82 (>99:1)
5	**1e**	phenyl	Me	30	**2e**	93 (>99:1)
6	**1f**	4-(OMe)phenyl	H	12	**2f**	82 (>99:1)
7	**1 g**	4-(OMe)phenyl	Me	25	**2g**	88 (>99:1)
8	**1h**	2-furyl	H	14	**2h**	82 (>99:1)
9	**1i**	2-furyl	Me	24	**2i**	95 (>99:1)

[a] Conditions: chlorodimethylvinylsilane (220 mol %), Et_3N (400 mol %), DMAP (catalytic amount)/MeCN, 0 °C to room temperature. [b] Based on products, which show very high purity by NMR diagnosis, obtained by exhaustively removing the volatiles under high vacuum after an aqueous workup; diastereomeric ratios (dr) determined by NMR are indicated in parentheses.

Unfortunately, however, those cycloadducts **2a**−**i** were too labile to be purified by silica gel chromatography or to be transformed to amino polyols under the conditions employed for reductive cleavage of two of N−O bonds or well-known oxidation of Si−C bonds by Tamao's procedures.[7] A difficult to identify, multicomponent mixture was obtained for these transformations.

After screening silylation agents for both the hydroxyl and nitro groups, we found that chlorodiphenylvinylsilane for the former and chlorotrimethylsilane for the latter gave a solution to this problem.[8] Thus, a hydroxyl group of **1a**−**f** was selectively silylated with chlorodiphenylvinylsilane and imi-

(3) When 4-hydroxy-2-isoxazoline-2-oxides, prepared through base-promoted reaction of aldehydes bearing a leaving group on the α carbon with *activated primary nitroalkanes*, were treated with TMS-Cl (1 equiv) and imidazole at room temperature, heterotricyclic compounds were obtained as precursors for linear aminopolyhydroxylated structures; see ref 1c. Tandem inter [4 + 2]/intra [3 + 2] cycloaddition between siloxynitroalkene and chiral vinyl ether was successfully used for the synthesis of cyclic polyhydroxylated amine structures; see ref 1d. For a review, see: Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp 263−274.

(4) (a) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261−1264. (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 321−340; see also the review in ref 3, pp 30−65.

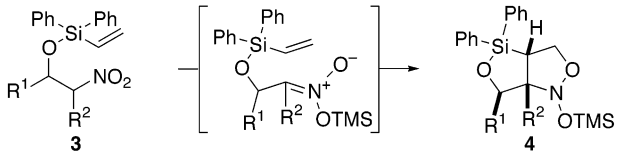
(5) (a) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372−10373. (b) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861−863 (c) For review, see: Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1075−1090.

(6) All of the products gave satisfactory spectroscopic data (NMR, IR, and MS). The stereochemistry of all of the cycloadducts was determined by NOE measurements and J_{H-H} values; see Supporting Information.

(7) For reviews, see: (a) Tamao, K. In *Advances in Silicon Chemistry*; Larson, G. L., Ed.; Jai Press: Greenwich, 1996; Vol. 3, pp 1−62. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *57*, 7599−7662. See also: (c) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694−1696.

dazole to **3a**−**f**, which were purified by passing through a silica gel pad. When thus-purified **3a**−**f** were dissolved in CH_3CN followed by the addition of TMS-Cl (150 mol %) and triethylamine (200 mol %) at 0 °C, the formation of silyl nitronate resulted, and the desired cycloaddition reactions immediately followed at 0 °C to room temperature. The results pertinent to this transformation are summarized in Table 2.

Table 2. Conversion of *O*-(Diphenylvinylsilyl)-2-nitroalkanols **3** to Isoxazolidines **4**[a]



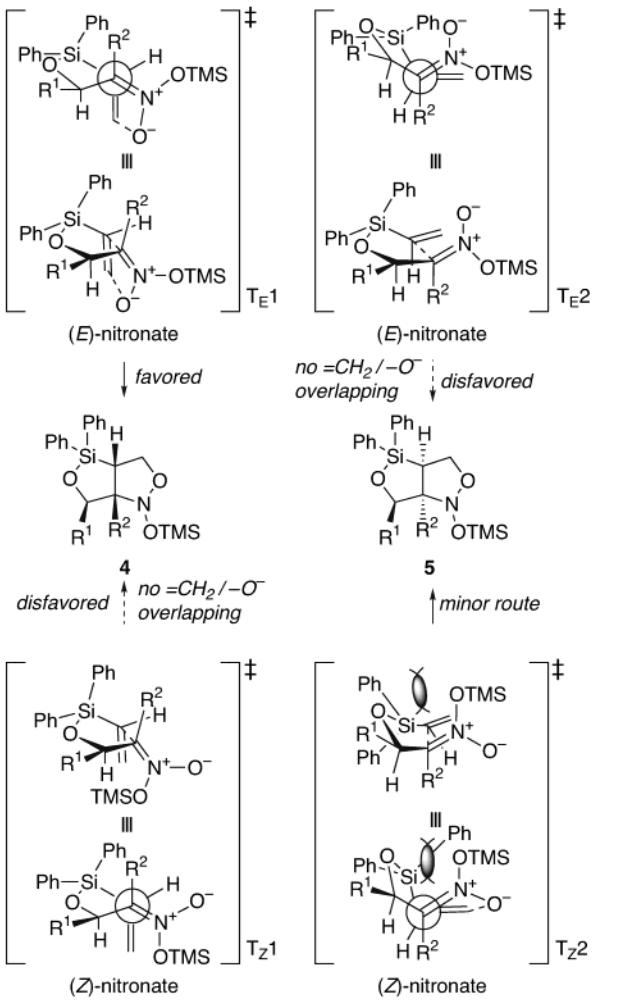
entry	**3**	R^1	R^2	time, h	**4**	yield, % (dr)[b]
1	**3a**	isopropyl	H	3	**4a**	99 (5:1)
2	**3b**	*n*-pentyl	H	9	**4b**	99 (5:1)
3	**3c**	*n*-pentyl	Me	96	**4c**	92 (>99:1)
4	**3d**	phenyl	H	5	**4d**	94 (>99:1)
5	**3e**	phenyl	Me	25	**4e**	95 (>99:1)
6	**3f**	4-(OMe)phenyl	H	9	**4f**	98 (>99:1)

[a] Chlorotrimethylsilane (150 mol %), Et_3N (200 mol %), MeCN, 0 °C to rt. [b] Based on products, which show very high purity by NMR diagnosis, obtained by exhaustively removing the volatiles under high vacuum after an aqueous workup; diastereomeric ratios (dr) determined by NMR are indicated in parentheses.

In every case the cycloadducts (isoxazolidines **4a**−**f**) were furnished in almost quantitative yields with diastereomeric ratios almost equal to those for the dimethylvinylsilyl version **1** (Table 1). In sharp contrast to **1**, however, the cycloadducts were so stable that they could be purified by silica gel column chromatography. It should also be pointed out that nitrogen-linked quaternary stereogenic centers were uneventfully introduced with a very high level of diastereomeric ratios (entries 3 and 5 in Table 2), although the reactions were rather sluggish. Thus, a novel route to fused-heterobicyclic ring systems involving 1,2-oxasilolane and *N*-(trimethylsiloxy)isoxazolidine rings has been established featuring the Henry reaction, an *O*-diphenylvinylsilylation, a trimethylsilyl nitronate formation, and a [3 + 2] cycloaddition reaction.

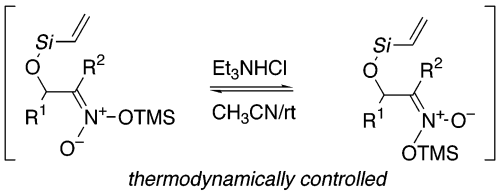
Scheme 2 shows possible transition states deduced from models leading to **4** (T_E1) and a minor diastereomer **5**[9] (T_Z2) (entries 1 and 2 in Tables 1 and 2): T_Z2 should suffer from severe $A^{1(3)}$-like strain between the N-OTMS and C-R^1 or C-OSi groups. For other transition states such as T_E2 and T_Z1, an expected cycloaddition seems impossible because of difficulty in overlapping between a terminal vinylic carbon and a negative end of the 1,3-dipole: this situation seems plausible when we represent T_E2 and T_Z1 by Newman projections arranging the developing carbon−carbon bond

Scheme 2



directly end on.[10] The formation of the minor product **5** may imply the existence of equilibrium between *E* and *Z* nitronates under the given reaction conditions as shown in Scheme 3.[11]

Scheme 3



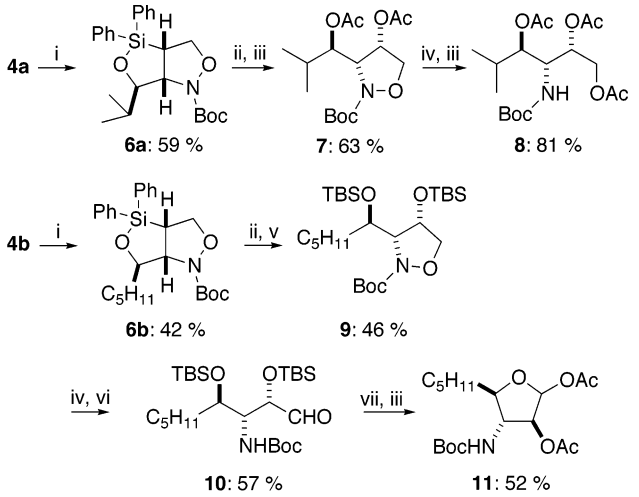
Transformations of cycloadducts **4** to amino polyols were successful, and representative examples are shown in Scheme

(8) When chlorodiphenylvinylsilane was employed as a bis-silylating agent, a difficult to separate, multicomponent mixture was furnished as products.

(9) The relative configuration of minor diastereomer was assigned as **5** by careful analysis of NMR spectra.

(10) It is possible to align the alkene with the dipole in T_Z1 and T_E2 by puckering the five-membered transition state structure down, instead of up. However, this leads to severe steric constraint between a phenyl group on the silicon atom and R^1 substituent in the transition state.

Scheme 4 [a]



[a] Conditions: (i) H_2, Pd−C, $(Boc)_2O$/AcOEt, rt, 45 h; (ii) KF, $KHCO_3$, 30% H_2O_2, THF−MeOH, rt, 30 min. (iii) Ac_2O, Et_3N, DMAP/CH_2Cl_2, rt 3 h; (iv) $Mo(CO)_6$, MeCN−H_2O, reflux, 8 h; (v) TBDMSOTf, Et_3N, CH_2Cl_2, rt; (vi) SO_3−Py, Et_3N/DMSO; (vii) TBAF, THF.

4. It turned out that a series of reactions involving reductive cleavage of an exocyclic N−O bond, oxidation of Si−C bond, and final cleavage of an endocyclic N−O bond was effective for this purpose in general.[12] For example, reductive cleavage of the exocyclic N−O bonds of **4a** or **4b** by means of catalytic hydrogenolysis in the presence of di-*tert*-butyl dicarbonate[13] afforded **6a** or **6b**, respectively. Tamao oxidation[7] of **6a** was followed by acetylation to give isoxazolidine **7**. $Mo(CO)_6$-mediated endocyclic N−O bond cleavage[14] of **7** gave **8** in acceptable yield. Similarly, **6b** was converted to **9** under the given reaction conditions. An N−O bond cleavage of **9** in a similar way as that of **7** to **8** conversion was followed by Palikh−Doering oxidation[15] to afford aldehyde **10**, which on treatment with TBAF in THF followed by acetylation led to 4-aminoribose derivatives **11** in good yield.

In conclusion, we have demonstrated that the intramolecular [3 + 2] cycloaddition reactions of silyl nitronate tethered to vinylsilyl group can provide a novel method for synthesizing fused heterobicyclic compounds involving 1,2-oxasilolane and *N*-(trimethylsiloxy)isoxazolidine rings as promising precursors for amino polyols. The 2-nitroalkanols available uneventfully through the Henry reaction can be employed as a starting material even in an optically active form if so desired.[5] Hence, the process will open a general strategy for the asymmetric synthesis of amino polyol derivatives including 5-substituted-4-aminoribose frameworks, a biologically important class of amino sugars.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for **2**, **4**, and **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) One promising indirect way of observing the existence of such geometrical isomers of the silyl nitronate is to analyze the products distribution for an appropriate intermolecular cycloaddition reaction. We have not done it yet. Two possible mechanisms deserve consideration for such a geometrical isomerization of the nitronate: one involves a protonation-deprotonation process and the other involves the 1,3-migration of a trimethylsilyl group from one oxygen to another oxygen. For discussion with respect to the 1,3-migration, see: Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697−710.

(12) No effort has been made to optimize each step of these transformations. It turned out that similar reaction conditions as those employed for **4a** or **4b** were ineffective for cycloadduct **4c** or **4e** having a tertiary carbon linking to the nitrogen atom,. We are now making extensive efforts to establish the reaction conditions applicable to the transformation of **4c** or **4e** to amino polyol derivatives, which will be published elsewhere.

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(14) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; Sarlo, F. D. *Tetrahedron Lett.* **1990**, *31*, 3351−3354.

(15) Parikh, J.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.