Silicon-Tethered 1,3-Dipolar Cycloaddition of 4-Hydroxy-2-isoxazoline 2-Oxides

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Recent reports from this laboratory have disclosed a stereocontrolled synthesis of *trans*- and *cis*-3-(ethoxycarbonyl)-4-hydroxy-5-substituted-2-isoxazoline 2-oxides **1** by a tandem nitroaldol (Henry)[1] -ring closure process from 2,3-epoxy aldehydes[2] and 2-bromo aldehydes[3] (Scheme 1).

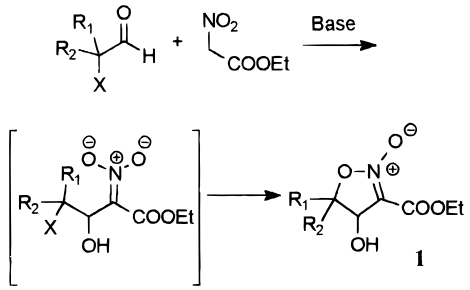
We anticipated that the dipolar character of these cyclic nitronates might be exploited for a regio- and stereospecific intramolecular 1,3-dipolar cycloaddition[4] with an olefinic counterpart aptly linked to the hydroxyl of the isoxazoline ring. In particular we were very attracted by the possibility to effect an unprecedented silicon-tethered[5] 1,3-dipolar cycloaddition.

The "temporary silicon connection" methodology, deeply investigated during the last few years by the Stork[6] and Tamao[7] groups, achieves the regio- and stereoselective formation of new bonds by temporarily linking together the two reactants by means of an eventually removable silicon atom.

We report here that racemic 4-hydroxy-2-isoxazoline 2-oxides **1** when treated with chlorodimethylvinylsilane[8] and imidazole in acetonitrile at room temperature gave previously unknown tricyclic compounds **2** in very good to excellent yields (Scheme 2). Table 1 summarizes the results obtained. To the best of our knowledge this is the first example of a silicon-tethered intramolecular 1,3-dipolar cycloaddition.[9,10]

The formation of tricyclic compounds occurs by a tandem process where the functionalization of the C(4) hydroxy group is followed by the intramolecular 1,3-dipolar cycloaddition where the cyclic nitronate acts as the dipole and the vinylsilane moiety as the dipolarophile. The cycloaddition step proceeds regiospecifically with the exclusive formation of the "fused" rings in opposition to the "bridged" system and stereospecifically with the exclusive formation of *cis*-fused isomers.[11]

Scheme 1. General Preparation of 4-Hydroxy-2-isoxazoline 2-Oxides



Scheme 2. General Preparation of Tricyclic Compounds **2**

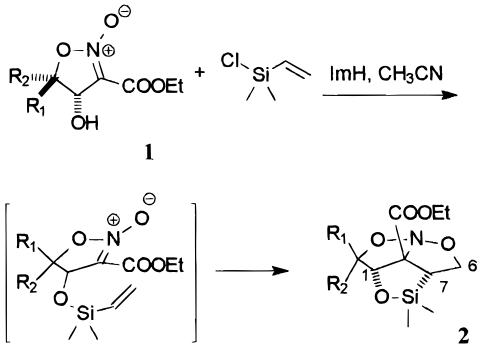


Table 1. Preparation of Tricyclic Compounds **2**

	t (h)	yield (%)
a: $R_1 = H$; $R_2 =$ *anti*-PhCH(OH)	48	95
b: $R_1 =$ *anti*-PhCH(OH); $R_2 = H$	53	>99
c: $R_1 = Ph$; $R_2 = CH_3$	15	99
d: $R_1 = n\text{-}C_{12}H_{25}$; $R_2 = H$ + *cis* isomer (2:1)	24	79
e: $R_1 = R_2 = (CH_2)_5$	24	>99
f: $R_1 = R_2 = CH_3$	46	96
g: $R_1 = R_2 = C_2H_5$	24	95
h: $R_1 = Bu$; $R_2 = H$ + *cis* isomer (5:1)	24	97

Compared to that of the other reported silicon-tethered cycloadditions,[5] the 1,3-dipolar cycloaddition step is extremely facile and proceeds spontaneously under the very mild conditions required for hydroxyl derivatization.[12] No appreciable amounts of *intermolecular* 1,3-dipolar cycloaddition products were observed when compound **1h** was allowed to react with 1,3-divinyl-1,1,3,3-tetramethyldisiloxane for three days under the same reaction conditions. Likely, entropic factors and the adequate length of the tether to achieve the appropriate geometries make the *intramolecular* 1,3-dipolar cycloaddition possible.

Tricyclic compounds of type **2** are not only examples of new heterocycles. They possess the framework of a hydroxylated amino acid already set up and a richness in functionalities (the ethoxycarbonyl group, the nitroso acetal bicyclic system,[13] and the cyclic silyl ether[14]) that could be exploited to unfold these tricyclic systems, obtaining, with "acyclic" stereoselection, very interesting linear structures such as polyhydroxylated nonnatural amino acids, and probably their cyclic variants.

(1) Rosini, G. The Henry (Nitroaldol) Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M.; Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, p 321.

(2) Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781−783.

(3) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J.-P. *J. Org. Chem.* **1991**, *56*, 6258−6260.

(4) Review: Wade, P. A. Intramolecular 1,3−Dipolar Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1111−1168 and references therein cited.

(5) Review on silicon-tethered reactions: Bols, M.; Skydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277.

(6) Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248. Stork, G.; Chan, T. Y.; Breault G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578−7579. Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054−7056. It has been recently reported that also magnesium or aluminum can serve as a temporary tether: Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595−6596.

(7) (a) Tamao, K.; Nakagawa, Y.; Ito, Y. *Org. Synth.* **1995**, *73*, 94−109. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478−6480.

(8) Very similar results were obtained with chlorodiphenylvinylsilane.

(9) The large majority of the reported silicon-tethered cycloadditons are of the Diels−Alder type: see ref 5.

(10) One of the reviewers pointed out that an earlier example of silicon-tethered 1,3-dipolar cycloaddition was presented by G. Stork at the 32nd National Organic Symposium held in 1991 in Minneapolis (Roger Adams Award lecture, *Book of Abstracts*, pp 120−121).

(11) The regiochemistry of the cycloaddition was established to give the "fused" isomer, observing a downfield methylene instead of a methyne both in ^1H and ^{13}C NMR spectra. The "*all-cis*-fused" stereochemistry of the tricyclic system was confirmed by NOE experiments: saturation of the C(7)H signal gave a ca. 2% enhancement of the C(1)H signal.

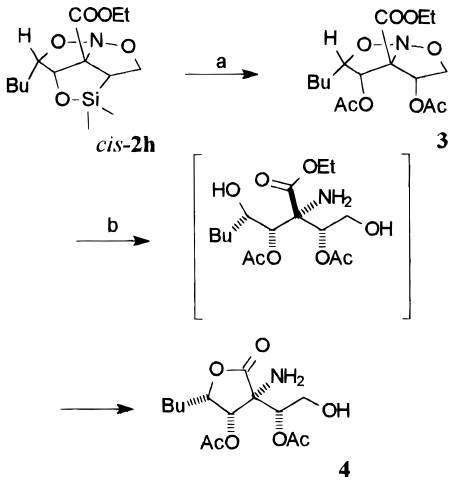
(12) It is possible to observe by TLC the formation of a transient species which smoothly interconverts to the tricyclic product.

(13) Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, *65*, 836−850. Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−166 and references cited therein.

(14) Tamao, K.; Yamauki, Y.; Ito, Y. *Chem. Lett.* **1987**, 171−174. See also ref 7a and references cited therein.

S0002-7863(96)01816-1 CCC: $12.00

Scheme 3[a]



cis-**2h** **3**

[a] Conditions: (a) (i) KF, $KHCO_3$, 30% H_2O_2, THF/MeOH; (ii) AcCl, Et_3N, DMAP. (b) 1 atm of H_2, Raney Ni, MeOH, KH_2PO_4.

As a preliminary attempt to investigate this potentiality, tricyclic compound *cis*-**2h** was converted to the corresponding bicyclic diol by an oxidative removal of the temporary silicon atom linker, under the conditions developed by Tamao.[15] The moderately unstable diol was protected immediately after isolation as the diacetate **3**. Reductive ring opening of the nitroso acetal moiety was performed with ambient pressure hydrogen in methanol, in the presence of a catalytic amount of Raney Ni, to afford the polyhydroxylated aminolactone derivative **4** in 52% isolated yield from starting isoxazoline **1h** (Scheme 3).

In this communication we have presented a new type of silicon-tethered cycloaddition that allows the preparation, in high yields, of a previously unknown type of heterotricyclic compound under very mild conditions. The net result of this cycloaddition is to deliver a two-atom fragment in a regio- and stereospecific fashion, achieving a great increase in structural complexity. Finally the many functionalities present on the tricyclic compounds could allow selective manipulation to give very interesting and potentially biologically active structures.

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Supporting Information Available: Procedure for the preparation of compounds **2a**−**h**, **3**, and **4** and actual ^1H and ^{13}C NMR spectra of compounds **2a**−**h**, **3**, and **4** (26 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96−105.