Silaketals in Intramolecular 1,3-Dipolar Cycloaddition of Nitrile Oxides

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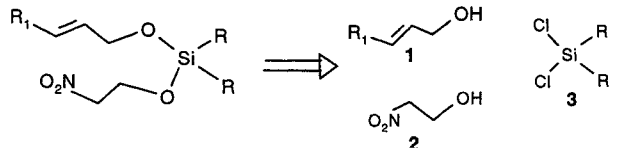
Abstract: A one pot synthesis of unsymmetrical silaketals having a 1,2-disubstituted double bond and a nitro-group is described. These compounds undergo, under mild conditions, regiospecific intramolecular 1,3-dipolar cycloaddition to give a single 2-isoxazoline.

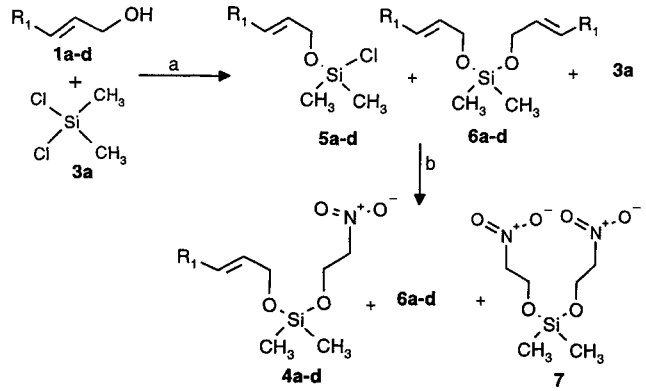
Intramolecular reaction processes which result from the linking of reactive species frequently lead to higher expressions of regio- and stereochemical preferences.[1] Subsequent removal of the linking species may produce compounds in which bond formation has been achieved with enhanced regio- and stereochemical control. However, it should be noted that tethers which impose intramolecularity may interfere with the bond forming process.[1] In this paper we present our first results applying such concepts to the realization of an intramolecular 1,3-dipolar cycloaddition: in this case we have used a silicone tether. To our knowledge, apart from intramolecular Diels-Alder reactions[2] and radical cyclization,[3] the use of silaketals in a 1,3-dipolar intramolecular cycloaddition has not yet been studied.[4]

The synthesis of the nitrosilaketals involved in the present reaction has been achieved by the temporary union of unsaturated alcohols **1** and nitrocompound **2** via dichlorosilanes **3** as shown below (Scheme 1).



Scheme 1

In the initial stages of our study, we chose dimethyldichlorosilane, **3a** (R=CH_3), based on the following criteria: the efficient substitution of the chlorine, the easy withdrawal of excess reagent, and the straightforward removal of the tether in the final 2-isoxazoline product. It is possible for the reaction to proceed without the generation of the free alcolate by a base.[5] Subsequently, when allylic alcohols **1** were treated with dichlorosilane **3a** and triethylamine in a 1:3:3 ratio, chlorosilanes **5** were formed along with a small amount of the symmetrical silaketals, **6,** (Scheme 2).



Scheme 2. (a) Et_3N (3eq), CH_2Cl_2, -78°C to r.t., 3 h;
(b) 2-nitroethanol, Et_3N, CH_2Cl_2, -78°C to r.t., overnight

The formation of these species can be readily monitored by the ^1H NMR signal of the methyl group. For example, in the case of cinnamyl alcohol **1a**, the proton NMR of the crude reaction mixture provides the following assignments: 0.50 ppm for **5a**, 0.13 ppm for **6a**, 0.85 ppm for **3a**. In order to minimize the formation of **6**, a three fold excess of **3a** and slow addition of the allylic alcohol is essential. After 3 hours, the removal of excess dichlorosilane **3a** from the reaction mixture is required before subsequent addition of a stoichiometric amount of 2-nitroethanol. Unfortunately, as chlorosilane **5** is readily hydrolyzed in contact with moist air, it is very important that the removal of dichlorodimethylsilane be carried out under an inert atmosphere. The partial hydrolysis of intermediate **5** leads to the formation of more silaketal **6** by the reaction of the liberated alcohol, **1**, with the chlorosilane **5** left in the reaction mixture. An attempt to isolate **5** by Kugelrohr distillation of the crude reaction product under vacuum yielded mainly silaketal **6**. The slow addition of 2-nitroethanol leads to the formation of the much more stable silaketals **4** which can be isolated in 30% yield for **4a** (Scheme 2, Table 1).[6a]

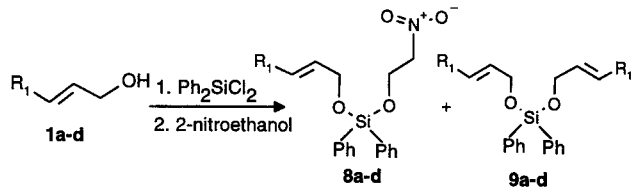
Table 1. Two-step synthesis of nitrosilaketals **4**.

Entry	R_1	Isolated yields of nitrosilaketals
1	Ph	**4a** (30%)
2	H	**4b** (25%)

^1H NMR analysis of a sample of the crude reaction mixture showed the presence of **4** as the only major component with approximately 25% of **6**. If dichlorosilane **3a** has not been completely removed, the unstable symmetrical compound **7** is formed and a dramatic drop in the yield of **4** (10%) is observed during the purification. We were delighted to find that nitrocompound aci-form substitution leading to the silylnitronate derivative doesn't take place.[7]

The low yields of tethered nitroalkene **4** prompted us to modify the criteria for the choice of the silicon tether and to devise a one pot procedure which would allow for the use of higher boiling dichlorodisubstituted silane derivatives. We chose the use of dichlorodiphenylsilane for the following reasons: the use of dichloromethylphenylsilane would afford a mixture of diastereoisomers of the 2-isoxazoline product because of the asymmetric centers generated at C-4 and C-5 and at the silicon atom. The use of dichlorodi-*tert*-butylsilane and of dichlorodiisopropylsilane was rejected because of the potential problems associated with the introduction of the second alcolate group[8] and with the expense of the reagents. The reaction of dichlorodiphenylsilane **3b** with allylic alcohols **1a-d** in presence of triethylamine in a 1:1:1 equivalent ratio followed by addition of 2-nitroethanol gave rise to more robust nitrosilaketals, **8a-d**, along with a small amount of symmetrical silaketals **9a-d**. The nitroalkenes can be isolated in good yields by circular chromatography on silica gel (Scheme 3, Table 2).[6b]

The tethered nitroalkenes **4a** and **8a-d** are easily transformed quantitatively[9] into 2-isoxazoline **10a** and **11a-d** under classic,[10] mild

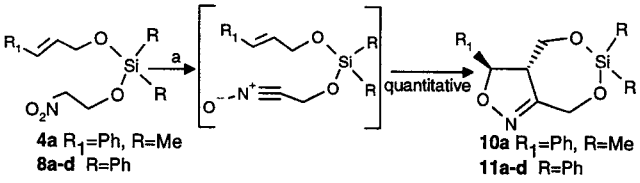


Scheme 3

Table 2. One pot synthesis of nitrosilaketals **8**.

Entry	R_1	Isolated yields of nitrosilaketals
1	Ph	**8a** (65%)
2	H	**8b** (75%)
3	Me	**8c** (67%)
4	CO_2Et	**8d** (70%)

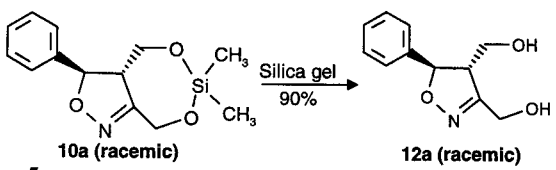
conditions: phenylisocyanate, along with a few drops of triethylamine at room temperature (Scheme 4, Table 3). The intermolecular cycloaddition involving a 1,2 unsymmetrically substituted alkene such as cinnamyl alcohol proceeds non-regioselectively to give a mixture of the two regioisomers,[11] or when chelated by Mg^{2+}, mainly yields the C-5 hydroxymethyl substituted 2-isoxazoline.[12] In contrast, the intramolecular version of this reaction was found to be stereo- and regiospecific. It provides a sole regioisomer of 2-isoxazoline having a C-5 phenyl group. The *trans* stereochemistry of the alkene was transposed to the 2-isoxazoline product as was supported by the observation of a coupling constant of 9 Hz between the protons at C-4 and C-5 in the ^1H NMR spectrum of **10a**.[13] During the purification of **10a**, cleavage of the silicon bridge occurs and the dihydroxylmethyl species, **12a**, is obtained (Scheme 5).[13] The spontaneous formation of **12a** reflects the ease by which the dimethylsilane moiety can be removed. In fact, aqueous treatment should be avoided if the isolation of **10** is required. The bicyclic derivatives, **11a-d**, having a diphenylsilane tether, are not subject to such rapid hydrolysis. However, perhaps some partial hydrolysis can account for the less than quantitative isolated yields as shown in Table 3.



Scheme 4. $PhNCO/NEt_3$, C_6H_6/CH_2Cl_2, r.t., 96 h

Table 3. Isolated yields of 2-isoxazoline **11a-d**.

Entry	R_1	Yields of Δ^2-isoxazoline
1	Ph	**11a** (65%)
2	H	**11b** (60%)
3	Me	**11c** (70%)
4	CO_2Et	**11d** (67%)



Scheme 5

In summary, the use of a silicon tether in an intramolecular 1,3-dipolar cycloaddition of nitrile oxides is a useful method for the regiospecific synthesis of 2-isoxazoline. We are currently investigating the diastereoselectivity of this reaction. Further uses of this new alternative for the regiocontrolled synthesis of 2-isoxazoline, and its application to the synthesis of natural products are also being studied.

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References and Notes

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(4) Recently, silyloxinitroalkene has been used in the key step of an asymmetric tandem inter [4 + 2] / intra [3 + 2] cycloaddition. See Denmark, Scott E.; Hurd Alexander R. and Sacha H. J., *J.Org. Chem*, **1997**, *62*, 1668-1674. For an example of use of silicon tether in [3 + 2] dipolar cycloadditions of nitronates see Righi, P.; Marotta, E.; Laduzzi, A.; Rossi, G., *J. Am. Chem. Soc.*, **1996**, *118*, 9446.

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(6) a) The low yields are probably due to partial hydrolysis during circular chromatography on silica gel.
Data for **4a**: colourless liquid, R_f = 0.40 (ethyl acetate/petroleum ether 1:5). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.16 (s, 6H, $2CH_3$); 4.2 (m, 2H, CH_2O); 4.3 (m, 2H, $CH_{2\ allyl}$); 4.46 (m, 2H, CH_2NO_2); 6.26 (dt, H, CH); 6.53 (d, 1H, J=13.75 Hz, Ph-CH); 7.3 (5 H_{arom}).^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -3.3 (2C, CH_3); 58.7; 63.3; 77.2; 126.4; 127.5; 127.9; 128.5; 130.5; 136.7. MS m/z: 281(M^+, 19%); 207(34%); 191(16%); 133(49%); 73(100%).
b) Typical procedure: one pot synthesis of nitrosilaketal **8a.** To a cooled (-78°C) solution of dichlorodiphenylsilane (0.93 mL, 7.46 mmol, 1.0 equiv) in dry dichloromethane (15 mL) under nitrogen, dry triethylamine (1.04 mL, 7.46 mmol, 1.0 equiv) was added and the mixture was stirred for 5 min. A solution of cinnamyl alcohol (1.0g, 7.46 mmol, 1.0 equiv) in 10 mL of dry dichloromethane under nitrogen, was slowly added. After complete addition, the reaction was then allowed to warm slowly at room temperature. After stirring for 3 hours, the crude mixture was cooled again at -78°C. Triethylamine (1.04 mL, 7.46 mmol, 1.0 equiv), and a solution of 2-nitroethanol (0.5 mL, 7.5 mmol, 1.0 equiv) in 10 mL of dry dichloromethane was added. After one night period stirring at room temperature, the solvent was evaporated in vacuo. The residue was diluted with diethyl ether (30 mL) and the precipitate formed was removed by filtration and the filtrate was concentrated. Circular chromatography on silica gel with ethyl acetate/petroleum ether (1:5) gave the pure nitrosilaketal **8a** (1.96 g, 65% yield).

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(9) The reaction was quenched when the ^1H NMR analysis of a sample of the crude reaction mixture showed a complete disappearance of the resonances attributed to the alkene function accompanied by the appearance of those attributed to the 2-isoxazoline product.

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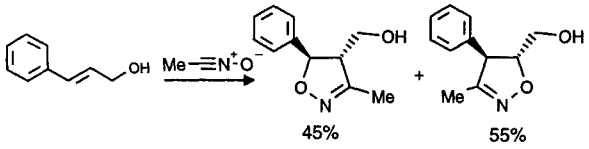
For example, the intermolecular reaction of *trans*-cinnamyl alcohol with acetonitrile oxide, generated from nitroethane and phenylisocyanate under similar reaction conditions, gives a mixture of the corresponding 2-isoxazoline with poor regioselectivity (i.e.1:1.2 ratio).



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(13) Data for **10a**: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.48 (s, 3H, CH_3); 0.5 (s, 3H, CH_3); 3.76 (m, 1H, H-4); 4.25 (dd, 1H, J_1=13Hz, J_2=4.5Hz,CH_2OSi); 4.72 (d, 1H, J_{gem}=13.75Hz, N=C-CH_2); 5.0 (d, 1H, J_{gem}=13.7Hz, N=C-CH_2); 5.38 (d, 1H, $J_{H4\text{-}H5}$ = 8.8Hz, H-5); 7.5 (5 H_{arom}).^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -3.2 (1C, CH_3); -3.0 (1C, CH_3); 58.3; 61.3; 62.9; 84.8; 125.8; 128.8; 129.0;139.1; 158.3.

Data for **12a**: colourless liquid, R_f = 0.18 (ethyl acetate/petroleum ether 1:1). IR(neat) 3370 (b), 2930, 1602, 1495, 1456, 1207 and 1048 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.90 (m, 2H, 2OH); 3.45 (m, 1H, H-4); 3.82 (dd, 1H, J_{gem}=11.2Hz, $J_{H4\text{-}H}$ = 6.8 Hz, CH_2OH); 4.0 (dd, 1H, J_{gem}=11.23Hz, $J_{H4\text{-}H}$ = 4.43Hz, CH_2OH); 4.38 (d, 1H, J_{gem}=13.46Hz, N=C-CH_2); 5.3 (d, 1H, $J_{H4\text{-}H5}$=8.8Hz, H-5); 7.35 (5 H_{arom}).^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 57.4; 60.2; 61.6; 85.2; 125.8; 128.4; 128.8; 139.7; 158.4. MS m/z: 207(M^+, 9%); 147(16%); 133(15%); 73(100%).