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CHEMISTRY OF ALDOLATE DIANIONS. β-SILYLOXY SILYL ENOL ETHERS AS BIFUNCTIONAL NUCLEOPHILIC EQUIVALENTS FOR OXYGEN HETEROCYCLE SYNTHESIS

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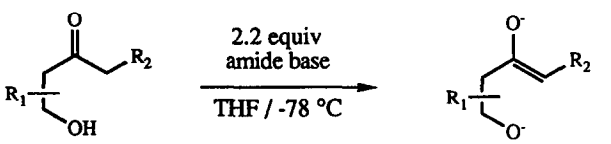
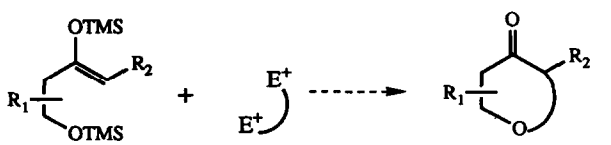
Summary: A variety of β-silyloxy silyl enol ethers (**3**) are easily produced by double deprotonation of readily available β-hydroxyketones. These substances undergo cyclization reactions with dioxenium cations to provide 2-alkoxy-tetrahydropyranones, thus confirming the use of **3** as bifunctional reagents for oxygen heterocycle synthesis.

We recently described the generation of distal aldolate dianions (**2**) by double deprotonation of β-hydroxyketones with 2.2 equivalents of amide base at low temperature.[1] These species are quite stable at -78 °C and in some cases can be warmed to room temperature for a number of hours without significant side reactions occurring. Additionally, the presence of the β-hydroxy group promotes the regioselective formation of distal enolates in cases of symmetrical substitution at the α position. Our interest in such dianions is centered around the potential of such species in oxygen heterocycle synthesis. One can easily imagine the reaction of the bis-nucleophilic **2** with a bis-electrophile to form functionalized oxygen heterocycles of many types. Toward this



1 **2**

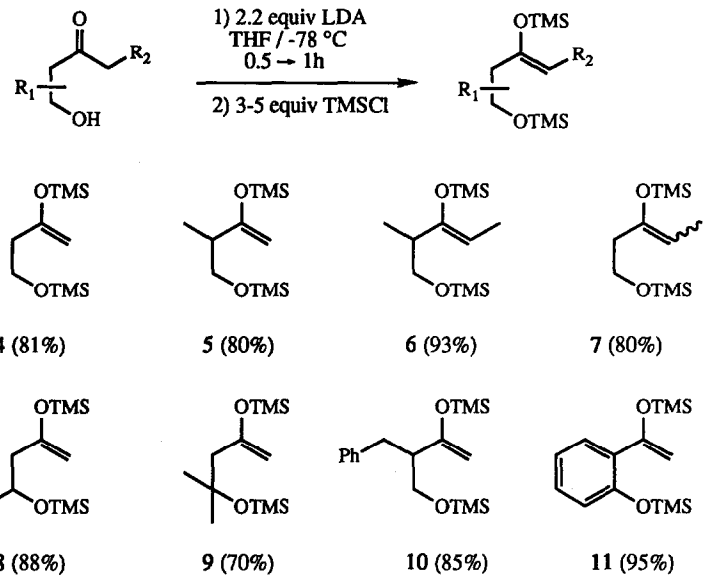
end, we have prepared β-silyloxy silyl enol ethers **3** derived from aldolate dianions, with the expectation that **3** will act as a mild synthetic equivalent of **2**. We wish to report further preliminary findings on the formation of **3** and their utility in oxygen heterocycle synthesis.



3

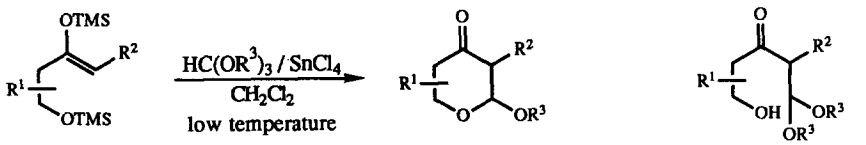
The *in situ* trapping of distal aldolate dianions with silyl chlorides provides a range of β-silyloxy silyl enol ethers **3** in good to excellent yield. The substrates prepared for this study are shown in Scheme 1. All of the silyl ethers were prepared by what can be described as the standard procedure for the formation and trapping of ketone enolates: the β-hydroxyketone was added to an excess of LDA at -78 °C and stirred for 30 min to an hour before quenching with excess TMSCl followed by addition of saturated aqueous $NaHCO_3$ solution and extraction with CH_2Cl_2.[2] The silyl ethers (**4** - **11**) generally required no further purification except for **9** which was chromatographed on silica (HPLC) with hexane/EtOAc (99:1) as the eluant. The formation of **6** and **7** deserve

Scheme 1



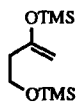
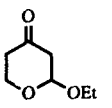
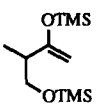
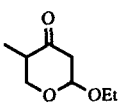
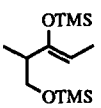
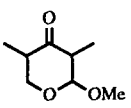
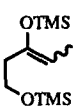
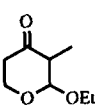
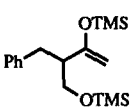
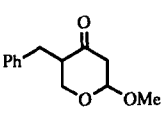
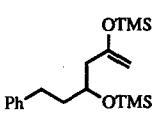
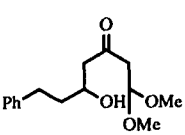
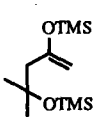
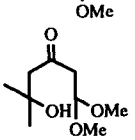
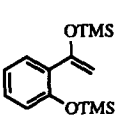
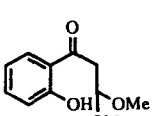
further comment. When prepared in a THF / HMPA solvent system, compound **6** was the only isomer produced, which was assigned a *Z* geometry on the basis of ^1H NMR allylic and homoallylic coupling constants.[3] Compound **7** was similarly prepared as a 2.2 : 1 *(Z : E)* mixture with >95% regioselectivity when the enolate solution was allowed to warm to 25 °C for 15 minutes. *This indicates that a β-hydroxy group may be used as a regio-control element in the enolization of symmetrically α-substituted ketones.*

Previous studies in our laboratory have been concerned with the chemistry of dioxenium cations in cationic cyclization processes. We felt that the addition of **3** to solutions of dioxenium cations (**12**) could result in the formation of **14** *via* a pathway previously confirmed for the reaction of homoallylic alcohols with **12**.[4] However, initial reaction of **12** at the β-carbon of the silyl enol ether is also reasonable.[5] The intermediate **14** can be expected to cyclize and desilylate resulting in 2-alkoxy-tetrahydropyran-4-ones **15**, which can also arise by transacetalization of **13**. Such heterocycles and their carbonyl-reduced analogs are ubiquitous substructures found in a variety of biomedicinally important natural products.[6] When solutions of dioxenium cations (generated from trialkyl

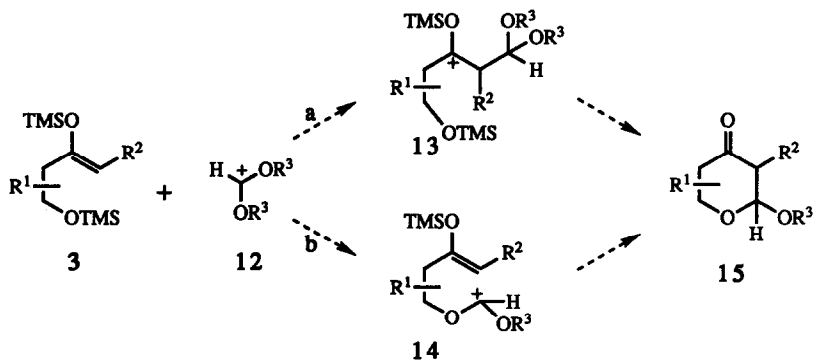


3 15 16

Results of the Reaction between β-Silyloxy Silyl Enol Ethers and Dioxenium Cations

SUBSTRATE	CONDITIONS	PRODUCT RATIOS AND YIELDS[a]
	1.1 equiv $HC(OEt)_3$ 1.2 equiv $SnCl_4$ -78 °C / 30 min	 60%
	1.1 equiv $HC(OEt)_3$ 1.2 equiv $SnCl_4$ -78 °C / 30 min	 88% 93 : 7 (*cis : trans*)
	1.2 equiv $HC(OMe)_3$ 0.6 equiv $SnCl_4$ -78 °C / 15 min	 62% (mixture of 4 isomers)
	1.1 equiv $HC(OEt)_3$ 1.2 equiv $SnCl_4$ -78 °C / 30 min	 92% 77 : 23 (*cis : trans*)
	1.0 equiv $HC(OMe)_3$ 0.6 equiv $SnCl_4$ 25 °C / 5 min	 75% 95 : 5 (*cis : trans*)[b]
	1.2 equiv $HC(OMe)_3$ 0.6 equiv $SnCl_4$ -78 °C / 15 min	 72%[c]
	1.2 equiv $HC(OMe)_3$ 0.6 equiv $SnCl_4$ -78 °C / 15 min	 69%[c]
	1.2 equiv $HC(OMe)_3$ 0.6 equiv $SnCl_4$ -78 °C / 15 min	 70%[c]

[a] Product ratios determined by ^1H NMR; [b] When run at -78 °C for 30 min the ratio was 72 : 28; [c] The cyclic product was produced as a mixture with elimination and other byproducts when > 1 equiv of $SnCl_4$ was used.



orthoformates and a Lewis acid) in CH_2Cl_2 were treated with a β-silyloxy silyl enol ether at -78 °C, the oxygen heterocycles **15** were isolated in good to excellent yield. The results of several cyclizations are shown in the Table. Since uncyclized products corresponding to **13** can be intercepted in many cases, it appears that the reaction is proceeding *via* pathway **a**. The reaction of **3** with dioxenium cations derived from higher orthoesters led to recovery of the original β-hydroxyketone from which the silyl ethers originated. This agrees with other information we have obtained, indicating the (unfortunate) hyper-stability of carbonium ions stabilized by two alkoxy and one alkyl group. ^1H NMR spectroscopy indicates that the predominant products (*cis*) in entries 2,4 and 5 exhibit equatorial alkyl groups and an axial -OR group. Our observations indicate that this stereoselectivity is due to equilibration of the anomeric center under the conditions of the reaction. Shorter reaction times, lower temperatures and smaller amounts of Lewis acid led to lower stereoselectivity in several experiments (for example, see entry 5).

To summarize, β-silyloxy silyl enol ethers (**3**) can be produced in high yields from regiospecifically formed distal aldolate dianions. These substances in turn react with dioxenium cations to provide 2-alkoxy-tetrahydropyran-4-ones in a moderately stereoselective process. This confirms the utility of **3** as mildly basic bis-nucleophilic equivalents for oxygen heterocycle synthesis. Further studies in this area are in progress.

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References

1) Martin, V. A.; Albizati, K. F. *J. Org. Chem.* **1988**, *53*, 5986.

2) Unless otherwise noted, all yields refer to isolated and purified substances. All new compounds were fully characterized by ^1H, ^{13}C and IR spectroscopy and gave satisfactory high resolution mass spectral data.

3) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

4) a. Perron, F., Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128; b. Perron, F.; Gahman, T.; Albizati, K. F. *Tetrahedron Lett.* **1988**, *29*, 2023.

5) Mukaiyama, T. *Org. React.* **1981**, *28*, 203.

6) For a summary of relevant structures, see Perron, F.; Albizati, K.F. *Chem. Rev.* **1989**, *89*, (November issue).

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