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PROTIODESILYLATION REACTIONS OF β- AND γ-HYDROXYSILANES: DEUTERIUM LABELING AND SILICON-DIRECTED EPOXIDE OPENINGS

Paul F. Hudrlik,* Peter E. Holmes, and Anne M. Hudrlik

Department of Chemistry, Howard University, Washington, D. C. 20059

Summary: Protiodesilylation reactions of β-hydroxysilanes are catalyzed by crown ether, can be used to introduce deuterium, and can be used to prepare silicon-free products of silicon-directed epoxide openings; similar reactions of γ-hydroxysilanes are possible.

We previously demonstrated that simple β-hydroxysilanes undergo protiodesilylation (replacement of the silyl group by hydrogen) when treated with KOtBu in aqueous dimethylsulfoxide (DMSO) at room temperature.[1] The presence of the hydroxyl group was found to be necessary for the reaction to occur, and a pathway involving a 4-membered ring species analogous to that postulated for the β-elimination reactions of β-hydroxysilanes was suggested. Water was found to slow down the reaction and favor protiodesilylation over β-elimination. We also demonstrated that simple α-hydroxysilanes undergo protiodesilylation in reactions faster than those of the β-hydroxysilanes.[1] We now wish to report improved reaction conditions, use of the reaction to introduce deuterium, the stereochemistry of the reaction in an unsubstituted system, and the analogous (but slower) base-induced protiodesilylation of γ-hydroxysilanes.

Reaction conditions. We have found that a small amount of 18-crown-6 facilitates the reactions for unreactive substrates without significantly increasing the amount of elimination product. Reaction of β-hydroxysilane **1**[1] with 5% KOtBu in 19:1 DMSO:H_2O at room temperature to give 2-octanol was complete in about 8 h (although normally left overnight for preparative runs). However, when 5 mole % of 18-crown-6 was added to the reaction mixture, the reaction time was reduced to 4-5 h.

Deuteriodesilylation. We have been interested in the possibility of replacing $SiMe_3$ by electrophiles other than H^+. Because of the significance of methods to prepare labelled compounds for biological studies, we were interested in replacing the $SiMe_3$ group with deuterium. Although treatment of β-hydroxysilane **1** as above with 5% KOtBu in 19:1 DMSO:D_2O (in the presence of 5 mole % 18-crown-6) yielded 2-octanol having only 5-10% deuterium incorporation by MS analysis, a similar reaction using DMSO-d_6:H_2O yielded 2-octanol having about 99% deuterium incorporation. These results are consistent with a rapid exchange of protons between DMSO and water under these conditions. When DMSO-d_6:D_2O was used, a 80% yield of 1-deuterio-2-octanol[2a,b] (about 100% deuterium incorporation) was obtained.

We found that the protiodesilylation reactions can also be carried out in aqueous hexamethylphosphoramide (HMPA), although the reactions are a little slower for a given percentage of water than those with aqueous DMSO, and that the reaction of **1** with KOtBu in HMPA/D_2O can be used to introduce deuterium. The product isolation was easier using DMSO, so we did not pursue the use of HMPA, although we expect it might be useful for higher molecular weight and less polar products, and for the introduction of other electrophiles.

1

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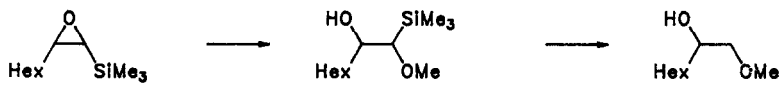
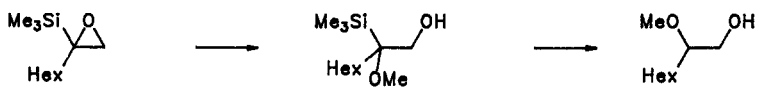
Stereochemistry. We previously demonstrated that protiodesilylation reactions take place with retention of configuration at carbon using α-methoxy-β-hydroxysilanes.[1] Using deuteriodesilylation, we have now demonstrated the stereochemistry in an unsubstituted system, the cyclic β-hydroxysilane **2**. Treatment of **2**[1] with 5% KOtBu in 19:1 DMSO-d_6:D_2O containing 18-crown-6 at room temperature resulted in a very slow reaction (2:3 mixture of starting material and product after 15 days). After aqueous workup, the product was isolated by preparative VPC. From the MS analysis, which indicated complete deuterium incorporation, and the ^2H NMR analysis (CCl_4), which showed one signal at δ 1.21, the product was assigned the structure cis-2-deuteriocyclohexanol,[3] demonstrating retention of configuration at the carbon bearing silicon.

Epoxide openings. Since the regiochemistry of many epoxide openings of α,β-epoxysilanes has been shown to be directed by silicon,[4] subsequent protiodesilylation reactions should be useful in obtaining products of directed epoxide opening. Treatment of 1,2-epoxyoctane with MeOH/CF_3CO_2H gave nearly a 1:1 mixture of regioisomers **5** and **8** (92% yield).[5] A similar reaction of epoxysilane **3**[4] in MeOH/CF_3CO_2H (0.2 ml of CF_3COOH in 50 ml anhydrous MeOH, room temp, 75 min) gave β-hydroxysilane **4**[2a,4] which, upon treatment with 5% KOtBu in 19:1 DMSO:H_2O, (10 min, room temp) gave 1-methoxy-2-octanol (**5**)[2a,5] in 77% overall yield, with none of regioisomer **8** detected by VPC analysis. Similarly, the reaction of epoxysilane **6**[4] with MeOH/CF_3CO_2H gave β-hydroxysilane **7**[2a,4] which, upon treatment with 5% KOtBu in 4:1 DMSO:H_2O (0.05 mole 18-crown-6, room temp, 48 h) gave 2-methoxy-1-octanol (**8**)[2a,5] in 61% overall yield, with none of regioisomer **5** detected by VPC analysis.



3 **4** **5**



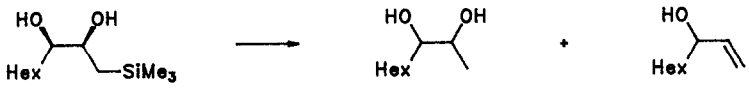
6 **7** **8**

γ-Hydroxysilanes. Under the conditions where **1** was converted to 2-octanol in 4-5 h (5% KOtBu in 19:1 DMSO:H_2O, crown ether, room temperature), γ-hydroxysilanes **9**[2a,c,6] and **10**[2a,c,7,8] were unchanged for up to 48 h (analysis by VPC relative to 2-octanol as an internal standard or with no standard). However, at 80°C, reaction was complete in 20 h for **9** and 12 h for **10**. [Under these conditions, β-hydroxysilane **1** was found to be totally consumed within 5 min.] On a preparative scale, **9** was converted to 3-nonanol in 72% yield, and **10** was converted to 2-methylcyclohexanol[7] in 78% yield.

9 10

Anionic 1,4 migrations of silicon are well known,[9] and a number of protiodesilylations of γ-hydroxysilanes are known where the silicon is attached to a double bond or an epoxide ring.[10] Stork and Sofia have reported a synthetic method involving protiodesilylation of a 1,2-oxasilacyclopentane using KOtBu in DMSO (via a presumed γ-hydroxysilane).[11]

When β,γ-dihydroxysilane **11**[2a,b,12] was treated with 5% KOtBu in 19:1 DMSO:H_2O containing 5 mole % 18-crown-6 at room temperature, reaction was complete by the first aliquot (30 min), to give a 3:1 mixture of diol **12**,[2a,b] (mp 48-49°C) product of protiodesilylation, and allylic alcohol **13**,[2a,14] product of β-elimination. The faster rate of this reaction than that of the β-hydroxysilane **1** could be due to a bicyclic hexacoordinate silicon species, or to intramolecular proton transfer from the second hydroxyl.



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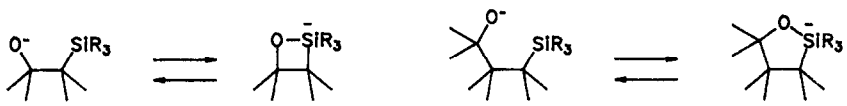
The considerably lower reactivity of γ-hydroxysilanes **9** and **10** compared with that of β-hydroxysilane **1** was initially surprising in view of the results of Eaborn and Mahmoud.[15] They studied the rates of cleavage of the compounds $PhCH_2SiMe_2(CH_2)_nOH$ by NaOMe/MeOH to form toluene. The β- and γ-hydroxysilanes (n = 2 and 3) were cleaved 0.75 and 95-135 times, respectively, as fast as $PhCH_2SiMe_3$ by NaOMe/MeOH at 50°C. [We found compounds **1** and **9** to be unreactive to these conditions.]

This apparent discrepancy can be resolved by the following considerations: In an equilibrium between an open chain alkoxide and the ring closed form, formation of the five-membered ring species (**17**) from the γ-oxidosilane (**16**) should be more favorable than formation of the 4-membered ring (**15**) from the β-oxidosilane (**14**), and loss of the benzyl group would be expected to be more rapid from the γ-oxidosilane if formation of the cyclic species is an important factor in the rate of the reaction. In contrast, our protiodesilylations must involve cleavage of a bond within the ring, and relief of the ring strain must be an important factor.



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7. Compound **10** was prepared, as a 4:1 trans:cis mixture, by $LiAlH_4$ reduction (ether, 2 h, 66% yield) of 2-(trimethylsilylmethyl)cyclohexanone (I. Fleming and J. Goldhill, J. Chem. Soc., Perkin I, 1493-1498 (1980); P. F. Hudrlik, A. M. Hudrlik, G. Nagendrappa, T. Yimenu, E. T. Zellers, and E. Chin, J. Am. Chem. Soc., **102**, 6894-6896 (1980)). The stereochemical assignment of **10** was determined by VPC comparison of its protiodesilylation product, trans- and cis-2-methylcyclohexanol (70:30), with an authentic sample obtained from the $LiAlH_4$ reduction of 2-methylcyclohexanone, known to give predominantly the trans isomer (H. C. Brown and H. R. Deck, J. Am. Chem. Soc., **87**, 5620-5625 (1965)).

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