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LETTERS

A MILD METHOD FOR PROTODESILYLATION OF α-DIMETHYLPHENYLSILYL ESTER SUBSTRATES

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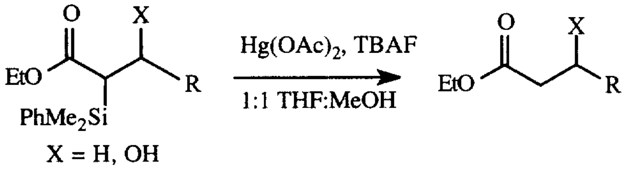
Abstract: Mild conditions (1.2 eq. $Hg(OAc)_2$, 1.2 eq. TBAF in 1:1 MeOH/THF; 35 min at 0 °C) have been developed for the protodesilylation of α-dimethylphenylsilyl esters. An enolate-dependent mechanism for the reaction was supported through studies indicating the clean incorporation of deuterium. To further investigate the mechanism, the optimal conditions as well as the kinetics of the reaction were explored.

Our interest in the oxidation chemistry of α-silyl-β-hydroxy esters has led us to the development of a mild method for protodesilylation of α-dimethylphenylsilyl esters.[1] A variety of methods have been developed for oxidation of a silane to an alcohol,[2-4] but few mild methods for protodesilylation have been reported.[5-9] In most cases, both transformations require an activating substituent on silicon (such as an alkoxy group) and are effected by fluoride. The oxidations have been exploited in natural product syntheses, as silicon's ability to act as a "masked" hydroxyl group allows it to be used in situations in which the presence of an alcohol is not desired.[10,11] We report a mild method for the replacement of the dimethylphenylsilyl moiety by hydrogen, which should increase the versatility of the silane in synthesis.



(eq. 1)

To effect protodesilylation of α-silylesters, treatment with $Hg(OAc)_2$ and TBAF cleanly substitutes the dimethylphenylsilyl group with hydrogen.[12] These conditions are an adaptation of one of Fleming's oxidation

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procedures in which the phenyl group is replaced *in situ* with acetate using $Hg(OAc)_2$ prior to oxidation by H_2O_2.[4] Using a variety of ester substrates, we have explored the scope of this reaction and its dependence on solvent, fluoride source, and mercuric acetate (Table 1).

Table 1. Representative Yields of Protodesilylation Products

Entry		**% Yield of 2**
a	X = OH R = $CH(CH_3)_2$	48
b	X = OH R = Ph	50
c	X = NCOPh R = Ph	99
d	X = H R = Ph	86
e	X = H R = CH_2CH_3	62

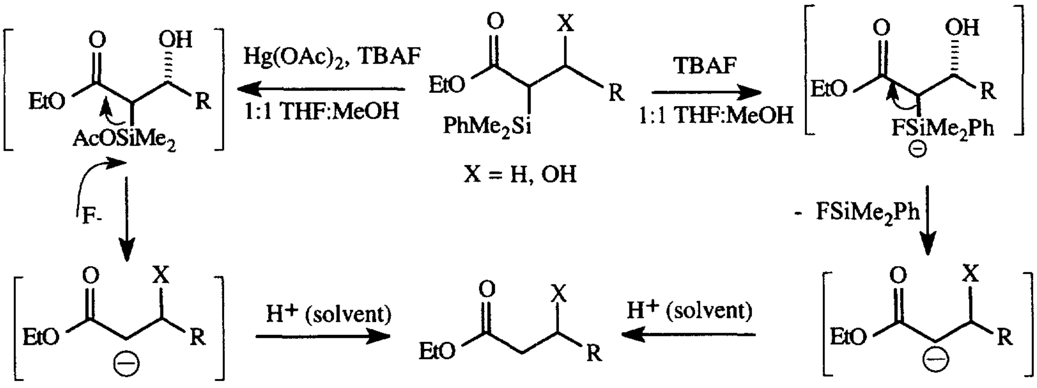
The reaction is clean with no evidence of elimination byproducts in any case. Unprotected alcohols are compatible with the reaction conditions (entries **a** and **b**), as are aromatic substituents not on silicon (entries **b**, **c** and **d**). Not surprisingly, siloxane and silanol byproducts were observed in the crude mixtures by ^1H NMR and GC/MS.

Our first observations of this reaction indicated that incipient enolate formation plays a critical role in the mechanism. It is important to note that the reaction occurs in the absence of a β-hydroxy group, indicating that the mechanism does not necessarily involve a Brook rearrangement as is the case in at least one other protodesilylation method.[7] In addition, no reaction was observed when dimethylphenylsilyloctane, which possesses no stabilizing substituents, was treated under the same conditions.

A protic solvent is required for these reactions, to both solubilize the fluoride and to serve as a proton donor to the enolate intermediate. The optimal solvent system is 1:1 MeOH:THF. To confirm the role played by the protic solvent, the reaction of **1d** with $Hg(OAc)_2$ and KF was monitored by ^1H NMR at 0 °C in 1:1 MeOH-d_4:CH_3CN-d_3, and the carbon alpha to the ester clearly showed incorporation of deuterium.

Slightly more than one equivalent of fluoride is necessary for these reactions, and a variety of fluoride sources are tolerated. The fluoride sources may be: TBAF (as a 1.0 M solution in THF, and in solid form), ammonium fluoride, and potassium fluoride. The yields are comparable in all cases, and selection of fluoride is determined by its solubility in the reaction mixture.

Somewhat suprisingly, protodesilylation will occur in the absence of $Hg(OAc)_2$, but the reaction is noticeably slower. Monitoring this reaction by ^1H NMR reveals that protodesilylation by fluoride alone results in $t_{1/2}$ that is seven-fold greater than with $Hg(OAc)_2$ and fluoride together. We also believe that in the absence of $Hg(OAc)_2$ the mechanism for protodesilylation must be slightly different, although both likely proceed via an enolate (Scheme 1). In the case of fluoride alone, the enolate could form by displacement of the silane by fluoride, or by stepwise formation of a pentacoordinate silicon species which then collapses to the enolate.[13,14]



Scheme 1. Proposed Mechanisms of Protodesilylation Reactions

In conclusion, we have determined that $Hg(OAc)_2$ and fluoride effect the protodesilylation of arylsilanes. The stabilization of an incipient anion appears to be important, and ongoing work is focussed on expanding the scope of dimethylphenylsilyl substrates which can undergo this reaction. The mild, neutral conditions are potentially applicable for removal of arylsilane linkers employed in combinatorial chemistry[15-17] and arylsilanes substituents in natural product synthesis.

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(12) A solution of the silane (0.209 mmol) in 1:1 THF:MeOH (2.0 mL) at 0 °C was treated with Hg(OAc)$_2$ (0.0795 g, 0.250 mmol) followed by 1.0 M TBAF (250 μL, 0.250 mmol). The yellow homogeneous solution was stirred for 35 min at 0 °C and then diluted with EtOAc (10 mL). The mixture was washed with 3 mL each: sat'd NH$_4$Cl, H$_2$0, and brine. A yellow precipitate which formed upon addition of EtOAc dissolved upon addition of the NH$_4$Cl solution. The organic phase was dried and concentrated by rotary evaporation to yield an oil which was purified by flash column chromatography.

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