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Stereoconservative protodesilylation of substituted silyl dithianes

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Abstract—Protodesilylaton of substituted silyl dithianes occurs with clean retention of configuration. In the case of the 2-phenyl derivative, epimerization of C-2 occurs. Selective functionalization of 2,2-bis trimethylsilyl derivatives can be efficiently obtained.

1,3-Dithiane anions have been widely used in umpolung reactivity as masked acyl carbanions, and have had significant impact on synthetic organic chemistry,[1] while, on the other hand, the lability under basic conditions of the parent dithiolane systems has always hampered their functionalization and consequently their use in umpolung reactivity. Actually the metallation of such molecules is reported to occur at C-2[2] or at C-4[3] followed by ring fragmentation.

Our interest in the synthesis and reactivity of organosilanes, in connection with the very mild functionalization conditions of the carbon–silicon bond under fluoride ion catalysis,[4] led us recently to disclose a protocol for the dithiolane functionalization through the 2-silyl-1,3-dithiolane that opened new perspectives in the chemistry of such heterocyclic rings.[5] Actually, these 2-silyl-1,3-dithiolanes can efficiently transfer the dithiolane moiety onto electrophiles, such as aldehydes, affording the corresponding protected α-hydroxy aldehydes and showing that under the present conditions, silyl dithiolane can be considered as a synthetic equivalent of a dithiolane anion. Such results then outline the peculiarity of the silicon moiety in promoting these reactions, and evidence this methodology as a possible general one for the functionalization of otherwise not easily functionalizable heterocycles.

Furthermore, the fluoride initiated functionalization of silyl dithiolanes and dithianes has been shown to occur with the retention of configuration.[6] These findings disclose a novel example of functionalization of a C–Si to a new C–C bond, with the retention of configuration. They appear particularly interesting, taking into account that, with the exception of allylsilanes,[7] there are only a few cases of stereoselective synthetic transformations of sp^3 carbon–silicon bonds to carbon–carbon bonds. Such examples include conversions of C–Si bonds of epoxysilanes to C–C bonds upon reaction with aldehydes[8] stereoselective insertion into strained bonds,[9] palladium-catalyzed conversions of chiral trifluoro benzyl silanes to chiral diaryl silanes,[10] diastereoselective intramolecular reaction of a benzyl silane,[11] the retention of configuration in the desilylative hydroxymethylation of α-silyl sulfides,[12] and, more recently, the reactivity of chiral benzyl silanes[13] and silylated aziridines[14] with aldehydes.

Nonetheless, even if some examples of protodesilylation with retention of configuration have been reported to occur,[15] no investigation has ever been performed on silyldithianes and dithiolanes.

On the other hand, it is firmly established that metallation of 1,3-dithianes[16] and 1,3-diselenanes[17] occurs regioselectively at C-2 at the equatorial rather than the axial hydrogen, and that their metallo derivatives lead, upon reaction with electrophiles, to products bearing the incoming group invariably at the equatorial position, whatever the other substituent present eventually at C-2. Krief and Defrere[18] have deeply investigated the related 4,6-disubstituted six-membered rings, 1,3-dithianes and diselenanes, and found that their treatment even at very low temperatures (up to

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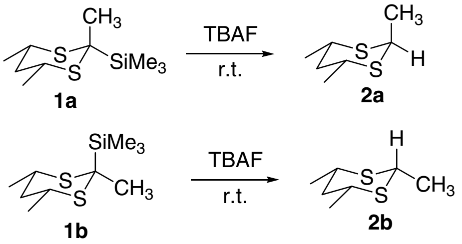
−130 °C) still affords invariably the equatorially functionalized products, irrespective of the configuration of the 2-substituted starting compound.

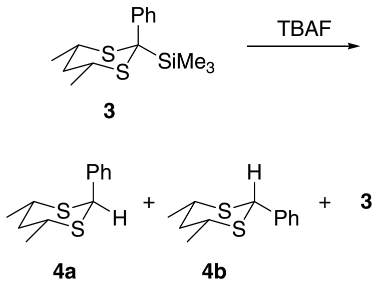
We then decided to undertake a more detailed investigation on the fluoride ion induced proto-desilylation of sterically defined silyl dithianes, in order to determine the stereochemical fate of such reactions.

Thus, we prepared both *cis* **1a** and *trans* **1b** 2-silyl-2,4,6-trimethyl dithiane and subjected them to fluoride-induced desilyltation with TBAF at rt for 4 h.[19] Both stereoisomers reacted smoothly to afford the corresponding 2,4,6-trimethyl 1,3-dithianes **2a** and **2b**, respectively, in almost quantitative yields, with a clean retention of configuration (Scheme 1).

With the aim to seek a generality for such behaviour, we moved towards a differently substituted system, and we took into consideration 2-trimethylsilyl-2-phenyl-4,6-dimethyl-1,3-dithiane **3**. In this case, the results of the desilylation reaction were less straightforward, appearing as a function of the temperature and the equivalents of TBAF used (Scheme 2). When, in fact, the desilylation is carried out at −5 °C with 0.02 equiv of TBAF, and for a short period of time (15 min), protodesilylation occurs, as already observed in the case of the methyl substituted system, with the clean retention of configuration. Under these conditions, large amounts of unreacted starting dithiane have been recovered (84%). On the other hand, when raising the temperature to 15 °C and increasing the amount of TBAF to 0.2 equiv, the inversion configuration product is formed in a nearly equimolar amount, and no starting dithiane has been obtained. Finally, if the temperature is further raised to 25 °C and 0.4 equiv of TBAF was used, the sole product deriving from the inversion of configuration is observed. Such peculiar behaviour could be possibly rationalized through the hypothesis that desilylation still occurs with retention of configuration, but due to the enhanced acidity of the thioacetalic proton induced by the presence of an aromatic ring,[20] it can be removed by the fluoride ion, this leading to epimerization of the molecule.



Scheme 1.



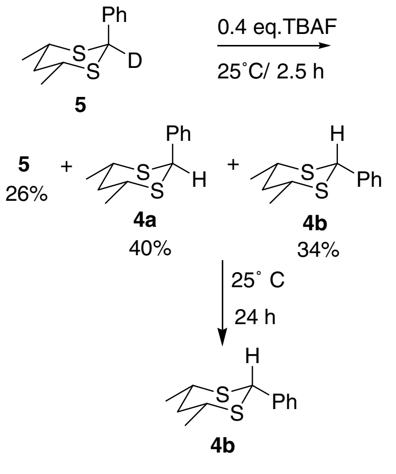
Conditions	4a	4b	3
0.02 eq.TBAF -5˚C/ 15'	13%	3%	84%
0.2 eq.TBAF 15˚C/ 120'	44%	56%	—
0.4 eq.TBAF 25˚C/ 90'	—	100%	—

Scheme 2.

In order to verify such a possible hypothesis, we prepared the deutero derivative **5**, and subjected it to fluoride ion conditions (Scheme 3).

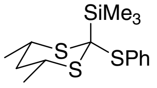
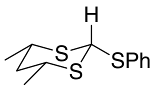
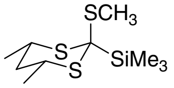
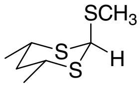
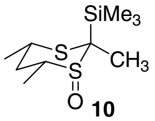
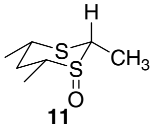
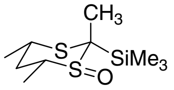
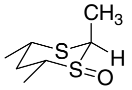
When the reaction is quenched after a reasonable *short* time (2.5 h), the starting material still being present, almost equimolar amounts of exchange products with the retention and inversion of configuration are obtained. If the so obtained mixture is let in the presence of TBAF for longer reaction times (24 h), a complete epimerization occurs, this according to the hypothesis of higher acidic character of the thioacetalic proton α to the aromatic ring. This result clearly shows that in the present case the increased acidity of the C-2 hydrogen indeed favours the exchange under TBAF conditions. Furthermore, both **4a** and **4b** being present after 2.5 h, the epimerization must occur at a different intermediate level than D/H exchange, it thus being a separate process.

This observation is supported also by an additional reaction performed on 2-methyl- substituted dithiane **2a**, which when treated with 0.8 equiv of TBAF for 24 h led again to the product of stereoconservative protodesilylation, with no trace of the epimer being detected.



Scheme 3.

Table 1. Protodesilylation of dithiane derivatives

Substrate	Product	Yield (%)
 **6**	 **7**	100
 **8**	 **9**	98
 **10**	 **11**	98
 **12**	 **13**	90

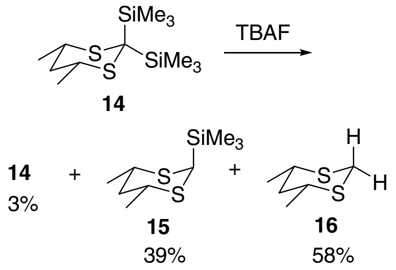
These results thus most likely outline that all the reported reactions proceed through a pentacoordinated silicon intermediate, rather than through a free carbanion, which should be expected to epimerize easily.

In order to check whether the presence of a carbanion stabilizing species on carbon 2 could affect the reported stereoconservative reactivity, we synthesized and subjected other different substrates to fluoride desilylation, which is presented in Table 1.

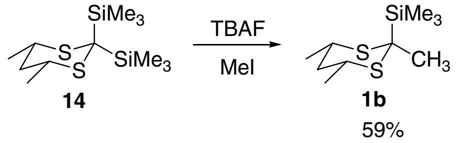
As it can be seen from Table 1, even in the presence of a further sulphurated moiety, or a sulphoxide group, no trace of epimerization was ever detected, thus showing that even with such substrates, the pentacoordinated silicon species seems the preferred reaction pathway.

Finally, in order to investigate deeper the chemical behaviour of such silylated species under fluoride ion conditions, we decided to investigate the 2,2-bis-trimethylsilyl-1,3-dithiane **14**, in order to ascertain whether there could be a possible discrimination between the two identical silyl groups.

Thus, upon reaction of compound **14** at −0.5 °C in the presence of a catalytic amount of TBAF (0.02 equiv), it has been observed that after 15 min from the mixture a 39% of the axially substituted dithiane together with the completely desilylated product as a major compound (Scheme 4) can be isolated. This result thus shows again that the silicon moiety in the equatorial position is more reactive than the one in axial position, no trace of the equatorial substituted system being detected in the reaction mixture. Thus, once established that a selective functionalization is possible, we checked such behaviour in the formation of a C–C bond and reacted **14** with methyl iodide in the presence of TBAF: such reaction afforded the isolation of a 59% of 2-trimethylsilyl-2,4,6-trimethyl-1,3-dithiane **1b** (Scheme 5).



Scheme 4.



Scheme 5.

In conclusion, we may say that we have shown that desilylation of functionalized dithianes occurs with strict retention of configuration, the stereochemistry of the original C–Si bond being retained in the newly formed C–C bond, and that such reactivity seems rather general.

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19. *Typical procedure:* A solution of 1 mmol of dithiane, **1a** or **1b**, prepared following Eliel's procedure,[16d] in 10 mL of dry THF is added portionwise every 1 h with 0.5 mL of 0.2 M THF solution of TBAF, and the progress of the reaction was monitored by TLC (petroleum ether/diethyl ether 98:2). After the addition of 0.4 equiv of TBAF a complete desilylation was observed. The mixture was then treated with a 5% solution of NH_4Cl, extracted with diethyl ether and dried over $MgSO_4$. Filtration and evaporation of solvent gave crude dithianes **2a** (95% on the crude) and **2b** (87% on the crude), respectively, whose NMR spectra were identical with an authentic sample.[16d]
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