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Tetrabutylammonium phenoxide induced reaction of silyl nucleophiles

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ABSTRACT

Reaction of silyl dithiolanes with electrophiles can be efficiently promoted by catalytic amounts of tetrabutylammonium phenoxide (PhON*n*–Bu$_4$), leading to a convenient access to functionalized dithiolanes. PhON*n*–Bu$_4$ proved effective also in promoting reactions of silylated sulfides such as PhSTMS and HMDST as well as silylated selenides such as PhSeTMS and HMDSS toward epoxides. The present reactivity is also observed on using ILs as reaction media.

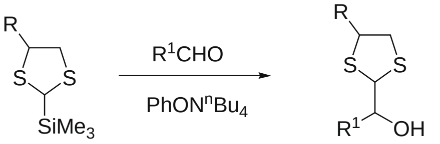
Fluoride ion-induced reactivity of a carbon silicon bond as a convenient methodology for the formation, under mild conditions, of novel carbon–carbon bonds has attracted a great deal of attention.

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,[1] 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.[2] Direct functionalization of dithiolane moieties being prevented by the lability of the generated dithiolane anion, which decompose through a cycloreversion reaction upon its generation[3], we explored different procedures, and we found that under the influence of fluoride ion, these 2-silyl-1,3- dithiolanes can efficiently transfer the dithiolane moiety onto electrophiles, such as aldehydes, affording the corresponding protected α-hydroxy aldehydes. These results showed that under the present conditions, silyl dithiolane can be considered as a synthetic equivalent of a dithiolane anion. Furthermore, when using stereodefined dithiolanes, the stereochemistry of the carbon–silicon bond is retained throughout the process and transferred to the newly formed carbon–carbon bond.[4]

Such results then outline the peculiarity of the silicon moiety in promoting these reactions, and evidence the fluoride ion-induced functionalization of the C–Si bond as a possible general tool for the functionalization of otherwise not easily functionalizable heterocycles.

In this context, several fluoride ion sources were evaluated, ranging from CsF, TASF, TBAT, and TBAF, and we found TBAF to be, at least in our hands, the best choice. Several drawbacks are nevertheless linked to the use of TBAF, such as the difficulties in having an anhydrous solution, and its stability along with time.[5] This is why we began to look for different catalytic systems. A recent investigation by Mukayama and coworkers[6] on the phenoxide-catalyzed reactivity of silyldithianes, prompted us to report our own results in this direction that show how phenoxide ion can be efficiently used in replacement of TBAF in promoting the reactions of silyl dithiolanes thus overcoming the mentioned drawbacks.

Both PhONa and PhON*n*-Bu$_4$ were used as catalysts in the reactions of silyl dithiolanes **1a,b** with aldehydes, and different solvents taken into consideration and we also found the best choice being PhON*n*-Bu$_4$ in polar solvents such as DMF (Scheme 1).[7] The use of PhONa generally leads to the formation of variable amounts of desilylation products, and solvents like THF to low yields of the expected products. Moreover, reactions in DMF were faster than those in THF (2–4 h in DMF, 12–24 h in THF).



1a: R = H
1b: R = CH$_2$O^{i}Pr

2a-g
R^1 = see Table 1

Scheme 1.

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Table 1
Carbodesilylation of silyldithiolanes

Entry	Dithiolane	R^1CHO	Catalyst	Solvent	Product	Yield (%)[a,b]
1	**1a**	PhCHO	PhONa	DMF	**2a**	42
2	**1a**	PhCHO	$PhONBu_4$	THF	**2a**	10
3	**1a**	PhCHO	$PhONBu_4$	DMF	**2a**	87
4	**1b**	PhCHO	$PhONBu_4$	DMF	**2b**	49[c]
5	**1a**	Thenyl-CHO	$PhONBu_4$	DMF	**2c**	88
6	**1a**	p-Br-C_6H_4–CHO	$PhONBu_4$	DMF	**2d**	70
7	**1a**	E-PhCH=CHCHO	$PhONBu_4$	DMF	**2e**	78
8	**1a**	$C_6H_{11}CHO$	$PhONBu_4$	DMF	**2f**	60
9	**1a**	$(CH_3)_2CHCH_2CHO$	$PhONBu_4$	DMF	**2g**	30[d]

[a] Based on isolated yield.

[b] All the products were characterized by ^1H, ^{13}C NMR and mass spectroscopy.

[c] Mixture of cis and trans isomers.

[d] 1,3-Dithiolane was recovered (ca. 25%) together with traces of condensation products (<5%).

Results of this investigation are summarized in Table 1.

Reactivity proved general, occurring smoothly with aromatic, heteroaromatic, and aliphatic aldehydes. In all reactions no trace of decomposition of the dithiolane ring was observed, thus showing that also under the influence of phenoxide ion a real carbanion is not generated in the present conditions. The substituted 2-silyl-4-(isopropoxymethyl)-1,3-dithiolane **1b** was reacted as well with benzaldehyde, leading to the formation of the 4-substituted-α-hydroxy-dithiolane **2b** as a mixture of cis/trans isomers (Table 1, entry 4), that can be separated on silica gel. It should be mentioned that when reacting substituted dithiolanes a greater amount of protodesilylation was observed.

Usually, dithiolane adducts were obtained as a mixture of hydroxy compounds and trimethylsilyl ethers. The use of saturated aqueous NH_4Cl solution during the work-up led to the exclusive formation of the corresponding alcohols.

Once established the efficiency of phenoxide ion in promoting the functionalization of silyl dithiolanes, we turned our attention to different organosilanes, namely those containing an heteroatom-silicon bond, such as S–Si.

We have in fact recently been interested in the functionalization of the S–Si bond in the regio- and stereoselective ring opening of oxiranes by HMDST, for the synthesis of mercapto alcohols.[8] Such investigation showed that sulfurated moieties can easily and efficiently be transferred onto different electrophiles, such as epoxides, by using the corresponding silyl derivatives under fluoride ion conditions.

Thus, when phenylthiotrimethylsilane was reacted with benzylglycidol **3** and a catalytic amount of PhONn-Bu$_4$ (20%),[9] a clean reaction occurred, leading to the isolation in good yield of compound **4**, arising from a regioselective attack on the less hindered side of the oxirane ring (Scheme 2). Then, the above-described procedure may represent a simple and efficient approach to access β-hydroxy sulfides, that behave as useful intermediates in different synthetic transformations.

The efficiency of the methodology is further demonstrated by the use in such reactions of the much more labile chalcogen derivative hexamethyldisilathiane [HMDST, $(Me_3Si)_2S$], which in turn reacted smoothly with oxirane **3**, affording the β-hydroxythiol **5** in comparable yields with those already reported under fluoride ion conditions (Scheme 2). Interestingly, epoxide functionalization reactions could be conveniently performed in THF instead of DMF. In some cases, products were isolated as their trimethylsilyl ethers.

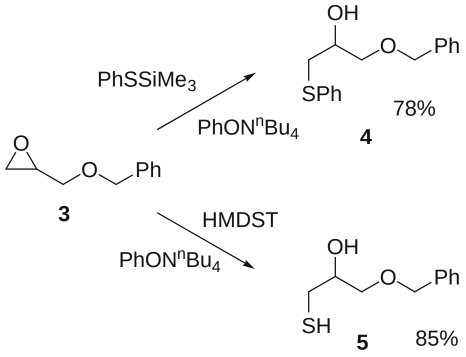
As a further step, we decided to evaluate the possible extension to the reactivity of selenosilanes.

To the best of our knowledge, while several papers have reported the reaction of thiosilanes with oxiranes,[10] only very few examples have been described dealing with the reactivity of selenosilanes.[11]

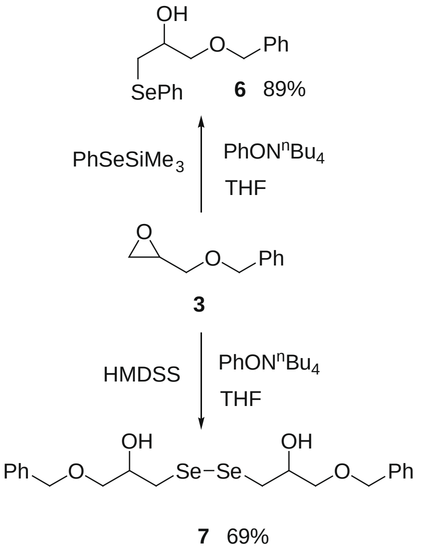
Very recently we found that bis(trimethylsilyl)selenide [$(TMS)_2Se$, HMDSS] acts as an efficient reagent in the TBAF-catalyzed reaction with three-membered heterocycles, leading to β-functionalized diselenides.[12]

Thus, benzylglycidol **3** was reacted with phenylselenotrimethylsilane under the catalysis of phenoxide ion, the reaction led to the isolation of the corresponding β-phenylselenoalcohol **6** in 89% yield (Scheme 3).

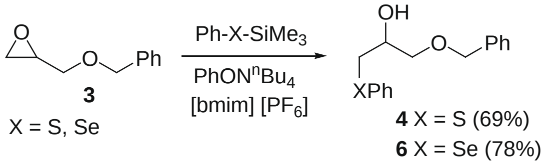
Again, when moving to the more intriguing hexamethyldisilaselenane (HMDSS) a smooth reaction was observed with benzylglyc-



Scheme 2.



Scheme 3.



Scheme 4.

idol **3**, leading this time to hydroxydiselenide **7**, arising from oxidation of the transient selenol obtained in the reaction (Scheme 3). Attempts to isolate the β-hydroxy silyl selenide (or selenol) intermediate were unsuccessful. It is interesting to note that in the case of silyl selenides, only a 2% of the catalyst was necessary to achieve complete transformation of the oxirane. As a consequence, compounds **6** and **7** are recovered from the reaction medium pure enough to undergo subsequent reactions.

Finally, we were interested to evaluate the efficiency of such protocol also in different reaction media. Due to their peculiar properties, ionic liquids (ILs) are regarded as eco-friendly novel and alternative solvents of increasing interest.[13]

To the best of our knowledge, besides few examples of ring opening of epoxides with sulfurated[14] or silylated[15] nucleophiles in ILs, no example has been described for the reactions of oxiranes with selenosilanes. Very recently a paper dealing with ring-opening reactions of epoxides with aryselenols has been reported.[14e]

Thus, we reacted benzylglycidol **3** with phenylthiotrimethylsilane and phenylselenotrimethylsilane under the catalysis of phenoxide ion (0.4–0.2 equiv, respectively) in ionic liquids such as [bmim][PF$_6$] (Scheme 4), and we found that the reaction proved quite efficient, leading to the β-hydroxy phenylthio- (**4**) and phenylseleno- (**6**) derivatives in good yields, thus confirming the versatility of this new catalytic system. Performing the reaction in ILs, no trimethylsilyl ether formation was observed, but only hydroxy compounds were isolated.

In conclusion, the use of phenoxide ion in promoting the reactivity of silyl derivatives proved quite efficient and general, thus disclosing an interesting alternative to the use of tetrabutylammonium fluoride.

The use of different ILs as well as different ring strained heterocyclics as substrates is now under investigation.

Acknowledgments

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7. *Typical procedure*: A solution of PhONBu$_4$ (30 mg, 0.09 mmol) in dry DMF (0.2 mL) was added under inert atmosphere dropwise to benzaldehyde (26 mg, 0.24 mmol) and 2-trimethylsilyl-1,3-dithiolane **1a** (40 mg, 0.22 mmol). Progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate 5:1) and GC/MS, and after 3.5 h the mixture was then diluted with diethyl ether and washed with water. The aqueous phase was extracted with diethyl ether and the combined organic phases were washed with brine and dried over Na$_2$SO$_4$. Filtration and evaporation of the solvent gave the crude α-hydroxy dithiolane **2a** as a yellow oil, that can be purified on TLC (petroleum ether/ethyl acetate 5:1) to afford the pure compound (87%). ^{1}H NMR (200 MHz, CDCl$_3$) δ: 3.14–3.32 (m, 4H), 4.62 (d, 1H, *J* = 7.0 Hz), 4.79 (d, 1H, *J* = 7.0 Hz), 7.30–7.46 (m, 5H). MS *m/z* (%): 135 (M$^+$−77, 0.5), 107 (18), 105 (100), 79 (15), 77 (22). The reaction was repeated on larger scale (178 mg of silyl-dithiolane **1a** (1 mmol), 116 mg of PhCHO (1.09 mmol) and 143 mg of PhONBu$_4$ (0.41 mmol) in 0.9 mL of dry DMF) affording 172 mg of **2a** (81%) after chromatographic purification.
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9. *Typical procedure:* A solution of 13 mg of PhONBu$_4$ (0.04 mmol) in dry THF (0.7 mL) was treated under inert atmosphere with benzylglycidol **3** (30 mg, 0.18 mmol) and phenylthio-trimethylsilane (36 mg, 0.20 mmol). The mixture was stirred at rt. and progression of the reaction was monitored by TLC. After quenching with water, the product was extracted with diethyl ether. The resulting organic phase was washed with brine, dried over Na$_2$SO$_4$ and the solvent evaporated under vacuum. TLC purification (petroleum ether/ethyl acetate 9:1) afforded 39 mg (78%) of adduct **4** as a pale yellow oil. ^{1}H NMR (200 MHz, CDCl$_3$) δ (ppm): 7.39–7.17 (m, 10H), 4.5 (br s, 2H), 3.96–3.84 (ap. pent, 1H), 3.57 (dd, 1H, *J* = 4 Hz, *J* = 9.6 Hz), 3.50 (dd, 1H, *J* = 5.4 Hz, *J* = 9.6), 3.12 (dd, 1H, *J* = 6 Hz, *J* = 13 Hz), 3.02 (dd, 1H, *J* = 7 Hz, *J* = 13 Hz), 2.67 (br s, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ (ppm): 37.5, 68.9, 72.4, 73.4, 127.4, 127.7, 128.4, 128.9, 129.6, 135.3, 137.7. MS *m/z* (%): 274 (M$^+$, 13), 165 (12), 123 (51), 109 (29), 91 (100), 77 (25). The reaction was repeated on larger scale (164 mg of benzylglycidol **3** (1 mmol), 202 mg of PhSSiMe$_3$ (1.11 mmol) and 77 mg of PhONBu$_4$ (0.22 mmol) in 3.9 mL of dry THF) affording 246 mg of **4** (90%).
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