

A General Access to 2-Silylthiazolidines and Their Reactions Under Fluoride Ion Conditions

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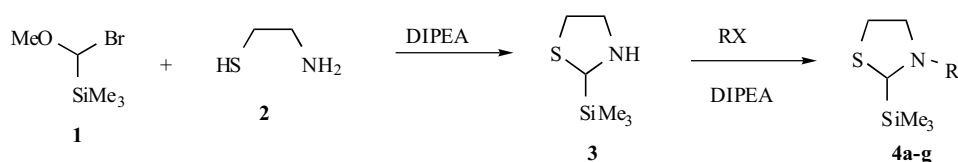
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Abstract: 2-Trimethylsilylthiazolidines were readily obtained through reaction of aminoethanethiol with (bromomethoxymethyl)trimethylsilane and efficiently *N*-functionalized with a variety of protecting groups. Such *N*-protected thiazolidines can then be satisfactorily reacted with several organic electrophiles under fluoride ion conditions, with a clean transfer of the thiazolidine moiety, to afford good yields of 2-functionalized heterocycles.

The thiazolidine ring system derives special importance from the fact that it is an integral part of medically important compounds like the penicillins [1] and some antiradiation drugs [2]. Substituted thiazolidine derivatives represent important key intermediates for the synthesis of pharmacologically active drugs [3]. Recently a number of thiazolidines have been claimed to be retroviral protease inhibitors [3b,4] and have also been investigated as possible substitute for the carbohydrate moiety in the synthesis of new antiviral nucleosides [5]. More recently they have also been shown as antitussive active molecules [6]. Thiazolidines are also relevant in food chemistry, as far as

best of our knowledge, deal with such functionalization, and their efficiency seems related to the presence of specific *N*-protecting groups. Meyers reports efficient metallation of the thiazolidine ring when on the nitrogen atom is present a *tert*-butylformamide group [11], while, more recently, Gawley has reported a nice functionalization of thiazolidines, bearing an *N*-BOC system [12], showing their possible use as chiral acyl anion synthons.

Our interest in the synthesis and reactivity of organosilanes, in connection with the very mild functionalization conditions of the carbon-silicon bond under



	R (Overall yield)		R (Overall yield)
a	CH ₃ SO ₂ (34%)	e	PhCH=CHCO (22%)
b	<i>p</i> -CH ₃ C ₆ H ₄ SO ₂ (32%)	f	BOC (45%)
c	CH ₃ CO (31%)	g	Cbz (56%)
d	PhCO (30%)	h	<i>o</i> -(CHO)C ₆ H ₄ CO (31%)

Scheme 1.

they are incorporated in flavor enhancing additives [7], and their synthetic utility is shown by their use as blocking groups [8], and as intermediates in the synthesis of aldehydes [9] and aminoethane thiols [10].

Despite the utility of the thiazolidine moiety, still very few methodologies for the functionalization of position 2 of the heterocyclic ring exist. Only two reports, in fact, to the

fluoride ion catalysis [13], led us recently to disclose a protocol for the dithiolane functionalization through the 2-silyl-1,3-dithiolane that opens new perspectives in the chemistry of such heterocyclic ring [14]. Actually, these 2-silyl-1,3-dithiolanes can be efficiently functionalized in the presence of fluoride ion with subsequent transfer of the dithiolane moiety onto different electrophiles, such as aldehydes, affording the corresponding protected α -hydroxy aldehydes, and showing that under the present conditions, silyl dithiolane can be considered a synthetic equivalent of a dithiolane anion. Furthermore, fluoride initiated functionalization of silyl dithiolanes and dithianes has been shown to occur with retention of configuration [15]. Such

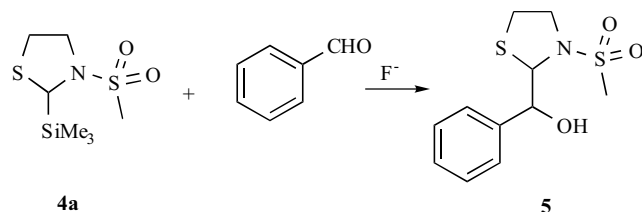
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results then outline the unicity of the silicon moiety in promoting these reactions, and evidence this methodology as a possible general one for the functionalization of otherwise not easily functionalizable heterocycles.

In this context, due to the greater importance of the thiazolidine ring system, and the efficiency, together with the mildness of the fluoride ion based procedure, we wondered whether such reactivity could have been satisfactorily applied to this heterocyclic system, thus leading to a possible general procedure of thiazolidine functionalization, and we undertook an investigation in such direction.

In order to obtain a general access to the variously functionalized thiazolidines, we had to devise a different synthetic approach with respect to those reported in the literature. In this context we could take advantage of the already experienced procedure that allowed the synthesis of the silyl dithiolane system [14]. We found that freshly prepared methoxy bromo methyltrimethylsilane (**1**) reacts smoothly *in situ* with aminoethanethiol (**2**) to afford a simple and direct access to the thiazolidine ring system (**3**) (Scheme 1). The thiazolidine thus obtained, again *in situ*, can be easily protected at the nitrogen atom with different groups, such as mesyl, tosyl, acetyl, benzoyl, cinnamoyl, BOC and Cbz, to afford a general access to variously *N*-functionalized 2-silylthiazolidines (**4a-g**) [16] through a simple one pot procedure (Scheme 1).

Then we moved to the evaluation of the possible functionalization of the so obtained silyl thiazolidines, and when compound (**4a**) was reacted with benzaldehyde, in the presence of fluoride ion, a smooth reaction occurred, leading to the corresponding functionalized α -hydroxy thiazolidine (**5**), in 52% yield, so disclosing a clean and mild functionalization of the heterocyclic ring and the generation of a novel class of acyl anion synthons (Scheme 2) [17]. Reaction occurs in the presence of catalytic amount of TBAF (10%), and we observed that the yields are not affected by the increase in the amount of fluoride. Then such reaction showed that a smooth functionalization may occur under the present conditions. In order to try a generalization of such reactional behaviour, and ascertain whether such functionalization could be dependent on the presence of a specific nitrogen protecting group, we reacted several differently *N*-protected thiazolidines with electrophiles.



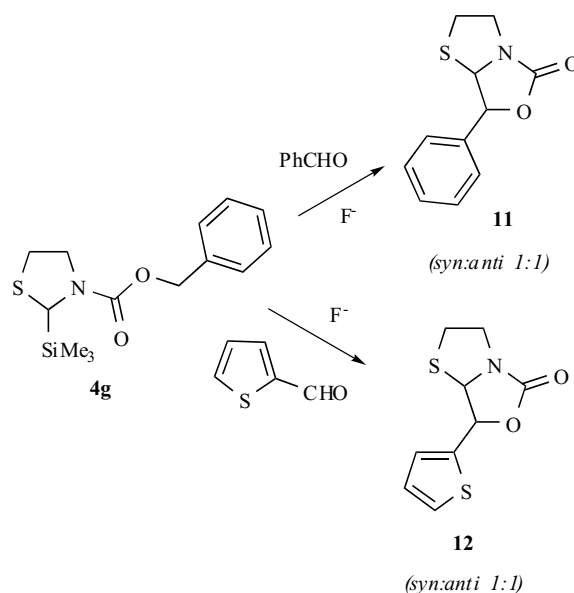
Scheme 2.

The results are summarized in Table 1.

The reactivity seemed rather general, and occurred smoothly in the presence of different *N*-protecting groups such as tosyl, mesyl, acetyl and BOC. No reaction was observed when the protecting groups were benzoyl and cinnamoyl, but only the desilylated thiazolidine was recovered from the reaction mixture.

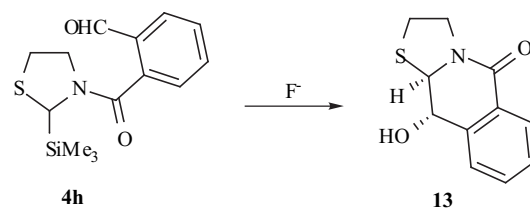
While compounds (**4a,c**) afforded the adducts as mixtures of diastereomers, compound (**4b**) showed a 20% d.e., but much more interestingly, the reaction of (**4f**) both with benzaldehyde and thienylaldehyde afforded, as estimated from the NMR of the crude reaction mixture, only a single diastereomer, thus evidencing a possible application of the present reaction in diastereoselective synthesis.

A different behaviour was observed when the protecting group was Cbz. In fact, in that case, under the same experimental conditions, a clean cyclization to oxazolidinones (**11**) and (**12**) was observed (Scheme 3) [18].



Scheme 3.

The versatility of the present methodology is further illustrated by another example. When the protecting group contains itself an electrophilic centre, a clean cyclization occurs, leading in good yields to polycyclic compounds. Thus, when reacting *N*-*o*-formylbenzoyl-2-trimethylsilylthiazolidine (**4h**) with fluoride ion, the polycyclic compound (**13**) can be isolated in very good yield, and with an interesting d.e. of 70% of the isomer with the two protons in anti configuration, as evidenced by the X-ray crystallographic structure. Such reaction then discloses the route to an easy and diastereoselective access to polycyclic derivatives with possible biological activity.



Scheme 4.

In conclusion, we may state that the fluoride ion based methodology of the carbon-silicon bond functionalization offers a simple and mild strategy for the functionalization of position 2 of the thiazolidine heterocyclic ring, differently protected at nitrogen, affording various products depending on the nature of the protecting group, thus opening a potentially useful route to interesting molecules.

Table 1.

Entry	Thiazolidine	Electrophile	Product ^a	d.r.	Yield (%) ^b
1		PhCHO		0%	52 ^c
2		PhCHO		20%	43 ^c
3		PhCHO		0%	30 ^c
4		<i>p</i> -NO ₂ -C ₆ H ₄ CHO		0%	35 ^c
5		PhCHO		>95%	50
6				>95%	41

^a Compounds showed spectroscopical and analytical data consistent with the assigned structure.

^b Yields refer to chromatographically pure material.

^c Mixture of diastereomers.

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- [16] To a solution of *in situ* prepared (bromomethoxymethyl) trimethylsilane (**1**) (obtained starting from 303 mg, 2.57 mmol of (methoxymethyl)trimethylsilane in 15 ml of CCl₄ and 404 mg, 2.53 mmol, of Br₂ in 5 ml of CCl₄), was added a suspension of 2-amino-ethanethiol hydrochloride (292 mg, 2.57 mmol) in dichloromethane (9 ml), DIPEA (536 μL, 3.08 mmol), and the mixture stirred overnight. The formation of thiazolidine (**3**) was followed by TLC on silica gel (AcOEt), or GC-MS m/z (%): 161 (M⁺, 2), 133 (23), 118 (35), 88 (100), 73 (36). The mixture was then added, at 0°C, with 2.6 ml of a 1M solution of methanesulfonyl chloride and stirred at room temperature until disappearance of the starting material and then was washed twice with H₂O, once with brine, dried and evaporated. The crude mixture was purified on silica gel (3:1 hexanes/AcOEt) to give the *N*-mesyl thiazolidine (**4a**) (206 mg, 0.86 mmol, overall yield: 34%) as a crystalline solid (m.p. 85-87°C). ¹H-NMR (CDCl₃, 200 MHz) δ (ppm): 0.13 (9H, s), 2.86 (3H, s), 2.92-3.10 (2H, m), 3.29 (1H, ddd, J=7, 9.2, 13.2 Hz), 4.16 (1H, dddd, J=0.6, 3, 6.8, 13.6 Hz), 4.48 (1H, s); ¹³C-NMR (CDCl₃, 50 MHz) δ (ppm): -3.1, 31.3, 36.5, 51.6, 54.9; MS m/z (%): 224 (2, M⁺-15), 196 (8), 166 (10), 160 (29), 137(31), 133 (23), 88 (24), 73 (100); Anal. Calc. for C₇H₁₇NO₂S₂Si: C, 35.11; H, 7.16; N, 5.85. Found: C, 34.90; H, 7.20; N, 5.67.
- [17] A solution of (**4a**) (50 mg, 0.21 mmol) and benzaldehyde (45 mg, 0.42 mmol) in freshly distilled anhydrous THF was treated with TBAF (21 μL of a 1M solution in THF) and stirred overnight. Diethyl ether (2 ml) was then added and the resulting organic layer washed once with brine and evaporated after drying over Na₂SO₄. Chromatographic purification (2:1 hexanes/ethyl acetate) gave 23 mg (52%) of (**5**) as a 1:1 mixture of diastereoisomers. ¹H-NMR (CDCl₃, 200 MHz) δ (ppm): 2.66 (3H, s), 2.80 (3H, s), 2.86-3.01 (6H, m), 3.33-3.52 (2H, m), 4.02-4.18 (2H, m), 4.68 (1H, d, J=8Hz), 4.81 (1H, d, J=4Hz), 5.26 (1H, d, J=8Hz), 5.28 (1H, d, J=4Hz), 7.33 – 7.48 (10H, m); ¹³C-NMR (CDCl₃, 50 MHz) δ (ppm): 32.2, 32.3, 38.0, 38.1, 51.1, 51.6, 70.9, 71.9, 76.6, 77.0, 126.8, 127.6, 128.3, 128.3, 128.4, 128.5, 138.6, 139.7; MS m/z (%): 255 (M⁺-18, 3), 207 (13), 176 (14), 166 (100), 88 (77), 77 (34); Anal. Calc. for C₁₁H₁₅NO₃S₂: C, 48.33; H, 5.53; N, 5.12. Found: C, 48.15; H, 5.60; N, 5.00.
- [18] A freshly distilled THF solution of (**4g**) (44 mg, 0.15 mmol) and benzaldehyde (32 mg, 0.30 mmol) was added with TBAF (30 μL of a 1M solution in THF) and stirred overnight. Diethyl ether (2 ml) was then added and the resulting organic layer was washed one time with brine, dried over Na₂SO₄ and evaporated. Chromatographic purification (4:1 hexanes/ethyl acetate) afforded 9 mg (27%) of **11-anti** and 9 mg (27%) of **11-syn**. Isomer *anti*: ¹H-NMR (CDCl₃, 200 MHz) δ (ppm): 3.04-3.15 (3H, m), 4.42-4.53 (1H, m), 4.99 (1H, d, J=1.8Hz), 5.53 (1H, d, J=1.8Hz), 7.36-7.43 (5H, m); MS m/z (%): 221 (M⁺, 29), 130 (32), 115 (45), 87 (100), 77 (34), 60 (84). Isomer *syn*: ¹H-NMR (CDCl₃, 200 MHz) δ (ppm): 2.93-3.01 (2H, m), 3.15-3.29 (1H, m), 4.36-4.47 (1H, m), 5.42 (1H, d, J=5.8Hz), 5.92 (1H, d, J=5.8Hz), 7.36-7.40 (5H, m); MS m/z (%): 221 (M⁺, 51), 130 (36), 115 (39), 87 (100), 77 (38), 60 (71); Anal. Calc. for C₁₁H₁₁NO₂S; C, 59.71; H, 5.01; N, 6.33. Found: C, 59.49; H, 5.10; N, 6.17.