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Straightforward access to 4-membered sulfurated heterocycles: introducing a strategy for the single and double functionalization of thietane 1-oxide

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A strategy for the stereoselective functionalization of thietane 1-oxide has been developed. Mono (C2 substituted) and doubly (C2, C4 disubstituted) functionalized thietanes have been obtained from the readily available thietane 1-oxide by using the corresponding organometallic intermediates that reacted with electrophiles leaving intact the 4-membered ring.

Four-membered heterocycles (FMH) have recently been recognized as privileged scaffolds in the drug-discovery process.[1] However, in striking contrast with five- and six-membered heterocycles, the number of FMH found in appropriate databases of lead compunds or fragment libraries is much smaller.[2] One can speculate that the ring strain associated to those systems, likely frightened medicinal chemists to use them in their researches. Furthermore, the scarcity of suitable building blocks and lengthy synthetic procedures for their introduction contributed to a reduced use of this kind of scaffolds. Moreover, with respect to oxetanes and azetidines, thietanes have received much less attention as sulfur-bearing compounds displaying biological activity.[3] Nevertheless, the importance of the thietane ring has been proven recently, leading to the development of several bioactive compounds (Figure 1).

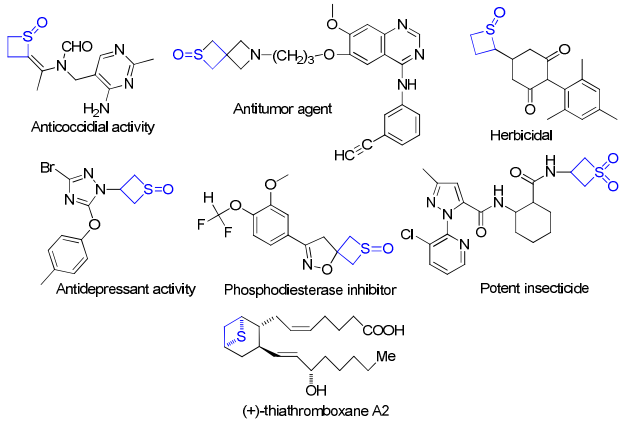
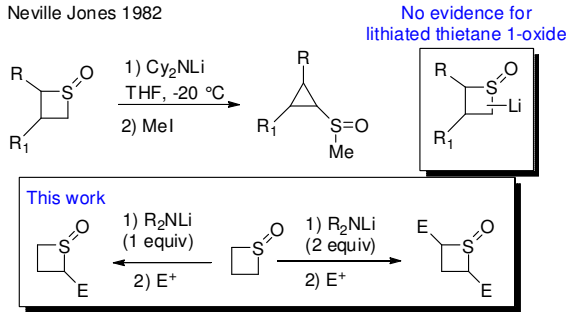


Figure 1 Bioactive compounds bearing a thietane moiety.

For example, (+)-thiathromboxane A2 showed a prolonged half-life with respect to thromboxane A2, in the platelet aggregation and vasoconstriction activity.[4] Oxidized thietanes were described as powerful insecticides,[5] anticoccidials,[5d] herbicidals,[5e] antitumor agents,[6] antidepressants[7] or enzyme inhibitors.[8] However most of the reported strategies are centered on thietanes devoid of C2- and/or C4-functionalization. In addition, there are still shortfalls in available strategies for the direct functionalization of FMH.[9]

In continuation of a research program aimed at developing new synthetic methodologies by using metalated small heterocycles,[10] we became interested in the direct C2-functionalization of FMH such as azetidines and thietanes. We envisaged that thietane 1-oxide **1** could be a suitable system to be investigated for two reasons: a) the biological importance of this system requires the development of new strategies for its functionalization, expanding the number of readily available derivatives in the drug-discovery process; b) to the best of our knowledge, efficient methodologies for the metalation/functionalization of simple thietane 1-oxides are rare. One isolated example reported by Neville Jones and coworkers in 1982 relies on the anionic rearrangement of lithiated diastereoisomeric 2,3- and 3-substituted thietane 1-oxides leading to functionalized cyclopropanes (Scheme 1).[11] In this work, it was demonstrated that the stereochemistry of the starting thietane 1-oxide affects that of the products, and a preliminary lithiation *syn* to the sulfinyl oxygen was proposed. However, the authors did not mention the possibility to capture the lithiated intermediates with electrophiles. We wish to report here our preliminary results on the first effective lithiation/trapping

sequence on thietane 1-oxide and stereochemical features emerged during this investigation (Scheme 1).



Scheme 1 Examples of lithiation of thietane 1-oxides.

An important aspect, we focused on while studying the metalation of FMH, is related to the presence of dynamic phenomena, associated to the ring substitution and/or ring-puckering, that could affect in some way the reactivity and stereoselectivity of the reaction.[12] In fact, crystallographic, experimental and computational studies assesed the ring puckering in four-membered rings,[13a-c] and in the case of thietane 1-oxide values of 21.2° and 16.8° have been calculated for the angle of puckering of the two main conformations.[13d] In the case of thietane **1** such ring puckering leads to conformations **1eq** and **1ax** (Figure 2). In addition, the presence of a prochiral sulfur atom makes diastereotopic the two removable protons and so two lithiated intermediates are, in principle, obtainable. Previously reported low temperature NMR studies demonstrated that **1** adopts one preferential puckered conformation with a pseudo-equatorial oxygen (**1eq** in Figure 2).[14] We confirmed such a preference by simulating the ^{1}H NMR spectra of the optimized geometries of **1eq** and **1ax** (see ESI).

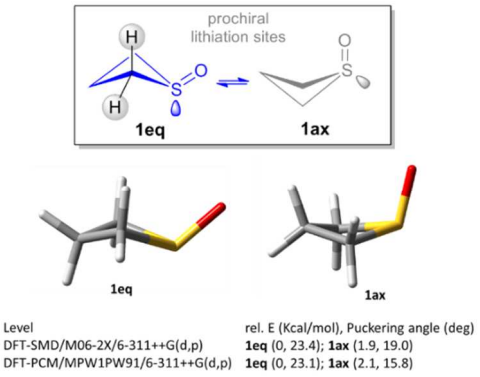


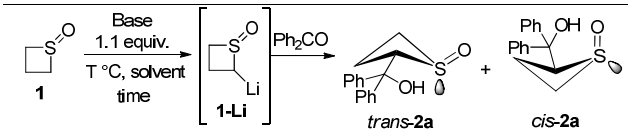
Figure 2 Ring puckering of **1** and optimized structures of conformers **1ax** and **1eq**.

With such evidences in hand, we speculated that the deprotonation should involve conformer **1eq** and that one main lithiated intermediate could be obtained as a consequence of a stereoselective lithiation *syn* to the sulfinyl oxygen atom.[15] In this case, only one stereoisomer would be expected from the reaction with the electrophile. Of course, a more complicated situation may result in the presence of a configurational instability of the lithiated intermediates or a non-stereoselective deprotonation.

In order to confirm or deny our hypotheses, and develop a strategy for the direct functionalization of thietanes, readily available thietane 1-oxide **1** was subjected to deprotonation under different reaction conditions reported in Table 1. Benzophenone was used as external electrophile, in place of D^+, for practical reasons because of the volatility and solubility in water of **1**.

As reported in Table 1 (entries 1,2), the use of MeLi or *n*-BuLi was unsuccessful giving only complex reaction mixtures perhaps as a consequence of a nucleophilic attack of the organolithium to the sulphur atom. We solved this problem by using lithium amides, such as LDA or LTMP, as bases for the deprotonation of **1** (entries 3-5). We were happy to find that both bases were able to deprotonate thietane **1** in 15 min. at -78 °C in THF, affording the putative lithiated intermediate **1-Li** trapped with benzophenone. However, we noticed that the reaction turned out not very stereoselective leading to two diastereomeric α-functionalized thietanes *trans*-**2a** and *cis*-**2a** in reasonable trans/cis ratios and with good yields (see Table 1).[16] Similar results, in terms of yield and stereoselectivity, were obtained using LDA in a less polar solvent such as toluene (entry 7). The structures of *trans*-**2a** and *cis*-**2a** were carefully ascertained by 1D and 2D-NMR experiments (see ESI) and confirmed by X-ray analysis in the case of the minor isomer *cis*-**2a**.[17]

Table 1. Stereoselective lithiations of **1**.



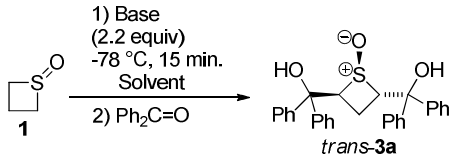
entry	Base	Solvent	T °C	time	Ratio *trans*/*cis*	Yield (%)[a]
1	*n*-BuLi	THF	-78	15 min	-[b]	-
2	MeLi	THF	-78	15 min	-[b]	-
3	LDA	THF	-98	15 min	77/23	78
4	LDA	THF	-78	15 min	83/17	80
5	LTMP	THF	-78	15 min	86/14	75
6	LDA	THF	-78	0[c]	70/30[d]	35
7	LDA	toluene	-78	15 min	70/30	80

[a]Overall yield of isolated products **2**. [b]Complex mixture. [c]Lithiated intermediates generated in presence of the electrophile. [d]The disubstituted derivative *trans*-**3a** was observed (see infra). Ratio **2a/3a** 70/30 ascertained by ^{1}H NMR.

Against our initial expectations (see above), the presence of *trans*-**2a** as the main product, suggested that the deprotonation might have occurred trans to the sulfinyl oxygen atom assuming a reaction with retention of configuration.[18] In addition, because we assumed that the deprotonation should involve **1ax** (Fig.2), the presence of *cis*-**2a** might also be explained.

Any hypothesis, to explain the stereoselectivity of the reaction, at this point could be only speculative needing mechanistic and stereochemical investigations that are out of the scope of this work.[19] Another interesting result was found in the reaction run under internal quenching conditions (Table 1, entry 6). In fact, adding a mixture of **1** and benzophenone in THF to a cooled (-78 °C) THF solution of LDA, the formation of 2,4-disubstituted thietane *trans*-**3a** was observed (20% yield).[20] We explained this result considering that the reaction was occurring in the presence of an excess of base likely favouring the double functionalization. In order to prove this hypothesis, **1** was reacted with 2.2 equivalents of LDA (or LTMP) (Table 2).

Table 2. Double functionalization of **1**.



entry	Base	Solvent	Ratio trans/cis [a]	Ratio **2a/3a**[b]	Yield (%)[c]
1	LDA	THF	>99:1	9/91	70
2	LTMP	THF	>99:1	10/90	65
3	LDA	toluene	>99:1	86/14	12

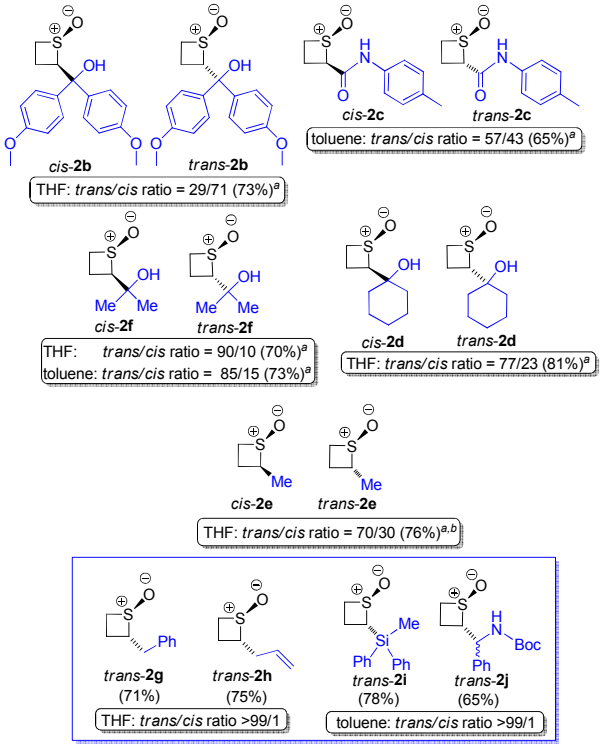
[a]Ratio of disubstituted thietanes **3**. [b]Ratio between mono- (*trans*-**2a** + *cis*-**2a**) and di-substituted (*trans*-**3a**) thietanes. [c]Yield of isolated product *trans*-**3a**.

We were happy to find that double functionalized product *trans*-**3a** could be obtained as the far predominating isomer performing the reaction in THF (entries 1, 2). The use of toluene resulted in low conversion and low selectivity (Table 2, entries 3) being the mono substituted thietanes *trans*-**2a** and *cis*-**2a** (63/37 ratio) the main reaction products.[21]

This result is, in our opinion, remarkable because it represents the first example of double direct one-pot C2, C4 functionalization of a thietane 1-oxide.

With the optimized conditions for the single and double functionalization in hand, we evaluated the scope of the methodology exploring first the single functionalization of **1** under the reaction conditions reported in Table 1 (entry 4 or 7) using 1.1 equiv. of LDA. In Scheme 2 the new C2-functionalized thietanes obtained are reported.

As reported in Scheme 2, lithiated thietane **1-Li** smoothly reacted with several electrophiles (ketones, isocyanates, imines, alkyl halides, silyl halides) leading to α-functionalized thietanes **2b-j**. The reaction proceeded with a selectivity depending on the electrophile. However, with the exception of **2b**, where cis selectivity was observed, all the other electrophiles gave mainly the corresponding trans stereoisomers.[22] In the reactions with BnBr, allylCl and $Ph_2MeSiCl$ only derivatives *trans*-**2g-i** were observed. In the reaction with imine PhCH=NBoc only the trans stereoisomer *trans*-**2j** was isolated as a mixture of diastereoisomers (75:25 ratio) considering the the newly created chiral center.



Scheme 2 Scope of the single functionalization of thietane **1**. [a]Overall isolated yields. [b]Inseparable mixture of stereosiomers.

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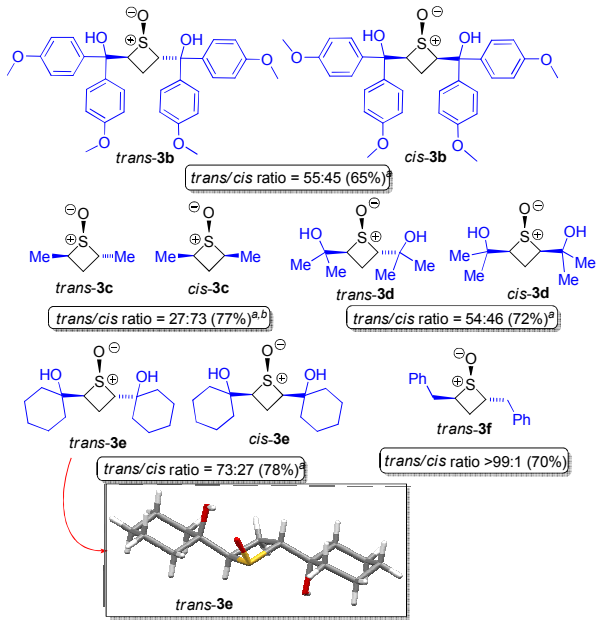
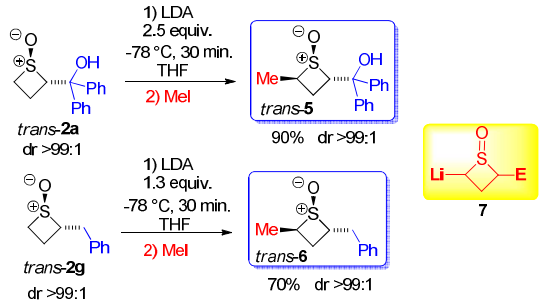
Similarly, the scope of the double functionalization was explored performing the lithiation of **1** under the optimized reaction conditions (Table 2, entry 1) obtaining new 2,4-disubstituted thietanes **3b-f** (Scheme 3).

The reaction was tested with ketones obtaining the corresponding bis-hydroxyalkylated products with variable stereoselectivity. In the case of *trans*-**3e**, X-ray analysis confirmed its structure and stereochemistry.[23] In the reaction with alkyl halides, variable degrees of stereoselectivity were also observed. The reaction with MeI resulted in the formation of *trans*-**3c** and *cis*-**3c** (trans/cis ratio: 27/73) while in the reaction with BnBr only *trans*-**3f** was obtained.



Scheme 3 Scope of the double functionalization of thietane **1**. [a]Overall isolated yields. [b]Inseparable mixture of stereoisomers.

Moreover, we were keen to find an explanation for the double functionalization of thietane **1**. In principle two possibilities could be envisaged: a) a stepwise lithiation/functionalization; b) the involvement of a dilithio species. This last hypothesis seems unlikely because it should involve a 2,4-dilithiated sulfoxide that, to the best of our knowledge, has not previously been observed. With the aim to get more insights on this double direct functionalization of thietanes, we attempted a further lithiation/trapping sequence on mono-substituted thietanes **2**. In particular when the main diastereoisomers *trans*-**2a** and *trans*-**2g** were reacted respectively with 2.5 equiv. and 1.3 equiv. of LDA at -78 °C for 30 min, the corresponding lithiated intermediate was generated and trapped with MeI (Scheme 4). The reaction resulted highly stereoselective and only trans disubstituted thietanes *trans*-**5** and *trans*-**6**, were obtained, as ascertained by NOESY experiments (see ESI), with very good yields.[20]



Scheme 4 Investigation on the double functionalization.

From our preliminary results it seems that the double functionalization could proceed stepwise involving the putative lithiated intermediates such as **7** (Scheme 4). Those results are important from a reactivity and stereochemical point of view and for planning stereoselective synthesis by using such heterosubstituted organolithiums.

In conclusion, this work tries to fill the gap in knowledge on the direct single and double functionalization of thietanes. An effective methodology for selective C2- and C2, C4-functionalizations of thietane 1-oxide has been developed for the first time. The mono (C2) functionalization as well as the double (C2, C4) functionalization occurred mainly with trans selectivity. Further studies will rely on the application of this methodology in stereoselective synthesis and in understanding the nature of the lithiated intermediates involved in the described processes.

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‡ Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data and copies of $^{1}H/^{13}C$ NMR spectra of new compounds. See DOI: 10.1039/c000000x/

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16) We use the trans/cis descriptors with reference to the spatial relationship between the introduced electrophile and the oxygen atom of the S=O group.

17) CCDC 978293 number of *cis*-**2a**. The crystallographic analysis of the *cis*-**2a**, revealed a puckered conformation for the four-membered ring, an equatorial benzhydryl group and an intramolecular hydrogen bond between the hydroxyl group and the axial oxygen atom of the sulfinyl group (see ESI).

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22) The relative stereochemistry has been assigned as reported in the supplementary material (see ESI).

23) CCDCD 978292 deposit number of *trans*-**3e**. A planarized four-membered ring resulted from X-ray analysis.

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