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Does an Oxygen Function Stabilize the Sulfonyl Carbanion? Metalation of 1,3-Oxathiane 3,3-Dioxides

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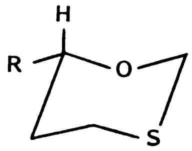
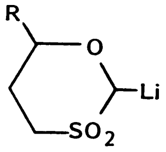
1,3-Oxathiane 3,3-dioxides were lithiated not at C-2 but at C-4 preferentially, which revealed that the oxygen function destabilizes the sulfonyl carbanion in this ring system.

Since we reported 1,3-oxathiane (1) was lithiated at C-2 but not at C-4 when treated with *s*-BuLi in tetrahydrofuran (THF),[1] attention has been paid for the chemistry of 2-lithiated 1,3-oxathianes.[2] Particularly, elegant applications of 2-lithio-1,3-oxathiane derivatives as a chiral acyl anion equivalent have been reported by Eliel and coworkers.[3] On the other hand, no report on the lithiation of the corresponding sulfone, 1,3-oxathiane 3,3-dioxide (2), has appeared. Here we describe the observation that, in contrast to 1,3-oxathiane (1), monometalation of 1,3-oxathiane 3,3-dioxide (2) occurs not at the carbon atom between the hetero atoms in the ring, but at the one adjacent to the sulfone group predominantly.



1, R = H
6, R = CH_3



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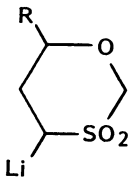

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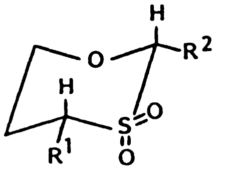
1,3-Oxathiane 3,3-dioxides 2[5] and 5 were obtained by the oxidation of the corresponding 1,3-oxathianes 1 and 6[6] with *t*-butyl hydroperoxide and a catalytic amount of molybdenyl acetylacetonate[7] in 83% and 81% yields, respectively. Sulfonyl carbanions generated by the addition of *n*-BuLi (1.1 equiv.) in THF at -78 °C were stirred at the given temperature for 1 h and the products were analyzed after quenched with electrophiles. The results are listed in Table 1. The most striking feature of the results in Table 1 is that the product substituted at C-4 was obtained predominantly in every case, regardless of the reaction conditions and electrophiles. Although we don't have conclusive evidence to determine whether this preference is largely kinetic or whether it is thermodynamic, involving the formation of a more stable C-4 lithium species 4, both factors seem to be responsible.

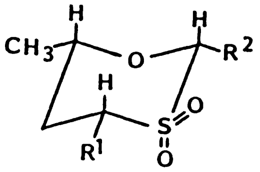
Table 1. Lithiation of 1,3-Oxathiane 3,3-Dioxides **2** and **5**

Entry	Starting material	Reaction temp/°C	Additive	Electrophile	Total yield/%	Product (Relative ratio)	Product ratio C-4 : C-2
1	**2**	-78	non	CD_3COOD[a]	99	**7**(67), **8**(29), **2**(4)	2.3 : 1
2	**2**	-78	12-crown-4	CD_3COOD[a]	96	**7**(58), **8**(42), **2**(0)[b]	1.4 : 1
3	**2**	-78	non	TMSCl	98	**9**(62), **10**(18), **2**(20)	3.4 : 1
4	**2**	-78	12-crown-4	TMSCl	87	**9**(39), **10**(12), **2**(49)	3.3 : 1
5	**2**	-78	HMPA	TMSCl	100	**9**(61), **10**(19), **2**(20)	3.2 : 1
6	**2**	-78	non	CH_3I	90	**11**(57), **12**(0), **2**(43)	-
7[c]	**5**	-78	non	CD_3COOD	d	**13**(41), **14**(16), **2**(43)	2.6 : 1
8[e]	**5**	-78 -25	non	CD_3COOD	d	**13**(55), **14**(10), **2**(35)	5.5 : 1
9	**5**	-78	non	TMSCl	90	**15**(71), **16**(18), **5**(11)	3.9 : 1
10	**5**	-30 -45	non	TMSCl	98	**15**(72), **16**(22), **5**(6)	3.3 : 1
11	**5**	-78	non	TMSCl[f]	82	**15**(22), **16**(7), **5**(71)	3.1 : 1

a) The anion was added to the THF solution of electrophile at 0 °C. b) 2,4-Dideuterated 1,3-oxathiane 3,3-dioxide was obtained in 4% yield. c) 0.9 equiv. of n-BuLi, 10 min. d) Not determined. e) 0.9 equiv. of n-BuLi, 10 min at -78 °C + 10 min at -25 °C. f) To a mixture of **5** and TMSCl was added n-BuLi.



2, R^1 = R^2 = H
7, R^1 = D, R^2 = H
8, R^1 = H, R^2 = D
9, R^1 = TMS, R^2 = H
10, R^1 = H, R^2 = TMS
11, R^1 = CH_3, R^2 = H
12, R^1 = H, R^2 = CH_3



5, R^1 = R^2 = H
13, R^1 = D, R^2 = H
14, R^1 = H, R^2 = D
15, R^1 = TMS, R^2 = H
16, R^1 = H, R^2 = TMS

6-Substituted 1,3-oxathiane 3,3-dioxides are ideal substrates to test not only the position but also the stereochemistry of the metalation, because the equatorial substituent at C-6 gives a similar steric influence to C-2 and C-4, and also will lock the conformation of the six-membered ring. 6-Methyl-1,3-oxathiane 3,3-dioxide (**5**) was lithiated with 0.9 mol equiv. of n-BuLi, where the equilibrium between **3** (R = Me) and **4** (R = Me) can be attained via unlithiated species **5**. A portion of the reaction mixture was quenched with CD_3COOD after 10 min at -78 °C to give 4-deuterated species **13** and 2-deuterated species **14** in 2.6 : 1 ratio (entry 7), which changed to 5.5 : 1 after 10 min at -25 °C (entry 8). Metalation of **5** followed by the addition of trimethylsilyl chloride afforded cis-isomers **15** and **16** in a ratio of 3.9 : 1 at -78 °C (entry 9). The cis-relationship between the substituents in **15** and **16** was easily deduced from the ^1H NMR spectra including decoupling experiment.[8)] This result shows that the equatorial preference of lithium both at C-2 and C-4 in the carbanionic intermediate.[9)] Predominant formation of **15** over **16** was preserved when the reaction temperature was raised (entry 10). These facts indicate the thermodynamic stability of 4-lithio species **4** (R = Me) over 2-lithio species **3** (R = Me). Similar product ratio was observed under the conditions where the lithium species could be trapped with an electrophile immediately after the formation (entry 11), indicating the kinetic preference of the formation of C-4 lithium species.

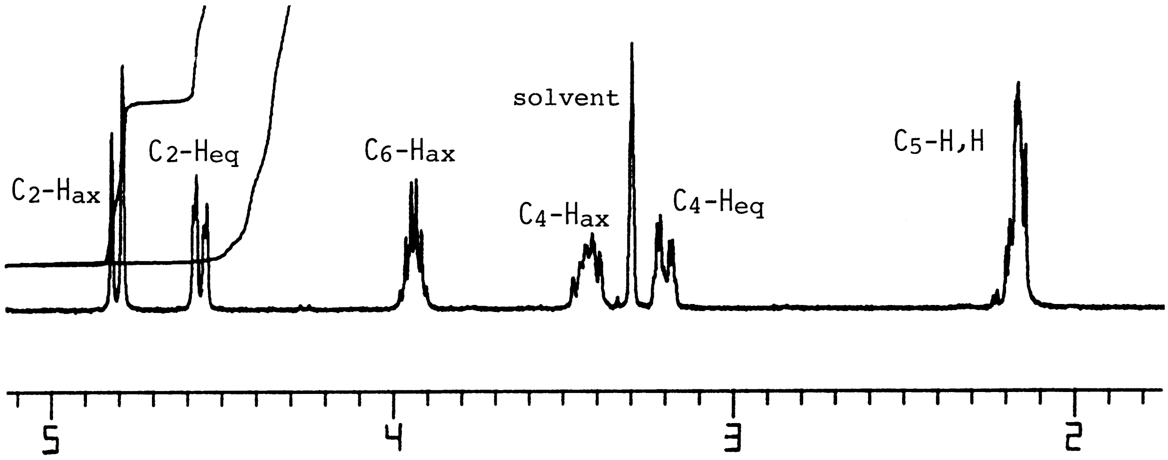


Fig. 1. ^{1}H NMR spectrum of **5** in CD$_3$OD with CD$_3$ONa after 70 min at 0 °C.

Table 2. Deuterium Exchange of **5** Measured in CD$_3$OD with CD$_3$ONa[a)]

	Deuterium incorporation/%			
Time/min	C$_2$-H*eq*	C$_2$-H*ax*	C$_4$-H*eq*	C$_4$-H*ax*
10[b)]	7.3	0	10.9	0
40[b)]	9.1	0	16.4	0
70[b,c)]	12.7	0	18.2	0
87	25.0	0	41.6	0
102	42.8	1.2	69.8	3.2
118	60.3	3.2	84.1	6.4
133	71.1	3.2	88.7	6.5
148	77.4	4.8	91.9	11.3
178	85.5	6.5	93.5	19.4
208	93.3	8.9	96.0	21.3

a) At 20 °C unless otherwise stated. b) At 0 °C. c) The tempeture was raised to 20 °C within a minute immediately after taking the spectrum.

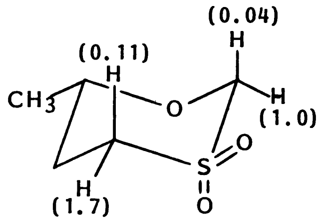


Fig. 2.
Numbersin parentheses indicate the relative rates for deuteration.

To determine the relative kinetic acidities of protons at C-2 and C-4 in **5**, ^{1}H NMR spectra were measured in CD$_3$OD with CD$_3$ONa. Each signal was well separated in the spectrum at 400 MHz as shown in Fig. 1 allowing the quantitative determination of deuteration for each signal. The initial relative rate for deuterium exchange was calculated from the data at 20 °C in Table 2 and the results are shown in Fig. 2. Thus, the equatorial proton at C-4 is more acidic than any other protons in **5** under the kinetically controlled conditions.

A conclusion from the present studies is that in the 1,3-oxathiane 3,3-dioxide system the α-oxygen functionality destabilizes the sulfonyl carbanion both kinetically and thermodynamically.

Theoretical ab initio studies of the lithiated species **3** and **4** and the corresponding bare anions are currently under way.

References

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5) Satisfactory spectral and analytical data were obtained on all new compounds reported herein.

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8) **13:** δ ($CDCl_3$, 100 MHz) 0.20 (s, 9H), 1.23 (d, J = 6 Hz, 3H), 1.73 - 2.43 (m, 2H), 2.65 (d,d, J = 12,4 Hz, C4-Hax), 3.49 - 3.77 (m, C6-Hax; d,d, J = 10,3 Hz on irradiation at 1.23 ppm indicating axial orientation of this proton), 4.42 (s, 2H). **14:** 0.26 (s, 9H), 1.27 (d, J = 6 Hz, 3H), 1.88 - 2.63 (m, 2H), 3.03 - 3.22 (m, 2H), 3.48 - 3.81 (m, C6-Hax; d,d, J = 10,3 Hz on irradiation at 1.27 ppm), 4.29 (s, 1H).

9) An alternative possible interpretation, in which the axial lithium intermediate was trimethylsilylated with complete inversion, is considered highly unlikely.

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