

QUANTITATIVE METALATIONS OF 2-SUBSTITUTED 1,3-DITHIANES AT -78°C USING *n*-BuLi/Na-O-*t*-Bu[#]

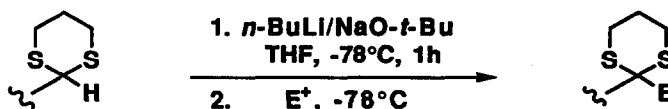
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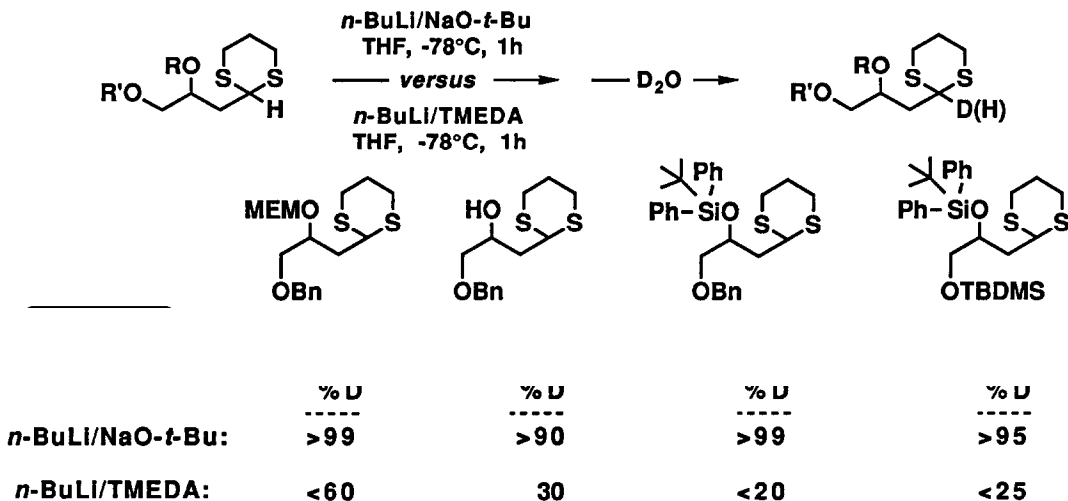
Abstract. Substituted dithianes can be metalated rapidly at -78°C in a virtually quantitative fashion using *n*-BuLi and Na-O-*t*-Bu in THF. Subsequent introduction of an electrophile affords fully substituted masked ketone equivalents.

As part of our efforts in the polyene macrolide area,¹ we were faced with the task of metalating a protected polyol dithiane for eventual coupling with an epoxide. Numerous attempts utilizing *n*-BuLi in various solvents with or without additives (e.g., TMEDA, DMPU, etc.) were uniformly low yielding. It occurred to us that an intrinsically stronger base, such as that expected from *n*-BuLi/Na-O-*t*-Bu,² potentially of a lower aggregation state³ versus *n*-BuLi,⁴ might make a difference. Moreover, while dithianes lithiate with a strong preference for the equatorial site,⁵ it is not obvious that the same stereoelectronic/steric demands operate with what may be the sodio analog. Once metalated, there was the added benefit of greater reactivity, assisted in part by less favorable driving forces for oxygen-sodium chelation. With these concepts in mind and the prospects for potentially solving a problem of a more general scope,⁶ a study was initiated on the use of *n*-BuLi/Na-O-*t*-Bu as a means of dithiane metalation.⁷ Herein, we report on our successful observations along these lines.

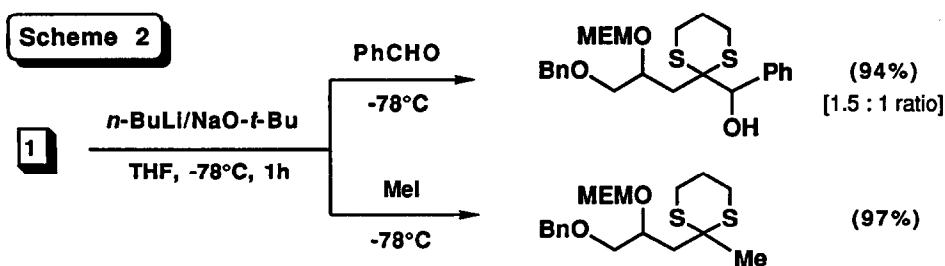


[#]Dedicated with admiration and appreciation to Professor Harry H. Wasserman in honor of his 70th birthday.

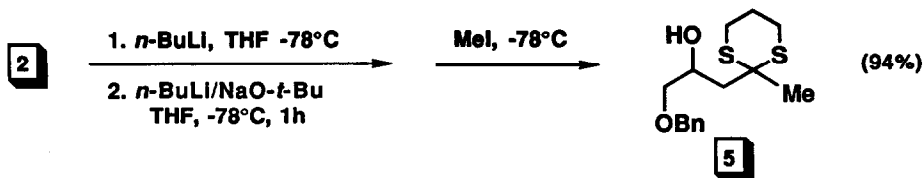
A series of substituted dithianes **1-4** were prepared, each containing partially or fully protected hydroxyl functionality. The extent of their metalation using the *in situ* Schlosser-type combination² of *n*-BuLi + NaO-*t*-Bu (~1.1 eq) under standardized conditions (THF, -78°C, 1h) was assessed relative to that realized using *n*-BuLi + TMEDA. Based on ¹H NMR analyses of D₂O quenched materials, all were essentially completely metalated, while lithiation proceeded to a consistently lesser degree (Scheme 1).



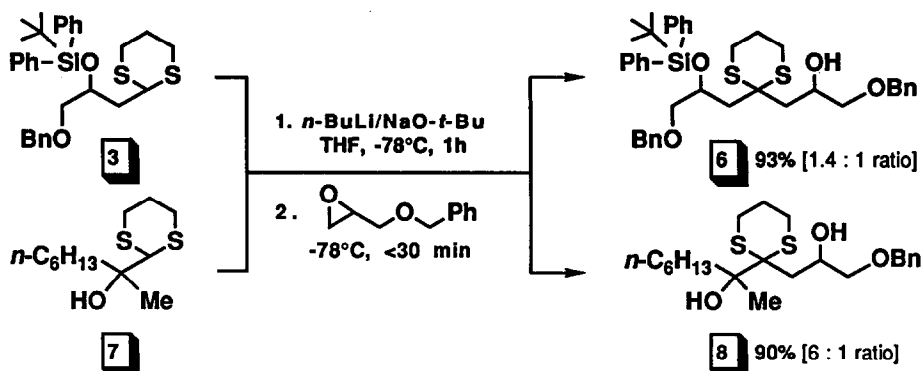
Other electrophiles were also screened for their compatibility and reaction efficiency with metalated dithianes generated under these conditions. MEM derivative **1** was metalated and then treated, in separate experiments, with PhCHO and MeI, to give the respective products shown (Scheme 2).



The mixed lithio sodio dianion of **2**, likewise, was converted to product **5** in high yield.



Most noteworthy are the reactions of these dithianes with functionalized epoxides. Exposure of **3** in metalated form to glycidol benzyl ether afforded the unsymmetrically protected adduct **6** in excellent yield. Hydroxy dithiane **7**, in its *bis*-metalated state (i.e., using 2.1 eq base), also reacted cleanly with this epoxide to give **8**. These ring openings all take place at -78°C in less than 30 minutes.



A typical procedure (for the preparation of **5**) is as follows: In a 5mL round bottom flask was placed $\text{NaO-}t\text{-Bu}$ (16.4mg, 0.18mmol, weighed out under Ar). Dry hexanes (0.4mL) were added, the flask was cooled to 0°C , and $n\text{-BuLi}$ (0.06mL, 0.17mmol) was introduced and the resulting slurry was stirred at 0°C for 1h and then for 1h at room temperature, followed by cooling to -78°C . In a separate flask was placed the dithiane (48.4mg, 0.17mmol) dissolved in 0.4mL THF and cooled to -78°C . $n\text{-BuLi}$ (0.06mL, 0.17mmol) was added and the solution stirred for 15 min. The alkoxide was then added to the slurry which turned dark brown after a few minutes at this temperature. After 1h at -78°C , MeI (0.014mL, 0.22mmol) was introduced *via* syringe, which led to an immediate color change. After 5 min, the mixture was quenched with water and warmed to ambient temperature. Usual extractive workup (Et_2O), drying (Na_2SO_4) and flash chromatography (SiO_2) using 5:1 hexanes/ Et_2O afforded 47.7mg (94%) of the desired product as a colorless oil; IR (neat) cm^{-1} 3420, 2900, 1290, 1070; $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.34 (m, 5H), 4.59 (d, 1H), 4.56 (d, 1H), 4.15 (m, 1H), 3.15 (m, 2H), 3.12 (d, 1H), 3.00-2.88 (m, 2H), 2.81-2.75 (m, 2H), 2.30-1.86 (m, 4H), 1.67 (s, 3H); MS: m/z (relative intensity) 298(M^+ , 5), 207(25), 147(44), 133(45), 91(100); HRCIMS calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2\text{S}_2$ 298.4693; found 298.4689.

That $n\text{-BuNa}$ is likely to be the species responsible for effecting the metalation is suggested by the initial isolation of this salt in purified form,^{3,8} followed by its dry box transfer and use in the sodiation of, e.g., **1** and **3**, under otherwise similar conditions. D_2O quenching led to >95% incorporation of deuterium in both cases, as seen employing the far more convenient $n\text{-BuLi} + \text{Na-O-}t\text{-Bu}$ combination (*vide supra*).

In summary, the trivial addition of $\text{Na-O-}t\text{-Bu}$ ⁹ to $n\text{-BuLi}$ allows for an especially mild method for metalating monosubstituted dithianes.¹⁰ Moreover, these derivatives are highly reactive toward carbon-based electrophiles and hence, show promise as intermediates in complex natural products total synthesis.

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References and Notes

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9. Obtained from Fluka. In contrast to K-O-*t*-Bu, which is oftentimes multiply sublimed prior to use,⁷ Na-O-*t*-Bu has been used here without further purification.
10. For a review of recent 1,3-dithiane chemistry, see Bullman Page, P.C., van Niel, M.B., Prodger, J.C., *Tetrahedron*, **1989**, 45, 7643; see also Trimitsis, G.B., Tuncay, A., Beyer, R.D., Ketterman, K.J., *J. Org. Chem.*, **1973**, 38, 1491.

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