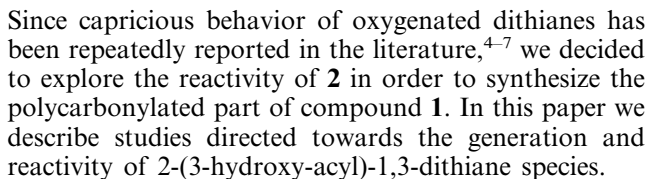
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**Abstract**—Lithium enolates of oxygenated acyl-dithiane undergo unexpected regiospecific reactions with electrophiles. Reaction of aldehydes with oxygenated acyl-dithiane leads to the formation of the corresponding monosubstituted  $\beta$ -hydroxy-acyl-dithiane.  
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The dithioacetal group is a valuable synthetic tool for the protection of aldehydes and ketones.<sup>1</sup> Monosubstituted dithianes are very useful since their anions can be coupled with a variety of electrophiles,<sup>2</sup> and many total syntheses of natural products involved the 1,3-dithiane linchpins.<sup>3</sup> During our ongoing studies directed towards the synthesis of complex, highly oxygenated species, we needed polycarbonylated compound **1** bearing a 1,3-dithiane functionality.



Compound **2** was obtained via a two step procedure by addition of *n*-BuLi-deprotonated 1,3-dithiane with  $\gamma$ -butyrolactone, followed by a *tert*-butyldimethylsilyl ether protection of the hydroxyl group.<sup>8</sup>

Deprotonation of 2-substituted dithianes often requires stronger bases,<sup>9</sup> solvent additives and a myriad of time and temperature regimes. The conditions developed by Smith (*t*-BuLi in 10% HMPA/THF,  $-78^{\circ}\text{C}$ ) were used to assure rapid metalation of substrate **2**.<sup>3d</sup> The enolates were then reacted with various electrophiles at  $-78^{\circ}\text{C}$  and quenched after 4 h with a saturated solution of ammonium chloride. The crude reaction mixtures were generally very clean and needed only a simple and rapid purification through a short silica gel column.<sup>10</sup>

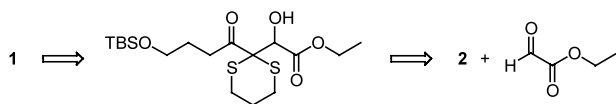
As expected, halogenoalkanes led to  $\alpha$ -alkylation producing the corresponding 2-alkyl-2-acyl-1,3-dithianes in good to excellent yields (data not shown). Curiously, no reaction was observed with diethyl oxalate even at higher temperature. To overcome this lack of reactivity, we decided to study the addition of various acid chlorides to the lithio derivative of compound **2**.

Interestingly, only the formation of the corresponding enol esters was observed (Table 1). This reactivity is independent of the dithiane (entry 4) and is in agreement with the HSAB concept. The most electronegative atom of the ambidentate nucleophile is the harder site. Consequently, the oxygen atom, which bears most of the negative charge, reacts with hard electrophiles such as acid chlorides to give the corresponding enol esters.<sup>11</sup> This result prompted us to opt for a two-step procedure to generate the polycarbonylated part of **1**. We planned to condense 2-lithio-2-acyl-1,3-dithiane with ethyl glyoxalate and oxidize subsequently the alcohol function into the corresponding ketone (Scheme 1).<sup>12</sup>

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**Table 1.** Reaction of acyl-dithiane with acyl-dithiane

Entry	Substrate	Acid Chloride	Product	Yield (%) <sup>a</sup>
1				90
2				75
3				68
4				87

<sup>a</sup> Isolated Yield**Scheme 1.** Synthesis of **1** by a two-step procedure.

Unexpectedly, we observed the formation of the  $\alpha'$ -addition product instead of the desired  $\alpha$ -product (Table 2). To understand this unprecedented result we undertook a systematic study of both structural and functional parameters of the reaction substrates. Similar regioselectivities were obtained with various aldehydes as shown in Table 2 to form diastereomeric mixtures of ( $\beta$ -hydroxy)-2-acyl-1,3-dithianes **3a–d** in good to fair yields (entries 1–4). Because kinetic considerations cannot explain this selectivity, we examined the stabilization of the lithium enolate by coordination with the oxygen atom on the side chain. Therefore we elongated the chain between the carbonyl and the ether function by one carbon atom, and observed a significant decrease in yield (entry 5). Complete deletion of the oxygen atom did not lead to the  $\alpha'$ -product, but only to the classical  $\alpha$ -addition product: 2,2-disubstituted-1,3-dithiane (entries 6 and 7).

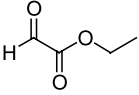
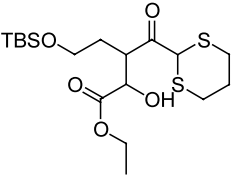
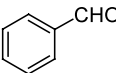
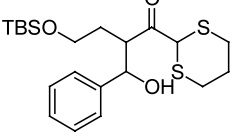
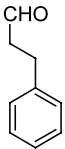
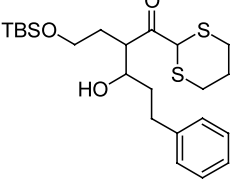

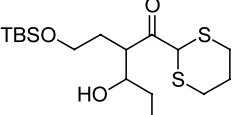
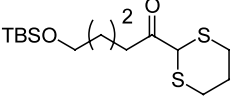
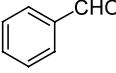
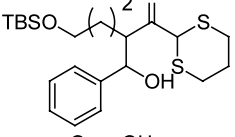
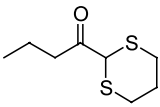
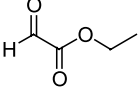
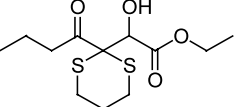
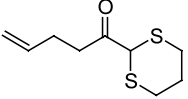
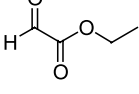
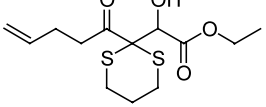
Although there are metalation/substitution processes reported in the literature, none is comparable to our system.<sup>13</sup> Clearly, our results are in agreement with a strong chelation effect of the oxygen atom of the *tert*-

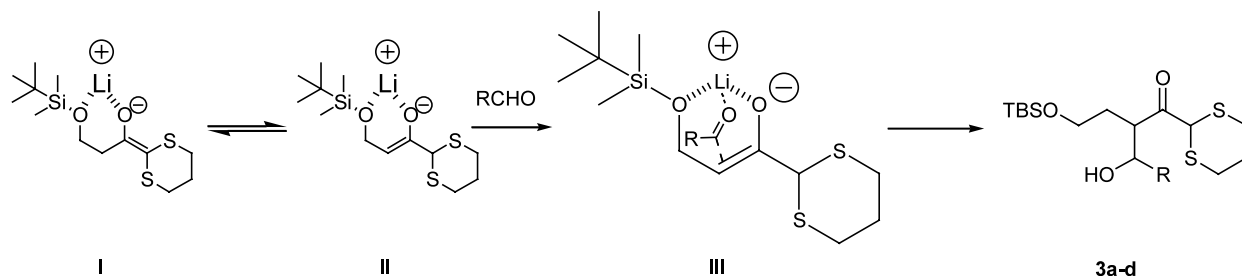
butyldimethylsilyl ether group. After deprotonation of **2**, structure **II** is the most stable intermediate, even as a 7-membered cyclic system including the lithium cation. The addition of aldehydes occurs through a classical carbonyl coordination with the lithium, which directs the approach as represented in **III** to lead to products **3a–d** (Scheme 2).

Finally, with the desired condensation product in hand (Table 2; entry 7) a hydroboration followed by oxidation of the secondary alcoholic function leads to the target compound **1**.

In conclusion, we showed in this study that the dithiane intermediate **2**, after metalation with *t*-BuLi reacts readily with various electrophiles. Three different types of products were obtained depending on the nature of the electrophile used. Alkyl halides and related compounds gave the expected  $\alpha$ -addition products, whereas acyl chlorides led to enol esters in which the double bond is exclusively tetrasubstituted. Notable was the unprecedented  $\alpha'$ -addition of aldehydes, which could be rationalized on the basis of a cyclic lithium enolate in which the oxygen chelation of the aldehydes directs the observed  $\alpha'$ -selectivity. Carbanions play an important role in chemical synthesis. Control of regio- and stereochemistry in the formation of carbon–carbon bonds and rationalization of structural effects on carbanion properties represent an important facet of organic chemistry. By developing effective solutions to our initial problem, we were able to expand the considerable potential of dithiane coupling reactions. These

**Table 2.** Reaction of acyl-dithiane with aldehydes

Entry	Substrate	Acid Chlorides	Product	Yield (%) <sup>a</sup>
1	2			92
2	2			70
3	2			55
4	2			30
5				45
6				78
7				80

<sup>a</sup> Isolated Yield**Scheme 2.** Proposed mechanism for the reaction of acyl-dithiane with aldehydes.

preliminary results show that metalated 2-(3-hydroxy-acyl)-1,3-dithiane display unexpected regioselectivities towards aldehydes, which paves the way for synthesis of various polyfunctionalized compounds of interest. Applications of these transformations are under way in our laboratory for the synthesis of natural products.

#### Acknowledgements

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10. Typical experimental procedure: To a solution of acyl-dithiane **2** in THF/HMPA (9/1, 0.4 M) at  $-78^{\circ}\text{C}$  a solution of *t*-BuLi in hexane (1.5 equiv.) is added dropwise. The solution is stirred 40 min at this temperature. The electrophile in THF (1 M) is then added dropwise and the reaction is left 4 h at  $-78^{\circ}\text{C}$ . Quenching with  $\text{NH}_4\text{Cl}$  (20 mL), followed by usual work up and flash chromatography give the expected products. Separation of the diastereoisomeric products was not usually possible by gel chromatography. All compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and mass spectrometry.
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