JOC Note

When Ethyl Is Infinitely Different from Methyl: Double Addition of Lithiated Dithianes to Aromatic Carboxylates Revisited

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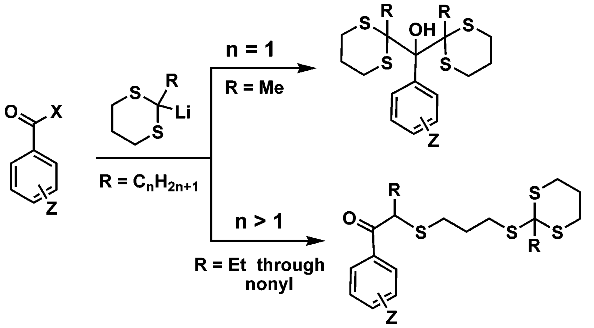
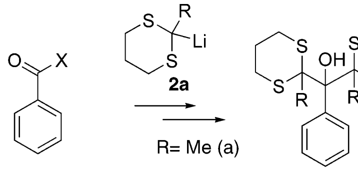


Addition of lithiated alkyl dithianes to benzoyl chloride or methyl benzoate does not produce the expected product of double addition, α,α-bis(alkyldithianyl) benzyl alcohol, for alkyls larger than methyl. Instead, the first step intermediate, i.e. 2-benzoylated dithiane, undergoes an electron-transfer reduction by the second molecule of the dithianyl anion. This reduction is followed by the ring-opening mesolytic fragmentation of the dithiane ring in the ketyl anion radical and subsequent radical recombination yielding acetophenone-tethered thioortho esters **4**, α-[3-(2-alkyl-1,3-dithiane-2-ylthio)propylthio]-α-alkyl-acetophenones. It appears that the Corey−Seebach bisaddition of lithiated dithianes to methyl benzoate is an exception rather than the rule in the alkyl dithiane series.

The Corey−Seebach umpolung approach, based on reactions of lithiodithianes with a variety of electrophiles, including carbonyl compounds, has secured a prominent place among the classical methodologies of synthetic organic chemistry.[1] One of its flavors, the methyl dithiane addition to alkyl benzoates or benzoyl chloride, offers access to tertiary alcohols **3** containing two dithiane moieties, much like the double addition of other organometallic reagents (Scheme 1). Unsubstituted dithiane was noted to react less efficiently because of possible deprotonation of the enolizable intermediate, benzoylated dithiane, by an excess dithiane anion.[2] Thus, it appears that the only known efficient double addition of lithiodithianes to benzoates is the case of methyl dithiane.

SCHEME 1



1
X = OMe, Cl

3a

Previously, we utilized such bisadducts of methyl dithiane in the development of a new generation of externally sensitized photocleavable latches possessing high quantum yields of fragmentation.[3]

Extension of this photochemical project required a series of different alkyl dithianes as labeling tags for mass-discriminating GCMS detection; thus, we proceeded with syntheses of nine bisdithiane adducts, using methyl- through nonyl-substituted dithianes. The reactions were run according to both the original Corey−Seebach procedure (i.e., at −20 °C[1d]) and a simpler method which we have developed for +20 °C experiments.[4] In subsequent benzophenone-sensitized photochemical experiments, all nine dithianes were released from their respective adducts, as expected. Similar photochemistry notwithstanding, the proton NMR spectrum of the *methyl* dithiane-based bisadduct was noticeably different from the ones obtained for the higher, ethyl through nonyl, homologues.

Although the integration ratio of the aromatic protons to the aliphatic protons indicated that two molecules of dithiane were indeed added, there was a triplet at approximately 4 ppm, $J = 7.3$ Hz, which was difficult to assign (Figure 1). Initially, this spectral inconsistency was attributed to the differences in the conformational behaviors of methyl vs ethyl dithiane adducts, which we have previously seen in the methyl/ethyl dithiane adducts of benzophenone;[5] the anisotropy associated with the aromatic ring and sulfur atoms caused some unusual chemical shifts. Yet, further spectroscopic investigation of the "anomalous" adducts revealed that they are not the α,α-bis(dithianyl) benzyl alcohols but rather rearranged products.

Figure 1 shows a comparison of aliphatic ^{1}H NMR signals for the bisadducts of methyl and ethyl dithianes with benzoyl chloride. In the bisadduct of methyl dithiane, **3a** (top spectrum), resonances of dithiane's CH$_2$S protons, both axial and equatorial pairs, are more compact, appearing in the 2.5−3.0 ppm range. In the ethyl dithiane bisadduct, **4b** (bottom spectrum), the two axial CH$_2$S protons of dithiane are found 0.7 ppm downfield

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(1) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075. (b) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1077. (c) Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434. (d) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (e) Groebel, B. T.; Seebach, D. *Synthesis* **1977**, 357.

(2) See ref 1d, although examples of high-yielding double addition of unsubstituted lithiodithiane to benzoyl chloride are known: Kita, Y.; Sekihachi, J.-I.; Hayashi, Y.; Da, Y.-Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108.

(3) Li, Z.; Kutateladze, A. G. *J. Org. Chem.* **2003**, *68* (21), 8236.

(4) We found that at room temperature addition of butyllithium to a THF solution of dithiane generates >90% anion within 15−20 min after which it slowly degrades. Most of the reactions with carbonyl compounds occur at room temperature at much higher rates, within minutes furnishing the desired adducts in excellent yields, even in the case of less-reactive aromatic ketones, for which the reaction time at low temperatures can be as long as 12−24 h (ref 1d).

(5) Gustafson, T. P.; Kurchan, A. N.; Kutateladze, A. G. *Tetrahedron* **2006**, *62*.

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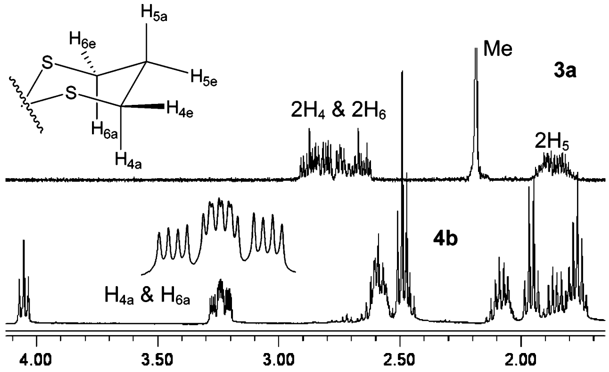


FIGURE 1. Partial ^{1}H NMR traces for bisadducts of methyl (**3a**, top) and ethyl (**4b**, bottom) dithiane addition to benzoyl chloride. The scale (ppm) is the same for both spectra.

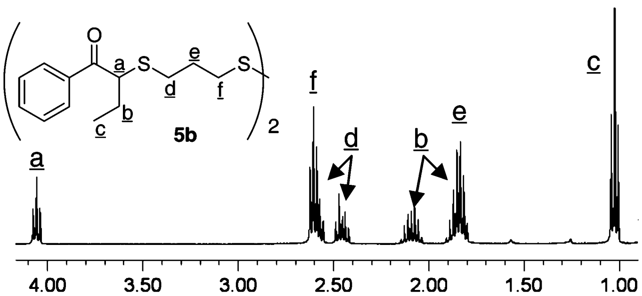


FIGURE 2. Aliphatic proton expansion of the monoadduct **5b**.

of the equatorial pair, at 3.25 and 3.23 ppm. Both H_{4a} and H_{6a} protons have spin−spin coupling constants of 14.2 Hz (geminal), 12.3 Hz (axial−axial, $H_{4/6a}$−H_{5a}), and 2.6 Hz (axial−equatorial). These axial dithiane protons integrate to 2H relative to the aromatic H's, which implies that only one dithiane ring survived.

Analysis of trace products, in the reaction at lower temperature, provided a critical clue in the form of a byproduct, which had a 5H:12H aromatic to aliphatic proton ratio, i.e., a monoadduct. (More of this byproduct is formed at low temperature than at high temperature.) The aliphatic portion of its ^{1}H NMR spectrum (Figure 2) clearly indicates that no *intact* dithiane ring is present in this compound.

The triplet at 4.05 is nearly identical to the triplet of the bisadduct above, and we assigned it to the α-proton (H_a) of the butyrophenone's aliphatic chain. Diastereotopic protons H_b and H_d have geminal spin−spin coupling constants of 12.5 and 14 Hz, respectively.

COSY cross-peaks indicate that there are two separate spin systems: 1H(a)−2H(b)−3H(c) and 2H(d)−2H(e)−2H(f). On the basis of NMR analysis, we assigned the structure to disulfide **5b** (Figure 2). Although we do not see a molecular ion in the mass spectrum of **5b**, it shows fragments with a molecular weight exceeding 268, i.e., greater than $M^+/2$, indicating that the molecule is indeed a dimeric disulfide. Both bisadduct **4b** and disulfide **5b** have typical acetophenone carbonyl resonances at approximately 195 ppm in the ^{13}C NMR spectra (see Supporting Information).

We assigned the structure of the bis-adduct to thioortho ester **4b**. The dithiane resonances for axial and equatorial CH_2S protons are in very good agreement with previously reported values for comparable methylthio dithiane.[6] We also synthesized 2-butylthio-2-ethyl dithiane, which has resonances matching the alkylthio dithianyl moiety of **4b**.

A likely mechanism accounting for all experimental observations is shown in Scheme 2. In the first step, benzoylation of a dithianyl anion, furnishing ketone **6**, occurs regardless of the size of substituent R. However, when R is ethyl or higher, the second addition of a dithiane anion (to **6**) is impeded because of steric congestion. Instead, a single-electron transfer (SET) reduction takes place to give anion radical **6**$^{\bullet -}$, which undergoes ring-opening mesolytic fragmentation into enolate **8**. The SET step also produces dithianyl radical **2**$^{\bullet}$ in the immediate proximity of **8**. Subsequent radical recombination furnishes the major product, thioortho ester **4**, in its enolate form, with a small amount of **8** escaping and dimerizing into **5**. Aqueous workup gives the final keto forms. Apparently, at lower temperature (−20 °C), more **8** escapes the solvent cage producing up to 50% of **5**.

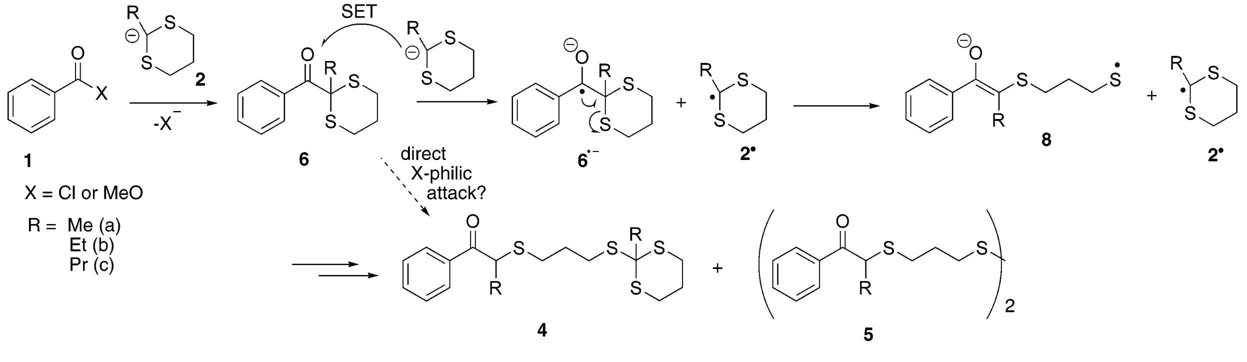
One cannot completely rule out a mechanism involving a direct X-philic attack[7] on sulfur in **6**, bypassing radical anion **8**. Yet, formation of **5** seems to point to a radical reaction.

The rearrangement appears to be general. In addition to **5a**−**c**, we have synthesized 2-alkyl-1,3-dithiane tags[8] (ethyl through nonyl) using monomethyl terephthalate **9** and obtained thioortho esters **10** outfitted with a carboxylate "handle" suitable for tethering them, when needed (Scheme 3).

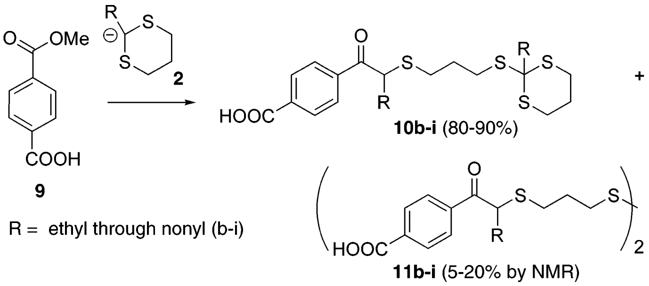
Only in cases when benzoylated methyl dithiane **12** was reacted with lithiated methyl dithiane or a less-substituted sulfur heterocycle did the "conventional" double addition occur. For example, a mixed trithiane−methyl dithiane adduct **13** was obtained with lithiated trithiane as shown in Scheme 4a.

Conventional bisaddition also takes place when less-congested ethyl formate is reacted with ethyl dithiane (Scheme 4b). The other nonenolizable carboxylic derivative that we tested was the more sterically demanding pivaloyl chloride, which gave the ring-opened adduct **15** (Scheme 4c).

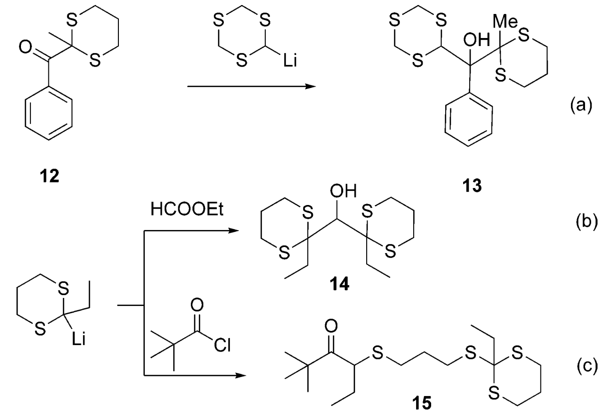
SCHEME 2. Most Plausible Mechanism Involving Ring-Opening Mesolytic Fragmentation in Ketyl 6•−



SCHEME 3



SCHEME 4



In conclusion, we have shown that bisaddition of lithiated 2-alkyl-1,3-dithianes to benzoates or benzoyl chloride is limited to methyl dithiane. Under the same reaction conditions, ethyl dithiane and higher homologues induce an efficient rearrangement via a ring-opening mesolytic fragmentation to yield α-[3-(2-alkyl-1,3-dithiane-2-ylthio)propylthio]-α-alkyl ketones. The rearrangement appears to be general. Studies are underway to elucidate the mechanism and evaluate the scope of photoinduced dithiane release from thioortho esters **4** and **10**.

Experimental Section

Common solvents were purchased from a commercial supplier and used as is, except for THF, which was refluxed over and distilled from potassium benzophenone ketyl prior to use. *n*-BuLi (as a 1.6 M solution in hexanes), 1,3-dithiane, 2-methyl-1,3-dithiane, benzoyl chloride, and monomethyl terephathalate were purchased from a commercial supplier. Propane-1,3-dithiol was purchased from a commercial supplier. Propanal through decanal were purchased from a commercial supplier. All reagents were used without purification. Alkyl dithianes were synthesized from propane-1,3-dithiol and an alkanal as described previously.[1d] ^{1}H NMR spectra were recorded at 25 °C on a Varian Mercury 400 MHz instrument in $CDCl_3$ with TMS as an internal standard (unless noted otherwise).

Typical Experimental Procedure for the Synthesis of 10(b−i): *n*-BuLi (8.96 mL, 14.3 mmol, 1.6 M solution in THF) was added at 20 °C to a solution of 2-alkyl-1,3-dithiane (14−17 mmol) in 50 mL of dry THF, and the resulting solution was stirred at this temperature for 15 min. Monomethyl terephthalate (516 mg, 2.86 mmol) in THF (30 mL) was added to the generated dithiane anion, and the solution was stirred overnight. Aqueous workup included a wash with saturated NH_4Cl (20 mL) followed by extraction with ethyl acetate (3 × 50 mL). The organic layer was dried over Na_2SO_4, and the solvent was removed in a vacuum. The crude product was purified by chromatography on a slurry-packed silica gel column using 10% EtOAc−hexane as eluent (yields for **10** were 80−90% with 10−15% of disulfide **11** recovered). For ^{1}H and ^{13}C NMR, see Supporting Information.

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Supporting Information Available: ^{1}H, ^{13}C, and COSY NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Bulman Page, P. C.; Wilkes, R. D.; Namwindwa, E. S.; Witty, M. J. *Tetrahedron* **1996**, *52*, 2125.

(7) For a review, see: Zefirov, N. S.; Makhon'kov, D. I. *Chem. Rev.* **1982**, *82*, 615.

(8) Photochemistry of tagged compounds will be described in detail elsewhere.