Novel Synthesis of 3,6-Disubstituted 1,2-Dithiin Molecules Involving a Direct Oxidative Deprotection−Cyclization Sequence from 1,4-Bis(*tert*-butylthio)-1,3-butadiene Precursors†

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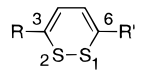
Over a dozen 1,2-dithiin (**1**) (1,5-dithia-3,5-cyclohexadiene)-containing natural products have been isolated primarily from the leaves and roots of the plants belonging to the *Asteraceae* genus.[1] Interestingly, all of these naturally occurring 1,2-dithiins isolated thus far contain acetylene and polyacetylene side chains at the C-3 and C-6 positions of the 8π, anti-aromatic 1,2-dithiin ring system[2] (see, e.g., thiarubrine A (**2**)). A number of these



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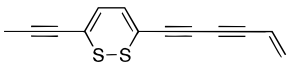

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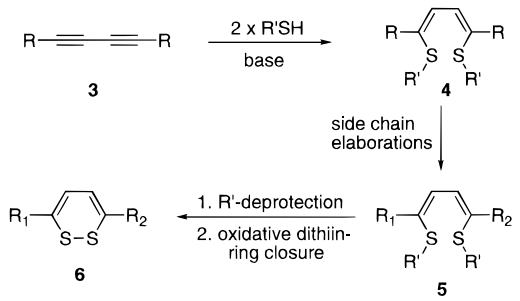
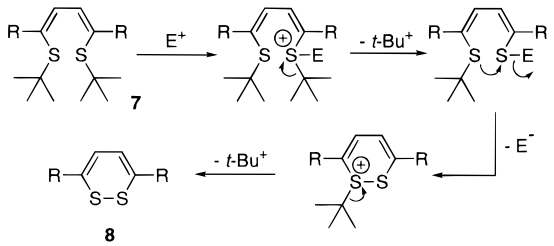
natural 1,2-dithiins as well as synthetic 1,2-dithiin molecules exhibit, in either the light or the dark, a wide spectrum of biological activities. These include antifungal,[3−5] antibacterial,[3,4,6] antiviral,[7,8] and antitumor activity[1d] and light-mediated activity against human immunodeficiency virus (HIV-1).[9]

Virtually all of the reported synthetic methods to access the 1,2-dithiin ring system follow the route summarized in Scheme 1. Thus, the initial stereo- and regiocontrolled bis-addition of a thiol (R′SH) to diyne **3** is followed by, after elaboration of the side chains if necessary, a two-step sequence of the 1,2-dithiin ring-formation involving deprotection of the R′S groups and oxidative ring closure of the resulting bis-thiol or bis-thiolate through the S−S bond formation. A number of protected thiols such as benzyl mercaptan,[10−12] 2-(trimethylsilyl)ethyl mercaptan,[13] and 2-mercaptopropionitrile[5] have been successfully employed for the synthesis of 1,2-dithiin compounds. However, it was felt that there may be a need for a more versatile, expedient method for the synthesis of 1,2-dithiin compounds that employs less expensive protected

Scheme 1



Scheme 2



thiols. In this paper, we describe a novel method for the synthesis of diverse 3,6-functionalized 1,2-dithiins that features the use of commercially available, inexpensive *tert*-butyl mercaptan as such a protected thiol[14] and the direct oxidative deprotection−1,2-dithiin ring formation[15] sequence from the bis-(*t*-BuSH)-adducted precursors.

It was envisioned that the bis-1,4-thio adducts (i.e., **7**) obtainable by the use of *tert*-butyl mercaptan as the source of the protected sulfur atoms may be directly converted into 1,2-dithiins **8** upon treatment with 1 equiv of an appropriate electrophile such as *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) (see Scheme 2). To this end, three diynes **3a**−**c** were treated with 2.2 equiv of *t*-BuSH in DMF in the presence of a catalytic amount of KOH or NaH,[11] which resulted in the exclusive formation of the corresponding (*Z*,*Z*)-1,4-bis-(*t*-BuSH) adducts **7a**−**7c** (see Table 1). It should be noted that 1,4-bis(trimethylsilyl)-1,3-butadiyne (**3b**) loses both TMS groups under these conditions (see Table 1, entry 2) in accord with earlier observations.[11,12]

The bis-*t*-BuSH adducts **7a** and **7b** were further transformed into several 1,2-dithiins having various functional groups at the C-3 and C-6 positions (see Scheme 3). The Swern oxidation[16] of diol **7a** provided dialdehyde **10** in excellent yield, which was directly converted into dimethyl ester **11** with MnO_2/NaCN in

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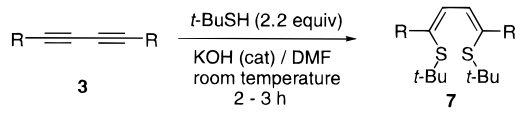
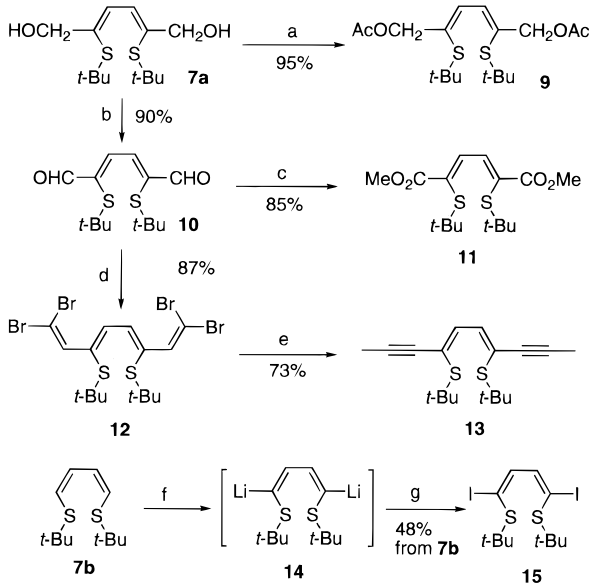
Table 1. Bis-*t*-BuSH Addition to Diynes 3



entry	diyne (**3**)	bis-*t*-BuSH adduct (**7**)	% yield[a]
1	**3a** (R = CH_2OH)	**7a** (R = CH_2OH)	78
2	**3b** (R = TMS)	**7b** (R = H)	66
3	**3c** (R = Ph)	**7c** (R = Ph)	56

[a] Yield of isolated, spectroscopically and microanalytically pure samples.

Scheme 3[a]

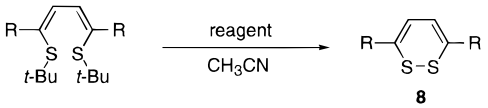


[a] Reagents and conditions: (a) Ac_2O/pyridine/CH_2Cl_2, room temperature, 2 h; (b) $(COCl)_2$/DMSO, Et_3N, −78 °C to room temperature; (c) MnO_2/NaCN/AcOH/MeOH, room temperature; (d) $CBr_4/PPh_3/CH_2Cl_2$, 0 °C, 0.5 h; (e) *n*-BuLi (4.4 equiv)/THF, −78 °C; then MeI (2.2 equiv), −78 °C to room temperature; (f) *t*-BuOK/*n*-BuLi (4.0 equiv each)/THF, −78 °C, 6 h; (g) I_2 (4.0 equiv)/THF, −78 °C, 0.5 h.

AcOH/MeOH.[17] The acetylene-containing analog **13** was prepared from dialdehyde **10** by the use of the Corey−Fuchs protocol[18] via its tetrabromide intermediate **12** in 64% overall yield. In an effort to introduce halogen atoms stereoselectively at the C-1 and C-4 positions of **7b**, a possibility of the double deprotonation of **7b** at these positions was explored. In keeping with the results of similar studies with *tert*-butyl vinyl sulfides, **7b** was treated with 4 equiv of a superbase[19] at −78 °C, producing dilithio species **14**,[19] which maintains its original *Z*,*Z*-stereochemistry ($^3J_{1,2}$ = 8.8 Hz[19a] in **7b**) as validated by the proton NMR spectroscopic analysis of its deuterium-quenched product. Treatment of the dilithio species **14** with excess iodine provided the 1,4-diiodo product **15** as a single stereoisomer in 48% overall yield from **7b**.[20]

The formation of 1,2-dithiins by the oxidative deprotection−cyclization method was realized in good to excellent yield by the treatment of bis(*t*-BuSH) adducts **7c**, **9**−**11**, and **15** with 1.1 equiv of electrophiles such as NIS, NBS, and iodine (see Table 2). In general, while acetonitrile was found to be the best solvent for the reaction in terms of yield and reaction time, dichloromethane or acetone may be used as a substitute or as a cosolvent in cases where the substrate is not soluble enough in acetonitrile. The rate of the reaction was found to be faster when substituents at C-1 and C-4 are electron withdrawing (see Table 2, entries 2, 3, and 5). The reaction of the 1,4-diiodo precursor (**15**) provided the

Table 2. Preparation of 1,2-Dithiins by Direct Oxidative Deprotection−Cyclization Sequence of 1,4-Bis(*tert*-butylthio) 1,3-Dienes



entry	1,4-bis(*tert*-butylthio) 1,3-diene	reagent[a]	reaction temp (°C)	reaction yield[b] time[a] (h)	(%)
1	**9** (R = CH_2OAc)	NIS	82	1.5	83
2	**10** (R = CHO)	NBS	rt	0.7	69
3	**11** (R = CO_2Me)	NBS	rt	0.3	91
4	**7c** (R = Ph)	I_2	82	10	56[c]
5	**15** (R = I)	NBS	rt	0.5	95

[a] Although only 1 equiv of the reagent is required for the reaction, 2 equiv of each reagent was used for the sake of expediency except entry 5. The reaction time given in this table represents that for the use of 2 equiv of the reagent. Only in entry 5, the use of 2 equiv of the reagent induced the decomposition of the product; thus, the reaction time given for entry 5 is for the reaction with 1 equiv of the reagent. [b] Yield of isolated, spectroscopically and microanalytically pure samples except the product from entry 5, whose microanalytically pure sample could not be obtained. [c] 80% yield based on recovered starting material **7c** (30%).

relatively unstable 3,4-diiodo-1,2-dithiin (**8**; R = I) in excellent yield. This diiodo product should serve as a versatile intermediate for the preparation of various 3,4-disubstituted 1,2-dithiins. In contrast, the unsubstituted 1,4-bis(*t*-BuSH)-adduct **7b** as well as diyne-containing disulfide **13** produced only a mixture of unidentifiable products under a variety of conditions using the electrophiles NIS, NBS, and iodine. In these cases, the electrophile seems to induce extensive decomposition of the starting sulfides through initial preferential interaction at the sites other than the two sulfur atoms.[21]

The novel method described above constitutes a highly efficient means for the synthesis of the 1,2-dithiins with various functionalized substituents at C-3 and C-6. The formation of the intial 1,4-bis-thiol adduct employs inexpensive, readily available *tert*-butyl mercaptan, and their one-step transformation into the corresponding 3,6-disubstituted 1,2-dithiins involves the electrophile-mediated oxidative deprotection−oxidative cyclization. The ready accessability of the reagents required and simple experimental procedures employed should make this unique sequence for the syntheses of the 3,6-disubstituted 1,2-dithiins amenable for their large-scale preparations.

Supporting Information Available: Experimental procedures and spectroscopic and microanalytical [except for **8** (R = I)] data for all new compounds and the proton and C-13 NMR spectra of **8** (R = I) (11 pages).

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(20) In addition to 1,4-diiodide **15**, the 1-iodide and starting diene **7b** were also obtained in 18 and 17% yield, respectively.
(21) The 1,4-bis[2-(trimethylsilyl)ethyl] mercaptan adducts, i.e., **4** (R′ = $TMSCH_2CH_2$), also may be amenable to a similar electrophile-initiated 1,2-dithiin synthesis as the silicon atom is capable of stabilizing the developing positive charge on the carbon β to silicon. However, in all cases, the reaction was found to be too sluggish with the exception of the 1,4-dicarbomethoxy derivative (**4**; R = COOMe, R′ = $TMSCH_2CH_2$), which provided 3,4-dicarbomethoxy-1,2-dithiin (**8**; R = COOMe) in 56% yield upon treatment with 2 equiv of NBS at room temperature in CH_3CN (10 min).