Synthetic Applications of 2-Chloro-1,3-dithiane. 2.[1,2] Reactions with Carbon Nucleophiles

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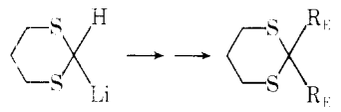
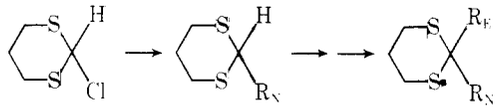
Reactions of 2-chloro-1,3-dithiane (**2**) with several carbon nucleophiles are described. Introduction not only of primary alkyl but also of aryl, vinyl, and secondary alkyl groups at C-2 of 1,3-dithiane can be effected by reaction with the corresponding Grignard reagents. In addition, the syntheses of 2-(1,3-dithianyl) derivatives of malonic esters and of electron-rich aromatic compounds are described.

The convergent synthesis of carbonyl compounds by using 2-lithio-1,3-dithiane (**1**)[3] and related reagents[4] as acyl anion equivalents has been the subject of considerable recent interest. This concept can be used for the introduction of groups R_E, originating from electrophilic reagents (e.g., alkyl halides and carbonyl compounds), to produce compounds of type **3a.** Recently, the possibility of using 2-chloro-1,3-dithiane (**2**) as a formyl *cation* equivalent was recognized independently by several groups.[1,5,6]



1 **3a**



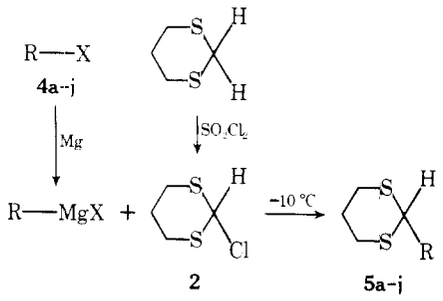
2 **3b** **3c**

Reaction of **2** with some S-, N-, P-, and C-nucleophiles leads to dithianes of type **3b,** which are in turn possible precursors for dithiane derivatives **3c.**[4] In this paper we present a study on the scope and limitations of the reactions of **2** with carbon nucleophiles.

Results and Discussion

Reaction with Grignard Reagents. Nucleophilic substitution reactions of **1** with compounds RX have become a standard method for the introduction of primary alkyl groups at the central carbon atom of 1,3-dithiane. Considerable limitations are imposed on this method by the fact that secondary alkyl halides tend to give elimination reactions,[7] while tertiary alkyl, aryl, and vinyl halides are not suitable at all.[8] This limitation might be eliminated by converting an organic halide RX into its Grignard reagent RMgX, which is subsequently reacted with a properly substituted *electrophilic* 1,3-dithiane. Recently, this approach led to the preparation of a number of structurally related dithioacetals.[9,10]

We have studied the reactions of **3** with a variety of Grignard reagents. The results have been compiled in Table I. The conversion of RX (**4**) into 1,3-dithianes (**5**) is most conveniently achieved by addition of **2** (from 1.0 equiv of 1,3-dithiane) to the Grignard reagent RMgX (from 1.0–1.2 equiv of RX) at −10 °C. By this procedure not only primary and acyclic secondary but also cyclohexyl, aryl, and vinyl groups can be introduced at C-2 of 1,3-dithiane.



4a–j **2** **5a–j**

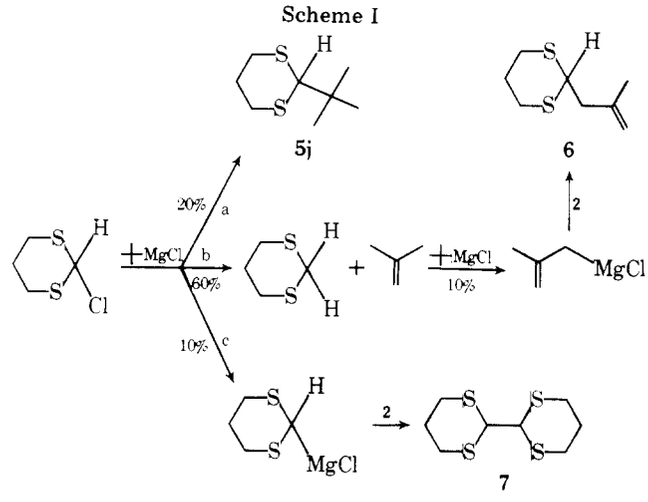
Good yields are obtained with aryl Grignard reagents. The conversion of the readily available bromides **4b–d** into the unknown dithioacetals of aromatic aldehydes **5b–d** illustrates the synthetic usefulness of this method. Styryl bromide likewise affords the dithioacetal of cinnamic aldehyde (**5e,** 70%). In this case, 15% of 1,4-diphenyl-1,3-butadiene is formed by reductive coupling of the starting vinylic bromide.[11]

When **2** is reacted with Grignard reagents derived from secondary alkyl bromides **4g, h,** small amounts (15–20%) of 1,3-dithiane are formed as a side product. Reaction with *tert*-butylmagnesium chloride gave a mixture of products, which contained, in addition to ~20% of the desired coupling product **5j,** 1,3-dithiane (60%) and ~10% of both 2-(methylallyl)-1,3-dithiane (**6**) and 2,2′-bis(1,3-dithiane) (**7**). This result can be rationalized by the reaction modes outlined in Scheme I.[12]

Apart from C–C bond formation to give **5j** (path a) and Grignard exchange reaction, ultimately resulting in the formation of **7** (path c), the major route consists of hydride transfer to produce 1,3-dithiane and isobutene (path b). An exchange reaction with the Grignard reagent then leads to (methylallyl)magnesium chloride and subsequently to **6.**

α-[2-(1,3-Dithianyl)]malonic Esters. The synthetic utility of **2** is also demonstrated by the possibility of introducing a 2-(1,3-dithianyl) group at the α-carbon atom of carbonyl compounds.[1,6] We have paid particular attention to the synthesis of protected α-formylmalonic esters **8a–e** because this type of compound cannot be prepared via the usual methods for 1,3-dithiane syntheses.[3b] The results are summarized in Table II.

Scheme I



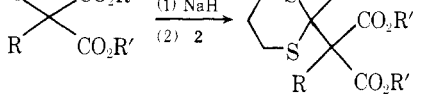
5j **6** **7**

Table I. Reaction of 2 with Grignard Reagents and Physical Properties of the Products

R	X	product	yield,[a] %	mp, °C	NMR data ($CDCl_3$), δ (ppm) and J (Hz) δ 2-H	δ 4,6-H- (a, e)	δ 5-H	δ/J R H	IR data, cm^{-1}
phenyl[b]	Br	**5a**	74	72	5.08	2.9, 2.7	1.75–1.9	7.35, 7.15 (m, 2, 3 H)	1480, 1470, 720, 690 (Ph); 900; 875
p-chlorophenyl[c]	Br	**5b**	70 (52)	85.5–86.5	5.11	3.0, 2.9	1.9–2.1	7.39, 7.29 (AA'BB', 4 H, ^3J = 8)	1480, 850, 750 (Ph); 1080 (PhCl); 905
m-chlorophenyl[d]	Br	**5c**	79	62.5–63.5	5.09	2.95, 2.8	1.9–2.05	7.47 (t, 1 H, ^4J = 1.5, *o*-arom), 7.25 (m, 3 H)	1570, 1470, 750, 680 (Ph); 1080 (PhCl); 905
α-naphthyl[e]	Br	**5d**	75 (57)	145–146	5.83	3.0, 2.8	1.85–2.0	8.29 (dd, 1 H, ^3J = 7, ^4J = 1.5), 7.7–7.8, 7.3–7.5 (m, 6 H)	1600, 1510, 780 (naphthyl); 905
(*E*)-styryl[f]	Br	**5e**	70 (63)		4.77	2.8	1.85–2.0	7.25 (m, 5 H, arom), 6.74 (dd, ^3J = 15.5, ^4J = 1.0, β-H), 6.23 (dd, 1 H, ^3J = 15.5, ^4J = 7.2, α-H)	
(*Z*)-styryl					5.09			6.56 (d, 1 H, ^3J = 11, β-H), 5.68 (t, 1 H, ^3J = 11, α-H)	
benzyl[g]	Cl	**5f**	64 (55)	34–36	4.18	2.7	1.75–1.9	7.17 (s, 5 H, arom), 2.95 (d, 2 H, ^3J = 7.0, $PhCH_2$)	1610, 1490, 1450, 735, 695 (Ph); 905
cyclohexyl[b]	Br	**5g**	60 (50)	52–53.5	4.04	2.85	~1.9	1.2–2.1 (m, 11 H), $^3J_{2\text{-H},\alpha\text{H}}$ = 5)	905
sec-butyl[i]	Br	**5h**	53 (48)		4.14	2.95, 2.85	~1.9	1.3–2.1 (m, 3 H), 1.07 (d, 3 H, ^3J = 6.5, $CHCH_3$), 0.92 (t, 3 H, ^3J = 7, CH_2CH_3), $^3J_{2\text{-H},\alpha\text{-H}}$ = 4.5)	900
tert-butyl[j]	Cl	**5j**	20		4.00	2.9	1.8–2.0	1.10 (s, 9 H)	1390, 1360 (*t*-Bu); 900; 775
		6			4.22	2.85	1.8–2.0	4.87 (m, 2 H, $=CH_2$), 2.55 (d, 2 H, ^3J = 7.5, α-CH_2), 1.78 (s, 3 H, CH_3)	

[a] From NMR of crude product; the yields in parentheses refer to pure products (see Experimental Section). [b] Identical with a sample prepared according to ref 3b. [c] Anal. Calcd for $C_{10}H_{11}S_2Cl$: C, 52.05; H, 4.80; S, 27.79; Cl, 15.36. Found: C, 51.91; H, 4.85, S, 28.17; Cl, 14.84. [d] Anal. Found: C, 52.19; H, 4.91; S, 28.38; Cl, 14.89. [e] NMR in acetone-d_6. Anal. Calcd for $C_{14}H_{14}S_2$: C, 68.28; H, 5.73; S, 25.99. Found: C, 68.06; H, 5.71; S, 26.00. [f] Composition of both **4e** and **5e**: 85% *E* and 15% *Z* isomer; 15% of 1,4-diphenyl-1,3-butadiene was obtained, mp 145–148 °C (lit.[11] mp 147–148 °C). [g] Yield based on converted **6f**: 80% (lit.[13] mp 34.5–34.9 °C). [h] Bp 87 °C/0.05 torr. Anal. Calcd for $C_{10}H_{18}S_2$: C, 59.35; H, 8.96; S, 31.69. Found: C, 59.05; H, 8.87; S, 31.77. [i] Bp 57–58 °C/0.008 torr; $n^{23}D$ 1.5355 (lit.[14] $n^{20}D$ 1.5387). [j] $n^{22}D$ 1.5370.

Table II. Reactions of 2 with Malonic Ester Anions and Physical Properties of 2-(1,3-Dithianyl)malonic Esters



8a-e

compd	R	R'	yield,[a] %	bp (°C)/torr or mp (°C)	NMR data ($CDCl_3$), δ (ppm)[b] $n^{20}D$	2-H	4,6-H(a, e)	5-H	R-H	IR data, cm^{-1}
8a	H	Et	90 (75)	137–138/0.15	1.5162	4.34	3.0, 2.7	1.95–2.05	4.09 (^3J = 11.8 Hz)	2980, 2920 (CH); 1740 (C=O); 1220, 1150, 1020, (COC); 905
8b	CH_3	Et	95 (85)	140/0.1	1.5107	4.80	3.0, 2.9	1.9–2.05	1.56	3000, 2920 (CH); 1745 (C=O); 1240, 1100 (COC); 910
8c	CH_3	*t*-Bu	76 (65)	135–140/0.1	1.4852	4.72	2.9	1.8–2.0	1.47	2980, 1440, 1390, 1365 (CH); 1730 (C=O); 1240, 1110 (COC); 900; 845
8d[c]	Ph	Et	95 (81)	82–83		4.98	2.7, 2.4	1.7–1.8	7.55 (*o*-arom), 7.35 (*m,p*-arom)	3050, 2980 (CH); 1750, (C=O); 1490, 770, 700 (Ph); 1220, 1170, 1020 (COC); 905
8e[d]	*p*-OCH_3Ph	Et	95 (85)	82.5–83.5		4.94	2.7, 2.5	1.75–1.85	7.43, 6.86 (AA'BB', ^3J = 8.7 Hz)	2980, 2840 (CH); 1750 (C=O); 1610, 1510, 830 (Ph); 1245, 1025 (PhOC); 1210, 1160 (COC); 905

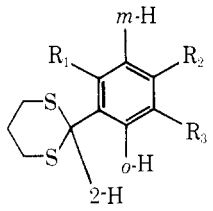
[a] From NMR of the crude product; in parentheses are given the yields after distillation (**8a–c**) or crystallization (**8d,e**). [b] δ(R'–H) in **8a,b,d,e**, 4.23 ± 0.03 (CH_2) and 1.25 ± 0.01 (CH_3), ^3J = 7.2 ± 0.2 Hz; and in **8c**, 1.44 (*t*-Bu). [c] Anal. Calcd for $C_{17}H_{22}O_5S_2$: C, 57.60; H, 6.26; S, 18.09. Found: C, 57.63; H, 6.34; S, 17.91. [d] Anal. Calcd for $C_{18}H_{24}O_5S_2$: C, 56.23; H, 6.29; S, 16.68. Found: C, 56.35; H, 6.41; S, 16.94.

Addition of **2** to a THF solution of a malonic ester anion results in a slightly exothermic reaction.[15] Excellent yields of products **8a,b,d,e** can be obtained. Reaction with the sterically more demanding di-*tert*-butyl methylmalonate affords **8c** in somewhat lower yield. Attempts to convert the 1,3-dithiane derivatives **8a,c** into the corresponding 2-lithio compounds were not successful.[16]

The conversion of malonic esters **8** into the corresponding acetic acid esters will be reported separately.[17]

Reaction of **2** with the dianion of ethyl acetoacetate was

Table III. Physical Properties of Protected Formyl Phenols



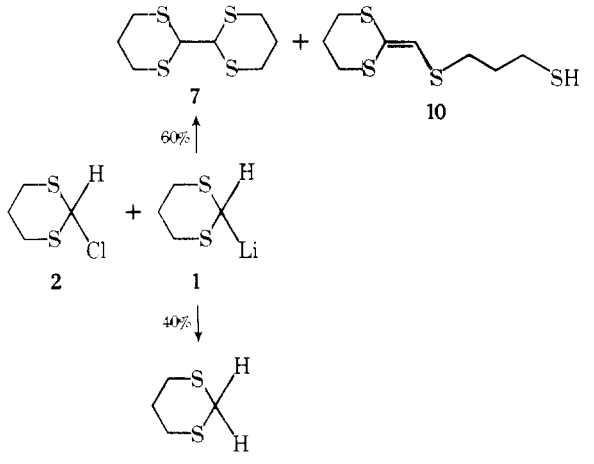
compd[b]	R_1	R_2	R_3	mp, °C	NMR data, δ (ppm)/J (Hz)[a] o-H	m-H	p-H	2-H	4,6-H(a, e)	5-H	IR data, cm^{-1}
11a[c]	o-H	OH	m-H	149–151	7.28 8.6	6.77 8.6		5.09	2.95, 2.9	1.9–2.1	3400, 1360 (OH); 1600, 1590, 1500, 1440, 850, 765 (Ph); 1230 (CO); 910
11c[d]	OH	p-H	OCH_3	124–125	6.98 2.5	6.79 9	6.65 9, 2.5	5.61	3.0, 2.85	1.85–2.0	3380, 1350 (OH); 1520, 1450, 880, 810 (Ph); 1220, 1040 (CO); 910
11d[e]	OH	p-H	CH_3	137–138	7.22 2	6.77 8	6.92 8, 2	5.63	3.05, 2.85	1.85–2.1	3350, 1330 (OH); 1610, 1500, 860, 805 (Ph); 1255 (CO); 900
11e[f]	OH	p-H	Cl	126–127	7.35 2.5	6.84 8.5	7.08 8.5, 2.5	5.59	3.1, 2.9	1.95–2.15	3300, 1320 (OH); 1500, 1410, 880, 810 (Ph); 1260 (CO); 1100 (CCl); 915
11f[g]	OH	OH	2-DT	230 dec	7.53	6.46		5.55	2.95, 2.85	1.7–1.95	3350, 1390 (OH); 1610, 1520, 1420, 830 (Ph); 1195 (CO); 915
11g[h]	1-(2-hydroxy-naphthyl)			134–136		7.1–8.1	(m)	6.21	3.05, 2.9	1.95–2.15	3300, 1340 (OH); 1610, 1490, 950, 810, 750, 740 (naphthyl); 1260 (CO); 900

[a] **11a,g** in $CDCl_3$, **11c–e** in $CDCl_3$–Me_2SO-d_6 (1:1), and **11f** in acetone-d_6–Me_2SO-d_6 (1:1). [b] **11b:** NMR ($CDCl_3$) δ 7.55, 7.15, 6.8 (m, 4 H, PhH), 5.62 (s, 1 H, 2-H); R_1 = OH, R_2 = R_3 = p,m-H. [c] Lit.[5b] mp 149–150 °C. [d] Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.54; H, 5.83; S, 26.42. Found: C, 54.24; H, 5.62; S, 26.23. [e] Anal. Calcd for $C_{11}H_{14}OS_2$: C, 58.40; H, 6.24; S, 28.29. Found: C, 57.87; H, 6.29; S, 27.77. [f] Anal. Calcd for $C_{10}H_{11}OS_2Cl$: C, 48.67; H, 4.49; S, 25.99; Cl, 14.37. Found: C, 49.38; H, 4.60; S, 25.88; Cl, 13.97. [g] Anal. Calcd for $C_{14}H_{14}OS_2$: C, 64.11; H, 5.38; S, 24.41. Found: C, 64.01; H, 5.47; S, 24.18. [h] Anal. Calcd for $C_{14}H_{18}O_2S_4$: C, 48.56; H, 5.24; S, 36.96. Found: C, 48.31; H, 5.23; S, 36.47.

reported to result in proton abstraction.[6] We have observed the same phenomenon when reacting **2** with other strongly basic nucleophiles such as aryl-, vinyl-, and (triphenylmethyl)lithium reagents. In these cases, **2** is converted into a mixture of products, mainly consisting of 1,3-bis(1′,3′-dithianyl-2′-thio)propane (**9**) and 2,2′-bis(1,3-dithianylidene). Thus, the successful alkylation of **2** seems to be limited to less strongly basic reagents, such as Grignard compounds.

The two modes of reactivity occur side by side when **2** is allowed to react with **1**.

Products both from C–C bond formation (**7** and its isomer **10**) and from proton transfer (1,3-dithiane) are obtained.[18]



Electrophilic Aromatic Substitution Reactions. Only a few examples of the direct introduction of a 2-(1,3-dithianyl) group into aromatic compounds can be found in the literature. Gassmann reported on the ortho formylation of phenols in poor yields via the corresponding 1,3-dithianes by reaction of phenols with 1,3-dithiane and *N*-chlorosuccinimide.[19] The Lewis acid catalyzed reaction of 2-methoxy-1,3-dithiane with indole was reported to proceed in 40% yield, but other substrates failed to react.[20] Oki described some interesting identification reactions of 2-chloro-1,3-dithiane; with excess phenol or dimethylaniline, para-substituted 2-(1,3-dithianyl) derivatives were isolated in 75 and 30% yields, respectively.[5b]

Electrophilic aromatic substitution reactions of **2** are of interest since a protected formyl group is introduced in one step. Hydrolysis to the aldehyde provides an alternative to the classical aromatic *formylations*,[13,21,22] while subsequent reaction via the 2-lithio-1,3-dithiane derivatives[3] followed by hydrolysis should give access to other *acyl* derivatives.

We have investigated the reactions of **2** with phenols (Scheme II, Table III) and other electron-rich aromatic compounds (Table IV).

Excellent yields of products **11a–g** are obtained by addition of 0.8 equiv of the requisite phenol to a chloroform solution of equal amounts of **2** and hydrogen chloride, obtained by the chlorination of 1,3-dithiane (1.0 equiv) with sulfuryl chloride. Upon reaction of **2** with phenol, the para-substituted product **11a** is mainly formed, but also ~20% of the ortho isomer **11b** shows up in the NMR spectrum of the reaction product.

The reaction with resorcinol to give **11f** was carried out with

Scheme II

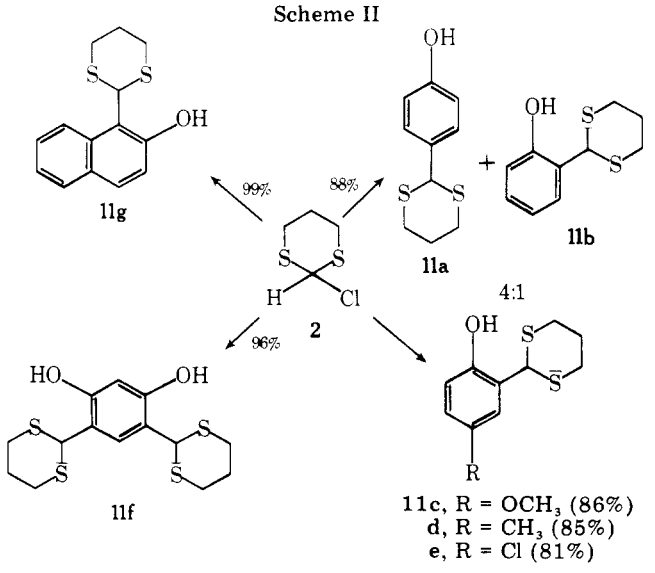


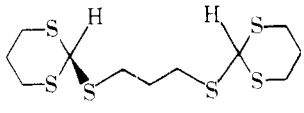
Table IV. Electrophilic Aromatic Substitution Reactions with 2

aromatic compd	equiv	product	substitution at	yield, %
N,N-diethylaniline	0.8	**13**	C-4	60[a]
thiophene	5	**14**	C-2	40[b]
N-methylpyrrole	2	**15**	C-2	30[b]

[a] Based on *N,N*-diethylaniline; yield after chromatography was 42%. [b] Based on **2**.

2.5 equiv of **2**.[23] It is of interest to note that the corresponding dialdehyde cannot be obtained by direct formylation of resorcinol.[24]

Reactions with para-substituted phenols proceed selectively to give *o*-2-(1,3-dithianyl) substituted derivatives **11c–e**.[25] However, when electron-withdrawing groups are present at the para position, the products of electrophilic substitution are formed in low yield (~10% with R = formyl) or not at all (R = nitro). In these cases, **2** is converted into a mixture of the known 1,3-bis(1′,3′-dithianyl-2′-thio)propane (**9**) and *S*-[3-(1′,3′-dithianyl-2′-thio)]propyl thioformate (**12**, major product).[26]



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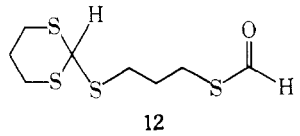

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The reactions of **2** with several other substrates, which are known to be reactive toward formylating agents,[22] were also studied. The aromatic compounds listed in Table IV exhibited the desired reactivity toward **2**, while others (phenanthrene, anisole, mesitylene, and 2-acetylthiophene) failed to react.

Again, best results are obtained when the substrate is added to a chloroform solution of **2** and hydrogen chloride at 20 °C.[27] The presence of hydrogen chloride retards the formation of **9** and **12**.[26] Reaction with indole, benzo[*b*]furan, and benzo[*b*]thiophene yields the desired products, albeit in modest yields (20–30%).

It can be concluded that electrophilic aromatic substitution reactions with **2** only proceed satisfactorily when the substrate is sufficiently nucleophilic to compete successfully with the attack of a sulfur atom of **2** on the central carbon atom of another molecule of **2** to give **9** and **12**.[26]

The results presented in this study justify the conclusion that considerable broadening of the synthetic scope of 1,3-dithiane chemistry can be realized by using 2-chloro-1,3-dithiane as a complementary reagent to 2-lithio-1,3-dithiane.

Experimental Section

General. Melting points are uncorrected. IR spectra (KBr disk or liquid film) were recorded on a Unicam SP-100 instrument. NMR spectra (δ relative to internal tetramethylsilane) were taken on a JEOL PS-100 instrument. Elemental analyses of the crystalline products were performed by Mr. W. J. Buys, TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands. For column chromatography silica gel MN (Mackery Nagel, 70–270 mesh) or silica gel G (Merck, 10–40 mesh) were used.

Materials. Solvents were purified and dried according to standard procedures. 1,3-Dithiane was synthesized as described in ref 2. Sulfuryl chloride was distilled in a nitrogen atmosphere before use. The Grignard reagents described in Table I were obtained by reactions of the distilled bromides **4a–e,g,h** or chlorides **4f,j** with equimolar amounts of magnesium (Fluka) in THF or ether. When necessary, the reactions were initiated by addition of 1,2-dibromoethane. The mixture of (*E*)- and (*Z*)-styryl bromides **4e** was prepared from cinnamic acid by a two-step procedure:[28] NMR ($CDCl_3$) (*E* isomer) δ 7.00 and 6.63 (AB, ^3J = 14 Hz), (*Z* isomer) 6.97 and 6.33 (AB, ^3J = 8 Hz). Diethyl phenyl- and (*p*-methoxyphenyl)malonate were synthesized by reaction of the corresponding acetates with diethyl carbonate (freshly distilled under nitrogen) and sodium hydride (2 equiv); yield in each case was 84% after distillation.[29] The other reagents were used as high-grade commercial products.

2-Chloro-1,3-dithiane (2). In an atmosphere of dry nitrogen, a solution of sulfuryl chloride (1.42 g, 10.5 mmol) in chloroform (5 mL) was added dropwise to a stirred solution of 1,3-dithiane (1.20 g, 10 mmol) in chloroform (25 mL). During the addition the temperature was kept at ~−30 °C. The white precipitate which formed instantly gradually dissolved when the stirred reaction mixture was allowed to warm to room temperature in 1 h. After being stirred for an additional 30 min, the ensuing reaction mixture was used directly for electrophilic aromatic substitution reactions. For the other synthetic conversions, the solvent was evaporated at 10 °C in vacuo under nitrogen, yielding **2** as a white or pale yellow solid (1.55 g, quantitative) of better than 95% purity (NMR): mp 50 °C dec; NMR ($CDCl_3$) δ 6.28 (s, 1 H, 2-H), 3.14 (m, 4 H, 4, 6-H), 2.16 (m, 2 H, 5-H).

General Procedure for the Reaction of 2 with Grignard Reagents. A 1 M solution of **2** in THF or ether was added dropwise to a stirred solution of the Grignard reagent (~1 M, from 1.0–1.2 equiv of **4a–g** or 2.0 equiv of **4h,j**) in the same solvent, which was cooled with an ice–salt bath. Invariably, an exothermic reaction occurred and a white precipitate was observed. The temperature was kept between 0 and −10 °C during the addition. After being stirred at 20 °C for 1 h, the reaction mixture was poured into an aqueous ammonium chloride–ether mixture. After separation of the organic layer and extraction of the aqueous layer, the combined ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo, giving the crude products which contained 60–90% of compounds **5a–j** (NMR). Purification was accomplished by column chromatography for **5b,e,f,g** (MN, benzene or ethyl acetate–hexane mixtures), by crystallization for **5d** (ethyl acetate), and by distillation for **5h**. All 1,3-dithianes showed the characteristic IR absorption at ~905 cm^{-1}.[3,13,14]

2-(1,3-Dithianyl)malonic Esters 8a–c. Malonic ester anions (1.0 equiv) were prepared in THF solution by additon of the requisite malonic ester (diethyl ester at 20 °C, di-*tert*-butyl ester at 50 °C) to a stirred suspension of sodium hydride in THF. A solution of **2** (obtained from 1.05 equiv of 1,3-dithiane) in THF was added in 10 min, and the resulting mixture was then heated at reflux temperature for 2 h.[15] The products were isolated after standard workup in the yields given in Table II.

Reaction of 2 with 1. A THF solution of **2** (10 mmol in 15 mL) was added dropwise to a stirred solution of **1** in THF (10 mmol in 20 mL) at −70 °C. The reaction mixture was allowed to warm to 20 °C and subsequently stirred for 1 h. Workup gave a mixture of 1,3-dithiane [NMR ($CDCl_3$) δ 3.7 (s, 2-H)], 2,2′-bis(1,3-dithiane) (**7**) [mp 137–139 °C (lit.[30] 140–141 °C); NMR ($CDCl_3$) δ 4.46 (s, 2-H)], and the trithioethene derivative **10** [NMR ($CDCl_3$) δ 6.36 (s)] in a ratio of 4:5:1.

General Procedure for the Reaction of 2 with Phenols. The requisite phenol was added in one portion to a stirred solution of equal amounts of **2** and hydrogen chloride in chloroform at 20 °C. A deeply orange-red colored reaction mixture resulted. After being stirred overnight at 20 °C, the mixture was diluted with chloroform and extracted (3×) with 1 N potassium hydroxide solution. The combined aqueous layers were acidified with diluted hydrochloric acid and then extracted (3×) with chloroform. Phenols **11a–e,g** were isolated after drying ($MgSO_4$) and evaporating the solvent in the yields indicated in Scheme II as products of better than 95% purity. Product **11f** was isolated most conveniently by direct concentration of the reaction mixture and treatment of the residue with cold ether. Analytical samples were obtained by crystallization from chloroform–hexane (**11a–e,g**) or acetic acid (**11f**).

NMR spectral data of 2-aryl-1,3-dithianes derived from aryl bromides (**5a–d**) and phenols (**11a–g**) are listed in Tables I and III. The absorption of 2-H in the 1,3-dithiane ring characteristically shifts from ~5.1 ppm (in **5a–c** and **11a**) to ~5.6 ppm (in **11b–f**) if one hydroxyl substituent is introduced at an ortho position. A similar difference is observed in the naphthalene derivatives **5d** (δ 5.83) and **11g** (δ 6.21). The axial protons at C-4 and C-6 are consistently found at lower field (δ 2.9–3.1) than the equatorial ones (δ 2.7–2.9).[13,31]

***p*-[2-(1,3-Dithianyl)]diethylaniline (13).** The addition of diethylaniline (0.8 equiv) to a chloroform solution of **2** caused the appearance of a green color, which gradually faded upon stirring of the reaction mixture for 16 h. Workup by addition of a sodium carbonate solution and extraction of the aqueous layer with chloroform (3×) gave the crude product, which was purified by dissolving in ether and extracting into diluted hydrochloric acid. Thus, a mixture of **13** (60%) and diethylaniline (40%) was obtained. An analytical sample was prepared by crystallization from benzene–hexane as blue needles: mp 88.5–89.5 °C; IR 2940, 2860 (CH), 1610, 1520, 815, 770 (phenyl), 1355,

1275 (PhNC), 905 cm^{-1}; NMR ($CDCl_3$) δ 7.33 and 6.61 (AA'BB', 4 H, ^3J = 9.5 Hz, PhH), 5.10 (s, 1 H, 2-H), 3.30 (q, 4 H, ^3J = 7.0 Hz, NCH_2), 2.8–2.95 (m, 4 H, 4, 6-H), 1.85–2.0 (m, 2 H, 5-H), 1.12 (t, 6 H, CH_3). Anal. Calcd for $C_{14}H_{21}NS_2$: C, 62.87; H, 7.91; N, 5.24; S, 23.98. Found: C, 63.00; H, 8.02; N, 5.32; S, 23.79.

2-[2'-(1',3'-Dithianyl)]thiophene (14). The crude product contained, besides **14** (~40%), considerable amounts of **9** and **12** [NMR ($CDCl_3$) δ 2-H in **9** and **12** 4.92 (s), and δ formyl-H in **12** 10.16 (s)].[1] Purification of **14** was achieved by careful column chromatography (G, benzene), followed by crystallization from hexane: white needles; mp 77–78 °C; IR 855, 760, 700 (thiophene), 905 cm^{-1}. The 2 substitution could be inferred from the NMR spectrum by analysis of the coupling constant magnitudes: NMR ($CDCl_3$) δ 7.22 (dd, 1 H, ^3J = 5.0, ^4J = 1.3 Hz, 5-H), 7.14 (ddd, 1 H, ^3J = 3.6, $^4J_{5\text{-H}}$ = 1.3, $^4J_{2'\text{-H}}$ = 0.7 Hz, 3-H), 6.92 (dd, 1 H, ^3J = 5.0 and 3.6 Hz, 4-H), 5.38 (d, 1 H, ^4J = 0.7 Hz, 2'-H), 2.95 (m, 4 H, 4',6'-H), 1.9–2.1 (m, 2 H, 5'-H). Anal. Calcd for $C_8H_{10}S_3$: C, 47.53; H, 4.99; S, 47.49. Found: C, 47.36; H, 4.99; S, 47.41.

1-Methyl-2-[2'-(1',3'-dithianyl)]pyrrole (15).[27] The crude product contained ~30% of this compound. An ~80% pure sample was obtained by column chromatography (G, 1:2 ethyl acetate–hexane). The NMR spectrum indicated the 2 substitution: NMR ($CDCl_3$) δ 6.48 (dd, 1 H, ^3J = 2.5, ^4J = 1.8 Hz, 5-H), 6.21 (dd, 1 H, ^3J = 3.5, ^4J = 1.8 Hz, 3-H), 6.00 (dd, 1 H, ^3J = 3.5 and 2.5 Hz, 4-H), 5.22 (s, 1 H, 2'-H), 2.85–3.0 (m, 4 H, 4',6'-H), 1.9–2.1 (m, 2 H, 5'-H).

NMR spectra of the products obtained by reaction of **2** with indole, benzo[*b*]furan, and benzo[*b*]thiophene indicated the presence of small amounts of dithianylated products besides products **9** and **12**.

Registry No.—**1**, 36049-90-8; **2**, 57529-04-1; **4a**, 108-86-1; **4b**, 106-39-8; **4c**, 108-37-2; **4d**, 90-11-9; **4e** (*E* isomer), 588-72-7; **4e** (*Z* isomer), 588-73-8; **4f**, 100-44,7; **4g**, 108-85-0; **4h**, 78-76-2; **4j**, 507-20-0; **5a**, 5425-44-5; **5b**, 10359-09-8; **5c**, 57009-71-9; **5d**, 57009-77-5; **5e** (*E* isomer), 69178-10-5; **5e** (*Z* isomer), 69178-11-6; **5f**, 31593-52-9; **5g**, 56698-00-1; **5h**, 69178-00-3; **5j**, 6007-21-2; **6**, 69178-01-4; **7**, 21875-49-0; **8a**, 63822-64-0; **8b**, 69178-02-5; **8c**, 69178-03-6; **8d**, 69178-04-7; **8e**, 69178-05-8; **9**, 38336-42-4; **10**, 69178-12-7; **11a**, 57529-05-2; **11b**, 6842-36-0; **11c**, 54810-45-6; **11d**, 54810-44-5; **11e**, 54810-43-4; **11f**, 69178-06-9; **11g**, 69178-07-0; **12**, 69178-13-8; **13**, 69178-08-1; **14**, 57009-79-7; **15**, 69178-09-2; sodium diethyl propanedioate, 996-82-7; sodium diethyl methylpropanedioate, 18424-77-6; sodium di-*tert*-butyl methylpropanedioate, 66702-41-8; sodium diethyl phenylpropanedioate, 28744-77-6; sodium diethyl (*p*-methoxyphenyl)propanedioate, 69178-14-9; phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-methylphenol, 106-44-5; *p*-chlorophenol, 106-48-9; resorcinol, 108-46-3; 2-naphthol, 135-19-3; sulfuryl chloride, 7791-25-5; 1,3-dithiane, 505-23-7; thiophene, 110-02-1; *N*-methylpyrrole, 96-54-8; *N*,*N*-diethylaniline, 91-66-7.

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Synthesis of (±)-Cacalol[1]

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The synthesis of cacalol (**1**), a structurally unusual sesquiterpenoid tetrahydronaphthofuran, is described. The starting compound for the synthesis, 6-acetyl-5-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**10**), was prepared in several steps from either 5-methoxy-8-methyl-1-tetralone (**5**) or 4,5-dimethyl-8-hydroxy-1-tetralone (**11**). The methyl ether of **10** (**13**) on Baeyer–Villiger oxidation followed by hydrolysis gave 5-methoxy-6-hydroxy-1,8-dimethyl-1,2,3,4-tetrahydronaphthalene (**15**). Hantzsche benzofuran synthesis gave a carbethoxy derivative of (±)-cacalol methyl ether (**17**) which on hydrolysis, decarboxylation, and ether cleavage afforded (±)-cacalol.

The structurally unusual sesquiterpene cacalol (**1**) is the parent member of a group of tetrahydronaphthofurans isolated from the roots of *Cacalia decomposita*, a shrub indigeneous to northern Mexico.[2] Following several revisions,[2] the indicated structure was proposed essentially simultaneously in three publications.[3] It has been suggested that cacalol is

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