Synthesis and Thermal Stability of 4-Substituted 1,2-Dithiolanes

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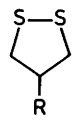
Disodium 2-cyano-3,3-bis(sulfido)propenamide (**6**) has been used as a double synthon for SH^- in the preparation of 1,3-dithiols. Oxidation of the dithiols gives 4-substituted 1,2-dithiolanes, e.g. asparagusic acid (**3**). The energy splits between the first and second ionization potentials in **3** and the other 1,2-dithiolanes (**8–11**) have been determined by ultraviolet photoelectron spectroscopy. The relative stabilities of these compounds do not correlate with the measured ΔE values. Hence, factors besides the S–S torsional angle must influence these stabilities.

Naturally occurring 4-substituted 1,2-dithiolanes exhibit a range of powerful biological activities including insecticidal and plant-growth regulating action.[1,2] For example charatoxin (**1**) from the green freshwater alga *Chara globularis*[3–6] and nereistoxin (**2**) from marine anelids of the genera *Lumbriconereis* and *Lumbrenereis*[7,8] are potent insecticides. A derivative of **2** is currently marketed as a highly successful insecticide.[9] Asparagusic acid (**3**), from etiolated *Asparagus officinalis*, inhibits growth of plants.[10] Synthetic procedures for the three compounds (**1**,[11] **2**[12–14] and **3**[15]) have been reported, however, all these procedures have inherent problems arising from the instability of the precursors and/or formation of product mixtures which are difficult to separate. We now report a modified procedure for the synthesis of 4-substituted 1,2-dithiolanes which allows a better controlled preparation.

Results and discussion

Asparagusic acid[15] (1,2-dithiolane-4-carboxylic acid, **3**) has been synthesized from 3-iodo-2-iodomethylpropionic acid prepared from diethyl bis(hydroxymethyl)malonate via 2-iodomethylacrylic acid.[16] Treatment of the isobutanoic acid derivative with *S*-potassium thioacetate gave the expected 2-(acetylthiomethyl)-3-acetylthiopropionic acid which after saponification left 2-(mercaptomethyl)-3-mercaptopropionic acid. Oxidation of the latter compound (O_2–$FeCl_3$) produced **3** in an overall yield (from malonate) of 8.5 %. Several modifications of the oxidation step have been reported.[17,18] Further modifications of the above procedure in which the preparation of the 2-iodomethyl-3-iodopropionic acid takes place in a single step from the malonate, and the mercapto groups are introduced via trithiocarbonate followed by acid hydrolysis, have raised the total yield to 31 %.[19]

The reaction of 1,3-dielectrophiles with S_4^{2-} followed by desulfurization with copper is known to produce 1,2-dithiolanes,[20–22] usually in good yield. Reaction of diethyl bis(*p*-tolylsulfonyloxymethyl)malonate by this procedure, however, resulted in a rather complex product mixture.



1: R = SMe
2: R = NMe_2
3: R = CO_2H

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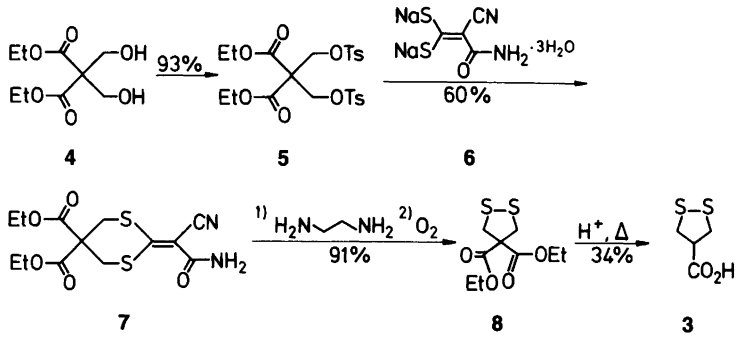


Scheme 1.

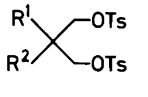
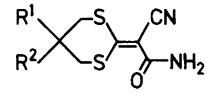
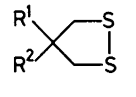
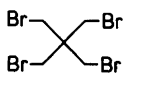
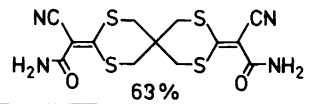
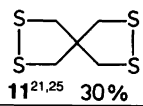
When the desulfurization step was omitted, the mixture contained the expected 1,2-dithiolane and the corresponding 1,2,3-trithiane and 1,2,3,4-tetrathiepane. The tetrathiepane represents a new heterocyclic system.[23]

In order to overcome these difficulties an alternative sulfur nucleophile was selected, namely the dianion 2-carbamoyl-2-cyano-1,1-ethylenedithiolate (**6**),[24] (Scheme 1). This procedure has a number of advantages: (*a*) the sulfur synthon **6** is available as a sodium salt and is easily handled; substitution of the 1,3-bis(toluene-*p*-sulfonates) is anchimerically assisted and hence disubstitution is favored; (*b*) the intermediate 1,3-dithianes are stable, easy to purify, and are cleaved by aminolysis with ethylenediamine under mild basic conditions, again making use of anchimeric assistance; (*c*) the 1,3-dithiols thus formed are oxidatively cyclized *in situ*. Furthermore, the only other product formed in the reaction, 2-[carbamoyl(cyano)methylene]imidazolidine, is easily removed owing to its insolubility in nonpolar solvents.

Following this method, four representative 4-substituted 1,2-dithiolanes were prepared (Table 1). All reagents used are cheap, easily accessible and easily handled. The intermediates are stable compounds which may be stored at ambient temperature for several years without decomposition.

The rather low yield of asparagusic acid (**3**) is results mainly from the elevated temperature used, which causes polymerization during hydrolysis. The polymer, however, can be induced to depolymerize by treatment with aqueous base.[17] Thus the yield can be improved by extraction of the polymeric material with saturated hydrogen carbonate solution. Once isolated in pure solid

Table 1. Synthesis and yields of 4-substituted 1,2-dithiolanes.

				Total yield %
$R^1 = R^2 = CO_2Et$ **5**	$R^1 = R^2 = CO_2Et$ **7**	60%	$R^1 = R^2 = CO_2Et$ **8**	91%	54.6
$R^1 = R^2 = Et$	$R^1 = R^2 = Et$	42%	$R^1 = R^2 = Et$ **9**	95%	39.9
$R^1 = Et, R^2 = H$	$R^1 = Et, R^2 = H$	80%	$R^1 = Et, R^2 = H$ **10**	34%	27.2
		63%	 **11**[21,25]	30%	18.9

form, **3** can be kept unchanged for long periods in the dark at low temperature. Asparagusic acid (**3**) is reported to melt in the range 76.5–77.5 °C.[15,18] We found that heating to this temperature resulted in rapid and quantitative polymerization producing a viscous mass which, on being cooled, hardened to an amorphous substance as evidenced by the absence of any discernible diffraction pattern during X-ray analysis. The polymer melted with sublimation at about 160 °C.

Dithiolanes **8**–**11** are prone to polymerization. The alkyl substituted 1,2-dithiolanes – especially 4-ethyl-1,2-dithiolane (**10**) – polymerize within a few minutes at room temperature, but they may be stored for a short time in a deep freeze. The polymers regenerate the monomer in refluxing toluene. The ester **8** is, on the other hand, relatively stable; after being stored in the dark at −16 °C for several years only a minor amount of polymer was found.

The enhanced reactivity of 1,2-dithiolanes compared with the open-chain disulfides is usually ascribed to the small dihedral angle in the 1,2-dithiolanes.[26] The value of the dihedral angle has been correlated with the size of the energy gap between the first- and the second-ionisation potentials (ΔIE) measured by photoelectron spectroscopy.[27,28] These data indicate that the smaller the dihedral angle, the greater the energy gap. It is therefore surprising that the most stable of the dithiolanes, i.e. **8**, exhibits the largest energy split (Table 2). These findings suggest either that a correlation between ΔIE and dihedral angle is not valid for these compounds or, more likely, that the stability of these compounds is governed to a greater extent by other factors, e.g. substituent effects.

Yet another apparent route for degradation is available to at least some 1,2-dithiolanes, namely spontaneous loss of sulfur. The result of this reaction is noticeable in the combustion analysis which gives rise to a lowered sulfur content. The effect is pronounced for 2,3,7,8-tetrathiaspiro[4,4]nonane (**11**) but less so for the ethyl substituted 1,2-dithiolanes (**9**, **10**). The nature of this transformation is not clear.

Table 2. First- and second-ionisation potentials determined by photoelectron spectroscopy of selected H-substituted 1,2-dithiolanes.

Compound	IE_I/eV	IE_{II}/eV	ΔIE/eV
8	8.09	9.90	1.81
9	8.06	9.74	1.68
10	8.07	9.68	1.61
11	8.07	9.73	1.66
3	8.26	10.00	1.74

Experimental

NMR spectra were recorded on a Jeol FX 90Q instrument (^{1}H at 90 MHz; ^{13}C at 22.5 MHz) or a Varian T-60A spectrometer. IR spectra were run on a Perkin–Elmer 580, MS spectra on a AEI-MS 902 instrument and UV spectra on a Unicam SP 1800 instrument. Photoelectron spectra were obtained using a Perkin–Elmer PS18 photoelectron spectrometer.

Diethyl bis(p-tolylsulfonyloxymethyl)malonate (**5**) was prepared from diethyl bis(hydroxymethyl)-malonate (**4**)[29] by analogy with described procedures.[22] Recrystallized tosyl chloride (100 g, 0.53 mol) was added in small portions over 2 h, whilst maintaining the temperature at 20–25 °C, to a solution of **4** (50 g, 0.23 mol) in dry pyridine (200 ml). The reaction mixture was kept at 40 °C for 2 h and, after being cooled, was poured into an ice-cold mixture of conc. hydrochloric acid (250 ml), water (310 ml) and methanol (620 ml). The resulting crystals were isolated and washed consecutively with the above mixture (50 ml), ice-cold water (1000 ml) and ice-cold methanol (300 ml). The product was dried *in vacuo* over conc. H_2SO_4 overnight: yield 113 g (93 %). M.p. 95–97.5 °C. Anal. $C_{23}H_{28}O_{10}S_2$: C, H, S. IR (KBr): 3040 (w), 2960 (m), 1735 (s), 1590 (m), 1375(s), 1305 (s), 1220 (s), 1180 (s) cm^{-1}. ^{1}H NMR (60 MHz; $CDCl_3$): δ 1.18 (6 H, t, CH_3CH_2), 2.24 (6 H, s, CH_3), 4.17 (4 H, q, CH_3CH_2), 7.68 (8 H, m, aromatic).

Diethyl 2-[carbamoyl(cyano)methylene]-1,3-dithiane-5,5-dicarboxylate (**7**). A mixture of **5** (40 g, 75.8 mmol) and **6** (19.56 g, 75.8 mmol) in Me_2SO (400 ml) was stirred for 6 days at room temperature. The reaction mixture was poured into ice–water (1600 ml) and left overnight at 5–10 °C. The white precipitate was isolated, washed thoroughly with water and dried *in vacuo* over conc. H_2SO_4 overnight. After being recrystallized from toluene the product yielded 15.6 g (60 %). M.p.

130–132 °C. Anal. $C_{13}H_{16}N_2O_5S_2$: C, H, N, S. MS: *m/z* 344 (M^+) IR (KBr): 3400 (m), 3160 (s), 2980 (m), 2200 (m), 1760 (m), 1730 (s), 1680 (s), 1615 (m) cm^{-1}. ^1H NMR (90 MHz; $CDCl_3$): δ 1.28 (6 H, t, CH_3CH_2), 3.45 (2 H, s, CH_2S), 3.55 (2 H, s, CH_2S), 4.63 (4 H, q, CH_3CH_2), 6.12 (2 H, br, NH_2). ^{13}C NMR: δ 13.4 (CH_3), 35.2 (CH_2S), 35.4 (CH_2S), 56.1 (C), 62.7 (CH_2O), 99.7 [=*C*(CN)], 115.8 (CN), 162.9 ($CONH_2$), 167.9 (CO_2Et), 177.5 (S_2C=).

Diethyl 1,2-dithiolane-4,4-dicarboxylate (**8**). A stirred suspension of **7** (1.4 g, 4 mmol) in absolute EtOH (25 ml) and ethylenediamine (0.55 ml, 8 mmol) was kept at 40–50 °C under a stream of O_2 for 6 h. A white precipitate was removed by filtration and the filtrate was evaporated using a rotary evaporator. A hexane extract of the residue was purified by passage through silica gel (5 g saturated with hexane) eluting with CH_2Cl_2–hexane (1:9). The yellow band was collected and yielded the product as a yellow oil after evaporation of the solvent. Yield 0.91 g (91 %). Anal. $C_9H_{14}O_4S_2$: C, H, S. MS: *m/z* 250 (M^+). IR (KBr) 2960 (w), 1735 (s), 1360 (w), 1245 (m), 1180 (m), 1160 (m) cm^{-1}. UV [EtOH(ε)]: 330 (150). ^1H NMR (90 MHz; $CDCl_3$): δ 1.27 (3 H, t, CH_3CH_2), 3.67 (2 H, s, CH_2S), 4.24 (2 H, q, OCH_2CH_3). ^{13}C NMR: δ 14.0 (CH_3), 45.4 (CH_2S), 62.5 (CH_2O), 67.4 (C), 168.7 (C=O). PES: IE_I 8.09, IE_{II} 9.90 eV; ΔIE 1.81 eV.

2-[Carbamoyl(cyano)methylene]-5,5-diethyl-1,3-dithiane was prepared analogously to compound **7** using 3,3-bis(*p*-tolylsulfonyloxymethyl)pentane[30] (5 g, 11.36 mmol) and **6** in Me_2SO (60 ml). The reaction time was 10 days. Yield 1.22 g (42 %). M.p. 128–130 °C. Anal. $C_{11}H_{16}N_2OS_2$: C, H, N, S. MS: *m/z* 256 (M^+). ^1H NMR (90 MHz; $CDCl_3$): δ 0.89 (6 H, t, CH_3CH_2), 1.58 (4 H, q, CH_3CH_2), 2.69 (2 H, s, SCH_2), 2.73 (2 H, s, SCH_2), 5.86 (2 H, br, NH_2). ^{13}C NMR: δ 7.8 (2×CH_3), 27.7 (2×CH_2), 40.3 (C), 41.5 (2×SCH_2), 98.0 [=*C*(CN)], 116.7 (CN), 163.3 ($CONH_2$), 181.4 (S_2C=).

4,4-Diethyl-1,2-dithiolane (**9**) was synthesized analogously to compound **8** using the corresponding 1,3-dithiane (1 g, 3.9 mmol) in EtOH (40 ml) and ethylenediamine (0.52 ml, 7.8 mmol). The reaction time was 3 h. Silica-gel chromatography eluting with CH_2Cl_2 gave a yellow oil, yield 0.6 g (95 %). Anal. $C_7H_{14}S_2$: C, H, S. MS: *m/z* 162 (M^+). UV [EtOH (ε)]: 330 (130). ^1H NMR (90 MHz; $CDCl_3$): δ 0.89 (3 H, t, CH_3CH_2), 1.57 (2 H, q, CH_3CH_2), 2.87 (2 H, s, CH_2S). ^{13}C NMR: δ 8.8 (CH_3), 28.1 (CH_2), 47.9 (CH_2S), 53.7 (C). PES: IE_I 8.06, IE_{II} 9.74 eV; ΔIE 1.68 eV.

2-[Carbamoyl(cyano)methylene]-5-ethyl-1,3-dithiane was prepared analogously to compound **7** using 2-ethyl-1,3-propanediylbis(*p*-toluenesulfonate)[30] (3 g, 7.28 mmol) and **6** (1.89 g, 7.28 mmol) in Me_2SO (36 ml). The reaction time was 3 days. Yield 1.32 g (80 %). M.p. 183–185 °C. Anal. $C_9H_{12}N_2OS_2$: C, H, N, S. MS: *m/z* 228 (M^+). ^1H NMR [90 MHz; $(CD_3)_2SO$]: δ 0.91 (3 H, t, CH_3CH_2), 1.44 (2 H, quintet, CH_3CH_2CH), 2.24 (1 H, m, CH_2CH), 2.56–3.36 (4 H, m, 2×CH_2S), 7.33 (1 H, NH, another presumably present in the water signal at 3.40 ppm). ^{13}C NMR: δ 11.0 (CH_3), 26.1 (CH_2), 34.5 (CH), 34.6 (CH_2S), 35.5 (CH_2S), 98.4 [=*C*(CN)] 116.1 (CN), 162.5 ($CONH_2$), 176.5 (S_2C=).

4-Ethyl-1,2-dithiolane (**10**) was prepared analogously to compound **9** from the corresponding 1,3-dithiane (1 g, 4.39 mmol) in EtOH (32 ml) and ethylenediamine (0.6 ml, 8.78 mmol). The eluent was CH_2Cl_2–hexane (1:4). The product was obtained as a yellow oil. Yield 0.2 g (34 %). Anal. $C_5H_{10}S_2$: C, H, S. MS: *m/z* 134 (M^+). UV [cyclohexane (ε)] 330 (106). ^1H NMR (90 MHz; $CDCl_3$): δ 1.00 (3 H, dt, CH_3CH_2), 1.54 (2 H, d quintet, CH_3CH_2CH), 2.46 (1 H, heptet, CH), 2.70–2.90 (2 H, m, 2×HC*H*S), 3.17–3.36 (2 H, m, 2×*H*CHS). ^{13}C NMR: δ 13.0 (CH_3), 26.8 (CH_2CH_3), 43.8 (CH_2S), 49.7 (CH).

3,9-Bis[carbamoyl(cyano)methylene]-2,4,8,10-tetrathiaspiro[5,5]undecane. A suspension of tetrakis(bromomethyl)methane (5 g, 12.9 mmol) and **6** (6.66 g, 25.8 mmol) in Me_2SO (45 ml) was stirred at room temperature for 6 days. The reaction mixture was poured into ice–water (200 ml) and left at 5–10 °C overnight. After being filtered and thoroughly washed with water, the product was dried *in vacuo* over conc. H_2SO_4 for 24 h. The product (3.3 g) was recrystallized from Me_2SO (25 ml) to yield 3.10 g (63 %). M.p. > 330 °C. Anal. $C_{13}H_{12}N_4O_2S_4 \cdot H_2O$: C, H, N, S. ^1H NMR [90 MHz; $(CD_3)_2SO$]: δ 2.92 (4 H, br, CH_2S), 3.07 (4 H, br, CH_2S), 11.5 (4 H, br, 2×NH_2).

2,3,7,8-Tetrathiaspiro[4,4]nonane (**11**). A suspension of the corresponding 1,3-dithiane (1.5 g, 3.9 mmol) and ethylenediamine (1.05 ml, 15.9 mmol) in DMF (40 ml) was stirred at room temperature for 5 days. Following the addition of EtOH (40 ml), the mixture was kept at −16 °C for 24 h to remove 2-[carbamoyl(cyano)methylene]imidazolidine. Filtration of the reaction mixture and evaporation of the EtOH left a residue which was mixed with an equal volume of water and then extracted with CH_2Cl_2 (4×10 ml). The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated to 5 ml. Hexane was added until the onset of precipitation and the mixture was left at −16 °C overnight. Crystals (yellow needles) were isolated and recrystallized from hexane to yield 0.23 g (30 %) of the product. M.p. 70 °C (subl.) (M.p. lit., [21] 80–80.5 °C). Anal. $C_5H_8S_4$: C, H, S. MS: *m/z* 196 (M^+). UV [EtOH (ε)]: 330 (160). ^1H NMR (60 MHz; $CDCl_3$): δ 3.21 (s). ^{13}C NMR: δ 47.7 (CH_2S), 66.7 (C). PES: IE_I 8.07, IE_{II} 9.73 eV; ΔIE 1.66 eV.

1,2-Dithiolane-4-carboxylic acid (**3**). Reflux of **8** (0.3 g, 1,2 mmol) in 6 M HCl (25 ml) was continued until all oil droplets had disappeared (2–3 h). Extraction of the reaction mixture with Et_2O (4×10 ml) followed by extraction of the combined ether extracts with saturated aqueous sodium hydrogen carbonate (3×10 ml), acidification of the latter with 1 M HCl and extraction of the acidified aqueous phases with benzene (3×10 ml) yielded, after drying over $MgSO_4$ and concentration to approximately 5 ml, a solution which was treated with hexane (1–2 ml) and kept at −16 °C overnight. The product, bright yellow prisms, was recrystallized from toluene to yield 0.06 g (33 %) of asparagusic acid. Anal. $C_4H_6O_2S_2$: C, H, S. MS: *m/z* 150 (M^+). IR (KBr): 3400 (sh), 3300–2800 (s), 1710 (s), 1430 (m), 1400 (m), 1230 (m) cm^{-1}. UV [EtOH (ε)] 330 (140). ^1H NMR: (90 MHz; $CDCl_3$): δ 3.18–3.68 (5 H, m, CH_2CHCH_2), 11.51 (1 H, s, CO_2H); (90 MHz; C_6D_6): δ 2.20–2.53 (3 H, m), 2.66–2.90 (2 H, m), 10.90 (1 H, s, CO_2H). ^{13}C NMR: δ 41.2 (CH_2S), 58.4 (CH), 178.3 (CO_2H).

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