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Mono-, bis-, and tris-1,3-dithiolane aromatic derivatives by esterification and amidation reactions

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RESEARCH ARTICLE

Mono-, bis-, and tris-1,3-dithiolane aromatic derivatives by esterification and amidation reactions

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We report the synthesis of new aromatic derivatives containing the 1,3-dithiolane moiety. The 1,3-dithiolane groups are attached by simple esterification or amidation reactions of 1,3-dithiolane-2-carbonyl chloride with hydroxybenzenes, aniline, or 2,6-diaminopyridine. The isolated yields of these compounds range from 40 to 87%. All of the reported compounds are white solids and stable to air and moisture.

Keywords: Dithiolane; Ligands; Multidentate

1. Introduction

Cyclic thioethers are popular ligands for the construction of discrete transition metal complexes, coordination polymers, and three-dimensional networks [1,2]. The presence and positioning of multiple sulfur atoms in the rings allow for a variety of multidentate binding modes to transition metals. Recent examples of cyclic thioethers used in this manner include 1,3,5-trithiane [3,4], 1,4-dithiane [5,6], 1,3-dithiane [7], 1,4,7-trithiacyclononane [8], 1,4,8,11-tetrathiacyclododecane [8], and various macrocyclic thioether-esters [9] and aza-thioethers [10]. Among cyclic thioethers, 1,3-dithiolanes have received very little attention as potential ligands for transition metal ions [11]. In a continuation of our research in the design of multidentate heteroaromatic ligands [12–14], we describe the synthesis and characterization of new aromatic derivatives containing the 1,3-dithiolane moiety. Such compounds contain multiple sulfur atoms in differing positions and thus have the potential to form new complex structures or networks from interactions with 'soft' transition metal ions.

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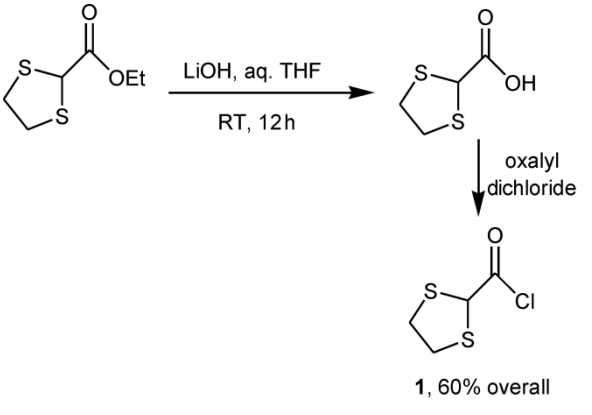
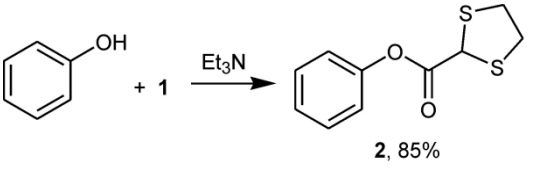
2. Results and discussion

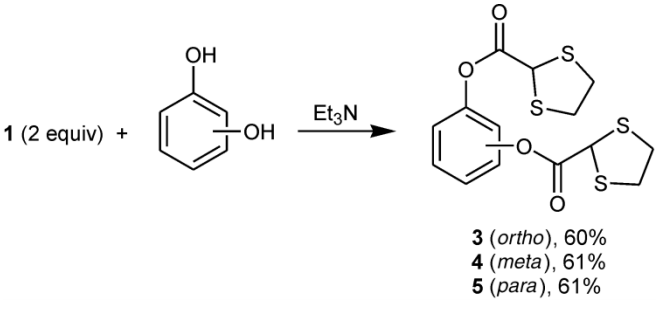
As a general synthetic plan, we sought to attach one or more 1,3-dithiolane moieties to a benzene ring through an ester linkage by treating hydroxybenzenes with 1,3-dithiolane-2-carbonyl chloride **1** [15], synthesized in two steps from commercially available ethyl 1,3-dithiolane-2-carboxylate (Scheme 1). We chose this approach because the ready availability of *ortho*-, *meta*-, and *para*-dihydroxybenzene would provide flexibility in positioning the dithiolane groups around the benzene ring. To test the feasibility of this method, we first treated compound **1** with phenol in the presence of triethylamine. We obtained the expected product **2** in 85% isolated yield [equation (1)]. Subsequently extending this reaction to *ortho*-, *meta*-, and *para*-dihydroxybenzene gave target compounds **3–5** in approximately 60% yield [equation (2)]. Based on the success of these reactions, we then attempted a reaction between **1** and phloroglucinol (1,3,5-trihydroxybenzene). In this case, sodium hydride was found to work effectively as the base and compound **6**, containing three dithiolane moieties on the benzene ring, was obtained in 40% isolated yield [equation (3)].



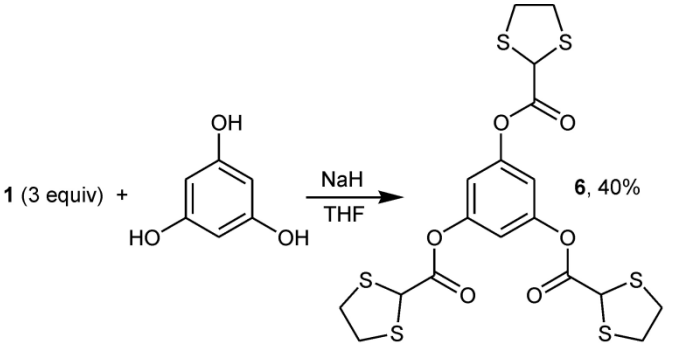
SCHEME 1



(1)

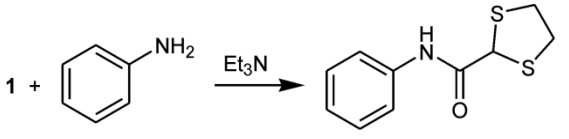


(2)



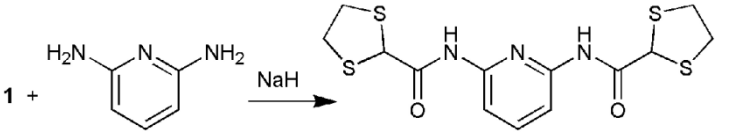
(3)

We also found that compound **1** reacted with aromatic amines to form amide linkages. Reaction of compound **1** with aniline gave amide **7** in 87% yield [equation (4)], and reaction of **1** with 2,6-diaminopyridine (using sodium hydride) gave the corresponding diamide **8** in 80% yield [equation (5)]. These compounds have the benefit of possessing nitrogen atoms as potential additional binding sites.



7, 87%

(4)



8, 80%

(5)

Compounds **2–8**, all new compounds, were isolated as air- and moisture-stable solids. All compounds were fully characterized using ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The solubilities of **2–7** were excellent in common organic solvents, but **8** was soluble only in DMSO or dilute hydrochloric acid solution.

These preparative reactions, though simple, may proceed by more than one type of mechanism. For the examples in which sodium hydride is used as the base, hydride ions initially deprotonate the -OH or -NH_2 groups prior to reaction with **1** (which is added in a later step). When triethylamine is used as the base, two mechanisms may be in competition. One mechanism is addition–elimination, consisting of the addition of ROH or RNH_2 to the carbonyl group of **1** followed by elimination of chloride ion to give the ester or amide. An addition–elimination mechanism may also proceed *via* a reactive acyl quaternary ammonium salt intermediate, a result of the reaction between **1** and triethylamine [16]. The other competing mechanism is elimination–addition, in which triethylamine deprotonates the α-carbon of **1** and eliminates the chloride ion to form a ketene [17]. Subsequent addition of ROH or RNH_2 gives the ester or amide. The presence of the two sulfur atoms bonded to the α-carbon of **1** increases the acidity of the hydrogen [18] and therefore should increase the likelihood of ketene formation [19]. However, in an experiment in which triethylamine was mixed with **1** in dichloromethane, no triethylammonium chloride precipitate was observed after three hours, suggesting that ketene

formation did not occur [17,20]. In the O- and N-acylation reactions described herein, the precipitation of triethylammonium chloride is instantaneous in dichloromethane. Consequently, we believe these reactions predominantly occur *via* an addition–elimination mechanism.

Preliminary experiments in which the acylation products were mixed with various silver salts resulted in the formation of insoluble suspensions that could not be recrystallized for X-ray crystallographic analysis. However, elemental analysis of the isolated suspensions confirms the presence of silver, suggesting that complexation reactions are indeed occurring.

3. Conclusions

We have prepared a series of new compounds containing one, two, or three dithiolane rings bonded to an aromatic core. The synthetic procedure is straightforward and the yields are moderate to good. All of these compounds possess multiple sulfur atoms and are thus capable of binding in a multidentate fashion to 'soft' transition metal ions. Reactions of these ligands with late transition metal ions are a current focus in our laboratory.

4. Experimental

^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Bruker Avance NMR spectrometer.

4.1 *Synthesis of 1*

Ethyl 1,3-dithiolane-2-carboxylate (15.0 g, 0.084 mol) was dissolved in THF/water (150 mL THF/75 mL water). Lithium hydroxide (10.2 g, 0.42 mol) was added, and the resulting mixture was stirred overnight at room temperature. The solvent was then removed under reduced pressure, and the residue was dissolved in water of pH > 10. This solution was extracted with diethyl ether to remove any unchanged ester and organic impurities, and the layer was discarded. The aqueous layer was then acidified to pH 2 with conc. HCl. After extracting with diethyl ether (2 × 200 mL), the combined organic layers were washed successively with water and brine, dried with anhydrous $MgSO_4$, and filtered. Removal of volatiles under reduced pressure gave the dithiolanecarboxylic acid [21] (8.5 g, 67%). A portion of the acid (1.0 g, 0.0066 mol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. Oxalyl dichloride (0.8 mL, 0.0073 mol) was added dropwise, and the resulting mixture was stirred and warmed to room temperature over 2 h. Volatiles were removed under reduced pressure to give **1** [15] as an oil (1.0 g, 89% from the acid). ^{1}H-NMR (400 MHz; $CDCl_3$) 5.17 (s, 1H), 3.40 (s, 4H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 170.5, 61.0, 38.8.

4.2 *General procedure for synthesis of 2–5*

The detailed synthetic procedure of **2** is representative of the procedures used to synthesize **3–5**. Phenol (0.60 g, 0.0063 mol) was dissolved in dichloromethane (15 mL) and cooled in an ice-bath under a nitrogen atmosphere. Triethylamine (1.1 mL, 0.0076 mol) was added and the clear solution was stirred for 15 min. A solution of **1** (1.1 g, 0.0065 mol) in dichloromethane (15 mL) was added dropwise over a period of 15 min. The resulting mixture was gradually warmed to room temperature and stirred for 3 h. The suspension was then poured into a beaker containing 100 mL of 10% aq. HCl. The aqueous layer was extracted with chloroform (100 mL) and the combined organic layers were washed successively with 4% aq. NaOH (100 mL),

water (100 mL), and brine (100 mL), and dried over anhydrous $MgSO_4$. After filtration, all volatiles were removed by rotary evaporation and the residual oil was chromatographed on silica gel (10:90 EtOAc:hexane) to give **2** as an oil that solidified in the freezer (1.2 g, 85%), mp 33–35 °C. IR (KBr) 2967 (m), 1748, 1591, 1277 (s), 943 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 7.30–7.28 (d, 2H, $J = 7.8$ Hz), 7.16–7.12 (t, 1H, $J = 7.3$ Hz), 7.04–7.02 (d, 2H, $J = 7.8$ Hz), 4.97 (s, 1H), 3.42–3.36 (m, 2H), 3.31–3.24 (m, 2H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 169.7, 150.6, 129.3, 126.0, 121.0, 50.5, 38.8 (Calc. for $C_{10}H_{10}O_4S_4$: C, 53.07, H, 4.45. Found: C, 53.25, H, 4.34%).

4.3 *Compound 3*

In the manner described above, compound **1** (1.01 g, 0.0059 mol) was treated with catechol (0.30 g, 0.0027 mol) in the presence of triethylamine (0.92 mL, 0.0065 mol). Column chromatography on silica gel (10:90 followed by 15:85 EtOAc:hexane) gave **3** as a white solid (0.61 g, 60%), mp 160 °C. IR (KBr) 2927 (m), 1758, 1492, 1288 (s), 954 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 7.29–7.28 (d, 2H, $J = 3.2$ Hz), 7.29–7.23 (d, 2H, $J = 2.0$ Hz), 5.13 (s, 2H), 3.53–3.49 (m, 4H), 3.43–3.39 (m, 4H). ^{13}C-NMR (100.6 MHz $CDCl_3$) 168.8, 142.0, 127.0, 123.0, 50.3, 38.9 (Calc. for $C_{14}H_{14}O_4S_4$: C, 44.90, H, 3.77. Found: C, 44.95, H, 3.84%).

4.4 *Compound 4*

In the manner described above, compound **1** (1.01 g, 0.0059 mol) was treated with resorcinol (0.30 g, 0.0027 mol) in the presence of triethylamine (0.92 mL, 0.0065 mol). Column chromatography on silica gel (10:90 followed by 15:85 EtOAc:hexane) gave **4** as a white solid (0.61 g, 61%), mp 89 °C. IR (KBr) 2931 (m), 1758, 1592, 1277 (s), 967 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 7.42–7.38 (t, 1H, $J = 8.2$ MHz), 7.06–7.04 (d, 2H, $J = 8.2$ MHz), 6.99 (d, 1H, $J = 1.8$ MHz), 5.06 (s, 2H), 3.53–3.48 (m, 4H), 3.43–3.37 (m, 4H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 169.3, 151.0, 129.7, 118.9, 114.7, 50.4, 38.8 (Found: C, 45.17, H, 3.76%).

4.5 *Compound 5*

In the manner described above, compound **1** (1.01 g, 0.0059 mol) was treated with hydroquinone (0.30 g, 0.0027 mol) in the presence of triethylamine (0.92 mL, 0.0065 mol). Column chromatography on silica gel (10:90 followed by 15:85 EtOAc:hexane) gave **5** as a white solid (0.63 g, 61%), mp 170 °C. IR (KBr) 2928 (m), 1752, 1507, 1273 (s), 942 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 7.16 (s, 4H), 5.07 (s, 2H), 3.55–3.49 (m, 4H), 3.45–3.38 (m, 4H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 169.6, 148.3, 122.1, 50.5, 38.9 (Found: C, 45.39, H, 3.83%).

4.6 *Compound 6*

Phloroglucinol (0.50 g, 0.0038 mol) was dissolved in THF (15 mL) and cooled in an ice-bath under a nitrogen atmosphere. Sodium hydride (0.343 g, 0.014 mol) was added and the resulting suspension was stirred for 15 min. A solution of compound **1** (2.2 g, 0.013 mol) in THF (15 mL) was added dropwise over 15 min and the mixture was then stirred overnight at room temperature. The THF was removed by rotary evaporation and the residue was quenched by the addition of water (100 mL) at 0 °C. The aqueous solution was extracted with ethyl acetate (2×100 mL) and the combined organic layers were washed successively with water (100 mL),

saturated aq. sodium hydrogen carbonate (100 mL), water (100 mL) again, and brine (100 mL). The organic solution was then dried over anhydrous $MgSO_4$ and filtered. The volatiles were removed under reduced pressure and the residue was chromatographed on silica gel (10:90 followed by 20:90 EtOAc:hexane) to give **6** as a white solid (0.82 g, 40%), mp 153–155 °C. IR (KBr) 2927 (m), 1758, 1604, 1454 (s), 994 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 6.93 (s, 3H), 5.04 (s, 3H), 3.54–3.50 (m, 6H), 3.44–3.38 (m, 6H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 168.9, 151.1, 112.6, 50.4, 38.9 (Calc. for $C_{18}H_{18}O_6S_6$: C, 41.36; H, 3.47. Found: C, 41.55, H, 3.62%).

4.7 *Compound 7*

Aniline (0.60 g, 0.0064 mol) was dissolved in dichloromethane (15 mL) and cooled in an ice-bath under a nitrogen atmosphere. Triethylamine (1.1 mL, 0.0077 mol) was added and the resulting clear solution was stirred for 15 min. A solution of compound **1** (1.2 g, 0.007 mol) in dichloromethane (15 mL) was added dropwise over 15 min. The resulting mixture was stirred at room temperature for 3 h, and then poured into a beaker containing 100 mL of 10% aq. HCl. The aqueous layer was extracted with chloroform (100 mL), and the combined organic layers were washed successively with 4% aq. NaOH (100 mL), water (100 mL), and brine (100 mL). The organic solution was then dried over anhydrous $MgSO_4$ and filtered. Removal of volatiles on a rotary evaporator gave a solid residue. Column chromatography using silica gel (10:90 EtOAc:hexane) gave **7** as a white solid (1.25 g, 87%), mp 134 ºC. IR (KBr) 3244, 2967 (m), 1647, 1552, 1442 (s), 962 (m) cm^{-1}. ^{1}H-NMR (400 MHz; $CDCl_3$) 8.66 (s, 1H, NH), 7.48–7.46 (d, 2H, $J = 7.8$ Hz), 7.27–7.23 (t, 1H, $J = 7.3$ Hz), 7.07–7.03 (t, 2H, $J = 7.8$ Hz), 4.92 (s, 1H), 3.33–3.23 (m, 4H). ^{13}C-NMR (100.6 MHz; $CDCl_3$) 167.5, 137.2, 128.9, 124.7, 119.8, 54.2, 39.2 (Calc. for $C_{12}H_{11}NOS_2$: C, 53.30, H, 4.92. Found: C, 53.42, H, 4.91%).

4.8 *Compound 8*

2,6-Diaminopyridine (0.30 g, 0.0027 mol) was dissolved in THF (15 mL) and cooled in an ice-bath under a nitrogen atmosphere. Sodium hydride (0.130 g, 0.0052 mol) was then added and the suspension was stirred for 15 min. A solution of **1** (1.02 g, 0.006 mol) in THF (15 mL) was added dropwise over 15 min, and the resulting suspension was stirred overnight at room temperature. The THF was removed on a rotary evaporator, and the residue was quenched by the addition of water (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the combined organic layers were washed successively with water (100 mL), saturated aq. sodium hydrogen carbonate (100 mL), water (100 mL) again, and brine (100 mL). The organic solution was then dried over anhydrous $MgSO_4$ and filtered. All volatiles were removed by rotary evaporation and the residue was chromatographed on silica gel (90:10 EtOAc:hexane) to give **8** as a white solid (0.80 g, 80%), mp 198 °C. IR (KBr) 3342, 2928 (m), 1690, 1586, 1496 (s), 804 (m) cm^{-1}. ^{1}H-NMR (400 MHz; DMSO-d_6) 10.21 (s, 2H, NH), 7.80–7.78 (t, 1H, $J = 7.8$ Hz), 7.71–7.69 (d, 2H, $J = 7.6$ Hz), 5.30 (s, 2H), 3.45–3.35 (m, 8H). ^{13}C-NMR (100.6 MHz; DMSO-d_6) 170.4, 150.7, 141.3, 110.2, 52.3, 39.4 (Calc. for $C_{13}H_{15}N_3O_2S_4$: C, 41.80; H, 4.05. Found: C, 41.56, H, 4.12%).

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