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Regioselective ring opening by propanethiolate of (methylenedioxy)benzenes with electron-withdrawing substituents

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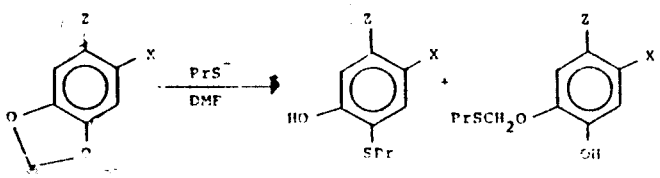
Abstract. The ring opening reaction of (methylenedioxy)benzenes **1** with propanethiolate in DMF leads to products **2** and/or **3**, depending on the nature of the electron-withdrawing substituent Z.

Aryl sulfides can be obtained by the action of alkanethiolates on aryl bromides[1]. This is a particularly advantageous process for the preparation of 2,5-dimethoxy-4-(alkylthio)benzaldehydes, a reaction which is carried out in DMF (dimethylformamide) at room temperature with excellent yield[2]. In trying to widen the scope of this smooth reaction, we reasoned that other *o*- or *p*-bromobenzaldehydes might be useful substrates for such a conversion. We were disappointed to discover that 2-bromo-4,5-dimethoxybenzaldehyde did not react with propenethiolate in DMF even after 12 h of stirring at room temperature. However, the analogous 2-bromo-4,5-(methylenedioxy)benzaldehyde** (a 1,3-benzodioxole derivative) behaved differently, yielding a product which was identified as 2-bromo-4-(propylthio)-5-hydroxybenzaldehyde. A survey of the literature revealed some examples of ring opening of the 1,3-benzodioxole system by alkoxides[3] and amines[4], but we could not find examples of this reaction with alkane- or arenethiolates.

Examples of dealkylation of aryl ethers with alkanethiolates are well known[5]. Instead, in our case, direct nucleophilic attack on the aromatic ring had taken place. We guessed that this mechanistic diversion was caused by the presence of the electron-withdrawing –CHO substituent and we, therefore, centered our efforts on investigation of the reactivity of 1,3-benzodioxole rings with electron-withdrawing substituents at position 5. We chose the propanethiolate anion, generated *in situ* by treatment of propanethiol with sodium hydride in DMF, as a common nucleophile for the series of substrates depicted in Scheme 1.

The products generally consisted of either **2** or **3**, and, in one case, of the mixture of the two. The product compositions depended largely on the nature of the electron-withdrawing group Z. The Table summarizes the results.

The nitro derivatives **1a** reacted smoothly at room temperature to give the corresponding hydroxyphenyl sulfide **2a** in quantitative yield. The less reactive aminocarbonyl deriva-



1 **2** **3**

a) X = H, Z = NO_2
b) X = H, Z = CHO
c) X = Br, Z = CHO
d) X = H, Z = CN
e) X = H, Z = $COCH_3$
f) X = H, Z = CO_2CH_3
g) X = H, Z = $CO_2C_6H_5$
h) X = H, Z = $CONH_2$

Scheme 1

Table. Products and yields of the reaction of (methylenedioxy)benzenes **1** *with propanethiolate in DMF.*

Substrate	Z	Yield (%) 2 + 3	Product	σ_p^-
1a	NO_2	98	**2a**	1.27
1b	CHO	20[a]	**2b**	1.13
1c	CHO	25[b]	**2c**	1.13
1d	CN	66	**2d** + **3d**[c]	1.00
1e	$COCH_3$	33[d]	**3e**	0.87
1f	CO_2CH_3	10[e]	**3f**	0.68
1g	$CO_2C_6H_5$	–[f]	–	–
1h	$CONH_2$	70[g]	**3h**	0.63

[a] In addition, competing Cannizzaro gave 38% yield of 3,4-(methylenedioxy)benzoic acid. [b] Competing Cannizzaro gave 36% yield of 2-bromo-4,5-(methylenedioxy)benzoic acid. [c] In a 1:1 ratio. The yield of **3d** was estimated on the basis of its hydrolysis product 3,4-dihydroxybenzonitrile. [d] 65% of the substrate recovered unchanged. [e] The product was a mixture of **3f** (10%) and 3,4-(methylenedioxy)benzoic acid (90%). [f] The product was 3,4-(methylenedioxy)benzoic acid (15%). [g] 30% of the substrate recovered unchanged.

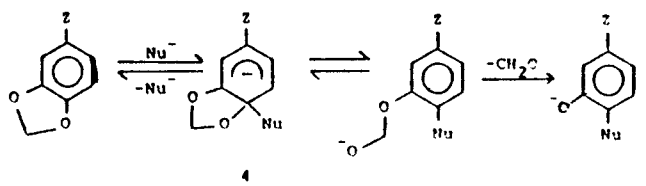
** Chem. Abstr. name: 6-bromo-1,3-benzodioxole-5-carboxaldehyde.

tive **1h** required higher temperature, and formed compound **3h** as the sole product of nucleophilic attack at the methylene carbon of the substrate.

The low yields obtained when substrate **1** was an aldehyde were due to the competing disproportionation of the substrate via Cannizzaro reaction. Sodium hydroxide generated in wet DMF consumed some of the reacting benzaldehyde, as shown by the large amounts of the corresponding benzoic acids isolated from the product mixtures.

In the case of the methyl ester **1f**, a low yield (10%) of the corresponding 4-hydroxybenzoate ester **3f** was obtained. We thought at first that hydrolysis by sodium hydroxide might also be responsible here for the low yield of the expected products. The corresponding 3,4-(methylenedioxy)benzoic acid was in fact the major product (90% yield) isolated from the reaction. However, the yield of **2f** could not be raised, nor was the amount of the isolated benzoic acid reduced by careful drying of the solvent. This was an indication that the propanethiolate anion itself was acting as a demethylating agent, in agreement with previous reports of ester dealkylations by thiolates[6]. This demethylation could be obviated by the use of a phenyl ester **1g**, but in this case rapid formation of the corresponding *S*-propyl thioester was the predominant process.

We also attempted the same reaction with a range of nucleophiles which included iodide, *O*-ethyl dithiocarbonate ($CH_3CH_2-O-CS_2^-$) and arenethiolates (4-$ClC_6H_4S^-$ and 4-$CH_3C_6H_4S^-$). Contact of these nucleophiles with substrates **1a** or **1b** at room temperature for 8–12 h in DMF did not form any products. The different behaviour of the arenethiolates, as compared to the successfully employed PrS^- anion is somewhat surprising. A possible explanation for the diminished reactivity of the former may be found in the S_NAr mechanism postulated for this conversion.



Scheme 2

Formation of intermediate **4** is reversible and its fate is determined by the relative leaving-group abilities of the two nucleofuges Nu^- and $ArOCH_2O^-$. When Nu^- is an arenethiolate, this competition favours a return of the intermediate **4** to the starting benzodioxole, as an arenethiolate is a much better nucleofuge than an alkoxide. The S_NAr process does not take place in this case, because the reactants do not go beyond the reversible first step.

As might be expected, the observed regioselectivity of substrate **1** is dependent on the nature of the activating group Z. The Table lists the values of the Hammett σ_p^- constants for the various substituents. A good correlation is observed between these values and the product compositions. Thus, substrates with strong electron-withdrawing substituents like $-NO_2$ or $-CHO$ yield exclusively hydrosulfides **2**, because of the strong activation of the carbon atom *para* to group Z. The cyano derivative **1d** offers an example of moderate activation with the consequent formation of a mixture of the two possible products **2d** and **3d** in an approximately 1:1 ratio. Finally, the aminocarbonyl group is too weakly activating to make formation of the corresponding S_NAr product **3h** an important outcome.

Experimental

Melting points were obtained with a Kofler hot-stage apparatus and were not corrected. IR spectra were recorded on a Perkin–Elmer 781 instrument, NMR spectra were obtained with a Varian EM 360 apparatus, employing tetramethylsilane as internal reference.

3,4-(Methylenedioxy)benzaldehyde (**1b**) and 3,4-(methylenedioxy)-acetophenone (**1e**) were purchased from Aldrich. The following compounds were prepared by reported procedures: 3,4-(methylenedioxy)nitrobenzene (**1a**), m.p. 147 °C, lit.[7] m.p. 147–149 °C; 2-bromo-4,5-(methylenedioxy)benzaldehyde (**1c**), m.p. 129 °C, lit.[8] m.p. 129 °C; 3,4-(methylenedioxy)benzonitrile (**1d**), m.p. 93 °C, lit.[9] m.p. 94–95 °C; methyl 3,4-(methylenedioxy)benzoate (**1f**), m.p. 52 °C, lit.[10] m.p. 53 °C; 3,4-(methylenedioxy)benzamide **1h**, m.p. 168 °C, lit.[11] m.p. 169 °C.

Phenyl 3,4-(methylenedioxy)benzoate (**1g**)

A mixture of 3,4-(methylenedioxy)benzoic acid (2.0 g, 12 mmol) and excess thionyl chloride (10 ml) was gently refluxed for 1 h. The solution was evaporated to dryness in a rotary evaporator and to the resulting crude acid chloride was added 15 ml of an aqueous solution of phenol (1.5 g, 16 mmol) and sodium hydroxide (0.8 g, 20 mmol). The suspension was shaken vigorously for 40 min and the precipitate filtered and washed with water to give, after drying, 2.0 g (70% yield) of the phenyl ester **1g**, recrystallized from hexane, m.p. 66 °C. Anal. calcd. for $C_{14}H_{10}O_4$: C 69.42, H 4.13; found: C 69.77, H 4.22%. IR $\bar{\nu}_{max}$(KBr): 1730 (C=O) cm^{-1}. ^1H NMR $\delta(CCl_4)$: 6.2 (2H, s, OCH_2); 7.1 (1H, d, *J* 8 Hz, ArH); 7.4–7.6 (5H, m, ArH); 7.9 (1H, d, *J* 1 Hz, ArH); 8.1 (1H, dd, *J* 8 Hz, *J'* 1 Hz, ArH).

Reaction of substrates **1** *with sodium propanethiolate; general procedure*

To a stirred solution of propanethiol (0.76 g, 10 mmol) in DMF (20 ml) was added sodium hydride (0.45 g of a 70% oil suspension, 13 mmol). After the evolution of H_2 had ceased, substrate **1** (5 mmol) was added and the resulting mixture was stirred for 12 h at 25 °C (for the less reactive substrates **1d**, **1e** and **1h**, the temperature was kept at 80 °C for 12 h). The mixture was then poured into ice–water (50 ml), acidified with 0.1M HCl and extracted with diethyl ether (3 × 30 ml). The crude product mixture, obtained after drying the ether extracts with anhydrous calcium chloride and removing the solvent in a rotary evaporator, was then analysed and purified by flash chromatography on silica 60H (Merck). The following compounds were obtained in his way:

2-(Propylthio)-5-nitrophenol (**2a**). The eluent was a mixture of hexane/diethyl-ether (4:1). Yield 1.0 g (98%); recrystallized in heptane, m.p. 48 °C. Anal. calcd. for $C_9H_{11}NO_3S$: C 50.70, H 5.16, N 6.57; found: C 50.92, H 5.37, N 6.37%. IR $\bar{\nu}_{max}$(KBr): 3350 (OH), 1600, 1500, 1325 (NO_2) cm^{-1}. ^1H NMR $\delta(CDCl_3)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2CH_2$); 2.8 2H, t, *J* 7 Hz, CH_2S); 6.8 (1H, s, OH) and 7.6–7.9 (3H, m, ArH).

3-Hydroxy-4-(propylthio)benzaldehyde (**2b**). The eluent was a mixture of hexane/diethyl-ether (4:1). Yield 0.2 g (20%); m.p. 84–86 °C. Anal. calcd. for $C_{10}H_{12}O_2S$: C 61.22, H 6.12; found: C 61.38, H 6.32%. IR $\bar{\nu}_{max}$(KBr): 3400 (OH), 1660 (C=O) cm^{-1}. ^1H NMR $\delta(CDCl_3)$: 1.0 (3H, t, *J* 7 Hz, $CH_3C\underline{H}_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2CH_2$); 2.8 (2H, t, *J* 7 Hz, CH_2S); 6.9 (1H, s, OH); 7.3–7.6 (3H, m, ArH); 9.9 (1H, s, CHO).

A second compound was also isolated from the product mixture and identified by its IR spectrum as 3,4-methylenedioxybenzoic acid (0.32 g, 38% yield), m.p. 225 °C, lit.[12] m.p. 227–228 °C.

2-Bromo-4-(propylthio)-5-hydroxybenzaldehyde (**2c**). Same eluent as for **2b**, yield 0.34 g (25%); m.p. 137 °C. Anal. calcd. for $C_{10}H_{11}BrO_2S$: C 43.64, H 4.04; found: C 43.92, H 4.09%. IR $\bar{\nu}_{max}$(KBr): 3400 (OH), 1660 (C=O) cm^{-1}. ^1H NMR $\delta(CDCl_3)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2CH_2$); 2.8 (2H, t, *J* 7 Hz, CH_2S); 6.6 (1H, s, OH); 7.4 (1H, s, ArH); 7.6 (1H, s, ArH); 10.2 (1H, s, CHO).

A second compound (0.44 g) was also isolated from the product mixture and identified as the 2-bromo-4,5-(methylenedioxy)benzoic acid: m.p. 202–203 °C, lit.[13] m.p. 204–205 °C.

3-Hydroxy-4-(propylthio)benzonitrile (**2d**). Chromatography using a mixture of hexane/chloroform (3:2) as eluent gave a viscous oil which was redissolved in a 1M methanolic solution of HCl and left standing at room temperature for 2 days to ensure complete hydrolysis of product **3d**. The crystals that separated were filtered to give, after drying, 0.32 g (33% yield) of compound **2d**; m.p.: 76–78°C. Anal. calcd. for $C_{10}H_{11}NOS$: C 62.18, H 5.70, N 7.25; found: C 62.50, H 5.69, N 7.30%. IR $\bar{\nu}_{max}$(KBr): 3350 (OH), 2200 (CN) cm^{-1}. ^1H NMR $\delta(CDCl_3)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2CH_2$); 2.8 (2H, t, *J* 7 Hz, CH_2S); 6.8 (1H, s, OH); 7.2 (1H, m, ArH); 7.6 (2H, m, ArH).

The methanolic filtrate was diluted with diethyl ether (70 ml) and washed with water. The ether extract was dried over $CaCl_2$ and evaporated to give 0.22 g of crude 3,4-dihydroxybenzonitrile (33% yield, based on substrate **1d**), recrystallized from water; m.p. 153°C, lit.[15] m.p. 152°C.

3-[(Propylthio)methoxy]-4-hydroxyacetophenone (**3e**). Purification by chromatography, using a mixture of hexane/ether (4:1) as eluent gave 0.53 g (65% recovery) of the unreacted substrate **1e**, besides 0.40 g (33% yield) of compound **3e**; m.p. 40–42°C. Anal. calcd. for $C_{12}H_{16}O_3S$: C 60.00, H 6.67; found: C 59.72, H 6.58%. IR $\bar{\nu}_{max}$(KBr): 3300 (OH), 1660 (C=O) cm^{-1}. ^1H NMR $\delta(CCl_4)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2CH_2$); 2.4 (3H, s, CH_3CO); 2.8 (2H, t, *J* 7 Hz, CH_2S); 5.5 (2H, s, OCH_2S); 6.8 (1H, s, OH); 7.2 (1H, m, ArH); 7.4–7.8 (2H, m, ArH).

Methyl 3-[(propylthio)methoxy]-4-hydroxybenzoate (**3f**). The eluent was a mixture of hexane/ether (2:1); yield 0.13 g (10%); m.p. 78–80°C. Anal. calcd. for $C_{12}H_{16}O_4S$: C 56.25, H 6.25; found: C 56.37, H 6.15%. IR $\bar{\nu}_{max}$(KBr): 3350 (OH) and 1675 (C=O) cm^{-1}. ^1H NMR $\delta(CCl_4)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.6 (2H, sextet, *J* 7 Hz, $CH_3C\underline{H}_2$); 2.8 (2H, t, *J* 7 Hz, CH_2S); 4.1 (3H, s, OCH_3); 5.5 (2H, s, OCH_2S); 6.4 (1H, s, OH); 7.6–7.9 (3H, m, ArH).

The major product was isolated and identified as the 3,4-(methylenedioxy)benzoic acid (0.75 g, 90°, yield); m.p. 226°C, lit.[13] m.p. 227–228°C.

S-Propyl 3,4-(methylenedioxy)benzothioate. After 2 h at room temperature, the reaction was interrupted and worked up as described. After elution with hexane/ether (2:1) the benzothioate was isolated in the form of an oil (0.9 g, 80% yield). Anal. calcd. for $C_{11}H_{12}O_3S$: C 58.93, H 5.36; found: C 58.84, H 5.51%. IR $\bar{\nu}_{max}$(neat): 1650 (C=O) cm^{-1}. ^1H NMR $\delta(CCl_4)$: 1.0 (3H, t, *J* 7 Hz, $C\underline{H}_3CH_2$); 1.5 (2H, sextet, $CH_3C\underline{H}_2$); 2.8 (2H, t, *J* 7 Hz, CH_2S); 6.0 (2H, s, OCH_2O); 6.7 (1H, d, *J* 8 Hz, ArH); 7.3 (1H, d, *J* 2 Hz, ArH); 7.5 (1H, dd, *J* 8 Hz and *J'* 2 Hz, ArH).

A second product (0.12 g) was isolated and identified as 3,4-(methylenedioxy)benzoic acid (15% yield); m.p. 226°C, lit.[13] m.p. 227–228°C.

3-[(Propylthio)methoxy]-4-hydroxybenzamide (**3h**). Elution with a mixture of hexane/ether (4:1) gave, besides the starting amide (0.25 g, 30% recovery), compound **3h** (0.84 g, 70% yield); m.p. 144°C. Anal. calcd. for $C_{11}H_{15}NO_3S$: C 54.77, H 6.22, N 5.81; found: C 54.89, H 6.44, N 5.72%. IR $\bar{\nu}_{max}$(KBr): 3340 (OH), 3170 (NH), 1630 (C=O) cm^{-1}. ^1H NMR $\delta[(CD_3)_2CO]$ 1.0 (3H, t, *J* 7 Hz, $CH_2C\underline{H}_3$); 1.7 (2H, sextet, *J* 7 Hz, $C\underline{H}_2CH_3$); 2.9 (2H, t, *J* 7 Hz, SCH_2); 5.6 (2H, s, OCH_2S); 7.1 (1H, m, ArH); 7.8–7.9 (2H, m, ArH); 8.8 (1H, s, ArOH).

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