

The Formylation of an Aromatic Nucleus by the Use of 2-Ethoxy-1,3-dithiolane

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The reaction of various phenols with 2-ethoxy-1,3-dithiolane proceeded smoothly in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to afford 1,3-dithiolan-2-ylated phenols, which were readily hydrolyzed to the corresponding aldehydes. This process was also extended to *N,N*-dimethylaniline and indole.

Considerable efforts have been devoted towards the discovery of methods for the introduction of a formyl moiety onto an aromatic nucleus. The Gattermann-Koch reaction,¹⁾ the Reimer-Tiemann reaction,²⁾ the Vilsmeier reaction,³⁾ the Duff reaction,⁴⁾ the Friedel-Crafts reaction with dichloromethyl alkyl ether or with trialkyl orthoformate,⁵⁾ etc. are well known and widely used. Recently, Gassman and Amick have reported a process which involves the reaction of phenols with a salt formed through the mixing of *N*-chlorosuccinimide and dithiane.⁶⁾ However, all these reactions give relatively poor yields or can be used only with electron-rich aromatic compounds. It is proper to say that no reaction for formylating aromatic compounds which would not be subjected to either one of the above limitations has been found.

We have now found that 2-ethoxy-1,3-dithiolane in dichloromethane with a Lewis acid catalyst is an efficient reagent for the introduction of the 1,3-dithiolan-2-yl group to some phenols and that the resulting cyclic thioacetal derivatives (protected formylated phenols) are easily hydrolyzed to the corresponding aldehydes. This process for the formylation of phenols could also be extended to *N,N*-dimethylaniline and indole. Although this formylation process is also subject to limitations similar to those of the earlier methods, that is, it is applicable only to electron-rich aromatic compounds, such as phenols, *N,N*-dimethylaniline, and indole, and the yields of the obtained aldehydes are roughly the same as those in the previously reported reactions, it has such advantages that

the starting 2-ethoxy-1,3-dithiolane is readily available, and can be stored for a long time, and the reaction smoothly proceeds under relatively mild conditions.

Results and Discussion

The first attempt was directed toward establishing the most effective Lewis acid catalyst for the reaction of *p*-cresol (**1d**) with 2-ethoxy-1,3-dithiolane in dichloromethane. The yields of 2-(1,3-dithiolan-2-yl)-*p*-cresol (**2d**) formed in the reaction with various Lewis acid catalysts are shown in Table 1.

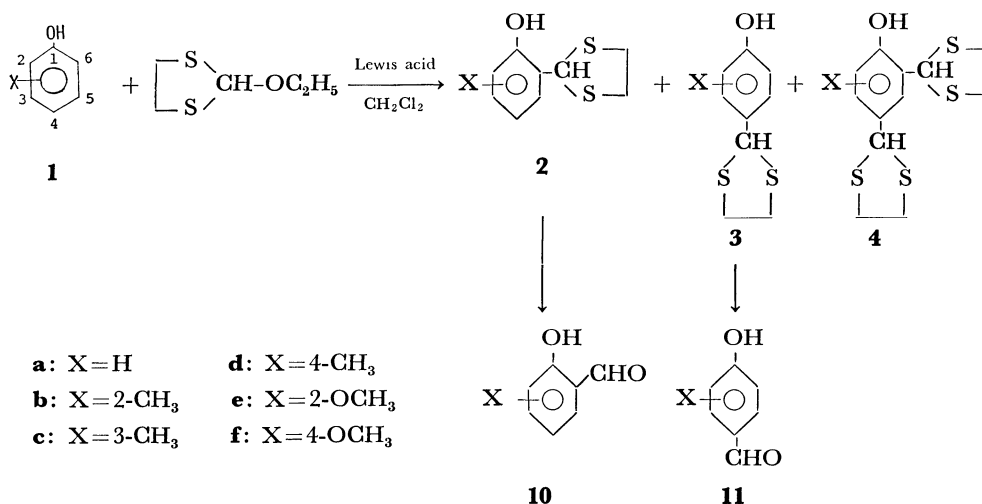
As is evident from Table 1, the best yield (55%) was achieved in a run involving a 1.5 molar ratio of 2-ethoxy-1,3-dithiolane and a 0.75 molar ratio of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ for **1d**. The $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyst, therefore, would be a very effective catalyst for the 1,3-dithiolan-2-ylation of phenols other than **1d**. Thus, we have studied the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed reaction of 2-ethoxy-1,3-dithiolane with several phenols in dichloromethane at room temperature. The results are summarized in Table 2.

It seems plausible that the reaction path involves the coordination of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ with 2-ethoxy-1,3-dithiolane to give the 1,3-dithiolan-2-ium ion and the subsequent attack on the aromatic nucleus. As can be seen from Table 2, the exclusive attack occurs in the 2- and 3-positions of **1d** and *p*-hydroxyanisole (**1f**) respectively and also in the 4-positions of *o*-cresol (**1b**) and guaiacol (**1e**). Phenol (**1a**) was 1,3-dithiolan-

TABLE 1. REACTION OF *p*-CRESOL (**1d**) WITH 2-ETHOXY-1,3-DITHIOLANE IN THE PRESENCE OF VARIOUS LEWIS-ACID CATALYSTS

Mole ratio, 2-ethoxy-1,3-dithiolane/ 1d	Lewis acid (Mole ratio, Lewis acid/ 2-ethoxy-1,3-dithiolane)	Reaction ^{a, b)}		Yield/% of 2d ^{c)}
		Temp/°C	Time/h	
1.0	ZnCl_2 (0.2)	rt	24	31 (61)
1.5	ZnCl_2 (0.2)	77 ^{d)}	8	37 (87)
1.5	ZnCl_2 (0.2)	rt	22	37 (90)
1.0	ZnCl_2 (1.0)	rt	1	27 (98)
1.5	ZnCl_2 (0.5)	rt	14	45 (84)
2.0	ZnCl_2 (0.5)	rt	14	34 (64)
1.5	FeCl_3 (0.5)	rt	6	41 (59)
1.5	HgCl_2 (0.5)	rt	6	22 (43)
1.5	$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.5)	rt	14	55 (94)
1.5	TiCl_4 (0.5)	rt	14	40 (66)

a) Dichloromethane was used as the solvent unless otherwise noted. b) In almost all runs, the formation of a small amount of 2,2'-[1,2-ethanediylbis(thio)]bis-1,3-dithiolane⁷⁾ as a by-product was observed. c) The values in parentheses are the percentages of conversion, corrected for the recovered **1d**. d) The solvent here is carbon tetrachloride.

TABLE 2. REACTION OF PHENOLS (**1**) WITH 2-ETHOXY-1,3-DITHIOLANE IN THE PRESENCE OF BF₃·Et₂O

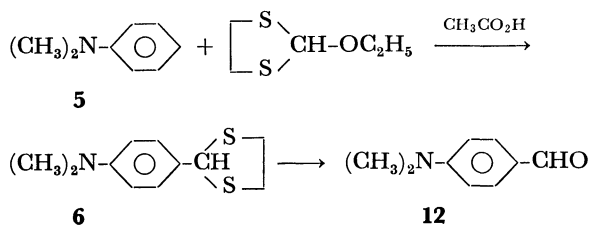
1, 20 mmol; 2-ethoxy-1,3-dithiolane, 30 mmol; BF₃·Et₂O, 15 mmol; dichloromethane, 40 ml. Reaction conditions: room temperature, 14 h.

Starting phenol	Total yield/% of products ^{a)}	Composition of product (%)			
1a	69 (100)	2a ^{b)} (22)	3a ^{b)} (65)	4a ^{b)} (13)	
1b	89 (96)	2b (0)	3b ^{c)} (94)	4b ^{d)} (6)	
1c	49 (58)	2c ^{b)} (33)	3c ^{b)} (49)	4c ^{b)} (18)	
1d	55 (94)	2d ^{c)} (100)	3d (0)	4d (0)	
1e	38 (81)	2e (0)	3e ^{c)} (100)	4e (0)	
1f	40 (74)	2f ^{c)} (100)	3f (0)	4f (0)	

a) The values in parentheses are the percentages of conversion, corrected for the recovered starting phenols. b) Isolated by column chromatography on silica gel, using dichloromethane as the eluent. c) Isolated by distillation. d) After the evaporation of **3b** from the crude reaction product, the residue was column-chromatographed on silica gel, using dichloromethane as the eluent, to afford **4b**.

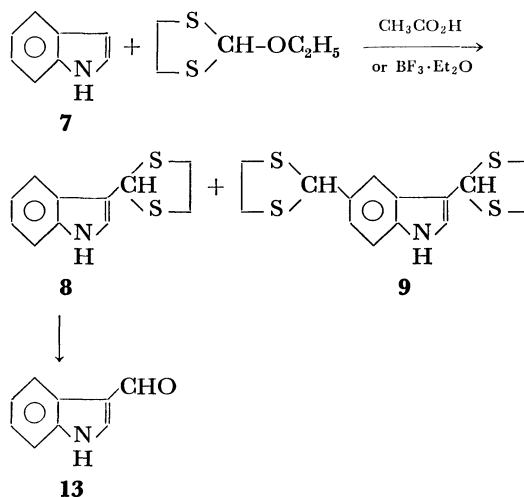
2-ylated in both the 2- and 4-positions in an approximate ratio of 1:3; *m*-cresol (**1c**) was attacked similarly in both the 6- and 4-positions in an approximate ratio of 2:3. These results are in accordance with the above suggestion that the reaction proceeds by means of a nucleophilic aromatic substitution.

The reaction of *N,N*-dimethylaniline (**5**) with 2-ethoxy-1,3-dithiolane proceeded smoothly in the presence of a large amount of acetic acid to afford *p*-(1,3-dithiolan-2-yl)-*N,N*-dimethylaniline (**6**), whereas the same reaction using ZnCl₂ as a catalyst gave only a trace of **6**.

TABLE 3. REACTION OF *N,N*-DIMETHYLANILINE (**5**) OR OF INDOLE (**7**) WITH 2-ETHOXY-1,3-DITHIOLANE **5** (or **7**), 13 mmol; 2-ethoxy-1,3-dithiolane, 20 mmol.

Starting aromatics	Catalyst	Reaction conditions	Products (yields % ^{a)})
5	ZnCl ₂	rt, 24 h, in dichloromethane	6 (trace)
5	Acetic acid	110 °C, 5 h, in acetic acid	6 (77)
7	BF ₃ ·Et ₂ O ^{b)}	rt, 24 h, in dichloromethane	8 (33) 9 (26)
7	Acetic acid	110 °C, 5 h, in acetic acid	8 (64) 9 (8)
7	Acetic acid	rt, 14 h, in acetic acid	8 (81)

a) Yield is based upon **5** or **7**. b) 0.75 molar ratio of BF₃·Et₂O for **7**.



The 1,3-dithiolan-2-ylation of indole (**7**) was also promoted by using acetic acid as both catalyst and solvent. When the reaction was carried out at 110 °C, the products were 3-(1,3-dithiolan-2-yl)indole (**8**) (64%) and 3,5-bis(1,3-dithiolan-2-yl)indole (**9**) (8%), a hitherto unknown compound; only the former was produced in a good yield (81%) in the reaction conducted at room temperature.

Most of the 1,3-dithiolan-2-ylated aromatics obtained in this work were hydrolyzed to the correspond-

TABLE 4. PHYSICAL PROPERTIES OF 1,3-DITHIOLAN-2-YLATED AROMATICS

Compound ^{a)}	Mp/°C or Bp/°C [Pressure/Torr]	¹ H-NMR(δ /ppm, CDCl ₃)					
		ArH	OH	Methine H	SCH ₂ CH ₂ S	CH ₃ or OCH ₃	Other
2a	— ^{b)}	7.4—6.7 (m, 4H)	6.76 (bs, 1H)	5.80 (s, 1H)	3.7—3.1 (m, 4H)		
3a	115—116.5 (chloroform) (lit, ⁸⁾ 119—120 °C)	7.6—7.4 (m, 2H) 6.9—6.7 (m, 2H)	5.62 (bs, 1H)	5.70 (s, 1H)	3.7—3.1 (m, 4H)		
4a	— ^{b)}	7.4—6.7 (m, 3H)	6.73 (bs, 1H)	5.74 (s, 1H) 5.52 (s, 1H)	3.7—3.1 (m, 8H)		
3b	168—170 [1.0]	7.2—7.0 (m, 2H) 6.6—6.4 (m, 1H)	5.30 (bs, 1H)	5.48 (s, 1H)	3.6—3.0 (m, 4H)	2.14 (s, 3H)	
4b	— ^{b)}	7.21 (bs, 2H)	6.86 (bs, 1H)	5.70 (s, 1H) 5.52 (s, 1H)	3.7—3.0 (m, 8H)	2.20 (s, 3H)	
2c	— ^{b)}	7.2—7.0 (m, 1H) 6.7—6.4 (m, 2H)	6.7—6.4 ^{c)} (bs, 1H)	5.72 (s, 1H)	3.6—3.0 (m, 4H)	2.18 (s, 3H)	
3c	173—174 [1.0]	7.6—7.4 (m, 1H) 6.6—6.4 (m, 2H)	6.28 (bs, 1H)	5.71 (s, 1H)	3.5—2.9 (m, 4H)	2.23 (s, 3H)	
4c	— ^{b)}	7.73 (bs, 1H) 6.57 (bs, 1H)	6.73 (bs, 1H)	5.73 (s, 2H)	3.7—3.0 (m, 8H)	2.30 (s, 3H)	
2d	173—173.5 [1.5]	7.1—6.7 (m, 3H)	6.50 (bs, 1H)	5.78 (s, 1H)	3.7—3.1 (m, 4H)	2.23 (s, 3H)	
3e	163—165 [1.5]	7.15 (bs, 1H) 7.0—6.9 (m, 2H)	5.94 (bs, 1H)	5.66 (s, 1H)	3.6—3.2 (m, 4H)	3.85 (s, 3H)	
2f	176—177 [0.5]	7.1—6.9 (m, 1H) 6.8—6.7 (m, 2H)	6.58 (bs, 1H)	5.81 (s, 1H)	3.4—3.1 (m, 4H)	3.69 (s, 3H)	
6	100—101 (ethanol) (lit, ⁹⁾ 105 °C)	7.5—7.3 (m, 2H) 6.7—6.5 (m, 2H)		5.62 (s, 1H)	3.5—3.1 (m, 4H)	2.90 (s, 6H)	
9	154—155.5 (50% diisopropyl ether-dichloro- methane)	7.2—7.0 (m, 3H)		6.41 (s, 1H) 6.29 (s, 1H)	3.8—3.0 (m, 8H)		8.57 (bs, 1H, NH) 8.0—7.7 (m, 1H, NCH)

a) The data of **8** can be seen in the literature.¹⁰⁾ b) The mp or bp could not be exactly determined because of the limited amounts. c) The line assigned to the OH is involved in that of the ArH.

ing aldehydes. The procedure used to accomplish the hydrolysis involved the treatment of the aromatic thioacetals with HgO and BF₃·Et₂O, followed by neutralization with aqueous Na₂CO₃.¹¹⁾ As can be seen from Table 6, the overall yields of the aldehydes from the starting aromatics (**1**, **5**, and **7**) ranged from 15 to 77%.

Experimental

Reaction of Phenols (**1**) with 2-Ethoxy-1,3-dithiolane.

General Procedure: To a mixture of **1** (20 mmol) and 2-

ethoxy-1,3-dithiolane (4.5 g, 30 mmol) in dichloromethane (40 ml), we added, drop by drop, BF₃·Et₂O (2.1 g, 15 mmol) at 0 °C. The mixture was brought to room temperature, stirred for 14 h, and then poured into about 200 ml of water. The organic layer was separated, and the aqueous phase was thoroughly extracted with dichloromethane. The combined dichloromethane solution was washed successively with water, 5% aqueous NaHCO₃, and again with water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give the crude product. The crude 1,3-dithiolan-2-ylated phenols thus obtained were purified by distillation under reduced pressure or by column chromatography on silica gel (see footnote to Table 2).

Reaction of N,N-Dimethylaniline (5) with 2-Ethoxy-1,3-dithiolane in Acetic Acid.

To a solution of **5** (1.6 g, 13 mmol) in acetic acid (30 ml) we added, drop by drop, 2-ethoxy-1,3-dithiolane (3.0 g, 20 mmol) at 110 °C. The mixture was stirred for 5 h at the same temperature, cooled, and then poured into about 150 ml of saturated brine. The resulting acidic solution was thoroughly extracted with ether and backwashed repeatedly with saturated brine containing Na₂CO₃, saturated brine, and a small amount of water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give a residue. It was chromatographed on silica gel, using 15% ether-hexane as eluent, to provide 2.3 g (77%) of **6**.

Reaction of Indole (7) with 2-Ethoxy-1,3-dithiolane in Acetic Acid.

To a solution of **7** (1.5 g, 13 mmol) in acetic acid (30 ml) we added, drop by drop, 2-ethoxy-1,3-dithiolane (3.0 g, 20 mmol) at 110 °C. The mixture was stirred for 5 h at the same temperature and then worked up as described in the above experiment using **5**. Subsequent column chromatography on silica gel, using 50% chloroform-hexane as the eluent, gave two products, **8** (1.8 g, 64%) and **9** (0.34 g, 8%). When the reaction temperature was

varied from 110 °C to room temperature, only the former, **8**, was obtained in an 81% yield.

Preparation of Aldehydes from 1,3-Dithiolan-2-ylated Aromatics.

To a suspension of red HgO (3.9 g, 18 mmol) in 20 ml of 15% aqueous tetrahydrofuran, maintained under N₂ at 0 °C, we added, drop by drop, BF₃·Et₂O (2.6 g, 18 mmol). The mixture was then allowed to warm to room temperature. A 1,3-dithiolan-2-ylated aromatic (9 mmol) was added over a period of 20 min, after which the mixture was stirred for 1 h. The resulting insoluble precipitate was filtered and washed thoroughly with a large amount of ether. The foregoing filtrate was extracted repeatedly with the washings and once with ether. The combined ethereal extracts were washed successively with saturated brine containing Na₂CO₃ (pH 10), saturated brine, and a small amount of water, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo* to give the crude aldehyde, which was then purified.

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TABLE 5. ANALYTICAL DATA OF 1,3-DITHIOLAN-2-YLATED AROMATICS

Compound	Found(%)			Calcd(%)		
	C	H	N	C	H	N
2a	54.09	5.32		54.51	5.08	
3a	54.41	5.30		54.51	5.08	
4a	47.60	4.90		47.65	4.66	
3b	56.47	5.61		56.57	5.70	
4b	49.14	5.26		49.33	5.10	
2c	56.37	5.57		56.57	5.70	
3c	56.57	5.90		56.57	5.70	
4c	49.67	5.02		49.33	5.10	
2d	56.53	5.72		56.57	5.70	
3e	52.44	5.32		52.60	5.30	
2f	52.53	5.43		52.60	5.30	
6	58.87	6.79	5.99	58.62	6.71	6.22
9	51.61	4.67	4.17	51.65	4.64	4.30

TABLE 6. PREPARATION OF ALDEHYDES FROM 1,3-DITHIOLAN-2-YLATED AROMATICS

1,3-Dithiolan-2-ylated aromatics	Aldehyde ^{a)}	Yield/% of aldehyde from 1,3-dithiolan-2-ylated aromatics ^{b)}	Overall yield/% of aldehyde from the starting aromatics	Chemical shift of aldehyde H (δ/ppm, CDCl ₃)
3a	11a	77	35	9.92
3b	11b	92	77	9.87
3c	11c	91	22	10.13
2d	10d	84	46	9.82
3e	11e	39	15	9.96
2f	10f	47	19	9.50
6	12	90	69	9.83
8	13	84	68	10.07 ^{c)}

a) All the aldehydes here are known compounds. Their ¹H-NMR spectra and analytical data satisfied all the given structures. b) Represents isolated yield. c) The solvent here was a mixture of CDCl₃ and DMSO-*d*₆.