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(1,3-Dithiolan-2-yl)trimethylammonium Iodide. An Electrophilic Dithiolanylating Reagent[1]

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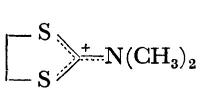
The reactions of (1,3-dithiolan-2-yl)trimethylammonium iodide (**5**), readily obtained by methylation of 2-dimethylamino-1,3-dithiolane (**2**), with aromatic amines were studied. It was found that **5** served as an electrophilic 1,3-dithiolanylating reagent; the reactions with aniline, *N*-methylaniline, and benzylamine gave *N*-dithiolanylated products while those with *N*,*N*-dimethylaniline and indole yielded exclusively *C*-dithiolanylated products *via* aromatic substitutions. Furthermore, *C*-dithiolanylated compounds were hydrolyzed to aldehydes using HgO–$BF_3 \cdot OEt_2$. The present aldehyde synthesis has been compared with an alternative electrophilic formylation method, the Vilsmeier reaction.

In a previous paper[2] we reported that the hydride reduction of various dithiocarbamidium ions including 2-dimethylamino-1,3-dithiolan-2-ylium ion (**1**) gave the corresponding formamide thioacetals in moderate yields. In the present work the synthetic utility of 2-dimethylamino-1,3-dithiolane (**2**) obtained from **1** has been studied.



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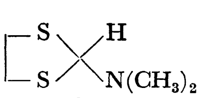

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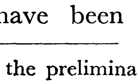
The utility of thioacetals, especially 1,3-dithianes, for the synthesis of aldehydes and ketones has been well established.[3] In most cases, however, the introduction of the dithianyl group was nucleophilically carried out by using dithianyl anion (**3**) and electrophiles such as alkyl halides. On the other hand, little information has been available on the electrophilic introduction of dithianyl or dithiolanyl group mainly because dithiolanyl cation (**4**) has not been characterized.[4] Recently the formation of **4** has been only observed in the mass spectrum of 1,3-dithiolane[5] and in the process of oxidation of 1,3-dithiolane derivatives by 2,3-dichloro-5,6-dicyano-1,4-quinone.[6]



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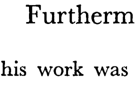

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In this work, in order to obtain a new electrophilic dithiolanylating reagent derived from **2**, the quarternary ammonium salts (**5**) were prepared by methylation of **2** with methyl iodide, and the reactions of **5** with various nucleophiles (NuH), mostly electron-rich aromatic compounds, have been investigated. Furthermore, the

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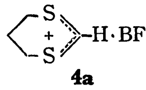
[1] Presented in part at the 26th Annual Meeting of the Chemical Society of Japan, Hiratsuka, 1 April, 1972; Preprint, Vol. III, p. 1114 (1972).

[2] K. Hiratani, T. Nakai, and M. Okawara, 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, 3 April, 1970; Preprint, Vol. III, p. 1499 (1970).

[3] For a review, See: D. Seebach, *Synthesis*, **1969**, 17.

[4] After the preliminary report[1] on this work was presented, E. J. Corey and S. W. Walinsky [*J. Amer. Chem. Soc.*, **94**, 8932 (1972)] reported on the isolation of 1,3-dithianyl tetrafluoroborate (**4a**) and its synthetic application as an electrophilic 1,3-dithianylating reagent eventually for aldehyde and ketone synthesis.

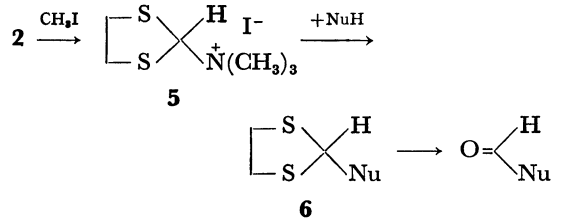


4a

[5] D. L. Coffen, K. C. Bank, and P. E. Garrett, *J. Org. Chem.*, **34**, 605 (1969).

[6] D. L. Coffen and P. E. Garrett, *Tetrahedron Lett.*, **1969**, 2043.

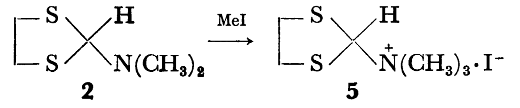
hydrolysis of some resultant 1,3-dithiolanes (**6**) to aldehydes has been studied.



The scope and limitation of the use of reagent **5** for dithiolanylating nucleophiles also described and compared with those of Vilsmeier's reagent, one of the most well-known of electrophilic formylating reagents.

Results and Discussion

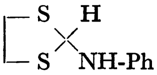
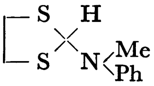
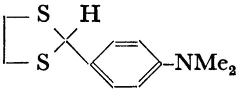
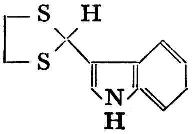
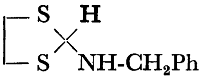
Preparation of (1,3-Dithiolan-2-yl)trimethylammonium Iodide (5). Dithiolane **2** was prepared by the hydride reduction of dithiolanylium perchlorate (**1**) using sodium dihydrobis(2-methoxyethoxy)aluminate (RDB).[2] **2** was also obtained by the following more convenient method. Treatment of dimethylformamide (DMF) in tetrahydrofuran (THF) with 1,2-ethanedithiol in the presence of an equimolar amount of benzoyl chloride gave **2** in 76% yield. This was quarternarized with methyl iodide in aprotic solvents giving (1,3-dithiolan-2-yl)trimethylammonium iodide (**5**) in 83% yield. The NMR spectrum of **5** in dimethyl sulfoxide-d_6 showed three singlet signals at δ 3.16 (N-CH$_3$), 3.60 (S-CH$_2$), and 6.83 ($\equiv$C-H).



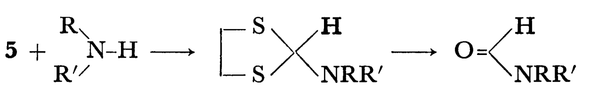
The NMR spectrum confirmed that the methylation occurred on the nitrogen, not on the sulfur atom of **2**. It should be noted that the methine proton of **5** has an absorption at a much lower field (δ 6.85) than that of **2** (δ 6.01) due to quarternarization of the dimethylamino group of **2**.

Reactions of the Ammonium Salt 5 with Various Aromatic Amines. Ammonium iodide **5** is expected to be capable of dithiolanylating nucleophiles analogously to cation **4**, accompanied by the elimination of trimethylamine. In this work, the reactions of **5** with the following aromatic amines were studied: aniline, *N*-methylaniline, *N,N*-dimethylaniline, indole, benzylamine, diphenylamine, and phenothiazine. The reactions were carried out in DMF at 40 °C for 1 hr giving products (**6**) having 1,3-dithiolanyl group along with trimethylammonium iodide except for the cases of diphenylamine and phenothiazine in which the reactants were recovered unchanged. The structures of **6** were elucidated by elemental analysis and spectroscopic methods. In particular the position of the dithiolanylation was determined by NMR and IR spectroscopic methods, and, in some cases, confirmed through identification of aldehydes obtained from the hydrolysis of the dithiolanylated products described below. The yields and physical properties of (**6**) are summarized in Table 1. We see that the position of the introduced 1,3-dithiolanyl group varies with the structure of the aromatic amine employed. In the cases of aniline, *N*-methylaniline, and benzylamine, only *N*-dithiolanylated products were obtained. On the other hand, the reactions of **5** with *N,N*-dimethylaniline and indole gave exclusively *C*-dithiolanylated products *via* aromatic displacement reactions. The former *N*-dithiolanylating reaction might provide a versatile method for synthesizing a variety of formamide thioacetals, eventually formamides from primary and secondary amines. The *N*-dithiolanyl group can be converted into the *N*-carbonyl groups by the hydrolysis: for example, treatment of *N*-(1,3-dithiolanyl)-*N*-methylaniline (**6b**) with HgO-BF$_3$·Et$_2$O gave *N*-phenyl-*N*-methylformamide in 78% yield.

TABLE 1. 1,3-DITHIOLANYLATION OF AROMATIC COMPOUNDS

Aromatics		Product	Yield %	Mp, °C (bp, °C/mmHg)
Aniline	**6a**		72	liq.[a]
N-Methyl-aniline	**6b**		51	liq.[a] (125—129/1.0)[b]
N,N-Dimethyl-aniline	**6c**		54	103—104
Indole	**6d**		78	116—119
Benzylamine	**6e**		57	liq.[a]
Diphenylamine Phenothiazine		No Reactions		

a) Purified by column chromatography. b) Prepared by the hydride reduction of carbonium ion, see Experimental.



The observed orientation of the aromatic *C*-dithiolanylation, on the other hand, is in agreement with the orientation observed with other electrophilic aromatic substitutions of these aromatic amines, *e.g.* the Vilsmeier reaction.[7]

Hydrolysis of the Dithiolanylated Products to Aldehydes. The hydrolysis of the *N*-dithiolanylated product (**6b**) and the *C*-dithiolanylated products (**6c** and **6d**) was studied. Hydrolysis was accomplished by using red mercury oxide–boron trifluoride etherate[8] in aqueous THF yielding the corresponding aldehydes in good yields. The aldehydes thus obtained were identified by IR spectra and comparisons of their physical properties with those of authentic samples. In short,

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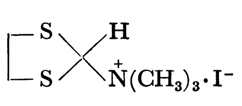
[7] The *para* position in *N,N*-dimethylaniline and the 3-position in indole are the most reactive sites for electrophilic substitution: For a review of the Vilsmeier reaction, see M.-R. Maheas, *Bull. Chim. Soc. Fr.*, **1962**, 1982.

[8] E. Vedejs and P. L. Fuchs, *J. Org. Chem.*, **36**, 366 (1971).

ammonium salt **5** can be used as an electrophilic formylating reagent just as Vilsmeier's reagent, *e.g.*, *N*-formyl-*N*-methylaniline–phosphorus oxychloride complex (**7**).[9]



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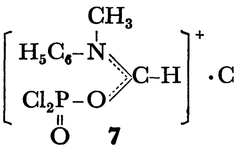
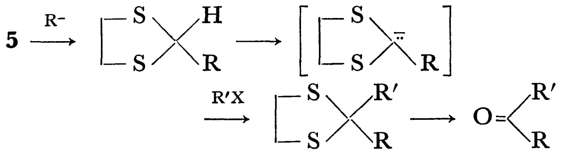


7

Let us compare the present aldehyde synthesis with the Vilsmeier reaction. First, it should be emphasized that a synthetic advantage of the present method over the Vilsmeier method is that aldehyde precursors, 1,3-dithiolanylated compounds, can be readily isolated, hence, a subsequent desirable reaction can be carried out under the protection of the aldehyde group by the 1,3-dithiolane ring. Isolation of the 1,3-dithiolanylated products might provide a unique method for ketone synthesis *via* the following sequences.



Secondly, it is concluded that the range of application of the present aldehyde synthesis covers more limited aromatics and heterocyclics, compared with Vilsmeier's reagent. Ammonium salt **5** did not react with diphenylamine, phenothiazine or anisole, while Vilsmeier's reagent is capable of undergoing aromatic substitution with these aromatics giving aldehydes. It can be said that the electrophilic reactivity of **5** is smaller and more selective than that of Vilsmeier's reagent (**7**).

Experimental

General. All melting and boiling points are uncorrected. IR and UV spectra were recorded with Hitachi EPI-S2 and EPS-3T spectrophotometers, respectively. NMR spectra were obtained with Japan Electron Optics JNN PS-100 and MH-60 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane as an internal standard.

2-Dimethylamino-1,3-dithiolane (2). Dithiolane **2** was prepared by the hydride reduction of the dithiolanylium salt **1** following previous procedures.[2] In a large scale experiment the following alternative method is recommended which is a modification of the procedures of R. Ohme[10] employed for the synthesis of trialkyl orthoformates.

In a 200-ml three-necked flask, equipped with a mechanical stirrer, dropping funnel and thermometer, was placed a solution of 7.3 g (0.10 mol) of DMF and 9.4 g (0.10 mol) of 1,2-ethanedithiol in 100 ml of THF, which was then cooled below 0 °C. To the stirred solution was added dropwise 14.1 g (0.10 mol) of benzoyl chloride over a period of 1 hr. The reaction temperature was then raised up to 40 °C and the mixture was stirred for 6 hr. The reaction flask was cooled to room temperature giving white precipitates which were filtered and washed three times with 50-ml portions of ether. The precipitates were then dissolved in cooled water and to the aqueous solution was added dropwise an aqueous sodium carbonate solution until the solution became weakly basic. The solution was extracted three times with100-ml portions of ether. The combined ether solutions were dried over anhydrous sodium sulfate. After removal of the drying agent followed by distillation of the ether, distillation of the liquid residue gave 11.4 g (76.5%) of **2**. bp 78—79 °C/2.0 mmHg (lit[2] 57—58 °C/1.5 mmHg). The physical properties and spectra data of this distillate were in agreement with those of an authentic sample.[2]

Preparation of (1,3-Dithiolan-2-yl)trimethylammonium Iodide (5). To a solution of 8.0 g (54 mmol) of **2** in 100 ml of THF was added excess methyl iodide. The mixture was stirred at room temperature for 3 hr giving white precipitates which were filtered and washed several times with THF. Recrystallization of the precipitates from anhydrous acetonitrile gave 13 g (83%) of white crystals, mp (dec.) 152 °C. Found: C, 24.91; H, 4.71; N, 4.95%. Calcd for $C_6H_{14}NS_2I$: C, 24.75; H, 4.85; N, 4.81%.

Reaction of 5 with Aniline. In a 50-ml three-necked flask equipped with a mechanical stirrer, condenser and thermometer was placed a solution of 1.50 g (5.1 mmol) of **5** in 20 ml of DMF. To the stirred solution was added 0.50 g (5.3 mmol) of aniline. The mixture was stirred at 40 °C for 1 hr, and then poured into water. The aqueous solution was extracted three times with 50-ml portions of ether. The combined ethereal solutions were washed four times with water and dried over anhydrous magnesium sulfate. Removal of the ether gave 1.0 g of a pale brown oil. The oil was subjected to chromatography on silica gel with chloroform giving 0.70 g (72%) of **6a**; IR (neat): 3340 cm^{-1} (N-H); NMR (CCl_4): δ 3.24 (m, 4H, S-CH_2), 4.1—4.5 (broad, 1H, N-H), 6.33 (d 1H C-H), and 6.5—7.4 (m, 5H, aromatic-H) UV (EtOH, nm): 248.5.

Reaction of 5 with N-*Methylaniline.* In a similar manner, the reaction of **5** (1.50 g, 5.1 mmol) with *N*-methylaniline (0.60 g, 5.6 mmol) in 20 ml of DMF at 40 °C for 1 hr gave an oil (0.90 g). The oil was subjected to chromatography on silica gel with chloroform. The first eluent gave 0.54 g (51%) of **6b**; n_D (25 °C) 1.640. The second eluent contained 0.24 g of the starting material, *N*-methylaniline. The IR and UV spectra of **6b** were in complete agreement with those of an authentic sample prepared by the reaction of 2-(*N*-methyl-*N*-phenylamino)-1,3-dithiolan-2-ylium perchlorate with sodium dihydrobis(2-methoxyethoxy)aluminate (yield, 66%), bp 125—129 °C/1.0 mmHg; n_D (25 °C) 1.639. **6b**; NMR (CCl_4): δ 2.92 (s, 3H, N-CH_3), 3.17 (m, 4H, S-CH_2), 6.98 (m, 1H, C-H), and 6.7—7.7 (m, 5H, aromatic-H); UV (EtOH, nm): 253. Found: C, 56.05; H, 6.10; N, 6.10%. Calcd for $C_{10}H_{13}NS_2$: C, 56.83; H, 6.20; N, 6.63%.

Reaction of 5 with N,N-*Dimethylaniline.* In a similar manner, the reaction of **5** (1.50 g, 5.1 mmol) with *N*,*N*-dimethylaniline (0.62 g, 5.1 mmol) in 20 ml of DMF at 30—40 °C for 2 hr gave 0.61 g (54%) of **6c** which was recrystallized from ethanol giving colorless plates, mp 103—104 °C; NMR ($CDCl_3$): δ 2.94 (s, 6H, N-CH_3), 3.44 (m, 4H, S-CH_2), 5.77 (s, 1H, C-H), 6.74 (d, 2H, aromatic-H), and 7.49 (d, 2H, aromatic-H); UV (EtOH, nm): 270. Found: C, 59.00; H, 6.72; N, 6.06%. Calcd for $C_{11}H_{15}NS_2$: C, 58.62; H, 6.71; N, 6.21%.

Reaction of 5 with Indole. In a similar manner, the reaction of **5** (1.50 g, 5.1 mmol) with indole (0.59 g, 5.0 mmol) in 20 ml of DMF at 40 °C for 2 hr gave 0.90 g (78%) of **6d** which was recrystallized from ethanol giving colorless plates, mp 116—119 °C; IR (KBr): 3400 cm^{-1} (N-H); NMR ($CDCl_3$): δ 3.50 (m, 4H, S-CH_2), 6.23 (s, 1H, C-H), 7.47 (m, 4H, aromatic-H), and 7.95—8.30 (broad, 2H, N-H

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[9] H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959); C. Jutz, *ibid.*, **91**, 850 (1958).

[10] R. Ohme, *Ann. Chem.*, **716**, 207 (1968).

and 2-C–H) ppm; UV (EtOH, nm): 221.5, 274, 280, and 290.5. Found: C, 59.36; H, 5.00; N, 6.27%. Calcd for $C_{11}H_{11}NS_2$: C, 59.69; H, 5.01; N, 6.33%.

*Reaction of **5** with Benzylamine.* In a similar manner, the reaction of **5** (1.50 g, 5.1 mmol) with benzylamine (0.50 g, 4.7 mmol) in 20 ml of acetonitrile at 60 °C for 3 hr gave 0.60 g (57%) of **6e** which was purified by means of column chromatography (silica gel) giving a colorless liquid; n_D (20 °C) 1.623; IR: 3330 cm^{-1} (N-H); NMR ($CDCl_3$): δ 1.94 (s, 1H, N-H), 3.23 (s, 4H, SCH_2), 3.93 (s, 2H, N-CH_2), 5.91 (s, 1H, C-H), and 7.38 (s, 5H, aromatic–H). Found: C, 56.83; H, 6.08; N, 6.43%. Calcd for $C_{10}H_{10}NS_2$: C, 56.83; H, 6.20; N, 6.63%.

Hydrolyses of 1,3-Dithiolanyl Compounds with Mercury Oxide (Red) Boron Trifluoride Etherate. a) p-*(1,3-Dithiolan-2-yl)*-N,N-*dimethylaniline (6c)*: In a 50-ml three-necked flask, equipped with a mechanical stirrer, dropping funnel, gas inlet, condenser and thermometer, was placed a suspension of 0.59 g (2.7 mmol) of red mercury oxide and 0.38 g (2.7 mmol) of boron trifluoride etherate in 1: 9 THF–water (10 ml). The mixture was stirred at room temperature under nitrogen atmosphere and then 0.30 g (1.3 mmol) of **6c** in 20 ml of THF was added dropwise to the mixture over a period of 0.5 hr. After the reaction mixture was stirred at room temperature for 1 hr, precipitates formed were filtered and the filtrate was poured into water. The aqueous solution was extracted three times with 50-ml portions of ether, and the combined ether solutions were washed three times with water and dried over anhydrous magnesium sulfate. After removal of the drying agent followed by distillation of the ether, 0.80 g of a yellow oil was obtained. The oil was subjected to chromatography on silica gel with benzene giving 0.17 g (85%) of *p-N,N*-dimethylaminobenzaldehyde; mp 71—73 °C (lit[11] 73 °C).

b) 3-(1,3-Dithiolan-2-yl)indole (6d): In a similar manner, the reaction of **6d** (0.30 g, 1.3 mmol) with red mercury oxide (0.59 g, 2.7 mmol) and boron trifluoride etherate (0.38 g, 2.7 mmol) gave 0.16 g (80%) of 3-formylindole; mp 189—191 °C (lit[12] 193—195 °C).

c) N-*(1,3-Dithiolan-2-yl)*-N-*methylaniline (6b)*: In a similar manner, the reaction of **6b** (1.05 g, 5.0 mmol) with red mercury oxide (2.0 g, 10 mmol) and boron trifluoride etherate (1.4 g, 10 mmol) gave 0.52 g (78%) of *N*-methylanilide. The IR spectrum of this product was in complete agreement with that of an authentic sample.

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[11] A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

[12] F. T. Tyson and J. T. Shaw, *J. Amer. Chem. Soc.*, **74**, 2273 (1952).