Dithioacetals and Related Derivatives of Tetrahydrofuran-2-carbaldehyde

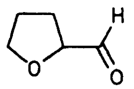
Alexander Mottoh and Colin B. Reese*

Department of Chemistry, King's College, Strand, London WC2R 2LS, U.K.

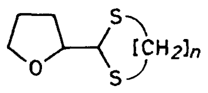
2,3-Dichlorotetrahydropyran (**3**) reacted with propane-1,3-dithiol, ethane-1,2-dithiol, and ethanethiol in the presence of titanium(IV) chloride to give the corresponding tetrahydrofuran-2-carbaldehyde dithioacetals [(**2a**), (**2b**), and (**4a**), respectively]; the action of strong base on (**2a**), its mono-sulphoxide (**7**), and (**9**) (the sulphone of an analogous monothioacetal) was examined.

In connection with some studies in nucleoside chemistry, we required the dithiane (**2a**), derived from tetrahydrofuran-2-carbaldehyde (**1**). As the literature methods[1] for the preparation of (**1**) are not particularly convenient to carry out in the laboratory, we sought an indirect method for the preparation of the desired dithioacetal (**2a**). We now report that when 2,3-dichlorotetrahydropyran (**3**), which may be prepared[2] in good yield by the addition of chlorine to commercially available 2,3-dihydro-4*H*-pyran, was heated under reflux for 1 h with a small excess each of propane-1,3-dithiol and titanium(IV) chloride[3] in dichloromethane solution, (**2a**) was obtained. The latter compound (**2a**) was isolated† as a pure colourless liquid in 73% yield.

This would appear to constitute a general procedure for the preparation of dithioacetals of tetrahydrofuran-2-carbaldehyde inasmuch as the reaction between (**3**), $TiCl_4$, and ethane-1,2-dithiol, under the same conditions, gave (**2b**) in 70% isolated yield and ethanethiol was similarly converted into (**4a**) in 53% isolated yield. The three dithioacetals [(**2a**), (**2b**), and (**4a**)] were subsequently prepared independently in 66, 65, and 76% yields, respectively, by allowing 2-(dimethoxymethyl)tetrahydrofuran (**4b**)‡ to react with the appropriate thiols in the presence of a catalytic quantity of toluene-4-sulphonic acid in acetonitrile solution at room temperature.



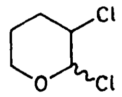
(**1**)



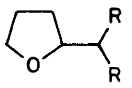
(**2**)

a; $n = 3$

b; $n = 2$



(**3**)



(**4**)

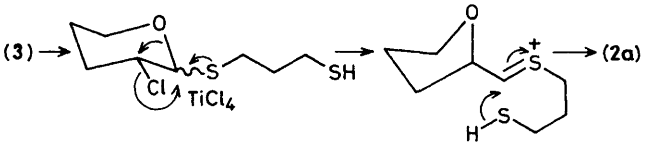
a; R = SEt

b; R = OMe

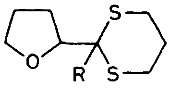
A possible mechanism for the conversion of (**3**) into (**2a**) is indicated in outline in Scheme 1. The preparation of other derivatives of (**1**) by ring contraction reactions has been reported.[2,4] However, none of the latter appears to be as efficient or as experimentally straightforward as the present method.

Our purpose in preparing 2-(tetrahydrofuran-2-yl)-1,3-dithiane (**2a**), was to determine whether, after treatment with a strong base, it would react[5] with an alkyl halide (RX) or another electrophile at C-2 to give derivatives of general formula (**5**). However, when (**2a**) was treated with n-butyllithium or lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) solution at −50 °C and the products subjected to aqueous work-up after 1 h, the unsaturated alcohol (**6a**) was obtained as the sole product. The latter compound (**6a**) was characterized spectroscopically and as its crystalline 3,5-dinitrobenzoate ester (**6b**), m.p. 72—73 °C.

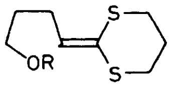
The dithiane (**2a**) was converted into its mono-sulphoxide (**7**) by treatment with sodium metaperiodate according to the literature procedure.[6] When (**7**) was treated with LDA in THF at 20 °C, and water was added to the products after 1 h, no starting material (**7**) was regenerated. It again appeared that opening of the tetrahydrofuran ring had occurred. In a final attempt to generate a tetrahydro-2-furoyl anion equivalent, the monothioacetal (**8**) was prepared, in 54% isolated yield, by allowing (**4b**) to react with 2-mercapto-2-methylpropan-1-ol[7,8] in the presence of toluene-4-sulphonic acid in acetonitrile solution at room temperature. Oxidation of (**8**) with an approximately two fold excess of 3-chloroperbenzoic acid in CH_2Cl_2 solution at room temperature gave the corresponding



Scheme 1



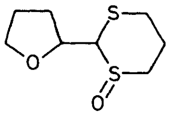
(**5**)



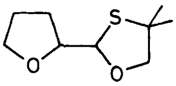
(**6**)

a; R = H

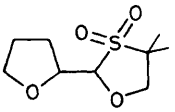
b; R = 3,5-$(O_2N)_2C_6H_3CO$



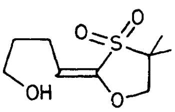
(**7**)



(**8**)



(**9**)



(**10**)

---

† The following experimental procedure was adopted. Propane-1,3-dithiol (2.20 ml, 21.9 mmol) was added dropwise and with the exclusion of moisture to a stirred solution of (**3**) (2.34 g, 15.1 mmol) and $TiCl_4$ (2.12 ml, 19.3 mmol) in CH_2Cl_2 (40 ml) at 0 °C (ice bath). The reactants were heated (reflux, 1 h), then cooled and shaken with ice (15 g). After separation, the organic layer was extracted with 10% aqueous sodium hydroxide (2 × 30 ml) and water (2 × 30 ml), and then dried ($MgSO_4$). Evaporation of the solvent and distillation of the residual oil gave (**2a**) (2.10 g, 73%), b.p. 104 °C at 0.25 mmHg; $\delta_C(CDCl_3)$ 26.00, 29.48, 29.58, 29.65, 51.93, 68.90, 80.58; M^+ = 190.0483, calc. for $C_8H_{14}OS_2$, 190.0486.

‡ (**4b**), b.p. 74 °C at 17 mmHg, was prepared in 71% isolated yield by hydrogenating 2-(dimethoxymethyl)furan in the presence of 5% Pd–C in diethyl ether.

sulphone (**9**), a pure crystalline diastereoisomer (m.p. 102—103 °C) of which was isolated in 38% yield. When the latter compound was treated[8] with n-butyl-lithium or LDA in THF solution at −50 °C, and water was added after 30 min, a mixture of the unsaturated alcohol (**10**) and its *E*-isomer was obtained in virtually quantitative yield.

One of us (A. M.) thanks the Nigerian Ministry of Education for the award of a scholarship.

Received, 11th May 1984; Com. 653

References

1 H. Scheibler, F. Sotscheck, and H. Friese, *Chem. Ber.*, 1924, **57**, 1443; H. Minné and H. Adkins, *J. Am. Chem. Soc.*, 1933, **55**, 299; J. G. M. Bremner, R. R. Coats, A. Robertson, and M. L. Allan, *J. Chem. Soc.*, 1949, S25.

2 R. Paul, *C. R. Acad. Sci.*, 1944, **218**, 122.

3 V. Kumar and S. Dev, *Tetrahedron Lett.*, 1983, **24**, 1289.

4 C. D. Hurd and O. E. Edwards, *J. Org. Chem.*, 1949, **14**, 680; 1954, **19**, 1319; E. H. Charlesworth and A. Giesinger, *Can. J. Chem.*, 1956, **34**, 376; A. Gerecs and J. Egyed, *Acta Chim. Acad. Sci. Hung.*, 1959, **19**, 195; A. Gerecs and L. Somogyi, *ibid.*, 1960, **24**, 73; A. McKillop, J. D. Hunt, F. Kienzle, E. Bigham, and E. C. Taylor, *J. Am. Chem. Soc.*, 1973, **95**, 3635; S. Antus, A. Gottsegen, M. Nórgrádi, and A. Gergely, *Chem. Ber.*, 1979, **112**, 3879.

5 D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231.

6 R. M. Carlson and P. M. Helquist, *J. Org. Chem.*, 1968, **33**, 2596.

7 W. Davies and W. E. Savige, *J. Chem. Soc.*, 1951, 774.

8 G. W. Gokel, H. M. Gerdes, D. E. Miles, J. M. Hufnal, and G. A. Zerby, *Tetrahedron Lett.*, 1979, 3375.