

SYNTHETIC APPLICATIONS OF 2-CHLORO-1,3-DITHIANE ¹

PREPARATION OF KETENE DITHIOACETALS.

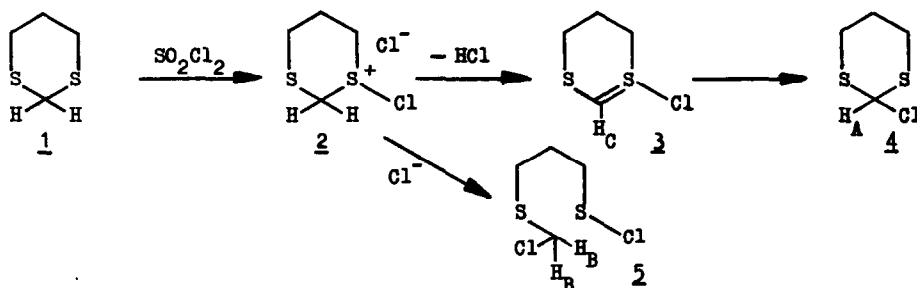
C.G. Kruse, N.L.J.M. Broekhof, A. Wijsman and A. van der Gen. [✉]

Department of Organic Chemistry, University of Leiden, The Netherlands.

(Received in UK 25 January 1977; accepted for publication 2 February 1977)

Since their original conception by Corey and Seebach, 2-lithio-1,3-dithianes have found widespread application in organic synthesis as masked carbonyl compounds with a nucleophilic central carbon atom.² Considerable broadening of the synthetic scope of 1,3-dithianes might be expected if this carbon atom could also be converted into an electrophilic centre. Recently, the first successful chlorination of 1,3-dithiane with *N*-chlorosuccinimide was reported by Arai and Oki.³ Although the resulting 2-chloro-1,3-dithiane was not isolated in a pure state, its identity was clearly shown by nmr studies and by its reactions with nucleophiles.

In this communication we report a simple, high yield synthesis of 2-chloro-1,3-dithiane which allows its isolation as a crystalline solid, and the conversion of this compound into a number of useful synthetic intermediates, in particular phosphorus ylids.



Reaction of 1,3-dithiane 1 in chloroform solution with sulfuryl chloride at -40°C results in precipitation of the chlorosulfonium chloride 2. Nmr-analysis shows that, when warmed to room temperature, this compound loses a proton to form the ylid 3, which is characterized by a sharp singlet at δ 6.90 for its vinylic proton. To our knowledge, this is the first experimental confirmation of the postulated mechanism for chlorination of thioethers.⁴ The ylid 3 gradually transforms into the 2-chloro compound 4. Upon evaporation of the solvent at 0°C 2-chloro-1,3-dithiane of better than 95 % purity is obtained as a white or pale-yellow solid; δ H_A 6.2 (CDCl_3), mp. 50°C (dec.). The only (minor) impurity (attack of chloride on the central carbon atom) is the sulfenyl chloride 5, recognized by its singlet at δ 4.8 (H_B -protons).

We have studied the reactivity of 2-chloro-1,3-dithiane 4 with the nucleophiles presented in Chart I. Not included is the reaction with thiophenol, where our results were identical with those obtained by Arai and Oki.³

When a solution of 4 in dry tetrahydrofuran is refluxed in an inert atmosphere, it is converted mainly into 1,3-bis-(1,3-dithianyl-2-mercapto)-propane 6. This compound, also easily available from reaction of 1,3-dimercaptopropane with triethylorthoformate 5, must have been formed from three molecules of 4, presumably with simultaneous loss of one molecule of chloroform in the last step.⁶ 2-Alkoxy-1,3-dithianes, initially formed from reaction of 4 with alcohols, could not be isolated. Apparently they are transformed into 6 or, if water is added, into the corresponding formic esters, which could be isolated in moderate yields. It is of interest to note here, that Arai and Oki³ observed that reaction with phenol resulted in attack on the aromatic ring, rather than on oxygen.

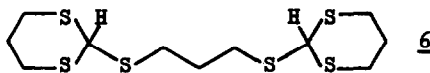
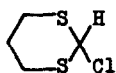
More promising appears to be the reaction of 4 with carbon nucleophiles. Reaction with 2-lithio-1,3-dithiane, with alkyl- and arylmagnesium halides and with sodium diethylmalonate gave the expected products in good yields. Of these, the dithiane-substituted malonate 7 in particular shows interesting synthetic potential.

Reaction of 4 with phosphorus nucleophiles proceeds smoothly at room temperature and the triphenylphosphonium chloride 8 as well as the diethylphosphonate 9 can be isolated in good yield. Both 8 and 9 were shown to be excellent precursors for the preparation of ketene dithioacetals. The synthesis of the latter compounds has been the subject of a number of recent publications.⁷ They possess an interesting π -electron system and their potential utility as synthetic intermediates has been stressed repeatedly.^{7,8}

Phosphonium salt 8 is easily and quantitatively converted into the bright-yellow ylid 10, even with a relatively weak base such as potassium hydroxide. This ylid reacts rapidly with aromatic aldehydes at 0°C and with aliphatic aldehydes at room temperature to give the corresponding ketene dithioacetals in high yield. Several examples are presented in Chart II (method A). Ylid 10 does not react with ketones⁹, but for these substrates the phosphonate carbanion 11, obtained by the action of n-butyllithium in tetrahydrofuran on phosphonate 9, turned out to be an excellent alternative. Chart II shows the results obtained with representative carbonyl compounds (method B). Thus, as ketene dithioacetals are easily converted into the corresponding acids and aldehydes^{7b}, 8 and 9 appear to be excellent reagents for the homologation of carbonyl compounds. Further applications of 2-chloro-1,3-dithiane and derived products are being studied.

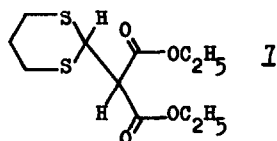
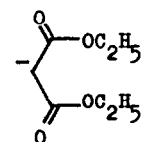
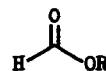
Chart I : Reactions of 2-chloro-1,3-dithiane with nucleophiles.

nucleophiles products (yield %)



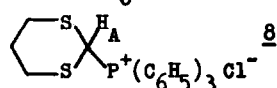
6

ROH



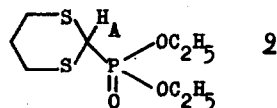
1

(80 %)

P(C₆H₅)₃

8

(78 %)

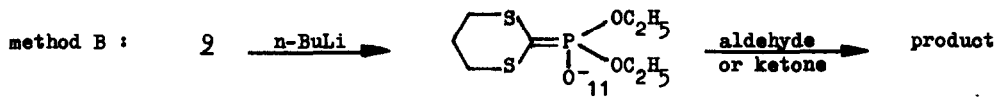
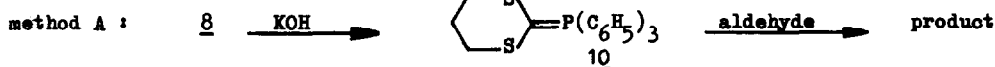
 δ_{H_A} 8.9 ; mp. 182-4°P(OC₂H₅)₃

9

(85 %)

 δ_{H_A} 3.6 ; n_D^{21} 1.5252

*) after two steps: chlorination and nucleophilic substitution.

Chart II : Conversion of aldehydes and ketones to ketene dithioacetals.

product	method	base-solvent	yield	mp. or n_D	δ_{H_A} (CDCl ₃)
	A	NaH - DMSO	87 %		
	A	KOH - H ₂ O - DMSO	82 %	n_D^{21} 1.6793	6.82 (s)
	A	NaH - DMSO	82 %	112-3°	6.67 (s)
	A	KOH - C ₂ H ₅ OH	96 %	76-78°	6.6 (d)
	B	n-BuLi - THF	85 %		J = 10.5 Hz
	A	KOH - C ₂ H ₅ OH	55 %	n_D^{21} 1.5332	5.65 (d)
	B	n-BuLi - THF	85 %		J = 9.5 Hz
	A	KOH - C ₂ H ₅ OH - DMSO	75 %	n_D^{21} 1.5783	5.8 (d)
					J = 8.5 Hz
	B	n-BuLi - THF	96 %	91-92°	-----
	B	n-BuLi - THF	88 %	n_D^{21} 1.6460	-----

Experimental Procedures.

2-Chloro-1,3-dithiane: Sulfuryl chloride (11 mmol) in 5 ml of chloroform is slowly added to 1,3-dithiane (10 mmol) in 25 ml of chloroform at -40°C in a nitrogen atmosphere. A white precipitate forms instantly. This precipitate gradually dissolves when the reaction mixture is allowed to warm to room temperature in 30 min. After stirring for an additional 30 min the solvent is evaporated at 0°C and 1.55 g of solid 2-chloro-1,3-dithiane of better than 95 % purity (nmr) is obtained.

Ketene dithioacetals. Method A: 2.2 ml of a 1.0 Molar solution of potassium hydroxide in ethanol or water is rapidly added to 2.2 mmol of phosphonium salt 8 in 10 ml of ethanol or dimethyl sulfoxide at room temperature. The yellow ylid 10 precipitates. The aldehyde (2.0 mmol in 5 ml of solvent) is added after 5 min and stirring is continued until the yellow colour has disappeared (0.1 - 5 hrs, depending on solvent and aldehyde). Work-up with water/hexane affords the desired product, contaminated with small amounts of triphenylphosphine oxide and 1,3-dithiane, which can easily be removed. Method B: 2.6 g of a 15 % solution of n-butyllithium in hexane (Merck) is added at -20°C to 5.5 mmol of phosphonate 9 in 20 ml of dry tetrahydrofuran. The red coloured solution is allowed to warm to room temperature in 30 min. After addition of the carbonyl compound (5.0 mmol) stirring is continued for 2 hrs. Work-up by addition of water and extraction with hexane affords the desired product.

References and Notes:

1. Part two of a series on the synthetic applications of cyclic α -chloro ethers and thioethers. Preceding paper: C.G.Kruse, N.L.Broekhof and A. van der Gen, *Tetrahedron Letters* 1976, 1725
2. For an extensive review see i.a.: D.Seebach, *Synthesis* 1969, 17
3. K.Arai and M.Oki, *Tetrahedron Letters* 1975, 2183
K.Arai and M.Oki, *Bull.Chem.Soc.Japan* 49, 553 (1976)
4. F.G.Bordwell and B.M.Pitt, *J.Am.Chem.Soc.* 77, 572 (1955). See also: W.E.Truce, C.H.Birum and E.T.MoBee, *J.Am.Chem.Soc.* 74, 3594 (1952) and D.L.Tuleen and V.C.Marcum, *J.Org.Chem.* 32, 204 (1967)
5. D.Seebach, *Angew.Chem.* 79, 468 (1967)
6. The mechanism of this transformation will be discussed in the forthcoming thesis of C.G.Kruse
7. a) E.J.Corey and D.Seebach, *Angew.Chem.* 77, 1134 (1965)
b) The approach to ketene dithioacetals via the Petersen olefin synthesis, using 2-lithio-2-trimethylsilyl-1,3-dithiane was published almost simultaneously by three different groups: F.A.Carey and A.S.Court, *J.Org.Chem.* 37, 1926 (1972); P.F.Jones and M.F.Lappert, *J.Chem.Soc.Perkin I*, 1973, 2272; D.Seebach, M.Kolb and B.T.Gröbel, *Ber.* 106, 2277 (1973)
8. F.A.Carey and J.R.Neergaard, *J.Org.Chem.* 36, 2731 (1971)
9. The corresponding trimethoxyphosphorane is also unreactive towards ketones: E.J.Corey and G.Märkl, *Tetrahedron Letters* 1967, 3201.