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DEOXYGENATIVE THIOACETALIZATION OF CARBONYL COMPOUNDS WITH ORGANIC DISULFIDE AND TRIBUTYLPHOSPHINE[1)]

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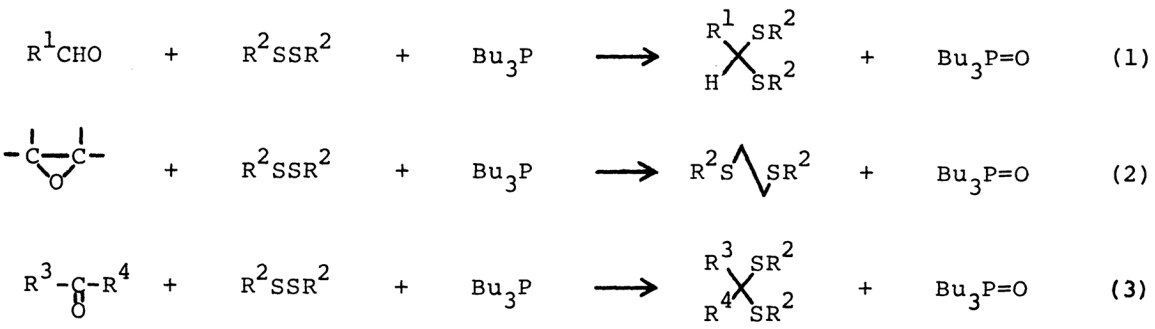
A new deoxygenative thioether formation from carbonyl compounds as well as epoxides is presented (eq. 1-3). The reaction proceeds with the combined use of alkyl or aryl disulfide and tributylphosphine under neutral and mild conditions. The reaction with aldehydes proceeds with special ease to give thioacetals in high yields, and can be a valuable synthetic reaction.

An equimolar reaction of aldehydes with organic disulfides in the presence of tributylphosphine was found to produce thioacetals and tributylphosphine oxide (eq. 1). Epoxides gave the vicinal dithioethers under similar conditions (eq. 2), but ketones gave the corresponding thioacetals only in very low yields (eq. 3).



The reaction procedure is very simple, and the work-up for product isolation is generally very easy. Followings are the examples:

Butyraldehyde phenylthioacetal To a mixture of 3.0 mmol of butyraldehyde and 3.1 mmol of diphenyl disulfide was added 3.3 mmol of commercial tributylphosphine by means of syringe with stirring under dry nitrogen atmosphere. Heat evolved and the reaction completed within a few minutes. Then, the mixture was subjected to silica-gel chromatography (Wakogel C-200), and was eluted with a hexane-benzene mixture to give pure thioacetal in the first fraction, 67 % yield.

5,5-Diethyl-2-tolyl-1,3-dithiane A mixture of 3.0 mmol of p-tolualdehyde, 3.1 mmol of 4,4-diethyl-1,2-dithiolane and 3.1 mmol of tributylphosphine was stirred under dry nitrogen at room temperature for 8 hr. Yellowish colour of the cyclic disulfide disappeared during the reaction. The resulting mixture was subjected to SiO_2 chromatography and eluted with benzene to give 5,5-diethyl-2-tolyl-1,3-dithiane

as colorless crystals. 67 %, mp 99-101 °C (from MeOH). Found: C, 67.34; H, 8.36 %. Calcd for $C_{15}H_{22}S_2$: C, 67.61; H, 8.32 %. IR (KBr disk) 2960, 2940, 2915, 2880, 1510, 1445, 1408, 1378, 1304, 1216, 1180, 1174, 1020, 978, 888, 853, 828 and 767 cm^{-1}. NMR (CCl_4, δ from TMS): 0.78 (3H, t, J = 7.5 Hz), 0.6-1.0 (3H, m), 1.1-1.55 (2H, m), 1.94 (2H, q, J = 7.5 Hz), 2.32 (3H, s), 2.51 (2H, d, J = 13.5 Hz), 2.73 (2H, d, J = 13.5 Hz), 4.90 (1H, s), 7.08 (2H, d, J = 7.8 Hz) and 7.33 (2H, d, J = 7.8 Hz).

Table 1 summarizes some of the typical experimental results. Generally, the reaction of aldehydes gave the corresponding thioacetals in nearly quantitative yields (direct glc analysis of the reaction mixture). The reduced yields in Table 1 are due to the loss in separation, since no special precautions were made to improve the recovery from the mixture. The reactivity was apparently unaffected by the structure of aldehydes, but was remarkably influenced by that of disulfides and phosphines employed. Thus the reactions with diphenyl disulfide and tributylphosphine proceeded exothermically within a few minutes even when a diluent such as benzene was used to control the reaction temperature. Dimethyl disulfide reacted similarly, but the reaction was retarded when diluted with inert solvent. Both cyclic and acyclic dialkyl disulfides other than dimethyl disulfide showed moderate reactivities. Naphthalene-1,8-disulfide never reacted even under severe conditions (120 °C). When tributylphosphine was replaced with triphenylphosphine, all of these reactions did not occur at all. From these results, the reactivities can be summarized as follows:

PhSSPh > MeSSMe > EtSSEt, BuSSBu,  >  (4)

Bu_3P > Ph_3P (5)

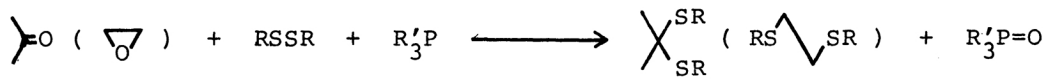
Ketones were much less reactive than aldehydes. Thus, cyclohexanone reacted with diphenyl disulfide and tributylphosphine only under severe conditions, giving the corresponding thioacetal in low yields. Esters and amides were unreactive.

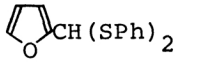
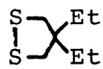
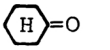
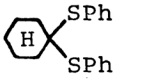
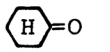
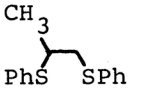
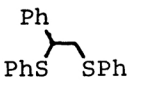
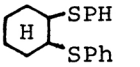
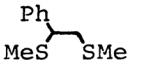
Epoxides reacted with diphenyl and dimethyl disulfide giving 1,2-bis(phenylthio)- and 1,2-bis(methylthio)ethanes, respectively. The effect of epoxide structure on reactivity was minor, and the reactivity was about intermediate between aldehydes and ketones.

aldehyde > epoxide > ketone > ester, amide (6)

The reaction of aldehydes is of special interest from the synthetic point of view, since it enables a ready access to thioacetals, whose synthetic utility as their lithio-derivatives increased in recent years.[2] The conventional synthetic method of making thioacetals was the reaction of aldehydes with excess thiols in the presence of Lewis acid catalyst such as $BF_3 \cdot OEt_2$.[3] In our procedure the reaction is

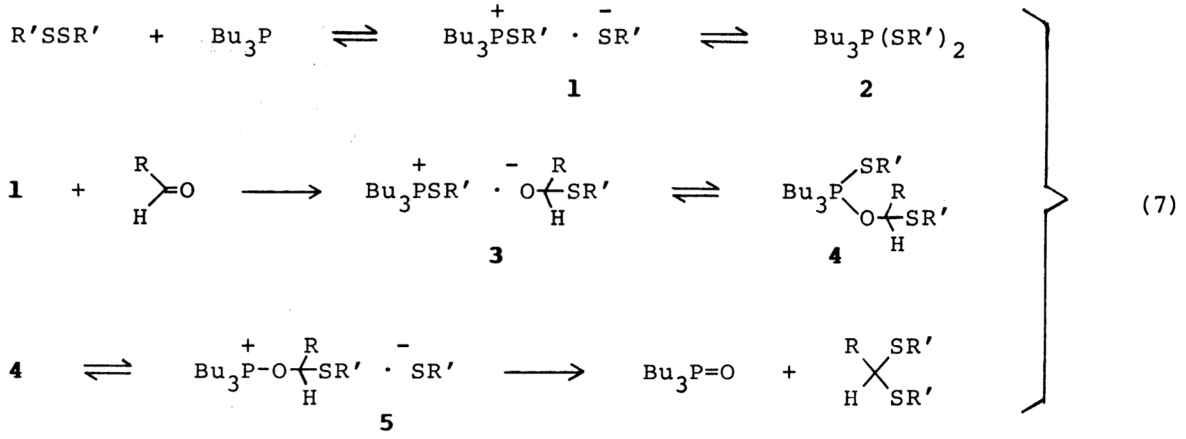
Table 1



Carbonyl compd	Disulfide	Phosphine	Temp	Time	Product (isolated yield, %)
n-PrCHO	PhSSPh	Bu_3P	rt	5min	n-PrCH(SPh)$_2$ (67)
t-BuCHO	"	"	"	"	t-BuCH(SPh)$_2$ (83)
	"	"	"	"	(76)
	"	"	"	"	 (83)
EtCHO	MeSSMe	"	"	"	EtCH(SMe)$_2$ (50)
n-PrCHO	"	"	"	"	n-PrCH(SMe)$_2$ (67)
i-PrCHO	"	"	"	"	i-PrCH(SMe)$_2$ (78)
	"	"	"	"	(81)
"	BuSSBu	"	"	8hr	(84)
"		"	"	"	(67)
"		"	120°C	"	no reaction
PhCHO	BuSSBu	Ph_3P	100°C	"	"
	PhSSPh	Bu_3P	80°C	15hr	 (15)
	EtSSEt	"	100°C	6hr	no reaction
	"	"	"	"	"
	PhSSPh	"	rt	3days	"
	"	"	"	12hr	 (69)
	"	"	"	5hr	 (51)
	"	"	"	7hr	 (53)
	MeSSMe	"	"	24hr	 (75)

performed at room temperature under essentially neutral conditions, so that undesired side-reactions can be avoided. Recently two novel procedures have been reported on the thioacetal synthesis which claims neutral and mild conditions similar to the present study. One employs orthothioborate $B(SR)_3$,[4] and the other makes use of Me_3SiSMe.[5] The accessibility and the handling of these reagents are not so easy as in the present method. With regard to reactivity toward carbonyl compounds, $B(SR)_3$ and Me_3SiSMe react with both ketone and aldehyde and cannot discriminate between the two carbonyl compounds. Thus our procedure may be a valuable tool for the selective thioacetalization of aldehydic groups in a compound which in addition contains ketone or epoxide functional groups within the molecule.

The tentative reaction mechanism is postulated as follows (eq. 7). Phosphine and disulfide are in equilibrium with thiophosphonium thiolate **1**, whose thiolate anion attacks carbonyl carbon to produce **3**. Then phosphonium cation in **3** undergoes a ligand exchange reaction with the external anion via pentacoordinate phosphorane **4** to form oxyphosphonium thiolate **5**, which further degrades into phosine oxide and thioacetal via Arbuzov-type reaction.



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