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SYNTHETIC METHOD OF FUNCTIONALIZED UNSYMMETRICAL SULFIDES AND DISULFIDES USING DIPHENYLPHOSPHINODITHIOATES

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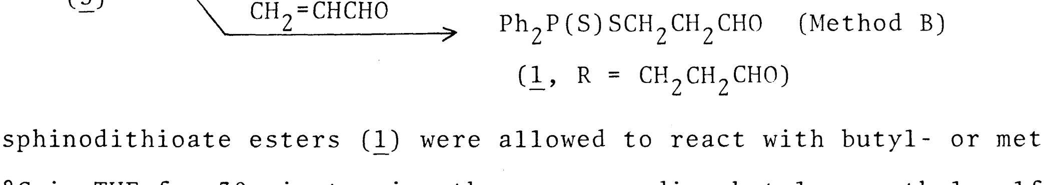
Various kinds of diphenylphosphinodithioates were prepared and allowed to react with some organolithium compounds under mild reaction conditions to give functionalized unsymmetrical sulfides and disulfides in good yields.

We have reported that butyl or phenyl sulfides are synthesized by the reactions of butyl- or phenyllithium with butyl or phenyl diphenylphosphinodithioate in good yields through direct attack of organolithium on the thiol sulfur atom.[1-3)]

$$\underset{(\underline{1})}{Ph_2P(S)SR} \quad + \quad R'Li \longrightarrow [Ph_2PS]Li \quad + \quad \underset{(\underline{2})}{RSR'}$$

In order to clarify the scope and limitation of this reaction, we carried out reactions between various kinds of diphenylphosphinodithioates ($\underline{1}$) and organolithium compounds under various reaction conditions. The present method turned out to be useful for preparation of functionalized unsymmetrical sulfides and disulfides.

Table 1 shows the results on preparation of substituted alkyl diphenylphosphinodithioates ($\underline{1}$). The preparation methods employed here are very simple: diphenylphosphinodithioic acid ($\underline{3}$) was allowed to react with alkyl halides in the absence (Method A) or in the presence (Method A') of phase-transfer catalyst (dodecylbenzyltrimethylammonium chloride), or $\underline{3}$ was allowed to react with propenal (Method B).



$$\underset{(\underline{3})}{Ph_2P(S)SH} \xrightarrow{RX,\ NaOH} \underset{(\underline{1})}{Ph_2P(S)SR} \qquad \text{(Methods A, A')}$$

$$\underset{(\underline{3})}{Ph_2P(S)SH} \xrightarrow{CH_2=CHCHO} \underset{(\underline{1},\ R\ =\ CH_2CH_2CHO)}{Ph_2P(S)SCH_2CH_2CHO} \qquad \text{(Method B)}$$

Phosphinodithioate esters ($\underline{1}$) were allowed to react with butyl- or methyllithium at - 40 °C in THF for 30 min to give the corresponding butyl or methyl sulfide $\underline{2}$ as shown in Table 2.

Table 1. Preparation of 1

R	X	Method	Yield (%)	Mp (°C)
CH_2CO_2Et	Cl	A'	63	oil
$CH_2CO_2Bu^t$	Br	A'	47	oil
CH_2CONH_2	Cl	A	38	105 - 106
CH_2CONEt_2	Br	A	85	76.5 - 79
CH_2COPh	Br	A	78	94 - 95
CH_2CN	Cl	A	64	80 - 81
$CH_2CH_2CH_2CN$	Br	A'	82	oil
$CH_2CH_2CH_2Cl$	Br	A'	95	oil
CH_2CH_2CHO	--	B	∿100	oil

Table 2. Reaction of 1 with R'Li

R	R'	Yield of 2 (%)
CH_2CO_2Et	Bu[a)]	22[b)]
$CH_2CO_2Bu^t$	Bu[a)]	61[b)]
CH_2CONH_2	Bu[a)]	21[b)]
CH_2CONEt_2	Bu[a)]	87[b)]
CH_2COPh	Bu[a)]	20[b)]
CH_2CN	Bu	68[b)]
$CH_2CH_2CH(OEt)_2$	Me	97[c)]
$CH_2CH_2CH_2CN$	Bu	70[c)]
$CH_2CH_2CH_2Cl$	Bu	81[c)]

a) Large excess of butyllithium was used. b) Yield by GLC. c) Isolated yield.

Phosphinodithioate esters functionalized by ethoxycarbonyl, carbamoyl, or carbonyl group gave the corresponding sulfides (2) only in a poor yield. Such groups compete with the thiol sulfur atom toward lithium reagent. Actually the reaction of β-formylethyl diphenylphosphinodithioate (4) with methyllithium gave 3-hydroxybutyl diphenylphosphinodithioate (5) almost quantitatively.

$$\underset{(4)}{\mathrm{Ph_2P(S)SCH_2CH_2CHO}} \quad + \quad \mathrm{MeLi} \longrightarrow \underset{(5)}{\mathrm{Ph_2P(S)SCH_2CH_2CH(Me)OH}}$$

Ethoxycarbonyl ester (1, R = $\mathrm{CH_2CO_2Et}$) was methylated almost quantitatively when it was allowed to react with one equivalent of the base at - 78 °C followed by quenching with methyl iodide to give 6.

$$\underset{(1,\ \mathrm{R} = \mathrm{CH_2CO_2Et})}{\mathrm{Ph_2P(S)SCH_2CO_2Et}} \xrightarrow[\text{2) MeI}]{\text{1) base}} \underset{(6)}{\mathrm{Ph_2P(S)SCH(Me)CO_2Et}}$$

However, t-butoxycarbonyl, N,N-diethylcarbamoyl, cyano, and chloro derivatives gave sulfides (2) in good yields. Reaction of methyllithium with diethyl acetal of 4 (1, R = $\mathrm{CH_2CH_2CH(OEt)_2}$), which was prepared from 4 and ethyl orthoformate almost quantitatively, gave the corresponding methyl sulfide (methional) in 97% yield, which could be converted to methionine by the Strecker synthesis.[4]

Table 3. Reaction of 1 with R'Li in THF-HMPA

R	R'	Yield of 2 (%)[a]
Me	$\mathrm{CMe_2CN}$	94[b]
Ph	$\mathrm{CMe_2CN}$	74
Ph	$\mathrm{CMe_2CO_2Et}$	94
Me	C≡CPh	89
Me	C≡CBu	76
Ph	$\mathrm{CH{=}CH_2}$	71

a) Isolated yield unless otherwise noted. b) Yield by GLC.

Table 3 shows the results on the reaction of methyl or phenyl diphenylphosphinodithioate (1, R = Me, Ph) with some organic lithium compounds. Cyano and ethoxycarbonyl substituted alkyllithiums, and ethynyl- and vinyllithiums reacted with 1 at -78 - -40 °C for 1 - 3 h to give the corresponding sulfides in good yields. The reactions shown in Table 3 proceeded only when HMPA was employed as a co-solvent with THF (vol %, 1:5). The present method is straightforward and very simple to employ and the reaction conditions are mild compared with traditional methods.[5]

When phenyl diphenylphosphinodithioate was allowed to react with lithium butanethiolate, the reaction gave butyl diphenylphosphinodithioate (1, R = Bu) in 91%

yield. However, the reaction in the presence of sulfur in THF-HMPA gave butyl phenyl disulfide almost quantitatively.

$$\underset{(1)}{\mathrm{Ph_2P(S)SR}} + \mathrm{R'SLi} + 1/8\ \mathrm{S_8} \longrightarrow \mathrm{[Ph_2PS_2]Li} + \underset{(7)}{\mathrm{RSSR'}}$$

Table 4 shows the results on some applications for the synthesis of unsymmetrical disulfides.

Table 4. Reaction of 1 with R'SLi in the Presence of Sulfur

R	R'	Yield of 7 (%)
Ph	Bu	∿100
Ph	t-Bu	92
Ph	s-Bu	87

Under similar conditions reaction of methyl ester (1, R = Me) with PhSLi failed to give 7 (R = Me, R'= Ph). Lithium compound generated from diphenylphosphine sulfide and one equivalent of butyllithium reacted with diethyl disulfide to give ethyl diphenylphosphinodithioate (1, R = Et) in 81% yield. Therefore, the presence of sulfur is necessary to prohibit the nucleophilic cleavage of desirable disulfide by diphenylphosphinothioyllithium formed during the reaction, which is converted to less nucleophilic lithium diphenylphosphinodithioate by addition of sulfur.

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