RELATIVE REACTIVITY OF 2-DIPHENYLPHOSPHINOYL- AND 2-DIPHENYL-THIOPHOSPHINOYL-2-[1,3]DITHIANYLLITHIUM AS REAGENTS WITTIG-HORNER/COREY-SEEBACH.¹

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Abstract.- The reaction of the title carbanions with several aldehydes and ketones to afford the corresponding ketene dithicketals was studied. It was found that the P=O organolithium reagent reacted with both types of carbonyl substrates in good to excellent yields. On the other hand, the P=S reagent reacted selectively with aldehydes although in poor yield. This contrasting behavior can not be ascribed to a greater stability of the latter carbanion since a $\Delta p K$ measurement showed that the more stable organolithium (by 0.33 ± 0.08 pK units) is also the more reactive. The lower reactivity of the P=S analog can be explained in terms of kinetic inhibition in the formation of the oxaphosphetane intermediate, and/or thermodynamic instability of this pentaccordinated phosphorus species with sulfur (vis-a-vis oxygen) as ligand.

Of the many organometallics employed in synthetic organic chemistry, the Wittig type reagents² and those derived from 1,3-dithiane³ are among the most widely used. It was soon recognized that a derivative combining both the 1,3-dithianyl and the phosphorus moieties could be useful as a precursor for ketene dithioketals (Equation 1),⁴ which are themselves convenient intermediates in the homologation of carbonyl compounds.⁵



In this report we describe the synthesis and use of 2-diphenylphosphinoyl-1,3-dithiane (1) as a new Wittig-Horner/Corey-Seebach reagent.⁶ In addition, the P=S analog 2 was studied and the results provide new insight into the chemistry of this relatively unknown functional group.⁷

RESULTS AND DISCUSSION

A. Preparation of the Wittig-Horner/Corey-Seebach Reagents.

2-[1,3]Dithianyldiphenylphosphine oxide (l) was prepared from 1,3-dithiane, <u>n</u>-butyllithium and chlorodiphenylphosphine; the phosphine intermediate oxidized spontaneously to l during workup:⁸ Scheme I. The sulfur analog l was similarly prepared, although the phosphine intermediate was now treated with an equivalent amount of elemental sulfur, prior to isolation: Scheme I. Isolated yields of l and l were 40% and 42.8%, respectively.



B. Preliminary Reactions.

It has been shown that the Ph_2P group is about as carbanion-stabilizing as a <u>p</u>-biphenylyl group.⁹ On the other hand, the conversion of a Ph_2P group to $Ph_2P(0)$ has a substantial acid strengthening effect in an alpha C-H bond of ca. 7 pK_a units.⁹ Since the pK_a of 2-(<u>p</u>-biphenylyl)--1,3-dithiane is 27.5,¹⁰ then the pK_a of 2-diphenylphosphinoyl-1,3-dithiane can be estimated as ca. 20. Accordingly, a strong base such as <u>n</u>-butyllithium effected a complete conversion of λ to its lithium derivative. Indeed, treatment of λ -Li with D₂0 or CH₃I afforded the deuterated and methylated derivatives in \geq 95% and 85% isolated yields, respectively (Scheme II). Similarly, the conversion of λ to 2-D and 2-CH₃ was effected via <u>n</u>-BuLi in \geq 95% and 80%, respectively (Scheme II).



C. Reaction of L-Li and 2-Li with Aldehydes and Ketones.

Table I summarizes the results from the reaction of l-Li and l-Li with several aldehydes and ketones (Scheme I). Several points merit comment: (1) l-Li reacts both with aldehydes and ketones to afford the corresponding ketene dithioketals in good to excellent yields,¹¹ (2) l-Li reacted selectively with aldehydes; the yields of ketene dithioketals in this case were poor.

The lower reactivity of χ -Li relative to χ -Li in their reaction with carbonyl compounds was confirmed in a competition experiment in which one equivalent of χ -Li and one equivalent of χ -Li were put to react with one equivalent of cyclohexanone; quenching of the reaction mixture with aqueous ammonium chloride afforded¹³ 2-cyclohexylidene-1,3-dithiane (67%), recovered χ (0.33 equivalents) and recovered χ (1.0 equivalent) (Scheme III). That the metallated species χ -Li was present during the competition reaction was shown by quenching with D_2O : χ -D was then isolated in essentially quantitative yield. This result indicates that in the reaction of χ -Li with enolizable ketones, enolate formation is not a side reaction preventing the desired (ketenedithioketal formation) pathway. (Scheme III).

Entry	$ \stackrel{R_1}{\underset{R_2}{\rightarrowtail}} = 0 \rightarrow \bigcirc S \xrightarrow{S} \stackrel{R_1}{\underset{R_2}{\rightthreetimes}} $	<u>% Conversion</u> from <u>l</u> -Li	on (by ¹ NMR) from 2-Li
1	$R_1 = C_6 H_5, R_2 = H$	80	63
2	$R_1 = C_2 H_5, R_2 = H$	93	33
3	$R_1 = n - C_6 H_{13}, R_2 = H$	93	24
4	$R_1 = CH_3, R_2 = H$	89	0
5	$R_1 = R_2 = C_6 H_5$	68	0
6	$R_1 - R_2 = (CH_2)_5$	100	0

Table I. Preparation of Ketenedithioketals from the Reaction of l-Li and 2-Li with Aldehydes and Ketones.

SCHEME III



D. Mechanistic Considerations.

Despite the considerable effort dedicated to the elucidation of the mechanism of Wittig-type reactions, ¹⁴ useful information is still being uncovered. ¹⁵ The present Wittig-Horner reaction can be discussed in terms of a reversible formation of an oxyanion intermediate (χ) that collapses to the alkene via an oxaphosphetane intermediate (g). (Scheme IV). ¹⁶ If carbanion 2-Li were much more stable than χ -Li, the lower reactivity of the former toward carbonyl compounds could be explained in terms of an unfavorable first step in Scheme IV.

The determination of $\Delta p K_a$ for dithianes λ and λ was achieved by the method of Conant and Wheland:¹⁷ λ -D and λ -D were equilibrated with their conjugated bases, and then quenched with aqueous HC1. The equilibrium constant was determined by integration of the proton NMR spectrum; $\Delta p K_a = p K_a(\lambda) - p K_a(\lambda) = -\log \{ [\lambda-Li] [\lambda-D] / [\lambda-D] \}$. (Scheme V).

SCHEME IV



Experimentally, $\Delta pK_a = -0.33 \pm 0.08$, l being stronger acid than 2. This result is in accord with those indicating that a $Ph_2P(0)$ group is slightly more electronegative than $Ph_2P(S)$, ¹⁹ and show that the more stable carbanion l-Li is also the more reactive.



(a) $k_2 \sim k_3 >>> k_1 \sim k_{-1}$.

It appears then that the higher reactivity of 1-L1 is due to either steric or electronic effects that inhibit the formation of the oxyanion (1) and/or oxaphosphetane (8) intermediates with X = S. (Scheme IV). In this respect, the kinetic studies of Larsen and Aksnes²⁰ have shown that the determining step in Wittig-Horner reactions is the formation of the pentacoordinated intermediate (8 in this case). This oxaphosphetane adopts a trigonal bipyramidal stereostructure with the attacking and leaving groups occupying apical positions.²¹ Therefore, in 8 it is expected that the four-membered ring occupies apical-equatorial positions, and $X^{T}Li^{+}$ (X = 0, S) an apical orientation:



With this information at hand, $^{20-22}$ it appears then reasonable that the lower reactivity of 2-Li relative to 1-Li is due to (1) a greater steric congestion during the formation of the critical oxaphosphetane (sulfur vis-a-vis oxygen), and/or (2) the trigonal bipyramid intermediate & is electronically more stable with $X^- = 0^-$ since this ligand has greater apicophilicity than $X^- = S^-$.^{23,24} In view of the long P-S bond distance, an argument based on steric congestion, i.e. (1), is perhaps less appealing.

EXPERIMENTAL SECTION

Melting points were obtained in a Mel-Temp and/or Electrothermal melting point apparatus with an open capillary tube.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on Varian EM-360 (60 MHz) or Varian EM-390 (90 MHz) spectrometers. Samples were prepared as 5-10% solutions in CDCl_3 with 2-5% Me₄Si as internal reference in 5- or 10-mm o.d. tubes. Data are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), integration. Carbon-13 NMR spectra were recorded on Varian XL-100 (25.12 MHz) or JEOL FX-90Q (22.49 MHz) instruments operated in pulsed Fourier transform mode and locked on solvent deuterium. Mass data were obtained on a Hewlett-Packard 5985-A spectrometer.

Flasks, stirring bars and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120°C and allowed to cool in a dessicator over anhydrous calcium sulfate. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl.²⁵

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37291.

<u>2-[1,3]Dithianyldiphenylphosphine Oxide</u> ($\frac{1}{2}$) was prepared according to the reported procedure.²⁶

<u>2-[1,3]Dithianyldiphenylphosphine Thiooxide</u> (2). One gram of 1,3-dithiane (8.33 mmol, freshly sublimed) was placed in a 25-mL round bottom flask provided with a rubber septum before the addition of 20 mL of THF under nitrogen. The flask was immersed in a carbon tetrachloride/dry ice bath (ca. -20°C) and then 6.67 mL of 1.5 M <u>n</u>-BuLi in hexane (20% excess) was added. The reaction mixture was stirred at -20°C for 1.5 h, and then treated with 2.206 g (10.0 mmol) of chlorodi-phenylphosphine in 15 mL of THF and TMEDA (0.968 g, 8.33 mmol). The reaction mixture was stirred at -20°C for 1.5 h and then transferred via cannula to another flask containing powdered sulfur (0.533 g, 8.33 mmol). Stirring was continued at -20°C for 4 h, at room temperature during one additional hour and then the reaction was quenched with saturated ammonium chloride. Extraction with chloroform and the usual work-up procedure yielded a yellowish solid (1.32 g, 46.9% yield), which was crystallized from methanol to afford 1.2 g (42.8%) of χ as white crystals, mp 177-178°C. ¹H NMR (90 MHz, CDCl₃) & 2.02 (m, 2 H), 2.68 (d of t, J_{gem} = 13.8 Hz, J_{gauche} = 5.4 Hz, 2 H), 3.50 (m, 2 H), 4.73 (d, ²J_{P-C-H} = 9 Hz, 1 H), 7.55 (m, 6 H), 8.02 (m, 4 H). ³¹P NMR (36.23 MHz, CDCl₃, H₃PO₄ external reference) & 48.81. ¹³C NMR (22.49 MHz, CDCl₃) & 24.65 (s, <u>CH₂(CH₂S)₂)</u>,

28.41 (d, ${}^{3}J_{CP} = 4 \text{ Hz}$, 2 $\underline{C}H_{2}S$), 42.50 (d, ${}^{1}J_{CP} = 52 \text{ Hz}$, S<u>C</u>HS), 128.34 (d, ${}^{3}J_{PC} = 12 \text{ Hz}$, meta C), 131.54 (d, ${}^{1}J_{CP} = 80 \text{ Hz}$, ipso C), ca. 131.70 (d, ${}^{4}J_{CP} = 2 \text{ Hz}$, para C), ca. 131.97 (d, ${}^{2}J_{CP} = 10 \text{ Hz}$, ortho C).

Anal. Calcd for C16H17PS3: C, 57.11; H, 5.09. Found: C, 57.03; H, 5.12.

Metallation of 1 and 2 to 1-Li and 2-Li. One millimol of the dithiane (320 mg of 1 or 336 mg of 2) was placed in a 25-mL round-bottom flask provided with a rubber septum and 15 mL of THF was added under nitrogen. The flask was immersed in a carbon tetrachloride/dry ice bath (ca. -20°C) and then 1.05 mmol (5% excess) of <u>n</u>-butyllithium in hexane was added. The reaction mixture was then stirred at -20°C for 1.5 h.

Deuteration of 1-Li and 2-Li to 1-D and 2-D. The lithium salts of the Wittig-Horner/Corey-Seebach precursors were prepared as described above and transferred to flasks containing deuterium oxide in excess. Extraction with chloroform and the usual work-up procedure yielded the deuterated dithianes (1-D or 2-D) with over 95% deuterium incorporation, as showed by integration of the ¹H NMR spectrum: no signal for C₂-H was observed.

Alkylation of 1-Li and 2-Li to $1-CH_3$ and $2-CH_3$. The carbanions prepared as described above were transferred to flasks containing an equimolar amount of methyl iodide in THF. The reaction mixture was stirred at -20°C for 1.5 h and then quenched with saturated ammonium chloride. Extraction with ether or methylene chloride and the usual work-up procedure afforded $1-CH_3$ and $2-CH_3$ in ca. 100% and 85% yields, respectively. $1-CH_3$ was purified by preparative thin layer chromatography (silica gel) in a chloroform/ethyl acetate (60:40) system: isolated yield = 85%; mp = 124-126°C. ¹H NMR (90 MHz, CDCl₃) & 1.6 (d, $^{3}J_{P-CC-H}$ = 13.5 Hz, 3 H), 2.0 (m, 2 H), 2.5 (d of t, J_{gem} = 14.4 Hz, J_{gauche} = 3.9 Hz, 2 H), 3.7 (m, 2 H), 7.3-8.0 (m, 10 H).

Anal. Calcd for $C_{17}H_{19}^{0}OPS_2$: C, 61.05; H, 5.72. Found: C, 61.45; H, 5.87. 2-CH₃ was similarly purified by thin layer chromatography with <u>n</u>-hexane/ethyl acetate (90:10) eluent, followed by crystallization from methanol to afford the desired product in 66% yield, mp = 112-113°C. ¹H NMR (90 MHz, CDCl₃) δ 1.91 (d, ³J_{p-C-C-H} = 15.6 Hz, 3 H), 1.95 (m, 2 H), 2.77 (distorted t, 4 H), 7.53 (m, 6 H), 8.35 (m, 4 H).

Anal. Calcd for C17H10PS3: C, 58.25; H, 5.46. Found: C, 58.01; H, 5.52.

<u>General Procedure for Wittig Reactions</u>. The lithium reagent (1-Li or 2-Li) was prepared as described above and transferred to a flask containing an equimolar amount of the carbonyl compound in 10-15 mL of dry THF at -20°C. The reaction mixture was stirred at this temperature during one additional hour and then heated gently until the reaction was complete (see below). The reaction was quenched with saturated ammonium chloride, extracted with ether or methylene chloride, the organic layer was dried (Na_2SO_4) and the solvent was removed in a rotary evaporator. The following compounds were prepared:

- a) 2-ethylidene-1,3-dithiane (1.5 h from L-Li), bp = 74°C/4 mm (lit.^{12a} bp = 48-52°C/0.3 mm).
 ¹H NMR (90 MHz, CDC1₃) & 1.81 (d, ³J = 6.6 Hz, 3 H), 2.15 (m, 2 H), 2.85 (m, 4 H), 6.0 (q, ³J = 6.6 Hz, 1 H).
- b) 2-benzylidene-1,3-dithiane (2 h from L-Li), bp = 142°C/0.1 mm (lit^{4a} bp = 142-145°C/0.1 mm); n_D = 1.6699 (lit.^{4b} n_D = 1.6793). ¹H NMR (90 MHz, CDCl₃) & 1.93-2.26 (m, 2 H), 2.8-3.03 (m, 4 H), 6.81 (s, 1 H), 7.15-7.60 (m, 5 H).
- c) $2-\underline{n}-\text{octylidene-1,3-dithiane}$ (4.5 h from $\underline{1}-\text{Li}$), bp = 80°C/0.9 mm. ¹H NMR (90 MHz, CDC1₃) δ 0.89 (t, ³J = 6.6 Hz, 3 H), 1.1-1.52 (m, 8 H), 2-2.45 (m, 4 H), 2.7-3.0 (m, 4 H), 5.88 (t, ³J = 12.0 Hz, 1 H).

Anal. Calcd for C₁₁H₂₀S₂: C, 61.09; H, 9.31. Found: C, 60.71; H, 9.43.

d) $2-\underline{n}-propylidene-1,3-dithiane (1.5 h from <math>l-Li$), bp = 46°C/4 mm. ¹H NMR (90 MHz, CDCl₃) δ 0.99 (t, ³J_{vic} = 6.3 Hz, 3 H), 1.95-2.4 (m, 4 H), 2.7-3.0 (m, 4 H), 5.92 (t, ³J_{vic} = 7.8 Hz, 1 H).

- e) 2-diphenylmethylene-1,3-dithiane (72 h from L-Li), mp = 131-133°C (lit.²⁷ mp = 134.5-135°C).
 ¹H NMR (90 MHz, CDCl₃) δ 2.10 (q, ³J = 6.3 Hz, 2 H), 2.94 (t, ³J = 6.3 Hz, 4 H), 7.3 (broad s, 10 H).
- f) 2-cyclohexylidene-1,3-dithiane (2 h from l-Li), mp = 89-90°C (lit.²⁷ mp = 93.6-94°C). ¹H NMR (90 MHz, CDCl₃) δ 1.35-1.7 (m, 6 H), 2-2.3 (m, 2 H), 2.3-2.6 (m, 4 H), 2.75-2.95 (m, 4 H).

Equilibration of 1-D, 2-D and their conjugated bases. Equimolar amounts of 1-D and 2-D (0.313 mmol) were placed in a 25-mL round-bottom flask provided with a rubber septum and 10 mL of THF was added under nitrogen. The flask was immersed in a carbon tetrachloride/dry ice bath (ca. -20°C) and then 0.313 mmol of <u>n</u>-butyllithium in hexane was added. The reaction mixture was stirred at -20°C for 1.5 h and then added dropwise (via cannula) to another flask containing aqueous 10% HC1. Neutralization was effected with aqueous Na₂CO₃, and the dithianes were then extracted with chloroform, dried (Na₂SO₄) and evaporated. Integration of the H(2) signals afforded the equilibrium concentrations of [1-Li], [1-D], [2-Li] and [2-D], from which ΔpK_a was evaluated (see Text).

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