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THE WITTIG REARRANGEMENT OF CHIRAL PHOSPHINOTHIOATES INDUCED BY THE TIN-LITHIUM TRANSMETALLATION

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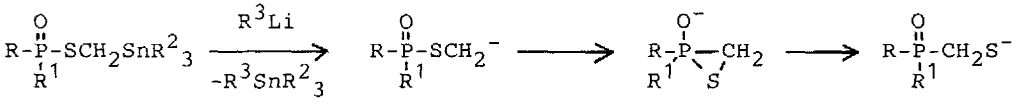
Abstract: The title reaction using optically active S-stannylmethyl phosphinothioates, followed by quenching with alkyl iodide affords mainly the corresponding (alkylthiomethyl)phosphine oxides with a retention of configuration.

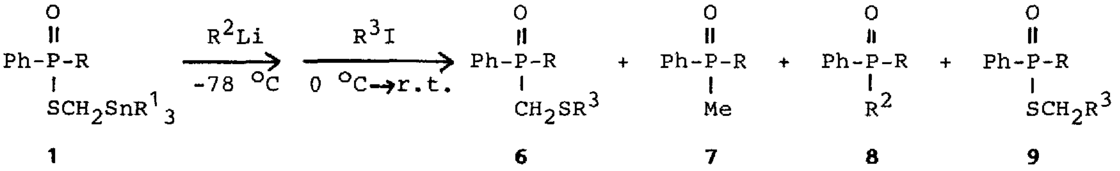
The tin-lithium transmetallation has been utilized as a useful method for the preparation of carbanions in the cases where direct metallation with lithium metal or deprotonation with other organolithium reagents is relatively difficult because of some reasons.[1] In the course of our investigations on the reactions of monothiophosphinates or dithiophosphinates with various nucleophiles, we have reported the first example for the Wittig rearrangement involving a phosphorus atom.[2] There have been reported many synthetic methods of optically active phosphorus compounds, based on the nucleophilic substitution on a phosphorus atom.[3] The stereochemistries and stereospecificities of those reactions extensively depend on the kinds of the substituent on the phosphorus atom and nucleophiles, which may affect the life time of a pentavalent intermediate.[4] If the transmetallation could be applied to S-stannylmethyl phosphinothioates (**1**), it would be expected to generate efficiently the carbanions at α-position of sulfur atom (**2**), which might undergo the Wittig rearrangement to give the corresponding thiolatomethylphosphine oxides (**4**) with a high stereospecificity, since the expected pentavalent intermediate (**3**) seems to be highly strained and too short lived to pseudorotate.



1 **2** **3** **4**

S-Tributylstannylmethyl 1-naphthylphenylphosphinothioate(**1a**), S-triphenylstannylmethyl 1-naphthylphenylphosphinothioate (**1b**), and S-tributylstannylmethyl t-butylphenylphosphinothioate (**1c**) were prepared by S-alkylation of the corresponding phosphinothioic acids (**5**) with the stannylmethyl iodides in 65, 86 and 85% yields, respectively.[5] To a solution of **1a** or **1b** in tetrahydrofuran (THF) were added various organolithium reagents at -78 °C, followed by treatment with alkyl iodides at 0 °C to afford the desired product, (alkylthiomethyl)-1-naphthylphenylphosphine oxides (**6a,b**),[5] methyl-1-naphthylphenylphosphine oxide (**7**), and/or the nucleophilic substitution product on the phosphorus atom by organolithium reagent (**8**), and/or the alkylation product of the first formed carbanion (**9**), together with the corresponding tin compounds. The results are shown in Table 1.

Table 1. Reactions of **1** with organolithium reagents, followed by treatment with alkyl iodides



$$\underset{\mathbf{1}}{\mathrm{Ph{-}\overset{\overset{O}{\|}}{\underset{\underset{SCH_2SnR^1_3}{|}}{P}}{-}R}} \xrightarrow[-78\ ^{\circ}\mathrm{C}]{\mathrm{R^2Li}} \xrightarrow[0\ ^{\circ}\mathrm{C}\rightarrow \mathrm{r.t.}]{\mathrm{R^3I}} \underset{\mathbf{6}}{\mathrm{Ph{-}\overset{\overset{O}{\|}}{\underset{\underset{CH_2SR^3}{|}}{P}}{-}R}} + \underset{\mathbf{7}}{\mathrm{Ph{-}\overset{\overset{O}{\|}}{\underset{\underset{Me}{|}}{P}}{-}R}} + \underset{\mathbf{8}}{\mathrm{Ph{-}\overset{\overset{O}{\|}}{\underset{\underset{R^2}{|}}{P}}{-}R}} + \underset{\mathbf{9}}{\mathrm{Ph{-}\overset{\overset{O}{\|}}{\underset{\underset{SCH_2R^3}{|}}{P}}{-}R}}$$

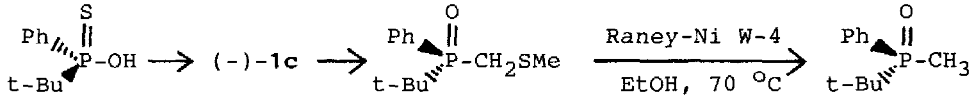
Run[b)]	R	R^1	R^2	R^3	Yields[a)]/% **6**	**7**	**8**	**9**
1	1-Np	n-Bu	Ph	Me	70	28	-	-
2	1-Np	n-Bu	Me	Me	79	11	-	-
3	1-Np	n-Bu	Me	Et	74	9	-	-
4	1-Np	n-Bu	n-Bu	Me	34	-	66	-
5	1-Np	Ph	Me	Me	50	18	-	-
6	1-Np	Ph	Ph	Me	15	20	-	47

a) Isolated yields based on consumed **1**. b) $R^1{}_3SnR^2$ was obtained almost quantitatively in all runs except Run 4, in which n-Bu_3SnCH_2SMe was obtained in addition to n-Bu_4Sn (2:1).

Butyllithium can attack on a phosphorus atom as well as on a tin atom, because of its stronger nucleophilicity to give the corresponding phosphine oxide (**8**) (see Run 4). Increasing a number of more electronegative phenyl groups on a tin atom makes an intermediate, "tin ate complex", more stable to increase the probability of the alkylation of the carbanion (**2**) formed via dissociation process (see Run 6). However, the intermediate could not be observed by ^{119}Sn-NMR spectroscopy.[6] Use of MeLi as an organolithium reagent and butyl group as a substituent on a tin atom gave the best results.

Optically active (-)-**1a**, (+)-**1a**, (-)-**1c**, and (+)-**1c** were readily prepared from (+)-, (-)-1-naphthylphenylphosphinothioic acids (**5a**),[7] (-)-(*S*)-, and (+)-(R)-t-butyl(phenyl)phosphinothioic acids (**5b**),[8a,9a] respectively. Reactions of (-)- and (+)-**1a** with MeLi, followed by methylation with iodomethane in the same reaction conditions as shown in Table 1 afforded optically active (-)- and (+)-**6a** (R=1-Np; R^3=Me), respectively. The similar reactions of (-)- and (+)-**1c** gave (-)- and (+)-t-butyl(methylthiomethyl)phenylphosphine oxides (**6b** (R=t-Bu; R^3=Me)), respectively, in 80% yield in addition with small amounts of S-methyl t-butyl(phenyl)phosphinothioate.

In order to determine stereochemistry and optical yield of the present rearrangement, **6b** was led to stereochemically-known t-butylmethylphenylphosphine oxide (**7b** (R=t-Bu))[8b,9b] as shown in the following scheme. That is, (-)-**1c** prepared from (-)-(S)-**5b** gave (+)-(R)-**7b**. As the step of preparation of **1** is known to be retention [12] and the reduction with Raney Ni seems not to affect stereochemistry at the chiral center, the result indicates that the present rearrangement proceeds with a retention of configuration on the phosphorus atom and in very high optical yield. It means that the intermediate **3** is too short-lived to pseudorotate as expected. But, it cannot rule out another possibility that the phosphorus-sulfur bond cleavage of **2** is followed by rapid recombination between the corresponding phosphinite ion and thioformaldehyde, though attempts to trap thioformaldehyde were unsuccessful.



(-)-(S)-**5b** $[\alpha]_D^{22}$ -27.8° (c 2.35, MeOH) o.y.[11] 98.9%

(-)-**6b**[10] $[\alpha]_D^{17}$ -81.0° (c 0.639, $CHCl_3$)

(+)-(R)-**7b**[10] $[\alpha]_D^{17}$ +21.0° (c 0.275, MeOH) o.y. 92.5%

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   (-)-**6a**: mp 151.8-154.2 °C. $[\alpha]_D^{24}$ -8.07° (c 0.405, $CHCl_3$). ^1H-NMR ($CDCl_3$): δ 2.17 (d, $^4J_{H,P}$=0.98 Hz, 3H, SMe), 3.41 (d, $^2J_{H,P}$=8.06 Hz, 2H, PCH_2S), 7.28-8.11 (m, 11H, aromatic protons except peri proton), and 8.43-8.66 (m, 1H, peri proton). ^{31}P-NMR ($CDCl_3$): δ_P 31.97. HRMS(70eV): m/z Found: 312.0731. Calcd for $C_{18}H_{17}OPS$: 312.0736.
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