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THE ORTHO-LITHIATION OF PHENYL GROUPS AND α-LITHIATION OF ALKYL GROUPS OF THIOPHOSPHORYL COMPOUNDS

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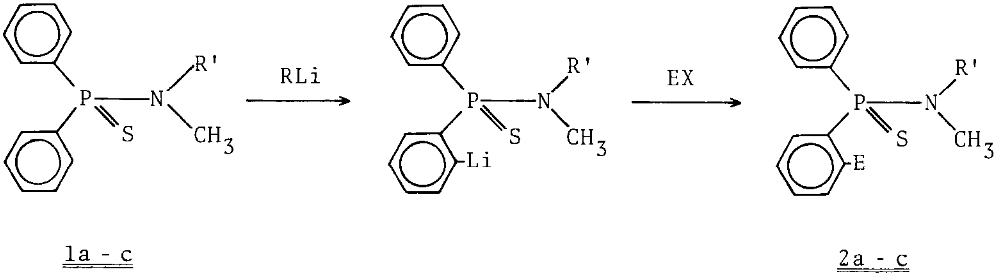
SUMMARY Diphenylphosphinothioyl compounds were ortho-lithiated and alkyldiphenyl phosphine sulfides were α-lithiated and the resulting lithio compounds reacted to give the corresponding o- and α-substituted products.

Very recently Dashan and Trippett[1] reported the ortho-lithiation of N,N,N',N'-tetramethylphenylphosphonic diamide. Now we wish to report promptly our preliminary results[2] on the reactions of phenyl-containing thiophosphoryl compounds with various alkyllithium reagents.

Attempted α-lithiations of N-alkyl groups in various thiophosphoryl amides under various conditions have been unsuccessful so far, although the corresponding reactions of 2-[bis(dimethylamino)phosphinoyl]-1,2,3,4-tetrahydroisoquinoline were successful.[3,4] In contrast, we found that o-lithiation occurs to the diphenylphosphinothioic amides of the type 1a - c to give 2a - c after quenching with electrophiles such as methyl iodide, D_2O, and H_2O as shown in Scheme I.

Scheme I



a: R' = Ph ; b: R' = CH_2Ph ; c: R' = CH_3
R = n-Bu, s-Bu, t-Bu
EX = MeI, D_2O, H_2O

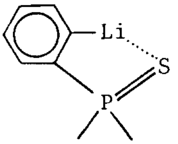
Under argon N-methyl-N-phenyldiphenylphosphinothioic amide (1a) was dissolved in dimethoxymethane (DMM) at -78°C and was added 1.0 eq. of s-butyllithium in cyclohexane in the presence of 1.0 eq. of N,N,N',N'-tetramethylethylenediamine (TMEDA) to give an orange-red homogeneous solution. After quenching with excess amount of methyl iodide and D_2O at that temperature gave 2a (E = Me) and 2a (E = D) in 50 and 45% yields, respectively. No doubly lithiated products were observed. Under similar reaction conditions, t-butyllithium in pentane did not react with 1a, however, at -10°C it started to react to give 2a (E = Me) in 74% yield after quenching with methyl iodide. In order to confirm the structure of 2a chemically it was cleaved with 2 eq. of n-butyllithium in THF at -50°C for 30 min, followed by quenching with water to form N-methylaniline and butylphenyl-o-tolylphosphine sulfide (3; see also Scheme II).

In a similar way, 1b was allowed to react with t-butyllithium in a mixture of DMM - TMEDA at -10°C, and after quenching with methyl iodide, 2b (E = Me) was obtained in 31% yield accompanied with recovered 1b. With s-butyllithium at -78°C for 30 min, the yield of 2b (E = Me) was only 15%. In tetrahydrofuran (THF) in the presence of TMEDA with n-butyllithium in hexane at -78°C for 30 min, 1b was recovered (67%) indicating that no lithiation occurred under such conditions. No lithiation in benzylic position was observed in 1b, either. The reaction of 1c with excess of t-butyllithium in DMM with 1 eq. of TMEDA at -10°C gave the corresponding o-methylated compound 2c (E = Me) in 78% yield, however, no α-lithiation to N-methyls was observed. In a mixture of THF - TMEDA, neither o-lithiation nor α-lithiation was observed even though 2 eq. of t-butyllithium was employed (89% recovery). Similarly s-butyllithium reacted with 1c in DMM - TMEDA at -78 → -50°C to give 2c (E = Me) (61% yield) after the quenching with methyl iodide.

In order to investigate the generality of the ortho-lithiation in thiophosphoryl compounds, triphenylphosphine sulfide (4) was allowed to react with s-butyllithium in a mixture of DMM - TMEDA - THF to give diphenyl-o-tolylphosphine sulfide (5) in 26% yield accompanied with the recovered 4.

Moreover, when hexamethylthiophosphoric triamide was allowed to react with s-butyllithium under the same reaction conditions as those reported by Magnus and Roy[5] for hexamethylphosphoric triamide, no reaction was observed.

$^{31}P\{^1H\}$ NMR of N,N-dimethyl-o-lithiophenylphenylphosphinothioic amide in DMM at -20°C appeared at δ_P 79.9 ppm and this peak gave the starting 1c (δ_P 69.5 ppm) after quenching with water indicating a contribution of a chelation structure (A).



(A)

Scheme II

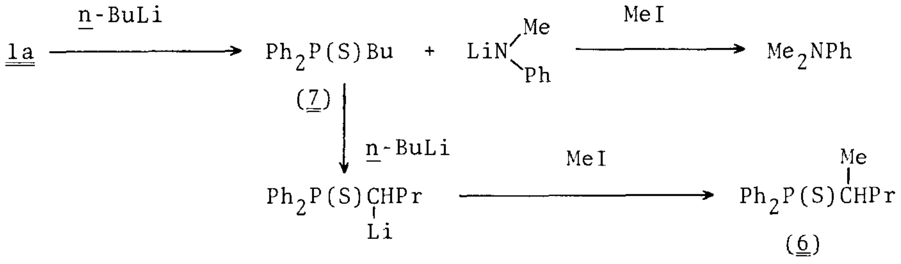


Table I. Some Important NMR Parameters ($CDCl_3$) in o-Lithiation Reactions

Compounds	^{31}P NMR δ_P/ppm a)	^1H NMR δ/ppm b)
1a	66.9	2.90 (Me, d, J = 12 Hz)
2a (E = Me)	66.5	2.40 (Me-arom., s) 3.10 (MeN, d, J = 10 Hz)
1b	71.2	2.40 (MeN, d, J = 14 Hz) 3.85 (CH_2N, d, J = 7 Hz)
2b (E = Me)	68.7	2.40 (Me-arom., s) 2.44 (MeN, d, J = 10 Hz) 4.32 (CH_2N, d, J = 8 Hz)
1c	71.1	2.43 (Me, d, J = 14 Hz)
2c (E = Me)	68.8	2.40 (Me-arom., s) 2.60 (MeN, d, J = 12 Hz)
3	42.9	2.40 (Me-arom., s)
4	43.3	
5	42.1	2.37 (Me-arom., s)

a) δ_P Values are indicated in ppm from external 85% H_3PO_4. b) All new compounds described here showed reasonable phenyl patterns in NMR and parent ion peaks in the mass spectra and/or correct elemental analyses.

Some important NMR characters of the starting materials and the products are shown in Table I.

When 1a was allowed to react with one equivalent of *n*-butyllithium in THF at -40 → -25°C for 3 h, followed by methyl iodide quenching to give 1-methylbutyldiphenylphosphine sulfide (6,[6] 14% yield) and N,N-dimethylaniline (29%). When 2 eq. of *n*-butyllithium was used, the yield of 6 was raised up to 62% indicating the nucleophilic attack of *n*-butyllithium on phosphorus atom to give butyldiphenylphosphine sulfide (7)[7] and lithium methylphenylamide as reaction intermediates. In a separate experiment 7 was first allowed to react with *n*-butyllithium and then with methyl iodide to give 6 in 91% yield indicating that α-lithiation of alkylphosphine sulfide is quite facile as shown in Scheme II.

When benzyldiphenylphosphine sulfide (8)[8] was lithiated with *n*-butyllithium followed by quenching with benzaldehyde to give trans-stilbene in 74% yield[10] after usual work-ups, whereas, methyldiphenylphosphine sulfide (9)[11] was lithiated on the methyl moiety, followed by quenching with benzophenone gave 2-hydroxy-2,2-diphenylethyldiphenylphosphine sulfide (10)[12] in 82% yield.

The results described here indicate that ortho-lithiation of diphenylphosphinothioyl compounds and α-lithiation of alkylthiophosphoryl compounds occur smoothly probably because of the chelation of sulfur to lithium.

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References and Notes

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11. 9 [oil; δ_P(CDCl$_3$) 35.8 ppm].[9]
12. 10 [mp 141 - 143°C; δ_P(CDCl$_3$) 34.7 ppm; ^{1}H NMR (CDCl$_3$) 3.53 (d, J = 10 Hz, 2H, CH$_2$), 6.47 ppm (s, 1H, OH)].

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