Unusual Demethylation of *O*,*O*′-Dimethyl Chlorothiophosphate with Aryllithiums

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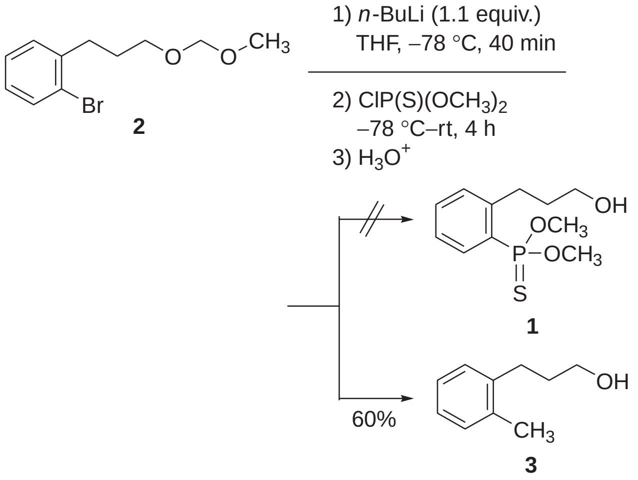
The reaction of *O*,*O*′-dimethyl chlorothiophosphate with aryllithiums took place easily to afford the corresponding methylated aryl compounds in place of expected *O*,*O*′-dimethyl aryl(thiophosphonate)s.

The *O*-thiophosphorylation/phosphorylation of alcohols with *O*,*O*′-dialkyl chlorothiophosphates/chlorophosphates are well-known reactions and were widely used for the synthesis of pentavalent phosphorus atom-containing insecticides[1] and so on. On the other hand, Miller has reported that benzenethiolate anion attacked the α-carbon of the ethyl group rather than the pentavalent phosphorus atom of *O*,*O*′-diethyl chlorothiophosphate to afford ethyl phenyl sulfide.[2] Later, it has been reported that the reactions of azaarenethiolate anions with *O*,*O*′-dimethyl chlorothiophosphate/chlorophosphate gave no expected S-thiophosphorylated/phosphorylated products and that the selective S-alkylation or S-preferential S/N-alkylation of the azaarenethiols occured.[3] These phenomena would be explained on the basis of the hard–soft acid–base principle; the soft thiolate anions, polarized to a large extent, preferentially attacked the alkyl α-carbon relatively softer than the pentavalent phosphorus atom in *O*,*O*′-dialkyl chlorothiophosphates/chlorophosphates.

In this paper, we describe the nucleophilic attack of aryllithiums to the methyl carbon of *O*,*O*′-dimethyl chlorothiophosphate, resulting in the methylation of the aryllithiums/the demethylation of the thiophosphate.

In the course of our study on the development of enantiopure *O*-alkyl arylphosphonothioic acids as efficient resolving agents for 1-arylethylamine derivatives,[4] we tried to synthesize a precursor of a cyclic phosphonothioic acid ester, *O*,*O*′-dimethyl [(3-hydroxypropyl)phenyl]thiophosphonate (**1**) by the reaction of 2-[(3-methoxymethoxy)propyl]phenyllithium, generated in situ from 1-bromo-2-[3-(methoxymethoxy)propyl]benzene (**2**) and butyllithium, with *O*,*O*′-dimethyl chlorothiophosphate. However, the reaction, followed by the treatment with an aqueous HCl solution to quench the reaction and to remove the protecting group, gave an unexpected methylated product, 3-*o*-tolylpropan-1-ol (**3**), in 60% isolated yield, accompanying the formation of only a small amount of **1** (Scheme 1). This result indicates that a demethylation of *O*,*O*′-dimethyl chlorothiophosphate underwent with the aryllithium. The result prompted us to examine the present unusual demethylation further, because no report described such a demethylation reaction with an aryllithium although the reactions of *O*,*O*′-dialkyl chlorothiophosphates/chlorophosphates with aryllithiums have been fragmentally reported.[5]

The reactions were carried out as follows: In order to prepare an aryllithium, *t*-butyllithium (2.1 equiv.) in pentane (or butyllithium (1.1 equiv.) in hexane) was dropwise added to a dry tetrahydrofuran solution (10 mL) of an aryl bromide (4 mmol) at −78 °C, and the mixture was stirred for 1 h at −78 °C. Then, *O*,*O*′-dimethyl chlorothiophosphate (1.1 equiv.) was added to the solution at −78 °C, and the reaction mixture was allowed to warm up to room temperature over a period of 4 h with stirring. After quenching the reaction with water, followed by extraction with dichloromethane, the crude product was purified by column chromatography on silica gel. The results are summarized in Table 1.



Scheme 1. Methylation of 2-[3-(methoxymethoxy)propyl]-phenyllithium with *O*,*O*′-dimethyl chlorothiophosphate (demethylation of *O*,*O*′-dimethyl chlorothiophosphate).

The reactions proceeded very smoothly to give the corresponding methylated aryl compounds in 60–80% yields; aryllithiums were found to be generally methylated with *O*,*O*′-dimethyl chlorothiophosphate without difficulty, namely, the demethylation of *O*,*O*′-dimethyl chlorothiophosphate could easily occur with aryllithiums.

In contrast to the demethylation, the deethylation of *O*,*O*′-diethyl chlorothiophosphate did not occur at all with 2-naphthyllithium, prepared from 2-bromonaphthalene (**4**) and *t*-butyllithium. The reaction led to the formation of the thiophosphorylated product **5**,[6] in 70% isolated yield (Scheme 2). Thus, the thiophosphorylation of aryllithiums/the dealkylation of *O*,*O*′-dialkyl chlorothiophosphate with aryllithium were strongly influenced by the alkyl group of *O*,*O*′-dialkyl chlorothiophosphate. It is noteworthy that such dependence is a contrast to the dealkylation with benzenethiolate anion.[2]

Such switch in alkylation/thiophosphorylation for the reaction of aryllithiums with *O*,*O*′-dialkyl chlorothiophosphate would be explained by the hard–soft acid–base principle for the substrate/reactant and/or by the steric repulsion between the substrate/reactant: The rather soft arylic carbanions would

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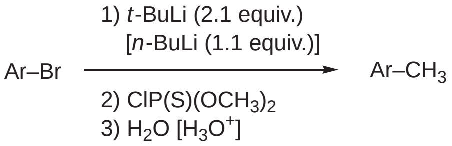
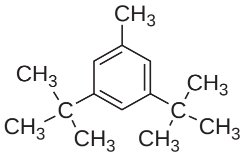
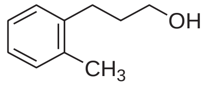
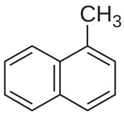
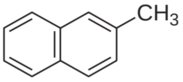
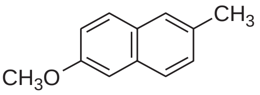
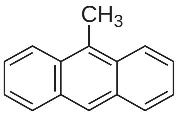
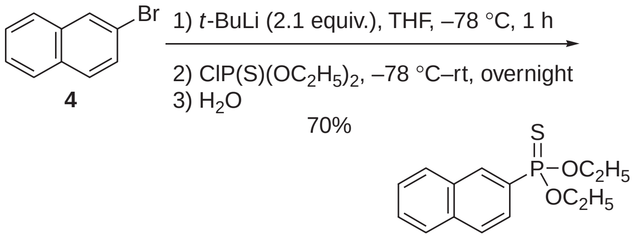
Table 1. Methylation of aryllithiums with *O*,*O*′-dimethyl chlorothiophosphate



$$\text{Ar–Br} \xrightarrow[\text{2) ClP(S)(OCH}_3)_2\text{; 3) H}_2\text{O [H}_3\text{O}^+]}]{\text{1) }t\text{-BuLi (2.1 equiv.) [}n\text{-BuLi (1.1 equiv.)]}} \text{Ar–CH}_3$$

Entry	Product[6]	Yield/%
1		80
2[a]		60
3		78
4		78
5		60
6		62 (62)[b]

[a] 1-Bromo-2-[3-(methoxymethoxy)propyl]benzene was used as a starting material. [b] Reaction with *O*,*O*′-dimethyl chlorophosphate.[7]



Scheme 2. Thiophosphorylation of 2-naphthyllithium with *O*,*O*′-diethyl chlorothiophosphate.

preferentially attack the methyl carbon softer than the pentavalent phosphorus atom in *O*,*O*′-dimethyl chlorothiophosphate. On the other hand, an ethyl carbon is relatively harder than a methyl carbon and an ethyl group is more bulky than a methyl group so that the nucleophilic attack of the arylic carbanion might take place at the pentavalent phosphorus atom in *O*,*O*′-diethyl chlorothiophosphate.

The phosphorylations of aryllithiums with *O*,*O*′-dialkyl chlorophosphates, reported fragmentally, resulted in rather low yields, especially when *O*,*O*′-dimethyl chlorophosphate was used.[5] The unsatisfactory results would arise from a competitive demethylation reaction of *O*,*O*′-dimethyl chlorophosphate with aryllithiums such as that observed in the present study (Table 1, Entry 6).[7]

In conclusion, we have clearly demonstrated that the unusual demethylation of *O*,*O*′-dimethyl chlorothiophosphate with aryllithiums took place easily, that is, the methylation of the aryllithiums with *O*,*O*′-dimethyl chlorothiophosphate proceeded smoothly to give their methylated compounds.

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References and Notes

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6 All products were characterized by ^{1}H NMR, ^{13}C NMR, and MS spectroscopies.
7 A similar methylation underwent, when 9-anthracenyllithium was allowed to react with *O*,*O*′-dimethyl chlorophosphonate in place of *O*,*O*′-dimethyl chlorothiophosphonate. In contrast, the reaction of 2-naphthyllithium with *O*,*O*′-dimethyl chlorophosphonate gave *O*,*O*′-dimethyl 2-naphthylphosphonate (28% yield) and a mixture of tri(2-naphthyl)phosphine oxide and *O*-methyl di(2-naphthyl)phosphinate (95:5; 59% yield), which would be produced by the multiple nucleophilic attack of the aryllithium to the pentavalent phosphorus atom of *O*,*O*′-dimethyl chlorophosphonate. These results indicate that in the case of the reaction with *O*,*O*′-dimethyl chlorophosphonate, the nucleophilic attack of aryllithiums was strongly influenced not only by hard–soft acid–base combination but also by steric hindrance.

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