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# Selenophosphonates as building blocks for the preparation of bis-methylene analogs of triphosphates

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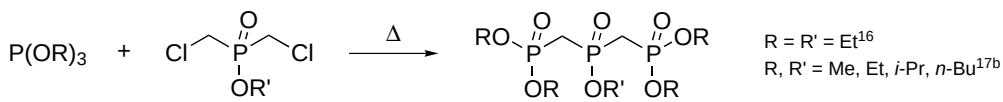
**Abstract**—A new route to bis-methylene analogs of triphosphate esters involving carbanion chemistry is described. Lithiated methaneselenophosphonate anion is condensed several times with chlorophosphites and phosphoramidous chlorides prior to esterification/transesterification and selenation or oxidation. 

Polyphosphates are key chemical species in living organisms. Nucleosides, dinucleosides, isoprenoids, vitamins and coenzymes, polyphosphates, nucleoside diphosphate sugars, etc. are some of the essential compounds for life incorporating one or more pyrophosphate moiety in their structure. The fine tuning of the activity of these substances results from the high sensitivity of the pyrophosphate bridge towards hydrolysis and nucleophilic displacement under physiological conditions. These reactions can occur spontaneously but most of the time they are enzymatically catalyzed. During recent decades much effort has been made to develop and design compounds able to specifically inhibit the enzymes involved in the metabolic pathway of polyphosphates.[1] A number of inhibitors are analogs of the substrate, incorporating structural changes within the polyphosphate chain (imidodiphosphates,[1d,2] thiophosphates,[3] methylene and halomethylene bisphosphonates[2e,4]). Even though they resist the enzymatic transformation, some of these compounds remain sensitive to chemical hydrolysis (imidodiphosphates, thiophosphates, pyrophosphonates). As far as it is concerned the methylene bis-phosphonate moiety is resistant to both enzymatic and chemical hydrolysis. Thus, the intrinsic stability of methylene-based analogs of polyphosphates makes them very interesting tools for investigating biological processes involving polyphosphates.

While a number of synthetic routes have been developed to prepare methylene analogs of diphosphates,[5–15] very few methodologies are available to prepare the bis-methylene analogs of triphosphates.[16–18] They all involve a double Michaelis–Arbuzov reaction between a bis-chloromethyl–phosphinic acid ester and trivalent phosphorus esters at high temperature. The pioneering studies by Shermergorn[16] and Maier[17] concern the preparation of bis(dialkyl-phosphonomethyl) phosphinic acid alkyl esters (Scheme 1).

The selective hydrolysis of one ester in these compounds is expected to be very difficult, if possible at all, and has not been described so far. Consequently, any modification of these molecules involves complete hydrolysis of the five esters prior to functionalization.[17b,19] An alternative route has been recently developed by Saady et al. who described the first use of tribenzyl phosphite in the Michaelis–Arbuzov reaction (Scheme 2).[18,20]




**Scheme 1.**

*Keywords*: triphosphate; methylene bisphosphonate; phosphonate; selenophosphonate; chlorophosphite; phosphoramidous chloride.
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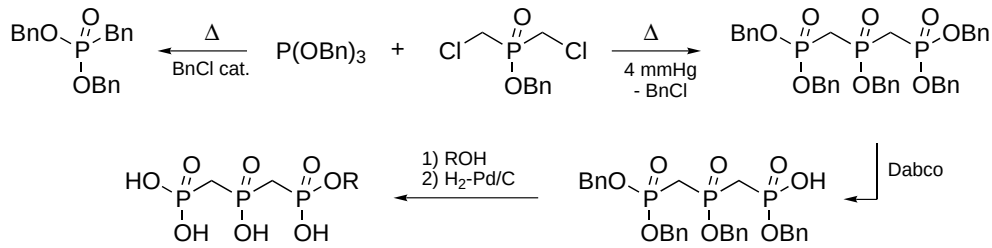



**Scheme 2.**

That strategy allows selective removal of one benzyl group prior to functionalization[21] and final debenzylation by hydrogenolysis.[22] The Michaelis–Arbuzov reaction, however, proves delicate to carry out as benzyl chloride formed in situ competes very efficiently with bis-chloromethylene phosphinate. It then autocatalytically reacts with the phosphite and quantitatively yields benzyl phosphonic acid dibenzyl ester if not removed quickly enough from the reaction mixture.

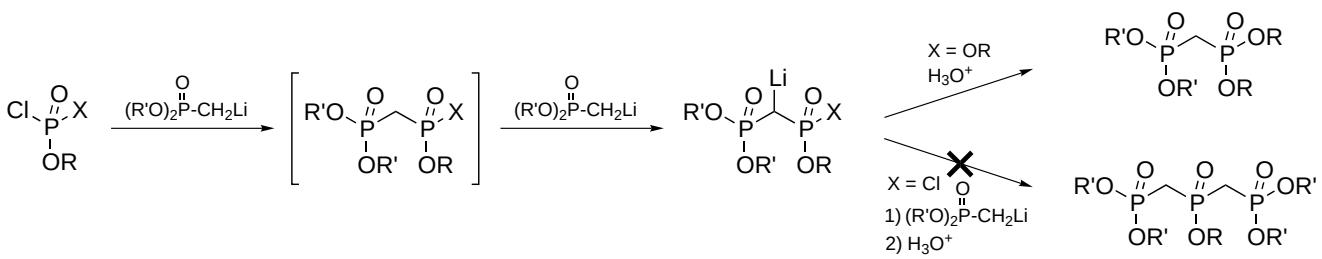
In order to carry out a more convenient and reproducible method for the preparation of the tittle compounds, we re-examined the chemistry of the methanephosphonate anion. Herein, we describe the synthesis of bis-methylene analogs of triphosphate using methaneselenophosphonates.

A major route in the preparation of methylene bisphosphonates involves the reaction between the anion of dialkyl methanephosphonate and a chlorophosphate (Scheme 3).[4c,23] The reaction sequence involves attack of the alkyllithium at the phosphorus center with expulsion of a chloride anion followed by deprotonation of the resulting methylene bis-phosphonate. The intermediate neutral bis-phosphonate is never observed in the reaction mixture and is regenerated upon aqueous work up. For that reason, the reaction cannot be extended to the preparation of triphosphate analogs. The deprotonation of the methylene group located between the two phosphorus atoms prevents any further attack of a second lithiated species and subsequent chloride displacement in the molecule.

As a typical class 'a' metal, lithium forms stable complexes with the P=O group.[24] The partial neutralization of the charge of the lithium cation through coordination with oxygen in P=O weakens the coulombic interaction between $Li^+$ and the negative carbon atom. Therefore, the latter is more basic and more reactive. In order to make possible a second alkylation reaction of the substrate, it is thus necessary to prevent the abstraction of a proton on the newly formed methylene bridge. This should be workable by lowering the basicity of the nucleophilic reagent. Considering that P=S species do not form stable complexes with $Li^+$,[25] we investigated the reactivity of the methanethiophosphonate anion and, in a wider sense, that of the methaneselenophosphonate anion in the course of the alkylation reaction with different phosphorus-containing substrates (Table 1).

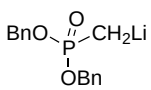
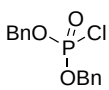
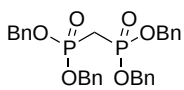
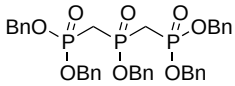
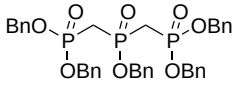
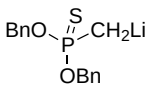
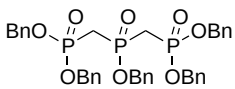
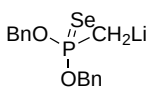
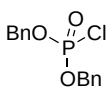
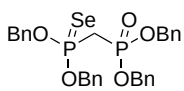
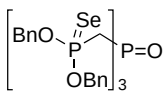
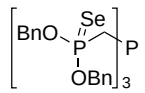
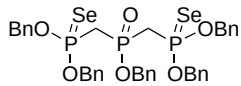
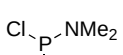
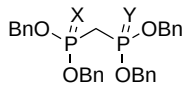
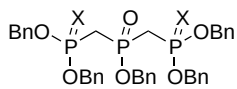
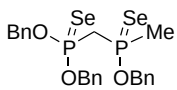
As expected, the reactivity of the selenophosphonate anion appears markedly decreased when compared to that of phosphonate and alkylation of the less reactive $P^V$ substrates proves unsuccessful (entries 1 and 5–6). Nevertheless, the more reactive $P^{III}$ substrates are alkylated (entries 7–14) in reasonable yields. On the other hand, in the case of polyfunctional substrates, second (entries 8, 12, and 13) and third (entry 7) alkylations indeed occur, which is definitely not the case with phosphonates (entries 2 and 3). In the particular case of phosphorus trichloride (entry 7), no product resulting from partial alkylation could be detected, indicating that the second and then third alkylations are likely to occur more easily than the first one.

In conclusion, we have described a new synthetic route to bis-methylene analogs of triphosphate esters involving carbanion chemistry. Whereas the transformation is not possible using methanephosphonate anions, two or three lithiated methanethiophosphonate and methaneselenophosphonate anions can condense with polyfunctional $P^{III}$ substrates, but not with less reactive $P^V$ compounds.




**Scheme 3.**

**Table 1.**

| Entry | Anion | Substrate | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  |  |  | 50[a] |
| 2 | |  |  | 0[b] |
| 3 | |  |  | 0[b,c] |
| 4 |  |  |  | 36[b,c] |
| 5 |  |  |  | 0[d] |
| 6 | |  |  | 0[e] |
| 7 | |  |  | 32[a] |
| 8 | |  |  | 23[f] |
| 9 | |  |  | X = Se, Y = Se : 69[c,g] |
| 10 | | | | X = Se, Y = O : 35[c,h] |
| 11 | | | | X = O, Y = O : 38[b,c] |
| 12 | |  |  | X = Se : 41[c,g,h] |
| 13 | | | | X = O : 37[b,c] |
| 14 | |  |  | 19[g] |

[a]Stoichiometric amounts of anion and substrate were used. [b]Oxidation was achieved using *m*CPBA. [c]Dimethylamino groups were displaced by heating with benzyl alcohol prior to oxidation or selenation. [d]Dibenzyl methaneselenophosphonate was quantitatively recovered after aqueous work up. [e]Dibenzyl chloromethaneselenophosphonate was isolated in 50% yield.[26] [f]Oxidation was achieved using DMSO. [g]Selenation was achieved with selenium dust. [h]Oxidation was achieved using *t*-butyl hydroperoxide.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