A New and Convenient Method for the Preparation of Functionalized Phosphorothioates

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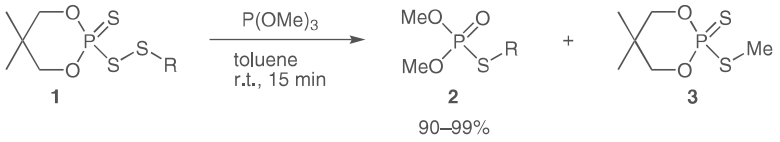
Abstract: A new and efficient method for the synthesis of alkyl and aryl phosphorothioates in high yields via the reaction of (5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorin-2-yl)disulfanyl derivatives with trimethyl phosphite is described.

Key words: phosphorothioates, trimethyl phosphite, Arbuzov reaction, thiols, L-cysteine



R = $(CH_2)_{11}Me$, Ph, 4-$MeOC_6H_4$, $(CH_2)_{11}OH$, $(CH_2)_{11}NHBoc$, $(CH_2)_{10}CO_2H$, $(CH_2)_{10}CO_2Me$, (*R*)-$CH_2CH(NHBoc)CO_2Et$

Scheme 1 Synthesis of functionalized phosphorothioates **2** and by-products **3**

Organophosphorus compounds play a significant role in many areas of chemistry.[1] Among these, phosphate esters are very useful substrates for the preparation of biologically active molecules,[2] and therefore are important targets in modern organic synthesis. Previous research has focused on phosphorothioate derivatives and their biological applications.[3] Reported methods for the preparation of phosphorothioate derivatives include reactions of trialkyl phosphites with thiols,[4] disulfides,[5] sulfenyl chlorides,[6] thiosuccinimides,[7] thiophthalimides,[7] and dialkyl or diaryl phosphites with disulfides.[8] Dinucleoside H-phosphonates react with *N*-phenylthio- and *N*-benzylthiosuccinimides[9] to provide the corresponding phosphorothioates. Rearrangements of organophosphorus thiono esters catalyzed by alkyl halides,[10a] Lewis acids,[10b] protic acids[10c] and palladium[10d] also lead to phosphorothioates. Furthermore, reactions of phosphorothioic acid with alcohols[11a,b] and ethers[11a] have been reported for the synthesis of phosphorothioates.

Most of the above methods, besides those of phosphorus and sulfur atom donors, require additional reagents or catalysts and they are applicable for the synthesis of alkyl or aryl phosphorothioates without additional functional groups.

We previously demonstrated various synthetic applications of readily available 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1**[12] leading to unsymmetrical molecules such as dialkyl disulfides,[13] alkyl–aryl disulfides,[13] 'bioresistant' disulfides,[14] unsymmetrical disulfides based on L-cysteine and L-cystine derivatives,[15] and diaryl disulfides.[16] We also developed methods for the synthesis of symmetrical trisulfides[12] and unsymmetrical alkyl trisulfides.[17]

Herein, we report a novel method for the preparation of functionalized phosphorothioates. We found that treatment of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinane-2-disulfanyl derivatives **1a–h** with trimethyl phosphite led to the corresponding functionalized phosphorothioates **2a–h** in excellent yields after purification (Scheme 1 and Table 1). The presence of electron-withdrawing and electron-donating groups or unprotected hydroxy and carboxy groups did not affect the formation of the products.

Isolation of the by-product, 5,5-dimethyl-2-(methylthio)-1,3,2-dioxaphosphinane 2-oxide (**3**) suggests an Arbuzov-type mechanistic pathway (Scheme 2). The phosphorodithioate **3** was unreactive and did not influence the formation or impact on the separation of functionalized phosphorothioates **2**.

We found that steric hindrance was an important factor influencing the reaction outcome and formation of the products. Reactions of trityl and *tert*-butyl disulfanyl derivatives **1i** and **1j** with trimethyl phosphite did not lead to the expected phosphorothioates. Starting materials **1i** and **1j** were recovered after stirring the reaction mixture for 24 hours at room temperature. When the reaction was

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