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Alkylthio-Fluoro-and Difluoromethylphosphonates: Synthesis and Reactivity

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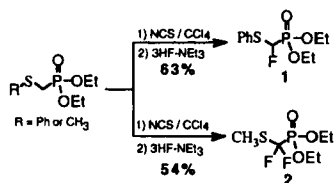
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Alkylthio-Fluoro-and Difluoromethylphosphonates : Synthesis and Reactivity

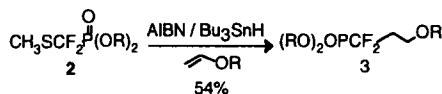
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The mimicry of reactive phosphate esters has become an established in the design of biologically-active compounds. Fluoromethylene and difluoromethylene-phosphonates have been prepared as non hydrolysable analogues of nucleosides or phosphoamino-acids. We have attempted to explore a new alternative approach using free radical chemistry from alkylthiofluoromethylphosphonate **1** and alkylthiodifluoromethylphosphonate **2**. We first developed a new preparation of fluorinated alkylthiophosphonate esters using electrophilic and nucleophilic fluorine sources. Using N-fluorobenzenesulfonimide **1** could be obtained in moderate yield (@40%). On the other hand Selectfluor™ allowed to obtain the difluoromethylphosphonate **2** but in relatively low yield (@10%). Using nucleophilic fluorine source¹ (3HF-NEt₃) we showed that phosphonate **1** and **2** could be obtained selectively from chloro- and dichloromethylphosphonate esters. By this way, diethyl alkylsulfanyl- fluoromethylphosphonate **1** and difluoromethylphosphonate **2** were respectively synthesized in 63% and 54% yields.



Using the strategy developed by Balczewski *et al.*², difluoromethylphosphonyl radical could be generated from **2**. Its electrophilic character allowed to trape it only with electron-rich alkenes. By this way, 3-alkoxy-1,1-difluoropropylphosphonate **3** were obtained in 54% yields.



References

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- [2] P. Balczewski, W.M. Pietrzykowski, *Tetrahedron* **1996**, *53*, 7291-7304.