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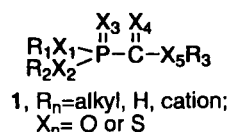
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The Preparation of Sulfur-Containing Phosphonoformate Derivatives

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Thio derivatives of organophosphorus compounds have long been of interest to chemists, not least because these compounds can be useful in agriculture or medicine, as well as in synthesis.^[1] The replacement in a phosphate, phosphonate or phosphinate molecule of one or more oxygen atoms by sulfur may lead to significant alteration in biological activity or related properties. One example is thiophosphonoformate (TPFA), a mono-sulfur analogue of the anti-viral agent phosphonoformic acid (PFA).^[2] As a class,



the sulfur-containing phosphonoformate derivatives **1** have received relatively little attention in the literature, although particular examples (chiefly triesters) have been made and shown to possess a range of useful applications in synthetic chemistry.^[3] Simple semi-empirical calculations of ΔH_f for a sampling of **1** (R_n = Me) predict an overall trend of decreasing stability as S replaces O, particularly when ΣS ≥ 3. Thus focused on the less thionated **1** trimethyl esters, we have compared synthesis of three (of four possible) mono-S structural isomers (X₁, X₄ or X₅ = S); three (of seven possible) di-S isomers (X_{3,4}, X_{3,5} or X_{4,5} = S); and one (seven possible) tri-S isomer (X_{3,4,5} = S). Also prepared were several mono-S (X₂, X₄ or X₅ = S), di-S (X_{2,4}, X_{2,5} or X_{4,5} = S) and tri-S (X_{2,4,5} = S) P,C-dimethyl esters of **1** (R_{2,3} = Me, R₁ = Na). It should be noted that NaI monodealkylation of trimethyl esters of **1** where X₃ = S invariably proceeded with an (RO)P=S → (RS)P=O rearrangement. All compounds were characterized by NMR (¹H, ¹³C and ³¹P) and by HRMS or combustion analysis.

Acknowledgments

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