N,S-Bridging Thiophosphoramidates: Synthesis and Reactivity

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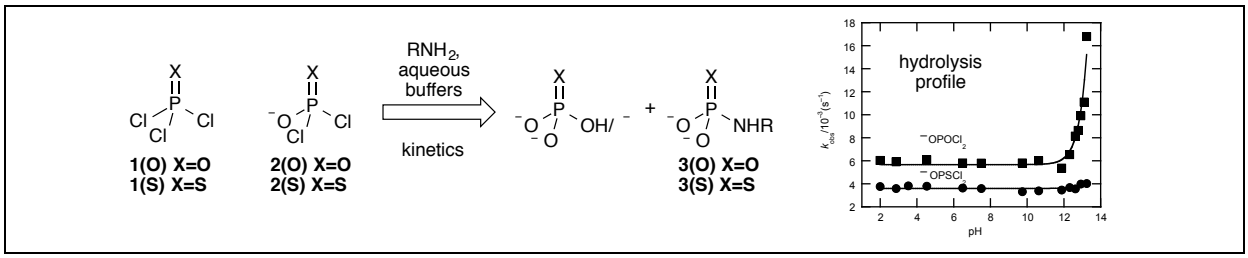
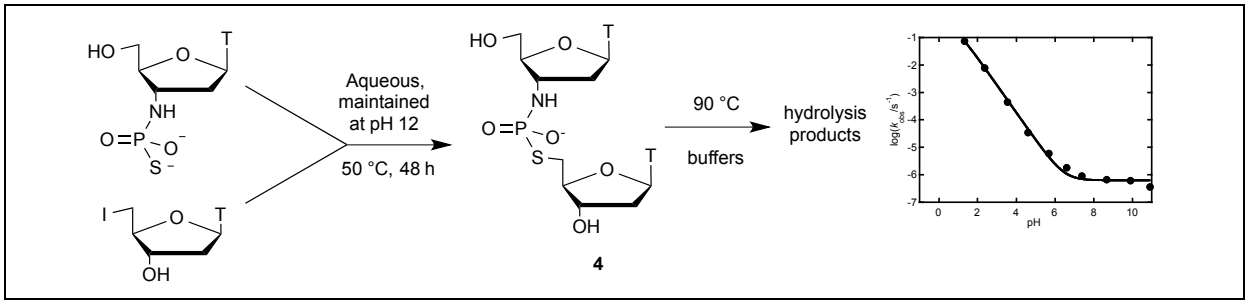
Phosphate analogues support mechanistic studies and biotechnologies such as nucleic acid ligation. We have prepared (thio)phosphoramidates **3** by reacting amines in aqueous media with $POCl_3$ **1(O)**, $PSCl_3$ **1(S)**, phosphodichloridate ion **2(O)** and thiophosphodichloridate ion **2(S)**.[1] Our kinetic and theoretical studies show that phosphodichloridate **1(O)** and thiophosphodichloridate **2(S)** ions discriminate significantly against hydroxide ion compared to water as a nucleophile.[2]



To explore the potential of thiophosphoramidate ions **3(S)** in ligations, we prepared dinuclotide analogue **4** through *S*-alkylation, and studied its stability towards hydrolysis. The pH-log k_{obs} profile of analogue **4** at 90 °C revealed a half-life of ~13 days between pH 7-10. Acid-promoted hydrolysis was evident at lower pHs.



(1) (a) Trmčić, M.; Hodgson, D. R. W. *Chem. Commun.* **2011**, *47*, 6156-6158. (b) Conway, L. P.; Delley, R. J.; Neville, J.; Freeman, G. R.; Maple, H. J.; Chan, V.; Hall, A. J.; Hodgson, D. R. W. *RSC Advances* **2014**, *4*, 38663-38671.

(2) (a) Delley, R. J.; O'Donoghue, A. C.; Hodgson, D. R. W. *J. Org. Chem.* **2012**, *77*, 5829–5831. (b) Carvalho, A.; O'Donoghue, A. C.; Hodgson, D. R. W.; Kamerlin, S. C. L. *Organic and Biomolecular Chemistry* **2015**, 10.1039/C1035OB00309A.