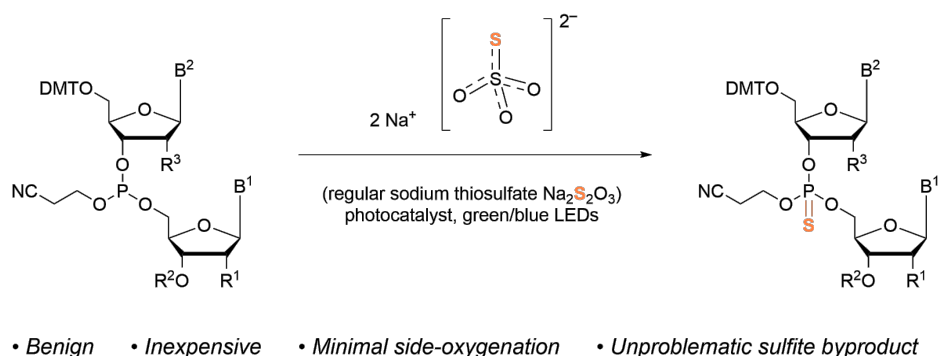


Synthesis of phosphorothioates by sulfur transfer from thiosulfate

Anton Budeev, Corentin Bon, Christof Sparr

Department of Chemistry, University of Basel, St. Johannis-Ring 19, Basel, Switzerland
anton.budeev@unibas.ch

With therapeutic oligonucleotides progressing from the treatment of rare genetic diseases to medications for common disorders, the synthesis of modified oligonucleotides is gaining significant momentum. To improve pharmacokinetic and pharmacodynamic properties, chemical modifications to the nucleotide backbone have thereby been particularly advantageous. Since Eckstein's pioneering discovery in 1966,¹ the phosphorothioate linkage has become the most useful oligonucleotide modification. Compared to phosphate, phosphorothioate is more resistant to cleavage by nucleases, resulting in improved elimination half-life of DNA or RNA sequence, extending from minutes to days. Moreover, the introduction of this moiety increases binding to serum proteins, amplifying the time available for uptake into target tissues.² This moiety can be found in 9 FDA-approved oligonucleotides.³



However, common reagents used for the sulfuration of phosphorothioate oligonucleotides have several disadvantages, including toxicity, cost- and atom-inefficiency, and compromised stability, underscoring the need for alternative sulfuration protocols. In this work, we developed a more sustainable, mild and general methodology for photocatalytic sulfuration to prepare phosphorothioates using regular thiosulfate as a benign sulfur source. Additionally, the protocol is switchable to oxygenation for the synthesis of phosphates by implementing aerobic reaction conditions. More importantly, the protocol was integrated into standard solid-phase phosphoramidite oligonucleotide synthesis using riboflavin (vitamin B2) as a photocatalyst in water. A variant of the reaction without the need of light irradiation was also developed. We believe the method represents a cost-efficient and sustainable means for the synthesis of DNA and RNA phosphorothioates and phosphates.⁴

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