Photocatalytic sulfur transfer enables the synthesis of phosphorothioate oligonucleotides

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With therapeutic oligonucleotides progressing from the treatment of rare genetic diseases to medications of 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 sulfurisation of phosphorothioate oligonucleotides have several disadvantages, including toxicity, cost- and atom-inefficiency, and compromised stability, underscoring the need for alternative sulfurisation protocols. In this work, we therefore developed a more sustainable, mild and general methodology for the photocatalytic sulfurisation to prepare phosphorothioates using regular thiosulfate as a benign sulfur source. Furthermore, the method was applied to standard solid-phase phosphoramidite oligonucleotide synthesis in pure water using riboflavin (vitamin B2) as photocatalyst, representing a sustainable alternative to existing sulfurisation methods.

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[2] Crooke S. T., Witztum J. L., Bennett C. F., Baker B. F. *Cell Metabolism* **2018** 27, 714-739.
[3] Obexer R., Nassir M., Moody E. R., Baran P. S., Lovelock S. L. *Science* **2024**, 384, eadl4015.