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Synthesis of 3'-Thioribouridine, 3'-Thioribocytidine, and Their Phosphoramidites

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SYNTHESIS OF 3'-THIORIBOURIDINE, 3'-THIO-RIBOCYTIDINE, AND THEIR PHOSPHORAMIDITES

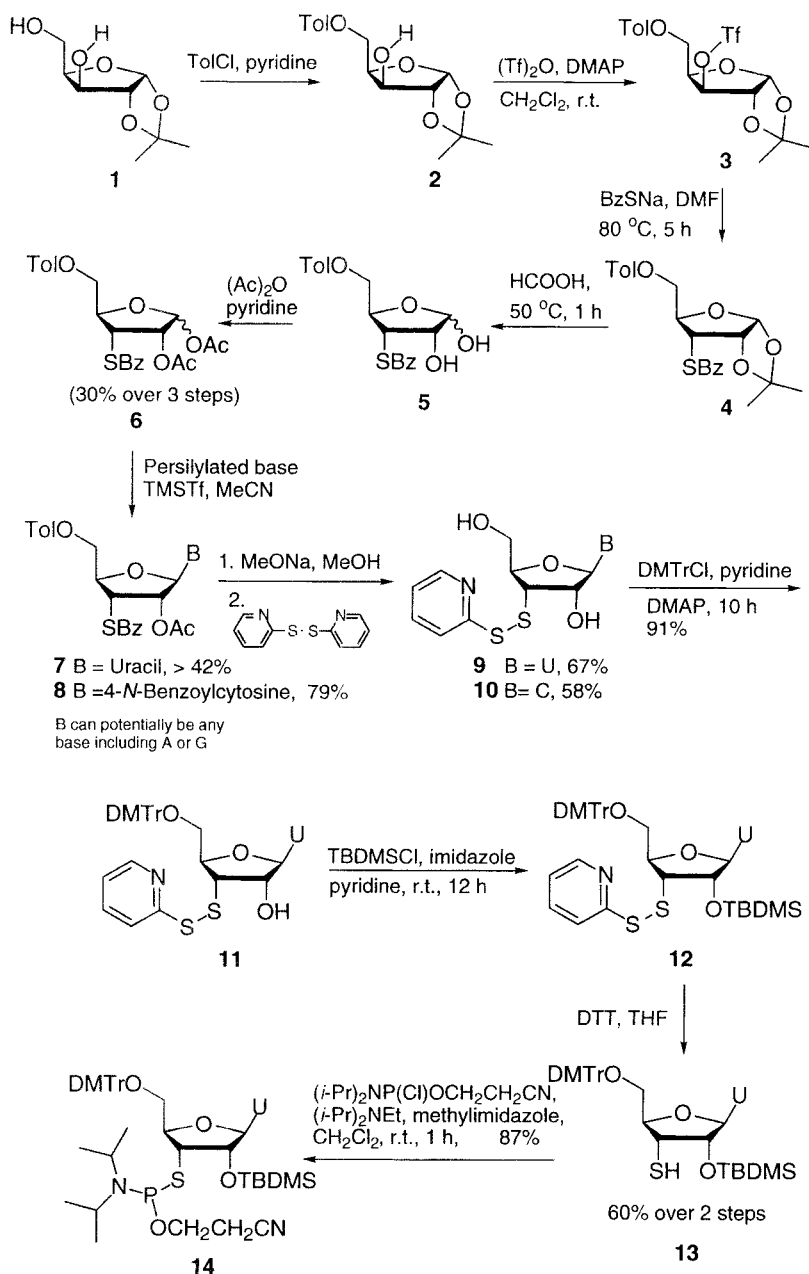
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ABSTRACT: 3'-Thio-3'-deoxyribonucleosides (U and C) have been synthesized *via* Vorbruggen-type glycosylation with 3-*S*-benzoyl-5-*O*-toluoyl-1,2-*O*-diacetylfuranose, which was obtained from 1,2-*O*-isopropylidene-5-*O*-toluoyl-3-*O*-trifluoromethanesulfonyl- α -D-xylofuranose. 3'-Thio-3'-deoxyuridine has been converted to its phosphoramidite.

3'-Thionucleosides have proven useful as mechanistic probes in phosphoryl transfer reactions in both protein enzymes¹ and ribozymes.² However, studies have been restricted to 2'-deoxy versions of these molecules. The 3'-thiol derivatives of adenosine^{3,4} and uridine⁵ have been previously reported, but not get incorporated into oligonucleotides by solid phase synthesis.

We have recently synthesized 3'-thio-3'-deoxyriboinosine and incorporated it at the 3'-splice site of a nuclear premessenger RNA *via* phosphoramidite chemistry followed by enzymatic ligation.⁶ Our interest in the mechanism of catalysis of RNA-mediated phosphoryl transfer reactions inspired us to develop a general procedure to access efficiently any of the 3'-thioribonucleoside analogs and their phosphoramidites (Scheme 1). The commercially available 1,2-*O*-isopropylidene- α -D-xylofuranose was transformed to 1,2-*O*-isopropylidene-5-*O*-toluoyl-3-*O*-trifluoromethanesulfonyl- α -D-xylofuranose.^{7,8} The triflate group was easily displaced by thiobenzoate to give the 3-*S*-benoylfuranose derivative. Removal of the isopropylidene group followed by acetylation gave a product **6**, which was used successfully in Vorbruggen-type reactions to glycosylate uridine and 4-*N*-benzoylcytosine. Removal of the acyl protecting groups followed by protection of the sulfhydryl as the pyridyl disulfide allowed 5'-dimethoxytritylation and 3'-silylation. Reduction of the disulfide followed by phosphitylation gave the phosphoramidite in very good yield.⁹



SCHEME 1

In conclusion, we have developed a useful procedure to synthesize 3'-thioribonucleosides. We are working to extend the procedure to prepare the corresponding guanosine and cytidine analogs.

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9. Every new compound was characterized by ^1H - and ^{13}C -NMR, and either a satisfactory molecular weight from high resolution mass spectrometry or a satisfactory elemental analysis was obtained. For the final thiouridine phosphoramidite **14**, ^{31}P -NMR (90 MHz, in CDCl_3 , using 85% H_3PO_4 as external standard): $\delta = 168.6, 157.4$; Anal. calcd for $\text{C}_{45}\text{H}_{61}\text{N}_4\text{O}_8\text{PSSi}$: C, 61.64; H, 6.96; N, 6.39; S, 3.65. Found: : C, 61.38; H, 6.95; N, 6.62; S, 3.49.