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Four Step Synthesis of a 5'-Deoxy-5'-iodomethylthymidine

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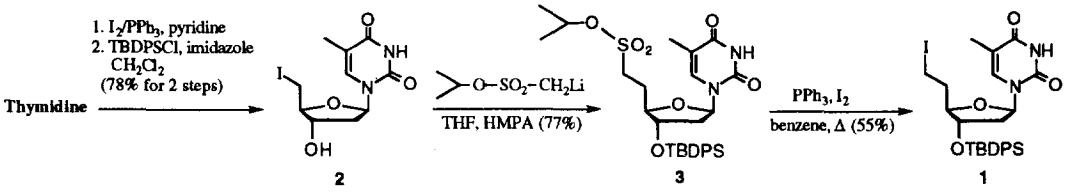
Abstract: The conversion of an alkylsulfonate to an iodide with triphenylphosphine/iodine in benzene has been performed for a nucleoside. Starting from thymidine, 3'-protected 5'-deoxy-5'-iodomethylthymidine was synthesized in 4 steps.

Modified nucleic acids are important biochemical and biomedical tools.[1] In oligonucleotides, the replacement of atoms of the phosphodiester linkage is one way of conferring hydrolytic stability and/or electrostatic neutrality, two properties believed to be advantageous for bioavailability.[2] While building blocks bearing heteroatoms at the 3'- and 5'-position are mostly accessible from natural nucleosides by functional group interconversions, the extension of the carbon backbone to homonucleosidic structures can be more challenging[3] and often necessitates target molecule assembly from modified sugars and nucleobases.[4]

In the course of our work on sulfone-linked oligonucleotides, a 3'-protected 5'-homonucleoside with a 6'-leaving group was needed as one of the two nucleoside precursors for incorporation of dimethylenesulfone linkages in natural DNA. 6'-Halonucleosides such as **1** (Scheme 1) were the preferred target molecules.[5]



Scheme 1

At the outset of our study, the nine-step synthesis of the base-protected bromo-derivative of **1**[6] had not yet been published. Other methods for the preparation of 5'-homonucleosides appeared either too laborious (>10 steps),[7] lead to nucleosides with 6'-functional groups with no obvious interconversion to leaving groups,[8] or to ribonucleosides[9] necessitating 2'-deoxygenations that were low yielding in our hands. Hydrogenation of a 6'-bromo-5',6'-didehydro-derivative of **1**[10] failed. We attempted homologization of 3'-silylated 5'-iodothymidine **2**[11] via its 5'-isopropoxydimethylsilylmethyl derivative, oxidative hydrolysis, and iodination under conditions described for terpenoids.[12] The low reactivity of the 5'-iodothymidine made this route unsuccessful. Analogous 5'-bromo- and 5'-chloro-thymidines suffered from the same drawback.

Sulfonate ester **3**[11] proved to be a useful intermediate in the synthesis of target molecule **1**. Under the conditions described for hydrocarbon substrates by Oae and Togo[13] **1** was obtained from **3** in acceptable yield. Interestingly, the sulfonate to iodide conversion, for which a mechanism has been proposed,[14] was unsuccessful in pyridine and acetonitrile and low yielding in toluene and THF. Further, the desired conversion occurred only in the presence of a precipitate (most probably $[PPh_3I]^+ I^-$) and the yield increased when as the solvent volume decreased. If full dissolution of the reagent was observed, the conversion stopped, indicating that the reaction may require the surface of the precipitate. Under the chosen conditions,[15] iodide **1** was isolated in 55% isolated yield on a 0.5 g scale. Higher yields based on recovered starting material were obtained when the reaction was stopped prior to full conversion of the educt. Building block **1** thus obtained was successfully incorporated in sulfone bridged oligonucleotides[16] and may in the future be used for other modified nucleic acids.[6,3]

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