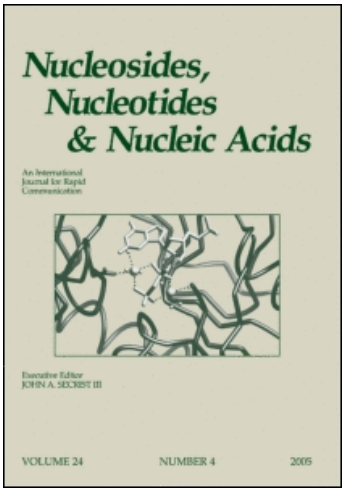

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A New *H*-Phosphonate Approach Using *N*-Unprotected Monomers and Phosphonium Condensing Reagents

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A NEW *H*-PHOSPHONATE APPROACH USING *N*-UNPROTECTED MONOMERS AND PHOSPHONIUM CONDENSING REAGENTS

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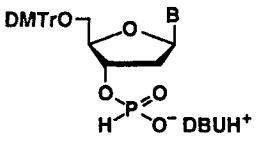
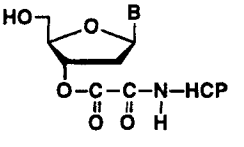
ABSTRACT: Oligodexyribonucleotides were synthesized by using *N*-unprotected *H*-phosphonate monomers and a phosphonium-type of new condensing reagent. In the present *H*-phosphonate approach, *N*-sulfonyloxaziridine derivatives were successfully employed as new reagents for oxidation of the *H*-phosphonate linkages in the presence of silylating reagents.

N-Protected *H*-phosphonate oligodeoxyribonucleotides have been used as versatile intermediates for the synthesis of DNA and a wide variety of backbone-modified DNA analogs. However, highly base-sensitive DNA analogs, which readily decompose under basic conditions prescribed for removal of the *N*-protecting groups, could not be synthesized with such protection modes. In this paper, we report a new *H*-phosphonate approach involving *O*-selective condensation using *N*-unprotected monomers (**1a**, **1c**, and **1g**), *N*-unprotected nucleosides anchored to a polymer support (**2a**, **2c**, and **2g**), and a phosphonium-type of new condensing reagent (SCHEME 1).[1-3] A new method for oxidation of *H*-phosphonate derivatives under anhydrous conditions using *N*-sulfonyloxaziridines will also be described.

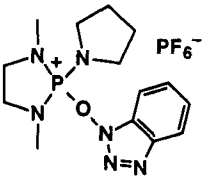
SCHEME 1



1a: B = Ad
1c: B = Cy
1g: B = Gu
1 t: B = Th



2a,c,g,t
HCP = highly cross-linked polystyrene



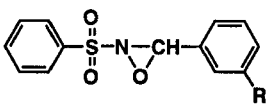
BOMP

The *H*-phosphonate monomers having the free amino groups (**1a**, **1c**, and **1g**) were synthesized in high yields by using diphenyl phosphonate[4] as an *O*-selective phosphonylating reagent. In contrast, trivalent phosphorus reagents commonly used for the synthesis of *H*-phosphonate monomers were found to react with the free amino groups of nucleosides.

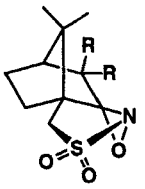
We have investigated several condensing reagents for *O*-selective internucleotidic bond formation. After extensive screening, we ultimately found that a benzotriazol-1-yl-oxy-carbonium or phosphonium condensing reagent and the activated monomers produced by these reagents did not affect the amino groups of nucleosides. The most effective condensing reagent for rapid internucleotidic bond formation was found to be BOMP (SCHEME 1).

During the oxidation of *H*-phosphonate linkages using aqueous I_2, the internucleotidic linkages are partially hydrolyzed to decrease the yield of oligomers. Therefore, a new oxidation method under anhydrous conditions should be explored. It was found that *N*-sulfonyloxaziridine derivatives found to be highly effective for the oxidation of *H*-phosphonate linkages in the presence of silylating reagents (SCHEME 2). The reaction proceeded *via* the trimethylsilyl phosphite intermediates and usually completed within 5 min. A new silylating reagent *N,O*-bis(trimethylsilyl)benzamide (BSB) found to be more reactive than BSA.[3]

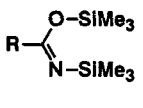
SCHEME 2



PPO: R = H
PNO: R = NO_2



CSO: R = H
DCSO: R = Cl



BSA: R = Me
BSB: R = Ph

The new condensation and oxidation methods were successfully applied to the solid-phase synthesis. The *N*-unprotected nucleosides anchored to the highly cross-linked polystyrene *via* an oxalyl linker (**2a**, **2c**, and **2g**) were used as the starting materials.[2] Oligodeoxyribonucleotides were synthesized in good yields and no base modifications were detected by the enzymatic characterization of the products.

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