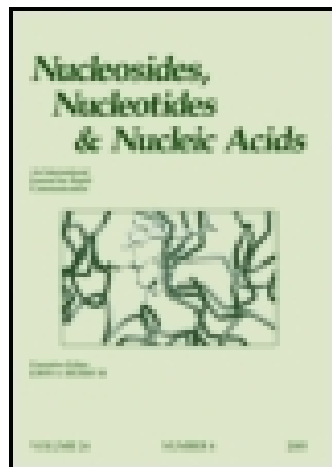




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Synthesis of 9-Fluorenemethyl Boranophosphonodiphosphate Via an H-Phosphonate Approach

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SYNTHESIS OF 9-FLUORENEMETHYL BORANOPHOSPHONO-DIPHOSPHATE VIA AN H-PHOSPHONATE APPROACH

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□ *9-Fluorenemethyl boranophosphonate 6 and its boranophosphonodiphosphate 7 were synthesized via an H-phosphonate approach. The method is efficient for the synthesis of acyclic compounds 6 & 7, and can be explored for the synthesis of nucleoside 5'-deoxy boranophosphonodiphosphate.*

Keywords Boranophosphonate; boranophosphonodiphosphate; antiviral; H-phosphonate; triphosphate analogues

INTRODUCTION

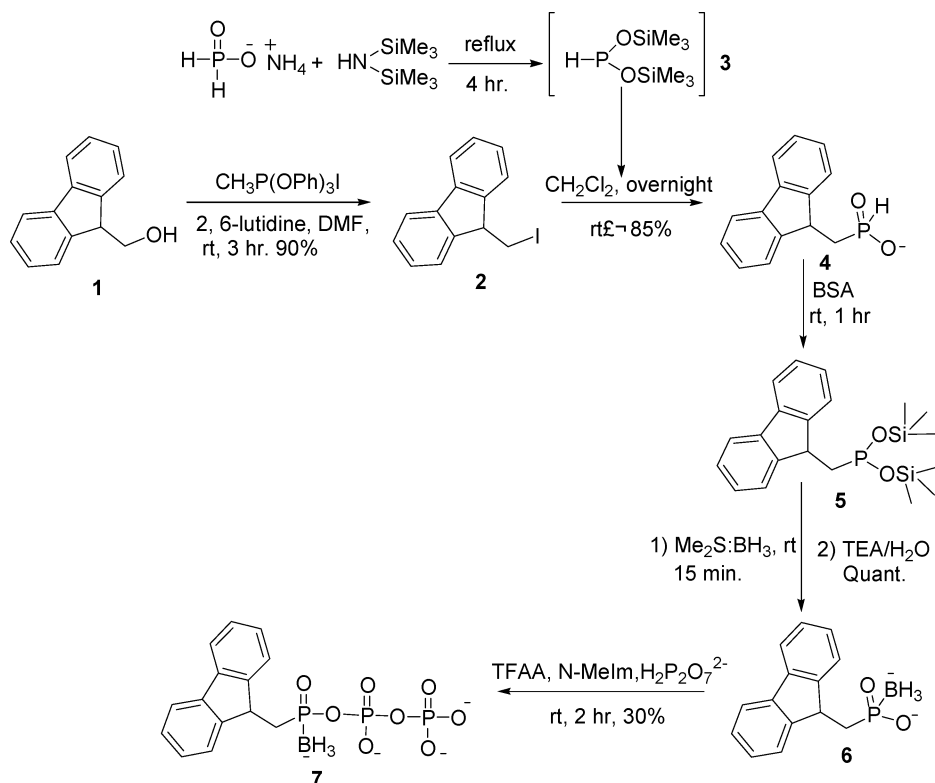
Phosphonate nucleoside analogues were first synthesized by A. Burger.^[1] Since then, numerous synthetic approaches and biological applications have been reported for various nucleoside phosphonates. Potent antiviral activity (HSV, CMV, HBV, HIV) has been associated with phosphonoalkylnucleobases, e.g., 9-[3-hydroxy-2-(phosphonylmethoxy)propyl]adenine (HPMPA) and 9-[2-(phosphonylmethoxy)ethyl]adenine (PMEA).^[2] The acyclic analogues possess a broad-spectrum anti-HSV activity and a potent anti-HIV activity, respectively. More recently, borane substitution of one of the non-bridging oxygens in a phosphate diester linkage has been shown to improve substrate properties, increase lipophilicity, and increase nuclease resistance compared to normal nucleotide diesters.^[3] Studies show that the presence of a BH₃ group at the α -phosphate position of di- and triphosphates of clinically relevant dideoxy compounds, such as AZT, d4T, and ddA, improves both phosphorylation by nucleoside diphosphate kinase and incorporation by wild-type and mutant HIV-1 reverse transcriptase (RT).^[4] Moreover, after a boranophosphate is incorporated into a DNA chain, repair of the blocked DNA chains by pyrophosphorolysis is reduced significantly with mutant RT enzymes from drug-resistant viruses.

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It, thus, is worthwhile to combine the borane with the phosphonate modification to study their antiviral properties. To our knowledge, no method has been reported for synthesis of a boranophosphonodiphosphate. Here we present the synthesis of a model compound, 9-fluorenemethyl boranophosphonodiphosphate **7**, via a modified H-phosphonate approach (Scheme 1).

As shown in Scheme 1, the commercially available 9-fluorenemethanol was reacted with methyltriphenoxyphosphonium iodide in the presence of 2,6-lutidine to give 9-fluorenemethyl iodide **2** in 90% yield. The iodide was then treated with bis(trimethylsilyl)phosphonite (BTSP) **3**^[5] (prepared by refluxing the mixture of ammonium phosphinite and hexamethyldisilazane under argon) to obtain 9-fluorenemethyl H-phosphonate **4** in 85% yield. Subsequent silylation, boronation, and hydrolysis gave 9-fluorenemethyl boranophosphonate **6** in quantitative yield.^[6] In the presence of trifluoroacetic anhydride and *N*-methylimidazole, 9-fluorenemethyl boranophosphonate **6** was further phosphorylated by tributylammonium pyrophosphate to give 9-fluorenemethyl boranophosphonodiphosphate **7** in 30% yield.^[7]



SCHEME 1 Synthesis of 9-fluorenemethyl boranophosphonate **6** and boranophosphonodiphosphate **7**.

In conclusion, a modified H-phosphonate approach was applied to synthesize the first fluorescent-labeled boranophosphonate compound, **6**, in good yield. It was further pyrophosphorylated to 9-fluorenemethyl boranophosphonodiphosphate **7**. This method is being explored to make cyclic and acyclic nucleoside boranophosphonodiphosphate compounds as triphosphate analogues.

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6. Compound **6**: ^1H NMR (D_2O) δ 7.65–7.23 (m, 8H, Ph), 4.12 (m, 1H, H-9), 1.96 (m, 2H, CH_2), (+)0.62(–)0.03 (br, 3H, BH_3); ^{31}P NMR (D_2O) δ 100.60 (br, 1P); LC-MS m/z 257.0, calcd for $\text{C}_{14}\text{H}_{14}\text{BO}_2\text{P}^-$ (M^-): 257.09.
7. Compound **7**: ^{31}P NMR (D_2O) δ 115.60 (br, 1P, P- α), -9.95 (s, 1P, P- γ), -20.23 (s, 1P, P- β); LC-MS m/z 416.6, calcd for $\text{C}_{14}\text{H}_{17}\text{BO}_8\text{P}_3^-$ (M^-): 417.02.