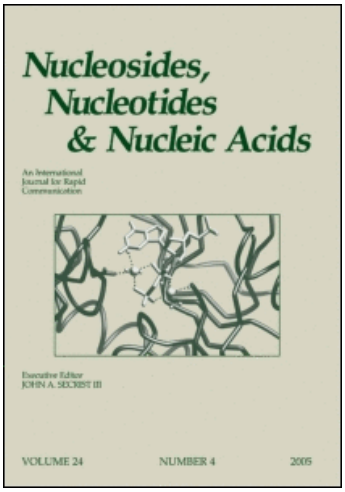



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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

Hongyan Liu[a]; Syed N. Hashmi[a]; Barbara Ramsay Shaw[a]
[a] Department of Chemistry, Duke University, Durham, North Carolina, USA

**To cite this Article** Liu, Hongyan , Hashmi, Syed N. and Shaw, Barbara Ramsay(2007) 'Synthesis of 9-Fluorenemethyl Boranophosphonodiphosphate Via an H-Phosphonate Approach', Nucleosides, Nucleotides and Nucleic Acids, 26: 10, 1455 — 1457
**To link to this Article: DOI:** 10.1080/15257770701542413
**URL:** http://dx.doi.org/10.1080/15257770701542413

*Nucleosides, Nucleotides, and Nucleic Acids*, 26:1455–1457, 2007

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770701542413

Taylor & Francis
Taylor & Francis Group

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

**Hongyan Liu, Syed N. Hashmi, and Barbara Ramsay Shaw** □ *Department of Chemistry, Duke University, Durham, North Carolina, USA*

□ *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 $BH_3$ group at the $\alpha$-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.

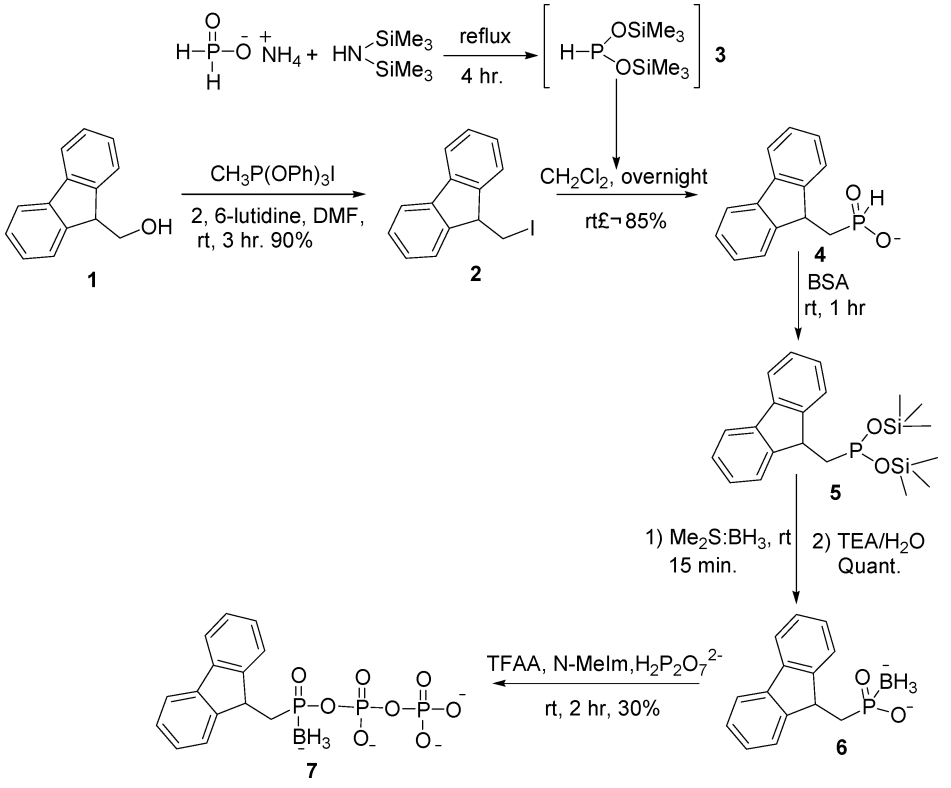
This research was supported by NIH grant GM-57693 to B.R.S. We thank Dr. Ping Li and Dr. Shoeb I. Khan for helpful discussion.

Address correspondence to Barbara Ramsay Shaw, Department of Chemistry, Duke University, Durham, NC 27708, USA. E-mail: brshaw@chem.duke.edu

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 phosphinate 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.

## REFERENCES

1. Parikh, J.R.; Wolff, M.E.; Burger, A. Analogs of nucleotides. II. phosphonate esters of ribose and glucopyranosyl purine derivatives. *J. Am. Chem. Soc.* **1957**, 79, 2778–2781.
2. De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C. A novel selective broad-spectrum anti-DNA virus agent. *Nature* **1986**, 323, 464–467.
3. Shaw, B.R.; Sergueev, D.; He, K.; Porter; K., Summers, J.; Sergueeva, Z.; Rait, V. Boranophosphate backbone: a mimic of phosphodiesters, phosphorothioates, and methylphosphonates. *Methods in Enzymology: Antisense Technology* **1999**, 313, 226–257.
4. Meyer, P.; Schneider, B.; Sarfati, S.; Deville-Bonne, D.; Guerreiro, C.; Boretto, J.; Janin, J.; Veron, M.; Canard, B. Structural basis for activation of alpha-boranophosphate nucleotide analogues targeting drug-resistant reverse transcriptase. *EMBO J.* **2000**, 19, 3520–3529.
5. An, H.; Wang, T.; Maier, M.A.; Manoharan, M.; Ross, B.S.; Cook, P.D.. Synthesis of novel 3′-*C*-methylene thymidine and 5-methyluridine/cytidine H-phosphonates and phosphonamidites for new backbone modification of oligonucleotides. *J. Org. Chem.* **2001**, 66, 2789–2801.
6. Compound **6**: $^{1}$H NMR ($D_2O$) $\delta$ 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 ($D_2O$) $\delta$ 100.60 (br, 1P); LC-MS m/z 257.0, calcd for $C_{14}H_{14}BO_2P^-$ ($M^-$): 257.09.
7. Compound **7**: $^{31}$P NMR ($D_2O$) $\delta$ 115.60 (br, 1P, P-$\alpha$), -9.95 (s, 1P, P-$\gamma$), -20.23 (s, 1P, P-$\beta$); LC-MS m/z 416.6, calcd for $C_{14}H_{17}BO_8P_3^-$ ($M^-$): 417.02.