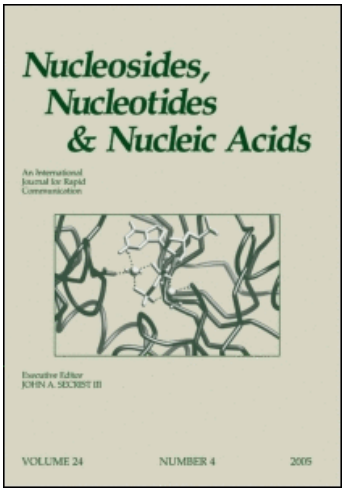

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EFFICIENT SYNTHESIS OF THYMIDINE BORANOPHOSPHORAMIDATES CONJUGATED WITH AMINO ACIDS

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□ *An efficient synthesis of a thymidine boranophosphoramidate prodrug was accomplished using a phosphoramidite approach in high yield. This new class of compounds is designed to have improved antiviral and anticancer advantages conferred by combining the boranophosphate and normal nucleoside amino acid phosphoramidate. Compounds were characterized by MS and* ^{31}P *NMR.*

Keywords Nucleoside-boranophosphoramidate; amino acids; prodrug; phosphoramidite

INTRODUCTION

Nucleoside boranophosphates (borane-phosphonates) have recently attracted attention due to their possible therapeutic applications as anticancer[1] and antiviral[2,3] prodrugs. The phosphoramidate delivery approach[4] has been conceived as a means to improve cellular penetration of nucleotides and to bypass the first step of kinase-mediated phosphorylation of nucleosides. Once in the cell, nucleoside boranophosphates have the potential to act as nucleotide prodrugs that could be phosphorylated to the α-P-BH_3-modified NTPs, which are good substrates for retroviral reverse transcriptases.[2] A *P—N* bond between the borano-nucleotide and amino containing compound results in a nucleoside boranophosphoramidate. Due to the presence of a borane group, the nucleoside boranophosphoramidates are expected to have increased lipophilicity relative to their parent phosphoramidate compounds and may facilitate the delivery of prodrugs containing antiviral nucleosides. The aim is to design and synthesize nucleotide prodrugs combining the best nucleoside inhibitors with the advantages of a boranophosphate modification.

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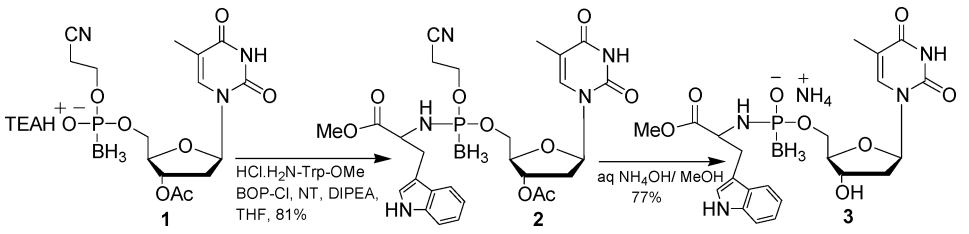
Our lab previously reported two strategies for the synthesis[5] of nucleoside boranophosphoramidates conjugated with amino acids that involve either H-phosphonate chemistry or an oxathiaphospholane approach. Due to the low yields and limitations of phosphorylating reagents and purification, here we present a third strategy to synthesize these nucleoside boranophosphoramidates in very good yields using conventional phosphoramidite chemistry.

RESULTS AND DISCUSSION

In order to explore the prodrug approach by conjugating amino acids to boranophosphates, first triethylammonium 2-cyanoethyl-3′-O-acetylthymidine 5′-boranophosphate **1** was synthesized from 3′-O-acetylthymidine and 2-cyanoethyldiisopropylchlorophophoramidite in the presence of tetrazole as an activator (Khan and Shaw, unpublished data). As shown in Scheme 1, compound **1** was further reacted with the amino group of tryptophane methyl ester hydrochloride in the presence of reagents N,N′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) and 3-nitro-1,2,4-triazole (NT)[6] to give 2-cyanoethyl-3′-O-acetylthymidine 5′-boranophosphoramidate tryptophane methyl ester **2** in 81% yield after purification. The appearance of a peak at δ 118.68 ppm in ^{31}P NMR confirmed the formation of the *P—N* bond Hydrolysis products of the BOP-Cl and NT reagents were efficiently removed from the desired nucleoside boranophosphoramidates **2** by water extraction during the purification step. Acetyl and cyanoethyl protecting groups were removed selectively in the presence of methyl ester by treatment with conc. NH_4OH (aq)/MeOH (1:1) for two hours to give the final ammonium salt of thymidine 5′-boranophosphoramidate tryptophane methyl ester **3,** in 77% yield as a mixture of stereoisomers.

In conclusion, we have accomplished the synthesis of thymidine boranophosphoramidate tryptophane methyl ester **3** using a clearly improved synthetic route. The yield was increased from 35% to 77% while avoiding the instability, unavailability, and hazardous nature associated with the previously reported phosphorylating reagents.[5,7]



SCHEME 1 Synthesis of nucleoside boranophosphoramidate.

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