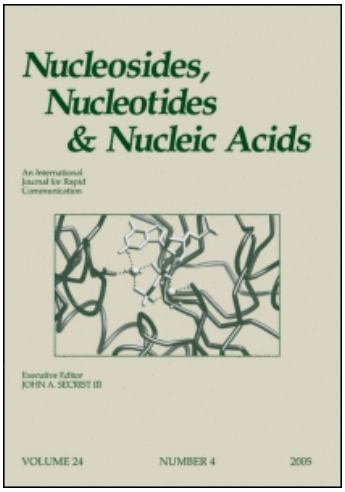

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N-PHENYLIMIDAZOLIUM TRIFLATE AS A HIGHLY EFFECTIVE PROMOTER FOR THE INTERRIBONUCLEOTIDE-BOND FORMATION VIA THE PHOSPHORAMIDITE METHOD

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N-PHENYLIMIDAZOLIUM TRIFLATE AS A HIGHLY EFFECTIVE PROMOTER FOR THE INTERRIBONUCLEOTIDE-BOND FORMATION VIA THE PHOSPHORAMIDITE METHOD

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ABSTRACT

N-Phenylimidazolium triflate has been invented as an extremely effective promoter for the construction of interribonucleotide linkage according to the phosphoramidite strategy.

Condensation of a ribonucleoside 3′-phosphoramidite and a 5′-*O*-free ribonucleoside is a key step in chemical synthesis of oligoribonucleotides via the phosphoramidite approach. In this reaction, invention of an effective promoter is one of important research subjects. Currently, 1*H*-tetrazole (1) or 5-(ethylthio)-1*H*-tetrazole (ETT) (2) is most conventionally employed as the promoter, but these tetrazole reagents are not quite useful because their reactivity is not sufficiently high and, accordingly, use of excess amounts of the phosphoramidite and the promoter toward the 5′-*O*-free ribonucleoside is generally required in order to achieve smooth and high-yield reaction. This paper discloses as a more efficient promoter *N*-phenylimidazolium triflate (PhIMT), which allows the interribonucleotide-linkage formation at an extremely high speed and in an excellent yield.

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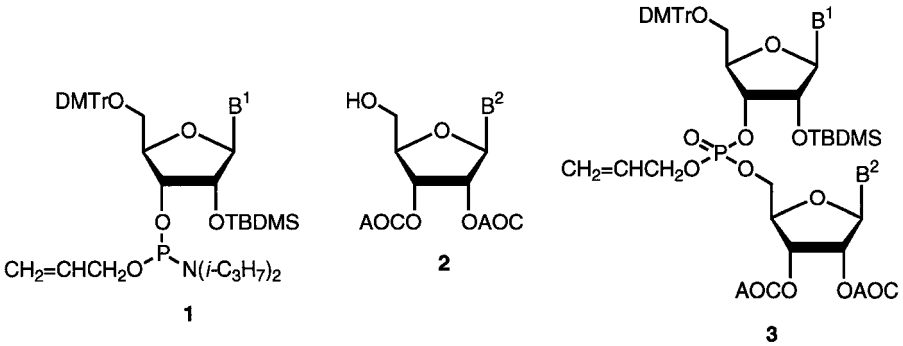

B^1, B^2 = Ade^{AOC}, Cyt^{AOC}, $Gua^{All, AOC}$, Ura
All = CH_2=$CHCH_2$; AOC = CH_2=$CHCH_2OCO$

RESULTS AND DISCUSSION

The condensation of a 2′-*O*-(*tert*-butyldimethylsilyl)ribonucleoside 3′-(allyl *N*,*N*-diisopropylphosphoramidite) and a 5′-*O*-free ribonucleoside promoted by PhIMT, where the promoter, the phosphoramidite, and the nucleoside are employed in *equimolar* amounts in a 0.1 M acetonitrile solution containing molecular sieves 3A was accomplished for 5 min at 25°C. For example, the 0.2 μmol-scale reaction of **1** (B^1 = Ade^{AOC}) and **2** (B^2 = Cyt^{AOC}) afforded, after oxidation with *tert*-butyl hydroperoxide (3), the fully protected dinucleoside phosphate **3** (B^1 = Ade^{AOC}; B^2 = Cyt^{AOC}) in >95% yield (^{31}P-NMR assay). This procedure can be applied to various kinds of nucleoside derivatives, such as those of B = Ade^{AOC}, Cyt^{AOC}, $Gua^{All, AOC}$, and Ura, and the corresponding dinucleoside phosphates were obtained generally in >95% yields. The reactivity of PhIMT is greatly higher than conventionally employed ETT and 1*H*-tetrazole. The above reaction of **1** (B^1 = Ade^{AOC}) and 2 (B^2 = Cyt^{AOC}) assisted by ETT was not finished for 5 min under the above conditions to give the phosphite intermediate in only 64% at this stage (^{31}P-NMR assay). This condensation required 40 min for the completion. Further, 1*H*-tetrazole could not complete the reaction even after 60 min.

PhIMT has also served as an efficient promoter for the solid-phase synthesis of oligoribonucleotides via the allyl-protected phosphoramidite method. For example, U_{10} was prepared in 99.6% average coupling yield (estimated by trityl assay). The results of the solid-phase synthesis of RNA oligomers including hetero-oligomers will be reported in detail in a separate paper.

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