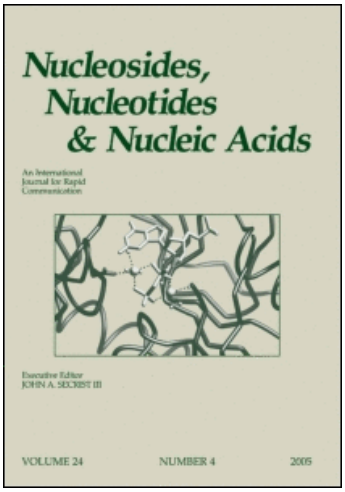

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SYNTHESIS OF N^2-ALKYLGUANOSINE USING MITSUNOBU REACTION AS A KEY STEP

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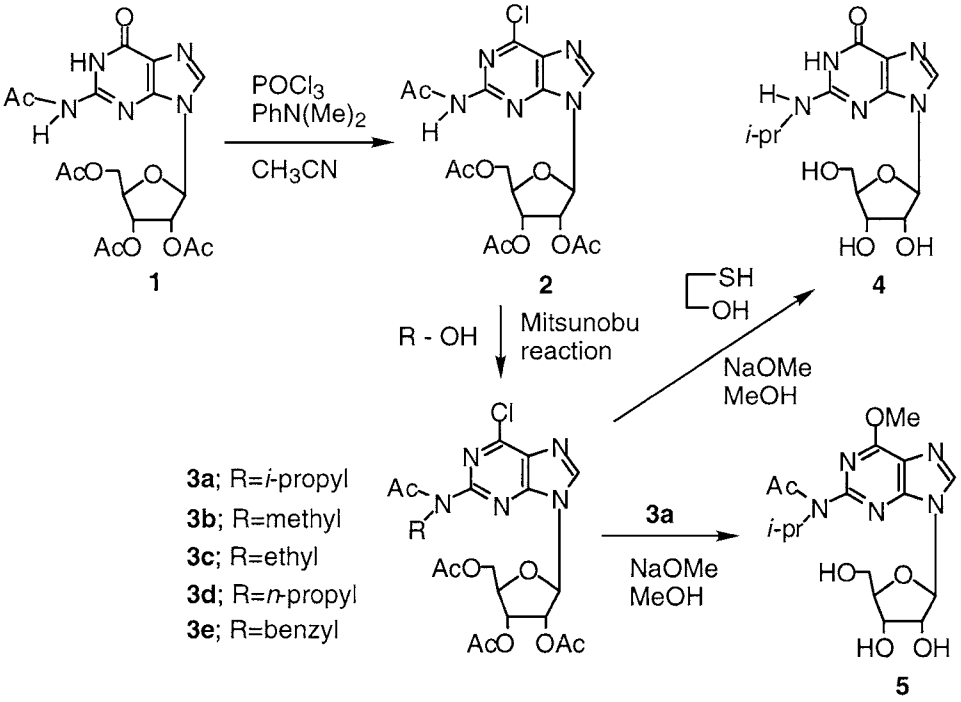
ABSTRACT

Peracetylated guanosine was reacted with $POCl_3$ to give an 2-acetamido-6-chloro-9*H*-purine derivative, which was condensed with primary or secondary alcohols to give N^2-alkylated analogues. The products were treated with mercaptoethanol in the presence of sodium methoxide to afford N^2-alkylguanosines.

Recently, N^2-alkylguanosine has attracted the attention of many chemists since the discovery of this type of compound in cells. The synthesis of N^2-alkylguanosine from guanosine has been achieved by several methods (1,2). However, those methods are limited to a primary alkyl group. For the synthesis of the guanosine analogue bearing a secondary alkyl group, a nucleophilic displacement of inosine-2-sulfonic acid or 2-halogeno-inosines has been used (3,4).

Reaction of N^2,$O^{2'}$,$O^{3'}$,$O^{5'}$-tetraacetylguanosine (**1**) with $POCl_3$ in the presence of *N,N*-dimethylaniline in CH_3CN gave 2-acetamide-6-chloro-9-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)purine (**2**) in 69% yield. Compound **2** was condensed with 2-propanol using 1,1′-azobis(*N,N*-dimethylformamide) and tri-*n*-butylphosphine as dehydrating reagents (5) to give 6-chloro-2-(*N*-isopropyl)acetamide-9-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)purine (**3a**) in 61% yield. Treatment of **3a** with 2-mercaptoethanol and NaOMe in MeOH gave N^2-isopropylguanosine (**4**) and 6-methoxy-2-methylamino-9-(beta-D-ribofuranosyl)purine (**5**) in 65% and 19%

*Corresponding author.



Scheme.

yields, respectively. However, reaction of **3a** with NaOMe in MeOH gave only **5** in quantitative yield. Compound **2** was also condensed with alcohols such as MeOH, EtOH, *n*-PrOH or benzyl alcohol using a similar method to give the N^2-alkyl derivatives (**3b–e**) in 50–60% yields. This is the first report that describes a general procedure to prepare the guanosine derivative bearing primary or secondary alkyl group at N2.

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