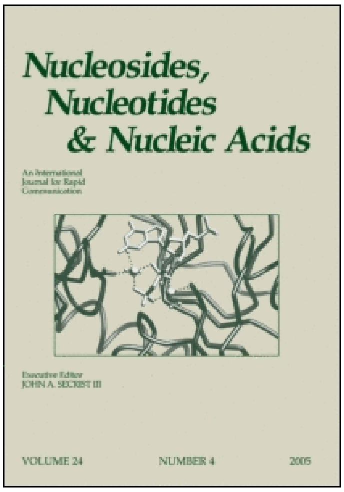

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Synthesis of 0^6-Alkylated Guanosine and Deoxyguanosinephosphoramidites

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SYNTHESIS OF O^6-ALKYLATED GUANOSINE AND DEOXYGUANOSINEPHOSPHORAMIDITES

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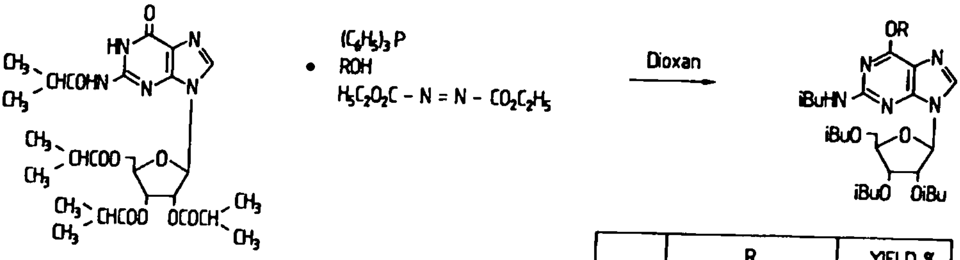
Since O^6-alkylguanine derivatives play a specific role in nucleic acids as potential sources of mutagenic (1) and carcinogenic (2) action the monomeric building blocks of this type of compounds are desirable for more detailed studies. The old route to O^6-alkyl ribonucleosides via the corresponding 6-chloro derivative worked with low yields in the 2'-deoxy series and could only just recently be improved by functionalizing the amide group first by sulfonylation on oxygen and followed by subsequent displacement of trimethylamine and various alkoxides (3).

Despite the fact that this sequence of reactions can be achieved as a one-pot procedure an even more simple method for modifying the O^6-position of guanosines has been found in the Mitsunobu reaction (4).

We found that N^2,2',3',5'-tetraisobutyryl-guanosine and N^2,3',5'-triisobutyryl-2'-deoxyguanosine respectively react smoothly at room temp. with a 20 % excess of triphenylphosphane, ethyl azodicarboxylate and the appropriate primary or secondary alcohol in absol. dioxane to the corresponding O^6-alkyl guanosine derivatives. The reaction proceeds in principle very well but isolation of the pure reaction products is sometimes problematic due to difficulties in chromatographical separation from triphenylphosphane oxide and ethyl hydrazinedicarboxylate.

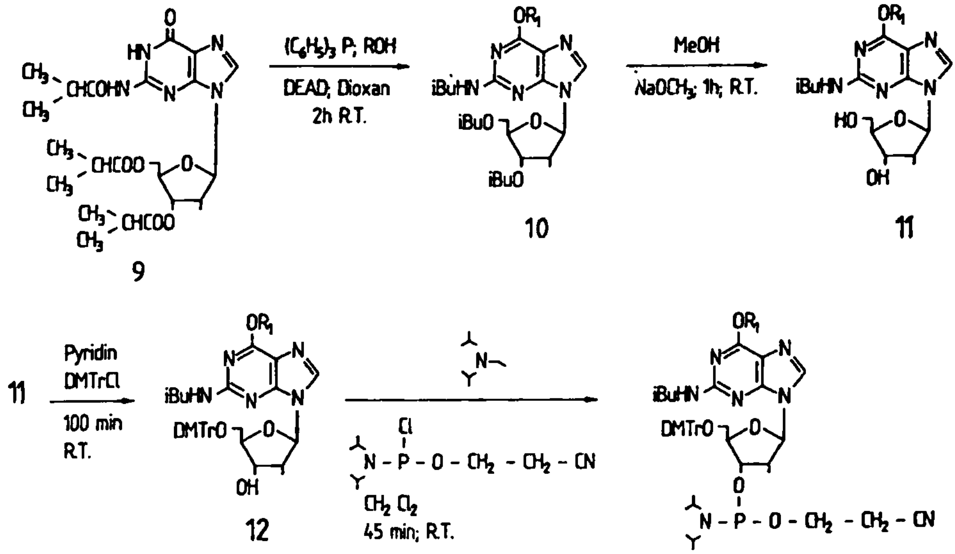
Methanol, ethanol, benzyl alcohol, ß-phenylethanol, allyl alcohol, propargyl alcohol and isopropanol reacted in a similar manner, but tertiary alcohols and aromatic phenols did not work from steric and mechanistic reasons respectively.

The O^6-alkylated 2'-deoxyguanosine derivatives have then chemically been modified to the corresponding cyanoethyl N-diisopropylphosphoramidites. First the sugar acyl groups were removed with methoxide/methanol followed by dimethoxytritylation and finally phosphitylation by means of chloro-cyanoethyl-N-diisopropylaminophosphane.



1

	R	YIELD %
2	CH_3	40
3	C_2H_5	64
4	CH_2-⌬	62
5	$CH_2-CH=CH_2$	42
6	$CH_2-C\equiv CH$	35
7	$CH(CH_3)_2$	82
8	CH_2-CH_2-⌬	73



9

10

11

12

13

	YIELD %			
	10	11	12	13
CH_3		35.3	92.8	91.8
CH_2-CH_3	71.4	95%	95.7	91.5
$CH(CH_3)_2$	81	96	88	92.7

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