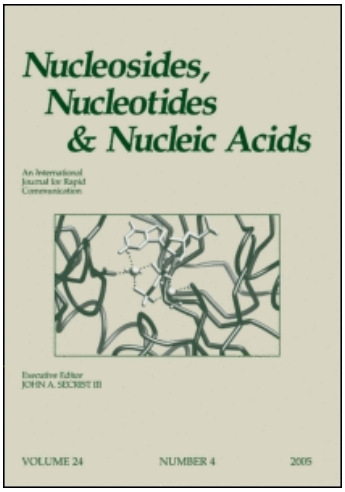

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Synthesis of Modified Thymidine Dimers

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SYNTHESIS OF MODIFIED THYMIDINE DIMERS

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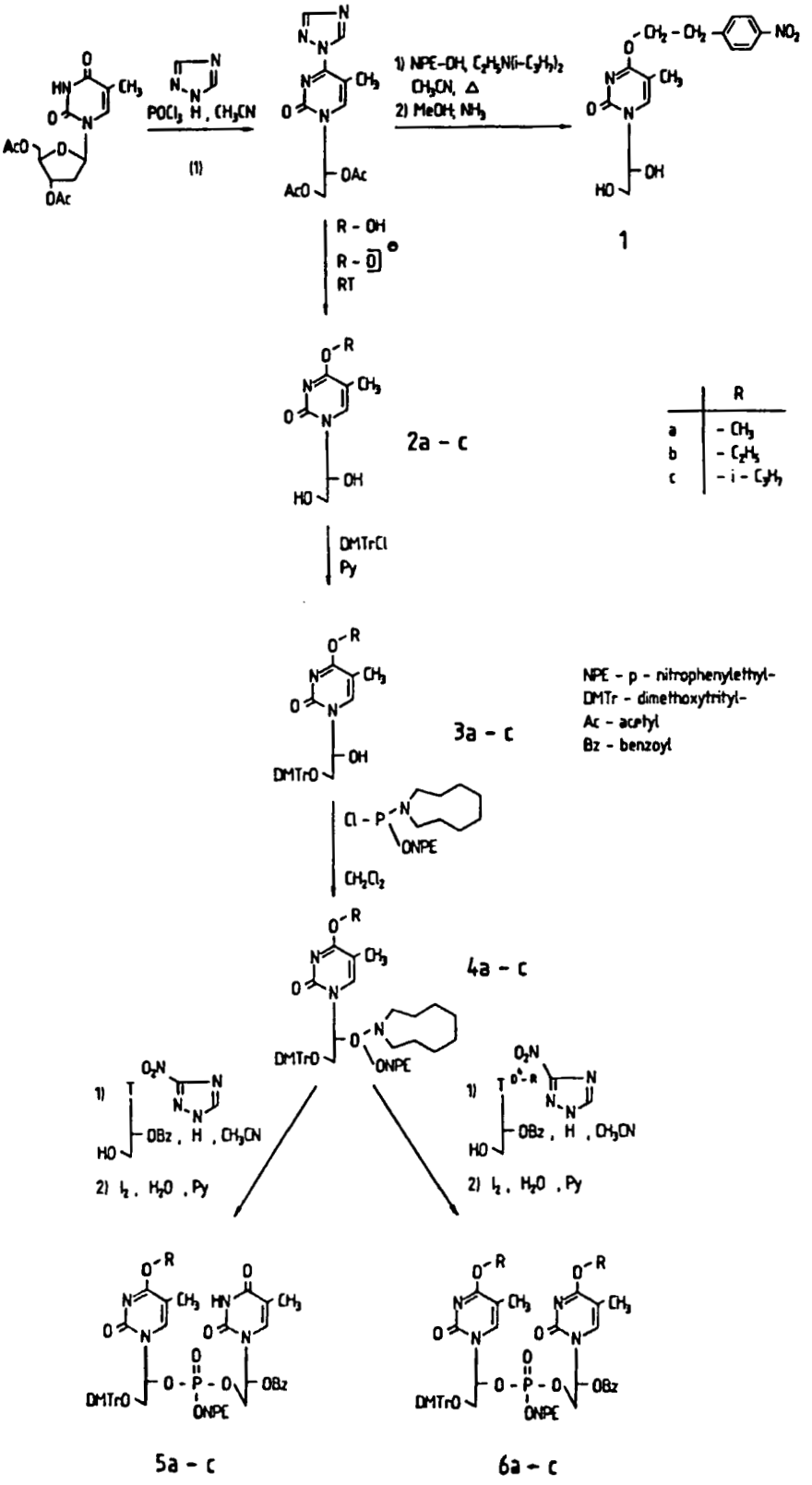
Alkylating agents are mutagenic and carcinogenic substances due to reaction with the pyrimidine and purine bases of the various nucleic acids. The thymine base can be alkylated at N^3-, O^2- or O^4-position. Their behaviour during transcription and replication is unknown (1).

The direct synthesis of O^4-alkylthymidine (2a-c) by normal alkylating agents is difficult, but the preparation can be achieved in good yields if 5-methyl-2-oxo-1-(3,5-di-O-acetyl-2-deoxyribofuranosyl)-4-(1,2,4-triazol-1-yl)-1,2-dihydropyrimidine (2) is treated with sodium methoxide, ethoxide, and isopropoxide respectively.

The 5'-O-dimethoxy-O^4-alkylthymidines (3a-c) and the corresponding phosphoramidites, O^4-alkyl-5'-O-dimethoxytrityl-3'-O-[(p-nitrophenylethoxy, N-octahydroazonino)phosphino]-thymidine, were prepared by analogous procedures according to the literature (3) in good yields. The phosphoramidites can be purified by silica gel chromatography and the resulting solid foam is quite stable and can be stored at room temp. for several months without decomposition.

The phosphoramidites (4a-c) were condensed with 3'-O-benzoylthymidine and 3'-O-benzoyl-O^4-alkylthymidine respectively to the corresponding dimers (5a-c) and (6a-c).

The introduction of the p-nitrophenylethyl group into O^4-position of thymidine was performed from 5-methyl-2-oxo-1-(3,5-di-O-acetyl-2-deoxyribofuranosyl)-4-(1,2,4-triazol-1-yl)-1,2-dihydropyrimidine with p-nitrophenylethanol in presence of Hünig's base followed by deacylation with ammonia in methanol to give the required O^4-p-nitrophenylethylpyrimidine in good yield.



R E F E R E N C E S

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