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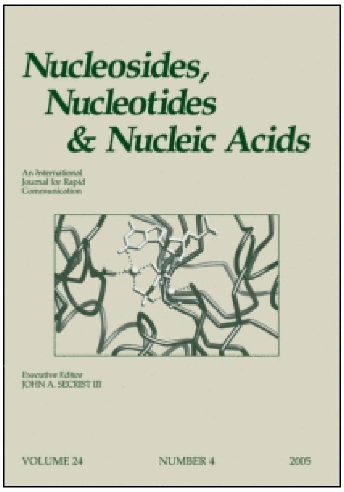

Nucleosides, Nucleotides and Nucleic Acids

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A Novel Class of 4'-Aza Analogues of 2',3'-Dideoxynucleosides as Potential Anti-HIV Drugs

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A NOVEL CLASS OF 4'-AZA ANALOGUES OF 2',3'-DIDEOXYNUCLEOSIDES AS POTENTIAL ANTI-HIV DRUGS

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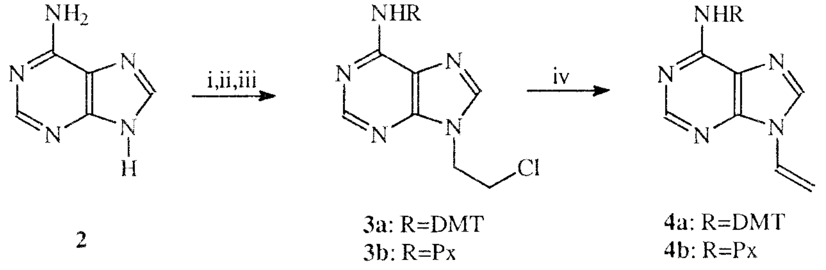
ABSTRACT. The 1,3 dipolar cycloaddition approach represents the most valuable strategy for the preparation of isoxazolidine nucleosides. The latter posses more conformational degrees of freedom than the corresponding dideoxyribosides. Side reactions due to the presence of formaldehyde in the reaction media can be avoided by proper derivatization of the vinyl-nucleobase.

INTRODUCTION

The synergic action of "drug cocktails" suitable to inhibit reverse transcriptase and protease in the replication cycle of HIV virus, seems to be the only therapeutic means available at the moment to delay the devastating action of AIDS.[1,2] 2',3'-dideoxy nuclesides are drugs directed against the reverse transcriptase and approved for clinical use in the treatment of HIV infections. The fast mutations of virus impose to have a number of different drugs alternative to one another. The 2',3'-dideoxy ribofuranosyl derivatives of adenine and thymine are effective in AIDS therapy, even though the lability of the glycosyl bond and their toxicity represent the major drawbacks in clinical applications, whereas various acyclic and carbocyclic adenosine analogues have proved to be active against a characteristic spectrum of virus.[3,4] In the 4'-aza-2',3'-dideoxy nucleosides analogues the asymmetric carbon atom responsible for D or L configuration of nucleosides is replaced with nitrogen atom. The structural features of the molecule ensure that[5,6] they can adopt conformations that would represent either the D or L of the carbon analogues, therefore they can supposedly adjust their configuration to the steric requirements of a macromolecular receptor. Moreover the hydroxylamino nitrogen atom



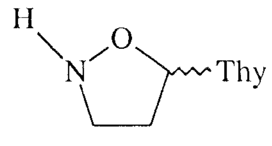
i: Ethylene carbonate, DMF dry, NaOH, Δ; ii: SOCl$_2$, Δ; iii: DMTCl (a) or PxCl (b), Pyridine dry; iv: dioxane dry, MeO$^-$/MeOH, r. t.

Scheme 1

might undergo phosphorylation and can be competitively protonated in acid media, thus enhancing the stability of the glycosyl linkage.

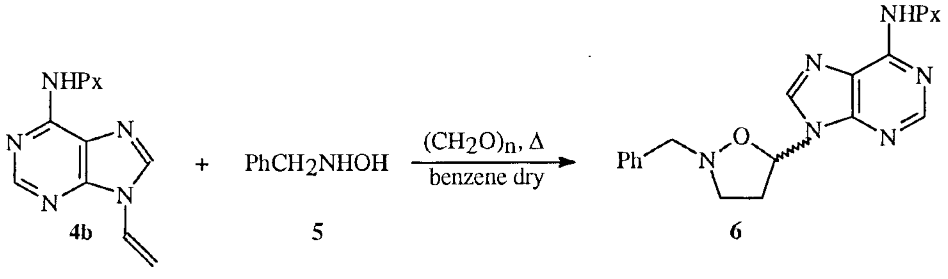
RESULTS AND DISCUSSION

[3+2]-dipolar cycloadditons of nitrones to vinyl thymine[5] and adenine[6,7] represent a unique approach to the synthesis of isoxazolidine nucleosides as potential antiviral drugs. In the case of thymine the appropriate dipolarophile is readily available[8] and the dipole can be obtained "in situ" by means of paraformaldehyde and the appropriate hydroxylamine. The activity of 4'-aza-2',3'-dideoxythymidine **1** has been tested in parallel with AZT in a CD4-lymphocytic cell line, C 8166, sensitive to the cytopathic effect of HIV. ADT inhibits HIV replication in C 8166, with an activity inversely related to the multiplicity of infection used. EC 50 of ADT is in general 10 fold greater than that of AZT. No toxicity was detected at concentration of ADT up to 50 μM.[9] The synthesis of adenine analog of **1** needs the protection of the 6-amino group of the dipolarophile. The 6-N-phtaloyl derivative gave poor yields, whereas the dimethoxytrityl analogue proved to be successful.[6]



1

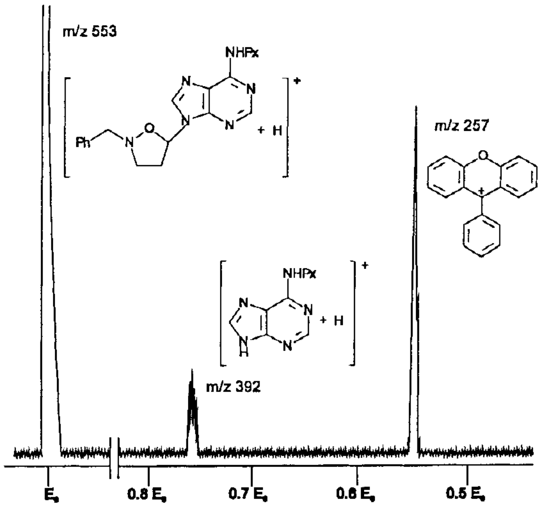
However the yields of the 9-N-(2'-chloroethyl)-6-N dimethoxytrityladenine (**3a**) were 58% and could not be improved. It has been demonstrated that 6-N-pixylation (Px) of deoxyadenosine can be advantageously used in the synthesis of 5'-phosphorothioate and -phosphorodithioate nucleotides.[10] A similar approach was used in the formation of **4b**



Scheme 2

(Scheme 1). The 9-N-(2'-chloroethyl)-6-N pixyladenine **3b** was obtained with 88% yield and directly used for the synthesis of the corresponded vinyl nucleoside **4b**, which was obtained as white glass solid with 92% yield.

Preliminary results have showed that N-benzyl nitrone produced *in situ* by means of paraformaldehyde reacts smoothly with **4b** affording satisfactory yield of the isoxazolidine nucleoside **6** (Scheme 2). The (+) FAB spectrum of **11** gave the expected $[M+H]^+$ and fragments and ions; its structure was thoroughly proved by MS/MS experiments (Figure).The MIKE spectra of the $(M+H)^+$ ion at m/z 553 afforded the product ions at m/z 257 and 392 with 80% and 20% relative yields which clearly indicate the presence of the protective group and of the nucleobase.



Figure

EXPERIMENTAL

Synthesis of 9-*N*-(2'-chloroethyl)-6-*N*-pixyladenine (3b)

Pixyl chloride (945 mg, 3.06 mmol) was dissolved in dry benzene (10 ml) and added to a solution of 9-*N*-(2'-chloroethyl)-adenine (504 mg, 2.55 mmol) in dry pyridine (10 ml) [TLC: CCl_4-MeOH 95:5 (v/v)]. After 45 min (r.t.), methanol (5 ml) was added and the reaction mixture concentrated under reduced pressure. The resulting crude oil was treated with 5% aqueous $NaHCO_3$ (20 ml) and brine (5 ml) then extracted with chloroform (3x15 ml). The organic layers were dried on Na_2SO_4 and evaporated to dryness. Trituration with n-hexane (100 ml) of the resulting crude yellow solid gave pure product as a pale yellow glass solid (1.02 g, 88% yield; $R_f = 0.38$). ^{1}H NMR: δ 8.10 (s, 8-CH; 1H), 7.84 (s, 2-CH; 1H), 6.92-7.43 (m, ArH; 13H), 4.47 (t, 2'-CH_2; 2H), 3.86 (t, 1'-CH_2; 2H) and 2.92 (s, 6-NH; 1H). FAB MS (+): *m/z* 454 [$(M+H)^+$, 3.7%], 453 [$(M^{+\cdot})$, 8.2], 392 (3), 257 (Px^+, 100) and 197 (7.2).

Synthesis of 9-*N*-vinyl-6-*N*-pixyladenine (4b).

A 10% methanolic solution of sodium methoxide (0.98 ml) was added dropwise to a magnetically stirred solution of 9-*N*-(2'-chloroethyl)-6-*N*-pixyladenine (330 mg, 0.756 mmol) in dry tetrahydrofuran (20 ml) at r.t. [TLC: CCl_4-MeOH 95:5 (v/v)]. After 26 h distilled water (15 ml) was added and the reaction mixture was extracted with diethyl ether (3x20 ml). Evaporation to dryness of the dried (Na_2SO_4) organic phase gave pure **17** as a white glass solid (289 mg, 92% yield; $R_f = 0.61$). ^{1}H NMR: δ 8.05 (s, 8-CH; 1H), 7.94 (s, 2-CH; 1H), 6.95-7.46 (m, ArH and 1'-CH; 13H+1H), 5.78 (dd, $J_{trans} = 16.0$ and $J_{gem} = 1.5$, 2-CH2; 1H), 5.10 (dd, $J_{cis} = 9.1$, 2-CH2; 1H) and 2.98 (s, 6-NH; 1H). FAB MS (+): *m/z* 418 [$(M+H)^+$, 7.8%], 257 (Px^+, 100) and 162 (6.2).

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