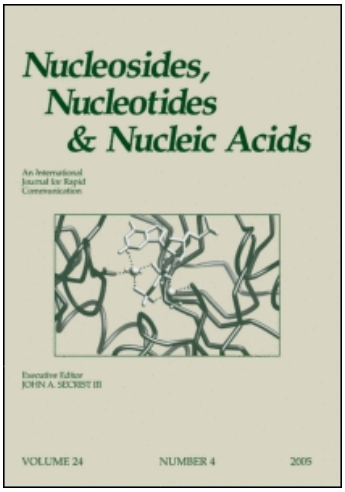

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Reactivity Models of 1-*N*-Vinyluracil and Synthesis of a New Class of Potential Antiviral Agents by the Use of 1,3-Dipolar Cycloaddition Reactions

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ABSTRACT

By the use of a convergent approach based on 1,3-dipolar cycloaddition reactions between *N*-protected formylnitrones generated in situ and 1-*N*-vinyluracil, a new class of 4′-aza-analogues of 2′,3′-dideoxynucleosides is synthesized. Competitive reaction for the endocyclic bond of uracil also brings to a new isoxazolidine derivative fused with the pyrimidine nucleus.

By a convergent approach based on 1,3-dipolar cycloaddition reactions between *N*-protected formylnitrones **1** generated in situ, starting from the corresponding hydroxylamines, and 1-*N*-vinylnucleobases **2** and **3**, a new class of 4′-*aza*-2′,3′-dideoxynucleosides **4** and **5** was synthesized[1,2] (Sch. 1).

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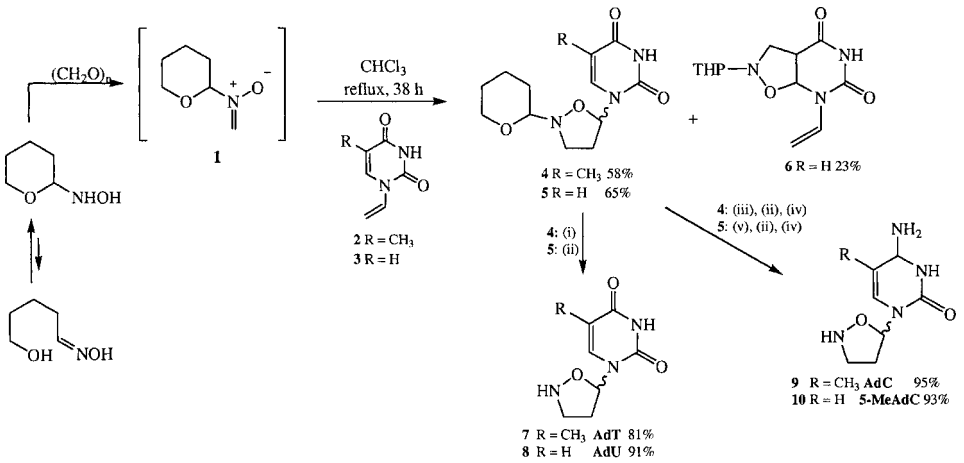

(i) *p*-TsOH, MeOH, $CHCl_3$; (ii) $HClO_4$ 60%, MeOH, $CHCl_3$; (iii) $POCl_3$, TEA, 1,2,4-(1*H*)-triazole, CH_3CN (quantitative yield); (ii) R = CH_3 92% yield; R = H 88% yield; (iv) NH_3, 1,4-dioxane; (v) $POCl_3$, 4-nitrophenol, *N*-methylpyrrolidine, 1,4-dioxane (90% yield).

Scheme 1.

The tandem mass spectra[3] of these compounds were similar to those of the wild-type nucleosides but all the protonated isoxazolidinyl nucleosides present a retrocycloaddition process, which can be considered a 'marker' of the chemistry of this class of compounds. The application of the convertible nucleoside approach (Sch. 1) was achieved in order to prepare 4′-*aza*-2′,3′-dideoxynucleosides **9** and **10**. A competitive reaction for the endocyclic bond of 1-*N*-vinyluracil **3** during 1,3-dipolar cycloaddition process, characterised by site selectivity affords a new isoxazolidinyl derivative fused with the pyrimidine nucleus (Sch. 1). The regiochemistry of nitrone attack on double bond C(5)–C(6) was demonstrated by two dimensional NMR and MS/MS experiments.[4]

On the bases of the above mentioned promising results, some other fused *N,O*-heterocycles (Table 1) have been prepared, using as dipolarophiles, modified uracils on 1-*N*-position by tetrahydropyranyloxyethyl and 2-benzyloxy-ethoxymethyl moieties. (Sch. 2).

Table 1.

	R_1	PG	Solvent	Yield (%)
13	$BnOCH_2CH_2OCH_2$-	THP	Toluene	20
14	$BnOCH_2CH_2OCH_2$-	Benzyl	Toluene	25
15	$THPOCH_2CH_2$-	THP	$CHCl_3$	15
16	$THPOCH_2CH_2$-	Benzyl	$CHCl_3$	19
17	$BnOCH_2CH_2OCH_2$-	–	$MeOH/CHCl_3$	72
18	$HOCH_2CH_2OCH_2$-	–	MeOH	85
19	$HOCH_2CH_2$-	–	$MeOH/CHCl_3$	70
20	$THPOCH_2CH_2$-	–	MeOH	92

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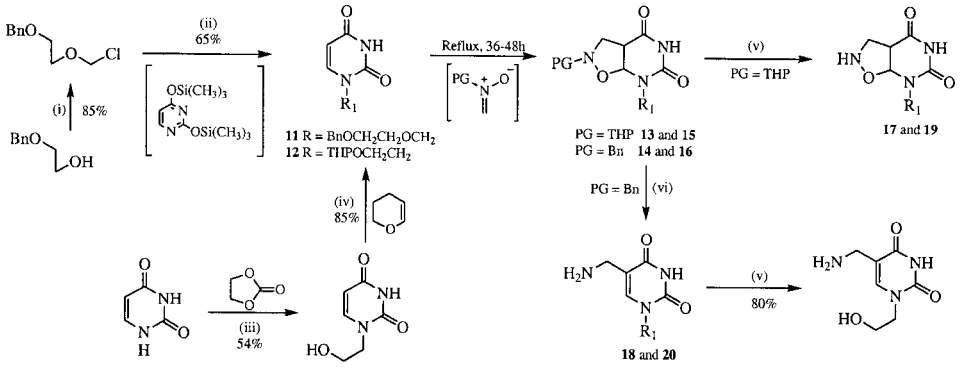

Scheme 2.

The subsequent reductive opening of fused isoxazolidine rings brought to some new acyclic uridine derivatives functionalised on C(5) by a methylamino group.

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