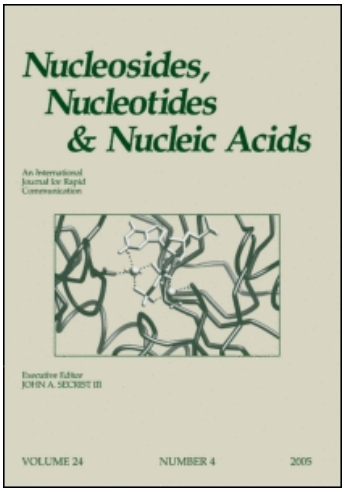

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SYNTHESIS OF NON-NATURAL PYRIMIDINE NUCLEOSIDES

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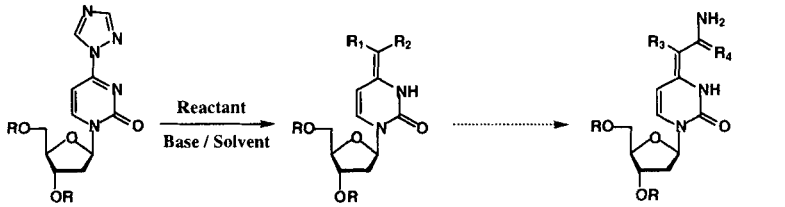
ABSTRACT : Two new non-natural nucleosides bearing an amide (**8**) or an amidine (**9**) function have been synthesized. Their properties and the geometry of the exocyclic double bond have been studied.

In order to recognize double-stranded DNA *via* a non-natural triple helix motif[1], we have become interested in non-natural nucleosides exhibiting an extended conjugation system and different hydrogen-bond donor (D) and acceptor (A) groups. In particular, nucleosides bearing an amide (D/A) or an amidine (D/D) function have been designed to recognize A-T and G-C base pairs, respectively.

The intermediates to the amide (**2, 3**) and amidine function (**4-6**) were prepared by a two-step process modified from a literature procedure[2]. This method allowed easy addition of malonate-type C-nucleophiles at the C-4 position of protected 2'-deoxyuridine *via* a triazolyl intermediate **1** (TABLE 1) in 50-70% yield[3].



1
R = TBDMS

2-7

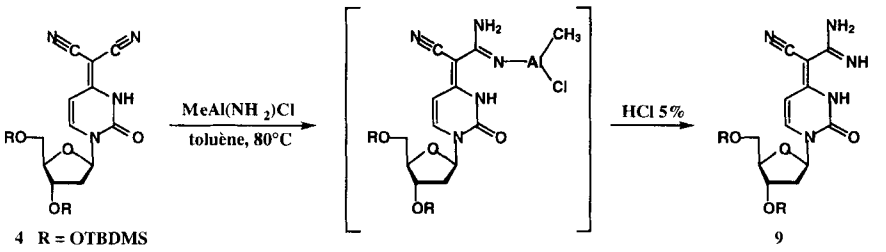
8 : R_3 = H, R_4 = O
9 : R_3 = CN, R_4 = NH

Compound	Reactant	Product	Base/Solvent	T	Yield
2	diethylmalonate	R_1=COOEt ; R_2=COOEt	NaH/THF	0°C	70%
3	ethylacetoacetate	R_1=COOEt ; R_2=$COCH_3$	NaH/THF	0°C	50%
4	malononitrile	R_1=CN ; R_2=CN	NaH/THF	0°C	67%
5	ethylcyanoacetate	R_1=CN ; R_2=COOEt	NaH/THF	0°C	56%
6	5-methylisoxazole	R_1=CN ; R_2=$COCH_3$	*t*-BuOK/*t*-BuOH	30°C	61%
7	acétonitrile	R_1=CN ; R_2=$C(NH)CH_3$	Na/THF	0°C	55%

TABLE 1 – Conditions for the synthesis of **2-7**

After desilylation, bis-ester **2** and keto-ester **3** were treated with concentrated aqueous ammonia at room temperature to afford the corresponding bis- and keto-amide. However, compounds **2** and **3** both underwent a retro-Claisen-type reaction to give the mono-amide **8**. Attempts to obtain the mono-nitrile from compounds **4-6** by the same method was unsuccessful and direct reaction of **1** with acetonitrile gave compound **7** instead as acetonitrile first dimerized in the presence of Na.

As a mild method for converting a nitrile into an amidine, we used Garigipati's reagent which was described for the conversion of weakly-reactive nitriles[4]. The reaction proceeded with compounds **4-6** using methylchloroaluminum amide in anhydrous toluene at 80°C for several hours, followed by acidic hydrolysis of the intermediate complex (SCHEME 1). This procedure lead to the mono-amidine product **9** in 75% yield from **4**, yet revealed to be inefficient in the case of **5** and **6**. A mechanism of action of the aluminium complex proceeding *via* interaction with N3-H could explain these results.



SCHEME 1

The non-natural nucleosides **8** and **9** have UV-absorption far away from typical nucleosides (λ=260 nm), respectively at 320 and 335 nm. The pKa value of the amidine group of **9** was determined spectroscopically to be 3.2 so, it should not be protonated at physiological pH. The geometry of the exocyclic double bond of compounds **3** and **5-9** is as shown above according to N3-H ^{1}H NMR shifts and NOESY correlations.

After incorporation of nucleoside analogs **8** and **9** into oligonucleotides, their hybridization with a duplex target has been studied[1].

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