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Synthesis of Isoguanosine Analogues

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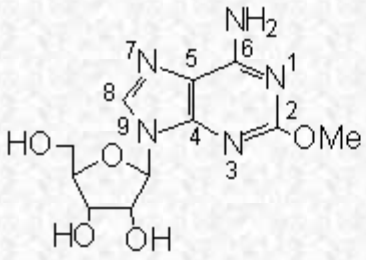
INTRODUCTION

An increasing number of isomeric (unnatural) nucleosides and nucleotides bearing an isomeric backbone, sugar or base have been characterized.[1]

A nucleobase isomer like isoguanine apparently makes feasible a non-standard base pair between 2`- deoxyisocytidine and 2`-deoxyisoguanosine when incorporated into oligomers. Some levels of functions by that isomeric replacement are retained and in some instances new functions are formed.[2] The results reported by Switzer et al have shown that various polimerases handle this nonstandard base pair while Horn et al[3] reported on the pairing in the absence of enzyme. Herein we report on a subtle change in a molecular shape by replacing N^3-nitrogen with more lipophylic CH^3-group and C^8-H by N^8-nitrogen.Though we do not prevent the Watson-Crick pairing the ring stacking might be altered. The absence of N^3-nitrogen introduces an incorrectness that would disrupt the minor groove spin of hydration what means that should eliminate the presence of any ordered water molecules or metal ions at this sequence position.[4] Recently,[5] it has been demonstrated that in dA-dT sequences, the spine of hydration should be considered an integral part of the helix and the possible metal ions binding in the minor groove is critical for the structural integrity of duplex DNA.

In the light of these statements, our intention to design and carry on efficient synthesis of 3-deaza-8-azaisoguanosin (**2**), seemed attractive and significant especialy when additional self-assembled properties are considered. G-quartets covalent assemblies[6] selectively coordinate monovalent and divalent cations to give extremely stable complexes, while the lack of one potential H-bond may considerably alter the binding affinity and selectivity of this potential ionophores.



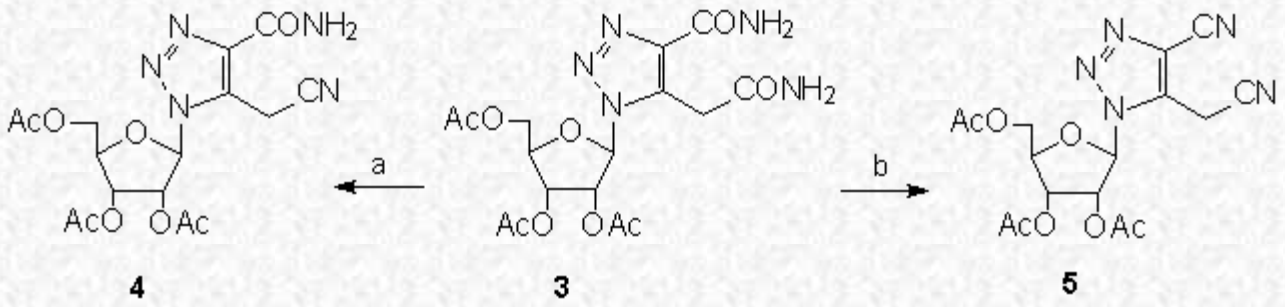
1

2

RESULTS AND DISCUSION

In spite of remarquable interest in isoguanosine and the 2-*O*-methylated congener spongosine[7] (**1**), there have been no attempts to the synthesis of 3-deaza analogues. Our efficient[8] high yield procedure for the preparation of 3-deaza-8-aza-guanosine analogues enabled us to select one of the two possible routes. The first would follow the obvious transformation of **11** , while the second *via* the intermediate **3** offered better option since **3** is readily transformed to compounds **5** or **6** (Scheme 1).

scheme 1



Reagents: (a) 1.1 eq $(CF_3CO)O$, pyridin, dry THF, -10-0°C ; (b) 2.2 eq $(CF_3CO)O$, pyridin, dry THF, -10-0°C

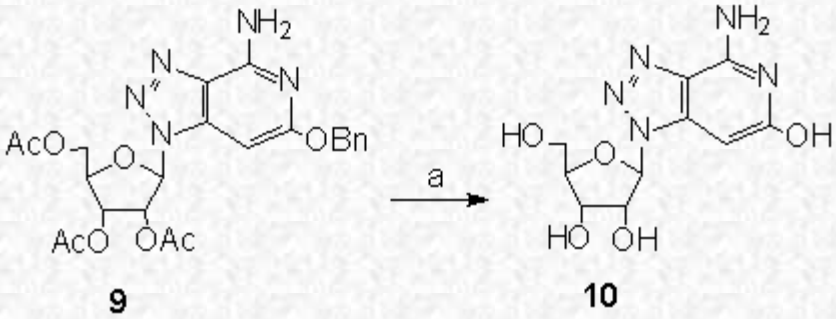
Intramolecular cyclisation between a cyanomethyl group and an adjacent cyano group located on imidazole[9] ring proceeded well by acid-catalysis with anhydrous hydrogen bromide in one direction when the aromatic nitrile becomes the ring nitrogen. This condensation has been reported as successful on a free base only, whether the alkoxide condensation of a dinitrile as was reported for the synthesis of aminoalkoxynaphthyridines[10] furnished the desired product just using sodium methoxide. This condensation employed for our purpuses is presented in Scheme 2.

Scheme 2

Reagents: NaOR in ROH (R=Me, Et, Pr and Bn)

This is the first successful example in nucleoside chemistry presenting a novel and efficient procedure in the chemistry of purine analogues mimicking guanosine framework. The use of different sodium alkoxides afforded 2-alkoxy-3-deaza-8-azaadenosine series **6**-**9** prepared as potentially coronary vasodilatatoris. Besides intermediate **9** is the anticipated precursor to provide the target nucleoside **2**. (Scheme 3).

Scheme 3



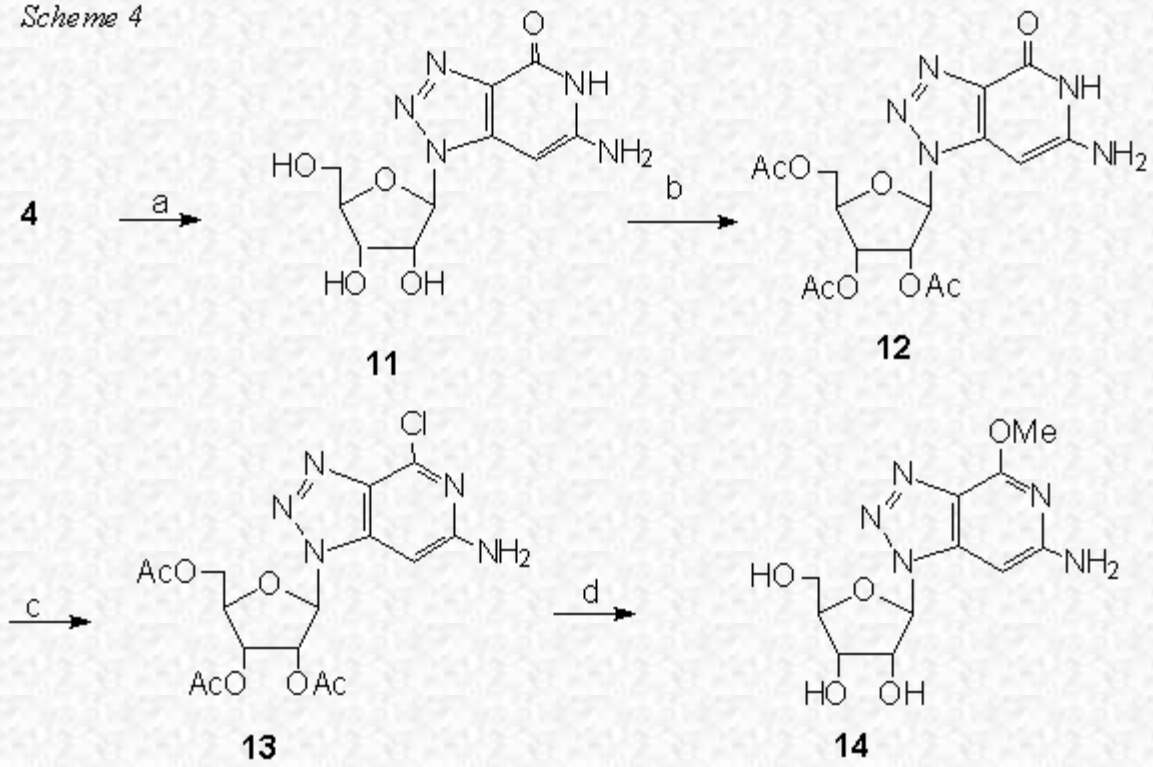
Reagents: (a) H_2 / 5% Pd/C, 80% EtOH

Comformation of obtained products was unambigously determined by the comparison of ^1H spectral data of **6** and **14**. (Table 1)

Table 1.

	δ (ppm)	
	6	**14**
-NH_2	7.25	6.18
-OMe	3.79	4.00
-H	6.30	6.07

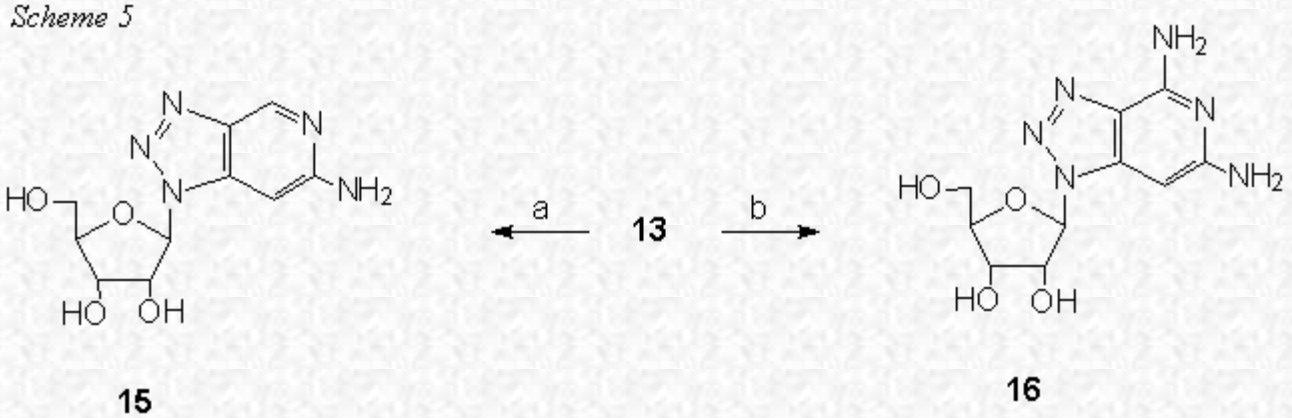
Scheme 4



Reagents: (a)1M NEt_3 in 80% MeOH; (b) Ac_2O, pyridin, DMF; (c) $POCl_3$, collidine, NEt_4Cl, MeCN; (d) MeONa in MeOH

The intermediate **13** is an interesting precursor. After careful hydrogenation it affords **15** and 4,6-diamino-9(b -D-ribofuranosil)-1,2,3-triazolo[4,5-c] pyridine **16** was obtained in liquid ammonia at 110° (Scheme 5)

Scheme 5



Reagents: (a) H_2 / 5% Pd/C; (b) NH_3 (l), 110°C

CONCLUSIONS

A novel alkoxide condensation of the new dinitrile synthon 2-[1-(2,3,5-tri-O-acetyl-b -D-ribofuranozil)-4-cyano-1,2,3-triazolo-5-il] acetonitrile was successfully applied to the synthesis of 3-deaza-8-aza isoguanosine analogue 4-amino-1-(b -D-ribofuranozil) triazolo[4,5-c] piridin-6(5H)-on. New spongosine analogues are reported as well.

ACKNOWLEDGMENTS

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