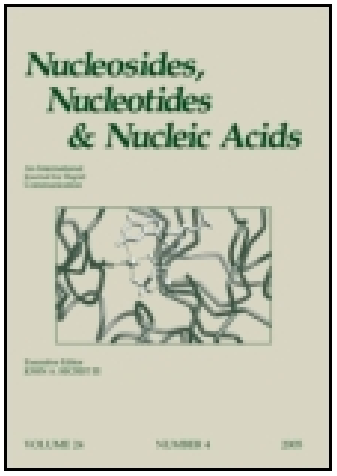

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Coupling of 2,6-Dichloropurine and 2,6-Dichlorodeazapurines with Ribose and Ribose Modified Sugars

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COUPLING OF 2,6-DICHLOROPURINE AND 2,6-DICHLORODEAZA-PURINES WITH RIBOSE AND RIBOSE MODIFIED SUGARS

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ABSTRACT: Substituted purine and deazapurine nucleosides are of great interest in medicinal chemistry. Furthermore, 3'-deoxynucleosides exhibit a number of biological activities. In this research the coupling of 2,6-dichloro-1- or 3-deazapurine with protected 3'-deoxyribose is reported. Depending upon coupling conditions and base structure, different anomeric and isomeric mixtures have been obtained. Extensive studies, utilizing chemical and physical methods, have been performed to assign the correct configuration to the resulting nucleosides.

INTRODUCTION

Purine and deazapurine nucleosides are widely investigated for their very promising properties in medicinal chemistry; 2- and/or 6-substituted nucleoside analogues show biological activity as agonists and antagonists of adenosine receptors,[1] inhibitors of viral and tumor cells replication agents,[2-4] and enzyme inhibitors.[4]

On the other hand, 3'-deoxynucleosides exhibit a number of biological activities, e. g. antifungal, antibacterial, antiparasitic, anticancer,[5] and high affinity for adenotin.[6,7]

Our research group has been involved since many years in this field; we have reported in some papers coupling of 2,6-dichloro purine and deazapurines with ribose,[1] 2-deoxyribose,[8] 3-deoxyribose[7] and 2,3-dideoxyribose[9] derivatives. The use of these versatile synthons allows the introduction of various substituents in 2- and 6-position; this is particularly useful in the case of the less reactive deazanucleosides. In this research the coupling of 2,6-dichloro-1- or 3-deazapurine with protected 3-deoxyribose is reported.

Depending upon coupling conditions and base structure, different anomeric and isomeric mixtures have been obtained. Extensive studies, using chemical and physical methods, have been performed to assign the correct configuration to the resulting nucleosides.

CHEMISTRY.

Coupling of 2,6-dichloro-1-deazapurine with protected 3-deoxyribose.

5,7-Dichloro-3H-imidazo[4,5-b]pyridine (**1**)[1] was treated with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**)[10] in dry acetonitrile using tin tetrachloride as catalyst (Scheme 1). The desired nucleoside **3** was obtained in 69% yield. Room temperature standing of **3** in methanol saturated at 0 °C with ammonia afforded the dichloro nucleoside **4** in 85% yield, which was converted to the 2-chloro-1-deaza-3'-deoxyAdo (**5**) by reaction with liquid ammonia at high temperature; moreover, the same derivative **5** was obtained by directly reacting **3** with liquid ammonia at 120° C.

Compounds **1** and **2** were also coupled under fusion reaction conditions, in the presence of a catalytic amount of *p*-toluenesulfonic acid, at 160 °C *in vacuo* for 10 min. Differently from the previously reported reaction conditions, the coupling gave a mixture of the N-3-β- and N-3-α-3'-deoxyribonucleosides **3** and **6**, with a total yield of 77%.

The anomeric mixture was reacted with methanolic ammonia at r. t. for several hours to yield 56% of 5,7-dichloro-3-deoxy-β-D-ribofuranosyl-3H-imidazo[4,5-b]pyridine (**4**) and 29% of the corresponding α-D-ribofuranosyl derivative **7** (Scheme 1).

The glycosylation site and the anomeric configuration were assigned on the basis of UV data and ^{1}H NMR spectra, including 1D ^{1}H n.O.e. difference spectra of the deprotected nucleosides **4** and **7**. The UV spectra of the two nucleosides were essentially identical.

Coupling of 2,6-dichloro-3-deazapurine with protected 3-deoxyribose.

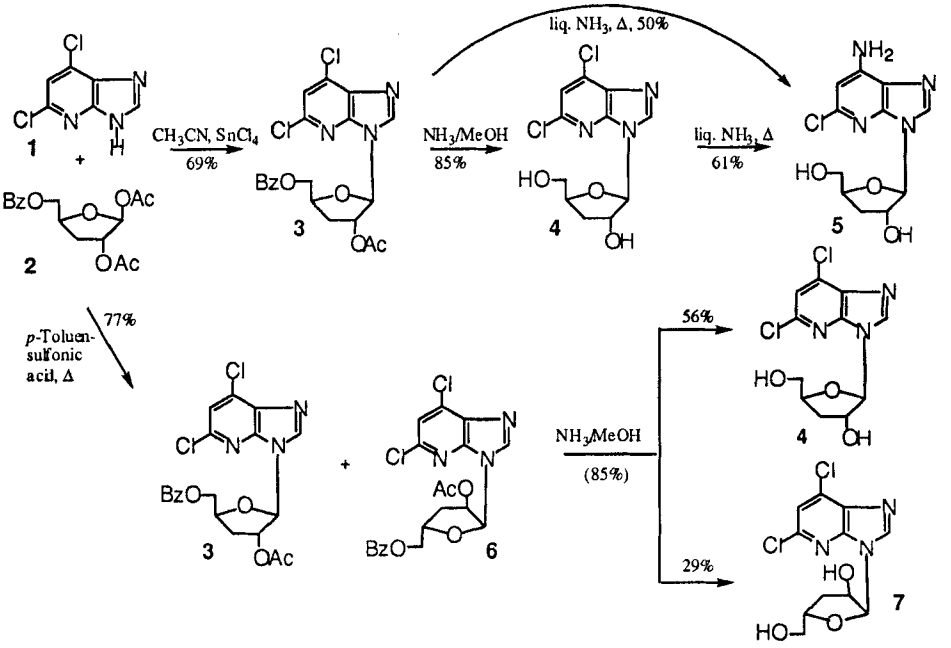
4,6-Dichloro-1H-imidazo[4,5-c]pyridine (**8**)[11] was treated with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**)[10] in the presence of a catalytic amount of *p*-toluenesulfonic acid at 160 °C *in vacuo* for 10 min. The coupling gave a mixture of N-1-β- and N-1-α- 3'-deoxyribonucleosides **9** and **10**. In the reaction mixture the N-1-α anomer **11** was also found, which proved to be 3'-deoxyarabinonucleoside deriving from epimerization at the C(2) of the sugar. Similar epimerization has been reported to occur under fusion reaction conditions in the case of ribose derivatives.[12] The total yield in nucleosides was 90%.

The glycosylation site and the anomeric configuration were assigned on the basis of UV data and ^{1}H NMR spectra, including 1D ^{1}H n.O.e. difference spectra, of the deprotected nucleosides **12**, **13**, **14** obtained by reacting **9**, **10**, and **11** with liquid ammonia (Scheme 2).

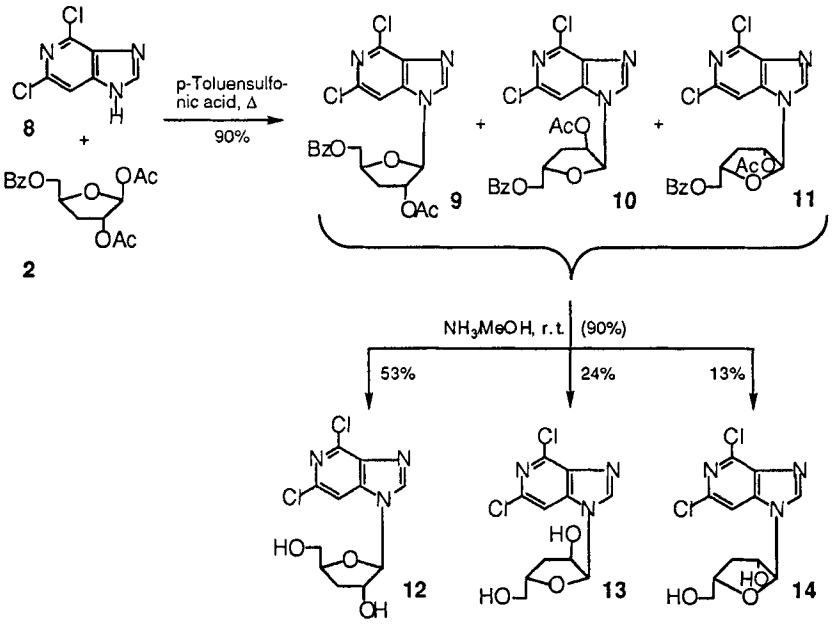
The UV spectra of the four nucleosides were essentially identical.

Furthermore, an n.O.e. at the H-C(2) and H-C(7) upon saturation of H-C(1') proves N(1) as glycosylation site in the case of all compounds.

SCHEME 1



SCHEME 2



Saturation of H-C(1') of compound **12** resulted in a n.O.e. at the H-C(4') and H-C(2') signal, while there was none at H-C(3'), establishing the β-D configuration. On the other hand, saturation of H-C(1') of compound **13** resulted in a n.O.e. at the H-C(3'a) signal, while there was none at H-C(4'), establishing the α-D configuration.

In the case of compound **14** irradiation of H-C(1') gave a n.O.e. effect at H-C(3'a) signal, while there was none at H-C(4'), establishing α-D configuration. Saturation of both H-C(2') and H-C(4') of the same nucleoside resulted in a n.O.e. at the H-C(3'b) signal, demonstrating that the sugar moiety of compound **14** is a deoxyarabinose derivative.

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